明細書

スルホン化されたアミノ酸誘導体およびそれを含有するメタロプロティナーゼ阻害剤

技術分野

本発明は、スルホン化されたアミノ酸誘導体およびそれらを含有するメタロプロテイナーゼ阻害剤に関する。

背景技術

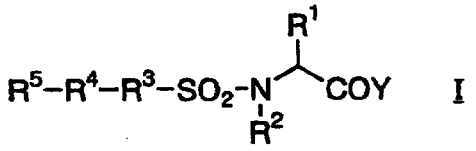
細胞外マトリックスはコラーゲン、プロテオグリカン等から構成され、組織支持機能とともに細胞の増殖、分化、接着等の細胞機能保持の役割を持つ。細胞外マトリックスの分解には、マトリックスメタロプロテイナーゼ（ＭＭＰ）であるゼラチナーゼ、ストロメリシンおよびコラゲナーゼ等が重要な役割を演じており、これらの酵素は生理学的状況下では成長および組織改革等で作動している。従って、これらの酵素は組織破壊や線維化を伴う各種病態、すなわち変形性関節症、関節リウマチ、角膜潰瘍、歯周病、腫瘍の転移または浸潤、あるいはウイルス感染症（例えば、ＨＩＶ感染症）の進行に関与すると考えられる。現在のところ、いずれの酵素が前記病態に深く関わっているかは明らかではないが、これらの酵素が組織破壊に関わっているという点では一致するところである。アミノ酸誘導体のメタロプロテイナーゼ阻害剤としては、例えば、アミノ酸のヒドロキサム酸誘導体（特開平６－２５６２９３）、アミノ酸のカルボン酸誘導体あるいはそのヒドロキサム酸誘導体（ＷＯ９５／３５２７６）等が開示されている。

発明の開示

上記のようなＭＭＰの活性を阻害し得るならば、その活性に起因または関連する前記病態の改善、あるいは進行の防止に大きく寄与すると考えられ、ＭＭＰ阻害剤の開発が望まれている。

本発明者らは以上の点に鑑み、鋭意検討を重ねた結果、ある種の新規なスルホンアミド誘導体が強いＭＭＰ阻害活性を示すことを見出した。すなわち、本発明は、

式Ⅰ：

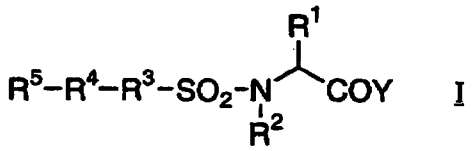


Ⅰ

［式中、R^1は置換されていてもよい低級アルキル、置換されていてもよいアリール、置換されていてもよいアラルキル、置換されていてもよいヘテロアリールまたは置換されていてもよいヘテロアリールアルキル；R^2は水素、置換されていてもよい低級アルキル、置換されていてもよいアリール、置換されていてもよいアラルキル、置換されていてもよいヘテロアリールまたは置換されていてもよいヘテロアリールアルキル；R^3は単結合、置換されていてもよいアリーレンまたは置換されていてもよいヘテロアリーレン；R^4は単結合、－（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－またはテトラゾールジイル；R^5は置換されていてもよい低級アルキル、置換されていてもよいC_3～C_8シクロアルキル、置換されていてもよいアリール、置換されていてもよいヘテロアリールまたは置換されていてもよい非芳香性複素環式基；R^Aは水素または低級アルキル；ＹはＮＨＯＨまたはＯＨ；ｍは

１または２；ただしＹがＮＨＯＨの時はR^2は水素である］で示される化合物、その光学活性体、もしくはそれらの製薬上許容される塩、またはそれらの水和物を含有するメタロプロテイナーゼ阻害剤に関する。さらに詳しくは、以下の発明ａ）～ｂ）、１）～１６）、およびＡ）～Ｃ）に関するものである。

ａ）式Ⅰ：



Ⅰ

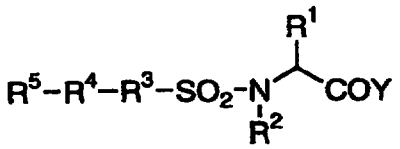
［式中、R^1は置換されていてもよい低級アルキル、置換されていてもよいアリール、置換されていてもよいアラルキル、置換されていてもよいヘテロアリールまたは置換されていてもよいヘテロアリールアルキル；R^2は水素、置換されていてもよい低級アルキル、置換されていてもよいアリール、置換されていてもよいアラルキル、置換されていてもよいヘテロアリールまたは置換されていてもよいヘテロアリールアルキル；R^3は単結合、置換されていてもよいアリーレンまたは置換されていてもよいヘテロアリーレン；R^4は単結合、－（CH_2）ｍ－、－ＣＨ＝ＣＨ－、－Ｃ≡Ｃ－、－ＣＯ－、－ＣＯ－ＮＨ－、－Ｎ＝Ｎ－、－Ｎ（R^A）－、－ＮＨ－ＣＯ－ＮＨ－、－ＮＨ－ＣＯ－、－Ｏ－、－Ｓ－、－SO_2ＮＨ－、－SO_2－ＮＨ－Ｎ＝ＣＨ－またはテトラゾールジイル；R^5は置換されていてもよい低級アルキル、置換されていてもよいC_3～C_8シクロアルキル、置換されていてもよいアリール、置換されていてもよいヘテロアリールまたは置換されていてもよい非芳香性複素環式基；R^Aは水素または低級アルキル；ＹはＮＨＯＨまたはＯＨ；ｍは１または２；ただしＹがＮＨＯＨの時はR^2は水素であり、R^3が置換されていてもよいアリーレンまたは置換されていてもよいヘテロアリーレ

ン、R^4が－CO－NH－または－NH－CO－の時、R^5は置換されていてもよいアリールまたは置換されていてもよいヘテロアリールであり、R^3が置換されていてもよいアリーレンまたは置換されていてもよいヘテロアリーレン、R^4がテトラゾールジイルの時、R^5は置換されていてもよいアリールまたは置換されていてもよいヘテロアリールであり、R^3が置換されていてもよいアリーレン、R^4が単結合の時、R^5は低級アルキル、低級アルキルもしくは置換されていてもよいアリールで置換されているアリール、または低級アルキルもしくは置換されていてもよいアリールで置換されているヘテロアリールであり、R^3およびR^4はともに単結合ではなく、R^3が置換されていてもよいアリーレンまたは置換されていてもよいヘテロアリーレンである時、R^4は－O－でない］で示される化合物、その光学活性体、もしくはそれらの製薬上許容される塩、またはそれらの水和物を含有するメタロプロテイナーゼ阻害剤。

b）ＩＶ型コラゲナーゼ阻害剤である上記のメタロプロテイナーゼ阻害剤。

本発明化合物を詳しく説明すると、以下の一般式で表わすことができる。

1）式Ⅰ：



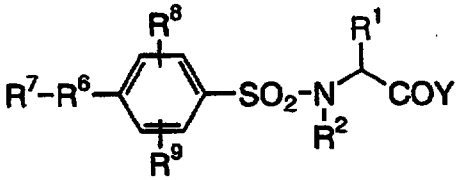
Ⅰ

［式中、R^1は置換されていてもよい低級アルキル、置換されていてもよいアリール、置換されていてもよいアラルキル、置換されていてもよいヘテロアリールまたは置換されていてもよいヘテロアリールアルキル；R^2は水素、置換されていてもよい低級アルキル、置換されていてもよいアリール、置換されていてもよいアラルキル、置換されていても

よいヘテロアリールまたは置換されていてもよいヘテロアリールアルキル；R^3は単結合、置換されていてもよいアリーレンまたは置換されていてもよいヘテロアリーレン；R^4は単結合、－（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－またはテトラゾールジイル；R^5は置換されていてもよい低級アルキル、置換されていてもよいC_3～C_8シクロアルキル、置換されていてもよいアリール、置換されていてもよいヘテロアリールまたは置換されていてもよい非芳香性複素環式基；R^Aは水素または低級アルキル；YはNHOHまたはOH；mは1または2；ただしYがNHOHの時はR^2は水素であり、R^3が置換されていてもよいアリーレンまたは置換されていてもよいヘテロアリーレン、R^4が－CO－NH－または－NH－CO－の時、R^5は置換されていてもよいアリールまたは置換されていてもよいヘテロアリールであり（R^3がフェニレン、R^4が－CO－NH－の時、R^1はメチルもしくはフェニルではなく、R^5は2－クロロフェニル、4－クロロフェニル、および2，4－ジクロロフェニルではない）、R^3が置換されていてもよいアリーレンまたは置換されていてもよいヘテロアリーレン、R^4がテトラゾールジイルの時、R^5は低級アルキル、置換されていてもよいアリール、または置換されていてもよいヘテロアリールであり、R^3が置換されていてもよいアリーレン、R^4が単結合の時、R^5は低級アルキル、低級アルキルもしくは置換されていてもよいアリールで置換されているアリール、または低級アルキルもしくは置換されていてもよいアリールで置換されているヘテロアリールであり、R^3およびR^4はともに単結合ではなく、R^3が置換されていてもよいアリーレンまたは置換されていてもよいヘテロアリーレンである時、R^4は－O－でない］で示さ

れる化合物、その光学活性体、もしくはそれらの製薬上許容される塩、またはそれらの水和物。

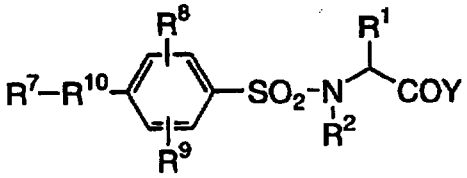
2）式II：



II

［式中、R^6は－CH＝CH－、－C≡C－、－N＝N－、－NH－CO－NH－、－S－、－SO_2NH－、または－SO_2－NH－N＝CH－；R^7は置換されていてもよいアリールまたは置換されていてもよいヘテロアリール；R^8およびR^9はそれぞれ独立して、水素、低級アルコキシ、またはニトロ；R^1、R^2およびYは前記と同意義］で示される化合物、その光学活性体、もしくはそれらの製薬上許容される塩、またはそれらの水和物。

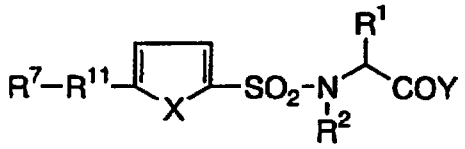
3）式III：



III

［式中、R^{10}は－（CH_2）m－、－CO－、－CO－NH－、－N（R^A）－、－NH－CO－、またはテトラゾールジイル；mは1または2；R^1、R^2、R^7、R^8、R^9、R^A、およびYは前記と同意義。ただし、R^{10}が－NH－CO－の時、R^1はメチルもしくはフェニルではなく、R^7は2－クロロフェニル、4－クロロフェニル、および2，4－ジクロロフェニルではない］で示される化合物、その光学活性体、もしくはそれらの製薬上許容される塩、またはそれらの水和物。

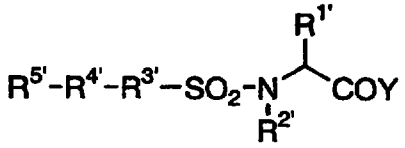
4）式IV：



IV

［式中、R^{11}は単結合、－CH＝CH－、または－C≡C－；Xは酸素原子または硫黄原子；R^1、R^2、R^7およびYは前記と同意義］で示される化合物、その光学活性体、もしくはそれらの製薬上許容される塩、またはそれらの水和物。

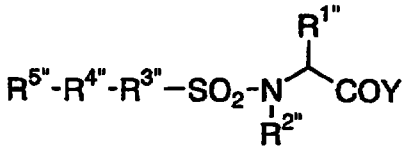
5）式I'：



I'

［式中、$R^{1'}$は、ベンジル、（インドール－3－イル）メチル、（1－メチルインドール－3－イル）メチル、（5－メチルインドール－3－イル）メチル、（5－フルオロインドール－3－イル）メチル、（1－アセチルインドール－3－イル）メチル、（1－メチルスルホニルインドール－3－イル）メチル、（1－アルコキシカルボニル－3－イル）メチル（例えば、エトキシカルボニルメチル）、またはi－プロピル；$R^{2'}$は水素原子、メチル、4－アミノブチル、またはベンジル；$R^{3'}$は1，4－フェニレン、$R^{4'}$は－O－、$R^{5'}$はフェニルまたは4－ヒドロキシフェニル；Yは前記と同意義］で示される化合物、その光学活性体、もしくはそれらの製薬上許容される塩、またはそれらの水和物。

6）式I''：



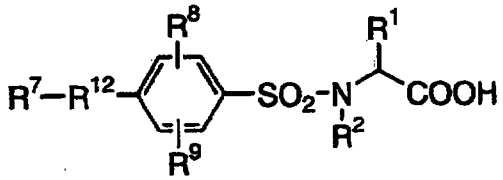
I''

［式中、$R^{1''}$は4－チアゾリルメチル、（インドール－3－イル）メ

訂正された用紙(規則91)

チル、（５－メトキシインドール－３－イル）メチル、１－ナフチルメチル、２－ナフチルメチル、４－ビフェニリルメチル、２，２，２－トリフルオロエチル、２－フェニルエチル、ベンジル、ｉ－プロピル、４－ニトロベンジル、４－フルオロベンジル、シクロヘキシルメチル、（１－メチルインドール－３－イル）メチル、（５－メチルインドール－３－イル）メチル、（５－フルオロインドール－３－イル）メチル、（ピリジン－４－イル）メチル、（ベンゾチアゾール－２－イル）メチル、（フェニル）（ヒドロキシ）メチル、フェニル、カルボキシメチル、２－カルボキシエチル、ヒドロキシメチル、フェニルメトキシメチル、４－カルボキシベンジル、（ベンゾイミダゾール－２－イル）メチル、（１－メチルスルホニルインドール－３－イル）メチル、または（１－エトキシカルボニルインドール－３－イル）メチル；$R^{2''}$は水素原子；$R^{3''}$は１，４－フェニレン；$R^{4''}$は単結合；$R^{5''}$はフェニル、３－メトキシフェニル、４－メトキシフェニル、４－メチルフェニル、４－ｔｅｒｔ－ブチルフェニル、４－トリフルオロメチルフェニル、４－フルオロフェニル、４－メチルチオフェニル、４－ビフェニル、２－チエニル、ベンゾオキサゾール－２－イル、ベンゾチアゾール－２－イル、またはテトラゾール－２－イル；Ｙは前記と同意義］で示される化合物、その光学活性体、もしくはそれらの製薬上許容される塩、またはそれらの水和物。

７）式Ⅴ：

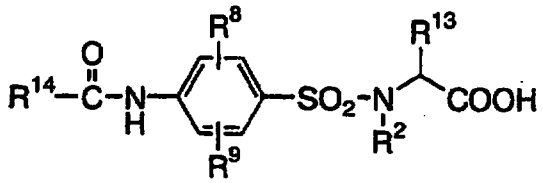


Ⅴ

［式中、R^{12}は－ＣＨ＝ＣＨ－または－Ｃ≡Ｃ－；R^{1}、R^{2}、R^{7}、R^{8}、およびR^{9}は前記と同意義］で示される化合物、その光学活性体、も

しくはそれらの製薬上許容される塩、またはそれらの水和物。

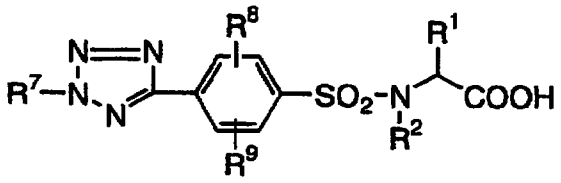
8）式VI：



VI

［式中、R^2、R^8、およびR^9は前記と同意義、R^{13}は置換されていてもよい低級アルキル、置換されていてもよいアリール、置換されていてもよいアラルキル、置換されていてもよいヘテロアリールまたは置換されていてもよいヘテロアリールアルキル、R^{14}は置換されていてもよいアリールまたは置換されていてもよいヘテロアリールを示す。ただし、R^{13}はメチルもしくはフェニルではなく、R^{14}は2－クロロフェニル、4－クロロフェニル、および2，4－ジクロロフェニルではない］で示される化合物、その光学活性体、もしくはそれらの製薬上許容される塩、またはそれらの水和物。

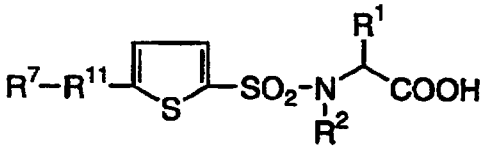
9）式VII：



VII

［式中、R^1、R^2、R^7、R^8、およびR^9は前記と同意義］で示される化合物、その光学活性体、もしくはそれらの製薬上許容される塩、またはそれらの水和物。

10）式VIII：

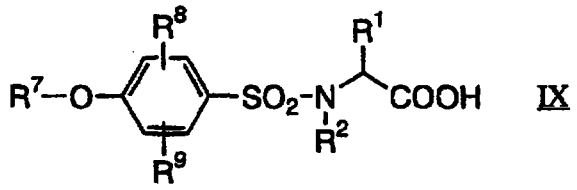


VIII

［式中、R^1、R^2、R^7、およびR^{11}は前記と同意義］で示される化合

物、その光学活性体、もしくはそれらの製薬上許容される塩、またはそれらの水和物。

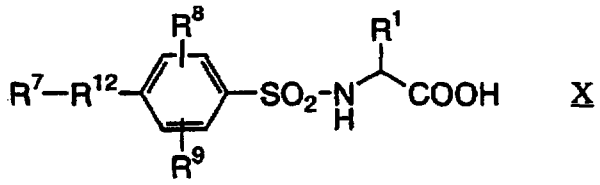
１１）式ＩＸ：



IX

［式中、R^1、R^2、R^7、R^8、およびR^9は前記と同意義］で示される化合物、その光学活性体、もしくはそれらの製薬上許容される塩、またはそれらの水和物。

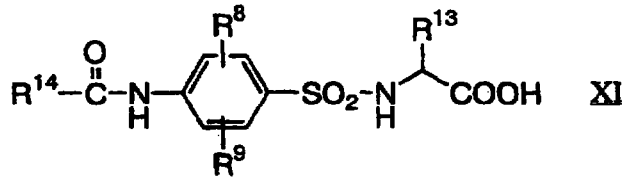
１２）式Ｘ：



X

［式中、R^{12}は－ＣＨ＝ＣＨ－または－Ｃ≡Ｃ－；R^1、R^7、R^8、およびR^9は前記と同意義］で示される化合物、その光学活性体、もしくはそれらの製薬上許容される塩、またはそれらの水和物。

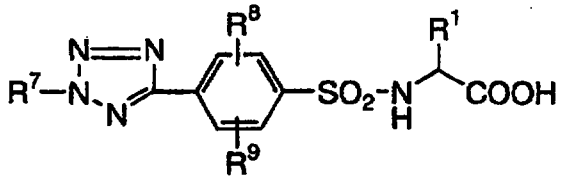
１３）式ＸＩ：



XI

［式中、R^8、R^9、R^{13}、およびR^{14}は前記と同意義。ただし、R^{13}はメチルもしくはフェニルではなく、R^{14}は２－クロロフェニル、４－クロロフェニル、および２，４－ジクロロフェニルではない］で示される化合物、その光学活性体、もしくはそれらの製薬上許容される塩、またはそれらの水和物。

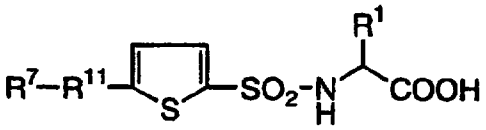
１４）式ＸＩＩ：



XII

［式中、R^1、R^7、R^8、およびR^9は前記と同意義］で示される化合物、その光学活性体、もしくはそれらの製薬上許容される塩、またはそれらの水和物。

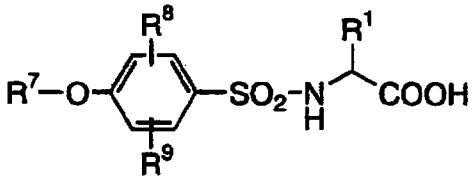
１５）式ＸＩＩＩ：



XIII

［式中、R^1、R^7、およびR^{11}は前記と同意義］で示される化合物、その光学活性体、もしくはそれらの製薬上許容される塩、またはそれらの水和物。

１６）式ＸＩＶ：



XIV

［式中、R^1、R^7、R^8、およびR^9は前記と同意義］で示される化合物、その光学活性体、もしくはそれらの製薬上許容される塩、またはそれらの水和物。

さらに本発明化合物を特定して示すと、

Ａ）R^1、$R^{1'}$、$R^{1''}$およびR^{13}がｉ－プロピル、ベンジル、または（インドール－３－イル）メチルである上記１）～１６）のいずれかに記載の化合物。

Ｂ）R^5、R^7、およびR^{14}がアルコキシ、アルキルチオ、またはアルキルで１または２以上置換されていてもよいフェニルである上記１）～

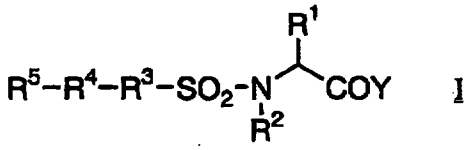
4）および7）～16）のいずれかに記載の化合物。

C）R^1、$R^{1'}$、$R^{1''}$およびR^{13}が結合している不斉炭素の配置がRである上記1）～16）記載のいずれかに記載の化合物。

さらに本発明は上記一般式1）～16）およびA）～C）に記載の化合物を含有する医薬組成物、メタロプロテイナーゼ、およびIV型コラゲナーゼに関する。

上記一般式1）～16）およびA）～C）に記載の化合物はすべて強いメタロプロテイナーゼ阻害活性を示すが、以下に示す化合物が特に好ましい。

式I：



I

1）R^1がi－プロピル、ベンジル、または（インドール－3－イル）メチル、R^2が水素原子、R^3が1，4－フェニレン、R^4が－C≡C－、R^5が置換されていてもよいフェニルで表わされる化合物。

2）R^1がi－プロピル、ベンジル、または（インドール－3－イル）メチル、R^2が水素原子、R^3が置換されていてもよい2，5－チオフェンジイル、R^4が－C≡C－、R^5が置換されていてもよいフェニルで表わされる化合物。

3）i－プロピル、ベンジル、または（インドール－3－イル）メチル、R^2が水素原子、R^3が1，4－フェニレン、R^4がテトラゾールジイル、R^5が置換されていてもよいフェニルで表わされる化合物。

本明細書中、「アルキル」とは直鎖状または分岐状のC_1～C_{10}のアルキルを意味し、例えば、メチル、エチル、n－プロピル、i－プロピル、n－ブチル、i－ブチル、sec－ブチル、tert－ブチル、n

ーペンチル、ｉーペンチル、ｎｅｏーペンチル、ｔｅｒｔーペンチル等が挙げられる。

本明細書中、「低級アルキル」とは、直鎖状または分枝状のC_1～C_6アルキルを意味し、例えば、メチル、エチル、ｎープロピル、ｉープロピル、ｎーブチル、ｉーブチル、ｓｅｃーブチル、ｔｅｒｔーブチル等が挙げられる。

本明細書中、「C_3～C_8シクロアルキル」とは、例えば、シクロプロピル、シクロブチル、シクロペンチル、シクロヘキシル、シクロヘプチル等が挙げられる。

本明細書中、「アリール」とは、単環状もしくは縮合環状芳香族炭化水素を意味し、例えば、フェニル、ナフチル等が挙げられる。

本明細書中、「アラルキル」とは、前記アルキル基に前記アリール基が置換したもので、これらは置換可能な全ての位置で結合しうる。例えば、ベンジル、フェネチル、フェニルプロピル（例えば、3-フェニルプロピル）、ナフチルメチル（例えば、α-ナフチルメチル）、アンスリルメチル（例えば、9-アンスリルメチル）等が挙げられる。中でもベンジルが好ましい。これらのアリール部分には任意の置換基を有していてもよい。

本明細書中、「ヘテロアリール」とは、任意に選ばれる、酸素原子、硫黄原子又は窒素原子を環内に１個以上含み、かつ炭素環もしくは他の複素環と縮合していてもよい５～６員の芳香環を意味し、これらは置換可能な全ての位置で結合しうる。例えば、ピロリル（例えば、1-ピロリル）、インドリル（例えば、2-インドリル）、カルバゾリル（例えば、3-カルバゾリル）、イミダゾリル（例えば、4-イミダゾリル）、ピラゾリル（例えば、1-ピラゾリル）、ベンゾイミダゾリル（例えば、2-ベンゾイミダゾリル）、インダゾリル（例えば、3-インダゾリル）、インド

リジニル（例えば、6-インドリジニル）、ピリジル（例えば、4-ピリジル）、キノリル（例えば、5-キノリル）、イソキノリル（例えば、3-イソキノリル）、アクリジル（例えば、1-アクリジル）、フェナンスリジニル（例えば、2-フェナンスリジニル）、ピリダジニル（例えば、3-ピリダジニル）、ピリミジニル（例えば、4-ピリミジニル）、ピラジニル（例えば、2-ピラジニル）、シンノリニル（例えば、3-シンノリニル）、フタラジニル（例えば、2-フタラジニル）、キナゾリニル（例えば、2-キナゾリニル）、イソキサゾリル（例えば、3-イソキサゾリル）、ベンゾイソキサゾリル（例えば、3-ベンゾイソキサゾリル）、オキサゾリル（例えば、2-オキサゾリル）、ベンゾオキサゾリル（例えば、2-ベンゾオキサゾリル）、ベンゾオキサジアゾリル（例えば、4-ベンゾオキサジアゾリル）、イソチアゾリル（例えば、3-イソチアゾリル）、ベンゾイソチアゾリル（例えば、2-ベンゾイソチアゾリル）、チアゾリル（例えば、2-チアゾリル）、ベンゾチアゾリル（例えば、2-ベンゾチアゾリル）、フリル（例えば、3-フリル）、ベンゾフリル（例えば、3-ベンゾフリル）、チエニル（例えば、2-チエニル）、ベンゾチエニル（例えば、2-ベンゾチエニル）、テトラゾリル等が挙げられる。これらのアリール部分には任意の置換基を有していてもよい。

本明細書中、「ヘテロアリールアルキル」とは、前記アルキル基の任意の位置に前記ヘテロアリール基が置換したもので、これらは置換可能な全ての位置で結合しうる。例えば、チアゾリルメチル（例えば、4-チアゾリルメチル）、チアゾリルエチル（例えば、5-チアゾリル-2-エチル）、インドリルメチル（例えば、2-インドリルメチル）、イミダゾリルメチル（例えば、4-イミダゾリルメチル）、ベンゾチアゾリルメチル（例えば、2-ベンゾチアゾリルメチル）、ベンゾピラゾリルメチル（例えば、1-ベンゾピラゾリルメチル）、ベンゾトリアゾリルメチル、（例えば、

4-ベンゾトリアゾリルメチル）、ベンゾキノリルメチル（例えば、2-ベンゾキノリルメチル）、ベンゾイミダゾリルメチル（例えば、2-ベンゾイミダゾリルメチル）、ピリジルメチル（例えば、2-ピリジルメチル）等が挙げられる。これらのアリール部分には任意の置換基を有していてもよい。

本明細書中、「アリーレン」とは、例えば、フェニレン、ナフチレン等を意味し、さらに詳しくは、１，２－フェニレン、１，３－フェニレン、１，４－フェニレン等が挙げられる。

本明細書中、「ヘテロアリーレン」とは、例えば、チオフェンジイル、フランジイル、ピリジンジイル等を意味し、さらに詳しくは、２，５－チオフェンジイル、２，５－フランジイル等が挙げられる。

本明細書中、「非芳香性複素環式基」とは、任意に選ばれる、酸素原子、硫黄原子又は窒素原子を環内に１個以上含み、非芳香性の５～６員環を意味し、これらは置換可能な全ての位置で結合しうる。例えば、モルホリノ、ピペリジノ、ピロリジノ等を意味する。

本明細書中、「アルコキシ」とは、アルキル部分が前記アルキルであるアルコキシ、例えば、メトキシ、エトキシ、プロポキシ、ブトキシ、ペンチルオキシ等を意味する。

本明細書中、「低級アルコキシ」とは、アルキル部分が前記低級アルキルであるアルコキシ、例えば、メトキシ、エトキシ、ｎ－プロポキシ、ｉ－プロポキシ、ｎ－ブトキシ、ｉ－ブトキシ、ｓｅｃ－ブトキシ、ｔｅｒｔ－ブトキシ等を意味する。

本明細書中、「ハロゲン」とはフッ素、塩素、臭素、およびヨウ素を意味する。

本明細書中、「アルキルチオ」とは、アルキル部分が前記低級アルキルであるアルキルチオ、例えば、メチルチオ、エチルチオ等を意味する。

本明細書中、「置換されていてもよいアルキル」、「置換されていてもよいC_3～C_8シクロアルキル」、または「置換されていてもよい非芳香性複素環式基」における置換基とはヒドロキシ、アルコキシ（例えば、メトキシ、エトキシ）、メルカプト、アルキルチオ（例えば、メチルチオ）、シクロアルキル（例えば、シクロプロピル、シクロブチル、シクロペンチル、シクロヘキシル）、ハロゲン（例えば、フッ素、塩素、臭素、ヨウ素）、カルボキシ、アルコキシカルボニル（例えば、メトキシカルボニル、エトキシカルボニル）、ニトロ、シアノ、ハロアルキル（例えば、トリフルオロメチル）、置換もしくは非置換アミノ（例えば、メチルアミノ、ジメチルアミノ、カルバモイルアミノ）、グアニジノ、フェニル、ベンジルオキシ等が挙げられる。これらは、全ての可能な位置で１個以上置換しうる。

本明細書中、「置換されていてもよいアリール」、「置換されていてもよいアラルキル」、「置換されていてもよいヘテロアリール」、「置換されていてもよいヘテロアリールアルキル」、「置換されていてもよいアリーレン」、および「置換されていてもよいヘテロアリーレン」における芳香環上の置換基とは、例えば、ヒドロキシ、アルコキシ（例えば、メトキシ、エトキシ）、メルカプト、アルキルチオ（例えば、メチルチオ）、シクロアルキル（例えば、シクロプロピル、シクロブチル、シクロペンチル）、ハロゲン（例えば、フッ素、塩素、臭素、ヨウ素）、カルボキシ、アルコキシカルボニル（例えば、メトキシカルボニル、エトキシカルボニル）、ニトロ、シアノ、ハロアルキル（例えば、トリフルオロメチル）、アリールオキシ（例えば、フェニルオキシ）、置換もしくは非置換アミノ（例えば、メチルアミノ、ジメチルアミノ、ジエチルアミノ、ベンジリデンアミノ）、グアニジノ、アルキル（例えば、メチル、エチル、ｎ－プロピル、ｉ－プロピル、ｎ－ブチル、ｉ－ブチル、

ｓｅｃ－ブチル、ｔｅｒｔ－ブチル、ｎ－ペンチル、ｉ－ペンチル、ｎｅｏ－ペンチル、ｔｅｒｔ－ペンチル）、アルケニル（例えば、ビニル、プロペニル）、アルキニル（例えば、エチニル、フェニルエチニル）、アルカノイル（例えば、ホルミル、アセチル、プロピオニル）、アシルオキシ（例えば、アセチルオキシ）、アシルアミノ、アルキルスルホニル（例えば、メチルスルホニル）フェニル、ベンジル、アゾ基（例えば、フェニルアゾ）、置換されていてもよいヘテロアリール（例えば、3-ピリジル）、置換されていてもよいウレイド（例えば、ウレイド、フェニルウレイド）等が挙げられる。これらは、全ての可能な位置で１個以上置換しうる。

発明を実施するための最良の形態

本発明化合物（Ｉａ）および（Ｉｂ）は、一般式（ＸＶ）で示される対応するα－アミノ酸を出発原料にして、以下に示す６種類の合成法により製造することができる。一般的にはＡ法を用いれば本発明化合物を合成することができるが、それぞれのタイプ別にＢ法～Ｆ法を用いても合成することができる。ただし、これらは化合物Ｉの製造方法の１例にすぎず、他の方法で製造された化合物Ｉも本発明の範囲に包含される。

Ａ法：化合物Ｉ全般についての合成法。

Ｂ法：R^3が置換されていてもよいアリーレンまたは置換されていてもよいヘテロアリーレン、R^4が－Ｃ≡Ｃ－、R^5が置換されていてもよいアリールまたは置換されていてもよいヘテロアリールである化合物についての合成法。

Ｃ法：R^3が置換されていてもよいアリーレンまたは置換されていてもよいヘテロアリーレン、R^4が単結合、R^5が置換されていてもよいアリールまたは置換されていてもよいヘテロアリールである化合物につい

ての合成法。

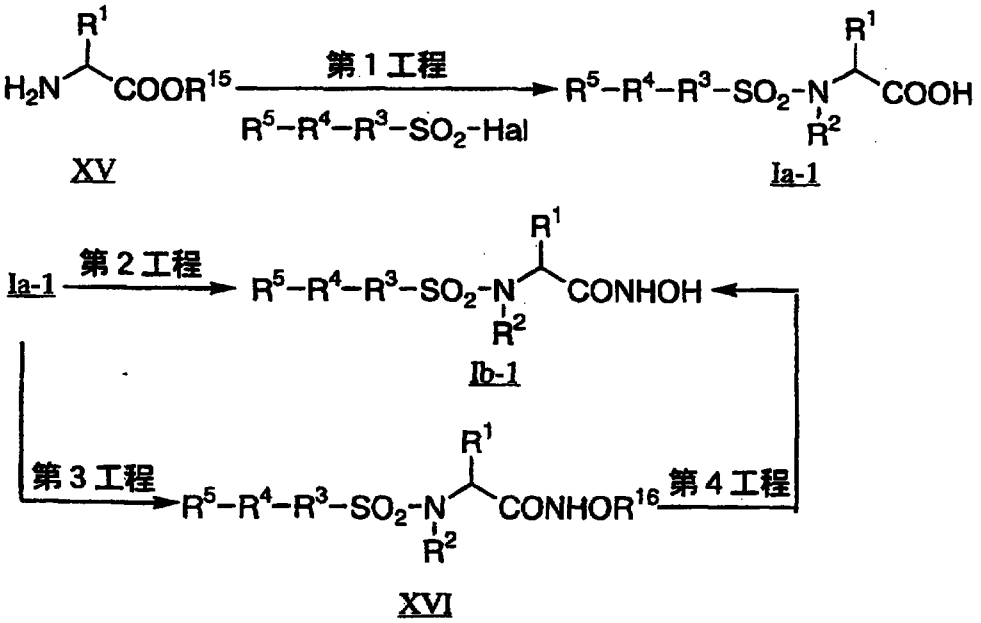
D法：R^3が置換されていてもよいアリーレンまたは置換されていてもよいヘテロアリーレン、R^4が－CO－NH－、R^5が置換されていてもよいアリールまたは置換されていてもよいヘテロアリールである化合物についての合成法。

E法：R^3が置換されていてもよいアリーレンまたは置換されていてもよいヘテロアリーレン、R^4がテトラゾールジイル、R^5が置換されていてもよいアリールまたは置換されていてもよいヘテロアリールである化合物についての合成法。

F法：R^3が置換されていてもよいアリーレンまたは置換されていてもよいヘテロアリーレン、R^4が－CH＝CH－、R^5が置換されていてもよいアリールまたは置換されていてもよいヘテロアリールである化合物についての合成法。

以下にこれらの方法について詳しく説明する。

（A法）



（式中、R^1、R^2、R^3、R^4、およびR^5は前記と同意義、R^{15}は水

素またはカルボキシ保護基を表わし、R^{16}はヒドロキシ保護基を表わし、Ｈａｌはハロゲンを表わす。）

化合物（XV）から化合物（Ia-1）への反応は、化合物（XV）のアミノ基をスルホニル化する反応（第１工程）であり、要すれば反応後、Ｎ－アルキル化等やカルボキシ保護基の除去を行う。化合物（Ia-1）から化合物（Ib-1）への反応はカルボキシル基をヒドロキサム酸化する反応（第２工程）である。また、化合物（Ia-1）から化合物（Ib-1）へは、化合物（Ia-1）にヒドロキシ保護基を有するヒドロキシルアミンまたはその酸付加塩を作用させて化合物（XVI）を得た後（第３工程）、脱保護反応（第４工程）に付してもよい。スルホニル化およびヒドロキサム酸化反応は常法に従って行なえばよい。例えば、式（XV）で示されるアミノ酸に、塩基の存在下、スルホニル化試薬、例えば、$R^5-R^4-R^3-SO_2Hal$（R^3、R^4、およびR^5は前記と同意義；Ｈａｌ＝ハロゲン）で表わされるスルホン酸ハロゲン化物等を反応させ、次いでヒドロキシルアミンを反応させる。各工程についてさらに詳しく述べれば以下の通りである。

（第１工程）

原料化合物の式（XV）で示されるアミノ酸またはその酸付加塩（例えば、塩酸塩、p-トルエンスルホン酸塩、トリフルオロ酢酸塩）の一部のものは市販品として入手できる。その他のものは実験化学講座２２巻、第４版（日本化学会編）に記載のアミノ酸合成法、 J. Med. Chem. 38, 1689-1700 (1995) Gary M. Ksander et. al.等に従って合成できる。また、スルホニル化試薬（例えば、スルホン酸ハロゲン化物）の一部のものは市販品として入手可能であり、その他のものは新実験化学講座１４巻、1787頁、(1978)、Synthesis 852-854 (1986) Tatsuo Hamada et. al.等に従って合成できる。保護されたカルボキシル基としては、例えば、エ

ステル（例えば、メチルエステル、ｔｅｒｔ－ブチルエステル、ベンジルエステル）化されたカルボキシル基が挙げられる。これらの保護基の脱離は、保護基に応じて酸（例えば、塩酸、トリフルオロ酢酸）または塩基（例えば、水酸化ナトリウム等）の存在下に加水分解するか、または接触還元（例えば、10%パラジウム-炭素触媒存在下）することによって実施されるが、化合物（Ib-1）を得るためには、エステルのまま第２工程のヒドロキサム酸化を行なってもよい。スルホニル化反応の溶媒としては、化合物（XV）においてＲ^{15}が水素であるアミノ酸の場合には、ジメチルホルムアミド、テトラヒドロフラン、ジオキサン、ジメチルスルホキシド、アセトニトリル、水またはそれら混合溶媒が好ましいが、Ｒ^{15}が保護基であるエステル体の場合には、この他に水不溶性溶媒（例えば、ベンゼン、ジクロロメタン）と上記溶媒との混合溶媒が挙げられる。スルホニル化反応に用いられる塩基は、トリエチルアミン、Ｎ－メチルモルホリン等の有機塩基、または水酸化ナトリウム、水酸化カリウム、炭酸カリウム等の無機塩基等である。反応温度は通常、氷冷～室温である。尚、化合物（Ia-1）におけるＲ^{1}、Ｒ^{3}、Ｒ^{4}、Ｒ^{5}またはＲ^{15}がスルホニル化に障害となる置換基（例えば、ヒドロキシ、メルカプト、アミノ、グアニジノ）を有する基である場合には、Protective Groups in Organic Synthesis, Theodora W Green (John Wiley & Sons) 等に記載の方法で予め保護し、望ましい段階でその保護基を除去すればよい。また、Ｒ^{2}が水素でない場合は、さらにジメチルホルムアミド、テトラヒドロフラン、ジオキサン等の溶媒中、氷冷下～８０℃、好ましくは氷冷下～室温でハロゲン化アルキル（例えば、ヨウ化メチル、ヨウ化エチル等）やハロゲン化アラルキル（例えば、ベンジルクロリド、ベンジルブロミド等）等を加え、３～３０時間、好ましくは１０～２０時間攪拌することにより目的のＮ－Ｒ^{2}体を得ることができる。

（第２工程）

ヒドロキサム酸（Ib-1）は、ヒドロキシルアミンを化合物（Ia-1）またはその反応性誘導体に作用させることによって製造されるが、ヒドロキシルアミンは通常、その酸付加塩（例えば、塩酸塩、リン酸塩、硫酸塩：市販品として入手可能）を塩基の存在下で反応に使用する。塩基としては、トリエチルアミン、N,N－ジメチルアニリン、N－メチルモルホリン等の有機塩基、または水酸化ナトリウム、水酸化カリウム、炭酸カリウム等の無機塩基が挙げられる。化合物（Ia-1）をそのままヒドロキサム酸化の原料として使用するときには、ペプチド縮合試薬（例えば、ジシクロヘキシルカルボジイミド、１－エチル－３－（３－ジメチルアミノプロピル）カルボジイミド、N,N'－カルボニルジイミダゾールまたはそれらのいずれかと１－ヒドロキシベンゾトリアゾール、N－ヒドロキシコハク酸イミド等との混合物）等の存在下に反応を行う。溶媒としては、ジメチルホルムアミド、テトラヒドロフラン、ジオキサン、ジメチルスルホキシド、アセトニトリル、水またはそれら混合溶媒が用いられ、反応温度は、－２０℃～４０℃、好ましくは氷冷～室温で、反応時間は１時間～１６時間である。

化合物（Ia-1）の反応性誘導体としては、酸無水物（特に、混合酸無水物）、酸ハロゲン化物、酸アジドまたはエステルを使用する。これらの反応性誘導体は通常の方法で製造されるが、酸無水物は、例えば、化合物（Ia-1）に塩基（例えば、トリエチルアミン）の存在下に酸ハロゲン化物（例えば、クロロ炭酸エチル）を作用させ、酸ハロゲン化物は、例えば、化合物（Ia-1）にハロゲン化試薬（例えば、オキサリルクロリド、チオニルクロリド）を作用させて製造できる。

また、エステルは非活性エステルもしくは活性エステルから選択することができるが、非活性エステルは第１工程で化合物（XV）においてR[1]

^{5}がカルボキシ保護基（例えば、メチル、ｔｅｒｔ－ブチル、ベンジル）であるものを、スルホニル化した生成物を脱保護せずそのまま使用すればよく、活性エステルは化合物（Ia-1）にカルボジイミド（例えば、ジシクロヘキシルカルボジイミド、１－エチル－３－（３－ジメチルアミノプロピル）カルボジイミド）と１－ヒドロキシベンゾトリアゾールまたはＮ－ヒドロキシコハク酸イミド等活性エステル残基に対応するヒドロキシ体とを作用させて製造できる。化合物（Ia-1）の反応性誘導体のヒドロキサム酸化の反応条件は、化合物（Ia-1）をそのまま用いるときのヒドロキサム酸化と同一でよい。なお、第１工程および第２工程の反応は単一反応槽（いわゆるワンポット）で行なってもよい。

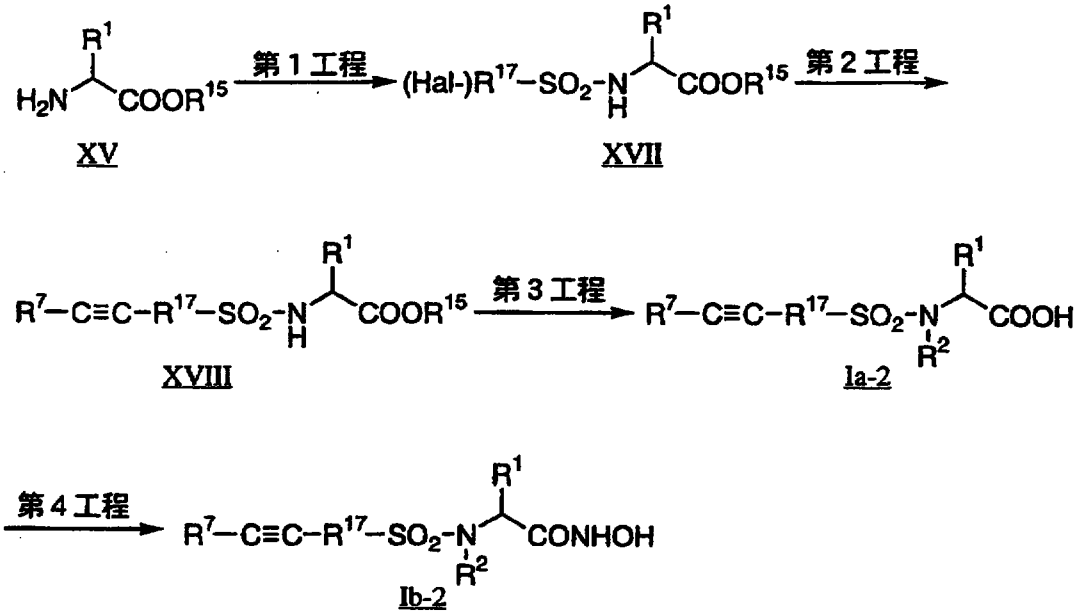
（第３工程）

本工程で使用される保護されたヒドロキシルアミンとしては、例えば、O-ベンジルヒドロキシルアミン、O-(p-メトキシベンジル)ヒドロキシルアミン、O-(tert-ブチル)ヒドロキシルアミン等が挙げられる。反応条件は第２工程における反応条件と同じでよい。

（第４工程）

本工程では水素雰囲気下での接触還元、あるいは濃塩酸またはトリフルオロ酢酸との処理によって保護基を除去し、目的の式（Ib-1）で示される化合物に導く。このように製造された本発明化合物（Ia-1）および（Ib-1）は公知の分離、精製手段（例えば、クロマトグラフィー、結晶化法等）により単離精製することができる。

（Ｂ法）



（式中、R^1、R^2、R^7、R^{15}、およびＨａｌは前記と同意義、R^{17}は置換されていてもよいアリールまたは置換されていてもよいヘテロアリールを表わす。）

化合物（XV）から化合物（XVII）への反応は、化合物（XV）のアミノ基をスルホニル化する反応（第１工程）であり、Ａ法第１工程と同様に行うことができる。化合物（XVII）から化合物（XVIII）への反応は、R^{17}のハロゲン置換基を足がかりにしてヘック（Ｈｅｃｋ）反応（K. Sonogashira, Y. Tohda, and N. Hagihara, Tetrahedron Lett., 4467(1975)等に記載）を用いて三重結合を導入する反応（第２工程）である。化合物（XVIII）から化合物（Ia-2）への反応は、化合物（XVIII）のＮ－アルキル化等やカルボキシ保護基の除去を行う反応（第３工程）であり、Ａ法第１工程と同様に行うことができる。化合物（Ia-2）から化合物（Ib-2）への反応はカルボン酸誘導体をヒドロキサム酸誘導体に変換する反応（第４工程）であり、Ａ法第２～第４工程と同様に行うことができる。各工程についてさらに詳しく述べれば以下の通りである。

（第１工程）

A法第１工程と同様に行うことができる。

（第２工程）

化合物（XVII）をジメチルホルムアミド、トルエン、キシレン、ベンゼン、テトラヒドロフラン等の溶媒中、パラジウム触媒（例えば、$Pd(Ph_3P)_2Cl_2$等）、２価の銅試薬（例えば、CuI等）、有機塩基（例えば、トリエチルアミン、ジイソプロピルエチルアミン等）の存在下、エチニルベンゼン等のエチニル基を有する、置換されていてもよいアリールまたは置換されていてもよいヘテロアリール誘導体を反応させることにより（Heck反応）、目的とする化合物（XVIII）へと変換することができる。反応温度は、室温～１００℃、好ましくは室温～８０℃、反応時間は、３～３０時間、好ましくは１０～２０時間である。置換されていてもよいアリールまたは置換されていてもよいヘテロアリール誘導体が本反応の障害となる置換基を有する場合には、Protective Groups in Organic Synthesis, Theodora W Green (John Wiley & Sons) 等に記載の方法で予め保護し、望ましい段階でその保護基を除去すればよい。

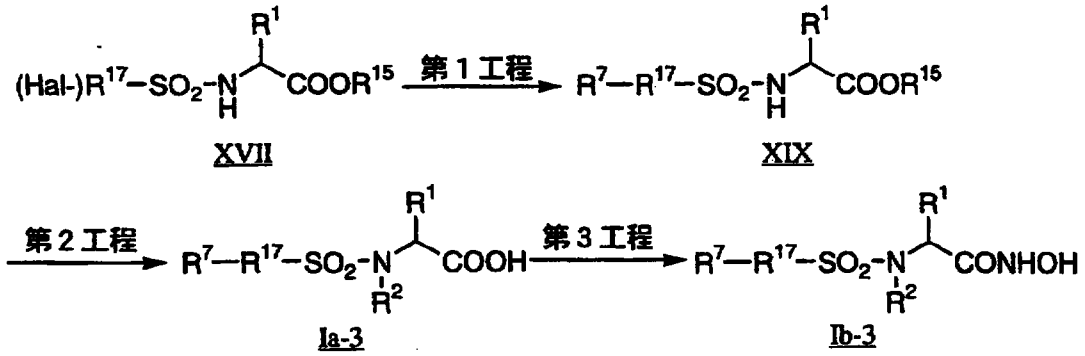
（第３工程）

A法第１工程と同様に行うことができる。

（第４工程）

A法第２～第４工程と同様に行うことができる。

（C法）



（式中、R^1、R^2、R^7、R^{15}、R^{17}、およびHａｌは前記と同意義。）

化合物（XVII）から化合物（XIX）への反応は、R^{17}のハロゲン置換基を足がかりにして鈴木反応（M.J. Sharp and V. Snieckus, Tetrahedron Lett. 26, 5997（1985）等に記載）を用いてアリールまたはヘテロアリールを導入する反応（第１工程）である。化合物（XIX）から化合物（Ia-3）への反応は、化合物（XIX）のＮ－アルキル化等やカルボキシ保護基の除去を行う反応（第２工程）であり、Ａ法第１工程と同様に行うことができる。化合物（Ia-3）から化合物（Ib-3）への反応はカルボン酸誘導体をヒドロキサム酸誘導体に変換する反応（第３工程）であり、Ａ法第２～第４工程と同様に行うことができる。各工程についてさらに詳しく述べれば以下の通りである。

（第１工程）

化合物（XVII）をジメチルホルムアミド、トルエン、キシレン、ベンゼン、テトラヒドロフラン等の溶媒中、パラジウム触媒（例えば、$Pd(Ph_3P)_4$等）、塩基（例えば、炭酸カリウム、炭酸カルシウム、トリエチルアミン、ナトリウムメトキシド等）の存在下、フェニルボロン酸等の $B(OH)_2$（他に $B(Et)_2$等）基を有する、置換されていてもよいアリールまたは置換されていてもよいヘテロアリール誘導体と反応させることにより（鈴木反応）、目的とする化合物（XIX）へと変換することができる。反応温度は、室温～１００℃、好ましくは室温～８０℃、反応時間は、５～５０時間、好ましくは１５～３０時間である。置換されていてもよいアリールまたは置換されていてもよいヘテロアリール誘導体が本反応の障害となる置換基を有する場合には、Protective Groups in Organic Synthesis, Theodora W Green (John Wiley & Sons) 等に記載の方法で予め保護し、望ましい段階でその保護基を除去すればよい。

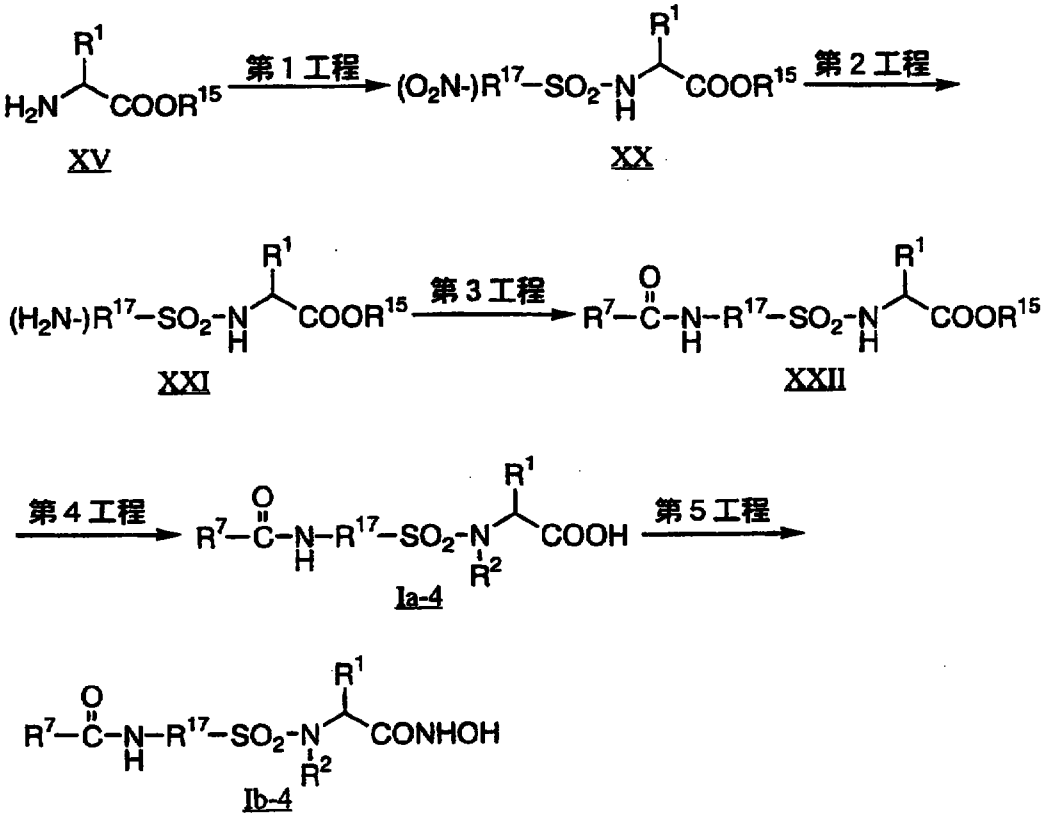
（第２工程）

A法第1工程と同様に行うことができる。

（第3工程）

A法第2～第4工程と同様に行うことができる。

（D法）



（式中、式中、R^1、R^2、R^7、R^{15}、R^{17}、およびHalは前記と同意義。）

化合物（XV）から化合物（XX）への反応は、化合物（XV）のアミノ基をスルホニル化する反応（第1工程）であり、A法第1工程と同様に行うことができる。化合物（XX）から化合物（XXI）への反応は、R^{17}のニトロ置換基をアミノ基へと還元する反応（第2工程）である。接触還元法または塩酸－鉄、塩酸－スズの反応条件等で行うことができる。化合物（XXI）から化合物（XXII）への反応は、R^{17}のアミノ基を足がかりにしてアミド結合を形成させる反応（第3工程）である。通常用い

られるアミド結合形成反応によって行うことができる。化合物（XXII）から化合物（Ia-4）への反応は、化合物（XXII）のＮ－アルキル化等やカルボキシ保護基の除去を行う反応（第４工程）であり、Ａ法第１工程と同様に行うことができる。化合物（Ia-4）から化合物（Ib-4）への反応はカルボン酸誘導体をヒドロキサム酸誘導体に変換する反応（第５工程）であり、Ａ法第２～第４工程と同様に行うことができる。各工程についてさらに詳しく述べれば以下の通りである。

（第１工程）

Ａ法第１工程と同様に行うことができる。

（第２工程）

化合物（XX）を、メタノール、エタノール、酢酸エチル,酢酸等の溶媒中、触媒（Pd-C, PtO2, Raney Ni等）の存在下、水素雰囲気下、常圧または加圧条件下で反応させることにより、目的とする化合物（XXI）を得ることができる。反応温度は、氷冷下～８０℃、好ましくは室温～５０℃、反応時間は、１～１０時間、好ましくは２～５時間である。

（第３工程）

化合物（XXI）を、ジメチルホルムアミド、テトラヒドロフラン、ジオキサン、ジメチルスルホキシド、アセトニトリル、キシレン、トルエン、ベンゼン、ジクロロメタン等の溶媒中、塩基（例えば、トリエチルアミン、Ｎ－メチルモルホリン、炭酸カリウム等）の存在下、ベンゾイルクロリド等の酸ハライド官能基（他に活性エステル等）を有する置換されていてもよいアリールまたは置換されていてもよいヘテロアリール誘導体を反応させることにより、目的とする化合物（XXII）へと変換することができる。反応温度は、氷冷下～１００℃、好ましくは室温～６０℃、反応時間は、３～３０時間、好ましくは１０～２５時間である。

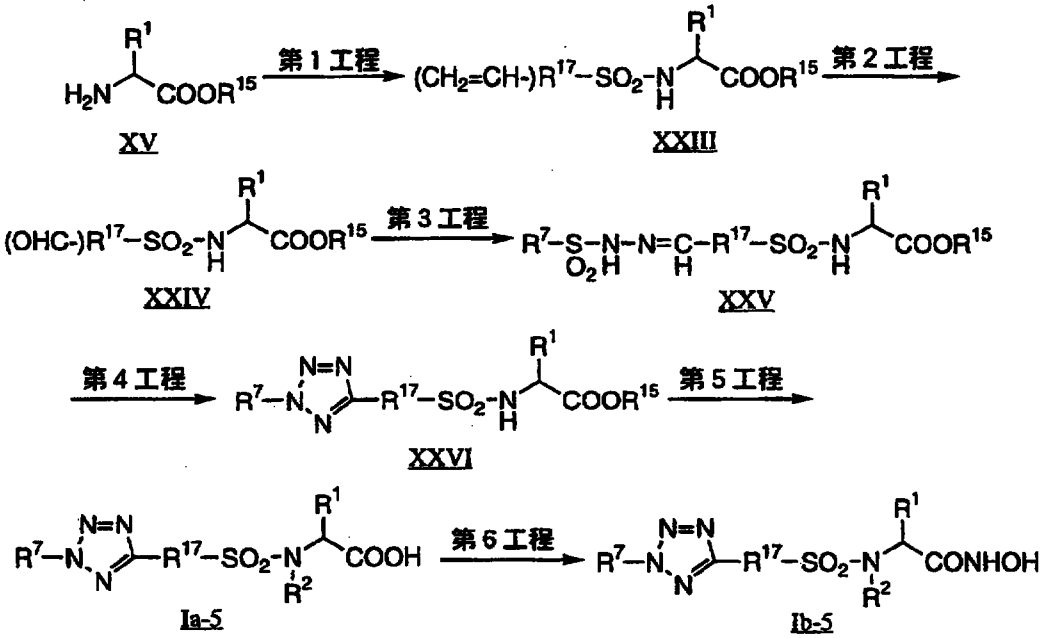
（第４工程）

A法第1工程と同様に行うことができる。

（第5工程）

A法第2～第4工程と同様に行うことができる。

（E法）



（式中、R^1、R^2、R^7、R^{15}、R^{17}、およびHa1は前記と同意義。）

化合物（XV）から化合物（XXIII）への反応は、化合物（XV）のアミノ基をスルホニル化する反応（第1工程）であり、A法第1工程と同様に行うことができる。化合物（XXIII）から化合物（XXIV）への反応は、R^{17}のエテニル置換基をアルデヒドへと変換する反応（第2工程）である。化合物（XXIV）から化合物（XXVI）への反応は、テトラゾール環を構築させる反応（第3、第4工程）である。化合物（XXVI）から化合物（Ia-5）への反応は、化合物（XXVI）のN－アルキル化等やカルボキシ保護基の除去を行う反応（第5工程）であり、A法第1工程と同様に行うことができる。化合物（Ia-5）から化合物（Ib-5）への反応はカルボン酸誘導体をヒドロキサム酸誘導体に変換する反応（第6工程）であり、A法第2～第4工程と同様に行うことができる。各工程についてさ

らに詳しく述べれば以下の通りである。

（第１工程）

Ａ法第１工程と同様に行うことができる。

（第２工程）

化合物（XXIII）をジクロロメタン、酢酸エチル、メタノール等の溶媒中、オゾンを添加することによりオゾニドを形成させ、引き続き同じ系中に亜鉛－酢酸、トリエチルホスフェート、あるいはジメチルスルフィド等を加えることにより還元的処理を行い、目的のアルデヒド誘導体（化合物（XXIV））へと変換することができる（還元的処理は接触水素添加でもよい）。反応温度は、－１００℃～室温、好ましくは－７８℃～氷冷下、反応時間は、０．５～１０時間、好ましくは１～３時間である。

（第３工程）

化合物（XXIV）を、テトラヒドロフラン、エーテル等の溶媒とメタノール、エタノール等の溶媒の混合溶媒中、ベンゼンスルホニルヒドラジドを反応させることにより目的とする化合物（XXV）へと変換することができる。反応温度は、氷冷下～８０℃、好ましくは室温～５０℃、反応時間は、３～３０時間、好ましくは１０～２０時間である。

（第４工程）

アニリン等のアミノ基を有する、置換されていてもよいアリールまたは置換されていてもよいヘテロアリール誘導体をアルコール（例えば、エタノール等）－水の混合溶媒に溶解し、系中の温度を－２０℃～１０℃、好ましくは０℃～５℃にて濃塩酸、および亜硝酸ナトリウム水溶液等のジアゾ化剤を加えて、ジアゾニウム塩に変換する。反応時間は５分～１時間、好ましくは１０～３０分である。この反応溶液を化合物（XXV）のピリジン溶液に加え、－３０℃～５０℃、好ましくは－１５℃～室温

で１～１０時間、好ましくは２～５時間反応させることにより、目的の化合物（XXVI）へと変換させることができる。置換されていてもよいアリールまたは置換されていてもよいヘテロアリール誘導体が本反応の障害となる置換基を有する場合には、Protective Groups in Organic Synthesis, Theodora W Green (John Wiley & Sons) 等に記載の方法で予め保護し、望ましい段階でその保護基を除去すればよい。

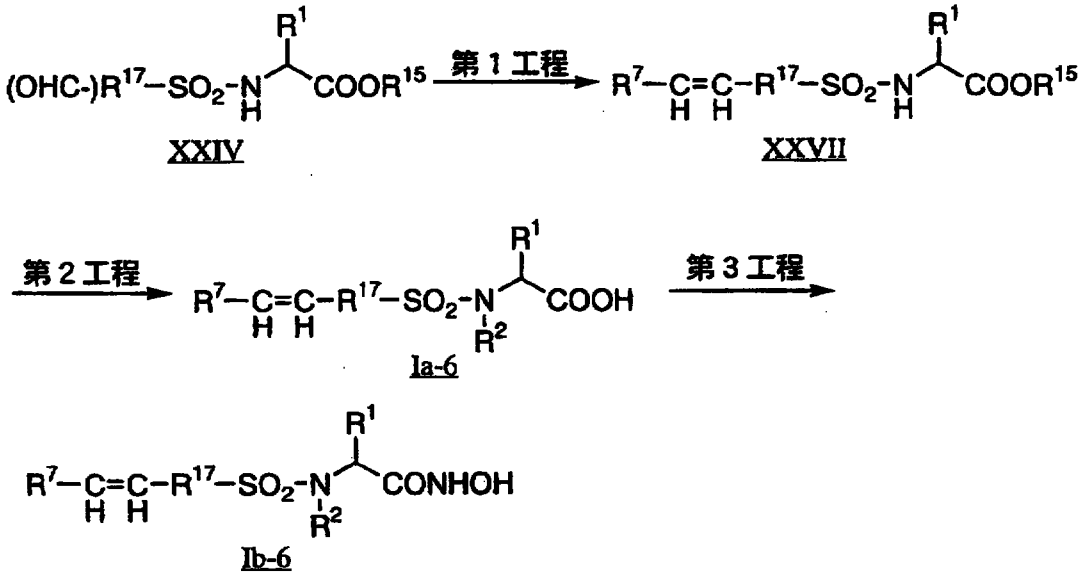
（第５工程）

Ａ法第１工程と同様に行うことができる。

（第６工程）

Ａ法第２～第４工程と同様に行うことができる。

（Ｆ法）



（式中、R^1、R^2、R^7、R^{15}、R^{17}、およびＨａｌは前記と同意義。）

化合物（XXIV）から化合物（XXVII）への反応は、R^{17}のアルデヒドを足がかりにして一般的に用いられるウィッティヒ（Wittig）反応（G Wittig et al., Chem. Berr. 87, 1318(1954)）の条件等を用い、二重結合を介してアリールまたはヘテロアリールを導入する反応（第１工程）で

ある。化合物（XXVII）から化合物（Ia-6）への反応は、化合物（XXVII）のN－アルキル化等やカルボキシ保護基の除去を行う反応（第２工程）であり、Ａ法第１工程と同様に行うことができる。化合物（Ia-6）から化合物（Ib-6）への反応はカルボン酸誘導体をヒドロキサム酸誘導体に変換する反応（第３工程）であり、Ａ法第２～第４工程と同様に行うことができる。各工程についてさらに詳しく述べれば以下の通りである。

（第１工程）

化合物（XXIV）のトルエン、キシレン、テトラヒドロフラン、エーテル、ジメチルホルムアミド等の溶媒中、－１００℃～室温、好ましくは－７８℃～氷冷下で、別途通常の方法により調製した$Ph_3P=CHPh$等の置換されていてもよいアリールまたは置換されていてもよいヘテロアリール誘導体のイリド体を加え、１～２０時間、好ましくは１～５時間攪拌することにより目的とする化合物（XXVII）へと変換することができる。置換されていてもよいアリールまたは置換されていてもよいヘテロアリール誘導体が本反応の障害となる置換基を有する場合には、Protective Groups in Organic Synthesis, Theodora W Green (John Wiley & Sons) 等に記載の方法で予め保護し、望ましい段階でその保護基を除去すればよい。

（第２工程）

Ａ法第１工程と同様に行うことができる。

（第３工程）

Ａ法第２～第４工程と同様に行うことができる。

「本発明化合物」という場合には、製薬上許容される塩、またはその水和物も抱含される。例えば、アルカリ金属（リチウム、ナトリウム、カリウム等）、アルカリ土類金属（マグネシウム、カルシウム等）、アンモニウム、有機塩基およびアミノ酸との塩、または無機酸（塩酸、臭

化水素酸、リン酸、硫酸等）、および有機酸（酢酸、クエン酸、マレイン酸、フマル酸、ベンゼンスルホン酸、ｐ－トルエンスルホン酸等）との塩が挙げられる。これらの塩は、通常行われる方法によって形成させることができる。

また、本発明化合物は特定の異性体に限定するものではなく、全ての可能な異性体やラセミ体を含むものである。

本発明化合物は後述する実験例の記載の通り、優れたメタロプロテイナーゼ阻害活性、とりわけＭＭＰ阻害活性を示し、マトリックス分解を阻害する。従って、本発明化合物はＭＭＰ、およびその類縁酵素であるＴＮＦ－αコンバーターゼ等に起因する疾患に有効である。

具体的には、変形性関節症、関節リウマチ、角膜潰瘍、歯周病、腫瘍の転移または浸潤、ウイルス感染症（例えば、ＨＩＶ感染症）の進行、閉塞性動脈硬化症、動脈硬化性動脈瘤、粥状動脈硬化症、再狭窄、敗血症、敗血症ショック、冠状血栓症、異常血管新生、強膜炎、多発性硬化症、開放角緑内障、網膜症、増殖性網膜症、血管新生緑内障、翼状皮膚、角膜炎、水泡性表皮剥離、乾癬、糖尿病、腎炎、神経性疾患、歯肉炎、腫瘍増殖、腫瘍血管新生、眼腫瘍、血管線維腫、血管腫、熱病、出血、凝固、悪液質、食欲不振、急性感染症、ショック、自己免疫症、マラリア、クローン病、髄膜炎、および胃腸潰瘍の予防または治療剤として使用することができる。

本発明化合物を、上記の疾患の治療あるいは予防を目的としてヒトに投与する場合は、散剤、顆粒剤、錠剤、カプセル剤、丸剤、液剤等として経口的に、または注射剤、坐剤、経皮吸収剤、吸入剤等として非経口的に投与することができる。また、本化合物の有効量にその剤型に適した賦形剤、結合剤、湿潤剤、崩壊剤、滑沢剤等の医薬用添加剤を必要に応じて混合し、医薬製剤とすることができる。注射剤の場合には、適当

な担体と共に滅菌処理を行って製剤とする。

投与量は疾患の状態、投与ルート、患者の年齢、または体重によっても異なり、最終的には医師の判断に委ねられるが、成人に経口で投与する場合、通常０．１～１００ mg／kg／日、好ましくは１～２０ mg／kg／日、非経口で投与する場合、通常０．０１～１０ mg／kg／日、好ましくは０．１～１ mg／kg／日を投与する。これを１回あるいは数回に分割して投与すればよい。

以下に実施例および実験例を挙げて本発明をさらに詳しく説明するが、本発明はこれらにより限定されるものではない。

実施例中、以下の略号を使用する。

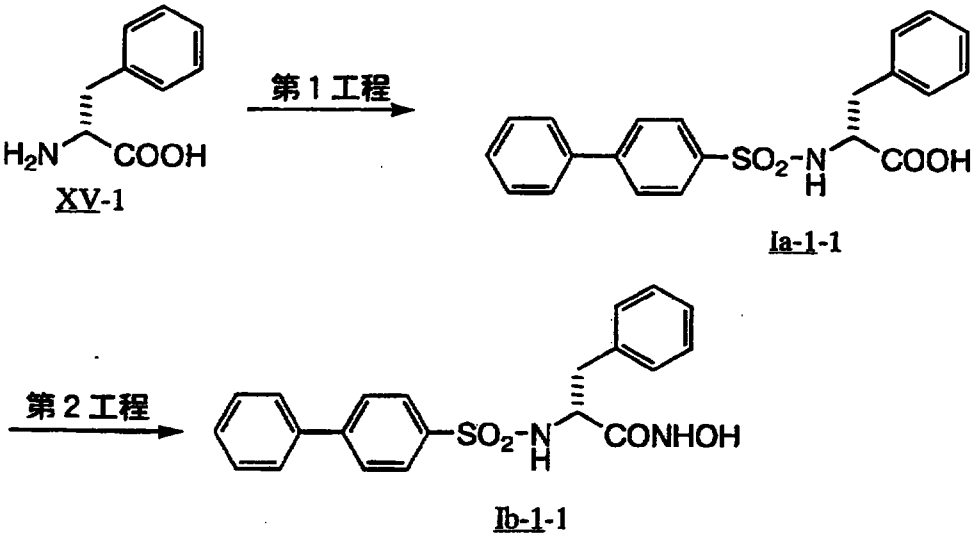
ｐ－ＴｓＯＨ：ｐ－トルエンスルホン酸

ＤＭＳＯ：ジメチルスルホキシド

Ｍｅ：メチル

^{t}Ｂｕ：ｔｅｒｔ－ブチル

実施例１（Ａ法）



(R)-(+)-フェニルアラニン(化合物 XV-1) 1.65g(10mmol)のジメチルホルムアミド 50ml、水 35ml懸濁液に、氷冷、撹拌下にトリエチルアミン

2.78ml(20mmol)を加えた。次いで 4-ビフェニルスルホニルクロリド 2.52g(10mmol)のジメチルホルムアミド 10ml溶液を5分間で加えた。同温度にて2時間撹拌後、1-ヒドロキシベンゾトリアゾールハイドレート 1.35g(10mmol)、1-エチル-3-(3-ジメチルアミノプロピル)カルボジイミド塩酸塩 2.1g(11mmol)、ヒドロキシルアミン塩酸塩 3.47g(50mmol)、トリエチルアミン 7ml(50mmol)を加えた。室温で16時間撹拌後、反応液を水に注ぎ込み酢酸エチルにて抽出した。2N-塩酸、5%炭酸水素ナトリウム水溶液、水にて順次洗浄した。減圧濃縮後、残渣をシリカゲルカラムクロマトグラフィーに付し、クロロホルム/メタノール=40/1 から 20/1 にて溶出する部分を集めると泡状の残渣(化合物 Ib-1-1) 1.70g を得た。収率 43%。融点 169-170℃。

元素分析値(%) C 2 1 H 2 0 N 2 O 4 S

計算値:C;63.62, H;5.08, N;7.07, S;8.09

実験値:C;63.61, H;5.12, N;6.98, S;8.06

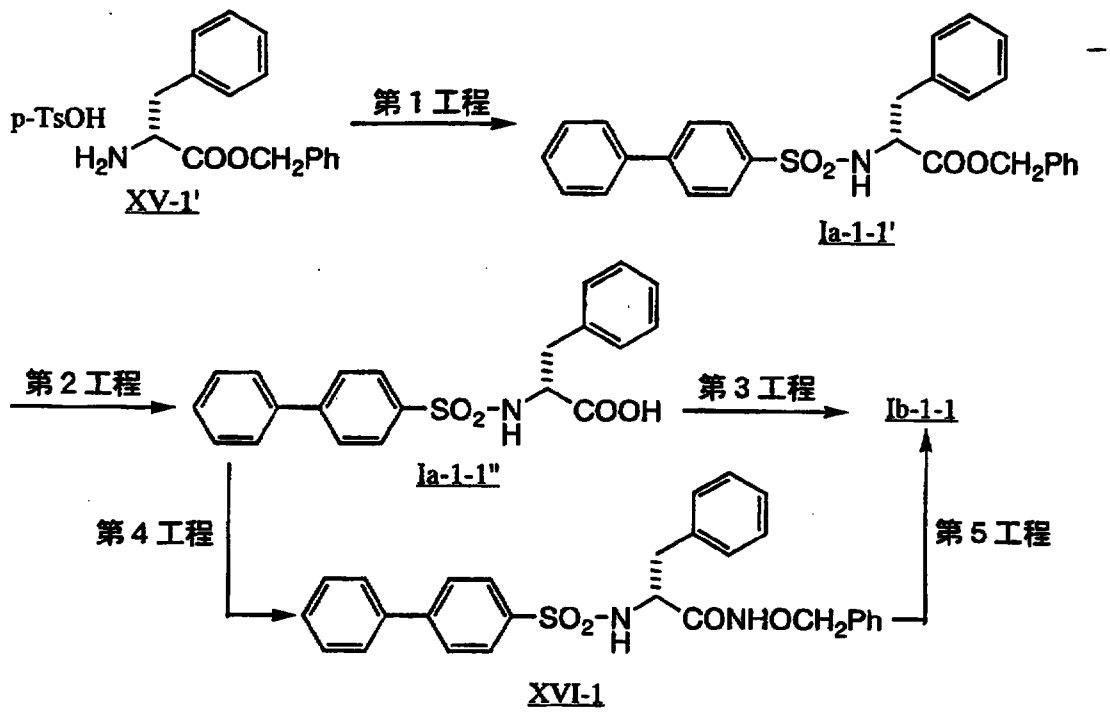
IR ν max(cm^{-1})(Nujol):3365, 3295, 3266, 1674, 1320, 1159

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)

[α]D : +18.5± 1.2(c=0.503%, 25℃, DMSO)

実施例 1 '

化合物 Ib-1-1 の別途合成法



第１工程

(R)-フェニルアラニンベンジルエステル･p-トルエンスルホン酸塩(化合物 ＸＶ-1')2.5g(5.85mmol)のジクロロメタン60ml溶液に、トリエチルアミン 1.8ml(12.87mmol)、次いで 4-ビフェニルスルホニルクロリド 1.63g(6.44mmol)を氷冷下に加えた。室温 2 時間撹拌後、2N-塩酸、5%炭酸水素ナトリウム水溶液、水にて順次洗浄した。減圧濃縮後、残渣をシリカゲルカラムクロマトグラフィーに付し、クロロホルム/メタノール=40/1 から 20/1 にて溶出する部分を集め、ジクロロメタン/ヘキサンより再結晶し、化合物 Ia-1-1' 2.32g を得た。収率 84.1%。融点 130-131℃。

元素分析値(%) C 2 8 H 2 5 NO 4 S

計算値:C;71.32, H;5.34, N;2.97, S;6.80

実測値: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)

[α]D：-16.4±1.1(c=0.506%, 25℃, MeOH)

第２工程

第１工程で得た化合物 Ia-1-1' 2.28g をメタノール/酢酸エチル=1/1 の 50ml 混液に溶解させ、10%パラジウム-炭素 200mg と共に 25 分間水添した。触媒を濾去後、減圧濃縮し残渣をジクロロメタン/ヘキサンより再結晶し、化合物 Ia-1-1" 1.83g を得た。収率 99.1%。融点 146-147℃。

元素分析値(%) C 2 1 H 1 9 NO 4 S

計算値:C;66.12, H;5.02, N;3.67, S;8.41

実測値: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)

[α]D：-4.0±0.4(c=1.000%, 25℃, MeOH)

第３工程

第２工程で得た化合物 Ia-1-1"1.0g(2.62mmol)のジクロロメタン 20ml 溶液にオキサリルクロリド 0.33ml(3.93mmol)、ジメチルホルムアミド 1 滴を加え室温 1 時間撹拌した。減圧濃縮後、テトラヒドロフラン 10ml に溶解させた。一方、ヒドロキシルアミン塩酸塩 911mg(13.1mmol)を、炭酸水素ナトリウム 1.54g(18.34mmol)を含むテトラヒドロフラン 10ml、水 10ml 混液中で氷冷下に 5 分間撹拌した。これに前記の酸クロリドのテトラヒドロフラン溶液を加え 30 分間撹拌した。反応液を水にあけ酢酸エチルにて抽出し、5%炭酸水素ナトリウム水溶液、水にて順次洗浄、減圧濃縮し、残渣 969mg(化合物 Ia-1)を得た。収率 93.3%。

第４工程

第２工程で得た化合物 Ia-1-1" 2.0g(5.24mmol)のジメチルホルムアミド 20ml 溶液に 1-ヒドロキシベンゾトリアゾールハイドレート

0.7g(5.24mmol)、N-メチルモルホリン 2.9ml(26.2mmol)、1-エチル-3-(3-ジイソプロピルアミノ)カルボジイミド塩酸塩(8mmol)、次いで O-ベンジルヒドロキシルアミン塩酸塩 1.67g(10.48mmol)を加え室温にて 6 時間撹拌した。反応液を水にあけ酢酸エチルで抽出、2N-塩酸、5%炭酸水素ナトリウム水溶液、水にて順次洗浄した。減圧濃縮後、残渣をシリカゲルカラムクロマトグラフィーに付し、酢酸エチル/ヘキサン=1/1 にて溶出する部分を集め、ジクロロメタン/ヘキサンより再結晶し、化合物 XVI-1 2.04g を得た。収率 80%。融点 171-173℃。

元素分析値(%) C 2 8 H 2 6 N 2 O 4 S

計算値:C;69.12, H;5.39, N;5.76, S;6.59

実測値: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)

[α]D: -40.2±1.6(c=0.505%, 25℃, DMSO)

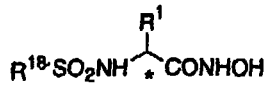
第 5 工程

第 4 工程で得た化合物 XVI-1 1.97g をメタノール/酢酸エチル=1/1 の 60ml 混液に溶解させ、10%パラジウム-炭素 200mg と共に 3.5 時間水添した。触媒を濾去後、減圧濃縮し残渣をジクロロメタン/ヘキサンより再結晶し、化合物 Ib-1-1 1.35g を得た。収率 84.4%。

実施例 2 ～ 9 1

実施例 1 ' と同様にして表 1 ～ 2 2 に示す化合物を合成した。

表 1



(Ib)

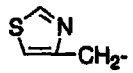
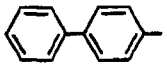
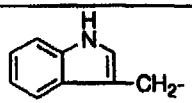
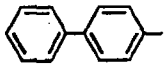
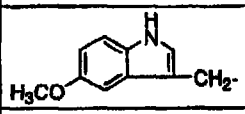
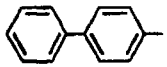
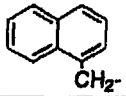
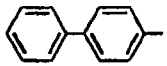
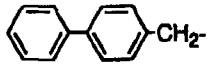
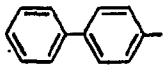
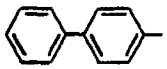
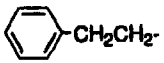
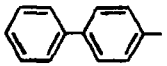
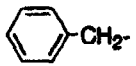
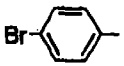
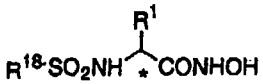
実施例 No.	R^1	R^{18}	*	融点（分解点） m.pt.(℃)	IR (ν cm-1) (KBr)	^{1}H-NMR(δ ppm) d_6-DMSO
2			RS	173 >	3258,1650,1377, 1348,1163 (Nujol)	2.87(dd,J=5.6,14.2Hz,1H), 2.98(dd, J=8.4,14.2Hz,1H),4.02(dd,J=2.2, 8.6Hz,1H), 7.24(d,J=2.0Hz,1H), 8.83(d,J=2.2Hz,1H)
3			R	203-206	3403,3386,3265,1673 ,1320,1162 (Nujol)	2.72(dd,J=7.2,13.8Hz,1H), 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),

表 2



(Ib)

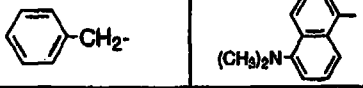
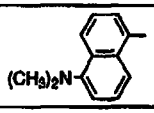
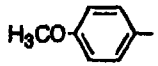
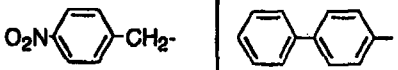
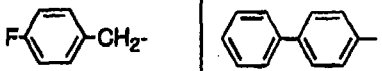
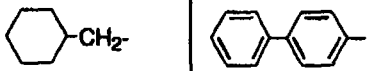
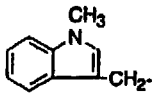
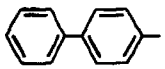
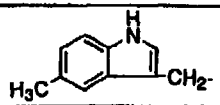
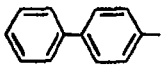
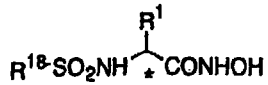
実施例 No.	R¹	R¹⁸	*	融点 (分解点) m.pt.(℃)	IR (ν cm-1) (KBr)	¹H-NMR(δ ppm) d₆-DMSO
10			R	116-118	3600-2400br,3257, 1743,1721,1323,1132,	2.60-2.82(m,2H),3.84(m,1H),7.00-7.18(m,5H),7.62-7.80(m,4H),
11			R	91-92	3700-2100br,3176, 1664,1320,1143,	2.70-2.93(m,2H),2.82(s,6H), 3.75(m,1H),
12	$(CH_3)_2CH$—		R	178-179	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)

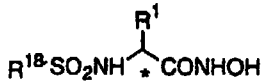
表 3



(Ib)

実施例 No.	R^1	R^{18}	*	融点（分解点） m.pt.(℃)	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)

表 4



(Ib)

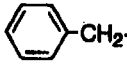
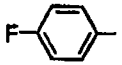
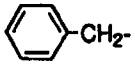
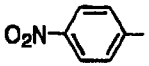
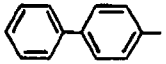
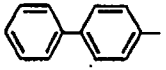
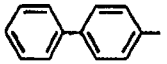
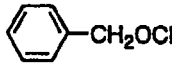
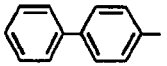
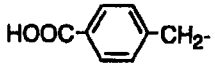
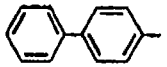
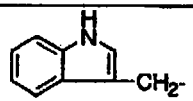
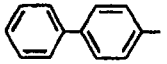
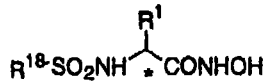
実施例 No.	R^1	R^{1B}	*	融点（分解点） m.pt.(℃)	IR（ν cm-1） (KBr)	^{1}H-NMR(δ ppm) d_6-DMSO
26			R	63-65	3700-2200(br),3362,1670, 1590,1336,1152	2.60(dd,J=9.0,13.8Hz,1H),2.79(dd, J=9.3,13.8Hz,1H),3.76(m,1H)
27			R	70-71	3700-2200br,3372,1674, 1531,1348,1310,1161	2.66(dd,J=9.5,13.6Hz,1H),2.79(dd,J=5.4,13.6Hz,1H),3.84(m,1H),7.73(A_2B_2q,J=8.9Hz,2H),8.20(A_2B_2q,J=8.9Hz,2H),8.72(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			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)

表 5



(Ib)

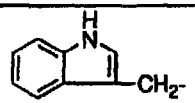
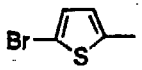
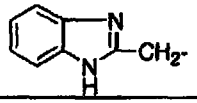
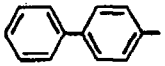
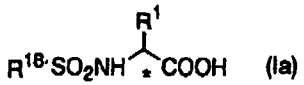
実施例 No.	R^1	R^{18}	*	融点 (分解点) m.pt.(℃)	IR (ν cm-1) (KBr)	^{1}H-NMR(δ ppm) d_6-DMSO
34			R	–	–	–
35			RS	141-145	3700-2400(br),1672, 1443,1327,1094	2.84-3.21(m,2H),4.29(m,1H)

表 6



(Ia)

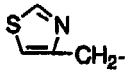
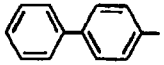
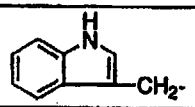
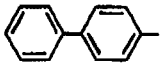
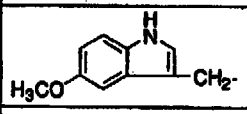
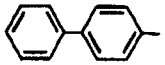
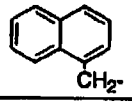
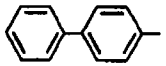
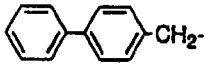
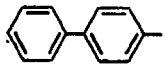
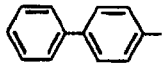
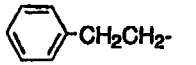
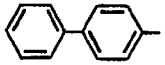
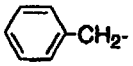
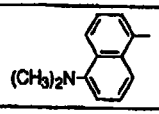
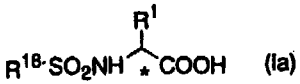
実施例 No.	R^1	R^{18}	*	融点 (分解点) m.pt.(℃)	IR (ν cm-1) (KBr)	^{1}H-NMR(δ ppm) d_6-DMSO
2			RS	159-161	3276,2503br,1897br, 1724,1344,1170(Nujol)	2.95(dd,J=9.0,14.0Hz,1H),3.12(dd, J=5.4,14.0Hz,1H),4.13(m,1H),7.29 (d,J=2.0Hz,1H),8.34(d,J=8.6Hz,1H),8.88(d,J=2.0Hz,1H),12.79(br,1H)
3			R	227-229	3386,3305,1747,1363, 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)

表 7



(Ia)

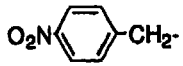
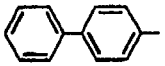
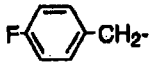
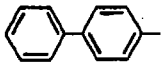
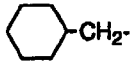
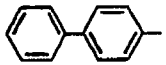
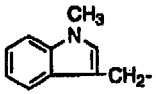
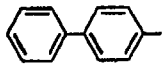
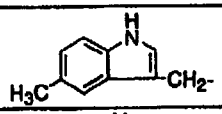
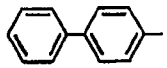
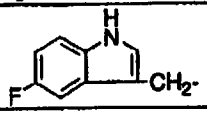
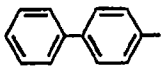
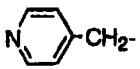
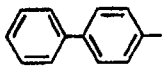
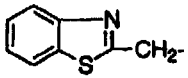
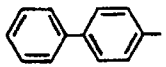
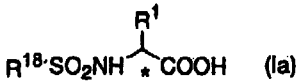
実施例 No.	R^1	R^{18}	*	融点（分解点） m.pt.(℃)	IR（ν cm-1） (KBr)	^{1}H-NMR(δ ppm) d_6-DMSO
13			RS	212-213	3113,1724,1520, 1345,1158	2.86(dd,J=10.2,13.2Hz,1H), 3.14(dd,J=4.5,13.7Hz,1H), 4.02(m,1H),8.42(d,J=8.4Hz,1H)
14			RS	164-165	3426,3114,1715, 1509,1224,1159	2.71(dd,J=9.9,13.7Hz,1H),2.96(dd, J=5.3,13.5Hz,1H),3.89(m,1H), 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)

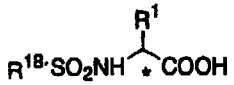
表 8



(Ia)

実施例 No.	R^1	R^{18}	*	融点（分解点） m.pt.(℃)	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	-CH_2OCH_2-		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	HOOC-C_6H_4-CH_2-		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)

表 9



(Ia)

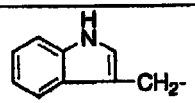
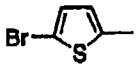
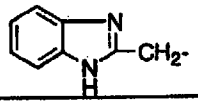
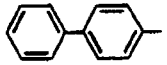
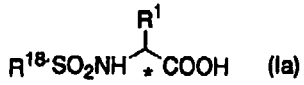
実施例 No.	R^1	R^{18}	*	融点（分解点） m.pt.(℃)	IR (ν cm-1) (KBr)	^{1}H-NMR(δ ppm) d_6-DMSO
34			R	243-246	3420,1588,1402, 1324,1151	3.06(dd,J=5.4,14.4Hz,1H),3.14(dd, J=5.1,14.4Hz,1H),3.65(t,J=5.4Hz, 1H),6.92(m,1H),10.72(s,1H)
35			RS	151-156	2200-3700br,1734, 1334,1161	3.17-3.50(m,2H),4.51(m,1H)

表 1 0



(Ia)

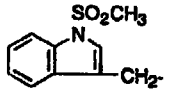
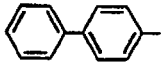
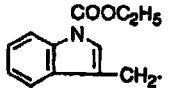
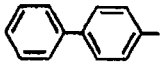
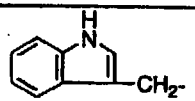
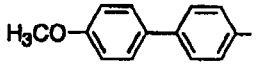
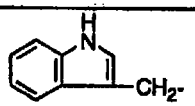
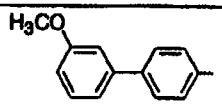
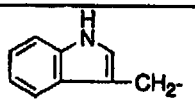
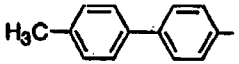
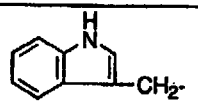
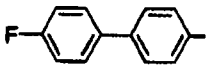
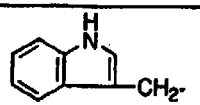
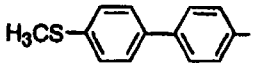
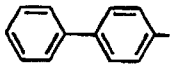
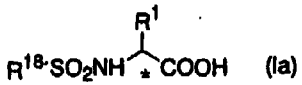
実施例 No.	R¹	R¹⁸	*	融点（分解点） m.pt.(℃)	IR (ν cm-1) (KBr)	元素分析
36			RS	>145	1726,1354 1326,1161	–
37			RS	–	1732,1594 1404,1155	–
38			R	188-190	1607,1594 1294,1153	$C_{24}H_{22}N_2O_5S \cdot 0.5H_2O$ Calc. C:62.73 H:5.04 N:6.10 S:6.98 Foun.C:62.75 H:5.08 N:6.31 S:7.05
39			R	90-93	1724,1594 1326,1159	$C_{24}H_{22}N_2O_5S \cdot 0.8H_2O$ 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

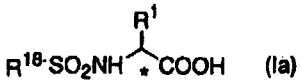
表 1 1



(Ia)

実施例 No.	R¹	R¹⁸	*	融点（分解点） m.pt.(℃)	IR (ν cm-1) (KBr)	元素分析
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

表 1 2



(Ia)

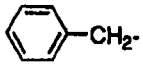
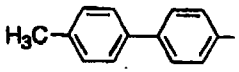
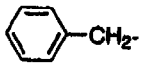
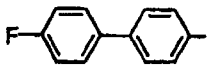
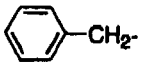
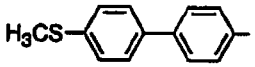
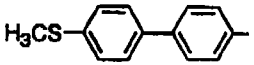
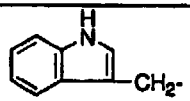
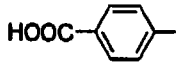
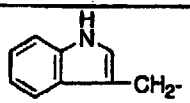
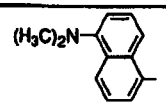
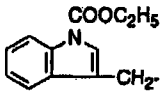
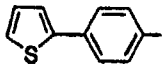
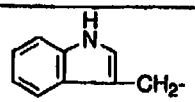
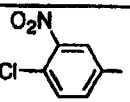
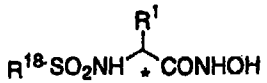
実施例 No.	R^1	R^{18}	*	融点（分解点） m.pt.(℃)	IR（ν cm-1） (KBr)	元素分析
52			R	157-160	1685,1349 1166	–
53			R	111-112	1691,1567 1390,1159	–
54			R	194-195	1749,1592 1323,1164	–
55	$(CH_3)_2CH$-		R	197-199	1746,1337 1164	$C_{18}H_{21}NO_4S_2 \cdot 0.2H_2O$ Calc. C:56.43 H:5.63 N:3.66 S:16.74 Foun.C:56.74 H:5.67 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

表 1 3



(Ib)

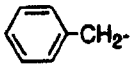
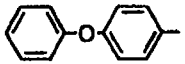
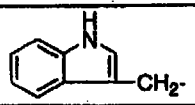
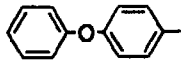
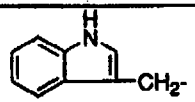
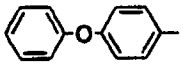
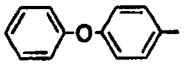
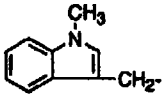
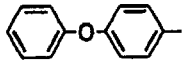
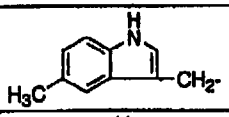
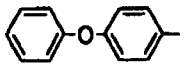
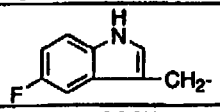
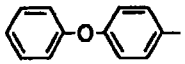
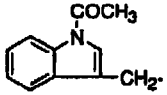
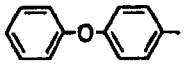
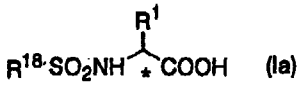
実施例 No.	R^1	R^{18}	*	融点（分解点） m.pt.(℃)	IR (ν cm-1) (KBr)	^{1}H-NMR(δ ppm) d_6-DMSO
60			R	foam	3700-2400br,3277, 1669,1325,1152	2.60(dd,J=8.7,13.7Hz,1H), 2.79(dd, J=6.0,13.7Hz,1H),3.75(ddd,J=6.0, 8.7,9.0,1H),6.94(d,J=8.9Hz.2H)
61			R	115-118	3302,1667,1324, 1153(Nujol)	2.71(dd,J=7.0,14.4Hz,1H), 2.96(dd, 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)

表 1 4



(Ia)

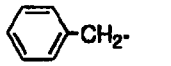
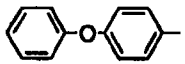
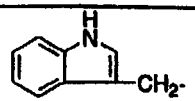
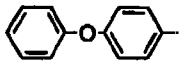
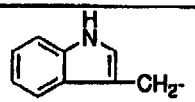
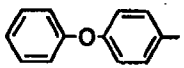
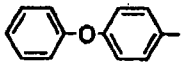
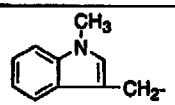
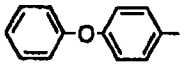
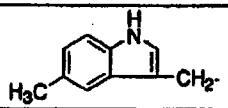
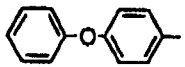
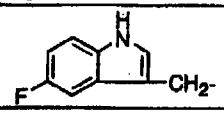
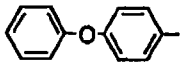
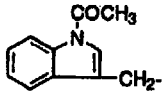
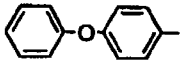
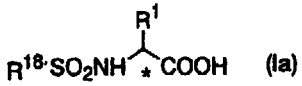
実施例 No.	R¹	R¹⁸	*	融点（分解点） m.pt.(℃)	IR (ν cm-1) (KBr)	¹H-NMR(δ ppm) d₆-DMSO
60			R	108-109	2400-3600br,3345,3213, 1735,1700,1346,1163	2.72(dd,J=8.7,13.6Hz,1H),2.94(dd, J=5.6,13.6Hz,1H),3.84(ddd,J=5.6, 8.7,8.7Hz,1H),8.23(d,J=8.7Hz,1H)
61			R	82-87	3410,3276,1724,1582, 1488,1331,1152(Nujol)	2.88(dd,J=7.4,15.2Hz,1H),3.07(dd, 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)

表 1 5



(Ia)

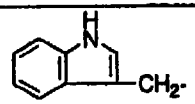
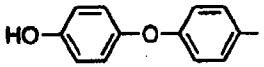
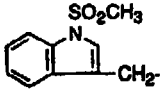
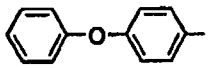
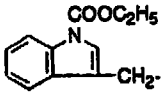
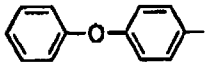
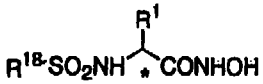
実施例 No.	R¹	R¹⁸	*	融点 (分解点) m.pt.(℃)	IR (ν cm-1) (KBr)	元素分析
68			R	>240	1608,1590 1507,1232 1157	–
69			RS	–	1735,1583 1362,1171	$C_{24}H_{22}N_2O_7S_2$ Calc. C:56.02 H:4.31 N:5.44 S:12.46 Foun.C:55.75 H:4.40 N:5.41 S:12.21
70			RS	–	1733,1583 1150	–

表 1 6



(Ib)

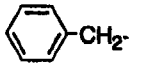
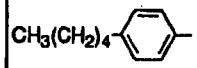
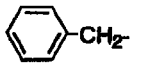
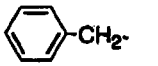
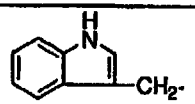
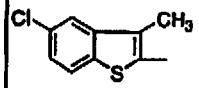
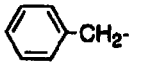
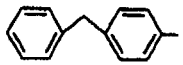
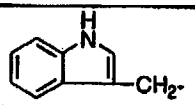
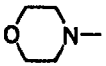
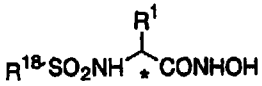
実施例 No.	R^1	R^{1a}	*	融点（分解点） m.pt.(℃)	IR (ν cm-1) (KBr)	^{1}H-NMR(δ ppm) d_6-DMSO
71			R	129-131	3700-2400br,3247, 1636,1337,1160	0.90(t,J=6.8Hz,3H),1.22-1.40(m,4H),1.52-1.67(m,2H),2.62(t,J=7.7Hz,2H),2.86(dd,J=8.4,13.7Hz,1H),3.02(dd,J=5.7,13.7Hz,1H) ($CDCl_3$)
72		$CH_3(CH_2)_7$—	R	oil	3700-2400br,1663, 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_2q,J=7.5Hz,2H),7.42(A_2B_2q,J=7.5Hz,2H)($CDCl_3$)
76			R	–	–	–

表 1 7



(Ib)

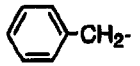
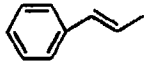
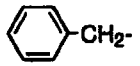
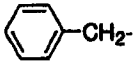
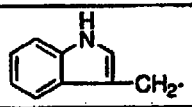
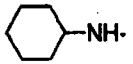
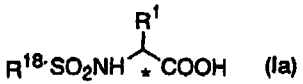
実施例 No.	R^1	R^{18}	*	融点（分解点） m.pt.(℃)	IR（ν cm-1） (KBr)	^{1}H-NMR(δ ppm) d_6-DMSO
77			R	138-139	3700-2400(br),3312, 1629,1329,1144	2.79(dd,J=8.5,13.4Hz,1H),2.89(dd, J=6.0,13.4Hz,1H),3.81(dd,J=6.0, 8.5Hz,1H),6.55(d,J=15.5Hz,1H)
78			R	69-70	3700-2200(br),1670, 1318,1152	2.78(dd,J=8.6,13.4Hz,1H),2.91(dd,J=6 .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	–	–	–

表 1 8



(Ia)

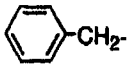
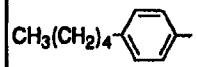
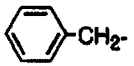
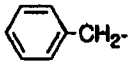
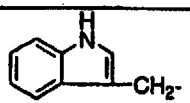
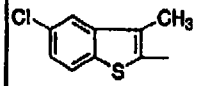
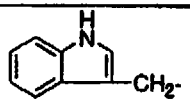
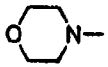
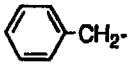
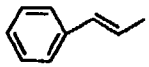
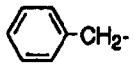
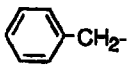
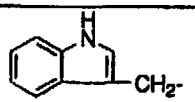
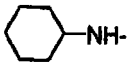
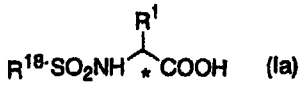
実施例 No.	R¹	R¹⁸	*	融点（分解点） m.pt.(℃)	IR (ν cm-1) (KBr)	¹H-NMR(δ ppm) d₆-DMSO
71			R	121-122	2300-3700br,3426,3318, 1713,1330,1159	0.89(t,J=6.7Hz,3H),2.62(t,J=7.6Hz,2H),2.96(dd,J=7.0,13.9Hz,1H),3.10(dd,J=5.4,13.9Hz,1H),4.19(dt,J=6.9,8.2Hz,1H),5.30(d,J=8.2Hz,1H),
72		$CH_3(CH_2)_7$—	R	oil	2400-3600br,3340,1736, 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)

表 1 9



(Ia)

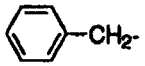
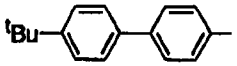
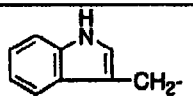
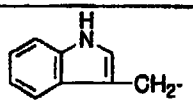
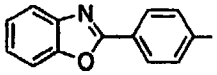
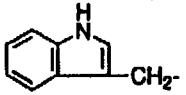
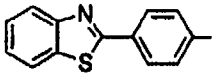
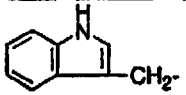
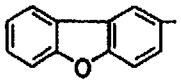
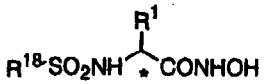
実施例 No.	R¹	R¹⁸	*	融点 (分解点) m.pt.(℃)	IR (ν cm-1) (KBr)	元素分析
80			R	153-155	1704,1596 1349,1164	–
81		n-C_8H_{17}-	R	>130	1576,1356 1139	–
82			R	128-130	1732,1342 1167	$C_{24}H_{19}N_3O_5S \cdot 1.3H_2O$ Calc. C:59.45 H:4.49 N:8.67 S:6.61 Foun.C:59.43 H:4.45 N:8.59 S:6.58
83			R	210-214	1745,1590 1316,1157	–
84			R	198-200	1594,1456 1200,1188	–

表 2 0



(Ib)

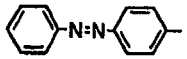
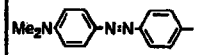
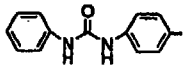
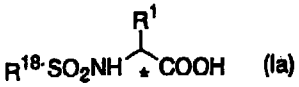
実施例 No.	R¹	R¹⁸	*	融点（分解点） m.pt.(℃)	IR (ν cm-1) (KBr)	¹H-NMR(δ ppm) d₆-DMSO
85			R	157-160	3700-2400br,3273, 1633,1338,1166	2.65(dd,J=8.9,13.6Hz,1H), 2.82(dd, J=6.6,13.6Hz,1H),3.86(m,1H),7.75 (d,J=7.8Hz,2H),7.87(d,J=8.7Hz,2H)
86			R	138-142	3700-2400br,2921, 1672,1314,1165,	2.62(dd,J=8.6,13.5Hz,1H),2.81(dd,J=6. 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,1 H),3.76(m,1H),8.02(d,J=8.7Hz,1H),8.80(s,1H),8.8 5(d,J=1.7Hz,1H),9.06(s,1H),10.59(d,J=1.7Hz,1H)

表 2 1



(Ia)

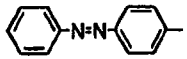
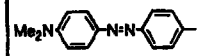
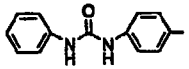
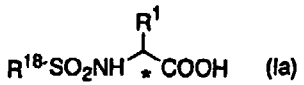
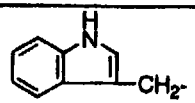
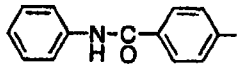
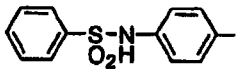
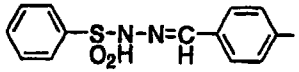
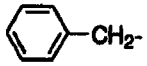
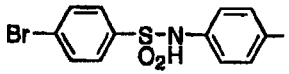
実施例 No.	R^1	R^{18}	*	融点（分解点） m.pt.(℃)	IR（ν cm-1） (KBr)	^{1}H-NMR(δ ppm) d_6-DMSO
85			R	172-174	2400-3600br,3426,3296, 1698,1350,1167	2.75(dd,J=9.1,13.7Hz,1H),2.98(dd, J=5.5,13.7Hz,1H),3.96(ddd,J=5.5, 9.1,9.1Hz,1H),8.51(d,J+9.1Hz,1H)
86			R	93-94	2200-3700br,3431, 1735,1391,1154	2.74(dd,J=9.1,13.6Hz,1H),2.96(dd,J =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)

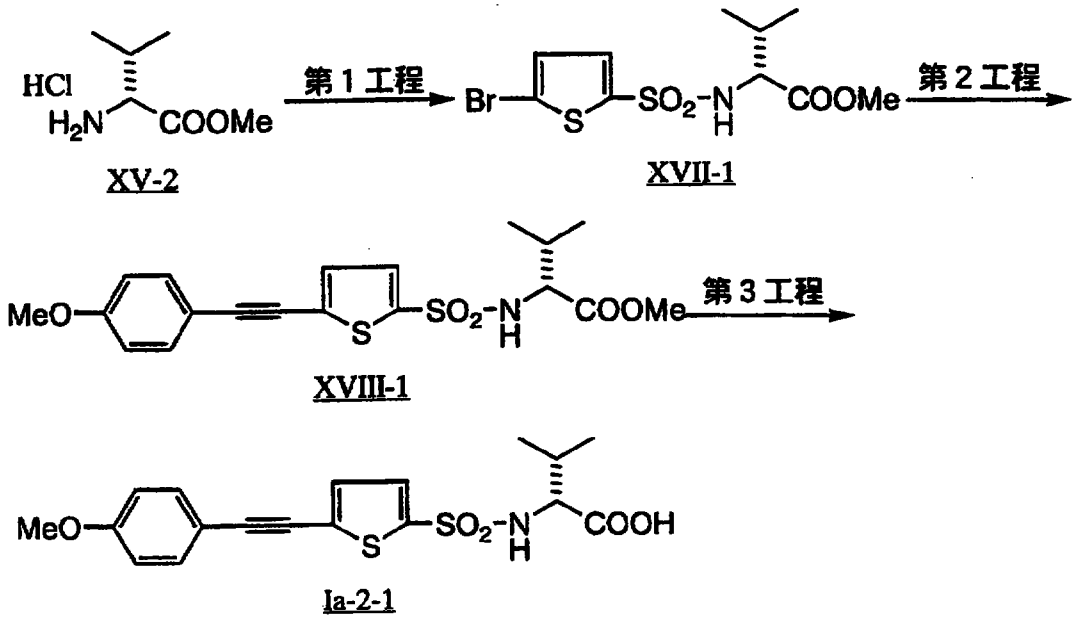
表 2 2



(Ia)

実施例 No.	R¹	R¹⁸	*	融点 (分解点) m.pt.(℃)	IR (ν cm-1) (KBr)	元素分析
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

実施例９２（Ｂ法）



第１工程

D-バリンメチルエステル塩酸塩(XV-2)755mg(4.5mmol)のジクロロメタン 12ml 溶液に、N-メチルモルホリン 1.49ml(3×4.5mmol)、次いで 5-ブロモチオフェン-2-スルホニルクロリド 1.24g(1.05×4.5mmol)を氷冷下に加えた。室温にて 15 時間撹拌した後 2N-塩酸、5%炭酸水素ナトリウム水、水にて順次洗浄した。芒硝にて乾燥後、減圧濃縮して得られた残渣をシリカゲルカラムクロマトグラフィーを行った。酢酸エチル/n-ヘキサン=1/3 にて溶出する部分を集め、n-ヘキサンにて洗浄し、融点 109-110℃の目的物(XVII-1)1.32g（収率 82%）を得た。

元素分析 $C_{10}H_{14}BrNO_4S_2$として

計算値：C;33.71 H;3.96 Br;22.43 N;3.93 S;18.00

実験値：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=6.8Hz,3H), 1.00(d,J=6.8Hz,3H), 2.00 (m,1H), 3.60(s,3H), 3.83(dd,J=5.2,10.0Hz,1H), 5.20(d,J=10.0Hz,1H), 7.04(d,J=4.1Hz,1H),7.32(d,J=4.1Hz,1H)

第２工程

化合物(XVII-1)400mg(1.12mmol)のジメチルホルムアミド5ml溶液に4-メトキシフェニルアセチレン 222mg(1.5×1.12mmol)、ヨウ化銅(I)21mg(0.1×1.12mmol)を加えアルゴンガス雰囲気下に良く脱気した。次いでビス(トリフェニルホスフィン)パラジウム(II)クロリド39mg(0.05×1.12mmol)、トリエチルアミン 0.47ml(3×1.12mmol)を加え、再度アルゴンガス雰囲気下に良く脱気した。この混合物を50℃、アルゴン雰囲気下に１夜加熱、撹拌した。反応液を酢酸エチルにて希釈し、1N-塩酸、5%炭酸水素ナトリウム水、水にて順次洗浄する。芒硝乾燥、減圧濃縮して得られる残渣をシリカゲルカラムクロマトグラフィーに付す。n-ヘキサン/酢酸エチル=2/1にて溶出する部分を集め、酢酸エチル/n-ヘキサンより再結晶し、融点131-132℃の目的物(XVIII-1)392mg（収率86%）を得た。

分析値 $C_{19}H_{21}NO_5S_2 \cdot 0.2H_2O$ として

計算値：C;55.51 H;5.25 N;3.41 S;15.60

実験値：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=6.6Hz,3H), 1.00(d,J=7.0Hz,3H), 2.00(m, 1H), 3.60(s,3H), 3.84(s,3H), 3.86(dd,J=5.0,10.2Hz,1H), 5.21(d,J=10.2 Hz,1H),6.90(d,J=9.0Hz,2H),7.44(d,J=9.0Hz,2H),7.12(d,J=4.0Hz,1H),7.44(d,J=4.0Hz,1H)

第３工程

化合物(XVII-1)407mg(1mmol)のテトラヒドロフラン8ml、メタノール

8ml混合溶液に1N-苛性ソーダ5.1mlを加え、60℃にて6時間加熱、撹拌した。反応液より減圧濃縮にて有機溶媒を除き、残渣を酢酸エチルで希釈した。クエン酸水溶液で酸性にした後、酢酸エチル抽出、ブラインにて洗浄した。芒硝乾燥、減圧濃縮し、化合物（Ia-2-1）373mg（収率100%）を得た。

融点：147～148℃

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

元素分析 $C_{18}H_{19}NO_5S_2 \cdot 0.2H_2O$ として

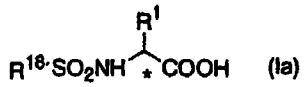
計算値：C;54.45 H;4.92 N;3.53 S;16.15

実験値：C;54.39 H;4.93 N;3.79 S;15.96

実施例９３～１５６

実施例９２と同様にして表２３～３０に示す化合物を合成した。

表２３



(Ia)

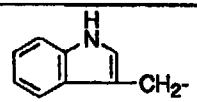
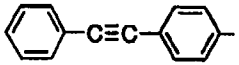
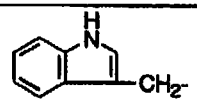
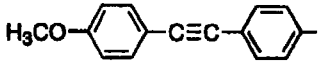
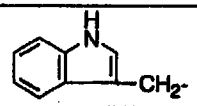
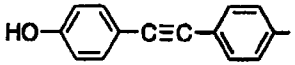
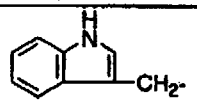
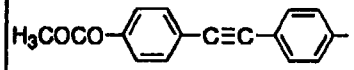
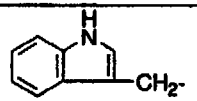
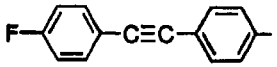
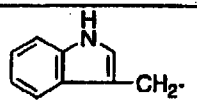
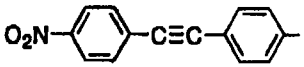
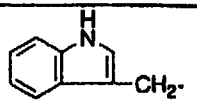
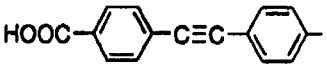
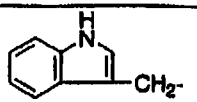
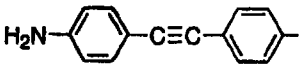
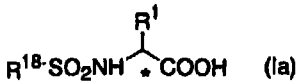
実施例 No.	R¹	R¹⁸	*	融点（分解点） m.pt.(℃)	IR (ν cm-1) (KBr)	元素分析
93			R	165-170	1590,1316 1137	–
94			R	223-226	1747,1323 1134	$C_{26}H_{22}N_2O_5S$ Calc. C:65.81 H:4.67 N:5.90 S:6.76 Foun.C:65.34 H:4.90 N:5.56 S:6.40
95			R	216-218	1724,1325 1135	–
96			R	111-114	1739,1336 1163	–
97			R	178-180	1710,1511 1329,1161	–
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

表 2 4



(Ia)

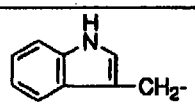
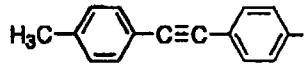
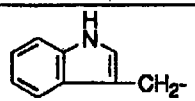
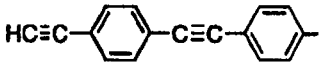
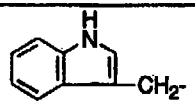
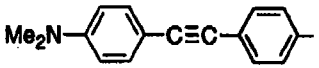
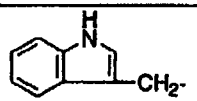
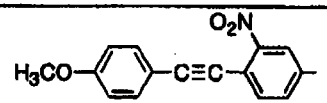
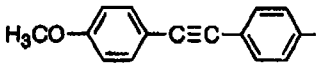
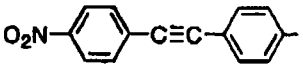
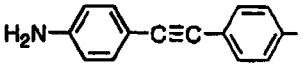
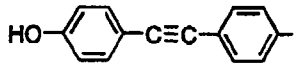
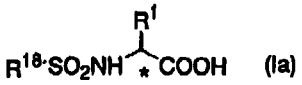
実施例 No.	R^1	R^{18}	*	融点（分解点） m.pt.(℃)	IR (ν cm-1) (KBr)	元素分析
101			R	227-229	1736,1618 1398,1168	$C_{26}H_{22}N_2O_4S \cdot 0.2H_2O$ Calc. C:67.57 H:4.89 N:6.06 S:6.94 Foun.C:67.66 H:4.77 N:6.09 S:6.71
102			R	230-233	1735,1654 1399,1164	–
103			R	234-236	1732,1631 1372,1148	–
104			R	>200 decomp.	1600,1558 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	–

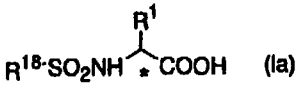
表 2 5



(Ia)

実施例 No.	R^1	R^{18}	*	融点（分解点） m.pt.(℃)	IR (ν cm-1) (KBr)	元素分析
109	$(CH_3)_2CH$-	H_3C-⟨⟩-C≡C-⟨⟩-	R	187-189	1720,1656 1319,1165	–
110	$(CH_3)_2CH$-	F-⟨⟩-C≡C-⟨⟩-	R	111-114	1724,1635 1366,1158	–
111	$(CH_3)_3C$-	H_3CO-⟨⟩-C≡C-⟨⟩-	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	$CH_3CH_2(CH_3)CH$-	H_3CO-⟨⟩-C≡C-⟨⟩-	R	157-159	1732,1680 1329,1167	–
113	⟨⟩-CH_2-	H_3CO-⟨⟩-C≡C-⟨⟩-	R	133-136	1735,1651 1348,1165	–
114	⟨⟩-CH_2-	H_3C-⟨⟩-C≡C-⟨⟩-	R	183-185	1727,1604 1335,1182	–
115	⟨⟩-CH_2-	F-⟨⟩-C≡C-⟨⟩-	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	$(CH_3)_2CH$-	HO-⟨⟩-C≡C-⟨⟩-	R	163-165	1728,1332 1172	–

表 2 6



(Ia)

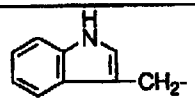
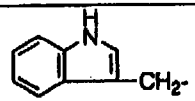
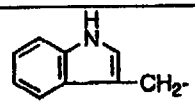
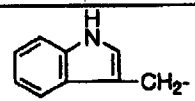
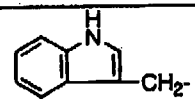
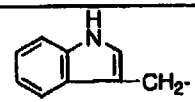
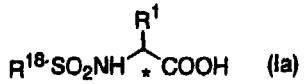
実施例 No.	R^1	R^{18}	*	融点 (分解点) m.pt.(℃)	IR (ν cm-1) (KBr)	元素分析
117	$(CH_3)_2CH$-	H_3C-C≡C-	R	187-189	1720,1656 1319,1165	–
118		F-C≡C-	R	111-114	1724,1635 1366,1158	–
119		C≡C-	R	167-169	1585,1318 1153	–
120		C≡C- NO_2	R	–	1605,1523 1340,1151	–
121		H_3CO-C≡C-	R	–	1604,1524 1336,1173	–
122		F-C≡C-	R	103-106	1721,1620 1339,1163	–
123		H_3C-C≡C-	R	180-182	1729,1675 1340,1168	–
124	$(CH_3)_2CH$-	H_3CO-C≡C-	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

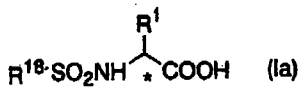
表 2 7



(Ia)

実施例 No.	R^1	R^{18}	*	融点（分解点） m.pt.(℃)	IR（ν cm-1） (KBr)	元素分析
125	$(CH_3)_2CH$-	H_3C-C≡C-S	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	$(CH_3)_2CH$-	F-C≡C-S	R	154-156	1710,1499 1356,1165	–
127	CH_2-	H_3CO-C≡C-S	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	CH_2-	H_3C-C≡C-S	R	161-164	1710,1329 1180	–
129	CH_2-	F-C≡C-S	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	CH_2-	C≡C-OCH_3-OCH_3	R	–	–	–
131	CH_2-	H_3CO-H_3CO-H_3CO-C≡C-	R	–	–	–
132	CH_2-	C≡C-NO_2	R	–	–	–

表 2 8



(Ia)

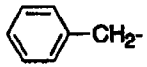
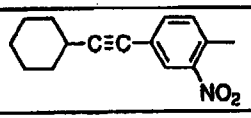
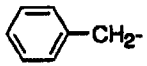
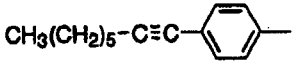
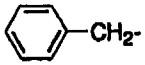
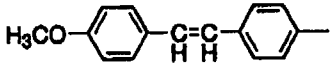
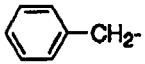
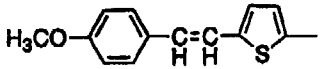
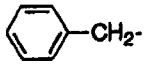
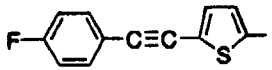
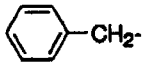
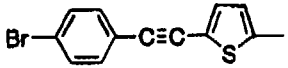
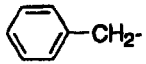
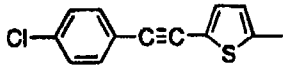
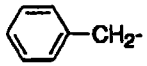
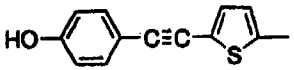
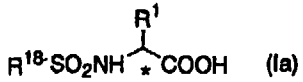
実施例 No.	R¹	R¹⁸	*	融点（分解点） m.pt.(℃)	IR (ν cm-1) (KBr)	元素分析
133			R	–	–	–
134			R	–	–	–
135			R	–	–	–
136			R	–	–	–
137			R	–	–	–
138			R	–	–	–
139			R	–	–	–
140			R	–	–	–

表 2 9



(Ia)

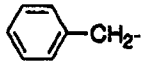
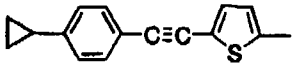
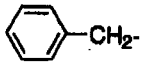
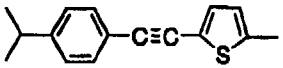
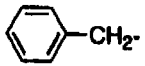
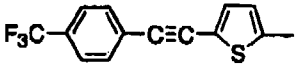
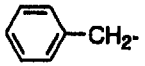
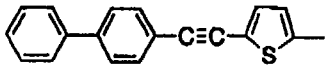
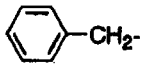
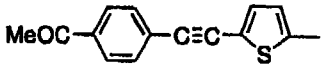
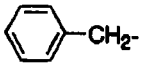
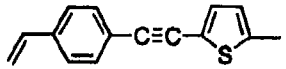
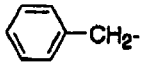
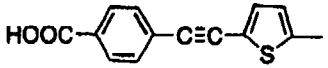
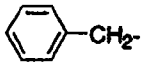
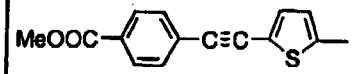
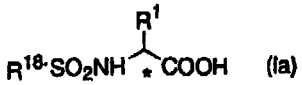
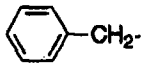
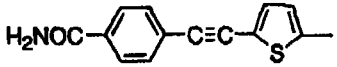
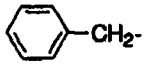
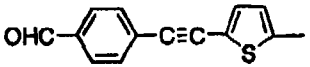
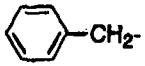
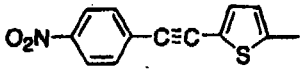
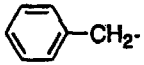
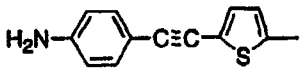
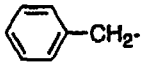
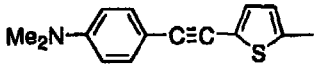
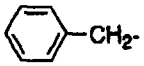
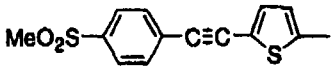
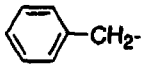
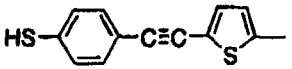
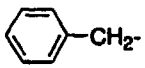
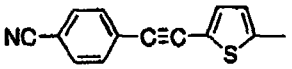
実施例 No.	R¹	R¹⁸	*	融点（分解点） m.pt.(℃)	IR (ν cm-1) (KBr)	元素分析
141			R	–	–	–
142			R	–	–	–
143			R	–	–	–
144			R	–	–	–
145			R	–	–	–
146			R	–	–	–
147			R	–	–	–
148			R	–	–	–

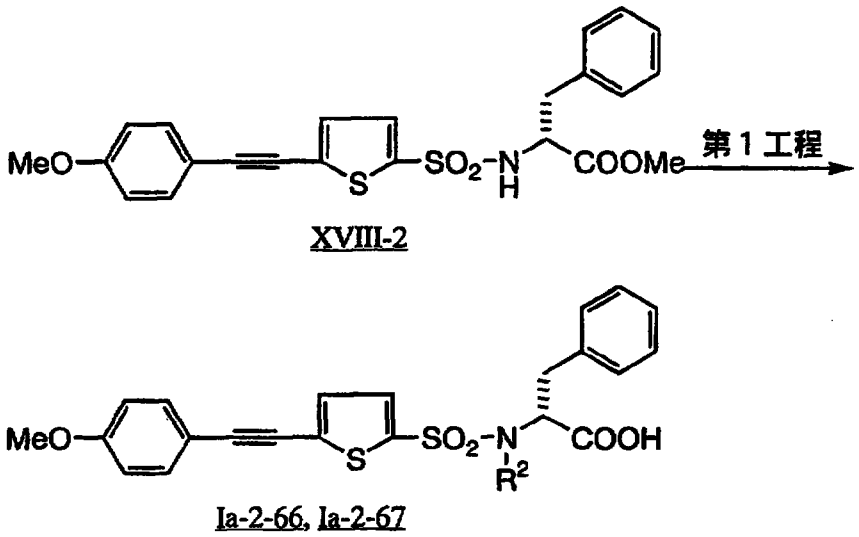
表３０



(Ia)

実施例 No.	R¹	R¹⁸	*	融点（分解点） m.pt.(℃)	IR (ν cm-1) (KBr)	元素分析
149			R	–	–	–
150			R	–	–	–
151			R	–	–	–
152			R	–	–	–
153			R	–	–	–
154			R	–	–	–
155			R	–	–	–
156			R	–	–	–

実施例１５７、１５８



第１工程（$R^2=CH_3$）

実施例９６と同様に合成した化合物(XVIII-2)150mg(0.33mmol)のジメチルホルムアミド 2ml 溶液に炭酸カリウム 227mg(5x0.33mmol)、ヨウ化メチル 0.1ml(5x0.33mmol)を加え、室温にて一夜攪拌した。反応液を水にあけ、酢酸エチルで抽出した。水洗、芒硝乾燥、減圧濃縮し、油状のＮ－メチル体化合物 373mg（収率 91%）を得た。

分析値 $C_{24}H_{23}NO_5S_2$ として

計算値：C;61.39 H;4.94 N;2.98 S;13.66

実験値：C;61.22 H;5.18 N;2.93 S;13.27

さらに上記で得た油状化合物 140mg のメタノール 2ml 溶液に 1N-NaOH 0.6ml を加え、室温にて一夜攪拌した。反応液を 2N-HCl にて酸性にした後、酢酸エチルで抽出した。水洗、芒硝乾燥、減圧濃縮し、融点 185～186℃の化合物(Ia-2-66)（R=Me）105mg（収率 77%）を得た。

分析値 $C_{23}H_{21}NO_5S$ として

計算値：C;60.64 H;4.65 N;3.07 S;14.08

実験値：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

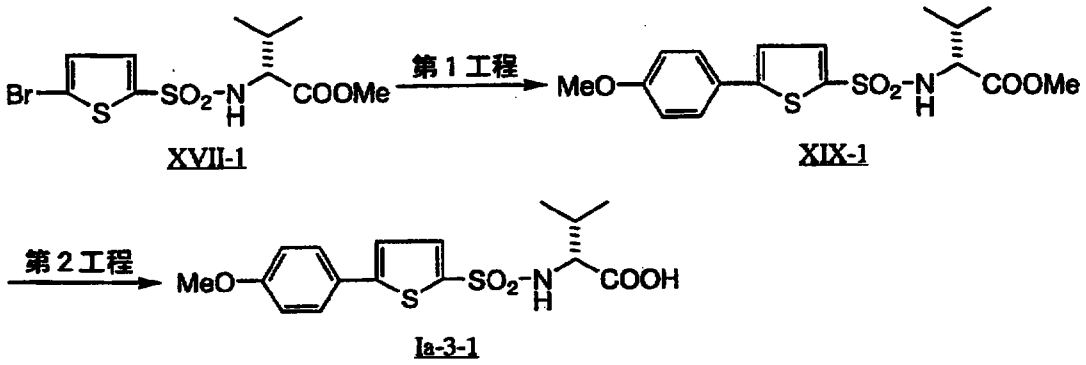
NMR(d_6-DMSO, δ ppm):2.88(s,3H),2.93(dd,J=12.0,10.2Hz,1H),3.19(dd,J=14.2,5.6Hz,1H), 3.81(s,3H), 4.74(dd,J=5.4,10.2Hz,1H), 6.99-7.04(m,2H),7.20-7.35(m,7H),7.52-7.56(m,2H),6.90(d,J=9.0Hz,2H),7.44(d,J=9.0Hz,2H),7.12(d,J=4.0Hz,1H),7.44(d,J=4.0Hz,1H)

同様に実施例１５７として、R^2＝CH_2Phの化合物(Ia-2-67)を合成した。

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

NMR(d_6-DMSO, δ ppm):2.94(dd,J=7.6,13.8Hz,1H),3.19 (dd,J=7.2,14.4Hz,1H), 3.83(s,3H), 4.29(d,J=16.2Hz,1H),4.62(d,J=16.2Hz,1H)(特徴的なピークのみ示した。)

実施例１５９（C法）



第１工程

実施例９６で得た化合物(XVII-2)500mg(1.4mmol)の乾燥テトラヒドロフラン 12ml 溶液に、粉末炭酸カリウム 387mg(2×1.4mmol)、4-メトキシフェニルボロン酸 319mg(1.5×1.4mmol),テトラキストリフェニルホスフィンパラジウム 81mg(0.05×1.4mmol)を加え、アルゴン雰囲気下に 75℃で 48 時間撹拌した。反応液を酢酸エチルで希釈し、1N-塩酸、

5%炭酸水素ナトリウム水、水にて順次洗浄した。芒硝乾燥、減圧濃縮した後、残渣をシリカゲルカラムクロマトグラフィーに付した。n-ヘキサン/酢酸エチル=3/1にて溶出する部分を集め、n-ヘキサンで結晶化し、融点122-123℃の目的物(XIX-1)447mg（収率83%）を得た。

元素分析 $C_{17}H_{21}NO_5S_2$として

計算値 C;53.25 H;5.52 N;3.65 S;16.72

実験値 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=7.0Hz,3H),1.00(d,J=6.6Hz,3H), 2.10(m,1H),3.54(s,3H),3.85(s,3H),3.87(dd,J=5.0,10.2Hz,1H),5.20(d,J=10.2Hz,1H),6.94(d,J=9.0Hz,2H),7.52(d,J=9.0Hz,2H),7.11(d,J=4.0Hz,1H),7.49(d,J=4.0Hz,1H)

第２工程

化合物(XIX-1)390mg(1.01mmol)のテトラヒドロフラン8ml、メタノール8ml混合溶液に1N-苛性ソーダ5.1mlを加え、60℃にて6時間加熱、撹拌した。反応液より減圧濃縮にて有機溶媒を除き、残渣を酢酸エチルで希釈した。クエン酸水溶液で酸性にした後、酢酸エチル抽出、ブラインにて洗浄した。芒硝乾燥、減圧濃縮し、373mg（収率 100%）の化合物(Ia-3-1)を得た。

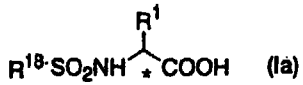
融点：174～176℃

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

実施例１６０～１７５

実施例１５９と同様にして表３１～３２に示す化合物を合成した。

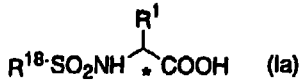
表３１



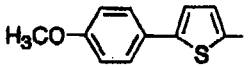
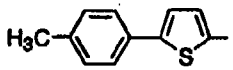
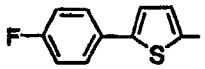
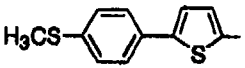
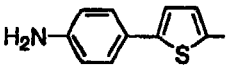
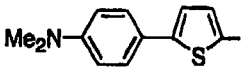
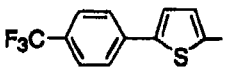
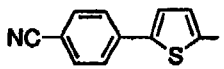
(Ia)

実施例 No.	R^1	R^{18}	*	融点（分解点） m.pt.(℃)	IR (ν cm-1) (KBr)	元素分析
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

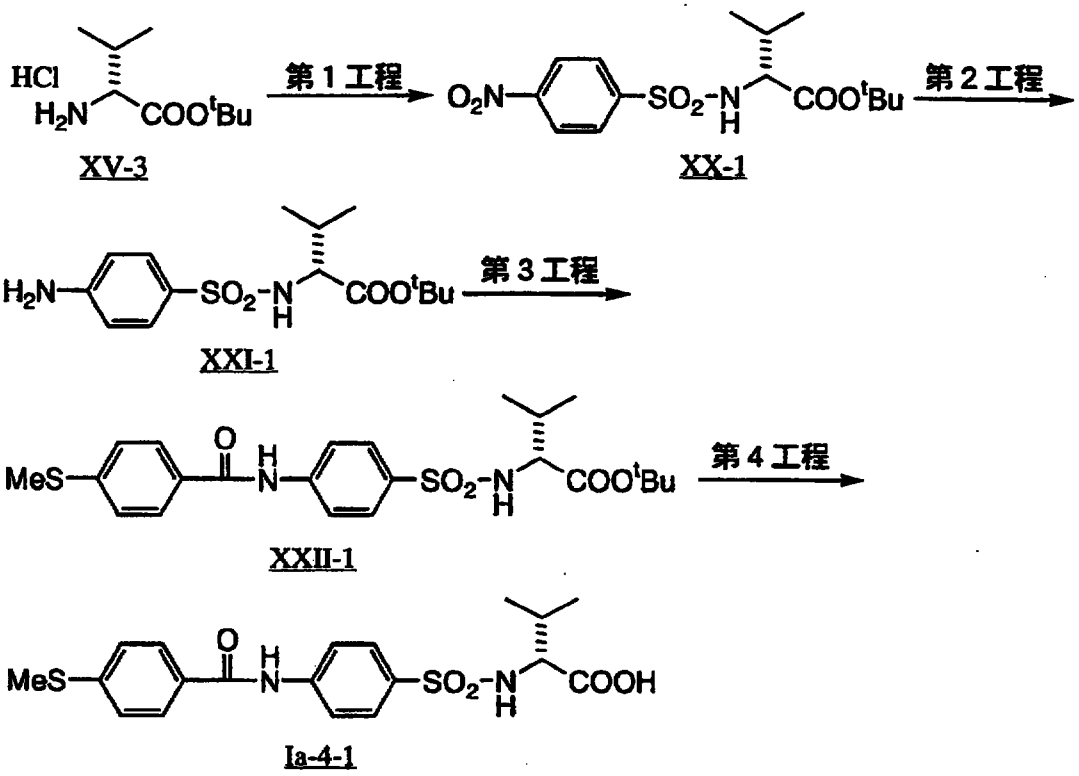
表 3 2



(Ia)

実施例 No.	R¹	R¹ᴬ	*	融点（分解点） m.pt.(℃)	IR (ν cm-1) (KBr)	元素分析
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	–	–	–

実施例１７６（Ｄ法）



第１工程

D-バリン-tert-ブチルエステル塩酸塩(XV-3)10g(47.68mmol)のジクロロメタン 100ml 溶液に N-メチルモルホリン 15.7ml(3×47.68mmol)、次いで 4-ニトロベンゼンスルホニルクロリド 14.1g(1.2×47.68mmol)を氷冷下に加えた。室温にて５時間撹拌後 2N-塩酸、5%炭酸水素ナトリウム水、水にて順次洗浄した。芒硝乾燥後、減圧濃縮し、残渣をジクロロメタン/n-ヘキサンから再結晶し、融点 89-90℃の目的物(XX-1)13.3g（収率 77.8%）を得た。

元素分析 $C_{15}H_{22}N_2O_6S$ として

計算値 C;50.27 H;6.19 N;7.82 S;8.95

実験値 C;50.04 H;6.10 N;7.89 S;8.84

[α]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

第2工程

化合物(XX-1)13.29g(37.08mmol)のメタノール200ml溶液に10%パラジウム/炭素 1g を加え、室温にて水素ガスと共に接触還元を行った。2時間後触媒を濾去し、減圧濃縮した。残渣をアセトン/n-ヘキサンから再結晶し、融点164-166℃のアミン体(XXI-1)11.5g（収率94.4%）を得た。

元素分析 $C_{15}H_{24}N_2O_4S$ として

計算値 C;54.86 H;7.37 N;8.53 S;9.76

実験値 C;54.84 H;7.33 N;8.63 S;9.50

[α]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=6.8Hz,3H),0.82(d,J=6.6Hz,3H),1.23(s,9H),1.83(m,1H),3.30(m,1H),5.86(s,2H),6.56(d,J=8.8Hz,2H),7.36(d,J=8.6Hz,2H),7.47(d,J=9.6Hz,1H)

第3工程

化合物(XXI-1)328mg(1mmol)のジクロロメタン10ml溶液にN-メチルモルホリン 0.33ml(3×1mmol)、次いで4-メチルチオベンゾイルクロリド280mg(1.5×1mmol)を氷冷下にて順次加えた。室温にて1夜撹拌し、エチルエーテルを加えた。析出した結晶を集め、氷水、エチルエーテルにて洗浄した。アセトン/エチルエーテルから再結晶し、融点235-238℃の目的物(XXII-1)433mg（収率90.5%）を得た。

元素分析 $C_{23}H_{30}N_2O_5S_2$ として

計算値 C;57.72 H;6.32 N;5.85 S;13.40

実験値 C;57.63 H;6.28 N;5.86 S;13.20

[α]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(d6-DMSO, δ ppm):0.82(d,J=6.6Hz,3H),0.84(d,J=6.8Hz,3H),1.22(s,9H),1.91(m,1H),2.55(s,3H),3.32(s,3H),3.44(dd,J=6.2,8.6Hz,1H),7.40(d,J=8.6Hz,2H),7.73(d,J=8.6Hz,2H),7.90-8.01(m,5H),10.48 (s,1H)

第４工程

化合物(XXII-1)405mg(0.85mmol)のジクロロメタン 3ml溶液に、トリフルオロ酢酸 3.3ml(50×0.85mmol)を加え、室温２時間撹拌した。減圧濃縮した後、残渣をエチルエーテルにて洗浄し、融点 231-234℃の目的物(Ia-4-1)340mg（収率 94.7%）を得た。

融点：231～234℃

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

元素分析 $C_{19}H_{22}N_2O_5S_2$・0.1CF_3COOH として

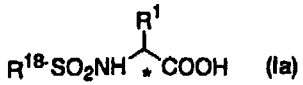
計算値：C;53.14 H;5.13 N;6.46 S;14.78

実験値：C;53.48 H;5.31 N;6.57 S;15.06

実施例１７７～２０８

実施例１７６と同様にして表３３～３６に示す化合物を合成した。

表３３



(Ia)

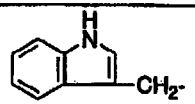
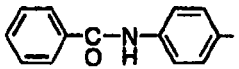
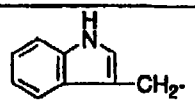
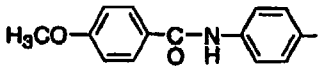
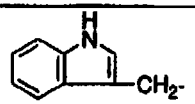
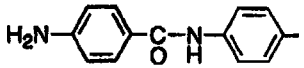
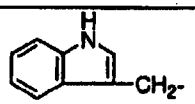
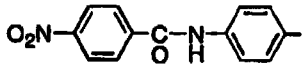
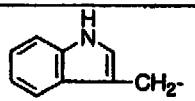
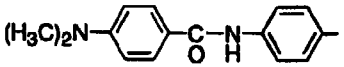
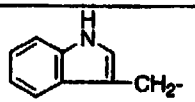
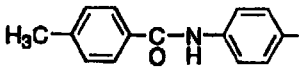
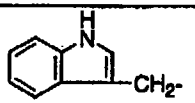
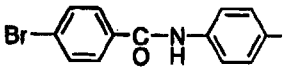
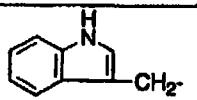
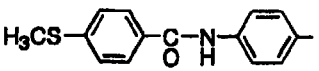
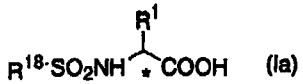
実施例 No.	R^1	R^{18}	*	融点（分解点） m.pt.(℃)	IR (ν cm-1) (KBr)	元素分析
177			R	215-217	1732,1641 1341,1163	–
178			R	233-234	1726,1655 1323,1177	$C_{25}H_{23}N_3O_6S \cdot 0.9H_2O$ Calc. C:58.91 H:4.90 N:8.24 S:6.29 Foun.C:58.97 H:5.07 N:7.95 S:6.10
179			R	216-218	1723,1633 1361,1149	–
180			R	211-213	1719,1629 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

表 3 4



(Ia)

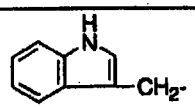
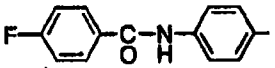
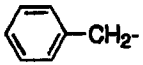
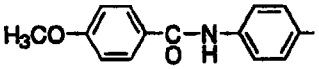
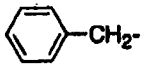
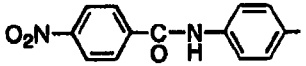
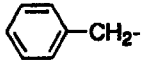
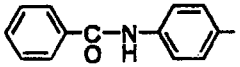
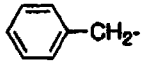
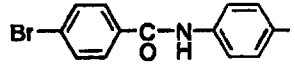
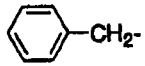
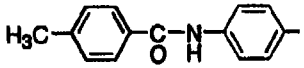
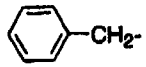
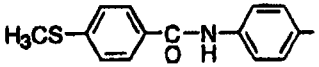
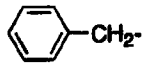
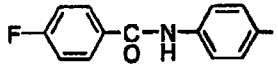
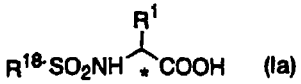
実施例 No.	R^1	R^{18}	*	融点（分解点） m.pt.(℃)	IR (ν cm-1) (KBr)	元素分析
185			R	170-175	1730,1651 1603,1333 1161	$C_{24}H_{20}FN_3O_5S \cdot 0.6H_2O$ Calc. C:58.55 H:4.34 F:3.86 N:8.54 S:6.51 Foun.C:58.67 H:4.51 F:3.77 N:8.42 S:6.47
186			R	237-239	1723,1651 1591,1322 1161	$C_{23}H_{22}N_2O_6S$ Calc. C:60.78 H:4.88 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

表３５



(Ia)

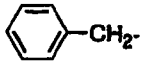
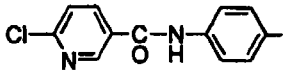
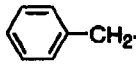
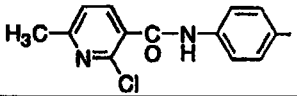
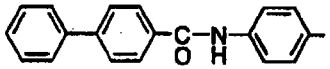
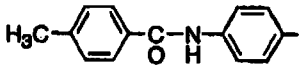
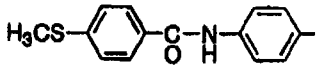
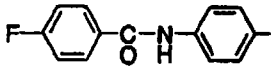
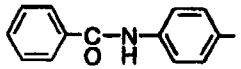
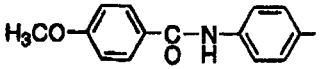
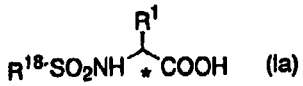
実施例 No.	R^1	R^{18}	*	融点（分解点） m.pt.(℃)	IR（ν cm-1） (KBr)	元素分析
193			R	201-203	1724,1673 1592,1326 1156	$C_{21}H_{18}ClN_3O_5S$ Calc. C:54.84 H:3.94 Cl:7.71 N:9.14 S:6.97 Foun.C:54.39 H:4.06 Cl:7.42 N:8.98 S:6.99
194			R	206-208	1725,1682 1592,1332 1160	$C_{22}H_{20}ClN_3O_5S \cdot 0.1CF_3COOH$ Calc. C:55.15 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	$C_{24}H_{24}N_2O_5S \cdot 0.5H_2O$ 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	$C_{19}H_{22}N_2O_5S \cdot 0.2H_2O$ 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	$C_{19}H_{22}N_2O_5S_2 \cdot 0.1CF_3COOH$ 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	$C_{18}H_{19}FN_2O_5S \cdot 0.1CF_3COOH$ 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	$C_{18}H_{20}N_2O_5S \cdot 0.1H_2O$ 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	$C_{19}H_{22}N_2O_6S \cdot 0.2H_2O$ 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

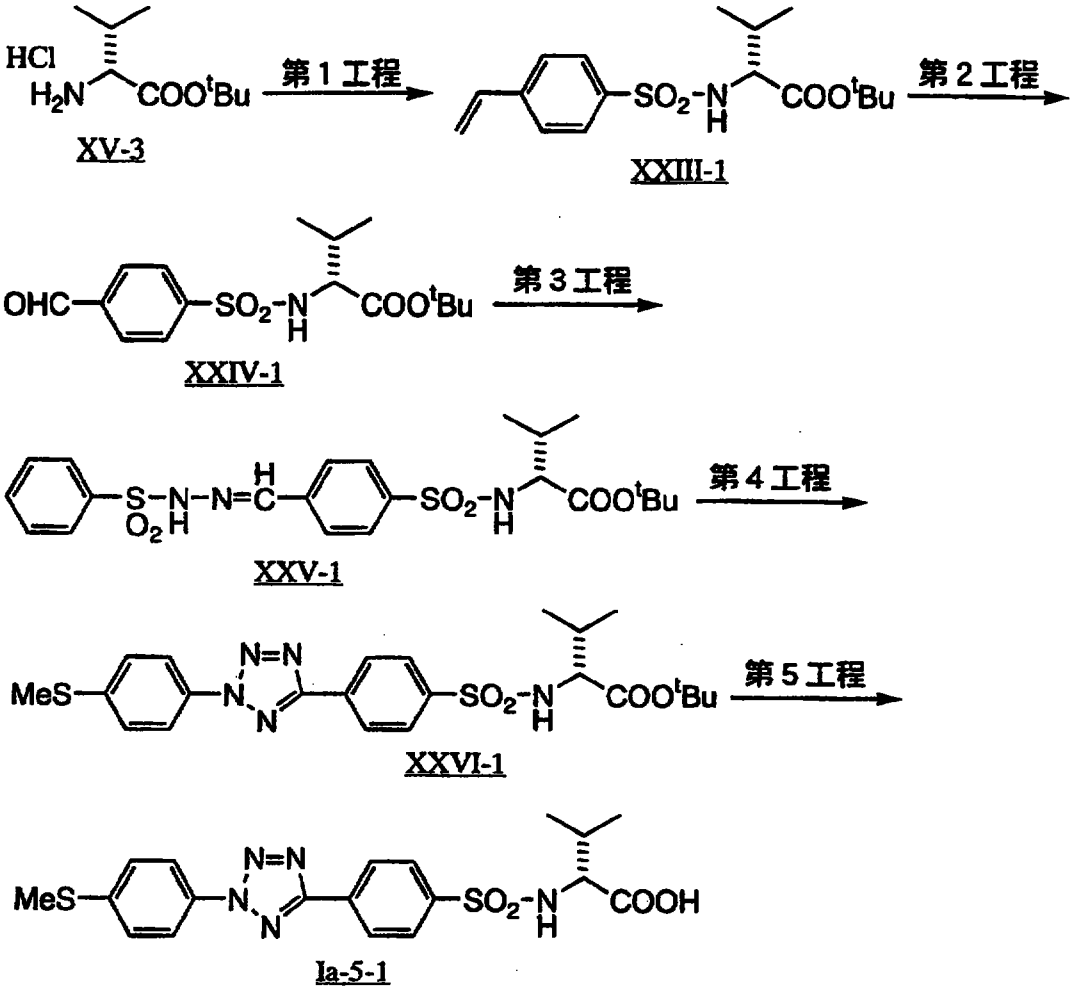
表 3 6



(Ia)

実施例 No.	R^1	R^{18}	*	融点 (分解点) m.pt.(℃)	IR (ν cm-1) (KBr)	元素分析
201	$(CH_3)_2CH$-	O_2N-C(=O)-NH-	R	240-242	1726,1688 1591,1347 1166	$C_{18}H_{19}N_3O_7S \cdot 0.4H_2O$ 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	$(CH_3)_2CH$-	Br-C(=O)-NH-	R	229-230	1726,1663 1592,1318 1159	$C_{18}H_{19}BrN_2O_5S \cdot 0.2$Ethylether 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	$(CH_3)_3C$-	H_3CO-C(=O)-NH-	R	214-216	1659,1591 1316,1159	$C_{20}H_{24}N_2O_6S \cdot 0.4H_2O$ 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-	H_3C-(N=C-N=C)-C(=O)-NH-	R	236-237	1723,1679 1590,1337 1162	$C_{21}H_{20}N_4O_5S \cdot 0.25CF_3COOH$ 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-	N-C(=O)-NH-	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-	H_3C-(N-O)-C(=O)-NH-	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-	Br-NH-C(=O)-NH-	R	217-220	1732,1679 1592,1312 1155	–
208	CH_2-	H_2N-C(=O)-NH-	R	–	–	–

実施例２０９（Ｅ法）



第１工程

D-バリンｔｅｒｔ－ブチルエステル塩酸塩(XV-3)20.94g(99.8mmol)のジクロロメタン 200ml 溶液に、N-メチルモルホリン 22ml(2×99.8mmol)、次いで p-スチレンスルホニルクロリド 20.27g(99.8mmol)を氷冷下に加えた。室温にて 15 時間撹拌した後、2N-塩酸、5%炭酸水素ナトリウム水、水にて順次洗浄した。芒硝にて乾燥後、減圧濃縮して得られた残渣をシリカゲルカラムクロマトグラフィーに付した。酢酸エチル/n-ヘキサン/クロロホルム=1/3/1 にて溶出する部分を集め、n-ヘキサ

ンにて洗浄し、融点 118-120℃の目的物(XXIII-1)28.93g（収率 85%）を得た。

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

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

第２工程

化合物(XXIII-1)5.09g(15mmol)のジクロロメタン 300ml 溶液に、－78℃にて 15 分間オゾンを通じた。次いでメチルスルフィド 22ml(20×15mmol)を加え、80 分を要して室温にした後、減圧濃縮し、6.03g のアルデヒド体(XXIV-1)を得た。

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

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

第３工程

化合物(XXIV-1)6.02g(15mmol)のエタノール 60ml、テトラヒドロフラン 15ml 混合溶液にベンゼンスルホニルヒドラジド 2.72g(1.05×15mmol)を加え、室温 2 時間撹拌した。減圧濃縮して得られた残渣を、シリカゲルカラムクロマトグラフィーに付し、クロロホルム/酢酸エチル=1/4 にて溶出する部分を集めた。酢酸エチルより再結晶を行い、融点 163-164℃の目的物(XXV-1)4.44g を得た。第２工程から 60%。

元素分析 $C_{22}H_{29}N_3O_6S_2$ として

計算値 C;53.32 H;5.90 N;8.48 S;12.94

実験値 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=6.9Hz,3H),0.99(d,J=6.6Hz,3H),1.19(s,9H),2.00(m,1H),3.63(dd,J=4.5,9.9Hz,1H),5.16(d,J=9.9Hz,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)

第4工程

4-メチルメルカプトアニリン0.14ml(1.11×1mmol)の50%エタノール水溶液に濃塩酸0.3mlを加え、内温0～5℃にて撹拌した。これに亜硝酸ソーダ78.4mg(1.14×1mmol)の水1ml溶液を加え、同温15分間撹拌した。一方、化合物(XXV-1)496mg(1mmol)の乾燥ピリジン5ml溶液を－25℃にて撹拌し、これに先の反応液を8分間で加えた。さらに－15℃から室温で4時間撹拌した。反応液を水に注ぎ込み酢酸エチルにて抽出した。2N-塩酸、5%炭酸水素ナトリウム水、水にて順次洗浄後、芒硝乾燥、減圧濃縮した。残渣をシリカゲルカラムクロマトグラフィーに付し、クロロホルム/酢酸エチル=1/9にて溶出する部分を集め、374mg(収率74%)の目的物(XXVI-1)を得た。

元素分析 $C_{23}H_{29}N_5O_4S_2 \cdot 0.3H_2O$ として

計算値 C;54.27 H;5.86 N;13.76 S;12.60

実験値 C;54.25 H;5.77 N;13.87 S;12.52

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

NMR(d6-DMSO, δ ppm):0.83(d,J=6.9Hz,3H),0.86(d,J=7.2Hz,3H),1.19(s,9H),2.00(m,1H),2.59(s,3H),3.54(dd,J=6.3,9.6Hz,1H),7.56(d,J=8.7Hz,2H),8.00(d,J=8.6Hz,2H),8.10(d,J=8.7Hz,2H),8.33(d,J=9.6Hz,2H),8.34(d,J=8.7Hz,2H)

第5工程

化合物(XXVI-1)353mgのジクロロメタン2.5ml、トリフルオロ酢酸2.5ml混合溶液を、室温にて3時間撹拌した。減圧濃縮後、残渣をエチ

ルエーテルにて洗浄し、化合物(Ia-5-1)308mg（収率 98%）を得た。

融点：194～195℃

IR(KBr, ν max cm^{-1}):1720,1343,1166

元素分析 $C_{19}H_{21}N_5O_4S_2 \cdot 1.1H_2O$ として

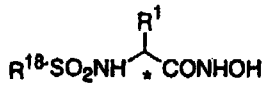
計算値：C;48.83 H;5.00 N;14.99 S;13.72

実験値：C;49.13 H;5.25 N;14.55 S;13.34

実施例２１０～２５１

実施例２０９と同様にして表３７～４３に示す化合物を合成した。

表３７



(Ib)

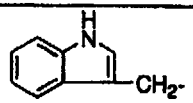
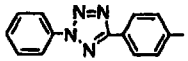
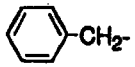
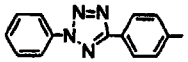
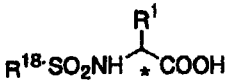
実施例 No.	R^1	R^{18}	*	融点（分解点） m.pt.(℃)	IR (ν cm-1) (KBr)	^{1}H-NMR(δ ppm) d_6-DMSO
210			R	–	–	–
211			R	194-195	3700-2200(br),3278, 1634,1337,1160	2.65(dd,J=9.3,13.1Hz,1H),2.82(dd, J=5.8,13.1Hz,1H),3.86(dt,J=5.8,9.3 Hz,1H),7.72(A_2B_2q,J=8.1Hz,2H), 8.19(A_2B_2q,J=8.1Hz,2H),8.49(d,J= 9.3Hz,1H),8.88(s,1H),10.69(s,1H)

表 3 8



(Ia)

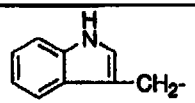
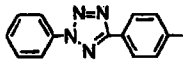
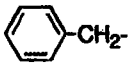
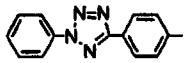
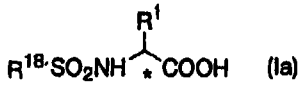
実施例 No.	R^1	R^{18}	*	融点（分解点） m.pt.(℃)	IR (ν cm-1) (KBr)	^{1}H-NMR(δ ppm) d_6-DMSO
210			R	–	–	–
211			R	215-216	2400-3700br,3422,3337, 1733,1698,1347,1170	2.75(dd,J=9.3,13.7Hz,1H),2.99(dd,J=5.3,13.7Hz,1H),3.96(dt,J= 5.3,9.3Hz,1H),8.53(d,J=9.3Hz, 1H)

表 3 9



(Ia)

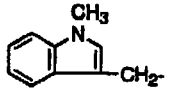
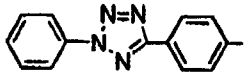
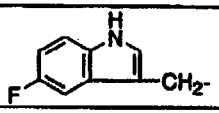
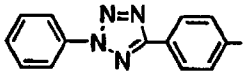
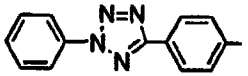
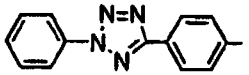
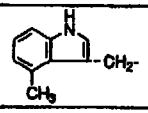
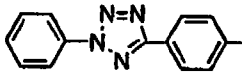
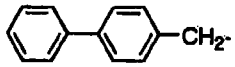
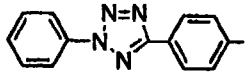
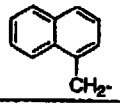
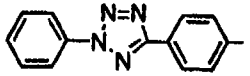
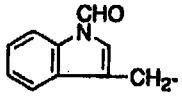
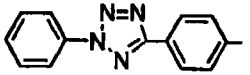
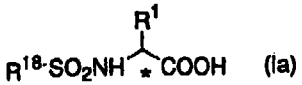
実施例 No.	R¹	R¹⁸	*	融点（分解点） m.pt.(℃)	IR (ν cm-1) (KBr)	元素分析
212			RS	199-202	1734,1337 1161	$C_{25}H_{22}N_6O_4S$•0.5Ethylether Calc. C:60.10 H:5.04 N:15.57 S:5.94 Foun.C:60.41 H:4.69 N:15.52 S:5.57
213			RS	224-225	1728,1338 1166	$C_{24}H_{19}FN_6O_4S$•0.4Ethylether Calc .C:57.35 H:4.32 F:3.54 N:15.67 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

表 4 0



(Ia)

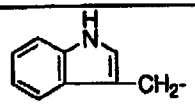
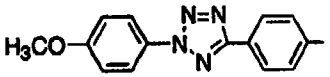
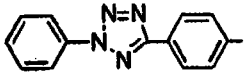
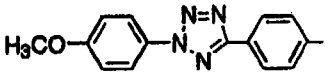
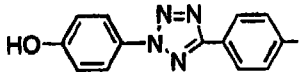
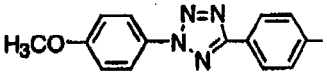
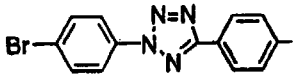
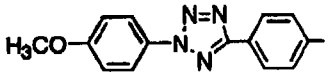
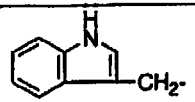
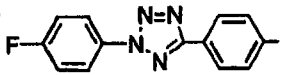
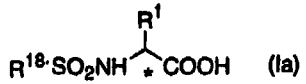
実施例 No.	R^1	R^{18}	*	融点 (分解点) m.pt.(℃)	IR (ν cm-1) (KBr)	元素分析
220			R	195-196	1749,1719 1331,1165	$C_{25}H_{22}N_6O_5S$ Calc. C:57.91 H:4.28 N:16.21 S:6.18 Foun.C:57.77 H:4.29 N:16.01 S:6.37
221	$CH_3CH_2(CH_3)CH$-		R	205-207	1730,1693 1349,1173	$C_{19}H_{21}N_5O_4S$ Calc. C:54.93 H:5.09 N:16.86 S:7.72 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	–

表 4 1



(Ia)

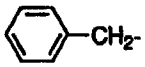
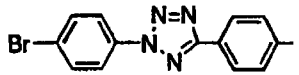
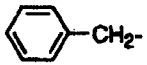
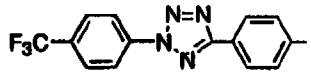
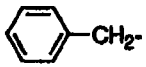
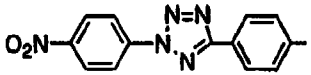
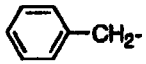
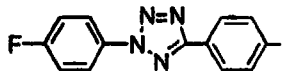
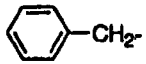
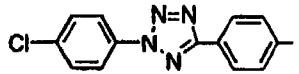
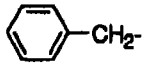
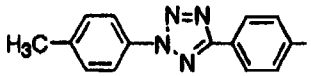
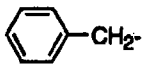
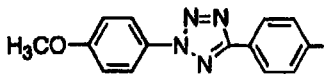
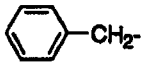
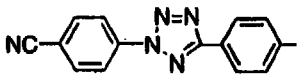
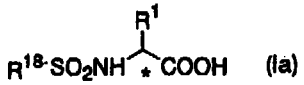
実施例 No.	R^1	R^{18}	*	融点（分解点） m.pt.(℃)	IR (ν cm-1) (KBr)	元素分析
228			R	197-199	1744,1325 1154	–
229			R	197-198	1738,1707 1328,1169	$C_{23}H_{18}F_3N_5O_4S$ Calc. C:53.38 H:3.51 F:11.01 N:13.53 S:6.20 Foun.C:53.11 H:3.55 F:10.89 N:13.66 S:6.31
230			R	190-191	1730,1597 1345,1161	$C_{22}H_{18}N_6O_6S$•0.4H_2O 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	$C_{22}H_{18}FN_5O_4S$•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	$C_{22}H_{18}ClN_5O_4S$•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	$C_{23}H_{21}N_5O_4S$•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	$C_{23}H_{21}N_5O_5S$•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	$C_{23}H_{18}N_6O_4S$•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

表 4 2



(Ia)

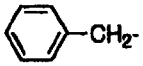
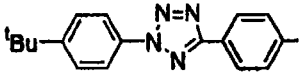
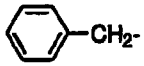
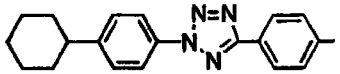
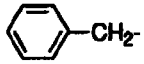
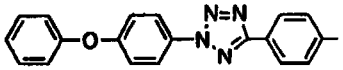
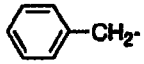
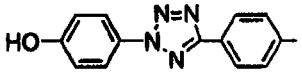
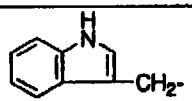
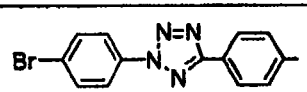
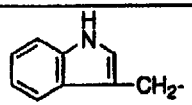
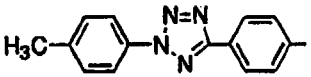
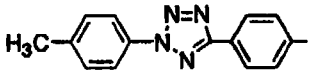
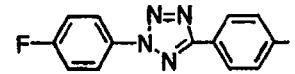
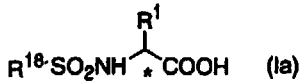
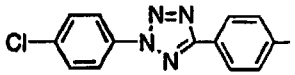
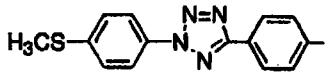
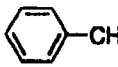
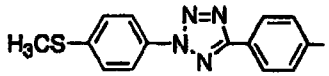
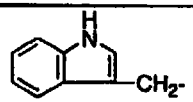
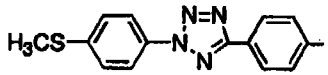
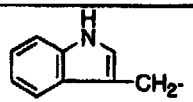
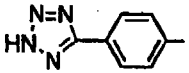
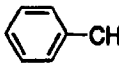
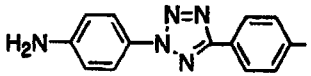
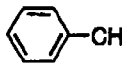
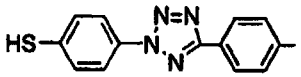
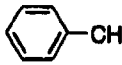
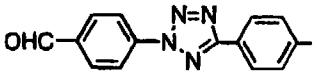
実施例 No.	R¹	R¹⁸	*	融点 (分解点) m.pt.(℃)	IR (ν cm-1) (KBr)	元素分析
236			R	224-226	1738,1328 1314,1149	$C_{26}H_{27}N_5O_4S$ Calc. C:61.77 H:5.38 N:13.85 S:6.34 Foun.C:61.59 H:5.45 N:13.89 S:6.27
237			R	225-227	1739,1512 1329,1178	$C_{28}H_{29}N_5O_4S\cdot0.3H_2O$ Calc. C:62.62 H:5.56 N:13.04 S:5.97 Foun.C:62.46 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	$C_{24}H_{19}BrN_6O_4S\cdot1.7H_2O$ 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	$C_{25}H_{22}N_6O_4S\cdot0.6H_2O$ 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	$C_{19}H_{21}N_5O_4S\cdot0.8H_2O$ 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	$C_{18}H_{18}FN_5O_4S\cdot0.2H_2O$ 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

表 4 3



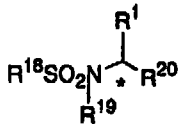
(Ia)

実施例 No.	R¹	R¹⁸	*	融点（分解点） m.pt.(℃)	IR (ν cm-1) (KBr)	元素分析
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	–	–	–

実施例２５２～２６６

実施例１５７と同様にして表４４～４５に示す化合物を合成した。

表４４



(I)

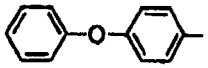
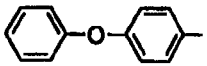
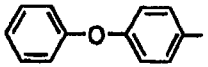
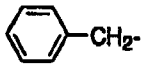
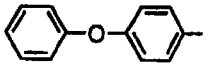
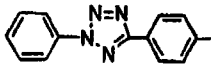
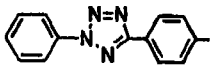
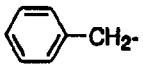
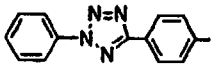
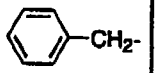
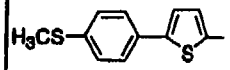
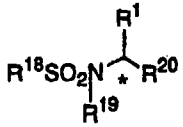
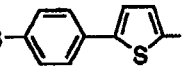
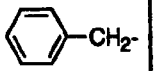
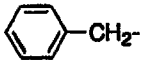
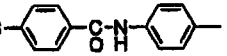
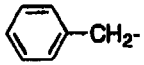
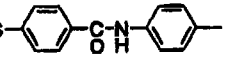
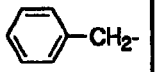
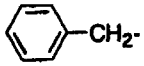
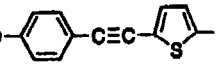
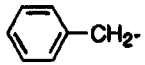
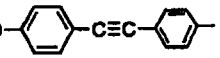
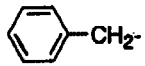
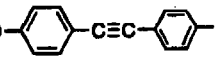
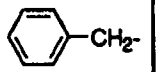
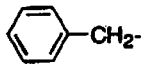
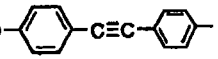
実施例 No.	R^1	R^{18}	R^{19}	R^{20}	*	融点（分解点） m.pt.(℃)	IR (ν cm-1) (KBr)	^{1}H-NMR(δ ppm) d_6-DMSO
252	$(CH_3)_2CH$-		-CH_3	-COOH	R	–	1715,1583 1340,1151	0.96(d,J=6.6Hz,3H) 1.01(d,6.8Hz,3H) 2.87(s,3H) 4.17(d,J=10.4Hz,1H)
253	$(CH_3)_2CH$-		-CH_3	-CONHOH	R	110-111	3323,1678 1328,1150	0.71(d,J=6.6Hz,3H) 0.88(d,6.4Hz,3H) 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)

表 4 5



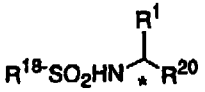
(I)

実施例 No.	R^1	R^{18}	R^{19}	R^{20}	*	融点（分解点） m.pt.(℃)	IR (ν cm-1) (KBr)	^{1}H-NMR(δ ppm) d_6-DMSO
260	$(CH_3)_2CH$-	H_3CS- 	 CH_2-	-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_2-	H_3CS- 	-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	 CH_2-	H_3CS- 	 CH_2-	-COOH	R	–	–	–
263	 CH_2-	H_3CO- 	-$(CH_2)_4NH_2$	-COOH	R	–	–	–
264	 CH_2-	H_3CO- 	-CH_3	-COOH	R	–	–	–
265	 CH_2-	H_3CO- 	 CH_2-	-COOH	R	–	–	–
266	 CH_2-	H_3CO- 	-$(CH_2)_4NH_2$	-COOH	R	–	–	–

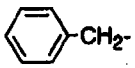
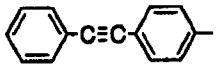
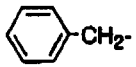
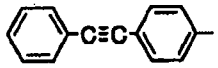
実施例２６７

実施例９２と同様にして表４６に示す化合物を合成した。

表４６



(I)

実施例 No.	R^1	R^{18}	R^{20}	*	融点（分解点） m.pt.(℃)	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)

以下に本発明化合物についての実験例を示すが、被験化合物は実施例および表中で用いたものと対応する。

実験例

(1) MMP-9(92kDa、ゼラチナーゼB)の単離・精製

以下の文献を参照し、IV型コラゲナーゼ(MMP-9)を精製した。

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 (SV40 で形質転換されたヒト肺繊維芽細胞は正常ヒトのマクロファージにより分泌されたものと同一の 92-kDa IV型コラゲナーゼを分泌する);Yasunori Okada et al, J. Biol. Chem., 267, 21712-21719, (1992) Matrix Metalloproteinase 9 (92-kDa Gelatinase/TypeIV Collagenase) from HT 1080 Human Fibrosarcoma Cells (HT 1080 株のヒトの線維芽肉腫細胞からのマトリックスメタロプロテイナーゼ 9 (92k-Da ゼラチナーゼ/IV 型コラゲナーゼ);Robin V. Ward et al,Biochem. J., (1991) 278, 179-187 The purification of tissue inhibitor of metalloproteinase-2 from its 72kDa progelatinase complex (72kDa プロゼラチナーゼ複合体からのメタロプロテイナーゼ-2の組織阻害剤の精製);

MMP-9はヒト線維芽肉腫 ATCC HT 1080株を 12-テトラデカノイルホルボル-13-アセテート(TPA)で刺激することにより培養液中に分泌される。この培養液にはゼラチンーザイモグラフィー法(Hidekazu Tanaka et al, (1993) Biochem. Biophys. Res. Commun., 190, 732-740, マウスの 105-kDa ゼラチナーゼ cDNA の分子クローニングおよび発現)でMMP-9 が産生している事を確認した。この HT1080 株の培養上清液を濃縮し、ゼラチンセファロース 4B、コンカナバリン A セファロース及

びセファクリル S-200で精製した。この精製pro-MMP-9(92kDa、ゼラチナーゼ B)はゼラチンーザイモグラフィ法で単一の活性バンドを示した。次いで、トリプシンで活性化を行い活性型MMP-9を得た。

(2) IV型 コラゲナーゼ阻害剤アッセイ方法

コラゲナーゼは前記 MMP-9、基質及び測定キットは(株)ヤガイの IV型コラゲナーゼ活性測定キットを使用し、アッセイ法は（株）ヤガイの処方に従った。阻害剤のアッセイは１つの化合物(阻害剤)について次の４つのアッセイを行う。

(A) 基質(IV型コラーゲン)、酵素(MMP-9)、阻害剤

(B) 基質(IV型コラーゲン)、阻害剤

(C) 基質(IV型コラーゲン)、酵素(MMP-9)

(D) 基質(IV型コラーゲン)

それぞれについて（株）ヤガイのアッセイ方法に従い、螢光強度を測定し、次式により阻害（％）を求めた。

阻害（％）＝｛１－（Ａ－Ｂ）／（Ｃ－Ｄ）｝×１００

ＩＣ５０は阻害（％）が５０％になる濃度を示す。結果を表４７～表５４に示す。

表４７

実施例No.	化合物No.	IC_{50} (μM)	化合物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

表４８

実施例No.	化合物No.	IC_{50} (μM)	化合物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

表49

実施例No.	化合物No.	IC_{50} (μM)	化合物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		

表５０

実施例No.	化合物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

表５１

実施例No.	化合物No.	IC_{50} (μM)
１７７	Ia-4-2	０．６８４
１７８	Ia-4-3	０．０２５２
１７９	Ia-4-4	２．３６
１８０	Ia-4-5	０．０４５
１８１	Ia-4-6	０．０５３９
１８２	Ia-4-7	０．００５９
１８３	Ia-4-8	０．００２７
１８４	Ia-4-9	０．００３２５
１８５	Ia-4-10	０．０４２２
１８６	Ia-4-11	０．０９８２
１８７	Ia-4-12	０．１７７
１８８	Ia-4-13	０．８４３
１８９	Ia-4-14	０．０３７５
１９０	Ia-4-15	０．０５９７
１９１	Ia-4-16	０．００９５
１９２	Ia-4-17	０．３２４
１９３	Ia-4-18	０．７２２
１９５	Ia-4-20	１．１
１９６	Ia-4-21	０．０５７３
１９７	Ia-4-22	０．０１６１
１９８	Ia-4-23	０．４９３
１９９	Ia-4-24	２．０６
２００	Ia-4-25	０．１７３
２０１	Ia-4-26	０．２５２
２０２	Ia-4-27	０．０１１４
２０３	Ia-4-28	０．１７３

表５２

実施例No.	化合物No.	IC_{50} (μM)	化合物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		

表５３

実施例No.	化合物No.	IC_{50} (μM)	化合物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

表５４

実施例No.	化合物No.	IC_{50} (μM)
２５２	1-252	０．２４
２５３	1-253	０．０００００３９
２５４	1-254	０．００００６３
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

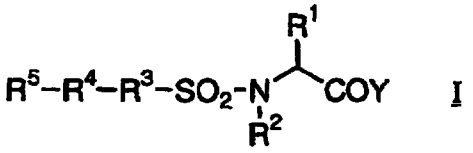
本発明化合物は、強いIV型コラゲナーゼ阻害活性を示した。

産業上の利用可能性

本発明化合物は、強いメタロプロテイナーゼ阻害活性、とりわけＭＭＰ阻害活性を有するので、変形性関節症、関節リウマチ、角膜潰瘍、歯周病、腫瘍の転移または浸潤、ウイルス感染症（例えば、ＨＩＶ感染症）の進行、閉塞性動脈硬化症、動脈硬化性動脈瘤、粥状動脈硬化症、再狭窄、敗血症、敗血症ショック、冠状血栓症、異常血管新生、強膜炎、多発性硬化症、開放角緑内障、網膜症、増殖性網膜症、血管新生緑内障、翼状皮膚、角膜炎、水泡性表皮剥離、乾癬、糖尿病、腎炎、神経性疾患、歯肉炎、腫瘍増殖、腫瘍血管新生、眼腫瘍、血管線維腫、血管腫、熱病、出血、凝固、悪液質、食欲不振、急性感染症、ショック、自己免疫症、マラリア、クローン病、髄膜炎、および胃腸潰瘍の予防または治療に有用と考えられる。

請求の範囲

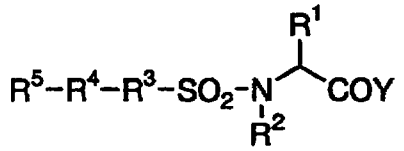
1．式I：



I

［式中、R^1は置換されていてもよい低級アルキル、置換されていてもよいアリール、置換されていてもよいアラルキル、置換されていてもよいヘテロアリールまたは置換されていてもよいヘテロアリールアルキル；R^2は水素、置換されていてもよい低級アルキル、置換されていてもよいアリール、置換されていてもよいアラルキル、置換されていてもよいヘテロアリールまたは置換されていてもよいヘテロアリールアルキル；R^3は単結合、置換されていてもよいアリーレンまたは置換されていてもよいヘテロアリーレン；R^4は単結合、－（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－またはテトラゾールジイル；R^5は置換されていてもよい低級アルキル、置換されていてもよいC_3～C_8シクロアルキル、置換されていてもよいアリール、置換されていてもよいヘテロアリールまたは置換されていてもよい非芳香性複素環式基；R^Aは水素または低級アルキル；YはNHOHまたはOH；mは1または2；ただしYがNHOHの時はR^2は水素である］で示される化合物、その光学活性体、もしくはそれらの製薬上許容される塩、またはそれらの水和物を含有するメタロプロテイナーゼ阻害剤。

2．式I：



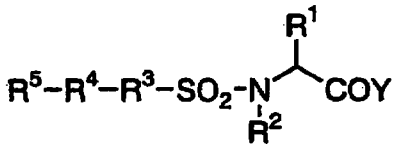
I

［式中、R^1は置換されていてもよい低級アルキル、置換されていてもよいアリール、置換されていてもよいアラルキル、置換されていてもよいヘテロアリールまたは置換されていてもよいヘテロアリールアルキル；R^2は水素、置換されていてもよい低級アルキル、置換されていてもよいアリール、置換されていてもよいアラルキル、置換されていてもよいヘテロアリールまたは置換されていてもよいヘテロアリールアルキル；R^3は単結合、置換されていてもよいアリーレンまたは置換されていてもよいヘテロアリーレン；R^4は単結合、－（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－またはテトラゾールジイル；R^5は置換されていてもよい低級アルキル、置換されていてもよいC_3～C_8シクロアルキル、置換されていてもよいアリール、置換されていてもよいヘテロアリールまたは置換されていてもよい非芳香性複素環式基；R^Aは水素または低級アルキル；YはNHOHまたはOH；mは1または2；ただしYがNHOHの時はR^2は水素であり、R^3が置換されていてもよいアリーレンまたは置換されていてもよいヘテロアリーレン、R^4が－CO－NH－または－NH－CO－の時、R^5は置換されていてもよいアリールまたは置換されていてもよいヘテロアリールであり、R^3が置換されていてもよいアリーレンまたは置換されていてもよいヘテロアリーレン、R^4がテトラゾールジイルの時、R^5は置換されていてもよいアリールまたは置換されていてもよいヘテロアリールであり、R^3が置換されていてもよいアリーレン、R^4が単結合の時、R^5は低級ア

ルキル、低級アルキルもしくは置換されていてもよいアリールで置換されているアリール、または低級アルキルもしくは置換されていてもよいアリールで置換されているヘテロアリールであり、R^3およびR^4はともに単結合ではなく、R^3が置換されていてもよいアリーレンまたは置換されていてもよいヘテロアリーレンである時、R^4は－O－でない］で示される化合物、その光学活性体、もしくはそれらの製薬上許容される塩、またはそれらの水和物を含有するメタロプロテイナーゼ阻害剤。

３．ＩＶ型コラゲナーゼ阻害剤である請求項１または２に記載のメタロプロテイナーゼ阻害剤。

４．式Ｉ：

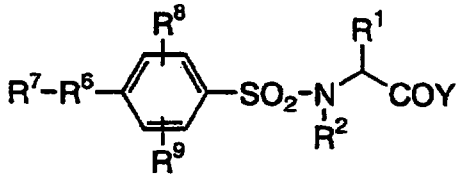


I

［式中、R^1は置換されていてもよい低級アルキル、置換されていてもよいアリール、置換されていてもよいアラルキル、置換されていてもよいヘテロアリールまたは置換されていてもよいヘテロアリールアルキル；R^2は水素、置換されていてもよい低級アルキル、置換されていてもよいアリール、置換されていてもよいアラルキル、置換されていてもよいヘテロアリールまたは置換されていてもよいヘテロアリールアルキル；R^3は単結合、置換されていてもよいアリーレンまたは置換されていてもよいヘテロアリーレン；R^4は単結合、－（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－またはテトラゾールジイル；R^5は置換されていてもよい低級アルキル、置換されていてもよいC_3～C_8シクロアルキル、置換されていてもよいアリール、置換されて

いてもよいヘテロアリールまたは置換されていてもよい非芳香性複素環式基；R^Aは水素または低級アルキル；YはNHOHまたはOH；mは1または2；ただしYがNHOHの時はR^2は水素であり、R^3が置換されていてもよいアリーレンまたは置換されていてもよいヘテロアリーレン、R^4が－CO－NH－または－NH－CO－の時、R^5は置換されていてもよいアリールまたは置換されていてもよいヘテロアリールであり（R^3がフェニレン、R^4が－CO－NH－の時、R^1はメチルもしくはフェニルではなく、R^5は2－クロロフェニル、4－クロロフェニル、および2，4－ジクロロフェニルではない）、R^3が置換されていてもよいアリーレンまたは置換されていてもよいヘテロアリーレン、R^4がテトラゾールジイルの時、R^5は低級アルキル、置換されていてもよいアリール、または置換されていてもよいヘテロアリールであり、R^3が置換されていてもよいアリーレン、R^4が単結合の時、R^5は低級アルキル、低級アルキルもしくは置換されていてもよいアリールで置換されているアリール、または低級アルキルもしくは置換されていてもよいアリールで置換されているヘテロアリールであり、R^3およびR^4はともに単結合ではなく、R^3が置換されていてもよいアリーレンまたは置換されていてもよいヘテロアリーレンである時、R^4は－O－でない］で示される化合物、その光学活性体、もしくはそれらの製薬上許容される塩、またはそれらの水和物。

5．式II：

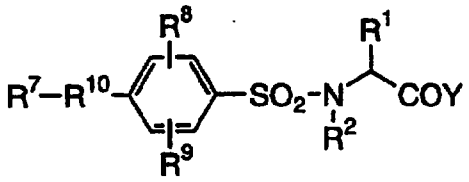


II

（式中、R^6は－CH＝CH－、－C≡C－、－N＝N－、－NH－CO－NH－、－S－、－SO_2NH－、または－SO_2－NH－N＝CH

－；R^7は置換されていてもよいアリールまたは置換されていてもよいヘテロアリール；R^8およびR^9はそれぞれ独立して、水素、低級アルコキシ、またはニトロ；R^1、R^2およびYは前記と同意義）で示される化合物、その光学活性体、もしくはそれらの製薬上許容される塩、またはそれらの水和物。

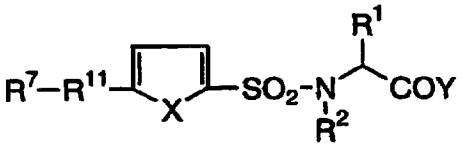
6．式III：



III

［式中、R^{10}は－（CH_2）m－、－CO－、－CO－NH－、－N（R^A）－、－NH－CO－、またはテトラゾールジイル；mは1または2；R^1、R^2、R^7、R^8、R^9、R^A、およびYは前記と同意義。ただし、R^{10}が－NH－CO－の時、R^1はメチルもしくはフェニルではなく、R^7は2－クロロフェニル、4－クロロフェニル、および2，4－ジクロロフェニルではない］で示される化合物、その光学活性体、もしくはそれらの製薬上許容される塩、またはそれらの水和物。

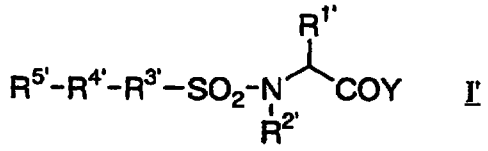
7．式IV：



IV

（式中、R^{11}は単結合、－CH＝CH－、または－C≡C－；Xは酸素原子または硫黄原子；R^1、R^2、R^7およびYは前記と同意義）で示される化合物、その光学活性体、もしくはそれらの製薬上許容される塩、またはそれらの水和物。

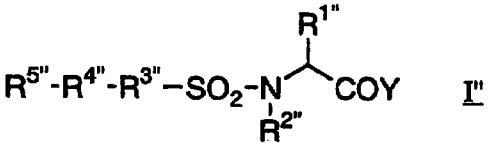
8．式I'：



I'

［式中、$R^{1'}$は、ベンジル、（インドール－３－イル）メチル、（１－メチルインドール－３－イル）メチル、（５－メチルインドール－３－イル）メチル、（５－フルオロインドール－３－イル）メチル、（１－アセチルインドール－３－イル）メチル、（１－メチルスルホニルインドール－３－イル）メチル、（１－アルコキシカルボニル－３－イル）メチル（例えば、エトキシカルボニルメチル）、またはｉ－プロピル；$R^{2'}$は水素原子、メチル、４－アミノブチル、またはベンジル；$R^{3'}$は１，４－フェニレン、$R^{4'}$は－Ｏ－、$R^{5'}$はフェニルまたは４－ヒドロキシフェニル；Ｙは前記と同意義］で示される化合物、その光学活性体、もしくはそれらの製薬上許容される塩、またはそれらの水和物。

９．式Ｉ''：



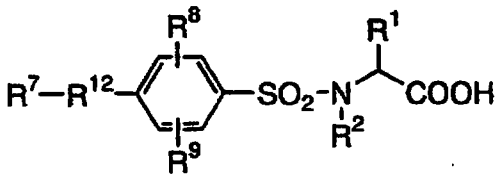
I''

［式中、$R^{1''}$は４－チアゾリルメチル、（インドール－３－イル）メチル、（５－メトキシインドール－３－イル）メチル、１－ナフチルメチル、２－ナフチルメチル、４－ビフェニリルメチル、２，２，２－トリフルオロエチル、２－フェニルエチル、ベンジル、ｉ－プロピル、４－ニトロベンジル、４－フルオロベンジル、シクロヘキシルメチル、（１－メチルインドール－３－イル）メチル、（５－メチルインドール－３－イル）メチル、（５－フルオロインドール－３－イル）メチル、（ピリジン－４－イル）メチル、（ベンゾチアゾール－２－イル）メチル、（フェニル）（ヒドロキシ）メチル、フェニル、カルボキシメチル、２

訂正された用紙(規則91)

ーカルボキシエチル、ヒドロキシメチル、フェニルメトキシメチル、4ーカルボキシベンジル、（ベンゾイミダゾールー2ーイル）メチル、（1ーメチルスルホニルインドールー3ーイル）メチル、または（1ーエトキシカルボニルインドールー3ーイル）メチル；$R^{2''}$は水素原子；$R^{3''}$は1，4ーフェニレン；$R^{4''}$は単結合；$R^{5''}$はフェニル、3ーメトキシフェニル、4ーメトキシフェニル、4ーメチルフェニル、4ーtertーブチルフェニル、4ートリフルオロメチルフェニル、4ーフルオロフェニル、4ーメチルチオフェニル、4ービフェニル、2ーチエニル、ベンゾオキサゾールー2ーイル、ベンゾチアゾールー2ーイル、またはテトラゾールー2ーイル；Yは前記と同意義〕で示される化合物、その光学活性体、もしくはそれらの製薬上許容される塩、またはそれらの水和物。

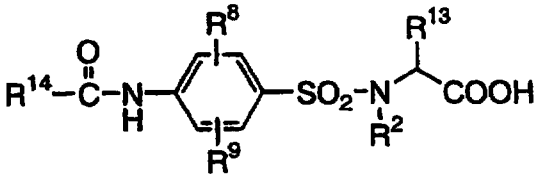
10．式V：



V

（式中、R^{12}は－CH＝CH－または－C≡C－；R^1、R^2、R^7、R^8、およびR^9は前記と同意義）で示される化合物、その光学活性体、もしくはそれらの製薬上許容される塩、またはそれらの水和物。

11．式VI：

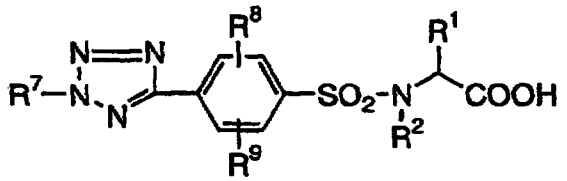


VI

（式中、R^2、R^8、およびR^9は前記と同意義、R^{13}は置換されていてもよい低級アルキル、置換されていてもよいアリール、置換されていてもよいアラルキル、置換されていてもよいヘテロアリールまたは置換さ

れていてもよいヘテロアリールアルキル、R^{14}は置換されていてもよいアリールまたは置換されていてもよいヘテロアリールを示す。ただし、R^{13}はメチルもしくはフェニルではなく、R^{14}は2－クロロフェニル、4－クロロフェニル、および2，4－ジクロロフェニルではない）で示される化合物、その光学活性体、もしくはそれらの製薬上許容される塩、またはそれらの水和物。

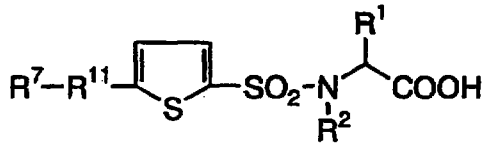
12．式VII：



VII

（式中、R^1、R^2、R^7、R^8、およびR^9は前記と同意義）で示される化合物、その光学活性体、もしくはそれらの製薬上許容される塩、またはそれらの水和物。

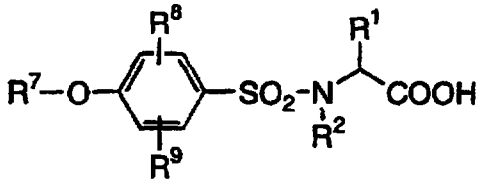
13．式VIII：



VIII

（式中、R^1、R^2、R^7、およびR^{11}は前記と同意義）で示される化合物、その光学活性体、もしくはそれらの製薬上許容される塩、またはそれらの水和物。

14．式IX：

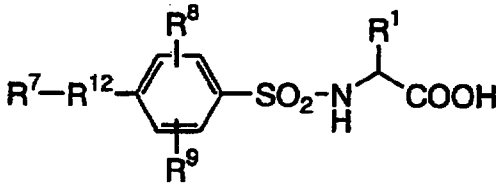


IX

（式中、R^1、R^2、R^7、R^8、およびR^9は前記と同意義）で示される化合物、その光学活性体、もしくはそれらの製薬上許容される塩、また

はそれらの水和物。

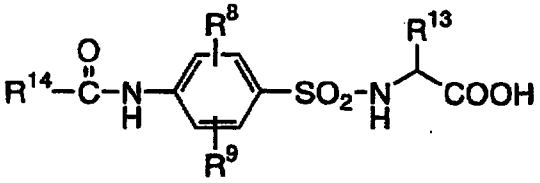
１５．式X：



X

（式中、R^{12}は－CH＝CH－または－C≡C－；R^1、R^7、R^8、およびR^9は前記と同意義）で示される化合物、その光学活性体、もしくはそれらの製薬上許容される塩、またはそれらの水和物。

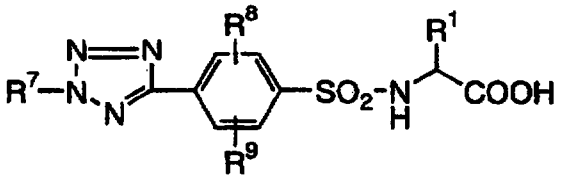
１６．式XI：



XI

（式中、R^1、R^8、R^9、R^{13}、およびR^{14}は前記と同意義。ただし、R^{13}はメチルもしくはフェニルではなく、R^{14}は２－クロロフェニル、４－クロロフェニル、および２，４－ジクロロフェニルではない）で示される化合物、その光学活性体、もしくはそれらの製薬上許容される塩、またはそれらの水和物。

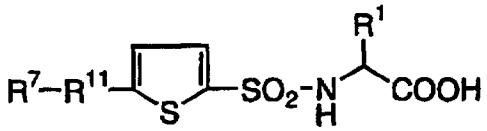
１７．式XII：



XII

（式中、R^1、R^7、R^8、およびR^9は前記と同意義）で示される化合物、その光学活性体、もしくはそれらの製薬上許容される塩、またはそれらの水和物。

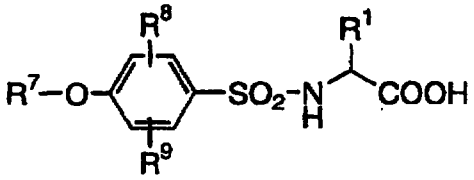
１８．式XIII：



XIII

（式中、R^1、R^7、およびR^{11}は前記と同意義）で示される化合物、その光学活性体、もしくはそれらの製薬上許容される塩、またはそれらの水和物。

１９．式ＸＩＶ：



XIV

（式中、R^1、R^7、R^8、およびR^9は前記と同意義）で示される化合物、その光学活性体、もしくはそれらの製薬上許容される塩、またはそれらの水和物。

２０．R^1、$R^{1'}$、$R^{1''}$およびR^{13}がｉ－プロピル、ベンジル、または（インドール－３－イル）メチルである請求項４～１９のいずれかに記載の化合物。

２１．R^5、R^7、およびR^{14}がアルコキシ、アルキルチオ、またはアルキルで１または２以上置換されていてもよいフェニルである請求項４～７および請求項１０～１９のいずれかに記載の化合物。

２２．R^1、$R^{1'}$、$R^{1''}$およびR^{13}が結合している不斉炭素の配置がＲである請求項４～１９記載のいずれかに記載の化合物。

２３．請求項４～１９記載のいずれかに記載の化合物を含有する医薬組成物。

２４．請求項４～１９記載のいずれかに記載の化合物を含有するメタロプロテイナーゼ阻害剤。

２５．請求項４～１９記載のいずれかに記載の化合物を含有するＩＶ型

コラゲナーゼ阻害剤。

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

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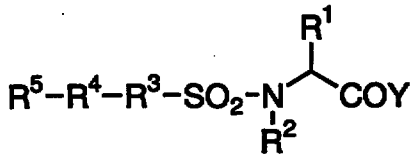
related to its activity. Therefore, development of MMP inhibitors has long been desired.

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:

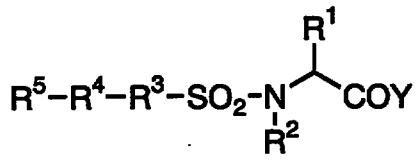


I

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

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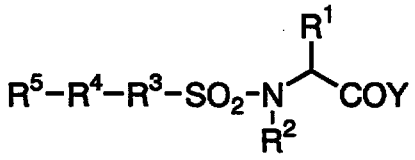
wherein R^1 is optionally substituted lower alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, or optionally substituted heteroarylalkyl; R^2 is hydrogen atom, optionally substituted lower alkyl, optionally substituted aryl, optionally substituted aralkyl,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

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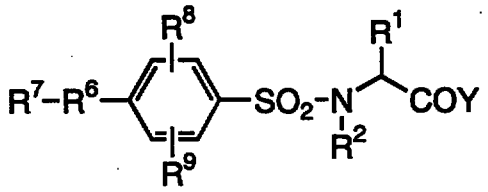
substituted aralkyl, optionally substituted heteroaryl, or optionally substituted heteroarylalkyl; R^2 is hydrogen atom, optionally substituted lower alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, or optionally substituted heteroarylalkyl; R^3 is 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

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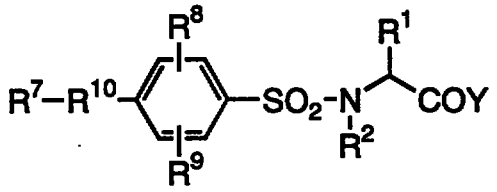
are each independently hydrogen atom, lower alkoxy, or nitro; R^1, R^2, and Y are as defined above, its optically active substance, their pharmaceutically acceptable salt, or hydrate thereof.

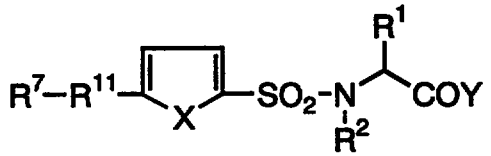
3) A compound of the formula III:



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.

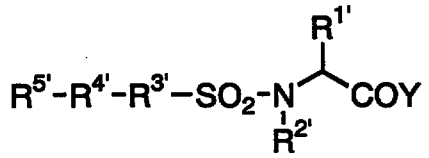
4) A compound of the formula IV:



IV

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

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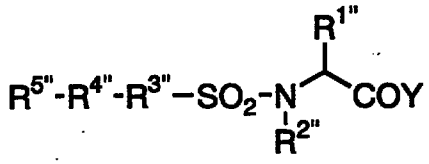
their pharmaceutically acceptable salt, or hydrate thereof.

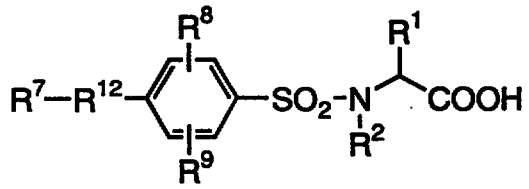
6) A compound of the formula I":



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:

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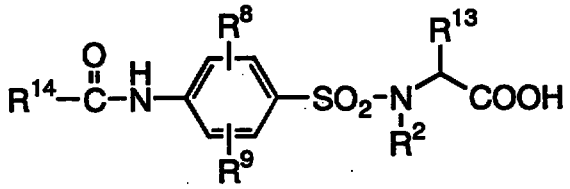
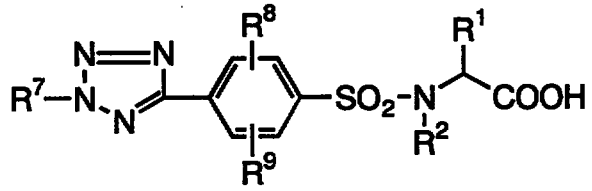


VI

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.

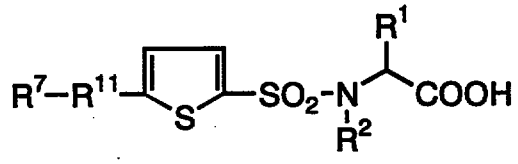
9) A compound of the formula VII:



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.

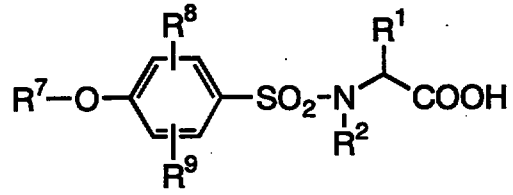
10) A compound of the formula VIII:



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

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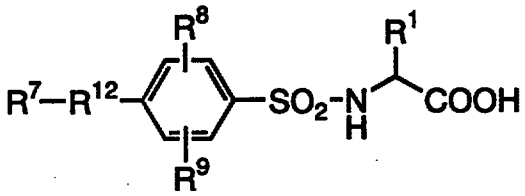
pharmaceutically acceptable salt, or hydrate thereof.

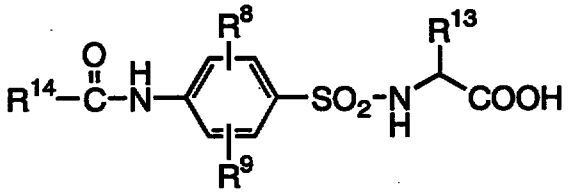
12) A compound of the formula X:



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.

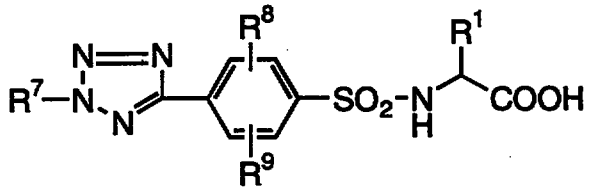
13) A compound of the formula XI:



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.

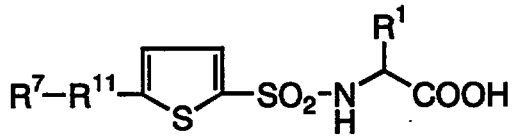
14) A compound of the formula XII:



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.

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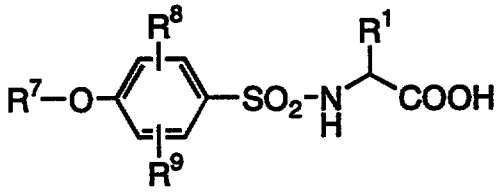
16) A compound of the formula XIV:



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:

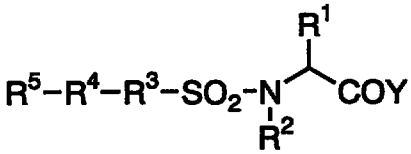
A) The compound of any one of above 1) to 16), wherein R^1, $R^{1'}$, $R^{1''}$, and R^{13} are i-propyl, benzyl, or (indol-3-yl) methyl.

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

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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.

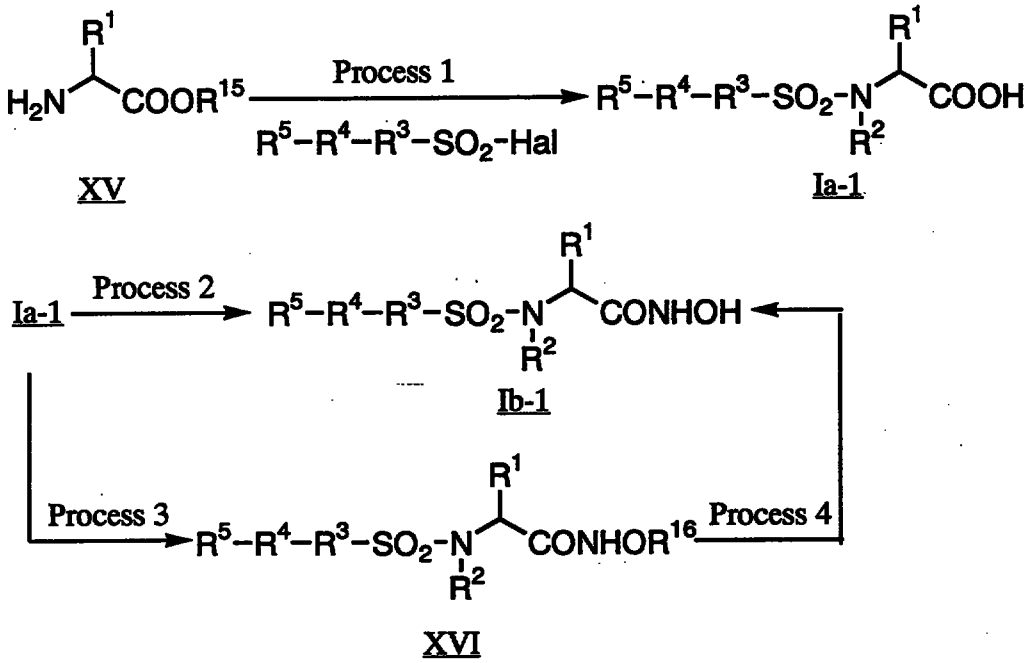
Method E: A synthetic method of the compound wherein R^3 is optionally substituted arylene or optionally substituted heteroarylene, R^4 is tetrazol-diyl, and R^5 is optionally substituted aryl or optionally substituted heteroaryl.

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.

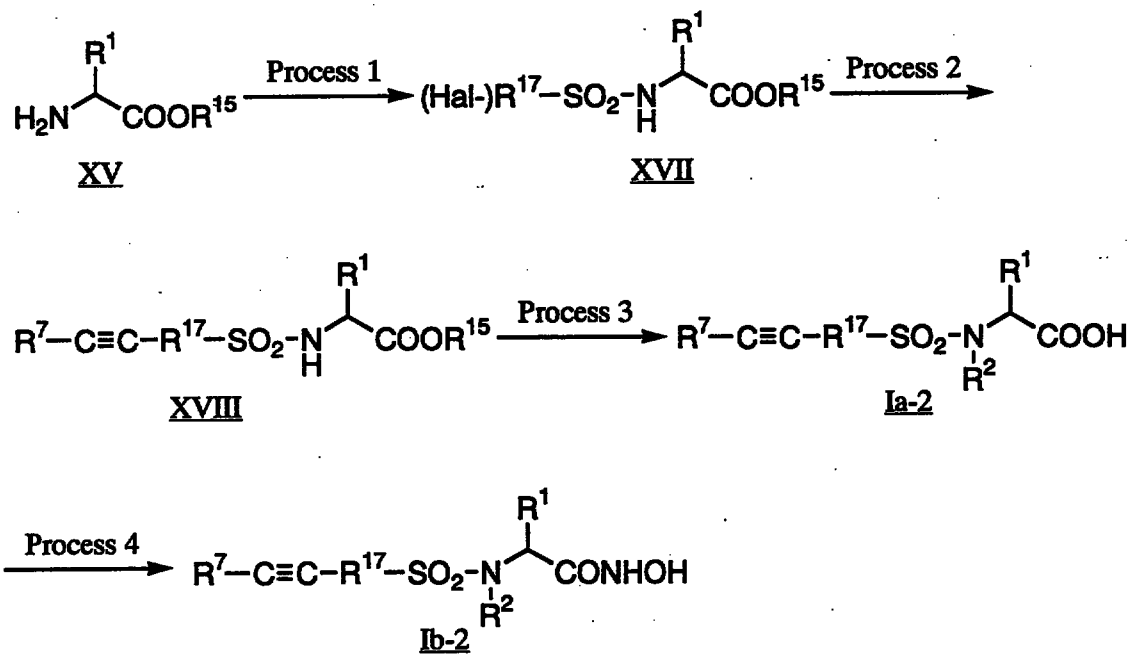
(Process 3)

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.

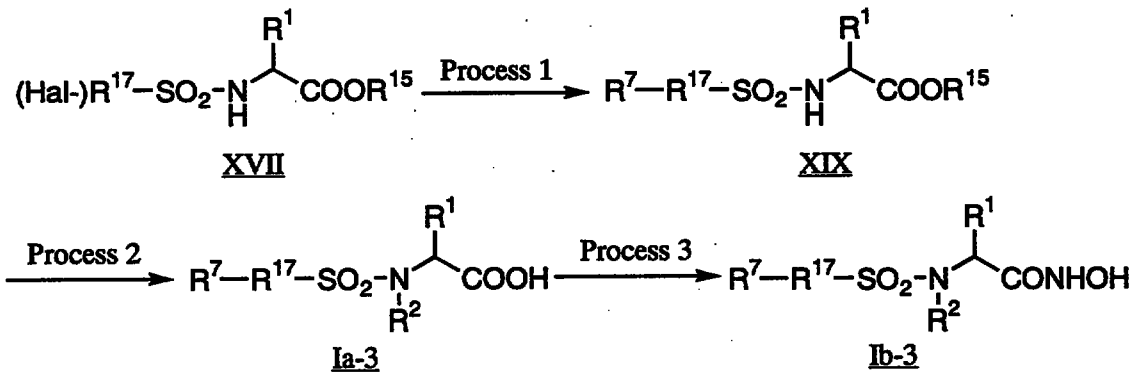
(Process 3)

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.

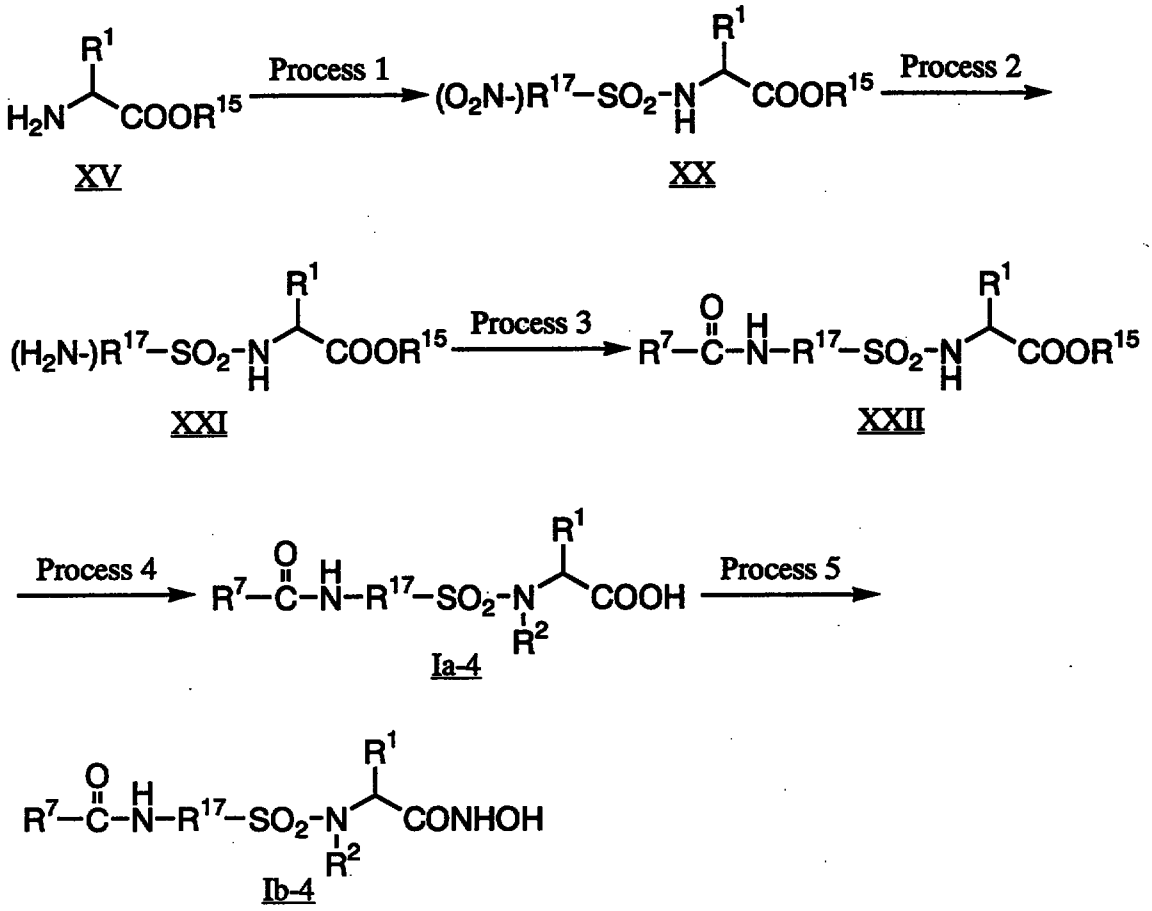
(Process 2)

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.

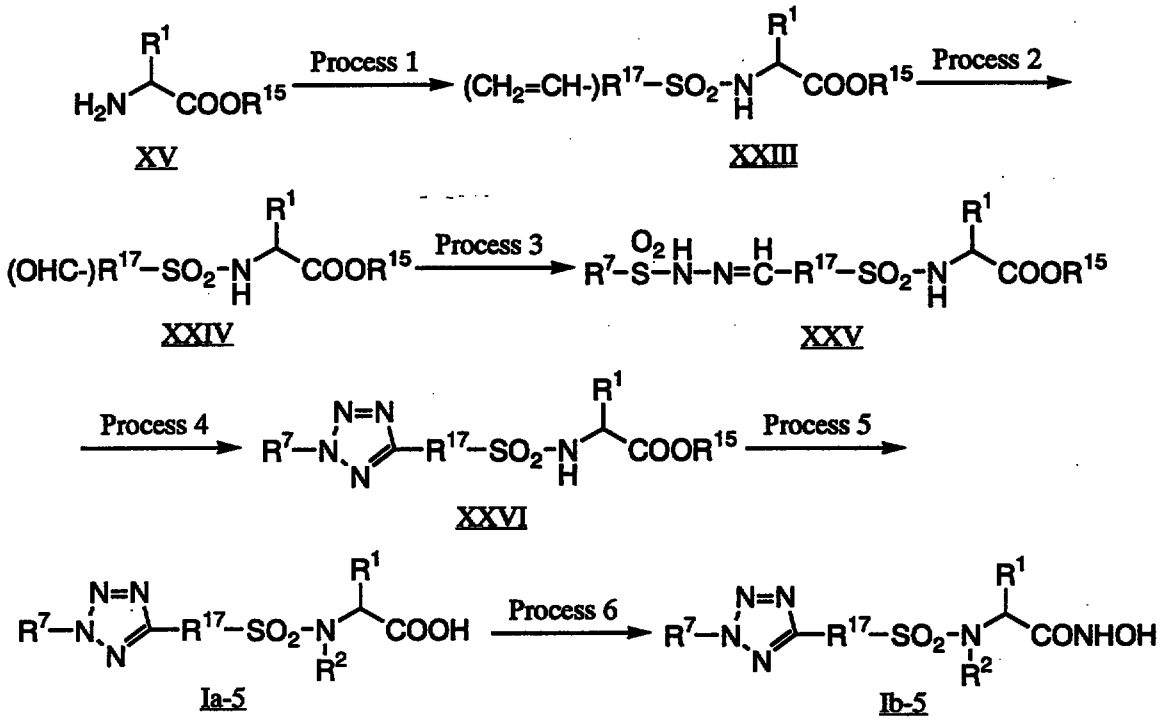
(Process 4)

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)

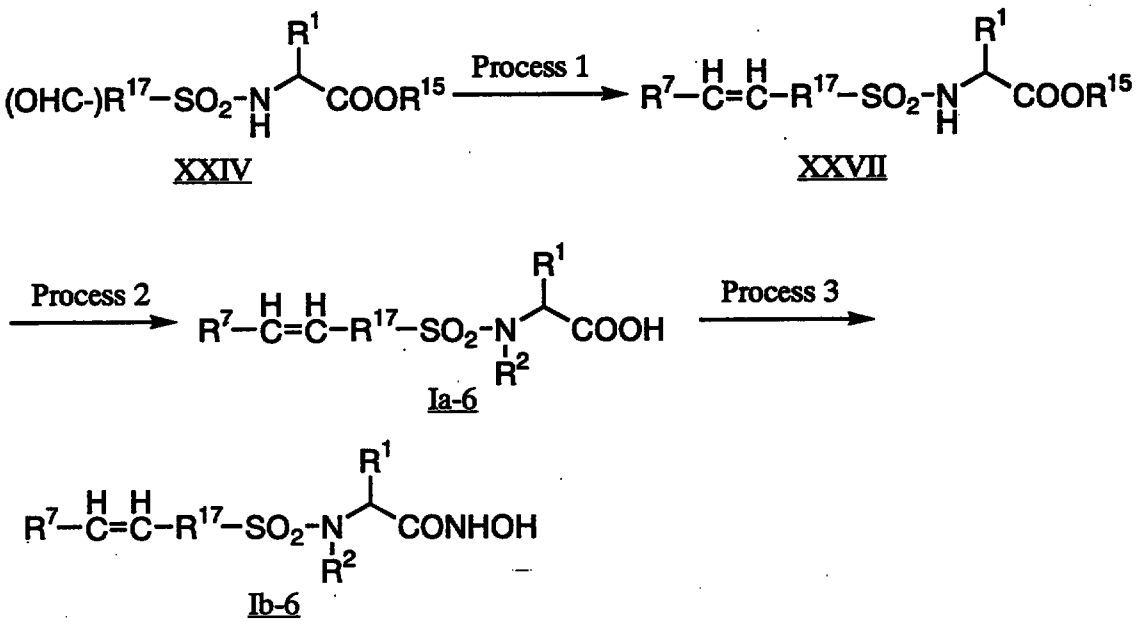
This process may be carried out in the same manner as that described in

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.

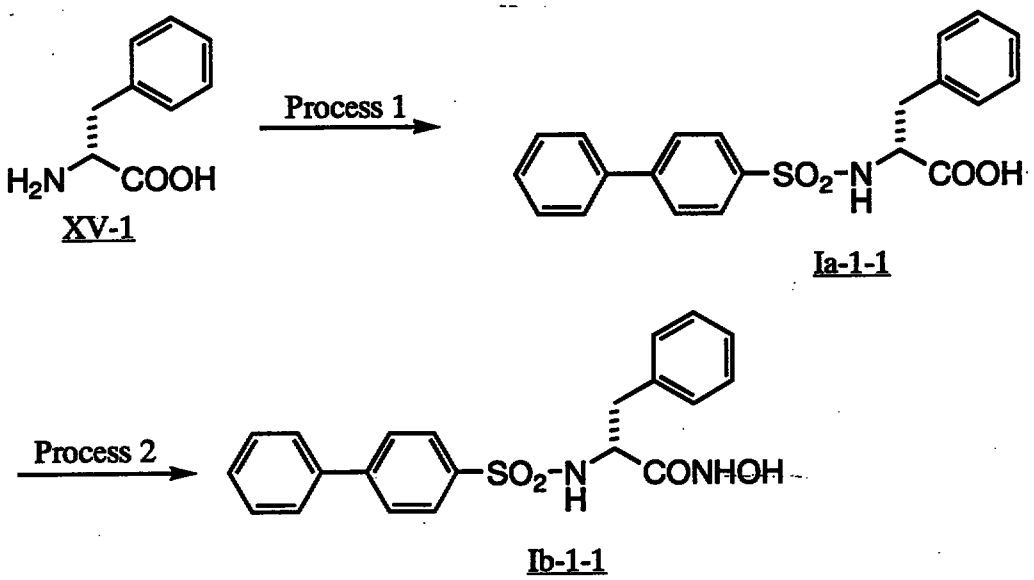
p-TsOH : p-toluenesulfonic acid

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

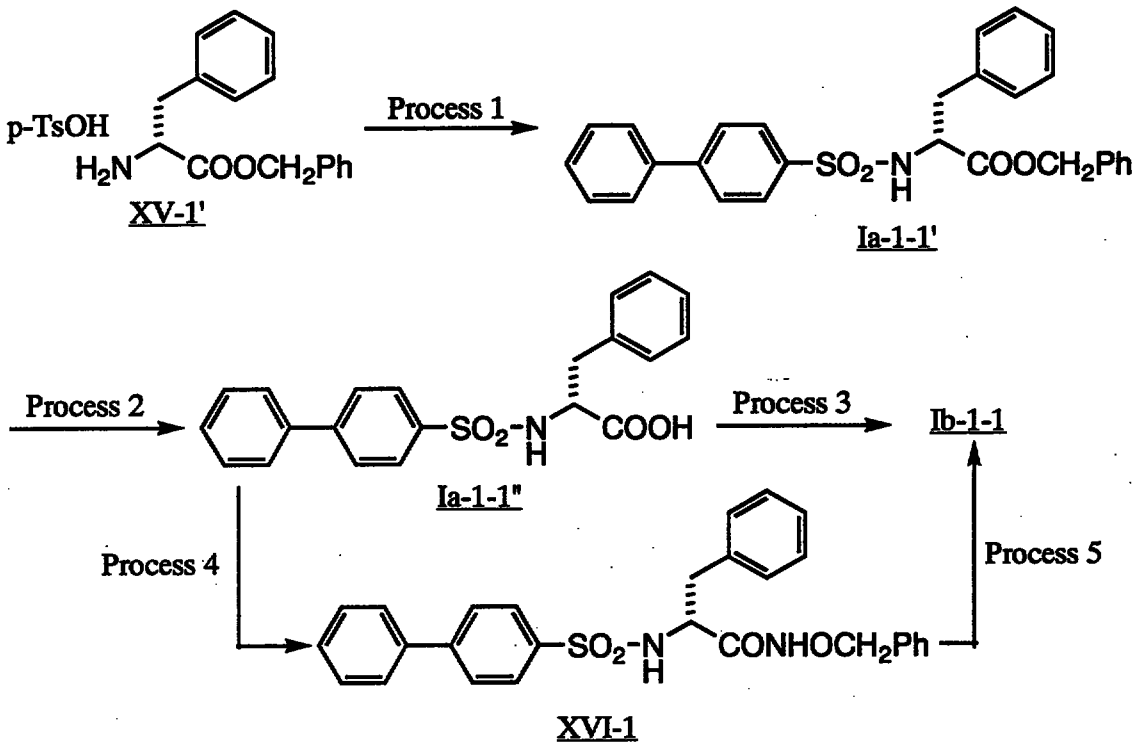
IR ν max (cm^{-1}) (Nujol) : 3365, 3295, 3266, 1674, 1320, 1159.

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)

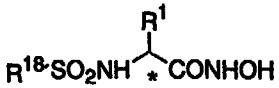
Process 5

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)

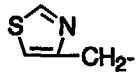
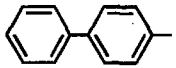
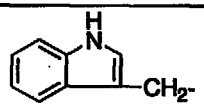
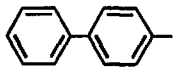
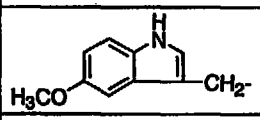
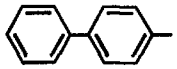
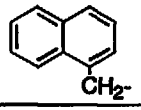
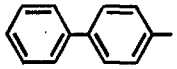
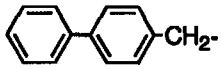
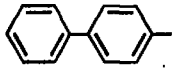
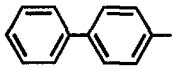
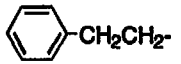
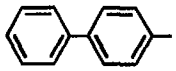
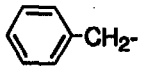
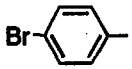
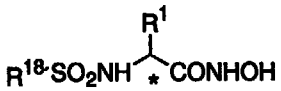
Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	^{1}H-NMR(δ ppm) d_6-DMSO
2			RS	173 >	3258,1650,1377, 1348,1163 (Nujol)	2.87(dd,J=5.6,14.2Hz,1H), 2.98(dd, J=8.4,14.2Hz,1H),4.02(dd,J=2.2, 8.6Hz,1H), 7.24(d,J=2.0Hz,1H), 8.83(d,J=2.2Hz,1H)
3			R	203-206	3403,3386,3265,1673 ,1320,1162 (Nujol)	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)

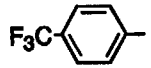
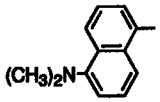
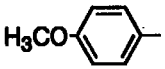
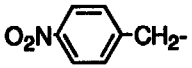
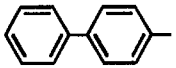
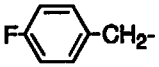
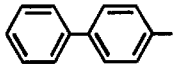
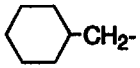
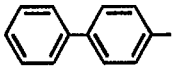
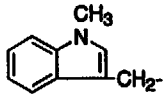
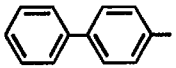
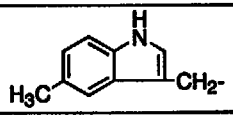
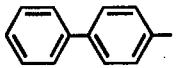
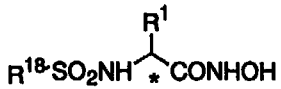
Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	^{1}H-NMR(δ ppm) d_6-DMSO
10			R	116-118	3600-2400br,3257, 1743,1721,1323,1132,	2.60-2.82(m,2H),3.84(m,1H),7.00-7.18(m,5H),7.62-7.80(m,4H),
11			R	91-92	3700-2100br,3176, 1664,1320,1143,	2.70-2.93(m,2H),2.82(s,6H), 3.75(m,1H),
12	$(CH_3)_2CH$—		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)

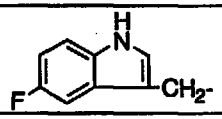
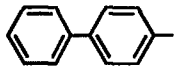
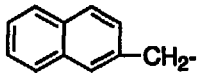
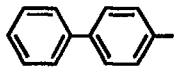
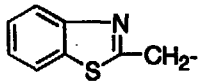
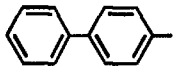
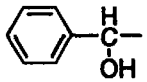
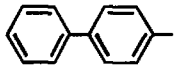
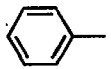
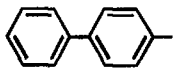
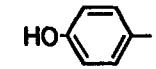
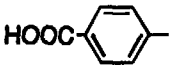
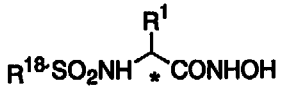
Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	^{1}H-NMR(δ ppm) d_6-DMSO
18			RS	–	3420,1670,1592, 1321,1159	2.72(dd,J=8.0,14.0Hz,1H),2.90(dd, J=6.2,14.2Hz,1H),3.82(m,1H)
19			RS	–	–	–
20			RS	154-158	3186,1593,1480, 1379	2.68(dd,J=9.8,13.7Hz,1H),2.79(dd, J=5.6,12.8Hz,1H),3.85(t,J=7.0Hz,1H),
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)

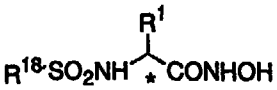
Table 4



(Ib)

Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	^{1}H-NMR(δ ppm) d_6-DMSO
26	$-CH_2-$	F-	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	$-CH_2-$	O_2N-	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_2q,J=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	$-CH_2OCH_2-$		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	H N CH_2-		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)

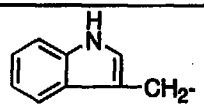
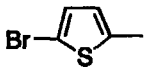
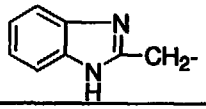
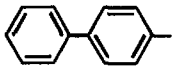
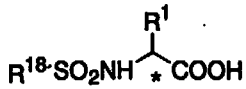
Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	^{1}H-NMR(δ ppm) d_6-DMSO
34			R	–	–	–
35			RS	141-145	3700-2400(br),1672, 1443,1327,1094	2.84-3.21(m,2H),4.29(m,1H)

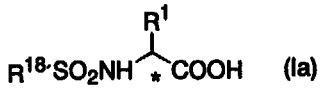
Table 6



(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)

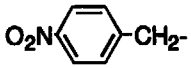
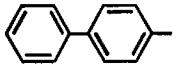
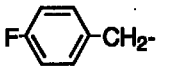
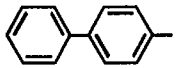
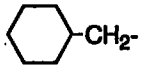
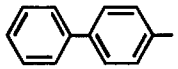
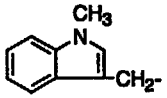
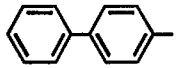
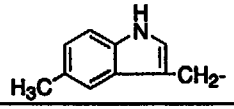
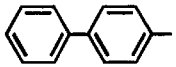
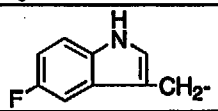
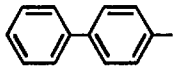
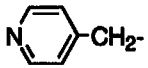
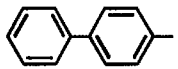
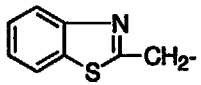
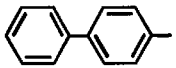
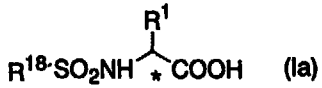
Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	^{1}H-NMR(δ ppm) d_6-DMSO
13			RS	212-213	3113,1724,1520, 1345,1158	2.86(dd,J=10.2,13.2Hz,1H), 3.14(dd,J=4.5,13.7Hz,1H), 4.02(m,1H),8.42(d,J=8.4Hz,1H)
14			RS	164-165	3426,3114,1715, 1509,1224,1159	2.71(dd,J=9.9,13.7Hz,1H),2.96(dd, J=5.3,13.5Hz,1H),3.89(m,1H), 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)

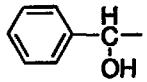
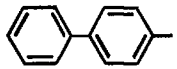
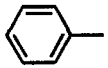
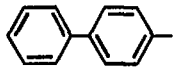
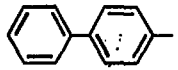
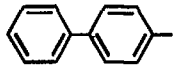
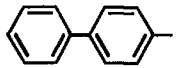
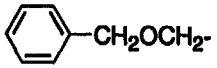
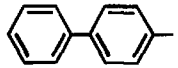
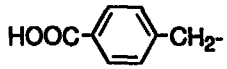
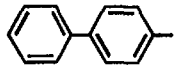
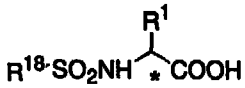
Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	^{1}H-NMR(δ ppm) d_6-DMSO
22			RS	141-143	3335,3246,1732, 1315,1152	4.10(d.J=3.2Hz,1H),5.13(d,J= 3.2Hz,1H)
23			R	211-214	3316,1734,1325, 1159(Nujol)	4.94(d,J=9.4Hz,1H),8.80(d,J= 9.4Hz,1H),13.0(br.s,1H)
28	HOOC-CH_2-		R	171-173	3353,1752,1326, 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)

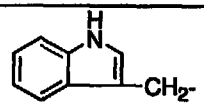
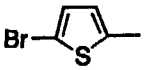
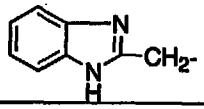
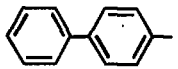
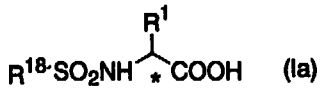
Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	^{1}H-NMR(δ ppm) d_6-DMSO
34			R	243-246	3420,1588,1402, 1324,1151	3.06(dd,J=5.4,14.4Hz,1H),3.14(dd, J=5.1,14.4Hz,1H),3.65(t,J=5.4Hz, 1H),6.92(m,1H),10.72(s,1H)
35			RS	151-156	2200-3700br,1734, 1334,1161	3.17-3.50(m,2H),4.51(m,1H)

Table 10



(Ia)

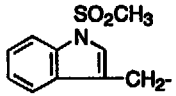
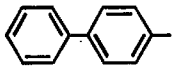
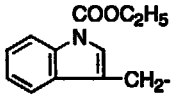
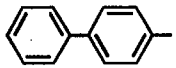
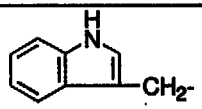
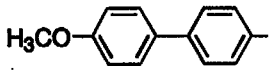
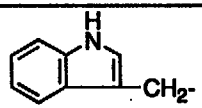
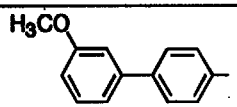
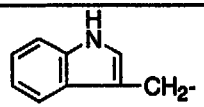
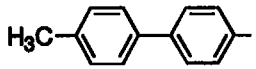
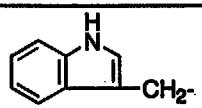
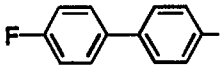
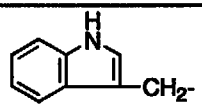
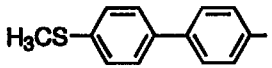
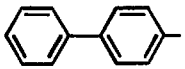
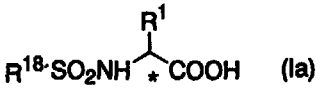
Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	Elemental analysis
36			RS	>145	1726,1354 1326,1161	–
37			RS	–	1732,1594 1404,1155	–
38			R	188-190	1607,1594 1294,1153	$C_{24}H_{22}N_2O_5S \cdot 0.5H_2O$ Calc. C:62.73 H:5.04 N:6.10 S:6.98 Foun.C:62.75 H:5.08 N:6.31 S:7.05
39			R	90-93	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

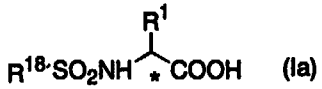
Table 11



(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)

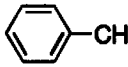
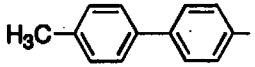
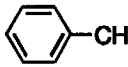
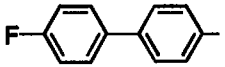
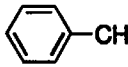
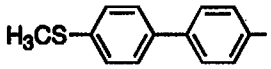
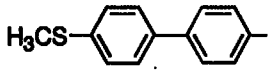
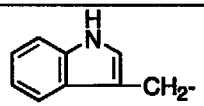
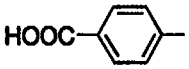
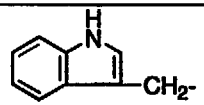
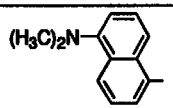
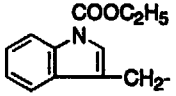
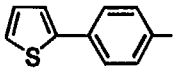
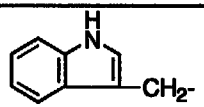
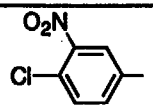
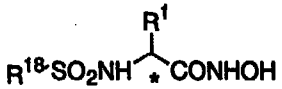
Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	Elemental analysis
52			R	157-160	1685,1349 1166	–
53			R	111-112	1691,1567 1390,1159	–
54			R	194-195	1749,1592 1323,1164	–
55	$(CH_3)_2CH$-		R	197-199	1746,1337 1164	$C_{18}H_{21}NO_4S_2 \cdot 0.2H_2O$ Calc. C:56.43 H:5.63 N:3.66 S:16.74 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)

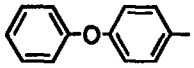
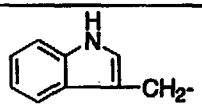
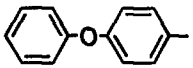
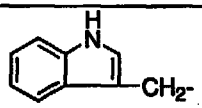
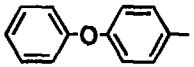
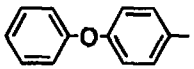
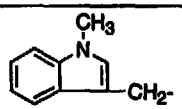
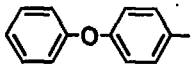
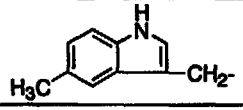
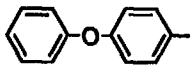
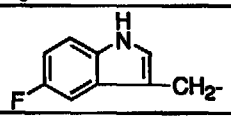
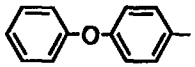
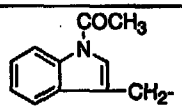
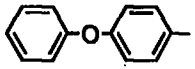
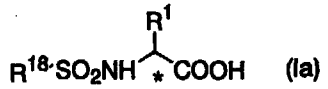
Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	^{1}H-NMR(δ ppm) d_6-DMSO
60			R	foam	3700-2400br,3277, 1669,1325,1152	2.60(dd,J=8.7,13.7Hz,1H), 2.79(dd, J=6.0,13.7Hz,1H),3.75(ddd,J=6.0, 8.7,9.0,1H),6.94(d,J=8.9Hz.2H)
61			R	115-118	3302,1667,1324, 1153(Nujol)	2.71(dd,J=7.0,14.4Hz,1H), 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)

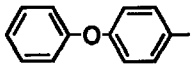
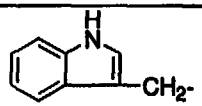
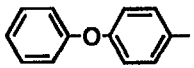
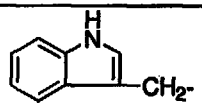
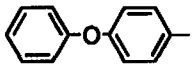
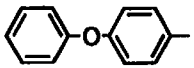
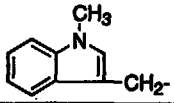
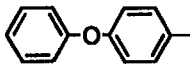
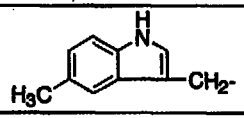
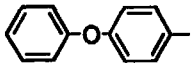
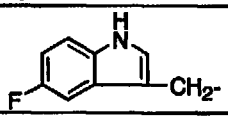
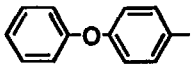
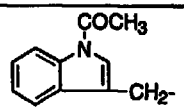
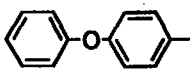
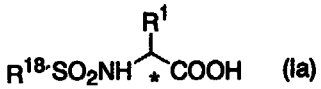
Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	^{1}H-NMR(δ ppm) d_6-DMSO
60			R	108-109	2400-3600br,3345,3213, 1735,1700,1346,1163	2.72(dd,J=8.7,13.6Hz,1H),2.94(dd, J=5.6,13.6Hz,1H),3.84(ddd,J=5.6, 8.7,8.7Hz,1H),8.23(d,J=8.7Hz,1H)
61			R	82-87	3410,3276,1724,1582, 1488,1331,1152(Nujol)	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)

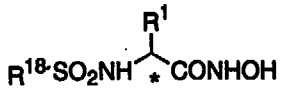
Table 15



(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)

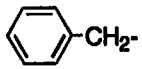
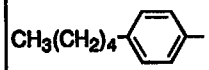
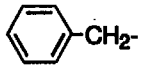
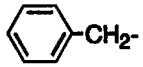
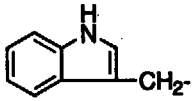
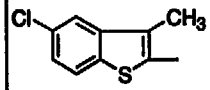
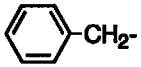
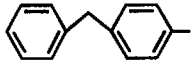
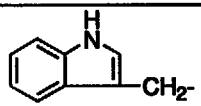
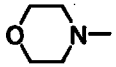
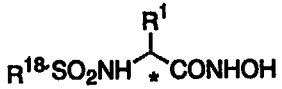
Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	^{1}H-NMR(δ ppm) d_6-DMSO
71			R	129-131	3700-2400br,3247, 1636,1337,1160	0.90(t,J=6.8Hz,3H),1.22-1.40(m,4H),1.52-1.67(m,2H),2.62(t,J=7.7Hz,2H),2.86(dd,J=8.4,13.7Hz,1H),3.02(dd,J=5.7,13.7Hz,1H) ($CDCl_3$)
72		$CH_3(CH_2)_7$—	R	oil	3700-2400br,1663, 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_2q,J=7.5Hz,2H),7.42(A_2B_2q,J=7.5Hz,2H)($CDCl_3$)
76			R	–	–	–

Table 17



(Ib)

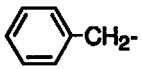
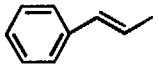
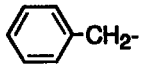
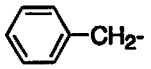
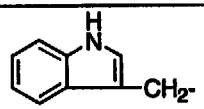
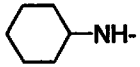
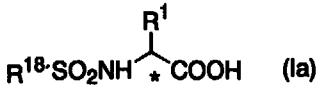
Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	^{1}H-NMR(δ ppm) d_6-DMSO
77			R	138-139	3700-2400(br),3312, 1629,1329,1144	2.79(dd,J=8.5,13.4Hz,1H),2.89(dd, J=6.0,13.4Hz,1H),3.81(dd,J=6.0, 8.5Hz,1H),6.55(d,J=15.5Hz,1H)
78			R	69-70	3700-2200(br),1670, 1318,1152	2.78(dd,J=8.6,13.4Hz,1H),2.91(dd,J=6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

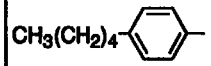
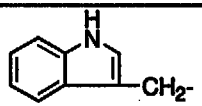
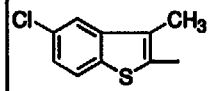
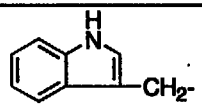
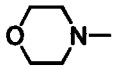
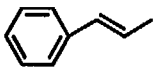
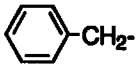
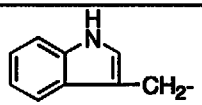
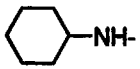
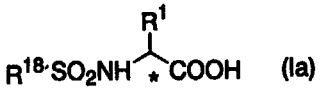
Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	^{1}H-NMR(δ ppm) d_6-DMSO
71			R	121-122	2300-3700br,3426,3318, 1713,1330,1159	0.89(t,J=6.7Hz,3H),2.62(t,J=7.6Hz,2H),2.96(dd,J=7.0,13.9Hz,1H),3.10(dd,J=5.4,13.9Hz,1H),4.19(dt,J=6.9,8.2Hz,1H),5.30(d,J=8.2Hz,1H),
72		$CH_3(CH_2)_7$—	R	oil	2400-3600br,3340,1736, 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)

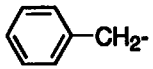
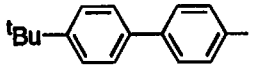
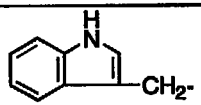
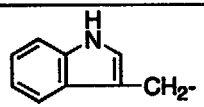
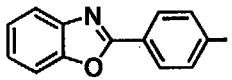
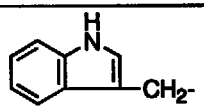
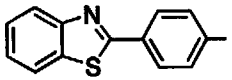
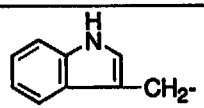
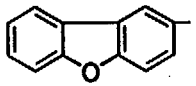
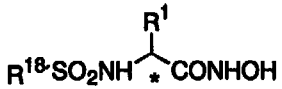
Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	Elemental analysis
80			R	153-155	1704,1596 1349,1164	–
81		n-C_8H_{17}-	R	>130	1576,1356 1139	–
82			R	128-130	1732,1342 1167	$C_{24}H_{19}N_3O_5S \cdot 1.3H_2O$ Calc. C:59.45 H:4.49 N:8.67 S:6.61 Foun.C:59.43 H:4.45 N:8.59 S:6.58
83			R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

Table 20



(Ib)

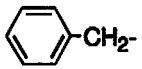
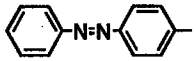
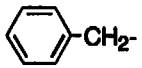
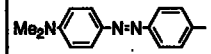
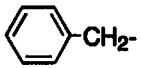
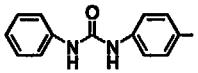
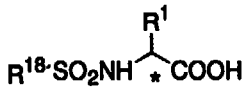
Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	^{1}H-NMR(δ ppm) d_6-DMSO
85			R	157-160	3700-2400br,3273, 1633,1338,1166	2.65(dd,J=8.9,13.6Hz,1H), 2.82(dd, J=6.6,13.6Hz,1H),3.86(m,1H),7.75 (d,J=7.8Hz,2H),7.87(d,J=8.7Hz,2H)
86			R	138-142	3700-2400br,2921, 1672,1314,1165,	2.62(dd,J=8.6,13.5Hz,1H),2.81(dd,J=6. 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,1 H),3.76(m,1H),8.02(d,J=8.7Hz,1H),8.80(s,1H),8.8 5(d,J=1.7Hz,1H),9.06(s,1H),10.59(d,J=1.7Hz,1H)

Table 21



(Ia)

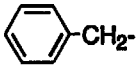
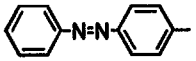
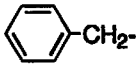
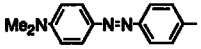
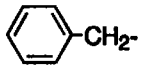
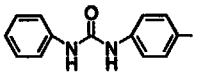
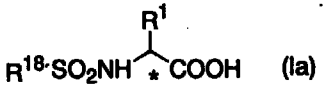
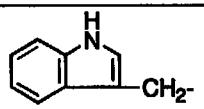
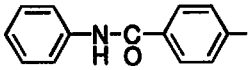
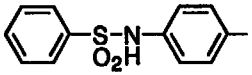
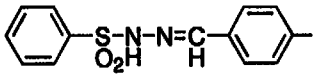
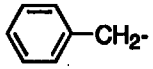
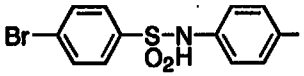
Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	^{1}H-NMR(δ ppm) d_6-DMSO
85			R	172-174	2400-3600br,3426,3296, 1698,1350,1167	2.75(dd,J=9.1,13.7Hz,1H),2.98(dd, J=5.5,13.7Hz,1H),3.96(ddd,J=5.5, 9.1,9.1Hz,1H),8.51(d,J+9.1Hz,1H)
86			R	93-94	2200-3700br,3431, 1735,1391,1154	2.74(dd,J=9.1,13.6Hz,1H),2.96(dd,J =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)

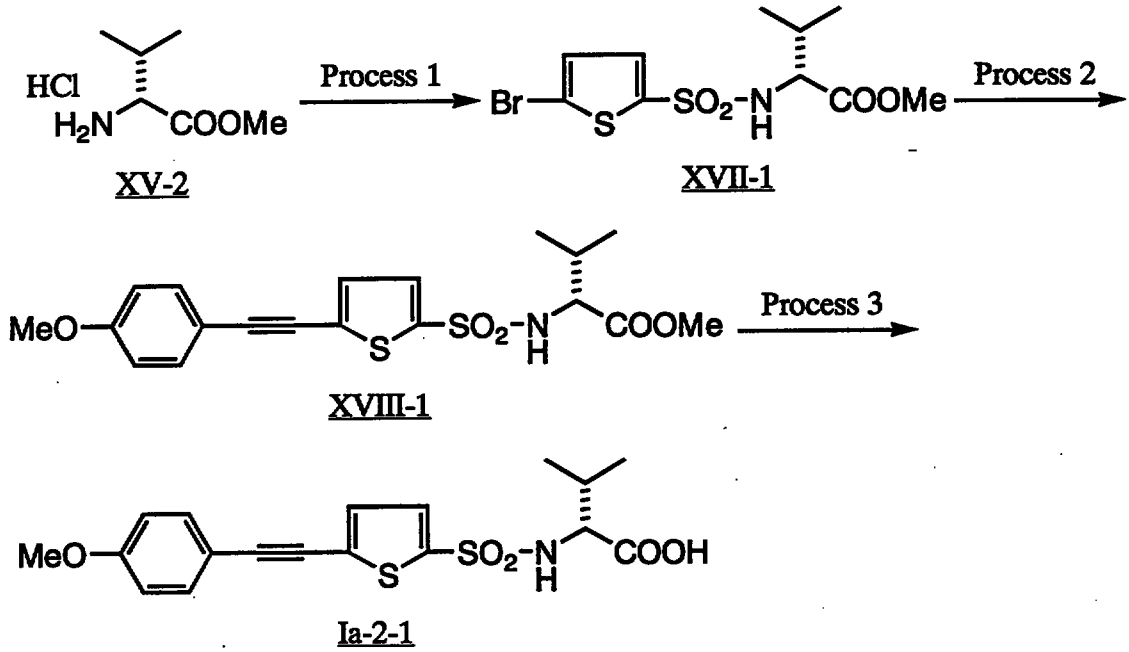
Table 22



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

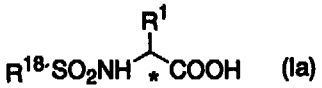
Calcd. : C; 54.45 H; 4.92 N; 3.53 S; 16.15

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)

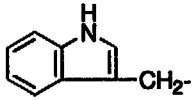
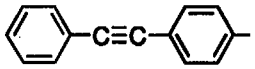
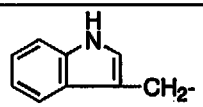
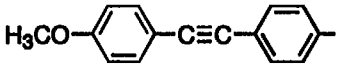
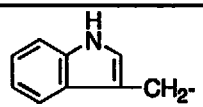
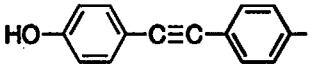
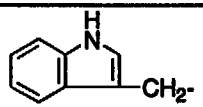
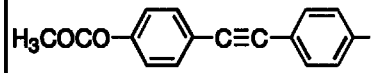
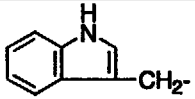
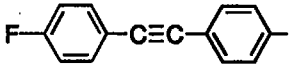
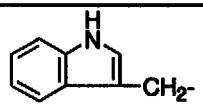
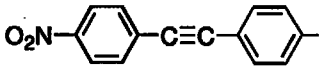
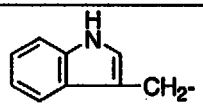
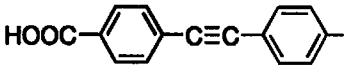
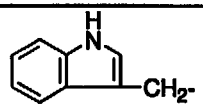
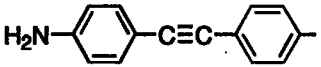
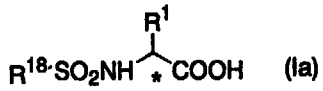
Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	Elemental analysis
93			R	165-170	1590,1316 1137	–
94			R	223-226	1747,1323 1134	$C_{26}H_{22}N_2O_5S$ Calc. C:65.81 H:4.67 N:5.90 S:6.76 Foun.C:65.34 H:4.90 N:5.56 S:6.40
95			R	216-218	1724,1325 1135	–
96			R	111-114	1739,1336 1163	–
97			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

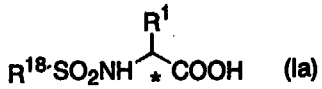
Table 24



(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	–

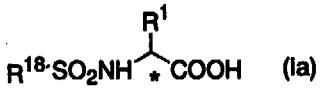
Table 25



(Ia)

Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	Elemental analysis
109	$(CH_3)_2CH$-	H_3C-C≡C-	R	187-189	1720,1656 1319,1165	–
110	$(CH_3)_2CH$-	F-C≡C-	R	111-114	1724,1635 1366,1158	–
111	$(CH_3)_3C$-	H_3CO-C≡C-	R	161-162	1711,1683 1600,1328 1159	$C_{21}H_{23}NO_5S$•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	$CH_3CH_2(CH_3)CH$-	H_3CO-C≡C-	R	157-159	1732,1680 1329,1167	–
113	-CH_2-	H_3CO-C≡C-	R	133-136	1735,1651 1348,1165	–
114	-CH_2-	H_3C-C≡C-	R	183-185	1727,1604 1335,1182	–
115	-CH_2-	F-C≡C-	R	166-168	1725,1663 1399,1197	$C_{23}H_{18}FNO_4S$•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	$(CH_3)_2CH$-	HO-C≡C-	R	163-165	1728,1332 1172	–

Table 26



(Ia)

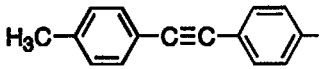
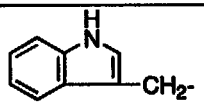
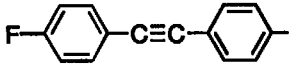
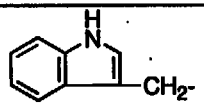
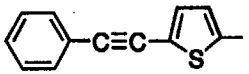
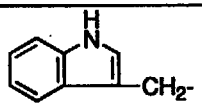
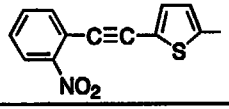
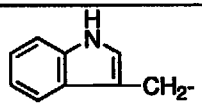
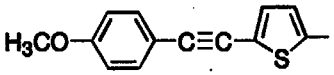
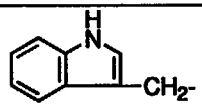
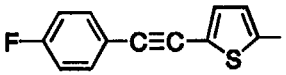
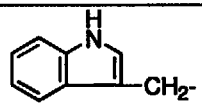
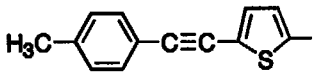
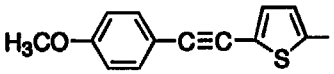
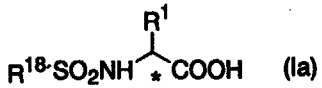
Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	Elemental analysis
117	$(CH_3)_2CH$-		R	187-189	1720,1656 1319,1165	–
118			R	111-114	1724,1635 1366,1158	–
119			R	167-169	1585,1318 1153	–
120			R	–	1605,1523 1340,1151	–
121			R	–	1604,1524 1336,1173	–
122			R	103-106	1721,1620 1339,1163	–
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)

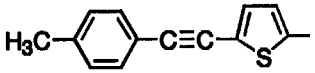
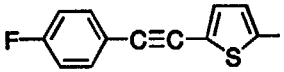
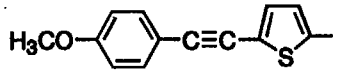
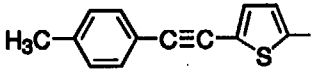
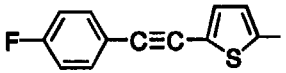
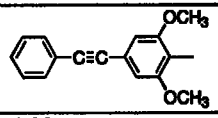
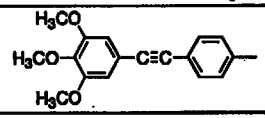
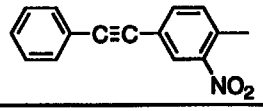
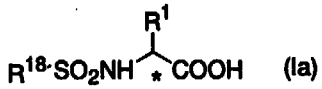
Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	Elemental analysis
125	$(CH_3)_2CH$-		R	157-158	1712,1350 1163	$C_{18}H_{19}NO_4S_2 \cdot 0.2H_2O$ Calc. C:56.73 H:5.13 N:3.68 S:16.83 Foun.C:57.03 H:5.30 N:3.89 S:16.56
126	$(CH_3)_2CH$-		R	154-156	1710,1499 1356,1165	–
127	CH_2-		R	149-150	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	CH_2-		R	161-164	1710,1329 1180	–
129	CH_2-		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	CH_2-		R	–	–	–
131	CH_2-		R	–	–	–
132	CH_2-		R	–	–	–

Table 28



(Ia)

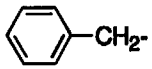
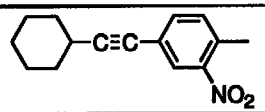
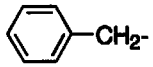
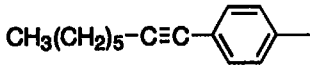
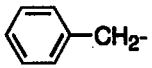
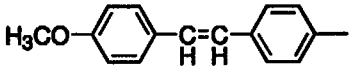
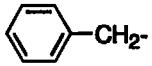
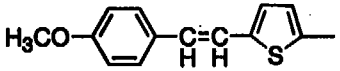
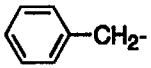
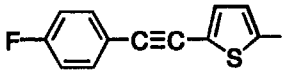
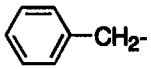
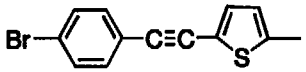
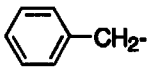
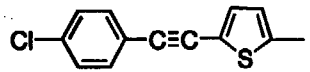
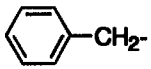
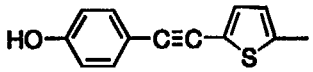
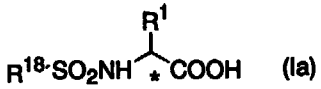
Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	Elemental analysis
133			R	–	–	–
134			R	–	–	–
135			R	–	–	–
136			R	–	–	–
137			R	–	–	–
138			R	–	–	–
139			R	–	–	–
140			R	–	–	–

Table 29



(Ia)

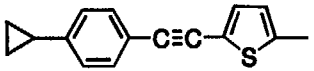
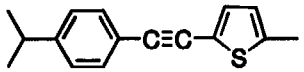
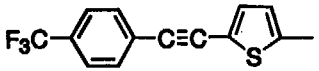
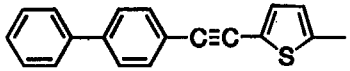
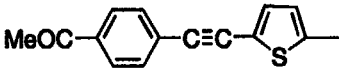
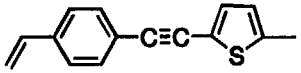
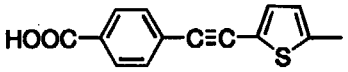
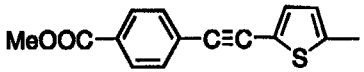
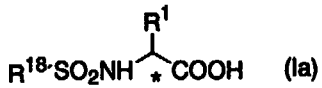
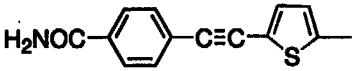
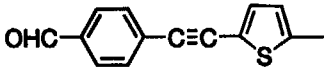
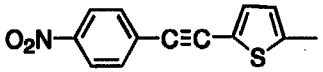
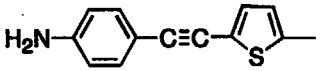
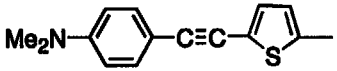
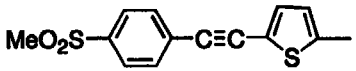
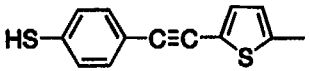
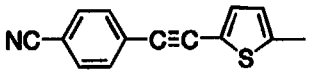
Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	Elemental analysis
141			R	–	–	–
142			R	–	–	–
143			R	–	–	–
144			R	–	–	–
145			R	–	–	–
146			R	–	–	–
147			R	–	–	–
148			R	–	–	–

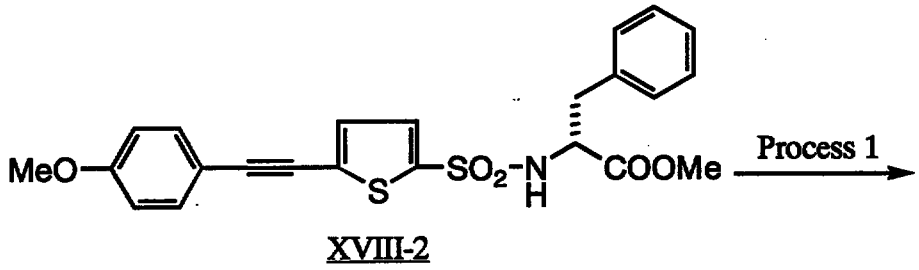
Table 30



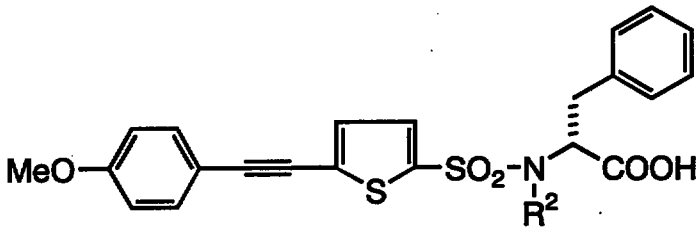
(Ia)

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



XVIII-2



Ia-2-66, Ia-2-67

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.

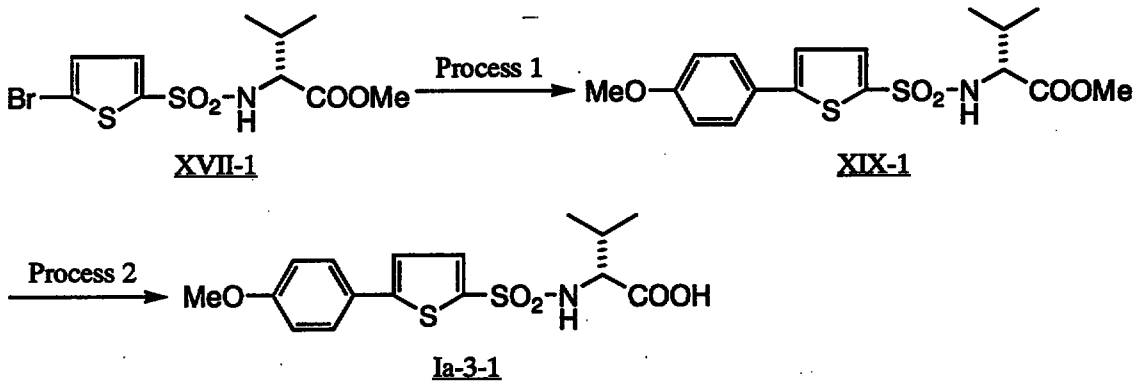
NMR (d_6-DMSO, δ ppm) : 2.88(s, 3H), 2.93(dd, J=12.0, 10.2 Hz, 1H), 3.19 (dd, J=14.2, 5.6 Hz, 1H), 3.81(s, 3H), 4.74(dd, J=5.4, 10.2 Hz, 1H), 6.99-7.04(m, 2H), 7.20-7.35(m, 7H), 7.52-7.56(m, 2H), 6.90(d, J=9.0 Hz, 2H), 7.44(d, J=9.0 Hz, 2H), 7.12(d, J=4.0 Hz, 1H), 7.44(d, J=4.0 Hz, 1H).

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

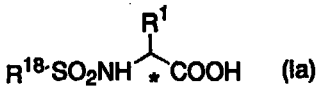
To a solution of 390 mg (1.01 mmol) of compound (XIX-1) in 8ml of tetrahydrofuran and 8ml of methanol was added 5.1 ml of 1N NaOH, and resulting mixture was stirred at 60℃ for 6 h. The reaction mixture was concentrated in vacuo to remove an organic solvent. The resulting residue was diluted with ethyl 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)

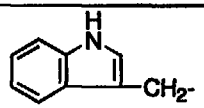
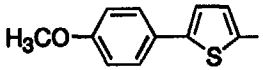
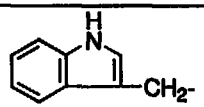
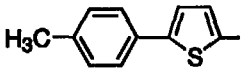
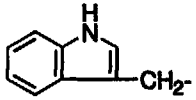
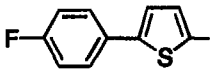
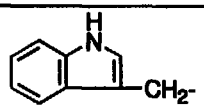
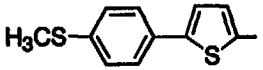
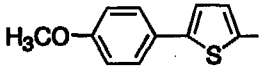
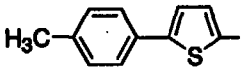
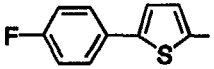
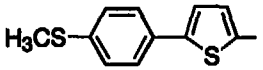
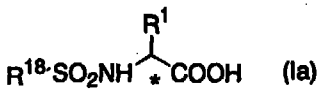
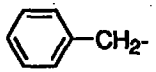
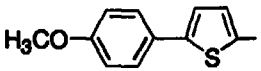
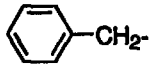
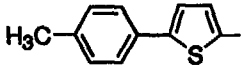
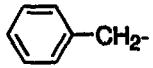
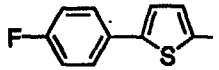
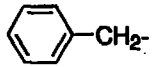
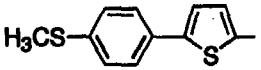
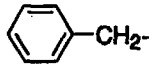
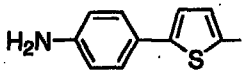
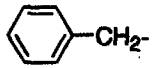
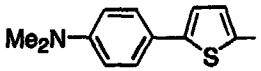
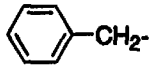
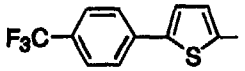
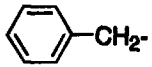
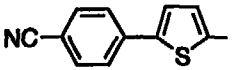
Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	Elemental analysis
160			R	93-96	1667,1337 1180	–
161			R	157-159	1670,1339 1194	–
162			R	168-171	1725,1598 1371,1185	–
163			R	226-230	1735,1341 1159	$C_{22}H_{20}N_2O_4S_3 \cdot 0.4H_2O$ Calc. C:55.07 H:4.37 N:5.84 S:20.05 Foun.C:55.35 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

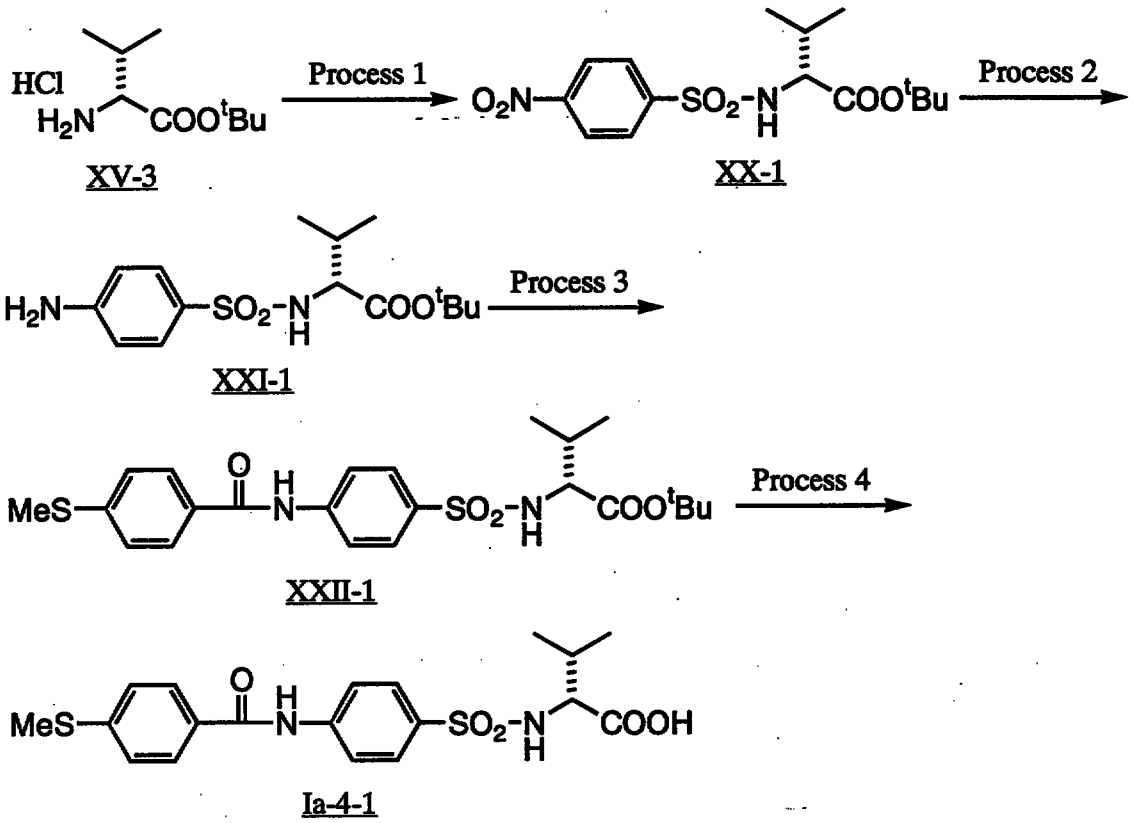
Table 32



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

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

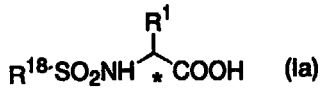
Calcd. : C; 53.14 H; 5.13 N; 6.46 S; 14.78

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)

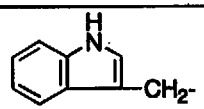
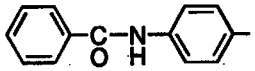
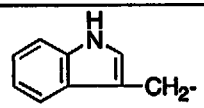
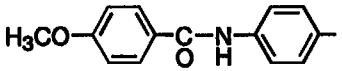
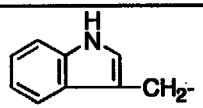
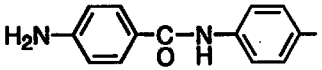
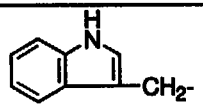
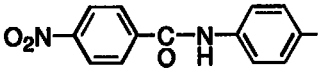
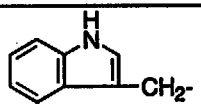
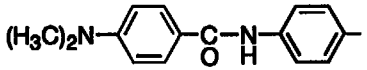
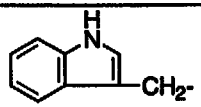
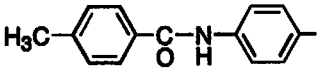
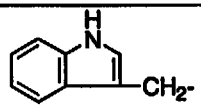
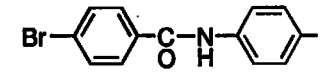
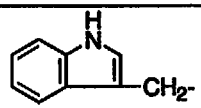
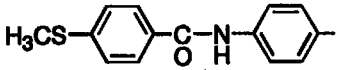
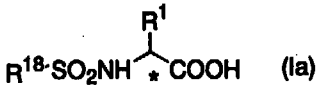
Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	Elemental analysis
177			R	215-217	1732,1641 1341,1163	–
178			R	233-234	1726,1655 1323,1177	$C_{25}H_{23}N_3O_6S \cdot 0.9H_2O$ Calc. C:58.91 H:4.90 N:8.24 S:6.29 Foun.C:58.97 H:5.07 N:7.95 S:6.10
179			R	216-218	1723,1633 1361,1149	–
180			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

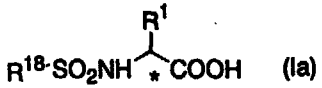
Table 34



(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)

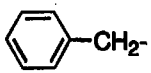
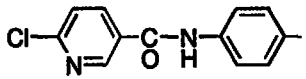
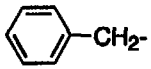
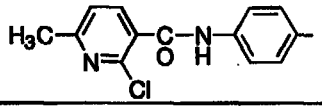
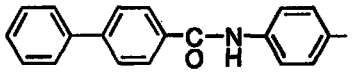
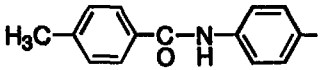
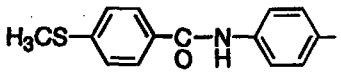
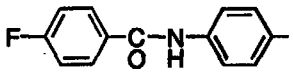
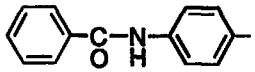
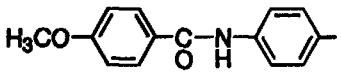
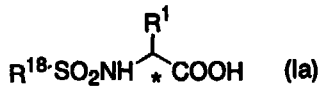
Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	Elemental analysis
193			R	201-203	1724,1673 1592,1326 1156	$C_{21}H_{18}ClN_3O_5S$ Calc. C:54.84 H:3.94 Cl:7.71 N:9.14 S:6.97 Foun.C:54.39 H:4.06 Cl:7.42 N:8.98 S:6.99
194			R	206-208	1725,1682 1592,1332 1160	$C_{22}H_{20}ClN_3O_5S \cdot 0.1CF_3COOH$ 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	$C_{24}H_{24}N_2O_5S \cdot 0.5H_2O$ 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	$C_{19}H_{22}N_2O_5S \cdot 0.2H_2O$ 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	$C_{19}H_{22}N_2O_5S_2 \cdot 0.1CF_3COOH$ 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	$C_{18}H_{19}FN_2O_5S \cdot 0.1CF_3COOH$ 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	$C_{18}H_{20}N_2O_5S \cdot 0.1H_2O$ 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	$C_{19}H_{22}N_2O_6S \cdot 0.2H_2O$ 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

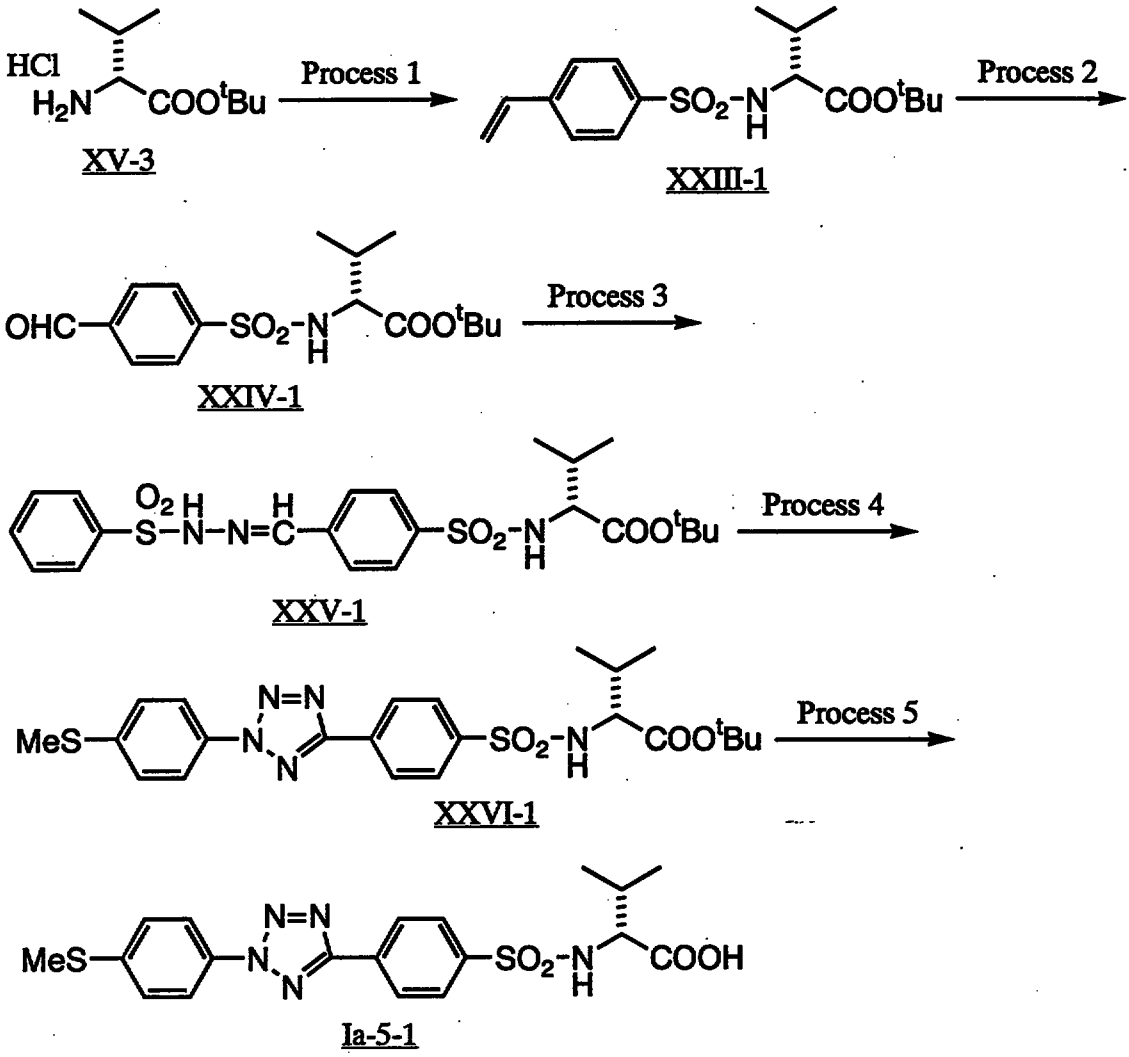
Table 36



(Ia)

Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	Elemental analysis
201	$(CH_3)_2CH$-	O_2N-C(=O)-NH-	R	240-242	1726,1688 1591,1347 1166	$C_{18}H_{19}N_3O_7S \cdot 0.4H_2O$ 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	$(CH_3)_2CH$-	Br-C(=O)-NH-	R	229-230	1726,1663 1592,1318 1159	$C_{18}H_{19}BrN_2O_5S \cdot 0.2$Ethylether 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	$(CH_3)_3C$-	H_3CO-C(=O)-NH-	R	214-216	1659,1591 1316,1159	$C_{20}H_{24}N_2O_6S \cdot 0.4H_2O$ 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	$C_6H_5CH_2$-	H_3C-pyrimidine-C(=O)-NH-	R	236-237	1723,1679 1590,1337 1162	$C_{21}H_{20}N_4O_5S \cdot 0.25CF_3COOH$ 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	$C_6H_5CH_2$-	pyridine-C(=O)-NH-	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	$C_6H_5CH_2$-	H_3C-isoxazole-C(=O)-NH-	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	$C_6H_5CH_2$-	Br-NH-C(=O)-NH-	R	217-220	1732,1679 1592,1312 1155	–
208	$C_6H_5CH_2$-	H_2N-C(=O)-NH-	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 $C_{19}H_{21}N_5O_4S_2 \cdot 1.1H_2O$

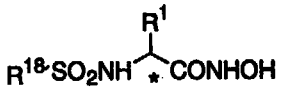
Calcd. : C; 48.83 H; 5.00 N; 14.99 S; 13.72

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)

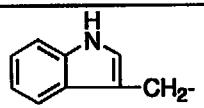
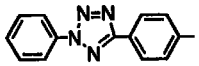
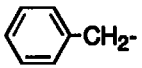
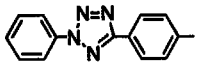
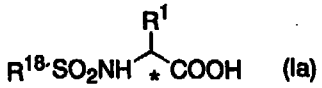
Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	^{1}H-NMR(δ ppm) d_6-DMSO
210			R	–	–	–
211			R	194-195	3700-2200(br),3278, 1634,1337,1160	2.65(dd,J=9.3,13.1Hz,1H),2.82(dd, J=5.8,13.1Hz,1H),3.86(dt,J=5.8,9.3 Hz,1H),7.72(A_2B_2q,J=8.1Hz,2H), 8.19(A_2B_2q,J=8.1Hz,2H),8.49(d,J= 9.3Hz,1H),8.88(s,1H),10.69(s,1H)

Table 38



(Ia)

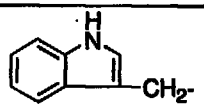
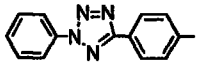
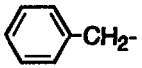
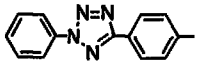
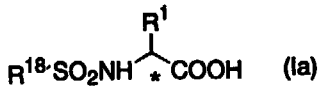
Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	^{1}H-NMR(δ ppm) d_6-DMSO
210			R	–	–	–
211			R	215-216	2400-3700br,3422,3337, 1733,1698,1347,1170	2.75(dd,J=9.3,13.7Hz,1H),2.99(dd,J=5.3,13.7Hz,1H),3.96(dt,J= 5.3,9.3Hz,1H),8.53(d,J=9.3Hz, 1H)

Table 39



(Ia)

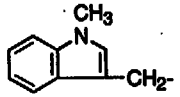
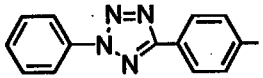
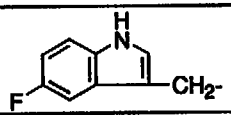
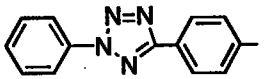
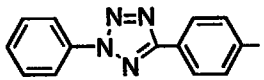
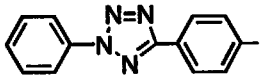
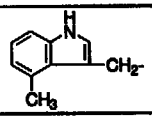
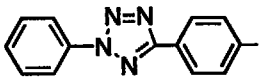
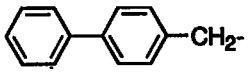
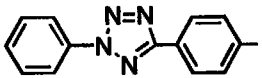
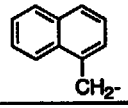
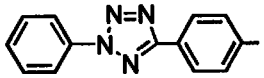
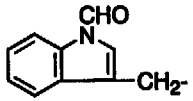
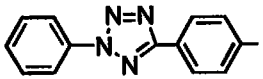
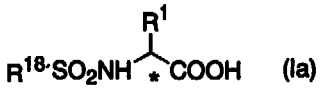
Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	Elemental analysis
212			RS	199-202	1734,1337 1161	$C_{25}H_{22}N_6O_4S$•0.5Ethylether Calc. C:60.10 H:5.04 N:15.57 S:5.94 Foun.C:60.41 H:4.69 N:15.52 S:5.57
213			RS	224-225	1728,1338 1166	$C_{24}H_{19}FN_6O_4S$•0.4Ethylether Calc .C:57.35 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)

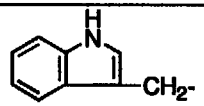
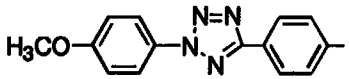
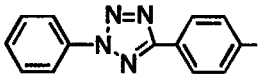
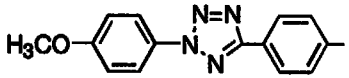
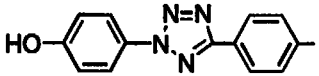
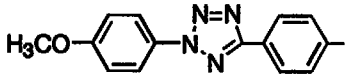
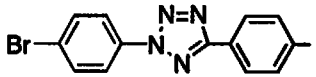
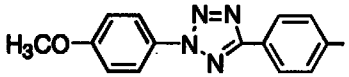
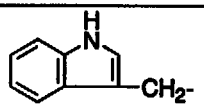
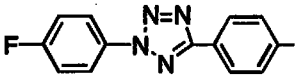
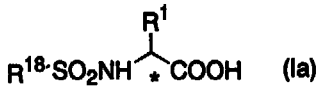
Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	Elemental analysis
220			R	195-196	1749,1719 1331,1165	$C_{25}H_{22}N_6O_5S$ Calc. C:57.91 H:4.28 N:16.21 S:6.18 Foun.C:57.77 H:4.29 N:16.01 S:6.37
221	$CH_3CH_2(CH_3)CH$-		R	205-207	1730,1693 1349,1173	$C_{19}H_{21}N_5O_4S$ Calc. C:54.93 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)

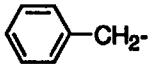
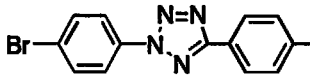
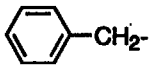
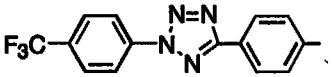
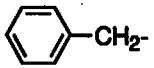
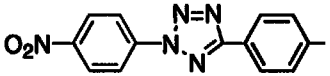
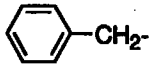
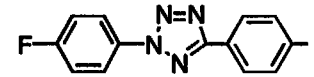
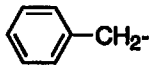
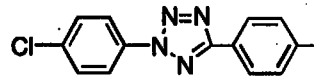
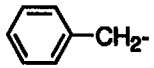
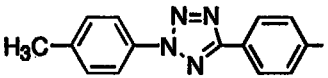
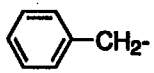
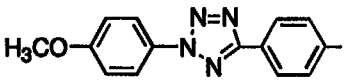
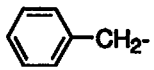
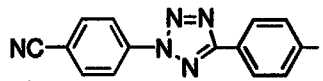
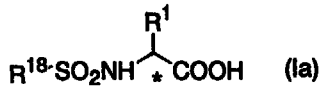
Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	Elemental analysis
228			R	197-199	1744,1325 1154	–
229			R	197-198	1738,1707 1328,1169	$C_{23}H_{18}F_3N_5O_4S$ Calc. C:53.38 H:3.51 F:11.01 N:13.53 S:6.20 Foun.C:53.11 H:3.55 F:10.89 N:13.66 S:6.31
230			R	190-191	1730,1597 1345,1161	$C_{22}H_{18}N_6O_6S{\cdot}0.4H_2O$ 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)

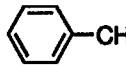
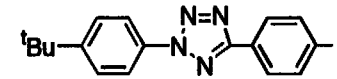
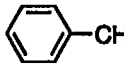
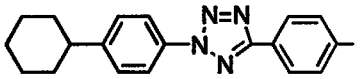
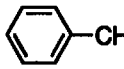
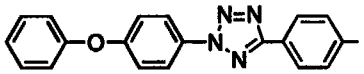
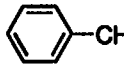
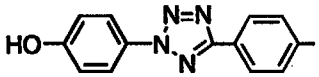
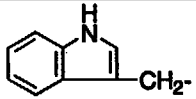
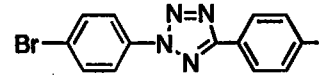
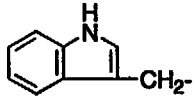
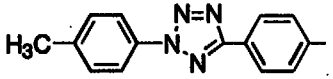
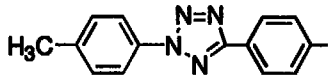
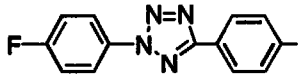
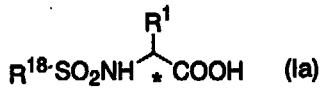
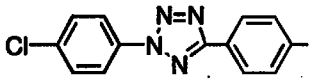
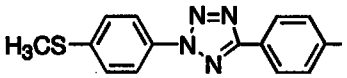
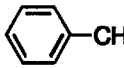
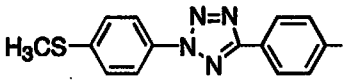
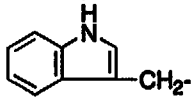
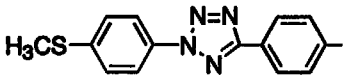
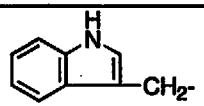
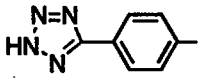
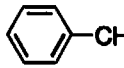
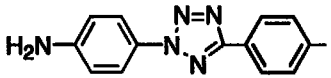
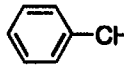
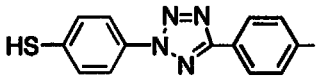
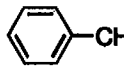
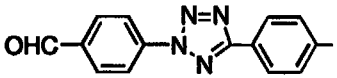
Example No.	R^1	R^{18}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	Elemental analysis
236			R	224-226	1738,1328 1314,1149	$C_{26}H_{27}N_5O_4S$ Calc. C:61.77 H:5.38 N:13.85 S:6.34 Foun.C:61.59 H:5.45 N:13.89 S:6.27
237			R	225-227	1739,1512 1329,1178	$C_{28}H_{29}N_5O_4S \cdot 0.3H_2O$ Calc. C:62.62 H:5.56 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



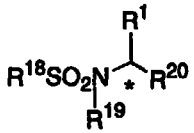
(Ia)

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)

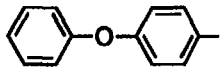
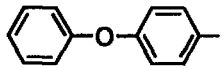
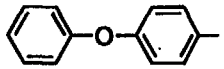
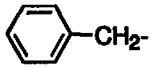
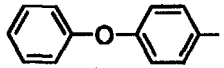
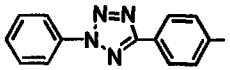
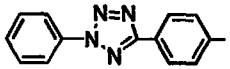
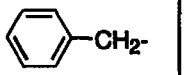
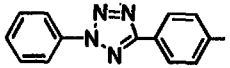
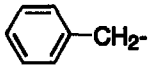
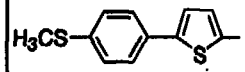
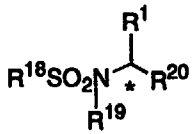
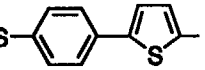
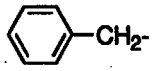
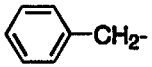
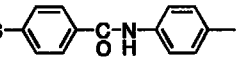
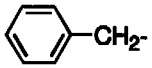
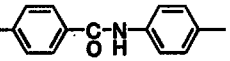
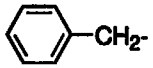
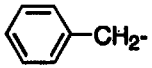
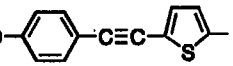
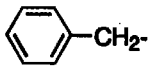
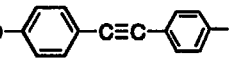
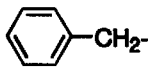
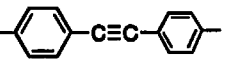
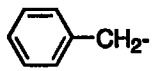
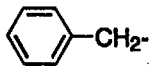
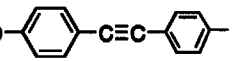
Example No.	R^1	R^{18}	R^{19}	R^{20}	*	mp (decomp.) (℃)	IR (ν cm^{-1}) (KBr)	^{1}H-NMR(δ ppm) d_6-DMSO
252	$(CH_3)_2CH$-		-CH_3	-COOH	R	–	1715,1583 1340,1151	0.96(d,J=6.6Hz,3H) 1.01(d,6.8Hz,3H) 2.87(s,3H) 4.17(d,J=10.4Hz,1H)
253	$(CH_3)_2CH$-		-CH_3	-CONHOH	R	110-111	3323,1678 1328,1150	0.71(d,J=6.6Hz,3H) 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



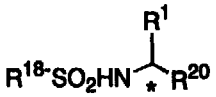
(I)

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	$(CH_3)_2CH$-	H_3CS- 	 CH_2-	-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_2-	H_3CS- 	-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	 CH_2-	H_3CS- 	 CH_2-	-COOH	R	–	–	–
263	 CH_2-	H_3CO- 	-$(CH_2)_4NH_2$	-COOH	R	–	–	–
264	 CH_2-	H_3CO- 	-CH_3	-COOH	R	–	–	–
265	 CH_2-	H_3CO- 	 CH_2-	-COOH	R	–	–	–
266	 CH_2-	H_3CO- 	-$(CH_2)_4NH_2$	-COOH	R	–	–	–

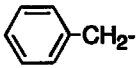
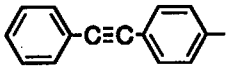
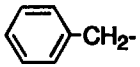
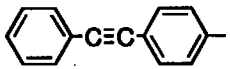
Example 267

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.

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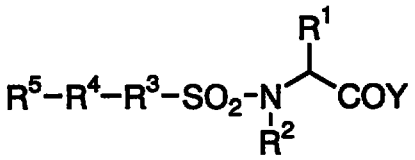
CLAIMS

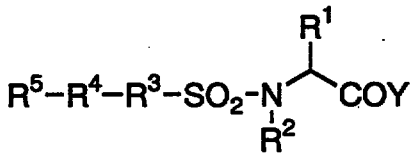
1. A composition for inhibiting metalloproteinase which contains a compound of the formula I:



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 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.

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 a bond, optionally substituted arylene, or

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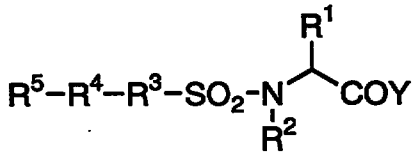
optionally substituted heteroarylene; R^4 is a bond, -(CH_2)m-, -CH=CH-, -C ≡ C-, -CO-, -CO-NH-, -N=N-, -N(R^A)-, -NH-CO-NH-, -NH-CO-, -O-, -S-, -SO_2NH-, -SO_2-NH-N=CH-, or tetrazol-diyl; R^5 is optionally substituted lower alkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted aryl, 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.

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 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-,

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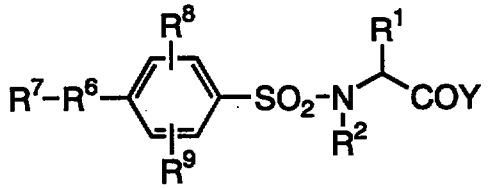
or tetrazol-diyl; R^5 is optionally substituted lower alkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, or an optionally substituted non-aromatic heterocyclic group; R^A is hydrogen atom or lower alkyl; Y is -NHOH or -OH; and m is 1 or 2; 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.

5. 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.

6. A compound of the formula III:

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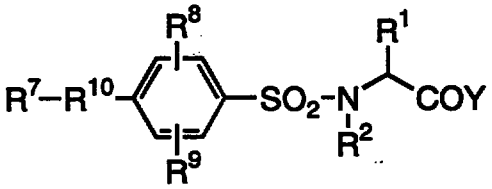
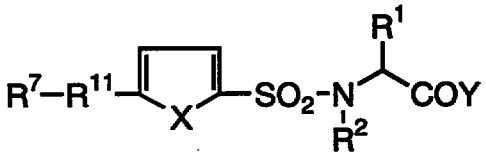


III

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.

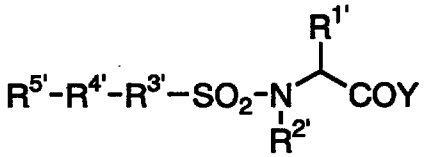
7. A compound of the formula IV:



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.

8. 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, (5-fluoroindole-3-yl)methyl, (1-acetylindol-3-yl)methyl, (1-methylsulfonylindol-3-yl)methyl, (1-alkoxycarbonyl-3-yl)methyl such as 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-hydroxyphenyl; and Y is as defined above, its optically active substance, their pharmaceutically acceptable salt, or hydrate thereof.

9. A compound of the formula I":

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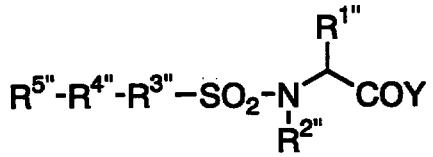
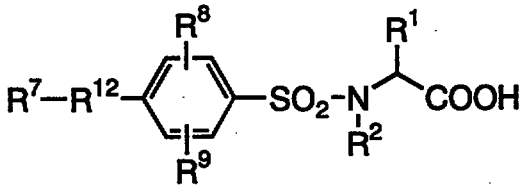


I"

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.

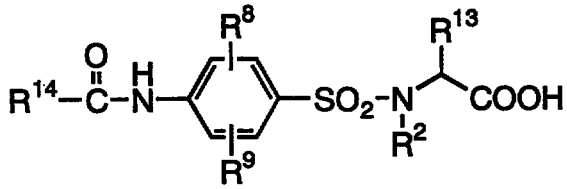
10. A compound of the formula V:



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.

11. 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,

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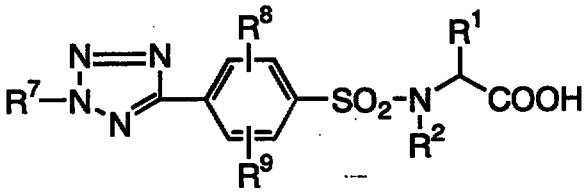
optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, or optionally substituted heteroarylalkyl; and R^{14} is optionally substituted aryl or optionally substituted heteroaryl; provided R^{13} is not methyl or phenyl and R^{14} is not 2-chlorophenyl, 4-chlorophenyl,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

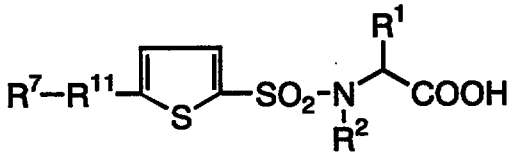
12. A compound of the formula VII:



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.

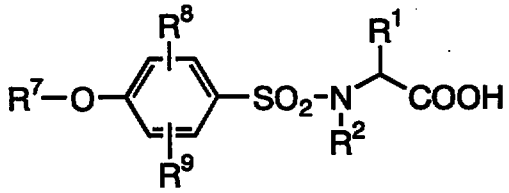
13. A compound of the formula VIII:



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.

14. A compound of the formula IX:



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.

15. A compound of the formula X:

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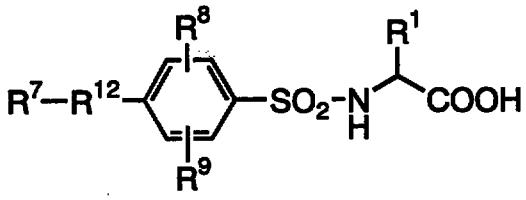
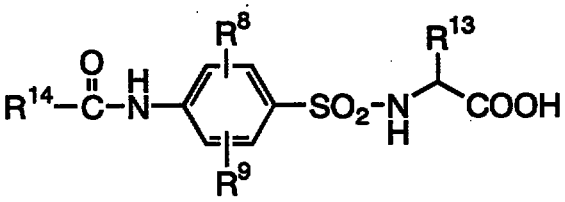


X

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.

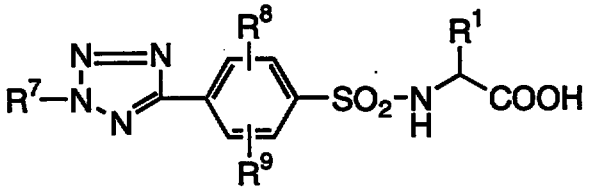
16. A compound of the formula XI:



XI

wherein R^1, 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.

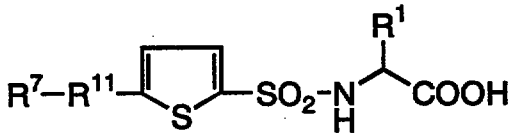
17. A compound of the formula XII:



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.

18. 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.

19. A compound of the formula XIV:

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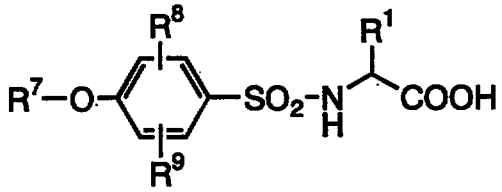

XIV

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.

20. The compound of any one of claims 4 to 19, wherein R^1, $R^{1'}$, $R^{1''}$, and R^{13} are i-propyl, benzyl, or (indole-3-yl)methyl.

21. The compound of any one of claims 4 to 7 and 10 to 19, 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.

22. The compound of any one of claims 4 to 19, wherein a configuration of asymmetric carbon atoms bonding with R^1, $R^{1'}$, $R^{1''}$, and R^{13} is R configuration.

23. A pharmaceutical composition containing a compound of any one of claims 4 to 19.

24. A composition for inhibiting metalloproteinase containing a compound of any one of claims 4 to 19.

25. A composition for inhibiting type IV collagenase containing a compound of any one of claims 4 to 19.

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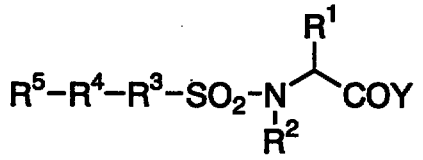
ABSTRACT

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

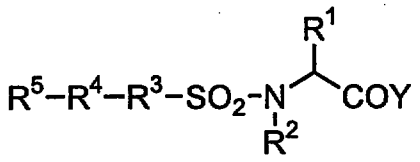


I

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:

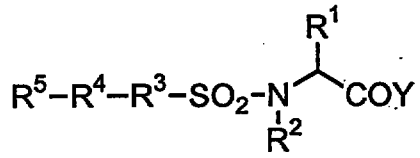


I

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, an optically active substance of the composition, a pharmaceutically acceptable salt of the composition or substance, or hydrate of the composition, substance or salt.

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:



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☒ Claim(s)	: paged 105 to paged 112a	
☐ Drawing(s)	: paged — to paged —	
☐ Abstract	: paged — to paged —	

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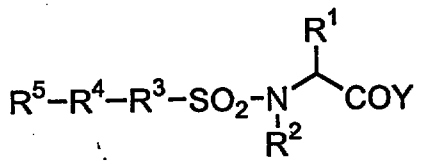
wherein R^1 is optionally substituted lower alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, or optionally substituted heteroarylalkyl; R^2 is hydrogen atom, optionally substituted lower alkyl, optionally substituted aryl, optionally substituted aralkyl, 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, an optically active substance of the composition, a pharmaceutically acceptable salt of the composition or substance, or hydrate of the composition, substance or salt.

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:



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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^1 is not carboxymethyl, alkylaminocarbonylalkyl, cycloalkylaminocarbonylalky, or phenylaminocarbonylalkyl when R^3 is phenylene and R^4 is -CONH- or -NH-CO-, 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, R^5 is not phenyl substituted with dimethylamino when R^4 is -N=N-, R^3 is not napthalenediyl when R^4 is -N=N-, R^5 is not phenyl when R^3 is 1,2-phenylene and R^4 is a bond, R^5 is not phenyl when R^3 is 1,3-phenylene and R^4 is -SO_2-, R^5 is not 1H-azepine when R^3 is 1,2-phenylene and R^4 is -CO-, R^5 is not optionally substituted heteroaryl when R^3 is phenylene and R^4 is -CH_2-, an optically active substance of the compound, a pharmaceutically acceptable

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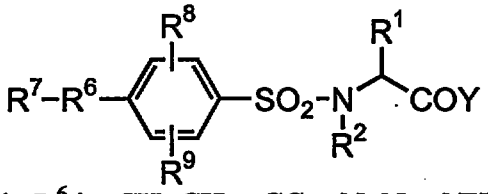
salt of the compound or the optically active substance, or a hydrate of the compound, substance or salt.

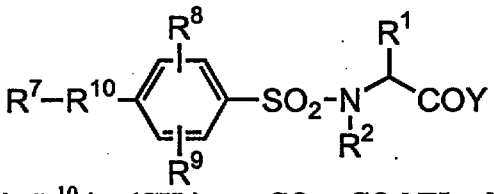
2) A compound of the formula II:



II

wherein R^6 is -CH=CH-, -CC-, -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, provided R^5 is not phenyl substituted with dimethylamino when R^4 is -N=N-, an optically active substance of the compound, a pharmaceutically acceptable salt of the compound or the optically active substance, or a hydrate of the compound, substance or salt.

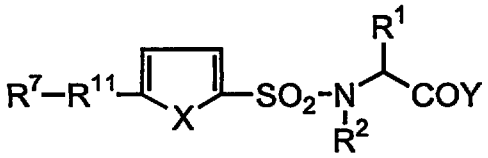
3) A compound of the formula III:



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-, R^1 is not carboxymethyl when R^{10} is -CONH- or -NH-CO-, an optically active substance of the compound, a pharmaceutically acceptable salt of the compound or the optically active substance, or a hydrate of the compound, substance or salt.

4) A compound of the formula IV:



IV

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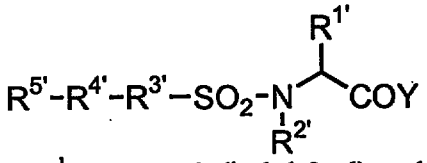
wherein R^{11} is a bond, -CH=CH-, or -C≡C-; X is oxygen atom or sulfur atom, R^1, R^2, R^7, and Y are as defined above, its optically active substance, their pharmaceutically acceptable salt, or hydrate thereof.

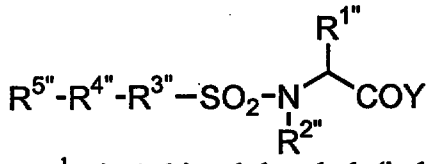
5) A compound of the formula I':



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

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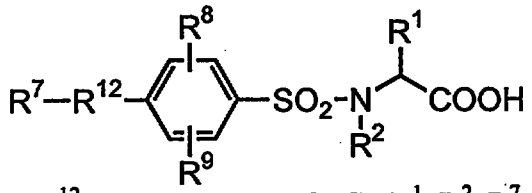
as defined above, its optically active substance, their pharmaceutically acceptable salt, or hydrate thereof.

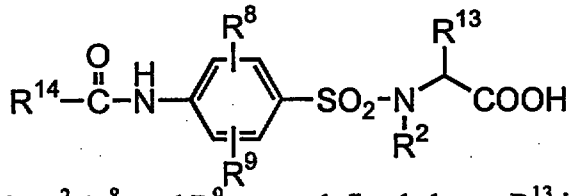
7) A compound of the formula V:



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.

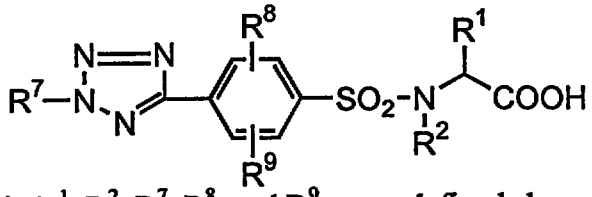
8) A compound of the formula VI:



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, phenyl, carboxymethyl, alkylaminocarbonylalkyl, cycloalkylaminocarbonylalkyl, or phenylaminocarbonylalkyl and R^{14} is not 2-chlorophenyl, 4-chlorophenyl, or 2,4-dichlorophenyl, an optically active substance of the compound, a pharmaceutically acceptable salt of the compound or the optically active substance, or a hydrate of the compound, substance or salt.

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.

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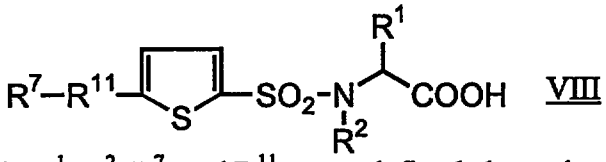
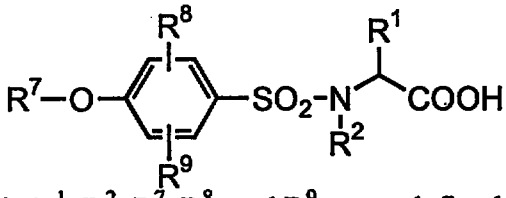
10) A compound of the formula VIII:



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.

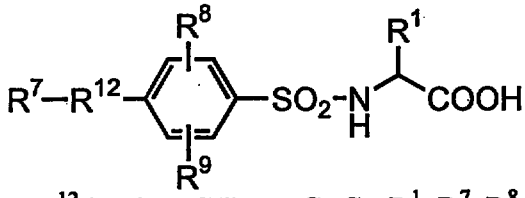
11) A compound of the formula VIII:



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.

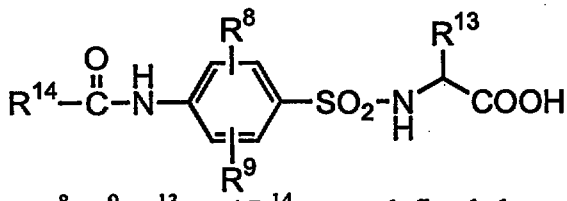
12) A compound of the formula X:



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, phenyl, carboxymethyl, alkylaminocarbonylalkyl, cycloalkylaminocarbonylalkyl, or phenylaminocarbonylalkyl and R^{14} is not 2-chlorophenyl, 4-chlorophenyl, or 2,4-dichlorophenyl, an optically active substance of the compound, a pharmaceutically

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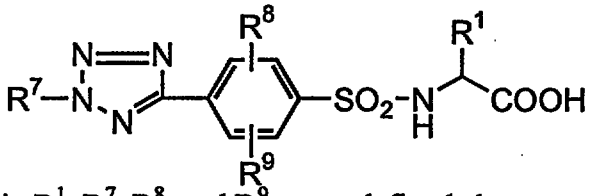
acceptable salt of the compound or the optically active substance, or a hydrate of the compound, substance or salt.

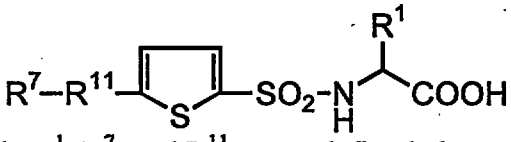
14) A compound of the formula XII:



XII

wherein R^1, R^7, R^8, and R^9 are as defined above, an optically active substance of the compound, a pharmaceutically acceptable salt of the compound or the optically active substance, or a hydrate of the compound, substance or salt.

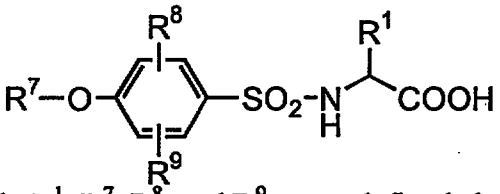
15) A compound of the formula XIII:



XIII

wherein R^1, R^7, and R^{11} are as defined above, an optically active substance of the compound, a pharmaceutically acceptable salt of the compound or the optically active substance, or a hydrate of the compound, substance or salt.

16) A compound of the formula XIV:



XIV

wherein R^1, R^7, R^8, and R^9 are as defined above, an optically active substance of the compound, a pharmaceutically acceptable salt of the compound or the optically active substance, or a hydrate of the compound, substance or salt.

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.

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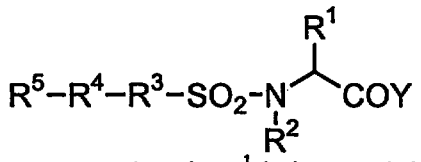
B) The compound of any one of above 1) to 4) and 7) to 16), wherein R^5, R^7, and R^{14} are phenyl optionally substituted with one or more substituents selected from the group consisting of alkoxy, alkylthio, and alkyl.

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

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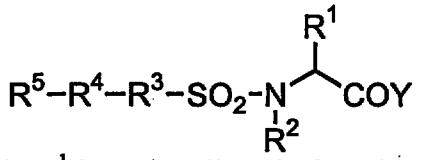
CLAIMS

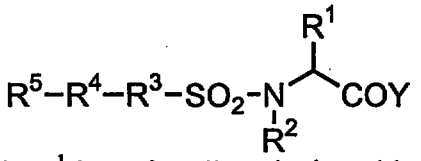
1. A composition for inhibiting metalloproteinase which contains a compound of the formula I:



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 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, an optically active substance of the composition, a pharmaceutically acceptable salt of the composition or substance, or hydrate of the composition, substance or salt.

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 a bond, optionally

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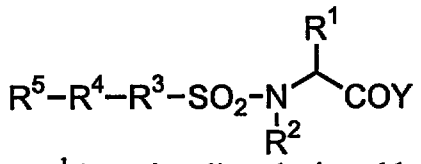
substituted arylene, or optionally substituted heteroarylene; R^4 is a bond, -(CH_2)m-, -CH=CH-, -C≡C-, -CO-, -CO-NH-, -N=N-, -N(R^A)-, -NH-CO-NH-, -NH-CO-, -O-, -S-, -SO_2NH-, -SO_2-NH-N=CH-, or tetrazol-diyl; R^5 is optionally substituted lower alkyl, optionally substituted C_3-C_8 cycloalkyl, optionally 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, an optically active substance of the composition, a pharmaceutically acceptable salt of the composition or substance, or hydrate of the composition, substance or salt.

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:

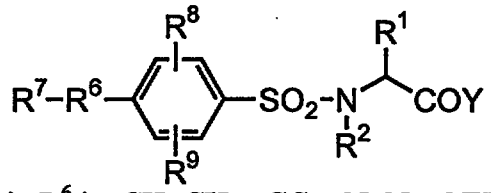


I

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 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^1 is not carboxymethyl, alkylaminocarbonylalkyl, cycloalkylaminocarbonylalky, or phenylaminocarbonylalkyl when R^3 is phenylene and R^4 is -CONH- or -NH-CO-, 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, R^5 is not phenyl substituted with dimethylamino when R^4 is -N=N-, R^3 is not napthalenediyl when R^4 is -N=N-, R^5 is not phenyl when R^3 is 1,2-phenylene and R^4 is a bond, R^5 is not phenyl when R^3 is 1,3-phenylene and R^4 is -SO_2-, R^5 is not 1H-azepine when R^3 is 1,2-phenylene and R^4 is -CO-, R^5 is not optionally substituted heteroaryl when R^3 is phenylene and R^4 is -CH_2-, an optically active substance of the compound, a pharmaceutically acceptable salt of the compound or the optically active substance, or a hydrate of the compound, substance or salt.

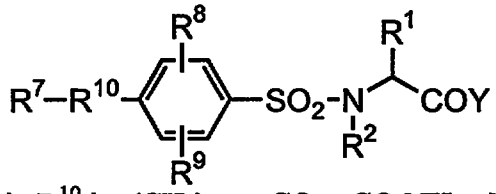
5. A compound of the formula II:



II

wherein R^6 is -CH=CH-, -CC-, -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; provided R^5 is not phenyl substituted with dimethylamino when R^4 is -N=N-, an optically active substance of the compound, a pharmaceutically acceptable salt of the compound or substance, or hydrate of the compound, substance or salt.

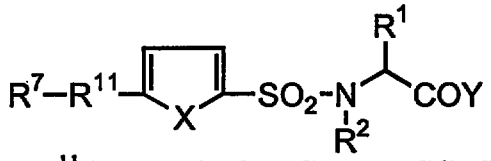
6. A compound of the formula III:



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-, R^1 is not carboxymethyl when R^{10} is -CONH- or -NH-CO-, an optically active substance of the compound, a pharmaceutically acceptable salt of the compound or substance, or hydrate of the compound, substance or salt.

7. A compound of the formula IV:

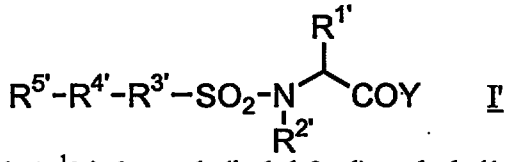


IV

wherein R^{11} is a bond, -CH=CH-, or -CC-; X is oxygen atom or sulfur atom; R^1, R^2, R^7, and Y are as defined above, an optically active substance of the compound, a

pharmaceutically acceptable salt of the compound or substance, or hydrate of the compound, substance or salt.

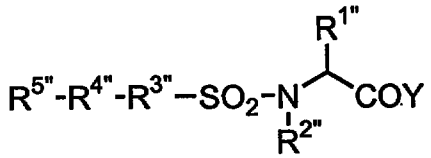
8. A compound of the formula I':



I'

wherein $R^{1'}$ is benzyl, (indol-3-yl)methyl, (1-methylindol-3-yl)methyl, (5-methylindol-3-yl)methyl, (5-fluoroindole-3-yl)methyl, (1-acetylindol-3-yl)methyl, (1-methylsulfonylindol-3-yl)methyl, (1-alkoxycarbonyl-3-yl)methyl such as 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-hydroxyphenyl; and Y is as defined above, an optically active substance of the compound, a pharmaceutically acceptable salt of the compound or substance, or hydrate of the compound, substance or salt.

9. 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

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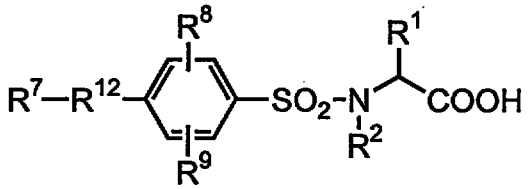
as defined above, an optically active substance of the compound, a pharmaceutically acceptable salt of the compound or substance, or hydrate of the compound, substance or salt.

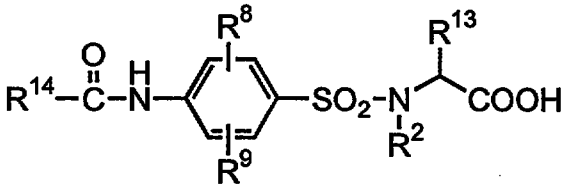
10. A compound of the formula V:



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, an optically active substance of the compound, a pharmaceutically acceptable salt of the compound or substance, or hydrate of the compound, substance or salt.

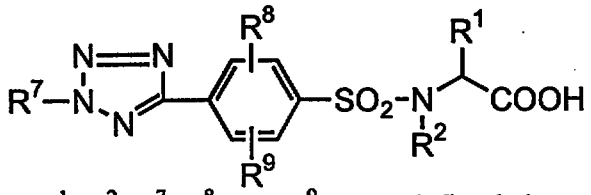
11. A compound of the formula VI:



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, phenyl, carboxymethyl, alkylaminocarbonylalkyl, cycloalkylaminocarbonylalkyl, or phenylaminocarbonylalkyl and R^{14} is not 2-chlorophenyl, 4-chlorophenyl, or 2,4-dichlorophenyl, an optically active substance of the compound, a pharmaceutically acceptable salt of the compound or substance, or hydrate of the compound, substance or salt.

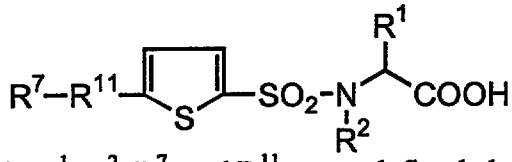
12. A compound of the formula VII:



VII

wherein R^1, R^2, R^7, R^8, and R^9 are as defined above, an optically active substance of the compound, a pharmaceutically acceptable salt of the compound or substance, or hydrate of the compound, substance or salt.

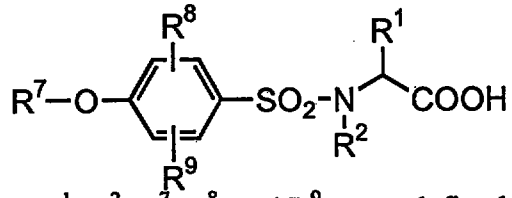
13. A compound of the formula VIII:



VIII

wherein R^1, R^2, R^7, and R^{11} are as defined above, an optically active substance of the compound, a pharmaceutically acceptable salt of the compound or substance, or hydrate of the compound, substance or salt.

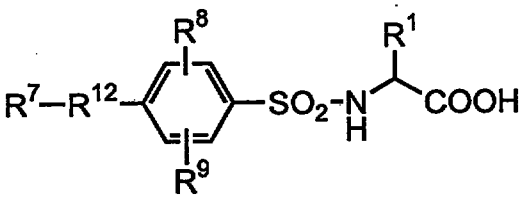
14. A compound of the formula IX:



IX

wherein R^1, R^2, R^7, R^8, and R^9 are as defined above, an optically active substance of the compound, a pharmaceutically acceptable salt of the compound or substance, or hydrate of the compound, substance or salt.

15. A compound of the formula X:



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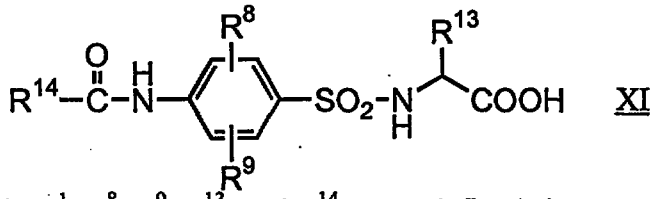
wherein R^{12} is -CH=CH- or -C≡C-; R^1, R^7, R^8, and R^9 are as defined above, an optically active substance of the compound, a pharmaceutically acceptable salt of the compound or substance, or hydrate of the compound, substance or salt.

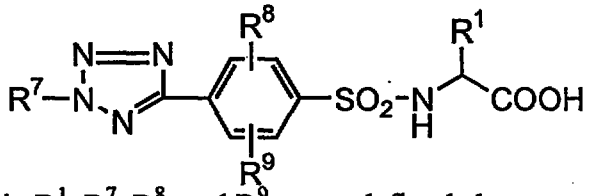
16. A compound of the formula XI:



XI

wherein R^1, R^8, R^9, R^{13}, and R^{14} are as defined above, provided R^{13} is not methyl, phenyl, carboxymethyl, alkylaminocarbonylalkyl, cycloalkylaminocarbonylalkyl, or phenylaminocarbonylalkyl and R^{14} is not 2-chlorophenyl, 4-chlorophenyl, or 2,4-dichlorophenyl, an optically active substance of the compound, a pharmaceutically acceptable salt of the compound or substance, or hydrate of the compound, substance or salt.

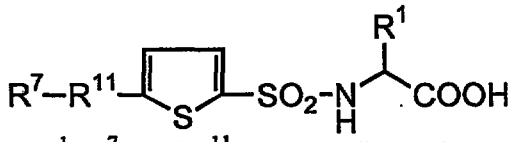
17. A compound of the formula XII:



XII

wherein R^1, R^7, R^8, and R^9 are as defined above, an optically active substance of the compound, a pharmaceutically acceptable salt of the compound or substance, or hydrate of the compound, substance or salt.

18. A compound of the formula XIII:



XIII

wherein R^1, R^7, and R^{11} are as defined above, an optically active substance of the compound, a pharmaceutically acceptable salt of the compound or substance, or hydrate of the compound, substance or salt.

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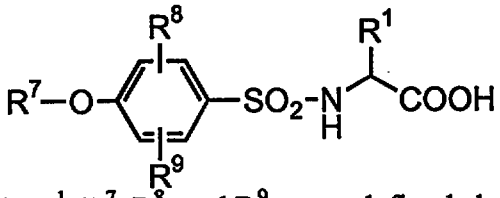
19. A compound of the formula XIV:



XIV

wherein R^1, R^7, R^8, and R^9 are as defined above, an optically active substance of the compound, a pharmaceutically acceptable salt of the substance or compound, or hydrate of the compound, substance or salt.

20. The compound of any one of claims 4 to 19, wherein R^1, $R^{1'}$, $R^{1''}$, and R^{13} are i-propyl, benzyl, or (indole-3-yl)methyl.

21. The compound of any one of claims 4 to 7 and 10 to 19, 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.

22. The compound of any one of claims 4 to 19, wherein a configuration of asymmetric carbon atoms bonding with R^1, $R^{1'}$, $R^{1''}$, and R^{13} is R configuration.

23. A pharmaceutical composition containing a compound of any one of claims 4 to 19.

24. A composition for inhibiting metalloproteinase containing a compound of any one of claims 4 to 19.

25. A composition for inhibiting type IV collagenase containing a compound of any one of claims 4 to 19.

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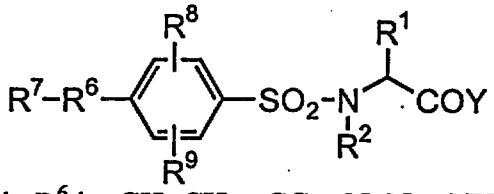
salt of the compound or the optically active substance, or a hydrate of the compound, substance or salt.

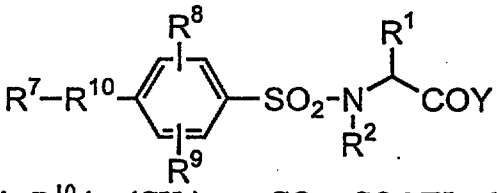
2) A compound of the formula II:



II

wherein R^6 is -CH=CH-, -CC-, -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, provided R^7 is not phenyl substituted with dimethylamino when R^6 is -N=N-, an optically active substance of the compound, a pharmaceutically acceptable salt of the compound or the optically active substance, or a hydrate of the compound, substance or salt.

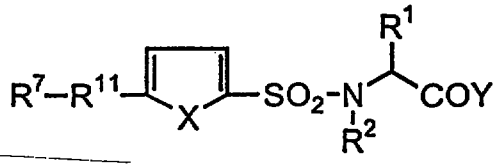
3) A compound of the formula III:



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-, R^1 is not carboxymethyl when R^{10} is -CONH- or -NH-CO-, an optically active substance of the compound, a pharmaceutically acceptable salt of the compound or the optically active substance, or a hydrate of the compound, substance or salt.

4) A compound of the formula IV:



IV

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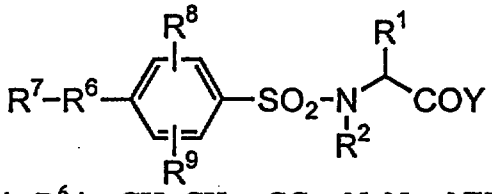
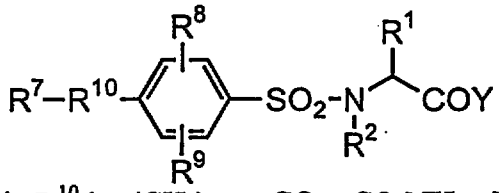
5. A compound of the formula II:



II

wherein R^6 is -CH=CH-, -CC-, -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; provided R^7 is not phenyl substituted with dimethylamino when R^6 is -N=N-, an optically active substance of the compound, a pharmaceutically acceptable salt of the compound or substance, or hydrate of the compound, substance or salt.

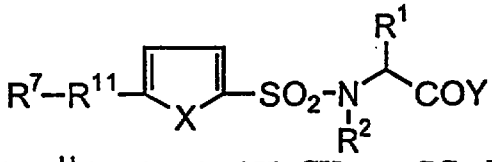
6. A compound of the formula III:



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-, R^1 is not carboxymethyl when R^{10} is -CONH- or -NH-CO-, an optically active substance of the compound, a pharmaceutically acceptable salt of the compound or substance, or hydrate of the compound, substance or salt.

7. A compound of the formula IV:



IV

wherein R^{11} is a bond, -CH=CH-, or -CC-; X is oxygen atom or sulfur atom; R^1, R^2, R^7, and Y are as defined above, an optically active substance of the compound, a

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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^1 is not carboxyalkyl alkylaminocarbonylalkyl, cycloalkylaminocarbonylalky, or phenylaminocarbonylalkyl when R^3 is phenylene and R^4 is -CONH- or -NH-CO-, 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, R^5 is not phenyl substituted with dimethylamino when R^4 is -N=N-, R^3 is not napthalenediyl when R^4 is -N=N-, R^5 is not phenyl when R^3 is 1,2-phenylene and R^4 is a bond, R^5 is not phenyl when R^3 is 1,3-phenylene and R^4 is $-SO_2-$, R^5 is not optionally substituted heteroaryl when R^3 is phenylene and R^4 is $-CH_2-$, and R^3 is not 1,2-phenylene, an optically active substance of the compound, a pharmaceutically acceptable

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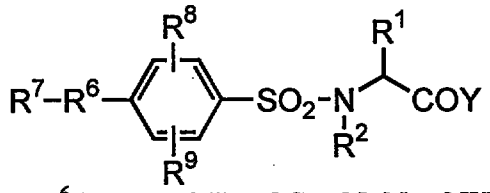
salt of the compound or the optically active substance, or a hydrate of the compound, substance or salt.

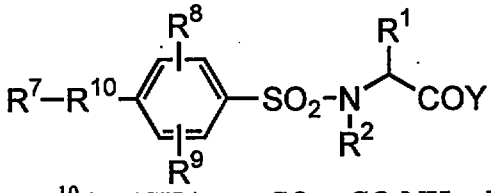
2) A compound of the formula II:



II

wherein R^6 is -CH=CH-, -CC-, -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, provided R^5 is not phenyl substituted with dimethylamino when R^4 is -N=N-, an optically active substance of the compound, a pharmaceutically acceptable salt of the compound or the optically active substance, or a hydrate of the compound, substance or salt.

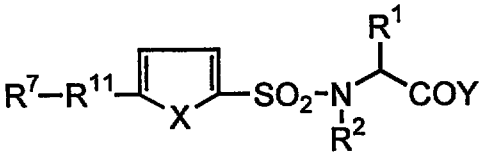
3) A compound of the formula III:



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-, R^1 is not carboxyalkyl, alkylaminocarbonylalkyl, cycloalkylamino carbonylalkyl, or phenylaminocarbonylalkyl when R^{10} is -CONH- and R^7 is not optionally subtituted heteroaryl when R^{10} is - CH_2 -, an optically active substance of the compound, a pharmaceutically acceptable salt of the compound or the optically active substance, or a hydrate of the compound, substance or salt.

4) A compound of the formula IV:



IV

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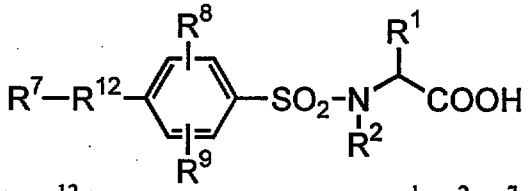
as defined above, its optically active substance, their pharmaceutically acceptable salt, or hydrate thereof.

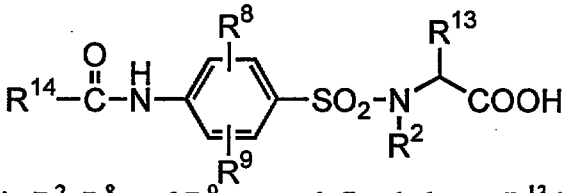
7) A compound of the formula V:



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.

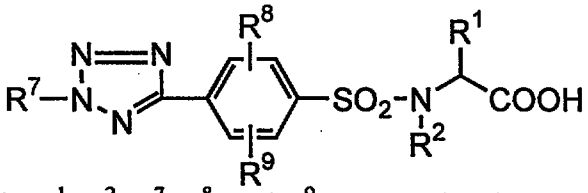
8) A compound of the formula VI:



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, phenyl, carboxyalkyl, alkylaminocarbonylalkyl, cycloalkylaminocarbonylalkyl, or phenylaminocarbonylalkyl and R^{14} is not 2-chlorophenyl, 4-chlorophenyl, or 2,4-dichlorophenyl, an optically active substance of the compound, a pharmaceutically acceptable salt of the compound or the optically active substance, or a hydrate of the compound, substance or salt.

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.

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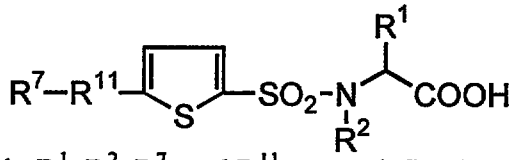
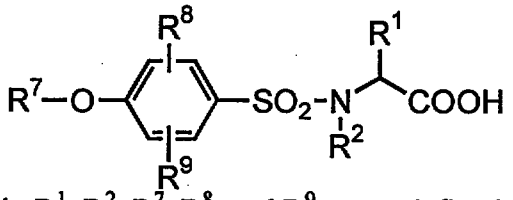
10) A compound of the formula VIII:



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.

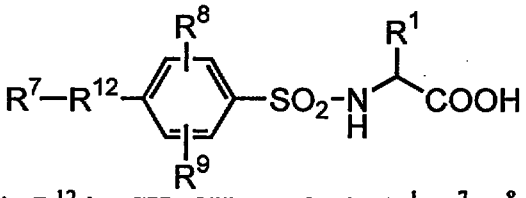
11) A compound of the formula VIII:



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.

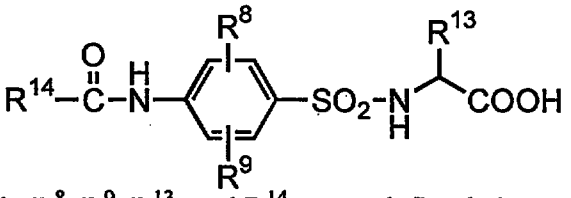
12) A compound of the formula X:



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, phenyl, carboxyalkyl, alkylaminocarbonylalkyl, cycloalkylaminocarbonylalkyl, or phenylaminocarbonylalkyl and R^{14} is not 2-chlorophenyl, 4-chlorophenyl, or 2,4-dichlorophenyl, an optically active substance of the compound, a pharmaceutically

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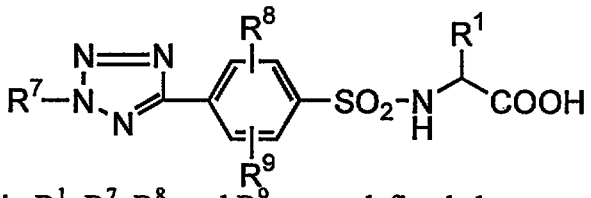
acceptable salt of the compound or the optically active substance, or a hydrate of the compound, substance or salt.

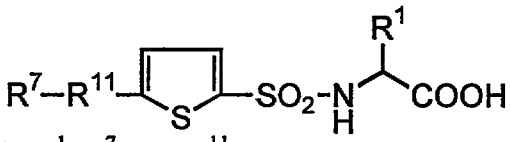
14) A compound of the formula XII:



XII

wherein R^1, R^7, R^8, and R^9 are as defined above, an optically active substance of the compound, a pharmaceutically acceptable salt of the compound or the optically active substance, or a hydrate of the compound, substance or salt.

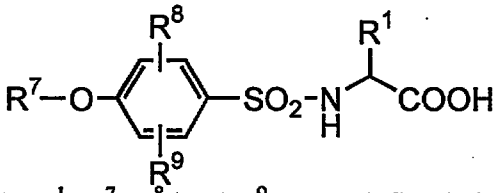
15) A compound of the formula XIII:



XIII

wherein R^1, R^7, and R^{11} are as defined above, an optically active substance of the compound, a pharmaceutically acceptable salt of the compound or the optically active substance, or a hydrate of the compound, substance or salt.

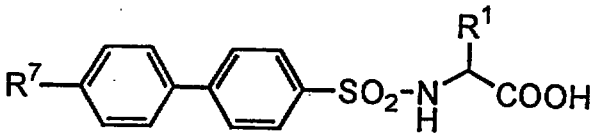
16) A compound of the formula XIV:



XIV

wherein R^1, R^7, R^8, and R^9 are as defined above, an optically active substance of the compound, a pharmaceutically acceptable salt of the compound or the optically active substance, or a hydrate of the compound, substance or salt.

17. A compound of the formula XXVIII :



XXVIII

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wherein R^1 and R^7 are as defined above, an optically active substance of the compound, a pharmaceutically acceptable salt of the substance or compound or hydrate of the compound, substance or salt.

A compound of the invention is more specifically illustrated below:

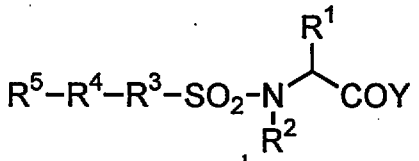
A) The compound of any one of above 1) to 16), wherein R^1, $R^{1'}$, $R^{1''}$, and R^{13} are i-propyl, benzyl, or (indol-3-yl) methyl.

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

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substituted arylene, or optionally substituted heteroarylene; R^4 is a bond, -(CH_2)m-, -CH=CH-, -CC-, -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^1 is not carboxyalkyl, alkylaminocarbonylalkyl, cycloalkylaminocarbonylalky, or phenylaminocarbonylalkyl when R^3 is phenylene and R^4 is -CONH- or -NH-CO-, 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, R^5 is not phenyl substituted with dimethylamino when R^4 is -N=N-, R^3 is not napthalenediyl when R^4 is -N=N-, R^5 is not phenyl when R^3 is 1,2-phenylene and R^4 is a bond, R^5 is not phenyl when R^3 is 1,3-phenylene and R^4 is -SO_2-, R^5 is not optionally substituted heteroaryl when R^3 is phenylene and R^4 is -CH_2-, and R^3 is not 1,2-phenylene, an optically active substance of the compound, a pharmaceutically acceptable salt of the compound or the optically active substance, or a hydrate of the compound, substance or salt.

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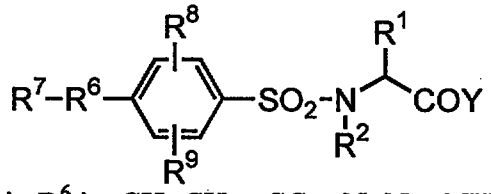
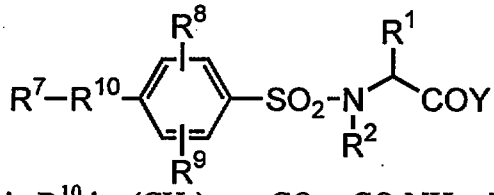
5. A compound of the formula II:



II

wherein R^6 is -CH=CH-, -CC-, -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; provided R^5 is not phenyl substituted with dimethylamino when R^4 is -N=N-, an optically active substance of the compound, a pharmaceutically acceptable salt of the compound or substance, or hydrate of the compound, substance or salt.

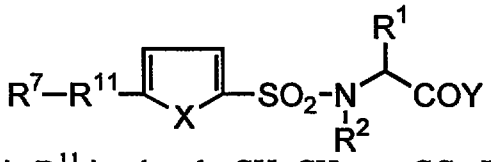
6. A compound of the formula III:



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-, R^1 is not carboxyalkyl, alkylaminocarbonylalkyl, cycloalkylamino carbonylalkyl, or phenoylaminocarbonylalkyl when R^{10} is -CONH- and R^7 is not optionally substituted heteroaryl when R^{10} is $- CH_2-$, an optically active substance of the compound, a pharmaceutically acceptable salt of the compound or substance, or hydrate of the compound, substance or salt.

7. A compound of the formula IV:



IV

wherein R^{11} is a bond, -CH=CH-, or -CC-; X is oxygen atom or sulfur atom; R^1, R^2, R^7, and Y are as defined above, an optically active substance of the compound, a

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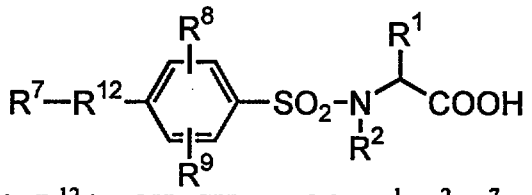
as defined above, an optically active substance of the compound, a pharmaceutically acceptable salt of the compound or substance, or hydrate of the compound, substance or salt.

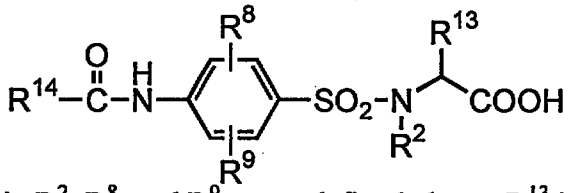
10. A compound of the formula V:



V

wherein R^{12} is -CH=CH- or -CC-; R^1, R^2, R^7, R^8, and R^9 are as defined above, an optically active substance of the compound, a pharmaceutically acceptable salt of the compound or substance, or hydrate of the compound, substance or salt.

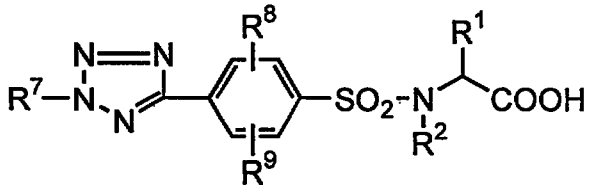
11. A compound of the formula VI:



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, phenyl carboxyalkyl, alkylaminocarbonylalkyl, cycloalkylaminocarbonylalkyl, or phenylaminocarbonylalkyl and R^{14} is not 2-chlorophenyl, 4-chlorophenyl, or 2,4-dichlorophenyl, an optically active substance of the compound, a pharmaceutically acceptable salt of the compound or substance, or hydrate of the compound, substance or salt.

12. A compound of the formula VII:



VII

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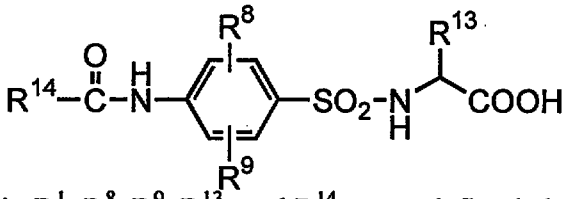
wherein R^{12} is -CH=CH- or -CC-; R^1, R^7, R^8, and R^9 are as defined above, an optically active substance of the compound, a pharmaceutically acceptable salt of the compound or substance, or hydrate of the compound, substance or salt.

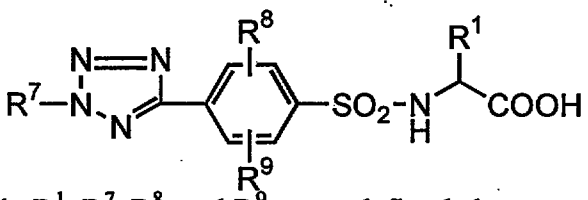
16. A compound of the formula XI:



XI

wherein R^1, R^8, R^9, R^{13}, and R^{14} are as defined above, provided R^{13} is not methyl, phenyl, carboxyalkyl, alkylaminocarbonylalkyl, cycloalkylaminocarbonylalkyl, or phenylaminocarbonylalkyl and R^{14} is not 2-chlorophenyl, 4-chlorophenyl, or 2,4-dichlorophenyl, an optically active substance of the compound, a pharmaceutically acceptable salt of the compound or substance, or hydrate of the compound, substance or salt.

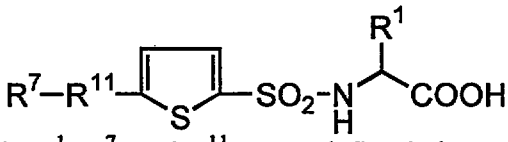
17. A compound of the formula XII:



XII

wherein R^1, R^7, R^8, and R^9 are as defined above, an optically active substance of the compound, a pharmaceutically acceptable salt of the compound or substance, or hydrate of the compound, substance or salt.

18. A compound of the formula XIII:



XIII

wherein R^1, R^7, and R^{11} are as defined above, an optically active substance of the compound, a pharmaceutically acceptable salt of the compound or substance, or hydrate of the compound, substance or salt.

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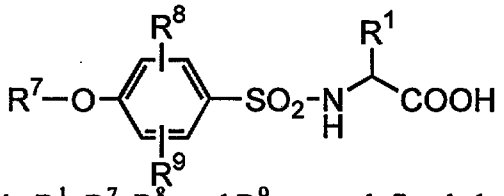
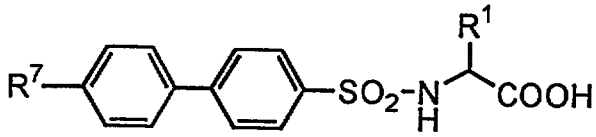
19. A compound of the formula XIV:



XIV

wherein R^1, R^7, R^8, and R^9 are as defined above, an optically active substance of the compound, a pharmaceutically acceptable salt of the substance or compound, or hydrate of the compound, substance or salt.

20. A compound of the formula XXVIII :



XXVIII

wherein R^1 and R^7 are as defined above, an optically active substance of the compound, a pharmaceutically acceptable salt of the substance or compound or hydrate of the compound, substance or salt.

21. The compound of any one of claims 4 to 20, wherein R^1, $R^{1'}$, $R^{1''}$, and R^{13} are i-propyl, benzyl, or (indole-3-yl)methyl.

22. The compound of any one of claims 4 to 7 and 10 to 20, 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.

23. The compound of any one of claims 4 to 20, wherein a configuration of asymmetric carbon atoms bonding with R^1, $R^{1'}$, $R^{1''}$, and R^{13} is R configuration.

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* C L M S *

24. A pharmaceutical composition containing a compound of any one of claims 4 to 20.

25. A composition for inhibiting metalloproteinase containing a compound of any one of claims 4 to 20.

26. A composition for inhibiting type IV collagenase containing a compound of any one of claims 4 to 20.

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特許協力条約に基づいて公開された国際出願

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添付公開書類
国際調査報告書

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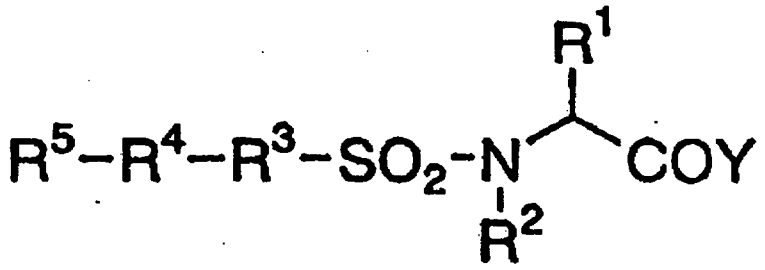
9804318-5

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

(54)発明の名称 スルホン化されたアミノ酸誘導体およびそれを含有するメタロプロティナーゼ阻害剤

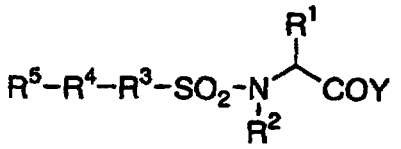


(I)

(57) Abstract
Compounds having a metalloproteinase inhibitory activity, represented by general formula (I), optically active isomers thereof, or pharmacologically acceptable salts thereof, or hydrates of these.

（５７）要約

式Ⅰ：



Ⅰ

で示される化合物、その光学活性体、もしくはそれらの製薬上許容される塩、またはそれらの水和物であって、メタロプロテイナーゼ阻害活性を有する化合物。

情報としての用途のみ

ＰＣＴに基づいて公開される国際出願をパンフレット第一頁にＰＣＴ加盟国を同定するために使用されるコード

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