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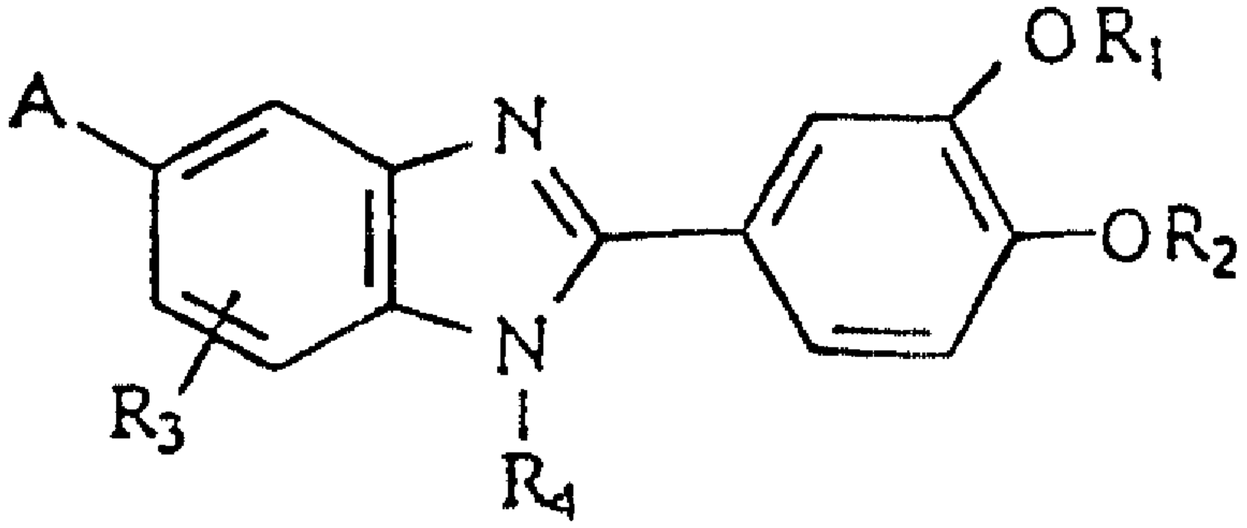
(54) Title: BENZIMIDAZOLE DERIVATIVES AND PHARMACOLOGICALLY ACCEPTABLE SALTS THEREOF

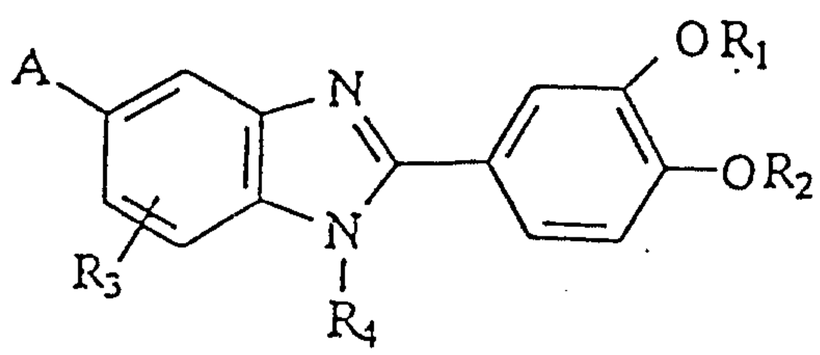


(I)

(57) Abrégé/Abstract:
This invention provides a compound having both IL-4 production inhibitory activity and PDE (IV) inhibitory activity, represented by formula (I): (see formula I) [wherein A represents a triazole group; R_1 and R_2 may be the same or different from each other and each represents an aliphatic hydrocarbon radical which may have an alicyclic or aromatic hydrocarbon radical or an alicyclic hydrocarbon radical; R_3 represents hydrogen atom or a substituent group; and R_4 represents a hydrogen atom or a protective group of the nitrogen atom], and a pharmaceutical composition, a therapeutic or preventive agent for acute and chronic inflammatory diseases and an anti-allergic or anti-inflammatory agent, each of which comprising an effective amount of the compound and a pharmacological carrier. It also provides a use of the compound of formula (I) for the production of the aforementioned pharmaceutical composition, therapeutic or preventive agent for acute and chronic inflammatory diseases and anti-allergic or anti-inflammatory agent, for preventing acute and chronic inflammatory diseases.

ABSTRACT

This invention provides a compound having both IL-4 production inhibitory activity and PDE (IV) inhibitory activity, represented by formula (I):



(I)

[wherein A represents a triazole group; R_1 and R_2 may be the same or different from each other and each represents an aliphatic hydrocarbon radical which may have an alicyclic or aromatic hydrocarbon radical or an alicyclic hydrocarbon radical; R_3 represents hydrogen atom or a substituent group; and R_4 represents a hydrogen atom or a protective group of the nitrogen atom], and a pharmaceutical composition, a therapeutic or preventive agent for acute and chronic inflammatory diseases and an anti-allergic or anti-inflammatory agent, each of which comprising an effective amount of the compound and a pharmacological carrier. It also provides a use of the compound of formula (I) for the production of the aforementioned pharmaceutical composition, therapeutic or preventive agent for acute and chronic inflammatory diseases and anti-allergic or anti-inflammatory agent, for preventing acute and chronic inflammatory diseases.

BENZIMIDAZOLE DERIVATIVES AND PHARMACOLOGICALLY ACCEPTABLE SALTS THEREOF

TECHNICAL FIELD

This invention relates to benzimidazole derivatives and pharmacologically acceptable salts thereof, both of which have interleukin (IL)-4 production inhibitory activity and phosphodiesterase IV (PDE (IV)) inhibitory activity, and are useful as therapeutic or preventive drugs for acute and chronic inflammatory diseases such as atopic dermatitis, allergic rhinitis, bronchial asthma and glomerulonephritis. The invention also relates to a pharmaceutical composition in which the benzimidazole derivative, or pharmacologically acceptable salt thereof, is used.

BACKGROUND ART

Regarding inflammatory diseases, various medicaments capable of inhibiting acute stage inflammations have been developed in recent years, but medicaments which can effectively inhibit chronic stage inflammations are still scarce so that their development is a pressing problem. Also, an anti-inflammatory drug which can be used without distinctions between acute stage and chronic stage is useful in the clinical field.

Under such circumstances, attempts are being made on the research and development of medicaments having phosphodiesterase IV (PDE (IV)) inhibitory activity. This is based on information that PDE (IV) is a concern in acute and chronic inflammatory diseases (see for example, *J. Pharmacol. Exp. Ther.*, 266(1), 306-313 (1993), *Br. J. Pharmacol.*, 120(2), 289-297 (1997) and *Am. J. Respir. Crit. Care Med.*, 149(5), 1153-1159 (1994)). In reality, however, drugs developed so far scarcely having such an activity are effective for acute inflammatory diseases but cannot exert sufficient effects on chronic inflammatory diseases. It is considered that certain members of cytokine produced by Th2 cells as one of the subgroups of CD4+ T cells play an important role in the onset

of inflammatory diseases, and interleukin (IL) -4, being among them, is particularly concerning in chronic stage inflammatory diseases (see for example, *Am. J. Physiol.*, 272 (2 Pt 1), L 253-261 (1997), *Am. J. Respir. Cell Mol. Biol.*, 10(5), 526-532 (1994) and ibid., 13(1), 54-59 (1995)).

Accordingly, development of a drug having both PDE (IV) inhibitory activity and IL-4 production inhibitory activity will result in an anti-inflammatory drug which is effective on both acute and chronic inflammatory diseases. At present, PDA-641 has been reported as such a compound (cf. *Allergy Clin. Immunol.*, 93, 286 (1994)), but this compound is not adequate enough because of its weak IL-4 production inhibitory activity.

Benzimidazole derivatives have been broadly studied as medicaments. JP-A-3-14579 describes a benzimidazole derivative having an imidazole group and a triazole group, however the compound is only disclosed as a therapeutic agent for heart diseases and for duodenal ulcer and not as an anti-inflammatory agent (the term "JP-A" as used herein means an "unexamined published Japanese patent application"). International Publication No. WO 94/12461 describes a benzimidazole derivative which has PDE (IV) inhibitory activity and is used in various inflammatory diseases, but the benzimidazole derivative is different from the compound of the present invention in terms of the presence or absence of triazole ring on the condensed phenyl ring. Thus, it is not expected to have an effect on both acute and chronic inflammatory diseases.

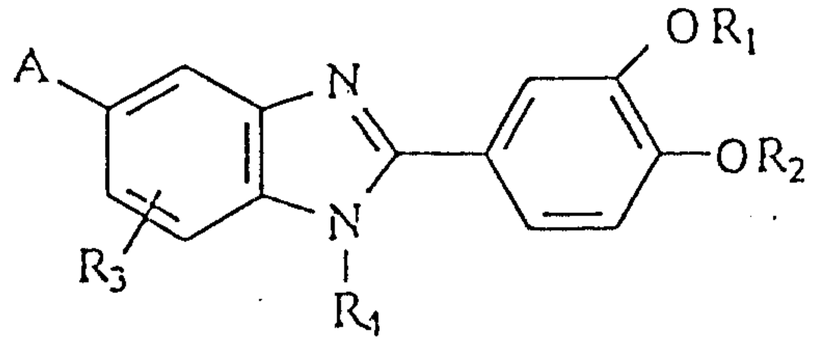
The present invention contemplates providing a compound which has both IL-4 production inhibitory activity and PDE (IV) inhibitory activity and is useful in treating or preventing acute and chronic inflammatory diseases.

SUMMARY OF THE INVENTION

As a result of extensive investigation, the inventors of the present invention have discovered that a compound having the aforementioned properties can be achieved by a novel

benzimidazole derivative in which a triazole group is introduced at the 5-position of the benzimidazole nucleus, and the positions of two alkoxy groups to be substituted on the phenyl group bonded to the 2-position are specified.

Accordingly, the present invention provides to a benzimidazole derivative represented by formula (I):



(I)

[wherein A represents a triazole group; R_1 and R_2 may be the same or different from each other and each represents an aliphatic hydrocarbon radical which may have an alicyclic or aromatic hydrocarbon radical or an alicyclic hydrocarbon radical; R_3 represents a hydrogen atom or a substituent group; and R_4 represents a hydrogen atom or a protective group of the nitrogen atom], or a pharmacologically acceptable salt thereof.

The benzimidazole derivative represented by formula (I), or a pharmacologically acceptable salt thereof, (hereinafter, referred to as "compound of the present invention") has excellent properties of both IL-4 production inhibitory activity and PDE (IV) inhibitory activity and is useful for the treatment of various acute and chronic inflammatory diseases.

Thus, the present invention provides a pharmaceutical composition which comprises an effective amount of the compound of the present invention and a pharmacological carrier.

In particular, there is provided an anti-allergic or anti-inflammatory agent which comprises an effective amount of the compound of the present invention and a pharmacological carrier.

The present invention also provides a use of the compound of the present invention for the production of the

aforementioned pharmaceutical composition, therapeutic or preventive agent for acute and chronic inflammatory diseases and anti-allergic or anti-inflammatory agent.

The present invention further provides a method for treating and/or preventing acute and chronic inflammatory diseases, which comprises the step of administering an effective amount of the aforementioned compound of the present invention to patients. Thus, another aspect of the invention provides use of the benzimidazole derivative of formula I or a pharmacologically acceptable salt thereof as defined above, a pharmaceutical composition containing such a benzimidazole derivative, a therapeutic or preventive agent containing such a benzimidazole derivative, or an anti-allergic or anti-inflammatory agent containing such a benzimidazole derivative, for treating and/or preventing acute and chronic inflammatory diseases.

According to the present invention, examples of the triazole group of A include 1,2,4-triazol-1-yl, 1,2,4-triazol-4-yl, 1,2,3-triazol-1-yl and 1,2,3-triazol-2-yl, of which 1,2,4-triazol-1-yl and 1,2,4-triazol-4-yl are preferred and 1,2,4-triazol-1-yl is more preferred.

Examples of the aliphatic hydrocarbon radical in R_1 or R_2 include straight- or branched-chain lower alkyl groups having 1 to 6 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl and n-hexyl; and straight-or branched-chain lower alkenyl groups having 2 to 6 carbon atoms, such as vinyl, 1-propenyl, allyl, dimethylallyl, isopropenyl, 1-butenyl, 2-butenyl, 1-methyl-2-butenyl, 1, 3-butanedienyl, 1-pentenyl, 2-pentenyl, 2-hexenyl and 1, 4-hexanedienyl; of which straight-or branched-chain lower alkyl groups having 1 to 6 carbon atoms are preferred, and methyl, isopropyl and isopentyl are particularly preferred.

Examples of the aliphatic hydrocarbon radical having an alicyclic hydrocarbon radical according to R_1 or R_2 include the aforementioned aliphatic hydrocarbon radicals further having

monocyclic alicyclic hydrocarbon radicals having 3 to 7 carbon atoms, which may have a straight- or branched-chain saturated lower alkyl group having 1 to 3 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, 3-isopropyl-cyclohexyl, cyclohexenyl, 2-methyl-2-cyclohexenyl, 3-methyl-2-cyclohexenyl, 4-ethyl-2-cyclohexenyl, cycloheptanyl and cycloheptenyl; or having alicyclic hydrocarbon radicals of cross-linked ring or polycyclic system, such as bicyclobutanyl, bicyclooctanyl, norbornyl, norborenyl and indanyl. Preferred radicals are straight- or branched lower alkyl groups having 1 to 6 carbon atoms substituted with a monocyclic alicyclic hydrocarbon radical having 3 to 7 carbon atoms, more preferably cyclopropylmethyl and cyclopentylmethyl.

Examples of the aliphatic hydrocarbon radical having an aromatic hydrocarbon radical according to R_1 or R_2 include the aforementioned aliphatic hydrocarbon radicals further having an aromatic hydrocarbon radical such as phenyl or naphthyl, of which an aliphatic hydrocarbon radical having phenyl group is preferred, and benzyl, phenylethyl, phenylpropyl and cinnamyl are particularly preferred.

Examples of the alicyclic hydrocarbon radical according to R_1 or R_2 include the aforementioned monocyclic alicyclic hydrocarbon radicals having 3 to 7 carbon atoms, which may have a straight- or branched-chain saturated lower alkyl group having 1 to 3 carbon atoms, and the aforementioned alicyclic hydrocarbon radicals of cross-linked ring or polycyclic system, of which monocyclic alicyclic hydrocarbon radicals having 3 to 7 carbon atoms are preferred, and cyclopentyl, whereby cyclopentenyl, cyclohexenyl and cycloheptenyl are particularly preferred.

Among the examples of the present invention, certain compounds have asymmetric carbons and thus exist in optical isomer forms and geometrical isomer forms, depending on the number of asymmetric carbons. All of the optical and geometrical isomers of these compounds are contemplated by the present invention. Although conventional optical resolution

methods can be used for the isolation of optically active substances of the compound of the present invention, the optically active substances can also be obtained by fractionation using HPLC and an optically active column. An example of the optically active column is CHIRALPAK* AD manufactured by Daicel Chemical Industries.

R_3 is a hydrogen atom or a substituent group, and examples of the substituent group include a lower alkoxy group, a lower alkyl group, a hydroxyl group, a nitro group, a cyano group, an amino group and a halogen atom. Preferably, R_3 is a hydrogen atom or a lower alkoxy group. Examples of a lower alkoxy group include straight- or branched-chain alkoxy groups having 1 to 6 carbon atoms, such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy, n-pentyloxy, cyclopentyloxy, isopentyloxy, n-hexyloxy and cyclohexyloxy, of which methoxy, ethoxy and pentyloxy are preferred, and methoxy and n-pentyloxy are more preferred. Examples of a lower alkyl group include straight- or branched-chain alkyl groups having 1 to 6 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl, isopentyl and n-hexyl, of which methl and ethyl are preferred. Examples of a halogen atom include fluorine, chlorine, bromine and iodine.

The R_3 substituent group can be substituted at one of the 4-, 6- and 7-positions of the benzimidazole nucleus, more preferably at the 6-position.

The nitrogen atom-protective group of R_4 may be any group which can be hydrolyzed easily in the living body, and examples include acyl groups such as acetyl, benzoyl and pivaloyl; alkoxycarbonyl groups such as methoxycarbonyl, ethoxycarbonyl and benzyloxycarbonyl; aryloxycarbonyl groups such as phenoxycarbonyl; straight- or branched-chain lower alkyl groups having 1 to 6 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl and n-hexyl; hydroxy lower alkyl groups such as hydroxymethyl and hydroxyethyl; aralkyl groups such as benzyl

* TRADEMARK

and trityl; alkoxyalkyl groups such as methoxymethyl, ethoxymethyl, methoxyethyl and ethoxyethyl; alkoxyalkoxyalkyl groups such as methoxymethoxymethyl, methoxyethoxymethyl, ethoxyethoxymethyl and ethoxyethoxyethyl; and aralkyloxyalkyl groups such as benzyloxymethyl, trityloxymethyl, benzyloxyethyl and trityloxyethyl.

Examples of a pharmacologically acceptable salt of the benzimidazole derivative of the present invention represented by the formula (I) include mineral acid salts such as hydrochloride, sulfate and nitrate, and organic acid salts such as fumarate, maleate, tartarate, toluenesulfonate and methanesulfonate.

The compound of the present invention may exist in tautomer forms based on the benzimidazole skeleton, and such isomers are also included in the present invention.

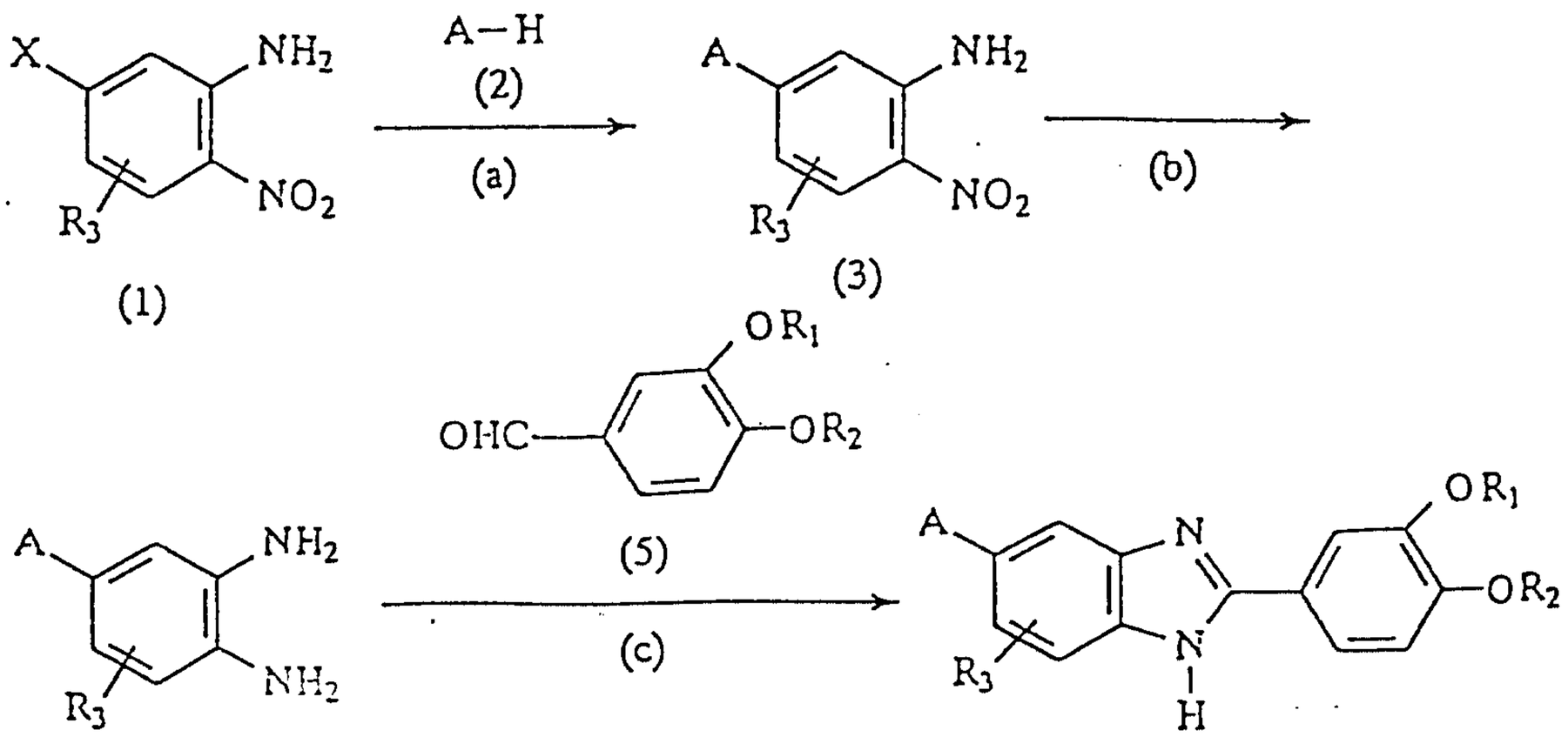
Moreover, the compound of the present invention may be in the form of solvates including hydrates, and amorphous or polymorphic forms.

With respect to the aforementioned formula (I), a benzimidazole derivative, or a pharmacologically acceptable salt thereof, is preferred in which A is 1, 2, 4-triazol-1-yl or 1, 2, 4-triazol-4-yl, R_1 and R_2 may be the same or different from each other and each is a straight- or branched lower alkyl group having 1 to 6 carbon atoms, which may have a monocylcic alicyclic hydrocarbon radical having 3 to 7 carbon atoms, or a monocyclic alicyclic hydrocarbon radical having 3 to 7 carbon atoms, R_3 is a hydrogen atom or a lower alkoxy group and R_4 is a hydrogen atom. Yet a more preferred benzimidazole derivative, or a pharmacologically acceptable salt thereof, is one in which A is 1, 2, 4-triazol-1-yl, R_1 and R_2 may be the same or different from each other and each is methyl, isopropyl, isopentyl, cyclopropylmethyl, cyclopentylmethyl, cyclopentyl, cyclopentenyl, cyclohexenyl or cycloheptenyl, R_3 is a hydrogen atom and R_4 is a hydrogen atom.

The benzimidazole derivative of the present invention represented by the formula (I) can be produced using various

compounds as the starting materials. For example, the benzimidazole derivative is produced by a method shown by the following "reaction process A", in accordance with the methods described in "Heterocyclic Compounds Benzimidazoles and Congeric Tricyclic Compounds, Part 1, 2" edited by P.N. Preston and "Comprehensive Heterocyclic Chemistry, Vol. 5" edited by A.R. Katritzky and C.W. Rees.

(Reaction process A)



In the above formulae, A, R_1, R_2 and R_3 are as defined as above, and X is a halogen atom.

Illustratively, each step of the above reaction process A is carried out in the following manner.

(Step a)

The compound represented by the formula (3) can be produced by allowing the known compound (1) as disclosed, for example, in *Journal of Chemical Society*, Perkin Trans I, 2751 (1994) to react with the known compound (2) in N, N-dimethylformamide in the presence of a base, in accordance with the method disclosed, for example, in *Journal of Medicinal Chemistry*, Vol. 35, No. 23, 4455 - 4463 (1992) and JP-A-3-14579.

Examples of the base include potassium carbonate, sodium carbonate and sodium hydride. In carrying out the reaction, 1 to 2 moles of the compound (2) and base are reacted with 1 mole of the compound (1). The reaction temperature is

generally from about 50 to 150°C, preferably from 100 to 120°C. The reaction time is generally from 0.5 to 24 hours, preferably from 3 to 6 hours.

(Step b)

The compound represented by the formula (4) is produced by reducing the compound represented by the formula (3). The reduction method may be selected from the following methods 1) to 3).

1) The compound is reduced by hydrogenation in an inert solvent in the presence of a catalyst. The choice of inert solvent is not particularly limited, with the proviso being that it does not take part in the reaction. Examples of the inert solvent include methanol, ethanol and ethyl acetate. Examples of the catalyst include palladium-carbon, Raney nickel and platinum oxide. The catalyst is used in an amount of from 0.1 to 0.5 g, based on 1 g of the compound of formula (3). The reaction is carried out under a hydrogen pressure of from 1 to 20 kg/cm^2 at a reaction temperature of from room temperature to 60°C for a period of from 1 to 4 hours.

2) The compound is reduced in an acidic or alkaline solvent in the presence of a metal or metal salt. Examples of the metal and metal salt include zinc, aluminum, tin, iron, stannous chloride, ferrous chloride and ferrous sulfate. Examples of the acidic solvent include acetic acid, hydrochloric acid and sulfuric acid, each alone or as a combination with water, methanol or ethanol. Examples of the alkaline solvent include liquid ammonia, sodium hydroxide aqueous solution and potassium hydroxide aqueous solution. The metal or metal salt is used in an amount of from 3 to 50 moles, preferably from 5 to 10 moles, based on compound (3). The temperature of this reaction is generally carried out from 50 to 150°C, preferably from 80 to 120°C. The reaction is carried out for a period of from 0.5 to 24 hours, preferably from 2 to 6 hours.

3) The compound is reduced by hydrazine in an appropriate solvent in the presence of a metal salt or metal oxide and activated carbon. Examples of the metal salt and

metal oxide include ferric chloride and ferric oxide. The choice of solvent is not particularly limited, with the proviso being that it does not take part in the reaction. Examples of the solvent include methanol, ethanol and ethyl acetate. The metal salt or metal oxide is used in an amount of from 0.6 to 1.0 mole %, activated carbon is used in an amount of 1/10 by weight and hydrazine is used in an amount of from 1.5 to 2.0 moles, based on compound (2). The temperature of this reaction is generally from 50 to 100°C, preferably the reflux temperature of the solvent used. The reaction is carried out for a period of from 0.5 to 24 hours, preferably from 2 to 6 hours.

(Step c)

The benzimidazole derivative of formula (Ia) is produced by allowing the compound of formula (4) to react with the benzaldehyde derivative of formula (5) in an appropriate solvent in the presence of an oxidizing agent or sodium hydrogen sulfite.

The choice of solvent is not particularly limited, with the proviso being that it does not take part in the reaction. Examples of the solvent include methanol, ethanol, dimethylformamide, dimethylacetamide and nitrobenzene. The benzaldehyde derivative (5) is used in an amount of from 1.0 to 1.5 moles, the oxidizing agent is used in an amount of from 1.0 to 2.0 moles and sodium hydrogen sulfite, if used, is used in the same amount, based on compound (4). The reaction temperature is from 70 to 150°C, and the reaction time is from 1 to 18 hours.

The benzaldehyde derivative of formula (5) can be produced in accordance with the method described in *Journal of Medicinal Chemistry*, Vol. 37, pp. 1696 - 1703 (1994), using vanillin or isovanillin as the material and carrying out its alkylation with a corresponding alkyl halide in N, N-dimethylformamide in the presence of a base. Examples of the base include potassium carbonate, sodium carbonate, sodium hydroxide, potassium hydroxide and sodium hydride. In carrying out the reaction, 1 to 2 moles of an alkyl halide and 1 to 2

moles of a base are reacted with 1 mole of the starting material. The temperature of this reaction is generally from 50 to 150°C, preferably from 60 to 90°C. The reaction time is generally from 0.5 to 24 hours, preferably from 4 to 8 hours.

The derivative can also be produced by carrying out alkylation of a corresponding alcohol compound with triphenylphosphine and diethyl azodicarboxylate in tetrahydrofuran under dehydration. In carrying out the reaction, 1 to 2 moles of the alcohol compound, triphenylphosphine and diethyl azodicarboxylate are used based on 1 mole of the starting material. The reaction temperature is from room temperature to reflux temperature of the solvent, and the reaction time is from 1 to 24 hours.

The compound (Ia) of the present invention thus obtained by the aforementioned reaction process A may have a protective group introduced at the nitrogen atom on the benzimidazole skeleton in accordance with ordinary methods as disclosed, for example, in International Publication No. WO93/14083.

The compound of the present invention thus obtained by the aforementioned reaction process A can be easily isolated and purified from the reaction mixture using separation and purification means such as column chromatography, recrystallization and evaporation under reduced pressure.

The pharmaceutical composition, therapeutic or preventive agent for acute and chronic inflammatory diseases and anti-allergic or anti-inflammatory agent of the present invention can be made into pharmaceutical preparation compositions in the usual way using appropriate pharmaceutical carriers. Examples of carriers to be used include those which are generally used in drugs, such as a filler, a binder, a disintegrating agent, a lubricant, a coloring agent, a flavor corrective, an order corrective and a surface active agent.

The dosage form of the pharmaceutical composition of the present invention, when used as a therapeutic agent in mammals including humans, is not particularly limited and can

be selected depending on each therapeutic purpose. Examples include parenteral preparations such as injections, suppositories, external preparations (e.g., ointments and adhesives) and aerosols, and oral preparations such as tablets, coated tablets, powders, granules, capsules, solutions, pills, suspensions and emulsions.

The aforementioned various pharmaceutical preparations can be made by conventional methods well known in the field.

In preparing oral solid dosage forms such as tablets, powders and granules, examples of the carriers to be used include fillers such as lactose, sucrose, sodium chloride, glucose, urea, starch, calcium carbonate, kaolin, crystalline cellulose, silicic acid, methyl cellulose, glycerol, sodium alginate and acacia, binders such as simple syrup, glucose solution, starch solution, gelatin solution, polyvinyl alcohol, polyvinyl ether, polyvinyl pyrrolidone, carboxymethyl cellulose, shellac, methyl cellulose, ethyl cellulose, hydroxypropyl cellulose, water, ethanol and potassium phosphate, disintegrating agents such as dry starch, sodium alginate, agar powder, laminaran powder, sodium bicarbonate, calcium carbonate, polyoxyethylene sorbitan fatty acid esters, sodium lauryl sulfate, stearic acid monoglyceride, starch and lactose, disintegration inhibitors such as sucrose, stearic acid, cacao butter and hydrogenated oil, absorption accelerating agents such as quaternary ammonium base and sodium lauryl sulfate, moisture keeping agents such as glycerol and starch, adsorbents such as starch, lactose, kaolin, bentonite and colloidal silica and lubricant such as purified talc, stearic acid salt, boric acid powder and polyethylene glycol. If required, tablets can be made into coated tablets using usual coatings, such as sugar coated tablets, gelatin coated tablets, enteric coated tablets, film coated tablets, double-layer tablets and multi-layer tablets. In preparing the dosage form of pills, examples of the carriers to be used include fillers such as glucose, lactose, starch, cacao butter, hardened plant oil, kaolin and talc, binders such as powdered acacia, powdered tragacanth, gelatin

and ethanol, and disintegrating agents such as laminaran and agar.

Capsules are prepared by mixing the active ingredient with the aforementioned various carriers and filling appropriate capsules such as hard gelatin capsules or soft capsules with the mixture.

The dosage form of suppositories can be prepared by adding an appropriate absorption accelerating agent to carriers such as polyethylene glycol, cacao butter, lanolin, higher alcohol, higher alcohol esters, gelatin, semi-synthetic glyceride and Witepsol (tradename, manufactured by Dynamite Novel).

Examples of the carriers to be used in preparing the dosage form of injections include diluents such as water, ethyl alcohol, macrogol, propylene glycol, ethoxylated isostearyl alcohol, polyoxylated isostearyl alcohol and polyoxyethylene sorbitan fatty acid esters, pH adjusting agents and buffers such as sodium citrate, sodium acetate and sodium phosphate, and stabilizing agents such as sodium pyrosulfite, ethylenediaminetetraacetic acid, thioglycollic acid and thiolactic acid. In this case, the pharmaceutical preparation may contain sodium chloride, glucose or glycerol in an amount sufficient enough for preparing isotonic solution. It may also contain other additives such as a solubilization assisting agent, a soothing agent and a local anaesthetic. By adding these carriers, subcutaneous, intramuscular and intravenous injections can be produced in the usual way.

The liquid preparations may be aqueous or oily suspensions, solutions, syrups or elixirs, and may be prepared in the usual way, using general additive agents.

When the dosage form of ointments such as pastes, creams and gels are prepared, materials which are generally used, such as a base, a stabilizing agent, a moistening agent and a preservative, are formulated and mixed in relation to each purpose and made into respective preparations. Examples of the base to be used include white petrolatum, paraffin, glycerol,

a cellulose derivative, polyethylene glycol, silicon and bentonite. Examples of the preservative to be used include methyl parahydroxybenzoate, ethyl parahydroxybenzoate and propyl parahydroxybenzoate.

Adhesive preparations can be produced in the usual way by coating the aforementioned ointments such as creams, gels or pastes on a conventional support. Examples of a suitable support include woven or non-woven fabrics made of cotton, rayon or chemical fiber and films and foam sheets of polymers such as soft vinyl chloride, polyethylene and polyurethane.

The amount of the compound of the present invention to be contained in the aforementioned pharmaceutical preparations varies depending on various conditions such as dosage form, route of administration and dosage regimen. Thus, the amount cannot be defined in a wholesale manner and may be selected from a broad range for each case; however, the pharmaceutical preparations should contain the compound generally in an amount of approximately from 1 to 70% by weight.

Administration methods of the aforementioned pharmaceutical preparations, such as intestinal application, oral administration, rectal administration, buccal application and percutaneous absorption, are not particularly limited but optionally decided depending, for example, on the dosage form, the age, sex and other conditions of each patient and the degree of symptoms of each patient. For example, tablets, pills, solutions, suspensions, emulsions, granules and capsules are used for oral administration, and suppositories are used for rectal administration. In the case of intravenous injections, the preparation may be used intact or after mixing with a usual replacement solution containing glucose or amino acids or, as occasion demands, administered alone by intraarterial infusion, intramuscular injection, intracutaneous injection, subcutaneous injection or intraperitoneal injection. Ointments are applied, for example, to the skin or oral mucous membrane.

The dose of the active ingredient of the pharmaceutical preparations of the present invention is selected

based on the application method, the age, sex and other conditions of each patient, as well as the kind of the compound of the present invention to be administered and other conditions. In general, the dose may be within the range of from 0.1 to 1,000 mg/kg/day, preferably from 0.5 to 500 mg/kg/day. The pharmaceutical preparations of the present invention can be administered by dividing the daily dose recited above into 1 to 4 doses per day.

BRIEF DESCRIPTION OF THE DRAWING

Fig. 1 is a graph showing powder x-ray diffraction of the compound 1-b obtained in Inventive Example 1b.

DETAILED DESCRIPTION OF THE INVENTION

The following reference, inventive test examples are provided for the purposes of illustration of the novel compounds of the present invention represented by the formula (1),and are not intended to limit the scope of the invention as defined by the appended claims.

[Reference Example 1] Synthesis of 5-(1,2,4-triazol-1-yl)-2-nitroaniline

A 10.0 g portion of 5-chloro-2-nitroaniline, 8.0 g of 1,2,4-triazole and 16.0 g of potassium carbonate were suspended in 50 ml of DMF and stirred for 5 hours while heating at 130°C. The reaction solution was poured into ice water, and the precipitated crystals were collected by filtration and washed with purified water. By washing the crystals with methanol, 10.0 g (84% in yield) of the subject compound was obtained. Its physical property values are shown below.

m.p. 259 - 261°C

^{1}H-NMR (DMSO-d_6) : δ (ppm) 7.18 (1 H, dd, J = 2.3, 9.4 Hz), 7.55 (1 H, d, J = 2.3 Hz), 7.69 (2 H, br-s), 8.15 (1 H, d, J = 9.2 Hz), 8.30 (1, H, s), 9.37 (1 H, s)

[Reference Example 2] Synthesis of 4-(1,2,4-triazol-1-yl)-o-phenylenediamine

(1) A 20.0 g portion of 5-(1,2,4-triazol-1-yl)-2-nitroaniline, obtained by the method of Reference Example 1, was suspended in 400 ml of methanol, and the suspension was mixed with 5.0 g of 10% palladium-carbon catalyst and subjected to hydrogenation using a Parr-type reducing apparatus. When absorption of hydrogen was completed, the reaction solution was mixed with activated carbon and filtered through Celite*. The solvent was evaporated from the resulting filtrate. The residue thus obtained was mixed with ethyl acetate and the subsequently formed crystals were collected by filtration, thereby resulting in 14.0 g (82% in yield) of the subject compound. Its physical property values are shown below.

m.p. 180 - 182°C

^{1}H-NMR (DMSO-d_6) : δ (ppm) 4.72 (2 H, br-s), 4.82 (2 H, br-s), 6.57 (1 H, d, J = 8.3 Hz), 6.77 (1 H, dd, J = 2.5, 8.3 Hz), 6.92 (1 H, d, J = 2.5Hz), 8.07 (1 H, s), 8.89 (1 H, s)

(2) A 49.5g portion of 5-(1,2,4-triazol-1-yl)-2-nitroaniline, obtained by the method of Example 1, was suspended in 250 ml of 95% ethanol, and the suspension was mixed with 37.0 ml of 5 mol/1 sodium hydroxide aqueous solution and heated to 80°C. Next, a total of 54.0 g of zinc powder was added thereto in 5 g portions at intervals of 10 minutes. After 1 hour of heating under reflux, the reaction mixture was filtered through Celite* while it was hot, and then the resulting filtrate was cooled.

Thereafter, the precipitated crystals were collected by filtration and washed with cold ethanol to obtain 37.6 g (89% in yield) of the subject compound. Its physical property values coincided with the aforementioned data.

(3) A 20.5g portion of 5-(1,2,4-triazol-1-yl)-2-nitroaniline, obtained by the method of Example 1, was suspended in 200 ml of methanol, and the suspension was mixed with 2.2 g of activated carbon and 160 mg of ferric chloride hexahydrate and refluxed for 15 minutes. Next, to this was added dropwise 15 g of 85% hydrazine monohydrate while continuing the reflux. After 2 hours of reflux, insoluble matter was removed by Celite*

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filtration, the solvent was evaporated from the filtrate, ethyl acetate was added to the resulting residue and then the crystals thus formed were collected by filtration to obtain 16.4 g (94% in yield) of the subject compound. Its physical property values coincided with the aforementioned data.

[Inventive Example 1a] Synthesis of 2-(3-isopropoxy-4-methoxyphenyl)-5-(1,2,4-triazol-1-yl) benzimidazole [compound 1-a]

(1) A 5.98 g portion of a known compound 3-isopropxy-4-methoxybenzaldehyde was added to 4.49 g of 4-(1,2,4-triazol-1-yl)-o-phenylenediamine obtained in Reference Example 2, and the mixture was stirred for 18 hours in 37 ml of nitrobenzene while heating at 150°C. After cooling, nitrobenzene was evaporated under a reduced pressure. By crystallizing the resulting residue with ethyl acetate/hexane, 4.90 g (55%) of the subject compound was obtained. Its physical property values are shown as the Compound No. 1 in Table 1.

(2) Under reflux, 20 ml of methanol solution containing 4.27 g of 3-isopropoxy-4-methoxybenzaldehyde and 10.81 g of ferric chloride hexahydrate was added dropwise to 35 ml of methanol solution containing 3.50 g of 4-(1,2,4-triazol-1-yl)-o-phenylenediamine obtained in Reference Example 2. The resulting mixture was refluxed for 1 hour and then cooled, and the insoluble matter was collected by filtration. This was suspended in ethyl acetate/water and alkalified with liquid ammonia, and then the insoluble matter was removed by Celite* filtration. The ethyl acetate layer was collected and dried over magnesium sulfate, and then the solvent was evaporated. By crystallizing the resulting residue with ethyl acetate/hexane, 4.92 g (70%) of the subject compound was obtained. Its physical property values coincided with the data obtained in the above step (1).

(3) A mixture consisting of 1.75 g of 4-(1,2,4-triazol-1-yl)-o-phenylenediamine obtained in Reference Example 2, 1.56 g of sodium hydrogen sulfite and 17 ml of dimethylacetamide was heated to 150°C, to which was subsequently

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added dropwise 17 ml of dimethylacetamide solution containing 1.94 g of 3-isopropoxy-4-methoxybenzaldehyde. After 2 hours of the reaction at the same temperature, the solvent was evaporated under a reduced pressure. The resulting residue was shaken in ethyl acetate and 10% sodium carbonate aqueous solution to effect separation of layers, and the resulting ethyl acetate layer was collected. The ethyl acetate layer was dried with magnesium sulfate, and then the solvent was evaporated. By crystallizing the resulting residue with ethyl acetate/hexane, 2.37 g (80% of the subject compound was obtained. Its physical property values coincided with the data obtained in the above step (1).

[Inventive Example 1b] Synthesis of amorphous 2-(3-isopropoxy-4-methoxyphenyl)-5-(1,2,4-triazol-1-yl) benzimidazole [compound 1-b]

A 20 g portion of the subject compound obtained by the above-mentioned production method was suspended in 100 ml of water and heated to 80°C. Next, this was dissolved by adding 70 ml of methanol and cooled to room temperature, and then the resulting precipitate was collected by filtration. This was air-dried and then heat-dried on phosphorous pentoxide under a reduced pressure to obtain 18.37 g (92%) of the subject compound. Its physical property values are shown below. Also, its powder X-ray diffraction is shown in Fig. 1, which confirmed that the thus obtained compound is amorphous.

m.p. 118 - 126°C

Elemental analysis data for $C_{19}H_{19}N_5O_2 \cdot O.2H_2O$:

	H	C	N
Calcd.	5.54	64.54	19.84
Found	5.49	64.53	20.02

[Inventive Example 2] Synthesis of 2-(3-cyclopentyloxy-4-methoxyphenyl)-5-(1,2,4-triazol-1-yl) benzimidazole [compound 2]

The procedure of Inventive Example 1a-(1) was repeated, except that 1.00 g of 3-cyclopentyloxy-4-methoxybenzaldehyde was

used instead of 3-isopropoxy-4-methoxybenzaldehyde, thereby obtaining 722 mg (34%) of the subject compound. Its physical property values are shown in Table 1.

[Inventive Example 3] Synthesis of 2-(4-cyclopentyloxy-3-methoxyphenyl)-5-(1,2,4-triazol-1-yl) benzimidazole [compound 3]

The procedure of Inventive Example 1a-(1) was repeated, except that 2.00 g of 4-cyclopentyloxy-3-methoxybenzaldehyde was used instead of 3-isopropoxy-4-methoxybenzaldehyde, thereby obtaining 1.46 g (34%) of the subject compound. Its physical property values are shown in Table 1.

[Inventive Example 4] Synthesis of 2-(3,4-dimethoxyphenyl)-5-(1,2,4-triazol-1-yl) benzimidazole [compound 4]

The procedure of Inventive Example 1a-(1) was repeated, except that 949 mg of veratraldehyde was used instead of 3-isopropoxy-4-methoxybenzaldehyde, thereby obtaining 523 mg (28%) of the subject compound. Its physical property values are shown in Table 1.

[Inventive Example 5] Synthesis of 2-(4-methoxy-3-n-pentyloxyphenyl)-5-(1,2,4-triazol-1-yl) benzimidazole [compound 5]

The procedure of Inventive Example 1a-(1) was repeated, except that 1.37 g of 4-methoxy-3-n-pentyloxybenzaldehyde was used instead of 3-isopropoxy-4-methoxybenzaldehyde, thereby obtaining 2.27 g (53%) of the subject compound. Its physical property values are shown in Table 1.

[Inventive Example 6] Synthesis of 2-(3,4-dimethoxyphenyl)-6-methoxy-5-(1,2,4-triazol-1-yl) benzimidazole [compound 6]

A 1.06 g portion of 4-(1,2,4-triazol-1-yl)-5-methoxy-o-phenylenediamine obtained in the same manner as described in Reference Examples 1 and 2 was allowed to react with 949 mg of veratraldehyde by the method of Inventive Example 1a-(1), thereby obtaining 454 mg (25%) of the subject compound. Its physical property values are shown in Table 1.

[Inventive Examples 7 to 21]

Each compound of the Compound Nos. 7 to 21 described in Table 1 was synthesized by the same method of Inventive Example 1a-(3), with their physical property values also shown in Table 1.

[Inventive Examples 22 to 26]

Each compound of the Compound Nos. 23 to 27 described in Table 1 was synthesized by the same method of Inventive Example 1a-(3), with their physical property values also shown in Table 1.

[Inventive Example 27] 2-{3-(2-Cyclohexenyloxy)-4-methoxyphenyl}-5-(1,2,4-triazol-1-yl) benzimidazole [compound 22]

The subject compound having low melting point was obtained from the high melting point compound obtained in Inventive Example 14, in accordance with the method of Inventive Example 1b. Its physical property values are shown in Table 1.

[Inventive Example 28] Resolution of optically active substances of 2-[3(2-cyclohexenyloxy)-4-methoxyphenyl]-5-(1,2,4-triazol-1-yl) benzimidazole [compound 14]

Using an optically active column, the compound 14 was fractionated by HPLC under the following conditions. As a result, the (R)-isomer of the compound 14 was obtained by collecting fractions of a retention time of about 35 minutes. Also, its (S)-isomer was obtained by collecting fractions at a retention time of about 40 minutes.

Column: CHIRALPAK* AD (mfd. by Daicel Chemical Industries)

Developing solvent: n-hexane/denatured ethanol = 90/10

Flow rate: 1.0 ml/min (L-6200 Intelligent Pump (mfd. by Hitachi Ltd.) was used)

Temperature: 40°C

Detection: UV 254 nm (L-4000 UV Detector (mfd. by Hitachi Ltd.) was used)

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Table 1

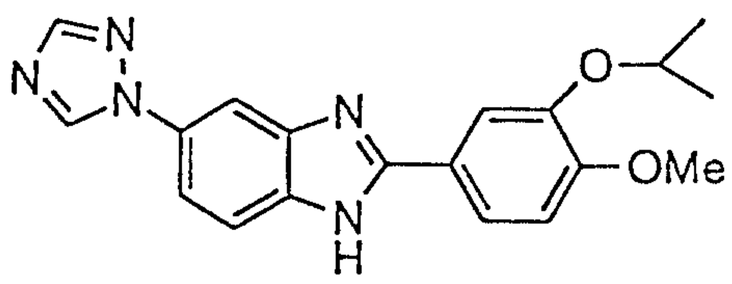
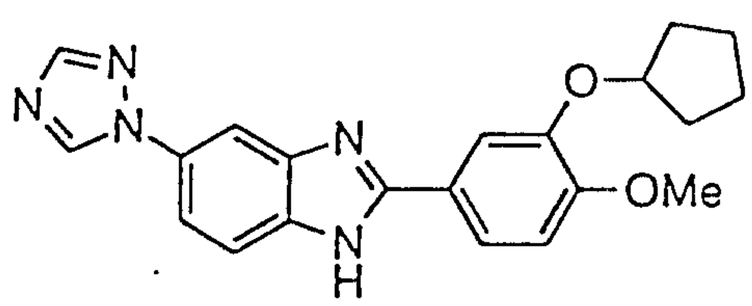
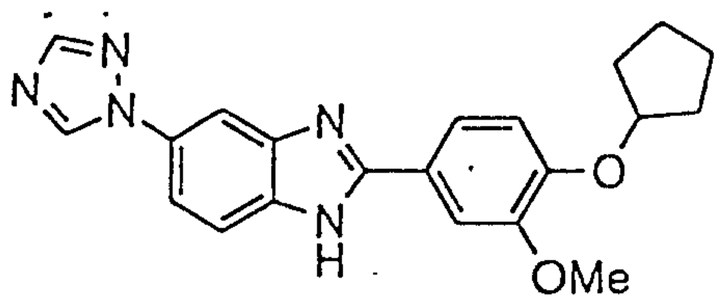
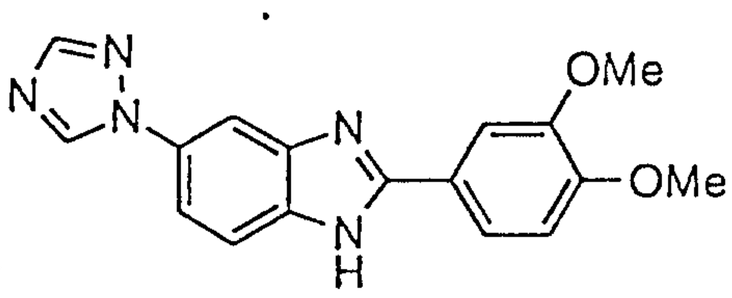
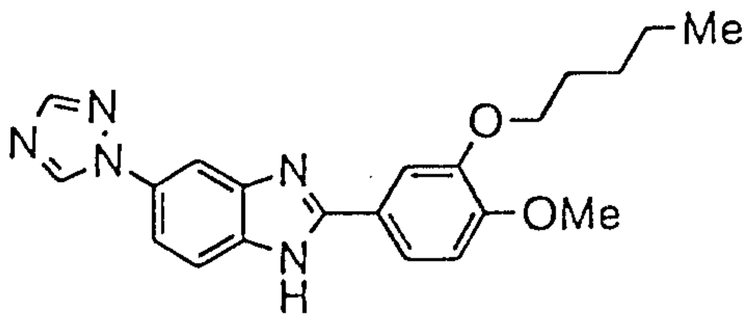
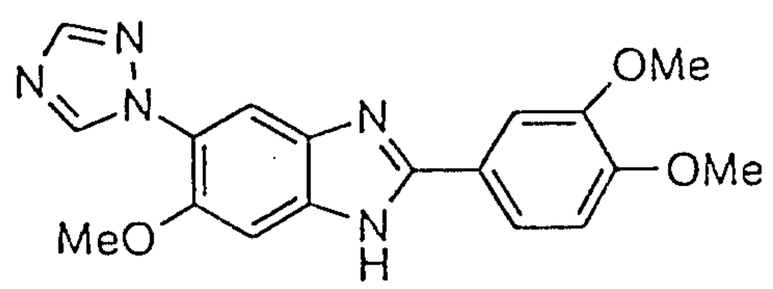
Comp. No.	Structure	Melting Point and NMR Chemical Shift Value
1		m.p. 187-188°C ^{1}H-NMR (DMSO-d_6) : δ (ppm) 1.34 (6H, d, J=6.1Hz), 3.85 (3H, s), 4.68 (1H, m), 7.16 (1H, d, J=7.0Hz), 7.66-7.79 (4H, m), 8.00 (1H, br-s), 8.23 (1H, s), 9.28 (1H, s), 13.00 (1H, br)
2		m.p. 122-127°C ^{1}H-NMR ($CDCl_3$) : δ (ppm) 1.55(2H, br-s), 1.79-1.86(6H, m), 3.89(3H, s), 4.79(1H, br-s), 6.94(1H, d, J=8.3Hz), 7.52-7.86(5H, m), 8.12(1H, s), 8.55(1H, s)
3		m.p. 194-196°C ^{1}H-NMR ($CDCl_3$) : δ (ppm) 1.60-1.98(8H, m), 3.86(3H, s), 4.83(1H, m), 6.95(1H, d, J=8.3Hz), 7.52-8.00(5H, m), 8.13(1H, s), 8.55(1H, s)
4		m.p. 213-215°C ^{1}H-NMR (DMSO-d_6) : δ (ppm) 3.86(3H, s), 3.90(3H, s), 7.16(1H, d, J=8.3Hz), 7.64-7.80(4H, m), 7.90(0.5H, br-s), 8.10(0.5H, br-s), 9.28(1H, d, J=17Hz), 13.04(1H, br)
5		m.p. 185-187°C ^{1}H-NMR (DMSO-d_6) : δ (ppm) 0.92 (3H, t, J=7.1Hz), 1.35-1.50 (4H, m), 1.76-1.87 (2H, m), 3.86 (3H, s), 4.05-4.10 (2H, m), 7.16 (1H, d, J=8.9Hz), 7.67 (1H, dd, J=1.7, 8.6Hz), 7.70 (1H, d, J=8.7Hz), 7.76-7.78 (2H, m), 8.23 (1H, s), 9.28 (1H, s), 13.01 (1H, br)
6		m.p. 242-246°C ^{1}H-NMR (DMSO-d_6) : δ (ppm) 3.33(3H,s) , 3.85(3H, s), 3.89(3H, s), 7.14(1H, d, J=8.3Hz), 7.35(1H,br-s), 7.72-7.76(3H, m), 8.19(1H, s), 8.87(1H,s), 12.89(1H, br)

Table 1 (continued)

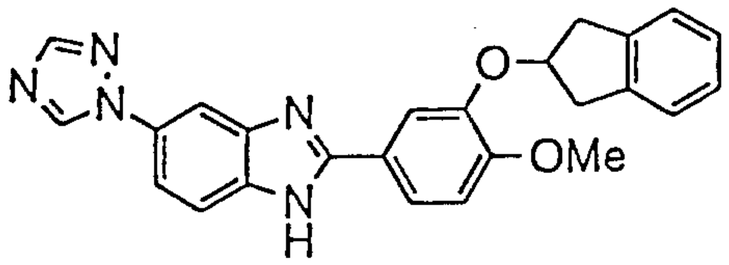
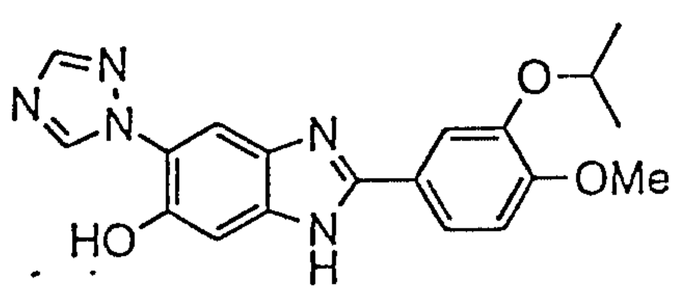
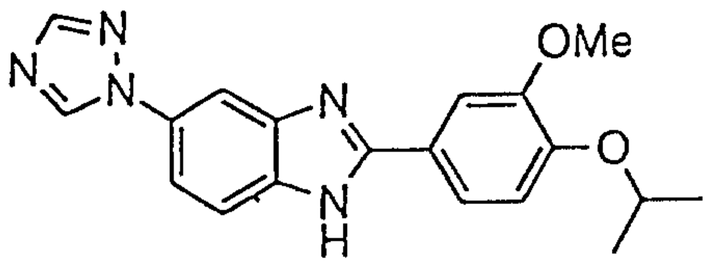
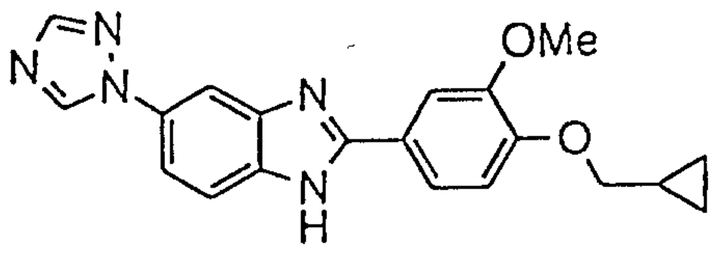
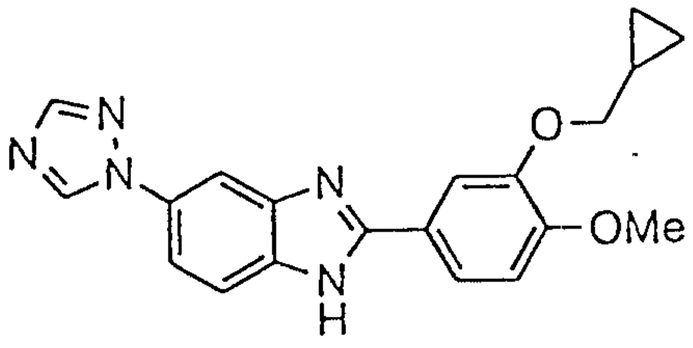
Comp. No.	Structure	Melting Point and NMR Chemical Shift Value
7		m.p. 134-136°C ^{1}H-NMR (DMSO-d_6) δ(ppm): 13.05(1H, br),9.29(1H, s), 8.24(1H,s), 8.00(1H,s), 7.85-7.69(4H, m), 7.32-7.28(2H, m), 7.23-7.15(3H, m), 5.34(1H, m), 3.80(3H, s), 3.45(2H, dd, J=17.2, 5.9Hz), 3.12(2H, dd, J=17.2, 2.3Hz)
8		m.p. 163-167°C ^{1}H-NMR (DMSO-d_6) δ(ppm): 12.75(1H, br),10.20(1H, s), 8.92(1H,s), 8.18(1H,s), 7.71-7.68(3H, m), 7.19(1H, s), 7.13(1H, d, J=9.2Hz), 4.67(1H, m), 3.83(3H, s), 1.32(6H, d, J=5.9Hz)
9		m.p. 185-186°C ^{1}H-NMR (DMSO-d_6) δ(ppm): 9.29(1H,s), 8.24(1H,s), 8.01(1H,br-s), 7.80-7.65(4H, m), 7.16(1H, d, J=9.0Hz), 4.69(1H, m), 3.89(3H, s), 1.31(6H, d, J=6.3Hz)
10		m.p. 118-120°C ^{1}H-NMR (DMSO-d_6) δ(ppm): 13.04(1H,br), 9.29(1H,s), 8.24(1H,s), 8.00(1H,br), 7.80-7.69(4H, m), 7.11(1H, d, J=8.6Hz), 3.91(3H, s), 3.90(2H, d, J=6.9Hz), 1.27(1H, m), 0.64-0.57(2H, m), 0.38-0.32(2H,m)
11		m.p. 193-194°C ^{1}H-NMR (DMSO-d_6) δ(ppm): 13.01(1H,br), 9.28(1H,s), 8.24(1H,s), 7.99(1H,br), 7.79-7.68(4H,m), 7.16(1H, d, J=8.4Hz), 3.93(2H, d, J=6.9Hz), 3.87(3H, s), 1.30(1H, m), 0.66-0.59(2H, m), 0.41-0.37(2H,m)

Table 1 (continued)

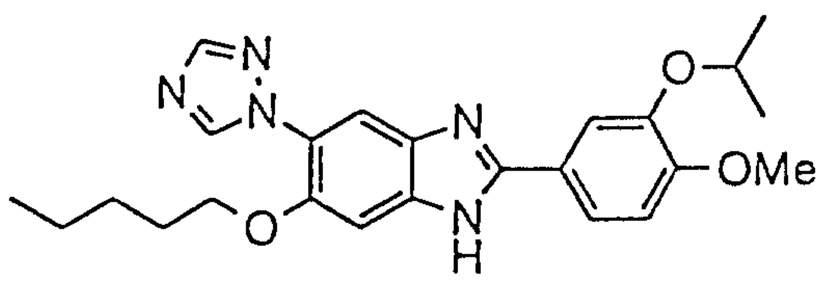
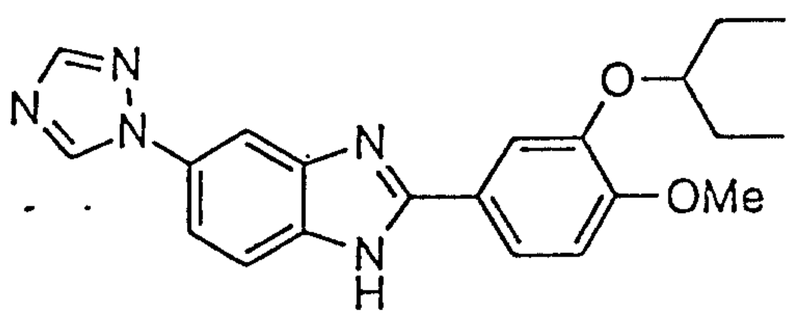
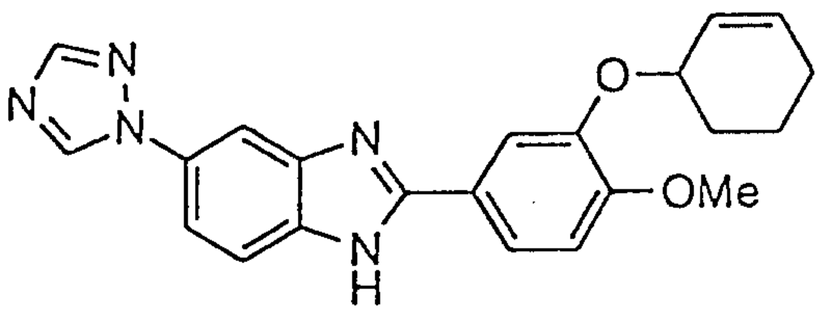
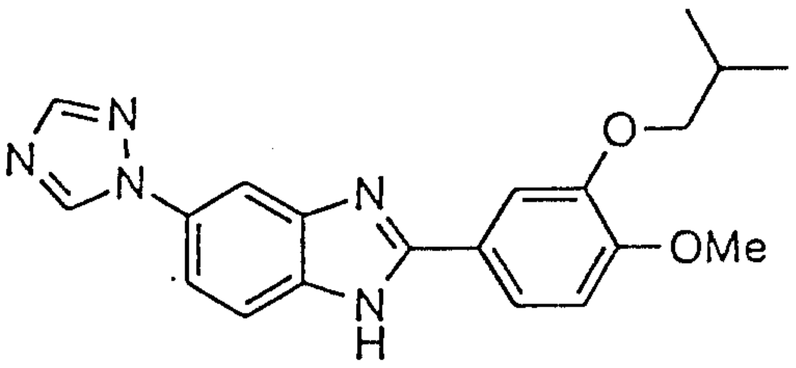
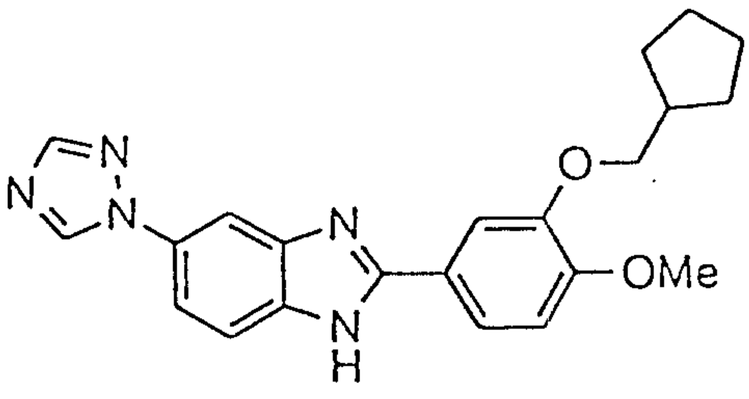
Comp. No.	Structure	Melting Point and NMR Chemical Shift Value
12		m.p. 161-164°C ^{1}H-NMR (DMSO-d_6) δ(ppm): 12.85(1H,br), 8.84(1H,s), 9.19(1H,s), 7.75(2H,s), 7.73(1H, s), 7.34(1H, br), 7.14(1H, d, J=8.9Hz), 4.67(1H, m), 4.09(2H, t, J=6.3Hz), 3.84(3H, s), 1.70(2H, m), 1.33(6H, d, J=6.1Hz), 1.32(4H, m), 0.86(3H, t, d=6.7Hz)
13		m.p. 143-146°C ^{1}H-NMR (DMSO-d_6) δ(ppm): 13.01(1H,br), 9.28(1H,s), 8.24(1H,s), 8.00(1H,br), 7.79-7.67(4H,m), 7.16(1H, d, J=8.9Hz), 4.32(1H, m), 3.86(3H, s), 1.99-1.63(4H,m), 0.98-0.92(6H,m)
14		m.p. 194-195 °C ^{1}H-NMR (DMSO-d_6) δ(ppm): 13.0(1H,br), 9.28(1H,s), 8.23(1H,s), 7.99(1H,br), 7.81-7.65(4H,m), 7.17(1H, d, J=8.2Hz), 6.00-5.86(2H, m), 4.93(1H, m), 3.85(3H, s), 2.06-1.65(6H, m)
15		m.p. 201°C ^{1}H-NMR (DMSO-d_6) δ(ppm): 13.02(1H,br), 9.28(1H,s), 8.24(1H,s), 7.98(1H,br), 7.80-7.77(4H,m), 7.15(1H, m)3.86(3H, s), 3.86(2H, d,J=6.8Hz), 2.10(1H,m), 1.03(6H,d, J=6.6Hz)
16		m.p. 204-206°C ^{1}H-NMR (DMSO-d_6) δ(ppm): 13.02(1H,br), 9.28(1H,s), 8.23(1H,s), 7.99(1H,br), 7.79-7.66(4H,m), 7.15(1H,m), 3.86(3H, s), 2.38(1H,m), 1.85-1.80(2H, m), 1.76-1.54(4H, m), 1.43-1.36(2H, m)

Table 1 (continued)

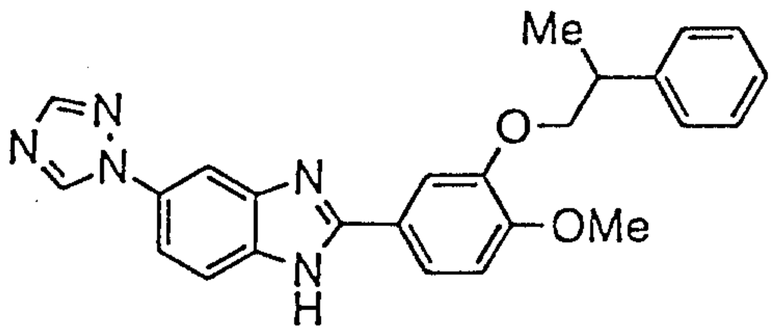
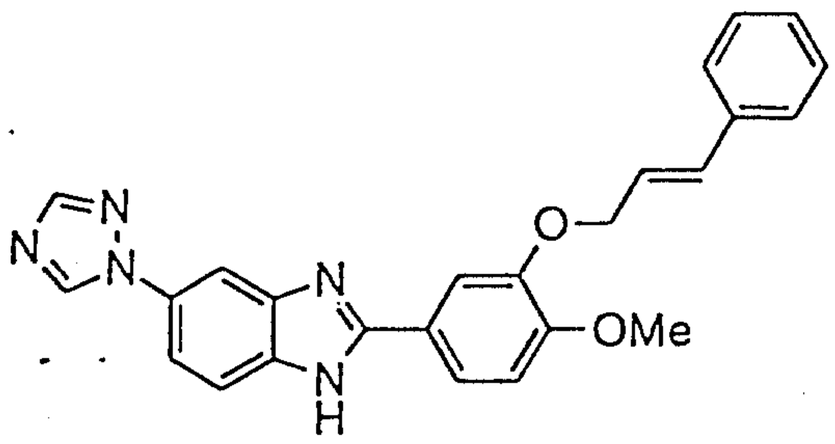
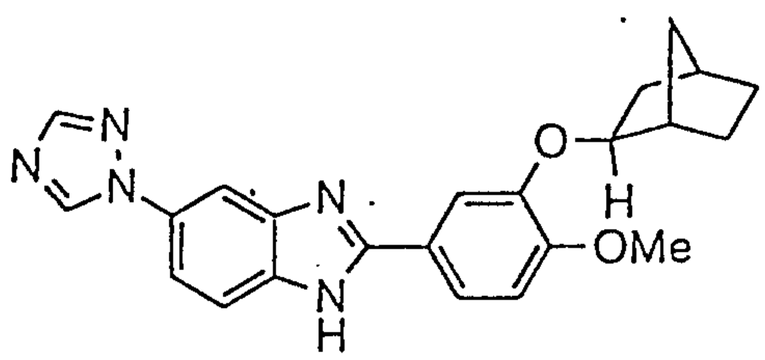
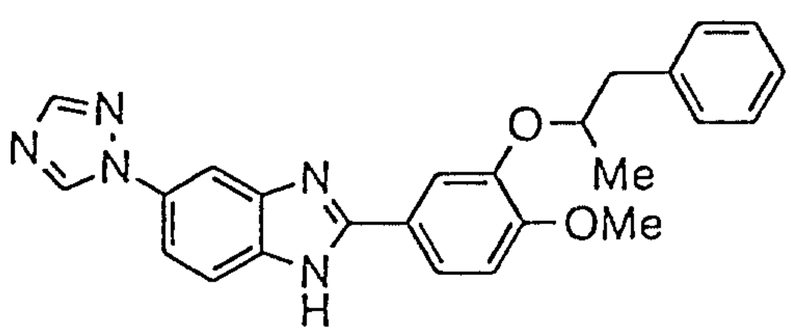
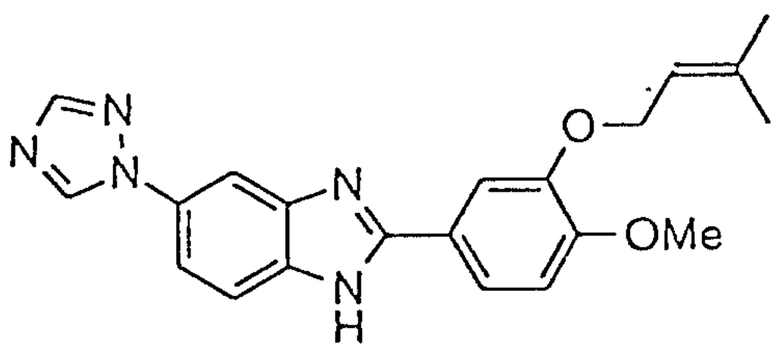
Comp. No.	Structure	Melting Point and NMR Chemical Shift Value
17		m.p. 191-192°C ^{1}H-NMR (DMSO-d_6) δ(ppm): 13.00(1H,br), 9.27(1H,s), 8.23(1H,s), 8.00(1H,br), 7.81-7.68(4H,m), 7.43-7.22(4H, m), 7.45(1H, d, J=9.0Hz), 4.22(1H, m), 3.84(3H, s), 3.29(1H, m), 1.39(3H, d, J=7.1Hz)
18		m.p. 214-216°C ^{1}H-NMR (DMSO-d_6) δ(ppm): 13.04(1H,br), 9.29(1H,s), 8.24(1H,s), 8.00(1H,br), 7.87-7.18(10H,m), 6.83(1H, d, J=16.0Hz), 6.58(1H, td, J=16.0, 5.9Hz), 4.84(2H, d, J=5.4Hz), 3.88(3H, s)
19		m.p. 232-234°C ^{1}H-NMR (DMSO-d_6) δ(ppm): 13.01(1H,br-s), 9.29(1H,s), 8.24(1H,s), 8.01(1H,br-s), 7.78-7.66(4H,m), 7.15(1H,d, J=8.6Hz), 4.36(1H, d, J=6.1Hz), 3.84(3H, s), 2.44(1H,br-s), 2.32(1H, s), 1.90-1.87(2H,m), 1.66-1.44(4H, m), 1.27-1.15(3H, m)
20		m.p. 101-105°C ^{1}H-NMR (DMSO-d_6) δ(ppm): 13.00(1H,br), 9.28(1H,s), 8.23(1H,s), 8.00(1H,br), 7.80-7.68(4H,m), 7.36-7.15(6H, m), 4.77(1H, m), 3.85(3H, s), 3.09(1H, dd,J=13.7, 6.3Hz), 2.91(1H, dd, J=13.5, 6.3Hz), 1.27(3H, d, J=5.9Hz)
21		m.p. 197-199°C ^{1}H-NMR (DMSO-d_6) δ(ppm): 13.02(1H,br-s), 9.29(1H,s), 8.25(1H,s), 8.01(1H,br), 7.82-7.67(4H, m), 7.15(1H,d,J=8.6Hz), 5.52(1H, m), 4.63(1H, d, J=6.8Hz), 3.85(3H, s), 1.77(6H, d, J=5.1Hz)

Table 1 (continued)

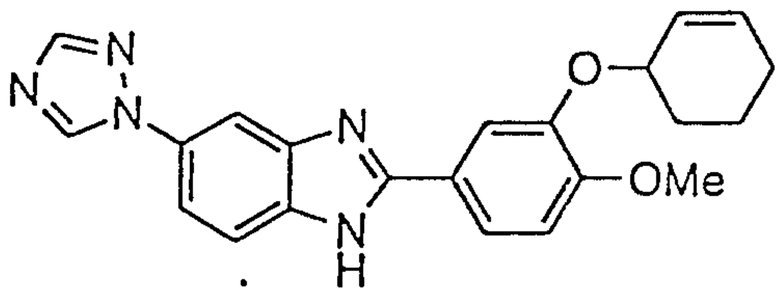
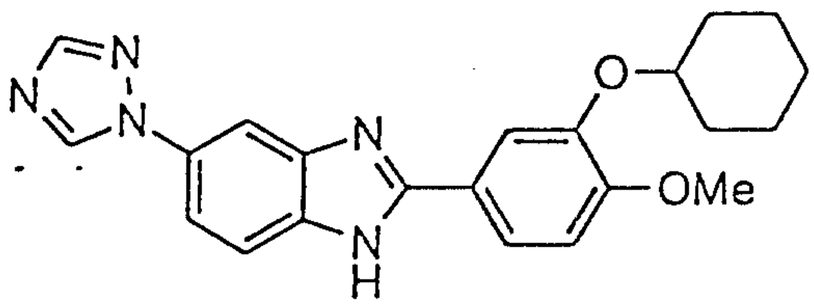
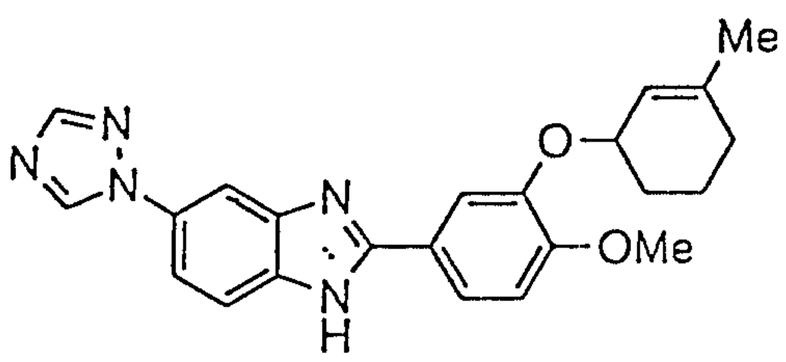
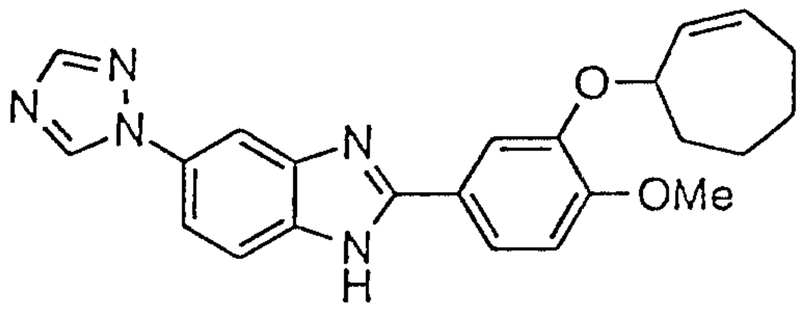
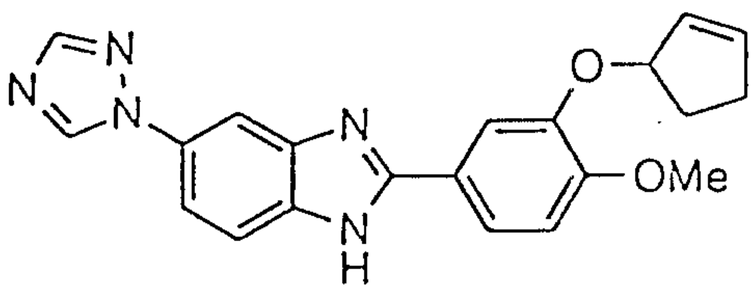
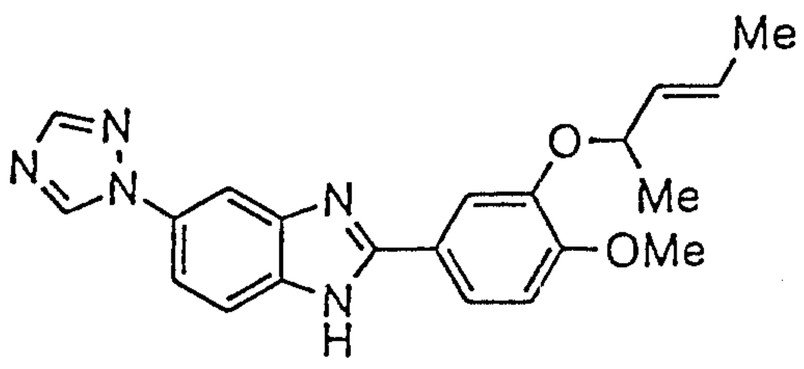
Comp. No.	Structure	Melting Point and NMR Chemical Shift Value
22		m.p. 122-123 °C ^{1}H-NMR (DMSO-d_6) δ(ppm): 13.01(1H, d, J=8.2Hz), 9.28(1H, d, J=10.7Hz), 8.24(1H, d, J=4.9Hz), 8.10-7.63(4H, m), 7.17(1H,d,J=8.2Hz), 5.97(1H, dt, J=7.1, 3.2Hz), 5.88(1H, m), 4.93(1H, br-s), 3.85(3H, s), 2.08-1.61(6H, m)
23		m.p. 197-198°C ^{1}H-NMR (DMSO-d_6) δ(ppm): 13.01(1H,br), 9.28(1H,s), 8.24(1H,s), 8.01(1H,br), 7.80-7.65(4H,m), 7.17(1H,d,J=9.1Hz), 4.39(1H, m), 3.85(3H, s), 1.99(2H, m), 1.55(2H, m), 1.78-1.30(6H, m)
24		m.p. 135-140°C ^{1}H-NMR (DMSO-d_6) δ(ppm): 13.01(1H, br), 9.28(1H, s), 8.24(1H, s), 8.01(1H, br), 7.81-7.69(4H, m), 7.16(1H, d, J=8.4Hz), 5.64(1H, br-s), 4.93(1H, br), 3.85(3H, s), 2.00-1.63(6H, m), 1.72(3H, m)
25		m.p. 188-189°C ^{1}H-NMR (DMSO-d_6) δ(ppm): 13.02(1H,br), 9.29(1H,s), 8.24(1H,s), 8.00(1H,br), 7.80-7.67(4H,m), 7.18(1H,d,J=8.6Hz), 5.95-5.78(2H,m), 5.08(1H, m), 3.86(3H, s), 2.27-2.19(2H, m), 2.04-2.02(2H, m), 1.80-1.69(3H, m), 1.40-1.35(1H, m)
26		m.p. 140-144°C ^{1}H-NMR (DMSO-d_6) δ(ppm): 13.03(1H, br), 9.29(1H,s), 8.24(1H,s), 8.02(1, br), 7.82-7.68 (4H, m), 7.16(1H, d, J=8.4Hz), 6.20(1H, m), 6.04(1H, m), 5.49(1H, br-s), 3.99(3H, s), 2.54-2.37(3H, m), 1.92-1.85(1H. m)

Table 1 (continued)

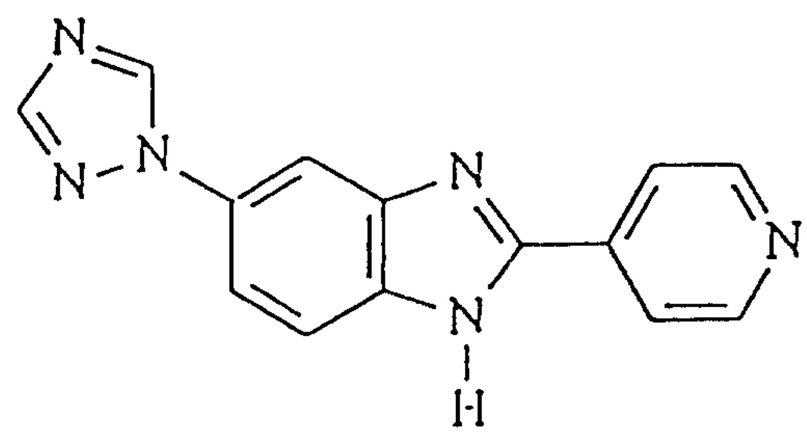
Comp. No.	Structure	Melting Point and NMR Chemical Shift Value
27		m.p. 132-134°C ^{1}H-NMR (DMSO-d_6) δ(ppm): 12.98(1H, br), 9.28(1H, s), 8.23(1H, s), 8.00(1H, br), 7.81-7.67(4H, m), 7.15(1H, d, J=9.0Hz), 5.80-5.57(2H, m), 4.97(1H, m), 3.85(3H, s), 1.64(3H, d, J=6.4Hz), 1.40(3H, d, 6.1Hz)

In the above table, "Me" means a methyl group.

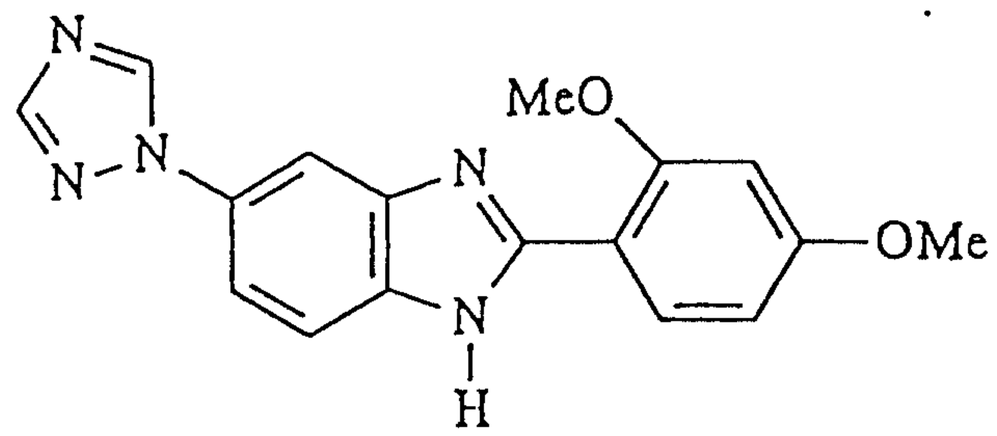
[Comparative Examples]

The following control compounds 1 to 5 were synthesized and used in pharmacological tests.

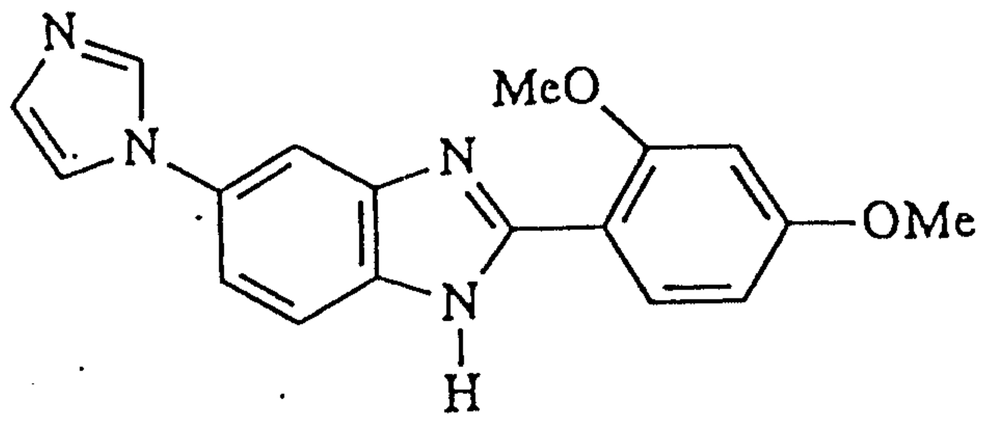
Control Compound 1:



Control Compound 2:

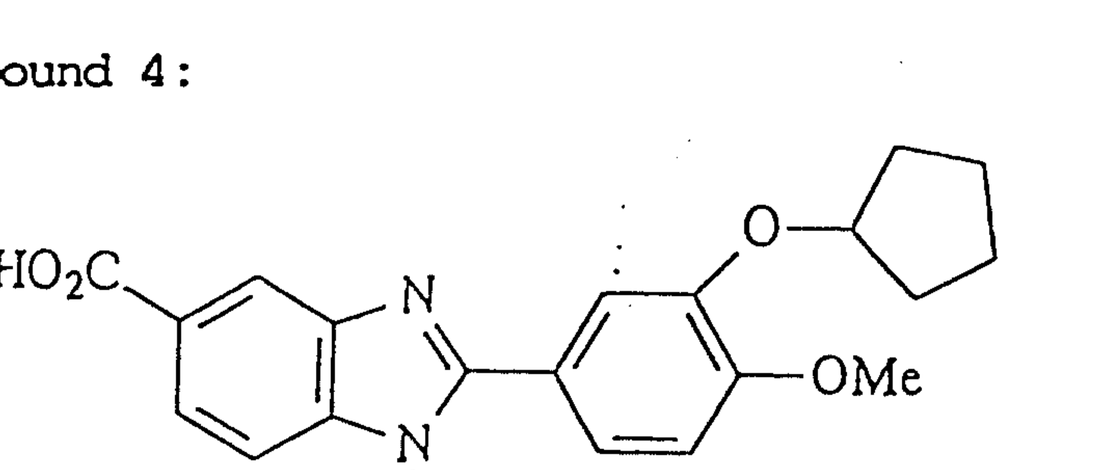


Control Compound 3:



Control Compound 4:

Control Compound 5:



(1) Each of the control compounds 1 to 3 was synthesized in accordance with the method described in JP-A-3-14579. Their physical property values are shown below.

(2) Each of the control compounds 4 and 5 was synthesized in accordance with the method described in International Publication No. WO 94/12461. Their physical property values are shown below.

Control compound 1

m.p. 264 - 266°C

^{1}H-NMR (DMSO-d_6) : δ (ppm) 7.77 - 7.86 (2 H, m), 8.12 - 8.14 (3 H, m), 8.26 (1 H, s), 8.79 - 8.81 (2 H, m), 9.34 (1 H, s)

Control compound 2

m.p. 230 - 232°C

^{1}H-NMR (DMSO-d_6) : δ (ppm) 3.88 (3 H, s), 4.05 (3 H, s), 6.73 - 6.79 (2 H, m), 7.64 - 7.72 (2 H, m), 8.04 (1 H, brs), 8.04 - 8.31 (2 H, m), 9.27 (1 H, s)

Control compound 3

m.p. 189 - 190°C

^{1}H-NMR (DMSO-d_6) : δ (ppm) 3.87 (3 H, s), 4.04 (3 H, s), 6.72 - 6.79 (2 H, m), 7.11 (1 H, s), 7.39 - 7.42 (1 H, m), 7.71 - 7.84 (3 H, m), 8.20 - 8.29 (2 H, m)

Control compound 4

m.p. 244 - 246°C

^{1}H-NMR (DMSO-d_6) : δ (ppm) 1.62 - 2.00 (8 H, m), 3.84 (3 H, s), 4.90 - 4.95 (1 H, m), 7.14 - 7.17 (1 H, m), 7.62 - 8.19 (5 H, m)

Control compound 5

m.p. 253 - 256°C

^{1}H-NMR (DMSO-d_6) : δ (ppm) 3.07 - 3.17 (2 H, m), 3.49 - 3.58 (2 H, m), 3.84 (3 H, s), 5.39 - 5.43 (1 H, m), 7.18 - 7.32 (5 H, m), 7.82 - 8.09 (4 H, m), 8.27 (1 H, s)

[Test Example 1] Interleukin-4 (IL-4) production inhibitory activity

This test was carried out in accordance with the method of Shelby et al. (*J. Allergy Clin. Immunol.*, Vol. 100, No. 4, 511 - 519 (1997)). Namely, $CD4^+$ T cells were purified from mouse spleen cells and suspended in 10% FCS-containing RPMI 1640 culture medium, and the cell suspension was deposited into wells of a 24 well culture plate, which had been coated with anti-rat IgG, at a density of 3×10^6 cells per well. Anti-mouse CD3 antibody and anti-mouse CD28 antibody were added thereto, and the cells were cultured at 37°C for 3 days in an atmosphere of 5% CO_2. The grown cells were recovered, washed three times with HBSS (Hank's balanced salt solution) and then suspended in 10% FCS-containing RPMI 1640 culture medium. The cell suspension was deposited into wells of a 24 well culture plate at a density of 1×10^6 cells per well, mixed with IL-2 and cultured for additional 3 days. The resulting cells were recovered, washed three times with HBSS and then suspended in 10% FCS-containing RPMI 1640 culture medium. The cell suspension was deposited into wells of a 24 well culture plate, which had been coated with anti-rat IgG, at a density of 2×10^6 cells per well, anti-mouse CD3 antibody and anti-mouse CD28 antibody were added thereto, and the cells were again cultured for 1 day. The culture supernatant was recovered from each well to measure the amount of IL-4 produced by ELISA. Each drug to be tested was treated at the time of the second addition of anti-mouse CD3 antibody and anti-mouse CD28 antibody to calculate its inhibition percentage based on the control IL-4 production by the addition of the solvent alone, and IC_{50} (50% inhibition concentration) of each drug to be tested was calculated based on the regression line. The results are shown in Table 2.

[Test Example 2] Phosphodiesterase IV (PDE(IV)) inhibitory activity

Purification of PDE (IV) and measurement of its activity were carried out by partially modifying the method of Saeki et al.(Biochem.Pharmacol., Vol. 46, 833 - 839, 1993). Namely, PDE(IV) was purified by centrifuging rat brain homogenate at 105,000 x g, applying the resulting supernatant to a Q-Sepharose*

* TRADEMARK

column and then eluting the protein with a density gradient of 0 to 0.5 M NaCl.

Activity of PDE (IV) was measured by the following two-step procedure. Using ^{3}H-cAMP (1 μM in final concentration) as the substrate, the reaction was carried out at 37°C for 10 minutes in a reaction solution containing tris (hydroxyl) aminomethane (50 nM, pH 8.0), EGTA (0.1 mM) and $MgCl_2$ (0.1 mM). The reaction was subsequently stopped by incubating the reaction solution at 95°C for 5 minutes. The 5' -AMP thus formed was hydrolyzed with 5' -nucleotidase, and AG1 X-8 resin was added thereto to effect adsorption of unreacted cAMP. After centrifugation, ^{3}H-adenosine was counted using a scintillation counter. Each of the drugs to be tested (compounds 1, 2 and 4) was added at the time of the commencement of reaction to calculate its inhibition percentage based on the control in which the solvent alone was added, and the IC_{50} (50% inhibition concentration) of each drug to be tested was calculated based on the regression line. The results are shown in Table 2.

Table 2

Compound No.	IL-4 production inhibition IC_{50} (μM)	PDE(IV) inhibition IC_{50} (μM)
1	4.3	0.02
11	5.5	1.6
14	6.1	0.54
18	5.1	0.051
25	2.8	0.73

[Text Example 3] Ear edema reaction inhibitory activity in mice [test on acute inflammation]

This test was carried out in accordance with the method of Sawada et al. (*Clin. Exp. Allergy*, Vol. 27, pp. 225 - 231, 1996). Each of the BALB/c mice was immunized by the intraperitoneal injection of 1 μg of egg albumin which had been adsorbed to 1 mg. of ALUM. Fourteen days following immunization, ear edema reaction was induced by intracutaneous

injection of 1 μg of egg albumin into mouse earlobe. Ear edema (x 10^{-2} mm) was calculated by measuring the thickness of the ear before and 1 hour after the induction with a dial thickness gage (Peacok). Each of the drugs to be tested (compounds 1 and 2) was suspended in 0.5% hydroxypropylmethylcellulose (HPMC) solution and orally administered 1 hour before the reaction induction. Ear edema caused by the antigen was calculated by subtracting ear edema thickness after the respective time of induction in the case of the same treatment of normal mice. The ear edema inhibition ratio (%) of the drugs to be tested was calculated based on the solvent-administered (control) group. The results are shown in Table 3.

The same test was carried out on the aforementioned control compounds 1 to 5. The results are also shown in Table 3.

[Test Example 4] Antigen-induced airway reactivity acceleration inhibitory activity in mice [test on chronic inflammation]

The model for this test was prepared in accordance with the method of Nagai et al. (*Life Sciences*, Vol. 54, pp. 471-475, 1994). Each of the BALB/c mice was immunized by an intraperitoneal injection of 1 μg of egg albumin which had been adsorbed to 1 mg of ALUM. Fourteen days following immunization, each animal was exposed to 1% egg albumin solution using an ultrasonic nebulizer, and this treatment was repeated three times at 3 day intervals. After 24 hours of the final exposure, the airway contraction reaction against intravenously injected acetycholine (30 μg /animal) was measured as overflow volume (x 0.01 ml) by the modified method of Konzett and Rossler under pentobarbital anesthesia. Each of the drugs to be tested (compounds 1 and 2) was suspended in 0.5% HPMC solution and orally administered once a day for a total of 10 days starting from the day before the antigen exposure until the day of final exposure. Accelerated quantity of the airway contraction reaction caused by the antigen exposure was calculated by subtracting the contraction reaction against intravenously injected acetylcholine in the case of the same treatment of

normal mice. The airway reactivity acceleration inhibition ratio (%) of the drugs to be tested was calculated based on the solvent-administered (control) group. The results are shown in Table 3.

The same test was carried out on the aforementioned control compounds 1 to 5. The results are also shown in Table 3.

Table 3

Compound No.	Mouse ear edema reaction inhibition (dose)	Airway reactivity acceleration inhibition (dose)
Compound 1	60% (30 mg/kg)	58% (10 mg/kg)
Compound 2	78% (30 mg/kg)	47% (30 mg/kg)
Control compound 1	2% (30 mg/kg)	26% (30 mg/kg)
Control compound 2	17% (30 mg/kg)	30% (30 mg/kg)
Control compound 3	37% (30 mg/kg)	6% (30 mg/kg)
Control compound 4	0% (100 mg/kg)	-17% (30 mg/kg)
Control compound 5	0% (100 mg/kg)	-3% (30 mg/kg)

Based on the results of the aforementioned Test Examples 1 and 2, it was confirmed that the benzimidazole compound of the present invention has excellent actions of both IL-4 production inhibitory activity and PDE (IV) inhibitory activity.

The compound of the present invention also showed excellent effects in the acute and chronic inflammation tests of Test Examples 3 and 4. However, none of the control compounds 1 to 5 showed similar effects in these tests.

Formulation examples of the compound of the present invention are shown as follows.

[Formulation Example 1] Tablets

Compound 1	200 mg
Corn starch	50 mg
Microcrystalline cellulose	50 mg
Hydroxypropylcellulose	15 mg
Lactose	47 mg
Talc	2 mg
Magnesium stearate	2 mg
Ethyl cellulose	30 mg

Unsaturated glyceride	2 mg
Titanium dioxide	2 mg

Tablets of 400 mg per one tablet having the above blending ratio were prepared in the usual way.

[Formulation Example 2] Granules

Compound 2	300 mg
Lactose	540 mg
Corn starch	100 mg
Hydroxypropylcellulose	50 mg
Talc	10 mg

Granules of 1,000 mg per one package having the above blending ratio were prepared in the usual way.

[Formulation Example 3] Capsules

Compound 3	200 mg
Lactose	30 mg
Corn starch	50 mg
Microcrystalline cellulose	10 mg
Magnesium stearate	3 mg

Capsules of 293 mg per one capsule having the above blending ratio were prepared in the usual way.

[Formulation Example 4] Injections

Compound 4	100 mg
Sodium chloride	3.5 mg
Distilled water for injection use	balance
(2 ml per one ampoule)	

Injections having the above blending ratio were prepared in the usual way.

[Formulation Example 5] Syrups

Compound 5	200 mg
Purified sucrose	60 mg
Ethyl parahydroxybenzoate	5 mg
Butyl parahydroxybenzoate	5 mg
Perfume	proper amount

Coloring agent	proper amount
Purified water	balance

Syrups having the above blending ratio were prepared in the usual way.

[Formulation Example 6] Suppositories

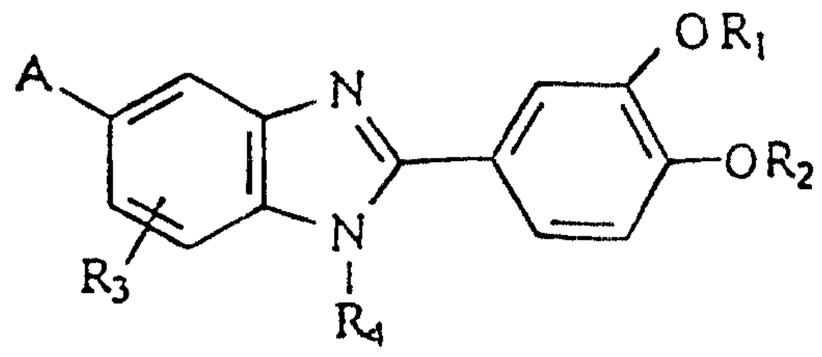
Compound 6	300 mg
Witepsol W-35	1,400 mg

(Trade name, a mixture of mono-, di- and tri-glycerides of from lauric acid to stearic acid, manufactured by Dynamite Novel)

Suppositories having the above blending ratio were prepared in the usual way.

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. A benzimidazole derivative represented by formula (I):



(I)

wherein A represents a triazole group; R_1 and R_2 may be the same or different from each other and each represents an aliphatic hydrocarbon radical or an alicyclic hydrocarbon radical, wherein:

- said aliphatic hydrocarbon radical is a straight- or branched-chain lower alkyl group having 1 to 6 carbon atoms, or a straight- or branched-chain lower alkenyl group having 2 to 6 carbon atoms, and optionally substituted by one or more of substituent groups selected from a monocyclic alicyclic hydrocarbon radical having 3 to 7 carbon atoms, which may have a straight- or branched-chain saturated lower alkyl group having 1 to 3 carbon atoms, an alicyclic hydrocarbon radical of cross-linked ring or polycyclic system, a phenyl group and a naphthyl group; and
- said alicyclic hydrocarbon radical is a monocyclic alicyclic hydrocarbon radical having 3 to 7 carbon atoms, which may have a straight- or branched-chain lower alkyl group having 1 to 3 carbon atoms or an alicyclic hydrocarbon radical of cross-linked ring or polycyclic system;

R_3 represents a hydrogen atom, a lower alkoxy group, a lower alkyl group, a hydroxyl group, a nitro group, a cyano group, an amino group, or a halogen atom; and R_4 represents a hydrogen

atom or a protective group of the nitrogen atom; or a pharmacologically acceptable salt thereof.

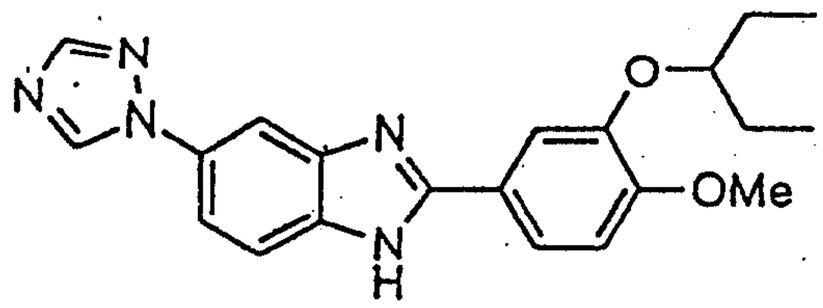
2. The benzimidazole derivative or a pharmacologically acceptable salt thereof according to claim 1, wherein A is 1,2,4-triazol-1-yl.

3. The benzimidazole derivative, or a pharmacologically acceptable salt thereof, according to claim 1 or 2, wherein R_1 and R_2 may be the same or different from each other and each is a methyl, isopropyl, isopentyl, cyclopropylmethyl, cyclopentylmethyl, benzyl, phenylethyl, phenylpropyl, cinnamyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl or cycloheptenyl group.

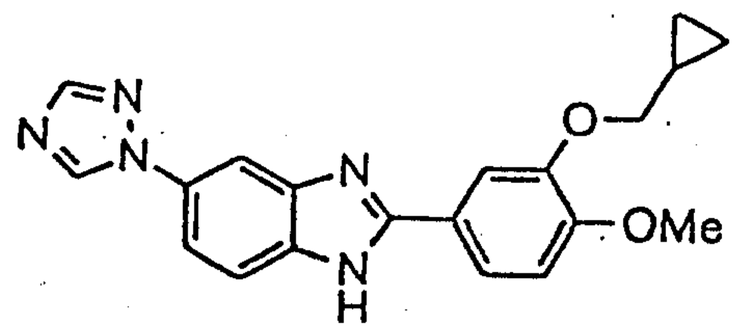
4. The benzimidazole derivative, or a pharmacologically acceptable salt thereof, according to claim 1, wherein A is 1,2,4-triazol-1-yl or 1,2,4-triazol-4-yl; R_1 and R_2 may be the same or different from each other and each is a straight- or branched lower alkyl group having 1 to 6 carbon atoms, which may have a monocyclic alicyclic hydrocarbon radical having 3 to 7 carbon atoms, or a monocyclic alicyclic hydrocarbon radical having 3 to 7 carbon atoms; R_3 is a hydrogen atom or a lower alkoxy group; and R_4 is a hydrogen atom.

5. The benzimidazole derivative or a pharmacologically acceptable salt thereof according to claim 4, wherein A is 1,2,4-triazol-1-yl; R_1 and R_2 may be the same or different from each other and each is a methyl, isopropyl, isopentyl, cyclopropylmethyl, cyclopentylmethyl, cyclopentyl, cyclopentenyl, cyclohexenyl or cycloheptenyl group; R_3 is a hydrogen atom; and R_4 is a hydrogen atom.

6. The benzimidazole derivative, or a pharmacologically acceptable salt thereof according to Claim 1, wherein the derivative has the formula

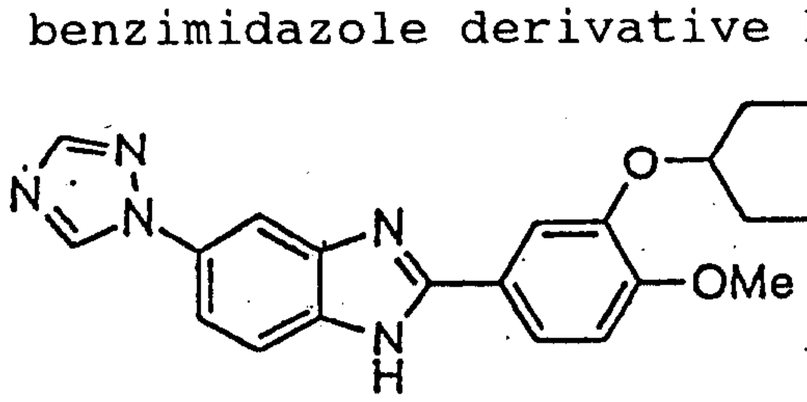


7. The benzimidazole derivative, or pharmacologically acceptable salt thereof according to Claim 1, where the derivative has the formula

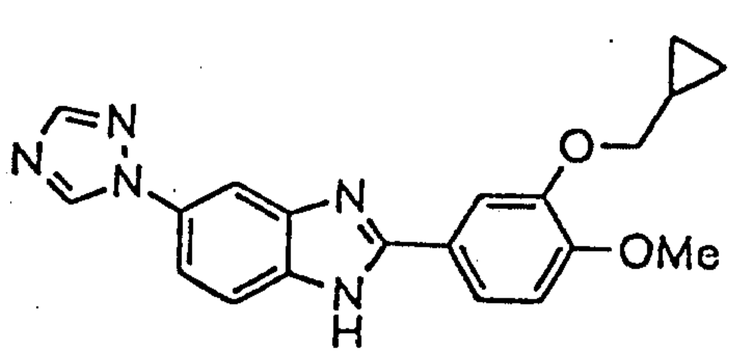


8. A pharmaceutical composition, which comprises an amount of the benzimidazole derivative represented by formula (I), or a pharmacologically acceptable salt thereof, defined in claim 1, and a pharmacological carrier.

9. The pharmaceutical composition according to Claim 8, wherein the benzimidazole derivative has the formula



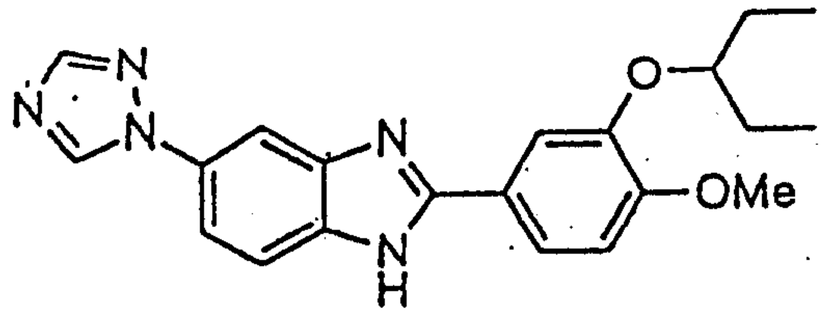
10. The pharmaceutical composition according to Claim 8, wherein the benzimidazole derivative has the formula



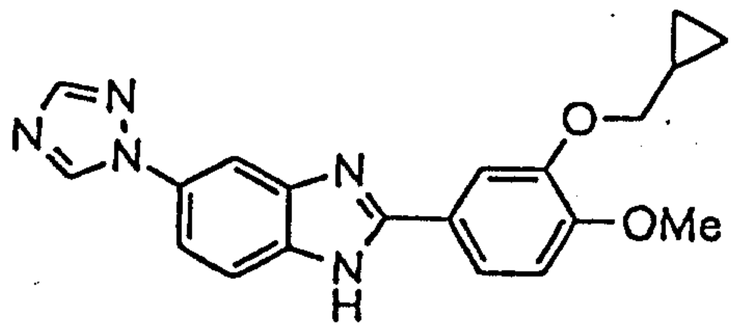
11. A therapeutic or preventive agent for acute and chronic inflammatory diseases, which comprises an amount of the benzimidazole derivative represented by formula (I), or a

pharmacologically acceptable salt thereof, defined in claim 1, and a pharmacological carrier.

12. The therapeutic or preventive agent according to Claim 11, wherein the benzimidazole derivative has the formula

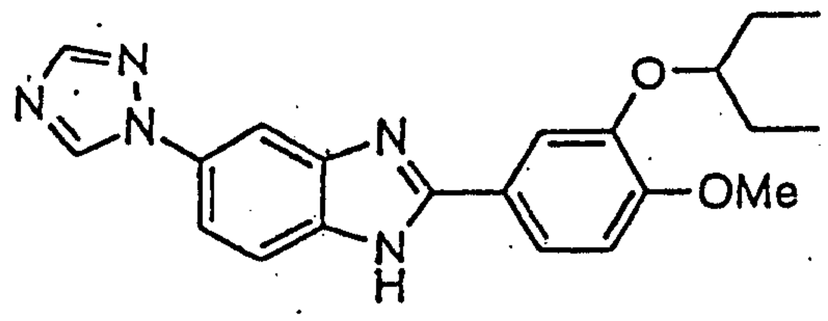


13. The therapeutic or preventive agent according to Claim 11, wherein the benzimidazole derivative has the formula

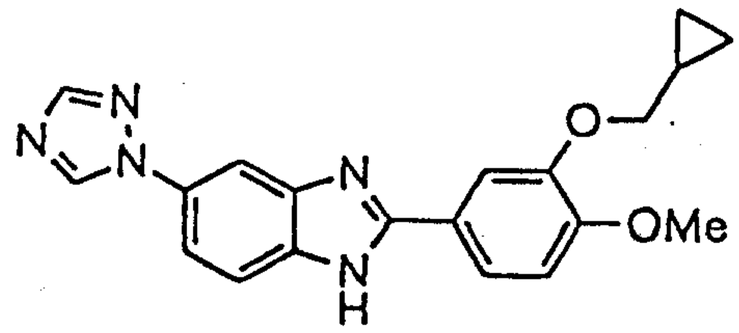


14. An anti-allergic or anti-inflammatory agent, which comprises an effective amount of the benzimidazole derivative represented by formula (I), or a pharmacologically acceptable salt thereof, defined in claim 1, and a pharmacological carrier.

15. The anti-allergic or anti-inflammatory agent according to Claim 14, wherein the benzimidazole derivative has the formula

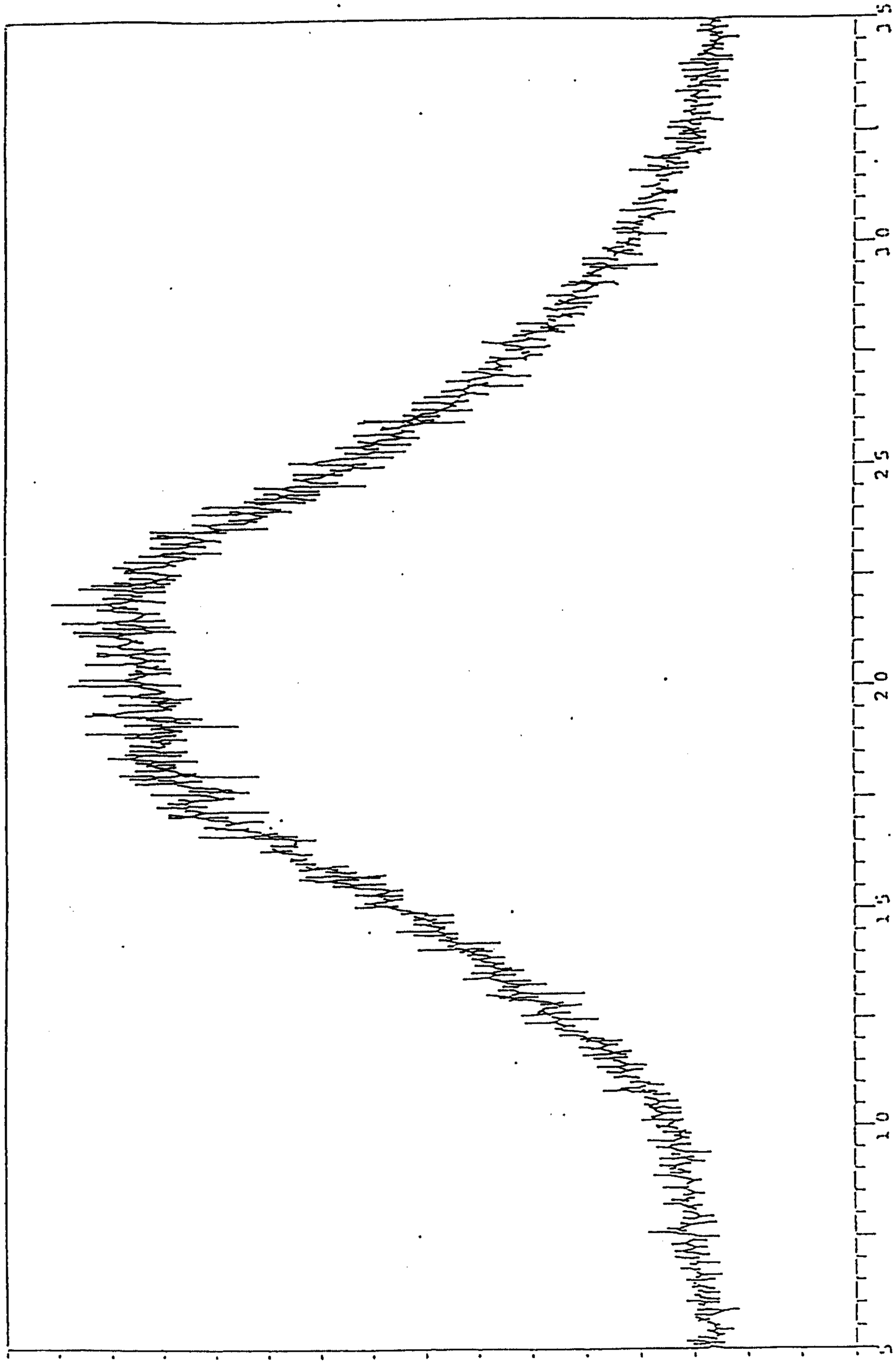


16. The anti-allergic or anti-inflammatory agent according to Claim 14, wherein the benzimidazole derivative has the formula



17. Use of the benzimidazole derivative or a pharmacologically acceptable salt thereof defined according to any one of claims 1 to 7, a pharmaceutical composition, according to claim 8, 9, or 10, a therapeutic or preventive agent, according to claim 11, 12, or 13, or an anti-allergic or anti-inflammatory agent, according to claim 14, 15, or 16, for treating and/or preventing acute and chronic inflammatory diseases.

Fig. 1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15
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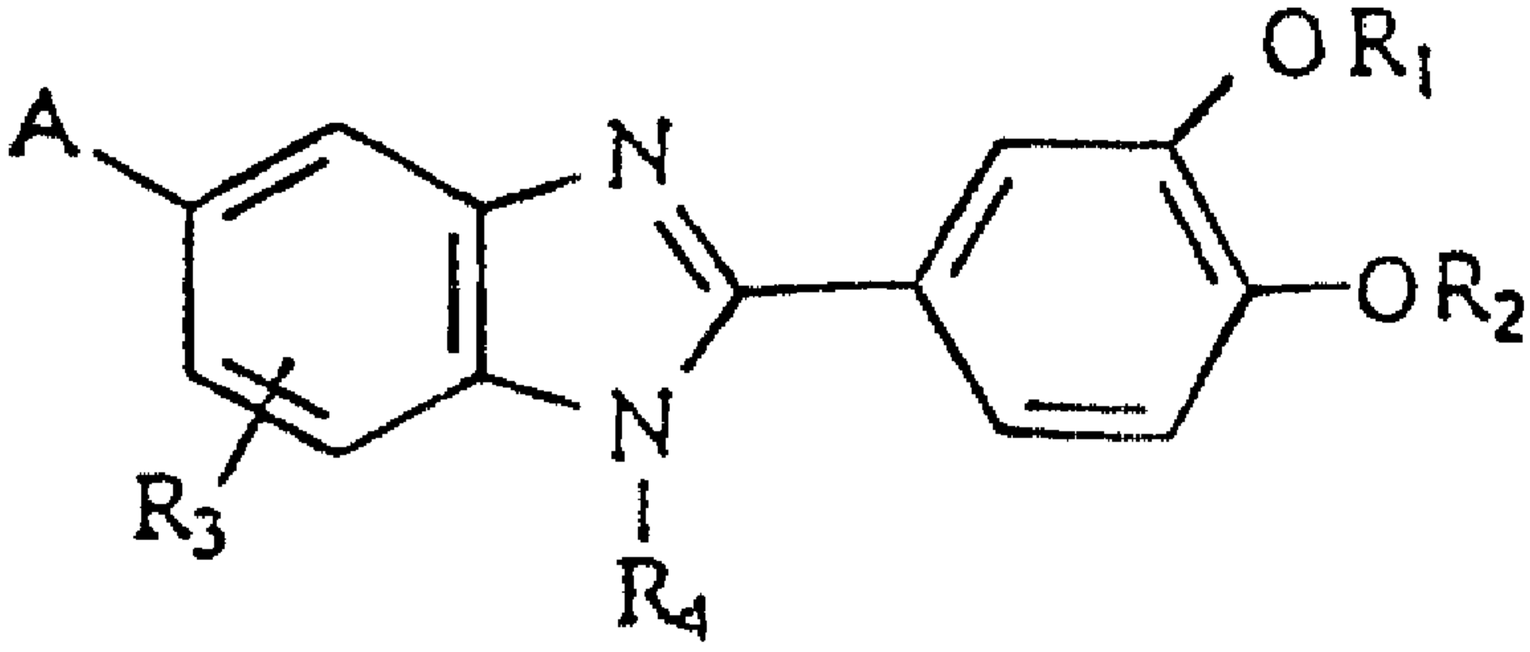

(I)