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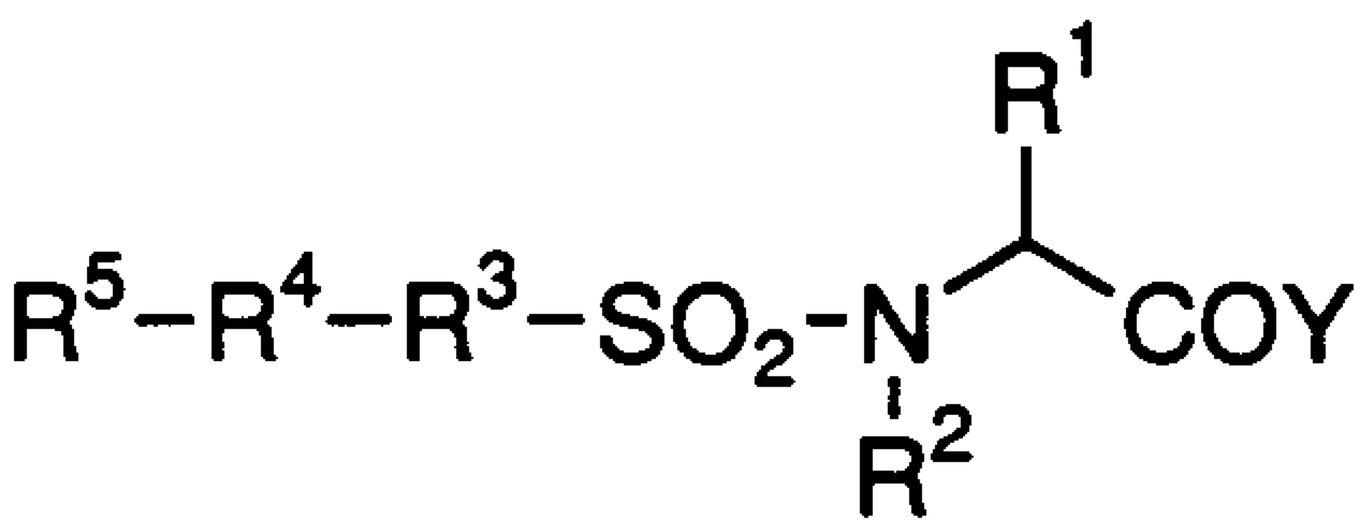
(54) Titre : DERIVES D'ACIDES AMINES SULFONES ET INHIBITEURS DE METALLOPROTEINASES CONTENANT CES DERIVES

(54) Title: SULFONATED AMINO ACID DERIVATIVES AND METALLOPROTEINASE INHIBITORS CONTAINING THE SAME



I

(57) Abrégé/Abstract:
Compounds having a metalloproteinase inhibitory activity, represented by the formula (I), its optically active isomers, their pharmaceutically acceptable salts, or hydrates thereof. (see formula I)

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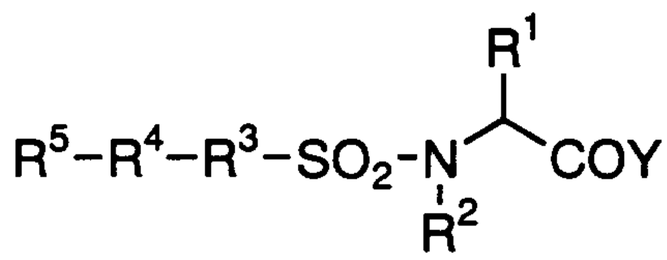
ABSTRACT

Compounds having a metalloproteinase inhibitory activity, represented by the formula (I), its optically active isomers, their pharmaceutically acceptable salts, or hydrates thereof.



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DESCRIPTION

SULFONATED AMINO ACID DERIVATIVES AND METALLOPROTEINASE INHIBITORS CONTAINING THE SAME

Technical Field

This application relates to sulfonated amino acid derivatives and metalloproteinase inhibitors containing the same.

Background Art

An extracellular matrix consists of collagen, proteoglycan, etc., has a function to support tissues, and plays a role in a maintaining of a cell functions , for example propagation, differentiation, adhesion, or the like. Matrix metalloproteinases (MMP) such as gelatinase, stromelysin, collagenase, and the like have an important role in degradation of an extracellular matrix, and these enzymes work for growth, tissue remodeling, etc. under physiological conditions. Therefore, it is considered that these enzymes participate in progression of various kind of diseases involving breakdown and fibrosis of tissues, such as osteoarthritis, rheumatoid arthritis, corneal ulceration, periodontitis, metastasis and invasion of tumor, and virus infection (for example, HIV infection). At the present time, it is not clear which enzyme participates in the above diseases seriously, but it is considered that these enzymes at least participate in tissue breakdown. As metalloproteinase inhibitors of amino acid derivatives, for example hydroxamic acid derivatives of amino acids (JP-A-6-2562939), carboxylic acid derivatives of amino acid and/or their hydroxamic acid derivatives (WO95/35276), etc. are disclosed.

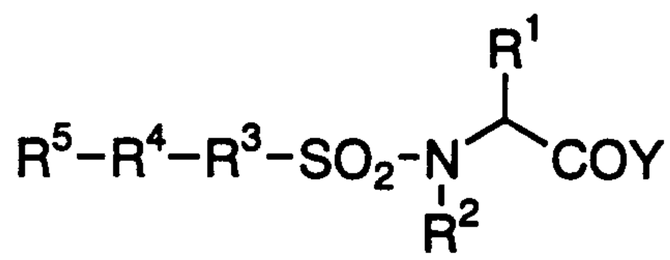
Disclosure of Invention

If it is able to inhibit the activity of MMP, it is considered that MMP inhibitors contribute to an improvement and prevention of the above diseases caused by or

related to its activity. Therefore, development of MMP inhibitors has long been desired.

In the above situation, the inventors of the present invention found that a kind of sulfonamide derivatives have strong activity to inhibit MMP.

The present invention relates to a composition for inhibiting metalloproteinase which contains a compound of the formula I:

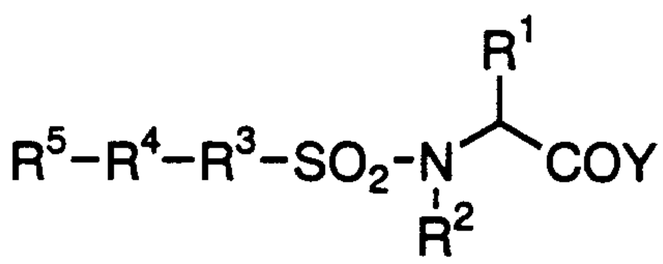


I

wherein R^1 is optionally substituted lower alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, or optionally substituted heteroarylalkyl; R^2 is hydrogen atom, optionally substituted lower alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, or optionally substituted heteroarylalkyl; R^3 is a bond, optionally substituted arylene, or optionally substituted heteroarylene; R^4 is a bond, -(CH_2)m-, -CH=CH-, -C ≡ C-, -CO-, -CO-NH-, -N=N-, -N(R^A)-, -NH-CO-NH-, -NH-CO-, -O-, -S-, -SO_2NH-, -SO_2-NH-N=CH-, or tetrazol-diyl; R^5 is optionally substituted lower alkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, or an optionally substituted non-aromatic heterocyclic group; R^A is hydrogen atom or lower alkyl; Y is -NHOH or -OH; and m is 1 or 2; provided R^2 is hydrogen atom when Y is -NHOH, its optically active substance, their pharmaceutically acceptable salt, or hydrate thereof.

Mentioned in more detail, the invention relates to the following a)-b), 1)-16), and A)-C).

a) A composition for inhibiting metalloproteinase which contains a compound of the formula I:



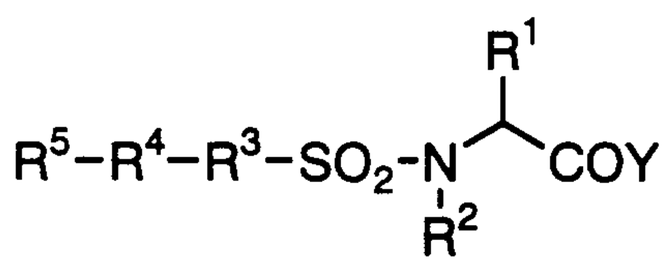
I

wherein R^1 is optionally substituted lower alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, or optionally substituted heteroarylalkyl; R^2 is hydrogen atom, optionally substituted lower alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, or optionally substituted heteroarylalkyl; R^3 is a bond, optionally substituted arylene, or optionally substituted heteroarylene; R^4 is a bond, -(CH_2)m-, -CH=CH-, -C ≡ C-, -CO-, -CO-NH-, -N=N-, -N(R^A)-, -NH-CO-NH-, -NH-CO-, -O-, -S-, -SO_2NH-, -SO_2-NH-N=CH-, or tetrazol-diyl; R^5 is optionally substituted lower alkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, or an optionally substituted non-aromatic heterocyclic group; R^A is hydrogen atom or lower alkyl; Y is -NHOH or -OH; and m is 1 or 2; provided R^2 is hydrogen atom when Y is -NHOH, R^5 is optionally substituted aryl or optionally substituted heteroaryl when R^3 is optionally substituted arylene or optionally substituted heteroarylene and R^4 is -CO-NH- or -NH-CO-, R^5 is optionally substituted aryl or optionally substituted heteroaryl when R^3 is optionally substituted arylene or optionally substituted heteroarylene and R^4 is tetrazol-diyl, R^5 is lower alkyl, aryl substituted by lower alkyl or optionally substituted aryl, or heteroaryl substituted by lower alkyl or optionally substituted aryl when R^3 is optionally substituted arylene and R^4 is a bond, both of R^3 and R^4 are not a bond at the same time, and R^4 is not -O- when R^3 is optionally substituted arylene or optionally substituted heteroarylene, its optically active substance, their pharmaceutically acceptable salt, or hydrate thereof.

b) A composition for inhibiting metalloproteinase as mentioned above, which is a composition for inhibiting type-IV collagenase.

Preferred embodiment of the present invention are as follows.

1) A compound of the formula I:

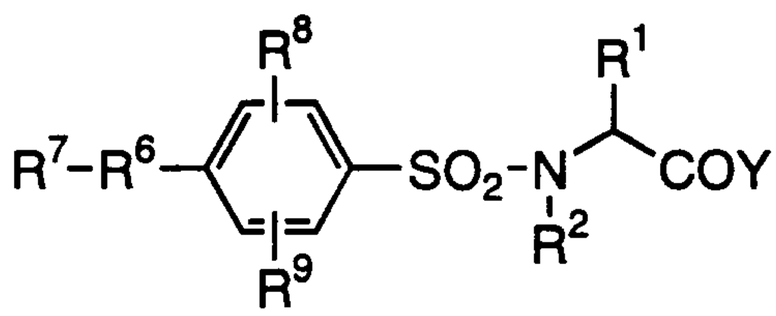


I

wherein R^1 is optionally substituted lower alkyl, optionally substituted aryl, optionally

substituted aralkyl, optionally substituted heteroaryl, or optionally substituted heteroarylalkyl; R^2 is hydrogen atom, optionally substituted lower alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, or optionally substituted heteroarylalkyl; R^3 is a bond, optionally substituted arylene, or optionally substituted heteroarylene; R^4 is a bond, -(CH_2)m-, -CH=CH-, -C ≡ C-, -CO-, -CO-NH-, -N=N-, -N(R^A)-, -NH-CO-NH-, -NH-CO-, -O-, -S-, -SO_2NH-, -SO_2-NH-N=CH-, or tetrazol-diyl; R^5 is optionally substituted lower alkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, or an optionally substituted non-aromatic heterocyclic group; R^A is hydrogen atom or lower alkyl; Y is -NHOH or -OH; and m is 1 or 2; provided R^2 is hydrogen atom when Y is -NHOH, R^5 is optionally substituted aryl or optionally substituted heteroaryl when R^3 is optionally substituted arylene or optionally substituted heteroarylene and R^4 is -CO-NH- or -NH-CO- (when R^3 is phenylene and R^4 is -CO-NH-, R^1 is not methyl or phenyl and R^5 is not 2-chlorophenyl, 4-chlorophenyl, or 2,4-dichlorophenyl), R^5 is lower alkyl, optionally substituted aryl, or optionally substituted heteroaryl when R^3 is optionally substituted arylene or optionally substituted heteroarylene and R^4 is tetrazol-diyl, R^5 is lower alkyl, aryl substituted with lower alkyl or optionally substituted aryl, or heteroaryl substituted with lower alkyl or optionally substituted aryl when R^3 is optionally substituted arylene and R^4 is a bond, both of R^3 and R^4 are not a bond at the same time, and R^4 is not -O- when R^3 is optionally substituted arylene or optionally substituted heteroarylene, its optically active substance, their pharmaceutically acceptable salt, or hydrate thereof.

2) A compound of the formula II:

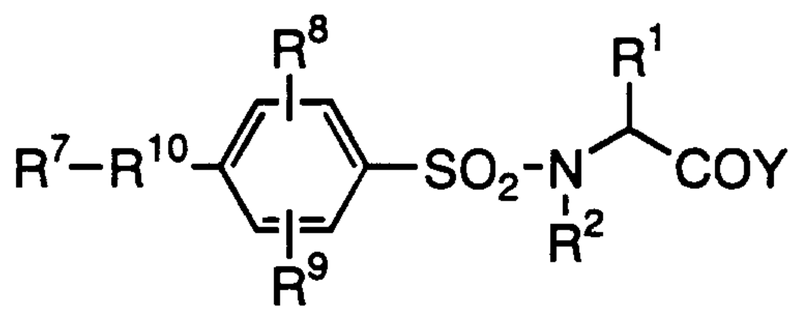


II

wherein R^6 is -CH=CH-, -C ≡ C-, -N=N-, -NH-CO-NH-, -S-, -SO_2NH-, or -SO_2-NH-N=CH-; R^7 is optionally substituted aryl or optionally substituted heteroaryl; R^8 and R^9

are each independently hydrogen atom, lower alkoxy, or nitro; R^1, R^2, and Y are as defined above, its optically active substance, their pharmaceutically acceptable salt, or hydrate thereof.

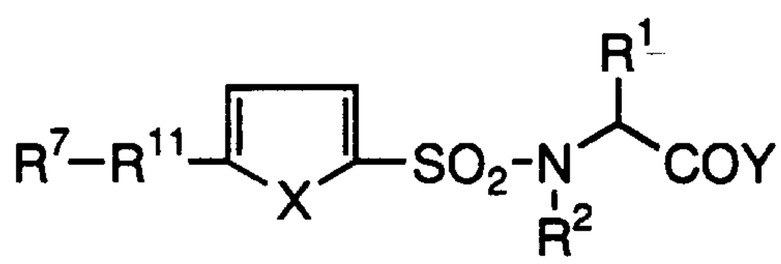
3) A compound of the formula III:



III

wherein R^{10} is -(CH_2)m-, -CO-, -CO-NH-, -N(R^A)-, -NHCO-, or tetrazol-diyl; m is 1 or 2; R^1, R^2, R^7, R^8, R^9, R^A, and Y are as defined above, provided R^1 is not methyl or phenyl and R^7 is not 2-chlorophenyl, 4-chlorophenyl, or 2,4-dichlorophenyl when R^{10} is -NH-CO-, its optically active substance, their pharmaceutically acceptable salt, or hydrate thereof.

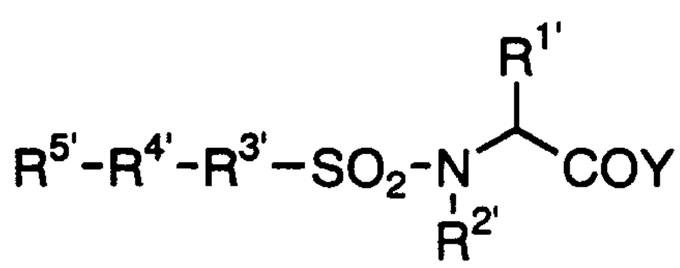
4) A compound of the formula IV:



IV

wherein R^{11} is a bond, -CH=CH-, or -C ≡ C-; X is oxygen atom or sulfur atom, R^1, R^2, R^7, and Y are as defined above, its optically active substance, their pharmaceutically acceptable salt, or hydrate thereof.

5) A compound of the formula I':

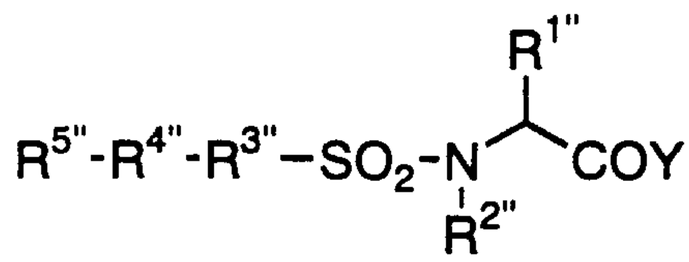


I'

wherein $R^{1'}$ is benzyl, (indol-3-yl)methyl, (1-methylindol-3-yl)methyl, (5-methylindol-3-yl)methyl, (1-acetylindol-3-yl)methyl, (1-methylsulfonylindol-3-yl)methyl, (1-alkoxycarbonyl-3-yl)methyl (for example ethoxycarbonylmethyl), or i-propyl; $R^{2'}$ is hydrogen atom, methyl, 4-aminobutyl, or benzyl; $R^{3'}$ is 1,4-phenylene; $R^{4'}$ is -O-; $R^{5'}$ is phenyl or 4-hydroxy-phenyl; and Y is as defined above, its optically active substance,

their pharmaceutically acceptable salt, or hydrate thereof.

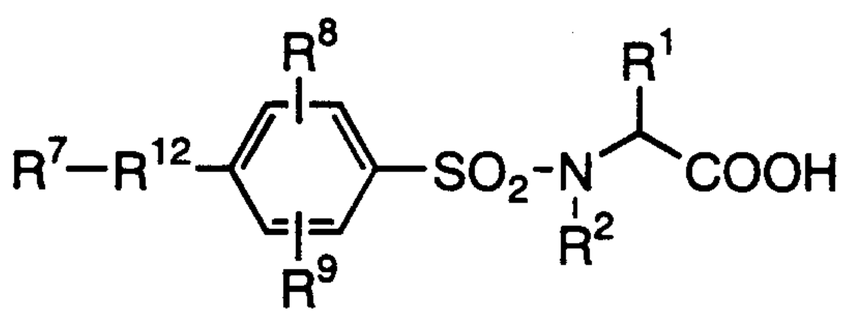
6) A compound of the formula I":



I"

wherein $R^{1"}$ is 4-thiazolylmethyl, (indol-3-yl)methyl, (5-methoxyindol-3-yl)methyl, 1-naphthylmethyl, 2-naphthylmethyl, 4-biphenylylmethyl, 2,2,2-trifluoroethyl, 2-phenylethyl, benzyl, i-propyl, 4-nitrobenzyl, 4-fluorobenzyl, cyclohexylmethyl, (1-methylindol-3-yl)methyl, (5-methylindol-3-yl)methyl, (5-fluoroindol-3-yl)methyl, (pyridin-4-yl)methyl, (benzothiazol-2-yl)methyl, (phenyl)(hydroxy)methyl, phenyl, carboxymethyl, 2-carboxyethyl, hydroxymethyl, phenylmethoxymethyl, 4-carboxybenzyl, (benzimidazol-2-yl)methyl, (1-methylsulfonylindol-3-yl)methyl, or (1-ethoxycarbonylindol-3-yl)methyl; $R^{2"}$ is hydrogen atom; $R^{3"}$ is 1,4-phenylene; $R^{4"}$ is a bond; $R^{5"}$ is phenyl, 3- methoxyphenyl, 4-methoxyphenyl, 4-methylphenyl, 4-tert-butylphenyl, 4-trifluoromethylphenyl, 4-fluorophenyl, 4-methylthiophenyl, 4-biphenylyl, 2-thienyl, benzoxazol-2-yl, benzothiazol-2-yl, or tetrazol-2-yl; and Y is as defined above, its optically active substance, their pharmaceutically acceptable salt, or hydrate thereof.

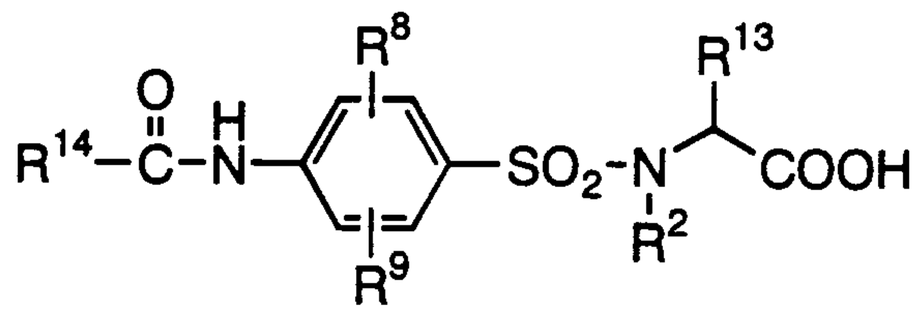
7) A compound of the formula V:



V

wherein R^{12} is -CH=CH- or -C ≡ C-; R^1, R^2, R^7, R^8, and R^9 are as defined above, its optically active substance, their pharmaceutically acceptable salt, or hydrate thereof.

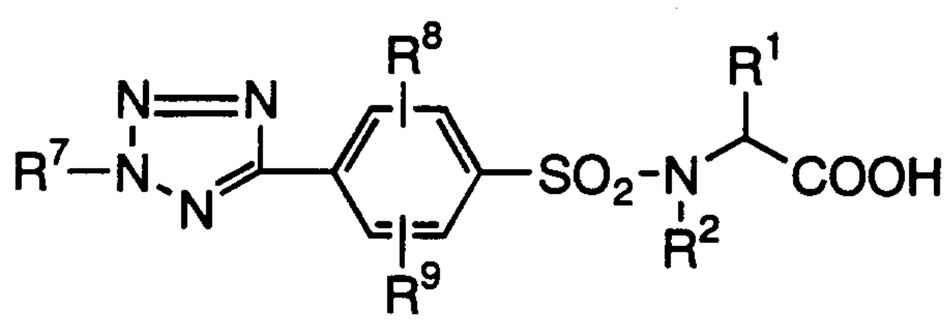
8) A compound of the formula VI:



VI

wherein R^2, R^8, and R^9 are as defined above, R^{13} is optionally substituted lower alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, or optionally substituted heteroarylalkyl; and R^{14} is optionally substituted aryl, or optionally substituted heteroaryl; provided R^{13} is not methyl or phenyl and R^{14} is not 2-chlorophenyl, 4-chlorophenyl, or 2,4-dichlorophenyl, its optically active substance, their pharmaceutically acceptable salt, or hydrate thereof.

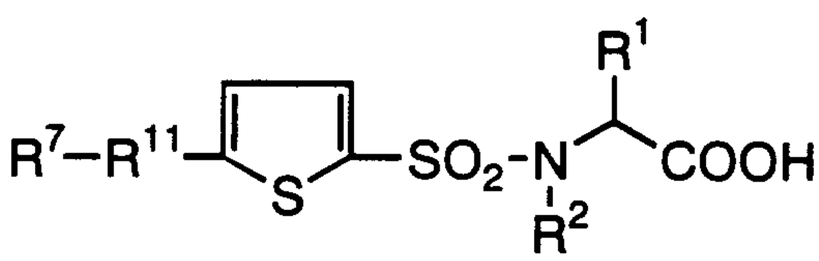
9) A compound of the formula VII:



VII

wherein R^1, R^2, R^7, R^8, and R^9 are as defined above, its optically active substance, their pharmaceutically acceptable salt, or hydrate thereof.

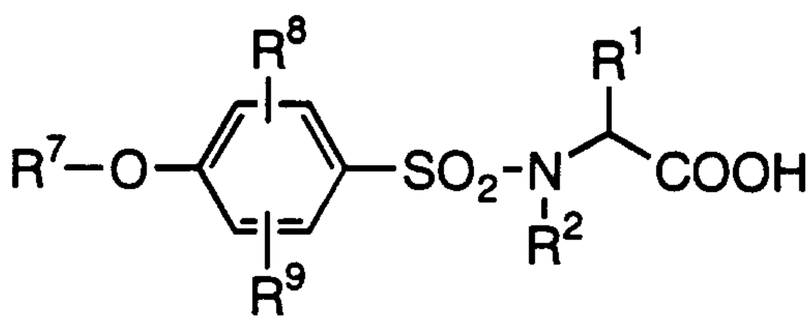
10) A compound of the formula VIII:



VIII

wherein R^1, R^2, R^7, and R^{11} are as defined above, its optically active substance, their pharmaceutically acceptable salt, or hydrate thereof.

11) A compound of the formula VIII:

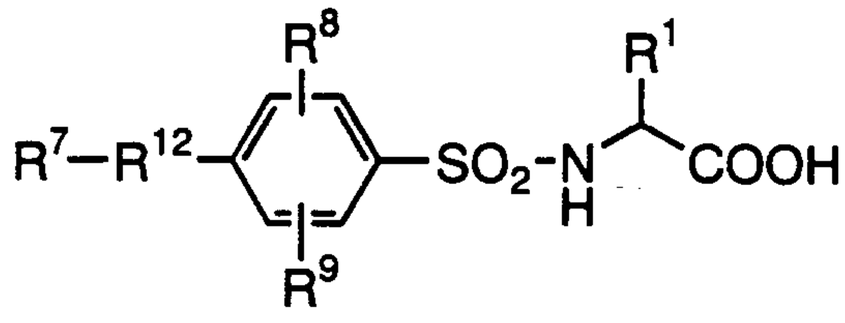


IX

wherein R^1, R^2, R^7, R^8, and R^9 are as defined above, its optically active substance, their

pharmaceutically acceptable salt, or hydrate thereof.

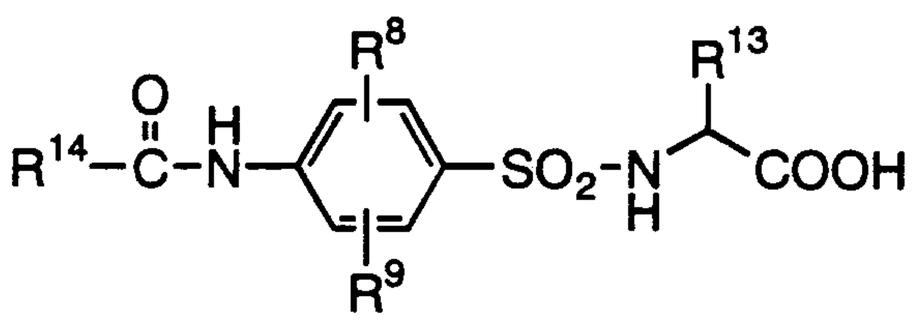
12) A compound of the formula X:



X

wherein R^{12} is -CH=CH- or -C ≡ C-; R^1, R^7, R^8, and R^9 are as defined above, its optically active substance, their pharmaceutically acceptable salt, or hydrate thereof.

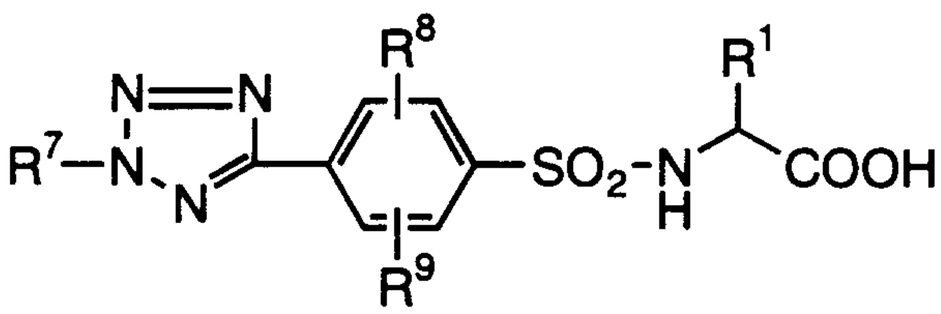
13) A compound of the formula XI:



XI

wherein R^8, R^9, R^{13}, and R^{14} are as defined above, provided R^{13} is not methyl or phenyl and R^{14} is not 2-chlorophenyl, 4-chlorophenyl, or 2,4-dichlorophenyl, its optically active substance, their pharmaceutically acceptable salt, or hydrate thereof.

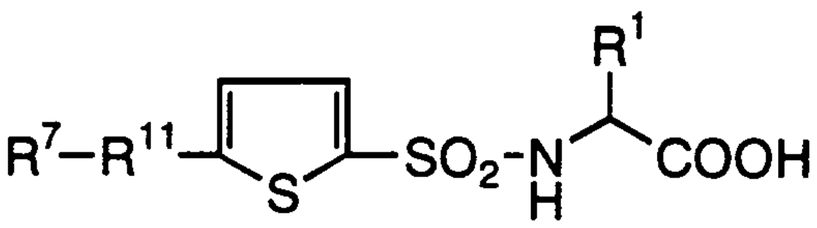
14) A compound of the formula XII:



XII

wherein R^1, R^7, R^8, and R^9 are as defined above, its optically active substance, their pharmaceutically acceptable salt, or hydrate thereof.

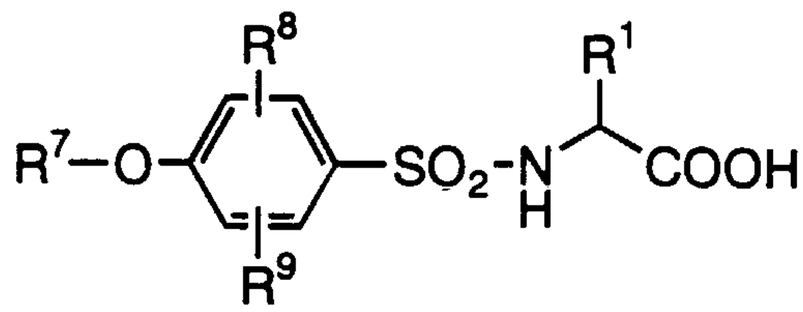
15) A compound of the formula XIII:



XIII

wherein R^1, R^7, and R^{11} are as defined above, its optically active substance, their pharmaceutically acceptable salt, or hydrate thereof.

16) A compound of the formula XIV:



XIV

wherein R^1, R^7, R^8, and R^9 are as defined above, its optically active substance, their pharmaceutically acceptable salt, or hydrate thereof.

A compound of the invention is more specifically illustrated below:

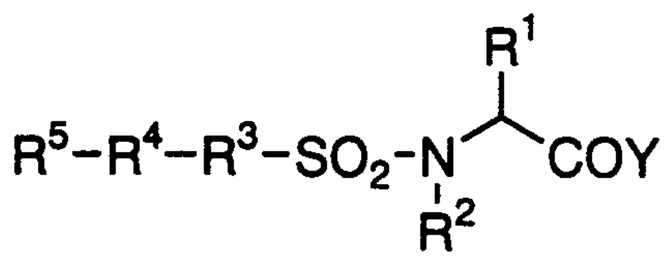
A) The compound of any one of above 1) to 16), wherein R^1, $R^{1'}$, $R^{1''}$, and R^{13} are i-propyl, benzyl, or (indol-3-yl) methyl.

B) The compound of any one of above 1) to 4) and 7) to 16), wherein R^5, R^7, and R^{14} are phenyl optionally substituted with one or more substituents selected from the group consisting of alkoxy, alkylthio, and alkyl.

C) The compound of any one of above 1) to 16), wherein a configuration of asymmetric carbon atoms bonding with R^1, $R^{1'}$, $R^{1''}$, and R^{13} is R configuration.

Further, this invention relates to a pharmaceutical composition , a composition for inhibiting metalloproteinase, and a composition for inhibiting type IV collagenase which contain the compound above 1) to 16) and A) to C)

All of compounds of above 1) to 16) and A) to C) have strong metalloproteinase inhibitory activity, and the following compound is more preferable:



I

1) A compound wherein R^1 is i-propyl, benzyl, or (indol-3-yl) methyl, R^2 is hydrogen atom, R^3 is 1,4-phenylene, R^4 is -C ≡ C-, and R^5 is optionally substituted phenyl.

2) A compound wherein R^1 is i-propyl, benzyl, or (indol-3-yl) methyl, R^2 is hydrogen atom, R^3 is optionally substituted 2,5-thiophen-diyl, R^4 is -C ≡ C-, and R^5 is optionally substituted phenyl.

3) A compound wherein R^1 is i-propyl, benzyl, or (indol-3-yl)methyl, R^2 is hydrogen

atom, R^3 is 1,4-phenylene, R^4 is tetrazol-diyl, and R^5 is optionally substituted phenyl.

The term "alkyl" herein used means C_1-C_{10} straight or branched chain alkyl, for example, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl, tert-butyl, n-pentyl, i-pentyl, neo-pentyl, tert-pentyl, and the like.

The term "lower alkyl" herein used means C_1-C_6 straight or branched chain alkyl, for example, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl, tert-butyl, and the like.

The term "C_3-C_8 cycloalkyl" herein used is exemplified by cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and the like.

The term "aryl" herein used means monocyclic or condensed ring aromatic hydrocarbons. Examples of the aryl are phenyl, naphthyl, and the like.

The term "aralkyl" herein used means the above mentioned alkyl substituted by the above mentioned aryl at any possible position. Examples of the aralkyl are benzyl, phenethyl, phenylpropyl (e.g., 3-phenylpropyl), naphthylmethyl (α-naphthylmethyl), anthrylmethyl (9-anthrylmethyl), and the like. Benzyl is preferred. The aryl part may optionally be substituted.

The term "heteroaryl" herein used means a 5 to 6 membered aromatic heterocyclic group which contains one or more hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms in the ring and may be fused with a carbocyclic ring or other heterocyclic ring at any possible position. Examples of the heteroaryl are pyrrolyl (e.g., 1-pyrrolyl), indolyl (e.g., 2-indolyl), carbazolyl (e.g., 3-carbazolyl), imidazolyl (e.g., 4- imidazolyl), pyrazolyl (e.g., 1-pyrazolyl), benzimidazolyl (e.g., 2-benzimidazolyl), indazolyl (e.g., 3-indazolyl), indolizinyl (e.g., 6-indolizinyl), pyridyl (e.g., 4-pyridyl), quinolyl (e.g., 5-quinolyl), isoquinolyl (e.g., 3-isoquinolyl), acridinyl (e.g., 1-acridinyl), phenanthridinyl (e.g., 2-phenanthridinyl), pyridazinyl (e.g., 3-pyridazinyl), pyrimidinyl (e.g., 4-pyrimidinyl), pyrazinyl (e.g., 2-pyrazinyl), cinnolinyl (e.g., 3-cinnolinyl), phthalazinyl (e.g., 2-phthalazinyl), quinazolinyl (e.g., 2-quinazolinyl), isoxazolyl (e.g., 3-isoxazolyl), benzisoxazolyl (e.g., 3-benzisoxazolyl), oxazolyl (e.g., 2-oxazolyl), benzoxazolyl (e.g., 2-benzoxazolyl), benzoxadiazolyl (e.g., 4-

benzoxadiazolyl), isothiazolyl (e.g., 3-isothiazolyl), benzisothiazolyl (e.g., 2-benzisothiazolyl), thiazolyl (e.g., 2-thiazolyl), benzothiazolyl (e.g., 2-benzothiazolyl), furyl (e.g., 3-furyl), benzofuryl (e.g., 3-benzofuryl), thienyl (e.g., 2-thienyl), benzothienyl (e.g., 2-benzothienyl), tetrazolyl, and the like. The aryl part of the above heteroaryl is optionally substituted.

The term "heteroarylalkyl" herein used means the above mentioned alkyl substituted with the above mentioned heteroaryl at any possible position. Examples of the heteroarylalkyl are thiazolylmethyl (e.g., 4-thiazolylmethyl), thiazolylethyl (e.g., 5-thiazolyl-2-ethyl), indolylmethyl (e.g., 2-indolylmethyl), imidazolylmethyl (e.g., 4-imidazolylmethyl), benzothiazolylmethyl (e.g., 2-benzothiazolylmethyl), benzopyrazolylmethyl (e.g., 1-benzopyrazolylmethyl), benzotriazolylmethyl (e.g., 4-benzotriazolylmethyl), benzoquinolylmethyl (e.g., 2-benzoquinolylmethyl), benzimidazolylmethyl (e.g., 2-benzimidazolylmethyl), pyridylmethyl (e.g., 2-pyridylmethyl), and the like. The aryl part of the above heteroaryl is optionally substituted.

The term "arylene" herein used is exemplified by phenylene, naphthylene, and the like. Mentioned in more detail, it is exemplified by 1,2-phenylene, 1,3-phenylene, 1,4-phenylene, and the like.

The term "heteroarylene" herein used is exemplified by thiophen-diyl, furan-diyl, pyridin-diyl, and the like, in more detail, by 2,5-thiophen-diyl, 2,5-furan-diyl, and the like.

The term "non-aromatic heterocyclic group" herein used means 5 to 6 membered non-aromatic heterocyclic group which contains one or more hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms in the ring, and may bind at any possible positin. Examples of the non-aromatic heterocyclic group are morpholino, piperidino, pyrrolidino, and the like.

The term "alkoxy" herein used means alkoxy of which alkyl part is the above mentioned alkyl. Examples of the alkoxy are methoxy, ethoxy, propoxy, butoxy, pentyloxy, and the like.

The term "lower alkoxy" herein used means alkoxy of which alkyl part is the above mentioned lower alkyl. Examples of the lower alkoxy are methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, sec-butoxy, tert-butoxy, and the like.

The term "halogen" herein used means fluoro, chloro, bromo, and iodo.

The term "alkylthio" herein used means alkylthio whose alkyl part is the above mentioned lower alkyl. Examples of the alkylthio are methylthio, ethylthio, and the like.

Substituents for "optionally substituted alkyl", "optionally substituted C_3-C_8 cycloalkyl", and "optionally substituted non-aromatic heterocyclic group" are hydroxy, alkoxy (e.g., methoxy and ethoxy), mercapto, alkylthio (e.g., methylthio), cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl), halogen (e.g., fluoro, chloro, bromo, and iodo), carboxy, alkoxycarbonyl (e.g., methoxycarbonyl and ethoxycarbonyl), nitro, cyano, haloalkyl (e.g., trifluoromethyl), substituted or unsubstituted amino (e.g., methylamino, dimethylamino, and carbamoylamino), guanidino, phenyl, benzyloxy, and the like. These substituents are able to bind them at one or more of any possible positions.

Substituents for the aromatic ring of "optionally substituted aryl", "optionally substituted aralkyl", "optionally substituted heteroaryl", "optionally substituted heteroarylalkyl", "optionally substituted arylene", and "optionally substituted heteroarylene" are, for example, hydroxy, alkoxy (e.g., methoxy and ethoxy), mercapto, alkylthio (e.g., methylthio), cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl), halogen (e.g., fluoro, chloro, bromo, and iodo), carboxy, alkoxycarbonyl (e.g., methoxycarbonyl and ethoxycarbonyl), nitro, cyano, haloalkyl (e.g., trifluoromethyl), aryloxy (e.g., phenyloxy) substituted or unsubstituted amino (e.g., methylamino, dimethylamino, diethylamino, and benzylidenamino), guanidino, alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl, tert-butyl, n-pentyl, i-pentyl, neo-pentyl, and tert-pentyl), alkenyl (e.g., vinyl and propenyl), alkynyl (e.g., ethynyl and phenylethynyl), alkanoyl (e.g., formyl, acetyl, and propionyl), acyloxy (e.g., acetyloxy), acylamino, alkylsulfonyl (e.g., methylsulfonyl), phenyl, benzyl, an azo group (e.g.,

phenylazo), optionally substituted heteroaryl (e.g., 3-pyridyl), optionally substituted ureido (e.g., ureido and phenylureido), and the like. These substituents are able to bind to it at one or more of any possible position.

Best Mode for Carrying Out the Invention

Compounds (Ia) and (Ib) of the invention are able to be synthesized from the corresponding α-amino acids represented by the formula (XV) by means of the following 6 synthetic methods. Generally, it is possible to produce the compounds of the invention by means of the method A. Each classified type of the compounds is possible to be produced by means of methods the B to F. However, these methods are only examples to produce the compounds represented by the formula I. A compound represented by the formula I produced by any other method is included in this invention.

Method A: A general synthetic method of the compound represented by the formula I.

Method B: A synthetic method of the compound wherein and R^3 is optionally substituted arylene or optionally substituted heteroarylene, R^4 is -C≡C-, and R^5 is optionally substituted aryl or optionally substituted heteroaryl.

Method C: A synthetic method of the compound wherein R^3 is optionally substituted arylene or optionally substituted heteroarylene, R^4 is a bond, and R^5 is optionally substituted aryl or optionally substituted heteroaryl.

Method D: A synthetic method of the compound wherein R^3 is optionally substituted arylene or optionally substituted heteroarylene, R^4 is -CO-NH-, and R^5 is optionally substituted aryl or optionally substituted heteroaryl.

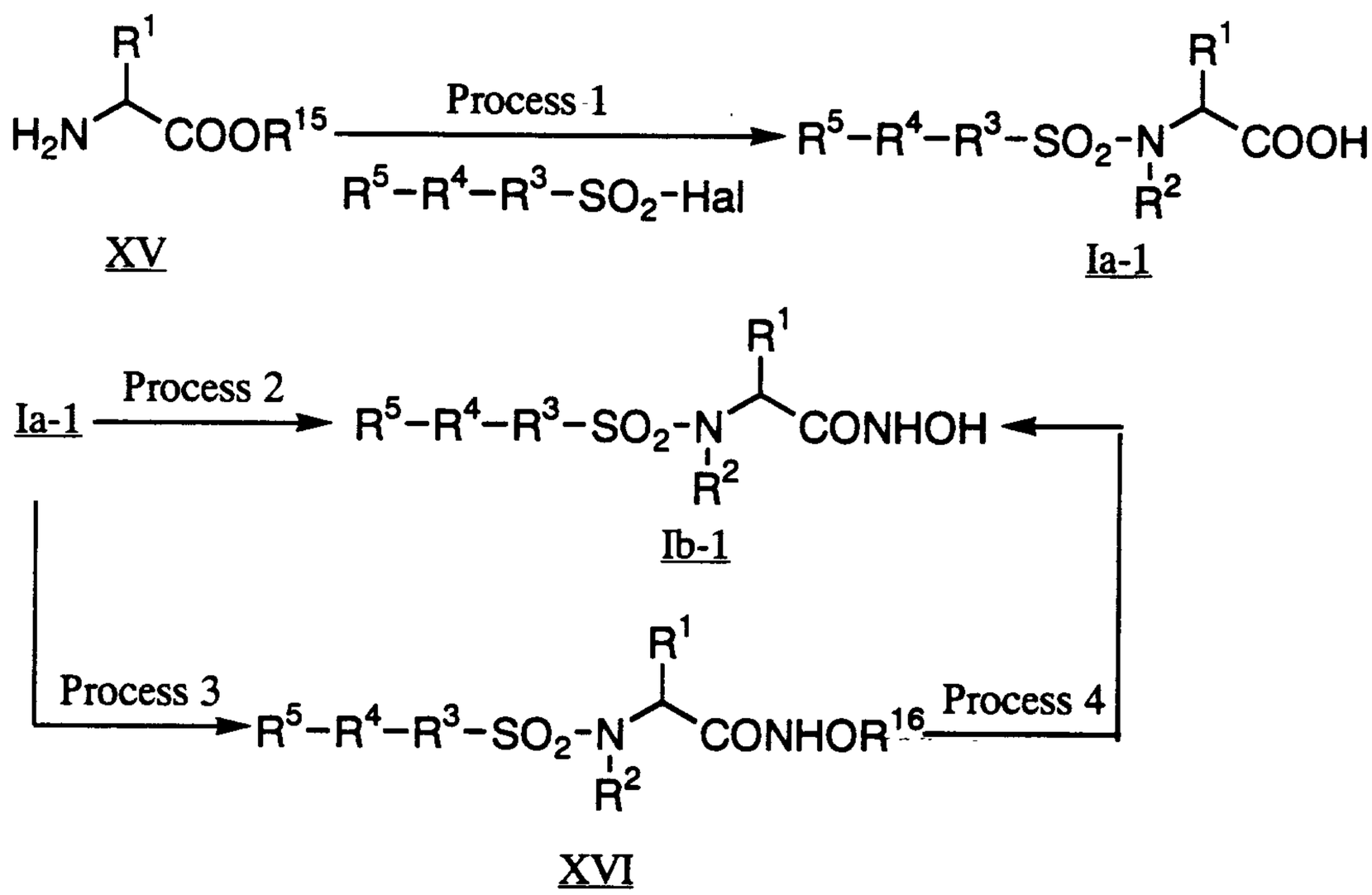
Method E: A synthetic method of the compound wherein R^3 is optionally substituted arylene or optionally substituted heteroarylene, R^4 is tetrazol-diyl, and R^5 is optionally substituted aryl or optionally substituted heteroaryl.

Method F: A synthetic method of the compound wherein R^3 is optionally substituted arylene or optionally substituted heteroarylene, R^4 is -CH=CH-, and R^5 is

optionally substituted aryl or optionally substituted heteroaryl.

Details of these methods are explained as follows.

(Method A)



wherein R^1, R^2, R^3, R^4, and R^5 are as defined above, R^{15} is hydrogen atom or a carboxy protective group, R^{16} is a hydroxy protective group, and Hal is halogen.

Conversion of compound (XV) to compound (Ia-1) is sulfonation of an amino group of the compound (XV) (process 1). If necessary, after this reaction, N-alkylation, deprotection of a carboxyl protective group, etc. are carried out. Conversion of compound (Ia-1) to compound (Ib-1) is to obtain hydroxamic acid derivatives from carboxylic acid derivatives (process 2). To obtain compound (Ib-1) from compound (Ia-1), compound (Ia-1) may also be reacted with hydroxylamine having a hydroxyl protective group or its acidic salts to give compound (XVI) (process 3), followed by and deprotection (process 4). Conversion to sulfonyl derivatives and hydroxamic acid derivatives are able to be carried out according to an usual method. For example, an amino acid represented by the formula (XV) is reacted with a sulfonating agent such as sulfonyl halide represented by R^5-R^4-R^3-SO_2Hal (R^3, R^4, and R^5 are as defined above; and Hal is halogen) and then hydroxylamine. Each process will hereinafter be described in more detail.

(Process 1)

Some of amino acids represented by the formula (XV) or its acidic salts (e.g., hydrochloride, p-toluenesulfonate, and trifluoroacetate) which are starting materials are commercially available. The other are able to be synthesized in accordance with a method described in Zikkenkagakukoza, vol. 22, IV (nihonkagakukai), J. Med. Chem. 38, 1689-1700, 1995, Gary M. Ksander et. al., etc. some of sulfonating agents are commercially available and the other are synthesized in accordance with a method described Shin-zikkenkagakukoza, vol. 14, 1787, 1978, Synthesis 852-854, 1986, etc. A carboxyl protective group is exemplified by esters (e.g., methyl ester , tert-butyl ester and benzyl ester). Deprotection of this protective group may be carried out by hydrolysis with acid (e.g., hydrochloride and trifluoroacetic acid) or base (e.g., sodium hydroxide) depending on the type of the group, or by catalytic reduction, e.g., under 10% palladium-carbon catalyst condition. To obtain a compound (Ib-1), the esters may directly be converted to hydroxamic acid by the method of process 2. When a compound (XV) is an amino acid wherein R^{15} is hydrogen atom, preferable solvents for this sulfonylation are dimethylformamide, tetrahydrofuran, dioxane, dimethylsulfoxide, acetonitrile, water, or mixed solvents thereof. When a compound (XV) is an amino acid wherein R^{15} is a protective group such as an ester, a solvent for this sulfonylation is exemplified by the above solvents and mixed solvents of water-insoluble solvents (e.g., benzene and dichloromethane) and the above solvents. A base to be used in this sulfonylation is exemplified by organic bases such as triethylamine, N-methylmorpholine, etc. and inorganic bases such as sodium hydroxide, potassium hydroxide, potassium carbonate, and the like. Usually this reaction can be carried out at ice-cooling to room temperature. When R^1, R^3, R^4, R^5, or R^{15} of compound (Ia-1) contains a functional group(s) possibly interfering this sulfonylation (e.g., hydroxy, mercapto, amino, and guanidino), it can previously be protected in accordance with a method described in " Protective Groups in Organic Synthesis" (Theodora W. Green (John Wiley & Sons)) and then deprotected at an appropriate process. When R^2 is not hydrogen atom, compound (Ia-1) wherein R^2 is hydrogen atom is further reacted with

haloalkyl (e.g., methyl iodide, and ethyl iodide) or haloaralkyl (e.g., benzyl chloride, and benzyl bromide) in dimethylformamide, tetrahydrofuran, dioxane, and the like at a temperature range of ice-cooling to 80 ℃, preferably ice-cooling to room temperature, for 3-10 hours, preferably 10-20 hours to give the desired N-R^2 derivative.

(Process 2)

A hydroxylamine is reacted with compound (Ia-1) or its reactive derivatives to give hydroxamic acid derivatives (Ib-1). A hydroxylamine is usually used as its acidic salts (e.g., hydrochloride, and phosphate, sulfate: commercially available) in the presence of a base. A base to be used in this reaction is exemplified by organic bases such as triethylamine, N, N-dimethylaniline, N-methylmorpholine, etc. and inorganic bases such as sodium hydroxide, potassium hydroxide, potassium carbonate, etc. When compound (Ia-1) is used as a starting material of conversion to hydroxamic acid, this reaction is carried out in the presence of a peptide condensing agent (e.g., dicyclohexylcarbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, N,N'-carbonyldiimidazole, or a mixture of one of the above agents with 1-hydroxybenzotriazole, N-hydroxy sucinicimide, etc.). A solvent for this reaction may be dimethylformamide, tetrahydrofuran, dioxane, dimethylsulfoxide, acetonitrile, water, and mixed solvent thereof. This reaction is carried out at -20 ℃ to 40 ℃, preferably ice-cooling to room temperature, for 1 to 16 hours.

Acid anhydrides (especially, mixed acid anhydrides), acid halides, acid azides, and esters can be utilized in this reaction as a reactive derivative of compound (Ia-1). These reactive derivatives are produced by usual methods. For example, the acid anhydride derivatives can be produced by a reaction of compound (Ia-1) with acid halide derivatives (e.g., ethyl chlorocarbonate) in the presence of a base (e.g., triethylamine), and acid halide derivatives can be produced by a reaction of compound (Ia-1) with a halogenation agent (e.g., oxalylchloride, and thionylchloride). Ester derivatives may be inactive or active. Sulfonyl derivatives converted from a compound (XV) wherein R^{15} is a carboxyl protective groups (e.g., methyl, tert-butyl, and benzyl) at process 1 can be used as inactive esters without deprotection. Active

esters can be produced by a reaction of compound (Ia-1), carbodiimide reagents (e.g., dicyclohexylcarbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide), and hydroxy derivatives corresponding to the active ester residue such as 1-hydroxybenzotriazole, N-hydroxysuccinimide, or the like. A reaction condition of conversion of the reactive derivatives of compound (Ia-1) to hydroxamic acid may be the same as that of conversion of compound (Ia-1) itself to hydroxamic acid . The reactions of processes 1 and 2 are able to continuously be carried out in one-pot reaction.

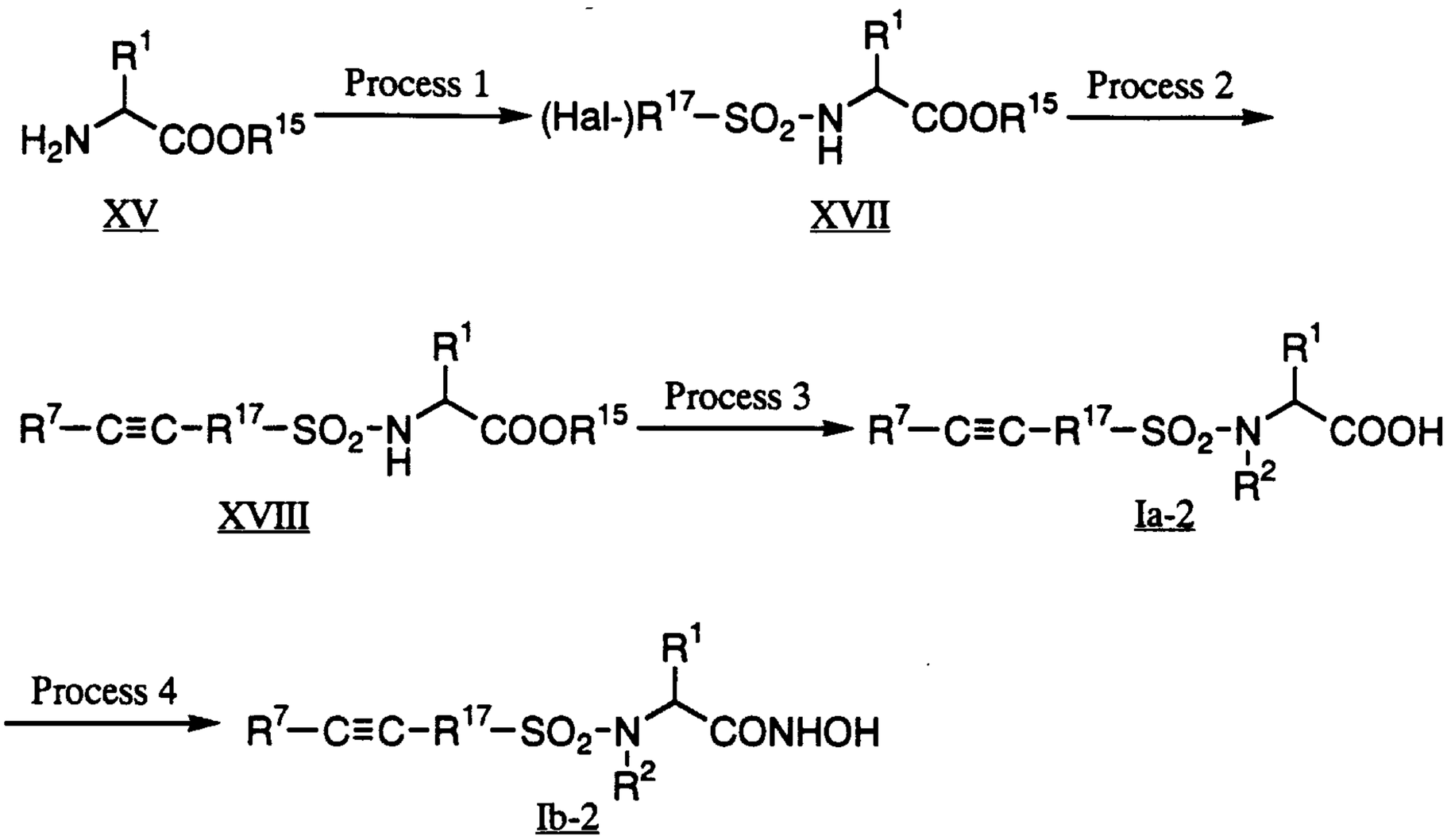
(Process 3)

A protected hydroxylamine to be used in this reaction includes O-benzylhydroxylamine, O-(p-methoxybenzyl)hydroxylamine, O-(tert-butyl)hydroxylamine, or the like. This reaction condition may be in the same manner as that of process 2.

(Process 4)

This process for deprotection is carried out by catalytic reduction, treatment with conc. hydrochloric acid, or treatment with trifluoroacetic acid to give the desired compound (Ib-1). The compounds of this invention (Ia-1) and (Ib-1) can be isolated and purified by usual separation methods and purification methods (e.g., chromatography, crystallization, etc.).

(Method B)



wherein R^1, R^2, R^7, R^{15}, and Hal are as defined above, R^{17} is optionally substituted aryl or optionally substituted heteroaryl.

Conversion of compound (XV) to compound (XVII) is performed by sulfonation of an amino group of compound (XV) (process 1) in the same manner as that described in process 1 of method A. Conversion of compound (XVII) to compound (XVIII) is performed by Heck reaction (K. Sonogashira, Y. Tohda, and N. Hagihara, Tetrahedron Lett., 4467(1975) etc.) wherein halogen of R^{17} is utilized to insert a triple bond (process 2). Conversion of compound (XVIII) to compound (Ia-2) is N-alkylation, deprotection of a carboxyl protective group, etc. (process 3), which can be carried out in the same manner as that described in process 1 of method A. Conversion of compound (Ia-2) to compound (Ib-2) is that of carboxylic acid derivatives to hydroxamic acid derivatives (process 4), which can be carried out in the same manner as those described in processes 2 to 4 of method A. Each process will hereinafter be described in more detail.

(Process 1)

This process may be carried out in the same manner as that described in process 1 of method A.

(Process 2)

Compound (XVII) is reacted with optionally substituted aryl or optionally substituted heteroaryl having an ethynyl group such as ethynylbenzene in a solvent such as dimethylformamide, toluene, xylene, benzene, tetrahydrofuran etc. in the presence of a palladium catalyst (e.g., $Pd(Ph_3P)_2Cl_2$), a divalent copper reagent (e.g., CuI), and an organic base (e.g., triethylamine, and diisopropylethylamine) to give a desired compound (XVIII) (Heck reaction). This reaction is carried out at room temperature to 100 ℃, preferably room temperature to 80 ℃. This reaction is completed for 3 to 30 hours, preferably 10 to 20 hours. When optionally substituted aryl or optionally substituted heteroaryl has a substituent(s) interfering this reaction, the substituent(s) can previously be protected in accordance with a method of " Protective Groups in Organic Synthesis " (Theodora W. Green (John Wiley & Sons)), and then deprotected at an appropriate step.

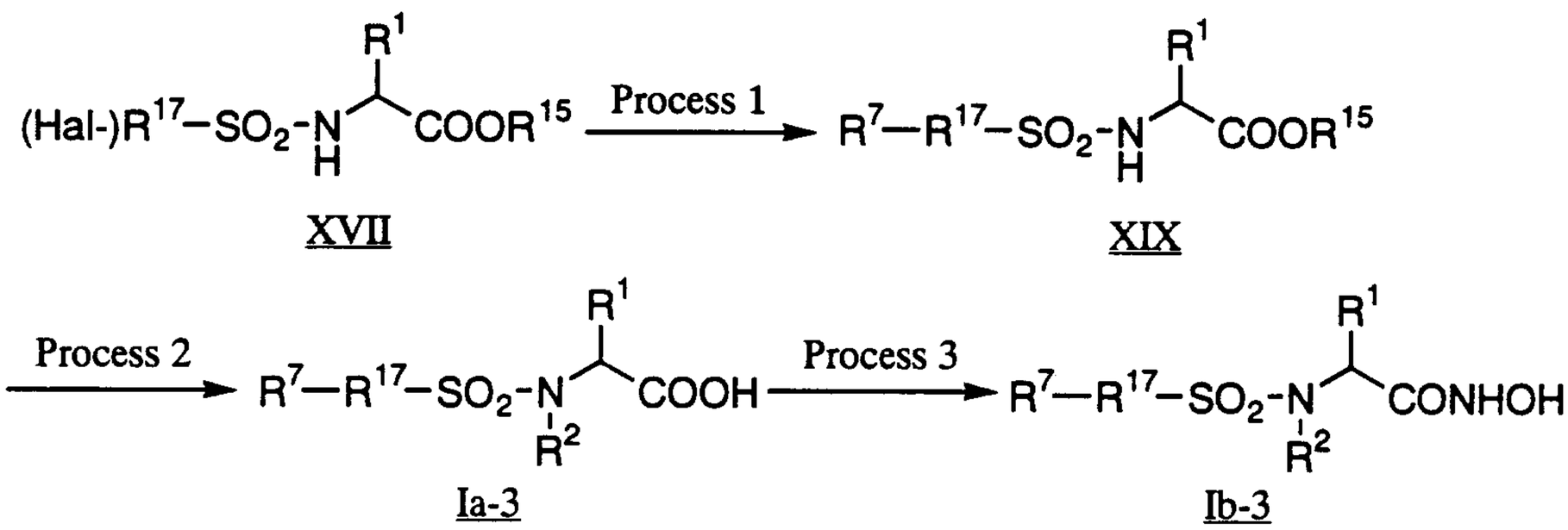
(Process 3)

This process may be carried out in the same manner as that described in process 1 of method A.

(Process 4)

This process may be carried out in the same manner as those described in processes 2 to 4 of method A.

(Method. C)



wherein R^1, R^2, R^7, R^{15}, R^{17}, and Hal are as defined above.

Conversion of compound (XVII) to compound (XIX) is performed by Suzuki reaction (M. J. Sharp and V. Shieckus, Tetrahedron Lett., 26, 5997 (1985) etc.) wherein

halogen of R^{17} is utilized to introduce aryl or heteroaryl (process 1). Conversion of compound (XIX) to compound (Ia-3) is N-alkylation, deprotection of a carboxyl protective group, etc. (process 2) and this process can be carried out in the same manner as that described in process 1 of method A. Conversion of compound (Ia-3) to compound (Ib-3) is that of carboxylic acid derivatives to hydroxamic acid derivatives (process 3), and this process can be carried out in the same manner as those described in processes 2 to 4 of method A. Each process will hereinafter be described in more detail.

(process 1)

Compound (XVII) is reacted with optionally substituted aryl or optionally substituted heteroaryl having a $B(OH)_2$ (otherwise $B(Et)_2$) group such as phenylboronic acid in a solvent such as dimethylformamide, toluene, xylene, benzene, tetrahydrofuran etc. in the presence of a palladium catalyst (e.g., $Pd(Ph_3P)_4$) and a base (e.g., potassium carbonate, calcium carbonate, triethylamine, sodium methoxide etc.) to give the desired compound (XIX) (Suzuki reaction). This reaction is carried out at room temperature to 100 ℃, preferably room temperature to 80 ℃. This reaction is completed for 5 to 50 hours, preferably 15 to 30 hours. When optionally substituted aryl or optionally substituted heteroaryl has a substituent(s) interfering this reaction, the substituent(s) can previously be protected in accordance with a method of " Protective Groups in Organic Synthesis " (Theodora W. Green (John Wiley & Sons)) and then deprotected at an appropriate step.

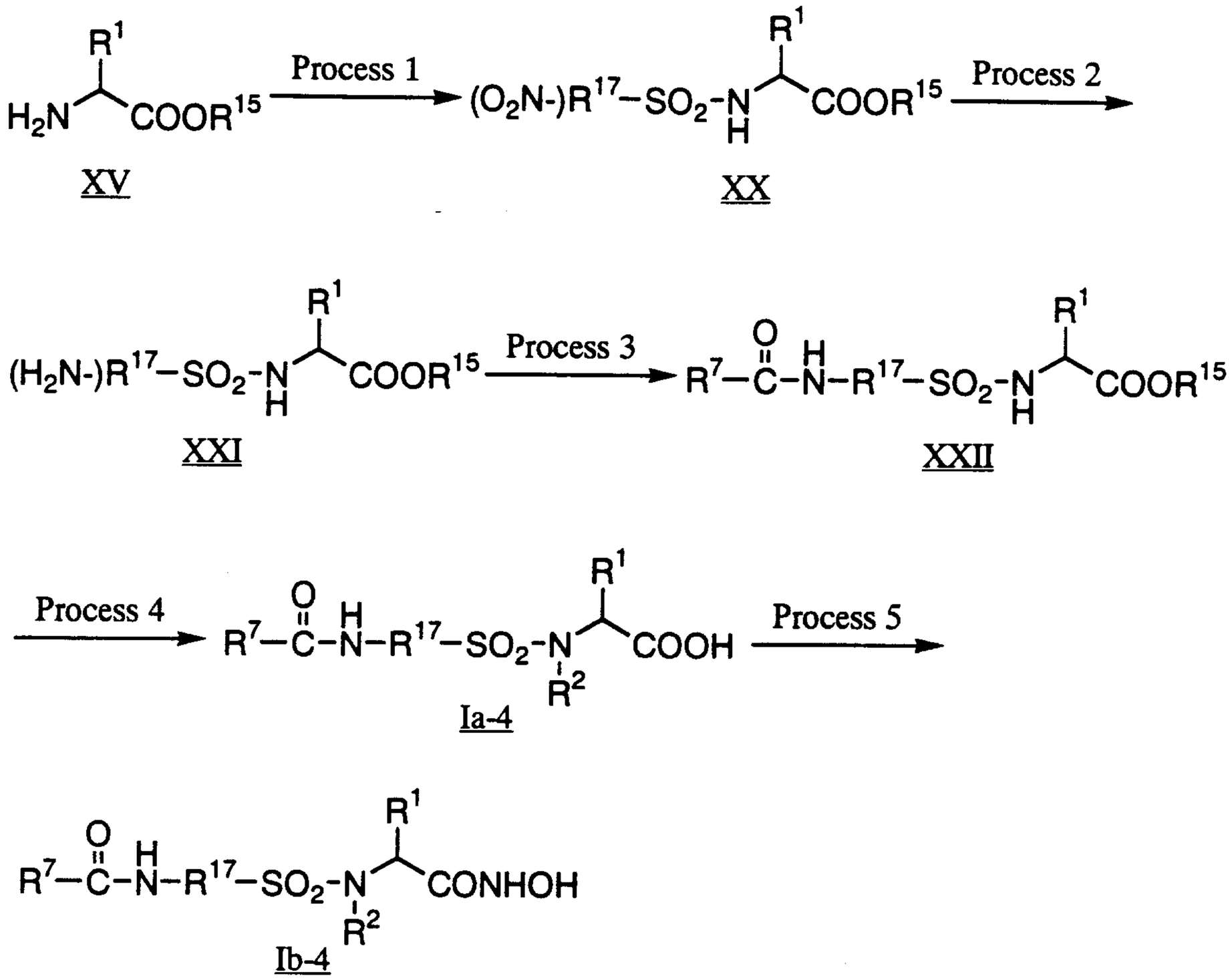
(Process 2)

This process may be carried out in the same manner as that described in process 1 of method A.

(Process 3)

This process may be carried out in the same manner as those described in processes 2 to 4 of method A.

(Method D)



wherein R^1, R^2, R^7, R^{15}, R^{17}, and Hal are as defined above.

Conversion of compound (XV) to compound (XX) is sulfonation of an amino group of the compound (XV) (process 1) and this process may be carried out in the same manner as that described in process 1 of method A. Conversion of compound (XX) to compound (XXI) is reduction of a nitro group of R^{17} to an amino group (process 2) and this process can be carried out by catalytic reduction or other reduction using hydrochloric chloride - Fe, hydrochloric chloride - Sn, etc. Conversion of compound (XXI) to compound (XXII) is performed by usual amide bond formation reaction wherein an amino group of R^{17} is utilized (process 3). Conversion of compound (XXII) to compound (Ia-4) is N-alkylation, deprotection of a carboxyl protective group, etc. (process 4) of compound (XXII) and this process can be carried out in the same manner as that described in process 1 of method A. Conversion of compound (Ia-4) to compound (Ib-4) is that of carboxylic acid derivatives to hydroxamic acid derivatives (process 5) and this process can be carried out in the same manner as those described

in processes 2 to 4 of method A. Each process will hereinafter be described in more detail.

(process 1)

This process may be carried out in the same manner as that described in process 1 of method A.

(Process 2)

Compound (XX) is treated with hydrogen in a solvent such as methanol, ethanol, ethyl acetate, acetic acid, etc. in the presence of a catalyst (e.g., Pd-C, PtO_2, Raney Ni etc.) , under a no-pressure or pressured condition to give the desired compound (XXI). This reaction is carried out at a temperature under ice-cooling to 80 ℃, preferably room temperature to 50 ℃, and is completed for 1 to 10 hours, preferably 2 to 5 hours.

(Process 3)

Compound (XXI) is reacted with optionally substituted aryl or optionally substituted heteroaryl having an acid halide (otherwise an active ester) group such as benzoyl chloride in a solvent such as dimethylformamide, tetrahydrofuran, dioxane, dimethylsulfoxide, acetonitrile, xylene, toluene, benzene, dichloromethane, etc. in the presence of a base (e.g., triethylamine, N-methylmorpholine, potassium carbonate etc.) to give the desired compound (XXII). This reaction is carried out at a temperature under ice-cooling to 100 ℃, preferably room temperature to 60 ℃, and is completed for 3 to 30 hours, preferably 10 to 25 hours.

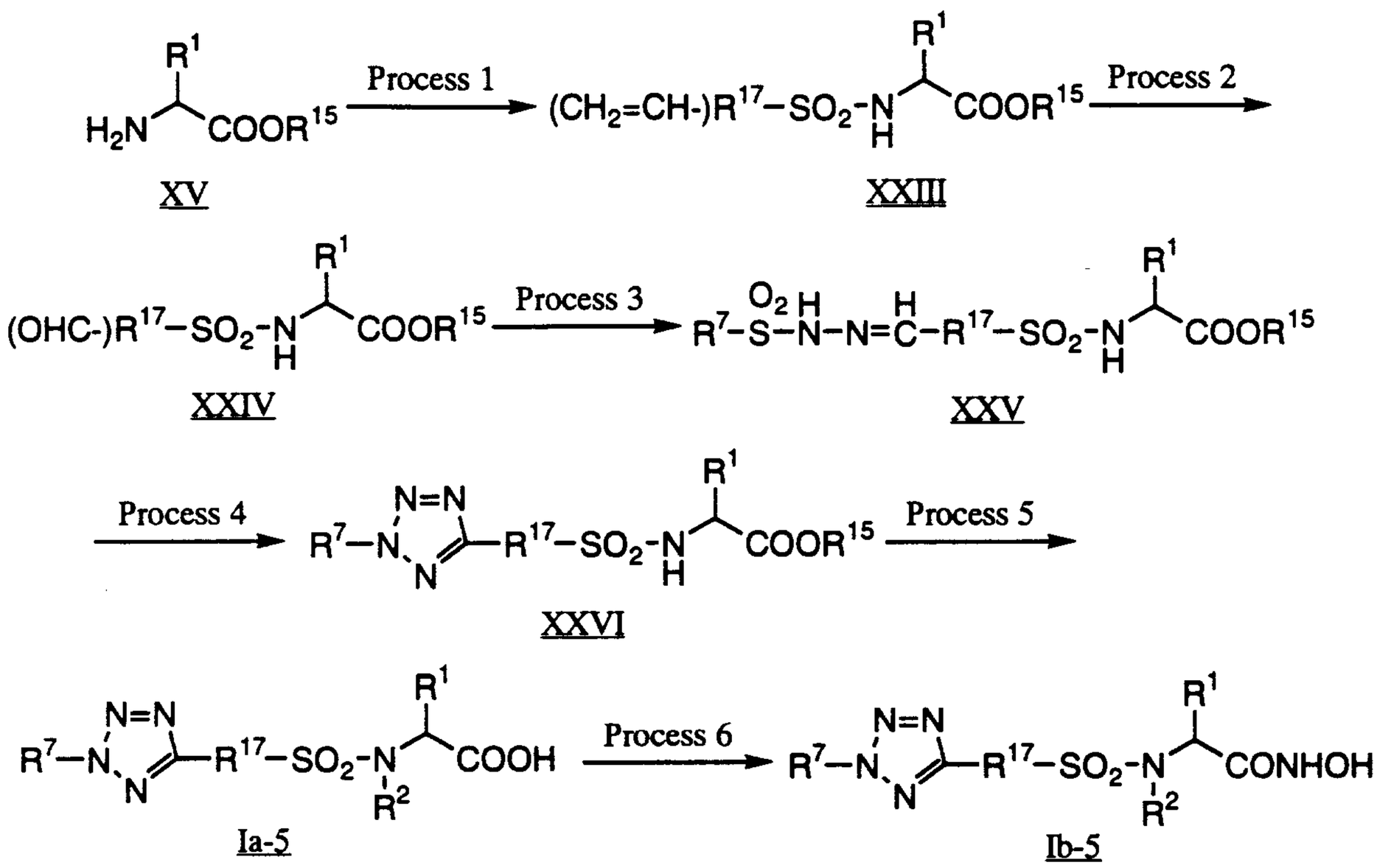
(Process 4)

This process may be carried out in the same manner as that described in process 1 of method A.

(Process 5)

This process may be carried out in the same manner as those described in processes 2 to 4 of method A.

(Method E)



wherein R^1, R^2, R^7, R^{15}, R^{17}, and Hal are as defined above.

Conversion of compound (XV) to compound (XXIII) is performed by sulfonating an amino group of the compound (XV) (process 1) in the same manner as that described in process 1 of method A. Conversion of compound (XXIII) to compound (XXIV) is done by the reduction wherein an ethenyl group of R^{17} is converted into an aldehyde group (process 2). Conversion of compound (XXIV) to compound (XXVI) is performed by a tetrazole ring formation reaction (processes 3 and 4). Conversion of compound (XXVI) to compound (Ia-5) is N-alkylation, deprotection of a carboxyl protective group, etc. of compound (XXVI) (process 5), and this process can be carried out in the same manner as that described in process 1 of method A. Conversion of compound (Ia-5) to compound (Ib-5) is that of carboxylic acid derivatives to hydroxamic acid derivatives (process 6), which can be carried out in the same manner as those described in processes 2 to 4 of method A. Each process will hereinafter be described in more detail.

(process 1)

This process may be carried out in the same manner as that described in process 1 of method A.

(Process 2)

A compound (XXIII) is treated with ozone in a solvent such as dichloromethane, ethyl acetate, methanol, etc. to form an ozonide, and then a reagent such as zinc-acetic acid, triethylphosphate, dimethylsulfide, etc. is added to this reaction mixture for reduction to give the desired aldehyde derivatives (XXIV) The reduction can also be carried out by catalytic hydrogenation. This reaction is carried out at -100 ℃ to room temperature, preferably -78 ℃ to a temperature under ice-cooling, and is completed for 0.5 to 10 hours, preferably 1 to 3 hours.

(Process 3)

A compound (XXIV) is reacted with benzensulfonylhydrazide in a solvent such as tetrahydrofuran, ether, etc. mixed with a solvent such as methanol, ethanol, etc. to give the desired compound (XXV). This reaction is carried out at a temperature under ice-cooling to 80 ℃, preferably room temperature to 50 ℃, and is completed for 3 to 30 hours, preferably 10 to 20 hours.

(Process 4)

Optionally substituted aryl or optionally substituted heteroaryl having amino group such as aniline is dissolved in a mixed solvent such as alcohol (e.g., ethanol) and water. To this mixture conc. hydrochloric acid and a diazotizing agent such as a sodium nitrite aqueous solution are added at -20 ℃ to 10 ℃, preferably 0 ℃ to 5 ℃, to give a diazonium salt. The reaction time is 5 min to 1 hr, preferably 10 to 30 min. This reaction mixture is added to a pyridine solution of compound (XXV) and allowed react for 1 to 10 hr, preferably 2 to 5 hr, at -30 ℃ to 50 ℃, preferably -15 ℃ to room temperature to give the desired compound (XXVI). When optionally substituted aryl or optionally substituted heteroaryl has a substituent(s) interfering this reaction, the substituent(s) can previously be protected in accordance with a method of " Protective Groups in Organic Synthesis " (Theodora W. Green (John Wiley & Sons)), and then deprotected at an appropriate step.

(Process 5)

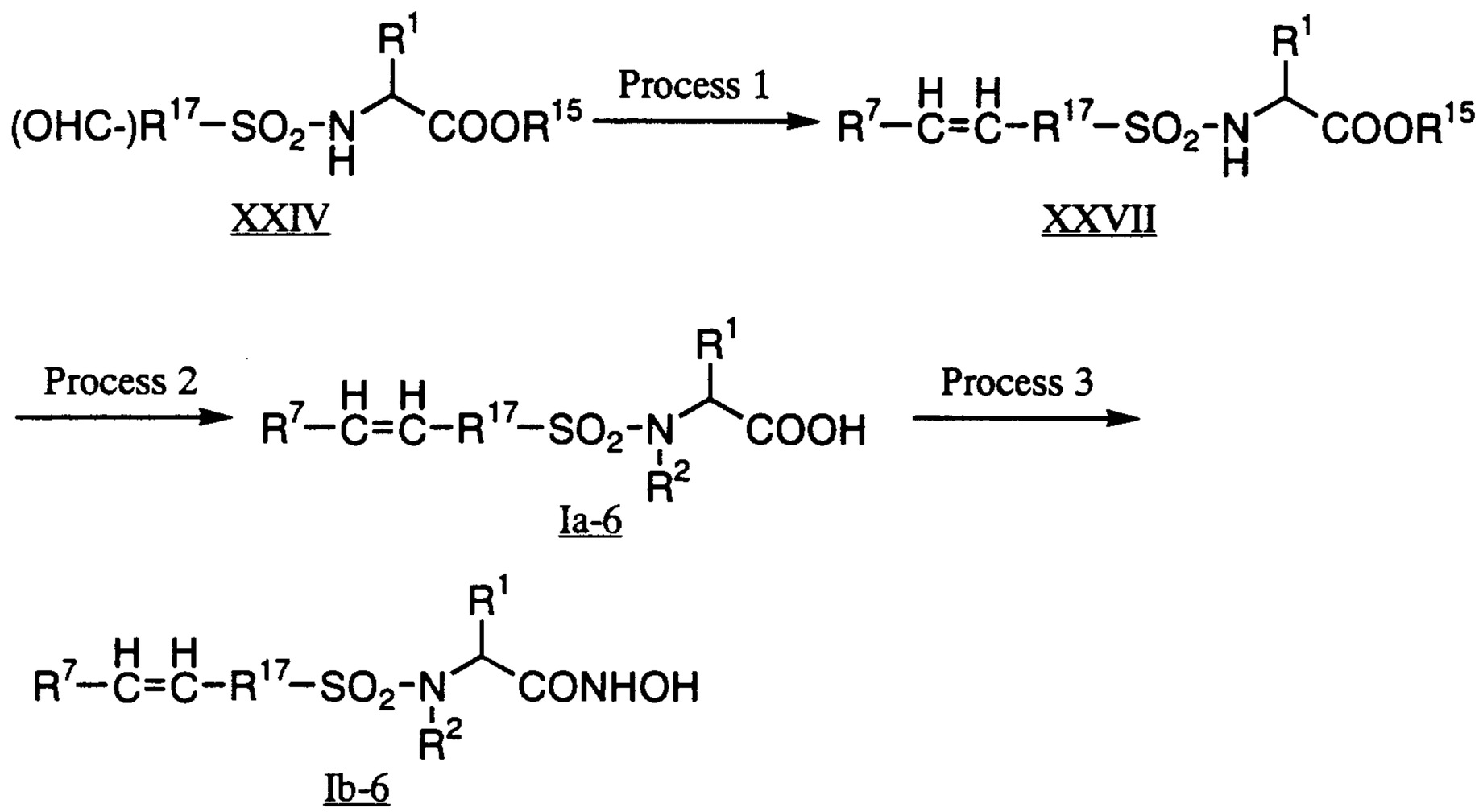
This process may be carried out in the same manner as that described in

process 1 of method A.

(Process 6)

This process may be carried out in the same manner as those described in processes 2 to 4 of method A.

(Method F)



wherein R^1, R^2, R^7, R^{15}, R^{17}, and Hal are as defined above.

Conversion of compound (XXIV) to compound (XXVII) is performed by Wittig reaction (G. Wittig et al., Chem. Berr. 87, 1318 (1954)) wherein an aldehyde group of R^{17} is utilized to introduce aryl or heteroaryl through a double bond (process 1). Conversion of compound (XXVII) to compound (Ia-6) is N-alkylation, deprotection, etc. of compound (XXVII) (process 2), and this process can be carried out the same similar as described in process 1 of method A. Conversion of compound (Ia-6) to compound (Ib-6) is that of carboxylic acid derivatives to hydroxamic acid derivatives (process 3), and this process can be carried out in the same manner as those described in processes 2 to 4 of method A. Each process will hereinafter be described in more detail.

(process 1)

Compound (XXIV) is reacted with ylide derivatives of optionally substituted aryl or optionally substituted heteroaryl such as Ph_3P=CHPh, etc., which is produced

by an usual method, in a solvent such as toluene, xylene, tetrahydrofuran, ether, dimethylformamide, etc. at -100 ℃ to room temperature, preferably -78 ℃ to ice-cooling for 1 to 20 hours, preferably 1 to 5 hours, to give the desired compound (XXVII). When optionally substituted aryl or optionally substituted heteroaryl has a substituent(s) interfering this reaction, the substituent(s) can previously be protected in accordance with a method of " Protective Groups in Organic Synthesis " (Theodora W. Green (John Wiley & Sons)), and deprotected at an appropriate step.

(Process 2)

This process may be carried out in the same manner as that described in process 1 of method A.

(Process 3)

This process may be carried out in the same manner as those described in processes 2 to 4 of method A.

The term " compound of the present invention " herein used includes pharmaceutically acceptable salt or hydrate of the compound. The salt is exemplified by a salt with alkali metals (e.g., lithium, sodium, and potassium), alkaline earth metals (e.g., magnesium and calcium), ammonium, organic bases, amino acids, mineral acids (e.g., hydrochloric acid, hydrobromic acid, phosphoric acid, and sulfuric acid), or organic acids (e.g., acetic acid, citric acid, mallein acid, fumaric acid, benzenesulfonic acid, and p-toluenesulfonic acid). These salts can be formed by the usual method.

The compound of the present invention is not restricted to any particular isomers but includes all possible isomers and racemic modifications.

The compound of the present invention has an excellent activity for inhibiting metalloproteinase, especially activity for inhibiting MMP, and inhibits matrix dissolution, as described in the following test example. Therefore, the compound of the present invention is useful to treat or prevent diseases which are caused by MMP and relative enzymes such as TNF-α converting enzyme, etc.

Definitely, the compounds of the present invention are useful in the prevention or treatment of diseases such as osteoarthritis, rheumatoid arthritis,

corneal ulceration, periodontal disease, metastasis and invasion of tumor, advanced virus infection (e.g., HIV), arteriosclerosis obliterans, arteriosclerotic aneurysm, atherosclerosis, restenosis, sepsis, septic shock, coronary thrombosis, aberrant angiogenesis, scleritis, multiple sclerosis, open angle glaucoma, retinopathies, proliferative retinopathy, neovascular glaucoma, pterygium, keratitis, epidermolysis bullosa, psoriasis, diabetes, nephritis, neurodegengerative disease, gingivitis, tumor growth, tumor angiogenesis, ocular tumor, angiofibroma, hemangioma, fever, hemorrhage, coagulation, cachexia, anorexia, acute infection, shock, autoimmune disease, malaria, Crohn disease, meningitis, and gastric ulcer.

When the compound of the present invention is administered to a person for treatment or prevention of the above diseases, they can be administered by oral administration such as powder, granules, tablets, capsules, pilulae, and liquid medicine, or by parenteral administration such as injections, suppository, percutaneous formulations, insufflation, or the like. An effective dose of the compound of the invention is formulated by being mixed with medicinal admixture such as excipient , penetrant, disintegrators, lubricant, and the like if necessary. When parenteral injection is prepared, the compound of the invention and an appropriate carrier are sterilized to prepare it.

An appropriate dosage varies with the conditions of the patients, an administration route, their age, their body weight and the like and should be determined by a physician in the end. In the case of oral administration, a daily dosage can generally be between 0.1 - 100 mg/kg/day, preferably 1 - 20 mg/kg/day. In the case of parenteral administration, the daily dosage can generally be between 0.01 - 10 mg/kg/day, preferably 0.1 - 1 mg/kg/day. The daily dosage can be administrated in one to several divisions.

The following examples are provided to further illustrate the present invention and are not to be constructed as limiting the scope thereof.

Abbreviations described below are used in the following examples.

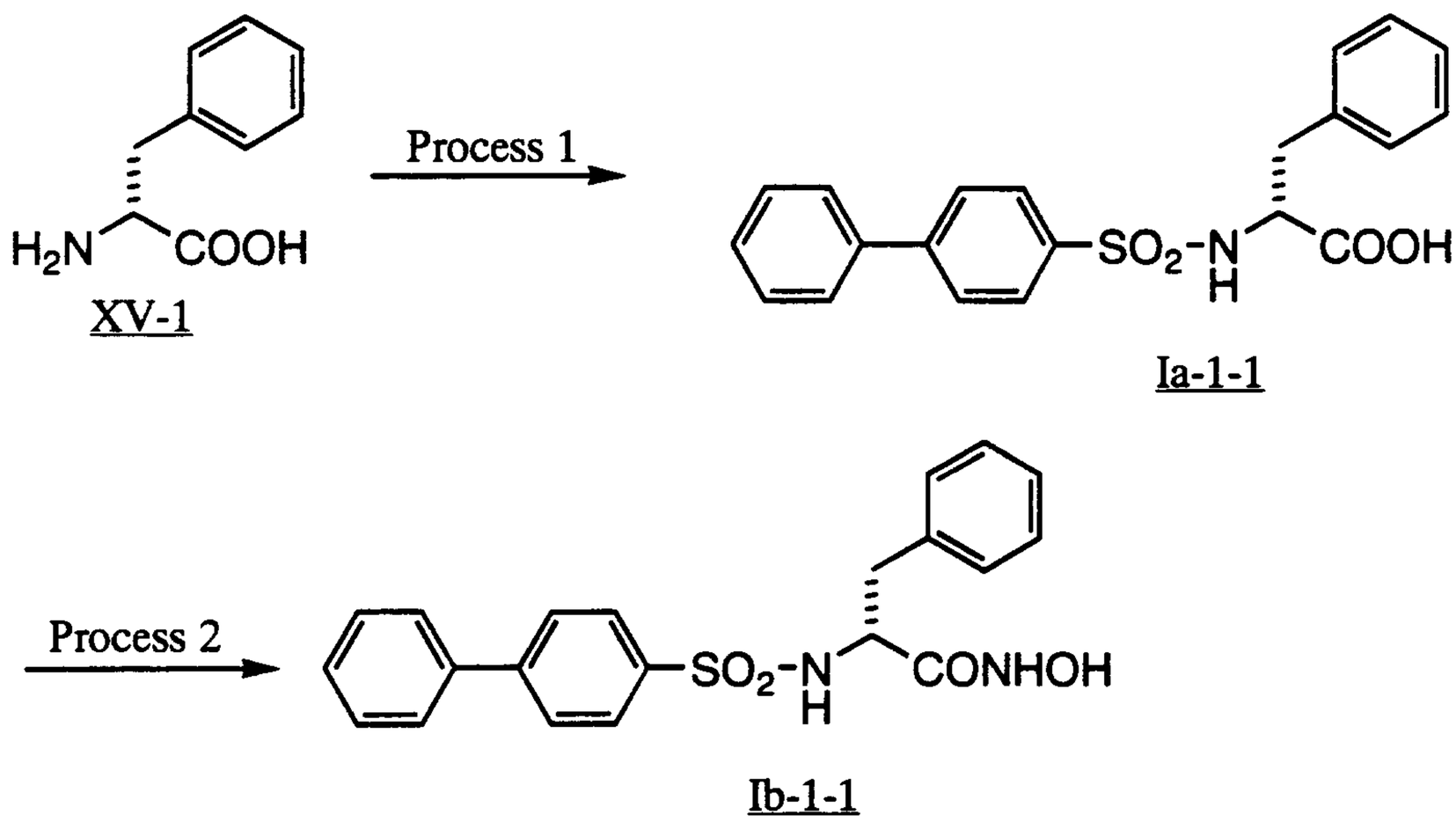
p-TsOH : p-toluenesulfonic acid

DMSO : dimethylsulfoxide

Me : methyl

^{t}Bu : tert-butyl

Example 1 (Method A)



To a suspension of (R)-(+)-phenylalanine (compound XV-1, 1.65g (10 mmol)) in 50 ml of dimethylformamide and 35 ml of water was stirred and treated with 2.78 ml (20 mmol) of triethylamine under ice-cooling. Then, 2.52g(10 mmol) of 4-biphenylsulfonyl chloride in 10 ml of dimethylformamide was added dropwise to the mixture over 5 min. After the reaction mixture was stirred for 2 h at the same temperature, 1.35 g (10 mmol) of 1-hydroxybenzotriazole hydrate, 2.1 g (11 mmol) of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, 3.47 g (50 mmol) of hydroxylamine hydrochloride, and 7 ml (50 mmol) of triethylamine were added to the mixture. After being stirred for 16 h at room temperature, the reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with 2N HCl, 5% $NaHCO_3$, and water, and concentrated in vacuo. The residue was subjected to silica gel column chromatography and the fractions eluting with $CHCl_3$ / MeOH = 40/1 to 20/1 were collected to yield 1.70 g of compound (Ib-1-1) as a foam. Yield 43%. mp. 169-170℃.

Elemental analysis (%) $C_{21}H_{20}N_2O_4S$

Calcd. : C; 63.62, H; 5.08, N; 7.07, S; 8.09

Found : C;63.61, H; 5.12, N; 6.98, S; 8.06

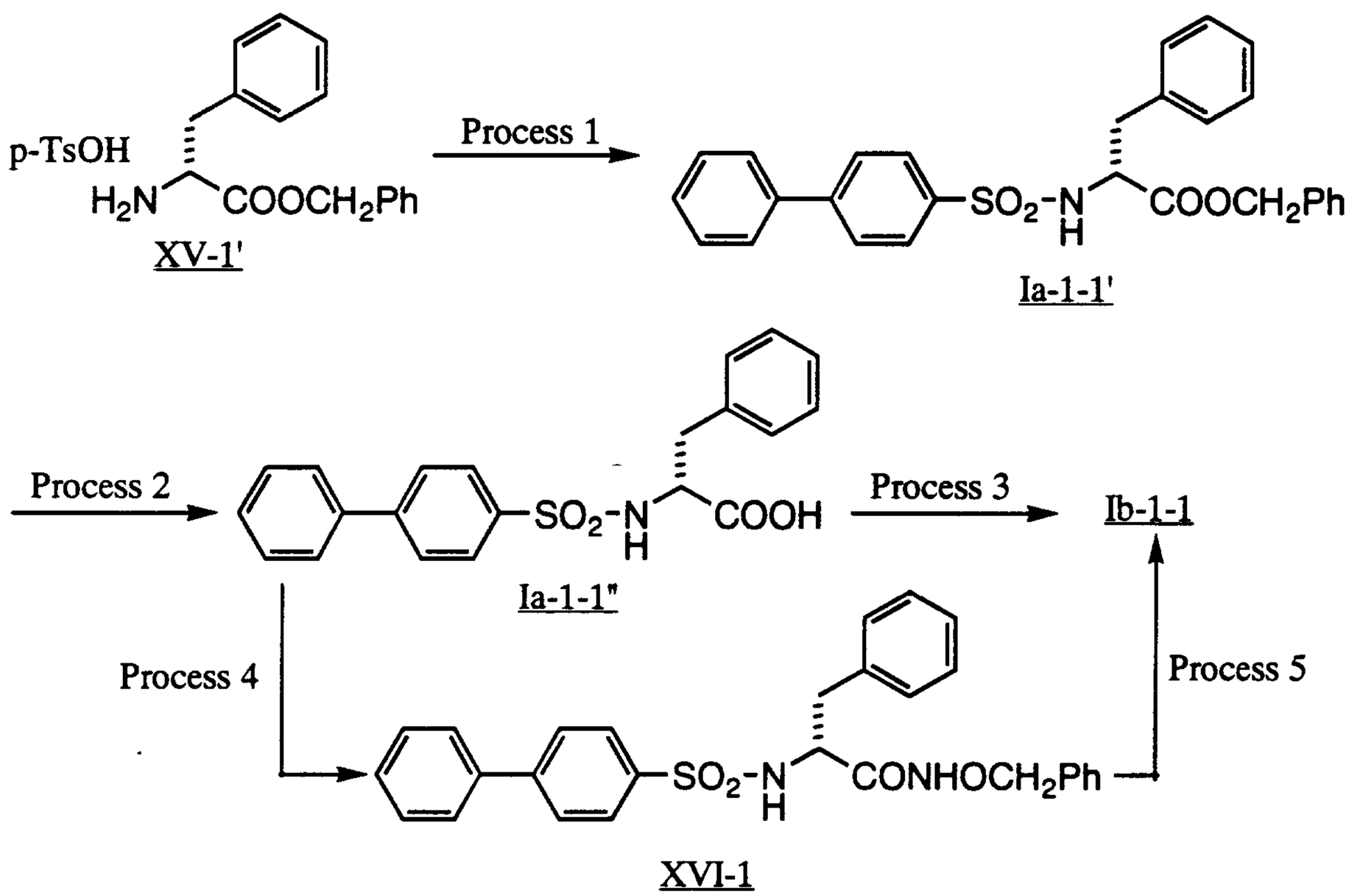
IR ν max (cm^{-1}) (Nujol) : 3365, 3295, 3266, 1674, 1320, 1159.

NMR (δ ppm) d_6-DMSO : 2.61 (dd, J=8.6, 13.4Hz, 1H), 2.80 (dd, J=6.0, 13.6Hz, 1H), 3.80 (m, 1H).

$[\alpha]_D$: +18.5±1.2 (c=0.503 %, 25℃, DMSO)

Example 1'

Another synthetic method of compound (Ib-1-1)



Process 1

To a solution of (R)-phenylalanine benzyl ester tosylate (compound XV-1', 2.5 g (5.85 mmol)) in 60 ml of dichloromethane was added triethylamine (1.8 ml, 12.87 mmol) and 4-biphenylsulfonyl chloride(1.63 g, 6.44 mmol) under ice-cooling. After being stirred for 2 h at room temperature, the reaction mixture was washed with 2N HCl, 5% $NaHCO_3$ and water, and concentrated in vacuo. The residue was subjected to silica gel column chromatography and the fractions eluting with $CHCl_3$ / MeOH = 40/1 to 20/1 were collected and crystallized from dichloromethane / hexane to give 2.32 g of

compound (Ia-1-1'). Yield 84.1%. mp. 130-131℃.

Elemental analysis (%) $C_{28}H_{25}NO_4S$

Calcd. : C; 71.32, H; 5.34, N; 2.97, S; 6.80

Found : C; 71.05, H; 5.41, N; 3.00, S; 6.81

IR ν max (cm^{-1}) (Nujol) : 3352, 1732, 1341, 1190, 1163.

NMR (δ ppm) ($CDCl_3$): 3.06 (d, J=5.8Hz, 2H), 4.30 (dt, J=6.0, 9.0Hz, 1H), 4.89 (s, 2H), 5.12 (d, J=9.0Hz, 1H), 6.98-7.81 (m, 14H).

$[\alpha]_D$: -16.4±1.1(c=0.506 %, 25℃, MeOH)

Process 2

A solution of compound (Ia-1-1') (2.28 g) which was obtained process 1 in 50 ml of mixed solvents of methanol / ethyl acetate =1/1, was hydrogenated using 10 % Pd/C (200 mg) for 25 min. The reaction mixture was filtered off, and the filtrate was concentrated in vacuo. The residue was recrystallized from dichloromethane / hexane to give 1.83 g of compound (Ia-1-1"). Yield 99.1 %. mp. 146-147℃.

Elemental analysis (%) $C_{21}H_{19}NO_4S$

Calcd.: C; 66.12, H; 5.02, N; 3.67, S; 8.41

Found: C;65.97, H; 5.06, N; 3.61, S; 8.48

IR ν max (cm^{-1}) (Nujol) : 3408, 3305, 1751, 1325, 1161, 1134.

NMR (δ ppm) ($CDCl_3$): 2.97 (dd, J=7.0, 13.8Hz, 1H), 3.14 (dd, J=5.2, 14.0Hz,1H), 4.13 (m, 1H), 7.03-7.78 (m, 14H).

$[\alpha]_D$: -4.0±0.4(c=1.000 %, 25℃, MeOH)

Process 3

To a solution of compound (Ia-1-1", 1.0 g (2.62 mmol)) which was obtained process 2 in dichloromethane (20 ml) was added 0.33 ml (3.93 mmol) of oxalyl chloride and one drop of dimethylformamide. After being stirred for stirred for 1 h at room temperature, the reaction mixture was concentrated in vacuo. The residue was dissolved in 10 ml of tetrahydrofuran. A solution of hydroxylamine hydrochloride (911 mg (13.1 mmol)) and $NaHCO_3$ 1.54 g (18.34 mmol) in 10ml of tetrahydrofuran and 10ml of water was stirred for 5 min under ice-cooling. To the mixture was added the

above solution of acid chloride in tetrahydrofuran and the resulting mixture was stirred for 30 min. The reaction mixture was poured into water, and extracted with ethyl acetate. The organic layer was washed with 5% $NaHCO_3$, and water, and concentrated in vacuo to give compound (Ia-1) (969 mg). Yield 93.3 %.

Process 4

To a solution of compound (Ia-1-1", 2.0 g, 5.24 mmol) which was obtained process 2 in dimethylformamide (20 ml) was added 1-hydroxybenzotriazole hydrate (0.7 g, 5.24 mmol), N-methylmorpholine (2.9 ml, 26.2 mmol), 1-ethyl-3-(3-diisopropylamino) carbodiimide hydrochloride (8 mmol), and O-benzylhydroxylamine hydrochloride (1.67 g, 10.48 mmol), and the resulting mixture was stirred for 6 h at room temperature. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with 2N HCl, 5% $NaHCO_3$, and water, and concentrated in vacuo. The residue was subjected to silica gel column chromatography and the fractions eluting with CH_2Cl_2 / hexane = 1/1 were collected and recrystallized from dichloromethane / hexane to give 2.04 g of compound (XVI-1). Yield 80 %. mp. 171-173℃.

Elemental analysis (%) $C_{28}H_{26}N_2O_4S$

Calcd.: C; 69.12, H; 5.39, N; 5.76, S; 6.59

Found :C; 68.85, H; 5.46, N; 5.76, S; 6.78

IR ν max (cm^{-1}) (Nujol) : 3248, 1661, 1594, 1333, 1163.

NMR (δ ppm) ($CDCl_3$): 2.85-3.60 (m, 2H), 3.86 (m, 1H), 4.77 (ABq-Apart, J=11.4Hz, 1H), 4.82 (ABq-Bpart, J=11.4Hz, 1H), 5.00 (m, 1H), 6.95-7.70 (m, 19H).

$[\alpha]_D$: -40.2±1.6 (c=0.505 %, 25℃, DMSO)

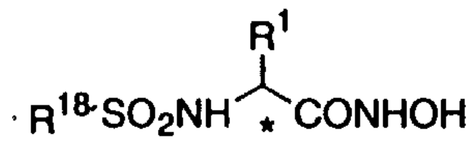
Process 5

A solution of compound (XVI-1) (1.97 g) which was obtained process 4 in a 60 ml of mixed solvents of methanol / ethyl acetate =1/1 was hydrogenated using 10 % Pd-C (200 mg) for 3.5 h. The reaction mixture was filtered off, and the filtrate was concentrated in vacuo. The residue was recrystallized from dichloromethane / hexane to give 1.35 g of compound (Ib-1-1). Yield 84.4 %.

Example 2 - 91

The compounds which were shown in Tables 1 to 22 were synthesized in a manner similar to those described in Example 1'

Table 1



(Ib)

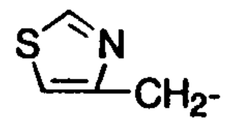
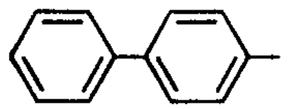
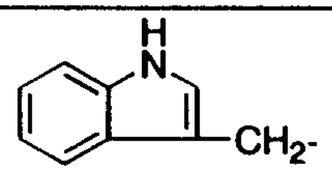
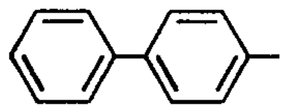
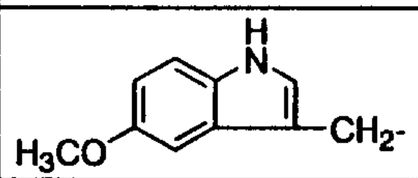
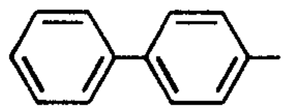
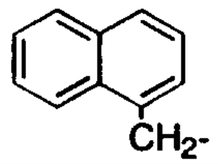
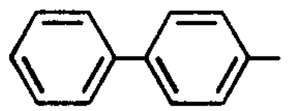
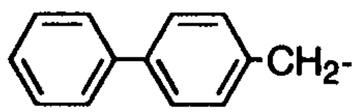
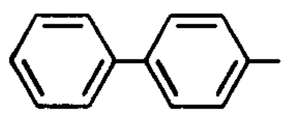
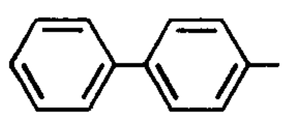
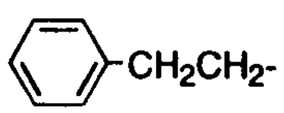
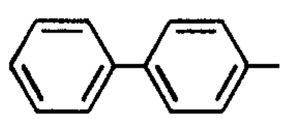
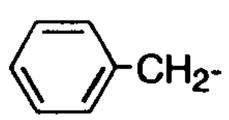
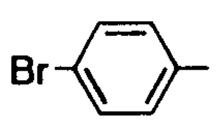
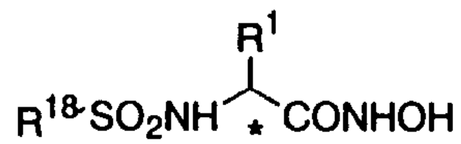
Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	^{1}H-NMR(δ ppm) d_6-DMSO
2			RS	173 >	3258,1650,1377, 1348,1163 (Nujol)	2.87(dd,J=5.6,14.2Hz,1H), 2.98(dd, J=8.4,14.2Hz,1H),4.02(dd,J=2.2, 8.6Hz,1H), 7.24(d,J=2.0Hz,1H), 8.83(d,J=2.2Hz,1H)
3			R	203-206	3403,3386,3265,1673 ,1320,1162 (Nujol)	2.72(dd,J=7.2,13.8Hz,1H), 2.97(dd, 7.0,14.8Hz,1H),3.81(m,1H),
4			RS	–	–	–
5			RS	124-126	3277,1669,1397, 1322,1159,	3.12(dd,J=10.3,14.3Hz,1H), 3.89(dd, J=3.3,13.5Hz,1H),4.20(m,1H), 5.90 (brs,1H)
6			R	139-141	3262,1663,1322, 1157,	2.67(dd,J=9.2,13.1Hz,1H), 2.84(dd, J=5.3,13.5Hz,1H),3.82(m,1H)
7	CF_3CH_2-		R	167-169	3265,1676,1642, 1337,1161 (Nujol)	2.2-2.7(m,2H),3.99(t,J=7.0Hz,1H)
8			RS	172-173	3403,3261,1669, 1321,1160	1.68(m,2H), 2.37(m,2H), 3.64(t, J=6.9Hz,1H)
9			R	144-146	3700-2200br,3264, 1635,1342,1164,	2.61(dd,J=9.4,13.8Hz,1H),2.78(dd, J=6.0,13.8Hz,1H),3.78(m,1H),7.43 (d,J=8.2Hz,2H),7.60(d,J=8.2Hz,2H),

Table 2



(Ib)

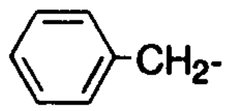
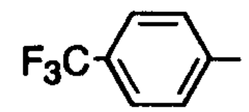
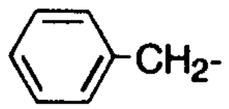
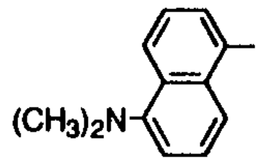
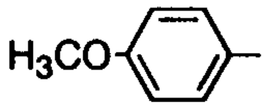
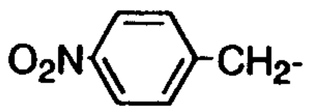
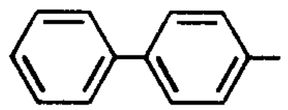
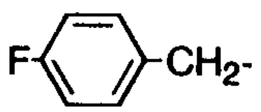
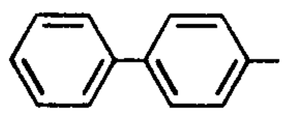
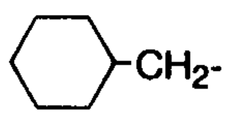
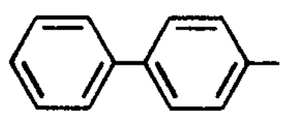
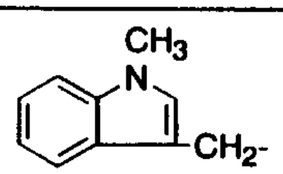
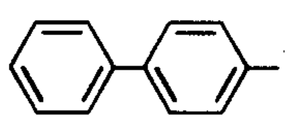
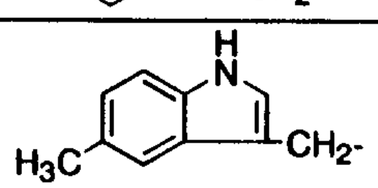
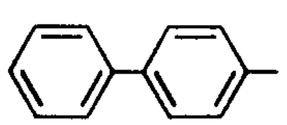
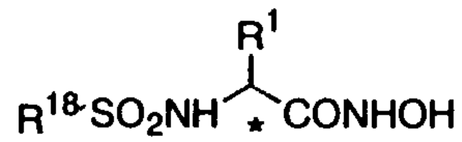
Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	^{1}H-NMR(δ ppm) d_6-DMSO
10			R	116-118	3600-2400br,3257, 1743,1721,1323,1132,	2.60-2.82(m,2H),3.84(m,1H),7.00-7.18(m,5H),7.62-7.80(m,4H),
11			R	91-92	3700-2100br,3176, 1664,1320,1143,	2.70-2.93(m,2H),2.82(s,6H), 3.75(m,1H),
12	$(CH_3)_2CH$—		R	178-179	3268,1632,1598, 1336,1162	0.71(d,J=6.8Hz,3H),0.74(d,J=5.4Hz,3H),1.73(m,1H),1.73(m,1H),3.22(m,1H),3.82(s,3H),7.05(d,J=9.0Hz,2H),7.69(d,J=9.0Hz,2H)
13			RS	184-185	3257,1662,1516, 1344,1322,1160,	2.80(dd,J=10.0,13.8Hz,1H),2.92(dd, J=5.0,12.8Hz,1H),3.90(dd,J=5.4, 9.6Hz,1H),
14			RS	128-130	3258,1669,1509, 1322,1157	2.62(dd,J=9.9,13.5Hz,1H),2.78(dd, J=5.8,13.0Hz,1H),3.77(t,J=6.2Hz, 1H),
15			R	165-166	3278,2920,1632, 1337,1161	0.50-1.62(m,13H), 3.56(t,J= 7.4Hz,1H)
16			RS	172-173	3272,1631,1332, 1161	2.71(dd,J=7.9,14.2Hz,1H),2.94(dd, J=6.9,14.2Hz,1H),3.57(s,3H),3.83 (dd,J=7.0,7.4Hz,1H)
17			RS	144-146	3404,1670,1320, 1159	2.25(s,3H),2.67(dd,J=7.5,14.2Hz, 1H),2.95(dd,J=7.7,14.6Hz,1H), 3.81(dd,J=6.2,14.2Hz,1H)

Table 3



(Ib)

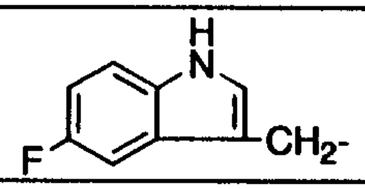
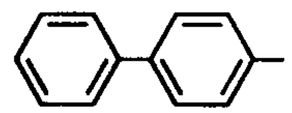
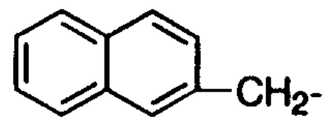
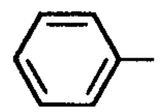
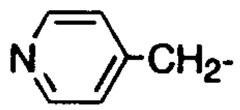
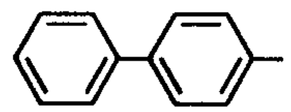
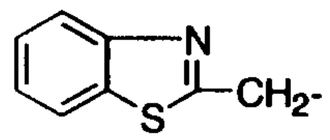
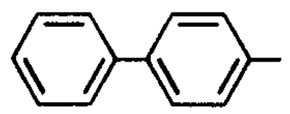
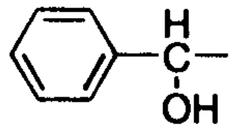
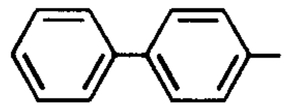
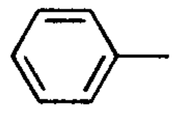
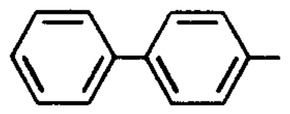
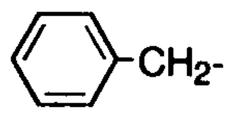
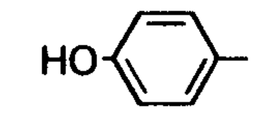
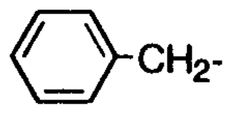
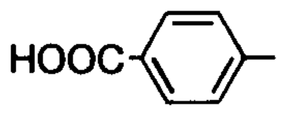
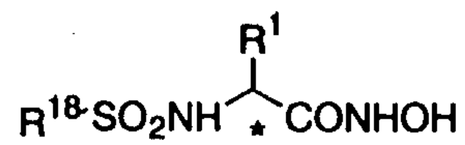
Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	^{1}H-NMR(δ ppm) d_6-DMSO
18			RS	–	3420,1670,1592, 1321,1159	2.72(dd,J=8.0,14.0Hz,1H),2.90(dd, J=6.2,14.2Hz,1H),3.82(m,1H)
19			RS	–	–	–
20			RS	154-158	3186,1593,1480, 1379	2.68(dd,J=9.8,13.7Hz,1H),2.79(dd, J=5.6,12.8Hz,1H),3.85(t,J=7.0Hz,1H),
21			RS	111-115	3700-2400br,3252, 1668,1326,1160	3.22-3.38(m,2H),4.17-4.24(m,2H), 7.80(d,J=8.0Hz,2H),7.96(d,J=6.4 Hz,2H)
22			RS	–	3455,3362,1672, 1398,1162	3.86(d,J=3.6Hz,1H),4.91 (d,J=3.6Hz,1H)
23			R	196-197	3404,3315,1669, 1594,1316,1162	4.88(d,J=9.4Hz,1H),8.74(d,J=9.4Hz,1H), 8.98(s,1H),10.92(s,1H)
24			R	197-199	3700-2400(br),3473, 1675,1310,1152	2.69(dd,J=7.6,13.5Hz,1H),2.93(dd, J=7.6,13.5Hz,1H),3.77(t,J=7.6Hz, 1H),(CD_3OD)
25			R	201-202	3700-2200(br),3278, 1706,1645,1322,1162	2.74(dd,J=8.3,13.5Hz,1H),2.95(dd, J=6.5,13.5Hz,1H),3.87(dd,J=6.5, 8.3Hz,1H),(CD_3OD)

Table 4



(Ib)

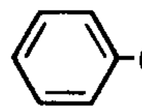
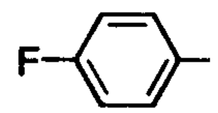
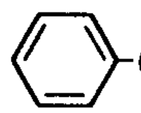
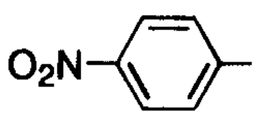
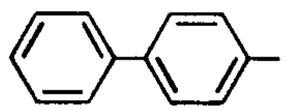
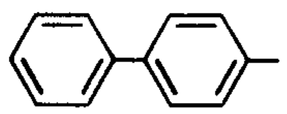
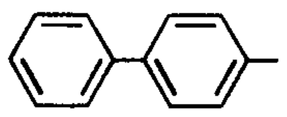
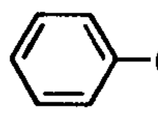
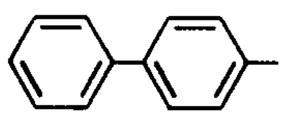
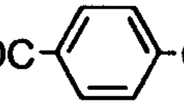
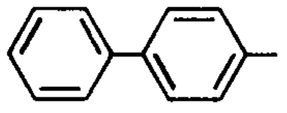
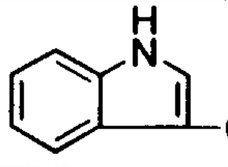
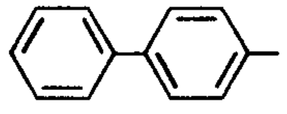
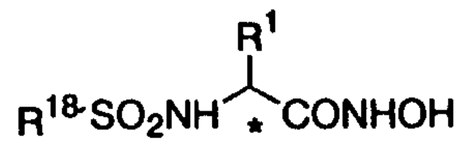
Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	^{1}H-NMR(δ ppm) d_6-DMSO
26			R	63-65	3700-2200(br),3362,1670, 1590,1336,1152	2.60(dd,J=9.0,13.8Hz,1H),2.79(dd, J=9.3,13.8Hz,1H),3.76(m,1H)
27			R	70-71	3700-2200br,3372,1674, 1531,1348,1310,1161	2.66(dd,J=9.5,13.6Hz,1H),2.79(dd,J=5.4,13.6Hz,1H),3.84(m,1H),7.73(A_2B_2qJ=8.9Hz,2H),8.20(A_2B_2q,J=8.9Hz,2H),8.72(d,J=9.0Hz,1H),8.86(s,1H),10.7(s,1H)
28	HOOC-CH_2-		R	–	–	–
29	HOOC-CH_2-CH_2-		R	–	–	–
30	$HOCH_2$-		R	192-193	3700-2400(br),3392, 1667,1320,1161	3.29(dd,J=5.7,10.7Hz,1H),3.43(dd,J=8.4,10.7Hz,1H),3.62(m,1H),7.85(A_2B_2q,J=8.7Hz,2H),7.88(A_2B_2q,J=8.7Hz,2H),7.98(d,J=7.8Hz,1H),10.61(s,1H)
31			R	69-70	3700-2200(br),1671, 1329,1163	2.69(dd,J=7.6,13.5Hz,1H),2.93(dd, J=7.6,13.5Hz,1H),3.77(t,J=7.6Hz, 1H),(CD_3OD)
32	HOOC-  -CH_2-		R	–	–	–
33			R	160-162	3401,3260,1673, 1316,1165	2.66(dd,J=7.5,13.4Hz,1H),2.96(dd, J=7.6,14.2Hz,1H),3.81(m,1H)

Table 5



(Ib)

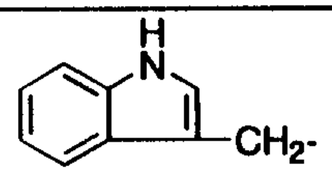
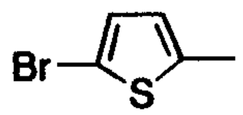
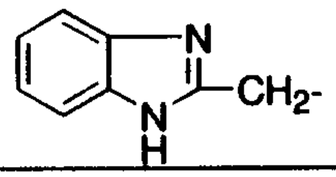
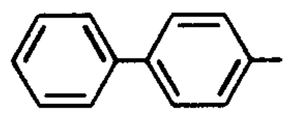
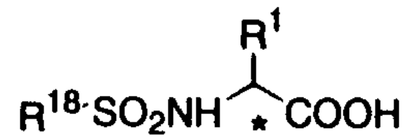
Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	^{1}H-NMR(δ ppm) d_6-DMSO
34			R	–	–	–
35			RS	141-145	3700-2400(br),1672, 1443,1327,1094	2.84-3.21(m,2H),4.29(m,1H)

Table 6



(Ia)

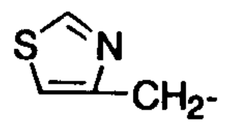
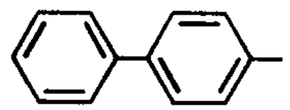
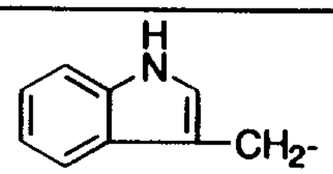
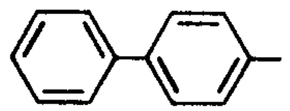
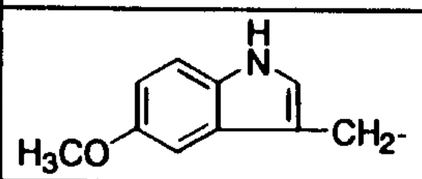
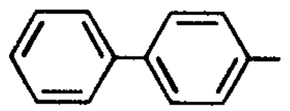
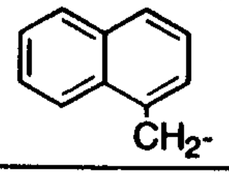
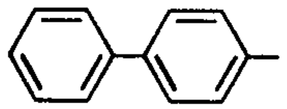
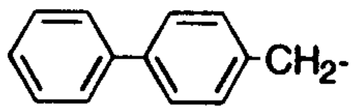
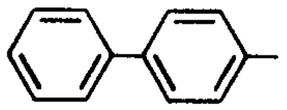
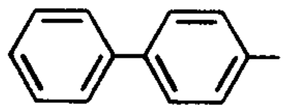
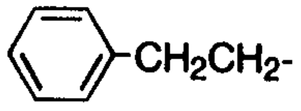
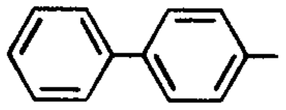
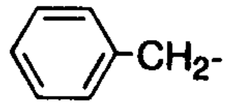
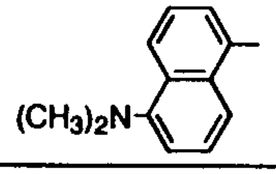
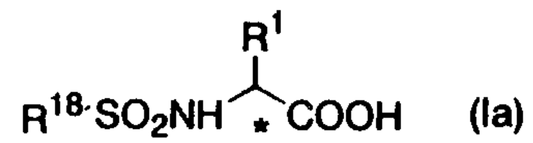
Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	^{1}H-NMR(δ ppm) d_6-DMSO
2			RS	159-161	3276,2503br,1897br, 1724,1344,1170(Nujol)	2.95(dd,J=9.0,14.0Hz,1H),3.12(dd, J=5.4,14.0Hz,1H),4.13(m,1H),7.29 (d,J=2.0Hz,1H),8.34(d,J=8.6Hz,1H),8.88(d,J=2.0Hz,1H),12.79(br,1H)
3			R	227-229	3386,3305,1747,1363, 1323,1161,1135(Nujol)	2.88(dd,J=8.0,14.0Hz,1H),3.09(dd, J=6.0,14.0Hz,1H),3.91(m,1H),8.23 (m,1H),10.79(s,1H),12.70(br,1H)
4			RS	181-189	2400-3700(br),1734, 1484,1327,1160	2.75-3.06(m,2H),3.69(s,3H),3.90 (m,1H)
5			RS	198-200	3446,3065,1594,1397, 1303,1154,1094	3.17(dd,J=7.4,13.8Hz,1H),3.57(dd, J=5.5,13.9Hz,1H),3.80(t,J=5.6Hz, 1H),8.11(d,J=7.4Hz,1H)
6			R	213-215	3184,1723,1337, 1317,1156	2.77(dd,J=9.7,13.7Hz,1H),3.03(dd, J=4.9,13.3Hz,1H),3.93(m,1H),8.38 (d,J=8.8Hz,1H)
7	CF_3CH_2-		R	176-177	3276,1706,1344, 1260,1165	2.40-2.90(m,2H),4.05(m,1H),8.51 (d,J=9.0Hz,1H),13.2(br,1H)
8			RS	153-156	3289,1739,1326, 1159,1089	1.83(m,2H),2.52(m,2H),3.70(m, 1H),8.32(d,J=9.0Hz,1H)
11			R	103-105	2200-3700br,3439,3288, 1725,1329,1143	2.86(m,1H),2.87(s,6H),2.98(dd,J= 5.1,13.8Hz,1H),4.15(m,1H),5.54 (m,1H)

Table 7



(Ia)

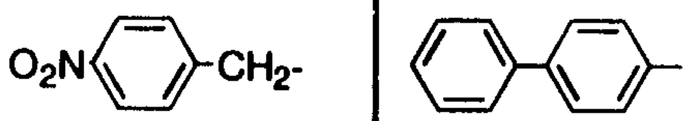
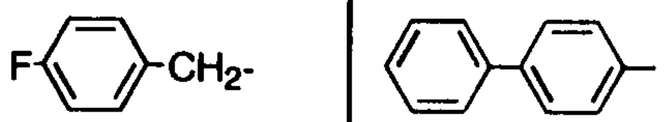
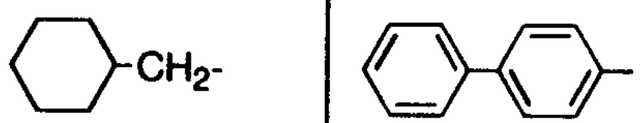
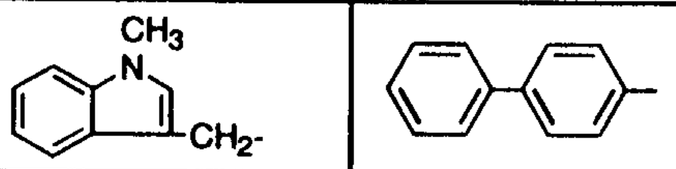
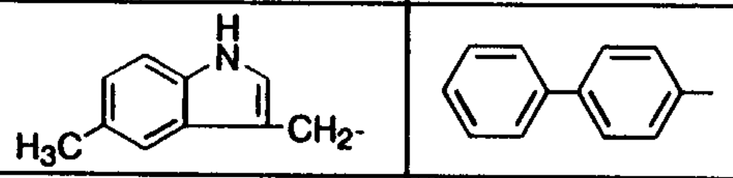
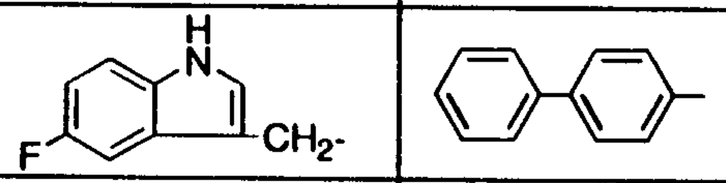
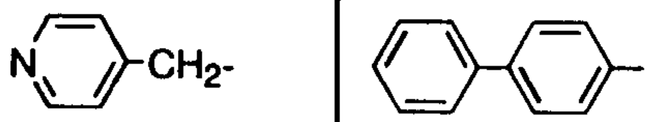
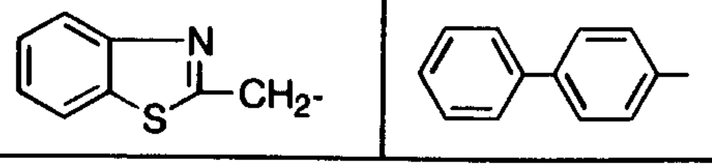
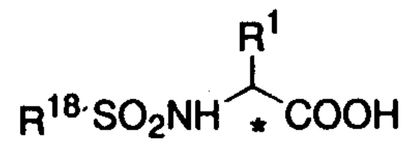
Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	^{1}H-NMR(δ ppm) d_6-DMSO
13			RS	212-213	3113,1724,1520, 1345,1158	2.86(dd,J=10.2,13.2Hz,1H), 3.14(dd,J=4.5,13.7Hz,1H), 4.02(m,1H),8.42(d,J=8.4Hz,1H)
14			RS	164-165	3426,3114,1715, 1509,1224,1159	2.71(dd,J=9.9,13.7Hz,1H),2.96(dd, J=5.3,13.5Hz,1H),3.89(m,1H), 8.34(d,J=9.0Hz,1H)
15			R	85-87	2919,1688,1448, 1335,1326,1169	0.52-1.72(m,13H),3.68(m,1H), 8.20(br.s,1H)
16			RS	179-183	3432,3294.1713, 1482,1341,1159	2.80-3.12(m,2H),3.61(s,3H), 3.94(m,1H),8.30(d,J=8.6Hz,1H)
17			RS	115-120	3419,3397,3291,1736, 1482,1336,1321,1165	2.28(s,3H),2.78-3.10(m,2H),3.91 (m,1H),8.29(d,J=8.3Hz,1H)
18			RS	208-211	3407,3285,1751,1735, 1703,1486,1321,1162	2.80-3.10(m,2H),3.92(m,1H), 8.29(d,J=8.2Hz,1H)
20			RS	197-205	2600-3700br,1635,1594, 1335,1163,1095	2.60-3.04(m,2H),3.98(m,1H)
21			RS	196-199	2200-3700br,1713br, 1345,1125	3.24-3.56(m,2H),4,34(m,1H)

Table 8



(Ia)

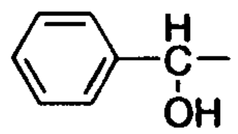
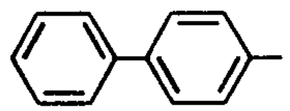
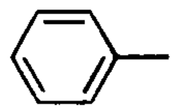
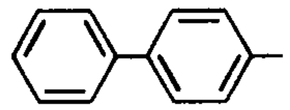
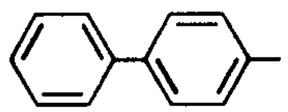
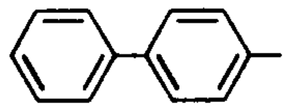
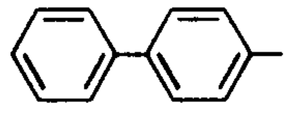
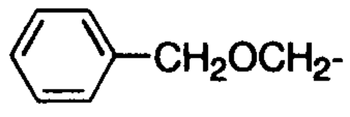
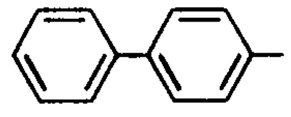
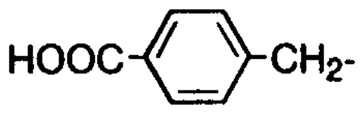
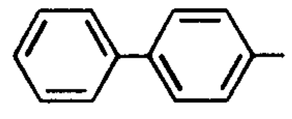
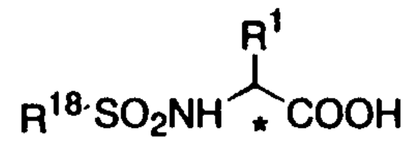
Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	^{1}H-NMR(δ ppm) d_6-DMSO
22			RS	141-143	3335,3246,1732, 1315,1152	4.10(d.J=3.2Hz,1H),5.13(d,J= 3.2Hz,1H)
23			R	211-214	3316,1734,1325, 1159(Nujol)	4.94(d,J=9.4Hz,1H),8.80(d,J= 9.4Hz,1H),13.0(br.s,1H)
28	HOOC-CH_2-		R	171-173	3353,1752,1326, 1155,1096	2.45(dd,J=6.2,16.4Hz,1H)2.63(dd, J=6.6,16.4Hz,1H),
29	HOOC-CH_2-CH_2-		R	185-187	3270.1709,1336, 1159,1093	1.68(dd,J=7.9,14.1Hz,1H),1.87(dd, J=6.0,13.4Hz,1H),2.22(t,J=7.2Hz, 2H),3.80(m,1H),
30	$HOCH_2$-		R	277-279	2200-3700br,3430, 3292,1728,1324,1162	3.51(dd,J=6.0,12.9Hz,1H),3.55(dd, J=5.4,12.9Hz,1H),3.80(m,1H), 8.06(d,J=8.7Hz,1H)
31			R	89-91	2200-3700br,3432, 3289,1733,1330,1165	3.54(dd,J=4.8,9.9Hz,1H),3.60(dd, J=5.7,9.9Hz,1H),4.04(m,1H), 4.39(s,2H),8.34(d,J=8.1Hz,1H)
32			R	>270	3319,3052,1701,1317, 1284,1162	2.81(dd,J=9.7,13.7Hz,1H),3.05(dd, J=4.8,13.4Hz,1H),3.96(m,1H), 8.40(d,J=9.0Hz,1H),12.88(br.s,1H)

Table 9



(Ia)

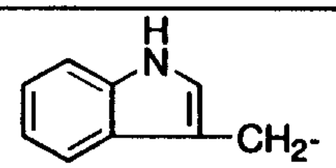
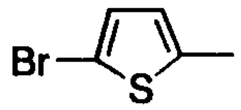
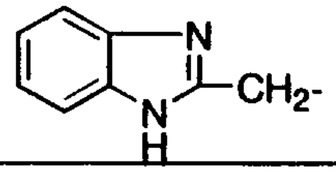
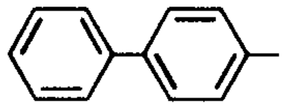
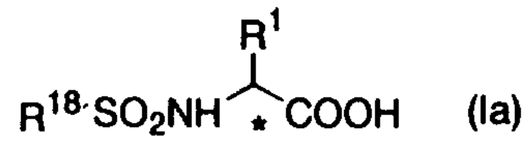
Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	^{1}H-NMR(δ ppm) d_6-DMSO
34			R	243-246	3420,1588,1402, 1324,1151	3.06(dd,J=5.4,14.4Hz,1H),3.14(dd, J=5.1,14.4Hz,1H),3.65(t,J=5.4Hz, 1H),6.92(m,1H),10.72(s,1H)
35			RS	151-156	2200-3700br,1734, 1334,1161	3.17-3.50(m,2H),4.51(m,1H)

Table 10



(Ia)

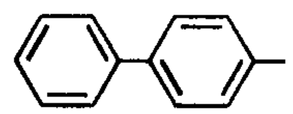
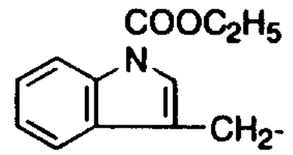
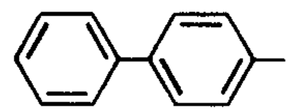
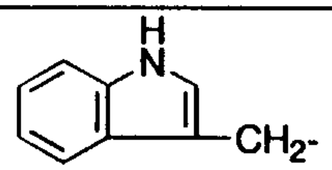
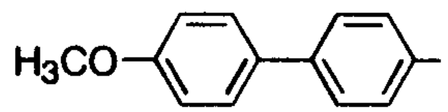
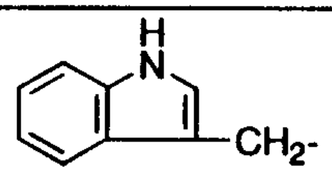
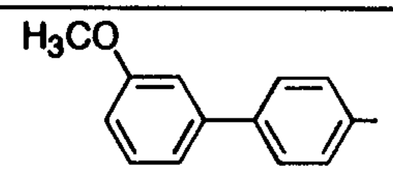
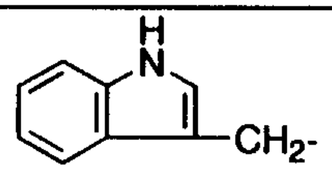
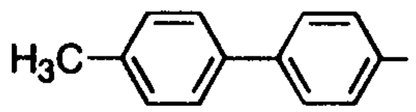
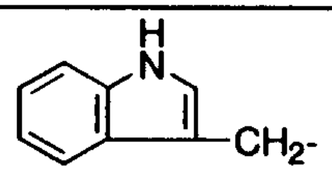
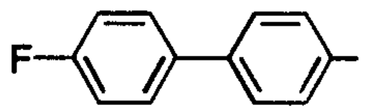
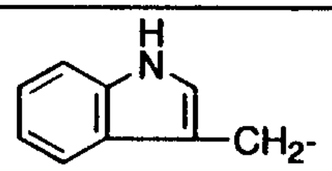
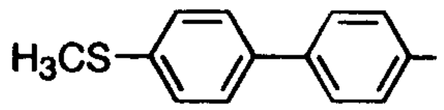
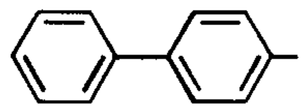
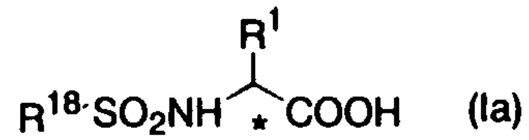
Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	Elemental analysis
36			RS	>145	1726,1354 1326,1161	–
37			RS	–	1732,1594 1404,1155	–
38			R	188-190	1607,1594 1294,1153	$C_{24}H_{22}N_2O_5S \cdot 0.5H_2O$ Calc. C:62.73 H:5.04 N:6.10 S:6.98 Foun.C:62.75 H:5.08 N:6.31 S:7.05
39			R	90-93	1724,1594 1326,1159	$C_{24}H_{22}N_2O_5S \cdot 0.8H_2O$ Calc. C:62.00 H:5.12 N:6.03 S:6.90 Foun.C:62.03 H:5.06 N:6.08 S:6.82
40			R	149-152	1685,1349 1166	–
41			R	104-107	1725,1599 1372,1173	–
42			R	167-169	1745,1653 1391,1147	–
43	$(CH_3)_2CH$-		R	155-157	1714,1594 1334.1166	$C_{17}H_{19}NO_4S \cdot 0.1CF_3COOH$ Calc. C:59.99 H:5.58 N:4.06 S:9.30 Foun.C:60.37 H:5.74 N:4.13 S:9.76

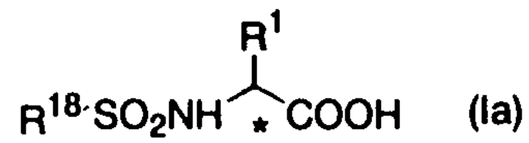
Table 11



(Ia)

Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	Elemental analysis
44	$(CH_3)_2CH$-	^tBu-	R	196-197	1724,1340 1328,1167	$C_{21}H_{27}NO_4S \cdot 0.3H_2O$ Calc. C:63.87 H:7.04 N:3.55 S:8.12 Foun.C:63.84 H:6.86 N:3.42 S:8.01
45	$(CH_3)_2CH$-		R	241-243	1734,1719 1324,1160	$C_{23}H_{23}NO_4S \cdot 0.3H_2O$ Calc. C:66.58 H:5.73 N:3.38 S:7.73 Foun.C:66.45 H:5.52 N:3.24 S:7.56
46	$(CH_3)_2CH$-	F_3C-	R	157-159	1670,1375 1148	–
47	$(CH_3)_2CH$-	H_3CO-	R	175-176	1717,1694 1349,1165	–
48	$(CH_3)_2CH$-	F-	R	145-147	1634,1334 1158	$C_{17}H_{18}FNO_4S$ Calc. C:58.11 H:5.16 F:5.41 N:3.99 S:9.12 Foun.C:58.11 H:5.17 F:5.86 N:3.92 S:9.69
49	$(CH_3)_2CH$-	H_3C-	R	183-186	1681,1319 1162	–
50	CH_2-	H_3CO-	R	183-184	1725,1340 1159	–
51	CH_2-		R	224-226	1750,1324 1159	$C_{27}H_{23}NO_4S \cdot 0.7H_2O$ Calc. C:68.98 H:5.23 N:2.98 S:6.82 Foun.C:69.08 H:5.09 N:2.91 S:6.73

Table 12



(Ia)

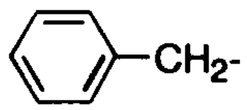
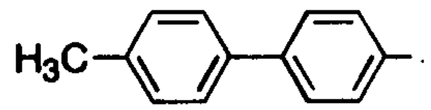
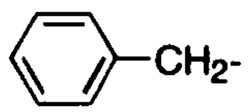
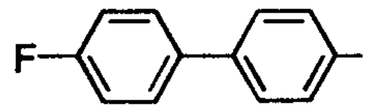
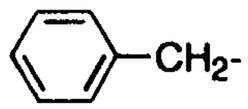
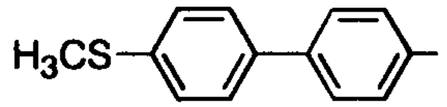
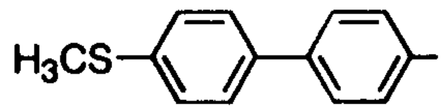
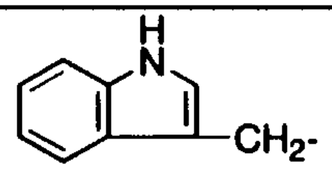
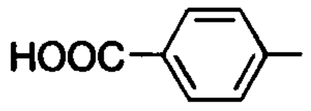
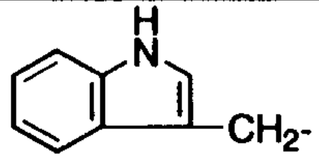
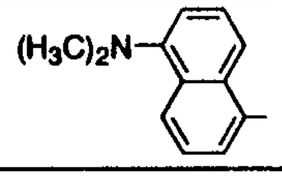
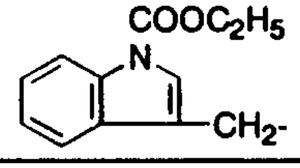
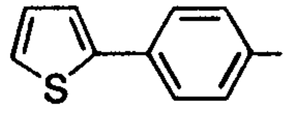
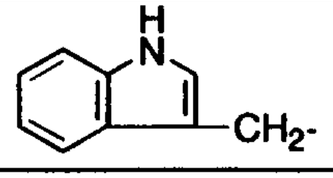
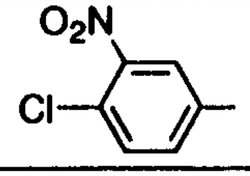
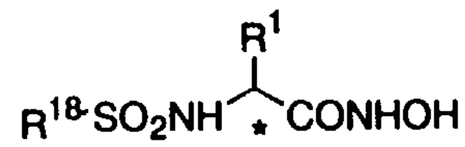
Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	Elemental analysis
52			R	157-160	1685,1349 1166	–
53			R	111-112	1691,1567 1390,1159	–
54			R	194-195	1749,1592 1323,1164	–
55	$(CH_3)_2CH$-		R	197-199	1746,1337 1164	$C_{18}H_{21}NO_4S_2 \cdot 0.2H_2O$ Calc. C:56.43 H:5.63 N:3.66 S:16.74 Foun.C:56.74 H:5.67 N:3.86 S:16.35
56			R	108-110	1649,1337 1165	–
57			R	187-190	1588,1308 1141	–
58			R	239-243	1744,1592 1323,1160	$C_{21}H_{18}N_2O_4S_2 \cdot 0.3H_2O$ Calc. C:58.40 H:4.34 N:6.45 S:14.85 Foun.C:58.40 H:4.44 N:6.58 S:14.57
59			R	222-224	1751,1734 1537,1347 1172	$C_{17}H_{14}ClN_3O_6S \cdot 0.3H_2O$ Calc. C:47.48 H:3.44 Cl:8.39 N:9.65 S:7.52 Foun.C:47.57 H:3.43 Cl:8.26 N:9.79 S:7.47

Table 13



(Ib)

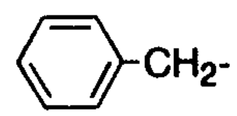
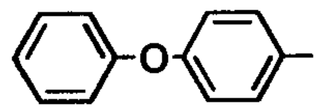
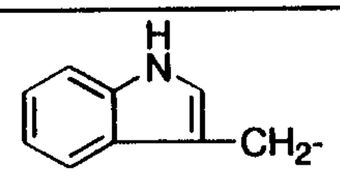
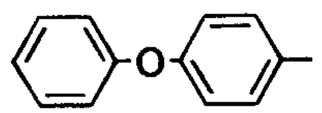
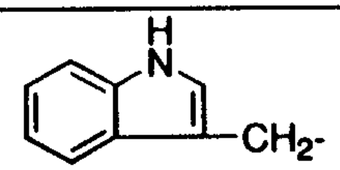
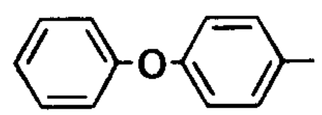
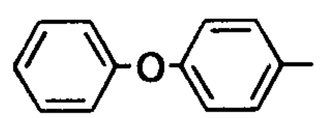
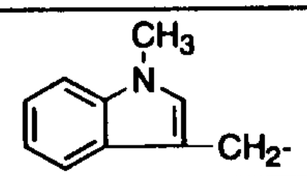
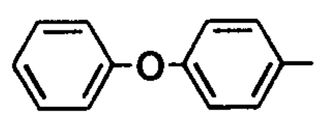
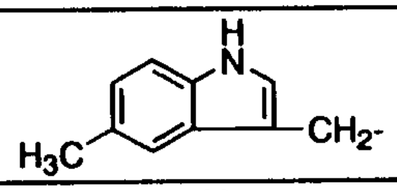
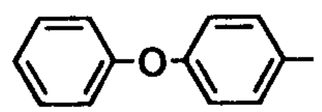
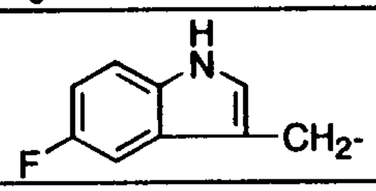
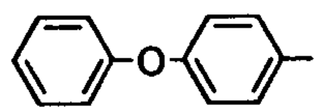
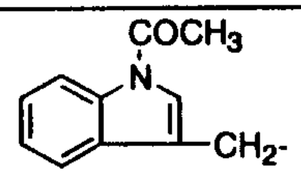
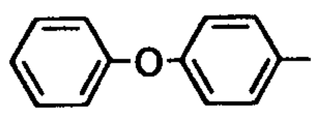
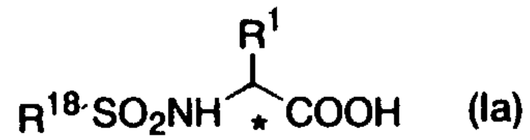
Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	^{1}H-NMR(δ ppm) d_6-DMSO
60			R	foam	3700-2400br,3277, 1669,1325,1152	2.60(dd,J=8.7,13.7Hz,1H), 2.79(dd, J=6.0,13.7Hz,1H),3.75(ddd,J=6.0, 8.7,9.0,1H),6.94(d,J=8.9Hz.2H)
61			R	115-118	3302,1667,1324, 1153(Nujol)	2.71(dd,J=7.0,14.4Hz,1H), 2.96(dd, J=7.0,14.2Hz,1H),3.78(t,J=7.6Hz, 1H)
62			S	–	3406,1670,1582, 1325,1153	2.71(dd,J=7.9,14.4Hz,1H),2.96(dd, J=7.6,14.4Hz,1H),3.78(dd,J=7.2, 7.3Hz,1H)
63	$(CH_3)_2CH$-		R	149-151	3268,1634,1584, 1336,1157	0.76(d,J=6.6Hz,6H), 1.77(m,1H), 3.26(m,1H)
64			RS	–	3314,1669,1582, 1420,1328,1154	2.71(dd,J=7.9,14.2Hz,1H),2.93(dd, J=6.5,14.3Hz,1H),3.65(s,3H),3.78 (dd,J=7.1,7.2Hz,1H)
65			RS	–	3405,1671,1582, 1487,1324,1154	2.34(s,3H),2.65(dd,J=7.8,14.1Hz, 1H),2.93(dd,J=7.6,14.4Hz,1H), 3.75(dd,J=6.8,7.7Hz,1H)
66			RS	–	3317,1670,1582, 1488,1323,1153	2.71(dd,J=8.9,14.4Hz,1H),2.89(dd, J=6.6,14.4Hz,1H),3.75(dd,J=6.5, 6.8Hz,1H)
67			RS	–	3421,1702,1676,1582, 1354,1328,1153	2.54(s,3H),2.69-2.89(m,2H),3.87 (m,1H)

Table 14



(Ia)

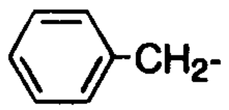
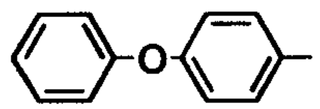
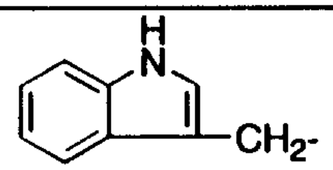
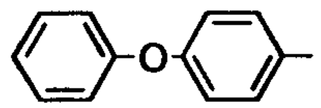
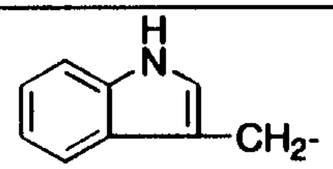
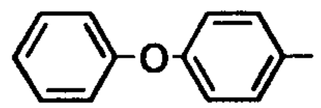
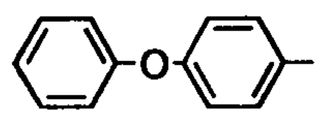
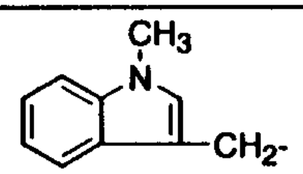
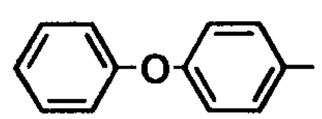
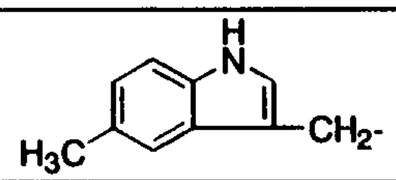
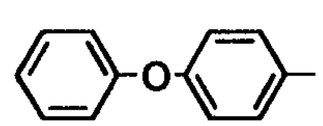
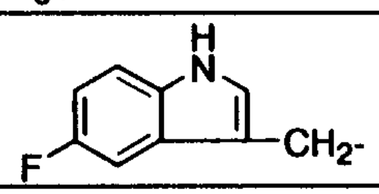
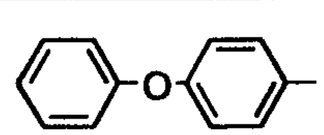
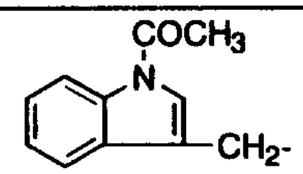
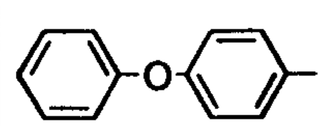
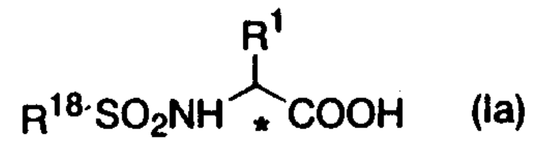
Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	^{1}H-NMR(δ ppm) d_6-DMSO
60			R	108-109	2400-3600br,3345,3213, 1735,1700,1346,1163	2.72(dd,J=8.7,13.6Hz,1H),2.94(dd, J=5.6,13.6Hz,1H),3.84(ddd,J=5.6, 8.7,8.7Hz,1H),8.23(d,J=8.7Hz,1H)
61			R	82-87	3410,3276,1724,1582, 1488,1331,1152(Nujol)	2.88(dd,J=7.4,15.2Hz,1H),3.07(dd, J=6.2,14.4Hz,1H),3.83(m,1H),8.08 (m,1H),10.80(s,1H),12.70(br,1H)
62			S	foam	3412,1724,1582,1488, 1332,1152	2.81-3.12(m,2H),3.88(m,1H),8.19 (d,J=8.4Hz,1H)
63	$(CH_3)_2CH$-		R	137-138	3154,1720,1688,1583, 1488,1251	0.89(d,J=7.0Hz,3H),0.98(d.J=6.8 Hz,3H),2.12(m,2H),3.80(dd,J=4.7 ,9.7Hz,1H),5.17(d,J=9.6Hz,1H)
64			RS	–	3273,1724,1582,1487. 1331,1198,1153	2.78-3.10(m,2H),3.67(s,3H), 3.86(m,1H)
65			RS	–	3409,3281,1725,1582, 1331,1197,1153	2.34(s,3H),2.75-3.08(m,2H),3.86(m,1H), 8.19(d,J=8.4Hz,1H)
66			RS	–	3415,1725,1582,1488, 1329,1196,1174,1152	2.78-3.08(m,2H),3.85(m,1H),8.18 (d,J=8.6Hz,1H)
67			RS	236-237	3296,1742,1647,1604, 1581,1342,1334,1152	2.55(s,3H),2.79-3.11(m,2H),3.98 (m,1H)

Table 15



(Ia)

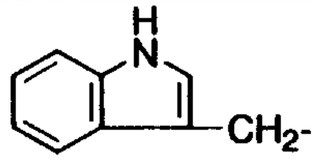
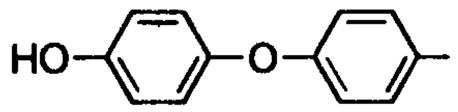
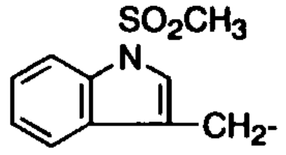
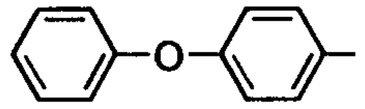
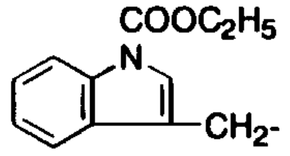
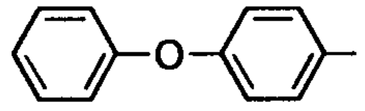
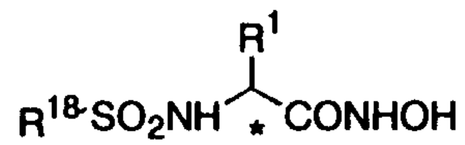
Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	Elemental analysis
68			R	>240	1608,1590 1507,1232 1157	–
69			RS	–	1735,1583 1362,1171	$C_{24}H_{22}N_2O_7S_2$ Calc. C:56.02 H:4.31 N:5.44 S:12.46 Foun.C:55.75 H:4.40 N:5.41 S:12.21
70			RS	–	1733,1583 1150	–

Table 16



(Ib)

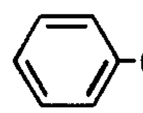
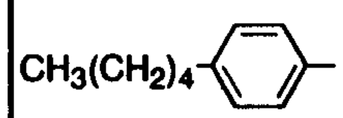
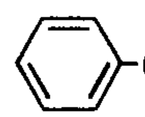
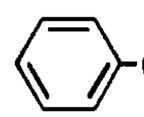
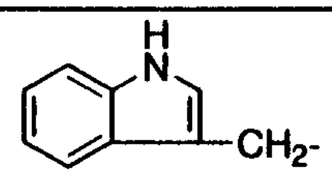
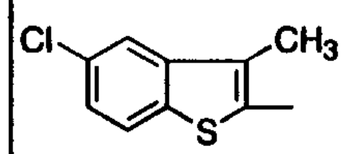
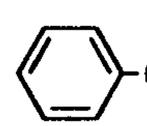
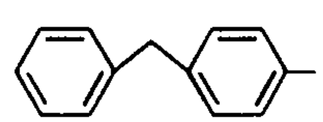
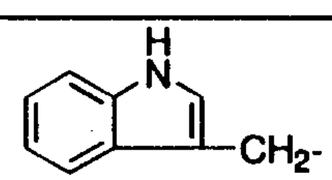
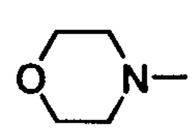
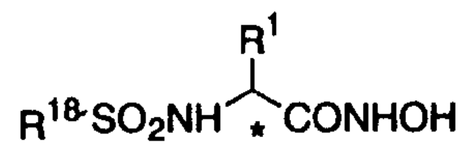
Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	^{1}H-NMR(δ ppm) d_6-DMSO
71			R	129-131	3700-2400br,3247, 1636,1337,1160	0.90(t,J=6.8Hz,3H),1.22-1.40(m,4H),1.52-1.67(m,2H),2.62(t,J=7.7Hz,2H),2.86(dd,J=8.4,13.7Hz,1H),3.02(dd,J=5.7,13.7Hz,1H) ($CDCl_3$)
72		$CH_3(CH_2)_7$—	R	oil	3700-2400br,1663, 1320,1145 (film)	0.87(t,J=6.3Hz,3H),2.50(t,J=7.4Hz,2H), 2.76(dd,J=9.6,14.0Hz,1H),2.87(dd,J=5.8,14.0Hz,1H),3.84(dd,J=5.8,9.6Hz,1H),
73		$CH_3(CH_2)_3$—	R	oil	3600-2400br,3262,1673, 1321,1142 ($CHCl_3$)	0.79(t,J=7.0Hz,3H),2.32-2.56(m,2H), 2.92(m,1H),3.26(m,1H),
74			R	–	–	–
75			R	85-86	3700-2200(br),3262, 1639,1332,1156	2.80(m,1H),2.96(m,1H),3.94(s,2H),3.86(m,1H),6.80-7.52(m,10H),7.08(A_2B_2qJ=7.5Hz,2H),7.42(A_2B_2q,J=7.5Hz,2H)($CDCl_3$)
76			R	–	–	–

Table 17



(Ib)

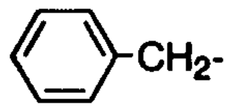
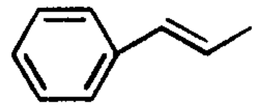
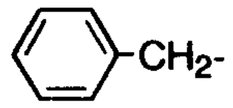
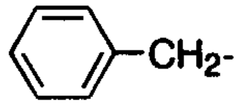
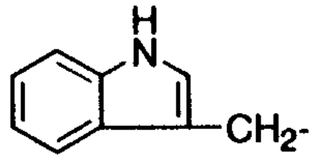
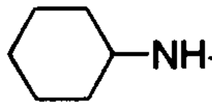
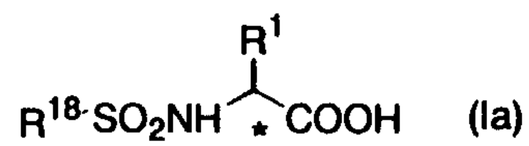
Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	^{1}H-NMR(δ ppm) d_6-DMSO
77			R	138-139	3700-2400(br),3312, 1629,1329,1144	2.79(dd,J=8.5,13.4Hz,1H),2.89(dd, J=6.0,13.4Hz,1H),3.81(dd,J=6.0, 8.5Hz,1H),6.55(d,J=15.5Hz,1H)
78			R	69-70	3700-2200(br),1670, 1318,1152	2.78(dd,J=8.6,13.4Hz,1H),2.91(dd,J=6 .0,13.4Hz,1H),3.92(ABq,J=13.5Hz,1H) ,3.90(m,1H),9.01(s,1H),10.78(s,1H)
79			R	–	–	–

Table 18



(Ia)

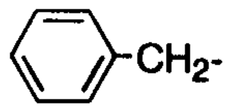
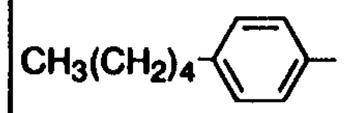
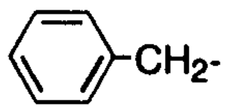
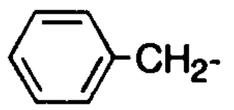
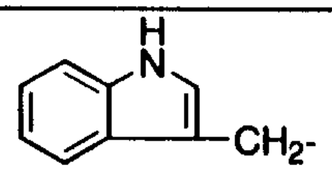
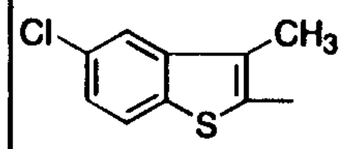
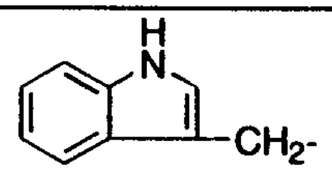
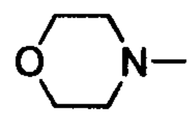
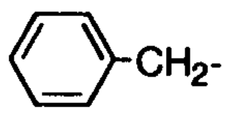
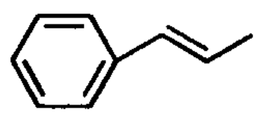
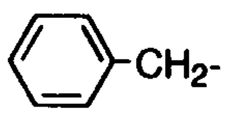
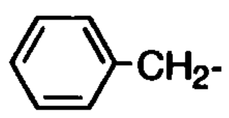
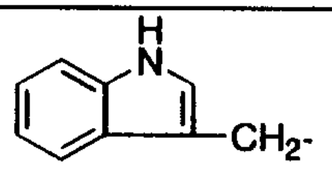
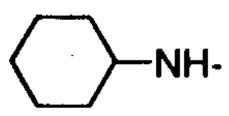
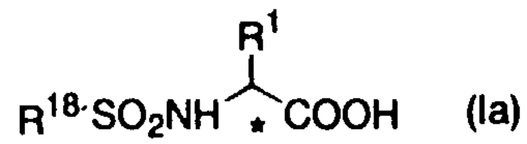
Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	^{1}H-NMR(δ ppm) d_6-DMSO
71			R	121-122	2300-3700br,3426,3318, 1713,1330,1159	0.89(t,J=6.7Hz,3H),2.62(t,J=7.6Hz,2H),2.96(dd,J=7.0,13.9Hz,1H),3.10(dd,J=5.4,13.9Hz,1H),4.19(dt,J=6.9,8.2Hz,1H),5.30(d,J=8.2Hz,1H),
72		$CH_3(CH_2)_7$—	R	oil	2400-3600br,3340,1736, 1334,1142($CHCl_3$)	0.88(t,J=6.9Hz,3H),2.55-2.73(m,2H),2.97(dd,J=8.4,13.8Hz,1H),3.24(dd,J=4.8,13.8Hz,1H),4.35(m,1H),4.98(m,1H) ($CDCl_3$)
73		$CH_3(CH_2)_3$—	R	89-90	2300-3700br,3240, 1725,1341,1144	0.84(t,J=7.1Hz,3H),2.57-2.70(m,2H),2.97(dd,J=8.4,13.9Hz,1H),3.25(dd,J=4.8,13.9Hz,1H),4.35(m,1H),4.96(d,J=9.6Hz,1H) ($CDCl_3$)
74			R	>250	3421,1580,1333, 1421,1153	2.41(s,3H),3.01(dd,J=6.0,14.4Hz,1H),3.12(dd,J=4.5,14.4Hz,1H),3.67(t,J=5.4Hz,1H),6.79(m,1H),6.89(m,1H),10.59(s,1H)
76			R	foam	3413,1594,1456, 1416,1157	3.03(dd,J=6.5,15.1Hz,1H),3.15(dd,J=4.7,14.1Hz,1H),3.64(t,J=5.1Hz,1H),10.68(s,1H)
77			R	–	2400-3700br,3252,1765, 1725,1301,1140	2.81(dd,J=9.2,13.7Hz,1H),3.03(dd,J=5.4,13.7Hz,1H),3.94(dt,J=5.4,9.2Hz,1H),6.66(d,J=15.2Hz,1H),7.16(d,J=15.2Hz,1H),8.01(d,J=9.2Hz,1H)
78			R	–	2200-3700br,3268,1726, 1321,1152(film)	2.81(dd,J=9.2,13.7Hz,1H),3.00(dd,J=5.6,13.7Hz,1H),4.01(ABq,J=13.7Hz,2H),4.01(m,1H),7.65(d,J=8.3Hz,1H)
79			R	–	3413,2931,1720,1585, 1455,1421,1313,1144	0.90-1.68(m,9H),1.78(m,1H),2.74(m,1H),3.00-3.20(m,2H),3.77(m,1H)6.45(br.s,1H),6.77(br.s,1H)

Table 19



(Ia)

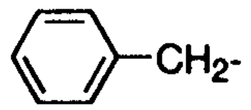
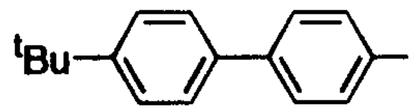
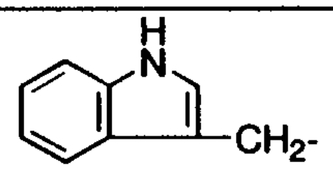
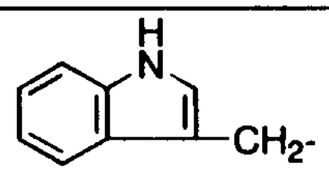
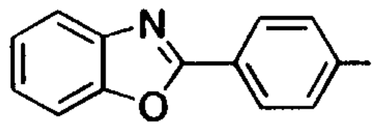
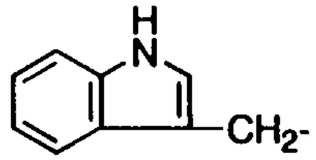
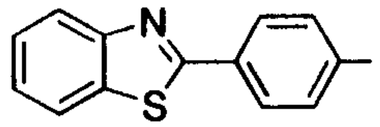
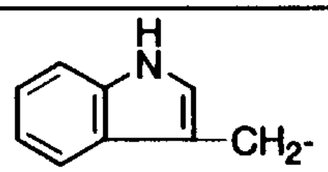
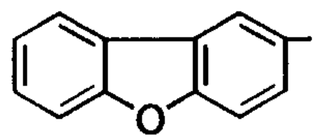
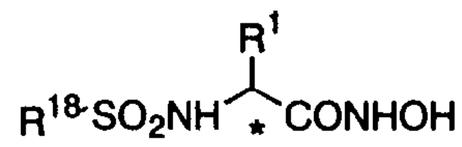
Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	Elemental analysis
80			R	153-155	1704,1596 1349,1164	–
81		n-C_8H_{17}-	R	>130	1576,1356 1139	–
82			R	128-130	1732,1342 1167	$C_{24}H_{19}N_3O_5S \cdot 1.3H_2O$ Calc. C:59.45 H:4.49 N:8.67 S:6.61 Foun.C:59.43 H:4.45 N:8.59 S:6.58
83			R	210-214	1745,1590 1316,1157	–
84			R	198-200	1594,1456 1200,1188	–

Table 20



(Ib)

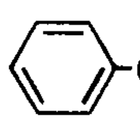
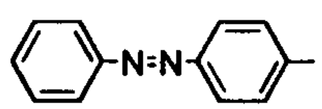
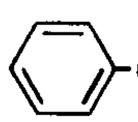
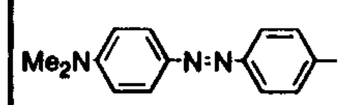
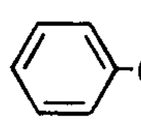
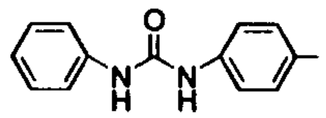
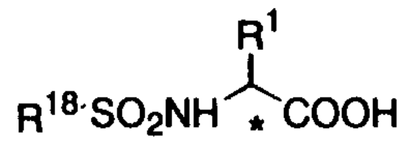
Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	^{1}H-NMR(δ ppm) d_6-DMSO
85			R	157-160	3700-2400br,3273, 1633,1338,1166	2.65(dd,J=8.9,13.6Hz,1H), 2.82(dd, J=6.6,13.6Hz,1H),3.86(m,1H),7.75 (d,J=7.8Hz,2H),7.87(d,J=8.7Hz,2H)
86			R	138-142	3700-2400br,2921, 1672,1314,1165,	2.62(dd,J=8.6,13.5Hz,1H),2.81(dd,J=6.5,13.6Hz,1H),3.09(s,6H),3.83(m,1H),6.86(d,J=9.0Hz,2H),7.83(d,J=8.8Hz,2H)
87			S	206-207	3700-2400(br),3357,1686, 1641,1314,1155	2.57(dd,J=8.3,13.6Hz,1H),2.79(dd,J=6.0,13.6Hz,1H),3.76(m,1H),8.02(d,J=8.7Hz,1H),8.80(s,1H),8.85(d,J=1.7Hz,1H),9.06(s,1H),10.59(d,J=1.7Hz,1H)

Table 21



(Ia)

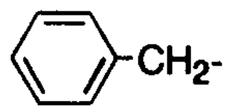
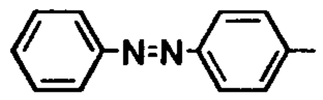
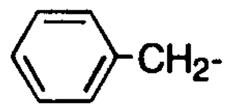
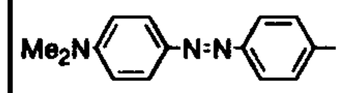
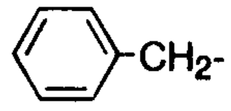
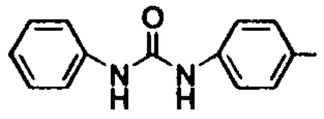
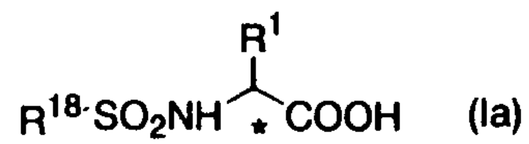
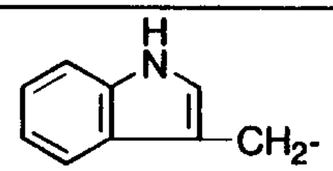
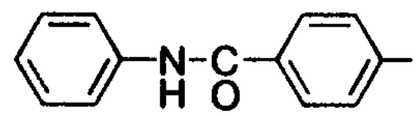
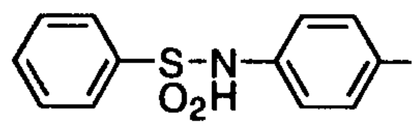
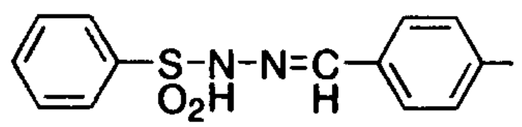
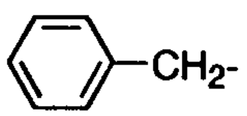
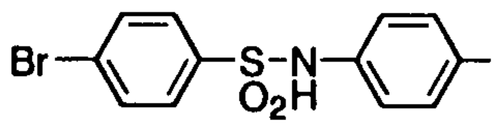
Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	^{1}H-NMR(δ ppm) d_6-DMSO
85			R	172-174	2400-3600br,3426,3296, 1698,1350,1167	2.75(dd,J=9.1,13.7Hz,1H),2.98(dd, J=5.5,13.7Hz,1H),3.96(ddd,J=5.5, 9.1,9.1Hz,1H),8.51(d,J+9.1Hz,1H)
86			R	93-94	2200-3700br,3431, 1735,1391,1154	2.74(dd,J=9.1,13.6Hz,1H),2.96(dd,J =5.7,13.6Hz,1H),3.09(s,6H),3.93(dt, J=5.7,9.1Hz,1H),8.39(d,J=9.1Hz,1H)
87			S	203-204	2300-3700br,3358, 3262,1718,1686, 1660,1313,1159	2.71(dd,J=9.1,13.7Hz,1H),2.93(dd,J=5.6 ,13.7Hz,1H),3.84(dt,J=5.6,9.1Hz,1H),8. 11(d,J=9.1Hz,1H),8.78(s,1H),9.06(s,1H)

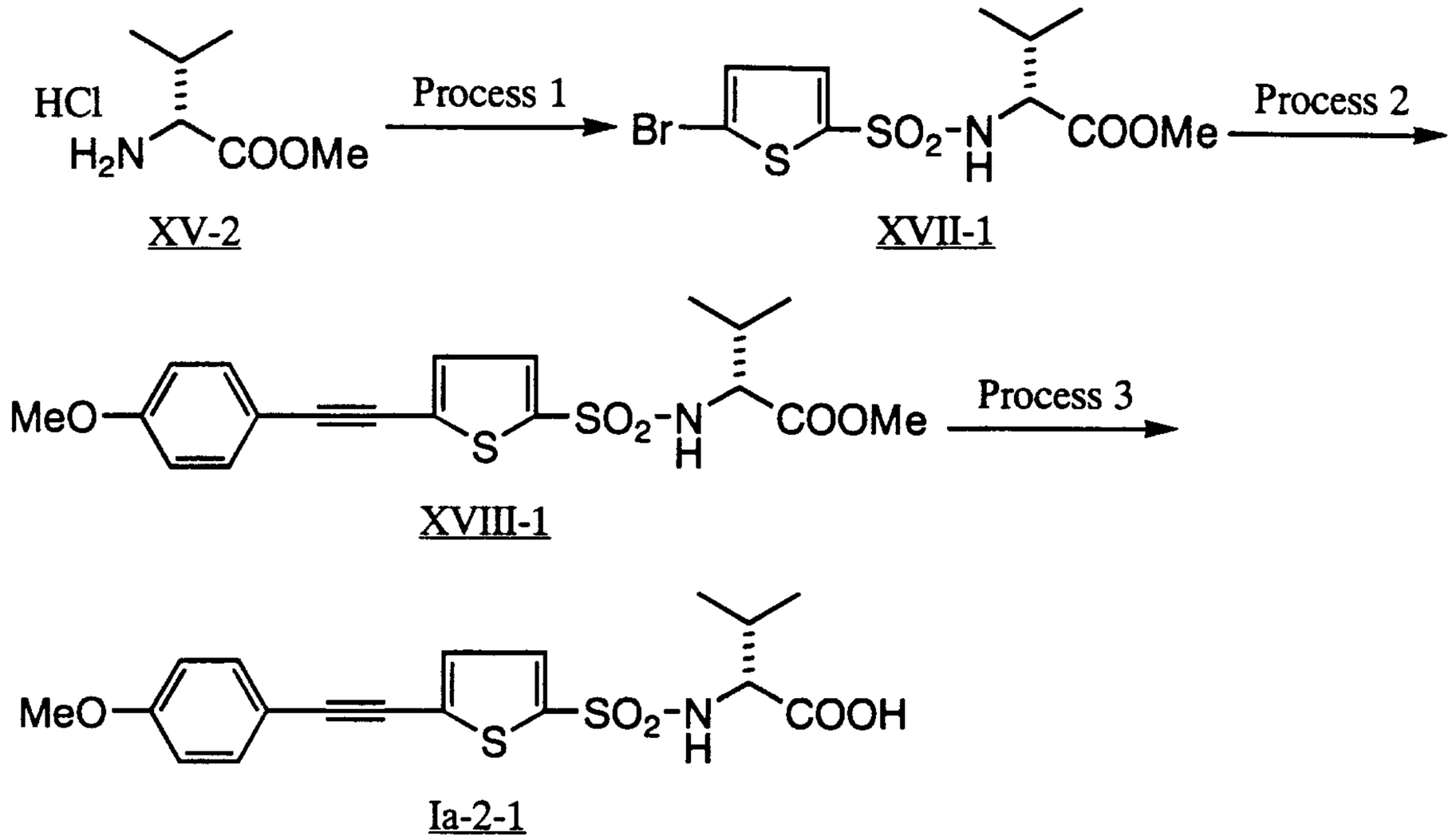
Table 22



(Ia)

Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	Elemental analysis
88			R	103-106	1719,1390 1229	–
89	$(CH_3)_2CH$-		R	96-99	1734,1461 1327,1158	$C_{17}H_{20}N_2O_6S_2$•0.9Ethylether Calc. C:51.63 H:6.10 N:5.85 S:13.38 Foun.C:51.23 H:6.17 N:5.87 S:13.11
90	$(CH_3)_2CH$-		R	110-112	1724,1325 1168	$C_{18}H_{21}N_3O_6S_2$•0.8Ethylether Calc. C:51.05 H:5.86 N:8.42 S:12.86 Foun.C:50.75 H:5.89 N:8.15 S:12.47
91			R	98-101	1735,1598 1327,1185	$C_{21}H_{19}BrN_2O_6S_2$•0.5CF_3COOH Calc. C:44.30 H:3.30 Br:13.40 N:4.70 S:10.75 Foun.C:44.62 H:3.52 Br:13.07 N:4.64 S:10.85

Example 92 (Method B)



Process 1

To a solution of D-valine methylester hydrochloride (XV-2) (755 mg, 4.5 mmol) in dichloromethane(12 ml) was added N-methylmorpholine (1.49 ml, 3×4.5 mmol) and 5-bromo-2-thiophensulfonyl chloride (1.24 g, 1.05×4.5 mmol) was added under ice-cooling. After being stirred for 15 h at room temperature, the reaction mixture was washed with 2N HCl, 5% $NaHCO_3$, and water. The organic layer was concentrated in vacuo, and dried over Na_2SO_4. The residue was subjected to silica gel column chromatography and the fractions eluting with ethyl acetate / hexane = 1/3 were collected and washed with n-hexane to give 1.32 g of the desired compound (XVII-1). Yield 82 %. mp. 109-110℃.

Elemental analysis $C_{10}H_{14}BrNO_4S_2$

Calcd. : C; 33.71 H; 3.96 Br; 22.43 N; 3.93 S;1 8.00

Found : C; 33.75 H; 3.89 Br; 22.43 N; 3.96 S; 17.86

$[\alpha]_D$: -34.5±0.7(c=1.012 $CHCl_3$ 25℃)

IR($CHCl_3$, ν max cm^{-1})1737,1356,1164,1138

NMR ($CDCl_3$, δ ppm): 0.89(d, J=6.8 Hz, 3H), 1.00(d, J=6.8 Hz, 3H), 2.00 (m, 1H), 3.60(s, 3H), 3.83(dd, J=5.2, 10.0 Hz, 1H), 5.20(d, J=10.0 Hz, 1H), 7.04(d, J=4.1 Hz, 1H), 7.32(d,

J=4.1 Hz, 1H)

Process 2

To a degassed solution of 400 mg (1.12 mmol) of compound (XVII-1) in 5 ml of dimethylformamide was added 222 mg (1.5 x 1.12 mmol) of 4-methoxyphenylacetylene and 21 mg(0.1 x 1.12 mmol) of copper iodide (I) under an argon atmosphere. Then 39 mg (0.05 x 1.12 mmol) of bis(triphenylphosphine)palladium dichloride (II) and 0.47 ml (3 x 1.12 mmol) of triethylamine were added to the reaction mixture. The resulting mixture was degassed and stirred overnight under an argon atmosphere at 50 ℃. The reaction mixture was diluted with ethyl acetate. The organic later was washed with 1N HCl, 5 % $NaHCO_3$, and water, dried over Na_2SO_4, and concentrated in vacuo. The resulting residue was column chromatographed on silica gel. The fractions eluting with n-hexane / ethyl acetate = 2/1 were collected and recrystallized from ethyl acetate / n-hexane to give 392 mg of the desired compound (XVIII-1). Yield 86 %. mp. 131-132℃.

Elemental analysis $C_{19}H_{21}NO_5S_2 \cdot 0.2\ H_2O$

Calcd. : C; 55.51 H; 5.25 N; 3.41 S; 15.60

Found : C; 55.80 H; 5.19 N; 3.38 S; 15.36

IR(KBr, ν max cm^{-1}) : 3268,2203,1736,1604,1524,1348,1164.

NMR($CDCl_3$, δ ppm) : 0.90(d, J=6.6 Hz, 3H), 1.00(d, J=7.0 Hz, 3H), 2.00(m, 1H), 3.60(s, 3H), 3.84(s, 3H), 3.86(dd, J=5.0, 10.2 Hz, 1H), 5.21(d, J=10.2 Hz, 1H), 6.90(d, J=9.0 Hz, 2H), 7.44(d, J=9.0 Hz, 2H), 7.12(d, J=4.0 Hz, 1H), 7.44(d, J=4.0 Hz, 1H).

Process 3

To a solution of 407 mg (1 mmol) of compound (XVII-1) in 8 ml of tetrahydrofuran and 8 ml of methanol was added 5.1 ml of 1N NaOH. The resulting mixture was stirred for 6 h at 60 ℃. The reaction mixture was concentrated in vacuo to remove an organic solvent, and the residue was diluted with ethyl acetate. The mixture was acidified with aqueous solution of citric acid and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo to give 373 mg of compound (Ia-2-1). Yield 100%. mp. 147-

148℃.

IR (KBr, ν max cm^{-1}) : 1710,1604,1351,1216.

Elemental analysis $C_{18}H_{19}NO_5S_2 \cdot 0.2H_2O$

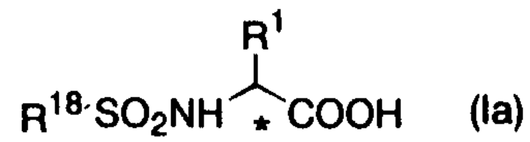
Calcd. : C; 54.45 H; 4.92 N; 3.53 S; 16.15

Found : C; 54.39 H; 4.93 N; 3.79 S; 15.96

Example 93 - 156

The compounds which were shown in Tables 23 to 30 were synthesized in a manner similar to those described in Example 92.

Table 23



(Ia)

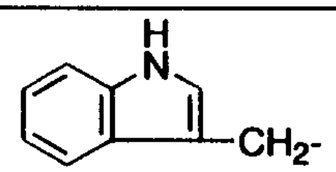
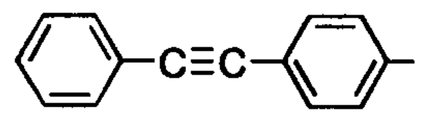
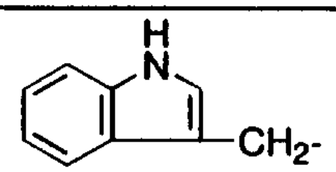
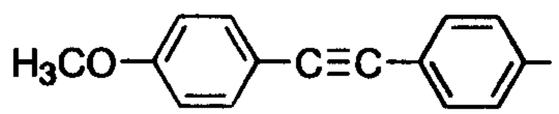
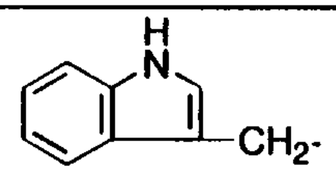
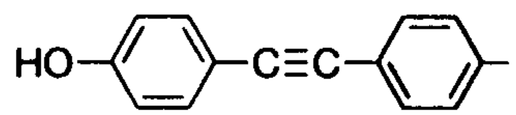
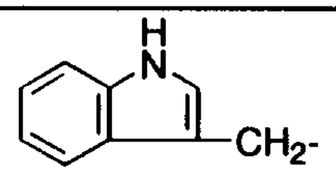
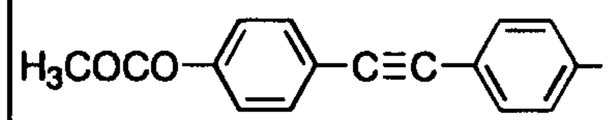
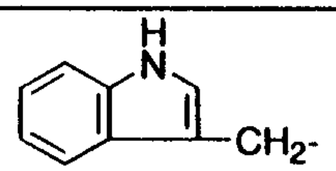
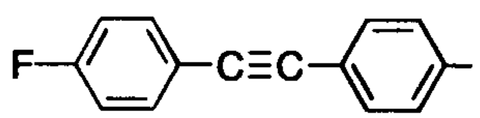
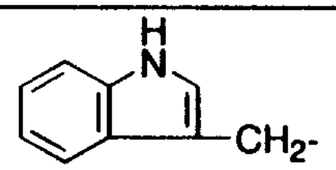
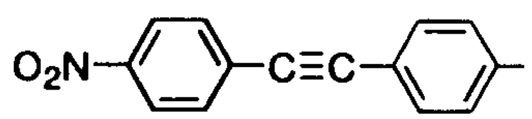
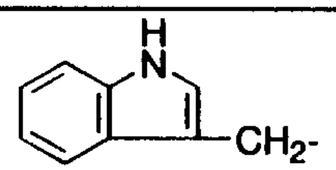
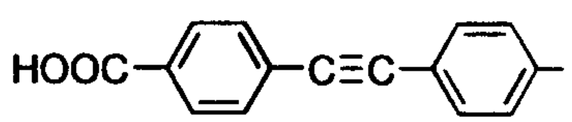
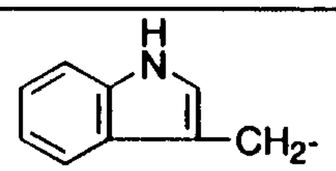
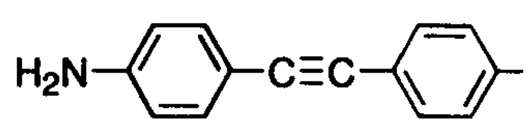
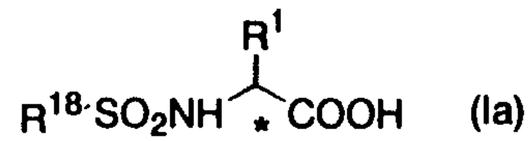
Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	Elemental analysis
93			R	165-170	1590,1316 1137	–
94			R	223-226	1747,1323 1134	$C_{26}H_{22}N_2O_5S$ Calc. C:65.81 H:4.67 N:5.90 S:6.76 Foun.C:65.34 H:4.90 N:5.56 S:6.40
95			R	216-218	1724,1325 1135	–
96			R	111-114	1739,1336 1163	–
97			R	178-180	1710,1511 1329,1161	–
98			R	105-108	1725,1618 1373,1163	–
99			R	>250	1706,1606 1350,1164	$C_{26}H_{20}N_2O_6S \cdot 0.4H_2O$ Calc. C:63.00 H:4.23 N:5.65 S:6.47 Foun.C:62.99 H:4.32 N:5.82 S:6.76
100			R	176-177	1735,1633 1321,1173	$C_{25}H_{21}N_3O_4S \cdot 0.8H_2O$ Calc. C:63.36 H:4.81 N:8.87 S:6.77 Foun.C:63.45 H:4.92 N:8.77 S:6.57

Table 24



(Ia)

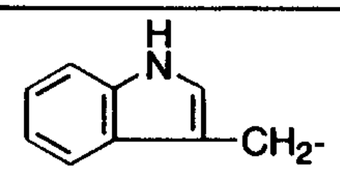
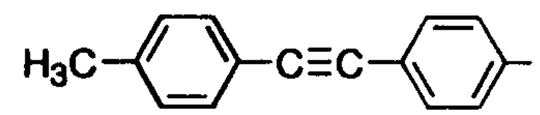
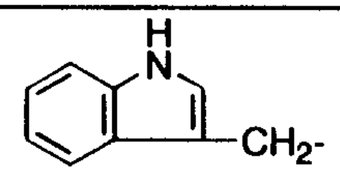
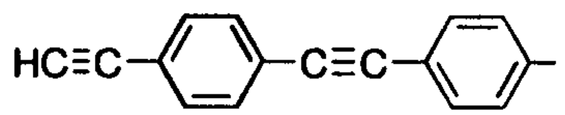
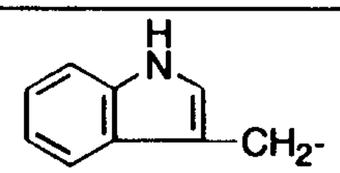
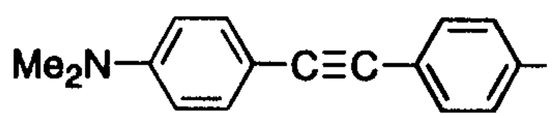
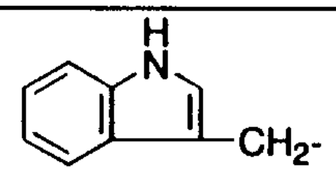
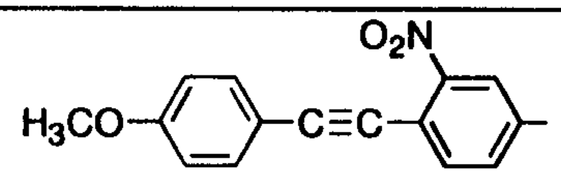
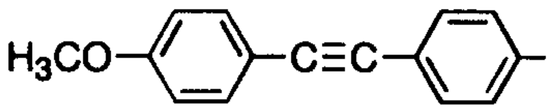
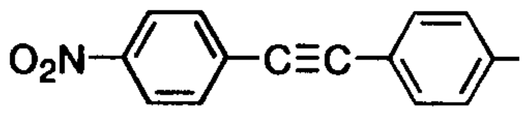
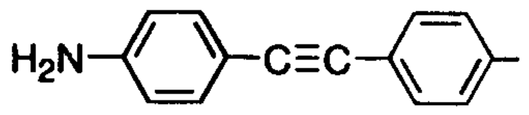
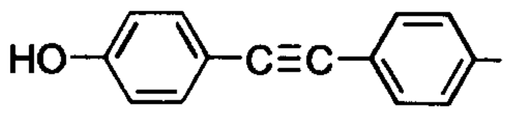
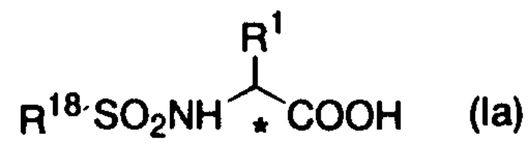
Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	Elemental analysis
101			R	227-229	1736,1618 1398,1168	$C_{26}H_{22}N_2O_4S \cdot 0.2H_2O$ Calc. C:67.57 H:4.89 N:6.06 S:6.94 Foun.C:67.66 H:4.77 N:6.09 S:6.71
102			R	230-233	1735,1654 1399,1164	–
103			R	234-236	1732,1631 1372,1148	–
104			R	>200 decomp.	1600,1558 1336,1171	–
105	$(CH_3)_2CH$-		R	146-149	1795,1718 1331,1166	–
106	$(CH_3)_2CH$-		R	231-232	1719,1595 1344,1167	$C_{19}H_{18}N_2O_6S \cdot 0.1H_2O$ Calc. C:56.46 H:4.54 N:6.93 S:7.93 Foun.C:56.30 H:4.37 N:7.14 S:7.85
107	$(CH_3)_2CH$-		R	166-169	1728,1631 1372,1148	–
108	$(CH_3)_2CH$-		R	163-165	1728,1332 1172	–

Table 25



(Ia)

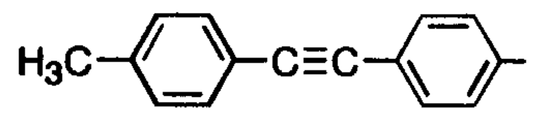
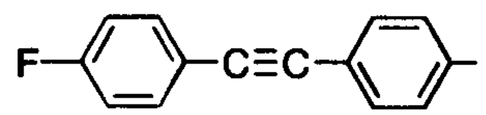
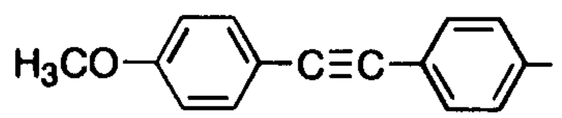
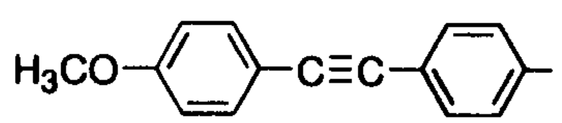
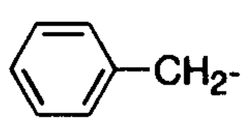
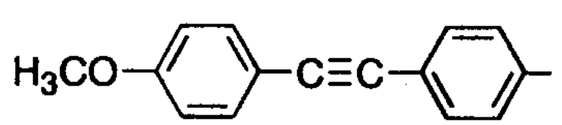
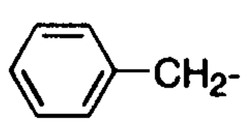
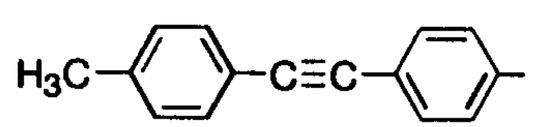
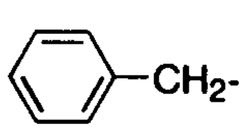
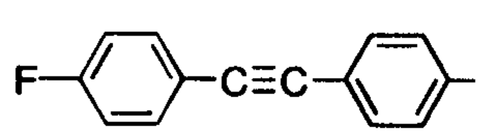
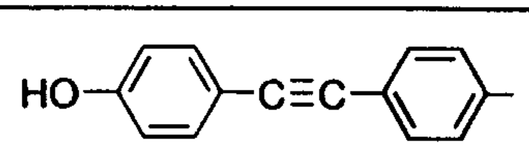
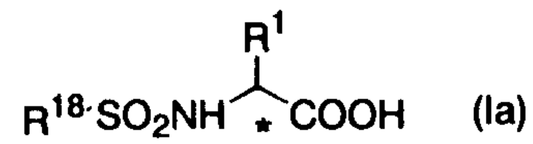
Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	Elemental analysis
109	$(CH_3)_2CH$-		R	187-189	1720,1656 1319,1165	–
110	$(CH_3)_2CH$-		R	111-114	1724,1635 1366,1158	–
111	$(CH_3)_3C$-		R	161-162	1711,1683 1600,1328 1159	$C_{21}H_{23}NO_5S \cdot 1.3H_2O$ Calc. C:59.36 H:6.07 N:3.30 S:7.55 Foun.C:59.36 H:6.06 N:3.50 S:7.44
112	$CH_3CH_2(CH_3)CH$-		R	157-159	1732,1680 1329,1167	–
113			R	133-136	1735,1651 1348,1165	–
114			R	183-185	1727,1604 1335,1182	–
115			R	166-168	1725,1663 1399,1197	$C_{23}H_{18}FNO_4S \cdot 0.3H_2O$ Calc. C:64.41 H:4.37 F:4.43 N:3.27 S:7.48 Foun.C:64.37 H:4.38 F:4.96 N:3.31 S:7.24
116	$(CH_3)_2CH$-		R	163-165	1728,1332 1172	–

Table 26



(Ia)

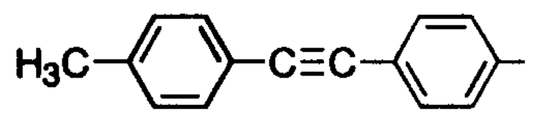
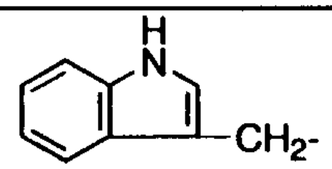
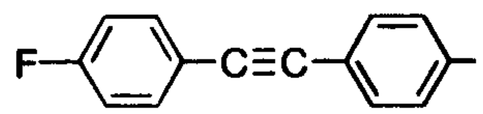
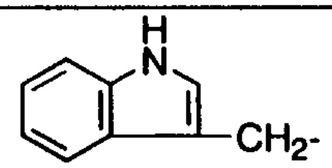
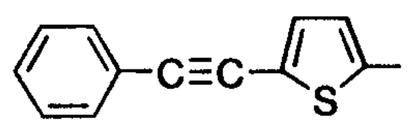
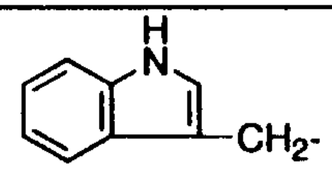
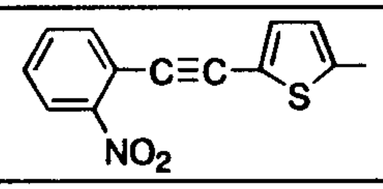
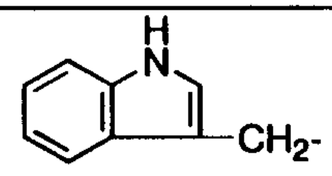
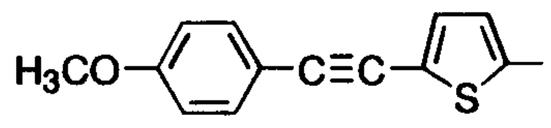
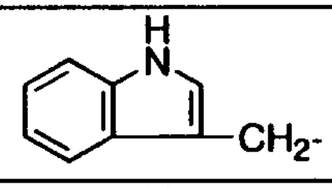
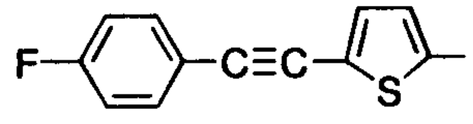
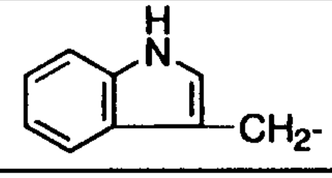
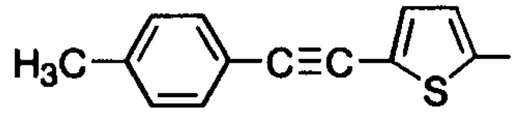
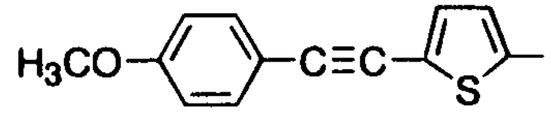
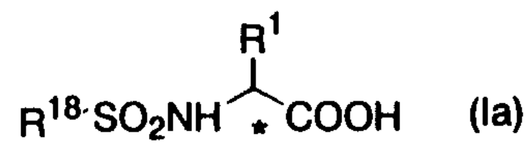
Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	Elemental analysis
117	$(CH_3)_2CH$-		R	187-189	1720,1656 1319,1165	–
118			R	111-114	1724,1635 1366,1158	–
119			R	167-169	1585,1318 1153	–
120			R	–	1605,1523 1340,1151	–
121			R	–	1604,1524 1336,1173	–
122			R	103-106	1721,1620 1339,1163	–
123			R	180-182	1729,1675 1340,1168	–
124	$(CH_3)_2CH$-		R	147-148	1710,1604 1351,1216	$C_{18}H_{19}NO_5S_2 \cdot 0.2H_2O$ Calc. C:54.45 H:4.92 N:3.53 S:16.15 Foun.C:54.39 H:4.93 N:3.79 S:15.96

Table 27



(Ia)

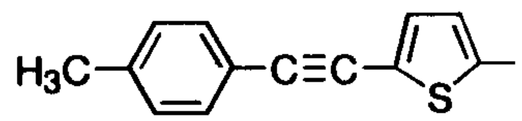
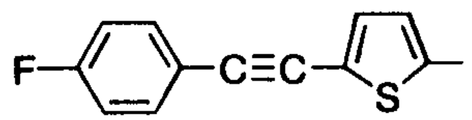
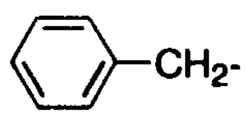
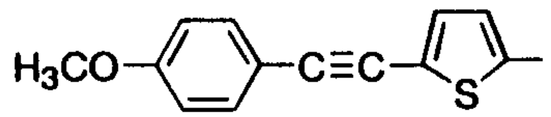
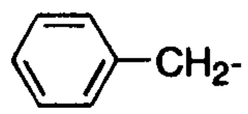
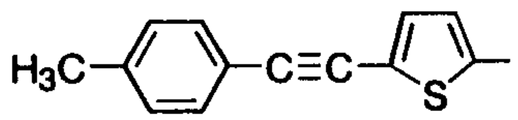
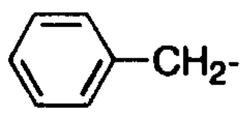
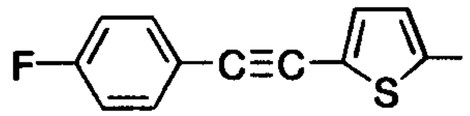
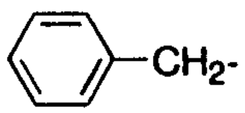
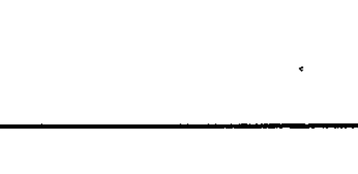
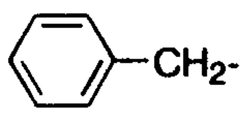
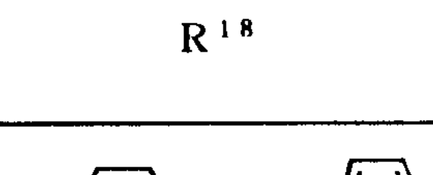
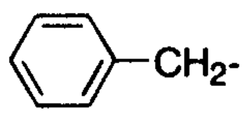
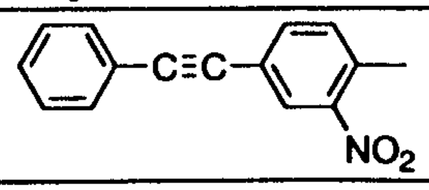
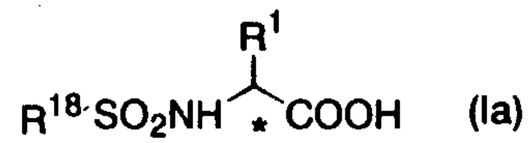
Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	Elemental analysis
125	$(CH_3)_2CH$-		R	157-158	1712,1350 1163	$C_{18}H_{19}NO_4S_2 \cdot 0.2H_2O$ Calc. C:56.73 H:5.13 N:3.68 S:16.83 Foun.C:57.03 H:5.30 N:3.89 S:16.56
126	$(CH_3)_2CH$-		R	154-156	1710,1499 1356,1165	–
127			R	149-150	1695,1334 1184	$C_{22}H_{19}NO_5S_2 \cdot 0.2H_2O$ Calc. C:59.36 H:4.39 N:3.15 S:14.41 Foun.C:59.43 H:4.61 N:3.25 S:14.02
128			R	161-164	1710,1329 1180	–
129			R	155-158	1734,1699 1324,1105	$C_{21}H_{16}FNO_4S_2$ Calc. C:58.73 H:3.75 F:4.42 N:3.26 S:14.93 Foun.C:58.66 H:3.93 F:4.52 N:3.33 S:14.41
130			R	–	–	–
131			R	–	–	–
132			R	–	–	–

Table 28



(Ia)

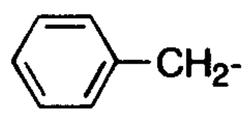
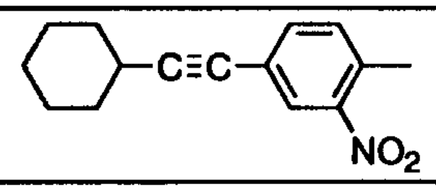
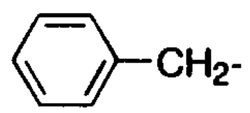
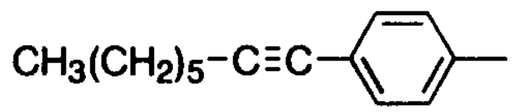
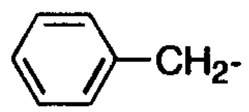
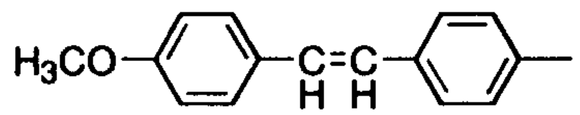
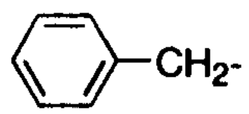
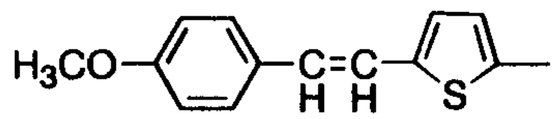
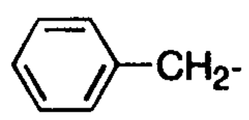
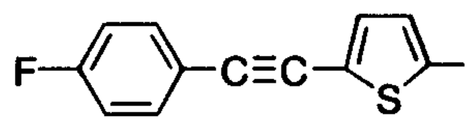
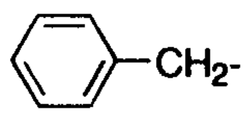
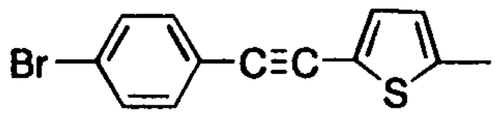
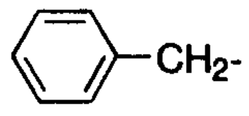
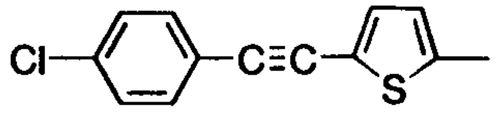
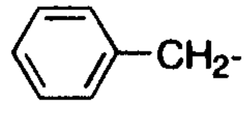
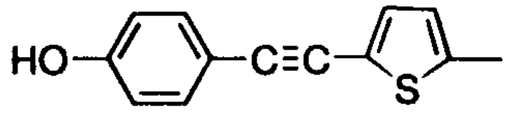
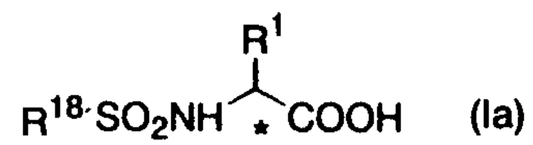
Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	Elemental analysis
133			R	–	–	–
134			R	–	–	–
135			R	–	–	–
136			R	–	–	–
137			R	–	–	–
138			R	–	–	–
139			R	–	–	–
140			R	–	–	–

Table 29



(Ia)

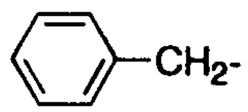
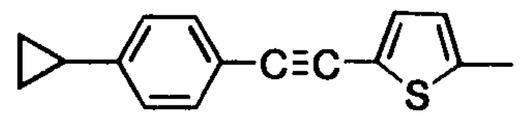
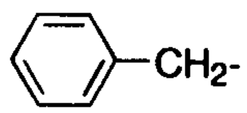
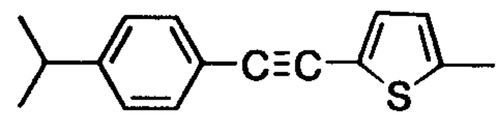
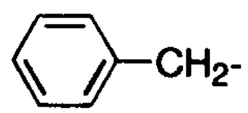
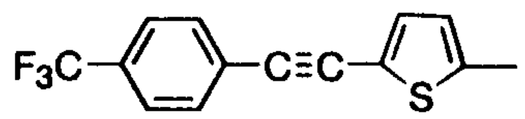
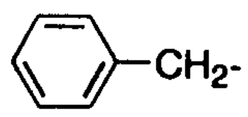
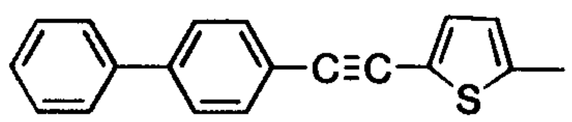
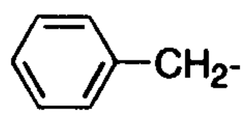
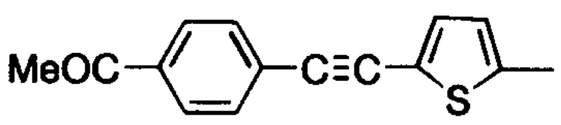
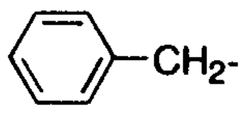
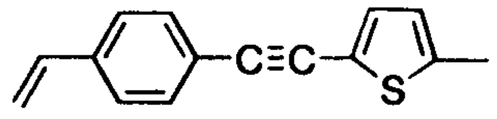
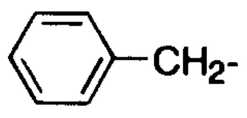
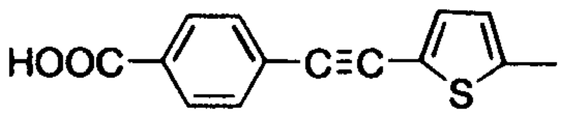
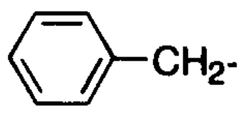
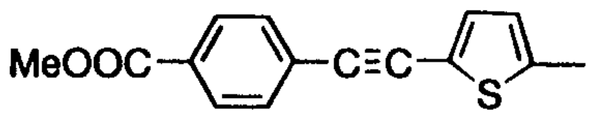
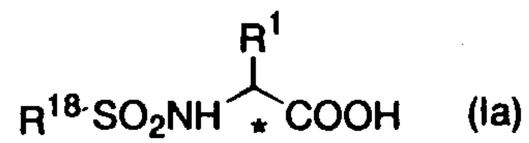
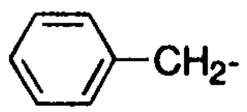
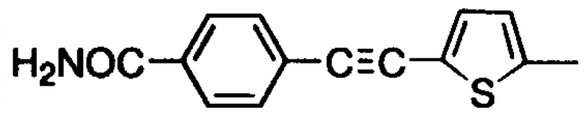
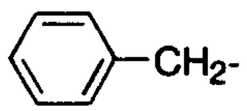
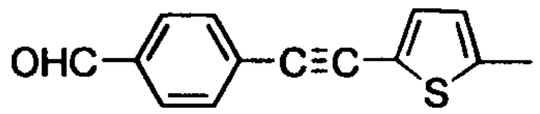
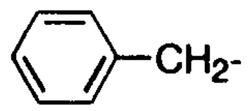
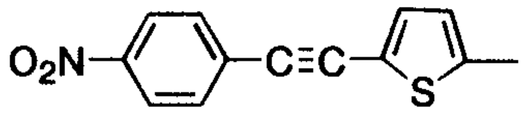
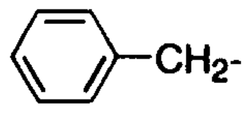
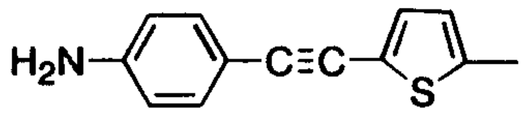
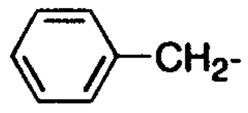
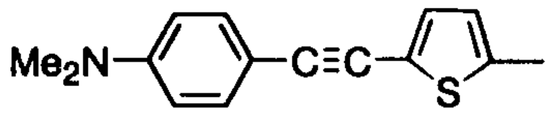
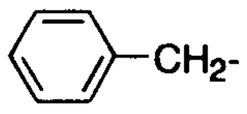
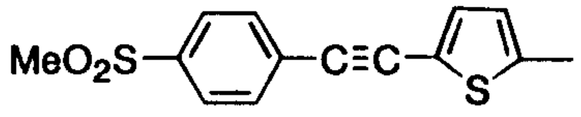
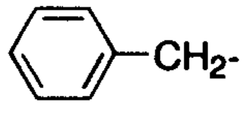
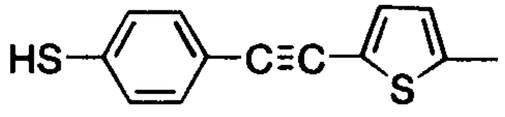
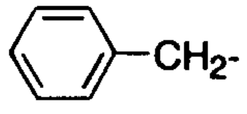
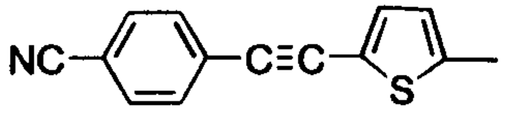
Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	Elemental analysis
141			R	–	–	–
142			R	–	–	–
143			R	–	–	–
144			R	–	–	–
145			R	–	–	–
146			R	–	–	–
147			R	–	–	–
148			R	–	–	–

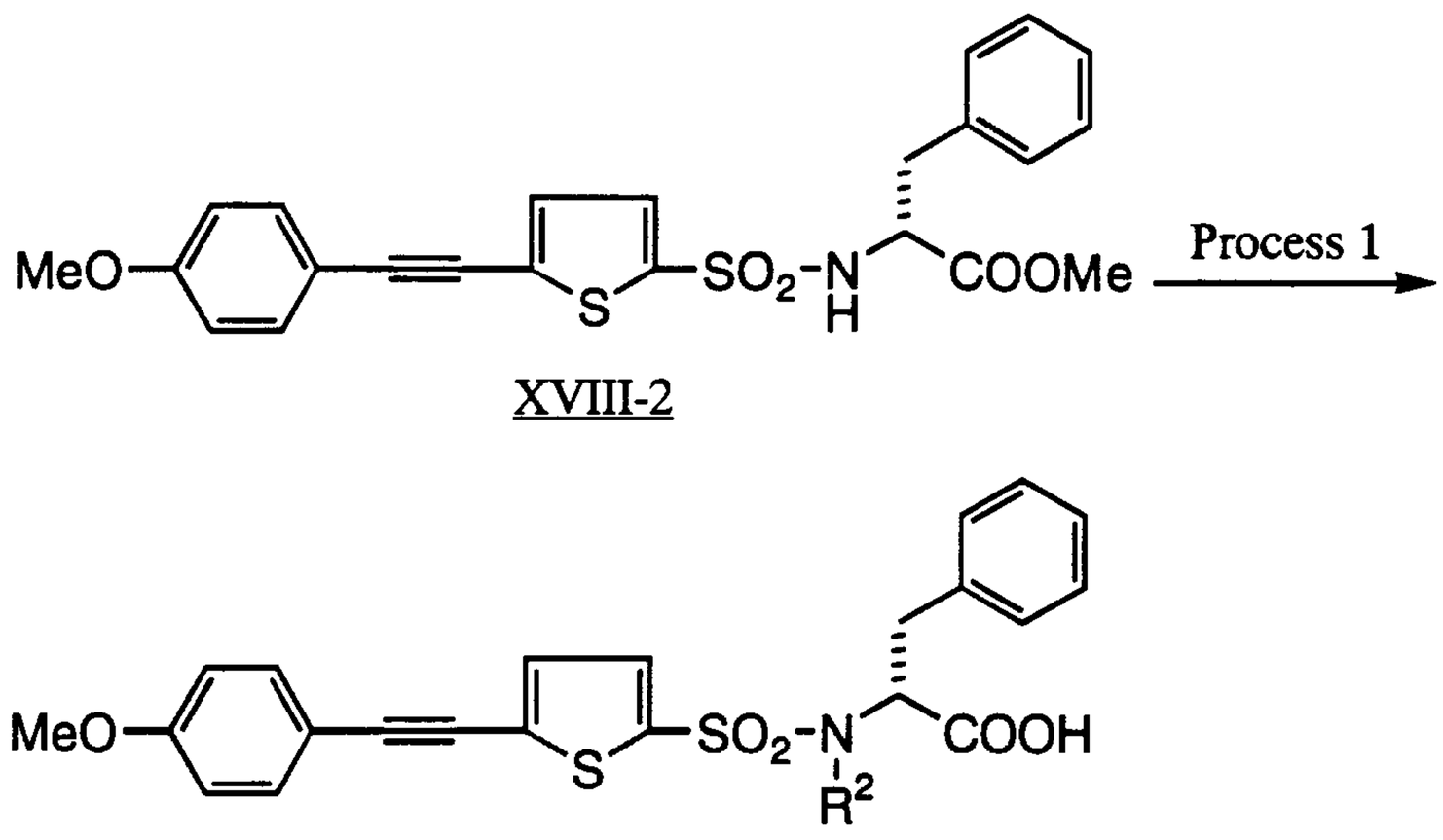
Table 30



(Ia)

Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	Elemental analysis
149			R	–	–	–
150			R	–	–	–
151			R	–	–	–
152			R	–	–	–
153			R	–	–	–
154			R	–	–	–
155			R	–	–	–
156			R	–	–	–

Example 157, 158



Process 1 ($R^2 = CH_3$)

To a solution of 150 mg (0.33 mmol) of compound (XVIII-2) in 2 ml of dimethylformamide which was synthesized the same manner as those described in Example 96 was added 227 mg (5 x 0.33 mmol) of potassium carbonate and 0.1 ml (5 x 0.33 mmol) of methyl iodide, and the resulting mixture was stirred overnight at room temperature. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with water, dried over Na_2SO_4, and concentrated in vacuo to give 373 mg of N-methyl derivative as an oil. Yield 91%.

Elemental analysis $C_{24}H_{23}NO_5S_2$

Calcd. : C; 61.39 H; 4.94 N; 2.98 S; 13.66

Found : C; 61.22 H; 5.18 N; 2.93 S; 13.27

Further, a solution of 140 mg of the above oily compound which was obtained the above process in 2 ml of methanol was added 0.6 ml of 1N NaOH, and the resulting mixture was stirred overnight at room temperature. The reaction mixture was acidified with 2N HCl and extracted with ethyl acetate. The organic layer was washed with water, dried over Na_2SO_4, and concentrated in vacuo to give 105 mg of compound (Ia-2-66) (R= Me). Yield 77 %. mp. 185 - 186℃.

Elemental analysis $C_{23}H_{21}NO_5S$

Calcd. : C; 60.64 H; 4.65 N; 3.07 S; 14.08

Found : C; 60.56 H; 4.84 N; 3.01 S; 13.94.

IR (KBr, ν max cm^{-1}) : 3600-2300br, 3426, 2203, 1710, 1604, 1503, 1344, 1151.

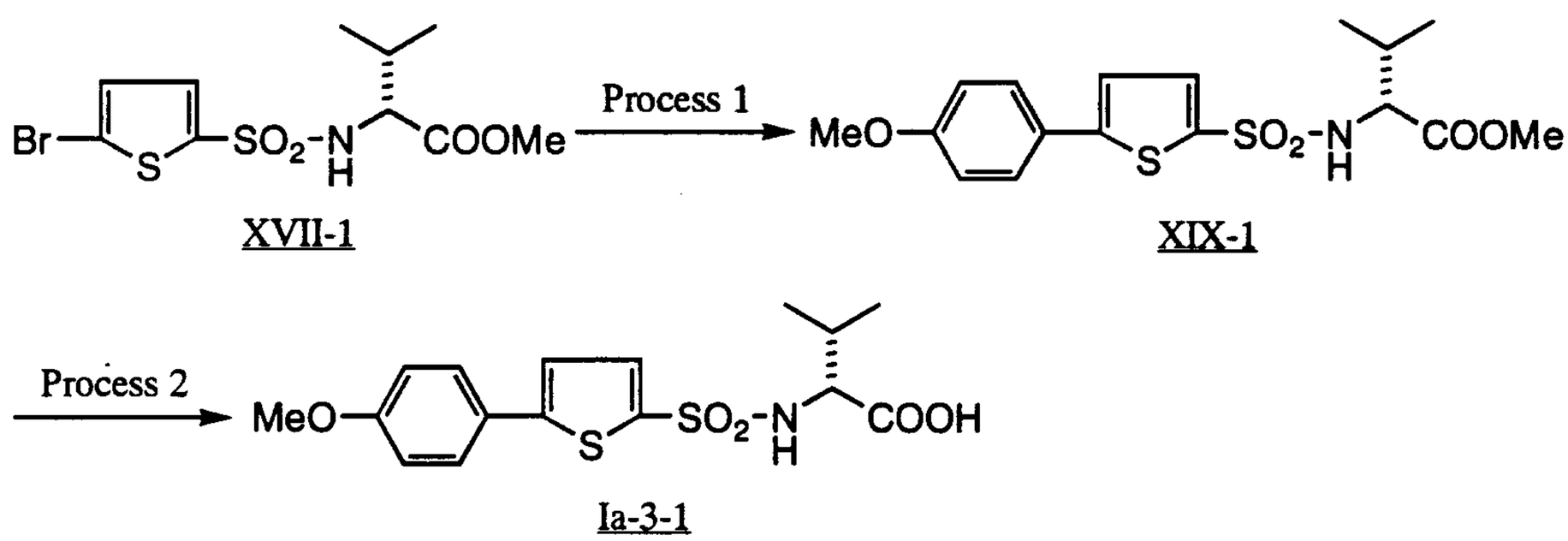
NMR (d_6-DMSO, δ ppm) : 2.88(s, 3H), 2.93(dd, J=12.0, 10.2 Hz, 1H), 3.19 (dd, J=14.2, 5.6 Hz, 1H), 3.81(s, 3H), 4.74(dd, J=5.4, 10.2 Hz, 1H), 6.99-7.04(m, 2H), 7.20-7.35(m, 7H), 7.52-7.56(m, 2H), 6.90(d, J=9.0 Hz, 2H), 7.44(d, J=9.0 Hz, 2H), 7.12(d, J=4.0 Hz, 1H), 7.44(d, J=4.0 Hz, 1H).

The compound (Ia-2-67) (R^2 = CH_2Ph) was synthesized in the same manner as those described in Example 157,.

IR(KBr, ν max cm^{-1}) : 2200,1722,1340,1151.

NMR (d_6-DMSO, δ ppm) : 2.94(dd, J=7.6, 13.8 Hz, 1H), 3.19(dd, J=7.2, 14.4 Hz, 1H), 3.83(s, 3H), 4.29(d, J=16.2 Hz, 1H), 4.62(d, J=16.2 Hz, 1H) (Only characteristic peaks are shown.)

Example 159 (Method C)



Process 1

To a solution of 500 mg (1.4 mmol) of compound(XVII-2) which was obtained Example 96 in 12 ml of dry tetrahydrofuran was added 387 mg (2 x 1.4 mmol) of powdery potassium carbonate, 319 mg (1.5x1.4 mmol) of 4-methoxyphenylboronic acid and 81 mg (0.05 x 1.4 mmol) of tetrakis(triphenylphosphine)palladium. The resulting mixture was stirred under argon atmosphere for 48 h at 75℃. The reaction mixture was diluted with ethyl acetate. The organic layer was washed with 1N HCl, 5% $NaHCO_3$ aq., and water, dried over Na_2SO_4, and concentrated in vacuo. The residue

was column chromatographed on silica gel. The fractions eluting with n-hexane / ethyl acetate = 3/1 were collected and recrystallized from n-hexane to give 447 mg of the desired compound (XIX-1). Yield 83 %. mp. 122-123℃.

Elemental analysis $C_{17}H_{21}NO_5S_2$

Calcd. : C; 53.25 H; 5.52 N; 3.65 S; 16.72

Found : C; 53.26 H; 5.50 N; 3.69 S; 16.63

$[\alpha]_D$ -21.7±0.6 (c=1.000 DMSO 25℃)

IR (KBr, ν max cm^{-1}) : 1735,1605,1505,1350,1167,1136

NMR ($CDCl_3$, δ ppm) : 0.90(d, J=7.0 Hz, 3H), 1.00(d, J=6.6 Hz, 3H), 2.10(m, 1H), 3.54(s, 3H), 3.85(s, 3H), 3.87(dd, J=5.0, 10.2 Hz, 1H), 5.20(d, J=10.2 Hz, 1H), 6.94(d, J=9.0 Hz, 2H), 7.52(d, J=9.0 Hz, 2H), 7.11(d, J=4.0 Hz, 1H), 7.49(d, J=4.0 Hz, 1H).

Process 2

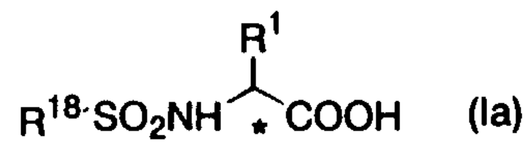
To a solution of 390 mg (1.01 mmol) of compound (XIX-1) in 8ml of tetrahydrofuran and 8ml of methanol was added 5.1 ml of 1N NaOH, and resulting mixture was stirred at 60℃ for 6 h. The reaction mixture was concentrated in vacuo to remove an organic solvent. The resulting residue was diluted with ethyl acetate. The mixture was acidified with aqueous solution of citric acid and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo to give 373 mg of compound (Ia-3-1). Yield 100%. mp. : 174 - 176℃

IR(KBr, ν max cm^{-1}) : 1735, 1503, 1343, 1163.

Example 160 - 175

The compounds which were shown in Tables 31 to 32 were synthesized in a manner similar to those described in Example 159,.

Table 31



(Ia)

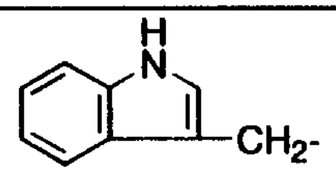
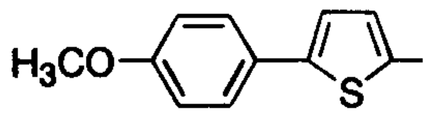
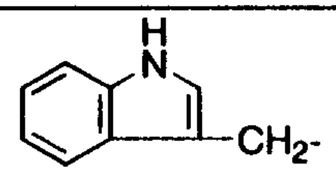
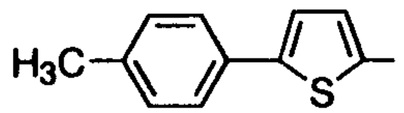
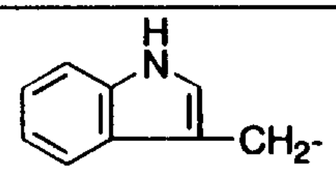
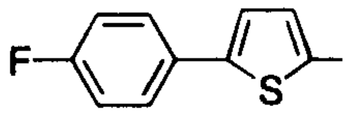
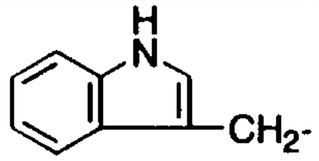
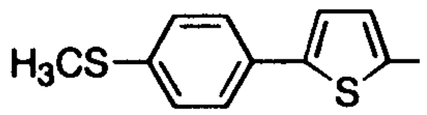
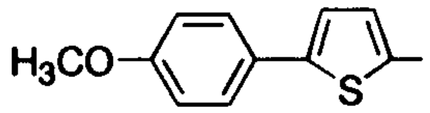
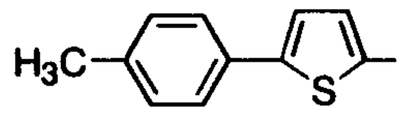
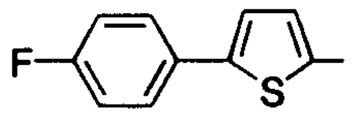
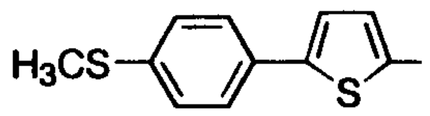
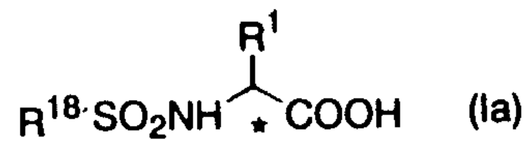
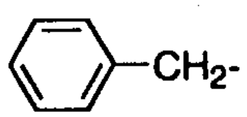
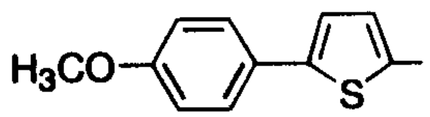
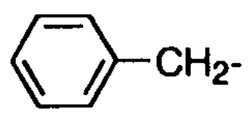
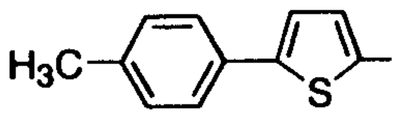
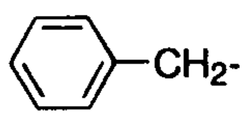
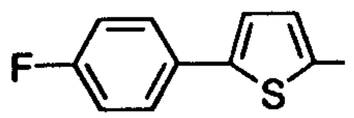
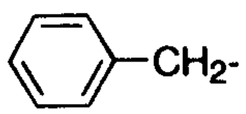
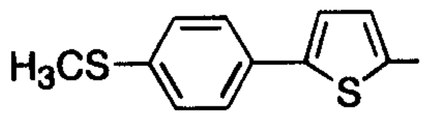
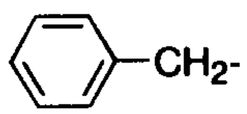
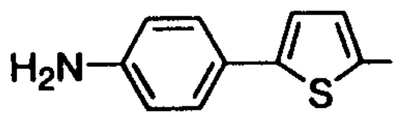
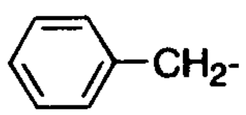
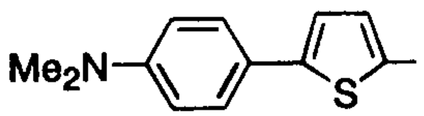
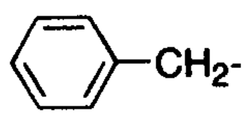
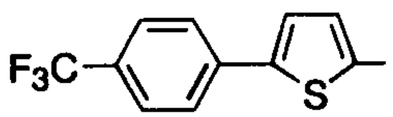
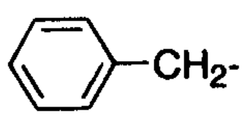
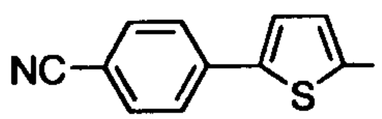
Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	Elemental analysis
160			R	93-96	1667,1337 1180	–
161			R	157-159	1670,1339 1194	–
162			R	168-171	1725,1598 1371,1185	–
163			R	226-230	1735,1341 1159	$C_{22}H_{20}N_2O_4S_3 \cdot 0.4H_2O$ Calc. C:55.07 H:4.37 N:5.84 S:20.05 Foun.C:55.35 H:4.43 N:6.04 S:19.65
164	$(CH_3)_2CH$-		R	174-176	1735,1503 1343,1163	–
165	$(CH_3)_2CH$-		R	165-167	1713,1353 1163	–
166	$(CH_3)_2CH$-		R	146-147	1702,1504 1352,1168	$C_{15}H_{16}FNO_4S_2 \cdot 0.1H_2O$ Calc. C:50.15 H:4.55 F:5.29 N:3.90 S:17.85 Foun.C:49.99 H:4.58 F:5.22 N:4.05 S:17.77
167	$(CH_3)_2CH$-		R	157-159	1747,1324 1159	$C_{16}H_{19}NO_4S_3$ Calc. C:49.85 H:4.97 N:3.63 S:24.95 Foun.C:49.70 H:5.00 N:3.93 S:24.96

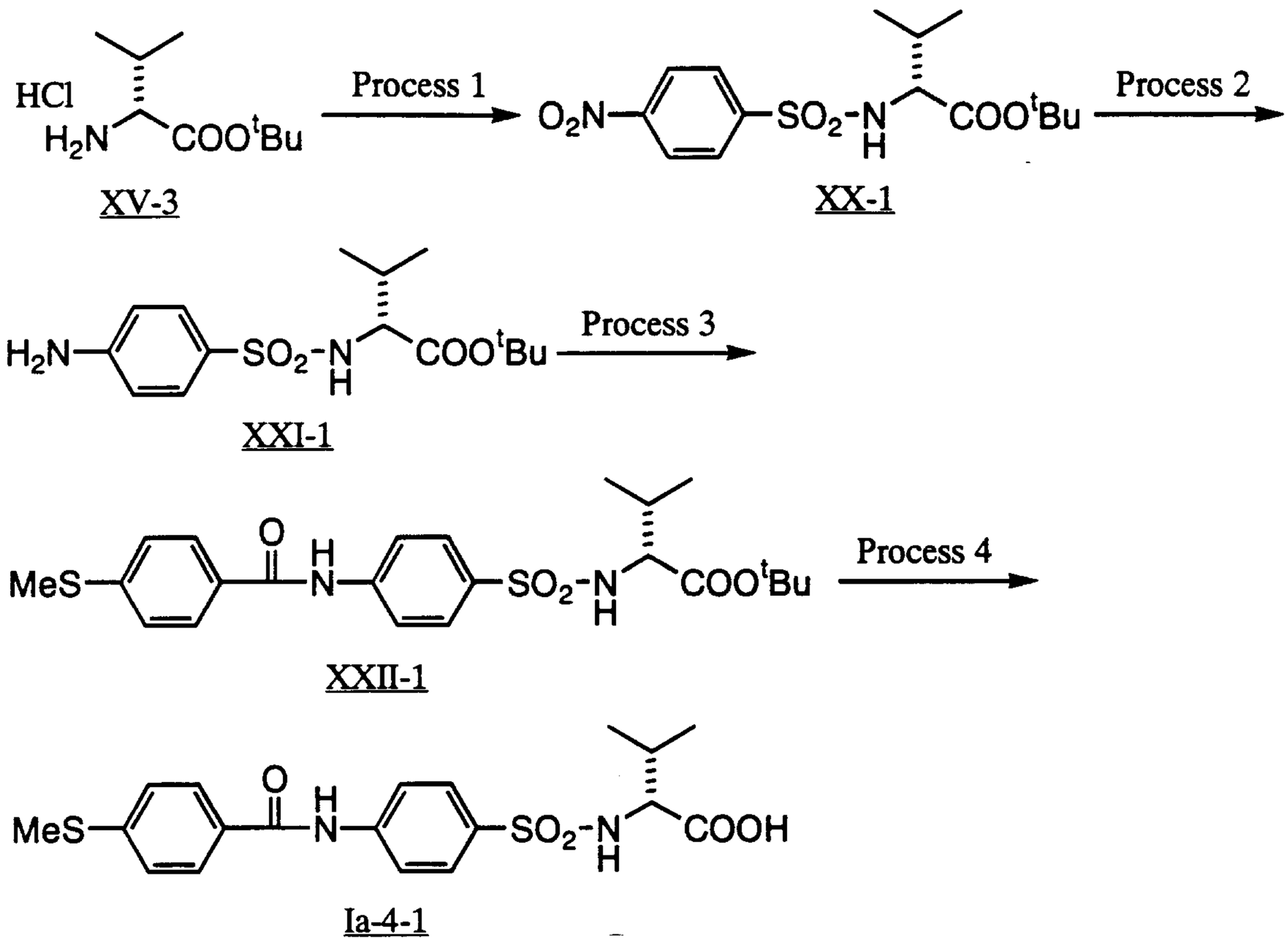
Table 32



(Ia)

Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	Elemental analysis
168			R	161-165	1735,1698 1374,1163	$C_{20}H_{19}NO_5S_2$ Calc. C:57.54 H:4.59 N:3.35 S:15.36 Foun.C:57.62 H:4.72 N:3.52 S:15.27
169			R	166-167	1713,1609 1378,1194	$C_{20}H_{19}NO_4S_2$ Calc. C:59.83 H:4.77 N:3.49 S:15.97 Foun.C:59.77 H:4.86 N:3.61 S:15.86
170			R	174-175	1721,1654 1365,1148	$C_{19}H_{16}FNO_4S_2$ Calc. C:56.28 H:3.98 F:4.09 N:3.45 S:15.82 Foun.C:56.33 H:4.09 F:4.65 N:3.65 S:15.84
171			R	203-205	1750,1730 1428,1325 1155	$C_{20}H_{19}NO_4S_3 \cdot 0.2H_2O$ Calc. C:54.95 H:4.47 N:3.20 S:22.00 Foun.C:55.05 H:4.52 N:3.34 S:22.04
172			R	–	–	–
173			R	–	–	–
174			R	–	–	–
175			R	–	–	–

Example 176 (Method D)



Process 1

To a solution of 10 g (47.68 mmol) of D-valine tert-butyl ester hydrochloride (XV-3) in 100 ml of dichloromethane was added 15.7 ml (3 x 47.68 mmol) of N-methylmorpholine and 14.1 g(1.2 x 47.68 mmol) of 4-nitrobenzenesulfonyl chloride under ice-cooling. After being stirred for 5 h at room temperature the reaction mixture was washed with 2N HCl, 5% $NaHCO_3$, water. The organic layer was dried over Na_2SO_4 and concentrated in vacuo, and the resulting residue was recrystallized from dichloromethane / n-hexane to give 13.3g of the desired compound (XX-1). Yield 77.8%. mp. 89-90℃.

Elemental analysis $C_{15}H_{22}N_2O_6S$

Calcd. : C; 50.27 H; 6.19 N; 7.82 S; 8.95

Found : C; 50.04 H; 6.10 N; 7.89 S; 8.84

$[\alpha]_D$ -2.9±0.8(c=0.512 DMSO 23℃)

IR(KBr, ν max cm^{-1}) : 3430br, 3301, 1722, 1698, 1525, 1362, 1348, 1181, 1174, 1159.

Process 2

A solution of 13.29 g (37.08 mmol) of compound (XX-1) in 200 ml of methanol was hydrogenated using 10% Pd/C (1g) for 2h at room temperature. The reaction mixture was filtered off and the filtrate was concentrated in vacuo. The residue was recrystallized from acetone / n-hexane to give 11.5g of amine derivative (XXI-1). Yield 94.4%. mp. 164-166℃

Elemental analysis$C_{15}H_{24}N_2O_4S$

Calcd. : C; 54.86 H; 7.37 N; 8.53 S; 9.76

Found : C; 54.84 H; 7.33 N; 8 63 S; 9.50

$[\alpha]_D$ +10.3±1.0(c=0.515 DMSO 23℃)

IR(KBr, ν max cm^{-1}) : 3461, 3375, 1716, 1638, 1598, 1344, 1313.

NMR(d-DMSO, δ ppm) : 0.80(d, J=6.8 Hz, 3H), 0.82(d, J=6.6 Hz, 3H), 1.23(s, 9H), 1.83(m, 1H), 3.30(m, 1H), 5.86(s, 2H), 6.56(d, J=8.8 Hz, 2H), 7.36(d, J=8.6 Hz, 2H), 7.47(d, J=9.6 Hz, 1H)

Process 3

To a solution of 328 mg (1mmol) of compound (XXI-1) in 10 ml of dichloromethane was added 0.33 ml (3 x 1 mmol) of N-methylmorpholine and 280 mg (1.5 x 1 mmol) of 4-(methylthio)benzoyl chloride under ice-cooling. The reaction mixture was stirred overnight at room temperature. To the reaction mixture was added ethyl ether and precipitation were collected and washed with ice-water and ethyl ether, The solid were recrystallized from acetone / ethyl ether to give 433 mg of the desired compound (XXII-1). Yield 90.5%. mp. 235-238℃.

Elemental analysis$C_{23}H_{30}N_2O_5S_2$

Calcd. : C; 57.72 H; 6.32 N; 5.85 S; 13.40

Found : C; 57.63 H; 6.28 N; 5.86 S; 13.20

$[\alpha]_D$ +5.7±0.9(c=0.512 DMSO 25℃)

IR(KBr, ν max cm^{-1}) : 3366, 3284, 1713, 1667, 1592, 1514, 1498, 1341, 1317.

NMR(d_6-DMSO, δ ppm) : 0.82(d, J=6.6 Hz, 3H), 0.84(d, J=6.8 Hz, 3H), 1.22(s, 9H), 1.91(m, 1H), 2.55(s, 3H), 3.32(s, 3H), 3.44(dd, J=6.2, 8.6 Hz, 1H), 7.40(d, J=8.6 Hz, 2H),

7.73(d, J=8.6 Hz, 2H), 7.90-8.01(m, 5H), 10.48 (s, 1H).

Process 4

To a solution of 405 mg (0.85 mmol) of compound (XXII-1) in 3 ml of dichloromethane was added 3.3 ml (50 x 0.85 mmol) of trifluoroacetic acid and resulting mixture was stirred for 2 h at room temperature. The reaction mixture was concentrated in vacuo and the resulting residue was washed with ethyl ether to give 340 mg of the desired compound (Ia-4-1). Yield 94.7 %. mp. 231-234℃

IR(KBr, ν max cm^{-1}) : 1748, 1655, 1592, 1323, 1161.

Elemental analysis $C_{19}H_{22}N_2O_5S_2 \cdot 0.1CF_3COOH$

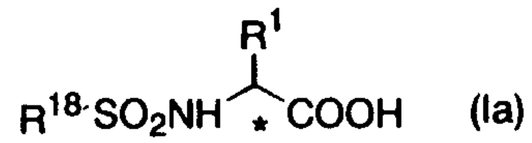
Calcd. : C; 53.14 H; 5.13 N; 6.46 S; 14.78

Found : C; 53.48 H; 5.31 N; 6.57 S; 15.06

Example 177 - 208

The compounds which were shown in Tables 33 to 36 were synthesized in a manner similar to those described in Example 176.

Table 33



(Ia)

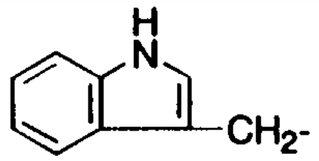
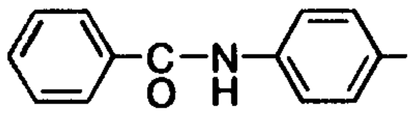
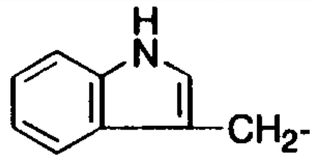
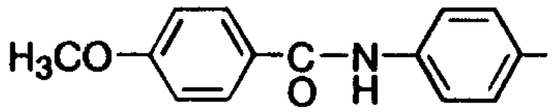
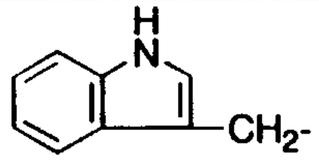
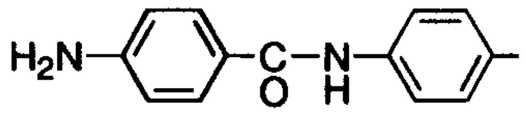
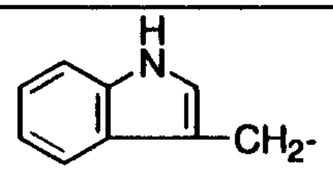
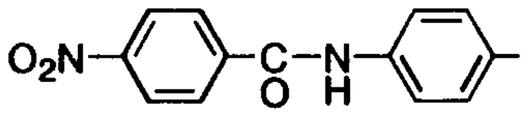
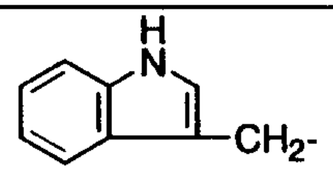
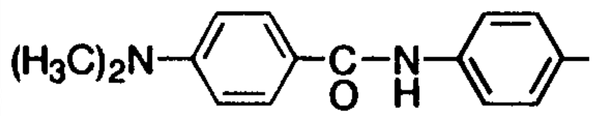
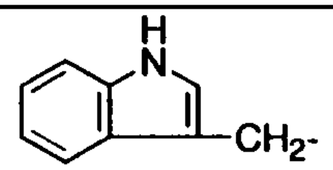
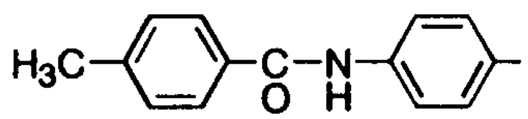
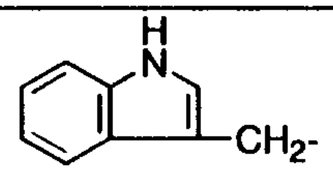
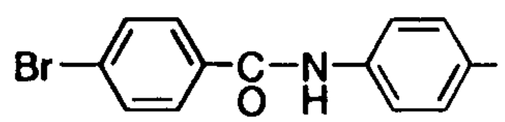
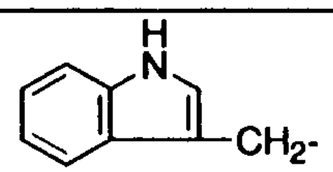
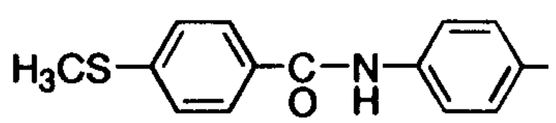
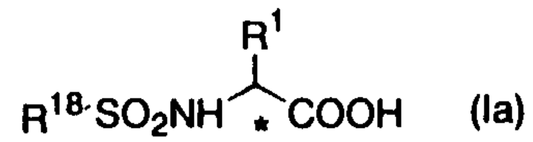
Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	Elemental analysis
177			R	215-217	1732,1641 1341,1163	–
178			R	233-234	1726,1655 1323,1177	$C_{25}H_{23}N_3O_6S \cdot 0.9H_2O$ Calc. C:58.91 H:4.90 N:8.24 S:6.29 Foun.C:58.97 H:5.07 N:7.95 S:6.10
179			R	216-218	1723,1633 1361,1149	–
180			R	211-213	1719,1629 1340,1156	$C_{24}H_{20}N_4O_7S \cdot 1.1H_2O$ Calc. C:54.56 H:4.24 N:10.60 S:6.07 Foun.C:54.51 H:4.32 N:10.83 S:6.15
181			R	236-238	1732,1653 1399,1199	$C_{26}H_{26}N_4O_5S \cdot 0.9H_2O$ Calc. C:59.73 H:5.36 N:10.72 S:6.13 Foun.C:59.58 H:5.23 N:10.85 S:6.47
182			R	240-244	1731,1656 1591,1327 1160	$C_{25}H_{23}N_3O_5S \cdot 0.9H_2O$ Calc. C:60.82 H:5.06 N:8.51 S:6.49 Foun.C:60.83 H:5.19 N:8.66 S:6.66
183			R	215-218	1727,1668 1590,1316 1154	$C_{24}H_{20}BrN_3O_5S \cdot 0.6H_2O$ Calc. C:52.11 H:3.86 Br:14.44 N:7.60 S:5.80 Foun.C:52.13 H:4.04 Br:14.57 N:7.43 S:5.70
184			R	244-249	1728,1653 1593,1323 1159	$C_{25}H_{23}N_3O_5S_2 \cdot 0.7H_2O$ Calc. C:57.50 H:4.71 N:8.05 S:12.28 Foun.C:57.63 H:4.79 N:8.00 S:12.08

Table 34



(Ia)

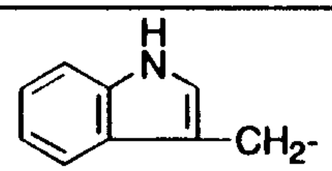
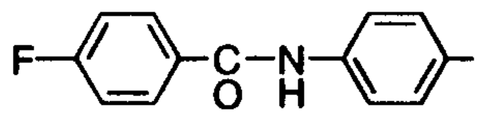
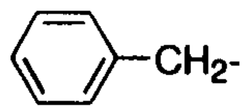
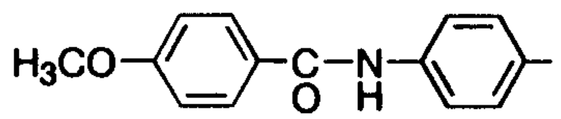
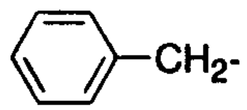
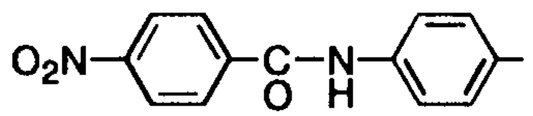
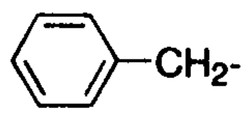
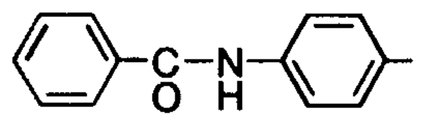
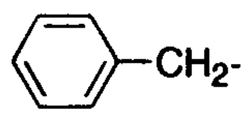
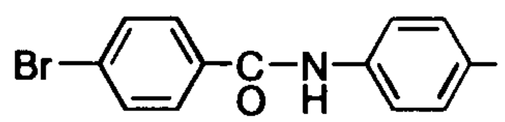
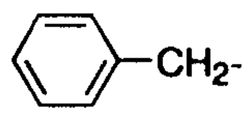
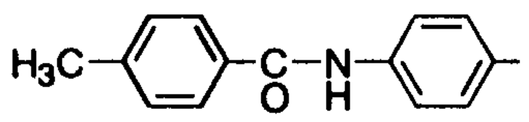
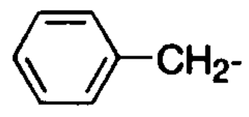
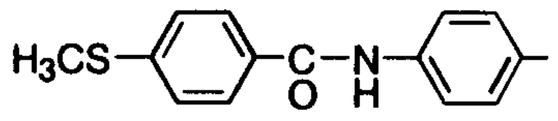
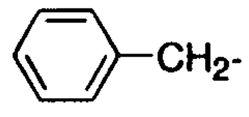
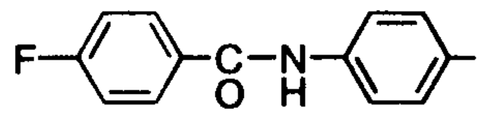
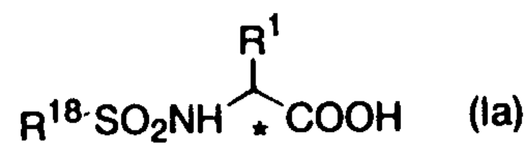
Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	Elemental analysis
185			R	170-175	1730,1651 1603,1333 1161	$C_{24}H_{20}FN_3O_5S \cdot 0.6H_2O$ Calc. C:58.55 H:4.34 F:3.86 N:8.54 S:6.51 Foun.C:58.67 H:4.51 F:3.77 N:8.42 S:6.47
186			R	237-239	1723,1651 1591,1322 1161	$C_{23}H_{22}N_2O_6S$ Calc. C:60.78 H:4.88 N:6.16 S:7.05 Foun.C:60.50 H:4.99 N:6.14 S:7.31
187			R	235-239	1719,1672 1593,1327 1159	$C_{22}H_{19}N_3O_7S$ Calc. C:56.29 H:4.08 N:8.95 S:6.83 Foun.C:56.01 H:4.09 N:8.93 S:6.75
188			R	114-115	1748,1658 1592,1325 1159	$C_{22}H_{20}N_2O_5S \cdot 0.5CF_3COOH$ Calc. C:57.37 H:4.29 N:5.82 S:6.66 Foun.C:57.53 H:4.45 N:5.75 S:7.11
189			R	242-243	1743,1670 1591,1335 1167	$C_{22}H_{19}BrN_2O_5S \cdot CF_3COOH$ Calc. C:46.69 H:3.27 Br:12.94 N:4.54 S:5.19 Foun.C:46.79 H:3.41 Br:12.86 N:4.57 S:5.37
190			R	242-244	1752,1726 1656,1591 1324,1160	$C_{23}H_{22}N_2O_5S$ Calc. C:63.00 H:5.06 N:6.39 S:7.31 Foun.C:62.70 H:5.13 N:6.36 S:7.36
191			R	232-235	1742,1667 1591,1334 1161	$C_{23}H_{22}N_2O_5S_2 \cdot 0.8CF_3COOH$ Calc. C:52.59 H:4.09 N:4.99 S:11.42 Foun.C:52.77 H:4.24 N:5.12 S:11.58
192			R	218-220	1737,1651 1598,1324 1160	$C_{22}H_{19}FN_2O_5S$ Calc. C:59.72 H:4.33 F:4.29 N:6.33 S:7.25 Foun.C:59.59 H:4.42 F:4.30 N:6.37 S:7.24

Table 35



(Ia)

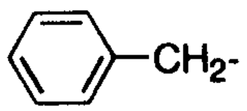
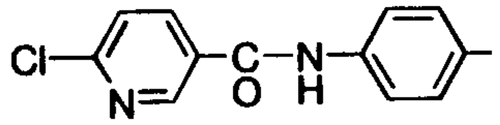
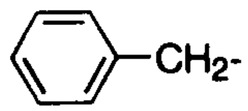
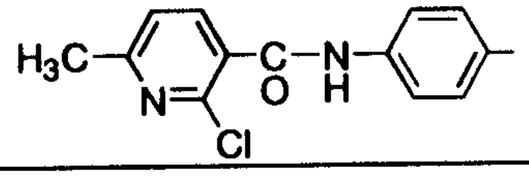
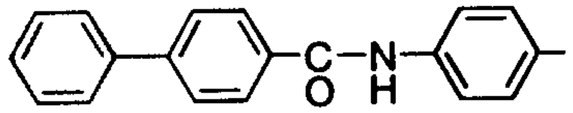
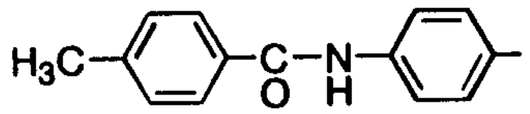
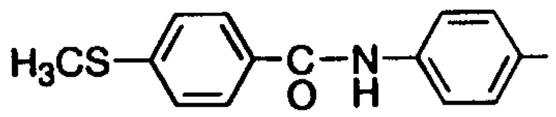
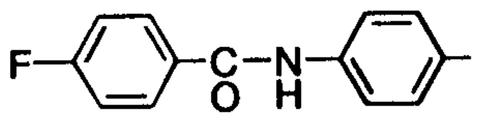
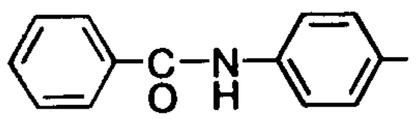
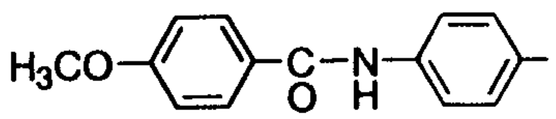
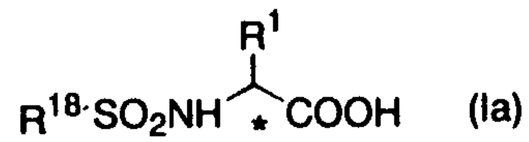
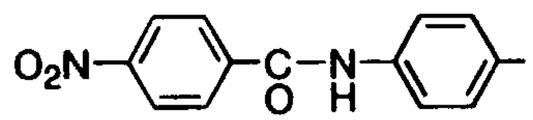
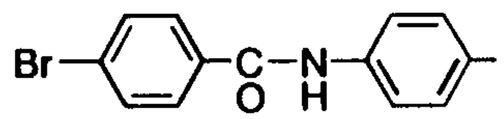
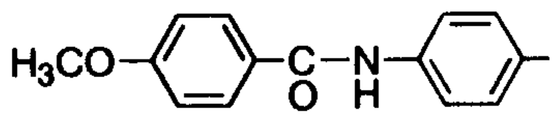
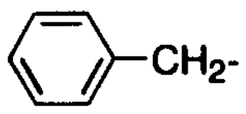
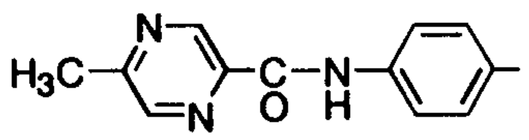
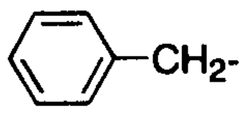
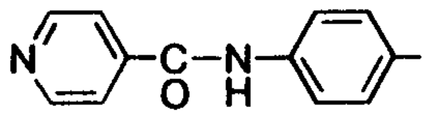
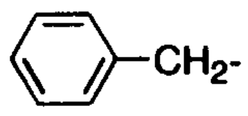
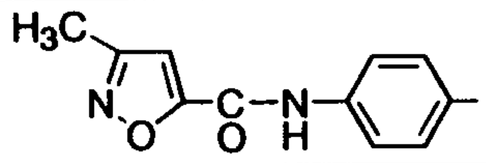
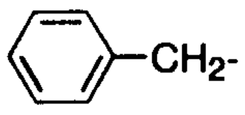
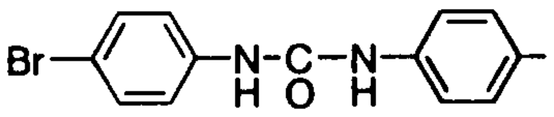
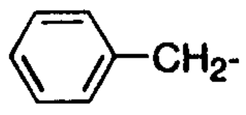
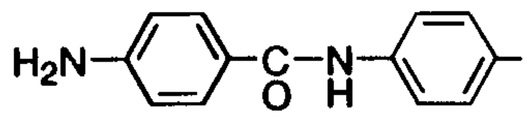
Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	Elemental analysis
193			R	201-203	1724,1673 1592,1326 1156	$C_{21}H_{18}ClN_3O_5S$ Calc. C:54.84 H:3.94 Cl:7.71 N:9.14 S:6.97 Foun.C:54.39 H:4.06 Cl:7.42 N:8.98 S:6.99
194			R	206-208	1725,1682 1592,1332 1160	$C_{22}H_{20}ClN_3O_5S\cdot0.1CF_3COOH$ Calc. C:55.15 H:4.19 Cl:7.33 N:8.69 S:6.63 Foun.C:55.25 H:4.28 Cl:7.10 N:8.80 S:6.80
195	$(CH_3)_2CH$-		R	254-256	1748,1659 1590,1324 1161	$C_{24}H_{24}N_2O_5S\cdot0.5H_2O$ Calc. C:62.46 H:5.46 N:6.07 S:6.95 Foun.C:62.42 H:5.54 N:6.26 S:6.97
196	$(CH_3)_2CH$-		R	227-229	1749,1658 1592,1323 1161	$C_{19}H_{22}N_2O_5S\cdot0.2H_2O$ Calc. C:57.91 H:5.73 N:7.11 S:8.14 Foun.C:57.94 H:5.69 N:7.03 S:8.14
197	$(CH_3)_2CH$-		R	231-234	1748,1655 1592,1323 1161	$C_{19}H_{22}N_2O_5S_2\cdot0.1CF_3COOH$ Calc. C:53.14 H:5.13 N:6.46 S:14.78 Foun.C:53.48 H:5.31 N:6.57 S:15.06
198	$(CH_3)_2CH$-		R	235-236	1749,1726 1668,1597 1322,1160	$C_{18}H_{19}FN_2O_5S\cdot0.1CF_3COOH$ Calc. C:53.86 H:4.74 F:6.09 N:6.90 S:7.90 Foun.C:53.82 H:4.85 F:5.60 N:6.93 S:7.78
199	$(CH_3)_2CH$-		R	226-227	1728,1661 1591,1317 1159	$C_{18}H_{20}N_2O_5S\cdot0.1H_2O$ Calc. C:57.16 H:5.38 N:7.41 S:8.48 Foun.C:57.01 H:5.46 N:7.57 S:8.57
200	$(CH_3)_2CH$-		R	220-221	1696,1654 1591,1317 1255	$C_{19}H_{22}N_2O_6S\cdot0.2H_2O$ Calc. C:55.65 H:5.51 N:6.83 S:7.82 Foun.C:55.63 H:5.48 N:7.03 S:7.75

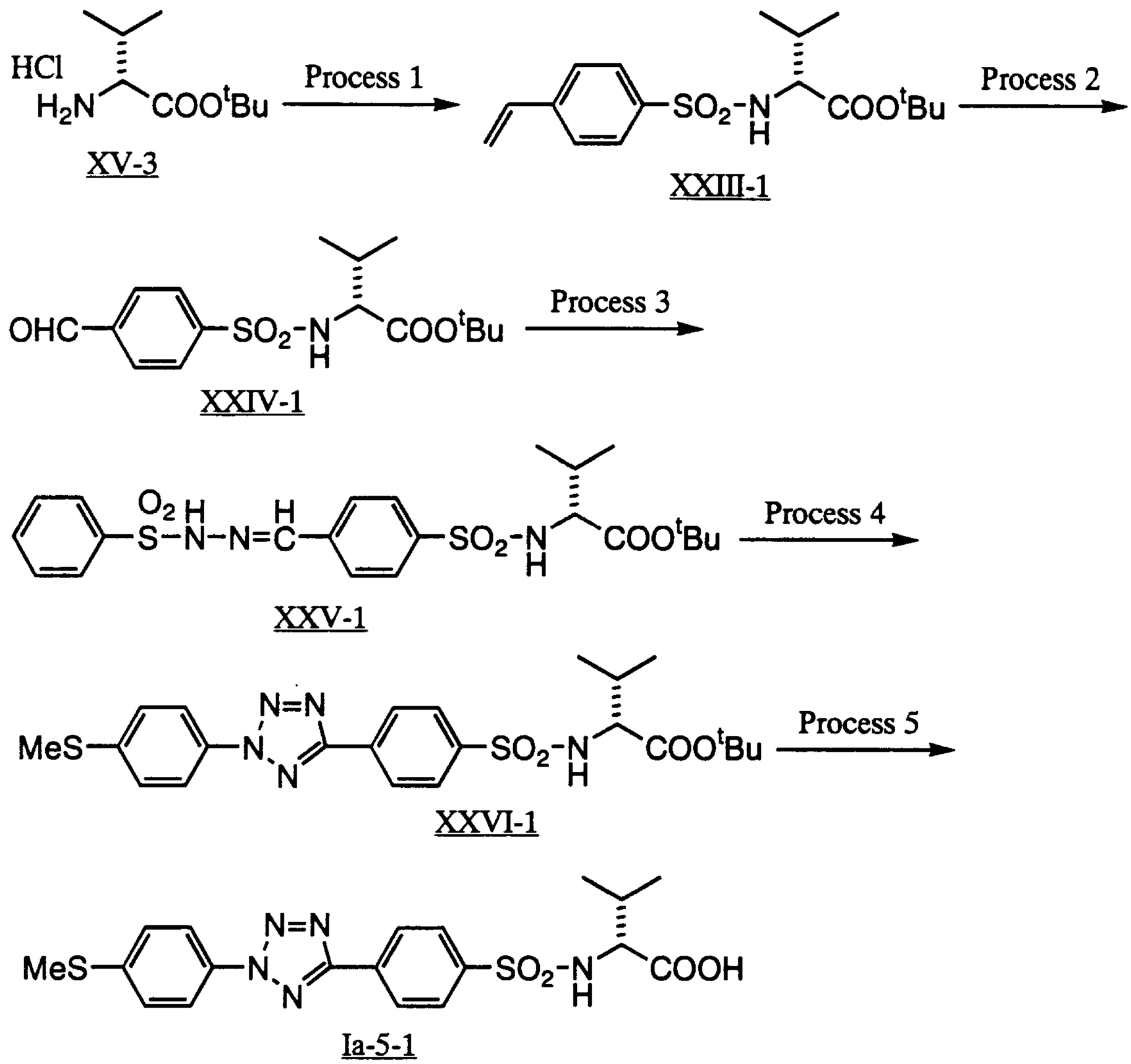
Table 36



(Ia)

Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	Elemental analysis
201	$(CH_3)_2CH$-		R	240-242	1726,1688 1591,1347 1166	$C_{18}H_{19}N_3O_7S$•0.4H_2O Calc. C:50.44 H:4.66 N:9.80 S:7.48 Foun.C:50.40 H:4.55 N:9.90 S:7.44
202	$(CH_3)_2CH$-		R	229-230	1726,1663 1592,1318 1159	$C_{18}H_{19}BrN_2O_5S$•0.2Ethylether Calc. C:48.03 H:4.50 Br:17.00 N:5.96 S:6.82 Foun.C:48.04 H:4.61 Br:16.83 N:5.96 S:6.86
203	$(CH_3)_3C$-		R	214-216	1659,1591 1316,1159	$C_{20}H_{24}N_2O_6S$•0.4H_2O Calc. C:56.17 H:5.84 N:6.55 S:7.50 Foun.C:56.21 H:6.02 N:6.50 S:7.33
204	 CH_2-		R	236-237	1723,1679 1590,1337 1162	$C_{21}H_{20}N_4O_5S$•0.25CF_3COOH Calc. C:55.06 H:4.35 N:11.95 S:6.84 Foun.C:54.80 H:4.90 N:12.16 S:7.10
205	 CH_2-		R	272-275	1719,1672 1594,1339 1165	$C_{21}H_{19}N_3O_5S$ Calc. C:59.28 H:4.50 N:9.88 S:7.54 Foun.C:58.84 H:4.56 N:9.71 S:7.36
206	 CH_2-		R	214-215	1733,1685 1594,1319 1154	$C_{20}H_{19}N_3O_6S$ Calc. C:55.94 H:4.46 N:9.78 S:7.47 Foun.C:55.50 H:4.47 N:9.74 S:7.31
207	 CH_2-		R	217-220	1732,1679 1592,1312 1155	—
208	 CH_2-		R	—	—	—

Example 209 (Method E)



Process 1

To a solution of 20.94 g (99.8 mmol) of D-valine tert-butyl ester hydrochloride (XV-3) in 200 ml of dichloromethane was added 22 ml (2 x 99.8 mmol) of N-methylmorpholine and 20.27 g (99.8 mmol) of p-styrenesulfonyl chloride under ice-cooling. After being stirred for 15 h at room temperature, the reaction mixture was washed with 2N HCl, 5% $NaHCO_3$, water. The organic layer was dried over Na_2SO_4 and concentrated in vacuo, and the resulting residue was column chromatographed on silica gel. The fractions eluting with ethyl acetate / n-hexane / chloroform = 1/3/1 were collected and washed with n-hexane to give 28.93 g of the desired compound (XXIII-1). Yield 85 %. mp. 118-120℃.

IR(KBr, ν max cm^{-1}) : 3419, 3283, 1716, 1348, 1168.

NMR($CDCl_3$, δ ppm) : 0.85(d, J=6.9 Hz, 3H), 1.00(d, J=6.6 Hz, 3H), 1.21(s, 9H), 2.04(m, 1H), 3.62(dd, J=9.8, 4.5 Hz, 1H), 5.09(d, J=9.8 Hz, 1H), 5.41(dd, J=0.5, 10.9 Hz, 1H), 5.84(dd, J=0.5, 17.6 Hz, 1H), 6.72(dd, J=10.9, 17.6 Hz, 1H), 7.49(d, J=8.4 Hz, 2H), 7.79(d, J=8.4 Hz, 2H).

Process 2

Ozone gas was bubbled through a solution of 5.09 g (15 mmol) of compound (XXIII-1) in 300 ml of dichloromethane for 15 h at -78℃. To this solution was added 22 ml (20 x 15 mmol) of methylsulfide, and the reaction mixture was allowed to warm to room temperature gradually over 80 min and concentrated in vacuo to give 6.03g aldehyde derivative (XXIV-1).

IR($CHCl_3$, ν max cm^{-1}) : 3322, 1710, 1351, 1170.

NMR($CDCl_3$, δ ppm) : 0.85(d, J=6.9 Hz, 3H), 1.00(d, J=6.9 Hz, 3H), 1.22(s, 9H), 2.07(m, 1H), 3.69(dd, J=4.5, 9.9 Hz, 1H), 8.01(s, 4H), 10.08(s, 1H).

Process 3

To a solution of 6.02 g(15 mmol) of compound (XXIV-1) in 60 ml of ethanol and 15 ml of tetrahydrofuran was added 2.72 g (1.05 x 15 mmol) of benzenesulfonyl hydrazide at room temperature. After being stirred for 2 h, the resulting mixture was concentrated in vacuo. The residue which was obtained by concentration in vacuo was column chromatographed on silica gel and the fractions eluting with chloroform / ethyl acetate = 1/4 were collected and recrystallized from ethyl acetate to give 4.44 g of the desired compound (XXV-1). Yield from process 2 60%. mp. 163-164℃.

Elemental analysis $C_{22}H_{29}N_3O_6S_2$

Calcd. : C; 53.32 H; 5.90 N; 8.48 S; 12.94

Found : C; 53.15 H; 5.87 N; 8.32 S; 12.82

$[\alpha]_D$ -11.6±1.0(c=0.509 DMSO 23.5℃)

IR(KBr, ν max cm^{-1}) : 3430, 3274, 1711, 1364, 1343, 1172.

NMR($CDCl_3$ δ ppm) : 0.84(d, J=6.9 Hz, 3H), 0.99(d, J=6.6 Hz, 3H), 1.19(s, 9H), 2.00(m, 1H), 3.63(dd, J=4.5, 9.9 Hz, 1H), 5.16(d, J=9.9 Hz, 1H), 7.50-7.68(m, 5H), 7.73(s, 1H),

7.78-7.84(m, 2H), 7.96-8.02(m, 2H), 8.16(brs, 1H).

Process 4

To a solution of 0.14 ml (1.11 x 1 mmol) of 4-(methylmercapto)aniline and 0.3 ml of conc. hydrochloric acid in 3 ml of aqueous 50% ethanol solution was added a solution of 78.4 mg (1.14 x 1 mmol) of sodium nitrite in 1 ml of water at 0 to 5 ℃ of the internal temperature and the reaction mixture was stirred for 15 min at the same temperature. To a solution of 496 mg (1 mmol) of compound (XXV-1) in 5 ml of dry pyridine was added the above reaction mixture over 8 min at -25℃. This reaction mixture was stirred for additional 4 h at -15℃ to rt, poured into water, and extracted with ethyl acetate. The organic layer was washed with 2N HCl, 5% $NaHCO_3$, and water, dried over Na_2SO_4, and concentrated in vacuo. The residue was column chromatographed on silica gel and the fractions eluting with chloroform / ethyl acetate = 1/9 were collected to give 374 mg of the desired compound (XXVI-1). Yield 74%.

Elemental analysis $C_{23}H_{29}N_5O_4S_2 \cdot 0.3H_2O$

Calcd. : C; 54.27 H; 5.86 N; 13.76 S; 12.60

Found : C; 54.25 H; 5.77 N; 13.87 S; 12.52

IR(KBr, ν max cm^{-1}) : 3422, 3310, 1705, 1345, 1171.

NMR(d_6-DMSO, δ ppm) : 0.83(d, J=6.9 Hz, 3H), 0.86(d, J=7.2 Hz, 3H), 1.19(s, 9H), 2.00(m, 1H), 2.59(s, 3H), 3.54(dd, J=6.3, 9.6 Hz, 1H), 7.56(d, J=8.7 Hz, 2H), 8.00(d, J=8.6 Hz, 2H), 8.10(d, J=8.7 Hz, 2H), 8.33(d, J=9.6 Hz, 2H), 8.34(d, J=8.7 Hz, 2H).

Process 5

A solution of 353 mg of compound (XXVI-1) in 2.5 ml of dichloromethane and 2.5 ml of trifluoroacetic acid was stirred for 3 h at room temperature. The reaction mixture was concentrated in vacuo and the resulting residue was washed with ethyl ether to give 308 mg of compound (Ia-5-1). Yield 98%. mp. 194 - 195℃.

IR(KBr, ν max cm^{-1}) : 1720, 1343, 1166.

Elemental analysis $C_{19}H_{21}N_5O_4S_2 \cdot 1.1H_2O$

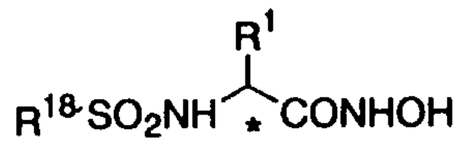
Calcd. : C; 48.83 H; 5.00 N; 14.99 S; 13.72

Found : C; 49.13 H; 5.25 N; 14.55 S; 13.34

Example 210 - 251

The compounds which were shown in Tables 37 to 43 were synthesized in a manner similar to those described in Example 209.

Table 37



(Ib)

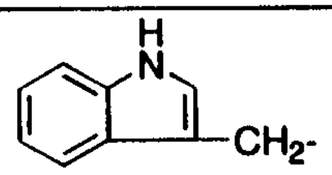
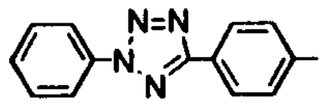
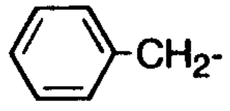
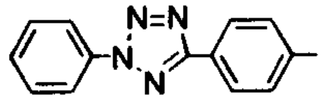
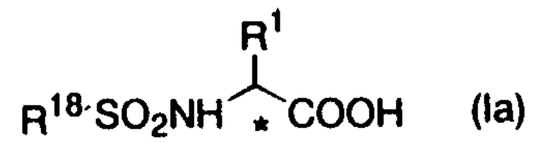
Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	^{1}H-NMR(δ ppm) d_6-DMSO
210			R	–	–	–
211			R	194-195	3700-2200(br),3278, 1634,1337,1160	2.65(dd,J=9.3,13.1Hz,1H),2.82(dd, J=5.8,13.1Hz,1H),3.86(dt,J=5.8,9.3 Hz,1H),7.72(A_2B_2q,J=8.1Hz,2H), 8.19(A_2B_2q,J=8.1Hz,2H),8.49(d,J= 9.3Hz,1H),8.88(s,1H),10.69(s,1H)

Table 38



(Ia)

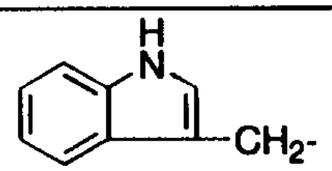
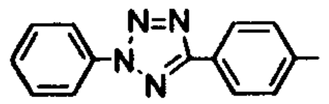
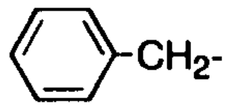
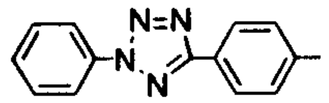
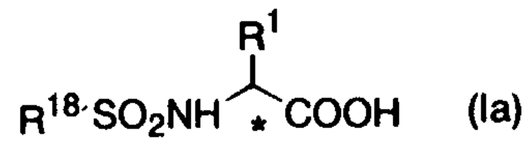
Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	^{1}H-NMR(δ ppm) d_6-DMSO
210			R	–	–	–
211			R	215-216	2400-3700br,3422,3337, 1733,1698,1347,1170	2.75(dd,J=9.3,13.7Hz,1H),2.99(dd,J=5.3,13.7Hz,1H),3.96(dt,J=5.3,9.3Hz,1H),8.53(d,J=9.3Hz,1H)

Table 39



(Ia)

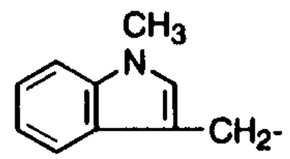
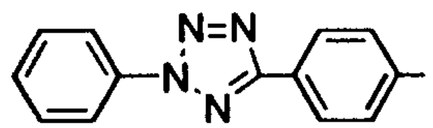
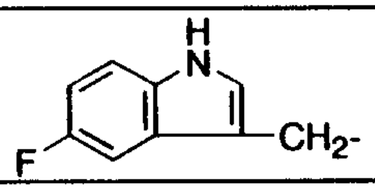
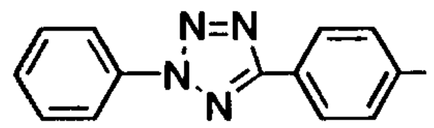
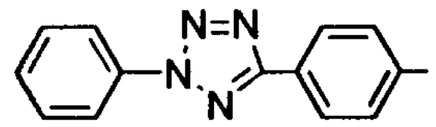
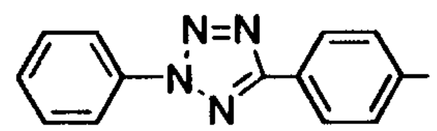
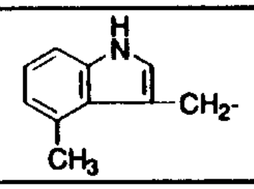
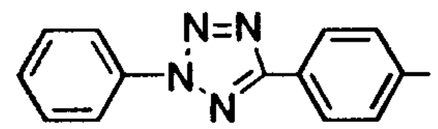
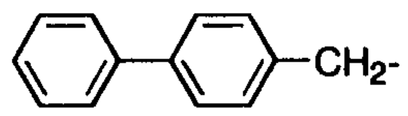
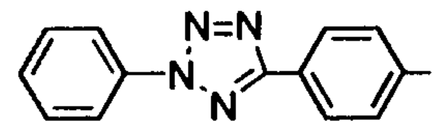
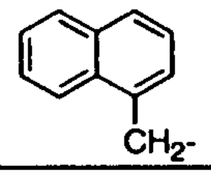
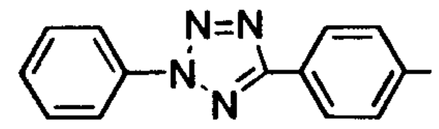
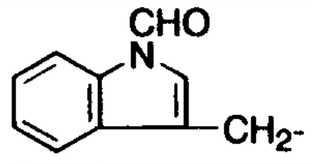
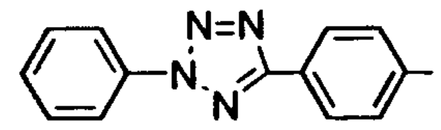
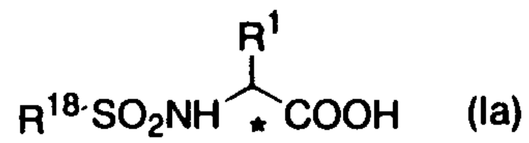
Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	Elemental analysis
212			RS	199-202	1734,1337 1161	$C_{25}H_{22}N_6O_4S$•0.5Ethylether Calc. C:60.10 H:5.04 N:15.57 S:5.94 Foun.C:60.41 H:4.69 N:15.52 S:5.57
213			RS	224-225	1728,1338 1166	$C_{24}H_{19}FN_6O_4S$•0.4Ethylether Calc .C:57.35 H:4.32 F:3.54 N:15.67 S:5.98 Foun.C:56.74 H:4.37 F:3.47 N:15.17 S:568
214	$(CH_3)_2CHCH_2$-		R	202-204	1720,1595 1338,1170	$C_{19}H_{21}N_5O_4S$ Calc. C:54.93 H:5.09 N:16.86 S:7.72 Foun.C:54.75 H:5.14 N:16.81 S:7.55
215	$(CH_3)_2CH$-		R	221-222	1696,1594 1349,1173	$C_{18}H_{19}N_5O_4S$ Calc. C:53.38 H:4.83 N:17.29 S:7.92 Foun.C:53.38 H:4.80 N:17.05 S:7.67
216			RS	145-148	1727,1337 1163	–
217			R	203-205	1735,1495 1336,1160	$C_{28}H_{23}N_5O_4S$•0.6H_2O Calc. C:62.70 H:4.55 N:13.06 S:5.98 Foun.C:62.61 H:4.50 N:13.29 S:5.87
218			RS	225-227	1721,1418 1344,1163	$C_{26}H_{21}N_5O_4S$•0.2H_2O Calc. C:62.07 H:4.29 N:13.92 S:6.37 Foun.C:61.93 H:4.30 N:14.01 S:6.43
219			R	111-114	1727,1703 1459,1332 1165	$C_{25}H_{20}N_6O_5S$•H_2O Calc. C:56.17 H:4.15 N:15.72 S:6.00 Foun.C:56.20 H:4.18 N:15.68 S:6.10

Table 40



(Ia)

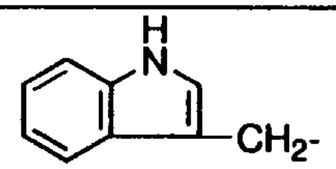
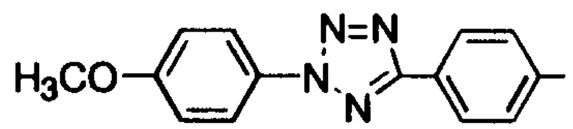
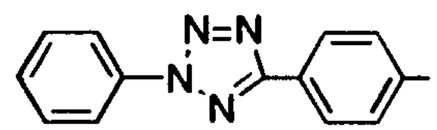
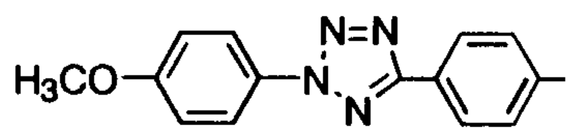
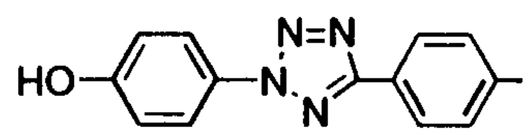
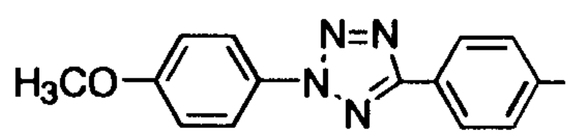
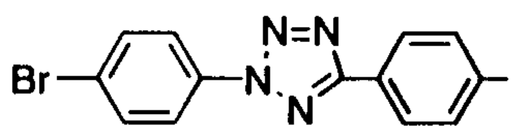
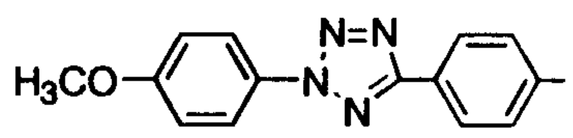
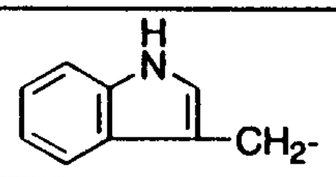
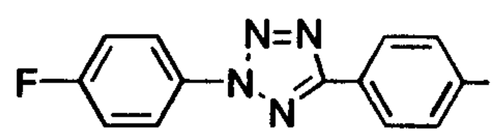
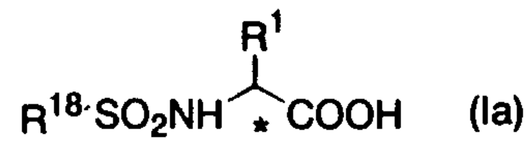
Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	Elemental analysis
220			R	195-196	1749,1719 1331,1165	$C_{25}H_{22}N_6O_5S$ Calc. C:57.91 H:4.28 N:16.21 S:6.18 Foun.C:57.77 H:4.29 N:16.01 S:6.37
221	$CH_3CH_2(CH_3)CH$-		R	205-207	1730,1693 1349,1173	$C_{19}H_{21}N_5O_4S$ Calc. C:54.93 H:5.09 N:16.86 S:7.72 Foun.C:54.71 H:5.09 N:16.70 S:7.56
222	$CH_3CH_2(CH_3)CH$-		R	204-207	1729,1693 1337,1170	$C_{20}H_{23}N_5O_5S \cdot 0.4H_2O$ Calc. C:53.06 H:5.30 N:15.47 S:7.08 Foun.C:53.13 H:5.13 N:15.12 S:7.14
223	$(CH_3)_2CH$-		R	190 decomp.	1718,1601 1385,1162	–
224	$(CH_3)_2CH$-		R	195-197	1719,1304 1162	$C_{20}H_{23}N_5O_5S \cdot 0.4H_2O$ Calc. C:53.06 H:5.30 N:15.47 S:7.08 Foun.C:53.13 H:5.13 N:15.12 S:7.14
225	$(CH_3)_2CH$-		R	227-228	1696,1348 1171	$C_{18}H_{18}BrN_5O_4S \cdot 0.8H_2O$ Calc. C:43.70 H:3.99 Br:16.15 N:14.16 S:6.48 Foun.C:43.93 H:3.85 Br:15.92 N:13.87 S:6.47
226	$(CH_3)_3C$-		R	204-207	1698,1344 1168	–
227			R	203-205	1757,1738 1331,1163	–

Table 41



(Ia)

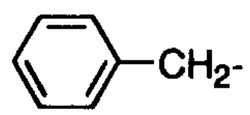
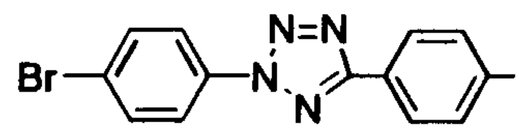
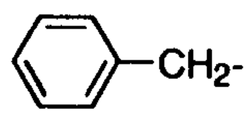
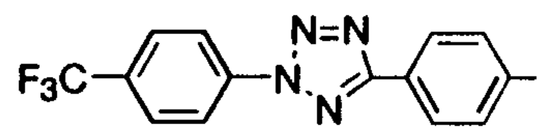
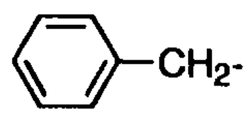
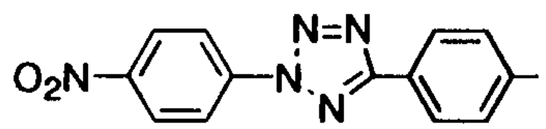
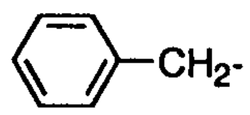
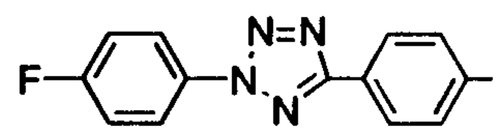
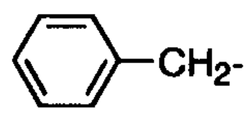
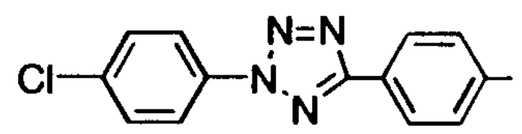
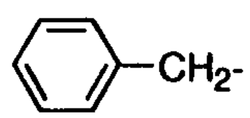
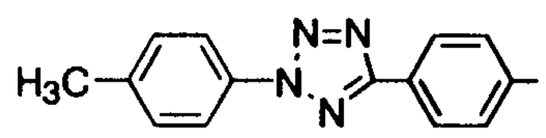
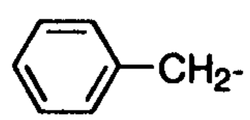
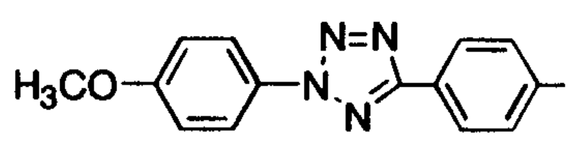
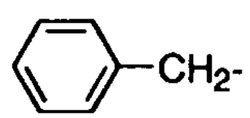
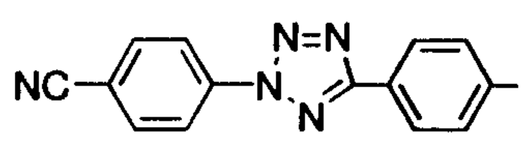
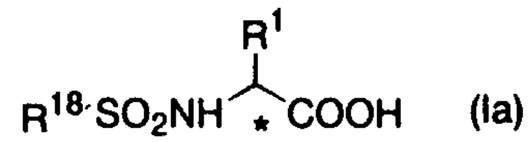
Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	Elemental analysis
228			R	197-199	1744,1325 1154	–
229			R	197-198	1738,1707 1328,1169	$C_{23}H_{18}F_3N_5O_4S$ Calc. C:53.38 H:3.51 F:11.01 N:13.53 S:6.20 Foun.C:53.11 H:3.55 F:10.89 N:13.66 S:6.31
230			R	190-191	1730,1597 1345,1161	$C_{22}H_{18}N_6O_6S{\cdot}0.4H_2O$ Calc. C:52.67 H:3.78 N:16.73 S:6.39 Foun.C:52.73 H:3.92 N:16.53 S:6.55
231			R	205-207	1730,1509 1236,1165	$C_{22}H_{18}FN_5O_4S{\cdot}0.2H_2O$ Calc. C:56.09 H:3.94 F:4.03 N:14.87 S:6.81 Foun.C:56.10 H:4.09 F:4.12 N:14.84 S:7.08
232			R	204-206	1730,1493 1346,1164	$C_{22}H_{18}ClN_5O_4S{\cdot}0.6H_2O$ Calc. C:53.41 H:3.91 Cl:7.17 N:14.16 S:6.48 Foun.C:53.33 H:3.90 Cl:7.22 N:14.19 S:6.68
233			R	226-227	1732,1697 1509,1373 1345,1170	$C_{23}H_{21}N_5O_4S{\cdot}1.2H_2O$ Calc. C:56.94 H:4.86 N:14.44 S:6.61 Foun.C:56.88 H:4.49 N:14.31 S:6.72
234			R	214-216	1732,1697 1345,1168	$C_{23}H_{21}N_5O_5S{\cdot}1.7H_2O$ Calc. C:54.15 H:4.82 N:13.73 S:6.29 Foun.C:54.05 H:4.35 N:13.60 S:6.77
235			R	190-192	1731,1605 1336,1160	$C_{23}H_{18}N_6O_4S{\cdot}0.8H_2O$ Calc. C:56.50 H:4.04 N:17.19 S:6.56 Foun.C:56.52 H:4.16 N:17.00 S:6.52

Table 42



(Ia)

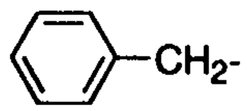
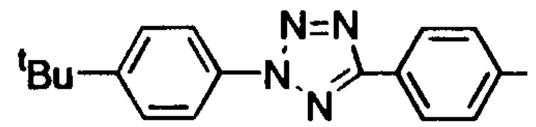
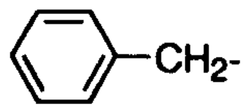
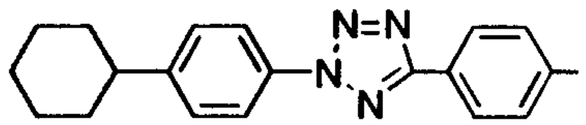
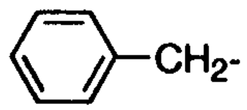
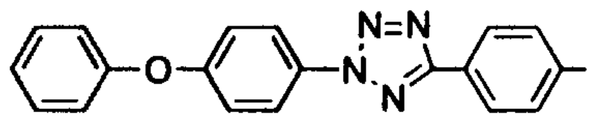
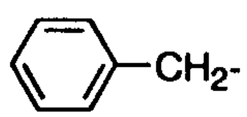
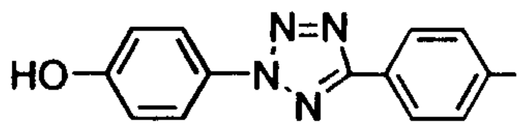
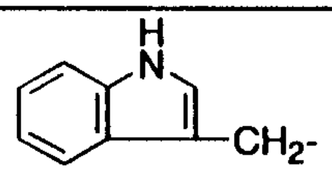
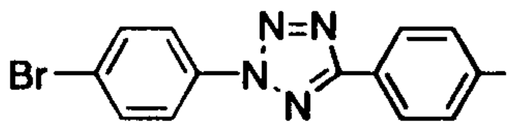
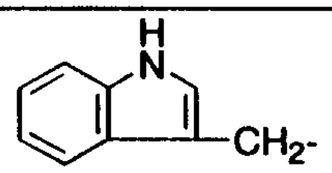
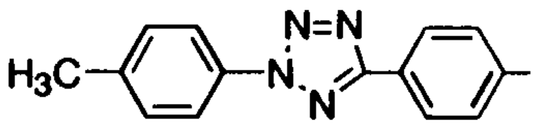
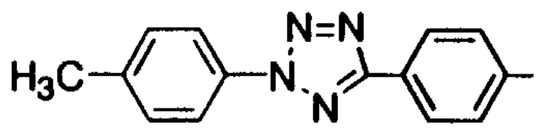
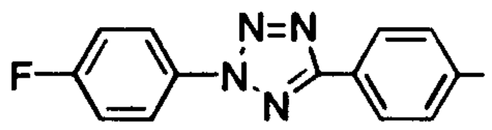
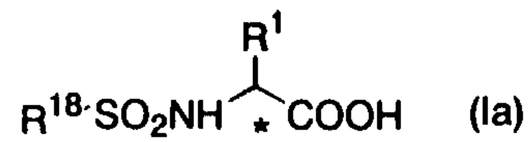
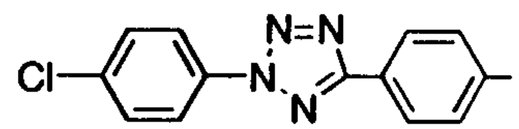
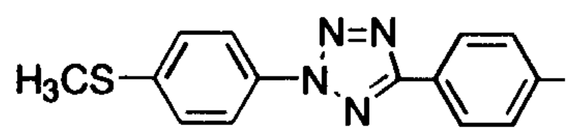
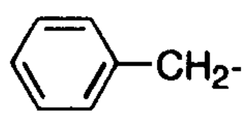
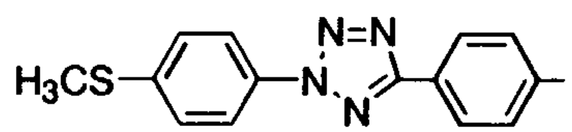
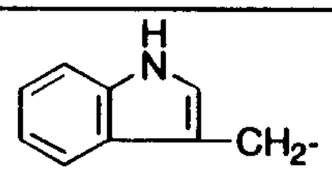
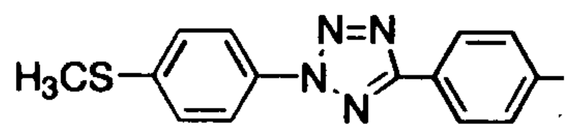
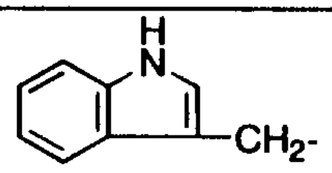
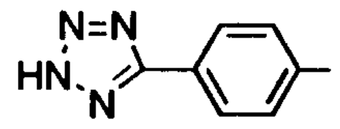
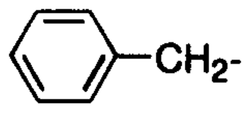
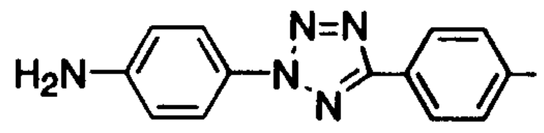
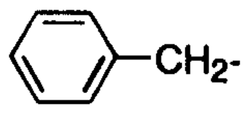
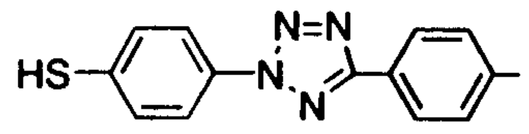
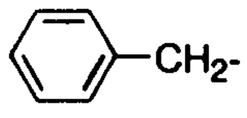
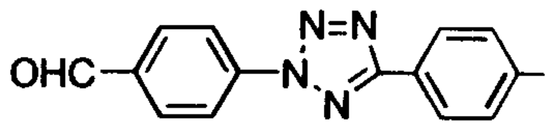
Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	Elemental analysis
236			R	224-226	1738,1328 1314,1149	$C_{26}H_{27}N_5O_4S$ Calc. C:61.77 H:5.38 N:13.85 S:6.34 Foun.C:61.59 H:5.45 N:13.89 S:6.27
237			R	225-227	1739,1512 1329,1178	$C_{28}H_{29}N_5O_4S \cdot 0.3H_2O$ Calc. C:62.62 H:5.56 N:13.04 S:5.97 Foun.C:62.46 H:5.52 N:13.43 S:6.28
238			R	182-184	1587,1506 1242,1159	—
239			R	226-228	1713,1514 1341,1159	—
240			R	205-207	1744,1716 1490,1327 1159	$C_{24}H_{19}BrN_6O_4S \cdot 1.7H_2O$ Calc. C:48.20 H:3.78 Br:13.36 N:14.05 S:5.36 Foun.C:48.27 H:3.75 Br:13.16 N:14.11 S:5.38
241			R	199-201	1718,1685 1334,1170	$C_{25}H_{22}N_6O_4S \cdot 0.6H_2O$ Calc. C:58.49 H:4.56 N:16.37 S:6.25 Foun.C:58.52 H:4.69 N:16.71 S:5.90
242	$(CH_3)_2CH$-		R	206-207	1716,1346 1165	$C_{19}H_{21}N_5O_4S \cdot 0.8H_2O$ Calc. C:53.09 H:5.30 N:16.29 S:7.46 Foun.C:53.20 H:5.14 N:16.06 S:7.70
243	$(CH_3)_2CH$-		R	208-209	1746,1726 1715,1334 1159	$C_{18}H_{18}FN_5O_4S \cdot 0.2H_2O$ Calc. C:51.11 H:4.38 F:4.49 N:16.55 S:7.58 Foun.C:50.90 H:4.37 F:4.89 N:16.28 S:7.46

Table 43



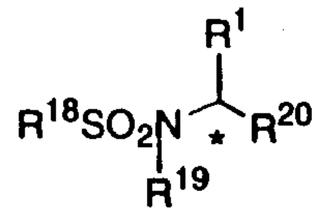
(Ia)

Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	Elemental analysis
244	$(CH_3)_2CH$-		R	223-225	1696,1348 1171	–
245	$(CH_3)_2CH$-		R	194-195	1720,1343 1166	$C_{19}H_{21}N_5O_4S_2$•1.1H_2O Calc. C:48.83 H:5.00 N:14.99 S:13.72 Foun.C:49.13 H:5.25 N:14.55 S:13.34
246			R	222-224	1753,1497 1325,1165	$C_{23}H_{21}N_5O_4S_2$•0.2H_2O Calc. C:55.34 H:4.32 N:14.03 S:12.85 Foun.C:55.37 H:4.35 N:14.00 S:12.86
247			R	213-216	1718,1677 1495,1333 1170	$C_{25}H_{22}N_6O_4S_2$•1.1H_2O Calc. C:54.16 H:4.40 N:15.16 S:11.57 Foun.C:54.20 H:4.66 N:15.09 S:11.62
248			R	>220	1698,1430 1327,1163	$C_{18}H_{16}N_6O_4S$•0.4H_2O Calc. C:51.52 H:4.04 N:20.03 S:7.64 Foun.C:51.34 H:3.96 N:19.76 S:8.02
249			R	–	–	–
250			R	–	–	–
251			R	–	–	–

Example 252 - 266

The compounds which were shown in Tables 44 to 45 were synthesized in a manner similar to those described in Example 157.

Table 44



(I)

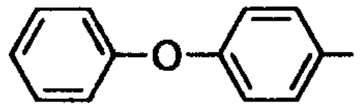
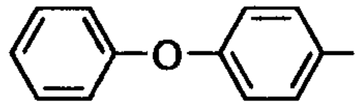
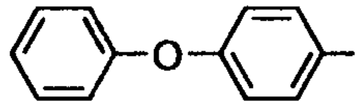
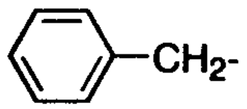
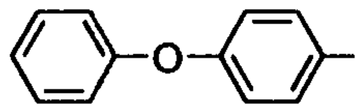
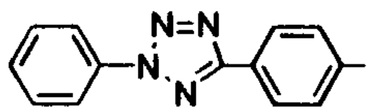
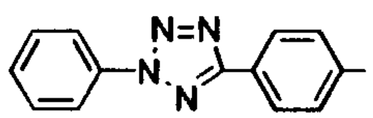
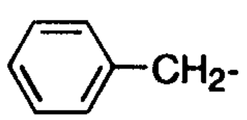
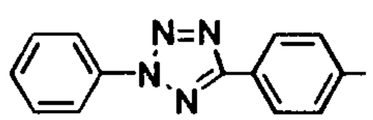
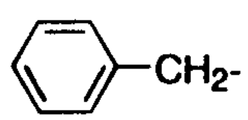
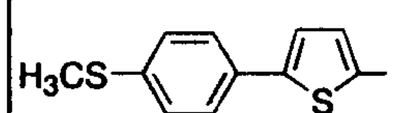
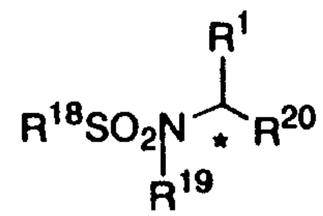
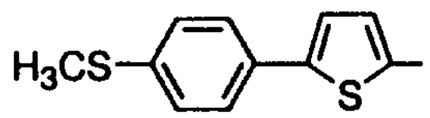
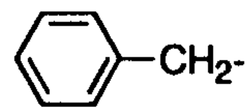
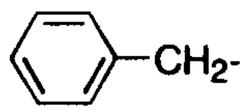
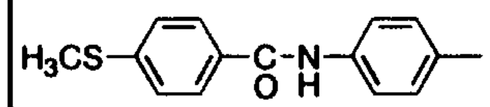
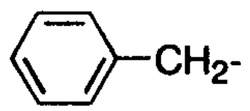
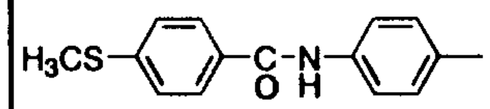
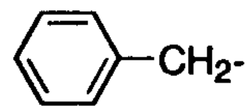
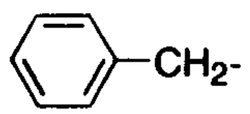
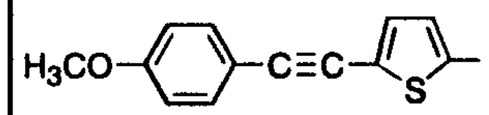
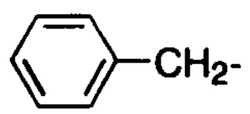
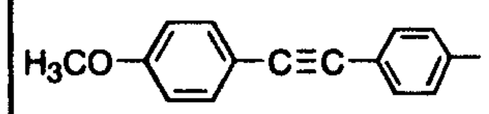
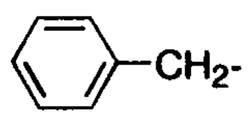
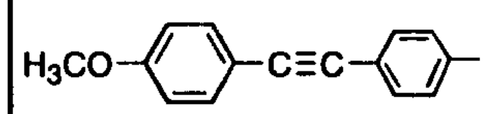
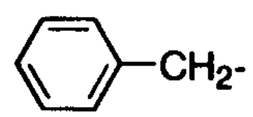
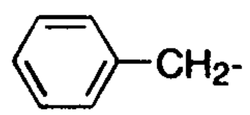
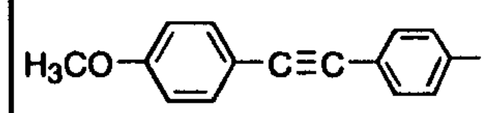
Example No.	R^1	R^{18}	R^{19}	R^{20}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	^{1}H-NMR(δ ppm) d_6-DMSO
252	$(CH_3)_2CH$-		-CH_3	-COOH	R	–	1715,1583 1340,1151	0.96(d,J=6.6Hz,3H) 1.01(d,6.8Hz,3H) 2.87(s,3H) 4.17(d,J=10.4Hz,1H)
253	$(CH_3)_2CH$-		-CH_3	-CONHOH	R	110-111	3323,1678 1328,1150	0.71(d,J=6.6Hz,3H) 0.88(d,6.4Hz,3H) 2.88(s,3H) 3.48(d,J=10.8Hz,1H)
254	$(CH_3)_2CH$-			-CONHOH	R	148-150	3344,1684 1323,1149	0.55(d,J=6.8Hz,3H) 0.82(d,6.6Hz,3H) 3.74(s,3H)
255	$(CH_3)_2CH$-		-$(CH_2)_4NH_2$	-COOH	R	–	3700-2200br 1681,1319 1212	0.91(d,J=5.6Hz,6H) 1.52-1.69(m,4H) 3.84(d,J=10.4Hz,1H)
256	$(CH_3)_2CH$-		-CH_3	-COOH	R	206-207	3300-2400br 1711,1336 1185	0.95(d,J=6.6Hz,3H) 0.97(d,6.8Hz,3H) 2.89(s,3H) 4.20(d,J=10.6Hz,1H)
257	$(CH_3)_2CHCH_2$-		-CH_3	-COOH	R	132-132.5	3300-2400br 1719,1340 1153	0.92(d,J=6.6Hz,3H) 0.97(d,6.6Hz,3H) 2.84(s,3H) 4.73(t,J=7.4Hz,1H)
258				-COOH	R	–	3640-2400br 1736,1717 1694,1346 1162	2.78(d.d,J=13.8,7.2Hz,1H) 3.14(d.d,J=14.8,7.4Hz,1H) 4.43(d,J=16.4Hz,1H) 4.68(d,J=16.4Hz,1H)
259	$(CH_3)_2CH$-		-CH_3	-COOH	R	141-144	3284br,1745 1714,1323 1131	0.96(d,J=6.4Hz,3H) 0.97(d,J=6.4Hz,3H) 2.52(s,3H),2.93(s,3H)

Table 45



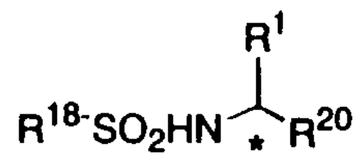
(I)

Example No.	R^1	R^{18}	R^{19}	R^{20}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	^{1}H-NMR(δ ppm) d_6-DMSO
260	$(CH_3)_2CH$-			-COOH	R	–	3600-2400br 1718,1344 1151	0.72(d,J=6.4Hz,3H)0.85(d,J=6.4Hz,3H)2.47(s,3),4.15(d,J=10.2Hz,1H)4.51(d,J=15.5Hz,1H)4.73(d,J=15.5Hz,1H)
261			-CH_3	-COOH	R	–	3600-2400br 1719,1655 1592,1320 1154	2.54(s,3H),2.78(s,3H) 2.85(d.d,J=14.0,9.4Hz,1H) 3.16(d.d,J=14.0,6.0Hz,1H) 4.76(d.d,J=10.0,5.8Hz,1H)
262				-COOH	R	–	–	–
263			-$(CH_2)_4NH_2$	-COOH	R	–	–	–
264			-CH_3	-COOH	R	–	–	–
265				-COOH	R	–	–	–
266			-$(CH_2)_4NH_2$	-COOH	R	–	–	–

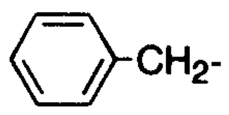
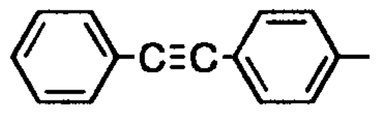
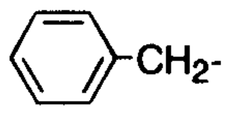
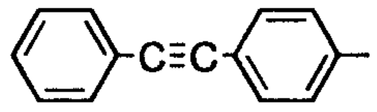
Example 267

The compounds which were shown in Tables 46 were synthesized in a manner similar to those described in Example 92.

Table 46



(I)

Example No.	R^1	R^{18}	R^{20}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	^{1}H-NMR(δ ppm) d_6-DMSO
267			−CONHOH	R	156-158	3700-2400br,3267, 2217,1671,1321,1161	2.62(dd,J=8.4,13.5Hz,1H), 2.80(dd, J=6.0,13.5Hz,1H),3.82(ddd,J=6.0, 8.4,8.7Hz,1H),8.38(d,J=8.7Hz,1H)
267			−COOH	R	176-178	2200-3700br,3430, 3292,1728,1324,1162	2.73(dd,J=9.3,13.6Hz,1H),2.96(dd, J=5.4,13.5Hz,1H),3.92(dt,J=5.4, 9.3Hz,1H),8.42(d,J=9.3Hz,1H)

Test examples on the compounds of the present invention are described below. The test compounds are the ones described in the Examples and Tables.

Test example

(1) Isolation and purification of MMP-9 (92 kDa, gelatinase B)

Type IV collagenase (MMP-9) was purified according to the methods descrived in the following literature. Scott M. Wilhelm et al., J. Biol. Chem., 264, 17213-17221, (1989), SV40-transformed Human Lung Fibroblasts Secrete a 92-kDa Type IV Collagenase Which Is Identical to That Secreted by Normal Human Macrophages; Yasunori Okada et al., J. Biol. Chem., 267, 21712-21719, (1992), Matrix Metalloproteinase 9 (92-kDa Gelatinase / Type IV Collagenase) from HT 1080 Human Fibrosarcoma Cells; Robin V. Ward et al., Biochem. J., (1991) 278, 179-187, The purification of tissue inhibitor of metalloproteinase-2 from its 72 kDa progelatinase complex.

MMP-9 is secreted from human fibrosarcoma cell line ATCC HT 1080, into its culture medium when it is stimulated with 12-tetradecanoylphorbol-13-acetate (TPA). The production of MMP-9 in this culture was verified by the gelatin zymography as described in the following literature (Hidekazu Tanaka et al., (1993) Biochem. Biophys. Res. Commun., 190, 732-740, Molecular cloning and manifestation of mouse 105-kDa gelatinase cDNA). The condition medium of the stimulated HT 1080 was concentrated and was purified with gelatin-Sepharose 4B, concanavalin A-sepharose, and Sephacryl S-200. The purified pro-MMP-9 (92 kDa, gelatinase B) thus obtained gave a single positive band in the gelatin zymography. Subsequently, activated MMP-9 was obtained by treating the pro-MMP-9 with trypsin.

(2) Assay methods of type IV collagenase inhibitors

Collagenase assay was performed using the activated MMP-9 described above and the substrate supplied in the type IV collagenase activity kit (YAGAI, inc.), according to the manufacturer's protocol. The following 4 assays are performed per compound (inhibitor).

(A) substrate (type IV collagenase), enzyme (MMP-9), inhibitor

(B) substrate (type IV collagenase), inhibitor

(C) substrate (type IV collagenase), enzyme (MMP-9)

(D) substrate (type IV collagenase)

According to the manufacturer's protocol, fluorescent intensity was measured and percent inhibition was determined by the following equation.

Inhibition (%) = {1 - (A - B) / (C - D)} x 100

IC_{50} is a concentration at which the percent inhibition reaches 50 %. The results are shown in Tables 47 to 54.

Table 47

Example No.	Compound No.	IC_{50} (μM)	Compound No.	IC_{50} (μM)
1	1a-1-1	0. 24	1b-1-1	0. 030
2	1a-1-2	2. 6	1b-1-2	0. 04
3	1a-1-3	0. 18	1b-1-3	0. 005
4	1a-1-4	2. 25		
5	1a-1-5	0. 81	1b-1-5	0. 041
6	1a-1-6	0. 68	1b-1-6	0. 034
7			1b-1-7	0. 028
8	1a-1-8	2. 0	1b-1-8	2. 0
9			1b-1-9	0. 41
10			1b-1-10	2. 1
11			1b-1-11	1. 7
12			1b-1-12	0. 085
13			1b-1-13	0. 38
14	1a-1-14	3. 7	1b-1-14	0. 11
15			1b-1-15	0. 027
16	1a-1-16	0. 520	1b-1-16	0. 0108
17	1a-1-17	0. 205	1b-1-17	0. 0203
18	1a-1-18	0. 500	1b-1-18	0. 0282
20			1b-1-20	0. 134
21	1a-1-21	4. 65	1b-1-21	0. 0041
23			1b-1-23	0. 073
24			1b-1-24	0. 2
26			1b-1-26	1. 3
27			1b-1-27	3. 0
30	1a-1-30	1. 16	1b-1-30	0. 213
31			1b-1-31	0. 0129

Table 48

Example No.	Compound No.	IC_{50} (μM)	Compound No.	IC_{50} (μM)
33	1a-1-33	0.24	1b-1-33	0.005
35	1a-1-35	2.6	1b-1-35	0.0216
38	1a-1-38	0.018		
40	1a-1-40	0.076		
41	1a-1-41	0.312		
42	1a-1-42	0.0123		
43	1a-1-43	0.625		
44	1a-1-44	1.910		
45	1a-1-45	0.040		
46	1a-1-46	1.12		
47	1a-1-47	0.389		
48	1a-1-48	1.15		
49	1a-1-49	0.249		
50	1a-1-50	0.553		
51	1a-1-51	0.110		
52	1a-1-52	0.329		
53	1a-1-53	1.8		
54	1a-1-54	0.075		
55	1a-1-55	0.0398		
60	1a-1-60	1.31	1b-1-60	0.0012
61	1a-1-61	0.247	1b-1-61	0.247
62			1b-1-62	3.50
63	1a-1-63	1.05	1b-1-63	0.00039
64	1a-1-64	1.90	1b-1-64	0.0037
65	1a-1-65	0.291	1b-1-65	0.0035

Table 49

Example No.	Compound No.	IC_{50} (μM)	Compound No.	IC_{50} (μM)
67	1a-1-67		1b-1-67	0.0061
68	1a-1-68	0.231		
80	1a-1-80	1.91		
83	1a-1-83	1.77		
85	1a-1-85	1.2	1b-1-85	0.013
86	1a-1-86	0.35	1b-1-86	0.0053
87			1b-1-87	0.940
93	1a-2-2	0.237		
94	1a-2-3	0.0109		
95	1a-2-4	0.0759		
96	1a-2-5	0.123		
97	1a-2-6	0.088		
98	1a-2-7	0.0699		
100	1a-2-9	0.0577		
101	1a-2-10	0.023		
102	1a-2-11	0.0475		
103	1a-2-12	0.0981		
104	1a-2-13	3.28		
105	1a-2-14	2.98		
106	1a-2-15	0.133		
107	1a-2-16	0.325		
109	1a-2-18	1.19		
110	1a-2-19	0.203		
111	1a-2-20	3.41		
112	1a-2-21	3.74		
114	1a-2-23	0.929		

Table 50

Example No.	Compound No.	IC_{50} (μM)
115	1a-2-24	0.161
117	1a-2-26	1.19
118	1a-2-27	0.088
119	1a-2-28	1.11
120	1a-2-29	1.53
121	1a-2-30	0.0736
122	1a-2-31	0.224
123	1a-2-32	0.0234
124	1a-2-33	0.0218
125	1a-2-34	0.0144
126	1a-2-35	0.156
127	1a-2-36	0.0243
128	1a-2-37	0.0922
129	1a-2-38	0.222
160	1a-3-2	0.040
161	1a-3-3	0.0108
162	1a-3-4	0.873
163	1a-3-5	0.0126
164	1a-3-6	0.0965
165	1a-3-7	0.230
166	1a-3-8	1.28
167	1a-3-9	0.014
168	1a-3-10	0.0083
169	1a-3-11	0.244
170	1a-3-12	2.03
171	1a-3-13	0.0395

Table 51

Example No.	Compound No.	IC_{50} (μM)
177	1a-4-2	0.684
178	1a-4-3	0.0252
179	1a-4-4	2.36
180	1a-4-5	0.045
181	1a-4-6	0.0539
182	1a-4-7	0.0059
183	1a-4-8	0.0027
184	1a-4-9	0.00325
185	1a-4-10	0.0422
186	1a-4-11	0.0982
187	1a-4-12	0.177
188	1a-4-13	0.843
189	1a-4-14	0.0375
190	1a-4-15	0.0597
191	1a-4-16	0.0095
192	1a-4-17	0.324
193	1a-4-18	0.722
195	1a-4-20	1.1
196	1a-4-21	0.0573
197	1a-4-22	0.0161
198	1a-4-23	0.493
199	1a-4-24	2.06
200	1a-4-25	0.173
201	1a-4-26	0.252
202	1a-4-27	0.0114
203	1a-4-28	0.173

Table 52

Example No.	Compound No.	IC_{50} (μM)	Compound No.	IC_{50} (μM)
204	1a-4-29	3.95		
207	1a-4-30	4.44		
210	1a-5-2	0.024		
211	1a-5-3	0.210	1b-211	0.00565
212	1a-5-4	0.393		
213	1a-5-5	0.128		
214	1a-5-6	0.832		
215	1a-5-7	0.110		
216	1a-5-8	0.107		
218	1a-5-10	0.744		
219	1a-5-11	0.574		
220	1a-5-12	0.0167		
221	1a-5-13	0.316		
222	1a-5-14	0.078		
223	1a-5-15	0.349		
224	1a-1-16	0.0101		
225	1a-5-17	0.0122		
226	1a-5-18	0.166		
227	1a-5-19	0.0198		
228	1a-5-20	0.106		
229	1a-5-21	0.215		
230	1a-5-22	0.281		
231	1a-5-23	0.197		
232	1a-5-24	0.144		
233	1a-5-25	0.0864		
234	1a-5-26	0.153		

Table 53

Example No.	Compound No.	IC_{50} (μM)	Compound No.	IC_{50} (μM)
235	1a-5-27	0.265		
236	1a-5-28	0.304		
237	1a-5-29	1.32		
238	1a-5-30	2.85		
239	1a-5-31	0.243		
240	1a-5-32	0.0041		
241	1a-5-33	0.0131		
242	1a-5-34	0.0239		
243	1a-5-35	0.0529		
244	1a-5-36	0.0165		
245	1a-5-37	0.0059		
246	1a-5-38	0.0108		
247	1a-5-39	0.0035		
267	1a-2-66	1.5	1b-2-66	0.011

Table 54

Example No.	Compound No.	IC_{50} (μM)
252	1-252	0.24
253	1-253	0.000039
254	1-254	0.00063
255	1-255	0.529
256	1-256	0.601
257	1-257	0.776
258	1-258	0.908
259	1-259	0.130
260	1-260	0.159
261	1-260	0.182

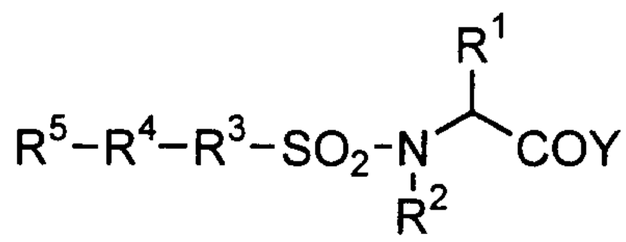
The compound of the present invention showed strong activity for inhibiting type IV collagenase.

Industrial Applicability

It is considered that the compound of the present invention is useful to prevent or treat osteoarthritis, rheumatoid arthritis, corneal ulceration, periodontal disease, metastasis and invasion of tumor, advanced virus infection (e.g., HIV), arteriosclerosis obliterans, arteriosclerotic aneurysm, atherosclerosis, restenosis, sepsis, septic shock, coronary thrombosis, aberrant angiogenesis, scleritis, multiple sclerosis, open angle glaucoma, retinopathies, proliferative retinopathy, neovascular glaucoma, pterygium, keratitis, epidermolysis bullosa, psoriasis, diabetes, nephritis, neurodegengerative disease, gingivitis, tumor growth, tumor angiogenesis, ocular tumor, angiofibroma, hemangioma, fever, hemorrhage, coagulation, cachexia, anorexia, acute infection, shock, autoimmune disease, malaria, Crohn disease, meningitis, and gastric ulcer, because the compound of the present invention has strong inhibitory activity against metalloproteinase, especially MMP.

CLAIMS

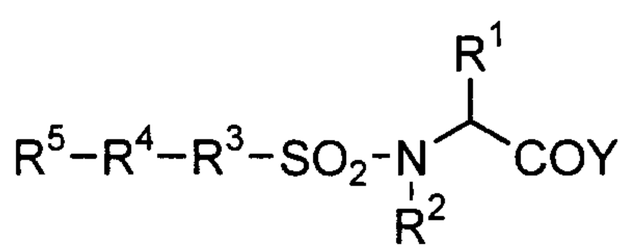
1. A composition for inhibiting metalloproteinase which contains a compound of the formula I:



I

wherein R^1 is optionally substituted lower alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, or optionally substituted heteroarylalkyl;
R^2 is hydrogen atom, optionally substituted lower alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, or optionally substituted heteroarylalkyl;
R^3 is optionally substituted arylene, or optionally substituted heteroarylene;
R^4 is a bond, -CH=CH-, or –C≡C-;
R^5 is optionally substituted C_3-C_8 cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, or an optionally substituted non-aromatic heterocyclic group; and
Y is -NHOH or -OH;
provided R^2 is hydrogen atom when Y is -NHOH,
its optically active substance, their pharmaceutically acceptable salt, or hydrate thereof, together with a pharmaceutically acceptable carrier therefor.

2. A composition for inhibiting metalloproteinase which contains a compound of the formula I:



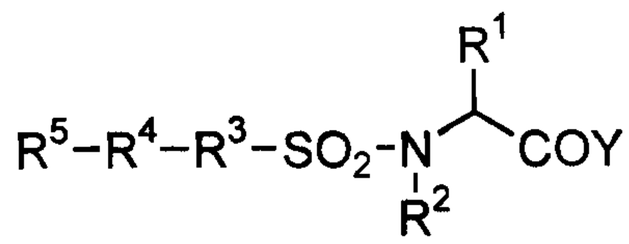
I

wherein R^1 is optionally substituted lower alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, or optionally substituted heteroarylalkyl;
R^2 is hydrogen atom, optionally substituted lower alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, or optionally substituted heteroarylalkyl;

R^3 is optionally substituted arylene, or optionally substituted heteroarylene;
R^4 is a bond, -CH=CH-, or –C≡C-;
R^5 is optionally substituted C_3-C_8 cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, or an optionally substituted non-aromatic heterocyclic group; and
Y is -NHOH or -OH;
provided R^2 is hydrogen atom when Y is -NHOH, and
R^5 is lower alkyl, aryl substituted by lower alkyl or optionally substituted aryl, or heteroaryl substituted by lower alkyl or optionally substituted aryl when R^3 is optionally substituted arylene and R^4 is a bond,
its optically active substance, their pharmaceutically acceptable salt, or hydrate thereof, together with a pharmaceutically acceptable carrier therefor.

3. A composition for inhibiting metalloproteinase of claim 1 or 2, which is a composition for inhibiting type-IV collagenase.

4. A compound of the formula I:



I

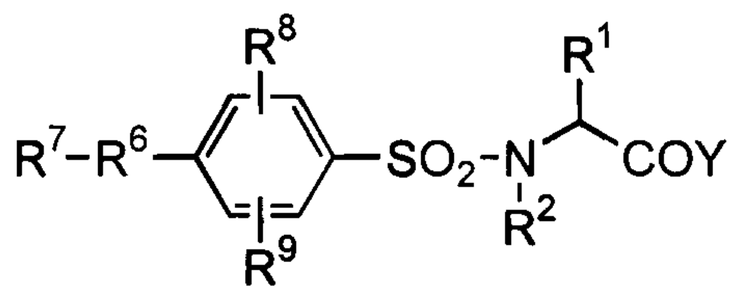
wherein R^1 is optionally substituted lower alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, or optionally substituted heteroarylalkyl;
R^2 is hydrogen atom, optionally substituted lower alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, or optionally substituted heteroarylalkyl;
R^3 is optionally substituted arylene, or optionally substituted heteroarylene;
R^4 is a bond, -CH=CH-, or –C≡C-;
R^5 is optionally substituted C_3-C_8 cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, or an optionally substituted non-aromatic heterocyclic group; and
Y is -NHOH or -OH;
provided R^2 is hydrogen atom when Y is -NHOH,
R^5 is aryl substituted with lower alkyl or optionally substituted aryl, or heteroaryl substituted with lower alkyl or optionally substituted aryl when R^3 is optionally

substituted arylene and R^4 is a bond, and

R^3 is not thiazolyl when R^4 is a bond,

its optically active substance, their pharmaceutically acceptable salt, or hydrate thereof.

5. A compound of the formula II:



II

wherein R^6 is -CH=CH- or –C≡C-;

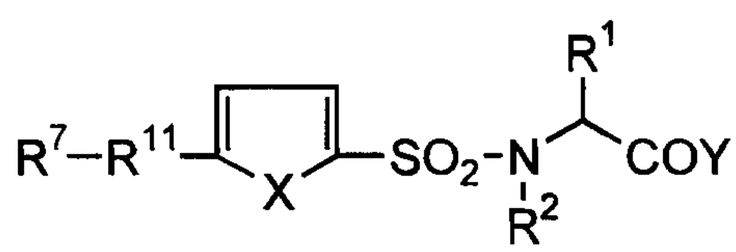
R^7 is optionally substituted aryl or optionally substituted heteroaryl;

R^8 and R^9 are each independently hydrogen atom, lower alkoxy, or nitro;

R^1, R^2, and Y are as defined in claim 4;

its optically active substance, their pharmaceutically acceptable salt, or hydrate thereof.

6. A compound of the formula IV:



IV

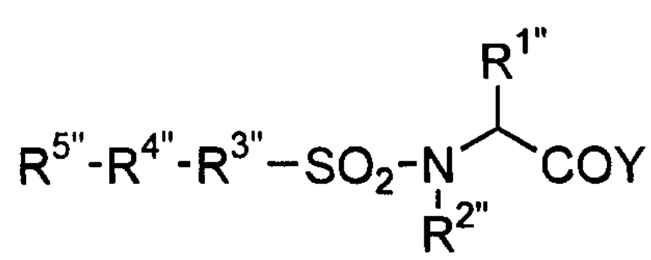
wherein R^{11} is a bond, -CH=CH-, or -C≡C-;

X is oxygen atom or sulfur atom;

R^1, R^2, and Y are as defined in claim 4 and R^7 is as defined in claim 5,

its optically active substance, their pharmaceutically acceptable salt, or hydrate thereof.

7. A compound of the formula I":

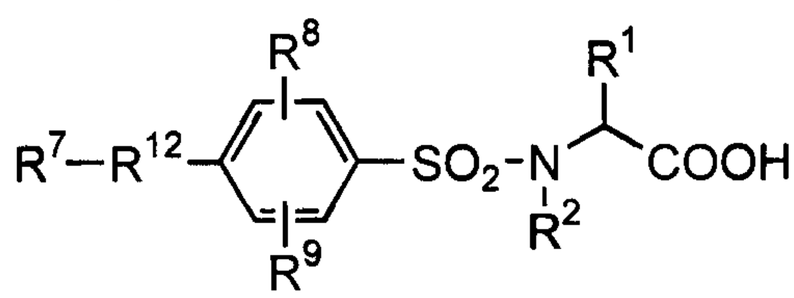


I"

wherein $R^{1"}$ is 4-thiazolylmethyl, (indol-3-yl)methyl, (5-methoxyindol-3-yl)methyl, 1-naphthylmethyl, 2-naphthylmethyl, 4-biphenylylmethyl, 2,2,2-trifluoroethyl, 2-phenylethyl, benzyl, i-propyl, 4-nitrobenzyl, 4-fluorobenzyl, cyclohexylmethyl, (1-methylindol-3-yl)methyl, (5-methylindol-3-yl)methyl, (5-fluoroindol-3-yl)methyl, (pyridin-4-yl)methyl, (benzothiazol-2-yl)methyl, (phenyl)(hydroxy)methyl, phenyl, carboxymethyl, 2-carboxyethyl, hydroxymethyl, phenylmethoxymethyl, 4-carboxybenzyl,

(benzimidazol-2-yl)methyl, (1-methylsulfonylindol-3-yl)methyl, or
(1-ethoxycarbonylindol-3-yl)methyl;
$R^{2''}$ is hydrogen atom;
$R^{3''}$ is 1,4-phenylene;
$R^{4''}$ is a bond;
$R^{5''}$ is phenyl, 3-methoxyphenyl, 4-methoxyphenyl, 4-methylphenyl, 4-tert-butylphenyl, 4-trifluoromethylphenyl, 4-fluorophenyl, 4-methylthiophenyl, 4-biphenylyl, 2-thienyl, benzoxazol-2-yl, benzothiazol-2-yl, or tetrazol-2-yl; and
Y is as defined in claim 4,
its optically active substance, their pharmaceutically acceptable salt, or hydrate thereof.

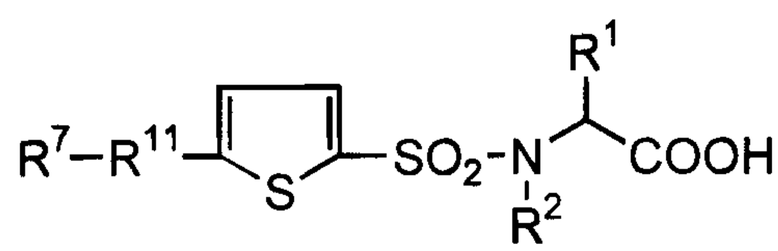
8. A compound of the formula V:



V

wherein R^{12} is -CH=CH- or -C≡C-;
R^1, and R^2 are as defined in claim 1, and R^7, R^8, and R^9 are as defined in claim 5,
its optically active substance, their pharmaceutically acceptable salt, or hydrate thereof.

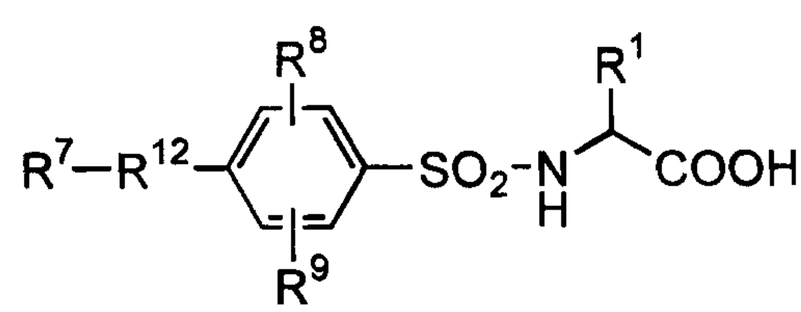
9. A compound of the formula VIII:



VIII

wherein R^1, and R^2 are as defined in claim 4, R^7 is as defined in claim 5, and R^{11} is as defined in claim 6,
its optically active substance, their pharmaceutically acceptable salt, or hydrate thereof.

10. A compound of the formula X:

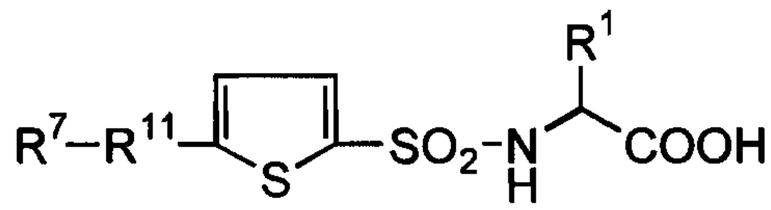


X

wherein R^{12} is -CH=CH- or -C≡C-;

R^1 is as defined in claim 4, and R^7, R^8, and R^9 are as defined in claim 5,
its optically active substance, their pharmaceutically acceptable salt, or hydrate thereof.

11. A compound of the formula XIII:



XIII

wherein R^1 is as defined in claim4, R^7 is as defined in claim 5, and R^{11} is as defined in claim 6,
its optically active substance, their pharmaceutically acceptable salt, or hydrate thereof.

12. The compound of any one of claims 4 to 6 and 8 to 11, wherein R^1 is i-propyl, benzyl, or (indole-3-yl)methyl.

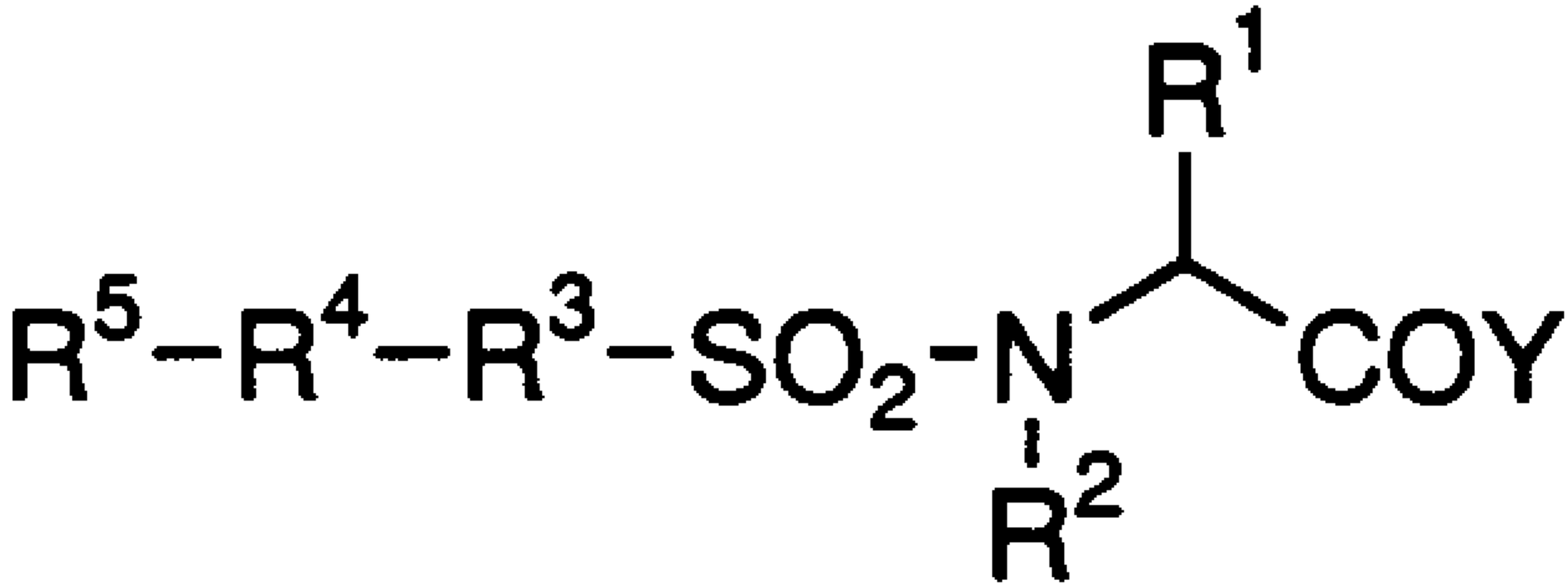
13. The compound of any one of claims 5, 6 and 8 to 11, wherein R^7 is phenyl optionally substituted with one or more substituents selected from the group consisting of alkoxy, alkylthio, and alkyl.

14. The compound of any one of claims 4 to 6 and 8 to 11, wherein the configuration of the asymmetric carbon atom bonding with R^1 has R configuration.

15. A pharmaceutical composition containing a compound of any one of claims 4 to 11, together with a pharmaceutically acceptable carrier therefor.

16. A composition for inhibiting metalloproteinase containing a compound of any one of claims 4 to 11, together with a pharmaceutically acceptable carrier therefor.

17. A composition for inhibiting type IV collagenase containing a compound of any one of claims 4 to 11, together with a pharmaceutically acceptable carrier therefor.



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