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(54) Title: TREATMENT OF T–HELPER CELL TYPE 2 MEDIATED IMMUNE DISEASES

(57) Abstract

Retinoids with retinoid receptor antagonistic activity called retinoid antagonists, pharmaceutically acceptable salts and pharmaceutically acceptable hydrolyzable esters thereof, have been found to be efficacious in the treatment of T–helper cell type 2 (Th2)–mediated immune diseases, such as immunoglobulin E (IgE)–mediated allergic diseases.

Treatment of T-Helper Cell Type 2 Mediated Immune Diseases

The present invention relates to the use of retinoid antagonists comprising retinoids with selective Retinoic Acid Receptor (RAR) antagonistic activity, Retinoid X Receptor (RXR) antagonistic activity or mixed RAR-RXR antagonistic activity, for the manufacture of a medicament for the treatment of T-helper cell type 2 (Th2)-mediated immune diseases such as immunoglobulin E (IgE)-mediated allergic diseases, as well as to the use of said active substances for the treatment of such diseases.

Retinoids are a class of compounds structurally related to vitamin A, comprising natural and synthetic compounds. Retinoids have been found to be clinically useful in the treatment of dermatological and oncological diseases.

The activity of retinoids is thought to be mediated by the nuclear retinoid receptors RARα, β, γ and RXRα, β, γ, belonging to the superfamily of steroid, thyroid hormone, vitamin D, peroxisome proliferator-activated receptors [Pfahl et al., Vitamins and Hormones 49, 327-382 (1994)]. Retinoids with receptor agonistic activity bind and activate receptors, whereas retinoids with receptor antagonistic activity bind receptors but do not activate them.

Experimentally, retinoids with retinoid receptor agonistic activity have been shown to be active not only in model systems for the treatment of dermatological and oncological diseases but also in models for the treatment of immunological diseases. Retinoids with retinoid receptor agonistic activity are active in the treatment of adjuvant arthritis [Brinckerhoff et al., Science 221, 756-758 (1983)] and experimental allergic encephalomyelitis [Massacesi et al.,

J. Clin. Invest. 88, 1331-1337 (1991); Racke et al., J. Immunol. 154, 450-458 (1995)], animal models for rheumatoid arthritis and multiple sclerosis, respectively. Both diseases are considered to belong to Th1-mediated, cell-mediated immune diseases.

Experimentally, retinoids with retinoid receptor antagonistic activity (retinoid antagonists) are effective in counteracting many properties of retinoids with retinoid receptor agonistic activity (retinoid agonists) such as inhibition of cell proliferation, induction of cell differentiation, induction of apoptosis and inhibition of angiogenesis [Bollag et al., Int. J. Cancer 70, 470-472 (1997)]. Retinoid antagonists are also suppressing toxic side effects of retinoid agonists such as the signs and symptoms of the hypervitaminosis A syndrome and teratogenesis [Standeven et al., Toxicol. Appl. Pharmacol. 138, 169-175 (1996); Eckhardt and Schmitt, Toxicol. Letters 70, 299-308 (1994)]. Therefore, they may be useful clinically in preventing or treating adverse events caused by retinoid agonists.

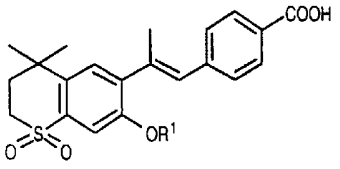
Retinoid antagonists have been proposed for clinical use in prevention and therapy of retinoid-induced toxicity and side effects, particularly of the so-called hypervitaminosis A syndrome. Retinoid antagonists have also been proposed to be used in combination with retinoid receptor agonists or other nuclear receptor agonists for prevention and treatment of preneoplastic or neoplastic lesions, vitreo-retinopathy and retinal detachment. In addition, retinoid antagonists could be used as single agents, based on their anti-proliferative effect, for treatment of certain neoplasms insensitive to retinoid receptor agonists [WO 97/09297].

For the first time, quite unexpectedly, it has now been found that retinoid antagonists are efficacious in the treatment of T-helper cell type 2 (Th2)-mediated immune diseases, such as immunoglobulin E (IgE)-mediated allergic diseases or diseases mediated by the Th2-related cytokines.

In the scope of the present invention the term "retinoid antagonists" is used for retinoids or compounds with RAR, RXR or mixed RAR-RXR antagonistic activity. It includes compounds with receptor neutral antagonistic activity (neutral antagonists), receptor inverse agonistic activity (inverse agonists) and negative hormone activity (negative hormones) [Klein et al., J. biol. Chem. 271, 22692-22696 (1996)].

In the scope of the present invention the term "retinoid antagonists" encompass compounds of formulae

a) RAR α-antagonists of formulae



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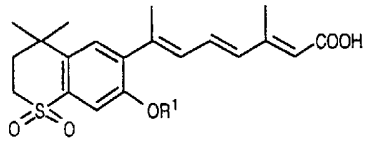
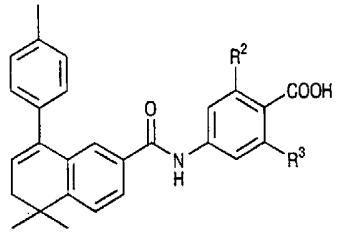
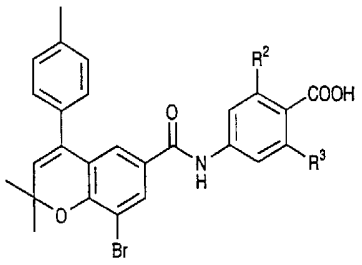


II;



III; and

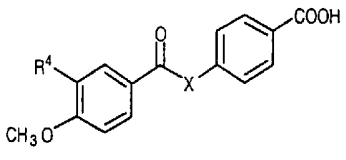


IV,

wherein R^1 is C_{5-10}-alkyl, and R^2 and R^3 independently of each other are hydrogen or fluorine;

such compounds are described in US patent no. 5 391 766 and J. Med. Chem. 1997, 40, 2445;

b) RAR α,β antagonists of formulae



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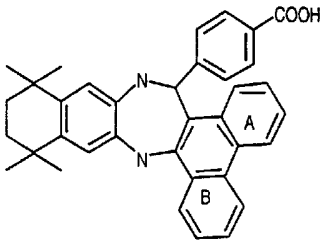
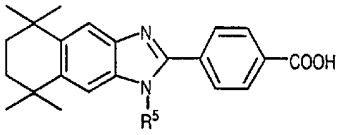


VI; and

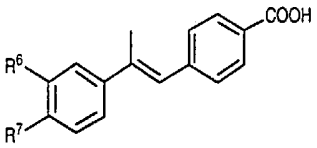


VII,

wherein R^4 is diamantyl, X is O or NH, R^5 is phenyl or benzyl, and wherein optionally either ring A or ring B is present;

such compounds are described in Med. Chem. Res. 1991, 1, 220; Biochem. Biophys. Res. Com. 1997, 231, 243; J. Med. Chem. 1994, 37, 1508;

c) RAR β,γ antagonists of formula

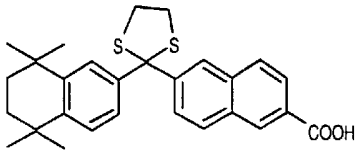


VIII,

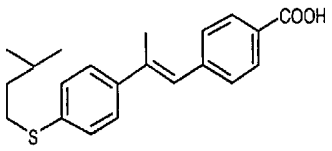
wherein R^6 and R^7 independently of each other hydroxy, C_{1-4}-alkoxy, optionnaly branched C_{1-5}-alkyl or adamantyl;

such compounds are described in J. Med. Chem. 1995, 38, 4993;

d) RAR γ antagonists of formulae



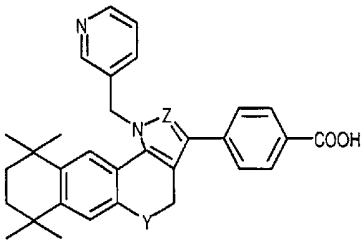
IX; and



X

such compounds are described in Cancer Res. 1995, 55, 4446;

e) RAR α,β,γ antagonists of formulae



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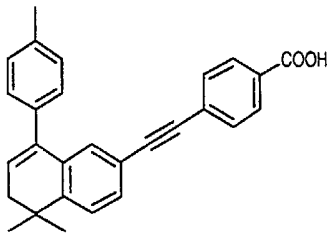
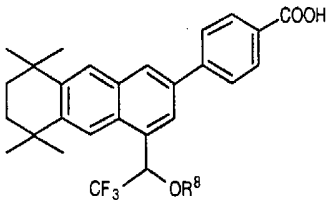


XII,



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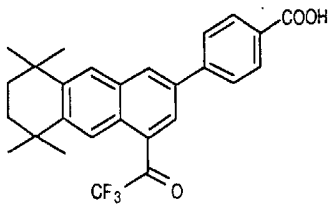
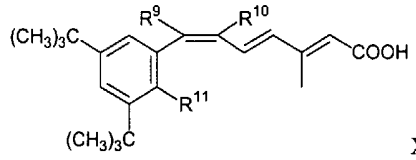


XIV

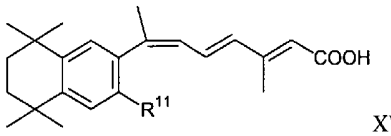
wherein Y is -CH_2- or sulfur and Z is -CH= or nitrogen, and R^8 is hydrogen or C_{1-4}-alkyl;

such compounds are described in J. Med. Chem. 1995, 38, 3163 and 4764; J. Biol. Chem. 1996, *271*, 11897 and 22692;

f) RXR antagonists of formulae



XV; and



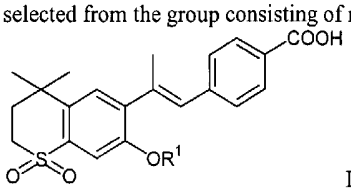
XVI;

wherein the dotted bond is optional; and, when the dotted bond is present, R^9 is methyl and R^{10} is hydrogen; and, when the dotted bond is absent, R^9 and R^{10} taken together are methylene to form a cis-substituted cyclopropyl ring; R^{11} is C^{1-4}-alkoxy;

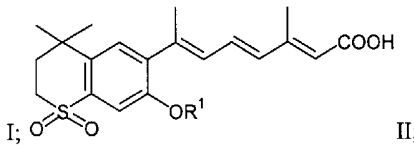
such compounds are described in EP patent appl. No. 97 107 843.1; J. Med. Chem. 1996, 39, 3229; and Nature 1996, 383, 450.

In accordance with this invention, it has thus been found that administration of retinoid antagonists, pharmaceutically acceptable salts, and pharmaceutically acceptable hydrolysable esters thereof, are efficacious in treating patients with T-helper cell type 2 (Th2)-mediated diseases. It has also been found that the administration of retiniod antagonists is efficacious in treating patients with diseases mediated by Th2-related cytokines, such as interleukin-4 (IL-4) and IL-4.

Accordingly, a first aspect of the present invention provides the use of a compound selected from the group consisting of retinoid antagonists of formulae



I;



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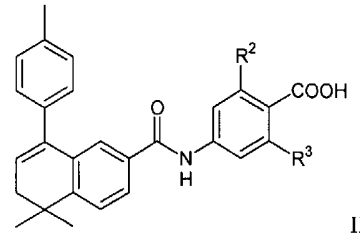

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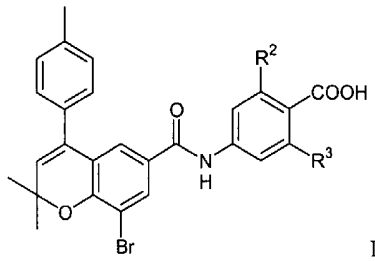
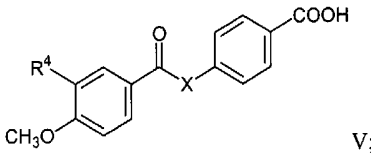


IV,

wherein R^1 is C_{5-10}-alkyl, and R^2 and R^3 independently of each other are hydrogen or fluorine;



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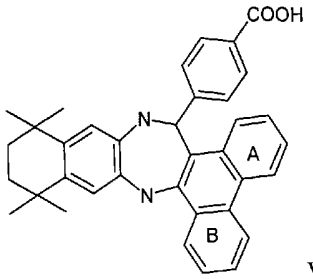
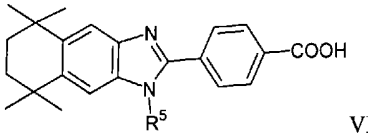
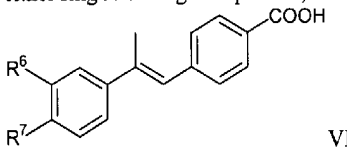


VI; and



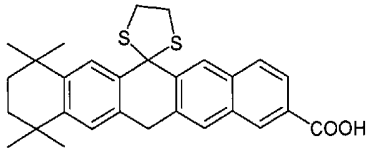
VII,

wherein R^4 is diamantyl, X is O or NH, R^5 is phenyl or benzyl, and wherein optionally either ring A or ring B is present;

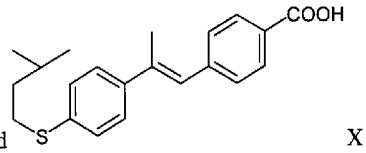


VIII,

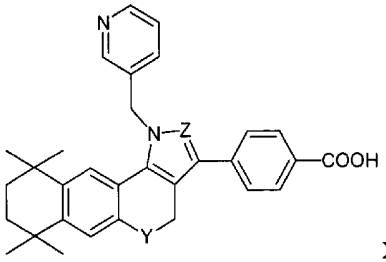
wherein R^6 and R^7 independently of each other hydroxy, C_{1-4}-alkoxy, optionally branched C_{1-5}-alkyl or adamantyl;



IX; and



X



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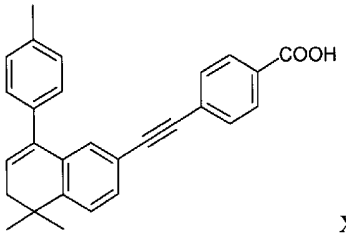
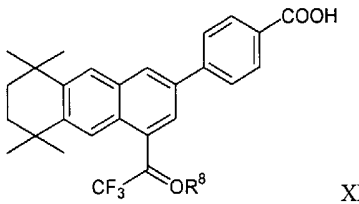


XII,



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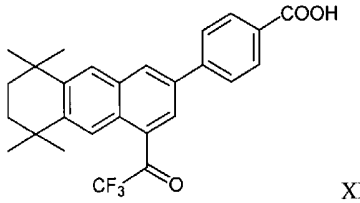
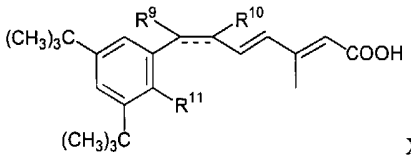
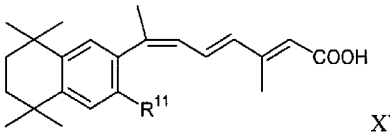


XIV

wherein Y is $-CH_2-$ or sulfur and Z is –CH= or nitrogen, and R^8 is hydrogen or C_{1-4}-alkyl;



XV; and



XVI;

wherein the dotted bond is optional; and, when the dotted bond is present, R^9 is methyl and R^{10} is hydrogen; and, when the dotted bond is absent, R^9 and R^{10} taken together are methylene to form a cis-substituted cyclopropyl ring; R^{11} is C_{1-4}-alkoxy; and pharmaceutically acceptable salts and pharmaceutically acceptable hydrolysable esters thereof, as active ingredient for the manufacture of a medicament for the treatment of T-helper cell type 2 (Th2)-mediated immune diseases, such as immunoglobulin E (IgE)-mediated allergic diseases or for the treatment of diseases mediated by Th2-related cytokines such as IL-4 and IL-5.

A second aspect of the present invention provides a method of treating T-helper cell type 2 (Th2)-mediated immune diseases, such as immunoglobulin E (IgE)-mediated allergic diseases or for the treatment of diseases mediated by Th2-related cytokines such as IL-4 and IL-5, said method comprising administering an effective amount of a compound selected from the group of retinoid antagonists of formulae I to XVI as defined in the first aspect of the invention above or a pharmaceutically acceptable hydrolysable ester thereof, to a patient in need thereof.

A third aspect of the present invention provides a compound selected from the group of retinoid antagonists of formulae I to XVI as defined in the first aspect of the invention above or a pharmaceutically acceptable hydrolysable ester thereof or a medicament containing the compound together with a pharmaceutically acceptable carrier when used for the treatment of T-helper cell type 2 (Th2)-mediated immune diseases, such as immunoglobulin E (IgE)-mediated allergic diseases or for the treatment of diseases mediated by Th2-related cytokines such as IL-4 and IL-5 in a patient in need thereof.

The invention also relates to a method for treating patients having T-helper cell type 2 (Th2)- mediated immune diseases comprising administering

to said human patient a compound selected from the group of retinoid antagonists, pharmaceutically acceptable salts and pharmaceutically acceptable hydrolyzable esters thereof, said compound being administered in an amount effective to treat said disease. The term „treatment" or „treating" includes preventive and/or therapeutic treatment.

As used herein, the term „T-helper cell type 2-mediated immune diseases" relates to diseases involving immunoglobulin E (IgE) and mast cells due to the development and activation of allergen-specific Th2 cells and it encompasses allergic diseases, such as atopic dermatitis, other dermatological diseases associated with atopy; allergic rhinitis or hay fever, allergic bronchial asthma in its acute or chronic, mild or severe forms, with or without acute or chronic bronchitis. Elevated serum levels of immunoglobulin E (IgE) and hypereosinophilia can be associated with these diseases. Retinoid antagonists are effective in all those immune diseases which are linked with an increase of Th2 cell activity and an increased secretion of the related cytokines, such as IL-4 and IL-5. The therapeutic effect of retinoid antagonists is due to a decrease in Th2 cell activity, a decreased secretion of the related cytokines, such as IL-4 and IL-5, and/or an increase in Th1 cell activity due to the enhancement of IL-12 production by activated myelomonocytic cells. [S. Romagnani, Ann. Rev. Immunol. 12, 227-257 (1994); Romagnani, ed., Th1 and Th2 Cells in Health and Disease. Chem. Immunol., Karger, Basel, 63, pp. 187-203 (1996); Abbas et al., Nature 383, 787-793 (1996)].

The efficacy of the retinoid antagonists in accordance with the present invention can be shown by their ability to either upregulate Th1 cell activity or induce/stimulate the production of cytokines, such as IL-12, IFNγ, TNF; and/or down-regulate Th2 cell activity, or inhibit the production of cytokines, such as IL-4 and IL-5.

Retinoid antagonists are active in the treatment of allergic bronchial asthma. The hallmarks of inflammation associated with asthmatic disease are the presence of activated eosinophils, an increased sensitivity of the airways (hyperresponsiveness), edema, mucus hypersecretion and cough. This inflammatory process is mediated by the generation and activation of Th2-type cells. The ability of retinoid antagonists to promote a Th1-type response and thereby to suppress the Th2-type response is thought to be the mechanism underlying the efficacy of these compounds in allergic lung inflammation/asthma. Retinoid antagonists are acting on Th1-type cells, in inhibiting the signs and symptoms of allergic lung inflammation/asthma

[Gavett et al., J. exp. Med. 182, 1527-1536 (1995); Kips et al., Am. J. Respir. Crit. Care Med. 153, 535-539 (1996)]. They are active in antigen/allergen (e.g. ovalbumin)-sensitized and challenged animals. Retinoid antagonists, given either systemically or topically by aerosol, are efficacious in attenuating, inhibiting or reversing bronchoconstriction, airway edema and mucus hypersecretion, airway inflammation, accumulation of eosinophils and neutrophils in the broncho-alveolar tissue and broncho-alveolar lavage respectively, as well as airway hyperresponsiveness to non-specific stimuli.

For the treatment, the active compound, i.e. a retinoid antagonist, a pharmaceutically acceptable salt or a pharmaceutically acceptable hydrolyzable ester thereof, is administered either systemically or topically. Preferably, said compound is administered as a composition containing said active compound and a pharmaceutically acceptable carrier or diluent compatible with said active compound. In preparing such composition, any conventional pharmaceutically acceptable carrier can be utilized. When the drug is administered orally, it is generally administered at regular intervals, conveniently at mealtimes or once daily. It has been established that this compound is effective in doses which show no or only mild side effects when given orally or when given topically. Therefore, oral or topical administration of the active compound is generally preferred. For treating diseases of the skin, mouth, nose, pharynx, larynx, bronchus etc. oral combined with topical administration may also be used advantageously.

In the treatment of T-helper cell type 2-mediated immune diseases, retinoid antagonists, when administered orally do not induce the adverse events belonging to the toxic syndrome of hypervitaminosis A, such as mucocutaneous, musculoskeletal, neurologic manifestations and elevation of transaminases, triglycerides and cholesterol. In addition, they are not or less teratogenic in contrast to the receptor agonistic retinoids clinically useful in the treatment of dermatological and oncological diseases, such as all-trans retinoic acid (tretinoin), 13-cis retinoic acid (isotretinoin), etretinate and acitretin.

In the treatment of T-helper cell type 2-mediated immune diseases, retinoid antagonists, pharmaceutically acceptable salts or pharmaceutically acceptable hydrolyzable esters thereof, can be used alone or in combination with other measures, e.g. in combination with other pharmaceutically active substances such as topical or systemic corticosteroids, antihistaminics and bronchodilating agents. If used in combination with other substances, retinoid

antagonists and said other substances can be administered separately or incorporated in effective amounts into one pharmaceutical composition.

In the scope of the present invention, the „pharmaceutically acceptable salts" includes any salt chemically permissible in the art for retinoid antagonists and applicable to human patients in a pharmaceutically acceptable preparation. Any such conventional pharmaceutically acceptable salt of retinoid antagonists can be utilized. Among the conventional salts which can be utilized, there are the base salts included, for example, alkali metal salts such as the sodium or potassium salt, alkaline earth metal salts such as the calcium or magnesium salt, and ammonium or alkyl ammonium salts.

In accordance with this invention the retinoid antagonists can also be administered in the form of its pharmaceutically acceptable hydrolyzable esters. Any pharmaceutically acceptable hydrolyzable ester can be used in the compositions and methods of this invention. Among the preferred esters are: the aromatic esters such as benzyl esters in which the benzyl moiety is unsubstituted or substituted with lower alkyl, halo, nitro, thio, or substituted thio; or lower alkyl esters, e.g. ethyl, t-butyl, cyclopentyl, cyclohexyl or cycloheptyl ester; or 9-fluorenylmethyl ester.

In the scope of the present invention the term „alkyl" means straight-chain, branched or cyclic alkyl residues, in particular those containing from 1 to 12 carbon atoms, such as methyl, ethyl, propyl, isopropyl, t-butyl, decyl, dodecyl, cyclopentyl, cyclohexyl, cycloheptyl and the like. The term „lower alkyl" means alkyl groups containing from 1 to 7 carbon atoms.

The aforementioned retinoid antagonists, the salts and esters thereof are useful especially in pharmaceutically acceptable oral or topical modes. These pharmaceutical compositions contain said active compound in association with a compatible pharmaceutically acceptable carrier material. Any conventional carrier material can be utilized. The carrier material can be organic or inorganic inert carrier material suitable for oral administration. Suitable carriers include water, gelatine, gum arabic, lactose, starch, magnesium stearate, talc, vegetable oils, polyalkylene-glycols, petroleum jelly and the like. Furthermore, the pharmaceutically active preparations may contain other pharmaceutically active agents. Additionally, additives such as flavouring agents, preservatives, stabilizers, emulsifying agents, buffers and the like may

be added in accordance with accepted practices of pharmaceutical compounding.

The pharmaceutical preparations can be made up in any conventional form including inter alia: (a) a solid form for oral administration such as tablets, capsules (e.g. hard or soft gelatine capsules), pills, sachets, powders, granules, and the like; (b) preparations for topical administrations such as solutions, suspensions, ointments, creams, gels, micronized powders, sprays, aerosols and the like. The pharmaceutical preparations may be sterilized and/or may contain adjuvants such as preservatives, stabilizers, wetting agents, emulsifiers, salts for varying the osmotic pressure and/or buffers.

For topical administration to the skin or mucous membrane the aforementioned derivative is preferably prepared as ointments, tinctures, creams, gels, solution, lotions, sprays; aerosols and dry powder for inhalation, suspensions, shampoos, hair soaps, perfumes and the like. In fact, any conventional composition can be utilized in this invention. Among the preferred methods of applying the composition containing the agents of this invention is in the form of an ointment, gel, cream, lotion, spray; aerosol or dry powder for inhalation. The pharmaceutical preparation for topical administration to the skin can be prepared by mixing the aforementioned active ingredient with non-toxic, therapeutically inert, solid or liquid carriers customarily used in such preparation. These preparations generally contain 0.01 to 5.0 percent by weight, preferably 0.1 to 1.0 percent by weight, of the active ingredient, based on the total weight of the composition.

In preparing the topical preparations described above, additives such as preservatives, thickeners, perfumes and the like conventional in the art of pharmaceutical compounding of topical preparation can be used. In addition, conventional antioxidants or mixtures of conventional antioxidants can be incorporated into the topical preparations containing the aforementioned active agent. Among the conventional antioxidants which can be utilized in these preparations are included N-methyl-α-tocopherolamine, tocopherols, butylated hydroxyanisole, butylated hydroxytoluene, ethoxyquin and the like. Cream-base pharmaceutical formulations containing the active agent, used in accordance with this invention, are composed of aqueous emulsions containing a fatty acid alcohol, semi-solid petroleum hydrocarbon, ethylene glycol and an emulsifying agent.

Ointment formulations containing the active agent in accordance with this invention comprise admixtures of a semi-solid petroleum hydrocarbon with a solvent dispersion of the active material. Cream compositions containing the active ingredient for use in this invention preferably comprise emulsions formed from a water phase of a humectant, a viscosity stabilizer and water, an oil phase of a fatty acid alcohol, a semi-solid petroleum hydrocarbon and an emulsifying agent and a phase containing the active agent dispersed in an aqueous stabilizer-buffer solution. Stabilizers may be added to the topical preparation. Any conventional stabilizer can be utilized in accordance with this invention. In the oil phase, fatty acid alcohol components function as a stabilizer. These fatty acid alcohol components function as a stabilizer. These fatty acid alcohol components are derived from the reduction of a long-chain saturated fatty acid containing at least 14 carbon atoms. Also, conventional perfumes and lotions generally utilized in topical preparation for the hair can be utilized in accordance with this invention. Furthermore, if desired, conventional emulsifying agents can be utilized in the topical preparations of this invention.

For topical treatment of allergic rhinitis and allergic bronchial asthma nasal and inhalation aerosols are used. Formulations for such aerosols are described in Drugs and Pharmaceutical Sciences, Marcel Dekker, New York, 1996, Vol. 72, pp. 547-574. Furthermore, the active compound can be delivered by dry powder inhalation. Such formulations and devices are described in Pharmaceutical Technology, June 1997, pp. 117-125.

A preferred oral dosage form comprises tablets, pills, sachets, or capsules of hard or soft gelatine, methylcellulose or of another suitable material easily dissolved in the digestive tract. Each tablet, pill, sachet or capsule can preferably contain from about 5 to about 200 mg, more preferably from about 20 to about 100 mg, of active ingredient. The oral dosages contemplated in accordance with the present invention will vary in accordance with the needs of the individual patient as determined by the prescribing physician. Generally, however, a daily dosage of from 0.05 to 20 mg per kg of body weight, preferably 0.1 to 7 mg, and most preferably from about 0.3 mg to about 1.5 mg per kg of body weight of the patient is utilized. This dosage may be administered according to any dosage schedule determined by the physician in accordance with the requirements of the patient.

The dosage for treatment typically depends on the route of administration, the age, weight and disease condition of the individual.

Suitable dosage forms are known in the art or can be easily obtained in a manner known per se. Formulations of lotions, gels, creams, sprays; aerosols and dry powder for inhalation, hard or soft gelatine capsules, tablets and sachets that are particularly suitable in the scope of the present invention or that can be easily adjusted in accordance with the above teaching are in the art.

Experimental Methods

I. *In vitro* assay for IL-12 induction by retinoid antagonists

THP-1 cells were obtained from American Tissue Culture Collection and cultured in complete medium. To assay for IL-12 production, THP-1 cells, 1.25 x 10^6 cells/ml, were stimulated with *S. aureus* Cowan strain (SAC) (1/1000) and human recombinant interferon-γ (huIFN-γ) (1000 U/ml) [Ma et al., *J. Exp. Med.* 183, 147-157 (1996)]. Alternatively, 0.5 x 10^6 human peripheral blood mononuclear cells (PBMC) (1 ml culture in 48 well plates) were primed with huIFN-γ (1000 U/ml) for 16 hours at 37°C, and then stimulated with SAC (1/1000). Supernatants were collected after 48 hours, and freezed at -20°C until assayed [Panina-Bordignon et al., *J. Clin. Invest.* 100, 1513-1519 (1997)].

IL-12 production was measured by specific enzyme linked immuno sorbant assay (ELISA), using 20C2 antibody (rat anti human IL-12 heterodimer p40-p35), at 2.5 µg/ml in coating buffer, and peroxidase-conjugated 4D6 antibody (rat anti human IL-12) at 250 ng/ml in assay buffer as described [Zhang et al., *J. Clin. Invest.* 93, 1733-1739 (1994)]. Standard (recombinant human IL-12, 800 pg/ml to 6 pg/ml) and samples (100 µl) diluted in assay buffer were added to duplicate wells. Absorbance was read at 450-650 nm. The unknown IL-12 concentrations of the samples were read from the corresponding standard curve and multiplied by the corresponding dilution factor. Maximal IL-12 production varied between 200 and 400 pg/ml.

Lyophilized retinoid antagonists were diluted in DMSO under yellow light, on ice at a concentration of 2 mM. Serial dilutions (1 µM-1 pM) were prepared in complete RPMI medium. 10 µl of each dilution was added to 1 ml culture.

The results of the experiments indicate that the tested retinoid antagonists influence IL-12 production. In particular, the tested retinoid antagonists stimulate IL-12 production by activated human monocytes, see Table I and II.

Table I

Retinoid antagonists specifically enhance IL-12 production by activated monocytes

	nM	IL-12 (pg/ml)	IL-10 (pg/ml)	TNF-α (pg/ml)
medium		0	<10	<10
SAC+IFN-γ		120	1040	1840
RAR α antagonist	1000	251	1343	1912
Compound A	100	102	1050	1600
	10	n.d.	1060	1392
medium		0	<10	<10
SAC+IFN-γ		126	1040	2000
RAR αβγ antagonist	1000	321	1116	2884
Compound B	100	205	983	2752
	10	173	971	2592
medium		0	<10	<10
SAC+IFN-γ		120	1040	1840
RXR antagonist	1000	298	1700	1560
Compound C	100	161	1521	1812
	10	106	1020	1484

Table II

Retinoid antagonists enhance IL-12 production by PBMC and THP-1 cells that have been primed with IFNγ and stimulated with SAC

Compound	Receptor Specificity	Activity	Stimuli	Time * (hrs)	PBMC IL-12	THP-1 (pg/ml)
A	RARα	antagonist	IFNγ+	0	503	306
			SAC	16	401	nd
B	RARα,β,γ	antagonist	IFNγ+	0	371	364
			SAC	16	367	nd
C	RXR	antagonist	IFNγ+	0	568	577
			SAC	16	367	nd
none			none		<12	<2
			IFNγ+		360	275
			SAC			

* retinoid antagonists (1 μg) were added at time 0 together with IFNγ or after 16 hours together with SAC.

Compound A p-[(E)-2-[3',4'-Dihydro-4',4'-dimethyl-7'-(heptyloxy)-2'H-1-benzothiopyran-6'-yl]propenyl]benzoic acid 1',1'-dioxide

Compound B 4-(7,7,10,10-Tetramethyl-1-pyridin-3-ylmethyl-4,5,7,8,9,10-hexahydro-1H-naphto[2,3-g]indol-3-yl)-benzoic acid

Compound C (2E,4E,6Z)-7-[2-Butoxy-3,5-bis(1,1-dimethylethyl)phenyl]-3-methyl-2,4,6-octatrienoic acid

II In vitro assay for inhibition of differentiation of human naive T cells into T helper 2 (Th2) cells by retinoid antagonists.

Naive T cells from cord blood were isolated and treated as described [Panina-Bordignon et al. *J. Clin. Invest.* 100. 1513-1519 (1997)]. Briefly, cord blood derived mononuclear cells were incubated with anti-CD45RA and anti-CD4 monoclonal antibodies. After a 20 minute incubation, cells were washed and incubated with goat anti-mouse Ig-coated magnetic beads. Positive cells were separated and seeded at 1 x 10^6 cells/ml in a 24 well plate, together with autologous adherent cells, PHA, and IL-4 in the presence or absence of p-[(E)-2-[3',4'-Dihydro-4',4'-dimethyl-7'-(heptyloxy)-2'H-1-benzothiopyran-6'-yl]propenyl]benzoic acid 1',1'-dioxide (Compound A) or (2E,4E,6Z)-7-[2-Butoxy-3,5-bis(1,1-dimethylethyl)phenyl]-3-methyl-2,4,6-octatrienoic acid (Compound C) at 1mM for 5 days. Cells were then washed and put back in culture in the presence of IL-2 (100 U/ml). After 10 days, the cells were collected and restimulated with PMA (50 ng/ml) and ionomycin (1 μg/ml) for 4 hours. Brefeldin A (10 μg/ml) was added for the last 2 hours. Then the cells were fixed with 4% paraformaldehyde and permeabilized with saponin. Fixed cells were stained with FITC-anti IFNγ and PE-anti-IL-4mAbs and subjected to cytofluorimetric analysis.

The results of the experiment indicate that the tested retinoid antagonists reduce the differentiation of naive T cells into IL-4-secreting Th2 cells. (Table III)

Table III

Suppression of IL-4 expression in Th2 cells by retinoid antagonists

	IL-4 expressing cells	
	% gated cells	% Th2 cells
Th2	26.32	100
Th2 + Compound A	10.8	41
Th2 + Compound C	8.5	32

III. Murine model of allergen-induced airway inflammation and hyperresponsiveness.

C57BL/6 mice (8-9 weeks old) are actively sensitized to ovalbumin (OA) on day 0 and on day 14 by a intraperitoneal injection of 10 μg OA + 1 mg $Al(OH)_3$ (gel suspension) in 0.2 ml sterile saline. On day 21, the mice were challenged with 5.0 % OA aerosol for 18 minutes. The aerosol is generated by a De Vilbiss Ultra-Neb 90 ultrasonic nebulizer, the outlet of which is connected to a small plexiglass chamber containing the animals. The mice are dosed with the RXR antagonist Compound C (10 and 30 mg/kg intraperitoneally) daily for three days, 48 hours, 24 hours, and immediately prior to OA challenge. Animals are used on day 21.

- **Airway Inflammatory Cell Accumulation**

On day 24, three days after the challenge with OA aerosol, animals are anesthetized with urethane (2.4 g/kg) and tracheotomized with a 23 gauge catheter. Lungs are lavaged with aliquots (2 x 1 ml) of sterile Hank's balanced salt solution without Ca^{++} and Mg^{++}. Lavage fluid is recovered after 30 sec by gentle aspiration and pooled for each animal. Samples then are centrifuged at 2000 rpm for 15 minutes at 5 °C. Red blood cells are lysed from the resulting pellet with 0.5 ml distilled water and the cells remaining in the pellet are reconstituted with 5 ml HBSS. Samples are centrifuged a second time at 2000 rpm for 15 minutes at 5 °C. The resulting pellet is suspended in 1 ml of HBSS. Total cell number is determined from an aliquot of the cell suspension using a hemocytometer. For cytological preparations, the cells are fixed on cytocentrifuged slides stained with a modified Wright's stain. Differential counts on at least 300 cells are made using standard morphological criteria to classify cells.

The results of the experiments indicate that the tested retinoid antagonists inhibit the allergen-induced accumulation of airway inflammatory cells (Table IV)

Table IV

Suppression of airway inflammatory cell accumulation by retinoid antagonists in a mouse model of allergen-induced airway inflammation

	Cell Influx (cells/ml)			Percent of reduction	
	Vehicle	Compound C		Compound C	
		10 mg/kg	30 mg/kg	10 mg/kg	30 mg/kg
Total leukocytes	795000	488000	271000	39%	66%
Macrophages	443000	289000	172000	35%	62%
Eosinophils	335000	176000	91000	48%	73%

- **Airway Hyperresponsiveness**

On day 24, three days after the challenge with OA aerosol, animals are anesthetized with pentobarbital sodium (100 mg/kg, i.p.) and tracheotomized (PE-190). A jugular vein is cannulated with a sylastic tubing for i.v. drug delivery. Animals are placed in a whole body plethysmograph with a built-in pneumotachograph and mechanically ventilated (V_f=150/min., V_t=0.3ml; Model 683, Harvard Apparatus, S. Natic, MA) immediately following pancuronium bromide (0.1 mg/kg, i.v.) treatment. Tidal volume is obtained from an integration of the respiratory flow signal using a differential pressure transducer (Validyne DP 103-08, Northridge, CA). Transpulmonary pressure is measured with a differential pressure transducer (Validyne DP 45-30, Northridge. CA) as the difference between intratracheal pressure and intrapleural pressure (obtained from a cannula inserted into the intercostal space). Changes in lung resistance (cm H_2O / ml / s) to increasing doses of methacholine (30, 100, 300, 1000 µg/kg, i.v.) are calculated from transpulmonary pressure, tidal volume, and respiratory flow measurements using a Modular Instrument Signal Processing System (Malvern, PA).

The results of the experiments indicate that retinoid antagonists can prevent or reverse allergic airway inflammation and inhibit antigen-induced bronchoconstriction, typical for allergic airway diseases, such as allergic bronchial asthma.

Examples for formulations: capsules, tablets, sachets, lotions, gels, creams, aerosols and dry powder for inhalation. The active compounds in the following examples are

p-[(E)-2-[3',4'-Dihydro-4,4'-dimethyl-7'-(heptyloxy)-2'H-1-benzothio-pyran-6'-yl]propenyl]benzoic acid 1,1'-dioxide

or

(2E,4E,6Z)-7-[2-Butoxy-3,5-bis(1,1-dimethylethyl)phenyl]-3-methyl-2,4,6-octatrienoic acid

Example 1

Lotion (solution)		preferred	
Active compound	0.1-2.0 g		
Propylene Glycol	5.00-20.00 g	10.00 g	
PEG-Glyceryl Cocoate *	0.00-20.00 g	10.00 g	
dl-a-Tocopherol	0.001-0.50 g	0.02 g	
Ascorbyl Palmitate	0.01-0.20 g	0.10 g	
Propyl Gallate	0.001-0.02 g	0.002 g	
Citric acid, anhydr. **	0.00-0.20 g	0.01 g	
Isopropanol ***	40.00-90.00 g	50.00 g	
Water, dem. ad	100.00 g	100.00 g	resp. ml

* or other tensides

** or other complexing agents e.g. EDTA

*** or other alcohols e.g. Ethanol

Example 2

Gel		preferred	
Active compound	0.1-2.0 g		
Propylene Glycol	5.00-20.00 g	10.00 g	
PEG-Glyceryl Cocoate *	0.00-20.00 g	10.00 g	
dl-α-Tocopherol	0.001-0.50 g	0.02 g	
Ascorbyl Palmitate	0.01-0.20 g	0.10 g	
Propyl Gallate	0.001-0.02 g	0.002 g	
Citric acid, anhydr. **	0.00-0.20 g	0.01 g	
Isopropanol ***	40.00-90.00 g	50.00 g	
HPMC ****	0.50-5.00 g	3.00 g	
Preservative *****	q.s.	q.s.	
Water, dem. ad	100.00 g	100.00 g	resp. ml

* or other tensides

** or other complexing agents e.g. EDTA

*** or other alcohols e.g. Ethanol

**** Hydroxypropyl Methylcellulose or other polymers e.g. neutralised Carbomer, Methyl Cellulose, Sodium Carboxymethylcellulose

***** Preservatives e.g., Paraben esters (methyl, ethyl, propyl, butyl). Sorbic Acid. Benzoic Acid

Example 3

Cream		preferred
Active compound	0.1-2.0 g	
Glycerol	0.00-10.00 g	5.00 g
Na_2 EDTA	0.001-0.50 g	0.03 g
Glycerides *	5.00-20.00 g	10.00 g
Cetyl Alcohol	0.50-5.00 g	1.00 g
Stearyl Alcohol	0.50-5.00 g	1.00 g
Glycerol mono Stearate	1.00-8.00 g	4.00 g
Ceteareth **	0.50-5.00 g	2.00 g
dl-α-Tocopherol	0.001-0.50 g	0.02 g
Preservative ***	q.s.	q.s.
Water, dem. ad	100.00 g	100.00 g

* e.g. Caprylic/Capric/Triglyceride, Caprylic/Capric/Linoleic Triglycerides, natural glycerides, as well as e.g. Propylene Glycol, Dicaprylate/Dicaprate and waxes, such as Stearyl, Stearate,

Oleyl Oleate, Isopropyl Myristate

** Ceteareth 5-30, or other emulsifiers such as Polysorbase 20-80, Sorbitane esters of fatty acids, fatty acid esters of PEG.

*** Preservatives e.g., Paraben esters (methyl, ethyl, propyl, butyl). Sorbic Acid. Benzoic Acid

Example 4

Fill mass for soft gelatin capsules

Active compound	5.0-200.0 mg
Oil * 1-3 parts	
Wax mixture **	1-5 parts
Fill volume	1-6 minims

* natural vegetable oils, e.g. soy oil, peanut oil, and artificial glycerides

** composition of natural and artificial waxes or partially hydrated fats

20 mg Soft Gelatin Capsules

Ingredients	mg/capsule
Active compound	20.000
dl-α-Tocopherol	0.028
Hydrogenated Castor Oil	4.200
Caprylic/Capric/Stearic Triglyceride (Synthetic Triglyceride)	56.000
Triglyceride, Medium Chain	199.772
	Total 280.000 mg

Example 5

Hard Gelatine capsules containing 20 mg active substance:

Composition: One Capsule contains:

Active compound	20.0 mg
Gelatine Bloom 30	70.0 mg
Maltodextrin MD 05	108.0 mg
dl-α-Tocopherol	2.0 mg
Sodium ascorbate	10.0 mg
Microcrystalline cellulose	48.0 mg
Magnesium stearate	2.0 mg
(weight capsule content)	260.0 mg

Procedure:

The active substance is wet milled in a solution of gelatine, maltodextrin, dl-α-Tocopherol and sodium ascorbate.
The wet milled suspension is spray-dried.
The spray-dried powder is mixed with microcrystalline cellulose and magnesium stearate.
260 mg each of this mixture are filled into hard gelatine capsules of suitable size and color.

Example 6

Tablet containing 20 mg active substance:

Composition:

Tablet kernel:

Active compound	20.0 mg
Anhydrous lactose	130.5 mg
Microcrystalline Cellulose	80.0 mg
dl-α-Tocopherol	2.0 mg
Sodium ascorbate	10.0 mg
Polyvinylpyrrolidone K30	5.0 mg
Magnesium stearate	2.5 mg
(Kernel weight)	250.0 mg

Film coat:

Hydroxypropyl methylcellulose	3.5 mg
Polyethylenglycol 6000	0.8 mg
Talc	1.3 mg
Irone oxide, yellow	0.8 mg
Titanium dioxide	0.8 mg
(weight of the film)	7.4 mg

Procedure:

The compound is mixed with anhydrous lactose and microcrystalline cellulose.
The mixture is granulated in water with a solution/dispersion of polyvinyl-pyrrolidone, dl-α-Tocopherol and sodium ascorbate.
The granular material is mixed with magnesium stearate and afterwards pressed as kernels with 250 mg weight.
The kernels are film coated with a solution/suspension of above-mentioned compositions.

Example 7

Sachet containing active substance

Composition:

Active compound	200.0 mg
Lactose, fine powder	990.0 mg
Microcrystalline Cellulose	1250.0 mg
Sodium Carboxymethyl cellulose	14.0 mg
dl-α-Tocopherol	5.0 mg
Sodium ascorbate	20.0 mg
Polyvinylpyrrolidone K30	10.0 mg
Magnesium stearate	10.0 mg

Example 8

Aerosol for inhalation, metered dose inhaler

Active compound	0.5 % (0.1-2.0%)
Sorbitantrioleate	5 %
dl-α-Tocopherol	0.4%
Propellant (mixture of Trichlorofluoro-methane and Dichlorodifluoromethane)	94.1 %

Example 9

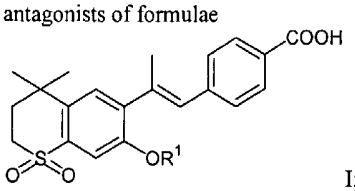
Dry powder inhaler

Active compound *	0.5 mg (0.1 mg - 2.0 mg)
Lactose monohydrate	25 mg

* jet-milled, spray-dried

The claims defining the invention are as follows:

1. The use of a compound selected from the group consisting of retinoid antagonists of formulae



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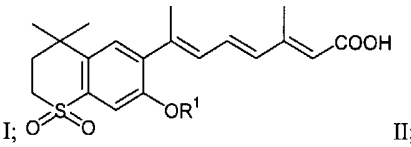

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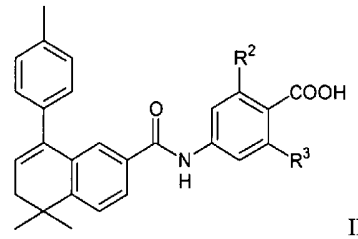
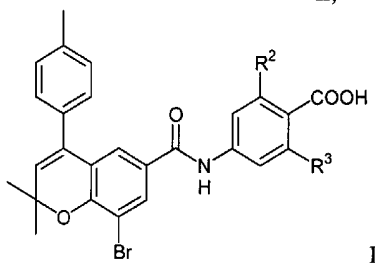
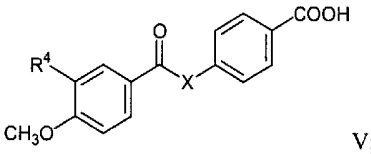


III; and

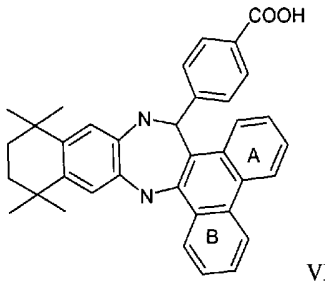


IV,

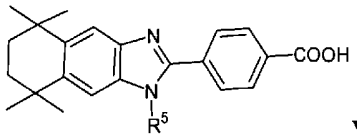
wherein R^1 is C_{5-10}-alkyl, and R^2 and R^3 independently of each other are hydrogen or fluorine;



V;

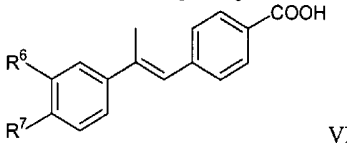


VI; and



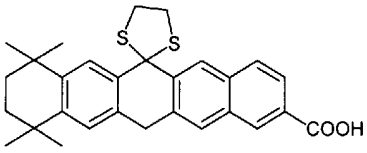
VII,

wherein R^4 is diamantyl, X is O or NH, R^5 is phenyl or benzyl, and wherein optionally either ring A or ring B is present;

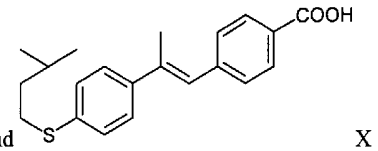


VIII,

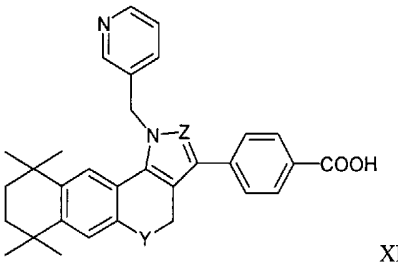
wherein R^6 and R^7 independently of each other hydroxy, C_{1-4}-alkoxy, optionally branched C_{1-5}-alkyl or adamantyl;



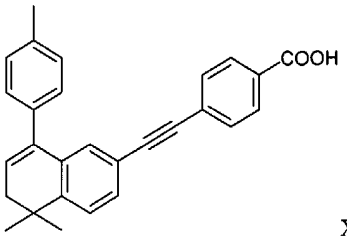
IX; and



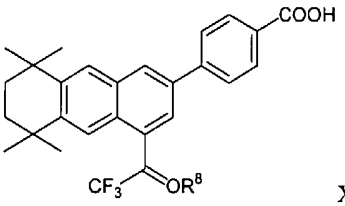
X



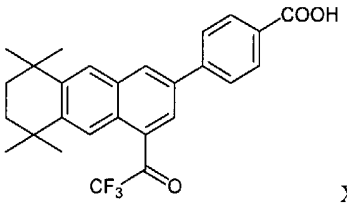
XI;



XII,

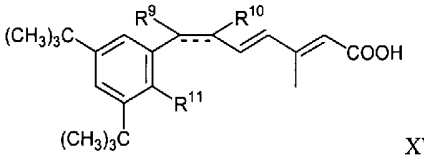


XIII; and

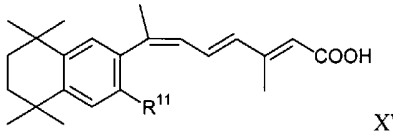


XIV

wherein Y is $-CH_2-$ or sulfur and Z is –CH= or nitrogen, and R^8 is hydrogen or C_{1-4}-alkyl;



XV; and



XVI;

wherein the dotted bond is optional; and, when the dotted bond is present, R^9 is methyl and R^{10} is hydrogen; and, when the dotted bond is absent, R^9 and R^{10} taken together are methylene to form a cis-substituted cyclopropyl ring; R^{11} is C_{1-4}-alkoxy; and pharmaceutically acceptable salts and pharmaceutically acceptable hydrolysable esters thereof, as active ingredient for the manufacture of a medicament for the treatment of T-helper cell type 2 (Th2)-mediated immune diseases, such as immunoglobulin E (IgE)-mediated allergic diseases or for the treatment of diseases mediated by Th2-related cytokines such as IL-4 and IL-5.

2. The use according to claim 1, wherein the active ingredient is used in combination with a pharmaceutically acceptable carrier.

3. The use according to claim 1 or 2, wherein the medicament is manufactured for oral or topical administration.

4. The use according to any one of claims 1 to 3, wherein the medicament is manufactured as a tablet, capsule, pill, sachet, ointment, cream, lotion, spray; nasal aerosol and aerosol or dry powder for inhalation.

5. The use according to any one of claims 1 to 4, wherein the medicament is manufactured as a tablet, capsule, pill or sachet containing 5 to 200 mg, of active ingredient.

6. The use according to claim 5, wherein the medicament is manufactured as a tablet, capsule, pill or sachet containing 20 to 100 mg, of active ingredient.

7. The use according to any one of claims 1 to 6, wherein the medicament is manufactured for oral daily dosage of from 0.05 mg to 20 mg, per kg of body weight.

8. The use according to claim 7, wherein the medicament is manufactured for oral daily dosage of from 0.3 mg to 1.5 mg, per kg of body weight.

9. The use according to any one of claims 1 to 4, wherein the medicament is manufactured as an ointment, cream, lotion, spray; nasal aerosol and aerosol or dry powder for inhalation containing 0.01 to 5 percent by weight, of the active ingredient.

10. The use according to claim 9 wherein the medicament is manufactured as an ointment, cream, lotion, spray; nasal aerosol and aerosol or dry powder for inhalation containing 0.1 to 1.0 percent by weight, of the active ingredient.

11. The use according to any one of claims 1 to 10, wherein the active ingredient is selected from the group consisting of retinoid antagonists of formulae I to XVI as defined in claim 1 and the alkali metal salts, alkaline earth metal salts, benzyl esters, lower alkyl esters and 9-fluorenylmethyl esters thereof.

12. The use according to any one of claims 1 to 11, wherein the medicament is manufactured for the treatment of immunoglobulin E (IgE)-mediated allergic diseases, including atopic dermatitis, allergic rhinitis and allergic bronchial asthma.

13. A method of treating T-helper cell type 2 (Th2)-mediated immune diseases, such as immunoglobulin E (IgE)-mediated allergic diseases or for the treatment of diseases mediated by Th2-related cytokines such as IL-4 and IL-5, said method comprising administering an effective amount of a compound selected from the group of retinoid antagonists of formulae I to XVI as defined in claim 1 or a pharmaceutically acceptable salt or pharmaceutically acceptable hydrolysable ester thereof, to a patient in need thereof.

14. The method according to claim 13, wherein the active ingredient is used in combination with a pharmaceutically acceptable carrier such that a medicament is administered.

15. The method according to claim 14, wherein the medicament is manufactured for oral or topical administration.

16. The method according to claim 15, wherein the medicament is manufactured as a tablet, capsule, pill, sachet, ointment, cream, lotion, spray; nasal aerosol and aerosol or dry powder for inhalation.

17. The method according to any one of claims 13 to 16, wherein the medicament is manufactured as a tablet, capsule, pill or sachet containing 5 to 200 mg, of active ingredient.

18. The method according to claim 17, wherein the medicament is manufactured as a tablet, capsule, pill or sachet containing 20 to 100 mg, of active ingredient.

19. The method according to any one of claims 13 to 18, wherein the medicament is manufactured for oral daily dosage of from 0.05 mg to 20 mg, per kg of body weight.

20. The method according to claim 19, wherein the medicament is manufactured for oral daily dosage of from 0.3 mg to 1.5 mg, per kg of body weight.

21. The method according to any one of claims 13 to 16, wherein the medicament is manufactured as an ointment, cream, lotion, spray; nasal aerosol and aerosol or dry powder for inhalation containing 0.01 to 5 percent by weight, of the active ingredient.

22. The method according to claim 21, wherein the medicament is manufactured as an ointment, cream, lotion, spray; nasal aerosol and aerosol or dry powder for inhalation containing 0.1 to 1.0 percent by weight, of the active ingredient.

23. The method according to any one of claims 13 to 21, wherein the active ingredient is selected from the group consisting of retinoid antagonists of formulae I to XVI as defined in claim 1 and the alkali metal salts, alkaline earth metal salts, benzyl esters, lower alkyl esters and 9-fluorenylmethyl esters thereof.

24. The method according to any one of claims 13 to 23, wherein the medicament is manufactured for the treatment of immunoglobulin E (IgE)-mediated allergic diseases, including atopic dermatitis, allergic rhinitis and allergic bronchial asthma.

25. A compound selected from the group of retinoid antagonists of formulae I to XVI as defined in claim 1 or a pharmaceutically acceptable salt or pharmaceutically acceptable hydrolysable ester thereof or a medicament containing the compound together with a pharmaceutically acceptable carrier when used for the treatment of T-helper cell type 2 (Th2)-mediated immune diseases, such as immunoglobulin E (IgE)-mediated allergic diseases or for the treatment of diseases mediated by Th2-related cytokines such as IL-4 and IL-5 in a patient in need thereof.

26. A compound or medicament when used as claimed in claim 25, wherein the medicament is manufactured for oral or topical administration.

27. A compound or medicament when used as claimed in claim 25 or claim 26, wherein the medicament is manufactured as a tablet, capsule, pill, sachet, ointment, cream, lotion, spray; nasal aerosol and aerosol or dry powder for inhalation.

28. A compound or medicament when used as claimed in any one of claims 25 to 27, wherein the medicament is manufactured as a tablet, capsule, pill or sachet containing 5 to 200 mg, of active ingredient.

29. A compound or medicament when used according to claim 28, wherein the medicament is manufactured as a tablet, capsule, pill or sachet containing 20 to 100 mg, of active ingredient.

30. A compound or medicament when used as claimed in any one of claims 25 to 29, wherein the medicament is manufactured for oral daily dosage of from 0.05 mg to 20 mg, per kg of body weight.

31. A compound or medicament when used as claimed in claim 30, wherein the medicament is manufactured for oral daily dosage of from 0.3 mg to 1.5 mg, per kg of body weight.

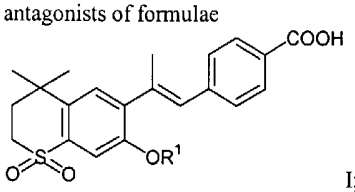
32. A compound or medicament when used as claimed in claim 25 or claim 26, wherein the medicament is manufactured as an ointment, cream, lotion, spray; nasal aerosol and aerosol or dry powder for inhalation containing 0.01 to 5 percent by weight, of the active ingredient.

33. A compound or medicament when used as claimed in claim 32, wherein the medicament is manufactured as an ointment, cream, lotion, spray; nasal aerosol and aerosol or dry powder for inhalation containing 0.1 to 1.0 percent by weight, of the active ingredient.

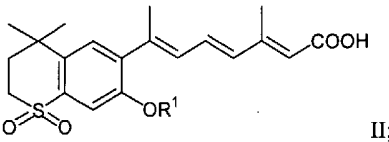
34. A compound or medicament when used as claimed in any one of claims 25 to 32, wherein the active ingredient is selected from the group consisting of retinoid antagonists of formulae I to XVI as defined in claim 1 and the alkali metal salts, alkaline earth metal salts, benzyl esters, lower alkyl esters and 9-fluorenylmethyl esters thereof.

35. A compound or medicament when used as claimed in any one of claims 25 to 34, wherein said treatment is of immunoglobulin E (IgE)-mediated allergic diseases, including atopic dermatitis, allergic rhinitis and allergic bronchial asthma.

36. The use of a compound selected from the group consisting of retinoid antagonists of formulae



I;



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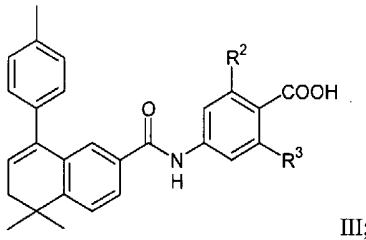
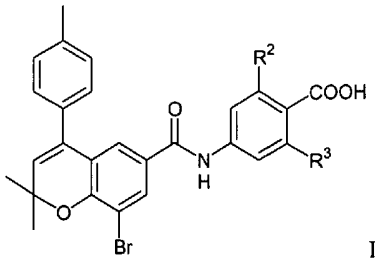
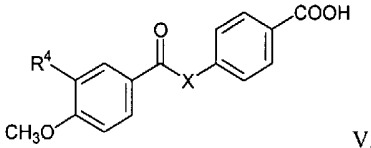


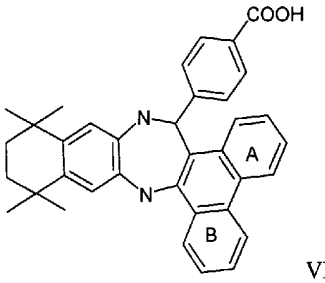


III; and IV,

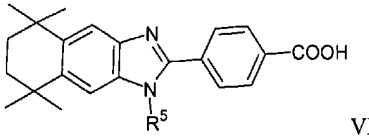
wherein R^1 is C_{5-10}-alkyl, and R^2 and R^3 independently of each other are hydrogen or fluorine;



V;

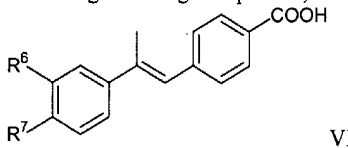


VI; and



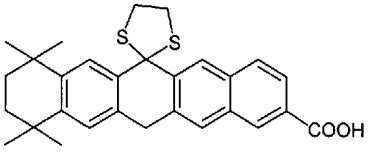
VII,

wherein R^4 is diamantyl, X is O or NH, R^5 is phenyl or benzyl, and wherein optionally either ring A or ring B is present;

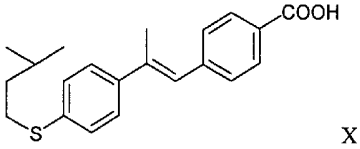


VIII,

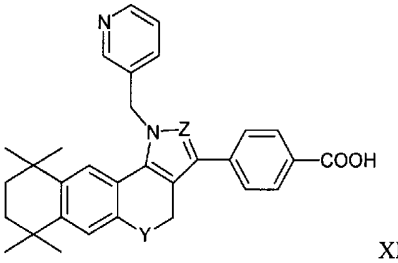
wherein R^6 and R^7 independently of each other hydroxy, C_{1-4}-alkoxy, optionally branched C_{1-5}-alkyl or adamantyl;

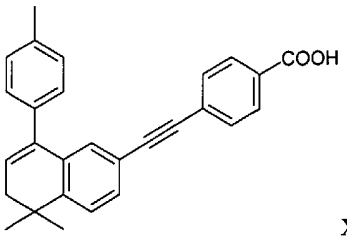


IX; and

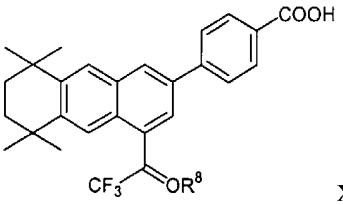


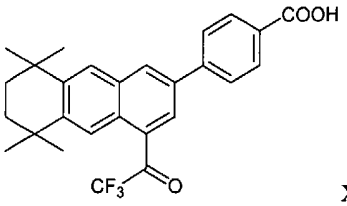
X





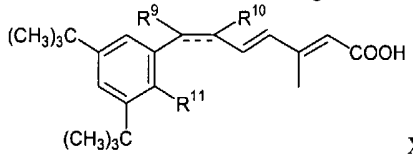
XI; XII,



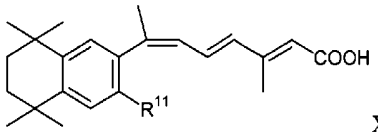


XIII; and XIV

wherein Y is $-CH_2-$ or sulfur and Z is –CH= or nitrogen, and R^8 is hydrogen or C_{1-4}-alkyl;



XV; and



XVI;

wherein the dotted bond is optional; and, when the dotted bond is present, R^9 is methyl and R^{10} is hydrogen; and, when the dotted bond is absent, R^9 and R^{10} taken together are methylene to form a cis-substituted cyclopropyl ring; R^{11} is C_{1-4}-alkoxy; and pharmaceutically acceptable salts and pharmaceutically acceptable hydrolysable esters thereof, as active ingredient for the manufacture of a medicament for the treatment of T-helper cell type 2 (Th2)-mediated immune diseases, such as immunoglobulin E (IgE)-mediated allergic diseases or for the treatment of diseases mediated by Th2-related cytokines such as IL-4 and IL-5, substantially as hereinbefore described with reference to any one of Examples 1 to 9.

Dated 6 March, 2002
F. Hoffmann-La Roche AG

Patent Attorneys for the Applicant/Nominated Person
SPRUSON & FERGUSON