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Amide derivative

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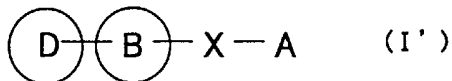
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ABSTRACT

This invention relates to a medicament, particularly an amide derivative by the following general formula (I') having an action to inhibit Ca^{2+} release activated Ca^{2+} channel, and a pharmaceutical composition containing the same as an active ingredient, particularly a Ca^{2+} release activated Ca^{2+} channel inhibitor.



(symbols in the formula having the following meanings:

D represents a pyrazolyl group which may have 1 to 3 halogen-substituted or unsubstituted lower alkyl groups as substituent groups,

B represents a phenylene or thiophenediyl group,

X represents a group of a formula -NH-CO- or -CO-NH- ,
and

A represents a phenyl group which may be substituted with one or more halogen atoms, or a five- or six-membered monocyclic heteroaryl group which may be substituted with one or more lower alkyl groups.)

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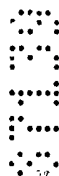
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Invention Title:

Amide derivative

The following statement is a full description of this invention, including the best method of performing it known to me:-

AMIDE DERIVATIVE

TECHNICAL FIELD

5 This invention relates to a medicament, particularly an amide derivative having an action to inhibit Ca^{2+} release-activated Ca^{2+} channel, and a pharmaceutical composition containing the same as an active ingredient, particularly a Ca^{2+} release activated Ca^{2+} channel inhibitor.

BACKGROUND ART

10 It has been known for a long time that calcium ion (Ca^{2+}) is important for an intracellular second messenger in the activation of various cells. Intracellular Ca^{2+} also acts as an important regulatory factor in inflammatory cells. 15 It has been suggested, however, that voltage-operated Ca^{2+} channel (to be referred to as "VOCC" hereinafter) inhibitors such as nifedipine does not show inhibitory activity against the activation of inflammatory cells and that a Ca^{2+} influx mechanism other than VOCC exist in inflammatory cells.

20 Hoth et al. have reported that a Ca^{2+} -selective and Ca^{2+} store depletion-activated Ca^{2+} channel, namely Ca^{2+} release-activated Ca^{2+} channel (to be referred to as "CRACC" hereinafter; also called store-dependent Ca^{2+} channel), is present in mast cells and lymphocytes, and these cells are 25 insensitive to membrane potential (*Pflugers Arch.*, 430, pp. 315 - 322 (1995)). It is known that CRACC is present in

several inflammatory cells such as mast cells, lymphocytes,
astrocytes (*J. Biol. Chem.*, 270, pp. 29 - 32 (1995)) and the
like, and that it is deeply concerned in, for example,
cytokine production and lipid mediator release (*J. Immunol.*,
5 155, pp. 285 - 296 (1995) and *Br. J. Pharmacol.*, 114, pp. 598
- 601 (1995)).

Recently, it has been revealed that an anti-arthritis
agent tenidap has a potency of CRACC inhibitor (*Cell Calcium*,
14, pp. 1 - 16 (1993)). Therefore, a CRACC inhibitor has a
10 possibility of therapeutic potency on chronic inflammatory
diseases including rheumatoid arthritis.

It is known that CRACC is also present in endothelial
cells (*Am. J. Physiol.*, 269, C 733 - 738 (1995)) and
epithelial cells (*J. Biol. Chem.*, 270, pp. 29169 - 175 (1995)).
15 Since it has been reported that sustained calcium influx
takes a role in the radical affection of endothelial cells
(*Am. J. Physiol.*, 261, C 889 - 896 (1991)), it is suggested
that a CRACC inhibitor should have protective efficacy on
endothelial cell-concerned tissue damage.

In addition, it has been reported that blockades of
calcium influx inhibit cell proliferation and interleukin 2
20 (IL-2) production (*Br. J. Pharmacol.*, 113, pp. 861 - 868
(1994)). Therefore, a CRACC inhibitor is useful as an agent
for the prevention and treatment of proliferative or
25 progressive diseases (e.g., malignant tumor and the like) and



autoimmune diseases, and also as a suppresser for tissue rejection in transplantation.

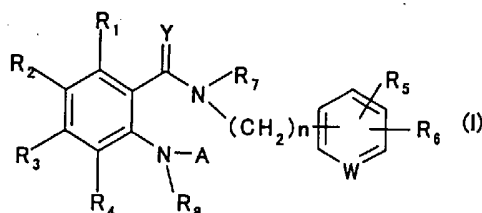
On the other hand, it is known that in excitable cells such as smooth muscle cells and nerve cells, intracellular calcium is mainly regulated with VOCC not with CRACC. Therefore, it is expected that a calcium channel blocker having CRACC selectivity against VOCC should be an useful agent for the prevention or treatment of various inflammatory diseases, allergic diseases, autoimmune diseases, tissue damages, proliferative diseases and the like without undesirable actions on cardiovascular and central nervous system.

Recently, some compounds showing CRACC inhibitory activity have been reported, such as a cycloalkyl-piperazinyethanol derivative disclosed in a published German patent publication 4404249 and a 2-(3,4-dihydro-1-isoquinolyl)acetamide derivative disclosed in WO 94/00435. It has also reported that 5-amino-1-[[3,5-dichloro-4-(4-chlorobenzoyl)phenyl]methyl]-1H-1,2,3-triazole-4-carboxamide inhibits CRACC (*J. Pharm. Exp. Ther.*, 257, pp. 967 - 971 (1991)). However, there are no reports on a compound whose CRACC selectivity over VOCC has been confirmed.

On the other hand, a published German patent publication 2525024 discloses a 5-(heterocycloylaminophenyl)-1-phenylpyrazole derivative which shows an anti-inflammatory activity. However, this patent does not disclose or suggest

about its inhibitory activities against CRACC and IL-2 production.

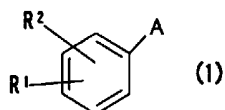
WO 95/18097 discloses an anthranilic acid derivative represented by the following formula (I), which inhibits a cyclic GMP phosphodiesterase. In the formula, R_1 to R_4 represent H, a halogen, ..., pyrazolyl which may be substituted, ..; n is 0 to 6, W represents N or CH, Y represents O or S, ... (see said published patent application for details).



An unexamined published Japanese patent application 9-59236 discloses an R^1 , R^2 -di-substituted benzamide derivative represented by the following formula (1), which is useful for the prevention and treatment of rheumatic, allergic and other inflammatory diseases. In the formula, R^1 represents a substituted or unsubstituted aromatic heterocyclic ring, ..., R^2 represents a halogen, a nitro, $-NR^3R^6$, ..., A represents $-C(=Z)NR^3R^4$ or $-NR^4C(=Z)R^3$, R^3 represents a substituted or unsubstituted aromatic hydrocarbon ring, a substituted or unsubstituted aromatic heterocyclic ring ... (see said published patent application

for details). However, there is no illustrative disclosure about pyrazolyl as the aromatic heterocyclic ring group. In addition, there is no disclosure about inhibitory activities against CRACC and/or IL-2 production.

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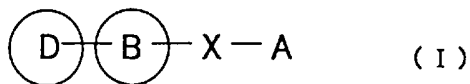


DISCLOSURE OF THE INVENTION

The inventors of the present invention have conducted extensive studies on the screening of compounds having excellent CRACC inhibitory activity. As a result of the efforts, certain amide derivatives which possess entirely different structures from those of the reported CRACC inhibitors have been found to show excellent CRACC inhibitory activity. The present invention has been accomplished by further finding that these compounds have high CRACC selectivity over VOCC.

Accordingly, this invention relates to a novel amide derivative represented by the following general formula (I)

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[symbols in the formula having the following meanings:

D represents a pyrazolyl group which may have 1 to 3 halogen-substituted or unsubstituted lower alkyl groups as substituent(s),

B represents a phenylene or thiophenediyl group,

X represents a group of a formula -NH-CO- or -CO-NH-,

and

A represents a phenyl group which may be substituted with one or more halogen atoms, or a five- or six-membered monocyclic heteroaryl group which may be substituted with one or more lower alkyl groups, with the proviso that 4-methyl-4'[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]-1,2,3-thiadiazole-5-carboxyanilide (to be referred to as "compound A" hereinafter) and 4'-chloro-5-(1-methyl-5-trifluoromethyl-1H-pyrazol-3-yl)thiophene-2-carboxyanilide (to be referred to as "compound B" hereinafter) are excluded; the same shall apply hereinafter] or a pharmaceutically acceptable salt thereof.

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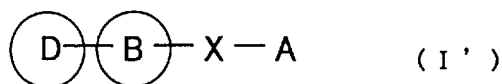
In this connection, the compounds A and B are known compounds described as SEW 04225 and KM 02904 in a reagent

catalog published by MAYBRIDGE (UK, Cornwall, August, 1995).
However, there are no reports on these pharmaceutical use and
other applications.

5 A preferred compound of the general formula (I) of
the present invention is an amide derivative or a
pharmaceutically acceptable salt thereof, in which D is a
pyrazolyl group substituted with at least one trifluoromethyl
group or D is 1-methyl-3-trifluoromethyl-1H-pyrazol-5-yl or
3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl, and A is phenyl
10 group which may be substituted with one or more halogen
atoms, or a five- or six-membered monocyclic heteroaryl group
selected from the group consisting of thiazolyl,
thiadiazolyl, thienyl and pyridyl, which may be substituted
with one or more lower alkyl groups.

15 This invention also relates to a pharmaceutical
composition which comprises an amide derivative represented
by the following general formula (I') including the compounds
A and B, or a pharmaceutically acceptable salt thereof, and a
pharmaceutically acceptable carrier, particularly to a
20 pharmaceutical composition for use in the inhibition of Ca^{2+}
release-activated Ca^{2+} channel.

Preferably, it is an IL-2 production inhibitor, an
agent for use in the prevention or treatment of allergic,
chronic inflammatory or autoimmune diseases or an agent for
25 use in the prevention or treatment of bronchial asthma or
rheumatoid arthritis.



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[symbols in the formula having the following meanings:

D represents a pyrazolyl group which may have 1 to 3 halogen-substituted or unsubstituted lower alkyl groups as substituent(s),

B represents a phenylene or thiophenediyl group,

X represents a group of a formula -NH-CO- or -CO-NH-,

and

A represents a phenyl group which may be substituted with one or more halogen atoms, or a five- or six-membered monocyclic heteroaryl group which may be substituted with one or more lower alkyl groups; the same shall apply hereinafter.]

Unless otherwise noted, the term "lower" as used herein means a straight or branched carbon chain having 1 to 6 carbon atoms. The "lower alkyl group" is preferably methyl, ethyl or propyl. The "five- or six-membered monocyclic heteroaryl group" is a five- or six-membered monocyclic heteroaryl group containing 1 to 4 hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom, and is preferably thienyl, thiazolyl, thiadiazolyl or

pyridyl. Preferably, the "phenylene group" is 1,4-phenylene and the "thiophenediyl group" is 2,5-thiophenediyl.

The "halogen" is preferably F or Cl. The "halogen-substituted lower alkyl group" is preferably trifluoromethyl.

5 The compound of this invention may exist in the form of geometrical isomers or tautomers depending on the kinds of substituent groups, and these isomers in separated forms or mixtures thereof are included in the present invention.

Also, the compound of the present invention may have
10 asymmetric carbon atoms, so that it may exist in (R) and (S) optical isomer forms based on such carbon atoms. All of the mixtures and the isolated forms of these optical isomers are included in the present invention.

15 The compound (I) or (I') of this invention may form an acid addition salt or, depending on the kinds of substituent groups, a salt with a base. Such salts are pharmaceutically acceptable ones, and their preferred
20 examples include acid addition salts with inorganic acids (e.g., hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid and the like) or with organic acids (e.g., formic acid, acetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid, lactic acid, malic acid, tartaric acid, citric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic
25 acid, aspartic acid, glutamic acid and the like) and salts with inorganic bases (e.g., sodium, potassium, magnesium,

calcium, aluminum and the like) or with organic bases (e.g., methylamine, ethylamine, ethanolamine, lysine, ornithine and the like), as well as ammonium salts.

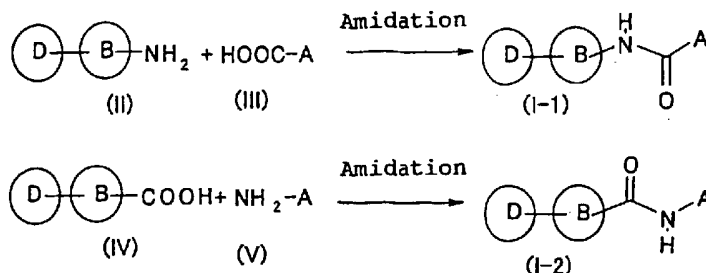
5 In addition, various hydrates and solvates and polymorphism of the compound (I) or (I') and salts thereof are also included in this invention.

(Production Method)

10 The compound of the present invention and a pharmaceutically acceptable salt thereof can be produced by making use of the features of its basic structure or the kinds of its substituents and by employing various known synthesis methods. In that case, depending on the kind of each functional group, it may sometimes be effective from the viewpoint of production techniques to replace said functional group with an appropriate protecting group, namely a group which can be converted into said functional group easily, at the stage of raw materials or intermediates. Thereafter, the compound of interest can be obtained by removing the protecting group as occasion demands. Examples of such functional groups include a hydroxyl group, a carboxyl group and the like and examples of their protecting groups include those which are described in "Protective Groups in Organic Synthesis", 2nd edition, edited by Greene and Wuts, which may be optionally used depending on the reaction conditions.

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25 The following describes typical methods for the preparation of the compound of the present invention.

Production Method 1



In this method, as shown in the above reaction formula, the compound (I-1) or (I-2) of the present invention is obtained by subjecting an amine derivative represented by the general formula (II) or (V) and a carboxylic acid derivative represented by the general formula (III) or (IV) to amidation reaction.

The carboxylic acid derivative (III) or (IV) which can be used in the production method 1 is a free carboxylic acid or a reactive derivative thereof, and examples of the reactive derivative include acid halides such as acid chlorides, acid bromides and the like; acid azides; active esters which can be prepared using methanol, ethanol, benzyl alcohol, phenol which may be substituted, 1-hydroxybenzotriazole, N-hydroxysuccinimide and the like; symmetric acid anhydrides; and mixed acid anhydrides with ethoxycarbonyl chloride, isobutylcarbonyl chloride, alkylcarboxylic acid, p-toluenesulfonic acid and the like.



These reactive derivatives are commercially available or can be produced by the usual procedures.

The amidating reaction can be carried out by the usual procedures.

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When the reaction is carried out using a free carboxylic acid, it is necessary to use a condensing agent such as N,N'-dicyclohexylcarbodiimide (DCC), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (WSCD) or the like or carboxylic acid activating agent such as 1,1'-carbonyldiimidazole, N,N'-disuccinimidyl carbonate, diphenylphosphoryl azide, phosphorus oxychloride, phosphorus trichloride, triphenylphosphine/N-bromosuccinimide or the like.

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The reaction is carried out using an amine derivative represented by the general formula (II) or (V) and a carboxylic acid derivative represented by the general formula (III) or (IV), in equimolar amounts or one of them in excess amount, in a reaction inert organic solvent such as pyridine, tetrahydrofuran (THF), dioxane, ether, benzene, toluene, dichloromethane, 1,2-dichloroethane (DCE), chloroform, dimethylformamide (DMF), ethyl acetate, acetonitrile or the like. The reaction temperature is optionally selected depending on the kinds of reaction derivatives.

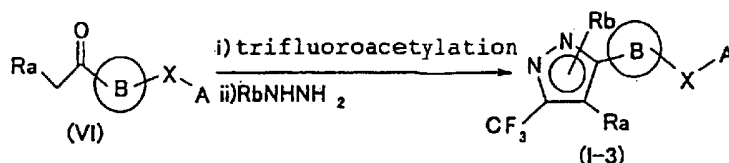
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Depending on the kinds of reaction derivatives, addition of a base such as triethylamine, pyridine, picoline, N,N-dimethylaniline, potassium carbonate, sodium hydroxide or

the like may be advantageous in some cases from the viewpoint of accelerating the reaction. It is possible to use pyridine also as the solvent.

Production Method 2

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10 (In the above reaction formula, each of Ra and Rb represents H or a lower alkyl group.)

15 In this production method, the compound (I-3) of the present invention is obtained by carrying out trifluoroacetylation of the carbon atom adjacent to the ketone of a compound represented by the general formula (VI) and then effecting cyclization by reacting it with a hydrazine derivative.

20 The first step trifluoroacetylation can be carried out by allowing the compound to react with a trifluoroacetylation agent (for example, ethyl trifluoroacetate, trifluoroacetic anhydride or the like) at a temperature of from -78°C to reflux temperature in a solvent such as methanol, ethanol, 1,3-dimethylimidazolidin-2-one (DMI), THF, DMF or the like, in the presence of a base
25 such as sodium methoxide, sodium ethoxide, alkali metal



hexamethyldisilazide, sodium hydride, alkyl lithium, triethylamine or the like.

5 The second step cyclization reaction can be carried out by allowing the compound obtained in the first step to react with a hydrazine derivative in a solvent such as methanol, ethanol or the like, or without solvent, in the presence or absence of an acid such as acetic acid, hydrochloric acid or the like or Lewis acid such as titanium(IV) isopropoxide, titanium(IV) chloride, boron trifluoride-diethyl ether complex or the like. This reaction can be carried out at a temperature of from cooling temperature to reflux temperature.

(Production Method of Starting Compounds)

Starting compounds of the aforementioned production methods are commercially available or can be produced easily by methods well known to those skilled in the art.

Each of the reaction products obtained by the aforementioned production methods is isolated and purified as a free compound, a salt thereof, a hydrate thereof or a solvate thereof. The salt can be produced by a usual salt forming method. The isolation and purification are carried out by employing usually used chemical techniques such as extraction, concentration, evaporation, crystallization, filtration, recrystallization, various types of chromatography and the like. Various forms of isomers can be isolated by the usual procedures making use of

physicochemical differences among isomers. For example, optical isomers can be separated by means of a conventional racemic resolution method such as fractional crystallization or a chromatography. In addition, an optical isomer can also be synthesized from an appropriate optically active starting compound.

INDUSTRIAL APPLICABILITY

The compound of the present invention is useful as an active ingredient of pharmaceutical compositions. Since it has inhibitory activities on CRACC and IL-2 production, it is particularly useful as an inhibitor of CRACC or IL-2 production.

It also is particularly useful as an agent for use in the prevention and treatment of allergic, chronic inflammatory or autoimmune diseases in which CRACC and/or IL-2 production are concerned. In this connection, examples of the allergic, chronic inflammatory or autoimmune diseases include various diseases in which CRACC and/or IL-2 production are concerned such as bronchial asthma, psoriasis, atopic diseases including atopic dermatitis, inflammatory bowel diseases including Crohn disease, peptic ulcer, glomerular nephritis, hepatitis, pancreatitis, collagen disease, rheumatoid arthritis; osteoarthritis, rejection on transplantation and the like.

Applicability of the compound of the present invention to the aforementioned diseases is evident from the results of *in vitro* tests on inhibition of CRACC and IL-2 production, which will be described later, as well as the

5 results of various tests carried out using animal models for diseases such as an antigen-induced airway eosinophilia as a typical model for bronchial asthma, some T-cell-dependent disease models and a collagen-induced arthritis in mice. In addition, since the compounds of the present invention also

10 have inhibitory effects on IL-4, IL-5, MMP-1 and TNF α production, such results also support its applicability to the aforementioned diseases.

On the other hand, anti-proliferative effect of the CRACC inhibitor suggests that it should be useful in

15 preventing or treating proliferative or progressive diseases such as malignant tumor, arteriosclerosis, multiple organ sclerosis, various types of fibrosis, burn keloid and the like. Also, since the CRACC inhibitor inhibits activation of inflammatory cells such as mast cells, leukocytes and

20 astrocytes, which concern with inflammation in several peripheral or brain tissues, its action to protect tissues from their damages such as ischemia-reperfusion injury, head injury, cerebral infarction and myocardial infarction can be expected.

25 In particular, the compound of the present invention which is possessed of CRACC selective inhibitory activity

over VOCC is useful, because it can cause CRACC inhibition without VOCC activation-induced undesirable reactions in central nerve system and cardiovascular system and the like.

5 The following shows certain tests and their results in order to confirm pharmacological actions of the compound of the present invention.

(1) CRACC inhibitory activity

10 Jurkat cells ($6 \times 10^6/\text{ml}$) suspension loaded with a calcium indicator fluorescence dye fura-2 ($1 \mu\text{M}$) was dispensed in $100 \mu\text{l}$ portions into wells of a 96 well microplate. Intracellular calcium increase stimulated with a calcium pump inhibitor (thapsigargin) was induced by adding to each well a $100 \mu\text{l}$ of Hanks' balanced salt solution containing a drug to be tested in two times higher concentration than the final concentration and $2 \mu\text{M}$ of thapsigargin (final concentration, $1 \mu\text{M}$), and, after 30 minutes of the addition, a fluorescence intensity ratio (R) was calculated from two fluorescence intensities obtained at excitation wave lengths of $340 \text{ nm}/500 \text{ nm}$ and $380 \text{ nm}/500 \text{ nm}$, respectively. In calculating R, self-fluorescence of the drug to be tested was measured in a cell-free system, and the effect of the self-fluorescence on the fura-2 fluorescence was corrected.

20 The intracellular calcium concentration was obtained by the following calculation formula based on a maximum reaction of R (R_{max}) obtained by $25 \mu\text{M}$ ionomycin stimulation,

a minimum reaction of R (Rmin) obtained by 5 μ M ionomycin +
1 mM EGTA stimulation, a fluorescence efficiency (Sb2) of a
calcium binding dye at an excitation wave length of
380 nm/500 nm and a fluorescence efficiency (Sf2) of a
calcium dissociation dye at an excitation wave length of
380 nm/500 nm.

Calculation formula: Intracellular calcium concentration (nM)
$$= 224 \times [(R - R_{min}) / (R_{max} - R)] \times [Sf2 / Sb2]$$

Using the thus calculated intracellular calcium
concentration in the presence of a predetermined
concentration of each of the drugs and that of the control
solvent, a ratio of inhibiting calcium influx (CRACC
inhibition) was obtained to calculate its concentration to
inhibit 50% of CRACC (IC₅₀ value).

The IC₅₀ value of the compounds of Examples 1 to 6
was within the range of from 0.51 to 0.050 μ M.

(2) Selectivity of CRACC inhibition against VOCC

A suspension of rat neuroblasts PC12-h5 (2×10^6 /ml)
loaded with a calcium indicator fluorescence dye fura-2
(1 μ M) was dispensed in 100 μ l portions into wells of a 96
well microplate. Intracellular calcium increase stimulated
with high concentration potassium chloride was induced by
adding to each well a 100 μ l of Hanks' balanced salt solution
containing a drug to be tested in two times higher
concentration than the final concentration and 100 mM of KCl
(final concentration, 50 mM), and, after 30 minutes of the

addition, a fluorescence intensity ratio (R) was calculated from two fluorescence intensities obtained at excitation wavelengths of 340 nm/500 nm and 380 nm/500 nm, respectively. In calculating R, self-fluorescence of the drug to be tested was measured in a cell-free system, and the effect of the self-fluorescence on the fura-2 fluorescence was corrected.

The IC_{50} value of VOCC inhibition was calculated in the same manner as the case of the aforementioned CRACC inhibition, and compared with that of CRACC inhibition.

The VOCC inhibition of the compounds of Examples 1 to 6 was 16 times or more weaker than their CRACC inhibition.

(3) Inhibitory effect on IL-2 production

Inhibitory effect of the invention compound on IL-2 production from Jurkat cells was tested in accordance with the method described by S. Clare Chung *et al.* in *Br. J. Pharmacol.*, 113: 861 - 868, 1994, and its IC_{50} value was calculated.

Compounds of this invention showed IC_{50} values of 1 μ M or less.

(4) Effect on TNCB-induced contact hypersensitivity model

In five-week-old male ICR mice, effect of the invention compound on TNCB-induced contact hypersensitivity was tested in almost the same manner as the method described in Current Protocols in Immunology (John Wiley & Sons, Inc., 1994). Compounds of this invention inhibited TNCB-induced contact hypersensitivity in a dose-dependent manner.

(5) Inhibitory effect on concanavalin A (ConA)-induced hepatitis in mice

In four to five-week-old female Balb/c mice (SLC), this test was carried out by employing a method similar to the method reported by G. Tiegs *et al.* in *J. Clin. Invest.*, 1992, 90: 196 - 203. Compounds of this invention inhibited ConA-induced hepatitis in a dose-dependent manner.

(6) Inhibitory effect on collagen-induced arthritis in mice

In five-week-old male DBA/1J mice (Charles River Japan), inhibitory effect on arthritis was tested in the similar manner as the methods reported by Fumio Nishikaku and Yoshihiko Koga in *Immunopharmacology*, 25, 65 - 74 (1993) and by Fuminori Kato, Masanao Nomura and Kyoko Nakamura in *Annals of the Rheumatic Disease*, 55, 535 - 539 (1996). Compounds of this invention showed significant inhibition on arthritis.

(7) Inhibitory effect on antigen-induced airway eosinophilia in rat

In four-week-old male BN rats, inhibitory effect on antigen-induced airway eosinophilia was tested in almost the same manner as the method reported by W. Elwood *et al.* in *Inflamm. Res.*, 44: 83 - 86, 1995. In this connection, the drug was administered 30 minutes before the antigen exposure in the case of intravenous injection or 1 hour before and 3 hours after the antigen exposure in the case of oral administration.

In this model, compounds of this invention inhibited numbers of infiltrated total leukocytes and that of infiltrated eosinophils into airways.

5 A pharmaceutical composition which contains the compound (I') of the present invention or a salt thereof and a pharmaceutically acceptable carrier can be prepared by a usually used method using at least one of compounds represented by the general formula (I') or salts thereof and a carrier for medicinal use, a filler and other additives usually used in pharmaceutical preparations. Its administration may be effected either by oral administration in the form of tablets, pills, capsules, granules, powders, solutions and the like or by parenteral administration in the form of intravenous, intramuscular and the like injections, suppositories, percutaneous absorption preparations and the like.

 The solid composition for use in the oral administration according to the present invention is used in the form of tablets, powders, granules and the like. In such a solid composition, one or more active substances are mixed with at least one inert diluent such as lactose, mannitol, glucose, hydroxypropylcellulose, microcrystalline cellulose, starch, polyvinyl pyrrolidone or aluminum magnesium silicate. By the usual procedures, the composition may contain other additives than the inert diluent, such as a lubricant (e.g.,

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magnesium stearate or the like), a disintegrating agent (e.g., calcium cellulose glycolate or the like), a stabilizing agent (e.g., lactose or the like) and a solubilization assisting agent (e.g., glutamic acid, aspartic acid or the like). If necessary, tablets or pills may be coated with films of a sugar or a gastric or enteric substance such as sucrose, gelatin, hydroxypropylcellulose, hydroxypropylmethylcellulose phthalate or the like.

The liquid composition for oral administration use includes pharmaceutically acceptable emulsions, solutions, suspensions, syrups, elixirs and the like and contains a generally used inert diluent such as purified water or ethanol. In addition to the inert diluent, this composition may also contain auxiliary agents such as a moistening agent, a suspending agent and the like, as well as sweeteners, flavors, aromatics and antiseptics.

The injections for parenteral administration use include aseptic aqueous or non-aqueous solutions, suspensions and emulsions. Examples of the diluent for use in the aqueous solutions and suspensions include distilled water for injection use and physiological saline. Examples of the diluent for use in the non-aqueous solutions and suspensions include propylene glycol, polyethylene glycol, plant oil (e.g., olive oil or the like), alcohol (e.g., ethanol and the like), and polysorbate 80. Such a composition may further contain auxiliary agents such as an antiseptic, a moistening

agent, an emulsifying agent, a dispersing agent, a stabilizing agent (lactose for example) and a solubilization assisting agent (glutamic acid or aspartic acid for example). These compositions are sterilized by filtration through a bacteria retaining filter, blending of a germicide or irradiation. Alternatively, they may be used by firstly making into sterile solid compositions and then dissolving them in sterile water or a sterile solvent for injection use prior to their use.

In the case of oral administration, suitable daily dose is usually from about 0.001 to 10 mg/kg body weight, and the daily dose is administered once a day or divided into 2 to 4 doses per day. In the case of intravenous injection, suitable daily dose is usually from about 0.0001 to 1 mg/kg body weight, and the daily dose is administered once a day or divided into a plurality of doses per day. The dose is optionally decided by taking into consideration symptoms, age, sex and the like of each patient to be treated.

BEST MODE OF CARRYING OUT THE INVENTION

The present invention is described further in detail based on the following examples. It is to be understood, however, that the compounds of the present invention are not limited to the compounds described in the following examples.

Example 1

A mixture of 4-methylthiazole-5-carboxylic acid (108 mg), 4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]aniline (223 mg), WSCD hydrochloride (152 mg) and DCE (5 ml) was stirred overnight at room temperature. Water (10 ml) was added to the reaction mixture, and the thus formed product was extracted with a mixed solvent of diethyl ether (5 ml) and ethyl acetate (10 ml). The extract was washed with 1 N hydrochloric acid, saturated sodium hydrogencarbonate aqueous solution and saturated brine in that order. The resulting organic layer was dried over anhydrous magnesium sulfate and then concentrated under a reduced pressure. The thus obtained residue was purified by a silica gel column chromatography (eluent; n-hexane:ethyl acetate = 2:1) and then recrystallized from a mixed solvent of ethyl acetate and n-hexane to give 4-methyl-4'-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]thiazole-5-carboxyanilide (143 mg) as colorless needles.

Example 2

A mixture of 5-(1-methyl-3-trifluoromethyl-1H-pyrazol-5-yl)thiophene-2-carbonyl chloride (150 mg) with dichloromethane (1.5 ml) was added to a mixture of 2-chloroaniline (68 mg), pyridine (42 mg) and dichloromethane (2 ml) and stirred for 30 minutes at room temperature. Saturated sodium hydrogencarbonate aqueous solution was added to the reaction mixture, the thus formed product was

extracted with ethyl acetate and then the extract was washed with saturated brine. The resulting organic layer was dried over anhydrous magnesium sulfate and then concentrated under a reduced pressure. The resulting residue was recrystallized from ethanol to give 2'-chloro-5-(1-methyl-3-trifluoromethyl-1H-pyrazol-5-yl)thiophene-2-carboxyanilide (80 mg) as colorless crystals. In this case, the aforementioned starting compound 5-(1-methyl-3-trifluoromethyl-1H-pyrazol-5-yl)thiophene-2-carbonyl chloride was obtained as brown solid by a treatment of 5-(1-methyl-3-trifluoromethyl-1H-pyrazol-5-yl)thiophene-2-carboxylic acid with oxalyl chloride.

Example 3

Sodium methoxide (257 mg) was added to a mixture of 4'-acetyl-4-chlorobenzanilide (1.00 g) and DMI (10 ml) at 0°C, and the thus prepared mixture was stirred for 2 hours at room temperature. Ethyl trifluoroacetate (0.522 ml) was added to the reaction solution and stirred for 2 days at 60°C. Water (50 ml) and 1 N hydrochloric acid (10 ml) were added to the reaction mixture, the thus formed product was extracted with ethyl acetate, and then the extract was washed with water and saturated brine in that order. The thus obtained organic layer was dried over anhydrous sodium sulfate and then concentrated under a reduced pressure. A mixture of the thus obtained residue with methylhydrazine (0.206 ml), acetic acid (2 ml) and ethanol (20 ml) was stirred for 21 hours at room temperature. After

concentration of the reaction mixture under a reduced pressure, the thus obtained residue was added ethyl acetate (100 ml) and washed with saturated sodium hydrogencarbonate aqueous solution and saturated brine in that order. The thus
5 obtained organic layer was dried over anhydrous sodium sulfate and then concentrated under a reduced pressure. The thus obtained residue was purified by a silica gel column chromatography (eluent; n-hexane:ethyl acetate = 3:1) and then recrystallized from a mixed solvent of ethyl acetate and n-hexane to give 4-chloro-4'-(1-methyl-3-trifluoromethyl-1H-pyrazol-5-yl)benzanilide (440 mg) as colorless powder
10 crystals.

Compounds of Example 4: (4-methyl-4'-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]-1,2,3-thiadiazole-5-carboxyanilide), Example 5: (3-methyl-4'-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]thiophene-2-carboxyanilide) and Example 6: (4'-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]nicotinilide) shown in the following Table
15 1 were respectively obtained in the same manner as described
20 in Example 1.

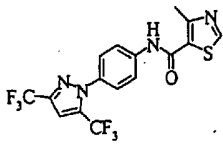
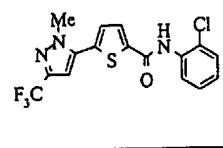
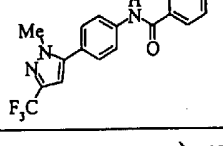
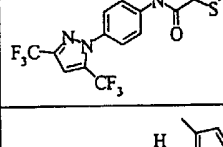
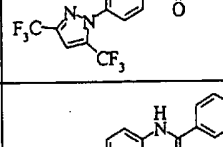
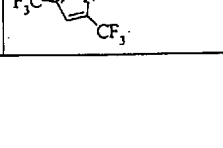
Structures and physicochemical properties of the compounds of Examples are shown in Table 1. In the table, Ex means Example No., Str means structural formula, Dat means physicochemical properties, mp. means melting point, NMR
25 means nuclear magnetic resonance spectrum (DMSO-d₆, TMS internal standard) δ ppm and NMR (CDCl₃) means nuclear

δ ppm

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

The figure shows four 5x5 dot patterns arranged vertically. The first pattern represents the digit '3', the second '5', the third '2', and the fourth '0'. Each pattern is formed by black dots on a white background.

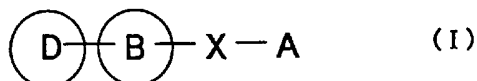
Table 1

Ex	Str	Dat
1		mp.: 144-145°C NMR: 2.64(3H, s), 7.61(2H, d, J=8.8Hz), 7.82(1H, s), 7.90(2H, d, J=8.8Hz), 9.17(1H, s), 10.57(1H, s)
2		mp.: 156°C NMR(CDCl ₃): 4.08(3H, s), 6.74(1H, s), 7.13(1H, td, J=7.8, 1.5Hz), 7.26(1H, d, J=3.4Hz), 7.35(1H, td, J=7.8, 1.4Hz), 7.44(1H, dd, J=7.8, 1.5Hz), 7.66(1H, d, J=3.9Hz), 8.32(1H, s), 8.48(1H, dd, J=8.3, 1.4Hz)
3		mp.: 187-188°C NMR(CDCl ₃): 3.93(3H, s), 6.56(1H, s), 7.42-7.45(2H, m), 7.48-7.51(2H, m), 7.75-7.79(2H, m), 7.82-7.86(2H, m), 7.91(1H, brs)
4		mp.: 166-168°C NMR: 2.84(3H, s), 7.65(2H, d, J=8.8Hz), 7.83(1H, s), 7.91(2H, d, J=9.2Hz), 11.05(1H, s)
5		mp.: 169-172°C NMR: 2.48(3H, s), 7.06(1H, d, J=4.9Hz), 7.59(2H, d, J=8.8Hz), 7.72(1H, d, J=4.9Hz), 7.82(1H, s), 7.90(2H, d, J=8.8Hz), 10.32(1H, s)
6		mp.: 188-190°C NMR: 7.58-7.66(3H, m), 7.83(1H, s), 8.00(2H, d, J=9.3Hz), 8.33(1H, dt, J=7.8, 2.0Hz), 8.80(1H, dd, J=4.6, 1.7Hz), 9.14(1H, d, J=1.5Hz), 10.77(1H, s)

The Claims defining the invention are as follows:

1. An amide derivative represented by the following general formula (I)

5



(symbols in the formula having the following meanings:

D represents a pyrazolyl group which may have 1 to 3 halogen-substituted or unsubstituted lower alkyl groups as substituent(s),

B represents a phenylene or thiophenediyl group,

X represents a group of a formula -NH-CO- or -CO-NH-, and

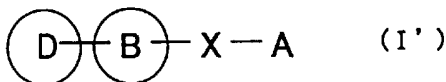
A represents a phenyl group which may be substituted with one or more halogen atoms, or a five- or six-membered monocyclic heteroaryl group which may be substituted with one or more lower alkyl groups, with the proviso that 4-methyl-4'[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]-1,2,3-thiadiazole-5-carboxyanilide and 4'-chloro-5-(1-methyl-5-trifluoromethyl-1H-pyrazol-3-yl)thiophene-2-carboxyanilide are excluded) or a pharmaceutically acceptable salt thereof.

2. The amide derivative or a pharmaceutically acceptable salt thereof according to claim 1, wherein D is a

pyrazolyl group substituted with at least one trifluoromethyl group.

3. The amide derivative or a pharmaceutically acceptable salt thereof according to claim 1, wherein D is 1-methyl-3-trifluoromethyl-1H-pyrazol-5-yl or 3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl, and A is a phenyl group which may be substituted with a halogen atom, or a five- or six-membered monocyclic heteroaryl group selected from the group consisting of thiazolyl, thiadiazolyl, thienyl and pyridyl, which may be substituted with a lower alkyl group.

4. A pharmaceutical composition for inhibiting Ca^{2+} release activated Ca^{2+} channel, which comprises an amide derivative represented by the following general formula (I') or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier



(symbols in the formula having the following meanings:

D represents a pyrazolyl group which may have 1 to 3 halogen-substituted or unsubstituted lower alkyl groups as substituent(s),

B represents a phenylene or thiophenediyl group,

X represents a group of a formula $-\text{NH}-\text{CO}-$ or $-\text{CO}-\text{NH}-$, and

A represents a phenyl group which may be substituted with one or more halogen atoms, or a five- or six-membered monocyclic heteroaryl group which may be substituted with one or more lower alkyl groups.

5 5. The pharmaceutical composition according to claim 4, wherein it is an IL-2 production inhibitor.

6. The pharmaceutical composition according to claim 5, wherein it is an agent for the prevention or treatment of allergic, chronic inflammatory or autoimmune diseases.

7. The pharmaceutical composition according to claim 6, wherein it is an agent for the prevention or treatment of bronchial asthma.

8. The pharmaceutical composition according to claim 6, wherein it is an agent for the prevention or treatment of rheumatoid arthritis.

9. The pharmaceutical composition according to any one of claims 4 to 8, wherein it comprises an amide derivative selected from the group consisting of 4-methyl-4'-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]thiazole-5-carboxyanilide, 2'-chloro-5-(1-methyl-3-trifluoromethyl-1H-pyrazol-5-yl)thiophene-2-carboxyanilide, 4-chloro-4'-(1-methyl-3-trifluoromethyl-1H-pyrazol-5-yl)benzanilide, 4-methyl-4'-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]-1,2,3-thiadiazole-5-carboxyanilide, 3-methyl-4'-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]thiophene-2-

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- 32 -

carboxyanilide and 4'-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]nicotinilide, or
pharmaceutically acceptable salt thereof.

10. Amide derivatives of the formula (I), methods for their manufacture or pharmaceutical
5 compositions or methods of treatment involving/containing them, substantially as hereinbefore
described with reference to the Examples.

DATED this 28th day of September 1998

10 **YAMANOUCHI PHARMACEUTICAL CO., LTD**

By Its Patent Attorneys

DAVIES COLLISON CAVE

