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(54) SUBSTITUTED AROMATIC-RING COMPOUNDS, PROCESS FOR PRODUCING THE SAME, AND USE

SUBSTITUIERTE AROMATISCHE RINGVERBINDUNGEN, VERFAHREN ZU IHRER HERSTELLUNG UND IHRE ANWENDUNG

COMPOSES A CYCLE AROMATIQUE SUBSTITUES, PROCEDE DE PRODUCTION, ET UTILISATION

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(56) References cited:
WO-A1-96/31492 **WO-A1-99/46242**
US-A- 5 378 703

- **GRAAFLAND TEUN ET AL.: 'Structure and reactivity in intramolecular catalysis. Catalysis of sulfonamide hydrolysis by the neighboring carboxyl group' J. AM. CHEM. SOC. vol. 101, no. 23, 1979, pages 6981 - 6991**

EP 1 209 149 B9

Description

Technical Field

[0001] The present invention relates to a novel cycloalkene derivative having a suppressive activity on the production of inducible nitric oxide synthase-derived nitric oxide (NO) production and/or a suppressive activity on the production of inflammatory cytokines such as TNF-α, IL-1, IL-6, which is useful as an agent for the prophylaxis and treatment of diseases such as cardiac disease, autoimmune disease, inflammatory disease, central nervous system disease, infectious disease, sepsis and septic shock, and a production method thereof and use thereof.

Background Art

[0002] Nitric oxide (NO) has been reported to play various roles in the physiological activity in the body of mammal; for example, as a vasodilator in the vascular system [Pharmacol. Rev., vol. 43, 109-142 (1991)], as a factor showing tumor cell eradicating activity in the leukocyte system [Curr. Opin. Immunol., vol. 3, 65-70 (1991)], and as a neurotransmitter in the nervous system [Neuron, vol. 8, 3-11 (1992)]. Basically, NO is produced from L-arginine by NO synthase (NOS), and to date, the presence of three kinds of isoforms of genetically nerve NOS, vascular endothelial NOS and inducible NOS (iNOS) has been clarified [Cell, vol. 70, pp. 705-707 (1992)]. Based on the mode of presence, the former two are also referred to as constitutive NOS (cNOS) as contrasted with the latter as iNOS.

[0003] The cNOS is considered to be present in the vascular endothelial cell and neurocyte, be calcium calmodulin-dependant, produce a small amount of NO by activation of various receptor stimulations, and to be responsible for the aforementioned physiological control. In contrast, iNOS is known to be induced by various cytokines, bacterial lipopolysaccharides (LPS) to produce a large amount of NO in a sustained manner in macrophage, neutrophile, and to damage and hurt cells and tissues at a production site, while showing the above-mentioned physiological activity [Immunol. Today, vol. 13, 157-160 (1992)]. Known cells and tissues that express iNOS are the aforementioned cells, as well as hepatocyte, kupffer's cell, glia cell, vascular smooth muscle cell, vascular endothelial cell, inner membrane of cardiac muscle, cardiac muscle cell, mesangial cell, chondrocyte, synovial cell, pancreatic β cell, osteoclast and the like [FASEB J., vol. 6, 3051-3064 (1992), Arch Surg., vol. 128, 396-401 (1993), J. Biol. Chem., vol. 44, 27580-27588 (1994), J. Cell. Biochem., vol. 57, 399-408 (1995)].

[0004] Heretofore, L-arginine analogs [Pharmacol. Rev., vol. 43, 109-142 (1991)], aminoguanidine [Br. J. Pharmacol., vol. 110, 963-968 (1993)], S-ethylisothiourea [J. Biol. Chem., vol. 43, 26669-26676 (1994)] have been reported to inhibit iNOS.

[0005] It is also known that cytokines, such as TNF-α, IL-1, IL-6, are secreted by various cells such as monocyte, macrophage, lymphocyte, neutrophile, fibroblast, vascular endothelial cell and widely involved in biological defense and immune system based on inflammation [The Cytokine Handbook, 2nd ed Academic Press Limited (1994), Advances Immunol., vol. 62, 257-304 (1996)].

[0006] It has been clarified that TNF-α and IL-1 show activities such as (1) fever, (2) activation and promoted chemotaxis of inflammatory cells such as macrophage, neutrophile, (3) induction of inflammatory cytokines such as IL-1, IL-6, IL-8, TNF, CSF and acute protein, (4) promotion of production of various chemical mediators such as NO, O_2^-, PAF, prostaglandin, leukotriene, protease ; and that IL-6 shows activity such as (1) introduction of acute protein, (2) increasing blood platelet, (3) differentiation and activation of lymphocyte and NK cell, (4) growth of osteoclast. However, excess production of these cytokines and production thereof at inappropriate sites and time is inconvenient for organisms. For example, these cytokines have been found to be involved in various diseases such as cachexia, allergic disease, rheumatoid arthritis, abscess, graft rejection, anemia, arteriosclerosis, autoimmune disease, diabetes, central nervous system disease, inflammatory bowel disease, cardiac disease, hepatitis, cirrhosis, nephritis, osteoporosis, psoriasis, septic shock, caused by protozoan, bacteria, fungi, virus and cancer. It has been described that a substance that suppresses or antagonizes production of TNF-α, IL-1, IL-6 can be a therapeutic drug of these diseases [Eur. J. Immunol., vol. 18, 951-956 (1991), Immunol., vol. 83, 262-267 (1994), Proc. Natl. Acad. Sci., vol. 93, 3967-3971 (1997), J. Immunol., vol. 147, 1530-1536 (1991), Immunol. Today, vol. 12, 404-410 (1991)].

[0007] Because substances that suppress NO production by iNOS inducible cell, thereby to treat cardiac disease, autoimmune disease, inflammatory disease, septic shock are considered to be effective as a prophylactic and therapeutic drug of various diseases, such as arteriosclerosis, myocarditis, cardiac myopathy, brain ischemic disorder, Alzheimer's disease, multiple sclerosis, septic shock, rheumatoid arthritis, osteoarthritis, gastric ulcer, duodenal ulcer, ulcerative colitis, diabetes, glomerular nephritis, osteoporosis, pneumonia, hepatitis, psoriasis, graft rejection, pain, and because the cells targeted by cytokines are diversified over, for example, the inflammation system, the vascular system, the central nervous system, the hematopoietic system, the endocrine system, the biological activities thereof are considered to be diversified, too. These compounds, however, are not entirely satisfactory from the aspect of activity, and are associated with problems that they inhibit not only iNOS but also cNOS responsible for physiological activity.

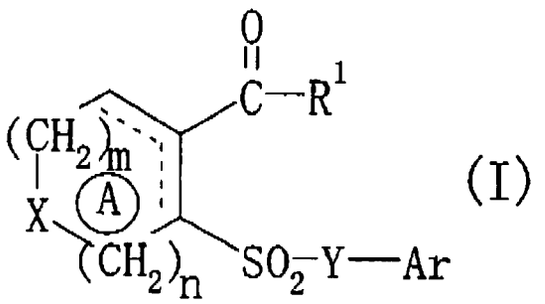
[0008] Therefore, the invention provides an improved agent for the prophylaxis or treatment of diseases such as cardiac disease, autoimmune disease, inflammatory disease and septic shock.

Disclosure of the Invention

[0009] In view of the current situation, the present inventors have conducted researches and study of an agent for the prophylaxis or treatment of the aforementioned diseases, which suppresses NO production from iNOS inducible cells and/or production of inflammatory cytokines, and synthesized, for the first time, the compound of the present invention and found that the obtained compound unexpectedly has, based on its chemical structure, a superior inhibitory activity on NO and/or cytokine production, has a superior action of inhibiting not only NO production from iNOS inducible cell but also production of inflammatory cytokines, can be a prophylactic and therapeutic agent more effective than conventional drugs, and that the compound has superior properties of a clinically useful pharmaceutical agent against the diseases such as cardiac disease, autoimmune disease, inflammatory disease, septic shock, where inflammatory cytokine, such as TNF-α, IL-1, IL-6, and NO are considered to not act independently from each other but cause progression of the diseases because of their complicated relationship.

[0010] Accordingly, the present invention relates to:

[1] A compound of the formula:



(I)

wherein

R^1 is (i) an aliphatic hydrocarbon group selected from C_{1-20} alkyl group, C_{3-10} cycloalkyl group, C_{4-12} cycloalkylalkyl group, C_{3-6} alkenyl group and C_{3-6} alkynyl group, wherein these aliphatic hydrocarbon groups optionally have 1 to 4 substituent(s) selected from the group consisting of heterocyclic group, oxo group, hydroxy group, C_{1-6} alkoxy group, C_{3-10}, cycloalkyloxy group, C_{6-10} aryloxy group, C_{7-19} aralkyloxy group, heterocyclyloxy group, C_{1-6} alkylthio group (the sulfur atom being optionally oxidized), C_{3-10} cycloalkylthio group (the sulfur atom being optionally oxidized), C_{6-10} arylthio (the sulfur atom being optionally oxidized), C_{7-19} aralkylthio group (the sulfur atom being optionally oxidized), heterocyclylthio group, heterocyclylsulfinyl group, heterocyclylsulfonyl group, nitro group, halogen atom, cyano group, carboxyl group, C_{1-10} alkoxy-carbonyl group, C_{3-6} cycloalkyloxycarbonyl group, C_{6-10} aryloxy-carbonyl group, C_{7-19} aralkyloxy-carbonyl group, heterocyclic oxycarbonyl group, C_{6-10} arylcarbonyl group, C_{1-6} alkanoyl group, C_{3-5} alkenoyl group, C_{6-10} aryl- carbonyloxy group, C_{2-6} alkanoyloxy group, C_{3-5} alkenoyloxy group, carbamoyl group (optionally substituted by 1 or 2 substituent(s) selected from C_{1-4} alkyl, phenyl, C_{1-7} acyl and C_{1-4} alkoxy- phenyl), thiocarbamoyl group (optionally substituted by 1 or 2 substituent(s) selected from C_{1-4} alkyl and phenyl), carbamoyloxy group (optionally substituted by 1 or 2 substituent(s) selected from C_{1-4} alkyl and phenyl), C_{1-6} alkanoylamino group, C_{6-10} aryl-carbonylamino group, C_{1-10} alkoxy-carboxamido group, C_{6-10} aryloxy-carboxamido group, C_{7-19} aralkyloxy- carboxamido group, C_{1-10} alkoxy-carbonyloxy group, C_{6-10} aryloxy-carbonyloxy group, C_{7-19} aralkyloxy- carbonyloxy group, C_{3-10} cycloalkyloxy-carbonyloxy group and ureido group (optionally having 1 to 3 substituent(s) selected from C_{1-4} alkyl group and phenyl group) (hereinafter substituent group A) and a group consisting of C_{6-10} aryl group optionally having 1 to 4 substituent(s) selected from substituent group A (hereinafter substituent group B), said heterocyclic group is a 5 to 8-membered heterocyclic group having, besides carbon atoms, 1 to 4 hetero atom(s) selected from a nitrogen atom (optionally oxidized), an oxygen atom and a sulfur atom, or a fused ring thereof, which optionally has 1 to 3 substituent(s) selected from C_{1-4} alkyl, hydroxy, oxo and C_{1-4} alkoxy, and said substituents may form, together with an aliphatic hydrocarbon group, a fused ring optionally

having 1 to 4 substituent(s) selected from substituent group B, (ii) C_{6-14} aryl group optionally having 1 to 5 substituent(s) selected from a group consisting of halogen atom, C_{1-4} alkyl group, C_{1-4} alkoxy group, C_{1-4} alkoxy-carbonyl group, carboxyl group, nitro group, cyano group, hydroxy group, C_{1-4} alkanoylamino group, C_{3-6} cycloalkyl group, C_{6-10} aryl group, halogeno C_{1-4} alkyl group, halogeno C_{1-4} alkoxy group, C_{1-4} alkylthio group, C_{1-4} alkylsulfonyl group, C_{1-4} alkanoyl group, 5-membered aromatic heterocyclic group, carbamoyl group, C_{1-4} alkyl-carbamoyl group, C_{1-4} alkoxy-carbonyl-C_{1-4} alkyl- carbamoyl group and 1,3-diacylguanidino-C_{1-4} alkyl group (hereinafter substituent group C), (iii) a 5 to 8-membered heterocyclic ring having, besides carbon atoms, 1 to 4 hetero atom(s) selected from a nitrogen atom (optionally oxidized), an oxygen atom and a sulfur atom, or a fused ring thereof, which heterocyclic group may have 1 to 3 substituent(s) selected from C_{1-4} alkyl, hydroxy, oxo and C_{1-4}, alkoxy, (iv) a group of the formula: OR^{1a} wherein R^{1a} is a hydrogen atom or an aliphatic hydrocarbon group selected from C_{1-20} alkyl group, C_{3-10} cycloalkyl group, C_{4-12} cycloalkylalkyl group, C_{3-6} alkenyl group and C_{3-6} alkynyl group optionally having substituent(s) selected from substituent group B, or (v) a group of the formula:

(a)

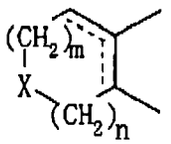
wherein R^{1b} and R^{1c} are the same or different and each is a hydrogen atom or an aliphatic hydrocarbon group

X selected from C_{1-20} alkyl group, C_{3-10} cycloalkyl group, C_{4-12} cycloalkylalkyl group, C_{3-6} alkenyl group and C_{3-6} alkynyl group optionally having substituent(s) selected from substituent group B; is a methylene group, a nitrogen atom, a sulfur atom or an oxygen atom; and

Y is (i) a methylene group optionally having substituent(s) selected from C_{1-6} alkyl group, hydroxy substituted-C_{1-6} alkyl group and C_{1-4} alkoxy-carbonyl- C_{1-4} alkyl group or (ii) a nitrogen atom optionally having substituent(s) selected from C_{1-6} alkyl group, hydroxy substituted- C_{1-6} alkyl group and C_{1-4} alkoxy-carbonyl-C_{1-4} alkyl group;

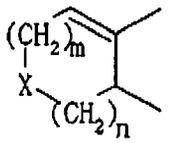
ring A is optionally substituted by 1 to 4 substituent(s) selected from the following (1) to (4): (1) an aliphatic hydrocarbon group selected from C_{1-20} alkyl group, C_{3-10} cycloalkyl group, C_{4-12} cycloalkylalkyl group, C_{3-6} alkynyl group and C_{3-6} alkynyl group optionally having substituent(s) selected from substituent group B, (2) C_{6-14} aryl group optionally having substituent(s) selected from substituent group C, (3) a group of the formula: OR^2 wherein R^2 is a hydrogen atom, or an aliphatic hydrocarbon group selected from C_{1-20} alkyl group, C_{3-10} cycloalkyl group, C_{4-12} cycloalkylalkyl group, C_{3-6} alkenyl group and C_{3-6} alkynyl group, optionally having substituent(s) selected from substituent group B and (4) a halogen atom;

Ar is a C_{6-14} aryl group optionally having substituent(s) selected from substituent group C; and the group of the formula:



(b)

is a group of the formula:



(b1)

wherein

m is 1; and

n is 1

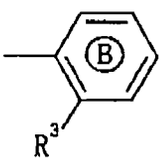
provided that when X is a methylene group, Y is a methylene group optionally having substituent(s) selected from C_{1-6} alkyl group, hydroxy substituted-C_{1-6} alkyl group and C_{1-4} alkoxy-carbonyl-C_{1-4} alkyl group, or a salt thereof.

[2] The compound of [1], wherein the ring A is optionally substituted by C_{1-6} alkyl, phenyl or halogen, R^1 is OR^{1a} wherein R^{1a} is a C_{1-6} alkyl group, and Ar is a phenyl group optionally having substituent(s) selected from substituent group C.

[3] The compound of [2], wherein R^{1a} is an ethyl group.

[4] The compound of [2], wherein Ar is a halogeno phenyl group, a C_{1-4} alkylphenyl group or a phenyl group substituted by halogen and C_{1-4} alkyl.

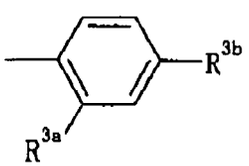
[5] The compound of [2], wherein Ar is a group of the formula:



(c)

wherein R^3 is a halogen atom or a C_{1-4} alkyl group and ring B are optionally further substituted by halogen atom.

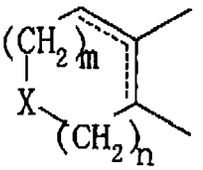
[6] The compound of [5], wherein Ar is a group of the formula:



(c1)

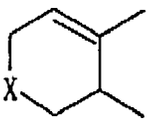
wherein R^{3a} and R^{3b} are the same or different and each is a halogen atom.

[7] The compound of [1], wherein R^1 is a group of the formula: $OR^{1a'}$ wherein $R^{1a'}$ is a C_{1-6} alkyl group, a group of the formula:



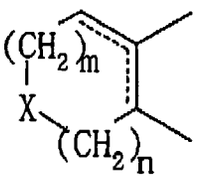
(b)

is a group of the formula:



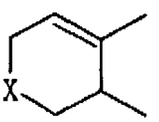
X is methylene or an oxygen atom, Y is methylene or -NH-, Ar is a phenyl group optionally having 1 or 2 substituent (s) selected from the group consisting of halogen atom and C_{1-6} alkoxy.

[8] The compound of [1], wherein R^1 is a group of the formula: $OR^{1a'}$ wherein $R^{1a'}$ is a C_{1-6} alkyl group, a group of the formula:



(b)

is a group of the formula:



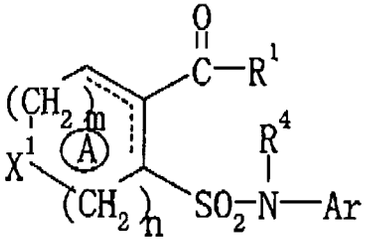
X is methylene and Y is methylene, or X is an oxygen atom and Y is -NH-, and Ar is a phenyl group optionally having two halogen atoms.

[9] Ethyl 6-[(2-chloro-4-fluorobenzyl)sulfonyl]-1-cyclahexene-1-carboxylate.

[10] Ethyl (+)-6-[(2-chloro-4-fluorobenzyl)sulfonyl]-1-cyclohexene-1-carboxylate.

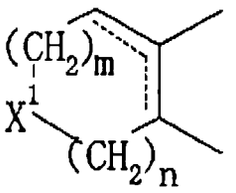
[11] Ethyl 3-[(2-chloro-4-fluorophenyl)sulfamoyl]-3,6-dihydro-2H-pyran-4-carboxylate, or a salt thereof.

[12] A production method of a compound of the formula:



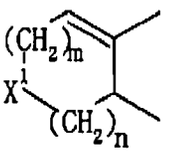
(Ia)

wherein
the group of the formula:



(b')

is a group of the formula:



(b1')

wherein

m is 1;

n is 1;

R^1 is (i) an aliphatic hydrocarbon group selected from C_{1-20} alkyl group, C_{3-10} cycloalkyl group, C_{1-12} cycloalkylalkyl group, C_{3-6} alkenyl group and C_{3-6} alkynyl group, wherein these aliphatic hydrocarbon groups optionally have 1 to 4 substituent(s) selected from the group consisting of heterocyclic group, oxo group, hydroxy group, C_{1-6} alkoxy group, C_{3-10} cycloalkyloxy group, C_{5-10} aryloxy group, C_{7-19} aralkyloxy group, heterocyclyloxy group, C_{1-6} alkylthio group (the sulfur atom being optionally oxidized), C_{3-10} cycloalkylthio group (the sulfur atom being optionally oxidized), C_{6-10} arylthio (the sulfur atom being optionally oxidized), C_{7-19} aralkylthio group (the sulfur atom being optionally oxidized), heterocyclylthio group, heterocyclylsulfinyl group, heterocyclylsulfonyl group, nitro group, halogen atom, cyano group, carboxyl group, C_{1-10} alkoxy-carbonyl group, C_{3-6} cycloalkyloxycarbonyl group, C_{6-10} aryloxy-carbonyl group, C_{7-19} aralkyloxy-carbonyl group, heterocyclic oxycarbonyl group, C_{6-10} arylcarbonyl group, C_{1-6} alkanoyl group, C_{3-5} alkenoyl group, C_{6-10} aryl- carbonyloxy group, C_{2-6} alkanoyloxy group, C_{3-5} alkenoyloxy group, carbamoyl group (optionally substituted by 1 or 2 substituent(s) selected from C_{1-4} alkyl, phenyl, C_{1-7} acyl and C_{1-4} alkoxy- phenyl), thiocarbamoyl group (optionally substituted by 1 or 2 substituent(s) selected from C_{1-4} alkyl and phenyl), carbamoyloxy group (optionally substituted by 1 or 2 substituent(s) selected from C_{1-4} alkyl and phenyl), C_{1-6} alkanoylamino group, C_{6-10} aryl-carbonylamino group, C_{1-10} alkoxy-carboxamido group, C_{6-10} aryloxy-carboxamido group, C_{7-19} aralkyloxy- carboxamido group, C_{1-10} alkoxy-carbonyloxy group, C_{6-10} aryloxy-carbonyloxy group, C_{7-19} aralkyloxy- carbonyloxy group, C_{3-10} cycloalkyloxy-carbonyloxy group and ureido group (optionally having 1 to 3 substituent(s) selected from C_{1-4} alkyl group and

phenyl group) (hereinafter substituent group A) and a group consisting of C_{6-10} aryl group optionally having 1 to 4 substituent(s) selected from substituent group A (hereinafter substituent group B), said heterocyclic group is a 5 to 8-membered heterocyclic group having, besides carbon atoms, 1 to 4 hetero atom(s) selected from a nitrogen atom (optionally oxidized), an oxygen atom and a sulfur atom, or a fused ring thereof, which optionally has 1 to 3 substituent (s) selected from C_{1-4} alkyl, hydroxy, oxo and C_{1-4} alkoxy, and said substituents may form, together with an aliphatic hydrocarbon group, a fused ring optionally having 1 to 4 substituent(s) selected from substituent group B, (ii) C_{6-14} aryl group optionally having 1 to 5 substituerit(s) selected from a group consisting of halogen atom, C_{1-4} alkyl group, C_{1-4} alkoxy group, C_{1-4} alkoxy-carbonyl group, carboxyl group, nitro group, cyano group, hydroxy group, C_{1-4}, alkanoylamino group, C_{3-6} cycloalkyl group, C_{6-10} aryl group, halogeno C_{1-4} alkyl group, halogeno C_{1-4} alkoxy group, C_{1-4} alkylthio group, C_{1-4} alkylsulfonyl group, C_{1-4} alkanoyl group, 5-membered aromatic heterocyclic group, carbamoyl group, C_{1-4} alkyl-carbamoyl group, C_{1-4}, alkoxy- carbonyl-C_{1-4} alkyl-carbamoyl group and 1,3- diacylguanidino-C_{1-4} alkyl group (hereinafter substituent group C), (iii) a 5 to 8-membered heterocyclic ring having, besides carbon atoms, 1 to 4 hetero atom(s) selected from a nitrogen atom (optionally oxidized), an oxygen atom and a sulfur atom, or a fused ring thereof, which heterocyclic group may have 1 to 3 substituent(s) selected from C_{1-4} alkyl, hydroxy, oxo and C_{1-4} alkoxy, (iv) a group of the formula: OR^{1a} wherein R^{1a} is a hydrogen atom or an aliphatic hydrocarbon group selected from C_{1-20} alkyl group, C_{3-10} cycloalkyl group, C_{4-12} cycloalkylalkyl group, C_{3-6} alkenyl group and C_{3-6} alkynyl group optionally having substituent(s) selected from substituent group B, or (v) a group of the formula:

(a)

wherein R^{1b} and R^{1c} are the same or different and each is a hydrogen atom or an aliphatic hydrocarbon group selected from C_{1-20} alkyl group, C_{3-10} cycloalkyl group, C_{4-12} cycloalkylalkyl group, C_{3-6} alkenyl group and C_{3-6}
alkynyl group optionally having substituent(s) selected from substituent group B;

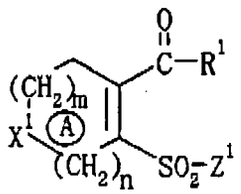
x^1 is a nitrogen atom, a sulfur atom or an oxygen atom; and

ring A is optionally substituted further by 1 to 4 substituent(s) selected from the following (1) to (4): (1) an aliphatic hydrocarbon group selected from C_{1-20} alkyl group, C_{3-10} cycloalkyl group, C_{4-12} cycloalkylalkyl group, C_{3-6} alkenyl group and C_{3-6} alkynyl group optionally having substituent(s) selected from substituent group B, (2) C_{6-14} aryl group optionally having substituent(s) selected from substituent group C, (3) a group of the formula: OR^2 wherein R^2 is a hydrogen atom, or an aliphatic hydrocarbon group selected from C_{1-20} alkyl group, C_{3-10} cycloalkyl group, C_{4-12} cycloalkylalkyl group, C_{3-6} alkenyl group and C_{3-6} alkynyl group, optionally having substituent(s) selected from substituent group B and (4) a halogen atom;

R^4 is a hydrogen atom or a C_{1-6} alkyl group which may be substituted with hydroxyl, or C_{1-4}-alkoxy carbonyl; and

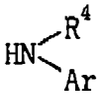
Ar is a C_{6-14} aryl group optionally having substituent(s) selected from substituent group C;

or a salt thereof, which method comprises reacting a compound of the formula:



(II)

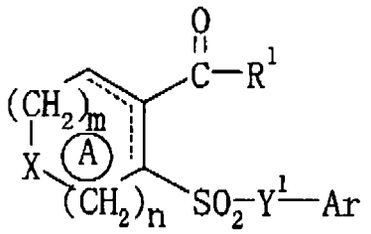
wherein Z^1 is a leaving group and other symbols are as defined above, or a salt thereof and a compound of the formula:



(III)

wherein each symbol is as defined above, or a salt thereof.

[13] A production method of a compound of the formula:



(Ib)

wherein

R^1 is (i) an aliphatic hydrocarbon group selected from C_{1-20} alkyl group, C_{3-10} cycloalkyl group, C_{4-12} cycloalkylalkyl group, C_{3-6} alkenyl group and C_{3-6} alkynyl group, wherein these aliphatic hydrocarbon groups optionally have 1 to 4 substituent(s) selected from the group consisting of heterocyclic group, oxo group, hydroxy group, C_{1-6} alkoxy group, C_{3-10} cycloalkyloxy group, C_{6-10} aryloxy group, C_{7-19} aralkyloxy group, heterocyclyloxy group, C_{1-6} alkylthio group (the sulfur atom being optionally oxidized), C_{3-10} cycloalkylthio group (the sulfur atom being optionally oxidized), C_{6-10} arylthio (the sulfur atom being optionally oxidized), C_{7-19} aralkylthio group (the sulfur atom being optionally oxidized), heterocyclylthio group, heterocyclylsulfinyl group, heterocyclylsulfonyl group, nitro group, halogen atom, cyano group, carboxyl group, C_{1-10} alkoxy-carbonyl group, C_{3-6} cycloalkyloxycarbonyl group, C_{6-10} aryloxy-carbonyl group, C_{7-19} aralkyloxy-carbonyl group, heterocyclic oxycarbonyl group, C_{6-10} arylcarbonyl group, C_{1-6} alkanoyl group, C_{3-5} alkenoyl group, C_{6-10} aryl- carbonyloxy group, C_{2-6} alkanoyloxy group, C_{3-5} alkenoyloxy group, carbamoyl group (optionally substituted by 1 or 2 substituent(s) selected from C_{1-4} alkyl, phenyl, C_{1-7} acyl and C_{1-4} alkoxy- phenyl), thiocarbamoyl group (optionally substituted by 1 or 2 substituent(s) selected from C_{1-4} alkyl and phenyl), carbamoyloxy group (optionally substituted by 1 or 2 substituent(s) selected from C_{1-4} alkyl and phenyl), C_{1-6} alkanoylamino group, C_{1-10} aryl-carbonylamino group, C_{1-10} alkoxy-carboxamido group, C_{6-10} aryloxy-carboxamido group, C_{7-19} aralkyloxy- carboxamido group, C_{1-10} alkoxy-carbonyloxy group, C_{6-10} aryloxy-carbonyloxy group, C_{7-19} aralkyloxy- carbonyloxy group, C_{3-10} cycloalkyloxy-carbonyloxy group and ureido group (optionally having 1 to 3 substituent(s) selected from C_{1-4} alkyl group and phenyl group) (hereinafter substituent group A) and a group consisting of C_{6-10} aryl group optionally having 1 to 4 substituent(s) selected from substituent group A (hereinafter substituent group B), said heterocyclic group is a 5 to 8-membered heterocyclic group having, besides carbon atoms, 1 to 4 hetero atom(s) selected from a nitrogen atom (optionally oxidized), an oxygen atom and a sulfur atom, or a fused ring thereof, which optionally has 1 to 3 substituent(s) selected from C_{1-4} alkyl, hydroxy, oxo and C_{1-4} alkoxy, and said substituents may form, together with an aliphatic hydrocarbon group, a fused ring optionally having 1 to 4 substituent(s) selected from substituent group B, (ii) C_{6-14} aryl group optionally having 1 to 5 substituent(s) selected from a group consisting of halogen atom, C_{1-4} alkyl group, C_{1-4} alkoxy group, C_{1-4} alkoxy-carbonyl group, carboxyl group, nitro group, cyano group, hydroxy group, C_{1-4} alkanoylamino group, C_{3-6} cycloalkyl group, C_{6-10} aryl group, halogeno C_{1-4} alkyl group, halogeno C_{1-4} alkoxy group, C_{1-4} alkylthio group, C_{1-4} alkylsulfonyl group, C_{1-4} alkanoyl group, 5-membered aromatic heterocyclic group, carbamoyl group, C_{1-4} alkyl-carbamoyl group, C_{1-4} alkoxy-carbonyl-C_{1-4} alkyl- carbamoyl group and 1,3-diacylguanidino-C_{1-4} alkyl group (hereinafter substituent group C), (iii) a 5 to 8-membered heterocyclic ring having, besides carbon atoms, 1 to 4 hetero atom(s) selected from a nitrogen atom (optionally oxidized), an oxygen atom and a sulfur atom, or a fused ring thereof, which heterocyclic group may have

1 to 3 substituent(s) selected from C_{1-4} alkyl, hydroxy, oxo, and C_{1-4} alkoxy, (iv) a group of the formula: OR^{1a} wherein R^{1a} is a hydrogen atom or an aliphatic hydrocarbon group selected from C_{1-20} alkyl group, C_{1-10} cycloalkyl group, C_{4-12} cycloalkylalkyl group, C_{3-6} alkenyl group and C_{3-6} alkynyl group optionally having substituent(s) selected from substituent group B, or (v) a group of the formula:

(a)

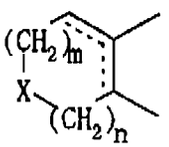
wherein R^{1b} and R^{1c} are the same or different and each is a hydrogen atom or an aliphatic hydrocarbon group selected from C_{1-20} alkyl group, C_{3-10} cycloalkyl group, C_{4-12} cycloalkylalkyl group, C_{3-6} alkenyl group and C_{3-6} alkynyl group optionally having substituent(s) selected from substituent group B;

X is a methylene group, a nitrogen atom, a sulfur atom or an oxygen atom; and

ring A is optionally substituted by 1 to 4 subetituent(s) selected from the following (1) to (4): (1) an aliphatic hydrocarbon group selected from C_{1-20} alkyl group, C_{3-10} cycloalkyl group, C_{4-12} cycloalkylalkyl group, C_{3-6} alkenyl group and C_{3-6} alkynyl group optionally having substituent(s) selected from substituent group B, (2) C_{6-14} aryl group optionally having substituent(s) selected from substituent group C, (3) a group of the formula: OR^2 wherein R^2 is a hydrogen atom, or an aliphatic hydrocarbon group selected from C_{1-20} alkyl group, C_{3-10} cycloalkyl group, C_{4-12} cycloalkylalkyl group, C_{3-15} alkenyl group and C_{3-6} alkynyl group, optionally having substituent(s) selected from substituent group B and (4) a halogen atom;

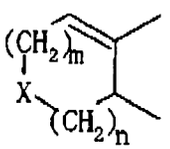
Y^1 is a methylene group optionally having substituent(s) selected from C_{1-6} alkyl group, hydroxy substituted-C_{1-6} alkyl group and C_{1-4} alkoxy-carbonyl-C_{1-4} alkyl group

Ar is a C_{6-14} aryl group optionally having substituent(s) selected from substituent group C; and the group of the formula:



(b)

is a group of the formula:

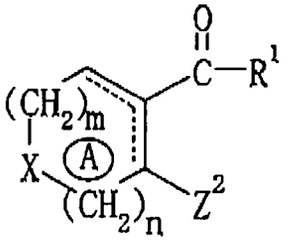


(b1)

wherein

m is 1; and

n is 1 or a salt thereof, which method comprises reacting a compound of the formula:



(IV)

wherein Z^2 is a leaving group and other symbols are as defined above, or a salt thereof, and a compound of the formula:

$$HS—Y^1—Ar \qquad (V1)$$

wherein each symbol is as defined above, or a salt thereof, and oxidizing the obtained sulfide.

[14] A pharmaceutical composition comprising a compound as defined in any of [1] to [11].

[15] The compound as defined in any of [1 to 11] or the composition as defined in [14] used for suppressing nitric oxide (NO) and/or cytokine production.

[16] The compound as defined in any of [1] to [11] or the composition as defined in [14] used for the prophylaxis or treatment of a cardiac disease, an autoimmune disease or septic shock.

[17] Use of the compound of any of [1] to [11] for the production of an agent for suppressing nitric oxide (NO) and/or cytokine production.

[18] Use of the compound of any of [1] to [11] for the production of an agent for the prophylaxis or treatment of a cardiac disease, an autoimmune disease or septic shock.

Best Mode for Embodying the Invention

[0011] In the present specification, R^1 is an aliphatic hydrocarbon group optionally having substituent(s), an aromatic hydrocarbon group optionally having substituent(s), an heterocyclic group optionally having substituent(s), a group of the formula: OR^{1a}, or a group of the formula (a). Particularly, a group of the formula: OR^{1a} is preferable.

[0012] The "aliphatic hydrocarbon group" of the "aliphatic hydrocarbon group optionally having substituent(s)" represented by R^1 is selected from alkyl group, cycloalkyl group, cycloalkylalkyl group, alkenyl group, and alkynyl group.

[0013] The alkyl group is a straight chain or branched alkyl group having 1 to 20 carboy atoms (e.g., methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, isobutyl group, sec-butyl group, tert-butyl group, pentyl group, hexyl group, heptyl group, octyl group, nonyl group, decyl group, dodecyl group). For example, alkyl group having 1 to 6 carbon atoms (e.g., methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, isobutyl group, sec-butyl group, tert-butyl group) are particularly preferable.

[0014] The cycloalkyl group is a cycloalkyl group having 3 to 10 carbon atoms (e.g., cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group, cycloheptyl group, cyclooctyl group). For example, cycloalkyl group having 3 to 6 carbon atoms (e.g., cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group) are particularly preferable.

[0015] The cycloalkylalkyl group is a cycloalkylalkyl group having 4 to 12 carbon atoms (e.g., cyclopropylmethyl group, cyclopentylmethyl group, cyclohexylmethyl group, cycloheptylmethyl group). For example, cycloalkylalkyl group having 4 to 8 (particularly 4 to 7) carbon atoms (e.g., cyclopropylmethyl group, cyclopentylmethyl group, cyclohexylmethyl group), are particularly preferable.

[0016] The alkenyl group is a alkenyl group having 3 to 6 carbon atoms (e.g., propenyl group, butenyl group, pentenyl group).

[0017] For example, lower alkenyl group having 3 or 4 carbon atoms (e.g., propenyl group, butenyl group) are particularly preferable.

[0018] The alkynyl group is a alkynyl group having 3 to 6 carbon atoms (e.g., propynyl group, butynyl group, pentynyl group).

[0019] For example, lower alkynyl group having 3 or 4 carbon atoms (e.g., propynyl group, butynyl group) are particularly preferable.

[0020] As the aforementioned "substituent" of the "aliphatic hydrocarbon group optionally having substituent(s)" heterocyclic group, oxo group, hydroxy group, C_{1-6} alkoxy group, C_{3-10} (particularly C_{3-6}) cycloalkyloxy group, C_{6-10} aryloxy group, C_{7-19} (particularly C_{7-12}) aralkyloxy group, heterocyclyloxy group, C_{1-6} alkylthio group (the sulfur atom being optionally oxidized), C_{3-10} (particularly C_{3-6}) cycloalkylthio group (the sulfur atom being optionally oxidized), C_{6-10} arylthio group (the sulfur atom being optionally oxidized), C_{7-19} (particularly C_{7-12}) aralkylthio group (the sulfur atom being optionally oxidized), heterocyclic thio group, heterocyclic sulfinyl group, heterocyclic sulfonyl group, nitro group, halogen atom, cyano group, carboxyl group, C_{1-10} (particularly C_{1-6}) alkoxy-carbonyl group, C_{3-5} cycloalkyloxy-carbonyl group, C_{6-10} aryloxy-carbonyl group, C_{7-19} (particularly C_{7-12}) aralkyloxy-carbonyl group, heterocyclic oxycarbonyl group, C_{6-10} aryl-carbonyl group, C_{1-6} alkanoyl group, C_{3-5} alkenoyl group, C_{6-10} aryl-carbonyloxy group, C_{2-6}alkanoyloxy group, C_{3-5} alkenoyloxy group, optionally substituted carbamoyl group, optionally substituted thiocarbamoyl group, optionally substituted carbamoyloxy group, C_{1-6} alkanoylamino group, C_{6-10} aryl-carbonylamino group, C_{1-10} (particularly C_{1-6}) alkoxy-carboxamido group, C_{6-10} aryloxy-carboxamido group, C_{7-19} (particularly C_{7-12})aralkyloxy-carboxamido group, C_{1-10} (particularly C_{1-6}) alkoxy-carbonyloxy group, C_{6-10} aryloxy-carbonyloxy group, C_{7-19} (particularly C_{7-12}) aralkyloxy-carbonyloxy group, C_{3-10} (particularly C_{3-6}) cycloalkyloxy-carbonyloxy group, optionally substituted ureido group, optionally substituted C_{6-10} aryl group are used.

[0021] These substituents are substituted at substitutable positions of the aforementioned "aliphatic hydrocarbon group". The substituent is not limited to one but may be in plurality (2 to 4), which may be the same or different.

[0022] As the "C_{1-6} alkoxy group", for example, methoxy group, ethoxy group, n-propoxy group, isopropoxy group, n-butoxy group, tert-butoxy group, n-pentyloxy group, n-hexyloxy group are preferable; as the "C_{3-10} cycloalkyloxy group", for example, cyclopropyloxy group, cyclohexyloxy group are preferable; as the "C_{6-10} aryloxy group", for example, phenoxy group, naphthyloxy group are preferable; as the "C_{7-19} aralkyloxy group", for example, benzyloxy group, 1-phenylethyloxy group, 2-phenylethyloxy group, benzhydryloxy group, 1-naphthylmethyloxy group are preferable; as the "C_{1-6} alkylthio group (the sulfur atom being optionally oxidized)", for example, methylthio group, ethylthio group, n-propylthio group, n-butylthio group, methylsulfinyl group, methylsulfonyl group are preferable; as the "C_{3-10} cycloalkylthio group (the sulfur atom being optionally oxidized)", for example, cyclopropylthio group, cyclohexylthio group, cyclopentylsulfinyl group, cyclohexylsulfonyl group are preferable; as the "C_{6-10} arylthio group (the sulfur atom being optionally oxidized)", for example, phenylthio group, naphthylthio group, phenylsulfinyl group, phenylsulfonyl group are preferable; as the "C_{7-19} aralkylthio group (the sulfur atom being optionally oxidized)", for example, benzylthio group, phenylethylthio group, benzhydrylthio group, benzylsulfinyl group, benzylsulfonyl group are preferable; as the "halogen atom", for example, fluorine atom, chlorine atom, bromine atom, iodine atom are preferable; as the "C_{1-10} alkoxy-carbonyl group", for example, methoxycarbonyl group, ethoxycarbonyl group, n-propoxycarbonyl group, isopropoxycarbonyl group, n-butoxycarbonyl group, isobutoxycarbonyl group, tert-butoxycarbonyl group are preferable; as the "C_{3-6} cycloalkyloxy-carbonyl group", for example, cyclopropyloxycarbonyl group, cyclopentyloxycarbonyl group, cyclohexyloxycarbonyl group, norbornyloxycarbonyl group are preferable; as the "C_{6-10} aryloxy-carbonyl group", for example, phenoxycarbonyl group, naphthyloxycarbonyl group are preferable; as the "C_{7-19} aralkyloxy-carbonyl group", for example, benzyloxycarbonyl group, benzhydryloxycarbonyl group, 2-phenethyloxycarbonyl group are preferable; as the "C_{6-10} aryl-carbonyl group", for example, benzoyl group, naphthoyl group, phenylacetyl group are preferable; as the "C_{1-6} alkanoyl group", for example, formyl group, acetyl group, propionyl, group, butyryl group, valeryl group, pivaloyl group are preferable; and as the "C_{3-5} alkenoyl group", for example, acryloyl group, crotonoyl group are preferable; as the "C_{6-10} aryl-carbonyloxy group", for example, benzoyloxy group, naphthoyloxy group, phenylacetoxy group are preferable; as the "C_{2-6}alkanoyloxy group", for example, acetoxy group, propionyloxy group, butyryloxy group, valeryloxy group, pivaloyloxy group are preferable; as the "C_{3-5} alkenoyloxy group", for example, acryloyloxy group, crotonoyloxy group are preferable.

[0023] The "optionally substituted carbamoyl group", for example, carbamoyl group, cyclic aminocarbonyl group is optionally substituted by 1 or 2 substituent(s) selected from C_{1-4} alkyl (e.g., methyl, ethyl), phenyl, C_{1-7} acyl (e.g., acetyl, propionyl, benzoyl), C_{1-4} alkoxy-phenyl (e.g., methoxyphenyl) which is specifically, for example, carbamoyl group, N-methylcarbamoyl group, N-ethylcarbamoyl group, N,N-dimethylcarbamoyl group, N,N-diethylcarbamoyl group, N-phenylcarbamoyl group, N-acetylcarbamoyl group, N-benzoylcarbamoyl group, N-(p-methoxyphenyl)carbamoyl group, 1-pyrrolidinylcarbonyl group, piperidinocarbonyl group, 1-piperazinylcarbonyl group, morpholinocarbonyl group. The "optionally substituted thiocarbamoyl group", for example, thiocarbamoyl group is optionally substituted by 1 or 2 substituent (s) selected from C_{1-4} alkyl (e.g., methyl, ethyl), phenyl, which is specifically, for example, thiocarbamoyl group, N-methylthiocarbamoyl group, N-phenylthiocarbamoyl group. The "optionally substituted carbamoyloxy group", for example, carbamoyloxy group is optionally substituted by 1 or 2 substituent(s) selected from C_{1-4} alkyl (e.g., methyl, ethyl), phenyl which is specifically, for example, carbamoyloxy group, N-methylcarbamoyloxy group, N',N-dimethylcarbamoyloxy group, N-ethylcarbamoyloxy group and N-phenylcarbamoyloxy group.

[0024] As the "C_{1-6} alkanoylamino group", for example, acetamido group, propionamido group, butyramido group, valeramido group, pivalamido group are used; as the "C_{6-10} aryl-carbonyl amino group", for example, benzamido group,

naphthamido group, phthalimido group are used; as the "C_{1-10} alkoxy-carboxamide group", for example, methoxycarboxamido group (CH_3OCONH-), ethoxycarboxamido group, tert-butoxycarboxamido group are used; as the "C_{6-10} aryloxy-carboxamido group", for example, phenoxycarboxamido group (C_6H_5OCONH-) are used; as the "C_{7-10} aralkyloxy-carboxamido group", for example, benzyloxycarboxamido group ($C_6H_5CH_2OCONH$-), benzhydryloxycarboxamido group are used; as the "C_{1-10} alkoxy-carbonyloxy group", for example, methoxycarbonyloxy group, ethoxycarbonyloxy group, n-propoxycarbonyloxy group, isopropoxycarbonyloxy group, n-butoxycarbonyloxy group, tert-butoxycarbonyloxy group, n-pentyloxycarbonyloxy group, n-hexyloxycarbonyloxy group are used; as the "C_{6-10} aryloxy-carbonyloxy group", for example, phenoxycarbonyloxy group, naphthyloxycarbonyloxy group are used; as the "C_{7-19} aralkyloxy-carbonyloxy group", for example, benzyloxycarbonyloxy group, 1-phenylethyloxycarbonyloxy group, 2-phenylethyloxycarbonyloxy group, benzhydryloxycarbonyloxy group are used; and as the "C_{3-10} cycloalkyloxy-carbonyloxy group", for example, cyclopropyloxycarbonyloxy group, cyclohexyloxycarbonyloxy group are used.

[0025] The "optionally substituted ureido group", for example, ureido group is optionally substituted by 1 to 3 (particularly 1 or 2) substituent(s) selected from C_{1-4} alkyl (e.g., methyl, ethyl), phenyl is used. Examples thereof include ureido group, 1-methylureido group, 3-methylureido group, 3,3-dimethylureido group, 1,3-dimethylureido group and 3-phenylureido group.

[0026] When heterocyclic group, heterocyclic oxy group, heterocyclic thio group, heterocyclic sulfinyl group, heterocyclic sulfonyl group or heterocyclic oxycarbonyl group is used as the "substituent" of the "aliphatic hydrocarbon group optionally having substituent(s)", the heterocyclic group means a group obtained by removing one of hydrogen atoms linked to the heterocyclic ring, and is a 5 to 8-membered ring (particularly 5 to 6-membered ring) containing 1 to several, preferably 1 to 4, hetero atom(s) such as nitrogen atom (optionally oxidized), oxygen atom, sulfur atom, or a fused ring thereof. Examples of heterocyclic group include pyrrolyl group, pyrazolyl group, imidazolyl group, 1,2,3-triazolyl group, 1,2,4-triazolyl group, tetrazolyl group, furyl group, thienyl group, oxazolyl group, isoxazolyl group, 1,2,3-oxadiazolyl group, 1,2,4-oxadiazolyl group, 1,2,5-oxadiazolyl group, 1,3,4-oxadiazolyl group, thiazolyl group, isothiazolyl group, 1,2,3-thiadiazolyl group, 1,2,4-thiadiazolyl group, 1,2,5-thiadiazolyl group, 1,3,4-thiadiazolyl group, pyridyl group, pyridazinyl group, pyrimidinyl group, pyrazinyl group, indolyl group, pyranyl group, thiopyranyl group, dioxynyl group, dioxolyl group, quinolyl group, pyrido[2,3-d]pyrimidyl group, 1,5-, 1,6-, 1,7-, 1,8-, 2,6- or 2,7-naphthyridyl group, thieno[2,3-d] pyridyl group, benzopyranyl group, tetrahydrofuryl group, tetrahydropyranyl group, dioxolanyl group and dioxanyl group.

[0027] These heterocyclic groups may be substituted by 1 to 3 substituent(s) selected from C_{1-4} alkyl (e.g., methyl and ethyl, hydroxy, oxo, C_{1-4} alkoxy (e.g., methoxy and ethoxy) at substitutable position(s).

[0028] As the "C_{6-10} aryl group" of the "optionally substituted C_{6-10} aryl group", for example, phenyl group, naphthyl group are used. The C_{6-10} aryl group may be substituted by substituent(s) selected from the "substituents" of the aforementioned "aliphatic hydrocarbon group optionally having substituent(s)" (except optionally substituted C_{6-10} aryl group) at substitutable position(s). Such substituents are substituted at substitutable position(s) of the C_{6-10} aryl group. The substituent is not limited to one but may be in plurality (2 to 4), which may be the same or different.

[0029] With regard to the "aliphatic hydrocarbon group optionally having substituent(s)", the substituent may form, together with aliphatic hydrocarbon group, an optionally substituted fused ring. As such fused ring, indanyl group, 1,2,3,4-tetrahydronaphthyl group are used. This fused ring may be substituted by substituent(s) selected from the "substituents" of the aforementioned "aliphatic hydrocarbon group optionally having substituent(s)" and optionally substituted at substitutable position(s). These substituents are substituted at substitutable positions of the fused ring, wherein the substituent is not limited to one but may be in plurality (2 to 4), which may be the same or different.

[0030] The "aromatic hydrocarbon group" of the "aromatic hydrocarbon group optionally having substituent(s)" represented by R^1, has 6 to 14 carbon atoms (e.g., phenyl group, naphthyl group, biphenyl group, anthryl group, indenyl group). Among others, for example, aryl group having 6 to 10 carbon atoms (e.g., phenyl group, naphthyl group) are preferable. Of these, phenyl group are particularly preferable.

[0031] The "substituent" of the "aromatic hydrocarbon group optionally having substituent(s)" represented by R^1 is selected from halogen atom (e.g., fluorine, chlorine, bromine, iodine), (C_{1-4}) alkyl group (e.g., methyl group, ethyl group, propyl group, butyl group), (C_{1-4})alkoxy group (e.g., methoxy group, ethoxy group, propoxy group, butoxy group), (C_{1-4}) alkoxy-carbonyl group (e.g., methoxycarbonyl group, ethoxycarbonyl group, propoxycarbonyl group, butoxycarbonyl group and the like), carboxyl group, nitro group, cyano group, hydroxy group, acylamino group (e.g., alkanoylamino group having 1 to 4 carbon atom(s) such as acetylamino group, propionylamino group, butyrylamino group), cycloalkyl group having 3 to 6 carbon atoms (e.g., cyclopropyl group, cyclopentyl group), aryl group having 6 to 10 carbon atoms (e.g., phenyl group, naphthyl group, indenyl group), halogeno (C_{1-4})alkyl group (e.g., trifluoromethyl group, trifluoroethyl group), halogeno (C_{1-4})alkoxy group (e.g., trifluoromethoxy group, 1,1,2,2-tetrafluoroethoxy group, 2,2,3,3,3-pentafluoropropoxy group), (C_{1-4})alkylthio group (e.g., methylthio group, ethylthio group, propionylthio group), (C_{1-4})alkylsulfonyl group (e.g., methanesulfonyl group, ethanesulfonyl group, propanesulfonyl group), (C_{1-4})alkanoyl group (e.g., formyl group, acetyl group, propionyl group), 5-membered aromatic heterocyclic group (e.g., 1,2,3-triazolyl group, 1,2,4-triazolyl group, tetrazolyl group, thiazolyl group, isothiazolyl group, oxazolyl group, isoxazolyl group, thiadiazolyl group, thienyl group, furyl group), carbamoyl group, (C_{1-4})alkyl-carbamoyl group (e.g., methylcarbamoyl group, dimethylcarbamoyl

group, propionylcarbamoyl group), (C_{1-4})alkoxy-carbonyl-(C_{1-4})alkyl-carbamoyl group (e.g., butoxycarbonylmethylcarbamoyl group, ethoxycarbonylmethylcarbamoyl group), 1,3-diacylguanidino-(C_{1-4})alkyl group (e.g., 1,3-diacetylguanidinomethyl group, 1,3-bis-tert-butoxycarbonylguanidinomethyl group),

[0032] with preference given to halogen atom (e.g., fluorine atom, chlorine atom, bromine atom, iodine atom), (C_{1-4}) alkyl group (e.g., methyl group, ethyl group, propyl group, butyl group), and more preference given to fluorine atom, chlorine atom and methyl group.

[0033] These substituents are substituted at substitutable positions of the aromatic hydrocarbon, wherein the number of the substituent is preferably 1 to 5, more preferably 1 to 3, most preferably 1 or 2. When two or more substituents are present, they may be the same or different.

[0034] The "heterocyclic group" of the "heterocyclic group optionally having substituent(s)" represented by R^1 is, a 5 to 8-membered ring (particularly 5 to 6-membered ring) containing 1 to several, preferably 1 to 4, hetero atom(s) from nitrogen atom (optionally oxidized), oxygen atom, sulfur atom, or a fused ring thereof. These heterocyclic groups are, for example, pyrrolyl group, pyrazolyl group, imidazolyl group, 1,2,3-triazolyl group, 1,2,4-triazolyl group, tetrazolyl group, furyl group, thienyl group, oxazolyl group, isoxazolyl group, 1,2,3-oxadiazolyl group, 1,2,4-oxadiazolyl group, 1,2,5-oxadiazolyl group, 1,3,4-oxadiazolyl group, thiazolyl group, isothiazolyl group, 1,2,3-thiadiazolyl group, 1,2,4-thiadiazolyl group, 1,2,5-thiadiazolyl group, 1,3,4-thiadiazolyl group, pyridyl group, pyridazinyl group, pyrimidinyl group, pyrazinyl group, indolyl group, pyranyl group, thiopyranyl group, dioxinyl group, dioxolyl group, quinolyl group, pyrido[2,3-d]pyrimidyl group, 1,5-, 1,6-, 1,7-, 1,8-, 2,6- or 2,7-naphthyridyl group, thieno[2,3-d]pyridyl group, benzopyranyl group, tetrahydrofuryl group, tetrahydropyranyl group, dioxolanyl group, dioxanyl group. These heterocyclic groups may be substituted by 1 to 3 substituent(s) selected from C_{1-4} alkyl (e.g., methyl, ethyl), hydroxy, oxo, C_{1-4} alkoxy group (e.g., methoxy, ethoxy) at substitutable position(s).

[0035] As the "aliphatic hydrocarbon group optionally having substituent(s)" represented by R^{1a}, those of the aforementioned "aliphatic hydrocarbon group optionally having substituent(s)" represented by R^1 are used. As R^{1a}, for example, optionally substituted alkyl group having 1 to 6 carbon atom(s) (e.g., methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, isobutyl group, tert-butoxycarbonylmethyl group, hydroxyethyl group) are preferably used. Of these, for example, methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, isobutyl group and the like are preferably used. Particularly, for example, methyl group, ethyl group, n-propyl group are preferable, and ethyl group are specifically preferable.

[0036] As the "aliphatic hydrocarbon group optionally having substituent(s)" represented by R^{1b} and R^{1c}, those of the aforementioned "aliphatic hydrocarbon group optionally having substituent(s)" represented by R^1 are used. As R^{1b} and R^{1c}, for example, optionally substituted alkyl group having 1 to 6 carbon atom(s) (e.g., methyl group; ethyl group, n-propyl group, isopropyl group, n-butyl group, isobutyl group, tert-butoxycarbonylmethyl group, hydroxyethyl group) are preferably used. Of these, for example, methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, isobutyl group are preferable. Particularly, for example, methyl group, ethyl group, n-propyl group are preferable, and ethyl group are specifically preferable.

[0037] As R^1, for example, optionally substituted alkyl group having 1 to 6 carbon atom(s) (e.g., methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, isobutyl group, tert-butoxycarbonylmethyl group, hydroxyethyl group) are preferably used. Of these, for example, methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, isobutyl group are preferably used. Particularly, for example, methyl group, ethyl group, n-propyl group are preferable, and ethyl group are specifically preferable.

[0038] As the substituent of the optionally substituted methylene group represented by Y, there are mentioned, C_{1-6} alkyl group such as methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, isobutyl group, hydroxy substituted-C_{1-6} alkyl group such as hydroxymethyl group, hydroxyethyl group, C_{1-4}, alkoxy-carbonyl-C_{1-4} alkyl group such as methoxycarbonylmethyl group, ethoxycarbonylmethyl group, tert-butoxycarbonylmethyl group, methoxycarbonylethyl group, ethoxycarbonylethyl group, tert-butoxycarbonylethyl group, with preference given to hydrogen atom and methyl group, and particularly hydrogen atom is preferable.

[0039] As the substituent of the optionally substituted nitrogen atom represented by Y, there are mentioned, C_{1-6} alkyl group such as methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, isobutyl group, hydroxy, substituted-C_{1-6} alkyl group such as hydroxymethyl group, hydroxyethyl group, C_{1-4} alkoxy-carbonyl-C_{1-4} alkyl group such as methoxycarbonylmethyl group, ethoxycarbonylmethyl group, tert-butoxycarbonylmethyl group, methoxycarbonylethyl group, ethoxycarbonylethyl group, tert-butoxycarbonylethyl group. Of these, hydrogen atom and methyl group are preferable, and particularly hydrogen atom is preferable.

[0040] As the "aromatic hydrocarbon group" of the "aromatic hydrocarbon group optionally having substituent(s)" represented by Ar, there are mentioned, aromatic hydrocarbon group having 6 to 14 carbon atoms (e.g., phenyl group, naphthyl group, biphenyl group, anthryl group, indenyl group). Of these, for example, aryl group having 6 to 10 carbon atoms (e.g., phenyl group, naphthyl group) are preferable, and phenyl group are particularly preferable.

[0041] As the "substituent" of the "aromatic hydrocarbon group optionally having substituent(s)" represented by Ar, halogen atom (e.g., fluorine, chlorine, bromine, iodine), lower (C_{1-4})alkyl group (e.g., methyl group, ethyl group, propyl

group, butyl group), (C_{1-4})alkoxy group (e.g., methoxy group, ethoxy group, propoxy group, butoxy group), (C_{1-4})alkoxy-carbonyl group (e.g., methoxycarbonyl group, ethoxycarbonyl group, propoxycarbonyl group, butoxycarbonyl group), carboxyl group, nitro group, cyano group, hydroxy group, acylamino group (e.g., alkanoylamino group having 1 to 4 carbon atom(s) such as acetylamino group, propionylamino group, butyrylamino group), cycloalkyl group having 3 to 6 carbon atoms (e.g., cyclopropyl group, cyclopentyl group), aryl group having 6 to 10 carbon atoms (e.g., phenyl group, naphthyl group, indenyl group), halogeno (C_{1-4})alkyl group (e.g., trifluoromethyl group, trifluoroethyl group), halogeno (C_{1-4})alkoxy group (e.g., trifluoromethoxy group, 1,1,2,2-tetrafluoroethoxy group, 2,2,3,3,3-pentafluaropropoxy group), (C_{1-4})alkylthio group (e.g., methylthio group, ethylthio group, propionylthio group), (C_{1-4})alkylsulfonyl group (e.g., methanesulfonyl group, ethanesulfonyl group, propanesulfonyl group), (C_{1-4})alkanoyl group (e.g., formyl group, acetyl group, propionyl group), 5-membered aromatic heterocyclic group (e.g., 1,2,3-thiazolyl group, 1,2,4-triazolyl group, tetrazolyl group, thiazolyl group, isothiazolyl group, oxazolyl group, isoxazolyl group, thiadiazolyl group, thienyl group, furyl group), carbamoyl group, (C_{1-4})alkyl-carbamoyl group (e.g., methylcarbamoyl group, dimethylcarbamoyl group, propionylcarbamoyl group), (C_{1-4})alkoxy-carbonyl- (C_{1-4})alkyl-carbamoyl group (e.g., butoxycarbonylmethylcarbamoyl group, ethoxycarbonylmethylcarbamoyl group), 1,3-diacylguanidino-lower (C_{1-4})alkyl group (e.g., 1,3-diacetylguanidinomethyl group, 1,3-bia-tert-butoxycarbonylguanidinomethyl group) are . Preferably, halogen atom (e.g., fluorine atom, chlorine atom, bromine atom, iodine atom), (C_{1-4})alkyl group (e.g., methyl group, ethyl group, propyl group, butyl group) are used and more preferably, fluorine atom, chlorine atom and methyl group are used.

[0042] These substituents are substituted at substitutable positions of the aromatic hydrocarbon group, where the number of the substituent is preferably 1 to 5, more preferably 1 to 3, and particularly preferably 1 or 2. When two or more substituents are present, they may be the same or different.

[0043] As Ar, phenyl, group, halogeno phenyl group, (C_{1-4})alkyl-phenyl group, (C_{1-4})alkoxy-phenyl group, (C_{1-4})alkoxy-carbonylphenyl group, carboxylphenyl group, nitrophenyl group, cyanophenyl group, halogeno (C_{1-4})alkyl-phenyl group, halogeno (C_{1-4})alkoxy-phenyl group, (C_{1-4})alkanoyl-phenyl group, phenyl group substituted by 5-membered aromatic heterocyclic group, (C_{1-4})alkoxy-carbonyl-(C_{1-4})alkyl-carbamoylphenyl group, 1,3-diacylguanidino- (C_{1-4})alkyl-phenyl group, phenyl group substituted by halogen and (C_{1-4})alkyl, phenyl group substituted by halogen and (C_{1-4})alkoxy-carbonyl, phenyl group substituted by halogen and cyano, phenyl group substituted by halogen and 5-membered aromatic heterocyclic group, phenyl group substituted by halogen and (C_{1-4})alkoxy-carbonyl-lower (C_{1-4})alkyl-carbamoyl are used.

[0044] As the halogeno phenyl group, for example, 2,3-difluorophenyl group, 2,3-dichlorophenyl group, 2,4-difluorophenyl group, 2,4-dichlorophenyl group, 2,5-difluorophenyl group, 2,5-dichlorophenyl group, 2,6-difluorophenyl group, 2,6-dichlorophenyl group, 3,4-difluorophenyl group, 3,4-dichlorophenyl group, 3,5-difluorophenyl group, 3,5-dichlorophenyl group, 2-fluorophenyl group, 2-chlorophenyl group, 3-fluorophenyl group, 3-chlorophenyl group, 4-fluorophenyl group, 4-chlorophenyl group, 2-fluoro-4-ohlorophenyl group, 2-chloro-4-fluorophenyl group, 4-bromo-2-fluoxophenyl group, 2,3,4-trifluorophenyl group, 2,4,5-trifluorophenyl group, 2,4,6-trifluorophenyl group are used.

[0045] As the (C_{1-4})alkyl-phenyl group, for example, 2-ethylphenyl group, 2,6-diisopropylphenyl group are preferably used, and as the (C_{1-4})alkoxy-phenyl group, for example, 4-methoxyphenyl are preferably used.

[0046] As the (C_{1-4})alkoxy-carbonylphenyl group, for example, 2-ethoxycarbonylphenyl group, 2-methoxycarbonylphenyl group, 4-methoxycarbonylphenyl group are preferably used; as the halogeno (C_{1-4}) alkylphenyl group, for example, 2-trifluoromethylphenyl group are preferably used; and as the halogeno (C_{1-4})alkoxy-phenyl group, for example, 2-trifluoromethoxyphenyl group, 4-(2,2,3,3,3-pentafluoropropoxy)phenyl group are preferably used.

[0047] As the (C_{1-4})alkanoyl-phenyl group, for example, 2-acetylphenyl group are preferably used; as the phenyl group substituted by 5-membered aromatic heterocyclic group, for example, 4-(2H-1,2,3-triazol-2-yl)phenyl group, 4-(2H-tetrazol-2-yl)phenyl group, 4-(1H-tetrazol-1-yl)phenyl group, 4-(1H-1,2,3-triazol-1-yl)phenyl group are preferably used; as the (C_{1-4})alkoxy-carbonyl-lower (C_{1-4})alkyl-carbamoylphenyl group, for example, 4-(N-ethoxycarbonylmethylcarbamoyl) phenyl group are preferably used; and as the 1,3-diacylguanidino-(C_{1-4})alkyl-phenyl group, for example, 4-(1,3-bis-tert-butoxycarbonylguanidinomethyl)phenyl group are preferably used.

[0048] As the phenyl group substituted by halogen and (C_{1-4})alkyl group, for example, 2-fluoro-4-methylphenyl group, 2-chloro-4-methylphenyl group, 4-fluoro-2-methylphenyl group are preferably used; as the phenyl group substituted by halogen and (C_{1-4})alkoxy-carbonyl, for example, 2-chloro-4-methoxycarbonylphenyl group are preferably used; as the phenyl group substituted by halogen and cyano, 2-chloro-4-cyanophenyl group are preferably used; as the phenyl group substituted by halogen and 5-membered aromatic heterocyclic group, for example, 2-fluoro-4-(1H-1,2,4-triazol-1-yl) phenyl are preferably used; and as the phenyl group substituted by halogen and (C_{1-4})alkoxy-carbonyl-(C_{1-4})-alkyl-carbamoyl, for example, 2-chloro-4-(N-tert-butoxycarbonylmethylcarbamoyl)phenyl group, 2-chloro-4-(N-ethoxycarbonylmethylcarbamoyl)phenyl group are preferably used.

[0049] As Ar, halogeno phenyl group, phenyl group substituted by (C_{1-4})alkyl-phenyl group, halogen and (C_{1-4})alkoxy-carbonyl are preferably used.

[0050] More specifically, as Ar, phenyl group, phenyl group substituted by 1 to 3 (particularly 1 or 2) halogen (e.g., 2,3-difluorophenyl group, 2,3-dichlorophenyl group, 2,4-difluorophenyl group, 2,4-dichlorophenyl group, 2,5-difluorophenyl group, 2,5-dichlorophenyl group, 2,6-difluorophenyl group, 2,6-dichlorophenyl group, 3,4-difluorophenyl group, 3,4-

dichlorophenyl group, 3,5-difluorophenyl group, 3,5-dichlorophenyl group, 4-bromo-2-fluorophenyl group, 2-fluorophenyl group, 2-chlorophenyl group, 3-fluorophenyl group, 3-chlorophenyl group, 4-fluorophenyl group, 4-chlorophenyl group, 2-fluoro-4-chlorophenyl group, 2-chloro-4-fluorophenyl group, 2,3,4-trifluorophenyl group, 2,4,5-trifluorophenyl group), phenyl group substituted by halogen and (C_{1-4})alkyl (e.g., 2-chloro-4-methylphenyl group, 4-fluoro-2-methylphenyl group) are preferable. Of these, phenyl group substituted by 1 to 3 (particularly 1 or 2) halogen (e.g., 2,3-dichlorophenyl group, 2,4-difluorophenyl group, 2,4-dichlorophenyl group, 2,6-dichlorophenyl group, 2-fluorophenyl group, 2-chlorophenyl group, 3-chlorophenyl group, 2-chloro-4-fluorophenyl group, 2,4,5-trifluorophenyl group), phenyl group substituted by halogen and (C_{1-4})alkyl (e.g., 2-chloro-4-methylphenyl group, 4-fluoro-2-methylphenyl group) are preferable. Particularly, as Ar, a group represented by the formula (c) is preferable and a group represented by the formula (cl) is more preferable. As the halogen atom which is a substituent represented by R^3 in the formula (c) and ring B, and halogen atom represented by R^{3a} and R^{3b} in the formula (c1), fluorine atom and chlorine atom are preferable. As the alkyl group represented by R^3 in the formula (c), C_{1-4} alkyl group such as methyl, ethyl, propyl are used. Of the groups represented by the formula (c), 2,4-difluorophenyl group, 2-chloro-4-fluorophenyl group, 2-methyl-4-chlorophenyl group are preferable. Of the groups represented by the formula (cl), 2,4-difluorophenyl group, 2-chloro-4-fluorophenyl group are preferable.

[0051] X shows methylene group, nitrogen atom, sulfur atom or oxygen atom. Of these, nitrogen atom, sulfur atom and oxygen atom are preferable.

[0052] The ring A is a 5 to 8-membered ring substituted by a group of the formula: -CO-R^1 wherein R^1 is as defined above and a group of the formula: -SO_2-Y-Ar wherein Y and Ar are as defined above, which is optionally substituted by 1 to 4 substituent(s) selected from (i) aliphatic hydrocarbon group optionally having substxtuent(s), (ii) aromatic hydrocarbon group optionally having substituent(s), (iii) a group of the formula: OR^2 wherein R^2 is as defined above and (iv) halogen atom. It is preferably a 5 to 8-membered ring optionally substituted by 1 to 4 substituent(s) selected from (i) aliphatic hydrocarbon group optionally having substituent(s), (ii) aromatic hydrocarbon group optionally having substituent (s) and (iv) halogen atom.

[0053] These substituents may be substituted at substitutable positions on ring A. When X constituting the ring is nitrogen atom or methylene, the nitrogen atom or methylene may be substituted. When ring A is substituted by plural substituents, these substituents may be of the same kind or otherwise. It is also possible that two substituents be substituted at the same carbon atom.

[0054] As the "aliphatic hydrocarbon group optionally having substituent(s)" and "aromatic hydrocarbon group optionally having substituent(s)", which are substituents of ring A, those mentioned with regard to the aforementioned "aliphatic hydrocarbon group optionally having substituent(s)" and "aromatic hydrocarbon group optionally having substituent(s)" represented by R^1 can be used.

[0055] As the substituent of ring A, 1 or 2 C_{1-6} alkyl group(s) (e.g., C_{1-4} alkyl group such as methyl group, tert-butyl group), phenyl group, halogen atom (e.g., fluorine, chlorine, bromine, iodine) and the like are preferably used.

[0056] The m is l and n is 1.

[0057] As the "alkyl group" of the "optionally substituted alkyl group" represented by R^4, C_{1-6} alkyl group such as methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, isobutyl group are mentioned, and as the "substituent", for example, hydroxyl group, C_{1-4} alkoxy-carbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, tert-butoxy-carbonyl) are mentioned.

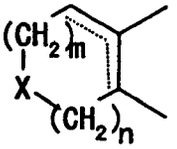
[0058] As the R^4, hydrogen atom and methyl group are preferable from among those mentioned above, and hydrogen atom is particularly preferable.

[0059] As the leaving group represented by Z^1, for example, halogen atom (e.g., chlorine, bromine and iodine) are preferable, and chlorine atom is particularly preferable.

[0060] The leaving group represented by Z^2 includes, for example, (1) a group of the formula: -$SO_2N(R^2)$-Ar wherein R^2 and Ar are as defined above, (2) halogen atom, such as chlorine, bromine, iodine, fluorine, (3) C_{1-6} alkylsulfonyloxy group optionally substituted by 1 to 4 halogen atom(s), such as methanesulfonyloxy, ethanesulfonyloxy, butanesulfonyloxy, trifluoromethanesulfonyloxy, (4) C_{6-10} arylsulfonyloxy group optionally substituted by 1 to 4 halogen atom(s), such as benzenesulfonyloxy, p-toluenesulfonyloxy, p-bromobenzenesulfonyloxy, mesitylenesulfonyloxy, (5) C_{1-6} acyl-sulfonyloxy group optionally substituted by 1 to 3 halogen atom(s), such as acetyloxy, propionyloxy, trifluoroacetyloxy, (6) C_{6-10} aryl-carbonylcarbonyloxy group, such as benzoylcarbonyloxy, phenylcarbonylcarbonyloxy.

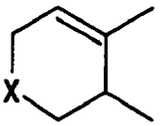
[0061] As the compound represented by the formula (I), for example, the following compound are preferable.

(1) A compound (I) wherein R^1 is a group of the formula: $OR^{1a'}$ ($R^{1a'}$ is C_{1-6} alkyl group), a group of the formula:



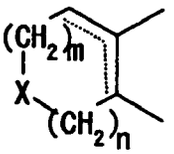
(b)

is a group of the formula:



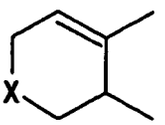
X is methylene or an oxygen atom, Y is methylene or -NH-, and Ar is phenyl group optionally substituted by 1 or 2 substituent(s) selected from the group consisting of halogen atom and C_{1-6} alkoxy.

(2) A compound (I) wherein R^1 is a group of the formula: $OR^{1a'}$ ($R^{1a'}$ is C_{1-6} alkyl group), a group of the formula:



(b)

is a group of the formula:



X in methylene and Y is methylene, or X is an oxygen atom and Y is -NH-, and Ar is a phenyl group optionally having two halogen atoms (e.g., 2-chloro-4-fluorophenyl group).

(3) Ethyl 6-(benzylsulfonyl)-1-cyclohexene-1-carboxylate (compound 1), ethyl 6-[(4-methoxybenzyl)sulfonyl]-1-cyclohexene-1-carboxylate (compound 2), ethyl 6-[(2,4-difluorobenzyl)sulfonyl]-1-cyclohexene-1-carboxylate (compound 3), ethyl 6-[(2-chloro-4-fluorobenzyl)sulfonyl]-1-cyclohexene-1-carboxylate (compound 4), ethyl (-)-6-[(2-chloro-4-fluorobenzyl)sulfonyl]-1-cyclohexene-1-carboxylate (compound 5), ethyl (+)-6-[(2-chloro-4-fluorobenzyl)sulfonyl]-1-cyclohexene-1-carboxylate (compound 6), ethyl 3-[(2,4-difluorophenyl)sulfamoyl]-3,6-dihydro-2H-pyran-4-carboxylate (compound 7) or ethyl 3-[(2-chloro-4-fluorophenyl)sulfamoyl]-3,6-dihydro-2H-pyran-4-carboxylate (compound 8).

(4) Ethyl 6-[(2-chloro-4-fluorobenzyl)sulfonyl]-1-cyclohexene-1-carboxylate (compound 4), ethyl (+)-6-[(2-chloro-4-fluorobenzyl)sulfonyl]-1-cyclohexene-1-carboxylate (compound 6) or ethyl 3-[(2-chloro-4-fluorophenyl)sulfamoyl]-3,6-dihydro-2H-pyran-4-carboxylate (compound 8).

[0062] The salt of the compound of the formula (I) is exemplified by a salt with inorganic base, a salt with organic base, a salt with inorganic acid, a salt with organic acid, and a salt with basic or acidic amino acid. Examples of the salt with inorganic base include alkali metal salts such as sodium salt, potassium salt , alkaline earth metal salts such as calcium salt, magnesium salt, aluminum salt and ammonium salt, examples of the salt with organic base include salts with trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, N,N'-dibenzylethylenediamine , examples of the salt with inorganic acid include salts with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, examples of the salt with organic acid include salts with formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, meth-

anesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid , examples of the salt with basic amino acid include salts with arginine, lysine, ornithine , and examples of the salt with acidic amino acid include salts with aspartic acid, glutamic acid.

[0063] When the compound of the formula (I) or a salt thereof has a stereoisomer, each stereoisomer thereof and a mixture of the stereoisomers are encompassed in the present invention.

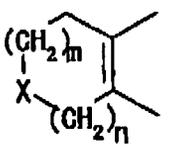
[0064] While the compound of the formula (I) and a salt thereof have an enantiomer, each enantiomer thereof and a mixture of the enantiomers are encompassed in the present invention.

[0065] The production method of compound (I) of the formula (I) and a salt thereof [hereinafter sometimes to be referred to as compound (I)] is explained in the following.

[0066] A compound of the formula (I) wherein X is nitrogen atom, sulfur atom or oxygen atom and Y is an optionally substituted nitrogen atom, or a salt thereof, namely, a compound of the formula (Ia) and a salt thereof [hereinafter sometimes to be referred to as compound (Ia)] can be produced by, for example, reacting a compound of the formula (II) or a salt thereof [hereinafter sometimes to be referred to as compound (II)] and a compound of the formula (III) or a salt thereof [hereinafter sometimes to be referred to as compound (III)], and where necessary, hydrolyzing the resulting product by a method known *per se*. The salt of a compound of the formula (II) and the salt of a compound of the formula (III) are exemplified by those similar to the salts mentioned with regard to the aforementioned compound of the formula (I).

[0067] The reaction between compound (II) and compound (III) can be carried out without solvent but it is generally carried out in a solvent inert to the reaction. The solvent includes, for example, sulfoxides (e.g., dimethyl sulfoxide), ethers (e.g., diethyl ether, tetrahydrofuran, dioxane), nitriles (e.g., acetonitrile), aromatic hydrocarbons (e.g., benzene toluene, xylene), halogenated hydrocarbons (e.g., dichloromethane, chloroform, 1,2-dichloroethane), esters (e.g., ethyl acetate etc.), amides (e.g., dimethylformamide, acetamide, dimethylacetamide, 1,3-dimethyl-2- imidazolidinone, 1-methyl-2-pyrrolidone). Only one kind of these solvents may be used, or two or more kinds thereof may be mixed at a suitable ratio and used. While the amount of the solvent to be used is not particularly limited, generally, it is preferably 2-300 times the weight of compound (II). This reaction is preferably carried out in the presence of a base, and as the base, an inorganic base (e.g., sodium hydride, potassium hydride, sodium hydroxide), and an organic base (e.g., triethylamine, pyridine, diisopropylethylamine, DBU) can be used. Particularly, an organic base such as triethylamine is preferably used. When a base is used, the amount thereof is preferably 0.5 to 5-fold amount (molar ratio), more preferably 0.9 to 2-fold amount (molar ratio), relative to compound (II). The amount of use of compound (III) is preferably 1 to 5-fold amount (molar ratio), more preferably 1 to 2-fold amount (molar ratio), based on compound (II). The reaction temperature is preferably -10 to 100˚C, more preferably 0 to 60˚C. The reaction time is preferably 0.5 to 50 hours, more preferably 0.5 to 30 hours.

[0068] During the course of reaction between compound (II) and compound (III), compound (Ia) may be synthesized due to isomerization of a group of the formula (b2) of



(b2)

compound (II) to a group of the formula (b1).

(Note: Groups of formula (b2) are not according to the invention.)

[0069] In this reaction, when a compound of the formula (Ia) wherein R^1 is OR^{1a}, where R^{1a} is an optionally substituted aliphatic hydrocarbon, is obtained, this compound is hydrolyzed to give a compound of the formula (Ia) wherein R^1 is OH. The hydrolysis can be performed according to a method known *per se.*

[0070] When compound (Ia) thus obtained has a free acidic group or basic group, it can be converted, where necessary, to a salt by a conventional method.

[0071] A compound of the formula (I) wherein Y is optionally substituted methylene group and a salt thereof can be produced by, for example, reacting a compound of the formula (IV) or a salt thereof [hereinafter sometimes to be also referred to as compound (IV)] and a compound of the formula (V1) or a salt thereof [hereinafter sometimes to be also referred to as compound (V1)], oxidizing the resulting sulfide with an oxidizing agent, and, where necessary, subjecting the product to hydrolysis. The salt of a compound of the formula (IV) and the salt of a compound of the formula (V1) are exemplified by those similar to the salts mentioned with regard to the aforementioned compound of the formula (I).

[0072] The reaction between compound (IV) and compound (V1) can be carried out without solvent or in a solvent that does not inhibit the reaction. The solvent includes, for example, sulfoxides (e.g., dimethyl sulfoxide), ethers (e.g., diethyl ether, tetrahydrofuran, dioxane), nitriles (e.g., acetonitrile), aromatic hydrocarbons (e.g., benzene, toluene, xy-

lene), halogenated hydrocarbons (e.g., dichloromethane, chloroform, 1,2-dichloroethane), esters (e.g., ethyl acetate), amides (e.g., dimethylformamide, acetamide, dimethylacetamide, 1,3-dimethyl-2-imidazolidinone, 1-methyl-2-pyrrolidone) . Only one kind of these solvents may be used, or two or more kinds thereof may be mixed at a suitable ratio and used. While the amount of the solvent to be used is not particularly limited, generally, it is preferably 2-300 times the weight of compound (IV).

[0073] This reaction is preferably carried out in the presence of a base, and as the base, an inorganic base (e.g., potassium carbonate, sodium hydride, potassium hydride, sodium hydroxide) or an organic base (e.g., triethylamine, pyridine, diisopropylethylamine, DBU, potassium t-butoxide) is preferably used. The amount of use when a base is present is preferably 0,5 to 5-told amount (molar ratio), more preferably 0.9 to 2-fold amount (molar ratio), relative to compound (VI). The amount of use of the compound (V1) is preferably 1 to 5-fold amount (molar ratio), more preferably 1 to 2-fold amount (molar ratio), based on compound (IV). The reaction temperature is preferably from -10 to 100˚C, more preferably from 0 to 60˚C. The reaction time is preferably from 0.1 to 50 hours, more preferably from 0.5 to 10 hours.

[0074] As a result of the above-mentioned reaction, sulfide is produced. The reaction to oxidize this sulfide is generally carried out in a solvent that does not inhibit the reaction. As the solvent, aromatic hydrocarbons (e.g., benzene, toluene, xylene), halogenated hydrocarbons (e.g., dichloromethane, chloroform, 1,2-dichloroethane), esters (e.g., ethyl acetate) are used. Only one kind of these solvents may be used, or two or more kinds thereof may be mixed at a suitable ratio and used. Examples of the oxidizing agent include oxygen-light, hydrogen peroxide, perbenzoic acids such as perbenzoic acid, m-chloroperbenzoic acid, for example perchlorate such as lithium perchlorate, silver perchlorate, mercury(II) perchlorate, tetrabutylammonium perchlorate and the like, nitrosylsulfuric acid, alkylnitrite such as isoamyl nitrite, halogen such as iodine, bromine, chlorine, N-bromosuccinic imide, sulfuryl chloride, chloramine T. The reaction temperature is preferably from -30 to 30˚C, more preferably from -10 to 10˚C. The reaction time is preferably from 0.1 to 50 hours, more preferably from 0.5 to 10 hours.

[0075] In this reaction, when a compound of the formula (Ia), wherein R^1 is OR^{1a} and R^{1a} is an optionally substituted aliphatic hydrocarbon, is obtained, this compound is hydrolyzed to give a compound of the formula (Ia) wherein R^1 is OH. This hydrolysis is performed by a method known *per se*.

[0076] When the thus-obtained compound (Ia) has a free acidic group or basic group, it can be converted to a salt as necessary by a conventional method.

[0077] The thus-obtained compound (I) of the present invention can be isolated and purified from the reaction mixture by a method known *per se*, such as extraction, concentration, neutralization, filtration, recrystallization, chromatography.

[0078] The prodrug of the compound (I) of the present invention is a compound that is converted to compound (I) by a reaction with an enzyme, gastric acid and the like in the body under physiological conditions. In other words, it is a compound that undergoes enzymatic oxidation, reduction, hydrolysis into compound (I), or a compound that undergoes hydrolysis and the like due to gastric acid and the like into compound (I). The prodrug of compound (I) is a compound (I) wherein amino group is acylated, alkylated or phosphorylated (e.g., a compound (I) wherein amino group is eicosanoylated, alanylated, pentylaminocarbonylated, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxycarbonylated, tetrahydrofuranylated, pyrrolidylmethylated, pivaloyloxymethylated, tert-butylated); a compound (I) wherein hydroxyl group is acylated, alkylated, phosphorylated or borated (e.g., a compound (I) wherein hydroxyl group is acetylated, palmitoylated, propanoylated, pivaloylated, succinylated, fumarylated, alanylated, dimethylaminomethylcarbonylated); a compound (I) wherein carboxyl group is esterified or amidated (e.g., a compound (I) wherein carboxyl group is ethyl esterified, phenyl esterified, carboxymethyl esterified, dimethylaminomethyl esterified, pivaloyloxymethyl esterified, ethoxycarbonyloxyethyl esterified, phthalidyl esterified, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl esterified, cyclohexyloxycarbonylethyl esterified, methyl amidated. These compounds can be produced from compound (I) by a method known *per se.*

[0079] The prodrug of compound (I) may be a compound that is converted to compound (I) under the physiological conditions described in Development of Pharmaceutical Products, vol. 7, Molecule Design, pp. 163-198, Hirokawa Shoten (1990).

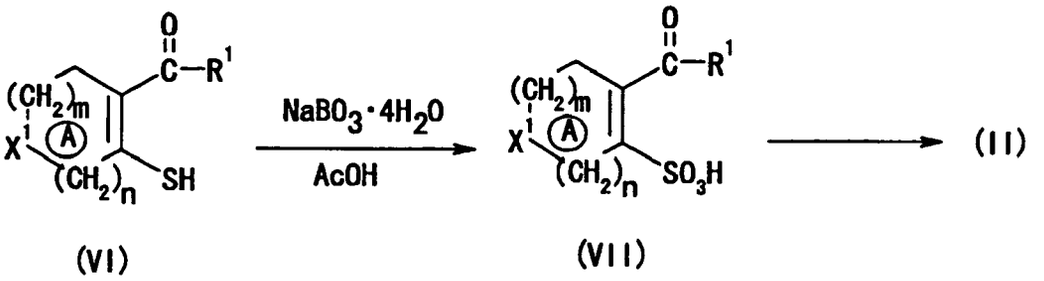
[0080] The compound (I) of the present invention may be a hydrate or anhydride.

[0081] The compound (I) of the present invention may be labeled with an isotope (e.g., ^{3}H, ^{14}C, ^{35}S, ^{125}I).

[0082] When the compound (I) of the present invention has an asymmetric carbon in ring A, at least two stereoisomers or enantiomers can exist, which isomers can be individually produced when desired.

[0083] When the compound (I) is a mixture of two or more kinds of isomers, these can be separated into each isomer by a typical separation method, such as a method for generating a salt with an optically active acid (e.g., camphor sulfonic acid) or an optically active base (e.g., 1-methylbenzylamine) or a separation method using various chromatographys (e.g., liquid chromatography using an optically active column), fractional recrystallization.

[0084] The starting compound (II) in the present invention can be produced by, for example, a method shown by the following reaction formula:



wherein each symbol is as defined above.

[0085] The compound (VI) is oxidized with sodium perborate in acetic acid to give compound (VII). The compound (VII) is reacted with thionyl halide (e.g., thionyl chloride) or substituted sulfonyl chloride (e.g., methanesulfonyl chloride, benzenesulfonyl chloride) to give compound (II).

[0086] The starting compound or synthetic intermediate obtained by the aforementioned method can be isolated and purified from a reaction mixture by a method known *per se,* such as extraction, concentration, neutralization, filtration, recrystallization, column chromatography, thin-layer chromatography.

[0087] It is also possible to use the reaction mixture without isolation in the next step.

[0088] In each of the above-mentioned reactions, a protecting group of amino group, carboxyl group and hydroxy group, which are not involved in the reaction, may be used for the compound or a salt thereof subjected to the reaction. The addition and removal of the protecting group can be performed according to a known method.

[0089] The protecting group of the amino group is, for example, formyl and respectively optionally substituted C_{1-6} alkylcarbonyl (for example, acetyl, propionyl), phenylcarbonyl, C_{1-6} alkyl-oxycarbonyl (e.g., methoxycarbonyl, ethoxycarbonyl), phenyloxycarbonyl, C_{7-10} aralkyloxy-carbonyl (e.g., phenyl-C_{1-4} alkyloxy-carbonyl such as benzyloxycarbonyl), trityl, phthaloyl or N,N-dimethylaminomethylene. As a substituent thereof, halogen atom (e.g., fluorine, chlorine, bromine, iodine), formyl, C_{1-6} alkyl-carbonyl (e.g., acetyl, propionyl, valeryl), nitro group are used, wherein the number of substituent is about 1 to 3.

[0090] The protecting group of carboxyl group is, for example, optionally substituted C_{1-6} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, tert-butyl), phenyl, trityl or silyl. As a substituent thereof, halogen atom (e.g., fluorine, chlorine), formyl, C_{1-6} alkyl-carbonyl (e.g., acetyl, propionyl, valeryl), nitro group are used, wherein the number of substituent is about 1 to 3.

[0091] The protecting group of hydroxy group is, for example, optionally substituted C_{1-6} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, tert-butyl), phenyl, C_{7-10} aralkyl (e.g. , phenyl-C_{1-4} alkyl such as benzyl), formyl, C_{1-6} alkyl-carbonyl (e.g., acetyl, propionyl), phenyloxycarbonyl, benzoyl, (C_{7-10} aralkyloxy)carbonyl (e.g., phenyl-C_{1-4} alkyloxy-carbonyl such as benzyloxycarbonyl), pyranyl, furanyl, silyl. As a substituent thereof, halogen atom ((e.g., fluorine, chlorine), C_{1-6} alkyl (e.g., methyl, ethyl, propyl), phenyl, C_{7-10} aralkyl (e.g., phenyl-C_{1-4} alkyl such as benzyl), nitro group are used, wherein the number of substituent is about 1 to 4.

[0092] The protecting group can be removed by a method known *per se* or a similar method. For example, a method including treating with acid, base, reduction, ultraviolet, hydrazine, phenylhydrazine, sodium N-methyldithiocarbamate, tetrabutylammonium fluoride, palladium acetate is used.

[0093] The compound (I) of the present invention, a salt thereof (hereinafter the compound (I) of the present invention) show low toxicity, and have a nitric oxide (NO) production-inhibitory activity and an inhibitory activity on the production of inflammatory cytokine such as TNF-α, IL-1, IL-6. They are useful as a drug for the treatment and/or prophylaxis of diseases such as cardiac disease, autoimmune disease, inflammatory disease, central nervous system disease, infectious disease, sepsis, septic shock in mammals (e.g., cat, cattle, dog, horse, goat, monkey, human), for example, ichorrhemia, endotoxin shock, exotoxin shock, heart failure, shock, hypotension, rheumatoid arthritis, arthrosteitis, gastritis, ulcerative colitis, peptic ulcer, stress gastric ulcer, Crohn's disease, autoimmune disease, tissue injury and rejection after organ transplantation, ischemic reperfusion disorder, acute coronary microvascular occlusion, shock vascular occlusion (disseminated intravascular coagulation syndrome (DIC) and the like), ischemic brain disorder, arteriosclerosis, pernicious anemia, Fanconi's anemia, sickle cell anemia, pancreatitis, nephrotic syndrome, nephritis, renal failure, insulin-dependent diabetes mellitus, non-insulin dependent diabetes mellitus, hepatic porphyria, alcoholism, Parkinson's disease, chronic leukemia, acute leukemia, tumor, myeloma, relief of side effects of anticancer agent, infant and adult respiratory distress syndrome, pulmonary emphysema, dementia, Alzheimer's disease, multiple sclerosis, vitamin E deficiency, aging, sunburn, myodystrophy, myocarditis, cardiac myopathy, myocardial infarction, sequela of myocardial infarction, osteoporosis, pneumonia, hepatitis, psoriasis, pain, cataract, influenza infection, malaria, human immunodeficiency virus (HIV) infection, radiation injury, burn, improved efficiency of in vitro fertilization, hypercalcemia, ankylosing spondylitis, osteopenia, bone Behcet's disease, osteomalacia, bone fracture, acute bacterial meningitis, Helicobacter

pylori infection, invasive staphylococcal infection, tuberculosis, systemic mycotic infection, herpes simplex virus infection, varicella-zoster virus infection, human papilloma virus infection, acute virus encephalitis, encephalitis, asthma, atopic dermatitis, allergic rhinitis, reflux esophagitis, fever, hypercholesterolemia, hyperglyceridemia, hyperlipidemia, diabetic complications, diabetic nephropathy, diabetic

[0094] neuropathy, diabetic retinopathy, gout, gastric atony, hemorrhoid, systemic lupus erythematodes, spinal trauma, agrypnia, schizophrenia, epilepsy, cirrhosis, hepatic failure, unstable angina pectoris, valvular disease of heart, thrombocytopenia derived from dialysis, acute ischemic stroke, acute brain thrombosis, cancer metastasis, bladder cancer, breast cancer, cervical cancer, colon cancer, stomach cancer, ovarian cancer, prostate cancer, small cell lung cancer, non-small cell lung cancer, malignant melanoma, Hodgkin's disease and non-Hodgkin's lymphoma.

[0095] When the compound (I) of the present invention is administered to human, the compound itself or the compound after admixing with a suitable pharmacologically acceptable carrier, excipient, diluent and the like can be administered orally or parenterally as a safe pharmaceutical composition, such as an oral administration agent (e.g., powder, granule, tablet and capsule), a parenteral administration agent (e.g., injection, an external preparation (e.g., nasal preparation, percutaneous preparation), a suppository (e.g., rectal suppository and vaginal suppository).

[0096] These preparations can be produced by, for example, applying a method known *per se* generally employed for the production of pharmaceutical preparations.

[0097] The content of the compound (I) of the present invention in the preparation varies depending on the dosage form. For example, the content thereof in the aforementioned oral administration agent is 1 to 99 wt%, preferably 10 to 99 wt%, more preferably 10 to 95 wt%. In the aforementioned parenteral administration agent, for example, it is 0.001 to 99 wt%, preferably 0.001 to 95 wt%.

[0098] The content of the components other than compound (I) in the preparation is generally 1 to 99.999 wt%, preferably 10 to 90 wt%.

[0099] For injection, for example, an aqueous injection can be prepared using the compound (I) of the present invention together with a solubilizer (e.g., β-cyclodextrins etc.), a dispersing agent (e.g., Tween 80 (Atlas Powder Co., USA), HCO60 (Nikko Chemicals Co., Ltd.), carboxymethylcellulose, sodium alginate), a preservative (e.g., methylparabene, propylparabene, benzyl alcohol, chlorobutanol), an isotonic agent (e.g., sodium chloride, glycerine, sorbitol, glucose) according to a conventional method. Alternatively, an oily injection can be formed by dissolving, suspending or emulsifying as appropriate the compound in a vegetable oil (e.g., olive oil, sesame oil, peanut oil, cottonseed oil, corn oil), propylene glycol.

[0100] An oral administration agent can be produced by adding, for example, an excipient (e.g., lactose, sucrose, starch), a disintegrant (e.g., starch, calcium carbonate), a binde,r (e.g., starch, gum arabic, carboxymethylcellulose, polyvinylpyrrolidone, hydroxypropylcellulose), a lubricant (e.g., talc, magnesium stearate, polyethylene glycol 6000) as appropriate to compound (I) of the present invention, compression-shaping, and where necessary, applying a coating aiming at masking of taste, enteric property or sustained release according to a method known *per se.* Examples of the coating agent include hydroxypropylmethylcellulose, ethylcellulose, hydroxymethylcellulose, hydroxypropylcellulose, polyoxyethylene glycol, Tween 80, pluronic F68, cellulose acetate phthalate, hydroxypropylmethyl cellulose phthalate, hydroxymethylcellulose acetate succinate, Eudragit (Rohm Pharm GmbH, Germany, a copolymer of methacrylic acid with acrylic acid), pigment (e.g., titanium oxide, bengara).

[0101] The compound (I) of the present invention can be also used as a solid, semi-solid or liquid external agent.

[0102] For example, a solid external agent can be produced from the compound (I) of the present invention as it is, or by adding an excipient (e.g., glycol, mannitol, starch, crystalline cellulose), a thickener (e.g., natural gums, cellulose derivative, acrylic polymer etc.), mixing the same and preparing into a powdery composition. A semi-solid external agent can be produced by a conventional method and preferably used as an aqueous or oily gel, or an ointment. A liquid external preparation can be produced by preparing into an oily or aqueous suspension according to a method employed for production of injection or a similar method.

[0103] In addition, a pH-adjusting agent (e.g., carbonic acid, phosphoric acid, citric acid, hydrochloric acid, sodium hydroxide), a preservative (e.g., p-oxybenzoic acid esters, chlorobutanol, benzalkonium chloride) may be added as appropriate to a solid, semi-solid or liquid external agent. To be specific, for example, an ointment can be prepared, which contains the compound (I) of the present invention generally by 0.1 to 100 mg per 1 g, using petrolatum, lanolin and the like as a base material.

[0104] The compound (I) of the present invention can be also prepared into an oily or aqueous solid, semi-solid or liquid suppository. The oily base used as appropriate for producing suppository is, for example, higher fatty acid glyceride (e.g., cacao butter, Witepsols (Dynamitnobel Ltd.)), middle fatty acid (e.g., migriol acid (Dynamitnobel Co., Ltd.)), vegetable oil (e.g., sesame oil, soybean oil, cottonseed oil).

[0105] As an aqueous base, for example, polyethylene glycols, propylene glycol are used, and as an aqueous gel base, for example, natural gums, cellulose derivative, vinyl polymer, acrylic polymer are used as appropriate.

[0106] While the dose of the compound (I) of the present invention varies depending on the age, body weight, condition, dosage form, administration method, administration period, for example, it is generally 0.01 to 1000 mg/kg, preferably

0.01 to 100 mg/kg, more preferably 0.1 to 100 mg/kg, particularly 0.1 to 50 mg/kg, specifically 1.5 to 30 mg/kg per day, as the amount of compound (I) of the present invention, for one patient (adult, body weight about 60 kg) with sepsis, which is orally or parenterally administered once to several times a day. It is needless to say that the dose varies depending on various conditions as mentioned above, and in some cases an amount smaller than the aforementioned dose is sufficient and in other cases administration beyond the above range may be necessary.

[0107] The present invention is explained in detail by the following Reference Examples, Examples, Formulation Examples and Experimental Examples. These examples do not limit the present invention.

[0108] The ^{1}H-NMR spectrum was measured with Varian Gemini 200 (200 MHz) type spectrometer using tetramethylsilane as an internal standard, and all δ values are shown in ppm. The figures in parentheses for mixed solvents are mixing volume ratios of respective solvents. The room temperature is 15-25°C and % means percent by weight, unless specifically indicated. The ratio of the solvents for silica gel chromatography shows the volume ratio of the solvents mixed.

[0109] Each symbol in Examples means the following. s: singlet, d: doublet, t: triplet, q: quartet, dd: double doublet, td: triple doublet, m: multiplet, br: broad, J: coupling constant

Examples

Reference Example 1

[0110] To a solution of ethyl 6-[N-(2,4-difluorophenyl)sulfamoyl]-1-cyclohexene-1-carboxylate (1 g, synthesized according to the method disclosed in JP-A-10-056492) and phenylmethanethiol (719 mg) in N,N-dimethylformamide (20 ml) was added dropwise under ice-cooling 1,8-diazabicyclo[5,4,0]-7-undecene (441 mg) and the mixture was stirred at room temperature for 18 h. The reaction mixture was diluted with ethyl acetate (100 ml), washed with water (70 ml $\times$ 2) and saturated brine (70 ml), and dried over anhydrous sodium sulfate. The solvent was evaporated and the obtained residue was purified by flash silica gel column chromatography (eluent: toluene) to give ethyl 6-(benzylsulfanyl)-1-cyclohexene-1-carboxylate (673 mg) as a colorless oil. ^{1}H-NMR($CDCl_3$)δ: 1.27 (3H, t, J = 7.0Hz), 1.55-2.36 (6H, m), 3.76 (1H, m), 3.86 (2H, s), 4.19 (2H, q, J = 7.0Hz), 6.95 (1H, t, J = 4.0Hz), 7.22-7.39 (5H, m).

Reference Example 2

[0111] In the same manner as in Reference Example 1, ethyl 6-[N-(2,4-difluorophenyl)sulfamoyl]-1-cyclohexene-1-carboxylate (1 g) and (4-methoxyphenyl)methanethiol (893 mg) were reacted to give ethyl 6-[(4-methoxybenzyl)-sulfanyl]-1-cyclohexene-1-carboxylate (848 mg) as a colorless oil.
^{1}H-NMR($CDCl_3$) δ: 1.28 (3H, t, J = 7.0Hz), 1.57-2.32 (6H, m), 3.74 (1H, m), 3.80 (3H, s), 3.82 (2H, s), 4.20 (2H, q, J = 7.0Hz), 6.84 (2H, d, J = 8.4Hz), 6.94 (1H, t, J = 4.0Hz), 7.29 (2H, d, J = 8.4Hz).

Reference Example 3

[0112] In the same manner as in Reference Example 1, ethyl 6-[N-(2,4-difluorophenyl)sulfamoyl]-1-cyclohexene-1-carboxylate (455 mg) and (2,4-difluorophenyl)-methanethiol (421 mg) were reacted to give ethyl 6-[(2,4-difluorobenzyl) sulfanyl]-1-cyclohexene-1-carboxylate (185 mg) as a colorless oil.
^{1}H-NMR ($CDCl_3$) δ:1.26 (3H, t, J = 7.0Hz), 1.60-2.40 (6H, m), 3.78 (1H, m), 3.84 (2H, s), 4.18 (2H, q, J = 7.0Hz), 6.76-6.88 (2H, m), 6.97 (1H, t, J = 4.4Hz), 7.34-7.46 (1H, m).

Reference Example 4

[0113] In the same manner as in Reference Example 1, ethyl 6-[N-(2,4-difluorophenyl)sulfamoyl]-1-cyclohexene-1-carboxylate (835 mg) and (2-chloro-4-fluorophenyl)-methanethiol (853 mg) were reacted to give ethyl 6-[(2-chloro-4-fluorobenzyl)sulfanyl]-1-cyclohexene-1-carboxylate (625 mg) as a colorless oil.
^{1}H-NMR ($CDCl_3$) δ: 1.26 (3H, t, J = 7.0Hz), 1.56-2.36 (6H, m), 3.82 (1H, m), 3.94 (2H, s), 4.19 (2H, q, J = 7.0Hz), 6.96 (1H, td, J = 8.6Hz, 2.6Hz), 6.98 (1H, m), 7.12 (1H, dd, J= 8.6Hz, 2.6Hz), 7.46 (1H, dd, J= 8.6Hz, 6.0Hz).

Reference Example 5

[0114] 3-Pyranone (20.0 g) was reacted in the same manner as described in Tetrahedron., vol. 19, p. 1625 (1963) to give ethyl 5-hydroxy-3,6-dihydro-2H-pyran-4-carboxylate (7.52 g) as a colorless oil.
^{1}H-NMR ($CDCl_3$) δ: 1.32 (3H, t, J = 7.2 Hz), 2.31-2.38 (2H, m), 3.79 (2H, t, J = 5.6 Hz), 4.14 (2H, t, J = 1.8 Hz), 4.24 (2H, q, J = 7.2 Hz), 11.85 (1H, s).
SIMS:172 (M^+).

Reference Example 6

[0115] Ethyl 5-hydroxy-3,6-dihydro-2H-pyran-4-carboxylate (12.9 g) was reacted in the same manner as described in Tetrahedron., vol. 30, p. 3753 (1974) to give ethyl 5-sulfanyl-3,6-dihydro-2H-pyran-4-carboxylate (12.0 g) as a pale-blue oil.
^{1}H-NMR ($CDCl_3$) δ: 1.32 (3H, t, J = 7.2 Hz), 2.42-2.50 (2H, m), 3.70 (1H, s), 3.84 (2H, t, J = 5.6 Hz), 4.22 (2H, t, J = 2.2 Hz), 4.25 (2H, q, J = 7.2 Hz).
elemental analysis value: as $C_8H_{12}O_3S$
Calculated (%):C,51.04; H,6.43; S, 17.03.
Found (%):C,50.99; H,6.54; S, 16.91.

Reference Example 7

[0116] Sodium perborate tetrahydrate (24.5 g) was added to acetic acid (130 ml) and the mixture was heated to 50-55˚C. Thereto was added dropwise a solution of ethyl 5-sulfanyl-3,6-dihydro-2H-pyran-4-carboxylate (10.0 g) in acetic acid (30 ml) over 2 h. The mixture was stirred at 50-55˚C for 3 h, and the reaction mixture was concentrated under reduced pressure. To the residue was added acetonitrile (230 ml) and the mixture was stirred at room temperature for 2 days, and the resultant insoluble material was removed off by filtration and washed with acetonitrile (70 ml). The filtrate and washing were combined and the mixture was concentrated under reduced pressure. The residue was dissolved in acetonitrile (160 ml) and the mixture was stirred at room temperature for 6 h. The obtained insoluble material was removed off by filtration, and the filtrate was concentrated under reduced pressure. To the residue was added diisopropyl ether (100 ml), and the precipitated insoluble material was filtered off to give 4-(ethoxycarbonyl)-5,6-dihydro-2H-pyran-3-sulfonic acid as a pale-yellow oil (27.6 g) containing an inorganic product.
^{1}H-NMR(DMSO-d_6) δ: 1.19 (3H, t, J = 7.2 Hz), 2.17-2.21 (2H, m), 3.65 (2H, t, J = 5.5 Hz), 4.04 (2H, q, J = 7.2 Hz), 4.16 (2H, t, J = 2.4 Hz).

Reference Example 8

[0117] 4-(Ethoxycarbonyl)-5,6-dihydro-2H-pyran-3-sulfonic acid (27.5 g) was dissolved in thionyl chloride (82.6 ml) and the mixture was stirred at room temperature → 85˚C for 3 h. The reaction mixture was concentrated to dryness under reduced pressure and the residue was dissolved in ethyl acetate (100 ml). The obtained solution was partitioned by adding diluted brine (120 ml). The ethyl acetate layer was washed twice with saturated brine (50 ml) and dried over anhydrous sodium sulfate. The solvent was evaporated and the obtained residue was purified by silica gel column chromatography (eluent:ethyl acetate/hexane=1/7→1/5). The objective product was concentrated under reduced pressure and the crystals produced by freezing were washed with hexane to give ethyl 5-(chlorosulfonyl)-3,6-dihydro-2H-pyran-4-carboxylate (7.81 g) as pale-yellow crystals.
^{1}H-NMR ($CDCl_3$) δ: 1.37 (3H, t, J = 7.2 Hz), 2.62-2.70 (2H, m), 3.87 (2H, t, J = 5.5 Hz), 4.34 (2H, q, J = 7.2 Hz), 4.53 (2H, t, J = 2.6 Hz).
elemental analysis value: as $C_8H_{11}ClO_5S$
Calculated (%): C,37.73; H,4.35.
Found (%): C,37.64; H,4.27.

Example 1

[0118] To a solution of ethyl 6-(benzylsulfanyl)-1-cyclohexene-1-carboxylate (100 mg) obtained in Reference Example 1 in methylene chloride (3 ml) was added m- chloroperbenzoic acid (196 mg) under ice-cooling, and the mixture was stirred at room temperature for 1 h. To the reaction solution was added saturated aqueous sodium hydrogencarbonate solution (20 ml) and the mixture was extracted with ethyl acetate (20 ml × 2). The ethyl acetate layer was washed with saturated aqueous sodium hydrogencarbonate solution (20 ml), water (20 ml) and saturated brine (20 ml), and dried over anhydrous sodium sulfate. The solvent was evaporated and the obtained residue was purified by flash silica gel chromatography (eluent: hexane→ethyl acetate/hexane = 1/30) and crystallized from hexane to give ethyl 6-(benzylsulfonyl)-1-cyclohexene-1-carboxylate (compound 1, 106 mg) as white crystals.
^{1}H-NMR ($CDCl_3$) δ: 1.34 (3H, t, J = 7.2Hz), 1.41-2.50 (6H, m), 4.28 (2H, q, J = 7.2Hz), 4.29 (1H, d, J= 13.8Hz), 4.35 (1H, m), 4.55 (1H, d, J= 13.8Hz), 7.37-7.45 (4H, m), 7.50-7.55 (2H, m).
elemental analysis value: as $C_{16}H_{20}O_4S{\cdot}0.5H_2O$
Calculated (%): C, 60.55; H, 6.67
Found (%): C, 60.98; H, 6.32.

Example 2

[0119] In the same manner as in Example 1, ethyl 6-[(4-methoxybenzyl)sulfanyl]-1-cyclohexene-1-carboxylate (98 mg) obtained in Reference Example 2 was reacted to give ethyl 6-[(4-methoxybenzyl)sulfonyl]-1-cyclohexene-1-carboxylate (compound 2, 88 mg) as white crystals.
^{1}H-NMR ($CDCl_3$)d: 1.34 (3H, t, J = 7.0Hz), 1.42-2.50 (6H, m), 3.82 (3H, s), 4.21 (1H, d, J = 13.6Hz), 4.28 (2H, q, J = 7.0Hz), 4.31 (1H, m), 4.50 (1H, d, J = 13.6Hz), 6.92 (2H, d, J = 8.8Hz), 7.41 (1H, t, J = 3.6Hz), 7.47 (2H, d, J = 8.8Hz).
Elemental analysis value: as $C_{17}H_{22}O_5S$
Calculated (%): C, 60.33; H, 6.55
Found (%): C, 60.42; H, 6.58.

Example 3

[0120] In the same manner as in Example 1, ethyl 6-[(2,4-difluorobenzyl)sulfanyl]-1-cyclohexene-1-carboxylate (161 mg) obtained in Reference Example 3 was reacted to give ethyl 6-[(2,4-difluorobenzyl)sulfonyl]-1-cyclohexene-1-carboxylate (compound 3, 134 mg) as white crystals.
^{1}H-NMR ($CDCl_3$) δ: 1.32 (3H, t, J = 7.0Hz), 1.59-2.50 (6H, m), 4.27 (2H, q, J = 7.0Hz), 4.35 (1H, d, J = 14.0Hz), 4.39 (1H, m), 4.51 (1H, d, J = 14.0Hz), 6.83-6.96 (2H, m), 7.42 (1H, t, J = 4.0Hz), 7.49-7.61 (1H, m).
Elemental analysis value: as $C_{16}H_{18}F_2O_4S$
Calculated (%) : C, 55.80; H, 5.27
Found (%) : C, 55.95; H, 5.40.

Example 4

[0121] In the same manner as in Example 1, ethyl 6-[(2-chloro-4-fluorobenzyl)sulfanyl]-1-cyclohexene-1-carboxylate (509 mg) obtained in Reference Example 4 was reacted to give ethyl 6-[(2-chloro-4-fluorobenzyl)-sulfonyl]-1-cyclohexene-1-carboxylate (compound 4, 422 mg) as white crystals.
^{1}H-NMR ($CDCl_3$) δ: 1.32 (3H, t, J = 7.0Hz), 1.55-2.52 (6H, m), 4.25 (2H, q, J = 7.0Hz), 4.41 (1H, d, J = 5.6Hz), 4.59 (2H, s), 7.03 (1H, td, J = 8.4Hz, 2.6Hz), 7.21 (1H, dd, J= 8.4Hz, 2.6Hz), 7.42 (1H, t, J = 4.0Hz), 7.62 (1H, dd, J = 8.4Hz, 6.2Hz).
Elemental analysis value: as $C_{16}H_{18}ClFO_4S$
Calculated (%): C, 53.26; H, 5.03
Found (%): C, 53.08; H, 4.95.

Example 5

[0122] Ethyl 6-[(2-chloro-4-fluorobenzyl)sulfonyl]-1-cyclohexene-1-carboxylate (compound 4, 100 mg) obtained in Example 4 was resolved in two enantiomer by high performance liquid chromatography (CHIRALPAK AD; eluent: hexane/ethanol 8/2). The eluants were filtered through a 0.45 μm filter, concentrated and crystallized from hexane to respectively give ethyl (-)-6-[(2-chloro-4-fluorobenzyl)sulfonyl]-1-cyclohexene-1-carboxylate (compound 5, 50 mg) and ethyl (+)-6-[(2-chloro-4-fluorobenzyl)sulfonyl]-1-cyclohexene-1-carboxylate (compound 6, 49 mg) each as white crystals.

Compound 5

[0123] ^{1}H-NMR ($CDCl_3$) δ: 1.32 (3H, t, J = 7.0Hz), 1.56-2.55 (6H, m), 4.26 (2H, q, J = 7.0Hz), 4.42 (1H, d, J = 5.6Hz), 4.59 (2H, s), 7.03 (1H, td, J = 8.6Hz, 2.4Hz), 7.21 (1H, dd, J= 8.6Hz, 2.4Hz), 7.42 (1H, t, J = 4.2Hz), 7.61 (1H, dd, J = 8.6Hz, 6.0Hz).
Elemental analysis value: as $C_{16}H_{18}ClFO_4S$
Calculated (%): C, 53.26; H, 5.03
Found (%): C, 53.24; H, 4.85.
$[\alpha]_D^{20}$ -97.0°(c = 0.5, in methanol).

Compound 6

[0124] ^{1}H-NMR ($CDCl_3$) δ: 1.32 (3H, t, J = 7.0Hz), 1.56-2.55 (6H, m), 4.26 (2H, q, J = 7.0Hz), 4.42 (1H, d, J = 6.2Hz), 4.59 (2H, s), 7.03 (1H, td, J = 8.6Hz, 2.4Hz), 7.21 (1H, dd, J= 8.6Hz, 2.4Hz), 7.42 (1H, t, J = 4.4Hz), 7.60 (1H, dd, J = 8.6Hz, 6.0Hz).
Elemental analysis value: as $C_{16}H_{18}ClFO_4S$
Calculated (%): C, 53.26; H, 5.03

Found (%): C, 53.29; H, 4.82.
$[\alpha]_D^{20}$ +95.0° (c = 0.5, in methanol).

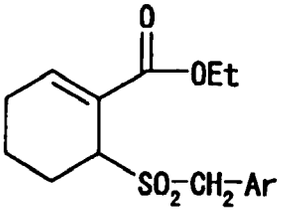
Example 6

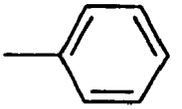
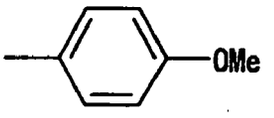
[0125] 2,4-Difluoroaniline (0.45g) was dissolved in ethyl acetate (10 ml) and triethylamine (0.55 mg) was added to the obtained solution under ice-cooling. Then, a solution of ethyl 5-(chlorosulfonyl)-3,6-dihydro-2H-pyran-4-carboxylate (0.69 g) obtained in Reference Example 8 in ethyl acetate (4 ml) was added dropwise. The reaction mixture was stirred under a nitrogen stream at 0°C for 30 min and at room temperature for 5.8 h. The reaction mixture was diluted with ethyl acetate and washed successively with water (50 ml), 0.5N hydrochloric acid (50 ml), water (50 ml × 2) and saturated brine (50 ml). The ethyl acetate layer was dried over magnesium sulfate and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: ethyl acetate/hexane=1/2). The objective fraction was concentrated under reduced pressure and the residue was crystallized from a mixture of ethyl acetate and diisopropyl ether to give ethyl 3-[(2,4-difluorophenyl)-sulfamoyl]-3,6-dihydro-2H-pyran-4-carboxylate (compound 7; 0.57 g) as white crystals.
^{1}H-NMR(DMSO-d_6) δ: 1.14 (3H, t, J = 7.0 Hz), 3.69 (1H, dd, J = 12.8 Hz, 3.0 Hz), 4.08 (2H, q, J = 7.0 Hz), 4.25 (2H, s), 4.33 (1H, d, J = 1.8 Hz), 4.41-4.48 (1H, m), 7.00-7.05 (1H, m), 7.12 (1H, br), 7.22-7.33 (1H, m), 7.43-7.55 (1H, m), 9.82 (1H, s).
Elemental analysis value: as $C_{14}H_{15}F_2NO_5S$
Calculated (%): C,48.41; H,4.35; N,4.03.
Found (%): C,48.47; H,4.35; N,3.96.

Example 7

[0126] In the same manner as in Example 6, ethyl 5-(chlorosulfonyl)-3,6-dihydro-2H-pyran-4-carboxylate (0.70 g) obtained in Reference Example 8 was reacted with 2-chloro-4-fluoroaniline (0.52 g) to give ethyl 3-[(2-chloro-4-fluorophenyl)sulfamoyl]-3,6-dihydro-2H-pyran-4-carboxylate (compound 8; 0.54 g) as white crystals.
^{1}H-NMR(DMSO-d_6) δ: 1.11 (3H, t, J = 7.0 Hz), 3.72 (1H, dd, J = 12.8 Hz, 3.0 Hz), 4.07 (2H, q, J = 7.0 Hz), 4.15-4.25 (2H, m), 4.37 (1H, d, J = 2.2 Hz), 4.46-4.55 (1H, m), 7.15 (1H, br), 7.22-7.26 (1H, m), 7.46-7.59 (2H, m), 9.68(1H, s).
Elemental analysis value: as $C_{14}H_{15}ClFNO_5S$
Calculated (%): C,46.22; H,4.16; N,3.85.
[0127] Found (%): C,46.35; H,4.11; N,3.73.
[0128] Specific examples of the compound of the present invention that can be synthesized in the same manner as in the aforementioned Examples are shown in Table 1 and Table 2. The present invention is not limited to the compounds exemplarily shown in Table 1 and Table 2.

Table 1



Compound No.	Ar
1	
2	

(continued)

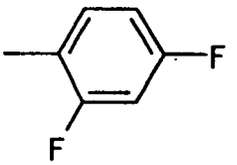
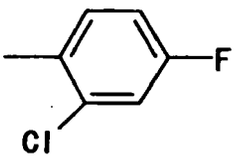
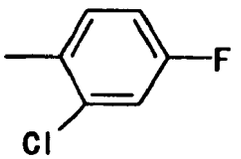
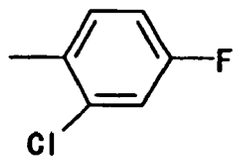
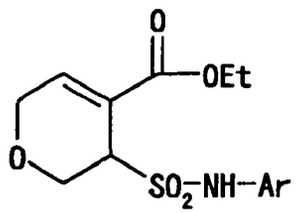
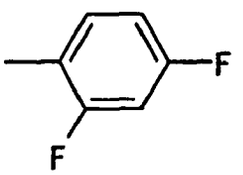
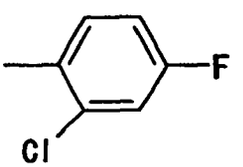
Compound No.	Ar
3	
4	
5 (-)-form	
6 (+)-form	

Table 2



Compound No.	Ar
7	
8	

Formulation Example 1

[0129]

(1) Compound 6	10	mg
(2) lactose	60	mg
(3) cornstarch	35	mg
(4) gelatin	3	mg
(5) magnesium stearate	2	mg

[0130] A mixture of compound 6 (10 mg), lactose (60 mg) and cornstarch (35 mg) was granulated using a 10% aqueous gelatin solution (0.03 ml, 3 mg of gelatin) by passing through a 1 mm mesh sieve, which granules were dried at 40˚C and passed through the sieve again. The thus-obtained granules were mixed with magnesium stearate (2 mg) and compressed. The obtained core tablet was coated with a sugar coating containing an aqueous suspension of sucrose, titanium dioxide, talc and gum arabic. The coated tablets were polished with beeswax to give coated tablets.

Formulation Example 2

[0131]

(1) Compound 6	10	mg
(2) lactose	70	mg
(3) cornstarch	50	mg
(4) soluble starch	7	mg
(5) magnesium stearate	3	mg

[0132] Compound 6 (10 mg) and magnesium stearate (3 mg) were granulated using an aqueous soluble starch solution (0.07 ml, 7 mg of soluble starch), dried and mixed with lactose (70 mg) and cornstarch (50 mg). The mixture was compressed to give tablets.

Formulation Example 3

[0133]

(1) Compound 8	10	mg
(2) lactose	60	mg
(3) cornstarch	35	mg
(4) gelatin	3	mg
(5) magnesium stearate	2	mg

[0134] A mixture of compound 8 (10 mg), lactose (60 mg) and cornstarch (35 mg) was granulated using a 10% aqueous gelatin solution (0.03 ml, 3 mg of gelatin) by passing through a 1 mm mesh sieve, which granules were dried at 40˚C and passed through the sieve again. The thus-obtained granules were mixed with magnesium stearate (2 mg) and compressed. The obtained core tablet was coated with a sugar coating containing an aqueous suspension of sucrose, titanium dioxide, talc and gum arabic. The coated tablets were polished with beeswax to give coated tablets.

Formulation Example 4

[0135]

(1) Compound 8	10	mg
(2) lactose	70	mg
(3) cornstarch	50	mg
(4) soluble starch	7	mg
(5) magnesium stearate	3	mg

[0136] Compound 8 (10 mg) and magnesium stearate (3 mg) were granulated using an aqueous soluble starch solution (0.07 ml, 7 mg of soluble starch), dried and mixed with lactose (70 mg) and cornstarch (50 mg). The mixture was

compressed to give tablets.

Experimental Example 1 inhibitory activity on NO production

[0137] Using mouse macrophage cell line, RAW264.7 as iNOS inducible cells, percent inhibition of NO production by the test compound was measured. The test compound was dissolved in N,N-dimethylformamide to 10 mM and diluted with RPMI-1640 medium to 0.1 mM. Furthermore, it was prepared with a medium to make a final concentration from 10 μM to 10 nM by diluting 10-fold, and added to the culture. The day before the experiment, the cells were prepared with RPMI-1640 medium supplemented with heat-inactivated 10% fetal calf serum to a concentration of 5×10^5 cells/ml and plated to a 96-well plate by 1×10^5 cells/0.2 ml per well. After culturing at 37˚C under 5% CO_2/95% air overnight, the medium was changed to RPMI-1640 medium supplemented with heat-inactivated 1% fetal calf serum. Thereto was added the prepared test compound, and LPS and interferon-γ were added to a final concentrations of 5 ng/ml and 1 U/ml, respectively. After incubation overnight, the concentration of nitrite ion (stable metabolite of NO) in the culture supernatant was measured and used as an index of NO production. The nitrite concentration was quantitatively measured by adding 20 μg/ml 2,3-diaminonaphtalene (DAN) by 25 μl to the culture supernatant (50 μl), incubating at room temperature for 10 min, adding 0.5N NaOH (25 μl) and measuring the fluorescence at 450 nm (excitation wavelength 365 nm). The results are shown in Table 3, wherein IC_{50} shows the concentration of the test compound necessary for inhibiting NO production by 50%.

Table 3

Compound No.	IC_{50} (μM)
1	0.24
2	3.2
3	0.047
4	0.029
5	1.0
6	0.0093
7	0.018
8	0.0031

[0138] The test compound strongly inhibited NO production by RAW264.7 cells, which shows that the cycloalkene derivative of the present invention has a superior NO production inhibitory activity.

Experimental Example 2 inhibitory activity on cytokine production

[0139] Using human monocyte cell line P31/FUJ (JCRB0091, establisher: Fujioka, obtained from the Human Science Research Resource Bank), the percent inhibition of cytokine production by the test compound was measured. The test compound was dissolved in N,N-dimethylformamide to 10 mM and diluted with RPMI-1640 medium to 0.1 mM. Furthermore, it was prepared with a medium to make a final concentration from 10 μM to 10 nM by diluting 10fold, and added to the culture. The day before the experiment, the cells were prepared with RPMI-1640 medium supplemented with 10% fetal calf serum to a concentration of 2×10^6 cells/ml and plated to a 96-well plate by 2×10^5 cells/0.1 ml per well. The abovementioned medium (0.1 ml) supplemented with 40 nM phorbol 12-myristate 13-acetate (PMA) was added and the mixture was cultured at 37˚C under 5% CO_2/95% air overnight. The cells were washed with the above-mentioned medium to remove PMA and the prepared test compound was added, and LPS and interferon-γ were added to a final concentrations of 100 ng/ml and 10 U/ml, respectively. After culturing overnight, the concentration of TNF-α and IL-1β in the culture supernatant was measured. For quantitative determination of each cytokine, a quantitative determination kit by Amersham was used. The results are shown in Table 4, wherein IC_{50} shows the concentration of the test compound necessary for inhibiting cytokine production by 50%.

Table 4

Compound No.	IC_{50} (μM)	
	TNF-α	IL-1β
4	0.20	0.58
6	0.15	0.23
8	0.02	0.011

Experimental Example 3 Effect against increase in blood nitrogen oxide concentration

[0140] When a biological defense response against infection and the like, immunopathy and the like causes NO production in the body, it is quickly metabolized into nitrous acid and nitric acid, whereby blood nitrogen oxide concentration (NOx) increases. Using test animals, the effect of the test compound against increase in blood NOx concentration was examined.

[0141] Female BALB/c mice (7-week-old) were divided into 6-8 mice per group. For the test compound group, the test compound was suspended in 0.5% aqueous methylcellulose solution and 10 mg/kg thereof was orally administered. For the control group, a solvent was similarly administered. One hour later, LPS (10 mg/kg) was intraperitoneally administered to the test compound group and the control group. At 6 h after LPS administration, blood was drawn and nitrate ion + nitrite ion concentration in sera was measured. The nitrate ion was converted to nitrous acid ion with nitrate reductase and quantitatively measured as a total nitrite ion , concentration by fluorescence method using the aforementioned DAN. The percent inhibition of the test compound group relative to the control group is shown in Table 5.

Table 5

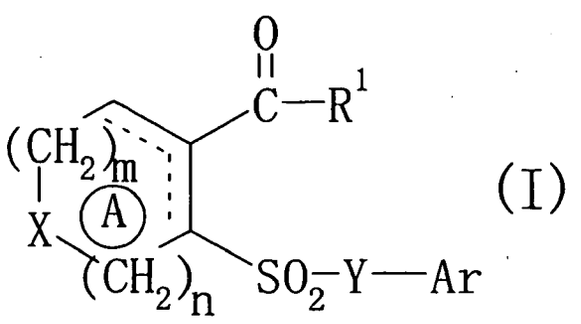
Compound No.	Blood NO_X inhibition (%)
4	62
8	80

Industrial Applicability

[0142] The compound (I) of the present invention has an inhibitory activity on nitric oxide (NO) production and cytokine production, and is useful as an agent for the prophylaxis and/or treatment of diseases such as cardiac disease, autoimmune disease, inflammatory disease, central nervous system disease, infectious disease, sepsis, septic shock and the like.

Claims

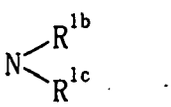
1. A compound of the formula:



(I)

wherein

R^1 is (i) an aliphatic hydrocarbon group selected from C_{1-20} alkyl group, C_{3-10} cycloalkyl group, C_{4-12} cycloalkylalkyl group, C_{3-6} alkenyl group and C_{3-6} alkynyl group, wherein these aliphatic hydrocarbon groups optionally have 1 to 4 substituent(s) selected from the group consisting of heterocyclic group, oxo group, hydroxy group, C_{1-6} alkoxy group, C_{3-10} cycloalkyloxy group, C_{6-10} aryloxy group, C_{7-19} aralkyloxy group, heterocyclyloxy group, C_{1-6} alkylthio group (the sulfur atom being optionally oxidized), C_{3-10} cycloalkylthio group (the sulfur atom being optionally oxidized), C_{6-10} arylthio (the sulfur atom being optionally oxidized), C_{7-19} aralkylthio group (the sulfur atom being optionally oxidized), heterocyclylthio group, heterocyclylsulfinyl group, heterocyclylsulfonyl group, nitro group, halogen atom, cyano group, carboxyl group, C_{1-10} alkoxy-carbonyl group, C_{3-6} cycloalkyloxycarbonyl group, C_{6-10} aryloxy-carbonyl group, C_{7-19} aralkyloxy-carbonyl group, heterocyclic oxycarbonyl group, C_{6-10} arylcarbonyl group, C_{1-6} alkanoyl group, C_{3-5} alkenoyl group, C_{6-10} aryl- carbonyloxy group, C_{2-6} alkanoyloxy group, C_{3-5} alkenoyloxy group, carbamoyl group (optionally substituted by 1 or 2 substituent(s) selected from C_{1-4} alkyl, phenyl, C_{1-7} acyl and C_{1-4} alkoxy- phenyl), thiocarbamoyl group (optionally substituted by 1 or 2 substituent(s) selected from C_{1-4} alkyl and phenyl), carbamoyloxy group (optionally substituted by 1 or 2 substituent(s) selected from C_{1-4} alkyl and phenyl), C_{1-6} alkanoylamino group, C_{6-10} aryl-carbonylamino group, C_{1-10} alkoxy-carboxamido group, C_{6-10} aryloxy-carboxamido group, C_{7-19} aralkyloxy- carboxamido group, C_{1-10} alkoxy-carbonyloxy group, C_{6-10} aryloxy-carbonyloxy group, C_{7-19} aralkyloxy- carbonyloxy group, C_{3-10} cycloalkyloxy-carbonyloxy group and ureido group (optionally having 1 to 3 substituent(s) selected from C_{1-4} alkyl group and phenyl group) (hereinafter substituent group A) and a group consisting of C_{6-10} aryl group optionally having 1 to 4 substituent(s) selected from substituent group A (hereinafter substituent group B), said heterocyclic group is a 5 to 8-membered heterocyclic group having, besides carbon atoms, 1 to 4 hetero atom(s) selected from a nitrogen atom (optionally oxidized), an oxygen atom and a sulfur atom, or a fused ring thereof, which optionally has 1 to 3 substituent(s) selected from C_{1-4} alkyl, hydroxy, oxo and C_{1-4} alkoxy, and said substituents may form, together with an aliphatic hydrocarbon group, a fused ring optionally having 1 to 4 substituent(s) selected from substituent group B, (ii) C_{6-14} aryl group optionally having 1 to 5 substituent(s) selected from a group consisting of halogen atom, C_{1-4} alkyl group, C_{1-4} alkoxy group, C_{1-4} alkoxy-carbonyl group, carboxyl group, nitro group, cyano group, hydroxy group, C_{1-4} alkanoylamino group, C_{3-6} cycloalkyl group, C_{6-10} aryl group, halogeno C_{1-4} alkyl group, halogeno C_{1-4} alkoxy group, C_{1-4} alkylthio group, C_{1-4} alkylsulfonyl group, C_{1-4} alkanoyl group, 5-membered aromatic heterocyclic group, carbamoyl group, C_{1-4} alkyl-carbamoyl group, C_{1-4} alkoxy-carbonyl-C_{1-4} alkyl- carbamoyl group and 1,3-diacylguanidino-C_{1-4} alkyl group (hereinafter substituent group C), (iii) a 5 to 8-membered heterocyclic ring having, besides carbon atoms, 1 to 4 hetero atom(s) selected from a nitrogen atom (optionally oxidized), an oxygen atom and a sulfur atom, or a fused ring thereof, which heterocyclic group may have 1 to 3 substituent(s) selected from C_{1-4} alkyl, hydroxy, oxo and C_{1-4} alkoxy, (iv) a group of the formula: OR^{1a} wherein R^{1a} is a hydrogen atom or an aliphatic hydrocarbon group selected from C_{1-20} alkyl group, C_{3-10} cycloalkyl group, C_{4-12} cycloalkylalkyl group, C_{3-6} alkenyl group and C_{3-6} alkynyl group optionally having substituent(s) selected from substituent group B, or (v) a group of the formula:



(a)

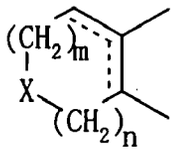
wherein R^{1b} and R^{1c} are the same or different and each is a hydrogen atom or an aliphatic hydrocarbon group selected from C_{1-20} alkyl group, C_{3-10} cycloalkyl group, C_{4-12} cycloalkylalkyl group, C_{3-6} alkenyl group and C_{3-6} alkynyl group optionally having substituent(s) selected from substituent group B; X is a methylene group, a nitrogen atom, a sulfur atom or an oxygen atom; and

Y is (i) a methylene group optionally having substituent(s) selected from C_{1-6} alkyl group, hydroxy substituted-C_{1-6} alkyl group and C_{1-4} alkoxy-carbonyl- C_{1-4} alkyl group or (ii) a nitrogen atom optionally having substituent (s) selected from C_{1-6} alkyl group, hydroxy substituted- C_{1-6} alkyl group and C_{1-4} alkoxy-carbonyl-C_{1-4} alkyl group;

ring A is optionally substituted by 1 to 4 substituent(s) selected from the following (1) to (4): (1) an aliphatic hydrocarbon group selected from C_{1-20} alkyl group, C_{3-10} cycloalkyl group, C_{4-12} cycloalkylalkyl group, C_{3-6} alkenyl group and C_{3-6} alkynyl group optionally having substituent(s) selected from substituent group B, (2) C_{6-14} aryl group optionally having substituent(s) selected from substituent group C, (3) a group of the formula: OR^2 wherein R^2 is a hydrogen atom, or an aliphatic hydrocarbon group

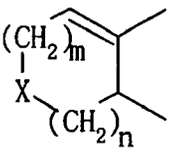
selected from C_{1-20} alkyl group, C_{3-10} cycloalkyl group, C_{4-12} cycloalkylalkyl group, C_{3-6} alkenyl group and C_{3-6} alkynyl group, optionally having substituent(s) selected from substituent group B and (4) a halogen atom;

Ar is a C_{6-14} aryl group optionally having substituent(s) selected from substituent group C; and the group of the formula:



(b)

is a group of the formula:



(b1)

wherein
m is 1; and
n is 1

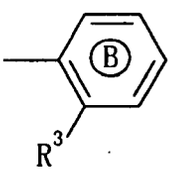
provided that when X is a methylene group, Y is a methylene group optionally having substituent(s) selected from C_{1-6} alkyl group, hydroxy substituted-C_{1-6} alkyl group and C_{1-4} alkoxy-carbonyl-C_{1-4} alkyl group, or a salt thereof.

2. The compound of claim 1, wherein the ring A is optionally substituted by C_{1-6} alkyl, phenyl or halogen, R^1 is OR^{1a} wherein R^{1a} is a C_{1-6} alkyl group, and Ar is a phenyl group optionally having substituent(s) selected from substituent group C.

3. The compound of claim 2, wherein R^{1a} is an ethyl group.

4. The compound of claim 2, wherein Ar is a halogeno phenyl group, a C_{1-4} alkylphenyl group or a phenyl group substituted by halogen and C_{1-4} alkyl.

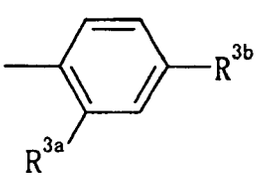
5. The compound of claim 2, wherein Ar is a group of the formula:



(c)

wherein R^3 is a halogen atom or a C_{1-4} alkyl group and ring B are optionally further substituted by halogen atom.

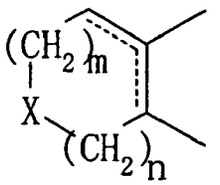
6. The compound of claim 5, wherein Ar is a group of the formula:



(c1)

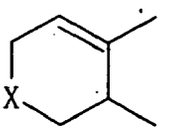
wherein R^{3a} and R^{3b} are the same or different and each is a halogen atom.

7. The compound of claim 1, wherein R^1 is a group of the formula: $OR^{1a'}$ wherein $R^{1a'}$ is a C_{1-6} alkyl group, a group of the formula:



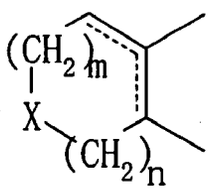
(b)

is a group of the formula:



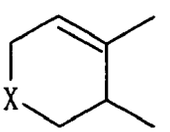
X is methylene or an oxygen atom, Y is methylene or -NH-, Ar is a phenyl group optionally having 1 or 2 substituent (s) selected from the group consisting of halogen atom and C_{1-6} alkoxy.

8. The compound of claim 1, wherein R^1 is a group of the formula: $OR^{1a'}$ wherein $R^{1a'}$ is a C_{1-6} alkyl group, a group of the formula:



(b)

is a group of the formula:



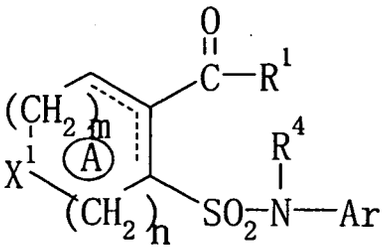
X is methylene and Y is methylene, or X is.an oxygen atom and Y is -NH-, and Ar is a phenyl group optionally having two halogen atoms.

9. Ethyl 6-[(2-chloro-4-fluorobenzyl)sulfonyl]-1-cyclohexene-1-carboxylate.

10. Ethyl (+)-6-[(2-chloro-4-fluorobenzyl)sulfonyl]-1-cyclohexene-1-carboxylate.

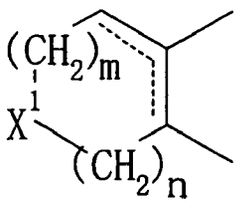
11. Ethyl 3-[(2-chloro-4-fluorophenyl)sulfamoyl]-3,6-dihydro-2H-pyran-4-carboxylate, or a salt thereof.

12. A production method of a compound of the formula:



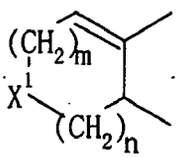
(Ia)

wherein
the group of the formula:



(b')

is a group of the formula:

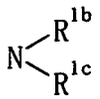


(b1')

wherein

m is 1;
n is 1;
R^1 is (i) an aliphatic hydrocarbon group selected from C_{1-20} alkyl group, C_{3-10} cycloalkyl group, C_{4-12} cycloalkylalkyl group, C_{3-6} alkenyl group and C_{3-6} alkynyl group, wherein these aliphatic hydrocarbon groups optionally have 1 to 4 substituent(s) selected from the group consisting of heterocyclic group, oxo group, hydroxy group, C_{1-6} alkoxy group, C_{3-10} cycloalkyloxy group, C_{6-10} aryloxy group, C_{7-19} aralkyloxy group, heterocyclyloxy group, C_{1-6} alkylthio group (the sulfur atom being optionally oxidized), C_{3-10} cycloalkylthio group (the sulfur atom being optionally oxidized), C_{6-10} arylthio (the sulfur atom being optionally oxidized), C_{7-19} aralkylthio group (the sulfur atom being optionally oxidized), heterocyclylthio group, heterocyclylsulfinyl group, heterocyclylsulfonyl group, nitro group, halogen atom, cyano group, carboxyl group, C_{1-10} alkoxy-carbonyl group, C_{3-6} cycloalkyloxycarbonyl group, C_{6-10} aryloxy-carbonyl group, C_{7-19} aralkyloxy-carbonyl group, heterocyclic oxycarbonyl group, C_{6-10} arylcarbonyl group, C_{1-6} alkanoyl group, C_{3-5} alkenoyl group, C_{6-10} aryl- carbonyloxy group, C_{2-6} alkanoyloxy group, C_{3-5} alkenoyloxy group, carbamoyl group (optionally substituted by 1 or 2 substituent(s) selected from C_{1-4} alkyl, phenyl, C_{1-7} acyl and C_{1-4} alkoxy- phenyl), thiocarbamoyl group (optionally substituted by 1 or 2 substituent(s) selected from C_{1-4} alkyl and phenyl), carbamoyloxy group (optionally substituted by 1 or 2 substituent(s) selected from C_{1-4} alkyl and phenyl), C_{1-6} alkanoylamino group, C_{6-10} aryl-carbonylamino group, C_{1-10} alkoxy-carboxamido group, C_{6-10} aryloxy-carboxamido group, C_{7-19} aralkyloxy- carboxamido group, C_{1-10} alkoxy-carbonyloxy group, C_{6-10} aryloxy-carbonyloxy group, C_{7-19} aralkyloxy- carbonyloxy group, C_{3-10} cycloalkyloxy-carbonyloxy group and ureido group (optionally having 1 to 3 substituent(s) selected from C_{1-4} alkyl group and phenyl group) (hereinafter substituent group A) and a group consisting of C_{6-10} aryl group optionally having 1 to 4 substituent(s) selected from substituent group A (hereinafter substituent group B), said heterocyclic group is a 5 to 8-membered heterocyclic group having, besides carbon atoms, 1 to 4 hetero atom(s) selected

from a nitrogen atom (optionally oxidized), an oxygen atom and a sulfur atom, or a fused ring thereof, which optionally has 1 to 3 substituent(s) selected from C_{1-4} alkyl, hydroxy, oxo and C_{1-4} alkoxy, and said substituents may form, together with an aliphatic hydrocarbon group, a fused ring optionally having 1 to 4 substituent(s) selected from substituent group B, (ii) C_{6-14} aryl group optionally having 1 to 5 substituent(s) selected from a group consisting of halogen atom, C_{1-4} alkyl group, C_{1-4} alkoxy group, C_{1-4} alkoxy-carbonyl group, carboxyl group, nitro group, cyano group, hydroxy group, C_{1-4} alkanoylamino group, C_{3-6} cycloalkyl group, C_{6-10} aryl group, halogeno C_{1-4} alkyl group, halogeno C_{1-4} alkoxy group, C_{1-4} alkylthio group, C_{1-4} alkylsulfonyl group, C_{1-4} alkanoyl group, 5-membered aromatic heterocyclic group, carbamoyl group, C_{1-4} alkyl-carbamoyl group, C_{1-4} alkoxy- carbonyl-C_{1-4} alkyl-carbamoyl group and 1,3- diacylguanidino-C_{1-4} alkyl group (hereinafter substituent group C), (iii) a 5 to 8-membered heterocyclic ring having, besides carbon atoms, 1 to 4 hetero atom (s) selected from a nitrogen atom (optionally oxidized), an oxygen atom and a sulfur atom, or a fused ring thereof, which heterocyclic group may have 1 to 3 substituent(s) selected from C_{1-4} alkyl, hydroxy, oxo and C_{1-4} alkoxy, (iv) a group of the formula: OR^{1a} wherein R^{1a} is a hydrogen atom or an aliphatic hydrocarbon group selected from C_{1-20} alkyl group, C_{3-10} cycloalkyl group, C_{4-12} cycloalkylalkyl group, C_{3-6} alkenyl group and C_{3-6} alkynyl group optionally having substituent(s) selected from substituent group B, or (v) a group of the formula:



(a)

wherein R^{1b} and R^{1c} are the same or different and each is a hydrogen atom or an aliphatic hydrocarbon group selected from C_{1-20} alkyl group, C_{3-10} cycloalkyl group, C_{4-12} cycloalkylalkyl group, C_{3-6} alkenyl group and C_{3-6} alkynyl group optionally having substituent(s) selected from substituent group B;

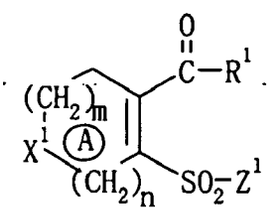
X^1 is a nitrogen atom, a sulfur atom or an oxygen atom; and

ring A is optionally substituted further by 1 to 4 substituent(s) selected from the following (1) to (4): (1) an aliphatic hydrocarbon group selected from C_{1-20} alkyl group, C_{3-10} cycloalkyl group, C_{4-12} cycloalkylalkyl group, C_{3-6} alkenyl group and C_{3-6} alkynyl group optionally having substituent(s) selected from substituent group B, (2) C_{6-14} aryl group optionally having substituent(s) selected from substituent group C, (3) a group of the formula: OR^2 wherein R^2 is a hydrogen atom, or an aliphatic hydrocarbon group selected from C_{1-20} alkyl group, C_{3-10} cycloalkyl group, C_{4-12} cycloalkylalkyl group, C_{3-6} alkenyl group and C_{3-6} alkynyl group, optionally having substituent(s) selected from substituent group B and (4) a halogen atom;

R^4 is a hydrogen atom or a C_{1-6} alkyl group which may be substituted with hydroxyl, or C_{1-4}-alkoxy carbonyl; and

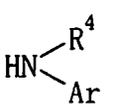
Ar is a C_{6-14} aryl group optionally having substituent(s) selected from substituent group C;

or a salt thereof, which method comprises reacting a compound of the formula:



(II)

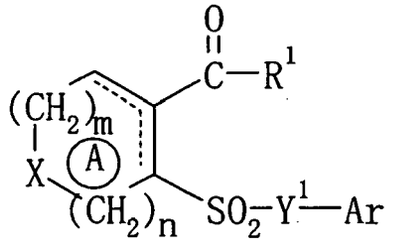
wherein Z^1 is a leaving group and other symbols are as defined above, or a salt thereof and a compound of the formula:



(III)

wherein each symbol is as defined above, or a salt thereof.

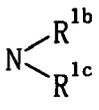
13. A production method of a compound of the formula:



(Ib)

wherein

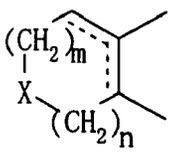
R^1 is (i) an aliphatic hydrocarbon group selected from C_{1-20} alkyl group, C_{3-10} cycloalkyl group, C_{4-12} cycloalkylalkyl group, C_{3-6} alkenyl group and C_{3-6} alkynyl group, wherein these aliphatic hydrocarbon groups optionally have 1 to 4 substituent(s) selected from the group consisting of heterocyclic group, oxo group, hydroxy group, C_{1-6} alkoxy group, C_{3-10} cycloalkyloxy group, C_{6-10} aryloxy group C_{7-19} aralkyloxy group, heterocyclyloxy group, C_{1-6} alkylthio group (the sulfur atom being optionally oxidized), C_{3-10} cycloalkylthio group (the sulfur atom being optionally oxidized), C_{6-10} arylthio (the sulfur atom being optionally oxidized), C_{7-19} aralkylthio group (the sulfur atom being optionally oxidized), heterocyclylthio group, heterocyclylsulfinyl group, heterocyclylsulfonyl group, nitro group, halogen atom, cyano group, carboxyl group, C_{1-10} alkoxy-carbonyl group, C_{3-6} cycloalkyloxycarbonyl group, C_{6-10} aryloxy-carbonyl group, C_{7-19} aralkyloxy-carbonyl group, heterocyclic oxycarbonyl group, C_{6-10} arylcarbonyl group, C_{1-6} alkanoyl group, C_{3-5} alkenoyl group, C_{6-10} aryl- carbonyloxy group, C_{2-6} alkanoyloxy group, C_{3-5} alkenoyloxy group, carbamoyl group (optionally substituted by 1 or 2 substituent(s) selected from C_{1-4} alkyl, phenyl, C_{1-7} acyl and C_{1-4} alkoxy- phenyl), thiocarbamoyl group (optionally substituted by 1 or 2 substituent(s) selected from C_{1-4} alkyl and phenyl), carbamoyloxy group (optionally substituted by 1 or 2 substituent(s) selected from C_{1-4} alkyl and phenyl), C_{1-6} alkanoylamino group, C_{6-10} aryl-carbonylamino group, C_{1-10} alkoxy-carboxamido group, C_{6-10} aryloxy-carboxamido group, C_{7-19} aralkyloxy- carboxamido group, C_{1-10} alkoxy-carbonyloxy group, C_{6-10} aryloxy-carbonyloxy group, C_{7-19} aralkyloxy- carbonyloxy group, C_{3-10} cycloalkyloxy-carbonyloxy group and ureido group (optionally having 1 to 3 substituent(s) selected from C_{1-4} alkyl group and phenyl group) (hereinafter substituent group A) and a group consisting of C_{6-10} aryl group optionally having 1 to 4 substituent(s) selected from substituent group A (hereinafter substituent group B), said heterocyclic group is a 5 to 8-membered heterocyclic group having, besides carbon atoms, 1 to 4 hetero atom(s) selected from a nitrogen atom (optionally oxidized), an oxygen atom and a sulfur atom, or a fused ring thereof, which optionally has 1 to 3 substituent(s) selected from C_{1-4} alkyl, hydroxy, oxo and C_{1-4} alkoxy, and said substituents may form, together with an aliphatic hydrocarbon group, a fused ring optionally having 1 to 4 substituent(s) selected from substituent group B, (ii) C_{6-14} aryl group optionally having 1 to 5 substituent(s) selected from a group consisting of halogen atom, C_{1-4} alkyl group, C_{1-4} alkoxy group, C_{1-4} alkoxy-carbonyl group, carboxyl group, nitro group, cyano group, hydroxy group, C_{1-4} alkanoylamino group, C_{3-6} cycloalkyl group, C_{6-10} aryl group, halogeno C_{1-4} alkyl group, halogeno C_{1-4} alkoxy group, C_{1-4} alkylthio group, C_{1-4} alkylsulfonyl group, C_{1-4} alkanoyl group, 5-membered aromatic heterocyclic group, carbamoyl group, C_{1-4} alkyl-carbamoyl group, C_{1-4} alkoxy-carbonyl-C_{1-4} alkyl- carbamoyl group and 1,3-diacylguanidino-C_{1-4} alkyl group (hereinafter substituent group C), (iii) a 5 to 8-membered heterocyclic ring having, besides carbon atoms, 1 to 4 hetero atom(s) selected from a nitrogen atom (optionally oxidized), an oxygen atom and a sulfur atom, or a fused ring thereof, which heterocyclic group may have 1 to 3 substituent(s) selected from C_{1-4} alkyl, hydroxy, oxo and C_{1-4} alkoxy, (iv) a group of the formula: OR^{1a} wherein R^{1a} is a hydrogen atom or an aliphatic hydrocarbon group selected from C_{1-20} alkyl group, C_{3-10} cycloalkyl group, C_{4-12} cycloalkylalkyl group, C_{3-6} alkenyl group and C_{3-6} alkynyl group optionally having substituent(s) selected from substituent group B, or (v) a group of the formula:



(a)

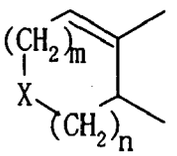
wherein R^{1b} and R^{1c} are the same or different and each is a hydrogen atom or an aliphatic hydrocarbon group selected from C_{1-20} alkyl group, C_{3-10} cycloalkyl group, C_{4-12} cycloalkylalkyl group, C_{3-6} alkenyl group and C_{3-6} alkynyl group optionally having substituent(s) selected from substituent group B;
X is a methylene group, a nitrogen atom, a sulfur atom or an oxygen atom; and
ring A is optionally substituted by 1 to 4 substituent(s) selected from the following (1) to (4): (1) an aliphatic hydrocarbon group selected from C_{1-20} alkyl group, C_{3-10} cycloalkyl group, C_{4-12} cycloalkylalkyl group, C_{3-6} alkenyl group and C_{3-6} alkynyl group optionally having substituent(s) selected from substituent group B, (2) C_{6-14} aryl group optionally having substituent(s) selected from substituent group C, (3) a group of the formula: OR^2 wherein R^2 is a hydrogen atom, or an aliphatic hydrocarbon group selected from C_{1-20} alkyl group, C_{3-10} cycloalkyl group, C_{4-12} cycloalkylalkyl group, C_{3-6} alkenyl group and C_{3-6} alkynyl group, optionally having substituent(s) selected from substituent group B and (4) a halogen atom;
Y^1 is a methylene group optionally having substituent(s) selected from C_{1-6} alkyl group, hydroxy substituted-C_{1-6} alkyl group and C_{1-4} alkoxy-carbonyl-C_{1-4} alkyl group
Ar is a C_{6-14} aryl group optionally having substituent(s) selected from substituent group C; and

the group of the formula:



(b)

is a group of the formula:

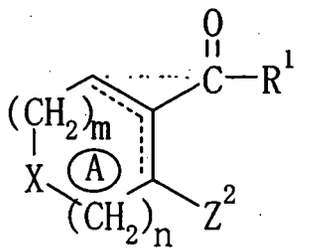


(b1)

wherein

m is 1; and
n is 1

or a salt thereof, which method comprises reacting a compound of the formula:



(IV)

wherein Z^2 is a leaving group and other symbols are as defined above, or a salt thereof, and a compound of the formula:

$$HS\text{-}Y^1\text{-}Ar \qquad (V1)$$

wherein each symbol is as defined above, or a salt thereof, and oxidizing the obtained sulfide.

14. A pharmaceutical composition comprising a compound as defined in any of claims 1 to 11.

15. The compound as defined in any of claims 1 to 11 or the composition as defined in claim 14 used for suppressing nitric oxide (NO) and/or cytokine production.

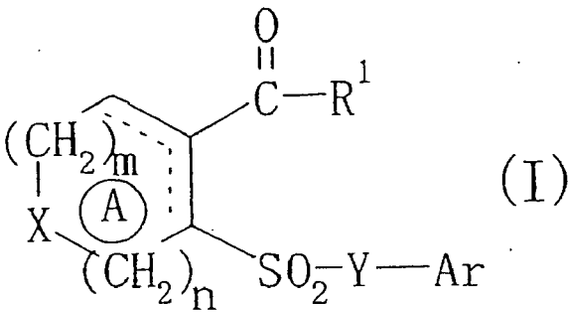
16. The compound as defined in any of claims 1 to 11 or the composition as defined in claim 14 used for the prophylaxis or treatment of a cardiac disease, an autoimmune disease or septic shock.

17. Use of the compound of any of claims 1 to 11 for the production of an agent for suppressing nitric oxide (NO) and/or cytokine production.

18. Use of the compound of any of claims 1 to 11 for the production of an agent for the prophylaxis or treatment of a cardiac disease, an autoimmune disease or septic shock.

Patentansprüche

1. Verbindung der Formel

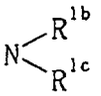


(I)

wobei

R^1 Folgendes ist: (i) eine aliphatische Kohlenwasserstoffgruppe, die aus einer C_{1-20}- Alkylgruppe, C_{3-10}-Cycloalkylgruppe, C_{4-12}-Cycloalkylalkylgruppe, C_{3-6}-Alkenylgruppe und C_{3-6}-Alkinylgruppe ausgewählt ist, wobei diese aliphatischen Kohlenwasserstoffgruppen gegebenenfalls 1 bis 4 Substituenten aufweisen, die aus der Gruppe ausgewählt sind, die aus einer heterocyclischen Gruppe, Oxogruppe, Hydroxygruppe, C_{1-6}-Alkoxygruppe, C_{3-10}-Cycloalkyloxygruppe, C_{6-10}-Aryloxygruppe, C_{7-19}-Aralkyloxygruppe, Heterocyclyloxygruppe, C_{1-6}-Alkylthiogruppe (wobei das Schwefelatom gegebenenfalls oxidiert ist), C_{3-10}- Cycloalkylthiogruppe (wobei das Schwefelatom gegebenenfalls oxi- diert ist), C_{6-10}-Arylthio (wobei das Schwefelatom gegebenenfalls oxidiert ist), C_{7-19}-Aralkylthiogruppe (wobei das Schwefelatom ge- gebenenfalls oxidiert ist), Heterocyclylthiogruppe, Heterocyclyl- sulfinylgruppe, Heterocyclylsulfonylgruppe, Nitrogruppe, einem Ha- logenatom, einer Cyanogruppe, Carboxygruppe, C_{1-10}-Alkoxycarbo- nylgruppe, C_{3-6}-Cycloal kyloxycarbonylgruppe, C_{5-10}-Aryloxycarbonylgruppe, C_{7-19}-Aralkyloxycarbonylgruppe, Heterocyclyloxycarbonyl- gruppe, C_{6-10}-Arylcarbonylgruppe, C_{1-6}-Alkanoylgruppe, C_{3-5}- Alkenoylgruppe, C_{6-10}-Arylcarbonyloxygruppe, C_{2-6}-Alkanoyloxy- gruppe, C_{3-5}-Alkenoyloxygruppe, Carbamoylgruppe (gegebenenfalls mit 1 oder 2 Substituenten substituiert, die aus C_{1-4}-Alkyl, Phenyl, C_{1-7}-Acyl und C_{1-4}-Alkoxyphenyl ausgewählt sind), Thiocarbamoyl- gruppe (gegebenenfalls mit 1 oder 2 Substituenten substituiert, die aus C_{1-4}-Alkyl und Phenyl ausgewählt sind), Carbamoyloxygruppe (gegebenenfalls mit 1 oder 2 Substituenten substituiert, die aus C_{1-4}-Alkyl und Phenyl ausgewählt sind), C_{1-6}-Alkanoylaminogruppe, C_{6-10}-Arylcarbonylaminogruppe, C_{1-10}-Alkoxycarboxamidogruppe, C_{6-10}-Aryloxycarboxamidogruppe, C_{7-19}-Aralkyloxycarboxamido- gruppe, C_{1-10}-Alkoxycarbonyloxygruppe, C_{6-10}-Aryloxycarbonyloxy- gruppe, C_{7-19}-Aralkyloxycarbonyloxygruppe, C_{3-10}-Cycloalkyloxycar- bonyloxygruppe und Ureidogruppe (die gegebenenfalls 1 bis 3 Sub- stituenten aufweist, die aus einer C_{1-4}-Alkylgruppe und einer Phe- nylgruppe ausgewählt sind) (im Folgenden Substituentengruppe A) und einer Gruppe, die aus einer C_{6-10}-Arylgruppe, die gegebenenfalls 1 bis 4 Substituenten aufweist, die aus Substituentengruppe A ausgewählt sind (im Folgenden Substituentengruppe B), besteht, wobei die heterocyclische Gruppe eine fünf- bis achtgliedrige heterocyclische Gruppe,

die neben Kohlenstoffatomen 1 bis 4 Hete- roatome aufweist, die aus einem Stickstoffatom (gegebenenfalls oxidiert), einem Sauerstoffatom und einem Schwefelatom ausge- wählt sind, oder ein kondensierter Ring davon ist und gegebenen- falls 1 bis 3 Substituenten aufweist, die aus C_{1-4}-Alkyl, Hydroxy, Oxo und C_{1-4}-Alkoxy ausgewählt sind, und die Substituenten zusammen mit einer aliphatischen Kohlenwasser- stoffgruppe einen kondensierten Ring bilden können, der gegebe- nenfalls 1 bis 4 Substituenten aufweist, die aus Substituentengruppe B ausgewählt sind; (ii) eine C_{6-14}-Arylgruppe, die gegebenenfalls 1 bis 5 Substituenten aufweist, die aus der Gruppe ausgewählt sind, die aus einem Halo- genatom, einer C_{1-4}-Alkylgruppe, C_{1-4}-Alkoxygruppe, C_{1-4}-Alkoxy- carbonylgruppe, Carboxygruppe, Nitrogruppe, Cyanogruppe, Hydroxygruppe, C_{1-4}-Alkanoylaminogruppe, C_{3-6}-Cycloalkylgruppe, C_{6-10}-Arylgruppe, Halogen-C_{1-4}-alkylgruppe, Halogen-C_{1-4}-alkoxy- gruppe, C_{1-4}-Alkylthiogruppe, C_{1-4}-Alkylsulfonylgruppe, C_{1-4}-Alka- noylgruppe, fünfgliedrigen aromatischen heterocyclischen Gruppe, Carbamoylgruppe, C_{1-4}-Alkylcarbamoylgruppe, C_{1-4}-Alkoxycarbonyl- C_{1-4}-alkylcarbamoylgruppe und 1,3-Diacylguanidino-C_{1-4}-alkyl- gruppe besteht (im Folgenden Substituentengruppe C); (iii) ein fünf- bis achtgliedriger heterocyclischer Ring, der neben Kohlenstoffatomen 1 bis 4 Heteroatome aufweist, die aus einem Stickstoffatom (gegebenenfalls oxidiert), einem Sauerstoffatom und einem Schwefelatom ausgewählt sind, oder ein kondensierter Ring davon ist, wobei die heterocyclische Gruppe 1 bis 3 Substituenten aufweisen kann, die aus C_{1-4}-Alkyl, Hydroxy, Oxo und C_{1-4}-Alkoxy ausgewählt sind; (iv) eine Gruppe der Formel OR^{1a}, wobei R^{1a} ein Wasserstoffatom oder eine aliphatische Kohlenwasserstoffgruppe ist, die aus einer C_{1-20}-Alkylgruppe, C_{3-10}-Cycloalkylgruppe, C_{4-12}-Cycloalkylalkyl- gruppe, C_{3-6}-Alkenylgruppe und C_{3-6}-Alkinylgruppe, die gegebenen- falls einen oder mehrere Substituenten aufweist, die aus Sub- stituentengruppe B ausgewählt sind, ausgewählt ist; oder (v) eine Gruppe der Formel:



(a)

X wobei R^{1b} und R^{1c} gleich oder verschieden sind und jeweils ein Wasserstoffatom oder eine aliphatische Kohlenwasserstoffgruppe sind, die aus einer C_{1-20}-Alkylgruppe, C_{3-10}-Cycloalkylgruppe, C_{4-12}- Cycloalkylalkylgruppe, C_{3-6}-Alkenylgruppe und C_{3-6}-Alkinylgruppe, die gegebenenfalls einen oder mehrere Substituenten aufweist, die aus Substituentengruppe B ausgewählt sind, ausgewählt ist; eine Methylengruppe, ein Stickstoffatom, ein Schwefelatom oder ein Sauerstoffatom ist; und

Y Folgendes ist: (i) eine Methylengruppe, die gegebenenfalls einen oder mehrere Substituenten aufweist, die aus einer C_{1-6}-Alkylgruppe, hydroxy- substituierten C_{1-6}-Alkylgruppe und C_{1-4}-Alkoxycarbonyl-C_{1-4}-alkyl- gruppe ausgewählt sind, oder (ii) ein Stickstoffatom, das gegebenenfalls einen oder mehrere Substituenten aufweist, die aus einer C_{1-6}-Alkylgruppe, hydroxy- substituierten C_{1-6}-Alkylgruppe und C_{1-4}-Alkoxycarbonyl-C_{1-4}-alkylgruppe ausgewählt sind;

Ring A gegebenenfalls mit 1 bis 4 Substituenten substituiert ist, die aus den folgenden (1) bis (4) ausgewählt sind:

(1) einer aliphatischen Kohlenwasserstoffgruppe, die aus einer C_{1-20}-Alkylgruppe, C_{3-10}-Cycloalkylgruppe, C_{4-12}-Cycloalkylalkyl- gruppe, C_{3-6}-Alkenylgruppe und C_{3-6}-Alkinylgruppe, die gegebenen- falls einen oder mehrere aus Substituentengruppe B ausgewählte Substituenten aufweisen, ausgewählt ist;

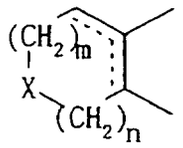
(2) einer C_{6-14}-Arylgruppe, die gegebenenfalls einen oder mehrere Substituenten aufweist, die aus Substituentengruppe C ausgewählt sind;

(3) einer Gruppe der Formel OR^2, wobei R^2 ein Wasserstoffatom oder eine aliphatische Kohlenwasserstoffgruppe ist, die aus einer C_{1-20}-Alkylgruppe, C_{3-10}-Cycloalkylgruppe, C_{4-12}-Cycloalkylalkylgruppe, C_{3-6}-Alkenylgruppe und C_{3-6}-Alkinylgruppe, die gegebenenfalls einen oder mehrere aus Substituentengruppe B ausgewählte Substituenten aufweisen, ausgewählt ist; und

(4) einem Halogenatom;

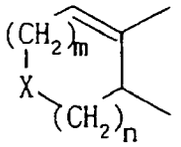
Ar eine C_{6-14}-Arylgruppe ist, die gegebenenfalls einen oder mehrere aus Substituentengruppe C ausgewählte Substituenten aufweist; und

die Gruppe der Formel



(b)

eine Gruppe der Formel



(b1)

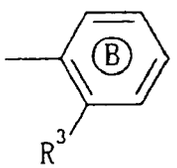
ist, wobei m = 1 ist; und n = 1 ist;
mit der Maßgabe, dass, wenn X eine Methylengruppe ist, dann Y eine Methylengruppe ist, die gegebenenfalls einen oder mehrere Substituenten aufweist, die aus einer C_{1-6}-Alkylgruppe, hydroxysubstituierten C_{1-6}-Alkylgruppe und C_{1-4}-Alkoxycarbonyl-C_{1-4}-alkylgruppe ausgewählt sind;
oder ein Salz davon.

2. Verbindung gemäß Anspruch 1, wobei Ring A gegebenenfalls mit C_{1-6}-Alkyl, Phenyl oder Halogen substituiert ist, $R^1 = OR^{1a}$ ist, wobei R^{1a} eine C_{1-6}-Alkylgruppe ist, und Ar eine Phenylgruppe ist, die gegebenenfalls einen oder mehrere Substituenten aufweist, die aus Substituentengruppe C ausgewählt sind.

3. Verbindung gemäß Anspruch 2, wobei R^{1a} eine Ethylgruppe ist.

4. Verbindung gemäß Anspruch 2, wobei Ar eine Halogenphenylgruppe, eine C_{1-4}-Alkylphenylgruppe oder eine mit Halogen oder C_{1-4}-Alkyl substituierte Phenylgruppe ist.

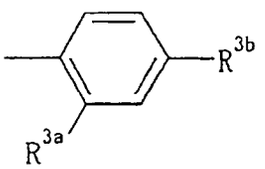
5. Verbindung gemäß Anspruch 2, wobei Ar eine Gruppe der Formel



(c)

ist, wobei R^3 ein Halogenatom oder eine C_{1-4}-Alkylgruppe ist und Ring B gegebenenfalls weiterhin mit einem Halogenatom substituiert ist.

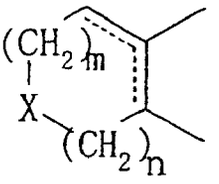
6. Verbindung gemäß Anspruch 5, wobei Ar eine Gruppe der Formel



(c1)

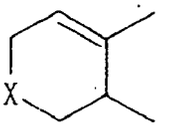
ist, wobei R^{3a} und R^{3b} gleich oder verschieden sind und jeweils ein Halogenatom sind.

7. Verbindung gemäß Anspruch 1, wobei R^1 eine Gruppe der Formel $OR^{1a'}$ ist, wobei $R^{1a'}$ eine C_{1-6}-Alkylgruppe ist, die Gruppe der Formel



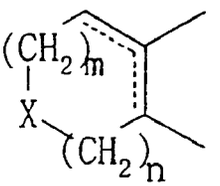
(b)

eine Gruppe der Formel



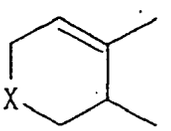
ist, X Methylen oder ein Sauerstoffatom ist, Y Methylen oder -NH- ist, Ar eine Phenylgruppe ist, die gegebenenfalls 1 oder 2 Substituenten aufweist, die aus der Gruppe ausgewählt sind, die aus einem Halogenatom und C_{1-6}-Alkoxy besteht.

8. Verbindung gemäß Anspruch 1, wobei R^1 eine Gruppe der Formel $OR^{1a'}$ ist, wobei $R^{1a'}$ eine C_{1-6}-Alkylgruppe ist, die Gruppe der Formel



(b)

eine Gruppe der Formel



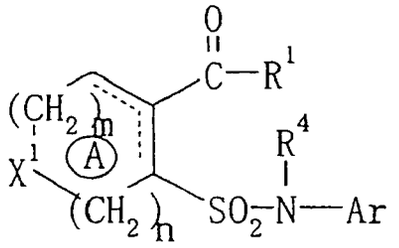
ist, X Methylen ist und Y Methylen ist oder X ein Sauerstoffatom ist und Y = -NH- ist und Ar eine Phenylgruppe ist, die gegebenenfalls zwei Halogenatome aufweist.

9. Ethyl-6-[(2-chlor-4-fluorbenzyl)sulfonyl]-1-cyclohexen-1-carboxylat.

10. Ethyl-(+)-6-[(2-chlor-4-fluorbenzyl)sulfonyl]-1-cyclohexen-1-carboxylat.

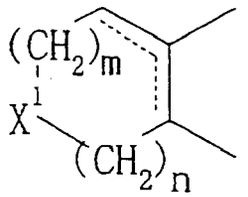
11. Ethyl-3-[(2-chlor-4-fluorphenyl)sulfamoyl]-3,6-dihydro-2H-pyran-4-carboxylat oder ein Salz davon.

12. Herstellungsverfahren für eine Verbindung der Formel



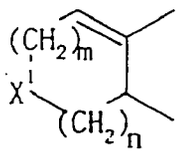
(Ia)

wobei die Gruppe der Formel



(b')

eine Gruppe der Formel

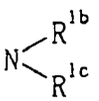


(b1')

ist, wobei

m = 1 ist;
n = 1 ist;
R^1 Folgendes ist: (i) eine aliphatische Kohlenwasserstoffgruppe, die aus einer C_{1-20}- Alkylgruppe, C_{3-10}-Cycloalkylgruppe, C_{4-12}-Cycloalkylalkylgruppe, C_{3-6}-Alkenylgruppe und C_{3-6}-Alkinylgruppe ausgewählt ist, wobei diese aliphatischen Kohlenwasserstoffgruppen gegebenenfalls 1 bis 4 Substituenten aufweisen, die aus der Gruppe ausgewählt sind, die aus einer heterocyclischen Gruppe, Oxogruppe, Hydroxygruppe, C_{1-6}-Alkoxygruppe, C_{3-10}-Cycloalkyloxygruppe, C_{6-10}-Aryloxygruppe, C_{7-19}-Aralkyloxygruppe, Heterocyclyloxygruppe, C_{1-6}-Alkylthiogruppe (wobei das Schwefelatom gegebenenfalls oxidiert ist), C_{3-10}- Cycloalkylthiogruppe (wobei das Schwefelatom gegebenenfalls oxi- diert ist), C_{6-10}-Arylthio (wobei das Schwefelatom gegebenenfalls oxidiert ist), C_{7-19}-Aralkylthiogruppe (wobei das Schwefelatom ge- gebenenfalls oxidiert ist), Heterocyclylthiogruppe, Heterocyclyl- sulfinylgruppe, Heterocyclylsulfonylgruppe, Nitrogruppe, einem Ha- logenatom, einer Cyanogruppe, Carboxygruppe, C_{1-10}-Alkoxycarbo- nylgruppe, C_{3-6}-Cycloalkyloxycarbonylgruppe, C_{6-10}-Aryloxycarbonylgruppe, C_{7-19}-Aralkyloxycarbonylgruppe, Heterocyclyloxycarbonyl- gruppe, C_{6-10}-Arylcarbonylgruppe, C_{1-6}-Alkanoylgruppe, C_{3-5}- Alkenoylgruppe, C_{6-10}-Arylcarbonyloxygruppe, C_{2-6}-Alkanoyloxy- gruppe, C_{3-5}-Alkenoyloxygruppe, Carbamoylgruppe (gegebenenfalls mit 1 oder 2 Substituenten substituiert, die aus C_{1-4}-Alkyl, Phenyl, C_{1-7}Acyl und C_{1-4}-Alkoxyphenyl ausgewählt sind), Thiocarbamoyl- gruppe (gegebenenfalls mit 1 oder 2 Substituenten substituiert, die aus C_{1-4}-Alkyl und Phenyl ausgewählt sind), Carbamoyloxygruppe (gegebenenfalls mit 1 oder 2 Substituenten substituiert, die aus C_{1-4}-Alkyl und Phenyl ausgewählt sind), C_{1-6}-Alkanoylaminogruppe, C_{6-10}-Arylcarbonylaminogruppe, C_{1-10}-Alkoxycarboxamidogruppe, C_{6-10}-Aryloxycarboxamidogruppe, C_{7-19}-Aralkyloxycarboxamido- gruppe, C_{1-10}-Alkoxycarbonyloxygruppe, C_{6-10}-Aryloxycarbonyloxy- gruppe, C_{7-19}-Aralkyloxycarbonyloxygruppe, C_{3-10}-Cycloalkyloxycar- bonyloxygruppe und Ureidogruppe (die gegebe-

nenfalls 1 bis 3 Sub- stituenten aufweist, die aus einer C_{1-4}-Alkylgruppe und einer Phe- nylgruppe ausgewählt sind) (im Folgenden Substituentengruppe A) und einer Gruppe, die aus einer C_{6-10}-Arylgruppe, die gegebenenfalls 1 bis 4 Substituenten aufweist, die aus Substituentengruppe A ausgewählt sind (im Folgenden Substituentengruppe B), besteht, wobei die heterocyclische Gruppe eine fünf- bis achtgliedrige heterocyclische Gruppe, die neben Kohlenstoffatomen 1 bis 4 Hete- roatome aufweist, die aus einem Stickstoffatom (gegebenenfalls oxidiert), einem Sauerstoffatom und einem Schwefelatom ausge- wählt sind, oder ein kondensierter Ring davon ist und gegebenen- falls 1 bis 3 Substituenten aufweist, die aus C_{1-4}-Alkyl, Hydroxy, Oxo und C_{1-4}-Alkoxy ausgewählt sind, und die Substituenten zusammen mit einer aliphatischen Kohlenwasser- stoffgruppe einen kondensierten Ring bilden können, der gegebe- nenfalls 1 bis 4 Substituenten aufweist, die aus Substituentengruppe B ausgewählt sind; (ii) eine C_{6-14}-Arylgruppe, die gegebenenfalls 1 bis 5 Substituenten aufweist, die aus der Gruppe ausgewählt sind, die aus einem Halo- genatom, einer C_{1-4}-Alkylgruppe, C_{1-4}-Alkoxygruppe, C_{1-4}-Alkoxy- carbonylgruppe, Carboxygruppe, Nitrogruppe, Cyanogruppe, Hydroxygruppe, C_{1-4}-Alkanoylaminogruppe, C_{3-6}-Cycloalkylgruppe, C_{6-10}-Arylgruppe, Halogen-C_{1-4}-alkylgruppe, Halogen-C_{1-4}-alkoxy- gruppe, C_{1-4}-Alkylthiogruppe, C_{1-4}-Alkylsulfonylgruppe, C_{1-4}-Alka- noylgruppe, fünfgliedrigen aromatischen heterocyclischen Gruppe, Carbamoylgruppe, C_{1-4}-Alkylcarbamoylgruppe, C_{1-4}-Alkoxycarbonyl- C_{1-4}-alkylcarbamoylgruppe und 1,3-Diacylguanidino-C_{1-4}-alkyl- gruppe besteht (im Folgenden Substituentengruppe C); (iii) ein fünf- bis achtgliedriger heterocyclischer Ring, der neben Kohlenstoffatomen 1 bis 4 Heteroatome aufweist, die aus einem Stickstoffatom (gegebenenfalls oxidiert), einem Sauerstoffatom und einem Schwefelatom ausgewählt sind, oder ein kondensierter Ring davon ist, wobei die heterocyclische Gruppe 1 bis 3 Substituenten aufweisen kann, die aus C_{1-4}-Alkyl, Hydroxy, Oxo und C_{1-4}-Alkoxy ausgewählt sind; (iv) eine Gruppe der Formel OR^{1a}, wobei R^{1a} ein Wasserstoffatom oder eine aliphatische Kohlenwasserstoffgruppe ist, die aus einer C_{1-20}-Alkylgruppe, C_{3-10}-Cycloalkylgruppe, C_{4-12}-Cycloalkylalkyl- gruppe, C_{3-6}-Alkenylgruppe und C_{3-6}-Alkinylgruppe, die gegebenen- falls einen oder mehrere Substituenten aufweist, die aus Sub- stituentengruppe B ausgewählt sind, ausgewählt ist; oder (v) eine Gruppe der Formel:



(a)

wobei R^{1b} und R^{1c} gleich oder verschieden sind und jeweils ein Wasserstoffatom oder eine aliphatische Kohlenwasserstoffgruppe sind, die aus einer C_{1-20}-Alkylgruppe, C_{3-10}-Cycloalkylgruppe, C_{4-12}- Cycloalkylalkylgruppe, C_{3-6}-Alkenylgruppe und C_{3-6}-Alkinylgruppe, die gegebenenfalls einen oder mehrere Substituenten aufweist, die aus Substituentengruppe B ausgewählt sind, ausgewählt ist;

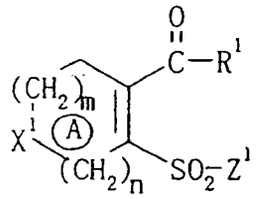
X^1 ein Stickstoffatom, ein Schwefelatom oder ein Sauerstoffatom ist; und

Ring A gegebenenfalls weiterhin mit 1 bis 4 Substituenten substituiert ist, die aus den folgenden (1) bis (4) ausgewählt sind: (1) einer aliphatischen Kohlenwasserstoffgruppe, die aus einer C_{1-20}-Alkylgruppe, C_{3-10}-Cycloalkylgruppe, C_{4-12}-Cycloalkylalkyl- gruppe, C_{3-6}-Alkenylgruppe und C_{3-6}-Alkinylgruppe, die gegebenen- falls einen oder mehrere aus Substituentengruppe B ausgewählte Substituenten aufweisen, ausgewählt ist; (2) einer C_{6-14}-Arylgruppe, die gegebenenfalls einen oder mehrere Substituenten aufweist, die aus Substituentengruppe C ausgewählt sind; (3) einer Gruppe der Formel OR^2, wobei R^2 ein Wasserstoffatom oder eine aliphatische Kohlenwasserstoffgruppe ist, die aus einer C_{1-20}-Alkylgruppe, C_{3-10}-Cycloalkylgruppe, C_{4-12}-Cycloalkylalkylgruppe, C_{3-6}-Alkenylgruppe und C_{3-6}-Alkinylgruppe, die gegebenen- falls einen oder mehrere aus Substituentengruppe B ausgewählte Substituenten aufweisen, ausgewählt ist; und (4) einem Halogenatom;

R^4 ein Wasserstoffatom oder eine C_{1-6}-Alkylgruppe, die mit Hydroxy substituiert sein kann, oder ein C_{1-4}-Alkoxycarbonyl ist; und

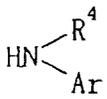
Ar eine C_{6-14}-Arylgruppe ist, die gegebenenfalls einen oder mehrere aus Substituentengruppe C ausgewählte Substituenten aufweist;

oder ein Salz davon, wobei das Verfahren das Umsetzen einer Verbindung der Formel



(II)

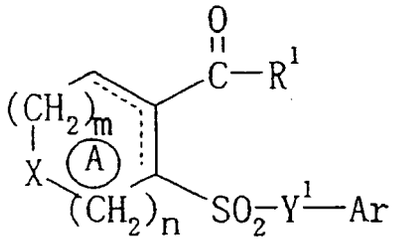
wobei Z^1 eine Abgangsgruppe ist und die anderen Symbole wie oben definiert sind, oder eines Salzes davon mit einer Verbindung der Formel



(III)

wobei jedes Symbol wie oben definiert ist, oder einem Salz davon umfasst.

13. Herstellungsverfahren für eine Verbindung der Formel

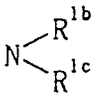


(Ib)

wobei

R^1 Folgendes ist: (i) eine aliphatische Kohlenwasserstoffgruppe, die aus einer C_{1-20}- Alkylgruppe, C_{3-10}-Cycloalkylgruppe, C_{4-12}-Cycloalkylalkylgruppe, C_{3-6}-Alkenylgruppe und C_{3-6}-Alkinylgruppe ausgewählt ist, wobei diese aliphatischen Kohlenwasserstoffgruppen gegebenenfalls 1 bis 4 Substituenten aufweisen, die aus der Gruppe ausgewählt sind, die aus einer heterocyclischen Gruppe, Oxogruppe, Hydroxygruppe, C_{1-6}-Alkoxygruppe, C_{3-10}-Cycloalkyloxygruppe, C_{6-10}-Aryloxygruppe, C_{7-19}-Aralkyloxygruppe, Heterocyclyloxygruppe, C_{1-6}-Alkylthiogruppe (wobei das Schwefelatom gegebenenfalls oxidiert ist), C_{3-10}- Cycloalkylthiogruppe (wobei das Schwefelatom gegebenenfalls oxi- diert ist), C_{6-10}-Arylthio (wobei das Schwefelatom gegebenenfalls oxidiert ist), C_{7-19}-Aralkylthiogruppe (wobei das Schwefelatom ge- gebenenfalls oxidiert ist), Heterocyclylthiogruppe, Heterocyclyl- sulfinylgruppe, Heterocyclylsulfonylgruppe, Nitrogruppe, einem Ha- logenatom, einer Cyanogruppe, Carboxygruppe, C_{1-10}-Alkoxycarbo- nylgruppe, C_{3-6}-Cycloalkyloxycarbonylgruppe, C_{6-10}-Aryloxycarbonylgruppe, C_{7-19}-Aralkyloxycarbonylgruppe, Heterocyclyloxycarbonyl- gruppe, C_{6-10}-Arylcarbonylgruppe, C_{1-6}-Alkanoylgruppe, C_{3-5}- Alkenoylgruppe, C_{6-10}-Arylcarbonyloxygruppe, C_{2-6}-Alkanoyloxy- gruppe, C_{3-5}-Alkenoyloxygruppe, Carbamoylgruppe (gegebenenfalls mit 1 oder 2 Substituenten substituiert, die aus C_{1-4}-Alkyl, Phenyl, C_1-$_7$-Acyl und C_{1-4}-Alkoxyphenyl ausgewählt sind), Thiocarbamoyl- gruppe (gegebenenfalls mit 1 oder 2 Substituenten substituiert, die aus C_{1-4}-Alkyl und Phenyl ausgewählt sind), Carbamoyloxygruppe (gegebenenfalls mit 1 oder 2 Substituenten substituiert, die aus C_{1-4}-Alkyl und Phenyl ausgewählt sind), C_{1-6}-Alkanoylaminogruppe, C_{6-10}-Arylcarbonylaminogruppe, C_{1-10}-Alkoxycarboxamidogruppe, C_{6-10}-Aryloxycarboxamidogruppe, C_{7-19}-Aralkyloxycarboxamido- gruppe, C_{1-10}-Alkoxycarbonyloxygruppe, C_{6-10}-Aryloxycarbonyloxy- gruppe, C_{7-19}-Aralkyloxycarbonyloxygruppe, C_{3-10}-Cycloalkyloxycar- bonyloxygruppe und Ureidogruppe (die gegebenenfalls 1 bis 3 Sub- stituenten aufweist, die aus einer C_{1-4}-Alkylgruppe und einer Phe- nylgruppe ausgewählt sind) (im Folgenden Substituentengruppe A) und einer Gruppe, die aus einer C_{6-10}-Arylgruppe, die gegebenen-

falls 1 bis 4 Substituenten aufweist, die aus Substituentengruppe A ausgewählt sind (im Folgenden Substituentengruppe B), besteht, wobei die heterocyclische Gruppe eine fünf- bis achtgliedrige heterocyclische Gruppe, die neben Kohlenstoffatomen 1 bis 4 Hete- roatome aufweist, die aus einem Stickstoffatom (gegebenenfalls oxidiert), einem Sauerstoffatom und einem Schwefelatom ausge- wählt sind, oder ein kondensierter Ring davon ist und gegebenen- falls 1 bis 3 Substituenten aufweist, die aus C_{1-4}-Alkyl, Hydroxy, Oxo und C_{1-4}-Alkoxy ausgewählt sind, und die Substituenten zusammen mit einer aliphatischen Kohlenwasser- stoffgruppe einen kondensierten Ring bilden können, der gegebe- nenfalls 1 bis 4 Substituenten aufweist, die aus Substituentengruppe B ausgewählt sind; (ii) eine C_{6-14}-Arylgruppe, die gegebenenfalls 1 bis 5 Substituenten aufweist, die aus der Gruppe ausgewählt sind, die aus einem Halo- genatom, einer C_{1-4}-Alkylgruppe, C_{1-4}-Alkoxygruppe, C_{1-4}-Alkoxy- carbonylgruppe, Carboxygruppe, Nitrogruppe, Cyanogruppe, Hydroxygruppe, C_{1-4}-Alkanoylaminogruppe, C_{3-6}-Cycloalkylgruppe, C_{6-10}-Arylgruppe, Halogen-C_{1-4}-alkylgruppe, Halogen-C_{1-4}-alkoxy- gruppe, C_{1-4}-Alkylthiogruppe, C_{1-4}-Alkylsulfonylgruppe, C_{1-4}-Alka- noylgruppe, fünfgliedrigen aromatischen heterocyclischen Gruppe, Carbamoylgruppe, C_{1-4}-Alkylcarbamoylgruppe, C_{1-4}-Alkoxycarbonyl- C_{1-4}-alkylcarbamoylgruppe und 1,3-Diacylguanidino-C_{1-4}-alkyl- gruppe besteht (im Folgenden Substituentengruppe C); (iii) ein fünf- bis achtgliedriger heterocyclischer Ring, der neben Kohlenstoffatomen 1 bis 4 Heteroatome aufweist, die aus einem Stickstoffatom (gegebenenfalls oxidiert), einem Sauerstoffatom und einem Schwefelatom ausgewählt sind, oder ein kondensierter Ring davon ist, wobei die heterocyclische Gruppe 1 bis 3 Substituenten aufweisen kann, die aus C_{1-4}-Alkyl, Hydroxy, Oxo und C_{1-4}-Alkoxy ausgewählt sind; (iv) eine Gruppe der Formel OR^{1a}, wobei R^{1a} ein Wasserstoffatom oder eine aliphatische Kohlenwasserstoffgruppe ist, die aus einer C_{1-20}-Alkylgruppe, C_{3-10}-Cycloalkylgruppe, C_{4-12}-Cycloalkylalkyl- gruppe, C_{3-6}-Alkenylgruppe und C_{3-6}-Alkinylgruppe, die gegebenen- falls einen oder mehrere Substituenten aufweist, die aus Sub- stituentengruppe B ausgewählt sind, ausgewählt ist; oder (v) eine Gruppe der Formel:



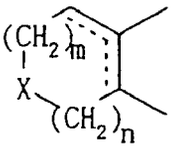
(a)

wobei R^{1b} und R^{1c} gleich oder verschieden sind und jeweils ein Wasserstoffatom oder eine aliphatische Kohlenwasserstoffgruppe sind, die aus einer C_{1-20}-Alkylgruppe, C_{3-10}-Cycloalkylgruppe, C_{4-12}- Cycloalkylalkylgruppe, C_{3-6}-Alkenylgruppe und C_{3-6}-Alkinylgruppe, die gegebenenfalls einen oder mehrere Substituenten aufweist, die aus Substituentengruppe B ausgewählt sind, ausgewählt ist;
X eine Methylengruppe, ein Stickstoffatom, ein Schwefelatom oder ein Sauerstoffatom ist; und
Ring A gegebenenfalls mit 1 bis 4 Substituenten substituiert ist, die aus den folgenden (1) bis (4) ausgewählt sind:

(1) einer aliphatischen Kohlenwasserstoffgruppe, die aus einer C_{1-20}-Alkylgruppe, C_{3-10}-Cycloalkylgruppe, C_{4-12}-Cycloalkylalkylgruppe, C_{3-6}-Alkenylgruppe und C_{3-6}-Alkinylgruppe, die gegebenenfalls einen oder mehrere aus Substituentengruppe B ausgewählte Substituenten aufweisen, ausgewählt ist;
(2) einer C_{6-14}-Arylgruppe, die gegebenenfalls einen oder mehrere Substituenten aufweist, die aus Substituentengruppe C ausgewählt sind;
(3) einer Gruppe der Formel OR^2, wobei R^2 ein Wasserstoffatom oder eine aliphatische Kohlenwasserstoffgruppe ist, die aus einer C_{1-20}-Alkylgruppe, C_{3-10}-Cycloalkylgruppe, C_{4-12}-Cycloalkylalkylgruppe, C_{3-6}-Alkenylgruppe und C_{3-6}-Alkinylgruppe, die gegebenenfalls einen oder mehrere aus Substituentengruppe B ausgewählte Substituenten aufweisen, ausgewählt ist; und
(4) einem Halogenatom;

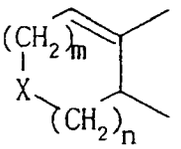
Y^1 eine Methylengruppe, die gegebenenfalls einen oder mehrere Substituenten aufweist, die aus einer C_{1-6}-Alkylgruppe, hydroxy- substituierten C_{1-6}-Alkylgruppe und C_{1-4}-Alkoxycarbonyl-C_{1-4}-alkyl- gruppe ausgewählt sind, ist;
Ar eine C_{6-14}-Arylgruppe ist, die gegebenenfalls einen oder mehrere aus Substituentengruppe C ausgewählte Substituenten aufweist; und

die Gruppe der Formel



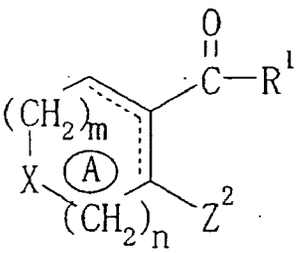
(b)

eine Gruppe der Formel



(b1)

ist, wobei
m = 1 ist; und
n = $_1$ ist;
oder ein Salz davon, wobei das Verfahren das Umsetzen einer Verbindung der Formel



(IV)

wobei Z^2 eine Abgangsgruppe ist und die anderen Symbole wie oben definiert sind, oder eines Salzes davon mit einer Verbindung der Formel

$$HS\text{-}Y^1\text{-}Ar \qquad (VI)$$

wobei jedes Symbol wie oben definiert ist, oder einem Salz davon und das Oxidieren des erhaltenen Sulfids umfasst.

14. Pharmazeutische Zusammensetzung, die eine Verbindung gemäß einem der Ansprüche 1 bis 11 umfasst.

15. Verbindung gemäß einem der Ansprüche 1 bis 11 oder Zusammensetzung gemäß Anspruch 14 zur Verwendung zum Unterdrücken der Produktion von Stickstoffoxid (NO) und/oder Cytokin.

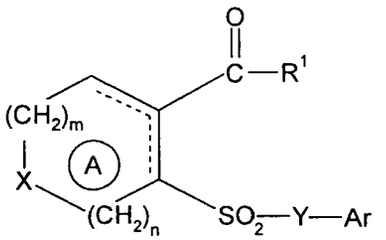
16. Verbindung gemäß einem der Ansprüche 1 bis 11 oder Zusammensetzung gemäß Anspruch 14 zur Verwendung für die Prophylaxe oder Behandlung einer Herzkrankheit, einer Autoimmunkrankheit oder eines septischen Schocks.

17. Verwendung der Verbindung gemäß einem der Ansprüche 1 bis 11 zur Herstellung eines Mittels zum Unterdrücken der Produktion von Stickstoffoxid (NO) und/oder Cytokin.

18. Verwendung der Verbindung gemäß einem der Ansprüche 1 bis 11 zur Herstellung eines Mittels zur Prophylaxe oder Behandlung einer Herzkrankheit, einer Autoimmunkrankheit oder eines septischen Schocks.

Revendications

1. Composé de formule :



(I)

dans laquelle

- R^1 représente :

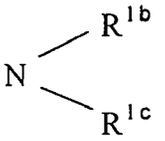
i) un groupe hydrocarboné aliphatique, choisi parmi les groupes alkyle en C_{1-20}, cycloalkyle en C_{3-10}, cycloalkyl-alkyle en C_{4-12}, alcényle en C_{3-6} et alcynyle en C_{3-6}, lesquels groupes hydrocarbonés aliphatiques peuvent, en option, porter 1 à 4 substituant(s) choisi(s) dans un ensemble formé par les groupes hétérocycliques, le substituant oxo, le groupe hydroxyle, les groupes alcoxy en C_{1-6}, cycloalcoxy en C_{3-10}, aryloxy en C_{6-10}, aryl-alkyl-oxy en C_{7-19} et hétérocyclyl-oxy, les groupes alkyl-thio en C_{1-6} dont l'atome de soufre peut en option être oxydé, cycloalkyl-thio en C_{3-10} dont l'atome de soufre peut en option être oxydé, aryl-thio en C_{6-10} dont l'atome de soufre peut en option être oxydé, aryl-alkyl-thio en C_{7-19} dont l'atome de soufre peut en option être oxydé, hétérocyclyl-thio, hétérocycyl-sulfinyle et hétérocyclyl-sulfonyle, le groupe nitro, les atomes d'halogène, le groupe cyano, le groupe carboxyle, les groupes (alcoxy en C_{1-10})-carbonyle, (cycloalcoxy en C_{3-6})-carbonyle, (aryl-oxy en C_{6-10})-carbonyle, (aryl-alkyl-oxy en C_{7-19})-carbonyle et hétérocyclyl-oxy-carbonyle, les groupes (aryle en C_{6-10})-carbonyle, alcanoyle en C_{1-6} et alcénoyle en C_{3-5}, les groupes (aryle en C_{6-10})-carbonyl-oxy, alcanoyl-oxy en C_{2-6} et alcénoyl-oxy en C_{3-5}, le groupe carbamyle qui peut en option porter 1 ou 2 substituant(s) choisi(s) parmi les groupes alkyle en C_{1-4}, phényle, acyle en C_{1-7} et (alcoxy en C_{1-4})-phényle, le groupe thiocarbamyle qui peut en option porter 1 ou 2 substituant (s) choisi(s) parmi les groupes alkyle en C_{1-4} et phényle, le groupe carbamyl-oxy qui peut en option porter 1 ou 2 substituants choisi(s) parmi les groupes alkyle en C_{1-4} et phényle, les groupes (alcanoyle en C_{1-6})-amino, (aryle en C_{6-10})-carbonyl-amino, (alcoxy en C_{1-10})-carboxamido, (aryl-oxy en C_{6-10})-carboxamido et (aryl-alkyl-oxy en C_{7-19})-carboxamido, les groupes (alcoxy en C_{1-10})-carbonyl-oxy, (aryl-oxy en C_{6-10})-carbonyl-oxy, (aryl-alkyl-oxy en C_{7-19})-carbonyl-oxy et (cycloalcoxy en C_{3-10})-carbonyl-oxy, et le groupe uréido qui peut en option porter 1 à 3 substituant(s) choisi(s) parmi les groupes alkyle en C_{1-4} et phényle (ce qu'on appelle dans ce qui suit "ensemble A de substituants"), et dans un ensemble formé par les groupes aryle en C_{6-10}, qui peuvent en option porter 1 à 4 substituant(s) choisi(s) dans l'ensemble A de substituants (ce qu'on appelle dans ce qui suit "ensemble B de substituants"), étant entendu
que chacun des groupes hétérocycliques cités ci-dessus est un groupe hétérocyclique comportant de 5 à 8 chaînons, qui comporte, en plus de son ou ses atome(s) de carbone, 1 à 4 hétéroatome(s) choisi(s) parmi les atomes d'azote, éventuellement oxydé, d'oxygène et de soufre,
ou un tel groupe avec lequel un autre cycle est condensé, qui peut en option porter 1 à 3 substituant(s) choisi(s) parmi le substituant oxo et les groupes alkyle en C_{1-4}, hydroxyle et alcoxy en C_{1-4},
et que lesdits substituants peuvent constituer, conjointement avec un groupe hydrocarboné aliphatique, un cycle condensé qui peut en option porter 1 à 4 substituant(s) choisi(s) dans l'ensemble B de substituants,

ii) un groupe aryle en C_{6-14}, qui peut en option porter 1 à 5 substituant(s) choisi(s) dans l'ensemble formé par les atomes d'halogène, les groupes alkyle en C_{1-4}, alcoxy en C_{1-4}, (alcoxy en C_{1-4})-carbonyle, carboxyle, nitro, cyano, hydroxyle, (alcanoyle en C_{1-4})-amino, aryle en C_{6-10}, cycloalkyle en C_{3-6}, halogéno-alkyle en C_{1-4}, halogéno-alcoxy en C_{1-4}, alkylthio en C_{1-4}, alkyl-sulfonyle en C_{1-4} et alcanoyle en C_{1-4}, les groupes hétérocycliques aromatiques à 5 chaînons, et les groupes carbamyle, (alkyle en C_{1-4})-carbamyle, (alcoxy en C_{1-4})-carbonyl-(alkyle en C_{1-4})-carbamyle et 1,3-diacyl-guanidino-(alkyle en C_{1-4}) (ce qu'on appelle dans ce qui suit "ensemble C de substituants"),

iii) un groupe hétérocyclique comportant de 5 à 8 chaînons, qui comporte, en plus de son ou ses atome(s) de carbone, 1 à 4 hétéroatome(s) choisi(s) parmi les atomes d'azote, éventuellement oxydé, d'oxygène et de soufre, ou un tel groupe avec lequel un autre cycle est condensé, lequel groupe hétérocyclique peut en option porter 1 à 3 substituant(s) choisi(s) parmi le substituant oxo et les groupes alkyle en C_{1-4}, hydroxyle et alcoxy en C_{1-4},

iv) un groupe de formule $-OR^{1a}$ dans laquelle R^{1a} représente un atome d'hydrogène ou un groupe hydrocarboné aliphatique, choisi parmi les groupes alkyle en C_{1-20}, cycloalkyle en C_{3-10}, cycloalkyl-alkyle en

C_{4-12}, alcényle en C_{3-6} et alcynyle en C_{3-6}, qui peut en option porter un ou des substituant(s) choisi(s) dans l'ensemble B de substituants,
v) ou un groupe de formule



(a)

dans laquelle R^{1b} et R^{1c} représentent des entités identiques ou différentes et représentent chacun un atome d'hydrogène ou un groupe hydrocarboné aliphatique, choisi parmi les groupes alkyle en C_{1-20}, cycloalkyle en C_{3-10}, cycloalkyl-alkyle en C_{4-12}, alcényle en C_{3-6} et alcynyle en C_{3-6}, qui peut en option porter un ou des substituant(s) choisi(s) dans l'ensemble B de substituants ;

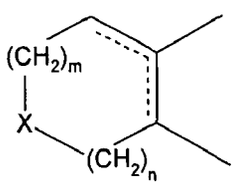
- X représente un groupe méthanediyle, ou un atome d'azote, de soufre ou d'oxygène ;
- Y représente :

i) un groupe méthanediyle, qui peut en option porter un ou des substituant(s) choisi(s) parmi les groupes alkyle en C_{1-6}, hydroxy-alkyle en C_{1-6} et (alcoxy en C_{1-4})-carbonyl-(alkyle en C_{1-4}),
ii) ou un atome d'azote, qui peut en option porter un ou des substituant(s) choisi(s) parmi les groupes alkyle en C_{1-6}, hydroxy-alkyle en C_{1-6} et (alcoxy en C_{1-4})-carbonyl-(alkyle en C_{1-4}) ;

- le cycle A peut en option porter 1 à 4 substituant(s) choisi(s) parmi les substituants (1) à (4) suivants :

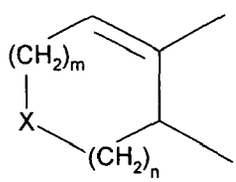
1) un groupe hydrocarboné aliphatique, choisi parmi les groupes alkyle en C_{1-20}, cycloalkyle en C_{3-10}, cycloalkyl-alkyle en C_{4-12}, alcényle en C_{3-6} et alcynyle en C_{3-6}, qui peut en option porter un ou des substituant (s) choisi(s) dans l'ensemble B de substituants,
2) un groupe aryle en C_{6-14}, qui peut en option porter un ou des substituant(s) choisi(s) dans l'ensemble C de substituants,
3) un groupe de formule $-OR^2$ dans laquelle R^2 représente un atome d'hydrogène ou un groupe hydrocarboné aliphatique, choisi parmi les groupes alkyle en C_{1-20}, cycloalkyle en C_{3-10}, cycloalkyl-alkyle en C_{4-12}, alcényle en C_{3-6} et alcynyle en C_{3-6}, qui peut en option porter un ou des substituant(s) choisi(s) dans l'ensemble B de substituants,
4) et un atome d'halogène ;

- Ar représente un groupe aryle en C_{6-14}, qui peut en option porter un ou des substituant(s) choisi(s) dans l'ensemble C de substituants ;
- et le groupe de formule



(b)

est un groupe de formule



(b1)

où l'indice m vaut 1 et l'indice n vaut 1 ;

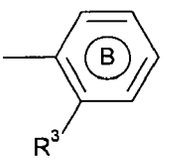
sous réserve que, si X représente un groupe méthanediyle, Y représente un groupe méthanediyle qui peut en option porter un ou des substituant(s) choisi(s) parmi les groupes alkyle en C_{1-6}, hydroxy-alkyle en C_{1-6} et (alcoxy en C_{1-4})-carbonyl-(alkyle en C_{1-4}) ;
ou sel d'un tel composé.

2. Composé conforme à la revendication 1, dans lequel le cycle A peut en option porter en tant que substituant un groupe alkyle en C_{1-6}, un groupe phényle ou un atome d'halogène, R^1 représente un groupe de formule $-OR^{1a}$ dans laquelle R^{1a} représente un groupe alkyle en C_{1-6}, et Ar représente un groupe phényle, qui peut en option porter un ou des substituant(s) choisi(s) dans l'ensemble C de substituants.

3. Composé conforme à la revendication 2, dans lequel R^{1a} représente un groupe éthyle.

4. Composé conforme à la revendication 2, dans lequel Ar représente un groupe halogénophényle, un groupe (alkyle en C_{1-4})-phényle, ou un groupe phényle qui porte, en tant que substituants, un atome d'halogène et un groupe alkyle en C_{1-4}.

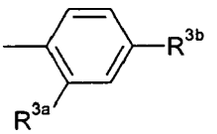
5. Composé conforme à la revendication 2, dans lequel Ar représente un groupe de formule



(c)

dans laquelle R^3 représente un atome d'halogène ou un groupe alkyle en C_{1-4} et le cycle B peut en option porter encore un autre atome d'halogène en tant que substituant.

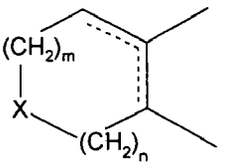
6. Composé conforme à la revendication 5, dans lequel Ar représente un groupe de formule



(c1)

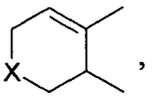
dans laquelle R^{3a} et R^{3b} représentent chacun un atome d'halogène, lesquels atomes peuvent être identiques ou différents.

7. Composé conforme à la revendication 1, dans lequel R^1 représente un groupe de formule $-OR^{1a'}$ dans laquelle $R^{1a'}$ représente un groupe alkyle en C_{1-6}, le groupe de formule



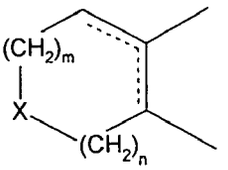
(b)

est un groupe de formule



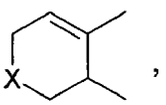
X représente un groupe méthanediyle ou un atome d'oxygène, Y représente un groupe méthanediyle ou un groupe symbolisé par -NH-, et Ar représente un groupe phényle, qui peut en option porter 1 ou 2 substituant(s) choisi(s) dans l'ensemble formé par les atomes d'halogène et les groupes alcoxy en C_{1-6}.

8. Composé conforme à la revendication 1, dans lequel R^1 représente un groupe de formule $-OR^{1a'}$ dans laquelle $R^{1a'}$ représente un groupe alkyle en C_{1-6}, le groupe de formule



(b)

est un groupe de formule



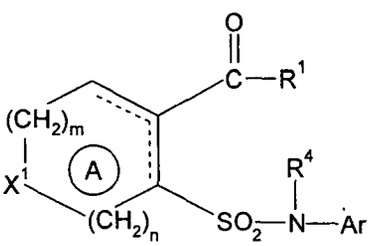
X représente un groupe méthanediyle et Y représente un groupe méthanediyle, ou bien X représente un atome d'oxygène et Y représente un groupe symbolisé par -NH-, et Ar représente un groupe phényle, qui peut en option porter deux atomes d'halogène en tant que substituants.

9. 6-[(2-chloro-4-fluoro-benzyl)sulfonyl]-cyclohex-1-ène-1-carboxylate d'éthyle.

10. (+)-6-[(2-chloro-4-fluoro-benzyl)sulfonyl]-cyclohex-1-ène-1-carboxylate d'éthyle.

11. 3-[(2-chloro-4-fluoro-phényl)sulfamyl]-3,6-dihydro-2H-pyrane-4-carboxylate d'éthyle, ou l'un de ses sels.

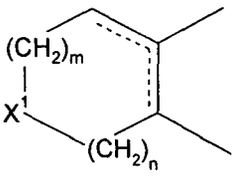
12. Procédé de préparation d'un composé de formule :



(Ia)

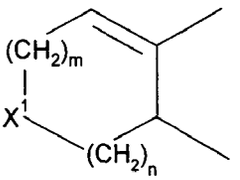
dans laquelle

- le groupe de formule



(b')

est un groupe de formule

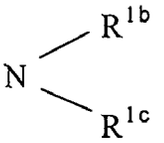


(b1')

où l'indice m vaut 1 et l'indice n vaut 1 ;
- R^1 représente :

i) un groupe hydrocarboné aliphatique, choisi parmi les groupes alkyle en C_{1-20}, cycloalkyle en C_{3-10}, cycloalkyl-alkyle en C_{4-12}, alcényle en C_{3-6} et alcynyle en C_{3-6}, lesquels groupes hydrocarbonés aliphatiques peuvent, en option, porter 1 à 4 substituant(s) choisi(s) dans un ensemble formé par les groupes hétérocycliques, le substituant oxo, le groupe hydroxyle, les groupes alcoxy en C_{1-6}, cycloalcoxy en C_{3-10}, aryl-oxy en C_{6-10}, aryl-alkyl-oxy en C_{7-19} et hétérocyclyl-oxy, les groupes alkyl-thio en C_{1-6} dont l'atome de soufre peut en option être oxydé, cycloalkyl-thio en C_{3-10} dont l'atome de soufre peut en option être oxydé, aryl-thio en C_{6-10} dont l'atome de soufre peut en option être oxydé, aryl-alkyl-thio en C_{7-19} dont l'atome de soufre peut en option être oxydé, hétérocyclyl-thio, hétérocycyl-sulfinyle et hétérocyclyl-sulfonyle, le groupe nitro, les atomes d'halogène, le groupe cyano, le groupe carboxyle, les groupes (alcoxy en C_{1-10})-carbonyle, (cycloalcoxy en C_{3-6})-carbonyle, (aryl-oxy en C_{6-10})-carbonyle, (aryl-alkyl-oxy en C_{7-19})-carbonyle et hétérocyclyl-oxy-carbonyle, les groupes (aryle en C_{6-10})-carbonyle, alcanoyle en C_{1-6} et alcénoyle en C_{3-5}, les groupes (aryle en C_{6-10})-carbonyl-oxy, alcanoyl-oxy en C_{2-6} et alcénoyl-oxy en C_{3-5}, le groupe carbamyle qui peut en option porter 1 ou 2 substituant(s) choisi(s) parmi les groupes alkyle en C_{1-4}, phényle, acyle en C_{1-7} et (alcoxy en C_{1-4})-phényle, le groupe thiocarbamyle qui peut en option porter 1 ou 2 substituant (s) choisi(s) parmi les groupes alkyle en C_{1-4} et phényle, le groupe carbamyl-oxy qui peut en option porter 1 ou 2 substituants choisi(s) parmi les groupes alkyle en C_{1-4} et phényle, les groupes (alcanoyle en C_{1-6})-amino, (aryle en C_{6-10})-carbonyl-amino, (alcoxy en C_{1-10})-carboxamido, (aryl-oxy en C_{6-10})-carboxamido et (aryl-alkyl-oxy en C_{7-19})-carboxamido, les groupes (alcoxy en C_{1-10})-carbonyl-oxy, (aryl-oxy en C_{6-10})-carbonyl-oxy, (aryl-alkyl-oxy en C_{7-19})-carbonyl-oxy et (cycloalcoxy en C_{3-10})-carbonyl-oxy, et le groupe uréido qui peut en option porter 1 à 3 substituant(s) choisi(s) parmi les groupes alkyle en C_{1-4} et phényle (ce qu'on appelle dans ce qui suit "ensemble A de substituants"), et dans un ensemble formé par les groupes aryle en C_{6-10}, qui peuvent en option porter 1 à 4 substituant(s) choisi(s) dans l'ensemble A de substituants (ce qu'on appelle dans ce qui suit "ensemble B de substituants"), étant entendu
que chacun des groupes hétérocycliques cités ci-dessus est un groupe hétérocyclique comportant de 5 à 8 chaînons, qui comporte, en plus de son ou ses atome(s) de carbone, 1 à 4 hétéroatome(s) choisi(s) parmi les atomes d'azote, éventuellement oxydé, d'oxygène et de soufre,
ou un tel groupe avec lequel un autre cycle est condensé, qui peut en option porter 1 à 3 substituant(s) choisi(s) parmi le substituant oxo et les groupes alkyle en C_{1-4}, hydroxyle et alcoxy en C_{1-4},
et que lesdits substituants peuvent constituer, conjointement avec un groupe hydrocarboné aliphatique, un cycle condensé qui peut en option porter 1 à 4 substituant(s) choisi(s) dans l'ensemble B de substituants,
ii) un groupe aryle en C_{6-14}, qui peut en option porter 1 à 5 substituant(s) choisi(s) dans l'ensemble formé par les atomes d'halogène, les groupes alkyle en C_{1-4}, alcoxy en C_{1-4}, (alcoxy en C_{1-4})-carbonyle, carboxyle, nitro, cyano, hydroxyle, (alcanoyle en C_{1-4})-amino, aryle en C_{6-10}, cycloalkyle en C_{3-6}, halogéno-alkyle en C_{1-4}, halogéno-alcoxy en C_{1-4}, alkylthio en C_{1-4}, alkyl-sulfonyle en C_{1-4} et alcanoyle en C_{1-4}, les groupes hétérocycliques aromatiques à 5 chaînons, et les groupes carbamyle, (alkyle en C_{1-4})-carbamyle, (alcoxy en C_{1-4})-carbonyl-(alkyle en C_{1-4})-carbamyle et 1,3-diacyl-guanidino-(alkyle en C_{1-4}) (ce qu'on appelle dans

ce qui suit "ensemble C de substituants"),
iii) un groupe hétérocyclique comportant de 5 à 8 chaînons, qui comporte, en plus de son ou ses atome(s) de carbone, 1 à 4 hétéroatome(s) choisi(s) parmi les atomes d'azote, éventuellement oxydé, d'oxygène et de soufre, ou un tel groupe avec lequel un autre cycle est condensé, lequel groupe hétérocyclique peut en option porter 1 à 3 substituant(s) choisi(s) parmi le substituant oxo et les groupes alkyle en C_{1-4}, hydroxyle et alcoxy en C_{1-4},
iv) un groupe de formule $-OR^{1a}$ dans laquelle R^{1a} représente un atome d'hydrogène ou un groupe hydrocarboné aliphatique, choisi parmi les groupes alkyle en C_{1-20}, cycloalkyle en C_{3-10}, cycloalkyl-alkyle en C_{4-12}, alcényle en C_{3-6} et alcynyle en C_{3-6}, qui peut en option porter un ou des substituant(s) choisi(s) dans l'ensemble B de substituants,
v) ou un groupe de formule



(a)

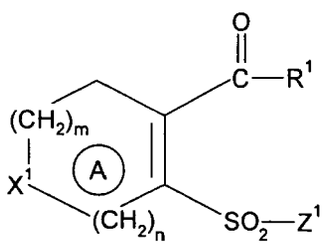
dans laquelle R^{1b} et R^{1c} représentent des entités identiques ou différentes et représentent chacun un atome d'hydrogène ou un groupe hydrocarboné aliphatique, choisi parmi les groupes alkyle en C_{1-20}, cycloalkyle en C_{3-10}, cycloalkyl-alkyle en C_{4-12}, alcényle en C_{3-6} et alcynyle en C_{3-6}, qui peut en option porter un ou des substituant(s) choisi(s) dans l'ensemble B de substituants ;

- X^1 représente un atome d'azote, de soufre ou d'oxygène ;
- le cycle A peut en option porter encore 1 à 4 substituant(s) choisi(s) parmi les substituants (1) à (4) suivants :

1) un groupe hydrocarboné aliphatique, choisi parmi les groupes alkyle en C_{1-20}, cycloalkyle en C_{3-10}, cycloalkyl-alkyle en C_{4-12}, alcényle en C_{3-6} et alcynyle en C_{3-6}, qui peut en option porter un ou des substituant(s) choisi(s) dans l'ensemble B de substituants,
2) un groupe aryle en C_{6-14}, qui peut en option porter un ou des substituant(s) choisi(s) dans l'ensemble C de substituants,
3) un groupe de formule $-OR^2$ dans laquelle R^2 représente un atome d'hydrogène ou un groupe hydrocarboné aliphatique, choisi parmi les groupes alkyle en C_{1-20}, cycloalkyle en C_{3-10}, cycloalkyl-alkyle en C_{4-12}, alcényle en C_{3-6} et alcynyle en C_{3-6}, qui peut en option porter un ou des substituant(s) choisi(s) dans l'ensemble B de substituants,
4) et un atome d'halogène ;

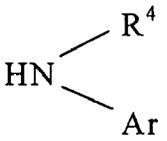
- R^4 représente un atome d'hydrogène ou un groupe alkyle en C_{1-6} qui peut porter en tant que substituant un groupe hydroxyle ou (alcoxy en C_{1-4})-carbonyle ;
- et Ar représente un groupe aryle en C_{6-14}, qui peut en option porter un ou des substituant(s) choisi(s) dans l'ensemble C de substituants ;

ou d'un sel d'un tel composé, lequel procédé comporte le fait de faire réagir un composé de formule :



(II)

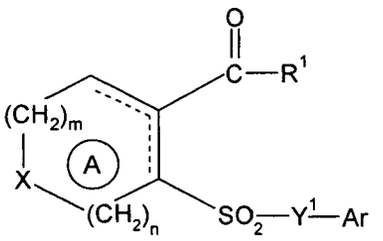
dans laquelle Z^1 représente un groupe partant et les autres symboles ont les significations indiquées ci-dessus, ou un sel d'un tel composé, avec un composé de formule



(III)

dans laquelle chacun des symboles a la signification indiquée ci-dessus, ou avec un sel d'un tel composé.

13. Procédé de préparation d'un composé de formule :



(Ib)

dans laquelle

- R^1 représente :

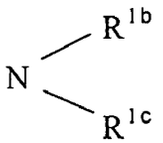
i) un groupe hydrocarboné aliphatique, choisi parmi les groupes alkyle en C_{1-20}, cycloalkyle en C_{3-10}, cycloalkyl-alkyle en C_{4-12}, alcényle en C_{3-6} et alcynyle en C_{3-6}, lesquels groupes hydrocarbonés aliphatiques peuvent, en option, porter 1 à 4 substituant(s) choisi(s) dans un ensemble formé par les groupes hétérocycliques, le substituant oxo, le groupe hydroxyle, les groupes alcoxy en C_{1-6}, cycloalcoxy en C_{3-10}, aryloxy en C_{6-10}, aryl-alkyl-oxy en C_{7-19} et hétérocyclyl-oxy, les groupes alkyl-thio en C_{1-6} dont l'atome de soufre peut en option être oxydé, cycloalkyl-thio en C_{3-10} dont l'atome de soufre peut en option être oxydé, aryl-thio en C_{6-10} dont l'atome de soufre peut en option être oxydé, aryl-alkyl-thio en C_{7-19} dont l'atome de soufre peut en option être oxydé, hétérocyclyl-thio, hétérocycyl-sulfinyle et hétérocyclyl-sulfonyle, le groupe nitro, les atomes d'halogène, le groupe cyano, le groupe carboxyle, les groupes (alcoxy en C_{1-10})-carbonyle, (cycloalcoxy en C_{3-6})-carbonyle, (aryl-oxy en C_{6-10})-carbonyle, (aryl-alkyl-oxy en C_{7-19})-carbonyle et hétérocyclyl-oxy-carbonyle, les groupes (aryle en C_{6-10})-carbonyle, alcanoyle en C_{1-6} et alcénoyle en C_{3-5}, les groupes (aryle en C_{6-10})-carbonyl-oxy, alcanoyl-oxy en C_{2-6} et alcénoyl-oxy en C_{3-5}, le groupe carbamyle qui peut en option porter 1 ou 2 substituant(s) choisi(s) parmi les groupes alkyle en C_{1-4}, phényle, acyle en C_{1-7} et (alcoxy en C_{1-4})-phényle, le groupe thiocarbamyle qui peut en option porter 1 ou 2 substituant (s) choisi(s) parmi les groupes alkyle en C_{1-4} et phényle, le groupe carbamyl-oxy qui peut en option porter 1 ou 2 substituants choisi(s) parmi les groupes alkyle en C_{1-4} et phényle, les groupes (alcanoyle en C_{1-6})-amino, (aryle en C_{6-10})-carbonyl-amino, (alcoxy en C_{1-10})-carboxamido, (aryl-oxy en C_{6-10})-carboxamido et (aryl-alkyl-oxy en C_{7-19})-carboxamido, les groupes (alcoxy en C_{1-10})-carbonyl-oxy, (aryl-oxy en C_{6-10})-carbonyl-oxy, (aryl-alkyl-oxy en C_{7-19})-carbonyl-oxy et (cycloalcoxy en C_{3-10})-carbonyl-oxy, et le groupe uréido qui peut en option porter 1 à 3 substituant(s) choisi(s) parmi les groupes alkyle en C_{1-4} et phényle (ce qu'on appelle dans ce qui suit "ensemble A de substituants"), et dans un ensemble formé par les groupes aryle en C_{6-10}, qui peuvent en option porter 1 à 4 substituant(s) choisi(s) dans l'ensemble A de substituants (ce qu'on appelle dans ce qui suit "ensemble B de substituants"), étant entendu
que chacun des groupes hétérocycliques cités ci-dessus est un groupe hétérocyclique comportant de 5 à 8 chaînons, qui comporte, en plus de son ou ses atome(s) de carbone, 1 à 4 hétéroatome(s) choisi(s) parmi les atomes d'azote, éventuellement oxydé, d'oxygène et de soufre,
ou un tel groupe avec lequel un autre cycle est condensé, qui peut en option porter 1 à 3 substituant(s) choisi(s) parmi le substituant oxo et les groupes alkyle en C_{1-4}, hydroxyle et alcoxy en C_{1-4},
et que lesdits substituants peuvent constituer, conjointement avec un groupe hydrocarboné aliphatique, un cycle condensé qui peut en option porter 1 à 4 substituant(s) choisi(s) dans l'ensemble B de substituants,
ii) un groupe aryle en C_{6-14}, qui peut en option porter 1 à 5 substituant(s) choisi(s) dans l'ensemble formé par les atomes d'halogène, les groupes alkyle en C_{1-4}, alcoxy en C_{1-4}, (alcoxy en C_{1-4})-carbonyle, carboxyle,

nitro, cyano, hydroxyle, (alcanoyle en C_{1-4})-amino, aryle en C_{6-10}, cycloalkyle en C_{3-6}, halogéno-alkyle en C_{1-4}, halogéno-alcoxy en C_{1-4}, alkylthio en C_{1-4}, alkyl-sulfonyle en C_{1-4} et alcanoyle en C_{1-4}, les groupes hétérocycliques aromatiques à 5 chaînons, et les groupes carbamyle, (alkyle en C_{1-4})-carbamyle, (alcoxy en C_{1-4})-carbonyl-(alkyle en C_{1-4})-carbamyle et 1,3-diacyl-guanidino-(alkyle en C_{1-4}) (ce qu'on appelle dans ce qui suit "ensemble C de substituants"),

iii) un groupe hétérocyclique comportant de 5 à 8 chaînons, qui comporte, en plus de son ou ses atome(s) de carbone, 1 à 4 hétéroatome(s) choisi(s) parmi les atomes d'azote, éventuellement oxydé, d'oxygène et de soufre, ou un tel groupe avec lequel un autre cycle est condensé, lequel groupe hétérocyclique peut en option porter 1 à 3 substituant(s) choisi(s) parmi le substituant oxo et les groupes alkyle en C_{1-4}, hydroxyle et alcoxy en C_{1-4},

iv) un groupe de formule $-OR^{1a}$ dans laquelle R^{1a} représente un atome d'hydrogène ou un groupe hydrocarboné aliphatique, choisi parmi les groupes alkyle en C_{1-20}, cycloalkyle en C_{3-10}, cycloalkyl-alkyle en C_{4-12}, alcényle en C_{3-6} et alcynyle en Z3.6, qui peut en option porter un ou des substituant(s) choisi(s) dans l'ensemble B de substituants,

v) ou un groupe de formule



(a)

dans laquelle R^{1b} et R^{1c} représentent des entités identiques ou différentes et représentent chacun un atome d'hydrogène ou un groupe hydrocarboné aliphatique, choisi parmi les groupes alkyle en C_{1-20}, cycloalkyle en C_{3-10}, cycloalkyl-alkyle en C_{4-12}, alcényle en C_{3-6} et alcynyle en C_{3-6}, qui peut en option porter un ou des substituant(s) choisi(s) dans l'ensemble B de substituants ;

- X représente un groupe méthanediyle, ou un atome d'azote, de soufre ou d'oxygène ;
- le cycle A peut en option porter 1 à 4 substituant(s) choisi(s) parmi les substituants (1) à (4) suivants :

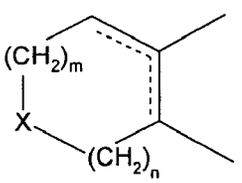
1) un groupe hydrocarboné aliphatique, choisi parmi les groupes alkyle en C_{1-20}, cycloalkyle en C_{3-10}, cycloalkyl-alkyle en C_{4-12}, alcényle en C_{3-6} et alcynyle en C_{3-6}, qui peut en option porter un ou des substituant (s) choisi(s) dans l'ensemble B de substituants,

2) un groupe aryle en C_{6-14}, qui peut en option porter un ou des substituant(s) choisi(s) dans l'ensemble C de substituants,

3) un groupe de formule $-OR^2$ dans laquelle R^2 représente un atome d'hydrogène ou un groupe hydrocarboné aliphatique, choisi parmi les groupes alkyle en C_{1-20}, cycloalkyle en C_{3-10}, cycloalkyl-alkyle en C_{4-12}, alcényle en C_{3-6} et alcynyle en C_{3-6}, qui peut en option porter un ou des substituant(s) choisi(s) dans l'ensemble B de substituants,

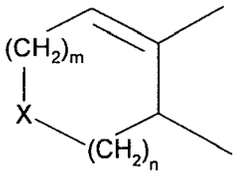
4) et un atome d'halogène ;

- Y^1 représente un groupe méthanediyle, qui peut en option porter un ou des substituant(s) choisi(s) parmi les groupes alkyle en C_{1-6}, hydroxy-alkyle en C_{1-6} et (alcoxy en C_{1-4})-carbonyl-(alkyle en C_{1-4}),
- Ar représente un groupe aryle en C_{6-14}, qui peut en option porter un ou des substituant(s) choisi(s) dans l'ensemble C de substituants ;
- et le groupe de formule



(b)

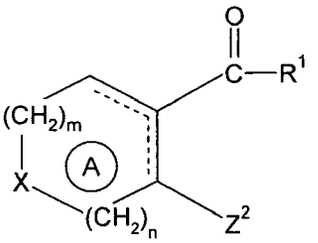
est un groupe de formule



(b1)

où l'indice m vaut 1 et l'indice n vaut 1 ;

ou d'un sel d'un tel composé, lequel procédé comporte le fait de faire réagir un composé de formule :



(IV)

dans laquelle Z^2 représente un groupe partant et les autres symboles ont les significations indiquées ci-dessus, ou un sel d'un tel composé, avec un composé de formule

$$HS—Y^1—Ar \qquad (VI)$$

dans laquelle chacun des symboles a la signification indiquée ci-dessus, ou avec un sel d'un tel composé, et le fait d'oxyder le sulfure ainsi obtenu.

14. Composition pharmaceutique comprenant un composé conforme à l'une des revendications 1 à 11.

15. Composé conforme à l'une des revendications 1 à 11, ou composition conforme à la revendication 14, utilisé(e) pour supprimer la production d'oxyde nitrique NO et/ou la production de cytokines.

16. Composé conforme à l'une des revendications 1 à 11, ou composition conforme à la revendication 14, utilisé(e) pour la prophylaxie ou le traitement d'une maladie cardiaque, d'une affection auto-immune ou d'un choc septique.

17. Utilisation d'un composé conforme à l'une des revendications 1 à 11, en vue de la préparation d'un agent conçu pour supprimer la production d'oxyde nitrique NO et/ou la production de cytokines.

18. Utilisation d'un composé conforme à l'une des revendications 1 à 11, en vue de la préparation d'un agent conçu pour la prophylaxie ou le traitement d'une maladie cardiaque, d'une affection auto-immune ou d'un choc septique.

REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

- JP 10056492 A **[0110]**

Non-patent literature cited in the description

- *Pharmacol. Rev.,* 1991, vol. 43, 109-142 **[0002] [0004]**
- *Curr. Opin. Immunol.,* 1991, vol. 3, 65-70 **[0002]**
- *Neuron,* 1992, vol. 8, 3-11 **[0002]**
- *Cell,* 1992, vol. 70, 705-707 **[0002]**
- *Immunol. Today,* 1992, vol. 13, 157-160 **[0003]**
- *FASEB J.,* 1992, vol. 6, 3051-3064 **[0003]**
- *Arch Surg.,* 1993, vol. 128, 396-401 **[0003]**
- *J. Biol. Chem.,* 1994, vol. 44, 27580-27588 **[0003]**
- *J. Cell. Biochem.,* 1995, vol. 57, 399-408 **[0003]**
- *Br. J. Pharmacol.,* 1993, vol. 110, 963-968 **[0004]**
- *J. Biol. Chem.,* 1994, vol. 43, 26669-26676 **[0004]**
- The Cytokine Handbook. Academic Press Limited, 1994 **[0005]**
- *Advances Immunol.,* 1996, vol. 62, 257-304 **[0005]**
- *Eur. J. Immunol.,* 1991, vol. 18, 951-956 **[0006]**
- *Immunol.,* 1994, vol. 83, 262-267 **[0006]**
- *Proc. Natl. Acad. Sci.,* 1997, vol. 93, 3967-3971 **[0006]**
- *J. Immunol.,* 1991, vol. 147, 1530-1536 **[0006]**
- *Immunol. Today,* 1991, vol. 12, 404-410 **[0006]**
- Development of Pharmaceutical Products, vol. 7, Molecule Design. Hirokawa Shoten, 1990, vol. 7, 163-198 **[0079]**
- *Tetrahedron,* 1963, vol. 19, 1625 **[0114]**
- *Tetrahedron,* 1974, vol. 30, 3753 **[0115]**