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(54) **NOVEL MALONIC ACID SULFONAMIDE DERIVATIVE AND PHARMACEUTICAL USE THEREOF**  
**NEUES MALONSÄURE-SULFONAMID-DERIVAT UND SEINE PHARMAZEUTISCHE**  
**VERWENDUNG**  
**NOUVEAU DÉRIVÉ SULFAMIDE D'ACIDE MALONIQUE ET SON USAGE PHARMACEUTIQUE**

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**no. 24, 2006, pages 7160 - 7168, XP008126707**

**EP 2 172 450 B9**

**Description****TECHNICAL FIELD OF THE INVENTION**

5 **[0001]** The present invention relates to a sulfonyl malonamide derivative that is a ligand for an angiotensin type 2 receptor (hereinafter to be indicated as AT<sub>2</sub> receptor), preferably having an agonist action at AT<sub>2</sub> receptor, and a pharmaceutical agent containing same.

**[BACKGROUND OF THE INVENTION]**

10 **[0002]** Biologically, angiotensinogen is converted via renin to angiotensin I, which is subsequently converted to angiotensin II (AngII) by converting enzymes such as angiotensin converting enzyme (ACE) and the like in vivo, resulting AngII has a potent and pleiotropic physiological action.

15 **[0003]** As receptors for AngII, the angiotensin type 1 receptor (hereinafter to be indicated as AT<sub>1</sub> receptor) and AT<sub>2</sub> receptor have been identified. It has been generally understood that conventionally well-known actions of AngII such as pressor effect on blood pressure, vasoconstriction and other effects are mainly mediated by classical AT<sub>1</sub> receptors. On the other hand, the physiological roles of AT<sub>2</sub> receptor have been rapidly revealed in recent years. The action via AT<sub>2</sub> receptor mostly opposes the effect mediated by AT<sub>1</sub> receptor in a number of cells and tissues and AT<sub>2</sub> receptor mainly acts toward the prevention of diseases progression in the course of the onset and the development, as evidenced by  
20 its antiproliferative, antihypertrophic and antihypertensive effects, promotion of apoptosis, inhibition of extracellular matrix production and the like. While AT<sub>2</sub> receptor is highly expressed in a wide range in fetal life, the expression level rapidly decreases after birth. However, it has become known that tissue-specific re-expression of AT<sub>2</sub> under pathological conditions, such as vascular injury, cardiovascular remodeling after myocardial infarction and the like, thereby the significance of AT<sub>2</sub> receptor involved in the prevention of the onset and progress of various diseases is much attracting attention.

25 **[0004]** Predicted pharmacological actions generally via AT<sub>2</sub> receptor activation have been reported in several papers including a paper from de Gasparo et al. (see non-patent reference 1). Thus, a variety of therapeutic or preventive effects in several diseases could be expected as pharmaceutical use of AT<sub>2</sub> receptor agonist. As its target diseases, various groups of disorders involving the renin-angiotensin-aldosterone system (hereinafter to be indicated as RAAS), such as metabolic diseases, cardiovascular diseases and the like are considered, and stroke, renal disease, cardiac disease,  
30 hypertension, diabetes, metabolic syndrome and the like can be given as examples.

**[0005]** As nonpeptidic AT<sub>2</sub> receptor agonist, 3-phenyl-2-thiophene sulfonamide or biphenyl sulfonamide compounds have heretofore been disclosed (see non-patent references 2, 3, patent references 1, 2, 3, 4, 5, 6, 7, 8, 9). However, the compounds described in these non-patent references and patent references are all characterized by a combination of a bisaryl structure and a sulfonamide group and the like, and a sulfonyl malonamide derivative is not clearly indicated  
35 or suggested.

**[0006]** While sulfonyl malonamide derivatives are known as herbicides (see patent reference 10), all of them are unsubstituted sulfonyl malonamide derivatives, and no reference is made to an AT<sub>2</sub> receptor agonist for a sulfonyl malonamide derivative having a substituent at 2-position of the malonamide structure.

40 **[0007]** The AT<sub>2</sub> receptor agonists reported up to current times have not been confirmed regarding the selectivity to other target molecules, pharmacokinetic property and/or safety. In addition, none of compounds successfully available or under development as a pharmaceutical product has been disclosed based on the mechanism of agonist action at AT<sub>2</sub> receptor.

**[0008]**

45 non-patent reference 1: Pharmacol. Rev., 52, 415-472 (2000)

non-patent reference 2: J. Med. Chem., 47, 5995-6008 (2004)

non-patent reference 3: J. Med. Chem., 49, 7160-7168 (2006)

patent reference 1: WO-A-02/096883

patent reference 2: WO-A-06/109058

50 patent reference 3: WO-A-03/064414

patent reference 4: WO-A-04/046128

patent reference 5: WO-A-04/046137

patent reference 6: WO-A-04/085420

patent reference 7: WO-A-06/109056

55 patent reference 8: WO-A-06/109058

patent reference 9: WO-A-04/046141

patent reference 10: Indian patent No. 178290

## Disclosure of the Invention

## Problems to be Solved by the Invention

5 **[0009]** It is therefore an object of the present invention to provide a novel ligand, preferably a novel agonist, for an AT<sub>2</sub> receptor, which is expected as a pharmaceutical product, whereby to contribute to the development of therapeutic and/or preventive methods for various diseases.

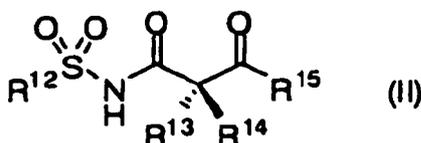
[Means of Solving the Problems]

10 **[0010]** The present inventors have found that a certain kind of sulfonyl malonamide derivative has an agonist action at AT<sub>2</sub> receptor and conducted intensive studies. As a result, they have found that a novel sulfonyl malonamide derivative having a potent and selective agonist action at AT<sub>2</sub> receptor can be expected as a pharmaceutical product, which resulted in the completion of the present invention.

15 **[0011]** Accordingly, the present invention relates to the following sulfonyl malonamide derivative or a pharmacologically acceptable salt thereof, and use of a ligand, agonist and the like comprising the same.

**[0012]** In particular, the present invention provides the following:

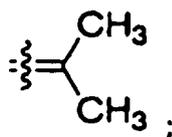
20 1. A sulfonyl malonamide derivative represented by the following formula (II)



wherein R<sup>12</sup> is 2-naphthyl, trans-β-styryl, phenethyl, 3-phenoxypropyl or 4-phenylbutyl;

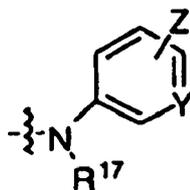
one of R<sup>13</sup> and R<sup>14</sup> is a hydrogen atom, and the other is isopropyl, isobutyl, neopentyl, allyl, -CH<sub>2</sub>-R<sup>16</sup> wherein R<sup>16</sup> is optionally substituted C<sub>3-10</sub> cycloalkyl, optionally substituted heterocycle or -CO-NR<sup>5</sup>R<sup>6</sup> (wherein R<sup>5</sup> and R<sup>6</sup> are the same or different and each is a hydrogen atom, C<sub>1-6</sub> alkyl, optionally substituted aryl or optionally substituted heteroaryl, or R<sup>5</sup> and R<sup>6</sup> optionally form optionally substituted cyclic amino together with a nitrogen atom bonded thereto),

30 -(CH<sub>2</sub>)<sub>2</sub>-R<sup>16'</sup> (wherein R<sup>16'</sup> is cyano or C<sub>1-6</sub> alkoxy), or -(CH<sub>2</sub>)<sub>n</sub>-Ar<sup>2</sup> (wherein n is an integer of 1 to 3, and Ar<sup>2</sup> is substituted phenyl or optionally substituted heteroaryl), or R<sup>13</sup> and R<sup>14</sup> optionally form, together with a carbon atom bonded thereto, the following formula



and

R<sup>15</sup> is di(C<sub>1-6</sub> alkyl)amino or the following formula

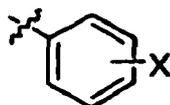


55 wherein Z is a hydrogen atom, a halogen atom or trifluoromethyl, Y is a nitrogen atom or CH, R<sup>17</sup> is ethyl, isopropyl or 3-pentyl, provided that when Y is a nitrogen atom, then Z is a hydrogen atom, or a pharmacologically acceptable salt thereof.

2. The sulfonyl malonamide derivative of item 1, wherein Ar<sup>2</sup> for R<sup>13</sup> or R<sup>14</sup> is substituted phenyl represented by the

following formula

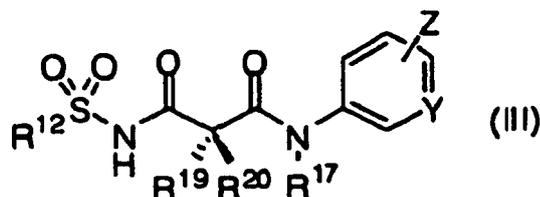
5



wherein X is a fluorine atom, a chlorine atom, a bromine atom, cyano, nitro, amino (excluding substitution at the ortho-position),  $-\text{NHCOAr}^3$ ,  $-\text{NHCOOAr}^3$ ,  $-\text{NHCONHAr}^3$ ,  $-\text{NHSO}_2\text{Ar}^3$ ,  $-\text{OAr}^3$  (wherein  $\text{Ar}^3$  is optionally substituted aryl or optionally substituted heteroaryl),  $-\text{NHCOR}^{18}$  (wherein  $\text{R}^{18}$  is optionally substituted  $\text{C}_{1-6}$  alkyl, optionally substituted  $\text{C}_{3-10}$  cycloalkyl, or optionally substituted heterocycle), optionally substituted  $\text{C}_{1-6}$  alkoxy, optionally substituted heterocycle, optionally substituted aryl or optionally substituted heteroaryl, or a pharmacologically acceptable salt thereof.

3. The sulfonyl malonamide derivative of item 1, which is represented by the following formula (III)

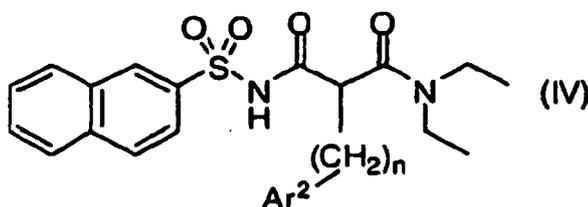
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wherein  $\text{R}^{12}$ ,  $\text{R}^{17}$ , Y and Z are as defined in item 1, one of  $\text{R}^{19}$  and  $\text{R}^{20}$  is a hydrogen atom, and the other is isopropyl, isobutyl, neopentyl, allyl, cyclopropylmethyl or  $-\text{CH}_2-\text{Ar}^2$ , wherein  $\text{Ar}^2$  is as defined in item 1, or a pharmacologically acceptable salt thereof.

4. The sulfonyl malonamide derivative of item 1, which is represented by the following formula (IV)

30



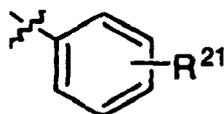
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wherein n is an integer of 1 to 3,  $\text{Ar}^2$  is as defined in item 1, or a pharmacologically acceptable salt thereof.

40

5. The sulfonyl malonamide derivative of Item 4, wherein  $\text{Ar}^2$  is substituted phenyl represented by the following formula

45



wherein  $\text{R}^{21}$  is a fluorine atom, a chlorine atom, nitro, cyano, amino (excluding substitution at the ortho-position), dimethylamino, methoxy, trifluoromethoxy, methoxycarbonyl, phenyl, 2-pyridyloxy, 1-imidazolyl, 2-isindolinyl, 1-oxo-2-isindolinyl or the following formula

50



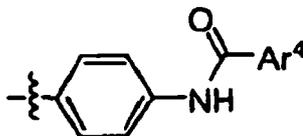
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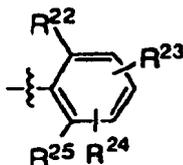
wherein  $\text{Ar}^3$  is as defined in item 2,

or a pharmacologically acceptable salt thereof.

6. The sulfonyl malonamide derivative of item 4, wherein Ar<sup>2</sup> is substituted phenyl represented by the following formula



wherein Ar<sup>4</sup> is 2-thienyl, 2-furyl, 4-pyridyl, 3-pyridyl, 2-pyridyl or the following formula



wherein R<sup>22</sup> and R<sup>25</sup> are the same or different and each is a hydrogen atom, amino, a fluorine atom, hydroxy, methoxy, methyl or a chlorine atom, R<sup>23</sup> is a hydrogen atom or a fluorine atom, and R<sup>24</sup> is a hydrogen atom, a fluorine atom, a chlorine atom, methyl, amino, methoxy or cyano, and n is 1, or a pharmacologically acceptable salt thereof.

7. The sulfonyl malonamide derivative of item 1, which is a compound selected from:

N,N-diethyl-2-{4-[(2,6-difluorobenzoyl)amino]benzyl}-N'-(2-naphthylsulfonyl)malonamide,  
 (2S)-2-[4-(benzoylamino)benzyl]-N,N-diethyl-N'-(2-naphthylsulfonyl)malonamide,  
 (2S)-N,N-diethyl-2-{4-[(2-fluorobenzoyl)amino]benzyl}-N'-(2-naphthylsulfonyl)malonamide,  
 (2S)-N,N-diethyl-2-{4-[(3-fluorobenzoyl)amino]benzyl}-N'-(2-naphthylsulfonyl)malonamide,  
 (2S)-N,N-diethyl-2-{4-[(2,4-difluorobenzoyl)amino]benzyl}-N'-(2-naphthylsulfonyl)malonamide,  
 (2S)-N,N-diethyl-2-{4-[(4-methylbenzoyl)amino]benzyl}-N'-(2-naphthylsulfonyl)malonamide,  
 (2S)-N,N-diethyl-N'-(2-naphthylsulfonyl)-2-{4-[(2-thienoyl)amino]benzyl}malonamide,  
 (2S)-N,N-diethyl-2-{4-[(2-furoyl)amino]benzyl}-N'-(2-naphthylsulfonyl)malonamide,  
 (2S)-2-{4-[(2-amino-5-fluorobenzoyl)amino]benzyl}-N,N-diethyl-N'-(2-naphthylsulfonyl)malonamide,  
 (2S)-2-{4-[(2-amino-6-fluorobenzoyl)amino]benzyl}-N,N-diethyl-N'-(2-naphthylsulfonyl)malonamide,  
 (2S)-N,N-diethyl-N'-(2-naphthylsulfonyl)-2-{4-[(2-pyridylcarbonyl)amino]benzyl}malonamide,  
 (2S)-2-{4-[(2-amino-4-chlorobenzoyl)amino]benzyl}-N,N-diethyl-N'-(2-naphthylsulfonyl)malonamide,  
 (2S)-2-{4-[(2-aminobenzoyl)amino]benzyl}-N,N-diethyl-N'-(2-naphthylsulfonyl)malonamide,  
 (2S)-2-{4-[(2-amino-5-chlorobenzoyl)amino]benzyl}-N,N-diethyl-N'-(2-naphthylsulfonyl)malonamide,  
 (2S)-2-{4-[(2-amino-4,5-difluorobenzoyl)amino]benzyl}-N,N-diethyl-N'-(2-naphthylsulfonyl)malonamide,  
 (2S)-2-{4-[(2-amino-4-fluorobenzoyl)amino]benzyl}-N,N-diethyl-N'-(2-naphthylsulfonyl)malonamide,  
 (2S)-2-{4-[(2-amino-5-methylbenzoyl)amino]benzyl}-N,N-diethyl-N'-(2-naphthylsulfonyl)malonamide,  
 2-[(4-fluorobenzyl)-N-isopropyl-N-(3-pyridyl)-N'-((E)-styrylsulfonyl)malonamide,  
 2-allyl-N-(4-fluorophenyl)-N-isopropyl-N'-((E)-styrylsulfonyl)malonamide, N-(4-fluorophenyl)-2-isobutyl-N-isopropyl-N'-((E)-styrylsulfonyl)malonamide,  
 N-(4-fluorophenyl)-2-isobutyl-N-isopropyl-N'-phenethylsulfonylmalonamide,  
 N-(4-fluorophenyl)-2-isobutyl-N-isopropyl-N'-(2-naphthylsulfonyl)malonamide, (2S or 2R)-2-cyclopropylmethyl-N-(4-fluorophenyl)-N-isopropyl-N'-((E)-2-styrylsulfonyl)malonamide,  
 2-cyclopropylmethyl-N-(4-fluorophenyl)-N-isopropyl-N'-phenethylsulfonylmalonamide, or  
 2-cyclopropylmethyl-N-(4-fluorophenyl)-N-isopropyl-N'-(2-naphthylsulfonyl)malonamide,

or a pharmacologically acceptable salt thereof.

8. A pharmaceutical composition comprising the sulfonyl malonamide derivative of any of the items 1 to 7, or a pharmacologically acceptable salt thereof, as an active ingredient.

9. The sulfonyl malonamide derivative of any of items 1 to 7, or a pharmacologically acceptable salt thereof for use

as an AT<sub>2</sub> receptor agonist.

10. The sulfonyl malonamide derivative of item 7, or a pharmacologically acceptable salt thereof for use as an AT<sub>2</sub> receptor agonist.

11. The sulfonyl malonamide derivative of item 10, wherein the AT<sub>2</sub> receptor agonist is AT<sub>2</sub> receptor selective.

12. The sulfonyl malonamide derivative of any of items 1 to 7, or a pharmacologically acceptable salt thereof for use in the treatment and prophylaxis of a disorder involving the renin-angiotensin-aldosterone system.

13. The sulfonyl malonamide derivative of item 12, wherein the disorder involving the renin-angiotensin-aldosterone system is selected from stroke, renal disease, cardiac disease, hypertension, diabetes, diabetic complications, hyperlipidemia and metabolic syndrome.

**[0013]** The present invention is directed to the sulfonyl malonamide derivatives as defined in Formulae (II), (III) and (IV). In as far as the following description relates to sulfonyl malonamide derivatives other than those defined by Formulae (II), (III) and (IV), such disclosure is for the purpose of providing illustration and enablement only.

[Effect of the Invention]

**[0014]** The sulfonyl malonamide derivative of the present invention has a potent and selective agonist action at AT<sub>2</sub> receptor, and is useful as a therapeutic or preventive drug for various diseases. As the target diseases, various groups of disorders involving RAAS, such as metabolic and cardiovascular diseases and the like are considered, and particularly stroke, renal disease, cardiac disease, hypertension, diabetes, metabolic syndrome and the like can be mentioned.

**[0015]** Each symbol used in the present specification is explained below.

**[0016]** Being optionally substituted means optionally having one or more substituents or being unsubstituted.

**[0017]** C<sub>1-6</sub> alkyl means a linear or branched chain hydrocarbon group having a carbon number of 1 to 6, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, isohexyl and the like.

**[0018]** C<sub>2-6</sub> alkenyl means a linear or branched unsaturated hydrocarbon group having a carbon number of 2 to 6 and containing one or more carbon-carbon double bonds, such as vinyl, allyl, 1-propenyl, isopropenyl, 2-butenyl, 1,3-butadienyl, 2-methyl-2-propenyl, prenyl, isopentenyl, 2-hexenyl and the like.

**[0019]** C<sub>2-6</sub> alkynyl means a linear or branched unsaturated hydrocarbon group having a carbon number of 2 to 6 and containing one or more carbon-carbon triple bond, such as ethynyl, 2-propynyl, 2-butyne, 3-butyne, 3-pentyne, 5-hexyne and the like.

**[0020]** C<sub>3-10</sub> cycloalkyl means a saturated cyclic hydrocarbon group having a carbon number of 3 to 10, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and the like. In addition, the cycloalkyl may be condensed with a benzene ring to form indane (e.g., indan-1-yl, indan-2-yl etc.), tetrahydronaphthalene (e.g., tetrahydronaphthalen-5-yl, tetrahydronaphthalen-6-yl etc.) and the like.

**[0021]** C<sub>3-10</sub> cycloalkyl C<sub>1-6</sub> alkyl means the above-mentioned "C<sub>2-6</sub> alkyl" substituted with the above-mentioned "C<sub>3-10</sub> cycloalkyl". The "C<sub>1-6</sub> alkyl" is preferably alkyl having a carbon number of 1 to 3, such as cyclopropylmethyl, 2-cyclobutylethyl, 3-cyclopentylpropyl, cyclohexylmethyl, 2-cyclohexylethyl, cycloheptylmethyl and the like.

**[0022]** Aryl means an aromatic hydrocarbon group preferably having a carbon number of 6 to 14, such as phenyl, naphthyl and the like. This group encompasses an ortho-fused bicyclic group having a ring atom of 8 to 10 wherein at least one ring is an aromatic ring (e.g., indenyl etc.) and the like.

**[0023]** Aryl C<sub>1-6</sub> alkyl means the above-mentioned "C<sub>1-6</sub> alkyl" substituted with the above-mentioned "aryl". Examples thereof include benzyl, benzhydryl, phenethyl, 1-phenylethyl, 3-phenylpropyl, 4-phenylbutyl, 5-phenylpentyl, 6-phenylhexyl, 1-naphthylmethyl, 2-naphthylmethyl, 2-(1-naphthyl)ethyl, 2-(2-naphthyl)ethyl, 3-(2-naphthyl)propyl, 4-(2-naphthyl)butyl and the like.

**[0024]** Aryloxy C<sub>1-6</sub> alkyl means the above-mentioned "C<sub>1-6</sub> alkyl" substituted with "aryloxy", wherein the aryl moiety of the "aryloxy" is as defined above for "aryl". The "C<sub>1-6</sub> alkyl" is preferably alkyl having a carbon number of 1 to 3, such as 2-phenoxyethyl, 3-phenoxypropyl, 2-(1-naphthoxy)ethyl, 2-(2-naphthoxy)ethyl, 3-(1-naphthoxy)propyl, 3-(2-naphthoxy)propyl and the like.

**[0025]** Aryl C<sub>2-6</sub> alkenyl means the above-mentioned "C<sub>2-6</sub> alkenyl" substituted with the above-mentioned "aryl". The "C<sub>2-6</sub> alkenyl" is preferably alkenyl having a carbon number of 2 to 4, such as trans-β-styryl, cinnamyl, 3-(1-naphthyl)-2-propenyl, 3-(2-naphthyl)-2-propenyl and the like.

**[0026]** Heteroaryl means an aromatic group containing, besides carbon atom, one or more (preferably 1 to 4) hetero atoms selected from an oxygen atom, a sulfur atom and a nitrogen atom. The group includes a 5- or 6-membered

monocyclic group, an ortho-fused bicyclic group having 8 to 10 ring atoms (particularly benzo derivative) derived therefrom, a group obtained by fusion thereof with propenylene, trimethylene or tetramethylene, its stable N-oxide and the like. Examples of the group include pyrrolyl, furyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl, tetrazolyl, 1,3,5-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,4-thiadiazolyl, pyridyl (2-pyridyl, 3-pyridyl, 4-pyridyl), pyrazinyl, pyrimidinyl, pyridazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, 1,3,5-triazinyl, benzoxazolyl, benzoisoxazolyl, benzothiazolyl, benzoisothiazolyl, benzoimidazolyl, oxazolopyridyl, imidazopyridazinyl, isothianaphthenyl, benzofuranyl, isobenzofuranyl, benzothieryl, chromenyl, isoindolyl, indolyl, indazolyl, isoquinolyl, quinolyl, phthalazinyl, quinoxalinyl, quinazolinyl, cinnolinyl, 2,1,3-benzoxadiazolyl, benzoxazinyl, pteridinyl and the like.

**[0027]** Heteroaryl C<sub>1-6</sub> alkyl means the above-mentioned "C<sub>1-6</sub> alkyl" substituted with the above-mentioned "heteroaryl". The "C<sub>1-6</sub> alkyl" is preferably alkyl having a carbon number of 1 to 5, such as 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethyl, 2-(2-pyridyl)ethyl, 2-(3-pyridyl)ethyl, 2-(4-pyridyl)ethyl, 3-(2-pyridyl)propyl, 3-(3-pyridyl)propyl, 3-(4-pyridyl)propyl, 2-thienylmethyl, 3-thienylmethyl, 2-(2-thienyl)ethyl, 3-(2-thienyl)propyl, 4-pyrazolylmethyl, 2-(4-pyrazolyl)ethyl, 3-(4-pyrazolyl)propyl, 2-thiazolylmethyl, 4-thiazolylmethyl, 5-thiazolylmethyl, 2-(2-thiazolyl)ethyl, 3-(2-thiazolyl)propyl, 2-(4-thiazolyl)ethyl, 3-(4-thiazolyl)propyl, 2-(5-thiazolyl)ethyl, 3-(5-thiazolyl)propyl, 2-oxazolylmethyl, 4-oxazolylmethyl, 5-oxazolylmethyl, 2-(2-oxazolyl)ethyl, 3-(2-oxazolyl)propyl, 2-(4-oxazolyl)ethyl, 3-(4-oxazolyl)propyl, 2-(5-oxazolyl)ethyl, 3-(5-oxazolyl)propyl, 4-(1,2,3-triazolyl)methyl, 5-tetrazolylmethyl, 2-(5-tetrazolyl)ethyl, 1-imidazolylmethyl, 2-(1-imidazolyl)ethyl, 6-benzoxazolylmethyl, 1-benzoimidazolylmethyl and the like.

**[0028]** Heteroaryl C<sub>2-6</sub> alkenyl means the above-mentioned "C<sub>2-6</sub> alkenyl" substituted with the above-mentioned "heteroaryl". The "C<sub>2-6</sub> alkenyl" is preferably alkenyl having a carbon number of 2 to 4, such as 2-pyridylethenyl, 3-pyridylethenyl, 4-pyridylethenyl, 2-thiazolylethenyl, 2-oxazolylethenyl, 3-(2-pyridyl)-2-propenyl, 3-(3-pyridyl)-2-propenyl, 3-(4-pyridyl)-2-propenyl, 3-(3-thienyl)-2-propenyl, 3-(4-isoquinolyl)-2-propenyl, 3-(3-benzothieryl)-2-propenyl and the like.

**[0029]** Heterocycle means a cyclic hydrocarbon group having 1 to 3 hetero atoms selected from a nitrogen atom, an oxygen atom, a sulfur atom and the like. The group is nonaromatic, and optionally saturated or partially unsaturated. The group includes not only monocycle but also spiro ring, with preference given to a 4- to 7-membered monocyclic group and a 10- or 11-membered spiro ring group. Examples of the group include azetidyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholino, 1,4-diazepanyl, 1,2,5,6-tetrahydropyridyl, tetrahydropyranyl, cyclopentanespiro-4'-piperidinyl and the like.

Furthermore, the above-mentioned heterocycle may be condensed with an aromatic ring. Examples of the fused ring include indolinyl, isoindolinyl, 1,2,3,4-tetrahydroquinolyl, 1,2,3,4-tetrahydroisoquinolyl, spiro[indane-1,4'-piperidin]-1'-yl and the like.

**[0030]** Heterocycle C<sub>1-6</sub> alkyl means the above-mentioned "C<sub>1-6</sub> alkyl" substituted with the above-mentioned "heterocycle". The "C<sub>1-6</sub> alkyl" is preferably alkyl having a carbon number of 1 to 3, such as 4-piperidinylmethyl, 2-(4-piperidinyl)ethyl, 2-(1-piperazinyl)ethyl and the like.

**[0031]** Cyclic amino means a cyclic hydrocarbon group containing at least one nitrogen atom, wherein the nitrogen atom is a bond of the group. The ring may further contain, besides the aforementioned nitrogen atom, 1 to 3 homologous or heterologous hetero atoms selected from, for example, a nitrogen atom, an oxygen atom and a sulfur atom. The group is nonaromatic, and optionally saturated or partially unsaturated. The group contains not only monocycle but also spiro ring, with preference given to a 4- to 7-membered monocyclic group and a 10- or 11-membered spiro ring group. Examples of the group include azetidino, pyrrolidino, piperidino, piperazino, morpholino, 1,4-diazepan-1-yl, 1,2,5,6-tetrahydropyridino, tetrahydroimidazolino, cyclopentanespiro-4'-piperidino and the like.

Furthermore, the above-mentioned cyclic amino may be condensed with an aromatic ring. Examples of the fused ring include indolino, isoindolino, 1,2,3,4-tetrahydroquinolino, 1,2,3,4-tetrahydroisoquinolino, spiro[indane-1,4'-piperidin]-1'-yl and the like.

**[0032]** Examples of the halogen atom include a chlorine atom, a bromine atom, a fluorine atom and an iodine atom.

**[0033]** Examples of the substituent of the "optionally substituted C<sub>1-6</sub> alkyl", "optionally substituted C<sub>2-6</sub> alkenyl", "optionally substituted C<sub>2-6</sub> alkynyl", "optionally substituted C<sub>3-10</sub> cycloalkyl", "optionally substituted heterocycle", "optionally substituted aryl" and "optionally substituted heteroaryl" include 1 to 3 substituents selected from substituent group A shown below, and the like.

**[0034]** Substituent group A: a halogen atom (as defined above), a hydroxyl group, nitro, cyano, trifluoromethyl, trifluoromethoxy, C<sub>1-6</sub> alkyl (as defined above), C<sub>2-6</sub> alkenyl (as defined above), C<sub>2-6</sub> alkynyl (as defined above), C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> alkylthio, C<sub>1-6</sub> alkylsulfanyl, C<sub>3-10</sub> cycloalkyl (as defined above), C<sub>3-10</sub> cycloalkyl C<sub>1-6</sub> alkyl (as defined above), aryl (as defined above), aryloxy, aryl C<sub>1-6</sub> alkyl (as defined above), aryl C<sub>2-6</sub> alkenyl (as defined above), aryl C<sub>2-6</sub> alkynyl, heteroaryl (as defined above), heteroaryloxy, heteroaryl C<sub>1-6</sub> alkyl (as defined above), heterocycle (as defined above), oxo, -COOR<sup>a</sup>, -CH<sub>2</sub>COOR<sup>a</sup>, -OCH<sub>2</sub>COOR<sup>a</sup>, -CONR<sup>b</sup>R<sup>c</sup>, -CH<sub>2</sub>CONR<sup>b</sup>R<sup>c</sup>, -OCH<sub>2</sub>CONR<sup>b</sup>R<sup>c</sup>, -COO(CH<sub>2</sub>)<sub>2</sub>NR<sup>e</sup>R<sup>f</sup>, -CONR<sup>d</sup>SO<sub>2</sub>T<sup>1</sup>, -NR<sup>e</sup>R<sup>f</sup>, -NR<sup>g</sup>CHO, -NR<sup>g</sup>COT<sup>2</sup>, -NR<sup>g</sup>COOT<sup>2</sup>, -NR<sup>g</sup>CONR<sup>i</sup>R<sup>j</sup>, -NR<sup>h</sup>SO<sub>2</sub>T<sup>3</sup>, -NHC(=NH)NH<sub>2</sub>, -COT<sup>2</sup>, -SO<sub>2</sub>T<sup>3</sup>, methylenedioxy, and ethyleneoxy.

The above-mentioned substituents may have 1 to 3 substituents selected from substituent group A at substitutable

position(s).

**[0035]** Here, the "C<sub>1-6</sub> alkyl" moiety of the C<sub>1-6</sub> alkoxy is as defined above for "C<sub>1-6</sub> alkyl", and examples thereof include methoxy, ethoxy, propoxy, isopropoxy, butoxy, pentyloxy, hexyloxy and the like.

**[0036]** The "C<sub>1-6</sub> alkyl" moiety of the C<sub>1-6</sub> alkylthio is as defined above for "C<sub>1-6</sub> alkyl", and examples thereof include methylthio, ethylthio, propylthio, isopropylthio, butylthio, pentylthio, hexylthio and the like.

**[0037]** The "C<sub>1-6</sub> alkyl" moiety of the C<sub>1-6</sub> alkylsulfinyl is as defined above for "C<sub>1-6</sub> alkyl", and examples thereof include methylsulfinyl, ethylsulfinyl, propylsulfinyl, isopropylsulfinyl, butylsulfinyl, pentylsulfinyl, hexylsulfinyl and the like.

**[0038]** The aryl moiety of the aryloxy is as defined above for "aryl", and examples thereof include phenoxy, 1-naphthoxy, 2-naphthoxy and the like.

**[0039]** The aryl C<sub>2-6</sub> alkynyl means the above-mentioned "C<sub>2-6</sub> alkynyl" substituted with the above-mentioned "aryl". The "C<sub>2-6</sub> alkynyl" is preferably alkynyl having a carbon number of 2 to 4, such as phenylethynyl and the like.

**[0040]** The "heteroaryl" moiety of the heteroaryloxy is as defined above for "heteroaryl", and examples thereof include 2-pyridyloxy, 2-benzothiazolyloxy and the like.

**[0041]** In addition, R<sup>a</sup> - R<sup>j</sup> are each a hydrogen atom, C<sub>1-6</sub> alkyl (as defined above), aryl (as defined above), aryl C<sub>1-6</sub> alkyl (as defined above), heteroaryl (as defined above) or heteroaryl C<sub>1-6</sub> alkyl (as defined above), respectively. These groups may further have 1 to 3 substituents selected from substituent group A, at substitutable position(s).

**[0042]** R<sup>b</sup> and R<sup>c</sup>, R<sup>e</sup> and R<sup>f</sup>, and R<sup>i</sup> and R<sup>j</sup> in -NR<sup>b</sup>R<sup>c</sup>, -NR<sup>e</sup>R<sup>f</sup>, -NR<sup>i</sup>R<sup>j</sup> may form, together with a nitrogen atom bonded thereto, cyclic amino (as defined above) optionally further having 1 to 3 substituents selected from substituent group A at substitutable position(s). In addition, cyclic amino formed by -NR<sup>e</sup>R<sup>f</sup> contains cyclic amino having oxo (e.g., 2-pyrrolidinon-1-yl, 1-oxoisindolin-2-yl, succinimido, oxazolidin-2-on-3-yl, 2-benzoxazolinon-3-yl, phthalimido, 4-quinazolinon-3-yl etc.).

**[0043]** T<sup>1</sup> - T<sup>3</sup> are each C<sub>1-6</sub> alkyl (as defined above), C<sub>2-6</sub> alkenyl (as defined above), C<sub>2-6</sub> alkynyl (as defined above), C<sub>3-10</sub> cycloalkyl (as defined above), C<sub>3-10</sub> cycloalkyl C<sub>1-6</sub> alkyl (as defined above), aryl (as defined above), aryl C<sub>1-6</sub> alkyl (as defined above), heteroaryl (as defined above), heteroaryl C<sub>1-6</sub> alkyl (as defined above), cyclic amino (as defined above) or heterocycle (as defined above). These groups may further have 1 to 3 substituents selected from substituent group A at substitutable position(s), and examples of aryl or heteroaryl having 1 to 3 substituent selected from substituent group A include 2-aminophenyl, 2-amino-5-fluorophenyl, 2-amino-6-fluorophenyl, 2-fluorophenyl, 4-methoxyphenyl, 5-chloro-2-pyridyl and the like.

**[0044]** Embodiments of the present invention encompass the sulfonyl malonamide derivatives represented by the above-mentioned formulas (II), (III) and (IV), and a pharmacologically acceptable salt thereof.

**[0045]** Particularly preferable sulfonyl malonamide derivatives are the following compounds:

N,N-diethyl-2-{4-[(2,6-difluorobenzoyl)amino]benzyl}-N'-(2-naphthylsulfonyl)malonamide,  
 (2S)-2-[4-(benzoylamino)benzyl]-N,N-diethyl-N'-(2-naphthylsulfonyl)malonamide,  
 (2S)-N,N-diethyl-2-{4-[(2-fluorobenzoyl)amino]benzyl}-N'-(2-naphthylsulfonyl)malonamide,  
 (2S)-N,N-diethyl-2-{4-[(3-fluorobenzoyl)amino]benzyl}-N'-(2-naphthylsulfonyl)malonamide,  
 (2S)-N,N-diethyl-2-{4-[(2,4-difluorobenzoyl)amino]benzyl}-N'-(2-naphthylsulfonyl)malonamide,  
 (2S)-N,N-diethyl-2-{4-[(4-methylbenzoyl)amino]benzyl}-N'-(2-naphthylsulfonyl)malonamide,  
 (2S)-N,N-diethyl-N'-(2-naphthylsulfonyl)-2-{4-[(2-thienoyl)amino]benzyl}malonamide,  
 (2S)-N,N-diethyl-2-{4-[(2-furoyl)amino]benzyl}-N'-(2-naphthylsulfonyl)malonamide,  
 (2S)-2-{4-[(2-amino-5-fluorobenzoyl)amino]benzyl}-N,N-diethyl-N'-(2-naphthylsulfonyl)malonamide,  
 (2S)-2-{4-[(2-amino-6-fluorobenzoyl)amino]benzyl}-N,N-diethyl-N'-(2-naphthylsulfonyl)malonamide,  
 (2S)-N,N-diethyl-N'-(2-naphthylsulfonyl)-2-{4-[(2-pyridylcarbonyl)amino]benzyl}malonamide,  
 (2S)-2-{4-[(2-amino-4-chlorobenzoyl)amino]benzyl}-N,N-diethyl-N'-(2-naphthylsulfonyl)malonamide,  
 (2S)-2-{4-[(2-aminobenzoyl)amino]benzyl}-N,N-diethyl-N'-(2-naphthylsulfonyl)malonamide,  
 (2S)-2-{4-[(2-amino-5-chlorobenzoyl)amino]benzyl}-N,N-diethyl-N'-(2-naphthylsulfonyl)malonamide,  
 (2S)-2-{4-[(2-amino-4,5-difluorobenzoyl)amino]benzyl}-N,N-diethyl-N'-(2-naphthylsulfonyl)malonamide,  
 (2S)-2-{4-[(2-amino-4-fluorobenzoyl)amino]benzyl}-N,N-diethyl-N'-(2-naphthylsulfonyl)malonamide,  
 (2S)-2-{4-[(2-amino-5-methylbenzoyl)amino]benzyl}-N,N-diethyl-N'-(2-naphthylsulfonyl)malonamide,  
 2-[(4-fluorobenzyl)-N-isopropyl-N-(3-pyridyl)-N'-((E)-styrylsulfonyl)malonamide,  
 2-allyl-N-(4-fluorophenyl)-N-isopropyl-N'-((E)-styrylsulfonyl)malonamide,  
 N-(4-fluorophenyl)-2-isobutyl-N-isopropyl-N'-((E)-styrylsulfonyl)malonamide,  
 N-(4-fluorophenyl)-2-isobutyl-N-isopropyl-N'-phenethylsulfonylmalonamide,  
 N-(4-fluorophenyl)-2-isobutyl-N-isopropyl-N'-(2-naphthylsulfonyl)malonamide,  
 (2S or 2R)-2-cyclopropylmethyl-N-(4-fluorophenyl)-N-isopropyl-N'-((E)-2-styrylsulfonyl)malonamide,  
 2-cyclopropylmethyl-N-(4-fluorophenyl)-N-isopropyl-N'-phenethylsulfonylmalonamide, and  
 2-cyclopropylmethyl-N-(4-fluorophenyl)-N-isopropyl-N'-(2-naphthylsulfonyl)malonamide.

[0046] AT<sub>2</sub> receptor is an angiotensin type 2 receptor.

[0047] Being AT<sub>2</sub> receptor selective means that affinity of the compound for AT<sub>2</sub> receptor, expressed by Ki value, is at least 5-fold, preferably at least 20-fold, more potent than that for AT<sub>1</sub> receptor.

[0048] AT<sub>2</sub> receptor agonist is a substance that binds to AT<sub>2</sub> receptor and evokes intracellular signal transduction similar to natural ligand, angiotensin II.

[0049] Being pharmacologically acceptable means generally safe and harmless. Even if biologically undesirable, a substance might be preferable from other aspects, and includes those advantageous for not only use as pharmaceutical agents for human but also animal medicine. It means being useful for preparation of pharmaceutical compositions.

[0050] Examples of the pharmacologically acceptable salt include inorganic acid addition salts (e.g., salts with hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid etc.), organic acid addition salts (e.g., salts with methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, formic acid, acetic acid, trifluoroacetic acid, oxalic acid, citric acid, malonic acid, fumaric acid, glutaric acid, adipic acid, maleic acid, tartaric acid, succinic acid, mandelic acid, malic acid, pantothenic acid, methylsulfuric acid etc.), inorganic base addition salts (e.g., salts with sodium, potassium, calcium, magnesium etc.), salts with amino acid (e.g., salts with glutamic acid, aspartic acid, arginine, lysin etc.) and the like.

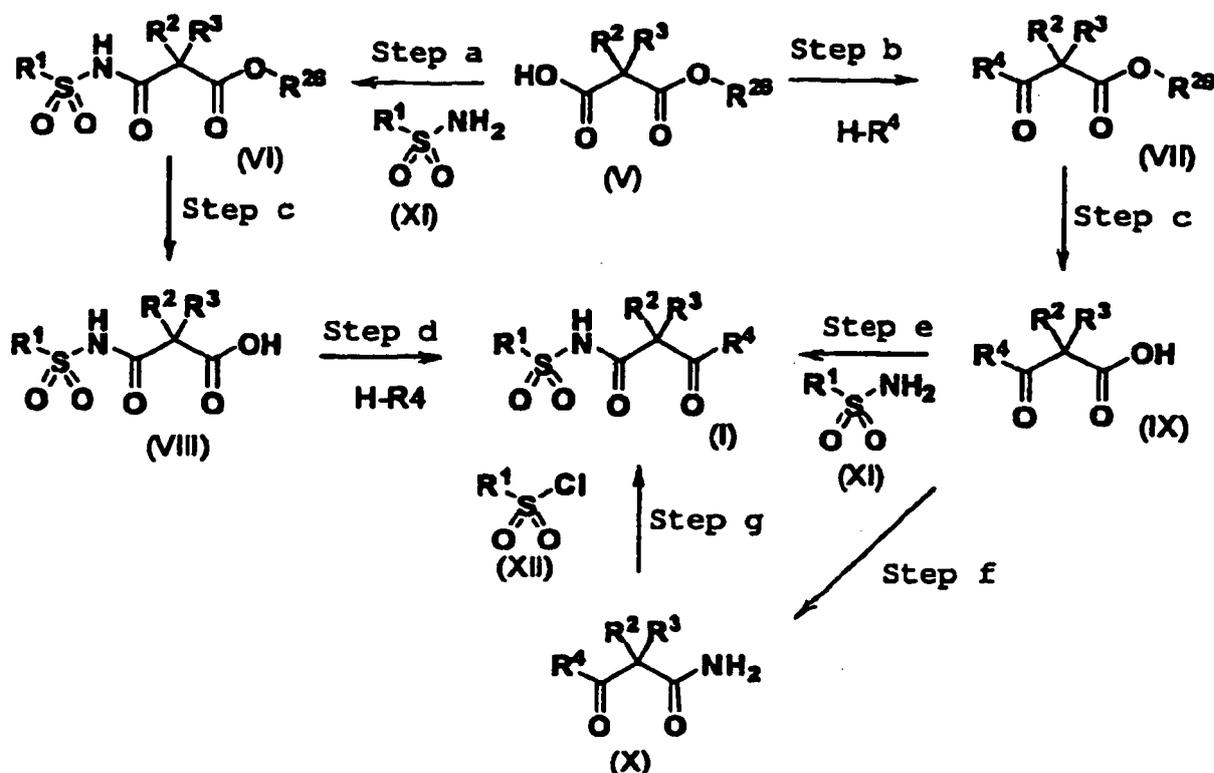
[0051] The sulfonyl malonamide derivative represented by the formula (I), or a pharmacologically acceptable salt thereof, can show polymorphism. The compound of the present invention can be present as an optical isomer and a stereo isomer when it has an asymmetric carbon in molecule. Furthermore, the compound of the present invention can be present as one or more tautomer depending on unsaturated bond, kind of substituent, pH and the like. Therefore, the present invention encompasses any of the above-mentioned stereoisomers, optical isomers, polymorphs, tautomers, optional mixtures thereof and the like.

[0052] The compound of the present invention can be produced by various methods shown below.

Each symbol in the following reaction schemes is as defined above unless otherwise indicated. Each compound in the reaction schemes also includes salts as long as the reaction is not inhibited. While the compound obtained by each reaction can be directly used for the next reaction in the form of a reaction mixture or a crude product, or can be isolated from a reaction mixture according to conventional methods and can be easily purified by general separation means (e.g., recrystallization, distillation, chromatography etc.)

[0053] The production method of the compound represented by the formula (I) is shown in Scheme 1.

Scheme 1



[0054] wherein R<sup>26</sup> is a carboxyl-protecting group (e.g., methyl, ethyl, benzyl, tert-butyl etc.).

[0055] Step a: In this step, a compound represented by the formula (VI) is produced by subjecting a compound represented by the formula (V) and a compound represented by the formula (XI) to dehydration-condensation by a method well known in the field. For example, this step can be performed according to the methods described in Ishizuka et al., *Synthesis*, No. 6, 784-788 (2000), Jansen et al., *Eur. J. Med. Chem.*, Vol. 38, 855-865 (2003), Chakravarty et al., *Bioorg. Med. Chem. Lett.*, Vol. 4, 75-80 (1994), Sakaki et al., *Bioorg. Med. Chem. Lett.*, Vol. 8, 2241-2246 (1998), Donkor et al., *Eur. J. Med. Chem.*, Vol.33, 15-22 (1998), or a method analogous thereto.

[0056] The compound represented by the formula (VI) can be produced by reacting an acidic compound represented by the formula (V) or a reactive derivative thereof with a compound represented by the formula (XI) using a dehydration-condensation agent in a solvent, in the presence of a base.

[0057] Examples of the reactive derivative of the acidic compound include acid anhydrides, activate esters (e.g., p-nitrophenyl ester, N-hydroxysuccinimide ester, pentafluorophenyl ester, 1-hydroxybenzotriazole ester etc.), acid halides (e.g., acid chloride, acid bromide etc.), imidazolide, mixed acid anhydrides (e.g., anhydrides with methyl carbonate, anhydride with ethyl carbonate etc.) and the like.

[0058] Examples of the solvent to be used include ether solvents (e.g., diethyl ether, tetrahydrofuran (THF), dioxane etc.), hydrocarbon solvents (e.g., benzene, toluene, hexane, heptane etc.), halogen solvents (e.g., dichloromethane, dichloroethane, chloroform, carbon tetrachloride etc.), acetonitrile, N,N-dimethylformamide (DMF) and the like, and a mixed solvent thereof.

[0059] Examples of the base to be used include organic bases such as triethylamine (TEA), 4-dimethylaminopyridine (DMAP), N,N-diisopropylethylamine (DIPEA), triethylenediamine, 4-methylmorpholine, 1,8-diazabicyclo[5.4.0]undec-7-ene and the like, inorganic bases such as alkali metal or alkaline earth metal carbonates (e.g., sodium carbonate, potassium carbonate, cesium carbonate etc.), alkali metal or alkaline earth metal hydrogen carbonates (e.g., sodium hydrogen carbonate, potassium hydrogen carbonate etc.), alkali metal or alkaline earth metal hydroxides (e.g., sodium hydroxide, potassium hydroxide, cesium hydroxide etc.), alkali metal or alkaline earth metal hydrides (e.g., lithium hydride, sodium hydride, potassium hydride, calcium hydride etc.), metal amides (e.g., sodium amide, lithium diisopropylamide, lithium hexamethyldisilazide etc.), alkali metal alkoxides (e.g., potassium tert-butoxide, sodium tert-butoxide etc.) and the like.

[0060] Examples of the dehydration-condensation agent include condensation agents to be used for peptide synthesis and the like. Specific examples thereof include dicyclohexylcarbodiimide (DCC), N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide (EDC) or a hydrochloride salt thereof, 2-chloro-1-methylpyridinium iodide, 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ), carbodiimidazole (CDI), diethylphosphoryl cyanide, benzotriazol-1-yloxy-trispyrrolidinophosphonium hexafluorophosphate (PyBOP), diphenylphosphoryl azide (DPPA), propanephosphonic acid anhydride (PPA), isobutyl chloroformate, diethylacetyl chloride, trimethylacetyl chloride and the like. These condensation agents are used alone, or in combination with an activator such as N-hydroxysuccinimide (HONSu), hydroxybenzotriazole (HOBT), 3-hydroxy-4-oxo-3,4-dihydro-1,2,3-benzotriazine (HOBT), DMAP and the like, preferably DMAP.

[0061] The compound represented by the formula (XI) is used in a proportion of about 50 to 1000 mol%, preferably about 100 to 600 mol%, per 1 mol of the compound represented by the formula (V), the condensation agent is used in a proportion of about 50 to 1000 mol%, preferably about 100 to 500 molM, per 1 mol of the compound represented by the formula (V), and the base is used in a proportion of about 50 to 1000 mol%, preferably about 100 to 500 mol%, per 1 mol of the compound represented by the formula (V). The reaction temperature is about -30°C to 100°C, preferably -10°C to 80°C, and the reaction time is about 30 min to 96 hr, preferably 30 min to 48 hr.

[0062] Step b: In this step, a compound represented by the formula (VII) is produced by subjecting the compound represented by the formula (V) and amine (H-R<sup>4</sup>) wherein R<sup>4</sup> is as defined above to dehydration-condensation.

[0063] The compound represented by the formula (VII) can be produced by reacting the acidic compound represented by the formula (V) or a reactive derivative with amine (H-R<sup>4</sup>) using a dehydration-condensation agent in a solvent, in the presence of a base as necessary. The reactive derivative of acidic compound, the solvent, the base and the dehydration-condensation agent to be used are in the same manner as in Step a.

[0064] Step c: In this step, a compound represented by the formula (VIII) or the formula (IX) is produced by deprotecting the ester-protected carboxyl group of a compound represented by the formula (VI) or the formula (VII).

[0065] The reaction can be carried out according to a general deprotection to a carboxyl group. Examples of the base to be used include alkali metal or alkaline earth metal carbonates (e.g., sodium carbonate, potassium carbonate, cesium carbonate etc.), alkali metal or alkaline earth metal hydroxides (e.g., lithium hydroxide, sodium hydroxide, potassium hydroxide, cesium hydroxide etc.) and the like.

[0066] When R<sup>26</sup> is a benzyl group, it can be deprotected according to catalytic hydrogenation reaction using a metal catalyst such as palladium and the like. Examples of the solvent to be used for the reaction include alcohol solvents (e.g., methanol, ethanol etc.), ether solvents (e.g., THF, dioxane etc.) and the like, and a mixed solvent of these and water as necessary. The reaction temperature is about 0°C to 100°C.

[0067] When R<sup>26</sup> is tert-butyl, it can be deprotected under acidic conditions of hydrochloric acid, trifluoroacetic acid

and the like. Examples of the solvent to be used for the reaction include halogen solvents (e.g., dichloromethane, dichloroethane, chloroform, carbon tetrachloride etc.) and the like. The reaction temperature is about -10°C to 60°C.

[0068] Step d: In this step, a compound represented by the formula (I) is produced from a compound represented by the formula (VIII) in the same manner as in Step b or according to a method analogous thereto.

[0069] Step e: In this step, a compound represented by the formula (I) is produced from a compound represented by the formula (IX) in the same manner as in step a or according to a method analogous thereto.

[0070] Step f: In this step, a compound represented by the formula (X) is produced from a compound represented by the formula (IX) in the same manner as in Step b or according to a method analogous thereto, using ammonia gas, an ammonia mixed solution (e.g., aqueous ammonia, ammonia/dioxane solution, ammonia/methanol solution etc.), or an ammonium salt (e.g., ammonium carbonate, ammonium hydrogen carbonate, ammonium chloride etc.) as an amine.

[0071] Step g: In this step, a compound represented by the formula (I) is produced by reacting a compound represented by the formula (X) with a compound represented by the formula (XII).

[0072] The compound represented by the formula (I) can be produced by reacting a compound represented by the formula (X) with a compound represented by the formula (XII) without solvent or in an appropriate solvent, in the presence of a base.

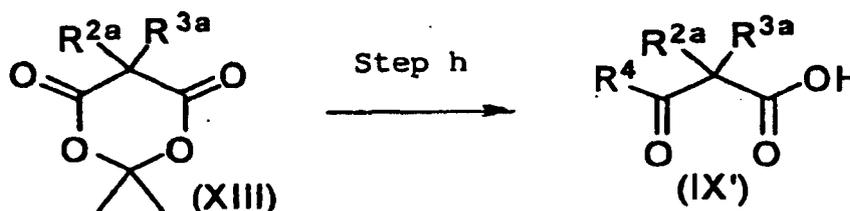
[0073] Examples of the base to be used include organic bases such as pyridine, TEA, DMAP, DIPEA, triethylenediamine, 4-methylmorpholine, 1,8-diazabicyclo[5.4.0]undec-7-ene and the like, alkali metal or alkaline earth metal carbonates (e.g., sodium carbonate, potassium carbonate, cesium carbonate etc.), alkali metal or alkaline earth metal hydrogen carbonates (e.g., sodium hydrogen carbonate, potassium hydrogen carbonate etc.), alkali metal or alkaline earth metal hydroxides (e.g., sodium hydroxide, potassium hydroxide, cesium hydroxide etc.), alkali metal or alkaline earth metal hydrides (e.g., lithium hydride, sodium hydride, potassium hydride, calcium hydride etc.), metal amides (e.g., sodium amide, lithium diisopropylamide, lithium hexamethyl disilazide etc.), alkali metal alkoxides (e.g., potassium tert-butoxide, sodium tert-butoxide etc.) and the like.

[0074] Examples of the solvent to be used include ether solvents (e.g., diethyl ether, THF, dioxane etc.), hydrocarbon solvents (e.g., benzene, toluene etc.), halogen solvents (e.g., dichloromethane, dichloroethane, chloroform, carbon tetrachloride etc.), acetonitrile, DMF and the like, and a mixed solvent thereof.

[0075] The compound represented by the formula (XII) is used in a proportion of about 50 to 1000 mol%, preferably about 100 to 600 mol%, per 1 mol of the compound represented by the formula (X), and the base is used in a proportion of about 50 to 2000 mol%, preferably about 200 to 1000 mol%, per 1 mol of the compound represented by the formula (X). The reaction temperature is about -30°C to 100°C, preferably -10°C to 80°C, and the reaction time is about 30 min to 96 hr, preferably 30 min to 48 hr.

[0076] When the compound represented by the formula (IX) in Scheme 1 is a compound represented by the formula (IX'), the compound can also be produced from a Meldrum's acid derivative represented by the formula (XIII) as shown in Scheme 2.

Scheme 2



[0077] wherein R<sup>2a</sup> and R<sup>3a</sup> may form, together with the carbon atom they are bonded to, C=CX'Y' wherein X' and Y' are as defined above, or one of R<sup>2a</sup> and R<sup>3a</sup> is a hydrogen atom, and the other is alkyl, alkenyl, alkynyl, cycloalkylalkyl, arylalkyl, aryloxyalkyl, heteroarylalkyl, heteroaryloxyalkyl or heterocyclyl, each of which is optionally substituted, and R<sup>4</sup> is as defined above.

[0078] The Meldrum's acid derivative represented by the formula (XIII) can be produced according to methods well known in the field, for example, the methods described in Toth et al., Synth. Commun., Vol.25, 3067-3074 (1995), Smrcina et al., Tetrahedron, Vol.53, 12867-12874 (1997), Hin et al., J. Org. Chem., Vol.67, 7365-7368 (2002), Desai et al., Synth. Commun., Vol.34, 25-32 (2004), Hrubowchak et al., Tetrahedron Lett., Vol.24, 4951-4954 (1983) and the like, or a method analogous thereto.

[0079] Step h: In this step, a compound represented by the formula (IX') is produced by reacting a Meldrum's acid derivative represented by the formula (XIII) with amine (H-R<sup>4</sup>).

[0080] The compound represented by the formula (IX') can be produced by reacting a Meldrum's acid derivative represented by the formula (XIII) with amine (H-R<sup>4</sup>) without solvent or in an appropriate solvent, in the presence of a silylating agent and, where necessary, an additive.

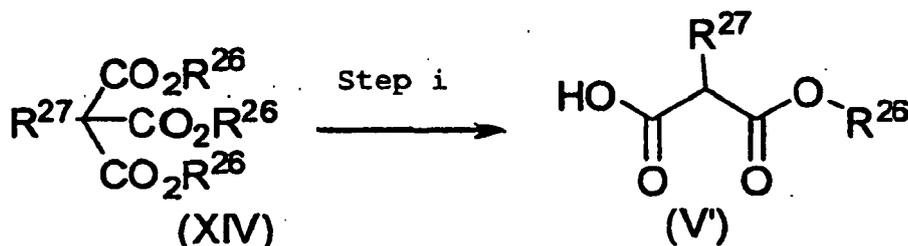
[0081] Examples of the solvent to be used include ether solvents (e.g., diethyl ether, THF, dioxane etc.), aromatic hydrocarbon solvents (e.g., benzene, toluene, chlorobenzene etc.), halogen solvents (e.g., dichloromethane, dichloroethane, chloroform, carbon tetrachloride etc.), acetonitrile, DMF, dimethyl sulfoxide (DMSO) and the like, and a mixed solvent thereof.

[0082] Examples of the silylating agent include N,O-bis(trimethylsilyl)trifluoroacetamide (BSTFA), N,O-bis(trimethylsilyl)acetamide (BSA), N-methyl-N-trimethylsilyl trifluoroacetamide (MSTFA), N-trimethylsilyl acetamide (TMSA) and the like. Preferred as the additive are DMAP and the like.

[0083] In this case, amine (H-R<sup>4</sup>) is used in a proportion of about 50 to 1000 mol%, preferably about 100 to 600 mol%, per 1 mol of the compound represented by the formula (XIII), the silylating agent is used in a proportion of about 50 to 1000 mol%, preferably about 100 to 600 mol%, per 1 mol of the compound represented by the formula (XIII), and DMAP is used in a proportion of about 50 to 1000 mol%, preferably about 100 to 600 mol%, per 1 mol of the compound represented by the formula (XIII). The reaction temperature is about -30°C to 100°C, preferably -10°C to 80°C, and the reaction time is about 30 min to 96 hr, preferably 60 min to 48 hr.

[0084] The compound represented by the formula (V) in Scheme 1 is commercially available, or can be easily produced from commercially available malonic acid diester, for example, according to the methods described in Strube, Org. Synth. Coll. Vol. IV, 417 (1963), Niwayama, J. Org. Chem., Vol. 65, 5834-5836 (2000) and the like or a method analogous thereto. Alternatively, the compound represented by the formula (V'), i.e., the compound represented by the formula (V) wherein one of R<sup>2</sup> and R<sup>3</sup> is a hydrogen atom, can also be produced from the tricarboxylic acid triester derivative represented by the formula (XIV) as shown in Scheme 3.

Scheme 3



[0085] wherein R<sup>26</sup> is as defined above, and when one of R<sup>2</sup> and R<sup>3</sup> is a hydrogen atom, R<sup>27</sup> is as defined for the other.

[0086] The tricarboxylic acid triester derivative represented by the formula (XIV) can be produced according to the methods well known in the field, for example, the methods described in Cravotto et al., Tetrahedron, Vol. 52, 13007-13016 (1996), Cravotto et al., Tetrahedron, Vol. 54, 1639-1646 (1998), Padgett et al., J. Org. Chem., Vol. 44, 3492-3496 (1979), Skarzewski, Synthesis, Vol. 12, 1125-1127 (1990) and the like, or a method analogous thereto.

[0087] Step i: In this step, a compound represented by the formula (V') is produced from a tricarboxylic acid triester derivative represented by the formula (XIV) by hydrolysis and decarboxylation reaction.

[0088] The reaction can be carried out according to a general deprotection to a carboxyl group, and a decarboxylation reaction proceeds following the deprotection. Examples of the base to be used include alkali metal or alkaline earth metal carbonates (e.g., sodium carbonate, potassium carbonate, cesium carbonate etc.), alkali metal or alkaline earth metal hydroxides (e.g., lithium hydroxide, sodium hydroxide, potassium hydroxide etc.) and the like. Examples of the solvent to be used for the reaction include alcohol solvents (e.g., methanol, ethanol etc.), ether solvents (e.g., THF, dioxane etc.) and the like, and a mixed solvent of these and water as necessary. The base is used in a proportion of about 200 mol% per 1 mol of the compound represented by the formula (XIV), and the reaction temperature is about 0°C to 100°C.

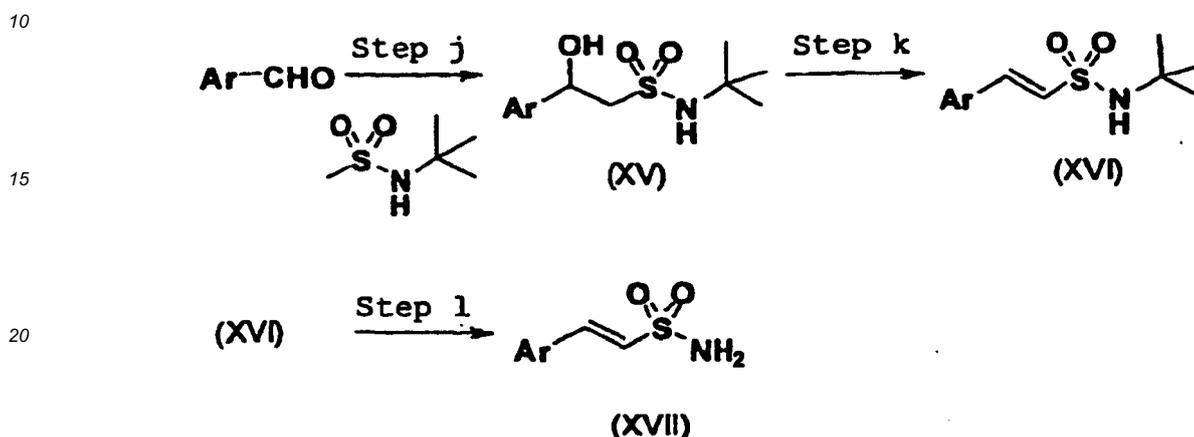
[0089] The compounds represented by the formulas (XI) and (XII) in Scheme 1 are commercially available, or can be produced according to a method known per se, for example, the methods described in Harada et al., Bioorg. Med. Chem., Vol. 9, 2955-2968 (2001) and the like or a method analogous thereto.

[0090] For example, a compound represented by the formula (XVII), i.e. a compound represented by the formula (XI) wherein R<sup>1</sup> is a group represented by the following formula



5 [0091] wherein Ar is as defined above, can be produced from Ar-CHO shown in Scheme 4.

Scheme 4



25 [0092] wherein Ar is as defined above.

[0093] Step j: In this step, a compound represented by the formula (XV) is produced by subjecting Ar-CHO and N-tert-butyl methanesulfonamide to aldol reaction.

30 [0094] The reaction can be carried out according to a general aldol reaction. Examples of the solvent to be used include ether solvents (e.g., THF, dioxane etc.) and the like. Examples of the base to be used include organic lithiums (e.g., methyl lithium, n-butyl lithium, sec-butyl lithium, tert-butyl lithium etc.), metal amides (e.g., lithium diisopropylamide, lithium hexamethyl disilazide etc.) and the like. The N-tert-butyl methanesulfonamide is used in a proportion of about 100 to 500 mol% per 1 mol of Ar-CHO, and the base is used in a proportion of about 200 to 1000 mol% per 1 mol of Ar-CHO. The reaction temperature is about -80°C to 20°C, and the reaction time is about 30 min to 48 hr.

35 [0095] Step k: In this step, a compound represented by the formula (XVI) is produced by subjecting a compound represented by the formula (XV) to dehydration reaction.

40 [0096] The compound represented by the formula (XVI) can be produced by converting the hydroxyl group of a compound represented by the formula (XV) to a leaving group in a solvent in the presence of a base. Examples of the solvent to be used include ether solvents (e.g., diethyl ether, THF, dioxane etc.), aromatic hydrocarbon solvents (e.g., benzene, toluene, chlorobenzene etc.), halogen solvents (e.g., dichloromethane, dichloroethane, chloroform, carbon tetrachloride etc.), acetonitrile, DMF, DMSO and the like.

[0097] The conversion of the hydroxyl group to a leaving group is carried out using, for example, sulfonyl chlorides such as mesyl chloride, tosyl chloride and the like. Examples of the base include organic bases such as pyridine, TEA, DMAP, DIPEA, triethylenediamine, 4-methylmorpholine, 1,8-diazabicyclo[5.4.0]undec-7-ene and the like, alkali metal or alkaline earth metal carbonates (e.g., sodium carbonate, potassium carbonate, cesium carbonate etc.), alkali metal or alkaline earth metal hydrogen carbonates (e.g., sodium hydrogen carbonate, potassium hydrogen carbonate etc.), alkali metal or alkaline earth metal hydroxides (e.g., sodium hydroxide, potassium hydroxide, cesium hydroxide etc.) and the like.

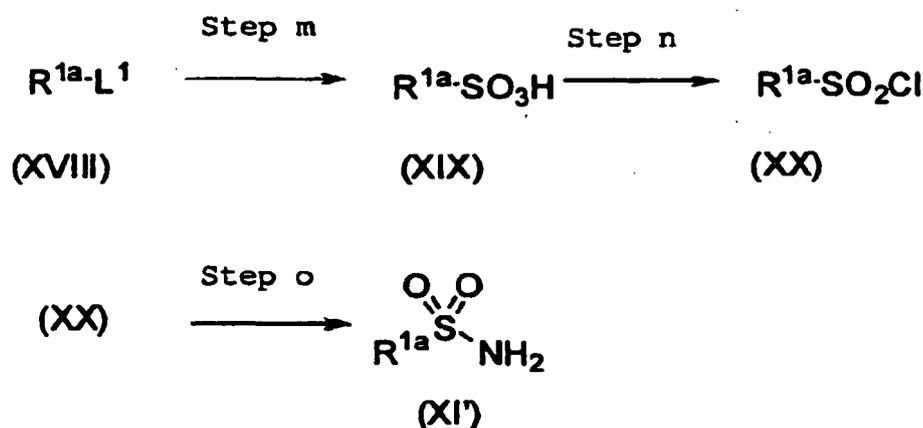
50 [0098] The sulfonyl chloride is used in a proportion of about 100 to 500 mol% per 1 mol of the compound represented by the formula (XV), and the base is used in a proportion of about 200 to 1000 mol% per 1 mol of the compound represented by the formula (XV). The reaction temperature is about 0°C to 100°C, and the reaction time is about 60 min to 48 hr.

[0099] Step 1: In this step, a compound represented by the formula (XVII) is produced by removing the tert-butyl group from the compound represented by the formula (XVI).

55 [0100] The compound represented by the formula (XVII) can be produced by removing the tert-butyl group from the compound represented by the formula (XVI) using an acid such as hydrochloric acid, sulfuric acid, trifluoroacetic acid and the like, without solvent or in a halogen solvent (e.g., dichloromethane, dichloroethane, chloroform, carbon tetrachloride etc.).

[0101] A compound represented by the formula (XI'), i.e., a compound represented by the formula (XI) wherein R<sup>1</sup> is alkyl, arylalkyl, aryloxyalkyl or heteroarylalkyl, each of which is optionally substituted, can also be produced as shown in Scheme 5.

Scheme 5



[0102] wherein R<sup>1a</sup> is alkyl, arylalkyl, aryloxyalkyl or heteroarylalkyl, each of which is optionally substituted, and L<sup>1</sup> is a leaving group.

[0103] Examples of the leaving group for L<sup>1</sup> include halogen atom, sulfonyloxy (e.g., methanesulfonyloxy, p-toluenesulfonyloxy etc.) and the like.

[0104] Step m: In this step, a compound represented by the formula (XIX) is produced from a compound represented by the formula (XVIII).

[0105] The compound represented by the formula (XIX) can be produced by reacting a compound represented by the formula (XVIII) with a sulfite in a solvent. Examples of the solvent include water, or a mixed solvent of water and an alcohol solvent (e.g., methanol, ethanol, propanol, isopropanol, n-butanol etc.), an ether solvent (e.g., THF, dioxane etc.), acetonitrile, DMF, DMSO and the like. Examples of the sulfite include sodium sulfite, potassium sulfite and the like. The sulfite is used in a proportion of about 100 to 1000 mol% per 1 mol of the compound represented by the formula (XVIII). The reaction temperature is about 30°C to 100°C, and the reaction time is about 60 min to 48 hr.

[0106] Step n: In this step, a compound represented by the formula (XX) is produced from a compound represented by the formula (XIX).

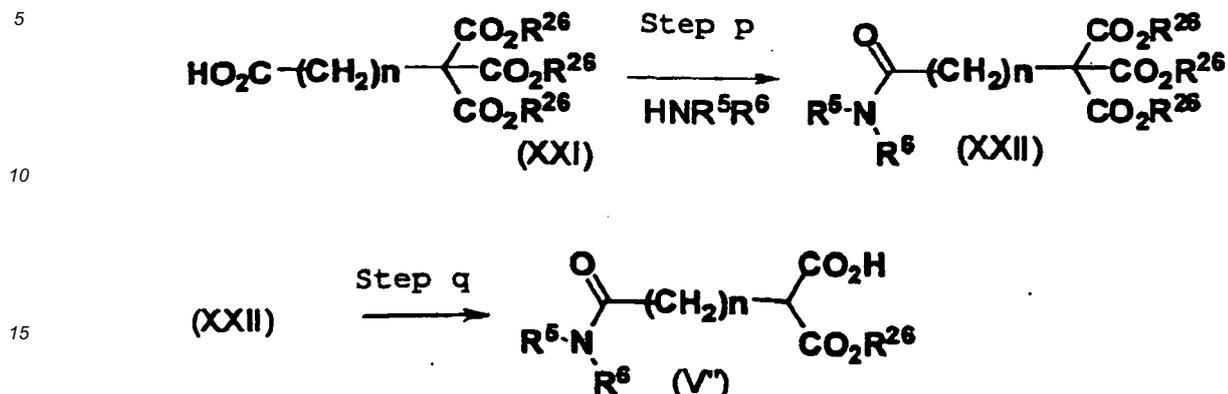
[0107] The compound represented by the formula (XX) can be produced by reacting a compound represented by the formula (XIX) with a chlorinating agent without solvent or in a solvent. Examples of the solvent include aromatic hydrocarbon solvents (e.g., benzene, toluene, chlorobenzene etc.), halogen solvents (e.g., dichloromethane, dichloroethane, chloroform, carbon tetrachloride etc.), DMF and the like. Examples of the chlorinating agent include thionyl chloride, phosphorus oxychloride, phosphorus pentachloride and the like. After completion of the reaction, the compound represented by the formula (XX) is generally obtained by evaporating the solvent and a chlorinating agent (in the case of thionyl chloride or phosphorus oxychloride). The chlorinating agent is used in excess per 1 mol of the compound represented by the formula (XIX). The reaction temperature is about 30°C to 150°C, and the reaction time is about 60 min to 48 hr.

[0108] Step o: In this step, a compound represented by the formula (XI') is produced from a compound represented by the formula (XX).

[0109] The compound represented by the formula (XI') is produced by treating a compound represented by the formula (XX) with ammonia in a solvent. Examples of the solvent include halogen solvents (e.g., dichloromethane, dichloroethane, chloroform, carbon tetrachloride etc.) and the like. The compound can be produced by reacting a compound represented by the formula (XX) with ammonia gas or an ammonia mixed solution (e.g., aqueous ammonia, ammonia/dioxane solution, ammonia/methanol solution etc.) and the like.

[0110] A compound represented by the formula (V''), i.e., a compound represented by the formula (V) wherein one of R<sup>2</sup> and R<sup>3</sup> is a hydrogen atom, and the other is -(CH<sub>2</sub>)<sub>n</sub>-C(O)-NR<sup>5</sup>R<sup>6</sup>, can also be produced from a compound represented by the formula (XXI) as shown in Scheme 6. The compound represented by the formula (XXI) can be produced in the same manner as in the production of the aforementioned compound represented by the formula (XIV), or according to a method analogous thereto.

## Scheme 6

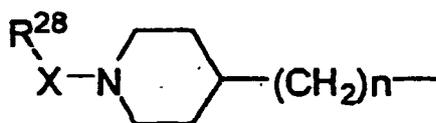


[0111] wherein  $R^5$ ,  $R^6$  and  $R^{26}$  are as defined above, and  $n$  is an integer of 0 to 6.

[0112] Step p: In this step, a compound represented by the formula (XXII) is produced from a compound represented by the formula (XXI) in the same manner as in Step b, or according to a method analogous thereto.

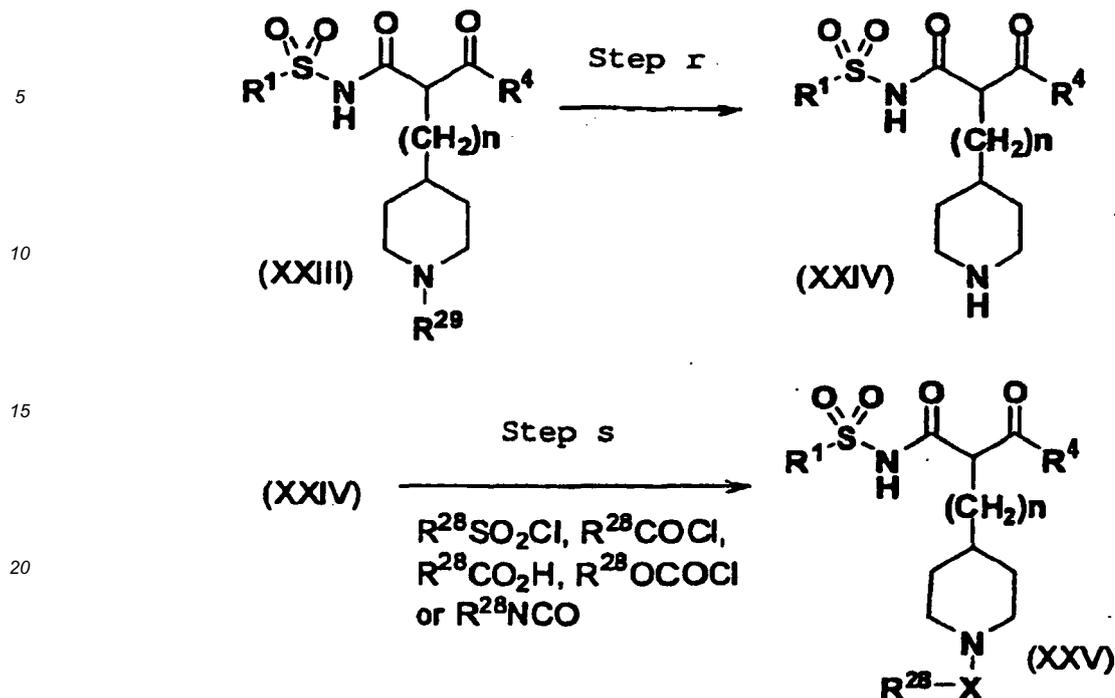
[0113] Step q: In this step, a compound represented by the formula (V'') is produced from a compound represented by the formula (XXII) in the same manner as in Step i, or according to a method analogous thereto.

[0114] The production method of a compound represented by the formula (XXV), i.e., a compound represented by the formula (I) wherein one of  $R^2$  and  $R^3$  is a hydrogen atom, and the other is a group represented by the following formula



[0115] wherein  $n$  is an integer of 0 to 6,  $X$  is CO,  $\text{SO}_2$ , COO or CONH,  $R^{28}$  is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl or heterocyclyl, each of which is optionally substituted, and the cycloalkyl and heterocycle are optionally fused with a aromatic ring, is shown in Scheme 7.

## Scheme 7



[0116] wherein  $R^1$ ,  $R^4$ ,  $R^{28}$  and  $X$  are as defined above,  $n$  is an integer of 0 to 6, and  $R^{29}$  is a conventional amino-protecting group.

[0117] Step r: In this step, a compound represented by the formula (XXIV) or a salt thereof is produced by subjecting a compound represented by the formula (XXIII) to deprotection.

[0118] For the reaction, general conditions for the deprotection of an amino-protecting group can be employed. For example, when  $R^{29}$  is tert-butyloxycarbonyl (Boc), the deprotection can be carried out using an acid such as hydrochloric acid, sulfuric acid, trifluoroacetic acid and the like without solvent or in a halogen solvent (e.g., dichloromethane, dichloroethane, chloroform, carbon tetrachloride etc.). For example, when  $R^{29}$  is benzyloxycarbonyl (Cbz), the deprotection can be carried out according to catalytic hydrogenation reaction using a palladium-carbon catalyst and the like to deprotect Cbz. Examples of the solvent to be used for the reaction include alcohol solvents (e.g., methanol, ethanol, isopropanol etc.), ether solvents (e.g., THF, dioxane etc.) and the like, and any reaction is generally carried out  $-20^\circ\text{C}$  to  $80^\circ\text{C}$ .

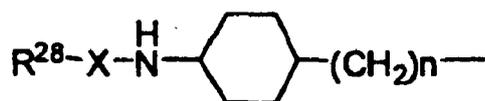
[0119] Step s: In this step, a compound represented by the formula (XXV) is produced by reacting a compound represented by the formula (XXIV) or a salt thereof with a sulfonyl chloride derivative:  $R^{28}SO_2Cl$ , carboxylic acid chloride derivative:  $R^{28}COCl$ , carboxylic acid derivative:  $R^{28}CO_2H$ , chloro carbonate derivative:  $R^{28}OCOCi$  or isocyanate derivative:  $R^{28}NCO$ .

[0120] When the compound represented by the formula (XXV) is an amide derivative ( $X=CO$ ), the reaction can be carried out using  $R^{28}CO_2H$  in the same manner as in Step b, or according to a method analogous thereto. Alternatively, the reaction can be carried out using  $R^{28}COCl$ , in the presence of an organic base such as TEA, pyridine and the like, or an inorganic base such as alkali metal or alkaline earth metal carbonate (e.g., sodium carbonate, potassium carbonate, cesium carbonate etc.), alkali metal or alkaline earth metal hydroxide (e.g., sodium hydroxide, potassium hydroxide, cesium hydroxide etc.) and the like, in a solvent such as toluene, chloroform, dichloromethane, THF and the like, or in a mixed solvent thereof with water, at generally  $-20$  to  $80^\circ\text{C}$ .

[0121] When the compound represented by the formula (XXV) is a sulfonamide derivative ( $X=SO_2$ ), the reaction can be carried out using  $R^{28}SO_2Cl$ , in the same manner as in the above-mentioned reaction with  $R^{28}COCl$ , or according to a method analogous thereto.

[0122] When the compound represented by the formula (XXV) is a carbamate derivative ( $X=COO$ ), the reaction can be carried out using  $R^{28}OCOCi$ , in the same manner as in the above-mentioned reaction with  $R^{28}COCl$ , or according to a method analogous thereto. When the compound represented by the formula (XXV) is a carbamide derivative ( $X=CONH$ ), the reaction can be carried out using  $R^{28}NCO$ , in the same manner as in the above-mentioned reaction with  $R^{28}COCl$ , or according to a method analogous thereto.

[0123] The production method of a compound represented by the formula (XXVIII), i.e., a compound represented by the formula (I) wherein one of  $R^2$  and  $R^3$  is a hydrogen atom, and the other is a group represented by the following formula



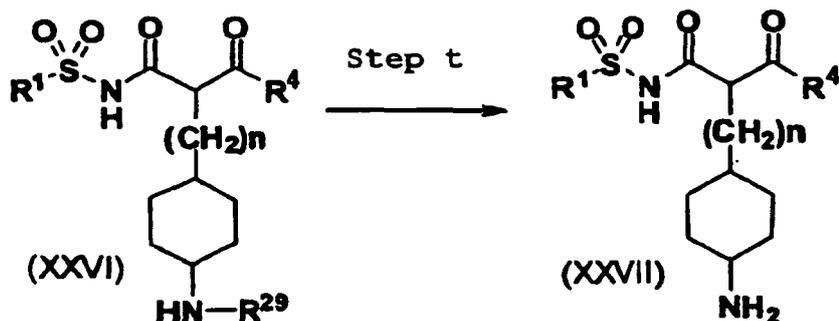
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[0124] wherein  $R^{28}$  and  $X$  are as defined above,  $n$  is an integer of 0 to 6, and the steric configuration of the cyclohexane ring is cis or trans, is shown in Scheme 8.

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Scheme 8

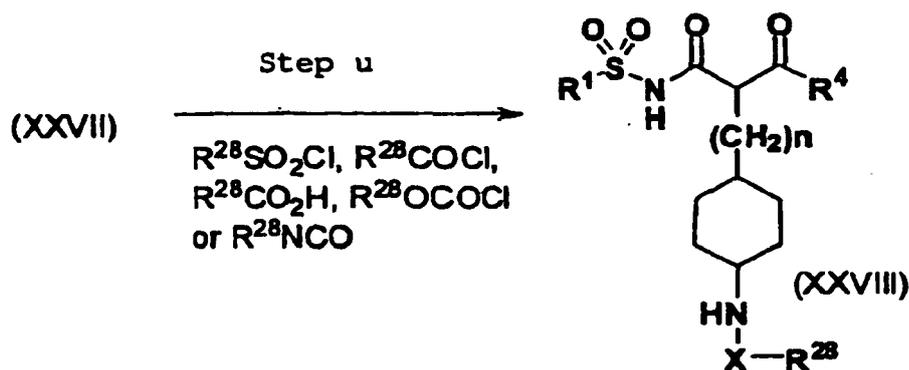
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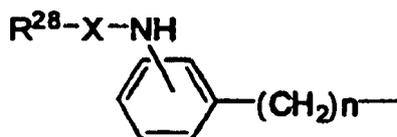
[0125] wherein  $R^1$ ,  $R^4$ ,  $R^{28}$ ,  $R^{29}$  and  $X$  are as defined above, and  $n$  is an integer of 0 to 6.

[0126] Step t: In this step, a compound represented by the formula (XXVII) or a salt thereof is produced from a compound represented by the formula (XXVI), in the same manner as in Step r, or according to a method analogous thereto.

[0127] Step u: In this step, a compound represented by the formula (XXVIII) is produced from a compound represented by the formula (XXVII) or a salt thereof, in the same manner as in Step s, or according to a method analogous thereto.

[0128] The production method of a compound represented by the formula (XXXI), i.e., a compound represented by the formula (I) wherein one of  $R^2$  and  $R^3$  is a hydrogen atom, and the other is a group represented by the following formula

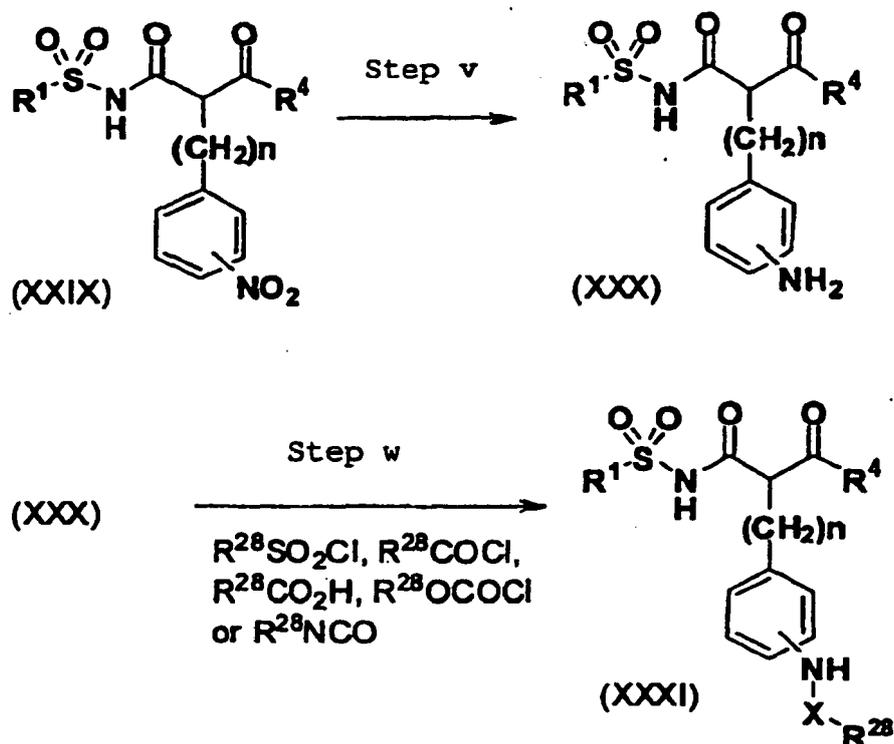
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[0129] wherein  $R^{28}$  and  $X$  are as defined above,  $n$  is an integer of 0 to 6, and ortho-substitution is excluded, is shown in Scheme 9.

## Scheme 9



[0130] wherein  $R^1$ ,  $R^4$ ,  $R^{28}$  and X are as defined above, and n is an integer of 0 to 6.

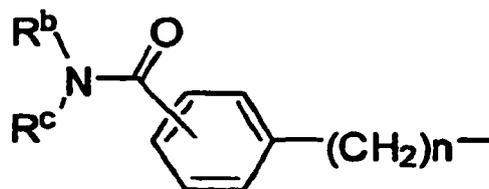
[0131] Step v: In this step, a compound represented by the formula (XXX) or a salt thereof is produced by reducing a nitro compound represented by the formula (XXIX).

[0132] The reaction can be carried out according to a general reduction reaction of a nitro group. For example, a nitro compound represented by the formula (XXIX) can also be reduced according to catalytic hydrogenation reaction using a metal catalyst such as palladium and the like. Examples of the solvent to be used for the reaction include ethyl acetate, aromatic hydrocarbon solvents (e.g., benzene, toluene etc.), alcohol solvents (e.g., methanol, ethanol, isopropanol etc.), ether solvents (e.g., THF, dioxane etc.) and the like and, where necessary, a base such as TEA and the like may be added. The reaction temperature is generally  $0^\circ\text{C}$  to  $100^\circ\text{C}$ .

[0133] Alternatively, the nitro compound can also be reduced using a metal such as zinc, iron and the like, or tin chloride. Examples of the solvent to be used for the reaction include DMF, acetic acid, alcohol solvents (e.g., methanol, ethanol, isopropanol etc.) and the like and, where necessary, a mixed solvent with an aqueous dilute hydrochloric acid can be used. Alternatively, the nitro compound can also be reduced using a metal catalyst such as iron chloride and the like in a mixed solvent of hydrazine and an alcohol solvent (e.g., methanol, ethanol, isopropanol etc.). Any reaction is carried out at generally  $0^\circ\text{C}$  to  $100^\circ\text{C}$ .

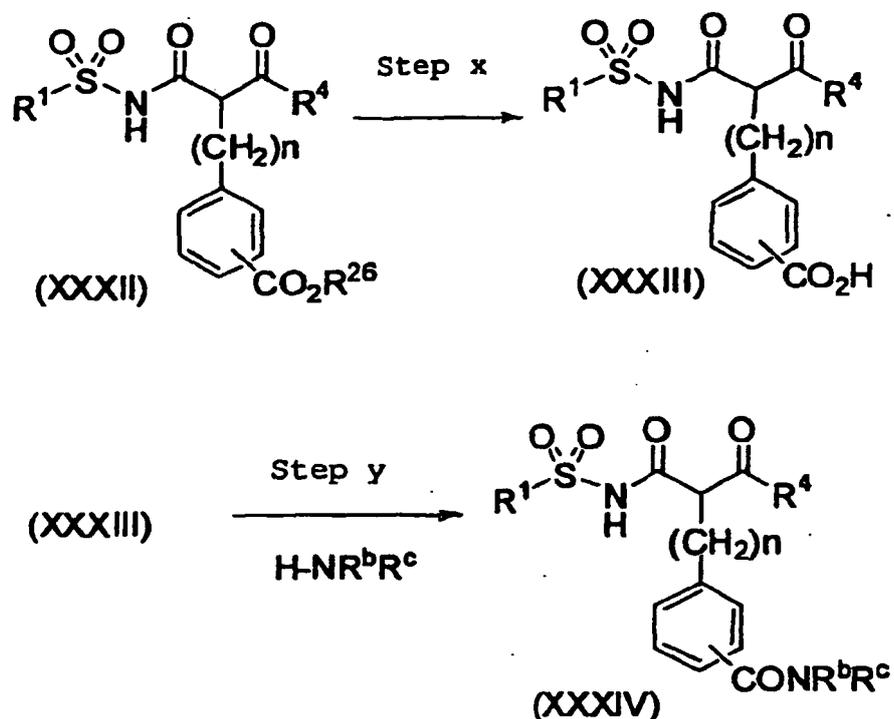
[0134] Step w: In this step, a compound represented by the formula (XXXI) is produced from a compound represented by the formula (XXX) or a salt thereof in the same manner as in Step s, or according to a method analogous thereto.

[0135] The production method of a compound represented by the formula (XXXIV), i.e., a compound represented by the formula (I) wherein one of  $R^2$  and  $R^3$  is a hydrogen atom, and the other is a group represented by the following formula



[0136] wherein  $R^b$  and  $R^c$  are as defined above, is shown in Scheme 10.

## Scheme 10

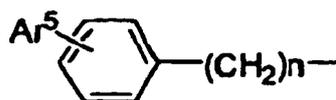


[0137] wherein  $R^1$ ,  $R^4$ ,  $R^{26}$ ,  $R^b$  and  $R^c$  are as defined above, and  $n$  is an integer of 0 to 6.

[0138] Step x: In this step, a compound represented by the formula (XXXIII) is produced from a compound represented by the formula (XXXII) in the same manner as in Step c, or according to a method analogous thereto.

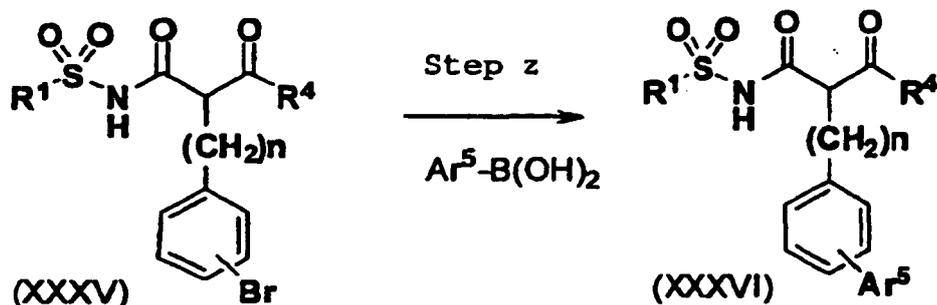
[0139] Step y: In this step, a compound represented by the formula (XXXIV) is produced from a compound represented by the formula (XXXIII) in the same manner as in Step b, or according to a method analogous thereto.

[0140] The production method of a compound represented by the formula (XXXVI), i.e., a compound represented by the formula (I) wherein one of  $R^2$  and  $R^3$  is a hydrogen atom, and the other is a group represented by the following formula



[0141] wherein  $\text{Ar}^5$  is aryl, heteroaryl and the like, each of which is optionally substituted, and  $n$  is an integer of 0 to 6, is shown in Scheme 11.

Scheme 11

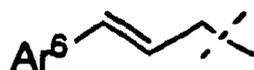


[0142] wherein  $R^1$ ,  $R^4$  and  $Ar^5$  are as defined above, and  $n$  is an integer of 0 to 6.

[0143] Step z: In this step, a compound represented by the formula (XXXVI) is produced by subjecting a compound represented by the formula (XXXV) and  $Ar^5\text{-B(OH)}_2$  to coupling reaction.

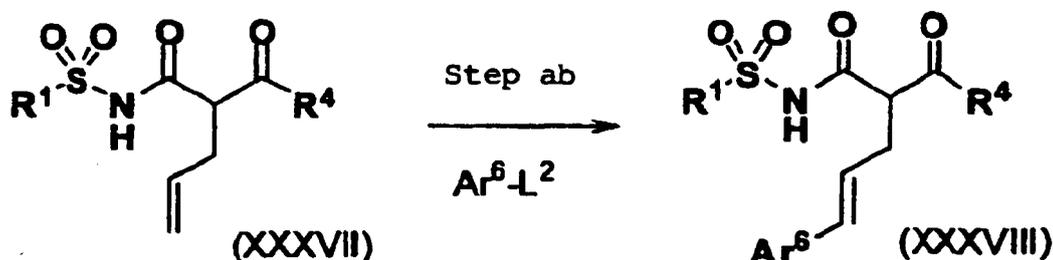
[0144] The reaction can be carried out according to a general Suzuki coupling reaction. Examples of the solvent to be used for the reaction include benzene, toluene, xylene, ethanol, DMF, DMSO, ethylene glycol dimethyl ether, water, dioxane and the like and a mixed solvent thereof. Examples of the coupling catalyst to be used include palladium catalysts (e.g.,  $Pd(PPh_3)_4$ ,  $Pd(OAc)_2$ /ligand (the ligand is, for example,  $PPh_3$ ,  $P(o-Tol)_3$ , 1,1'-bis(diphenylphosphino)ferrocene and the like) and the like. Examples of the base to be used include inorganic bases such as sodium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate and the like, or organic bases such as TEA, DIPEA and the like.  $Ar^5\text{-B(OH)}_2$  is used in a proportion of about 100 to 500 mol% per 1 mol of the compound represented by the formula (XXXV), the coupling catalyst is used in a proportion of about 1 to 100 mol% per 1 mol of the compound represented by the formula (XXXV), and the base is used in a proportion of about 200 to 1000 mol% per 1 mol of the compound represented by the formula (XXXV). The reaction temperature is about 20°C to 150°C, and the reaction time is about 1 to 100 hr.

[0145] The production method of a compound represented by the formula (XXXVIII), i.e., a compound represented by the formula (I) wherein one of  $R^2$  and  $R^3$  is a hydrogen atom, and the other is a group represented by the following formula



[0146] wherein  $Ar^6$  is aryl, heteroaryl and the like, each of which is optionally substituted, is shown in Scheme 12.

Scheme 12



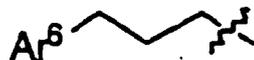
[0147] wherein  $R^1$ ,  $R^4$  and  $Ar^6$  are as defined above, and  $L^2$  is a leaving group (a halogen atom, trifluoromethanesulfonyloxy etc.).

[0148] Step ab: In this step, a compound represented by the formula (XXXVIII) is produced by subjecting a compound represented by the formula (XXXVII) and  $Ar^6\text{-L}^2$  to coupling reaction.

[0149] The reaction can be carried out according to a general Heck reaction using a palladium catalyst (e.g.,  $Pd(PPh_3)_4$ ,

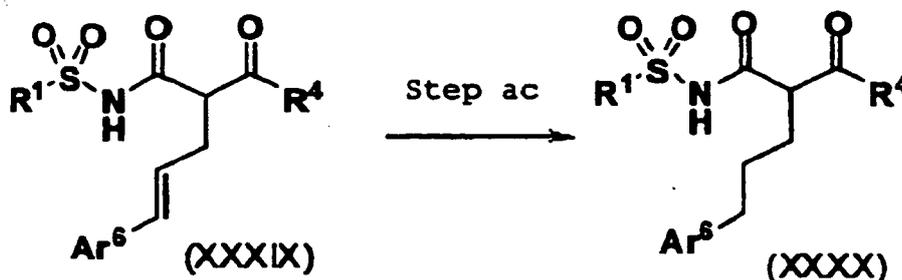
Pd(OAc)<sub>2</sub>/PPh<sub>3</sub> etc.), in the presence of a base (e.g., potassium carbonate, calcium carbonate, TEA, diisopropylamine etc.), in a solvent such as THF, acetonitrile, N,N'-dimethylacetamide, DMF, 1-methyl-2-pyrrolidinone and the like, at room temperature to about 100°C. Where necessary, an additive (e.g., silver carbonate, potassium acetate etc.) may be added.

[0150] A compound represented by the formula (XXXX), i.e., a compound represented by the formula (I) wherein one of R<sup>2</sup> and R<sup>3</sup> is a hydrogen atom, and the other is a group represented by the following formula



[0151] wherein Ar<sup>6</sup> is as defined above, can also be produced as shown in Scheme 13.

Scheme 13



[0152] wherein R<sup>1</sup>, R<sup>4</sup> and Ar<sup>6</sup> are as defined above.

[0153] Step ac: In this step, a compound represented by the formula (XXXX) is produced by reducing a compound represented by the formula (XXXIX).

[0154] The reaction can be carried out according to a general catalytic hydrogenation reaction using a palladium-carbon catalyst and the like. Examples of the solvent to be used for the reaction include ethyl acetate, aromatic hydrocarbon solvents (e.g., benzene, toluene etc.), alcohol solvents (e.g., methanol, ethanol, isopropanol etc.), ether solvents (e.g., THF, dioxane etc.) and the like, and the reaction temperature is generally 0°C to 100°C.

[0155] A compound represented by the formula (XXXXII), i.e., a compound represented by the formula (I) wherein R<sup>1</sup> is a group represented by the following formula



[0156] wherein Ar is as defined above, can also be produced as shown in Scheme 14.

Scheme 14



[0157] wherein R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and Ar are as defined above.

[0158] Step ad: In this step, a compound represented by the formula (XXXXII) is produced from a compound repre-

sented by the formula (XXXXI) in the same manner as in Step ac, or according to a method analogous thereto.

**[0159]** When the compound represented by the formula (I) is a racemate, it can also be resolved by a general optical resolution means well known in the pertinent field [for example, resolution using chiral amine ((+)-dehydroabiethylamine, optically active 2-amino-1-(4-nitrophenyl)-1,3-propanediol, optically active phenylethylamine and the like) described in CRC Handbook of Optical Resolution via Diastereomeric Salt Formation (CRC Press), resolution by chiral column chromatography] to give an S form or R form. Alternatively, a compound represented by the formula (IX) is resolved by a general optical resolution means and an S form or R form of the compound represented by the formula (I) can be produced according to a method described in, for example, Ishizuka et al., Synthesis, No. 6, 784-788 (2000), or a method analogous thereto.

**[0160]** The thus-produced compound of the present invention can be obtained at any purity by appropriately applying a known separation and purification means, such as concentration, extraction, chromatography, reprecipitation, recrystallization and the like.

**[0161]** Where necessary, the compound represented by the formula (I) can be converted to an inorganic base addition salt with sodium, potassium, calcium, magnesium etc., an inorganic acid addition salt with hydrochloric acid, sulfuric acid, phosphoric acid, hydrobromic acid etc., an organic acid addition salt with methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, acetic acid etc., or a salt with amino acid such as glutamic acid, aspartic acid, arginine, lysin and the like. In addition, the compound represented by the formula (I) or a salt thereof can also be present as a solvate such as hydrate and the like.

**[0162]** The compound of the present invention has a potent agonist action at AT<sub>2</sub> receptor in mammals (e.g., human, monkey, dog, rat etc.).

**[0163]** Therefore, the compound of the present invention is useful as a novel AT<sub>2</sub> receptor agonist for the treatment or prevention of various diseases. Expected target diseases include various groups of disorders involving RAAS, such as metabolic and cardiovascular diseases and the like, particularly stroke, renal disease, cardiac disease, hypertension, diabetes, metabolic syndrome and the like.

**[0164]** Moreover, the compound of the present invention can be administered to a single subject simultaneously with other therapeutic or preventive drug(s), for example, a therapeutic or preventive drug for stroke, renal disease, cardiac disease, hypertension, diabetes, diabetic complications, hyperlipidemia and/or metabolic syndrome and the like, or in a staggered manner.

**[0165]** When the compound of the present invention is used in combination with other therapeutic or preventive drug(s), the compounding ratio thereof can be appropriately determined according to the subject to be administered, age, body weight and condition of the subject, administration time, dosage form, method of administration, pattern of combination and the like.

**[0166]** When the compound of the present invention is used as a therapeutic or preventive drug, the compound itself or a mixture of the compound and appropriate pharmacologically acceptable carrier, excipient, diluent and the like can be administered orally or parenterally in the form of powder, granule, tablet, capsule, injection and the like. The above-mentioned preparation contains an effective amount of the compound of the present invention.

**[0167]** The dose of the compound of the present invention varies depending on the administration route, target disease, condition, body weight or age of the subject and the like and can also be appropriately set according to the object. Generally, the dose for oral administration to an adult is 0.01 - 1000 mg/kg body weight/day, more preferably 0.05 - 500 mg/kg body weight/day, and an appropriate dose is preferably administered once a day or in several portions a day.

[Examples]

**[0168]** The present invention is explained in more detail in the following by referring to Examples, which are not to be construed as limitative.

In the following as well as in the subsequent Tables 1 to 4, the following Examples are not according to the present invention and merely serve for illustration:

2 to 5, 123, 146, 148, 151, 152, 174 to 199, 203, 215, 223 to 228, 230, 231, 233, 234, 244 to 247, 252 to 263, 306, 307, 324 to 327, 331 to 334, 339 to 342, 349 to 352, 398 to 400, 402, 403, 405 to 407, 409, 411 to 417, 419 to 423, 445 to 451, 454 to 460, 462, 464, 465, 467 to 474, 477, 478, 480, 485 to 489, 492, 494, 498 to 500, 503 to 511, 513, 517 to 528, 534 to 541, 545 to 549, 551, 553 to 555, 557, 559 to 562, 564, 568 to 572, 574, 575 and 588.

**[0169]** <sup>1</sup>H-NMR was measured at 300 or 400 MHz. The chemical shift of <sup>1</sup>H-NMR was expressed as relative delta (δ) value in parts per million (ppm) using tetramethylsilane (TMS) as the internal standard. For the coupling constant J, obvious multiplicity is shown using s (singlet), d (doublet), t (triplet), q (quartet), sept (septet), m (multiplet), dd (doublet of doublets), td (triplet of doublets), dt (doublet of triplets), brs (broad singlet) and the like in hertz (Hz). Mass spectrum (MS) was measured by liquid chromatography mass spectrometry and on a positive ion mode. The optical purity was

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measured by high performance liquid chromatography using a chiral column, and expressed by enantiomer excess (% e.e.) or diastereomer excess (% d.e.) based on the area value of R form and S form thereof. The optical rotation was represented by specific optical rotation  $[\alpha]_D$ . The thin-layer chromatography was performed using silica gel manufactured by Merck, and column chromatography was performed using silica gel manufactured by Fuji Silysia Chemical.

**[0170]** In extraction, moreover, organic solutions were dried over anhydrous sodium sulfate or anhydrous magnesium sulfate unless otherwise specified.

**[0171]** The solvents and reagents used for the experiments are shown by the following abbreviations.

tetrahydrofuran: THF

N,N-dimethylformamide: DMF

1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride:

WSCI-HCl

1,1'-carbonyldiimidazole: CDI

1-hydroxybenzotriazole 1-hydrate: HOBt-H<sub>2</sub>O

1,8-diazabicyclo[5.4.0]undec-7-ene: DBU

Example 1 Synthesis of 2-benzyl-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

(1) monoethyl benzylmalonate

**[0172]** To a solution of diethyl benzylmalonate (27.1 g) in ethanol (70 mL) was added a solution of potassium hydroxide (6.1 g) in ethanol (70 mL), and the mixture was stirred at room temperature for 18 hr. After concentration under reduced pressure, water (300 ml) and ether (100 mL) were added to extract the mixture. The aqueous layer was adjusted to pH = 1-2 by the addition of concentrated hydrochloric acid, and the mixture was extracted with ethyl acetate (200 mL×2). The organic layer was washed with saturated brine and concentrated under reduced pressure to give the title compound (19.3 g) as an oil.

<sup>1</sup>H-NMR(300MHz, DMSO-d<sub>6</sub>)δ1.08(3H, t, J = 7.2Hz), 3.05(2H, dd, J = 9.3, 4.8Hz), 3.67-3.72(1H, m), 4.04(2H, q, J=7.2Hz), 7.17-7.30(5H, m), 12.94(1H, brs).

(2) ethyl 2-benzyl-3-[(2-naphthylsulfonyl)amino]-3-oxopropionate

**[0173]** To a solution of the above-mentioned compound (5.53 g) in THF (100 mL) was added CDI (6.46 g), and the mixture was heated under reflux for 1 hr. The reaction mixture was allowed to cool to room temperature, naphthalene-2-sulfonamide (5.15 g) and DBU (4.10 mL) were added, and the mixture was stirred at room temperature for 20 hr. The reaction mixture was concentrated, 1 mol/L hydrochloric acid (100 mL) and ethyl acetate (200 mL) were added to extract the residue, and the organic layer was washed with saturated brine. After concentration, chloroform was added to the residue, and insoluble material was removed by filtration. The filtrate was concentrated, and the residue was purified by silica gel column chromatography to give the title compound (3.30 g) as an oil.

<sup>1</sup>H-NMR(300MHz, DMSO-d<sub>6</sub>)δ0.94(3H, t, J = 7.0Hz), 2.92-2.95(2H, m), 3.71-3.78(1H, m), 3.95(2H, q, J = 7.0Hz), 6.99-7.08(5H, m), 7.70-7.77(3H, m), 8.07-8.25(3H, m), 8.53(1H, s), 12.53(1H, brs).

(3) 2-benzyl-3-[(2-naphthylsulfonyl)amino]-3-oxopropionic acid

**[0174]** To a mixed solution of the above-mentioned compound (3.30 g) in THF (10 mL)/ethanol (50 mL) was added a solution of sodium hydroxide (1.0 g) in water (4 mL), and the mixture was stirred at room temperature for 15 hr. After concentration under reduced pressure, the residue was adjusted to pH = 1-2 by the addition of 1 mol/L hydrochloric acid, and the mixture was extracted with ethyl acetate (100 mL×2). The organic layer was washed with saturated brine, and concentrated under reduced pressure to give the title compound (2.91 g) as a white solid.

<sup>1</sup>H-NMR(300MHz, DMSO-d<sub>6</sub>)δ2.50-2.98(2H, m), 3.67(1H, dd, J = 9.3, 6.0Hz), 6.95-7.06(5H, m), 7.69-7.79(3H, m), 8.07-8.22(3H, m), 8.51(1H, s), 12.47(1H, brs), 12.90(1H, brs).

(4) 2-benzyl-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

**[0175]** To a solution of the above-mentioned compound (690 mg) in DMF (10 mL) were added diethylamine (690 μL), HOBt-H<sub>2</sub>O (330 mg) and WSCI-HCl (420 mg), and the mixture was stirred at room temperature for 18 hr. The mixture was adjusted to pH = 1-2 by the addition of dilute hydrochloric acid (20 mL), and extracted with ethyl acetate (100 mL). The organic layer was washed with saturated brine and concentrated under reduced pressure. A mixed solution of hexane/ethyl acetate was added to the residue, and the precipitate was collected by filtration to give the title compound (473 mg) as a white solid.

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<sup>1</sup>H-NMR(300MHz, DMSO-d<sub>6</sub>)δ0.81-0.88(6H, m), 2.91(2H, d, J = 7.2Hz), 3.08-3.23(4H, m), 3.80-3.85(1H, m), 7.02-7.09(5H, m), 7.70-7.80(3H, m), 8.06-8.21(3H, m), 8.53(1H, s), 12.33(1H, brs).  
MS: 439(M+H)<sup>+</sup>.

5 Example 2 Synthesis of N-{2-benzyl-3-[(2-naphthylsulfonyl)amino]-3-oxopropanoyl}-N-ethylglycine ethyl ester

(1) N-ethylglycine ethyl ester hydrochloride

10 **[0176]** To ethanol (30 mL) was added dropwise thionyl chloride (2.6 mL) at -10°C, and the mixture was stirred for 15 min. N-ethylglycine (1.0 g) was added to this solution at -10°C, and the mixture was allowed to warm to room temperature while stirring for 17 hr. The reaction mixture was concentrated under reduced pressure to give the title compound (1.63 g) as a white solid.

<sup>1</sup>H-NMR(300MHz, DMSO-d<sub>6</sub>)δ1.19-1.27(6H, m), 2.96(2H, q, J = 7.2Hz), 3.93(2H, s), 4.21(2H, q, J = 6.9Hz), 9.54(2H, brs).

15 (2) N-{2-benzyl-3-[(2-naphthylsulfonyl)amino]-3-oxopropanoyl}-N-ethylglycine ethyl ester

**[0177]** In the same manner as in Example 1 (4), a crude product was obtained using the compound (582 mg) obtained by Example 1 (3) and the above-mentioned compound (310 mg). This was purified by silica gel column chromatography to give the title compound (342 mg) as a white solid.

20 <sup>1</sup>H-NMR(300MHz, DMSO-d<sub>6</sub>)δ0.89(3H, t, J = 7.0Hz), 1.08-1.22(3H, m), 2.78-3.00(2H, m), 3.22-3.35(2H, m), 3.79-4.36(5H, m), 6.90-7.10(5H, m), 7.70-7.80(3H, m), 8.08-8.24(3H, m), 8.54(1H, d, J = 1.6Hz), 12.36(1H, brs).

MS: 525(M+Na)<sup>+</sup>.

Example 3 Synthesis of N-{2-benzyl-3-[(2-naphthylsulfonyl)amino]-3-oxopropanoyl}-N-ethylglycine

25 **[0178]** To a mixture of the compound (250 mg) obtained by Example 2 in THF (10 mL)/water (3 mL) was added 1 mol/L aqueous sodium hydroxide solution (1.5 mL) at room temperature, and the mixture was stirred for 2.5 hr. After concentration under reduced pressure, the residue was adjusted to pH = 1-2 by the addition of 1 mol/L hydrochloric acid and extracted with ethyl acetate (50 mLx2). The organic layer was washed with saturated brine and concentrated under reduced pressure to give the title compound (211 mg) as a white solid.

30 <sup>1</sup>H-NMR(300MHz, DMSO-d<sub>6</sub>)δ0.88(3H, t, J = 6.9Hz), 2.78-2.98(2H, m), 3.19-3.34(2H, m), 3.74-4.24(3H, m), 6.91-7.08(5H, m), 7.70-7.79(3H, m), 8.07-8.22(3H, m), 8.51-8.52(1H, m), 12.30(1H, brs), 12.51(1H, brs).

MS: 469(M+H)<sup>+</sup>.

35 Example 4 Synthesis of N-benzyl-N-{2-benzyl-3-[(2-naphthylsulfonyl)amino]-3-oxopropanoyl}glycine

(1) N-benzyl-N-{2-benzyl-3-[(2-naphthylsulfonyl)amino]-3-oxopropanoyl}glycine ethyl ester

40 **[0179]** In the same manner as in Example 1 (4), the title compound (1.29 g) was obtained as a white solid using the compound (930 mg) obtained by Example 1 (3) and N-benzylglycine ethyl ester (570 mg).

MS:559 (M+H)<sup>+</sup>.

(2) N-benzyl-N-{2-benzyl-3-[(2-naphthylsulfonyl)amino]-3-oxopropanoyl}glycine

45 **[0180]** In the same manner as in Example 3, the title compound (1.13 g) was obtained as a white solid using the above-mentioned compound (1.29 g).

<sup>1</sup>H-NMR(300MHz, DMSO-d<sub>6</sub>)δ2.80-3.05(2H, m), 3.75-4.25(3H, m), 4.50-4.80(2H, m), 6.84-7.25(10H, m), 7.70-7.80(3H, m), 8.07-8.10(2H, m), 8.20-8.23(1H, m), 8.52-8.53(1H, m), 12.38(2H, brs).

MS: 531(M+H)<sup>+</sup>.

50 Example 5 Synthesis of 2-benzyl-N-(2-naphthylsulfonyl)-3-[4-(2-naphthylsulfonyl)piperazin-1-yl]-3-oxopropanamide (1) 2-benzyl-N-(2-naphthylsulfonyl)-3-(piperazin-1-yl)-3-oxopropanamide trifluoroacetate

**[0181]** To a solution of the compound (1.0 g) obtained by Example 1 (3) in DMF (20 mL) were added 1-tert-butyloxy-carbonylpiperazine (590 mg), HOBT·H<sub>2</sub>O (480 mg), WSCI·HCl (600 mg) and N-methylmorpholine (290 μL), and the mixture was stirred at room temperature for 3.5 hr. The reaction mixture was adjusted to pH = 4 by the addition of dilute hydrochloric acid (20 mL), and the precipitate was collected by filtration. Trifluoroacetic acid (10 mL) was added to this, and the mixture was stirred at room temperature for 13 hr. After concentration under reduced pressure, ether was added

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to the residue, and the mixture was subjected to decantation to give the title compound (1.47 g) as a white powder. MS: 452(M+H)<sup>+</sup>.

(2) 2-benzyl-N-(2-naphthylsulfonyl)-3-[4-(2-naphthylsulfonyl)piperazin-1-yl]-3-oxopropanamide

**[0182]** To a solution of the above-mentioned compound (600 mg) in pyridine (5 mL) were added 4-dimethylaminopyridine (130 mg) and 2-naphthalenesulfonyl chloride (240 mg), and the mixture was stirred at room temperature for 16 hr. After concentration under reduced pressure, dilute hydrochloric acid was added to the residue, and the precipitate was collected by filtration. This was purified by silica gel column chromatography to give the title compound (265 mg) as a white powder.

<sup>1</sup>H-NMR(300MHz, DMSO-d<sub>6</sub>)δ2.55-3.68(10H, m), 3.88-3.97(1H, m), 6.48-6.52(1H, m), 6.75-6.79(2H, m), 6.90-6.92(2H, m), 7.63-8.51(14H, m), 12.27(1H, brs).

MS: 642(M+H)<sup>+</sup>.

Example 6 Synthesis of N, N-diethyl-N'-(2-naphthylsulfonyl)-2-(4-nitrobenzyl)malonamide

(1) dimethyl (4-nitrobenzyl)malonate

**[0183]** To a solution of dimethyl malonate (5.53 g) in THF (100 mL) was added 60% sodium hydride (1.84 g) under ice-cooling, and the mixture was stirred for 30min. 4-Nitrobenzyl bromide (9.04 g) was added to this mixture under ice-cooling, and the mixture was allowed to warm to room temperature while stirring for 4 hr. The reaction mixture was adjusted to pH = 2-3 by the addition of dilute hydrochloric acid, the precipitate was removed by filtration, and the filtrate was extracted with ethyl acetate (200 mL). The organic layer was washed with saturated brine and concentrated under reduced pressure to give the title compound (7.66 g) as a pale-yellow solid. <sup>1</sup>H-NMR(300MHz, DMSO-d<sub>6</sub>)δ3.21(2H, d, J = 7.8Hz), 3.60(6H, s), 4.00(1H, t, J = 7.8Hz), 7.51(2H, d, J = 8.4Hz), 8.13(2H, d, J = 8.4Hz).

(2) monomethyl (4-nitrobenzyl)malonate

**[0184]** To a solution (30 mL) of the above-mentioned compound (7.62 g) in methanol was added a solution of potassium hydroxide (1.45 g) in methanol (20 mL), and the mixture was stirred at room temperature for 56 hr. After concentration under reduced pressure, water (300 ml) and ether (100 mL) were added to extract the residue. The aqueous layer was adjusted to pH = 1-2 by the addition of concentrated hydrochloric acid, and extracted with ethyl acetate (200 mL×2). The organic layer was washed with saturated brine and concentrated under reduced pressure to give the title compound (4.32 g) as a yellow solid. <sup>1</sup>H-NMR(300MHz, DMSO-d<sub>6</sub>)δ3.20(2H, d, J = 7.9Hz), 3.61(3H, s), 3.89(1H, t, J = 7.9Hz), 7.53(2H, d, J = 8.5Hz), 8.15(2H, d, J = 8.5Hz), 13.00(1H, brs).

(3) methyl 3-[(2-naphthylsulfonyl)amino]2-(4-nitrobenzyl)-3-oxopropionate

**[0185]** In the same manner as in Example 1 (2), the title compound (5.49 g) was obtained as a pale-yellow powder using the above-mentioned compound (4.24 g).

<sup>1</sup>H-NMR(300MHz, DMSO-d<sub>6</sub>)δ3.00-3.19(2H, m), 3.57(3H, s), 3.86-3.95(1H, m), 7.23(2H, d, J = 8.5Hz), 7.69-7.82(5H, m), 8.03-8.07(2H, m), 8.17-8.19(1H, m), 8.48(1H, s), 12.60(1H, brs).

(4) 3-[(2-naphthylsulfonyl)amino]-2-(4-nitrobenzyl)-3-oxopropionic acid

**[0186]** To a solution of the above-mentioned compound (5.49 g) in THF (100 mL) was added a solution of sodium hydroxide (1.54 g) in water (12 mL). In the same manner as in Example 1 (3), the title compound (5.31 g) as a pale-yellow powder was obtained. <sup>1</sup>H-NMR(300MHz, DMSO-d<sub>6</sub>)δ2.97-3.18(2H, m), 3.74-3.80(1H, m), 7.22(2H, d, J = 8.5Hz), 7.67-7.73(3H, m), 7.78(2H, d, J = 8.5Hz), 8.03(2H, d, J = 8.8Hz), 8.16(1H, d, J = 7.9Hz), 8.47(1H, s), 12.54(2H, brs).

(5) N, N-diethyl-N'-(2-naphthylsulfonyl)-2-(4-nitrobenzyl)malonamide

**[0187]** To the residue obtained in the same manner as in Example 1 (4) using the above-mentioned compound (5.31 g) was added methanol, and the precipitate was collected by filtration to give the title compound (2.63 g) as a white solid. <sup>1</sup>H-NMR(300MHz, DMSO-d<sub>6</sub>)δ0.86(6H, t, J = 7.6Hz), 3.05(2H, d, J = 7.3Hz), 3.12-3.20(4H, m), 3.95(1H, t, J = 7.6Hz), 7.31(2H, d, J = 8.6Hz), 7.70-7.79(3H, m), 7.88(2H, d, J = 8.6Hz), 8.08(2H, t, J = 9.0Hz), 8.19(1H, d, J = 7.9Hz), 8.52(1H, s), 12.40(1H, brs).

MS: 484(M+H)<sup>+</sup>.

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### Example 7 Synthesis of 2-(4-aminobenzyl)-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

**[0188]** To a mixed suspension of the compound (2.53 g) obtained in Example 6 in ethanol (200 mL)/ethyl acetate (100 mL) was added 10% palladium/carbon (500 mg), and the mixture was heated under reflux under hydrogen atmosphere for 6 hr. After allowing to cool to room temperature, insoluble material was removed by filtration, and the filtrate was concentrated under reduced pressure to give the title compound (2.37 g) as a white powder. In some cases, the compound was further converted to a hydrochloride salt with 4 mol/L hydrochloric acid/ethyl acetate and used.

<sup>1</sup>H-NMR(300MHz, DMSO-d<sub>6</sub>)δ0.82-0.88(6H, m), 2.74(2H, d, J = 6.9Hz), 3.06-3.20(4H, m), 3.72(1H, t, J = 6.9Hz), 6.37(2H, d, J = 8.4Hz), 6.71(2H, d, J = 8.4Hz), 7.65-7.78(3H, m), 8.07(1H, d, J = 7.8Hz), 8.13(1H, d, J = 9.0Hz), 8.20(1H, d, J = 7.8Hz), 8.54(1H, s).

MS: 454(M+H)<sup>+</sup>.

### Example 8 Synthesis of N, N-diethyl-2-(4-guanidinobenzyl)-N'-(2-naphthylsulfonyl)malonamide trifluoroacetic acid salt (1) [4-(N",N"-di-tert-butylloxycarbonylguanidino)benzyl]-N, N-diethyl-2-N'-(2-naphthylsulfonyl)malonamide

**[0189]** To a solution of the compound (1.09 g) obtained in Example 7 in ethanol (10 mL) was added N,N'-di-tert-butylloxycarbonyl-1H-pyrazole-1-carboxamide (745 mg) at room temperature, and the mixture was stirred for 2 hr. The precipitate was collected by filtration from the reaction mixture to give the title compound (1.44 g) as a white solid. MS:696(M+H)<sup>+</sup>.

### (2) N, N-diethyl-2-(4-guanidinobenzyl)-N'-(2-naphthylsulfonyl)malonamide trifluoroacetic acid salt

**[0190]** To the above-mentioned compound (1.44 g) was added 95% trifluoroacetic acid (20 mL), and the mixture was stirred at room temperature for 3 hr. The reaction mixture was concentrated under reduced pressure, ether was added to the residue, and the precipitate was collected by filtration to give the title compound (1.26 g) as a white solid. <sup>1</sup>H-NMR(300MHz, DMSO-d<sub>6</sub>)δ0.86(6H, t, J = 6.6Hz), 2.93(2H, d, J = 6.9Hz), 3.10-3.21(4H, m), 3.87(1H, t, J = 6.9Hz), 6.95(2H, d, J = 8.1Hz), 7.12(2H, d, J = 8.1Hz), 7.36(4H, brs), 7.69-7.79(3H, m), 8.07-8.08(1H, d, J = 8.1Hz), 8.14(1H, d, J = 8.7Hz), 8.22(1H, d, J = 7.8Hz), 8.56(1H, s), 9.67(1H, s), 12.24(1H, brs).

MS: 496(M+H)<sup>+</sup>.

### Example 9 Synthesis of 2-[4-(benzoylamino)benzyl]-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

**[0191]** To a solution of the compound (500 mg) obtained in Example 7 in pyridine (5 mL) were added benzoyl chloride (160 mg) and 4-dimethylaminopyridine in catalytic amount at room temperature, and the mixture was stirred for 3 hr. The reaction mixture was adjusted to pH = 2-3 by the addition of dilute hydrochloric acid, the precipitate was collected by filtration, and washed with water to give the title compound (527 mg) as a white solid.

<sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.86(6H, t, J = 6.9Hz), 2.86-2.95(2H, m), 3.09-3.22(4H, m), 3.87(1H, t, J = 7.2Hz), 7.05(2H, d, J = 8.2Hz), 7.52-7.79(8H, m), 7.96(2H, d, J = 8.2Hz), 8.05(1H, d, J = 8.1Hz), 8.14(1H, d, J = 8.8Hz), 8.21(1H, d, J = 8.1Hz), 8.56(1H, s), 10.16(1H, s), 12.37(1H, brs).

MS: 558(M+H)<sup>+</sup>.

### Example 10 Synthesis of 2-[4-(acetylamino)benzyl]-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

**[0192]** In the same manner as in Example 9, the title compound (261 mg) was obtained as a white solid using hydrochloride salt (300 mg) of the compound obtained in Example 7 and acetic anhydride (70 μL).

<sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.82-0.87(6H, m), 2.02(3H, s), 2.86(2H, dd, J = 7.2, 2.4Hz), 3.07-3.20(4H, m), 3.83(1H, t, 7.2Hz), 6.97(2H, d, J = 8.4Hz), 7.33(2H, d, J = 8.4Hz), 7.69-7.78(3H, m), 8.07(1H, d, J = 8.0Hz), 8.12(1H, d, J = 8.8Hz), 8.21(1H, d, J = 8.0Hz), 8.54(1H, s), 9.81(1H, s), 12.39(1H, brs). MS:496(M+H)<sup>+</sup>.

### Example 11 Synthesis of N, N-diethyl-2-[4-(isobutrylamino)benzyl]-N'-(2-naphthylsulfonyl)malonamide

**[0193]** In the same manner as in Example 9, the title compound (217 mg) was obtained as a white solid using hydrochloride salt (300 mg) of the compound obtained in Example 7 and isobutryl chloride (77 μL).

<sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.84-0.86(6H, m), 1.10(6H, d, J = 7.2Hz), 2.55(1H, sept, J = 7.2Hz), 2.85-2.90(2H, m), 3.08-3.17(4H, m), 3.83(1H, t, J = 6.8Hz), 6.98(2H, d, J = 8.4Hz), 7.38(2H, d, J = 8.4Hz), 7.68-7.78(3H, m), 8.06(1H, d, J = 8.4Hz), 8.11(1H, d, J = 8.8Hz), 8.21(1H, d, J = 8.0Hz), 8.55(1H, s), 9.72(1H, s), 12.26(1H, brs).

MS: 524(M+H)<sup>+</sup>.

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### Example 12 Synthesis of N, N-diethyl-N'-(2-naphthylsulfonyl)-2-[4-(pivaloylamino)benzyl]malonamide

**[0194]** In the same manner as in Example 9, the title compound (307 mg) was obtained as a white solid using the compound (460 mg) obtained in Example 7 and trimethylacetyl chloride (128  $\mu$ L).  $^1\text{H-NMR}$ (400MHz, DMSO- $d_6$ ) $\delta$ 0.85(6H, t, J = 6.4Hz), 1.22(9H, s), 2.80-2.92(2H, m), 3.10-3.30(4H, m), 3.83(1H, t, J = 7.2Hz), 6.99(2H, d, J = 8.4Hz), 7.40(2H, d, J = 8.4Hz), 7.69-7.78(3H, m), 8.05(1H, d, J = 8.0Hz), 8.11(1H, d, J = 8.4Hz), 8.20(1H, d, J = 8.0Hz), 8.54(1H, s), 9.07(1H, s), 12.27(1H, brs).

MS: 538 (M+H) $^+$ .

### Example 13 Synthesis of N, N-diethyl-N'-(2-naphthylsulfonyl)-2-[4-(propioloylamino)benzyl]malonamide

**[0195]** To a solution of hydrochloride salt (240 mg) of the compound obtained in Example 7 in DMF (5 mL) were added WSCI·HCl (115 mg), 4-dimethylaminopyridine (120 mg) and propiolic acid (36  $\mu$ L) at room temperature, and the mixture was stirred for 16 hr. The mixture was adjusted to pH = 1-2 by the addition of dilute hydrochloric acid (30 mL) and extracted with ethyl acetate (50 mL $\times$ 2). The organic layer was washed with saturated brine, concentrated under reduced pressure, and the residue was purified by silica gel column chromatography to give the title compound (46 mg) as a pale-yellow solid.  $^1\text{H-NMR}$ (300MHz, DMSO- $d_6$ ) $\delta$ 0.81-0.87(6H, m), 2.85-2.90(2H, m), 3.08-3.18(4H, m), 3.84(1H, t, J = 7.2Hz), 4.41(1H, s), 6.99(2H, d, J = 7.8Hz), 7.34(2H, d, J = 7.8Hz), 7.68-7.79(3H, m), 8.06-8.12(2H, m), 8.21(1H, d, J = 8.0Hz), 8.54(1H, s), 10.70(1H, s), 12.30(1H, brs).

MS: 506(M+H) $^+$ .

### Example 14 Synthesis of 2-{4-[(2-butynoyl)amino]benzyl}-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

**[0196]** In the same manner as in Example 13, the reaction mixture was obtained using hydrochloride salt (300 mg) of the compound obtained in Example 7 and 2-butynoic acid (57 mg). Dilute hydrochloric acid was added, and the precipitate was collected by filtration to give the title compound (170 mg) as a white solid.

$^1\text{H-NMR}$ (300MHz, DMSO- $d_6$ ) $\delta$ 0.81-0.86(6H, m), 1.88(3H, s), 2.82-2.85(2H, m), 3.08-3.18(4H, m), 3.80(1H, t, J = 7.2Hz), 6.95(2H, d, J = 8.4Hz), 7.32(2H, d, J = 8.4Hz), 7.67-7.76(3H, m), 8.04(1H, d, J = 7.8Hz), 8.09(1H, d, J = 8.7Hz), 8.18(1H, d, J = 7.8Hz), 8.52(1H, s), 10.48(1H, s), 12.31(1H, brs). MS: 520 (M+H) $^+$ .

### Example 15 Synthesis of 2-[4-(cyclopropylcarbonylamino)benzyl]-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

**[0197]** In the same manner as in Example 9, the title compound (81 mg) was obtained as a white solid using the compound (337 mg) obtained in Example 7 and cyclopropanecarbonyl chloride (67  $\mu$ L).

$^1\text{H-NMR}$ (400MHz, DMSO- $d_6$ ) $\delta$ 0.72-0.95(10H, m), 1.67-1.80(1H, m), 2.79-2.95(2H, m), 3.03-3.25(4H, m), 3.82(1H, t, J = 7.2Hz), 6.97(2H, d, J = 8.4Hz), 7.34(2H, d, J = 8.4Hz), 7.66-7.82(3H, m), 8.05(1H, d, J = 8.4Hz), 8.10(1H, d, J = 8.4Hz), 8.19(1H, d, J = 8.4Hz), 8.53(1H, s), 10.03(1H, s), 12.28(1H, brs).

MS: 522 (M+H) $^+$ .

### Example 16 Synthesis of N, N-diethyl-2-[4-[(1-methylcyclopropyl)carbonylamino]benzyl]-N'-(2-naphthylsulfonyl)malonamide

**[0198]** In the same manner as in Example 13, the title compound (366 mg) was obtained as a white solid using hydrochloride salt (430 mg) of the compound obtained in Example 7 and 1-methylcyclopropane-1-carboxylic acid (88 mg).

$^1\text{H-NMR}$ (400MHz, DMSO- $d_6$ ) $\delta$ 0.58-0.68(2H, m), 0.74-0.95(6H, m), 1.02-1.13(2H, m), 1.40(3H, s), 2.54(2H, s), 2.78-2.93(2H, m), 3.01-3.23(4H, m), 3.83(1H, t, J = 7.2Hz), 6.97(2H, d, J = 8.4Hz), 7.37(2H, d, J = 8.4Hz), 7.62-7.82(3H, m), 8.06(1H, d, J = 8.4Hz), 8.11(1H, d, J = 8.4Hz), 8.20(1H, d, J = 8.4Hz), 8.54(1H, s), 9.03(1H, s), 12.30(1H, brs).

MS: 536(M+H) $^+$ .

### Example 17 Synthesis of 2-[4-[(1-tert-butyloxycarbonyl-4-piperidinylcarbonyl)amino]benzyl]-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

**[0199]** In the same manner as in Example 1 (4), the reaction mixture was obtained using hydrochloride salt (430 mg) of the compound obtained in Example 7, N-tert-butyloxycarbonylisonipecotic acid (200 mg) and N-methylmorpholine (190  $\mu$ L). Dilute hydrochloric acid was added, and the precipitate was collected by filtration to give the title compound (410 mg) as a white solid.

$^1\text{H-NMR}$ (400MHz, DMSO- $d_6$ ) $\delta$ 0.82-0.86(6H, m), 1.41(9H, s), 1.41-1.52(2H, m), 1.72-1.76(2H, m), 2.67-2.89(4H, m), 3.06-3.32(5H, m), 3.72-3.78(1H, m), 3.94-4.00(2H, m), 6.98(2H, d, J = 8.8Hz), 7.37(2H, d, J = 8.8Hz), 7.67-7.76(3H,

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m), 8.02-8.16(3H, m), 8.49(1H, brs), 9.80(1H, s), 12.32(1H, brs).

Example 18 Synthesis of N, N-diethyl-N'-(2-naphthylsulfonyl)-2-{4-[(4-piperidinylcarbonyl)amino]benzyl}malonamide trifluoroacetic acid salt

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**[0200]** To a solution of the compound (250 mg) obtained in Example 17 in methylene chloride (10 mL) was added trifluoroacetic acid (3 mL) at room temperature, and the mixture was stirred for 16 hr. After concentration under reduced pressure, an ether/chloroform mixture was added, and the precipitate was collected by filtration to give the title compound (247 mg) as a white solid.

10 <sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.81-0.87(6H, m), 1.75-1.97(4H, m), 2.57-2.63(1H, m), 2.78-3.28(10H, m), 3.82(1H, t, J = 7.2Hz), 7.01(2H, d, J = 8.4Hz), 7.37 (2H, d, J = 8.4Hz), 7.68-7.77 (3H, m), 8.05(1H, d, J = 8.0Hz), 8.10(1H, d, J = 8.4Hz), 8.20(1H, d, J = 8.0Hz), 8.26-8.33(1H, brs), 8.54(1H, s), 8.54-8.58(1H, brs), 9.93(1H, s), 12.34(1H, brs). MS: 565(M+H)<sup>+</sup>.

15 Example 19 Synthesis of N, N-diethyl-2-{4-[(2-fluorobenzoyl)amino]benzyl}-N'-(2-naphthylsulfonyl)malonamide

**[0201]** In the same manner as in Example 9, the title compound (204 mg) was obtained as a white solid using the compound (332 mg) obtained in Example 7 and 2-fluorobenzoyl chloride (87 μL). <sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.87(6H, t, J = 7.2Hz), 2.83-2.98(2H, m), 3.05-3.28(4H, m), 3.86(1H, t, J = 7.2Hz), 7.04(2H, d, J = 8.4Hz), 7.28-7.40(2H, m), 20 7.49(2H, d, J = 8.4Hz), 7.53-7.80(5H, m), 8.06(1H, d, J = 8.4Hz), 8.12(1H, d, J = 8.4Hz), 8.21(1H, d, J = 8.4Hz), 8.56(1H, s), 10.29(1H, s), 12.27(1H, brs).

MS: 576(M+H)<sup>+</sup>.

25 Example 20 Synthesis of N, N-diethyl-2-{4-[(4-fluorobenzoyl)amino]benzyl}-N'-(2-naphthylsulfonyl)malonamide

**[0202]** In the same manner as in Example 9, the title compound (261 mg) was obtained as a white solid using hydrochloride salt (300 mg) of the compound obtained in Example 7 and 4-fluorobenzoyl chloride (87 μL).

30 <sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.86(6H, t, J = 6.8Hz), 2.85-2.92(2H, m), 3.09-3.35(4H, m), 3.87(1H, t, J = 7.2Hz), 7.04(2H, d, J = 8.4Hz), 7.36-7.40(2H, m), 7.52(2H, d, J = 8.4Hz), 7.66-7.79(3H, m), 8.02-8.06(3H, m), 8.13(1H, d, J = 8.8Hz), 8.21(1H, d, J = 8.0Hz), 8.55(1H, s), 10.16(1H, s), 12.28(1H, brs). MS: 576(M+H)<sup>+</sup>.

Example 21 Synthesis of N, N-diethyl-2-{4-[(3-fluorobenzoyl)amino]benzyl}-N'-(2-naphthylsulfonyl)malonamide

**[0203]** In the same manner as in Example 9, the title compound (192 mg) was obtained as a white solid using hydrochloride salt (196 mg) of the compound obtained in Example 7 and 3-fluorobenzoyl chloride (48 μL).

35 <sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.86(6H, t, J = 6.8Hz), 2.82-2.96(2H, m), 3.04-3.23(4H, m), 3.87(1H, t, J = 7.2Hz), 7.06(2H, d, J = 8.4Hz), 7.40-7.49(1H, m), 7.53(2H, d, J = 8.4Hz), 7.57-7.86(6H, m), 8.06(1H, d, J = 8.0Hz), 8.13(1H, d, J = 8.4Hz), 8.20(1H, d, J = 8.4Hz), 8.55(1H, s), 10.19(1H, s). MS: 576(M+H)<sup>+</sup>.

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Example 22 Synthesis of N, N-diethyl-2-{4-[(2,6-difluorobenzoyl)amino]benzyl}-N'-(2-naphthylsulfonyl)malonamide

**[0204]** In the same manner as in Example 9, the title compound (184 mg) was obtained as a white solid using hydrochloride salt (207 mg) of the compound obtained in Example 7 and 2, 6-difluorobenzoyl chloride (53 μL).

45 <sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.87(6H, t, J = 6.8Hz), 2.80-2.98(2H, m), 3.04-3.23(4H, m), 3.85(1H, t, J = 7.2Hz), 7.06(2H, d, J = 8.4Hz), 7.25(2H, t, J = 8.0Hz), 7.46(2H, d, J = 8.4Hz), 7.51-7.80(4H, m), 8.06(1H, d, J = 8.0Hz), 8.11(1H, d, J = 8.8Hz), 8.21(1H, d, J = 8.0Hz), 8.56(1H, s), 10.69(1H, s). MS: 594 (M+H)<sup>+</sup>.

50 Example 23 Synthesis of N, N-diethyl-2-{4-[(2, 4-difluorobenzoyl)amino]benzyl}-N'-(2-naphthylsulfonyl)malonamide

**[0205]** In the same manner as in Example 13, the title compound (269 mg) was obtained as a white solid using hydrochloride salt (257 mg) of the compound obtained in Example 7 and 2, 4-difluorobenzoic acid (83 mg).

55 <sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.78-0.92(6H, m), 2.81-2.97(2H, m), 3.04-3.23(4H, m), 3.72(1H, m), 7.05(2H, d, J = 8.4Hz), 7.22(2H, t, J = 8.4Hz), 7.41(1H, t, J = 8.4Hz), 7.48(1H, d, J = 8.4Hz), 7.60-7.7.83(4H, m), 8.03(2H, t, J = 8.4Hz), 8.13(1H, d, J = 8.0Hz), 8.45(1H, brs), 10.27(1H, s). MS: 594(M+H)<sup>+</sup>.

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Example 24 Synthesis of N, N-diethyl-2-{4-[(2-fluoro-4-methylbenzoyl)amino]benzyl}-N'-(2-naphthylsulfonyl)malonamide

**[0206]** In the same manner as in Example 13, the title compound (193 mg) was obtained as a white solid using hydrochloride salt (252 mg) of the compound obtained in Example 7 and 2-fluoro-4-methylbenzoic acid (88 mg).  
<sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.86(6H, t, J = 7.2Hz), 2.39(3H, s), 2.83-3.00(2H, m), 3.07-3.25(4H, m), 3.86(1H, t, J = 7.2Hz), 7.03(2H, d, J = 8.0Hz), 7.11-7.22(2H, m), 7.48(2H, d, J = 8.0Hz), 7.56(1H, t, J = 8.0Hz), 7.66-7.82(3H, m), 8.06(1H, d, J = 8.0Hz), 8.12(1H, d, J = 8.8Hz), 8.20(1H, d, J = 8.0Hz), 8.55(1H, s), 10.16(1H, s), 12.33(1H, brs).  
MS:590(M+H)<sup>+</sup>.

Example 25 Synthesis of N, N-diethyl-2-{4-[(2-methoxybenzoyl)amino]benzyl}-N'-(2-naphthylsulfonyl)malonamide

**[0207]** In the same manner as in Example 9, the title compound (178 mg) was obtained as a white solid using the compound (505 mg) obtained in Example 7 and 2-methoxybenzoyl chloride (200 μL).  
<sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.86(6H, t, J = 7.0Hz), 2.89(2H, d, J = 7.0Hz), 3.08-3.23(4H, m), 3.86(1H, t, J = 7.0Hz), 3.91(3H, s), 7.02(2H, d, J = 8.4Hz), 7.08(1H, t, J = 7.4Hz), 7.19(1H, d, J = 8.4Hz), 7.47-7.55(3H, m), 7.62-7.80(4H, m), 8.06(1H, d, J = 8.1Hz), 8.13(1H, d, J = 8.8Hz), 8.21(1H, d, J = 8.1Hz), 8.55(1H, s), 10.01(1H, s), 12.36(1H, brs).  
MS: 588(M+H)<sup>+</sup>.

Example 26 Synthesis of N, N-diethyl-2-{4-[(4-methoxybenzoyl)amino]benzyl}-N'-(2-naphthylsulfonyl)malonamide

**[0208]** In the same manner as in Example 9, the title compound (485 mg) was obtained as a white solid using the compound (488 mg) obtained in Example 7 and 4-methoxybenzoyl chloride (145 μL).  
<sup>1</sup>H-NMR(300MHz, DMSO-d<sub>6</sub>)δ0.86(6H, t, J = 7.0Hz), 2.89(2H, d, J = 6.9Hz), 3.03-3.23(4H, m), 3.79-3.95(4H, m), 7.03(2H, d, J = 8.7Hz), 7.06(2H, d, J = 8.7Hz), 7.53(2H, d, J = 8.7Hz), 7.62-7.80(3H, m), 7.96(2H, d, J = 8.7Hz), 8.05(1H, d, J = 8.1Hz), 8.13(1H, d, J = 8.1Hz), 8.21(1H, d, J = 8.1Hz), 8.55(1H, s), 9.99(1H, s), 13.26(1H, brs).  
MS: 588 (M+H)<sup>+</sup>.

Example 27 Synthesis of N, N-diethyl-2-{4-[(3-methoxybenzoyl)amino]benzyl}-N'-(2-naphthylsulfonyl)malonamide

**[0209]** In the same manner as in Example 9, the title compound (199 mg) was obtained as a white solid using the compound (453 mg) obtained in Example 7 and 3-methoxybenzoyl chloride (135 μL).  
<sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.86(3H, t, J = 7.2Hz), 0.86(3H, t, J = 6.8Hz), 2.86-2.97(2H, m), 3.07-3.24(4H, m), 3.84(3H, s), 3.87(1H, t, J = 7.2Hz), 7.04(2H, d, J = 8.4Hz), 7.16(1H, dd, J = 8.4, 2.0Hz), 7.42-7.57(5H, m), 7.64-7.81(3H, m), 8.05(1H, d, J = 8.4Hz), 8.13(1H, d, J = 8.4Hz), 8.21(1H, d, J = 8.2Hz), 8.56(1H, s), 10.13(1H, s), 12.36(brs).  
MS: 588 (M+H)<sup>+</sup>.

Example 28 Synthesis of N, N-diethyl-2-{4-[(2, 6-dimethoxybenzoyl)amino]benzyl}-N'-(2-naphthylsulfonyl)malonamide

**[0210]** In the same manner as in Example 9, the title compound (463 mg) was obtained as a white solid using the compound (520 mg) obtained in Example 7 and 2, 6-dimethoxybenzoyl chloride (241 mg).  
<sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.76-0.90(6H, m), 2.80-2.97(2H, m), 3.04-3.25(4H, m), 3.76(6H, s), 3.85(1H, d, J = 7.2Hz), 6.74(2H, d, J = 8.8Hz), 6.99(2H, d, J = 8.4Hz), 7.36(1H, t, J = 8.4Hz), 7.50(2H, d, J = 8.4Hz), 7.66-7.84(3H, m), 8.06(1H, d, J = 8.0Hz), 8.13(1H, d, J = 8.8Hz), 8.22(1H, d, J = 8.0Hz), 8.55(1H, s), 10.14(1H, s).  
MS: 618 (M+H)<sup>+</sup>.

Example 29 Synthesis of N, N-diethyl-2-{4-[(2-hydroxybenzoyl)amino]benzyl}-N'-(2-naphthylsulfonyl)malonamide

**[0211]** In the same manner as in Example 1 (4), a crude product was obtained using hydrochloride salt (357 mg) of the compound obtained in Example 7, 2-hydroxybenzoic acid (120 mg) and triethylamine (120 μL). This was purified by silica gel column chromatography to give the title compound (198 mg) as a white solid.  
<sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.86(6H, t, J = 7.0Hz), 2.89-2.92(2H, m), 3.12-3.21(4H, m), 6.96-7.00(4H, m), 7.41-7.47(3H, m), 7.65-7.79(3H, m), 7.97(1H, dd, J = 7.9, 1.3Hz), 8.05(1H, d, J = 8.2Hz), 8.12(1H, d, J = 8.7Hz), 8.20(1H, d, J = 8.2Hz), 8.54(1H, d, J = 1.0Hz), 10.26(1H, s), 11.85(1H, s), 12.32(1H, brs).  
MS: 574(M+H)<sup>+</sup>.

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Example 30 Synthesis of N, N-diethyl-2-(4-[(3-methyl-2-hydroxybenzoyl)amino]benzyl)-N'-(2-naphthylsulfonyl)malonamide

**[0212]** In the same manner as in Example 1 (4), a crude product was obtained using the compound (530 mg) obtained in Example 7 and 3-methyl-2-hydroxybenzoic acid (150 mg). This was purified by silica gel column chromatography to give the title compound (467 mg) as a white solid.

<sup>1</sup>H-NMR(300MHz, DMSO-d<sub>6</sub>)δ0.87(6H, t, J = 6.9Hz), 2.21(3H, s), 2.92(2H, d, J = 7.8Hz), 3.12-3.20(4H, m), 3.87(1H, t, J = 7.8Hz), 6.88(1H, t, J = 7.8Hz), 7.06(2H, d, J = 8.4Hz), 7.37-7.43(3H, m), 7.65-7.92(4H, m), 8.05(1H, d, J = 8.0Hz), 8.13(1H, d, J = 8.7Hz), 8.20(1H, d, J = 8.0Hz), 8.54(1H, d, J = 0.9Hz), 10.29(1H, s), 12.28(1H, brs), 12.63(1H, s).

MS: 588(M+H)<sup>+</sup>.

Example 31 Synthesis of N, N-diethyl-2-(4-[(2-methylbenzoyl)amino]benzyl)-N'-(2-naphthylsulfonyl)malonamide

**[0213]** In the same manner as in Example 9, the title compound (534 mg) was obtained as a white solid using the compound (525 mg) obtained in Example 7 and 2-methylbenzoyl chloride (159 μL). <sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.86(6H, t, J = 7.2Hz), 2.35(3H, s), 2.89(2H, d, J = 6.8Hz), 3.01-3.25(4H, m), 3.85(1H, d, J = 6.8Hz), 7.02(2H, d, J = 8.4Hz), 7.31(2H, d, J = 7.6Hz), 7.30-7.48(2H, m), 7.44(2H, d, J = 7.6Hz), 7.63-7.70(1H, m), 7.76(2H, d, J = 7.2Hz), 8.06(1H, d, J = 8.0Hz), 8.13(1H, d, J = 8.0Hz), 8.24(1H, d, J = 8.0Hz), 8.57(1H, s), 10.20(1H, s), 12.37(1H, brs).

MS: 572 (M+H)<sup>+</sup>.

Example 32 Synthesis of N, N-diethyl-2-(4-[(4-methylbenzoyl)amino]benzyl)-N'-(2-naphthylsulfonyl)malonamide

**[0214]** In the same manner as in Example 9, the title compound (525 mg) was obtained as a white solid using the compound (497 mg) obtained in Example 7 and 4-methylbenzoyl chloride (146 μL). <sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.78-0.95 (6H, m), 2.39(3H, s), 2.82-2.96(2H, m), 3.05-3.28(4H, m), 3.86(1H, t, J = 7.4Hz), 7.03(2H, d, J = 8.4Hz), 7.34(2H, d, J = 8.4Hz), 7.53(2H, d, J = 8.4Hz), 7.61-7.82(3H, m), 7.87(2H, d, J = 8.4Hz), 8.05(1H, d, J = 8.4Hz), 8.13(1H, d, J = 8.4Hz), 8.22(1H, d, J = 8.4Hz), 8.55(1H, s), 10.07(1H, s), 12.36(1H, brs).

MS: 572(M+H)<sup>+</sup>.

Example 33 Synthesis of N, N-diethyl-2-(4-[(3-methylbenzoyl)amino]benzyl)-N'-(2-naphthylsulfonyl)malonamide

**[0215]** In the same manner as in Example 9, the title compound (416 mg) was obtained as a white solid using the compound (454 mg) obtained in Example 7 and 3-methylbenzoyl chloride (131 μL). <sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.86(6H, t, J = 7.0Hz), 2.41(3H, s), 2.90(2H, dd, J = 4.2, 2.7Hz), 3.06-3.28(4H, m), 3.86(1H, t, J = 7.0Hz), 7.03(2H, d, J = 8.4Hz), 7.38-7.46(2H, m), 7.53(2H, d, J = 8.4Hz), 7.68(1H, t, J = 7.4Hz), 7.71-7.80(4H, m), 8.05(1H, d, J = 8.1Hz), 8.13(1H, d, J = 8.1Hz), 8.21(1H, d, J = 8.1Hz), 8.55(1H, s), 10.11(1H, s), 12.36(1H, brs).

MS: 572(M+H)<sup>+</sup>.

Example 34 Synthesis of N, N-diethyl-2-(4-[(2, 6-dimethylbenzoyl)amino]benzyl)-N'-(2-naphthylsulfonyl)malonamide

**[0216]** In the same manner as in Example 9, the title compound (141 mg) was obtained as a white solid using the compound (950 mg) obtained in Example 7 and 2, 6-dimethylbenzoyl chloride (390 mg).

<sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.87(6H, t, J = 6.8Hz), 2.27(6H, s), 2.89(2H, d, J = 6.8Hz), 3.08-3.22(4H, m), 3.85(1H, d, J = 6.8Hz), 7.02(2H, d, J = 8.4Hz), 7.10(2H, d, J = 8.4Hz), 7.22(1H, q, J = 7.6Hz), 7.51(2H, d, J = 8.4Hz), 7.63-7.81(3H, m), 8.66(1H, d, J = 8.0Hz), 8.13(1H, d, J = 8.0Hz), 8.22(1H, d, J = 8.0Hz), 8.58(1H, s), 10.26(1H, s), 12.34(1H, brs).

MS: 586(M+H)<sup>+</sup>.

Example 35 Synthesis of 2-(4-[(4-chlorobenzoyl)amino]benzyl)-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

**[0217]** In the same manner as in Example 9, the title compound (484 mg) was obtained as a white solid using the compound (450 mg) obtained in Example 7 and 4-chlorobenzoyl chloride (126 μL). <sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.85(3H, t, J = 7.2Hz), 0.86(3H, t, J = 7.2Hz), 2.90(2H, dd, J = 7.0, 2.0Hz), 3.05-3.24 (4H, m), 3.87(1H, t, J = 7.2Hz), 7.04(2H, d, J = 8.5Hz), 7.52(2H, d, J = 8.4Hz), 7.62(2H, d, J = 8.5Hz), 7.66-7.80(3H, m), 7.98(2H, d, J = 8.5Hz), 8.05(1H, d, J = 8.1Hz), 8.13(1H, d, J = 8.8Hz), 8.20(1H, d, J = 8.1Hz), 8.55(1H, s), 10.22(1H, s), 12.37(1H, brs).

MS: 592(M+H)<sup>+</sup>.

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Example 36 Synthesis of 2-{4-[(2-chlorobenzoyl)amino]benzyl}-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

5 **[0218]** In the same manner as in Example 9, the title compound (300 mg) was obtained as a white solid using the compound (501 mg) obtained in Example 7 and 2-chlorobenzoyl chloride (140  $\mu$ L).  $^1\text{H-NMR}$ (400MHz, DMSO- $d_6$ ) $\delta$ 0.86(6H, t, J = 7.2Hz), 2.84-2.95(2H, m), 3.07-3.24(4H, m), 3.85(1H, t, J = 7.2Hz), 7.03(2H, d, J = 8.5Hz), 7.44-7.54(4H, m), 7.56-7.60(2H, m), 7.68-7.79(3H, m), 8.06(1H, d, J = 8.0Hz), 8.13(1H, d, J = 8.0Hz), 8.22(1H, d, J = 8.0Hz), 8.57(1H, d, J = 1.0Hz), 10.42(1H, s), 12.33(1H, brs). MS: 592(M+H) $^+$ .

10 Example 37 Synthesis of 2-{4-[(3-chlorobenzoyl)amino]benzyl}-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

15 **[0219]** In the same manner as in Example 9, the title compound (461 mg) was obtained as a white solid using the compound (503 mg) obtained in Example 7 and 3-chlorobenzoyl chloride (142  $\mu$ L).  $^1\text{H-NMR}$ (400MHz, DMSO- $d_6$ ) $\delta$ 0.86(6H, t, J = 7.2Hz), 2.91(2H, dd, J = 7.2, 2.5Hz), 3.06-3.23(4H, m), 3.86(1H, t, J = 7.2Hz), 7.05(2H, d, J = 8.5Hz), 7.52(2H, d, J = 8.4Hz), 7.54-7.61(1H, m), 7.65-7.76(3H, m), 7.77(1H, dd, J = 8.6, 1.6Hz), 7.91(1H, d, J = 7.8Hz), 7.98-8.02(1H, m), 8.05(1H, d, J = 8.2Hz), 8.12(1H, d, J = 8.7Hz), 8.19(1H, d, J = 8.0Hz), 8.54(1H, s), 10.22(1H, s), 12.34(1H, brs). MS: 592(M+H) $^+$ .

20 Example 38 Synthesis of 2-{4-[(3, 4-dichlorobenzoyl)amino]benzyl}-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

25 **[0220]** In the same manner as in Example 9, the title compound (401 mg) was obtained as a white solid using the compound (503 mg) obtained in Example 7 and 3, 4-dichlorobenzoyl chloride (243 mg).  $^1\text{H-NMR}$ (400MHz, DMSO- $d_6$ ) $\delta$ 0.86(6H, t, J = 7.2Hz)2.91(2H, dd, J = 7.0, 2.1Hz), 3.05-3.26(4H, m), 3.87(1H, t, J = 7.2Hz), 7.05(2H, d, J = 8.4Hz), 7.50(2H, d, J = 8.5Hz), 7.65-7.76(2H, m), 7.77(1H, dd, 8.7, 1.7Hz), 7.83(1H, d, J = 8.4Hz), 7.94(1H, dd, J = 8.5, 2.2Hz), 8.05(1H, d, J = 8.0Hz), 8.12(1H, d, J = 8.8Hz), 8.18-8.24(2H, m), 8.54(1H, s), 10.27(1H, s), 12.31(1H, brs). MS: 626(M+H) $^+$ .

30 Example 39 Synthesis of N, N-diethyl-2-{4-[(5-fluoro-2-methoxybenzoyl)amino]benzyl}-N'-(2-naphthylsulfonyl)malonamide

35 **[0221]** In the same manner as in Example 1 (4), a crude product was obtained using the compound (530 mg) obtained in Example 7 and 5-fluoro-2-methoxybenzoic acid (298 mg). This was purified by silica gel column chromatography to give the title compound (398 mg) as a white solid.  $^1\text{H-NMR}$ (400MHz, DMSO- $d_6$ ) $\delta$ 0.87(6H, t, J = 7.2Hz), 2.41-2.95(2H, m), 3.07-3.22(4H, m), 3.85(1H, t, J = 7.2Hz), 3.90(3H, s), 7.03(2H, d, J = 7.2Hz), 7.14-7.25(1H, m), 7.30-7.40(1H, m), 7.40-7.53(3H, m), 7.62-7.80(3H, m), 8.05(1H, d, J = 8.0Hz), 8.12(1H, d, J = 8.0Hz), 8.20(1H, d, J = 8.0Hz), 8.55(1H, s), 10.07(1H, s), 12.30(1H, brs). MS: 606(M+H) $^+$ .

40 Example 40 Synthesis of N, N-diethyl-N'-(2-naphthylsulfonyl)-2-{4-[(2-trifluoromethylbenzoyl)amino]benzyl}malonamide

45 **[0222]** In the same manner as in Example 9, the title compound (322 mg) was obtained as a white solid using the compound (292 mg) obtained in Example 7 and 2-trifluoromethylbenzoyl chloride (94  $\mu$ L).  $^1\text{H-NMR}$ (400MHz, DMSO- $d_6$ ) $\delta$ 0.86(3H, t, J = 7.2Hz), 0.86(3H, t, J = 7.2), 2.85-2.95(2H, m), 3.05-3.24(4H, m), 3.86(1H, t, J = 7.2Hz), 7.04(2H, d, J = 8.4Hz), 7.48(2H, d, J = 8.4Hz), 7.60-7.92(7H, m), 8.06(1H, d, J = 8.4Hz), 8.12(1H, d, J = 8.4Hz), 8.20(1H, d, J = 8.4Hz), 8.57(1H, s), 10.11(1H, s). MS: 626(M+H) $^+$ .

Example 41 Synthesis of 2-{4-[(3-cyanobenzoyl)amino]benzyl}-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

50 **[0223]** In the same manner as in Example 13, the reaction mixture was obtained using hydrochloride salt (250 mg) of the compound obtained in Example 7 and 3-cyanobenzoic acid (80 mg). Dilute hydrochloric acid was added, and the mixture was extracted with ethyl acetate. The organic layer was concentrated under reduced pressure to give the title compound (249 mg) as a white solid.  $^1\text{H-NMR}$ (400MHz, DMSO- $d_6$ ) $\delta$ 0.86(6H, t, J = 7.2Hz), 2.81-2.95(2H, m), 3.04-3.28(4H, m), 3.84(1H, t, J = 7.2Hz), 7.07(2H, d, J = 8.4Hz), 7.53(2H, d, J = 8.4Hz), 7.60-7.83(4H, m), 7.98-8.15(3H, m), 8.19(1H, d, J = 8.4Hz), 8.25(1H, d, J = 8.4Hz), 8.40(1H, s), 8.52(1H, s), 10.30(1H, s), 12.35(1H, brs). MS: 583(M+H) $^+$ .

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Example 42 Synthesis of N, N-diethyl-N'-(2-naphthylsulfonyl)-2-{4-[(2-nitrobenzoyl)amino]benzyl}malonamide

**[0224]** In the same manner as in Example 13, the reaction mixture was obtained using hydrochloride salt (2.01 g) of the compound obtained in Example 7 and 2-nitrobenzoic acid (695 mg). Dilute hydrochloric acid was added, and the mixture was extracted with ethyl acetate. The organic layer was concentrated under reduced pressure to give the title compound (1.20 g) as a white solid.

<sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.86(6H, t, J = 7.2Hz), 2.81-2.99(2H, m), 3.05-3.27(4H, m), 3.86(1H, t, J = 7.2Hz), 7.04(2H, d, J = 8.4Hz), 7.45(2H, d, J = 8.4Hz), 7.67-7.92(6H, m), 8.07(1H, d, J = 8.0Hz), 8.13(1H, d, J = 8.4Hz), 8.15(1H, d, J = 8.4Hz), 8.22(1H, d, J = 8.4Hz), 8.57(1H, s), 10.57(1H, s), 12.32(1H, brs).

MS: 603(M+H)<sup>+</sup>.

Example 43 Synthesis of 2-{4-[(2-aminobenzoyl)amino]benzyl}-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

**[0225]** To a mixture of the compound (538 mg) obtained in Example 42 in ethanol (10 mL)/ethyl acetate (10 mL) was added 10% palladium/carbon (100 mg), and the mixture was stirred under hydrogen atmosphere at room temperature for 11 hr. Insoluble material was removed by filtration, and the filtrate was concentrated under reduced pressure to give the title compound (456 mg) as a brown powder.

<sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.87(6H, t, J = 7.2Hz), 2.88-2.93(2H, m), 3.05-3.23(4H, m), 3.86(1H, t, J = 7.2Hz), 6.57(1H, t, J = 7.2Hz), 6.76(1H, d, J = 8.4Hz), 7.00(2H, d, J = 8.4Hz), 7.46(1H, t, J = 7.2Hz), 7.47(2H, d, J = 8.4Hz), 7.61(1H, d, J = 7.6Hz), 7.65-7.88(3H, m), 8.06(1H, d, J = 8.0Hz), 8.13(1H, d, J = 8.8Hz), 8.20(H, d, J = 8.0H), 8.55(1H, s), 9.88(1H, s). MS: 573(M+H)<sup>+</sup>.

Example 44 Synthesis of 2-{4-[(4-aminobenzoyl)amino]benzyl}-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

(1) N, N-diethyl-N'-(2-naphthylsulfonyl)-2-{4-[(4-nitrobenzoyl)amino]benzyl}malonamide

**[0226]** In the same manner as in Example 13, the reaction mixture was obtained using hydrochloride salt (491 mg) of the compound obtained in Example 7 and 4-nitrobenzoic acid (197 mg). Dilute hydrochloric acid was added, and the mixture was extracted with ethyl acetate. The organic layer was concentrated under reduced pressure to give the title compound (462 mg) as a white solid.

(2) 2-{4-[(4-aminobenzoyl)amino]benzyl}-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

**[0227]** In the same manner as in Example 43, the title compound (284 mg) was obtained as a pale-yellow powder using the above-mentioned compound (462 mg).

<sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.86(3H, t, J = 7.2Hz), 0.86(3H, t, J = 7.2Hz), 2.80-2.97(2H, m), 3.05-3.25(4H, m), 3.85(1H, t, J = 7.2Hz), 6.60(2H, d, J = 8.0Hz), 6.99(2H, d, J = 8.0Hz), 7.52(2H, d, J = 8.0Hz), 7.62-7.81(5H, m), 8.05(1H, d, J = 8.0Hz), 8.12(1H, d, J = 8.4Hz), 8.20(1H, d, J = 8.0Hz), 8.54(1H, s), 9.64(1H, s).

MS: 573(M+H)<sup>+</sup>.

Example 45 Synthesis of 2-{4-[(3-aminobenzoyl)amino]benzyl}-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

(1) N, N-diethyl-N'-(2-naphthylsulfonyl)-2-{4-[(3-nitrobenzoyl)amino]benzyl}malonamide

**[0228]** In the same manner as in Example 13, the reaction mixture was obtained using hydrochloride salt (500 mg) of the compound obtained in Example 7 and 3-nitrobenzoic acid (195 mg). Dilute hydrochloric acid was added, and the mixture was extracted with ethyl acetate. The organic layer was concentrated under reduced pressure to give the title compound (444 mg) as a white solid.

(2) 2-{4-[(3-aminobenzoyl)amino]benzyl}-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

**[0229]** In the same manner as in Example 43, a crude product was obtained using the above-mentioned compound (444 mg). This was purified by silica gel column chromatography to give the title compound (293 mg) as a pale-yellow powder.

<sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.86(6H, t, J = 7.2), 2.83-2.97(2H, m), 3.04-3.25(4H, m), 3.86(1H, t, J = 7.2Hz), 6.75(1H, d, J = 8.0Hz), 7.01(2H, d, J = 8.4Hz), 7.04-7.21(3H, m), 7.54(2H, d, J = 8.4Hz), 7.62-7.78(3H, m), 8.05(2H, d, J = 8.4Hz), 8.12(1H, d, J = 8.8Hz), 8.20(1H, d, J = 8.4Hz), 8.54(1H, s), 9.95(1H, s).

MS: 573(M+H)<sup>+</sup>.

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Example 46 Synthesis of 2-{4-[(2-amino-3-methylbenzoyl)amino]benzyl}-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

5 **[0230]** In the same manner as in Example 13, the reaction mixture was obtained using hydrochloride salt (187 mg) of the compound obtained in Example 7 and 3-methylantranilic acid (61 mg). Dilute hydrochloric acid was added, and the mixture was extracted with ethyl acetate. The organic layer was concentrated under reduced pressure to give the title compound (77 mg) as a white solid.

<sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.81-0.90(6H, m), 2.12(3H, s), 2.83-2.95(2H, m), 3.05-3.21(4H, m), 3.81-3.89(1H, m), 6.10(2H, brs), 6.52-6.58(1H, m), 7.01(2H, d, J = 8.2Hz), 7.08-7.14(1H, m), 7.46-7.50(3H, m), 7.64-7.78(3H, m), 8.05(1H, d, J = 8.1Hz), 8.13(1H, d, J = 8.7Hz), 8.21(1H, d, J = 8.1Hz), 8.54(1H, s), 9.89(1H, s), 12.24(1H, brs).  
10 MS:587(M+H)<sup>+</sup>.

Example 47 Synthesis of 2-{4-[(2-amino-5-chlorobenzoyl)amino]benzyl}-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

15 **[0231]** In the same manner as in Example 13, the title compound (45 mg) was obtained as a white solid using hydrochloride salt (187 mg) of the compound obtained in Example 7 and 5-chloroantranilic acid (69 mg).

<sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.87(6H, t, d = 7.0Hz), 2.90(2H, d, J = 7.0Hz), 3.06-3.22(4H, m), 3.82-3.87(1H, m), 6.45(2H, brs), 6.78(1H, d, J = 8.8Hz), 7.02(2H, d, J = 8.4Hz), 7.21-7.24(1H, m), 7.44(2H, d, J = 8.4Hz), 7.66-7.79(4H, m), 8.05(1H, d, J = 8.0Hz), 8.12(1H, d, J = 8.7Hz), 8.20(1H, d, J = 8.0Hz), 8.54(1H, s), 9.97(1H, s), 12.22(1H, brs).  
20 MS: 607(M+H)<sup>+</sup>.

Example 48 Synthesis of 2-{4-[(2-amino-5-fluorobenzoyl)amino]benzyl}-N,N-diethyl-N'-(2-naphthylsulfonyl)malonamide

25 **[0232]** In the same manner as in Example 13, the title compound (51 mg) was obtained as a white solid using hydrochloride salt (187 mg) of the compound obtained in Example 7 and 5-fluoroantranilic acid (63 mg).

<sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.8(6H, t, J = 7.0Hz), 2.85-2.92 (2H, m), 3.07-3.25(4H, m), 3.85(1H, t, J = 7.1Hz), 6.21(2H, brs), 6.77(1H, dd, J = 8.9Hz, 5.0Hz), 7.02(2H, d, J = 8.4Hz), 7.09-7.14(1H, m), 7.44-7.50(3H, m), 7.68-7.79(3H, m), 8.05(1H, d, J = 8.0Hz), 8.13(1H, d, J = 8.7Hz), 8.20(1H, d, J = 8.0Hz), 8.55(1H, s), 9.91(1H, s), 12.21(H, brs).  
30 MS: 591(M+H)<sup>+</sup>.

Example 49 Synthesis of 2-{4-[(2-amino-3-chlorobenzoyl)amino]benzyl}-N,N-diethyl-N'-(2-naphthylsulfonyl)malonamide

35 **[0233]** In the same manner as in Example 13, the reaction mixture was obtained using hydrochloride salt (187 mg) of the compound obtained in Example 7 and 3-chloroantranilic acid (69 mg). Dilute hydrochloric acid was added, and the mixture was extracted with ethyl acetate. The organic layer was concentrated under reduced pressure to give the title compound (182 mg) as a white solid.

<sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.80-0.91(6H, m), 2.90(2H, d, J = 7.4Hz), 3.09-3.28(4H, m), 3.79-3.88(1H, m), 6.39(2H, brs), 6.68(1H, t, J = 7.8Hz), 7.02(2H, d, J = 8.4Hz), 7.44-7.47(3H, m), 7.58-7.80(4H, m), 8.05(1H, d, J = 8.0Hz), 8.11(1H, d, J = 8.7Hz), 8.19(1H, d, J = 8.0Hz), 8.53(1H, s), 10.07(1H, s), 12.27(1H, brs).  
40 MS: 607(M+H)<sup>+</sup>.

Example 50 Synthesis of 2-{4-[(2-amino-5-methylbenzoyl)amino]benzyl}-N,N-diethyl-N'-(2-naphthylsulfonyl)malonamide

45 **[0234]** In the same manner as in Example 13, the title compound (74 mg) was obtained as a white solid using hydrochloride salt (300 mg) of the compound obtained in Example 7 and 5-methylantranilic acid (111 mg).

<sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.87(6H, t, J = 7.0Hz), 2.22(3H, s), 2.85-2.94(2H, m), 3.07-3.28(4H, m), 3.81-3.89(1H, m), 6.08(2H, brs), 6.68(2H, d, J = 8.4Hz), 6.98-7.08(3H, m), 7.42(1H, s), 7.46(2H, d, J = 8.4Hz), 7.64-7.80(3H, m), 8.05(1H, d, J = 8.0Hz), 8.13(1H, d, J = 8.8Hz), 8.20(1H, d, J = 8.0Hz), 8.54(1H, s), 9.85(1H, s), 12.23(1H, brs).  
50 MS: 587(M+H)<sup>+</sup>,

Example 51 Synthesis of 2-{4-[(2-amino-4-chlorobenzoyl)amino]benzyl}-N,N-diethyl-N'-(2-naphthylsulfonyl)malonamide

55 **[0235]** In the same manner as in Example 13, the title compound (86 mg) was obtained as a white solid using hydrochloride salt (300 mg) of the compound obtained in Example 7 and 4-chloroantranilic acid (126 mg).

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<sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.80-0.91(6H, m), 2.85-2.92(2H, m), 3.07-3.25(4H, m), 3.79-3.87(1H, m), 6.56-6.64(1H, m), 6.60(2H, brs), 6.82(1H, d, J = 1.8Hz), 7.01(2H, d, J = 8.5Hz), 7.44(2H, d, J = 8.5Hz), 7.62-7.79(4H, m), 8.05(1H, d, J = 8.0Hz), 8.12(1H, d, J = 8.2Hz), 8.20(1H, d, J = 8.0Hz), 8.53(1H, s), 9.92(1H, s), 12.30(1H, brs).  
MS: 607(M+H)<sup>+</sup>.

5

Example 52 Synthesis of 2-{4-[(2-amino-4-fluorobenzoyl)amino]benzyl}-N,N-diethyl-N'-(2-naphthylsulfonyl)malonamide

**[0236]** In the same manner as in Example 13, the title compound (87 mg) was obtained as a white solid using hydrochloride salt (300 mg) of the compound obtained in Example 7 and 4-fluoroanthranilic acid (114 mg).

10 <sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.88(6H, t, J = 7.0Hz), 2.85-2.92(2H, m), 3.05-3.24(4H, m), 3.84(1H, t, J = 6.9Hz), 6.40(1H, td, J = 8.9, 2.4Hz), 6.52(1H, dd, J = 11.8, 2.4Hz), 6.67(2H, brs), 7.01(2H, d, J = 8.4Hz), 7.44(2H, d, J = 8.4Hz), 7.65-7.80(3H, m), 8.05(1H, d, J = 8.0Hz), 8.12(1H, d, J = 8.7Hz), 8.20(1H, d, J = 8.0Hz), 8.54(1H, s), 9.86(1H, s), 12.29(1H, brs).  
MS: 591(M+H)<sup>+</sup>.

15 Example 53 Synthesis of 2-{4-[(2-amino-3, 5-dichlorobenzoyl)amino]benzyl}-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

**[0237]** In the same manner as in Example 13, the reaction mixture was obtained using hydrochloride salt (300 mg) of the compound obtained in Example 7 and 3, 5-dichloroanthranilic acid (151 mg). Dilute hydrochloric acid was added, and the mixture was extracted with ethyl acetate. The organic layer was concentrated under reduced pressure to give the title compound (141 mg) as a white solid.

20 <sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.87(6H, t, J = 7.0Hz), 2.90(2H, d, J = 7.1Hz), 3.07-3.25(4H, m), 3.85(1H, t, J = 7.1Hz), 6.51(2H, brs), 7.03(2H, d, J = 8.4Hz), 7.43(2H, d, J = 8.4Hz), 7.58(1H, d, J = 2.2Hz), 7.68-7.80(4H, m), 8.05(1H, d, J = 8.0Hz), 8.12(1H, d, J = 8.7Hz), 8.20(1H, d, J = 8.0Hz), 8.54(1H, s), 10.16(1H, s), 12.32(1H, brs).

25 MS: 641(M+H)<sup>+</sup>.

Example 54 Synthesis of 2-{4-[(2-amino-4, 5-difluorobenzoyl)amino]benzyl}-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

**[0238]** In the same manner as in Example 13, the title compound (79 mg) was obtained as a white solid using hydrochloride salt (300 mg) of the compound obtained in Example 7 and 4, 5-difluoroanthranilic acid (127 mg).

30 <sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.86(6H, t, J = 7.0Hz), 2.85-2.93(2H, m), 3.07-3.24(4H, m), 3.81-3.89(1H, m), 6.55(2H, brs), 6.72(1H, dd, J = 13.2, 7.3Hz), 7.02(2H, d, J = 8.4Hz), 7.43(2H, d, J = 8.4Hz), 7.63-7.80(4H, m), 8.05(1H, d, J = 8.0Hz), 8.12(1H, d, J = 8.8Hz), 8.20(1H, d, J = 8.0Hz), 8.54(1H, s), 9.86(1H, s), 12.32(1H, brs).

35 MS: 609(M+H)<sup>+</sup>.

Example 55 Synthesis of 2-{4-[(2-amino-6-fluorobenzoyl)amino]benzyl}-N,N-diethyl-N'-(2-naphthylsulfonyl)malonamide

**[0239]** In the same manner as in Example 13, the title compound (94 mg) was obtained as a white solid using hydrochloride salt (338 mg) of the compound obtained in Example 7 and 6-fluoroanthranilic acid (120 mg).

40 <sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.87(6H, t, J = 6.9Hz), 2.85-2.94(2H, m), 3.05-3.24(4H, m), 3.85(1H, t, J = 7.0Hz), 5.76(2H, brs), 6.40(1H, t, J = 9.0Hz), 6.57(1H, d, J = 8.2Hz), 7.02(2H, d, J = 8.2Hz), 7.08-7.16(1H, m), 7.49(2H, d, J = 8.2Hz), 7.64-7.80(3H, m), 8.06(1H, d, J = 8.0Hz), 8.12(1H, d, J = 8.7Hz), 8.20(1H, d, J = 8.0Hz), 8.55(1H, s), 10.16(1H, s), 12.03(1H, brs).

45 MS: 591(M+H)<sup>+</sup>.

Example 56 Synthesis of N, N-diethyl-2-{4-[(2-methylaminobenzoyl)amino]benzyl}-N'-(2-naphthylsulfonyl)malonamide

**[0240]** In the same manner as in Example 13, the title compound (100 mg) was obtained as a white solid using hydrochloride salt (242 mg) of the compound obtained in Example 7 and N-methylantranilic acid (83 mg).

50 <sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.86(6H, t, J = 7.2Hz), 2.81(3H, s), 2.90(2H, d, J = 6.0Hz), 3.02-3.27(4H, m), 3.85(1H, t, J = 7.2Hz), 6.59-6.74(2H, m), 7.02(2H, d, J = 8.4Hz), 7.24-7.42(2H, m), 7.47(2H, d, J = 8.4Hz), 7.60-7.83(3H, m), 8.05(1H, d, J = 8.0Hz), 8.13(1H, d, J = 8.8Hz), 8.20(1H, d, J = 8.0Hz), 8.54(1H, s), 9.95(1H, s), 12.32(1H, brs).

55 MS: 587(M+H)<sup>+</sup>.

Example 57 Synthesis of 2-{4-[(2-acetylaminobenzoyl)amino]benzyl}-N,N-diethyl-N'-(2-naphthylsulfonyl)malonamide

**[0241]** In the same manner as in Example 13, the title compound (103 mg) was obtained as a white solid using

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hydrochloride salt (239 mg) of the compound obtained in Example 7 and N-acetylanthranilic acid (81 mg).

<sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.86(3H, t, J = 7.2Hz), 0.88(3H, t, J = 7.2Hz), 2.05(3H, s), 2.91-3.28(6H, m), 3.57(1H, m), 7.17(2H, d, J = 8.4Hz), 7.19-7.31(2H, m), 7.43-7.61(3H, m), 7.65(1H, d, J = 8.0Hz), 7.74-8.06(6H, m), 8.09(1H, d, J = 8.0Hz), 8.29(1H, brs).

MS: 615(M+H)<sup>+</sup>.

Example 58 Synthesis of 2-{4-[(2-acetylamino-5-fluorobenzoyl)amino]benzyl}-N,N-diethyl-N'-(2-naphthylsulfonyl)malonamide

**[0242]** In the same manner as in Example 13, the title compound (94 mg) was obtained as a white solid using hydrochloride salt (227 mg) of the compound obtained in Example 7 and N-acetyl-5-fluoroanthranilic acid (98 mg).

<sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.86(3H, t, J = 7.2Hz), 0.88(3H, t, J = 7.2Hz), 2.04(3H, s), 2.90-3.28(6H, m), 3.59(1H, m), 7.18(2H, d, J = 8.0Hz), 7.20-7.32(2H, m), 7.49-7.66(2H, m), 7.66-7.84(4H, m), 7.86-8.09(3H, m), 8.32(1H, s).

MS: 633(M+H)<sup>+</sup>.

Example 59 Synthesis of N, N-diethyl-N'-(2-naphthylsulfonyl)-2-[4-(nicotinoylamino)benzyl]malonamide hydrochloride

**[0243]** In the same manner as in Example 9, a white solid was obtained using the compound (310 mg) obtained in Example 7 and nicotinic acid chloride hydrochloride (365 mg). This was dissolved in ethanol (3 ml), 4 mol/L hydrochloric acid-ethyl acetate, (200 μL) was added, and the precipitate was collected by filtration to give the title compound (255 mg) as a white solid.

<sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.86(6H, t, J = 7.2Hz), 2.85-2.94(2H, m), -3.05-3.24(4H, m), 3.90(1H, t, J = 7.2Hz), 7.08(2H, d, J = 8.4Hz), 7.54(2H, d, J = 8.4Hz), 7.64-7.80(4H, m), 8.06(1H, d, J = 8.0Hz), 8.13(1H, d, J = 8.8Hz), 8.21(1H, d, J = 8.0Hz), 8.50(1H, d, J = 8.0Hz), 8.55(1H, d, J = 1.2Hz), 8.85(1H, dd, J = 4.4, 1.2Hz), 9.20(1H, d, J = 2.0Hz), 10.47(1H, s), 12.34(1H, brs).

MS: 559(M+H)<sup>+</sup>.

Example 60 Synthesis of N, N-diethyl-N'-(2-naphthylsulfonyl)-2-[4-[(2-pyridylcarbonyl)amino]benzyl]malonamide hydrochloride

**[0244]** In the same manner as in Example 9, the reaction mixture was obtained using the compound (340 mg) obtained in Example 7 and picolinic acid chloride hydrochloride (400 mg). The reaction mixture was adjusted to pH = 1-2 by the addition of dilute hydrochloric acid and extracted with ethyl acetate (50 mL×2). After concentration under reduced pressure, the residue was dissolved in ethanol (3 ml), 4 mol/L hydrochloric acid-ethyl acetate (300 μL) was added, and the precipitate was collected by filtration to give the title compound (228 mg) as a pale-yellow solid.

<sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.87(6H, t, J = 7.1Hz), 2.91(2H, d, J = 7.2Hz), 3.10-3.24(4H, m), 3.89(1H, t, J = 7.2Hz), 7.03(2H, d, J = 8.4Hz), 7.62(2H, d, J = 8.4Hz), 7.64-7.78(4H, m), 8.04-8.12(3H, m), 8.15(1H, d, J = 9.6Hz), 8.19(1H, d, J = 8.7Hz), 8.53(1H, s), 8.76(1H, d, J = 4.6Hz), 10.46(1H, s), 12.31(1H, brs).

MS: 559(M+H)<sup>+</sup>.

Example 61 Synthesis of N,N-diethyl-2-[4-(isonicotinoylamino)benzyl]-N'-(2-naphthylsulfonyl)malonamide hydrochloride

**[0245]** In the same manner as in Example 9, the title compound (16 mg) as a pale-brown solid was obtained using the compound (299 mg) obtained in Example 7 and isonicotinic acid chloride (128 mg).

<sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.80-0.95(6H, m), 2.85-2.96(2H, m), 3.07-3.27(4H, m), 3.85(1H, m), 7.01(2H, d, J = 7.6Hz), 7.50-7.63(3H, m), 7.64-7.88(4H, m), 8.06(1H, d, J = 8.1Hz), 8.13(1H, d, J = 8.12Hz), 8.21(1H, d, J = 8.1Hz), 8.55(2H, s), 10.42(1H, s), 12.40(1H, brs).

MS: 573(M+H)<sup>+</sup>.

Example 62 Synthesis of N, N-diethyl-N'-(2-naphthylsulfonyl)-2-[4-(pyrazinylcarbonylamino)benzyl]malonamide

**[0246]** In the same manner as in Example 13, the reaction mixture was obtained using hydrochloride salt (245 mg) of the compound obtained in Example 7 and pyrazinecarboxylic acid (66 mg). Dilute hydrochloric acid was added, and the mixture was extracted with ethyl acetate. The organic layer was concentrated under reduced pressure to give the title compound (213 mg) as a white solid.

<sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.80-0.90(6H, m), 2.91(2H, d, J = 7.2Hz), 3.10-3.25(4H, m), 3.87(1H, t, J = 7.2Hz), 7.04(2H, d, J = 8.4Hz), 7.62(2H, d, J = 8.4Hz), 7.66-7.78(3H, m), 8.04(1H, d, J = 8.0Hz), 8.12(1H, d, J = 8.7Hz), 8.19(1H, d, J = 8.0Hz), 8.53(1H, s), 8.82-8.83(1H, m), 8.95(1H, d, J = 2.4Hz), 9.30(1H, d, J = 1.2Hz), 10.57(1H, s), 12.31(1H, brs).

MS: 560(M+H)<sup>+</sup>.

Example 63 Synthesis of N,N-diethyl-2-{4-[(5-methyl-2-pyrazinylcarbonyl)amino]benzyl}-N'-(2-naphthylsulfonyl)malonamide

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**[0247]** In the same manner as in Example 13, the reaction mixture was obtained using hydrochloride salt (245 mg) of the compound obtained in Example 7 and 5-methyl-2-pyrazinecarboxylic acid (73 mg). Dilute hydrochloric acid was added, and the mixture was extracted with ethyl acetate. The organic layer was concentrated under reduced pressure to give the title compound (211 mg) as a white solid.

10 <sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.87(6H, t, J = 7.0Hz), 2.65(3H, s), 2.90(2H, d, J = 7.2Hz), 3.10-3.25(4H, m), 3.87(1H, t, J = 7.2Hz), 7.03(2H, d, J = 8.4Hz), 7.61(2H, d, J = 8.4Hz), 7.66-7.78(3H, m), 8.04(1H, d, J = 8.0Hz), 8.12(1H, d, J = 8.7Hz), 8.19(1H, d, J = 8.0Hz), 8.53(1H, s), 8.71(1H, s), 9.17(1H, d, J = 1.1Hz), 10.48(1H, s), 12.31(1H, brs).  
MS: 574(M+H)<sup>+</sup>.

15 Example 64 Synthesis of N, N-diethyl-N'-(2-naphthylsulfonyl)-2-{4-[(5-pyrimidinylcarbonyl)amino]benzyl}malonamide

**[0248]** In the same manner as in Example 13, the reaction mixture was obtained using hydrochloride salt (245 mg) of the compound obtained in Example 7 and 5-pyrimidinecarboxylic acid (66 mg). Dilute hydrochloric acid was added, and the mixture was extracted with ethyl acetate. The organic layer was concentrated under reduced pressure to give the title compound (230 mg) as a white solid.

20 <sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.80-0.90(6H, m), 2.85-2.96(2H, m), 3.07-3.25(4H, m), 3.86(1H, t, J = 7.2Hz), 7.08(2H, d, J = 8.4Hz), 7.52(2H, d, J = 8.4Hz), 7.66-7.79(3H, m), 8.05(1H, d, J = 8.0Hz), 8.12(1H, d, J = 8.8Hz), 8.20(1H, d, J = 8.0Hz), 8.54(1H, s), 9.23(2H, s), 9.37(1H, s), 10.97(1H, s), 12.31(1H, brs).  
MS: 560(M+H)<sup>+</sup>.

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Example 65 Synthesis of 2-{4-[(3-amino-2-pyrazinylcarbonyl)amino]benzyl}-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

**[0249]** In the same manner as in Example 13, the reaction mixture was obtained using hydrochloride salt (500 mg) of the compound obtained in Example 7 and 3-amino-2-pyrazinecarboxylic acid (142 mg). Dilute hydrochloric acid was added, and the precipitate was collected by filtration to give the title compound (519 mg) as a white solid.

30 <sup>1</sup>H-NMR(300MHz, DMSO-d<sub>6</sub>)δ0.87(6H, t, J = 7.2Hz), 2.99(2H, d, J = 7.2Hz), 3.08-3.27(4H, m), 3.83(1H, t, J = 7.2Hz), 7.01(2H, d, J = 8.7Hz), 7.54(2H, d, J = 8.7Hz), 7.58-7.78(5H, m), 7.94(1H, d, J = 2.7Hz), 8.05(1H, d, J = 8.1Hz), 8.13(1H, d, J = 8.7Hz), 8.20(1H, d, J = 8.1Hz), 8.30(1H, d, J = 2.4Hz), 8.53(1H, s), 10.34(1H, s), 12.31(1H, brs).

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Example 66 Synthesis of N, N-diethyl-2-{4-[(1-ethyl-1H-pyrazolyl-4-carbonyl)amino]benzyl}-N'-(2-naphthylsulfonyl)malonamide

**[0250]** In the same manner as in Example 13, the reaction mixture was obtained using hydrochloride salt (530 mg) of the compound obtained in Example 7 and 1-ethyl-1H-pyrazole-4-carboxylic acid (151 mg). Dilute hydrochloric acid was added, and the precipitate was collected by filtration to give the title compound (273 mg) as a white solid.

40 <sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.80-0.90(6H, m), 1.41(3H, t, J = 7.2Hz), 2.84-2.94(2H, m), 3.06-3.26(4H, m), 3.80-3.87(1H, m), 4.19(2H, q, J = 7.2Hz), 7.02(2H, d, J = 8.4Hz), 7.47(2H, d, J = 8.4Hz), 7.66-7.78(3H, m), 8.02(1H, s), 8.05(1H, d, J = 8.0Hz), 8.12(1H, d, J = 8.8Hz), 8.20(1H, d, J = 8.0Hz), 8.35(1H, s), 8.54(1H, s), 9.70(1H, s), 12.33(1H, brs). MS: 576(M+H)<sup>+</sup>.

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Example 67 Synthesis of N, N-diethyl-2-{4-[(5-methyl-1H-pyrazolyl-3-carbonyl)amino]benzyl}-N'-(2-naphthylsulfonyl)malonamide

**[0251]** In the same manner as in Example 13, the reaction mixture was obtained using hydrochloride salt (280 mg) of the compound obtained in Example 7 and 5-methyl-1H-pyrazole-3-carboxylic acid (80 mg). Dilute hydrochloric acid was added, and the mixture was extracted with ethyl acetate. The organic layer was concentrated under reduced pressure to give the title compound (205 mg) as a white solid.

50 <sup>1</sup>H-NMR(300MHz, DMSO-d<sub>6</sub>)δ0.84(6H, t, J = 6.9Hz), 2.28(3H, s), 2.86(2H, d, J = 7.2Hz), 3.05-3.25(4H, m), 3.84(1H, t, J = 7.2Hz), 6.51(1H, brs), 6.97(2H, d, J = 8.4Hz), 7.53(2H, d, J = 8.4Hz), 7.65-7.75(3H, m), 8.04(1H, d, J = 7.8Hz), 8.11(1H, d, J = 8.7Hz), 8.19(1H, d, J = 7.8Hz), 8.52(1H, s), 9.82(1H, s), 12.33(1H, brs), 13.06(1H, brs).  
MS: 562 (M+H)<sup>+</sup>.

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Example 68 Synthesis of N, N-diethyl-2-{4-[(3-methyl-4-isoxazolylcarbonyl)amino]benzyl}-N'-(2-naphthylsulfonyl)malonamide

5 **[0252]** In the same manner as in Example 13, the title compound (328 mg) was obtained as a white solid using the compound (493 mg) obtained in Example 7 and 3-methyl-4-isoxazole carboxylic acid (161 mg).

<sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.84(3H, t, J = 7.2Hz), 0.86(3H, t, J = 7.2Hz), 2.69(3H, s), 2.82-2.93(2H, m), 3.05-3.28(4H, m), 3.85(1H, d, J = 7.2Hz), 7.05(2H, d, J = 8.8Hz), 7.44(2H, d, J = 8.4Hz), 7.60-7.82(3H, m), 8.05(1H, d, J = 8.0Hz), 8.12(1H, d, J = 8.8Hz), 8.20(1H, d, J = 8.0Hz), 9.05(1H, s), 9.91(1H, s), 12.31(1H, brs).

MS: 563(M+H)<sup>+</sup>.

10 Example 69 Synthesis of N, N-diethyl-2-{4-[(2-furoyl)amino]benzyl}-N'-(2-naphthylsulfonyl)malonamide

15 **[0253]** In the same manner as in Example 9, the title compound (270 mg) was obtained as a white solid using the compound (275 mg) obtained in Example 7 and 2-furoyl chloride (60 μL). <sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.86(6H, t, J = 7.2Hz), 2.81-2.93(2H, m), 3.02-3.25(4H, m), 3.86(1H, t, J = 7.2Hz), 7.04(2H, d, J = 8.4Hz), 7.47(2H, d, J = 8.4Hz), 7.62-7.90(6H, m), 7.93(1H, s), 8.06(1H, d, J = 8.4Hz), 8.12(1H, d, J = 8.4Hz), 8.20(1H, d, J = 8.4Hz), 8.57(1H, s), 10.45(1H, s).

MS: 548(M+H)<sup>+</sup>.

20 Example 70 Synthesis of N, N-diethyl-2-{4-[(5-methyl-2-furoyl)amino]benzyl}-N'-(2-naphthylsulfonyl)malonamide

25 **[0254]** In the same manner as in Example 13, the reaction mixture was obtained using hydrochloride salt (297 mg) of the compound obtained in Example 7 and 5-methyl-2-furancarboxylic acid (80 mg). Dilute hydrochloric acid was added, and the mixture was extracted with ethyl acetate. The organic layer was concentrated under reduced pressure to give the title compound (192 mg) as a white solid.

<sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.86(6H, t, J = 7.2Hz), 2.39(3H, s), 2.60-2.95(2H, m), 3.04-3.26(4H, m), 3.85(1H, t, J = 7.2Hz), 6.32(1H, d, J = 2.8Hz), 7.01(2H, d, J = 8.4Hz), 7.22(1H, d, J = 2.8Hz), 7.49(2H, d, J = 8.4Hz), 7.61-7.80(3H, m), 8.05(1H, d, J = 8.0Hz), 8.12(1H, d, J = 8.8Hz), 8.20(1H, d, J = 8.0Hz), 8.54(1H, s), 9.87(1H, s), 12.32(1H, brs).

MS: 562(M+H)<sup>+</sup>.

30 Example 71 Synthesis of N, N-diethyl-2-{4-[(3-methyl-2-furoyl)amino]benzyl}-N'-(2-naphthylsulfonyl)malonamide

35 **[0255]** In the same manner as in Example 13, the reaction mixture was obtained using hydrochloride salt (303 mg) of the compound obtained in Example 7 and 3-methyl-2-furancarboxylic acid (107 mg). Dilute hydrochloric acid was added, and the mixture was extracted with ethyl acetate. The organic layer was concentrated under reduced pressure to give the title compound (277 mg) as a white solid.

<sup>1</sup>H-NMR(300MHz, DMSO-d<sub>6</sub>)δ0.83(6H, t, J = 7.2Hz), 2.33(3H, s), 2.86(2H, d, J = 6.9Hz), 3.02-3.28(4H, m), 3.69-3.84(1H, m), 6.57(1H, s), 6.98(2H, d, J = 8.4Hz), 7.50(2H, d, J = 8.4Hz), 7.58-7.85(3H, m), 8.02(1H, d, J = 8.1Hz), 8.08(1H, d, J = 9.0Hz), 8.16(1H, d, J = 8.1Hz), 8.48(1H, s), 9.88(1H, s), 12.39(1H, brs).

MS: 562(M+H)<sup>+</sup>.

40 Example 72 Synthesis of N, N-diethyl-N'-(2-naphthylsulfonyl)-2-{4-[(5-nitro-2-furoyl)amino]benzyl}malonamide

45 **[0256]** In the same manner as in Example 13, the reaction mixture was obtained using hydrochloride salt (296 mg) of the compound obtained in Example 7 and 5-nitro-2-furancarboxylic acid (130 mg). Dilute hydrochloric acid was added, and the mixture was extracted with ethyl acetate. The organic layer was concentrated under reduced pressure to give the title compound (318 mg) as a white solid.

<sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.86(3H, t, J = 7.2Hz), 0.86(3H, t, J = 7.2Hz), 2.91(2H, d, J = 7.2Hz), 3.03-3.24(4H, m), 3.87(1H, t, J = 7.2Hz), 7.07(2H, d, J = 8.4Hz), 7.48(2H, d, J = 8.4Hz), 7.63(1H, d, J = 4.0Hz), 7.64-7.80(3H, m), 7.82(1H, d, J = 4.0Hz), 8.06(1H, d, J = 8.4Hz), 8.12(1H, d, J = 8.4Hz), 8.19(1H, d, J = 8.0Hz), 8.53(1H, s), 10.49(1H, s), 12.32(1H, brs).

MS: 593(M+H)<sup>+</sup>.

55 Example 73 Synthesis of 2-{4-[(5-bromo-2-furoyl)amino]benzyl}-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

**[0257]** In the same manner as in Example 13, the reaction mixture was obtained using hydrochloride salt (288 mg) of the compound obtained in Example 7 and 5-bromo-2-furancarboxylic acid (150 mg). Dilute hydrochloric acid was added, and the mixture was extracted with ethyl acetate. The organic layer was concentrated under reduced pressure to give

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the title compound (330 mg) as a white solid.

<sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.85(3H, t, J = 7.2Hz), 0.86(3H, t, J = 7.2Hz), 2.90(2H, d, J = 4.8Hz), 2.82-2.97(4H, m), 3.86(1H, t, J = 7.2Hz), 6.84(1H, d, J = 3.2Hz), 7.03(2H, d, J = 8.4Hz), 7.36(1H, d, J = 3.2Hz), 7.47(2H, d, J = 8.4Hz), 7.62-7.83(3H, m), 8.05(1H, d, J = 8.0Hz), 8.02(1H, d, J = 8.4Hz), 8.20(1H, d, J = 8.0Hz), 8.54(1H, s), 10.08(1H, s), 12.30(1H, brs).

MS: 626(M+H)<sup>+</sup>.

Example 74 Synthesis of N, N-diethyl-N'-2-{4-[(4, 5-dimethyl-2-furoyl)amino]benzyl}-(2-naphthylsulfonyl)malonamide

**[0258]** In the same manner as in Example 13, the reaction mixture was obtained using hydrochloride salt (308 mg) of the compound obtained in Example 7 and 4, 5-dimethyl-2-furancarboxylic acid (84 mg). Dilute hydrochloric acid was added, and the mixture was extracted with ethyl acetate. The organic layer was concentrated under reduced pressure to give the title compound (222 mg) as a white solid.

<sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.86(3H, t, J = 7.2Hz), 0.87(3H, t, J = 7.2Hz), 1.98(3H, s), 2.31(3H, s), 2.81-2.96(2H, m), 3.04-3.27(4H, m), 3.85(1H, t, J = 7.2Hz), 7.00(2H, d, J = 8.8Hz), 7.12(1H, s), 7.49(2H, d, J = 8.4Hz), 7.65-7.81(3H, m), 8.05(1H, d, J = 8.0Hz), 8.12(1H, d, J = 8.4Hz), 8.20(1H, d, J = 8.0Hz), 8.54(1H, s), 9.80(1H, s), 12.30(1H, brs).

MS: 576(M+H)<sup>+</sup>.

Example 75 Synthesis of N, N-diethyl-N'-(2-naphthylsulfonyl)-2-{4-[(2-thienoyl)amino]benzyl}malonamide

**[0259]** In the same manner as in Example 9, the title compound (296 mg) was obtained as a white solid using the compound (301 mg) obtained in Example 7 and thiophene-2-carbonyl chloride (71 μL).

<sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.85(3H, t, J = 7.2Hz), 0.86(3H, t, J = 7.2Hz), 2.81-2.96(2H, m), 3.03-3.25(4H, m), 3.88(1H, t, J = 7.2Hz), 7.05(2H, d, J = 8.4Hz), 7.19-7.57(1H, m), 7.48(2H, d, J = 8.4Hz), 7.60-7.92(3H, m), 7.95-8.07(2H, m), 8.12(1H, d, J = 8.4Hz), 8.20(1H, d, J = 8.4Hz), 8.55(1H, s), 8.66-8.25(1H, m), 10.12(1H, s).

MS: 564(M+H)<sup>+</sup>.

Example 76 Synthesis of N, N-diethyl-2-{4-[(5-methyl-2-thienoyl)amino]benzyl}-N'-(2-naphthylsulfonyl)malonamide

**[0260]** In the same manner as in Example 13, the reaction mixture was obtained using hydrochloride salt (245 mg) of the compound obtained in Example 7 and 5-methyl-2-thiophenecarboxylic acid (84 mg). Dilute hydrochloric acid was added, and the precipitate was collected by filtration to give the title compound (257 mg) as a white solid.

<sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.83-0.88(6H, m), 2.85-2.94(2H, m), 2.89(3H, s), 3.07-3.23(4H, m), 3.88(1H, t, J = 7.2Hz), 6.92(1H, d, J = 3.8Hz), 7.04(2H, d, J = 8.5Hz), 7.47(2H, d, J = 8.5Hz); 7.60-7.79(3H, m), 7.83(1H, d, J = 3.8Hz), 8.05(1H, d, J = 8.0Hz), 8.12(1H, d, J = 8.8Hz), 8.20(1H, d, J = 8.0Hz), 8.54(1H, d, J = 1.0Hz), 10.00(1H, s), 12.34(1H, brs).

MS: 578(M+H)<sup>+</sup>.

Example 77 Synthesis of 2-{4-[(5-chloro-2-thienoyl)amino]benzyl}-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

**[0261]** In the same manner as in Example 13, the reaction mixture was obtained using hydrochloride salt (245 mg) of the compound obtained in Example 7 and 5-chloro-2-thiophenecarboxylic acid (98 mg). Dilute hydrochloric acid was added, and the precipitate was collected by filtration to give the title compound (278 mg) as a white solid.

<sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.83-0.88(6H, m), 2.85-2.94(2H, m), 3.07-3.24(4H, m), 3.85(1H, t, J = 7.2Hz), 7.05(2H, d, J = 8.5Hz), 7.27(1H, d, J = 4.0Hz), 7.44(2H, d, J = 8.5Hz), 7.65-7.79(3H, m), 7.90(1H, d, J = 4.0Hz), 8.04(1H, d, J = 8.2Hz), 8.11(1H, d, J = 8.4Hz), 8.19(1H, d, J = 8.2Hz), 8.53(1H, s), 10.17(1H, s), 12.30(1H, brs).

MS: 598(M+H)<sup>+</sup>.

Example 78 Synthesis of N, N-diethyl-2-{4-[(2, 4-dimethyl-5-oxazolylcarbonyl)amino]benzyl}-N'-(2-naphthylsulfonyl)malonamide

**[0262]** In the same manner as in Example 13, the reaction mixture was obtained using hydrochloride salt (245 mg) of the compound obtained in Example 7 and 2, 4-dimethyl-5-oxazolecarboxylic acid (74 mg). Dilute hydrochloric acid was added, and the mixture was extracted with ethyl acetate. The organic layer was concentrated under reduced pressure to give the title compound (217 mg) as a white solid.

<sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.83-0.87(6H, m), 2.38(3H, s), 2.50(3H, s), 2.85-2.93(2H, m), 3.07-3.24(4H, m), 3.80-3.90(1H, m), 7.01(2H, d, J = 8.5Hz), 7.49(2H, d, J = 8.5Hz), 7.65-7.78(3H, m), 8.05(1H, d, J = 8.1Hz), 8.12(1H, d, J = 8.7Hz), 8.20(1H, d, J = 8.1Hz), 8.54(1H, s), 9.97(1H, s), 12.28(1H, brs).

MS: 577(M+H)<sup>+</sup>.

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Example 79 Synthesis of N, N-diethyl-2-{4-[(2, 4-dimethyl-5-thiazolylcarbonyl)amino]benzyl}-N'-(2-naphthylsulfonyl)malonamide

5 **[0263]** In the same manner as in Example 13, the reaction mixture was obtained using hydrochloride salt (245 mg) of the compound obtained in Example 7 and 2, 4-dimethyl-5-thiazolecarboxylic acid (83 mg). Dilute hydrochloric acid was added, and the mixture was extracted with ethyl acetate. The organic layer was concentrated under reduced pressure to give the title compound (239 mg) as a white solid.

<sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.86(6H, t, J = 6.8Hz), 2.54(3H, s), 2.66(3H, s), 2.85-2.92(2H, m), 3.06-3.23(4H, m), 3.80-3.89(1H, m), 7.02(2H, d, J = 8.3Hz), 7.40(2H, d, J = 8.3Hz), 7.69-7.79(3H, m), 8.05(1H, d, J = 8.0Hz), 8.12(1H, d, J = 8.8Hz), 8.20(1H, d, J = 8.0Hz), 8.54(1H, s), 9.95(1H, s), 12.30(1H, brs).

10 MS: 593(M+H)<sup>+</sup>.

Example 80 Synthesis of N, N-diethyl-N'-(2-naphthylsulfonyl)-2-{4-(1-naphthoyl)amino}benzyl}malonamide

15 **[0264]** In the same manner as in Example 9, the title compound (307 mg) was obtained as a white solid using hydrochloride salt (280 mg) of the compound obtained in Example 7 and 1-naphthoyl chloride (91 μL).

<sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.81-0.93(6H, m), 2.92(2H, d, J = 6.8Hz), 3.10-3.25(4H, m), 3.87(1H, t, J = 6.8Hz), 7.06(2H, d, J = 8.4Hz), 7.57-7.80(9H, m), 8.01-8.24(6H, m), 8.57(1H, s), 10.46(1H, s), 12.35(1H, brs).

20 MS: 608 (M+H)

Example 81 Synthesis of N, N-diethyl-N'-(2-naphthylsulfonyl)-2-{4-[(8-quinolylcarbonyl)amino]benzyl}malonamide

25 **[0265]** In the same manner as in Example 13, the reaction mixture was obtained using hydrochloride salt (245 mg) of the compound obtained in Example 7 and 8-quinolinecarboxylic acid (91 mg). Dilute hydrochloric acid was added, and the mixture was extracted with ethyl acetate. The organic layer was concentrated under reduced pressure to give the title compound (129 mg) as a white solid.

30 <sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.84-0.90(6H, m), 2.93(2H, d, J = 7.2Hz), 3.10-3.25(4H, m), 3.88(1H, t, J = 7.2Hz), 7.08(2H, d, J = 8.3Hz), 7.60(2H, d, J = 8.3Hz), 7.63-7.71(2H, m), 7.76-7.85(3H, m), 8.03(1H, d, J = 8.0Hz), 8.13(1H, d, J = 8.8Hz), 8.20(1H, d, J = 8.0Hz), 8.28(1H, d, J = 8.0Hz), 8.54(1H, s), 8.65(1H, d, J = 7.5Hz), 9.18(1H, d, J = 4.4Hz), 12.31(1H, brs), 13.10(1H, s).

35 MS: 609(M+H)<sup>+</sup>.

Example 82 Synthesis of N, N-diethyl-2-{4-[(2-methyl-1H-benzimidazolyl-5-carbonyl)amino]benzyl}-N'-(2-naphthylsulfonyl)malonamide

40 **[0266]** In the same manner as in Example 13, the reaction mixture was obtained using hydrochloride salt (245 mg) of the compound obtained in Example 7 and 2-methyl-1H-benzimidazole-5-carboxylic acid (93 mg). Dilute hydrochloric acid was added, and the mixture was extracted with ethyl acetate. The organic layer was concentrated under reduced pressure to give the title compound (14 mg) as a white solid.

<sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.84-0.89(6H, m), 2.55(3H, s), 2.86-2.94(2H, m), 3.07-3.25(4H, m), 3.80-3.88(1H, m), 7.03(2H, d, J = 8.5Hz), 7.53-7.60(3H, m), 7.67-7.79(4H, m), 8.05(1H, d, J = 8.1Hz), 8.11-8.14(2H, m), 8.20(1H, d, J = 8.1Hz), 8.53(1H, s), 10.08(1H, s), 12.50(2H, brs).

45 MS: 612(M+H)<sup>+</sup>.

Example 83 Synthesis of 2-{4-[(1H-benzimidazolyl-2-carbonyl)amino]benzyl}-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

50 **[0267]** In the same manner as in Example 13, the reaction mixture was obtained using hydrochloride salt (245 mg) of the compound obtained in Example 7 and 1H-benzimidazole-2-carboxylic acid (85 mg). Dilute hydrochloric acid was added, and the mixture was extracted with ethyl acetate. The organic layer was concentrated under reduced pressure to give the title compound (188 mg) as a white solid.

<sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.80-0.92(6H, m), 2.85-2.94(2H, m), 3.06-3.25(4H, m), 3.88(1H, t, J = 7.2Hz), 7.04(2H, d, J = 8.5Hz), 7.28-7.40(2H, m), 7.52-7.89(7H, m), 8.05(1H, d, J = 8.1Hz), 8.13(1H, d, J = 8.7Hz), 8.20(1H, d, J = 8.1Hz), 8.54(1H, s), 10.74(1H, s), 12.29(1H, brs), 13.40(1H, brs). MS: 598(M+H)<sup>+</sup>.

55 Example 84 Synthesis of N, N-diethyl-2-[4-(mesylamino)benzyl]-N'-(2-naphthylsulfonyl)malonamide

**[0268]** In the same manner as in Example 9, the title compound (304 mg) as an orange solid was obtained using

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hydrochloride salt (300 mg) of the compound obtained in Example 7 and mesyl chloride (57  $\mu$ L).

$^1\text{H-NMR}$ (400MHz, DMSO- $d_6$ ) $\delta$ 0.81-0.86(6H, m), 2.83-2.92(2H, m), 2.90(3H, s), 3.06-3.20(4H, m), 3.83(1H, t, J = 7.2Hz), 6.98-7.03(4H, m), 7.50-7.53(3H, m), 8.08(1H, d, J = 8.0Hz), 8.14(1H, d, J = 8.8Hz), 8.22 (1H, d, J = 8.0Hz), 8.57(1H, d, J = 1.2Hz), 9.60(1H, s).

5 MS: 532(M+H) $^+$ .

Example 85 Synthesis of N, N-diethyl-N'-(2-naphthylsulfonyl)-2-[4-(phenylsulfonylamino)benzyl]malonamide

**[0269]** In the same manner as in Example 9, the title compound (234 mg) as a pale-brown solid was obtained using hydrochloride salt (210 mg) of the compound obtained in Example 7 and benzenesulfonyl chloride (57  $\mu$ L).

10  $^1\text{H-NMR}$ (400MHz, DMSO- $d_6$ ) $\delta$ 0.73(3H, t, J = 7.2Hz), 0.78(3H, t, J = 7.2Hz), 2.75-2.87(2H, m), 2.94-3.20(4H, m), 3.76(1H, t, J = 7.4Hz), 6.86-6.91(4H, m), 7.45-7.59(3H, m), 7.69-7.78(5H, m), 8.08(2H, t, J = 9.4Hz), 8.20(1H, d, J = 8.0Hz), 8.56(1H, s), 10.16(1H, s), 12.29(1H, brs).

15 MS: 594(M+H) $^+$ .

Example 86 Synthesis of N, N-diethyl-N'-(2-naphthylsulfonyl)-2-[4-(tosylamino)benzyl]malonamide

**[0270]** In the same manner as in Example 9, the title compound (574 mg) as a pale-brown solid was obtained using hydrochloride salt (500 mg) of the compound obtained in Example 7 and tosyl chloride (215 mg).

20  $^1\text{H-NMR}$ (400MHz, DMSO- $d_6$ ) $\delta$ 0.70-0.81(6H, m), 2.31(3H, s), 2.73-2.86(2H, m), 2.93-3.20(4H, m), 3.71-3.78(1H, m), 6.83-6.90(4H, m), 7.30(2H, d, J = 8.4Hz), 7.59(2H, d, J = 8.4Hz), 7.67-7.78(3H, m), 8.03-8.10(2H, m), 8.20(1H, d, J = 8.0Hz), 8.54(1H, s), 10.07(1H, s), 12.22(1H, brs).

MS: 608(M+H) $^+$ .

25 Example 87 Synthesis of N, N-diethyl-N'-(2-naphthylsulfonyl)-2-[4-(phenoxy-carbonylamino)benzyl]malonamide

**[0271]** In the same manner as in Example 9, the title compound (185 mg) as a pale-brown solid was obtained using hydrochloride salt (260 mg) of the compound obtained in Example 7 and phenyl chlorocarbonate (70  $\mu$ L).

30  $^1\text{H-NMR}$ (300MHz, DMSO- $d_6$ ) $\delta$ 0.75-0.84(6H, m), 2.88(2H, d, J = 7.2Hz), 3.02-3.24(4H, m), 3.84(1H, t, J = 7.2Hz), 7.00(2H, d, J = 8.7Hz), 7.21-7.50(7H, m), 7.65-7.78(3H, m), 8.04-8.22(3H, m), 8.55(1H, s), 10.09(1H, s).

MS: 574(M+H) $^+$ .

Example 88 Synthesis of 2-[4-(anilino-carbonylamino)benzyl]-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

35 **[0272]** To a solution of the compound (478 mg) obtained in Example 7 in THF (10 mL) were added 1 mol/L aqueous sodium hydroxide solution (3 mL) and phenyl isocyanate (120  $\mu$ L), and the mixture was stirred at room temperature for 4 hr. The reaction mixture was adjusted to pH = 1-2 by the addition of dilute hydrochloric acid and extracted with ethyl acetate (30 mL $\times$ 2). The organic layer was washed with saturated brine, concentrated under reduced pressure, and washed with isopropanol (100 mL) to give the title compound (331 mg) as a white solid.

40  $^1\text{H-NMR}$ (400MHz, DMSO- $d_6$ ) $\delta$ 0.86(3H, t, J = 7.0Hz), 0.86(3H, t, J = 6.9Hz), 2.87(2H, d, J = 7.0Hz), 3.05-3.20(4H, m), 3.83(1H, t, J = 7.0Hz), 6.96(2H, d, J = 8.3Hz), 7.20(2H, d, J = 8.3Hz), 7.22-7.35(2H, m), 7.45(2H, d, J = 8.1Hz), 7.65-7.78(3H, m), 8.06(1H, d, J = 8.0Hz), 8.12(1H, d, J = 8.0Hz), 8.20(1H, d, J = 8.0Hz), 8.53(2H, m), 8.60(1H, s).

MS: 573(M+H) $^+$ .

45 Example 89 Synthesis of N, N-diethyl-2-[4-(1-indolinyl-carbonylamino)benzyl]-N'-(2-naphthylsulfonyl)malonamide

**[0273]** To a solution of the compound obtained in Example 87 (418 mg) in THF (6 mL) were added indoline (84  $\mu$ L) and triethylamine (540  $\mu$ L), and the mixture was heated under reflux for 5.5 hr. Dilute hydrochloric acid was added to the reaction mixture, and the mixture was extracted with ethyl acetate (50 mL $\times$ 2). The extract was washed with saturated brine and concentrated under reduced pressure, and the residue was purified by silica gel column chromatography to give the title compound (198 mg) as a white solid.

50  $^1\text{H-NMR}$ (300MHz, DMSO- $d_6$ ) $\delta$ 0.85(3H, t, J = 7.2Hz), 0.86(3H, t, J = 7.2Hz), 2.82-2.93(2H, m), 3.05-3.28(6H, m), 3.81(1H, t, J = 7.2Hz), 4.11(2H, t, J = 8.7Hz), 6.90(1H, m), 6.99(2H, d, J = 8.4Hz), 7.13(1H, m), 7.20(1H, m), 7.32(2H, d, J = 8.4Hz), 7.62-7.80(5H, m), 7.87(1H, d, J = 8.2Hz), 8.06(1H, d, J = 8.1Hz), 8.14(1H, d, J = 8.1Hz), 8.21(1H, d, J = 8.1Hz),

55 8.40(1H, s), 8.55(1H, s), 12.30(1H, brs).

MS: 599(M+H) $^+$ .

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Example 90 Synthesis of N, N-diethyl-2-[4-(N", N"-diethylaminocarbonylamino)benzyl]-N'-(2-naphthylsulfonyl)malonamide

5 [0274] To a mixed solution of the compound (520 mg) obtained in Example 87 in THF (40 mL)/pyridine (4 mL) were added diethylamine (2.0 mL) and 4-dimethylaminopyridine (14 mg), and the mixture was stirred at room temperature for 18 hr. Dilute hydrochloric acid was added to the reaction solution, and the mixture was extracted with ethyl acetate (50 mL×2). The extract was washed with saturated brine and concentrated under reduced pressure to give the title compound (256 mg) as a white solid. <sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ, 0.85(6H, t, J = 6.8), 1.15(6H, t, J = 6.8Hz), 2.75-2.94(2H, m), 3.03-3.24(4H, m), 3.82(1H, t, J = 6.8Hz), 6.92(2H, d, J = 8.4Hz), 7.25(2H, d, J = 8.4Hz), 7.64-7.85(3H, m), 8.05(1H, d, J = 8.0Hz), 8.12(1H, d, J = 8.4Hz), 8.20(1H, d, J = 8.0Hz), 8.54(1H, s), 12.28(1H, brs). MS: 553(M+H)<sup>+</sup>.  
10

Example 91 Synthesis of (2S)-N, N-diethyl-N'-(2-naphthylsulfonyl)-2-(4-nitrobenzyl)malonamide

15 [0275] To the compound (100 g) obtained in Example 6 and (+)-dehydroabiethylamine (70.8 g) was added methanol (2.7 L), and the mixture was dissolved by heating under reflux. The mixture was left standing and allowed to gradually cool to room temperature. Two days later, the precipitated solid was collected by filtration to give a (+)-dehydroabiethylamine salt (93.7 g, optical purity 43% d.e.) of the title compound as white crystals. 24.6 g thereof was dissolved in THF (400 mL) with heating, and the solution was allowed to gradually cool to room temperature and left standing for 1 day. The precipitate was collected by filtration. The filtrate was concentrated under reduced pressure and recrystallized from methanol (100 mL) in the same manner. The obtained crystals were combined, and recrystallized again from methanol (100 mL). The precipitate was collected by filtration to give a (+)-dehydroabiethylamine salt (12.3 g, optical purity >98% d.e.) of the title compound as white crystals. The salt (12.3 g) was suspended in ethanol (200 mL), 1 mol/L hydrochloric acid (50 mL) was added, and the mixture was desalted by stirring at room temperature for 3 hr. The precipitate was collected by filtration to give the title compound (7.23 g) as a white solid (optical purity >98% e.e.).  
20

25 <sup>1</sup>H-NMR and MS were the same as in Example 6.  
specific optical rotation:  $[\alpha]_D = +9^\circ$  (c = 1.28, chloroform).

Example 92 Synthesis of (2S)-2-[4-(benzoylamino)benzyl]-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

30 [0276] To a suspension of the compound (500 mg) obtained in Example 91 in THF (15 mL) were added triethylamine (160 μL) and 10% palladium/carbon (70 mg), and the mixture was stirred under hydrogen atmosphere at room temperature for 4 hr. Insoluble material was removed by filtration, benzoyl chloride (120 μL) was added to the filtrate under ice-cooling, and the mixture was stirred at room temperature for 17 hr. The mixture was concentrated under reduced pressure, dilute hydrochloric acid (30 mL) was added to the residue, and the precipitate was collected by filtration. The precipitate was triturated with ethanol/water to give the title compound (404 mg) as a white solid.  
35

<sup>1</sup>H-NMR and MS were same as in Example 9.  
specific optical rotation:  $[\alpha]_D = +42^\circ$  (c = 0.28, chloroform).

Example 93 Synthesis of (2S)-N, N-diethyl-2-{4-[(2-fluorobenzoyl)amino]benzyl}-N'-(2-naphthylsulfonyl)malonamide

40 [0277] In the same manner as in Example 92, the title compound (336 mg) was obtained as a white solid using the compound (500 mg) obtained in Example 91 and 2-fluorobenzoyl chloride (124 μL).

<sup>1</sup>H-NMR and MS were same as in Example 19.  
specific optical rotation:  $[\alpha]_D = +27^\circ$  (c = 0.61, chloroform).  
45

Example 94 Synthesis of (2S)-N, N-diethyl-2-{4-[(3-fluorobenzoyl)amino]benzyl}-N'-(2-naphthylsulfonyl)malonamide

[0278] In the same manner as in Example 92, the title compound (327 mg) was obtained as a white solid using the compound (500 mg) obtained in Example 91 and 3-fluorobenzoyl chloride (124 μL).

<sup>1</sup>H-NMR and MS were same as in Example 21.  
specific optical rotation:  $[\alpha]_D = +31^\circ$  (c = 0.37, chloroform).  
50

Example 95 Synthesis of (2S)-N, N-diethyl-2-{4-[(2, 4-difluorobenzoyl)amino]benzyl}-N'-(2-naphthylsulfonyl)malonamide

55 [0279] In the same manner as in Example 92, the title compound (489 mg) was obtained as a white solid using the compound (500 mg) obtained in Example 91 and 2, 4-difluorobenzoyl chloride (127 μL).

<sup>1</sup>H-NMR and MS were same as in Example 23.  
specific optical rotation:  $[\alpha]_D = +28^\circ$  (c = 0.56, chloroform).

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Example 96 Synthesis of (2S)-N, N-diethyl-2-(4-[(4-methylbenzoyl)amino]benzyl)-N'-(2-naphthylsulfonyl)malonamide

**[0280]** In the same manner as in Example 92, the title compound (273 mg) was obtained as a white solid using the compound (500 mg) obtained in Example 91 and 4-methylbenzoyl chloride (137  $\mu$ L).

<sup>1</sup>H-NMR and MS were same as in Example 32.

specific optical rotation:  $[\alpha]_D = +35^\circ$  (c = 0.32, chloroform).

Example 97 Synthesis of (2S)-N, N-diethyl-N'-(2-naphthylsulfonyl)-2-{4-[(2-thienoyl)amino]benzyl}malonamide

**[0281]** In the same manner as in Example 92, the title compound (382 mg) was obtained as a white solid using the compound (500 mg) obtained in Example 91 and thiophene-2-carbonyl chloride (111  $\mu$ L).

<sup>1</sup>H-NMR and MS were same as in Example 75.

specific optical rotation:  $[\alpha]_D = +33^\circ$  (c = 0.35, chloroform).

Example 98 Synthesis of (2S)-N, N-diethyl-2-{4-[(2-furoyl)amino]benzyl}-N'-(2-naphthylsulfonyl)malonamide

**[0282]** In the same manner as in Example 92, the title compound (352 mg) was obtained as a white solid using the compound (500 mg) obtained in Example 91 and 2-furoyl chloride (102  $\mu$ L).

<sup>1</sup>H-NMR and MS were same as in Example 69.

specific optical rotation:  $[\alpha]_D = +33^\circ$  (c = 0.53, chloroform).

Example 99 Synthesis of (2S)-2-{4-[(2-amino-5-fluorobenzoyl)amino]benzyl}-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

**[0283]** The compound (5.79 g) obtained in Example 48 and (1S, 2S)-(+)-2-amino-1-(4-nitrophenyl)-1, 3-propanediol (2.08 g) were dissolved with heating in methanol (100 mL), and the solution was concentrated under reduced pressure to give an oil. The oil was dissolved with heating in isopropanol (100 mL), and the solution was stirred at 60°C for 12 hr.

The precipitate was collected by filtration and recrystallized from isopropanol (100 mL) to give (1S, 2S)-(+)-2-amino-1-(4-nitrophenyl)-1, 3-propanediol salt (2.20 g) of the title compound as white crystals (optical purity >98% d.e.). 0.5 mol/L Hydrochloric acid (200 mL) was added to a salt (15.6 g) obtained by repeating a similar operation, and the mixture was extracted with ethyl acetate (300 mL). After concentration under reduced pressure, the residue was triturated with ethanol to give the title compound (10.5 g) as a white solid (optical purity >98% e.e.).

<sup>1</sup>H-NMR and MS were same as in Example 48.

specific optical rotation:  $[\alpha]_D = +30^\circ$  (c = 0.325, chloroform).

Example 100 Synthesis of (2S)-2-{4-[(2-amino-6-fluorobenzoyl)amino]benzyl}-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

**[0284]** Resolution in the same manner as in Example 91 and using the compound (10.28 g) obtained in Example 55, (+)-dehydroabiethylamine (6.30 g) and ethanol gave a (+)-dehydroabiethylamine salt (3.62 g) (optical purity >98% d.e.) of the title compound as white crystals. A salt (6.80 g) obtained by repeating a similar operation was desalted in the same manner as in Example 91 to give the title compound (4.51 g) as a white solid (optical purity >98% e.e.).

<sup>1</sup>H-NMR and MS were same as in Example 55.

specific optical rotation:  $[\alpha]_D = +25^\circ$  (c = 0.515, chloroform).

Example 101 Synthesis of (2S)-N, N-diethyl-N'-(2-naphthylsulfonyl)-2-{4-[(2-pyridylcarbonyl)amino]benzyl}malonamide

**[0285]** Resolution in the same manner as in Example 91 and using a free form of the compound (18.2 g) obtained in Example 60, (+)-dehydroabiethylamine (12.1 g) and methanol gave a (+)-dehydroabiethylamine salt (12.3 g) (optical purity >98% d.e.) of the title compound as white crystals. The salt was desalted with 2 equivalent amounts of hydrochloric acid in the same manner as in Example 91 to give the title compound (4.81 g) as a white solid (optical purity >98% e.e.).

<sup>1</sup>H-NMR(400MHz, CDCl<sub>3</sub>) $\delta$ 0.81(3H, t, J = 7.2Hz), 1.03(3H, t, J = 7.2Hz), 2.80-2.88(2H, m), 3.01(1H, dd, J = 13.2, 5.0Hz), 3.07-3.18(2H, m), 3.44-3.53(1H, m), 3.57(1H, dd, J = 10.1, 5.0Hz), 7.05(2H, d, J = 8.4Hz), 7.50(1H, dd, J = 8.0, 4.6Hz), 7.56(2H, d, J = 8.4Hz), 7.60-7.68(2H, m), 7.90-7.94(2H, m), 7.97-8.04(3H, m), 8.28(1H, d, J = 7.8Hz), 8.62(1H, d, J = 4.6Hz), 8.68(1H, s), 9.93(1H, s), 10.97(1H, s).

MS was the same as in Example 60.

specific optical rotation:  $[\alpha]_D = +33^\circ$  (c = 0.32, chloroform).

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Example 102 Synthesis of (2S)-2-(4-aminobenzyl)-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

5 **[0286]** To a mixed suspension of the compound (9.12 g) obtained in Example 91 in ethanol (50 mL)/ethyl acetate (50 mL) was added 10% palladium/carbon (1.00 g), and the mixture was stirred at room temperature under hydrogen atmosphere for 3 hr. The white precipitate was dissolved in chloroform, insoluble material was removed by filtration, and the filtrate was concentrated under reduced pressure to give the title compound (8.53 g) as a white powder.

<sup>1</sup>H-NMR and MS were same as in Example 7.

specific optical rotation:  $[\alpha]_D = +32^\circ$  (c = 0.65, chloroform).

10 Example 103 Synthesis of (2S)-2-{4-[(2-amino-4-chlorobenzoyl)amino]benzyl}-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

**[0287]** In the same manner as in Example 13, the title compound (668 mg) was obtained as a white solid using the compound (1.01 g) obtained in Example 102 and 4-chloroanthranilic acid (381 mg).

15 <sup>1</sup>H-NMR and MS were same as in Example 51.

specific optical rotation:  $[\alpha]_D = +33^\circ$  (c = 0.445, chloroform).

Example 104 Synthesis of (2S)-2-{4-[(2-aminobenzoyl)amino]benzyl}-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

20 **[0288]** In the same manner as in Example 13, the title compound (178 mg) was obtained as a white solid using the compound (1.02 g) obtained in Example 102 and anthranilic acid (309 mg).

<sup>1</sup>H-NMR and MS were same as in Example 43.

specific optical rotation:  $[\alpha]_D = +29^\circ$  (c = 0.385, chloroform).

25 Example 105 Synthesis of (2S)-2-{4-[(2-amino-5-chlorobenzoyl)amino]benzyl}-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

**[0289]** In the same manner as in Example 13, the title compound (396 mg) was obtained as a white solid using the compound (1.01 g) obtained in Example 102 and 5-chloroanthranilic acid (382 mg).

30 <sup>1</sup>H-NMR and MS were same as in Example 47.

specific optical rotation:  $[\alpha]_D = +21^\circ$  (c = 0.475, chloroform).

Example 106 Synthesis of (2S)-2-{4-[(2-amino-4, 5-difluorobenzoyl)amino]benzyl}-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

35 **[0290]** In the same manner as in Example 13, the title compound (503 mg) was obtained as a white solid using the compound (1.01 g) obtained in Example 102 and 4, 5-difluoroanthranilic acid (424 mg).

<sup>1</sup>H-NMR and MS were same as in Example 54.

specific optical rotation:  $[\alpha]_D = +27^\circ$  (c = 0.575, chloroform).

40 Example 107 Synthesis of (2S)-2-{4-[(2-amino-4-fluorobenzoyl)amino]benzyl}-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

**[0291]** In the same manner as in Example 13, the title compound (715 mg) was obtained as a white solid using the compound (1.01 g) obtained in Example 102 and 4-fluoroanthranilic acid (340 mg).

45 <sup>1</sup>H-NMR and MS were same as in Example 52.

specific optical rotation:  $[\alpha]_D = +29^\circ$  (c = 0.525, chloroform).

50 Example 108 Synthesis of (2S)-2-{4-[(2-amino-5-methylbenzoyl)amino]benzyl}-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

**[0292]** In the same manner as in Example 13, the title compound (276 mg) was obtained as a white solid using the compound (1.80 g) obtained in Example 102 and 5-methylanthranilic acid (607 mg).

55 <sup>1</sup>H-NMR and MS were same as in Example 50.

specific optical rotation:  $[\alpha]_D = +25^\circ$  (c = 0.445, chloroform).

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Example 109 Synthesis of N, N-diethyl-2-(4-dimethylaminobenzyl)-N'-(2-naphthylsulfonyl)malonamide

**[0293]** To a solution of the compound (122 mg) obtained in Example 7 in THF (5 mL) were added 37% aqueous formaldehyde solution (0.5 mL) and sodium triacetoxyborohydride (230 mg), and the mixture was stirred at room temperature for 16 hr. Water (50 mL) was added to the reaction mixture, and the mixture was extracted with ethyl acetate (50 mL×2). The organic layer was washed with saturated brine and concentrated under reduced pressure to give the title compound (110 mg) as a white solid.

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.88(6H, t, J = 7.1Hz), 2.69-2.90(2H, m), 2.75(6H, s), 3.07-3.29(4H, m), 3.68-3.75(1H, m), 6.37(2H, d, J = 8.6Hz), 6.78(2H, d, J = 8.6Hz), 7.68-7.82(3H, m), 8.05-8.25(3H, m), 8.53(1H, s), 12.26(1H, brs).

MS: 482(M+H)<sup>+</sup>.

Example 110 Synthesis of 2-(4-chlorobenzyl)-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

(1) diethyl 4-chlorobenzylmalonate

**[0294]** In the same manner as in Example 6 (1), a crude product was obtained using diethyl malonate (13.6 g) and 4-chlorobenzyl bromide (17.5 g). This was purified by silica gel column chromatography to give the title compound (10.1 g) as an oil.

<sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ1.22(6H, t, J = 6.9Hz), 3.18(2H, d, J = 7.8Hz), 3.60(1H, t, J = 7.7Hz), 4.05-4.30(4H, m), 7.14(2H, d, J = 8.4Hz), 7.25(2H, d, J = 9.0Hz).

(2) monomethyl 4-chlorobenzylmalonate

**[0295]** In the same manner as in Example 6 (2), the title compound (8.29 g) was obtained as an oil using the above-mentioned compound (10.1 g).

<sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ3.10-3.29(2H, m), 3.55-3.87(4H, m), 7.08-7.32(4H, m).

(3) methyl 2-(4-chlorobenzyl)-3-[(2-naphthylsulfonyl)amino]-3-oxopropionate

**[0296]** In the same manner as in Example 1 (2), the title compound (3.12 g) was obtained as an oil using the above-mentioned compound (2.00 g).

<sup>1</sup>H-NM(300Mz, CDCl<sub>3</sub>)δ3.00-3.90(6H, m), 6.80(2H, d, J = 8.5Hz), 6.90(2H, d, J = 8.7Hz), 7.56-7.77(2H, m), 7.84-8.08(4H, m), 8.63(1H, d, J = 1.7Hz).

(4) 2-(4-chlorobenzyl)-3-[(2-naphthylsulfonyl)amino]-3-oxopropionic acid disodium salt

**[0297]** To a solution of the above-mentioned compound (3.12 g) in THF/ethanol (10 mL/20 mL) was added a solution of sodium hydroxide (0.867 g) in water (6 mL), and the mixture was stirred at room temperature for 18 hr. The precipitate was collected by filtration to give the title compound (2.41 g) as a white powder.

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ2.75-2.96(3H, m), 6.94-7.10(4H, m), 7.49-7.64(2H, m), 7.70-8.03(7H, m), 8.24(1H, s).

(5) 2-(4-chlorobenzyl)-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

**[0298]** In the same manner as in Example 1 (4), a crude product was obtained using the above-mentioned compound (300 mg). This was purified by silica gel column chromatography to give the title compound (164 mg) as a white powder.

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.74-0.92(6H, m), 2.90(2H, d, J = 7.2Hz), 3.01-3.29(4H, m), 3.83(1H, t, J = 6.9Hz), 7.00-7.14(4H, m), 7.63-7.82(3H, m), 8.01-8.29(3H, m), 8.53(1H, s), 12.38(1H, brs).

MS: 473(M+H)<sup>+</sup>.

Example 111 Synthesis of 2-(4-cyanobenzyl)-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

(1) diethyl 4-cyanobenzylmalonate

**[0299]** In the same manner as in Example 6 (1), a crude product was obtained using diethyl malonate (13.6 g) and 4-cyanobenzyl bromide (16.7 g). This was purified by silica gel column chromatography to give the title compound (15.5 g) as an oil.

<sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ1.22(6H, t, J = 7.2Hz), 3.27(2H, d, J = 7.8Hz), 3.64(1H, t, J = 7.5Hz), 4.07-4.29(4H, m), 7.34(2H, d, J = 8.1Hz), 7.59(2H, d, J = 8.1Hz).

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### (2) monoethyl (4-cyanobenzyl)malonate

**[0300]** To a solution of the above-mentioned compound (15.5 g) in ethanol (100 mL) were added a solution of potassium hydroxide (3.71 g) in ethanol (100 mL) and ethanol (50 mL), and the mixture was stirred at room temperature for 18 hr. The reaction mixture was concentrated under reduced pressure, water (100 mL) and ether (30 mL) were added to extract the residue. The aqueous layer was adjusted to pH = 1-2 by the addition of 1 mol/L hydrochloric acid (100 mL), and extracted with ethyl acetate (200 mL). The organic layer was washed with brine and concentrated under reduced pressure to give the title compound (12.2 g) as an oil.

<sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ1.22(3H, t, J = 6.9Hz), 3.18-3.35(2H, m), 3 - 70(1H, t, J = 7.6Hz), 4.00-4.30(2H, m), 7.35(2H, d, J = 8.2Hz), 7.60(2H, d, J = 8.2Hz).

### (3) ethyl 2-(4-cyanobenzyl)-3-[(2-naphthylsulfonyl)amino]-3-oxopropionate

**[0301]** In the same manner as in Example 1 (2), the title compound (6.25 g) was obtained as an oil using the above-mentioned compound (4.00 g).

<sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ1.17(3H, J = 7.2Hz), 3.18(2H, d, J = 7.8Hz), 3.52(1H, t, J = 7.2Hz), 4.00-4.30(2H, m), 7.01(2H, d, J = 8.1Hz), 7.22(2H, d, J = 8.4Hz), 7.52-7.79(2H, m), 7.82-8.11(4H, m), 8.63(1H, s).

### (4) 2-(4-cyanobenzyl)-3-[(2-naphthylsulfonyl)amino]-3-oxopropionic acid

**[0302]** To a solution of the above-mentioned compound (6.25 g) in THF/ethanol (20 mL/40 mL) was added a solution of sodium hydroxide (1.79 g) in water (12 mL), and the mixture was stirred at room temperature for 18 hr. The precipitate was collected by filtration, 0.5 mol/L hydrochloric acid (80 mL) and ethyl acetate (200 mL) were added to extract the precipitate. The organic layer was washed with brine and concentrated under reduced pressure to give the title compound (4.64 g) as a white powder.

<sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ2.82-2.67(2H, m), 3.63-3.81(1H, m), 7.16(2H, d, J = 8.2Hz), 7.39(2H, d, J = 8.2Hz), 7.61-7.82(3H, m), 8.09(2H, d, J = 8.6Hz), 8.20(1H, d, J = 7.7Hz), 8.50(1H, d, J = 1.2H), 12.00-13.40(1H, brs).

### (5) 2-(4-cyanobenzyl)-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

**[0303]** In the same manner as in Example 1 (4), a crude product was obtained using the above-mentioned compound (300 mg). This was purified by silica gel column chromatography to give the title compound (174 mg) as a white powder.

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.76-0.91(6H, m), 3.00(2H, d, J = 7.2Hz), 3.02-3.31(4H, m), 3.90(1H, t, J = 7.2Hz), 7.24(2H, d, J = 8.4Hz), 7.49(2H, d, J = 8.4Hz), 7.86-7.81(3H, m), 8.00-8.25(3H, m), 8.52(1H, s), 12.39(1H, brs).

## Example 112 Synthesis of N, N-diethyl-2-(4-methoxybenzyl)-N'-(2-naphthylsulfonyl)malonamide

### (1) diethyl 4-methoxybenzylmalonate

**[0304]** In the same manner as in Example 6 (1), a crude product was obtained using diethyl malonate (25.6 g) and 4-methoxybenzyl chloride (25.0 g). This was purified by silica gel column chromatography to give the title compound (25.0 g) as an oil.

<sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ1.21(6H, t, J = 7.5Hz), 3.15(2H, d, J = 7.8Hz), 3.60(1H, t, J = 7.8Hz), 3.78(3H, s), 4.02-4.27(4H, m), 6.81(2H, d, J = 8.4Hz), 7.12(2H, d, J = 8.1Hz).

### (2) monoethyl (4-methoxybenzyl)malonate

**[0305]** In the same manner as in Example 111 (2), the title compound (18.0 g) was obtained as an oil using the above-mentioned compound (25.0 g).

<sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ1.22(3H, t, J = 7.1Hz), 3.18(2H, d, J = 7.3Hz), 3.65(1H, t, J = 7.5Hz), 3.78(3H, s), 4.17(2H, q, J = 7.2Hz), 6.82(2H, d, J = 8.6Hz), 7.12(2H, d, J = 8.6Hz).

### (3) ethyl 2-(4-methoxybenzyl)-3-[(2-naphthylsulfonyl)amino]-3-oxopropionate

**[0306]** In the same manner as in Example 1 (2), the title compound (7.14 g) was obtained as an oil using the above-mentioned compound (4.08 g).

<sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ1.14(3H, t, J = 7.1Hz), 3.02-3.15 (2H, m), 3.45(1H, t, J = 7.0Hz), 3.68(3H, s), 4.01-4.20(2H, m), 6.55(2H, d, J = 8.7Hz), 6.81(2H, J = 8.6Hz), 7.56-7.75(2H, m), 7.95-8.10(4H, m), 8.65(1H, s).

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(4) 2-(4-methoxybenzyl)-3-[(2-naphthylsulfonyl)amino]-3-oxopropionic acid

**[0307]** In the same manner as in Example 111 (4), the title compound (5.66 g) was obtained as a white powder using the above-mentioned compound (7.14 g).

<sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ2.99-3.19(2H, m), 3.58(1H, t, J = 6.7Hz), 3.62(3H, s), 6.47(2H, d, J = 8.7Hz), 6.81(2H, d, J = 8.5Hz), 7.53-7.72(2H, m), 7.80-8.05(4H, m), 7.00-8.00(1H, brs), 8.63(1H, s), 9.40-10.30(1H, brs).

(5) N, N-diethyl-2-(4-methoxybenzyl)-N'-(2-naphthylsulfonyl)malonamide

**[0308]** In the same manner as in Example 1 (4), a crude product was obtained using the above-mentioned compound (550 mg). This was purified by silica gel column chromatography to give the title compound (189 mg) as a white powder. <sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.80-0.94(6H, m), 2.70-2.95(2H, m), 3.08-3.30(4H, m), 3.63(3H, s), 3.68-3.82(1H, m), 6.59(2H, d, J = 8.7Hz), 6.92(2H, d, J = 8.4Hz), 7.64-7.84(3H, m), 8.01-8.29(3H, m), 8.54(1H, s), 12.31(1H, brs). MS: 469(M+H)<sup>+</sup>.

Example 113 Synthesis of N, N-diethyl-N'-(2-naphthylsulfonyl)-2-(4-pyridylmethyl)malonamide

(1) diethyl (4-pyridylmethyl)malonate

**[0309]** In the same manner as in Example 6 (1), a crude product was obtained using diethyl malonate (6.41 g) and 4-(bromomethyl)pyridine hydrobromide (10.1 g). This was purified by silica gel column chromatography to give the title compound (3.86 g) as an oil.

<sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ1.22(6H, t, J = 7.1Hz), 3.21(2H, d, J = 7.8Hz), 3.58-3.71(1H, m), 4.07-4.27(4H, m), 7.09-7.17(2H, m), 8.44-8.56(2H, m).

(2) monoethyl (4-pyridylmethyl)malonate

**[0310]** In the same manner as in Example 111 (2), the title compound (1.89 g) was obtained as a white powder using the above-mentioned compound (3.86 g).

<sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ0.97-1.16(3H, m), 2.92-3.19(2H, m), 3.70-4.15(3H, m), 7.26(2H, d, J = 5.7Hz), 8.46(2H, d, J = 5.4Hz), 12.30-13.80(1H, brs).

(3) ethyl 3-[(2-naphthylsulfonyl)amino]-3-oxo-2-(4-pyridylmethyl)propionate

**[0311]** In the same manner as in Example 1 (2), the title compound (2.44 g) was obtained as an oil using the above-mentioned compound (1.89 g).

<sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ1.04(3H, t, J = 7.2Hz), 3.00-3.75 (3H, m), 3.91-4.09(2H, m), 7.04(2H, d, J = 5.9Hz), 7.40-8.05(6H, m), 8.27(2H, d, J = 6.0Hz), 8.24(1H, s).

(4) 3-[(2-naphthylsulfonyl)amino]-3-oxo-2-(4-pyridylmethyl)propionic acid disodium salt

**[0312]** In the same manner as in Example 110 (4), the title compound (1.27 g) was obtained as a white powder using the above-mentioned compound (3.86 g).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ2.79-3.00(2H, m), 3.10-4.70(1H, brs), 6.98-7.09(2H, m), 7.50-7.63(2H, m), 7.70-8.06(4H, m), 8.18-8.29(3H, m).

(5) N, N-diethyl-N'-(2-naphthylsulfonyl)-2-(4-pyridylmethyl)malonamide

**[0313]** In the same manner as in Example 1 (4), a crude product was obtained using the above-mentioned compound (200 mg). This was purified by silica gel column chromatography to give the title compound (38 mg) as a white powder. <sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.85(6H, t, J = 6.9Hz), 2.95(2H, d, J = 7.2Hz), 3.00-3.30(4H, m), 3.89(1H, t, J = 7.5Hz), 7.08(2H, d, J = 5.7Hz), 7.60-7.80(3H, m), 8.01-8.30(5H, m), 8.54(1H, s), 12.60(1H, brs). MS: 440(M+H)<sup>+</sup>.

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Example 114 Synthesis of N, N-diethyl-N'-(2-naphthylsulfonyl)-2-(3-nitrobenzyl)malonamide

(1) diethyl 3-nitrobenzylmalonate

5 **[0314]** In the same manner as in Example 6 (1), the title compound (7.02 g) was obtained as an oil using diethyl malonate (6.57 g) and 3-nitrobenzyl bromide (8.87 g).

(2) monoethyl (3-nitrobenzyl)malonate

10 **[0315]** In the same manner as in Example 111 (2), the title compound (4.00 g) was obtained as an oil using the above-mentioned compound (7.02 g).

$^1\text{H-NMR}$ (400Mz,  $\text{CDCl}_3$ ) $\delta$ 1.22-1.33(6H, m), 3.15-3.20(2H, m), 3.74(1H, t, J = 7.5Hz), 4.18-4.28(4H, m), 7.47-7.51(1H, m), 7.58(1H, d, J = 7.7Hz), 8.07-8.12(2H, m).

15 (3) ethyl 3-(N, N-diethylamino)-2-(3-nitrobenzyl)-3-oxopropionate

**[0316]** To a solution of the above-mentioned compound (3.92 g) in methylene chloride (50 mL) was added oxalyl chloride (2.60 mL) under ice-cooling, and the mixture was stirred at room temperature for 1.5 hr. After concentration under reduced pressure, THF (50 mL) was added to the residue, and diethylamine (4.60 mL) was added under ice-cooling. After stirring for 20 min under the condition, the reaction mixture was adjusted to pH = 2-3 by the addition of dilute hydrochloric acid and extracted with ethyl acetate (50 mL $\times$ 2). The extract was washed with saturated brine and concentrated under reduced pressure, and the residue was purified by silica gel column chromatography to give the title compound (3.43 g) as an oil.

20  $^1\text{H-NMR}$ (300Mz,  $\text{CDCl}_3$ ) $\delta$ 0.99(3H, t, J = 7.5Hz), 1.04(3H, t, J = 7.2Hz), 1.25(3H, t, J = 7.2Hz), 3.04-3.18(1H, m), 3.25-3.48(5H, m), 3.82(1H, dd, J = 9.0, 6.0Hz), 4.19(2H, q, J = 7.2Hz), 7.42-7.47(1H, m), 7.60(1H, d, J = 7.5Hz), 8.09(1H, d, J = 7.5Hz), 8.10(1H, s).

(4) 3-(N, N-diethylamino)-2-(3-nitrobenzyl)-3-oxopropionic acid

30 **[0317]** To a solution of the above-mentioned compound (2.99 g) in methanol (50 mL) was added 1 mol/L aqueous sodium hydroxide solution (14 mL), and the mixture was stirred at room temperature for 2 hr. After concentration under reduced pressure, the residue was adjusted to pH = 2-3 by the addition of dilute hydrochloric acid and extracted with ethyl acetate (50 mL $\times$ 2). The extract was washed with saturated brine and concentrated under reduced pressure to give the title compound (2.67 g) as a white solid.

35  $^1\text{H-NMR}$ (400Mz,  $\text{CDCl}_3$ ) $\delta$ 1.05(3H, t, J = 7.2Hz), 1.08(3H, t, J = 7.2Hz), 3.00-3.09(2H, m), 3.09-3.22(1H, m), 3.27-3.41(2H, m), 3.49-3.61(1H, m), 3.80-3.83(1H, m), 7.48-7.52(1H, m), 7.57(1H, d, J = 7.5Hz), 8.05(1H, s), 8.14(1H, d, J = 8.2Hz).

(5) N, N-diethylamino-2-(3-nitrobenzyl)malonamide

40 **[0318]** To a solution of the above-mentioned compound (2.66 g) in methylene chloride (50 mL) were added oxalyl chloride (1.60 mL) and DMF (50  $\mu\text{L}$ ) under ice-cooling, and the mixture was stirred at room temperature for 2 hr. After concentration under reduced pressure, THF (50 mL) was added to the residue, and 28% aqueous ammonia (1.00 mL) was added under ice-cooling. After stirring at room temperature for 12 hr, the mixture was concentrated under reduced pressure, water was added to the residue, and the precipitate was collected by filtration to give the title compound (2.27 g) as a white solid.  $^1\text{H-NMR}$ (400Mz,  $\text{DMSO-d}_6$ ) $\delta$ 0.88-0.95(6H, m), 3.05-3.40(6H, m), 3.77(1H, dd, J = 8.7, 6.2Hz), 7.12(1H, brs), 7.37(1H, brs), 7.54-7.58(1H, m), 7.71(1H, d, J = 7.7Hz), 8.06(1H, d, J = 7.8Hz), 8.11(1H, s).

(6) N,N-diethyl-N'-(2-naphthylsulfonyl)-2-(3-nitrobenzyl)malonamide

50 **[0319]** To a solution of the above-mentioned compound (250 mg) in THF (20 mL) was added 60% sodium hydride (40 mg) under ice-cooling, and the mixture was stirred at room temperature for 20 min. 2-Naphthalenesulfonyl chloride (230 mg) was added to the mixture at room temperature, and the mixture was stirred for 30 min. Additional 60% sodium hydride (40 mg) was added under ice-cooling, and the mixture was stirred at room temperature for 3 days. Water (50 mL) was added to the reaction mixture, and the mixture was extracted with ethyl acetate (50 mL $\times$ 2). The extract was washed with saturated brine and concentrated under reduced pressure, and the residue was purified by silica gel column chromatography to give the title compound (144 mg) as a white solid.

55  $^1\text{H-NMR}$ (400Mz,  $\text{CDCl}_3$ ) $\delta$ 0.88(3H, t, J = 7.0Hz), 1.02(3H, t, J = 7.0Hz), 2.91-3.03(2H, m), 3.09-3.20(2H, m), 3.28(1H, dd, J = 13.2, 9.2Hz), 3.42-3.51(1H, m), 3.61(1H, dd, J = 9.2, 6.0Hz), 7.20-7.32(3H, m), 7.62-7.71(2H, m), 7.92-8.03(5H,

m), 8.66(1H, s), 10.72(1H, s).  
MS: 484(M+H)<sup>+</sup>.

Example 115 Synthesis of 2-(3-aminobenzyl)-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

**[0320]** In the same manner as in Example 7, the title compound (83 mg) was obtained as a white powder using the compound (104 mg) obtained in Example 114 at room temperature. <sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ0.75-0.84(3H, m), 0.97-1.06(3H, m), 2.78-3.12(5H, m), 3.47-3.55(2H, m), 6.36(1H, d, J = 2.0Hz), 6.43(1H, d, J = 7.6Hz), 6.48(1H, dd, J = 7.6, 2.0Hz), 6.93(1H, t, J = 7.6Hz), 7.60-7.69(2H, m), 7.91-8.02(4H, m), 8.67(1H, s). MS: 454(M+H)<sup>+</sup>.

Example 116 Synthesis of N, N-diethyl-N'-(2-naphthylsulfonyl)-2-(2-nitrobenzyl)malonamide

(1) diethyl 2-nitrobenzylmalonate

**[0321]** In the same manner as in Example 6 (1), a crude product was obtained using diethyl malonate (10.1 g) and 2-nitrobenzyl bromide (13.6 g). This was purified by silica gel column chromatography to give the title compound (13.9 g) as an oil. <sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.19-1.24(6H, m), 3.51(2H, d, J = 7.6Hz), 3.87(1H, t, J = 7.6Hz), 4.10-4.24(4H, m), 7.39-7.44(2H, m), 7.51-7.55(1H, m), 8.01(1H, d, J = 7.6Hz).

(2) monoethyl (2-nitrobenzyl)malonate

**[0322]** In the same manner as in Example 111 (2), a crude product was obtained using the above-mentioned compound (13.8 g). This was purified by silica gel column chromatography to give the title compound (3.75 g) as an oil. <sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.22(3H, t, J = 7.2Hz), 3.45-3.56(2H, m), 3.95(1H, t, J = 7.2Hz), 4.14-4.22(2H, m), 7.42-7.46(2H, m), 7.55(1H, dd, J = 8.0, 7.8Hz), 8.03(1H, d, J = 8.0Hz).

(3) ethyl 3-[(2-naphthylsulfonyl)amino]-2-(2-nitrobenzyl)-3-oxopropionate

**[0323]** In the same manner as in Example 1 (2), the title compound (860 mg) was obtained as a pale-yellow powder using the above-mentioned compound (910 mg). <sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.10-1.17(3H, m), 3.34-3.48(2H, m), 3.74(1H, t, J = 7.2Hz), 4.06-4.18(2H, m), 7.14-7.32(3H, m), 7.63-7.69(2H, m), 7.70-8.04(5H, m), 8.64(1H, s), 9.25(1H, brs).

(4) N, N-diethyl-N'-(2-naphthylsulfonyl)-2-(2-nitrobenzyl)malonamide

**[0324]** To a solution of the above-mentioned compound (852 mg) in THF (10 mL) was added a solution of sodium hydroxide (292 mg) in water (2 mL), and the mixture was stirred at room temperature for 18 hr. After concentration under reduced pressure, the residue was adjusted to pH = 2-3 by the addition of dilute hydrochloric acid and extracted with ethyl acetate (50 mL × 2). After concentration under reduced pressure, the residue was subjected to the same manner as in Example 1 (4) to give a crude product. The crude product was purified by silica gel column chromatography to give the title compound (230 mg) as a pale-yellow powder. <sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.00-1.10(6H, m), 3.12-3.41(4H, m), 3.41-3.52(2H, m), 3.95(1H, dd, J = 9.2, 6.4Hz), 6.88-6.91(2H, m), 7.21-7.25(1H, m), 7.61-7.72(2H, m), 7.93-8.03(5H, m), 8.64(1H, s), 11.01(1H, s). MS: 484(M+H)<sup>+</sup>.

Example 117 Synthesis of N, N-diethyl-N'-(2-naphthylsulfonyl)-2-[4-(trifluoromethoxy)benzyl]malonamide

(1) triethyl 2-[4-(trifluoromethoxy)phenyl]ethane-1, 1, 1-tricarboxylate

**[0325]** To a solution of triethyl methanetricarboxylate (4.55 g) in DMF (40 mL) were added 4-(trifluoromethoxy)benzyl bromide (5.00 g), potassium iodide in catalytic amount and potassium carbonate (4.07 g), and the mixture was stirred at room temperature for 3 hr. Ethyl acetate (200 mL) and water (100 mL) were added to extract the reaction mixture. The extract was washed sequentially with water and brine, and concentrated under reduced pressure to give the title compound (7.97 g) as an oil. <sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ1.20(9H, t, J = 7.3Hz), 3.51(2H, s), 4.20(6H, q, J = 7.5Hz), 7.09(2H, d, J = 8.7Hz), 7.33(2H, d, J = 8.8Hz).

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(2) monoethyl (4-trifluoromethoxybenzyl)malonate

**[0326]** To a solution of the above-mentioned compound (7.97 g) in ethanol (30 mL) was added a solution of potassium hydroxide (2.20 g) in ethanol (50 mL), and the mixture was stirred at room temperature for 18 hr. The reaction mixture was concentrated, and the residue was adjusted to pH = 2-3 by the addition of dilute hydrochloric acid and extracted with ethyl acetate (200 mL). The extract was washed with saturated brine and concentrated under reduced pressure to give the title compound (5.94 g) as an oil.

<sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ1.20(3H, t, J = 7.2Hz), 3.24(2H, d, J = 7.5Hz), 3.68(1H, t, J = 7.5Hz), 4.17(2H, q, J = 7.2Hz), 7.14(2H, d, J = 8.4Hz), 7.16-7.30(2H, m).

(3) ethyl 3-[(2-naphthylsulfonyl)amino]-3-oxo-2-[4-(trifluoromethoxy)benzyl]propionate

**[0327]** In the same manner as in Example 1 (2), the title compound (3.27 g) was obtained as an oil using the above-mentioned compound (2.97 g).

<sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ1.12(3H, t, J = 6.8Hz), 3.13(2H, d, J = 7.3Hz), 3.48(1H, t, J = 6.9Hz), 4.27(2H, q, J = 7.5Hz), 6.85(2H, d, J = 8.1Hz), 6.94(2H, d, J = 8.8Hz), 7.57-7.75(2H, m), 7.84-8.08(4H, m), 8.65(1H, s).

(4) 3-[(2-naphthylsulfonyl)amino]-3-oxo-2-[4-(trifluoromethoxy)benzyl]propionic acid

**[0328]** In the same manner as in Example 111 (4), the title compound (2.36 g) was obtained as a white solid using the above-mentioned compound (3.27 g).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ2.73-3.15(2H, m), 3.50-3.85(1H, m), 6.95(2H, d, J = 8.2Hz), 7.08(2H, d, J = 8.5Hz), 7.58-7.89(3H, m), 7.93-8.18(2H, m), 8.20(1H, d, J = 8.0Hz), 8.53(1H, s), 11.60-13.80(1H, brs).

(5) N, N-diethyl-N'-(2-naphthylsulfonyl)-2-[4-(trifluoromethoxy)benzyl]malonamide

**[0329]** In the same manner as in Example 1 (4), a crude product was obtained using the above-mentioned compound (1.18 g). This was purified by silica gel column chromatography to give the title compound (530 mg) as a white powder.

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.68-0.90(6H, m), 2.95(2H, d, J = 7.2Hz), 3.00-3.27(4H, m), 3.86(1H, t, J = 7.2Hz), 7.03(2H, d, J = 8.4Hz), 7.15(2H, d, J = 9.0Hz), 7.63-7.83(3H, m), 8.02-8.26(3H, m), 8.55(1H, s), 12.34(1H, brs).

MS: 523(M+H)<sup>+</sup>.

Example 118 Synthesis of N, N-diethyl-2-(4-fluorobenzyl)-N'-(2-naphthylsulfonyl)malonamide

(1) triethyl 2-(4-fluorophenyl)ethane-1, 1,1-tricarboxylate

**[0330]** In the same manner as in Example 117 (1), the title compound (13.5 g) was obtained as an oil using triethyl methanetricarboxylate (9.29 g) and 4-fluorobenzyl bromide (7.56 g).

<sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ1.22(9H, t, J = 7.1Hz), 3.49(2H, s), 4.20(6H, q, J = 7.1Hz), 6.92(2H, t, J = 8.7Hz), 7.18-7.32(2H, m).

(2) monoethyl (4-fluorobenzyl)malonate

**[0331]** In the same manner as in Example 117 (2), the title compound (10.0 g) was obtained as an oil using the above-mentioned compound (13.5 g).

<sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ1.21(3H, t, J = 7.4Hz), 3.10-3.27(2H, m), 3.60-3.74(1H, m), 4.15(2H, q, J = 6.9Hz), 6.97(2H, t, J = 8.6Hz), 7.10-7.24(2H, m).

(3) ethyl 3-(N, N-diethylamino)-2-(4-fluorobenzyl)-3-oxopropionate

**[0332]** In the same manner as in Example 1 (4), the reaction mixture was obtained using the above-mentioned compound (3.30 g). Ethyl acetate (150 mL) and aqueous sodium hydrogen carbonate solution (120 mL) were added to extract the reaction mixture, and the organic layer was washed sequentially with 0.5 mol/L hydrochloric acid, water and brine. The organic layer was concentrated under reduced pressure to give the title compound (3.11 g) as an oil.

<sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ0.96(3H, t, J = 7.3Hz), 1.04(3H, t, J = 7.4Hz), 1.23(3H, t, J = 7.4Hz), 2.87-3.43(6H, m), 3.66-3.78(1H, m), 4.17(2H, q, J = 7.4Hz), 6.94(2H, t, J = 8.9Hz), 7.10-7.27(2H, m).

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(4) 3-(N, N-diethylamino)-2-(4-fluorobenzyl)-3-oxopropionic acid

**[0333]** To a solution of the above-mentioned compound (3.11 g) in THF (50 mL) were added 1 mol/L aqueous sodium hydroxide solution (12.6 mL) and ethanol (20 mL), and the mixture was stirred at room temperature for 3 days. After concentration under reduced pressure, 1 mol/L hydrochloric acid (50 mL) and ethyl acetate (100 mL) were added sequentially to extract the residue, and the organic layer was washed with brine. The organic layer was concentrated to give the title compound (2.77 g) as an oil.

$^1\text{H-NMR}$ (300Mz,  $\text{CDCl}_3$ ) $\delta$ 0.98(3H, t, J = 7.4Hz), 1.07(3H, t, J = 7.3Hz), 2.74-3.30(6H, m), 3.65-3.78(1H, m), 6.89-7.05(2H, m), 7.10-7.24(2H, m).

(5) N, N-diethyl-2-(4-fluorobenzyl)-N'-(2-naphthylsulfonyl)malonamide

**[0334]** In the same manner as in Example 1 (2), the title compound (1.29 g) was obtained as a white powder using the above-mentioned compound (1.39 g).

$^1\text{H-NMR}$ (300Mz,  $\text{DMSO-d}_6$ ) $\delta$ 0.70-0.96(6H, m), 2.91(2H, d, J = 7.2Hz), 3.00-3.38(4H, m), 3.84(1H, t, J = 7.5Hz), 6.85(2H, t, J = 8.7Hz), 6.99-7.14(2H, m), 7.60-7.83(3H, m), 8.02-8.16(2H, m), 8.21(1H, d, J = 8.1Hz), 8.54(1H, s), 12.29(1H, brs). MS:457 (M+H) $^+$ .

Example 119 Synthesis of N, N-diethyl-2-(3, 4-dimethoxybenzyl)-N'-(2-naphthylsulfonyl)malonamide

(1) 5-(3, 4-dimethoxybenzyl)-2, 2-dimethyl-1, 3-dioxane-4, 6-dione

**[0335]** Under ice-cooling, to formic acid (20 mL) was added dropwise triethylamine (29.6 mL). Then, 3, 4-dimethoxybenzaldehyde (9.22 g) and Meldrum's acid (8.00 g) were added under ice-cooling, and the mixture was stirred at room temperature for 18 hr. The reaction mixture was poured into a mixture of ice (80 g) and 1 mol/L hydrochloric acid (50 mL), and the precipitate was collected by filtration to give the title compound (14.4 g) as a white solid.

$^1\text{H-NMR}$ (300Mz,  $\text{CDCl}_3$ ) $\delta$ 1.70(3H, s), 1.77(3H, s), 3.38(2H, d, J = 5.6Hz), 3.86(3H, s), 3.87(3H, s), 4.14(1H, t, J = 5.8Hz), 6.77-6.90(1H, m), 6.92-7.09(2H, m).

(2) 3-(N, N-diethylamino)-2-(3, 4-dimethoxybenzyl)-3-oxopropionic acid

**[0336]** To a solution of diethylamine (1.99 g) in methylene chloride (40 mL) were added N, O-bis(trimethylsilyl)acetamide (6.66 mL) and 4-dimethylaminopyridine (1.66 g) under ice-cooling, and the mixture was stirred at room temperature for 2 hr. The above-mentioned compound (2.00 g) was added to the reaction mixture under ice-cooling, and the mixture was stirred at room temperature for 3 days. Under ice-cooling, methanol (10 mL) and water (50 mL) were added to extract the reaction mixture. The aqueous layer was acidified with 1 mol/L hydrochloric acid, and methylene chloride (50 mL) was added to extract the mixture. The organic layer was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography to give the title compound (1.52 g) as a white powder.

$^1\text{H-NMR}$ (300Mz,  $\text{CDCl}_3$ ) $\delta$ 0.80-1.00(6H, m), 2.80-2.97(1H, m), 2.99-3.40(5H, m), 3.74(3H, s), 3.77(3H, s), 3.78-3.89(1H, m), 6.66-6.77(1H, m), 6.80-6.98(2H, m), 11.20-13.50(1H, brs).

(3) N, N-diethyl-2-(3, 4-dimethoxybenzyl)-N'-(2-naphthylsulfonyl)malonamide

**[0337]** In the same manner as in Example 1 (2), the title compound (518 mg) was obtained as a white powder using the above-mentioned compound (760 mg).

$^1\text{H-NMR}$ (300Mz,  $\text{DMSO-d}_6$ ) $\delta$ 0.91(3H, t, J = 7.0Hz), 0.97(3H, t, J = 7.0Hz), 2.77-2.98(2H, m), 3.08-3.45(4H, m), 3.60(3H, s), 3.74(3H, s), 3.78-3.89(1H, m), 6.37-6.45(1H, m), 6.60(1H, t, J = 7.8Hz), 6.78(1H, dd, J = 8.2, 1.4Hz), 7.64-7.84(3H, m), 8.02-8.12(2H, m), 8.13-8.22(1H, m), 8.50(1H, s), 12.20(1H, brs).

MS: 499(M+H) $^+$ .

Example 120 Synthesis of N, N-diethyl-2-(4-methoxycarbonylbenzyl)-N'-(2-naphthylsulfonyl)malonamide (1) 5-(4-methoxycarbonylbenzyl)-2, 2-dimethyl-1, 3-dioxane-4, 6-dione

**[0338]** In the same manner as in Example 119 (1), the title compound (8.57 g) was obtained as a white powder using methyl 4-formylbenzoate (9.11 g).

$^1\text{H-NMR}$ (300Mz,  $\text{CDCl}_3$ ) $\delta$ 1.59(3H, s), 1.76(3H, s), 3.53(2H, d, J = 5.0Hz), 3.79(1H, t, J = 4.9Hz), 3.90(3H, s), 7.41(2H, d, J = 8.3Hz), 7.96(2H, d, J = 8.3Hz).

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(2) 3-(N, N-diethylamino)-2-(4-methoxycarbonylbenzyl)-3-oxopropionic acid

**[0339]** In the same manner as in Example 119 (2), the title compound (1.82 g) was obtained as a white powder using the above-mentioned compound (2.34 g).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>) $\delta$ 0.71-0.97(6H, m), 2.97-3.36(6H, m), 3.83(3H, s), 3.90-4.02(1H, m), 7.35(2H, d, J = 8.1Hz), 7.84(2H, d, J = 8.4Hz).

(3) N, N-diethyl-2-(4-methoxycarbonylbenzyl)-N'-(2-naphthylsulfonyl)malonamide

**[0340]** In the same manner as in Example 1 (2), the title compound (470 mg) was obtained as a white powder using the above-mentioned compound (909 mg).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>) $\delta$ 0.77-0.98(6H, m), 2.99(2H, d, J = 7.5Hz), 3.09-3.35(4H, m), 3.83(3H, s), 3.82-3.97(1H, m), 7.16(2H, d, J = 8.4Hz), 7.62(2H, d, J = 8.1Hz), 7.67-7.83(3H, m), 8.04-8.15(2H, m), 8.18(1H, d, J = 7.8Hz), 8.51(1H, s), 12.35(1H, brs).

MS: 497(M+H)<sup>+</sup>.

Example 121 Synthesis of 2-(4-carboxybenzyl)-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

**[0341]** To the compound (300 mg) obtained in Example 120 were added THF (20 mL), methanol (10 mL) and 1 mol/L aqueous sodium hydroxide solution (2.66 mL), and the mixture was stirred at room temperature for 3 days. The reaction mixture was concentrated, and water (30 mL) and chloroform (30 mL) were added to extract the residue. The aqueous layer was adjusted to pH = 1-2 by the addition of 1 mol/L hydrochloric acid, and chloroform (30 mL) was added to extract the mixture. The organic layer was concentrated under reduced pressure to give the title compound (242 mg) as a white powder.

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>) $\delta$ 0.63-0.94(6H, m), 2.90-3.30(6H, m), 3.89(1H, t, J = 7.2Hz), 7.17(2H, d, J = 8.1Hz), 7.60-7.82(5H, m), 8.01-8.10(2H, m), 8.19(1H, d, J = 7.8Hz), 8.53(1H, s), 12.34(1H, brs), 12.78(1H, brs).

MS: 483(M+H)<sup>+</sup>.

Example 122 Synthesis of N, N-diethyl-2-[(2-methoxy-5-pyridyl)methyl]-N'-(2-naphthylsulfonyl)malonamide

(1) 5-(2-methoxy-5-pyridylmethyl)-2, 2-dimethyl-1, 3-dioxane-4, 6-dione

**[0342]** Under ice-cooling, to formic acid (10 mL) was added dropwise triethylamine (14.8 mL). Then, 6-methoxy-3-pyridinecarboxyaldehyde (3.81 g) and Meldrum's acid (4.00 g) were added under ice-cooling, and the mixture was stirred at room temperature for 18 hr. The reaction mixture was poured into ice-water, and ethyl acetate was added to extract the mixture. The organic layer was concentrated under reduced pressure. THF and then, ether were added to the residue, and the precipitate was collected by filtration to give the title compound (2.54 g) as a white powder.

<sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>) $\delta$ 1.62(3H, s), 1.76(3H, s), 3.41(2H, d, J = 4.8Hz), 3.72(1H, t, J = 4.5Hz), 3.91(3H, s), 6.67(1H, d, J = 8.7Hz), 7.59(1H, dd, J = 8.4, 2.7Hz), 8.13(1H, d, J = 2.4Hz).

(2) 3-(N, N-diethylamino)-2-(2-methoxy-5-pyridyl)methyl-3-oxopropionic acid

**[0343]** In the same manner as in Example 119 (2), the title compound (1.41 g) was obtained as an oil using the above-mentioned compound (2.12 g).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>) $\delta$ 0.77-0.96(6H, m), 2.88-3.32(6H, m), 3.79(3H, s), 3.84-3.96(1H, m), 6.70(1H, d, J = 8.4Hz), 7.55(1H, dd, J = 8.4, 2.4Hz), 7.96(1H, d, J = 2.4Hz).

(3) N, N-diethyl-2-[(2-methoxy-5-pyridyl)methyl]-N'-(2-naphthylsulfonyl)malonamide

**[0344]** In the same manner as in Example 1 (2), the title compound (649 mg) was obtained as a white powder using the above-mentioned compound (705 mg).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>) $\delta$ 0.70-0.95(6H, m), 2.70-2.90(2H, m), 3.00-3.27(4H, m), 3.75(3H, s), 3.76-3.85(1H, m), 6.50(1H, d, J = 8.6Hz), 7.35(1H, dd, J = 8.6, 2.3Hz), 7.63-7.89(4H, m), 7.99-8.10(2H, m), 8.21(H, d, J = 7.9Hz), 8.54(1H, s), 12.34(1H, brs).

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Example 123 Synthesis of N, N-diethyl-2-(2-naphthylmethyl)-N'-(2-naphthylsulfonyl)malonamide

(1) diethyl (2-naphthylmethyl)malonate

5 **[0345]** In the same manner as in Example 6 (1), a crude product of the title compound was obtained using diethyl malonate (7.46 g) and 2-(bromomethyl)naphthalene (10.3 g).

(2) monoethyl (2-naphthylmethyl)malonate

10 **[0346]** In the same manner as in Example 1 (1), the title compound (2.88 g) was obtained as an oil using the above-mentioned crude product.

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.18(3H, t, J = 7.2Hz), 3.35-3.45(2H, m), 3.81(1H, J = 7.7Hz), 9.09-4.20(2H, m), 7.33(1H, dd, J = 8.5, 1.4Hz), 7.41-7.49(2H, m), 7.66(1H, s), 7.76-7.81(3H, m).

15 (3) ethyl 2-(2-naphthylmethyl)-3-[(2-naphthylsulfonyl)amino]-3-oxopropionate

**[0347]** In the same manner as in Example 1 (2), the title compound (290 mg) was obtained as a white powder using the above-mentioned compound (280 mg).

20 <sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.00(3H, t, J = 7.2Hz), 3.22-3.31 (2H, m), 3.73(1H, t, J = 7.2Hz), 4.02(2H, q, J = 7.2Hz), 7.04(1H, dd, J = 8.4, 1.2Hz), 7.27-7.45(5H, m), 7.50-7.54(1H, m), 7.59-7.86(6H, m), 8.60(1H, s), 10.04(1H, s).

(4) 2-(2-naphthylmethyl)-3-[(2-naphthylsulfonyl)amino]-3-oxopropionic acid

25 **[0348]** In the same manner as in Example 1 (3), the title compound (272 mg) was obtained using the above-mentioned compound (290 mg).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ3.30-3.38(2H, m), 3.67(1H, t, J = 7.2Hz), 7.02-7.05(1H, m), 7.32-7.52 (5H, m), 7.63-7.74(3H, m), 7.86-8.00(4H, m), 8.61(1H, s).

(5) N, N-diethyl-2-(2-naphthylmethyl)-N'-(2-naphthylsulfonyl)malonamide

30 **[0349]** In the same manner as in Example 1 (4), a crude product was obtained using the above-mentioned compound (290 mg). This was purified by silica gel column chromatography to give the title compound (151 mg) as a white powder.  
<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ0.78-0.88(6H, m), 3.06-3.23(6H, m), 3.98(1H, t, J = 7.2Hz), 7.24(1H, dd, J = 8.8, 1.6Hz), 7.40-7.47(2H, m), 7.54(1H, s), 7.62-7.81(6H, m), 7.96(1H, d, J = 8.8Hz), 8.04(1H, d, J = 8.0Hz), 8.17(1H, d, J = 8.0Hz), 8.53(1H, s), 12.37(1H, brs).  
35 MS: 489(M+H)<sup>+</sup>.

Example 124 Synthesis of 2-(4-biphenylmethyl)-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

40 (1) diethyl (4-biphenylmethyl)malonate

**[0350]** In the same manner as in Example 6 (1), a crude product of the title compound was obtained using diethyl malonate (5.02 g) and 4-(bromomethyl)biphenyl (7.75 g).

45 (2) monoethyl (4-biphenylmethyl)malonate

**[0351]** In the same manner as in Example 1 (1), the title compound (1.05 g) was obtained as a white solid using the above-mentioned crude product.

50 <sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ1.18(3H, t, J = 6.8Hz), 3.07-3.15(2H, m), 3.74(1H, t, J = 8.0Hz), 4.01-4.12(2H, m), 7.31-7.36(3H, m), 7.43-7.47(2H, m), 7.58(2H, d, J = 8.0Hz), 7.64(2H, d, J = 8.0Hz), 12.86(1H, brs).

(3) ethyl 2-(4-biphenylmethyl)-3-[(2-naphthylsulfonyl)amino]-3-oxopropionate

55 **[0352]** In the same manner as in Example 1 (2), the title compound (910 mg) was obtained as a white powder using the above-mentioned compound (1.01 g).

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ1.00(3H, t, J = 7.2Hz), 2.94-3.03(2H, m), 3.76-3.79(1H, m), 4.01(2H, q, J = 7.2Hz), 7.06(2H, d, J = 8.0Hz), 7.29(2H, d, J = 8.0Hz), 7.33-7.37(1H, m), 7.43-7.51(4H, m), 7.63-7.81(3H, m), 8.02(1H, d, J = 8.4Hz), 8.10(1H, d, J = 8.8Hz), 8.19(1H, d, J = 8.0Hz), 8.54(1H, d, J = 0.8Hz), 12.55(1H, brs).

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(4) 2-(4-biphenylmethyl)-3-[(2-naphthylsulfonyl)amino]-3-oxopropionic acid

**[0353]** In the same manner as in Example 1 (3), the title compound (859 mg) was obtained using the above-mentioned compound (910 mg).

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ2.91-3.01(2H, m), 3.67-3.71(1H, m), 7.02(2H, d, J = 8.0Hz), 7.22(2H, d, J = 8.0Hz), 7.33-7.38(1H, m), 7.42-7.47(4H, m), 7.64-7.91(3H, m), 8.00(1H, d, J = 8.4Hz), 8.07(1H, d, J = 8.8Hz), 8.18(1H, d, J = 8.0Hz), 8.53(1H, s), 12.47(1H, brs), 13.00(1H, brs).

(5) 2-(4-biphenylmethyl)-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

**[0354]** In the same manner as in Example 1 (4), the title compound (760 mg) was obtained as a white solid using the above-mentioned compound (782 mg).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ0.84(3H, t, J = 7.2Hz), 1.03(3H, t, J = 7.2Hz), 2.88-2.93(2H, m), 3.04-3.19(3H, m), 3.43-3.52(1H, m), 3.59-3.63(1H, m), 7.06(2H, d, J = 8.0Hz), 7.31(2H, d, J = 8.0Hz), 7.31-7.35(1H, m), 7.39-7.47(4H, m), 7.58-7.68(2H, m), 7.89-8.05(4H, m), 8.67(1H, s).

MS: 515(M+H)<sup>+</sup>.

Example 125 Synthesis of N, N-diethyl-2-[4-(1H-imidazol-1-yl)benzyl]-N'-(2-naphthylsulfonyl)malonamide hydrochloride

**[0355]** To a solution of hydrochloride salt (550 mg) of the compound obtained in Example 7 in ethanol (4 mL) were added 35% aqueous formaldehyde solution (350 μL), 40% aqueous paraformaldehyde solution (600 μL) and 28% aqueous ammonia (250 μL), and the mixture was stirred at 50°C for 3 hr. The mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography. This was dissolved in ethyl acetate (5 mL), 4 mol/L hydrochloric acid/ethyl acetate (1 mL) was added, and the precipitate was collected by filtration to give the title compound (295 mg) as a white solid.

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ0.87(6H, t, J = 7.2Hz), 2.96-3.10(2H, m), 3.11-3.23(4H, m), 4.03(1H, t, J = 7.2Hz), 7.35(2H, d, J = 8.4Hz), 7.52(2H, d, J = 8.4Hz), 7.64-7.74(2H, m), 7.81-7.84(1H, m), 7.89(1H, s), 8.03(1H, d, J = 8.4Hz), 8.12(1H, d, J = 8.8Hz), 8.17(1H, s), 8.18(1H, d, J = 8.4Hz), 8.54(1H, d, J = 0.8Hz), 9.56(1H, s), 12.80(1H, brs).

MS: 505 (M+H)<sup>+</sup>.

Example 126 Synthesis of 2-[4-(5-chloro-2-pyridyloxy)benzyl]-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

(1) triethyl 2-[4-(5-chloro-2-pyridyloxy)phenyl]ethane-1, 1, 1-tricarboxylate

**[0356]** In the same manner as in Example 117 (1), the title compound (4.60 g) was obtained as an oil using triethyl methanetricarboxylate (2.60 g) and 4-(5-chloro-2-pyridyloxy)benzyl chloride (2.77 g).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.23(9H, t, J = 7.2Hz), 3.52(2H, s), 4.21(6H, q, J = 7.2Hz), 6.83(1H, d, J = 8.8Hz), 6.99(2H, d, J = 8.4Hz), 7.32(2H, d, J = 8.4Hz), 7.61(1H, dd, J = 8.8, 2.8Hz), 8.10(1H, d, J = 2.8Hz).

(2) monoethyl [4-(5-chloro-2-pyridyloxy)benzyl]malonate

**[0357]** In the same manner as in Example 117 (2), the title compound (2.96 g) was obtained as an oil using the above-mentioned compound (4.60 g).

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)1.12(3H, t, J = 7.2Hz), 3.02-3.12(2H, m), 3.71(1H, t, J = 8.0Hz), 4.07(2H, q, J = 7.2Hz), 7.03-7.27(5H, m), 7.94(1H, dd, J = 8.8, 2.8Hz), 8.19(1H, d, J = 2.8Hz), 12.90(1H, brs).

(3) ethyl 2-[4-(5-chloro-2-pyridyloxy)benzyl]-3-(N, N-diethylamino)-3-oxopropionate

**[0358]** In the same manner as in Example 1 (4), the reaction mixture was obtained using the above-mentioned compound (2.67 g). The reaction mixture was adjusted to pH = 1-2 by the addition of dilute hydrochloric acid (50 mL) and extracted with ethyl acetate (100 mL). The organic layer was washed with water and saturated brine, and concentrated under reduced pressure to give the title compound (2.40 g) as an oil.

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ0.88-0.93(6H, m), 1.13(3H, t, J = 7.2Hz), 3.01-3.28(6H, m), 4.02-4.09(3H, m), 7.01-7.03(3H, m), 7.24(2H, d, J = 8.8Hz), 7.93(1H, dd, J = 8.4, 2.4Hz), 8.17(1H, d, J = 2.4Hz).

(4) 2-[4-(5-chloro-2-pyridyloxy)benzyl]-3-(N, N-diethylamino)-3-oxopropionic acid

**[0359]** In the same manner as in Example 1 (3), the title compound (1.91 g) was obtained as an oil using the above-

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mentioned compound (2.40 g).

$^1\text{H-NMR}$ (400Mz, DMSO- $d_6$ ) $\delta$ 0.85-0.96(6H, m), 2.97-3.34(6H, m), 3.91(1H, dd, J = 9.2, 6.0Hz), 7.00-7.03(3H, m), 7.24(1H, d, J = 8.4Hz), 7.93(1H, dd, J = 8.8, 2.8Hz), 8.17(1H, d, J = 2.8Hz), 12.56(1H, brs).

5 (5) 2-[4-(5-chloro-2-pyridyloxy)benzyl]-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

**[0360]** In the same manner as in Example 1 (2), the title compound (1.03 g) was obtained as a white solid using the above-mentioned compound (1.91 g).

10  $^1\text{H-NMR}$ (400Mz, DMSO- $d_6$ ) $\delta$ 0.88(6H, t, J = 7.2Hz), 2.93(2H, d, J = 7.2Hz), 3.10-3.25(4H, m), 3.87(1H, t, J = 7.2Hz), 6.81(2H, d, J = 8.4Hz), 7.02-7.06(3H, m), 7.65-7.74(2H, m), 7.81(1H, dd, J = 8.8, 1.6Hz), 7.93-7.96(1H, m), 8.04(1H, d, J = 8.0Hz), 8.12(1H, d, J = 8.8Hz), 8.16-8.19(2H, m), 8.55(1H, s), 12.30(1H, brs).

MS: 566(M+H) $^+$ .

Example 127 Synthesis of N, N-diethyl-N'-(2-naphthylsulfonyl)-2-[4-(2-pyridyloxy)benzyl]malonamide

15 **[0361]** To a mixed solution of the compound (720 mg) obtained in Example 126 in ethanol (30 mL)/ethyl acetate (10 mL) was added 10% palladium/carbon (350 mg), and the mixture was stirred under hydrogen atmosphere for 42 hr. Insoluble material was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound (265 mg) as a white solid.

20  $^1\text{H-NMR}$ (300Mz, DMSO- $d_6$ ) $\delta$ 0.88(6H, t, J = 6.9Hz), 2.92(2H, d, J = 6.9Hz), 3.05-3.23(4H, m), 3.87(1H, t, J = 6.9Hz), 6.78(2H, d, J = 8.4Hz), 6.97(1H, d, J = 8.1Hz), 7.03(2H, d, J = 8.4Hz), 7.07-7.13(1H, m), 7.60-7.87(4H, m), 8.02-8.19(4H, m), 8.55(1H, s), 12.35(1H, brs).

MS: 532(M+H) $^+$ .

25 Example 128 Synthesis of N, N-diethyl-N'-(2-naphthylsulfonyl)-2-[(2-phenyl-1, 3-benzoxazol-6-yl)methyl]malonamide (1) ethyl 2-phenyl-1, 3-benzoxazole-6-carboxylate

30 **[0362]** To a solution of ethyl 3-hydroxy-4-nitrobenzoate (3.56 g) in ethyl acetate (100 mL) was added 10% palladium/carbon (600 mg), and the mixture was stirred under hydrogen atmosphere for 5 hr. Insoluble material was removed by filtration, and the filtrate was concentrated under reduced pressure. To a solution of the residue in methanol (100 mL) were added benzaldehyde (1.50 mL) and sodium sulfate (1.00 g), and the mixture was stirred at 45°C for 16 hr. Insoluble material was removed by filtration, and the filtrate was concentrated under reduced pressure. To a solution of the residue in methylene chloride (100 mL) was added 2, 3-dichloro-5, 6-dicyano-1, 4-benzoquinone (DDQ) (4.21 g), and the mixture was stirred at room temperature for 30 min. Saturated aqueous sodium hydrogen carbonate solution (300 mL) was added to the reaction mixture, and the mixture was extracted with chloroform (100 mL $\times$ 2). The organic layer was washed with saturated brine. After concentration under reduced pressure, the residue was purified by silica gel column chromatography to give the title compound (3.60 g) as a pale-yellow solid.

35  $^1\text{H-NMR}$ (300Mz, CDCl $_3$ ) $\delta$ 1.44(3H, t, J = 7.1Hz), 4.43(2H, q, J = 7.1Hz), 7.53-7.59(3H, m), 7.90(1H, d, J = 8.4Hz), 8.11(1H, dd, J = 8.4, 1.4Hz), 8.27-8.30(3H, m).

40

(2) 6-hydroxymethyl-2-phenyl-1, 3-benzoxazole

45 **[0363]** To a solution of the above-mentioned compound (3.58 g) in THF (100 mL) was added lithium aluminum hydride (510 mg) under ice-cooling, and the mixture was stirred at room temperature for 39 hr. Saturated aqueous (+)-potassium sodium tartrate solution (300 mL) was added to the reaction mixture, and the mixture was extracted with ethyl acetate (200 mL $\times$ 2). The organic layer was washed with saturated brine and concentrated under reduced pressure to give the title compound (2.60 g) as a white solid.

50  $^1\text{H-NMR}$ (400Mz, DMSO- $d_6$ ) $\delta$ 4.65(2H, d, J = 5.6Hz), 5.36(1H, t, J = 5.6Hz), 7.37(1H, d, J = 8.0Hz), 7.62-7.64(3H, m), 7.71(1H, s), 7.75(1H, d, J = 8.0Hz), 8.19-8.22(2H, m).

55

(3) 6-chloromethyl-2-phenyl-1, 3-benzoxazole

**[0364]** To a solution of the above-mentioned compound (2.56 g) in chloroform (200 mL) was added thionyl chloride (2.73 mL), and the mixture was heated under reflux for 8 hr. Saturated aqueous sodium hydrogen carbonate solution (100 mL) was added to extract the reaction mixture. The organic layer was washed with saturated brine and concentrated under reduced pressure to give the title compound (2.69 g) as a pale-yellow solid.  $^1\text{H-NMR}$ (400Mz, DMSO- $d_6$ ) $\delta$ 4.94(2H, s), 7.51(1H, dd, J = 8.0, 1.2Hz), 7.52-7.66(3H, m), 7.81(1H, d, J = 8.0Hz), 7.90(1H, s), 8.20-8.23(2H, m).

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(4) triethyl 2-(2-phenyl-1, 3-benzoxazol-6-yl)ethane-1, 1, 1-tricarboxylate

**[0365]** In the same manner as in Example 117 (1), the title compound (4.83 g) was obtained as an oil using triethyl methanetricarboxylate (2.56 g) and the above-mentioned compound (2.69 g).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.22 (9H, t, J = 7.2Hz), 3.67 (2H, s), 4.22(6H q, J = 7.2Hz), 7.24-7.27 (1H, m), 7.50-7.54(3H, m), 7.61-7.63(2H, m), 8.22-8.25 (2H, m).

(5) monoethyl [(2-phenyl-1, 3-benzoxazol-6-yl)methyl]malonate

**[0366]** In the same manner as in Example 117 (2), the title compound (3.55 g) was obtained as a pale-yellow solid using the above-mentioned compound (4.83 g).

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ1.03-1.10(3H, m), 3.17-3.26(2H, m), 3.82 (1H, t, J = 8.0Hz), 4.00-4.11(2H, m), 7.29(1H, dd, J = 8.0, 1.2Hz), 7.59-7.72(5H, m), 8.18-8.20(2H, m), 12.92(1H, brs).

(6) ethyl 3-(N, N-diethylamino)-3-oxo-2-[(2-phenyl-1, 3-benzoxazol-6-yl)methyl]propionate

**[0367]** In the same manner as in Example 1 (4), the reaction mixture was obtained using the above-mentioned compound (820 mg). The reaction mixture was adjusted to pH = 1-2 by the addition of dilute hydrochloric acid (50 mL) and extracted with ethyl acetate (100 mL). The organic layer was washed with water and saturated brine, and concentrated under reduced pressure to give the title compound (860 mg) as an oil. <sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ0-94(3H, t, J = 7.2Hz), 1.04(3H, t, J = 7.2Hz), 3.00-3.25(2H, m), 3.25-3.49(4H, m), 3.80-3.87(1H, m), 4.19(2H, q, J = 7.2Hz), 7.22(1H, dd, J = 8.1, 1.2Hz), 7.48(1H, d, J = 1.2Hz), 7.52-7.54(3H, m), 7.66(1H, d, J = 8.1Hz), 8.22-8.26(2H, m).

(7) 3-(N, N-diethylamino)-3-oxo-2-[(2-phenyl-1, 3-benzoxazol-6-yl)methyl]propionic acid

**[0368]** In the same manner as in Example 1 (3), the title compound (630 mg) was obtained as a white powder using the above-mentioned compound (860 mg).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ0.95(3H, t, J = 7.2Hz), 1.07(3H, t, J = 7.2Hz), 2.67-2.75(1H, m), 2.84-2.93(1H, m), 3.06-3.14(1H, m), 3.07-3.12(2H, m), 3.56-3.64(1H, m), 3.80(1H, dd, J = 9.6, 5.2Hz), 7.20 (1H, dd, J = 8.0, 1.2Hz), 7.44(1H, d, J = 1.2Hz), 7.52-7.56(3H, m), 7.69(1H, d, J = 8.0Hz), 8.23-8.26(2H, m).

(8) N, N-diethyl-N'-(2-naphthylsulfonyl)-2-[(2-phenyl-1, 3-benzoxazol-6-yl)methyl]malonamide

**[0369]** In the same manner as in Example 1 (2), the title compound (361 mg) was obtained as a white solid using the above-mentioned compound (630 mg).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.88(3H, t, J = 6.5Hz), 3.09-3.24(6H, m), 3.98(1H, t, J = 7.2Hz), 7.12(1H, d, J = 8.3Hz), 7.44(1H, s), 7.51(1H, d, J = 8.3Hz), 7.64-7.72(6H, m), 7.94-8.02(2H, m), 8.15-8.17(3H, m), 8.52(1H, s), 12.33(1H, brs). MS: 556(M+H)<sup>+</sup>.

Example 129 Synthesis of N, N-diethyl-2-[4-(1, 3-dihydro-2H-isoindol-2-yl)benzyl]-N'-(2-naphthylsulfonyl)malonamide hydrochloride

**[0370]** To a solution of hydrochloride salt (200 mg) of the compound obtained in Example 7 in DMF (5 mL) were added O-xylene dibromide (110 mg) and potassium carbonate (260 mg), and the mixture was stirred at room temperature for 17 hr. The reaction mixture was adjusted to pH = 1-2 by the addition of dilute hydrochloric acid, and the precipitate was collected by filtration to give the title compound (188 mg) as a white solid.

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.88-0.92(6H, m), 2.67-2.88(2H, m), 3.00-3.62(5H, m), 4.46(4H, s), 6.37(2H, d, J = 8.1Hz), 6.90(2H, d, J = 8.1Hz), 7.29-7.41(4H, m), 7.55-7.68(2H, m), 7.80(1H, d, J = 8.6Hz), 7.83-8.07(3H, m), 8.33(1H, s), 12.22(1H, brs).

MS: 556(M+H)<sup>+</sup>.

Example 130 Synthesis of N, N-diethyl-N'-(2-naphthylsulfonyl)-2-[4-(1-oxo-1, 3-dihydro-2H-isoindol-2-yl)benzyl]malonamide

(1) N, N-diethyl-2-[4-(1, 3-dioxo-1, 3-dihydro-2H-isoindol-2-yl)benzyl]-N'-(2-naphthylsulfonyl)malonamide

**[0371]** To a solution of hydrochloride salt (500 mg) of the compound obtained in Example 7 in pyridine (10 mL) was added phthaloyl chloride (150 μL) under ice-cooling, and the mixture was stirred at room temperature for 1.5 hr. The

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reaction mixture was adjusted to pH = 1-2 by the addition of dilute hydrochloric acid, and the precipitate was collected by filtration. This was purified by silica gel column chromatography to give the title compound (140 mg) as a pale-yellow powder.

<sup>1</sup>H-NMR (300Mz, CDCl<sub>3</sub>) δ0.80 (3H, t, J = 7.2Hz), 1.02(3H, t, J = 7.2Hz), 2.85(2H, q, J = 7.2Hz), 2.94-3.19(3H, m), 3.39-3.61(2H, m), 7.04(2H, d, J = 8.4Hz), 7.17(2H, d, J = 8.4Hz), 7.21-7.27(1H, m), 7.53-8.04(9H, m), 8.65(1H, s).

(2) N, N-diethyl-N'-(2-naphthylsulfonyl)-2-[4-(1-oxo-1, 3-dihydro-2H-isoindol-2-yl)benzyl]malonamide

**[0372]** To a solution of the above-mentioned compound (140 mg) in acetic acid (10 mL) was added zinc (300 mg), and the mixture was heated under reflux for 1 hr. Insoluble material was removed by filtration and, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound (22 mg) as a white solid.

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>) δ0.88-0.92 (6H, m), 2.98-2.97 (2H, m), 3.10-3.26(4H, m), 8.85-3.92(1H, m), 4.84(2H, d, J = 16.0Hz), 7.08(2H, d, J = 8.4Hz), 7.57(2H, d, J = 8.4Hz), 7.56-7.70(5H, m), 7.78-7.81(2H, m), 8.03-8.05(1H, m), 8.13(1H, d, J = 8.8Hz), 8.17-8.20(1H, m), 8.53(1H, s), 12.31(1H, brs).

MS: 570(M+H)<sup>+</sup>.

Example 131 Synthesis of N, N-diethyl-2-(4-[(1, 3-benzoxazol-2-yl)amino]benzyl)-N'-(2-naphthylsulfonyl)malonamide

**[0373]** To a solution of the compound (450 mg) obtained in Example 7 in N-methyl-2-pyrrolidinone (2 mL) were added 2-chloro-1, 3-benzoxazole (230 μL) and diisopropyl ethyl amine (500 μL), and the mixture was stirred at 100°C for 10 hr. The reaction mixture was adjusted to pH = 2-3 by the addition of dilute hydrochloric acid, and extracted with ethyl acetate (50 mL). The organic layer was washed with saturated brine and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound (256 mg) as a white solid.

<sup>1</sup>H-NMR(300MHz, DMSO-d<sub>6</sub>)δ0.85(3H, t, J = 7.3Hz), 1.05 (3H, t, J = 7.3Hz), 2.80-3.30(5H, m), 3.28-3.63(2H, m), 7.02(2H, d, J = 8.4Hz), 7.05-7.40(6H, m), 7.49(1H, d, J = 7.4Hz), 7.50-7.70(2H, m), 7.85-8.08(4H, m), 8.67(1H, brs).

MS: 571 (M+H)<sup>+</sup>.

Example 132 Synthesis of N, N-diethyl-N'-(2-naphthylsulfonyl)-2-[4-(phenylethynyl)benzyl]malonamide

(1) 2, 2-dimethyl-5-[4-(phenylethynyl)benzyl]-1, 3-dioxane-4, 6-dione

**[0374]** To a mixture of Meldrum's acid (688 mg) and 4-phenylethynylbenzoic acid (955 mg) in methylene chloride (30 mL) was added a solution of 4-dimethylaminopyridine (830 mg) and N, N'-dicyclohexylcarbodiimide (976 mg) in methylene chloride (15 mL) under ice-cooling, and the mixture was stirred at room temperature for 66 hr. Insoluble material was removed by filtration, and the filtrate was washed with 10% potassium hydrogen sulfate (30 mL) and saturated brine and concentrated under reduced pressure. The residue was dissolved in acetic acid (5 mL), and the solution was cooled to 0°C. Sodium borohydride (408 mg) was added, and the mixture was stirred at room temperature for 6 hr. Water (50 mL) was added to the reaction mixture, and the mixture was extracted with methylene chloride (50 mL×2). The organic layer was washed with saturated brine and concentrated under reduced pressure. The residue was washed with isopropanol, and the resulting precipitate was collected by filtration to give the title compound (654 mg) as a white solid.

<sup>1</sup>H-NMR(300MHz, CDCl<sub>3</sub>)δ1.56 (3H, s), 1.75 (3H, s), 3.50(2H, d, J = 4.8Hz), 3.76(1H, t, J = 4.8Hz), 7.28-7.40 (5H, m), 7.44-7.55(4H, m).

(2) 3-(N, N-diethylamino)-3-oxo-2-[4-(phenylethynyl)benzyl]propionic acid

**[0375]** In the same manner as in Example 119 (2), the title compound (470 mg) was obtained as a white solid using the above-mentioned compound (654 mg).

<sup>1</sup>H-NMR(300MHz, CDCl<sub>3</sub>)δ0.97(3H, t, J = 7.2Hz), 1.09(3H, t, J = 7.2Hz), 2.70-3.01(2H, m), 3.05-3.19(1H, m), 3.19-3.37(1H, m), 3.52-3.68(1H, m), 3.73(1H, dd, J = 9.6, 5.4Hz), 7.18(2H, d, J = 8.1Hz), 7.34 (3H, dd, J = 6.0, 3.6Hz), 7.46 (2H, d, J = 8.1Hz), 7.48-7.60(2H, m).

(3) N, N-diethyl-N'-(2-naphthylsulfonyl)-2-[4-(phenylethynyl)benzyl]malonamide

**[0376]** In the same manner as in Example 1 (2), a crude product was obtained using the above-mentioned compound (470 mg). This was washed with ethyl acetate, and the resulting precipitate was collected by filtration to give the title compound (365 mg) as a white solid.

<sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.82(3H, t, J = 7.2Hz), 1.03(3H, t, J = 7.2Hz), 2.85(2H, q, J = 7.2Hz), 3.02(1H, dd, J =

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14.4, 4.8Hz), 3.08-3.22(2H, m), 3.40-3.52(1H, m), 3.56(1H, q, J = 10.2Hz), 7.01 (2H, d, J = 8.1Hz), 7.14 (2H, d, J = 9.6Hz), 7.31-7.40 (3H, m), 7.45-7.55(2H, m), 7.58-7.70(2H, m), 7.86-8.08(5H, m), 8.67(1H, brs).  
MS: 539(M+H)<sup>+</sup>.

### 5 Example 133 Synthesis of N, N-diethyl-N'-(2-naphthylsulfonyl)-2-{4-[(E)-2-phenylvinyl]benzyl}malonamide

(1) triethyl 2-{4-[(E)-2-phenylvinyl]phenyl}ethane-1, 1, 1-tricarboxylate

10 **[0377]** In the same manner as in Example 117 (1), the title compound (4.69 g) was obtained as an oil using triethyl methanetricarboxylate (2.5 mL) and 4-chloromethylstilbene (2.29 g).  
<sup>1</sup>H-NMR(300MHz, CDCl<sub>3</sub>) δ1.22(9H, t, J = 6.9Hz), 3.53(2H, s), 4.21(6H, dd, J = 14.1, 6.9Hz), 7.07 (2H, s), 7.25-7.30 (2H, m), 7.37-7.42(5H, m), 7.46-7.55(2H, m).

15 (2) monoethyl {4-[(E)-2-phenylvinyl]benzyl}malonate

**[0378]** In the same manner as in Example 117 (2), the title compound (2.14 g) was obtained as a white solid using the above-mentioned compound (4.69 g).  
<sup>1</sup>H-NMR(300MHz, CDCl<sub>3</sub>) δ1.22 (3H, t, J = 7.2Hz), 3.26 (2H, d, J = 7.5Hz), 3.70(1H, t, J = 7.5Hz), 4.18(2H, q, J = 7.2Hz), 7.18-7.30(3H, m), 7.35(2H, t, J = 7.2Hz), 7.46(2H, d, J = 8.1Hz), 7.49(2H, d, J = 8.1Hz).

20

(3) ethyl 3-(N, N-diethylamino)-3-oxo-2-{4-[(E)-2-phenylvinyl]benzyl}propionate

**[0379]** In the same manner as in Example 1 (4), the reaction mixture was obtained using the above-mentioned compound (2.14 g). The reaction mixture was adjusted to pH = 1-2 by the addition of dilute hydrochloric acid (50 mL), and extracted with ethyl acetate (100 mL). The organic layer was washed with water and saturated brine, and concentrated under reduced pressure to give the title compound (2.63 g) as a white solid. <sup>1</sup>H-NMR(300MHz, CDCl<sub>3</sub>) δ0.98(3H, t, J = 7.2Hz), 1.06(3H, t, J = 7.2Hz), 1.24(3H, t, J = 7.2Hz), 3.15-3.46(6H, m), 3.78(1H, dd, J = 8.7, 2.4Hz), 4.17(2H, q, J = 6.9Hz), 7.07(2H, d, J = 3.3Hz), 7.14-7.28(2H, m), 7.28-7.49(5H, m), 7.50(2H, d, J = 7.5Hz).

25

30 (4) 3-(N, N-diethylamino)-3-oxo-2-{4-[(E)-2-phenylvinyl]benzyl}propionic acid

**[0380]** In the same manner as in Example 1 (3), the title compound (2.53 g) was obtained as a white powder using the above-mentioned compound (2.63 g).

35 (5) N, N-diethyl-N'-(2-naphthylsulfonyl)-2-{4-[(E)-2-phenylvinyl]benzyl}malonamide

**[0381]** In the same manner as in Example 1 (2), the title compound (448 mg) was obtained as a white solid using the above-mentioned compound (2.53 g).  
<sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>) δ0.83(3H, t, J = 7.5Hz), 1.04(3H, t, J = 7.2Hz), 2.86(2H, q, J = 7.5Hz), 3.00(1H, dd, J = 7.4, 5.4Hz), 3.05-3.22 (2H, m), 3.39-3.50(1H, m), 3.57(1H, m), 6.97 (2H, d, J = 7.2Hz), 6.96(2H, d, J = 7.2Hz), 7.21(2H, d, J = 8.1Hz), 7.36(2H, dd, J = 15.0, 7.2Hz), 7.48(1H, d, J = 7.2Hz), 7.58-7.70(2H, m), 7.85-8.08(4H, m), 8.67(1H, s), 10.96(1H, brs).  
MS: 541(M+H)<sup>+</sup>.

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45 Example 134 Synthesis of N, N-diethyl-N'-(2-naphthylsulfonyl)-2-(4-phenethylbenzyl)malonamide

**[0382]** To a solution of the compound (412 mg) obtained in Example 133 in ethanol (40 mL) was added 10% palladium/carbon (100 mg), and the mixture was stirred under hydrogen atmosphere at room temperature for 14 hr. Insoluble material was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound (279 mg) as a white solid.  
NMR(400MHz, DMSO-d<sub>6</sub>) δ0.60-0.98(6H, m), 2.67-2.80(4H, m), 2.80-2.95(2H, m), 3.05-3.26(4H, m), 3.82(1H, t, J = 7.2Hz), 6.88(4H, dd, J = 13.0, 8.0Hz), 7.14-7.22(3H, m), 7.23-7.30(2H, t, J = 7.7Hz), 7.71(1H, t, J = 7, 7Hz)7.77(1H, t, J = 7.0Hz), 7.81(1H, dd, J = 8.6, 1.3Hz), 8.09(1H, d, J = 8.1Hz), 8.14(1H, d, J = 8.7Hz), 8.20(1H, d, J = 8.1Hz), 8.31(1H, s), 12.26(1H, brs). MS: 543(M+H)<sup>+</sup>.

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Example 135 Synthesis of N, N-diethyl-2-[4-(2, 5-dioxo-3-phenylimidazolidin-1-yl)benzyl]-N'-(2-naphthylsulfonyl)malonamide

(1) N, N-diethyl-2-[4-[(N"-ethoxycarbonyl-N"-phenyl)aminoacetyl]aminobenzyl]-N'-(2-naphthylsulfonyl)malonamide

**[0383]** To a solution of N-phenylglycine (1.57 g) in THF (30 mL) were added ethyl chloroformate (1.60 mL) and triethylamine (4.00 mL) under ice-cooling, and the mixture was stirred at room temperature for 4 hr. The compound (453 mg) obtained in Example 7 was added to the reaction mixture, and the mixture was stirred at room temperature for 24 hr. The reaction solution was adjusted to pH = 2-3 by the addition of dilute hydrochloric acid, and the mixture was extracted with ethyl acetate (100 mL×2). The organic layer was washed with saturated brine and concentrated under reduced pressure, and the residue was purified by silica gel column chromatography to give the title compound (587 mg) as a white solid. <sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.84(3H, t, J = 7.2Hz), 0.85 (3H, t, J = 7.2Hz), 1.13(3H, t, J = 7.2Hz), 2.80-2.94(2H, m), 3.05-3.25(4H, m), 3.84(1H, t, J = 7.4Hz), 4.07(2H, q, J = 7.2Hz), 4.38(2H, s), 6.99(2H, d, J = 8.4Hz), 7.10-7.43(7H, m), 7.63-7.80(3H, m), 8.04(1H, d, J = 8.0Hz), 8.09(1H, d, J = 8.8Hz), 8.19(1H, d, J = 8.0Hz), 8.53(1H, s), 9.95(1H, s), 12.96(1H, brs).

(2) N, N-diethyl-2-[4-(2, 5-dioxo-3-phenylimidazolidin-1-yl)benzyl]-N'-(2-naphthylsulfonyl)malonamide

**[0384]** To a solution of the above-mentioned compound (587 mg) in pyridine (10 mL) was added DBU (138 μL), and the mixture was heated under reflux. The reaction solution was adjusted to pH = 2-3 by the addition of dilute hydrochloric acid and extracted with ethyl acetate (50 mL×2). The organic layer was washed with saturated brine and concentrated under reduced pressure, and the residue was purified by silica gel column chromatography to give the title compound (462 mg) as a white solid.

<sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.57-0.73(6H, m), 2.97(2H, d, J = 7.2Hz), 3.03-3.45(4H, m), 3.90(1H, d, J = 7.2Hz), 4.64(2H, s), 7.05-7.26(6H, m), 7.44(2H, t, J = 8.4Hz), 7.60-7.81(5H, m), 8.07(1H, d, J = 8.4Hz), 8.14(1H, d, J = 8.4Hz), 8.19 (1H, d, J = 8.4Hz), 8.54(1H, s), 12.34(1H, brs).

MS: 613(M+H)<sup>+</sup>.

Example 136 Synthesis of 2-[4-[benzoyl(methyl)amino]benzyl]-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

(1) 4-[benzoyl(methyl)amino]benzoic acid

**[0385]** To a mixture of 4-(methylamino)benzoic acid (1.50 g) in THF (30 mL) and 1 mol/L aqueous sodium hydroxide solution (30 mL) was added dropwise benzoyl chloride (1.20 mL) under ice-cooling, and the mixture was stirred at room temperature for 14 hr. The reaction mixture was adjusted to pH = 1-2 by the addition of dilute hydrochloric acid, and extracted with ethyl acetate (50 mL×2). The organic layer was washed with saturated brine and concentrated under reduced pressure. The residue was washed with a chloroform /hexane mixture and collected by filtration to give the title compound (1.81 g) as a white solid.

(2) 5-[4-[benzoyl(methyl)amino]benzyl]-2, 2-dimethyl-1, 3-dioxane-4, 6-dione

**[0386]** In the same manner as in Example 132 (1), the title compound (2.05 g) was obtained as a white solid using the above-mentioned compound (1.81 g).

<sup>1</sup>H-NMR(300MHz, CDCl<sub>3</sub>)δ1.54 (3H, s), 1.74 (3H, s), 3.41 (2H, d, J = 4.8Hz), 3.45(3H, s), 3.70(1H, t, J = 5.1Hz), 6.96(2H, d, J = 8.4Hz), 7.08-7.35(7H, m).

(3) 2-[4-[benzoyl(methyl)amino]benzyl]-3-(N, N-diethylamino)-3-oxopropionic acid

**[0387]** In the same manner as in Example 119 (2), the title compound (1.53 g) was obtained as an oil using the above-mentioned compound (2.05 g).

<sup>1</sup>H-NMR(300MHz, CDCl<sub>3</sub>)δ0.96(3H, t, J = 6.9Hz), 0.98(3H, t, J = 6.9Hz), 2.55-2.90 (2H, m), 2.98-3.10 (1H, m), 3.16(2H, d, J = 7.5Hz), 3.45 (3H, s), 3.46-72 (2H, m), 6.97(2H, d, J = 8.4Hz), 7.00(2H, d, J = 8.4Hz), 7.10-7.36 (5H, m).

(4) 2-[4-[benzoyl(methyl)amino]benzyl]-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

**[0388]** In the same manner as in Example 1 (2), the title compound (2.29 g) was obtained as a white solid using the above-mentioned compound (1.53 g).

<sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>) δ0.70-0.92 (6H, m), 2.84 (2H, d, J = 8.0H), 2.95-3.22(4H, m), 3.25(3H, s), 3.76(1H, t, J =

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7.2Hz), 6.82(2H, d, J = 8.4Hz), 6.89(2H, d, J = 8.4Hz), 7.12-7.28(5H, m), 7.64-7.84(3H, m), 8.08(1H, d, J = 8.0Hz), 8.13(1H, d, J = 8.8Hz), 8.20(1H, d, J = 8.4Hz), 8.55(1H, s), 12.23(1H, brs). MS: 572 (M+H)<sup>+</sup>.

Example 137 Synthesis of 2-[4-(benzoylamino)-3, 5-dimethylbenzyl]-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

(1) 5-(3, 5-dimethyl-4-nitrobenzyl)-2, 2-dimethyl-1, 3-dioxane-4, 6-dione

**[0389]** In the same manner as in Example 132 (1), the title compound (1.30 g) was obtained as a yellow solid using 3, 5-dimethyl-4-nitrobenzoic acid (1.10 g).

<sup>1</sup>H-NMR(400MHz, CDCl<sub>3</sub>)δ1.67(3H, s), 1.78(3H, s), 2.28(6H, s), 3.43(2H, d, J = 4.8H), 3.72(1H, t, J = 4.8H), 7.11(2H, s).

(2) 3-(N, N-diethylamino)-2-(3, 5-dimethyl-4-nitrobenzyl)-3-oxopropionic acid

**[0390]** In the same manner as in Example 119 (2), the title compound (1.66 g) was obtained as a yellow powder using the above-mentioned compound (1.30 g).

<sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.88(3H, t, J = 6.8Hz), 0.90(3H, t, J = 6.8Hz), 2.19(6H, s), 2.95-3.40(6H, m), 3.98(1H, t, J = 6.8Hz), 7.11(2H, s).

(3) N, N-diethyl-2-(3, 5-dimethyl-4-nitrobenzyl)-N'-(2-naphthylsulfonyl)malonamide

**[0391]** In the same manner as in Example 1 (2), the title compound (2.06 g) was obtained as a yellow powder using the above-mentioned compound (1.66 g).

<sup>1</sup>H-NMR(300MHz, DMSO-d<sub>6</sub>)δ0.85(3H, t, J = 6.9Hz), 0.87(3H, t, J = 6.9Hz), 2.07(6H, s), 2.92(2H, d, J = 7.2Hz), 3.02-3.27(4H, m), 3.90(1H, t, J = 6.9Hz), 6.98(2H, s), 7.63-7.80(3H, m), 8.06(1H, d, J = 8.1Hz), 8.09(1H, d, J = 8.1Hz), 8.20(1H, d, J = 8.1Hz), 8.56(1H, s), 12.38(1H, brs).

(4) 2-(4-amino-3, 5-dimethylbenzyl)-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

**[0392]** To a solution of the above-mentioned compound (1.91 g) in DMF (30 mL) was added tin(II) chloride dehydrate (4.18 g), and the mixture was heated at 60°C for 6 hr. Water (50 mL) and chloroform (50 mL) were added to the reaction mixture, and the mixture was stirred for 30 min. After stirring, the mixture was neutralized to pH7 with 1 mol/L aqueous sodium hydroxide solution, and extracted with chloroform (50 mL×2). The organic layer was washed with saturated brine and concentrated under reduced pressure, and the residue was purified by silica gel column chromatography to give the title compound (631 mg) as a pale-yellow solid.

<sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.79(3H, t, J = 7.2Hz), 1.01(3H, t, J = 7.2Hz), 2.04(6H, s), 2.68-3.09(5H, m), 3.45-3.60(2H, m), 6.64(2H, s), 7.60-7.75(2H, m), 7.88-8.09(5H, m), 8.68(1H, s).

(5) 2-[4-(benzoylamino)-3, 5-dimethylbenzyl]-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

**[0393]** In the same manner as in Example 9, a crude product was obtained using the above-mentioned compound (300 mg). This was purified by silica gel column chromatography to give the title compound (170 mg) as a white solid.

<sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.88(6H, t, J = 6.8Hz), 2.03(6H, s), 2.89(2H, d, J = 6.8Hz), 3.03-3.25(4H, m), 3.87(1H, t, J = 7.2Hz), 6.83(2H, s), 7.45-3.88(6H, m), 7.98(2H, d, J = 8.0Hz), 8.06(1H, d, J = 8.0H), 8.14(1H, d, J = 8.4Hz), 8.22(1H, d, J = 7.6Hz), 8.59(1H, s), 9.64(1H, s), 12.37(1H, brs). MS: 586(M+H)<sup>+</sup>.

Example 138 Synthesis of N, N-diethyl-2-[4-[(2-fluorobenzoyl)amino]-3, 5-dimethylbenzyl]-N'-(2-naphthylsulfonyl)malonamide

**[0394]** In the same manner as in Example 9, a crude product was obtained using the compound (331 mg) obtained in Example 137 (4) and 4-fluorobenzoyl chloride (82 μL). This was purified by silica gel column chromatography to give the title compound (239 mg) as a white solid.

<sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.87(6H, t, J = 7.2Hz), 2.07(6H, s), 2.88(2H, d, J = 6.8Hz), 3.04-3.28(4H, m), 3.87(1H, t, J = 7.2Hz), 6.83(2H, s), 7.28-7.40(2H, m), 7.64-7.80(4H, m), 8.06(1H, d, J = 8.4Hz), 8.13(1H, d, J = 8.4Hz), 8.22(1H, d, J = 8.0Hz), 8.58(1H, s), 9.62(1H, s), 12.35(1H, brs). MS: 604 (M+H)<sup>+</sup>.

Example 139 Synthesis of N, N-diethyl-N'-(2-naphthylsulfonyl)-2-[4-(4-oxoquinazolin-3(4H)-yl)benzyl]malonamide

**[0395]** The compound (429 mg) obtained in Example 43 was dissolve in a mixed solution (1.5 mL) of ethanol/acetic

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acid (10/1), ethyl ortho-formate (187  $\mu$ L) was added, and the mixture was heated under reflux for 7 hr. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography to give the title compound (175 mg) as a white solid.

<sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>) $\delta$ 0.78-0.99(6H, m), 3.01(2H, d, J = 7.2Hz), 3.08-3.28(4H, m), 3.94(1H, t, J = 7.2Hz), 7.12-7.28(4H, m), 7.75-7.95 (6H, m), 8.04 (1H, d, J = 8.4Hz) , 8.07-8.29 (4H, m), 8.56(1H, s), 12.39(1H, brs). MS: 583(M+H)<sup>+</sup>.

Example 140 Synthesis of N, N-diethyl-2-[4-(2-methyl-4-oxoquinazoline-3(4H)-yl)benzyl]-N'-(2-naphthylsulfonyl)malonamide

**[0396]** In the same manner as in Example 139, the title compound (132 mg) was obtained as a white solid using the compound (211 mg) obtained in Example 43 and ethyl orthoacetate (105  $\mu$ L). <sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>) $\delta$ 0.86(3H, t, J = 7.2Hz), 0.87(3H, t, J = 7.2Hz), 2.03(3H, s), 2.95-3.08(2H, m), 3.08-3.28(4H, m), 3.93(1H, t, J = 7.2Hz), 7.13-7.30(4H, m), 7.52(1H, t, J = 8.0Hz), 7.59-7.75(3H, m), 7.79-7.88(2H, m), 8.06(1H, d, J = 8.0Hz), 8.11(1H, d, J = 8.4Hz), 8.15(1H, d, J = 8.4Hz), 8.21(1H, d, J = 8.4Hz), 8.56(1H, s), 12.36(1H, brs). MS: 597 (M+H)<sup>+</sup>.

Example 141 Synthesis of N, N-diethyl-N'-(2-naphthylsulfonyl)-2-[4-(4-oxopteridin-3(4H)-yl)benzyl]malonamide

**[0397]** In the same manner as in Example 139, the title compound (130 mg) was obtained as a white solid using the compound (214 mg) obtained in Example 65.

<sup>1</sup>H-NMR(300MHz, DMSO-d<sub>6</sub>) $\delta$ 0.89(3H, t, J = 6.9Hz), 0.90(3H, t, J = 6.9Hz), 3.02 (2H, d, J = 6.9Hz) , 3.08-3.28 (4H, m), 3.95(1H, t, J = 6.9Hz), 7.23(2H, d, J = 8.4Hz), 7.27(2H, d, J = 8.4Hz), 7.62(1H, t, J = 7.2Hz), 7.71(1H, t, J = 7.2Hz), 7.82(1H, d, J = 8.7Hz), 8.06(1H, d, J = 8.1Hz), 8.16(1H, d, J = 9.0Hz), 8.19(1H, d, J = 8.1Hz), 8.50(1H, s), 8.57(1H, s), 8.94(1H, d, J = 2.1Hz), 9.08(1H, d, J = 2.1Hz), 12.43(1H, brs) .

MS: 585(M+H)<sup>+</sup>.

Example 142 Synthesis of N, N-diethyl-2-[4-(2-methyl-4-oxopteridin-3(4H)-yl)benzyl]-N'-(2-naphthylsulfonyl)malonamide

**[0398]** In the same manner as in Example 139, the title compound (71 mg) was obtained as a white solid using the compound (221 mg) obtained in Example 65 and ethyl orthoacetate (305  $\mu$ L).

<sup>1</sup>H-NMR(300MHz, DMSO-d<sub>6</sub>) $\delta$ 0.85(3H, t, J = 7.2Hz), 0.87(3H, t, J = 7.2Hz), 2.10(3H, s), 2.92-3.29(6H, m), 3.95(1H, t, J = 6.9Hz), 7.10-7.35(4H, m), 7.55-7.78(2H, m), 7.84(1H, d, J = 9.0Hz), 8.06(1H, d, J = 8.1Hz), 8.16(1H, d, J = 8.1Hz), 8.22(1H, d, J = 8.1Hz), 8.59 (1H, s), 8.85 (1H, s), 9.04 (1H, m), 12.38(1H, brs).

MS: 599(M+H)<sup>+</sup>.

Example 143 Synthesis of N, N-diethyl-N'-(2-naphthylsulfonyl)-2-[4-(4-quinazolinylamino)benzyl]malonamide

**[0399]** To a solution of hydrochloride salt (378 mg) of the compound obtained in Example 7 in isopropanol (10 mL) were added 4-chloroquinazoline (127 mg) and diisopropylethylamine (410  $\mu$ L), and the mixture was heated under reflux for 5.5 hr. Additional 4-chloroquinazoline (127 mg) was added, and the mixture was heated under reflux for 7 hr. The reaction mixture was adjusted to pH = 2-3 by the addition of dilute hydrochloric acid, and extracted with ethyl acetate (50 mL $\times$ 2). The organic layer was washed with saturated brine and concentrated under reduced pressure, and the residue was purified by silica gel column chromatography to give the title compound (186 mg) as a white solid.

<sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>) $\delta$ 0.87-0.91(6H, m), 2.97(2H, d, J = 7.1Hz), 3.13-3.25(4H, m), 3.93(1H, t, J = 7.1Hz), 7.14(2H, d, J = 7.7Hz) , 7.48 (2H, d, J = 7.7Hz), 7.56-7.70 (2H, m), 7.75-7.91(3H, m), 7.97-8.07(2H, m), 8.16(1H, d, J = 8.7Hz), 8.18(1H, d, J = 8.2Hz), 8.55(1H, s), 8.64-8.73(1H, m), 8.73-8.82(1H, m), 10.81(1H, brs).

MS: 582 (M+H)<sup>+</sup>.

Example 144 Synthesis of N, N-diethyl-N'-(2-naphthylsulfonyl)-2-(4-nitrophenethyl)malonamide

(1) triethyl 3-(4-nitrophenyl)propane-1, 1, 1-tricarboxylate

**[0400]** To a solution of triethyl methanetricarboxylate (16.6 g) in ether (350 mL) were added 4-nitrophenethyl alcohol (8.00 g) and triphenylphosphine (25.0 g). 40% Diisopropyl azodicarboxylate/toluene solution (48.4 g) was added dropwise to the mixture under ice-cooling, and the mixture was stirred at room temperature for 18 hr. Insoluble material was removed by filtration, and the filtrate was washed with saturated aqueous sodium hydrogen carbonate solution (300 mL) and saturated brine. After concentration under reduced pressure, the residue was purified by silica gel column chroma-

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tography to give the title compound (12.2 g) as an oil.

$^1\text{H-NMR}$ (400MHz,  $\text{CDCl}_3$ ) $\delta$ 1.28-1.33(9H, m), 2.39-2.43(2H, m), 2.93-2.97(2H, m), 4.29 (6H, q, J = 7.2Hz), 7.38 (2H, d, J = 8.8Hz), 8.15(2H, d, J = 8.8Hz).

5 (2) monoethyl (4-nitrophenethyl)malonate

**[0401]** In the same manner as in Example 117 (2), the title compound (2.34 g) was obtained as an oil using the above-mentioned compound (3.17 g).

10  $^1\text{H-NMR}$ (400MHz,  $\text{DMSO-d}_6$ ) $\delta$ 1.19(3H, t, J = 7.2Hz), 2.01-2.10(2H, m), 2.74 (2H, dd, J = 8.8, 6.0H), 3.31-3.37(1H, m), 4.12 (2H, q, J = 7.2Hz), 7.49(2H, d, J = 8.4Hz), 8.17(2H, d, J = 8.4Hz), 12.90(1H, brs).

(3) ethyl 2-[(2-naphthylsulfonyl)amino]carbonyl]-4-(4-nitrophenyl)butyrate

15 **[0402]** In the same manner as in Example 1 (2), the title compound (1.34 g) was obtained as an oil using the above-mentioned compound (2.34 g).

$^1\text{H-NMR}$ (400MHz,  $\text{CDCl}_3$ ) $\delta$ 1.24 (3H, t, J = 7.2Hz), 2.13-2.20 (2H, m), 2.65(1H, t, J = 8.0Hz), 3.21(1H, t, J = 7.2Hz), 4.19(2H, q, J = 7.2Hz), 7.19 (2H, d, J = 8.4Hz), 7.65-7.71(2H, m), 7.92 (2H, d, J = 8.0Hz), 7.97-8.04(3H, m), 8.08 (2H, d, J = 8.4Hz), 8.69(1H, s), 9.61(1H, s).

20 (4) 2-[(2-naphthylsulfonyl)amino]carbonyl]-4-(4-nitrophenyl)butyric acid

**[0403]** To a solution of the above-mentioned compound (1.33 g) in THF (30 mL) was added a solution of sodium hydroxide (333 mg) in water (1.5 mL) at room temperature, and the mixture was stirred for 3 hr. The reaction mixture was adjusted to pH = 1-2 by the addition of dilute hydrochloric acid and extracted with ethyl acetate (50 mLx2). The organic layer was concentrated under reduced pressure to give the title compound (1.24 g) as a white powder.

25  $^1\text{H-NMR}$ (400MHz,  $\text{CDCl}_3$ ) $\delta$ 2.18-2.25(2H, m), 2.68(2H, t, J = 8.0Hz), 3.31(1H, t, J = 6.8Hz), 7.20(2H, d, J = 8.8Hz), 7.63-7.72(2H, m), 7.93(1H, d, J = 7.6Hz), 8.02-8.08(5H, m), 8.70(1H, s), 9.70 (1H, brs).

30 (5) N, N-diethyl-N'-(2-naphthylsulfonyl)-2-(4-nitrophenethyl)malonamide

**[0404]** In the same manner as in Example 1 (4), the reaction mixture was obtained using the above-mentioned compound (350 mg). The reaction mixture was adjusted to pH = 1-2 by the addition of dilute hydrochloric acid, and the precipitate was collected by filtration to give the title compound (316 mg) as a white solid.

35  $^1\text{H-NMR}$  (400MHz,  $\text{DMSO-d}_6$ ) $\delta$ 0.83-0.95(6H, m), 1.86-1.97(2H, m), 2.45-2.55(2H, m), 3.06-3.25(4H, m), 3.55(1H, t, J = 6.8Hz), 7.29(2H, d, J = 8.8Hz), 7.68-7.77(2H, m), 7.89(1H, dd, J = 8.8, 1.6Hz), 8.07(1H, d, J = 8.0Hz), 8.10(2H, d, J = 8.8Hz), 8.16 (1H, d, J = 8.0H), 8.23 (1H, d, J = 8.0H), 8.62(1H, s), 12.44(1H, brs).

MS: 498(M+H) $^+$ .

Example 145 Synthesis of 2-(4-aminophenethyl)-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

40 **[0405]** In the same manner as in Example 7, the title compound (244 mg) was obtained as a white powder using the compound (292 mg) obtained in Example 144 at room temperature.

$^1\text{H-NMR}$ (300MHz,  $\text{DMSO-d}_6$ ) $\delta$ 0.86-0.93(6H, m), 1.66-1.86(2H, m), 2.11-2.25(2H, m), 2.95-3.30(4H, m), 3.45(1H, t, J = 7.0Hz), 6.44 (2H, d, J = 8.2Hz), 6.62 (2H, d, J = 8.2Hz), 7.67-7.77(2H, m), 7.87(1H, dd, J = 8.5, 1.5Hz), 8.07(1H, d, J = 7.7Hz), 8.15 (1H, d, J = 8.7Hz), 8.22(1H, d, J = 7.7Hz), 8.60(1H, s). MS: 468(M+H) $^+$ .

Example 146 Synthesis of N, N-diethyl-N'-(2-naphthylsulfonyl)-2-[(2E)-3-(4-nitrophenyl)-2-propen-1-yl]malonamide (1) triethyl (3E)-4-(4-nitrophenyl)-3-butene-1, 1, 1-tricarboxylate

50 **[0406]** In the same manner as in Example 144 (1), the title compound (8.56 g) was obtained as an oil using triethyl methanetricarboxylate (10.1 g) and trans-4-nitrocinnamyl alcohol (5.18 g).

$^1\text{H-NMR}$ (400MHz,  $\text{CDCl}_3$ ) $\delta$ 1.24-1.30(9H, m), 3.08 (2H, d, J = 6.8Hz), 4.24-4.31(6H, m), 6.53(1H, d, J = 16.0Hz), 6.60(1H, dd, J = 16.0, 6.8Hz), 7.46(2H, d, J = 8.8Hz), 8.15(2H, d, J = 8.8Hz).

55 (2) monoethyl (trans-4-nitrocinnamyl)malonate

**[0407]** In the same manner as in Example 117 (2), a crude product was obtained using the above-mentioned compound (8.56 g). This was purified by silica gel column chromatography to give the title compound (2.33 g) as an oil.

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<sup>1</sup>H-NMR(400MHz, CDCl<sub>3</sub>)δ1.28(3H, t, J = 7.2Hz), 2.85-2.93(2H, m), 3.59(1H, t, J = 7.2Hz), 4.25(2H, q, J = 7.2Hz), 6.37(1H, dt, J = 16.0, 7.2Hz), 6.57(1H, d, J = 16.0Hz), 7.46(2H, d, J = 8.8Hz), 8.17(2H, d, J = 8.8Hz).

(3) ethyl (4E)-2-[(2-naphthylsulfonyl)amino]carbonyl]-5-(4-nitrophenyl)-4-pentenoate

**[0408]** In the same manner as in Example 1 (2), the title compound (195 mg) was obtained as an oil using the above-mentioned compound (2.32 g).

<sup>1</sup>H-NMR(400MHz, CDCl<sub>3</sub>)δ1.13-1.21(3H, m), 2.80 (2H, t, J = 7.2Hz), 3.55(1H, t, J = 7.2Hz), 4.14-4.21(2H, m), 6.12(1H, dt, J = 16.0, 7.2Hz), 6.30(1H, d, J = 16.0Hz), 7.12(2H, d, J = 8.8Hz), 7.54-7.66(2H, m), 7.80-7.84(2H, m), 7.92(2H, d, J = 8.8Hz), 7.91-8.00(2H, m), 8.64(1H, d, J = 1.2Hz), 9.89(1H, brs).

(4) N, N-diethyl-N'-(2-naphthylsulfonyl)-2-[(2E)-3-(4-nitrophenyl)-2-propen-1-yl]malonamide

**[0409]** The above-mentioned compound (195 mg) was subjected to hydrolysis in the same manner as in Example 144 (4) to give a carboxylic acid. The carboxylic acid was concentrated in the same manner as in Example 1 (4). After completion of the reaction, the reaction mixture was adjusted to pH = 1-2 by the addition of dilute hydrochloric acid, and the precipitate was collected by filtration to give the title compound (100 mg) as a pale-yellow solid.

<sup>1</sup>H-NMR(400MHz, CDCl<sub>3</sub>)δ1.10-1.54(6H, m), 2.65-2.76(2H, m), 3.26-3.35(4H, m), 3.54 (1H, t, J = 7.2Hz), 6.02 (1H, dt, J = 16.0, 8.0Hz), 6.24(1H, d, J = 16.0Hz), 7.07(2H, d, J = 8.4Hz), 7.55-7.65(2H, m), 7.79-7.85(2H, m), 7.93-7.99(4H, m), 8.62(1H, s). MS: 510(M+H)<sup>+</sup>.

Example 147 Synthesis of 2-[3-(4-aminophenyl)propyl]-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

**[0410]** In the same manner as in Example 7, the title compound (24 mg) was obtained as a white solid using the compound (40 mg) obtained in Example 146.

<sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.86-0.92(6H, m), 1.12-1.40(2H, m), 1.50-1.62(2H, m), 2.20-2.35(2H, m), 3.05-3.27(4H, m), 3.52(1H, t, J = 6.8Hz), 6.49(2H, d, J = 8.0Hz), 6.69(2H, d, J = 8.0Hz), 7.69-7.78(2H, m), 7.83(1H, dd, J = 8.8, 1.9Hz), 8.07(1H, d, J = 8.0Hz), 8.11(1H, d, J = 8.7Hz), 8.20(1H, d, J = 8.0Hz), 8.58(1H, s).

MS: 482 (M+H)<sup>+</sup>.

Example 148 Synthesis of 2-[(2E)-3-(4-aminophenyl)-2-propen-1-yl]-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

**[0411]** In the same manner as in Example 137 (4), the title compound (4 mg) was obtained as a pale-yellow solid using the compound (58 mg) obtained in Example 146 at room temperature. <sup>1</sup>H-NMR(400MHz, CDCl<sub>3</sub>)δ1.08(6H, t, J = 7.2Hz), 2.57-2.72 (2H, m), 3.15-3.34(4H, m), 3.47-3.55(3H, m), 5.69(1H, dt, J = 15.6, 8.0Hz), 6.18 (1H, d, J = 15.6Hz), 6.58(2H, d, J = 8.4Hz), 6.93(2H, d, J = 8.4Hz), 7.60-7.66(2H, m), 7.88(2H, d, J = 8.8Hz), 7.96-8.00(2H, m), 8.65(1H, s). MS: 502 (M+Na)<sup>+</sup>.

Example 149 Synthesis of 2-[3-(4-tert-butyloxycarbonylamino)phenyl]propyl]-N,N-diethyl-N'-(2-naphthylsulfonyl)malonamide

(1) triethyl 4-(4-tert-butyloxycarbonylamino)phenyl)butane-1, 1, 1-tricarboxylate

**[0412]** To a solution of the compound (3.95 g) obtained in Example 146 (1) in ethyl acetate (100 mL) was added di-tert-butyl dicarbonate (2.19 g), and the mixture was subjected to the same manner as in Example 7 at room temperature to give a crude product. This was purified by silica gel column chromatography to give the title compound (3.59 g) as an oil. <sup>1</sup>H-NMR(300MHz, CDCl<sub>3</sub>)δ1.26(9H, t, J = 7.3Hz), 1.51(9H, s), 1.72-1.85(2H, m), 2.08-2.15(2H, m), 2.59(2H, t, J = 8.6Hz), 4.23(6H, q, J = 7.3Hz), 7.09(2H, d, J = 8.6Hz), 7.25(2H, d, J = 8.6Hz).

(2) monoethyl [3-(4-tert-butyloxycarbonylamino)phenyl]propyl]malonate

**[0413]** In the same manner as in Example 117 (2), the title compound (2.77 g) was obtained as an oil using the above-mentioned compound (3.53 g).

<sup>1</sup>H-NMR (400MHz, CDCl<sub>3</sub>)δ1.28(3H, t, J = 7.2Hz), 1.51(9H, s), 1.60-1.74(2H, m), 1.88-2.02(2H, m), 2.60(2H, t, J = 7.2Hz), 3.39(1H, t, J = 7.2Hz), 4.22(2H, q, J = 7.2Hz), 6.49(1H, brs), 7.08(2H, d, J = 8.4Hz), 7.25 (2H, d, J = 8.4Hz).

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(3) ethyl 5-(4-tert-butyloxycarbonylamino)phenyl-2-[(2-naphthylsulfonyl)amino]carboxylate.

**[0414]** In the same manner as in Example 1 (2), the title compound (2.42 g) was obtained as a white powder using the above-mentioned compound (2.77 g).

<sup>1</sup>H-NMR(400MHz, CDCl<sub>3</sub>) δ1.21(3H, t, J = 7.2Hz), 1.42-1.49(2H, m), 1.52(9H, s), 2.45(2H, t, J = 7.2Hz), 3.19(1H, t, J = 7.2Hz), 4.16(2H, q, J = 7.2Hz), 6.39(1H, s), 6.92(2H, d, J = 8.0Hz), 7.19(2H, d, J = 8.0Hz), 7.61-7.70(2H, m), 7.92(1H, d, J = 8.0Hz), 7.96-7.97(2H, m), 8.01(1H, d, J = 8.0Hz), 8.67(1H, s), 9.70(1H, brs).

(4) 5-(4-tert-butyloxycarbonylamino)phenyl-2-[(2-naphthylsulfonyl)amino]valeric acid

**[0415]** In the same manner as in Example 144 (4), the title compound (2.28 g) was obtained as a white powder using the above-mentioned compound (2.40 g).

<sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>) δ1.23-1.38(2H, m), 1.48(9H, s), 1.48-1.64(2H, m), 2.29-2.41(2H, m), 3.25-3.35(1H, m), 6.84(2H, d, J = 8.4Hz), 7.28(2H, d, J = 8.4Hz), 7.67-7.78(2H, m), 7.84(1H, dd, J = 8.4, 1.6Hz), 8.06(1H, d, J = 8.4Hz), 8.09(1H, d, J = 8.8Hz), 8.20(1H, d, J = 8.4Hz), 8.59(1H, s), 9.22(1H, s), 12.52(1H, brs), 12.76(1H, brs).

(5) 2-[3-(4-tert-butyloxycarbonylamino)phenyl]propyl-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

**[0416]** The above-mentioned compound (2.28 g) was subjected to the same manner as in Example 1 (4) to give the reaction mixture. The reaction mixture was adjusted to pH = 3 - 4 by the addition of dilute hydrochloric acid, and the precipitate was collected by filtration to give the title compound (2.48 g) as a white solid.

<sup>1</sup>H-NMR(300MHz, DMSO-d<sub>6</sub>) δ0.86-0.93(6H, m), 1.11-1.41(2H, m), 1.47(9H, s), 1.50-1.62(2H, m), 2.28-2.42(2H, m), 3.08-3.22(4H, m), 3.50-3.59(1H, m), 6.87(2H, d, J = 8.4Hz), 7.29(2H, d, J = 8.4Hz), 7.68-7.78(2H, m), 7.83(1H, dd, J = 8.7, 1.5Hz), 8.07(1H, d, J = 8.1Hz), 8.11(1H, d, J = 9.0Hz), 8.20(1H, d, 8.1Hz), 8.58 (1H, s), 9.22 (1H, s), 12.38 (1H, brs). MS:604 (M+Na)<sup>+</sup>.

Example 150 Synthesis of 2-[3-(4-acetylamino)phenyl]propyl-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

**[0417]** To a solution of the compound (210 mg) obtained in Example 147 in pyridine (4 mL) was added acetic anhydride (46 μL) at room temperature, and the mixture was stirred for 19 hr. The reaction mixture was adjusted to pH = 1-2 by the addition of dilute hydrochloric acid, and the precipitate was collected by filtration to give the title compound (213 mg) as a white solid.

<sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>) δ0.85-0.94(6H, m), 1.19-1.30(1H, m), 1.30-1.42(1H, m), 1.52-1.63(2H, m), 2.02(3H, s), 2.32-2.45(2H, m), 3.06-3.24 (4H, m), 3.54 (1H, t, J = 6.8Hz), 6.91(2H, d, J = 8.9Hz), 7.41(2H, d, J = 8.4Hz), 7.69-7.85(3H, m), 8.07(1H, d, J = 8.0Hz), 8.11(1H, d, J = 8.8Hz), 8.20(1H, d, J = 8.0Hz), 8.58(1H, s), 9.83(1H, s), 12.40(1H, brs). MS: 524 (M+H)<sup>+</sup>.

Example 151 Synthesis of 2-butyl-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

(1) monoethyl butylmalonate

**[0418]** In the same manner as in Example 1 (1), the title compound (20.0 g) was obtained as an oil using diethyl butylmalonate (25.3 g).

<sup>1</sup>H-NMR(300MHz, DMSO-d<sub>6</sub>) δ0.85(3H, t, J = 6.9Hz), 1.15-1.33(4H, m), 1.18(3H, t, J = 7.4Hz), 1.69-1.78(2H, m), 3.30(1H, t, J = 7.5Hz), 4.11(2H, q, J = 6.9Hz), 12.80(1H, brs).

(2) 2-[(2-naphthylsulfonyl)amino]hexanoic acid

**[0419]** In the same manner as in Example 1 (2), a crude product was obtained using the above-mentioned compound (1.15 g). This was subjected to hydrolysis in the same manner as in Example 1 (3) to give the title compound (1.61 g) as a white solid. <sup>1</sup>H-NMR(300MHz, DMSO-d<sub>6</sub>) δ0.86(3H, t, J = 6.9Hz), 1.17-1.34(4H, m), 1.61-1.75(2H, m), 3.14-3.21(1H, m), 7.67-7.90(3H, m), 8.05-8.25(3H, m), 8.59(1H, s), 12.56(2H, brs).

(3) 2-butyl-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

**[0420]** In the same manner as in Example 1 (4), a crude product was obtained using the above-mentioned compound (350 mg). This was purified by silica gel column chromatography to give the title compound (64 mg) as a white solid.

<sup>1</sup>H-NMR(300MHz, DMSO-d<sub>6</sub>) δ0.70 (3H, t, J = 7.2Hz), 0.86-0.95 (6H, m), 1.00-1.18(4H, m), 1.49-1.63(2H, m),

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3.05-3.30(4H, m), 3.46-3.55(1H, m), 7.68-7.79(2H, m), 7.85-7.88(1H, m), 8.07(1H, d, J = 7.9Hz), 8.16 (1H, d, J = 8.4Hz), 8.22 (1H, d, J = 7.9Hz), 8.59 (1H, s), 12.37(1H, brs).

MS: 405(M+H)<sup>+</sup>.

### 5 Example 152 Synthesis of N, N-diethyl-N'-(2-naphthylsulfonyl)-2-(2-propynyl)malonamide

#### (1) diethyl (2-propynyl)malonate

10 **[0421]** To a mixed solution of triethyl methanetricarboxylate sodium salt (25.0 g) in toluene/DMF (120 mL/120 mL) was added propargyl bromide (25.0 g), and the mixture was stirred at 80°C for 1.5 hr. After allowing to cool, dilute hydrochloric acid was added to the reaction mixture, and the mixture was extracted with ethyl acetate (60 mL). The organic layer was washed with saturated brine and concentrated under reduced pressure. The residue was dissolved in THF (30 mL), sodium ethoxide (7.60 g) was added, and the mixture was stirred at room temperature for 1 hr. 1 mol/L Hydrochloric acid (150 mL) was added, and the mixed solution was extracted with chloroform (100 mL). The organic layer was concentrated, and the residue was purified by silica gel column chromatography to give the title compound (35.0 g) as an oil.

<sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ1.26-1.32(6H, m), 2.04(1H, s), 2.89-3.02(3H, m), 4.22-4.32(4H, m).

#### (2) monoethyl (2-propynyl)malonate

20 **[0422]** In the same manner as in Example 1 (1), the title compound (8.20 g) was obtained as an oil using the above-mentioned compound (19.8 g).

<sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ1.23-1.33(3H, m), 2.18(1H, s), 2.80-2.87(2H, m), 3.60-3.65(1H, m), 4.16-4.30(2H, m).

#### 25 (3) ethyl 2-[(2-naphthylsulfonyl)amino]carbonyl-4-pentynoate

30 **[0423]** To a solution of the above-mentioned compound (8.19 g) in DMF (30 mL) were added naphthalene-2-sulfonamide (9.97 g), 2-chloro-1-methylpyridinium iodide (14.7 g), diisopropyl ethyl amine (13.3 mL) and 4-dimethylaminopyridine (0.59 g), and the mixture was stirred at room temperature for 18 hr. The reaction mixture was adjusted to pH = 2-3 by the addition of dilute hydrochloric acid, and ethyl acetate was added to extract the mixture. The organic layer was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography to give the title compound (9.97 g) as a white powder.

<sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ1.21-1.33(3H, m), 1.95(1H, s), 2.72-2.75(2H, m), 3.38-3.43(1H, m), 4.18-4.29(2H, m), 7.60-7.69(2H, m), 7.90-8.03(4H, m), 8.68(1H, s), 9.62(1H, brs).

#### 35 (4) 2-[(2-naphthylsulfonyl)amino]carbonyl-4-pentynoic acid

**[0424]** In the same manner as in Example 1 (3), the title compound (9.78 g) was obtained as a white powder using the above-mentioned compound (9.97 g).

40 <sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ2.75-2.77(1H, m), 3.47-3.52(1H, m), 3.72-3.77(2H, m), 7.60-7.70(2H, m), 7.90-8.03(5H, m), 8.68(1H, s).

#### (5) N, N-diethyl-N'-(2-naphthylsulfonyl)-2-(2-propynyl)malonamide

45 **[0425]** In the same manner as in Example 1 (4), a crude product was obtained using the above-mentioned compound (1.82 g). This was purified by silica gel column chromatography to give the title compound (860 mg) as a white powder.

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.09-1.12(6H, m), 1.92(1H, s), 2.63-2.77(2H, m), 3.21-3.32 (2H, m), 3.34-3.42(1H, m), 3.45-3.52(1H, m), 3.57-3.68(1H, m), 7.59-7.68(2H, m), 7.89-8.02(4H, m), 8.65(1H, s), 10.58(1H, brs).

MS: 387(M+H)<sup>+</sup>.

### 50 Example 153 Synthesis of 2-(2-cyanoethyl)-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

#### (1) monoethyl (2-cyanoethyl)malonate

55 **[0426]** In the same manner as in Example 1 (1), the title compound (4.29 g) was obtained as an oil using diethyl (2-cyanoethyl)malonate (5.00 g).

<sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ1.24-1.33(3H, m), 2.26-2.32(2H, m), 2.51-2.56(2H, m), 3.56-3.59(1H, m), 4.15-4.30(2H, m).

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(2) ethyl 4-cyano-2-[[2-(naphthylsulfonyl)amino]carbonyl]butyrate

**[0427]** In the same manner as in Example 152 (3), the title compound (2.43 g) was obtained as a white powder using the above-mentioned compound (2.50 g).

<sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ1.20-1.32(3H, m), 2.22-2.28(2H, m), 2.49-2.58(2H, m), 3.50-3.57(1H, m), 4.18-4.28 (2H, m), 7.62-7.71(2H, m), 7.72-7.94(1H, m), 7.99-8.04 (3H, m), 8.67(1H, s), 9.44(1H, brs).

(3) 4-cyano-2-[[2-(naphthylsulfonyl)amino]carbonyl]butyric acid

**[0428]** In the same manner as in Example 1 (3), the title compound (1.94 g) was obtained as a white powder using the above-mentioned compound (2.43 g).

<sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ2.21-2.25(2H, m), 2.41-2.46(2H, m), 3.01-3.52(1H, m), 7.62-7.71(2H, m), 7.71-7.92(1H, m), 7.94-8.04 (3H, m), 8.68(1H, s).

(4) 2-(2-cyanoethyl)-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

**[0429]** In the same manner as in Example 1 (4), a crude product was obtained using the above-mentioned compound (1.00 g). This was purified by silica gel column chromatography to give the title compound (470 mg) as a white powder.

<sup>1</sup>H-NM(400Mz, CDCl<sub>3</sub>)δ1.09-1.14(6H, m), 2.17-2.21(2H, m), 2.27-2.39(2H, m), 3.22-3.41(3H, m), 3.43-3.55(2H, m), 7.61-7.69(2H, m), 7.91-8.03(4H, m), 8.65(1H, s), 10.56(1H, s). MS: 402(M+H)<sup>+</sup>.

Example 154 Synthesis of N, N-diethyl-N'-(2-naphthylsulfonyl)-2-(4-piperidinylmethyl)malonamide trifluoroacetic acid salt (1) 5-(1-tert-butyloxycarbonyl-4-piperidinylmethyl)-2, 2-dimethyl-1, 3-dioxane-4, 6-dione

**[0430]** In the same manner as in Example 132 (1), the title compound (10.8 g) was obtained as a white solid using N-(tert-butyloxycarbonyl)isonipecotic acid (8.68 g).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.07-1.22(2H, m), 1.45(9H, s), 1.57-1.73(2H, m), 2.04-2.08 (2H, m), 2.63-2.7.4 (2H, m), 3.48(1H, t, J = 5.6Hz), 4.00-4.18(2H, m).

(2) 2-(1-tert-butyloxycarbonyl-4-piperidinylmethyl)-3-(N, N-diethylamino)-3-oxopropionic acid

**[0431]** In the same manner as in Example 119 (2), the title compound (3.07 g) was obtained as a white solid using the above-mentioned compound (2.94 g).

<sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.90-1.05(5H, m), 1.11(3H, t, J = 7.2Hz), 1.37(9H, s), 1.52-1.76(5H, m), 2.50-2.73(2H, m), 3.23-3.48(4H, m), 3.63(1H, t, J = 7.2Hz), 3.81-3.95(2H, m), 12.48(1H, brs).

(3) 2-(1-tert-butyloxycarbonyl-4-piperidinylmethyl)-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

**[0432]** In the same manner as in Example 1 (4), a crude product was obtained using the above-mentioned compound (2.93 g). This was purified by silica gel column chromatography to give the title compound (1.73 g) as a white powder.

<sup>1</sup>H-NMR(300MHz, DMSO-d<sub>6</sub>)δ0.75-1.75(7H, m), 0.89(3H, t, J = 7.2Hz), 0.96(3H, t, J = 7.2Hz), 1.36(9H, s), 2.23-2.54(2H, m), 3.05-3.25(4H, m), 3.55-3.64(1H, m), 3.64-3.95(2H, m), 7.67-7.79(2H, m), 7.85-7.88(1H, m), 8.07(1H, d, J = 7.1Hz), 8.16(1H, d, J = 8.7Hz), 8.22(1H, d, J = 7.5Hz), 8.59(1H, d, J = 1.2Hz), 12.32(1H, brs).

(4) N, N-diethyl-N'-(2-naphthylsulfonyl)-2-(4-piperidinylmethyl)malonamide trifluoroacetic acid salt

**[0433]** In the same manner as in Example 18, the title compound (1.77 g) was obtained as a white solid using the above-mentioned compound (1.73 g).

<sup>1</sup>H-NMR(300MHz, DMSO-d<sub>6</sub>)δ0.85-0.93(6H, m), 1.00-1.88(7H, m), 2.57-2.84(2H, m), 3.03-3.28(6H, m), 3.55-3.64(1H, m), 7.67-7.79(2H, m), 7.85-7.89(1H, m), 7.97-8.17(1H, m), 8.07(1H, d, J = 8.0Hz), 8.16(1H, d, J = 8.9Hz), 8.22(1H, d, J = 8.0Hz), 8.30-8.47(H, m), 8.60(1H, d, J = 1.0Hz), 12.40 (1H, brs). MS: 446(M+H)<sup>+</sup>.

Example 155 Synthesis of 2-(1-benzoyl-4-piperidinylmethyl)-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

**[0434]** To a mixed solution of the compound (250 mg) obtained in Example 154 in THF, (10 mL) and 1 mol/L aqueous sodium hydroxide (1.5 mL) was added benzoyl chloride (104 μL) at room temperature, and the mixture was stirred for 24 hr. The reaction mixture was adjusted to pH = 2-3 by the addition of dilute hydrochloric acid, and extracted with ethyl acetate (50 mL×2). The organic layer was washed with saturated brine and concentrated under reduced pressure to

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give the title compound (188 mg) as a white solid.

<sup>1</sup>H-NMR(300MHz, DMSO-d<sub>6</sub>)δ0.80-1.08(7H, m), 1.08-1.70(6H, m), 3.10-3.49(8H, m), 3.56-3.68 (1H, m), 7.29-7.45 (5H, m), 7.63-7.77(2H, m), 7.85-7.88(1H, m), 8.03-8.05(1H, m), 8.14(1H, d, J = 8.8Hz), 8.21(1H, d, J = 7.7Hz), 8.59(1H, d, J = 1.0Hz), 12.35(1H, brs).

MS: 550(M+H)<sup>+</sup>.

Example 156 Synthesis of N, N-diethyl-N'-(2-naphthylsulfonyl)-2-(1-phenylsulfonyl-4-piperidinylmethyl)malonamide

**[0435]** In the same manner as in Example 155, the title compound (205 mg) was obtained as a white solid using the compound (250 mg) obtained in Example 154 and benzenesulfonyl chloride (114 μL).

<sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.74-1.08(7H, m), 1.24-1.59(4H, m), 1.80-1.86(1H, m), 1.94-2.00(1H, m), 3.08-3.19(4H, m), 3.21-3.47(3H, m), 3.50-3.56(2H, m), 7.66-7.81(8H, m), 7.96(1H, d, J = 9.6Hz), 7.99(1H, d, J = 9.2Hz), 8.17(1H, d, J = 8.4Hz), 8.55(1H, d, J = 0.8H), 12.30(1H, brs).

MS: 586(M+H)<sup>+</sup>.

Example 157 Synthesis of N, N-diethyl-N'-(2-naphthylsulfonyl)-2-(1-phenoxyacetyl-4-piperidinylmethyl)malonamide

**[0436]** In the same manner as in Example 155, a crude product was obtained using the compound (250 mg) obtained in Example 154 and phenyl chloroformate (112 μL). This was purified by silica gel column chromatography to give the title compound (208 mg) as a white solid.

<sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.84-1.06(7H, m), 1.10-1.68(6H, m), 2.46-2.81(2H, m), 3.12-3.29(4H, m), 3.64(1H, t, J = 6.8Hz), 3.78-4.08(2H, m), 7.06-7.23(3H, m), 7.36-7.40(2H, m), 7.66-7.78(2H, m), 7.87-7.90(1H, m), 8.07(1H, d, J = 8.0Hz), 8.18 (1H, d, J = 8.8Hz), 8.23(1H, d, J = 7.6Hz), 8.61(1H, s), 12.35 (1H, brs).

MS: 566(M+H)<sup>+</sup>.

Example 158 Synthesis of N, N-diethyl-N'-(2-naphthylsulfonyl)-2-(1-phenylacetyl-4-piperidinylmethyl)malonamide

**[0437]** In the same manner as in Example 155, the title compound (302 mg) was obtained as a white solid using the compound (373 mg) obtained in Example 154 and phenylacetic acid chloride (106 μL).

<sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.67-0.99(8H, m), 1.03-1.60(5H, m), 2.16-2.33(1H, m), 2.50-2.73(1H, m), 3.08-3.28(4H, m), 3.56-3.84(4H, m), 4.18-4.30(1H, m), 7.14-7.26(3H, m), 7.28-7.32(2H, m), 7.66-7.78 (2H, m), 7.86(1H, d, J = 8.8Hz), 8.02-8.23(3H, m), 8.60(1H, s), 12.30(1H, brs).

MS: 564(M+H)<sup>+</sup>.

Example 159 Synthesis of 2-(1-anilinoacetyl-4-piperidinylmethyl)-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

**[0438]** In the same manner as in Example 155, the title compound (223 mg) was obtained as a white solid using the compound (305 mg) obtained in Example 154 and phenyl isocyanate (72 μL).

<sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.88-0.99(8H, m), 1.05-1.19(1H, m), 1.23-1.41(1H, m), 2.39-2.52(2H, m), 3.11-3.26(4H, m), 3.60-3.68(1H, m), 3.91-4.06(2H, m), 6.92(1H, d, J = 8.0H), 7.21(2H, t, J = 8.0Hz), 7.43(2H, d, J = 8.0Hz), 7.77-7.78(2H, m), 7.86-7.89(1H, m), 8.07 (1H, d, J = 8.0Hz), 8.17(1H, d, J = 8.8Hz), 8.22(1H, d, J = 8.0Hz), 8.35(1H, s), 8.60(1H, s), 12.32(1H, brs).

MS: 565(M+H)<sup>+</sup>.

Example 160 Synthesis of N, N-diethyl-2-[1-(1-naphthoyl)-4-piperidinylmethyl]-N'-(2-naphthylsulfonyl)malonamide

**[0439]** In the same manner as in Example 155, the title compound (169 mg) was obtained as a white solid using the compound (272 mg) obtained in Example 154 and 1-naphthoyl chloride (73 μL).

<sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.66-1.02(7H, m), 1.02-1.39(3H, m), 1.48-1.79(3H, m), 2.45-2.78(2H, m), 2.92-3.29(5H, m), 3.57-3.66(1H, m), 4.45-4.61(1H, m), 7.30-7.43(1H, m), 7.50-7.78(6H, m), 7.81-7.88(1H, m), 7.95-8.22(5H, m), 8.59(1H, s), 12.32(1H, brs).

MS: 600(M+H)<sup>+</sup>.

Example 161 Synthesis of 2-(1-benzyl-4-piperidinylmethyl)-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide hydrochloride

**[0440]** To a solution of the compound (365 mg) obtained in Example 154 in chloroform, (10 mL) were added benzaldehyde (67 μL) and sodium triacetoxyborohydride (280 mg), and the mixture was stirred at room temperature for 4 days.

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Water (50 mL) was added to the reaction mixture, and the mixture was extracted with chloroform (50 mL×2). The organic layer was washed with saturated brine and concentrated under reduced pressure. The residue was purified by silica gel column chromatography and converted to a hydrochloride salt with 4 mol/L hydrochloric acid-ethyl acetate (1 mL) to give the title compound (58 mg) as a white solid.

<sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.82-0.95(6H, m), 1.23-1.82(7H, m), 2.62-2.79(2H, m), 2.96-3.40(6H, m), 3.60-3.69(1H, m), 4.11-4.22(2H, m), 7.46-7.54(5H, m), 7.68-7.76(2H, m), 7.85-7.89(1H, m), 8.04(1H, d, J = 8.0Hz), 8.11(1H, d, J = 8.8Hz), 8.20(1H, d, J = 8.4Hz), 8.58(1H, s), 10.03(1H, brs), 12.50(1H, brs).

MS: 536(M+H)<sup>+</sup>.

Example 162 Synthesis of 2-(1-benzylsulfonyl-4-piperidinylmethyl)-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

**[0441]** In the same manner as in Example 155, the title compound (68 mg) was obtained as a white solid using the compound (290 mg) obtained in Example 154 and benzylsulfonyl chloride (100 mg).

<sup>1</sup>H-NMR(300MHz, DMSO-d<sub>6</sub>)δ0.80-1.01(8H, m), 1.37-1.62 (5H, m), 2.28-2.51(2H, m), 3.08-3.50(6H, m), 3.56-3.63(1H, m), 4.29(2H, s), 7.30-7.40(5H, m), 7.70-7.79(2H, m), 7.87(1H, dd, J = 8.7, 1.8Hz), 8.09(1H, d, J = 7.8Hz), 8.17(1H, d, J = 8.7Hz), 8.24 (1H, d, J = 7.5Hz), 8.61 (1H, d, J = 1.8H), 12.35(1H, brs).

MS: 600(M+H)<sup>+</sup>.

Example 163 Synthesis of 2-[1-(2-benzothiazolyl)-4-piperidinylmethyl]-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

**[0442]** To a solution of the compound (1.01 g) obtained in Example 154 in N-methylpyrrolidone (10 mL) were added 2-chlorobenzothiazole (445 μL) and diisopropyl ethyl amine (1.54 mL), and the mixture was stirred under nitrogen atmosphere at 100°C for 2 hr. After allowing to cool, the reaction mixture was adjusted to pH = 2-3 by the addition of dilute hydrochloric acid, and extracted with ethyl acetate (50 mL×2). The organic layer was washed with saturated brine and concentrated under reduced pressure, and the residue was purified by silica gel column chromatography to give the title 163 compound (515 mg) as a white solid.

<sup>1</sup>H-NMR(300MHz, DMSO-d<sub>6</sub>)δ0.83-1.70(13H, m), 2.72-2.96(2H, m), 3.10-3.25(4H, m), 3.62-3.69(1H, m), 3.71-3.96(2H, m), 7.02-7.11(1H, m), 7.21-7.30(1H, m), 7.42(1H, d, J = 7.8Hz), 7.66-7.77(3H, m), 7.88(1H, dd, J = 8.7, 1.8Hz), 8.09(1H, d, J = 8.1Hz), 8.18(1H, d, J = 9.0Hz), 8.23(1H, d, J = 7.5Hz), 8.61(H, d, J = 1.8H), 12.39(1H, brs).

MS: 579(M+H)<sup>+</sup>.

Example 164 Synthesis of 2-[cis-4-(tert-butyloxycarbonylamino)cyclohexylmethyl]-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

(1) 5-[cis-4-(tert-butyloxycarbonylamino)cyclohexylmethyl]-2, 2-dimethyl-1, 3-dioxane-4, 6-dione

**[0443]** In the same manner as in Example 132 (1), the title compound (5.51 g) was obtained as a white solid using cis-4-(tert-butyloxycarbonylamino)cyclohexanecarboxylic acid (4.55 g).

<sup>1</sup>H-NMR(300MHz, DMSO-d<sub>6</sub>)δ1.30-1.75(9H, m), 1.38(9H, s), 1.66(3H, s), 1.80(3H, s), 1.85-1.94(2H, m), 3.38-3.49(1H, m), 4.10-4.16(1H, m), 6.76-6.75(1H, m).

(2) 2-[cis-4-(tert-butyloxycarbonylamino)cyclohexylmethyl]-3-(N, N-diethylamino)-3-oxopropionic acid

**[0444]** In the same manner as in Example 119 (2), the title compound (3.35 g) was obtained as an oil using the above-mentioned compound (4.00 g).

<sup>1</sup>H-NMR(300MHz, DMSO-d<sub>6</sub>)δ0.93(3H, t, J = 7.2Hz), 1.11(3H, t, J = 7.2Hz), 1.20-1.78(11H, m), 1.36(9H, s), 3.19-3.48(5H, m), 3.54-3.60(1H, m), 6.60-6.70(1H, m), 12.40(1H, brs).

(3) 2-[cis-4-(tert-butyloxycarbonylamino)cyclohexylmethyl]-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

**[0445]** In the same manner as in Example 1 (2), the title compound (870 mg) was obtained as a white powder using the above-mentioned compound (3.34 g).

<sup>1</sup>H-NMR(300MHz, DMSO-d<sub>6</sub>)δ0.81-1.76 (17H, m), 1.37(9H, s), 3.06-3.21(5H, m), 3.50-3.60(1H, m), 6.58-6.66(1H, m), 7.66-7.75(2H, m), 7.82-7.90(1H, m), 8.02-8.25(3H, m), 8.58(1H, s), 12.30(1H, brs).

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Example 165 Synthesis of 2-(cis-4-aminocyclohexylmethyl)-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide trifluoroacetic acid salt

**[0446]** In the same manner as in Example 18, the title compound (790 mg) was obtained as a white solid using the compound (850 mg) obtained in Example 164.

<sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.82-0.94(6H, m), 1.18-1.65 (11H, m), 3.00-3.27(5H, m), 3.55-3.59(1H, m), 7.64(3H, brs), 7.67-7.78(2H, m), 7.86(1H, dd, J = 8.4, 1.6Hz), 8.07(1H, d, J = 8.0Hz), 8.15(1H, d, J = 8.8Hz), 8.21(1H, d, J = 8.0Hz), 8.59(1H, s), 12.37 (1H, brs).

MS: 460 (M+H)<sup>+</sup>.

Example 166 Synthesis of 2-[cis-4-(benzoylamino)cyclohexylmethyl]-N, N-diethyl-N'-(2-naphthylsulfonyl) malonamide

**[0447]** In the same manner as in Example 155, the title compound (100 mg) was obtained as a white powder using the compound (119 mg) obtained in Example 165 and benzoyl chloride (27 μL).

<sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.84-0.98(6H, m), 1.09-1.45 (7H, m), 1.45-1.71(4H, m), 3.07-3.29(4H, m), 3.59(1H, t, J = 6.8Hz), 3.78-3.85(1H, m), 7.41-7.52(3H, m), 7.67-7.80(4H, m), 7.86-7.88(1H, m), 7.98(1H, d, J = 7.6Hz), 8.07 (1H, d, J = 8.4Hz), 8.16(1H, d, J = 8.8Hz), 8.22(1H, d, J = 8.0Hz), 8.60(1H, d, J = 1.2Hz), 12.32(1H, brs).

MS: 564(M+H)<sup>+</sup>.

Example 167 Synthesis of N, N-diethyl-N'-(2-naphthylsulfonyl)-2-[cis-4-(3-phenylureido)cyclohexylmethyl]malonamide

**[0448]** In the same manner as in Example 155, the title compound (100 mg) was obtained as a white solid using the compound (126 mg) obtained in Example 165 and phenyl isocyanate (27 μL).

<sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.83-1.63(17H, m), 3.10-3.29(4H, m), 3.57-3.67(2H, m), 6.15(1H, d, J = 7.6Hz), 6.85-6.89(1H, m), 7.19-7.22(2H, m), 7.35(2H, d, J = 8.0Hz), 7.68-7.50(2H, m), 7.87(1H, dd, J = 9.2, 2.0Hz), 8.06(1H, d, J = 8.8Hz), 8.16(1H, d, J = 8.8Hz), 8.21-8.23(2H, m), 8.60(1H, s), 12.31(1H, brs).

MS: 579(M+H)<sup>+</sup>.

Example 168 Synthesis of N, N-diethyl-N'-(2-naphthylsulfonyl)-2-[cis-4-(pivaloylamino)cyclohexylmethyl]malonamide

**[0449]** In the same manner as in Example 155, the title compound (86 mg) was obtained as a white solid using the compound (106 mg) obtained in Example 165 and pivaloyl chloride (25 μL).

<sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.83-0.96(6H, m), 1.06(9H, s), 1.06-1.47(9H, m), 1.57-1.70(2H, m), 3.06-3.25(4H, m), 3.50-3.60(2H, m), 6.82(1H, d, J = 7.6Hz), 7.70-7.75(2H, m), 7.85-7.88(1H, m), 8.07(1H, d, J = 8.0Hz), 8.16(1H, d, J = 8.8Hz), 8.22(1H, d, J = 8.0Hz), 8.59(1H, d, J = 0.8Hz), 12.32(1H, brs).

MS: 544(M+H)<sup>+</sup>.

Example 169 Synthesis of 2-[trans-4-(tert-butyloxycarbonylamino)cyclohexylmethyl]-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

(1) 5-[trans-4-(tert-butyloxycarbonylamino)cyclohexylmethyl]-2, 2-dimethyl-1, 3-dioxane-4, 6-dione

**[0450]** In the same manner as in Example 132 (1), the title compound (18.9 g) was obtained as a white solid using trans-4-(tert-butyloxycarbonylamino)cyclohexanecarboxylic acid (15.2 g).

<sup>1</sup>H-NMR(300MHz, DMSO-d<sub>6</sub>)δ0.83-1.16(4H, m), 1.37(9H, s), 1.37-1.90(7H, m), 1.66(3H, s), 1.80(3H, s), 3.07-3.33(1H, m), 4.12-4.20(1H, m), 6.60-6.70(1H, m).

(2) 2-[trans-4-(tert-butyloxycarbonylamino)cyclohexylmethyl]-3-(N, N-diethylamino)-3-oxopropionic acid

**[0451]** In the same manner as in Example 119 (2), the title compound (8.40 g) was obtained as a white powder using the above-mentioned compound (10.2 g).

<sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.82-1.13(11H, m), 1.35(9H, s), 1.50-1.77(6H, m), 3.04-3.17(1H, m), 3.20-3.49(4H, m), 3.59(1H, t, J = 7.2Hz), 6.55-6.63(1H, m), 12.43(1H, brs).

(3) 2-[trans-9-(tert-butyloxycarbonylamino)cyclohexylmethyl]-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

**[0452]** In the same manner as in Example 1 (2), the title compound (7.20 g) was obtained as a white powder using the above-mentioned compound (8.30 g).

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<sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.74-1.05(11H, m), 1.37(9H, s), 1.37-1.72(6H, m), 3.00-3.27(5H, m), 3.59(1H, t, J = 7.2Hz), 6.50-6.60(1H, m), 7.65-7.77(2H, m), 7.83-7.86(1H, m), 8.07(1H, d, J = 8.0Hz), 8.18(1H, d, J = 8.8Hz), 8.22(1H, d, J = 7.6Hz), 8.59(1H, d, J = 0.8Hz), 12.30(1H, brs).

5 Example 170 Synthesis of 2-(trans-4-aminocyclohexylmethyl)-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide trifluoroacetic acid salt

**[0453]** In the same manner as in Example 18, the title compound (6.45 g) was obtained as a white solid using the compound (6.80 g) obtained in Example 169.

10 <sup>1</sup>H-NMR(300MHz, DMSO-d<sub>6</sub>)δ0.78-1.23(11H, m), 1.40-1.91(6H, m), 2.79-2.93(1H, m), 3.04-3.27(4H, m), 3.60(1H, t, J = 6.8Hz), 7.68(3H, brs), 7.68-7.78(2H, m), 7.85(1H, d, J = 8.6Hz), 8.07(1H, d, J = 7.9Hz), 8.16(1H, d, J = 8.8Hz), 8.22(1H, d, J = 8.0Hz), 8.59(1H, s), 12.40(1H, brs).  
MS: 460(M+H)<sup>+</sup>.

15 Example 171 Synthesis of 2-[trans-4-(benzoylamino)cyclohexylmethyl]-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

**[0454]** In the same manner as in Example 155, the title compound (269 mg) was obtained as a white solid using the compound (323 mg) obtained in Example 170 and benzoyl chloride (27 μL). <sup>1</sup>H-NMR(300MHz, DMSO-d<sub>6</sub>)δ0.85-1.04(9H, m), 1.07-1.29(2H, m), 1.44-1.60(3H, m), 1.66-1.81(3H, m), 3.08-3.27(4H, m), 3.59-3.71(2H, m), 7.43-7.51(3H, m), 7.68-7.76(2H, m), 7.81-7.83(2H, m), 7.86-7.88(1H, m), 8.08(1H, d, J = 7.9Hz), 8.18(1H, d, J = 8.8Hz), 8.23(1H, d, J = 7.8Hz), 8.60(1H, s), 12.34(1H, brs). MS: 564 (M+H)<sup>+</sup>.

Example 172 Synthesis of N, N-diethyl-2-[trans-4-(2-methoxybenzoylamino)cyclohexylmethyl]-N'-(2-naphthylsulfonyl)malonamide

25 **[0455]** In the same manner as in Example 13, the title compound (454 mg) was obtained as a white solid using the compound (655 mg) obtained in Example 170 and 2-methoxybenzoic acid (174 mg).

30 <sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.81-1.14(11H, m), 1.39-1.82(6H, m), 3.09-3.27(4H, m), 3.55-3.66(2H, m), 3.89(3H, s), 7.00-7.04(1H, m), 7.13(1H, d, J = 8.3Hz), 7.43-7.47 (1H, m), 7.66-7.79(4H, m), 7.86-7.89(1H, m), 8.07(1H, d, J = 8.0Hz), 8.17(1H, d, J = 8.7Hz), 8.23(1H, d, J = 8.0H), 8.60(1H, s), 12.32(1H, brs).  
MS: 594(M+H)<sup>+</sup>.

Example 173 Synthesis of 2-(trans-4-[(2-benzoxazolyl)amino]cyclohexylmethyl)-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

35 **[0456]** In the same manner as in Example 163, the title compound (245 mg) was obtained as a pale-yellow solid using the compound (333 mg) obtained in Example 170 and 2-chlorobenzoxazole (140 μL).

40 <sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.82-1.24(11H, m), 1.42-2.00 (6H, m), 3.08-3.27(4H, m), 3.36-3.46(1H, m), 3.62(1H, t, J = 7.4Hz), 6.94-6.98(1H, m), 7.08-7.11(1H, m), 7.22(1H, d, J = 7.5Hz), 7.31(1H, d, J = 7.8Hz), 7.67-7.74(3H, m), 7.85-7.88(1H, m), 8.07(1H, d, J = 7.9Hz), 8.18(H, d, J = 8.7Hz), 8.22(1H, d, J = 7.8H), 8.60(1H, s), 12.34(1H, brs).  
MS: 577 (M+H)<sup>+</sup>.

Example 174 Synthesis of 2-[2-(1-benzoyl-4-piperidinyl)ethyl]-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

45 (1) 5-[2-(1-tert-butyloxycarbonyl-4-piperidinyl)ethyl]-2, 2-dimethyl-1, 3-dioxane-4, 6-dione

**[0457]** In the same manner as in Example 132 (1), the title compound (3.15 g) was obtained as a white solid using 1-tert-butyloxycarbonyl-4-piperidinylacetic acid (4.96 g). <sup>1</sup>H-NMR(300MHz, DMSO-d<sub>6</sub>)δ0.83-1.41(5H, m), 1.36(9H, s), 1.55-1.96(4H, m), 1.64(3H, s), 1.77(3H, s), 2.54-2.74(2H, m), 3.80-3.94(2H, m), 4.38-4.45(1H, m).

50 (2) 2-[2-(1-tert-butyloxycarbonyl-4-piperidinyl)ethyl]-3-(N, N-diethylamino)-3-oxopropionic acid

**[0458]** In the same manner as in Example 119 (2), the title compound (1.23 g) was obtained as an oil using the above-mentioned compound (3.13 g).

55 <sup>1</sup>H-NMR(300MHz, DMSO-d<sub>6</sub>)δ0.80-1.20(11H, m), 1.37(9H, s), 1.52-1.74(4H, m), 2.55-2.70(2H, m), 3.18-3.53(5H, m), 3.81-3.93(2H, m), 12.43(1H, brs).

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(3) 2-[2-(1-tert-butyloxycarbonyl-4-piperidinyl)ethyl]-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

**[0459]** In the same manner as in Example 1 (2), the title compound (880 mg) was obtained as a white powder using the above-mentioned compound (1.22 g).

<sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.63-1.31(13H, m), 1.38(9H, s), 1.50-1.67(2H, m), 2.43-2.62(2H, m), 3.08-3.25(4H, m), 3.45-3.50(1H, m), 3.73-3.84(2H, m), 7.65-7.78(2H, m), 7.85-7.88(1H, m), 8.06(1H, d, J = 8.0Hz), 8.15(1H, d, J = 8.8Hz), 8.21(1H, d, J = 8.0Hz), 8.59(1H, s), 12.30(1H, brs).

(4) N, N-diethyl-N'-(2-naphthylsulfonyl)-2-[2-(4-piperidinyl)ethyl]malonamide trifluoroacetic acid salt

**[0460]** In the same manner as in Example 18, the title compound (900 mg) was obtained as a white powder using the above-mentioned compound (880 mg).

<sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.87-0.92(6H, m), 0.89-1.17(4H, m), 1.31-1.40(1H, m), 1.53-1.69(4H, m), 2.68-2.82(2H, m), 3.07-3.50(7H, m), 7.67-7.77(2H, m), 7.85-7.88(1H, m), 7.95-8.08(1H, m), 8.07(1H, d, J = 8.4Hz), 8.16(1H, d, J = 8.4Hz), 8.22(1H, d, J = 7.6Hz), 8.31-8.40(1H, m), 8.59(1H, s), 12.33(1H, brs).

(5) 2-[2-(1-benzoyl-4-piperidinyl)ethyl]-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

**[0461]** In the same manner as in Example 155, the title compound (152 mg) was obtained as a white solid using the above-mentioned compound (175 mg) and benzoyl chloride (39 μL).

<sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.70-1.10(11H, m), 1.20-1.65(6H, m), 2.52-2.93(2H, m), 3.08-3.25(4H, m), 3.45-3.51(2H, m), 4.22-4.42(1H, m), 7.30-7.33(2H, m), 7.42-7.44(3H, m), 7.65-7.75(2H, m), 7.87(1H, dd, J = 8.8, 1.6H), 8.06(1H, d, J = 8.0H), 8.16(1H, d, J = 8.8Hz), 8.22(1H, d, J = 8.0Hz), 8.60(1H, d, J = 1.6Hz), 12.30(1H, brs).

MS: 564(M+H)<sup>+</sup>.

Example 175 Synthesis of 2-[2-(1-anilinoacarbonyl-4-piperidinyl)ethyl]-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

**[0462]** In the same manner as in Example 155, the title compound (151 mg) was obtained as a white solid using the compound (178 mg) obtained in Example 174 (4) and phenyl isocyanate (37 μL).

<sup>1</sup>H-NMR (400MHz, DMSO-d<sub>6</sub>)δ0.71-1.08(9H, m), 1.17-1.30(2H, m), 1.40-1.66(4H, m), 2.58-2.68(2H, m), 3.07-3.26(4H, m), 3.46-3.52(1H, m), 3.95-4.04(2H, m), 6.88-6.94(1H, m), 7.19-7.23(2H, m), 7.44-7.46(2H, m), 7.68-7.71(2H, m), 7.86-7.88(1H, m), 8.01-8.07(1H, m), 8.14(1H, d, J = 8.8Hz), 8.17-8.23(1H, m), 8.36(1H, s), 8.59(1H, d, J = 0.8Hz), 12.32(1H, brs).

MS: 579(M+H)<sup>+</sup>.

Example 176 Synthesis of N, N-diethyl-N'-(2-naphthylsulfonyl)-2-[2-(1-nicotinoyl-4-piperidinyl)ethyl]malonamide hydrochloride

**[0463]** To a solution of the compound (350 mg) obtained in Example 174 (4) in pyridine (2 mL) was added nicotinic acid chloride hydrochloride (326 mg) under ice-cooling, and the mixture was stirred at room temperature for 2 hr. The mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography. This was converted to a hydrochloride salt with 4 mol/L hydrochloric acid-ethyl acetate to give the title compound (63 mg) as a white powder.

<sup>1</sup>H-NMR(300MHz, DMSO-d<sub>6</sub>)δ0.76-1.68(15H, m), 2.59-2.73(1H, m), 2.84-3.05(1H, m), 3.05-3.28(4H, m), 3.28-3.48(1H, m), 3.59(1H, t, J = 6.6Hz), 4.23-4.40(2H, m), 7.65-7.78(2H, m), 7.78-7.90(2H, m), 8.07(1H, d, J = 7.9Hz), 8.16(1H, d, J = 8.8Hz), 8.21-8.25(3H, m), 8.60(1H, s), 8.83-8.85(2H, m), 12.48(1H, brs).

MS: 565(M+H)<sup>+</sup>.

Example 177 Synthesis of 2-benzyl-N, N-diethyl-N'-(4-isobutylphenylsulfonyl)malonamide

(1) 4-isobutylbenzenesulfonamide

**[0464]** To chlorosulfonic acid (10 mL) was added dropwise isobutylbenzene (1.00 mL) under ice-cooling, and the mixture was stirred for 1 hr. Ice-water (100 mL) was added to the reaction mixture, and the mixture was extracted with ethyl acetate (100 mL×2). The organic layer was washed with saturated brine and concentrated under reduced pressure. 28% Aqueous ammonia (50 mL) was added dropwise to a solution of the residue in THF (20 mL) under ice-cooling, and the mixture was stirred at room temperature for 15 hr. The reaction mixture was adjusted to pH = 1-2 by the addition of dilute hydrochloric acid, and extracted with ethyl acetate (100 mL×2). The organic layer was washed with saturated

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brine and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound (690 mg) as a white solid.

$^1\text{H-NMR}$ (300MHz,  $\text{DMSO-d}_6$ ) $\delta$ 0.86(6H, d, J = 6.6Hz), 1.79-1.94(1H, m), 2.52(2H, d, J = 7.2Hz), 7.28 (2H, brs), 7.35(2H, d, J = 8.1Hz), 7.73 (2H, d, J = 8.1Hz).

5

(2) ethyl 2-benzyl-3-[(4-isobutylphenylsulfonyl)amino]-3-oxopropionate

**[0465]** In the same manner as in Example 1 (2), the title compound (118 mg) was obtained as an oil using the above-mentioned compound (680 mg) and the compound (710 mg) obtained in Example 1 (1).

$^1\text{H-NMR}$ (300MHz,  $\text{CDCl}_3$ ) $\delta$ 0.92(6H, d, J = 6.6Hz), 1.11(3H, t, J = 7.1Hz), 1.83-1.93(1H, m), 2.56(2H, d, J = 6.6Hz), 3.14(2H, d, J = 7.2Hz), 3.53(1H, t, J = 7.2Hz), 4.08(2H, q, J = 7.1Hz), 6.97-7.00(2H, m), 7.15-7.18(3H, m), 7.29(2H, d, J = 8.3Hz), 7.92 (2H, d, J = 8.3Hz).

15

(3) 2-benzyl-3-[(4-isobutylphenylsulfonyl)amino]-3-oxopropionic acid

**[0466]** In the same manner as in Example 1 (3), the title compound (110 mg) was obtained as an oil using the above-mentioned compound (118 mg).

$^1\text{H-NMR}$ (300MHz,  $\text{DMSO-d}_6$ ) $\delta$ 0.87(6H, d, J = 6.9Hz), 1.81-1.98(1H, m), 2.56(2H, d, J = 7.2Hz), 2.84-3.00(2H, m), 3.60-3.70(1H, m), 6.97-7.00(2H, m), 7.14-7.16(3H, m), 7.37(2H, d, J = 8.4Hz), 7.67(2H, d, J = 8.4Hz), 12.32 (1H, brs), 12.92(1H, brs).

20

(4) 2-benzyl-N, N-diethyl-N'-(4-isobutylphenylsulfonyl)malonamide

**[0467]** In the same manner as in Example 1 (4), the title compound (67 mg) was obtained as an oil using the above-mentioned compound (110 mg).

$^1\text{H-NMR}$ (300MHz,  $\text{CDCl}_3$ ) $\delta$ 0.78(3H, t, J = 7.1Hz), 0.90 (6H, d, J = 6.6Hz), 1.00(3H, t, J = 7.1Hz), 1.85-1.97(1H, m), 2.55(2H, d, J = 7.2Hz), 2.78-2.88(2H, m), 2.98-3.20(3H, m), 3.38-3.52(1H, m), 3.55-3.63(1H, m), 7.05-7.08(2H, m), 7.19-7.21(3H, m), 7.30(2H, d, J = 8.4Hz), 7.97(2H, d, J = 8.4Hz), 10.08(1H, brs).  
MS: 445 (M+H) $^+$ .

30

Example 178 Synthesis of N, N-diethyl-2-(4-nitrobenzyl)-N'-tosylmalonamide

(1) diethyl (4-nitrobenzyl)malonate

**[0468]** In the same manner as in Example 6 (1), the title compound (27.2 g) was obtained as an oil using diethyl malonate (18.5 g).

$^1\text{H-NMR}$ (300Mz,  $\text{CDCl}_3$ ) $\delta$ 1.22(6H, t, J = 7.1Hz), 3.32(2H, d, J = 7.8Hz), 3.66(1H, t, J = 7.8Hz), 4.05-4.29(4H, m), 7.39(2H, d, J = 8.7Hz), 8.15(2H, d, J = 8.7Hz).

40

(2) monoethyl (4-nitrobenzyl)malonate

**[0469]** In the same manner as in Example 111 (2), the title compound (5.10 g) was obtained as an oil using the above-mentioned compound (7.40 g).

$^1\text{H-NMR}$ (300Mz,  $\text{CDCl}_3$ ) $\delta$ 1.23 (3H, t, J = 7.1Hz), 3.23-3.41 (2H, m), 3.74(1H, t, J = 7.7Hz), 4.04-4.35(2H, m), 7.40(2H, d, J = 8.6Hz), 8.15 (2H, d, J = 8.7Hz), 9.65(1H, brs).

45

(3) ethyl 2-(4-nitrobenzyl)-3-oxo-3-tosylaminopropionate

**[0470]** In the same manner as in Example 1 (2), the title compound (4.72 g) was obtained as an oil using the above-mentioned compound (3.00 g) and p-toluene-2-sulfonamide (1.92 g).

$^1\text{H-NMR}$ (300Mz,  $\text{CDCl}_3$ ) $\delta$ 1.23(3H, t, J = 7.0Hz), 2.43(3H, s), 2.98-3.36(2H, m), 3.73(1H, t, J = 7.56Hz), 4.14-4.25(2H, m), 7.30-7.33(2H, m), 7.39-7.42(2H, m), 7.79-7.83(2H, m), 8.14-8.19(2H, m).

55

(4) N, N-diethyl-2-(4-nitrobenzyl)-N'-tosylmalonamide

**[0471]** The above-mentioned compound (4.72 g) was subjected to hydrolysis in the same manner as in Example 1 (3). In the same manner as in Example 1 (4), the title compound (1.06 g) was obtained as a white powder using the obtained carboxylic acid (2.16 g).

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<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.88(6H, t, J = 7.2Hz), 2.38(3H, s), 3.03-3.05(2H, m), 3.11-3.19(4H, m), 3.91(1H, t, J = 7.2Hz), 7.30-7.36(4H, m), 7.65(2H, d, J = 8.1Hz), 7.97(2H, d, J = 8.4Hz), 12.22 (1H, brs).  
MS: 448(M+H)<sup>+</sup>.

### 5 Example 179 Synthesis of 2-(4-aminobenzyl)-N, N-diethyl-N'-tosylmalonamide

**[0472]** In the same manner as in Example 7, the title compound (92 mg) was obtained as a white powder using the compound (120 mg) obtained in Example 178 at room temperature.

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>3</sub>)δ0.83-0.90(6H, m), 2.39(3H, s), 2.72(2H, d, J = 6.9Hz), 3.10-3.17(4H, m), 3.66-3.67(1H, m), 6.35(2H, d, J = 8.1Hz), 6.67 (2H, d, J = 8.1Hz), 7.38(2H, d, J = 8.1Hz), 7.66(2H, d, J = 8.1Hz).  
MS: 418(M+H)<sup>+</sup>.

### Example 180 Synthesis of N'-(4-chlorophenylsulfonyl)-N, N-diethyl-2-(4-nitrobenzyl)malonamide

#### 15 (1) ethyl 3-[(4-chlorophenylsulfonyl)amino]-2-(4-nitrobenzyl)-3-oxopropionate

**[0473]** In the same manner as in Example 152 (3), the title compound (1.95 g) was obtained as a white powder using the compound (2.00 g) obtained in Example 178(2) and 4-chlorobenzenesulfonamide (1.44 g).

<sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ1.20-1.25(3H, m), 3.25-3.28(2H, m), 3.56-3.61(1H, m), 4.14-4.19(2H, m), 7.39-7.42(1H, m), 7.48-7.52(2H, m), 7.85-7.88(1H, m), 7.94-7.96(2H, m), 8.13-8.16(2H, m).

#### (2) 3-[(4-chlorophenylsulfonyl)amino]-2-(4-nitrobenzyl)-3-oxopropionic acid

**[0474]** In the same manner as in Example 1 (3), the title compound (1.01 g) was obtained as a white powder using the above-mentioned compound (1.95 g).

<sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ3.31-3.39(2H, m), 3.59-3.64(1H, m), 7.20-7.23(1H, m), 7.44-7.49(1H, m), 7.49-7.54(2H, m), 7.85-7.88(1H, m), 7.94-7.97(1H, m), 8.04-8.07(1H, m), 8.16-8.19(1H, m).

#### 30 (3) N'-(4-chlorophenylsulfonyl)-N, N-diethyl-2-(4-nitrobenzyl)malonamide

**[0475]** In the same manner as in Example 1 (4), the title compound (140 mg) was obtained as a white powder using the above-mentioned compound (1.01 g).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.85-0.97(6H, m), 3.05-3.11(2H, m), 3.13-3.23 (4H, m), 3.93(1H, t, J = 7.5Hz), 7.34 (2H, d, J = 8.4Hz), 7.63(2H, d, J = 8.4Hz), 7.78 (2H, d, J = 8.7Hz), 7.99(2H, d, J = 8.7Hz), 12.40(1H, brs).  
MS: 468 (M+H)<sup>+</sup>.

### Example 181 Synthesis of 2-(4-aminobenzyl)-N'-(4-chlorophenylsulfonyl)-N, N-diethylmalonamide

**[0476]** In the same manner as in Example 137 (4), the title compound (8 mg) was obtained as a white powder using the compound (116 mg) obtained in Example 180 at room temperature.

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.86-0.87(6H, m), 2.71-2.75(1H, m), 3.03-3.15(4H, m), 3.33-3.37(2H, m), 6.41(1H, d, J = 7.8Hz), 6.71(1H, d, J = 8.4Hz), 7.33(1H, d, J = 8.7Hz), 7.57(1H, d, J = 8.1Hz), 7.65(1H, d, J = 8.7Hz), 7.75-7.78(2H, m), 7.99(1H, d, J = 8.7Hz).

MS: 438(M+H)<sup>+</sup>.

### Example 182 Synthesis of N, N-diethyl-N'-(4-methoxyphenylsulfonyl)-2-(4-nitrobenzyl)malonamide

#### (1) ethyl 3-[(4-methoxyphenylsulfonyl)amino]-2-(4-nitrobenzyl)-3-oxopropionate

**[0477]** In the same manner as in Example 152 (3), the title compound (2.82 g) was obtained as a white powder using the compound (2.00 g) obtained in Example 178 (2) and 4-methoxybenzenesulfonamide (1.40 g).

<sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ1.20(3H, t, J = 7.2Hz), 2.17(3H, s), 3.24-3.27(2H, m), 3.51-3.55(1H, m), 4.13-4.20(2H, m), 6.97-6.99(3H, m), 7.14-7.17(1H, m), 7.85-7.88(1H, m), 7.93-8.02(3H, m).

#### 55 (2) 3-[(4-methoxyphenylsulfonyl)amino]-2-(4-nitrobenzyl)-3-oxopropionic acid

**[0478]** In the same manner as in Example 1 (3), the title compound (2.64 g) was obtained as a white powder using the above-mentioned compound (2.82 g).

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<sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ2.07(3H, s), 2.99-3.15(2H, m), 3.68-3.71(1H, m), 6.99-7.08(2H, m), 7.16-7.26(2H, m), 7.61-7.74(2H, m), 7.92-7.95(1H, m), 8.10-8.12(1H, m).

(3) N, N-diethyl-N'-(4-methoxyphenylsulfonyl)-2-(4-nitrobenzyl)malonamide

**[0479]** In the same manner as in Example 1 (4), the title compound (980 mg) was obtained as a white powder using the above-mentioned compound (2.64 g).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.86-0.90(6H, m), 3.03-3.13(2H, m), 3.16-3.21(4H, m), 3.32(3H, s), 3.87-3.92(1H, m), 7.06(2H, d, J = 9.0Hz), 7.32(2H, d, J = 8.7Hz), 7.71 (2H, d, J = 8.7Hz), 7.98(2H, d, J = 9.0Hz), 12.14(1H, brs).

MS: 464(M+H)<sup>+</sup>.

Example 183 Synthesis of 2-(4-aminobenzyl)-N, N-diethyl-N'-(4-methoxyphenylsulfonyl)malonamide

**[0480]** In the same manner as in Example 7, the title compound (170 mg) was obtained as a white powder using the compound (200 mg) obtained in Example 182 at room temperature.

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.83-0.90(6H, m), 2.72(2H, d, J = 6.9Hz), 3.06-3.31(4H, m), 3.64-3.62(1H, m), 3.84(3H, s), 6.36(2H, d, J = 8.4Hz), 6.68(2H, d, J = 8.4Hz), 7.10(2H, d, J = 8.7Hz), 7.73 (2H, d, J = 8.7Hz).

MS: 434 (M+H)<sup>+</sup>.

Example 184 Synthesis of N, N-diethyl-N'-(1-naphthylsulfonyl)-2-(4-nitrobenzyl)malonamide

(1) ethyl 3-[(1-naphthylsulfonyl)amino]-2-(4-nitrobenzyl)-3-oxopropionate

**[0481]** In the same manner as in Example 152 (3), the title compound (3.17 g) was obtained as a white powder using the compound (2.00 g) obtained in Example 178 (2) and naphthalene-1-sulfonamide (1.55 g).

<sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ0.88(3H, t, J = 6.9Hz), 2.93-3.00(2H, m), 3.76-3.89(3H, m), 7.09-7.12(2H, m), 7.55-7.72(5H m), 8.01-8.04(1H m), 8.21-8.28(2H, m), 8.34-8.36(1H, m), 12.75(1H, brs).

(2) 3-[(1-naphthylsulfonyl)amino]-2-(4-nitrobenzyl)-3-oxopropionic acid

**[0482]** In the same manner as in Example 1 (3), the title compound (2.61 g) was obtained as a white powder using the above-mentioned compound (3.17 g).

<sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ3.05-3.20(2H, m), 3.64-3.66(1H, m), 6.87-6.89(2H, m), 7.48-7.65(5H, m), 7.96-7.99(1H, m), 8.18-8.21(1H, m), 8.34-8.37(1H, m), 8.48-8.51(1H, m), 10.18(1H, brs).

(3) N,N-diethyl-N'-(1-naphthylsulfonyl)-2-(4-nitrobenzyl)malonamide

**[0483]** In the same manner as in Example 1 (4), the title compound (1.18 g) was obtained as a white powder using the above-mentioned compound (2.61 g).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.68(3H, t, J = 6.9Hz), 0.76(3H, t, J = 6.9Hz), 2.89-3.09(6H, m), 3.84-3.86(1H, m), 7.21-7.24(2H, m), 7.60-7.70(3H, m), 7.82-7.85(2H, m), 8.00-8.07(1H, m), 8.26-8.30(2H, m), 8.44(1H, d, J = 8.4Hz), 12.67(1H, brs). MS: 484(M+H)<sup>+</sup>.

Example 185 Synthesis of 2-(4-aminobenzyl)-N,N-diethyl-N'-(1-naphthylsulfonyl)malonamide

**[0484]** In the same manner as in Example 7, the title compound (290 mg) was obtained as a white powder using the compound (400 mg) obtained in Example 184.

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.61-0.71(6H, m), 2.63-2.71(2H, m), 3.00-3.02(4H, m), 3.60-3.63(1H, m), 6.36(2H, d, J = 7.8Hz), 6.71(2H, d, J = 7.8Hz), 7.67-7.69(3H, m), 8.09-8.29(3H, m), 8.56(1H, d, J = 8.4Hz).

MS: 454(M+H)<sup>+</sup>.

Example 186 Synthesis of N, N-diethyl-N'-(7-methoxy-2-naphthylsulfonyl)-2-(4-nitrobenzyl)malonamide

(1) 3-[(7-methoxy-2-naphthylsulfonyl)amino]-2-(4-nitrobenzyl)-3-oxopropionic acid

**[0485]** In the same manner as in Example 152 (3), the ester form of the title compound was obtained using the compound (1.55 g) obtained in Example 178 (2) and 7-methoxynaphthalene-2-sulfonamide (1.37 g). In the same manner as in Example 1 (3), the title compound (1.53 g) was obtained as a white powder using this.

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<sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ2.97-3.13(2H, m), 3.72-3.75(1H, m), 3.89(3he s), 7.16-7.19(1H, m), 7.34-7.38(1H, m), 7.46-7.56(3H, m), 7.73-7.76(2H, m), 7.89-7.92(2H, m), 8.11-8.14(1H, m), 8.33(1H, s), 12.77(1H, brs).

(2) N, N-diethyl-N'-(7-methoxy-2-naphthylsulfonyl)-2-(4-nitrobenzyl)malonamide

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**[0486]** In the same manner as in Example 1 (4), the title compound (450 mg) was obtained as a white powder using the above-mentioned compound (1.53 g).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.86(6H, t, J = 6.9Hz), 3.04(2H, d, J = 7.5Hz), 3.12-3.18(4H, m), 3.90(3H, s), 3.92-3.95(1H, m), 7.26-7.29(2H, m), 7.35-7.39(1H, m), 7.58-7.61(2H, m), 7.83-7.86(2H, m), 7.93-8.00(2H, m), 8.38(1H, s), 12.30(1H, brs).

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MS: 514(M+H)<sup>+</sup>.

Example 187 Synthesis of 2-(4-aminobenzyl)-N, N-diethyl-N'-(7-methoxy-2-naphthylsulfonyl)malonamide

15 **[0487]** In the same manner as in Example 7, the title compound (46 mg) was obtained as a white powder using the compound (320 mg) obtained in Example 186.

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.82-0.84(6H, m), 2.73(2H, d, J = 6.0Hz), 3.09-3.12(4H, m), 3.65-3.70(1H, m), 3.90(3H, s), 6.34(2H, d, J = 8.1Hz), 6.70(2H, d, J = 8.4Hz), 7.36(1H, d, J = 9.0Hz), 7.57-7.60(2H, m), 7.94-8.03(2H, m), 8.42(1H, s). MS: 484 (M+H)<sup>+</sup>.

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Example 188 Synthesis of N'-(4-biphenylsulfonyl)-N, N-diethyl-2-(4-nitrobenzyl)malonamide

(1) ethyl 3-(N, N-diethylamino)-2-(4-nitrobenzyl)-3-oxopropionate

25 **[0488]** In the same manner as in Example 1 (4), the title compound (1.53 g) was obtained as a white powder using the compound (2.00 g) obtained in Example 178 (2).

<sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ0.94-1.07(6H, m), 1.22-1.26(3H, m), 3.05-3.10(2H, m), 3.30-3.42(4H, m), 3.75-3.78(1H, m), 4.15-4.22(2H, m), 7.36-7.42(2H, m), 8.12-8.14(2H, m).

30 (2) 3-(N, N-diethylamino)-2-(4-nitrobenzyl)-3-oxopropionic acid

**[0489]** In the same manner as in Example 1 (3), the title compound (1.09 g) was obtained as a pale-yellow powder using the above-mentioned compound (1.53 g).

<sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ0.82-0.86(6H, m), 3.05-3.14 (4H, m), 3.20-3.33(2H, m), 3.99-4.04(1H, m), 7.47-7.50(2H, m), 8.09-8.12(2H, m), 12.70(1H, brs).

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(3) N, N-diethyl-2-(4-nitrobenzyl)malonamide

**[0490]** To a solution of the above-mentioned compound (400 mg) in methylene chloride (10 mL) was added oxalyl chloride (180 μL) under ice-cooling, and the mixture was stirred at room temperature for 1 hr. The reaction mixture was concentrated under reduced pressure. THF (50 mL) was added, and the mixture was ice-cooled. 28% Aqueous ammonia (1 mL) was added, and the mixture was stirred for 1 hr. 1 mol/L Hydrochloric acid (100 mL) was added, and the mixture was extracted with ethyl acetate (50 mL). The organic layer was washed with saturated brine and concentrated under reduced pressure to give the title compound (250 mg) as a white powder.

45 <sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ0.87-0.94(6H, m), 3.04-3.10(2H, m), 3.19-3.24(4H, m), 3.37-3.76(1H, m), 7.09(1H, brs), 7.35(1H, brs), 7.47-7.50(2H, m), 8.10-8.13(2H, m).

(4) N'-(4-biphenylsulfonyl)-N, N-diethyl-2-(4-nitrobenzyl)malonamide

50 **[0491]** To a solution of the above-mentioned compound (300 mg) and 4-biphenylsulfonyl chloride (260 mg) in THF (25 mL) was added 60% sodium hydride (80 mg) under ice-cooling, and the mixture was stirred at room temperature for 1 hr. 1 mol/L Hydrochloric acid (20 mL) was added to the reaction mixture under ice-cooling, and the mixture was extracted with ethyl acetate (20 mL). The organic layer was washed with saturated brine and concentrated under reduced pressure, and the residue was purified by silica gel column chromatography to give the title compound (380 mg) as a white powder.

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<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.84-0.89(6H, m), 3.01-3.15(4H, m), 3.33-3.49(1H, m), 3.49-3.62(2H, m), 7.34-7.39(3H, m), 7.44-7.49(2H, m), 7.60-7.74(6H, m), 7.98(2H, d, J = 8.4Hz).

MS: 510(M+H)<sup>+</sup>.

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Example 189 Synthesis of 2-(4-aminobenzyl)-N'-(4-biphenylsulfonyl)-N, N-diethylmalonamide

**[0492]** In the same manner as in Example 7, the title compound (230 mg) was obtained as a white powder using the compound (300 mg) obtained in Example 188 at room temperature.

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.89-0.90(6H, m), 2.16(1H, d, J = 7.2Hz), 3.16-3.18(4H, m), 3.28-3.29(2H, m), 6.39-6.43(2H, m), 6.71-6.74(2H, m), 7.94-7.54(3H, m), 7.73-7.84(2H, m), 7.86-7.87 (4H, m).

MS: 480(M+H)<sup>+</sup>.

Example 190 Synthesis of N, N-diethyl-2-(4-nitrobenzyl)-N'-(2-tolylsulfonyl)malonamide

**[0493]** In the same manner as in Example 188 (4), the title compound (170 mg) was obtained as a white powder using the compound (300 mg) obtained in Example 188 (3) and 2-methylbenzenesulfonyl chloride (150 μL).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.86-0.91(6H, m), 2.48(3H, s), 3.04-3.06(2H, m), 3.11-3.30(4H, m), 3.93-3.97(1H, m), 7.30-7.39(4H, m), 7.54-7.56(1H, m), 7.65-7.67(1H, m), 7.90-8.05(2H, m).

MS: 448(M+H)<sup>+</sup>.

Example 191 Synthesis of 2-(4-aminobenzyl)-N, N-diethyl-N'-(2-tolylsulfonyl)malonamide

**[0494]** In the same manner as in Example 7, the title compound (158 mg) was obtained as a white powder using the compound (170 mg) obtained in Example 190 at room temperature.

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.84-0.92(6H, m), 2.43(3H, s), 2.72-2.74(2H, m), 3.12-3.17(4H, m), 3.71(1H, t, J = 6.9Hz), 6.38(2H, d, J = 8.3Hz), 6.69(2H, d, J = 8.3Hz), 7.35-7.38 (2H, m), 7.53-7.58(1H, m), 7.86(1H, d, J = 8.1Hz).

MS: 418(M+H)<sup>+</sup>.

Example 192 Synthesis of N'-(4-tert-butylphenylsulfonyl)-N, N-diethyl-2-(4-nitrobenzyl)malonamide

**[0495]** In the same manner as in Example 188 (4), the title compound (187 mg) was obtained as a white powder using the compound (300 mg) obtained in Example 188 (3) and 4-tert-butylbenzenesulfonyl chloride (230 mg).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.82-0.90(6H, m), 1.28(9H, s), 3.07-3.29(6H, m), 3.91(1H, t, J = 7.2Hz), 7.33(2H, d, J = 8.7Hz), 7.58(2H, d, J = 8.7Hz), 7.71(2H, d, J = 8.7Hz), 7.98(2H, d, J = 8.7Hz), 12.20(1H, brs).

MS: 490(M+H)<sup>+</sup>.

Example 193 Synthesis of 2-(4-aminobenzyl)-N'-(4-tert-butylphenylsulfonyl)-N, N-diethylmalonamide

**[0496]** In the same manner as in Example 7, the title compound (100 mg) was obtained as a white powder using the compound (130 mg) obtained in Example 192 at room temperature.

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.79-0.88(6H, m), 1.29(9H, s), 2.74(2H, d, J = 6.9Hz), 3.08-3.32(4H, m), 3.67-3.69(1H, m), 6.37(2H, d, J = 8.4Hz), 6.69(2H, d, J = 8.4Hz), 7.60(2H, d, J = 8.7Hz), 7.71(2H, d, J = 8.7Hz).

MS: 460(M+H)<sup>+</sup>.

Example 194 Synthesis of N, N-diethyl-2-(4-nitrobenzyl)-N'-(2-thienylsulfonyl)malonamide

**[0497]** In the same manner as in Example 188 (4), the title compound (390 mg) was obtained as a white powder using the compound (300 mg) obtained in Example 188 (3) and 2-thiophenesulfonyl chloride (180 mg).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.84-0.91(6H, m), 3.06-3.21(6H, m), 3.91(1H, t, J = 7.5Hz), 7.14-7.17(1H, m), 7.36(2H, d, J = 8.7Hz), 7.67-7.68(1H, m), 8.00-8.03(3H, m).

MS:440(M+H)<sup>+</sup>.

Example 195 Synthesis of 2-(4-aminobenzyl)-N, N-diethyl-N'-(2-thienylsulfonyl)malonamide

**[0498]** In the same manner as in Example 137 (4), the title compound (52 mg) was obtained as a white powder using the compound (230 mg) obtained in Example 194 at room temperature.

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.85-0.91(6H, m), 2.74(2H, d, J = 6.3Hz), 3.12-3.14(9H, m), 3.65-3.67(1H, m), 6.41(2H, d, J = 7.6Hz), 6.73(2H, d, J = 7.6Hz), 7.16(1H, brs), 7.64(1H, brs), 7.98(1H brs).

MS: 410 (M+H)<sup>+</sup>.

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Example 196 Synthesis of N, N-diethyl-2-(4-nitrobenzyl)-N'-(4-trifluoromethylphenylsulfonyl)malonamide

**[0499]** In the same manner as in Example 188 (4), the title compound (260 mg) was obtained as a white powder using the compound (300 mg) obtained in Example 188 (3) and 4-trifluoromethylbenzenesulfonyl chloride (240 mg).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.85-0.92(6H, m), 3.07(2H, d, J = 7.5Hz), 3.12-3.21(4H, m), 3.95(1H, t, J = 7.5Hz), 7.34(2H, d, J = 8.7Hz), 7.93-8.02(6H, m).

MS: 502 (M+H)<sup>+</sup>.

Example 197 Synthesis of 2-(4-aminobenzyl)-N, N-diethyl-N'-(4-trifluoromethylphenylsulfonyl)malonamide

**[0500]** In the same manner as in Example 7, the title compound (120 mg) was obtained as a white powder using the compound (310 mg) obtained in Example 196.

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.84(3H, s), 0.86(3H, s), 2.76(2H, d, J = 5.4Hz), 3.12-3.17(4H, m), 3.69(1H, brs), 6.46(2H, d, J = 7.2Hz), 6.76(2H, d, J = 7.2Hz), 7.95-7.96(4H, m).

MS: 472 (M+H)<sup>+</sup>.

Example 198 Synthesis of N, N-diethyl-N'-(5-dimethylaminonaphthyl-1-sulfonyl)-2-(4-nitrobenzyl)malonamide

**[0501]** In the same manner as in Example 188 (4), the title compound (390 mg) was obtained as a white powder using the compound (300 mg) obtained in Example 188 (3) and 5-dimethylaminonaphthalene-1-sulfonyl chloride (270 mg).

<sup>1</sup>H-NMR(300mz, DMSO-d<sub>6</sub>)δ0.69(3H, brs), 0.76(3H, brs), 2.81(6H, s), 2.87-3.18(6H, m), 3.85(1H, brs), 7.16-7.24(3H, m), 7.51-7.54(1H, m), 7.61-7.66(1H, m), 7.83-7.85(2H, m), 8.05-8.08(1H, m), 8.22-8.29(1H, m), 8.48-8.51(1H, m), 12.62(1H, brs).

MS: 527(M+H)<sup>+</sup>.

Example 199 Synthesis of 2-(4-aminobenzyl)-N, N-diethyl-N'-(5-dimethylaminonaphthyl-1-sulfonyl)malonamide

**[0502]** In the same manner as in Example 7, the title compound (100 mg) was obtained as a white powder using the compound (260 mg) obtained in Example 198 at room temperature.

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.57-0.59(3H, brs), 0.68-0.70(3H, brs), 2.64-2.81(9H, m), 2.99-3.01(3H, m), 3.63(1H, brs), 6.35-6.38(2H, m), 6.71-6.74(2H, m), 7.23-7.25(1H, m), 7.57-7.66(2H, m), 8.19-8.30(2H, m), 8.48-8.50(1H, m).

MS: 497(M+H)<sup>+</sup>.

Example 200 Synthesis of N, N-diethyl-2-(4-nitrobenzyl)-N'-(E)-styrylsulfonyl)malonamide

**[0503]** In the same manner as in Example 188 (4), the title compound (310 mg) was obtained as a white powder using the compound (600 mg) obtained in Example 188 (3) and trans-β-styrenesulfonyl chloride (410 mg).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.87-0.97(6H, m), 3.14-3.30(6H, m), 3.94-3.96(1H, m), 7.26(1H, d, J = 15.3Hz), 7.43-7.48(6H, m), 7.68-7.70(2H, m), 8.03(2H, d, J = 8.4Hz), 12.07(1H, brs).

MS: 460(M+H)<sup>+</sup>.

Example 201 Synthesis of 2-(4-aminobenzyl)-N, N-diethyl-N'-(E)-styrylsulfonyl)malonamide

**[0504]** In the same manner as in Example 137 (4), the title compound (60 mg) was obtained as a white powder using the compound (200 mg) obtained in Example 200 at room temperature.

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.88-0.95(6H, m), 2.83(2H, d, J = 6.6Hz), 3.13-3.22(4H, m), 3.73-3.74(1H, m), 6.90(2H, d, J = 8.3Hz), 6.81(2H, d, J = 8.3Hz), 7.20(1H, d, J = 15.3Hz), 7.45-7.55(4H, m), 7.70-7.71(2H, m).

MS: 430(M+H)<sup>+</sup>.

Example 202 Synthesis of 2-[4-(benzoylamino)benzyl]-N, N-diethyl-N'-(E)-styrylsulfonyl)malonamide

**[0505]** In the same manner as in Example 9, the title compound (187 mg) was obtained as a white solid using the compound (193 mg) obtained in Example 201.

<sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.86-1.05(6H, m), 3.01(2H, d, J = 6.8Hz), 3.08-3.40(4H, m), 3.90(1H, t, J = 7.2Hz), 7.10-7.28(3H, m), 7.40-7.80(11H, m), 7.94(2H, d, J = 7.2Hz), 10.15(1H, s), 12.00(1H, brs).

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Example 203 Synthesis of 2-[4-(benzoylamino)benzyl]-N'-(4-tert-butylphenylsulfonyl)-N,N-diethylmalonamide

**[0506]** In the same manner as in Example 92, the title compound (1.70 g) was obtained as a white solid using the compound (1.62 g) obtained in Example 192.

<sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.85-0.92(6H, m), 1.29(9H, s), 2.93(2H, d, J = 7.1Hz), 3.10-3.24(4H, m), 3.85(1H, t, J = 7.1Hz), 7.05(2H, d, J = 8.4Hz), 7.52-7.62(7H, m), 7.72(2H, d, J = 8.4Hz), 7.95(2H, d, J = 7.4Hz), 10.19(1H, s), 12.19(1H, brs).

MS: 564(M+H)<sup>+</sup>.

Example 204 Synthesis of N, N-diethyl-2-(3-nitrobenzyl)-N'-(E)-styrylsulfonylmalonamide

(1) N, N-diethyl-2-(3-nitrobenzyl)malonamide

**[0507]** In the same manner as in Example 188 (3), the title compound (2.27 g) was obtained as a white solid using the compound (2.66 g) obtained in Example 114 (4).

<sup>1</sup>H-NMR(300MHz, DMSO-d<sub>6</sub>)δ0.88-0.95(6H, m), 3.05-3.40(6H, m), 3.77(1H, dd, J = 6.5, 4.7Hz), 7.12(1H, brs), 7.37(1H, brs), 7.56(1H, t, J = 7.9Hz), 7.72(1H, d, J = 7.9Hz), 8.06(1H, d, J = 7.9Hz), 8.11(1H, s).

(2) N, N-diethyl-2-(3-nitrobenzyl)-N'-(E)-styrylsulfonylmalonamide

**[0508]** In the same manner as in Example 188 (4), the title compound (150 mg) was obtained as a white solid using the above-mentioned compound (830 mg) and trans-β-styrenesulfonyl chloride (1.26 g).

<sup>1</sup>H-NMR(300MHz, CDCl<sub>3</sub>)δ0.95(3H, t, J = 7.1Hz), 1.04(3H, t, J = 7.1Hz), 2.96-3.60(6H, m), 3.75(1H, dd, J = 9.0, 6.1Hz), 7.04(1H, d, J = 15.4Hz), 7.35-7.54(7H, m), 7.71(1H, d, J = 15.4Hz), 8.06-8.08(2H, m), 10.56(1H, brs).

Example 205 Synthesis of 2-(3-aminobenzyl)-N, N-diethyl-N'-(E)-styrylsulfonylmalonamide hydrochloride

**[0509]** The compound (470 mg) obtained in Example 204 was reduced at room temperature in the same manner as in Example 137 (4), and the reduced product was converted to a hydrochloride salt with 4 mol/L hydrochloric acid-ethyl acetate (1 mL) to give the title compound (89 mg) as a pale-yellow powder.

<sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.85-1.03(6H, m), 2.98-3.30(6H, m), 3.93-3.97(1H, m), 7.00-7.20(3H, m), 7.20-7.36(2H, m), 7.37(1H, d, J = 15.2Hz), 7.45-7.50(2H, m), 7.58(1H, d, J = 15.2Hz), 7.74-7.76(2H, m), 9.58(3H, brs), 12.13(1H, brs).  
MS:430 (M+H)<sup>+</sup>.

Example 206 Synthesis of N, N-diethyl-2-(4-methoxybenzyl)-N'-(E)-styrylsulfonylmalonamide

(1) ethyl 2-(4-methoxybenzyl)-3-oxo-3-(((E)-styrylsulfonyl)amino]propionate

**[0510]** In the same manner as in Example 1 (2), the title compound (5.01 g) was obtained as an oil using the compound (4.08 g) obtained in Example 112 (2) and trans-β-styrenesulfonamide (2.74 g).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ1.08(3H, t, J = 7.0H), 2.88-3.03(2H, m), 3.56-3.80(4H, m), 3.90-4.19(2H, m), 6.73(2H, d, J = 8.5Hz), 7.07(2H, d, J = 8.6Hz), 7.28(1H, d, J = 15.5Hz), 7.35-7.60(4H, m), 7.67-7.81(2H, m), 12.23(1H, brs).

(2) 2-(4-methoxybenzyl)-3-oxo-3-(((E)-styrylsulfonyl)amino]propionic acid

**[0511]** In the same manner as in Example 1 (3), the title compound (3.56 g) was obtained as a white powder using the above-mentioned compound (5.01 g).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ2.88-3.03(2H, m), 3.50-3.70(4H, m), 6.70(2H, d, J = 8.7Hz), 7.06(2H, d, J = 8.6Hz), 7.23(1H, J = 15.4Hz), 7.40-7.58(4H, m), 7.61-7.79(2H, m), 12.00(1H, brs), 12.80(1H, brs).

(3) N, N-diethyl-2-(4-methoxybenzyl)-N'-(E)-styrylsulfonylmalonamide

**[0512]** In the same manner as in Example 1 (4), the title compound (980 mg) was obtained as a white powder using the above-mentioned compound (1.25 g).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.80-1.00(6H, m), 2.83-3.31(6H, m), 3.64(3H, s), 3.71-3.88(1H, m), 6.72(2H, d, J = 8.4Hz), 7.08(2H, d, J = 8.4Hz), 7.29(1H, d, J = 15.7Hz), 7.40-7.59(4H, m), 7.74(2H, d, J = 7.7Hz), 12.00 (1H, brs).

MS: 445(M+H)<sup>+</sup>.

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Example 207 Synthesis of N, N-diethyl-N'-((E)-styrylsulfonyl)-2-(4-trifluoromethoxybenzyl)malonamide

(1) ethyl 3-oxo-3-(((E)-styrylsulfonyl)amino)-2-[4-(trifluoromethoxy)benzyl]propionate

5 **[0513]** In the same manner as in Example 1 (2), the title compound (3.34 g) was obtained as an oil using the compound (2.97 g) obtained in Example 117 (2) and trans- $\beta$ -styrenesulfonamide (1.64 g).

$^1\text{H-NMR}$ (300Mz,  $\text{CDCl}_3$ ) $\delta$ 1.16(3H, t, J = 7.1Hz), 3.09-3.31(2H, m), 3.48-3.61(1H, m), 4.15(2H, q, J = 7.2Hz), 6.89-7.64(10H, m), 7.72(1H, d, J = 15.4Hz).

10 (2) 3-oxo-3-(((E)-styrylsulfonyl)amino)-2-[4-(trifluoromethoxy)benzyl]propionic acid

**[0514]** In the same manner as in Example 1 (3), the title compound (2.44 g) was obtained as a white powder using the above-mentioned compound (3.34 g).

15  $^1\text{H-NMR}$ (300Mz,  $\text{DMSO-d}_6$ ) $\delta$ 2.93-3.20(2H, m), 3.60-3.78(1H, m), 6.97-7.60(9H, m), 7.60-7.80(2H, m), 10.90-13.80(2H, brs).

(3) N, N-diethyl-N'-((E)-styrylsulfonyl)-2-(4-trifluoromethoxybenzyl)malonamide

20 **[0515]** In the same manner as in Example 1 (4), the title compound (280 mg) was obtained as a white powder using the above-mentioned compound (1.22 g).

$^1\text{H-NMR}$ (300Mz,  $\text{DMSO-d}_6$ ) $\delta$ 0.80-1.00(6H, m), 3.00-3.40(6H, m), 3.89(1H, t, J = 7.2Hz), 7.16(2H, d, J = 8.7Hz), 7.20-7.35(3H, m), 7.38-7.60(4H, m), 7.65-7.80(2H, m), 12.05(1H, brs).

MS : 499(M+H) $^+$ .

25 Example 208 Synthesis of N, N-diethyl-2-(4-fluorobenzyl)-N'-((E)-styrylsulfonyl)malonamide

**[0516]** In the same manner as in Example 1 (2), the title compound (755 mg) was obtained as a white powder using the compound (1.39 g) obtained in Example 118 (4) and trans-p-styrenesulfonamide (878 mg).

30  $^1\text{H-NMR}$ (300Mz,  $\text{DMSO-d}_6$ ) $\delta$ 0.80-1.00(6H, m), 2.90-3.40(6H, m), 3.86(1H, t, J = 7.2Hz), 6.99(2H, t, J = 9.0Hz), 7.11-7.33(3H, m), 7.39-7.60(4H, m), 7.64-7.79(2H, m), 12.01(1H, brs).

MS: 433(M+H) $^+$ .

Example 209 Synthesis of N, N-diethyl-2-(3, 4-dimethoxybenzyl)-N'-((E)-styrylsulfonyl)malonamide

35 **[0517]** In the same manner as in Example 1 (2), the title compound (495 mg) was obtained as a white powder using the compound (760 mg) obtained in Example 119 (2) and trans- $\beta$ -styrenesulfonamide (416 mg).

$^1\text{H-NMR}$ (300Mz,  $\text{DMSO-d}_6$ ) $\delta$ 0.96(3H, t, J = 7.2Hz), 1.04(3H, t, J = 7.2Hz), 2.88-3.09(2H, m), 3.10-3.47(4H, m), 3.71(3H, s), 3.75(3H, s), 3.80-3.94(1H, m), 6.58-6.69(1H, m), 6.71-6.90(2H, m), 7.20(1H, d, J = 15.3Hz), 7.39-7.59(4H, m), 7.65-7.78(2H, m), 11.91(1H, brs).

40 MS : 475(M+H) $^+$ .

Example 210 Synthesis of N, N-diethyl-2-(4-methoxycarbonylbenzyl)-N'-((E)-styrylsulfonyl)malonamide

45 **[0518]** In the same manner as in Example 1 (2), the title compound (759 mg) was obtained as a white powder using the compound (909 mg) obtained in Example 120 (2) and trans- $\beta$ -styrenesulfonamide (500 mg).

$^1\text{H-NMR}$ (300Mz,  $\text{DMSO-d}_6$ ) $\delta$ 0.79-1.00(6H, m), 2.09(3H, s), 3.00-3.37(6H, m), 3.81(3H, s), 3.94(1H, t, J = 7.5H), 7.25(1H, d, J = 15.3Hz), 7.29-7.39(2H, m), 7.40-7.58(4H, m), 7.67-7.84(4H, m), 12.05(1H, brs).

MS: 473(M+H) $^+$ .

50 Example 211 Synthesis of N, N-diethyl-2-(4-hydroxycarbonylbenzyl)-N'-((E)-styrylsulfonyl)malonamide

**[0519]** In the same manner as in Example 121, the title compound (254 mg) was obtained as a white powder using the compound (300 mg) obtained in Example 210.

55  $^1\text{H-NMR}$ (300Mz,  $\text{DMSO-d}_6$ ) $\delta$ 0.80-1.05(6H, m), 3.00-3.45(6H, m), 3.82-4.00(1H, m), 7.18-7.34(3H, m), 7.39-7.59(4H, m), 7.64-7.85(4H, m), 12.05(1H, brs), 12.76(1H, brs).

MS: 459(M+H) $^+$ .

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Example 212 Synthesis of N, N-diethyl-2-[(2-methoxy-5-pyridyl)methyl]-N'-((E)-styrylsulfonyl)malonamide

**[0520]** In the same manner as in Example 1 (2), the title compound (502 mg) was obtained as a white powder using the compound (705 mg) obtained in Example 122 (2) and trans- $\beta$ -styrenesulfonamide (425 mg).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>) $\delta$ 0.83-1.03(6H, m), 2.86-3.01(2H, m), 3.04-3.33(4H, m), 3.76(3H, s), 3.84(1H, t, J = 7.2Hz), 6.64(1H, d, J = 8.4Hz), 7.26(1H, d, J = 15.4Hz), 7.43-7.60(5H, m), 7.68-7.79(2H, m), 7.96(1H, s), 12.01(1H, brs).  
MS: 446(M+H)<sup>+</sup>.

Example 213 Synthesis of 2-[4-(5-chloro-2-pyridyloxy)benzyl]-N, N-diethyl-N'-((E)-styrylsulfonyl)malonamide

**[0521]** In the same manner as in Example 1 (2), the title compound (450 mg) was obtained as a white powder using the compound (770 mg) obtained in Example 126 (4) and trans- $\beta$ -styrenesulfonamide (375 mg).

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>) $\delta$ 0.88-1.02(6H, m), 3.05(2H, d, J = 7.2Hz), 3.10-3.31(4H, m), 3.90(1H, t, J = 7.2Hz), 6.94(2H, d, J = 8.4Hz), 7.03(1H, d, J = 8.8Hz), 7.21(2H, d, J = 8.4Hz), 7.27(1H, d, J = 15.2Hz), 7.40-7.48(3H, m), 7.56(1H, d, J = 15.2Hz), 7.70-7.72(2H, m), 7.92-7.95(1H, m), 8.15(1H, d, J = 2.9H), 12.02(1H, brs).  
MS: 542(M+H)<sup>+</sup>.

Example 214 Synthesis of 2-cyclopropylmethyl-N, N-diethyl-N'-((E)-styrylsulfonyl)malonamide

(1) 5-cyclopropylmethyl-2, 2-dimethyl-1, 3-dioxane-4, 6-dione

**[0522]** To a solution of cyclopropanecarboxylic acid (17.2 g) in methylene chloride (800 mL) were added Meldrum's acid (28.8 g), WSCI·HCl (42.2 g) and 4-dimethylaminopyridine (39.1 g), and the mixture was stirred at room temperature for 18 hr. Water and then hydrochloric acid were added to acidify the reaction mixture, and the aqueous layer was removed by partitioning. Under ice-cooling, acetic acid (114 mL) and then sodium borohydride (18.9 g) were added slowly to the organic layer, and the mixture was stirred at room temperature for 3 days. Water and then hydrochloric acid were added to the reaction mixture, and the aqueous layer was removed by partitioning. The organic layer was concentrated to give a yellow powder. This was washed with ether/hexane to give the title compound (25.8 g) as a yellow powder.

<sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>) $\delta$ 0.14-0.27(2H, m), 0.43-0.52(2H, m), 0.96-1.13(1H, m), 1.78(3H, s), 1.81(3H, s), 1.97-2.09(2H, m), 3.54(1H, t, J = 5.4Hz).

(2) 2-cyclopropylmethyl-3-(N, N-diethylamino)-3-oxopropionic acid

**[0523]** In the same manner as in Example 119 (2), the title compound (1.05 g) was obtained as an oil using the above-mentioned compound (991 mg).

<sup>1</sup>H-NMR (300Mz, DMSO-d<sub>6</sub>) $\delta$ (-0.20)-1.20(11H, m), 1.35-1.71(2H, m), 3.02-3.48(4H, m), 3.50-3.65(1H, m), 12.40(1H, brs).

(3) 2-cyclopropylmethyl-N,N-diethyl-N'-((E)-styrylsulfonyl)malonamide

**[0524]** In the same manner as in Example 1 (2), the title compound (137 mg) was obtained as a white powder using the above-mentioned compound (1.05 g) and trans- $\beta$ -styrenesulfonamide (694 mg).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>) $\delta$ (-0.07)-0.11(2H, m), 0.18-0.42(2H, m), 0.50-0.78(1H, m), 0.96(3H, t, J = 6.9Hz), 1.08(3H, t, J = 6.9Hz), 1.31-1.54(1H, m), 1.68-1.89(1H, m), 3.02-3.97(4H, m), 3.56-3.77(1H, m), 7.32-7.62(5H, m), 7.62-7.88(2H, m), 12.08(1H, brs).  
MS: 379(M+H)<sup>+</sup>.

Example 215 Synthesis of N, N-diethyl-2-(2-propynyl)-N'-((E)-styrylsulfonyl)malonamide

(1) ethyl 2-[[[(E)-styrylsulfonyl]amino]carbonyl]-4-pentynoate

**[0525]** In the same manner as in Example 152 (3), the title compound (1.99 g) was obtained as a white powder using the compound (5.55 g) obtained in Example 152 (2) and trans- $\beta$ -styrenesulfonamide (5.97 g).

<sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>) $\delta$ 1.25-1.30(3H, m), 2.05-2.07(1H, m), 2.84-2.86(2H, m), 3.48-3.52(1H, m), 4.24-4.31(2H, m), 7.04(1H, d, J = 15.6Hz), 7.39-7.46(3H, m), 7.51-7.54(2H, m), 7.75(1H, d, J = 15.6Hz), 9.45(1H, brs).

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(2) 2-(((E)-styrylsulfonyl)amino)carbonyl-4-pentynoic acid

**[0526]** In the same manner as in Example 1 (3), the title compound (2.08 g) was obtained as a white powder using the above-mentioned compound (1.99 g).

<sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ2.09-2.12(1H, m), 2.87-2.90(2H, m), 3.61-3.57(1H, m), 7.04(1H, d, J = 15.6Hz), 7.42-7.46(3H, m), 7.52-7.54(2H, m), 7.76(1H, d, J = 15.6Hz).

(3) N,N-diethyl-2-(2-propynyl)-N'-((E)-styrylsulfonyl)malonamide

**[0527]** In the same manner as in Example 1 (4), a crude product was obtained using the above-mentioned compound (1.04 g). This was purified by silica gel column chromatography to give the title compound (140 mg) as a white powder. <sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.08-1.28(6H, m), 2.05(1H, s), 2.80-2.85(2H, m), 3.25-3.73(4H, m), 4.21-4.22(1H, m), 7.03(1H, d, J = 15.6Hz), 7.39-7.47(3H, m), 7.51-7.53(2H, m), 7.71(1H, d, J = 15.6Hz), 10.40(1H, brs). MS: 363(M+H)<sup>+</sup>.

Example 216 Synthesis of 2-(2-cyanoethyl)-N, N-diethyl-N'-((E)-styrylsulfonyl)malonamide

(1) ethyl 4-cyano-2-(((E)-styrylsulfonyl)amino)carbonylbutyrate

**[0528]** In the same manner as in Example 152 (3), the title compound (880 mg) was obtained as a white powder using the compound (2.50 g) obtained in Example 153 (1) and trans-β-styrenesulfonamide (2.47 g).

<sup>1</sup>H-NMR (300Mz, CDCl<sub>3</sub>)δ1.26-1.32(3H, m), 2.26-2.32(2H, m), 2.49-2.53(2H, m), 3.48-3.52(1H, m), 4.24-4.32(2H, m), 7.04 (1H, d, J = 15.2Hz), 7.26-7.57(5H, m), 7.75(1H, d, J = 15.2Hz), 9.38(1H, brs).

(2) 4-cyano-2-(((E)-styrylsulfonyl)amino)carbonylbutyric acid

**[0529]** In the same manner as in Example 1 (3), the title compound (700 mg) was obtained as a white powder using the above-mentioned compound (800 mg).

<sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ2.31-2.34(2H, m), 2.54-2.57(2H, m), 3.57-3.60(1H, m), 7.04(1H, d, J = 15.6Hz), 7.26-7.48(3H, m), 7.53-7.55(2H, m), 7.77(1H, d, J = 15.6Hz).

(3) 2-(2-cyanoethyl)-N, N-diethyl-N'-((E)-styrylsulfonyl)malonamide

**[0530]** In the same manner as in Example 1 (4), a crude product was obtained using the above-mentioned compound (1.00 g). This was purified by silica gel column chromatography to give the title compound (210 mg) as a white powder. <sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.17(3H, t, J = 7.2Hz), 1.23(3H, t, J = 7.2Hz), 2.21-2.26(2H, m), 2.42-2.52(2H, m), 3.31-3.50(4H, m), 3.63-3.67(1H, m), 7.04(1H, d, J = 15.6Hz), 7.41-7.46(3H, m), 7.52-7.54(2H, m), 7.72(1H, d, J = 15.6Hz), 10.41(1H, brs). MS: 378(M+H)<sup>+</sup>.

Example 217 Synthesis of N,N-diethyl-2-(4-nitrophenethyl)-N'-((E)-styrylsulfonyl)malonamide

(1) ethyl 4-(4-nitrophenyl)-2-(((E)-styrylsulfonyl)amino)carbonylbutyrate

**[0531]** In the same manner as in Example 1 (2), the title compound (1.52 g) was obtained as an oil using the compound (3.30 g) obtained in Example 144 (2) and trans-β-styrenesulfonamide (2.30 g).

<sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ1.30(3H, t, J = 7.2Hz), 2.24-2.31(2H, m), 2.76-2.81(2H, m), 3.31(1H, t, J = 7.2Hz), 4.25(2H, q, J = 7.2Hz), 7.05(1H, d, J = 15.6Hz), 7.33(2H, d, J = 8.7Hz), 7.41-7.55(5H, m), 7.76(1H, d, J = 15.6Hz), 8.15(2H, d, J = 8.7Hz), 9.41(1H, brs).

(2) 4-(4-nitrophenyl)-2-(((E)-styrylsulfonyl)amino)carbonylbutyric acid

**[0532]** In the same manner as in Example 1 (3), the title compound (1.42 g) was obtained as a white powder using the above-mentioned compound (1.52 g).

<sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ2.15-2.36(2H, m), 2.80-2.85(2H, m), 3.36-3.42(1H, m), 7.05-(1H, d, J = 15.6Hz), 7.33(2H, d, J = 8.7Hz), 7.38-7.55(5H, m), 7.77(1H, d, J = 15.6Hz), 8.12-8.15(2H, m), 9.40(1H, brs).

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(3) N, N-diethyl-2-(4-nitrophenethyl)-N'-((E)-styrylsulfonyl)malonamide

**[0533]** In the same manner as in Example 1 (4), the title compound (773 mg) was obtained as a white solid using the above-mentioned compound (800 mg).

<sup>1</sup>H-NMR (400Mz, DMSO-d<sub>6</sub>) δ0.95-1.03(6H, m), 1.99-2.08 (2H, m), 2.60-2.73(2H, m), 3.13-3.59(4H, m), 3.59(1H, t, J = 6.8Hz), 7.41-7.48(6H, m), 7.60(1H, d, J = 15.6Hz), 7.50-7.77(1H, m), 8.15(2H, d, J = 8.8Hz), 12.13(1H, brs).  
MS: 474(M+H)<sup>+</sup>.

Example 218 Synthesis of 2-(4-aminophenethyl)-N,N-diethyl-N'-((E)-styrylsulfonyl)malonamide

**[0534]** In the same manner as in Example 137 (4), the title compound (40 mg) was obtained as a white powder using the compound (452 mg) obtained in Example 217 at room temperature. <sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>) δ0-94-1.03(6H, m), 1.79-1.97(2H, m), 2.29-2.37(2H, m), 3.11-3.34(4H, m), 3.51(1H, t, J = 6.8Hz), 6.48(2H, d, J = 8.4Hz), 6.77(2H, d, J = 8.4Hz), 7.42(H, d, J = 15.6Hz), 7.45-7.48(3H, m), 7.58(1H, d, J = 15.6), 7.74-7.77(2H, m).

MS: 444(M+H)<sup>+</sup>.

Example 219 Synthesis of 2-(4-aminobenzyl)-N, N-diethyl-N'-phenethylsulfonylmalonamide

**[0535]** In the same manner as in Example 7, the title compound (29 mg) was obtained as a white powder using the compound (130 mg) obtained in Example 200 at room temperature.

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>) δ0.89-0.91(6H, m), 2.79-2.89(2H, m), 3.16-3.38(8H, m), 3.73-3.74(1H, m), 6.43(2H, d, J = 7.6Hz), 6.82(2H, d, J = 7.6Hz), 6.95(1H, brs), 7.14-7.27(1H, m), 7.46-7.54(2H, m), 7.69(1H, brs).

MS: 432 (M+H)<sup>+</sup>.

Example 220 Synthesis of 2-[4-(benzoylamino)benzyl]-N, N-diethyl-N'-phenethylsulfonylmalonamide

**[0536]** In the same manner as in Example 92, a crude product was obtained using the compound (1.53 g) obtained in Example 200. To a mixed solution of this in ethanol (50 mL) and acetic acid (5 mL) was added 20% palladium hydroxide/carbon (500 mg), and the mixture was stirred under hydrogen atmosphere for 3 hr. Insoluble material was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound (27 mg) as a white solid.

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>) δ0.96-1.05(6H, m), 2.78-3.12(4H, m), 3.20-3.34(4H, m), 3.51-3.64(2H, m), 3.93-4.00(1H, m), 7.19-7.31(7H, m), 7.51-7.59 (3H, m), 7.68(2H, d, J = 8.5Hz), 7.92(2H, d, J = 7.1Hz), 10.18(1H, s), 11.92(1H, brs).

MS: 536(M+H)<sup>+</sup>.

Example 221 Synthesis of N, N-diethyl-2-(4-methoxybenzyl)-N'-phenethylsulfonylmalonamide

**[0537]** To a mixed solution of the compound (660 mg) obtained in Example 206 in ethyl acetate (10 mL) and ethanol (10 mL) was added palladium black (400 mg), and the mixture was stirred under hydrogen atmosphere at room temperature for 21 hr. Insoluble material was removed by filtration, and the filtrate was concentrated under reduced pressure to give the title compound (339 mg) as a white solid.

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>) δ0.83-1.07(6H, m), 2.63-3.07(4H, m), 3.10-3.39(4H, m), 3.45-3.62(2H, m), 3.64(3H, s), 3.80-3.93(1H, m), 6.80(2H, d, J = 9.0Hz), 7.09-7.38(7H, m), 11.90(1H, brs). MS:447(M+H)<sup>+</sup>.

Example 222 Synthesis of 2-(4-aminophenethyl)-N, N-diethyl-N'-phenethylsulfonylmalonamide

**[0538]** In the same manner as in Example 221, a crude product was obtained using the compound (300 mg) obtained in Example 217. This was purified by silica gel column chromatography to give the title compound (95 mg) as a white solid.

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>) δ1.00(3H, t, J = 7.0Hz), 1.07(3H, t, J = 7.0Hz), 1.80-1.91(1H, m), 2.00-2.11(1H, m), 2.90-3.07(2H, m), 3.11-3.34(6H, m), 3.57-3.72(3H, m), 6.98(2H, d, J = 7.6Hz), 7.12(2H, d, J = 7.6Hz), 7.20-7.32(5H, m).

MS: 446(M+H)<sup>+</sup>.

Example 223 Synthesis of N, N-diethyl-2-(4-nitrobenzyl)-N'-((4-phenoxyphenylsulfonyl)malonamide

**[0539]** In the same manner as in Example 188 (4), the title compound (200 mg) was obtained as a white powder using the compound (300 mg) obtained in Example 188 (3) and 4-phenoxybenzenesulfonyl chloride (270 mg).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>) δ0.84-0.91(6H, m), 3.06-3.08(2H, m), 3.14-3.15(4H, m), 3.92(1H, t, J = 6.9Hz), 7.04-7.15(4H, m), 7.25-7.37(3H, m), 7.45-7.50(2H, m), 7.79(2H, d, J = 8.5Hz), 8.02(2H, d, J = 8.5Hz), 12.25(1H, brs).

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MS: 526(M+H)<sup>+</sup>.

Example 224 Synthesis of 2-(4-aminobenzyl)-N, N-diethyl-N'-(4-phenoxyphenylsulfonyl)malonamide

5 **[0540]** In the same manner as in Example 7, the title compound (120 mg) was obtained as a white powder using the compound (160 mg) obtained in Example 223 at room temperature.

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.83-0.91(6H, m), 2.73-2.75(2H, m), 3.12-3.18(4H, m), 3.66-3.68(1H, m), 6.38(2H, d, J = 8.0Hz), 6.71(2H, d, J = 8.0Hz), 7.08-7.14(4H, m), 7.24-7.28(1H, m), 7.45-7.50(2H, m), 7.79(2H, d, J = 9.0Hz).

MS: 496(M+H)<sup>+</sup>.

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Example 225 Synthesis of N, N-diethyl-N'-(5-isobutyl-2-thienylsulfonyl)-2-(4-nitrobenzyl)malonamide

(1) ethyl 3-[(5-isobutyl-2-thienylsulfonyl)amino]-2-(4-nitrobenzyl)-3-oxopropionate

15 **[0541]** In the same manner as in Example 152 (3), the title compound (2.22 g) was obtained as a white powder using the compound (2.40 g) obtained in Example 178 (2) and 5-isobutyl-2-thiophenesulfonamide (2.00 g).

<sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ0.94(3H, s), 0.95(3H, s), 1.18-1.28 (3H, m), 1.96-1.98(1H, m), 2.72-2.75(2H, m), 3.29-3.32(2H, m), 3.54-3.61(1H, m), 4.14-4.19(2H, m), 6.79-6.81(1H, m), 7.21-7.24(1H, m), 7.36-7.39(1H, m), 7.70-7.71(1H, m), 8.05-8.16(2H, m), 9.41(1H, brs).

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(2) N, N-diethyl-N'-(5-isobutyl-2-thienylsulfonyl)-2-(4-nitrobenzyl)malonamide

**[0542]** The above-mentioned compound (2.22 g) was subjected to hydrolysis in the same manner as in Example 1 (3). In the same manner as in Example 1 (4), a crude product was obtained using this. The crude product was purified

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by silica gel column chromatography to give the title compound (620 mg) as a white powder.

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.86(6H, brs), 0.89(6H, brs), 1.80-1.84(1H, m), 2.70(2H, d, J = 6.9Hz), 3.08-3.21(6H, m), 3.92(1H, t, J = 6.9Hz), 6.89(1H, d, J = 3.9Hz), 7.38(2H, d, J = 8.7Hz), 7.53(1H, d, J = 3.9Hz), 8.03(1H, d, J = 8.7Hz), 12.31(1H, brs).

MS: 496(M+H)<sup>+</sup>.

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Example 226 Synthesis of 2-(4-aminobenzyl)-N, N-diethyl-N'-(5-isobutyl-2-thienylsulfonyl)malonamide

**[0543]** In the same manner as in Example 137 (4), the title compound (140 mg) as a brown solid was obtained using the compound (200 mg) obtained in Example 225.

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<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.84-0.90(12H, m), 1.82-1.86(1H, m), 2.72(2H, d, J = 6.9Hz), 2.77(2H, d, J = 7.2Hz), 3.28-3.35(4H, m), 3.67(1H, t, J = 7.2Hz), 6.40(2H, d, J = 8.4Hz), 6.73(2H, d, J = 8.4Hz), 6.90(1H, d, J = 3.7Hz), 7.50(1H, d, J = 3.7Hz).

MS: 466(M+H)<sup>+</sup>.

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Example 227 Synthesis of 2-(4-cyanobenzyl)-N-cyclohexyl-N'-(2-naphthylsulfonyl)malonamide

**[0544]** In the same manner as in Example 1 (4), the title compound (184 mg) was obtained as a white powder using the compound (300 mg) obtained in Example 111 (4) and cyclohexylamine (87 mg).

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<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.89-0.1.27(5H, m), 1.34-1.70(5H, m), 2.29(2H, d, J = 7.6Hz), 3.28-3.60(2H, m), 7.25(2H, d, J = 8.1Hz), 7.54(2H, d, J = 8.0Hz), 7.59-7.84(4H, m), 8.00-8.26(3H, m), 8.53(1H, s), 12.20(1H, brs).

MS: 490(M+H)<sup>+</sup>.

Example 228 Synthesis of 2-(4-cyanobenzyl)-N-(2-naphthylsulfonyl)-3-[4-(4-nitrophenyl)-1-piperazinyl]-3-oxopropanamide

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**[0545]** In the same manner as in Example 1 (4), a crude product was obtained using the compound (300 mg) obtained in Example 111 (4) and 1-(4-nitrophenyl)piperazine (183 mg). This was purified by silica gel column chromatography to give the title compound (358 mg) as a white powder.

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<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ2.91-3.74(10H, m), 3.98-4.15(1H, m), 6.83(2H, d, J = 9.3Hz), 7.31(2H, J = 8.1Hz), 7.56(2H, d, J = 8.1Hz), 7.63-8.20(8H, m), 8.55(1H, s), 12.50(1H, brs).

MS: 597(M+H)<sup>+</sup>.

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### Example 229 Synthesis of 2-(4-cyanobenzyl)-N-ethyl-N'-(2-naphthylsulfonyl)-N-phenylmalonamide

**[0546]** In the same manner as in Example 1 (4), a crude product was obtained using the compound (300 mg) obtained in Example 111 (4) and N-ethylaniline (107 mg). This was purified by silica gel column chromatography to give the title compound (344 mg) as a white powder.

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.87(3H, t, J = 7.2Hz), 2.40-3.70(5H, m), 6.93(2H, d, J = 7.5Hz), 7.21(2H, J = 8.1Hz), 7.10-8.30(11H, m), 8.53(1H, s), 12.10(1H, brs).

MS: 512(M+H)<sup>+</sup>.

### Example 230 Synthesis of 2-(4-cyanobenzyl)-3-[4-(5-cyano-2-pyridyl)-1-piperazinyl]-N-(2-naphthylsulfonyl)-3-oxopropanamide

**[0547]** In the same manner as in Example 1 (4), a crude product was obtained using the compound (300 mg) obtained in Example 111 (4) and N-(5-cyano-2-pyridyl)piperazine (166 mg). This was purified by silica gel column chromatography to give the title compound (284 mg) as a white powder.

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ2.80-3.00(2H, m), 3.06-3.67(8H, m), 3.88-4.00(1H, m), 6.66(1H, J = 9.1Hz), 7.20(2H, J = 8.3Hz), 7.45(2H, d, J = 8.2Hz), 7.49-7.80(4H, m), 7.86-8.15(3H, m), 8.38(1H, d, J = 2.3Hz), 8.43(1H, s), 12.32(1H, brs).

MS: 579(M+H)<sup>+</sup>.

### Example 231 Synthesis of 2-(4-cyanobenzyl)-N-(2-naphthylsulfonyl)-3-oxo-3-[4-(4-pyridyl)-1-piperazinyl]propanamide

**[0548]** In the same manner as in Example 1 (4), a crude product was obtained using the compound (300 mg) obtained in Example 111 (4) and 1-(4-pyridyl)piperazine (144 mg). This was purified by silica gel column chromatography to give the title compound (109 mg) as a white powder.

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ2.90-3.10(2H, m), 3.13-3.95(9H, m), 7.01(2H, d, J = 7.4Hz), 7.31(2H, d, J = 8.2Hz), 7.43-7.60(4H, m), 7.76(1H, dd, J = 8.9, 1.4Hz), 7.91(2H, d, J = 8.9Hz), 7.95-8.06(1H, m), 8.22(2H, d, J = 7.3Hz), 8.30(1H, s), 13.20(1H, brs).

MS: 574(M+H)<sup>+</sup>.

### Example 232 Synthesis of N-ethyl-2-(4-methoxybenzyl)-N'-(2-naphthylsulfonyl)-N-phenylmalonamide

**[0549]** In the same manner as in Example 1 (4), a crude product was obtained using the compound (550 mg) obtained in Example 112 (4) and N-ethylaniline (161 mg). This was purified by silica gel column chromatography to give the title compound (456 mg) as a white powder.

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.88(3H, t, J = 6.9Hz), 2.66-2.90(2H, m), 3.30-3.70(6H, m), 6.50-6.70(4H, m), 6.95(2H, d, J = 7.2Hz), 7.20-7.43(3H, m), 7.61-7.83(3H, m), 8.01-8.29(3H, m), 8.54(1H, s), 12.06(1H, brs).

MS: 517(M+H)<sup>+</sup>.

### Example 233 Synthesis of 3-[4-(3, 4-dicyanophenyl)-1-piperazinyl]-2-(4-methoxybenzyl)-N-(2-naphthylsulfonyl)-3-oxopropanamide

**[0550]** In the same manner as in Example 1 (4), a crude product was obtained using the compound (550 mg) obtained in Example 112 (4) and N-(3, 4-dicyanophenyl)piperazine (282 mg). This was purified by silica gel column chromatography to give the title compound (480 mg) as a yellow powder.

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ2.70-3.70(10H, m), 3.60(3H, s), 3.88-4.06(1H, m), 6.65(2H, dd, J = 7.0, 1.9Hz), 6.98(2H, d, J = 8.7Hz), 7.04-7.19(1H, m), 7.45(1H, d, J = 2.4Hz), 7.60-8.30(7H, m), 8.56(1H, s), 12.40(1H, brs).

MS: 608(M+H)<sup>+</sup>.

### Example 234 Synthesis of N-diphenylmethyl-2-(4-methoxybenzyl)-N'-(2-naphthylsulfonyl)malonamide

**[0551]** In the same manner as in Example 1 (4), a crude product was obtained using the compound (300 mg) obtained in Example 112 (4) and benzhydrylamine (133 mg). This was purified by silica gel column chromatography to give the title compound (390 mg) as a white powder.

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ2.79-2.95(2H, m), 3.51-3.70(4H, m), 5.95(1H, d, J = 7.8Hz), 6.63(2H, d, J = 8.4Hz), 6.85-7.09(4H, m), 7.10-7.40(8H, m), 7.64-7.84(3H, m), 8.00-8.23(3H, m), 8.55(1H, s), 8.65(1H, d, J = 7.8Hz), 12.19(1H, brs).

MS: 579(M+H)<sup>+</sup>.

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### Example 235 Synthesis of N-ethyl-N'-(2-naphthylsulfonyl)-2-(4-nitrobenzyl)-N-phenylmalonamide

**[0552]** In the same manner as in Example 1 (4), a crude product was obtained using the compound (500 mg) obtained in Example 6 (4) and N-ethylaniline (141 mg). This was purified by silica gel column chromatography to give the title compound (242 mg) as a white powder.

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.87(3H, t, J = 7.2Hz), 2.88-3.12(2H, m), 3.25-3.69(3H, m), 6.94(2H, d, J = 7.5Hz), 7.11(2H, d, J = 8.6Hz), 7.29-7.48(3H, m), 7.66-7.85(3H, m), 7.94(2H, d, J = 8.8Hz), 8.00-8.25(3H, m), 8.51(1H, s), 12.12(1H, brs). MS: 532 (M+H)<sup>+</sup>.

### Example 236 Synthesis of 2-(4-aminobenzyl)-N-ethyl-N'-(2-naphthylsulfonyl)-N-phenylmalonamide

**[0553]** In the same manner as in Example 7, the title compound (178 mg) was obtained as a white powder using the compound (198 mg) obtained in Example 235 at room temperature.

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.88(3H, t, J = 7.1Hz), 2.57-2.78(2H, m), 3.20-3.61(3H, m), 6.32(2H, d, J = 8.1Hz), 6.46(2H, d, J = 8.1Hz), 6.92(2H, d, J = 7.6Hz), 7.20-7.43(3H, m), 7.62-7.84(3H, m), 8.10(1H, d, J = 7.8Hz), 8.17(1H, d, J = 8.8Hz), 8.23(1H, d, J = 7.8Hz), 8.55(1H, s). MS: 501(M+H)<sup>+</sup>.

### Example 237 Synthesis of N, N-diisopropyl-N'-(2-naphthylsulfonyl)-2-(4-nitrobenzyl)malonamide

(1) 2, 2-dimethyl-5-(4-nitrobenzyl)-1, 3-dioxane-4, 6-dione

**[0554]** In the same manner as in Example 119 (1), the title compound (38.4 g) was obtained as a white powder using 4-nitrobenzaldehyde (25.0 g).

<sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ1.67(3H, s), 1.79(3H, s), 3.58(2H, d, J = 5.1Hz), 3.82(1H, t, J = 5.1Hz), 7.54(2H, d, J = 8.7Hz), 8.15(2H, d, J = 8.7Hz).

(2) 3-(N, N-diisopropylamino)-2-(4-nitrobenzyl)-3-oxopropionic acid

**[0555]** In the same manner as in Example 119 (2), the title compound (550 mg) was obtained as a white powder using the above-mentioned compound (2.07 g) and diisopropylamine (3.00 g).

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ0.74(3H, d, J = 6.4Hz), 1.04-1.07(6H, m), 1.23(3H, d, J = 6.2Hz), 3.08-3.20(2H, m), 3.30-3.40(1H, m), 3.98-4.07(1H, m), 4.08-4.16(1H, m), 7.50(2H, d, J = 8.6Hz), 8.12(2H, d, J = 8.6Hz), 12.64(1H, brs).

(3) N, N-diisopropyl-N'-(2-naphthylsulfonyl)-2-(4-nitrobenzyl)malonamide

**[0556]** In the same manner as in Example 1 (2), the title compound (356 mg) was obtained as a white solid using the above-mentioned compound (520 mg).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.82(3H, d, J = 6.3Hz), 1.01(3H, d, J = 6.6Hz), 1.15(3H, d, J = 6.6Hz), 1.19(3H, d, J = 6.6Hz), 3.04(2H, d, J = 7.5Hz), 3.27-3.40(1H, m), 3.81-3.99(2H, m), 7.29(2H, d, J = 8.4Hz), 7.63-7.80(3H, m), 7.85(2H, d, J = 8.4Hz), 8.05-8.10(2H, m), 8.19(1H, d, J = 7.8Hz), 8.52(1H, s), 12.30(1H, brs). MS: 512(M+H)<sup>+</sup>.

### Example 238 Synthesis of 2-[4-(benzoylamino)benzyl]-N, N-diisopropyl-N'-(2-naphthylsulfonyl)malonamide

(1) 2-(4-aminobenzyl)-N, N-diisopropyl-N'-(2-naphthylsulfonyl)malonamide

**[0557]** In the same manner as in Example 7, the title compound (281 mg) was obtained as a white solid using the compound (300 mg) obtained in Example 237.

(2) 2-[4-(benzoylamino)benzyl]-N, N-diisopropyl-N'-(2-naphthylsulfonyl)malonamide

**[0558]** In the same manner as in Example 9, the title compound (121 mg) was obtained as a white solid using the above-mentioned compound (281 mg).

<sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.83(3H, d, J = 6.4Hz), 1.00(3H, d, J = 6.4Hz), 1.18(6H, t, J = 6.8Hz), 2.81-2.95(2H, m), 3.32-3.40(1H, m), 3.82-3.94(1H, m), 3.86(1H, t, J = 6.8Hz), 7.02(2H, d, J = 8.4Hz), 7.25-7.80(8H, m), 7.90-8.00(3H, m), 8.04(1H, d, J = 8.8Hz), 8.12(1H, d, J = 8.8Hz), 8.20(1H, d, J = 8.8Hz), 10.13(1H, s), 12.22(1H, brs). MS: 586(M+H)<sup>+</sup>.

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Example 239 Synthesis of 2-[4-(benzoylamino)benzyl]-N-ethyl-N'-(2-naphthylsulfonyl)-N-phenylmalonamide

**[0559]** In the same manner as in Example 9, the title compound (187 mg) was obtained as a white solid using the compound (155 mg) obtained in Example 236.

<sup>1</sup>H-NMR(400MHz, DMSO-d<sub>6</sub>)δ0.80-0.93(3H, m), 2.72-2.94(2H, m), 3.39-3.62(3H, m), 6.79(2H, d, J = 8.0Hz), 6.95(2H, d, J = 8.0Hz), 7.26-7.42(3H, m), 7.46-7.62(4H, m), 7.69-7.80(3H, m), 7.94(1H, d, J = 7.2Hz), 8.08(1H, d, J = 7.6Hz), 8.17(1H, d, J = 8.8Hz), 8.23(1H, d, J = 8.0Hz), 8.55(1H, s), 10.11(1H, s), 12.12(1H, brs).

MS: 606(M+H)<sup>+</sup>.

Example 240 Synthesis of 2-[4-(benzoylamino)benzyl]-N, N-dimethyl-N'-(2-naphthylsulfonyl)malonamide

(1) ethyl 3-[(2-naphthylsulfonyl)amino]-2-(4-nitrobenzyl)-3-oxopropionate

**[0560]** In the same manner as in Example 1 (2), the title compound (9.02 g) as a pale-yellow powder was obtained using the compound (7.21 g) obtained in Example 178 (2).

<sup>1</sup>H-NMR(300Hz, CDCl<sub>3</sub>)δ1.18(3H, t, J = 7.3Hz), 3.12-3.29(2H, m), 3.57(1H, t, J = 7.0Hz), 4.03-4.30(2H, m), 7.06(2H, d, J = 8.8Hz), 7.56-7.92(4H, m), 7.92-8.08(4H, m), 8.63(1H, d, J = 1.0Hz).

(2) ethyl 2-(4-aminobenzyl)-3-[(2-naphthylsulfonyl)amino]-3-oxopropionate

**[0561]** In the same manner as in Example 7, the title compound (15.4 g) as a pale-yellow powder was obtained using the above-mentioned compound (16.8 g) at room temperature.

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.93(3H, t, J = 7.1Hz), 2.66-2.89(2H, m), 3.54-3.68(1H, m), 3.93(2H, q, J = 7.1Hz), 6.43(2H, d, J = 8.3Hz), 6.74(2H, d, J = 8.2Hz), 7.59-7.82(3H, m), 7.97-8.32(3H, s), 8.54(1H, s).

(3) ethyl 2-[4-(benzoylamino)benzyl]-3-[(2-naphthylsulfonyl)amino]-3-oxopropionate

**[0562]** In the same manner as in Example 9, the title compound (14.3 g) was obtained as a pale-yellow solid using the above-mentioned compound (15.4 g).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.95(3H, t, J = 7.2Hz), 2.79-3.00(2H, m), 3.60-3.80(1H, m), 3.96(2H, q, J = 7.2Hz), 7.03(2H, d, J = 8.4Hz), 7.40-7.78(8H, m), 7.82-8.29(4H, m), 8.54(1H, s), 10.17(1H, s), 12.50(1H, brs).

(4) 2-[4-(benzoylamino)benzyl]-3-[(2-naphthylsulfonyl)amino]-3-oxopropionic acid

**[0563]** In the same manner as in Example 1 (3), the title compound (13.3 g) was obtained as a white powder using the above-mentioned compound (14.3 g).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ2.74-3.04(2H, m), 3.57-3.76(1H, m), 6.99(2H, d, J = 8.4Hz), 7.40-7.78(8H, m), 7.87-8.29(5H, m), 8.52(1H, s), 10.15(1H, s), 12.40(1H, brs), 12.95(1H, brs).

(5) 2-[4-(benzoylamino)benzyl]-N, N-dimethyl-N'-(2-naphthylsulfonyl)malonamide

**[0564]** In the same manner as in Example 13, the title compound (102 mg) was obtained as a white powder using the above-mentioned compound (503 mg), dimethylamine hydrochloride (489 mg) and triethylamine (833 μL).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ2.73(3H, s), 2.76(3H, s), 2.65-2.99(2H, m), 3.93(1H, t, J = 7.5Hz), 7.05(2H, d, J = 8.4Hz), 7.60-7.81(8H, m), 7.89-8.26(5H, m), 8.56(1H, s), 10.17(1H, s), 12.33(1H, brs).

MS: 530(M+H)<sup>+</sup>.

Example 241 Synthesis of 2-[4-(benzoylamino)benzyl]-N-ethyl-N-methyl-N'-(2-naphthylsulfonyl)malonamide

**[0565]** In the same manner as in Example 13, the title compound (188 mg) was obtained as a white powder using the compound (503 mg) obtained in Example 240 (4) and N-ethylmethylamine (515 μL).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.74-0.98(3H, m), 2.69, 2.73(total 3H, each s), 2.77-3.00(2H, m), 3.00-3.55(2H, m), 3.78-4.02(1H, m), 7.05(2H, d, J = 8.1Hz), 7.39-7.84(8H, m), 7.95(2H, d, J = 7.2Hz), 8.06(1H, d, J = 7.8Hz), 8.13(1H, d, J = 8.7Hz), 8.21(1H, d, J = 7.8Hz), 8.55(1H, s), 10.16(1H, s), 12.35(1H, brs).

MS: 544(M+H)<sup>+</sup>.

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Example 242 Synthesis of 2-[4-(benzoylamino)benzyl]-N, N-dipropyl-N'-(2-naphthylsulfonyl)malonamide

**[0566]** In the same manner as in Example 13, the title compound (351 mg) was obtained as a white powder using the compound

(503 mg) obtained in Example 240 (4) and dipropylamine (165  $\mu$ L).  $^1\text{H-NMR}$ (300Mz, DMSO- $d_6$ ) $\delta$ 0.60(3H, t, J = 7.5Hz), 0.69(3H, t, J = 5Hz), 1.00-1.38(4H, m), 2.70-3.20(6H, m), 3.77-3.98(1H, m), 7.05(2H, d, J = 8.4Hz), 7.40-7.80(8H, m), 7.96(2H, d, J = 7.2Hz), 8.06(1H, d, J = 8.1Hz), 8.13(1H, d, J = 8.7Hz), 8.21(1H, d, J = 8.1Hz), 8.55(1H, s), 10.16(1H, s), 12.36(1H, brs).

MS: 586(M+H) $^+$ .

Example 243 Synthesis of 2-[4-(benzoylamino)benzyl]-N, N-dipentyl-N'-(2-naphthylsulfonyl)malonamide

**[0567]** In the same manner as in Example 13, the title compound (256 mg) was obtained as a white powder using the compound (503 mg) obtained in Example 240 (4) and dipentylamine (189  $\mu$ L).

$^1\text{H-NMR}$ (300Mz, DMSO- $d_6$ ) $\delta$ 0.60-1.39(18H, m), 2.70-3.24(6H, m), 3.74-3.96(1H, m), 7.05(2H, d, J = 8.4Hz), 7.43-7.86(8H, m), 7.88-7.98(2H, m), 7.98-8.27(3H, m), 8.56(1H, s), 10.15(1H, s), 12.34(1H, brs).

MS: 642 (M+H) $^+$ .

Example 244 Synthesis of 2-[(4-benzoylamino)benzyl]-N-(2-naphthylsulfonyl)-3-oxo-3-pyrrolidinopropanamide

**[0568]** In the same manner as in Example 13, the title compound (264 mg) was obtained as a white powder using the compound (503 mg) obtained in Example 240 (4) and pyrrolidine (100  $\mu$ L).

$^1\text{H-NMR}$ (300Mz, DMSO- $d_6$ ) $\delta$ 1.41-1.80(4H, m), 2.70-3.52(6H, m), 3.61-3.81(1H, m), 7.05(2H, d, J = 8.4Hz), 7.38-7.83(8H, m), 7.88-8.31(5H, m), 8.55 (1H, s), 10.16(1H, s), 12.31(1H, brs). MS: 556(M+H) $^+$ .

Example 245 Synthesis of 2-[(4-benzoylamino)benzyl]-N-(2-naphthylsulfonyl)-3-oxo-3-piperidinopropanamide

**[0569]** In the same manner as in Example 13, the title compound (314 mg) was obtained as a white powder using the compound (503 mg) obtained in Example 240 (4) and piperidine (119  $\mu$ L).

$^1\text{H-NMR}$ (300Mz, DMSO- $d_6$ ) $\delta$ 0.91-1.53(6H, m), 2.73-2.99(2H, m), 3.03-3.49(4H, m), 3.93(1H, t, J = 6.9Hz), 7.05(2H, d, J = 8.4Hz), 7.40-7.88(8H, m), 7.96(2H, d, J = 6.9Hz), 8.06(1H, d, J = 8.1Hz), 8.14(1H, d, J = 8.7Hz), 8.21(1H, d, J = 7.8Hz), 8.56(1H, s), 10.17(1H, s), 12.29(1H, brs).

MS: 570 (H+H) $^+$ .

Example 246 Synthesis of 2-[(4-benzoylamino)benzyl]-3-morpholino-N-(2-naphthylsulfonyl)-3-oxopropanamide

**[0570]** In the same manner as in Example 13, the title compound (346 mg) was obtained as a white powder using the compound (503 mg) obtained in Example 240 (4) and morpholine (105  $\mu$ L).

$^1\text{H-NMR}$ (300Mz, DMSO- $d_6$ ) $\delta$ 2.72-3.00(2H, m), 3.00-3.55 (8H, m), 3.96(1H, t, J = 7.2Hz), 7.08(2H, d, J = 8.4Hz), 7.41-7.88(8H, m), 7.88-8.30(5H, m), 8.57(1H, s), 10.18(1H, s), 12.35(1H, brs).

MS: 572(M+H) $^+$ .

Example 247 Synthesis of 2-[(4-benzoylamino)benzyl]-3-(4-methylpiperazino)-N-(2-naphthylsulfonyl)-3-oxopropanamide

**[0571]** In the same manner as in Example 13, the title compound (256 mg) was obtained as a white powder using the compound (503 mg) obtained in Example 240 (4) and 1-methylpiperazine (133  $\mu$ L).

$^1\text{H-NMR}$ (300Mz, DMSO- $d_6$ ) $\delta$ 2.00-3.90(14H, m), 7.08(2H, d, J = 7.5Hz), 7.35-8.15(13H, m), 8.32(1H, s), 10.15(1H, s).

MS: 585(M+H) $^+$ .

Example 248 Synthesis of 2-[4-(benzoylamino)benzyl]-N-ethyl-N-(4-fluorophenyl)-N'-(2-naphthylsulfonyl)malonamide

**[0572]** In the same manner as in Example 13, the title compound (555 mg) was obtained as a white powder using the compound (503 mg) obtained in Example 240 (4) and N-ethyl-N-(4-fluorophenyl)amine (167 mg).

$^1\text{H-NMR}$ (300Mz, DMSO- $d_6$ ) $\delta$ 0.88(3H, t, J = 7.0Hz), 2.66-3.00(2H, m), 3.20-3.64(3H, m), 6.67-6.89(2H, m), 6.89-7.26(4H, m), 7.38-7.82(8H, m), 7.82-8.00(2H, m), 8.00-8.30 (3H, m), 8.55(1H, s), 10.12(1H, s), 12.03(1H, brs).

MS: 624 (M+H) $^+$ .

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Example 249 Synthesis of 2-[4-(benzoylamino)benzyl]-N-(4-fluorophenyl)-N-isopropyl-N'-(2-naphthylsulfonyl)malonamide

**[0573]** In the same manner as in Example 13, the title compound (473 mg) was obtained as a white powder using the compound (503 mg) obtained in Example 240 (4) and N-(4-fluorophenyl)-N-isopropylamine (184 mg).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.60-1.00(6H, m), 2.60-2.80(1H, m), 2.80-3.00(1H, m), 3.10-3.39(1H, m), 4.45-4.77(1H, m), 6.65-7.00(5H, m), 7.18-7.39(1H, m), 7.39-7.64(5H, m), 7.64-7.85(3H, m), 7.95(2H, d, J = 6.9Hz), 8.00-8.30(3H, m), 8.56(1H, s), 10.15(1H, s), 12.00(1H, brs).

MS: 638 (M+H)<sup>+</sup>.

Example 250 Synthesis of 2-[4-(benzoylamino)benzyl]-N-isopropyl-N'-(2-naphthylsulfonyl)-N-(3-trifluoromethylphenyl)malonamide

**[0574]** In the same manner as in Example 13, the title compound (439 mg) was obtained as a white powder using the compound (503 mg) obtained in Example 240 (4) and N-isopropyl-3-trifluoromethylaniline (244 mg).

<sup>1</sup>H-NMR(300Hz, DMSO-d<sub>6</sub>)δ0.60-1.09(6H, m), 2.65-3.07(2H, m), 3.09-3.50(1H, m), 4.55-4.82(1H, m), 6.58-6.94(2H, m), 6.98-8.33(17H, m), 8.56(1H, s), 10.15(1H, s), 12.08(1H, brs).

MS: 688 (M+H)<sup>+</sup>.

Example 251 Synthesis of 2-[4-(benzoylamino)benzyl]-N-isopropyl-N'-(2-naphthylsulfonyl)-N-(3-pyridyl)malonamide

**[0575]** In the same manner as in Example 13, the title compound (339 mg) was obtained as a white powder using the compound (503 mg) obtained in Example 240 (4) and N-isopropyl-N-(3-pyridyl)amine (163 mg).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.69-1.05(6H, m), 2.60-3.08(2H, m), 3.20-3.56(1H, m), 4.54-4.83(1H, m), 6.60-6.98(2H, m), 6.98-8.38(16H, m), 8.40-8.80(2H, m), 10.16(1H, s), 12.08(1H, brs).

MS: 621(M+H)<sup>+</sup>.

Example 252 Synthesis of 3-morpholino-N-(2-naphthylsulfonyl)-2-(4-nitrobenzyl)-3-oxopropanamide

**[0576]** In the same manner as in Example 1 (4), a crude product was obtained using the compound (500 mg) obtained in Example 6 (4) and morpholine (204 μL). This was purified by silica gel column chromatography to give the title compound (304 mg) as a white powder.

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ2.91-3.43(11H, m), 4.5(1H, t, J = 7.4Hz), 7.35(2H, d, J = 8.7Hz), 7.63-7.84(3H, m), 7.93(2H, d, J = 8.7Hz), 8.00-8.25(3H, m), 8.53(1H, s).

MS: 498(M+H)<sup>+</sup>.

Example 253 Synthesis of 2-(4-aminobenzyl)-3-morpholino-N-(2-naphthylsulfonyl)-3-oxopropanamide

**[0577]** In the same manner as in Example 7, the title compound (164 mg) was obtained as a white powder using the compound (198 mg) obtained in Example 252 at room temperature.

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ2.60-2.89(2H, m), 2.95-3.55(8H, m), 3.78(1H, t, J = 7.1Hz), 6.39(2H, d, J = 8.3Hz), 6.74(2H, d, J = 8.3Hz), 7.64-7.87(3H, m), 8.07(1H, d, J = 7.7Hz), 8.12(1H, d, J = 7.5Hz), 8.20(1H, d, J = 7.6Hz), 8.59(1H, s).

MS: 468(M+H)<sup>+</sup>.

Example 254 Synthesis of 3-(4-methylpiperazino)-N-(2-naphthylsulfonyl)-2-(4-nitrobenzyl)-3-oxopropanamide

**[0578]** In the same manner as in Example 1 (4), the title compound (355 mg) was obtained as a white powder using the compound (500 mg) obtained in Example 6 (4) and 1-methylpiperazine (234 mL).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ2.00-5.00(6H, m), 2.60(3H, brs), 2.94-3.11(4H, m), 3.81(1H, t, J = 6.9Hz), 7.34(2H, d, J = 5.6Hz), 7.52-7.68(2H, m), 7.75(1H, d, J = 8.4Hz), 7.80-8.00(4H, m), 8.03(1H, d, J = 6.8Hz), 8.29(1H, s).

MS: 511(M+H)<sup>+</sup>.

Example 255 Synthesis of 2-(4-aminobenzyl)-3-(4-methylpiperazino)-N-(2-naphthylsulfonyl)-3-oxopropanamide

**[0579]** In the same manner as in Example 7, the title compound (168 mg) was obtained as a white powder using the compound (270 mg) obtained in Example 254 at room temperature.

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ2.00-4.00(14H, m), 6.37(2H, d, J = 8.2Hz), 6.74(2H, d, J = 8.2Hz), 7.54-7.70(2H, m), 7.77(1H, dd, J = 8.6, 1.4Hz), 7.90-8.10(3H, m), 8.32(1H, s).

MS: 481(M+H)<sup>+</sup>.

Example 256 Synthesis of N-(2-hydroxyethyl)-N-methyl-N'-(2-naphthylsulfonyl)-2-(4-nitrobenzyl)malonamide

5 **[0580]** In the same manner as in Example 1 (4), a crude product was obtained using the compound (400 mg) obtained in Example 6 (4) and N-methylethanolamine (140 mg). This was purified by silica gel column chromatography to give the title compound (322 mg) as a white powder.

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ2.76-2.87(total 3H, each s), 2.90-3.70(6H, m), 3.90-4.30(1H, m), 7.22-7.40(2H, m), 7.64-7.92(5H, m), 8.00-8.24(3H, m), 8.52(1H, s), 11.90-12.60(1H, m).

10 MS: 486(M+H)<sup>+</sup>.

Example 257 Synthesis of 2-(4-aminobenzyl)-N-(2-hydroxyethyl)-N-methyl-N'-(2-naphthylsulfonyl)malonamide

15 **[0581]** In the same manner as in Example 7, the title compound (209 mg) was obtained as a white powder using the compound (270 mg) obtained in Example 256.

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ2.50-2.82(5H, m), 3.06-3.59(4H, m), 3.68-4.00(1H, m), 4.38, 4.60(total 1H, each brs), 6.29-6.40(2H, m), 6.70(2H, d, J = 8.0Hz), 7.64-7.88(3H, m), 8.04-8.30(3H, m), 8.53(1H, m).

MS: 456(M+H)<sup>+</sup>.

20 Example 258 Synthesis of N-diphenylmethyl-N'-(2-naphthylsulfonyl)-2-(4-nitrobenzyl)malonamide

**[0582]** In the same manner as in Example 1 (4), a crude product was obtained using the compound (400 mg) obtained in Example 6 (4) and benzhydrylamine (171 mg). This was purified by silica gel column chromatography to give the title compound (155 mg) as a white powder.

25 <sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ3.09(2H, d, J = 7.5Hz), 3.69-3.89(1H, m), 5.95(1H, d, J = 7.8Hz), 6.97-7.76(12H, m), 7.65-7.84(3H, m), 7.91(2H, d, J = 8.5Hz), 8.00-8.21(3H, m), 8.54(1H, m), 8.73(1H, d, J = 7.8Hz), 12.32(1H, brs).

MS: 594(M+H)<sup>+</sup>.

30 Example 259 Synthesis of 2-(4-aminobenzyl)-N-diphenylmethyl-N'-(2-naphthylsulfonyl)malonamide

**[0583]** In the same manner as in Example 7, the title compound (91 mg) was obtained as a white powder using the compound (135 mg) obtained in Example 258 at room temperature.

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ2.63-2.92(2H, m), 3.39-3.47(1H, m), 5.94(1H, d, J = 7.7Hz), 6.36(2H, d, J = 8.3Hz), 6.66-8.18(19H, m), 8.56(1H, d, J = 7.9Hz).

35 MS: 564(M+H)<sup>+</sup>.

Example 260 Synthesis of N-ethyl-N'-(2-naphthylsulfonyl)-2-(4-nitrobenzyl)malonamide

40 **[0584]** In the same manner as in Example 1 (4), a crude product was obtained using the compound (400 mg) obtained in Example 6 (4) and 40% ethylamine-methanol solution (500 μL). This was purified by silica gel column chromatography to give the title compound (205 mg) as a white powder.

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.91(3H, t, J = 6.9Hz), 2.86-3.10(4H, m), 3.54(1H, t, J = 7.7Hz), 7.30(2H, d, J = 8.5Hz), 7.62-7.80(3H, m), 7.81-7.98(3H, m), 8.05(2H, t, J = 7.7Hz), 8.18(1H, d, J = 8.1Hz), 8.52(1H, s), 12.29(1H, brs).

MS: 456(M+H)<sup>+</sup>.

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Example 261 Synthesis of 2-(4-aminobenzyl)-N-ethyl-N'-(2-naphthylsulfonyl)malonamide

**[0585]** In the same manner as in Example 7, the title compound (100 mg) was obtained as a white powder using the compound (145 mg) obtained in Example 260 at room temperature.

50 <sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.89(3H, t, J = 7.2Hz), 2.62-3.10(4H, m), 3.34-3.52(1H, m), 6.33(2H, d, J = 8.3Hz), 6.69(2H, d, J = 8.3Hz), 7.60-7.84(4H, m), 8.07(2H, t, J = 9.2Hz), 8.17(1H, d, J = 7.8Hz), 8.51(1H, s).

MS: 426(M+H)<sup>+</sup>.

55 Example 262 Synthesis of N-(2-naphthylsulfonyl)-2-(4-nitrobenzyl)-3-oxo-3-(3-oxospiro[indane-1, 4'-piperidin]-1'-yl)propanamide

**[0586]** In the same manner as in Example 1 (4), a crude product was obtained using the compound (300 mg) obtained in Example 6 (4) and 3-oxospiro[indane-1, 4'-piperidin] (141 mg). This was purified by silica gel column chromatography

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to give the title compound (90 mg) as a white powder.

$^1\text{H-NMR}$ (300Mz, DMSO- $d_6$ ) $\delta$ 0.80-4.50(13H, m), 7.09-8.25(14H, m), 8.52(1H, s), 12.47(1H, brs).

MS: 612(M+H) $^+$ .

5 Example 263 Synthesis of 2-(4-aminobenzyl)-N-(2-naphthylsulfonyl)-3-oxo-3-(3-oxospiro[indane-1, 4'-piperidine]-1'-yl)propanamide

**[0587]** In the same manner as in Example 7, the title compound (17 mg) was obtained as a white powder using the compound (72 mg) obtained in Example 262 at room temperature.

10  $^1\text{H-NMR}$ (300Hz, DMSO- $d_6$ ) $\delta$ 0.80-4.48(13H, m), 6.38(1H, d, J = 8.2Hz), 6.47(2H, d, J = 8.2Hz), 6.76(1H, d, J = 8.2Hz), 6.82(2H, d, J = 8.2Hz), 7.15-8.20(10H, m), 8.49(1H, brs).

MS: 582 (M+H) $^+$ .

Example 264 Synthesis of 2-(4-aminobenzyl)-N, N-dipentyl-N'-(2-naphthylsulfonyl)malonamide

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(1) N, N-dipentyl-N'-(2-naphthylsulfonyl)-2-(4-nitrobenzyl)malonamide

**[0588]** In the same manner as in Example 1 (4), a crude product was obtained using the compound (400 mg) obtained in Example 6 (4) and diamylamine (147 mg). This was purified by silica gel column chromatography to give the title compound (125 mg) as an oil.

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$^1\text{H-NMR}$ (300Mz,  $\text{CDCl}_3$ ) $\delta$ 0.60-1.90(18H, m), 2.70-3.75(7H, m), 7.13(2H, d, J = 8.6Hz), 7.50-8.10(8H, m), 8.64(1H, s), 10.60(1H, brs).

(2) 2-(4-aminobenzyl)-N, N-dipentyl-N'-(2-naphthylsulfonyl)malonamide

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**[0589]** In the same manner as in Example 7, the title compound (91 mg) as a pale-green powder was obtained using the above-mentioned compound (125 mg).

$^1\text{H-NMR}$ (300Mz, DMSO- $d_6$ ) $\delta$ 0.60-1.50(18H, m), 2.35-3.30(6H, m), 3.59-3.72(1H, m), 6.35(2H, d, J = 8.2Hz), 6.71(2H, d, J = 8.2Hz), 7.65-7.83(3H, m), 8.06(2H, t, J = 8.3Hz), 8.16(1H, d, J = 7.7Hz), 8.52(1H, s).

30

MS: 538(M+H) $^+$ .

Example 265 Synthesis of N-ethyl-2-(4-methoxybenzyl)-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

**[0590]** In the same manner as in Example 1 (4), a crude product, was obtained using the compound (1.25 g) obtained in Example 206 (2) and N-ethylaniline (364 mg). This was purified by silica gel column chromatography to give the title compound (610 mg) as a white powder.

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$^1\text{H-NMR}$ (300Mz, DMSO- $d_6$ ) $\delta$ 0.92(3H, t, J = 7.2Hz), 2.71-2.96(2H, m), 3.30-3.70(6H, m), 6.68(2H, d, J = 8.4Hz), 6.79(2H, d, J = 8.4Hz), 6.99-7.17(2H, m), 7.30(1H, d, J = 15.7Hz), 7.35-7.82(7H, m), 7.70-7.89(2H, m), 11.78(1H, brs).

MS: 493(M+H) $^+$ .

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Example 266 Synthesis of N-ethyl-2-(4-methoxybenzyl)-N'-phenethylsulfonyl-N-phenylmalonamide

**[0591]** In the same manner as in Example 221, the title compound (72 mg) was obtained as a white powder using the compound (390 mg) obtained in Example 265.

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$^1\text{H-NMR}$ (300Mz, DMSO- $d_6$ ) $\delta$ 0.98(3H, t, J = 7.2Hz), 2.65-3.01(4H, m), 3.28-3.82(8H, m), 6.59-6.95(4H, m), 7.09-7.54(10H, m), 11.75(1H, brs).

MS: 495(M+H) $^+$ .

Example 267 Synthesis of 2-(9-chlorobenzyl)-N-ethyl-N'-(2-naphthylsulfonyl)-N-phenylmalonamide

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(1) 2-(4-chlorobenzyl)-3-[(2-naphthylsulfonyl)amino]-3-oxopropionic acid

**[0592]** To the compound (2.10 g) obtained in Example 110 (4) were added 0.5 mol/L hydrochloric acid (40 mL) and ethyl acetate (80 mL), and the organic layer was collected by partitioning and washed with brine. The organic layer was concentrated under reduced pressure to give the title compound (1.90 g) as a white solid.

55

$^1\text{H-NMR}$ (300Mz, DMSO- $d_6$ ) $\delta$ 2.55-3.00(2H, m), 3.58-3.74(1H, m), 6.88-7.07(4H, m), 7.60-7.87(3H, m), 8.09(2H, d, J = 8.9Hz), 8.20(1H, d, J = 7.7Hz), 8.51(1H, d, J = 1.3Hz), 12.44(1H, brs), 13.00(1H, brs).

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(2) 2-(4-chlorobenzyl)-N-ethyl-N'-(2-naphthylsulfonyl)-N-214 phenylmalonamide

**[0593]** In the same manner as in Example 1 (4), a crude product was obtained using the above-mentioned compound (244 mg) and N-ethylaniline (71 mg). This was purified by silica gel column chromatography to give the title compound

(125 mg) as a white powder.

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.88(3H, t, J = 7.2Hz), 2.67-3.61(5H, m), 6.83(2H, d, J = 8.4Hz), 6.94(2H, d, J = 8.1Hz), 7.11(2H, d, J = 8.1Hz), 7.26-7.50(3H, m), 7.69-7.87(3H, m), 8.08-8.30(3H, m), 8.54(1H, s), 12.11(1H, brs).

MS: 521 (M+H)<sup>+</sup>.

Example 268 Synthesis of N-ethyl-N'-(2-naphthylsulfonyl)-N-phenyl-2-(4-pyridylmethyl)malonamide

(1) 3-[(2-naphthylsulfonyl)amino]-3-oxo-2-(4-pyridyl)propionic acid

**[0594]** To the compound (513 mg) obtained in Example 113 (4) were added 1 mol/L hydrochloric acid (2.5 mL) and water (10 mL), and the mixture was stirred at room temperature. The precipitate was collected by filtration to give the title compound (224 mg) as a white solid.

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ2.80-3.02(2H, m), 3.60-3.75(1H, m), 7.01(2H, d, J = 5.9Hz), 7.59-7.80(3H, m), 7.96-8.24(5H, m), 8.51(1H, d, J = 1.1Hz).

(2) N-ethyl-N'-(2-naphthylsulfonyl)-N-phenyl-2-(4-pyridylmethyl)malonamide

**[0595]** In the same manner as in Example 1 (4), a crude product was obtained using the above-mentioned compound (224 mg) and N-ethylaniline (71 mg). This was purified by silica gel column chromatography to give the title compound (65 mg) as a white powder.

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.87(3H, t, J = 7.0Hz), 2.70-3.98(2H, m), 3.19-3.60(3H, m), 6.85(2H, d, J = 5.7Hz), 6.94(2H, d, J = 7.7Hz), 7.18-7.40(3H, m), 7.59-7.82(3H, m), 8.00-8.40(5H, m), 8.53(1H, s), 12.28 (1H, brs).

MS: 487(M+H)<sup>+</sup>.

Example 269 Synthesis of N-ethyl-N'-(2-naphthylsulfonyl)-N-phenyl-2-(4-trifluoromethoxybenzyl)malonamide

**[0596]** In the same manner as in Example 1 (4), a crude product was obtained using the compound (1.18 g) obtained in Example 117 (4) and N-ethylaniline (305 mg). This was purified by silica gel column chromatography to give the title compound (519 mg) as a white powder.

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.87(3H, t, J = 7.2Hz), 2.70-3.00(2H, m), 3.25-3.66 (3H, m), 6.80-6.98(4H, m), 7.06(2H, d, J = 8.4Hz), 7.19-7.43(3H, m), 7.65-7.84(3H, m), 8.00-8.30(3H, m), 8.59(1H, s), 12.08 (1H, brs).

MS: 571(M+H)<sup>+</sup>.

Example 270 Synthesis of N-ethyl-N-phenyl-N'-(E)-styrylsulfonyl)-2-(4-trifluoromethoxybenzyl)malonamide

**[0597]** In the same manner as in Example 1 (4), a crude product was obtained using the compound (1.22 g) obtained in Example 207 (2) and N-ethylaniline (333 mg). This was purified by silica gel column chromatography to give the title compound (544 mg) as a white powder.

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.91(3H, t, J = 7.2Hz), 2.80-3.10(2H, m), 3.26-3.67(3H, m), 6.93-7.61(14H, m), 7.69-7.88(2H, m), 11.76(1H, brs).

MS: 547(M+H)<sup>+</sup>.

Example 271 Synthesis of N-ethyl-2-(3, 4-dimethoxybenzyl)-N'-(2-naphthylsulfonyl)-N-phenylmalonamide

(1) 3-(N-ethyl-N-phenylamino)-2-(3, 4-dimethoxybenzyl)-3-oxopropionic acid

**[0598]** In the same manner as in Example 119 (2), the title compound (428 mg) was obtained as a white powder using the compound (2.00 g) obtained in Example 119 (1) and N-ethylaniline (1.65 g).

<sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ1.06(3H, t, J = 7.2Hz), 2.97-3.29(2H, m), 3.46-3.84(6H, m), 3.87(3H, s), 6.65-7.50(8H, m).

(2) N-ethyl-2-(3, 4-dimethoxybenzyl)-N'-(2-naphthylsulfonyl)-N-phenylmalonamide

**[0599]** In the same manner as in Example 1 (2), the title compound (9 mg) was obtained as a white powder using the above-mentioned compound (214 mg).

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<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.90(3H, t, J = 7.2Hz), 2.70-3.00(2H, m), 3.30-3.70(6H, m), 3.71(3H, s), 6.22-6.34(1H, m), 6.66-6.81(2H, m), 6.83-7.10(2H, m), 7.19-7.42(3H, m), 7.63-7.80(3H, m), 8.01-8.27(3H, m), 8.52(1H, s), 11.97(1H, brs). MS: 547(M+H)<sup>+</sup>.

5 Example 272 Synthesis of N-ethyl-2-(3, 4-dimethoxybenzyl)-N-phenyl-N'-(E)-styrylsulfonylmalonamide

**[0600]** In the same manner as in Example 1 (2), the title compound (69 mg) was obtained as a white powder using the compound (214 mg) obtained in Example 271 (1) and trans-β-styrenesulfonamide (101 mg).

10 <sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.93(3H, t, J = 6.9Hz), 2.75-3.10(2H, m), 3.30-3.70(6H, m), 3.73(3H, s), 6.38-6.50(1H, m), 6.77-6.94(2H, m), 6.97-7.15(2H, m), 7.25(1H, d, J = 15.3Hz), 7.30-7.66(7H, m), 7.63-7.80(2H, m), 11.64(1H, brs). MS: 523(M+H)<sup>+</sup>.

Example 273 Synthesis of N-ethyl-2-(3, 4-methylenedioxybenzyl)-N'-(2-naphthylsulfonyl)-N-phenylmalonamide

15 (1) 2, 2-dimethyl-5-(3, 4-methylenedioxybenzyl)-1, 3-dioxane-4, 6-dione

**[0601]** In the same manner as in Example 119 (1), the title compound (8.34 g) was obtained as a white powder using 3, 4-methylenedioxybenzaldehyde (8.33 g).

20 <sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ1.54(3H, s), 1.74(3H, s), 3.41(2H, d, J = 4.8Hz), 3.71(1H, t, J = 4.8Hz), 5.92(2H, s), 6.68-6.87(3H, m).

(2) 3-(N-ethyl-N-phenylamino)-2-(3, 4-methylenedioxybenzyl)-3-oxopropionic acid

25 **[0602]** In the same manner as in Example 119 (2), the title compound (1.92 g) was obtained as a white solid using the above-mentioned compound (2.00 g) and N-ethylaniline (3.48 g).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.93(3H, t, J = 7.2Hz), 2.86(2H, d, J = 7.5Hz), 3.08-3.71(3H, m), 5.98(2H, s), 6.31-6.51(2H, m), 6.54-6.96(3H, m), 7.28-7.45(3H, m), 12.45(1H, brs).

(3) N-ethyl-2-(3, 4-methylenedioxybenzyl)-N'-(2-naphthylsulfonyl)-N-phenylmalonamide

30 **[0603]** In the same manner as in Example 1 (2), the title compound (563 mg) was obtained as a white powder using the above-mentioned compound (811 mg).

35 <sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.89(3H, t, J = 7.2Hz), 2.61-2.89(2H, m), 3.20-3.69(3H, m), 5.80-5.97(2H, m), 6.17-6.34(2H, m), 6.54(1H, d, J = 6.5Hz), 6.96(2H, d, J = 7.2Hz), 7.20-7.47(3H, m), 7.60-7.85(3H, m), 8.09(1H, d, J = 7.8Hz), 8.16(1H, d, J = 8.7Hz), 8.22(1H, d, J = 7.8Hz), 8.53(1H, s), 12.03(1H, brs). MS : 531(M+H)<sup>+</sup>.

Example 274 Synthesis of N-ethyl-2-(3, 4-methylenedioxybenzyl)-N-phenyl-N'-(E)-styrylsulfonylmalonamide

40 **[0604]** In the same manner as in Example 1 (2), the title compound (277 mg) was obtained as a white powder using the compound (811 mg) obtained in Example 273 (2) and trans-β-styrenesulfonamide (402 mg).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.93(3H, t, J = 7.2Hz), 2.65-2.89(2H, m), 3.30-3.72(3H, m), 5.91(2H, s), 6.29-6.47(2H, m), 6.66(1H, d, J = 8.4Hz), 7.00-7.19(2H, m), 7.27(1H, d, J = 15.6Hz), 7.36-7.81(7H, m), 7.70-7.86(2H, m), 11.72(1H, brs). MS: 507 (M+H)<sup>+</sup>.

45 Example 275 Synthesis of N-ethyl-2-(4-methoxycarbonylbenzyl)-N'-(2-naphthylsulfonyl)-N-phenylmalonamide

(1) 3-(N-ethyl-N-phenylamino)-2-(4-methoxycarbonylbenzyl)-3-oxopropionic acid

50 **[0605]** In the same manner as in Example 119 (2), the title compound (1.50 g) was obtained as a white powder using the compound (2.34 g) obtained in Example 120 (1) and N-ethylaniline (3.88 g).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.91(3H, t, J = 7.2Hz), 2.90-3.10(2H, m), 3.20-3.68(3H, m), 3.85(3H, s), 6.35-7.00(2H, m), 7.14(2H, d, J = 8.1Hz), 7.20-7.50(3H, m), 7.85(2H, d, J = 8.1Hz).

55 (2) N-ethyl-2-(4-methoxycarbonylbenzyl)-N'-(2-naphthylsulfonyl)-N-phenylmalonamide

**[0606]** In the same manner as in Example 1 (2), the title compound (542 mg) was obtained as a white powder using the above-mentioned compound (750 mg).

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<sup>1</sup>H-NMR(300Hz, DMSO-d<sub>6</sub>)δ0.87(3H, t, J = 7.2Hz), 2.80-3.09(2H, m), 3.20-3.70(3H, m), 3.82(3H, s), 6.83-7.01(4H, m), 7.20-7.46(3H, m), 7.59-7.81(5H, m), 8.05-8.30(3H, m), 8.52(1H, s), 12.09(1H, brs).  
MS: 545(M+H)<sup>+</sup>.

### 5 Example 276 Synthesis of 2-(4-carboxybenzyl)-N-ethyl-N'-(2-naphthylsulfonyl)-N-phenylmalonamide

**[0607]** In the same manner as in Example 121, the title compound (193 mg) was obtained as a white powder using the compound (300 mg) obtained in Example 275.

10 <sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.86(3H, t, J = 6.9Hz), 2.78-3.07(2H, m), 3.20-3.77(3H, m), 6.83-7.01(4H, m), 7.18-7.47(3H, m), 7.59-7.87(5H, m), 8.03-8.34(3H, m), 8.45(1H, s), 12.12(1H, brs), 12.79(1H, brs).  
MS: 531(M+H)<sup>+</sup>.

### Example 277 Synthesis of N-ethyl-2-(4-methoxycarbonylbenzyl)-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

15 **[0608]** In the same manner as in Example 1 (2), the title compound (237 mg) was obtained as a white powder using the compound (750 mg) obtained in Example 275 (1) and trans-β-styrenesulfonamide (357 mg).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.91(3H, t, J = 7.2Hz), 2.90-3.15(2H, m), 3.35-3.68(3H, m), 3.82(3H, s), 7.00-7.13(4H, m), 7.29(1H, d, J = 15.3Hz), 7.34-7.60(7H, m), 7.70-7.86(4H, m), 11.80(1H, brs).  
MS: 521(M+H)<sup>+</sup>.

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### Example 278 Synthesis of 2-(4-carboxybenzyl)-N-ethyl-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

**[0609]** In the same manner as in Example 121, the title compound (116 mg) was obtained as a white powder using the compound (180 mg) obtained in Example 277.

25 <sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.91(3H, t, J = 7.2Hz), 2.81-3.12(2H, m), 3.35-3.69(3H, m), 6.89-7.11(4H, m), 7.28(1H, d, J = 15.3Hz), 7.30-7.62(7H, m), 7.65-7.90(4H, m), 11.79(1H, brs)12.80(1H, brs).  
MS: 507(M+H)<sup>+</sup>.

### 30 Example 279 Synthesis of N-ethyl-2-[(2-methoxy-5-pyridyl)methyl]-N'-(2-naphthylsulfonyl)-N-phenylmalonamide (1) 3-(N-ethyl-N-phenylamino)-2-[(2-methoxy-5-pyridyl)methyl]-3-oxopropionic acid

**[0610]** In the same manner as in Example 119 (2), the title compound (1.46 g) was obtained as a white powder using the compound (2.12 g) obtained in Example 122 (1) and N-ethylaniline (3.87 g).

35 <sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.93(3H, t, J = 7.1Hz), 2.89(2H, d, J = 7.5Hz), 3.20-3.69(3H, m), 3.82(3H, s), 6.71(1H, d, J = 8.4Hz), 6.60-7.04(2H, m), 7.29(1H, dd, J = 6.1, 2.3Hz), 7.30-7.50(3H, m), 7.77(1H, d, J = 2.2Hz).

### (2) N-ethyl-2-[(2-methoxy-5-pyridyl)methyl]-N'-(2-naphthylsulfonyl)-N-phenylmalonamide

**[0611]** In the same manner as in Example 1 (2), the title compound (536 mg) was obtained as a white powder using the above-mentioned compound (728 mg).

40 <sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.88(3H, t, J = 6.9Hz), 2.61-2.90(2H, m), 3.30-3.65(3H, m), 3.75(3H, s), 6.49(1H, d, J = 9.0Hz), 6.90-7.01(2H, m), 7.07-7.15(1H, m), 7.22-7.45(3H, m), 7.61(1H, s), 7.65-7.84(3H, s), 8.04-8.30(3H, m), 8.53(1H, s), 12.04(1H, brs).  
MS: 518(M+H)<sup>+</sup>.

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### Example 280 Synthesis of N-ethyl-2-[(2-methoxy-5-pyridyl)methyl]-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

**[0612]** In the same manner as in Example 1 (2), the title compound (346 mg) was obtained as a white powder using the compound (728 mg) obtained in Example 279 (1) and trans-β-styrenesulfonamide (375 mg).

50 <sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.92(3H, t, J = 6.9Hz), 2.70-3.05(2H, m), 3.18-3.75(3H, m), 3.76(3H, s), 6.61(1H, d, J = 8.7Hz), 7.00-7.14(2H, m), 7.19-7.31(2H, m), 7.32-7.61(7H, m), 7.65-7.86(3H, m), 11.73(1H, brs).  
MS: 494(M+H)<sup>+</sup>.

### Example 281 Synthesis of 2-[4-(benzyloxy)benzyl]-N-ethyl-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

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### (1) 5-[4-(benzyloxy)benzyl]-2, 2-dimethyl-1, 3-dioxane-4, 6-dione

**[0613]** In the same manner as in Example 119 (1), the title compound (10.4 g) was obtained as a pale-yellow powder

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using 4-benzyloxybenzaldehyde (11.8 g).

$^1\text{H-NMR}$ (300Hz,  $\text{CDCl}_3$ ) $\delta$ 1.46(3H, s), 1.72(3H, s), 3.44(2H, d,  $J = 4.8\text{Hz}$ ), 3.72(1H, t,  $J = 4.5\text{Hz}$ ), 5.03(2H, s), 6.89(2H, d,  $J = 8.7\text{Hz}$ ), 7.17-7.49(7H, m).

5 (2) 2-[4-(benzyloxy)benzyl]-3-(N-ethyl-N-phenylamino)-3-oxopropionic acid

**[0614]** In the same manner as in Example 119 (2), the title compound (354 mg) was obtained as a white powder using the above-mentioned compound (681 mg) and N-ethylaniline (969 mg).

10  $^1\text{H-NMR}$ (300Mz,  $\text{DMSO-d}_6$ ) $\delta$ 0.88(3H, t,  $J = 7.1\text{Hz}$ ), 2.73-2.95(2H, m), 3.10-3.69(3H, m), 5.12(2H, s), 6.35-7.00(6H, m), 7.10-7.50(8H, m).

(3) 2-[4-(benzyloxy)benzyl]-N-ethyl-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

15 **[0615]** In the same manner as in Example 1 (2), the title compound (167 mg) was obtained as a white powder using the above-mentioned compound (462 mg) and trans- $\beta$ -styrenesulfonamide (462 mg).

$^1\text{H-NMR}$ (300Mz,  $\text{DMSO-d}_6$ ) $\delta$ 0.91(3H, t,  $J = 6.9\text{Hz}$ ), 2.60-3.78(5H, m), 5.00(2H, s), 6.70-6.90(4H, m), 6.90-7.14(2H, m), 7.18-7.58(13H, m), 7.65-7.90(2H, m), 11.76(1H, brs).

MS: 569(M+H) $^+$ .

20 Example 282 Synthesis of 2-[3-(benzyloxy)benzyl]-N-ethyl-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

(1) 5-[3-(benzyloxy)benzyl]-2, 2-dimethyl-1, 3-dioxane-4, 6-dione

25 **[0616]** In the same manner as in Example 119 (1), the title compound (371 mg) was obtained as a white powder using 3-benzyloxybenzaldehyde (950 mg).

$^1\text{H-NMR}$ (300Mz,  $\text{CDCl}_3$ ) $\delta$ 1.50(3H, s), 1.73(3H, s), 3.47(2H, d,  $J = 4.9\text{Hz}$ ), 3.74(1H, t,  $J = 4.9\text{Hz}$ ), 5.05(2H, s), 6.79-7.00(3H, m), 7.16-7.52(6H, m).

(2) 2-[3-(benzyloxy)benzyl]-3-(N-ethyl-N-phenylamino)-3-oxopropionic acid

30 **[0617]** In the same manner as in Example 119 (2), the title compound (400 mg) was obtained as an oil using the above-mentioned compound (371 mg) and N-ethylaniline (528 mg).

$^1\text{H-NMR}$ (300Mz,  $\text{DMSO-d}_6$ ) $\delta$ 0.92(3H, t,  $J = 7.2\text{Hz}$ ), 2.80-2.98(2H, m), 3.20-3.70(3H, m), 5.01(2H, s), 6.43-7.52(14H, m), 12.60(1H, brs).

35 (3) 2-[3-(benzyloxy)benzyl]-N-ethyl-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

**[0618]** In the same manner as in Example 1 (2), the title compound (57 mg) was obtained as a white powder using the above-mentioned compound (400 mg) and trans- $\beta$ -styrenesulfonamide (168 mg).

40  $^1\text{H-NMR}$ (300Mz,  $\text{DMSO-d}_6$ ) $\delta$ 0.92(3H, t,  $J = 6.9\text{Hz}$ ), 2.65-3.70(5H, m), 4.97(2H, s), 6.40-6.90(3H, m), 6.94-7.20(3H, m), 7.20-7.65(13H, m), 7.69-7.90(2H, m), 11.80(1H, brs).

MS: 569(M+H) $^+$ .

45 Example 283 Synthesis of N-ethyl-2-(4-methoxy-3-nitrobenzyl)-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

(1) 5-(4-methoxy-3-nitrobenzyl)-2, 2-dimethyl-1, 3-dioxane-4, 6-dione

50 **[0619]** In the same manner as in Example 214 (1), a crude product was obtained using 4-methoxy-3-nitrobenzoic acid (3.94 g). This was purified by silica gel column chromatography to give the title compound (1.08 g) as a pale-yellow solid.

$^1\text{H-NMR}$ (300Mz,  $\text{DMSO-d}_6$ ) $\delta$ 1.64(3H, s), 1.82(3H, s), 3.27(2H, d,  $J = 5.3\text{Hz}$ ), 3.89(3H, s), 4.81(1H, t,  $J = 5.4\text{Hz}$ ), 7.28(1H, d,  $J = 8.6\text{Hz}$ ), 7.59(1H, dd,  $J = 8.8, 1.6\text{Hz}$ ), 7.83(1H, d,  $J = 1.2\text{Hz}$ ).

(2) 3-(N-ethyl-N-phenylamino)-2-(4-methoxy-3-nitrobenzyl)-3-oxopropionic acid

55 **[0620]** In the same manner as in Example 119 (2), the title compound (310 mg) was obtained as a white powder using the above-mentioned compound (1.08 g) and N-ethylaniline (1.69 g).

$^1\text{H-NMR}$ (300Mz,  $\text{DMSO-d}_6$ ) $\delta$ 0.91(3H, t,  $J = 7.0\text{Hz}$ ), 2.96(2H, d,  $J = 7.5\text{Hz}$ ), 3.20-3.70(3H, m), 3.91(3H, s), 6.25-7.10(2H, m), 7.20-7.40(5H, m), 7.46(1H, s), 12.70(1H, brs).

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(3) N-ethyl-2-(4-methoxy-3-nitrobenzyl)-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

**[0621]** In the same manner as in Example 1 (2), the title compound (22 mg) was obtained as a white powder using the above-mentioned compound (310 mg) and trans- $\beta$ -styrenesulfonamide (141 mg).

$^1\text{H-NMR}$ (300Mz, DMSO- $d_6$ ) $\delta$ 0.91(3H, t, J = 7.2Hz), 2.78-3.16(2H, m), 3.25-3.70(3H, m), 3.84(3H, s), 6.94-7.05(2H, m), 7.17(H, d, J = 8.7Hz), 7.20-7.84(10H, m), 7.86-7.92(2H, m), 11.74(1H, brs).

MS: 538 (M+H) $^+$ .

Example 284 Synthesis of N-ethyl-2-(4-methoxy-3-nitrobenzyl)-N'-(2-naphthylsulfonyl)-N-phenylmalonamide

**[0622]** In the same manner as in Example 1 (2), the title compound (210 mg) was obtained as a white powder using the compound (294 mg) obtained in Example 283 (2).

$^1\text{H-NMR}$ (300Mz, DMSO- $d_6$ ) $\delta$ 0.86(3H, t, J = 7.2Hz), 2.70-3.07(2H, m), 3.23-3.64(3H, m), 3.83(3H, s), 6.87(2H, d, J = 7.5Hz), 6.99-7.18(2H, m), 7.18-7.46(4H, m), 7.60-7.85(3H, m), 8.00-8.29(3H, m), 8.55(1H, s), 12.02(1H, brs).

MS: 562(M+H) $^+$ .

Example 285 Synthesis of 2-(3-amino-4-methoxybenzyl)-N-ethyl-N'-(2-naphthylsulfonyl)-N-phenylmalonamide

**[0623]** In the same manner as in Example 7, the title compound (132 mg) was obtained as a white powder using the compound (156 mg) obtained in Example 284 at room temperature.

$^1\text{H-NMR}$ (300Mz, DMSO- $d_6$ ) $\delta$ 0.89(3H, t, J = 7.1Hz), 2.50-2.90(2H, m), 3.25-3.75(3H, m), 3.65(3H, s), 5.91(1H, d, J = 7.7Hz), 6.17(1H, d, J = 1.0Hz), 6.43(1H, d, J = 8.2Hz), 6.88-7.01(2H, m), 7.22-7.46(3H, m), 7.61-7.87(3H, m), 8.02-8.24(3H, m), 8.53(1H, s). MS: 532(M+H) $^+$ .

Example 286 Synthesis of N-ethyl-2-(3-methoxy-4-nitrobenzyl)-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

(1) 5-(3-methoxy-4-nitrobenzyl)-2, 2-dimethyl-1, 3-dioxane-4, 6-dione

**[0624]** In the same manner as in Example 214 (1), the title compound (3.49 g) was obtained as a white powder using 3-methoxy-4-nitrobenzoic acid (3.94 g).

$^1\text{H-NMR}$ (300Mz, DMSO- $d_6$ ) $\delta$ 1.67(3H, s), 1.84(3H, s), 3.34(2H, d, J = 5.5Hz), 3.90(3H, s), 4.84(1H, t, J = 5.6Hz), 7.03(1H, d, J = 8.3Hz), 7.32(1H, s), 7.80(1H, d, J = 8.3Hz).

(2) 3-(N-ethyl-N-phenylamino)-2-(3-methoxy-4-nitrobenzyl)-3-oxopropionic acid

**[0625]** In the same manner as in Example 119 (2), the title compound (962 mg) was obtained as a white powder using the above-mentioned compound (1.08 g) and N-ethylaniline (1.69 g).  $^1\text{H-NMR}$ (300Mz, DMSO- $d_6$ ) $\delta$ 0.91(3H, t, J = 7.1Hz), 2.89-3.09(2H, m), 3.09-3.74(3H, m), 3.76(3H, s), 6.74(2H, brs), 6.73(1H, dd, J = 8.3, 1.3Hz), 6.95(1H, d, J = 0.9Hz), 7.20-7.43(3H, m), 7.79(1H, d, J = 8.2Hz), 12.80(1H, brs).

(3) N-ethyl-2-(3-methoxy-4-nitrobenzyl)-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

**[0626]** In the same manner as in Example 1 (2), the title compound (200 mg) was obtained as a white powder using the above-mentioned compound (310 mg) and trans- $\beta$ -styrenesulfonamide (141 mg).

$^1\text{H-NMR}$ (300Mz, DMSO- $d_6$ ) $\delta$ 0.92(3H, t, J = 7.1Hz), 2.79-3.20(2H, m), 3.26-3.70(3H, m), 3.79(3H, s), 6.70(1H, d, J = 8.3Hz), 6.87(1H, s), 6.90-7.88(13H, m), 11.80(1H, brs).

MS: 538(M+H) $^+$ .

Example 287 Synthesis of N-ethyl-2-(3-methoxy-4-nitrobenzyl)-N'-(2-naphthylsulfonyl)-N-phenylmalonamide

**[0627]** In the same manner as in Example 1 (2), the title compound (318 mg) was obtained as a white powder using the compound (294 mg) obtained in Example 286 (2).

$^1\text{H-NMR}$ (300Mz, DMSO- $d_6$ ) $\delta$ 0.88(3H, t, J = 7.1Hz), 2.80-3.09(2H, m), 3.26-3.69(3H, m), 3.70(3H, s), 6.54(1H, d, J = 8.3Hz), 6.75(1H, s), 6.89-7.00(2H, m), 7.20-7.50(3H, m), 7.58(1H, d, J = 8.3Hz), 7.65-7.83(3H, m), 8.02-8.29(3H, m), 8.55(1H, s), 11.10(1H, brs).

MS: 562(M+H) $^+$ .

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Example 288 Synthesis of 2-(4-amino-3-methoxybenzyl)-N-ethyl-N'-(2-naphthylsulfonyl)-N-phenylmalonamide

**[0628]** In the same manner as in Example 7, the title compound (204 mg) was obtained as a white powder using the compound (240 mg) obtained in Example 287 at room temperature.

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.88(3H, t, J = 6.9Hz), 2.60-2.80(2H, m), 3.24-3.67(3H, m), 3.53(3H, s), 6.05-6.20(2H, m), 6.35(1H, d, J = 8.1Hz), 6.90-7.05(2H, m), 7.20-7.40(3H, m), 7.62-7.80(3H, m), 8.03-8.26(3H, m), 8.55(1H, s).  
MS: 532(M+H)<sup>+</sup>.

Example 289 Synthesis of N-ethyl-2-(3-methoxy-2-nitrobenzyl)-N-phenyl-N'-(E)-styrylsulfonylmalonamide

(1) 5-(3-methoxy-2-nitrobenzyl)-2, 2-dimethyl-1, 3-dioxane-4, 6-dione

**[0629]** In the same manner as in Example 214 (1), the title compound (864 mg) was obtained as a white powder using 3-methoxy-2-nitrobenzoic acid (3.94 g).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ1.68(3H, s), 1.84(3H, s), 3.18(2H, d, J = 5.5Hz), 3.87(3H, s), 4.77(1H, t, J = 5.5Hz), 7.07(1H, d, J = 7.9Hz), 7.18(1H, d, J = 8.4Hz), 7.48(1H, t, J = 8.1Hz).

(2) 3-(N-ethyl-N-phenylamino)-2-(3-methoxy-2-nitrobenzyl)-3-oxopropionic acid

**[0630]** In the same manner as in Example 119 (2), the title compound (714 mg) was obtained as a white powder using the above-mentioned compound (864 mg) and N-ethylaniline (1.36 g).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.93(3H, t, J = 7.1Hz), 2.66-2.80(1H, m), 2.90-3.05(1H, m), 3.25-3.70(3H, m), 3.90(3H, s), 6.15-7.60(8H, m), 12.95(1H, brs).

(3) N-ethyl-2-(3-methoxy-2-nitrobenzyl)-N-phenyl-N'-(E)-styrylsulfonylmalonamide

**[0631]** In the same manner as in Example 1 (2), the title compound (285 mg) was obtained as a white powder using the above-mentioned compound (714 mg) and trans-β-styrenesulfonamide (392 mg).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.92(3H, t, J = 7.1Hz), 2.70-3.10(2H, m), 3.35-3.70(3H, m), 3.82(3H, s), 6.60(1H, d, J = 7.8Hz), 6.99-7.20(3H, m), 7.22-7.60(9H, m), 7.68-7.89(2H, m), 11.75(1H, brs).  
MS: 538(M+H)<sup>+</sup>.

Example 290 Synthesis of N-ethyl-2-(4-methyl-3-nitrobenzyl)-N-phenyl-N'-(E)-styrylsulfonylmalonamide

(1) triethyl 2-(4-methyl-3-nitrophenyl)ethane-1, 1, 1-tricarboxylate

**[0632]** In the same manner as in Example 117 (1), the title compound (16.5 g) was obtained as an oil using 4-methyl-3-nitrobenzyl chloride (8.06 g).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.25(9H, t, J = 7.2Hz), 2.56(3H, s), 3.53(2H, s), 7.22(1H, d, J = 8.0Hz), 7.47(1H, dd, J = 8.0, 1.6Hz), 7.92(1H, d, J = 1.6Hz).

(2) monoethyl (4-methyl-3-nitrobenzyl)malonate

**[0633]** In the same manner as in Example 117 (2), the title compound (12.2 g) was obtained as a yellow solid using the above-mentioned compound (16.5 g).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.25(3H, t, J = 7.2Hz), 2.57 (3H, s), 3.23-3.33(2H, m), 3.70(1H, t, J = 7.6Hz), 4.15-4.23(2H, m), 7.27(1H, d, J = 8.0Hz), 7.37(1H, dd, J = 8.0, 1.6Hz), 7.85(1H, d, J = 1.6Hz).

(3) ethyl 3-(N-ethyl-N-phenylamino)-2-(4-methyl-3-nitrobenzyl)-3-oxopropionate

**[0634]** In the same manner as in Example 1 (4), the title compound (1.84 g) was obtained as a yellow solid using the above-mentioned compound (2.02 g) and N-ethylaniline (1.00 mL). <sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ0.92(3H, t, J = 7.2Hz), 1.12(3H, t, J = 7.2Hz), 2.50(3H, s), 3.00-3.09(2H, m), 3.43-3.65(3H, m), 4.00(2H, q, J = 7.2Hz), 6.76(2H, brs), 7.26-7.28(1H, m), 7.31-7.46(4H, m), 7.60(1H, d, J = 1.2Hz).

(4) 3-(N-ethyl-N-phenylamino)-2-(4-methyl-3-nitrobenzyl)-3-oxopropionic acid

**[0635]** In the same manner as in Example 1 (3), the title compound (1.54 g) was obtained as an oil using the above-

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mentioned compound (1.84 g).

$^1\text{H-NMR}$ (400Mz, DMSO- $d_6$ ) $\delta$ 0.90(3H, t, J = 7.2Hz), 2.50(3H, s), 3.02(2H, d, J = 7.6Hz), 3.32-3.39(1H, m), 3.43-3.64(2H, m), 6.72(2H, brs), 7.26(1H, dd, J = 7.6, 1.6Hz), 7.35(3H, brs), 7.40(1H, d, J = 7.6Hz), 7.58(1H, d, J = 1.6Hz), 12.70(1H, brs).

5 (5) N-ethyl-2-(4-methyl-3-nitrobenzyl)-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

**[0636]** In the same manner as in Example 1 (2), the title compound (296 mg) was obtained as a white solid using the above-mentioned compound (420 mg) and trans- $\beta$ -styrenesulfonamide (216 mg).

10  $^1\text{H-NMR}$ (400Mz, DMSO- $d_6$ ) $\delta$ 0.82-0.96(3H, m), 2.42(3H, s), 2.86-2.99(1H, m), 3.05-3.16(1H, m), 3.43-3.64(3H, m), 7.03-7.05(2H, m), 7.24-7.60(11H, m), 7.78-7.80(2H, m), 11.75(1H, brs).

Example 291 Synthesis of 2-(3-amino-4-methylbenzyl)-N-ethyl-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

15 **[0637]** In the same manner as in Example 137 (4), the title compound (130 mg) was obtained as a pale-yellow solid using the compound (204 mg) obtained in Example 290 at room temperature.

$^1\text{H-NMR}$ (400Mz, DMSO- $d_6$ ) $\delta$ 0.89-0.98(3H, m), 1.96(3H, s), 2.70-2.87(2H, m), 3.40-3.53(2H, m), 3.60-3.70(1H, m), 6.01(1H, d, J = 7.2Hz), 6.26(1H, s), 6.69(1H, d, J = 7.2Hz), 7.09-7.11(2H, m), 7.29(1H, d, J = 15.6Hz), 7.36-7.50(6H, m), 7.55(1H, d, J = 15.6Hz), 7.77-7.78(2H, m).

MS: 492(M+H) $^+$ .

20

Example 292 Synthesis of 2-(3-benzoylamino-4-methylbenzyl)-N-ethyl-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

**[0638]** In the same manner as in Example 9, the title compound (71 mg) was obtained as a white solid using the compound (75 mg) obtained in Example 291.

25  $^1\text{H-NMR}$ (400Mz, DMSO- $d_6$ ) $\delta$ 0.87-0.95(3H, m), 2.49(3H, s), 2.80-2.91(1H, m), 2.96-3.07(1H, m), 3.40-3.70(3H, m), 6.76(1H, d, J = 7.9Hz), 6.95(1H, s), 7.04-7.10(3H, m), 7.29-7.60(10H, m), 7.73-7.82(3H, m), 7.98(2H, d, J = 7.2Hz), 9.79(1H, s), 11.80(1H, brs).

MS: 596(M+H) $^+$ .

30 Example 293 Synthesis of N-ethyl-2-(4-methyl-3-nitrobenzyl)-N'-(2-naphthylsulfonyl)-N-phenylmalonamide

**[0639]** In the same manner as in Example 1 (2), the title compound (962 mg) was obtained as a white solid using the compound (1.12 g) obtained in Example 290 (4).

35  $^1\text{H-NMR}$ (400Mz, DMSO- $d_6$ ) $\delta$ 0.81-0.90(3H, m), 2.40(3H, s), 2.85(1H, dd, J = 13.6, 5.6Hz), 2.99(1H, dd, J = 13.6, 8.8Hz), 3.39-3.57(3H, m), 6.89(2H, d, J = 7.6Hz), 7.08-7.15(2H, m), 7.20-7.41(3H, m), 7.52(1H, s), 7.65-7.84(3H, m), 8.11(1H, d, J = 8.0Hz), 8.17(1H, d, J = 8.8Hz), 8.24(1H, d, J = 8.0Hz), 8.54(1H, s), 12.07(1H, brs).

MS: 546(M+H) $^+$ .

40 Example 294 Synthesis of 2-(3-amino-4-methylbenzyl)-N-ethyl-N'-(2-naphthylsulfonyl)-N-phenylmalonamide

**[0640]** In the same manner as in Example 7, the title compound (620 mg) was obtained as a white solid using the compound (670 mg) obtained in Example 293 at room temperature.

45  $^1\text{H-NMR}$ (400Mz, DMSO- $d_6$ ) $\delta$ 0.80-0.95(3H, m), 1.94(3H, s), 2.64-2.74(2H, m), 3.36-3.49(2H, m), 3.49-3.63(1H, m), 5.87(1H, d, J = 7.6Hz), 6.15(1H, s), 6.58(1H, d, J = 7.6Hz), 6.90-6.99(2H, m), 7.25-7.39(3H, m), 7.76-7.80(3H, m), 8.10(1H, d, J = 8.0Hz), 8.16(1H, d, J = 8.8Hz), 8.22(1H, d, J = 8.0Hz), 8.54(1H, s).

MS: 516(M+H) $^+$ .

Example 295 Synthesis of 2-(3-benzoylamino-4-methylbenzyl)-N-ethyl-N'-(2-naphthylsulfonyl)-N-phenylmalonamide

50 **[0641]** In the same manner as in Example 9, the title compound (148 mg) was obtained as a white solid using the compound (146 mg) obtained in Example 294.

$^1\text{H-NMR}$ (400Mz, DMSO- $d_6$ ) $\delta$ 0.86(3H, t, J = 7.2Hz), 2.15(3H, s), 2.70-2.81(1H, m), 2.86-2.96(1H, m), 3.37-3.61(3H, m), 6.66(1H, d, J = 7.3Hz), 6.89-6.98(4H, m), 7.18-7.40(3H, m), 7.49-7.62(3H, m), 7.70-7.82(3H, m), 7.97-7.99(2H, m), 8.09(1H, d, J = 8.0Hz), 8.18(1H, d, J = 8.8Hz), 8.24(1H, d, J = 8.0Hz), 8.56(1H, s), 9.78(1H, s), 12.10(1H, brs).

55 MS: 620 (M+H) $^+$ .

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### Example 296 Synthesis of N-ethyl-2-(4-fluorobenzyl)-N'-(2-naphthylsulfonyl)-N-phenylmalonamide

#### (1) ethyl 3-(N-ethyl-N-phenylamino)-2-(4-fluorobenzyl)-3-oxopropionate

5 **[0642]** The compound (884 mg) obtained in Example 118 (2) and N-ethylaniline (1.67 g) were subjected to the same manner as in Example 1 (4) to give the reaction mixture. Ethyl acetate (150 mL) and aqueous sodium hydrogen carbonate solution (120 mL) were added to extract the mixture, and the organic layer was washed sequentially with 0.5 mol/L hydrochloric acid, water and saturated brine. The organic layer was concentrated under reduced pressure to give the title compound (940 mg) as an oil. <sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ1.03(3H, t, J = 7.2Hz), 1.25(3H, t, J = 7.5Hz), 2.93-3.09(1H, m), 3.13-3.28(1H, m), 3.32-3.46(1H, m), 3.66(2H, q, J = 7.2Hz), 4.14(2H, q, J = 6.9Hz), 6.80-7.09(4H, m), 7.09-7.50(5H, m).

#### (2) 3-(N-ethyl-N-phenylamino)-2-(4-fluorobenzyl)-3-oxopropionic acid

15 **[0643]** In the same manner as in Example 111 (4), the title compound (837 mg) was obtained as an oil using the above-mentioned compound (940 mg).  
<sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ1.06(3H, t, J = 7.2Hz), 2.90-3.04(1H, m), 3.04-3.20(1H, m), 3.35-3.48(1H, m), 3.52-3.79(2H, m), 6.80-7.50(9H, m).

#### (3) N-ethyl-2-(4-fluorobenzyl)-N'-(2-naphthylsulfonyl)-N-phenylmalonamide

20 **[0644]** In the same manner as in Example 1 (2), the title compound (274 mg) was obtained as a white powder using the above-mentioned compound (418 mg).  
<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.87(3H, t, J = 6.9Hz), 2.65-2.94(2H, m), 3.20-3.66(3H, m), 6.71-6.97(6H, m), 7.38-7.40(3H, m), 7.63-7.82(3H, m), 8.00-8.29(3H, m), 8.54(1H, s), 12.08(1H, brs).  
25 MS: 505(M+H)<sup>+</sup>.

### Example 297 Synthesis of N-ethyl-2-(4-fluorobenzyl)-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

30 **[0645]** In the same manner as in Example 1 (2), the title compound (98 mg) was obtained as a white powder using the compound (418 mg) obtained in Example 296 (2) and trans-β-styrenesulfonamide (224 mg).  
<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.91(3H, t, J = 7.2Hz), 2.79-3.09(2H, m), 3.38-3.70(3H, m), 6.85-7.10(6H, m), 7.29(1H, d, J = 15.3Hz), 7.34-7.60(7H, m), 7.70-7.89(2H, m), 11.76(1H, brs). MS: 481(M+H)<sup>+</sup>.

### Example 298 Synthesis of N-ethyl-2-[3-(4-fluorophenoxy)benzyl]-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

#### (1) triethyl 2-[3-(4-fluorophenoxy)phenyl]ethane-1, 1, 1-tricarboxylate

35 **[0646]** In the same manner as in Example 117 (1), the title compound (1.56 g) was obtained as an oil using 3-(4-fluorophenoxy)benzyl bromide (1.01 g).  
40 <sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.20(9H, t, J = 7.2Hz), 3.48(2H, s), 4.17(2H, q, J = 7.2Hz), 6.80-6.88(2H, m), 7.91-7.02(5H, m), 7.14-7.21(1H, m).

#### (2) monoethyl [3-(4-fluorophenoxy)benzyl]malonate

45 **[0647]** In the same manner as in Example 117 (2), the title compound (1.19 g) was obtained as an oil using the above-mentioned compound (1.55 g).  
<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.22(3H, t, J = 7.2Hz), 3.23(2H, dd, J = 7.6, 4.4Hz), 3.67(1H, t, J = 7.6Hz), 4.17 (2H, q, J = 7.2Hz), 6.82-6.84(2H, m), 6.92-6.97(3H, m), 7.01-7.05(2H, m), 7.22-7.26(1H, m).

#### (3) ethyl 3-(N-ethyl-N-phenylamino)-2-[3-(4-fluorophenoxy)benzyl]-3-oxopropionate

50 **[0648]** In the same manner as in Example 1 (4), the title compound (1.07 g) was obtained as an oil using the above-mentioned compound (1.19 g) and N-ethylaniline (550 μL).  
55 <sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ1.05(3H, t, J = 7.2Hz), 1.24(3H, t, J = 7.2Hz), 3.03(1H, dd, J = 13.2, 5.1Hz), 3.20(1H, dd, J = 13.2, 9.6Hz), 3.42(1H, dd, J = 9.6, 5.1Hz), 3.67(2H, q, J = 7.2Hz), 4.13(2H, q, J = 7.2Hz), 6.60-6.68(2H, m), 6.77-7.05(8H, m), 7.18-7.30(3H, m).

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(4) 3-(N-ethyl-N-phenylamino)-2-[3-(4-fluorophenoxy)benzyl]-3-oxopropionic acid

**[0649]** In the same manner as in Example 1 (3), the title compound (1.00g) was obtained as an oil using the above-mentioned compound (1.07 g).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.92(3H, t, J = 7.2Hz), 2.91-2.94(2H, m), 3.26-3.31(1H, m), 3.41-3.68(2H, m), 6.50-7.10(6H, m), 7.10-7.44(6H, m), 12.60(1H, brs).

(5) N-ethyl-2-[3-(4-fluorophenoxy)benzyl]-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

**[0650]** In the same manner as in Example 1 (2), the title compound (260 mg) was obtained as a white powder using the above-mentioned compound (1.00 g) and trans-β-styrenesulfonamide (450 mg).

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ0.88-0.95(3H, m), 2.84-2.92(1H, m), 2.98-3.06(1H, m), 3.45-3.54(2H, m), 3.54-3.65(1H, m), 6.59(1H, s), 6.74-6.82(2H, m), 6.98-7.03(4H, m), 7.12-7.60(11H, m), 7.76-7.82(2H, m), 11.74(1H, brs).

MS: 573(M+H)<sup>+</sup>.

Example 299 Synthesis of N-ethyl-2-[3-(1H-imidazol-1-ylmethyl)benzyl]-N-phenyl-N'-((E)-styrylsulfonyl)malonamide (1) triethyl 2-[3-(1H-imidazol-1-ylmethyl)phenyl]ethane-1, 1, 1-tricarboxylate

**[0651]** In the same manner as in Example 144 (1), the title compound (1.13 g) was obtained as an oil using 3-(1H-imidazol-1-ylmethyl)benzyl alcohol (1.05 g).

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ1.10(9H, t, J = 7.2Hz), 3.37(2H, s), 4.09(6H, q, J = 7.2Hz), 5.14(2H, s), 6.90(1H, s), 7.06(1H, s), 7.10-7.17(3H, m), 7.22-7.28(1H, m), 7.70(1H, s).

(2) ethyl 3-(N-ethyl-N-phenylamino)-2-[3-(1H-imidazol-1-ylmethyl)benzyl]-3-oxopropionate

**[0652]** The above-mentioned compound (1.10 g) was subjected to hydrolysis in the same manner as in Example 117 (2). In the same manner as in Example 1 (4), a crude product was obtained using this and N-ethylaniline (360 μL). The crude product was purified by silica gel column chromatography to give the title compound (655 mg) as an oil.

<sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ1.02(3H, t, J = 7.2Hz), 1.25(3H, t, J = 7.2Hz), 3.00-3.10(1H, m), 3.16-3.28(1H, m), 3.37-3.45(1H, m), 3.53-3.72(3H, m), 4.14(2H, q, J = 7.2Hz), 5.04(2H, s), 6.58(2H, m), 6.88-6.92(2H, m), 7.02-7.04(2H, m), 7.08(1H, s), 7.18-7.35(4H, m), 7.51(1H, s).

(3) N-ethyl-2-[3-(1H-imidazol-1-ylmethyl)benzyl]-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

**[0653]** The above-mentioned compound (655 g) was subjected to hydrolysis in the same manner as in Example 1 (3). In the same manner as in Example 1 (2), the title compound (440 mg) was obtained as a white powder using this and trans-β-styrenesulfonamide (300 mg).

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ0.82-0.93(3H, m), 2.90(1H, dd, J = 13.2, 5.6Hz), 3.00(1H, dd, J = 13.2, 8.0Hz), 3.40-3.64(3H, m), 5.33(2H, s), 6.91-7.07(4H, m), 7.17-7.81(14H, m), 9.19(1H, s), 11.83(1H, brs).

MS: 543(M+H)<sup>+</sup>.

Example 300 Synthesis of N-ethyl-2-{3-[(2-methyl-1H-benzimidazolyl-1-yl)methyl]benzyl}-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

(1) methyl 3-[(2-methyl-1H-benzimidazolyl-1-yl)methyl]benzoate

**[0654]** To a solution of 2-methyl-1H-benzimidazolyle (2.25 g) in THF (100 mL) was added 60% sodium hydride (750 mg) under ice-cooling, and the mixture was stirred for 20 min. Methyl 3-(bromomethyl)benzoate (3.90 g) was added to the reaction mixture under ice-cooling, and the mixture was stirred at room temperature for 2 days. Water (100 mL) was added to the reaction mixture, and the mixture was extracted with ethyl acetate (100 mLx2). The organic layer was washed with saturated brine and concentrated under reduced pressure to give the title compound (3.97 g) as a pale-brown solid. <sup>1</sup>H-NMR(400Hz, DMSO-d<sub>6</sub>)δ2.50(3H, s), 3.81(3H, s), 5.58(2H, s), 7.15-7.18 (2H, m), 7.36(1H, d, J = 7.6Hz), 7.45-7.57(3H, m), 7.74(1H, s), 7.87(1H, d, J = 8.0Hz).

(2) 3-[(2-methyl-1H-benzimidazolyl-1-yl)methyl]benzyl alcohol

**[0655]** To a solution of the above-mentioned compound (3.97 g) in THF (50 mL) lithium aluminum hydride (540 mg) was added in small amounts under ice-cooling, and the mixture was allowed to warm to room temperature while stirring

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for 20 hr. Water (100 mL) was added to the reaction mixture, and the mixture was extracted with ethyl acetate (100 mL). The organic layer was washed with saturated brine and concentrated under reduced pressure to give the title compound (2.62 g) as a pale-yellow solid.

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ2.51(3H, s), 4.43(2H, d, J = 5.7Hz), 5.16(1H, t, J = 5.7Hz), 5.45(2H, s), 6.95-7.00(1H, m), 7.12-7.30(5H, m), 7.44-7.56(2H, m).

(3) 3-[(2-methyl-1H-benzimidazolyl-1-yl)methyl]benzyl chloride

**[0656]** To a solution of the above-mentioned compound (2.61 g) in chloroform (50 mL) was added thionyl chloride (4.0 mL), and the mixture was heated under reflux for 4 hr. Ice-water (200 mL), saturated sodium hydrogen carbonate (100 mL) and chloroform (100 mL) were added to extract the reaction mixture. The organic layer was washed with saturated brine, treated with activated carbon, and concentrated under reduced pressure to give the title compound (1.92 g) as a pale-brown solid.

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ2.52(3H, s), 4.72(2H, s), 5.49(2H, s), 7.00-7.17(3H, m), 7.25(1H, s), 7.27-7.35(2H, m), 7.45-7.57(2H, m).

(4) triethyl 2-{3-[(2-methyl-1H-benzimidazolyl-1-yl)methyl]phenyl}ethane-1, 1, 1-tricarboxylate

**[0657]** In the same manner as in Example 117 (1), a crude product was obtained using the above-mentioned compound (1.65 g). This was purified by silica gel column chromatography to give the title compound (2.68 g) as an oil.

<sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ1.15(9H, t, J = 7.1Hz), 2.56(3H, s), 4.08(6H, q, J = 7.1Hz), 5.27(2H, s), 6.90-7.00(2H, m), 7.08-7.33(5H, m), 7.65-7.76(1H, m).

(5) monoethyl {3-[(2-methyl-1H-benzimidazolyl-1-yl)methyl]benzyl}malonate

**[0658]** In the same manner as in Example 117 (2), a crude product was obtained using the above-mentioned compound (2.65 g). This was purified by silica gel column chromatography to give the title compound (800 mg) as an oil.

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ0.99-1.06(3H, m), 2.85(3H, s), 2.97-3.09(2H, m), 3.67-3.71(1H, m), 3.92-4.00(2H, m), 5.67(2H, s), 7.16-7.31(4H, m), 7.49-7.56(2H, m), 7.78-7.82(2H, m).

(6) ethyl 3-(N-ethyl-N-phenylamino)-2-{3-[(2-methyl-1H-benzimidazolyl-1-yl)methyl]benzyl}-3-oxopropionate

**[0659]** In the same manner as in Example 1 (4), a crude product was obtained using the above-mentioned compound (800 mg) and N-ethylaniline (300 μL). This was purified by silica gel column chromatography to give the title compound (600 mg) as an oil.

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ0.87(3H, t, J = 7.2Hz), 1.08(3H, t, J = 7.2Hz), 2.50(3H, s), 2.84-2.96(2H, m), 3.35-3.47(3H, m), 3.94(2H, q, J = 7.2Hz), 5.39(2H, s), 6.62(2H, brs), 6.84(1H, s), 6.90(1H, d, J = 8.0Hz), 7.02(1H, d, J = 7.9Hz), 7.13-7.31(6H, m), 7.41-7.44(1H, m), 7.53-7.55(1H, m).

(7) 3-(N-ethyl-N-phenylamino)-2-{3-[(2-methyl-1H-benzimidazolyl-1-yl)methyl]benzyl}-3-oxopropionic acid

**[0660]** In the same manner as in Example 1 (3), the title compound (430 mg) was obtained as a white solid using the above-mentioned compound (655 mg).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.85(3H, t, J = 7.2Hz), 2.51(3H, s), 2.80-2.97(2H, m), 3.23-3.45(3H, m), 5.39(2H, s), 6.60(2H, brs), 6.86-6.90(2H, m), 7.01(1H, d, J = 7.5Hz), 7.13-7.36(6H, m), 7.43-7.57 (2H, m), 12.61 (1H, brs).

(8) N-ethyl-2-{3-[(2-methyl-1H-benzimidazolyl-1-yl)methyl]benzyl}-N-phenyl-N'-(E)-styrylsulfonylmalonamide

**[0661]** In the same manner as in Example 1 (2), the title compound (182 mg) was obtained as a white solid using the above-mentioned compound (427 mg) and trans-β-styrenesulfonamide (177 mg).

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ0.80-0.90(3H, m), 2.83(3H, s), 2.83-3.01(2H, m), 3.37-3.59(3H, m), 5.60(2H, s), 6.88-6.98(4H, m), 7.11(1H, d, J = 7.6Hz), 7.19(1H, t, J = 7.6Hz), 7.27-7.40(4H, m), 7.46-7.58(6H, m), 7.73-7.83(4H, m), 11.80(1H, brs).

MS: 607(M+H)<sup>+</sup>.

Example 301 Synthesis of N-ethyl-2-(4-nitrophenethyl)-N-phenyl-N'-(E)-styrylsulfonylmalonamide

**[0662]** In the same manner as in Example 1 (4), the title compound (524 mg) was obtained as a white solid using the

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compound (690 mg) obtained in Example 217 (2) and N-ethylaniline (230  $\mu$ L).

$^1\text{H-NMR}$ (400Mz, DMSO- $d_6$ ) $\delta$ 0.97(3H, t, J = 6.8Hz), 1.80-2.08(2H, m), 2.53-2.57(2H, m), 3.14 (1H, t, J = 7.2Hz), 3.49-3.71(2H, m), 7.14-7.16(2H, m), 7.27(2H, d, J = 8.8Hz), 7.34-7.38(4H, m), 7.48-7.49(3H, m), 7.58(1H, d, J = 15.6Hz), 7.80-7.82(2H, m), 8.10(2H, d, J = 8.8Hz), 11.72(1H, brs).

MS: 522(M+H) $^+$ .

Example 302 Synthesis of 2-(4-aminophenethyl)-N-ethyl-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

**[0663]** In the same manner as in Example 137 (4), the title compound (29 mg) was obtained as a white solid using the compound (257 mg) obtained in Example 301 at room temperature.

$^1\text{H-NMR}$ (400Mz, DMSO- $d_6$ ) $\delta$ 0.97(3H, t, J = 7.2Hz), 1.67-1.94(2H, m), 2.15-2.27(2H, m), 3.09-3.18(1H, m), 3.52-3.67(2H, m), 6.43(2H, d, J = 8.0H), 6.63(2H, d, J = 8.0Hz), 7.12-7.14(2H, m), 7.30-7.36(4H, m), 7.48-7.49(3H, m), 7.55(1H, d, J = 15.6Hz), 7.78-7.80(2H, m).

MS: 492(M+H) $^+$ .

Example 303 Synthesis of 2-(4-aminophenethyl)-N-ethyl-N'-phenethylsulfonyl-N-phenylmalonamide

**[0664]** In the same manner as in Example 221, a crude product was obtained using the compound (240 mg) obtained in Example 301. The crude product was purified by silica gel column chromatography to give the title compound (86 mg) as a white solid.

$^1\text{H-NMR}$ (400Mz, DMSO- $d_6$ ) $\delta$ 1.01(3H, t, J = 7.2Hz), 1.76-1.82(2H, m), 2.07-2.26(2H, m), 2.85-3.08(2H, m), 3.24(1H, t, J = 6.8Hz), 3.47-3.80(4H, m), 6.43(2H, d, J = 8.0Hz), 6.59(2H, d, J = 8.0Hz), 7.20-7.42(10H, m).

MS: 494(M+H) $^+$ .

Example 304 Synthesis of N-ethyl-N'-(2-naphthylsulfonyl)-2-(4-nitrophenethyl)-N-phenylmalonamide

**[0665]** In the same manner as in Example 1 (4), the title compound (710 mg) was obtained as a white solid using the compound (850 mg) obtained in Example 144 (4) and N-ethylaniline (290  $\mu$ L).

$^1\text{H-NMR}$ (400Mz, DMSO- $d_6$ ) $\delta$ 0.88-0.98(3H, m), 1.72-1.98(2H, m), 2.35-2.48(2H, m), 3.11(1H, t, J = 6.8Hz), 3.43-3.67(2H, m), 7.69-7.08(2H, m), 7.14(2H, d, J = 8.8Hz), 7.18-7.38(3H, m), 7.70-7.85(3H, m), 8.00(2H, d, J = 8.8Hz), 8.06-8.11(1H, m), 8.20(H, d, J = 8.8Hz), 8.26(1H, d, J = 8.0H), 8.59(1H, s), 12.03(1H, brs).

MS: 546(M+H) $^+$ .

Example 305 Synthesis of 2-(4-aminophenethyl)-N-ethyl-N'-(2-naphthylsulfonyl)-N-phenylmalonamide

**[0666]** In the same manner as in Example 7, the title compound (600 mg) was obtained as a white solid using the compound (650 mg) obtained in Example 304 at room temperature.

$^1\text{H-NMR}$ (400Mz, DMSO- $d_6$ ) $\delta$ 0.93(3H, t, J = 7.2Hz), 1.60-1.85(2H, m), 2.09(2H, t, J = 7.6Hz), 3.11(1H, t, J = 6.8Hz), 3.45-3.63(2H, m), 6.41(2H, d, J = 8.4Hz), 6.51(2H, d, J = 8.4Hz), 6.99(2H, d, J = 7.6Hz), 7.18-7.35(3H, m), 7.70-7.83(3H, m), 8.09(1H, d, J = 8.0Hz), 8.19 (1H, d, J = 8.8Hz), 8.24(1H, d, J = 8.0Hz), 8.56(H, s).

MS: 516(M+H) $^+$ .

Example 306 Synthesis of N-ethyl-N-phenyl-2-(2-propynyl)-N'-((E)-styrylsulfonyl)malonamide

**[0667]** In the same manner as in Example 1 (4), a crude product was obtained using the compound (1.04 g) obtained in Example 215 (2) and N-ethylaniline (430  $\mu$ L). This was purified by silica gel column chromatography to give the title compound (95 mg) as a white powder.

$^1\text{H-NMR}$ (400Mz,  $\text{CDCl}_3$ ) $\delta$ 1.17(3H, brs), 2.04(1H, s), 2.63-2.64(1H, m), 2.65-2.71(1H, m), 3.35-3.39(1H, m), 3.74-3.84(2H, m), 7.02(1H, d, J = 15.2Hz), 7.15-7.17(2H, m), 7.39-7.47(7H, m), 7.51-7.53(2H, m), 7.71(1H, d, J = 15.2Hz).

MS: 411(M+H) $^+$ .

Example 307 Synthesis of N-ethyl-N'-(2-naphthylsulfonyl)-N-phenyl-2-(2-propynyl)malonamide

**[0668]** In the same manner as in Example 1 (4), a crude product was obtained using the compound (4.00 g) obtained in Example 152 (4) and N-ethylaniline (1.53 mL). This was purified by silica gel column chromatography to give the title compound (98 mg) as a white powder.

$^1\text{H-NMR}$ (400Mz,  $\text{CDCl}_3$ ) $\delta$ 1-10(3H, brs), 1.18-1.20(1H, m), 1.88(1H, s), 2.49-2.62(1H, m), 2.63-2.88(1H, m), 3.67-3.85(2H, m), 6.67-7.19(2H, m), 7.35-7.42(3H, m), 7.60-7.69(2H, m), 7.90-8.01(4H, m), 8.66(1H, s).

MS: 435(M+H)<sup>+</sup>.

Example 308 Synthesis of N-ethyl-2-(4-fluorobenzyl)-N-(4-fluorophenyl)-N'-((E)-styrylsulfonyl)malonamide (1) ethyl 2-(4-fluorobenzyl)-3-oxo-3-(((E)-styrylsulfonyl)amino)propionate

**[0669]** In the same manner as in Example 152 (3), the title compound (3.72 g) was obtained as an oil using the compound (10.0 g) obtained in Example 118 (2) and trans-β-styrenesulfonamide (7.06 g).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ1.07(3H, t, J = 6.9Hz), 3.04 (2H, d, J = 8.3Hz), 3.75(1H, t, J = 7.6Hz), 4.05(2H, q, J = 6.8Hz), 6.80-7.80(11H, m), 12.20(1H, brs).

(2) 2-(4-fluorobenzyl)-3-oxo-3-(((E)-styrylsulfonyl)amino)propionic acid

**[0670]** In the same manner as in Example 1 (3), the title compound (2.58 g) was obtained as an oil using the above-mentioned compound (3.72 g).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ2.91-3.11(2H, m), 3.58-3.72(1H, m), 6.85-7.80(11H, m), 12.10(1H, brs), 12.50(1H, brs).

(3) N-ethyl-2-(4-fluorobenzyl)-N-(4-fluorophenyl)-N'-((E)-styrylsulfonyl)malonamide

**[0671]** In the same manner as in Example 13, the title compound (358 mg) was obtained as a white solid using the above-mentioned compound (755 mg) and N-ethyl-4-fluoroaniline (334 mg).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.91(3H, t, J = 7.2Hz), 2.78-3.08(2H, m), 3.11-3.67 (3H, m), 6.80-7.38(9H, m), 7.38-7.61 (4H, m), 7.64-7.89(2H, m), 11.70(1H, brs).

MS: 499(M+H)<sup>+</sup>.

Example 309 Synthesis of 2-(4-fluorobenzyl)-N-(4-fluorophenyl)-N-isopropyl-N'-((E)-styrylsulfonyl)malonamide

**[0672]** In the same manner as in Example 13, the title compound (432 mg) was obtained as a white solid using the compound (755 mg) obtained in Example 308 (2) and 4-fluoro-N-isopropylaniline (368 mg).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.69-1.00(6H, m), 2.76-2.93(1H, m), 2.93-3.10(1H, m), 3.12-3.45(1H, m), 4.52-4.80(1H, m), 6.60-7.19(7H, m), 7.19-7.40(2H, m), 7.40-7.63(4H, m), 7.69-7.89(2H, m), 11.67(1H, brs).

MS: 513(M+H)<sup>+</sup>.

Example 310 Synthesis of 2-(3-fluorobenzyl)-N-(4-fluorophenyl)-N-isopropyl-N'-((E)-styrylsulfonyl)malonamide (1) 5-(3-fluorobenzyl)-2, 2-dimethyl-1, 3-dioxane-4, 6-dione

**[0673]** In the same manner as in Example 119 (1), the title compound (9.96 g) was obtained as a white solid using 3-fluorobenzaldehyde (8.60 g).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.58(3H, s), 1.76(3H, s), 3.48 (2H, d, J = 4.9Hz), 3.73-3.76(1H, m), 6.91-6.96(1H, m), 7.01-7.11(2H, m), 7.23-7.28(1H, m).

(2) 3-[N-(4-fluorophenyl)-N-isopropylamino]-2-(3-fluorobenzyl)-3-oxopropionic acid

**[0674]** In the same manner as in Example 119 (2), the title compound (740 mg) was obtained as a white solid using the above-mentioned compound (1.31 g) and 4-fluoro-N-isopropylaniline (1.68 g).

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ0.70-0.88(6H, m), 2.90-3.01(2H, m), 3.16-3.18(1H, m), 4.73-4.79(1H, m), 5.95-5.99(1H, m), 6.81-6.87(2H, m), 7.03-7.10(2H, m), 7.13-7.20(1H, m), 7.29-7.35(2H, m), 12.63(1H, brs).

(3) 2-(3-fluorobenzyl)-N-(4-fluorophenyl)-N-isopropyl-N'-((E)-styrylsulfonyl)malonamide

**[0675]** In the same manner as in Example 1 (2), the title compound (95 mg) was obtained as a white powder using the above-mentioned compound (260 mg) and trans-β-styrenesulfonamide (140 mg).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ0.90(6H, brs), 2.95-2.97(1H, m), 3.13-3.21(2H, m), 4.88-4.99(1H, m), 5.69-5.73(1H, m), 6.74(1H, d, J = 9.4Hz), 6.81-7.19(5H, m), 7.22-7.26(2H, m), 7.34-7.56(6H, m), 7.71(1H, d, J = 15.0Hz).

MS: 513(M+H)<sup>+</sup>.

Example 311 Synthesis of 2-(3-fluorobenzyl)-N-(4-fluorophenyl)-N-isopropyl-N'-(2-naphthylsulfonyl)malonamide

**[0676]** In the same manner as in Example 1 (2), the title compound (200 mg) was obtained as a white powder using

the compound (480 mg) obtained in Example 310 (2).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ0.89(6H, brs), 2.75-2.78(1H, m), 3.00-3.10(2H, m), 4.87-4.90(1H, m), 5.69-5.73(1H, m), 6.61-6.69(3H, m), 6.77-6.82(1H, m), 6.87-6.94(2H, m), 7.11-7.25(1H, m), 7.62-7.69(2H, m), 7.91-8.02(4H, m), 8.66(1H, s), 10.34(1H, s).

MS: 537(M+H)<sup>+</sup>.

Example 312 Synthesis of 2-(4-cyanobenzyl)-N-(4-fluorophenyl)-N-isopropyl-N'-((E)-styrylsulfonyl)malonamide

(1) 2-(4-cyanobenzyl)-3-oxo-3-[[E)-styrylsulfonyl]amino]propionic acid

**[0677]** In the same manner as in Example 152 (3), the object compound was obtained using the compound (1.57 g) obtained in Example 111 (2) and trans-β-styrenesulfonamide (1.25 g). This was subjected to hydrolysis in the same manner as in Example 1 (3) to give the title compound (2.30 g) as a white powder.

(2) 2-(4-cyanobenzyl)-N-(4-fluorophenyl)-N-isopropyl-N'-((E)-styrylsulfonyl)malonamide

**[0678]** In the same manner as in Example 1 (4), the title compound (395 mg) was obtained as a white powder using the above-mentioned compound (2.30 g) and 4-fluoro-N-isopropylaniline (920 mg).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ0.96(6H, m), 3.15-3.25(2H, m), 4.87-4.94(1H, m), 5.98-6.02(1H, m), 6.89-7.13(6H, m), 7.26-7.53(8H, m), 7.72(1H, d, J = 15.5Hz), 10.16(1H, brs).

MS: 520 (M+H)<sup>+</sup>.

Example 313 Synthesis of 2-(4-cyanobenzyl)-N-(4-fluorophenyl)-N-isopropyl-N'-(2-naphthylsulfonyl)malonamide

(1) 2-(4-cyanobenzyl)-3-oxo-3-[[2-naphthylsulfonyl]amino]propionic acid

**[0679]** In the same manner as in Example 152 (3), the object compound was obtained using the compound (1.57 g) obtained in Example 111 (2). This was subjected to hydrolysis in the same manner as in Example 1 (3) to give the title compound (2.51 g) as a white powder.

(2) 2-(4-cyanobenzyl)-N-(4-fluorophenyl)-N-isopropyl-N'-(2-naphthylsulfonyl)malonamide

**[0680]** In the same manner as in Example 1 (4), the title compound (969 mg) was obtained as a white powder using the above-mentioned compound (2.51 g) and 4-fluoro-N-isopropylaniline (940 mg).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ0.96(6H, brs), 2.82-2.86(1H, m), 3.02-3.14(2H, m), 4.84-4.91(1H, m), 6.04-6.08(1H, m), 6.69-6.73(1H, m), 6.87-6.95(3H, m), 7.31-7.33(2H, m), 7.62-7.68(2H, m), 7.69-8.02(5H, m), 8.49(1H, s), 12.03(1H, brs).

MS: 544 (M+H)<sup>+</sup>.

Example 314 Synthesis of 2-(3-cyanobenzyl)-N-(4-fluorophenyl)-N-isopropyl-N'-((E)-styrylsulfonyl)malonamide

(1) monoethyl (3-cyanobenzyl)malonate

**[0681]** In the same manner as in Example 117 (1), the object compound was obtained using 3-cyanobenzyl bromide (4.22 g). This was subjected to hydrolysis in the same manner as in Example 117 (2) to give the title compound (6.32 g) as an oil.

(2) 2-(3-cyanobenzyl)-3-oxo-3-[[E)-styrylsulfonyl]amino]propionic acid

**[0682]** In the same manner as in Example 152 (3), the object compound was obtained using the above-mentioned compound (3.16 g) and trans-β-styrenesulfonamide (2.47 g). This was subjected to hydrolysis in the same manner as in Example 1 (3) to give the title compound (4.04 g) as a white powder.

(3) 2-(3-cyanobenzyl)-N-(4-fluorophenyl)-N-isopropyl-N'-((E)-styrylsulfonyl)malonamide

**[0683]** In the same manner as in Example 1 (4), the title compound (668 mg) was obtained as a white powder using the above-mentioned compound (4.04 g) and 4-fluoro-N-isopropylaniline (1.61 g).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ0.96(6H, brs), 2.99-3.03(1H, m), 3.15-3.25(2H, m), 4.87-4.93(1H, m), 5.82-5.85(1H, m), 6.89-6.96(2H, m), 7.01-7.10(2H, m), 7.30-7.37(3H, m), 7.39-7.43(3H, m), 7.46-7.58(3H, m), 7.73(1H, d, J = 15.6Hz),

10.14(1H, brs).  
MS: 520 (M+H)<sup>+</sup>.

Example 315 Synthesis of 2-(3-cyanobenzyl)-N-(4-fluorophenyl)-N-isopropyl-N'-(2-naphthylsulfonyl)malonamide

(1) 2-(3-cyanobenzyl)-3-oxo-3-[(2-naphthylsulfonyl)amino]propionic acid

**[0684]** In the same manner as in Example 152 (3), the object compound was obtained using the compound (3.16 g) obtained in Example 314 (1). This was subjected to hydrolysis in the same manner as in Example 1 (3) to give the title compound (3.96 g) as a white powder.

(2) 2-(3-cyanobenzyl)-N-(4-fluorophenyl)-N-isopropyl-N'-(2-naphthylsulfonyl)malonamide

**[0685]** In the same manner as in Example 1 (4), the title compound (2.05 g) was obtained as a white powder using the above-mentioned compound (3.96 g) and 4-fluoro-N-isopropylaniline (1.49 g).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ0.97(6H, brs), 2.85-2.97(1H, m), 3.03-3.14(2H, m), 4.84-4.91(1H, m), 5.90-5.86(1H, m), 6.65-6.69(1H, m), 6.86-6.94(2H, m), 7.10-7.12(1H, m), 7.21-7.24 (1H, m), 7.44-7.50(2H, m), 7.62-7.69(3H, m), 7.71-8.07(4H, m), 8.70(1H, s).

MS: 544(M+H)<sup>+</sup>.

Example 316 Synthesis of 2-(4-chlorobenzyl)-N-(4-fluorophenyl)-N-isopropyl-N'-(2-naphthylsulfonyl)malonamide

**[0686]** In the same manner as in Example 13, the title compound (358 mg) was obtained as a white powder using the compound (418 mg) obtained in Example 267 (1) and 4-fluoro-N-isopropylaniline (184 mg).

<sup>1</sup>H-MMR(300Mz, DMSO-d<sub>6</sub>)δ0.62-0.98(6H, m), 2.60-2.82(1H, m), 2.82-3.13(1H, m), 3.15-3.45(1H, m), 4.49-4.78(1H, m), 6.60-7.00(5H, m), 7.00-7.19(2H, m), 7.19-7.40(1H, m), 7.60-7.85(3H, m), 7.97-8.35(3H, m), 8.54(1H, s), 11.98(1H, brs).

MS: 553(M+H)<sup>+</sup>.

Example 317 Synthesis of 2-(4-chlorobenzyl)-N-isopropyl-N'-(2-naphthylsulfonyl)-N-(3-pyridyl)malonamide hydrochloride

**[0687]** In the same manner as in Example 13, the object compound was obtained using the compound (418 mg) obtained in Example 267 (1) and 3-(isopropylamino)pyridine (163 mg). This was dissolved in ethanol, 1 mol/L hydrochloric acid was added, and the mixture was concentrated under reduced pressure to give the title compound (74 mg) as a white solid.

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.60-1.08(6H, m), 2.39-3.10(2H, m), 3.20-3.53(1H, m), 4.48-4.78(1H, m), 6.60-7.20(4H, m), 7.25-7.90(5H, m), 7.95-8.30(3H, m), 8.30-8.60(2H, m), 8.68-8.91(1H, m), 12.00(1H, brs).

MS: 536(M+H)<sup>+</sup>.

Example 318 Synthesis of 2-(3-chlorobenzyl)-N-(4-fluorophenyl)-N-isopropyl-N'-((E)-styrylsulfonyl)malonamide

(1) monoethyl (3-chlorobenzyl)malonate

**[0688]** In the same manner as in Example 117 (1), the object compound was obtained using 3-chlorobenzyl bromide (3.46 g). This was subjected to hydrolysis in the same manner as in Example 117 (2) to give the title compound (5.72 g) as an oil.

(2) 2-(3-chlorobenzyl)-3-oxo-3-[(E)-styrylsulfonyl]amino]propionic acid

**[0689]** In the same manner as in Example 152 (3), the object compound was obtained using the above-mentioned compound (2.86 g) and trans-β-styrenesulfonamide (2.16 g). This was subjected to hydrolysis in the same manner as in Example 1 (3) to give the title compound (4.36 g) as a white powder.

(3) 2-(3-chlorobenzyl)-N-(4-fluorophenyl)-N-isopropyl-N'-((E)-styrylsulfonyl)malonamide

**[0690]** In the same manner as in Example 1 (4), the title compound (1.89 g) was obtained as a white powder using the above-mentioned compound (4.36 g) and 4-fluoro-N-isopropylaniline (1.70 g).

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<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ0.92(6H, brs), 1.55-2.98(1H, m), 3.12-3.20 (2H, m), 4.89-4.93(1H, m), 5.63-5.67(1H, m), 6.83-6.95(3H, m), 7.01-7.07(3H, m), 7.18-7.26(1H, m), 7.27-7.29(1H, m), 7.40-7.45(3H, m), 7.52-7.54(2H, m), 7.73(1H, d, J = 15.4Hz), 10.24(1H, brs).  
MS: 531(M+H)<sup>+</sup>.

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Example 319 Synthesis of 2-(3-chlorobenzyl)-N-(4-fluorophenyl)-N-isopropyl-N'-(2-naphthylsulfonyl)malonamide

(1) 2-(3-chlorobenzyl)-3-oxo-3-[(2-naphthylsulfonyl)amino]propionic acid

10 **[0691]** In the same manner as in Example 152 (3), the object compound was obtained using the compound (2.86 g) obtained in Example 318 (1). This was subjected to hydrolysis in the same manner as in Example 1 (3) to give the title compound (4.37 g) as a white powder.

(2) 2-(3-chlorobenzyl)-N-(4-fluorophenyl)-N-isopropyl-N'-(2-naphthylsulfonyl)malonamide

15 **[0692]** In the same manner as in Example 1 (4), the title compound (970 mg) was obtained as a white powder using the above-mentioned compound (4.37 g) and 4-fluoro-N-isopropylaniline (1.61 g).

20 <sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ0.88(6H, brs), 2.73-2.76(1H, m), 2.99-3.09(2H, m), 4.86-4.89(1H, m), 5.62-5.66(1H, m), 6.65-6.70(1H, m), 6.79-6.84(2H, m), 6.88-6.93(2H, m), 7.09-7.21(1H, m), 7.22-7.26(1H, m), 7.61-7.70(2H, m), 7.91-8.00(5H, m), 8.67(1H, s), 10.37(1H, brs).  
MS: 555(M+H)<sup>+</sup>.

Example 320 Synthesis of N-(4-fluorophenyl)-N-isopropyl-N'-((E)-styrylsulfonyl)-2-(3-trifluoromethylbenzyl)malonamide  
(1) monoethyl (3-trifluoromethylbenzyl)malonate

25 **[0693]** In the same manner as in Example 117 (1), the object compound was obtained using 3-trifluoromethylbenzyl bromide (5.00 g). This was subjected to hydrolysis in the same manner as in Example 117 (2) to give the title compound (6.72 g) as an oil.

30 <sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1-19-1.27(3H, m), 3.30-3.34(2H, m), 3.69-3.77(1H, m), 4.10-4.21(2H, m), 7.41-7.51(4H, m).

(2) 3-[N-(4-fluorophenyl)-N-isopropylamino]-3-oxo-2-(3-trifluoromethylbenzyl)propionic acid

35 **[0694]** In the same manner as in Example 1 (4), the object compound was obtained using the above-mentioned compound (6.72 g) and 4-fluoro-N-isopropylaniline (3.55 g). This was subjected to hydrolysis in the same manner as in Example 1 (3) to give the title compound (348 mg) as a white powder.

(3) N-(4-fluorophenyl)-N-isopropyl-N'-((E)-styrylsulfonyl)-2-(3-trifluoromethylbenzyl)malonamide

40 **[0695]** In the same manner as in Example 1 (2), the title compound (47 mg) was obtained as a white powder using the above-mentioned compound (800 mg) and trans-β-styrenesulfonamide (370 mg).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ0.92-0.94(6H, m), 3.05-3.06(1H, m), 3.17-3.23(2H, m), 4.90-4.91(1H, m), 6.80-6.82(1H, m), 6.93(2H, m), 7.00-7.05(2H, m), 7.12-7.14(2H, m), 7.41-7.57(7H, m), 7.73(1H, d, J = 15.4Hz).  
MS: 563(M+H)<sup>+</sup>.

45 Example 321 Synthesis of N-(4-fluorophenyl)-N-isopropyl-N'-(2-naphthylsulfonyl)-2-(3-trifluoromethylbenzyl)malonamide

**[0696]** In the same manner as in Example 1 (2), the title compound (193 mg) was obtained as a white powder using the compound (800 mg) obtained in Example 320 (2).

50 <sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ0.88-0.93(6H, m), 1.56-2.86(1H, m), 3.02-3.12(2H, m), 5.82-5.85(1H, m), 6.70-6.72(1H, m), 6.73-6.83(1H, m), 6.89-6.95(3H, m), 7.32-7.34(2H, m), 7.62-7.71(3H, m), 7.89-8.00(4H, m), 8.50(1H, s), 8.66(1H, brs).  
MS: 587(M+H)<sup>+</sup>.

Example 322 Synthesis of 2-(4-fluorobenzyl)-N-isopropyl-N-(3-pyridyl)-N'-((E)-styrylsulfonyl)malonamide

55 **[0697]** In the same manner as in Example 13, the title compound (390 mg) was obtained as a white powder using the compound (1.00 g) obtained in Example 308 (2) and 3-(isopropylamino)pyridine (433 mg).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.69-0.97(6H, m), 2.70-3.43(3H, m), 4.57-4.80(1H, m), 6.80-7.60(11H, m), 7.60-7.86(2H,

m), 7.91-8.32(1H, m), 8.66(1H, s), 11.10-12.40(1H, m).

MS: 496(M+H)<sup>+</sup>.

Example 323 Synthesis of 2-(4-fluorobenzyl)-N-(4-fluorophenyl)-N'-(E)-styrylsulfonylmalonamide

**[0698]** In the same manner as in Example 13, the title compound (250 mg) was obtained as a white powder using the compound (377 mg) obtained in Example 308 (2) and 4-fluoro-N-(3-pentyl)aniline (218 mg).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.59(3H, t, J = 7.2Hz), 0.78(3H, t, J = 7.2Hz), 0.90-1.33(4H, m), 2.69-2.90(1H, m), 2.90-3.10(1H, m), 3.15-3.50(1H, m), 4.20-4.43(1H, m), 6.58-7.84(13H, m), 7.84-7.96(2H, m), 11.69(1H, brs).

MS: 541(M+H)<sup>+</sup>.

Example 324 Synthesis of N-cyclohexyl-2-(4-fluorobenzyl)-N-(4-fluorophenyl)-N'-(E)-styrylsulfonylmalonamide

**[0699]** In the same manner as in Example 13, the title compound (217 mg) was obtained as a white powder using the compound (377 mg) obtained in Example 308 (2) and 4-fluoro-N-cyclohexylaniline (232 mg).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.60-0.98(3H, m), 1.02-1.35(2H, m), 1.35-1.75(5H, m), 2.70-2.90(1H, m), 2.90-3.10(1H, m), 3.18-3.47(1H, m), 4.14-4.37(1H, m), 6.68-6.90(1H, m), 6.90-7.17(6H, m), 7.17-7.40(2H, m), 7.40-7.68(4H, m), 7.69-7.90(2H, m), 11.68(1H, brs).

MS: 553(M+H)<sup>+</sup>.

Example 325 Synthesis of 2-(4-fluorobenzyl)-N-(4-fluorophenyl)-N'-(E)-styrylsulfonyl-N-(4-tetrahydropyranyl)malonamide

**[0700]** In the same manner as in Example 13, the title compound (184 mg) was obtained as a white powder using the compound (377 mg) obtained in Example 308 (2) and 4-fluoro-N-(4-tetrahydropyranyl)aniline (234 mg).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.90-1.20(2H, m), 1.33-1.68(2H, m), 2.74-2.92(1H, m), 2.92-3.10(1H, m), 3.15-3.54(3H, m), 3.64-3.85(2H, m), 4.19-4.30(1H, m), 6.70-7.16(7H, m), 7.16-7.38(2H, m), 7.38-7.67(4H, m), 7.67-7.90(2H, m), 11.70(1H, brs).

MS: 555(M+H)<sup>+</sup>.

Example 326 Synthesis of 2-(4-fluorobenzyl)-N-(4-fluorophenyl)-N'-(E)-styrylsulfonyl-N-(1-methyl-4-piperidinyl)malonamide

**[0701]** In the same manner as in Example 13, the title compound (250 mg) was obtained as a white powder using the compound (377 mg) obtained in Example 308 (2) and 4-fluoro-N-(1-methyl-4-piperidinyl)aniline (250 mg).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ1.00-1.40(2H, m), 1.51-1.70(1H, m), 1.70-1.90(1H, m), 2.60(3H, s), 2.70-3.70(7H, m), 4.45-4.70(1H, m), 6.10(1H, brs), 6.77-7.25(8H, m), 7.25-7.63(6H, m), 8.80(1H, brs).

MS: 568 (M+H)<sup>+</sup>.

Example 327 Synthesis of 2-(4-fluorobenzyl)-N-(4-fluorophenyl)-N-isobutyl-N'-(E)-styrylsulfonylmalonamide

**[0702]** In the same manner as in Example 13, the title compound (160 mg) was obtained as a white powder using the compound (377 mg) obtained in Example 308 (2) and 4-fluoro-N-isobutylaniline (201 mg).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.67(3H, t, J = 6.6Hz), 0.77(3H, t, J = 6.6Hz), 1.37-1.60(1H, m), 2.77-2.92(1H, m), 2.92-3.10(1H, m), 3.14-3.55(3H, m), 6.80-7.37(9H, m), 7.37-7.65(4H, m), 7.68-7.89(2H, m), 11.72(1H, brs).

MS:527(M+H)<sup>+</sup>.

Example 328 Synthesis of 2-(4-fluorobenzyl)-N-isopropyl-N'-(E)-styrylsulfonyl-N-(3-trifluoromethylphenyl)malonamide

**[0703]** In the same manner as in Example 13, the title compound (158 mg) was obtained as a white powder using the compound (377 mg) obtained in Example 308 (2) and N-isopropyl-3-trifluoromethylaniline (244 mg).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.68-1.03(6H, m), 2.75-3.53(3H, m), 4.59-4.89(1H, m), 6.74-7.96(15H, m), 11.70(1H, brs).

MS: 563(M+H)<sup>+</sup>.

Example 329 Synthesis of 2-(4-fluorobenzyl)-N, N-diisopropyl-N'-(E)-styrylsulfonylmalonamide

**[0704]** In the same manner as in Example 13, the title compound (88 mg) was obtained as a white powder using the compound (870 mg) obtained in Example 308 (2) and diisopropylamine (646 μL).

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<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ1.01(6H, d, J = 6.6Hz), 1.09-1.30(6H, m), 2.89-3.10(2H, m), 3.19-3.48(1H, m), 3.74-3.89(1H, m), 3.89-4.05(1H, m), 6.98(2H, t, J = 8.7Hz), 7.10-7.34(3H, m), 7.37-7.60(4H, m), 7.60-7.92(2H, m), 11.94(1H, brs).  
MS:461(M+H)<sup>+</sup>.

5 Example 330 Synthesis of N-ethyl-2-(4-fluorobenzyl)-N-isopropyl-N'-((E)-styrylsulfonyl)malonamide

**[0705]** In the same manner as in Example 13, the title compound (104 mg) was obtained as a white powder using the compound (377 mg) obtained in Example 308 (2) and N-ethylisopropylamine (174 mg).

10 <sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.75-1.15(9H, m), 2.90-3.25(4H, m), 3.68-4.40(2H, m), 6.91-7.08(2H, m), 7.12-7.38(3H, m), 7.38-7.58(4H, m), 7.64-7.80(2H, m), 12.01 (1H, brs).  
MS: 447(M+H)<sup>+</sup>.

15 Example 331 Synthesis of N-ethyl-N'-[(5-isobutyl-2-biphenyl)sulfonyl]-2-(4-nitrobenzyl)-N-phenylmalonamide (1) 3-[[[(5-isobutyl-2-biphenyl)sulfonyl]amino]-2-(4-nitrobenzyl)-3-oxopropionic acid

20 **[0706]** In the same manner as in Example 1 (2), the object compound was obtained using the compound (1.01 g) obtained in Example 178 (2) and 5-isobutylbiphenyl-2-sulfonamide (1.09 g). This was subjected to hydrolysis in the same manner as in Example 1 (3) to give the title compound (1.58 g) as an oil. <sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ0.85-0.98(6H, m), 1.90-1.94(1H, m), 2.54-2.59(2H, m), 3.19-3.23(1H, m), 3.35-3.37(2H, m), 7.05-7.07(2H, m), 7.11-7.43(6H, m), 8.06-8.15(2H, m), 8.17-8.20(2H, m).

(2) N-ethyl-N'-[(5-isobutyl-2-biphenyl)sulfonyl]-2-(4-nitrobenzyl)-N-phenylmalonamide

25 **[0707]** In the same manner as in Example 1 (4), the title compound (323 mg) was obtained as a white powder using the above-mentioned compound (1.58 g) and N-ethylaniline (380 mg).

30 <sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.85-0.92(9H, m), 1.85-1.87(1H, m), 2.54(2H, d, J = 6.9Hz), 2.75-2.76(1H, m), 2.88-2.91(1H, m), 3.19-3.20(1H, m), 3.31-3.39(1H, m), 3.64-3.65(1H, m), 7.02-7.05(7H, m), 7.27-7.42(7H, m), 7.95-8.05(3H, m), 11.68(1H, brs).  
MS: 614(M+H)<sup>+</sup>.

35 Example 332 Synthesis of 2-(4-aminobenzyl)-N-ethyl-N'-[(5-isobutyl-2-biphenyl)sulfonyl]-N-phenylmalonamide

**[0708]** In the same manner as in Example 7, the title compound (183 mg) was obtained as a white powder using the compound (250 mg) obtained in Example 331 at room temperature.

40 <sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.86-0.93(9H, m), 1.86-1.93(2H, m), 2.55-2.57(2H, m), 2.69-2.76(2H, m), 3.64-3.71(1H, m), 3.97-4.02(1H, m), 6.75(2H, d, J = 8.1Hz), 7.05-7.07(6H, m), 7.19-7.43(8H, m), 7.97(1H, d, J = 8.1Hz).  
MS: 584(M+H)<sup>+</sup>.

45 Example 333 Synthesis of N'-(3-biphenylsulfonyl)-N-ethyl-2-(4-nitrobenzyl)-N-phenylmalonamide

(1) 3-[[[(3-biphenylsulfonyl)amino]-2-(4-nitrobenzyl)-3-oxopropionic acid

50 **[0709]** In the same manner as in Example 1 (2), the object compound was obtained using the compound (1.01 g) obtained in Example 178 (2) and biphenyl-3-sulfonamide (880 mg). This was subjected to hydrolysis in the same manner as in Example 1 (3) to give the title compound (1.17 g) as an oil.

(2) N'-(3-biphenylsulfonyl)-N-ethyl-2-(4-nitrobenzyl)-N-phenylmalonamide

55 **[0710]** In the same manner as in Example 1 (4), the title compound (382 mg) was obtained as a white powder using the above-mentioned compound (1.17 g) and N-ethylaniline (330 mg).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.87 (3H, t, J = 6.9Hz), 2.94-2.96(1H, m), 3.02-3.05(1H, m), 3.37-3.58(3H, m), 6.94(2H, d, J = 7.2Hz), 7.10(2H, d, J = 8.4Hz), 7.27-7.30(3H, m), 7.45-7.53(3H, m), 7.68-7.79(4H, m), 7.95-7.98(2H, m), 8.04-8.05(2H, m), 12.07(1H, brs).  
MS: 558 (M+H)<sup>+</sup>.

Example 334 Synthesis of 2-(4-aminobenzyl)-N'-(3-biphenylsulfonyl)-N-ethyl-N-phenylmalonamide

**[0711]** In the same manner as in Example 7, the title compound (237 mg) was obtained as a white powder using the

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compound (280 mg) obtained in Example 333 at room temperature.

$^1\text{H-NMR}$ (300Mz,  $\text{DMSO-d}_6$ ) $\delta$ 0.87-0.88(3H, brs), 2.67-2.68(2H, m), 3.55-3.57(3H, m), 6.29-6.41(4H, m), 6.94-6.50(2H, m), 7.29-7.30(3H, m), 7.44-7.51(3H, m), 7.71-7.79(4H, m), 8.01-8.06(2H, m).

MS: 528(M+H) $^+$ .

5

Example 335 Synthesis of N-ethyl-2-(4-nitrobenzyl)-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

(1) ethyl 3-(N-ethyl-N-phenylamino)-2-(4-nitrobenzyl)-3-oxopropionate

10 **[0712]** To a solution of the compound (3.00 g) obtained in Example 178 (2) in methylene chloride (10 mL) were added oxalyl chloride (1.43 mL) and DMF in catalytic amount under ice-cooling, and the mixture was stirred for 1 hr. After concentration under reduced pressure, the residue was dissolved in THF (10 mL), N-ethylaniline (1.55 mL) was added, and the mixture was stirred at room temperature for 1 hr. 1 mol/L Hydrochloric acid (100 mL) and ethyl acetate (100 mL) were added to extract the reaction mixture, and the organic layer was concentrated. The residue was purified by silica gel column chromatography to give the title compound (2.43 g) as an oil.

15  $^1\text{H-NMR}$ (300Mz,  $\text{CDCl}_3$ ) $\delta$ 1.01-1.06(3H, m), 1.23-1.28(3H, m), 3.18-3.20(1H, m), 3.46-3.47(1H, m), 3.60-3.63(1H, m), 3.68-3.71(2H, m), 4.12-4.16(2H, m), 7.21-7.32(7H, m), 8.10-8.13(2H, m).

(2) 3-(N-ethyl-N-phenylamino)-2-(4-nitrobenzyl)-3-oxopropionic acid

20 **[0713]** In the same manner as in Example 1 (3), the title compound (1.35 g) was obtained as a white powder using the above-mentioned compound (2.43 g).

$^1\text{H-NMR}$ (300Mz,  $\text{CDCl}_3$ ) $\delta$ 1.04-1.09(3H, m), 3.13-3.18(1H, m), 3.26-3.29(1H, m), 3.52-3.65(2H, m), 3.75-3.77(1H, m), 7.17-7.20(3H, m), 7.34-7.36(4H, m), 8.11-8.14(2H, m).

25

(3) N-ethyl-2-(4-nitrobenzyl)-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

30 **[0714]** To a solution of the above-mentioned compound (340 mg) in methylene chloride (10 mL) were added oxalyl chloride (500  $\mu\text{L}$ ) and DMF in catalytic amount under ice-cooling, and the mixture was stirred for 1 hr. After concentration under reduced pressure, the residue was dissolved in THF (10 mL) under ice-cooling, trans- $\beta$ -styrenesulfonamide (180 mg) and 60% sodium hydride (80 mg) were added, and the mixture was stirred for 1 hr. 1 mol/L Hydrochloric acid (100 mL) and ethyl acetate (50 mL) were added to extract the reaction mixture, and the organic layer was concentrated. The residue was purified by silica gel column chromatography to give the title compound (270 mg) as a white powder.

35  $^1\text{H-NMR}$ (300Mz,  $\text{DMSO-d}_6$ ) $\delta$ 0.89(3H, t, J = 6.9Hz), 2.97-3.01 (1H, m), 3.11-3.19(1H, m), 3.48-3.60(3H, m), 7.00-7.07(2H, m), 7.21-7.28(3H, m), 7.38-7.39(3H, m), 7.45-7.47(4H, m), 7.74-7.75(2H, m), 8.02-8.04(2H, m), 11.73(1H, brs).

Example 336 Synthesis of 2-(4-aminobenzyl)-N-ethyl-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

40 **[0715]** In the same manner as in Example 137 (4), the title compound (93 mg) was obtained as a white powder using the compound (110 mg) obtained in Example 335 at room temperature.

$^1\text{H-NMR}$ (300Mz,  $\text{DMSO-d}_6$ ) $\delta$ 0.89(3H, brs), 2.70-2.71(1H, m), 2.86-2.87(1H, m), 3.00-3.04(1H, m), 3.54-3.55(2H, m), 7.01-7.10(4H, m), 7.12-7.13(2H, m), 7.28(1H, d, J = 15.3Hz), 7.37-7.38(3H, m), 7.48-7.49(3H, m), 7.56(1H, d, J = 15.3Hz), 7.92-7.93(2H, m).

MS: 478(M+H) $^+$ .

45

Example 337 Synthesis of 2-[4-(benzoylamino)benzyl]-N-ethyl-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

**[0716]** In the same manner as in Example 9, the title compound (32 mg) was obtained as a white solid using the compound (33 mg) obtained in Example 336.

50  $^1\text{H-NMR}$ (400Mz,  $\text{DMSO-d}_6$ ) $\delta$ 0.93(3H, t, J = 7.2Hz), 2.82-3.03(2H, m), 3.43-3.57(2H, m), 2.57-2.69(1H, m), 6.88(2H, d, J = 8.0Hz), 7.10 (2H, brs), 7.28(1H, d, J = 15.2Hz), 7.36-7.63 (12H, m), 7.73-7.83(2H, m), 7.93(2H, d, J = 7.2Hz), 10.13(1H, s), 11.76(1H, brs).

MS: 582 (M+H) $^+$ .

55

Example 338 Synthesis of 2-(4-aminobenzyl)-N-ethyl-N'-phenethylsulfonyl-N-phenylmalonamide

**[0717]** In the same manner as in Example 7, the title compound (118 mg) was obtained as a white powder using the compound (130 mg) obtained in Example 335 at room temperature.  $^1\text{H-NMR}$ (400Mz,  $\text{DMSO-d}_6$ ) $\delta$ 0.89(3H, brs),

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2.84-3.00(3H, m), 3.55-3.62(6H, m), 6.89-7.03(3H, m), 7.14-7.31(4H, m), 7.38-7.44(3H, m), 7.49-7.59(3H, m), 7.78-7.79(1H, m).  
MS: 480(M+H)<sup>+</sup>.

### 5 Example 339 Synthesis of N'-benzylsulfonyl-N-ethyl-2-(4-nitrobenzyl)-N-phenylmalonamide

**[0718]** In the same manner as in Example 1 (2), the title compound (112 mg) was obtained as a white powder using the compound (100 mg) obtained in Example 335 (2) and benzylsulfonamide (50 mg).

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ0.95(3H, brs), 2.90-2.95(1H, m), 3.08-3.19(1H, m), 3.44-3.64(2H, m), 3.66-3.73(1H, m), 4.63(2H, s), 7.12-7.21(2H, m), 7.30-7.32(4H, m), 7.34-7.37(3H, m), 7.47-7.50(3H, m), 8.12-8.22(2H, m), 11.57(1H, brs).  
MS: 496(M+H)<sup>+</sup>.

### Example 340 Synthesis of 2-(4-aminobenzyl)-N'-benzylsulfonyl-N-ethyl-N-phenylmalonamide

**[0719]** In the same manner as in Example 7, the title compound (310 mg) was obtained as a white powder using the compound (490 mg) obtained in Example 339 at room temperature.

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ0.95(3H, brs), 2.74-2.79 (2H, m), 3.38-3.43(1H, m), 3.46-3.55(1H, m), 3.66-3.75(1H, m), 4.58(2H, s), 6.38-6.52(4H, m), 7.10-7.28(4H, m), 7.30-7.37(3H, m), 7.45-7.48(3H, m).  
MS: 466(M+H)<sup>+</sup>.

20

### Example 341 Synthesis of N-ethyl-2-(4-nitrobenzyl)-N-phenyl-N'-propylsulfonylmalonamide

**[0720]** In the same manner as in Example 1 (2), the title compound (379 mg) was obtained as a white powder using the compound (500 mg) obtained in Example 335 (2) and propylsulfonamide (180 mg).

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ0.95(6H, m), 1.46-1.61(2H, m), 3.01-3.05(1H, m), 3.13-3.19(1H, m), 3.23-3.32(2H, m), 3.49-3.56(1H, m), 3.61-3.67(2H, m), 7.17 (2H, d, J = 6.4Hz), 7.23(2H d, J = 8.4Hz), 7.48-7.51(3H, m), 8.12(2H, d, J = 8.4Hz), 11.59(1H, brs).  
MS: 448 (M+H)<sup>+</sup>.

### 30 Example 342 Synthesis of 2-(4-aminobenzyl)-N-ethyl-N-phenyl-N'-propylsulfonylmalonamide

**[0721]** In the same manner as in Example 7, the title compound (127 mg) was obtained as a white powder using the compound (200 mg) obtained in Example 341 at room temperature.

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ0.95(6H, m), 1.56-1.70(2H, m), 2.76(2H, d, J = 6.8Hz), 3.21-3.25(2H, m), 3.37-3.66(2H, m), 3.68-3.71(1H, m), 6.36(2H d, J = 8.0Hz), 6.48 (2H, d, J = 8.0Hz), 7.17-7.28(2H, m), 7.43-7.49(3H, m).  
MS: 418(M+H)<sup>+</sup>.

### Example 343 Synthesis of 2-(3-bromobenzyl)-N-ethyl-N'-(2-naphthylsulfonyl)-N-phenylmalonamide

#### 40 (1) diethyl (3-bromobenzyl)malonate

**[0722]** In the same manner as in Example 6 (1), the title compound (12.5 g) was obtained as an oil using 3-bromobenzyl bromide (35.0 g).

<sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ1.15-1.31(6H, m), 3.16-3.19(2H, m), 3.60-3.62(1H, m), 4.09-4.22(4H, m), 7.10-7.15(2H, m), 7.30-7.34(1H, m), 7.63-7.39(1H, m).

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#### (2) monoethyl (3-bromobenzyl)malonate

**[0723]** In the same manner as in Example 1 (1), the title compound (6.54 g) was obtained as an oil using the above-mentioned compound (7.00 g).

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#### (3) 2-(3-bromobenzyl)-3-(N-ethyl-N-phenylamino)-3-oxopropionic acid

**[0724]** In the same manner as in Example 335 (1), the object compound was obtained using the above-mentioned compound (6.54 g). This was subjected to hydrolysis in the same manner as in Example 1 (3) to give the title compound (5.36 g) as a white powder.

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<sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ1.20-1.27(3H, m), 2.99-3.03(1H, m), 3.13-3.19 (1H, m), 3.45-3.49(1H, m), 3.66-3.71(2H, m), 6.99-7.00 (1H, m), 7.14-7.26(3H, m), 7.33-7.47(5H, m).

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(4) 2-(3-bromobenzyl)-N-ethyl-N'-(2-naphthylsulfonyl)-N-phenylmalonamide

**[0725]** In the same manner as in Example 1 (2), the title compound (284 mg) was obtained as a white powder using the above-mentioned compound (300 mg).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.94-0.97(3H, m), 2.92-2.95(2H, m), 3.49-3.54(2H, m), 3.62-3.70(1H, m), 6.83-6.89(2H, m), 6.97-7.04(2H, m), 7.13-7.53(5H, m), 7.60-7.80(3H, m), 8.10-8.30(3H, m), 12.12(1H, brs).

MS: 567(M+H)<sup>+</sup>.

Example 344 Synthesis of 2-(3-bromobenzyl)-N-ethyl-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

**[0726]** In the same manner as in Example 1 (2), the title compound (307 mg) was obtained as a white powder using the compound (540 mg) obtained in Example 343 (3) and trans-β-styrenesulfonamide (260 mg).

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ1.17(3H, t, J = 7.2Hz), 2.86-2.90(1H, m), 2.97-3.03(1H, m), 3.39-3.57(3H, m), 6.95-6.97(1H, m), 7.03(2H, brs), 7.08-7.15(2H, m), 7.22-7.35(2H, m), 7.42-7.50(3H, m), 7.50-7.59(4H, m), 7.80-7.89(2H, m), 11.78(1H, brs).

MS: 545(M+H)<sup>+</sup>.

Example 345 Synthesis of 2-(4-bromobenzyl)-N-ethyl-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

(1) monoethyl (4-bromobenzyl)malonate

**[0727]** In the same manner as in Example 6 (1), the object compound was obtained using 4-bromobenzyl bromide (25.0 g). This was subjected to hydrolysis in the same manner as in Example 1 (1) to give the title compound (12.9 g) as an oil. <sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ1.21-1.28(3H, m), 3.18-3.21(2H, m), 3.80-3.83(1H, m), 4.08-4.16(2H, m), 7.07-7.10(2H, m), 7.39-7.43(2H, m).

(2) 2-(4-bromobenzyl)-3-(N-ethyl-N-phenylamino)-3-oxopropionic acid

**[0728]** In the same manner as in Example 1 (4), the object compound was obtained using the above-mentioned compound (5.00 g) and N-ethylaniline (2.40 g). This was subjected to hydrolysis in the same manner as in Example 1 (3) to give the title compound (5.28 g) as a white powder.

(3) 2-(4-bromobenzyl)-N-ethyl-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

**[0729]** In the same manner as in Example 1 (2), the title compound (965 mg) was obtained as a white powder using the above-mentioned compound (2.00 g) and trans-β-styrenesulfonamide (970 mg).

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ1.09(3H, t, J = 7.2Hz), 2.83-2.88(1H, m), 2.95-3.00(1H, m), 3.44-3.59(2H, m), 3.61-3.66(1H, m), 6.90(2H, d, J = 8.4Hz), 7.08(2H, brs), 7.27-7.50(6H, m), 7.50-7.80(4H, m), 8.31-8.32(2H, m), 11.77(1H, brs).

MS: 543 (M+H)<sup>+</sup>.

Example 346 Synthesis of 2-(4-bromobenzyl)-N-ethyl-N'-((E)-styrylsulfonyl)-N-phenylmalonamide

**[0730]** In the same manner as in Example 1 (2), the title compound (825 mg) was obtained as a white powder using the compound (2.00 g) obtained in Example 345 (2).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.85(3H, t, J = 7.2Hz), 2.76-2.84(2H, m), 3.40-3.52(3H, m), 6.74(2H, d, J = 8.1Hz), 6.92(2H, d, J = 7.5Hz), 7.19-7.30(5H, m), 7.71-7.78(3H, m), 8.07-8.23(3H, m), 8.53(1H, s), 12.06(1H, brs).

MS: 567(M+H)<sup>+</sup>.

Example 347 Synthesis of 2-(2-bromobenzyl)-N-ethyl-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

(1) monoethyl (2-bromobenzyl)malonate

**[0731]** In the same manner as in Example 6 (1), the object compound was obtained using 2-bromobenzyl bromide (25.0 g). This was subjected to hydrolysis in the same manner as in Example 1 (1) to give the title compound (25.9 g) as an oil.

<sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ1.18-1.26(3H, m), 3.35-3.39(2H, m), 3.88-3.93(1H, m), 4.11-4.20(2H, m), 7.08-7.14(1H, m), 7.20-7.24(2H, m), 7.53-7.56(1H, m).

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(2) 2-(2-bromobenzyl)-3-(N-ethyl-N-phenylamino)-3-oxopropionic acid

**[0732]** In the same manner as in Example 1 (4), the object compound was obtained using the above-mentioned compound (5.00 g) and N-ethylaniline (2.40 g). This was subjected to hydrolysis in the same manner as in Example 1 (3) to give the title compound (4.22 g) as a white powder.

<sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ1.00-1.06(3H, m), 3.22-3.28(2H, m), 3.61-3.62(1H, m), 3.71-3.74(2H, m), 7.14-7.24(3H, m), 7.32-7.48(1H, m).

(3) 2-(2-bromobenzyl)-N-ethyl-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

**[0733]** In the same manner as in Example 1 (2), the title compound (1.02 g) was obtained as a white powder using the above-mentioned compound (2.17 g) and trans-β-styrenesulfonamide (1.05 g).

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ0.93(3H, t, J = 6.8Hz), 2.98-3.01(2H, m), 3.56-3.81(3H, m), 7.09-7.12(4H, m), 7.19-7.37(2H, m), 7.47-7.48(3H, m), 7.50-7.55(5H, m), 7.78-7.78(2H, m), 11.63(1H, brs).

MS: 543 (M+H)<sup>+</sup>.

Example 348 Synthesis of 2-(2-bromobenzyl)-N-ethyl-N'-(2-naphthylsulfonyl)-N-phenylmalonamide

**[0734]** In the same manner as in Example 1 (2), the title compound (1.18 g) was obtained as a white powder using the compound (2.04 g) obtained in Example 347 (2).

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ0.90(3H, brs), 2.91-2.92(1H, m), 3.05-3.06(1H, m), 3.62-3.79(3H, m), 6.82-7.05(5H, m), 7.19-7.28(3H, m), 7.33-7.44(1H, m), 7.74-7.78(3H, m), 8.10-8.13(3H, m), 8.52(1H, s), 11.97(1H, brs).

MS: 567 (M+H)<sup>+</sup>.

Example 349 Synthesis of N-ethyl-2-[2-(1-naphthyl)ethyl]-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

(1) 2, 2-dimethyl-5-[2-(1-naphthyl)ethyl]-1,3-dioxane-4, 6-dione

**[0735]** In the same manner as in Example 132 (1), the title compound (3.02 g) was obtained as a pale-yellow powder using 1-naphthaleneacetic acid (3.72 g).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.76(3H, s), 1.79 (3H, s), 2.51-2.56(2H, m), 3.27-3.31(2H, m), 3.57-3.60(1H, m), 7.37-7.58(4H, m), 7.34-7.76(1H, m), 7.85-7.87(1H, m), 8.19-8.21(1H, m).

(2) 3-(N-ethyl-N-phenylamino)-2-[2-(1-naphthyl)ethyl]-3-oxopropionic acid

**[0736]** In the same manner as in Example 119 (2), the title compound (2.50 g) was obtained as an oil using the above-mentioned compound (2.05 g) and N-ethylaniline (3.50 g). <sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.11-1.23(3H, m), 1.23-1.25(1H, m), 2.89-2.93(1H, m), 3.09-3.16(1H, m), 3.29-3.31(1H, m), 3.45-3.49(1H, m), 3.63-3.70(1H, m), 3.82-3.87(1H, m), 6.96-6.97(2H, m), 7.29-7.32(5H, m), 7.48-7.51(2H, m), 7.66-7.69(1H, m), 7.82-7.84(2H, m).

(3) N-ethyl-2-[2-(1-naphthyl)ethyl]-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

**[0737]** In the same manner as in Example 1 (2), the title compound (44 mg) was obtained as a white powder using the above-mentioned compound (1.00 g) and trans-β-styrenesulfonamide (530 mg).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.07(3H, brs), 2.14-2.23(2H, m), 2.60-2.71(2H, m), 3.18-3.22(1H, m), 3.64-3.77(1H, m), 3.79-3.82(1H, m), 6.91(2H, m), 7.04-7.16(4H, m), 7.39-7.52(6H, m), 7.53-7.54(2H, m), 7.65-7.68(3H, m), 7.73-7.78(2H, m), 10.49(1H, brs).

MS: 527(M+H)<sup>+</sup>.

Example 350 Synthesis of N-ethyl-2-[2-(1-naphthyl)ethyl]-N-phenyl-N'-(2-naphthylsulfonyl)malonamide

**[0738]** In the same manner as in Example 1 (2), the title compound (251 mg) was obtained as a white powder using the compound (1.00 g) obtained in Example 349 (2).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.10(3H, brs), 2.08-2.19(2H, m), 2.68-2.81(1H, m), 2.85-2.88(1H, m), 3.12-3.16(1H, m), 3.59-3.68(1H, m), 3.76-3.84(1H, m), 6.81-6.83(2H, m), 6.99-7.02(1H, m), 7.15-7.26(4H, m), 7.36-7.59(2H, m), 7.60-7.70(4H, m), 7.75-7.95(3H, m), 8.05-8.15(2H, m), 8.79(1H, s), 10.80(1H, brs). MS: 551(M+H)<sup>+</sup>.

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Example 351 Synthesis of N-ethyl-2-[2-(2-naphthyl)ethyl]-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

(1) 2, 2-dimethyl-5-[2-(2-naphthyl)ethyl]-1, 3-dioxane-4, 6-dione

5 **[0739]** In the same manner as in Example 132 (1), the title compound (6.55 g) was obtained as a pale-yellow powder using 2-naphthaleneacetic acid (3.72 g).

$^1\text{H-NMR}$ (400Mz,  $\text{CDCl}_3$ ) $\delta$ 1.72(3H, s), 1.76(3H, s), 2.49-2.54(2H, m), 3.01-3.05(2H, m), 3.50-3.53(1H, m), 7.38-7.48(3H, m), 7.67(1H, s), 7.78-7.83(3H, m).

10 (2) 3-(N-ethyl-N-phenylamino)-2-[2-(2-naphthyl)ethyl]-3-oxopropionic acid

**[0740]** In the same manner as in Example 119 (2), the title compound (2.19 g) was obtained as an oil using the above-mentioned compound (2.09 g) and N-ethylaniline (3.50 g).  $^1\text{H-NMR}$ (400Mz,  $\text{CDCl}_3$ ) $\delta$ 1.12-1.20(3H, m), 2.17-2.22(1H, m), 2.23-2.28(1H, m), 2.63-2.71(1H, m), 2.74-2.80(1H, m), 3.27-3.30(1H, m), 3.61-3.70(1H, m), 3.81-3.90(1H, m),

15 6.98-7.00(2H, m), 7.05-7.09(1H, m), 7.15-7.20(3H, m), 7.41-7.48(3H, m), 7.67-7.72(2H, m), 7.78-7.80(1H, m).

(3) N-ethyl-2-[2-(2-naphthyl)ethyl]-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

**[0741]** In the same manner as in Example 1 (2), the title compound (185 mg) was obtained as a white powder using the above-mentioned compound (1.00 g) and trans- $\beta$ -styrenesulfonamide (910 mg).

20  $^1\text{H-NMR}$ (400Mz,  $\text{CDCl}_3$ ) $\delta$ 1.12(3H, brs), 2.14-2.23(2H, m), 2.60-2.71(2H, m), 3.18-3.22(1H, m), 3.64-3.77(1H, m), 3.78-3.82(1H, m), 6.90-6.92(2H, m), 7.04-7.16(5H, m), 7.26-7.52(6H, m), 7.53-7.54(2H, m), 7.65-7.68(2H, m), 7.73-7.78(2H, m), 10.49(1H, brs).

MS:527(M+H) $^+$ .

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Example 352 Synthesis of N-ethyl-2-[2-(2-naphthyl)ethyl]-N'-(2-naphthylsulfonyl)-N-phenylmalonamide

**[0742]** In the same manner as in Example 1 (2), the title compound (284 mg) was obtained as a white powder using the compound (1.00 g) obtained in Example 351 (2).

30  $^1\text{H-NMR}$ (400Mz,  $\text{CDCl}_3$ ) $\delta$ 1.10(3H, brs), 2.03-2.10(2H, m), 2.42-2.52(2H, m), 3.06-3.09(1H, m), 3.58-3.65(1H, m), 3.74-3.81(1H, m), 6.75-6.77(2H, m), 7.00-7.02(4H, m), 7.30-7.35(1H, m), 7.41-7.44(2H, m), 7.59-7.76(4H, m), 7.89-7.91(1H, m), 7.95-7.97(1H, m), 8.01-8.03(1H, m), 8.04-8.05(2H, s), 8.70(1H, s), 10.62(1H, brs).

MS: 551(M+H) $^+$ .

35 Example 353 Synthesis of N-ethyl-2-[2-(4-methoxyphenyl)ethyl]-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

(1) 5-[2-(4-methoxyphenyl)ethyl]-2, 2-dimethyl-1, 3-dioxane-4, 6-dione

**[0743]** In the same manner as in Example 132 (1), the title compound (4.59 g) was obtained as a pale-yellow powder using 4-methoxyphenylacetic acid (3.32 g).

40  $^1\text{H-NMR}$ (400Mz,  $\text{CDCl}_3$ ) $\delta$ 1.73(3H, s), 1.79(3H, s), 2.34-2.41(2H, m), 2.77-2.83(2H, m), 3.44-3.47(1H, m), 3.79(3H, s), 6.83-6.86(2H, m), 7.16-7.25(2H, m).

(2) 3-(N-ethyl-N-phenylamino)-2-[2-(4-methoxyphenyl)ethyl]-3-oxopropionic acid

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**[0744]** In the same manner as in Example 119 (2), the title compound (2.10 g) was obtained as an oil using the above-mentioned compound (2.00 g) and N-ethylaniline (3.50 g).  $^1\text{H-NMR}$ (400Mz,  $\text{CDCl}_3$ ) $\delta$ 1.10-1.15(3H, m), 1.92-2.05(2H, m), 2.31-2.45(1H, m), 2.49-2.55(1H, m), 3.23-3.27(1H, m), 3.64-3.72(1H, m), 3.79(3H, s), 3.82-3.88(1H, m),

6.72-6.76(2H, m), 6.90-7.02(2H, m), 7.11-7.15(2H, m), 7.37-7.43(3H, m).

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(3) N-ethyl-2-[2-(4-methoxyphenyl)ethyl]-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

**[0745]** In the same manner as in Example 1 (2), the title compound (303 mg) was obtained as a white powder using the above-mentioned compound (1.00 g) and trans- $\beta$ -styrenesulfonamide (940 mg).

55  $^1\text{H-NMR}$ (400Mz,  $\text{CDCl}_3$ ) $\delta$ 1.15(3H, brs), 2.06-2.08(2H, m), 2.09-2.49(2H, m), 3.17(1H, t, J = 7.2Hz), 3.67-3.84(5H, m), 6.69-6.73(2H, m), 6.90-6.93(2H, m), 7.00-7.08(3H, m), 7.33-7.34(3H, m), 7.39-7.44(3H, m), 7.51-7.53(2H, m), 7.71-7.75(1H, m), 10.44(1H, brs).

MS: 507(M+H) $^+$ .

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### Example 354 Synthesis of N-ethyl-2-[2-(4-methoxyphenyl)ethyl]-N'-(2-naphthylsulfonyl)-N-phenylmalonamide

**[0746]** In the same manner as in Example 1 (2), the title compound (527 mg) was obtained as a white powder using the compound (1.00 g) obtained in Example 353 (2).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.09(3H, brs), 1.95-1.97(2H, m), 2.20-2.30(2H, m), 3.04(1H, t, J = 7.6Hz), 3.59-3.67(1H, m), 3.75-3.83(4H, m), 6.64-6.67(2H, m), 6.77-6.79(2H, m), 6.84-6.86(2H, m), 7.22-7.30(3H, m), 7.60-7.90(2H, m), 7.92-8.68(4H, m), 8.68(1H, s), 10.56(1H, brs).

MS: 531(M+H)<sup>+</sup>.

### Example 355 Synthesis of 2-[2-(3-bromophenyl)ethyl]-N-ethyl-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

(1) 5-[2-(3-bromophenyl)ethyl]-2, 2-dimethyl-1, 3-dioxane-4, 6-dione

**[0747]** In the same manner as in Example 132 (1), the title compound (4.74 g) was obtained as a pale-yellow powder using 3-bromophenylacetic acid (4.30 g).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.77(6H, s), 2.37-2.42(2H, m), 2.79-2.83(2H, m), 3.45-3.51(1H, m), 7.17-7.20(2H, m), 7.34-7.39(2H, m).

(2) 2-[2-(3-bromophenyl)ethyl]-3-(N-ethyl-N-phenylamino)-3-oxopropionic acid

**[0748]** In the same manner as in Example 119 (2), the title compound (2.31 g) was obtained as an oil using the above-mentioned compound (2.30 g) and N-ethylaniline (3.50 g). <sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.09-1.17(3H, m), 1.91-2.09(1H, m), 2.10-2.18(1H, m), 2.43-2.50(1H, m), 2.55-2.61(1H, m), 3.20-3.23(1H, m), 3.64-3.71(1H, m), 6.98-7.00(1H, m), 7.04-7.68(3H, m), 7.08(1H, s), 7.27-7.29(2H, m), 7.38-7.41(3H, m).

(3) 2-[2-(3-bromophenyl)ethyl]-N-ethyl-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

**[0749]** In the same manner as in Example 1 (2), the title compound (11 mg) was obtained as a white powder using the above-mentioned compound (1.00 g) and trans-β-styrenesulfonamide (810 mg).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.10(3H, brs), 2.02-2.12(2H, m), 2.40-2.50(2H, m), 3.11-3.15(1H, m), 3.65-3.78(1H, m), 3.79-3.85(1H, m), 6.93-6.99(5H, m), 7.01-7.05(1H, m), 7.16-7.36(4H, m), 7.40-7.45(3H, m), 7.52-7.54(2H, m), 7.73(1H, d, J = 15.6Hz), 10.47(1H, brs).

MS: 555(M+H)<sup>+</sup>.

### Example 356 Synthesis of 2-[2-(3-bromophenyl)ethyl]-N-ethyl-N'-((E)-styrylsulfonyl)-N-phenylmalonamide

**[0750]** In the same manner as in Example 1 (2), the title compound (56 mg) was obtained as a white powder using the compound (1.00 g) obtained in Example 355 (2).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.09(3H, brs), 1.90-2.02(2H, m), 2.19-2.34(2H, m), 2.98-3.02(1H, m), 3.57-3.66(1H, m), 3.77-3.86(1H, m), 6.78-6.85(3H, m), 6.95-6.99(2H, m), 7.03-7.30(4H, m), 7.60-7.69(2H, m), 7.90-8.04(4H, m), 8.68(1H, m), 10.59(1H, brs).

MS: 579(M+H)<sup>+</sup>.

### Example 357 Synthesis of 2-[2-(4-bromophenyl)ethyl]-N-ethyl-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

(1) 5-[2-(4-bromophenyl)ethyl]-2, 2-dimethyl-1, 3-dioxane-4, 6-dione

**[0751]** In the same manner as in Example 132 (1), the title compound (3.72 g) was obtained as a pale-yellow powder using 4-bromophenylacetic acid (4.30 g).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.76(3H, s), 1.77(3H, s), 2.36-2.41(2H, m), 2.78-2.82(2H, m), 3.45-3.51(1H, m), 7.10-7.14(2H, m), 7.41-7.44(2H, m).

(2) 2-[2-(4-bromophenyl)ethyl]-3-(N-ethyl-N-phenylamino)-3-oxopropionic acid

**[0752]** In the same manner as in Example 119 (2), the title compound (2.57 g) was obtained as an oil using the above-mentioned compound (2.30 g) and N-ethylaniline (3.50 g).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.09-1.15(3H, m), 1.92-1.99(1H, m), 2.08-2.18(1H, m), 2.42-2.49(1H, m), 2.54-2.61(1H, m), 3.18-3.21(1H, m), 3.62-3.69(1H, m), 3.83-3.92(1H, m), 6.89-6.91(2H, m), 7.01-7.03(2H, m), 7.27-7.41(5H, m).

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### (3) 2-[2-(4-bromophenyl)ethyl]-N-ethyl-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

**[0753]** In the same manner as in Example 1 (2), the title compound (57 mg) was obtained as a white powder using the above-mentioned compound (1.00 g) and trans- $\beta$ -styrenesulfonamide (810 mg).

$^1\text{H-NMR}$ (400Mz,  $\text{CDCl}_3$ ) $\delta$ 1.10(3H, brs), 1.90-2.07(1H, m), 2.09-2.19(1H, m), 2.36-2.44(1H, m), 2.48-2.62(1H, m), 3.11-3.14(1H, m), 3.64-3.71(1H, m), 3.76-3.83(1H, m), 6.87(2H, d, J = 8.0Hz), 6.94-6.96(2H, m), 7.06(1H, d, J = 15.6Hz), 7.29-7.39(5H, m), 7.40-7.45(3H, m), 7.52-7.54(2H, m), 7.73(1H, d, J = 15.6Hz), 10.51(1H, brs).

MS: 555(M+H) $^+$ .

### Example 358 Synthesis of 2-[2-(4-bromophenyl)ethyl]-N-ethyl-N'-(2-naphthylsulfonyl)-N-phenylmalonamide

**[0754]** In the same manner as in Example 1 (2), the title compound (52 mg) was obtained as a white powder using the compound (1.00 g) obtained in Example 357 (2).

$^1\text{H-NMR}$ (400Mz,  $\text{CDCl}_3$ ) $\delta$ 1.07(3H, brs), 1.90-2.01(2H, m), 2.20-2.3,2(2H, m), 2.98-3.02(1H, m), 3.58-3.63(1H, m), 3.77-3.82(1H, m), 6.73(2H, d, J = 8.4Hz), 6.81(2H, d, J = 7.6Hz), 7.19-7.26(4H, m), 7.29-7.32(1H, m), 7.61-7.69(2H, m), 7.90-8.04(4H, m), 8.68(1H, s), 10.63(1H, brs).

MS: 579(M+H) $^+$ .

### Example 359 Synthesis of 2-(3-biphenylmethyl)-N-ethyl-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

**[0755]** To a mixed solution of the compound (131 mg) obtained in Example 344 in toluene (10 mL)/ethanol (5 mL) were added phenylboronic acid (29 mg), tetrakis(triphenylphosphine)palladium (12 mg) and sodium carbonate (133 mg), and the mixture was heated under reflux for 8 hr. 1 mol/L Hydrochloric acid (10 mL) and ethyl acetate (30 mL) were added to extract the reaction mixture, and the organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound (20 mg) as a white powder.

$^1\text{H-NMR}$ (300Mz,  $\text{CDCl}_3$ ) $\delta$ 0.94-1.04(3H, m), 2.98-3.09(1H, m), 3.17-3.78(1H, m), 3.31-3.34(1H, m), 3.61-3.67(2H, m), 6.83-7.02(5H, m), 7.21-7.25(7H, m), 7.44-7.53(8H, m), 7.69-7.75(2H, m), 10.40(1H, brs).

MS: 539(M+H) $^+$ .

### Example 360 Synthesis of 2-(3-biphenylmethyl)-N-ethyl-N'-(2-naphthylsulfonyl)-N-phenylmalonamide

**[0756]** In the same manner as in Example 359, the title compound (21 mg) was obtained as a white powder using the compound (239 mg) obtained in Example 343.

$^1\text{H-NMR}$ (400Mz,  $\text{CDCl}_3$ ) $\delta$ 0.90-1.03(3H, m), 2.85-3.30(3H, m), 3.56-3.64(2H, m), 6.81-6.99(2H, m), 7.01-7.03(2H, m), 7.12-7.13(1H, m), 7.15-7.37(4H, m), 7.40-7.49(4H, m), 7.61-7.69(2H, m), 7.90-8.03(4H, m), 8.70(1H, s), 10.60(1H, brs).

MS: 563(M+H) $^+$ .

### Example 361 Synthesis of N-ethyl-2-[(4'-methoxy-4-biphenyl)methyl]-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

**[0757]** In the same manner as in Example 359, the title compound (60 mg) was obtained as a white powder using the compound (228 mg) obtained in Example 345 and (4-methoxyphenyl)boronic acid (456 mg).

$^1\text{H-NMR}$ (300Mz,  $\text{CDCl}_3$ ) $\delta$ 0.92(3H, t, J = 6.9Hz), 2.94-3.01(2H, m), 3.32-3.46(2H, m), 3.61-3.76(H, m), 3.83(3H, s), 6.90-6.98(4H, m), 7.10-7.20(2H, m), 7.30-7.56(12H, m), 7.74-7.77(2H, m), 11.76(1H, brs).

MS: 569(M+H) $^+$ .

### Example 362 Synthesis of N-ethyl-2-[(4'-methoxy-4-biphenyl)methyl]-N'-(2-naphthylsulfonyl)-N-phenylmalonamide

**[0758]** In the same manner as in Example 359, the title compound (167 mg) was obtained as a white powder using the compound (239 mg) obtained in Example 346 and (4-methoxyphenyl)boronic acid (456 mg).

$^1\text{H-NMR}$ (300Mz,  $\text{DMSO-d}_6$ ) $\delta$ 0.88(3H, t, J = 6.9Hz), 2.85(2H, d, J = 6.9Hz), 3.43-3.50(2H, m), 3.55-3.57(1H, m), 3.77(3H, s), 6.75(2H, d, J = 8.1Hz), 6.95-7.01(4H, m), 7.19-7.22(2H, m), 7.31-7.44(5H, m), 7.68-7.78(3H, m), 8.03-8.04(1H, m), 8.12-8.19(2H, m), 8.53(1H, m), 12.07(1H, brs).

MS: 593(M+H) $^+$ .

### Example 363 Synthesis of N-ethyl-2-[(4'-methoxy-4-biphenyl)methyl]-N'-phenethylsulfonyl-N-phenylmalonamide

**[0759]** In the same manner as in Example 7, the title compound (43 mg) was obtained as a white powder using the compound (115 mg) obtained in Example 361 at room temperature.  $^1\text{H-NMR}$ (300Mz,  $\text{DMSO-d}_6$ ) $\delta$ 0.92(3H, t, J = 6.9Hz),

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2.94-2.95(2H, m), 3.39-3.44(5H, m), 3.47-3.60(2H, m), 3.77(3H, s), 6.89-6.98(3H, m), 7.11-7.51(13H, m), 7.75(2H, d, J = 6.9Hz), 11.77(1H, brs). MS: 571(M+H)<sup>+</sup>.

Example 364 Synthesis of 2-(2-biphenylmethyl)-N-ethyl-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

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**[0760]** In the same manner as in Example 359, the title compound (263 mg) was obtained as a white powder using the compound (228 mg) obtained in Example 347.

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.86(3H, t, J = 7.2Hz), 2.70-2.90(1H, m), 2.92-3.12(1H, m), 3.15-3.34(1H, m), 3.47-3.46(2H, m), 6.71-6.74(2H, m), 6.97-7.16(2H, m), 7.18-7.19(1H, m), 7.21-7.23(3H, m), 7.32-7.46(4H, m), 7.47-7.75(6H, m), 8.28-8.29(2H, m), 9.30(1H, s), 11.67(1H, brs).

MS: 539(M+H)<sup>+</sup>.

Example 365 Synthesis of 2-(2-biphenylmethyl)-N-ethyl-N'-(2-naphthylsulfonyl)-N-phenylmalonamide

15 **[0761]** In the same manner as in Example 359, the title compound (264 mg) was obtained as a white powder using the compound (239 mg) obtained in Example 348.

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.84(3H, t, J = 6.9Hz), 2.61-2.78(1H, m), 2.80-3.01(1H, m), 3.44-3.50(3H, m), 6.74(2H, d, J = 8.1Hz), 6.85-6.86(2H, m), 7.07-7.18(5H, m), 7.31-7.35(1H, m), 7.56-7.63(4H, m), 7.67-7.72(3H, m), 8.12-8.20(2H, m), 8.49(1H, s), 9.31(1H, s), 11.86(1H, brs).

20 MS: 563(M+H)<sup>+</sup>.

Example 366 Synthesis of 2-[(2-biphenyl)methyl]-N-ethyl-N'-phenethylsulfonyl-N-phenylmalonamide

25 **[0762]** In the same manner as in Example 7, the title compound (44 mg) was obtained as a white powder using the compound (63 mg) obtained in Example 364.

<sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ0.99-1.04(3H, m), 1.45-1.58(2H, m), 3.01-3.23(4H, m), 3.51-3.57(2H, m), 3.69-3.74(1H, m), 6.70-6.76(2H, m), 6.80-7.00(1H, m), 7.13-7.49(15H, m), 7.60-7.62(1H, m), 9.89-9.93(1H, m).

MS: 541(M+H)<sup>+</sup>.

30 Example 367 Synthesis of 2-[2-(3-biphenyl)ethyl]-N-ethyl-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

**[0763]** In the same manner as in Example 359, the title compound (29 mg) was obtained as a white powder using the compound (279 mg) obtained in Example 355.

35 <sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.09-1.12(3H, m), 2.22-2.78(2H, m), 2.49-2.62(2H, m), 3.21(1H, t, J = 7.2Hz), 3.66-3.77(1H, m), 3.79-3.84(1H, m), 6.98-7.01(3H, m), 7.07(1H, d, J = 15.6Hz), 7.23-7.28(5H, m), 7.32-7.43(7H, m), 7.44-7.53(4H, m), 7.73(1H, d, J = 15.6Hz), 10.44(1H, brs).

MS: 553(M+H)<sup>+</sup>.

40 Example 368 Synthesis of 2-[2-(4-biphenyl)ethyl]-N-ethyl-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

**[0764]** In the same manner as in Example 359, the title compound (18 mg) was obtained as a white powder using the compound (279 mg) obtained in Example 357.

45 <sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.09-1.11(3H, m), 2.09-2.17(2H, m), 2.46-2.62(2H, m), 3.21(1H, t, J = 6.0Hz), 3.68-3.84(2H, m), 6.98-6.99(2H, m), 7.01-7.09(3H, m), 7.29-7.36(4H, m), 7.39-7.46(7H, m), 7.52-7.56(4H, m), 7.74(1H, d, J = 15.6Hz), 10.48(1H, brs).

MS: 553 (M+H)<sup>+</sup>.

Example 369 Synthesis of 2-[2-(4-biphenyl)ethyl]-N-ethyl-N'-(2-naphthylsulfonyl)-N-phenylmalonamide

50 **[0765]** In the same manner as in Example 359, the title compound (50 mg) was obtained as a white powder using the compound (300 mg) obtained in Example 358.

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.10-1.12(3H, m), 2.00-2.10(2H, m), 2.30-2.41(2H, m), 3.06-3.09(1H, m), 3.51-3.68(1H, m), 3.76-3.85(1H, m), 6.84-6.85(2H, m), 6.93-6.95(2H, m), 7.18-7.22(3H, m), 7.31-7.36(3H, m), 7.41-7.45(2H, m), 7.52-7.62(2H, m), 7.64-7.65(2H, m), 7.68-7.66(1H, m), 7.89-7.82(1H, m), 7.96-8.06(2H, m), 8.72(1H, s), 10.6(1H, brs).

55 MS: 577 (M+H)<sup>+</sup>.

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Example 370 Synthesis of 2-[2-(3-biphenyl)ethyl]-N-ethyl-N'-(2-naphthylsulfonyl)-N-phenylmalonamide

**[0766]** In the same manner as in Example 359, the title compound (55 mg) was obtained as a white powder using the compound (300 mg) obtained in Example 356.

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.02-1.09(3H, m), 2.03-2.07(2H, m), 2.30-2.42 (2H, m), 3.08(1H, t, J = 7.2Hz), 3.58-3.67(1H, m), 3.76-3.85(1H, m), 6.83-6.87(3H, m), 7.12(1H, s), 7.16-7.24(4H, m), 7.32-7.36(2H, m), 7.41-7.48(2H, m), 7.49-7.50(2H, m), 7.58-7.87(2H, m), 7.89-7.94(1H, m), 7.96-7.99(1H, m), 8.02-8.05(2H, m), 8.69(1H, s), 10.56(1H, brs). MS: 577(M+H)<sup>+</sup>.

Example 371 Synthesis of 2-[(1-benzyl-1H-pyrazol-4-yl)methyl]-N-ethyl-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

(1) ethyl 1-(tert-butoxycarbonyl)pyrazole-4-carboxylate

**[0767]** To a solution of ethyl pyrazolecarboxylate (20.5 g) in ethanol (150 mL) were added a solution of di-tert-butyl dicarbonate (32.0 g) in ethanol (150 mL) and triethylamine (22 mL) at room temperature, and the mixture was stirred for 3 hr. After concentration under reduced pressure, 10% aqueous citric acid solution (500 mL) was added to the residue, and the mixture was extracted with ethyl acetate (200 mL×2) and washed with saturated brine. The organic layer was concentrated under reduced pressure to give the title compound (34.7 g) as an oil. <sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.37(3H, t, J = 7.2Hz), 1.67(9H, s), 4.33(2H, q, J = 7.2Hz), 8.06(1H, s), 8.56(1H, s).

(2) [1-(tert-butoxycarbonyl)-1H-pyrazol-4-yl]methanol

**[0768]** To a solution of the above-mentioned compound (34.7 g) in ether (400 mL) was added dropwise 1 mol/L diisobutylaluminum hydride-hexane solution (300 mL) at -78°C for 1 hr, and the mixture was allowed to warm to room temperature and stirred for 3 days. The reaction mixture was washed with saturated aqueous (+)-potassium sodium tartrate solution (500 mL), and the organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound (4.15 g) as an oil.

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ1.57(9H, s), 4.38(2H, d, J = 5.6Hz), 5.07(1H, t, J = 5.6Hz), 7.73(1H, s), 8.09(1H, s).

(3) triethyl 2-[1-(tert-butoxycarbonyl)-1H-pyrazol-4-yl]ethane-1, 1, 1-tricarboxylate

**[0769]** To a solution of the above-mentioned compound (4.12 g) in methylene chloride (100 mL) were added mesyl chloride (1.69 mL) and triethylamine (3.19 mL) under ice-cooling, and the mixture was stirred at room temperature for 3 hr. After the reaction mixture was concentrated under reduced pressure, the residue was dissolved in DMF (50 mL). Triethyl methanetricarboxylate (4.83 g), potassium carbonate (4.31 g) and potassium iodide in catalytic amount were added at room temperature, and the mixture was stirred for 16 hr. Water (300 mL) and hexane/ethyl acetate (1/1) (200 mL×2) were added to extract the reaction mixture, and the organic layer was washed with saturated brine. The organic layer was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography to give the title compound (3.87 g) as an oil.

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ1.17(9H, t, J = 7.2Hz), 1.56(9H, s), 3.24(2H, s), 4.18(6H, q, J = 7.2Hz), 7.61(1H, s), 7.99(1H, s).

(4) triethyl 2-(4-pyrazolyl)ethane-1, 1, 1-tricarboxylate

**[0770]** To a solution of the above-mentioned compound (2.72 g) in methylene chloride (50 mL) was added trifluoroacetic acid (20 mL) at room temperature, and the mixture was stirred for 17 hr. The reaction mixture was concentrated under reduced pressure, saturated aqueous sodium hydrogen carbonate solution (100 mL) was added to the residue, and the mixture was extracted with chloroform (100 mL×2). The organic layer was concentrated under reduced pressure to give the title compound (2.06 g) as an oil.

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ1.16(9H, t, J = 7.2Hz), 3.20(2H, s), 4.14(6H, q, J = 7.2Hz), 7.37(2H, brs), 12.58(1H, brs).

(5) triethyl 2-(1-benzyl-1H-pyrazol-4-yl)ethane-1, 1, 1-tricarboxylate

**[0771]** To a solution of the above-mentioned compound (710 mg) in DMF (10 mL) were added benzyl bromide (325 μL) and potassium carbonate (380 mg), and the mixture was stirred at 60°C for 24 hr. Water (100 mL) was added to the reaction mixture, and the mixture was extracted with ethyl acetate (50 mL). The organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound (350 mg) as an oil.

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<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.19(9H, t, J = 7.2Hz), 3.29(2H, s), 4.16(6H, q, J = 7.2Hz), 5.21(2H, s), 7.15-7.16(2H, m), 7.25-7.32(3H, m), 7.36(1H, s), 7.40(1H, s).

(6) monoethyl [(1-benzyl-1H-pyrazol-4-yl)methyl]malonate

**[0772]** In the same manner as in Example 117 (2), the title compound (248 mg) was obtained as an oil using the above-mentioned compound (330 mg).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.16(3H, t, J = 7.2Hz), 3.01-3.09(2H, m), 3.51-3.56(1H, m), 4.08-4.17(2H, m), 5.22(2H, s), 7.11-7.17(2H, m), 7.24(1H, s), 7.24-7.31(4H, m), 7.43(1H, s), 10.07(1H, brs).

(7) ethyl 2-[(1-benzyl-1H-pyrazol-4-yl)methyl]-3-(N-ethyl-N-phenylamino)-3-oxopropionate

**[0773]** In the same manner as in Example 1 (4), the title compound (200 mg) was obtained as an oil using the above-mentioned compound (248 mg) and N-ethylaniline (124 μL).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.01(3H, t, J = 7.2Hz), 1.23(3H, t, J = 7.2Hz), 2.87(1H, dd, J = 14.4, 4.8Hz), 3.10(1H, dd, J = 14.4, 10.4Hz), 3.33(1H, dd, J = 10.4, 4.8Hz), 3.56-3.72(2H, m), 4.11(2H, q, J = 7.2Hz), 5.23(2H, dd, J = 16.8, 14.8Hz), 6.72(2H, brs), 7.17(1H, s), 7.21(1H, s), 7.26-7.36(8H, m).

(8) 2-[(1-benzyl-1H-pyrazol-4-yl)methyl]-3-(N-ethyl-N-phenylamino)-3-oxopropionic acid

**[0774]** In the same manner as in Example 1 (3), the title compound (167 mg) was obtained as an oil using the above-mentioned compound (180 mg).

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ0.89(3H, t, J = 7.2Hz), 7.68-2.85 (2H, m), 3.10-3.18(1H, m), 3.47-3.57(2H, m), 5.26(2H, s), 6.71(2H, brs), 7.07(1H, s), 7.27-7.39(8H, m), 7.39(1H, s).

(9) 2-[(1-benzyl-1H-pyrazol-4-yl)methyl]-N-ethyl-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

**[0775]** In the same manner as in Example 1 (2), the title compound (90 mg) was obtained as a white powder using the above-mentioned compound (168 mg) and trans-β-styrenesulfonamide (82 mg).

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ0.89-0.96(3H, m), 2.70(1H, dd, J = 13.6, 5.2Hz), 2.87(1H, dd, J = 13.6, 8.4Hz), 3.30-3.33(1H, m), 3.48-3.63(2H, m), 5.19(2H, s), 7.00(3H, brs), 7.15(2H, d, J = 7.2Hz), 7.26-7.32(8H, m), 7.45-7.52(3H, m), 7.57(1H, d, J = 15.2Hz), 7.78-7.80(2H, m), 11.73(1H, brs).

MS: 543(M+H)<sup>+</sup>.

Example 372 Synthesis of N-ethyl-2-[(1-ethyl-1H-pyrazol-4-yl)methyl]-N-phenyl-N'-((E)-styrylsulfonyl)malonamide (1) triethyl 2-(1-ethyl-1H-pyrazol-4-yl)ethane-1, 1, 1-tricarboxylate

**[0776]** In the same manner as in Example 371 (5), the title compound (240 mg) was obtained as an oil using the compound (710 mg) obtained in Example 371 (4) and ethyl iodide (440 μL). <sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.24(9H, t, J = 7.2Hz), 1.43(3H, t, J = 7.2Hz), 3.30(2H, s), 4.09(2H, q, J = 7.2Hz), 4.22(6H, q, J = 7.2Hz), 7.33(1H, s), 7.37(1H, s).

(2) monoethyl [(1-ethyl-1H-pyrazol-4-yl)methyl]malonate

**[0777]** In the same manner as in Example 117 (2), the title compound (151 mg) was obtained as an oil using the above-mentioned compound (240 mg).

<sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ1.27(3H, t, J = 7.3Hz), 1.44(3H, t, J = 7.1Hz), 3.10(2H, d, J = 7.3Hz), 3.57(1H, t, J = 7.3Hz), 4.10-4.25(4H, m), 5.62(1H, brs), 7.28(1H, s), 7.38(1H, s).

(3) ethyl 3-(N-ethyl-N-phenylamino)-2-[(1-ethyl-1H-pyrazol-4-yl)methyl]-3-oxopropionate

**[0778]** In the same manner as in Example 1 (4), the title compound (90 mg) was obtained as an oil using the above-mentioned compound (151 mg) and N-ethylaniline (95 μL). <sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.04-1.10(3H, m), 1.22-1.28(3H, m), 1.46(3H, t, J = 7.2Hz), 2.86-3.94(1H, m), 3.08(1H, dd, J = 14.0, 10.0Hz), 3.37(1H, dd, J = 10.0, 5.2Hz), 3.71(2H, q, J = 7.2Hz), 4.07-4.19(4H, m), 6.83(2H, brs), 7.17 (2H, s), 7.29-7.38 (3H, m).

(4) 3-(N-ethyl-N-phenylamino)-2-[(1-ethyl-1H-pyrazol-4-yl)methyl]-3-oxopropionic acid

**[0779]** In the same manner as in Example 1 (3), the title compound (82 mg) was obtained as an oil using the above-

mentioned compound (90 mg).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.05-1.12(3H, m), 1.46(3H, t, J = 7.2Hz), 2.91(1H, dd, J = 15.0, 5.2Hz), 3.10(1H, dd, J = 15.0, 10.0Hz), 3.42(1H, dd, J = 10.0, 5.2Hz), 3.68-3.77 (2H, m), 4.09-4.18(2H, m), 6.85(2H, brs), 7.19(1H, s), 7.21(1H, s), 7.31-7.42(3H, m), 8.76(1H, brs).

5

(5) N-ethyl-2-[(1-ethyl-1H-pyrazol-4-yl)methyl]-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

**[0780]** In the same manner as in Example 1 (2), the title compound (87 mg) was obtained as a white powder using the above-mentioned compound (82 mg) and trans-β-styrenesulfonamide (50 mg).

10 <sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ0.96(3H, t, J = 7.2Hz), 1.23(3H, t, J = 7.2Hz), 2.65-2.83(2H, m), 3.50-3.69(2H, m), 3.94(2H, q, J = 7.2Hz), 6.88(1H, s), 7.10-7.16(2H, m), 7.17(1H, s), 7.28-7.60(8H, m), 7.75-7.85(2H, m), 11.72(1H, brs).  
MS: 481(M+H)<sup>+</sup>.

Example 373 Synthesis of N-ethyl-2-[(1-methyl-1H-pyrazol-4-yl)methyl]-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

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(1) triethyl 2-(1-methyl-1H-pyrazol-4-yl)ethane-1, 1, 1-tricarboxylate

**[0781]** In the same manner as in Example 371 (5), the title compound (220 mg) was obtained as an oil using the compound (710 mg) obtained in Example 371 (4) and methyl iodide (340 μL). <sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.25(3H, t, J = 7.2Hz), 3.29(2H, s), 3.83(3H, s), 4.22(2H, q, J = 7.2Hz), 7.33(1H, s), 7.36(1H, s).

20

(2) monoethyl [(1-methyl-1H-pyrazol-4-yl)methyl]malonate

**[0782]** In the same manner as in Example 117 (2), the title compound (120 mg) was obtained as an oil using the above-mentioned compound (220 mg).

25

(3) ethyl 3-(N-ethyl-N-phenylamino)-2-[(1-methyl-1H-pyrazol-4-yl)methyl]-3-oxopropionate

**[0783]** In the same manner as in Example 1 (4), the title compound (90 mg) was obtained as an oil using the above-mentioned compound (120 mg) and N-ethylaniline (80 μL).

30

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.08(3H, t, J = 7.2Hz), 1.25(3H, t, J = 7.2Hz), 2.90(1H, dd, J = 14.0, 5.6Hz), 3.06(1H, dd, J = 14.0, 10.0Hz), 3.38(1H, dd, J = 10.0, 5.6Hz), 3.67-3.75(2H, m), 3.85(3H, s), 4.13(2H, q, J = 7.2Hz), 6.89(2H, brs), 7.12(1H, s), 7.15(1H, s), 7.31-7.38(3H, m).

35

(4) 3-(N-ethyl-N-phenylamino)-2-[(1-methyl-1H-pyrazol-4-yl)methyl]-3-oxopropionic acid

**[0784]** In the same manner as in Example 1 (3), the title compound (77 mg) was obtained as an oil using the above-mentioned compound (90 mg).

40

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.09(3H, t, J = 7.2Hz), 2.91(1H, d, J = 14.4, 5.6Hz), 3.06(1H, dd, J = 14.4, 9.6Hz), 3.43(1H, dd, J = 9.6, 5.6Hz), 3.67-3.79(2H, m), 3.87(3H, s), 6.91(2H, brs), 7.14(1H, s), 7.19(1H, s), 7.33-7.41(3H, m), 8.57(1H, brs).

(5) N-ethyl-2-[(1-methyl-1H-pyrazol-4-yl)methyl]-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

**[0785]** In the same manner as in Example 1 (2), the title compound (54 mg) was obtained as a white powder using the above-mentioned compound (77 mg) and trans-β-styrenesulfonamide (50 mg).

45

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ0.95(3H, t, J = 7.2Hz), 2.67-2.71(1H, m), 2.79(1H, dd, J = 14.0, 7.6Hz), 3.25-3.39(1H, m), 3.46-3.59(1H, m), 3.59-3.72(1H, m), 3.65(3H, s), 6.87(1H, s), 7.14 (3H, brs), 7.30(1H, d, J = 15.6Hz), 7.35-7.51(6H, m), 7.56(1H, d, J = 15.6Hz), 7.74-7.82(2H, m), 11.73(1H, brs).

50

MS: 467(M+H)<sup>+</sup>.

Example 374 Synthesis of 2-[[1-(4-chlorophenyl)-1H-pyrazol-4-yl]methyl]-N-ethyl-N-phenyl-N'-((E)-styrylsulfonyl)malonamide (1) triethyl 2-[1-(4-chlorophenyl)-1H-pyrazol-4-yl]ethane-1, 1, 1-tricarboxylate

**[0786]** In the same manner as in Example 117 (1), the title compound (1.71 g) was obtained as an oil using 4-(chloromethyl)-1-(4-chlorophenyl)-1H-pyrazole (920 mg). <sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ1.16(9H, t, J = 7.2Hz), 3.28(2H, s), 4.18(2H, q, J = 7.2Hz), 7.54(2H, d, J = 8.8Hz), 7.56(1H, s), 7.79(2H, d, J = 8.8Hz), 8.25(1H, s).

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(2) monoethyl {[1-(4-chlorophenyl)-1H-pyrazol-4-yl]methyl}malonate

**[0787]** In the same manner as in Example 117 (2), the title compound (1.31 g) was obtained as a white solid using the above-mentioned compound (1.71 g).

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ1.13(3H, t, J = 7.2Hz), 2.97(2H, d, J = 8.0Hz), 3.69(1H, t, J = 8.0Hz), 4.10(2H, q, J = 7.2Hz), 7.54(2H, d, J = 8.8Hz), 7.61(1H, s), 7.80(2H, d, J = 8.8Hz), 8.34(1H, s), 12.98(1H, brs).

(3) ethyl 2-[[1-(4-chlorophenyl)-1H-pyrazol-4-yl]methyl]-3-(N-ethyl-N-phenylamino)-3-oxopropionate

**[0788]** In the same manner as in Example 1 (4), the title compound (310 mg) was obtained as an oil using the above-mentioned compound (410 mg) and N-ethylaniline (176 μL). <sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ0.96(3H, t, J = 7.2Hz), 1.12(3H, t, J = 7.2Hz), 2.85-2.97(2H, m), 3.34-3.40(1H, m), 3.52-3.68(2H, m), 3.96-4.07(2H, m), 6.90(2H, brs), 7.33-7.42(4H, m), 7.55(2H, d, J = 8.8Hz), 7.80(2H, d, J = 8.8H), 8.14(1H, s).

(4) 2-[[1-(4-chlorophenyl)-1H-pyrazol-4-yl]methyl]-3-(N-ethyl-N-phenylamino)-3-oxopropionic acid

**[0789]** In the same manner as in Example 1 (3), the title compound (247 mg) was obtained as a white solid using the above-mentioned compound (310 mg).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.95(3H, t, J = 7.8Hz), 2.83-2.95(2H, m), 3.18-3.33(1H, m), 3.56-3.65(2H, m), 6.88(2H, brs), 7.36(3H, brs), 7.37(1H, s), 7.55(2H, d, J = 8.8Hz), 7.80(2H, d, J = 8.8Hz), 8.11(1H, s), 12.63(lh, brs).

(5) 2-[[1-(4-chlorophenyl)-1H-pyrazol-4-yl]methyl]-N-ethyl-N-phenyl-N'-(E)-styrylsulfonylmalonamide

**[0790]** In the same manner as in Example 1 (2), the title compound (135 mg) was obtained as a white powder using the above-mentioned compound (240 mg) and trans-β-styrenesulfonamide (110 mg).

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ0.97(3H, t, J = 7.2Hz), 2.84(1H, dd, J = 14.4, 6.0Hz), 2.95(1H, dd, J = 14.4, 7.6Hz), 3.46-3.70(3H, m), 7.17-7.19(2H, m), 7.29(1H, s), 7.30(1H, d, J = 15.6Hz), 7.36-7.51(8H, m), 7.57(1H, d, J = 15.6Hz), 7.71-7.78(4H, m), 8.01(1H, s), 11.76(1H, brs).

MS: 563(M+H)<sup>+</sup>.

Example 375 Synthesis of N-ethyl-2-[[1-(4-fluorobenzyl)-1H-pyrazol-4-yl]methyl]-N-phenyl-N'-(E)-styrylsulfonylmalonamide

(1) ethyl 1-(4-fluorobenzyl)-1H-pyrazole-4-carboxylate

**[0791]** To a solution of ethyl pyrazolecarboxylate (10.1 g) in THF (200 mL) was added slowly 60% sodium hydride (3.17 g) under ice-cooling, and the mixture was stirred for 20 min. A solution of 4-fluorobenzyl bromide (14.3 g) in THF (25 mL) was added to the reaction mixture under ice-cooling, and the mixture was stirred at room temperature for 19 hr. Dilute hydrochloric acid was added to the reaction mixture, and the precipitate was collected by filtration to give the title compound (11.9 g) as a pale-yellow solid.

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ1.25(3H, t, J = 7.2Hz), 4.20(2H, q, J = 7.2Hz), 5.35(2H, s), 7.16-7.21(2H, m), 7.33-7.36(2H, m), 7.87(1H, s), 8.48(1H, s).

(2) [1-(4-fluorobenzyl)-1H-pyrazol-4-yl]methanol

**[0792]** In the same manner as in Example 128 (2), the title compound (4.99 g) was obtained as an oil using the above-mentioned compound (6.00 g).

<sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ4.57(2H, s), 5.24(2H, s), 7.00-7.06(2H, m), 7.19-7.27(2H, m), 7.38(1H, s), 7.53(1H, s).

(3) 4-(chloromethyl)-1-(4-fluorobenzyl)-1H-pyrazole

**[0793]** To a solution of the above-mentioned compound (4.99 g) in chloroform (100 mL) was added thionyl chloride (2.10 mL), and the mixture was heated under reflux for 2 hr. The reaction mixture was concentrated under reduced pressure to give the title compound (5.44 g) as an oil.

<sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ4.53(2H, s), 5.24(2H, s), 7.01-7.07(2H, m), 7.19-7.26(2H, m), 7.41(1H, s), 7.56(1H, s).

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(4) triethyl 2-[1-(4-fluorobenzyl)-1H-pyrazol-4-yl]ethane-1, 1, 1-tricarboxylate

**[0794]** In the same manner as in Example 117 (1), the title compound (10.1 g) was obtained as an oil using the above-mentioned compound (5.44 g).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.21(9H, t, J = 7.2Hz), 3.29(2H, s), 4.18(6H, q, J = 7.2Hz), 5.19(2H, s), 6.97-7.02(2H, m), 7.13-7.16(2H, m), 7.35(1H, s), 7.38(1H, s).

(5) monoethyl {[1-(4-fluorobenzyl)-1H-pyrazol-4-yl]methyl}malonate

**[0795]** In the same manner as in Example 117 (2), the title compound (7.75 g) was obtained as a white solid using the above-mentioned compound (5.44 g).

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ1.08(3H, t, J = 7.2Hz), 2.84-2.89(2H, m), 3.54(1H, t, J = 7.2Hz), 5.23(2H, s), 7.12-7.17(2H, m), 7.21-7.24(2H, m), 7.28(1H, s), 7.57(1H, s), 12.84(1H, brs).

(6) ethyl 3-(N-ethyl-N-phenylamino)-2-[[1-(4-fluorobenzyl)-1H-pyrazol-4-yl]methyl]-3-oxopropionate

**[0796]** In the same manner as in Example 1 (4), the title compound (1.40 g) was obtained as an oil using the above-mentioned compound (1.49 g) and N-ethylaniline (700 μL).

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ0.91(3H, t, J = 7.2Hz), 1.10(3H, t, J = 7.2Hz), 2.73-2.89(2H, m), 3.22(1H, dd, J = 9.6, 5.6Hz), 3.50-3.59(2H, m), 3.98(2H, q, J = 7.2Hz), 5.24(2H, s), 6.76(2H, brs), 7.08(1H, s), 7.14-7.19(2H, m), 7.21-7.37(5H, m), 7.40(1H, s).

(7) 3-(N-ethyl-N-phenylamino)-2-[[1-(4-fluorobenzyl)-1H-pyrazol-4-yl]methyl]-3-oxopropionic acid

**[0797]** In the same manner as in Example 1 (3), the title compound (1.21 g) was obtained as a white powder using the above-mentioned compound (1.37 g).

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ0.89(3H, t, J = 7.2Hz), 2.72(1H, dd, J = 14.0, 5.2Hz), 2.82(1H, dd, J = 14.0, 9.6Hz), 3.15(1H, d, J = 9.6, 5.2Hz), 3.50-3.57(2H, m), 5.24(2H, s), 6.70(2H, brs), 7.06(1H, s), 7.15-7.20(2H, m), 7.30-7.39(5H, m), 7.39(1H, s), 12.53(1H, brs).

(B) N-ethyl-2-[[1-(4-fluorobenzyl)-1H-pyrazol-4-yl]methyl]-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

**[0798]** In the same manner as in Example 1 (2), the title compound (730 mg) was obtained as a white powder using the above-mentioned compound (1.20 g) and trans-β-styrenesulfonamide (550 mg).

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ0.92(3H, t, J = 6.8Hz), 2.70(1H, dd, J = 13.6, 4.4Hz), 2.86(1H, dd, J = 13.6, 8.4Hz), 3.25-3.38(1H, m), 3.51-4.04(2H, m), 5.18(2H, s), 7.00(3H, brs), 7.12-7.42(9H, m), 7.49(3H, brs), 7.58(1H, d, J = 15.6Hz), 7.79(2H, brs), 11.69(1H, brs).  
MS:561(M+H)<sup>+</sup>.

Example 376 Synthesis of 2-[[1-(2, 4-difluorobenzyl)-1H-pyrazol-4-yl]methyl]-N-ethyl-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

(1) ethyl 1-(2, 4-difluorobenzyl)-1H-pyrazole-4-carboxylate

**[0799]** In the same manner as in Example 375 (1), the title compound (6.29 g) was obtained as a white solid using 2, 4-difluorobenzyl bromide (5.02 g).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ1.26(3H, t, J = 6.9Hz), 4.21(2H, q, J = 6.9Hz), 5.41(2H, s), 7.07-7.15(1H, m), 7.24-7.40(2H, m), 7.87(1H, s), 8.44(1H, s).

(2) [1-(2, 4-difluorobenzyl)-1H-pyrazol-4-yl]methanol

**[0800]** In the same manner as in Example 128 (2), the title compound (3.76 g) was obtained as an oil using the above-mentioned compound (4.69 g).

<sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ4.58(2H, s), 5.28(2H, s), 6.78-6.90(2H, m), 7.16-7.24(1H, m), 7.45(1H, s), 7.52(1H, s).

(3) 4-(chloromethyl)-1-(2, 4-difluorobenzyl)-1H-pyrazole

**[0801]** In the same manner as in Example 375 (3), the title compound (3.01 g) was obtained as a white solid using

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the above-mentioned compound (3.72 g).

$^1\text{H-NMR}$ (300Mz, DMSO- $d_6$ ) $\delta$ 4.69(2H, s), 5.33(2H, s), 7.03-7.14(1H, m), 7.24-7.35(2H, m), 7.52(1H, s), 7.90(1H, s).

(4) triethyl 2-[1-(2, 4-difluorobenzyl)-1H-pyrazol-4-yl]ethane-1, 1, 1-tricarboxylate

**[0802]** In the same manner as in Example 117 (1), the title compound (5.32 g) was obtained as an oil using the above-mentioned compound (2.88 g).

$^1\text{H-NMR}$ (400Mz,  $\text{CDCl}_3$ ) $\delta$ 1.22(9H, t, J = 7.2Hz), 3.29(2H, s), 4.19(2H, q, J = 7.2Hz), 5.23(2H, s), 6.78-6.84(2H, m), 7.05-7.10(1H, m), 7.38(1H, s), 7.41(1H, s).

(5) monoethyl {[1-(2,4-difluorobenzyl)-1H-pyrazol-4-yl]methyl}malonate

**[0803]** In the same manner as in Example 117 (2), the title compound (4.09 g) was obtained as an oil using the above-mentioned compound (5.32 g).

$^1\text{H-NMR}$ (300Mz, DMSO- $d_6$ ) $\delta$ 1.10(3H, t, J = 7.2Hz), 2.87(2H, d, J = 7.8Hz), 3.55(1H, t, J = 7.8Hz), 4.05(2H, q, J = 7.2Hz), 5.27(2H, s), 7.01-7.09(1H, m), 7.16-7.28(2H, m), 7.30(1H, s), 7.57(1H, s), 12.87(1H, brs).

(6) ethyl 2-[[1-(2,4-difluorobenzyl)-1H-pyrazol-4-yl]methyl]-3-(N-ethyl-N-phenylamino)-3-oxopropionate

**[0804]** In the same manner as in Example 1 (4), the title compound (2.40 g) was obtained as an oil using the above-mentioned compound (2.70 g) and N-ethylaniline (1.20 mL).

$^1\text{H-NMR}$ (300Mz, DMSO- $d_6$ ) $\delta$ 0.92(3H, t, J = 7.1Hz), 1.10(3H, t, J = 7.1Hz), 2.70-2.89(2H, m), 3.23(1H, dd, J = 9.0, 6.0Hz), 3.55(2H, q, J = 7.1Hz), 3.98(2H, q, J = 7.1Hz), 5.29(2H, s), 6.77(2H, brs), 7.07(1H, s), 7.07-7.12(1H, m), 7.23-7.43(5H, m), 7.38(1H, s).

(7) 2-[[1-(2,4-difluorobenzyl)-1H-pyrazol-4-yl]methyl]-3-(N-ethyl-N-phenylamino)-3-oxopropionic acid

**[0805]** In the same manner as in Example 1 (3), the title compound (2.25 g) was obtained as an oil using the above-mentioned compound (2.40 g).

$^1\text{H-NMR}$ (300Mz, DMSO- $d_6$ ) $\delta$ 0.91(3H, t, J = 7.1Hz), 2.68-2.87(2H, m), 3.13-3.20(1H, m), 3.55(2H, q, J = 7.1Hz), 5.29(2H, s), 6.73(2H, brs), 7.06(1H, s), 7.06-7.13(1H, m), 7.25-7.40(5H, m), 7.36(1H, s), 12.50(1H, brs).

(8) 2-[[1-(2,4-difluorobenzyl)-1H-pyrazol-4-yl]methyl]-N-ethyl-N-phenyl-N'-(E)-styrylsulfonylmalonamide

**[0806]** In the same manner as in Example 1 (2), the title compound (1.01 g) was obtained as a white solid using the above-mentioned compound (2.25 g) and trans- $\beta$ -styrenesulfonamide (1.00 g).

$^1\text{H-NMR}$ (300Mz, DMSO- $d_6$ ) $\delta$ 0.92(3H, t, J = 7.2Hz), 2.60-2.76(1H, m), 2.79-2.95(1H, m), 3.21-3.32(1H, m), 3.46-3.78(2H, m), 5.22(2H, s), 6.92-7.13(4H, m), 7.13-7.62(11H, m), 7.79-7.81(2H, m), 11.72(1H, brs).  
MS:579(M+H) $^+$ .

Example 377 Synthesis of 2-[[1-(2-chlorobenzyl)-1H-pyrazol-4-yl]methyl]-N-ethyl-N-phenyl-N'-(E)-styrylsulfonylmalonamide (1) triethyl 2-[1-(2-chlorobenzyl)-1H-pyrazol-4-yl]ethane-1, 1, 1-tricarboxylate

**[0807]** In the same manner as in Example 371 (5), the title compound (1.12 g) was obtained as an oil using hydrochloride salt (2.15 g) of the compound obtained in Example 371 (4) and 2-chlorobenzyl bromide (800  $\mu\text{L}$ ).

$^1\text{H-NMR}$ (400Mz,  $\text{CDCl}_3$ ) $\delta$ 1.22(9H, t, J = 7.2Hz), 3.31(2H, s), 4.19(2H, q, J = 7.2Hz), 5.35(2H, s), 6.89-6.91(1H, m), 7.17-7.24(2H, m), 7.35-7.38(1H, m), 7.42(2H, s).

(2) monoethyl {[1-(2-chlorobenzyl)-1H-pyrazol-4-yl]methyl}malonate

**[0808]** In the same manner as in Example 117 (2), the title compound (840 mg) was obtained as an oil using the above-mentioned compound (1.12 g).

$^1\text{H-NMR}$ (400Mz,  $\text{CDCl}_3$ ) $\delta$ 1.24(3H, t, J = 7.2Hz), 3.10-3.13(2H, m), 3.55-3.59(1H, m), 4.15-4.22(2H, m), 5.38(2H, s), 6.95-6.97(1H, m), 7.18-7.24(2H, m), 7.31(1H, s), 7.34-7.39(1H, m), 7.41(1H, s).

(3) ethyl 2-[[1-(2-chlorobenzyl)-1H-pyrazol-4-yl]methyl]-3-(N-ethyl-N-phenylamino)-3-oxopropionate

**[0809]** In the same manner as in Example 1 (4), the title compound (430 mg) was obtained as an oil using the above-

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mentioned compound (400 mg) and N-ethylaniline (180  $\mu$ L).  $^1\text{H-NMR}$ (400Mz,  $\text{CDCl}_3$ ) $\delta$ 1.03(3H, t, J = 7.2Hz), 1.23(3H, t, J = 7.2Hz), 2.89(1H, dd, J = 14.4, 5.2Hz), 3.10(1H, dd, J = 14.4, 10.0Hz), 3.35(1H, dd, J = 10.0, 5.2Hz), 4.12(2H, q, J = 7.2Hz), 5.37(2H, s), 6.80(2H, brs), 7.10-7.12(1H, m), 7.21-7.29(7H, m), 7.38-7.40(1H, m).

5 (4) 2-[[1-(2-chlorobenzyl)-1H-pyrazol-4-yl]methyl]-3-(N-ethyl-N-phenylamino)-3-oxopropionic acid

**[0810]** In the same manner as in Example 1 (3), the title compound (260 mg) was obtained as a white powder using the above-mentioned compound (430 mg).

10  $^1\text{H-NMR}$ (400Mz,  $\text{DMSO-d}_6$ ) $\delta$ 0.91(3H, t, J = 7.2Hz), 2.70-2.87(2H, m), 3.13-3.21(1H, m), 3.50-3.60(2H, m), 5.37(2H, s), 6.81(2H, brs), 7.05-7.14(1H, m), 7.10(1H, s), 7.28-7.43(5H, m), 7.37(1H, s), 7.47-7.52(1H, m), 12.54(1H, brs).

(5) 2-[[1-(2-chlorobenzyl)-1H-pyrazol-4-yl]methyl]-N-ethyl-N-phenyl-N'-(E)-styrylsulfonylmalonamide

15 **[0811]** In the same manner as in Example 1 (2), the title compound (107 mg) was obtained as a white solid using the above-mentioned compound (255 mg) and trans- $\beta$ -styrenesulfonamide (106 mg).

$^1\text{H-NMR}$ (400Mz,  $\text{DMSO-d}_6$ ) $\delta$ 0.92(3H, t, J = 7.2Hz), 2.70(1H, dd, J = 14.0, 4.8Hz), 2.87(1H, dd, J = 14.0, 8.4Hz), 3.29-3.38(1H, m), 3.48-3.66(2H, m), 5.29(2H, s), 6.91(1H, d, J = 7.6Hz), 7.01-7.04(3H, m), 7.29-7.36(7H, m), 7.43-7.51(4H, m), 7.56(1H, d, J = 15.6Hz), 7.76-7.82(2H, m), 11.67(1H, brs).

MS: 577(M+H) $^+$ .

20 Example 378 Synthesis of 2-[[1-(2-chloro-5-pyridylmethyl)-1H-pyrazol-4-yl]methyl]-N-ethyl-N-phenyl-N'-(E)-styrylsulfonylmalonamide

(1) ethyl 1-(2-chloro-5-pyridylmethyl)-1H-pyrazole-4-carboxylate

25 **[0812]** In the same manner as in Example 375 (1), the title compound (9.93 g) was obtained as a white solid using 2-chloro-5-(chloromethyl)pyridine (10.1 g).

$^1\text{H-NMR}$ (400Mz,  $\text{CDCl}_3$ ) $\delta$ 1.33(3H, t, J = 7.2Hz), 4.29(2H, q, J = 7.2Hz), 5.30(2H, s), 7.33(1H, d, J = 8.4Hz), 7.54(1H, dd, J = 8.4, 1.6Hz), 7.91(1H, s), 7.95(1H, s), 8.35(1H, d, J = 1.6Hz).

30 (2) [1-(2-chloro-5-pyridylmethyl)-1H-pyrazol-4-yl]methanol

**[0813]** In the same manner as in Example 128 (2), a crude product was obtained using the above-mentioned compound (9.90 g). This was purified by silica gel column chromatography to give the title compound (4.87 g) as an oil.

35  $^1\text{H-NMR}$ (300Mz,  $\text{CDCl}_3$ ) $\delta$ 1.69(1H, t, J = 5.1Hz), 4.59(2H, d, J = 5.1Hz), 5.27(2H, s), 7.31(1H, d, J = 8.4Hz), 7.43(1H, s), 7.52(1H, s), 7.55(1H, s), 8.30(1H, d, J = 2.4Hz).

(3) 4-(chloromethyl)-1-(2-chloro-5-pyridylmethyl)-1H-pyrazole

40 **[0814]** In the same manner as in Example 375 (3), the title compound (4.59 g) was obtained as a white solid using the above-mentioned compound (4.84 g).

$^1\text{H-NMR}$ (300Mz,  $\text{DMSO-d}_6$ ) $\delta$ 4.69(2H, s), 5.37(2H, s), 7.52(1H, d, J = 8.2Hz), 7.56(1H, s), 7.71(1H, dd, J = 8.2, 2.3Hz), 7.98(1H, s), 8.35(1H, d, J = 2.3Hz).

45 (4) triethyl 2-[1-(2-chloro-5-pyridylmethyl)-1H-pyrazol-4-yl]ethane-1, 1, 1-tricarboxylate

**[0815]** In the same manner as in Example 117 (1), a crude product was obtained using the above-mentioned compound (4.52 g). This was purified by silica gel column chromatography to give the title compound (7.33 g) as an oil.

50  $^1\text{H-NMR}$ (300Mz,  $\text{CDCl}_3$ ) $\delta$ 1.22(9H, t, J = 7.2Hz), 3.29(2H, s), 4.19(6H, q, J = 7.2Hz), 5.22(2H, s), 7.28(1H, d, J = 8.1Hz), 7.38-7.47(1H, m), 7.38(1H, s), 7.43(1H, s), 8.25(1H, s).

(5) monoethyl {[1-(2-chloro-5-pyridylmethyl)-1H-pyrazol-4-yl]methyl}malonate

55 **[0816]** In the same manner as in Example 117 (2), the title compound (5.54 g) was obtained as an oil using the above-mentioned compound (7.23 g).

$^1\text{H-NMR}$ (300Mz,  $\text{DMSO-d}_6$ ) $\delta$ 1.08(3H, t, J = 7.1Hz), 2.87(2H, d, J = 7.8Hz), 3.56(1H, t, J = 7.8Hz), 4.05(2H, q, J = 7.1Hz), 5.32(2H, s), 7.32(1H, s), 7.49(1H, d, J = 7.6Hz), 7.62-7.65(1H, s), 7.65(1H, s), 8.27(1H, d, J = 2.0Hz), 12.91(1H, brs).

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(6) ethyl 2-[[1-(2-chloro-5-pyridylmethyl)-1H-pyrazol-4-yl]methyl]-3-(N-ethyl-N-phenylamino)-3-oxopropionate

**[0817]** In the same manner as in Example 1 (4), the title compound (3.84 g) was obtained as an oil using the above-mentioned compound (3.87 g) and N-ethylaniline (1.73 mL).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.03(3H, t, J=7.2Hz), 1.24(3H, t, J = 7.2Hz), 2.10(1H, dd, J = 14.4, 5.6Hz), 3.07(1H, dd, J = 14.4, 9.6Hz), 3.35(1H, dd, J = 9.6, 5.6Hz), 3.61-3.73(2H, m), 4.11(2H, q, J = 7.2Hz), 5.22(2H, s), 6.80(2H, brs), 7.20-7.32(6H, m), 7.53(1H, dd, J = 8.0, 2.4Hz), 8.31(1H, d, J = 2.4Hz).

(7) 2-[[1-(2-chloro-5-pyridylmethyl)-1H-pyrazol-4-yl]methyl]-3-(N-ethyl-N-phenylamino)-3-oxopropionic acid

**[0818]** In the same manner as in Example 1 (3), the title compound (3.10 g) was obtained as a white solid using the above-mentioned compound (3.83 g).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.87(3H, t, J = 7.2Hz), 2.66-2.87(2H, m), 3.13-3.16(1H, m), 3.42-3.62(2H, m), 5.33(2H, s), 6.71(2H, brs), 7.10(1H, s), 7.33(3H, brs), 7.48(1H, s), 7.52(1H, d, J = 8.4Hz), 7.76(1H, dd, J = 8.4, 2.4Hz), 8.37(1H, d, J = 2.4Hz), 12.56(1H, brs).

(8) 2-[[1-(2-chloro-5-pyridylmethyl)-1H-pyrazol-4-yl]methyl]-N-ethyl-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

**[0819]** In the same manner as in Example 1 (2), the title compound (1.23 g) was obtained as a white solid using the above-mentioned compound (3.06 g) and trans-β-styrenesulfonamide (1.35 g).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.92(3H, t, J = 7.2Hz), 2.62-2.96(2H, m), 3.30-3.36(1H, m), 3.46-3.65(2H, m), 5.27(2H, s), 7.00-7.03(3H, m), 7.30-7.67(11H, m), 7.79-7.81(2H, m), 8.25(1H, d, J = 2.1Hz), 11.73(1H, brs).  
MS:578 (M+H)<sup>+</sup>.

Example 379 Synthesis of N-ethyl-N-phenyl-2-[[1-(3-pyridylmethyl)-1H-pyrazol-4-yl]methyl]-N'-((E)-styrylsulfonyl)malonamide hydrochloride

**[0820]** To a solution of the compound (340 mg) obtained in Example 378 in acetic acid (20 mL) was added zinc powder (780 mg), and the mixture was heated under reflux for 2 hr. Insoluble material was removed by filtration, and the filtrate was concentrated under reduced pressure. Ethyl acetate (10 mL) was added to the residue, and the precipitate was collected by filtration. This was purified by silica gel column chromatography to give the object compound, and this was converted to a hydrochloride salt with 1 mol/L hydrochloric acid-ethyl acetate to give the title compound (83 mg) as a white solid.

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ0.92(3H, t, J = 7.2Hz), 2.71(1H, dd, J = 14.0, 5.2Hz), 2.85(1H, dd, J = 14.0, 8.0Hz), 3.33-3.36(1H, m), 3.48-3.65(4H, m), 5.40(2H, s), 7.04-7.06(3H, m), 7.29(1H, d, J = 15.6Hz), 7.36-7.38(3H, m), 7.46-7.49(4H, m), 7.56(1H, d, J = 15.6Hz), 7.78-7.83(3H, m), 8.03(1H, d, J = 8.0Hz), 8.65(1H, s), 8.74(1H, d, J = 5.6Hz), 11.69(1H, brs).  
MS: 544 (M+H)<sup>+</sup>.

Example 380 Synthesis of N-ethyl-N-phenyl-2-[[1-(2-pyridylmethyl)-1H-pyrazol-4-yl]methyl]-N'-((E)-styrylsulfonyl)malonamide hydrochloride

(1) triethyl 2-[1-(2-pyridylmethyl)-1H-pyrazol-4-yl]ethane-1, 1, 1-tricarboxylate

**[0821]** In the same manner as in Example 371 (5), the title compound (600 mg) was obtained as an oil using hydrochloride salt (2.00 g) of the compound obtained in Example 371 (4) and 2-(chloromethyl)pyridine hydrochloride (990 mg). <sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.23(9H, t, J = 7.2Hz), 3.16(2H, s), 4.20(6H, q, J = 7.2Hz), 5.37(2H, s), 6.89(1H, d, J = 7.6Hz), 7.16-7.21(1H, m), 7.44(1H, s), 7.49(1H, s), 7.59-7.64(1H, m), 8.54-8.56(1H, m).

(2) monoethyl {[1-(2-pyridylmethyl)-1H-pyrazol-4-yl]methyl}malonate

**[0822]** In the same manner as in Example 117 (2), the title compound (300 mg) was obtained as an oil using the above-mentioned compound (600 mg).

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ1.12(3H, t, J = 7.2Hz), 2.90(2H, d, J = 8.0Hz), 3.56(1H, t, J = 8.0Hz), 5.34(2H, s), 6.90(1H, d, J = 7.6Hz), 7.29(1H, dd, J = 7.6, 4.8Hz), 7.31(1H, s), 7.62(1H, s), 7.71-7.75(1H, m), 8.52(1H, d, J = 4.8Hz), 12.85(1H, brs).

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(3) ethyl 3-(N-ethyl-N-phenylamino)-3-oxo-2-[[1-(2-pyridylmethyl)-1H-pyrazol-4-yl]methyl]propionate

**[0823]** In the same manner as in Example 1 (4), the title compound (340 mg) was obtained as an oil using the above-mentioned compound (297 mg) and N-ethylaniline (150  $\mu$ L).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>) $\delta$ 1.04(3H, t, J = 7.2Hz), 1.23(3H, t, J = 7.2Hz), 2.91(1H, dd, J = 14.4, 5.2Hz), 3.11(1H, dd, J = 14.4, 9.6Hz), 3.37(1H, dd, J = 9.6, 5.2Hz), 3.60-3.78 (2H, m), 4.12(2H, q, J = 7.2Hz), 5.37 (2H, s), 6.84(2H, brs), 7.06(1H, d, J = 7.6Hz), 7.17-7.23(1H, m), 7.23-7.30(5H, m), 7.59-7.66(1H, m), 8.56(1H, d, J = 4.4Hz).

(4) N-ethyl-N-phenyl-2-[[1-(2-pyridylmethyl)-1H-pyrazol-4-yl]methyl]-N'-((E)-styrylsulfonyl)malonamide hydrochloride

**[0824]** The above-mentioned compound (330 mg) was subjected to hydrolysis in the same manner as in Example 1 (3). The reaction mixture was neutralized with dilute hydrochloric acid and concentrated under reduced pressure. In the same manner as in Example 1 (2), the object compound was obtained using the residue and trans- $\beta$ -styrenesulfonamide (150 mg). This was converted to a hydrochloride salt with 1 mol/L hydrochloric acid-ethyl acetate to give the title compound (80 mg) as a white solid.

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>) $\delta$ 0.87-0.98(3H, m), 2.73(1H, dd, J = 14.0, 5.6Hz), 2.88(1H, dd, J = 14.0, 7.6Hz), 3.38(1H, dd, J = 7.6, 5.6Hz), 3.51-3.64(2H, m), 5.52(2H, s), 7.07-7.09(3H, m), 7.17(1H, d, J = 8.0Hz), 7.29(1H, d, J = 15.6Hz), 7.37-7.38(3H, m), 7.45-7.49(4H, m), 7.56(1H, d, J = 15.6Hz), 7.62-7.66(1H, m), 7.78-7.94(2H, m), 8.10-8.14(1H, m), 8.71(1H, d, J = 4.8Hz), 11.72(1H, brs).

MS: 544(M+H)<sup>+</sup>.

Example 381 Synthesis of 2-[[1-(2-chloro-5-pyridylmethyl)-1H-pyrazol-4-yl]methyl]-N-ethyl-N-(4-fluorophenyl)-N'-((E)-styrylsulfonyl)malonamide

(1) ethyl 2-[[1-(2-chloro-5-pyridylmethyl)-1H-pyrazol-4-yl]methyl]-3-[N-ethyl-N-(4-fluorophenyl)amino]-3-oxopropionate

**[0825]** In the same manner as in Example 1 (4), the title compound (2.12 g) was obtained as an oil using the compound (2.51 g) obtained in Example 378 (5) and N-ethyl-4-fluoroaniline (1.24 g).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>) $\delta$ 0.99-1.03(3H, m), 1.23(3H, t, J = 7.2Hz), 2.89(1H, dd, J = 14.4, 5.2Hz), 3.09(1H, dd, J = 14.4, 10.0Hz), 3.32(1H, dd, J = 10.0, 5.2Hz), 3.60-3.70(2H, m), 4.09-4.14(2H, m), 5.23(2H, s), 6.94-7.05(2H, m), 7.22-7.31(5H, m), 7.52-7.55(1H, m), 8.31(1H, d, J = 1.6Hz).

(2) 2-[[1-(2-chloro-5-pyridylmethyl)-1H-pyrazol-4-yl]methyl]-3-[N-ethyl-N-(4-fluorophenyl)amino]-3-oxopropionic acid

**[0826]** In the same manner as in Example 1 (3), the title compound (1.93 g) was obtained as a white solid using the above-mentioned compound (2.11 g).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>) $\delta$ 0.88(3H, t, J = 7.1Hz), 2.69-2.87(2H, m), 3.14-3.20(1H, m), 3.41-3.63(2H, m), 5.33(2H, s), 6.76(2H, brs), 7.04-7.21(3H, m), 7.49-7.53(2H, m), 7.76(1H, dd, J = 8.3, 2.3Hz), 8.36(1H, d, J = 2.3Hz), 12.53(1H, brs).

(3) 2-[[1-(2-chloro-5-pyridylmethyl)-1H-pyrazol-4-yl]methyl]-N-ethyl-N-(4-fluorophenyl)-N'-((E)-styrylsulfonyl)malonamide

**[0827]** In the same manner as in Example 1 (2), the title compound (1.27 g) was obtained as a white powder using the above-mentioned compound (1.91 g) and trans- $\beta$ -styrenesulfonamide (810 mg).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>) $\delta$ 0.90(3H, t, J = 7.1Hz), 2.63-2.92(2H, m), 3.19-3.31(1H, m), 3.47-3.60(2H, m), 5.25(2H, s), 7.00-7.21 (5H, m), 7.31(1H, d, J = 15.4Hz), 7.41-7.59(7H, m), 7.77-7.80(2H, m), 8.24(1H, d, J = 2.1Hz), 11.65(1H, brs). MS: 596(M+H)<sup>+</sup>.

Example 382 Synthesis of N-ethyl-N-(4-fluorophenyl)-2-[[1-(3-pyridylmethyl)-1H-pyrazol-4-yl]methyl]-N'-((E)-styrylsulfonyl)malonamide hydrochloride

**[0828]** In the same manner as in Example 379, the title compound (51 mg) was obtained as a white solid using the compound (1.24 g) obtained in Example 381.

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>) $\delta$ 0.91(3H, t, J = 7.2Hz), 2.64-2.90(2H, m), 3.30-3.37(1H, m), 3.98-3.60(2H, m), 5.38(2H, s), 7.08-7.21(5H, m), 7.31(1H, d, J = 15.6Hz), 7.48-7.49(4H, m), 7.56(1H, d, J = 15.6Hz), 7.73-7.80(3H, m), 7.96(1H, d, J = 7.6Hz), 8.61(1H, s), 8.71(1H, d, J = 0.8Hz), 11.68(1H, brs).

MS: 562(M+H)<sup>+</sup>.

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Example 383 Synthesis of 2-[[1-(2-aminobenzyl)-1H-pyrazol-4-yl]methyl]-N-ethyl-N-phenyl-N'-((E)-styrylsulfonyl)malonamide (1) triethyl 2-[1-(2-nitrobenzyl)-1H-pyrazol-4-yl]ethane-1, 1, 1-tricarboxylate

5 **[0829]** In the same manner as in Example 371 (5), the title compound (810 mg) was obtained as an oil using hydrochloride salt (1.13 g) of the compound obtained in Example 371 (4) and 2-nitrobenzyl bromide (700 mg).  
<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.25(9H, t, J = 1.8Hz), 4.22(6H, q, J = 1.8Hz), 5.67(2H, s), 6.69(1H, d, J = 7.6Hz), 7.43-7.53(2H, m), 7.46(1H, s), 7.51(1H, s), 8.09-8.11(1H, m).

10 (2) monoethyl {[1-(2-nitrobenzyl)-1H-pyrazol-4-yl]methyl}malonate

**[0830]** In the same manner as in Example 117 (2), the title compound (630 mg) was obtained as an oil using the above-mentioned compound (810 mg).  
<sup>1</sup>H-NMR(400Mz) DMSO-d<sub>6</sub>)δ1.12(3H, t, J=7.2Hz), 2.91(2H, d, J = 8.0Hz), 3.54-3.60(1H, m), 4.07(2H, q, J = 7.2Hz), 5.64(2H, s), 6.70-6.75(1H, m), 7.37(1H, s), 7.51-7.70(2H, m), 7.63(1H, s), 8.06-8.11(1H, m), 12.85(1H, brs).

15 (3) ethyl 3-(N-ethyl-N-phenylamino)-2-[[1-(2-nitrobenzyl)-1H-pyrazol-4-yl]methyl]-3-oxopropionate

**[0831]** In the same manner as in Example 1 (4), the title compound (568 mg) was obtained as an oil using the above-mentioned compound (630 mg) and N-ethylaniline (280 μL). <sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ1.08(3H, t, J = 7.1Hz), 1.24(3H, t, J = 7.1Hz), 2.88-3.17(2H, m), 3.35-3.42(1H, m), 3.60-3.82(2H, m), 4.13(2H, q, J = 7.1Hz), 5.67(2H, s), 6.83-6.95(3H, m), 7.26-7.36(5H, m), 7.40-7.56(2H, m), 8.11(1H, d, J = 7.8Hz).

20 (4) 3-(N-ethyl-N-phenylamino)-2-[[1-(2-nitrobenzyl)-1H-pyrazol-4-yl]methyl]-3-oxopropionic acid

25 **[0832]** In the same manner as in Example 1 (3), the title compound (450 mg) was obtained as a white powder using the above-mentioned compound (568 mg).  
<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ0.93(3H, t, J = 7.2Hz), 2.72-2.89(2H, m), 3.18-3.25(1H, m), 3.52-3.61(2H, m), 5.64(2H, s), 6.87(2H, brs), 6.92-7.00(1H, m), 7.14(1H, s), 7.36(3H, brs), 7.45(1H, s), 7.53-7.61(1H, m), 7.64-7.72(1H, m), 8.05-8.10(1H, m), 12.56(1H, brs).

30 (5) N-ethyl-2-[[1-(2-nitrobenzyl)-1H-pyrazol-4-yl]methyl]-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

**[0833]** In the same manner as in Example 1 (2), the title compound (450 mg) was obtained as a pale-yellow solid using the above-mentioned compound (450 mg) and trans-β-styrenesulfonamide (200 mg).  
<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ0.88-0.98(3H, m), 2.66-3.93(2H, m), 3.30-3.42(1H, m), 3.49-3.65(2H, m), 5.58(2H, s), 6.70-6.77(1H, m), 7.03-7.12(3H, m), 7.27-7.69(11H, m), 7.79-7.81(2H, m), 8.06-8.11(1H, m), 11.70(1H, brs).

(6) 2-[[1-(2-aminobenzyl)-1H-pyrazol-4-yl]methyl]-N-ethyl-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

40 **[0834]** To a solution of the above-mentioned compound (430 mg) in ethanol (20 mL) were added acetic acid (1.0 mL) and zinc powder (500 mg), and the mixture was heated under reflux for 30 min. Insoluble material was removed by filtration, and the filtrate was concentrated under reduced pressure. Ethyl acetate (30 mL) was added to the residue, and the mixture was stirred. The precipitate was collected by filtration to give the title compound (187 mg) as a white solid.  
<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.84(3H, t, J = 7.1Hz), 2.58-2.90(2H, m), 3.24-3.28(1H, m), 3.39-3.50(2H, m), 5.09(2H, s), 5.24(2H, brs), 6.48-6.55(1H, m), 6.63-6.69(1H, m), 6.80(2H, brs), 6.95-7.42(12H, m), 7.49-7.54(2H, m).  
MS: 558(M+H)<sup>+</sup>.

50 Example 384 Synthesis of 2-[[1-(3-aminobenzyl)-1H-pyrazol-4-yl]methyl]-N-ethyl-N-phenyl-N'-((E)-styrylsulfonyl)malonamide (1) triethyl 2-[1-(3-nitrobenzyl)-1H-pyrazol-4-yl]ethane-1, 1, 1-tricarboxylate

**[0835]** In the same manner as in Example 371 (5), the title compound (600 mg) was obtained as an oil using hydrochloride salt (1.13 g) of the compound obtained in Example 371 (4) and 3-nitrobenzyl bromide (560 mg).  
<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.23(9H, t, J = 7.2Hz), 3.31(2H, s), 4.20(2H, q, J = 7.2Hz), 5.33(2H, s), 7.42-7.52(4H, m), 8.01(1H, s), 8.12-8.16(1H, m).

55 (2) monoethyl {[1-(3-nitrobenzyl)-1H-pyrazol-4-yl]methyl}malonate

**[0836]** In the same manner as in Example 117 (2), the title compound (465 mg) was obtained as an oil using the

above-mentioned compound (600 mg).

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ1.09(3H, t, J = 7.2Hz), 2.89(2H, d, J = 8.0Hz), 3.56(1H, t, J = 8.0Hz), 4.05(2H, q, J = 7.2Hz), 5.42(2H, s), 7.34(1H, s), 7.58-7.69(3H, m), 8.05(1H, s), 8.14(1H, d, J = 7.6Hz), 12.88(1H, brs).

5 (3) ethyl 3-(N-ethyl-N-phenylamino)-2-[[1-(3-nitrobenzyl)-1H-pyrazol-4-yl]methyl]-3-oxopropionate

**[0837]** In the same manner as in Example 1 (4), the title compound (400 mg) was obtained as an oil using the above-mentioned compound (465 mg) and N-ethylaniline (210 μL). <sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.02(3H, t, J = 7.2Hz), 1.23(3H, t, J = 7.2Hz), 2.91(1H, dd, J = 14.4, 5.6Hz), 3.10(1H, dd, J = 14.4, 9.6Hz), 3.37(1H, dd, J = 9.6, 5.6Hz), 3.61-3.72(2H, m), 4.12(2H, q, J = 7.2Hz), 5.34(2H, s), 6.83(2H, brs), 7.24-7.38(5H, m), 7.50-7.56(2H, m), 8.09(1H, s), 8.15-8.17(1H, m).

(4) 3-(N-ethyl-N-phenylamino)-2-[[1-(3-nitrobenzyl)-1H-pyrazol-4-yl]methyl]-3-oxopropionic acid

**[0838]** In the same manner as in Example 1 (3), the title compound (384 mg) was obtained as an oil using the above-mentioned compound (400 mg).

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ0.86(3H, t, J = 7.2Hz), 2.69-2.89(2H, m), 3.12-3.20(1H, m), 3.42-3.63(2H, m), 4.03(2H, q, J = 7.2Hz), 5.44(2H, s), 6.71(2H, brs), 7.13(1H, s), 7.21-7.36(3H, m), 7.50(1H, s), 7.62-7.77(2H, m), 8.13-8.17(2H, m), 12.55(1H, brs).

20 (5) N-ethyl-2-[[1-(3-nitrobenzyl)-1H-pyrazol-4-yl]methyl]-N-phenyl-N'-(E)-styrylsulfonylmalonamide

**[0839]** In the same manner as in Example 1 (2), the title compound (272 mg) was obtained as a white solid using the above-mentioned compound (375 mg) and trans-β-styrenesulfonamide (163 mg).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.89(3H, t, J = 7.2Hz), 2.62-2.93(2H, m), 7.15-3.31(1H, m), 3.45-3.62(2H, m), 5.37(2H, s), 6.90-7.08(3H, m), 7.20-7.64(11H, m), 7.70-7.82(2H, m), 8.03(1H, s), 8.01-8.18(1H, m), 11.68(1H, brs).

(6) 2-[[1-(3-aminobenzyl)-1H-pyrazol-4-yl]methyl]-N-ethyl-N-phenyl-N'-(E)-styrylsulfonylmalonamide

**[0840]** In the same manner as in Example 383 (6), the title compound (107 mg) was obtained as a white solid using the above-mentioned compound (260 mg).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.88(3H, t, J = 7.1Hz), 2.58-2.94(2H, m), 3.24-3.30(1H, m), 3.40-3.57(2H, m), 5.02(2H, s), 5.06(2H, s), 6.32-6.50(3H, m), 6.75-7.22(10H, m), 7.29-7.43(3H, m), 7.49-7.56(2H, m).  
MS: 558(M+H)<sup>+</sup>.

35 Example 385 Synthesis of 2-[[1-(benzyl-1H-pyrazol-4-yl)methyl]-N, N-diethyl-N'-(E)-styrylsulfonylmalonamide

(1) ethyl 2-[[1-(benzyl-1H-pyrazol-4-yl)methyl]-3-(N, N-diethylamino)-3-oxopropionate

**[0841]** In the same manner as in Example 1 (4), the title compound (3.62 g) was obtained as an oil using the compound (3.48 g) obtained in Example 371 (6).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.86-0.92(6H, m), 1.12(3H, t, J = 7.1Hz), 2.87(2H, d, J = 7.4Hz), 3.15-3.24(4H, m), 3.86(1H, t, J = 7.4Hz), 4.04(2H, q, J = 7.4Hz), 5.23(2H, s), 7.15(2H, d, J = 7.2Hz), 7.26-7.33(4H, m), 7.50(1H, s).

(2) 2-[[1-(benzyl-1H-pyrazol-4-yl)methyl]-3-(N, N-diethylamino)-3-oxopropionic acid

**[0842]** In the same manner as in Example 1 (3), the title compound (3.32 g) was obtained as an oil using the above-mentioned compound (3.62 g).

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ0.82-0.91(6H, m), 2.81-2.89(2H, m), 3.11-3.30(4H, m), 3.75(1H, t, J = 7.2Hz), 5.23(2H, s), 7.15(2H, d, J = 6.4Hz), 7.25-7.33(4H, m), 7.49(1H, s), 12.56(1H, brs).

(3) 2-[[1-(benzyl-1H-pyrazol-4-yl)methyl]-N, N-diethyl-N'-(E)-styrylsulfonylmalonamide

**[0843]** In the same manner as in Example 1 (2), the title compound (2.02 g) was obtained as a white solid using the above-mentioned compound (3.32 g) and trans-β-styrenesulfonamide (1.85 g).

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ0.90-0.96(6H, m), 2.86(2H, d, J = 7.2Hz), 3.11-3.27(4H, m), 3.73(1H, t, J = 7.2Hz), 5.17(2H, s), 7.13(2H, d, J = 7.2Hz), 7.23-7.32(5H, m), 7.43-7.50(4H, m), 7.56(1H, d, J = 15.2Hz), 7.72(2H, d, J = 7.2Hz), 11.99(1H, brs).  
MS: 495(M+H)<sup>+</sup>.

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Example 386 Synthesis of N, N-diethyl-2-[[1-(4-fluorobenzyl)-1H-pyrazol-4-yl]methyl]-N'-((E)-styrylsulfonyl)malonamide

(1) ethyl 3-(N, N-diethylamino)-2-[[1-(4-fluorobenzyl)-1H-pyrazol-4-yl]methyl]-3-oxopropionate

5 **[0844]** In the same manner as in Example 1 (4), the title compound (1.71 g) was obtained as an oil using the compound (2.12 g) obtained in Example 375 (5).

$^1\text{H-NMR}$ (400Mz,  $\text{CDCl}_3$ ) $\delta$ 0.93-1.07(6H, m), 1.26(3H, t, J = 7.2Hz), 3.00-3.17(3H, m), 3.24-3.40(3H, m), 3.62-3.66(1H, m), 4.15(2H, q, J = 7.2Hz), 5.18(2H, s), 6.97-7.03(2H, m), 7.14-7.20(2H, m), 7.21(1H, s), 7.36(1H, s).

10 (2) 3-(N, N-diethylamino)-2-[[1-(4-fluorobenzyl)-1H-pyrazol-4-yl]methyl]-3-oxopropionic acid

**[0845]** In the same manner as in Example 1 (3), the title compound (1.48 g) was obtained as a pale-yellow solid using the above-mentioned compound (1.70 g).

15  $^1\text{H-NMR}$ (300Mz,  $\text{DMSO-d}_6$ ) $\delta$ 0.83-0.90(6H, m), 2.83(2H, d, J = 7.2Hz), 3.05-3.32(4H, m), 3.74(1H, t, J = 7.2Hz), 5.22(2H, s), 7.11-7.25(5H, m), 7.49(1H, s), 12.58(1H, brs).

(3) N, N-diethyl-2-[[1-(4-fluorobenzyl)-1H-pyrazol-4-yl]methyl]-N'-((E)-styrylsulfonyl)malonamide

20 **[0846]** In the same manner as in Example 1 (2), the title compound (740 mg) was obtained as a white solid using the above-mentioned compound (1.48 g) and trans- $\beta$ -styrenesulfonamide (780 mg).

$^1\text{H-NMR}$ (400Mz,  $\text{DMSO-d}_6$ ) $\delta$ 0.89-0.95(6H, m), 2.86(2H, d, J = 7.2Hz), 3.11-3.27(4H, m), 3.72(1H, t, J = 7.2Hz), 5.16(2H, s), 7.09-7.23(5H, m), 7.30(1H, d, J = 15.2Hz), 7.43-7.48(4H, m), 7.56(1H, d, J = 15.2Hz), 7.73(2H, dd, J = 7.6, 1.6Hz), 11.99(1H, brs).

25 MS: 513(M+H) $^+$ .

Example 387 Synthesis of 2-[[1-(4-chlorobenzyl)-1H-pyrazol-4-yl]methyl]-N,N-diethyl-N'-((E)-styrylsulfonyl)malonamide

(1) ethyl 1-(4-chlorobenzyl)-1H-pyrazole-4-carboxylate

30 **[0847]** In the same manner as in Example 375 (1), the title compound (33.8 g) was obtained as a white solid using 4-chlorobenzyl chloride (25.0 g).

$^1\text{H-NMR}$ (400Mz,  $\text{DMSO-d}_6$ ) $\delta$ 1.26(3H, t, J = 7.2Hz), 4.21(2H, q, J = 7.2Hz), 5.37(2H, s), 7.29(2H, d, J = 8.4Hz), 7.42(2H, d, J = 8.4Hz), 7.87(1H, s), 8.47(1H, s).

35 (2) [1-(4-chlorobenzyl)-1H-pyrazol-4-yl]methanol

**[0848]** In the same manner as in Example 128 (2), the title compound (8.20 g) was obtained as an oil using the above-mentioned compound (1.00 g).

40  $^1\text{H-NMR}$ (400Mz,  $\text{CDCl}_3$ ) $\delta$ 4.58(2H, d, J = 4.0Hz), 5.24(2H, s), 7.16(2H, d, J = 8.4Hz), 7.30-7.34(2H, m), 7.38(1H, s), 7.53(1H, s).

(3) 1-(4-chlorobenzyl)-4-(chloromethyl)-1H-pyrazole

**[0849]** In the same manner as in Example 375 (3), the title compound (8.19 g) was obtained as a white solid using the above-mentioned compound (7.97 g).

45  $^1\text{H-NMR}$ (400Mz,  $\text{CDCl}_3$ ) $\delta$ 4.52(2H, s), 5.24(2H, s), 7.15(2H, d, J = 8.4Hz), 7.29-7.34(2H, m), 7.40(1H, s), 7.55(1H, s).

(4) triethyl 2-[1-(4-chlorobenzyl)-1H-pyrazol-4-yl]ethane-1, 1, 1-tricarboxylate

50 **[0850]** In the same manner as in Example 117 (1), a crude product was obtained using the above-mentioned compound (8.18 g). The crude product was purified by silica gel column chromatography to give the title compound (12.3 g) as an oil.

$^1\text{H-NMR}$ (400Mz,  $\text{CDCl}_3$ ) $\delta$ 1.21(9H, t, J = 7.2Hz), 3.29(2H, s), 4.18(6H, q, J = 7.2Hz), 5.19(2H, s), 7.09(2H, d, J = 8.4Hz), 7.28(2H, d, J = 8.4Hz), 7.36(1H, s), 7.39(1H, s).

(5) monoethyl[[1-(4-chlorobenzyl)-1H-pyrazol-4-yl]methyl]malonate

55 **[0851]** In the same manner as in Example 117 (2), the title compound (9.30 g) was obtained as a white solid using the above-mentioned compound (12.3 g).

$^1\text{H-NMR}$ (400Mz,  $\text{CDCl}_3$ ) $\delta$ 1.21(3H, t, J = 6.8Hz), 3.07-3.09(2H, m), 3.55(1H, t, J = 7.2Hz), 4.15-4.20(2H, m), 5.21(2H,

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s), 7.09(2H, d, J = 8.0Hz), 7.24-7.28(2H, m), 7.29(1H, s), 7.39(1H, s).

(6) ethyl 2-[[1-(4-chlorobenzyl)-1H-pyrazol-4-yl]methyl]-3-(N, N-diethylamino)-3-oxopropionate

5 **[0852]** In the same manner as in Example 1 (4), the title compound (3.90 g) was obtained as an oil using the above-mentioned compound (4.71 g).

<sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ0.98(3H, t, J = 7.2Hz), 1.04(3H, t, J = 7.1Hz), 1.22(3H, t, J = 7.1Hz), 3.00-3.39(6H, m), 4.15(2H, q, J = 7.1Hz), 5.18(2H, s), 7.11(2H, d, J = 8.3Hz), 7.22(1H, s), 7.28(2H, d, J = 8.3Hz), 7.36(1H, s).

10 (7) 2-[[1-(4-chlorobenzyl)-1H-pyrazol-4-yl]methyl]-3-(N, N-diethylamino)-3-oxopropionic acid

**[0853]** In the same manner as in Example 1 (3), the title compound (3.60 g) was obtained as a white solid using the above-mentioned compound (3.88 g).

15 <sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.04(6H, t, J = 7.2Hz), 2.95-3.22(5H, m), 3.46-3.55(1H, m), 3.60-3.66(1H, m), 5.20(2H, s), 7.10-7.15(2H, m), 7.22-7.36(4H, m).

(8) 2-[[1-(4-chlorobenzyl)-1H-pyrazol-4-yl]methyl]-N, N-diethyl-N'-((E)-styrylsulfonyl)malonamide

20 **[0854]** In the same manner as in Example 1 (2), the title compound (1.79 g) was obtained as a white solid using the above-mentioned compound (3.51 g) and trans-β-styrenesulfonamide (1.76 g).

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ0.89-0.96(6H, m), 2.86(2H, d, J = 7.2Hz), 3.09-3.28(4H, m), 3.73(1H, t, J = 7.2Hz), 5.18(2H, s), 7.15(2H, d, J = 8.0Hz), 7.24-7.36(4H, m), 7.43-7.49(4H, m), 7.56(1H, d, J = 15.6Hz), 7.37(2H, d, J = 8.0Hz), 11.99(1H, brs).

MS: 529(M+H)<sup>+</sup>.

25

Example 388 Synthesis of 2-[[1-(2-chloro-5-pyridylmethyl)-1H-pyrazol-4-yl]methyl]-N, N-diethyl-N'-((E)-styrylsulfonyl)malonamide

(1) ethyl 2-[[1-(2-chloro-5-pyridylmethyl)-1H-pyrazol-4-yl]methyl]-3-(N, N-diethylamino)-3-oxopropionate

30

**[0855]** In the same manner as in Example 1 (4), the title compound (1.15 g) was obtained as a white powder using the compound (1.63 g) obtained in Example 378 (5).

35 <sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ0.99(3H, t, J = 7.2Hz), 1.04(3H, t, J = 7.2Hz), 1.22(3H, t, J = 7.2Hz), 3.00-3.44(6H, m), 3.62-3.69(1H, m), 4.16(2H, q, J = 7.2Hz), 5.21(2H, s), 7.26-7.29(2H, m), 7.38(1H, s), 7.47(1H, dd, J = 8.1, 2.4Hz), 8.25(1H, d, J = 2.4Hz).

(2) 2-[[1-(2-chloro-5-pyridylmethyl)-1H-pyrazol-4-yl]methyl]-3-(N, N-diethylamino)-3-oxopropionic acid

40 **[0856]** In the same manner as in Example 1 (3), the title compound (850 mg) was obtained as a white powder using the above-mentioned compound (1.15 g).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.81-0.89(6H, m), 2.83(2H, d, J = 7.2Hz), 3.10-3.31(4H, m), 3.75(1H, t, J = 7.2Hz), 5.30(2H, s), 7.27(1H, s), 7.49(1H, d, J = 8.1Hz), 7.56(1H, s), 7.64(1H, dd, J = 8.1, 2.4Hz), 8.26(1H, d, J = 2.4Hz), 12.56(1H, brs).

(3) 2-[[1-(2-chloro-5-pyridylmethyl)-1H-pyrazol-4-yl]methyl]-N, N-diethyl-N'-((E)-styrylsulfonyl)malonamide

45

**[0857]** In the same manner as in Example 1 (2), the title compound (442 mg) was obtained as a white solid using the above-mentioned compound (850 mg) and trans-β-styrenesulfonamide (430 mg).

50 <sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ.86-0.94(6H, m), 2.86(2H, d, J = 6.6Hz), 3.07-3.30(4H, m), 3.71(1H, t, J = 6.6Hz), 5.25(2H, s), 7.26(1H, s), 7.34(1H, d, J = 15.6Hz), 7.45-7.47(4H, m), 7.54-7.61(2H, m), 7.73-7.76(2H, m), 8.25(1H, d, J = 2.1Hz), 12.07(1H, brs). MS: 530(M+H)<sup>+</sup>.

Example 389 Synthesis of 2-[[1-(benzyl-1H-pyrazol-4-yl)methyl]-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

55 **[0858]** In the same manner as in Example 1 (2), the title compound (2.05 g) was obtained as a white solid using the compound (2.14 g) obtained in Example 358 (2).

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ0.78-0.98(6H, m), 2.73(2H, m), 3.06-3.21(4H, m), 3.70(1H, t, J = 7.2Hz), 5.08(1H, d, J = 10.2Hz), 5.14(1H, d, J = 10.2Hz), 7.11(2H, d, J = 6.8Hz), 7.15(1H, s), 7.23-7.32(3H, m), 7.34(1H, s), 7.68-7.77(2H, m), 7.81(1H, dd, J = 8.4, 1.6Hz), 8.07(1H, d, J = 8.0Hz), 8.12(1H, d, J = 8.4Hz), 8.21(1H, d, J = 8.0Hz), 8.57(1H, d, J =

1.6H), 12.29(1H, brs).

MS: 519(M+H)<sup>+</sup>.

Example 390 Synthesis of N, N-diethyl-2-[[1-(2-fluorobenzyl)-1H-pyrazol-4-yl]methyl]-N'-(2-naphthylsulfonyl)malonamide (1) ethyl 1-(2-fluorobenzyl)-1H-pyrazole-4-carboxylate

**[0859]** In the same manner as in Example 375 (1), the title compound (1.90 g) was obtained as an oil using 2-fluorobenzyl bromide (1.53 g).

<sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ1.33(3H, t, J=7.2Hz), 4.28(2H, q, J = 7.2Hz), 5.36(2H, s), 7.06-7.38(4H, m), 7.92(1H, s), 7.93(1H, s).

(2) [1-(2-fluorobenzyl)-1H-pyrazol-4-yl]methanol

**[0860]** In the same manner as in Example 128 (2), a crude product was obtained using the above-mentioned compound (1.90 g), and the crude product was purified by silica gel column chromatography to give the title compound (860 mg) as an oil. <sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.54(3H, t, J = 5.2Hz), 4.57(2H, d, J = 5.2Hz), 5.33(2H, s), 7.05-7.13(2H, m), 7.17-7.20(1H, m), 7.25-7.33(1H, m), 7.44(1H, s), 7.52(1H, s).

(3) 1-(2-fluorobenzyl)-4-(chloromethyl)-1H-pyrazole

**[0861]** In the same manner as in Example 375 (3), the title compound (937 mg) was obtained as an oil using the above-mentioned compound (860 mg).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ4.53(2H, s), 5.33(2H, s), 7.06-7.34(4H, m), 7.47(1H, s), 7.54(1H, s).

(4) triethyl 2-[1-(2-fluorobenzyl)-1H-pyrazol-4-yl]ethane-1, 1, 1-tricarboxylate

**[0862]** In the same manner as in Example 117 (1), the title compound (1.70 g) was obtained as an oil using the above-mentioned compound (937 mg).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.21(9H, t, J = 7.2Hz), 3.30(2H, s), 4.18(6H, q, J = 7.2Hz), 5.28(2H, s), 7.03-7.09(3H, m), 7.25-7.28(1H, m), 7.39(1H, s), 7.40(1H, s).

(5) monoethyl {[1-(2-fluorobenzyl)-1H-pyrazol-4-yl]methyl}malonate

**[0863]** In the same manner as in Example 117 (2), the title compound (1.24 g) was obtained as an oil using the above-mentioned compound (1.68 g).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.23(3H, t, J = 7.2Hz), 3.09-3.14(2H, m), 3.56(1H, t, J = 7.2Hz), 4.17(2H, q, J = 7.2Hz), 5.30(2H, s), 7.04-7.13(3H, m), 7.26-7.30(1H, m), 7.30(1H, s), 7.38(1H, s).

(6) ethyl 3-(N, N-diethylamino)-2-[[1-(2-fluorobenzyl)-1H-pyrazol-4-yl]methyl]-3-oxopropionate

**[0864]** In the same manner as in Example 1 (4), the title compound (1.06 g) was obtained as an oil using the above-mentioned compound (1.24 g).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.85-0.92(6H, m), 1.12(3H, t, J = 7.0Hz), 2.87(2H, d, J = 7.4Hz), 3.15-3.23(4H, m), 3.86(1H, t, J = 7.4Hz), 4.04(2H, q, J = 7.0Hz), 5.29(2H, s), 7.03-7.22(3H, m), 7.26(1H, s), 7.30-7.39(1H, m), 7.49(1H, s).

(7) 3-(N, N-diethylamino)-2-[[1-(2-fluorobenzyl)-1H-pyrazol-4-yl]methyl]-3-oxopropionic acid

**[0865]** In the same manner as in Example 1 (3), the title compound (962 mg) was obtained as an oil using the above-mentioned compound (1.04 g).

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ0.83-0.91(6H, m), 2.83-2.85(2H, m), 3.12-3.27(4H, m), 3.74(1H, dd, J = 8.0, 7.2Hz), 5.28(2H, s), 7.07-7.22(3H, m), 7.24(1H, s), 7.32-7.36(1H, m), 7.47(1H, s).

(8) N, N-diethyl-2-[[1-(2-fluorobenzyl)-1H-pyrazol-4-yl]methyl]-N'-(2-naphthylsulfonyl)malonamide

**[0866]** In the same manner as in Example 1 (2), the title compound (577 mg) was obtained as a white solid using the above-mentioned compound (930 mg).

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ0.77-0.88(6H, m), 2.71-2.82(2H, m), 3.04-3.20(4H, m), 3.70(1H, t, J = 7.2Hz), 5.15(1H, d, J = 10.2Hz), 5.29(1H, d, J = 10.2Hz), 7.01-7.05(1H, m), 7.10-7.21(3H, m), 7.31-7.37(2H, m), 7.68-7.76(2H, m), 7.82(1H,

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dd, J = 8.8, 1.6Hz), 8.06(1H, d, J = 8.0Hz), 8.13(1H, d, J = 8.8Hz), 8.21(1H, d, J = 8.0Hz), 8.57(1H, d, J = 1.6Hz), 12.31(1H, brs).  
MS:537 (M+H)<sup>+</sup>.

- 5 Example 391 Synthesis of 2-[[1-(2-chlorobenzyl)-1H-pyrazol-4-yl]methyl]-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide (1) ethyl 2-[[1-(2-chlorobenzyl)-1H-pyrazol-4-yl]methyl]-3-(N, N-diethylamino)-3-oxopropionate

**[0867]** In the same manner as in Example 1 (4), the title compound (389 mg) was obtained as an oil using the compound (410 mg) obtained in Example 377 (2).

- 10 <sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ0.99-1.07(6H, m), 1.22(3H, t, J = 7.2Hz), 3.03-3.18(3H, m), 3.23-3.42(3H, m), 3.66(1H, dd, J = 9.6, 6.0Hz), 4.16(2H, q, J = 7.2Hz), 5.34(2H, s), 6.98(1H, dd, J = 7.2, 1.2Hz), 7.19-7.28(3H, m), 7.36-7.38(2H, m).

(2) 2-[[1-(2-chlorobenzyl)-1H-pyrazol-4-yl]methyl]-3-(N, N-diethylamino)-3-oxopropionic acid

- 15 **[0868]** In the same manner as in Example 1 (3), the title compound (351 mg) was obtained as an oil using the above-mentioned compound (378 mg).

<sup>1</sup>H-NMR (400Mz, DMSO-d<sub>6</sub>)δ0.90(6H, t, J = 7.2Hz), 2.83-2.90(2H, m), 3.10-3.30(4H, m), 3.73-3.79(1H, m), 5.33(2H, s), 6.85-6.92(1H, m), 7.24-7.36(3H, m), 7.45-7.52(2H, m), 12.52(1H, brs).

- 20 (3) 2-[[1-(2-chlorobenzyl)-1H-pyrazol-4-yl]methyl]-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

**[0869]** In the same manner as in Example 1 (2), the title compound (150 mg) was obtained as a white solid using the above-mentioned compound (351 mg).

- 25 <sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ0.75-0.88(6H, m), 2.74-2.84(2H, m), 3.07-3.21(4H, m), 3.73(1H, t, J = 7.2Hz), 5.22(2H, s), 6.84(1H, d, J = 7.6Hz), 7.20(1H, s), 7.23-7.33(2H, m), 7.36(1H, s), 7.45(1H, d, J = 8.0Hz), 7.67-7.84(3H, m), 8.06(1H, d, J = 8.0Hz), 8.12(1H, d, J = 8.8Hz), 8.20(1H, d, J = 8.0Hz), 8.57(1H, s), 12.30(1H, brs).

MS: 553(M+H)<sup>+</sup>.

- 30 Example 392 Synthesis of N, N-diethyl-N'-(2-naphthylsulfonyl)-2-[[1-((2E)-3-phenyl-2-propen-1-yl)-1H-pyrazol-4-yl]methyl]malonamide

(1) triethyl 2-[1-((2E)-3-phenyl-2-propen-1-yl)-1H-pyrazol-4-yl]ethane-1, 1, 1-tricarboxylate

**[0870]** In the same manner as in Example 371 (5), the title compound (1.04 g) was obtained as an oil using hydrochloride salt (1.50 g) of the compound obtained in Example 371 (4) and trans-cinnamyl chloride (630 μL).

- 35 <sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ1.23(9H, t, J = 7.1Hz), 3.31(2H, s), 4.20(6H, q, J = 7.1Hz), 4.82(1H, d, J = 8.8Hz), 6.26-6.54(2H, m), 7.22-7.42(7H, m).

(2) monoethyl {[1-((2E)-3-phenyl-2-propen-1-yl)-1H-pyrazol-4-yl]methyl}malonate

- 40 **[0871]** In the same manner as in Example 117 (2), the title compound (540 mg) was obtained as an oil using the above-mentioned compound (1.04 g).

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ1.11(3H, t, J = 7.2Hz), 2.89(2H, d, J = 7.6Hz), 3.55(1H, t, J = 7.6Hz), 4.05(2H, q, J = 7.2Hz), 4.83(1H, d, J = 5.6Hz), 6.37-6.52(2H, m), 7.22-7.46(6H, m), 7.53(1H, s), 12.79(1H, brs).

- 45 (3) ethyl 3-(N, N-diethylamino)-3-oxo-2-[[1-((2E)-3-phenyl-2-propen-1-yl)-1H-pyrazol-4-yl]methyl]propionate

**[0872]** In the same manner as in Example 1 (4), the title compound (496 mg) was obtained as an oil using the above-mentioned compound (530 mg).

- 50 <sup>1</sup>H-NMR (400Mz, CDCl<sub>3</sub>)δ0.98-1.11 (6H, m), 1.22(3H, t, J = 7.2Hz), 3.04-3.20(3H, m), 3.31-3.38(3H, m), 3.67(1H, dd, J = 8.8, 6.4Hz), 4.16(2H, q, J = 7.2Hz), 4.81(2H, d, J = 6.4Hz), 6.27-6.34(1H, m), 6.54(1H, d, J = 16.0Hz), 7.23-7.37(7H, m).

(4) 3-(N, N-diethylamino)-3-oxo-2-[[1-((2E)-3-phenyl-2-propen-1-yl)-1H-pyrazol-4-yl]methyl]propionic acid

- 55 **[0873]** In the same manner as in Example 1 (3), the title compound (430 mg) was obtained as a white powder using the above-mentioned compound (493 mg).

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ0.92(6H, t, J = 7.2Hz), 2.86(2H, d, J = 7.2Hz), 3.10-3.26(4H, m), 3.71-3.79(1H, m), 4.81(2H, d, J = 6.0Hz), 6.33-6.53(2H, m), 7.25-7.41(6H, m), 7.45(1H, s), 12.48(1H, brs).

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(5) N, N-diethyl-N'-(2-naphthylsulfonyl)-2-[[1-((2E)-3-phenyl-2-propen-1-yl)-1H-pyrazol-4-yl]methyl]malonamide

**[0874]** In the same manner as in Example 1 (2), the title compound (315 mg) was obtained as a white powder using the above-mentioned compound (423 mg).

5 <sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ0.83-0.88(6H, m), 2.78(2H, d, J = 7.2Hz), 3.07-3.25(4H, m), 3.71(1H, t, J = 7.2Hz), 4.68-4.71(2H, m), 6.27-6.35(1H, m), 6.47(1H, d, J = 16.0Hz), 7.15(1H, s), 7.25-7.41(6H, m), 7.65-7.83(3H, m), 8.06(1H, d, J = 8.0Hz), 8.13(1H, d, J = 8.8Hz), 8.21(1H, d, J = 8.0Hz), 8.56(1H, s), 12.28(1H, brs).  
MS: 545(M+H)<sup>+</sup>.

10 Example 393 Synthesis of N, N-diethyl-N'-(2-naphthylsulfonyl)-2-[[1-(3-phenylpropyl)-1H-pyrazol-4-yl]methyl]malonamide

**[0875]** In the same manner as in Example 7, the title compound (150 mg) was obtained as a white powder using the compound (170 mg) obtained in Example 392 at room temperature.

15 <sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.83-0.87 (6H, m), 1.85-1.99(2H, m), 2.44(2H, t, J = 7.8Hz), 2.75(2H, d, J = 7.2Hz), 3.06-3.27(4H, m), 3.70(1H, t, J = 7.2Hz), 3.77-3.92(2H, m), 7.13-7.29(7H, m), 7.65-7.83(3H, m), 8.05-8.23(3H, m), 8.57(1H, s), 12.34(1H, brs).  
MS: 547(M+H)<sup>+</sup>.

20 Example 394 Synthesis of 2-[(1-ethyl-1H-pyrazol-4-yl)methyl]-N-(4-fluorophenyl)-N-isopropyl-N'-((E)-styrylsulfonyl)malonamide

(1) 5-[(1-ethyl-1H-pyrazol-4-yl)methyl]-2, 2-dimethyl-1, 3-dioxane-4, 6-dione

25 **[0876]** In the same manner as in Example 132 (1), the title compound (12.6 g) was obtained as a yellow solid using 1-ethyl-1H-pyrazole-4-carboxylic acid (10.0 g).  
<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ1.30(3H, t, J = 7.2Hz), 1.58(3H, s), 1.78(3H, s), 3.08(2H, d, J = 4.4Hz), 4.03(2H, q, J = 7.2Hz), 4.71(1H, t, J = 4.4Hz), 7.18(1H, s), 7.43(1H, s).

30 (2) 2-[(1-ethyl-1H-pyrazol-4-yl)methyl]-3-[N-(4-fluorophenyl)-N-isopropylamino]-3-oxopropionic acid

**[0877]** In the same manner as in Example 119 (2), a crude product was obtained using the above-mentioned compound (2.19 g) and 4-fluoro-N-isopropylaniline (5.33 g). This was purified by silica gel column chromatography to give the title compound (1.77 g) as a white powder.

35 <sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ9.86-0.96(6H, m), 1.33(3H, t, J = 7.2Hz), 2.71(1H, dd, J = 14.0, 5.6Hz), 2.80(1H, dd, J = 14.0, 9.6Hz), 3.01(1H, dd, J = 9.6, 5.6Hz), 4.07(2H, q, J = 7.2Hz), 4.75-4.83(1H, m), 6.26-6.34(1H, m), 7.03(1H, s), 7.15-7.24(2H, m), 7.26-7.32(1H, m), 7.32(1H, s), 12.52(1H, brs).

(3) 2-[(1-ethyl-1H-pyrazol-4-yl)methyl]-N-(4-fluorophenyl)-N-isopropyl-N'-((E)-styrylsulfonyl)malonamide

40 **[0878]** In the same manner as in Example 1 (2), the title compound (843 mg) was obtained as a white solid using the above-mentioned compound (1.76 g) and trans-β-styrenesulfonamide (930 mg).

45 <sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ0.82-0.96(6H, m), 1.24(3H, t, J = 7.2Hz), 2.70(1H, dd, J = 14.0, 5.6Hz), 2.84(1H, dd, J = 14.0, 8.0Hz), 3.18(1H, dd, J = 8.0, 5.6Hz), 3.95(2H, q, J = 7.2Hz), 4.70-4.77(1H, m), 6.97(1H, s), 6.97-7.15(3H, m), 7.22(1H, s), 7.26-7.36(1H, m), 7.31(1H, d, J = 15.2Hz), 7.46-7.50(3H, m), 7.56(1H, d, J = 15.2Hz), 7.79-7.81(2H, m), 11.61(1H, brs).  
MS: 513(M+H)<sup>+</sup>.

50 Example 395 Synthesis of N-(4-fluorophenyl)-N-isopropyl-2-[(1-isopropyl-1H-pyrazol-4-yl)methyl]-N'-((E)-styrylsulfonyl)malonamide

(1) 5-[(1-isopropyl-1H-pyrazol-4-yl)methyl]-2, 2-dimethyl-1, 3-dioxane-4, 6-dione

**[0879]** In the same manner as in Example 132 (1), the title compound (11.2 g) was obtained as a yellow solid using 1-isopropyl-1H-pyrazole-4-carboxylic acid (7.98 g).

55 <sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ1.34(6H, d, J = 6.9Hz), 1.57(3H, s), 1.78(3H, s), 3.08(2H, d, J = 4.5Hz), 4.40(1H, sept, J = 6.9Hz), 4.69(1H, t, J = 4.5Hz), 7.18(1H, s), 7.44(1H, s).

(2) 3-[N-(4-fluorophenyl)-N-isopropylamino]-2-[(1-isopropyl-1H-pyrazol-4-yl)methyl]-3-oxopropionic acid

**[0880]** In the same manner as in Example 119 (2), the title compound (2.31 g) was obtained as a pale-yellow powder using the above-mentioned compound (3.06 g) and 4-fluoro-N-isopropylaniline (7.04 g).

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ0.82-0.95(6H, m), 1.38(6H, d, J = 6.4Hz), 2.71(1H, dd, J = 14.0, 5.2Hz), 2.81(1H, dd, J = 14.0, 9.6Hz), 3.01(1H, dd, J = 9.6, 5.2Hz), 4.44(1H, sept, J = 6.4Hz), 4.76-4.83(1H, m), 6.22-6.26(1H, m), 7.04(1H, s), 7.11-7.21(2H, m), 7.27-7.32(1H, m), 7.35(1H, s), 12.52(1H, brs).

(3) N-(4-fluorophenyl)-N-isopropyl-2-[(1-isopropyl-1H-pyrazol-4-yl)methyl]-N'-((E)-styrylsulfonyl)malonamide

**[0881]** In the same manner as in Example 1 (2), the title compound (1.53 g) was obtained as a white solid using the above-mentioned compound (2.29 g) and trans-β-styrenesulfonamide (1.16 g).

<sup>1</sup>H-NMR(300Hz, DMSO-d<sub>6</sub>)δ0.86-0.92(6H, m), 1.29(6H, d, J = 6.5Hz), 2.64-2.89(2H, m), 3.14-3.20(1H, m), 4.32(1H, sept, J = 6.5Hz), 4.68-4.79(1H, m), 6.96(1H, s), 6.96-7.16(3H, m), 7.23(1H, s), 7.27-7.39(1H, m), 7.31(1H, d, J = 15.4Hz), 7.43-7.52(3H, m), 7.56(1H, d, J = 15.4Hz), 7.79-7.81(2H, m), 11.61(1H, brs).

MS: 527(M+H)<sup>+</sup>.

Example 396 Synthesis of N-isopropyl-2-[(1-isopropyl-1H-pyrazol-4-yl)methyl]-N-(3-trifluoromethylphenyl)-N'-((E)-styrylsulfonyl)malonamide

(1) 3-[N-isopropyl-N-(3-trifluoromethylphenyl)amino]-2-[(1-isopropyl-1H-pyrazol-4-yl)methyl]-3-oxopropionic acid

**[0882]** In the same manner as in Example 119 (2), the title compound (931 mg) was obtained as a pale-yellow powder using the compound (2.00 g) obtained in Example 395 (1) and N-isopropyl-3-trifluoromethylaniline (6.10 g).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.87-0.96(6H, m), 1.28-1.46(6H, m), 2.64-3.00(3H, m), 4.32-4.50(1H, m), 4.65-4.90(1H, m), 6.42-6.60(1H, m), 7.03(1H, d, J = 5.7Hz), 7.35-7.82(4H, m), 12.94(1H, brs).

(2) N-isopropyl-2-[(1-isopropyl-1H-pyrazol-4-yl)methyl]-N-(3-trifluoromethylphenyl)-N'-((E)-styrylsulfonyl)malonamide

**[0883]** In the same manner as in Example 1 (2), the title compound (643 mg) was obtained as a white solid using the above-mentioned compound (931 mg) and trans-β-styrenesulfonamide (410 mg).

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ0.85-1.01(6H, m), 1.27(6H, d, J = 6.4Hz), 2.68-2.91(2H, m), 3.08-3.17(1H, m), 4.29(1H, sept, J = 6.4Hz), 4.78(1H, sept, J = 6.7Hz), 6.83-6.93(1H, m), 7.14-7.86(12H, m), 11.65(1H, brs).

MS: 577(M+H)<sup>+</sup>.

Example 397 Synthesis of N-(4-fluorophenyl)-N-isopropyl-2-[(1-isopropyl-1H-pyrazol-4-yl)methyl]-N'-(2-naphthylsulfonyl)malonamide

**[0884]** In the same manner as in Example 1 (2), the title compound (1.00 g) was obtained as a white solid using the compound (1.38 g) obtained in Example 395 (2).

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ0.78-0.90(6H, m), 1.29-1.32(6H, m), 2.62(1H, dd, J = 14.0, 5.8Hz), 2.75(1H, dd, J = 14.0, 7.6Hz), 3.10-3.18(1H, m), 4.24(1H, sept, J = 6.6Hz), 4.68(1H, sept, J = 6.7Hz), 6.79-6.97(3H, m), 6.89(1H, s), 7.09(1H, s), 7.25-7.34(1H, m), 7.67-7.82(3H, m), 8.07-8.28(3H, m), 8.56(1H, s), 11.92(1H, brs).

MS: 551(M+H)<sup>+</sup>.

Example 398 Synthesis of 2-[(1-benzyl-1H-pyrazol-4-yl)methyl]-N-ethyl-N-phenyl-N'-((E)-2-(2-thiazolyl)ethenyl)sulfonylmalonamide

(1) N-tert-butyl-2-hydroxy-2-(2-thiazolyl)ethanesulfonamide

**[0885]** To a solution of N-(tert-butyl)methanesulfonamide (3.44 g) in THF (30 mL) was added a 2.0 mol/L solution of lithium diisopropylamide in heptane/THF/ethylbenzene at -78°C, and the mixture was stirred at -40°C for 45 min. The reaction mixture was again cooled to -78°C, and a solution of 2-thiazolecarboxyaldehyde (2.57 g) in THF (20 mL) was added dropwise. The reaction mixture was stirred at -78°C for 1 hr, and then at room temperature for 1 hr, and poured into 1 mol/L hydrochloric acid (50 mL) containing ice, and the mixture was concentrated under reduced pressure. 1 mol/L Hydrochloric acid (50 mL) and ethyl acetate (300 mL) were added to extract the residue, and the organic layer was washed with saturated brine and concentrated under reduced pressure to give the title compound (3.05 g) as a pale-brown powder.

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$^1\text{H-NMR}$ (300Mz,  $\text{CDCl}_3$ ) $\delta$ 1.41(9H, s), 3.40-3.57(1H, m), 3.80-3.92(1H, m), 4.28(1H, brs), 4.42(1H, brs), 5.48-5.60(1H, m), 7.37(1H, d, J = 3.6Hz), 7.76(1H, d, J = 3.3Hz).

(2) N-tert-butyl-[(E)-2-(2-thiazolyl)ethylene]sulfonamide

**[0886]** To a solution of the above-mentioned compound (3.05 g) in methylene chloride (30 mL) were added triethylamine (4.80 mL) and methanesulfonyl chloride (1.34 mL) under ice-cooling, and the mixture was heated under reflux for 3 hr. 1 mol/L Hydrochloric acid (100 mL) and methylene chloride were added to extract the reaction mixture, and the organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound (2.84 g) as an oil.

$^1\text{H-NMR}$ (400Mz,  $\text{CDCl}_3$ ) $\delta$ 1.39(9H, s), 4.40(1H, brs), 7.20(1H, d, J = 15.0Hz), 7.48(1H, d, J = 3.3Hz), 7.56(1H, d, J = 15.0Hz), 7.94(1H, d, J = 3.3Hz).

(3) [(E)-2-(2-thiazolyl)ethylene]sulfonamide

**[0887]** To the above-mentioned compound (2.84 g) was added trifluoroacetic acid (30 mL), and the mixture was stirred at room temperature for 18 hr. The reaction mixture was concentrated under reduced pressure, and the residue was adjusted to pH = 8-9 by the addition of aqueous sodium hydrogen carbonate solution under ice-cooling. Ethyl acetate (100 mL) was added to extract the mixture, and the organic layer was washed with saturated brine, and concentrated under reduced pressure to give the title compound (1.39 g) as a red powder.

$^1\text{H-NMR}$ (300Mz,  $\text{DMSO-d}_6$ ) $\delta$ 7.29(2H, brs), 7.36(1H, d, J = 14.5Hz), 7.49(1H, d, J = 15.3Hz), 7.94(1H, d, J = 3.1Hz), 8.00(1H, d, J = 3.1Hz).

(4) 2-[(1-benzyl-1H-pyrazol-4-yl)methyl]-N-ethyl-N-phenyl-N'-{[(E)-2-(2-thiazolyl)ethenyl]sulfonyl}malonamide

**[0888]** In the same manner as in Example 152 (3), a condensed product was obtained using the above-mentioned compound (380 mg) and the compound (604 mg) obtained in Example 371 (6). This was subjected to hydrolysis in the same manner as in Example 1 (3) to give a white solid (578 mg). This and N-ethylaniline (156 mg) were condensed in the same manner as in Example 1 (4) to give a crude product, and the crude product was purified by silica gel column chromatography to give the title compound (60 mg) as a white powder.

$^1\text{H-NMR}$ (400Mz,  $\text{DMSO-d}_6$ ) $\delta$ 0.89-0.92(3H, m), 2.50-2.70(1H, m), 2.76-2.82(1H, m), 2.95-2.97(1H, m), 3.25-3.57(2H, m), 5.22(2H, s), 6.86-6.88(2H, m), 7.04(1H, s), 7.15-7.39(11H, m), 7.84-7.94(2H, m).

MS: 550(M+H) $^+$ .

Example 399 Synthesis of 2-[(1-benzyl-1H-pyrazol-4-yl)methyl]-N-ethyl-N-phenyl-N'-{[(E)-2-(3-pyridyl)ethenyl]sulfonyl}malonamide

(1) N-tert-butyl-2-hydroxy-2-(3-pyridyl)ethanesulfonamide

**[0889]** In the same manner as in Example 398 (1), the title compound (2.93 g) was obtained as a white powder using 3-pyridinecarboxyaldehyde (2.43 g).

$^1\text{H-NMR}$ (300Mz,  $\text{CDCl}_3$ ) $\delta$ 1.41(9H, s), 3.21-3.52(2H, m), 4.06(1H, brs), 4.56(1H, brs), 5.28-5.41(1H, m), 7.28-7.39(1H, m), 7.70-7.81(1H, m), 8.49-8.68(2H, m).

(2) N-tert-butyl-[(E)-2-(3-pyridyl)ethylene]sulfonamide

**[0890]** In the same manner as in Example 398 (2), the title compound (2.43 g) was obtained as a pale-brown powder using the above-mentioned compound (2.93 g).

$^1\text{H-NMR}$ (300Mz,  $\text{CDCl}_3$ ) $\delta$ 1.38(9H, s), 4.41(1H, brs), 6.90(1H, d, J = 15.7Hz), 7.29-7.40(1H, m), 7.46(1H, d, J = 15.5Hz), 7.72-7.88(1H, m), 8.56-8.69(1H, m), 8.72(1H, d, J = 2.1Hz).

(3) [(E)-2-(3-pyridyl)ethylene]sulfonamide

**[0891]** In the same manner as in Example 398 (3), the title compound (433 mg) was obtained as a pale-brown powder using the above-mentioned compound (2.43 g).

$^1\text{H-NMR}$ (300Mz,  $\text{DMSO-d}_6$ ) $\delta$ 7.19(2H, brs), 7.25-7.53(3H, m), 8.17(1H, dd, J = 6.1, 2.0Hz), 8.59(1H, dd, J = 4.5, 1.3Hz), 8.85(1H, d, J = 1.9Hz).

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(4) 2-[(1-benzyl-1H-pyrazol-4-yl)methyl]-N-ethyl-N-phenyl-N'-{[(E)-2-(3-pyridyl)ethenyl]sulfonyl}malonamide

**[0892]** In the same manner as in Example 152 (3), a condensed product was obtained using the above-mentioned compound (368 mg) and the compound (604 mg) obtained in Example 371 (6). This was subjected to hydrolysis in the same manner as in Example 1 (3) to give a white solid (228 mg). This and N-ethylaniline (66 mg) were condensed in the same manner as in Example 1 (4) to give a crude product, and the crude product was purified by silica gel column chromatography to give the title compound (28 mg) as a white powder.

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.90(3H, t, J = 6.8Hz), 2.67-2.72(2H, m), 2.82-2.88(1H, m), 3.38-3.40(2H, m), 5.20(2H, s), 6.98-6.99(3H, m), 7.13-7.15(2H, m), 7.28-7.36(7H, m), 7.54-7.65(3H, m), 8.35-8.36(1H, m), 8.68-8.69(1H, m), 8.97-8.98(1H, m), 11.78(1H, brs).  
MS: 544 (M+H)<sup>+</sup>.

Example 400 Synthesis of 2-[(1-benzyl-1H-pyrazol-4-yl)methyl]-N-ethyl-N-phenyl-N'-{[(E)-2-(4-fluorophenyl)ethenyl]sulfonyl}malonamide

(1)N-tert-butyl-2-(4-fluorophenyl)-2-hydroxyethanesulfonamide

**[0893]** In the same manner as in Example 398 (1), the title compound (9.27 g) was obtained as a pale-brown powder using 4-fluorobenzaldehyde (5.49 g).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.38(9H, s), 3.29-3.31(1H, m), 3.35-3.38(1H, m), 4.11-4.13(1H, m), 4.66-4.68(1H, m), 5.24-5.30(1H, m), 7.02-7.09(2H, m), 7.32-7.38(2H, m).

(2) N-tert-butyl-[(E)-2-(4-fluorophenyl)ethylene]sulfonamide

**[0894]** In the same manner as in Example 398 (2), the title compound (6.58 g) was obtained as an oil using the above-mentioned compound (9.27 g).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.38(9H, s), 4.20(1H, brs), 6.73(1H, d, J = 15.2Hz), 7.04-7.12(2H, m), 7.39-7.40(1H, m), 7.44-7.48(2H, m).

(3) [(E)-2-(4-fluorophenyl)ethylene]sulfonamide

**[0895]** In the same manner as in Example 398 (3), the title compound (1.56 g) was obtained as a red powder using the above-mentioned compound (6.58 g).

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ7.09(2H, brs), 7.19-7.34(4H, m), 7.74-7.78(2H, m).

(4) 2-[(1-benzyl-1H-pyrazol-4-yl)methyl]-N-ethyl-N-phenyl-N'-{[(E)-2-(4-fluorophenyl)ethenyl]sulfonyl}malonamide

**[0896]** In the same manner as in Example 1 (2), the title compound (548 mg) was obtained as a white powder using the above-mentioned compound (302 mg) and the compound obtained in Example 371 (8).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.04(3H, t, J = 6.8Hz), 2.85-2.89(1H, m), 3.01-3.07(1H, m), 3.35-3.39(1H, m), 3.55-3.57(1H, m), 3.73-3.76(1H, m), 4.73-4.75(2H, m), 5.24(2H, s), 6.85(1H, d, J = 15.6Hz), 7.08-7.21(3H, m), 7.28-7.35(8H, m), 7.47-7.52(4H, m).  
MS: 561(M+H)<sup>+</sup>.

Example 401 Synthesis of N-ethyl-N-phenyl-2-[[1-(1-phenylethyl)-1H-pyrazol-4-yl]methyl]-N'-((E)-styrylsulfonyl)malonamide

(1) (1-benzyl-1H-pyrazol-4-yl)methoxy-tert-butyltrimethylsilane

**[0897]** To a solution of (1-benzyl-1H-pyrazol-4-yl)methanol (3.84 g) in methylene chloride (100 mL) were added triethylamine (2.80 mL), 4-dimethylaminopyridine (100 mg) and tertbutyldimethylsilyl chloride (3.80 g) at room temperature, and the mixture was stirred for 2 hr. Saturated aqueous sodium hydrogen carbonate solution was added to the reaction mixture, and insoluble material was removed by filtration. Ethyl acetate (100 mL) was added to extract the filtrate, and the organic layer was washed with brine. The organic layer was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography to give the title compound (6.00 g).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ0.08-0.10(6H, m), 0.87-0.89(9H, m), 0.91-0.94(3H, m), 1.87-1.89(2H, m), 4.57-4.61(2H, m), 7.17-7.26(2H, m), 7.29-7.33(2H, m), 7.41-7.52(2H, m).

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### (2) [1-(1-phenylethyl)-1H-pyrazol-4-yl]methanol

**[0898]** To a solution of the above-mentioned compound (1.00 g) in THF (50 mL) was added 2.6 mol/L n-butyl lithium-hexane solution (1.70 mL) under cooling to -78°C, and the mixture was stirred for 1 hr. Methyl iodide (1.20 mL) was added to the reaction mixture, and the mixture was stirred for 1 hr. After allowing to warm to room temperature, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate (100 mL). The organic layer was washed with saturated brine. The organic layer was concentrated under reduced pressure. The residue was dissolved in THF (20 mL), tetrabutylammonium fluoride (5.0 mL) was added at room temperature, and the mixture was stirred for 1 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate (100 mL). The organic layer was washed with saturated brine. The organic layer was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography to give the title compound (2.76 g).  
<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.88-1.90(3H, m), 2.35(2H, s), 4.52-4.56(2H, m), 5.46-5.49(1H, m), 7.13-7.25(3H, m), 7.29-7.41(2H, m), 7.55(1H, s).

### (3) 4-(chloromethyl)-1-(1-phenylethyl)-1H-pyrazole

**[0899]** In the same manner as in Example 375 (3), the title compound (1.57 g) was obtained using the above-mentioned compound (2.16 g).

### (4) monoethyl {[1-(1-phenylethyl)-1H-pyrazol-4-yl]methyl}malonate

**[0900]** In the same manner as in Example 117 (1), the object compound was obtained using the above-mentioned compound (1.57 g). This was subjected to hydrolysis in the same manner as in Example 117 (2) to give the title compound (1.59 g) as an oil.  
<sup>1</sup>H-NMR(400Hz, CDCl<sub>3</sub>)δ1.23-1.33(3H, m), 1.84(3H, s), 3.15(2H, s), 3.54-3.57(1H, m), 4.25-4.27(2H, m), 5.49-5.51(2H, m), 7.11-7.13(2H, m), 7.28-7.40(4H, m).

### (5) 3-oxo-2-[[1-(1-phenylethyl)-1H-pyrazol-4-yl]methyl]-3-[(E)-styrylsulfonyl]amino]propionic acid

**[0901]** In the same manner as in Example 152 (3), the object compound was obtained using the above-mentioned compound (1.57 g) and trans-β-styrenesulfonamide (1.35 g). This was subjected to hydrolysis in the same manner as in Example 1 (3) to give the title compound (2.02 g) as a white solid.

### (6) N-ethyl-N-phenyl-2-[[1-(1-phenylethyl)-1H-pyrazol-4-yl]methyl]-N'-((E)-styrylsulfonyl)malonamide

**[0902]** In the same manner as in Example 1 (4), the title compound (69 mg) was obtained as a white powder using the above-mentioned compound (1.46 g) and N-ethylaniline (400 mg).  
<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.00-1.03(3H, m), 1.84-1.87(3H, m), 2.81-2.86(1H, m), 3.01-3.07(1H, m), 3.22-3.26(1H, m), 3.51-3.59(1H, m), 3.65-3.71(1H, m), 5.38-5.44(1H, m), 7.02(1H, d, J = 15.6Hz), 7.16-7.20(3H, m), 7.24-7.35(5H, m), 7.39-7.41(5H, m), 7.43-7.52(3H, m), 7.71(1H, d, J = 15.6Hz), 10.20(1H, brs). MS: 557(M+H)<sup>+</sup>.

### Example 402 Synthesis of 2-[[1-(1-benzyl-1H-pyrazol-4-yl)methyl]-N-ethyl-N-phenyl-N'-(4-tolylsulfonyl)malonamide

#### (1) 2-[[1-(1-benzyl-1H-pyrazol-4-yl)methyl]-3-oxo-3-[(4-tolylsulfonyl)amino]propionic acid

**[0903]** In the same manner as in Example 152 (3), a condensed product was obtained using p-toluenesulfonamide (283 mg) and the compound (500 mg) obtained in Example 371 (6). This was subjected to hydrolysis in the same manner as in Example 1 (3) to give the title compound (670 mg) as a white solid.

#### (2) 2-[[1-(1-benzyl-1H-pyrazol-4-yl)methyl]-N-ethyl-N-phenyl-N'-(4-tolylsulfonyl)malonamide

**[0904]** In the same manner as in Example 1 (4), the title compound (170 mg) was obtained as a white powder using the above-mentioned compound (670 mg) and N-ethylaniline (190 mg).  
<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ0.99(3H, t, J = 7.6Hz), 2.42(3H, s), 2.65-2.70(1H, m), 2.90-2.96(1H, m), 3.11-3.14(1H, m), 3.46-3.53(1H, m), 3.64-3.72(1H, m), 5.20(2H, m), 7.02(1H, s), 7.11(1H, s), 7.20-7.25(2H, m), 7.25-7.37(10H, m), 7.93(2H, d, J = 8.0Hz), 10.24(1H, brs).

MS: 531(M+H)<sup>+</sup>.

Example 403 Synthesis of 2-[(1-benzyl-1H-pyrazol-4-yl)methyl]-N'-(4-chlorophenylsulfonyl)-N-ethyl-N-phenylmalonamide

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(1) 2-[(1-benzyl-1H-pyrazol-4-yl)methyl]-3-[(4-chlorophenylsulfonyl)amino]-3-oxopropionic acid

**[0905]** In the same manner as in Example 152 (3), a condensed product was obtained using 4-chlorobenzenesulfonamide (317 mg) and the compound (500 mg) obtained in Example 371 (6). This was subjected to hydrolysis in the same manner as in Example 1 (3) to give the title compound (617 mg) as a white solid.

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(2) 2-[(1-benzyl-1H-pyrazol-4-yl)methyl]-N'-(4-chlorophenylsulfonyl)-N-ethyl-N-phenylmalonamide

**[0906]** In the same manner as in Example 1 (4), the title compound (94 mg) was obtained as a white powder using the above-mentioned compound (617 mg) and N-ethylaniline (167 mg).

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<sup>1</sup>H-NMR(400Hz, CDCl<sub>3</sub>)δ1.01-1.03(3H, m), 2.63-2.72(1H, m), 2.88-2.93(1H, m), 3.13-3.17(1H, m), 3.45-3.61(1H, m), 3.65-3.72(1H, m), 5.24(2H, m), 6.95(1H, s), 6.96(1H, s), 7.00-7.26(4H, m), 7.31-7.47(6H, m), 7.48-7.52(2H, m), 7.98(2H, d, J = 8.8Hz), 10.47(1H, brs).

20 MS: 551(M+H)<sup>+</sup>.

Example 404 Synthesis of N-ethyl-N-(4-fluorophenyl)-2-[[1-(3-methyl-2-buten-1-yl)-1H-pyrazol-4-yl]methyl]-N'-((E)-styrylsulfonyl)malonamide

25 (1) [1-(3-methyl-2-buten-1-yl)-1H-pyrazol-4-yl]methanol

**[0907]** In the same manner as in Example 375 (1), the object compound (7.98 g) was obtained using 1-bromo-3-methyl-2-butene (5.00 g). In the same manner as in Example 128 (2), the title compound (4.92 g) was obtained as an oil using this. <sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ0.84-0.88(1H, m), 1.77(3H, s), 1.79(3H, s), 4.57(2H, s), 4.69-4.71(2H, m), 5.42-5.45(1H, m), 7.39(1H, s), 7.49(1H, s).

30

(2) 4-(chloromethyl)-1-(3-methyl-2-buten-1-yl)-1H-pyrazole

**[0908]** In the same manner as in Example 375 (3), the title compound (4.95 g) was obtained as an oil using the above-mentioned compound (4.92 g).

35

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.77(3H, s), 1.79(3H, s), 4.54(2H, s), 4.68-4.71(2H, m), 5.41-5.45(1H, m), 7.42(1H, s), 7.51(1H, s).

(3) monoethyl {[1-(3-methyl-2-buten-1-yl)-1H-pyrazol-4-yl]methyl}malonate

40

**[0909]** In the same manner as in Example 117 (1), the object compound was obtained using the above-mentioned compound (4.95 g). This was subjected to hydrolysis in the same manner as in Example 117 (2) to give the title compound (6.04 g) as an oil.

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<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.25-1.33(3H, m), 1.74(3H, s), 1.77 (3H, s), 3.09-3.11(2H, m), 3.54-3.58(1H, m), 4.20-4.29(2H, m), 4.66-4.68(2H, m), 5.37-5.41(H, m), 7.23(1H, s), 7.35(1H, s).

(4) 2-[[1-(3-methyl-2-buten-1-yl)-1H-pyrazol-4-yl]methyl]-3-[(E)-styrylsulfonyl]amino]-3-oxopropionic acid

**[0910]** In the same manner as in Example 152 (3), a condensed product was obtained using the above-mentioned compound (3.00 g) and trans-β-styrenesulfonamide (1.96 g). This was subjected to hydrolysis in the same manner as in Example 1 (3) to give the title compound (2.35 g) as a white solid.

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(5) N-ethyl-N-(4-fluorophenyl)-2-[[1-(3-methyl-2-buten-1-yl)-1H-pyrazol-4-yl]methyl]-N'-((E)-styrylsulfonyl)malonamide

**[0911]** In the same manner as in Example 1 (4), the title compound (158 mg) was obtained as a white powder using the above-mentioned compound (834 mg) and N-ethyl-4-fluoroaniline (278 mg).

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<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.08(3H, brs), 1.72-1.79(6H, m), 2.85-2.89(1H, m), 3.02-3.08(1H, m), 3.22-3.26(1H, m), 3.64-3.71(2H, m), 4.65(2H, d, J = 7.2Hz), 5.37-5.41(1H, m), 7.00-7.05(4H, m), 7.12(1H, s), 7.18(1H, s), 7.31-7.46(3H,

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m), 7.48-7.54(3H, m), 7.72(1H, d, J = 15.6Hz), 10.23(1H, brs).

MS: 539(M+H)<sup>+</sup>.

Example 405 Synthesis of 2-[(1-benzyl-1H-pyrazol-4-yl)methyl]-N-ethyl-N-(1-naphthyl)-N'-((E)-styrylsulfonyl)malonamide

(1) ethyl 2-[(1-benzyl-1H-pyrazol-4-yl)methyl]-3-[N-ethyl-N-(1-naphthyl)amino]-3-oxopropionate

**[0912]** To a solution of the compound (4.70 g) obtained in Example 371 (6) in toluene (80 mL) was added thionyl chloride (1.36 mL), and the mixture was stirred at 85°C for 2 hr. After completion of the reaction, the mixture was concentrated under reduced pressure. 1.28 g of the residue was dissolved in acetonitrile (10 mL), triethylamine (666 μL) and N-ethyl-1-naphthylamine (685 mg) were added, and the mixture was stirred at room temperature for 1 hr. Ethyl acetate (50 mL) and dilute hydrochloric acid were added to extract the reaction mixture, and the organic layer was washed sequentially with 1 mol/L hydrochloric acid, aqueous sodium hydrogen carbonate solution and saturated brine. The organic layer was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography to give the title compound (1.23 g) as an oil.

<sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ0.88-1.33(6H, m), 2.70-3.40(4H, m), 3.75-4.40(3H, m), 5.00-5.35(2H, m), 6.20-8.00(14H, m).

(2) 2-[(1-benzyl-1H-pyrazol-4-yl)methyl]-3-[N-ethyl-N-(1-naphthyl)amino]-3-oxopropionic acid

**[0913]** In the same manner as in Example 1 (3), the title compound (1.18 g) was obtained as a pale-yellow solid using the above-mentioned compound (1.23 g).

<sup>1</sup>H-NMR(300Hz, DMSO-d<sub>6</sub>)δ0.80-1.10(3H, m), 2.55-3.40(4H, m), 3.90-4.20(1H, m), 5.05-5.45(2H, m), 6.25-8.10(14H, m), 12.50(1H, brs).

(3) 2-[(1-benzyl-1H-pyrazol-4-yl)methyl]-N-ethyl-N-(1-naphthyl)-N'-((E)-styrylsulfonyl)malonamide

**[0914]** In the same manner as in Example 1 (2), the title compound (33 mg) was obtained as a white solid using the above-mentioned compound (622 mg) and trans-β-styrenesulfonamide (246 mg).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.96(3H, t, J = 6.9Hz), 2.78-3.06(2H, m), 3.06-3.48(2H, m), 3.85-4.09(1H, m), 5.23(2H, s), 6.96(1H, s), 7.00-8.09(20H, m), 11.49(1H, brs).

MS: 593 (M+H)<sup>+</sup>.

Example 406 Synthesis of 2-[(1-benzyl-1H-pyrazol-4-yl)methyl]-N-ethyl-N-(2-naphthyl)-N'-((E)-styrylsulfonyl)malonamide

(1) ethyl 2-[(1-benzyl-1H-pyrazol-4-yl)methyl]-3-[N-ethyl-N-(2-naphthyl) amino] -3-oxopropionate

**[0915]** In the same manner as in Example 405 (1), the title compound (1.27 g) was obtained as an oil using N-ethyl-2-naphthylamine hydrobromide (1.01 g).

<sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ1.04(3H, t, J = 7.0Hz), 1.23(3H, t, J = 7.4Hz), 2.75-2.90(1H, m), 3.03-3.20(1H, m), 3.30-3.44(1H, m), 3.70(2H, brs), 4.01-4.20(2H, m), 5.17-5.35(2H, m), 7.10-7.89(14H, m).

(2) 2-[(1-benzyl-1H-pyrazol-4-yl)methyl]-3-[N-ethyl-N-(2-naphthyl)amino]-3-oxopropionic acid

**[0916]** In the same manner as in Example 1 (3), the title compound (1.15 g) was obtained as a pale-yellow solid using the above-mentioned compound (1.27 g).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.95(3H, t, J = 7.1Hz), 2.60-2.78(1H, m), 2.78-2.98(1H, m), 3.09-3.30(1H, m), 3.48-3.84(2H, m), 5.28(2H, s), 6.35-8.00(14H, m), 12.55(1H, brs).

(3) 2-[(1-benzyl-1H-pyrazol-4-yl)methyl]-N-ethyl-N-(2-naphthyl)-N'-((E)-styrylsulfonyl)malonamide

**[0917]** In the same manner as in Example 1 (2), the title compound (140 mg) was obtained as a white powder using the above-mentioned compound (630 mg) and trans-β-styrenesulfonamide (249 mg).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.97(3H, t, J = 6.9Hz), 2.57-3.02(2H, m), 3.25-3.80(3H, m), 5.18(2H, s), 6.90-7.65(16H, m), 7.69-8.00(5H, m), 11.60(1H, brs).

MS: 593(M+H)<sup>+</sup>.

Example 407 Synthesis of 2-[(1-benzyl-1H-pyrazol-4-yl)methyl]-3-(2, 3-dihydro-1H-indol-1-yl)-3-oxo-N-((E)-styrylsulfonyl)propanamide

(1) ethyl 2-[(1-benzyl-1H-pyrazol-4-yl)methyl]-3-oxo-3-[(E)-styrylsulfonyl]amino]propionate

**[0918]** In the same manner as in Example 152 (3), the title compound (4.31 g) was obtained as an oil using the compound (3.00 g) obtained in Example 371 (6) and trans- $\beta$ -styrenesulfonamide (1.68 g).

$^1\text{H-NMR}$ (300Mz, DMSO- $d_6$ ) $\delta$ 1.06(3H, t, J = 7.1Hz), 2.78-2.95(2H, m), 3.54-3.68(1H, m), 3.92-4.10(2H, m), 5.00-5.32(2H, m), 6.90-7.80(14H, m), 12.25(1H, brs).

(2) 2-[(1-benzyl-1H-pyrazol-4-yl)methyl]-3-oxo-3-[(E)-styrylsulfonyl]amino]propionic acid

**[0919]** In the same manner as in Example 1 (3), the title compound (2.32 g) was obtained as a white powder using the above-mentioned compound (4.31 g).

$^1\text{H-NMR}$ (300Mz, DMSO- $d_6$ ) $\delta$ 2.85(2H, d, J = 7.5Hz), 3.55(1H, t, J = 7.2Hz), 5.00-5.30(2H, m), 7.00-7.95(14H, m), 12.18(1H, brs), 12.80(1H, brs).

(3) 2-[(1-benzyl-1H-pyrazol-4-yl)methyl]-3-(2, 3-dihydro-1H-indol-1-yl)-3-oxo-N-((E)-styrylsulfonyl)propanamide

**[0920]** In the same manner as in Example 13, the title compound (47 mg) was obtained as a white solid using the above-mentioned compound (110 mg) and indoline (32 mg).

$^1\text{H-NMR}$ (300Mz, DMSO- $d_6$ ) $\delta$ 2.80-4.22(7H, m), 5.16(2H, s), 6.90-7.66(15H, m), 7.66-7.76(2H, m), 8.00-8.15(1H, m), 12.15(1H, brs).

MS: 541 (M+H) $^+$ .

Example 408 Synthesis of 2-[(1-benzyl-1H-pyrazol-4-yl)methyl]-N-ethyl-N-(4-fluorophenyl)-N'-((E)-styrylsulfonyl)malonamide

**[0921]** In the same manner as in Example 13, the title compound (111 mg) was obtained as a white solid using the compound (220 mg) obtained in Example 407 (2) and N-ethyl-4-fluoroaniline (84 mg).

$^1\text{H-NMR}$ (300Mz, DMSO- $d_6$ ) $\delta$ 0.90(3H, t, J = 7.1Hz), 2.58-2.92(2H, m), 3.18-3.64(3H, m), 5.18(2H, s), 6.90-7.64(16H, m), 7.66-7.85(2H, m), 11.68(1H, brs).

MS : 561(M+H) $^+$ .

Example 409 Synthesis of 2-[(1-benzyl-1H-pyrazol-4-yl)methyl]-3-(3, 4-dihydroquinolin-1(2H)-yl)-3-oxo-N-((E)-styrylsulfonyl)propanamide

**[0922]** In the same manner as in Example 13, the title compound (235 mg) was obtained as a white solid using the compound (310 mg) obtained in Example 407 (2) and 1, 2, 3, 4-tetrahydroquinoline (113 mg).

$^1\text{H-NMR}$ (300Mz, DMSO- $d_6$ ) $\delta$ 1.52-1.83(2H, m), 1.86-2.98(4H, m), 3.18-4.10(3H, m), 5.17(2H, s), 6.40-7.65(16H, m), 7.65-7.85(2H, m), 12.05(1H, brs).

MS: 555(M+H) $^+$ .

Example 410 Synthesis of 2-[(1-benzyl-1H-pyrazol-4-yl)methyl]-N-ethyl-N-(3-pyridyl)-N'-((E)-styrylsulfonyl)malonamide hydrochloride

**[0923]** In the same manner as in Example 13, the object compound was obtained using the compound (220 mg) obtained in Example 407 (2) and 3-(ethylamino)pyridine (73 mg). The compound was converted to a hydrochloride salt with hydrochloric acid-methanol solution to give the title compound (151 mg) as a white powder.

$^1\text{H-NMR}$ (300Mz, DMSO- $d_6$ ) $\delta$ 0.93(3H, t, J = 7.2Hz), 2.65-2.95(2H, m), 3.20-3.80(3H, m), 5.16(2H, s), 6.95-7.86(14H, m), 7.93-8.08(2H, m), 8.54(1H, brs), 8.66-8.79(1H, s), 11.70(1H, brs).

MS: 544(M+H) $^+$ .

Example 411 Synthesis of 2-[(1-benzyl-1H-pyrazol-4-yl)methyl]-N-(4-ethoxycarbonylphenyl)-N-ethyl-N'-((E)-styrylsulfonyl) malonamide

**[0924]** In the same manner as in Example 13, the title compound (338 mg) was obtained as a white solid using the compound (439 mg) obtained in Example 407 (2) and ethyl 4-(ethylamino)benzoate (232 mg).

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<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.91(3H, t, J = 7.2Hz), 1.31(3H, t, J = 7.2Hz), 2.58-2.95(2H, m), 3.10-3.45(1H, m), 3.59(2H, q, J = 6.9Hz), 4.32(2H, q, J = 7.2Hz), 5.19(2H, s), 6.82-7.38(10H, m), 7.40-7.58(4H, m), 7.69-7.81(2H, m), 7.89(2H, d, J = 8.4Hz), 11.68(1H, brs).  
MS: 615(M+H)<sup>+</sup>.

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Example 412 Synthesis of 2-[(1-benzyl-1H-pyrazol-4-yl)methyl]-N-(4-carboxyphenyl)-N-ethyl-N'-((E)-styrylsulfonyl)malonamide

**[0925]** In the same manner as in Example 121, the title compound (191 mg) was obtained as a white powder using the compound (200 mg) obtained in Example 411.

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<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.92(3H, t, J = 7.0Hz), 2.58-2.92(2H, m), 3.10-3.78(3H, m), 5.18(2H, s), 6.88-7.62(14H, m), 7.65-7.81(2H, m), 7.91(2H, d, J = 8.5Hz), 11.65(1H, brs), 13.10(1H, brs). MS: 587(M+H)<sup>+</sup>.

Example 413 Synthesis of 2-[(1-benzyl-1H-pyrazol-4-yl)methyl]-N-(3-ethoxycarbonylphenyl)-N-ethyl-N'-((E)-styrylsulfonyl)malonamide

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**[0926]** In the same manner as in Example 13, the title compound (165 mg) was obtained as a white solid using the compound (439 mg) obtained in Example 407 (2) and ethyl 3-(ethylamino)benzoate (232 mg).

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<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.92(3H, t, J = 6.9Hz), 1.32(3H, t, J = 7.2Hz), 2.60-2.94(2H, m), 3.16-3.45(1H, m), 3.59(2H, q, J = 6.9Hz), 4.20-4.40(2H, m), 5.17(2H, s), 6.88-7.62(14H, m), 7.62-7.80(3H, m), 7.86-8.00(1H, m), 11.65(1H, brs). MS: 615(M+H)<sup>+</sup>.

Example 414 Synthesis of 2-[(1-benzyl-1H-pyrazol-4-yl)methyl]-N-(3-carboxyphenyl)-N-ethyl-N'-((E)-styrylsulfonyl)malonamide

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**[0927]** In the same manner as in Example 121, the title compound (76 mg) was obtained as a white powder using the compound (100 mg) obtained in Example 413.

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.91(3H, t, J = 6.9Hz), 2.55-2.95(2H, m), 3.15-3.80(3H, m), 5.16(2H, s), 6.85-7.82(17H, m), 7.85-8.00(1H, m), 11.71(1H, brs), 13.30(1H, brs).

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MS: 587(M+H)<sup>+</sup>.

Example 415 Synthesis of 2-[(1-benzyl-1H-pyrazol-4-yl)methyl]-N-ethyl-N-[4-(hydroxymethyl)phenyl]-N'-((E)-styrylsulfonyl)malonamide

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**[0928]** In the same manner as in Example 13, the title compound (108 mg) was obtained as a white powder using the compound (220 mg) obtained in Example 407 (2) and 4-(ethylamino)benzyl alcohol (108 mg).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.90(3H, t, J = 7.2Hz), 2.55-2.97(2H, m), 3.20-3.65(3H, m), 4.36-4.56(2H, m), 5.19(2H, s), 5.18-5.36(1H, m), 6.74-7.65(16H, m), 7.65-7.89(2H, m), 11.72(1H, brs).

MS: 573(M+H)<sup>+</sup>.

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Example 416 Synthesis of 2-[(1-benzyl-1H-pyrazol-4-yl)methyl]-N-ethyl-N-[3-(hydroxymethyl)phenyl]-N'-((E)-styrylsulfonyl)malonamide

**[0929]** In the same manner as in Example 13, the title compound (180 mg) was obtained as a white powder using the compound (220 mg) obtained in Example 407 (2) and 3-(ethylamino)benzyl alcohol (91 mg).

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<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.93(3H, t, J = 6.9Hz), 2.54-2.97(2H, m), 3.17-3.70(3H, m), 4.49(2H, s), 5.17(2H, s), 5.30(1H, brs), 6.77-7.62(16H, m), 7.67-7.83(2H, m), 11.72(1H, brs).

MS: 573(M+H)<sup>+</sup>.

Example 417 Synthesis of 2-[(1-benzyl-1H-pyrazol-4-yl)methyl]-N-(2-hydroxyethyl)-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

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**[0930]** In the same manner as in Example 13, the title compound (172 mg) was obtained as a white powder using the compound (220 mg) obtained in Example 407 (2) and N-phenylethanolamine (82 mg).

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<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ2.60-2.98(2H, m), 3.19-3.70(5H, m), 4.63(1H, brs), 5.17(2H, s), 6.79-7.63(17H, m), 7.63-7.89(2H, m), 11.72(1H, brs).

MS: 559(M+H)<sup>+</sup>.

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Example 418 Synthesis of 2-[(1-benzyl-1H-pyrazol-4-yl)methyl]-N-isopropyl-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

5 **[0931]** In the same manner as in Example 13, the title compound (162 mg) was obtained as a white powder using the compound (220 mg) obtained in Example 407 (2) and N-isopropylaniline (81 mg).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.75-0.95(6H, m), 2.50-2.70(1H, m), 2.75-2.98(1H, m), 3.00-3.20(1H, m), 4.59-4.80(1H, m), 5.20(2H, s), 6.63-6.81(1H, m), 6.83-7.64(16H, m), 7.67-7.90(2H, m), 11.63(1H, brs).

MS: 557(M+H)<sup>+</sup>.

10 Example 419 Synthesis of N-allyl-2-[(1-benzyl-1H-pyrazol-4-yl)methyl]-N-methyl-N'-((E)-styrylsulfonyl)malonamide

**[0932]** In the same manner as in Example 13, the title compound (74 mg) was obtained as a white powder using the compound (220 mg) obtained in Example 407 (2) and N-methylallylamine (143 μL).

15 <sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ2.64-2.94(5H, m), 3.67-3.96(3H, m), 4.86-5.10(2H, m), 5.17(2H, s), 5.50-5.70(1H, m), 7.09-7.62(12H, m), 7.66-7.80(2H, m), 12.04(1H, brs).

MS: 493(M+H)<sup>+</sup>.

Example 420 Synthesis of 2-[(1-benzyl-1H-pyrazol-4-yl)methyl]-N-ethyl-N-(2-methoxyethyl)-N'-(2-naphthylsulfonyl)malonamide

20 (1) ethyl 2-[(1-benzyl-1H-pyrazol-4-yl)methyl]-3-[(2-naphthylsulfonyl)amino]-3-oxopropionate

**[0933]** In the same manner as in Example 152 (3), the title compound (4.62 g) was obtained as an oil using the compound (3.00 g) obtained in Example 371 (6).

25 <sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.93(3H, t, J = 7.1Hz), 2.69-2.88(2H, m), 3.50-3.70(1H, m), 2.82-4.20(2H, m), 4.98-5.32(2H, m), 6.90-8.65(14H, m), 12.55(1H, brs).

(2) 2-[(1-benzyl-1H-pyrazol-4-yl)methyl]-3-[(2-naphthylsulfonyl)amino]-3-oxopropionic acid

30 **[0934]** In the same manner as in Example 1 (3), the title compound (2.23 g) was obtained as a white powder using the above-mentioned compound (4.62 g).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ2.62-2.84(2H, m), 3.40-3.60(1H, m), 4.94-5.18(2H, m), 7.00-8.20(13H, m), 8.56(1H, s), 12.65(2H, brs).

35 (3) 2-[(1-benzyl-1H-pyrazol-4-yl)methyl]-N-ethyl-N-(2-methoxyethyl)-N'-(2-naphthylsulfonyl)malonamide

**[0935]** In the same manner as in Example 13, the title compound (62 mg) was obtained as a white powder using the above-mentioned compound (232 mg) and N-(2-methoxyethyl)ethylamine (62 mg).

40 <sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.70-0.90(3H, m), 2.63-2.86(2H, m), 2.97-3.48(9H, m), 3.68-3.90(1H, m), 5.00-5.20(2H, m), 7.00-7.19(3H, m), 7.19-7.43(4H, m), 7.61-7.88(3H, m), 8.00-8.29(3H, m), 8.57(1H, s), 12.10(1H, brs).

MS: 549(M+H)<sup>+</sup>.

Example 421 Synthesis of 2-[(1-benzyl-1H-pyrazol-4-yl)methyl]-N-[2-(dimethylamino)ethyl]-N-ethyl-N'-(2-naphthylsulfonyl)malonamide trifluoroacetic acid salt

45 **[0936]** In the same manner as in Example 13, the object compound was obtained using the compound (232 mg) obtained in Example 420 (2) and N, N-dimethyl-N'-ethylethylenediamine (70 mg). This was treated with trifluoroacetic acid to give the title compound (41 mg) as a white powder.

MS: 562 (M+H)<sup>+</sup>.

50 Example 422 Synthesis of 2-[(1-benzyl-1H-pyrazol-4-yl)methyl]-N-(2-hydroxyethyl)-N-methyl-N'-(2-naphthylsulfonyl)malonamide

**[0937]** In the same manner as in Example 13, the title compound (69 mg) was obtained as a white powder using the compound (232 mg) obtained in Example 420 (2) and N-methylethanolamine (45 mg).

55 <sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ2.55-2.90(5H, m), 2.95-4.05(5H, m), 4.95-5.20(2H, m), 6.96-7.40(7H, m), 7.58-7.86(3H, m), 7.97-8.30(3H, m), 8.56(1H, s), 12.30(2H, brs).

MS: 521 (M+H)<sup>+</sup>.

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Example 423 Synthesis of 2-[(1-benzyl-1H-pyrazol-4-yl)methyl]-3-morpholino-N-(2-naphthylsulfonyl)-3-oxopropanamide

**[0938]** In the same manner as in Example 13, the title compound (160 mg) was obtained as a white powder using the compound (232 mg) obtained in Example 420 (2) and morpholine (52 mg).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ2.55-2.80(2H, m), 2.97-3.50(8H, m), 3.79(1H, t, J = 6.9Hz), 5.00-5.25(2H, m), 6.89-7.49(7H, m), 7.78-7.87(3H, m), 7.92-8.23(3H, m), 8.58(1H, s), 12.30(1H, brs).

MS: 532(M+H)<sup>+</sup>.

Example 424 Synthesis of 2-[(1-benzyl-1H-pyrazol-4-yl)methyl]-N-ethyl-N'-(2-naphthylsulfonyl)-N-phenylmalonamide

**[0939]** In the same manner as in Example 13, the title compound (261 mg) was obtained as a white powder using the compound (200 mg) obtained in Example 420 (2) and N-ethylaniline (52 mg).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ0.99(3H, t, J = 7.2Hz), 2.64-2.69(1H, m), 2.88-2.96(1H, m), 3.09-3.13(1H, m), 3.46-3.52(1H, m), 3.66-3.71(1H, m), 5.10(2H, s), 6.94(1H, s), 7.08(1H, s), 7.15-7.26(5H, m), 7.29-7.35(3H, m), 7.61-7.68(3H, m), 7.89-8.01(5H, m), 8.65(1H, s), 10.39(1H, brs).

MS: 567(M+H)<sup>+</sup>.

Example 425 Synthesis of N-ethyl-2-[[2-(2, 4-difluorophenyl)-4-thiazolyl]methyl]-N-phenyl-N'-((E)-styrylsulfonyl)malonamide (1) [2-(2, 4-difluorophenyl)-4-thiazolyl]methanol

**[0940]** In the same manner as in Example 128 (2), the title compound (1.23 g) was obtained as an orange solid using ethyl 2-(2,4-difluorophenyl)thiazolyl-4-carboxylate (1.93 g).

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ4.66(2H, d, J = 6.0Hz), 5.43(1H, t, J = 6.0Hz), 7.25-7.30(1H, m), 7.48-7.54(1H, m), 7.61(1H, s), 8.21-8.27(1H, m).

(2) monoethyl [[2-(2, 4-difluorophenyl)-4-thiazolyl]methyl]malonate

**[0941]** In the same manner as in Example 371 (3), the object compound was obtained using the above-mentioned compound (1.19 g). This was subjected to hydrolysis in the same manner as in Example 117 (2) to give the title compound (251 mg) as a white solid.

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ1.13(3H, t, J = 7.2Hz), 3.27(2H, d, J = 7.6Hz), 4.10(2H, q, J = 7.2Hz), 7.27-7.31(1H, m), 7.48-7.55(2H, m), 8.20-8.26(1H, m), 13.00(1H, brs).

(3) ethyl 3-(N-ethyl-N-phenylamino)-2-[[2-(2,4-difluorophenyl)-4-thiazolyl]methyl]-3-oxopropionate

**[0942]** In the same manner as in Example 335 (1), the title compound (157 mg) was obtained as an oil using the above-mentioned compound (250 mg) and N-ethylaniline (200 μL). <sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.94(3H, t, J = 7.1Hz), 1.13(3H, t, J = 7.1Hz), 3.10-3.30(3H, m), 3.58(2H, q, J = 7.1Hz), 3.69-3.78(1H, m), 4.03(2H, q, J = 7.1Hz), 6.92(2H, brs), 7.22-7.55(6H, m), 7.96-8.06(1H, m).

(4) 3-(N-ethyl-N-phenylamino)-2-[[2-(2,4-difluorophenyl)-4-thiazolyl]methyl]-3-oxopropionic acid

**[0943]** In the same manner as in Example 1 (3), the title compound (81 mg) was obtained as an oil using the above-mentioned compound (156 mg).

<sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ1.05(3H, t, J = 7.2Hz), 3.31(1H, dd, J = 13.8, 4.8Hz), 3.43(1H, dd, J = 13.8, 9.3Hz), 3.60-3.79(2H, m), 3.89(1H, dd, J = 9.3, 4.8Hz), 6.85(2H, brs), 6.93-7.03(2H, m), 7.15(1H, s), 7.15-7.30(3H, m), 7.85(1H, brs), 8.04-8.12(1H, m).

(5) N-ethyl-2-[[2-(2, 4-difluorophenyl)-4-thiazolyl]methyl]-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

**[0944]** In the same manner as in Example 1 (2), the title compound (95 mg) was obtained as a white powder using the above-mentioned compound (81 mg) and trans-β-styrenesulfonamide (36 mg).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.96(3H, t, d = 7.1Hz), 3.07-3.30(2H, m), 3.46-3.72(2H, m), 3.80-3.91(1H, m), 7.08-7.50(12H, m), 7.57(1H, d, J = 16.1Hz), 7.64-7.85(2H, m), 8.06-8.20(1H, m), 11.85(1H, brs).

MS: 582(M+H)<sup>+</sup>.

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Example 426 Synthesis of 2-[(2-anilino-4-thiazolyl)methyl]-N-ethyl-N-phenyl-N'-((E)-styrylsulfonyl)malonamide (1) triethyl 2-(2-anilino-4-thiazolyl)ethane-1, 1, 1-tricarboxylate

5 [0945] In the same manner as in Example 117 (1), the title compound (940 mg) was obtained as an oil using 2-anilino-4-(chloromethyl)thiazole (920 mg).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ1.14(9H, t, J = 7.2Hz), 3.38(2H, s), 4.17(6H, q, J = 7.2Hz), 6.55(1H, s), 6.87-6.94(1H, m), 7.19-7.30(2H, m), 7.56(2H, d, J = 8.4Hz), 10.01(H, s).

10 (2) monoethyl [(2-anilino-4-thiazolyl)methyl]malonate

[0946] In the same manner as in Example 117 (2), the title compound (522 mg) was obtained as a pale-brown powder using the above-mentioned compound (910 mg).

15 <sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ1.27(3H, t, J = 7.0Hz), 3.20-3.36(2H, m), 3.74(1H, t, J = 7.3Hz), 4.22(2H, q, J = 7.0H), 6.30(1H, s), 7.10-7.20(1H, m), 7.26-7.40(5H, m).

(3) ethyl 2-[(2-anilino-4-thiazolyl)methyl]-3-(N-ethyl-N-phenylamino)-3-oxopropionate

[0947] In the same manner as in Example 1 (4), the title compound (317 mg) was obtained as a pale-brown powder using the above-mentioned compound (510 mg) and N-ethylaniline (320 μL).

20 <sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ1.07(3H, t, J = 7.0Hz), 1.25(3H, t, J = 7.0Hz), 3.09(1H, dd, J = 13.9, 4.5Hz), 3.23(1H, dd, J = 13.9, 10.0Hz), 3.61-3.80(3H, m), 4.15(2H, q, J = 7.0Hz), 6.32(1H, s), 6.90(2H, brs), 7.04-7.09(1H, m), 7.16-7.38(8H, m).

(4) 2-[(2-anilino-4-thiazolyl)methyl]-3-(N-ethyl-N-phenylamino)-3-oxopropionic acid

25 [0948] In the same manner as in Example 1 (3), the title compound (292 mg) was obtained as a pale-brown powder using the above-mentioned compound (313 mg).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.06(3H, t, J = 7.2Hz), 2.95-3.24(2H, m), 3.57-3.75(3H, m), 6.26(1H, s), 6.94(2H, brs), 7.07-7.14(1H, m), 7.20-7.42(8H, m).

30 (5) 2-[(2-anilino-4-thiazolyl)methyl]-N-ethyl-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

[0949] In the same manner as in Example 1 (2), the title compound (81 mg) was obtained as a white solid using the above-mentioned compound (292 mg) and trans-β-styrenesulfonamide (135 mg).

35 <sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ0.95(3H, t, J = 7.2Hz), 2.83-3.05(2H, m), 3.47-3.53(1H, m), 3.66-3.76(2H, m), 6.27(1H, s), 6.92-6.95(1H, m), 7.18-7.20(2H, m), 7.27-7.38(6H, m), 7.47-7.58(6H, m), 7.77-7.79(2H, m), 10.04(1H, s), 11.80(1H, brs). MS: 561(M+H)<sup>+</sup>.

Example 427 Synthesis of 2-[[2-(4-chlorobenzyl)-4-thiazolyl]methyl]-N, N-diethyl-N'-((E)-styrylsulfonyl)malonamide

40 (1) 2-(4-chlorobenzyl)-4-(chloromethyl)thiazole

[0950] To a solution of 2-(4-chlorophenyl)thioacetamide (3.51 g) in 1, 4-dioxane (20 mL) were added dichloroacetone (2.64 g) and sodium hydrogen carbonate (1.75 g) at room temperature, and the mixture was stirred for 3 days. Insoluble material was removed by filtration, thionyl chloride (1.52 mL) was added to the filtrate, and the mixture was heated at 45 70°C for 30 min. The reaction mixture was adjusted to pH = 8-9 by the addition of saturated aqueous sodium hydrogen carbonate solution, and extracted with ethyl acetate/hexane (1/1)(100 mL×2). The organic layer was washed with saturated brine, and concentrated under reduced pressure to give the title compound (4.19 g) as a pale-yellow solid.

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ4.34(2H, s), 4.78(2H, s), 7.36-7.42(4H, m), 7.61(1H, s).

50 (2) triethyl 2-[2-(4-chlorobenzyl)-4-thiazolyl]ethane-1, 1, 1-tricarboxylate

[0951] In the same manner as in Example 117 (1), the title compound (7.35 g) was obtained as an oil using the above-mentioned compound (3.77 g).

55 <sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ1.11(9H, t, J = 7.2Hz), 3.48(2H, s), 4.11(6H, q, J = 7.2Hz), 4.34(2H, s), 7.21(1H, s), 7.30-7.40(4H, m).

(3) monoethyl {[2-(4-chlorobenzyl)-4-thiazolyl]methyl}malonate

**[0952]** In the same manner as in Example 117 (2), the title compound (4.56 g) was obtained as an oil using the above-mentioned compound (7.35 g).

5 <sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ1.08-1.13(3H, m), 3.15(2H, d, J = 7.6Hz), 3.77(1H, t, J = 7.6Hz), 4.00-4.11(2H, m), 4.28(2H, s), 7.18(1H, s), 7.32-7.40(4H, m), 12.92(1H, brs).

(4) ethyl 2-[[2-(4-chlorobenzyl)-4-thiazolyl]methyl]-3-(N, N-diethylamino)-3-oxopropionate

10 **[0953]** In the same manner as in Example 1 (4), the title compound (570 mg) was obtained as an oil using the above-mentioned compound (1.16 g).

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ0.85(3H, t, J = 7.2Hz), 0.94(3H, t, J = 7.2Hz), 1.12(3H, t, J = 7.2Hz), 3.07-3.30(6H, m), 4.01-4.13(3H, m), 4.27(2H, s), 7.11(1H, s), 7.30-7.40(4H, m).

15 (5) 2-[[2-(4-chlorobenzyl)-4-thiazolyl]methyl]-3-(N, N-diethylamino)-3-oxopropionic acid

**[0954]** In the same manner as in Example 1 (3), the title compound (480 mg) was obtained as an oil using the above-mentioned compound (570 mg).

20 <sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ0.84(3H, t, J = 7.2Hz), 0.95(3H, t, J = 7.2Hz), 3.04-3.29(6H, m), 3.99-4.04(1H, m), 4.27(2H, s), 7.08(1H, s), 7.31-7.40(4H, m), 12.58(1H, brs).

(6) 2-[[2-(4-chlorobenzyl)-4-thiazolyl]methyl]-N,N-diethyl-N'-((E)-styrylsulfonyl)malonamide

25 **[0955]** In the same manner as in Example 1 (2), the title compound (250 mg) was obtained as a pale-brown powder using the above-mentioned compound (480 mg) and trans-β-styrenesulfonamide (230 mg).

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ0.92(3H, t, J = 7.2Hz), 1.01(3H, t, J = 7.2Hz), 3.07-3.33(6H, m), 4.11(1H, t, J = 7.2Hz), 4.23(2H, s), 7.08(1H, s), 7.29-7.49(8H, m), 7.58(1H, d, J = 15.6Hz), 7.70(2H, d, J = 6.8Hz), 12.05(1H, brs).

MS: 546(M+H)<sup>+</sup>.

30 Example 428 Synthesis of N-ethyl-2-[[2-(4-fluorophenyl)-4-oxazolyl]methyl]-N-phenyl-N'-((E)-styrylsulfonyl)malonamide (1) triethyl 2-[2-(4-fluorophenyl)-4-oxazolyl]ethane-1, 1, 1-tricarboxylate

**[0956]** In the same manner as in Example 117 (1), the title compound (1.00 g) was obtained as an oil using 4-(chloromethyl)-2-(4-fluorophenyl)oxazole (520 mg).

35 <sup>1</sup>H-NMR (400Mz, CDCl<sub>3</sub>)δ1.26(9H, t, J = 7.2Hz), 3.49(2H, s), 4.27(6H, q, J = 7.2Hz), 7.09-7.14(2H, m), 7.57(1H, s), 7.95-7.98(2H, m).

(2) monoethyl {[2-(4-fluorophenyl)-4-oxazolyl]methyl}malonate

40 **[0957]** In the same manner as in Example 117 (2), the title compound (750 mg) was obtained as a pale-yellow solid using the above-mentioned compound (1.00 g).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ1.15(3H, t, J = 7.1Hz), 3.02(2H, d, J = 7.6Hz), 3.74(1H, t, J = 7.6Hz), 4.12(2H, q, J = 7.1Hz), 7.34-7.40(2H, m), 7.96(1H, s), 7.96-8.01(2H, m), 11.99(1H, brs).

45 (3) ethyl 3-(N-ethyl-N-phenylamino)-2-[[2-(4-fluorophenyl)-4-oxazolyl]methyl]-3-oxopropionate

**[0958]** In the same manner as in Example 1 (4), the title compound (690 mg) was obtained as an oil using the above-mentioned compound (750 mg) and N-ethylaniline (370 μL).

50 <sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.96(3H, t, J = 7.2Hz), 1.31(3H, t, J = 7.2Hz), 2.84-3.08(2H, m), 3.57-3.68(3H, m), 4.03(2H, q, J = 7.2Hz), 7.06(2H, brs), 7.36-7.42(5H, m), 7.88(1H, s), 7.91-7.96(2H, m).

(4) 3-(N-ethyl-N-phenylamino)-2-[[2-(4-fluorophenyl)-4-oxazolyl]methyl]-3-oxopropionic acid

55 **[0959]** In the same manner as in Example 1 (3), the title compound (614 mg) was obtained as a white powder using the above-mentioned compound (660 mg).

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ0.96(3H, t, J = 7.2Hz), 2.86(1H, dd, J = 14.4, 4.8Hz), 2.99(1H, dd, J = 14.4, 9.6Hz), 3.56-3.62(3H, m), 7.02(2H, brs), 7.34-7.43(5H, m), 7.86(1H, s), 7.92-7.96(2H, m), 12.75(1H, brs).

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(5) N-ethyl-2-[[2-(4-fluorophenyl)-4-oxazolyl]methyl]-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

**[0960]** In the same manner as in Example 1 (2), the title compound (311 mg) was obtained as a white solid using the above-mentioned compound (614 mg) and trans- $\beta$ -styrenesulfonamide (295 mg).

$^1\text{H-NMR}$ (300Mz, DMSO- $d_6$ ) $\delta$ 0.96(3H, t, J = 7.2Hz), 2.86(1H, dd, J = 15.0, 5.4Hz), 3.02(1H, dd, J = 15.0, 7.8Hz), 3.55-3.69(3H, m), 7.21(2H, brs), 7.29-7.48(9H, m), 7.56(1H, d, J = 15.6Hz), 7.73-7.78(3H, m), 7.88-7.93(2H, m), 11.77(1H, brs).

MS: 548(M+H) $^+$ .

10 Example 429 Synthesis of 2-[(1-benzyl-1H-1, 2, 3-triazol-4-yl)methyl]-N-ethyl-N-phenyl-N'-((E)-styrylsulfonyl)malonamide (1) ethyl 1-benzyl-1H-1, 2, 3-triazole-4-carboxylate

**[0961]** To a mixed solvent of toluene (100 mL)/ethanol (100 mL)/water (50 mL) were added benzyl bromide (10.7 g) and sodium azide (10.1 g), and the mixture was heated under reflux for 5 hr. A solution of ethyl acrylate (38.8 mL) in ethanol (200 mL) was added dropwise to the reaction mixture, and the mixture was heated under reflux for 12 hr. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography to give the title compound (5.66 g) as an oil.

$^1\text{H-NMR}$ (400Mz,  $\text{CDCl}_3$ ) $\delta$ 1.37-1.40(3H, m), 4.40-4.42(2H, m), 5.58(2H, s), 7.28-7.56(5H, m), 7.96(1H, s).

20 (2) 1-benzyl-4-(hydroxymethyl)-1H-1, 2, 3-triazole

**[0962]** In the same manner as in Example 128 (2), the title compound (4.15 g) was obtained as an oil using the above-mentioned compound (5.32 g).

$^1\text{H-NMR}$ (400Mz,  $\text{CDCl}_3$ ) $\delta$ 2.43-2.46(1H, m), 4.75-4.77(2H, m), 5.52(2H, s), 7.27-7.28(2H, m), 7.34-7.40(3H, m), 7.44(1H, s).

(3) 1-benzyl-4-(chloromethyl)-1H-1, 2, 3-triazole

**[0963]** In the same manner as in Example 128 (3), the title compound (3.66 g) was obtained as an oil using the above-mentioned compound (4.15 g).

$^1\text{H-NMR}$ (400Mz,  $\text{CDCl}_3$ ) $\delta$ 4.68(2H, s), 5.52(2H, s), 7.27-7.29(2H, m), 7.36-7.41(3H, m), 7.48(1H, s).

(4) monoethyl [(1-benzyl-1H-1, 2, 3-triazol-4-yl)methyl]malonate

**[0964]** In the same manner as in Example 117 (1), the object compound was obtained using the above-mentioned compound (4.10 g). This was subjected to hydrolysis in the same manner as in Example 117 (2) to give the title compound (3.25 g) as an oil.

$^1\text{H-NMR}$ (400Mz,  $\text{CDCl}_3$ ) $\delta$ 1.23-1.31(3H, m), 3.32-3.34(2H, m), 3.84-3.88(1H, m), 4.11-4.27(2H, m), 5.48(2H, m), 7.22-7.25(3H, m), 7.33(1H, s), 7.35-7.38(2H, m).

(5) 2-[(1-benzyl-1H-1, 2, 3-triazol-4-yl)methyl]-3-oxo-3-[(E)-styrylsulfonyl]amino]propionic acid

**[0965]** In the same manner as in Example 152 (3), the object compound was obtained using the above-mentioned compound (3.25 g) and trans- $\beta$ -styrenesulfonamide (2.04 g). This was subjected to hydrolysis in the same manner as in Example 1 (3) to give the title compound (1.68 g) as a white powder.

$^1\text{H-NMR}$ (400Mz,  $\text{CDCl}_3$ ) $\delta$ 3.44-3.52(3H, m), 3.76-3.84(1H, m), 5.49(2H, s), 7.00(1H, d, J = 15.2Hz), 7.17-7.19(2H, m), 7.23-7.43(5H, m), 7.47-7.52(4H, m), 7.67(1H, d, J = 15.2Hz).

(6) 2-[(1-benzyl-1H-1, 2, 3-triazol-4-yl)methyl]-N-ethyl-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

**[0966]** In the same manner as in Example 1 (4), the title compound (606 mg) was obtained as a white powder using the above-mentioned compound (1.68 g) and N-ethylaniline (479  $\mu\text{L}$ ).

$^1\text{H-NMR}$ (400Mz,  $\text{CDCl}_3$ ) $\delta$ 1.01-1.05(3H, m), 3.13-3.15(1H, m), 3.24-3.26(H, m), 3.47-3.51(1H, m), 3.64-3.68(2H, m), 5.38-5.45(2H, m), 6.80-6.95(2H, m), 6.99(1H, d, J = 15.6Hz), 7.22-7.26(2H, m), 7.32-7.36(7H, m), 7.42-7.50(3H, m), 7.51-7.52(2H, m), 7.67(1H, d, J = 15.6Hz), 11.20(1H, brs).

MS: 544(M+H)<sup>+</sup>.

Example 430 Synthesis of 2-[(1-benzyl-1H-1, 2, 3-triazol-4-yl)methyl]-N-ethyl-N-(4-fluorophenyl)-N'-((E)-styrylsulfonyl)malonamide

**[0967]** In the same manner as in Example 1 (4), the title compound (182 mg) was obtained as a white powder using the compound (1.27 g) obtained in Example 429 (5) and N-ethyl-4-fluoroaniline (418 mg).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.01-1.09(3H, m), 3.09-3.14(1H, m), 3.25-3.31(1H, m), 3.49-3.53(1H, m), 3.57-3.68(2H, m), 5.36-5.46(2H, m), 6.88-6.89(1H, m), 6.94-7.06(3H, m), 7.23-7.25(1H, m), 7.26-7.33(3H, m), 7.39-7.44(3H, m), 7.40-7.44(3H, m), 7.46-7.52(2H, m), 7.68(1H, d, J = 15.2Hz), 10.11(1H, brs).

MS: 562(M+H)<sup>+</sup>.

Example 431 Synthesis of 2-[(1-cyclohexyl-1H-tetrazol-5-yl)methyl]-N-ethyl-N-phenyl-N'-((E)-styrylsulfonyl)malonamide (1) triethyl 2-(1-cyclohexyl-1H-tetrazol-5-yl)ethane-1, 1, 1-tricarboxylate

**[0968]** In the same manner as in Example 117 (1), the title compound (5.14 g) was obtained as an oil using 5-(chloromethyl)-1-cyclohexyl-1H-tetrazole (2.91 g).

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ1.17(9H, t, J = 7.2Hz), 1.20-1.31(1H, m), 1.40-1.52(2H, m), 1.63-1.87(5H, m), 1.94-2.03(2H, m), 3.66(2H, s), 4.20(6H, q, J = 7.2Hz), 4.48-4.57(1H, m).

(2) monoethyl [(1-cyclohexyl-1H-tetrazol-5-yl)methyl]malonate

**[0969]** In the same manner as in Example 117 (2), the title compound (3.85 g) was obtained as an oil using the above-mentioned compound (5.14 g).

<sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ1.20-1.56(6H, m), 1.73-2.12(7H, m), 3.41(2H, d, J = 7.4Hz), 4.08-4.39(4H, m).

(3) ethyl 2-[(1-cyclohexyl-1H-tetrazol-5-yl)methyl]-3-(N-ethyl-N-phenylamino)-3-oxopropionate

**[0970]** In the same manner as in Example 1 (4), the title compound (1.08 g) was obtained as an oil using the above-mentioned compound (3.85 g) and N-ethylaniline (2.00 mL).

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ0.96-1.04(3H, m), 1.07-1.30(4H, m), 1.37-1.52(2H, m), 2.63-2.02(7H, m), 3.22-3.42(2H, m), 3.55-3.71(2H, m), 3.87-3.95(1H, m), 3.95-4.07(2H, m), 4.40-4.50(1H, m), 7.29(2H, d, J = 7.2Hz), 7.36-7.51(3H, m).

(4) 2-[(1-cyclohexyl-1H-tetrazol-5-yl)methyl]-3-(N-ethyl-N-phenylamino)-3-oxopropionic acid

**[0971]** In the same manner as in Example 1 (3), the title compound (1.00 g) was obtained as a white powder using the above-mentioned compound (1.07 g).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.07(3H, t, J = 7.6Hz), 1.23-1.52(3H, m), 1.73-2.11(7H, m), 3.25(1H, dd, J = 15.6, 5.2Hz), 3.48(1H, dd, J = 15.6, 9.6Hz), 3.69-4.09(2H, m), 4.12(1H, dd, J = 9.6, 5.2Hz), 4.20-4.33(1H, m), 7.21-7.29(2H, m), 7.37-7.50(3H, m).

(5) 2-[(1-cyclohexyl-1H-tetrazol-5-yl)methyl]-N-ethyl-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

**[0972]** In the same manner as in Example 1 (2), the title compound (168 mg) was obtained as a white solid using the above-mentioned compound (970 mg) and trans-β-styrenesulfonamide (480 mg).

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ0.86-1.00(3H, m), 1.17-1.31(1H, m), 2.35-2.52(2H, m), 1.62-2.05(7H, m), 3.08(1H, dd, J = 16.0, 4.8Hz), 3.38(1H, dd, J = 16.0, 9.6Hz), 3.49-3.61(2H, m), 4.02(1H, dd, J = 9.6, 4.8Hz), 4.46-4.52(1H, m), 7.15-7.44(5H, m), 7.31(1H, d, J = 15.6Hz), 7.44-7.45(3H, m), 7.58(1H, d, J = 15.6Hz), 7.75-7.88(2H, m), 11.88(1H, brs).  
MS: 537(M+H)<sup>+</sup>.

Example 432 Synthesis of 2-[(1-benzyl-1H-tetrazol-5-yl)methyl]-N-ethyl-N-phenyl-N'-((E)-styrylsulfonyl)malonamide (1) 3, 3, 3-(triethoxycarbonyl)propionic acid

**[0973]** In the same manner as in Example 117 (1), the object compound was obtained using tert-butyl bromoacetate (10.4 g). This was dissolved in methylene chloride (100 mL), trifluoroacetic acid (30 mL) was added at room temperature, and the mixture was stirred for 20 hr. The reaction mixture was concentrated under reduced pressure, and water (200 mL) and chloroform (100 mL) were added to extract the residue. The organic layer was washed with saturated brine, and concentrated under reduced pressure to give the title compound (9.90 g) as an oil.

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$^1\text{H-NMR}$ (400Mz,  $\text{DMSO-d}_6$ ) $\delta$ 1.18(9H, t, J = 7.2Hz), 2.96(2H, s), 4.18(6H, q, J = 7.2Hz), 12.52(1H, brs).

(2) N-benzyl-3, 3, 3-(triethoxycarbonyl)propanamide

5 **[0974]** In the same manner as in Example 1 (4), the title compound (2.99 g) was obtained as a white solid using the above-mentioned compound (2.45 g) and benzylamine (1.10 mL).  $^1\text{H-NMR}$ (400Mz,  $\text{DMSO-d}_6$ ) $\delta$ 1.17(9H, t, J = 7.2Hz), 2.97(2H, s), 4.15(6H, q, J = 7.2Hz), 4.25(2H, d, J = 6.0H), 7.21-7.33(5H, m), 8.44(1H, t, J = 6.0Hz).

10 (3) triethyl 2-(1-benzyl-1H-tetrazol-5-yl)ethane-1, 1, 1-tricarboxylate

**[0975]** To a solution of the above-mentioned compound (2.99 g) in methylene chloride (40 mL) was added phosphorus pentachloride (1.64 g) under ice-cooling, and the mixture was stirred at room temperature for 3 hr. Trimethylsilylazide (2.10 mL) was added to the reaction mixture under ice-cooling, and the mixture was stirred at room temperature for 28 hr. The reaction mixture was adjusted to pH = 8 by the addition of saturated aqueous sodium hydrogen carbonate solution and extracted with chloroform (100 mL). The organic layer was washed with saturated brine, and concentrated under reduced pressure to give the title compound (3.19 g) as an oil.  $^1\text{H-NMR}$ (300Mz,  $\text{CDCl}_3$ ) $\delta$ 1.27(9H, t, J = 7.2Hz), 3.50(2H, s), 4.28(6H, q, J = 7.2Hz), 5.62(2H, s), 7.22-7.26(3H, m), 7.36-7.38(2H, m).

20 (4) monoethyl [(1-benzyl-1H-tetrazol-5-yl)methyl]malonate

**[0976]** In the same manner as in Example 117 (2), the title compound (2.40 g) was obtained as an oil using the above-mentioned compound (3.19 g).  $^1\text{H-NMR}$ (300Mz,  $\text{DMSO-d}_6$ ) $\delta$ 1.11-1.20(3H, m), 3.29-3.37(2H, m), 3.94-4.17(3H, m), 5.70(2H, s), 7.26-7.43(5H, m), 13.05(1H, brs).

25 (5) ethyl 2-[(1-benzyl-1H-tetrazol-5-yl)methyl]-3-(N-ethyl-N-phenylamino)-3-oxopropionate

**[0977]** In the same manner as in Example 1 (4), the title compound (1.19 g) was obtained as an oil using the above-mentioned compound (2.40 g) and N-ethylaniline (1.20 mL).  $^1\text{H-NMR}$ (400Mz,  $\text{CDCl}_3$ ) $\delta$ 1.06(3H, t, J = 7.2Hz), 1.22(3H, t, J = 7.2Hz), 3.12(1H, dd, J = 15.6, 5.6Hz), 3.39(1H, dd, J = 15.6, 10.0Hz), 3.65-3.75(2H, m), 4.02(1H, dd, J = 10.0, 5.6Hz), 4.11(2H, q, J = 7.2Hz), 5.56(1H, d, J = 15.6Hz), 5.66(1H, d, J = 15.6Hz), 7.21-7.26(4H, m), 7.32-7.45(6H, m).

35 (6) 2-[(1-benzyl-1H-tetrazol-5-yl)methyl]-3-(N-ethyl-N-phenylamino)-3-oxopropionic acid

**[0978]** In the same manner as in Example 1 (3), the title compound (1.08 g) was obtained as a white powder using the above-mentioned compound (1.17 g).  $^1\text{H-NMR}$ (400Mz,  $\text{DMSO-d}_6$ ) $\delta$ 0.94-1.02(3H, m), 3.22-3.28(2H, m), 3.56-3.70(2H, m), 3.76-3.80(1H, m), 5.60(1H, d, J = 15.6Hz), 5.65(1H, d, J = 15.6Hz), 7.22-7.27(4H, m), 7.34-7.49(6H, m), 12.89(1H, brs).

40 (7) 2-[(1-benzyl-1H-tetrazol-5-yl)methyl]-N-ethyl-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

**[0979]** In the same manner as in Example 1 (2), the title compound (460 mg) was obtained as a white solid using the above-mentioned compound (1.08 g) and trans- $\beta$ -styrenesulfonamide (520 mg).  $^1\text{H-NMR}$ (300Mz,  $\text{DMSO-d}_6$ ) $\delta$ 0.94(3H, t, J = 7.1Hz), 3.01-3.14(1H, m), 3.36-3.45(1H, m), 3.51-3.64(2H, m), 3.95-4.04(1H, m), 5.65(2H, s), 7.16-7.51(14H, m), 7.58(1H, d, J = 15.6Hz), 7.78-7.88(2H, m), 11.88(1H, brs).  
MS: 545 (M+H)<sup>+</sup>.

50 Example 433 Synthesis of 2-[(1-ethyl-1H-tetrazol-5-yl)methyl]-N-(4-fluorophenyl)-N-isopropyl-N'-((E)-styrylsulfonyl)malonamide

(1) N-ethyl-3, 3, 3-(triethoxycarbonyl)propanamide

**[0980]** In the same manner as in Example 1 (4), the title compound (2.04 g) was obtained as an oil using the compound (2.31 g) obtained in Example 432 (1) and 70% aqueous ethylamine solution (640 mg).  $^1\text{H-NMR}$ (400Mz,  $\text{DMSO-d}_6$ ) $\delta$ 1.00(3H, t, J = 7.2Hz), 1.17(9H, t, J = 7.2Hz), 2.73(2H, s), 2.99-3.06(2H, m), 4.15(6H, q, J = 7.2Hz), 7.87-7.92(1H, m).

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(2) triethyl 2-(1-ethyl-1H-tetrazol-5-yl)ethane-1, 1, 1-tricarboxylate

**[0981]** In the same manner as in Example 432 (3), the title compound (2.13 g) was obtained as an oil using the above-mentioned compound (1.97 g).

5  $^1\text{H-NMR}$ (400Mz,  $\text{CDCl}_3$ ) $\delta$ 1.29(9H, t, J = 7.2Hz), 1.58(3H, t, J = 7.2Hz), 3.60(2H, s), 4.31(6H, q, J = 7.2Hz), 4.40(2H, q, J = 7.2Hz).

(3) monoethyl [(1-ethyl-1H-tetrazol-5-yl)methyl]malonate

10 **[0982]** In the same manner as in Example 117 (2), the title compound (1.07 g) was obtained as an oil using the above-mentioned compound (2.13 g).

$^1\text{H-NMR}$ (400Mz,  $\text{DMSO-d}_6$ ) $\delta$ 1.22(3H, t, J = 6.8Hz), 1.42(3H, t, J = 7.2Hz), 3.35-3.42(2H, m), 3.99(1H, t, J = 7.6Hz), 4.09-4.37(2H, m), 4.37-4.43(2H, m), 13.21(1H, brs).

15 (4) ethyl 2-[(1-ethyl-1H-tetrazol-5-yl)methyl]-3-[N-(4-fluorophenyl)-N-isopropylamino]-3-oxopropionate

**[0983]** In the same manner as in Example 13, the title compound (940 mg) was obtained as an oil using the above-mentioned compound (1.05 g) and 4-fluoro-N-isopropylaniline (800 mg).

20  $^1\text{H-NMR}$ (300Mz,  $\text{DMSO-d}_6$ ) $\delta$ 0.90(3H, d, J = 6.9Hz), 1.00(3H, d, J = 6.9Hz), 1.14(3H, t, J = 7.2Hz), 1.38(3H, t, J = 7.2Hz), 3.24-3.27(2H, m), 3.71(1H, dd, J = 10.8, 6.9Hz), 3.94-4.10(2H, m), 4.35(2H, q, J = 7.2Hz), 4.75(1H, sept, J = 6.9Hz), 7.23-7.39(4H, m).

(5) 2-[(1-ethyl-1H-tetrazol-5-yl)methyl]-3-[N-(4-fluorophenyl)-N-isopropylamino]-3-oxopropionic acid

25 **[0984]** In the same manner as in Example 1 (3), the title compound (852 mg) was obtained as a white powder using the above-mentioned compound (920 mg).

$^1\text{H-NMR}$ (300Mz,  $\text{DMSO-d}_6$ )  $\delta$ 0.90(3H, d, J = 6.7Hz), 0.96(3H, d, J = 6.7Hz), 1.34(3H, t, J = 7.2Hz), 3.13-3.29(2H, m), 3.58-3.67(1H, m), 4.34(2H, q, J = 7.2Hz), 4.75(1H, sept, J = 6.7Hz), 7.18-7.36(4H, m), 12.96(1H, brs).

30 (6) 2-[(1-ethyl-1H-tetrazol-5-yl)methyl]-N-(4-fluorophenyl)-N-isopropyl-N'-((E)-styrylsulfonyl)malonamide

**[0985]** In the same manner as in Example 1 (2), the title compound (480 mg) was obtained as a white solid using the above-mentioned compound (852 mg) and trans- $\beta$ -styrenesulfonamide (440 mg).

35  $^1\text{H-NMR}$ (300Mz,  $\text{DMSO-d}_6$ ) $\delta$ 0.88(6H, t, J = 7.4Hz), 1.39(3H, t, J = 7.2Hz), 3.06(1H, dd, J = 15.9, 4.8Hz), 3.34-3.42(1H, m), 3.81(1H, dd, J = 9.5, 4.8Hz), 4.37(2H, q, J = 7.2Hz), 4.57-4.73(1H, m), 6.94-7.15(2H, m), 7.33-7.62(7H, m), 7.69-7.88(2H, m), 11.80(1H, brs).

MS: 515(M+H)<sup>+</sup>.

40 Example 434 Synthesis of N-(4-fluorophenyl)-N-isopropyl-2-[(1-methyl-1H-tetrazol-5-yl)methyl]-N'-((E)-styrylsulfonyl)malonamide

(1) N-methyl-3, 3, 3-(triethoxycarbonyl)propanamide

45 **[0986]** In the same manner as in Example 1 (4), the title compound (3.51 g) was obtained as an oil using the compound (5.04 g) obtained in Example 432 (1) and 2 mol/L methylamine-THF solution (9.55 mL).

$^1\text{H-NMR}$ (300Mz,  $\text{CDCl}_3$ ) $\delta$ 1.29(9H, t, J = 7.2Hz), 2.31(2H, s), 3.06(3H, s), 4.29(6H, q, J = 7.2Hz), 5.85(1H, brs).

(2) triethyl 2-(1-methyl-1H-tetrazol-5-yl)ethane-1, 1, 1-tricarboxylate

50 **[0987]** In the same manner as in Example 432 (3), the title compound (1.47 g) was obtained as an oil using the above-mentioned compound (3.45 g).

$^1\text{H-NMR}$ (400Mz,  $\text{CDCl}_3$ ) $\delta$ 1.29(9H, t, J = 7.2Hz), 3.61(2H, s), 4.08(3H, s), 4.31(6H, q, J = 7.2Hz).

(3) monoethyl [(1-methyl-1H-tetrazol-5-yl)methyl]malonate

55 **[0988]** In the same manner as in Example 117 (2), the title compound (760 mg) was obtained as an oil using the above-mentioned compound (1.47 g).

$^1\text{H-NMR}$ (300Mz,  $\text{DMSO-d}_6$ ) $\delta$ 1.17(3H, t, J = 7.1Hz), 3.29-3.36(2H, m), 3.96(1H, t, J = 7.7Hz), 4.02(3H, s), 4.13(2H, q, J

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= 7.1Hz), 13.07(1H, brs).

(4) ethyl 3-[N-(4-fluorophenyl)-N-isopropylamino]-2-[(1-methyl-1H-tetrazol-5-yl)methyl]-3-oxopropionate

5 **[0989]** In the same manner as in Example 13, the title compound (1.09 g) was obtained as an oil using the above-mentioned compound (760 mg) and 4-fluoro-N-isopropylaniline (620 mg).

<sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ0.90(3H, d, J = 6.9Hz), 1.05(3H, d, J = 6.9Hz), 1.27(3H, t, J = 7.2Hz), 3.20(1H, dd, J = 15.3, 4.8Hz), 3.48(1H, dd, J = 15.3, 10.2Hz), 3.90(1H, dd, J = 10.2, 4.8Hz), 4.06(3H, s), 4.15(2H, q, J = 7.2Hz), 4.84(1H, sept, J = 6.9Hz), 7.01-7.24(4H, m).

10

(5) 3-[N-(4-fluorophenyl)-N-isopropylamino]-2-[(1-methyl-1H-tetrazol-5-yl)methyl]-3-oxopropionic acid

**[0990]** In the same manner as in Example 1 (3), the title compound (820 mg) was obtained as a white powder using the above-mentioned compound (1.08 g).

15 <sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ0.87-1.00(6H, m), 3.17-3.31(2H, m), 3.60(1H, dd, J = 8.4, 6.4Hz), 3.96(3H, s), 4.75(1H, sept, J = 6.8Hz), 7.14-7.36(4H, m), 12.91(1H, brs).

(6) N-(4-fluorophenyl)-N-isopropyl-2-[(1-methyl-1H-tetrazol-5-yl)methyl]-N'-((E)-styrylsulfonyl)malonamide

20 **[0991]** In the same manner as in Example 1 (2), the title compound (432 mg) was obtained as a white solid using the above-mentioned compound (765 mg) and trans-β-styrenesulfonamide (420 mg).

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ0.86-0.91(6H, m), 3.06(1H, dd, J = 15.6, 5.2Hz), 3.35(1H, dd, J = 15.6, 9.2Hz), 3.62-3.81(1H, m), 3.98(3H, s), 4.67(1H, sept, J = 6.8Hz), 7.00-7.10(2H, m), 7.27-7.43(3H, m), 7.43-7.52(3H, m), 7.57(1H, d, J = 15.6Hz), 7.78-7.87(2H, m), 11.77(1H, brs).

25 MS: 501(M+H)<sup>+</sup>.

Example 435 Synthesis of N-(4-fluorophenyl)-N-isopropyl-2-[(1-phenyl-1H-tetrazol-5-yl)methyl]-N'-((E)-styrylsulfonyl)malonamide

30 (1) N-phenyl-3, 3, 3-(triethoxycarbonyl)propanamide

**[0992]** In the same manner as in Example 1 (4), the title compound (2.22 g) was obtained as a yellow solid using the compound (2.00 g) obtained in Example 432 (1) and aniline (750 μL).

35 <sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ.18(9H, t, J = 7.2Hz), 3.14(2H, s), 4.19(6H, q, J = 7.2Hz), 7.03(1H, t, J = 7.6Hz), 7.28(2H, t, J = 7.6Hz), 7.52(2H, d, J = 7.6Hz), 10.05(1H, s).

(2) triethyl 2-(1-phenyl-1H-tetrazol-5-yl)ethane-1, 1, 1-tricarboxylate

**[0993]** In the same manner as in Example 432 (3), the title compound (2.19 g) was obtained as an oil using the above-mentioned compound (2.05 g).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.28(9H, t, J = 7.2Hz), 3.63(2H, s), 4.30(6H, q, J = 7.2Hz), 7.47-7.50(2H, m), 7.57-7.61(3H, m).

(3) monoethyl [(1-phenyl-1H-tetrazol-5-yl)methyl]malonate

45 **[0994]** In the same manner as in Example 117 (2), the title compound (1.40 g) was obtained as an oil using the above-mentioned compound (2.19 g).

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ1.13-1.19(3H, m), 3.29-3.89(2H, m), 4.00-4.13(3H, m), 7.62-7.75(5H, m), 13.24(1H, brs).

(4) ethyl 3-[N-(4-fluorophenyl)-N-isopropylamino]-3-oxo-2-[(1-phenyl-1H-tetrazol-5-yl)methyl]propionate

50

**[0995]** In the same manner as in Example 13, the title compound (974 mg) was obtained as an oil using the above-mentioned compound (1.31 g) and 4-fluoro-N-isopropylaniline (830 mg).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.91(3H, d, J = 6.9Hz), 1.00(3H, d, J = 6.9Hz), 1.10(3H, t, J = 7.2Hz), 3.18-3.38(2H, m), 3.75-3.82(1H, m), 3.91-4.02(2H, m), 4.72(1H, sept, J = 6.9Hz), 7.21-7.41(5H, m), 7.63-7.70(5H, m).

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(5) 3-[N-(4-fluorophenyl)-N-isopropylamino]-3-oxo-2-[(1-phenyl-1H-tetrazol-5-yl)methyl]propionic acid

**[0996]** In the same manner as in Example 1 (3), the title compound (690 mg) was obtained as a white powder using

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the above-mentioned compound (974 mg).

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ0.88-1.02(6H, m), 3.18-3.32(2H, m), 3.72(1H, t, J = 7.6Hz), 4.68-4.78(lah, m), 7.21-7.40(5H, m), 7.62-7.69(5H, m), 12.93(1H, brs).

5 (6) N-(4-fluorophenyl)-N-isopropyl-2-[(1-phenyl-1H-tetrazol-5-yl)methyl]-N'-((E)-styrylsulfonyl)malonamide

**[0997]** In the same manner as in Example 1 (2), the title compound (255 mg) was obtained as a white solid using the above-mentioned compound (690 mg) and trans-β-styrenesulfonamide (320 mg).

10 <sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.87(6H, t, J = 7.2Hz), 3.09-3.30(2H, m), 3.87-3.96(1H, m), 4.64(1H, sept, J = 7.2Hz), 6.98-7.08(2H, m), 7.23-7.60(7H, m), 7.67(5H, brs), 7.80-7.82(2H, m), 11.87(1H, brs).  
MS: 563(M+H)<sup>+</sup>.

Example 436 Synthesis of N, N-diethyl-N'-(2-naphthylsulfonyl)-2-[(1-phenyl-1H-tetrazol-5-yl)methyl]malonamide

15 (1) ethyl 3-(N, N-diethylamino)-3-oxo-2-[(1-phenyl-1H-tetrazol-5-yl)methyl]propionate

**[0998]** In the same manner as in Example 13, the title compound (1.82 g) was obtained as an oil using the compound (2.96 g) obtained in Example 435 (3) and diethylamine (1.30 mL). <sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ1.06(3H, t, J = 7.1Hz), 1.24(3H, t, J = 7.1Hz), 1.33(3H, t, J = 7.2Hz), 3.19-3.30(1H, m), 3.36-3.70(5H, m), 4.17(2H, q, J = 7.2Hz), 4.63(1H, dd, J = 8.1, 5.7Hz), 7.59(5H, brs).

20

(2) 3-(N, N-diethylamino)-3-oxo-2-[(1-phenyl-1H-tetrazol-5-yl)methyl]propionic acid

**[0999]** In the same manner as in Example 1 (3), the title compound (1.63 g) was obtained as a white powder using the above-mentioned compound (1.80 g).

25

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ0.88-0.96(3H, m), 1.20(3H, t, J = 7.2Hz), 3.17-3.45(5H, m), 3.54-3.62(1H, m), 4.37-4.41(1H m), 7.66-7.71(5H, m), 12.97(1H, brs).

(3) N, N-diethyl-N'-(2-naphthylsulfonyl)-2-[(1-phenyl-1H-tetrazol-5-yl)methyl]malonamide

30

**[1000]** In the same manner as in Example 1 (2), the title compound (1.21 g) was obtained as a white solid using the above-mentioned compound (1.60 g).

35

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ0.79(3H, t, J = 7.0Hz), 0.98(3H, t, J = 7.0Hz), 3.06-3.25(6H, m), 4.41-4.45(1H, m), 7.52-7.62(5H, m), 7.68-7.82(3H, m), 8.06(1H, d, J = 7.9Hz), 8.11(1H, d, J = 8.7Hz), 8.20(1H, d, J = 7.9Hz), 8.55(1H, s), 12.73(1H, brs). MS: 507(M+H)<sup>+</sup>.

Example 437 Synthesis of N-isopropyl-2-[(1-methyl-1H-tetrazol-5-yl)methyl]-N'-(2-naphthylsulfonyl)-N-(3-trifluoromethylphenyl)malonamide

40 (1) ethyl 3-[N-isopropyl-N-(3-trifluoromethylphenyl)amino]-2-[(1-methyl-1H-tetrazol-5-yl)methyl]-3-oxopropionate

**[1001]** In the same manner as in Example 13, the title compound (1.22 g) was obtained as a white solid using the compound (1.23 g) obtained in Example 434 (3) and N-isopropyl-3-trifluoromethylaniline (1.32 g).

45

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ0.89-0.95(3H, m), 0.96-1.04(3H, m), 1.12-1.20(3H, m), 3.23(1H, dd, J = 16.0, 5.9Hz), 3.33-3.42(1H, m), 3.97(3H, s), 4.00-4.08(2H, m), 4.79(1H, sept, J = 6.8Hz), 7.50-7.66(2H, m), 7.75-7.79(1H, m), 7.82-7.90(1H, m).

(2) 3-[N-isopropyl-N-(3-trifluoromethylphenyl)amino]-2-[(1-methyl-1H-tetrazol-5-yl)methyl]-3-oxopropionic acid

50

**[1002]** In the same manner as in Example 1 (3), the title compound (1.01 g) was obtained as a white powder using the above-mentioned compound (1.22 g).

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ0.89-1.02(6H, m), 3.17-3.38 (2H, m), 3.51-3.55(1H, m), 3.95(3H, s), 4.79(1H, sept, J = 6.8Hz), 7.51-7.59(2H, m), 7.73-7.77(1H, m), 7.80-7.89(1H, m), 13.05(1H, brs).

55

(3) N-isopropyl-2-[(1-methyl-1H-tetrazol-5-yl)methyl]-N'-(2-naphthylsulfonyl)-N-(3-trifluoromethylphenyl)malonamide

**[1003]** In the same manner as in Example 1 (2), the title compound (830 mg) was obtained as a white solid using the above-mentioned compound (1.00 g).

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<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ0.78-0.96(6H, m), 2.95-3.24 (2H, m), 3.64-3.80(1H, m), 3.91(3H, s), 4.60-4.75(1H, m), 6.94-7.32(1H, m), 7.42-7.92(6H, m), 8.02-8.30(3H, m), 8.56(1H, s), 12.12(1H, brs).  
MS: 575(M+H)<sup>+</sup>.

5 Example 438 Synthesis of N-ethyl-2-{2-[4-(4-nitrophenyl)-1-piperazinyl]-2-oxoethyl}-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

(1) triethyl 3-[4-(4-nitrophenyl)-1-piperazinyl]-3-oxopropane-1, 1, 1-tricarboxylate

10 **[1004]** In the same manner as in Example 1 (4), the title compound (1.86 g) was obtained as a yellow solid using the compound (1.23 g) obtained in Example 432 (1) and 4-(4-nitrophenyl)piperazine (930 mg).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ1.18(9H, t, J = 7.2Hz), 3.17(2H, s), 3.42-3.71(8H, m), 4.16(6H, q, J = 7.2Hz), 7.02(2H, d, J = 9.6Hz), 8.08(2H, d, J = 9.6Hz).

15 (2) monoethyl {2-[4-(4-nitrophenyl)-1-piperazinyl]-2-oxoethyl}malonate

**[1005]** In the same manner as in Example 117 (2), the title compound (1.47 g) obtained as a yellow solid was using the above-mentioned compound (1.86 g).

20 <sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ1.18(3H, t, J = 7.2Hz), 2.92(2H, d, J = 8.0Hz), 3.48-3.71(9H, m), 4.05-4.15(2H, m), 7.02(2H, d, J = 9.6Hz), 8.08(2H, d, J = 9.6Hz), 12.95(1H, brs).

(3) ethyl 3-(N-ethyl-N-phenylamino)-2-(2-[4-(4-nitrophenyl)-1-piperazinyl]-2-oxoethyl)-3-oxopropionate

25 **[1006]** In the same manner as in Example 1 (4), the title compound (330 mg) was obtained as a yellow powder using the above-mentioned compound (500 mg) and N-ethylaniline (175 μL). <sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.15(3H, t, J = 7.2Hz), 1.24(3H, t, J = 7.2Hz), 2.82(1H, dd, J = 16.4, 4.8Hz), 3.15(1H, dd, J = 16.4, 9.2Hz), 3.40-3.57(4H, m), 3.70-3.83(6H, m), 3.92(1H, dd, J = 9.2, 4.8Hz), 4.11(2H, q, J = 7.2Hz), 6.79-6.83(2H, m), 7.34-7.47(5H, m), 8.08-8.12(2H, m).

(4) 3-(N-ethyl-N-phenylamino)-2-[2-[4-(4-nitrophenyl)-1-piperazinyl]-2-oxoethyl]-3-oxopropionic acid

30 **[1007]** In the same manner as in Example 1 (3), the title compound (260 mg) was obtained as a yellow powder using the above-mentioned compound (330 mg).

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ1.00(3H, t, J = 7.2Hz), 2.73-2.90(2H, m), 3.46-3.66(11H, m), 7.01(2H, d, J = 9.6Hz), 7.37-7.48(5H, m), 8.08(2H, d, J = 9.6Hz), 12.57(1H, brs).

35 (5) N-ethyl-2-(2-[4-(4-nitrophenyl)-1-piperazinyl]-2-oxoethyl)-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

**[1008]** In the same manner as in Example 1 (2), the title compound (153 mg) was obtained as a yellow solid using the above-mentioned compound (251 mg) and trans-β-styrenesulfonamide (100 mg).

40 <sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ0.96(3H, t, J = 7.2Hz), 2.56-2.66(H, m), 2.88-2.98(1H, m), 3.40-3.69(11H, m), 7.01(2H, d, J = 9.6Hz), 7.19-7.60(10H, m), 7.72-7.88(2H, m), 8.08(2H, d, J = 9.6Hz), 11.72(1H, brs).

MS: 620 (M+H)<sup>+</sup>.

45 Example 439 Synthesis of 2-{2-[4-(4-aminophenyl)-1-piperazinyl]-2-oxoethyl}-N-ethyl-N-phenyl-N'-((E)-styrylsulfonyl)malonamide 2 hydrochloride

**[1009]** In the same manner as in Example 137 (4), the object compound was obtained using the compound (135 mg) obtained in Example 438. This was converted to a hydrochloride salt with 4 mol/L hydrochloric acid-dioxane to give the title compound (45 mg) as a pale-brown solid.

50 <sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ0.95(3H, t, J = 7.2Hz), 2.61(1H, dd, J = 16.4, 4.4Hz), 2.92-3.20(5H, m), 3.46-3.68(7H, m), 7.05(2H, d, J = 9.2Hz), 7.22-7.58(12H, m), 7.80-7.82(2H, m), 9.98(3H, brs), 11.70(1H, brs).

MS: 590(M+H)<sup>+</sup>.

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Example 440 Synthesis of 2-{2-[4-(5-cyano-2-pyridyl)-1-piperazinyl]-2-oxoethyl}-N-ethyl-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

(1) triethyl 3-[4-(5-cyano-2-pyridyl)-1-piperazinyl]-3-oxopropane-1,1,1-tricarboxylate

**[1010]** In the same manner as in Example 1 (4), the title compound (2.08 g) was obtained as a white solid using the compound (1.31 g) obtained in Example 432 (1) and 1-(5-cyano-2-pyridyl)piperazine (1.02 g).

$^1\text{H-NMR}$ (400Mz, DMSO- $d_6$ ) $\delta$ 1.18(9H, t, J = 7.2Hz), 3.17(2H, s), 3.53-3.74(8H, m), 4.15(6H, q, J = 7.2Hz), 6.94(2H, d, J = 9.2Hz), 7.89(1H, dd, J = 9.2, 2.4Hz), 8.52(1H, d, J = 2.4Hz).

(2) ethyl 2-{2-[4-(5-cyano-2-pyridyl)-1-piperazinyl]-2-oxoethyl}-3-(N-ethyl-N-phenylamino)-3-oxopropionate

**[1011]** In the same manner as in Example 117 (2), the object compound was obtained using the above-mentioned compound (2.08 g). This and N-ethylaniline (625  $\mu\text{L}$ ) were condensed in the same manner as in Example 1 (4) to give the title compound (422 mg) as an oil.

$^1\text{H-NMR}$ (300Mz,  $\text{CDCl}_3$ ) $\delta$ 1.15(3H, t, J = 7.1Hz), 1.22-1.29(3H, m), 2.76-2.87(1H, m), 3.07-3.19(1H, m), 3.68-3.96(11H, m), 4.07-4.14(2H, m), 6.63-6.67(1H, m), 7.35-7.45(5H, m), 7.63-7.68(1H, m), 8.40(1H, d, J = 1.9Hz).

(3) 2-{2-[4-(5-cyano-2-pyridyl)-1-piperazinyl]-2-oxoethyl}-3-(N-ethyl-N-phenylamino)-3-oxopropionic acid

**[1012]** In the same manner as in Example 1 (3), the title compound (140 mg) was obtained as a white powder using the above-mentioned compound (400 mg).

$^1\text{H-NMR}$ (400Mz,  $\text{CDCl}_3$ ) $\delta$ 1.15(3H, t, J = 7.2Hz), 2.82-2.90(1H, m), 3.07-3.15(1H, m), 3.62-3.86(11H, m), 6.59(2H, d, J = 9.2Hz), 7.35-7.45(5H, m), 7.65(1H, dd, J = 9.2, 2.0Hz), 8.42(1H, d, J = 2.0Hz).

(4) 2-{2-[4-(5-cyano-2-pyridyl)-1-piperazinyl]-2-oxoethyl}-N-ethyl-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

**[1013]** In the same manner as in Example 1 (2), the title compound (50 mg) was obtained as a white solid using the above-mentioned compound (140 mg) and trans- $\beta$ -styrenesulfonamide (60 mg).

$^1\text{H-NMR}$ (400Mz, DMSO- $d_6$ ) $\delta$ 0.96(3H, t, J = 7.2Hz), 2.56-2.64(1H, m), 2.90-2.98(1H, m), 3.40-3.77(11H, m), 6.92(1H, d, J = 8.8Hz), 7.19-7.60(10H, m), 7.80(2H, brs), 7.85-7.92(1H, m), 8.50(1H, d, J = 2.0Hz), 11.65(1H, brs).

MS: 601(M+H) $^+$ .

Example 441 Synthesis of 2-[2-(3,4-dihydroisoquinolin-2(1H)-yl)-2-oxoethyl]-N-ethyl-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

(1) triethyl 3-(3,4-dihydroisoquinolin-2(1H)-yl)-3-oxopropane-1,1,1-tricarboxylate

**[1014]** In the same manner as in Example 1 (4), the title compound (2.08 g) was obtained as an oil using the compound (1.70 g) obtained in Example 432 (1) and 1,2,3,4-tetrahydroisoquinoline (890  $\mu\text{L}$ ).

$^1\text{H-NMR}$ (300Mz,  $\text{CDCl}_3$ ) $\delta$ 1.28(9H, t, J = 7.1Hz), 2.80-3.00(2H, m), 3.27-3.28(2H, m), 3.70-3.85(2H, m), 4.28(2H, q, J = 7.1Hz), 4.67-4.72(2H, m), 7.06-7.22(4H, m).

(2) monoethyl [2-(3,4-dihydroisoquinolin-2(1H)-yl)-2-oxoethyl]malonate

**[1015]** In the same manner as in Example 117 (2), the title compound (394 mg) was obtained as an oil using the above-mentioned compound (1.97 g).

$^1\text{H-NMR}$ (300Mz, DMSO- $d_6$ ) $\delta$ 1.17(3H, t, J = 7.2Hz), 2.70-2.97(4H, m), 3.64-3.73(3H, m), 4.09(2H, q, J = 7.2Hz), 4.57(1H, s), 4.68(1H, s), 7.18-7.21(4H, m), 12.88(1H, brs).

(3) ethyl 2-[2-(3,4-dihydroisoquinolin-2(1H)-yl)-2-oxoethyl]-3-(N-ethyl-N-phenylamino)-3-oxopropionate

**[1016]** In the same manner as in Example 1 (4), the title compound (204 mg) was obtained as an oil using the above-mentioned compound (390 mg) and N-ethylaniline (200  $\mu\text{L}$ ).  $^1\text{H-NMR}$ (400Mz,  $\text{CDCl}_3$ ) $\delta$ 1.09-1.29(6H, m), 2.78-2.95(3H, m), 3.15-3.24(1H, m), 3.66-3.95(5H, m), 4.10(2H, q, J = 7.2Hz), 4.61-4.74(2H, m), 7.08-7.22(4H, m), 7.31-7.48(5H, m).

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(4) 2-[2-(3, 4-dihydroisoquinolin-2(1H)-yl)-2-oxoethyl]-3-(N-ethyl-N-phenylamino)-3-oxopropionic acid

**[1017]** In the same manner as in Example 1 (3), the title compound (190 mg) was obtained as a white powder using the above-mentioned compound (204 mg).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.99(3H, t, J = 7.1Hz), 2.68-2.97 (4H, m), 3.53-3.72(5H, m), 4.54-4.64(2H, m), 7.17-7.21(4H, m), 7.36-7.50(5H, m), 12.47(1H, brs).

(5) 2-[2-(3,4-dihydroisoquinolin-2(1H)-yl)-2-oxoethyl]-N-ethyl-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

**[1018]** In the same manner as in Example 1 (2), the title compound (112 mg) was obtained as a white solid using the above-mentioned compound (190 mg) and trans-β-styrenesulfonamide (91 mg).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.95(3H, t, J = 7.2Hz), 2.54-2.75(2H, m), 2.79-2.88(1H, m), 2.92-3.05(1H, m), 3.45-3.74(5H, m), 4.52-4.62(2H, m), 7.10-7.59(14H, m), 7.74-7.85(2H, m), 11.65(1H, brs).

MS: 546(M+H)<sup>+</sup>.

Example 442 Synthesis of 2-[(dimethylaminocarbonyl)methyl]-N-(4-fluorophenyl)-N-isopropyl-N'-((E)-styrylsulfonyl)malonamide (1) triethyl 2-(dimethylaminocarbonyl)ethane-1, 1, 1-tricarboxylate

**[1019]** In the same manner as in Example 1 (4), the title compound (4.52 g) was obtained as an oil using the compound (4.17 g) obtained in Example 432 (1) and dimethylamine hydrochloride (1.41 g).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.29(9H, t, J = 7.2Hz), 2.95(3H, s), 3.06(3H, s), 3.18(2H, s), 4.28(6H, q, J = 7.2Hz).

(2) monoethyl [(dimethylaminocarbonyl)methyl]malonate

**[1020]** In the same manner as in Example 117 (2), the title compound (2.48 g) was obtained as an oil using the above-mentioned compound (4.52 g).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.29(3H, t, J = 7.2Hz), 2.97-3.11(2H, m), 2.99(3H, s), 3.08(3H, s), 3.81(1H, dd, J = 7.2, 4.8Hz), 4.22-4.28 (2H, m).

(3) ethyl 2-[(dimethylaminocarbonyl)methyl]-3-[N-(4-fluorophenyl)-N-isopropylamino]-3-oxopropionate

**[1021]** In the same manner as in Example 13, the title compound (462 mg) was obtained as an oil using the above-mentioned compound (521 mg) and 4-fluoro-N-isopropylaniline (410 mg). <sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ1.01(3H, d, J = 6.8Hz), 1.10(3H, d, J = 6.8Hz), 1.23(3H, t, J = 7.1Hz), 2.63-2.73(1H, m), 2.91(3H, s), 3.02(3H, s), 3.08-3.18(1H, m),

3.67-3.73(1H, m), 4.09(2H, q, J = 7.1Hz), 4.92-5.05(1H, m), 7.00-7.21(3H, m), 7.45-7.54(1H, m).

(4) 2-[(dimethylaminocarbonyl)methyl]-3-[N-(4-fluorophenyl)-N-isopropylamino]-3-oxopropionic acid

**[1022]** In the same manner as in Example 1 (3), the title compound (412 mg) was obtained as a white powder using the above-mentioned compound (462 mg).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.91(3H, d, J = 6.6Hz), 0.96(3H, d, J = 6.6Hz), 2.58-2.81(2H, m), 2.66(3H, s), 2.92(3H, s), 3.32-3.37(1H, m), 4.76(1H, sept, J = 6.6Hz), 7.16-7.44(4H, m), 12.43(1H, brs).

(5) 2-[(dimethylaminocarbonyl)methyl]-N-(4-fluorophenyl)-N-isopropyl-N'-((E)-styrylsulfonyl)malonamide

**[1023]** In the same manner as in Example 1 (2), the title compound (250 mg) was obtained as a white solid using the above-mentioned compound (400 mg) and trans-β-styrenesulfonamide (226 mg).

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ0.89-0.91(6H, m), 2.42-2.51(1H, m), 2.75(3H, s), 2.83-2.92(1H, m), 2.93(3H, s), 3.42-3.50(1H, m), 4.67-4.77(1H, m), 6.96-7.07(2H, m), 7.28-7.40(3H, m), 7.47-7.60(4H, m), 7.78-7.86(2H, m), 11.60(1H, brs).

MS: 490(M+H)<sup>+</sup>.

Example 443 Synthesis of N-(4-fluorophenyl)-N-isopropyl-2-[(pyrrolidinocarbonyl)methyl]-N'-((E)-styrylsulfonyl)malonamide

(1) triethyl 2-(pyrrolidinocarbonyl)ethane-1, 1, 1-tricarboxylate

**[1024]** In the same manner as in Example 1 (4), the title compound (5.60 g) was obtained as an oil using the compound

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(4.74 g) obtained in Example 432 (1) and pyrrolidine (1.64 mL).  $^1\text{H-NMR}$ (300Mz,  $\text{CDCl}_3$ ) $\delta$ 1.29(9H, t, J = 7.1Hz), 1.80-2.00(4H, m), 3.11 (2H, s), 3.48(4H, t, J = 6.7Hz), 4.28(6H, q, J = 7.1H).

(2) monoethyl [(pyrrolidinocarbonyl)methyl]malonate

5

**[1025]** In the same manner as in Example 117 (2), the title compound (3.46 g) was obtained as an oil using the above-mentioned compound (5.60 g).

$^1\text{H-NMR}$ (400Mz,  $\text{CDCl}_3$ ) $\delta$ 1.25-1.32(3H, m), 1.88-2.07(4H, m), 2.91(1H, dd, J = 16.8, 4.0Hz), 3.03(1H, dd, J = 16.8, 7.2Hz), 3.44-3.57(4H, m), 3.82(1H, dd, J = 7.2, 4.0Hz), 4.20-4.30(2H, m).

10

(3) ethyl 3-[N-(4-fluorophenyl)-N-isopropylamino]-3-oxo-2-[(pyrrolidinocarbonyl)methyl]propionate

**[1026]** In the same manner as in Example 13, the title compound (1.09 g) was obtained as an oil using the above-mentioned compound (980 mg) and 4-fluoro-N-isopropylaniline (680 mg).  $^1\text{H-NMR}$ (300Mz,  $\text{DMSO-d}_6$ ) $\delta$ 0.92(3H, d, J = 6.9Hz), 1.00(3H, d, J = 6.9Hz), 1.14(3H, t, J = 7.2Hz), 1.69-1.90(4H, m), 2.55-2.80(2H, m), 3.18-3.47(5H, m), 3.93-4.03(2H, m), 4.77(1H, sept, 6.9Hz), 7.18-7.45(4H, m).

15

(4) 3-[N-(4-fluorophenyl)-N-isopropylamino]-3-oxo-2-[(pyrrolidinocarbonyl)methyl]propionic acid

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**[1027]** In the same manner as in Example 1(3), the title compound (963 mg) was obtained as a white powder using the above-mentioned compound (1.09 g).

$^2\text{H-NMR}$ (400Mz,  $\text{DMSO-d}_6$ ) $\delta$ 0.98-1.01(6H, m), 1.69-1.90(4H, m), 2.53-2.78(2H, m), 3.20-3.30(2H, m), 3.32-3.42(3H, m), 4.71-4.82(1H, m), 7.20-7.49(4H, m), 12.49(1H, brs).

25

(5) N-(4-fluorophenyl)-N-isopropyl-2-[(pyrrolidinocarbonyl)methyl]-N'-((E)-styrylsulfonyl)malonamide

**[1028]** In the same manner as in Example 1 (2), the title compound (930 mg) was obtained as a white solid using the above-mentioned compound (1.05 g) and trans- $\beta$ -styrenesulfonamide (550 mg).

$^1\text{H-NMR}$ (400Mz,  $\text{DMSO-d}_6$ ) $\delta$ 0.87-0.93(6H, m), 1.69-1.90(4H, m), 2.44(1H, dd, J = 16.0, 4.4Hz), 2.81(1H, dd, J = 16.0, 9.6Hz), 3.17-3.24(2H, m), 3.31-3.42(2H, m), 3.49(1H, dd, J = 9.6, 4.4Hz), 4.69-4.76(1H, m), 6.97-7.07(2H, m), 7.28-7.38(3H, m), 7.47-7.50(3H, m), 7.56(1H, d, J = 15.6Hz), 7.80-7.82(2H, m), 11.62 (1H, brs).

30

MS: 516(M+H) $^+$ .

Example 444 Synthesis of 2-allyl-N-ethyl-N'-(2-naphthylsulfonyl)-N-phenylmalonamide

35

(1) monoethyl allylmalonate

**[1029]** In the same manner as in Example 1 (1), the title compound (7.50 g) was obtained as an oil using diethyl allylmalonate (10.0 g).

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$^1\text{H-NMR}$ (300Mz,  $\text{CDCl}_3$ ) $\delta$ 1.22-1.28(3H, m), 2.04-2.70(2H, m), 3.46-3.50(1H, m), 4.09-4.16(1H, m), 4.19-4.24(2H, m), 5.07-5.17(2H, m), 5.74-5.85(1H, m).

(2) ethyl 2-allyl-3-[(2-naphthylsulfonyl)amino]-3-oxopropionate

45

**[1030]** In the same manner as in Example 152 (3), the title compound (15.5 g) was obtained as a white powder using the above-mentioned compound (7.50 g).

$^1\text{H-NMR}$ (300Mz,  $\text{CDCl}_3$ ) $\delta$ 1.23(3H, t, J = 7.2Hz), 2.55-2.59(2H, m), 3.27-3.31(1H, t, J = 7.2Hz), 4.14-4.22(2H, m), 4.94-4.99(2H, m), 5.54-5.59(1H, m), 7.59-7.70(2H, m), 7.90-8.03(4H, m), 8.67(1H, s), 9.74(1H, s).

50

(3) 2-allyl-3-[(2-naphthylsulfonyl)amino]-3-oxopropionic acid

**[1031]** In the same manner as in Example 1 (3), the title compound (15.0 g) was obtained as a white powder using the above-mentioned compound (15.5 g).

55

$^1\text{H-NMR}$ (300Mz,  $\text{CDCl}_3$ ) $\delta$ 2.62-2.64(2H, m), 3.38(1H, t, J = 6.9Hz), 4.95-5.01(2H, m), 5.57-5.66(1H, m), 7.60-7.70(2H, m), 7.90-8.03(4H, m), 8.67(1H, s).

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### (4) 2-allyl-N-ethyl-N'-(2-naphthylsulfonyl)-N-phenylmalonamide

**[1032]** In the same manner as in Example 1 (4), the title compound (15.5 g) was obtained as a white powder using the above-mentioned compound (14.3 g) and N-ethylaniline (5.40 mL).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ0.95(3H, brs), 2.13-2.25(1H, m), 2.28-2.40(1H, m), 3.46-3.51(1H, m), 3.56-3.66(2H, m), 4.71-4.79(2H, m), 5.45-5.64(1H, m), 7.03-7.05(2H, m), 7.27-7.46(3H, m), 7.71-7.96(3H, m), 8.14-8.19(1H, m), 8.21-8.30(2H, m), 8.60(1H, s), 12.02(1H, brs).

MS: 437(M+H)<sup>+</sup>.

### Example 445 Synthesis of 2-allyl-N-(2-hydroxyethyl)-N-methyl-N'-(E)-styrylsulfonylmalonamide

#### (1) 2-allyl-3-oxo-3-[(E)-styrylsulfonyl]amino]propionic acid

**[1033]** In the same manner as in Example 152 (3), the object compound was obtained using the compound (9.05 g) obtained in Example 444 (1) and trans-β-styrenesulfonamide (9.16 g). This was subjected to hydrolysis in the same manner as in Example 1 (3) to give the title compound (7.86 g) as a white powder. <sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ2.71-2.75(2H, m), 3.46(1H, t, J = 6.9Hz), 5.11-5.18(2H, m), 5.70-5.79(1H, m), 6.92(1H, d, J = 15.3Hz), 7.42-7.77(5H, m), 7.74(1H, d, J = 1.5.3H), 9.52(1H, brs).

#### (2) 2-allyl-N-(2-hydroxyethyl)-N-methyl-N'-(E)-styrylsulfonylmalonamide

**[1034]** In the same manner as in Example 1 (4), the title compound (169 mg) was obtained as a white powder using the above-mentioned compound (500 mg) and 2-(methylamino)ethanol (240 mg).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ2.65(3H, s), 3.01-3.13(2H, m), 3.58-3.71(2H, m), 3.77-3.87(3H, m), 5.04-5.17(2H, m), 5.68-5.78(1H, m), 6.99-7.06(1H, m), 7.39-7.42(3H, m), 7.42-7.52(2H, m), 7.66-7.72(1H, m).

MS: 367(M+H)<sup>+</sup>.

### Example 446 Synthesis of 2-allyl-3-[4-(5-cyano-2-pyridyl)piperazino]-3-oxo-N-(E)-styrylsulfonylpropanamide

**[1035]** In the same manner as in Example 1 (4), the title compound (485 mg) was obtained as a white powder using the compound (500 mg) obtained in Example 445 (1) and 1-(5-cyano-2-pyridyl)piperazine (301 mg).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ2.66-2.69(2H, m), 3.59-3.67(5H, m), 3.68-3.82(4H, m), 5.11-5.19(2H, m), 5.67-5.77(1H, m), 6.59(1H, d, J = 9.2Hz), 7.03(1H, d, J = 15.2Hz), 7.26-7.46(3H, m), 7.50-7.51(2H, m), 7.52-7.73(2H, m), 8.42(1H, s), 10.42(1H, brs).

MS: 480(M+H)<sup>+</sup>.

### Example 447 Synthesis of 2-allyl-3-[4-(2-benzothiazolyl)piperazino]-3-oxo-N-(E)-styrylsulfonylpropanamide

**[1036]** In the same manner as in Example 1 (4), the title compound (860 mg) was obtained as a white powder using the compound (500 mg) obtained in Example 445 (1) and 1-(2-benzothiazolyl)piperazine (351 mg).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ2.63-2.73(2H, m), 3.60-3.62(2H, m), 3.66-3.71(5H, m), 3.73-3.85(2H, m), 5.12-5.19(2H, m), 5.67-5.77(1H, m), 7.04(1H, d, J = 15.6Hz), 7.11-7.15(1H, m), 7.31-7.49(4H, m), 7.51-7.59(2H, m), 7.61-7.63(2H, m), 7.72(1H, d, J = 15.6Hz), 10.43(1H brs).

MS: 511(M+H)<sup>+</sup>.

### Example 448 Synthesis of 2-allyl-3-oxo-N-(E)-styrylsulfonyl-3-[4-(7-trifluoromethyl-4-quinolyl)piperazino]propanamide

**[1037]** In the same manner as in Example 1 (4), the title compound (558 mg) was obtained as a white powder using the compound (500 mg) obtained in Example 445 (1) and 1-(7-trifluoromethyl-4-quinolyl)piperazine (341 mg).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ3.70-3.80(5H, m), 3.82-4.02(4H, m), 4.05-4.18(2H, m), 5.13-5.21(2H, m), 5.68-5.84(1H, m), 6.90-7.07(2H, m), 7.39-7.48(4H, m), 7.49-7.53(2H, m), 6.51-6.73(1H, m), 7.01-7.85(1H, m), 8.11-8.19(1H, m), 8.63(1H, s), 8.98(1H, brs). MS: 573(M+H)<sup>+</sup>.

### Example 449 Synthesis of 2-allyl-3-[4-(3, 4-dimethylphenyl)piperazino]-3-oxo-N-(E)-styrylsulfonylpropanamide

**[1038]** In the same manner as in Example 1 (4), the title compound (366 mg) was obtained as a white powder using the compound (500 mg) obtained in Example 445 (1) and 1-(3, 4-dimethylphenyl)piperazine (303 mg).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.50-1.70(2H, m), 1.82-1.99(2H, m), 2.21-2.23(6H, m), 2.65-2.72(4H, m), 3.12-3.23(1H, m),

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3.69-3.72(1H, m), 3.96-3.99(1H, m), 4.76-4.80(1H, m), 5.08-5.21(2H, m), 5.69-5.79(1H, m), 6.88-6.95(2H, m), 7.03-7.09(2H, m), 7.38-7.41(3H, m), 7.42-7.46(2H, m), 7.53-7.71(1H, m), 10.80-11.00(1H, m).  
MS : 481(M+H)<sup>+</sup>.

### 5 Example 450 Synthesis of 2-allyl-N-diphenylmethyl-N'-((E)-styrylsulfonyl)malonamide

**[1039]** In the same manner as in Example 1 (4), the title compound (8 mg) was obtained as a white powder using the compound (500 mg) obtained in Example 445 (1) and benzhydramine (352 mg).

10 <sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ2.67-2.69(2H, m), 3.16-3.18(1H, m), 5.07-5.14(2H, m), 5.60-5.77(1H, m), 6.17-6.19(1H, m), 6.45-6.49(1H, m), 7.00(1H, d, J = 15.6Hz), 7.17-7.18(4H, m), 7.28-7.32(6H, m), 7.42-7.49(3H, m), 7.50-7.51(2H, m), 7.71(1H, d, J = 15.6Hz), 10.09(1H, m).  
MS: 475(M+H)<sup>+</sup>.

### 15 Example 451 Synthesis of 2-allyl-3-[4-(3-methyl-1-phenyl-5-pyrazolyl)piperazino]-3-oxo-N-((E)-styrylsulfonyl)propanamide

**[1040]** In the same manner as in Example 1 (4), the title compound (20 mg) was obtained as a white powder using the compound (500 mg) obtained in Example 445 (1) and 1-(3-methyl-1-phenyl-5-pyrazolyl)piperazine (388 mg).

20 <sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ2.28(3H, s), 2.60-2.64(3H, m), 2.81-2.88(4H, m), 3.48-3.53(2H, m), 3.68-3.70(2H, m), 5.09-5.15(2H, m), 5.64-5.71(1H, m), 7.02(1H, d, J = 15.2Hz), 7.27-7.31(2H, m), 7.39-7.45(5H, m), 7.50-7.52(2H, m), 7.68-7.72(3H, m), 10.45(1H, brs).  
MS: 534(M+H)<sup>+</sup>.

### 25 Example 452 Synthesis of 2-allyl-N, N-diethyl-N'-((E)-styrylsulfonyl)malonamide

**[1041]** In the same manner as in Example 1 (4), the title compound (119 mg) was obtained as a white powder using the compound (500 mg) obtained in Example 445 (1). <sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.05-1.20(6H, m), 2.60-2.66(2H, m), 3.21-3.38(3H, m), 3.51-3.58(2H, m), 5.07-3.15(2H, m), 5.65-5.76(1H, m), 7.03(1H, d, J = 15.6Hz), 7.39-7.46(3H, m), 7.51-7.53(2H, m), 7.71(1H, d, J = 15.6Hz), 10.70(1H, brs).

30 MS: 365(M+H)<sup>+</sup>.

### Example 453 Synthesis of 2-allyl-N-ethyl-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

**[1042]** In the same manner as in Example 1 (4), the title compound (515 mg) was obtained as a white powder using the compound (500 mg) obtained in Example 445 (1) and N-ethylaniline (240 μL).

35 <sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.10-1.17(3H, m), 2.40-2.66(2H, m), 3.20-3.32(1H, m), 3.67-3.85(2H, m), 5.01-5.06(2H, m), 5.49-5.60(1H, m), 7.03(1H, d, J = 15.6Hz), 7.09-7.12(2H, m), 7.30-7.42(6H, m), 7.48-7.51(2H, m), 7.69(1H, d, J = 15.6Hz), 10.47(1H, brs).  
MS: 413(M+H)<sup>+</sup>.

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### Example 454 Synthesis of 2-allyl-N-ethyl-N-(1-naphthyl)-N'-((E)-styrylsulfonyl)malonamide

**[1043]** In the same manner as in Example 1 (4), the title compound (108 mg) was obtained as a white powder using the compound (500 mg) obtained in Example 445 (1) and N-ethyl-1-naphthylamine (277 μL).

45 <sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.15-1.22(3H, m), 2.34-2.70(2H, m), 2.92-3.30(1H, m), 3.32-3.53(1H, m), 4.19-4.40(1H, m), 4.85-5.08(2H, m), 5.31-5.59(1H, m), 6.98-7.04(1H, m), 7.22-7.76(11H, m), 7.80-7.99(2H, m), 10.10-10.04(1H, brs).  
MS: 463(M+H)<sup>+</sup>.

### 50 Example 455 Synthesis of 2-allyl-N-ethyl-N-(1-naphthyl)-N'-(2-naphthylsulfonyl) malonamide

**[1044]** In the same manner as in Example 1 (4), the title compound (108 mg) was obtained as a white powder using the compound (540 mg) obtained in Example 444 (3) and N-ethyl-1-naphthylamine (279 μL).

55 <sup>1</sup>H-MMR(400Mz, CDCl<sub>3</sub>)δ1.12-1.20(3H, m), 2.19-2.45(2H, m), 2.79-2.94(1H, m), 3.21-3.53(1H, m), 4.11-4.40(1H, m), 4.66-4.88(2H, m), 5.15-5.47(1H, m), 6.82-6.97(1H, m), 7.24-8.03(12H, m), 8.62-8.67(1H, m), 10.14-10.67(1H, m).  
MS: 487(M+H)<sup>+</sup>.

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Example 456 Synthesis of 2-allyl-N-ethyl-N-(2-naphthyl)-N'-{[(E)-2-(2-thiazolyl)ethenyl]sulfonyl}malonamide

**[1045]** The compound (344 mg) obtained in Example 444 (1) and [(E)-2-(2-thiazolyl)ethylene]sulfonamide (380 mg) were condensed in the same manner as in Example 152 (3), and the condensed product was subjected to hydrolysis in the same manner as in Example 1 (3) to give a white powder (469 mg). In the same manner as in Example 1 (4), the title compound (84 mg) was obtained as a white powder using this and N-ethyl-2-naphthylamine (373 mg).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.30(3H, m), 2.48-2.53(1H, m), 2.56-2.64(1H, m), 3.29(1H, t, J = 6.8Hz), 3.82-3.89(2H, m), 5.03-5.08(2H, m), 5.49-5.59(1H, m), 7.18-7.21(1H, m), 7.39(1H, d, J = 14.8Hz), 7.52-7.78(4H, m), 7.81-7.83(2H, m), 7.87-7.93(2H, m), 7.97-7.98(1H, m), 10.61(1H, brs).

MS: 470(M+H)<sup>+</sup>.

Example 457 Synthesis of 2-allyl-N-ethyl-N-(1-naphthyl)-N'-{[(E)-2-(2-thiazolyl)ethenyl]sulfonyl}malonamide

**[1046]** In the same manner as in Example 456, the title compound (116 mg) was obtained as a white powder using N-ethyl-1-naphthylamine (514 μL).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1-17-1.21(3H, m), 2.30-2.70(2H, m), 2.90-3.10(1H, m), 4.20-4.40(2H, m), 4.90-5.10(2H, m), 5.30-5.60(1H, m), 7.36-7.40(1H, m), 7.47-7.59(5H, m), 7.78-7.81(1H, m), 7.91-7.94(1H, m), 7.97-7.98(3H, m), 10.25(1H, brs).

MS: 470(M+H)<sup>+</sup>.

Example 458 Synthesis of 2-allyl-N-ethyl-N-(2-naphthyl)-N'-{[(E)-2-(3-pyridyl)ethenyl]sulfonyl}malonamide

**[1047]** The compound (344 mg) obtained in Example 444 (1) and [(E)-2-(3-pyridyl)ethylene]sulfonamide (369 mg) were condensed in the same manner as in Example 152 (3), and the condensed product was subjected to hydrolysis in the same manner as in Example 1 (3). In the same manner as in Example 1 (4), the title compound (25 mg) was obtained as a white powder using this and N-ethyl-2-naphthylamine (504 mg).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.22(3H, t, J = 7.2Hz), 2.47-2.52(2H, m), 2.56-2.63(2H, m), 3.45-3.50(1H, m), 3.69-3.87(2H, m), 5.02-5.06(2H, m), 5.51-5.58(1H, m), 7.10-7.20(2H, m), 7.35-7.38(1H, m), 7.52-7.73(2H, m), 7.81-7.83(1H, m), 7.88-7.93(4H, m), 8.65(1H, s), 8.75(1H, s).

MS: 464 (M+H)<sup>+</sup>.

Example 459 Synthesis of 2-allyl-N-(2, 3-dichlorophenyl)-N-ethyl-N'-{(E)-styrylsulfonyl}malonamide

**[1048]** In the same manner as in Example 1 (4), the title compound (44 mg) was obtained as a white powder using the compound (928 mg) obtained in Example 445 (1) and 2, 3-dichloro-N-ethylaniline (570 mg).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.12-1.18(3H, m), 2.42-2.68(2H, m), 3.02-3.10(1H, m), 3.43-4.50(1H, m), 3.93-4.26(1H, m), 4.98-5.25(2H, m), 5.50-5.79(1H, m), 6.97-7.12(2H, m), 7.21-7.31(1H, m), 7.40-7.50(3H, m), 7.55-7.65(3H, m), 7.72(1H, d, J = 15.2Hz).

MS: 480(M+H)<sup>+</sup>.

Example 460 Synthesis of 2-allyl-N-(2, 3-dimethylphenyl)-N-ethyl-N'-{(E)-styrylsulfonyl}malonamide

**[1049]** In the same manner as in Example 1 (4), the title compound (92 mg) was obtained as a white powder using the compound (928 mg) obtained in Example 445 (1) and 2, 3-dimethyl-N-ethylaniline (448 mg).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.10-1.15(3H, m), 2.09(3H, s), 2.30(3H, s), 2.40-2.45(1H, m), 2.50-2.55(1H, m), 3.04-3.15(2H, m), 4.21-4.26(1H, m), 4.97-5.04(2H, m), 5.50-5.57(1H, m), 6.78-6.80(1H, m), 7.02(1H, d, J = 15.2Hz), 7.07-7.11(1H, m), 7.18-7.19(1H, m), 7.39-7.44(3H, m), 7.49-7.52(2H, m), 7.70(1H, d, J = 15.2Hz), 10.12(1H, brs).

MS: 441(M+H)<sup>+</sup>.

Example 461 Synthesis of 2-allyl-N-ethyl-N-(4-fluorophenyl)-N'-{(E)-styrylsulfonyl}malonamide

**[1050]** In the same manner as in Example 1 (4), the title compound (110 mg) was obtained as a white powder using the compound (928 mg) obtained in Example 445 (1) and N-ethyl-4-fluoroaniline (418 mg).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.13(3H, brs), 2.45-2.59(2H, m), 3.17-3.21(1H, m), 3.66-3.81(2H, m), 5.03-5.07(2H, m), 5.49-5.58(1H, m), 7.02(1H, d, J = 15.2Hz), 7.09-7.15(4H, m), 7.42-7.47(3H, m), 7.50-7.52(2H, m), 7.71(1H, d, J = 15.2Hz), 10.28(1H, brs).

MS: 431(M+H)<sup>+</sup>.

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### Example 462 Synthesis of 2-allyl-N-methyl-N-(1-naphthyl)-N'-((E)-styrylsulfonyl)malonamide

**[1051]** In the same manner as in Example 1 (4), the title compound (458 mg) was obtained as a white powder using the compound (928 mg) obtained in Example 445 (1) and N-methyl-1-naphthylamine (581 mg).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ2.91-2.49(2H, m), 3.12-3.16(1H, m), 3.44(3H, s), 4.87-5.08(2H, m), 5.29-5.40(1H, m), 7.03(1H, d, J = 15.6Hz), 7.27-7.31(1H, m), 7.32-7.61(6H, m), 7.66-7.34(2H, m), 7.89-7.91(2H, m), 7.93-7.96(2H, m), 10.06(1H, brs). MS: 449(M+H)<sup>+</sup>.

### Example 463 Synthesis of 2-allyl-N-(4-chlorophenyl)-N-ethyl-N'-((E)-styrylsulfonyl)malonamide

**[1052]** In the same manner as in Example 1 (4), the title compound (707 mg) was obtained as a white powder using the compound (928 mg) obtained in Example 445 (1) and 4-chloro-N-ethylaniline (467 mg).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1-14(3H, brs), 2.46-2.59(2H, m), 3.17-3.21(1H, m), 3.66-3.71(1H, m), 3.76-3.82(1H, m), 5.03-5.07(2H, m), 5.51-5.57(1H, m), 7.00-7.06(3H, m), 7.26-7.45(5H, m), 7.51-7.53(2H, m), 7.71(1H, d, J = 15.6Hz), 10.25(1H, brs). MS: 447(M+H)<sup>+</sup>.

### Example 464 Synthesis of 2-allyl-N-(2, 5-difluorophenyl)-N-ethyl-N'-((E)-styrylsulfonyl)malonamide

**[1053]** In the same manner as in Example 1 (4)', the title compound (92 mg) was obtained as a white powder using the compound (928 mg) obtained in Example 445 (1) and 2, 5-difluoro-N-ethylaniline (425 mg).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.10-1.15(3H, m), 2.40-2.70(2H, m), 3.12-3.29(1H, m), 3.47-3.67(1H, m), 3.82-3.89(1H, m), 4.97-5.10(2H, m), 5.53-5.70(1H, m), 6.91-6.94(1H, m), 6.99-7.21(4H, m), 7.31-7.43(2H, m), 7.51-7.53(2H, m), 7.71(1H, d, J = 15.6Hz), 10.04-10.14(1H, m).

MS: 449(M+H)<sup>+</sup>.

### Example 465 Synthesis of 2-allyl-N-(4-chlorophenyl)-N-methyl-N'-((E)-styrylsulfonyl)malonamide

**[1054]** In the same manner as in Example 1 (4), the title compound (178 mg) was obtained as a white powder using the compound (928 mg) obtained in Example 445 (1) and 4-chloro-N-methylaniline (425 mg).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ2.47-2.59(2H, m), 3.27-3.31(4H, m), 5.03-5.08(2H, m), 5.48-5.57(1H, m), 7.00-7.09(3H, m), 7.39-7.45(5H, m), 7.51-7.53(2H, m), 7.71(1H, d, J = 15.6Hz), 10.18(1H, brs). MS: 432(M+H)<sup>+</sup>.

### Example 466 Synthesis of 2-allyl-N-ethyl-N-(2-fluorophenyl)-N'-((E)-styrylsulfonyl)malonamide

**[1055]** In the same manner as in Example 1 (4), the title compound (263 mg) was obtained as a white powder using the compound (928 mg) obtained in Example 445 (1) and N-ethyl-2-fluoroaniline (418 mg).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.09-1.11(3H, m), 2.40-2.70(2H, m), 3.12-3.20(1H, m), 3.51-3.57(1H, m), 3.80-3.95(1H, m), 4.96-5.08(2H, m), 5.51-5.71(1H, m), 6.99-7.04(1H, m), 7.14-7.24(4H, m), 7.50-7.55(3H, m), 7.58-7.62(2H, m), 7.88(1H, d, J = 15.2Hz), 10.18-10.30(1H, brs).

MS: 431(M+H)<sup>+</sup>.

### Example 467 Synthesis of 2-allyl-N-ethyl-N-(2, 4, 6-trifluorophenyl)-N'-((E)-styrylsulfonyl)malonamide

**[1056]** In the same manner as in Example 1 (4), the title compound (108 mg) was obtained as a white powder using the compound (928 mg) obtained in Example 445 (1) and N-ethyl-2, 4, 6-trifluoroaniline (525 mg).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.17(3H, brs), 2.46-2.53(1H, m), 2.57-2.63(1H, m), 3.05-3.09(1H, m), 3.49-3.58(1H, m), 3.84-3.93(1H, m), 5.03-5.08(2H, m), 5.51-5.61(1H, m), 6.74-6.84(2H, m), 7.00(1H, d, J = 15.6Hz), 7.26-7.45(3H, m), 7.51-7.53(2H, m), 7.71(1H, d, J = 15.6Hz), 9.91(1H, brs).

MS: 467(M+H)<sup>+</sup>.

### Example 468 Synthesis of 2-allyl-N-ethyl-N-(2, 4-difluorophenyl)-N'-((E)-styrylsulfonyl)malonamide

**[1057]** In the same manner as in Example 1 (4), the title compound (5 mg) was obtained as a white powder using the compound (928 mg) obtained in Example 445 (1) and N-ethyl-2, 4-difluoroaniline (550 mg).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.26-1.30(3H, m), 2.66-2.70(2H, m), 3.37-3.41(1H, m), 4.20-4.25(2H, m), 5.08-5.14(2H, m), 5.70-5.72(1H, m), 7.04(1H, d, J = 15.2Hz), 7.40-7.45(4H, m), 7.51-7.53(4H, m), 7.73(1H, d, J = 15.2Hz), 9.60(1H, brs).

MS: 449(M+H)<sup>+</sup>.

Example 469 Synthesis of 2-allyl-N-ethyl-N-(3, 4-methylenedioxyphenyl)-N'-((E)-styrylsulfonyl)malonamide

5 **[1058]** In the same manner as in Example 1 (4), the title compound (627 mg) was obtained as a white powder using the compound (928 mg) obtained in Example 445 (1) and N-ethyl-3, 4-methylenedioxyaniline (496 mg).  
<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.10(3H, brs), 2.45-2.61(2H, m), 3.29-3.32(1H, m), 3.69-3.70(2H, m), 5.03-5.08(2H, m), 5.53-5.63(1H, m), 6.04(2H, s), 6.54-6.56(2H, m), 6.78-6.80(1H, m), 7.03(1H, d, J = 15.6Hz), 7.32-7.40(3H, m), 7.41-7.52(2H, m), 7.70(1H, d, J = 15.6Hz), 10.38(1H, brs).  
 10 MS: 457(M+H)<sup>+</sup>.

Example 470 Synthesis of 2-allyl-3-(5-bromo-2, 3-dihydro-1H-indol-1-yl)-3-oxo-N-((E)-styrylsulfonyl)propanamide

15 **[1059]** In the same manner as in Example 1 (4), the title compound (96 mg) was obtained as a white powder using the compound (928 mg) obtained in Example 445 (1) and 5-bromoindoline (594 mg).  
<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ2.69-2.78(2H, m), 3.17-3.21(2H, m), 3.58-3.62(1H, m), 4.05-4.21(2H, m), 5.10-5.21(2H, m), 5.71-5.81(1H, m), 7.03(1H, d, J = 15.6Hz), 7.33-7.39(2H, m), 7.40-7.46(3H, m), 7.50-7.52(2H, m), 7.72(1H, d, J = 15.6Hz), 8.11(1H, d, J = 8.4Hz), 10.35(1H, brs).  
 20 MS: 491(M+H)<sup>+</sup>.

Example 471 Synthesis of 2-allyl-3-(6-fluoro-2-methyl-3, 4-dihydroquinolin-1(2H)-yl)-3-oxo-N-((E)-styrylsulfonyl)propanamide

25 **[1060]** In the same manner as in Example 1 (4), the title compound (236 mg) was obtained as a white powder using the compound (618 mg) obtained in Example 445 (1) and 6-fluoro-2-methyl-1, 2, 3, 4-tetrahydroquinoline (330 mg).  
<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.12(3H, brs), 1.20-1.32(1H, m), 2.34-2.61(5H, m), 3.73-3.78(H, m), 4.75-4.80(1H, m), 4.93-4.99(2H, m), 5.30-5.39(1H, m), 6.92-6.96(3H, m), 7.07(1H, d, J = 15.2Hz), 7.41-7.46(3H, m), 7.53-7.55(2H, m), 7.75(1H, d, J = 15.2Hz), 10.29(1H, brs).  
 30 MS: 457(M+H)<sup>+</sup>.

Example 472 Synthesis of 2-allyl-N-benzyl-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

35 **[1061]** In the same manner as in Example 1 (4), the title compound (268 mg) was obtained as a white powder using the compound (741 mg) obtained in Example 445 (1) and N-benzylaniline (439 mg).  
<sup>2</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ2.46-2.53(1H, m), 2.57-2.64(1H, m), 3.24-3.27(1H, m), 4.78-4.82(1H, m), 4.93-5.07(3H, m), 5.49-5.59(1H, m), 6.87(2H, d, J = 2.4Hz), 7.01(1H, d, J = 15.2Hz), 7.13-7.23(2H, m), 7.28-7.36(6H, m), 7.39-7.46(3H, m), 7.49-7.52(2H, m), 7.71(1H, d, J = 15.2Hz), 10.36(1H, brs).  
 40 MS: 475(M+H)<sup>+</sup>.

Example 473 Synthesis of 2-allyl-3-(3,4-dihydroisoquinolin-2(1H)-yl)-3-oxo-N-((E)-styrylsulfonyl)propanamide

45 **[1062]** In the same manner as in Example 1 (4), the title compound (650 mg) was obtained as a white powder using the compound (674 mg) obtained in Example 445 (1) and 1, 2, 3, 4-tetrahydroisoquinoline (266 mg).  
<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ2.62-2.75(2H, m), 2.85-2.96(2H, m), 3.71-3.78(3H, m), 4.59-4.80(2H, m), 4.98-5.17(2H, m), 5.63-5.76(1H, m), 7.03(1H, d, J = 15.6Hz), 7.06-7.23(4H, m), 7.26-7.45(3H, m), 7.52-7.64(2H, m), 7.72(1H, d, J = 15.6Hz), 10.70-10.80(1H, m).  
 50 MS: 425(M+H)<sup>+</sup>.

Example 474 Synthesis of 2-allyl-N-ethyl-N-(4-methylthiophenyl)-N'-((E)-styrylsulfonyl)malonamide

55 **[1063]** In the same manner as in Example 1 (4), the title compound (282 mg) was obtained as a white powder using the compound (618 mg) obtained in Example 445 (1) and N-ethyl-4-methylthioaniline (1.00 g).  
<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.14(3H, brs), 2.45-2.60(5H, m), 3.23-3.26(1H, m), 3.65-3.81(2H, m), 5.02-5.07(2H, m), 5.51-5.58(1H, m), 6.99-7.05(3H, m), 7.25-7.40(2H, m), 7.40-7.45(3H, m), 7.51-7.53(2H, m), 7.71(1H, d, J = 15.2Hz), 10.42(1H, brs).  
 60 MS: 459(M+H)<sup>+</sup>.

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Example 475 Synthesis of 2-allyl-N-ethyl-N'-((E)-styrylsulfonyl)-N-(3-trifluoromethylphenyl)malonamide

**[1064]** In the same manner as in Example 1 (4), the title compound (321 mg) was obtained as a white powder using the compound (618 mg) obtained in Example 445 (1) and N-ethyl-3-trifluoromethylaniline (1.00 g).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.14(3H, brs), 2.45-2.51(1H, m), 2.52-2.63(1H, m), 3.10-3.14(1H, m), 3.73-3.82(2H, m), 5.05-5.24(2H, m), 5.49-5.59(1H, m), 7.03(1H, d, J = 15.6Hz), 7.29-7.31(1H, m), 7.33-7.46(4H, m), 7.51-7.62(2H, m), 7.65-7.70(1H, m), 7.74-8.06(2H, m), 10.31(1H, brs).

MS: 481(M+H)<sup>+</sup>.

Example 476 Synthesis of 2-allyl-N-ethyl-N'-((E)-styrylsulfonyl)-N-(4-trifluoromethylphenyl)malonamide

**[1065]** In the same manner as in Example 1 (4), the title compound (398 mg) was obtained as a white powder using the compound (618 mg) obtained in Example 445 (1) and N-ethyl-4-trifluoromethylaniline (1.00 g).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.10-1.16(3H, m), 2.45-2.52(1H, m), 2.53-2.63(1H, m), 3.16(1H, t, J = 7.2Hz), 3.68-3.87(2H, m), 5.04-5.08(2H, m), 5.48-5.57(1H, m), 7.02(1H, d, J = 15.6Hz), 7.24-7.28(2H, m), 7.39-7.45(3H, m), 7.51-7.53(2H, m), 7.61-7.73(3H, m), 10.17(1H, s).

MS: 481(M+H)<sup>+</sup>.

Example 477 Synthesis of 2-allyl-N-methyl-N-(1-naphthylmethyl)-N'-((E)-styrylsulfonyl)malonamide

**[1066]** In the same manner as in Example 1 (4), the title compound (89 mg) was obtained as a white powder using the compound (618 mg) obtained in Example 445 (1) and N-methyl-1-naphthylmethylamine hydrochloride (415 mg).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ2.60-2.80(2H, m), 2.88-3.15(3H, m), 3.53-3.73(1H, m), 4.93-5.28(4H, m), 5.58-5.77(1H, m), 6.99(1H, d, J = 15.6Hz), 7.33-7.58(9H, m), 7.71-8.09(4H, m), 10.40-10.82(1H, m).

MS: 463(M+H)<sup>+</sup>.

Example 478 Synthesis of 2-allyl-N, N-dibenzyl-N'-((E)-styrylsulfonyl)malonamide

**[1067]** In the same manner as in Example 1 (4), the title compound (288 mg) was obtained as a white powder using the compound (618 mg) obtained in Example 445 (1) and dibenzylamine (394 mg).

<sup>1</sup>H-NMR (400Mz, CDCl<sub>3</sub>)δ2.62-2.67(2H, m), 3.65-3.69(1H, m), 4.39-4.54(3H, m), 4.84-4.88(1H, m), 5.04-5.12(2H, m), 5.60-5.66(1H, m), 7.02(1H, d, J = 15.2Hz), 7.07-7.09(2H, m), 7.19-7.21(2H, m), 7.29-7.34(6H, m), 7.42-7.47(3H, m), 7.51-7.53(2H, m), 7.72(1H, d, J = 15.2Hz), 10.43(1H, brs).

MS: 489(M+H)<sup>+</sup>.

Example 479 Synthesis of 2-allyl-N-ethyl-N-(3-fluorophenyl)-N'-((E)-styrylsulfonyl)malonamide

**[1068]** In the same manner as in Example 1 (4), the title compound (372 mg) was obtained as a white powder using the compound (618 mg) obtained in Example 445 (1) and N-ethyl-3-fluoroaniline (278 mg).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.12(3H, brs), 2.40-2.80(2H, m), 3.21-3.69(1H, m), 3.71-3.84(2H, m), 5.04-5.22(2H, m), 5.50-5.82(1H, m), 6.85-6.93(2H, m), 7.03(1H, d, J = 15.6Hz), 7.11-7.16(1H, m), 7.30-7.41(5H, m), 7.42-7.47(3H, m), 7.70(1H, d, J = 15.6Hz), 10.30(1H, brs).

MS: 431(M+H)<sup>+</sup>.

Example 480 Synthesis of 2-allyl-N-ethyl-N-(4'-fluoro-4-biphenyl)-N'-((E)-styrylsulfonyl)malonamide

**[1069]** In the same manner as in Example 1 (4), the title compound (241 mg) was obtained as a white powder using the compound (337 mg) obtained in Example 445 (1) and N-(4'-fluoro-4-biphenyl)-N-ethylamine (430 mg).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.12(3H, brs), 2.40-2.65(2H, m), 3.27-3.49(1H, m), 3.70-3.89(2H, m), 5.03-5.25(2H, m), 5.52-5.85(1H, m), 7.03(1H, d, J = 15.6Hz), 7.09-7.22(4H, m), 7.39-7.49(3H, m), 7.51-7.54(6H, m), 7.75(1H, d, J = 15.6Hz), 10.40(1H, brs).

MS: 507(M+H)<sup>+</sup>.

Example 481 Synthesis of 2-allyl-N-(4-fluorophenyl)-N-isopropyl-N'-((E)-styrylsulfonyl)malonamide

**[1070]** In the same manner as in Example 1 (4), the title compound (265 mg) was obtained as a white powder using the compound (618 mg) obtained in Example 445 (1) and 4-fluoro-N-isopropylaniline (306 mg).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.00(3H, d, J = 6.8Hz), 1.09(3H, d, J = 6.8Hz), 2.17-2.49(1H, m), 2.52-2.58(1H, m),

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3.02-3.06(1H, m), 4.93-4.97(1H, m), 5.03-5.07(2H, m), 5.50-5.57(1H, m), 6.99-7.05(3H, m), 7.09-7.14(2H, m), 7.39-7.45(3H, m), 7.50-7.52(2H, m), 7.70(1H, d, J = 15.6Hz), 10.29(1H, brs).  
MS: 445(M+H)<sup>+</sup>.

### 5 Example 482 Synthesis of 2-allyl-N-isopropyl-N'-((E)-styrylsulfonyl)-N-(3-trifluoromethylphenyl)malonamide

**[1071]** In the same manner as in Example 13, the title compound (96 mg) was obtained as a white powder using the compound (309 mg) obtained in Example 445 (1) and N-isopropyl-3-trifluoromethylaniline (244 mg).

10 <sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.74-1.51(6H, m), 2.15-2.60(2H, m), 2.96-3.22(1H, m), 4.67-5.00(3H, m), 5.42-5.75(1H, m), 7.13-7.95(11H, m), 11.59(1H, brs).  
MS: 495(M+H)<sup>+</sup>.

### Example 483 Synthesis of 2-allyl-N-(4-fluorophenyl)-N-(3-pentyl)-N'-((E)-styrylsulfonyl)malonamide

15 **[1072]** In the same manner as in Example 13, the title compound (357 mg) was obtained as a white powder using the compound (619 mg) obtained in Example 445 (1) and 4-fluoro-N-(3-pentyl)aniline (435 mg).

20 <sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.69-0.90(6H, m), 0.90-1.38(4H, m), 2.11-2.32(1H, m), 2.36-2.56(1H, m), 3.06-3.23(1H, m), 4.25-4.50(1H, m), 4.78-4.99(2H, m), 5.50-5.76(1H, m), 6.84-7.04(1H, m), 7.04-7.23(2H, m), 7.23-7.40(2H, m), 7.40-7.63(4H, m), 7.69-7.91(2H, m), 11.59(1H, brs).  
MS: 473(M+H)<sup>+</sup>.

### Example 484 Synthesis of 2-allyl-N-isopropyl-N-(3-pyridyl)-N'-((E)-styrylsulfonyl)malonamide

25 **[1073]** In the same manner as in Example 13, the title compound (170 mg) was obtained as a white powder using the compound (619 mg) obtained in Example 445 (1) and 3-(isopropylamino)pyridine (327 mg).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.75-1.00(6H, m), 2.13-2.55(2H, m), 2.60-3.08(1H, m), 4.60-5.00(3H, m), 5.48-5.74(1H, m), 7.00-7.90(9H, m), 8.38(1H, brs), 8.59(1H, brs), 11.58(1H, brs).  
MS: 428(M+H)<sup>+</sup>.

### 30 Example 485 Synthesis of 2-allyl-N-cyclohexyl-N-ethyl-N'-((E)-styrylsulfonyl)malonamide

**[1074]** In the same manner as in Example 13, the title compound (113 mg) was obtained as a white powder using the compound (619 mg) obtained in Example 445 (1) and N-ethylcyclohexylamine (305 mg).

35 <sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.82-1.80(13H, m), 2.31-2.52(2H, m), 2.98-4.10(4H, m), 4.89-5.05(2H, m), 5.57-5.88(1H, m), 7.23-7.61(5H, m), 7.61-7.79(2H, m), 12.14(1H, brs).  
MS: 419(M+H)<sup>+</sup>.

### 40 Example 486 Synthesis of N-ethyl-N-(4-fluorophenyl)-2-(3-methyl-2-butenyl)-N'-((E)-styrylsulfonyl)malonamide (1) monoethyl (3-methyl-2-butenyl)malonate

**[1075]** In the same manner as in Example 117 (1), the object compound was obtained using 1-bromo-3-methyl-2-butene (5.00 g). This was subjected to hydrolysis in the same manner as in Example 117 (2) to give the title compound (5.08 g) as an oil.

45 <sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.26-1.33(3H, m), 1.64(3H, s), 1.69(3H, s), 2.59-2.68(2H, m), 3.37-3.43(1H, m), 4.19-4.27(2H, m), 5.06-5.10(1H, m).

### (2) 2-(3-methyl-2-butenyl)-3-oxo-3-(((E)-styrylsulfonyl)amino)propionic acid

**[1076]** In the same manner as in Example 152 (3), the object compound was obtained using the above-mentioned compound (3.00 g) and trans-β-styrenesulfonamide (2.75 g). This was subjected to hydrolysis in the same manner as in Example 1 (3) to give the title compound (3.84 g) as a white powder.

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ2.11(3H, s), 2.21(3H, s), 3.39-3.45(1H, m), 3.47-3.52(1H, m), 5.01-5.10(2H, m), 7.03(1H, d, J = 15.6Hz), 7.21-7.54(5H, m), 7.74(1H, d, J = 15.6Hz), 9.42(1H, brs).

### 55 (3) N-ethyl-N-(4-fluorophenyl)-2-(3-methyl-2-butenyl)-N'-((E)-styrylsulfonyl)malonamide

**[1077]** In the same manner as in Example 1 (4), the title compound (201 mg) was obtained as a white powder using the above-mentioned compound (674 mg) and N-ethyl-4-fluoroaniline (278 mg).

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<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.10-1.14(3H, m), 1.50(3H, s), 1.63(3H, s), 2.41-2.44(1H, m), 2.52-2.54(1H, m), 3.11-3.15(1H, m), 3.69-3.76(2H, m), 4.86-4.88(1H, m), 7.02-7.13(5H, m), 7.41-7.45(3H, m), 7.51-7.53(2H, m), 7.71(1H, d, J = 15.2Hz), 10.36(1H, brs).  
MS: 459(M+H)<sup>+</sup>.

5

Example 487 Synthesis of N-ethyl-N-(1-naphthyl)-2-propyl-N'-((E)-styrylsulfonyl)malonamide

(1) monoethyl propylmalonate

10 **[1078]** In the same manner as in Example 1 (1), the title compound (4.31 g) was obtained as an oil using diethyl propylmalonate (5.00 g).

<sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ0.95(3H, t, J = 7.5Hz), 1.08-1.48(5H, m), 1.74-2.02(2H, m), 3.39(1H, t, J = 7.2Hz), 4.23(2H, q, J = 7.2Hz), 7.27(1H, brs).

15 (2) ethyl 3-oxo-2-propyl-3-[(E)-styrylsulfonyl]amino]propionate

**[1079]** In the same manner as in Example 152 (3), the title compound (8.17 g) was obtained as an oil using the above-mentioned compound (4.31 g) and trans-β-styrenesulfonamide (4.18 g).

20 <sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ0.92(3H, t, J = 7.4Hz), 1.07-1.48(5H, m), 1.74-2.00(2H, m), 3.32(1H, t, J = 7.4Hz), 4.22(2H, q, J = 7.4Hz), 6.89-7.79(7H, m), 9.60(1H, brs).

(3) 3-oxo-2-propyl-3-[(E)-styrylsulfonyl]amino]propionic acid

25 **[1080]** In the same manner as in Example 1 (3), the title compound (4.13 g) was obtained as an oil using the above-mentioned compound (8.17 g).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.84(3H, t, J = 7.4Hz), 1.08-1.34(2H, m), 1.50-1.78(2H, m), 3.36(1H, t, J = 7.4Hz), 7.07-7.80(7H, m), 12.45(2H, brs).

(4) N-ethyl-N-(1-naphthyl)-2-propyl-N'-((E)-styrylsulfonyl)malonamide

30

**[1081]** In the same manner as in Example 13, the title compound (186 mg) was obtained as a white powder using the above-mentioned compound (1.25 g) and N-ethyl-1-naphthylamine (822 mg).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.62(3H, t, J = 6.9Hz), 0.80-1.47(6H, m), 1.60-1.86(1H, m), 2.70-2.87(1H, m), 3.04-3.45(1H, m), 3.97-4.18(1H, m), 7.08-8.14(14H, m), 11.36(1H, brs).

35 MS: 465(M+H)<sup>+</sup>.

Example 488 Synthesis of N-ethyl-N-(4-fluorophenyl)-2-propyl-N'-((E)-styrylsulfonyl)malonamide

40 **[1082]** In the same manner as in Example 13, the title compound (274 mg) was obtained as a white powder using the compound (1.25 g) obtained in Example 487 (3) and N-ethyl-4-fluoroaniline (668 mg).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.70(3H, t, J = 7.2Hz), 0.96(3H, t, J = 7.2Hz), 1.00-1.20(2H, m), 1.40-1.83(2H, m), 3.00-3.72(3H, m), 6.97-7.61(9H, m), 7.63-7.88(2H, m), 11.62(1H, brs).

MS: 432(M+H)<sup>+</sup>.

45 Example 489 Synthesis of N-(4-fluorophenyl)-N-isopropyl-2-propyl-N'-((E)-styrylsulfonyl)malonamide

**[1083]** In the same manner as in Example 13, the title compound (627 mg) was obtained as a white powder using the compound (623 mg) obtained in Example 487 (3) and 4-fluoro-N-isopropylaniline (368 mg).

50 <sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.71(3H, t, J = 7.5Hz), 0.77-0.97(6H, m), 0.97-1.20(2H, m), 1.33-1.57(1H, m), 1.57-1.78(1H, m), 2.89-3.08(1H, m), 4.61-4.86(1H, m), 6.80-7.40(5H, m), 7.40-7.60(4H, m), 7.68-7.89(2H, m), 11.54(1H, brs).

MS: 447(M+H)<sup>+</sup>.

Example 490 Synthesis of N-(4-fluorophenyl)-N-isopropyl-2-isopropyl-N'-((E)-styrylsulfonyl)malonamide

55 (1) monoethyl isopropylmalonate

**[1084]** In the same manner as in Example 1 (1), the title compound (4.35 g) was obtained as an oil using diethyl isopropylmalonate (5.06 g).

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<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.93(6H, t, J = 6.5Hz), 1.18(3H, t, J = 7.2Hz), 2.09-2.30(1H, m), 3.07(1H, d, J = 8.3Hz), 4.11(2H, q, J = 7.3Hz), 12.80(1H, brs).

(2) ethyl 2-[N-(4-fluorophenyl)-N-isopropylamino]carbonyl-3-methylbutyrate

**[1085]** In the same manner as in Example 13, the title compound (1.63 g) was obtained as an oil using the above-mentioned compound (1.39 g) and N-isopropyl-4-fluoroaniline (1.47 g). <sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ0.83(3H, d, J = 6.6Hz), 0.92(3H, d, J = 6.9Hz), 1.01(3H, d, J = 6.6Hz), 1.07(3H, d, J = 6.6Hz), 1.24(3H, t, J = 7.2Hz), 2.33-2.55(1H, m), 2, 79(1H, d, J = 9.6Hz), 4.00-4.24(2H, m), 4.90-5.14(1H, m), 6.95-7.24(4H, m).

(3) 2-[N-(4-fluorophenyl)-N-isopropylamino]carbonyl-3-methylbutyric acid

**[1086]** In the same manner as in Example 1 (3), the title compound (1.48 g) was obtained as an oil using the above-mentioned compound (1.63 g).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.76(3H, d, J = 6.6Hz), 0.83(3H, d, J = 6.7Hz), 0.92(3H, d, J = 6.8Hz), 1.00(3H, d, J = 6.8Hz), 2.00-2.32(1H, m), 2, 65(1H, d, J = 9.5Hz), 4.66-4.95(1H, m), 7.05-7.40(2H, m), 12.40(1H, brs).

(4) N-(4-fluorophenyl)-N-isopropyl-2-isopropyl-N'-((E)-styrylsulfonyl)malonamide

**[1087]** In the same manner as in Example 1 (2), the title compound (517 mg) was obtained as a white powder using the above-mentioned compound (1.48 g) and trans-β-styrenesulfonamide (890 mg).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.65-0.80(12H, m), 2.11-2.37(1H, m), 2.64-2.89(1H, m), 4.63-4.83(1H, m), 6.77-7.02(1H, m), 7.05-7.25(2H, m), 7.25-7.66(6H, m), 7.66-7.89(2H, m), 11.29(1H, brs).

MS: 447(M+H)<sup>+</sup>.

Example 491 Synthesis of N-(4-fluorophenyl)-2-isobutyl-N-isopropyl-N'-((E)-styrylsulfonyl)malonamide

(1) 4-methyl-2-(((E)-styrylsulfonyl)amino)carbonyl}valeric acid

**[1088]** In the same manner as in Example 1 (1), the object compound was obtained using diethyl isobutylmalonate (10.0 g). This and trans-β-styrenesulfonamide (2.91 g) were condensed in the same manner as in Example 152 (3). The condensed product was subjected to hydrolysis in the same manner as in Example 1 (3) to give the title compound (4.99 g) as an oil.

(2) N-(4-fluorophenyl)-2-isobutyl-N-isopropyl-N'-((E)-styrylsulfonyl)malonamide

**[1089]** In the same manner as in Example 1 (4), the title compound (269 mg) was obtained as a white powder using the above-mentioned compound (651 mg) and 4-fluoro-N-isopropylaniline (306 mg).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ0.62(3H, d, J = 7.2Hz), 0.75(3H, d, J = 7.2Hz), 0.94(3H, d, J = 7.2Hz), 1.03(3H, d, J = 7.2Hz), 1.43-1.49(1H, m), 1.63-1.72(2H, m), 3.03-3.06(1H, m), 4.90-4.97(1H, m), 7.01-7.05(3H, m), 7.06-7.14(2H, m), 7.39-7.51(3H, m), 7.51-7.53(2H, m), 7.71(1H, d, J = 15.5Hz), 10.19(1H, brs).

MS: 461(M+H)<sup>+</sup>.

Example 492 Synthesis of N-(4-fluorophenyl)-N'-(((E)-2-(4-fluorophenyl) ethenyl)sulfonyl)-2-isobutyl-N-isopropyl-malonamide

(1) ethyl 2-([N-(4-fluorophenyl)-N-isopropylamino]carbonyl)-4-methylvalerate

**[1090]** In the same manner as in Example 1 (4), the title compound (5.97 g) was obtained as an oil using intermediate monoethyl isobutylmalonate (5.00 g) obtained in Example 491 (1) and 4-fluoro-N-isopropylaniline (4.08 g).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ0.97-0.98(6H, m), 1.01-1.08(6H, m), 1.24-1.31(3H, m), 1.44-1.47(1H, m), 1.66-1.79(2H, m), 3.11(1H, t, J = 7.3Hz), 4.08-4.13(2H, m), 5.02(1H, t, J = 6.7Hz), 7.07-7.14(3H, m), 7.18-7.21(1H, m).

(2) 2-([N-(4-fluorophenyl)-N-isopropylamino]carbonyl)-4-methylvaleric acid

**[1091]** In the same manner as in Example 1 (3), the title compound (2.94 g) was obtained as an oil using the above-mentioned compound (5.00 g).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ0.50-0.55(3H, m), 0.71-0.77(3H, m), 1.04-1.52(3H, m), 1.11-1.13(3H, m), 1.47-1.60(2H, m),

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1.75-1.86(1H, m), 2.35-3.13(1H, m), 4.94-5.01(1H, m), 7.09-7.26(4H, m).

(3) N-(4-fluorophenyl)-N'-{[(E)-2-(4-fluorophenyl)ethenyl]sulfonyl}-2-isobutyl-N-isopropylmalonamide

- 5 **[1092]** In the same manner as in Example 1 (2), the title compound (261 mg) was obtained as a white powder using the above-mentioned compound (295 mg) and [(E)-2-(4-fluorophenyl)ethylene]sulfonamide (201 mg).  
<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ0.62(3H, d, J = 6.4Hz), 0.75(3H, d, J = 6.4Hz), 1.00(3H, d, J = 6.4Hz), 1.10(3H, d, J = 6.4Hz), 1.60-1.72(2H, m), 3.02-3.06(1H, m), 4.09-4.15(1H, m), 4.90-4.97(1H, m), 6.95(1H, d, J = 15.5Hz), 7.03-7.15(6H, m), 7.50-7.54(2H, m), 7.67(1H, d, J = 15.5Hz), 10.22(1H, brs).  
10 MS: 479(M+H)<sup>+</sup>.

Example 493 Synthesis of N-(4-fluorophenyl)-2-isobutyl-N-isopropyl-N'-phenethylsulfonylmalonamide

- 15 **[1093]** In the same manner as in Example 1 (2), the title compound (70 mg) was obtained as a white powder using the compound (295 mg) obtained in Example 492 (2) and phenethylsulfonamide (185 mg).  
<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ0.66(3H, d, J = 6.4Hz), 0.77(3H, d, J = 6.4Hz), 1.02(3H, d, J = 6.4Hz), 1.10(3H, d, J = 6.4Hz), 1.46-1.53(1H, m), 1.61-1.66(1H, m), 3.04-3.17(4H, m), 3.63-3.70(2H, m), 4.92-4.95(1H, m), 7.06-7.07(2H, m), 7.08-7.23(4H, m), 7.24-7.25(1H, m), 7.30-7.34(2H, m), 10.20(1H, brs).  
20 MS: 463(M+H)<sup>+</sup>.

Example 494 Synthesis of N-(4-fluorophenyl)-2-isobutyl-N-isopropyl-N'-phenylsulfonylmalonamide

- 25 **[1094]** In the same manner as in Example 1 (2), the title compound (78 mg) was obtained as a white powder using the compound (443 mg) obtained in Example 492 (2) and benzenesulfonamide (338 mg).  
<sup>1</sup>H-NMR (400Mz, CDCl<sub>3</sub>)δ0.56(3H, d, J = 6.6Hz), 0.66(3H, d, J = 6.6Hz), 0.98(3H, d, J = 6.6Hz), 1.07(3H, d, J = 6.6Hz), 1.22-1.27(1H, m), 1.49-1.59(2H, m), 2.91(1H, t, J = 7.4Hz), 4.87-4.94(1H, m), 6.77-6.99(1H, m), 7.01-7.11(3H, m), 7.51-7.55(2H, m), 7.61-7.63(1H, m), 8.04-8.06(2H, m), 10.21(1H, brs).  
30 MS: 435(M+H)<sup>+</sup>.

Example 495 Synthesis of N-(4-fluorophenyl)-2-isobutyl-N-isopropyl-N'-(2-naphthylsulfonyl)malonamide

- 35 **[1095]** In the same manner as in Example 1 (2), the title compound (278 mg) was obtained as a white powder using the compound (443 mg) obtained in Example 492 (2) and naphthalene-2-sulfonamide (311 mg).  
<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ0.54(3H, d, J = 6.7Hz), 0.63(3H, d, J = 6.7Hz), 0.94(3H, d, J = 6.7Hz), 1.06(3H, d, J = 6.7Hz), 1.20-1.28(1H, m), 1.52-1.58(2H, m), 2.90(1H, t, J = 7.8Hz), 4.86-4.93(1H, m), 6.67-6.71(1H, m), 6.88-6.93(1H, m), 6.97-7.01(H, m), 7.04-7.08(1H, m), 7.60-7.69(2H, m), 7.91-8.02(4H, m), 8.65(1H, s), 10.28(1H, brs).  
40 MS: 485(M+H)<sup>+</sup>.

Example 496 Synthesis of N-(4-fluorophenyl)-2-isobutyl-N-isopropyl-N'-(3-phenoxypropylsulfonyl)malonamide

45 (1) 3-phenoxypropanesulfonamide

- [1096]** To a solution of 3-phenoxypropyl bromide (6.74 g) in water (67 mL) was added sodium sulfite (5.30 g), and the mixture was heated under reflux for 24 hr. Toluene was added to the reaction mixture, and the organic layer was concentrated under reduced pressure. The residue was dissolved in benzene (100 mL), and DMF (0.67 g) was added. Thionyl chloride (4.40 g) was added dropwise with stirring, and the mixture was heated under reflux for 4 hr. The reaction mixture was concentrated under reduced pressure, THF (100 mL) was added to the residue, and 28% aqueous ammonia was slowly added dropwise under ice-cooling. After completion of the reaction, the mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography to give the title compound (3.75 g).  
50 <sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ2.09-2.17(2H, m), 3.11-3.15(2H, m), 4.00-4.10(2H, m), 6.91-6.93(2H, m), 7.26-7.31(3H, m), 7.43-7.46(2H, m).

(2) N-(4-fluorophenyl)-2-isobutyl-N-isopropyl-N'-(3-phenoxypropylsulfonyl)malonamide

- 55 **[1097]** In the same manner as in Example 1 (2), the title compound (208 mg) was obtained as a white powder using the compound (295 mg) obtained in Example 492 (2) and the above-mentioned compound (215 mg).  
<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ0.65(3H, d, J = 6.5Hz), 0.77(3H, d, J = 6.5Hz), 1.01(3H, d, J = 6.5Hz), 1.10(3H, d, J = 6.5Hz), 1.44-1.52(1H, m), 1.62-1.72(2H, m), 2.26-2.33(2H, m), 3.08(1H, t, J = 7.2Hz), 3.60-3.64(2H, m), 4.07-4.09(2H, m),

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4.90-4.95(1H, m), 6.94-6.98(2H, m), 7.01-7.02(1H, m), 7.04-7.08(2H, m), 7.12-7.17(2H, m), 7.28-7.30(2H, m), 10.08(1H, brs).

MS: 493(M+H)<sup>+</sup>.

### 5 Example 497 Synthesis of N-(4-fluorophenyl)-2-isobutyl-N-isopropyl-N'-(4-phenylbutylsulfonyl)malonamide

(1)4-phenylbutanesulfonamide

10 **[1098]** In the same manner as in Example 496 (1), the title compound (5.93 g) was obtained using 4-phenylbutyl bromide (5.00 g).

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ1.69-1.74(2H, m), 2.49-2.50(2H, m), 2.53-2.61(2H, m), 2.98-3.11(2H, m), 6.71-6.72(2H, m), 7.15-7.21(3H, m), 7.26-7.29(2H, m).

(2) N-(4-fluorophenyl)-2-isobutyl-N-isopropyl-N'-(4-phenylbutylsulfonyl)malonamide

15 **[1099]** In the same manner as in Example 1 (2), the title compound (288 mg) was obtained as a white powder using the compound (443 mg) obtained in Example 492 (2) and the above-mentioned compound (398 mg).

20 <sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ0.76(3H, d, J = 6.5Hz), 0.91(3H, d, J = 6.5Hz), 1.02(3H, d, J = 6.5Hz), 1.10(3H, d, J = 6.5Hz), 1.42-1.54(1H, m), 1.60-1.66(2H, m), 1.75-1.88(4H, m), 2.62-2.66(2H, m), 3.05(1H, t, J = 7.6Hz), 3.36-3.44(2H, m), 4.89-4.96(1H, m), 7.01-7.08(2H, m), 7.11-7.18(5H, m), 7.28-7.29(2H, m), 9.93(1H, brs).

MS: 491(M+H)<sup>+</sup>.

Example 498 Synthesis of N'-(4-biphenylsulfonyl)-N-(4-fluorophenyl)-2-isobutyl-N-isopropylmalonamide

25 **[1100]** In the same manner as in Example 1 (2), the title compound (568 mg) was obtained as a white powder using the compound (586 mg) obtained in Example 492 (2) and 4-biphenylsulfonamide (467 mg).

30 <sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ0.56(3H, d, J = 6.4Hz), 0.67(3H, d, J = 6.4Hz), 0.98(3H, d, J = 6.4Hz), 1.08(3H, d, J = 6.4Hz), 1.26-1.27(2H, m), 1.58-1.60(1H, m), 2.92-2.96(1H, m), 4.89-4.93(1H, m), 6.80-6.87(1H, m), 7.02-7.09(3H, m), 7.42-7.50(3H, m), 7.59-7.61(2H, m), 7.72-7.74(2H, m), 8.10-8.12(2H, m), 10.27(1H, brs).

MS: 511(M+H)<sup>+</sup>.

Example 499 Synthesis of N-ethyl-N-(3-hydroxymethylphenyl)-2-isobutyl-N'-(E)-styrylsulfonylmalonamide

35 **[1101]** In the same manner as in Example 13, the title compound (262 mg) was obtained as a white powder using the compound (325 mg) obtained in Example 491 (1) and 3-(ethylamino)benzyl alcohol (181 mg).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.55(3H, d, J = 6.3Hz), 0.65(3H, d, J = 6.6Hz), 0.99(3H, t, J = 7.2Hz), 1.12-1.70(3H, m), 3.10-3.56(2H, m), 3.59-3.80(1H, m), 4.40-4.60(2H, m), 5.15-5.38(1H, m), 6.98-7.14(1H, m), 7.19(1H, s), 7.27-7.65(7H, m), 7.65-7.86(2H, m), 11.77(1H, brs).

MS: 459(M+H)<sup>+</sup>.

40

Example 500 Synthesis of N-(3-hydroxymethylphenyl)-2-isobutyl-N-isopropyl-N'-(E)-styrylsulfonylmalonamide

**[1102]** In the same manner as in Example 13, the title compound (33 mg) was obtained as a white powder using the compound (325 mg) obtained in Example 491 (1) and 3-(isopropylamino)benzyl alcohol (198 mg).

45 <sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.58(3H, d, J = 6.3Hz), 0.67(3H, d, J = 6.3Hz), 0.74-1.03(3H, m), 0.99(3H, d, J = 6.6Hz), 1.12-1.49(2H, m), 1.49-1.75(1H, m), 2.89-3.18(1H, m), 4.38-4.61(2H, m), 4.61-4.83(1H, m), 5.12-5.37(1H, m), 6.73-7.92(11H, m), 11.68(1H, brs).

MS: 473(M+H)<sup>+</sup>.

### 50 Example 501 Synthesis of 2-isobutyl-N-isopropyl-N'-(E)-styrylsulfonyl-N-(3-trifluoromethylphenyl)malonamide

**[1103]** In the same manner as in Example 13, the title compound (111 mg) was obtained as a white powder using the compound (325 mg) obtained in Example 491 (1) and N-isopropyl-3-trifluoromethylaniline (244 mg).

55 <sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.24-0.78(6H, m), 0.78-1.77(9H, m), 2.84-3.15(1H, m), 4.64-4.90(1H, m), 7.16-7.95(11H, m), 11.75(1H, brs).

MS: 511(M+H)<sup>+</sup>.

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Example 502 Synthesis of 2-isobutyl-N-isopropyl-N'-(3-pyridyl)-N'-((E)-styrylsulfonyl)malonamide hydrochloride

**[1104]** In the same manner as in Example 13, the object compound was obtained using the compound (325 mg) obtained in Example 491 (1) and 3-(isopropylamino)pyridine (136 mg). 1 mol/L Hydrochloric acid was added to this, and the mixture was concentrated to give the title compound (45 mg) as a white powder.

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.37-1.14(12H, m), 1.14-1.75(3H, m), 2.90-3.15(1H, m), 4.61-4.91(1H, m), 7.10-8.02(9H, m), 8.30-8.88(2H, m), 11.76(1H, brs).

MS: 444(M+H)<sup>+</sup>.

Example 503 Synthesis of 2-isobutyl-N-(2-hydroxyethyl)-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

**[1105]** In the same manner as in Example 13, the title compound (221 mg) was obtained as a white powder using the compound (325 mg) obtained in Example 491 (1) and N-phenylethanolamine (165 mg).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.53(3H, d, J = 6.3Hz), 0.64(3H, d, J = 6.6Hz), 1.17-1.67(3H, m), 3.07-3.52(3H, m), 3.52-3.71(2H, m), 4.49-4.73(1H, m), 1.14-1.60(10H, m), 7.65-7.85(2H, m), 11.77(1H, brs).

MS: 445(M+H)<sup>+</sup>.

Example 504 Synthesis of N-benzyl-2-isobutyl-N-isopropyl-N'-((E)-styrylsulfonyl)malonamide

**[1106]** In the same manner as in Example 13, the title compound (50 mg) was obtained as a white powder using the compound (325 mg) obtained in Example 491 (1) and N-isopropylbenzylamine (179 mg).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.50-1.10(12H, m), 1.18-1.80(3H, m), 3.10-4.68(4H, m), 7.00-7.89(12H, m), 12.19(1H, brs).

MS: 457(M+H)<sup>+</sup>.

Example 505 Synthesis of N-(4-fluorobenzyl)-2-isobutyl-N-isopropyl-N'-((E)-styrylsulfonyl)malonamide

**[1107]** In the same manner as in Example 13, the title compound (91 mg) was obtained as a white powder using the compound (325 mg) obtained in Example 491 (1) and 4-fluoro-N-isopropylbenzylamine (201 mg).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.50-1.15(12H, m), 1.15-1.80(3H, m), 3.10-4.64(4H, m), 6.85-7.80(11H, m), 12.19(1H, brs).

MS: 475(M+H)<sup>+</sup>.

Example 506 Synthesis of N-(3-fluorobenzyl)-2-isobutyl-N-isopropyl-N'-((E)-styrylsulfonyl)malonamide

**[1108]** In the same manner as in Example 13, the title compound (89 mg) was obtained as a white powder using the compound (325 mg) obtained in Example 491 (1) and 3-fluoro-N-isopropylbenzylamine (201 mg).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.50-1.18(12H, m), 1.18-1.81(3H, m), 3.13-4.64(4H, m), 6.80-7.80(11H, m), 12.22(1H, brs).

MS: 475(M+H)<sup>+</sup>.

Example 507 Synthesis of 2-isobutyl-N-isopropyl-N-phenethyl-N'-((E)-styrylsulfonyl)malonamide

**[1109]** In the same manner as in Example 13, the title compound (28 mg) was obtained as a white powder using the compound (325 mg) obtained in Example 491 (1) and N-isopropylphenethylamine (196 mg).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.69-0.89(6H, m), 0.89-1.18(6H, m), 1.35-1.75(3H, m), 2.45-4.22(6H, m), 7.10-7.80(12H, m), 12.11(1H, brs).

MS: 471(M+H)<sup>+</sup>.

Example 508 Synthesis of N-[2-(4-fluorophenyl)ethyl]-2-isobutyl-N-isopropyl-N'-((E)-styrylsulfonyl)malonamide

**[1110]** In the same manner as in Example 13, the title compound (40 mg) was obtained as a white powder using the compound (325 mg) obtained in Example 491 (1) and 2-(4-fluorophenyl)-N-isopropylethylamine (218 mg).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.68-0.91(6H, m), 0.91-1.20(6H, m), 1.33-1.77(3H, m), 2.57-4.38(6H, m), 6.98-7.82(11H, m), 12.08(1H, brs).

MS: 489(M+H)<sup>+</sup>.

Example 509 Synthesis of N-(4-fluorophenyl)-2-isobutyl-N-isopropyl-N'-{[(E)-2-(2-thiazolyl)ethenyl]sulfonyl}malonamide

**[1111]** In the same manner as in Example 1 (2), the title compound (57 mg) was obtained as a white powder using the compound (295 mg) obtained in Example 492 (2) and [(E)-2-(2-thiazolyl)ethylene]sulfonamide (190 mg).

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<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.61(3H, d, J = 6.3Hz), 0.69(3H, d, J = 6.3Hz), 0.88(3H, d, J = 6.9Hz), 0.96(3H, d, J = 6.6Hz), 1.25-1.48(2H, m), 1, 54-1.75(1H, m), 2.91-3.17(1H, m), 4.60-4.88(1H, m), 6.92-7.51(5H, m), 7.60-7.89(1H, m), 7.97-8.18(2H, m), 11.92(1H, brs).  
MS: 468(M+H)<sup>+</sup>.

5  
Example 510 Synthesis of N-(4-fluorophenyl)-2-isobutyl-N-isopropyl-N'-[[2-(2-thiazolyl)ethyl]sulfonyl]malonamide (1)  
2-(2-thiazolyl)ethanesulfonamide

10  
[1112] In the same manner as in Example 7, the title compound (270 mg) was obtained as a white powder using [(E)-2-(2-thiazolyl)ethylene]sulfonamide (500 mg) at room temperature. <sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ3.29-3.54(4H, m), 6.98(2H, brs), 7.64(1H, d, J = 3.2Hz), 7.73(1H, d, J = 3.2Hz).

(2) N-(4-fluorophenyl)-2-isobutyl-N-isopropyl-N'-[[2-(2-thiazolyl)ethyl]sulfonyl]malonamide

15  
[1113] In the same manner as in Example 1 (2), the title compound (177 mg) was obtained as a white powder using the above-mentioned compound (270 mg) and the compound (415 mg) obtained in Example 492 (2).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.54(3H, d, J = 6.6Hz), 0.69(3H, d, J = 6.6Hz), 0.93(3H, d, J = 6.6Hz), 0.99(3H, d, J = 6.6Hz), 1.16-1.39(1H, m), 1.39-1.67(2H, m), 3.10(1H, t, J = 6.6Hz), 3.25-3.53(2H, m), 3.82(2H, t, J = 7.5Hz), 4.62-4.87(1H, m), 7.12-7.40(4H, m), 7.65(1H, d, J = 3.3Hz), 7.74(1H, d, J = 3.6Hz), 11.70(1H, brs).

20  
MS: 470(M+H)<sup>+</sup>.

Example 511 Synthesis of N-(4-fluorophenyl)-2-isobutyl-N-isopropyl-N'-[(E)-2-(3-pyridyl)ethenyl]sulfonyl]malonamide

25  
[1114] In the same manner as in Example 1 (2), the title compound (266 mg) was obtained as a white powder using the compound (295 mg) obtained in Example 492 (2) and [(E)-2-(3-pyridyl)ethylene]sulfonamide (184 mg).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.68(3H, d, J = 6.3Hz), 0.83(3H, d, J = 6.3Hz), 0.88(3H, d, J = 6.3Hz), 0.96(3H, d, J = 6.6Hz), 1.18-1.49(2H, m), 1.51-1.78(1H, m), 2.92-3.14(1H, m), 4.59-4.88(1H, m), 7.04-7.42(4H, m), 7.43-7.70(3H, m), 8.28(1H, d, J = 8.1Hz), 8.57-8.70(1H, m), 8.95(1H, s), 11.80(1H, brs).

30  
MS: 462(M+H)<sup>+</sup>.

Example 512 Synthesis of N-(4-fluorophenyl)-2-isopentyl-N-isopropyl-N'-((E)-2-styrylsulfonyl)malonamide

(1) 5-isopentyl-2, 2-dimethyl-1,3-dioxane-4,6-dione

35  
[1115] In the same manner as in Example 214 (1), the title compound (10.0 g) was obtained as a pale-yellow powder using isovaleric acid (12.3 g).

<sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ0.92(6H, d, J = 6.6Hz), 1.26-1.37(2H, m), 1.48-1.70(1H, m), 1.76(3H, s), 1.78(3H, s), 2.02-2.19(2H, m), 3.49(1H, t, J = 4.8Hz).

40  
(2) 2-[N-(4-fluorophenyl)-N-isopropylamino]carbonyl-5-methylhexanoic acid

[1116] In the same manner as in Example 119 (2), the title compound (660 mg) was obtained as an oil using the above-mentioned compound (1.07 g) and 4-fluoro-N-isopropylaniline (2.14 g).

45  
<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.79(6H, d, J = 6.6Hz), 0.80-1.10(8H, m), 1.20-1.43(1H, m), 1.49-1.73(2H, m), 2.84(1H, t, J = 7.4Hz), 4.65-4.90(1H, m), 7.10-7.40(4H, m), 12.40(1H, brs).

(3) N-(4-fluorophenyl)-2-isopentyl-N-isopropyl-N'-((E)-2-styrylsulfonyl)malonamide

50  
[1117] In the same manner as in Example 1 (2), the title compound (382 mg) was obtained as a white powder using the above-mentioned compound (660 mg) and trans-β-styrenesulfonamide (361 mg).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.62-0.83(6H, m), 0.83-1.02(8H, m), 1.25-1.40(1H, m), 1.40-1.58(1H, m), 1.58-1.78(1H, m), 2.86-3.03(1H, m), 4.62-4.82(1H, m), 6.90-7.17(2H, m), 7.17-7.40(3H, m), 7.40-7.61(4H, m), 7.69-7.90(2H, m), 11.54(1H, brs).

55  
MS: 475(M+H)<sup>+</sup>.

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Example 513 Synthesis of N-(4-fluorophenyl)-N-isopropyl-2-neopentyl-N'-((E)-2-styrylsulfonyl)malonamide

(1) 2, 2-dimethyl-5-neopentyl-1, 3-dioxane-4, 6-dione

5 **[1118]** In the same manner as in Example 119 (1), the title compound (8.52 g) was obtained as a white solid using trimethylacetaldehyde (90 mL).

$^1\text{H-NMR}$ (300Mz,  $\text{CDCl}_3$ ) $\delta$ 0.97(9H, s), 1.76(3H, s), 1.84(3H, s), 2.12(2H, d, J = 5.2Hz), 3.30(1H, t, J = 5.2Hz).

(2) 4, 4-dimethyl-2-[[N-(4-fluorophenyl)-N-isopropylamino]carbonyl]valeric acid

10 **[1119]** In the same manner as in Example 119 (2), the title compound (472 mg) was obtained as a white solid using the above-mentioned compound (3.01 g) and 4-fluoro-N-isopropylaniline (8.47 g).

$^1\text{H-NMR}$ (400Mz,  $\text{DMSO-d}_6$ ) $\delta$ 0.66(9H, s), 0.93(3H, d, J = 6.8Hz), 0.99(3H, d, J = 6.8Hz), 1.06(2H, t, J = 6.7Hz), 2.90(1H, t, J = 6.0Hz), 4.78(1H, m), 7.64(2H, brs), 8.31(2H, brs).

15 (3) N-(4-fluorophenyl)-N-isopropyl-2-neopentyl-N'-((E)-2-styrylsulfonyl)malonamide

**[1120]** In the same manner as in Example 1 (2), the title compound (212 mg) was obtained as a white solid using the above-mentioned compound (472 mg) and trans- $\beta$ -styrenesulfonamide (291 mg).

20  $^1\text{H-NMR}$ (400Mz,  $\text{DMSO-d}_6$ ) $\delta$ 0.59(9H, s), 0.83(3H, d, J = 6.8Hz), 0.97(3H, d, J = 6.8Hz), 1.53(1H, dd, J = 13.7, 5.7Hz), 1.77(1H, dd, J = 13.7, 6.4Hz), 3.06(1H, t, J = 5.9Hz), 4.65-4.76(1H, m), 7.10-7.40(5H, m), 7.44-7.51(3H, m), 7.55-7.62(1H, m), 7.76-7.82(2H, m), 11.73(1H, s).

MS: 475(M+H) $^+$ .

25 Example 514 Synthesis of 2-cyclopropylmethyl-N-ethyl-N-(4-fluorophenyl)-N'-((E)-2-styrylsulfonyl)malonamide (1) 2-cyclopropylmethyl-3-[N-ethyl-N-(4-fluorophenyl)amino]-3-oxopropionic acid

**[1121]** In the same manner as in Example 119 (2), the title compound (750 mg) was obtained as an oil using the compound (740 mg) obtained in Example 214 (1) and N-ethyl-4-fluoroaniline (2.08 g).

30  $^1\text{H-NMR}$ (300Mz,  $\text{DMSO-d}_6$ ) $\delta$ (-0.20)-(-0.02)(2H, m), 0.20-0.38(2H, m), 0.40-0.61(1H, m), 1.18(3H, t, J = 7.5Hz), 1.54(2H, d, J = 7.2Hz), 3.10-3.20(1H, m), 3.65(2H, q, J = 7.2Hz), 7.25-7.45(4H, m), 12.50(1H, brs).

(2) 2-cyclopropylmethyl-N-ethyl-N-(4-fluorophenyl)-N'-((E)-2-styrylsulfonyl)malonamide

35 **[1122]** In the same manner as in Example 1 (2), the title compound (357 mg) was obtained as a white powder using the above-mentioned compound (750 mg) and trans- $\beta$ -styrenesulfonamide (486 mg).

$^1\text{H-NMR}$ (300Mz,  $\text{DMSO-d}_6$ ) $\delta$ (-0.35)-(-0.20)(1H, m), (-0.20)-(-0.02)(1H, m), 0.15-0.34(2H, m), 0.45-0.64(1H, m), 0.97(3H, t, J = 7.2Hz), 1.20-1.43(1H, m), 1.56-1.77(1H, m), 3.18-3.75(3H, m), 7.06-7.64(9H, m), 7.66-7.95(2H, m), 11.64(1H, brs).

MS: 445(M+H) $^+$ .

40 Example 515 Synthesis of 2-cyclopropylmethyl-N-(4-fluorophenyl)-N-isopropyl-N'-((E)-2-styrylsulfonyl)malonamide (1) 2-cyclopropylmethyl-3-[N-(4-fluorophenyl)-N-isopropylamino]-3-oxopropionic acid

**[1123]** In the same manner as in Example 119 (2), the title compound (570 mg) was obtained as an oil using the compound (793 mg) obtained in Example 214 (1) and 4-fluoro-N-isopropylaniline (613 mg).

45  $^1\text{H-NMR}$ (300Mz,  $\text{DMSO-d}_6$ ) $\delta$ (-0.26)-(-0.10)(2H, m), 0.19-0.38(2H, m), 0.40-0.64(1H, m), 0.88-1.06(6H, m), 1.54(2H, t, J = 7.2Hz), 3.01(1H, t, J = 6.9Hz), 4.70-4.90(1H, m), 7.15-7.40(4H, m), 12.40(1H, brs).

(2) 2-cyclopropylmethyl-N-(4-fluorophenyl)-N-isopropyl-N'-((E)-2-styrylsulfonyl)malonamide

50 **[1124]** In the same manner as in Example 1 (2), the title compound (450 mg) was obtained as a white powder using the above-mentioned compound (570 mg) and trans- $\beta$ -styrenesulfonamide (329 mg).

$^1\text{H-NMR}$ (300Mz,  $\text{DMSO-d}_6$ ) $\delta$ (-0.30)-(-0.02)(2H, m), 0.18-0.36(2H, m), 0.47-0.70(1H, m), 0.80-1.06(6H, m), 1.17-1.40(1H, m), 1.65-1.86(1H, m), 3.05-3.17(1H, m), 4.62-4.86(1H, m), 6.95-7.40(5H, m), 7.40-7.63(4H, m), 7.69-7.89(2H, m), 11.55(1H, brs).

55 MS: 459(M+H) $^+$ .

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Example 516 Synthesis of (2S or 2R)-2-cyclopropylmethyl-N-(4-fluorophenyl)-N-isopropyl-N'-((E)-2-styrylsulfonyl)malonamide

**[1125]** To a suspension of the compound (19.2 g) obtained in Example 515 in methanol (300 mL) was added (S)-phenylethylamine (5.33 mL), and the mixture was stirred at room temperature to give a solution. The reaction mixture was concentrated under reduced pressure, diisopropylether (300 mL) was added to the residue, and the mixture was stirred at 60°C for 20 min. Insoluble material was collected by filtration, and the obtained solid was subjected to the same operation with diisopropylether (100 mLx3) to give (S)-phenylethylamine salt (8.12 g) of the title compound as a white solid (optical purity >98% d.e.). To (S)-phenylethylamine salt (19.9 g) of the title compound obtained in the same manner as above were added ethyl acetate (500 mL) and 1 mol/L hydrochloric acid (500 mL), and the mixture was extracted. The organic layer was washed with saturated brine. The organic layer was concentrated under reduced pressure to give the title compound (16.2 g) as a white powder (optical purity >98% e.e.).

<sup>1</sup>H-NMR and MS were same as in Example 5 15. specific optical rotation:[α]<sub>D</sub> = -64°(c = 0.54, chloroform).

Example 517 Synthesis of N'-(3, 5-dichlorophenylsulfonyl)-2-cyclopropylmethyl-N-(4-fluorophenyl)-N-isopropylmalonamide (1) 2-cyclopropylmethyl-N-(4-fluorophenyl)-N-isopropylmalonamide

**[1126]** In the same manner as in Example 114 (5), the title compound (864 mg) was obtained as a white powder using the compound (1.00 g) obtained in Example 515 (1).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ(-0.01)-0.01(1H, m), 0.08-0.12(1H, m), 0.39-0.46(2H, m), 0.58-0.63(1H, m), 1.02-1.04(3H, m), 1.10-1.12(3H, m), 1.65-1.69(1H, m), 1.79-1.87(1H, m), 3.03-3.07(1H, m), 4.97-5.04(1H, m), 5.24(1H, brs), 7.05-7.17(5H, m).

(2) N'-(3, 5-dichlorophenylsulfonyl)-2-cyclopropylmethyl-N-(4-fluorophenyl)-N-isopropylmalonamide

**[1127]** In the same manner as in Example 114 (6), the title compound (170 mg) was obtained as a white powder using the above-mentioned compound (585 mg) and 3, 5-dichlorobenzenesulfonyl chloride (491 mg).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ(-0.12)-(-0.10)(2H, m), 0.33-0.36(2H, m), 0.46-0.49(1H, m), 1.01(3H, d, J = 6.4Hz), 1.09(3H, d, J = 6.4Hz), 1.59-1.64(2H, m), 3.03(1H, t, J = 6.8Hz), 4.91-4.98(1H, m), 6.94-6.96(1H, m), 7.03-7.06(1H, m), 7.10-7.16(2H, m), 7.59(1H, s), 7.94(2H, s), 10.68(1H, brs).

MS: 501(M+H)<sup>+</sup>.

Example 518 Synthesis of N'-(3, 4-dichlorophenylsulfonyl)-2-cyclopropylmethyl-N-(4-fluorophenyl)-N-isopropylmalonamide

**[1128]** In the same manner as in Example 114 (6), the title compound (191 mg) was obtained as a white powder using the compound (200 mg) obtained in Example 517 (1) and 3, 4-dichlorobenzenesulfonyl chloride (167 mg).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ(-0.29)-(-0.08)(2H, m), 0.29-0.38(2H, m), 0.44-0.50(1H, m), 1.00(3H, d, J = 6.4Hz), 1.10(3H, d, J = 6.4Hz), 1.53-1.67(2H, m), 3.02(1H, t, J = 7.2Hz), 4.91-4.98(1H, m), 6.94-6.96(1H, m), 7.02-7.06(1H, m), 7.09-7.15(2H, m), 7.60(1H, d, J = 8.8Hz), 7.90(1H, d, J = 8.8Hz), 8.16(1H, s), 10.62(1H, brs).

MS: 501(M+H)<sup>+</sup>.

Example 519 Synthesis of N'-(4-chlorophenylsulfonyl)-2-cyclopropylmethyl-N-(4-fluorophenyl)-N-isopropylmalonamide

**[1129]** In the same manner as in Example 1 (2), the title compound (105 mg) was obtained as a white powder using the compound (587 mg) obtained in Example 515 (1) and 4-chlorobenzenesulfonamide (383 mg).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ(-0.13)-(-0.12) (2H, m), 0.30-0.34 (2H, m), 0.45-0.46(1H, m), 1.00(3H, d, J = 6.4Hz), 1.09(3H, d, J = 6.4Hz), 1.53-1.61(2H, m), 2.99(1H, t, J = 7.2Hz), 4.92-4.95(1H, m), 6.91-6.92(1H, m), 7.03-7.05(1H, m), 7.08-7.13(2H, m), 7.50 (2H, d, J = 8.4Hz), 7.99-8.02 (2H, m), 10.48(1H, brs).

MS: 467(M+H)<sup>+</sup>.

Example 520 Synthesis of N'-(4-tert-butylphenylsulfonyl)-2-cyclopropylmethyl-N-(4-fluorophenyl)-N-isopropylmalonamide

**[1130]** In the same manner as in Example 114 (6), the title compound (552 mg) was obtained as a white powder using the compound (584 mg) obtained in Example 517 (1) and 4-tert-butylbenzenesulfonyl chloride (465 mg).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ(-0.18)-(-0.14)(2H, m), 0.24-0.30(2H, m), 0.40-0.42(1H, m), 0.99(3H, d, J = 5.2Hz), 1.07(3H, d, J = 5.2Hz), 1.33(9H, s), 1.53-1.63(2H, m), 2.95-2.97(1H, m), 4.91-4.96(1H, m), 6.80-6.81(1H, m), 7.02-7.06(3H, m),

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7.52-7.54(2H, m), 7.96-7.98(2H, m), 10.22(1H, brs).

MS: 489(M+H)<sup>+</sup>.

5 Example 521 Synthesis of 2-cyclopropylmethyl-N-(4-fluorophenyl)-N-isopropyl-N'-(4-trifluoromethoxyphenylsulfonyl)malonamide

**[1131]** In the same manner as in Example 114 (6), the title compound (211 mg) was obtained as a white powder using the compound (585 mg) obtained in Example 517 (1) and 4-trifluoromethoxybenzenesulfonyl chloride (521 mg).

10 <sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ(-0.16)-(-0.14) (2H, m), 0.28-0.32(2H, m), 0.42-0.45(1H, m), 0.99(3H, d, J = 6.8Hz), 1.09(3H, d, J = 6.8Hz), 1.57-1.61(2H, m), 2.99(1H, t, J = 7.2Hz), 4.90-4.97(1H, m), 6.87-6.91(1H, m), 7.01-7.05(1H, m), 7.08-7.12(2H, m), 7.34(2H, d, J = 8.8Hz), 8.13(2H, d, J = 8.8Hz), 10.49(1H, brs).

MS: 517(M+H)<sup>+</sup>.

15 Example 522 Synthesis of 2-cyclopropylmethyl-N-(4-fluorophenyl)-N-isopropyl-N'-(4-tolylsulfonyl)malonamide

**[1132]** In the same manner as in Example 1 (2), the title compound (267 mg) was obtained as a white powder using the compound (587 mg) obtained in Example 515 (1) and 4-toluenesulfonamide (342 mg).

20 <sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ(-0.22)-(-0.09)(2H, m), 0.28-0.33(2H, m), 0.43-0.44(1H, m), 1.00(3H, d, J = 6.8Hz), 1.08(3H, d, J = 6.8Hz), 1.54-1.57(2H, m), 2.43(3H, s), 2.98(1H, t, J = 7.2Hz), 4.94(1H, t, J = 6.8Hz), 6.86-6.89(1H, m), 7.02-7.11(3H, m), 7.30-7.32(2H, m), 7.93-7.95(2H, m), 10.27(1H, brs).

MS: 447(M+H)<sup>+</sup>.

25 Example 523 Synthesis of 2-cyclopropylmethyl-N-(4-fluorophenyl)-N'-(4-isobutylphenylsulfonyl)-N-isopropylmalonamide

**[1133]** In the same manner as in Example 1 (2), the title compound (202 mg) was obtained as a white powder using the compound (587 mg) obtained in Example 515 (1) and 4-isobutylbenzenesulfonamide (427 mg).

30 <sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ(-0.19)-(-0.14)(2H, m), 0.24-0.30(2H, m), 0.40-0.42(1H, m), 0.89(6H, d, J = 6.4Hz), 0.99(3H, d, J = 6.4Hz), 1.08(3H, d, J = 6.4Hz), 1.55-1.61(2H, m), 1.87-1.90(1H, m), 2.54(2H, d, J = 7.2Hz), 2.97(1H, t, J = 7.2Hz), 4.92-4.96(1H, m), 6.84-6.87(1H, m), 7.02-7.09(3H, m), 7.27-7.29(2H, m), 7.95(2H, d, J = 6.4Hz), 10.26(1H, brs).

MS: 489(M+H)<sup>+</sup>.

35 Example 524 Synthesis of N'-(4-benzylsulfonyl)-2-cyclopropylmethyl-N-(4-fluorophenyl)-N-isopropylmalonamide

**[1134]** In the same manner as in Example 1 (2), the title compound (193 mg) was obtained as a white powder using the compound (587 mg) obtained in Example 515 (1) and benzylsulfonamide (342 mg).

40 <sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ0.41-0.43(2H, m), 0.49-0.55(1H, m), 0.98(3H, d, J = 6.8Hz), 1.07(3H, d, J = 6.8Hz), 1.49-1.50(2H, m), 1.53-1.67(2H, m), 3.05-3.13(1H, m), 4.62(2H, s), 4.82-4.91(1H, m), 7.00-7.09(2H, m), 7.10-7.23(2H, m), 7.37(5H, brs), 9.84(1H, brs).

MS: 447(M+H)<sup>+</sup>.

45 Example 525 Synthesis of 2-cyclopropylmethyl-N-(4-fluorophenyl)-N-isopropyl-N'-(4-methoxyphenylsulfonyl)malonamide

**[1135]** In the same manner as in Example 1 (2), the title compound (70 mg) was obtained as a white powder using the compound (587 mg) obtained in Example 515 (1) and 4-methoxybenzenesulfonamide (374 mg).

50 <sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ(-0.20)-(-0.09)(2H, m), 0.33-0.37(2H, m), 0.39-0.48(1H, m), 0.99(3H, d, J = 6.8Hz), 1.64(3H, d, J = 6.8Hz), 1.59-1.79(2H, m), 2.98(1H, t, J = 7.2Hz), 3.87(3H, s), 4.89-5.01(1H, m), 6.96-6.97(1H, m), 6.98-7.01(2H, m), 7.03-7.05(1H, m), 7.07-7.52(2H, m), 7.97-8.00(2H, m), 10.23(1H, brs).

MS: 463(M+H)<sup>+</sup>.

55 Example 526 Synthesis of 2-cyclopropylmethyl-N-(4-fluorophenyl)-N-isopropyl-N'-propylsulfonylmalonamide

**[1136]** In the same manner as in Example 1 (2), the title compound (37 mg) was obtained as a white powder using the compound (587 mg) obtained in Example 515 (1) and propylsulfonamide (648 mg).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ0.01-0.08(2H, m), 0.42-0.49(2H, m), 0.58-0.62(1H, m), 1.03-1.12(9H, m), 1.67-1.81(2H, m), 1.83-1.91(2H, m), 3.12(1H, t, J = 6.8Hz), 3.34-3.38(2H, m), 4.94-5.01(1H, m), 7.05-7.20(4H, m), 10.06(1H, brs).

MS: 399(M+H)<sup>+</sup>.

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Example 527 Synthesis of 2-cyclopropylmethyl-N-(4-fluorophenyl)-N-isopropyl-N'-(4-phenoxyphenylsulfonyl)malonamide

5 **[1137]** In the same manner as in Example 114 (6), the title compound (85 mg) was obtained as a white powder using the compound (200 mg) obtained in Example 517 (1) and 4-phenoxybenzenesulfonyl chloride (183 mg).  
<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ(-0.13)-(-0.12)(2H, m), 0.25-0.30(2H, m), 0.41-0.49(1H, m), 1.00(3H, d, J = 7.2Hz), 1.09(3H, d, J = 7.2Hz), 1.59-1.61(2H, m), 2.99-3.01(1H, m), 4.94-4.96(1H, m), 6.88-6.95(1H, m), 7.02-7.13(7H, m), 7.22-7.25(1H, m), 7.38-7.43(2H, m), 8.01(2H, d, J = 7.2Hz), 10.32(1H, brs). MS: 525(M+H)<sup>+</sup>.

10 Example 528 Synthesis of N'-(4-biphenylsulfonyl)-2-cyclopropylmethyl-N-(4-fluorophenyl)-N-isopropylmalonamide

15 **[1138]** In the same manner as in Example 114 (6), the title compound (131 mg) was obtained as a white powder using the compound (200 mg) obtained in Example 517 (1) and 4-biphenylsulfonyl chloride (172 mg).  
<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ(-0.15)-(-0.12)(2H, m), 0.27-0.33(2H, m), 0.45-0.46(1H, m), 1.00(3H, d, J = 6.8Hz), 1.09(3H, d, J = 6.8Hz), 1.59-1.64(2H, m), 3.00(1H, t, J = 7.2Hz), 4.93-4.97(1H, m), 6.85-6.92(1H, m), 7.03-7.09(3H, m), 7.42-7.50(3H, m), 7.59-7.62(2H, m), 7.62-7.75(2H, m), 8.11-8.13(2H, m), 10.38(1H, brs).  
MS: 509(M+H)<sup>+</sup>.

20 Example 529 Synthesis of 2-cyclopropylmethyl-N-(4-fluorophenyl)-N-isopropyl-N'-phenethylsulfonylmalonamide

25 **[1139]** In the same manner as in Example 1 (2), the title compound (237 mg) was obtained as a white powder using the compound (587 mg) obtained in Example 515 (1) and phenethylsulfonamide (370 mg).  
<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ0-02-0.07(2H, m), 0.42-0.45(2H, m), 0.54-0.59(1H, m), 1.02(3H, d, J = 6.8Hz), 1.11(3H, d, J = 6.8Hz), 1.60-1.74(2H, m), 3.09-3.15(3H, m), 3.61-3.71(2H, m), 4.93-5.00(1H, m), 7.06-7.24(7H, m), 7.29-7.33(2H, m), 10.16(1H, brs).  
MS: 461(M+H)<sup>+</sup>.

30 Example 530 Synthesis of 2-cyclopropylmethyl-N-(4-fluorophenyl)-N-isopropyl-N'-(2-naphthylsulfonyl)malonamide

35 **[1140]** In the same manner as in Example 1 (2), the title compound (195 mg) was obtained as a white powder using the compound (587 mg) obtained in Example 515 (1) and naphthalene-2-sulfonamide (415 mg).  
<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ(-0.20)-(-0.10)(2H, m), 0.21-0.33(2H, m), 0.40-0.47(1H, m), 0.97(3H, d, J = 6.9Hz), 1.07(3H, d, J = 6.9Hz), 1.56-1.65(2H, m), 2.97(1H, t, J = 7.3Hz), 4.91-4.97(1H, m), 6.75-6.82(1H, m), 6.97-7.09(3H, m), 7.61-7.69(2H, m), 7.91-8.02(4H, m), 8.66(1H, s), 10.43(1H, brs).  
MS: 483(M+H)<sup>+</sup>.

40 Example 531 Synthesis of 2-cyclopropylmethyl-N-(4-fluorophenyl)-N-isopropyl-N'-(3-phenoxypropylsulfonyl)malonamide

45 **[1141]** In the same manner as in Example 1 (2), the title compound (188 mg) was obtained as a white powder using the compound (587 mg) obtained in Example 515 (1) and 3-phenoxypropanesulfonamide (430 mg).  
<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ0.01-0.05(2H, m), 0.42-0.45(2H, m), 0.57-0.60(1H, m), 1.02(3H, d, J = 6.9Hz), 1.11(3H, d, J = 6.9Hz), 1.67-1.77(2H, m), 2.27-2.33(2H, m), 3.12-3.15(1H, m), 3.59-3.66(2H, m), 4.06-4.11(2H, m), 4.93-5.00(1H, m), 6.86-6.88(2H, m), 6.94-7.15(5H, m), 7.28-7.30(2H, m), 10.21(1H, brs). MS: 491 (M+H)<sup>+</sup>.

50 Example 532 Synthesis of 2-cyclopropylmethyl-N-(4-fluorophenyl)-N-(3-pentyl)-N'-(E)-styrylsulfonylmalonamide

(1) 2-cyclopropylmethyl-3-[N-(4-fluorophenyl)-N-(3-pentyl)amino]-3-oxopropionic acid

55 **[1142]** In the same manner as in Example 119 (2), the title compound (970 mg) was obtained as an oil using the compound (991 mg) obtained in Example 214 (1) and 4-fluoro-N-(3-pentyl)aniline (1.81 g).  
<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ(-0.24)-(-0.05)(2H, m), 0.20-0.42(2H, m), 0.42-0.60(1H, m), 0.78-1.00(6H, m), 1.07-1.70(6H, m), 2.98-3.11(1H, m), 4.34-4.57(1H, m), 7.08-7.40(4H, m), 12.45(1H, brs).

(2) 2-cyclopropylmethyl-N-(4-fluorophenyl)-N-(3-pentyl)-N'-(E)-styrylsulfonylmalonamide

**[1143]** In the same manner as in Example 1 (2), the title compound (92 mg) was obtained as a white powder using the above-mentioned compound (970 mg) and trans-β-styrenesulfonamide (426 mg).

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<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ(-0.28)-0.04(2H, m), 0.13-0.39(2H, m), 0.47-0.68(1H, m), 0.68-0.98(6H, m), 0.98-1.40(5H, m), 1.70-1.96(1H, m), 3.00-3.25(1H, m), 4.29-4.51(1H, m), 6.80-7.29(3H, m), 7.29-7.70(6H, m), 7.70-7.92(2H, m), 11.58(1H, brs).  
MS: 487(M+H)<sup>+</sup>.

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Example 533 Synthesis of 2-cyclopropylmethyl-N, N-diisopropyl-N'-((E)-styrylsulfonyl)malonamide

(1) 2-cyclopropylmethyl-3-(N, N-diisopropylamino)-3-oxopropionic acid

10 **[1144]** In the same manner as in Example 119 (2), the title compound (1.21 g) was obtained as an oil using the compound (991 mg) obtained in Example 214 (1) and diisopropylamine (1.40 mL).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ(-0.06)-0.09(2H, m), 0.20-0.40(2H, m), 0.49-0.72(1H, m), 0.93-1.35(12H, m), 1.38-1.58(1H, m), 1.58-1.77(1H, m), 3.32-3.50(1H, m), 3.55-3.77(1H, m), 4.08-4.30(1H, m), 12.42(1H, brs).

15 (2) 2-cyclopropylmethyl-N, N-diisopropyl-N'-((E)-styrylsulfonyl)malonamide

**[1145]** In the same manner as in Example 1 (2), the title compound (320 mg) was obtained as a white powder using the above-mentioned compound (1.21 g) and trans-β-styrenesulfonamide (707 mg).

20 <sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ(-0.18)-0.10(2H, m), 0.19-0.38(2H, m), 0.45-0.75(1H, m), 0.99(3H, t, J = 6.6Hz), 1.07(3H, t, J = 6.6Hz), 1.10-1.43(7H, m), 1.60-1.80(1H, m), 3.19-3.47(1H, m), 3.59(1H, t, J = 6.9Hz), 3.75-4.00(1H, m), 7.27-7.60(5H, m), 7.60-7.80(2H, m), 12.02(1H, brs).

MS: 407 (M+H)<sup>+</sup>.

Example 534 Synthesis of N-cyclohexyl-2-cyclopropylmethyl-N-isopropyl-N'-((E)-styrylsulfonyl)malonamide

25

(1) 3-(N-cyclohexyl-N-isopropylamino)-2-cyclopropylmethyl-3-oxopropionic acid

**[1146]** In the same manner as in Example 119 (2), the title compound (880 mg) was obtained as an oil using the compound (991 mg) obtained in Example 214 (1) and N-isopropylcyclohexylamine (2.83 g).

30 <sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ(-0.10)-0.10(2H, m), 0.20-0.42(2H, m), 0.49-0.70(1H, m), 0.70-1.80(18H, m), 2.10-2.46(1H, m), 2.80-4.30(2H, m), 12.40(1H, brs).

(2) N-cyclohexyl-2-cyclopropylmethyl-N-isopropyl-N'-((E)-styrylsulfonyl)malonamide

35 **[1147]** In the same manner as in Example 1 (2), the title compound (120 mg) was obtained as a white powder using the above-mentioned compound (880 mg) and trans-β-styrenesulfonamide (524 mg).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ(-0.18)-0.45(4H, m), 0.50-1.88(19H, m), 2.05-3.00(1H, m), 3.15-4.00(2H, m), 7.25-7.63(5H, m), 7.63-7.79(2H, m), 12.16(1H, brs).

MS: 447(M+H)<sup>+</sup>.

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Example 535 Synthesis of N'-butylsulfonyl-2-cyclopropylmethyl-N-(4-fluorophenyl)-N-isopropylmalonamide

**[1148]** In the same manner as in Example 1 (2), the title compound (124 mg) was obtained as a white powder using the compound (587 mg) obtained in Example 515 (1) and 1-butanefulfonamide (274 mg).

45 <sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ(-0.38)-(-0.20) (1H, m), (-0.14)-0.02(1H, m), 0.15-0.33(2H, m), 0.45-0.67(1H, m), 0.88(3H, t, J = 7.2Hz), 0.96(6H, t, J = 7.2Hz), 1.30-1.77(6H, m), 3.08-3.20(1H, m), 3.20-3.44(2H, m), 4.64-4.88(1H, m), 7.10-7.42(4H, m), 11.37(1H, brs).

MS: 413(M+H)<sup>+</sup>.

50 Example 536 Synthesis of 2-cyclopropylmethyl-N-(4-fluorophenyl)-N-isopropyl-N'-octylsulfonylmalonamide

**[1149]** In the same manner as in Example 1 (2), the title compound (490 mg) was obtained as a white powder using the compound (587 mg) obtained in Example 515 (1) and 1-octanesulfonamide (387 mg).

55 <sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ(-0.39)-(-0.20)(1H, m), (-0.17)-0.02(1H, m), 0.13-0.39(2H, m), 0.42-0.67(1H, m), 0.86(3H, t, J = 6.9Hz), 0.96(6H, t, J = 7.2Hz), 1.13-1.76(14H, m), 3.13(1H, t, J = 6.6Hz), 3.17-3.40(2H, m), 4.63-4.89(1H, m), 7.10-7.47(4H, m), 11.36(1H, brs).

MS: 469(M+H)<sup>+</sup>.

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Example 537 Synthesis of 2-cyclopropylmethyl-N-(4-fluorophenyl)-N-isopropyl-N'-(2-methyl-2-propenylsulfonyl)malonamide

(1) 2-methyl-2-propenesulfonamide

**[1150]** To 2-methyl-2-propenesulfonic acid sodium salt (7.91 g) was added DMF (50 mL), thionyl chloride (7.26 mL) was added under ice-cooling, and the mixture was stirred at room temperature for 6 hr. The reaction mixture was poured into a mixed solution of ice-water (100 mL) and toluene (100 mL), and the mixture was extracted. The organic layer was concentrated under reduced pressure. THF (60 mL) was added to the residue, and then aqueous ammonia (40 mL) was added under ice-cooling. The mixture was stirred at room temperature for 18 hr. The reaction mixture was concentrated, and water and ethyl acetate were added to extract the residue. The organic layer was washed with saturated brine, and concentrated under reduced pressure to give the title compound (3.11 g) as an oil. <sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ1.86(3H, s), 3.69(2H, s), 5.00(1H, brs), 5.08(1H, brs), 6.80(2H, brs).

(2) 2-cyclopropylmethyl-N-(4-fluorophenyl)-N-isopropyl-N'-(2-methyl-2-propenylsulfonyl)malonamide

**[1151]** In the same manner as in Example 1 (2), the title compound (390 mg) was obtained as a white powder using the compound (587 mg) obtained in Example 515 (1) and the above-mentioned compound (270 mg).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ(-0.40)-(-0.20)(1H, m), (-0.17)-0.02(1H, m), 0.15-0.35(2H, m), 0.46-0.69(1H, m), 0.81-1.09(6H, m), 1.27-1.44(1H, m), 1.60-1.79(1H, m), 1.82(3H, s), 2.97-3.19(1H, m), 3.88-4.15(2H, m), 4.66-4.88(1H, m), 4.95(1H, s), 5.12(1H, s), 7.05-7.44(4H, m), 11.42(1H, brs).

MS: 411(M+H)<sup>+</sup>.

Example 538 Synthesis of N-(4-fluorophenyl)-N-isopropyl-2-(2-methoxyethyl)-N'-((E)-styrylsulfonyl)malonamide

(1) 5-(2-methoxyethyl)-2, 2-dimethyl-1, 3-dioxane-4, 6-dione

**[1152]** In the same manner as in Example 214 (1), the title compound (930 mg) was obtained as an oil using methoxyacetic acid (3.60 g).

<sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ1.76(3H, s), 1.81(3H, s), 5.61(2H, q, J = 5.6Hz), 3.32(3H, s), 3.63(2H, t, J = 5.9Hz), 3.74(1H, t, J = 5.5Hz).

(2) 2-[[N-(4-fluorophenyl)-N-isopropylamino]carbonyl]-4-methoxybutyric acid

**[1153]** In the same manner as in Example 119 (2), the title compound (600 mg) was obtained as a white powder using the above-mentioned compound (930 mg) and 4-fluoro-N-isopropylaniline (2.82 g).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.84-1.05(6H, m), 1.70-2.01(2H, m), 2.95-3.30(6H, m), 4.65-4.90(1H, m), 7.10-7.40(4H, m), 12.50(1H, brs).

(3) N-(4-fluorophenyl)-N-isopropyl-2-(2-methoxyethyl)-N'-((E)-styrylsulfonyl)malonamide

**[1154]** In the same manner as in Example 1 (2), the title compound (164 mg) was obtained as a white powder using the above-mentioned compound (600 mg) and trans-β-styrenesulfonamide (341 mg).

<sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.77-1.00(6H, m), 1.67-1.85(1H, m), 1.85-2.04(1H, m), 2.97-3.26(6H, m), 4.62-4.84(1H, m), 6.95-7.15(2H, m), 7.15-7.29(1H, m), 7.29-7.40(2H, m), 7.40-7.60(4H, m), 7.69-7.90(2H, m), 11.62(1H, brs).

MS: 963(M+H)<sup>+</sup>.

Example 539 Synthesis of N-(4-fluorophenyl)-N-isopropyl-2-[2-(methylthio)ethyl]-N'-((E)-styrylsulfonyl)malonamide (1) 2, 2-dimethyl-5-[2-(methylthio)ethyl]-1,3-dioxane-4, 6-dione

**[1155]** In the same manner as in Example 214 (1), the title compound (3.62 g) was obtained as a white powder using methylthioacetic acid (3.48 mL).

<sup>1</sup>H-NMR(300Mz, CDCl<sub>3</sub>)δ1.78(3H, s), 1.84(3H, s), 2.09(3H, s), 2.40(2H, q, J = 5.7Hz), 2.80(2H, t, J = 6.9Hz), 4.02(1H, t, J = 5.4Hz).

(2) 2-[[N-(4-fluorophenyl)-N-isopropylamino]carbonyl]-4-methylthiobutyric acid

**[1156]** In the same manner as in Example 119 (2), the title compound (1.02 g) was obtained as a white solid using

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the above-mentioned compound (1.00 g) and 4-fluoro-N-isopropylaniline (2.82 g).

$^1\text{H-NMR}$ (300Mz, DMSO- $d_6$ ) $\delta$ 0.82-1.02(6H, m), 1.76-2.00(5H, m), 2.31(2H, t, J = 7.1Hz), 3.12(1H, t, J = 7.4Hz), 4.68-4.88(1H, m), 7.13-7.40(4H, m), 12.60(1H, brs).

### 5 (3) N-(4-fluorophenyl)-N-isopropyl-2-[2-(methylthio)ethyl]-N'-((E)-styrylsulfonyl)malonamide

**[1157]** In the same manner as in Example 1 (2), the title compound (339 mg) was obtained as a white powder using the above-mentioned compound (1.02 g) and trans- $\beta$ -styrenesulfonamide (551 mg).

10  $^1\text{H-NMR}$ (300Mz, DMSO- $d_6$ ) $\delta$ 0.78-1.00(6H, m), 1.68-1.85(1H, m), 1.85-2.09(4H, m), 2.14-2.40(2H, m), 3.00-3.19(1H, m), 4.60-4.84(1H, m), 6.94-7.18(2H, m), 7.18-7.40(3H, m), 7.40-7.67(4H, m), 7.67-7.89(2H, m), 11.66(1H, brs).  
MS: 479 (M+H) $^+$ .

### Example 540 Synthesis of N-(4-fluorophenyl)-N-isopropyl-2-[2-(methylsulfinyl)ethyl]-N'-((E)-styrylsulfonyl)malonamide

15 **[1158]** To a solution of the compound (100 mg) obtained in Example 539 in methanol (5 mL) was added a solution of sodium periodate (49 mg) in water (1 mL) under ice-cooling, and the mixture was stirred under ice-cooling for 2 hr. The reaction mixture was concentrated under reduced pressure, and 1 mol/L hydrochloric acid and ethyl acetate were added to extract the residue. The organic layer was washed with saturated brine, and concentrated under reduced pressure to give the title compound (103 mg) as a white powder.

20  $^1\text{H-NMR}$ (300Mz, DMSO- $d_6$ ) $\delta$ 0.80-1.00(6H, m), 1.75-1.95(1H, m), 1.95-2.20(1H, m), 2.35-2.58(4H, m), 2.58-2.78(1H, m), 3.09-3.33(1H, m), 4.64-4.88(1H, m), 6.91-7.17(2H, m), 7.17-7.40(3H, m), 7.40-7.67(4H, m), 7.69-7.90(2H, m), 11.68(1H, brs).  
MS: 495 (M+H) $^+$ .

### 25 Example 541 Synthesis of N-(4-fluorophenyl)-N-isopropyl-2-[2-(methylsulfonyl)ethyl]-N'-((E)-styrylsulfonyl)malonamide

**[1159]** To a solution of the compound (100 mg) obtained in Example 539 in methylene chloride (5 mL) was added m-chloroperbenzoic acid (79 mg), and the mixture was stirred at room temperature for 18 hr. Water, 1 mol/L hydrochloric acid and chloroform were added to extract the reaction mixture, and the organic layer was concentrated under reduced pressure. The residue was washed with THF-chloroform mixture to give the title compound (12 mg) as a white powder.

30  $^1\text{H-NMR}$ (300Mz, DMSO- $d_6$ ) $\delta$ 0.92(6H, d, J = 6.7Hz), 1.80-2.00(1H, m), 2.00-2.28(1H, m), 2.80-3.08(5H, m), 3.08-3.35(1H, m), 4.68-4.87(1H, m), 6.88-7.09(2H, m), 7.09-7.60(7H, m), 7.62-7.89-(2H, m), 11.70(1H, brs).  
MS: 511(M+H) $^+$ .

### 35 Example 542 Synthesis of 2-(2-cyanoethyl)-N-ethyl-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

**[1160]** In the same manner as in Example 1 (4), a crude product was obtained using the compound (300 mg) obtained in Example 216 (2) and N-ethylaniline (123  $\mu\text{L}$ ). This was purified by silica gel column chromatography to give the title compound (145 mg) as a white powder.

40  $^1\text{H-NMR}$ (400Mz,  $\text{CDCl}_3$ ) $\delta$ 1.13(3H, m), 2.15-2.40(4H, m), 3.25-3.28(1H, m), 3.67-3.76(1H, m), 3.83-3.92(1H, m), 7.04(1H, d, J = 15.6Hz), 7.13-7.15(2H, m), 7.41-7.54(8H, m), 7.73(1H, d, J = 15.6Hz), 10.14(1H, brs).  
MS: 426(M+H) $^+$ .

### 45 Example 543 Synthesis of 2-(2-cyanoethyl)-N-ethyl-N'-(2-naphthylsulfonyl)-N-phenylmalonamide

**[1161]** In the same manner as in Example 1 (4), a crude product was obtained using the compound (1.00 g) obtained in Example 153 (3) and N-ethylaniline (379  $\mu\text{L}$ ). This was purified by silica gel column chromatography to give the title compound (687 mg) as a white powder.

50  $^1\text{H-NMR}$ (400Mz,  $\text{CDCl}_3$ ) $\delta$ 1.09(3H, m), 1.91-2.02(1H, m), 2.09-2.21(3H, m), 3.11-3.15(1H, m), 3.60-3.69(1H, m), 3.82-3.91(1H, m), 6.95-6.99(2H, m), 7.35-7.62(3H, m), 7.63-7.71(2H, m), 7.92-7.93(1H, m), 7.99-8.04(3H, m), 8.67(1H, s), 10.16(1H, s).  
MS: 450(M+H) $^+$ .

### 55 Example 544 Synthesis of 2-(2-cyanoethyl)-N-(4-fluorophenyl)-N-isopropyl-N'-((E)-styrylsulfonyl)malonamide

**[1162]** In the same manner as in Example 1 (4), a crude product was obtained using the compound (657 mg) obtained in Example 216 (2) and 4-fluoro-N-isopropylaniline (306 mg). This was purified by silica gel column chromatography to give the title compound (334 mg) as a white powder.

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$^1\text{H-NMR}$ (400Hz,  $\text{CDCl}_3$ ) $\delta$ 1-05(3H, d, J = 6.8Hz), 1.11(3H, d, J = 6.8Hz), 2.03-2.09(1H, m), 2.16-2.39(3H, m), 3.09-3.14(1H, m), 4.94-4.97(1H, m), 7.00-7.09(2H, m), 7.10-7.19(3H, m), 7.43-7.47(3H, m), 7.52-7.55(2H, m), 7.72(1H, d, J = 15.6Hz), 9.96(1H, brs).  
MS : 458(M+H)<sup>+</sup>.

5

Example 545 Synthesis of 2-cyanomethyl-N-ethyl-N'-(2-naphthylsulfonyl)-N-phenylmalonamide

(1) monoethyl (2-cyanomethyl)malonate

10 **[1163]** In the same manner as in Example 117 (1), the object compound was obtained using chloroacetonitrile (1.63 mL). This was subjected to hydrolysis in the same manner as in Example 117 (2) to give the title compound (3.81 g) as an oil.

$^1\text{H-NMR}$ (400Mz,  $\text{CDCl}_3$ ) $\delta$ 1.32-1.36(3H, m), 2.91-2.99(2H, m), 3.69-3.79(1H, m)4.25-4.34(2H, m).

15 (2) 2-cyanomethyl-3-(N-ethyl-N-phenylamino)-3-oxopropionic acid

**[1164]** In the same manner as in Example 1 (4), the object compound was obtained using the above-mentioned compound (3.81 g) and N-ethylaniline (2.70 mL). This was subjected to hydrolysis in the same manner as in Example 1 (3) to give the title compound (1.07 g) as an oil.

20

(3) 2-cyanomethyl-N-ethyl-N'-(2-naphthylsulfonyl)-N-phenylmalonamide

**[1165]** In the same manner as in Example 1 (2), the title compound (1.25 g) was obtained as a white powder using the above-mentioned compound (500 mg).

25  $^1\text{H-NMR}$ (400Mz,  $\text{CDCl}_3$ ) $\delta$ 1.19(3H, m), 2.51-2.56(1H, m), 2.80-2.87(1H, m) 3.38-3.42(1H, m), 3.73-3.87(2H, m), 6.87-7.05(2H, m), 7.39-7.40(3H, m), 7.66-7.71(2H, m), 7.92-8.03(4H, m), 8.65(1H, s), 9.77(1H, brs).

MS: 436(M+H)<sup>+</sup>.

Example 546 Synthesis of 2-cyanomethyl-N-ethyl-N-phenyl-N'-((E)-styrylsulfonyl)malonamide

30

**[1166]** In the same manner as in Example 1 (2), the title compound (66 mg) was obtained as a white powder using the compound (500 mg) obtained in Example 545 (2) and trans- $\beta$ -styrenesulfonamide (372 mg).

$^1\text{H-NMR}$ (400Mz,  $\text{CDCl}_3$ ) $\delta$ 1.10-1.15(3H, m), 2.61-2.74(1H, m), 2.87-2.97(1H, m), 3.47-3.53(1H, m), 3.74-3.89(2H, m), 6.91-7.02(1H, m), 7.15-7.18(2H, m), 7.21-7.57(8H, m), 7.73(1H, d, J = 15.6Hz), 9.48(1H, brs).

35 MS: 412(M+H)<sup>+</sup>.

Example 547 Synthesis of N-(4-fluorophenyl)-N-isopropyl-2-(2-propynyl)-N'-((E)-styrylsulfonyl)malonamide

40 **[1167]** In the same manner as in Example 152 (3), the object compound was obtained using the compound (3.00 g) obtained in Example 152 (2) and trans- $\beta$ -styrenesulfonamide (3.23 g). This was subjected to hydrolysis in the same manner as in Example 1 (3), and condensed with 4-fluoro-N-isopropylaniline (1.29 g) in the same manner as in Example 1 (4) to give a crude product. This was purified by silica gel column chromatography to give the title compound (1.25 g) as a white powder.

45  $^1\text{H-NMR}$ (400Mz,  $\text{CDCl}_3$ ) $\delta$ 1.04(3H, d, J = 6.8Hz), 1.11(3H, d, J = 6.8Hz), 2.04(1H, s)2.57-2.64(1H, m), 2.70-2.77(1H, m), 3.18-3.22(1H, m), 4.94-4.99(1H, m), 6.99-7.05(2H, m), 7.09-7.15(3H, m), 7.39-7.45(3H, m), 7.50-7.53(2H, m), 7.71(1H, d, J = 15.6Hz), 9.87(1H, brs).

MS: 443(M+H)<sup>+</sup>.

Example 548 Synthesis of 2-cyclopentyl-N-(4-fluorophenyl)-N-isopropyl-N'-((E)-styrylsulfonyl)malonamide

50

(1) monoethyl cyclopentylmalonate

**[1168]** In the same manner as in Example 1 (1), the title compound (8.6 g) was obtained as an oil using diethyl cyclopentylmalonate (10.0 g).

55

(2) 2-cyclopentyl-N-(4-fluorophenyl)-N-isopropyl-N'-((E)-styrylsulfonyl)malonamide

**[1169]** In the same manner as in Example 152 (3), the object compound was obtained using the above-mentioned

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compound (540 mg) and trans- $\beta$ -styrenesulfonamide (500 mg). This was subjected to hydrolysis in the same manner as in Example 1 (3), and condensed with 4-fluoro-N-isopropylaniline (414 mg) in the same manner as in Example 1 (4) to give a crude product. This was purified by silica gel column chromatography to give the title compound (103 mg) as a white powder.

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>) $\delta$ 1.00(3H, d, J = 5.4Hz), 1.03-1.10(1H, m), 1.12(3H, d, J = 5.4Hz), 1.26-1.31(1H, m), 1.48-1.49(4H, m), 1.55-1.62(1H, m), 1.61-1.79(1H, m), 2.31-2.42(1H, m), 2.76(1H, d, J = 10.4Hz), 4.93-5.02(1H, m), 6.96-7.14(5H, m), 7.39-7.50(3H, m), 7.52-7.69(2H, m), 7.71(1H, d, J = 15.4Hz), 9.90(1H, brs).

MS: 473(M+H)<sup>+</sup>.

Example 549 Synthesis of N-ethyl-N'-(2-naphthylsulfonyl)-N-phenyl-2-[(2E)-3-(3-pyridyl)-2-propenyl]malonamide

**[1170]** To a solution of the compound (436 mg) obtained in Example 444 in DMF (5 mL) were added 3-bromopyridine (237 mg), palladium acetate (145 mg), tetra-n-butylammonium chloride (416 mg), triphenylphosphine (52 mg) and potassium acetate (294 mg), and the mixture was stirred at 80°C for 18 hr. Water and ethyl acetate were added to extract the reaction mixture, and the organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound (345 mg) as a white powder.

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>) $\delta$ 0.92(3H, brs), 2.39-2.45(1H, m), 3.53-3.61(3H, m), 6.23(2H, s), 7.01-7.03(2H, m), 7.08-7.40(5H, m), 7.55-7.57(1H, m), 7.59-7.79(3H, m), 7.98-8.03(2H, m), 8.14-8.16(1H, m), 8.30-8.40(2H, m), 8.52(1H, s).

MS: 514 (M+H)<sup>+</sup>.

Example 550 Synthesis of N-ethyl-N'-(2-naphthylsulfonyl)-N-phenyl-2-[3-(3-pyridyl)propyl]malonamide

**[1171]** In the same manner as in Example 7, the title compound (89 mg) was obtained as a white powder using the compound (100 mg) obtained in Example 549.

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>) $\delta$ 1.09(3H, brs), 1.29-1.36(2H, m), 1.67-1.76(2H, m), 2.27-2.38(2H, m), 3.01-3.04(1H, m), 3.57-3.82(1H, m), 3.84-3.37(1H, m), 6.89-6.90(2H, m), 7.07-7.10(1H, m), 7.17-7.19(1H, m), 7.32-7.34(3H, m), 7.60-7.69(2H, m), 7.90-8.01(4H, m), 8.21(1H, s), 8.39(1H, d, J = 4.4Hz), 8.67(1H, s).

MS: 516(M+H)<sup>+</sup>.

Example 551 Synthesis of N-ethyl-2-[(2E)-3-[4-(1H-imidazol-1-ylmethyl)phenyl]-2-propenyl]-N'-(2-naphthylsulfonyl)-N-phenylmalonamide

**[1172]** In the same manner as in Example 549, the title compound (108 mg) was obtained as a white powder using the compound (436 mg) obtained in Example 444 and 1-(4-bromobenzyl)imidazole (356 mg).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>) $\delta$ 1.10(3H, brs), 2.61-2.64(2H, m), 3.60-3.69(1H, m), 3.77-3.84(1H, m), 5.24(2H, s), 5.76-5.82(1H, m), 6.09-6.20(1H, m), 6.94-6.95(1H, m), 7.03-7.20(5H, m), 7.30-7.40(5H, m), 7.58-7.67(3H, m), 7.85-8.01(5H, m), 8.65(1H, s), 8.85(1H, brs).

MS: 593(M+H)<sup>+</sup>.

Example 552 Synthesis of N-ethyl-2-[3-[4-(1H-imidazol-1-ylmethyl)phenyl]propyl]-N'-(2-naphthylsulfonyl)-N-phenylmalonamide

**[1173]** In the same manner as in Example 7, the title compound (17 mg) was obtained as a white powder using the compound (108 mg) obtained in Example 551 at room temperature.

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>) $\delta$ 1.05-1.10(3H, m), 1.35-1.40(2H, m), 1.69-1.74(2H, m), 2.36-2.42(2H, m), 3.60-3.62(2H, m), 3.82-3.84(1H, m), 5.20(2H, s), 6.89-6.90(2H, m), 6.99-7.02(2H, m), 7.07-7.08(2H, m), 7.10-7.24(2H, m), 7.31-7.32(3H, m), 7.37-7.38(1H, m), 7.63-7.65(2H, m), 7.67-8.03(4H, m), 8.65(1H, s), 8.69(1H, brs).

MS: 595(M+H)<sup>+</sup>.

Example 553 Synthesis of N-ethyl-2-[(2E)-3-(2-naphthyl)-2-propenyl]-N'-(2-naphthylsulfonyl)-N-phenylmalonamide

**[1174]** In the same manner as in Example 549, the title compound (14 mg) was obtained as a white powder using the compound (436 mg) obtained in Example 444 and 2-bromonaphthalene (310 mg).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>) $\delta$ 1.10(3H, brs), 2.47-2.56(1H, m), 2.60-2.81(1H, m), 3.23-3.27(1H, m), 3.63-3.66(1H, m), 3.68-3.85(1H, m), 5.81-5.87(1H, m), 6.29(1H, d, J = 16.0Hz), 6.95-6.97(2H, m), 7.30-7.60(7H, m), 7.65-7.85(7H, m), 7.89-7.99(2H, m), 8.67(1H, s), 10.82(1H, brs).

MS: 563(M+H)<sup>+</sup>.

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### Example 554 Synthesis of N-ethyl-2-[3-(2-naphthyl)propyl]-N'-(2-naphthylsulfonyl)-N-phenylmalonamide

**[1175]** In the same manner as in Example 7, the title compound (33 mg) was obtained as a white powder using the compound (34 mg) obtained in Example 553 at room temperature.

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.08(3H, m), 1.76-1.82(2H, m), 2.46-2.53(2H, m), 3.01-3.04(2H, m), 3.52-3.60(1H, m), 3.77-3.86(1H, m), 6.81(2H, d, J = 7.6Hz), 6.99-7.03(3H, m), 7.05-7.31(2H, m), 7.37-7.38(2H, m), 7.41-7.43(1H, m), 7.44-7.71(4H, m), 7.74-8.01(5H, m), 8.70(1H, s)10.60(1H, brs).

MS: 565(M+H)<sup>+</sup>.

### 10 Example 555 Synthesis of N-ethyl-2-[(2E)-3-(4-methoxyphenyl)-2-propenyl]-N'-(2-naphthylsulfonyl)-N-phenylmalonamide

**[1176]** In the same manner as in Example 549, the title compound (11 mg) was obtained as a white powder using the compound (436 mg) obtained in Example 444 and 4-bromoanisole (281 mg).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.05(3H, brs), 2.42-2.52(1H, m), 2.54-2.70(1H, m), 3.11-3.25(1H, m), 3.64-3.71(1H, m), 3.77-3.83(4H, m), 5.17-5.76(1H, m), 6.08-6.17(1H, m), 6.65-6.78(2H, m), 6.87-6.98(3H, m), 7.29-7.41(4H, m), 7.60-7.70(2H, m), 7.85-7.90(2H, m), 7.97-8.07(2H, m), 8.67(1H, s), 10.60(1H, brs).

MS: 543(M+H)<sup>+</sup>.

### 20 Example 556 Synthesis of N-ethyl-2-[3-(4-methoxyphenyl)propyl]-N'-(2-naphthylsulfonyl)-N-phenylmalonamide

**[1177]** In the same manner as in Example 7, the title compound (11 mg) was obtained as a white powder using the compound (84 mg) obtained in Example 555 at room temperature.

<sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ0.97(3H, brs), 1.07-1.30(2H, m), 1.45-1.70(2H, m), 2.29-2.33(2H, m), 3.10-3.20(1H, m), 3.56-3.59(2H, m), 3.72(3H, s), 6.54-6.59(1H, m), 6.71-6.75(2H, m), 6.80-6.87(H, m), 7.01-7.09(2H, m), 7.33-7.37(2H, m), 7.47-7.51(1H, m), 7.72-7.81(3H, m), 8.11-8.16(1H, m), 8.18-8.22(1H, m), 8.24-8.35(1H, m), 8.54(1H, s), 11.98(1H, brs).

MS:545(M+H)<sup>+</sup>.

### 30 Example 557 Synthesis of 2-[(2E)-3-(4-biphenyl)-2-propenyl]-N-ethyl-N'-(2-naphthylsulfonyl)-N-phenylmalonamide

**[1178]** In the same manner as in Example 549, the title compound (10 mg) was obtained as a white powder using the compound (436 mg) obtained in Example 444 and 4-bromobiphenyl (350 mg).

<sup>1</sup>H-MMR(400Mz, CDCl<sub>3</sub>)δ1.10(3H, brs), 2.52-2.61(1H, m), 3.20-3.24(1H, m), 3.64-3.69(1H, m), 3.80-3.85(1H, m), 5.71-5.75(1H, m), 6.18(1H, d, J = 15.6Hz), 6.96-7.06(1H, m), 7.09-7.12(2H, m), 7.33-7.41(4H, m), 7.43-7.54(5H, m), 7.55-7.63(5H, m), 7.82-7.86(2H, m), 7.95-7.99(2H, m), 8.62(1H, s).

MS: 589(M+H)<sup>+</sup>.

### 40 Example 558 Synthesis of 2-[3-(4-biphenyl)propyl]-N-ethyl-N'-(2-naphthylsulfonyl)-N-phenylmalonamide

**[1179]** In the same manner as in Example 7, the title compound (19 mg) was obtained as a white powder using the compound (94 mg) obtained in Example 557 at room temperature.

<sup>1</sup>H-NMR (400Mz, DMSO-d<sub>6</sub>)δ0.93(3H, brs), 1.12-1.40 (2H, m), 1.43-1.70(2H, m), 2.33-2.51(2H, m), 3.50-3.86(3H, m), 7.04-7.06(4H, m), 7.32-7.38(2H, m), 7.44-7.50(2H, m), 7.56-7.63(4H, m), 7.71-7.76(2H, m), 7.79-8.10(3H, m), 8.16-8.55(3H, m), 11.95(1H, s), 12.28(1H, brs).

MS: 591(M+H)<sup>+</sup>.

### Example 559 Synthesis of N-ethyl-2-[(2E)-3-(4-isoquinoly)-2-propenyl]-N'-(2-naphthylsulfonyl)-N-phenylmalonamide

**[1180]** In the same manner as in Example 549, the title compound (61 mg) was obtained as a white powder using the compound (436 mg) obtained in Example 444 and 4-bromoisoquinoline (363 mg).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ0.99(3H, brs), 2.77-2.79(1H, m), 3.28-3.30(1H, m), 3.63-3.84(1H, m), 3.86-3.93(1H, m), 5.79-5.85(1H, m), 6.69-6.65(1H, m), 6.95-7.00(2H, m), 7.30-7.37(2H, m), 7.42-7.48(3H, m), 7.48-7.58(2H, m), 7.59-7.31(3H, m), 7.73-8.05(5H, m), 8.29(1H, s), 8.65(1H, s), 9.05(1H, s).

MS: 564(M+H)<sup>+</sup>.

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Example 560 Synthesis of 2-[3-(benzothiophen-3-yl)-2-propenyl]-N-ethyl-N'-(2-naphthylsulfonyl)-N-phenylmalonamide

**[1181]** In the same manner as in Example 549, the title compound (10 mg) was obtained as a white powder using the compound (436 mg) obtained in Example 444 and 3-bromobenzothiophene (319 mg). <sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.10(3H, brs), 2.50-2.60(1H, m), 2.60-2.70(1H, m), 3.23-3.32(1H, m), 3.60-3.69(1H, m), 3.80-3.89(1H, m), 5.72-5.79(1H, m), 6.35(1H, d, J = 15.6Hz), 6.96-6.99(2H, m), 7.01-7.02(1H, m), 7.30-7.37(5H, m), 7.48-7.55(2H, m), 7.58-7.80(3H, m), 7.82-7.98(3H, m), 8.60(1H, s), 10.70(1H, brs).

MS: 569(M+H)<sup>+</sup>.

Example 561 Synthesis of N-ethyl-N'-(2-naphthylsulfonyl)-N-phenyl-2-[(2E)-3-(3-thienyl)-2-propenyl]malonamide

**[1182]** In the same manner as in Example 549, the title compound (1 mg) was obtained as a white powder using the compound (436 mg) obtained in Example 444 and 3-bromothiophene (244 mg).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.08(3H, brs), 2.40-2.48(1H, m), 2.51-2.65(1H, m), 3.16-3.19(1H, m), 3.61-3.69(1H, m), 3.78-3.85(1H, m), 5.49-5.57(1H, m), 6.16(1H, d, J = 15.6Hz), 6.83-6.99(4H, m), 7.16-7.18(1H, m), 7.31-7.34(3H, m), 7.52-7.68(2H, m), 7.86-7.88(2H, m), 7.92-7.99(2H, m), 8.65(1H, s), 10.60(1H, brs).

MS: 519 (M+H)<sup>+</sup>.

Example 562 Synthesis of N-ethyl-2-[(2E)-3-(4-ethoxycarbonylphenyl)-2-propenyl]-N'-(2-naphthylsulfonyl)-N-phenylmalonamide

**[1183]** In the same manner as in Example 549, the title compound (1.12 g) was obtained as a white powder using the compound (1.31 g) obtained in Example 444 and ethyl 4-bromobenzoate (1.24 g).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.07(3H, brs), 1.42(3H, brs), 2.49-2.55(1H, m), 2.59-2.64(1H, m), 3.19-3.23(1H, m), 3.63-3.70(1H, m), 3.78-3.85(1H, m), 4.35-4.41(2H, m), 5.75-5.83(1H, m), 6.15(1H, d, J = 16.0Hz), 6.93-6.96(2H, m), 7.03-7.05(2H, m), 7.31-7.37(3H, m), 7.57-7.65(2H, m), 7.81-7.84(4H, m), 7.94-7.98(2H, m), 8.63(1H, s), 10.65(1H, brs).

MS: 585(M+H)<sup>+</sup>.

Example 563 Synthesis of N-ethyl-2-[3-(4-ethoxycarbonylphenyl)propyl]-N'-(2-naphthylsulfonyl)-N-phenylmalonamide

**[1184]** In the same manner as in Example 7, the title compound (158 mg) was obtained as a white powder using the compound (1.10 g) obtained in Example 562 at room temperature.

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.09(3H, brs), 1.22-1.32(2H, m), 1.41(3H, brs), 1.68-1.73(2H, m), 2.31-2.42(2H, m), 2.99-3.03(1H, m), 3.56-3.63(1H, m), 3.82-3.87(1H, m), 4.35-4.40(2H, m), 6.87-6.94(4H, m), 7.29-7.34(3H, m), 7.61-7.69(2H, m), 7.83-8.02(6H, m), 8.67(1H, s), 10.61(1H, brs).

MS: 587(M+H)<sup>+</sup>.

Example 564 Synthesis of N-ethyl-2-[(2E)-3-(4-fluorophenyl)-2-propenyl]-N'-(2-naphthylsulfonyl)-N-phenylmalonamide

**[1185]** In the same manner as in Example 549, the title compound (52 mg) was obtained as a white powder using the compound (436 mg) obtained in Example 444 and 4-bromo-1-fluorobenzene (263 mg).

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.09(3H, brs), 2.41-2.52(1H, m), 2.54-2.67(1H, m), 3.20-3.21(1H, m), 3.61-3.70(1H, m), 3.77-3.86(1H, m), 5.54-5.72(1H, m), 6.08(1H, d, J = 16.0Hz), 6.71-6.88(2H, m), 6.92-6.99(4H, m), 7.31-7.35(3H, m), 7.52-7.65(2H, m), 7.82-7.89(2H, m), 7.91-8.00(2H, m), 8.65(1H, s), 10.61(1H, brs).

MS: 531 (M+H)<sup>+</sup>.

Example 565 Synthesis of N-ethyl-2-[3-(4-fluorophenyl)propyl]-N'-(2-naphthylsulfonyl)-N-phenylmalonamide

**[1186]** In the same manner as in Example 7, the title compound (11 mg) was obtained as a white powder using the compound (40 mg) obtained in Example 564 at room temperature.

<sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.10(3H, brs), 1.20-1.36(2H, m), 1.61-1.82(2H, m), 2.22-2.37(2H, m), 2.98-3.02(1H, m), 3.55-3.63(1H, m), 3.79-3.88(1H, m), 6.79-6.89(5H, m), 7.13-7.20(1H, m), 7.29-7.36(3H, m), 7.60-7.63(2H, m), 7.65-8.00(4H, m), 8.71(1H, s), 10.60(1H, brs).

MS: 533(M+H)<sup>+</sup>.

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Example 566 Synthesis of N-ethyl-N'-(2-naphthylsulfonyl)-2-{2-[4-(4-nitrophenyl)piperazino]ethyl}-N-phenylmalonamide  
(1) N-ethyl-5-hydroxy-1-(2-naphthylsulfonyl)-2-oxo-N-phenylpyrrolidine-3-carboxamide

5 **[1187]** To a mixture of the compound (10.1 g) obtained in Example 444 in ethanol (60 mL)/water (60 mL) were added osmium tetroxide (200 mg) and sodium periodate (8.90 g), and the mixture was stirred at room temperature for 1.5 hr. Ethyl acetate and water were added to the reaction mixture, and the precipitate was collected by filtration to give the title compound (439 mg) as a white powder.

10 <sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ0.91-0.97(3H, m), 1.89-1.95(1H, m), 2.63-2.67(1H, m), 3.59-3.63(2H, m), 3.65-3.70(1H, m), 5.89-5.93(1H, m), 6.91-6.93(1H, m), 7.25-7.30(2H, m), 7.33-7.37(1H, m), 7.41-7.45(2H, m), 7.69-7.78(2H, m), 7.93-7.95(1H, m), 8.05(1H, d, J = 8.0Hz), 8.12-8.21(2H, m), 8.63(1H, brs).

(2) N-ethyl-N'-(2-naphthylsulfonyl)-2-{2-[4-(4-nitrophenyl)piperazino]ethyl}-N-phenylmalonamide

15 **[1188]** To a solution of the above-mentioned compound (439 mg) in methylene chloride (5 mL) were added 1-(4-nitrophenyl)piperazine (228 mg), acetic acid (580 μL) and sodium triacetoxyborohydride (1.02 g), and the mixture was stirred at room temperature for 2 days. Water and chloroform were added to extract the reaction mixture, and the organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound (227 mg) as a white powder.

20 <sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.07(3H, t, J = 7.2Hz), 1.80-1.95(1H, m), 1.97-2.04(1H, m), 2.28-2.34(1H, m), 2.46-2.53(1H, m), 2.56-2.58(4H, m), 3.39-3.42(4H, m), 3.47-3.50(1H, m), 3.56-3.64(1H, m), 3.77-3.86(1H, m), 6.77-6.81(2H, m), 6.97-6.99(2H, m), 7.29-7.32(3H, m), 7.58-7.66(2H, m), 7.88-8.01(4H, m), 8.09-8.14(2H, m), 8.64(1H, brs).

MS: 630(M+H)<sup>+</sup>.

25 Example 567 Synthesis of 2-{2-[4-(4-aminophenyl)piperazino]ethyl}-N-ethyl-N'-(2-naphthylsulfonyl)-N-phenylmalonamide

**[1189]** In the same manner as in Example 7, the title compound (89 mg) was obtained as a white powder using the compound (154 mg) obtained in Example 566 at room temperature.

30 <sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ0.96(3H, t, J = 6.4Hz), 1.06-1.19(3H, m), 1.91-1.99(2H, m), 2.82-2.84(2H, m), 3.36-3.43(3H, m), 3.51-3.61(4H, m), 4.02-4.04(1H, m), 6.50-6.52(2H, m), 6.67-6.69(2H, m), 7.18-7.28(5H, m), 7.60-7.61(2H, m), 7.80-7.82(1H, m), 7.96-7.98(2H, m), 8.05-8.06(1H, m), 8.34(1H, s).

MS: 600 (M+H)<sup>+</sup>.

35 Example 568 Synthesis of N-ethyl-2, 2-difluoro-N-(1-naphthyl)-N'-(E)-styrylsulfonylmalonamide

**[1190]** Diethyl difluoromalonate (1.00 g) was subjected to hydrolysis in the same manner as in Example 1 (1) to give the object compound as an oil. This and trans-β-styrenesulfonamide (1.94 g) were condensed in the same manner as in Example 152 (3), and the condensed product was subjected to hydrolysis in the same manner as in Example 1 (3). In the same manner as in Example 1 (4), a crude product was obtained using this and N-ethyl-1-naphthylamine (805 mg). This was purified by silica gel column chromatography to give the title compound (22 mg) as a white powder.

40 <sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.85(3H, t, J = 6.8Hz), 3.30-3.34(1H, m), 4.35-4.38(1H, m), 6.87(1H, d, J = 15.6Hz), 7.27-7.30(1H, m), 7.41-7.58(8H, m), 7.67-7.87(2H, m), 7.89-7.91(2H, m).

MS: 459(M+H)<sup>+</sup>.

45 Example 569 Synthesis of N-(4-fluorophenyl)-N-isopropyl-2, 2-dimethyl-N'-(E)-styrylsulfonylmalonamide

(1) 2, 2-dimethyl-3-oxo-3-[(E)-styrylsulfonyl]amino]propionic acid

50 **[1191]** Diethyl dimethylmalonate (10.0 g) was subjected to hydrolysis in the same manner as in Example 1 (1) to give the object compound as an oil. The carboxylic acid form (3.20 g) and trans-β-styrenesulfonamide (3.67 g) were condensed in the same manner as in Example 152 (3), and the condensed product was subjected to hydrolysis in the same manner as in Example 1 (3) to give the title compound (1.38 g) as a white powder. <sup>1</sup>H-NMR(400Mz, CDCl<sub>3</sub>)δ1.48(6H, s), 7.07(1H, d, J = 14.4H), 7.27-7.29(3H, m), 7.40-7.42(2H, m), 7.52-7.54(2H, m), 7.71(1H, d, J = 14.4H).

55 (2) N-(4-fluorophenyl)-N-isopropyl-2,2-dimethyl-N'-(E)-styrylsulfonylmalonamide

**[1192]** In the same manner as in Example 1 (4), a crude product was obtained using the above-mentioned compound (594 mg) and 4-fluoro-N-isopropylaniline (306 mg). This was purified by silica gel column chromatography to give the

title compound (57 mg) as a white powder.

$^1\text{H-NMR}$ (400Mz,  $\text{CDCl}_3$ ) $\delta$ 1.02 (3H, s), 1.04(3H, s), 1.90(6H, brs), 4.89-4.93(1H, brs), 6.99-7.10(5H, m), 7.41-7.52(3H, m), 7.53-7.55(2H, m), 7.72(1H, d, J = 15.2Hz), 8.45-8.48(1H, brs).

MS: 433(M+H) $^+$ .

5

Example 570 Synthesis of N-benzyl-N-phenyl-N'-((E)-styrylsulfonyl)cyclobutane-1, 1-dicarboxamide

(1) 1-[[((E) - styrylsulfonyl)amino]carbonyl]cyclobutanecarboxylic acid

**[1193]** Diethyl 1, 1-cyclobutanedicarboxylate (10.0 g) was subjected to hydrolysis in the same manner as in Example 1 (1) to give the object compound as an oil. The carboxylic acid form (3.44 g) and trans- $\beta$ -styrenesulfonamide (3.67 g) were condensed in the same manner as in Example 152 (3), and the condensed product was subjected to hydrolysis in the same manner as in Example 1 (3) to give the title compound (3.02 g) as a white powder.

$^1\text{H-NMR}$ (400Mz,  $\text{CDCl}_3$ ) $\delta$ 1.97-2.07(2H, m), 2.60-2.65(2H, m), 2.70-2.73(2H, m), 7.09(1H, d, J = 13.4Hz), 7.31-7.34(2H, m), 7.41-7.42(3H, m), 7.53-7.54(2H, m), 7.71(1H, d, J = 13.4Hz).

15

(2) N-benzyl-N-phenyl-N'-((E)-styrylsulfonyl)cyclobutane-1, 1-dicarboxamide

**[1194]** In the same manner as in Example 1 (4), a crude product was obtained using the above-mentioned compound (618 mg) and N-benzylaniline (367 mg). This was purified by silica gel column chromatography to give the title compound (249 mg) as a white powder.

$^1\text{H-NMR}$ (400Mz,  $\text{CDCl}_3$ ) $\delta$ 1.48-1.51(2H, m), 1.87-1.89(2H, m), 2.29-2.32(2H, m), 4.88(2H, s), 6.70-6.75(2H, m), 6.85(1H, d, J = 15.6Hz), 7.05-7.09(2H, m), 7.16-7.20(3H, m), 7.29-7.31(3H, m), 7.41-7.46(5H, m), 7.71(1H, d, J = 15.6Hz), 8.75(1H, brs).

MS: 475(M+H) $^+$ .

25

Example 571 Synthesis of N, N-diethyl-N'-((E)-styrylsulfonyl)cyclobutane-1,1-dicarboxamide

**[1195]** In the same manner as in Example 1 (4), a crude product was obtained using the compound (618 mg) obtained in Example 570 (1). This was purified by silica gel column chromatography to give the title compound (26 mg) as a white powder.

$^1\text{H-NMR}$ (400Mz,  $\text{CDCl}_3$ ) $\delta$ 1.04-1.13(6H, m), 1.70-1.90(1H, m), 1.93-1.96(1H, m), 2.57-2.63(4H, m), 3.02-3.08(2H, m), 3.33-3.38(2H, m), 7.04(1H, d, J = 15.6Hz), 7.41-7.52(3H, m), 7.53-7.72(2H, m), 7.74(1H, d, J = 15.6Hz), 8.30(1H, brs).

MS: 365(M+H) $^+$ .

35

Example 572 Synthesis of N-(4-fluorophenyl)-N-isopropyl-N'-((E)-styrylsulfonyl)cyclobutane-1,1-dicarboxamide

**[1196]** In the same manner as in Example 1 (4), a crude product was obtained using the compound (1.00 g) obtained in Example 570 (1) and 4-fluoro-N-isopropylaniline (490 mg). This was purified by silica gel column chromatography to give the title compound (71 mg) as a white powder.

$^1\text{H-NMR}$ (400Mz,  $\text{CDCl}_3$ ) $\delta$ 1.04-1.06(6H, m), 1.49-1.53(1H, m), 1.69-1.75(1H, m), 1.82-1.86(2H, m), 2.30-2.38(2H, m), 4.89-4.92(1H, m), 6.96-6.98(4H, m), 7.09(1H, d, J = 15.6Hz), 7.42-7.47(3H, m), 7.54-7.56(2H, m), 7.76(1H, d, J = 15.6Hz), 8.63(1H, brs).

MS: 445(M+H) $^+$ .

45

Example 573 Synthesis of N-(4-fluorophenyl)-N-isopropyl-2-(1-methylethylidene)-N'-((E)-styrylsulfonyl)malonamide

**[1197]** Diethyl (1-methylethylidene)malonate (5.00 g) was subjected to hydrolysis in the same manner as in Example 1 (1). The obtained carboxylic acid and trans- $\beta$ -styrenesulfonamide (953 mg) were condensed in the same manner as in Example 152 (3), and the condensed product was subjected to hydrolysis in the same manner as in Example 1 (3). This and 4-fluoro-N-isopropylaniline (805 mg) were condensed in the same manner as in Example 1 (4) to give a crude product. This was purified by silica gel column chromatography to give the title compound (13 mg) as a white powder.

$^1\text{H-NMR}$ (400Mz,  $\text{CDCl}_3$ ) $\delta$ 0.80-1.10(6H, m), 2.40-2.50(6H, m), 5.50-5.80(1H, m), 6.99-7.06(2H, m), 7.09-7.14(1H, m), 7.40-7.45(4H, m), 7.50-7.54(3H, m), 7.68-7.74(1H, m), 10.30(1H, brs). MS: 445(M+H) $^+$ .

55

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Example 574 Synthesis of N, N-diethyl-N'-(2-naphthylsulfonyl)-2-(4-nitrobenzylidene)malonamide

(1) 2, 2-dimethyl-5-(4-nitrobenzylidene)-1, 3-dioxane-4, 6-dione

5 **[1198]** To 4-nitrobenzaldehyde (15.1 g) were added a toluene (180 mL) solution, Meldrum's acid (14.4 g), piperidine (300  $\mu$ L) and acetic acid (300  $\mu$ L) at room temperature, and the mixture was stirred for 5 hr. Insoluble material was collected by filtration, and the obtained solid was washed with ethyl acetate (80 mL). The resulting precipitate was collected by filtration to give the title compound (19.3 g) as a pale yellow solid.

$^1\text{H-NMR}$ (300Mz, DMSO- $d_6$ ) $\delta$ 1.61(6H, s), 8.07(1H, d, J = 8.7Hz), 8.30(2H, d, J = 8.8Hz), 8.51(1H, s).

10

(2) 3-(N, N-diethylamino)-2-(4-nitrobenzylidene)-3-oxopropionic acid

**[1199]** In the same manner as in Example 119 (2), the title compound (1.22 g) was obtained as a white powder using the above-mentioned compound (15.2 g).

15  $^1\text{H-NMR}$ (300Mz, DMSO- $d_6$ ) $\delta$ 0.83(3H, t, J = 7.1Hz), 1.07(3H, t, J = 7.1Hz), 3.00-3.70(4H, m), 7.67(1H, s), 7.79(2H, d, J = 8.8Hz), 8.27(2H, d, J = 8.7Hz).

(3) N, N-diethyl-N'-(2-naphthylsulfonyl)-2-(4-nitrobenzylidene)malonamide

20 **[1200]** In the same manner as in Example 1 (2), the title compound (930 mg) was obtained as a white powder using the above-mentioned compound (1.22 g).

$^1\text{H-NMR}$ (300Mz, DMSO- $d_6$ ) $\delta$ 0.59(3H, t, J = 7.0Hz), 0.97(3H, t, J = 7.0Hz), 2.84-3.60(4H, m), 7.50-8.39(11H, m), 8.67(1H, s).

MS: 482(M+H) $^+$ .

25

Example 575 Synthesis of 2-[4-(benzoylamino)benzylidene]-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

(1) 2-(4-aminobenzylidene)-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

30 **[1201]** In the same manner as in Example 137 (4), the title compound (50 mg) was obtained as a white powder using the compound (560 mg) obtained in Example 574.

$^1\text{H-NMR}$ (300Mz,  $\text{CDCl}_3$ ) $\delta$ 0.84(3H, t, J = 7.2Hz), 1.23(3H, t, J = 7.2Hz), 2.80-2.99(1H, m), 3.04-3.39(2H, m), 3.69-3.91(1H, m), 6.55(2H, d, J = 8.7Hz), 7.17(2H, d, J = 8.7Hz), 7.46(H, s), 7.50-7.75(2H, m), 7.83-8.12(4H, m), 8.70(1H, s).

35 (2) 2-[4-(benzoylamino)benzylidene]-N,N-diethyl-N'-(2-naphthylsulfonyl)malonamide

**[1202]** In the same manner as in Example 9, the title compound (36 mg) was obtained as a white powder using the above-mentioned compound (50 mg).

40  $^1\text{H-NMR}$ (300Mz, DMSO- $d_6$ ) $\delta$ 0.64(3H, t, J = 7.2Hz), 1.03(3H, t, J = 7.2Hz), 2.80-3.60(4H, m), 7.37-8.30(16H, m), 8.62(1H, s), 10.45(1H, s).

MS: 556(M+H) $^+$ .

Example 576 Synthesis of 2-[3-(benzoylamino)benzyl]-N, N-diethyl-N'-(2-naphthylsulfonyl)malonamide

45 **[1203]** In the same manner as in Example 9, a crude product was obtained using the compound (170 mg) obtained in Example 115. This was purified by silica gel column chromatography to give the title compound (27 mg) as a white powder.

50  $^1\text{H-NMR}$ (400MHz,  $\text{CDCl}_3$ ) $\delta$ 0.87(3H, t, J = 7.2Hz), 1.02(3H, t, J = 7.1Hz), 2.92-3.20(5H, m), 3.41-3.47(1H, m), 3.61(1H, dd, J = 9.2, 5.8Hz), 6.80(1H, d, J = 7.7Hz), 7.14(1H, t, J = 7.7Hz), 7.34(1H, s), 7.49(2H, t, J = 7.2Hz), 7.53-7.69(4H, m), 7.79(1H, brs), 7.85(2H, d, J = 7.2Hz), 7.90(1H, d, J = 7.9Hz), 7.96(1H, d, J = 8.8Hz), 7.99-8.04(2H, m), 8.67(1H, s), 10.98(1H, brs).

MS: 558(M+H) $^+$ .

Example 577 Synthesis of N, N-diethyl-N'-(2-naphthylsulfonyl)-2-{3-[(2-pyridylcarbonyl)amino]benzyl}malonamide

55

**[1204]** The compound (150 mg) obtained in Example 115 and picolinic acid chloride hydrochloride (67 mg) were subjected to the same manner as in Example 9 to give the reaction mixture. The reaction mixture was adjusted to pH = 1-2 by the addition of dilute hydrochloric acid and extracted with ethyl acetate (50 mL $\times$ 2). After concentration under

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reduced pressure, and the residue was purified by silica gel column chromatography to give the title compound (84 mg) as a white powder.

<sup>1</sup>H-NMR(400MHz, CDCl<sub>3</sub>)δ0.81(3H, t, J = 7.2Hz), 0.99(3H, t, J = 7.1Hz), 2.78-2.97(2H, m), 3.01-3.21(3H, m), 3.42-3.53(1H, m), 3.63(1H, dd, J = 10.2, 5.1Hz), 6.80(1H, d, J = 7.8Hz), 7.13(1H, t, J = 7.8Hz), 7.46-7.51(2H, m), 7.58-7.69(3H, m), 7.88-7.94(2H, m), 7.97(1H, d, J = 8.8Hz), 8.00-8.05(2H, m), 8.27(1H, d, J = 7.8Hz), 8.61(1H, d, J = 4.6Hz), 8.68(1H, s), 9.95(1H, brs), 10.94(1H, brs).

MS: 559(M+H)<sup>+</sup>.

Example 578 Synthesis of 2-{3-[(2-amino-5-fluorobenzoyl)amino]benzyl}-N,N-diethyl-N'-(2-naphthylsulfonyl)malonamide

**[1205]** In the same manner as in Example 1 (4), a crude product was obtained using the compound (300 mg) obtained in Example 115 and 5-fluoroanthranilic acid (100 mg). This was purified by silica gel column chromatography to give the title compound (160 mg) as a white solid.

<sup>1</sup>H-NMR(400MHz, CDCl<sub>3</sub>)δ0.86(3H, t, J = 7.2Hz), 1.02(3H, t, J = 7.1Hz), 2.85-3.20(5H, m), 3.42-3.53(1H, m), 3.60(1H, dd, J = 9.5, 5.6Hz), 6.69(1H, dd, J = 8.9, 4.6Hz), 6.81(1H, d, J = 7.9Hz), 7.02(1H, ddd, J = 8.9, 7.8, 2.8Hz), 7.13(1H, t, J = 7.9Hz), 7.16(1H, dd, J = 9.2, 2.8Hz), 7.33(1H, s), 7.46(1H, d, J = 7.9Hz), 7.58-7.69(2H, m), 7.75(1H, brs), 7.90(1H, d, J = 8.0Hz), 7.96(1H, d, J = 8.8Hz), 7.98-8.04(2H, m), 8.67(1H, s).

MS: 591(M+H)<sup>+</sup>.

Example 579 Synthesis of 2-{3-[(2-amino-6-fluorobenzoyl)amino]benzyl}-N,N-diethyl-N'-(2-naphthylsulfonyl)malonamide

**[1206]** In the same manner as in Example 1 (4), a crude product was obtained using the compound (250 mg) obtained in Example 115 and 6-fluoroanthranilic acid (86 mg). This was purified by silica gel column chromatography to give the title compound (64 mg) as an oil.

<sup>1</sup>H-NMR(400MHz, CDCl<sub>3</sub>)δ0.81(3H, t, J = 7.2Hz), 1.01(3H, t, J = 7.1Hz), 2.78-2.97(2H, m), 2.98-3.20(3H, m), 3.42-3.55(1H, m), 3.61(1H, dd, J = 10.0, 5.0Hz), 5.95(2H, brs), 6.40(1H, dd, J = 13, 8.1Hz), 6.48(1H, d, J = 8.3Hz), 6.81(1H, d, J = 7.6Hz), 7.07-7.19(2H, m), 7.36(1H, s), 7.42(1H, d, J = 8.2Hz), 7.58-7.68(2H, m), 7.90(1H, d, J = 7.8Hz), 7.96(1H, d, J = 8.7Hz), 7.99-8.05(2H, m), 8.23(1H, d, J = 17Hz), 8.67(1H, s), 10.95(1H, brs).

MS: 591(M+H)<sup>+</sup>.

Example 580 Synthesis of 2-[4-(benzoylamino)phenethyl]-N,N-diethyl-N'-(2-naphthylsulfonyl)malonamide

**[1207]** In the same manner as in Example 9, a crude product was obtained using the compound (200 mg) obtained in Example 145. This was purified by silica gel column chromatography to give the title compound (180 mg) as a white solid.

<sup>1</sup>H-NMR(400MHz, CDCl<sub>3</sub>)δ0.94(3H, t, J = 7.2Hz), 1.09(3H, t, J = 7.1Hz), 1.97-2.08(1H, m), 2.08-2.19(1H, m), 2.44-2.58(2H, m), 2.94-3.13(2H, m), 3.20-3.30(1H, m), 3.35(1H, dd, J = 8.3, 6.2Hz), 3.39-3.50(1H, m), 7.06(2H, d, J = 8.4Hz), 7.46-7.53(4H, m), 7.56(1H, t, J = 7.3Hz), 7.59-7.69(2H, m), 7.74(1H, brs), 7.86(2H, d, J = 7.0Hz), 7.91(1H, d, J = 8.0Hz), 7.96(1H, d, J = 9.2Hz), 7.99-8.05(2H, m), 8.68(1H, s), 10.94(1H, brs).

MS: 572(M+H)<sup>+</sup>.

Example 581 Synthesis of N,N-diethyl-N'-(2-naphthylsulfonyl)-2-{4-[(2-pyridylcarbonyl)amino]phenethyl}malonamide

**[1208]** In the same manner as in Example 577, the title compound (89 mg) was obtained as an oil using the compound (200 mg) obtained in Example 145.

<sup>1</sup>H-NMR(400MHz, CDCl<sub>3</sub>)δ0.93(3H, t, J = 7.2Hz), 1.09(3H, t, J = 7.1Hz), 1.97-2.09(1H, m), 2.09-2.20(1H, m), 2.44-2.58(2H, m), 2.90-3.10(2H, m), 3.18-3.30(1H, m), 3.35(1H, dd, J = 8.3, 6.2Hz), 3.38-3.50(1H, m), 7.07(2H, d, J = 8.4Hz), 7.48(1H, ddd, J = 7.5, 4.7, 1.1Hz), 7.59-7.69(4H, m), 7.88-7.93(2H, m), 7.96(1H, d, J = 8.8Hz), 8.00-8.04(2H, m), 8.28(1H, d, J = 7.8Hz), 8.61(1H, d, J = 4.4Hz), 8.68(1H, s), 9.96(1H, brs), 10.94 (1H, brs).

MS: 573 (M+H)<sup>+</sup>.

Example 582 Synthesis of 2-{4-[(2-amino-5-fluorobenzoyl)amino]phenethyl}-N,N-diethyl-N'-(2-naphthylsulfonyl)malonamide

**[1209]** In the same manner as in Example 578, the title compound (91 mg) was obtained as a white solid using the compound (250 mg) obtained in Example 145.

<sup>1</sup>H-NMR(400MHz, CDCl<sub>3</sub>)δ0.95(3H, t, J=7.1Hz), 1.10(3H, t, J = 7.1Hz), 1.95-2.20(2H, m), 2.45-2.58(2H, m),

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2.95-3.15(2H, m), 3.20-3.32(1H, m), 3.36(1H, dd, J = 8.2, 6.3Hz), 3.40-3.50(1H, m), 6.69(1H, dd, J = 8.8, 4.5Hz), 6.99-7.10(3H, m), 7.17(1H, dd, J = 9.2, 2.7Hz), 7.42(2H, d, J = 8.1Hz), 7.59-7.73(3H, m), 7.91(1H, d, J = 8.2Hz), 7.96(1H, d, J = 8.7Hz), 8.00-8.06(2H, m), 8.68(1H, s).  
MS: 605(M+H)<sup>+</sup>.

5

Example 583 Synthesis of 2-{4-[(2-amino-6-fluorobenzoyl)amino]phenethyl}-N,N-diethyl-N'-(2-naphthylsulfonyl)malonamide

**[1210]** In the same manner as in Example 579, the title compound (170 mg) was obtained as a white solid using the compound (250 mg) obtained in Example 145.

<sup>1</sup>H-NMR(400MHz, CDCl<sub>3</sub>)δ0.95(3H, t, J = 7.2Hz), 1.09(3H, t, J = 7.1Hz), 1.95-2.18(2H, m), 2.43-2.57(2H, m), 2.93-3.14(2H, m), 3.20-3.30(1H, m), 3.35(1H, dd, J = 8.3, 6.3Hz), 3.39-3.50(1H, m), 5.95(2H, brs), 6.40(1H, dd, J = 13, 8.2Hz), 6.48(1H, d, J = 8.2Hz), 7.04(2H, d, J = 8.4Hz), 7.13(1H, td, J = 8.2, 6.5Hz), 7.44(2H, d, J = 8.4Hz), 7.59-7.69(2H, m), 7.91(1H, d, J = 7.9Hz), 7.96(1H, d, J = 8.8Hz), 8.00-8.04(2H, m), 8.25(1H, d, J = 17H), 8.68(1H, s), 10.92(1H, brs).  
MS: 605(M+H)<sup>+</sup>.

15

Example 584 Synthesis of 2-{3-[4-(benzoylamino)phenyl]propyl}-N,N-diethyl-N'-(2-naphthylsulfonyl)malonamide

**[1211]** In the same manner as in Example 9, a crude product was obtained using the compound (200 mg) obtained in Example 147. This was purified by silica gel column chromatography to give the title compound (160 mg) as a white solid.

<sup>1</sup>H-NMR(400MHz, CDCl<sub>3</sub>)δ1.05(3H, t, J = 7.2Hz), 1.09(3H, t, J = 7.1Hz), 1.44-1.55(2H, m), 1.76-1.85(2H, m), 2.41-2.57(2H, m), 3.19(2H, q, J = 7.2Hz), 3.23-3.48(3H, m), 6.98(2H, d, J = 8.4Hz), 7.44-7.69(7H, m), 7.73(1H, brs), 7.87(2H, d, J = 7.0Hz), 7.91(1H, d, J = 8.1Hz), 7.94(1H, d, J = 8.8Hz), 7.96-8.04(2H, m), 8.68(1H, s), 10.83(1H, brs).  
MS: 586(M+H)<sup>+</sup>.

25

Example 585 Synthesis of N,N-diethyl-N'-(2-naphthylsulfonyl)-2-{3-[4-((2-pyridylcarbonyl)amino)phenyl]propyl}malonamide

**[1212]** In the same manner as in Example 577, the title compound (180 mg) was obtained as an oil using the compound (200 mg) obtained in Example 147.

<sup>1</sup>H-NMR(400MHz, CDCl<sub>3</sub>)δ1.05(3H, t, J = 7.3Hz), 1.09(3H, t, J = 7.2Hz), 1.43-1.54(2H, m), 1.76-1.87(2H, m), 2.40-2.57(2H, m), 3.18(2H, q, J = 7.2Hz), 3.23-3.33(1H, m), 3.35(1H, t, J = 7.4Hz), 3.37-3.48(1H, m), 6.99(2H, d, J = 8.4Hz), 7.49(1H, ddd, J = 7.7, 4.8, 1.1Hz), 7.57-7.70(4H, m), 7.89-8.03(5H, m), 8.30(1H, d, J = 7.7Hz), 8.63(1H, d, J = 4.8Hz), 8.66(1H, s), 9.96(1H, brs), 10.88(1H, brs).  
MS: 587(M+H)<sup>+</sup>.

35

Example 586 Synthesis of 2-{3-[4-((2-amino-5-fluorobenzoyl)amino)phenyl]propyl}-N,N-diethyl-N'-(2-naphthylsulfonyl)malonamide

**[1213]** In the same manner as in Example 578, the title compound (210 mg) was obtained as a white solid using the compound (200 mg) obtained in Example 147.

<sup>1</sup>H-NMR(400MHz, CDCl<sub>3</sub>)δ1.06(3H, t, J = 7.1Hz), 1.09(3H, t, J = 7.2Hz), 1.43-1.54(2H, m), 1.76-1.85(2H, m), 2.40-2.58(2H, m), 3.20(2H, q, J = 7.1Hz), 3.23-3.48(3H, m), 6.69(1H, dd, J = 8.9, 4.6Hz), 6.97(2H, d, J = 8.4Hz), 7.02(1H, ddd, J = 8.9, 7.9, 2.9Hz), 7.19(1H, dd, J = 9.1, 2.9Hz), 7.38(2H, d, J = 8.4Hz), 7.59-7.72(3H, m), 7.92(1H, d, J = 8.1Hz), 7.95(1H, d, J = 8.8Hz), 7.97-8.04(2H, m), 8.66(1H, s).  
MS: 619(M+H)<sup>+</sup>.

45

Example 587 Synthesis of 2-{3-[4-((2-amino-6-fluorobenzoyl)amino)phenyl]propyl}-N,N-diethyl-N'-(2-naphthylsulfonyl)malonamide

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**[1214]** In the same manner as in Example 579, the title compound (130 mg) was obtained as a white solid using the compound (200 mg) obtained in Example 147.

<sup>1</sup>H-NMR(400MHz, CDCl<sub>3</sub>)δ1.05(3H, t, J = 7.1Hz), 1.09(3H, t, J = 7.2Hz), 1.40-1.53(2H, m), 1.76-1.87(2H, m), 2.40-2.56(2H, m), 3.19(2H, q, J = 7.1Hz), 3.23-3.50(3H, m), 5.96(2H, brs), 6.42(1H, dd, J = 13, 8.2Hz), 6.49(1H, d, J = 8.2Hz), 6.96(2H, d, J = 8.2Hz), 7.14(1H, td, J = 8.2, 6.9Hz), 7.39(2H, d, J = 8.2Hz), 7.60-7.70(2H, m), 7.91(1H, d, J = 8.0Hz), 7.94(1H, d, J = 8.9Hz), 7.97-8.05(2H, m), 8.24(1H, d, J = 17H), 8.66(1H, s), 10.84(1H, brs).  
MS: 619(M+H)<sup>+</sup>.

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Example 588 Synthesis of 2-[4-(benzoylamino)benzyl]-N'-cyclohexylsulfonyl-N, N-diethylmalonamide

(1) cyclohexanesulfonamide

5 **[1215]** To a suspension of cyclohexanesulfonic acid sodium salt (2.5 g) in DMF (15 mL) was added thionyl chloride (1.96 mL) under ice-cooling, and the mixture was stirred at room temperature for 29 hr. The reaction mixture was added to a mixture of ice-cooled water (100 mL) and toluene (100 mL), and the mixture was extracted. The organic layer was concentrated under reduced pressure. THF (50 mL) was added to the residue, 28% aqueous ammonia (10 mL) was added dropwise to the solution under ice-cooling, and the mixture was stirred at room temperature for 17 hr. After concentration under reduced pressure, water (100 mL) and ethyl acetate (100 mL) were added to extract the residue. The organic layer was concentrated under reduced pressure to give the title compound (760 mg) as a white solid. <sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ1.04-1.37(5H, m), 1.61-1.64(1H, m), 1.77-1.80(2H, m), 2.04-2.07(2H, m), 2.70-2.77(1H, m), 6.62(2H, brs).

15 (2) N'-cyclohexylsulfonyl-N, N-diethyl-2-(4-nitrobenzyl)malonamide

**[1216]** To a suspension of the compound (1.37 g) obtained in Example 188 (2) in methylene chloride (50 mL) were added oxalyl chloride (800 μL) and DMF in catalytic amount under ice-cooling, and the mixture was stirred at room temperature for 1.5 hr. After concentration under reduced pressure, methylene chloride (8 mL) was added to the residue. Under ice-cooling, the solution was added dropwise to a mixture of the above-mentioned compound (760 mg) in THF (50 mL) and 4-dimethylaminopyridine (1.71 g). After stirring at room temperature for 17 hr, dilute hydrochloric acid (100 mL) was added, and the mixture was extracted with ethyl acetate (100 mL×2). The organic layer was concentrated under reduced pressure, and the residue was purified by silica gel chromatography to give the title compound (1.67 g) as a white solid. <sup>1</sup>H-NMR(300Mz, DMSO-d<sub>6</sub>)δ0.94-1.98(17H, m), 3.17-3.33(6H, m), 4.06(1H, t, J = 7.5H), 7.54(2H, d, J = 9.0Hz), 8.18(2H, d, J = 9.0Hz), 11.76(1H, brs).

(3) 2-[4-(benzoylamino)benzyl]-N'-cyclohexylsulfonyl-N, N-diethylmalonamide

30 **[1217]** To a mixed solution of the above-mentioned compound (1.67 g) in THF (50 mL) and triethylamine (1.06 mL) was added 10% palladium carbon (500 mg) under nitrogen atmosphere, and the mixture was stirred under hydrogen atmosphere at room temperature for 4 hr. Insoluble material was removed by filtration, benzoyl chloride (465 μL) was added to the filtrate under ice-cooling, and the mixture was stirred at room temperature for 15 hr. The reaction mixture was adjusted to pH = 1-2 by the addition of dilute hydrochloric acid, and extracted with ethyl acetate (100 mL×2). The organic layer was concentrated under reduced pressure, and the residue was purified by silica gel chromatography to give the title compound (617 mg) as a white solid. <sup>1</sup>H-NMR(400Mz, DMSO-d<sub>6</sub>)δ0.97-1.35(12H, m), 1.54-1.61(2H, m), 1.67-1.81(2H, m), 1.94-2.00(1H, m), 2.96(1H, dd, J = 13.6, 6.4Hz), 3.08(1H, dd, J = 13.6, 8.3Hz), 3.19-3.28(4H, m), 3.94-4.02(1H, m), 7.20(2H, d, J = 8.5Hz), 7.51-7.61(3H, m), 7.69(2H, d, J = 8.5H), 7.92(1H, d, J = 1.3H), 7.94(1H, s), 10.21(1H, s), 11.64(1H, s). MS:514(M+H)<sup>+</sup>.

**[1218]** The structures of the aforementioned Example compounds are shown in the following Tables 1 to 4.

[Table 1]

Table 1				
Example	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>
1			H	

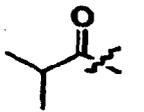
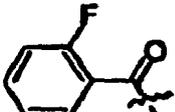
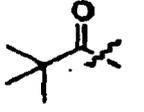
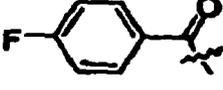
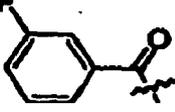
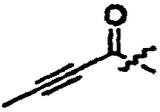
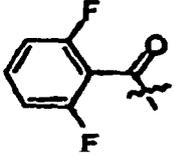
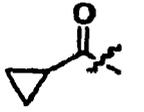
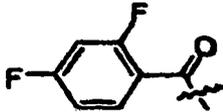
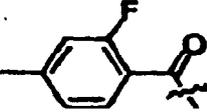
(continued)

Example	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>
2	↑	↑	↑	
3	↑	↑	↑	
4	↑	↑	↑	
5	↑	↑	↑	
6	↑		↑	
7	↑		↑	↑
8	↑		↑	↑

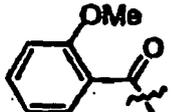
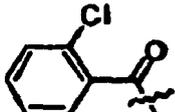
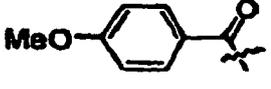
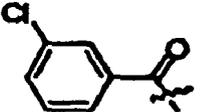
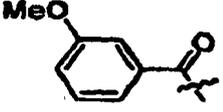
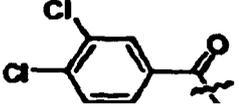
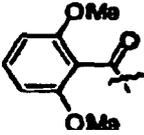
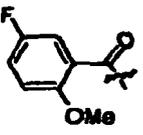
[Table 2-1]

Table 2			
Example	Q <sup>1</sup>	Example	Q <sup>1</sup>
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10	Ac	18	

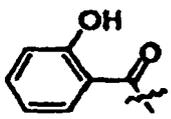
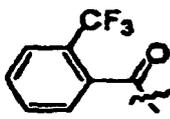
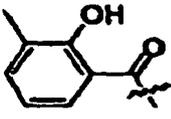
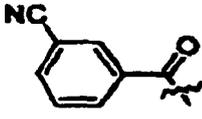
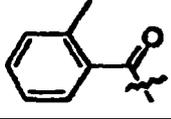
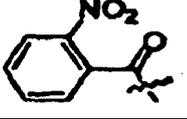
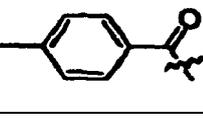
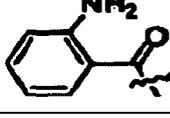
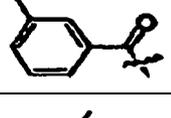
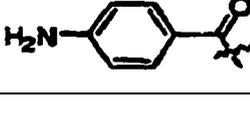
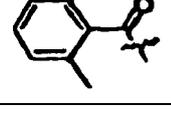
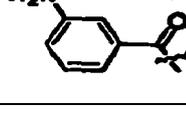
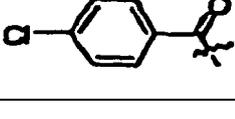
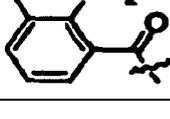
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Example	Q <sup>1</sup>	Example	Q <sup>1</sup>
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12		20	
13		21	
14		22	
15		23	
16		24	

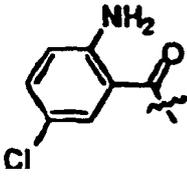
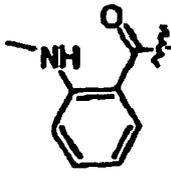
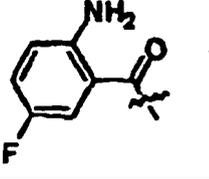
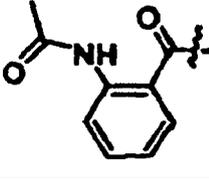
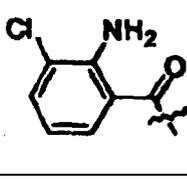
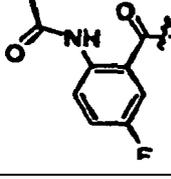
[Table 2-2]

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26		37	
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28		39	

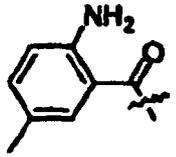
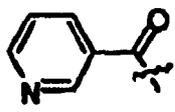
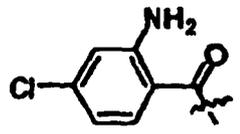
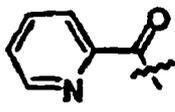
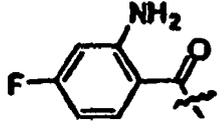
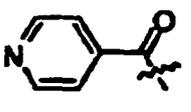
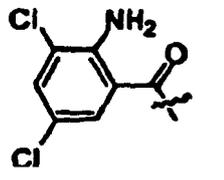
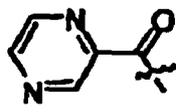
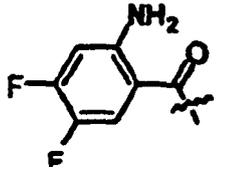
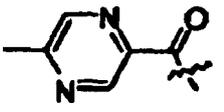
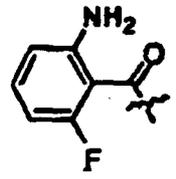
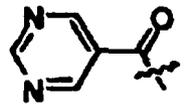
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29		40	
30		41	
31		42	
32		43	
33		44	
34		45	
35		46	

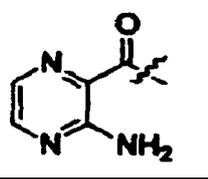
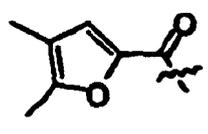
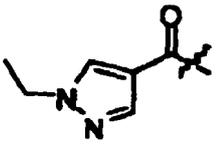
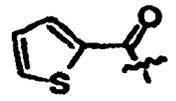
[Table 2-3]

47		56	
48		57	
49		58	

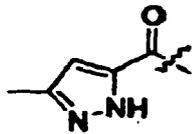
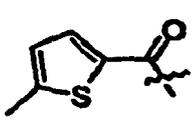
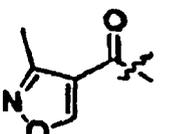
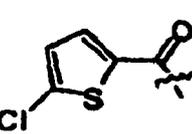
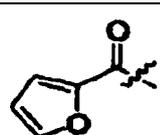
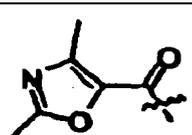
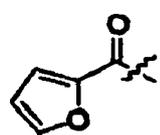
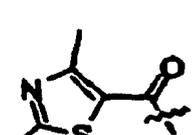
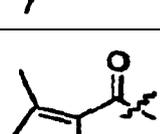
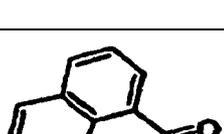
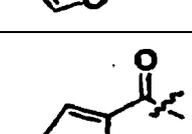
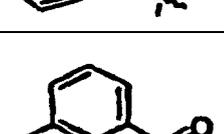
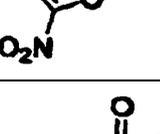
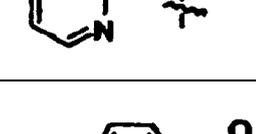
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50		59	HCl 
51		60	HCl 
52		61	HCl 
53		62	
54		63	
55		64	

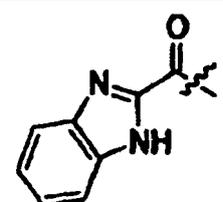
[Table 2-4]

65		74	
66		75	

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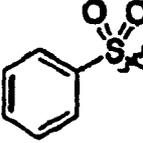
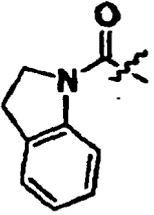
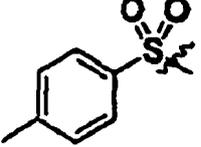
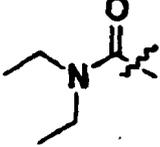
67		76	
68		77	
69		78	
70		79	
71		80	
72		81	
73		82	

[Table 2-5]

83		87	PhOCO
84		88	PhNHCO

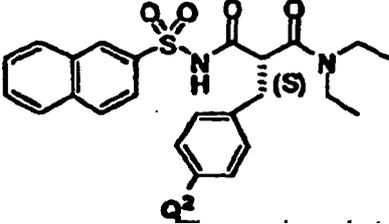
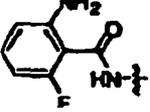
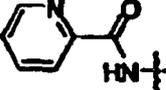
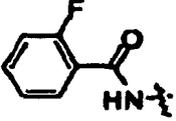
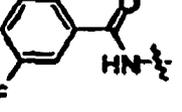
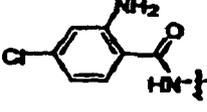
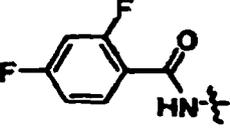
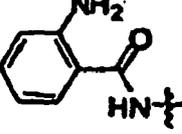
(continued)

Table 2 (-continue)

85		89	
86		90	

[Table 3]

Table 3

			
Example	Q <sup>2</sup>	Example	Q <sup>2</sup>
91	NO <sub>2</sub>	100	
92	PhCONH	101	
93		102	NH <sub>2</sub>
94		103	
95		104	

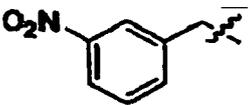
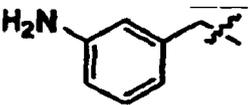
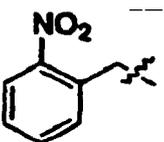
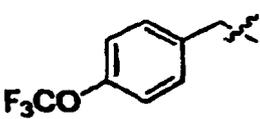
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Example	Q <sup>2</sup>	Example	Q <sup>2</sup>
96		105	
97		106	
98		107	
99		108	

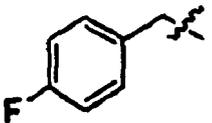
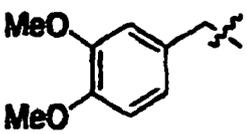
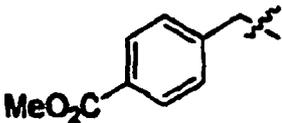
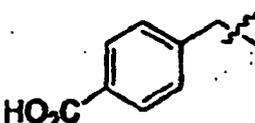
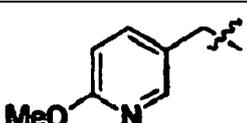
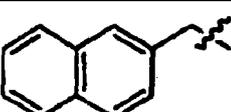
[Table 4-1]

Table 4				
↑ : same substituent as above				
Example	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>
109			H	
110	↑		↑	↑
111	↑		↑	↑
112	↑		↑	↑
113	↑		↑	↑

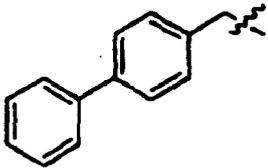
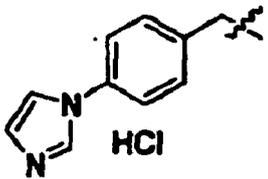
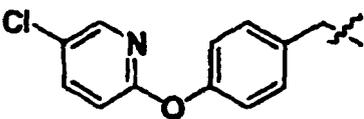
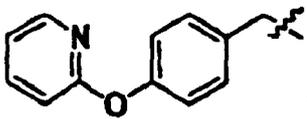
(continued)

Example	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>
			↑ :	same substituent as above
114	↑		↑	↑
115	↑		↑	↑
116	↑		↑	↑
117	↑		↑	↑

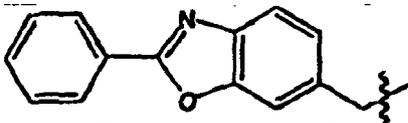
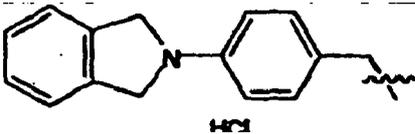
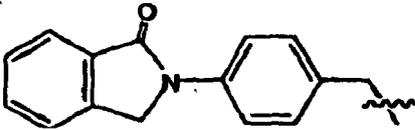
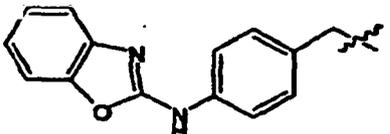
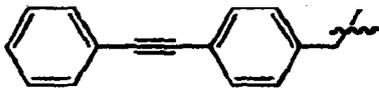
[Table 4-2]

Table 4 (-continue)				
118	↑		↑	↑
119	↑		↑	↑
120	↑		↑	↑
121	↑		↑	↑
122	↑		↑	↑
123	↑		↑	↑

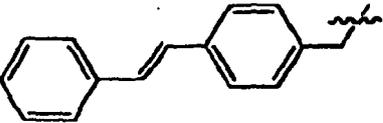
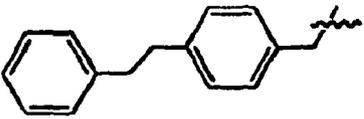
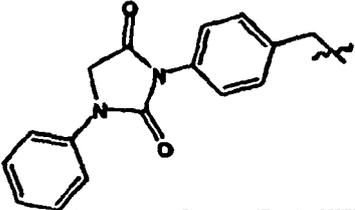
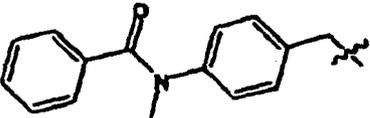
(continued)

Table 4 (-continue)				
124	↑		↑	↑
125	↑		↑	↑
126	↑		↑	↑
127	↑		↑	↑

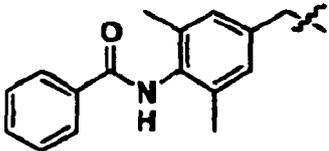
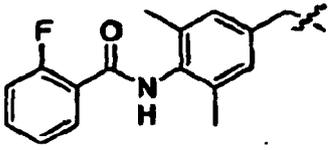
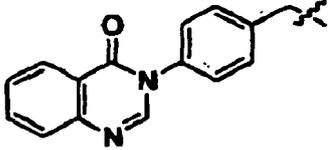
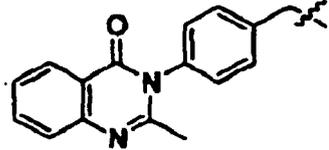
[Table 4-3]

Table 4 (-continue)				
128	↑		↑	↑
129	↑		↑	↑
130	↑		↑	↑
131	↑		↑	↑
132	↑		↑	↑

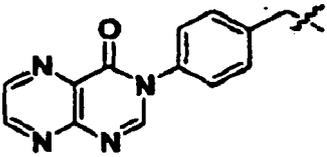
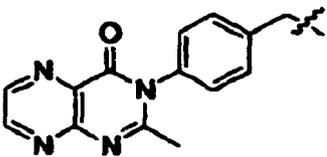
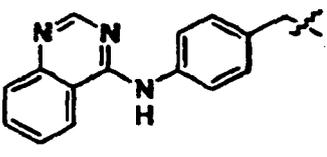
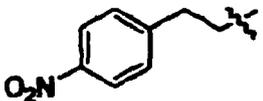
(continued)

Table 4 (-continue)					
5	133	↑		↑	↑
10	134	↑		↑	↑
15	135	↑		↑	↑
20	136	↑		↑	↑
25					

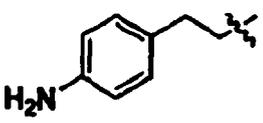
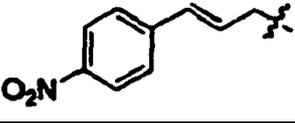
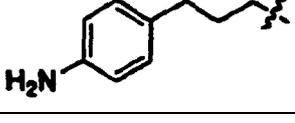
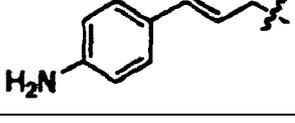
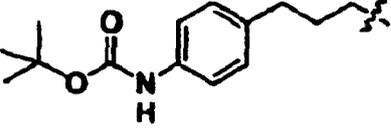
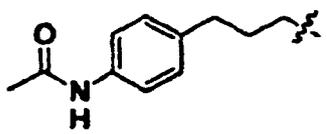
[Table 4-4]

Table 4 (-continue)					
30	137	↑		↑	↑
35	138	↑		↑	↑
40	139	↑		↑	↑
45	140	↑		↑	↑
50					
55					

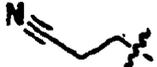
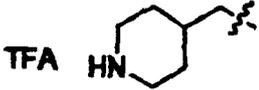
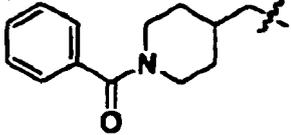
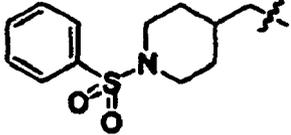
(continued)

5 141	↑		↑	↑
10 142	↑		↑	↑
15 143	↑		↑	↑
20 144	↑		↑	↑

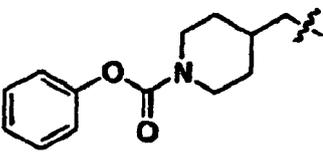
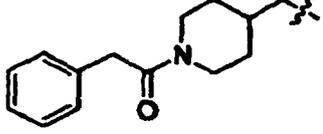
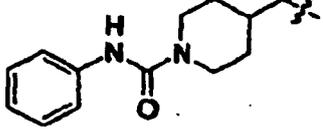
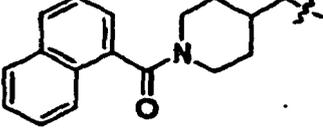
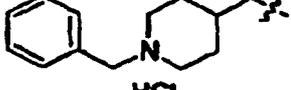
[Table 4-5]

30 145	↑		↑	↑
35 146	↑		↑	↑
40 147	↑		↑	↑
45 148	↑		↑	↑
50 149	↑		↑	↑
55 150	↑		↑	↑

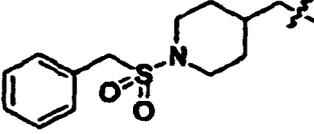
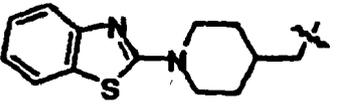
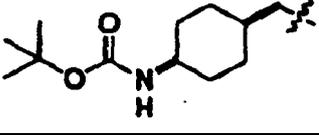
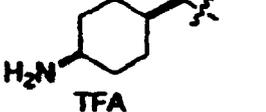
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Table 4 (-continue)					
5	151	↑		↑	↑
	152	↑		↑	↑
10	153	↑		↑	↑
15	154	↑	<b>TFA</b> 	↑	↑
20	155	↑		↑	↑
25	156	↑		↑	↑

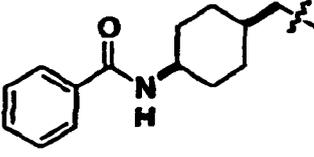
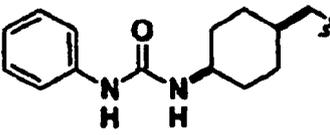
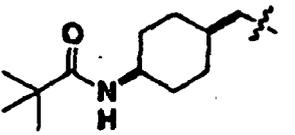
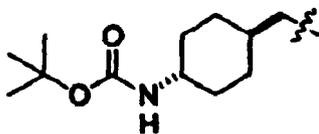
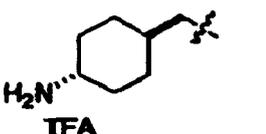
[Table 4-6]

Table 4 (-continue)					
30	157	↑		↑	↑
35	158	↑		↑	↑
40	159	↑		↑	↑
45	160	↑		↑	↑
50	161	↑	 <b>HCl</b>	↑	↑
55					

(continued)

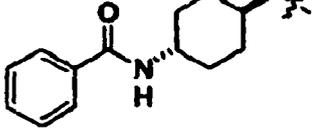
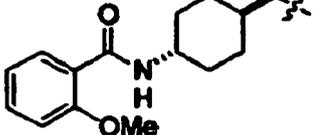
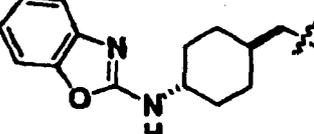
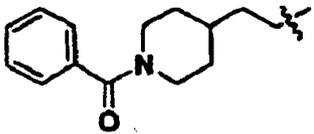
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5	162	↑		↑	↑
10	163	↑		↑	↑
15	164	↑		↑	↑
20	165	↑		↑	↑

[Table 4-7]

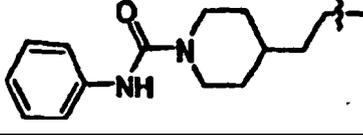
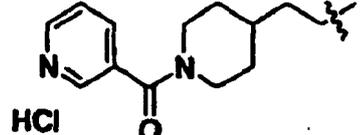
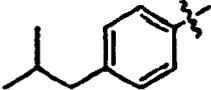
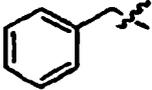
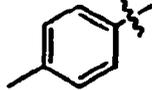
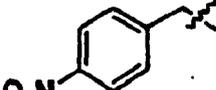
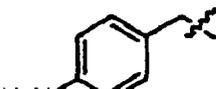
Table 4 (-continue)					
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35	167	↑		↑	↑
40	168	↑		↑	↑
45	169	↑		↑	↑
50	170	↑		↑	↑

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(continued)

Table 4 (-continue)					
5	171	↑		↑	↑
10	172	↑		↑	↑
15	173	↑		↑	↑
20	174	↑		↑	↑

[Table 4-8]

Table 4 (-continue)					
30	175	↑		↑	↑
35	176	↑		↑	↑
40	177			↑	↑
45	178			↑	↑
50	179	↑		↑	↑

25

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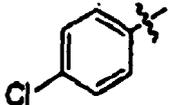
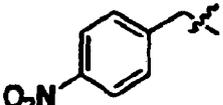
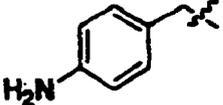
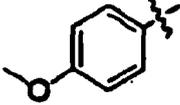
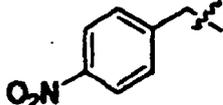
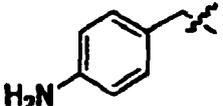
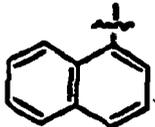
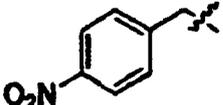
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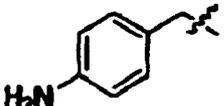
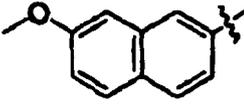
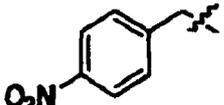
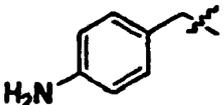
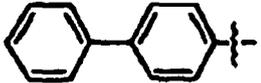
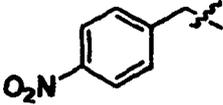
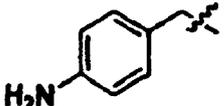
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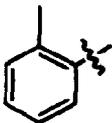
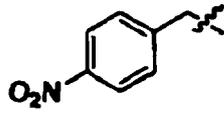
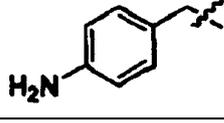
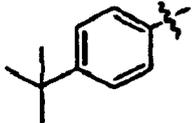
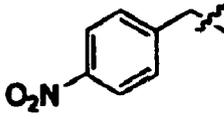
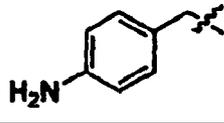
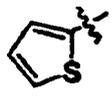
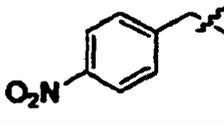
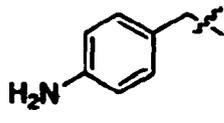
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15	182			↑	↑
20	183	↑		↑	↑
25	184			↑	↑

[Table 4-9]

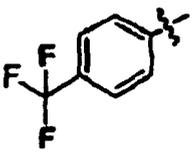
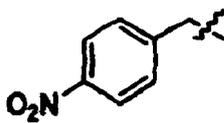
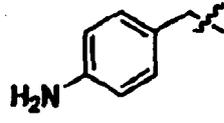
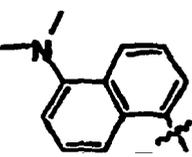
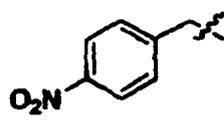
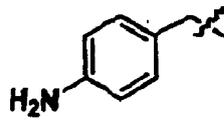
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40	187	↑		↑	↑
45	188			↑	↑
50	189	↑		↑	↑

55

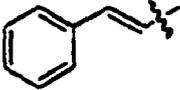
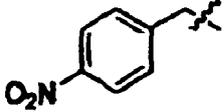
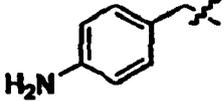
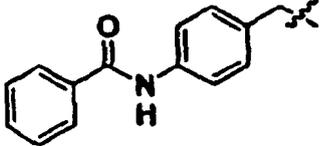
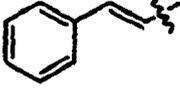
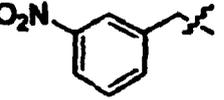
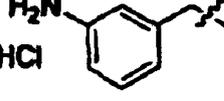
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5	190			↑	↑
10	191	↑		↑	↑
15	192			↑	↑
20	193	↑		↑	↑
25	194			↑	↑
30	195	↑		↑	↑

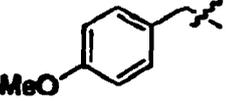
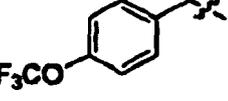
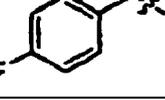
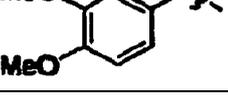
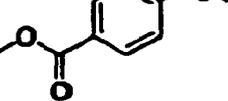
[Table 4-10]

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40	197	↑		↑	↑
45	198			↑	↑
50	199	↑		↑	↑
55					

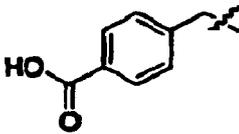
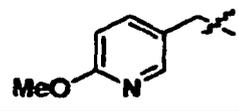
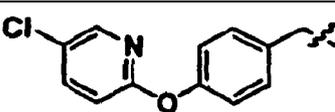
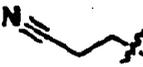
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200			↑	↑
201	↑		↑	↑
202	↑		↑	↑
203		↑	↑	↑
204			↑	↑
205	↑		↑	↑

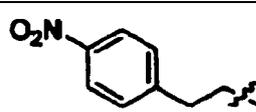
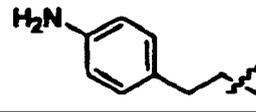
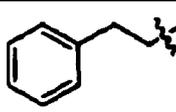
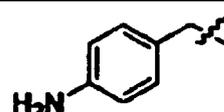
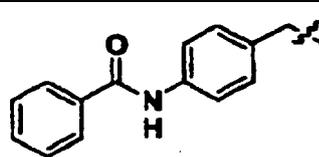
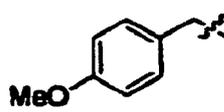
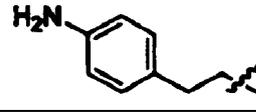
[Table 4-11]

206	↑		↑	↑
207	↑		↑	↑
208	↑		↑	↑
209	↑		↑	↑
210	↑		↑	↑

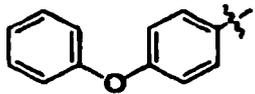
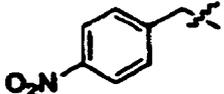
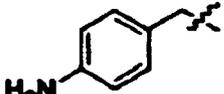
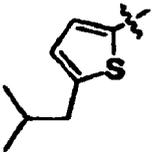
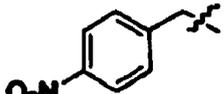
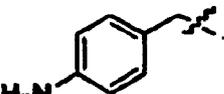
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Table 4 (-continue)				
211	↑		↑	↑
212	↑		↑	↑
213	↑		↑	↑
214	↑		↑	↑
215	↑		↑	↑
216	↑		↑	↑

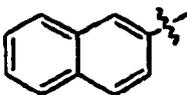
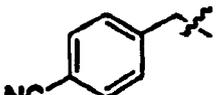
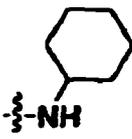
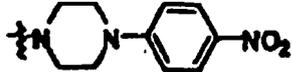
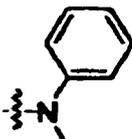
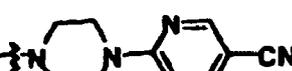
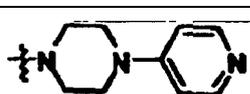
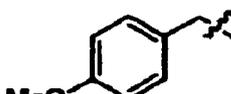
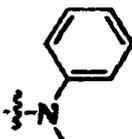
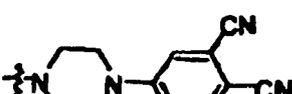
[Table 4-12]

Table 4 (-continue)				
217	↑		↑	↑
218	↑		↑	↑
219			↑	↑
220	↑		↑	↑
221	↑		↑	↑
222	↑		↑	↑

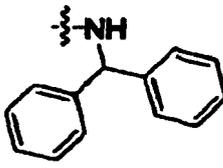
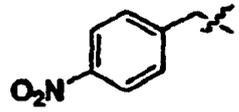
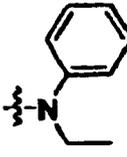
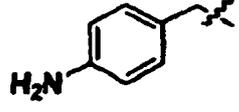
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223			↑	↑
224	↑		↑	↑
225			↑	↑
226	↑		↑	↑

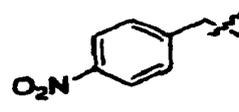
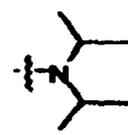
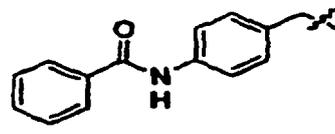
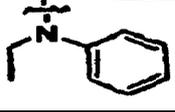
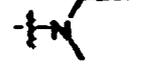
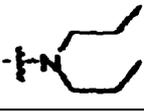
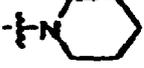
[Table 4-13]

227			↑	
228	↑	↑	↑	
229	↑	↑	↑	
230	↑	↑	↑	
231	↑	↑	↑	
232	↑		↑	
233	↑	↑	↑	

(continued)

Table 4 (-continue)				
234	↑	↑	↑	
235	↑		↑	
236	↑		↑	↑

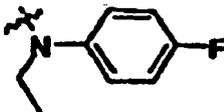
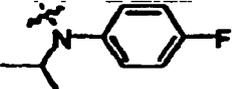
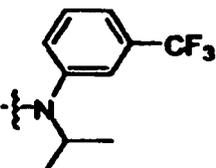
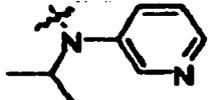
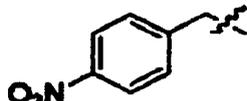
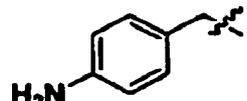
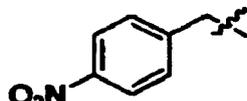
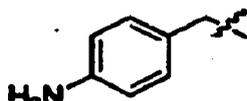
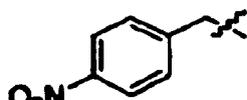
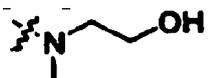
[Table 4-14]

Table 4 (-continue)				
237	↑			
238	↑		↑	↑
239	↑	↑		
240	↑	↑	↑	
241	↑	↑	↑	
242	↑	↑	↑	
243	↑	↑	↑	
244	↑	↑	↑	
245	↑	↑	↑	

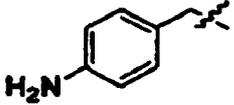
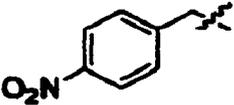
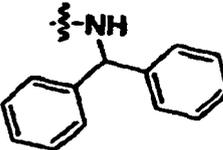
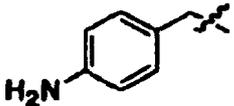
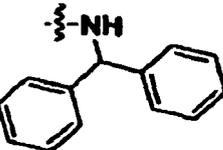
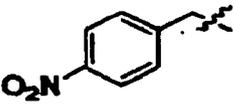
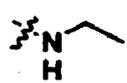
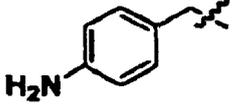
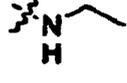
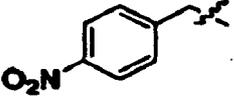
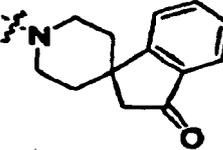
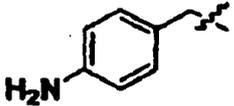
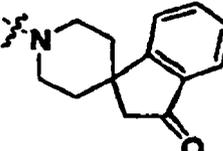
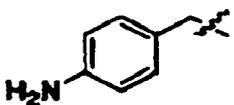
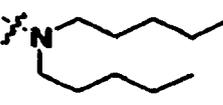
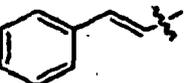
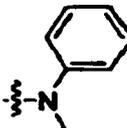
(continued)

Table 4 (-continue)				
246	↑	↑	↑	

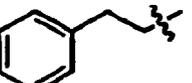
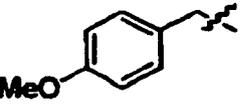
[Table 4-15]

Table 4 (-continue)				
247	↑	↑	↑	
248	↑	↑	↑	
249	↑	↑	↑	
250	↑	↑	↑	
251	↑	↑	↑	
252	↑		↑	
253	↑		↑	
254	↑		↑	
255	↑		↑	
256	↑		↑	

[Table 4-16]

Table 4 (-continue)				
5	257		↑	
10	258		↑	
15	259		↑	
20	260		↑	
25	261		↑	
30	262		↑	
35	263		↑	
40	264		↑	
45	265		↑	

[Table 4-17]

Table 4 (-continue)					
55	266			↑	↑

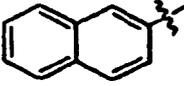
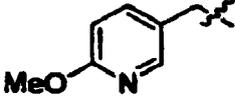
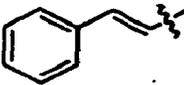
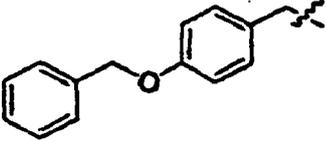
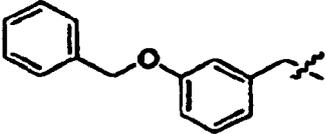
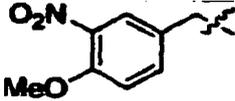
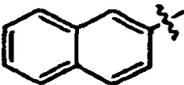
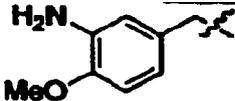
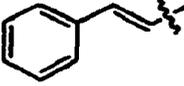
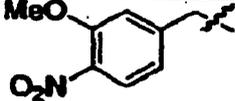
(continued)

Table 4 (-continue)					
5	267			↑	↑
	268	↑		↑	↑
10	269	↑		↑	↑
15	270			↑	↑
20	271			↑	↑
25	272			↑	↑
30	273			↑	↑
35	274			↑	↑
40	275			↑	↑
45	276	↑		↑	↑

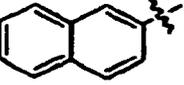
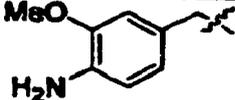
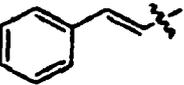
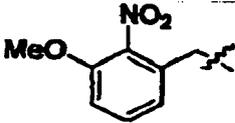
[Table 4-18]

Table 4 (-continue)					
50	277			↑	↑
55	278	↑		↑	↑

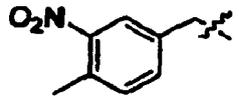
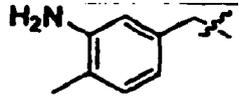
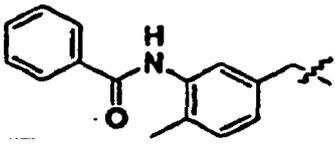
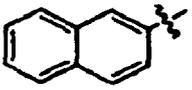
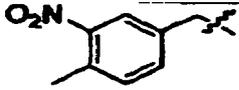
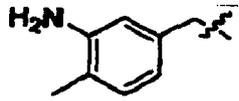
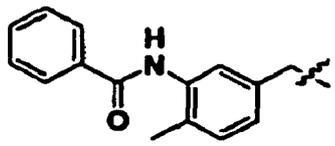
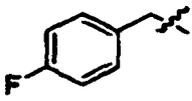
(continued)

Table 4 (-continue)					
5	279			↑	↑
10	280		↑	↑	↑
15	281	↑		↑	↑
20	282	↑		↑	↑
25	283	↑		↑	↑
30	284		↑	↑	↑
35	285	↑		↑	↑
40	286			↑	↑

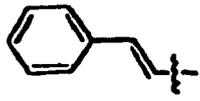
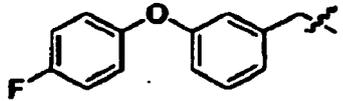
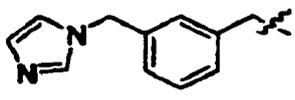
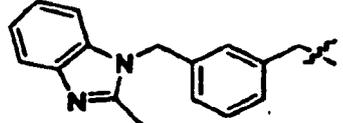
[Table 4-19]

Table 4 (-continue)					
45	287		↑	↑	↑
50	288	↑		↑	↑
55	289			↑	↑

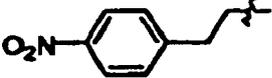
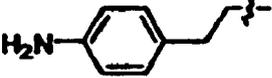
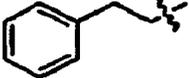
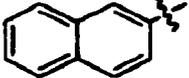
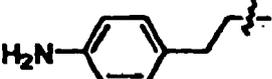
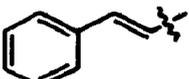
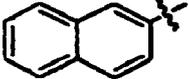
(continued)

Table 4 (-continue)					
5	290	↑		↑	↑
10	291	↑		↑	↑
15	292	↑		↑	↑
20	293			↑	↑
25	294	↑		↑	↑
30	295	↑		↑	↑
35	296	↑		↑	↑

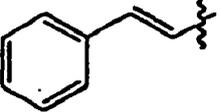
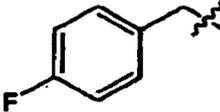
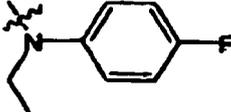
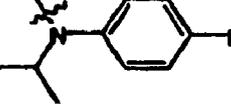
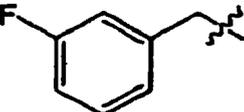
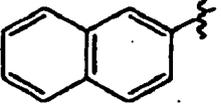
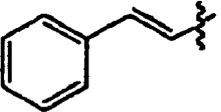
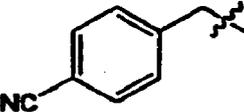
[Table 4-20]

Table 4 (-continue)					
40	297		↑	↑	↑
45	298	↑		↑	↑
50	299	↑		↑	↑
55	300	↑		↑	↑

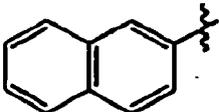
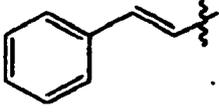
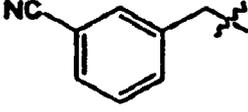
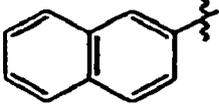
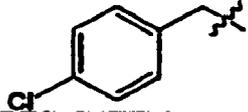
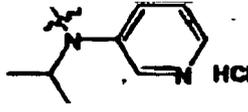
(continued)

Table 4 (-continue)					
5	301	↑		↑	↑
10	302	↑		↑	↑
15	303			↑	↑
20	304			↑	↑
25	305	↑		↑	↑
30	306			↑	↑
	307		↑	↑	↑

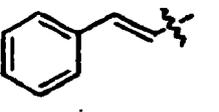
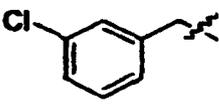
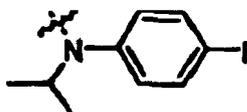
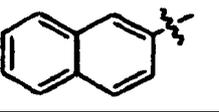
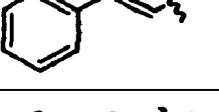
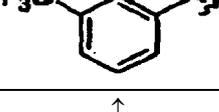
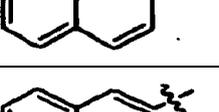
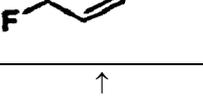
[Table 4-21]

Table 4 (-continue)					
35	308			↑	
40	309	↑	↑	↑	
45	310	↑		↑	↑
50	311		↑	↑	↑
55	312			↑	↑

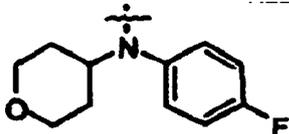
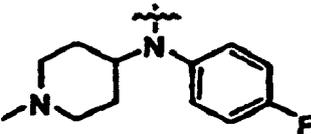
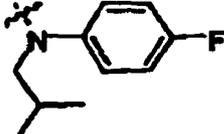
(continued)

5	313		↑	↑	↑
10	314			↑	↑
15	315		↑	↑	↑
20	316	↑		↑	↑
25	317	↑	↑	↑	

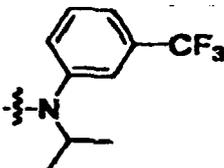
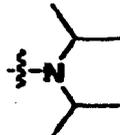
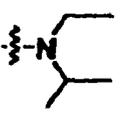
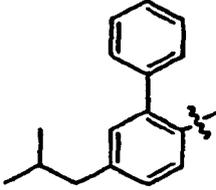
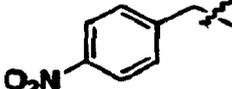
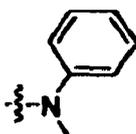
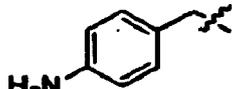
[Table 4-22]

30	318			↑	
35	319		↑	↑	↑
40	320			↑	↑
45	321		↑	↑	↑
50	322			↑	
55	323	↑	↑	↑	

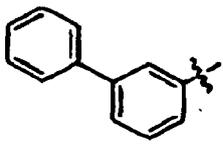
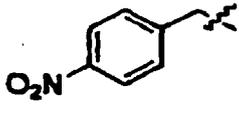
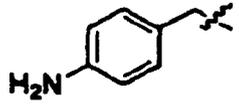
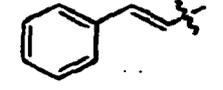
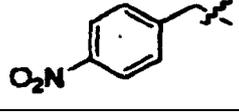
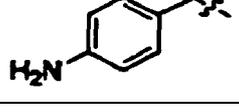
(continued)

Table 4 (-continue)					
5	324	↑	↑	↑	
10	325	↑	↑	↑	
15	326	↑	↑	↑	
20	327	↑	↑	↑	
25					

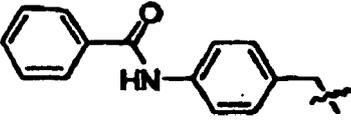
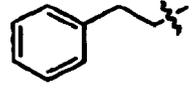
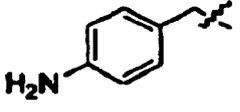
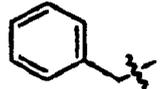
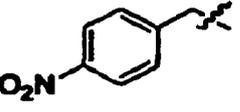
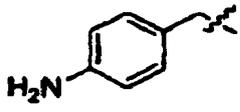
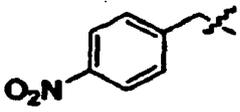
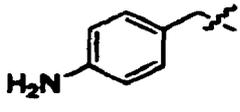
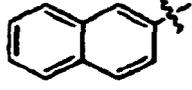
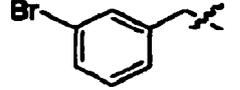
[Table 4-23]

Table 4 (-continue)					
30	328	↑	↑	↑	
35	329	↑	↑	↑	
40	330	↑	↑	↑	
45	331			↑	
50	332	↑		↑	↑
55					

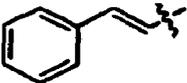
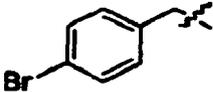
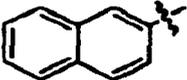
(continued)

Table 4 (-continue)					
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10	334	↑		↑	↑
15	335			↑	↑
20	336	↑		↑	↑

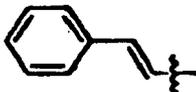
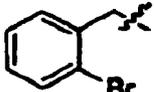
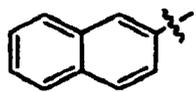
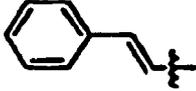
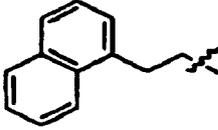
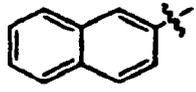
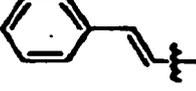
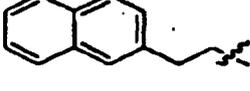
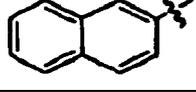
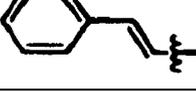
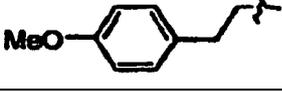
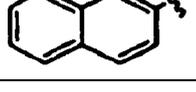
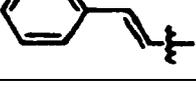
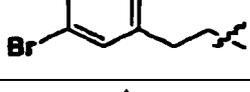
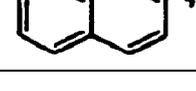
[Table 4-24]

Table 4 (-continue)					
25	337	↑		↑	↑
30	338			↑	↑
35	339			↑	↑
40	340	↑		↑	↑
45	341			↑	↑
50	342	↑		↑	↑
55	343			↑	↑

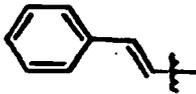
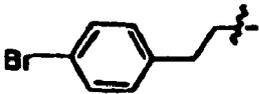
(continued)

Table 4 (-continue)				
5 344		↑	↑	↑
10 345	↑		↑	↑
15 346		↑	↑	↑

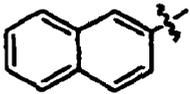
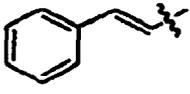
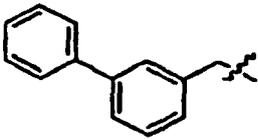
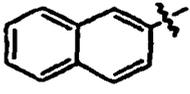
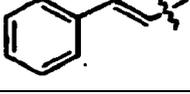
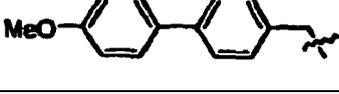
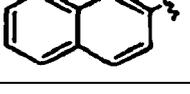
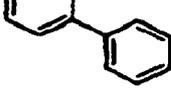
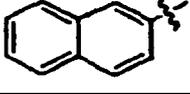
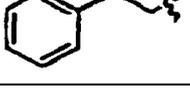
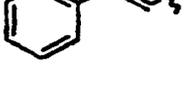
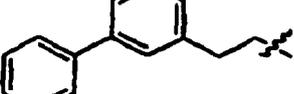
[Table 4-25]

Table 4 (-continue)				
20 347			↑	↑
25 348		↑	↑	↑
30 349			↑	↑
35 350		↑	↑	↑
40 351			↑	↑
45 352		↑	↑	↑
50 353			↑	↑
55 354		↑	↑	↑
355			↑	↑
356		↑	↑	↑

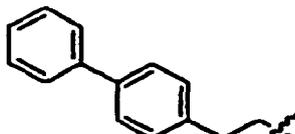
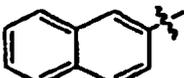
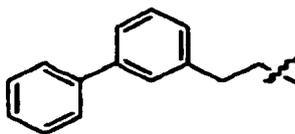
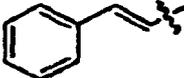
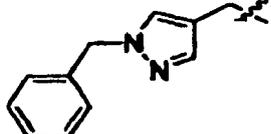
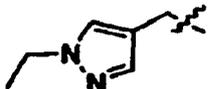
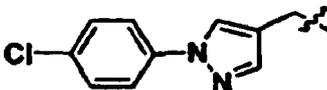
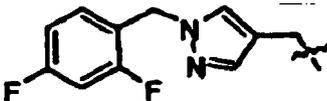
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Table 4 (-continue)				
5 357			↑	↑

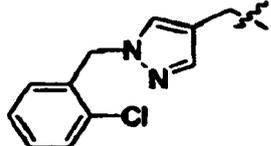
[Table 4-26]

Table 4 (-continue)				
15 358		↑	↑	↑
20 359			↑	↑
25 360		↑	↑	↑
30 361			↑	↑
35 362		↑	↑	↑
40 363		↑	↑	↑
45 364			↑	↑
50 365		↑	↑	↑
55 366		↑	↑	↑
367			↑	↑

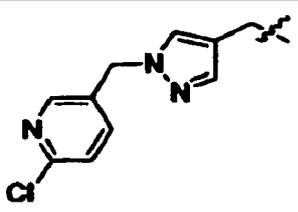
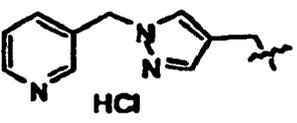
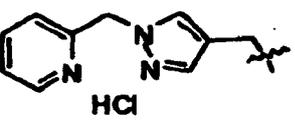
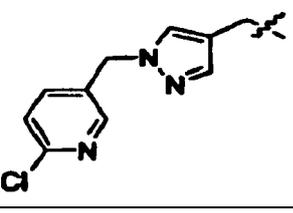
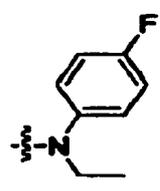
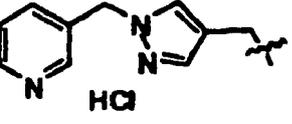
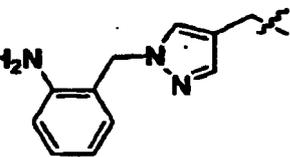
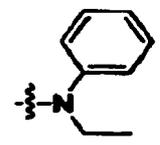
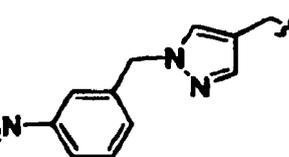
[Table 4-27]

Table 4 (-continue)					
5	368	↑		↑	↑
10	369		↑	↑	↑
15	370	↑		↑	↑
20	371			↑	↑
25	372	↑		↑	↑
30	373	↑		↑	↑
35	374	↑		↑	↑
40	375	↑		↑	↑
45	376	↑		↑	↑

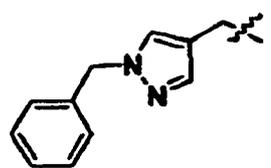
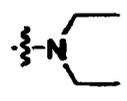
[Table 4-28]

Table 4 (-continue)					
50	377	↑		↑	↑

(continued)

Table 4 (-continue)				
378	↑		↑	↑
379	↑		↑	↑
380	↑		↑	↑
381	↑		↑	
382	↑		↑	↑
383	↑		↑	
384	↑		↑	↑

[Table 4-29]

Table 4 (-continue)				
385	↑		↑	

(continued)

Table 4 (-continue)				
5	↑		↑	↑
10	↑		↑	↑
15	↑		↑	↑
20			↑	↑
25	↑		↑	↑
30	↑		↑	↑
35	↑		↑	↑
40				

[Table 4-30]

Table 4 (-continue)				
45	↑		↑	↑
50			↑	
55	↑		↑	↑

(continued)

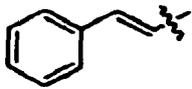
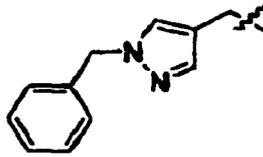
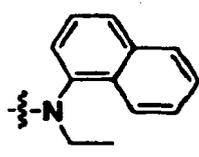
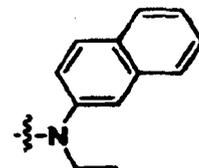
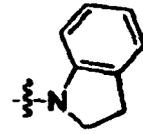
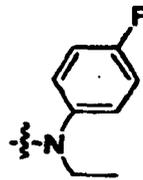
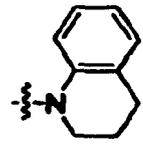
Table 4 (-continue)				
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15			↑	
20		↑	↑	↑
25		↑	↑	↑
30			↑	↑

[Table 4-31]

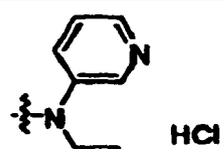
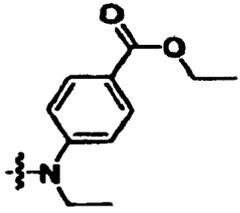
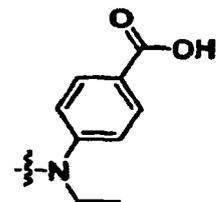
Table 4 (-continue)				
40			↑	↑
45		↑	↑	↑
50			↑	

55

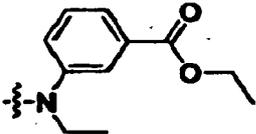
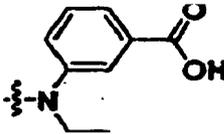
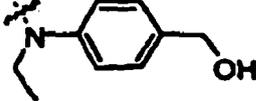
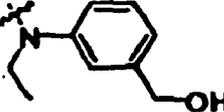
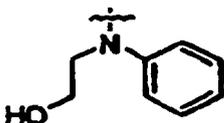
(continued)

5 405			↑	
10 406	↑	↑	↑	
15 407	↑	↑	↑	
20 408	↑	↑	↑	
25 409	↑	↑	↑	

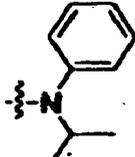
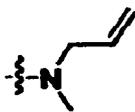
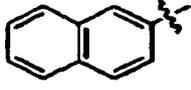
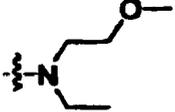
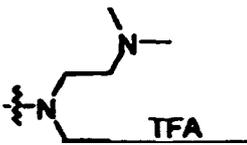
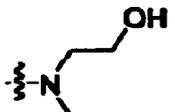
[Table 4-32]

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45 411	↑	↑	↑	
50 412	↑	↑	↑	

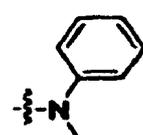
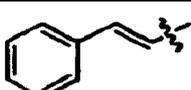
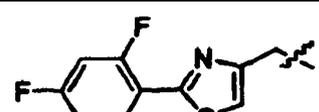
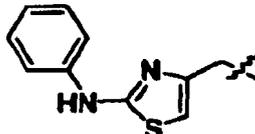
(continued)

5 413	↑	↑	↑	
10 414	↑	↑	↑	
15 415	↑	↑	↑	
20 416	↑	↑	↑	
25 417	↑	↑	↑	

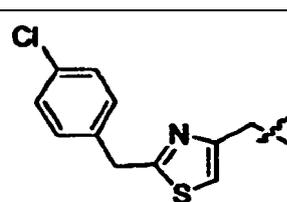
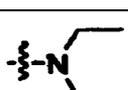
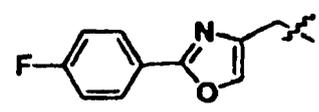
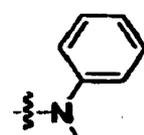
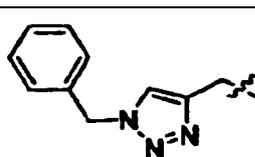
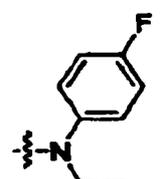
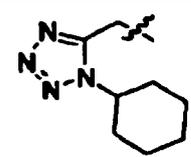
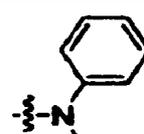
[Table 4-33]

35 418	↑	↑	↑	
40 419	↑	↑	↑	
45 420		↑	↑	
50 421	↑	↑	↑	 TFA
55 422	↑	↑	↑	

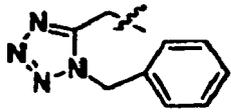
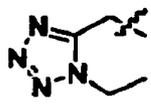
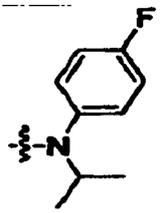
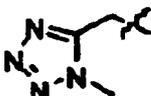
(continued)

Table 4 (-continue)					
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10	424	↑	↑	↑	
15	425			↑	↑
20	426	↑		↑	↑

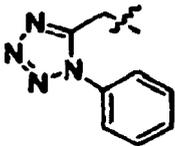
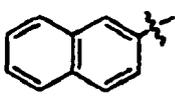
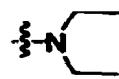
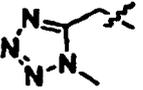
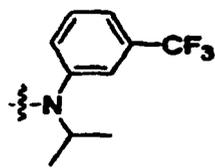
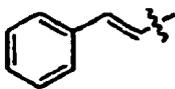
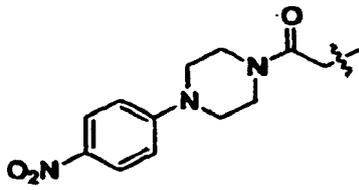
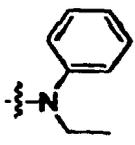
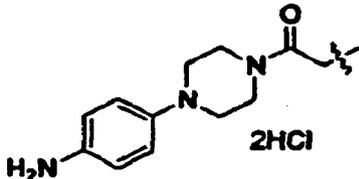
[Table 4-34]

Table 4 (-continue)					
25	427	↑		↑	
30	428	↑		↑	
35	429	↑		↑	↑
40	430	↑	↑	↑	
45	431	↑		↑	
50					
55					

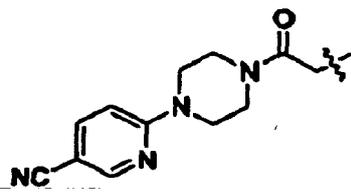
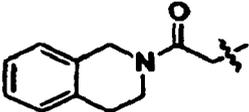
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Table 4 (-continue)				
432	↑		↑	↑
433	↑		↑	
434	↑		↑	↑

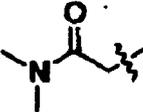
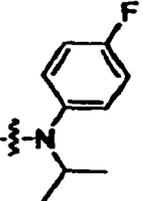
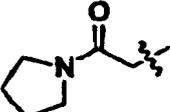
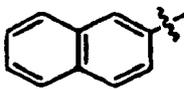
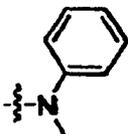
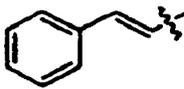
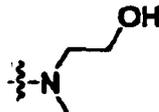
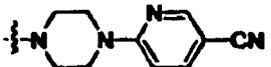
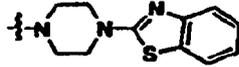
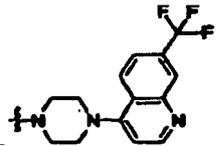
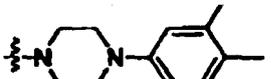
[Table 4-35]

Table 4 (-continue)				
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436		↑	↑	
437	↑		↑	
438			↑	
439	↑		↑	↑

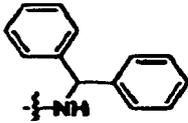
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Table 4 (-continue)				
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10 441	↑		↑	↑

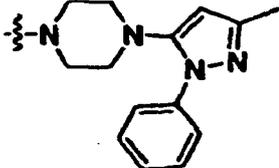
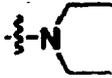
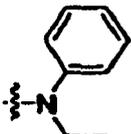
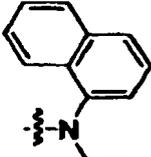
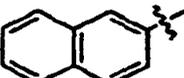
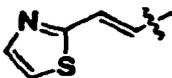
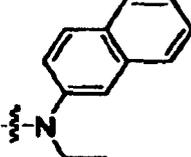
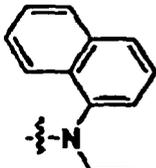
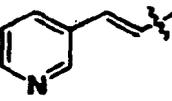
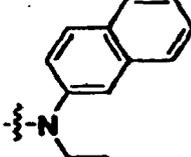
[Table 4-36]

Table 4 (-continue)				
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25 443	↑		↑	↑
30 444			↑	
35 445		↑	↑	
40 446	↑	↑	↑	
45 447	↑	↑	↑	
50 448	↑	↑	↑	
55 449	↑	↑	↑	

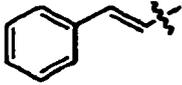
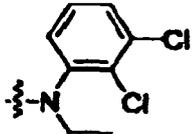
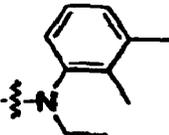
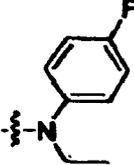
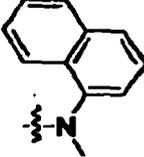
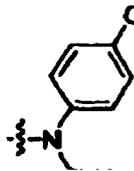
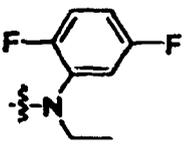
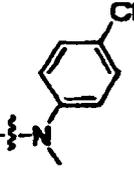
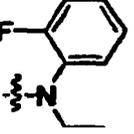
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Table 4 (-continue)				
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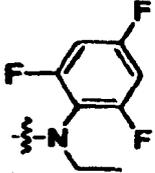
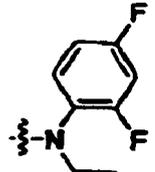
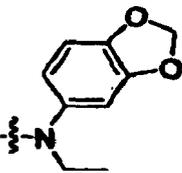
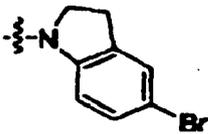
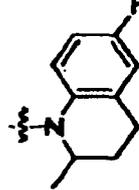
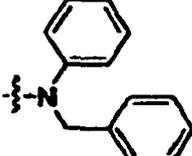
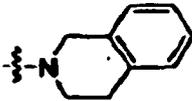
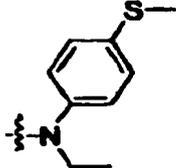
[Table 4-37]

Table 4 (-continue)				
15 451	↑	↑	↑	
20 452	↑	↑	↑	
25 453	↑	↑	↑	
30 454	↑	↑	↑	
35 455		↑	↑	↑
40 456		↑	↑	
45 457	↑	↑	↑	
50 458		↑	↑	

[Table 4-38]

Table 4 (-continue)				
5 459		↑	↑	
10 460	↑	↑	↑	
15 461	↑	↑	↑	
20 462	↑	↑	↑	
25 463	↑	↑	↑	
30 464	↑	↑	↑	
35 465	↑	↑	↑	
40 466	↑	↑	↑	

[Table 4-39]

Table 4 (-continue)				
5 467	↑	↑	↑	
10 468	↑	↑	↑	
15 469	↑	↑	↑	
20 470	↑	↑	↑	
25 471	↑	↑	↑	
30 472	↑	↑	↑	
35 473	↑	↑	↑	
40 474	↑	↑	↑	

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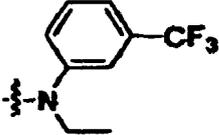
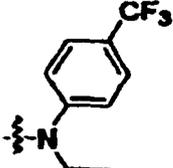
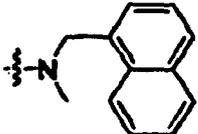
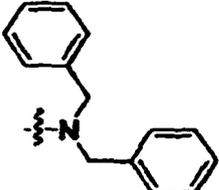
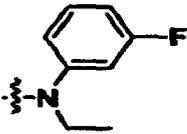
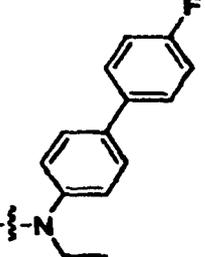
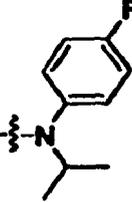
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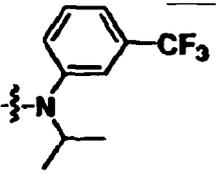
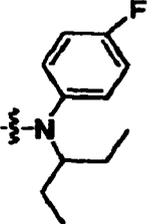
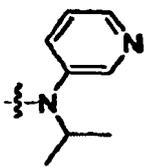
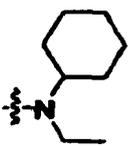
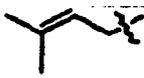
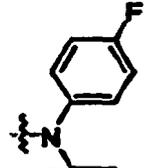
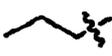
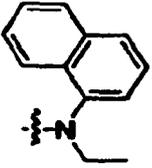
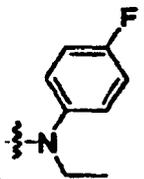
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[Table 4-40]

475	↑	↑	↑	
476	↑	↑	↑	
477	↑	↑	↑	
478	↑	↑	↑	
479	↑	↑	↑	
480	↑	↑	↑	
481	↑	↑	↑	

[Table 4-41]

Table 4 (-continue)				
5 482	↑	↑	↑	
10 483	↑	↑	↑	
15 484	↑	↑	↑	
20 485	↑	↑	↑	
25 486	↑		↑	
30 487	↑		↑	
35 488	↑	↑	↑	

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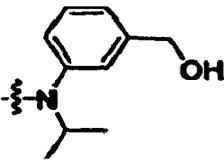
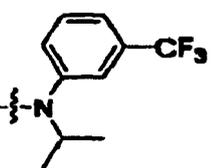
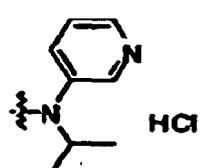
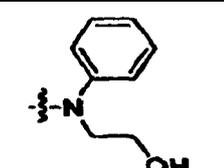
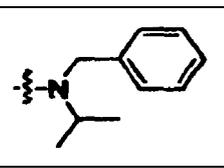
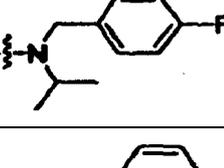
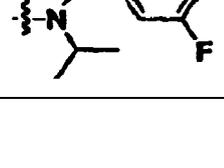
[Table 4-42]

Table 4 (-continue)				
5 489	↑	↑	↑	
10 490	↑		↑	↑
15 491	↑		↑	↑
20 492		↑	↑	↑
25 493		↑	↑	↑
30 494		↑	↑	↑
35 495		↑	↑	↑
40 496		↑	↑	↑
45 497		↑	↑	↑
50 498		↑	↑	↑

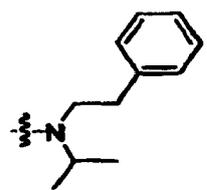
[Table 4-43]

Table 4 (-continue)				
50 499		↑	↑	

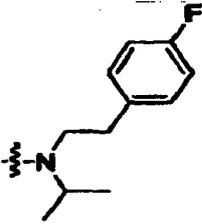
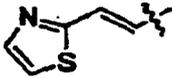
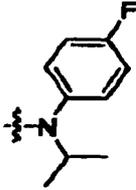
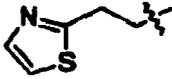
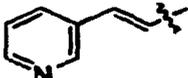
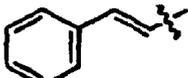
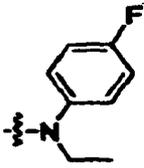
(continued)

Table 4 (-continue)				
500	↑	↑	↑	
501	↑	↑	↑	
502	↑	↑	↑	
503	↑	↑	↑	
504	↑	↑	↑	
505	↑	↑	↑	
506	↑	↑	↑	

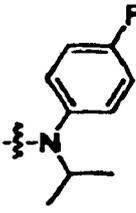
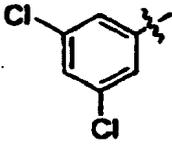
[Table 4-44]

Table 4 (-continue)				
507	↑	↑	↑	

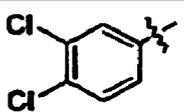
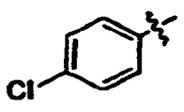
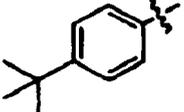
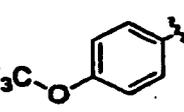
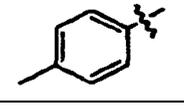
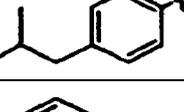
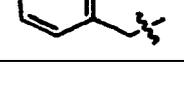
(continued)

Table 4 (-continue)				
508	↑	↑	↑	
509		↑	↑	
510		↑	↑	↑
511		↑	↑	↑
512			↑	↑
513	↑		↑	↑
514	↑		↑	

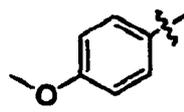
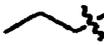
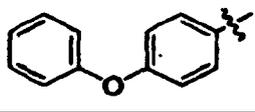
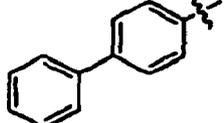
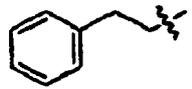
[Table 4-45]

Table 4 (-continue)				
515	↑	↑	↑	
516	↑	↑ (optically active form)	↑	↑
517			↑	↑

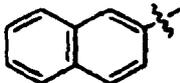
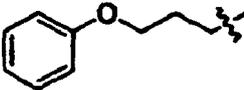
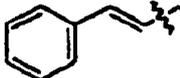
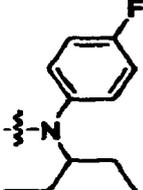
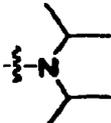
(continued)

5	518		↑	↑	↑
10	519		↑	↑	↑
15	520		↑	↑	↑
20	521		↑	↑	↑
25	522		↑	↑	↑
30	523		↑	↑	↑
	524		↑	↑	↑

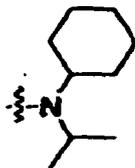
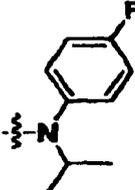
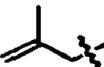
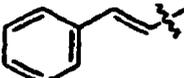
[Table 4-46]

35	525		↑	↑	↑
40	526		↑	↑	↑
45	527		↑	↑	↑
50	528		↑	↑	↑
55	529		↑	↑	↑

(continued)

Table 4 (-continue)				
530		↑	↑	↑
531		↑	↑	↑
532		↑	↑	
533	↑	↑	↑	

[Table 4-47]

Table 4 (-continue)				
534	↑	↑	↑	
535		↑	↑	
536		↑	↑	↑
537		↑	↑	↑
538			↑	↑
539	↑		↑	↑
540	↑		↑	↑

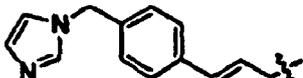
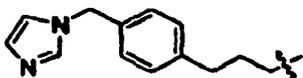
(continued)

Table 4 (-continue)				
541	↑		↑	↑
542	↑		↑	
543		↑	↑	↑

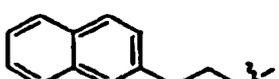
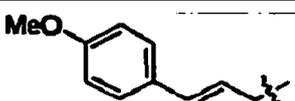
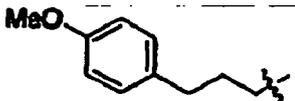
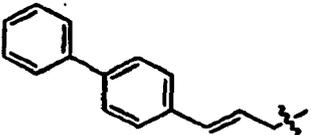
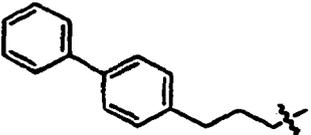
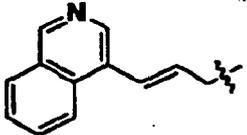
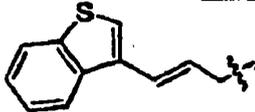
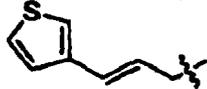
[Table 4-48]

Table 4 (-continue)				
544		↑	↑	
545			↑	
546		↑	↑	↑
547	↑		↑	
548	↑		↑	↑
549			↑	
550	↑		↑	↑

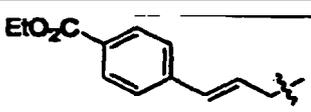
(continued)

Table 4 (-continue)					
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10	552	↑		↑	↑

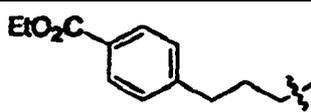
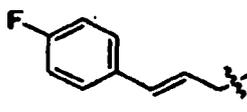
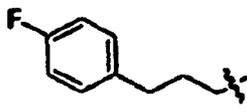
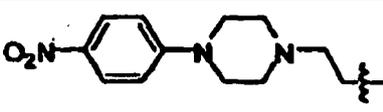
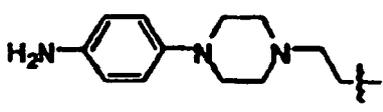
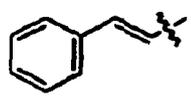
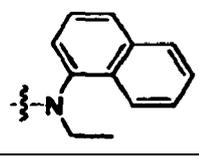
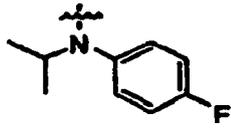
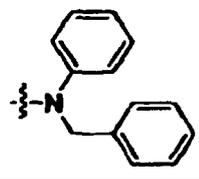
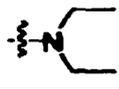
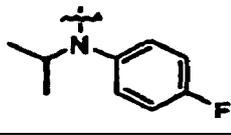
[Table 4-49]

Table 4 (-continue)					
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20	554	↑		↑	↑
25	555	↑		↑	↑
30	556	↑		↑	↑
35	557	↑		↑	↑
40	558	↑		↑	↑
45	559	↑		↑	↑
50	560	↑		↑	↑
55	561	↑		↑	↑

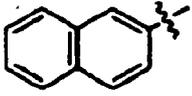
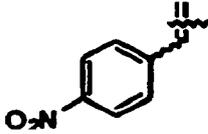
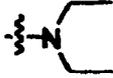
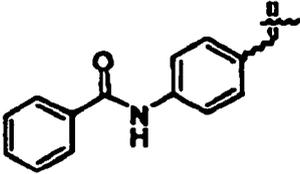
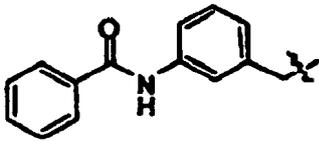
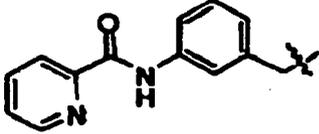
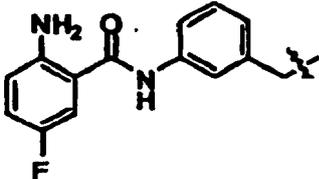
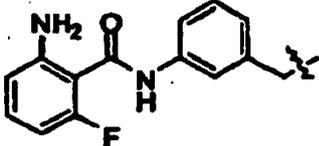
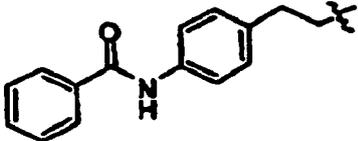
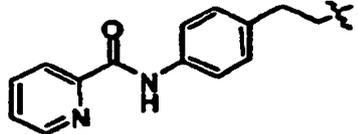
(continued)

Table 4 (-continue)				
562	↑		↑	↑

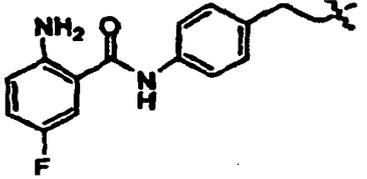
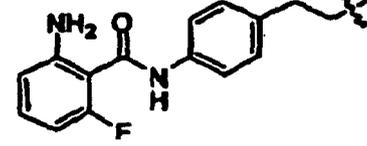
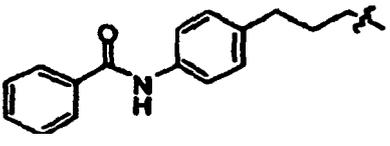
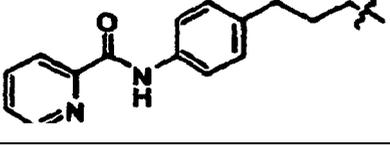
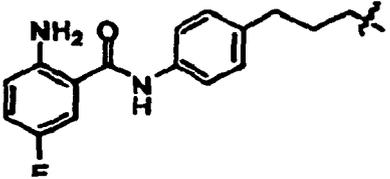
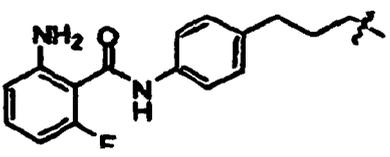
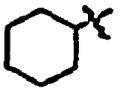
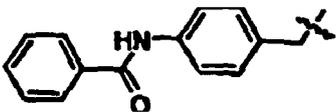
[Table 4-50]

Table 4 (-continue)				
563	↑		↑	↑
564	↑		↑	↑
565	↑		↑	↑
566	↑		↑	↑
567	↑		↑	↑
568		F, F		
569	↑	Me, Me		
570	↑			
571	↑	↑		
572	↑	↑		
573	↑		↑	

[Table 4-51]

Table 4 (-continue)				
5	574			
10		↑		↑
15	575			
20		↑		↑
25	576			H
30		↑		↑
35	577			↑
40		↑		↑
45	578			↑
50		↑		↑
55	579			↑
60		↑		↑
65	580			↑
70		↑		↑
75	581			↑

[Table 4-52]

Table 4 (-continue)				
5	↑		↑	↑
10	↑		↑	↑
15	↑		↑	↑
20	↑		↑	↑
25	↑		↑	↑
30	↑		↑	↑
35	↑		↑	↑
40			↑	↑

45 **[1219]** It was clarified from the following Experimental Examples 1 to 3 that the compound of the present invention selectively binds to AT<sub>2</sub> receptor and/or shows an agonist action at AT<sub>2</sub> receptor.

#### Experimental Example 1 (affinity for AT<sub>1</sub> receptor)

50 **[1220]** Using a commercially available receptor membrane fraction (PerkinElmer, Cat No. 6110533) obtained from CHO cells expressing human recombinant AT<sub>1</sub> receptor, a receptor binding assay was performed. <sup>125</sup>I]-[Sar<sup>1</sup>, Ile<sup>8</sup>]-Ang II (2.4 kBq, final concentration 0.3 nmol/L) and various concentrations of the compound of the present invention were added to a solution of 50 mmol/L Tris-HCl (pH 7.4), 125 mmol/L NaCl, 6.5 mmol/L MgCl<sub>2</sub> and 1 mmol/L EDTA containing the receptor membrane fraction, and the mixture was incubated at room temperature for 60 min. Bound or free <sup>125</sup>I]-[Sar<sup>1</sup>, Ile<sup>8</sup>]-Ang II was separated with a glass fiber filter (Millipore, MultiScreen FB Plate), and the radioactivity of <sup>125</sup>I]-[Sar<sup>1</sup>, Ile<sup>8</sup>]-Ang II bound to the receptor was determined. IC<sub>50</sub> value which shows the concentration of the compound of the present invention necessary for inhibiting the binding of <sup>125</sup>I]-[Sar<sup>1</sup>, Ile<sup>8</sup>]-Ang II to the receptor by 50% was calculated from the concentration-response curve. On the other hand, K<sub>d</sub> value of <sup>125</sup>I]-[Sar<sup>1</sup>, Ile<sup>8</sup>]-Ang II for AT<sub>1</sub> receptor in the

absence of the compound of the present invention was determined by Scatchard analysis. Using the IC<sub>50</sub> value obtained from the concentration-response curve and the K<sub>d</sub> value of <sup>125</sup>I-[Sar<sup>1</sup>, Ile<sup>8</sup>]-Ang II, the K<sub>i</sub> value of the compound of the present invention was calculated and used as an index of the affinity for AT<sub>1</sub> receptor.

5 Experimental Example 2 (affinity for AT<sub>2</sub> receptor)

[1221] Using a commercially available receptor membrane fraction (PerkinElmer, Cat No. 6110538) obtained from HeLa cells expressing human recombinant AT<sub>2</sub> receptor, a receptor binding assay was performed. <sup>125</sup>I-[Sar<sup>1</sup>, Ile<sup>8</sup>]-Ang II (0.8 kBq, final concentration 0.1 nmol/L) and various concentrations of the compound of the present invention were added to a solution of 50 mmol/L Tris-HCl (pH 7.4), 125 mmol/L NaCl, 6.5 mmol/L MgCl<sub>2</sub> and 1 mmol/L EDTA containing the receptor membrane fraction, and the mixture was incubated at room temperature for 90 min. Bound or free <sup>125</sup>I-[Sar<sup>1</sup>, Ile<sup>8</sup>]-Ang II was separated with a glass fiber filter (Millipore, MultiScreen FB Plate), and the radioactivity of <sup>125</sup>I-[Sar<sup>1</sup>, Ile<sup>8</sup>]-Ang II bound to the receptor was determined. IC<sub>50</sub> value which shows the concentration of the compound of the present invention necessary for inhibiting the binding of <sup>125</sup>I-[Sar<sup>1</sup>, Ile<sup>8</sup>]-Ang II to the receptor by 50% was calculated from the concentration-response curve. On the other hand, K<sub>d</sub> value of <sup>125</sup>I-[Sar<sup>1</sup>, Ile<sup>8</sup>]-Ang II for AT<sub>2</sub> receptor in the absence of the compound of the present invention was determined by Scatchard analysis. Using the IC<sub>50</sub> value obtained from the concentration-response curve and the K<sub>d</sub> value of <sup>125</sup>I-[Sar<sup>1</sup>, Ile<sup>8</sup>]-Ang II, the K<sub>i</sub> value of the compound of the present invention was calculated and used as an index of the affinity for AT<sub>2</sub> receptor.

20 Experimental Example 3 (agonist action at AT<sub>2</sub> receptor)

[1222] According to the method of Stroth et al (Mol. Brain Res. 78 (2000), 175-180), the agonist action at AT<sub>2</sub> receptor of the compound of the present invention was examined. To be specific, PC12W cells (rat adrenal pheochromocytoma) cultured in a growth medium were subsequently cultured in a low-serum medium, and finally serum-deprived for 3 hr. Then, NGF (final concentration 3 - 30 ng/mL) and various concentrations of the compound of the present invention were added, and they were incubated at 37°C, 5% CO<sub>2</sub> for 10 min. Thereafter, the cells were lysed on ice for 30 min, and the amount of phosphorylated ERK in the cell lysis solution was detected by a Phospho-p44/42 MAPK-recognizing antibody. Using the decreasing effect on phosphorylated ERK as an index, the agonist action at AT<sub>2</sub> receptor of the compound of the present invention was examined.

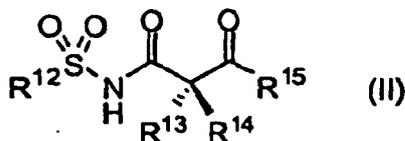
[1223] The affinity (K<sub>i</sub> value) of the compounds of the present invention for AT<sub>2</sub> receptor as determined by the aforementioned method is shown in the following. All the compounds showed an agonist action at AT<sub>2</sub> receptor and the affinity for AT<sub>1</sub> receptor of K<sub>i</sub>>500 nmol/L.

[Table 5]

Example No.	Affinity for AT <sub>2</sub> receptor (K <sub>i</sub> , nmol/L)	Example No.	Affinity for AT <sub>2</sub> receptor (K <sub>i</sub> , nmol/L)
22	8.0	441	11
87	23	475	13
92	2.3	481	9.0
99	0.9	491	9.2
100	1.6	493	5.2
101	16	495	8.4
103	3.2	496	12
104	3.3	518	6.1
105	5.4	529	10
106	1.6	530	13
107	1.6		
108	9.7		
147	34		
322	6.4		
371	12		

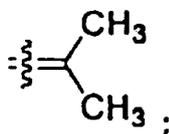
## Claims

1. A sulfonyl malonamide derivative represented by the following formula (II)

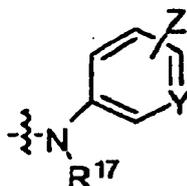


15

wherein R<sup>12</sup> is 2-naphthyl, trans-β-styryl, phenethyl, 3-phenoxypropyl or 4-phenylbutyl;  
 one of R<sup>13</sup> and R<sup>14</sup> is a hydrogen atom, and the other is isopropyl, isobutyl, neopentyl, allyl, -CH<sub>2</sub>-R<sup>16</sup> wherein  
 R<sup>16</sup> is optionally substituted C<sub>3-10</sub> cycloalkyl, optionally substituted heterocycle or -CO-NR<sup>5</sup>R<sup>6</sup> (wherein R<sup>5</sup> and  
 R<sup>6</sup> are the same or different and each is a hydrogen atom, C<sub>1-6</sub> alkyl, optionally substituted aryl or optionally  
 20 substituted heteroaryl, or R<sup>5</sup> and R<sup>6</sup> optionally form optionally substituted cyclic amino together with a nitrogen  
 atom bonded thereto), -(CH<sub>2</sub>)<sub>2</sub>-R<sup>16'</sup> (wherein R<sup>16'</sup> is cyano or C<sub>1-6</sub> alkoxy), or -(CH<sub>2</sub>)<sub>n</sub>-Ar<sup>2</sup> (wherein n is an integer  
 of 1 to 3, and Ar<sup>2</sup> is substituted phenyl or optionally substituted heteroaryl), or R<sup>13</sup> and R<sup>14</sup> optionally form,  
 together with a carbon atom bonded thereto, the following formula



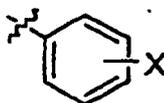
and  
 R<sup>15</sup> is di(C<sub>1-6</sub> alkyl)amino or the following formula



wherein Z is a hydrogen atom, a halogen atom or trifluoromethyl, Y is a nitrogen atom or CH, R<sup>17</sup> is ethyl,  
 isopropyl or 3-pentyl, provided that when Y is a nitrogen atom, then Z is a hydrogen atom,

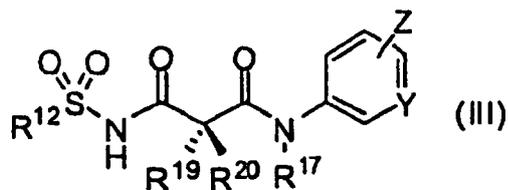
40 or a pharmacologically acceptable salt thereof.

2. The sulfonyl malonamide derivative of claim 1, wherein Ar<sup>2</sup> for R<sup>13</sup> or R<sup>14</sup> is substituted phenyl represented by the  
 following formula



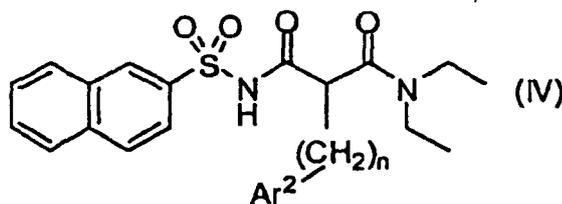
wherein X is a fluorine atom, a chlorine atom, a bromine atom, cyano, nitro, amino (excluding substitution at the  
 ortho-position), -NHCOAr<sup>3</sup>, -NHCOOAr<sup>3</sup>, -NHCONHAr<sup>3</sup>, -NHCO<sub>2</sub>Ar<sup>3</sup>, -OAr<sup>3</sup> (wherein Ar<sup>3</sup> is optionally substituted  
 aryl or optionally substituted heteroaryl), -NHCOR<sup>18</sup> (wherein R<sup>18</sup> is optionally substituted C<sub>1-6</sub> alkyl, optionally  
 55 substituted C<sub>3-10</sub> cycloalkyl, or optionally substituted heterocycle), optionally substituted C<sub>1-6</sub> alkoxy, optionally substituted heterocycle, optionally substituted aryl or op-  
 tionally substituted heteroaryl,  
 or a pharmacologically acceptable salt thereof.

3. The sulfonyl malonamide derivative of claim 1, which is represented by the following formula (III)



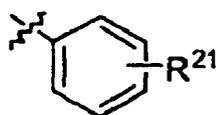
10 wherein R<sup>12</sup>, R<sup>17</sup>, Y and Z are as defined in claim 1, one of R<sup>19</sup> and R<sup>20</sup> is a hydrogen atom, and the other is isopropyl, isobutyl, neopentyl, allyl, cyclopropylmethyl or -CH<sub>2</sub>-Ar<sup>2</sup>, wherein Ar<sup>2</sup> is as defined in claim 1, or a pharmacologically acceptable salt thereof.

- 15 4. The sulfonyl malonamide derivative of claim 1, which is represented by the following formula (IV)-

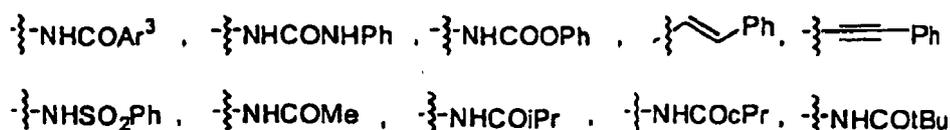


25 wherein n is an integer of 1 to 3, Ar<sup>2</sup> is as defined in claim 1, or a pharmacologically acceptable salt thereof.

- 30 5. The sulfonyl malonamide derivative of claim 4, wherein Ar<sup>2</sup> is substituted phenyl represented by the following formula

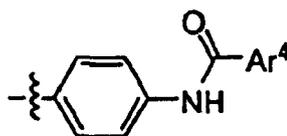


40 wherein R<sup>21</sup> is a fluorine atom, a chlorine atom, nitro, cyano, amino (excluding substitution at the ortho-position), dimethylamino, methoxy, trifluoromethoxy, methoxycarbonyl, phenyl, 2-pyridyloxy, 1-imidazolyl, 2-isindolyl, 1-oxo-2-isindolyl or the following formula

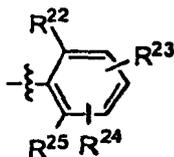


50 wherein Ar<sup>3</sup> is as defined in claim 2, or a pharmacologically acceptable salt thereof.

- 55 6. The sulfonyl malonamide derivative of claim 4, wherein Ar<sup>2</sup> is substituted phenyl represented by the following formula



wherein Ar<sup>4</sup> is 2-thienyl, 2-furyl, 4-pyridyl, 3-pyridyl, 2-pyridyl or the following formula



wherein  $R^{22}$  and  $R^{25}$  are the same or different and each is a hydrogen atom, amino, a fluorine atom, hydroxy, methoxy, methyl or a chlorine atom,  $R^{23}$  is a hydrogen atom or a fluorine atom, and  $R^{24}$  is a hydrogen atom, a fluorine atom, a chlorine atom, methyl, amino, methoxy or cyano, and  $n$  is 1, or a pharmacologically acceptable salt thereof.

7. The sulfonyl malonamide derivative of claim 1, which is a compound selected from:

N,N-diethyl-2-[4-[(2, 6-difluorobenzoyl)amino]benzyl]-N'-(2-naphthylsulfonyl)malonamide,  
 (2S)-2-[4-(benzoylamino)benzyl]-N,N-diethyl-N'-(2-naphthylsulfonyl)malonamide,  
 (2S)-N,N-diethyl-2-[4-[(2-fluorobenzoyl)amino]benzyl]-N'-(2-naphthylsulfonyl)malonamide,  
 (2S)-N,N-diethyl-2-[4-[(3-fluorobenzoyl)amino]benzyl]-N'-(2-naphthylsulfonyl)malonamide,  
 (2S)-N,N-diethyl-2-[4-[(2,4-difluorobenzoyl)amino]benzyl]-N'-(2-naphthylsulfonyl)malonamide,  
 (2S)-N,N-diethyl-2-[4-[(4-methylbenzoyl)amino]benzyl]-N'-(2-naphthylsulfonyl)malonamide,  
 (2S)-N,N-diethyl-N'-(2-naphthylsulfonyl)-2-[4-[(2-thienoyl)amino]benzyl]malonamide,  
 (2S)-N,N-diethyl-2-[4-[(2-furoyl)amino]benzyl]-N'-(2-naphthylsulfonyl)malonamide,  
 (2S)-2-[4-[(2-amino-5-fluorobenzoyl)amino]benzyl]-N,N-diethyl-N'-(2-naphthylsulfonyl)malonamide,  
 (2S)-2-[4-[(2-amino-6-fluorobenzoyl)amino]benzyl]-N,N-diethyl-N'-(2-naphthylsulfonyl)malonamide,  
 (2S)-N,N-diethyl-N'-(2-naphthylsulfonyl)-2-[4-[(2-pyridylcarbonyl)amino]benzyl]malonamide,  
 (2S)-2-[4-[(2-amino-4-chlorobenzoyl)amino]benzyl]-N,N-diethyl-N'-(2-naphthylsulfonyl)malonamide,  
 (2S)-2-[4-[(2-aminobenzoyl)amino]benzyl]-N,N-diethyl-N'-(2-naphthylsulfonyl)malonamide,  
 (2S)-2-[4-[(2-amino-5-chlorobenzoyl)amino]benzyl]-N,N-diethyl-N'-(2-naphthylsulfonyl)malonamide,  
 (2S)-2-[4-[(2-amino-4,5-difluorobenzoyl)amino]benzyl]-N,N-diethyl-N'-(2-naphthylsulfonyl)malonamide,  
 (2S)-2-[4-[(2-amino-4-fluorobenzoyl)amino]benzyl]-N,N-diethyl-N'-(2-naphthylsulfonyl)malonamide,  
 (2S)-2-[4-[(2-amino-5-methylbenzoyl)amino]benzyl]-N,N-diethyl-N'-(2-naphthylsulfonyl)malonamide,  
 2-[(4-fluorobenzyl)-N-isopropyl-N-(3-pyridyl)-N'-((E)-styrylsulfonyl)malonamide,  
 2-allyl-N-(4-fluorophenyl)-N-isopropyl-N'-((E)-styrylsulfonyl)malonamide,  
 N-(4-fluorophenyl)-2-isobutyl-N-isopropyl-N'-((E)-styrylsulfonyl)malonamide,  
 N-(4-fluorophenyl)-2-isobutyl-N-isopropyl-N'-phenethylsulfonylmalonamide,  
 N-(4-fluorophenyl)-2-isobutyl-N-isopropyl-N'-(2-naphthylsulfonyl)malonamide,  
 (2S or 2R)-2-cyclopropylmethyl-N-(4-fluorophenyl)-N-isopropyl-N'-((E)-2-styrylsulfonyl)malonamide,  
 2-cyclopropylmethyl-N-(4-fluorophenyl)-N-isopropyl-N'-phenethylsulfonylmalonamide, or  
 2-cyclopropylmethyl-N-(4-fluorophenyl)-N-isopropyl-N'-(2-naphthylsulfonyl)malonamide,

or a pharmacologically acceptable salt thereof.

8. A pharmaceutical composition comprising the sulfonyl malonamide derivative of any of the claims 1 to 7, or a pharmacologically acceptable salt thereof, as an active ingredient.

9. The sulfonyl malonamide derivative of any of claims 1 to 7, or a pharmacologically acceptable salt thereof for use as an  $AT_2$  receptor agonist.

10. The sulfonyl malonamide derivative of claim 7, or a pharmacologically acceptable salt thereof for use as an  $AT_2$  receptor agonist.

11. The sulfonyl malonamide derivative of claim 10, wherein the  $AT_2$  receptor agonist is  $AT_2$  receptor selective.

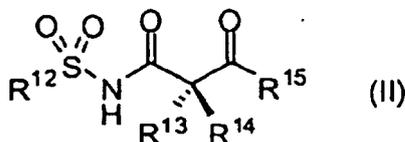
12. The sulfonyl malonamide derivative of any of claims 1 to 7, or a pharmacologically acceptable salt thereof for use in the treatment and prophylaxis of a disorder involving the renin-angiotensin-aldosterone system.

13. The sulfonyl malonamide derivative of claim 12, wherein the disorder involving the renin-angiotensin-aldosterone system is selected from stroke, renal disease, cardiac disease, hypertension, diabetes, diabetic complications,

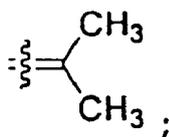
hyperlipidemia and metabolic syndrome.

### Patentansprüche

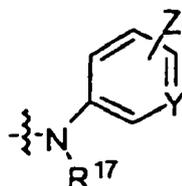
1. Sulfonylmalonamid-Derivat, das durch die folgende Formel (II)



dargestellt wird, wobei R<sup>12</sup> für 2-Naphthyl, trans-β-Styryl, Phenethyl, 3-Phenoxypropyl oder 4-Phenylbutyl steht; eines von R<sup>13</sup> und R<sup>14</sup> ein Wasserstoffatom ist und das andere Isopropyl, Isobutyl, Neopentyl, Allyl, -CH<sub>2</sub>-R<sup>16</sup>, wobei R<sup>16</sup> gegebenenfalls substituiertes C<sub>3-10</sub>-Cycloalkyl, ein gegebenenfalls substituierter Heterocyclus oder -CO-NR<sup>5</sup>R<sup>6</sup> (wobei R<sup>5</sup> und R<sup>6</sup> gleich oder verschieden sind und jeweils ein Wasserstoffatom, C<sub>1-6</sub>-Alkyl, gegebenenfalls substituiertes Aryl oder gegebenenfalls substituiertes Heteroaryl sind oder R<sup>5</sup> und R<sup>6</sup> gegebenenfalls zusammen mit einem daran gebundenen Stickstoffatom gegebenenfalls substituiertes cyclisches Amino bilden) ist, -(CH<sub>2</sub>)<sub>2</sub>-R<sup>16'</sup> (wobei R<sup>16'</sup> Cyano oder C<sub>1-6</sub>-Alkoxy ist) oder -(CH<sub>2</sub>)<sub>n</sub>-Ar<sup>2</sup> (wobei n eine ganze Zahl von 1 bis 3 ist und Ar<sup>2</sup> substituiertes Phenyl oder gegebenenfalls substituiertes Heteroaryl ist) ist oder R<sup>13</sup> und R<sup>14</sup> gegebenenfalls zusammen mit einem daran gebundenen Kohlenstoffatom die folgende Formel bilden:



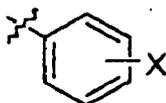
und  
R<sup>15</sup> für Di(C<sub>1-6</sub>-alkyl)amino oder die folgende Formel steht:



wobei Z ein Wasserstoffatom, ein Halogenatom oder Trifluormethyl ist, Y ein Stickstoffatom oder CH ist, R<sup>17</sup> Ethyl, Isopropyl oder 3-Pentyl ist, mit der Maßgabe, dass Z ein Wasserstoffatom ist, wenn Y ein Stickstoffatom ist;

oder ein pharmakologisch annehmbares Salz davon.

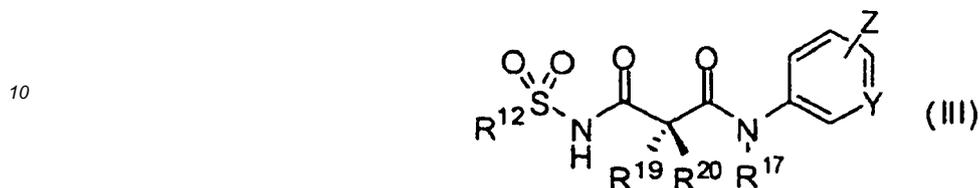
2. Sulfonylmalonamid-Derivat gemäß Anspruch 1, wobei Ar<sup>2</sup> für R<sup>13</sup> oder R<sup>14</sup> substituiertes Phenyl ist, das durch die folgende Formel



dargestellt wird, wobei X ein Fluoratom, ein Chloratom, ein Bromatom, Cyano, Nitro, Amino (wobei eine Substitution auf der ortho-Position ausgeschlossen ist), -NHCOAr<sup>3</sup>, -NHCOOAr<sup>3</sup>, -NHCONHAr<sup>3</sup>, -NHCO<sub>2</sub>Ar<sup>3</sup>, -OAr<sup>3</sup> (wobei Ar<sup>3</sup> gegebenenfalls substituiertes Aryl oder gegebenenfalls substituiertes Heteroaryl ist), -NHCOR<sup>18</sup> (wobei R<sup>18</sup> gegebenenfalls substituiertes C<sub>1-6</sub>-Alkyl, gegebenenfalls substituiertes C<sub>3-10</sub>-Cycloalkyl oder ein gegebenenfalls substituierter Heterocyclus ist), gegebenenfalls substituiertes C<sub>1-6</sub>-Alkoxy-carbonyl, Di(C<sub>1-6</sub>-alkyl)amino, gegebenenfalls

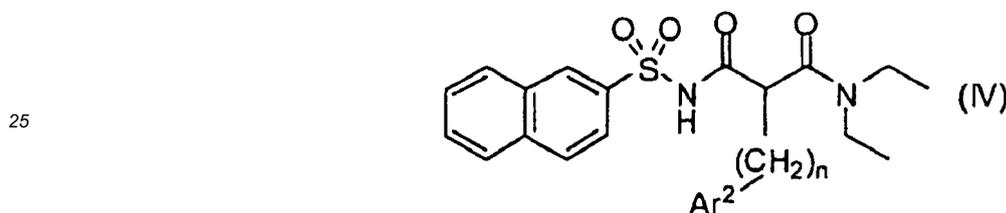
substituiertes C<sub>1-6</sub>-Alkoxy, ein gegebenenfalls substituierter Heterocyclus, gegebenenfalls substituiertes Aryl oder gegebenenfalls substituiertes Heteroaryl ist; oder ein pharmakologisch annehmbares Salz davon.

- 5 3. Sulfonylmalonamid-Derivat gemäß Anspruch 1, das durch die folgende Formel (III)



15 dargestellt wird, wobei R<sup>12</sup>, R<sup>17</sup>, Y und Z wie in Anspruch 1 definiert sind, eines von R<sup>19</sup> und R<sup>20</sup> ein Wasserstoffatom ist und das andere Isopropyl, Isobutyl, Neopentyl, Allyl, Cyclopropylmethyl oder -CH<sub>2</sub>-Ar<sup>2</sup> ist, wobei Ar<sup>2</sup> wie in Anspruch 1 definiert ist, oder ein pharmakologisch annehmbares Salz davon.

- 20 4. Sulfonylmalonamid-Derivat gemäß Anspruch 1, das durch die folgende Formel (IV)

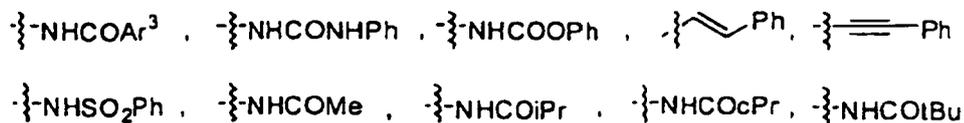


30 dargestellt wird, wobei n eine ganze Zahl von 1 bis 3 ist, Ar<sup>2</sup> wie in Anspruch 1 definiert ist, oder ein pharmakologisch annehmbares Salz davon.

- 35 5. Sulfonylmalonamid-Derivat gemäß Anspruch 4, wobei Ar<sup>2</sup> substituiertes Phenyl ist, das durch die folgende Formel

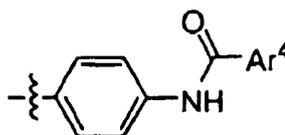


dargestellt wird, wobei R<sup>21</sup> ein Fluoratom, ein Chloratom, Nitro, Cyano, Amino (wobei eine Substitution auf der ortho-Position ausgeschlossen ist), Dimethylamino, Methoxy, Trifluormethoxy, Methoxycarbonyl, Phenyl, 2-Pyridyloxy, 1-Imidazolyl, 2-Isoindolinyl, 1-Oxo-2-isoindolinyl ist oder der folgenden Formel

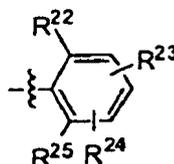


entspricht, wobei Ar<sup>3</sup> wie in Anspruch 2 definiert ist, oder ein pharmakologisch annehmbares Salz davon.

- 55 6. Sulfonylmalonamid-Derivat gemäß Anspruch 4, wobei Ar<sup>2</sup> substituiertes Phenyl ist, das durch die folgende Formel



dargestellt wird, wobei Ar<sup>4</sup> für 2-Thienyl, 2-Furyl, 4-Pyridyl, 3-Pyridyl, 2-Pyridyl steht oder der folgenden Formel



entspricht, wobei R<sup>22</sup> und R<sup>25</sup> gleich oder verschieden sind und jeweils ein Wasserstoffatom, Amino, ein Fluoratom, Hydroxy, Methoxy, Methyl oder ein Chloratom sind, R<sup>23</sup> ein Wasserstoffatom oder ein Fluoratom ist und R<sup>24</sup> ein Wasserstoffatom, ein Fluoratom, ein Chloratom, Methyl, Amino, Methoxy oder Cyano ist und n = 1 ist, oder ein pharmakologisch annehmbares Salz davon.

7. Sulfonylmalonamid-Derivat gemäß Anspruch 1, bei dem es sich um eine Verbindung handelt, die ausgewählt ist aus:

N,N-Diethyl-2-{4-[(2,6-difluorbenzoyl)amino]benzyl}-N'-(2-naphthylsulfo-nyl)malonamid,  
 (2S)-2-[4-(Benzoylamino)benzyl]-N,N-diethyl-N'-(2-naphthylsulfonyl)-malonamid,  
 (2S)-N,N-Diethyl-2-{4-[(2-fluorbenzoyl)amino]benzyl}-N'-(2-naphthylsulfonyl)malonamid,  
 (2S)-N,N-Diethyl-2-{4-[(3-fluorbenzoyl)amino]benzyl}-N'-(2-naphthylsulfonyl)malonamid,  
 (2S)-N,N-Diethyl-2-{4-[(2,4-difluorbenzoyl)amino]benzyl}-N'-(2-naphthylsulfonyl)malonamid,  
 (2S)-N,N-Diethyl-2-{4-[(4-methylbenzoyl)amino]benzyl}-N'-(2-naphthylsulfonyl)malonamid,  
 (2S)-N,N-Diethyl-N'-(2-naphthylsulfonyl)-2-{4-[(2-thienoyl)amino]benzyl}malonamid,  
 (2S)-N,N-Diethyl-2-{4-[(2-furoyl)amino]benzyl}-N'-(2-naphthylsulfonyl)-malonamid,  
 (2S)-2-{4-[(2-Amino-5-fluorbenzoyl)amino]benzyl}-N,N-diethyl-N'-(2-naphthylsulfonyl)malonamid,  
 (2S)-2-{4-[(2-Amino-6-fluorbenzoyl)amino]benzyl}-N,N-diethyl-N'-(2-naphthylsulfonyl)malonamid,  
 (2S)-N,N-Diethyl-N'-(2-naphthylsulfonyl)-2-{4-[(2-pyridylcarbonyl)-amino]benzyl}malonamid,  
 (2S)-2-{4-[(2-Amino-4-chlorbenzoyl)amino]benzyl}-N,N-diethyl-N'-(2-naphthylsulfonyl)malonamid,  
 (2S)-2-{4-[(2-Aminobenzoyl)amino]benzyl}-N,N-diethyl-N'-(2-naphthylsulfonyl)malonamid,  
 (2S)-2-{4-[(2-Amino-5-chlorbenzoyl)amino]benzyl}-N,N-diethyl-N'-(2-naphthylsulfonyl)malonamid,  
 (2S)-2-{4-[(2-Amino-4,5-difluorbenzoyl)amino]benzyl}-N,N-diethyl-N'-(2-naphthylsulfonyl)malonamid,  
 (2S)-2-{4-[(2-Amino-4-fluorbenzoyl)amino]benzyl}-N,N-diethyl-N'-(2-naphthylsulfonyl)malonamid,  
 (2S)-2-{4-[(2-Amino-5-methylbenzoyl)amino]benzyl}-N,N-diethyl-N'-(2-naphthylsulfonyl)malonamid,  
 2-[(4-Fluorbenzyl)-N-isopropyl-N-(3-pyridyl)-N'-((E)-styrylsulfonyl)malonamid,  
 2-Allyl-N-(4-fluorphenyl)-N-isopropyl-N'-((E)-styrylsulfonyl)malonamid,  
 N-(4-Fluorphenyl)-2-isobutyl-N-isopropyl-N'-((E)-styrylsulfonyl)malonamid,  
 N-(4-Fluorphenyl)-2-isobutyl-N-isopropyl-N'-phenethylsulfonylmalonamid,  
 N-(4-Fluorphenyl)-2-isobutyl-N-isopropyl-N'-(2-naphthylsulfonyl)malonamid,  
 (2S oder 2R)-2-Cyclopropylmethyl-N-(4-fluorphenyl)-N-isopropyl-N'-((E)-2-styrylsulfonyl)malonamid,  
 2-Cyclopropylmethyl-N-(4-fluorphenyl)-N-isopropyl-N'-phenethylsulfonylmalonamid oder  
 2-Cyclopropylmethyl-N-(4-fluorphenyl)-N-isopropyl-N'-(2-naphthylsulfonyl)malonamid,

oder ein pharmakologisch annehmbares Salz davon.

8. Pharmazeutische Zusammensetzung, die das Sulfonylmalonamid-Derivat gemäß einem der Ansprüche 1 bis 7 oder ein pharmakologisch annehmbares Salz davon als Wirkstoff umfasst.

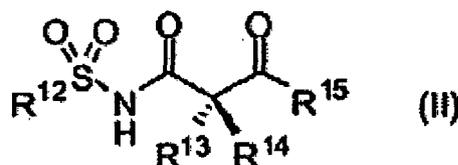
9. Sulfonylmalonamid-Derivat gemäß einem der Ansprüche 1 bis 7 oder ein pharmakologisch annehmbares Salz davon zur Verwendung als AT<sub>2</sub>-Rezeptor-Agonist.

10. Sulfonylmalonamid-Derivat gemäß Anspruch 7 oder ein pharmakologisch annehmbares Salz davon zur Verwendung als AT<sub>2</sub>-Rezeptor-Agonist.

11. Sulfonylmalonamid-Derivat gemäß Anspruch 10, wobei der AT<sub>2</sub>-Rezeptor-Agonist AT<sub>2</sub>-Rezeptor-selektiv ist.
12. Sulfonylmalonamid-Derivat gemäß einem der Ansprüche 1 bis 7 oder ein pharmakologisch annehmbares Salz davon zur Verwendung bei der Behandlung und Prophylaxe einer Störung, die das Renin-Angiotensin-Aldosteron-System betrifft.
13. Sulfonylmalonamid-Derivat gemäß Anspruch 12, wobei die Störung, die das Renin-Angiotensin-Aldosteron-System betrifft, aus einem Schlaganfall, einer Nierenerkrankung, einer Herzkrankheit, Bluthochdruck, Diabetes, Diabetes-Komplikationen, Hyperlipidämie und metabolischem Syndrom ausgewählt ist.

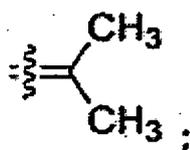
### Revendications

1. Dérivé de sulfonyl-malonamide représenté par la formule (II) suivante



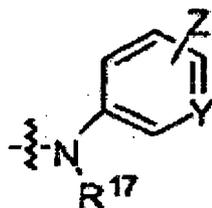
dans laquelle R<sup>12</sup> représente un groupe 2-naphtyle, trans-β-styryle, phénéthyle, 3-phénoxypropyle ou 4-phénylbutyle ;

l'un de R<sup>13</sup> et de R<sup>14</sup> représente un atome d'hydrogène, et l'autre représente un groupe isopropyle, isobutyle, néopentyle, allyle, -CH<sub>2</sub>-R<sup>16</sup> où R<sup>16</sup> représente un groupe cycloalkyle en C<sub>3</sub> à C<sub>10</sub> éventuellement substitué, hétérocycle éventuellement substitué ou -CO-NR<sup>5</sup>R<sup>6</sup> (où R<sup>5</sup> et R<sup>6</sup> sont identiques ou différents et chacun représente un atome d'hydrogène, un groupe alkyle en C<sub>1</sub> à C<sub>6</sub>, aryle éventuellement substitué ou hétéroaryle éventuellement substitué, ou R<sup>5</sup> et R<sup>6</sup> forment éventuellement un groupe amino cyclique éventuellement substitué conjointement avec un atome d'azote qui y est lié), -(CH<sub>2</sub>)<sub>2</sub>-R<sup>16'</sup> (où R<sup>16'</sup> représente un groupe cyano ou alcoxy en C<sub>1</sub> à C<sub>6</sub>), ou -(CH<sub>2</sub>)<sub>n</sub>-Ar<sup>2</sup> (où n est un nombre entier de 1 à 3, et Ar<sup>2</sup> représente un groupe phényle substitué ou hétéroaryle éventuellement substitué), ou R<sup>13</sup> et R<sup>14</sup> forment éventuellement, conjointement avec un atome de carbone qui y est lié, la formule suivante



et

R<sup>15</sup> représente un groupe di (alkyl en C<sub>1</sub> à C<sub>6</sub>)amino ou la formule suivante

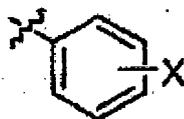


dans laquelle Z représente un atome d'hydrogène, un atome d'halogène ou un groupe trifluorométhyle, Y représente un atome d'azote ou CH, R<sup>17</sup> représente un groupe éthyle, isopropyle ou 3-pentyle, à condition que lorsque Y représente un atome d'azote, alors Z représente un atome d'hydrogène,

ou un sel pharmacologiquement acceptable de celui-ci.

2. Dérivé de sulfonyl-malonamide selon la revendication 1, où  $Ar^2$  pour  $R^{13}$  ou  $R^{14}$  représente un groupe phényle substitué représenté par la formule suivante

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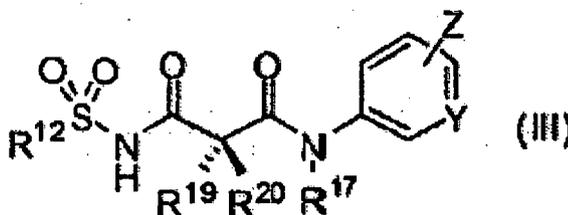


10 dans laquelle X représente un atome de fluor, un atome de chlore, un atome de brome, un groupe cyano, nitro, amino (en excluant une substitution au niveau de la position ortho),  $-NHCOAr^3$ ,  $-NHCOOAr^3$ ,  $-NHCONHAr^3$ ,  $-NHSO_2Ar^3$ ,  $-OAr^3$  (où  $Ar^3$  représente un groupe aryle éventuellement substitué ou hétéroaryle éventuellement substitué),  $-NHCOR^{18}$  (où  $R^{18}$  représente un groupe alkyle en  $C_1$  à  $C_6$  éventuellement substitué, cycloalkyle en  $C_3$  à  $C_{10}$  éventuellement substitué ou hétérocycle éventuellement substitué), alcoxy en  $C_1$  à  $C_6$ -carbonyle éventuellement substitué, di(alkyl en  $C_1$  à  $C_6$ )amino, alcoxy en  $C_1$  à  $C_6$  éventuellement substitué, hétérocycle éventuellement substitué, aryle éventuellement substitué ou hétéroaryle éventuellement substitué, ou un sel pharmacologiquement acceptable de celui-ci.

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3. Dérivé de sulfonyl-malonamide selon la revendication 1, qui est représenté par la formule (III) suivante

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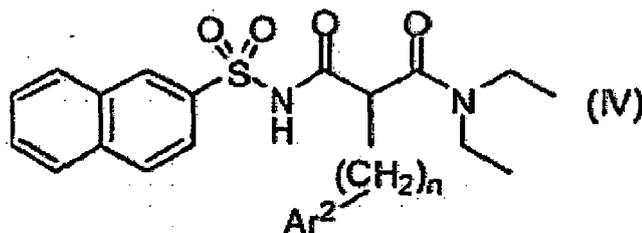
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30 dans laquelle  $R^{12}$ ,  $R^{17}$ , Y et Z sont tels que définis dans la revendication 1, l'un de  $R^{19}$  et de  $R^{20}$  représente un atome d'hydrogène, et l'autre représente un groupe isopropyle, isobutyle, néopentyle, allyle, cyclopropylméthyle ou  $-CH_2-Ar^2$ , où  $Ar^2$  est tel que défini dans la revendication 1, ou un sel pharmacologiquement acceptable de celui-ci.

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4. Dérivé de sulfonyl-malonamide selon la revendication 1, qui est représenté par la formule (IV) suivante

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dans laquelle n est un nombre entier de 1 à 3,  $Ar^2$  est tel que défini dans la revendication 1, ou un sel pharmaceutiquement acceptable de celui-ci.

5. Dérivé de sulfonyl-malonamide selon la revendication 4, où  $Ar^2$  représente un groupe phényle substitué représenté par la formule suivante

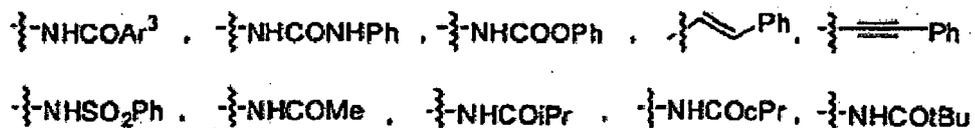
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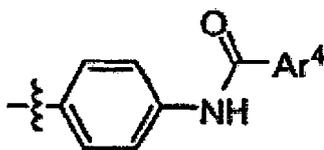
dans laquelle  $R^{21}$  représente un atome de fluor, un atome de chlore, un groupe nitro, cyano, amino (en excluant

une substitution au niveau de la position ortho), diméthylamino, méthoxy, trifluorométhoxy, méthoxycarbonyle, phényle, 2-pyridyloxy, 1-imidazolyle, 2-isoindolinyne, 1-oxo-2-isoindolinyne ou la formule suivante

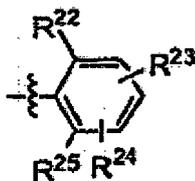


où Ar<sup>3</sup> est tel que défini dans la revendication 2, ou un sel pharmacologiquement acceptable de celui-ci.

6. Dérivé de sulfonyl-malonamide selon la revendication 4, où Ar<sup>2</sup> représente un groupe phényle substitué représenté par la formule suivante



dans laquelle Ar<sup>4</sup> représente un groupe 2-thiényle, 2-furyle, 4-pyridyle, 3-pyridyle, 2-pyridyle ou la formule suivante



dans laquelle R<sup>22</sup> et R<sup>25</sup> sont identiques ou différents et chacun représente un atome d'hydrogène, un groupe amino, un atome de fluor, un groupe hydroxy, méthoxy, méthyle ou un atome de chlore, R<sup>23</sup> représente un atome d'hydrogène ou un atome de fluor, et R<sup>24</sup> représente un atome d'hydrogène, un atome de fluor, un atome de chlore, un groupe méthyle, amino, méthoxy ou cyano, et n vaut 1, ou un sel pharmacologiquement acceptable de celui-ci.

7. Dérivé de sulfonyl-malonamide selon la revendication 1, qui est un composé choisi parmi :

le N,N-diéthyl-2-{4-[(2,6-difluorobenzoyl)amino]benzyl}-N'-(2-naphtylsulfonyl)malonamide,  
 le (2S)-2-[4-(benzoylamino)benzyl]-N,N-diéthyl-N'-(2-naphtylsulfonyl)malonamide,  
 le (2S)-N,N-diéthyl-2-[4-[(2-fluorobenzoyl)amino]benzyl]-N'-(2-naphtylsulfonyl)malonamide,  
 le (2S)-N,N-diéthyl-2-[4-[(3-fluorobenzoyl)amino]benzyl]-N'-(2-naphtylsulfonyl)malonamide,  
 le (2S)-N,N-diéthyl-2-[4-[(2,4-difluorobenzoyl)amino]benzyl]-N'-(2-naphtylsulfonyl)malonamide,  
 le (2S)-N,N-diéthyl-2-[4-[(4-méthylbenzoyl)amino]benzyl]-N'-(2-naphtylsulfonyl)malonamide,  
 le (2S)-N,N-diéthyl-N'-(2-naphtylsulfonyl)-2-[4-[(2-thiényle)amino]benzyl]malonamide,  
 le (2S)-N,N-diéthyl-2-[4-[(2-furoyle)amino]benzyl]-N'-(2-naphtylsulfonyl)malonamide,  
 le (2S)-2-[4-[(2-amino-5-fluorobenzoyl)amino]benzyl]-N,N-diéthyl-N'-(2-naphtylsulfonyl)malonamide,  
 le (2S)-2-[4-[(2-amino-6-fluorobenzoyl)amino]benzyl]-N,N-diéthyl-N'-(2-naphtylsulfonyl)malonamide,  
 le (2S)-N,N-diéthyl-N'-(2-naphtylsulfonyl)-2-[4-[(2-pyridylcarbonyl)amino]benzyl]malonamide,  
 le (2S)-2-[4-[(2-amino-4-chlorobenzoyl)amino]benzyl]-N,N-diéthyl-N'-(2-naphtylsulfonyl)malonamide,  
 le (2S)-2-[4-[(2-aminobenzoyl)amino]benzyl]-N,N-diéthyl-N'-(2-naphtylsulfonyl)malonamide,  
 le (2S)-2-[4-[(2-amino-5-chlorobenzoyl)amino]benzyl]-N,N-diéthyl-N'-(2-naphtylsulfonyl)malonamide,  
 le (2S)-2-[4-[(2-amino-4,5-difluorobenzoyl)amino]benzyl]-N,N-diéthyl-N'-(2-naphtylsulfonyl)malonamide,  
 le (2S)-2-[4-[(2-amino-4-fluorobenzoyl)amino]benzyl]-N,N-diéthyl-N'-(2-naphtylsulfonyl)malonamide,  
 le (2S)-2-[4-[(2-amino-5-méthylbenzoyl)amino]benzyl]-N,N-diéthyl-N'-(2-naphtylsulfonyl)malonamide,  
 le 2-(4-fluorobenzyl)-N-isopropyl-N-(3-pyridyl)-N'-((E)-styrylsulfonyl)malonamide,

le 2-allyl-N-(4-fluorophényl)-N-isopropyl-N'-((E)-styrylsulfonyl)malonamide,  
le N-(4-fluorophényl)-2-isobutyl-N-isopropyl-N'-((E)-styrylsulfonyl)malonamide,  
le N-(4-fluorophényl)-2-isobutyl-N-isopropyl-N'-phénéthylsulfonylmalonamide,  
le N-(4-fluorophényl)-2-isobutyl-N-isopropyl-N'-(2-naphtylsulfonyl)malonamide,  
5 le (2S ou 2R)-2-cyclopropylméthyl-N-(4-fluorophényl)-N-isopropyl-N'-((E)-2-styrylsulfonyl)malonamide,  
le 2-cyclopropylméthyl-N-(4-fluorophényl)-N-isopropyl-N'-phénéthylsulfonylmalonamide, ou  
le 2-cyclopropylméthyl-N-(4-fluorophényl)-N-isopropyl-N'-(2-naphtylsulfonyl)malonamide,

ou un sel pharmacologiquement acceptable de celui-ci.

- 10
- 8.** Composition pharmaceutique comprenant le dérivé de sulfonyl-malonamide selon l'une quelconque des revendications 1 à 7, ou un sel pharmacologiquement acceptable de celui-ci, en tant que principe actif.
- 9.** Dérivé de sulfonyl-malonamide selon l'une quelconque des revendications 1 à 7, ou un sel pharmacologiquement acceptable de celui-ci pour une utilisation en tant qu'agoniste du récepteur AT<sub>2</sub>.
- 15
- 10.** Dérivé de sulfonyl-malonamide selon la revendication 7, ou un sel pharmacologiquement acceptable de celui-ci pour une utilisation en tant qu'agoniste du récepteur AT<sub>2</sub>.
- 11.** Dérivé de sulfonyl-malonamide selon la revendication 10, où l'agoniste du récepteur AT<sub>2</sub> est sélectif du récepteur AT<sub>2</sub>.
- 20
- 12.** Dérivé de sulfonyl-malonamide selon l'une quelconque des revendications 1 à 7, ou un sel pharmacologiquement acceptable de celui-ci pour une utilisation dans le traitement et la prophylaxie d'un trouble impliquant le système rénine-angiotensine-aldostérone.
- 25
- 13.** Dérivé de sulfonyl-malonamide selon la revendication 12, où le trouble impliquant le système rénine-angiotensine-aldostérone est choisi parmi un accident vasculaire cérébral, une maladie rénale, une maladie cardiaque, l'hypertension, le diabète, des complications diabétiques, une hyperlipidémie et un syndrome métabolique.

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