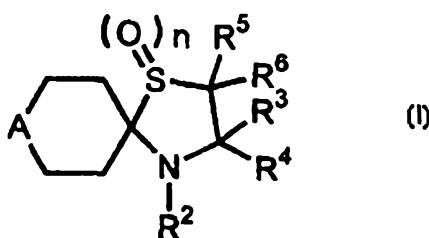




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			(43) 国際公開日 1999年11月18日(18.11.99)
(21) 国際出願番号 PCT/JP99/02262		西尾守弘(NISHIO, Morihiro)[JP/JP] 〒930-2237 富山県富山市打出819-5 Toyama, (JP)	
(22) 国際出願日 1999年4月28日(28.04.99)		黒田 宏(KURODA, Hiroshi)[JP/JP] 〒920-0935 石川県金沢市石引4丁目10-20 Isikawa, (JP)	
(30) 優先権データ 特願平10/142200 1998年5月8日(08.05.98) 特願平10/179649 1998年6月11日(11.06.98)		JP	田中啓一(TANAKA, Keiichi)[JP/JP] 〒930-0802 富山県富山市下新北町1-31 Toyama, (JP)
		JP	梶田哲也(KAJITA, Tetsuya)[JP/JP] 〒933-0874 富山県高岡市京田110 Toyama, (JP)
(71) 出願人 (米国を除くすべての指定国について) 富山化学工業株式会社 (TOYAMA CHEMICAL CO., LTD.)[JP/JP] 〒160-0023 東京都新宿区西新宿3丁目2-5 Tokyo, (JP)		広野修一(HIRONO, Shuichi)[JP/JP] 〒175-0093 東京都板橋区赤塚新町3丁目16-29 Tokyo, (JP)	
(72) 発明者 ; および (75) 発明者／出願人 (米国についてのみ) 茶木久晃(CHAKI, Hisaaki)[JP/JP] 〒930-1328 富山県上新川郡大山町小原屋455-1 Toyama, (JP)		塩澤俊一(SHIOZAWA, Shunichi)[JP/JP] 〒651-2274 兵庫県神戸市西区竹の台2丁目11-6 Hyogo, (JP)	
(81) 指定国 AU, CA, JP, KR, NZ, US, 欧州特許 (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE)			
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(54) Title: NOVEL SPIRO COMPOUNDS OR SALTS THEREOF, AND PREVENTIVES/REMEDIES FOR AUTOIMMUNE DISEASES AND AP-1 INHIBITORS CONTAINING THE SAME Agent for preventing and/or treating autoimmune diseases and AP-1 inhibitors containing the same

(54)発明の名称 新規なスピロ化合物またはその塩、それらを含有する自己免疫疾患の予防・治療剤およびAP-1阻害剤



(57) Abstract

(c) Spiro compounds represented by general formula (I), wherein A, R², R³, R⁴, R⁵, R⁶ and n are each as defined in the specification; which exert an AP-1 activity inhibitory effect. Owing to this effect, these compounds are useful as remedies/preventives for autoimmune diseases which inhibit the expression of various genes and show little side effect.

DESCRIPTION

NOVEL SPIRO COMPOUNDS OR SALTS THEREOF, AGENT FOR PREVENTING AND/OR TREATING AUTOIMMUNE DISEASES AND AP-1 INHIBITOR CONTAINING THE SAME

TECHNICAL FIELD

The present invention relates to novel spiro compounds or salts thereof that inhibit the activity of a transcription factor AP-1 and are useful as agents

- 5 for treating autoimmune diseases, agents for preventing and/or treating autoimmune diseases and an AP-1 inhibitor containing the same.

BACKGROUND ART

Up to today, therapeutic drugs for many diseases have been developed to control the functions of proteins such as enzymes and receptors. For example, for treating inflammatory diseases such as rheumatoid arthritis, etc., cyclooxygenase synthesizing prostaglandins from arachidonic acid or 5-lipoxygenase synthesizing leucotrienes have been taken as a target, and a number of non-steroidal antiinflammatory drugs such as indomethacin have been developed and put to therapeutic uses (J. Pharm. Sci., Vol. 73, Pages 579-589, 1984). Inflammatory cytokines such as interleukins (IL)-1 and IL-6 and tumor necrotic factor (TNF) have attracted intention as amplifying or



aggravating factors in inflammatory reaction. As agents for regulating the functions of these proteins, monoclonal antibodies for respective proteins (Arthritis Rheum., Vol. 36, Pages 1681-1690, 1993), low 5 molecular weight cytokine production inhibitors (Ann. Rep. Med. Chem., Vol. 27, Pages 209-218, 1992), etc. are being developed. Further, the use of antibodies for those cytokine receptors is also being attempted clinically (Rheumatism, Vol. 37, No. 2, Page 174, 10 1997).

In the diseases caused by a quantitative abnormality of functional proteins existing in cells or on cell membranes or of functional molecules secreted from cells, however, it is considered that a therapy in 15 the true sense is to regulate the quantity of transcription of functional molecule gene and thereby normalize the quantity of expression rather than to inhibit the activity of the functional molecules. It is known that not only the quantitative abnormalities 20 of the above-mentioned inflammatory cytokines and lipid mediators synthesized from arachidonic acid but also the quantitative abnormalities of many functional proteins such as adhesion molecules and matrix metallo proteinases take part in the cause of autoimmune 25 diseases such as rheumatoid arthritis and chronic inflammatory diseases (N. Engl. J. Med., Vol. 322, Pages 1277-1289, 1990). Although gene expression and production of these functional proteins are regulated



by a plurality of transcription factors, it is known that the promoter region of a majority of such genes commonly involves a consensus sequences of transcription factor AP-1 (TRE sequence). Further, it has been 5 reported that expression of some of these functional proteins is regulated by binding of AP-1 to the promoter region (Nature, Vol. 337, Pages 661-663, 1989).

A living body exhibits various defensive 10 reactions against outer stimulation and attack, and shows immune responses and inflammatory reactions.

Cellular and molecular analyses of such reactions have made a surprising progress in the recent years, due to which it has become apparent that gene 15 expression and production of proteins to make sure the physiological functions was induced the stimulation in all the cells constituting a living body.

The immune responses and inflammatory reactions are amplified and regulated by the 20 interaction of these genes including inflammatory cytokines such as IL-1 and TNF α , cell surface molecules such as cell-adhesion molecules and various cytokine receptors and enzymes such as matrix metallo-proteinases. On the other hand, autoimmune diseases 25 typified by rheumatoid arthritis and other intractable chronic inflammatory diseases are considered caused by an excessive immunity and inflammatory reactions. That is, it is prospected that, in these inflammatory



diseases, such a wide variety of genes directly relating to the etiology of disease are expressed in an excessive quantity, so that a mere inhibition or control of only one genetic product (protein) is 5 incapable of realizing a sufficient therapy (radical therapy).

At the present time, non-steroidal anti-inflammatory agents and steroidal agents are used for the pharmaceutical treatment of chronic inflammatory 10 diseases such as rheumatoid arthritis. Non-steroidal anti-inflammatory agents such as indomethacin and the like inhibit cyclooxygenase and thereby suppress the production of lipid mediators such as prostaglandin E₂ and the like. However, such a treatment is not 15 sufficient as a radical therapy because the use of these drugs is to suppress only one inflammatory mediator, cyclooxygenase, and the effect thereof is nothing but an expectation of a conservative treatment. On the other hand, steroidal agents are known to 20 exhibit regulating effect at the stage of expression of gene through intermediation of a glucocorticoid receptor, and it has actually been reported that these agents inhibit the activity of transcription factor AP-1 and thereby suppress the production of cytokines and 25 other proteins (Cell, Vol. 62, Pages 1189-1204, 1990). Although effectiveness of such steroidal agents are sufficiently recognized, the use of such steroidal agents is restricted by the hormonal and side effects



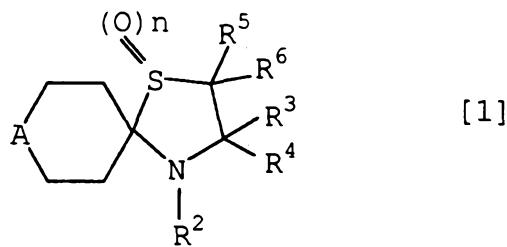
thereof, and they cannot be administered over a long period of time. Especially, the inflammatory diseases such as autoimmune diseases are generally chronic and require a long-term therapy, so that drugs having 5 intense side effects cannot be used at least at the present time.

Thus, it has been desired to develop an agent for treating and/or preventing autoimmune diseases which inhibits AP-1 activity and can suppress the 10 expression of a wide variety of genes through inhibiting AP-1 activity thereof, with lessened side reactions.

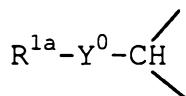
DISCLOSURE OF THE INVENTION

The present inventors have conducted 15 extensive studies with the aim of developing an agent for treating and/or preventing autoimmune diseases which inhibits AP-1 activity and can suppress the expression of a wide variety of genes through inhibiting AP-1 activity thereof, with lessened side 20 reactions. As a result, it has been found that spiro compounds having a spiro ring skeleton represented by the following general formula [1]:

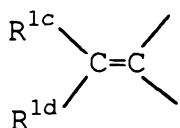




wherein A is a group of the following general formula:



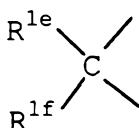
wherein R^{1a} represents hydrogen atom, halogen atom, cyano group, nitro group, an unprotected or protected carboxyl group, an unprotected or protected hydroxyl group, or an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, acyl, alkoxycarbonyl, aryloxycarbonyl, carbamoyl, amino or heterocyclic group; and Y⁰ represents oxygen atom, sulfur atom, an unsubstituted or substituted imino group, carbonyl group, methylene group, vinylene group, sulfinyl group, sulfonyl group or group -CH(OH)-; or a group of the following general formula:



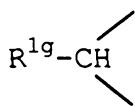
wherein R^{1c} and R^{1d}, same or different, each represents hydrogen atom, halogen atom, cyano group, nitro group,



an unprotected or protected carboxyl group, an unprotected or protected hydroxyl group, mercapto group, or an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, 5 acyl, alkoxycarbonyl, aryloxycarbonyl, carbamoyl, alkylthio, alkylsulfinyl, alkylsulfonyl, amino or heterocyclic group; or a group of the following general formula:



wherein R^{1e} and R^{1f} , same or different, each represents 10 halogen atom, cyano group, nitro group, an unprotected or protected carboxyl group, an unprotected or protected hydroxyl group, or an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, acyl, alkoxycarbonyl, aryloxycarbonyl, 15 carbamoyl, alkylthio, alkylsulfinyl, alkylsulfonyl, amino or heterocyclic group; or a group of the following general formula:



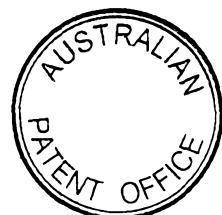
wherein R^{1g} represents an unsubstituted or substituted heterocyclic group;

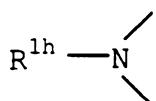
R^2 represents hydrogen atom or an



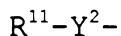
unsubstituted or substituted alkyl, alkenyl,
cycloalkyl, acyl, aryl, aralkyl, alkylsulfonyl,
arylsulfonyl or heterocyclic group; R³ and R⁴, same or
different, each represents hydrogen atom, halogen atom,
5 cyano group, an unprotected or protected carboxyl
group, an unprotected or protected hydroxyl group, or
an unsubstituted or substituted alkyl, alkenyl,
cycloalkyl, alkoxy, alkylthio, alkylsulfinyl,
alkylsulfonyl, acyl, alkoxycarbonyl, aryl, amino,
10 alkylamino, acylamino, carbamoyl or heterocyclic group
or R³ and R⁴, taken conjointly, represent an oxo group;
R⁵ and R⁶, same or different, each represents hydrogen
atom, halogen atom, cyano group, an unprotected or
protected carboxyl group, an unprotected or protected
15 hydroxyl group, or an unsubstituted or substituted
alkyl, alkenyl, cycloalkyl, alkoxy, alkylthio,
alkylsulfinyl, alkylsulfonyl, acyl, alkoxycarbonyl,
aryl, amino, alkylamino, acylamino, carbamoyl or
heterocyclic group or R⁵ and R⁶, taken conjointly with
20 the terminal carbon atom to which R⁵ and R⁶ are
combined, represent an alkenyl group; and n represents
0, 1 or 2;

spiro compounds represented by the general
formula [1] wherein A is a group represented by the
25 following general formula:

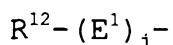




wherein R^{1h} represents a group of the following general formula:



wherein R^{11} represents hydrogen atom, halogen atom, 5 cyano group, an unprotected or protected carboxyl, hydroxyl or mercapto group or an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, alkoxy, alkylthio, alkylsulfonyl, arylsulfonyl, sulfamoyl, acyl, acyloxy, alkoxy carbonyl, aryloxycarbonyl, amino, 10 carbamoyl, carbamoyloxy or heterocyclic group; and Y^2 represents methylene group, an unsubstituted or substituted imino group, carbonyl group or sulfonyl group; or a group of the following general formula:

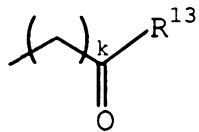


15 wherein E^1 represents amino acid residue; R^{12} represents hydrogen atom or a protecting group for amino group; and j represents 2 or 3;

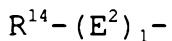
R^2 represents hydrogen atom, an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, acyl, aryl, 20 arylsulfonyl, alkylsulfonyl, aralkyl or heterocyclic group;

R^3 and R^4 , taken conjointly, represent an oxo group; R^5 represents hydrogen atom; R^6 represents a group of the following general formula:

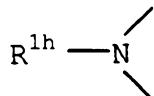




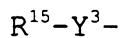
wherein R¹³ represents hydrogen atom, halogen atom, an unprotected or protected hydroxyl, hydroxyamino, amino, alkylamino, arylamino, acylamino, alkoxycarbonylamino, arylsulfonylamino or alkylsulfonylamino group, an 5 unsubstituted or substituted alkyl, aryloxy, aralkyloxy, alkylthio, alkoxy, aryl or heterocyclic group, or a group of the following general formula:



wherein E² represents amino acid residue; R¹⁴ represents 10 hydroxyl group or amino group; and l represents 1, 2 or 3; k represents 1, 2 or 3; and n represents 0, 1 or 2; spiro compounds represented by general formula [1] wherein A represents a group of the following general formula:



15 wherein R^{1h} represents a group of the following general formula:



wherein R¹⁵ represents hydrogen atom, halogen atom, cyano group, an unprotected or protected carboxyl, hydroxyl or mercapto group, or an unsubstituted or

substituted alkyl, alkenyl, cycloalkyl, aryl, alkoxy, alkylthio, alkylsulfonyl, arylsulfonyl, sulfamoyl, acyl, acyloxy, alkoxycarbonyl, aryloxycarbonyl, amino, carbamoyl, carbamoyloxy or heterocyclic group; and Y³

5 represents methylene group, an unsubstituted or substituted imino group, carbonyl group or sulfonyl group; or

a group of the following general formula:

R¹⁶-(E³)_s-

10 wherein E³ represents amino acid residue; R¹⁶ represents hydrogen atom or a protecting group for amino group; and s represents 2 or 3;

R² represents hydrogen atom, an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, acyl, aryl, 15 arylsulfonyl, alkylsulfonyl, aralkyl or heterocyclic group; R³ and R⁴, same or different, each represents hydrogen atom, halogen atom, cyano group, an unprotected or protected hydroxyl group or an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, acyl, alkoxycarbonyl, aryl, amino, alkylamino, acylamino, carbamoyl or heterocyclic group; or a group of the following general formula:

-CO-(E⁴)_t-R¹⁸

25 wherein E⁴ represents amino acid residue; R¹⁸ represents hydroxyl group or amino group; and t represents 1, 2 or 3; R⁵ and R⁶, same or different, each represents hydrogen atom, halogen atom, cyano group, an



unprotected or protected carboxyl group, an unprotected or protected hydroxyl group, an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, acyl, 5 alkoxycarbonyl, aryl, amino, alkylamino, acylamino, carbamoyl or heterocyclic group; and n represents 0, 1 or 2; and salts of the above-mentioned spiro compounds inhibit the activity of transcription factor AP-1 and are useful as an agent for preventing and/or treating 10 autoimmune diseases. Based on this finding, the present invention has been accomplished.

The compounds of the present invention inhibit the activity of transcription factor AP-1. That is to say, the compound of the present invention 15 inhibits the transcription of DNAs having a TRE alignment in the promoter region thereof. Thereby, it is possible to inhibit the production of proteins corresponding to the gene in genes having TRE sequence. Accordingly, the compounds of the present invention can 20 suppress the expression of genes of cytokines group such as IL-1 β , IL-2, IL-3, IL-8, TNF α , granulocyte-macrophage colony stimulating factor (GM-CSF), monocyte chemoattractant protein 1 (MCP-1), etc., MMPs such as collagenase (MMP-1), stromelysin (MMP-3), collagenase 25 IV (MMP-9), etc., cell surface molecules such as immunoglobulins, major histocompatibility complex (MHC) class II, vascular cell adhesion molecule 1 (VCAM-1), fibroblast growth factor (FGF) receptor, etc., growth



factors such as monocyte growth factor, insulin-related growth factor (IGF), nerve growth factor (NGF), etc., and metallothionein, collagen, osteocarcin, osteopontin, amyloid precursor protein, apolipoprotein-5 1, etc. Accordingly, the compounds of the present invention can prevent and/or treat the diseases is related to these genes.

As the diseases is related these genes, for example, collagen diseases (rheumatoid arthritis, 10 systemic lupus erythematosus, general scleroderma, rheumatic fever, multiple myositis, periarteritis nodosa, Sjögren's syndrome and Behçet's syndrome), idiopathic ulcerative colitis, glomerulonephritis, various autoimmune diseases such as autoimmune 15 hemolytic anemia and the like, active chronic hepatitis, osteoarthritis, gout, atherosclerosis, psoriasis, atopic dermatitis, lungal diseases accompanied by granuloma such as interstitial pneumonia, various meningitises, Alzheimer's disease, 20 and other intractable chronic inflammatory diseases can be referred to.

Hereunder, the compounds of the present invention will be detailed.

Unless otherwise referred to, the term 25 "halogen atom" used in this specification means fluorine atom, chlorine atom, bromine atom and iodine atom; the term "alkyl group" means a straight or branched chain C₁₋₁₂ alkyl group such as methyl, ethyl,



n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, pentyl, hexyl, heptyl, octyl and the like; the term "alkenyl group" means a straight or branched chain C₂₋₁₂ alkenyl group such as vinyl, allyl, propenyl, 5 isopropenyl, butenyl, isobutenyl, pentenyl, hexenyl, heptenyl, octenyl and the like; the term "cycloalkyl group" means a C₃₋₆ cycloalkyl group such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like; the term "aryl group" means a group such as phenyl, tolyl, 10 naphthyl and the like; the term "alkoxy group" means a straight or branched chain C₁₋₁₂ alkoxy group such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentyloxy, hexyloxy, heptyloxy, octyloxy and the like; the term 15 "alkoxyimino group" means a straight or branched chain C₁₋₁₂ alkoxyimino group such as methoxyimino, ethoxyimino and the like; the term "alkoxycarbonylamino group" means a straight or branched chain C₁₋₁₂ alkoxy- carbonylamino group such as methoxycarbonylamino, 20 ethoxycarbonylamino, n-propoxycarbonylamino, isopropoxycarbonylamino, n-butoxycarbonylamino, isobutoxycarbonylamino, sec-butoxycarbonylamino, tert- butoxycarbonylamino, pentyloxycarbonylamino, hexyloxycarbonylamino, heptyloxycarbonylamino, 25 octyloxycarbonylamino and the like; the term "arylsulfonylamino group" means an aryl-SO₂NH- group such as phenylsulfonylamino, naphthylsulfonylamino and the like; the term "alkylsulfonylamino group" means a



straight or branched chain C_{1-12} alkylsulfonylamino group such as methylsulfonylamino, ethylsulfonylamino, n-propylsulfonylamino, isopropylsulfonylamino, n-butylsulfonylamino, isobutylsulfonylamino, sec-
5 butylsulfonylamino, tert-butylsulfonylamino, pentylsulfonylamino, hexylsulfonylamino, heptylsulfonylamino, octylsulfonylamino and the like; the term "aryloxy group" means a group represented by aryl-O- such as phenoxy, tolyloxy, naphthoxy and the like;
10 the term "aryloxycarbonyl group" means a group represented by aryl-O-CO- such as phenoxy carbonyl, naphthoxycarbonyl and the like; the term "aryl amino group" means a group such as phenylamino, naphthylamino and the like; the term "alkylamino group" means a mono-
15 or di- C_{1-12} alkylamino group such as methylamino, ethylamino, propylamino, butylamino, pentylamino, hexylamino, heptylamino, octylamino, dimethylamino, diethylamino, methylethylamino, dipropylamino, dibutylamino, dipentylamino, dihexylamino,
20 diheptylamino, dioctylamino and the like; the term "aralkyl group" means an ar- C_{1-12} -alkyl group such as benzyl, phenethyl, 4-methylbenzyl, naphthylmethyl and the like; the term "alkylidene group" means a C_{1-12} alkylidene group such as methylene, ethylidene,
25 propylidene, isopropylidene, butylidene, hexylidene, octylidene and the like; the term "aralkyloxy group" means an ar- C_{1-12} -alkyloxy group such as benzyloxy, phenethyloxy, 4-methylbenzyloxy, naphthylmethyloxy and



the like; the term "aralkyloxycarbonyl group" means an ar-C₁₋₁₂-alkyloxycarbonyl group such as benzyloxy-carbonyl, phenethyloxycarbonyl, 4-methylbenzyloxy-carbonyl, naphthylmethyloxycarbonyl and the like; the 5 term "aralkylcarbonyloxy group" means an ar-C₁₋₁₂-alkylcarbonyloxy group such as benzylcarbonyloxy, phenethylcarbonyloxy, 4-methylbenzylcarbonyloxy, naphthylmethylcarbonyloxy and the like; the term "aralkylcarbonyl group" means a group represented by 10 aralkyl-CO- wherein aralkyl is as defined above; the term "acyl group" means acyl groups including C₂₋₁₂ alkanoyl groups such as formyl, acetyl, propionyl and the like, aralkylcarbonyl groups such as benzylcarbonyl and the like, aroyl groups such as benzoyl, naphthoyl 15 and the like and heterocycle-carbonyl groups such as nicotinoyl, thenoyl, pyrrolidinocarbonyl, furoyl and the like; the term "acyloxy group" means a group represented by acyl-O- wherein acyl is as defined above; the term "acylamino group" means a C₁₋₆ acylamino 20 group such as formylamino, acetylamino, propionylamino, butyrylamino and the like; the term "aralkyloxycarbonyl group" means an ar-C₁₋₁₂-alkyloxycarbonyl-CO- group such as benzyloxycarbonyl, phenethyloxycarbonyl, 4-methylbenzyloxycarbonyl, naphthylmethyloxycarbonyl and 25 the like; the term "cyclic amino group" means a cyclic amino group which may be any of saturated and unsaturated cyclic amino groups and may contain at least one heteroatom such as nitrogen atom, oxygen



atom, sulfur atom or the like and a carbonyl carbon in the ring thereof and may be any of monocyclic, bicyclic and tricyclic amino groups, of which more specific examples include saturated or unsaturated, monocyclic,

- 5 3- to 7-membered cyclic amino groups containing one nitrogen atom such as aziridin-1-yl, azetidin-1-yl, pyrrolidin-1-yl, pyrrolin-1-yl, pyrrol-1-yl, dihydropyridin-1-yl, piperidino, dihydroazepin-1-yl, perhydroazepin-1-yl and the like; saturated or
- 10 unsaturated, monocyclic, 3- to 7-membered cyclic amino groups containing two nitrogen atoms such as imidazol-1-yl, imidazolidin-1-yl, imidazolin-1-yl, pyrazolidin-1-yl, piperazin-1-yl, 1,4-dihydropyrazin-1-yl, 1,2-dihydropyrimidin-1-yl, perhydropyrazin-1-yl,
- 15 homopiperazin-1-yl and the like; saturated or unsaturated, monocyclic, 3- to 7-membered cyclic amino groups containing three or more nitrogen atoms such as 1,2,4-triazol-1-yl, 1,2,3-triazol-1-yl, 1,2-dihydro-1,2,4-triazin-1-yl, perhydro-S-triazin-1-yl and the
- 20 like; saturated or unsaturated, monocyclic, 3- to 7-membered cyclic amino groups containing 1 to 4 heteroatoms selected from the group consisting of oxygen atom and sulfur atom in addition to nitrogen atom such as oxazolidin-3-yl, isoxazolidin-2-yl,
- 25 morpholino, 1,3-oxazolidin-3-yl, thiazolidin-1-yl, isothiazolidin-1-yl, thiomorpholino, homothiomorpholin-1-yl, 1,2,4-thiadiazolin-2-yl and the like; saturated or unsaturated, bicyclic or tricyclic cyclic amino



groups such as isoindolin-2-yl, indolin-1-yl, 1H-indazol-1-yl, purin-7-yl, tetrahydroquinolin-1-yl and the like; and spiro or crosslinked, saturated or unsaturated, 5- to 12-membered cyclic amino groups such as 5-azaspiro[2.4]heptan-5-yl, 2,8-diazabicyclo[4.3.0]-nonan-8-yl, 3-azabicyclo[3.1.0]hexan-3-yl, 2-oxa-5,8-diazabicyclo[4.3.0]nonan-8-yl, 2,8-diazaspiro[4.4]-nonan-2-yl, 7-azabicyclo[2.2.1]heptan-7-yl and the like; the term "heterocyclic group" means a 4- to 7-membered or fused heterocyclic group containing at least one heteroatom selected from the group consisting of oxygen atom, nitrogen atom and sulfur atom such as azetidinyl, thienyl, furyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, 15 isoxazolyl, furazanyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiazidiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, thiatriazolyl, 20 pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, piperidinyl, piperazinyl, pyranyl, morpholinyl, 1,2,4-triazinyl, benzothienyl, naphthothienyl, benzofuryl, isobenzofuryl, chromenyl, indolidinyl, isoindolyl, indolyl, indazolyl, purinyl, quinolyl, isoquinolyl, 25 phthalazinyl, naphthylidinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, isochromanyl, chromanyl, indolinyl, isoindolinyl, benzoxazolyl, triazolopyridyl, tetrazolopyridazinyl,



tetrazolopyrimidinyl, thiazolopyridazinyl,
thiadiazolopyridazinyl, triazolopyridazinyl,
benzimidazolyl, benzothiazolyl, 1,2,3,4-
tetrahydroquinolyl, imidazo[1,2-b][1,2,4]triazinyl,
5 quinuclidinyl and the like; the term "alkanoyl group"
means a C_{2-12} alkanoyl group such as acetyl, propionyl
and the like; the term "aroyl group" means an aroyl
group such as benzoyl, naphthoyl and the like; the term
"heterocycle- carbonyl group" means a group represented
10 by heterocycle-CO- wherein heterocycle is as defined
above); the term "alkylthio group" means a straight or
branched chain C_{1-12} alkylthio group such as methylthio,
ethylthio, n-propylthio, isopropylthio, n-butylthio,
isobutylthio, sec-butylthio, tert-butylthio,
15 pentylthio, hexylthio, heptylthio, octylthio and the
like; the term "alkylsulfinyl group" means a straight
or branched chain C_{1-12} alkylsulfinyl group such as
methylsulfinyl, ethylsulfinyl, n-propylsulfinyl,
isopropylsulfinyl, n-butylsulfinyl, isobutylsulfinyl,
20 sec-butylsulfinyl, tert-butylsulfinyl, pentylsulfinyl,
hexylsulfinyl, heptylsulfinyl, octylsulfinyl and the
like; the term "alkylsulfonyl group" means a straight
or branched chain C_{1-12} alkylsulfonyl group such as
methylsulfonyl, ethylsulfonyl, n-propylsulfonyl,
isopropylsulfonyl, n-butylsulfonyl, isobutylsulfonyl,
25 sec-butylsulfonyl, tert-butylsulfonyl, pentylsulfonyl,
hexylsulfonyl, heptylsulfonyl, octylsulfonyl and the
like; the term "arylsulfonyl group" means, for example,



phenylsulfonyl group or naphthylsulfonyl group; the term "alkylsulfonyloxy group" means a straight or branched chain C_{1-12} alkylsulfonyloxy group such as methylsulfonyloxy, ethylsulfonyloxy, n-propyl-
 5 sulfonyloxy, isopropylsulfonyloxy, n-butylsulfonyloxy, isobutylsulfonyloxy, sec-butylsulfonyloxy, tert-butylsulfonyloxy, pentylsulfonyloxy, hexylsulfonyloxy, heptylsulfonyloxy, octylsulfonyloxy and the like; the term "arylsulfonyloxy group" means a group such as
 10 phenylsulfonyloxy, naphthylsulfonyloxy and the like; the term "alkoxycarbonyl group" means a straight or branched chain C_{1-12} alkyloxycarbonyl group such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl and the like; and the term "alkoxycarbonyloxy group" means
 15 a straight or branched chain C_{1-12} alkyloxycarbonyloxy group such as methoxycarbonyloxy, ethoxycarbonyloxy, propoxycarbonyloxy and the like.

As R^{1a} , R^{1b} , R^{1c} , R^{1d} , R^{1e} , R^{1f} , R^{1g} , R^{1aa} , R^{1ba} , R^{1ca} ,
 R^{1da} , R^{1ea} , R^{1fa} , R^{11a} , R^{aa} , R^{bb} , R^{cc} , R^{dd} , R^{ee} , R^{ff} , R^{aaa} , R^{bbb} ,
 20 R^{ccc} , R^{ddd} , R^{eee} , R^{fff} , R^2 , R^{2a} , R^3 , R^4 , R^5 , R^6 , R^{11} , R^{13} , R^{13a} ,
 R^{13aa} , R^{15} , R^{15a} , Y , Y^0 , Y^2 , Y^3 and the substituents used in the formulas of production processes, for example, halogen atom, cyano group, nitro group, sulfo group, mercapto group, an unprotected or protected carboxyl
 25 group, an unprotected or protected hydroxyl and hydroxyimino groups, an unprotected or protected amino group, an unprotected or protected imino group, an unsubstituted or substituted alkyl, alkoxy,



alkoxycarbonyl, alkoxyimino, acyl, acyloxy, carbamoyl, carbamoyloxy, aralkylcarbonyloxy, aryl, aryloxy-carbonyl, aralkyloxycarbonyl, cycloalkyl, alkenyl, aralkyl, alkylthio, alkylsulfonyl, alkylsulfonyloxy,

5 alkylidene and heterocyclic groups, an unprotected or protected cyclic amino, aminosulfonyl, aminosulfinyl, alkoxycarbonylamino and alkylamino groups can be referred to. If desired, these groups may be substituted with at least one of these substituents.

10 As the substituted alkyl group in R^{1b}, R^{1ba}, R^{bb} and R^{bbb}, the same groups as above can be referred to, and they are substituted with at least one of these substituents.

The protecting groups for carboxyl group

15 which can be used include all the groups conventionally usable as a protecting group for carboxyl group. As examples thereof, there can be referred to alkyl groups such as methyl, ethyl, n-propyl, iso-propyl, 1,1-dimethylpropyl, n-butyl, tert-butyl and the like; aryl groups such as phenyl, naphthyl and the like; aralkyl groups such as benzyl, diphenylmethyl, trityl, p-nitrobenzyl, p-methoxybenzyl, bis(p-methoxyphenyl)-methyl and the like; acyl-alkyl groups such as acetyl methyl, benzoylmethyl, p-nitrobenzoylmethyl, p-bromobenzoylmethyl, p-methanesulfonylbenzoylmethyl and the like; oxygen-containing heterocyclic groups such as 2-tetrahydropyranyl, 2-tetrahydrofuranyl and the like; halogeno-alkyl groups such as 2,2,2-trichloroethyl and



the like; alkylsilylalkyl groups such as 2-(trimethylsilyl)ethyl and the like; acyloxyalkyl groups such as acetoxyethyl, propionyloxymethyl, pivaloyloxymethyl and the like; nitrogen-containing heterocycle-alkyl groups such as phthalimidomethyl, succinimidomethyl and the like; cycloalkyl groups such as cyclohexyl and the like; alkoxy-alkyl groups such as methoxymethyl, methoxyethoxymethyl, 2-(trimethylsilyl)-ethoxymethyl and the like; ar-alkoxy-alkyl groups such as benzyloxymethyl and the like; alkylthio-alkyl groups such as methylthiomethyl, 2-methylthioethyl and the like; arylthio-alkyl groups such as phenylthiomethyl and the like; alkenyl groups such as 1,1-dimethyl-2-propenyl, 3-methyl-3-butenyl, allyl and the like; and substituted silyl groups such as trimethylsilyl, triethylsilyl, triisopropylsilyl, diethyl-isopropylsilyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl, diphenylmethylsilyl, tert-butylmethoxyphenylsilyl and the like.

The protecting groups for amino group which can be used include all the groups conventionally usable as a protecting group for amino group. As examples thereof, there can be referred to acyl groups such as trichloroethoxycarbonyl, tribromoethoxy-carbonyl, benzoyloxycarbonyl, p-nitrobenzylcarbonyl, o-bromobenzylloxycarbonyl, (mono-, di-, tri-)chloroacetyl, trifluoroacetyl, phenylacetyl, formyl, acetyl, benzoyl, tert-amyoxy carbonyl, tert-butoxycarbonyl, p-



methoxybenzyloxycarbonyl, 3,4-dimethoxybenzyloxy-
carbonyl, 4-(phenylazo)benzyloxycarbonyl, 2-
furfuryloxycarbonyl, diphenylmethoxycarbonyl, 1,1-
dimethylpropoxycarbonyl, isopropoxycarbonyl, phthaloyl,
5 succinyl, alanyl, leucyl, 1-adamantyloxycarbonyl, 8-
quinolyloxycarbonyl and the like; aralkyl groups such
as benzyl, diphenylmethyl, trityl and the like;
arylthio groups such as 2-nitrophenylthio, 2,4-
dinitrophenylthio and the like; alkyl- and aryl-
10 sulfonyl groups such as methanesulfonyl,
paratoluenesulfonyl and the like; dialkylamino-
alkylidene groups such as N,N-dimethylaminomethylene
and the like; aralkylidene groups such as benzylidene,
2-hydroxybenzylidene, 2-hydroxy-5-chlorobenzylidene, 2-
15 hydroxy-1-naphthylmethylen and the like; nitrogen-
containing heterocyclic alkylidene groups such as 3-
hydroxy-4-pyridylmethylen and the like; cyclo-
alkylidene groups such as cyclohexylidene, 2-
ethoxycarbonylcyclohexylidene, 2-ethoxycarbonyl-
20 cyclopentylidene, 2-acetylcyclohexylidene, 3,3-
dimethyl-5-oxycyclohexylidene and the like; diaryl- and
diaralkylphosphoryl groups such as diphenylphosphoryl,
dibenzylphosphoryl and the like; oxygen-containing
heterocyclic alkyl groups such as 5-methyl-2-oxo-2H-
25 1,3-dioxol-4-yl-methyl and the like; and substituted
silyl groups such as trimethylsilyl and the like.

The protecting groups for hydroxyl group
which can be used include all the groups conventionally



usable as a protecting group for hydroxyl group. As examples thereof, there can be referred to acyl groups such as benzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, 4-bromobenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl,

- 5 3,4-dimethoxybenzyloxycarbonyl, methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl, 1,1-dimethylpropoxycarbonyl, isopropoxycarbonyl, isobutyloxycarbonyl, diphenylmethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2,2,2-tribromoethoxycarbonyl,
- 10 2-(trimethylsilyl)-ethoxycarbonyl, 2-(phenylsulfonyl)-ethoxycarbonyl, 2-(triphenylphosphonio)ethoxycarbonyl, 2-furyloxycarbonyl, 1-adamantyloxycarbonyl, vinyloxycarbonyl, allyloxycarbonyl, S-benzylthiocarbonyl, 4-ethoxy-1-naphthyloxycarbonyl, 8-
- 15 quinolyloxycarbonyl, acetyl, formyl, chloroacetyl, dichloroacetyl, trichloroacetyl, trifluoroacetyl, methoxyacetyl, phenoxyacetyl, pivaloyl, benzoyl and the like; alkyl groups such as methyl, tert-butyl, 2,2,2-trichloroethyl, 2-trimethylsilylethyl and the like; alkenyl groups such as allyl and the like; aralkyl groups such as benzyl, p-methoxybenzyl, 3,4-dimethoxybenzyl, diphenylmethyl, trityl and the like; oxygen-containing and sulfur-containing heterocyclic groups such as tetrahydrofuryl, tetrahydropyranyl,
- 20 tetrahydrothiopyranyl and the like; alkoxy-alkyl groups such as methoxymethyl, methylthiomethyl, benzyloxymethyl, 2-methoxyethoxymethyl, 2,2,2-trichloroethoxymethyl, 2-(trimethylsilyl)ethoxymethyl,
- 25



1-ethoxyethyl and the like; alkyl- and aryl-sulfonyl groups such as methanesulfonyl, paratoluenesulfonyl and the like; and substituted silyl groups such as trimethylsilyl, triethylsilyl, triisopropylsilyl,
5 diethylisopropylsilyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl, diphenylmethyilsilyl, tert-butylmethoxyphenylsilyl and the like.

The term "amino acid residue" means an $-\text{NH}(\text{CHR})_z\text{CO}-$ part (R is an amino acid side chain, and Z is an integer of 1 to 6) which appears when an amino acid is introduced into a protein molecule or a peptide molecule while forming a peptide bonding with loss of a water molecule. Herein, the term "amino acid" means a compound having a carboxyl group and an amino group in
15 one molecule such as glycine, alanine, valine, leucine, isoleucine, serine, threonine, asparagine, aspartic acid, glutamine, glutamic acid, lysine, alginine, histidine, methionine, thyrosine, phenylalanine, tryptophane, proline, cysteine, homocysteine, β -alanine, γ -aminobutyric acid, ornithine, 3,4-dihydroxyphenylalanine and the like.
20

As the salt of the compound of general formula [1], usually known salts formed at the site of basic group such as amino group and the like and at the
25 site of acidic group such as hydroxyl or carboxyl group and the like can be referred to. As the salt formed at the site of a basic group, for example, salts of a mineral acid such as hydrochloric acid, hydrobromic



acid, sulfuric acid and the like; salts of an organic acid such as tartaric acid, formic acid, citric acid, trichloroacetic acid, trifluoroacetic acid and the like; and salts of a sulfonic acid such as

5 methanesulfonic acid, benzenesulfonic acid, paratoluenesulfonic acid, mesitylenesulfonic acid, naphthalenesulfonic acid and the like can be referred to. As the salts formed at the site of an acid group, for example, salts of alkali metals such as sodium,

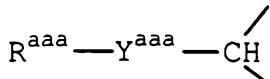
10 potassium and the like; salts of alkaline earth metals such as calcium, magnesium and the like; ammonium salts; and salts of nitrogen-containing organic bases such as trimethylamine, triethylamine, tributylamine, pyridine, N,N-dimethylaniline, N-methylpiperidine, N-

15 methylmorpholine, diethylamine, dicyclohexylamine, procaine, dibenzylamine, N-benzyl- β -phenethylamine, 1-ephedamine, and N,N'-dibenzylethylene-diamine and the like can be referred to. Of the salts mentioned above, preferred salts of the compound of general formula [1]

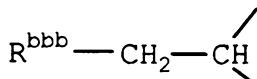
20 are pharmacologically acceptable ones.

Among the compounds of the present invention, preferred are the compounds in which A represents a group of the following general formula:

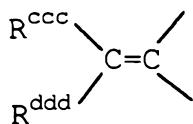




wherein R^{aaa} represents hydrogen atom, an unprotected or protected carboxyl group, an unprotected or protected hydroxyl group or an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, 5 acyl, alkoxycarbonyl, amino or heterocyclic group; and Y^{aaa} represents oxygen atom, sulfur atom, carbonyl group, vinylene group, sulfinyl group or sulfonyl group; a group of the following general formula:



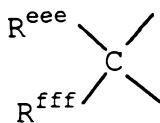
wherein R^{bbb} represents an unprotected or protected 10 carboxyl group, an unprotected or protected hydroxyl group, substituted alkyl group or an unsubstituted or substituted alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, acyl, alkoxycarbonyl, amino or heterocyclic group; a group of the following general formula:



15 wherein R^{ccc} and R^{ddd} , same or different, each represents hydrogen atom, an unprotected or protected carboxyl group or an unsubstituted or substituted alkyl,



alkenyl, cycloalkyl, aryl, alkoxy, acyl, alkoxycarbonyl, amino or heterocyclic group; or a group of the following general formula:

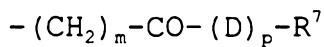


wherein R^{eee} and R^{fff} , same or different, each represents

5 an unprotected or protected carboxyl group, an unprotected or protected hydroxyl group or an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, alkoxy, acyl, alkoxycarbonyl, amino or heterocyclic group; R^2 represents hydrogen atom or an

10 unsubstituted or substituted alkyl, alkenyl, acyl, aryl, aralkyl, alkylsulfonyl, arylsulfonyl or heterocyclic group; R^3 and R^4 , same or different, each represents hydrogen atom, an unprotected or protected carboxyl group or an unsubstituted or substituted

15 alkyl, acyl, alkoxycarbonyl, carbamoyl group or a group of the following general formula:

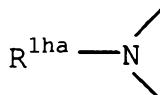


wherein D represents amino acid residue; R^7 represents hydroxyl group or amino group; p represents 1, 2 or 3; 20 and m represents 0, 1, 2 or 3, or R^3 and R^4 , taken conjointly, represent an oxo group; R^5 and R^6 , same or different, each represents hydrogen atom, halogen atom, cyano group, an unprotected or protected carboxyl group, an unprotected or protected hydroxyl group, or

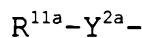


an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, acyl, alkoxycarbonyl, aryl, amino, alkylamino, acylamino, carbamoyl or heterocyclic group, 5 or R⁵ and R⁶, taken conjointly with the terminal carbon atom to which R⁵ and R⁶ are combined, represent an alkenyl group; and n represents 0, 1 or 2.

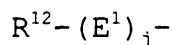
Also, preferred are the compounds in which A represents a group of the following general formula:



10 wherein R^{1ha} represents a group of the following general formula:

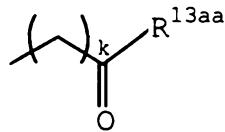


wherein R^{11a} represents an unsubstituted or substituted alkyl, alkenyl, aryl, alkoxy or heterocyclic group; and 15 Y^{2a} represents methylene group, carbonyl group or sulfonyl group; or a group represented by the following general formula:

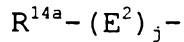


wherein E¹ represents amino acid residue; R¹² represents 20 hydrogen atom or a protecting group for amino group; and j represents 2 or 3; R² represents hydrogen atom or an unsubstituted or substituted alkyl, alkenyl, aryl, aralkyl or heterocyclic group; R⁶ represents a group of the following general formula:



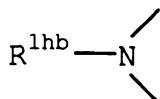


wherein R^{13aa} represents an unprotected or protected hydroxyl, amino, alkylamino, acylamino, alkoxy-carbonylamino, arylsulfonylamino or alkylsulfonylamino group or an unsubstituted or substituted alkyl or 5 alkoxy group; and k represents 1, 2 or 3; or a group of the following general formula:



wherein E^2 represents amino acid residue; R^{14a} represents hydroxyl group or amino group; and j represents 1, 2 or 10 3.

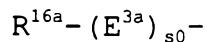
Also, preferred are the compounds in which A represents a group of the following general formula:



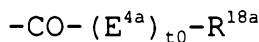
wherein R^{1hb} represents a group of the following general formula:

15 R^{15a}-Y^{3a}-

wherein R^{15a} represents an unsubstituted or substituted alkyl, alkenyl, aryl or heterocyclic group; and Y^{3a} represents carbonyl group or a group of the following general formula:

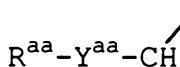


wherein E^{3a} represents amino acid residue; R^{16a} represents hydrogen atom or a protecting group for amino group; and s_0 represents 2 or 3; R^2 represents hydrogen atom or an unsubstituted or substituted acyl group; R^3 represents hydrogen atom; R^4 represents carbamoyl group or a group of the following general formula:

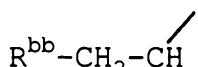


wherein E^{4a} represents amino acid residue; R^{18a} represents hydroxyl group or amino group; and t_0 represents 1, 2 or 3; R^5 and R^6 , same or different, each represents hydrogen atom, an unsubstituted or substituted alkyl group; and n represents 0.

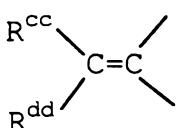
Among the compounds of the present invention, further preferred are the compounds in which A represents a group of the following general formula:



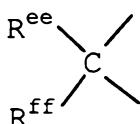
wherein R^{aa} represents an unsubstituted or substituted alkyl, alkenyl, aryl or heterocyclic group; and Y^{aa} represents oxygen atom or vinylene group; a group of the following general formula:



wherein R^{bb} represents an unsubstituted or substituted alkyl group or an unsubstituted or substituted alkenyl, aryl or heterocyclic group; a group of the following general formula:



5 wherein R^{cc} and R^{dd}, same or different, each represents hydrogen atom or an unsubstituted or substituted alkyl, alkenyl, aryl or heterocyclic group; or a group of the following general formula:



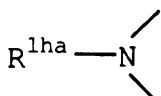
wherein R^{ee} and R^{ff}, same or different, each represents
 10 an unprotected or protected hydroxyl group or an unsubstituted or substituted aryl group; R² represents hydrogen atom, formyl group, alkanoyl group, aralkyl-carbonyl group or an unsubstituted or substituted alkyl, alkenyl, aroyl, heterocycle-carbonyl, aryl, aralkyl or heterocyclic group; R³ and R⁴, same or different, each represents hydrogen atom, an unsubstituted or substituted alkoxy carbonyl, carbamoyl group or a group of the following general formula:



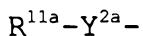
20 wherein D represents amino acid residue; R⁷ represents

hydroxyl group or amino group; p represents 1, 2 or 3; and m represents 0, 1, 2 or 3, or R³ and R⁴, taken conjointly, represent an oxo group; R⁵ and R⁶, same or different, each represents hydrogen atom or an 5 unsubstituted or substituted alkyl group; and n represents 0 or 2.

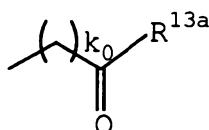
Also, further preferred are the compounds in which A represents a group of the following general formula:



10 wherein R^{1ha} represents a group of the following general formula:



wherein R^{11a} represents an unsubstituted or substituted alkyl, alkenyl, aryl or heterocyclic group; and Y^{2a} 15 represents methylene group, carbonyl group or sulfonyl group; R² represents hydrogen atom or an unsubstituted or substituted alkyl or aralkyl group; R⁶ represents a group of the following general formula:



wherein R^{13a} represents an unprotected or protected hydroxyl, amino, alkylamino, acylamino,

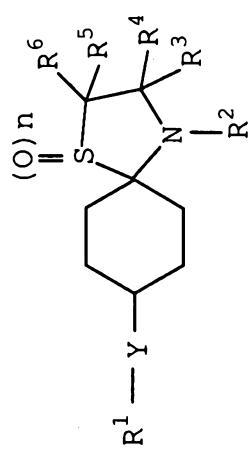
alkoxycarbonylamino, arylsulfonylamino or alkylsulfonylamino group or an unsubstituted or substituted alkoxy group; and k_0 represents 1; and n represents 0.

5 As representative examples of the compound of the present invention, the compounds of the following Tables 1 to 51 can be referred to.





[Table 1]



No.	n	R ¹ -Y-	R ²	R ³	R ⁴	R ⁵	R ⁶
1	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	H	COOH	H	H	H
2	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₃	COOH	H	H	H
3	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₃	COOH	H	H	H
4	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ CH ₃	COOH	H	H	H
5	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ CH ₂ CH ₃	COOH	H	H	H
6	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ CH ₂ CH ₂ CH ₃	COOH	H	H	H
7	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH(CH ₃)CH ₃	COOH	H	H	H
8	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH(CH ₃)CH ₃	COOH	H	H	H
9	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ CH(CH ₃)CH ₃	COOH	H	H	H
10	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ CH ₂ CH(CH ₃)CH ₃	COOH	H	H	H
11	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH(CH ₃)C ₂ H ₅	COOH	H	H	H
12	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ CH(CH ₃)C ₂ H ₅	COOH	H	H	H
13	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ CH(C ₂ H ₅)C ₂ H ₅	COOH	H	H	H
14	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ F	COOH	H	H	H
15	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ OH	COOH	H	H	H



[Table 2]

No.	n	R ¹ -Y-	R ²	R ³	R ⁴	R ⁵	R ⁶
16	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ OH	COOH	H	H	H
17	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ CH ₂ OH	COOH	H	H	H
18	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ CH ₂ CH ₂ OH	COOH	H	H	H
19	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ OH	COOH	H	H	H
20	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH(OH)CH ₂ OH	COOH	H	H	H
21	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH(OH)CH ₂ OH	COOH	H	H	H
22	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH(OH)CH ₂ CH ₂ OH	COOH	H	H	H
23	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ CH(OH)CH ₂ CH ₂ OH	COOH	H	H	H
24	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ OC(O)NH ₂	COOH	H	H	H
25	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ OC(O)CH ₃	COOH	H	H	H
26	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ COOH	COOH	H	H	H
27	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOH	COOH	H	H	H
28	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ CH ₂ COOH	COOH	H	H	H
29	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ CH ₂ CH ₂ COOH	COOH	H	H	H
30	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ CH ₂ CH ₂ COOH	COOH	H	H	H
31	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ COOCH ₃	COOH	H	H	H
32	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ COOC ₂ H ₅	COOH	H	H	H
33	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ COO-n-C ₃ H ₇	COOH	H	H	H
34	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ COO-i-C ₃ H ₇	COOH	H	H	H
35	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ COOC ₆ H ₅	COOH	H	H	H



[Table 3]

No.	n	R ¹ -Y-	R ²	R ³	R ⁴	R ⁵	R ⁶
36	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ COOCH ₂ C ₆ H ₅	COOH	H	H	H
37	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CONH ₂	COOH	H	H	H
38	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CONHOH	COOH	H	H	H
39	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CONHCH ₃	COOH	H	H	H
40	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CONHC ₂ H ₅	COOH	H	H	H
41	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CONH-n-C ₃ H ₇	COOH	H	H	H
42	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CONH-i-C ₃ H ₇	COOH	H	H	H
43	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CON(CH ₃) ₂	COOH	H	H	H
44	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CON(n-C ₃ H ₇) ₂	COOH	H	H	H
45	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CON(C ₂ H ₅) ₃	COOH	H	H	H
46	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CONHC ₆ H ₅	COOH	H	H	H
47	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₃	COOH	H	H	H
48	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	COOH	H	H	H
49	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH(CH ₃)COOH	COOH	H	H	H
50	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH(CH ₂ OH)COOH	COOH	H	H	H
51	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH(CH ₂ COOH)COOH	COOH	H	H	H
52	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH(CH ₂ CONH ₂)COOH	COOH	H	H	H
53	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH(CH ₂ CH ₂ COOH)COOH	COOH	H	H	H
54	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH(CH ₂ CH ₂ CONH ₂)COOH	COOH	H	H	H
55	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH(4-Imidazolylmethyl)COOH	COOH	H	H	H



Table 4]

No.	n	R ¹ -Y-	R ²	R ³	R ⁴	R ⁵	R ⁶
56	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH(CH(C ₂ H ₅)CH ₃)COOH	COOH	H	H	H
57	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH(CH ₂ CH(CH ₃)CH ₃)COOH	COOH	H	H	H
58	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH(CH ₂ CH ₂ SCH ₃)COOH	COOH	H	H	H
59	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH(CH(OH)CH ₃)COOH	COOH	H	H	H
60	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH(CH ₂ -(4-HO)C ₆ H ₅)COOH	COOH	H	H	H
61	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH(CH ₂ C ₆ H ₅)COOH	COOH	H	H	H
62	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH(3-Indolylmethyl)COOH	COOH	H	H	H
63	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH(i-C ₃ H ₇)COOH	COOH	H	H	H
64	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CN	COOH	H	H	H
65	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ NO ₂	COOH	H	H	H
66	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ COCH ₃	COOH	H	H	H
67	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ C(NOH)CH ₃	COOH	H	H	H
68	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ SO ₃ H	COOH	H	H	H
69	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ S(O) ₂ CH ₃	COOH	H	H	H
70	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ S(O)CH ₃	COOH	H	H	H
71	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ SO ₂ NH ₂	COOH	H	H	H
72	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ SO ₃ CH ₃	COOH	H	H	H
73	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ OCH ₃	COOH	H	H	H
74	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ OCH ₃	COOH	H	H	H
75	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ CH ₂ OCH ₃	COOH	H	H	H



[Table 5]

No.	n	R ¹ -Y-	R ²	R ³	R ⁴	R ⁵	R ⁶
76	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ SCH ₃	COOH	H	H	H
77	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CHCH ₂	COOH	H	H	H
78	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CHCH ₂	COOH	H	H	H
79	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CHCHCH ₃	COOH	H	H	H
80	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	Cyclopropyl	COOH	H	H	H
81	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	Cyclobutyl	COOH	H	H	H
82	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	Cyclopentyl	COOH	H	H	H
83	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	Cyclohexyl	COOH	H	H	H
84	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ C ₆ H ₅	COOH	H	H	H
85	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ C ₆ H ₅	COOH	H	H	H
86	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ C ₆ H ₁₁	COOH	H	H	H
87	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH(CH ₃)C ₆ H ₅	COOH	H	H	H
88	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	2-Thienylmethyl	COOH	H	H	H
89	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	2-Furfuryl	COOH	H	H	H
90	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	2-Pyranylmethyl	COOH	H	H	H
91	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	1-Isobenzofurylmethyl	COOH	H	H	H
92	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	2-Pyrrolylmethyl	COOH	H	H	H
93	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	1-Imidazolylmethyl	COOH	H	H	H
94	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	1-Pyrazolylmethyl	COOH	H	H	H
95	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	3-Isothiazolylmethyl	COOH	H	H	H



[Table 6]

No.	n	R ¹ -Y-	R ²	R ³	R ⁴	R ⁵	R ⁶
96	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	3-Isoxazolylmethyl	COOH	H	H	H
97	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	2-Pyridylmethyl	COOH	H	H	H
98	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	2-Pyrazinylmethyl	COOH	H	H	H
99	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	2-Pyrimidinylmethyl	COOH	H	H	H
100	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	3-Pyridazinylmethyl	COOH	H	H	H
101	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	1-Isoindolylmethyl	COOH	H	H	H
102	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	2-Indolylmethyl	COOH	H	H	H
103	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	3-(1H-Indazolyl)methyl	COOH	H	H	H
104	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	2-Purinylmethyl	COOH	H	H	H
105	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	1-Isoquinolylmethyl	COOH	H	H	H
106	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	2-Quinolylmethyl	COOH	H	H	H
107	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	1-Phthalazinylmethyl	COOH	H	H	H
108	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	2-Naphthylidinylmethyl	COOH	H	H	H
109	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	2-Quinoxalinylmethyl	COOH	H	H	H
110	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	2-Quinazolinylmethyl	COOH	H	H	H
111	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	3-Cinnolinylmethyl	COOH	H	H	H
112	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	2-Oxazolylmethyl	COOH	H	H	H
113	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	2-Thiazozylmethyl	COOH	H	H	H
114	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	2-Benzo[b]furylmethyl	COOH	H	H	H
115	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	2-Benzo[b]thienylmethyl	COOH	H	H	H



[Table 7]

No.	n	R ¹ -Y-	R ²	R ³	R ⁴	R ⁵	R ⁶
116	0	4-CH ₃ CH (CH ₃) C ₆ H ₄ O-	3-(1,2,4-Triazinyl)methyl	COOH	H	H	H
117	0	4-CH ₃ CH (CH ₃) C ₆ H ₄ O-	2-Benz [d] imidazolylmethyl	COOH	H	H	H
118	0	4-CH ₃ CH (CH ₃) C ₆ H ₄ O-	2-Benz [d] oxazolylmethyl	COOH	H	H	H
119	0	4-CH ₃ CH (CH ₃) C ₆ H ₄ O-	Phenyl	COOH	H	H	H
120	0	4-CH ₃ CH (CH ₃) C ₆ H ₄ O-	2-Thiazolyl	COOH	H	H	H
121	0	4-CH ₃ CH (CH ₃) C ₆ H ₄ O-	4-Imidazolyl	COOH	H	H	H
122	0	4-CH ₃ CH (CH ₃) C ₆ H ₄ O-	3-Pyrazolyl	COOH	H	H	H
123	0	4-CH ₃ CH (CH ₃) C ₆ H ₄ O-	3-Isoxazolyl	COOH	H	H	H
124	0	4-CH ₃ CH (CH ₃) C ₆ H ₄ O-	5-Isothiazolyl	COOH	H	H	H
125	0	4-CH ₃ CH (CH ₃) C ₆ H ₄ O-	2-Pyrimidinyl	COOH	H	H	H
126	0	4-CH ₃ CH (CH ₃) C ₆ H ₄ O-	3-(1,2,4-Triazolyl)	COOH	H	H	H
127	0	4-CH ₃ CH (CH ₃) C ₆ H ₄ O-	2-Pyridyl	COOH	H	H	H
128	0	4-CH ₃ CH (CH ₃) C ₆ H ₄ O-	2-Benzoxazolyl	COOH	H	H	H
129	0	4-CH ₃ CH (CH ₃) C ₆ H ₄ O-	3-Benzothienyl	COOH	H	H	H
130	0	4-CH ₃ CH (CH ₃) C ₆ H ₄ O-	2-Benzofuryl	COOH	H	H	H
131	0	4-CH ₃ CH (CH ₃) C ₆ H ₄ O-	5-Indolyl	COOH	H	H	H
132	0	4-CH ₃ CH (CH ₃) C ₆ H ₄ O-	2-Pyrazinyl	COOH	H	H	H
133	0	4-CH ₃ CH (CH ₃) C ₆ H ₄ O-	3-Quinolinyl	COOH	H	H	H
134	0	4-CH ₃ CH (CH ₃) C ₆ H ₄ O-	5-Tetrazolyl	COOH	H	H	H
135	0	4-CH ₃ CH (CH ₃) C ₆ H ₄ O-	Methylsulfonyl	COOH	H	H	H

[Table 8]



No.	n	R ¹ -Y-	R ²	R ³	R ⁴	R ⁵	R ⁶
136	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	Benzenesulfonyl	COOH	H	H	H
137	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COCH ₃	COOH	H	H	H
138	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COCH ₂ CH ₃	COOH	H	H	H
139	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COCH ₂ CH ₂ CH ₃	COOH	H	H	H
140	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COCH ₂ CH ₂ CH ₂ CH ₃	COOH	H	H	H
141	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COCH ₂ CH ₂ CH ₂ CH ₂ CH ₃	COOH	H	H	H
142	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COCH(CH ₃)CH ₃	COOH	H	H	H
143	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COCH ₂ CH(CH ₃)CH ₃	COOH	H	H	H
144	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COCH ₂ C ₆ H ₅	COOH	H	H	H
145	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	2-Thienylmethylcarbonyl	COOH	H	H	H
146	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	2-Furylmethylcarbonyl	COOH	H	H	H
147	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	2-Pyridylmethylcarbonyl	COOH	H	H	H
148	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	2-Quinolylmethylcarbonyl	COOH	H	H	H
149	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	2-Benzothienylmethylcarbonyl	COOH	H	H	H
150	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	2-Naphthylidinylmethylcarbonyl	COOH	H	H	H
151	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	2-thiazolylmethylcarbonyl	COOH	H	H	H
152	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	2-Pyrimidinylmethylcarbonyl	COOH	H	H	H
153	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	2-Benzoxazolylmethylcarbonyl	COOH	H	H	H
154	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	2-Indolylmethylcarbonyl	COOH	H	H	H
155	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	2-Thiazolylmethylcarbonyl	COOH	H	H	H



[Table 9]

No.	n	R ¹ -Y-	R ²	R ³	R ⁴	R ⁵	R ⁶
156	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	2-Pyrimidinylcarbonyl	COOH	H	H	H
157	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	2-Indolylcarbonyl	COOH	H	H	H
158	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	2-Benzothienylcarbonyl	COOH	H	H	H
159	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	5-Quinolylcarbonyl	COOH	H	H	H
160	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CONHCH ₂ C ₆ H ₅	COOH	H	H	H
161	0	4-FC ₆ H ₄ O-	COC ₆ H ₅	COOH	H	H	H
162	0	2-CH ₃ C ₆ H ₄ O-	COC ₆ H ₅	COOH	H	H	H
163	0	3-CH ₃ C ₆ H ₄ O-	COC ₆ H ₅	COOH	H	H	H
164	0	4-CH ₃ C ₆ H ₄ O-	COC ₆ H ₅	COOH	H	H	H
165	0	2, 4-(CH ₃) ₂ C ₆ H ₃ O-	COC ₆ H ₅	COOH	H	H	H
166	0	3, 4-(CH ₃) ₂ C ₆ H ₃ O-	COC ₆ H ₅	COOH	H	H	H
167	0	2, 3-(CH ₃) ₂ C ₆ H ₃ O-	COC ₆ H ₅	COOH	H	H	H
168	0	3, 5-(CH ₃) ₂ C ₆ H ₃ O-	COC ₆ H ₅	COOH	H	H	H
169	0	3, 6-(CH ₃) ₂ C ₆ H ₃ O-	COC ₆ H ₅	COOH	H	H	H
170	0	2, 6-(CH ₃) ₂ C ₆ H ₃ O-	COC ₆ H ₅	COOH	H	H	H
171	0	2, 5-(CH ₃) ₂ C ₆ H ₃ O-	COC ₆ H ₅	COOH	H	H	H
172	0	2, 4, 6-(CH ₃) ₃ C ₆ H ₂ O-	COC ₆ H ₅	COOH	H	H	H
173	0	2, 3, 5-(CH ₃) ₃ C ₆ H ₂ O-	COC ₆ H ₅	COOH	H	H	H
174	0	2, 4, 5-(CH ₃) ₃ C ₆ H ₂ O-	COC ₆ H ₅	COOH	H	H	H
175	0	2, 5, 6-(CH ₃) ₃ C ₆ H ₂ O-	COC ₆ H ₅	COOH	H	H	H



[Table 10]

No.	n	R ¹ -Y-	R ²	R ³	R ⁴	R ⁵	R ⁶
176	0	4-HOC ₆ H ₄ O-	COC ₆ H ₅	COOH	H	H	H
177	0	4-CH ₃ OC ₆ H ₄ O-	COCH ₆ H ₅	COOH	H	H	H
178	0	4-C ₂ H ₅ OC ₆ H ₄ O-	COCH ₆ H ₅	COOH	H	H	H
179	0	4-CH ₃ CH(CH ₃)OC ₆ H ₄ O-	COCH ₆ H ₅	COOH	H	H	H
180	0	4-C ₆ H ₅ OC ₆ H ₄ O-	COCH ₆ H ₅	COOH	H	H	H
181	0	4-C ₆ H ₅ CH ₂ OC ₆ H ₄ O-	COCH ₆ H ₅	COOH	H	H	H
182	0	4-HO ₂ CC ₆ H ₄ O-	COCH ₆ H ₅	COOH	H	H	H
183	0	4-CH ₃ COOC ₆ H ₄ O-	COCH ₆ H ₅	COOH	H	H	H
184	0	4-CH ₃ OC(O)C ₆ H ₄ O-	COCH ₆ H ₅	COOH	H	H	H
185	0	4-H ₂ NC(O)C ₆ H ₄ O-	COCH ₆ H ₅	COOH	H	H	H
186	0	4-HONHC(O)C ₆ H ₄ O-	COCH ₆ H ₅	COOH	H	H	H
187	0	4-H ₃ CNHC(O)C ₆ H ₄ O-	COCH ₆ H ₅	COOH	H	H	H
188	0	4-(H ₃ C) ₂ NC(O)C ₆ H ₄ O-	COCH ₆ H ₅	COOH	H	H	H
189	0	4-O ₂ NC ₆ H ₄ O-	COCH ₆ H ₅	COOH	H	H	H
190	0	4-H ₂ NC ₆ H ₄ O-	COCH ₆ H ₅	COOH	H	H	H
191	0	4-H ₃ CNHC ₆ H ₄ O-	COCH ₆ H ₅	COOH	H	H	H
192	0	4-(H ₃ C) ₂ NC ₆ H ₄ O-	COCH ₆ H ₅	COOH	H	H	H
193	0	4-OHCC ₆ H ₄ O-	COCH ₆ H ₅	COOH	H	H	H
194	0	4-CH(NOH)C ₆ H ₄ O-	COCH ₆ H ₅	COOH	H	H	H
195	0	4-OHCNHC ₆ H ₄ O-	COCH ₆ H ₅	COOH	H	H	H



[Table 11]

No.	n	R ¹ -Y-	R ²	R ³	R ⁴	R ⁵	R ⁶
196	0	4-CH ₃ C(O)NHC ₆ H ₄ O-	CO ₂ C ₆ H ₅	COOH	H	H	H
197	0	4-CH ₃ OC(O)NHC ₆ H ₄ O-	CO ₂ C ₆ H ₅	COOH	H	H	H
198	0	4-H ₂ NC(O)OC ₆ H ₄ O-	CO ₂ C ₆ H ₅	COOH	H	H	H
199	0	4-HSC ₆ H ₄ O-	CO ₂ C ₆ H ₅	COOH	H	H	H
200	0	4-H ₃ CSC ₆ H ₄ O-	CO ₂ C ₆ H ₅	COOH	H	H	H
201	0	4-H ₃ CS(O)C ₆ H ₄ O-	CO ₂ C ₆ H ₅	COOH	H	H	H
202	0	4-H ₃ CS(O) ₂ C ₆ H ₄ O-	CO ₂ C ₆ H ₅	COOH	H	H	H
203	0	3,4-(OCH ₂ O)C ₆ H ₃ O-	CO ₂ C ₆ H ₅	COOH	H	H	H
204	0	3,4-(CH ₂ CH ₂ CH ₂)C ₆ H ₃ O-	CO ₂ C ₆ H ₅	COOH	H	H	H
205	0	4-HO ₃ SC ₆ H ₄ O-	CO ₂ C ₆ H ₅	COOH	H	H	H
206	0	4-NCC ₆ H ₄ O-	CO ₂ C ₆ H ₅	COOH	H	H	H
207	0	4-H ₂ NC(NH)C ₆ H ₄ O-	CO ₂ C ₆ H ₅	COOH	H	H	H
208	0	3-Isoxazoloxy	CO ₂ C ₆ H ₅	COOH	H	H	H
209	0	2-Imidazoloxy	CO ₂ C ₆ H ₅	COOH	H	H	H
210	0	2-Benzimidazoloxy	CO ₂ C ₆ H ₅	COOH	H	H	H
211	0	2-Thiazoloxy	CO ₂ C ₆ H ₅	COOH	H	H	H
212	0	5-Benzo[b]thienyloxy	CO ₂ C ₆ H ₅	COOH	H	H	H
213	0	2-Thiazolylamino	CO ₂ C ₆ H ₅	COOH	H	H	H
214	0	4-Imidazolylamino	CO ₂ C ₆ H ₅	COOH	H	H	H
215	0	3-Pyrazolylamino	CO ₂ C ₆ H ₅	COOH	H	H	H



[Table 12]

No.	n	R ¹ -Y-	R ²	R ³	R ⁴	R ⁵	R ⁶
216	0	3-Isoxazolylamino	CO ₂ C ₆ H ₅	COOH	H	H	H
217	0	5-Iothiazolylamino	CO ₂ C ₆ H ₅	COOH	H	H	H
218	0	2-Pyrimidinylamino	CO ₂ C ₆ H ₅	COOH	H	H	H
219	0	3-(1,2,4-Triazolyl)amino	CO ₂ C ₆ H ₅	COOH	H	H	H
220	0	2-Pyridylamino	CO ₂ C ₆ H ₅	COOH	H	H	H
221	0	2-Benzoxazolylamino	CO ₂ C ₆ H ₅	COOH	H	H	H
222	0	3-Benzothienylamino	CO ₂ C ₆ H ₅	COOH	H	H	H
223	0	2-Benzofurylamino	CO ₂ C ₆ H ₅	COOH	H	H	H
224	0	5-Indolylamino	CO ₂ C ₆ H ₅	COOH	H	H	H
225	0	2-Pyrazinylamino	CO ₂ C ₆ H ₅	COOH	H	H	H
226	0	3-Quinolylamino	CO ₂ C ₆ H ₅	COOH	H	H	H
227	0	5-Tetrazolylamino	CO ₂ C ₆ H ₅	COOH	H	H	H
228	0	2-Imidazolylthioxy	CO ₂ C ₆ H ₅	COOH	H	H	H
229	0	2-Pyridylthioxy	CO ₂ C ₆ H ₅	COOH	H	H	H
230	0	2-Benzothiazolylthioxy	CO ₂ C ₆ H ₅	COOH	H	H	H
231	0	2-Benzothienylthienyl	CO ₂ C ₆ H ₅	COOH	H	H	H
232	0	2-Benzothienylmethyl	CO ₂ C ₆ H ₅	COOH	H	H	H
233	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ S(O) ₂ -	CO ₂ C ₆ H ₅	COOH	H	H	H
234	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ S-	CO ₂ C ₆ H ₅	COOH	H	H	H
235	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ NH-	CO ₂ C ₆ H ₅	COOH	H	H	H



[Table 13]

No.	n	R ¹ -Y-	R ²	R ³	R ⁴	R ⁵	R ⁶
236	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	COCH ₆ H ₅	COOH	H	H	H
237	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CH(OH)-	COCH ₆ H ₅	COOH	H	H	H
238	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CH ₂ OC(O)-	COCH ₆ H ₅	COOH	H	H	H
239	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ NHC(O)-	COCH ₆ H ₅	COOH	H	H	H
240	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ OC(O)NH-	COCH ₆ H ₅	COOH	H	H	H
241	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CH ₂ OC(O)NH-	COCH ₆ H ₅	COOH	H	H	H
242	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ C(O)NH-	COCH ₆ H ₅	COOH	H	H	H
243	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CH ₂ C(O)NH-	COCH ₆ H ₅	COOH	H	H	H
244	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CH ₂ CO-	COCH ₆ H ₅	COOH	H	H	H
245	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CH ₂ OCH ₂ -	COCH ₆ H ₅	COOH	H	H	H
246	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ C(NO _H)-	COCH ₆ H ₅	COOH	H	H	H
247	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CHCH-	COCH ₆ H ₅	COOH	H	H	H
248	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CH ₂ -	COCH ₆ H ₅	COOH	H	H	H
249	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COCH ₆ H ₅	CH ₂ OH	H	H	H
250	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COCH ₆ H ₅	CHFCOOH	H	H	H
251	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COCH ₆ H ₅	COCOOH	H	H	H
252	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COCH ₆ H ₅	C(NO _H)COOH	H	H	H
253	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COCH ₆ H ₅	CH(CH ₂ OH)COOH	H	H	H
254	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COCH ₆ H ₅	CH(NH ₂)COOH	H	H	H
255	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COCH ₆ H ₅	CH(NHCHO)COOH	H	H	H

[Table 14]



No.	n	R ¹ -Y-	R ²	R ³	R ⁴	R ⁵	R ⁶
256	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COCH ₃	CF ₂ COOH	H	H	H
257	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COCH ₃	CH(OH)COOH	H	H	H
258	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COCH ₃	CH(OCH ₃)COOH	H	H	H
259	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COCH ₃	CH(CH ₃)COOH	H	H	H
260	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COCH ₃	CH(C ₆ H ₅)COOH	H	H	H
261	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COCH ₃	C(CH ₃) ₂ COOH	H	H	H
262	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COCH ₃	C(C ₂ H ₄)COOH	H	H	H
263	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COCH ₃	C(C ₃ H ₆)COOH	H	H	H
264	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COCH ₃	C(C ₄ H ₆)COOH	H	H	H
265	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COCH ₃	C(C ₅ H ₁₀)COOH	H	H	H
266	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COCH ₃	CONHOH	H	H	H
267	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COCH ₃	CON(CH ₃) ₂	H	H	H
268	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COCH ₃	CONHC ₆ H ₅	H	H	H
269	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COCH ₃	COCH ₃	H	H	H
270	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COCH ₃	COCH ₃	H	H	H
271	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COCH ₃	CH ₂ COOH	H	H	H
272	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COCH ₃	CH ₂ COOCH ₃	H	H	H
273	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COCH ₃	CH ₂ CH ₂ COOH	H	H	H
274	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COCH ₃	CH ₂ CH(OH)COOH	H	H	H
275	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COCH ₃	CH(OH)CH ₂ COOH	H	H	H

[Table 15]



No.	n	R ¹ -Y-	R ²	R ³	R ⁴	R ⁵	R ⁶
276	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COC ₆ H ₅	CH ₂ CF ₂ COOH	H	H	H
277	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COC ₆ H ₅	CH ₂ CHFCOOH	H	H	H
278	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COC ₆ H ₅	CH ₂ CH ₂ OH	H	H	H
279	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COC ₆ H ₅	CH ₂ CH ₂ OCH ₃	H	H	H
280	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COC ₆ H ₅	CH ₂ CH ₂ OC ₆ H ₅	H	H	H
281	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COC ₆ H ₅	CH ₂ CH ₂ OCH ₂ C ₆ H ₅	H	H	H
282	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COC ₆ H ₅	CH ₂ CH ₂ F	H	H	H
283	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COC ₆ H ₅	CH ₂ F	H	H	H
284	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COC ₆ H ₅	CH ₂ NH ₂	H	H	H
285	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COC ₆ H ₅	CH ₂ CH ₂ NH ₂	H	H	H
286	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COC ₆ H ₅	CH ₂ CH ₂ NHCCHO	H	H	H
287	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COC ₆ H ₅	CH ₂ CH ₂ NHCOOCH ₃	H	H	H
288	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COC ₆ H ₅	CH ₂ CH ₂ N(CH ₃) ₂	H	H	H
289	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COC ₆ H ₅	CH ₂ CH ₂ NHCH ₃	H	H	H
290	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COC ₆ H ₅	CH ₂ SH	H	H	H
291	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COC ₆ H ₅	CH ₂ CH ₂ SH	H	H	H
292	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COC ₆ H ₅	CH ₂ SCH ₃	H	H	H
293	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COC ₆ H ₅	CH ₂ S(O) ₂ CH ₃	H	H	H
294	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COC ₆ H ₅	CH ₂ S(O)CH ₃	H	H	H
295	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COC ₆ H ₅	CONHCH(CH ₂ COOH)COOH	H	H	H



[Table 16]

No.	n	R ¹ -Y-	R ²	R ³	R ⁴	R ⁵	R ⁶
296	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COC ₆ H ₅	CONHCH(CH ₃)COOH	H	H	H
297	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COC ₆ H ₅	CONHCH(CH ₂ CH ₂ (CH ₃) ₂)COOH	H	H	H
298	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COC ₆ H ₅	CONHCH(CH ₂ OH)COOH	H	H	H
299	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COC ₆ H ₅	CONHCH(CH ₂ CH ₂ SCH ₃)COOH	H	H	H
300	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COC ₆ H ₅	CONHCH((CH ₂) ₄ NH ₂)COOH	H	H	H
301	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COC ₆ H ₅	CONHCH(C ₆ H ₅)COOH	H	H	H
302	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COC ₆ H ₅	CONHCH(CH ₂ CONH ₂)COOH	H	H	H
303	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COC ₆ H ₅	CONH ₂	H	H	H
304	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COC ₆ H ₅	CH ₂ CONH ₂	H	H	H
305	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COC ₆ H ₅	CONHCH ₃	H	H	H
306	0	CH ₃ C(O)S-	COC ₆ H ₅	COOH	H	H	H
307	0	OHC-	COC ₆ H ₅	COOH	H	H	H
308	0	O ₂ NCHCH-	COC ₆ H ₅	COOH	H	H	H
309	0	CH ₂ CHCHCH-	COC ₆ H ₅	COOH	H	H	H
310	0	CH ₃ OCHCH-	COC ₆ H ₅	COOH	H	H	H
311	0	CH ₃ COCHCH-	COC ₆ H ₅	COOH	H	H	H
312	0	CH ₂ CH-	COC ₆ H ₅	COOH	H	H	H
313	0	C1CH ₂ CH ₂ -	COC ₆ H ₅	COOH	H	H	H
314	0	NCCH ₂ -	COC ₆ H ₅	COOH	H	H	H
315	0	O ₂ NCH ₂ -	COC ₆ H ₅	COOH	H	H	H



[Table 17]

No.	n	R ¹ -Y-	R ²	R ³	R ⁴	R ⁵	R ⁶
316	0	CH ₃ OC(O)CH ₂ -	COC ₆ H ₅	COOH	H	H	H
317	0	HOOC(O)CH ₂ -	COC ₆ H ₅	COOH	H	H	H
318	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COCH ₃	COOH	H	CH ₃	CH ₃
319	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COCH ₂ CH ₃	COOH	H	CH ₃	CH ₃
320	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COCH ₂ CH ₂ CH ₃	COOH	H	CH ₃	CH ₃
321	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COCH ₂ CH ₂ CH ₂ CH ₃	COOH	H	CH ₃	CH ₃
322	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COCH ₂ CH ₂ CH ₂ CH ₂ CH ₃	COOH	H	CH ₃	CH ₃
323	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COCH(CH ₃)CH ₃	COOH	H	CH ₃	CH ₃
324	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COCH ₂ CH(CH ₃)CH ₃	COOH	H	CH ₃	CH ₃
325	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COCH ₂ C ₆ H ₅	COOH	H	CH ₃	CH ₃
326	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	2-Thienylmethylcarbonyl	COOH	H	CH ₃	CH ₃
327	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	2-Furylmethylcarbonyl	COOH	H	CH ₃	CH ₃
328	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	2-Pyridylmethylcarbonyl	COOH	H	CH ₃	CH ₃
329	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	2-Quinolylmethylcarbonyl	COOH	H	CH ₃	CH ₃
330	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	2-Benzothienylmethylcarbonyl	COOH	H	CH ₃	CH ₃
331	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	2-Naphthylidinylmethylcarbonyl	COOH	H	CH ₃	CH ₃
332	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	2-Thiazolylmethylcarbonyl	COOH	H	CH ₃	CH ₃
333	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	2-Pyrimidinylmethylcarbonyl	COOH	H	CH ₃	CH ₃
334	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	2-Benzoxazolylmethylcarbonyl	COOH	H	CH ₃	CH ₃
335	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	2-Indolylmethylcarbonyl	COOH	H	CH ₃	CH ₃



[Table 18]

No.	n	R ¹ -Y-	R ²	R ³	R ⁴	R ⁵	R ⁶
336	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	2-Thiazolylcarbonyl	COOH	H	CH ₃	CH ₃
337	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	2-Pyrimidinylcarbonyl	COOH	H	CH ₃	CH ₃
338	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	2-Indolylcarbonyl	COOH	H	CH ₃	CH ₃
339	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	2-Benzothienylcarbonyl	COOH	H	CH ₃	CH ₃
340	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	5-Quinolylcarbonyl	COOH	H	CH ₃	CH ₃
341	0	HO-	COC ₆ H ₅	COOH	H	H	H
342	0	O ₂ NO-	COC ₆ H ₅	COOH	H	H	H
343	0	H ₂ NC(O)O-	COC ₆ H ₅	COOH	H	H	H
344	0	HS-	COC ₆ H ₅	COOH	H	H	H
345	0	HOS-	COC ₆ H ₅	COOH	H	H	H
346	0	(HO ₂)CH-	COC ₆ H ₅	COOH	H	H	H
347	0	CH ₃ O-	COC ₆ H ₅	COOH	H	H	H
348	0	CH ₃ S-	COC ₆ H ₅	COOH	H	H	H
349	0	CH ₃ NH-	COC ₆ H ₅	COOH	H	H	H
350	0	CH ₃ CO-	COC ₆ H ₅	COOH	H	H	H
351	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COC ₆ H ₅	C(NO ₂)CH ₃	H	H	H
352	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COC ₆ H ₅	CHO	H	H	H
353	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COC ₆ H ₅	CH ₂ OC(O)NH ₂	H	H	H
354	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COC ₆ H ₅	CH ₂ OC(O)CH ₃	H	H	H
355	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COC ₆ H ₅	CH ₂ OC(O)C ₆ H ₅	H	H	H



[Table 19]

No.	n	R ¹ -Y-	R ²	R ³	R ⁴	R ⁵	R ⁶
356	1	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COCH ₃ H ₅	CH ₂ COOH	H	H	H
357	2	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COCH ₃ H ₅	CH ₂ COOH	H	H	H
358	0	CH ₃ COCH ₂ -	COCH ₃ H ₅	COOH	H	H	H
359	0	H ₂ NCH ₂	COCH ₃ H ₅	COOH	H	H	H
360	0	HOCH ₂ -	COCH ₃ H ₅	COOH	H	H	H
361	0	HONH-	COCH ₃ H ₅	COOH	H	H	H
362	0	CH ₃ C(O)NCl-	COCH ₃ H ₅	COOH	H	H	H
363	0	O ₂ NNH-	COCH ₃ H ₅	COOH	H	H	H
364	0	CH ₃ ONH-	COCH ₃ H ₅	COOH	H	H	H
365	0	H ₂ NNH-	COCH ₃ H ₅	COOH	H	H	H
366	0	H ₂ N-	COCH ₃ H ₅	COOH	H	H	H
367	0	C1CO-	COCH ₃ H ₅	COOH	H	H	H
368	0	C1CHCH	COCH ₃ H ₅	COOH	H	H	H
369	0	C1S(O) ₂ -	COCH ₃ H ₅	COOH	H	H	H
370	0	HOS(O) ₂ -	COCH ₃ H ₅	COOH	H	H	H
371	0	NCS(O) ₂ -	COCH ₃ H ₅	COOH	H	H	H
372	0	CH ₃ OS(O) ₂ -	COCH ₃ H ₅	COOH	H	H	H
373	0	H ₂ NS(O) ₂ -	COCH ₃ H ₅	COOH	H	H	H
374	0	NCCO-	COCH ₃ H ₅	COOH	H	H	H
375	0	NCCHCH-	COCH ₃ H ₅	COOH	H	H	H



[Table 20]

No.	n	R ¹ -Y-	R ²	R ³	R ⁴	R ⁵	R ⁶
376	0	NCS-	CO ₂ C ₆ H ₅	COOH	H	H	H
377	0	OCN-	CO ₂ C ₆ H ₅	COOH	H	H	H
378	0	HOC (O) CO-	CO ₂ C ₆ H ₅	COOH	H	H	H
379	0	CH ₃ OC (O) NH-	CO ₂ C ₆ H ₅	COOH	H	H	H
380	0	HOC (O) CHCH-	CO ₂ C ₆ H ₅	COOH	H	H	H
381	0	HOC (O) CH (OH) -	CO ₂ C ₆ H ₅	COOH	H	H	H
382	0	HOO-	CO ₂ C ₆ H ₅	COOH	H	H	H
383	0	HOC (O) -	CO ₂ C ₆ H ₅	COOH	H	H	H
384	0	CH ₃ C (O) OCHCH	CO ₂ C ₆ H ₅	COOH	H	H	H
385	0	CH ₃ C (O) SCHCH	CO ₂ C ₆ H ₅	COOH	H	H	H
386	0	CH ₃ OC (O) -	CO ₂ C ₆ H ₅	COOH	H	H	H
387	0	CH ₃ OC (O) CHCH-	CO ₂ C ₆ H ₅	COOH	H	H	H
388	0	CH ₃ C (O) NHCHCH -	CO ₂ C ₆ H ₅	COOH	H	H	H
389	0	4-CH ₃ CH (CH ₃) C ₆ H ₄ O -	CO ₂ C ₆ H ₅	COOH	H	C ₆ H ₅	C ₆ H ₅
390	0	4-CH ₃ CH (CH ₃) C ₆ H ₄ O -	CO ₂ C ₆ H ₅	COOH	H	H	C ₆ H ₅
391	0	CH ₃ CHCH -	CO ₂ C ₆ H ₅	COOH	H	H	H
392	0	C ₆ H ₅ S (O) -	CO ₂ C ₆ H ₅	COOH	H	H	H
393	0	CH ₃ S (O) -	CO ₂ C ₆ H ₅	COOH	H	H	H
394	0	CH ₃ S (O) ₂ -	CO ₂ C ₆ H ₅	COOH	H	H	H
395	0	NCCH (OH) -	CO ₂ C ₆ H ₅	COOH	H	H	H



[Table 21]

No.	n	R ¹ -Y-	R ²	R ³	R ⁴	R ⁵	R ⁶
396	0	CH ₃ OC(O)CH(OH)-	COC ₆ H ₅	COOH	H	H	H
397	0	CH ₃ COCH(OH)-	COC ₆ H ₅	COOH	H	H	H
398	0	CH ₃ CH(OH)-	COC ₆ H ₅	COOH	H	H	H
399	0	CH ₂ CHO-	COC ₆ H ₅	COOH	H	H	H
400	0	CH ₂ CHS-	COC ₆ H ₅	COOH	H	H	H
401	0	CH ₂ CHNH-	COC ₆ H ₅	COOH	H	H	H
402	0	CH ₂ CHCO-	COC ₆ H ₅	COOH	H	H	H
403	0	CH ₂ CHCH ₂ -	COC ₆ H ₅	COOH	H	H	H
404	0	CH ₂ CHS(O)-	COC ₆ H ₅	COOH	H	H	H
405	0	CH ₂ CHS(O) ₂ -	COC ₆ H ₅	COOH	H	H	H
406	0	2-Thiazolylsulfonyl	COC ₆ H ₅	COOH	H	H	H
407	0	CH ₂ CHCH(OH)-	COC ₆ H ₅	COOH	H	H	H
408	0	C ₆ H ₁₁ O-	COC ₆ H ₅	COOH	H	H	H
409	0	C ₆ H ₁₁ S-	COC ₆ H ₅	COOH	H	H	H
410	0	C ₆ H ₁₁ NH-	COC ₆ H ₅	COOH	H	H	H
411	0	C ₆ H ₁₁ CHCH-	COC ₆ H ₅	COOH	H	H	H
412	0	C ₆ H ₁₁ S(O)-	COC ₆ H ₅	COOH	H	H	H
413	0	C ₆ H ₁₁ S(O) ₂ -	COC ₆ H ₅	COOH	H	H	H
414	0	C ₆ H ₁₁ CH(OH)-	COC ₆ H ₅	COOH	H	H	H
415	0	CH ₃ C(O)O-	COC ₆ H ₅	COOH	H	H	H



[Table 22]

No.	n	R ¹ -Y-	R ²	R ³	R ⁴	R ⁵	R ⁶
416	0	C ₆ H ₅ CH ₂ C(O)O-	COCH ₆ H ₅	COOH	H	H	H
417	0	CH ₃ C(O)NH-	COCH ₆ H ₅	COOH	H	H	H
418	0	H ₂ NC(O)-	COCH ₆ H ₅	COOH	H	H	H
419	0	C ₆ H ₅ CH ₂ CH ₂ -	COCH ₆ H ₅	COOH	H	H	H
420	0	2-Pyridylethenyl	COCH ₆ H ₅	COOH	H	H	H
421	0	C ₆ H ₅ CHCH-	COCH ₆ H ₅	COOH	H	H	H
422	0	CH ₃ COCO-	COCH ₆ H ₅	COOH	H	H	H
423	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COCH ₆ H ₅	COOH	H	H	C1
424	0	Cyclohexanecarbonyl	COCH ₆ H ₅	COOH	H	H	H
425	0	2-Thienylcarbonyl	COCH ₆ H ₅	COOH	H	H	H
426	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COCH ₆ H ₅	COOH	CH ₃	CH ₃	CH ₃
427	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COCH ₆ H ₅	COOH	CH ₂ COOH	CH ₃	CH ₃
428	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COCH ₆ H ₅	COOH	CN	CH ₃	CH ₃
429	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COCH ₆ H ₅	COOH	CONH ₂	CH ₃	CH ₃
430	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COCH ₆ H ₅	COOH	F	CH ₃	CH ₃
431	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COCH ₆ H ₅	COOH	H	H	C ₆ H ₅
432	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COCH ₆ H ₅	COOH	C1	H	H
433	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COCH ₆ H ₅	COOH	CN	H	H
434	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COCH ₆ H ₅	COOH	COOH	H	H
435	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COCH ₆ H ₅	COOH	COOCH ₃	H	H

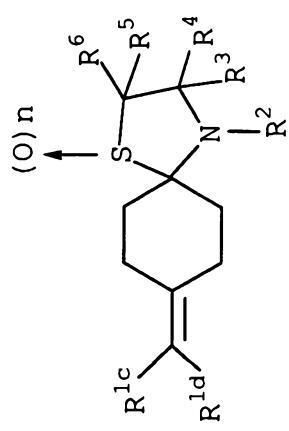
[Table 23]

No.	n	R ¹ -Y-	R ²	R ³	R ⁴	R ⁵	R ⁶
436	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COOC ₆ H ₅	COOH	CONH ₂	H	H
437	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COOC ₆ H ₅	COOH	CH ₃	H	H
438	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COOC ₆ H ₅	COOH	CHCH ₂	H	H
439	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COOC ₆ H ₅	COOH	C ₆ H ₁₁	H	H
440	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COOC ₆ H ₅	COOH	COCH ₃	H	H
441	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COOC ₆ H ₅	COOH	COC ₆ H ₅	H	H
442	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COOC ₆ H ₅	COOH	C ₆ H ₅	H	H
443	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COOC ₆ H ₅	COOH	2-Pyridyl	H	H





[Table 24]



No.	n	R^{1c}	R^{1d}	R²	R³	R⁴	R⁵	R⁶
444	0	CH ₃ S(O) ₂	H	COCH ₃	COOH	H	H	H
445	0	CH ₃	H	COCH ₃	COOH	H	CH ₃	CH ₃
446	0	C ₂ H ₅	H	COCH ₃	COOH	H	CH ₃	CH ₃
447	0	CH ₂ CH	H	COCH ₃	COOH	H	CH ₃	CH ₃
448	0	CH ₃ CHCH	H	COCH ₃	COOH	H	CH ₃	CH ₃
449	0	C ₆ H ₅	H	COCH ₃	COOH	H	CH ₃	CH ₃
450	0	2-Pyridyl	H	COCH ₃	COOH	H	CH ₃	CH ₃
451	0	C ₆ H ₅	H	COCH ₃	COOH	H	CH ₃	CH ₃
452	0	C ₆ H ₅ CO	H	COCH ₃	COOH	H	CH ₃	CH ₃
453	0	H	H	COCH ₃	COOH	H	H	H
454	0	H	C1	COCH ₃	COOH	H	H	H
455	0	H	NC	COCH ₃	COOH	H	H	H
456	0	H	HOC(O)	COCH ₃	COOH	H	H	H
457	0	H	CH ₃ OC(O)	COCH ₃	COOH	H	H	H
458	0	H	CH ₃	COCH ₃	COOH	H	H	H
459	0	H	CH ₃ O	COCH ₃	COOH	H	H	H
460	0	H	C ₆ H ₅ CH ₂	COCH ₃	COOH	H	H	H



[Table 25]

No.	n	R ^{1,c}	R ^{1,d}	R ²	R ³	R ⁴	R ⁵	R ⁶
461	0	H	CH ₂ CH	COCH ₆ H ₅	COOH	H	H	H
462	0	H	CH ₃ CHCH	COCH ₆ H ₅	COOH	H	H	H
463	0	H	C ₆ H ₅	COCH ₆ H ₅	COOH	H	H	H
464	0	H	2-Pyridyl	COCH ₆ H ₅	COOH	H	H	H
465	0	CH ₃	CH ₃	COCH ₆ H ₅	COOH	H	H	H
466	0	C ₂ H ₅	CH ₃	COCH ₆ H ₅	COOH	H	H	H
467	0	CH ₂ CH	CH ₃	COCH ₆ H ₅	COOH	H	H	H
468	0	CH ₃ CHCH	CH ₃	COCH ₆ H ₅	COOH	H	H	H
469	0	C ₆ H ₅	CH ₃	COCH ₆ H ₅	COOH	H	H	H
470	0	2-Pyridyl	CH ₃	COCH ₆ H ₅	COOH	H	H	H
471	0	CH ₃	CH ₃	CH ₂ C ₆ H ₅	COOH	CH ₃	H	H
472	0	CH ₃	CH ₃	CH ₂ C ₆ H ₅	COOH	H	CH ₃	CH ₃
473	0	CH ₃	CH ₃	CH ₂ C ₆ H ₅	COOH	CH ₃	CH ₃	CH ₃
474	0	CH ₃	CH ₃	C ₆ H ₅	COOH	CH ₃	CH ₃	CH ₃
475	0	CH ₃	CH ₃	S(O) ₂ C ₆ H ₅	COOH	CH ₃	CH ₃	CH ₃
476	0	CH ₃	CH ₃	2-Thiazolyl	COOH	CH ₃	CH ₃	CH ₃
477	0	C ₆ H ₅	C ₆ H ₅	COCH ₆ H ₅	COOH	H	H	H
478	0	C ₆ H ₅ CO	H	COCH ₆ H ₅	COOH	H	H	H
479	0	CH ₃ CO	H	COCH ₆ H ₅	COOH	H	H	H
480	0	CH ₃ NHC(O)	H	COCH ₆ H ₅	COOH	H	H	H
481	0	CH ₃ S	H	COCH ₆ H ₅	COOH	H	H	H
482	1	CH ₂ CH	H	COCH ₆ H ₅	COOH	H	CH ₃	CH ₃
483	1	CH ₃ CHCH	H	COCH ₆ H ₅	COOH	H	CH ₃	CH ₃
484	1	C ₆ H ₅	H	COCH ₆ H ₅	COOH	H	CH ₃	CH ₃



[Table 26]

No.	n	R ^{1c}	R ^{1d}	R ²	R ³	R ⁴	R ⁵	R ⁶
485	1	2-Pyridyl	H	COCH ₃	COOH	H	CH ₃	CH ₃
486	1	C ₆ H ₅	H	COCH ₃	COOH	H	CH ₃	CH ₃
487	1	C ₆ H ₅ CO	H	COCH ₃	COOH	H	CH ₃	CH ₃
488	1	CH ₃ CO	H	COCH ₃	COOH	H	CH ₃	CH ₃
489	1	CH ₃ NHC(O)	H	COCH ₃	COOH	H	CH ₃	CH ₃
490	1	CH ₃ S	H	COCH ₃	COOH	H	CH ₃	CH ₃
491	0	CH ₃ CO	H	COCH ₃	COOH	H	CH ₃	CH ₃
492	0	CH ₃ NHC(O)	H	COCH ₃	COOH	H	CH ₃	CH ₃
493	0	CH ₃ S	H	COCH ₃	COOH	H	CH ₃	CH ₃
494	0	CH ₃ S(O) ₂	H	COCH ₃	COOH	H	CH ₃	CH ₃
495	1	H	H	COCH ₃	COOH	H	H	H
496	1	H	CH ₃	COCH ₃	COOH	H	H	H
497	1	H	C ₂ H ₅	COCH ₃	COOH	H	H	H
498	1	H	CH ₂ CH	COCH ₃	COOH	H	H	H
499	1	H	CH ₃ CHCH	COCH ₃	COOH	H	H	H
500	1	H	C ₆ H ₅	COCH ₃	COOH	H	H	H
501	1	H	2-Pyridyl	COCH ₃	COOH	H	H	H
502	1	CH ₃	CH ₃	COCH ₃	COOH	H	H	H
503	1	C ₂ H ₅	CH ₃	COCH ₃	COOH	H	H	H
504	1	CH ₂ CH	CH ₃	COCH ₃	COOH	H	H	H
505	1	CH ₃ CHCH	CH ₃	COCH ₃	COOH	H	H	H
506	1	C ₆ H ₅	CH ₃	COCH ₃	COOH	H	H	H
507	1	2-Pyridyl	CH ₃	COCH ₃	COOH	H	H	H
508	1	CH ₃	CH ₃	COCH ₃	COOH	H	CH ₃	CH ₃

[Table 27]



No.	n	R ^{1c}	R ^{1d}	R ²	R ³	R ⁴	R ⁵	R ⁶
509	1	CH ₃	CH ₃	CH ₂ C ₆ H ₅	COOH	CH ₃	H	H
510	1	CH ₃	CH ₃	CH ₂ C ₆ H ₅	COOH	CH ₃	CH ₃	CH ₃
511	1	CH ₃	CH ₃	C ₆ H ₅	COOH	CH ₃	CH ₃	CH ₃
512	1	CH ₃	CH ₃	S(O) ₂ C ₆ H ₅	COOH	CH ₃	CH ₃	CH ₃
513	1	CH ₃	CH ₃	2-Thiazolyl	COOH	CH ₃	CH ₃	CH ₃
514	1	C ₆ H ₅	C ₆ H ₅	COC ₆ H ₅	COOH	H	H	H
515	1	C ₆ H ₅ CO	H	COC ₆ H ₅	COOH	H	H	H
516	1	CH ₃ CO	H	COC ₆ H ₅	COOH	H	H	H
517	1	CH ₃ NHC(O)	H	COC ₆ H ₅	COOH	H	H	H
518	1	CH ₃ S	H	COC ₆ H ₅	COOH	H	H	H
519	1	CH ₃ S(O) ₂	H	COC ₆ H ₅	COOH	H	H	H
520	1	CH ₃	H	COC ₆ H ₅	COOH	H	CH ₃	CH ₃
521	1	C ₂ H ₅	H	COC ₆ H ₅	COOH	H	CH ₃	CH ₃
522	2	C ₆ H ₅	H	COC ₆ H ₅	COOH	H	CH ₃	CH ₃
523	2	2-Pyridyl	H	COC ₆ H ₅	COOH	H	CH ₃	CH ₃
524	2	C ₆ H ₅	H	COC ₆ H ₅	COOH	H	CH ₃	CH ₃
525	2	C ₆ H ₅ CO	H	COC ₆ H ₅	COOH	H	CH ₃	CH ₃
526	2	CH ₃ CO	H	COC ₆ H ₅	COOH	H	CH ₃	CH ₃
527	2	CH ₃ NHC(O)	H	COC ₆ H ₅	COOH	H	CH ₃	CH ₃
528	2	CH ₃ S	H	COC ₆ H ₅	COOH	H	CH ₃	CH ₃
529	2	CH ₃ S(O) ₂	H	COC ₆ H ₅	COOH	H	CH ₃	CH ₃
530	1	CH ₃	CH ₃	COC ₆ H ₅	CH ₂ CH ₂ F	H	CH ₃	CH ₃
531	1	CH ₃ S(O) ₂	H	COC ₆ H ₅	COOH	H	CH ₃	CH ₃

[Table 28]



No.	n	R ^{1c}	R ²	R ³	R ⁴	R ⁵	R ⁶
532	2	H	H	COOH	H	H	H
533	2	H	CH ₃ O	COCH ₆ H ₅	COOH	H	H
534	2	H	CH ₃	COCH ₆ H ₅	COOH	H	H
535	2	H	C ₂ H ₅	COCH ₆ H ₅	COOH	H	H
536	2	H	CH ₂ CH	COCH ₆ H ₅	COOH	H	H
537	2	H	CH ₃ CHCH	COCH ₆ H ₅	COOH	H	H
538	2	H	C ₆ H ₅	COCH ₆ H ₅	COOH	H	H
539	2	H	2-Pyridyl	COCH ₆ H ₅	COOH	H	H
540	2	CH ₃	COCH ₆ H ₅	COOH	H	H	H
541	2	C ₂ H ₅	CH ₃	COCH ₆ H ₅	COOH	H	H
542	2	CH ₂ CH	CH ₃	COCH ₆ H ₅	COOH	H	H
543	2	CH ₃ CHCH	CH ₃	COCH ₆ H ₅	COOH	H	H
544	2	C ₆ H ₅	CH ₃	COCH ₆ H ₅	COOH	H	H
545	2	2-Pyridyl	CH ₃	COCH ₆ H ₅	COOH	H	H
546	2	CH ₃	CH ₃	CH ₂ C ₆ H ₅	COOH	H	CH ₃
547	2	CH ₃	CH ₃	CH ₂ C ₆ H ₅	COOH	CH ₃	H
548	2	CH ₃	CH ₃	CH ₂ C ₆ H ₅	COOH	CH ₃	CH ₃
549	2	CH ₃	CH ₃	C ₆ H ₅	COOH	CH ₃	CH ₃
550	2	CH ₃	CH ₃	S(O) ₂ C ₆ H ₅	COOH	CH ₃	CH ₃
551	2	CH ₃	CH ₃	2-Thiazolyl	COOH	CH ₃	CH ₃
552	2	C ₆ H ₅	C ₆ H ₅	COCH ₆ H ₅	COOH	H	H
553	2	C ₆ H ₅ CO	H	COCH ₆ H ₅	COOH	H	H
554	2	CH ₃ CO	H	COCH ₆ H ₅	COOH	H	H
555	2	CH ₃ NHC(O)	H	COCH ₆ H ₅	COOH	H	H



[Table 29]

No.	n	R ^{1c}	R ^{1d}	R ²	R ³	R ⁴	R ⁵	R ⁶
556	2	CH ₃ S	H	COCH ₆ H ₅	COOH	H	H	H
557	2	CH ₃ S(O) ₂	H	COCH ₆ H ₅	COOH	H	H	H
558	2	CH ₃	H	COCH ₆ H ₅	COOH	H	CH ₃	CH ₃
559	2	C ₂ H ₅	H	COCH ₆ H ₅	COOH	H	CH ₃	CH ₃
560	2	CH ₂ CH	H	COCH ₆ H ₅	COOH	H	CH ₃	CH ₃
561	2	CH ₃ CHCH	H	COCH ₆ H ₅	COOH	H	CH ₃	CH ₃
562	1	CH ₃	CH ₃	COCH ₆ H ₅	COC ₆ H ₅	H	CH ₃	CH ₃
563	1	CH ₃	CH ₃	COCH ₆ H ₅	COCH ₃	H	CH ₃	CH ₃
564	1	CH ₃	CH ₃	COCH ₆ H ₅	C(NO ₂)CH ₃	H	CH ₃	CH ₃
565	1	CH ₃	CH ₃	COCH ₆ H ₅	CHO	H	CH ₃	CH ₃
566	1	CH ₃	CH ₃	COCH ₆ H ₅	CH ₂ OC(O)NH ₂	H	CH ₃	CH ₃
567	1	CH ₃	CH ₃	COCH ₆ H ₅	CH ₂ OC(O)CH ₃	H	CH ₃	CH ₃
568	1	CH ₃	CH ₃	COCH ₆ H ₅	CH ₂ OC(O)C ₆ H ₅	H	CH ₃	CH ₃
569	1	CH ₃	CH ₃	COCH ₆ H ₅	CH ₂ COOH	H	CH ₃	CH ₃
570	1	CH ₃	CH ₃	COCH ₆ H ₅	CH ₂ COOH	H	CH ₃	CH ₃
571	1	CH ₃	CH ₃	COCH ₆ H ₅	CH ₂ CH ₂ OCH ₂ C ₆ H ₅	H	CH ₃	CH ₃
572	1	CH ₃	CH ₃	COCH ₆ H ₅	CH ₂ F	H	CH ₃	CH ₃
573	1	CH ₃	CH ₃	COCH ₆ H ₅	CH ₂ NH ₂	H	CH ₃	CH ₃
574	1	CH ₃	CH ₃	COCH ₆ H ₅	CH ₂ CH ₂ NH ₂	H	CH ₃	CH ₃
575	1	CH ₃	CH ₃	COCH ₆ H ₅	CH ₂ CH ₂ NHCHO	H	CH ₃	CH ₃
576	1	CH ₃	CH ₃	COCH ₆ H ₅	CH ₂ CH ₂ NHCOOCH ₃	H	CH ₃	CH ₃
577	1	CH ₃	CH ₃	COCH ₆ H ₅	CH ₂ CH ₂ N(CH ₃) ₂	H	CH ₃	CH ₃
578	1	CH ₃	CH ₃	COCH ₆ H ₅	CH ₂ CH ₂ NHCH ₃	H	CH ₃	CH ₃
579	1	CH ₃	CH ₃	COCH ₆ H ₅	CH ₂ CH ₂ NHCH ₂ C ₆ H ₅	H	CH ₃	CH ₃

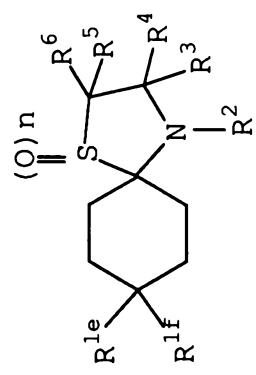


[Table 30]

No.	n	R ^{1c}	R ^{1d}	R ²	R ³	R ⁴	R ⁵	R ⁶
580	1	CH ₃	CH ₃	COC ₆ H ₅	CH ₂ SH	H	CH ₃	CH ₃
581	1	CH ₃	CH ₃	COC ₆ H ₅	CH ₂ CH ₂ SH	H	CH ₃	CH ₃
582	1	CH ₃	CH ₃	COC ₆ H ₅	CH ₂ SCH ₃	H	CH ₃	CH ₃
583	1	CH ₃	CH ₃	COC ₆ H ₅	CH ₂ S(O)CH ₃	H	CH ₃	CH ₃
584	1	CH ₃	CH ₃	COC ₆ H ₅	CH ₂ S(O)CH ₃	H	CH ₃	CH ₃
585	1	CH ₃	CH ₃	COC ₆ H ₅	CONHCH(CH ₂ COOH)COOH	H	CH ₃	CH ₃
586	1	CH ₃	CH ₃	COC ₆ H ₅	CONHCH(CH ₃)COOH	H	CH ₃	CH ₃
587	1	CH ₃	CH ₃	COC ₆ H ₅	CONHCH(CHCH ₂ (CH ₃) ₂)COOH	H	CH ₃	CH ₃
588	1	CH ₃	CH ₃	COC ₆ H ₅	CONHCH(CH ₂ OH)COOH	H	CH ₃	CH ₃
589	1	CH ₃	CH ₃	COC ₆ H ₅	CONHCH(CH ₂ CH ₂ SCH ₃)COOH	H	CH ₃	CH ₃
590	1	CH ₃	CH ₃	COC ₆ H ₅	CONHCH((CH ₂) ₄ NH ₂)COOH	H	CH ₃	CH ₃
591	1	CH ₃	CH ₃	COC ₆ H ₅	CONHCH(C ₆ H ₅)COOH	H	CH ₃	CH ₃
592	1	CH ₃	CH ₃	COC ₆ H ₅	CONHCH(CH ₂ CONH ₂)COOH	H	CH ₃	CH ₃
593	1	CH ₃	CH ₃	CONH ₂	CH ₂ CONH ₂	H	CH ₃	CH ₃
594	1	CH ₃	CH ₃	COC ₆ H ₅	CONHCH ₃	H	CH ₃	CH ₃
595	1	CH ₃	CH ₃	COC ₆ H ₅	CONHOH	H	CH ₃	CH ₃
596	1	CH ₃	CH ₃	COC ₆ H ₅	CON(CH ₃) ₂	H	CH ₃	CH ₃
597	1	CH ₃	CH ₃	COC ₆ H ₅	CONHC ₆ H ₅	H	CH ₃	CH ₃
598	1	CH ₃	CH ₃	COC ₆ H ₅				



[Table 31]



No.	n	R ^{1e}	R ^{1f}	R ²	R ³	R ⁴	R ⁵	R ⁶
599	0	CH ₃ O	C ₆ H ₅	COCH ₂ H ₅	COOH	H	H	H
600	0	H ₂ N	C ₆ H ₅	COCH ₂ H ₅	COOH	H	H	H
601	0	CH ₃ C(O)NH	C ₆ H ₅	COCH ₂ H ₅	COOH	H	H	H
602	0	2-Thienyl	C ₆ H ₅	COCH ₂ H ₅	COOH	H	H	H
603	0	C ₆ H ₅	OH	CH ₂ C ₆ H ₅	COOH	H	H	H
604	0	C ₆ H ₅	OH	COCH ₂ C ₆ H ₅	COOH	H	H	H
605	0	C ₆ H ₅	OH	CH ₂ CH ₂ C ₆ H ₅	COOH	H	H	H
606	0	C ₆ H ₅	OH	C ₆ H ₅	COOH	H	H	H
607	0	C ₆ H ₅	OH	S(O) ₂ C ₆ H ₅	COOH	H	H	H
608	0	F	C ₆ H ₅	COCH ₂ H ₅	COOH	H	H	H
609	0	C1	C ₆ H ₅	COCH ₂ H ₅	COOH	H	H	H
610	0	NC	C ₆ H ₅	COCH ₂ H ₅	COOH	H	H	H
611	0	HOC(O)	C ₆ H ₅	COCH ₂ H ₅	COOH	H	H	H
612	0	CH ₃ OC(O)	C ₆ H ₅	COCH ₂ H ₅	COOH	H	H	H
613	0	(CH ₃) ₂ NC(O)	C ₆ H ₅	COCH ₂ H ₅	COOH	H	H	H
614	0	HO	C ₆ H ₅	COCH ₂ H ₅	COOH	H	H	H
615	0	CH ₃	C ₆ H ₅	COCH ₂ H ₅	COOH	H	H	H



[Table 32]

No.	n	R ^{1e}	R ^{1f}	R ²	R ³	R ⁴	R ⁵	R ⁶
616	0	C ₂ H ₅	C ₆ H ₅	CO C ₆ H ₅	COOH	H	H	H
617	0	CH ₂ CH	C ₆ H ₅	CO C ₆ H ₅	COOH	H	H	H
618	0	C ₆ H ₁₁	C ₆ H ₅	CO C ₆ H ₅	COOH	H	H	H
619	0	C ₅ H ₉	C ₆ H ₅	CO C ₆ H ₅	COOH	H	H	H
620	0	C ₄ H ₇	C ₆ H ₅	CO C ₆ H ₅	COOH	H	H	H
621	0	C ₆ H ₅	C ₆ H ₅	CO C ₆ H ₅	COOH	H	H	H
622	0	C ₆ H ₅	OH	CO C ₆ H ₅	CONHCH(C ₆ H ₅)COOH	CH ₃	CH ₃	CH ₃
623	0	C ₆ H ₅	OH	CO C ₆ H ₅	CONHCH(CH ₂ CONH ₂)COOH	CH ₃	CH ₃	CH ₃
624	1	OH	C ₆ H ₅	CO C ₆ H ₅	COOH	H	H	H
625	1	C ₆ H ₅	OH	CO C ₆ H ₅	CONH ₂	CH ₃	H	H
626	1	C ₆ H ₅	OH	CO C ₆ H ₅	COOH	H	CH ₃	CH ₃
627	1	C ₆ H ₅	OH	CO C ₆ H ₅	CONH ₂	CH ₃	CH ₃	CH ₃
628	2	OH	C ₆ H ₅	CO C ₆ H ₅	COOH	H	H	H
629	2	C ₆ H ₅	OH	CO C ₆ H ₅	CONH ₂	CH ₃	H	H
630	2	C ₆ H ₅	OH	CO C ₆ H ₅	COOH	H	CH ₃	CH ₃
631	0	C ₆ H ₅	OH	CO C ₆ H ₅	COOH	H	H	H
632	0	C ₆ H ₅	OH	CO C ₆ H ₅	COOH	CH ₃	H	H
633	0	C ₆ H ₅	OH	CO C ₆ H ₅	COOH	H	CH ₃	CH ₃
634	0	C ₆ H ₅	OH	CO C ₆ H ₅	COOH	CH ₃	CH ₃	CH ₃
635	0	C ₆ H ₅	OH	CO C ₆ H ₅	COOH	CH ₃	CH ₃	CH ₃
636	0	C ₆ H ₅	OH	CO C ₆ H ₅	CO(O)CH ₂ C ₆ H ₅	CH ₃	CH ₃	CH ₃
637	0	C ₆ H ₅	OH	CO C ₆ H ₅	CO(O)C ₂ H ₅	CH ₃	CH ₃	CH ₃

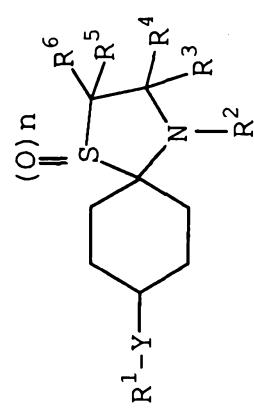
[Table 33]

No.	n	R ^{1e}	R ^{1f}	R ²	R ³	R ⁴	R ⁵	R ⁶
638	0	C ₆ H ₅	OH	COCH ₃	CONH ₂	CH ₃	CH ₃	CH ₃
639	0	C ₆ H ₅	OH	COCH ₂	CH ₂ CONH ₂	CH ₃	CH ₃	CH ₃
640	0	C ₆ H ₅	OH	COCH ₃	CONHCH ₃	CH ₃	CH ₃	CH ₃
641	0	C ₆ H ₅	OH	COCH ₅	CONHOH	CH ₃	CH ₃	CH ₃
642	0	C ₆ H ₅	OH	COCH ₅	CON (CH ₃) ₂	CH ₃	CH ₃	CH ₃
643	0	C ₆ H ₅	OH	COCH ₆ H ₅	CONHC ₆ H ₅	CH ₃	CH ₃	CH ₃
644	0	C ₆ H ₅	OH	COCH ₆ H ₅	COCH ₆ H ₅	CH ₃	CH ₃	CH ₃
645	0	C ₆ H ₅	OH	COCH ₆ H ₅	COCH ₃	CH ₃	CH ₃	CH ₃
646	0	C ₆ H ₅	OH	COCH ₆ H ₅	C (NOH) CH ₃	CH ₃	CH ₃	CH ₃
647	0	C ₆ H ₅	OH	COCH ₆ H ₅	CHO	CH ₃	CH ₃	CH ₃
648	0	C ₆ H ₅	OH	COCH ₆ H ₅	CH ₂ OC (O) NH ₂	CH ₃	CH ₃	CH ₃
649	0	C ₆ H ₅	OH	COCH ₆ H ₅	CH ₂ OC (O) CH ₃	CH ₃	CH ₃	CH ₃
650	0	C ₆ H ₅	OH	COCH ₆ H ₅	CH ₂ OC (O) C ₆ H ₅	CH ₃	CH ₃	CH ₃
651	0	C ₆ H ₅	OH	COCH ₆ H ₅	CH ₂ COOH	CH ₃	CH ₃	CH ₃
652	0	C ₆ H ₅	OH	COCH ₆ H ₅	CONHCH (CH ₂ COOH) COOH	CH ₃	CH ₃	CH ₃
653	0	C ₆ H ₅	OH	COCH ₆ H ₅	CONHCH (CH ₃) COOH	CH ₃	CH ₃	CH ₃
654	0	C ₆ H ₅	OH	COCH ₆ H ₅	CONHCH (CHCH ₂ (CH ₃) ₂) COOH	CH ₃	CH ₃	CH ₃
655	0	C ₆ H ₅	OH	COCH ₆ H ₅	CONHCH (CH ₂ OH) COOH	CH ₃	CH ₃	CH ₃
656	0	C ₆ H ₅	OH	COCH ₆ H ₅	CONHCH (CH ₂ CH ₂ SCH ₃) COOH	CH ₃	CH ₃	CH ₃
657	0	C ₆ H ₅	OH	COCH ₆ H ₅	CONHCH ((CH ₂) ₄ NH ₂) COOH	CH ₃	CH ₃	CH ₃
658	2	C ₆ H ₅	OH	COCH ₂	CONH ₂	CH ₃	CH ₃	CH ₃





[Table 34]



NO.	n	R ¹ -Y-	R ²	R ³ , R ⁴	R ⁵	R ⁶
659	0	H ₂ NNH-	CH ₂ C ₆ H ₅		O	H
660	0	H ₂ N-	CH ₂ C ₆ H ₅		O	H
661	0	C1CO-	CH ₂ C ₆ H ₅		O	H
662	0	C1CHCH-	CH ₂ C ₆ H ₅		O	H
663	0	C1SO ₂ -	CH ₂ C ₆ H ₅		O	H
664	0	HOS(O) ₂ -	CH ₂ C ₆ H ₅		O	H
665	0	NCS(O) ₂ -	CH ₂ C ₆ H ₅		O	H
666	0	CH ₃ OS(O) ₂ -	CH ₂ C ₆ H ₅		O	H
667	0	H ₂ NS(O) ₂ -	CH ₂ C ₆ H ₅		O	H
668	0	HO-	CH ₂ C ₆ H ₅		O	H
669	0	O ₂ NO-	CH ₂ C ₆ H ₅		O	H
670	0	H ₂ NC(O)O-	CH ₂ C ₆ H ₅		O	H
671	0	HS-	CH ₂ C ₆ H ₅		O	H
672	0	HOS-	CH ₂ C ₆ H ₅		O	H
673	0	CH ₃ (O)S-	CH ₂ C ₆ H ₅		O	H



[Table 35]

No.	n	R ¹ -Y-	R ²	R ³ , R ⁴	R ⁵	R ⁶
674	0	OHC-	CH ₂ C ₆ H ₅	O	H	CH ₂ COOH
675	0	O ₂ NCHCH-	CH ₂ C ₆ H ₅	O	H	CH ₂ COOH
676	0	CH ₂ CHCHCH-	CH ₂ C ₆ H ₅	O	H	CH ₂ COOH
677	0	CH ₃ OCHCH-	CH ₂ C ₆ H ₅	O	H	CH ₂ COOH
678	0	CH ₃ C(O)CHCH-	CH ₂ C ₆ H ₅	O	H	CH ₂ COOH
679	0	CH ₂ CH-	CH ₂ C ₆ H ₅	O	H	CH ₂ COOH
680	0	ClCH ₂ CH ₂ -	CH ₂ C ₆ H ₅	O	H	CH ₂ COOH
681	0	NCH ₂ -	CH ₂ C ₆ H ₅	O	H	CH ₂ COOH
682	0	O ₂ NCH ₂ -	CH ₂ C ₆ H ₅	O	H	CH ₂ COOH
683	0	CH ₃ OC(O)CH ₂ -	CH ₂ C ₆ H ₅	O	H	CH ₂ COOH
684	0	HOC(O)CH ₂ -	CH ₂ C ₆ H ₅	O	H	CH ₂ COOH
685	0	CH ₃ COCH ₂ -	CH ₂ C ₆ H ₅	O	H	CH ₂ COOH
686	0	H ₂ NCH ₂	CH ₂ C ₆ H ₅	O	H	CH ₂ COOH
687	0	HOCH ₂ -	CH ₂ C ₆ H ₅	O	H	CH ₂ COOH
688	0	HONH-	CH ₂ C ₆ H ₅	O	H	CH ₂ COOH
689	0	CH ₃ C(O)NCl-	CH ₂ C ₆ H ₅	O	H	CH ₂ COOH
690	0	O ₂ NNH-	CH ₂ C ₆ H ₅	O	H	CH ₂ COOH
691	0	CH ₃ ONH-	CH ₂ C ₆ H ₅	O	H	CH ₂ COOH
692	0	CH ₂ CHS(O)-	CH ₂ C ₆ H ₅	O	H	CH ₂ COOH
693	0	CH ₂ CHS(O) ₂ -	CH ₂ C ₆ H ₅	O	H	CH ₂ COOH
694	0	2-Thiazolylsulfonyl	CH ₂ C ₆ H ₅	O	H	CH ₂ COOH
695	0	CH ₂ CHCH(OH)-	CH ₂ C ₆ H ₅	O	H	CH ₂ COOH



[Table 36]

No.	n	R ¹ -Y-	R ²	R ³ , R ⁴	R ⁵	R ⁶
696	0	C ₆ H ₁₁ O-	CH ₂ C ₆ H ₅	O	H	CH ₂ COOH
697	0	C ₆ H ₁₁ S-	CH ₂ C ₆ H ₅	O	H	CH ₂ COOH
698	0	C ₆ H ₁₁ NH-	CH ₂ C ₆ H ₅	O	H	CH ₂ COOH
699	0	C ₆ H ₁₁ CHCH-	CH ₂ C ₆ H ₅	O	H	CH ₂ COOH
700	0	C ₆ H ₁₁ S (O) -	CH ₂ C ₆ H ₅	O	H	CH ₂ COOH
701	0	NCCO-	CH ₂ C ₆ H ₅	O	H	CH ₂ COOH
702	0	NCCCHCH-	CH ₂ C ₆ H ₅	O	H	CH ₂ COOH
703	0	NCS-	CH ₂ C ₆ H ₅	O	H	CH ₂ COOH
704	0	C ₆ H ₁₁ S (O) ₂ -	CH ₂ C ₆ H ₅	O	H	CH ₂ COOH
705	0	HOC (O) C (O) -	CH ₂ C ₆ H ₅	O	H	CH ₂ COOH
706	0	H ₃ COC (O) NH-	CH ₂ C ₆ H ₅	O	H	CH ₂ COOH
707	0	HOC (O) CHCH -	CH ₂ C ₆ H ₅	O	H	CH ₂ COOH
708	0	HOC (O) CH (OH) -	CH ₂ C ₆ H ₅	O	H	CH ₂ COOH
709	0	HOO -	CH ₂ C ₆ H ₅	O	H	CH ₂ COOH
710	0	HOC (O) -	CH ₂ C ₆ H ₅	O	H	CH ₂ COOH
711	0	CH ₃ OC (O) CHCH	CH ₂ C ₆ H ₅	O	H	CH ₂ COOH
712	0	CH ₃ OC (O) SCHCH	CH ₂ C ₆ H ₅	O	H	CH ₂ COOH
713	0	(HO) ₂ CH -	CH ₂ C ₆ H ₅	O	H	CH ₂ COOH
714	0	CH ₃ O -	CH ₂ C ₆ H ₅	O	H	CH ₂ COOH
715	0	CH ₃ S -	CH ₂ C ₆ H ₅	O	H	CH ₂ COOH
716	0	CH ₃ NH -	CH ₂ C ₆ H ₅	O	H	CH ₂ COOH
717	0	CH ₃ CO -	CH ₂ C ₆ H ₅	O	H	CH ₂ COOH



[Table 37]

No.	n	R ¹ -Y-	R ²	R ³ , R ⁴	R ⁵	R ⁶
718	0	CH ₃ CHCH-	CH ₂ C ₆ H ₅	0	H	CH ₂ COOH
719	0	C ₆ H ₅ S(O)-	CH ₂ C ₆ H ₅	0	H	CH ₂ COOH
720	0	CH ₃ S(O)-	CH ₂ C ₆ H ₅	0	H	CH ₂ COOH
721	0	CH ₃ S(O) ₂ -	CH ₂ C ₆ H ₅	0	H	CH ₂ COOH
722	0	NCCN(OH)-	CH ₂ C ₆ H ₅	0	H	CH ₂ COOH
723	0	CH ₃ OC(O)CH(OH)-	CH ₂ C ₆ H ₅	0	H	CH ₂ COOH
724	0	CH ₃ C(O)CH(OH)-	CH ₂ C ₆ H ₅	0	H	CH ₂ COOH
725	0	CH ₃ CH(OH)-	CH ₂ C ₆ H ₅	0	H	CH ₂ COOH
726	0	CH ₂ CHO-	CH ₂ C ₆ H ₅	0	H	CH ₂ COOH
727	0	CH ₂ CHS-	CH ₂ C ₆ H ₅	0	H	CH ₂ COOH
728	0	CH ₂ CHNH-	CH ₂ C ₆ H ₅	0	H	CH ₂ COOH
729	0	CH ₂ CHCO-	CH ₂ C ₆ H ₅	0	H	CH ₂ COOH
730	0	CH ₂ CHCH ₂ -	CH ₂ C ₆ H ₅	0	H	CH ₂ COOH
731	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ CH(C ₂ H ₅)C ₂ H ₅	0	H	CH ₂ COOH
732	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ F	0	H	CH ₂ COOH
733	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ OH	0	H	CH ₂ COOH
734	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ OH	0	H	CH ₂ COOH
735	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ CH ₂ OH	0	H	CH ₂ COOH
736	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ CH ₂ CH ₂ OH	0	H	CH ₂ COOH
737	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ CH ₂ CH ₂ OH	0	H	CH ₂ COOH
738	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH(OH)CH ₂ OH	0	H	CH ₂ COOH
739	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH(OH)CH ₂ OH	0	H	CH ₂ COOH
740	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH(OH)CH ₂ OH	0	H	CH ₂ COOH



[Table 38]

No.	n	R ¹ -Y-	R ²	R ³ , R ⁴	R ⁵	R ⁶
741	0	C ₆ H ₁₁ CH(OH) -	CH ₂ C ₆ H ₅	O	H	CH ₂ COOH
742	0	CH ₃ C(O)O -	CH ₂ C ₆ H ₅	O	H	CH ₂ COOH
743	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O -	CH ₂ CH ₂ CH(CH ₃)C ₂ H ₅	O	H	CH ₂ COOH
744	0	CH ₃ C(O)NH -	CH ₂ C ₆ H ₅	O	H	CH ₂ COOH
745	0	H ₂ NC(O) -	CH ₂ C ₆ H ₅	O	H	CH ₂ COOH
746	0	C ₆ H ₅ CH ₂ CH ₂ -	CH ₂ C ₆ H ₅	O	H	CH ₂ COOH
747	0	2-Pyridyletheny1	CH ₂ C ₆ H ₅	O	H	CH ₂ COOH
748	0	C ₆ H ₅ CHCH-	CH ₂ C ₆ H ₅	O	H	CH ₂ COOH
749	0	CH ₃ C(O)C(O) -	CH ₂ C ₆ H ₅	O	H	CH ₂ COOH
750	0	CH ₃ C(O)C(O) -	CH ₂ CH ₂ C ₆ H ₅	O	H	CH ₂ COOH
751	0	Cyclohexanecarbonyl	CH ₂ C ₆ H ₅	O	H	CH ₂ COOH
752	0	2-Thienylcarbonyl	CH ₂ C ₆ H ₅	O	H	CH ₂ COOH
753	0	CH ₃ OC(O) -	CH ₂ C ₆ H ₅	O	H	CH ₂ COOH
754	0	CH ₃ OC(O)CHCH-	CH ₂ C ₆ H ₅	O	H	CH ₂ COOH
755	0	CH ₃ C(O)NHCHCH-	CH ₂ C ₆ H ₅	O	H	CH ₂ COOH
756	0	CH ₃ SCHCH-	CH ₂ C ₆ H ₅	O	H	CH ₂ COOH
757	0	CH ₃ S(O)CHCH-	CH ₂ C ₆ H ₅	O	H	CH ₂ COOH
758	0	CH ₃ S(O) ₂ CHCH-	CH ₂ C ₆ H ₅	O	H	CH ₂ COOH
759	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O -	H	O	H	CH ₂ COOH
760	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O -	CH ₃	O	H	CH ₂ COOH
761	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O -	CH ₂ CH ₃	O	H	CH ₂ COOH
762	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O -	CH ₂ CH ₂ CH ₃	O	H	CH ₂ COOH



[Table 39]

No.	n	R ¹ -Y-	R ²	R ³ , R ⁴	R ⁵	R ⁶
763	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ CH ₂ CH ₃	O	H	CH ₂ COOH
764	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ CH ₂ CH ₂ CH ₃	O	H	CH ₂ COOH
765	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH(CH ₃)CH ₃	O	H	CH ₂ COOH
766	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH(CH ₃)CH ₃	O	H	CH ₂ COOH
767	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ CH(CH ₃)CH ₃	O	H	CH ₂ COOH
768	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ CH ₂ CH(CH ₃)CH ₃	O	H	CH ₂ COOH
769	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH(CH ₃)C ₂ H ₅	O	H	CH ₂ COOH
770	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH(CH ₂ OH)COOH	O	H	CH ₂ COOH
771	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH(CH ₂ COOH)COOH	O	H	CH ₂ COOH
772	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH(CH ₂ CONH ₂)COOH	O	H	CH ₂ COOH
773	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH(CH ₂ CH ₂ COOH)COOH	O	H	CH ₂ COOH
774	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH(CH ₂ CH ₂ CONH ₂)COOH	O	H	CH ₂ COOH
775	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH(4-Imidazolylmethyl)COOH	O	H	CH ₂ COOH
776	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH(CH(C ₂ H ₅)CH ₃)COOH	O	H	CH ₂ COOH
777	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH(CH ₂ CH(CH ₃)CH ₃)COOH	O	H	CH ₂ COOH
778	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH(CH ₂ CH ₂ SC ₂ H ₅)COOH	O	H	CH ₂ COOH
779	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH(CH(OH)CH ₃)COOH	O	H	CH ₂ COOH
780	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH(CH ₂ -(4-HO)C ₆ H ₅)COOH	O	H	CH ₂ COOH
781	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ CH(OH)CH ₂ CH ₂ OH	O	H	CH ₂ COOH
782	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ OC(O)NH ₂	O	H	CH ₂ COOH
783	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ OC(O)CH ₃	O	H	CH ₂ COOH
784	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ COOH	O	H	CH ₂ COOH

[Table 40]

No.	n	R ¹ -Y-	R ²	R ³ , R ⁴	R ⁵	R ⁶
785	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOH	O	H	CH ₂ COOH
786	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ CH ₂ COOH	O	H	CH ₂ COOH
787	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ CH ₂ CH ₂ COOH	O	H	CH ₂ COOH
788	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ COOH	O	H	CH ₂ COOH
789	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ COOCH ₃	O	H	CH ₂ COOH
790	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ COOC ₂ H ₅	O	H	CH ₂ COOH
791	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ COO-n-C ₃ H ₇	O	H	CH ₂ COOH
792	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ COO-i-C ₃ H ₇	O	H	CH ₂ COOH
793	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ COOC ₆ H ₅	O	H	CH ₂ COOH
794	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
795	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
796	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH(CH ₃)COOH	O	H	CH ₂ COOH
797	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CONH ₂	O	H	CH ₂ COOH
798	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CONHOH	O	H	CH ₂ COOH
799	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CONHCH ₃	O	H	CH ₂ COOH
800	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CONH ₂ H ₅	O	H	CH ₂ COOH
801	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CONH-n-C ₃ H ₇	O	H	CH ₂ COOH
803	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CONH-i-C ₃ H ₇	O	H	CH ₂ COOH
803	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CON(CH ₃) ²	O	H	CH ₂ COOH
804	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CON(n-C ₃ H ₇) ₂	O	H	CH ₂ COOH
805	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CON(C ₂ H ₅) ₂	O	H	CH ₂ COOH
806	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CONHC ₆ H ₅	O	H	CH ₂ COOH





[Table 41]

No.	n	R ¹ -Y-	R ²	R ³ , R ⁴	R ⁵	R ⁶
807	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₃	0	H	CH ₂ COOH
808	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	Cyclopentyl	0	H	CH ₂ COOH
809	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	Cyclohexyl	0	H	CH ₂ COOH
810	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ C ₆ H ₅	0	H	CH ₂ COOH
811	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ C ₆ H ₅	0	H	CH ₂ COOH
812	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ C ₆ H ₁₁	0	H	CH ₂ COOH
813	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH(CH ₃)C ₆ H ₅	0	H	CH ₂ COOH
814	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	2-Thienylmethyl	0	H	CH ₂ COOH
815	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	2-Furyl	0	H	CH ₂ COOH
816	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	2-Pyranylmethyl	0	H	CH ₂ COOH
817	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	1-Isobenzofurylmethyl	0	H	CH ₂ COOH
818	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	2-Pyrrolylmethyl	0	H	CH ₂ COOH
819	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	1-Imidazolylmethyl	0	H	CH ₂ COOH
820	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	1-Pyrazolylmethyl	0	H	CH ₂ COOH
821	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH(CH ₂ C ₆ H ₅)COOH	0	H	CH ₂ COOH
822	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH(3-Indolylmethyl)COOH	0	H	CH ₂ COOH
823	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH(1-C ₃ H ₇)COOH	0	H	CH ₂ COOH
824	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CN	0	H	CH ₂ COOH
825	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ NO ₂	0	H	CH ₂ COOH
826	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ COCH ₃	0	H	CH ₂ COOH
827	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ C(OCH ₂) ₂ CH ₃	0	H	CH ₂ COOH
828	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ C(SCH ₃) ₂ CH ₃	0	H	CH ₂ COOH

[Table 42]



No.	n	R ¹ -Y-	R ²	R ³ , R ⁴			R ⁵	R ⁶
829	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	C(NH)NH ₂	0	H		CH ₂ COOH	
830	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ C(NOH)CH ₃	0	H		CH ₂ COOH	
831	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ SH	0	H		CH ₂ COOH	
832	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ SO ₃ H	0	H		CH ₂ COOH	
833	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ S(O) ₂ CH ₃	0	H		CH ₂ COOH	
834	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ S(O)CH ₃	0	H		CH ₂ COOH	
835	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ S(O) ₂ NH ₃	0	H		CH ₂ COOH	
836	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	Cyclobutyl	0	H		CH ₂ COOH	
837	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ OCH ₃	0	H		CH ₂ COOH	
838	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ OCH ₃	0	H		CH ₂ COOH	
839	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ CH ₂ OCH ₃	0	H		CH ₂ COOH	
840	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ SCH ₃	0	H		CH ₂ COOH	
841	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ SCH ₃	0	H		CH ₂ COOH	
842	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ CH ₂ SCH ₃	0	H		CH ₂ COOH	
843	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CHCH ₂	0	H		CH ₂ COOH	
844	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CHCH ₂	0	H		CH ₂ COOH	
845	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CCH	0	H		CH ₂ COOH	
846	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	Cyclopropyl	0	H		CH ₂ COOH	
847	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	2-Thiazolyl	0	H		CH ₂ COOH	
848	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	4-Imidazolyl	0	H		CH ₂ COOH	
849	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	3-Pyrazolyl	0	H		CH ₂ COOH	
850	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	3-Isoxazolyl	0	H		CH ₂ COOH	



[Table 43]

No.	n	R ¹ -Y-	R ²	R ³ , R ⁴	R ⁵	R ⁶
851	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	5-Isothiazolyl	O	H	CH ₂ COOH
852	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	2-Pyrimidinyl	O	H	CH ₂ COOH
853	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	3-(1,2,4-Triazolyl)	O	H	CH ₂ COOH
854	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	2-Pyridyl	O	H	CH ₂ COOH
855	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	2-Benzoxazolyl	O	H	CH ₂ COOH
856	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	3-Benzothienyl	O	H	CH ₂ COOH
857	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	2-Benzofuryl	O	H	CH ₂ COOH
858	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	5-Indolyl	O	H	CH ₂ COOH
859	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	2-Pyrazinyl	O	H	CH ₂ COOH
860	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	3-Quinolyl	O	H	CH ₂ COOH
861	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	3-Isothiazolylmethyl	O	H	CH ₂ COOH
862	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	3-Isoxazolylmethyl	O	H	CH ₂ COOH
863	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	2-Pyridylmethyl	O	H	CH ₂ COOH
864	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	2-Pyrazinylmethyl	O	H	CH ₂ COOH
865	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	2-Pyrimidinylmethyl	O	H	CH ₂ COOH
866	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	3-Pyridazinylmethyl	O	H	CH ₂ COOH
867	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	1-Isindolylmethyl	O	H	CH ₂ COOH
868	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	2-Indolylmethyl	O	H	CH ₂ COOH
869	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	3-(1H-Indazolyl)methyl	O	H	CH ₂ COOH
870	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	2-Purinylmethyl	O	H	CH ₂ COOH
871	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	1-Isoquinolylmethyl	O	H	CH ₂ COOH
872	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	2-Quinolylmethyl	O	H	CH ₂ COOH



[Table 44]

No.	n	R ¹ -Y-	R ²	R ³ , R ⁴	R ⁵	R ⁶
873	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	1-Phthalazinylmethyl	O	H	CH ₂ COOH
874	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	2-Naphthylidinylmethyl	O	H	CH ₂ COOH
875	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	2-Quinoxalinylmethyl	O	H	CH ₂ COOH
876	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	2-Quinazolinylmethyl	O	H	CH ₂ COOH
877	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	3-Cinnolinylmethyl	O	H	CH ₂ COOH
878	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	2-Oxazolylmethyl	O	H	CH ₂ COOH
879	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	2-Thiazolylmethyl	O	H	CH ₂ COOH
880	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	2-Benzo[b]furlylmethyl	O	H	CH ₂ COOH
881	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	2-Benzo[b]thienylmethyl	O	H	CH ₂ COOH
882	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	3-(1,2,4-Triazinyl)methyl	O	H	CH ₂ COOH
883	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	2-Benz[d]imidazolylmethyl	O	H	CH ₂ COOH
884	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	2-Benz[d]oxazolylmethyl	O	H	CH ₂ COOH
885	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	Phenyl	O	H	CH ₂ COOH
886	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	2-Naphthyl	O	H	CH ₂ COOH
887	0	4-C ₆ H ₅ CH ₂ OOC ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
888	0	4-HO ₂ CC ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
889	0	4-H ₃ COC(O)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
890	0	4-H ₂ NC(O)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
891	0	4-HONHC(O)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
892	0	4-H ₃ CNHC(O)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
893	0	4-(H ₃ C) ₂ NC(O)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
894	0	4-O ₂ NC ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH



[Table 45]

No.	n	R ¹ -Y-	R ²	R ³ , R ⁴	R ⁵	R ⁶
895	0	4-H ₂ NC ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	CH ₂ COOH
896	0	4-H ₃ CNHC ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	CH ₂ COOH
897	0	4-(H ₃ C) ₂ NC ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	CH ₂ COOH
898	0	4-OHCC ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	CH ₂ COOH
899	0	4-HONCHC ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	CH ₂ COOH
900	0	4-OHCNHC ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	CH ₂ COOH
901	0	4-CH ₃ CH (CH ₃) C ₆ H ₄ O-	5-Tetrazolyl	0	H	CH ₂ COOH
902	0	4-CH ₃ CH (CH ₃) C ₆ H ₄ O-	Methylsulfonyl	0	H	CH ₂ COOH
903	0	4-CH ₃ CH (CH ₃) C ₆ H ₄ O-	Benzenesulfonyl	0	H	CH ₂ COOH
904	0	4-CH ₃ CH (CH ₃) C ₆ H ₄ O-	CH ₂ CONHCH ₂ C ₆ H ₅	0	H	CH ₂ COOH
905	0	4-FC ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	CH ₂ COOH
906	0	2-CH ₃ C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	CH ₂ COOH
907	0	3-CH ₃ C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	CH ₂ COOH
908	0	4-CH ₃ C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	CH ₂ COOH
909	0	2, 4-(CH ₃) ₂ C ₆ H ₃ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	CH ₂ COOH
910	0	3, 4-(CH ₃) ₂ C ₆ H ₃ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	CH ₂ COOH
911	0	2, 3-(CH ₃) ₂ C ₆ H ₃ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	CH ₂ COOH
912	0	3, 5-(CH ₃) ₂ C ₆ H ₃ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	CH ₂ COOH
913	0	3, 6-(CH ₃) ₂ C ₆ H ₃ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	CH ₂ COOH
914	0	2, 6-(CH ₃) ₂ C ₆ H ₃ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	CH ₂ COOH
915	0	2, 5-(CH ₃) ₂ C ₆ H ₃ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	CH ₂ COOH
916	0	2, 4, 6-(CH ₃) ₃ C ₆ H ₂ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	CH ₂ COOH



[Table 46]

No.	n	R ¹ -Y-	R ²	R ³ , R ⁴	R ⁵	R ⁶
917	0	2, 3, 5-(CH ₃) ₃ C ₆ H ₂ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
918	0	4-CH(OCH ₃) ₂ C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
919	0	4-CH(SCH ₃) ₂ C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
920	0	2, 4, 5-(CH ₃) ₃ C ₆ H ₂ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
921	0	2, 5, 6-(CH ₃) ₃ C ₆ H ₂ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
922	0	4-HOC ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
923	0	4-H ₃ COC ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
924	0	4-C ₂ H ₅ OC ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
925	0	4-CH ₃ CH(CH ₃)OC ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
926	0	4-C ₆ H ₅ OC ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
927	0	2-Benzoxazolylamino	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
928	0	3-Benzothienylamino	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
929	0	2-Benzofuryl amino	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
930	0	5-Indolylamino	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
931	0	2-Pyrazinylamino	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
932	0	3-Quinolylamino	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
933	0	5-Tetrazolylamino	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
934	0	2-Imidazolylthioxy	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
935	0	2-Pyridylthioxy	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
936	0	2-Benzothiazolylthioxy	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
937	0	2-Benzothienylthienyl	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
938	0	2-Benzothienyllethynyl	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH



[Table 47]

No.	n	R ¹ -Y-	R ²	R ³ , R ⁴	R ⁵	R ⁶
939	0	2-Benzothienylmethyl	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
940	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ S(O)-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
941	0	4-H ₃ CC(O)NHC ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
942	0	4-H ₃ COC(O)NHC ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
943	0	4-H ₂ NC(O)OC ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
944	0	4-HSC ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
945	0	4-H ₃ CSC ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
946	0	4-H ₃ CS(O)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
947	0	4-H ₃ CS(O) ₂ C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
948	0	3, 4-(OCH ₂ O)C ₆ H ₃ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
949	0	3, 4-(CH ₂ CH ₂ CH ₂)C ₆ H ₃ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
950	0	4-HO ₃ SC ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
951	0	4-NCC ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
952	0	4-H ₂ NC(NH)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
953	0	2-Pyridylamino	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
954	0	3-Isoxazoloxyl	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
955	0	2-Imidazoloxyl	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
956	0	2-Benzimidazoloxyl	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
957	0	2-Thiazoloxyl	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
958	0	5-Benzol[b]thienyloxy	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
959	0	2-Thiazolylamino	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
960	0	4-Imidazolylamino	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH

[Table 48]



No.	n	R ¹ -Y-	R ²	R ³ , R ⁴	R ⁵	R ⁶
961	0	3-Pyrazolylamino	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	CH ₂ COOH
962	0	3-Isoxazolylamino	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	CH ₂ COOH
963	0	5-Isothiazolylamino	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	CH ₂ COOH
964	0	2-Pyrimidinylamino	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	CH ₂ COOH
965	0	3-(1,2,4-Triazolyl)amino	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	CH ₂ COOH
966	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	CH(CH ₃)COOH
967	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	CH(C ₆ H ₅)COOH
968	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	C(CH ₃) ₂ COOH
969	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	C(C ₂ H ₄)COOH
970	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	C(C ₃ H ₆)COOH
971	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	C(C ₄ H ₈)COOH
972	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	C(C ₅ H ₁₀)COOH
973	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	C(O)COOH
974	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	C(NO) ₂ COOH
975	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	C(OCH ₃) ₂ COOH
976	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	C(SCH ₃) ₂ COOH
977	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	CH(CH ₂ OH)COOH
978	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	CH(NH ₂)COOH
979	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	CH(NHCHO)COOH
980	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	CH ₂ CH ₂ COOH
981	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ S(O) ₂ -	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	CH ₂ COOH
982	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ OS(O) ₂ -	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	CH ₂ COOH

[Table 49]



No.	n	R ¹ -Y-	R ²	R ³ , R ⁴	R ⁵	R ⁶
983	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ S-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	CH ₂ COOH
984	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	CH(OH)COOH
985	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ NH-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	CH ₂ COOH
986	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	CH ₂ COOH
987	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CH(OH)-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	CH ₂ COOH
988	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ OCH ₂ -	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	CH ₂ COOH
989	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ OC(O)-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	CH ₂ COOH
990	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CH ₂ OC(O)-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	CH ₂ COOH
991	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ NHC(O)-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	CH ₂ COOH
992	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ OC(O)NH-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	CH ₂ COOH
993	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CH ₂ OC(O)NH-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	CH ₂ COOH
994	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CONH-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	CH ₂ COOH
995	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CH ₂ CONH-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	CH ₂ COOH
996	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CH ₂ CO-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	CH ₂ COOH
997	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CH ₂ OCH ₂ -	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	CH ₂ COOH
998	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ C(NO _H)-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	CH ₂ COOH
999	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CHCH-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	CH ₂ COOH
1000	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	CH(OCH ₃)COOH
1001	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CH ₂ -	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	CH ₂ COOH
1002	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	CHFCOOH
1003	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	CF ₂ COOH
1004	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	CH ₂ CH ₂ NHCH ₂ C ₆ H ₅



Table 50]

No.	n	R ¹ -Y-	R ²	R ³ , R ⁴	R ⁵	R ⁶
1005	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ CH ₂ SH
1006	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ CH ₂ SCH ₃
1007	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ CH ₂ SO ₂ CH ₃
1008	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ CH ₂ S(O)CH ₃
1009	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ CONH ₂
1010	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ CONHCH(CH ₃)COOH
1011	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ CONHCH(CH ₂ CONH ₂)COOH
1012	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ CONHCH ₃
1013	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ CONHOH
1014	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ CON(CH ₃) ₂
1015	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ CONHC ₆ H ₅
1016	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COC ₆ H ₅
1017	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COCH ₃
1018	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ C(OCH ₃) ₂ CH ₃
1019	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ CH(OCH ₃) ₂
1020	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ C(NO ₂)CH ₃
1021	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ CH(OH)COOH
1022	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH(OH)CH ₂ COOH
1023	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ CHFCOOH
1024	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ CH ₂ OH
1025	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ CH ₂ OCH ₃
1026	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ CH ₂ OC ₆ H ₅



[Table 51]

No.	n	R ¹ -Y-	R ²	R ³ , R ⁴	R ⁵	R ⁶
1027	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	CH ₂ CH ₂ OCH ₂ C ₆ H ₅
1028	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	CH ₂ CH ₂ F
1029	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	CH ₂ CH ₂ NH ₂
1030	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	CH ₂ CH ₂ NHCHO
1031	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	CH ₂ CH ₂ NHCOOCH ₃
1032	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	CH ₂ CH ₂ N(CH ₃) ₂
1033	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	CH ₂ CH ₂ NH(CH ₃) ₂
1034	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	H
1035	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	CHCH ₂	H
1036	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	COCH ₃	H
1037	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	COCH ₃ H ₅	H
1038	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	C ₆ H ₅	H
1039	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	CH ₂ C ₆ H ₅	H
1040	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	C ₁	CH ₂ COOH
1041	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	CN	CH ₂ COOH
1042	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	COOH	CH ₂ COOH
1043	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	COOH	CH ₂ COOH
1044	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	CONH ₂	CH ₂ COOH
1045	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	CONHCH ₃	CH ₂ COOH
1046	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	CH ₃	CH ₂ COOH
1047	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	COCH ₃	CH ₂ COOH
1048	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	COC ₆ H ₅	CH ₂ COOH



[Table 52]

No.	n	R ¹ -Y-	R ²	R ³ , R ⁴	R ⁵	R ⁶
1049	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	C ₆ H ₅	CH ₂ COOH
1050	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	CH ₂ C ₆ H ₅	CH ₂ COOH
1051	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	CH ₂ CHO
1052	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	CH ₂ CH ₂ OCONH ₂
1053	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	CH ₂ CH ₂ OOCCH ₃
1054	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	CH ₂ CH ₂ OOCOC ₆ H ₅
1055	1	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	CH ₂ COOH
1056	2	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	CH ₂ COOH
1057	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	CH ₂ COOH
1058	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	C ₁	H
1059	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	CN	H
1060	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	COOH	H
1061	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	CONH ₂	H
1062	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	CONHCH ₃	H
1063	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	CH ₃	H



[Table 53]

No.	n	R ^{1c}	R ^{1d}	R ²	R ^{3, R⁴}	R ⁵	R ⁶
1064	0	CH ₃	CH ₃	CH ₂ CONH ₂	0	H	CH ₂ COOH
1065	0	CH ₃	CH ₃	CH ₂ CONHOH	0	H	CH ₂ COOH
1066	0	CH ₃	CH ₃	CH ₂ CONHCH ₃	0	H	CH ₂ COOH
1067	0	CH ₃	CH ₃	CH ₂ CONHC ₂ H ₅	0	H	CH ₂ COOH
1068	0	CH ₃	CH ₃	CH ₂ CONH-n-C ₃ H ₇	0	H	CH ₂ COOH
1069	0	CH ₃	CH ₃	CH ₂ CONH-i-C ₃ H ₇	0	H	CH ₂ COOH
1070	0	CH ₃	CH ₃	CH ₂ CON (CH ₃) ₂	0	H	CH ₂ COOH
1071	0	CH ₃	CH ₃	CH ₂ CON (n-C ₃ H ₇) ₂	0	H	CH ₂ COOH
1072	0	CH ₃	CH ₃	CH ₂ CON (C ₂ H ₅) ₂	0	H	CH ₂ COOH
1073	0	CH ₃	CH ₃	CH ₂ CONHC ₆ H ₅	0	H	CH ₂ COOH
1074	0	CH ₃	CH ₃	CH ₂ CH ₂ COOCH ₃	0	H	CH ₂ COOH
1075	0	CH ₃	CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	0	H	CH ₂ COOH
1076	0	CH ₃	CH ₃	CH (CH ₃) COOH	0	H	CH ₂ COOH
1077	0	CH ₃	CH ₃	CH (CH ₂ OH) COOH	0	H	CH ₂ COOH
1078	0	CH ₃	CH ₃	CH (CH ₂ COOH) COOH	0	H	CH ₂ COOH
1079	0	CH ₃	CH ₃	CH (CH ₂ CONH ₂) COOH	0	H	CH ₂ COOH
1080	0	CH ₃	CH ₃	CH (CH ₂ CH ₂ COOH) COOH	0	H	CH ₂ COOH
1081	0	CH ₃	CH ₃	CH ₂ COOH	0	H	CH ₂ COOH
1082	0	CH ₃	CH ₃	CH ₂ CH ₂ COOH	0	H	CH ₂ COOH
1083	0	CH ₃	CH ₃	CH ₂ CH ₂ CH ₂ COOH	0	H	CH ₂ COOH
1084	0	CH ₃	CH ₃	CH ₂ CH ₂ CH ₂ CH ₂ COOH	0	H	CH ₂ COOH
1085	0	CH ₃	CH ₃	CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ COOH	0	H	CH ₂ COOH

[Table 54]

No.	n	R ^{1c}	R ^{1d}	R ²	R ^{3, R⁴}		R ⁵	R ⁶
1086	0	CH ₃	CH ₃	CH ₂ COOCH ₃	0		H	CH ₂ COOH
1087	0	CH ₃	CH ₃	CH ₂ COOC ₂ H ₅	0		H	CH ₂ COOH
1088	0	CH ₃	CH ₃	CH ₂ COO-n-C ₃ H ₇	0		H	CH ₂ COOH
1089	0	CH ₃	CH ₃	CH ₂ COO-i-C ₃ H ₇	0		H	CH ₂ COOH
1090	0	CH ₃	CH ₃	CH ₂ COOC ₆ H ₅	0		H	CH ₂ COOH
1091	0	CH ₃	CH ₃	CH ₂ COOCH ₂ C ₆ H ₅	0		H	CH ₂ COOH
1092	0	CH ₃	CH ₃	H	0		H	CH ₂ COOH
1093	0	CH ₃	CH ₃	CH ₂ F	0		H	CH ₂ COOH
1094	0	CH ₃	CH ₃	CH(i-C ₃ H ₇)COOH	0		H	CH ₂ COOH
1095	0	CH ₃	CH ₃	CH ₂ CN	0		H	CH ₂ COOH
1096	0	CH ₃	CH ₃	CH ₂ NO ₂	0		H	CH ₂ COOH
1097	0	CH ₃	CH ₃	CH ₂ COCH ₃	0		H	CH ₂ COOH
1098	0	CH ₃	CH ₃	CH ₂ C(OCH ₃) ₂ CH ₃	0		H	CH ₂ COOH
1099	0	CH ₃	CH ₃	CH ₂ C(SCH ₃) ₂ CH ₃	0		H	CH ₂ COOH
1100	0	CH ₃	CH ₃	C(NH)NH ₂	0		H	CH ₂ COOH
1101	0	CH ₃	CH ₃	CH ₂ C(NO ₂)CH ₃	0		H	CH ₂ COOH
1102	0	CH ₃	CH ₃	CH ₂ SH	0		H	CH ₂ COOH
1103	0	CH ₃	CH ₃	CH ₂ SO ₃ H	0		H	CH ₂ COOH
1104	0	CH ₃	CH ₃	CH ₂ S(O) ₂ CH ₃	0		H	CH ₂ COOH
1105	0	CH ₃	CH ₃	CH ₂ S(O)CH ₃	0		H	CH ₂ COOH
1106	0	CH ₃	CH ₃	CH ₂ S(O) ₂ NH ₂	0		H	CH ₂ COOH
1107	0	CH ₃	CH ₃	CH ₂ SO ₃ CH ₃	0		H	CH ₂ COOH





[Table 55]

No.	n	R ^{1c}	R ^{1d}	R ²	R ^{3, R⁴}		R ⁵	R ⁶
1108	0	CH ₃	CH ₃	CH ₂ OCH ₃		0	H	CH ₂ COOH
1109	0	CH ₃	CH ₃	CH ₂ CH ₂ OCH ₃		0	H	CH ₂ COOH
1110	0	CH ₃	CH ₃	CH ₂ CH ₂ CH ₂ OCH ₃		0	H	CH ₂ COOH
1111	0	CH ₃	CH ₃	CH ₂ SCH ₃		0	H	CH ₂ COOH
1112	0	CH ₃	CH ₃	CH ₂ CH ₂ SCH ₃		0	H	CH ₂ COOH
1113	0	CH ₃	CH ₃	CH ₂ CH ₂ CH ₂ SCH ₃		0	H	CH ₂ COOH
1114	0	CH ₃	CH ₃	CHCH ₂		0	H	CH ₂ COOH
1115	0	CH ₃	CH ₃	CH ₂ CHCH ₂		0	H	CH ₂ COOH
1116	0	CH ₃	CH ₃	S(O) ₂ C ₆ C ₅		0	H	CH ₂ COOH
1117	0	CH ₃	CH ₃	Cyclopropyl		0	H	CH ₂ COOH
1118	0	CH ₃	CH ₃	Cyclobutyl		0	H	CH ₂ COOH
1119	0	CH ₃	CH ₃	Cyclopentyl		0	H	CH ₂ COOH
1120	0	CH ₃	CH ₃	Cyclohexyl		0	H	CH ₂ COOH
1121	0	CH ₃	CH ₃	CH(CH ₂ CH ₂ CONH ₂)COOH		0	H	CH ₂ COOH
1122	0	CH ₃	CH ₃	CH(4-Imidazolylmethyl)COOH		0	H	CH ₂ COOH
1123	0	CH ₃	CH ₃	CH(CH(C ₂ H ₅)CH ₃)COOH		0	H	CH ₂ COOH
1124	0	CH ₃	CH ₃	CH(CH ₂ CH(CH ₃)CH ₃)COOH		0	H	CH ₂ COOH
1125	0	CH ₃	CH ₃	CH(CH ₂ CH ₂ SCH ₃)COOH		0	H	CH ₂ COOH
1126	0	CH ₃	CH ₃	CH(CH(OH)CH ₃)COOH		0	H	CH ₂ COOH
1127	0	CH ₃	CH ₃	CH(CH ₂ -(4-HO)C ₆ H ₅)COOH		0	H	CH ₂ COOH
1128	0	CH ₃	CH ₃	CH(CH ₂ C ₆ H ₅)COOH		0	H	CH ₂ COOH
1129	0	CH ₃	CH ₃	CH(3-Indolylmethyl)COOH		0	H	CH ₂ COOH
1130	0	CH ₃	CH ₃	S(O) ₂ CH ₃		0	H	CH ₂ COOH



[Table 56]

No.	n	R ^{1c}	R ^{1d}	R ²	R ³ , R ⁴	R ⁵	R ⁶
1141	0	CH ₃	CH ₃	CH ₂ C ₆ H ₅	0	H	CH ₂ COOH
1142	0	CH ₃	CH ₃	CH ₂ CH ₂ C ₆ H ₅	0	H	CH ₂ COOH
1143	0	CH ₃	CH ₃	CH ₂ C ₆ H ₁₁	0	H	CH ₂ COOH
1144	0	CH ₃	CH ₃	CH(CH ₃)C ₆ H ₅	0	H	CH ₂ COOH
1145	0	CH ₃	CH ₃	2-Thienylmethyl	0	H	CH ₂ COOH
1146	0	CH ₃	CH ₃	2-Furfuryl	0	H	CH ₂ COOH
1147	0	CH ₃	CH ₃	2-Pyranylmethyl	0	H	CH ₂ COOH
1148	0	CH ₃	CH ₃	1-Isobenzofuranylmethyl	0	H	CH ₂ COOH
1149	0	CH ₃	CH ₃	2-Pyrrolylmethyl	0	H	CH ₂ COOH
1150	0	CH ₃	CH ₃	1-Imidazolylmethyl	0	H	CH ₂ COOH
1151	0	CH ₃	CH ₃	1-Pyrazolylmethyl	0	H	CH ₂ COOH
1152	0	CH ₃	CH ₃	3-Isothiazolylmethyl	0	H	CH ₂ COOH
1153	0	CH ₃	CH ₃	3-Isoxazolylmethyl	0	H	CH ₂ COOH
1154	0	CH ₃	CH ₃	2-Pyridylmethyl	0	H	CH ₂ COOH
1155	0	CH ₃	CH ₃	2-Pyrazinylmethyl	0	H	CH ₂ COOH
1156	0	CH ₃	CH ₃	2-Pyrimidinylmethyl	0	H	CH ₂ COOH
1157	0	CH ₃	CH ₃	3-Pyridazinylmethyl	0	H	CH ₂ COOH
1158	0	CH ₃	CH ₃	1-Isindolylmethyl	0	H	CH ₂ COOH
1159	0	CH ₃	CH ₃	2-Indolylmethyl	0	H	CH ₂ COOH
1160	0	CH ₃	CH ₃	3-(1H-Indazolyl)methyl	0	H	CH ₂ COOH
1161	0	CH ₃	CH ₃	2-Purinylmethyl	0	H	CH ₂ COOH
1162	0	CH ₃	CH ₃	1-Isoquinolylmethyl	0	H	CH ₂ COOH



[Table 57]

No.	n	R ^{1c}	R ^{1d}	R ²	R ^{3, R⁴}	R ⁵	R ⁶
1163	0	CH ₃	CH ₃	2-Quinolylmethyl	O	H	CH ₂ COOH
1164	0	CH ₃	CH ₃	1-Phthalazinylmethyl	O	H	CH ₂ COOH
1165	0	CH ₃	CH ₃	2-Naphthylidinylmethyl	O	H	CH ₂ COOH
1166	0	CH ₃	CH ₃	2-Quinoxalinylmethyl	O	H	CH ₂ COOH
1167	0	CH ₃	CH ₃	2-Quinazolinylmethyl	O	H	CH ₂ COOH
1168	0	CH ₃	CH ₃	3-Cinnolinylmethyl	O	H	CH ₂ COOH
1169	0	CH ₃	CH ₃	2-Oxazolylmethyl	O	H	CH ₂ COOH
1170	0	CH ₃	CH ₃	2-Thiazolylmethyl	O	H	CH ₂ COOH
1171	0	CH ₃	CH ₃	2-Benzo[b]furylmethyl	O	H	CH ₂ COOH
1172	0	CH ₃	CH ₃	2-Benzo[b]thienylmethyl	O	H	CH ₂ COOH
1173	0	CH ₃	CH ₃	3-(1,2,4-Triazinyl)methyl	O	H	CH ₂ COOH
1174	0	CH ₃	CH ₃	2-Benz[d]imidazolylmethyl	O	H	CH ₂ COOH
1175	0	CH ₃	CH ₃	2-Benz[d]oxazolylmethyl	O	H	CH ₂ COOH
1176	0	CH ₃	CH ₃	Phenyl	O	H	CH ₂ COOH
1177	0	CH ₃	CH ₃	2-Naphthyl	O	H	CH ₂ COOH
1178	0	CH ₃	CH ₃	2-Thiazoly1	O	H	CH ₂ COOH
1179	0	CH ₃	CH ₃	4-Imidazoly1	O	H	CH ₂ COOH
1180	0	CH ₃	CH ₃	3-Pyrazoly1	O	H	CH ₂ COOH
1181	0	CH ₃	CH ₃	3-Isoxazoly1	O	H	CH ₂ COOH
1182	0	CH ₃	CH ₃	5-Isothiazoly1	O	H	CH ₂ COOH
1183	0	CH ₃	CH ₃	2-Pyrimidinyl	O	H	CH ₂ COOH
1184	0	CH ₃	CH ₃	3-(1,2,4-Triazolyl)	O	H	CH ₂ COOH

[Table 58]

No.	n	R ^{1c}	R ^{1d}	R ²	R ^{3, R⁴}	R ⁵	R ⁶
1185	0	CH ₃	CH ₃	2-Pyridyl	O	H	CH ₂ COOH
1186	0	CH ₃	CH ₃	2-Benzoxazolyl	O	H	CH ₂ COOH
1187	0	CH ₃	CH ₃	3-Benzothienyl	O	H	CH ₂ COOH
1188	0	CH ₃	CH ₃	2-Benzofurinyl	O	H	CH ₂ COOH
1189	0	CH ₃	CH ₃	5-Indolyl	O	H	CH ₂ COOH
1190	0	CH ₃	CH ₃	2-Pyrazinyl	O	H	CH ₂ COOH
1191	0	CH ₃	CH ₃	3-Quinolyl	O	H	CH ₂ COOH
1192	0	CH ₃	CH ₃	5-Tetrazolyl	O	H	CH ₂ COOH
1193	0	CH ₃	CH ₃	Methylsulfonyl	O	H	CH ₂ COOH
1194	0	CH ₃	CH ₃	Benzenesulfonyl	O	H	CH ₂ COOH
1195	0	CH ₃	CH ₃	CH ₂ CONHCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
1196	0	CH ₃	CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CHFCOOH
1197	0	CH ₃	CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CF ₂ COOH
1198	0	CH ₃	CH ₃	CH ₂ CH ₂ OOCH ₂ C ₆ H ₅	O	H	CH(OH)COOH
1199	0	CH ₃	CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH(OCH ₃)COOH
1200	0	CH ₃	CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH(CH ₃)COOH
1201	0	CH ₃	CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH(C ₆ H ₅)COOH
1202	0	CH ₃	CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	C(CH ₃) ₂ COOH
1203	0	CH ₃	CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	C(C ₂ H ₄)COOH
1204	0	CH ₃	CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	C(C ₃ H ₆)COOH
1205	0	CH ₃	CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	C(C ₄ H ₈)COOH
1206	0	CH ₃	CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	C(C ₅ H ₁₀)COOH





[Table 59]

No.	n	R ^{1c}	R ^{1d}	R ²	R ³ , R ⁴	R ⁵	R ⁶
1207	0	CH ₃	CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	COCOOH
1208	0	CH ₃	CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	C(NOH)COOH
1209	0	CH ₃	CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	C(OCH ₃) ₂ COOH
1210	0	CH ₃	CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	C(SCH ₃) ₂ COOH
1211	0	CH ₃	CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH(CH ₂ OH)COOH
1212	0	CH ₃	CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH(NH ₂)COOH
1213	0	CH ₃	CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH(NHCHO)COOH
1214	0	CH ₃	CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ CH ₂ COOH
1215	0	CH ₃	CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ CH(OH)COOH
1216	0	CH ₃	CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH(OH)CH ₂ COOH
1217	0	CH ₃	CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ CHFCOOH
1218	0	CH ₃	CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ CH ₂ OH
1219	0	CH ₃	CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ CH ₂ OCH ₃
1220	0	CH ₃	CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ CH ₂ OC ₆ H ₅
1221	0	CH ₃	CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ CH ₂ OCH ₂ C ₆ H ₅
1222	0	CH ₃	CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ CH ₂ F
1223	0	CH ₃	CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ CH ₂ NH ₂
1224	0	CH ₃	CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ CH ₂ NHCHO
1225	0	CH ₃	CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ CH ₂ NHCOOCH ₃
1226	0	CH ₃	CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ CH ₂ N(CH ₃) ₂
1227	0	CH ₃	CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ CH ₂ NH(CH ₃)
1228	0	CH ₃		CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ CH ₂ NHCH ₂ C ₆ H ₅

[Table 60]

No.	n	R ^{1c}	R ^{1d}	R ²	R ³ , R ⁴	R ⁵	R ⁶
1229	0	CH ₃	CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ CH ₂ SH
1230	0	CH ₃	CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ CH ₂ SCH ₃
1231	0	CH ₃	CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ CH ₂ S(O)CH ₃
1232	0	CH ₃	CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ CH ₂ S(O)CH ₃
1233	0	CH ₃	CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ CONH ₂
1234	0	CH ₃	CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ CONCH(CH ₃)COOH
1235	0	CH ₃	CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ CONHCH ₃
1236	0	CH ₃	CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ CONHOH
1237	0	CH ₃	CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ CON(CH ₃) ₂
1238	0	CH ₃	CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ CONHC ₆ H ₅
1239	0	CH ₃	CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COC ₆ H ₅
1240	0	CH ₃	CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COCH ₃
1241	0	CH ₃	CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ C(OCH ₃) ₂ CH ₃
1242	0	CH ₃	CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ CH(OCH ₃) ₂
1243	0	CH ₃	CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ C(NOH)CH ₃
1244	0	CH ₃	CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ CHO
1245	0	CH ₃	CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ CH ₂ OC(O)NH ₂
1246	0	CH ₃	CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ CH ₂ OC(O)CH ₃
1247	0	CH ₃	CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ CH ₂ OC(O)C ₆ H ₅
1248	0	CH ₃	CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	C1	CH ₂ COOH
1249	0	CH ₃	CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	CN	CH ₂ COOH
1250	0	CH ₃	CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	COOH	CH ₂ COOH



[Table 61]

No.	n	R ^{1c}	R ^{1d}	R ²	R ³ , R ⁴	R ⁵	R ⁶
1251	0	CH ₃	CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	CH ₂ COOH	CH ₂ COOH
1252	0	CH ₃	CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	CONH ₂	CH ₂ COOH
1253	0	CH ₃	CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	CONHCH ₃	CH ₂ COOH
1254	0	CH ₃	CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	CH ₃	CH ₂ COOH
1255	0	CH ₃	CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	CHCH ₂	CH ₂ COOH
1256	0	CH ₃	CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	COCH ₃	CH ₂ COOH
1257	0	CH ₃	CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	COC ₆ H ₅	CH ₂ COOH
1258	0	CH ₃	CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	C ₆ H ₅	CH ₂ COOH
1259	0	CH ₃	CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	CH ₂ C ₆ H ₅	CH ₂ COOH
1260	0	H	H	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
1261	0	H	Cl	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
1262	0	H	NC	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
1263	0	H	HOC (O)	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
1264	0	H	CH ₃ OC (O)	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
1265	0	H	H ₂ NC (O)	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
1266	0	H	CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
1267	0	H	C ₆ H ₅ CH ₂	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
1268	0	H	CH ₃ CONH	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
1269	0	H	CH ₃ O	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
1270	0	H	CH ₂ CH	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
1271	0	H	CH ₃ CHCH	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
1272	0	H	C ₆ H ₅	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH



[Table 62]

No.	n	R ^{1c}	R ²	R ^{1d}	2-Pyridyl	R ²	R ³ , R ⁴	R ⁵	R ⁶
1273	0	H			CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O		H	CH ₂ COOH
1274	0	C1		CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O		H	CH ₂ COOH
1275	0	NC		CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O		H	CH ₂ COOH
1276	0	HOC(O)		CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O		H	CH ₂ COOH
1277	0	CH ₂ OC(O)		CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O		H	CH ₂ COOH
1278	0	H ₂ NC(O)		CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O		H	CH ₂ COOH
1279	0	CH ₃		CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O		H	CH ₂ COOH
1280	0	C ₂ H ₅		CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O		H	CH ₂ COOH
1281	0	CH ₂ CH		CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O		H	CH ₂ COOH
1282	0	CH ₃ CHCH		CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O		H	CH ₂ COOH
1283	0	C ₆ H ₅		CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O		H	CH ₂ COOH
1284	0	2-Pyridyl		CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O		H	CH ₂ COOH
1285	0	C ₆ H ₅		C ₆ H ₅	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O		H	CH ₂ COOH
1286	0	C ₆ H ₅ CO		H	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O		H	CH ₂ COOH
1287	0	CH ₃ CO		H	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O		H	CH ₂ COOH
1288	0	CH ₃ NHCO		H	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O		H	CH ₂ COOH
1289	0	CH ₃ S		H	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O		H	CH ₂ COOH
1290	0	CH ₃ S(O)		H	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O		H	CH ₂ COOH
1291	0	CH ₃ S(O) ₂		H	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O		H	CH ₂ COOH
1292	0	CH ₃		H	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O		H	CH ₂ COOH
1293	0	C ₂ H ₅		H	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O		H	CH ₂ COOH
1294	0	CH ₂ CH		H	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O		H	CH ₂ COOH



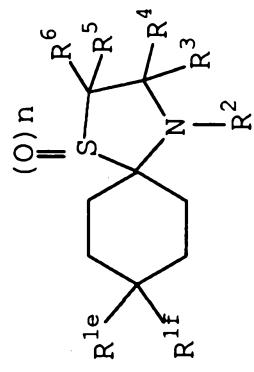
[Table 63]

No.	n	R ^{1c}	R ^{1d}	R ²	R ³ , R ⁴	R ⁵	R ⁶
1295	0	CH ₃ CHCH	H	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
1296	0	C ₆ H ₅	H	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
1297	0	2-Pyridyl	H	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
1298	1	H	H	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
1299	1	CH ₃	CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
1300	1	CH ₃	H	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
1301	1	C ₆ H ₅	C ₆ H ₅	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
1302	1	C ₆ H ₅	H	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
1303	2	H	H	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
1304	2	CH ₃	CH ₃	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
1305	2	CH ₃	H	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
1306	2	C ₆ H ₅	C ₆ H ₅	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH
1307	2	C ₆ H ₅	H	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	O	H	CH ₂ COOH





[Table 64]



No.	n	R ^{1e}	R ^{1f}	R ²	R ³ , R ⁴	R ⁵	R ⁶
1308	0	F	C ₆ H ₅	CH ₂ C ₆ H ₅		O	CH ₂ COOH
1309	0	C1	C ₆ H ₅	CH ₂ C ₆ H ₅		O	CH ₂ COOH
1310	0	NC	C ₆ H ₅	CH ₂ C ₆ H ₅		O	CH ₂ COOH
1311	0	HOC(O)	HOC(O)	CH ₂ C ₆ H ₅		O	CH ₂ COOH
1312	0	CH ₃ OC(O)	CH ₃ OC(O)	CH ₂ C ₆ H ₅		O	CH ₂ COOH
1313	0	(CH ₃) ₂ NO	(CH ₃) ₂ NCO	CH ₂ C ₆ H ₅		O	CH ₂ COOH
1314	0	HO	C ₆ H ₅	CH ₂ C ₆ H ₅		O	CH ₂ COOH
1315	0	CH ₃	C ₆ H ₅	CH ₂ C ₆ H ₅		O	CH ₂ COOH
1316	0	C ₂ H ₅	C ₆ H ₅	CH ₂ C ₆ H ₅		O	CH ₂ COOH
1317	0	CH ₂ CH	C ₆ H ₅	CH ₂ C ₆ H ₅		O	CH ₂ COOH
1318	0	Cyclohexyl	C ₆ H ₅	CH ₂ C ₆ H ₅		O	CH ₂ COOH
1319	0	Cyclopentyl	C ₆ H ₅	CH ₂ C ₆ H ₅		O	CH ₂ COOH
1320	0	Cyclobutyl	C ₆ H ₅	CH ₂ C ₆ H ₅		O	CH ₂ COOH
1321	0	C ₆ H ₅	C ₆ H ₅	CH ₂ C ₆ H ₅		O	CH ₂ COOH
1322	0	CH ₃ OC(O)	C ₆ H ₅	CH ₂ C ₆ H ₅		O	CH ₂ COOH

[Table 65]



No.	n	R ^{1e}	R ^{1f}	R ²	R ^{3, R⁴}	R ⁵	R ⁶
1323	0	CH ₃ S	C ₆ H ₅	CH ₂ C ₆ H ₅	0	H	CH ₂ COOH
1324	0	CH ₃ S(O)	C ₆ H ₅	CH ₂ C ₆ H ₅	0	H	CH ₂ COOH
1325	0	CH ₃ S(O) ₂	C ₆ H ₅	CH ₂ C ₆ H ₅	0	H	CH ₂ COOH
1326	0	H ₂ N	C ₆ H ₅	CH ₂ C ₆ H ₅	0	H	CH ₂ COOH
1327	0	CH ₃ CONH	C ₆ H ₅	CH ₂ C ₆ H ₅	0	H	CH ₂ COOH
1328	0	2-Thienyl	C ₆ H ₅	CH ₂ C ₆ H ₅	0	H	CH ₂ COOH
1329	0	C ₆ H ₅	HO	CH ₂ C ₆ H ₅	0	H	CHFCOOH
1330	0	C ₆ H ₅	HO	CH ₂ C ₆ H ₅	0	H	CF ₂ COOH
1331	0	C ₆ H ₅	HO	CH ₂ C ₆ H ₅	0	H	CH(OH)COOH
1332	0	C ₆ H ₅	HO	CH ₂ C ₆ H ₅	0	H	CH(OCH ₃)COOH
1333	0	C ₆ H ₅	HO	CH ₂ C ₆ H ₅	0	H	CH(CH ₃)COOH
1334	0	C ₆ H ₅	HO	CH ₂ C ₆ H ₅	0	H	CH(C ₆ H ₅)COOH
1335	0	C ₆ H ₅	HO	CH ₂ C ₆ H ₅	0	H	C(CH ₃) ₂ COOH
1336	0	C ₆ H ₅	HO	CH ₂ C ₆ H ₅	0	H	C(C ₂ H ₄)COOH
1337	0	C ₆ H ₅	HO	CH ₂ C ₆ H ₅	0	H	C(C ₃ H ₆)COOH
1338	0	C ₆ H ₅	HO	CH ₂ C ₆ H ₅	0	H	C(C ₄ H ₈)COOH
1339	0	C ₆ H ₅	HO	CH ₂ C ₆ H ₅	0	H	C(C ₅ H ₁₀)COOH
1340	0	C ₆ H ₅	HO	CH ₂ C ₆ H ₅	0	H	COCOOH
1341	0	C ₆ H ₅	HO	CH ₂ C ₆ H ₅	0	H	C(NOH)COOH
1342	0	C ₆ H ₅	HO	CH ₂ C ₆ H ₅	0	H	C(OCH ₃) ₂ COOH
1343	0	C ₆ H ₅	HO	CH ₂ C ₆ H ₅	0	H	C(SCH ₃) ₂ COOH
1344	0	C ₆ H ₅	HO	CH ₂ C ₆ H ₅	0	H	CH(CH ₂ OH)COOH



[Table 66]

No.	n	R ^{1e}	R ^{1f}	R ²	R ^{3, R⁴}	R ⁵	R ⁶
1345	0	C ₆ H ₅	HO	CH ₂ C ₆ H ₅	O	H	CH(NH ₂)COOH
1346	0	C ₆ H ₅	HO	CH ₂ C ₆ H ₅	O	H	CH(NHCHO)COOH
1347	0	C ₆ H ₅	HO	CH ₂ C ₆ H ₅	O	H	CH ₂ CH ₂ COOH
1348	0	C ₆ H ₅	HO	CH ₂ C ₆ H ₅	O	H	CH ₂ CH(OH)COOH
1349	0	C ₆ H ₅	HO	CH ₂ C ₆ H ₅	O	H	CH(OH)CH ₂ COOH
1350	0	C ₆ H ₅	HO	CH ₂ C ₆ H ₅	O	H	CH ₂ CHFCOOH
1351	0	C ₆ H ₅	HO	CH ₂ C ₆ H ₅	O	H	CH ₂ CH ₂ OH
1352	0	C ₆ H ₅	HO	CH ₂ C ₆ H ₅	O	H	CH ₂ CH ₂ OCH ₃
1353	0	C ₆ H ₅	HO	CH ₂ C ₆ H ₅	O	H	CH ₂ CH ₂ OC ₆ H ₅
1354	0	C ₆ H ₅	HO	CH ₂ C ₆ H ₅	O	H	CH ₂ CH ₂ OCH ₂ C ₆ H ₅
1355	0	C ₆ H ₅	HO	CH ₂ C ₆ H ₅	O	H	CH ₂ CH ₂ F
1356	0	C ₆ H ₅	HO	CH ₂ C ₆ H ₅	O	H	CH ₂ CH ₂ NH ₂
1357	0	C ₆ H ₅	HO	CH ₂ C ₆ H ₅	O	H	CH ₂ CH ₂ NHCHO
1358	0	C ₆ H ₅	HO	CH ₂ C ₆ H ₅	O	H	CH ₂ CH ₂ NHCOOCH ₃
1359	0	C ₆ H ₅	HO	CH ₂ C ₆ H ₅	O	H	CH ₂ CH ₂ N(CH ₃) ₂
1360	0	C ₆ H ₅	HO	CH ₂ C ₆ H ₅	O	H	CH ₂ CH ₂ NH(CH ₃)
1361	0	C ₆ H ₅	HO	CH ₂ C ₆ H ₅	O	H	CH ₂ CH ₂ NHCH ₂ C ₆ H ₅
1362	0	C ₆ H ₅	HO	CH ₂ C ₆ H ₅	O	H	CH ₂ CH ₂ SH
1363	0	C ₆ H ₅	HO	CH ₂ C ₆ H ₅	O	H	CH ₂ CH ₂ SCH ₃
1364	0	C ₆ H ₅	HO	CH ₂ C ₆ H ₅	O	H	CH ₂ CH ₂ S(O) ₂ CH ₃
1365	0	C ₆ H ₅	HO	CH ₂ C ₆ H ₅	O	H	CH ₂ CH ₂ S(O)CH ₃
1366	0	C ₆ H ₅	HO	CH ₂ C ₆ H ₅	O	H	CH ₂ CONH ₂

[Table 67]

No.	n	R ^{1e}	R ^{1f}	R ²	R ³ , R ⁴	R ⁵	R ⁶
1367	0	C ₆ H ₅	HO	CH ₂ C ₆ H ₅	O	H	CH ₂ CONHCH(CH ₃)COOH
1368	0	C ₆ H ₅	HO	CH ₂ C ₆ H ₅	O	H	CH ₂ CONHCH ₃
1369	0	C ₆ H ₅	HO	CH ₂ C ₆ H ₅	O	H	CH ₂ CONHOH
1370	0	C ₆ H ₅	HO	CH ₂ C ₆ H ₅	O	H	CH ₂ CON(CH ₃) ₂
1371	0	C ₆ H ₅	HO	CH ₂ C ₆ H ₅	O	H	CH ₂ CONHC ₆ H ₅
1372	0	C ₆ H ₅	HO	CH ₂ C ₆ H ₅	O	H	CH ₂ COC ₆ H ₅
1373	0	C ₆ H ₅	HO	CH ₂ C ₆ H ₅	O	H	CH ₂ COCH ₃
1374	0	C ₆ H ₅	HO	CH ₂ C ₆ H ₅	O	H	CH ₂ C(OCH ₃) ₂ CH ₃
1375	0	C ₆ H ₅	HO	CH ₂ C ₆ H ₅	O	H	CH ₂ CH(OCH ₃) ₂
1376	0	C ₆ H ₅	HO	CH ₂ C ₆ H ₅	O	H	CH ₂ C(NOH)CH ₃
1377	0	C ₆ H ₅	HO	CH ₂ C ₆ H ₅	O	H	CH ₂ CHO
1378	0	C ₆ H ₅	HO	CH ₂ C ₆ H ₅	O	H	CH ₂ CH ₂ OC(O)NH ₂
1379	0	C ₆ H ₅	HO	CH ₂ C ₆ H ₅	O	H	CH ₂ CH ₂ OC(O)CH ₃
1380	0	C ₆ H ₅	HO	CH ₂ C ₆ H ₅	O	H	CH ₂ CH ₂ OC(O)C ₆ H ₅
1381	0	C ₆ H ₅	HO	CH ₂ C ₆ H ₅	O	C1	CH ₂ COOH
1382	0	C ₆ H ₅	HO	CH ₂ C ₆ H ₅	O	CN	CH ₂ COOH
1383	0	C ₆ H ₅	HO	CH ₂ C ₆ H ₅	O	COOH	CH ₂ COOH
1384	0	C ₆ H ₅	HO	CH ₂ C ₆ H ₅	O	CH ₂ COOH	CH ₂ COOH
1385	0	C ₆ H ₅	HO	CH ₂ C ₆ H ₅	O	CONH ₂	CH ₂ COOH
1386	0	C ₆ H ₅	HO	CH ₂ C ₆ H ₅	O	CONHCH ₃	CH ₂ COOH
1387	0	C ₆ H ₅	HO	CH ₂ C ₆ H ₅	O	CH ₃	CH ₂ COOH
1388	0	C ₆ H ₅	HO	CH ₂ C ₆ H ₅	O	CHCH ₂	CH ₂ COOH

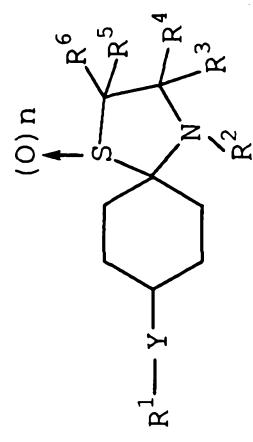


[Table 68]

No.	n	R ^{1e}	R ^{1f}	R ²	R ³ , R ⁴	R ⁵	R ⁶
1389	0	C ₆ H ₅	HO	CH ₂ C ₆ H ₅	O	OCH ₃	CH ₂ COOH
1390	0	C ₆ H ₅	HO	CH ₂ C ₆ H ₅	O	COC ₆ H ₅	CH ₂ COOH
1391	0	C ₆ H ₅	HO	CH ₂ C ₆ H ₅	O	C ₆ H ₅	CH ₂ COOH
1392	0	C ₆ H ₅	HO	CH ₂ C ₆ H ₅	O	CH ₂ C ₆ H ₅	CH ₂ COOH
1393	1	HO	C ₆ H ₅	CH ₂ C ₆ H ₅	O	H	CH ₂ COOH
1394	2	HO	C ₆ H ₅	CH ₂ C ₆ H ₅	O	H	CH ₂ COOH
1395	0	HO	C ₆ H ₅	H	O	H	CH ₂ COOH
1396	0	HO	C ₆ H ₅	CH ₃	O	H	CH ₂ COOH
1397	0	HO	C ₆ H ₅	C ₂ H ₅	O	H	CH ₂ COOH
1398	0	HO	C ₆ H ₅	CHCH ₂	O	H	CH ₂ COOH
1399	0	HO	C ₆ H ₅	Cyclohexyl	O	H	CH ₂ COOH
1400	0	HO	C ₆ H ₅	Cyclobutyl	O	H	CH ₂ COOH
1401	0	HO	C ₆ H ₅	C ₆ H ₅	O	H	CH ₂ COOH
1402	0	HO	C ₆ H ₅	S(O) ₂ CH ₃	O	H	CH ₂ COOH
1403	0	HO	C ₆ H ₅	S(O) ₂ C ₆ H ₅	O	H	CH ₂ COOH
1404	0	HO	C ₆ H ₅	2-Thienyl	O	H	CH ₂ COOH

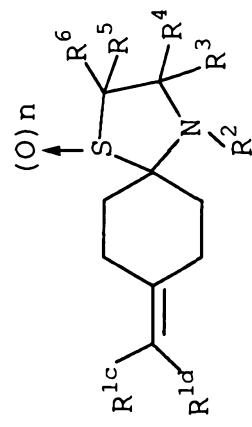


[Table 69]



No.	n	R ¹ -Y-	R ²	R ³	R ⁴	R ⁵	R ⁶
3001	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COCH ₂ CH ₂ CH(CH ₃) ₂	COOH	H	H	H
3002	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COCH ₂ CH ₂ CH(CH ₃) ₂	COOH	H	CH ₃	CH ₃
3003	1	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COCH ₂ CH ₂ CH(CH ₃) ₂	COOH	H	H	H
3004	1	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COCH ₂ CH ₂ CH(CH ₃) ₂	COOH	H	CH ₃	CH ₃
3005	2	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COCH ₂ CH ₂ CH(CH ₃) ₂	COOH	H	H	H
3006	2	4-CH ₃ CH(CH ₃)C ₆ H ₄ O-	COCH ₂ CH ₂ CH(CH ₃) ₂	COOH	H	CH ₃	CH ₃
3007	0	2, 3-Dihydro-1H-inden-5-yloxy	COCH ₂ CH ₂ CH(CH ₃) ₂	COOH	H	H	H
3009	0	2, 3-Dihydro-1H-inden-5-yloxy	COCH ₂ CH ₂ CH(CH ₃) ₂	COOH	H	CH ₃	CH ₃
3011	0	(CH ₃) ₂ CHOC(O)-	COCH ₂ CH ₂ CH(CH ₃) ₂	COOH	H	H	H
3012	0	(CH ₃) ₂ CHOC(O)-	COCH ₂ CH ₂ CH(CH ₃) ₂	COOH	H	CH ₃	CH ₃
3013	0	(CH ₃) ₂ CHC(O)O-	COCH ₂ CH ₂ CH(CH ₃) ₂	COOH	H	H	H
3014	0	(CH ₃) ₂ CHC(O)O-	COCH ₂ CH ₂ CH(CH ₃) ₂	COOH	H	CH ₃	CH ₃
3015	0	(CH ₃) ₂ CHNHC(O)-	COCH ₂ CH ₂ CH(CH ₃) ₂	COOH	H	H	H
3016	0	(CH ₃) ₂ CHNHC(O)-	COCH ₂ CH ₂ CH(CH ₃) ₂	COOH	H	CH ₃	CH ₃





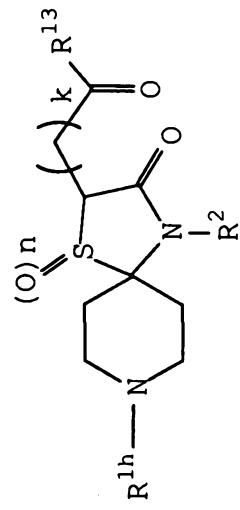
[Table 70]

No.	n	R ^{1c}	R ^{1d}	R ²	R ³	R ⁴	R ⁵	R ⁶
3017	0	(CH ₃) ₂ CH	H	COCH ₂ CH ₃	COOH	H	H	H
3018	0	(CH ₃) ₂ CH	H	COCH ₂ CH ₃	COOH	H	CH ₃	CH ₃
3019	0	(CH ₃) ₂ CHCH ₂	H	COCH ₂ CH ₃	COOH	H	H	H
3020	0	(CH ₃) ₂ CHCH ₂	H	COCH ₂ CH ₃	COOH	H	CH ₃	CH ₃
3021	0	(CH ₃) ₂ CHCH ₂ CH ₂	H	COCH ₂ CH ₃	COOH	H	H	H
3022	0	(CH ₃) ₂ CHCH ₂ CH ₂	H	COCH ₂ CH ₃	COOH	H	CH ₃	CH ₃
3023	0	CH ₃ CH ₂ CH ₂	H	COCH ₂ CH ₃	COOH	H	H	H
3024	0	CH ₃ CH ₂ CH ₂	H	COCH ₂ CH ₃	COOH	H	CH ₃	CH ₃
3025	0	(CH ₃) ₂ CH	H	COCH ₂ CH ₂ CH(CH ₃) ₂	COOH	H	H	H
3026	0	(CH ₃) ₂ CH	H	COCH ₂ CH ₂ CH(CH ₃) ₂	COOH	H	CH ₃	CH ₃
3027	0	(CH ₃) ₂ CHCH ₂	H	COCH ₂ CH ₂ CH(CH ₃) ₂	COOH	H	H	H
3028	0	(CH ₃) ₂ CHCH ₂	H	COCH ₂ CH ₂ CH(CH ₃) ₂	COOH	H	CH ₃	CH ₃
3029	0	(CH ₃) ₂ CHCH ₂ CH ₂	H	COCH ₂ CH ₂ CH(CH ₃) ₂	COOH	H	H	H
3030	0	(CH ₃) ₂ CHCH ₂ CH ₂	H	COCH ₂ CH ₂ CH(CH ₃) ₂	COOH	H	CH ₃	CH ₃
3031	0	CH ₃ CH ₂ CH ₂	H	COCH ₂ CH ₂ CH(CH ₃) ₂	COOH	H	H	H



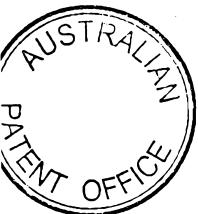
[Table 71]

No.	n	R ^{1c}	R ^{1d}	R ²	R ³	R ⁴	R ⁵	R ⁶
3032	0	CH ₃ CH ₂ CH ₂	H	COCH ₂ CH ₂ CH(CH ₃) ₂	COOH	H	CH ₃	CH ₃
3033	0	(CH ₃) ₂ CHCH ₂	H	COCH ₂ CH ₂ CH ₂ CH ₃	COOH	H	H	H
3034	0	(CH ₃) ₂ CHCH ₂	H	COCH ₂ CH ₂ CH ₂ CH ₃	COOH	H	CH ₃	CH ₃
3035	0	(CH ₃) ₂ CHCH ₂	H	COCH ₂ CH ₂ C ₅ H ₉	COOH	H	H	H
3036	0	(CH ₃) ₂ CHCH ₂	H	COCH ₂ CH ₂ C ₅ H ₉	COOH	H	CH ₃	CH ₃
3037	1	(CH ₃) ₂ CHCH ₂	H	COCH ₂ CH ₂ CH(CH ₃) ₂	COOH	H	H	H
3038	1	(CH ₃) ₂ CHCH ₂	H	COCH ₂ CH ₂ CH(CH ₃) ₂	COOH	H	CH ₃	CH ₃
3039	2	(CH ₃) ₂ CHCH ₂	H	COCH ₂ CH ₂ CH(CH ₃) ₂	COOH	H	H	H
3040	2	(CH ₃) ₂ CHCH ₂	H	COCH ₂ CH ₂ CH(CH ₃) ₂	COOH	H	CH ₃	CH ₃



[Table 72]

No.	n	R ^{1h}	R ²	R ¹³	k
2001	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	H	OH	1
2002	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₃	OH	1
2003	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ CH ₃	OH	1
2004	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ CH ₂ CH ₃	OH	1
2005	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ CH ₂ CH ₂ CH ₃	OH	1
2006	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ CH ₂ CH ₂ CH ₂ CH ₃	OH	1
2007	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH(CH ₃)CH ₃	OH	1
2008	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ CH(CH ₃)CH ₃	OH	1
2009	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ CH ₂ CH(CH ₃)CH ₃	OH	1
2010	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ CH ₂ CH ₂ CH(CH ₃)CH ₃	OH	1
2011	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ CH(CH ₃)C ₂ H ₅	OH	1
2012	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ CH ₂ CH(CH ₃)C ₂ H ₅	OH	1
2013	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ CH ₂ CH(C ₂ H ₅)C ₂ H ₅	OH	1
2014	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ F	OH	1
2015	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ OH	OH	1
2016	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ CH ₂ OH	OH	1



[Table 73]

No.	n	R ¹ⁿ	R ²	R ¹³	k
2017	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ CH ₂ CH ₂ OH	OH	1
2018	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ CH ₂ CH ₂ CH ₂ OH	OH	1
2019	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ OH	OH	1
2020	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH(OH)CH ₂ OH	OH	1
2021	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ CH(OH)CH ₂ OH	OH	1
2022	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ CH(OH)CH ₂ CH ₂ OH	OH	1
2023	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ CH ₂ CH(OH)CH ₂ CH ₂ OH	OH	1
2024	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ OC(O)NH ₂	OH	1
2025	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ OC(O)CH ₃	OH	1
2026	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ OC(O)CH ₂ C ₆ H ₅	OH	1
2027	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ COOH	OH	1
2028	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ CH ₂ COOH	OH	1
2029	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ CH ₂ CH ₂ COOH	OH	1
2030	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ CH ₂ CH ₂ CH ₂ COOH	OH	1
2031	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ COOH	OH	1
2032	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ COOCH ₃	OH	1
2033	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ COOC ₂ H ₅	OH	1
2034	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ COO-n-C ₃ H ₇	OH	1
2035	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ COO-i-C ₃ H ₇	OH	1
2036	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ COOC ₆ H ₅	OH	1
2037	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2038	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ CONH ₂	OH	1



[Table 74]

No.	n	R ^{1h}	R ²	R ¹³	k
2039	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ CONHOH	OH	1
2040	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ CONHCH ₃	OH	1
2041	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ CONHC ₂ H ₅	OH	1
2042	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ CONH-n-C ₃ H ₇	OH	1
2043	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ CONH-i-C ₃ H ₇	OH	1
2044	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ CON(CH ₃) ₂	OH	1
2045	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ CON(n-C ₃ H ₇) ₂	OH	1
2046	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ CON(C ₂ H ₅) ₂	OH	1
2047	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ CONHC ₆ H ₅	OH	1
2048	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ CH ₂ COOCH ₃	OH	1
2049	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2050	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH(CH ₃)COOH	OH	1
2051	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH(CH ₂ OH)COOH	OH	1
2052	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH(CH ₂ COOH)COOH	OH	1
2053	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH(CH ₂ CONH ₂)COOH	OH	1
2054	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH(CH ₂ CH ₂ COOH)COOH	OH	1
2055	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH(CH ₂ CH ₂ CONH ₂)COOH	OH	1
2056	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH(4-Imidazolylmethyl)COOH	OH	1
2057	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH(CH(C ₂ H ₅)CH ₃)COOH	OH	1
2058	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH(CH ₂ CH(CH ₃)CH ₃)COOH	OH	1
2059	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH(CH ₂ CH ₂ SC ₆ H ₅)COOH	OH	1
2060	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH(CH(OH)CH ₃)COOH	OH	1



[Table 75]

No.	n	R ^{1h}	R ²	R ¹³	k
2061	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH(CH ₂ -(4-HO)C ₆ H ₅)COOH	OH	1
2062	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH(CH ₂ C ₆ H ₅)COOH	OH	1
2063	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH(3-Indolylmethyl)COOH	OH	1
2064	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH(i-C ₃ H ₇)COOH	OH	1
2065	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ CN	OH	1
2066	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ NO ₂	OH	1
2067	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ COCH ₃	OH	1
2068	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ C(OCH ₃) ₂ CH ₃	OH	1
2069	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ C(SCH ₃) ₂ CH ₃	OH	1
2070	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ CH ₂ SH	OH	1
2071	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ C(NO _H)CH ₃	OH	1
2072	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ SH	OH	1
2073	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ SO ₃ H	OH	1
2074	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ S(O) ₂ CH ₃	OH	1
2075	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ S(O)CH ₃	OH	1
2076	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ S(O) ₂ NH ₂	OH	1
2077	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ OCH ₃	OH	1
2078	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ CH ₂ OCH ₃	OH	1
2079	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ CH ₂ CH ₂ OCH ₃	OH	1
2080	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ SCH ₃	OH	1
2081	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ CH ₂ SCH ₃	OH	1
2082	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ CH ₂ CH ₂ SCH ₃	OH	1



[Table 76]

No.	n	R ^{1b}	R ²	R ¹³	k
2083	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CHCH ₂	OH	1
2084	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ CHCH ₂	OH	1
2085	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	Cyclopropyl	OH	1
2086	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	Cyclobutyl	OH	1
2087	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	Cyclopentyl	OH	1
2088	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	Cyclohexyl	OH	1
2089	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ C ₆ H ₅	OH	1
2090	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ CH ₂ C ₆ H ₅	OH	1
2091	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ C ₆ H ₁₁	OH	1
2092	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH(CH ₃)C ₆ H ₅	OH	1
2093	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	2-Thienylmethyl	OH	1
2094	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	2-Furfuryl	OH	1
2095	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	2-Pyranylmethyl	OH	1
2096	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	1-Isobenzofurylmethyl	OH	1
2097	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	2-Pyrrolylmethyl	OH	1
2098	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	1-Imidazolylmethyl	OH	1
2099	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	1-Pyrazolylmethyl	OH	1
2100	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	3-Isothiazolylmethyl	OH	1
2101	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	3-Isoxazolylmethyl	OH	1
2102	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	2-Pyridylmethyl	OH	1
2103	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	2-Pyrazinylmethyl	OH	1
2104	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	2-Pyrimidinylmethyl	OH	1



[Table 77]

No.	n	R ^{1h}	R ²	R ¹³	k
2105	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	3-Pyridazinylmethyl	OH	1
2106	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	1-Isoindolylmethyl	OH	1
2107	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	2-Indolylmethyl	OH	1
2108	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	3-(1H-Indazolyl)methyl	OH	1
2109	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	2-Purinylmethyl	OH	1
2110	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	1-Isoquinolylmethyl	OH	1
2111	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	2-Quinolylmethyl	OH	1
2112	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	1-Phthalazinylmethyl	OH	1
2113	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	2-Naphthylidinylmethyl	OH	1
2114	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	2-Quinoxalinylmethyl	OH	1
2115	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	2-Quinazolinylmethyl	OH	1
2116	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	3-Cinnolinylmethyl	OH	1
2117	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	2-Oxazolylmethyl	OH	1
2118	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	2-Thiazolylmethyl	OH	1
2119	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	2-Benzo[b]furylmethyl	OH	1
2120	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	2-Benzo[b]thienylmethyl	OH	1
2121	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	3-(1,2,4-Triazinyl)methyl	OH	1
2122	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	2-Benz[d]imidazolylmethyl	OH	1
2123	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	2-Benz[d]oxazolylmethyl	OH	1
2124	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	Phenyl	OH	1
2125	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	2-Naphthyl	OH	1
2126	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	2-Thiazolyl	OH	1



[Table 78]

No.	n	R ^{1h}	R ²	R ¹³	k
2127	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	4-Imidazolyl	OH	1
2128	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	3-Pyrazolyl	OH	1
2129	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	3-Isoxazolyl	OH	1
2130	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	5-Isothiazolyl	OH	1
2131	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	2-Pyrimidinyl	OH	1
2132	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	3-(1,2,4-Triazolyl)	OH	1
2133	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	2-Pyridyl	OH	1
2134	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	2-Benzoxazolyl	OH	1
2135	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	3-Benzothienyl	OH	1
2136	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	2-Benzofuryl	OH	1
2137	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	5-Indolyl	OH	1
2138	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	2-Pyrazinyl	OH	1
2139	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	3-Quinolyl	OH	1
2140	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	5-Tetrazolyl	OH	1
2141	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ CONHCH ₂ C ₆ H ₅	OH	1
2142	0	FCH ₂	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2143	0	HOCH ₂	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2144	0	HOCH ₂ CH ₂	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2145	0	HOCH ₂ CH ₂ CH ₂	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2146	0	HOCH ₂ CH ₂ CH ₂ CH ₂	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2147	0	HOCH ₂ CH ₂ CH ₂ CH ₂	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2148	0	HOCH ₂ CH(OH)CH ₂	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1



[Table 79]

No.	n	R ^{1h}	R ²	R ¹³	k
2149	0	HOCH ₂ CH ₂ CH(OH)CH ₂	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2150	0	HOCH ₂ CH(OH)CH ₂ CH ₂ CH ₂	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2151	0	H ₂ NC(O)OCH ₂	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2152	0	CH ₃ C(O)OCH ₂	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2153	0	HOOCCH ₂	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2154	0	HOOCCH ₂ CH ₂	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2155	0	HOOCCH ₂ CH ₂ CH ₂	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2156	0	HOOCCH ₂ CH ₂ CH ₂ CH ₂	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2157	0	HOOCCH ₂ CH ₂ CH ₂ CH ₂ CH ₂	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2158	0	CH ₃ OC(O)CH ₂	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2159	0	C ₆ H ₅ CH ₂ OC(O)CH ₂	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2160	0	n-C ₃ H ₇ OC(O)CH ₂	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2161	0	i-C ₃ H ₇ OC(O)CH ₂	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2162	0	C ₆ H ₅ OC(O)CH ₂	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2163	0	H ₂ NC(O)CH ₂	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2164	0	HONHC(O)CH ₂	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2165	0	CH ₃ NHC(O)CH ₂	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2166	0	C ₂ H ₅ NHC(O)CH ₂	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2167	0	n-C ₃ H ₇ NHC(O)CH ₂	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2168	0	CH ₃ OC(O)CH ₂ CH ₂	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2169	0	C ₆ H ₅ OC(O)CH ₂ CH ₂	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2170	0	H ₂ N	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1



[Table 80]

No.	n	R ^{1h}	R ²	R ¹³	k
2171	0	NCCH ₂	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2172	0	CH ₃ COCH ₂	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2173	0	CH ₃ C(OCH ₃) ₂ CH ₂	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2174	0	CH ₃ C(SCH ₃) ₂ CH ₂	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2175	0	CH ₃ C(NO _H)CH ₂	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2176	0	NSCH ₂	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2177	0	CH ₃ S(O) ₂ CH ₂	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2178	0	H ₂ NS(O) ₂ CH ₂	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2179	0	CH ₃ CH ₂ S(O) ₂ CH ₂	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2180	0	CH ₃ OCH ₂	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2181	0	CH ₃ OCH ₂ CH ₂	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2182	0	CH ₃ OCH ₂ CH ₂ CH ₂	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2183	0	CH ₃ SCH ₂	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2184	0	CH ₃ SCH ₂ CH ₂	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2185	0	CH ₃ SCH ₂ CH ₂ CH ₂	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2186	0	C ₆ H ₅ CH ₂	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2187	0	C ₆ H ₅ CH ₂ CH ₂	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2188	0	C ₆ H ₁₁ CH ₂	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2189	0	2-Thienylmethyl	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2190	0	2-Furfuryl	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2191	0	2-Pyranylmethyl	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2192	0	1-Isobenzofurylmethyl	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1





[Table 81]

No.	n	R ^{1h}	R ²	R ¹³	k
2193	0	2-Pyrrolylmethyl	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2194	0	1-Imidazolylmethyl	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2195	0	1-Pyrazolylmethyl	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2196	0	3-Isothiazolylmethyl	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2197	0	3-Isoxazolylmethyl	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2198	0	2-Pyridylmethyl	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2199	0	2-Pyrazinylmethyl	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2200	0	2-Pyrimidinylmethyl	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2201	0	3-Pyridazinylmethyl	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2202	0	1-Isoindolylmethyl	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2203	0	2-Indolylmethyl	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2204	0	3-(1H-Indazolyl)methyl	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2205	0	2-Purinylmethyl	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2206	0	1-Isoquinolylmethyl	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2207	0	2-Quinolylmethyl	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2208	0	1-Phthalazinylmethyl	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2209	0	2-Naphthylidinylmethyl	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2210	0	2-Quinoxalinylmethyl	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2211	0	2-Quinazolinylmethyl	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2212	0	3-Cinnolinylmethyl	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2213	0	2-Oxazolylmethyl	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2214	0	2-Thiazolylmethyl	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1

[Table 82]

No.	n	R ^{1h}	R ²	R ¹³	k
2215	0	2-Benzo[b] furylmethyl	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2216	0	2-Benzo[b] thiienylmethyl	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2217	0	3-(1,2,4-triazinyl)methyl	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2218	0	2-Benz[d] imidazolylmethyl	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2219	0	2-Benz[d] oxazolylmethyl	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2220	0	C ₆ H ₅ CO	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2221	0	CH ₃ CO	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2222	0	CH ₃ CH ₂ CO	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2223	0	CH ₃ CH ₂ CH ₂ CO	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2224	0	CH ₃ CH ₂ CH ₂ CH ₂ CO	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2225	0	CH ₃ CH ₂ CH ₂ CH ₂ CH ₂ CO	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2226	0	CH ₃ CH(CH ₃)CO	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2227	0	CH ₃ CH ₂ CH(CH ₃)CO	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2228	0	C ₆ H ₅ CH ₂ CO	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2229	0	H ₂ NCH(CH ₂ OH)CO	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2230	0	H ₂ NCH(CH ₂ COOH)CO	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2231	0	H ₂ NCH(CH ₂ CONH ₂)CO	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2232	0	H ₂ NCH(CH ₂ CH ₂ COOH)CO	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2233	0	H ₂ NCH(CH ₂ CH ₂ CONH ₂)CO	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2234	0	H ₂ NCH(4-imidazolylmethyl)CO	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2235	0	H ₂ NCH(CH(C ₂ H ₅)CH ₃)CO	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2236	0	H ₂ NCH(CH ₂ CH(CH ₃)CH ₃)CO	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1



[Table 83]

No.	n	R ^{1h}	R ²	R ¹³	k
2237	0	H ₂ NCH(CH ₂ CH ₂ SCH ₃)CO	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2238	0	H ₂ NCH(CH(OH)CH ₃)CO	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2239	0	H ₂ NCH(CH ₂ -(4-HO)C ₆ H ₅)CO	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2240	0	H ₂ NCH(CH ₂ C ₆ H ₅)CO	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2241	0	H ₂ NCH(3-indolylmethyl)CO	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2242	0	2-Thienylmethylcarbonyl	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2243	0	2-Furfurylcarbonyl	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2244	0	2-Pyridylmethylcarbonyl	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2245	0	2-Quinolylmethylcarbonyl	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2246	0	2-Benzothienylmethylcarbonyl	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2247	0	2-Naphthylidinylmethylcarbonyl	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2248	0	2-Thiazolylmethylcarbonyl	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2249	0	2-Pyrimidinylmethylcarbonyl	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2250	0	2-Benzoxazolylmethylcarbonyl	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2251	0	2-Indolylmethylcarbonyl	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2252	0	2-Thiazolylcarbonyl	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2253	0	2-Pyrimidinylcarbonyl	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2254	0	2-Indolylcarbonyl	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2255	0	2-Benzothienylcarbonyl	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2256	0	5-Quinolylcarbonyl	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2257	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	S(O) ₂ CH ₃	OH	1
2258	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	S(O) ₂ C ₆ H ₅	OH	1



[Table 84]

No.	n	R ^{1h}	R ²	R ¹³	k
2259	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ SO ₂ -	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2260	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ SO ₂ -	S(O) ₂ CH ₃	OH	1
2261	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ SO ₂ -	S(O) ₂ C ₆ H ₅	OH	1
2262	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ SO ₂ -	H	OH	2
2263	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ CH ₂ OH	OH	2
2264	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ OCONH ₂	OH	2
2265	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ OOCCH ₃	OH	2
2266	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ COOH	OH	2
2267	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ CONH ₂	OH	2
2268	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ CH ₂ C ₆ H ₅	OH	3
2269	1	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	H	OH	1
2270	1	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ CH ₂ OH	OH	1
2271	1	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ OCONH ₂	OH	1
2272	1	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ OC(O)CH ₃	OH	1
2273	1	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ COOH	OH	1
2274	1	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ CONH ₂	OH	1
2275	1	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ S(O) ₂ CH ₃	OH	1
2276	2	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	H	OH	1
2277	2	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ CH ₂ OH	OH	1
2278	2	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ OCONH ₂	OH	1
2279	2	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ OC(O)CH ₃	OH	1
2280	2	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ COOH	OH	1



[Table 85]

No.	n	R ^{1h}	R ²	R ¹³	k
2281	2	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ CONH ₂	OH	1
2282	2	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ S(O) ₂ CH ₃	OH	1
2283	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ CH ₂ C ₆ H ₅	H	1
2284	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ CH ₂ C ₆ H ₅	C1	1
2285	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ CH ₂ C ₆ H ₅	OCH ₃	1
2286	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ CH ₂ C ₆ H ₅	OC ₂ H ₅	1
2287	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ CH ₂ C ₆ H ₅	OC ₆ H ₅	1
2288	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ CH ₂ C ₆ H ₅	OCH ₂ C ₆ H ₅	1
2289	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ CH ₂ C ₆ H ₅	SCH ₃	1
2290	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ CH ₂ C ₆ H ₅	NH ₂	1
2291	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ CH ₂ C ₆ H ₅	NHCOH	1
2292	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ CH ₂ C ₆ H ₅	NHCH ₃	1
2293	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ CH ₂ C ₆ H ₅	N(CH ₃) ₂	1
2294	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ CH ₂ C ₆ H ₅	NHCH ₂ C ₆ H ₅	1
2295	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ CH ₂ C ₆ H ₅	NHC ₆ H ₅	1
2296	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ CH ₂ C ₆ H ₅	CH ₃	1
2297	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ CH ₂ C ₆ H ₅	C ₂ H ₅	1
2298	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ CH ₂ C ₆ H ₅	C ₆ H ₅	1
2299	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ CH ₂ C ₆ H ₅	CH ₂ C ₆ H ₅	1
2300	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ CH ₂ C ₆ H ₅	2-Thienyl	1
2301	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ CH ₂ C ₆ H ₅	NHCH(CH ₃)COOH	1
2302	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ CH ₂ C ₆ H ₅	NHCH(CH ₃)CONH ₂	1
2303	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ CH ₂ C ₆ H ₅	NHCH(CH ₂ COOH)COOH	1
2304	0	4-CH ₃ CH(CH ₃)C ₆ H ₄ CO-	CH ₂ CH ₂ C ₆ H ₅	NHCH(CH ₂ C ₆ H ₅)COOH	1



[Table 86]

No.	n	R ^{1h}	R ²	R ¹³	k
2305	0	4-CH ₃ CH (CH ₃) C ₆ H ₄ CO-	CH ₂ CH ₂ C ₆ H ₅	Leu-Leu-OH	1
2306	0	4-CH ₃ CH (CH ₃) C ₆ H ₄ CO-	CH ₂ CH ₂ C ₆ H ₅	Leu-Ala-Leu-OH	1
2307	0	OHC-	CH ₂ CH ₂ C ₆ H ₅	OH	1
2308	0	HOCH ₂ -	CH ₂ CH ₂ C ₆ H ₅	OH	1
2309	0	H ₂ N-	CH ₂ CH ₂ C ₆ H ₅	OH	1
2310	0	C1S (O) ₂ -	CH ₂ CH ₂ C ₆ H ₅	OH	1
2311	0	NCCO-	CH ₂ CH ₂ C ₆ H ₅	OH	1
2312	0	HOC (O) C (O) -	CH ₂ CH ₂ C ₆ H ₅	OH	1
2313	0	H ₃ COC (O) NH-	CH ₂ CH ₂ C ₆ H ₅	OH	1
2314	0	HOC (O) -	CH ₂ CH ₂ C ₆ H ₅	OH	1
2315	0	CH ₃ NH-	CH ₂ CH ₂ C ₆ H ₅	OH	1
2316	0	CH ₃ CO-	CH ₂ CH ₂ C ₆ H ₅	OH	1
2317	0	CH ₂ CHNH-	CH ₂ CH ₂ C ₆ H ₅	OH	1
2318	0	CH ₂ CHCO-	CH ₂ CH ₂ C ₆ H ₅	OH	1
2319	0	CH ₂ CHCH ₂ -	CH ₂ CH ₂ C ₆ H ₅	OH	1
2320	0	CH ₂ CHS (O) ₂ -	CH ₂ CH ₂ C ₆ H ₅	OH	1
2321	0	C ₆ H ₁₁ NH-	CH ₂ CH ₂ C ₆ H ₅	OH	1
2322	0	C ₆ H ₁₁ S (O) ₂ -	CH ₂ CH ₂ C ₆ H ₅	OH	1
2323	0	H ₂ NCO-	CH ₂ CH ₂ C ₆ H ₅	OH	1
2324	0	CH ₃ OC (O) -	CH ₂ CH ₂ C ₆ H ₅	OH	1
2325	0	H-Leu-Leu-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1
2326	0	H-Leu-Ala-Leu-	CH ₂ CH ₂ COOCH ₂ C ₆ H ₅	OH	1



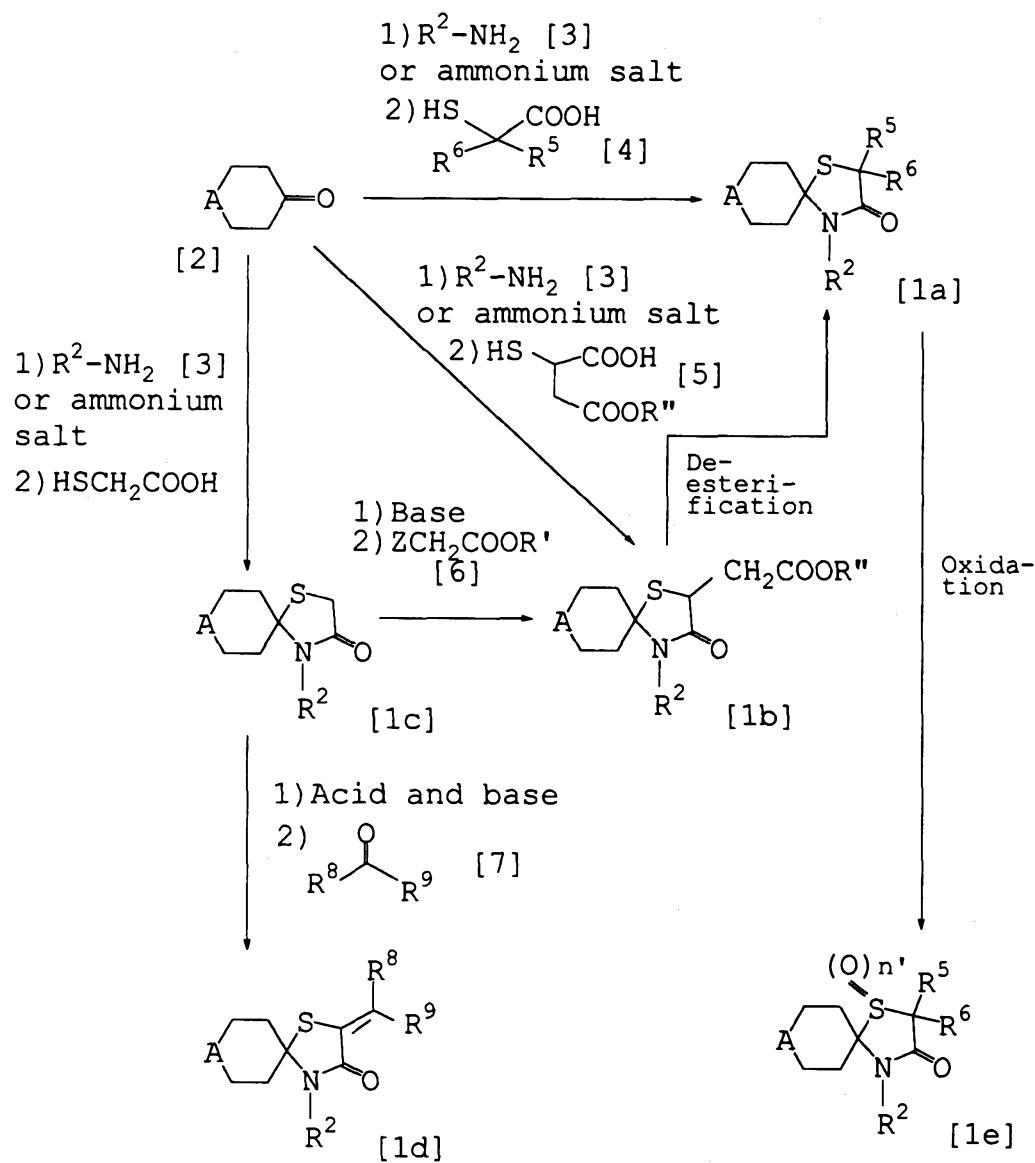
Some of the compounds of the present invention represented by general formula [1] or salts thereof have isomers such as optical isomers, geometrical isomers and tautomers. In such cases, the 5 present invention involves such isomers. Further, the present invention involves solvated products, hydrated products and a variety of crystal forms.

Next, the process for producing the compounds of the present invention will be described.

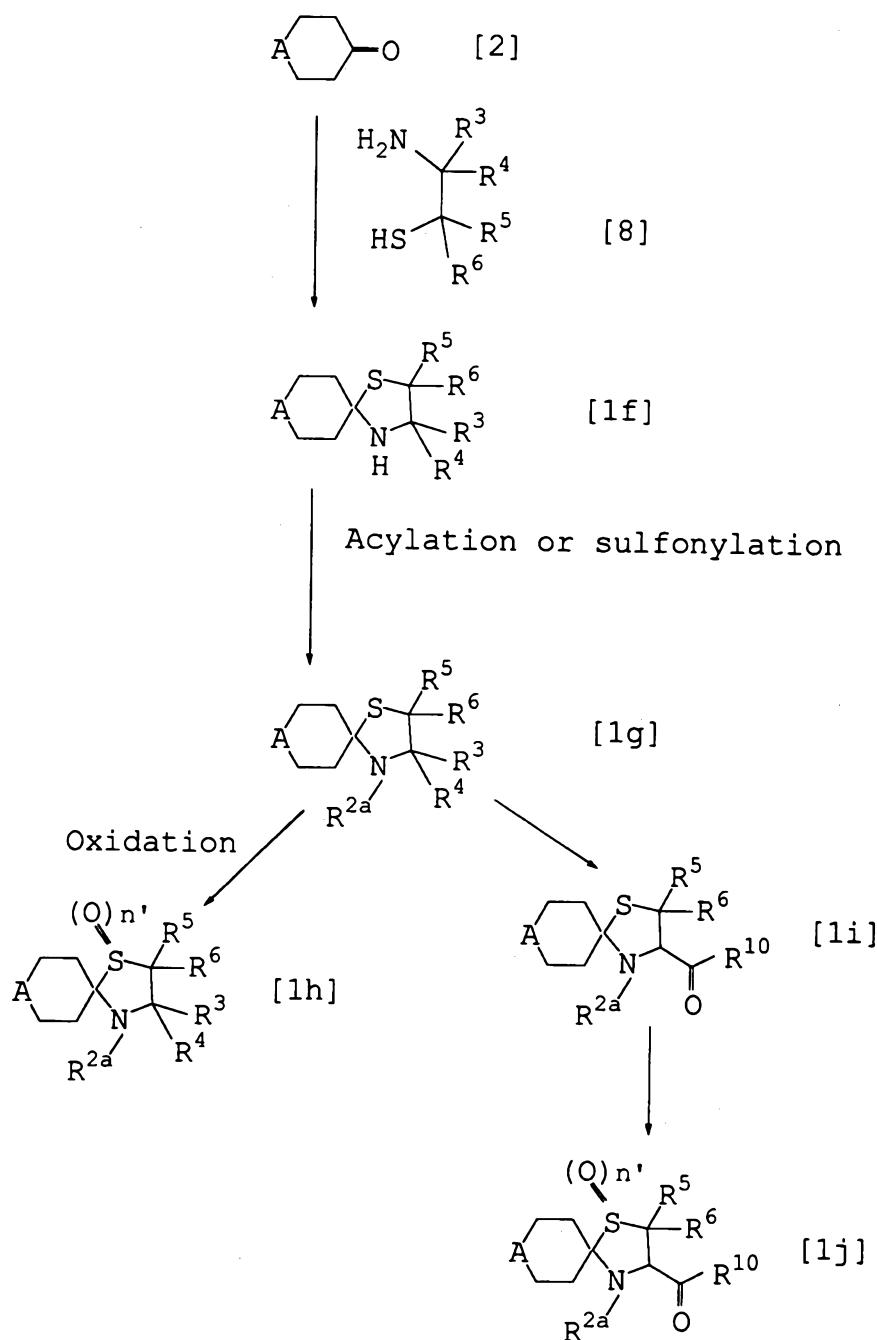
10 The compounds of the present invention can be synthesized according to, for example, the Production Processes 1 and 2 mentioned below.



[Production Process 1]



[Production Process 2]



wherein R^2 , R^3 , R^4 , R^5 , R^6 and A are as defined above; R^{2a} represents an unsubstituted or substituted acyl or sulfonyl group; R' represents an unsubstituted or substituted alkyl or aryl group; R'' represents tert-
5 butyl group or trichloroethyl group; R^8 and R^9 , same or different, each represents hydrogen atom or an unsubstituted or substituted alkyl, aryl or heterocyclic group; R^{10} represents an unsubstituted or substituted amino group, n' represents 1 or 2; and Z
10 represents halogen atom, alkylsulfonyloxy group or arylsulfonyloxy group.

[Production Process 1]

Next, the process for producing the compounds of the present invention will be described.

15 The compounds of the present invention can be produced by combining the processes which are known in themselves, namely, according to the production processes mentioned below, for example.

The compound of the general formula [1a] can
20 be produced by, for example, the process mentioned in Yakugaku Zasshi, Vol. 91, No. 3, Pages 363-383 (1971), or the like. More concretely speaking, the compounds of the present invention can be obtained by reacting a compound of general formula [2] with an amine
25 represented by general formula [3] or an ammonium salt and a compound represented by general formula [4] in the presence or absence of a dehydrating agent and/or a catalyst, and subjecting the reaction product to a



dehydrating ring closure.

As the amines which can be used in this reaction, primary amines such as methylamine, benzylamine, aniline, phenethylamine or the like and 5 amino acids such as leucine, asparagine, aspartic acid, β -alanine or the like can be referred to. As the ammonium salts, ammonium carbonate, ammonium sulfate and the like can be referred to. The amine of general formula [3] or the ammonium salt is used in an amount 10 of 1-10 mol and preferably 1-2 mol per mol of the compound of general formula [2]. The compound of general formula [4] is used in an amount of 1-10 mol and preferably 1-2 mol per mol of the compound of general formula [2]. As the dehydrating agent which 15 can be used according to the need, zeolam, molecular sieve, calcium chloride, magnesium sulfate, diphosphorus pentoxide and the like can be referred to, and the amount thereof is 1-10 times (w/w) and preferably 1-2 times (w/w) as much as the weight of the 20 compound of general formula [2]. As the catalyst which can be used according to the need, paratoluenesulfonic acid, benzenesulfonic acid, hydrochloric acid, sulfuric acid and the like can be referred to, and the amount thereof is 0.001-3 mol and preferably 0.01-0.1 mol per 25 mol of the compound of general formula [2]. The solvent used in this reaction is not particularly critical so far as the solvent exercises no adverse influence upon the reaction. Examples of the solvent



which can be used include aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as dioxane, tetrahydrofuran, anisole, diethylene glycol diethyl ether, dimethyl cellosolve and the like; esters 5 such as methyl acetate, ethyl acetate and the like; nitriles such as acetonitrile and the like; alcohols such as methyl alcohol, ethyl alcohol, isopropyl alcohol and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; 10 halogenated hydrocarbons such as chloroform, methylene chloride and the like; and sulfoxides such as dimethyl sulfoxide and the like. These solvents may be used alone or in mixture of two or more. This reaction is carried out usually at 0-150°C and preferably at 25- 15 120°C for a period of 30 minutes to 24 hours.

The compound of general formula [1b] can be obtained, for example, according to the process mentioned in *Yakugaku Zasshi*, Vol. 91, No. 3, Pages 363-383 (1971), or the like. More concretely speaking, 20 it can be obtained by reacting a compound of general formula [2] with an amine represented by general formula [3] or an ammonium salt and a compound represented by general formula [5] which can be synthesized according to the method described in 25 *SYNTHETIC COMMUNICATIONS*, Vol. 21, No. 2, Pages 249-263 (1991) or the like in the presence or absence of a dehydrating agent and/or a catalyst, and subjecting the reaction product to a dehydrating ring closure. As the



amines which can be used in this reaction, primary amines such as methylamine, benzylamine, aniline, phenethylamine and the like, amino acids such as leucine, asparagine, aspartic acid, β -alanine and the like, etc. can be referred to. As the ammonium salts, ammonium carbonate, ammonium sulfate and the like can be referred to. The amine represented by general formula [3] or the ammonium salt is used in an amount of 1-10 mol and preferably 1-2 mol per mol of the compound of general formula [2]. The compound of general formula [5] is used in an amount of 1-10 mol and preferably 1-2 mol per mol of the compound of general formula [2]. As the dehydrating agent, for example, zeolam, molecular sieve, calcium chloride, magnesium sulfate, diphosphorus pentoxide and the like can be used in an amount of 1-10 times (w/w) and preferably 1-2 times (w/w) as much as the weight of the compound of general formula [2]. As the catalyst which may be used according to the need, paratoluenesulfonic acid, benzenesulfonic acid, hydrochloric acid, sulfuric acid and the like can be referred to, and the amount thereof is 0.001-3 mol and preferably 0.01-0.1 mol per mol of the compound of general formula [2]. The solvent used in this reaction is not particularly critical so far as the solvent exercises no adverse influence upon the reaction. Examples of the solvent which can be used include aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as



dioxane, tetrahydrofuran, anisole, diethylene glycol diethyl ether, dimethyl cellosolve and the like; esters such as methyl acetate, ethyl acetate and the like; nitriles such as acetonitrile and the like; alcohols 5 such as methyl alcohol, ethyl alcohol, isopropyl alcohol and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; halogenated hydrocarbons such as chloroform, methylene chloride and the like; and sulfoxides such as dimethyl 10 sulfoxide and the like. These solvents may be used alone or in mixture of two or more. This reaction is carried out usually at 0-150°C and preferably at 25-120°C for a period of 30 minutes to 24 hours.

The compound of general formula [1c] can be 15 obtained, for example, according to the process mentioned in *Yakugaku Zasshi*, Vol. 91, No. 3, Pages 363-383 (1971), or the like. More concretely speaking, it can be obtained by reacting a compound of general formula [2] with an amine represented by general 20 formula [3] or an ammonium salt and mercaptoacetic acid in the presence or absence of a dehydrating agent and/or a catalyst, and subjecting the reaction product to a dehydrating ring closure. As the amines which can be used in this reaction, primary amines such as 25 methylamine, benzylamine, aniline, phenethylamine and the like, amino acids such as leucine, asparagine, aspartic acid, β -alanine and the like, etc. can be referred to. As the ammonium salts, ammonium



carbonate, ammonium sulfate and the like can be referred to. The amine represented by general formula [3] or the ammonium salt is used in an amount of 1-10 mol and preferably 1-2 mol per mol of the compound of general formula [2]. The mercaptoacetic acid is used in an amount of 1-10 mol and preferably 1-2 mol per mol of the compound of general formula [2]. As the dehydrating agent which may be used according to the need, for example, zeolam, molecular sieve, calcium 10 chloride, magnesium sulfate, diphosphorus pentoxide and the like can be used in an amount of 1-10 times (w/w) and preferably 1-2 times (w/w) as much as the weight of the compound of general formula [2]. As the catalyst which may be used according to the need, paratoluene- 15 sulfonic acid, benzenesulfonic acid, hydrochloric acid, sulfuric acid and the like can be referred to, and the amount thereof is 0.001-3 mol and preferably 0.01-0.1 mol per mol of the compound of general formula [2]. The solvent used in this reaction is not particularly 20 critical so far as the solvent exercises no adverse influence upon the reaction. Examples of the solvent which can be used include aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as dioxane, tetrahydrofuran, anisole, diethylene glycol 25 diethyl ether, dimethyl cellosolve and the like; esters such as methyl acetate, ethyl acetate and the like; nitriles such as acetonitrile and the like; alcohols such as methyl alcohol, ethyl alcohol, isopropyl



alcohol and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; halogenated hydrocarbons such as chloroform, methylene chloride and the like; and sulfoxides such as dimethyl sulfoxide and the like. These solvents may be used alone or in mixture of two or more. This reaction is carried out usually at 0-150°C and preferably at 25-120°C for a period of 30 minutes to 24 hours. If desired, this reaction may be carried out in an atmosphere of inert gas such as argon or nitrogen.

The compound of general formula [1b] can be obtained by, for example, reacting a compound of general formula [1c] with a compound of general formula [6] in the presence of a base. As the base used in this reaction, for example, there can be referred to organolithium compounds such as n-butyllithium, phenyllithium, lithium diisopropylamide and the like; alkali metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide and the like; alkali metal hydrides such as sodium hydride, potassium hydride and the like; alkali metal carbonates such as potassium carbonate, sodium carbonate and the like; alkali hydroxides such as sodium hydroxide, potassium hydroxide and the like; etc. The base is used in an amount of 1-5 mol per mol of the compound of general formula [1c]. The compound of general formula [6] is used in an amount of 1-10 mol and preferably 1-2 mol per mol of the compound of general formula [1c]. The



solvent used in this reaction is not particularly critical so far as the solvent exercises no adverse influence upon the reaction. Examples of the solvent which can be used include aromatic hydrocarbons such as 5 benzene, toluene, xylene and the like; ethers such as dioxane, tetrahydrofuran, anisole, diethylene glycol diethyl ether, dimethyl cellosolve and the like; nitriles such as acetonitrile and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide and the 10 like; halogenated hydrocarbons such as chloroform, methylene chloride and the like; and sulfoxides such as dimethyl sulfoxide and the like. These solvents may be used alone or in mixture of two or more. This reaction is carried out usually at -78°C to 150°C and preferably 15 at -50°C to 120°C, for a period of 30 minutes to 24 hours. If desired, the reaction may be carried out in an atmosphere of inert gas such as argon or nitrogen.

The compound of general formula [1d] can be obtained by reacting a compound of general formula [1c] 20 with an aldehyde or a ketone represented by general formula [7] in the presence or absence of an acid or a base.

As the acid which may be used in this reaction according to the need, for example, 25 paratoluenesulfonic acid, benzenesulfonic acid, hydrochloric acid, sulfuric acid and the like can be referred to. The amount thereof is 1-10 mol per mol of the compound of general formula [1c]. As the base



which may be used according to the need, for example, there can be referred to organolithium compounds such as n-butyllithium, phenyllithium, lithium diisopropylamide and the like; alkali metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide and the like; alkali metal hydrides such as sodium hydride, potassium hydride and the like; alkali metal carbonates such as potassium carbonate, sodium carbonate and the like; alkali hydroxides such as sodium hydroxide, potassium hydroxide and the like; etc. The base is used in an amount of 1-10 mol per mol of the compound of general formula [1c]. The compound of general formula [7] is used in an amount of 1-10 mol and preferably 1-2 mol per mol of the compound of general formula [1c]. The solvent used in this reaction is not particularly critical so far as the solvent exercises no adverse influence upon the reaction. Examples of the solvent which can be used include aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as dioxane, tetrahydrofuran, anisole, diethylene glycol diethyl ether, dimethyl cellosolve and the like; nitriles such as acetonitrile and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; halogenated hydrocarbons such as chloroform, methylene chloride and the like; and sulfoxides such as dimethyl sulfoxide and the like. These solvents may be used alone or in mixture of two or more. This reaction is



carried out usually at -78°C to 150°C and preferably at -50°C to 120°C, for a period of 30 minutes to 24 hours.

The compound of general formula [1a] can be obtained by, for example, subjecting a compound of 5 general formula [1b] to a de-esterification reaction in the presence or absence of an acid or a base. As the acid which may be used in this reaction according to the need, for example, hydrochloric acid, sulfuric acid, acetic acid, trifluoro-acetic acid, 10 paratoluenesulfonic acid and the like can be referred to, and the amount thereof is 1-50 mol and preferably 10-30 mol per mol of the compound of general formula [1b]. As the base which may be used according to the need, for example, there can be referred to 15 organolithium compounds such as n-butyllithium, phenyllithium, lithium diisopropylamide and the like; alkali metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide and the like; alkali metal hydrides such as sodium hydride, potassium 20 hydride and the like; alkali metal carbonates such as potassium carbonate, sodium carbonate and the like; alkali hydroxides such as sodium hydroxide, potassium hydroxide and the like; etc. The base is used in an amount of 1-50 mol and preferably 10-30 mol per mol of 25 the compound of general formula [1b].

The solvent used in this reaction is not particularly critical so far as the solvent exercises no adverse influence upon the reaction. Examples of



the solvent which can be used include aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as dioxane, tetrahydrofuran, anisole, diethylene glycol diethyl ether, dimethyl cellosolve and the like; nitriles such as acetonitrile and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; halogenated hydrocarbons such as chloroform, methylene chloride and the like; acetic acid; water; and sulfoxides such as dimethyl sulfoxide and the like. These solvents may be used alone or in mixture of two or more. This reaction is carried out usually at 0-150°C and preferably at 25-120°C, for a period of 30 minutes to 24 hours.

The compound of general formula [1e] can be obtained by, for example, oxidizing a compound of general formula [1a]. As the oxidant which can be used in this reaction, for example, peracids such as peracetic acid, trifluoro-peracetic acid, perbenzoic acid, m-chloroperbenzoic acid and the like; hydrogen peroxide; chromic acid; potassium permanganate and the like can be referred to. The oxidant is used in an amount of 0.5-5 mol and preferably 1-3 mol per mol of the compound of general formula [1a]. The solvent used in this reaction is not particularly critical so far as the solvent exercises no adverse influence upon the reaction. Examples of the solvent which can be used include aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as dioxane,



tetrahydrofuran, anisole, diethylene glycol diethyl ether, dimethyl cellosolve and the like; alcohols such as methanol, ethanol and the like; esters such as methyl acetate, ethyl acetate and the like; nitriles such as acetonitrile and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; halogenated hydrocarbons such as chloroform, methylene chloride and the like; water; and sulfoxides such as dimethyl sulfoxide and the like. These solvents may be used alone or in mixture of two or more. This reaction is carried out usually at a temperature ranging from 0°C to reflux temperature of the used solvent and preferably at 0-30°C, for a period of 30 minutes to 24 hours.

15 [Production Process 2]

The compound of general formula [1f] can be obtained by, for example, the process mentioned in JP-A 53-44574, or the like. More concretely speaking, it can be obtained by reacting a compound of general formula [2] with a compound of general formula [8] in the presence or absence of a base, a dehydrating agent and a catalyst, and subjecting the product to a dehydrating ring closure. Although the compound of general formula [8] used in this reaction is not particularly critical, D-cysteine, L-cysteine, D-penicillamine and L-penicillamine of which C-terminal may optionally be protected and salts thereof can be referred to, for example. The compound of general



formula [8] is used in an amount of 0.5-10 mol and preferably 1-2 mol per mol of the compound of general formula [2]. As the base which may be used according to the need, for example, organic amines such as

5 dimethylaminopyridine, triethylamine, pyridine and the like; alkali metal carbonates such as potassium carbonate, sodium carbonate and the like; etc. can be referred to, and the amount thereof is 0.5-10 mol and preferably 1-2 mol per mol of the compound of general

10 formula [2]. As the dehydrating agent which may be used according to the need, zeolam, molecular sieve, calcium chloride, magnesium sulfate, diphosphorus pentoxide and the like can be referred to, and the amount thereof is 1-10 times (w/w) and preferably 1-2

15 (w/w) times as much as the amount of the compound of general formula [2]. As the catalyst which may be used according to the need, paratoluenesulfonic acid, benzenesulfonic acid, hydrochloric acid, sulfuric acid and the like can be referred to, and the amount thereof

20 is 0.001-1 mol and preferably 0.01-0.1 mol per mol of the compound of general formula [2]. The solvent used in this reaction is not particularly critical so far as the solvent exercises no adverse influence upon the reaction. Examples of the solvent which can be used

25 include aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as dioxane, tetrahydrofuran, anisole, diethylene glycol diethyl ether, dimethyl cellosolve and the like; esters such as



methyl acetate, ethyl acetate and the like; nitriles such as acetonitrile and the like; alcohols such as methyl alcohol, ethyl alcohol, isopropyl alcohol and the like; amides such as N,N-dimethylformamide, N,N-5 dimethylacetamide and the like; halogenated hydrocarbons such as chloroform, methylene chloride and the like; water; and sulfoxides such as dimethyl sulfoxide and the like. These solvents may be used alone or in mixture of two or more. This reaction is 10 carried out usually at 0-150°C and preferably at 20-120°C, for a period of 30 minutes to 24 hours.

The compound of general formula [1g] can be obtained by, for example, subjecting a compound of general formula [1f] to an acylation reaction or a 15 sulfonylation reaction in the presence or absence of a base. As the acylating agent which can be used in this reaction, for example, acetic anhydride, acetyl chloride, benzoyl chloride, pyrrolecarbonyl chloride, thiazolecarbonyl chloride and the like can be referred to. As the sulfonylating agent, methanesulfonyl 20 chloride, benzenesulfonyl chloride and the like can be referred to. The amounts of said acylating agent and sulfonylating agent are 0.5-10 mol and preferably 1-3 mol per mol of the compound of general formula [1f]. 25 As the base which may be used according to the need, organic amines such as dimethylaminopyridine, triethylamine, pyridine and the like and alkali metal carbonates such as potassium carbonate, sodium



carbonate and the like can be referred to, and the amount thereof is 0.5-10 mol and preferably 1-3 mol per mol of the compound of general formula [1f].

The solvent used in this reaction is not particularly critical so far as the solvent exercises no adverse influence upon the reaction. Examples of the solvent which can be used include aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as dioxane, tetrahydrofuran, anisole, diethylene glycol diethyl ether, dimethyl cellosolve and the like; esters such as methyl acetate, ethyl acetate and the like; nitriles such as acetonitrile and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; halogenated hydrocarbons such as chloroform, methylene chloride and the like; and sulfoxides such as dimethyl sulfoxide and the like. These solvents may be used alone or in mixture of two or more. The reaction is carried out usually at -20°C to 150°C and preferably at 0-120°C, for a period of 30 minutes to 24 hours.

The compound of general formula [1h] can be obtained by, for example, oxidizing a compound of general formula [1g]. As the oxidant which can be used in this reaction, for example, peracids such as peracetic acid, trifluoro-peracetic acid, perbenzoic acid, m-chloroperbenzoic acid and the like, hydrogen peroxide, chromic acid, potassium permanganate and the like can be referred to. The oxidant is used in an



amount of 0.5-5 mol and preferably 1-3 mol per mol of the compound of general formula [1g]. The solvent used in this reaction is not particularly critical so far as the solvent exercises no adverse influence upon the 5 reaction. Examples of the solvent which can be used include aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as dioxane, tetrahydrofuran, anisole, diethylene glycol diethyl ether, dimethyl cellosolve and the like; alcohols such 10 as methanol, ethanol and the like; esters such as methyl acetate, ethyl acetate and the like; nitriles such as acetonitrile and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; halogenated hydrocarbons such as chloroform, methylene 15 chloride and the like; water; and sulfoxides such as dimethyl sulfoxide and the like. These solvents may be used alone or in mixture of two or more. The reaction is carried out usually at a temperature ranging from 0°C to the reflux temperature of the used solvent and 20 preferably at 0-30°C, for a period of 30 minutes to 24 hours.

The compound of general formula [1i] can be obtained by, for example, subjecting a compound of general formula [1g] to an amidation reaction.

25 This reaction is a usual amidation reaction, which can be carried out by, for example, a method via an acid chloride, a method via an acid anhydride, a method using a base, a condensing agent and an



additive, etc. In a case of using a base, a condensing agent and an additive, the amines which can be used in the reaction include primary amines such as methylamine, benzylamine, aniline, phenethylamine, 5 aminothiazole and the like; secondary amines such as dimethylamine, diethylamine, di-n-propylamine and the like; cyclic amines such as piperidine, morpholine and the like; amino acids such as leucine, asparagine, aspartic acid, β -alanine, methionine and the like; and 10 esters thereof. The amine is used in an amount of 0.5-10 mol and preferably 1-3 mol per mol of the compound of general formula [1g]. As the base which can be used in this reaction, organic amines such as dimethylaminopyridine, triethylamine, pyridine, N-15 methylmorphline and the like and alkali metal carbonates such as potassium carbonate, sodium carbonate and the like can be referred to, and the amount thereof is 0.5-10 mol and preferably 1-3 mol per mol of the compound of general formula [1g]. As the 20 condensing agent, dicyclohexyl-carbodiimide, diisopropyl-carbodiimide, N-ethyl-N'-3-dimethylaminopropyl carbodiimide, diphenyl phosphoryl azide and the like can be referred to, and as the additive, 1-hydroxybenzotriazole, N-hydroxysuccinimide 25 and the like can be referred to. The amounts of the condensing agent and the additive are both 0.5-10 mol and preferably 1-3 mol per mol of the compound of general formula [1g]. The solvent used in this



reaction is not particularly critical so far as the solvent exercises no adverse influence upon the reaction. Examples of the solvent which can be used include aromatic hydrocarbons such as benzene, toluene, 5 xylene and the like; ethers such as dioxane, tetrahydrofuran, anisole, diethylene glycol diethyl ether, dimethyl cellosolve and the like; esters such as methyl acetate, ethyl acetate and the like; nitriles such as acetonitrile and the like; amides such as N,N- 10 dimethylformamide, N,N-dimethylacetamide and the like; halogenated hydrocarbons such as chloroform, methylene chloride and the like; and sulfoxides such as dimethyl sulfoxide and the like. These solvents may be used alone or in mixture of two or more. The reaction is 15 carried out usually at a temperature of -20°C to 150°C and preferably at 0-120°C, for a period of 30 minutes to 24 hours.

The compound of [1j] can be obtained by, for example, oxidizing a compound of general formula [1i].

20 As the oxidant which can be used in this reaction, peracids such as peracetic acid, trifluoro-peracetic acid, perbenzoic acid, m-chloroperbenzoic acid and the like; hydrogen peroxide; chromic acid and potassium permanganate and the like can be referred to. 25 The oxidant is used in an amount of 0.5-5 mol and preferably 1-3 mol per mol of the compound of general formula [1i]. The solvent used in this reaction is not particularly critical so far as the solvent exercises

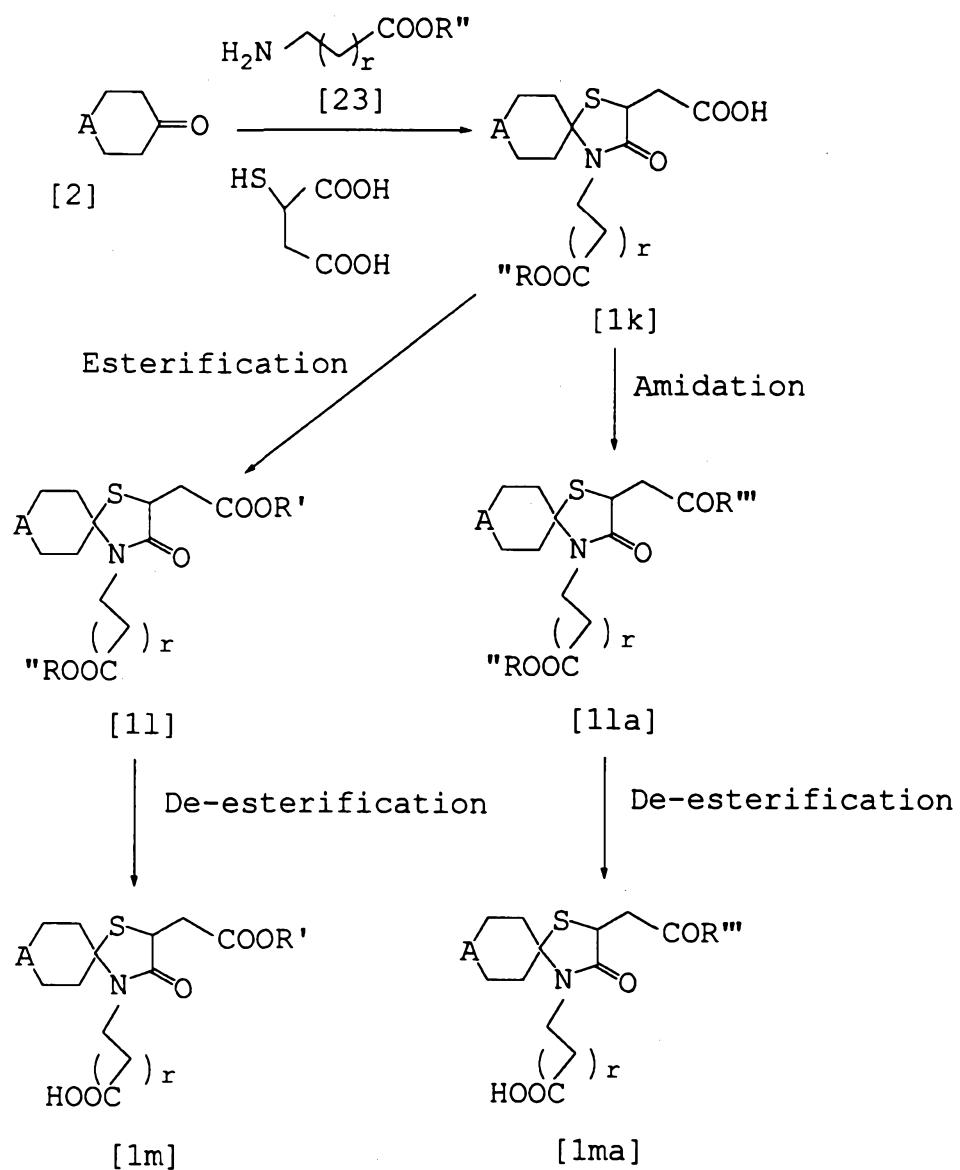


no adverse influence upon the reaction. Examples of the solvent which can be used include aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as dioxane, tetrahydrofuran, anisole, 5 diethylene glycol diethyl ether, dimethyl cellosolve and the like; alcohols such as methanol, ethanol and the like; esters such as methyl acetate, ethyl acetate and the like; nitriles such as acetonitrile and the like; amides such as N,N-dimethylformamide, N,N-10 dimethylacetamide and the like; halogenated hydrocarbons such as chloroform, methylene chloride and the like; water; and sulfoxides such as dimethyl sulfoxide and the like. These solvents may be used alone or in mixture of two or more. The reaction is 15 carried out usually at a temperature ranging from 0°C to the reflux temperature of the used solvent and preferably at 0-30°C, for a period of 30 minutes to 24 hours.

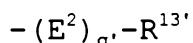
Furthermore, it is also possible to 20 synthesize the compounds of the present invention according to the Production Processes 1a and 2a described below.



[Production Process 1a]



wherein A is as defined above; R' represents an unsubstituted or substituted alkyl or aryl group; R" represents tert-butyl group; R''' represents an unprotected or protected amino, hydroxyamino, 5 alkylamino, arylamino, acylamino, alkoxycarbonylamino, arylsulfonylamino, alkylsulfonylamino or a group of the following general formula:



wherein E² represents amino acid residue; and R^{13'} 10 represents an unprotected or protected hydroxyl, amino, alkylamino, acylamino, alkoxycarbonylamino, arylsulfonylamino, alkylsulfonylamino, or an unsubstituted or substituted alkyl or alkoxy group; and q' represents 1, 2 or 3; and r represents 0, 1 or 2.

15 The compound of general formula [1k] can be obtained by, for example, the process mentioned in Yakugaku Zasshi, Vol. 91, No. 3, Pages 363-383 (1971), or the like. More concretely speaking, it can be obtained by reacting a compound of general formula [2] 20 with an amine represented by general formula [23] and mercaptosuccinic acid in the presence or absence of a dehydrating agent and/or a catalyst, and subjecting the product to a dehydrating ring closure.

As the amine which can be used in this 25 reaction, glycine tert-butyl ester, β -alanine tert-butyl ester and the like can be referred to. The amine of general formula [23] is used in an amount of 1-10 mol and preferably 1-2 mol per mol of the compound of



general formula [2]. The mercaptosuccinic acid is used in an amount of 1-10 mol and preferably 1-2 mol per mol of the compound of general formula [2]. As the dehydrating agent which may be used according to the 5 need, for example, zeolam, molecular sieve, calcium chloride, magnesium sulfate, diphosphorus pentoxide and the like can be referred to, and the amount thereof is 1-10 times (w/w) and preferably 1-2 times (w/w) as much as the amount of the compound of general formula [2].

10 As the catalyst which may be used according to the need, paratoluenesulfonic acid, benzenesulfonic acid, hydrochloric acid, sulfuric acid and the like can be referred to, and the amount thereof is 0.001-3 mol and preferably 0.01-0.1 mol per mol of the compound of

15 general formula [2]. The solvent used in this reaction is not particularly critical so far as the solvent exercises no adverse influence upon the reaction. Examples of the solvent which can be used include aromatic hydrocarbons such as benzene, toluene, xylene

20 and the like; ethers such as dioxane, tetrahydrofuran, anisole, diethylene glycol diethyl ether, dimethyl cellosolve and the like; esters such as methyl acetate, ethyl acetate and the like; nitriles such as acetonitrile and the like; alcohols such as methanol,

25 ethanol, isopropyl alcohol and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; halogenated hydrocarbons such as chloroform, methylene chloride and the like; and sulfoxides such as



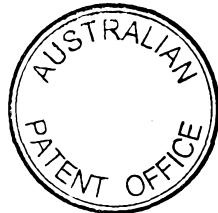
dimethyl sulfoxide and the like. These solvents may be used alone or in mixture of two or more. The reaction is carried out usually at 0-150°C and preferably at 25-120°C, for a period of 30 minutes to 24 hours.

5 The compound of general formula [11] can be obtained by subjecting a compound of general formula [1k] to an esterification reaction.

This reaction may be practiced according to the usual methods of esterification, such as the method 10 via an acid chloride, the method via an acid anhydride, the method using a base and an alkyl halide, the method of using a condensing agent and an additive, etc. In the case of using a base and an alkyl halide, the base which can be used include organic amines such as 15 dimethylaminopyridine, triethylamine, pyridine, N-methylmorpholine and the like; alkali metal carbonates such as potassium carbonate, sodium carbonate and the like; etc. The amount of the base is 0.5-10 mol and preferably 1-3 mol per mol of the compound of general 20 formula [1k]. As the alkyl halide which can be used in this reaction, methyl iodide, ethyl iodide, benzyl bromide and the like can be referred to, and the amount thereof is 0.5-10 mol and preferably 1-3 mol per mol of the compound of general formula [1k]. The solvent used 25 in this reaction is not particularly critical so far as the solvent exercises no adverse influence upon the reaction. Examples of the solvent which can be used include aromatic hydrocarbons such as benzene, toluene,



xylene and the like; ethers such as dioxane, tetrahydrofuran, anisole, diethylene glycol diethyl ether, dimethyl cellosolve and the like; esters such as methyl acetate, ethyl acetate and the like; nitriles such as acetonitrile and the like; amides such as N,N-dimethylformamide and the like; halogenated hydrocarbons such as chloroform, methylene chloride and the like; and sulfoxides such as dimethyl sulfoxide and the like. The reaction is carried out usually at 0-200°C and preferably at 25-150°C, for a period of 10 minutes to 24 hours. In the case of using a condensing agent and an additive, the objective compound can be obtained by subjecting an alcohol such as ethanol, benzyl alcohol or the like to a condensation reaction with a condensing agent and an additive. As the condensing agent used in this reaction, for example, dicyclohexyl carbodiimide, diisopropyl carbodiimide, N-ethyl-N'-3-dimethylaminopropyl carbodiimide, diphenyl phosphoryl azide and the like can be referred to. As the additive used in this reaction, for example, 1-hydroxybenzotriazole, N-hydroxysuccinimide and the like can be referred to. The alcohol, condensing agent and additive used in this reaction are used each in an amount of 0.5-10 mol and preferably 1-3 mol per mol of the compound of general formula [1k]. The solvent used in this reaction is not particularly critical so far as the solvent exercises no adverse influence upon the reaction. Examples of the solvent which can be used



include aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as dioxane, tetrahydrofuran, anisole, diethylene glycol diethyl ether, dimethyl cellosolve and the like; esters such as 5 methyl acetate, ethyl acetate and the like; nitriles such as acetonitrile and the like; amides such as N,N-dimethylformamide and the like; halogenated hydrocarbons such as chloroform, methylene chloride and the like; and sulfoxides such as dimethyl sulfoxide and 10 the like. The reaction is carried out usually at 0-200°C and preferably at 25-150°C, for a period of 10 minutes to 24 hours.

The compound of general formula [1m] can be obtained by, for example, subjecting a compound of 15 general formula [11] to a de-esterification reaction in the presence of an acid. As the acid which can be used in this reaction according to the need, for example, hydrochloric acid, sulfuric acid, acetic acid, trifluoroacetic acid, paratoluenesulfonic acid and the 20 like can be referred to. The amount thereof is 1-50 mol and preferably 10-30 mol per mol of the compound of general formula [11]. The solvent used in this reaction is not particularly critical so far as the solvent exercises no adverse influence upon the 25 reaction. Examples of the solvent which can be used include aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as dioxane, tetrahydrofuran, anisole, diethylene glycol diethyl



ether, dimethyl cellosolve and the like; nitriles such as acetonitrile and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; halogenated hydrocarbons such as chloroform, methylene chloride and the like; acetic acid; water; and sulfoxides such as dimethyl sulfoxide and the like.

These solvents may be used alone or in mixture of two or more. The reaction is carried out usually at 0-150°C and preferably at 25-120°C, for a period of 30 minutes to 24 hours.

The compound of general formula [1la] can be obtained by, for example, subjecting a compound of general formula [1k] to an amidation reaction.

This reaction is a usual amidation reaction, which can be carried out by, for example, a method via an acid chloride, a method via an acid anhydride, a method using a base, a condensing agent and an additive, etc. In the case of using a base, a condensing agent and an additive, the amines which can be used in the reaction include primary amines such as methylamine, benzylamine, aniline, phenethylamine, aminothiazole and the like; secondary amines such as dimethylamine, diethylamine, di-n-propylamine and the like; cyclic amines such as piperidine, morpholine and the like; amino acids such as leucine, asparagine, aspartic acid, β -alanine, methionine and the like; compounds prepared by substituting the C-terminal carboxyl group may be substituted of the above-



mentioned amino acids with an unsubstituted or substituted alkyloxycarbonyl or carbamoyl group; compounds prepared by condensing 2 or 3 amino acids such as alanylalanine, leucylalanine or the like of

5 which C-terminal carboxyl group may be substituted with an unsubstituted or substituted alkyloxycarbonyl or carbamoyl group; and the like. The amine is used in an amount of 0.5-10 mol and preferably 1-3 mol per mol of the compound of general formula [1k]. As the base

10 which can be used in this reaction, organic amines such as dimethylaminopyridine, triethylamine, pyridine, N-methylmorphline and the like and alkali metal carbonates such as potassium carbonate, sodium carbonate and the like can be referred to, and the

15 amount thereof is 0.5-10 mol and preferably 1-3 mol per mol of the compound of general formula [1k]. As the condensing agent, dicyclohexyl carbodiimide, diisopropyl carbodiimide, N-ethyl-N'-3-dimethylaminopropyl carbodiimide, diphenyl phosphoryl

20 azide and the like can be referred to, and as the additive, 1-hydroxybenzotriazole, N-hydroxysuccinimide and the like can be referred to. The amounts of the condensing agent and the additive are both 0.5-10 mol and preferably 1-3 mol per mol of the compound of

25 general formula [1k]. The solvent used in this reaction is not particularly critical so far as the solvent exercises no adverse influence upon the reaction. Examples of the solvent which can be used



include aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as dioxane, tetrahydrofuran, anisole, diethylene glycol diethyl ether, dimethyl cellosolve and the like; esters such as 5 methyl acetate, ethyl acetate and the like; nitriles such as acetonitrile and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; halogenated hydrocarbons such as chloroform, methylene chloride and the like; and sulfoxides such as dimethyl 10 sulfoxide and the like. These solvents may be used alone or in mixture of two or more. The reaction is carried out usually at a temperature of -20°C to 150°C and preferably at 0-120°C, for a period of 30 minutes to 24 hours.

15 The compound of general formula [1ma] can be obtained by, for example, subjecting a compound of general formula [1la] to a de-esterification reaction in the presence of an acid. As the acid which may be used in this reaction according to the need, for 20 example, hydrochloric acid, sulfuric acid, acetic acid, trifluoroacetic acid, paratoluenesulfonic acid and the like can be referred to, and the amount thereof is 1-50 mol and preferably 10-30 mol per mol of the compound of the general formula [1la]. The solvent used in this 25 reaction is not particularly critical so far as the solvent exercises no adverse influence upon the reaction. Examples of the solvent which can be used include aromatic hydrocarbons such as benzene, toluene,

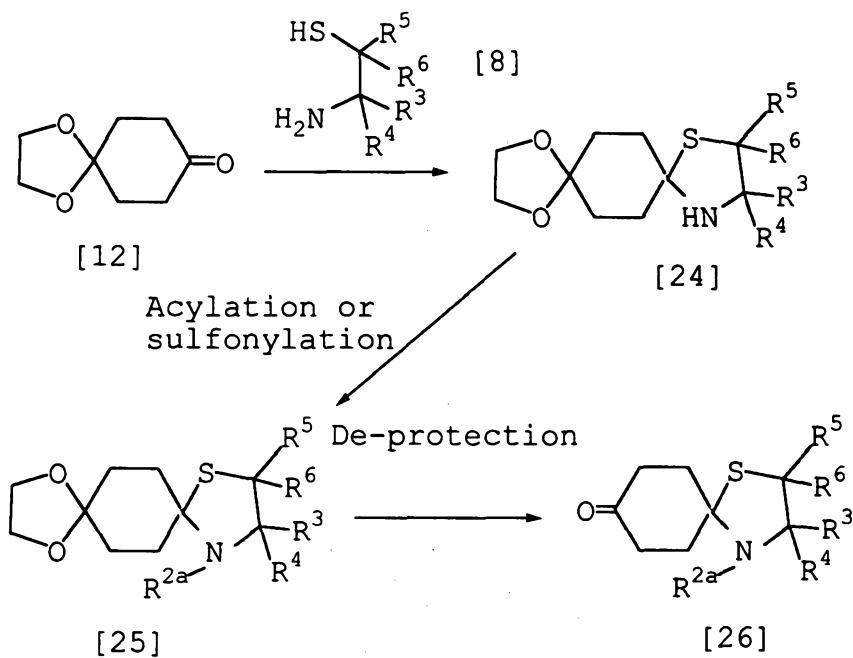


xylene and the like; ethers such as dioxane, tetrahydrofuran, anisole, diethylene glycol diethyl ether, dimethyl cellosolve and the like; nitriles such as acetonitrile and the like; amides such as N,N-

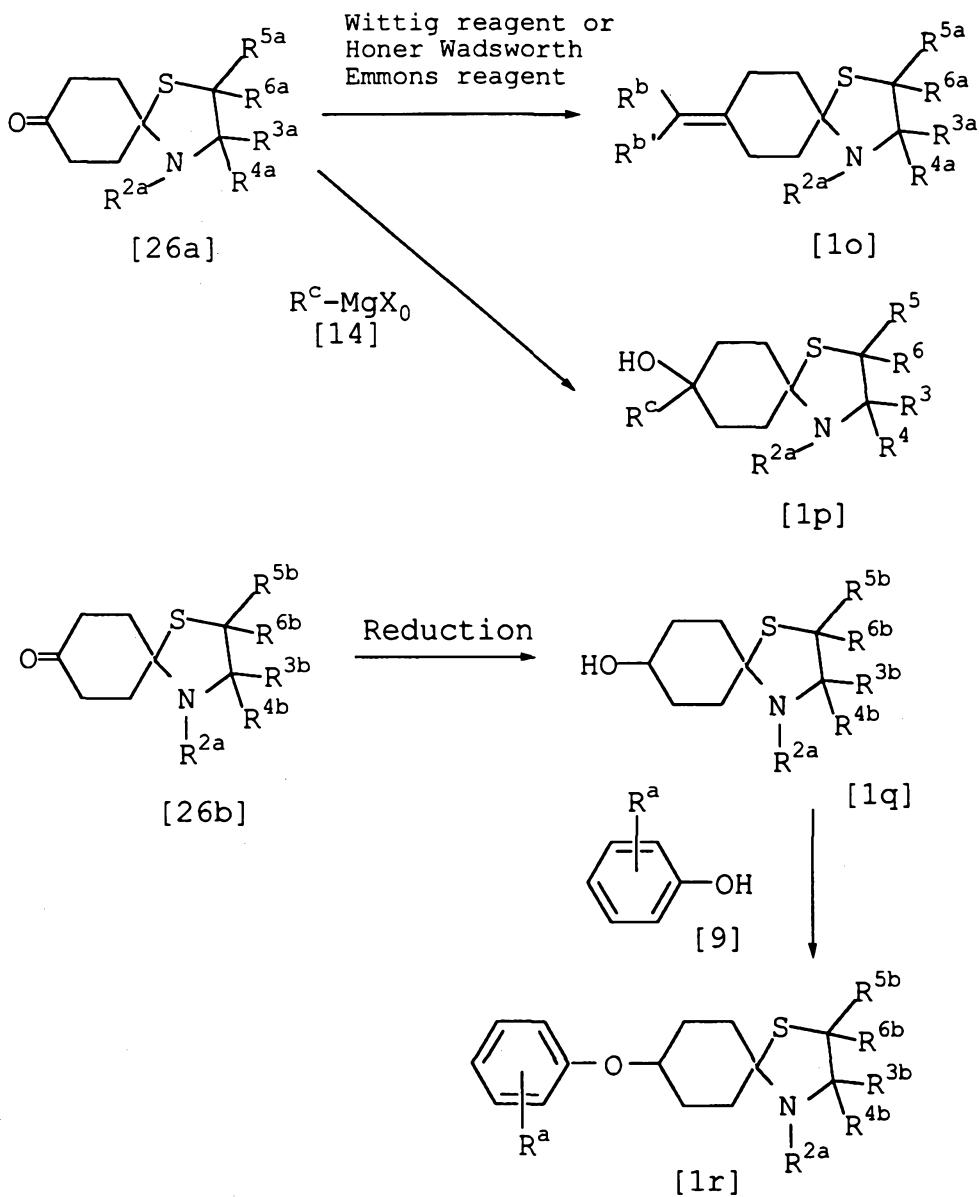
5 dimethylformamide, N,N-dimethylacetamide and the like; halogenated hydrocarbons such as chloroform, methylene chloride and the like; acetic acid; water; and sulfoxides such as dimethyl sulfoxide and the like.

These solvents may be used alone or in mixture of two
 10 or more. The reaction is carried out usually at 0-150°C and preferably at 25-120°C, for a period of 30 minutes to 24 hours.

[Production Process 2a]



[Production Process 2b]



wherein R³, R⁴, R⁵ and R⁶ are as defined above; R^{3a} and R^{4a}, same or different, each represents hydrogen atom, halogen atom, cyano group, an unprotected or protected carboxyl group, an unprotected or protected hydroxyl group, or an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkoxycarbonyl, aryl, amino, alkylamino, acylamino, carbamoyl or heterocyclic group or R^{3a} and R^{4a}, taken conjointly, represent an oxo group; R^{5a} and R^{6a}, same or different, each represents hydrogen atom, halogen atom, cyano group, an unprotected or protected carboxyl group, an unprotected or protected hydroxyl group, an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkoxycarbonyl, aryl, amino, alkylamino, acylamino, carbamoyl or heterocyclic group or R^{5a} and R^{6a}, taken conjointly with the terminal carbon atom to which R^{5a} and R^{6a} are combined, represent an alkenyl group; R^{3b} and R^{4b}, same or different, each represents hydrogen atom, halogen atom, cyano group, an unprotected or protected carboxyl group, protected hydroxyl group, or an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, acyl, alkoxycarbonyl, aryl, amino, alkylamino, acylamino, carbamoyl or heterocyclic group or R^{3b} and R^{4b}, taken conjointly, represent an oxo group; R^{5b} and R^{6b}, same or different, each represents hydrogen atom, halogen atom, cyano



group, an unprotected or protected carboxyl group, protected hydroxyl group, or an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, acyl, 5 alkoxycarbonyl, aryl, amino, alkylamino, acylamino, carbamoyl or heterocyclic group or R^{5b} and R^{6b} , taken conjointly with the terminal carbon atom to which R^{5b} and R^{6b} are combined, represent an alkenyl group; R^{2a} represents an unsubstituted or substituted acyl or 10 sulfonyl group; R^a represents hydrogen atom, halogen atom, cyano group, nitro group, protected carboxyl group, protected hydroxyl group or an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, acyl, alkoxycarbonyl, aryloxycarbonyl, 15 carbamoyl, amino or heterocyclic group; R^b and $R^{b'}$, same or different, each represents hydrogen atom, halogen atom, cyano group, nitro group, an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl or alkoxy group, protected amino group, or an 20 unprotected or protected carboxyl group; X_0 represents chlorine, bromine or iodine atom; and R^c represents an unsubstituted or substituted alkyl, alkenyl, cycloalkyl or aryl group.

The compound of general formula [24] can be 25 obtained by, for example, according to the method described in JP-A 53-44574, or the like. More concretely speaking, it can be obtained by reacting a compound [12] with a compound of general formula [8] in



the presence or absence of a base and a dehydrating agent and subjecting the product to a dehydrating ring closure. Although the compound of general formula [8] which can be used in this reaction is not particularly critical, D-cysteine, L-cysteine, D-penicillamine and L-penicillamine of which C-terminal may optionally be protected and salts thereof can be referred to, for example. The compound of general formula [8] is used in an amount of 0.5-10 mol and preferably 1-2 mol per 10 mol of the compound of general formula [12]. As the base which may be used according to the need, for example, organic amines such as dimethylaminopyridine, triethylamine, pyridine and the like; and alkali metal carbonates such as potassium carbonate, sodium 15 carbonate and the like can be referred to, and the amount thereof is 0.5-10 mol and preferably 1-2 mol per mol of the compound of general formula [12]. As the dehydrating agent which may be used according to the need, zeolam, molecular sieve, calcium chloride, 20 magnesium sulfate, diphosphorus pentoxide and the like can be referred to, and the amount thereof is 1-10 times (w/w) and preferably 1-2 times (w/w) as much as the weight of the compound of general formula [12]. The solvent used in this reaction is not particularly 25 critical so far as the solvent exercises no adverse influence upon the reaction. Examples of the solvent which can be used include aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as



dioxane, tetrahydrofuran, anisole, diethylene glycol
diethyl ether, dimethyl cellosolve and the like; esters
such as methyl acetate, ethyl acetate and the like;
nitriles such as acetonitrile and the like; alcohols
5 such as methanol, ethanol, isopropyl alcohol and the
like; amides such as N,N-dimethylformamide, N,N-
dimethylacetamide and the like; halogenated
hydrocarbons such as chloroform, methylene chloride and
the like; water; and sulfoxides such as dimethyl
10 sulfoxide and the like. These solvents may be used
alone or in mixture of two or more. The reaction is
carried out usually at 0-150°C and preferably at 20-
120°C, for a period of 30 minutes to 24 hours.

The compound of general formula [25] can be
15 obtained by, for example, subjecting a compound of
general formula [24] to an acylation reaction or
sulfonylation reaction in the presence or absence of a
base. As the acylating agent which can be used in this
reaction, for example, acetic anhydride, acetyl
20 chloride, benzoyl chloride, pyrrole carbonyl chloride,
thiazole carbonyl chloride and the like can be referred
to. As the sulfonylating agent, methanesulfonyl
chloride, benzenesulfonyl chloride and the like can be
referred to, and the amount thereof is 0.5-10 mol and
25 preferably 1-3 mol per mol of the compound of general
formula [24]. As the base which may be used according
to the need, organic amines such as dimethylamino-
pyridine, triethylamine, pyridine and the like; and



alkali metal carbonates such as potassium carbonate, sodium carbonate and the like can be referred to, and the amount thereof is 0.5-10 mol and preferably 1-3 mol per mol of the compound of general formula [24].

5 The solvent used in this reaction is not particularly critical so far as the solvent exercises no adverse influence upon the reaction. Examples of the solvent which can be used include aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as dioxane, tetrahydrofuran, anisole, diethylene glycol diethyl ether, dimethyl cellosolve and the like; esters such as methyl acetate, ethyl acetate and the like; nitriles such as acetonitrile and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; halogenated hydrocarbons such as chloroform, methylene chloride and the like; and sulfoxides such as dimethyl sulfoxide and the like. These solvents may be used alone or in mixture of two or more. The reaction is carried out

10 usually at -20°C to 150°C and preferably at 0-120°C, for a period of 30 minutes to 24 hours.

20 The compound of general formula [26] can be obtained by de-protecting a compound of general formula [25] in the presence of an acid. As the acid which can be used in this reaction, mineral acids such as hydrochloric acid, sulfuric acid, hydrobromic acid and the like, and organic acids such as paratoluenesulfonic acid and the like can be referred to, and the amount



thereof is 1-50 mol and preferably 5-20 mol per mol of the compound of general formula [25]. The solvent used in this reaction is not particularly critical so far as the solvent exercises no adverse influence upon the 5 reaction. Examples of the solvent which can be used include aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as dioxane, tetrahydrofuran, anisole, diethylene glycol diethyl ether, dimethyl cellosolve and the like; esters such as 10 methyl acetate, ethyl acetate and the like; nitriles such as acetonitrile and the like; alcohols such as methanol, ethanol, isopropyl alcohol and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; halogenated 15 hydrocarbons such as chloroform, methylene chloride and the like; water; and sulfoxides such as dimethyl sulfoxide and the like. These solvents may be used alone or in mixture of two or more. The reaction is carried out usually at 0-150°C and preferably at 25- 20 120°C, for a period of 30 minutes to 24 hours.

The compound of general formula [10] can be obtained by reacting a compound of general formula [26a] with Wittig reagent or Horner Wadsworth Emmons reagent.

25 More concretely speaking, the compound of general formula [10] can be obtained by reacting a compound of general formula [26a] with Wittig reagent which can be synthesized according to the method



mentioned in Organic Syntheses Collective Volume, Vol. 5, Pages 751-754 (1973) or Honer Wadsworth Emmons reagent which can be synthesized according to the method mentioned in Organic Syntheses Collective Volume, Vol. 5, Pages 509-513 (1973). The Wittig reagent and the Honer Wadsworth Emmons reagent are used in an amount of 0.5-5 mol and preferably 1-2 mol per mol of the compound of general formula [26a]. The solvent used in this reaction is not particularly critical so far as the solvent exercises no adverse influence upon the reaction. Examples of the solvent which can be used include aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as dioxane, tetrahydrofuran, anisole, diethylene glycol diethyl ether, dimethyl cellosolve and the like; esters such as methyl acetate, ethyl acetate and the like; nitriles such as acetonitrile and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; halogenated hydrocarbons such as chloroform, 20 methylene chloride and the like; and sulfoxides such as dimethyl sulfoxide and the like. These solvents may be used alone or in mixture of two or more. The reaction is carried out usually at -78°C to 120°C and preferably at -20°C to 30°C, for a period of 30 minutes to 24 hours. If desired, this reaction may be carried out in an atmosphere of inert gas such as argon or nitrogen.

The compound of general formula [1p] can be obtained by, for example, subjecting a compound of



general formula [26a] and a compound of general formula [14] to Grignard reaction. The Grignard reagent used in this reaction can be synthesized according to the method mentioned in *Organic Syntheses Collective*

5 Volume, Vol. 5, Page 226 (1955). Examples of the Grignard reagent include alkylmagnesium halides such as methylmagnesium bromide and the like and arylmagnesium halides such as phenylmagnesium bromide and the like.

In this reaction, the compound of general formula [14] is used in an amount of 0.5-5 mol and preferably 0.8-2 mol per mol of the compound of general formula [26a].

The solvent used in this reaction is not particularly critical so far as the solvent exercises 15 no adverse influence upon the reaction. Examples of the solvent which can be used include aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as dioxane, tetrahydrofuran, anisole, diethylene glycol diethyl ether, dimethyl cellosolve 20 and the like; halogenated hydrocarbons such as chloroform, methylene chloride and the like; and sulfoxides such as dimethyl sulfoxide and the like. These solvents may be used alone or in mixture of two or more. The reaction is carried out usually at -20°C 25 to 120°C and preferably at 0-70°C for a period of 30 minutes to 24 hours. If desired, this reaction may be carried out in an atmosphere of inert gas such as argon or nitrogen.



The compound of general formula [1q] can be obtained by reacting a compound of general formula [26b] with a reductant in the presence or absence of a salt. As the salt which may be used according to the 5 need, lithium chloride, magnesium chloride, calcium chloride and the like can be referred to, and the amount thereof is 1-10 mol per mol of the compound of general formula [26b]. As the reductant, sodium boron hydride, lithium boron hydride, aluminum diisobutyl 10 hydride and the like can be referred to, and the amount thereof is 1-10 mol and preferably 1-2 mol per mol of the compound of general formula [26b]. The solvent used in this reaction is not particularly critical so far as the solvent exercises no adverse influence upon 15 the reaction. Examples of the solvent which can be used include halogenated hydrocarbons such as methylene chloride, chloroform, carbon tetrachloride and the like; ethers such as tetrahydrofuran, diethyl ether and the like; alcohols such as methanol, ethanol, isopropyl 20 alcohol and the like; aromatic hydrocarbons such as toluene, benzene, xylene and the like; aliphatic hydrocarbons such as n-hexane, cyclohexane and the like; dimethyl sulfoxide, N,N-dimethylformamide, pyridine, water and the like. These solvents may be 25 used alone or in mixture of two or more. The reaction is carried out usually at a temperature ranging from -78°C to the reflux temperature of the used solvent and preferably at -78°C to 30°C, for a period of 30 minutes



to 24 hours.

The compound of general formula [1r] can be obtained by subjecting a compound of general formula [9] and a compound of general formula [1q] to a

5 Mitsunobu reaction.

This reaction is carried out by using, for example, an azodicarbonyl compound such as diethylazo dicarboxylate, azodicarbonyl dipiperidine or the like and a triaryl phosphine such as triphenyl phosphine or 10 the like or a trialkylphosphine such as tri-n-butyl phosphine or the like. The compound of general formula [9] is used in an amount of 1-5 mol and preferably 1-3 mol per mol of the compound of general formula [1q].

The solvent used in this reaction is not 15 particularly critical so far as the solvent exercises no adverse influence upon the reaction. Examples of the solvent which can be used include aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as dioxane, tetrahydrofuran, anisole, 20 diethylene glycol diethyl ether, dimethyl cellosolve and the like; esters such as methyl acetate, ethyl acetate and the like; nitriles such as acetonitrile and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; halogenated 25 hydrocarbons such as chloroform, methylene chloride and the like; and sulfoxides such as dimethyl sulfoxide and the like. These solvents may be used alone or in mixture of two or more. The reaction is carried out



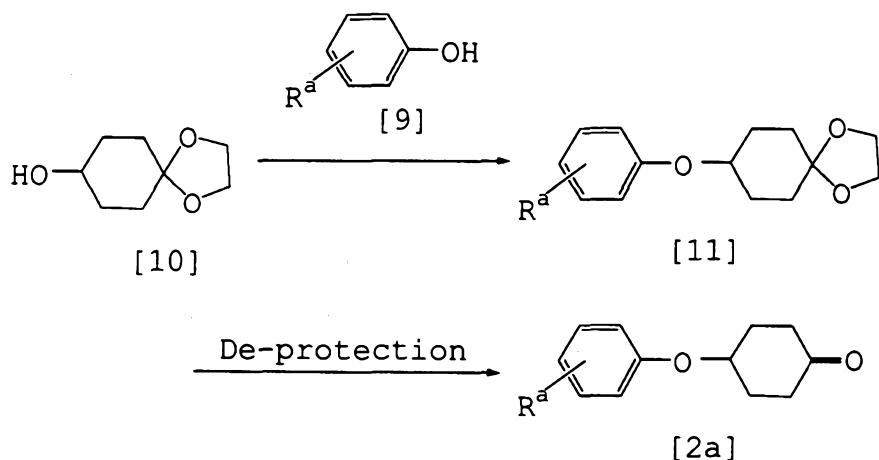
usually at -20°C to 120°C and preferably at 0°C to 30°C, for a period of 30 minutes to 24 hours.

The compounds of general formulas [1a], [1b], [1c], [1d], [1e], [1f], [1g], [1h], [1i], [1j], [1k], 5 [1l], [1la], [1m], [1ma], [1o], [1p], [1q] and [1r] which have been obtained in the above-mentioned manner can be converted to other compounds of general formula [1] by, for example, subjecting them to reactions known in themselves such as oxidation, reduction, 10 rearrangement, substitution, halogenation, dehydration, hydrolysis, etc. or appropriately combining these reactions. The compounds of general formula [1] or salts thereof thus obtained can be isolated and purified by the conventional procedures such as 15 extraction, crystallization and/or column chromatography, etc.

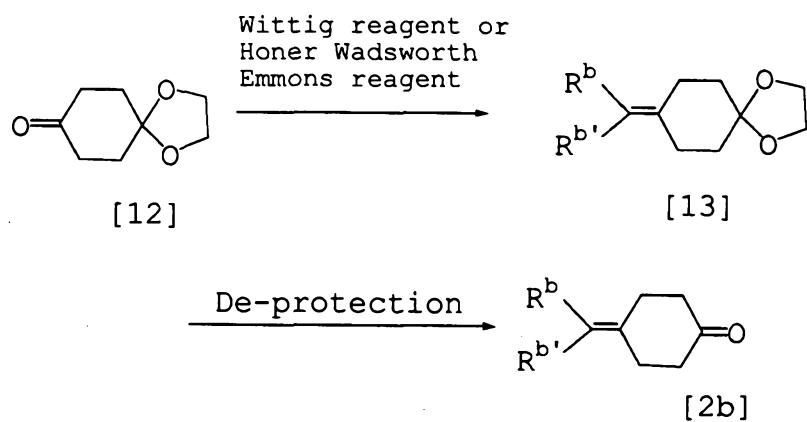
Next, the process for producing the compound of general formula [2] which is a starting material for producing the compound of the present invention will be 20 described. The compound of general formula [2] can be obtained by, for example, the following processes.



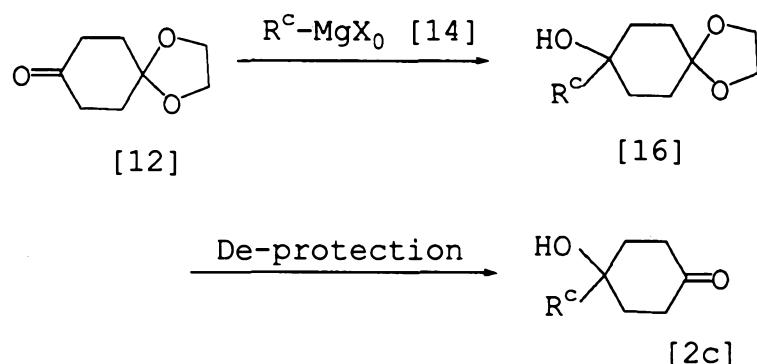
[Production Process A]



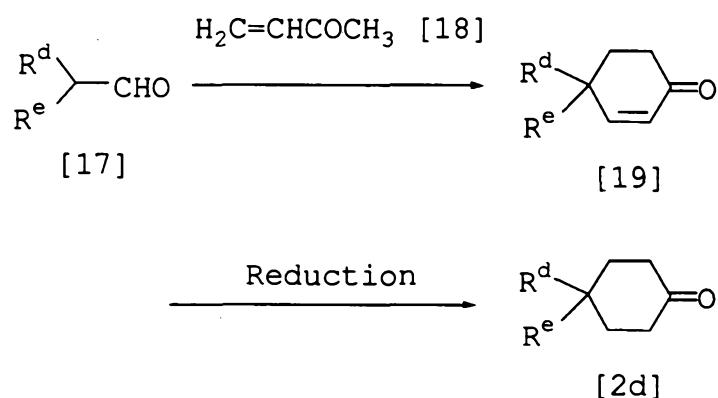
[Production Process B]



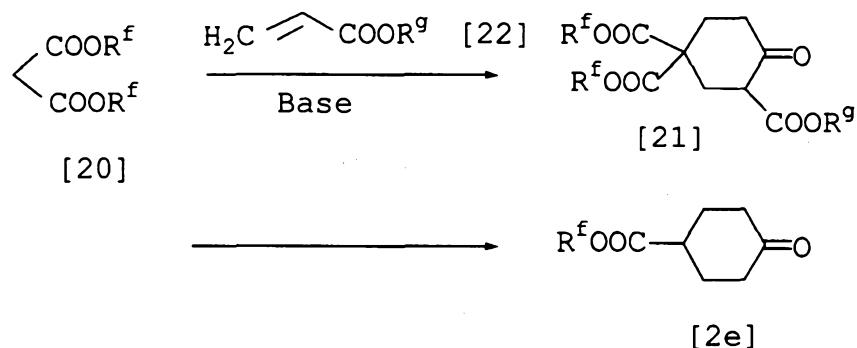
[Production Process C]



[Production Process D]



[Production Process E]



wherein R^a represents hydrogen atom, halogen atom, cyano group, nitro group, protected carboxyl group, protected hydroxyl group or an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, 5 aryloxy, acyl, alkoxycarbonyl, aryloxycarbonyl, carbamoyl, amino or heterocyclic group; R^b and R^{b'}, same or different, each represents hydrogen atom, halogen atom, cyano group, nitro group, an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl 10 or alkoxy group, protected amino group or an unprotected or protected carboxyl group; R^c represents an unsubstituted or substituted alkyl, alkenyl, cycloalkyl or aryl group; X₀ represents chlorine, bromine or iodine atom; R^d and R^e represent hydrogen 15 atom, an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl or aralkyl group; and R^f and R^g represent a protecting group for carboxyl group.

[Production Process A]

The compound of general formula [11] can be 20 obtained by subjecting a compound of general formula [9] and a compound of general formula [10] to a Mitsunobu reaction.

This reaction can be carried out by, for example, using an azodicarbonyl compound such as 25 diethylazo dicarboxylate, azodicarbonyl dipiperidine or the like and a triaryl phosphine such as triphenyl phosphine or the like or a trialkyl phosphine such as tri-n-butyl phosphine or the like. The compound of



general formula [9] is used in an amount of 1-5 mol and preferably 1-3 mol per mol of the compound of general formula [10].

The solvent used in this reaction is not particularly critical so far as the solvent exercises no adverse influence upon the reaction. Examples of the solvent which can be used include aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as dioxane, tetrahydrofuran, anisole, diethylene glycol diethyl ether, dimethyl cellosolve and the like; esters such as methyl acetate, ethyl acetate and the like; nitriles such as acetonitrile and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; halogenated hydrocarbons such as chloroform, methylene chloride and the like; and sulfoxides such as dimethyl sulfoxide and the like. These solvents may be used alone or in mixture of two or more. The reaction is carried out usually at -20°C to 120°C and preferably at 0°C to 30°C, for a period of 30 minutes to 24 hours.

The compound of general formula [2a] can be obtained by, for example, de-protecting a compound of general formula [11] in the presence of an acid. As the acid which can be used in this reaction, mineral acids such as hydrochloric acid, sulfuric acid, hydrobromic acid and the like; and organic acids such as paratoluenesulfonic acid and the like can be referred to, and the amount thereof is 1-50 mol and



preferably 5-20 mol per mol of the compound of general formula [11]. The solvent used in this reaction is not particularly critical so far as the solvent exercises no adverse influence upon the reaction. Examples of 5 the solvent which can be used include aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as dioxane, tetrahydrofuran, anisole, diethylene glycol diethyl ether, dimethyl cellosolve and the like; esters such as methyl acetate, ethyl 10 acetate and the like; nitriles such as acetonitrile and the like; alcohols such as methyl alcohol, ethyl alcohol, isopropyl alcohol and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; halogenated hydrocarbons such as chloroform, 15 methylene chloride and the like; water; and sulfoxides such as dimethyl sulfoxide and the like. These solvents may be used alone or in mixture of two or more. The reaction is carried out usually at 0-150°C and preferably at 25-120°C, for a period of 30 minutes 20 to 24 hours.

[Production Process B]

The compound of general formula [13] is obtained by reacting a compound of general formula [12] with Wittig reagent or Horner Wadsworth Emmons reagent.

25 More concretely speaking, the compound of formula [13] can be obtained by reacting a compound of general formula [12] with Wittig reagent which can be synthesized according to the method mentioned in



Organic Syntheses Collective Volume, Vol. 5, Pages 751-754 (1973) or Honer Wadsworth Emmons reagent which can be synthesized according to the method mentioned in Organic Syntheses Collective Volume, Vol. 5, Pages 509-513 (1973). The Wittig reagent and the Honer Wadsworth Emmons reagent are used in an amount of 0.5-5 mol and preferably 1-2 mol per mol of the compound of general formula [12]. The solvent used in this reaction is not particularly critical so far as the solvent exercises no adverse influence upon the reaction. Examples of the solvent which can be used include aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as dioxane, tetrahydrofuran, anisole, diethylene glycol diethyl ether, dimethyl cellosolve and the like; esters such as methyl acetate, ethyl acetate and the like; nitriles such as acetonitrile and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; halogenated hydrocarbons such as chloroform, methylene chloride and the like; and sulfoxides such as dimethyl sulfoxide and the like. These solvents may be used alone or in mixture of two or more. The reaction is carried out usually at -78°C to 120°C and preferably at -20°C to 30°C, for a period of 30 minutes to 24 hours. If desired, this reaction may be carried out in an atmosphere of inert gas such as argon or nitrogen.

The compound of general formula [2b] can be obtained by, for example, de-protecting a compound of



general formula [13] in the presence of an acid.

As the acid which can be used in this reaction, mineral acids such as hydrochloric acid, sulfuric acid, hydrobromic acid and the like, and 5 organic acids such as paratoluenesulfonic acid, methanesulfonic acid and the like can be referred, and the amount thereof is 1-50 mol and preferably 5-20 mol per mol of the compound of general formula [13]. The solvent used in this reaction is not particularly 10 critical so far as the solvent exercises no adverse influence upon the reaction. Examples of the solvent which can be used include aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as dioxane, tetrahydrofuran, anisole, diethylene glycol 15 diethyl ether, dimethyl cellosolve and the like; esters such as methyl acetate, ethyl acetate and the like; nitriles such as acetonitrile and the like; alcohols such as methyl alcohol, ethyl alcohol, isopropyl alcohol and the like; amides such as N,N- 20 dimethylformamide, N,N-dimethylacetamide and the like; halogenated hydrocarbons such as chloroform, methylene chloride and the like; water; and sulfoxides such as dimethyl sulfoxide and the like. These solvents may be used alone or in mixture of two or more. The reaction 25 is carried out usually at 0-150°C and preferably at 25-120°C, for a period of 30 minutes to 24 hours.

[Production Process C]

The compound of general formula [16] can be



obtained by, for example, subjecting a compound of general formula [12] and a compound of general formula [14] to Grignard reaction. The Grignard reagent used in this reaction can be synthesized according to the 5 method mentioned in Organic Syntheses Collective Volume, Vol. 5, Page 226 (1955). Examples of the Grignard reagent include alkylmagnesium halides such as methylmagnesium bromide and the like and arylmagnesium halides such as phenylmagnesium bromide and the like.

10 In this reaction, the compound of general formula [14] is used in an amount of 0.5-5 mol and preferably 0.8-2 mol per mol of the compound of general formula [12].

The solvent used in this reaction is not 15 particularly critical so far as the solvent exercises no adverse influence upon the reaction. Examples of the solvent which can be used include aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as dioxane, tetrahydrofuran, anisole, 20 diethylene glycol diethyl ether, dimethyl cellosolve and the like; halogenated hydrocarbons such as chloroform, methylene chloride and the like; and sulfoxides such as dimethyl sulfoxide and the like. These solvents may be used alone or in mixture of two 25 or more. The reaction is carried out usually at -20°C to 120°C and preferably at 0-70°C for a period of 30 minutes to 24 hours. If desired, this reaction may be carried out in an atmosphere of inert gas such as argon



or nitrogen.

The compound of general formula [2c] can be obtained by, for example, de-protecting a compound of general formula [16] in the presence of an acid. As 5 the acid which can be used in this reaction, mineral acids such as hydrochloric acid, sulfuric acid, hydrobromic acid and the like, and organic acids such as paratoluenesulfonic acid, methanesulfonic acid and the like can be referred to, and the amount thereof is 10 1-50 mol and preferably 5-20 mol per mol of the compound of general formula [16]. The solvent used in this reaction is not particularly critical so far as the solvent exercises no adverse influence upon the reaction. Examples of the solvent which can be used 15 include aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as dioxane, tetrahydrofuran, anisole, diethylene glycol diethyl ether, dimethyl cellosolve and the like; esters such as methyl acetate, ethyl acetate and the like; nitriles 20 such as acetonitrile and the like; alcohols such as methyl alcohol, ethyl alcohol, isopropyl alcohol and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; halogenated hydrocarbons such as chloroform, methylene chloride and 25 the like; water; and sulfoxides such as dimethyl sulfoxide and the like. These solvents may be used alone or in mixture of two or more. The reaction is carried out usually at 0-150°C and preferably at 25-



120°C, for a period of 30 minutes to 24 hours.

[Production Process D]

The compound of general formula [19] can be obtained by, for example, the process mentioned in J.

5 Org. Chem., Vol. 45, Pages 5399-5400 (1980), etc. More concretely speaking, it can be obtained by subjecting a compound of general formula [17] and a compound of general formula [18] to Robinson cyclization reaction. The compound of general formula [18] is used in an 10 amount of 1-10 mol and preferably 2-4 mol per mol of the compound of general formula [17].

The reagent used in this reaction is, for example, an aldehyde such as isobutylaldehyde, cyclohexylaldehyde, 2-phenylpropionaldehyde and the 15 like and a ketone such as methyl vinyl ketone, 3-penten-2-one and the like. The solvent used in this reaction is not particularly critical so far as the solvent exercises no adverse influence upon the reaction. Examples of the solvent which can be used 20 include aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as dioxane, tetrahydrofuran, anisole, diethylene glycol diethyl ether, dimethyl cellosolve and the like; esters such as methyl acetate, ethyl acetate and the like; nitriles 25 such as acetonitrile and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; halogenated hydrocarbons such as chloroform, methylene chloride and the like; and sulfoxides such as dimethyl



sulfoxide and the like. These solvents may be used alone or in mixture of two or more. The reaction is carried out usually at -20°C to 150°C and preferably at 0-120°C, for a period of 30 minutes to 24 hours.

5 The compound of general formula [2d] can be obtained by, for example, reducing a compound of general formula [19]. This reaction may be carried out according to the conventional method for reducing carbon-carbon double bonds, for example, by the method 10 of catalytic reduction using palladium-carbon, Raney nickel or platinum catalyst.

 In the case of using a palladium-carbon catalyst, the catalyst is used in an amount of 0.01-1 time (w/w) and preferably 0.05-0.2 time (w/w) as much 15 as the amount of the compound of general formula [19]. The solvent used in this reaction is not particularly critical so far as the solvent exercises no adverse influence upon the reaction. Examples of the solvent which can be used include aromatic hydrocarbons such as 20 benzene, toluene, xylene and the like; ethers such as dioxane, tetrahydrofuran, anisole, diethylene glycol diethyl ether, dimethyl cellosolve and the like; esters such as methyl acetate, ethyl acetate and the like; nitriles such as acetonitrile and the like; alcohols 25 such as methyl alcohol, ethyl alcohol, isopropyl alcohol and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; water; acetic acid, etc. These solvents may be used



alone or in mixture of two or more. The reaction is carried out usually at -20°C to 120°C under normal pressure or elevated pressure, and preferably at 25-50°C, for a period of 30 minutes to 24 hours.

5 [Production Process E]

It is also possible to obtain the compound of general formula [21] according to the method mentioned in SYNTHETIC COMMUNICATIONS, Vol. 15, Pages 141-149 (1985). More concretely speaking, it can be obtained 10 by subjecting a compound of general formula [20] and twice or more molar quantity, per mol of compound [20], of an acrylic ester represented by general formula [22] to Diekman condensation reaction. The solvent used in this reaction is not particularly critical so far as 15 the solvent exercises no adverse influence upon the reaction. Examples of the solvent which can be used include aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as dioxane, tetrahydrofuran, anisole, diethylene glycol diethyl 20 ether, dimethyl cellosolve and the like; esters such as methyl acetate, ethyl acetate and the like; nitriles such as acetonitrile and the like; and amides such as N,N-dimethylformamide, N,N-dimethylacetamide and the like. These solvents may be used alone or in mixture 25 of two or more. This reaction is carried out usually at -20°C to 150°C and preferably at 25-100°C, for a period of 30 minutes to 24 hours. If desired, the reaction may be carried out in an atmosphere of an



inert gas such as argon or nitrogen.

The compound of general formula [2e] can be obtained by, for example, subjecting a compound of general formula [21] to a de-carboxylation reaction.

5 The reagents used in this reaction are lithium chloride, lithium iodide, sodium chloride, pyridine and the like. The solvent used in this reaction is not particularly critical so far as the solvent exercises no adverse influence upon the reaction. Examples of 10 the solvent which can be used include aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as dioxane, tetrahydrofuran, anisole, diethylene glycol diethyl ether, dimethyl cellosolve and the like; esters such as methyl acetate, ethyl 15 acetate and the like; nitriles such as acetonitrile and the like; alcohols such as methyl alcohol, ethyl alcohol, isopropyl alcohol and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; water; acetic acid; and the like. These solvents 20 may be used alone or in mixture of two or more. This reaction is carried out usually at 25°C to 250°C and preferably at 100-190°C, for a period of 30 minutes to 24 hours.

Next, the processes for producing the 25 compounds of the present invention will be explained.

In the production processes mentioned above, the compounds of general formulas [2], [3], [4], [5], [6], [7], [8], [9], [10], [11], [12], [13], [14], [16],



[17], [18], [19], [20], [21], [22], [24], [25], [26], [26a], [26b], [1a], [1b], [1c], [1f], [1g], [1i], [1k], [1l], [1la], [1m], [1ma], [1o], [1p], [1q], [1r], [2a], [2b], [2c], [2d] and [2e] can be put to use in the form 5 of salts thereof, too. As salts thereof, the same salts as mentioned in the paragraph of the salts of compound of general formula [1] can be used.

In the production processes mentioned above, the compounds of general formulas [2], [3], [4], [5], 10 [6], [7], [8], [9], [10], [11], [12], [13], [14], [16], [17], [18], [19], [20], [21], [22], [24], [25], [26], [26a], [26b], [1a], [1b], [1c], [1f], [1g], [1i], [1k], [1l], [1la], [1m], [1ma], [1o], [1p], [1q], [1r], [2a], [2b], [2c], [2d] and [2e] can have isomers such as 15 optical isomers, geometrical isomers and tautomers. In such cases, these isomers can also be used in the present invention. Further, solvated products, hydrates, and various crystal forms of these compounds can also be used. Further, in the compounds of [2], [3], [4], [5], [6], [7], [8], [9], [10], [11], [12], 20 [13], [14], [16], [17], [18], [19], [20], [21], [22], [24], [25], [26], [26a], [26b], [1a], [1b], [1c], [1f], [1g], [1i], [1k], [1l], [1la], [1m], [1ma], [1o], [1p], [1q], [1r], [2a], [2b], [2c], [2d] and [2e], some of 25 the compounds can have an amino group, a hydroxyl group or a carboxyl group. It is also possible to protect these groups previously with conventional protecting groups and, after the reaction, to eliminate these

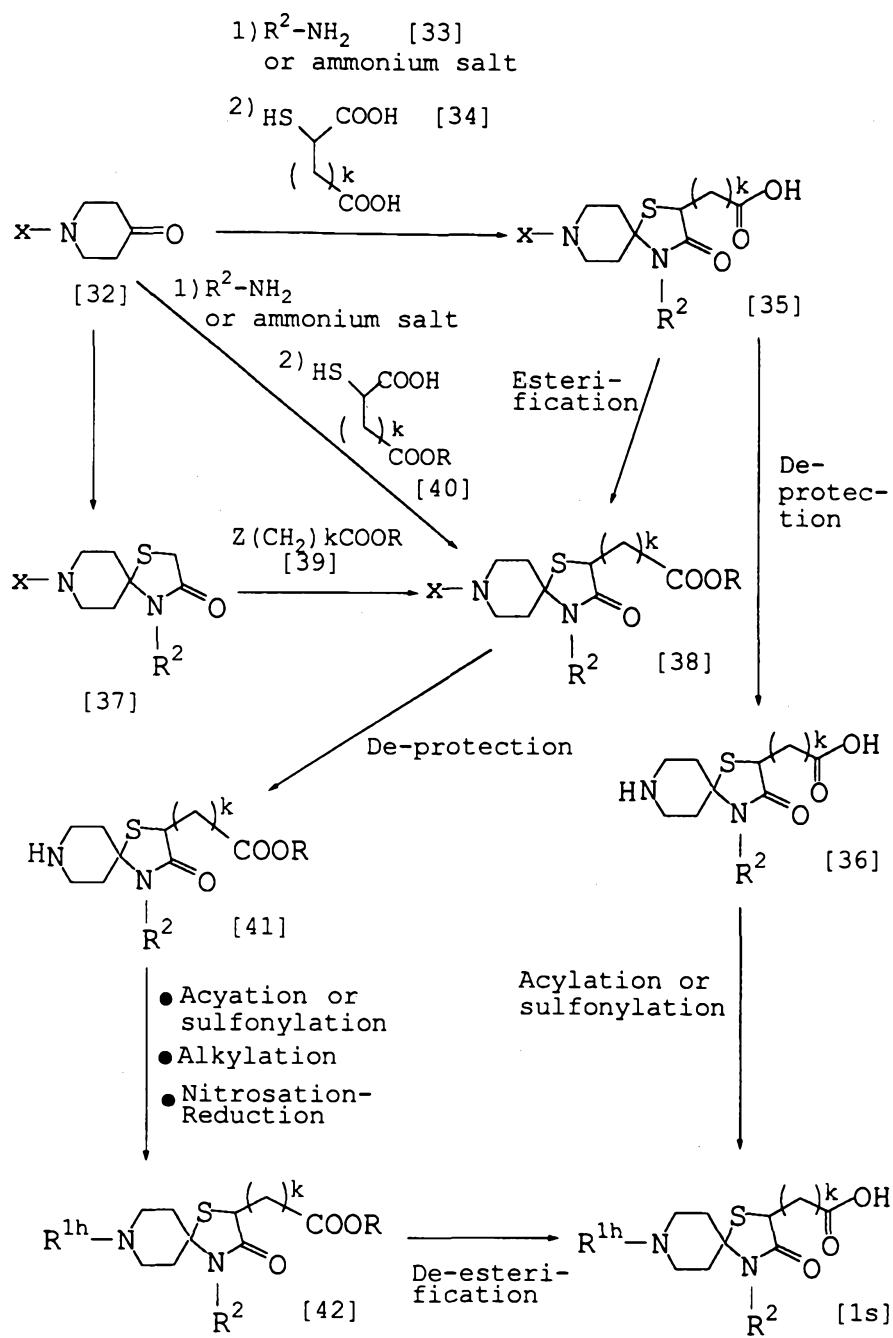


protecting groups according to the methods known in themselves.

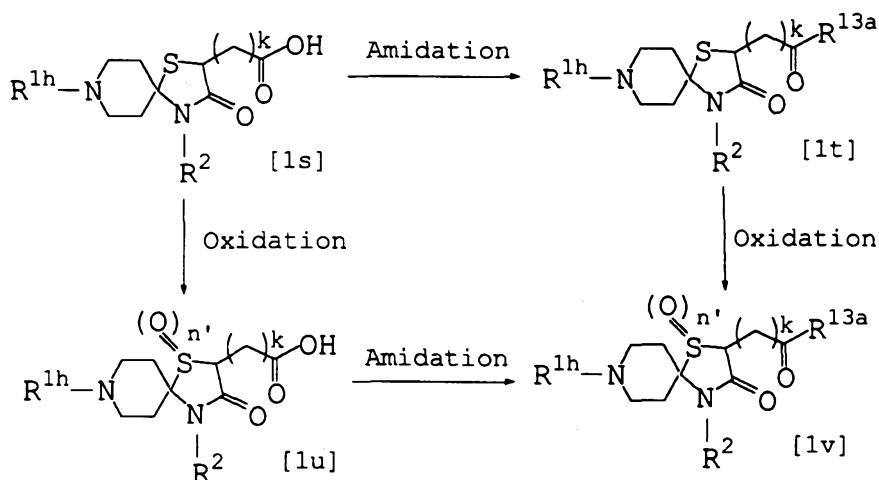
In cases where the compound of the present invention is a 1-thia-4,8-diazaspiro[4.5]decane derivative, such a compound can be synthesized according to the Production Processes 3 and 4 mentioned below, for example:



[Production Process 3]



[Production Process 4]

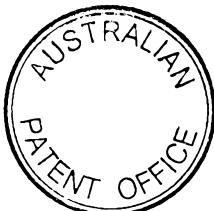


wherein R^{1h}, R², k and n' are as defined above; R^{13a} represents an unprotected or protected amino, alkylamino, arylamino, acylamino, alkoxy carbonylamino, arylsulfonylamino or alkylsulfonylamino group; R 5 represents a protecting group for carboxyl group; X represents a protecting group for amino group; and Z represents halogen atom, alkylsulfonyloxy group or arylsulfonyloxy group.

The compound of general formula [35] can be 10 obtained by, for example, the process mentioned in Yakugaku Zasshi, Vol. 91, No. 3, Pages 363-383 (1971), or the like. More concretely speaking, it can be obtained by reacting a compound of general formula [32] with an amine represented by general formula [33] or an ammonium salt and a compound represented by general formula [34] in the presence or absence of a

dehydrating agent and/or a catalyst, and subjecting the reaction product to a dehydrating ring closure.

As the amine represented by general formula [33] or the ammonium salt which can be used in this reaction, for example, primary amines such as methylamine, benzylamine, aniline, phenethylamine or the like, amino acids such as leucine, asparagine, aspartic acid, β -alanine or the like, and ammonium salts such as ammonium carbonate, ammonium sulfate and the like can be referred to. The amine of general formula [33] or the ammonium salt is used in an amount of 1-10 mol and preferably 1-2 mol per mol of the compound of general formula [32]. The compound of general formula [34] is used in an amount of 1-10 mol and preferably 1-2 mol per mol of the compound of general formula [32]. As the dehydrating agent which can be used according to the need, zeolam, molecular sieve, calcium chloride, magnesium sulfate, diphosphorus pentoxide and the like can be referred to, and the amount thereof is 1-10 times (w/w) and preferably 1-2 times (w/w) as much as the weight of the compound of general formula [32]. As the catalyst which can be used according to the need, paratoluenesulfonic acid, benzenesulfonic acid, hydrochloric acid, sulfuric acid and the like can be referred to, and the amount thereof is 0.001-3 mol and preferably 0.01-0.1 mol per mol of the compound of general formula [32]. The solvent used in this



reaction is not particularly critical so far as the solvent exercises no adverse influence upon the reaction. Examples of the solvent which can be used include aromatic hydrocarbons such as benzene, toluene, 5 xylene and the like; ethers such as dioxane, tetrahydrofuran, anisole, diethylene glycol diethyl ether, dimethyl cellosolve and the like; esters such as methyl acetate, ethyl acetate and the like; nitriles such as acetonitrile and the like; alcohols such as 10 methyl alcohol, ethyl alcohol, isopropyl alcohol and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; halogenated hydrocarbons such as chloroform, methylene chloride and the like; and sulfoxides such as dimethyl sulfoxide and 15 the like. These solvents may be used alone or in mixture of two or more. This reaction is carried out usually at 0-150°C and preferably at 25-120°C for a period of 30 minutes to 24 hours. If desired, this reaction may be carried out in an atmosphere of inert 20 gas such as argon or nitrogen.

It is also possible to obtain the compound of general formula [36] by de-protecting a compound of general formula [35] in the presence or absence of an acid or a base.

25 As the acid which may be used in this reaction according to the need, hydrochloric acid, sulfuric acid, acetic acid, trifluoroacetic acid, paratoluenesulfonic acid and the like can be referred



to, and the amount thereof is 1-50 mol and preferably 10-30 mol per mol of the compound of general formula [35]. As the base which may be used in this reaction according to the need, organolithium compounds such as

5 n-butyllithium, phenyllithium, lithium diisopropylamine and the like; alkali metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide and the like; alkali metal hydrides such as sodium hydride, potassium hydride and the like; alkali metal carbonates such as potassium carbonate, sodium carbonate and the like; and alkali hydroxides such as sodium hydroxide, potassium hydroxide and the like can be referred to, and the amount thereof is 1-50 mol and preferably 10-30 mol per mol of the compound of general formula [35].

15 The solvent used in this reaction is not particularly critical so far as the solvent exercises no adverse influence upon the reaction. Examples of the solvent which can be used include aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as

20 dioxane, tetrahydrofuran, anisole, diethylene glycol diethyl ether, dimethyl cellosolve and the like; nitriles such as acetonitrile and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; halogenated hydrocarbons such as chloroform,

25 methylene chloride and the like; water; and sulfoxides such as dimethyl sulfoxide and the like. These solvents may be used alone or in mixture of two or more. This reaction is carried out usually at 0-150°C



and preferably at 25-110°C for a period of 30 minutes to 24 hours.

The compound of general formula [1s] is obtained by, for example, subjecting a compound of 5 general formula [36] to an acylation reaction or sulfonylation reaction in the presence or absence of a base.

As the acylating agent which can be used in this reaction, for example, acetic anhydride, acetyl 10 chloride, benzoyl chloride, 4-isopropylbenzoyl chloride, ethylsuccinyl chloride and the like can be referred to. As the sulfonylating agent, methanesulfonyl chloride, benzenesulfonyl chloride and the like can be referred to. The amounts of said 15 acylating agent and sulfonylating agent are 1-20 mol and preferably 2-6 mol per mol of the compound of general formula [36]. As the base which may be used according to the need, organic amines such as dimethylaminopyridine, triethylamine, pyridine and the 20 like and alkali metal carbonates such as potassium carbonate, sodium carbonate and the like can be referred to, and the amount thereof is 0.5-10 mol and preferably 2-4 mol per mol of the compound of general formula [36]. The solvent used in this reaction is not 25 particularly critical so far as the solvent exercises no adverse influence upon the reaction. Examples of the solvent which can be used include aromatic hydrocarbons such as benzene, toluene, xylene and the



like; ethers such as dioxane, tetrahydrofuran, anisole, diethylene glycol diethyl ether, dimethyl cellosolve and the like; esters such as methyl acetate, ethyl acetate and the like; nitriles such as acetonitrile and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; halogenated hydrocarbons such as chloroform, methylene chloride and the like; and sulfoxides such as dimethyl sulfoxide and the like. These solvents may be used alone or in mixture of two or more. The reaction is carried out usually at -20°C to 150°C and preferably at 0-120°C, for a period of 30 minutes to 24 hours.

The compound of general formula [37] can be obtained by, for example, the process mentioned in 15 Yakugaku Zasshi, Vol. 91, No. 3, pages 363-383 (1971). More concretely speaking, it can be obtained by reacting a compound of general formula [32] with an amine represented by general formula [33] or an ammonium salt and mercaptoacetic acid in the presence 20 or absence of a dehydrating agent and/or a catalyst, and subjecting the product to a dehydrating ring closure.

As the amines represented by general formula [33] which can be used in this reaction, primary amines 25 such as methylamine, benzylamine, aniline, phenethylamine or the like and amino acids such as leucine, asparagine, aspartic acid, β -alanine or the like can be referred to. As the ammonium salts,



ammonium carbonate, ammonium sulfate and the like can be referred to. The amine of general formula [33] or the ammonium salt is used in an amount of 1-10 mol and preferably 1-2 mol per mol of the compound of general formula [32]. The mercaptoacetic acid is used in amount of 1-10 mol and preferably 1-2 mol per mol of the compound of general formula [32]. As the dehydrating agent which can be used according to the need, zeolam, molecular sieve, calcium chloride, magnesium sulfate, diphosphorus pentoxide and the like can be referred to, and the amount thereof is 1-10 times (w/w) and preferably 1-2 times (w/w) as much as the weight of the compound of general formula [32]. As the catalyst which can be used according to the need, paratoluene-15 sulfonic acid, benzenesulfonic acid, hydrochloric acid, sulfuric acid and the like can be referred to, and the amount thereof is 0.001-3 mol and preferably 0.01-0.1 mol per mol of the compound of general formula [32]. The solvent used in this reaction is not particularly critical so far as the solvent exercises no adverse influence upon the reaction. Examples of the solvent which can be used include aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as dioxane, tetrahydrofuran, anisole, diethylene glycol 20 diethyl ether, dimethyl cellosolve and the like; esters such as methyl acetate, ethyl acetate and the like; nitriles such as acetonitrile and the like; alcohols such as methyl alcohol, ethyl alcohol, isopropyl



alcohol and the like; amides such as N,N-dimethyl-formamide, N,N-dimethylacetamide and the like; halogenated hydrocarbons such as chloroform, methylene chloride and the like; and sulfoxides such as dimethyl 5 sulfoxide and the like. These solvents may be used alone or in mixture of two or more. This reaction is carried out usually at 0-150°C and preferably at 25-120°C for a period of 30 minutes to 24 hours. If desired, this reaction may be carried out in an 10 atmosphere of inert gas such as argon or nitrogen.

The compound of general formula [38] can be obtained by, for example, reacting a compound of general formula [37] with a compound of general formula [39] in the presence of a base. As the base used in 15 this reaction, for example, there can be referred to organolithium compounds such as n-butyllithium, phenyllithium, lithium diisopropylamide and the like; alkali metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide and the like; alkali 20 metal hydrides such as sodium hydride, potassium hydride and the like; alkali metal carbonates such as potassium carbonate, sodium carbonate and the like; alkali hydroxides such as sodium hydroxide, potassium hydroxide and the like; etc. The base is used in an 25 amount of 1-5 mol per mol of the compound of general formula [37]. The compound of general formula [39] is used in an amount of 1-10 mol and preferably 1-2 mol per mol of the compound of general formula [37]. The



solvent used in this reaction is not particularly critical so far as the solvent exercises no adverse influence upon the reaction. Examples of the solvent which can be used include aromatic hydrocarbons such as

5 benzene, toluene, xylene and the like; ethers such as dioxane, tetrahydrofuran, anisole, diethylene glycol diethyl ether, dimethyl cellosolve and the like; nitriles such as acetonitrile and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide and the

10 like; halogenated hydrocarbons such as chloroform, methylene chloride and the like; and sulfoxides such as dimethyl sulfoxide and the like. These solvents may be used alone or in mixture of two or more. This reaction is carried out usually at -78°C to 150°C and preferably

15 at -50°C to 120°C, for a period of 30 minutes to 24 hours. If desired, the reaction may be carried out in an atmosphere of inert gas such as argon or nitrogen.

It is also possible to obtain the compound of general formula [38] by the process mentioned in

20 Yakugaku Zasshi, Vol. 91, No. 3, Pages 363-383 (1971), or the like. More concretely speaking, it can be obtained by reacting a compound of general formula [32] in the presence or absence of a dehydrating agent and/or a catalyst with an amine represented by general

25 formula [33] or an ammonium salt and a compound represented by general formula [40] which can be synthesized according to the method mentioned in SYNTHETIC COMMUNICATIONS, Vol. 21, No. 2, Pages 249-263



(1991) or the like and subjecting the product to a dehydrating ring closure.

As the amine represented by general formula [33] used in this reaction, primary amines such as 5 methylamine, benzylamine, aniline, phenethylamine and the like and amino acids such as leucine, asparagine, aspartic acid, β -alanine and the like can be referred to. As the ammonium salt, ammonium carbonate, ammonium sulfate and the like can be referred to. The amine of 10 general formula [33] or the ammonium salt is used in an amount of 1-10 mol and preferably 1-2 mol per mol of the compound of general formula [32]. The compound of general formula [40] is used in an amount of 1-10 mol and preferably 1-2 mol per mol of the compound of 15 general formula [32]. As the dehydrating agent, for example, zeolam, molecular sieve, calcium chloride, magnesium sulfate, diphosphorus pentoxide and the like can be referred to, and the amount thereof is 1-10 times (w/w) and preferably 1-2 times (w/w) as much as 20 the amount of the compound of general formula [32]. As the catalyst which can be used according to the need, paratoluenesulfonic acid, benzenesulfonic acid, hydrochloric acid, sulfuric acid and the like can be referred to, and the amount thereof is 0.001-3 mol and 25 preferably 0.01-0.1 mol per mol of the compound of general formula [32]. The solvent used in this reaction is not particularly critical so far as the solvent exercises no adverse influence upon the



reaction. Examples of the solvent which can be used include aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as dioxane, tetrahydrofuran, anisole, diethylene glycol diethyl 5 ether, dimethyl cellosolve and the like; esters such as methyl acetate, ethyl acetate and the like; nitriles such as acetonitrile and the like; alcohols such as methyl alcohol, ethyl alcohol, isopropyl alcohol and the like; amides such as N,N-dimethylformamide, N,N-10 dimethylacetamide and the like; halogenated hydrocarbons such as chloroform, methylene chloride and the like; and sulfoxides such as dimethyl sulfoxide and the like. These solvents may be used alone or in mixture of two or more. This reaction is carried out 15 usually at 0-150°C and preferably at 25-120°C for a period of 30 minutes to 24 hours. If desired, the reaction may be carried out in an atmosphere of inert gas such as argon or nitrogen.

Further, it is also possible to obtain the 20 compound of general formula [38] by subjecting a compound of general formula [35] to an esterification reaction.

This reaction may be a usual esterification reaction, such as a method via an acid chloride, a 25 method via an acid anhydride, a method using a base and an alkyl halide, a method using a condensing agent and an additive, etc. In a case where a base and an alkyl halide are used, the base which can be used include



organic amines such as dimethylaminopyridine, triethylamine, pyridine, N-methylmorpholine and the like; alkali metal carbonates such as potassium carbonate, sodium carbonate and the like; etc. The 5 amount of the base is 0.5-10 mol and preferably 1-3 mol per mol of the compound of general formula [35]. As the alkyl halide which can be used in this reaction, methyl iodide, ethyl iodide, benzyl bromide and the like can be referred to, and the amount thereof is 0.5-10 mol and preferably 1-3 mol per mol of the compound of general formula [35]. The solvent used in this reaction is not particularly critical so far as the solvent exercises no adverse influence upon the reaction. Examples of the solvent which can be used 15 include aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as dioxane, tetrahydrofuran, anisole, diethylene glycol diethyl ether, dimethyl cellosolve and the like; esters such as methyl acetate, ethyl acetate and the like; nitriles such as acetonitrile and the like; amides such as N,N-dimethylformamide and the like; halogenated hydrocarbons such as chloroform, methylene chloride and the like; and sulfoxides such as dimethyl sulfoxide and the like. These solvents may be used alone or in mixture 20 of two or more. The reaction is carried out usually at 0-200°C and preferably at 25-150°C, for a period of 10 minutes to 24 hours. In a case where a condensing agent and an additive are used, the objective compound 25



can be obtained by subjecting an alcohol such as ethanol, benzyl alcohol, tert-butanol or the like to a condensation reaction with a condensing agent and an additive. As the condensing agent used in this reaction, for example, dicyclohexyl carbodiimide, diisopropyl carbodiimide, N-ethyl-N'-3-dimethylamino-propyl carbodiimide, diphenyl phosphoryl azide and the like can be referred to. As the additive used in this reaction, for example, 1-hydroxybenzotriazole, N-10 hydroxysuccinimide and the like can be referred to.

The alcohol, condensing agent and additive used in this reaction are used each in an amount of 0.5-10 mol and preferably 1-3 mol per mol of the compound of general formula [35]. The solvent used in this reaction is not 15 particularly critical so far as the solvent exercises no adverse influence upon the reaction. Examples of the solvent which can be used include aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as dioxane, tetrahydrofuran, anisole, 20 diethylene glycol diethyl ether, dimethyl cellosolve and the like; esters such as methyl acetate, ethyl acetate and the like; nitriles such as acetonitrile and the like; amides such as N,N-dimethylformamide and the like; halogenated hydrocarbons such as chloroform, 25 methylene chloride and the like; and sulfoxides such as dimethyl sulfoxide and the like. These solvents may be used alone or in mixture of two or more. The reaction is carried out usually at 0-200°C and preferably at 25-



150°C, for a period of 10 minutes to 24 hours.

The compound of general formula [41] can be obtained by de-protecting a compound of general formula [38] in the presence or absence of an acid or a base.

5 As the acid which may be used in this reaction according to the need, hydrochloric acid, sulfuric acid, acetic acid, trifluoroacetic acid, paratoluenesulfonic acid and the like can be referred to, and the amount thereof is 1-50 mol and preferably 10 10-30 mol per mol of the compound of general formula [38]. As the base which may be used in this reaction according to the need, organolithium compounds such as n-butyllithium, phenyllithium, lithium diisopropylamide and the like; alkali metal alkoxides such as sodium 15 methoxide, sodium ethoxide, potassium tert-butoxide and the like; alkali metal hydrides such as sodium hydride, potassium hydride and the like; alkali metal carbonates such as potassium carbonate, sodium carbonate and the like; and alkali hydroxides such as sodium hydroxide, 20 potassium hydroxide and the like can be referred to, and the amount thereof is 1-50 mol and preferably 1-30 mol per mol of the compound of general formula [38].

In a case where X is a tert-butyloxycarbonyl group and R is an ethyl group, the acids which can be 25 used are hydrochloric acid, sulfuric acid, trifluoroacetic acid and the like, and the amount thereof is 1-50 mol and preferably 10-30 mol per mol of the compound of general formula [38]. In a case where



X is a 9-fluorenylmethoxycarbonyl group and R is a tert-butyl group, the bases which can be used are piperidine, morpholine, dimethylaminopyridine and the like, and the amount thereof is 1-30 mol and preferably 5 1-5 mol per mol of the compound of general formula [38]. The solvent used in this reaction is not particularly critical so far as the solvent exercises no adverse influence upon the reaction. Examples of the solvent which can be used include aromatic 10 hydrocarbons such as benzene, toluene, xylene and the like; ethers such as dioxane, tetrahydrofuran, anisole, diethylene glycol diethyl ether, dimethyl cellosolve and the like; esters such as methyl acetate, ethyl acetate and the like; nitriles such as acetonitrile and 15 the like; alcohols such as methyl alcohol, ethyl alcohol, isopropyl alcohol and the like; amides such as N,N-dimethylformamide and the like; halogenated hydrocarbons such as chloroform, methylene chloride and the like; water; and sulfoxides such as dimethyl 20 sulfoxide and the like. These solvents may be used alone or in mixture of two or more. This reaction is carried out usually at 0-200°C and preferably at 20-70°C for a period of 10 minutes to 5 hours.

The compound of general formula [42] can be 25 obtained by, for example, subjecting a compound of general formula [41] to an acylation reaction or a sulfonylation reaction in the presence or absence of a base.



As the acylating agent which can be used in this reaction, for example, acetic anhydride, acetyl chloride, benzoyl chloride, ethylsuccinyl chloride and the like can be referred to. As the sulfonylating agent, methanesulfonyl chloride, benzenesulfonyl chloride and the like can be referred to. The amount of said acylating agent and sulfonylating agent is each 0.5-10 mol and preferably 1-3 mol per mol of the compound of general formula [41]. As the base used in this reaction, organic amines such as dimethylamino-pyridine, triethylamine, pyridine and the like and alkali metal carbonates such as potassium carbonate, sodium carbonate and the like can be referred to, and the amount thereof is 0.5-10 mol and preferably 1-3 mol per mol of the compound of general formula [41]. The solvent used in this reaction is not particularly critical so far as the solvent exercises no adverse influence upon the reaction. Examples of the solvent which can be used include aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as dioxane, tetrahydrofuran, anisole, diethylene glycol diethyl ether, dimethyl cellosolve and the like; esters such as methyl acetate, ethyl acetate and the like; nitriles such as acetonitrile and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; halogenated hydrocarbons such as chloroform, methylene chloride and the like; and sulfoxides such as dimethyl sulfoxide and the like. These solvents may be



used alone or in mixture of two or more. The reaction is carried out usually at -20°C to 150°C and preferably at 0-120°C, for a period of 30 minutes to 24 hours.

The compound of general formula [42] can be obtained by, for example, subjecting a compound of general formula [41] to an alkylation reaction in the presence of a base. As the alkylating agent which can be used in this reaction, for example, methyl iodide, benzyl bromide and the like can be referred to, and the amount thereof is 1-20 mol and preferably 1-4 mol per mol of the compound of general formula [41]. As the base used in this reaction, organic amines such as dimethylaminopyridine, triethylamine, pyridine and the like and alkali metal carbonates such as potassium carbonate, sodium carbonate and the like can be referred to, and the amount thereof is 2-20 mol and preferably 2-4 mol per mol of the compound of general formula [41]. The solvent used in this reaction is not particularly critical so far as the solvent exercises no adverse influence upon the reaction. Examples of the solvent which can be used include aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as dioxane, tetrahydrofuran, anisole, diethylene glycol diethyl ether, dimethyl cellosolve and the like; esters such as methyl acetate, ethyl acetate and the like; nitriles such as acetonitrile and the like; alcohols such as methyl alcohol, ethyl alcohol, isopropyl alcohol and the like; amides such as



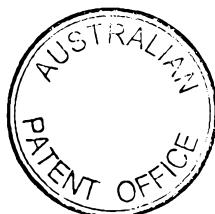
N,N-dimethylformamide and the like; halogenated hydrocarbons such as chloroform, methylene chloride and the like; and sulfoxides such as dimethyl sulfoxide and the like. These solvents may be used alone or in 5 mixture of two or more. The reaction is carried out usually at 0-200°C and preferably at 25-150°C, for a period of 10 minutes to 24 hours.

The compound of general formula [42] can be obtained by, subjecting a compound of general formula 10 [41] to a nitrosation reaction in the presence of a base and then reducing the product. The nitrosation reaction can be carried out according to the procedure mentioned in Organic Syntheses Collective Volume, Vol. 2, Page 211 (1943). As the nitrosating agent, for 15 example, nitrous acid and the like can be used. The nitrosating agent is used in an amount of 1-10 mol and preferably 1-4 mol per mol of the compound of general formula [41]. The solvent used in this reaction is not particularly critical so far as the solvent exercises 20 no adverse influence upon the reaction. Examples of the solvent which can be used include aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as dioxane, tetrahydrofuran, anisole, diethylene glycol diethyl ether, dimethyl cellosolve 25 and the like; esters such as methyl acetate, ethyl acetate and the like; nitriles such as acetonitrile and the like; alcohols such as methyl alcohol, ethyl alcohol, isopropyl alcohol and the like; amides such as



N,N-dimethylformamide and the like; halogenated hydrocarbons such as chloroform, methylene chloride and the like; water; and sulfoxides such as dimethyl sulfoxide and the like. These solvents may be used 5 alone or in mixture of two or more. The reaction is carried out usually at 0-200°C and preferably at 0-100°C, for a period of 10 minutes to 24 hours.

The reduction as a subsequent step can be carried out according to the description of Organic 10 Syntheses Collective Volume, Vol. 2., Page 211 (1943). That is, the objective product can be obtained by reacting the nitroso compound synthesized from the compound of general formula [41] with a reductant such as zinc powder. The solvent used in this reaction is 15 not particularly critical so far as the solvent exercises no adverse influence upon the reaction. Examples of the solvent which can be used include aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as dioxane, tetrahydrofuran, 20 anisole, diethylene glycol diethyl ether, dimethyl cellosolve and the like; esters such as methyl acetate, ethyl acetate and the like; nitriles such as acetonitrile and the like; alcohols such as methyl alcohol, ethyl alcohol, isopropyl alcohol and the like; 25 amides such as N,N-dimethylformamide and the like; halogenated hydrocarbons such as chloroform, methylene chloride and the like; water; and acetic acid. These solvents may be used alone or in mixture of two or



more. The reaction is carried out usually at 0-200°C and preferably at 0-100°C, for a period of 30 minutes to 24 hours.

The compound of general formula [1s] can be
5 obtained by, for example, subjecting a compound of
general formula [42] to a de-esterification reaction in
the presence or absence of an acid or a base.

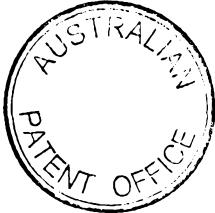
As the acid which can be used in this
reaction according to the need, for example,
10 hydrochloric acid, sulfuric acid, acetic acid,
trifluoroacetic acid, paratoluenesulfonic acid and the
like can be referred to. The amount thereof is 1-50
mol and preferably 10-30 mol per mol of the compound of
general formula [42]. As the base used in this
15 reaction according to the need, for example, there can
be referred to organolithium compounds such as n-
butyllithium, phenyllithium, lithium diisopropylamide
and the like; alkali metal alkoxides such as sodium
methoxide, sodium ethoxide, potassium tert-butoxide and
20 the like; alkali metal hydrides such as sodium hydride,
potassium hydride and the like; alkali metal carbonates
such as potassium carbonate, sodium carbonate and the
like; alkali hydroxides such as sodium hydroxide,
potassium hydroxide and the like; etc. The base is
25 used in an amount of 1-50 mol and preferably 10-30 mol
per mol of the compound of general formula [42]. The
solvent used in this reaction is not particularly
critical so far as the solvent exercises no adverse



influence upon the reaction. Examples of the solvent which can be used include aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as dioxane, tetrahydrofuran, anisole, diethylene glycol
5 diethyl ether, dimethyl cellosolve and the like; nitriles such as acetonitrile and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; halogenated hydrocarbons such as chloroform, methylene chloride and the like; acetic acid; water;
10 alcohols such as methyl alcohol, ethyl alcohol, isopropyl alcohol and the like; and sulfoxides such as dimethyl sulfoxide and the like. These solvents may be used alone or in mixture of two or more. The reaction is carried out usually at 0-150°C and preferably at 25-
15 120°C, for a period of 30 minutes to 24 hours.

The compound of general formula [1t] can be obtained by subjecting a compound of general formula [1s] to an amidation reaction.

This reaction may be a usual amidation
20 reaction, such as a method via an acid chloride, a method via an acid anhydride, a method using a base, a condensing agent and an additive, etc. For example, in the case of using a base, a condensing agent and an additive, the amines which can be used in the reaction
25 include primary amines such as methylamine, benzylamine, aniline, phenethylamine, aminothiazole and the like; secondary amines such as dimethylamine, diethylamine, di-n-propylamine and the like; cyclic



amines such as piperidine, morpholine and the like; and amino acids such as leucine, asparagine, aspartic acid, β -alanine and the like. The amine is used in an amount of 0.5-10 mol and preferably 1-3 mol per mol of the

5 compound of general formula [1s]. As the base which can be use in this reaction, organic amines such as dimethylaminopyridine, triethylamine, pyridine, N-methylmorpholine and the like and alkali metal carbonates such as potassium carbonate, sodium

10 carbonate and the like can be referred to, and the amount thereof is 0.5-10 mol and preferably 1-3 mol per mol of the compound of general formula [1s]. As the condensing agent, dicyclohexyl carbodiimide, diisopropyl carbodiimide, N-ethyl-N'-3-dimethyl-

15 aminopropyl carbodiimide, diphenyl phosphoryl azide and the like can be referred to, and as the additive, 1-hydroxybenzotriazole, N-hydroxysuccinimide and the like can be referred to. The amounts of the condensing agent and the additive are both 0.5-10 mol and

20 preferably 1-3 mol per mol of the compound of general formula [1s]. The solvent used in this reaction is not particularly critical so far as the solvent exercises no adverse influence upon the reaction. Examples of the solvent which can be used include aromatic

25 hydrocarbons such as benzene, toluene, xylene and the like; ethers such as dioxane, tetrahydrofuran, anisole, diethylene glycol diethyl ether, dimethyl cellosolve and the like; esters such as methyl acetate, ethyl



acetate and the like; nitriles such as acetonitrile and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; halogenated hydrocarbons such as chloroform, methylene chloride and the like; and sulfoxides such as dimethyl sulfoxide and the like. These solvents may be used alone or in mixture of two or more. The reaction is carried out usually at a temperature of -20°C to 150°C and preferably at 0-120°C, for a period of 30 minutes to 24 hours.

The compound of general formula [1u] can be obtained by, for example, oxidizing a compound of general formula [1s].

As the oxidant which can be used in this reaction, for example, peracids such as peracetic acid, trifluoro-peracetic acid, perbenzoic acid, m-chloroperbenzoic acid and the like; hydrogen peroxide; chromic acid; potassium permanganate and the like can be referred to. The oxidant is used in an amount of 0.5-5 mol and preferably 1-3 mol per mol of the compound of general formula [1s]. The solvent used in this reaction is not particularly critical so far as the solvent exercises no adverse influence upon the reaction. Examples of the solvent which can be used include aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as dioxane, tetrahydrofuran, anisole, diethylene glycol diethyl ether, dimethyl cellosolve and the like; alcohols such



as methanol, ethanol and the like; esters such as methyl acetate, ethyl acetate and the like; nitriles such as acetonitrile and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide and the like;

5 halogenated hydrocarbons such as chloroform, methylene chloride and the like; water; and sulfoxides such as dimethyl sulfoxide and the like. These solvents may be used alone or in mixture of two or more. This reaction is carried out usually at a temperature ranging from 0°C

10 to reflux temperature of the used solvent and preferably at 0-30°C, for a period of 30 minutes to 24 hours.

The compound of general formula [1v] can be obtained by subjecting a compound of general formula

15 [1u] to an amidation reaction. This reaction may be a usual amidation reaction, such as a method via an acid chloride, a method via an acid anhydride, a method using a base, a condensing agent and an additive, etc. For example, in the case of using a base, a condensing

20 agent and an additive, the amines which can be used in the reaction include primary amines such as methylamine, benzylamine, aniline, phenethylamine, aminothiazole and the like; secondary amines such as dimethylamine, diethylamine, di-n-propylamine and the

25 like; cyclic amines such as piperidine, morpholine and the like; and amino acids such as leucine, asparagine, aspartic acid, β -alanine and the like. The amine is used in an amount of 0.5-10 mol and preferably 1-3 mol



per mol of the compound of general formula [1u]. As the base which can be used in this reaction, organic amines such as dimethylaminopyridine, triethylamine, pyridine, N-methylmorpholine and the like and alkali 5 metal carbonates such as potassium carbonate, sodium carbonate and the like can be referred to, and the amount thereof is 0.5-10 mol and preferably 1-3 mol per mol of the compound of general formula [1u]. As the condensing agent, dicyclohexyl carbodiimide, 10 diisopropyl carbodiimide, N-ethyl-N'-3-dimethylaminopropyl carbodiimide, diphenyl phosphoryl azide and the like can be referred to, and as the additive, 1-hydroxybenzotriazole, N-hydroxysuccinimide and the like can be referred to. The amounts of the 15 condensing agent and the additive are both 0.5-10 mol and preferably 1-3 mol per mol of the compound of general formula [1u]. The solvent used in this reaction is not particularly critical so far as the solvent exercises no adverse influence upon the 20 reaction. Examples of the solvent which can be used include aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as dioxane, tetrahydrofuran, anisole, diethylene glycol diethyl ether, dimethyl cellosolve and the like; esters such as 25 methyl acetate, ethyl acetate and the like; nitriles such as acetonitrile and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; halogenated hydrocarbons such as chloroform, methylene



chloride and the like; and sulfoxides such as dimethyl sulfoxide and the like. These solvents may be used alone or in mixture of two or more. The reaction is carried out usually at a temperature of -20°C to 150°C 5 and preferably at 0-120°C, for a period of 30 minutes to 24 hours.

The compound of general formula [1v] can be obtained by, for example, oxidizing a compound of general formula [1t].

10 As the oxidant which can be used in this reaction, for example, peracids such as peracetic acid, trifluoro-peracetic acid, perbenzoic acid, m-chloroperbenzoic acid and the like; hydrogen peroxide; chromic acid; potassium permanganate and the like can 15 be referred to. The oxidant is used in an amount of 0.5-5 mol and preferably 1-3 mol per mol of the compound of general formula [1t]. The solvent used in this reaction is not particularly critical so far as the solvent exercises no adverse influence upon the 20 reaction. Examples of the solvent which can be used include aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as dioxane, tetrahydrofuran, anisole, diethylene glycol diethyl ether, dimethyl cellosolve and the like; alcohols such 25 as methanol, ethanol and the like; esters such as methyl acetate, ethyl acetate and the like; nitriles such as acetonitrile and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide and the like;



halogenated hydrocarbons such as chloroform, methylene chloride and the like; water; and sulfoxides such as dimethyl sulfoxide and the like. These solvents may be used alone or in mixture of two or more. This reaction 5 is carried out usually at a temperature ranging from 0°C to reflux temperature of the used solvent and preferably at 0-30°C, for a period of 30 minutes to 24 hours.

The compounds of general formulas [1s], [1t], 10 [1u] and [1v] which have been obtained in the above-mentioned manner can be converted to other compounds of general formula [1] by, for example, subjecting them to reactions known in themselves such as oxidation, reduction, rearrangement, substitution, halogenation, 15 dehydration, hydrolysis, etc. or appropriately combining these reactions. The compounds of general formula [1s], [1t], [1u] and [1v] or salts thereof thus obtained can be isolated and purified by the conventional procedures such as extraction, 20 crystallization and/or column chromatography, etc.

By converting the compound of [1s] or [1u], for example, to an acid halide by the conventional method, reacting the acid halide with diethyl malonate and magnesium chloride in the presence of a base such 25 as triethylamine and then subjecting the product to hydrolysis and decarboxylation, there can be obtained a compound in which R^{13a} is an unsubstituted or substituted alkyl group. By converting the compound of



[1s] or [1u] to an acid halide by the conventional method and then reacting the acid halide with alkylmercaptan, there can be obtained a compound in which R^{13a} is an unsubstituted or substituted alkylthio group. Further, by converting the compound of [1s] or [1u] to an acid halide by the conventional method and then subjecting the acid halide to Friedel-Crafts reaction with an aryl or heterocyclic group in the presence of an acid such as aluminum chloride or the like, there can be obtained a compound in which R^{13a} is an unsubstituted or substituted aryl or heterocyclic group.

The compound of general formula [32] which is a starting compound for production of the compound of the present invention can be produced according to the method described in, for example, *Synthesis*, Page 48 (1986) or the like or a similar method.

In the production processes mentioned above, the compounds of general formulas [32], [33], [34], [35], [36], [37], [38], [39], [40], [41], [42], [1s], [1t] and [1u] can be used in the form of a salt, too. As said salt, the same ones as mentioned in the paragraph of salts of the compound of general formula [1] can be referred to.

The compounds of general formulas [32], [33], [34], [35], [36], [37], [38], [39], [40], [41], [42], [1s], [1t], [1u] and [1v] can be converted to salts thereof. As said salts, the same ones as mentioned in



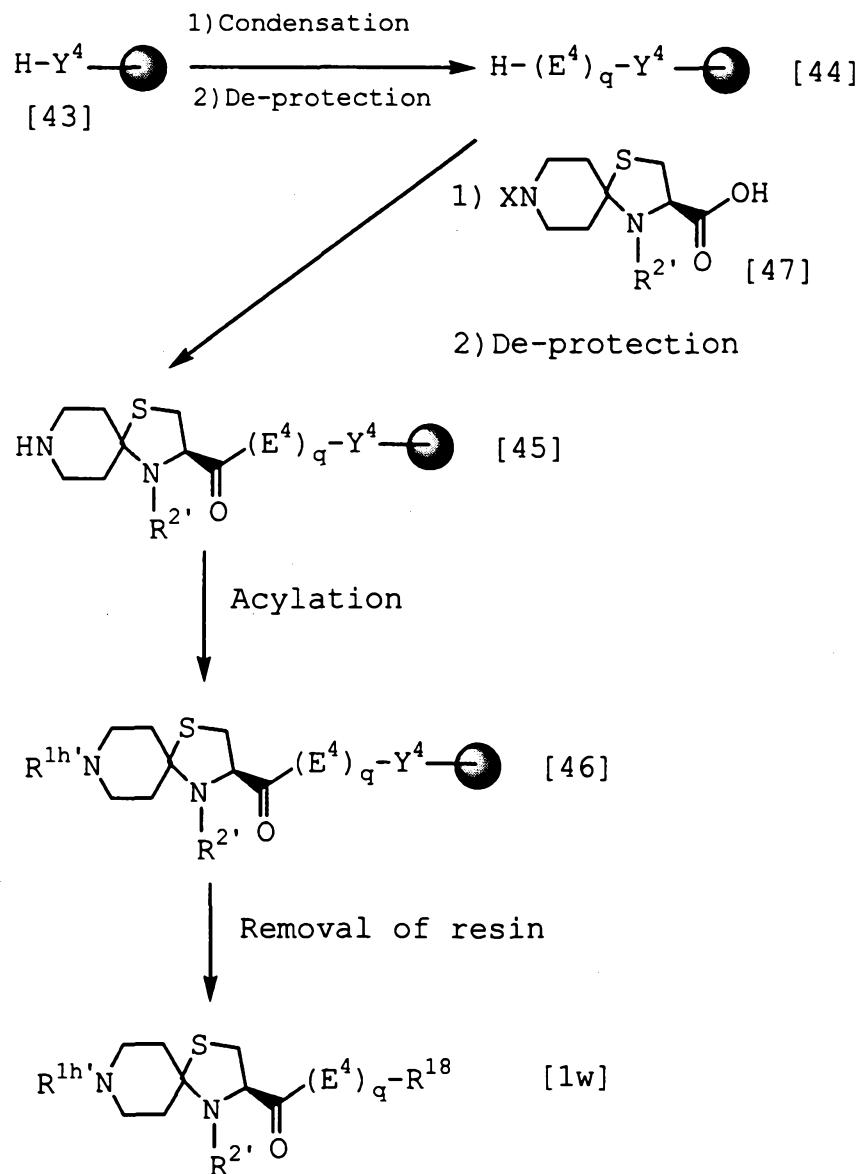
the paragraph of general formula [1] can be referred to.

In the above-mentioned production processes, some of the compounds of general formulas [32], [33], 5 [34], [35], [36], [37], [38], [39], [40], [41], [42], [1s], [1t] and [1u] have isomers such as optical isomer, geometrical isomer, tautomer, etc. In such cases, these isomers are also usable in the present invention. Further, solvated products, hydrates and 10 various crystal forms of these compounds are also usable. In the compounds of general formulas [32], [33], [34], [35], [36], [37], [38], [39], [40], [41], [42], [1s], [1t], [1u] and [1v], some compounds have an amino group, a hydroxyl group, a mercapto group or a 15 carboxyl group. It is possible, if desired, to protect these groups previously with a usual protecting group and, after the reaction, to eliminate the protecting group according to a method known in itself.

It is also possible to obtain the compounds 20 of general formulas [1w], [1x] and [1y] by, for example, the following Production Processes 5-7.



Production Process 5



wherein Y^4 represents O or NH; q represents 0, 1, 2 or 3, provided that when q is zero, Y^4 represents NH; E^4 represents amino acid residue; and R^{1h} represents a group of the following general formula:

5 $R^{15'}-Y^{3'}-$

wherein $Y^{3'}$ represents carbonyl group; and $R^{15'}$ represents hydrogen atom, cyano group, protected carboxyl, hydroxyl or mercapto group or an unsubstituted or substituted alkyl, alkenyl, 10 cycloalkyl, aryl, alkoxy, alkylthio, alkylsulfonyl, arylsulfonyl, sulfamoyl, acyl, acyloxy, alkoxy carbonyl, aryloxycarbonyl, amino, carbamoyl, carbamoyloxy or heterocyclic group; or a group of the following general formula:

15 $R^{16}-(E^3)_s-$

wherein R^{16} represents hydrogen atom or a protecting group for amino group; E^3 represents amino acid residue; and s represents 2 or 3; and X represents a protecting group for amino group; and R^2' represents hydrogen atom 20 or an unsubstituted or substituted acyl group.

The amino acid-bounded resin of general formula [44] can be obtained by reacting a resin of general formula [43] with an amino acid derivative, followed by de-protection. As the resin usable in this 25 reaction, the resins conventionally used in the solid phase method can be referred to, of which examples include benzhydrylamine resin, 4-methylbenzhydrylamine resin, Rink amide resin, oxymethyl resin,



oxymethylphenoxyethyl resin and the like. As the amino acid derivatives usable in this reaction, there can be referred to those amino acid derivatives in which t-butyloxycarbonyl (Boc) group or 9-

5 fluorenylmethoxycarbonyl (Fmoc) group is used as protecting group for an α -amino acid, those in which t-butyl ester group, benzyl ester group, cyclohexyl ester group or the like is used as protecting group for the side chain functional group such as the side chain 10 carboxyl group of aspartic acid or glutamic acid; those in which t-butyl group, benzyl group, 2,6-dibromobenzyl group or the like is used as a protecting group for the side chain hydroxyl group of serine, threonine, tyrosine; those in which trityl group, acetamidomethyl 15 group, t-butyl group or the like is used as a protecting group for the side chain thiol group of cysteine; etc. Among these amino acid derivatives, Fmoc-amino acids are preferred.

(1) An amino acid-bounded resin with protected N-terminal can be obtained by condensing a resin with an amino acid derivative. Concretely speaking, it can be obtained by introducing a resin into a reactor, adding a solvent thereto to swell the resin, filtering off the solvent, adding an amino acid derivative and a 25 condensation reagent, again adding a solvent, and then carrying out a reaction. As the condensation reagent used in this reaction, dicyclohexyl carbodiimide, diisopropyl carbodiimide, benzotriazole-1-yl-oxy-tris-



pyrrolidino-phosphonium hexafluorophosphate (PyBOP), bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBroP) and the like can be referred to, and the amount thereof is 1-10 equivalents per equivalent of 5 amino group in the resin. In the case of using PyBOP or PyBroP, an amine such as diisopropylethylamine, triethylamine or the like may be added, if desired, in an amount of 1-5 equivalents per equivalent of the condensing agent. It is also allowable to add 0.5-5 10 equivalents of an ester-activator such as N-hydroxybenzotriazole, N-hydroxy-7-azabenzotriazole or the like per equivalent of the condensation reagent. As the solvents used in this reaction, N,N-dimethylformamide, dichloromethane, chloroform, N-15 methylpyrrolidone and the like can be referred to. Although the amount of the solvent is not particularly critical, 5-100 ml and preferably 5-20 ml of solvent is used per gram of the resin when used for swelling the resin, and 5-100 ml, preferably 5-50 ml, of solvent is 20 used per gram of the resin when used for reaction. This reaction is carried out usually at 10-40°C and preferably at 20-30°C for a period of 5-120 minutes.

(2) An amino acid-bounded resin with de-protected N-terminal can be obtained by reacting an amino acid-bounded resin having a protected N-terminal with a de-protecting agent and thereby eliminating the protecting group for α -amino acid. Concretely speaking, a peptide-bonding resin having a protected N-terminal is



reacted in the presence of an acid or a base in the presence or absence of a solvent. The de-protecting group used in this reaction is properly selected in accordance with the kind of protecting group for α -amino acid. For example, in the case where the protecting group for α -amino acid to be eliminated is a Boc group, an acid such as trifluoroacetic acid, methanesulfonic acid and the like is used. In the case where the protecting group for α -amino acid to be eliminated is a Fmoc group, a base such as piperidine, 1,8-diazabicyclo[5.4.0]undec-7-ene or the like is used. The solvent used in this reaction is not critical so far as the solvent exercises no adverse influence on the reaction. When an acid is used for the elimination, dichloromethane, dichloroethane and the like can be used. When a base is used for the elimination, N,N-dimethylformamide, N-methylpyrrolidone and the like can be used. When a solvent is used, the solvent may be used in a proportion of 5-20 ml per one gram of the resin. The reaction is carried out usually at 10-40°C and preferably at 20-30°C for a period of 5-120 minutes.

For combining two or more amino acid residues, the procedure mentioned above is repeated.

The resin of general formula [45] can be obtained by reacting an amino acid-bounded resin of general formula [44] with a compound of general formula [47], followed by de-protection. This reaction can be



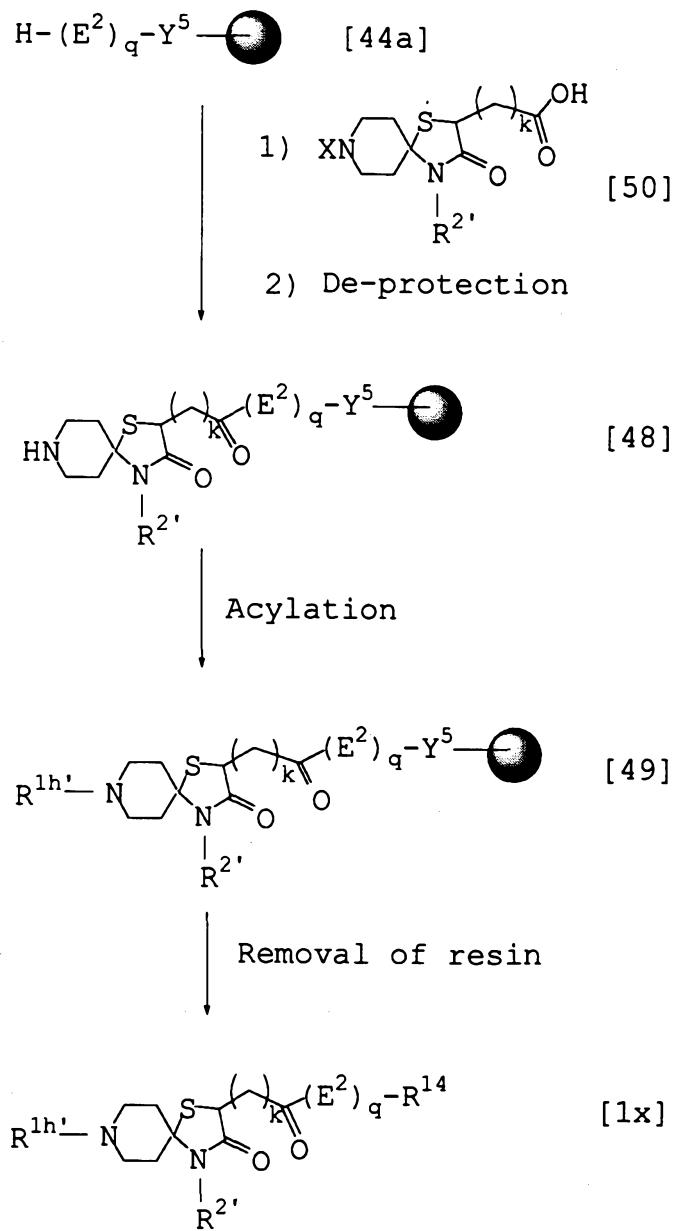
effected in the same manner as above.

The resin of general formula [46] can be obtained by acylating a resin of general formula [45]. This reaction can be effected in the same manner as 5 above. In a case where the functional group of the compound bonded to the resin of formula [46] is protected, conversion to other compound can be carried out by de-protection followed by acylation, sulfonylation or the like. These reactions may be 10 effected in the same manner as above.

The compound of general formula [1w] can be obtained by treating a resin of general formula [46] in the presence of an acid to remove the resin therefrom. The acid used in this reaction is properly selected in 15 accordance with the combination of the used resin and the protecting group for amino group. The acids include, for example, trifluoromethanesulfonic acid, anhydrous hydrogen fluoride, trifluoroacetic acid and the like. The solvent used in this reaction is not 20 critical so far as the solvent exercises no adverse influence on the reaction. For example, dichloromethane is used for this purpose. Although the amount of the solvent is not critical, 5-100 ml of the solvent may be used per gram of the resin. The reaction is 25 carried out at -10°C to 40°C and preferably at 0-20°C, for a period of 30-300 minutes.



Production Process 6



wherein Y^5 represents O or NH; q represents 0, 1, 2 or 3; E^2 represents amino acid residue; k represents 1, 2 or 3; and R^{1h} represents a group of the following formula:

5 $R^{11'}-Y^2'-$

wherein Y^2' represents carbonyl group; and $R^{11'}$ represents hydrogen atom, cyano group, protected carboxyl, hydroxyl or mercapto group, or an unsubstituted or substituted alkyl, alkenyl, 10 cycloalkyl, aryl, alkoxy, alkylthio, alkylsulfonyl, arylsulfonyl, sulfamoyl, acyl, acyloxy, alkoxy carbonyl, aryloxycarbonyl, amino, carbamoyl, carbamoyloxy or heterocyclic group; or a group of the following general formula:

15 $R^{12}-\left(E^1\right)_j-$

wherein R^{12} represents hydrogen atom or a protecting group for amino group; R^{14} represents hydroxyl group or amino group; E^1 represents amino acid residue; and j represents 2 or 3; and X represents a protecting group 20 for amino group; and R^2' represents hydrogen atom or an unsubstituted or substituted acyl group.

The resin of general formula [48] can be obtained by reacting a resin of general formula [44a] with a compound of general formula [50], followed by 25 de-protection. This reaction may be carried out in the same manner as mentioned in the paragraph of Production Process 5.

The resin of general formula [49] can be

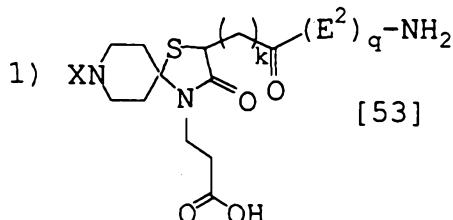


obtained by acylating a resin of the general formula [48]. This reaction may be carried out in the same manner as above. In a case where the functional group of the compound bonded to the resin of formula [48] is 5 protected, conversion to other compound can be carried out by de-protection, followed by acylation, sulfonylation or the like. These reaction may be carried out in the same manner as above.

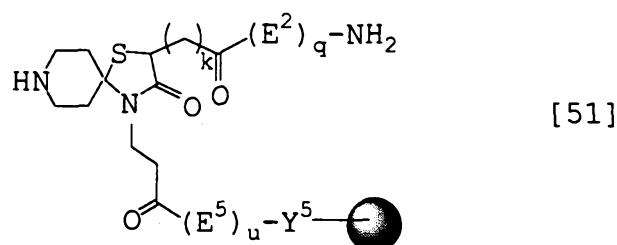
The compound of the general formula [1x] can 10 be obtained by treating a resin of general formula [49] in the presence of an acid to remove the resin therefrom. This reaction may be carried out in the same manner as mentioned in the paragraph of Production Process 5.



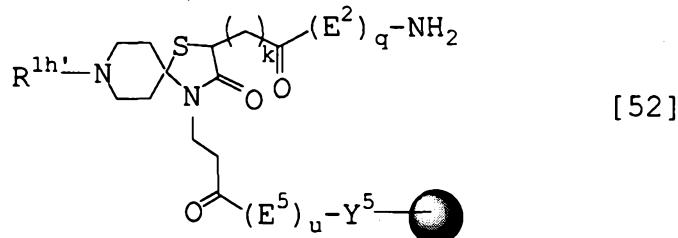
Production Process 7



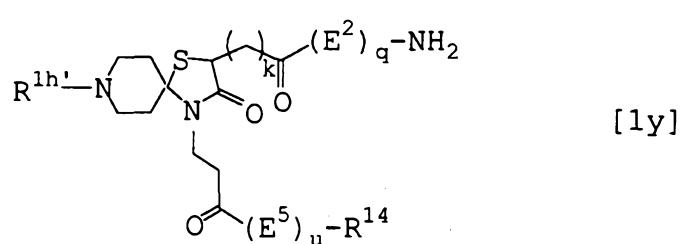
2) De-protection



Acylation



Removal of resin



wherein Y^5 represents O or NH; k represents 1, 2, or 3; q represents 0, 1, 2 or 3; u represents 0, 1, 2 or 3; and R^{1h} represents a group of the following general formula:

5 $R^{11'}-Y^{2'}-$

wherein $Y^{2'}$ represents carbonyl group; and $R^{11'}$ represents hydrogen atom, cyano group, protected carboxyl, hydroxyl or mercapto group, or an unsubstituted or substituted alkyl, alkenyl, 10 cycloalkyl, aryl, alkoxy, alkylthio, alkylsulfonyl, arylsulfonyl, sulfamoyl, acyl, acyloxy, alkoxy carbonyl, aryloxy carbonyl, amino, carbamoyl, carbamoyloxy or heterocyclic group; or a group of the following general formula:

15 $R^{12}-\left(E^1\right)_j-$

wherein R^{12} represents hydrogen atom or a protecting group for amino group; E^1 represents amino acid residue; and j represents 2 or 3; and $R^{2'}$ represents hydrogen atom, or an unsubstituted or substituted acyl group; R^{14} 20 represents hydroxyl group or amino group; E^2 and E^5 each represents amino acid residue; and X represents a protecting group for amino group.

The resin of general formula [51] can be obtained by reacting a resin of general formula [44b] 25 with a compound of general formula [53], followed by de-protection. This reaction may be carried out in the same manner as in the description of Production Process 5.



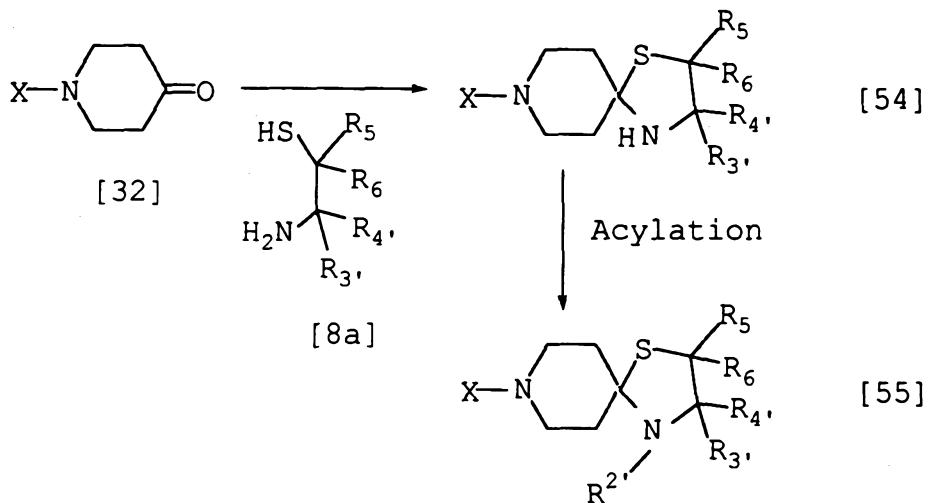
The resin of general formula [52] can be obtained by acylating a resin of general formula [51]. This reaction may be carried out in the same manner as above. In a case where the functional group of the 5 compound bonded to the resin of formula [52] is protected, conversion to other compounds can be carried out by de-protection, followed by acylation, sulfonylation, etc. These reactions may be carried out in the same manner as above.

10 The compound of general formula [1y] can be obtained by treating a resin of general formula [52] in the presence of an acid to remove the resin therefrom. This reaction may be carried out in the same manner as mentioned in the paragraph of Production Process 5.

15 The compound of general formula [55] which is a starting compound for production of the compound of the present invention can be obtained, for example, in the following manner.



[Production Process F]



wherein X represents a protecting group for amino group; R³, R⁴, R⁵ and R⁶ are as defined above; and R² represents an unsubstituted or substituted acyl group.

The compound of general formula [54] can be obtained according to, for example, the process mentioned in JP-A 53-44574, or the like. More concretely speaking, it can be obtained by reacting a compound of general formula [32] with a compound of general formula [8a] in the presence or absence of a base, a dehydrating agent and a catalyst, and subjecting the product to a dehydrating ring closure. Although the compound of general formula [8a] used in this reaction is not particularly critical, D-cysteine, L-cysteine, D-penicillamine and L-penicillamine and salts thereof can be referred to, for example. The compound of general formula [8a] is used in an amount of 0.5-10 mol and preferably 1-2 mol per mol of the compound of general formula [32]. As the base which



may be used according to the need, for example, organic amines such as dimethylaminopyridine, triethylamine, pyridine and the like, alkali metal carbonates such as potassium carbonate, sodium carbonate and the like;

5 etc. can be referred to, and the amount thereof is 0.5-10 mol and preferably 1-2 mol per mol of the compound of general formula [32]. As the dehydrating agent which may be used according to the need, zeolam, molecular sieve, calcium chloride, magnesium sulfate,

10 diphosphorus pentoxide and the like can be referred to, and the amount thereof is 1-10 times (w/w) and preferably 1-2 times (w/w) as much as the weight of the compound of general formula [32]. As the catalyst which may be used according to the need, paratoluene-

15 sulfonic acid, benzenesulfonic acid, hydrochloric acid, sulfuric acid and the like can be referred to, and the amount thereof is 0.001-1 mol and preferably 0.01-0.1 mol per mol of the compound of general formula [32]. The solvent used in this reaction is not particularly

20 critical so far as the solvent exercises no adverse influence upon the reaction. Examples of the solvent which can be used include aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as dioxane, tetrahydrofuran, anisole, diethylene glycol

25 diethyl ether, dimethyl cellosolve and the like; esters such as methyl acetate, ethyl acetate and the like; nitriles such as acetonitrile and the like; alcohols such as methyl alcohol, ethyl alcohol, isopropyl



alcohol and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; halogenated hydrocarbons such as chloroform, methylene chloride and the like; water; and sulfoxides such as 5 dimethyl sulfoxide and the like. These solvents may be used alone or in mixture of two or more. This reaction is carried out usually at 0-150°C and preferably at 20-120°C, for a period of 30 minutes to 24 hours.

The compound of general formula [55] can be 10 obtained by, for example, acylating a compound of general formula [54] in the presence or absence of a base. As the acylating agent which can be used in this reaction, for example, acetic anhydride, acetyl chloride, benzoyl chloride, pyrrolecarbonyl chloride, 15 thiazolecarbonyl chloride and the like can be referred to. The amount of said acylating agent is 0.5-10 mol and preferably 1-3 mol per mol of the compound of general formula [54]. As the base which may be used according to the need, organic amines such as 20 dimethylaminopyridine, triethylamine, pyridine and the like and alkali metal carbonates such as potassium carbonate, sodium carbonate and the like can be referred to, and the amount thereof is 0.5-10 mol and preferably 1-3 mol per mol of the compound of general 25 formula [54]. The solvent used in this reaction is not particularly critical so far as the solvent exercises no adverse influence upon the reaction. Examples of the solvent which can be used include aromatic



hydrocarbons such as benzene, toluene, xylene and the like; ethers such as dioxane, tetrahydrofuran, anisole, diethylene glycol diethyl ether, dimethyl cellosolve and the like; esters such as methyl acetate, ethyl acetate and the like; nitriles such as acetonitrile and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; halogenated hydrocarbons such as chloroform, methylene chloride and the like; and sulfoxides such as dimethyl sulfoxide and the like. These solvents may be used alone or in mixture of two or more. The reaction is carried out usually at -20°C to 150°C and preferably at 0-120°C, for a period of 30 minutes to 24 hours.

It is also possible, if desired, to eliminate the protecting group just after the compound [55] has been obtained and thereafter to convert it to other protecting group.

In the production processes mentioned above, the compounds of general formulas [8a], [32], [43], [44], [44a], [44b], [45], [46], [47], [48], [49], [50], [51], [52], [53], [54], [55], [1w], [1x] and [1y] can be used in the form of a salt, too. As said salt, the same ones as mentioned in the paragraph of salts of the compound of general formula [1] can be referred.

In the above-mentioned Production Processes 5, 6, 7 and F, some of the compounds of general formulas [8a], [32], [43], [44], [44a], [44b], [45], [46], [47], [48], [49], [50], [51], [52], [53], [54], [55], [1w], [1x] and [1y] can be referred.



[55], [1w], [1x] and [1y] have isomers such as optical isomer, geometrical isomer, tautomer, etc. In such cases, these isomers are also usable in the present invention. Further, solvated products, hydrates and 5 various crystal forms of these compounds are also usable.

In the compounds of general formulas [8a], [32], [43], [44], [44a], [44b], [45], [46], [47], [48], [49], [50], [51], [52], [53], [54], [55], [1w], [1x] 10 and [1y], some compounds have an amino group, a hydroxyl group, a mercapto group or a carboxyl group. It is possible, if desired, to protect these groups with a usual protecting group previously and, after the reaction, to eliminate the protecting group according 15 to a method known in itself.

When the compound of the present invention is used as a medical drug, conventional adjuvants for preparations such as an excipient, a carrier, a diluent and the like may be appropriately mixed into the 20 composition, and the preparations thus obtained can be orally or non-orally administered in the form of tablet, capsule, powder, syrup, granule, pill, suspension, emulsion, solution, powdery preparation, suppository, ointment, injection and the like according 25 to usual ways. The method, dosage and frequency of administration can properly be selected according to age, body weight and symptom of the patient. Usually, in case of adult patients, the preparation is orally or



non-orally (for example, by injection, instillation, rectal application and the like) administered at a dosage of 0.1 to 100 mg/kg per day, at once or in several portions.

5 Next, pharmacological activities of typical compounds of the present invention will be mentioned below.

[Testing Method]

Test Example 1: Preparation of transfectant

10 A reporter plasmid was prepared according to the method of R.I. Scheinman et al. [Mol. Cell. Biol., Vol. 15, Pages 943-953 (1995)]. That is, a plasmid p(TRE)₅TK-Luc was constructed by connecting a promoter of thymidine kinase (TK) at an upstream site of
15 luciferase (Luc) gene which is a reporter gene and a 5-times repeated TRE sequence at a further upstream site thereof. The plasmid was co-transfected simultaneously with p3'SS plasmid (prepared by Stratagene Co.) by the electrotranspolation method onto mouse 3T3 fibroblast
20 (ATCC: CCL-163) cultured in a Dulbecco's modified Eagle's medium (DMEM) containing 10% fetal calf serum (FCS). Then the cells were cultured in DMEM containing 10% FCS and 100 µg/ml of Hygromycin B. Using the expression of Hygromycin-resistant gene contained in
25 p3'SS as an indicator, cell strains of the transfectant into which the objective plasmid had been introduced stably were selected. Furthermore in the test mentioned below, cell strains showing expression of Luc



gene under stimulation of 12-O-tetradecanoylphorbol 13-acetate (TPA, prepared by Sigma Co.) were used, and DMEM containing 10% FCS and 100 µg/ml of Hygromycin B was used for the culture of cells.

5 Test Example 2: Luciferase assay

The cells prepared above were suspended in culture medium, and plated 96 well-plate at 1×10^4 cells/0.1 ml. After culturing it overnight, 50 µl of test compounds solution and 40 µl of culture medium 10 were added, and incubated. After one hour 10 µl of 200 ng/ml TPA solution was added and the culture was continued for an additional 16 hours to stimulate the cells. The end of culture, the cells were recovered, and cell lysis solutions were obtained. The Luc 15 activity of the cell lysates was measured with a chemilluminescent detection kit (Pica Gene; manufactured by Toyo Ink Co.). The suppressive effect of each test compound could be assessed as a decrease of Luc activity, and the inhibition rate (%) was 20 calculated according to the following formula:

Inhibition rate (%) =

$$(1 - \text{Luc activity of cells to which the compound is added} / \text{Luc activity of cells to which the compound is not added}) \times 100$$

25 Test Example 3: XTT assay (cytotoxicity test)

The same culture plate as above was prepared,



and test compound and TPA were added under the same conditions as above, after which a culture was carried out for 16 hours. The end of culture, XTT reagent prepared according to the method of D.A. Scudievo 5 [Cancer Res., Vol. 48, Pages 4827-4833 (1988)] was added and made to react for a prescribed period of time. Then, the amount of formazan formed by alive cells was analyzed by measuring absorbance at 450 nm using a micro plate reader. In this test, a decrease 10 in absorbance is observed when the test compounds show a cytotoxicic or a growth inhibitory activity. Cell viability (T/C %) was determined according to the following formula:

Cell viability rate (T/C %) =
15 (Absorbance of well to which compound is added/ Absorbance of well to which the compound was not added) X 100

The results are shown in Table 52.



[Table 52]

Example No.	Concentration $\mu\text{g/ml}$	Inhibition rate (%)	Cell viability (%)
1	50	80	80
2	100	38	81
6(3)	100	91	83
6(5)	30	60	106
12	100	74	84
13	100	40	80
14	30	23	100
15	100	79	87
16(11)	30	65	94
17	100	93	79
18(1)	100	89	97
18(4)	100	53	83
18(8)	100	86	86
18(17)	100	92	83
18(18)	100	87	78
18(19)	100	100	98
20(1)	30	72	98
20(2)	100	93	92
21	30	28	74
29	100	92	110
40	100	91	108
41(2)	100	94	71
41(3)	100	80	97
41(4)	100	96	82
41(5)	100	94	90
41(6)	100	49	97
41(7)	70	87	71
41(8)	50	53	78
41(9)	70	53	95
41(10)	50	73	75
41(11)	100	90	85
41(12)	100	87	79
41(13)	40	56	77
41(14)	100	92	73
41(15)	30	86	100
44	30	62	75
47	30	47	83
B-9	100	46	89
B-13	10	24	98



The compounds of Example No. 1, 6(3), 6(5), 13, 15, 17, 18(1), 18(8), 20(1) and 20(2) were converted to sodium salts according to the method of Example 42, and then used for the assay.

5 Test Example 4: type II collagen-induced arthritis in mice

The compound of Example 20 (1) was tested for the effect on type II collagen-induced arthritis, using 8 weeks old, male DBA/1J mice (Japan Charles River).

10 Emulsion was prepared by mixing an equal volume of bovine type II collagen (prepared by Koken) in 0.1N acetic acid (2 mg/ml) and Freund's complete adjuvant (prepared by Nacalai Tesque). Arthritis was induced by intradermal injection of 0.2 ml (the quantity of 15 antigen: 200 µg/head) of the emulsion into the skin of the tail root twice (day 0 and day 21). The test compound was suspended in 0.5% solution of methyl cellulose, and 100 mg/kg was orally administered once every day from day 21 to day 35. To the control group 20 (negative control group), 0.5% methyl cellulose solution was administered in the same manner as above.

Severity of the arthritis was scored 0: no change, 1: only one or two swelling of the joints or slight swelling of the ankle or toes, 2: swelling and/or rubor 25 in further joints, 3: extensive swelling of whole paw, and the maximum possible score for arthritis was 12 points. As to the severity of destruction of joints



and bones, X ray photographs of four paws were taken (Softex), and severity of destruction in the second to fifth articulationes interphalangeae, first to fifth articulationes metacarpophalangeae and

5 metatarsophalangeae, and calcaneus was scored by 0 or 1 in accordance with presence or absence of destruction, and the severity of destruction in the carpus and tarsal was scored by 0 to 3. Overall severity of destruction of joints and bones was evaluated by a
10 joint-bone destruction score, taking the total score of the four paws as 50 points [Method in Enzymology, 162, 361-373 (1988)].

The results are shown in Table 53, wherein the scores are mean values.

15 [Table 53]

Example No.	Dosage (mg/kg)	Arthritis score	Joint-bone destruction score
Control	—	10 ± 1	20 ± 3
20 (1)	100	8 ± 1	14 ± 3

BEST EMBODIMENT FOR CARRYING OUT THE INVENTION

Next, the present invention is explained by referring to referential examples and examples. The present invention is by no means limited by these
20 examples. In the paragraphs of eluents, all the mixing ratios are expressed by volume. The carrier used in



the column chromatography is Silica Gel 60, No. 7734 (product of Merck).

Amino acid residues are expressed according to the three-letter system prescribed by IUPAC and IUB.

5 Unless otherwise referred to, meanings of the abbreviations are as follows:

Fmoc: 9-Fluorenylmethoxycarbonyl

PyBOP: Benzotriazol-1-yl-oxy-tris-pyrrolidino-
phosphonium hexafluorophosphate

10 HOEt: N-Hydroxybenzotriazole

DMF: N,N-Dimethylformamide

DIEA: N,N-Diisopropylethylamine

DCM: Dichloromethane

TFA: Trifluoroacetic acid

15 DIPCDI: Diisopropyl carbodiimide

PMC: 2,2,5,7,8-Pentamethylchroman-6-sulfonyl

DMSO: Dimethyl sulfoxide

Ac: Acetyl

Py: Pyridyl

20 Cit: Citroline

Example 1

To 20 ml of toluene were added 1.90 g of 4-(3-methylbutylidene)-1-cyclohexanone and 2.05 g of benzyl 3-aminopropionate, and the mixture was stirred 25 at ambient temperature for one hour. Then, 1.72 g of mercaptosuccinic acid was added, and the resulting mixture was heated under reflux for one hour under the



condition of azeotropic dehydration by means of Dean Stark. The reaction mixture was added to a mixture of ice water and ethyl acetate, pH was adjusted to 2.0 with 2 mol/L hydrochloric acid, and the organic layer

5 was separated. The organic layer was washed successively with water and saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue thus obtained was

10 purified by column chromatography [eluent: chloroform:ethanol = 50:1] to obtain 3.10 g of 2-[4-[3-(benzyloxy)-3-oxopropyl]-8-(3-methylbutylidene)-3-oxo-1-thia-4-azaspiro[4.5]decan-2-yl]-acetic acid as a light yellow oily product.

15 NMR (CDCl₃+D₂O) δ: 0.89(6H,d,J=6.4Hz), 1.4-2.9(14H,m), 3.19(1H,dd,J=5.2Hz,17.0Hz), 3.4-3.7(2H,m), 4.14(1H,dd,J=5.2Hz,8.1Hz), 5.0-5.4(1H,m), 5.12(2H,s), 7.35(5H,s)

Example 2

20 The procedure of Example 1 was repeated to obtain the following compound:

2-[8-(3-methylbutylidene)-3-oxo-4-(5-phenylpentyl)-1-thia-4-azaspiro[4.5]decan-2-yl]-acetic acid

25 NMR (CDCl₃) δ: 0.88(6H,d,J=6.1Hz), 1.1-3.4(23H,m), 4.1-4.3(1H,m), 5.1-5.3(1H,m), 7.21(5H,s), 8.5-9.3(1H,bs)



Example 3

To 8 ml of toluene were added 0.75 g of 4-(3-methylbutylidene)-1-cyclohexanone and 0.89 g of benzyl 3-aminopropionate, and the mixture was stirred at 5 ambient temperature for one hour. Then, 1.02 g of β -tert-butyl 2-mercaptosuccinate was added, and the resulting mixture was heated under reflux for 8 hours under the condition of azeotropic dehydration by means of Dean Stark apparatus. The reaction mixture was 10 poured into a mixture of ice water and ethyl acetate, pH was adjusted to 2.0 with 2 mol/L hydrochloric acid, and the organic layer was separated. The organic layer was washed successively with water, saturated aqueous solution of sodium hydrogen carbonate and saturated 15 aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue thus obtained was purified by column chromatography [eluent: hexane:ethyl acetate = 6:1] to obtain 0.75 g of benzyl 20 3-[2-[2-(tert-butoxy)-2-oxoethyl-8-(3-methylbutylidene)-3-oxo-1-thia-4-azaspiro[4.5]decan-4-yl]-propionate as a light yellow oily product.

NMR (CDCl₃) δ : 0.88(6H,d,J=6.4Hz), 1.4-2.9(14H,m), 1.46(9H,s), 3.15(1H,dd,J=3.8Hz, 16.7Hz), 3.4-3.7(2H,m), 25 4.08(1H,dd,J=3.8Hz, 9.9Hz), 5.1-5.3(1H,m), 5.11(2H,s), 7.35(5H,s)



Example 4

The procedure of Example 3 was repeated to obtain the compounds of Tables 54 and 55.



[Table 54]

No.	A	R ²
4 (1)		
4 (2)		
4 (3)		
4 (4)		
4 (5)		
4 (6)		
4 (7)		

[Table 55]

No.	A	R ²
4 (8)		$-\text{CH}_2\text{CH}_2\text{COOCH}_2-$
4 (9)		$-\text{CH}_2\text{CH}_2\text{COOCH}_2-$
4 (10)		$-\text{CH}_2\text{CH}_2\text{COOCH}_2-$
4 (11)		$-\text{CH}_2\text{CH}_2\text{COOCH}_2-$
4 (12)		$-\text{CH}_2\text{CH}_2\text{COOCH}_2-$
4 (13)		$-\text{CH}_2\text{CH}_2-$
4 (14)		$-\text{CH}_2\text{CH}_2\text{CH}_3$
4 (15)		$-\text{CH}_2\text{CH}_2\text{OCH}_3$



Properties of the compounds of Tables 54 and 55 are shown below.

4 (1)

NMR (CDCl₃) δ: 0.89 (6H, d, J=6.3Hz), 1.3-3.7 (17H, m), 1.48
5 (9H, s), 4.13 (1H, dd, J=3.7Hz, 10.3Hz), 5.19
(1H, t, J=7.1Hz), 7.26 (5H, s)

4 (2)

NMR (CDCl₃) δ: 0.87 (6H, d, J=6.1Hz), 1.2-2.8 (12H, m), 1.48
(9H, s), 3.24 (1H, dd, J=3.8Hz, 16.7Hz), 4.22
10 (1H, dd, J=3.8Hz, 9.9Hz), 4.42 (1H, d, J=15.5Hz), 4.68
(1H, d, J=15.5Hz), 5.1-5.3 (1H, m), 7.1-7.4 (1H, m), 7.5-
7.8 (1H, m), 8.3-8.7 (2H, m)

4 (3)

NMR (CDCl₃) δ: 0.91 (6H, d, J=6.1Hz), 1.2-3.6 (13H, m), 1.48
15 (9H, s), 4.33 (1H, dd, J=3.9Hz, 9.3Hz), 5.1-5.5 (1H, m),
7.06 (1H, d, J=3.5Hz), 7.50 (1H, d, J=3.5Hz)

4 (4)

NMR (CDCl₃) δ: 0.7-1.0 (6H, m), 1.46 (9H, s), 1.5-3.0
(12H, m), 3.1-3.5 (1H, m), 3.73 (3H, s), 4.0-4.3 (1H, m),
20 4.84 (1H, bs), 5.0-5.3 (1H, m), 7.34 (5H, s)

4 (5)

NMR (CDCl₃) δ: 1.23 (6H, d, J=6.8Hz), 1.46 (9H, s), 1.4-3.0
(12H, m), 3.16 (1H, dd, J=3.7, 16.7Hz), 3.5-3.8 (2H, m),
4.07 (1H, dd, J=3.7Hz, 10.3Hz), 4.6-4.8 (1H, m), 5.13
25 (2H, s), 6.83 (2H, d, J=8.7Hz), 7.14 (2H, d, J=8.7Hz), 7.35
(5H, s)

4 (6)

NMR (CDCl₃) δ: 1.22 (6H, d, J=6.8Hz), 1.47 (9H, s), 1.5-2.3



(8H,m), 2.4-3.1 (5H,m), 3.2-3.5 (2H,m), 3.9-4.2 (2H,m),
6.81 (2H,d,J=8.6Hz), 7.13 (2H,d,J=8.6Hz), 7.27 (5H,s)
4(7)

NMR(CDCl₃) δ: 1.46 (9H,s), 1.4-2.9 (11H,m), 3.17
5 (1H,dd,J=3.7Hz,16.6Hz), 3.5-3.8 (2H,m), 4.08
(1H,dd,J=3.7Hz,10.0Hz), 4.4-4.6 (1H,m), 5.14 (2H,s),
6.8-7.6 (10H,m)

4(8)

NMR(CDCl₃) δ: 1.46 (9H,s), 1.67 (6H,s), 1.6-2.8 (11H,m),
10 3.15 (H,dd,J=3.8Hz,16.6Hz), 3.4-3.7 (2H,m), 4.08
(1H,dd,J=3.8Hz,10.0Hz), 5.12 (2H,s), 7.34 (5H,s)

4(9)

NMR(CDCl₃) δ: 1.46 (9H,s), 1.58 (3H,d,J=6.8Hz), 1.7-2.8
(11H,m), 3.15 (1H,dd,J=3.8Hz,16.7Hz), 3.4-3.7 (2H,m),
15 4.08 (1H,dd,J=3.8Hz,9.9Hz), 5.11 (2H,s), 5.1-5.3
(1H,m), 7.35 (5H,s)

4(10)

NMR(CDCl₃) δ: 0.91 (6H,d,J=6.4Hz), 1.2-2.8 (15H,m), 1.46
(9H,s), 3.0-3.3 (3H,m), 3.4-3.7 (2H,m), 4.02
20 (1H,dd,J=3.7Hz,10.0Hz), 5.12 (2H,s), 5.5-5.8 (1H,m),
7.36 (5H,s)

4(11)

NMR(CDCl₃) δ: 0.8-1.0 (6H,m), 1.2-2.8 (18H,m), 1.46
(9H,s), 3.0-3.7 (7H,m), 4.03 (1H,dd,J=3.7Hz,10.3Hz),
25 5.12 (2H,s), 7.36 (5H,s)

4(12)

NMR(CDCl₃) δ: 0.76 (6H,t,J=7.3Hz), 1.1-2.9 (15H,m), 1.46
(9H,s), 3.13 (1H,dd,J=3.7Hz,16.6Hz), 3.5-3.8 (2H,m),



4.03 (1H, dd, J=3.7Hz, 10.0Hz), 5.13 (2H, s), 7.36 (5H, s)

4 (13)

NMR (CDCl₃) δ: 0.76 (6H, t, J=7.3Hz), 1.1-2.3 (12H, m), 1.47 (9H, s), 2.52 (1H, dd, J=10.3Hz, 16.6Hz), 2.8-3.7 (5H, m),

5 4.08 (1H, dd, J=3.7Hz, 10.3Hz), 7.27 (5H, m)

Example 5

In 10 ml of methylene chloride was dissolved 0.50 g of benzyl 3-[2-[2-(tert-butoxy)-2-oxoethyl]-8-(3-methylbutylidene)-3-oxo-1-thia-4-azaspiro[4.5]decan-4-yl]-propionate. After adding 2 ml of trifluoroacetic acid at 0-5°C, the mixture was stirred at ambient temperature of 2 hours. Distillation of the solvent under reduced pressure, followed by an azeotropic distillation with toluene gave 0.37 g of 2-[4-[3-(benzyloxy)-3-oxopropyl]-8-(3-methylbutylidene)-3-oxo-1-thia-4-azaspiro[4.5]decan-2-yl]-acetic acid as a light yellow oily product.

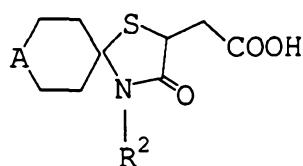
NMR (CDCl₃+D₂O) δ: 0.89 (6H, d, J=6.4Hz), 1.4-2.9 (14H, m), 3.19 (1H, dd, J=5.2Hz, 17.0Hz), 3.4-3.7 (2H, m), 4.14 (1H, dd, J=5.2Hz, 8.1Hz), 5.0-5.4 (1H, m), 5.12 (2H, s), 7.35 (5H, s)

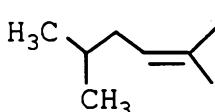
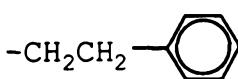
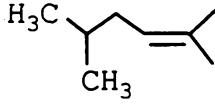
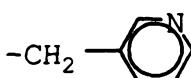
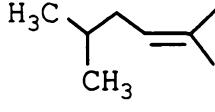
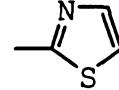
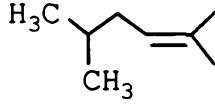
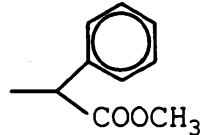
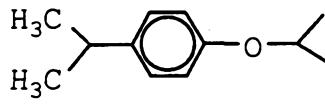
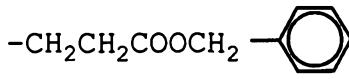
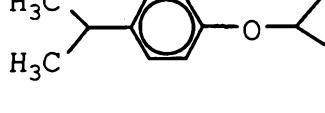
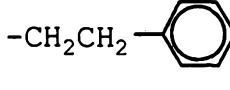
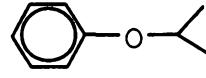
Example 6

The procedure of Example 5 was repeated to obtain the compounds of Tables 56 and 57.



[Table 56]



No.	A	R^2
6 (1)		
6 (2)		
6 (3)		
6 (4)		
6 (5)		
6 (6)		
6 (7)		



[Table 57]

No.	A	R ²
6 (8)		
6 (9)		
6 (10)		
6 (11)		
6 (12)		
6 (13)		
6 (14)		
6 (15)		



Properties of the compounds of Tables 56 and 57 are shown below.

6(1)

NMR(CDCl₃) δ: 0.89 (6H, d, J=6.1Hz), 1.3-3.7 (17H, m), 4.20
 5 (1H, dd, J=4.6Hz, 8.5Hz), 5.20 (1H, t, J=7.2Hz), 7.26
 (5H, s), 8.8-9.2 (1H, bs)

6(2)

NMR(CDCl₃) δ: 0.85 (6H, d, J=6.1Hz), 1.2-3.4 (13H, m), 4.1-
 5.6 (4H, m), 7.8-9.2 (4H, m), 11.5-12.4 (1H, bs)

10 6(3)

NMR(CDCl₃) δ: 0.91 (6H, d, J=5.4Hz), 1.2-3.6 (13H, m), 4.39
 (1H, dd, J=4.4Hz, 8.8Hz), 5.1-5.4 (1H, m), 7.09
 (1H, d, J=3.7Hz), 7.52 (1H, d, J=3.7Hz), 6.1-7.0 (1H, bs)

6(4)

15 NMR(CDCl₃) δ: 0.87 (6H, d, J=6.1Hz), 1.1-3.0 (12H, m), 3.1-
 3.5 (1H, m), 3.75 (3H, s), 4.1-4.4 (1H, m), 5.1-5.7
 (2H, m), 4.85 (1H, bs), 7.34 (5H, s)

6(5)

NMR(CDCl₃) δ: 1.23 (6H, d, J=6.8Hz), 1.4-3.0 (12H, m), 3.23
 20 (1H, dd, J=4.6Hz, 17.3Hz), 3.5-3.8 (2H, m), 4.13
 (1H, dd, J=4.6Hz, 8.8Hz), 4.3-4.6 (1H, m), 5.14 (2H, s), 6.83
 (2H, d, J=8.7Hz), 7.14 (2H, d, J=8.7Hz), 7.35 (5H, s), 8.6-
 9.4 (1H, bs)

6(6)

25 NMR(CDCl₃) δ: 1.22 (6H, d, J=6.8Hz), 1.6-2.3 (8H, m), 2.6-
 3.7 (7H, m), 3.9-4.3 (2H, m), 6.81 (2H, d, J=8.6Hz), 7.13
 (2H, d, J=8.6Hz), 7.27 (5H, s), 7.1-7.4 (1H, bs)



6(7)

NMR (CDCl₃+D₂O) δ: 1.4-2.9 (11H, m), 3.21 (1H, dd, J=4.6Hz, 17.1Hz), 3.5-3.8 (2H, m), 4.12 (1H, dd, J=4.6Hz, 8.4Hz), 4.4-4.6 (1H, m), 5.14 (2H, s),

5 6.8-7.6 (10H, m)

6(8)

NMR (CDCl₃) δ: 1.54 (6H, s), 1.6-2.2 (8H, m), 2.6-2.9 (3H, m), 3.21 (1H, dd, J=4.5Hz, 17.2Hz), 3.5-3.7 (2H, m), 4.11 (1H, dd, J=4.5Hz, 8.5Hz), 5.13 (2H, s), 7.36 (5H, s),
10 8.0-8.6 (1H, bs)

6(9)

NMR (CDCl₃) δ: 1.59 (3H, d, J=6.6Hz), 1.5-2.9 (11H, m), 3.21 (1H, dd, J=5.0Hz, 17.0Hz), 3.4-3.7 (2H, m), 4.14 (1H, dd, J=5.0Hz, 8.1Hz), 5.12 (2H, s), 5.1-5.4 (1H, m),
15 6.6-7.0 (1H, bs), 7.35 (5H, m)

6(10)

NMR (CDCl₃) δ: 0.91 (6H, d, J=6.6Hz), 1.2-2.3 (12H, m), 2.5-2.9 (3H, m), 3.0-3.8 (5H, m), 4.09 (1H, dd, J=4.0Hz, 8.9Hz), 5.13 (2H, s), 5.7-6.0 (1H, m), 6.3-6.7 (1H, bs), 7.35
20 (5H, s)

6(11)

NMR (CDCl₃) δ: 0.8-1.0 (6H, m), 1.2-2.9 (18H, m), 3.0-3.7 (7H, m), 4.09 (1H, dd, J=4.4Hz, 8.6Hz), 4.4-4.8 (1H, bs), 5.12 (2H, s), 7.35 (5H, s)

25 6(12)

NMR (CDCl₃+D₂O) δ: 0.76 (6H, t, J=7.3Hz), 1.1-2.3 (12H, m), 2.3-2.9 (3H, m), 3.19 (1H, dd, J=5.1Hz, 17.0Hz), 3.5-3.8 (2H, m), 4.09 (1H, dd, J=5.1Hz, 8.3Hz), 5.14 (2H, s), 7.36



(5H, s)

6 (13)

NMR (CDCl₃+D₂O) δ: 0.76 (6H, t, J=7.4Hz), 1.1-2.3 (12H, m),
2.5-3.7 (6H, m), 4.16 (1H, dd, J=5.3Hz, 8.4Hz), 7.26 (5H, s)

5 6 (14)

NMR (CDCl₃+D₂O) δ: 0.8-1.2 (9H, m), 1.2-3.4 (17H, m), 4.17
(1H, dd, J=4.2Hz, 9.0Hz), 5.1-5.4 (1H, m)

6 (15)

NMR (CDCl₃) δ: 0.88 (6H, d, J=6.1Hz), 1.2-3.7 (17H, m), 3.34
10 (3H, s), 4.17 (1H, dd, J=5.3Hz, 8.2Hz), 5.1-5.3 (1H, m),
7.8-8.2 (1H, bs)

Example 7

In an atmosphere of nitrogen, 3.32 g of 4-(3-methylbutylidene)-1-cyclohexanone and 5.35 g of benzyl 15 3-aminopropionate were added to 35 ml of dioxane and stirred at ambient temperature for 30 minutes, after which 2.25 g of mercaptoacetic acid was added and the resulting mixture was stirred under reflux for 3 hours. The reaction mixture was poured into a mixture of ice 20 water and ethyl acetate, pH was adjusted to 2.0 with 2 mol/L hydrochloric acid, and the organic layer was separated. The organic layer was washed successively with water, saturated aqueous solution of sodium hydrogen carbonate and saturated aqueous solution of 25 sodium chloride and then dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. Purification of the residue by



column chromatography (eluent: hexane:ethyl acetate = 6:1) gave 4.36 g of benzyl 3-[8-(3-methylbutylidene)-3-oxo-1-thia-4-azaspiro[4.5]decan-4-yl]-propionate as a light yellow oily product.

5 NMR (CDCl₃) δ: 0.88 (6H, d, J=6.1Hz), 1.4-2.8 (13H, m), 3.4-3.7 (2H, m), 3.51 (2H, s), 5.1-5.3 (1H, m), 5.12 (2H, s), 7.35 (5H, s)

Example 8

In 40 ml of dioxane was dissolved 4.11 g of 10 benzyl 3-[8-(3-methylbutylidene)-3-oxo-1-thia-4-azaspiro[4.5]decan-4-yl]-propionate. Then, 20.5 ml of 1 mol/L aqueous solution of sodium hydroxide was added at 0-5°C, and the resulting mixture was stirred at ambient temperature for one hour. The reaction mixture 15 was poured into a mixture of chloroform and water, the aqueous layer was separated, ethyl acetate was added to the aqueous layer, pH was adjusted to 2.0 with 2 mol/L hydrochloric acid, and the organic layer was separated. The organic layer was washed successively with water 20 and saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. Purification of the residue by column chromatography (eluent: chloroform:ethanol = 50:1) gave 2.72 g of 3-[8-(3-25 methylbutylidene)-3-oxo-1-thia-4-azaspiro[4.5]decan-4-yl]-propionic acid as a light yellow oily product.

NMR (CDCl₃) δ: 0.88 (6H, d, J=6.4Hz), 1.4-2.8 (13H, m), 3.4-



3.7 (2H, m), 3.56 (2H, s), 5.1-5.3 (1H, m), 7.4-8.1 (1H, bs)

Example 9

In an atmosphere of nitrogen, 1.97 ml of N,N-diisopropylamine was added to 10 ml of anhydrous tetrahydrofuran, to which was dropwise added 9.50 ml of a solution of n-butyllithium in hexane (1.58 mol/L) at -30°C. The mixture was stirred at the same temperature for 10 minutes and then cooled to -70°C, to which was dropwise added a solution of 1.56 g of 3-[8-(3-methylbutyldene)-3-oxo-1-thia-4-azaspiro[4.5]decan-4-yl]-propionic acid in 20 ml of anhydrous tetrahydrofuran. After stirring the resulting mixture at the same temperature as above for 30 minutes, 0.89 ml of tert-butyl bromoacetate was dropwise added at the same temperature. After elevating the temperature to 0°C, the reaction mixture was poured into a mixture of ice water and ethyl acetate, pH was adjusted to 2.0 with 2 mol/L hydrochloric acid, and the organic layer was separated. The organic layer was washed successively with water and saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. Thus, 2.23 g of 3-[2-[2-(tert-butoxy)-2-oxoethyl]-8-(3-methylbutyldene)-3-oxo-1-thia-4-azaspiro[4.5]decan-4-yl]-propionic acid was obtained as a yellow oily product.

NMR (CDCl₃) δ: 0.87 (6H, d, J=6.3Hz), 1.2-2.8 (14H, m),



1.46(9H,s), 3.13(1H,dd,J=3.9Hz,16.6Hz), 3.4-3.7(2H,m),
4.11 (1H,dd,J=3.9Hz,9.6Hz), 5.1-5.3(1H,m), 6.8-
7.6(1H,bs)

Example 10

5 In 10 ml of methylene chloride was dissolved 0.56 g of 3-[2-[2-(tert-butoxy)-2-oxoethyl]-8-(3-methylbutylidene)-3-oxo-1-thia-4-azaspiro[4.5]decan-4-yl]-propionic acid. At ambient temperature, 0.21 g of benzyl alcohol, 0.23 g of 1-hydroxybenzotriazole monohydrate and 0.31 g of dicyclohexyl carbodiimide were successively added. After stirring the resulting mixture for 24 hours at the same temperature as above, the insoluble matter was filtered off. The filtrate was washed successively with 2 mol/L hydrochloric acid, 15 water, saturated aqueous solution of sodium hydrogen carbonate and saturated aqueous solution of sodium chloride, and dried over anhydrous magnesium sulfate, and then the solvent was distilled off under reduced pressure. Purification of the residue by column chromatography [eluent: hexane:ethyl acetate = 6:1] gave 0.17 g of benzyl 3-[2-[2-(tert-butoxy)-2-oxoethyl]-8-(3-methylbutylidene)-3-oxo-1-thia-4-azaspiro[4.5]decan-4-yl]-propionate as a light yellow oily product.

20 25 NMR (CDCl₃) δ: 0.88(6H,d,J=6.4Hz), 1.4-2.9(14H,m), 1.46(9H,s), 3.15(1H,dd,J=3.8Hz,16.7Hz), 3.4-3.7(2H,m), 4.08(1H,dd,J=3.8Hz,9.9Hz), 5.1-5.3(1H,m), 5.11(2H,s),



7.35(5H,s)

Example 11

In 7 ml of N,N-dimethylformamide was added 0.70 g of 3-[2-[2-(tert-butoxy)-2-oxoethyl]-8-(3-methylbutylidene)-3-oxo-1-thia-4-azaspiro[4.5]decan-4-yl]-propionic acid. After adding 0.14 ml of ethyl iodide and 0.25 g of anhydrous potassium carbonate at 0-5°C, the resulting mixture was stirred at ambient temperature for 3 hours. The resulting mixture was 10 poured into a mixture of ice water and ethyl acetate, pH was adjusted to 2.0 with 2 mol/L hydrochloric acid, and the organic layer was separated. The organic layer was washed successively with water, saturated aqueous solution of sodium hydrogen carbonate and saturated 15 aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. Thus, 0.70 g of ethyl 3-[2-[2-(tert-butoxy)-2-oxoethyl]-8-(3-methylbutylidene)-3-oxo-1-thia-4-azaspiro[4.5]decan-4-yl]-propionate was obtained as a light yellow oily 20 product.

NMR (CDCl₃) δ: 0.88(6H,d,J=6.1Hz), 1.25(3H,t,J=7.1Hz), 1.46(9H,s), 1.6-2.8(14H,m), 3.15(1H,dd,J=3.9Hz,16.6Hz), 3.4-3.7(2H,m), 3.9-4.2(1H,m), 4.13(2H,q,J=7.1Hz), 5.1- 25 5.3(1H,m)



Example 12

The procedure of Example 11 was repeated to obtain benzyl 3-[2-[2-(methoxy-2-oxoethyl)-8-(3-methylbutylidene)-3-oxo-1-thia-4-azaspiro[4.5]decan-4-yl]-propionate.

NMR (CDCl₃) δ: 0.87 (6H, d, J=6.1Hz), 1.4-2.8 (14H, m), 3.19 (1H, dd, J=3.9Hz, 16.8Hz), 3.4-3.8 (2H, m), 3.71 (3H, s), 4.12 (1H, dd, J=3.9Hz, 9.4Hz), 5.11 (2H, s), 5.1-5.3 (1H, m), 7.34 (5H, s)

10 Example 13

The procedure of Example 5 was repeated to obtain 2-[4-[3-(ethoxy-3-oxopropyl)-8-(3-methylbutylidene)-3-oxo-1-thia-4-azaspiro[4.5]decan-2-yl]-acetic acid.

15 NMR (CDCl₃) δ: 0.88 (6H, d, J=5.4Hz), 1.26 (3H, t, J=7.1Hz), 1.4-3.8 (17H, m), 4.15 (2H, q, J=7.1Hz), 4.0-4.3 (1H, m), 5.1-5.3 (1H, m), 10.2 (1H, bs)

Example 14

In 10 ml of methylene chloride was dissolved 20 0.96 g of 2-[4-[3-(benzyloxy)-3-oxopropyl]-8-(3-methylbutylidene)-3-oxo-1-thia-4-azaspiro[4.5]decan-2-yl]-acetic acid. After adding 0.18 ml of thionyl chloride at ambient temperature, the resulting mixture was stirred for one hour under reflux. The reaction 25 mixture was concentrated under reduced pressure, and the concentrate was dissolved in 10 ml of dioxane. The



resulting solution was dropwise added at 0-5°C to an ethyl ether solution containing diazomethane prepared from 5.00 g of N-methylnitrosourea, 3.00 g of potassium hydroxide, 4.00 ml of water and 15 ml of ethyl ether,

5 and the resulting mixture was stirred at ambient temperature for 30 minutes. The reaction mixture was poured into a mixture of water, acetic acid and ethyl acetate, and the organic layer was separated. The organic layer thus obtained was washed successively

10 with water, saturated aqueous solution of sodium hydrogen carbonate and saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was dissolved in a

15 mixture of 10 ml dioxane and 10 ml water, and the resulting solution was added to a mixture of 0.16 g of silver benzoate and 3.00 ml of triethylamine at ambient temperature and stirred for 2 hours. The reaction mixture was poured into a mixture of water and ethyl

20 acetate, pH was adjusted to 2.0 with 2 mol/L hydrochloric acid, and the organic layer was separated. The organic layer thus obtained was washed successively with water and saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate,

25 and the solvent was distilled off under reduced pressure. Purification of the residue by column chromatography [eluent: chloroform: ethanol = 80:1] gave 0.36 g of 3-[4-[3-(benzyloxy)-3-oxopropyl]-8-(3-



methylbutylidene)-3-oxo-1-thia-4-azaspiro[4.5]decan-2-yl]-propionic acid as a light yellow oily product.

NMR (CDCl₃) δ: 0.89(6H,d,J=6.1Hz), 1.4-2.8(17H,m), 3.4-3.7 (2H,m), 3.8-4.0(1H,m), 5.12(2H,s), 5.1-5.3(1H,m),
5 7.35(5H,s), 8.1-8.9(1H,bs)

Example 15

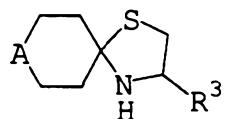
In a solvent mixture consisting of 21 ml of ethanol and 9 ml of water were dissolved 3.10 g of 4-(4-isopropylphenoxy)-1-cyclohexanone, 2.35 g of L-10 cysteine hydrochloride monohydrate and 1.10 g of sodium acetate. The mixture was stirred at ambient temperature for 6 hours. The reaction mixture was concentrated under reduced pressure, and water and ethyl ether were added to the concentrate. The 15 deposited crystal was collected by filtration, and there was obtained 2.45 g of (3R)-8-(4-isopropylphenoxy)-1-thia-4-azaspiro[4.5]decan-3-carboxylic acid as a colorless crystalline product.
NMR (d₆-DMSO+D₂O) δ: 1.17(6H,d,J=6.8Hz), 1.3-2.3(8H,m),
20 2.6-3.4(3H,m), 3.8-4.2(1H,m), 4.2-4.6(1H,m),
6.85(2H,d,J=8.5Hz), 7.13(2H,d,J=8.5Hz)

Example 16

The procedure of Example 15 was repeated to obtain the compound listed in Tables 58 to 60.



[Table 58]



No.	A	R ³
16(1)		COOH
16(2)		COOH
16(3)		COOH
16(4)		COOH
16(5)		COOH
16(6)		COOH



[Table 59]

No.	A	R ³
16(7)		▲ COOH
16(8)		▲ COOH
16(9)		▲ COOH
16(10)		▲ COOH
16(11)		▲ COOH
16(12)		▲ COOH
16(13)		···· COOH



[Table 60]

No.	A	R^{13}
16(14)		▲ COOH
16(15)		▲ COOH
16(16)		▲ COOH
16(17)		▲ COOH



Properties of the compounds shown in Tables 58-60 are as follows.

16(1)

NMR (d_6 -DMSO+D₂O) δ : 1.16 (6H, d, $J=6.8$ Hz), 1.3-2.3 (8H, m), 2.6-3.0 (2H, m), 3.1-3.4 (1H, m), 3.9-4.2 (1H, m), 4.2-4.6 (1H, m), 6.85 (2H, d, $J=8.5$ Hz), 7.13 (2H, d, $J=8.5$ Hz)

16(2)

NMR (d_6 -DMSO+D₂O) δ : 1.3-2.3 (8H, m), 2.7-3.0 (1H, m), 3.1-3.4 (1H, m), 3.81 (3H, s), 3.9-4.7 (2H, m), 7.06 (2H, d, $J=8.7$ Hz), 7.89 (2H, d, $J=8.7$ Hz)

16(3)

NMR (d_6 -DMSO) δ : 1.3-2.3 (8H, m), 2.7-3.0 (1H, m), 3.1-3.4 (1H, m), 3.69 (3H, s), 3.9-4.1 (1H, m), 4.2-4.5 (1H, m), 4.6-5.6 (2H, bs), 6.8-7.0 (4H, m)

15 16(4)

NMR (d_6 -DMSO) δ : 1.3-2.3 (8H, m), 2.42 (3H, s), 2.7-3.0 (1H, m), 3.1-3.4 (1H, m), 3.9-4.1 (1H, m), 4.2-4.6 (1H, m), 4.8-6.2 (2H, bs), 6.92 (2H, d, $J=8.7$ Hz), 7.23 (2H, d, $J=8.7$ Hz)

20 16(5)

NMR (d_6 -DMSO) δ : 1.4-2.4 (8H, m), 2.7-3.0 (1H, m), 3.1-3.4 (1H, m), 3.15 (3H, s), 3.9-4.1 (1H, m), 4.3-5.2 (3H, m), 7.18 (2H, d, $J=8.7$ Hz), 7.82 (2H, d, $J=8.7$ Hz)

16(6)

25 NMR (d_6 -DMSO) δ : 1.17 (3H, t, $J=7.1$ Hz), 1.4-2.5 (9H, m), 2.7-3.0 (1H, m), 3.1-3.4 (1H, m), 3.8-4.3 (1H, m), 5.2-7.2 (2H, bs), 4.05 (2H, q, $J=7.1$ Hz)



16(7)

NMR(d_6 -DMSO) δ : 1.27 (9H, s), 1.5-2.4 (8H, m), 2.7-3.0 (1H, m), 3.1-3.4 (1H, m), 3.9-4.2 (1H, m), 4.4-6.4 (3H, bs), 7.35 (4H, s)

5 16(11)

NMR($CDCl_3$) δ : 0.87 (6H, d, $J=6.4$ Hz), 1.2-2.8 (11H, m), 3.1-3.6 (2H, m), 4.35 (1H, t, $J=7.6$ Hz), 5.19 (1H, t, $J=7.3$ Hz), 7.7-8.2 (2H, m)

16(13)

10 NMR($CDCl_3$) δ : 0.87 (6H, d, $J=6.1$ Hz), 1.2-2.8 (11H, m), 3.1-3.6 (2H, m), 4.34 (1H, t, $J=7.8$ Hz), 5.19 (1H, t, $J=7.1$ Hz), 6.9-7.5 (2H, m)

16(14)

NMR(d_6 -DMSO) δ : 1.5-2.4 (10H, m), 2.7-3.0 (5H, m), 3.2-3.6 (1H, m), 3.9-4.6 (2H, m), 5.07 (2H, bs), 6.6-6.9 (2H, m), 7.0-7.2 (1H, m)

16(15)

NMR($CDCl_3$) δ : 0.6-2.8 (15H, m), 3.1-3.6 (2H, m), 4.35 (1H, dd, $J=6.8$ Hz, 7.6Hz), 5.18 (1H, t, $J=7.6$ Hz), 7.87

20 (1H, bs)

16(16)

NMR(d_6 -DMSO) δ : 0.89 (6H, d, $J=5.9$ Hz), 1.5-3.5 (11H, m), 3.8-4.2 (1H, m), 4.8-5.2 (1H, m)

16(17)

25 NMR($CDCl_3$) δ : 0.89 (6H, d, $J=6.3$ Hz), 1.0-2.8 (13H, m), 3.1-3.7 (2H, m), 4.2-4.5 (1H, m), 5.12 (1H, t, $J=3.5$ Hz), 6.36 (2H, bs)



Example 17

In 50 ml of methylene chloride were dissolved 2.40 g of (3R)-8-(4-isopropylphenoxy)-1-thia-4-azaspiro[4.5]decan-3-carboxylic acid and 2.23 ml of 5 triethylamine. To the solution thus obtained was dropwise added 1.41 g of benzoyl chloride at 0-5°C, and the resulting mixture was stirred at the same temperature as above for 3 hours. The reaction mixture was poured into ice water, pH was adjusted to 1.0 with 10 2 mol/L hydrochloric acid, and the organic layer was separated. The organic layer thus obtained was washed successively with water and saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate, and the solvent was distilled off under 15 reduced pressure. Ethyl ether was added to the residue thus obtained, and the deposited crystal was collected by filtration. Thus, 2.10 g of (3R)-4-benzoyl-8-(4-isopropylphenoxy)-1-thia-4-azaspiro[4.5]decan-3-carboxylic acid was obtained as a colorless crystalline 20 product.

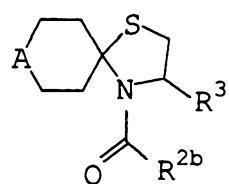
NMR (d_6 -DMSO+D₂O) δ : 1.17(6H,d,J=6.8Hz), 1.3-2.3(6H,m), 2.6-3.7(5H,m), 4.4-4.6(1H,m), 4.7-4.9(1H,m), 6.87(2H,d,J=8.6Hz), 7.15(2H,d,J=8.6Hz), 7.2-7.5(5H,m)

Example 18

25 The procedure of Example 17 was repeated to obtain the compounds listed in Tables 61 to 63.



[Table 61]



No.	A	R ^{2b}	R ³
18 (1)			••• COOH
18 (2)			▲ COOH
18 (3)			▲ COOH
18 (4)			▲ COOH
18 (5)			▲ COOH
18 (6)			▲ COOH
18 (7)			▲ COOH

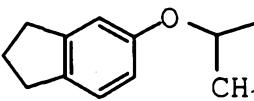
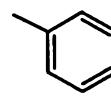
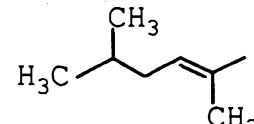
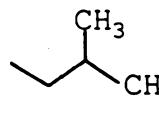
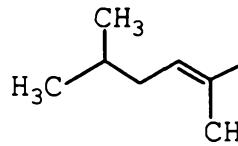
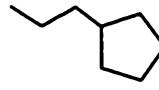


[Table 62]

No.	A	R ^{2b}	R ³
18 (8)			► COOH
18 (9)		-CH ₃	► COOH
18 (10)			► COOH
18 (11)			► COOH
18 (12)		-CH ₂ CH ₂ COOEt	► COOH
18 (13)		-CH ₂ (CH ₂) ₃	► COOH
18 (14)			► COOH
18 (15)		 COOH
18 (16)			► COOH



[Table 63]

No.	A	R ^{2b}	R ³
18(17)			— COOH
18(18)			— COOH
18(19)			— COOH

Properties of the compounds of Tables 61-63 are as follows.

18(1)

NMR (d₆-DMSO) δ: 1.17 (6H, d, J=6.8Hz), 1.3-2.3 (6H, m),
 5 2.6-3.7 (5H, m), 4.4-4.6 (1H, m), 4.7-4.9 (1H, m), 6.87
 (2H, d, J=8.6Hz), 7.15 (2H, d, J=8.6Hz), 7.2-7.6 (6H, m)

18(2)

NMR (d₆-DMSO+D₂O) δ: 1.4-2.4 (6H, m), 3.0-3.7 (4H, m), 3.82
 (3H, s), 4.6-4.9 (2H, m), 7.06 (2H, d, J=8.4Hz), 7.40
 10 (5H, s), 7.93 (2H, d, J=8.4Hz)

18(3)

NMR (d₆-DMSO+D₂O) δ: 1.3-2.3 (6H, m), 2.9-3.6 (4H, m), 3.69
 (3H, s), 4.3-4.6 (1H, m), 4.7-4.9 (1H, m), 6.7-7.0 (4H, m),
 7.2-7.6 (5H, m)



18 (4)

NMR (d_6 -DMSO+D₂O) δ : 1.3-2.3 (6H, m), 2.42 (3H, s), 2.9-3.7 (4H, m), 4.4-4.7 (1H, m), 4.7-4.9 (1H, m), 6.94 (2H, d, $J=8.7\text{Hz}$), 7.25 (2H, d, $J=8.7\text{Hz}$), 7.39 (5H, s)

5 18 (5)

NMR (d_6 -DMSO+D₂O) δ : 1.3-2.3 (6H, m), 2.8-3.7 (4H, m), 3.16 (3H, s), 4.6-4.9 (2H, m), 7.17 (2H, d, $J=8.7\text{Hz}$), 7.40 (5H, s), 7.86 (2H, d, $J=8.7\text{Hz}$)

18 (6)

10 NMR (CDCl₃) δ : 1.4-3.8 (15H, m), 4.6-4.9 (1H, m), 5.10 (2H, s), 6.7-7.1 (1H, m), 7.2-7.5 (10H, m), 8.93 (1H, bs)

18 (7)

NMR (d_6 -DMSO) δ : 1.28 (9H, s), 1.5-2.4 (6H, m), 2.9-3.8 (5H, m), 4.6-5.0 (2H, m), 7.37 (9H, s)

15 18 (8)

NMR (CDCl₃+D₂O) δ : 0.89 (6H, d, $J=5.9\text{Hz}$), 1.4-3.4 (13H, m), 4.7-4.9 (1H, m), 5.1-5.3 (1H, m), 7.2-7.7 (5H, m)

18 (9)

NMR (CDCl₃) δ : 1.21 (6H, d, $J=7.1\text{Hz}$), 1.4-2.6 (6H, m), 2.11 (3H, s), 2.6-3.6 (5H, m), 4.0-5.2 (3H, m), 6.82 (2H, d, $J=8.7\text{Hz}$), 7.12 (2H, d, $J=8.7\text{Hz}$)

18 (10)

NMR (d_6 -DMSO) δ : 1.3-3.8 (18H, m), 4.6-4.9 (1H, m), 5.0-5.3 (1H, m), 6.68 (1H, bs), 7.1-7.6 (5H, m)

25 18 (11)

NMR (CDCl₃) δ : 1.09 (3H, t, $J=7.5\text{Hz}$), 1.18 (3H, t, $J=7.5\text{Hz}$), 1.4-3.6 (20H, m), 4.6-4.9 (1H, m), 5.0-5.3 (1H, m), 7.32 (5H, s), 9.46 (1H, bs)



18 (12)

NMR (d_6 -DMSO+D₂O) δ : 1.19 (3H, t, $J=7.1$ Hz), 1.3-3.7 (14H, m), 3.82 (3H, s), 4.06 (2H, q, $J=7.1$ Hz), 4.6-4.8 (1H, m), 5.1-5.3 (1H, m), 7.06 (2H, d, $J=8.5$ Hz), 7.91 (2H, d, $J=8.5$ Hz)

5 (2H, d, $J=8.5$ Hz)

18 (14)

NMR (CDCl₃) δ : 1.26 (3H, t, $J=7.1$ Hz), 1.4-2.6 (7H, m), 2.9-3.4 (4H, m), 4.14 (2H, q, $J=7.1$ Hz), 4.7-4.9 (1H, m), 7.1-7.5 (5H, m), 8.57 (1H, bs)

10 18 (16)

NMR (d_6 -DMSO+D₂O) δ : 0.84 (6H, d, $J=6.6$ Hz), 1.3-2.2 (10H, m), 2.6-3.5 (6H, m), 4.6-4.8 (1H, m), 7.1-7.5 (5H, m)

18 (17)

NMR (CDCl₃) δ : 1.4-2.4 (10H, m), 2.6-3.0 (5H, m), 3.0-3.8

15 (1H, m), 4.0-4.5 (1H, m), 4.6-4.8 (1H, m), 6.6-6.9 (2H, m), 7.08 (1H, d, $J=7.6$ Hz), 7.35 (5H, bs), 8.2-8.8 (1H, m)

18 (18)

NMR (CDCl₃) δ : 0.7-1.1 (12H, m), 1.3-3.4 (16H, m), 4.8-5.3 (2H, m), 8.69 (1H, bs)

20 18 (19)

NMR (CDCl₃) δ : 0.88 (6H, d, $J=6.1$ Hz), 1.0-3.4 (26H, m), 4.9-5.3 (2H, m), 6.8-8.0 (1H, m)

Example 19(1)

In a mixture of 0.70 ml of ethanol and 0.30 ml of water were dissolved 0.30 g of 4-(4-isopropylphenoxy)-1-cyclohexanone and 0.21 g of D-penicillamine. The solution thus formed was stirred at



ambient temperature for 4 hours. The reaction mixture was poured into a solvent mixture consisting of water and ethyl acetate, and the organic layer was separated. The organic layer was washed successively with water 5 and saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. Hexane was added to the residue, and the deposited crystal was collected by filtration. Thus, 0.32 g of (3S)-8-(4-10 isopropylphenoxy)-2,2-dimethyl-1-thia-4-azaspiro[4.5]decane-3-carboxylic acid was obtained as a colorless crystalline product.

15 NMR (CDCl₃) δ: 1.1-2.5 (20H,m), 2.7-3.1(1H,m), 3.9-4.5(2H,m), 4.77(2H,bs), 6.7-7.2(4H,m)

19(2)

Using L-penicillamine, the procedure of 19 (1) was repeated to obtain (3R)-8-(4-isopropylphenoxy)-2,2-dimethyl-1-thia-4-azaspiro[4.5]decane-3-carboxylic acid.

20 NMR (CDCl₃) δ: 1.2-2.5(20H,m), 2.6-3.1(1H,m), 4.0-4.6(2H,m), 5.83(2H,bs), 6.7-7.4(4H,m)

Examples 20

The procedure of Example 17 was repeated to obtain the following compounds.

25 20(1)

(3S)-4-Benzoyl-8-(4-isopropylphenoxy)-2,2-dimethyl-1-thia-4-azaspiro[4.5]decane-3-carboxylic acid



NMR (CDCl₃) δ: 1.22 (6H, d, J=6.8Hz), 1.38 (3H, s), 1.69 (3H, s), 1.4-3.7 (9H, m), 4.0-4.6 (2H, m), 6.1-6.6 (1H, bs), 6.84 (2H, d, J=8.6Hz), 7.14 (2H, d, J=8.6Hz), 7.0-7.5 (5H, m)

5 20 (2)

(3R)-4-Benzoyl-8-(4-isopropylphenoxy)-2,2-dimethyl-1-thia-4-azaspiro[4.5]decane-3-carboxylic acid
NMR (CDCl₃) δ: 1.1-3.8 (21H, m), 4.0-4.8 (3H, m), 6.8-7.7 (9H, m)

10 Example 21

In 56 ml of methylene chloride was dissolved 2.80 g of (3R)-4-benzoyl-8-(4-isopropylphenoxy)-1-thia-4-azaspiro[4.5]decane-3-carboxylic acid, to which were successively added at 0-5°C 0.56 ml of ethanol, 0.16 g 15 of N,N-dimethylaminopyridine and 1.98 g of dicyclohexyl carbodiimide. After stirring the mixture at ambient temperature for 24 hours, the insoluble matter was filtered off. The filtrate was poured into ice water, pH was adjusted to 2.0 with 2 mol/L hydrochloric acid, 20 and the organic layer was separated. The organic layer thus obtained was washed successively with water, saturated aqueous solution of sodium hydrogen carbonate and saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate, and the solvent 25 was distilled off under reduced pressure. Purification of the residue by column chromatography [eluent: toluene:ethyl acetate = 50:1] gave 0.85 g of ethyl



(3R)-4-benzoyl-8-(4-isopropylphenoxy)-1-thia-4-azaspiro[4.5]decane-3-carboxylate as a colorless oily product.

NMR (CDCl₃) δ: 1.21 (6H, d, J=6.8Hz), 1.21 (3H, t, J=7.1Hz),
 5 1.4-2.4 (6H, m), 2.6-3.8 (5H, m), 4.13 (2H, q, J=7.1Hz), 4.4-
 4.6 (1H, m), 4.7-5.0 (1H, m), 6.88 (2H, d, J=8.7Hz),
 7.11 (2H, d, J=8.7Hz), 7.35 (5H, s)

Example 22

The procedure of Example 21 was repeated to
 10 obtain the following compounds.

22(1)

Ethyl (3S)-4-benzoyl-8-(4-isopropylphenoxy)-1-thia-4-azaspiro[4.5]decane-3-carboxylate
 NMR (CDCl₃) δ: 1.21 (6H, d, J=6.8Hz), 1.22 (3H, t, J=7.1Hz),
 15 1.4-2.4 (6H, m), 2.6-3.8 (5H, m), 4.13 (2H, q, J=7.1Hz), 4.4-
 4.6 (1H, m), 4.8-5.0 (1H, m), 6.89 (2H, d, J=8.8Hz),
 7.12 (2H, d, J=8.8Hz), 7.3-7.6 (5H, m)

22(2)

Ethyl (3R)-4-benzoyl-3-(tert-butoxycarbonyl)-1-thia-4-azaspiro[4.5]decane-8-carboxylate
 NMR (CDCl₃) δ: 1.25 (3H, t, J=7.1Hz), 1.39 (9H, s), 1.4-
 2.6 (7H, m), 2.9-3.5 (4H, m), 4.13 (2H, q, J=7.1Hz),
 4.67 (1H, dd, J=3.1Hz, 5.0Hz), 7.34 (5H, s)

Example 23

25 In a mixture consisting of 23 ml of ethanol and 23 ml of tetrahydrofuran was dissolved 2.30 g of



ethyl (3R)-4-benzoyl-3-(tert-butoxycarbonyl)-1-thia-4-azaspiro[4.5]decane-8-carboxylate. Then, 15.9 ml of 1 mol/L aqueous solution of sodium hydroxide was added at 0-5°C and the resulting mixture was stirred at ambient 5 temperature for 2 hours. The solvent was distilled off under reduced pressure, the residue thus obtained was added to a mixture of water and ethyl acetate, and the aqueous layer was separated. Ethyl acetate was added to the aqueous layer, pH was adjusted to 2.0 with 2 10 mol/L hydrochloric acid, and the organic layer was separated. The organic layer was washed successively with water and saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced 15 pressure. Isopropyl ether was added to the residue and the deposited crystal was collected by filtration. Thus, 1.78 g of (3R)-4-benzoyl-3-(tert-butoxycarbonyl)-1-thia-4-azaspiro[4.5]decane-8-carboxylic acid was obtained as a colorless crystalline product.

20 NMR (CDCl₃) δ: 1.39(9H,s), 1.4-2.6(7H,m), 2.9-3.5(4H,m), 4.68(1H,dd,J=3.2Hz,4.6Hz), 7.35(5H,s), 9.63(1H,bs)

Example 24

In 6 ml of methylene chloride was dissolved 0.40 g of (3R)-4-benzoyl-3-(tert-butoxycarbonyl)-1-thia-4-azaspiro[4.5]decane-8-carboxylic acid. After 25 adding 0.17 ml of oxalyl chloride and 0.06 ml of N,N-dimethylformamide at ambient temperature, the resulting



mixture was stirred at the same temperature as above for 2 hours. The solvent was distilled off under reduced pressure, and the residue was subjected to an azeotropic distillation treatment with toluene several 5 times. Thus, 0.40 g of a yellow oily product was obtained.

The 0.40 g of the yellow oily product obtained above dissolved in 4 ml of methylene chloride was dropwise added at 0-5°C to a solution of 0.28 g of 10 4-isopropylaniline and 0.15 ml of triethylamine in 4 ml of methylene chloride. The resulting mixture was stirred at the same temperature as above for 30 minutes and then at ambient temperature for one hour. The reaction mixture was poured into ice water, pH was 15 adjusted to 2.0 with 2 mol/L hydrochloric acid, and the organic layer was separated. The organic layer thus obtained was washed successively with water, saturated aqueous solution of sodium hydrogen carbonate and saturated aqueous solution of sodium chloride and dried 20 over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue thus obtained was purified by column chromatography [eluent: hexane:ethyl acetate = 3:1] and then treated with a mixture of hexane and isopropyl ether. The deposited 25 crystal was collected by filtration, and there was obtained 0.40 g of tert-butyl (3R)-4-benzoyl-8-[(4-isopropylanilino)carbonyl]-1-thia-4-azaspiro[4.5]- decane-3-carboxylate.



NMR (CDCl₃) δ: 1.21(6H, d, J=6.8Hz), 1.38(9H, s), 1.5-2.5(7H, m), 2.7-3.5(5H, m), 4.66(1H, dd, J=3.1Hz, 4.8Hz), 7.0-7.7(10H, m)

Example 25

5 The procedure of Example 24 was repeated to obtain tert-butyl (3R)-4-benzoyl-8-[(4,5-dimethyl-1,3-thiazol-2-yl)amino]carbonyl]-1-thia-4-azaspiro[4.5]-decane-3-carboxylate.

NMR (CDCl₃) δ: 1.39(9H, s), 1.5-2.5(7H, m), 2.31(6H, s),
10 2.9-3.5(4H, m), 4.66(1H, dd, J=3.2Hz, 4.6Hz), 7.34(5H, s),
7.8-8.5(1H, bs)

Example 26

In 7 ml of methylene chloride was dissolved 0.35 g of tert-butyl (3R)-4-benzoyl-8-[(4-isopropylanilino)-carbonyl]-1-thia-4-azaspiro[4.5]-decane-3-carboxylate. After adding 1.8 ml of trifluoroacetic acid at 0-5°C, the resulting mixture was stirred at ambient temperature for 6 hours. After distilling off the solvent under reduced pressure, the residue was several times subjected to an azeotropic distillation treatment together with toluene and then purified by column chromatography [eluent: chloroform:ethanol = 20:1]. The residue was treated with ethyl ether, and the deposited crystal was collected by filtration to obtain 0.12 g of (3R)-4-benzoyl-8-[(4-isopropylanilino)carbonyl]-1-thia-4-



azaspiro[4.5]decane-3-carboxylic acid as a colorless crystalline product.

NMR (d_6 -DMSO) δ : 1.17(6H, d, $J=6.8\text{Hz}$), 1.4-3.7(13H, m), 4.6-4.9(1H, m), 7.0-7.7(9H, m), 9.83(1H, bs)

5 Example 27

The procedure of Example 26 was repeated to obtain (3R)-4-benzoyl-8-[(4,5-dimethyl-1,3-thiazol-2-yl)amino]-carbonyl}-1-thia-4-azaspiro[4.5]decane-3-carboxylic acid.

10 NMR (d_6 -DMSO) δ : 1.6-2.5(7H, m), 2.15(3H, s), 2.22(3H, s), 2.8-3.8(4H, m), 4.6-4.8(1H, m), 7.38(5H, s), 7.6-8.0(1H, bs), 11.4-12.4(1H, bs)

Example 28

In 10 ml of anhydrous tetrahydrofuran was dissolved 0.50 g of (3R)-4-benzoyl-8-(4-isopropylphenoxy)-1-thia-4-azaspiro[4.5]decane-3-carboxylic acid. Then, at 0-5°C, 0.22 g of benzyl 3-aminopropionate, 0.19 g of 1-hydroxybenzotriazole monohydrate and 0.26 g of dicyclohexyl carbodiimide were added successively. After stirring the resulting mixture at the same temperature as above for 30 minutes and then at ambient temperature for 5 hours, the insoluble matter was filtered off. The filtrate was poured into a mixture of water and ethyl acetate, pH 25 was adjusted to 2.0 with 2 mol/L hydrochloric acid, and the organic layer was separated. The organic layer



thus obtained was washed successively with water, saturated aqueous solution of sodium hydrogen carbonate and saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate, and the solvent 5 was distilled off under reduced pressure. Purification of the residue by column chromatography [eluent: hexane:ethyl acetate = 2:1] gave 0.55 g of benzyl 3-{{(3R)-4-benzoyl-8-(4-isopropylphenoxy)-1-thia-4-azaspiro[4.5]decan-3-yl}carbonyl}amino-propionate as a 10 colorless oily product.

NMR (CDCl₃) δ: 1.21(6H,d,J=6.8Hz), 1.4-2.3(6H,m), 2.4-3.8(9H,m), 4.4-4.6(1H,m), 4.7-4.9(1H,m), 5.13(2H,s), 6.87(2H,d,J=8.8Hz), 6.6-7.0(1H,m), 7.12(2H,d,J=8.8Hz), 7.33(10H,s)

15 Example 29

In 8 ml of ethanol was dissolved 0.38 g of benzyl 3-{{(3R)-4-benzoyl-8-(4-isopropylphenoxy)-1-thia-4-azaspiro[4.5]decan-3-yl}carbonyl}amino)-propionate. Then, 1.90 ml of 1 mol/L aqueous solution 20 of sodium hydroxide was added at 0-5°C, and the resulting mixture was stirred at ambient temperature for 4 hours. The reaction mixture was poured into a mixture of ice water and ethyl acetate, and the aqueous layer was separated. Ethyl acetate was added to the 25 aqueous layer thus obtained, pH was adjusted to 2.0 with 2 mol/L hydrochloric acid, and the organic layer was separated. The organic layer thus obtained was



washed successively with water and saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. Thus, 0.30 g of 3-(([(3R)-4-
5 benzoyl-8-(4-isopropylphenoxy)-1-thia-4-azaspiro[4.5]-
decan-3-yl]carbonyl}amino)-propionic acid was obtained
as a colorless oily product.

NMR (CDCl₃) δ: 1.21 (6H, d, J=6.8Hz), 1.4-2.3 (6H, m), 2.4-
3.8 (9H, m), 4.4-4.6 (1H, m), 4.7-4.9 (1H, m), 6.83
10 (2H, d, J=8.8Hz), 7.0-7.5 (6H, m), 7.11 (2H, d, J=8.8Hz),
8.00 (1H, bs)

Example 30

In 4 ml of methanol was suspended 0.40 g of
(3R)-4-benzoyl-8-[4-(methoxycarbonyl)phenoxy]-1-thia-4-
15 azaspiro[4.5]decane-3-carboxylic acid. After adding
thereto 4.40 ml of 1 mol/L aqueous solution of sodium
hydroxide at 0-5°C, the resulting mixture was stirred at
ambient temperature for 6 hours. The reaction mixture
was poured into ice water, pH was adjusted to 2.0 with
20 2 mol/L hydrochloric acid, and then the product was
extracted with ethyl acetate. The organic layer was
washed successively with water and saturated aqueous
solution of sodium chloride and dried over anhydrous
magnesium sulfate, and the solvent was distilled off
25 under reduced pressure. Ethyl ether and ethyl acetate
was added to the residue, and the deposited crystal was
collected by filtration to obtain 0.30 g of (3R)-4-



benzoyl-8-(4-carboxyphenoxy)-1-thia-4-azaspiro[4.5]-
decane-3-carboxylic acid as a colorless crystalline
product.

NMR (d_6 -DMSO+D₂O) δ : 1.4-2.4 (6H, m), 3.0-3.7 (4H, m),
5 4.6-4.9 (2H, m), 7.04 (2H, d, J =8.6Hz), 7.40 (5H, s), 7.92
(2H, d, J =8.6Hz)

Example 31

The procedure of Example 30 was repeated to obtain the following compounds.

10 31(1)

(3R)-8-(4-Carboxyphenoxy)-4-(3-
carboxypropanoyl)-1-thia-4-azaspiro[4.5]decane-3-
carboxylic acid

NMR (d_6 -DMSO+D₂O) δ : 1.3-3.7 (14H, m) 4.5-4.8 (1H, m),
15 5.1-5.3 (1H, m), 7.04 (2H, d, J =8.5Hz), 7.90
(2H, d, J =8.5Hz)

31(2)

(3R)-4-Benzoyl-8-{[(2-carboxyethyl)amino]-
carbonyl}-1-thia-4-azaspiro[4.5]decane-3-carboxylic
20 acid

NMR (d_6 -DMSO+D₂O) δ : 1.3-3.6 (15H, m), 4.6-4.9 (1H, m), 7.1-
7.6 (5H, bs)

Example 32

In 9 ml of anhydrous tetrahydrofuran was
25 dissolved 0.60 g of (3R)-4-benzoyl-8-{[(3-(benzoyloxy)-
3-oxopropyl)-amino]carbonyl}-1-thia-4-



azaspiro[4.5]decane-3-carboxylic acid. At 0-5°C, 0.26 g of L-methionine methyl ester hydrochloride, 0.19 g of 1-hydroxybenzotriazole monohydrate and 0.14 ml of N-methylmorpholine were successively added. After

5 stirring the mixture at the same temperature as above for 30 minutes, 0.27 g of dicyclohexyl carbodiimide was added and the resulting mixture was stirred at the same temperature as above for 30 minutes and then at ambient temperature for 6 hours. The insoluble matter was

10 filtered off, the filtrate was added to a mixture of water and ethyl acetate, pH was adjusted to 2.0 with 2 mol/L hydrochloric acid, and the organic layer was separated. The organic layer was washed successively with water, saturated aqueous solution of sodium

15 hydrogen carbonate and saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. Purification of the residue by column chromatography [eluent: toluene:ethyl acetate =

20 1:2] gave 0.62 g of methyl (2S)-2-({[(3R)-4-benzoyl-8-({[3-(benzyloxy)-3-oxopropyl]amino}carbonyl)-1-thia-4-azaspiro[4.5]decan-3-yl]carbonyl}amino)-4-(methylthio)-butyrate as a colorless oily product.

NMR (CDCl₃) δ: 1.5-2.8 (13H, m), 2.06 (3H, s), 2.9-3.7

25 (6H, m), 3.79 (3H, s), 4.5-4.9 (2H, m), 5.15 (2H, s), 6.0-6.3 (1H, m), 6.6-6.9 (1H, m), 7.36 (10H, s)



Example 33

The procedure of Example 29 was repeated to obtain (2S)-2-{[(3R)-4-benzoyl-8-[(2-carboxyethyl)-amino]-carbonyl]-1-thia-4-azaspiro[4.5]decan-3-yl)carbonyl]amino}-4-(methylthio)butyric acid.

NMR (d_6 -DMSO) δ : 1.3-3.8 (19H, m), 2.00 (3H, s), 4.0-4.4 (1H, m), 4.5-4.8 (1H, m), 7.33 (5H, bs), 7.7-8.2 (2H, m), 11.6-13.0 (2H, bs)

Example 34

10 In 5 ml of anhydrous tetrahydrofuran was dissolved 0.50 g of 3-[8-(3-methylbutylidene)-3-oxo-1-thia-4-azaspiro[4.5]decan-4-yl]-propionic acid. After adding 0.25 ml of benzaldehyde and 0.45 g of potassium tert-butoxide at ambient temperature, the resulting
15 mixture was heated under reflux for 6 hours. The reaction mixture was poured into a mixture of water and ethyl acetate, pH was adjusted to 2.0 with 2 mol/L hydrochloric acid, and the organic layer was separated. The organic layer was washed successively with water
20 and saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. Isopropyl ether was added to the residue and the deposited crystal was collected by filtration. Thus, 0.32 g of
25 3-[8-(3-methylbutylidene)-3-oxo-2-(1-phenylmethylidene)-1-thia-4-azaspiro[4.5]decan-4-yl]-propionic acid was obtained as a colorless crystalline



product.

NMR (CDCl₃) δ: 0.91 (6H, d, J=6.4Hz), 1.4-3.0 (13H, m), 3.5-3.9 (2H, m), 5.1-5.3 (1H, m), 7.0-7.8 (7H, m)

Example 35

5 The procedure of Example 10 was repeated to obtain the following compounds.

35(1)

Benzyl 3-[8-(3-methylbutylidene)-3-oxo-2-(1-phenylmethylidene)-1-thia-4-azaspiro[4.5]decan-4-yl-

10 propionate

NMR (CDCl₃) δ: 0.91 (6H, d, J=6.1Hz), 1.4-3.0 (13H, m), 3.6-4.0 (2H, m), 5.1-5.3 (1H, m), 5.14 (2H, s), 7.2-7.7 (11H, m)

35(2)

15 tert-Butyl 2-[8-(4-isopropylphenoxy)-3-oxo-4-phenethyl-1-thia-4-azaspiro[4.5]decan-2-yl]-acetate

NMR (CDCl₃) δ: 1.22 (6H, d, J=6.8Hz), 1.47 (9H, s), 1.5-2.3 (8H, m), 2.4-3.1 (5H, m), 3.2-3.5 (2H, m), 3.9-4.2 (2H, m), 6.81 (2H, d, J=8.6Hz), 7.13 (2H, d, J=8.6Hz), 7.27 (5H, s)

20 Example 36

In 7 ml of methylene chloride was dissolved 0.32 g of tert-butyl 2-[8-(4-isopropylphenoxy)-3-oxo-4-phenethyl-1-thia-4-azaspiro[4.5]decan-2-yl]-acetate.

25 After adding 0.33 g of m-chloroperbenzoic acid at 0-5°C, the resulting mixture was stirred at ambient temperature for 24 hours. The reaction mixture was



poured into a saturated aqueous solution of sodium hydrogen carbonate, and the organic layer was separated. The organic layer was washed successively with water and saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. Purification of the residue by column chromatography [eluent: hexane:ethyl acetate = 8:1] gave 0.17 g of tert-butyl 2-[8-(4-isopropylphenoxy)-1,1,3-trioxo-4-phenethyl-1-thia-4-azaspiro[4.5]decan-2-yl]-acetate as a colorless oily product.

NMR (CDCl₃) δ: 1.24 (6H, d, J=6.8Hz), 1.50 (9H, s), 1.8-2.5 (8H, m), 2.6-3.9 (7H, m), 4.1-4.3 (1H, m), 4.5-4.7 (1H, m), 6.83 (2H, d, J=8.6Hz), 7.17 (2H, d, J=8.6Hz), 7.26 (5H, s)

15 Example 37

The procedure of Example 5 was repeated to obtain 2-[8-(4-isopropylphenoxy)-1,1,3-trioxo-4-phenethyl-1-thia-4-azaspiro[4.5]decan-2-yl]-acetic acid.

20 NMR (CDCl₃) δ: 1.24 (6H, d, J=6.8Hz), 1.8-2.5 (8H, m), 2.7-4.0 (7H, m), 4.1-4.4 (1H, m), 4.5-4.7 (1H, m), 6.83 (2H, d, J=8.7Hz), 6.6-6.8 (1H, bs), 7.17 (2H, d, J=8.7Hz), 7.27 (5H, s)

Example 38

25 In 4 ml of N,N-dimethylformamide was dissolved 0.29 g of 2-[8-(4-isopropylphenoxy)-3-oxo-4-



phenethyl-1-thia-4-azaspiro[4.5]decan-2-yl]-acetic acid. After adding 0.10 g of glycine methyl ester hydrochloride and 0.08 g of N-methylmorpholine at ambient temperature, the resulting mixture was stirred 5 at the same temperature as above for 5 minutes. Then, 0.14 g of 1-hydroxybenzotriazole monohydrate and 0.17 g of dicyclohexyl carbodiimide were added at 0-5°C, and the resulting mixture was stirred at ambient temperature for 24 hours. The reaction mixture was 10 poured into a mixture of water and ethyl acetate, pH was adjusted to 2.0 with 2 mol/L hydrochloric acid, and the organic layer was separated. The organic layer thus obtained was washed successively with water, saturated aqueous solution of sodium hydrogen carbonate 15 and saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. Purification of the residue thus obtained by column chromatography [eluent: toluene:ethyl acetate = 2:1] gave 0.35 g of 20 methyl 2-({[2-[8-(4-isopropylphenoxy)-3-oxo-4-phenethyl-1-thia-4-azaspiro[4.5]decan-2-yl]acetyl]-amino)-acetate as a colorless oily product.

NMR (CDCl₃) δ: 1.23 (6H, d, J=6.8Hz), 1.4-3.7 (15H, m), 3.77 (3H, s), 4.0-4.3 (3H, m), 4.4-4.6 (1H, m), 6.6-6.9 25 (1H, bs), 6.82 (2H, d, J=8.9Hz), 7.16 (2H, d, J=8.9Hz), 7.29 (5H, s)



Example 39

The procedure of Example 8 was repeated to obtain 2-({2-[8-(4-isopropylphenoxy)-3-oxo-4-phenethyl-1-thia-4-azaspiro[4.5]decan-2-yl]acetyl}amino)-acetic acid.

NMR (CDCl₃) δ: 1.23 (6H, d, J=6.8Hz), 1.4-3.1 (11H, m), 3.1-3.9 (4H, m), 4.0-4.3 (3H, m), 4.4-4.6 (1H, m), 6.82 (2H, d, J=8.5Hz), 7.15 (2H, d, J=8.5Hz), 7.2-7.5 (7H, m)

Example 40

In 15 ml of methylene chloride was suspended 0.30 g of 1H-2-pyrrolecarboxylic acid. To the suspension thus obtained were added at 0-5°C 0.28 ml of oxalyl chloride and 0.06 ml of N,N-dimethylformamide, and the resulting mixture was stirred at ambient temperature for 24 hours. The solvent was distilled off under reduced pressure from the reaction mixture, and the residue was subjected to an azeotropic distillation treatment with toluene. Thus, 0.36 g of 1H-2-pyrrolecarbonyl chloride was obtained as a brown crystalline product.

In 6 ml of methylene chloride were dissolved 0.30 g of (3R)-8-(4-isopropylphenoxy)-1-thia-4-azaspiro[4.5]decane-3-carboxylic acid and 0.47 ml of triethylamine. After adding 0.18 g of 1H-2-pyrrolecarbonyl chloride at 0-5°C, the resulting mixture was stirred at ambient temperature for 24 hours. The reaction mixture was poured into ice water, pH was



adjusted to 2.0 with 2 mol/L hydrochloric acid, and the organic layer was separated. The organic layer thus obtained was washed successively with water and saturated aqueous solution of sodium chloride and dried 5 over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. After purifying the residue by column chromatography [eluent: chloroform:ethanol = 200:1], isopropyl ether was added and the deposited crystal was collected by filtration. 10 Thus, 0.14 g of (3R)-8-(4-isopropylphenoxy)-4-(1H-2-pyrrolylcarbonyl)-1-thia-4-azaspiro[4.5]decane-3-carboxylic acid was obtained as a yellow crystalline product.

NMR (d_6 -DMSO) δ : 1.17 (6H, d, $J=6.8\text{Hz}$), 1.5-2.4 (6H, m), 15 2.4-3.8 (6H, m), 4.5-4.7 (1H, m), 5.3-5.6 (1H, m), 6.0-6.4 (2H, m), 6.8-7.4 (6H, m)

Example 41

The procedure of Example 40 was repeated to obtain the following compounds.

20 41(1)

(3R)-8-(4-Isopropylphenoxy)-4-(2-thienylcarbonyl)-1-thia-4-azaspiro[4.5]decane-3-carboxylic acid

NMR (CDCl_3) δ : 1.21 (6H, d, $J=6.8\text{Hz}$), 1.4-2.4 (6H, m), 2.6-25 3.8 (5H, m), 4.4-4.6 (1H, m), 5.1-5.3 (1H, m), 6.8-7.5 (8H, m)



41(2)

(3R)-8-(4-Isopropylphenoxy)-4-(3-quinolylcarbonyl)-1-thia-4-azaspiro[4.5]decane-3-carboxylic acid

5 NMR (CDCl₃) δ: 1.22 (6H, d, J=6.8Hz), 1.4-2.5 (6H, m), 2.7-4.0 (5H, m), 4.5-4.8 (2H, m), 6.8-7.3 (5H, m), 7.5-8.3 (5H, m), 9.2-9.4 (1H, m)

41(3)

(3R)-8-(4-Isopropylphenoxy)-4-[(2-methyl-1,3-thiazol-4-yl)carbonyl]-1-thia-4-azaspiro[4.5]decane-3-carboxylic acid

NMR (CDCl₃) δ: 1.22 (6H, d, J=6.8Hz), 1.4-2.3 (6H, m), 2.55 (3H, s), 2.6-3.9 (5H, m), 4.4-4.6 (1H, m), 5.9-6.0 (1H, m), 6.93 (2H, d, J=8.8Hz), 7.12 (2H, d, J=8.8Hz), 7.97 (1H, s), 15 8.9-9.2 (1H, bs)

41(4)

(3R)-8-(4-Isopropylphenoxy)-4-(2-pyrazinylcarbonyl)-1-thia-4-azaspiro[4.5]decane-3-carboxylic acid

20 NMR (d₆-DMSO) δ: 1.17 (6H, d, J=6.8Hz), 1.3-2.3 (6H, m), 2.4-3.8 (5H, m), 4.5-4.7 (1H, m), 5.4-5.6 (1H, m), 6.8-7.3 (5H, m), 8.5-9.0 (3H, m)

41(5)

(3R)-8-(4-Isopropylphenoxy)-4-(4-methoxybenzoyl)-1-thia-4-azaspiro[4.5]decane-3-carboxylic acid

NMR (CDCl₃) δ: 1.21 (6H, d, J=6.8Hz), 1.4-2.4 (6H, m), 2.7-3.6 (5H, m), 3.79 (3H, s), 4.4-4.5 (1H, m), 4.8-5.0



(1H, m), 6.7-7.4 (8H, m), 9.4-9.6 (1H, bs)

41 (6)

(3R)-4-{4-[(Diethylamino)carbonyl]benzoyl}-8-(4-isopropylphenoxy)-1-thia-4-azaspiro[4.5]decane-3-

5 carboxylic acid

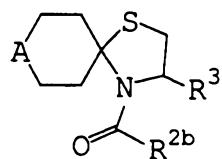
NMR (CDCl₃) δ: 1.0-1.3 (12H, m), 1.3-2.4 (6H, m) 2.7-3.8 (9H, m), 4.4-4.7 (2H, m), 6.91 (2H, d, J=8.5Hz), 7.12 (2H, d, J=8.5Hz), 7.36 (4H, s), 8.4-8.6 (1H, bs)

Further, in the same manner as above, the

10 compounds of Tables 64 and 65 were obtained.



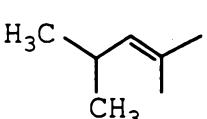
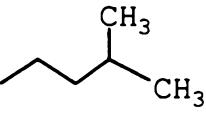
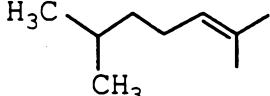
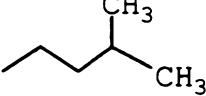
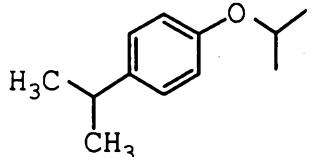
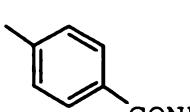
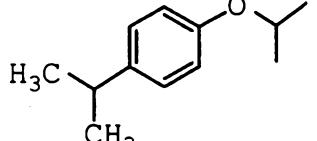
[Table 64]



No.	A	R^{2b}	R^3
41(7)			••• COOH
41(8)			▲ COOH
41(9)			▲ COOH
41(10)			▲ COOH
41(11)			▲ COOH



[Table 65]

No.	A	R ^{2b}	R ³
41(12)			··· COOH
41(13)			← COOH
41(14)			··· COOH
41(15)			··· COOH



Properties of the compounds shown in Tables 64 and 65 are as follows.

41(7)

NMR(CDCl₃) δ: 0.7-1.1 (12H,m), 1.2-3.4 (18H,m), 4.8-5.3
5 (2H,m), 6.9-7.4 (1H,m)

41(8)

NMR(CDCl₃) δ: 0.8-1.1 (12H,m), 1.3-3.5 (18H,m), 4.9-5.3
(2H,m), 8.0-8.2 (1H,m)

41(9)

10 NMR(CDCl₃) δ: 0.7-1.1 (9H,m), 1.1-3.6 (19H,m), 4.8-5.3
(2H,m), 8.37 (1H,bs)

41(10)

NMR(CDCl₃) δ: 0.87(12H,d,J=6.1Hz), 1.1-3.4 (20H,m), 4.8-
5.3 (2H,m), 6.05 (1H,bs)

15 41(11)

NMR(CDCl₃) δ: 0.7-1.1 (9H,m), 1.1-3.5 (19H,m), 4.8-5.3
(2H,m), 6.88 (1H,bs)

41(12)

NMR(CDCl₃) δ: 0.6-3.7 (28H,m), 4.8-5.1 (2H,m)

20 41(13)

NMR(CDCl₃) δ: 0.3-3.6 (32H,m), 4.8-5.5 (2H,m), 8.00
(1H,bs)

41(14)

NMR(CDCl₃) δ: 1.0-2.4 (23H,m), 2.6-3.7 (8H,m), 4.0-4.6
25 (1H,m), 4.9-5.2 (1H,m), 6.7-7.5 (9H,m)

41(15)

NMR(CDCl₃) δ: 1.1-4.8 (22H,m), 5.0-5.2 (1H,m), 6.0-6.3
(1H,m), 6.4-7.5 (6H,m), 10.0-10.8 (2H,m)



Example 42

In 80 ml of acetone was dissolved 8.50 g of 2-[4-[3-(benzyloxy)-3-oxopropyl]-8-(3-methylbutylidene)-3-oxo-1-thia-4-azapiro[4.5]decan-2-yl]-acetic acid. After adding thereto 40 ml of an aqueous solution containing 1.50 g of sodium hydrogen carbonate, the resulting mixture was stirred at ambient temperature for 30 minutes. The solvent was distilled off under reduced pressure and the residue was 10 subjected to an azeotropic distillation treatment with ethanol to obtain 8.00 g of sodium 2-[4-[3-(benzyloxy)-3-oxopropyl]-8-(3-methylbutylidene)-3-oxo-1-thia-4-azapiro[4.5]decan-2-yl]-acetate.

NMR (d_6 -DMSO) δ : 0.86 (6H, d, $J=6.4\text{Hz}$), 1.4-2.9 (13H, m), 15 3.2-3.7 (4H, m), 3.9-4.1 (1H, m), 5.09 (2H, s), 5.0-5.3 (1H, m), 7.37 (5H, s)

Example 43

The procedure of 19(2) was repeated to obtain (3R)-2,2-dimethyl-8-(3-methylbutylidene)-1-thia-4-20 azapiro[4.5]decan-3-carboxylic acid

NMR (CDCl_3) δ : 1.1-2.8 (17H, m), 4.03 (1H, s), 5.0-5.3 (1H, m)

Example 44

The procedure of Example 40 was repeated to obtain (3R)-2,2-dimethyl-8-(3-methylbutylidene)-4-(4-25 methylpentanoyl)-1-thia-4-azapiro[4.5]decan-3-carboxylic acid



NMR (CDCl₃) δ: 0.5-3.5 (34H, m), 4.52 (1H, s), 5.0-5.3 (1H, m), 8.96 (1H, bs)

Example 45

The procedure of Example 1 was repeated to
5 obtain 2-[4-[2-(tert-butoxy)-2-oxoethyl]-8-(3-
methylbutylidene)-3-oxo-1-thia-4-azaspiro[4.5]decan-2-
yl]-acetic acid.

NMR (CDCl₃) δ: 0.88 (6H, d, J=6.4Hz), 1.2-2.9 (21H, m),
3.32 (1H, dd, J=17.1, 4.9Hz), 3.89 (2H, d, J=2.2Hz), 4.24
10 (1H, dd, J=4.7, 5.4Hz), 5.0-5.4 (1H, m)

Example 46

In 10 ml of N,N-dimethylformamide was dissolved 1.0 g of 2-[4-[2-(tert-butoxy)-2-oxoethyl]-8-(3-methylbutylidene)-3-oxo-1-thia-4-azaspiro[4.5]decan-2-yl]-acetic acid. After adding 0.42 ml of 2-iodopropane and 0.67 g of anhydrous potassium carbonate at ambient temperature, the resulting mixture was stirred at ambient temperature for 17 hours. The reaction mixture was poured into a mixture of ice water and ethyl acetate, pH was adjusted to 2.0 with 2 mol/L hydrochloric acid, and the organic layer was separated. The organic layer thus obtained was washed successively with water, saturated aqueous solution of sodium hydrogen carbonate and saturated aqueous solution of 25 sodium chloride and dried over anhydrous magnesium sulfate, and the solvent was distilled off under



reduced pressure. Purification of the residue by column chromatography [eluent: hexane:ethyl acetate = 17:3] gave 1.0 g of isopropyl 2-[4-[2-(tert-butoxy)-2-oxoethyl]-8-(3-methylbutylidene)-3-oxo-1-thia-4-5 azaspiro[4.5]decan-2-yl]-acetate as a light yellow oily product.

NMR (CDCl₃) δ: 0.88 (6H, d, J=6.4Hz), 1.1-2.8 (26H, m), 3.26 (1H, dd, J=16.8, 3.7Hz), 3.8-4.3 (4H, m), 4.8-5.3 (2H, m)

10 Example 47

In 3 ml of diethyl ether was dissolved 0.33 g of isopropyl 2-[4-[2-(tert-butoxy)-2-oxoethyl]-8-(3-methylbutylidene)-3-oxo-1-thia-4-azaspiro[4.5]decan-2-yl]-acetate. Then, 1 ml of a 5.39 mol/L solution of dry hydrogen chloride in dioxane was added and the resulting mixture was stirred at the same temperature as above for 2 hours. Further, 1 ml of 5.39 mol/L solution of dry hydrogen chloride in dioxane was added and the resulting mixture was stirred for one hour, 15 after which 3 ml of 5.39 mol/L solution of dry hydrogen chloride in dioxane was added and the resulting mixture was stirred for one hour. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography [eluent: chloroform]. 20 Then, hexane was added, and the deposited crystal was collected by filtration. Thus, 0.08 g of 2-[2-(2-isopropoxy-2-oxoethyl)-8-(3-methylbutylidene)-3-oxo-1-



thia-4-azaspiro[4.5]decan-4-yl]-acetic acid was obtained as a colorless crystalline product.

NMR (CDCl₃) δ: 0.87 (6H, d, J=6.3Hz), 1.26 (6H, d, J=6.1Hz), 1.3-2.8 (11H, m), 3.21 (1H, dd, J=16.6, 3.8Hz), 3.9-4.4 5 (4H, m), 4.9-5.3 (2H, m), 7.10 (1H, bs)

Example B-1

In 5 ml of methylene chloride was suspended 0.25 g of 4-isopropylbenzoic acid. Then, at ambient temperature, 0.12 ml of thionyl chloride and 0.03 ml of 10 N,N-dimethylformamide were added. After stirring the mixture at the same temperature as above for one hour, the solvent was distilled off under reduced pressure, and an azeotropic distillation treatment using toluene was carried out to obtain 0.25 g of 4-isopropylbenzoic 15 acid chloride. To a suspension of 0.50 g of trifluoroacetic acid salt of 2-(4-benzyl-3-oxo-1-thia-4,8-diazaspiro[4.5]decan-2-yl]-acetic acid in 5 ml methylene chloride were successively added dropwise at 0-5°C 0.64 ml of triethylamine and a solution of 0.25 g 20 of 4-isopropylbenzoic acid chloride in 5 ml methylene chloride. The resulting mixture was stirred at ambient temperature for 24 hours. The reaction mixture was poured into ice water, pH was adjusted to 1.0 with 2 mol/L hydrochloric acid, and the organic layer was 25 separated. The organic layer was washed successively with water and saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate,



and the solvent was distilled off under reduced pressure. Purification of the residue by column chromatography [eluents: toluene:ethyl acetate = 1:1, followed by chloroform] gave 0.30 g of 2-[4-benzyl-8-5 (4-isopropylbenzoyl)-3-oxo-1-thia-4,8-diazaspiro[4.5]-decan-2-yl]-acetic acid as a light yellow solid product.

NMR (CDCl₃) δ: 1.24 (6H, d, J=6.8Hz), 1.4-2.4 (4H, m), 2.5-3.6 (5H, m), 3.6-4.8 (5H, m), 7.26 (9H, bs), 8.3-8.5 10 (1H, bs)

Example B-2

The procedure of Example B-1 was repeated to obtain the following compounds.

B-2(1)

15 2-[4-Benzyl-8-[4-(methoxycarbonyl)benzoyl]-3-oxo-1-thia-4,8-diazaspiro[4.5]decan-2-yl]-acetic acid
 NMR (CDCl₃) δ: 1.4-2.3 (4H, m), 2.5-3.8 (5H, m), 3.93 (3H, s), 4.2-4.9 (4H, m), 7.27 (5H, s), 7.40 (2H, d, J=8.1Hz), 8.07 (2H, d, J=8.1Hz), 7.8-8.0 (1H, bs)

B-2(2)

2-[4-Benzyl-8-[(4-methylphenyl)sulfonyl]-3-oxo-1-thia-4,8-diazaspiro[4.5]decan-2-yl]-acetic acid
 NMR (CDCl₃) δ: 1.5-1.8 (2H, m), 2.0-2.9 (5H, m), 2.44 (3H, s), 3.1-3.5 (1H, m), 3.7-4.0 (2H, m), 4.1-4.3 (1H, m), 25 4.46 (1H, d, J=14.0Hz), 4.68 (1H, d, J=14.0Hz), 7.1-7.5 (7H, m), 7.61 (2H, d, J=8.1Hz), 7.9-8.3 (1H, bs)



Example B-3

In 2.5 ml of ethanol was dissolved 0.51 g of ethyl 4-[2-(2-ethoxy-2-oxoethyl)-3-oxo-4-phenethyl-1-thia-4,8-diazaspiro[4.5]decan-8-yl]-oxobutanoate.

5 After adding 2.5 ml of 1 mol/L aqueous solution of sodium hydroxide at 0-5°C, the resulting mixture was stirred at ambient temperature for 1.5 hours. The reaction mixture was poured into a mixture of ice water and ethyl acetate, pH was adjusted to 2.0 with 2 mol/L 10 hydrochloric acid, and the organic layer was separated. The organic layer thus obtained was washed successively with water and saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced 15 pressure. Thus, 0.34 g of 4-[2-(carboxymethyl)-3-oxo-4-phenethyl-1-thia-4,8-diazaspiro[4.5]decan-8-yl]-4-oxobutanoic acid was obtained as a yellow oily product.

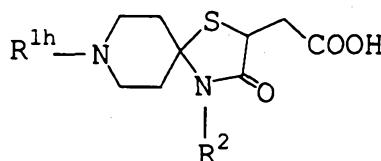
NMR (d_6 -DMSO) δ : 1.4-4.7 (19H, m), 7.2-7.8 (7H, m)

Example B-4

20 The procedure of Example B-3 was repeated to obtain the compounds shown in Table 66.



[Table 66]



No.	R^{1h}	R^2
4 (1)	$-\text{COCH}_2\text{C}_6\text{H}_5$	$-\text{CH}_2\text{CH}_2\text{C}_6\text{H}_5$
4 (2)	$-\text{COCH}_2\text{CH}_2\text{CH}_2\text{C}_6\text{H}_5$	$-\text{CH}_2\text{CH}_2\text{C}_6\text{H}_5$
4 (3)	$-\text{COCH}=\text{CHC}_6\text{H}_5$	$-\text{CH}_2\text{CH}_2\text{C}_6\text{H}_5$
4 (4)	$ \begin{array}{c} \text{NH}_2 \bullet \text{HCl} \\ \\ \text{C}_2 \text{H}_4 \text{COCH} \\ \\ \text{CH}_2\text{CH} \left(\text{CH}_3 \right)_2 \end{array} $	$-\text{CH}_2\text{CH}_2\text{C}_6\text{H}_5$
4 (5)	$ \begin{array}{c} \text{NHCOCH}_3 \\ \\ \text{C}_2 \text{H}_4 \text{COCH} \\ \\ \text{CH}_2\text{CH}_2\text{CONH}_2 \end{array} $	$-\text{CH}_2\text{CH}_2\text{CH} \left(\text{CH}_3 \right)_2$
4 (6)	$-\text{COCH}_2\text{CH}_2\text{COOH}$	$-\text{CH}_2\text{CH}_2\text{CH} \left(\text{CH}_3 \right)_2$
4 (7)	$-\text{COCH}(\text{OH})\text{C}_6\text{H}_5$	$-\text{CH}_2\text{CH}_2\text{C}_6\text{H}_5$
4 (8)	$-\text{CO-C}_6\text{H}_4-\text{COOH}$	$-\text{CH}_2\text{C}_6\text{H}_5$
4 (9)	$-\text{COO} \left(\text{CH}_3 \right)_3$	$-\text{CH}_2\text{CH}_2\text{COOH}$

Properties of the compounds of Table 66 are as follows.

B-4 (1)

NMR (CDCl₃) δ: 1.3-2.2 (4H, m), 2.6-3.6 (6H, m), 3.76 (2H, s), 3.8-4.8 (5H, m), 7.0-7.8 (11H, m)

5 B-4 (2)

NMR (CDCl₃) δ: 1.4-2.2 (6H, m), 2.2-4.0 (13H, m), 4.1-4.3 (1H, m), 4.6-4.9 (1H, m), 7.0-7.7 (11H, m)

B-4 (3)

NMR (CDCl₃) δ: 1.6-2.2 (4H, m), 2.4-3.8 (8H, m), 4.0-4.4 (2H, m), 4.6-5.0 (1H, m), 6.3-6.7 (1H, m), 6.85 (1H, d, J=15.4Hz), 7.1-7.6 (10H, m), 7.70 (1H, d, J=15.4Hz)

B-4 (4)

NMR (d₆-DMSO) δ: 0.8-1.1 (6H, m), 1.4-2.2 (7H, m), 2.3-4.7 (12H, m), 7.28 (5H, s), 8.1-8.6 (3H, bs)

15 B-4 (5) (Measured in the form of sodium salt)

NMR (d₆-DMSO) δ: 0.94 (6H, d, J=5.9Hz), 1.0-3.6 (17H, m), 1.83 (3H, s), 3.8-4.8 (4H, m), 6.7 (1H, bs), 8.0-8.4 (2H, m)

B-4 (6)

20 NMR (CDCl₃) δ: 0.93 (6H, d, J=5.4Hz), 1.1-2.5 (7H, m), 2.5-3.6 (10H, m), 3.9-4.9 (3H, m), 8.9 (2H, bs)

B-4 (7)

NMR (d₆-DMSO) δ: 1.2-2.0 (4H, m), 2.4-3.8 (8H, m), 3.8-4.2 (2H, m), 4.3-4.7 (1H, m), 5.4-5.8 (2H, m), 7.1-7.5 (11H, m)

25 B-4 (8)

NMR (CDCl₃) δ: 1.1-2.4 (4H, m), 2.4-3.8 (5H, m), 3.9-4.9 (4H, m), 7.28 (5H, s), 7.39 (2H, d, J=8.0Hz), 8.07 (2H, d, J=8.0Hz), 8.6-9.0 (2H, bs)



B-4 (9)

NMR (d_6 -DMSO+D₂O) δ : 1.2-3.7 (12H, m), 1.41 (9H, s), 3.6-4.3 (3H, m), 12.4 (2H, bs)

Example B-5

5 In 1.4 ml of ethanol was dissolved 0.31 g of 4-[2-(carboxymethyl)-3-oxo-4-phenethyl-1-thia-4,8-diazaspiro[4.5]decan-8-yl]-4-oxobutanoic acid. After adding 1.36 ml of 1 mol/L aqueous solution of sodium hydroxide at 0-5°C, the resulting mixture was stirred at 10 ambient temperature for 5 hours. The reaction mixture was poured into a mixture of ice water and ethyl acetate, and the aqueous layer was separated. The aqueous layer thus obtained was concentrated under reduce pressure to obtain 0.32 g of disodium 4-[2-(carboxymethyl)-3-oxo-4-phenethyl-1-thia-4,8-diazaspiro[4.5]decan-8-yl]-4-oxobutanoate as a colorless solid product.

Example C-1

DMF was added to 1.875 g (1.200 mmol) of Rink 20 Amide MBHA resin to swell the resin. Then, 2 ml of 20% piperidine/DMF solution was added and shaken for 20 minutes. The resin was six times washed with DMF, 1.28 g of Fmoc-Leu-OH, 552 mg of HOBr·H₂O, 0.58 ml of DIPCDI and 18 ml of DMF were added and shaken for 90 minutes. 25 After filtering off the liquid phase, the resin was six times washed with DMF. Then, 24 ml of 20% piperidine/DMF solution was added and shaken for 20



minutes. The resin was six times washed with DMF, and then 1.903 g of (3R)-4-benzoyl-8-[(9H-fluoren-9-ylmethoxy)carbonyl]-1-thia-4,8-diazaspiro[4.5]decan-3-carboxylic acid, 552 mg of HOBt·H₂O, 0.58 ml of DIPCDI and 18 ml of DMF were added and shaken for 90 minutes. After filtering off the liquid phase, the resin was six times washed with DMF. The resin was divided into 15 equal portions, and 2 ml of 20% piperidine/DMF solution was added to one of the portions and shaken for 20 minutes. The resin was six times washed with DMF, and 113 mg of Fmoc-Leu-OH, 37 mg of HOBt·H₂O, 39 μL of DIPCDI and 1.2 ml of DMF were added and shaken for 2 hours. After filtering off the liquid phase, the resin was washed with DMF six times. Then, 2 ml of 20% piperidine/DMF solution was added and shaken for 20 minutes. After filtering off the liquid phase, the resin was six times washed with DMF. Then, 1.2 ml of DMF-DCM (1:1) mixture, 0.29 ml of acetic anhydride and 0.53 ml of DIEA were added and shaken for one hour. After filtering off the liquid phase, the resin was washed four times with DMF and three times with DCM. The resin thus obtained was shaken for four hours together with 6 ml of TFA-methylene chloride (1:1). The insoluble matter was filtered off, the filtrate was concentrated under reduced pressure, 20 ml of diethyl ether was added to the residue, and the resulting crystal was collected by filtration to obtain 46 mg of (3R)-8-[(2S)-2-(acetylamino)-4-methylpentanoyl]-N-



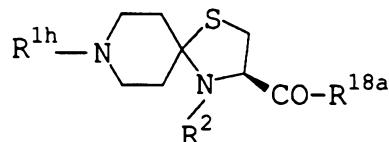
[(1S)-1-(aminocarbonyl)-3-methylbutyl]-4-benzoyl-1-thia-4,8-diazaspiro[4.5]decane-3-carboxamide.

Example C-2

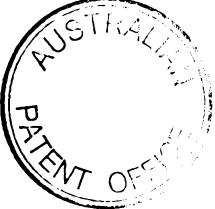
The procedure of Example C-1 was repeated to
5 obtain the following compounds.



[Table 67]



$\text{R}^{1\text{h}}$	$\text{R}^{18\text{a}}$	R^2	calcd.	found	
Ac-Leu	NH ₂	COC ₆ H ₅	460.6	461.4	M+H
Ac-Asp	NH ₂	COC ₆ H ₅			
Ac-Asn	NH ₂	COC ₆ H ₅			
Ac-Glu	NH ₂	COC ₆ H ₅			
Ac-Gln	NH ₂	COC ₆ H ₅			
Ac-Phe	NH ₂	COC ₆ H ₅			
Ac-Lys	NH ₂	COC ₆ H ₅			
Ac-Arg	NH ₂	COC ₆ H ₅			
Ac-His	NH ₂	COC ₆ H ₅			
Ac-Tyr	NH ₂	COC ₆ H ₅			
nC ₃ H ₇ CO	NH ₂	COC ₆ H ₅			
4-ClC ₆ H ₄ CHCHCO	NH ₂	COC ₆ H ₅	503.62	504.4	M+H
4-ClC ₆ H ₄ CH ₂ CO	NH ₂	COC ₆ H ₅			
3-PyCO	NH ₂	COC ₆ H ₅			
4-PyCO	NH ₂	COC ₆ H ₅			
Ac-Leu	Leu-NH ₂	COC ₆ H ₅	573.76	574.4	M+H
Ac-Asp	Leu-NH ₂	COC ₆ H ₅			
Ac-Asn	Leu-NH ₂	COC ₆ H ₅			
Ac-Glu	Leu-NH ₂	COC ₆ H ₅			
Ac-Gln	Leu-NH ₂	COC ₆ H ₅			
Ac-Phe	Leu-NH ₂	COC ₆ H ₅			
Ac-Lys	Leu-NH ₂	COC ₆ H ₅			
Ac-Arg	Leu-NH ₂	COC ₆ H ₅			
Ac-His	Leu-NH ₂	COC ₆ H ₅			
Ac-Tyr	Leu-NH ₂	COC ₆ H ₅			
nC ₃ H ₇ CO	Leu-NH ₂	COC ₆ H ₅			
4-ClC ₆ H ₄ CHCHCO	Leu-NH ₂	COC ₆ H ₅			
4-ClC ₆ H ₄ CH ₂ CO	Leu-NH ₂	COC ₆ H ₅			



Example C-3

DMF was added to 173 mg (0.100 mmol) of Wang resin to swell the resin. Then, 90 mg of Fmoc-Gly-OH, 1.22 mg of DMAP, 48 μ L of DIPCDI and 1.2 ml of DMF were added to the resin and shaken for 2 hours. After filtering off the liquid phase, the resin was six times washed with DMF. Then, 2 ml of 20% piperidine/DMF solution was added and shaken for 20 minutes. After washing the resin six times with DMF, 160 mg of (3R)-4-benzoyl-8-[(9H-fluoren-9-ylmethoxy)carbonyl]-1-thia-4,8-diazaspiro[4.5]decane-3-carboxylic acid, 46 mg of HOBT \cdot H₂O, 48 μ L of DIPCDI and 1.2 ml of DMF were added and shaken for 90 minutes. After filtering off the liquid phase, the resin was six times washed with DMF. Then, 2 ml of 20% piperidine/DMF solution was added and shaken for 20 minutes. The resin was six times washed with DMF, and then 266 mg of Fmoc-Arg(Pmc)-OH, 62 mg of HOBT \cdot H₂O, 64 μ L of DIPCDI and 1.2 ml of DMF were added and shaken for 2 hours. After filtering off the liquid phase, the resin was washed with DMF six times. Then, 2 ml of 20% piperidine/DMF solution was added and shaken for 20 minutes. After filtering off the liquid phase, the resin was washed with DMF six times. Then, 1.2 ml of DMF-DCM (1:1) mixture, 0.29 ml of acetic anhydride and 0.53 ml of DIEA were added and shaken for one hour. The liquid phase was filtered off, and the resin was washed four times with DMF and three times with DCM. Then, 6 ml of TFA-methylene chloride (1:1)



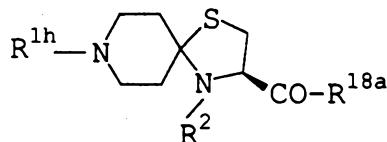
was added and shaken for 4 hours. The insoluble matter was filtered off, the filtrate was concentrated under reduced pressure, 20 ml of diethyl ether was added to the residue, and the resulting crystal was collected by 5 filtration to obtain 66 mg of trifluoroacetic acid salt of 2-({[(3R)-8-((2S)-2-(acetylamino)-5-{[amino(imino)-methyl]amino}pentanoyl)-4-benzoyl-1-thia-4,8-diazaspiro[4.5]decan-3-yl]-carbonyl}amino)-acetic acid.

Example C-4

10 The procedure of Example C-3 was repeated to obtain the following compounds.



[Table 68]



R ^{1h}	R ^{18a}	R ²	calcd.	found	
Ac-Leu	Leu-OH	COC ₆ H ₅	574.75	575.4	M+H
Ac-Asp	Leu-OH	COC ₆ H ₅			
Ac-Asn	Leu-OH	COC ₆ H ₅			
Ac-Gln	Leu-OH	COC ₆ H ₅			
Ac-Gln	Leu-OH	COC ₆ H ₅			
Ac-Phe	Leu-OH	COC ₆ H ₅			
Ac-Lys	Leu-OH	COC ₆ H ₅	589.76	590.4	M+H
Ac-Arg	Leu-OH	COC ₆ H ₅	617.77	618.4	M+H
Ac-His	Leu-OH	COC ₆ H ₅			
Ac-Tyr	Leu-OH	COC ₆ H ₅			
4-ClC ₆ H ₄ CHCHCO	Leu-OH	COC ₆ H ₅	584.3	584.4	M+H
4-ClC ₆ H ₄ CH ₂ CO	Leu-OH	COC ₆ H ₅			
Ac-Arg	Ala-OH	COC ₆ H ₅			
Ac-Arg	Asp-OH	COC ₆ H ₅			
Ac-Arg	Glu-OH	COC ₆ H ₅			
Ac-Arg	Phe-OH	COC ₆ H ₅			
Ac-Arg	Lys-OH	COC ₆ H ₅			
Ac-Arg	Tyr-OH	COC ₆ H ₅			
Ac-Arg	Pro-OH	COC ₆ H ₅			
Ac-Arg	β-Ala-OH	COC ₆ H ₅			
Ac-Arg	D-ala-OH	COC ₆ H ₅			
Ac-Arg	Leu-OH	COCH ₃			
H-Arg	Leu-OH	COCH ₃			
4-ClC ₆ H ₄ CHCHCO	Leu-OH	COCH ₃			
4-ClC ₆ H ₄ CH ₂ CO	Leu-OH	COCH ₃			
4-H ₂ N(HN)CC ₆ H ₄ CO	Leu-OH	COCH ₃			
3-(2-Thienyl)-2- propanoyl	Leu-OH	COCH ₃			
3-(3-Pyridyl)-2- propanoyl	Leu-OH	COCH ₃			
H-Arg	Leu-OH	COC ₆ H ₅			
4-H ₂ N(HN)CC ₆ H ₄ CO	Leu-OH	COC ₆ H ₅			



R ^{1h}	R ^{18a}	R ²	calcd.	found
3-(2-Thienyl)-2-propenoyl	Leu-OH	COC ₆ H ₅		
3-(3-Pyridyl)-2-propenoyl	Leu-OH	COC ₆ H ₅		
2-Oxo-2H-pyran-5-carbonyl	Leu-OH	COC ₆ H ₅		
3-Pyridylcarbonyl	Leu-OH	COC ₆ H ₅		
Ac-Arg	Gly-OH	COCH ₃		
Ac-Arg	Gly-Gly-OH	COCH ₃		
Ac-Arg	D-ala-OH	COCH ₃		
Ac-Arg	β-Ala-OH	COCH ₃		
H-Cit	Leu-OH	COCH ₃		
Ac-Cit	Leu-OH	COCH ₃		

Example C-5

DMF was added to 182 mg (0.100 mmol) of Rink amide MBHA resin to swell the resin. Then, 2 ml of 20% piperidine/DMF solution was added and shaken for 20 minutes. After washing the resin six times with DMF, 106 mg of Fmoc-Leu-OH, 46 mg of HOBr·H₂O, 47 μL of DIPCDI and 2 ml of DMF were added and shaken for 90 minutes. After filtering off the liquid phase, the resin was six times washed with DMF. Then, 2 ml of 20% piperidine/DMF solution was added and shaken for 20 minutes. After washing the resin with DMF six times, 190 mg of 2-{4-[3-(benzoyloxy)-3-oxopropyl]-8-[(9H-fluoren-9-ylmethoxy)carbonyl]-3-oxo-1-thia-4,8-diazaspiro[4.5]decan-2-yl}-acetic acid, 46 mg of HOBr·H₂O, 47 μL of DIPCDI and 2 ml of DMF were added and shaken for 90 minutes. After filtering off the liquid



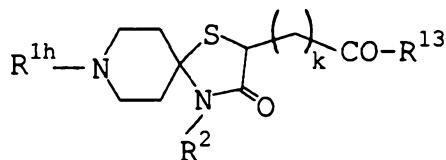
phase, the resin was washed six times with DMF. Then, 2 ml of 20% piperidine/DMF solution was added and shaken for 20 minutes. After washing the resin six times with DMF, 115 mg of Fmoc-Ser(tBu)-OH, 46 mg of 5 HOBt·H₂O, 47 μ L of DIPCDI and 2 ml of DMF were added and shaken for 90 minutes. After filtering off the liquid phase, the resin was washed six times with DMF. Then, 2 ml of 20% piperidine/DMF solution was added and shaken for 20 minutes. After filtering off the liquid 10 phase, the resin was washed six times with DMF. Then, 2 ml of DMF-DCM (1:1) mixture, 0.29 ml of acetic anhydride and 0.53 ml of DIEA were added, and shaken for 40 minutes. After filtering off the liquid phase, the resin was washed four times with DMF and three 15 times with DCM. Then, 6 ml of TFA-methylene chloride (1:1) was added and shaken for 4 hours. The insoluble matter was filtered off, the filtrate was concentrated under reduced pressure, 20 ml of diethyl ether was added to the residue, and the resulting crystal was 20 collected by filtration to obtain 45 mg of benzyl 3-[8-[(2S)-2-(acetylamino)-3-hydroxypropanoyl]-2-(2-[(1S)-1-(aminocarbonyl)-3-methylbutyl]amino)-2-oxoethyl]-3-oxo-1-thia-4,8-diazaspiro[4,5]decan-4-yl]-propionate.

Example C-6

25 The procedure of Example C-5 was repeated to obtain the following compounds.



[Table 69]



R^{1h}	R^{13}	R^2	k	calcd.	found	
Ac-Asn	Leu-NH ₂	CH ₂ CH ₂ CO ₂ CH ₂ C ₆ H ₅	1	660.79	661.4	M+H
Ac-Ala	Leu-NH ₂	CH ₂ CH ₂ CO ₂ CH ₂ C ₆ H ₅	1	617.77	618.3	M+H
Ac-Asp	Leu-NH ₂	CH ₂ CH ₂ CO ₂ CH ₂ C ₆ H ₅	1	661.78	662.3	M+H
Ac-Leu	Asp-NH ₂	CH ₂ CH ₂ CO ₂ CH ₂ C ₆ H ₅	1	661.78	662.3	M+H
Ac-Asp	Asp-NH ₂	CH ₂ CH ₂ CO ₂ CH ₂ C ₆ H ₅	1	663.72	662.4	M+H
Ac-Gln	Asp-NH ₂	CH ₂ CH ₂ CO ₂ CH ₂ C ₆ H ₅	1	676.75	677.3	M+H
Ac-Ser	Asp-NH ₂	CH ₂ CH ₂ CO ₂ CH ₂ C ₆ H ₅	1	635.71	636.3	M+H
Ac-Asn	Asp-NH ₂	CH ₂ CH ₂ CO ₂ CH ₂ C ₆ H ₅	1	662.72	663.3	M+H
Ac-Ala	Asp-NH ₂	CH ₂ CH ₂ CO ₂ CH ₂ C ₆ H ₅	1	619.71	620.2	M+H
Ac-Leu	Gln-NH ₂	CH ₂ CH ₂ CO ₂ CH ₂ C ₆ H ₅	1	674.82	675.4	M+H
Ac-Gln	Gln-NH ₂	CH ₂ CH ₂ CO ₂ CH ₂ C ₆ H ₅	1	689.79	690.3	M+H
Ac-Ser	Gln-NH ₂	CH ₂ CH ₂ CO ₂ CH ₂ C ₆ H ₅	1	648.74	649.3	M+H
Ac-Asn	Gln-NH ₂	CH ₂ CH ₂ CO ₂ CH ₂ C ₆ H ₅	1	675.77	676.3	M+H
Ac-Ala	Gln-NH ₂	CH ₂ CH ₂ CO ₂ CH ₂ C ₆ H ₅	1	632.74	633.3	M+H
Ac-Leu	Leu-NH ₂	CH ₂ CH ₂ CO ₂ CH ₂ C ₆ H ₅	1	659.85	660.4	M+H
Ac-Gln	Leu-NH ₂	CH ₂ CH ₂ CO ₂ CH ₂ C ₆ H ₅	1	674.82	675.4	M+H
Ac-Glu	Asp-NH ₂	CH ₂ CH ₂ CO ₂ CH ₂ C ₆ H ₅	1	677.74	678.4	M+H
Ac-Asp	Asn-NH ₂	CH ₂ CH ₂ CO ₂ CH ₂ C ₆ H ₅	1	662.72	661.4	M-H
Ac-Asn	Asn-NH ₂	CH ₂ CH ₂ CO ₂ CH ₂ C ₆ H ₅	1	661.74	660.4	M-H
Ac-Asp	Glu-NH ₂	CH ₂ CH ₂ CO ₂ CH ₂ C ₆ H ₅	1	677.74	676.4	M-H
Ac-Asn	Glu-NH ₂	CH ₂ CH ₂ CO ₂ CH ₂ C ₆ H ₅	1	676.75	675.4	M-H
Ac-Glu	Glu-NH ₂	CH ₂ CH ₂ CO ₂ CH ₂ C ₆ H ₅	1	691.77	690.4	M-H
Ac-Gln	Glu-NH ₂	CH ₂ CH ₂ CO ₂ CH ₂ C ₆ H ₅	1	690.78	689.4	M-H
Ac-Asp	Gln-NH ₂	CH ₂ CH ₂ CO ₂ CH ₂ C ₆ H ₅	1	676.75	675.4	M-H
Ac-Glu	Gln-NH ₂	CH ₂ CH ₂ CO ₂ CH ₂ C ₆ H ₅	1	690.78	689.4	M-H
Ac-D-Ala	D-Ala-NH ₂	CH ₂ CH ₂ CO ₂ CH ₂ C ₆ H ₅	1	575.7	598.4	M+Na
Ac-Asn	D-Ala-NH ₂	CH ₂ CH ₂ CO ₂ CH ₂ C ₆ H ₅	1	618.71	641.4	M+Na
Ac-D-Ala	Asn-NH ₂	CH ₂ CH ₂ CO ₂ CH ₂ C ₆ H ₅	1	618.71	641.4	M+Na



Example C-7

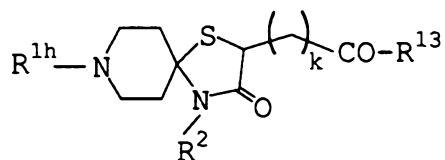
Using Wang resin, Fmoc-Leu-OH, Fmoc-Arg(Pmc)-OH and 2-{4-benzyl-8-[(9H-fluoren-9-ylmethoxy)carbonyl]-3-oxo-1-thia-4,8-diazaspiro[4.5]decan-2-yl}-acetic acid, the procedure of Example C-3 was repeated to obtain (2S)-2-({2-[8-((2S)-2-(acetylamino)-5-{[amino(imino)methyl]amino}-pentanoyl)-4-benzyl-3-oxo-1-thia-4,8-diazaspiro[4.5]decan-2-yl]acetyl}amino)-4-methylvaleric acid.

Example C-8

The procedure of Example C-7 was repeated to obtain the following compounds.



[Table 70]



R ^{1h}	R ¹³	R ²	k
Ac-Gln-Leu	Leu-Ala-Leu-OH	CH ₂ CH ₂ CO ₂ CH ₂ C ₆ H ₅	1
Ac-Gln	Leu-Ala-Leu-OH	CH ₂ CH ₂ CO ₂ CH ₂ C ₆ H ₅	1
Ac-Arg	OH	CH ₂ C ₆ H ₅	1
4-ClC ₆ H ₄ CHCHCO	OH	CH ₂ C ₆ H ₅	1
4-H ₂ N (HN) CC ₆ H ₄ CO	OH	CH ₂ C ₆ H ₅	1
4-ClC ₆ H ₄ CHCHCO	Leu-OH	CH ₂ C ₆ H ₅	1
4-H ₂ N (HN) CC ₆ H ₄ CO	Leu-OH	CH ₂ C ₆ H ₅	1
4-H ₂ N (HN) CC ₆ H ₄ CO	Leu-OH	CH ₂ C ₆ H ₅	1
Ac-Arg	OH	H	1
4-ClC ₆ H ₄ CHCHCO	OH	H	1
4-H ₂ N (HN) CC ₆ H ₄ CO	OH	H	1
Ac-Arg	Leu-OH	H	1
4-ClC ₆ H ₄ CHCHCO	Leu-OH	H	1
4-H ₂ N (HN) CC ₆ H ₄ CO	Leu-OH	H	1
4-H ₂ N (HN) CC ₆ H ₄ CO	Leu-OH	H	1
4-H ₂ N (HN) CC ₆ H ₄ OCH ₂ CO	OH	H	1
4-H ₂ N (HN) CC ₆ H ₄ OCH ₂ CO	OH	CH ₂ C ₆ H ₅	1



Example C-9

DMF was added to 157 mg (0.100 mmol) of Rink amide MBHA resin to swell the resin. Then, 2 ml of 20% piperidine/DMF solution was added and shaken for 20 minutes. After washing the resin six times with DMF, 106 mg of Fmoc-Leu-OH, 46 mg of HOBr·H₂O, 48 μL of DIPCDI and 1.5 ml of DMF were added and shaken for 90 minutes. After filtering off the liquid phase, the resin was six times washed with DMF. Then, 2 ml of 20% piperidine/DMF solution was added and shaken for 20 minutes. After washing the resin six times with DMF, 175 mg of 3-{2-{2-[(2-amino-2-oxoethyl)amino]-2-oxoethyl}-8-[(9H-fluoren-9-ylmethoxy)carbonyl]-3-oxo-1-thia-4,8-diazaspiro[4.5]decan-4-yl}-propionic acid, 46 mg of HOBr·H₂O, 48 μL of DIPCDI and 1.5 ml of DMF were added and shaken for 90 minutes. After filtering off the liquid phase, the resin was six times washed with DMF. Then, 2 ml of 20% piperidine/DMF solution was added and shaken for 20 minutes. After washing the resin six times with DMF, 106 mg of Fmoc-Leu-OH, 46 mg of HOBr·H₂O, 48 μL of DIPCDI and 1.5 ml of DMF were added and shaken for 90 minutes. After filtering off the liquid phase, the resin was washed six times with DMF. Then, 2 ml of 20% piperidine/DMF solution was added and shaken for 20 minutes. After filtering off the liquid phase, the resin was washed six times with DMF. Then, 2 ml of DMF-DCM (1:1) mixture, 0.29 ml of acetic anhydride and 0.53 ml of DIEA were added and



shaken for 90 minutes. After filtering off the liquid phase, the resin was washed four times with DMF and three times with DCM. Then, 6 ml of TFA-methylene chloride (1:1) was added and shaken for 2 hours. The 5 insoluble matter was filtered off, the filtrate was concentrated under reduced pressure, 20 ml of diethyl ether was added to the residue, and the resulting crystal was collected by filtration to obtain 55 mg of (2S)-2-{[3-(8-[(2S)-2-(acetylamino)-4-methylpentanoyl]-10 2-{2-[(2-amino-2-oxoethyl)amino]-2-oxoethyl}-3-oxo-1-thia-4,8-diazaspiro[4.5]decan-4-yl)propanoyl]amino}-4-methylpentanamide.

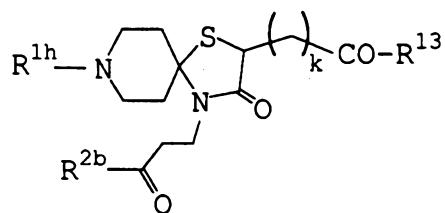
ESI-MS: m/z 626.4 for $(M+H)^+$ (calcd. 625.80 for $C_{28}H_{47}N_7O_7S$)

15 Example C-10

The procedure of Example C-9 was repeated to obtain the following compounds.



[Table 71]



R^{1h}	R^{2b}	R^{13}	k
Ac-Asp	Gly-NH ₂	Leu-NH ₂	1
Ac-Asn	Gly-NH ₂	Leu-NH ₂	1
Ac-Glu	Gly-NH ₂	Leu-NH ₂	1
Ac-Gln	Gly-NH ₂	Leu-NH ₂	1
Ac-Ser	Gly-NH ₂	Leu-NH ₂	1
Ac-Leu	Gly-NH ₂	Asp-NH ₂	1
Ac-Asp	Gly-NH ₂	Asp-NH ₂	1
Ac-Asn	Gly-NH ₂	Asp-NH ₂	1
Ac-Glu	Gly-NH ₂	Asp-NH ₂	1
Ac-Gln	Gly-NH ₂	Asp-NH ₂	1
Ac-Ser	Gly-NH ₂	Asp-NH ₂	1
Ac-Leu	Gly-NH ₂	Glu-NH ₂	1
Ac-Asp	Gly-NH ₂	Glu-NH ₂	1
Ac-Asn	Gly-NH ₂	Glu-NH ₂	1
Ac-Glu	Gly-NH ₂	Glu-NH ₂	1
Ac-Gln	Gly-NH ₂	Glu-NH ₂	1
Ac-Ser	Gly-NH ₂	Glu-NH ₂	1
Ac-Leu	Gly-NH ₂	Gln-NH ₂	1
Ac-Asp	Gly-NH ₂	Gln-NH ₂	1
Ac-Asn	Gly-NH ₂	Gln-NH ₂	1
Ac-Gln	Gly-NH ₂	Gln-NH ₂	1
Ac-Gln	Gly-NH ₂	Gln-NH ₂	1
Ac-Ser	Gly-NH ₂	Gln-NH ₂	1



Referential Example 1

In an atmosphere of nitrogen, 139 g of isobutyltriphenylphosphonium iodide was suspended in 350 ml of anhydrous tetrahydrofuran and cooled to -20°C.

- 5 At the same temperature as above, 176 ml of 1.66 mol/L solution of n-butyllithium in hexane was dropwise added and the resulting mixture was stirred for one hour.
- 10 After elevating the temperature up to the ambient temperature, 175 ml of a solution of 35.0 g of 1,4-cyclohexandione monoethylene ketal in anhydrous tetrahydrofuran was dropwise added while cooling the mixture with water. After stirring the mixture at the same temperature for one hour, the reaction mixture was poured into a mixture of ice water, aqueous solution of
- 15 ammonium chloride and ethyl acetate, and the organic layer was separated. The organic layer was washed successively with water and saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate, and the solvent was distilled off under
- 20 reduced pressure. Ethyl ether was added to the residue, the deposited insoluble matter was filtered off, and the filtrate was concentrated under reduced pressure. To the residue thus obtained were added 150 ml of anhydrous tetrahydrofuran and 150 ml of 6 mol/L
- 25 hydrochloric acid, and the resulting mixture was stirred at ambient temperature for 24 hours. The reaction mixture was poured into a mixture of water and ethyl acetate, and the organic layer was separated.



The organic layer was washed successively with water and saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. Purification

5 of the residue by column chromatography [eluent:

hexane:ethyl acetate = 20:1] gave 28.0 g of 4-(3-methylbutylidene)-1-cyclohexanone as a colorless oily product.

NMR (CDCl₃) δ: 0.91(6H,d,J=6.4Hz), 1.4-2.1(3H,m),

10 2.44(8H,bs), 5.3-5.5(1H,m)

Referential Example 2

In 40 ml of anhydrous tetrahydrofuran were dissolved 4.00 g of 4-isopropylphenol, 5.10 g of 1,4-dioxaspiro[4.5]decan-8-ol and 8.47 g of triphenylphosphine. Then, 14.1 g of 40% solution of diethyl azodicarboxylate in toluene was dropwise added at 0-5°C, and the resulting mixture was stirred at ambient temperature for 24 hours. The reaction mixture was poured into ice water and extracted with ethyl acetate. The organic layer was washed successively with water and saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. Ethyl ether was added to the residue, the deposited insoluble matter was filtered off, and the filtrate was concentrated under reduced pressure. The residue thus obtained was mixed with 60 ml of anhydrous



tetrahydrofuran and 40 ml of 6 mol/L hydrochloric acid and stirred at ambient temperature for 24 hours. The reaction mixture was poured in a mixture of water and ethyl acetate, and the organic layer was separated.

5 The organic layer was washed successively with water and saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. Purification of the residue by column chromatography [eluents: 10 toluene:ethyl acetate = 20:1, followed by hexane:ethyl acetate = 20:1] gave 2.40 g of 4-(4-isopropylphenoxy)-1-cyclohexanone as a colorless oily product.

NMR (CDCl₃) δ: 1.23 (6H, d, J=6.8Hz), 1.8-3.1 (9H, m), 4.5-4.8 (1H, m), 6.88 (2H, d, J=8.5Hz), 7.17 (2H, d, J=8.5Hz)

15 Referential Example 3

The procedure of Referential Example 1 was repeated to obtain the following compounds.

3(1)

4-(1-Methylethylidene)-1-cyclohexanone

20 NMR (CDCl₃) δ: 1.72 (6H, s), 2.2-2.7 (8H, m)

3(2)

4-Ethylidene-1-cyclohexanone

NMR (CDCl₃) δ: 1.65 (3H, d, J=6.8Hz), 2.2-3.2 (8H, m), 5.41 (1H, q, J=6.8Hz)

25 3(3)

5-(4-Oxocyclohexylidene)-valeric acid

NMR (CDCl₃) δ: 1.5-2.8 (14H, m), 5.34 (1H, t, J=7.1Hz), 9.6-



10.4 (1H, bs)

3 (4)

4-Butylenecyclohexanone

NMR (CDCl₃) δ: 0.7-2.7 (15H, m), 5.35 (1H, t, J=7.2Hz),

5 3 (5)

4-(2-Methylpropylidene)cyclohexanone

NMR (CDCl₃) δ: 0.98 (6H, d, J=6.8Hz), 1.5-2.8 (9H, m),

5.18 (1H, d, J=9.3Hz)

3 (6)

10 4-(4-Methylpentylidene)cyclohexanone

Referential Example 4

The procedure of Referential Example 2 was repeated to obtain the following compounds.

4 (1)

15 4-Phenoxy-1-cyclohexanone

NMR (CDCl₃) δ: 1.9-3.0 (8H, m), 4.5-4.9 (1H, m), 6.8-7.5 (5H, m)

4 (2)

Methyl 4-[(4-oxocyclohexyl)oxy]-benzoate

20 NMR (CDCl₃) δ: 1.9-3.0 (8H, m), 3.89 (3H, s), 4.7-5.0 (1H, m), 6.97 (2H, d, J=9.0Hz), 8.00 (2H, d, J=9.0Hz)

4 (3)

4-[4-(Methylthio)phenoxy]-1-cyclohexanone

NMR (CDCl₃) δ: 1.9-3.0 (8H, m), 2.46 (3H, s), 4.5-4.8 (1H, m),
25 6.91 (2H, d, J=8.9Hz), 7.28 (2H, d, J=8.9Hz)

4 (4)

4-(4-Methoxyphenoxy)-1-cyclohexanone



NMR (CDCl₃) δ: 1.8-3.0(8H,m), 3.77(3H,s), 4.4-4.7(1H,m),
6.9-7.0(4H,m)
4(5)

4-(2,3-Dihydro-1H-inden-5-yloxy)cyclohexanone

5 NMR (CDCl₃) δ: 1.8-3.1(14H,m), 4.5-4.8(1H,m), 6.6-
7.0(2H,m), 7.14(1H,d,J=8Hz)

Referential Example 5

In 50 ml of methylene chloride was dissolved 2.50 g of 4-[4-(methylthio)phenoxy]-1-cyclohexanone.

10 After adding 5.48 g of m-chloroperbenzic acid at 0-5°C, the resulting mixture was stirred at ambient temperature for 4 hours. The reaction mixture was poured into water, pH was adjusted to 8.0 with saturated aqueous solution of sodium hydrogen 15 carbonate, and the organic layer was separated. The organic layer thus obtained was washed successively with aqueous solution of sodium thiosulfate, water and saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate, and the solvent was 20 distilled off under reduced pressure.

Recrystallization of the residue from ethanol gave 2.05 g of 4-[4-(methylsulfonyl)phenoxy]-1-cyclohexanone as a colorless crystalline product.

NMR (CDCl₃) δ: 2.0-3.0(8H,m), 3.06(3H,s), 4.7-5.0(1H,m),

25 7.10 (2H,d,J=9.0Hz), 7.90(2H,d,J=9.0Hz)



Referential Example 6

In 21 ml of anhydrous tetrahydrofuran were dissolved 1.50 g of 5-(4-oxocyclohexylidene)-valeric acid and 1.17 ml of triethylamine. Then, 4.50 ml of a 5 solution of 0.80 ml of ethyl chloroformate in anhydrous tetrahydrofuran was dropwise added at -20°C, and the resulting mixture was stirred at the same temperature as above for one hour. Then, 4.50 ml of a solution of anhydrous tetrahydrofuran containing 2.00 ml of 10 diethylamine was dropwise added at the same temperature, and the resulting mixture was stirred at ambient temperature for one hour. The reaction mixture was poured into ice water, pH was adjusted to 2.0 with 2 mol/L hydrochloric acid, and the mixture was 15 extracted with ethyl acetate. The organic layer was washed successively with water, saturated aqueous solution of sodium hydrogen carbonate and saturate aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate, and the solvent was 20 distilled off under reduced pressure. Purification of the residue by column chromatography [eluent: toluene:ethyl acetate = 1:1] gave 1.30 g of N,N-diethyl-5-(4-oxocyclohexylidene)-valeramide as a colorless oily product.

25 NMR (CDCl_3) δ : 1.11(3H, t, $J=7.0\text{Hz}$), 1.17(3H, t, $J=7.0\text{Hz}$), 1.5-2.7(14H, m), 3.31(2H, q, $J=7.0\text{Hz}$), 3.38(2H, q, $J=7.0\text{Hz}$), 5.37(1H, t, $J=7.0\text{Hz}$)



Referential Example 7

The procedure of Referential Example 6 was repeated to obtain the following compounds.

7 (1)

5 5-(4-Oxocyclohexylidene)-valeramide

NMR (CDCl₃) δ: 1.5-2.8(14H,m), 5.34(1H,t,J=7.0Hz), 5.5-6.4(2H,m)

7 (2)

10 Benzyl 3-{{[(4-oxocyclohexyl)carbonyl]amino}- propionate

NMR (CDCl₃) δ: 1.6-2.8(11H,m), 3.4-3.7(2H,m), 5.14(2H,s), 6.1-6.5(1H,m), 7.35(5H,s)

7 (3)

15 N-Isobutyl-2-(4-oxocyclohexyl)acetamide

NMR (CDCl₃) δ: 0.92(6H,d,J=6.6Hz), 1.2-2.6(12H,m), 3.0-3.2(2H,m), 5.6-5.9(1H,bs)

7 (4)

N,N-Dipropyl-2-(4-oxocyclohexyl)-acetamide

20 NMR (CDCl₃) δ: 0.7-1.0(6H,m), 1.2-2.5(15H,m), 3.1-3.4(4H,m)

Referential Example 8

In an atmosphere of nitrogen, 0.23 g of magnesium powder was suspended in 2 ml of anhydrous ethyl ether. While refluxing the suspension, a 25 solution of 2.00 g of 4-tert-butyl-1-bromobenzene in 10 ml anhydrous ethyl ether was dropwise added. After stirring the resulting mixture under reflux for one



hour, a solution of 1.17 g of 1,4-cyclohexandione monoethylene ketal in 10 ml anhydrous tetrahydrofuran was dropwise added at 0-5°C, and the temperature was elevated to ambient temperature. After stirring the 5 mixture at the same temperature as above, the reaction mixture was poured into a mixture of water and acetic acid, stirred at ambient temperature for 20 minutes, and extracted with ethyl acetate. The organic layer was washed successively with water and saturated 10 aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. Purification of the residue by column chromatography [eluent: hexane:ethyl acetate = 3:1] gave 1.25 g of 8-[4-(tert- 15 butyl)phenyl]-1,4-dioxaspiro[4.5]decan-8-ol as a light yellow oily product.

NMR (CDCl₃) δ: 1.31(9H,s), 1.5-2.3(9H,m), 3.97(4H,s), 7.3-7.6(4H,m)

Referential Example 9

20 In 10 ml of tetrahydrofuran was dissolved 1.10 g of 8-[4-(tert-butyl)phenyl]-1,4-dioxaspiro[4.5]decan-8-ol. Then, 5.00 ml of 6 mol/L hydrochloric acid and 5.00 ml of water were added at an ice-cooled temperature and the resulting mixture was 25 stirred at ambient temperature for 2 hours. The reaction mixture was poured into a mixture of water and ethyl acetate, and the organic layer was separated.



The organic layer was washed successively with water and saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. Hexane was 5 added to the residue, and the resulting crystal was collected by filtration to obtain 0.67 g of 4-[4-(tert-butyl)phenyl]-4-hydroxy-1-cyclohexanone as a colorless crystalline product.

NMR (CDCl₃) δ: 1.32(9H,s), 2.0-2.5(7H,m), 2.6-3.2(2H,m),
10 7.43(4H,s)

Referential Example 10

In 75 ml of benzene was dissolved 15.0 g of 2-ethylbutanal, to which were added 10.5 g of 3-buten-2-one and 0.15 ml of concentrated sulfuric acid at 15 ambient temperature. While heating the mixture under reflux, an azeotropic distillation treatment was carried out for 3 hours by means of Dean Stark apparatus. The reaction mixture was poured into a mixture of ice water and ethyl acetate, pH was adjusted 20 to 7.0 with a saturated aqueous solution of sodium hydrogen carbonate, and the organic layer was separated. The organic layer was washed successively with water and saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate, 25 and the solvent was distilled off under reduced pressure. Purification of the residue by distillation under reduced pressure gave 4.90 g of 4,4-diethyl-2-



cyclohexen-1-one as a light yellow oily product.

NMR (CDCl₃) δ: 0.89(6H, t, J=7.3Hz), 1.85(2H, t, J=6.8Hz), 1.4-1.8(4H, m), 2.44(2H, t, J=6.8Hz), 5.92(1H, d, J=10.3Hz), 6.72(1H, d, J=10.3Hz)

5 Referential Example 11

In 22 ml of acetic acid was dissolved 2.20 g of 4,4-diethyl-2-cyclohexen-1-one, to which was added 0.22 g of 5% palladium-carbon. Under a pressure of 5 atmospheres, the mixture was stirred at ambient 10 temperature for one hour under a stream of hydrogen. The reaction mixture was filtered, and the solvent was distilled off under reduced pressure. Purification of the residue by column chromatography [eluent: hexane:ethyl acetate = 10:1] gave 1.90 g of 4,4-diethyl-1-cyclohexanone as a colorless oily product. 15 NMR (CDCl₃) δ: 0.84(6H, t, J=7.3Hz), 1.2-1.8(8H, m), 2.32(4H, t, J=6.8Hz)

Referential Example 12

In an atmosphere of nitrogen, 280 ml of 20 anhydrous tetrahydrofuran was added to 23.0 g of sodium hydride, to which was dropwise added a solution of 40.0 g of diethyl malonate in 80 ml of anhydrous tetrahydrofuran at 40°C over a period 30 minutes. After stirring the mixture at the same temperature as above for one 25 hour, the mixture was cooled to 15°C, and a solution of 52.5 g of ethyl acrylate in 80 ml of anhydrous



tetrahydrofuran was dropwise added thereto over a period of 30 minutes. After a reaction at 45°C for 30 minutes followed by cooling, the reaction mixture was poured into a mixture of ice water and ethyl acetate.

5 After adjusting pH value to 2.0 with 6 mol/L hydrochloric acid, the organic layer was separated. The organic layer was washed successively with water, saturated aqueous solution of sodium hydrogen carbonate and saturated aqueous solution of sodium chloride and 10 dried over anhydrous magnesium sulfate, the solvent was distilled off under reduced pressure. Purification of the residue by distillation under reduced pressure gave 61.8 g of 2,4,4-tricarbethoxy- cyclohexanone as a light yellow oily product.

15 Boiling point: 140-153°C (2.0-2.5 mmHg)

Referential Example 13

To 540 ml of dimethyl sulfoxide were added 21.9 g of lithium chloride, 13.9 ml of pyridine and 9.3 ml of water, and the resulting mixture was gently 20 heated under reflux. While refluxing the mixture, 100 ml of a solution of 54.0 g of 2,4,4-tricarbethoxycyclohexanone in dimethyl sulfoxide was dropwise added thereto over one hour. After a reaction at the same temperature as above for 2 hours, the mixture was 25 cooled and poured into a mixture of ice water and ethyl acetate, and the organic layer was separated. The organic layer was washed with saturated aqueous



solution of sodium chloride and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. Purification of the residue by distillation under reduced pressure gave 13.5 g of 4-5 carbethoxycyclohexanone as a light yellow oily product.

Boiling point: 103-107°C (2.5-3.5 mmHg)

Referential Example 14

In 120 ml of methylene chloride was suspended 6.0 g of 4-(methoxycarbonyl)-benzoic acid, to which 10 were added 3.5 ml of oxalyl chloride and 0.05 ml of N,N-dimethylformamide at 0-5°C. After a reaction at the same temperature as above for 3 hours, the mixture was stirred at ambient temperature for 24 hours. Then, a 90.7 g portion of the reaction mixture was taken out, 15 and 6.9 ml of diethylamine was added thereto. The mixture was stirred at ambient temperature for 3 hours, and then poured into ice water. pH was adjusted to 1.0 with 6 mol/L hydrochloric acid, and the organic layer was separated. The organic layer was washed 20 successively with water, saturated aqueous solution of sodium hydrogen carbonate and saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. Thus, 5.89 g of methyl 4-25 [(diethylamino)carbonyl]-benzoate was obtained as a red oily product.



Referential Example 15

In 25 ml of methanol was dissolved 5.44 g of methyl 4-[(diethylamino)carbonyl]-benzoate. After adding 25 ml of 1 mol/L aqueous solution of sodium hydroxide at 0-5°C, the mixture was stirred at ambient temperature for 2 hours. The reaction mixture was poured into a mixture of water and ethyl acetate, and the aqueous layer was separated. The aqueous layer was mixed with ethyl acetate, pH was adjusted to 1.5 with 6 mol/L hydrochloric acid, and the organic layer was separated. The organic layer was washed successively with water and saturated aqueous solution of sodium chloride and dried over magnesium sulfate, and the solvent was distilled off under reduced pressure.

Diisopropyl ether was added to the residue, and the deposited crystal was collected by filtration to obtain 2.94 g of 4-[(diethylamino)carbonyl]-benzoic acid as a colorless crystalline product.

Referential Example 16

In 2.3 ml of methylene chloride was added 0.470 g of 5-phenylvaleric acid, to which were added at ambient temperature 0.287 ml of thionyl chloride and 0.020 ml of N,N-dimethylformamide. After a reaction at the same temperature as above for 4 hours, the reaction mixture was concentrated under reduced pressure, 5.0 ml of toluene was added and the resulting mixture was further concentrated under reduced pressure. Thus,



0.510 g of 5-phenylvaleric acid chloride was obtained as a light yellow oily product.

Referential Example 17

In 20 ml of N,N-dimethylformamide was suspended 1.11 g of 60% sodium hydride, to which was dropwise added 5.0 ml of ethyl diethylphosphonoacetate over 5 minutes at an ice-cooled temperature. The resulting mixture was stirred at ambient temperature for 90 minutes. Then, 2.49 ml of isovalerylaldehyde was dropwise added at an ice-cooled temperature over a period of 5 minutes, and the resulting mixture was stirred at ambient temperature for one hour. The reaction mixture was poured into a mixture of chloroform and water, pH was adjusted to 1.0 with 2 mol/L hydrochloric acid, and the organic layer was separated. The organic layer was washed successively with water and saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. Purification of the residue by silica gel column chromatography [eluent: n-hexane:ethyl acetate = 10:1] gave 3.27 g of ethyl (E)-5-methyl-2-hexenoate as a colorless oily product.

NMR (CDCl₃) δ : 0.93(6H, d, J=6.3Hz), 1.29(3H, t, J=7.1Hz), 1.5-1.9(1H, m), 2.0-2.3(2H, m), 4.19(2H, q, J=7.1Hz), 5.7-5.9(1H, m), 6.9-7.0(1H, m)



Referential Example 18

In 15 ml of ethanol was dissolved ethyl (E)-5-methyl-2-hexenoate, to which was added 0.50 g of 5% palladium-carbon. Under a stream of hydrogen, the 5 mixture was stirred at ambient temperature for 2 hours. The reaction mixture was filtered with Celite, and the solvent was distilled off under reduced pressure. Thus, 2.2 g of ethyl 5-methylhexanoate was obtained as a colorless oily product.

10 NMR (CDCl₃) δ: 0.88 (6H, d, J=6.3Hz), 1.1-2.1 (8H, m), 2.28 (2H, t, J=7.4Hz), 4.12 (2H, q, J=7.2Hz)

Referential Example 19

In 20 ml of ethanol was dissolved 2.0 g of ethyl 5-methylhexanoate. After adding 10 ml of 2 mol/L 15 aqueous solution of sodium hydroxide at ambient temperature, the resulting mixture was stirred for 30 minutes. The ethanol was distilled off under reduced pressure, the residue was poured into a mixture of water and chloroform, pH was adjusted to 1.0 with 2 mol/L hydrochloric acid, and the organic layer was 20 separated. The organic layer was washed successively with water and saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced 25 pressure. Diisopropyl ether was added to the residue, and the deposited crystal was collected by filtration. Thus, 1.56 g of 5-methylhexanoic acid was obtained as a



colorless oily product.

NMR (CDCl₃) δ: 0.89(6H,d,J=6.1Hz), 1.1-2.1(5H,m),
2.34(2H,t,J=7.3Hz)

Referential Example B-1

5 In 200 ml of toluene were dissolved 20.00 g of tert-butyl 4-oxo-1-piperidinecarboxylate and 12.6 ml of β -phenethylamine. After stirring the resulting solution at ambient temperature for 30 minutes, 15.07 g of mercaptosuccinic acid was added, and the resulting
10 mixture was subjected to an azeotropic distillation treatment under reflux for 6 hours. The reaction mixture was poured into a mixture of ice water and ethyl acetate, and the organic layer was separated. The organic layer was washed successively with water
15 and saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. Purification of the residue by column chromatography [eluent: toluene:ethyl acetate = 5:1] gave 22.10 g of 2-[8-
20 (tert-butoxycarbonyl)-3-oxo-4-phenethyl-1-thia-4,8-diazaspiro[4.5]decan-2-yl]-acetic acid as a yellow oily product.

NMR (CDCl₃) δ: 1.47(9H,s), 1.4-2.2(4H,m), 2.4-3.8(8H,m),
3.8-4.4(3H,m), 7.1-7.4(6H,m)

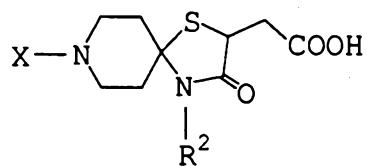


Referential Example B-2

The procedure of Referential Example B-1 was repeated to obtain the compounds listed in Table 72.



[Table 72]



No.	X	R ²
2 (1)	$-\text{COO} \begin{array}{c} \text{CH}_3 \\ \\ \text{---} \\ \\ \text{CH}_3 \end{array}$	$-\text{CH}_2\text{CH}_2\text{COOCH}_2 \text{---} \text{C}_6\text{H}_5$
2 (2)	$-\text{COO} \begin{array}{c} \text{CH}_3 \\ \\ \text{---} \\ \\ \text{CH}_3 \end{array}$	$-\text{CH}_2 \text{---} \text{C}_6\text{H}_5$
2 (3)	$-\text{COO} \begin{array}{c} \text{CH}_3 \\ \\ \text{---} \\ \\ \text{CH}_3 \end{array}$	$-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$
2 (4)	$-\text{COO} \begin{array}{c} \text{CH}_3 \\ \\ \text{---} \\ \\ \text{CH}_3 \end{array}$	$-\text{CH}_2\text{CH}_2\text{OCH}_3$
2 (5)	$-\text{COCH}_3$	$-\text{CH}_2\text{CH}_2\text{COOCH}_2 \text{---} \text{C}_6\text{H}_5$
2 (6)	$-\text{COOCH}_2\text{CH} \begin{array}{c} \text{CH}_3 \\ \\ \text{---} \\ \\ \text{CH}_3 \end{array}$	$-\text{CH}_2\text{CH}_2\text{COOCH}_2 \text{---} \text{C}_6\text{H}_5$
2 (7)	$-\text{COO} \begin{array}{c} \text{CH}_3 \\ \\ \text{---} \\ \\ \text{CH}_3 \end{array}$	H
2 (8)	$-\text{COO} \begin{array}{c} \text{CH}_3 \\ \\ \text{---} \\ \\ \text{CH}_3 \end{array}$	$-\text{CH}_2\text{CH}_2\text{CH} \begin{array}{c} \text{CH}_3 \\ \\ \text{---} \\ \\ \text{CH}_3 \end{array}$



Properties of the compounds of Table 72 are as mentioned below.

B-2 (1)

NMR (CDCl₃) δ: 1.1-2.3 (4H, m), 1.46 (9H, s), 2.3-3.8
 5 (8H, m), 3.8-4.4 (3H, m), 5.12 (2H, s), 6.0-6.7 (1H, bs),
 7.0-7.2 (5H, m)

B-2 (2)

NMR (CDCl₃) δ: 1.44 (9H, s), 1.5-2.2 (4H, m), 2.6-3.5
 (4H, m), 3.9-4.3 (3H, m), 4.48 (1H, d, J=16.8Hz), 4.69
 10 (1H, d, J=16.8Hz), 7.27 (5H, s), 9.13 (1H, bs)

B-2 (3)

NMR (CDCl₃) δ: 0.92 (3H, t, J=7.2Hz), 1.1-2.3 (8H, m), 1.47
 (9H, s), 2.3-3.6 (6H, m), 3.9-4.4 (3H, m), 6.0-6.4 (1H, bs)

B-2 (4)

15 NMR (CDCl₃) δ: 1.2-2.3 (4H, m), 1.46 (9H, s), 2.5-3.7
 (8H, m), 3.47 (3H, s), 4.0-4.4 (3H, m), 5.9-6.5 (1H, bs)

B-2 (5)

NMR (CDCl₃) δ: 2.12 (3H, s), 1.6-2.2 (4H, m), 2.5-4.0
 (9H, m), 4.14 (1H, dd, J=3.9Hz, 8.8Hz), 4.6-4.9 (1H, m),
 20 5.12 (2H, s), 6.4 (1H, bs), 7.3-7.6 (5H, s)

B-2 (7)

NMR (d₆-DMSO) δ: 1.39 (9H, s), 1.4-2.2 (4H, m), 2.3-3.5
 (4H, m), 3.5-4.2 (2H, m), 4.04 (1H, dd, J=3.8Hz, 9.9Hz),
 8.89 (1H, s), 12.48 (1H, bs)

25 B-2 (8)

NMR (CDCl₃) δ: 0.93 (6H, d, J=5.9Hz), 1.0-2.4 (7H, m), 1.47
 (9H, s), 2.5-3.5 (6H, m), 4.0-4.4 (3H, m), 6.2-6.8 (1H, bs)



Referential Example B-3

In 200 ml of N,N-dimethylformamide was dissolved 22.0 g of 2-[8-(tert-butoxycarbonyl)-3-oxo-4-phenethyl-1-thia-4,8-diazaspiro[4.5]decan-2-yl]-acetic acid. After adding 8.40 g of anhydrous potassium carbonate at 0-5°C, 4.90 ml of ethyl iodide was dropwise added over a period of 5 minutes. The resulting mixture was stirred at the same temperature as above for 10 minutes and then at ambient temperature for 2 hours, the reaction mixture was poured into a mixture of ice water and ethyl acetate, pH was adjusted to 2.0 with 6 mol/L hydrochloric acid, and the organic layer was separated. The organic layer was washed successively with water and saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. Purification of the residue by column chromatography [eluent: hexane:ethyl acetate = 2:1] gave 19.85 g of tert-butyl 2-(2-ethoxy-2-oxoethyl)-3-oxo-4-phenethyl-1-thia-4,8-diazaspiro[4.5]decan-8-carboxylate as a yellow oily product.

NMR (CDCl₃, δ: 1.47(9H,s), 1.28(3H,t,J=7.2Hz), 1.4-2.2(4H,m), 2.5-3.6(8H,m), 4.0-4.4(5H,m), 7.27(5H,s)

25 Referential Example B-4

The procedure of Referential Example B-3 was repeated to obtain the following compound:



tert-Butyl 2-(2-ethoxy-2-oxoethyl)-4-isopentyl-3-oxo-1-thia-4,8-diazaspiro[4.5]decan-8-carboxylate

NMR (CDCl₃) δ: 0.93 (6H, d, J=5.9Hz), 1.0-3.4 (13H, m),
5 1.27 (3H, t, J=7.1Hz), 1.47 (9H, s), 3.9-4.4 (5H, m)

Referential Example B-5

In 56 ml of methylene chloride was dissolved 18.50 g of tert-butyl 2-(2-ethoxy-2-oxoethyl)-3-oxo-4-phenethyl-1-thia-4,8-diazaspiro[4.5]decan-8-carboxylate. After adding 56 ml of trifluoroacetic acid at 0-5°C, the resulting mixture was stirred at the same temperature as above for 30 minutes and then at ambient temperature for 5 hours. The solvent was distilled off under reduced pressure, the residue was poured into a mixture of ice water and ethyl acetate, pH was adjusted to 8.0 with saturated aqueous solution of sodium hydrogen carbonate, and the organic layer was separated. The organic layer was washed successively with water and saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate and the solvent was distilled off under reduced pressure. Thus, 7.26 g of ethyl 2-(3-oxo-4-phenethyl-1-thia-4,8-diazaspiro[4.5]decan-2-yl)-acetate was obtained as a yellow oily product.

25 NMR (CDCl₃) δ: 1.29 (3H, t, J=7.0Hz), 1.2-1.8 (2H, m), 2.2-3.6 (13H, m), 4.0-4.4 (3H, m), 7.25 (5H, s)



Referential Example B-6

The procedure of Referential Example B-5 was repeated to obtain the following compounds.

B-6(1)

5 Trifluoroacetic acid salt of 2-(4-benzyl-3-oxo-1-thia-4,8-diazaspiro[4.5]decan-2-yl)-acetic acid
NMR (d_6 -DMSO) δ : 1.6-2.0(2H,m), 2.2-3.6(8H,m),
4.32(1H,dd, J =3.9Hz, 9.5Hz), 4.44(1H,d, J =16.5Hz),
4.68(1H,d, J =16.5Hz), 7.29(5H,s), 8.6-9.1(2H,bs)

10 B-6(2)

Ethyl 2-(4-isopentyl-3-oxo-1-thia-4,8-diazaspiro[4.5]deecan-2-yl)-acetate
NMR ($CDCl_3$) δ : 0.93(6H,d, J =5.6Hz), 1.27(3H,t, J =7.2Hz),
1.4-3.4(16H,m), 4.0-4.4(3H,m)

15 Referential Example B-7

In 5 ml of methylene chloride was dissolved 0.50 g of ethyl 2-(3-oxo-4-phenethyl-1-thia-4,8-diazaspiro[4.5]decan-2-yl)-acetate. After adding 0.25 ml of triethylamine at 0-5°C, 0.26 ml of ethyl succinyl chloride was dropwise added. After stirring at ambient temperature for 5 hours, the reaction mixture was poured into ice water, pH was adjusted to 2.0 with 2 mol/L hydrochloric acid, and the organic layer was separated. The organic layer was washed successively with water and saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced



pressure. Purification of the residue by column chromatography [eluent: hexane:ethyl acetate = 1:1] gave 0.65 g of ethyl 4-[2-(2-ethoxy-2-oxoethyl)-3-oxo-4-phenethyl-1-thia-4,8-diazaspiro[4.5]decan-8-yl]-4-oxobutanoate as a yellow oily product..

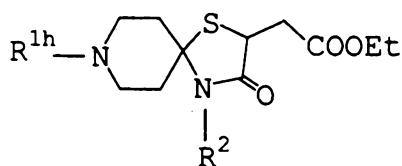
NMR (CDCl₃) δ: 1.26(3H,t,J=7.1Hz), 1.29(3H,t,J=7.1Hz), 1.2-2.5(4H,m), 2.6-5.0(19H,m), 7.26(5H,s)

Referential Example B-8

The procedure of Referential Example B-7 was 10 repeated to obtain the compounds listed in Table 73.



[Table 73]



No.	R^{1h}	R^2
8 (1)	$-\text{COCH}_2-\text{C}_6\text{H}_5$	$-\text{CH}_2\text{CH}_2-\text{C}_6\text{H}_5$
8 (2)	$-\text{COCH}_2\text{CH}_2\text{CH}_2-\text{C}_6\text{H}_5$	$-\text{CH}_2\text{CH}_2-\text{C}_6\text{H}_5$
8 (3)	$-\text{COCH}=\text{CH}-\text{C}_6\text{H}_5$	$-\text{CH}_2\text{CH}_2-\text{C}_6\text{H}_5$
8 (4)	$ \begin{array}{c} \text{NH}_2 \bullet \text{HCl} \\ \\ -\text{COCH} \\ \\ \text{CH}_2\text{CH} \begin{array}{l} \diagup \text{CH}_3 \\ \diagdown \text{CH}_3 \end{array} \end{array} $	$-\text{CH}_2\text{CH}_2-\text{C}_6\text{H}_5$
8 (5)	$ \begin{array}{c} \text{NHCOCH}_3 \\ \\ -\text{COCH} \\ \\ \text{CH}_2\text{CH}_2\text{CONH}_2 \end{array} $	$-\text{CH}_2\text{CH}_2\text{CH} \begin{array}{l} \diagup \text{CH}_3 \\ \diagdown \text{CH}_3 \end{array}$
8 (6)	$-\text{COCH}_2\text{CH}_2\text{COOEt}$	$-\text{CH}_2\text{CH}_2\text{CH} \begin{array}{l} \diagup \text{CH}_3 \\ \diagdown \text{CH}_3 \end{array}$
8 (7)	$ \begin{array}{c} \text{OCOCH}_3 \\ \\ -\text{COCH} \\ \\ \text{C}_6\text{H}_5 \end{array} $	$-\text{CH}_2\text{CH}_2-\text{C}_6\text{H}_5$



Properties of the compounds of Table 73 are as follows.

B-8(1)

NMR (CDCl₃) δ: 1.24 (3H, t, J=7.0Hz), 1.2-2.0 (4H, m), 2.5-5 4.9 (11H, m), 3.73 (2H, s), 4.14 (2H, q, J=7.0Hz), 7.0-7.8 (10H, m)

B-8(2)

NMR (CDCl₃) δ: 1.28 (3H, t, J=7.1Hz), 1.5-2.2 (6H, m), 2.2-4.0 (13H, m), 4.0-4.9 (4H, m), 7.0-7.4 (10H, m)

10 B-8(3)

NMR (CDCl₃) δ: 1.29 (3H, t, J=7.0Hz), 1.5-2.3 (4H, m), 2.5-3.8 (8H, m), 4.0-4.9 (5H, m), 6.86 (1H, d, J=15.4Hz), 7.1-7.7 (10H, m), 7.69 (1H, d, J=15.4Hz)

B-8(5)

15 NMR (CDCl₃) δ: 0.93 (6H, d, J=5.6Hz), 1.28 (3H, t, J=7.2Hz), 1.2-3.6 (17H, m), 2.10 (3H, s), 4.0-4.4 (4H, m), 4.5-5.2 (2H, m), 5.4-7.0 (3H, m)

B-8(6)

NMR (CDCl₃) δ: 0.93 (6H, d, J=5.8Hz), 1.27 (6H, t, J=7.1Hz), 20 1.1-2.4 (7H, m), 2.5-3.7 (10H, m), 3.8-4.9 (7H, m)

B-8(7)

NMR (CDCl₃) δ: 1.26 (3H, t, J=7.2Hz), 1.4-2.2 (2H, m), 2.18 (3H, s), 2.4-4.9 (13H, m), 4.17 (2H, q, J=7.2Hz), 6.21 (1H, s), 7.0-7.6 (10H, m)

25 Referential Example C-1

Using 9H-fluoren-9-ylmethyl 4-oxo-1-piperidinecarboxylate, the procedure of Referential



Example B-1 was repeated to obtain 2-[4-[3-(tert-butoxy)-3-oxopropyl]-8-[(9H-fluoren-9-ylmethoxy)-carbonyl]-3-oxo-1-thia-4,8-diazaspiro[4.5]decan-2-yl]-acetic acid.

5 Referential Example C-2

The procedure of Example 38 was repeated to obtain 9H-fluoren-9-ylmethyl 2-[2-[(2-amino-2-oxoethyl)amino]-2-oxoethyl]-4-[3-(tert-butoxy)-3-oxopropyl]-3-oxo-1-thia-4,8-diazaspiro[4.5]decan-8-10 carboxylate.

Referential Example C-3

The procedure of Example 5 was repeated to obtain 3-[2-[(2-amino-2-oxoethyl)amino]-2-oxoethyl]-8-[(9H-fluoren-9-ylmethoxy)carbonyl]-3-oxo-1-thia-4,8-15 diazaspiro[4.5]decan-4-yl]-propionic acid.

Referential Example C-4

The procedure of Example 15 was repeated to obtain (3R)-8-(tert-butoxycarbonyl)-1-thia-4,8-diazaspiro[4.5]decan-3-carboxylic acid.

20 Referential Example C-5

The procedure of Example 17 was repeated to obtain (3R)-4-benzoyl-8-(tert-butoxycarbonyl)-1-thia-4,8-diazaspiro[4.5]decan-3-carboxylic acid.

Referential Example C-6

The procedure of Referential Example B-5 was repeated to obtain (3R)-4-benzoyl-1-thia-4,8-diazaspiro[4.5]decane-3-carboxylic acid.

5 Referential Example C-7

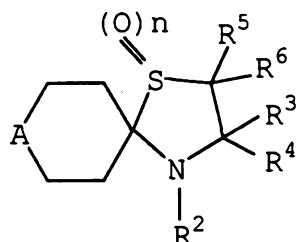
Using 9-fluorenylmethyloxycarbonyl-N-hydroxysuccinimide, the procedure of Referential Example B-7 was repeated to obtain (3R)-4-benzoyl-8-[(9H-fluoren-9-ylmethoxy)carbonyl]-1-thia-4,8-diazaspiro[4.5]decane-3-carboxylic acid.

INDUSTRIAL UTILIZABILITY

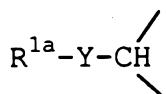
The compounds of the present invention exhibit an AP-1 activity-inhibitory action and, based on the AP-1 inhibitory action thereof, suppress the expression of a wide variety of genes and are useful as an agent for treating and preventing autoimmune diseases with lessened side reactions.

CLAIMS

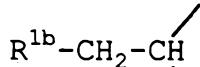
1. A spiro compound represented by the following general formula:



wherein A represents a group of the following general formula:

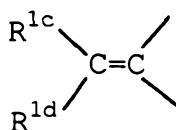


wherein R^{1a} represents a hydrogen atom, a halogen atom, a cyano group, a nitro group, an unprotected or protected carboxyl group, an unprotected or protected hydroxyl group or an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, acyl, alkoxycarbonyl, aryloxycarbonyl, carbamoyl, amino or heterocyclic group; and Y represents an oxygen atom, a sulfur atom, an unsubstituted or substituted imino group, a carbonyl group, a vinylene group, a sulfinyl group, a sulfonyl group or a group -CH(OH)-; a group of the following general formula:



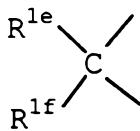
wherein R^{1b} represents a halogen atom, a cyano group, a nitro group, an unprotected or protected carboxyl group, an unprotected or protected hydroxyl group, a substituted alkyl group, or an unsubstituted or substituted alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, acyl, alkoxycarbonyl, aryloxycarbonyl, carbamoyl, amino or heterocyclic group;

a group of the following general formula:

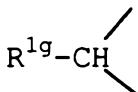


wherein R^{1c} and R^{1d} , which may be the same or different, each represents a hydrogen atom, a halogen atom, a cyano group, a nitro group, an unprotected or protected carboxyl group, an unprotected or protected hydroxyl group, a mercapto group, or an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, acyl, alkoxycarbonyl, aryloxycarbonyl, carbamoyl, alkylthio, alkylsulfinyl, alkylsulfonyl, amino or heterocyclic group;

a group of the following general formula:



wherein R^{1e} and R^{1f} , which may be the same or different, each represents a halogen atom, a cyano group, a nitro group, an unprotected or protected carboxyl group, an unprotected or protected hydroxyl group, or an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, acyl, alkoxycarbonyl, aryloxycarbonyl, carbamoyl, alkylthio, alkylsulfinyl, alkylsulfonyl, amino or heterocyclic group; or a group of the following general formula:



wherein R^{1g} represents an unsubstituted or substituted heterocyclic group; R^2 represents a hydrogen atom, a formyl group, an alkanoyl group, an aralkylcarbonyl group, or an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aroyl, heterocyclic carbonyl, aryl, aralkyl, alkylsulfonyl, arylsulfonyl or heterocyclic group; R^3 and R^4 , which may be the same or different, each represents a hydrogen atom, a halogen atom, a cyano

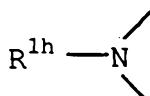
group, an unprotected or protected carboxyl group, an unprotected or protected hydroxyl group or an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, acyl, alkoxycarbonyl, aryl, amino, alkylamino, acylamino, carbamoyl or heterocyclic group, or alternatively, R^3 and R^4 , taken conjointly, represent an oxo group;

R^5 and R^6 , which may be the same or different, each represents a hydrogen atom, a halogen atom, a cyano group, an unprotected or protected carboxyl group, an unprotected or protected hydroxyl group, an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, acyl, alkoxycarbonyl, aryl, amino, alkylamino, acylamino, carbamoyl or heterocyclic group, or alternatively, R^5 and R^6 , taken conjointly with the terminal carbon atom to which R^5 and R^6 are connected, represent an alkenyl group; and

n represents 0, 1 or 2;

a spiro compound represented by the same general formula as above,

wherein A represents a group of the following general formula:



wherein R^{1h} represents a group of the following general formula:

$R^{11}-Y^2-$

wherein R^{11} represents a hydrogen atom, a halogen atom, a cyano group, an unprotected or protected carboxyl, hydroxyl or mercapto group, or an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, alkoxy, alkylthio, alkylsulfonyl, arylsulfonyl, sulfamoyl, acyl, acyloxy, alkoxycarbonyl, aryloxycarbonyl, amino, carbamoyl, carbamoyloxy or heterocyclic group; and

Y^2 represents a methylene group, an unsubstituted or substituted imino group, a carbonyl group or a sulfonyl group or a group of the following general formula:

$R^{12}-(E^1)_j-$

wherein E^1 represents an amino acid residue; R^{12} represents a hydrogen atom or an amino-protecting group; and

j represents 2 or 3;

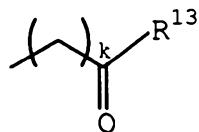
R^2 represents a hydrogen atom, an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, acyl, aryl, arylsulfonyl, alkylsulfonyl, aralkyl or heterocyclic group;

R^3 and R^4 , taken conjointly, represent an oxo group;

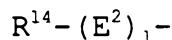
R^5 represents a hydrogen atom;

R^6 represents a group of the following general

formula:

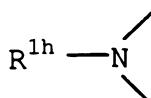


wherein R¹³ represents a hydrogen atom, a halogen atom, an unprotected or protected hydroxyl, hydroxyamino, amino, alkylamino, arylamino, acylamino, alkoxy carbonylamino, arylsulfonylamino or alkylsulfonylamino group, an unsubstituted or substituted alkyl, aryloxy, aralkyloxy, alkylthio, alkoxy, aryl or heterocyclic group, or a group of the following general formula:



wherein E² represents an amino acid residue; R¹⁴ represents a hydroxyl group or an amino group; 1 represents 1, 2 or 3; and k represents 1, 2 or 3; and n represents 0, 1 or 2; and a spiro compound represented by the same general formula as above,

wherein A represents a group of the following general formula:



wherein R¹⁴ represents a group of the following general formula:

$R^{15}-Y^3-$

wherein R^{15} represents a hydrogen atom, a halogen atom, a cyano group, an unprotected or protected carboxyl, hydroxyl or mercapto group or an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, alkoxy, alkylthio, alkylsulfonyl, arylsulfonyl, sulfamoyl, acyl, acyloxy, alkoxycarbonyl, aryloxycarbonyl, amino, carbamoyl, carbamoyloxy or heterocyclic group; and

Y^3 represents a methylene group, an unsubstituted or substituted imino group, a carbonyl group or a sulfonyl group or a group of the following general formula:

 $R^{16}-(E^3)_s-$

wherein E^3 represents an amino acid residue;

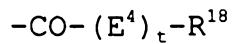
R^{16} represents a hydrogen atom or an amino-protecting group; and

s represents 2 or 3;

R^2 represents a hydrogen atom, or an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, acyl, aryl, arylsulfonyl, alkylsulfonyl, aralkyl or heterocyclic group;

R^3 and R^4 , which may be the same or different, each represents a hydrogen atom, a halogen atom, a cyano group, an unprotected or protected hydroxyl group, an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, alkoxy, alkylthio, alkylsulfinyl,

alkylsulfonyl, acyl, alkoxycarbonyl, aryl, amino, alkylamino, acylamino, carbamoyl or heterocyclic group, or a group of the following general formula:



wherein E^4 represents an amino acid residue;

R^{18} represents a hydroxyl group or an amino group; and

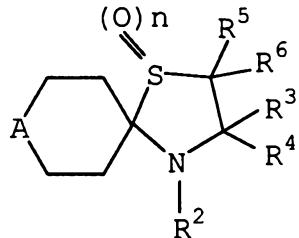
t represents 1, 2 or 3;

R^5 and R^6 , which may be the same or different, each represents a hydrogen atom, a halogen atom, a cyano group, an unprotected or protected carboxyl group, an unprotected or protected hydroxyl group, an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, acyl, alkoxycarbonyl, aryl, amino, alkylamino, acylamino, carbamoyl or heterocyclic group; and

n represents 0, 1 or 2;

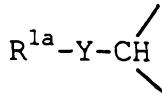
and salts of these spiro compounds.

2. A spiro compound represented by the following general formula:



wherein A represents a group of the following general

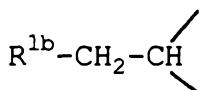
formula:



wherein R^{1a} represents a hydrogen atom, a halogen atom, a cyano group, a nitro group, an unprotected or protected carboxyl group, an unprotected or protected hydroxyl group, or an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, acyl, alkoxycarbonyl, aryloxycarbonyl, carbamoyl, amino or heterocyclic group; and

Y represents an oxygen atom, a sulfur atom, an unsubstituted or substituted imino group, a carbonyl group, a vinylene group, a sulfinyl group, a sulfonyl group or a group $-\text{CH}(\text{OH})-$;

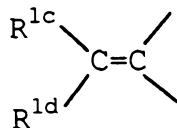
a group of the following general formula:



wherein R^{1b} represents a halogen atom, a cyano group, a nitro group, an unprotected or protected carboxyl group, an unprotected or protected hydroxyl group, a substituted alkyl group, or an unsubstituted or substituted alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, acyl, alkoxycarbonyl, aryloxycarbonyl, carbamoyl, amino

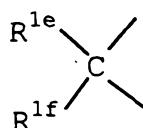


or heterocyclic group;
a group of the following general formula:



wherein R^{1c} and R^{1d} , which may be the same or different, each represents a hydrogen atom, a halogen atom, a cyano group, a nitro group, an unprotected or protected carboxyl group, an unprotected or protected hydroxyl group, a mercapto group, or an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, acyl, alkoxycarbonyl, aryloxycarbonyl, carbamoyl, alkylthio, alkylsulfinyl, alkylsulfonyl, amino or heterocyclic group;

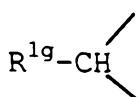
a group of the following formula:



wherein R^{1e} and R^{1f} , which may be the same or different, each represents a halogen atom, a cyano group, a nitro group, an unprotected or protected carboxyl group, an unprotected or protected hydroxyl group, or an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, acyl, alkoxycarbonyl, aryloxycarbonyl,



carbamoyl, alkylthio, alkylsulfinyl, alkylsulfonyl, amino or heterocyclic group; or a group of the following general formula;



wherein R^{1g} represents an unsubstituted or substituted heterocyclic group;

R^2 represents a hydrogen atom, a formyl group, an alkanoyl group, an aralkylcarbonyl group, or an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aroyl, heterocyclic carbonyl, aryl, aralkyl, alkylsulfonyl, arylsulfonyl or heterocyclic group;

R^3 and R^4 , which may be the same or different, each represents a hydrogen atom, a halogen atom, a cyano group, an unprotected or protected carboxyl group, an unprotected or protected hydroxyl group, or an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, acyl, alkoxy carbonyl, aryl, amino, alkylamino, acylamino, carbamoyl or heterocyclic group, or alternatively, R^3 and R^4 , taken conjointly, represent an oxo group;

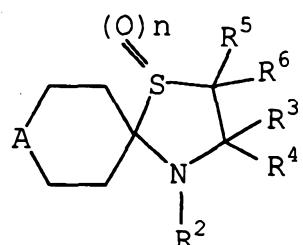
R^5 and R^6 , which may be the same or different, each represents a hydrogen atom, a halogen atom, a cyano group, an unprotected or protected carboxyl group, an



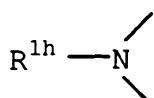
unprotected or protected hydroxyl group, an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, acyl, alkoxy carbonyl, aryl, amino, alkylamino, acylamino, carbamoyl or heterocyclic group, or alternatively, R^5 and R^6 , taken conjointly with the terminal carbon atom to which R^5 and R^6 are combined, represent an alkenyl group; and
 n represents 0, 1 or 2;

or a salt thereof.

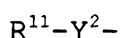
3. A spiro compound represented by the following general formula:



wherein A represents a group of the following general formula:



wherein R^{11} represents a group of the following general formula:

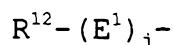


wherein R^{11} represents a hydrogen atom, a halogen atom, a cyano group, an unprotected or protected



carboxyl, hydroxyl or mercapto group, or an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, alkoxy, alkylthio, alkylsulfonyl, arylsulfonyl, sulfamoyl, acyl, acyloxy, alkoxycarbonyl, aryloxycarbonyl, amino, carbamoyl, carbamoyloxy or heterocyclic group; and

Y^2 represents a methylene group, an unsubstituted or substituted imino group, a carbonyl group or a sulfonyl group, or a group of the following formula:



wherein E^1 represents an amino acid residue;

R^{12} represents a hydrogen atom or an amino-protecting group; and

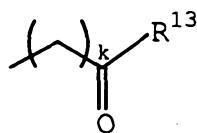
j represents 2 or 3;

R^2 represents a hydrogen atom, an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, acyl, aryl, arylsulfonyl, alkylsulfonyl, aralkyl or heterocyclic group;

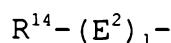
R^3 and R^4 , taken conjointly, represent an oxo group;

R^5 represents a hydrogen atom; and

R^6 represents a group of the following general formula:



wherein R^{13} represents a hydrogen atom, a halogen atom, an unprotected or protected hydroxyl, hydroxyamino, amino, alkylamino, arylamino, acylamino, alkoxy carbonylamino, arylsulfonylamino or alkylsulfonylamino group, an unsubstituted or substituted alkyl, aryloxy, aralkyloxy, alkylthio, alkoxy, aryl or heterocyclic group, or a group of the following general formula:



wherein E^2 represents an amino acid residue;

R^{14} represents a hydroxyl group or amino group; and

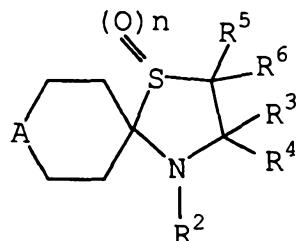
k represents 1, 2 or 3; and

l represents 1, 2 or 3; and

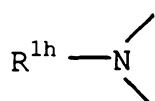
n represents 0, 1 or 2;

or a salt thereof.

4. A spiro compound represented by the following general formula:



wherein A represents a group of the following general formula:



wherein R^{1h} represents a group of the following general formula:

$R^{15}-Y^3-$

wherein R^{15} represents a hydrogen atom, a halogen atom, a cyano group, an unprotected or protected carboxyl, hydroxyl or mercapto group, or an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, alkoxy, alkylthio, alkylsulfonyl, arylsulfonyl, sulfamoyl, acyl, acyloxy, alkoxycarbonyl, aryloxycarbonyl, amino, carbamoyl, carbamoyloxy or heterocyclic group; and

Y^3 represents a methylene group, an unsubstituted or substituted imino group, a carbonyl group or sulfonyl group or a group of the following general formula:

$R^{16}-(E^3)_s-$

wherein E^3 represents an amino acid residue;

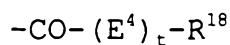
R^{16} represents a hydrogen atom or an amino-protecting group; and

s represents 2 or 3;

R^2 represents a hydrogen atom, an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, acyl, aryl, arylsulfonyl, alkylsulfonyl, aralkyl or heterocyclic group;

R^3 and R^4 , which may be the same or different, each represents a hydrogen atom, a halogen atom, a cyano group, an unprotected or protected hydroxyl group, an

unsubstituted or substituted alkyl, alkenyl, cycloalkyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, acyl, alkoxycarbonyl, aryl, amino, alkylamino, acylamino, carbamoyl or heterocyclic group, or a group of the following general formula:



wherein E^4 represents an amino acid residue;

R^{18} represents a hydroxyl group or an amino group;

and

t represents 1, 2 or 3;

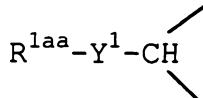
R^5 and R^6 , which may be the same or different, each represents a hydrogen atom, a halogen atom, a cyano group, an unprotected or protected carboxyl group, an unprotected or protected hydroxyl group, an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, acyl, alkoxycarbonyl, aryl, amino, alkylamino, acylamino, carbamoyl or heterocyclic group; and

n represents 0, 1 or 2;

or a salt thereof.

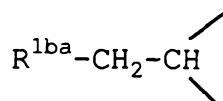
5. A spiro compound or a salt thereof according to Claim 2, wherein A represents

a group of the following general formula:



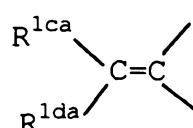
wherein R^{1aa} represents an unsubstituted or substituted alkyl, alkenyl, aryl or heterocyclic group; and

Y^1 represents an oxygen atom or a vinylene group; a group of the following general formula:



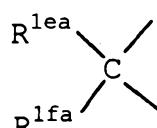
wherein R^{1ba} represents a substituted alkyl group or an unsubstituted or substituted alkenyl, aryl or heterocyclic group;

a group of the following general formula:



wherein R^{1ca} and R^{1da} , which may be the same or different, each represents a hydrogen atom, an unsubstituted or substituted alkyl, alkenyl, aryl or heterocyclic group; or

a group of the following general formula:



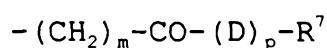
wherein R^{1ea} and R^{1fa} , which may be the same or different, each represents an unprotected or



protected hydroxyl group, or an unsubstituted or substituted aryl group;

R^2 represents a hydrogen atom, a formyl group, an alkanoyl group, an aralkylcarbonyl group, or an unsubstituted or substituted alkyl, alkenyl, aroyl, heterocyclic carbonyl, aryl, aralkyl or heterocyclic group;

R^3 and R^4 , which may be the same or different, each represents a hydrogen atom, an unsubstituted or substituted alkoxy carbonyl or carbamoyl group, or a group of the following general formula:



wherein D represents an amino acid residue;

R^7 represents a hydroxyl group or an amino group;

p represents 1, 2 or 3; and

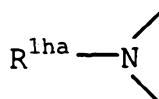
m represents 0, 1, 2 or 3;

or alternatively, R^3 and R^4 , taken conjointly, represent an oxo group;

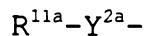
R^5 and R^6 , which may be the same or different, each represents a hydrogen atom or an unsubstituted or substituted alkyl group; and

n represents 0 or 2.

6. A spiro compound or a salt thereof according to Claim 3, wherein A represents a group of the following general formula:



wherein R^{1ha} represents a group of the following general formula:

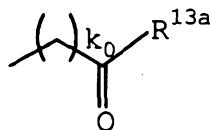


wherein R^{11a} represents an unsubstituted or substituted alkyl, alkenyl, aryl or heterocyclic group; and

Y^{2a} represents a methylene group, a carbonyl group or a sulfonyl group;

R^2 represents a hydrogen atom, an unsubstituted or substituted alkyl or aralkyl group;

R^6 represents a group of the following general formula:

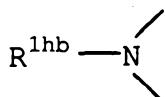


wherein R^{13a} represents an unprotected or protected hydroxyl, amino, alkylamino, acylamino, alkoxy-carbonylamino, arylsulfonylamino or alkylsulfonylamino group, or an unsubstituted or substituted alkoxy group; and

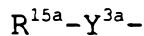
k_0 represents 1; and

n represents 0.

7. A spiro compound or a salt thereof according to Claim 4, wherein A represents a group of the following general formula:

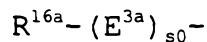


wherein R^{1hb} represents a group of the following general formula:



wherein R^{15a} represents an unsubstituted or substituted alkyl, alkenyl, aryl or heterocyclic group; and

Y^{3a} represents a carbonyl group or a group of the following general formula:



wherein E^{3a} represents an amino acid residue;

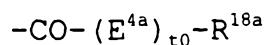
R^{16a} represents a hydrogen atom or an amino-protecting group; and

$s0$ represents 2 or 3;

R^2 represents a hydrogen atom, or an unsubstituted or substituted acyl group;

R^3 represents a hydrogen atom;

R^4 represents a carbamoyl group or a group of the following general formula:



wherein E^{4a} represents an amino acid residue;

R^{18a} represents a hydroxyl group or an amino group; and $t0$ represents 1, 2 or 3;

R^5 and R^6 , which may be the same or different, each represents a hydrogen atom, or an unsubstituted or substituted alkyl group; and

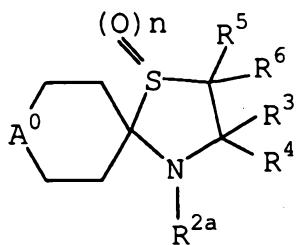
n represents 0.

8. An agent for preventing and/or treating autoimmune diseases, which comprises a spiro compound

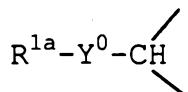
or a salt thereof according to any one of Claims 1 to 7.

9. An AP-1 inhibitor, which comprises a spiro compound or a salt thereof according to any one of Claims 1 to 7.

10. An agent for preventing and treating autoimmune diseases, which comprises a spiro compound represented by the following general formula:



wherein A^0 represents a group of the following general formula:

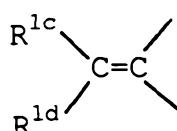


wherein R^{1a} represents hydrogen atom, a halogen atom, a cyano group, a nitro group, an unprotected or protected carboxyl group, an unprotected or protected hydroxyl group, or an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, acyl, alkoxycarbonyl, aryloxycarbonyl, carbamoyl, amino or heterocyclic group; and

Y^0 represents an oxygen atom, sulfur atom, an

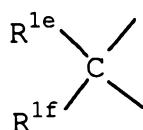
unsubstituted or substituted imino group, a carbonyl group, a methylene group, a vinylene group, a sulfinyl group, a sulfonyl group or a group $-\text{CH}(\text{OH})-$;

a group of the following general formula:



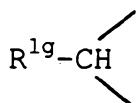
wherein R^{1c} and R^{1d} , which may be the same or different, each represents a hydrogen atom, a halogen atm, a cyano group, a nitro group, an unprotected or protected carboxyl group, an unprotected or protected hydroxyl group, a mercapto group, or an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, acyl, alkoxycarbonyl, aryloxycarbonyl, carbamoyl, alkylthio, alkylsulfinyl, alkylsulfonyl, amino or heterocyclic group;

a group of the following general formula:



wherein R^{1e} and R^{1f} , which may be the same or different, each represents a halogen atom, a cyano group, a nitro group, an unprotected or protected carboxyl group, an unprotected or protected

hydroxyl group, or an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, acyl, alkoxycarbonyl, aryloxycarbonyl, carbamoyl, alkylthio, alkylsulfinyl, alkylsulfonyl, amino or heterocyclic group; or a group of the following general formula:



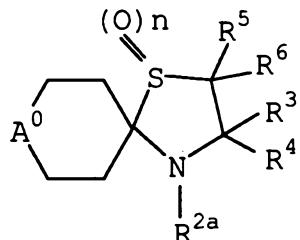
wherein R^{1g} represents an unsubstituted or substituted heterocyclic group; R^{2a} represents a hydrogen atom or an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, acyl, aryl, aralkyl, alkylsulfonyl, arylsulfonyl or heterocyclic group; R^3 and R^4 , which may be the same or different, each represents a hydrogen atom, a halogen atom, a cyano group, an unprotected or protected carboxyl group, an unprotected or protected hydroxyl group, or an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, acyl, alkoxycarbonyl, aryl, amino, alkylamino, acylamino, carbamoyl or heterocyclic group, or alternatively, R^3 and R^4 , taken conjointly, represent an oxo group; R^5 and R^6 , which may be the same or different, each represents a hydrogen atom, a halogen atom, a cyano



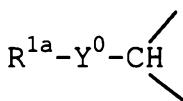
group, an unprotected or protected carboxyl group, an unprotected or protected hydroxyl group, an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, acyl, alkoxycarbonyl, aryl, amino, alkylamino, acylamino, carbamoyl or heterocyclic group, or alternatively, R^5 and R^6 , taken conjointly with the terminal carbon atom to which R^5 and R^6 are connected, represent an alkenyl group; and n represents 0, 1 or 2;

or a salt thereof.

11. An AP-1 inhibitor, which comprises a spiro compound represented by the following general formula:



wherein A^0 represents a group of the following general formula:



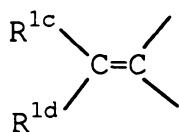
wherein R^{1a} represents a hydrogen atom, a halogen atom, a cyano group, a nitro group, an unprotected or protected carboxyl group, an unprotected or protected hydroxyl group, or an unsubstituted or



substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, acyl, alkoxycarbonyl, aryloxycarbonyl, carbamoyl, amino or heterocyclic group; and

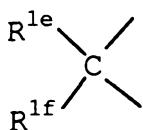
Y^0 represents an oxygen atom, a sulfur atom, an unsubstituted or substituted imino group, a carbonyl group, a methylene group, a vinylene group, a sulfinyl group, a sulfonyl group or an group $-\text{CH}(\text{OH})-$;

a group of the following general formula:

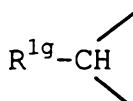


wherein R^{1c} and R^{1d} , which may be the same or different, each represents a hydrogen atom, a halogen atm, a cyano group, a nitro group, an unprotected or protected carboxyl group, an unprotected or protected hydroxyl group, a mercapto group, or an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, acyl, alkoxycarbonyl, aryloxycarbonyl, carbamoyl, alkylthio, alkylsulfinyl, alkylsulfonyl, amino or heterocyclic group;

a group of the following general formula:



wherein R^{1e} and R^{1f} , which may be the same or different, each represents a halogen atom, a cyano group, a nitro group, an unprotected or protected carboxyl group, an unprotected or protected hydroxyl group, or an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, acyl, alkoxycarbonyl, aryloxycarbonyl, carbamoyl, alkylthio, alkylsulfinyl, alkylsulfonyl, amino or heterocyclic group; or a group of the following general formula:



wherein R^{1g} represents an unsubstituted or substituted heterocyclic group; R^{2a} represents a hydrogen atom or an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, acyl, aryl, aralkyl, alkylsulfonyl, arylsulfonyl or heterocyclic group; R^3 and R^4 , which may be the same or different, each represents a hydrogen atom, a halogen atom, a cyano group, an unprotected or protected carboxyl group, an unprotected or protected hydroxyl group, or an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, acyl, alkoxycarbonyl, aryl, amino, alkylamino, acylamino, carbamoyl or heterocyclic



group, or alternatively, R³ and R⁴, taken conjointly, represent an oxo group;

R⁵ and R⁶, which may be the same or different, each represents a hydrogen atom, a halogen atom, a cyano group, an unprotected or protected carboxyl group, an unprotected or protected hydroxyl group, an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, acyl, alkoxycarbonyl, aryl, amino, alkylamino, acylamino, carbamoyl or heterocyclic group, or alternatively, R⁵ and R⁶, taken conjointly with the terminal carbon atom to which R⁵ and R⁶ are connected, represent an alkenyl group; and

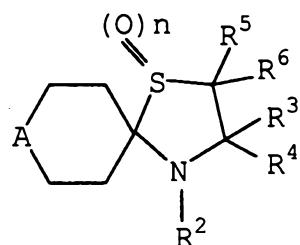
n represents 0, 1 or 2;

or a salt thereof.



ABSTRACT

The spiro compounds of the present invention represented by the following general formula:



wherein A, R², R³, R⁴, R⁵, R⁶ and n are as defined in the specification, exhibit an AP-1 activity inhibitory action and, based on the AP-1 inhibitory action, suppresses the expression of a wide variety of genes and are useful as an agent for treating and preventing autoimmune diseases with lessened side reactions.

