METHOD OF MITIGATING THE ADVERSE EFFECTS OF INTERLEUKIN-2

CROSS REFERENCE

This is a continuation-in-part of USSN 60/098,341, filed August 28, 1998.

INTRODUCTION

Technical Field

This invention relates to mitigating adverse effects induced by interleukin-2 through the administration of an effective amount of a leukotriene receptor antagonist.

Background

Recombinant interleukin-2 (PROLEUKIN® or "IL-2") is an analogue of human native interleukin-2. While human native interleukin-2 is present in a human in small amounts, under certain conditions, i.e., the administration of IL-2 to treat certain conditions, excess levels (i.e., higher than normal levels) of IL-2 will be present in a subject's system. IL-2 is approved for the treatment of certain human malignancies including melanoma and renal cell carcinoma and is useful in treating certain viral conditions. The administration of IL-2 has been associated with "vascular leak syndrome" (VLS), which results from extravasation of plasma proteins and fluid into the extravascular space. It is known that, among other adverse signs or symptoms, VLS can cause generalized edema, systemic hypotension, reduced organ perfusion, and subsequent dysfunction of one or more organs. When sufficiently severe, VLS may cause significant disability or even death. The adverse effects of IL-2 may necessitate using a lower dose of IL-2, thereby diminishing the potential for therapeutic benefit from IL-2. An effective means of mitigating IL-2 toxicity would be beneficial.

Empirical approaches to treating VLS have included the use of corticosteroids, which, unfortunately, can reduce the antitumor effects of IL-2. The pluripotent filaricide diethylcarbamazine (DEC) has also been studied experimentally, but because of its

diverse pharmacological effects, the role of DEC in VLS is unclear. The antifolate methotrexate has also been suggested as a means of mitigating VLS. Unfortunately, methotrexate itself is quite toxic.

As the variety of potential interventions suggests, the pathogenesis of VLS is unknown. It has been demonstrated, however, that IL-2 increases plasma levels of leukotrienes, including leukotriene B4. It is also known that leukotrienes may unfavorably alter vascular permeability. Therefore, blocking leukotriene effects with a leukotriene antagonist (LA) during IL-2 therapy may mitigate VLS and lessen the adverse effects of IL-2.

Relevant Literature

1. Vetto J.T., et al. Reduction of Toxicity of Interleukin-2 and Lymphokine-Activated Killer Cells in Humans by the Administration of Corticosteroids. J. Clin Oncol 1987;5:496-503

2. Klausner J.M., et al. Interleukin-2-Induced Lung Permeability is Mediated by Leukotriene B4. Cancer 1990;66:2357-64.

3. Spiro R.C., et al. Inhibition of post-translational modification and surface expression of a melanoma-associated chondroitin sulfate proteoglycan by diethylcarbamazine or ammonium chloride. J. Biol. Chem. 1986;261:5121-9.

4. U.S. Patent No. 5,593,671.

5. U.S. Patent No. 4,889,871.

6. Staub N.D. et al. Preparation of chronic lung lymph fistula in sheep. J Surg Res 1975;19:315-20.

7. Edwards, M.J., et al. Interleukin Acutely Reduces Platelet and Neutrophil-Endothelial Adherence and Macromolecular Leakage, Cancer Research 52: 1992 3425-31.

Objects of the Invention

An object of this invention is to mitigate IL-2-associated adverse signs or symptoms, particularly those associated with VLS.

Another object of this invention is to reduce diagnostic testing required to monitor patient responses to IL-2 and to determine the success of therapeutic interventions required to mitigate IL-2-related adverse events.

Still another object of this invention is to reduce diagnostic testing needed to demonstrate that certain events are caused by IL-2 rather than by another agent,

Still another object is to reduce the costs associated with treating IL-2-induced adverse events, particularly those associated with VLS.

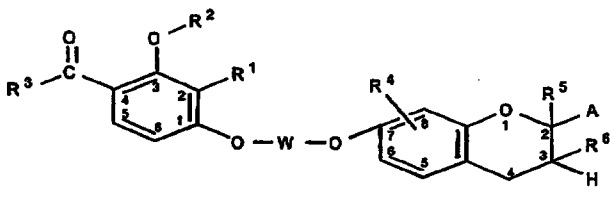
Other objects and advantages of the invention may be apparent to one of skill in the art upon reading the following specification and claims.

SUMMARY OF THE INVENTION

One aspect of this invention is a method of mitigating an adverse pharmacological effect of IL-2 in a subject. The method comprises administering to a subject receiving exogenous IL-2 an amount of a leukotriene receptor antagonist that is sufficient to mitigate the adverse effects. Another aspect is treating a malignancy or viral infection in a mammal by administering a therapeutically effective amount of IL-2 in combination with a leukotriene receptor antagonist in an amount sufficient to reduce IL-2 – induced adverse pharmacological effects, e.g., increased vascular permeability.

The preferred leukotriene receptor antagonist is represented by the Formula (I), or a stereoisomer or pharmaceutically acceptable salt thereof, wherein

(I)



R^1 represents alkyl having 2 to 6 carbon atoms, alkenyl having 2 to 6 carbon atoms, alkynyl having 2 to 6 carbon atoms, or $(CH_2)_nR$ wherein R represents cycloalkyl of 3 to 5 carbon atoms and n is 1 or 2;

R^2 represents hydrogen, methyl or ethyl;

R^3 represents alkyl having 1 to 5 carbon atoms;

W represents a bridging group such as $(CH_2)_x$ where x is 2 to 7, alkenylene having 3 to 7 carbon atoms, alkynylene having 3 to 7 carbon atoms or cyclopentyl;

R^4 represents hydrogen, alkyl having 2 to 5 carbon atoms, alkynyl having 2 to 5 carbon atoms, alkenyl having 2 to 5 carbon atoms, alkanoyl of 2 to 5 carbon atoms, or aralkanoyl of 7 to 9 carbon atoms;

R^5 represents hydrogen, alkyl having 1 to 6 carbon atoms, or R^5 represents alkanoyl having 2 to 4 carbon atoms, or $(CH_2)_y - CO_2R^8$ wherein y is 0 to 4 and R^8 is hydrogen or alkyl having 1 to 6 carbon atoms;

R^6 represents hydrogen or together with R^5 represents a carbon to carbon bond; and

A represents - Z - CO_2R^7 wherein R^7 represents hydrogen or alkyl having 1 to 6 carbon atoms, and wherein Z is absent or represents straight or branched chain alkylene or alkenylene having up to 6 carbon atoms.

Other leukotriene receptor antagonists include those set forth in U.S. Patent 4,788,214 and are incorporated herein by reference.

Another aspect of the invention may be viewed as an improvement in a method of treatment. In a method of treating a malignancy or viral infection in a mammal, which method comprises administering a therapeutically effective amount of IL-2, which administration also induces adverse pharmacological effects in the mammal, the

improvement comprises administering a leukotriene receptor antagonist in an amount sufficient to mitigate IL-2 induced adverse pharmacological effects.

Another aspect of this invention is a process for preparing a pharmaceutical composition. The process comprises combining a leukotriene receptor antagonist with a pharmaceutical excipient to form a composition useful for mitigating IL-2 induced, adverse pharmacological effects in a subject receiving exogenous IL-2.

Still another aspect of this invention is an article of manufacture that comprises a pharmaceutical composition comprising a leukotriene receptor antagonist as a unit dosage in combination with printed labeling instructions for administering the composition to a mammal undergoing treatment of a malignancy or viral infection with IL-2, wherein the amount of the composition administered is sufficient to mitigate IL-2 induced adverse pharmacological effects in the mammal being treated.

DESCRIPTION OF THE FIGURES

Figure 1: This figure presents comparative *in vivo* results showing the effects of a compound useful in this invention on the reduction of oxygention of arterial blood by IL-2 administration.

DETAILED DESCRIPTION AND PRESENTLY PREFERRED EMBODIMENTS

For purposes of this application the following definitions apply:

Alkyl means a fully saturated hydrocarbon radical having the number of carbon atoms indicated. For example, alkyl of 1 to 6 includes, e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl, n-pentyl, amyl, n-hexyl, and the like.

Alkenyl means a radical derived from an alkene, *i.e.*, hydrocarbon having a single double bond and having the number of carbons indicated. For example, alkenyl of 2-6 carbon atoms includes radicals derived from ethylene, propylene, 1-butene, 2-butene, isobutylene, 3, 3- dimethylpropylene, and the like.

Alkynyl means a radical derived from an alkyne, i.e., hydrocarbon having a single triple bond and having the number of carbons indicated. For example alkynyl of 1-6 carbon atoms includes acetylenyl, propynyl, 1-butynyl, 1 pentynyl, 1-hexynyl and the like.

Alkanoyl means a radical represented by the formula RC(O)- where R is alkyl of the number of carbons indicated.

Aralkanoyl means a radical represented by the formula ArC(O) – where Ar is an aryl group of the number of carbons indicated, e.g., phenyl (6 carbons).

LA is the abbreviation for leukotriene receptor antagonist.

Pharmaceutically-acceptable salts are those that are physiologically acceptable for pharmaceutical purposes and include, e.g., ammonium, potassium, sodium, alkaline earth, and the like.

A stereoisomer is one of a set of isomers whose molecules have the same atoms bonded to each other but differ in the way these atoms are arranged in space. Included in this are enantiomers, i.e., compounds that are mirror images of each other but that are not superimposable upon each other.

Compounds Useful in the Invention

While the LA useful in this invention may be any compound that antagonizes (i.e., blocks) a leukotriene receptor, preferably the compound is one that blocks the effects mediated by the leukotriene B4 receptor. A preferred class of compounds is represented by Formula (I) as set forth in the "Summary of the Invention" section of this application or a pharmaceutically acceptable salt thereof. In Formula (I),

R^1 represents hydrogen, alkyl having 1 to 6 carbon atoms, alkenyl having 2 to 6 carbon atoms, alkynyl having 2 to 6 carbon atoms, or $(CH_2)_nR$ wherein R represents cycloalkyl of 3 to 5 carbon atoms and n is 1 or 2;

R^2 represents hydrogen, methyl or ethyl;

R^3 represents alkyl having 1 to 5 carbon atoms;

W represents $(CH_2)_x$ where x is 2 to 7, alkenylene having 3 to 7 carbon atoms, alkynylene having 3 to 7 carbon atoms or cyclopentylene;

R^4 represents hydrogen, alkyl having 2 to 5 carbon atoms, alkynyl having 2 to 5 carbon atoms, alkenyl having 2 to 5 carbon atoms, alkanoyl of 2 to 5 carbon atoms or aralkanoyl;

R^5 represents hydrogen, alkyl having 1 to 6 carbon atoms, or R^5 represents alkanoyl having 2 to 4 carbon atoms, or $(CH_2)_Y$ - CO_2R^8 wherein $_Y$ is 0 to 4 and R^8 is hydrogen or alkyl having 1 to 6 carbon atoms;

R^6 represents hydrogen or together with R^5 represents a carbon to carbon bond; and

A represents - Z - CO_2R^7 wherein R^7 represents hydrogen or alkyl having 1 to 6 carbon atoms, and wherein Z is absent or represents straight or branched chain alkylene or alkenylene having up to 6 carbon atoms.

A preferred subgroup is represented by Formula (I) wherein R^1 represents alkyl having 2-4 carbon atoms; R^2 represents hydrogen, methyl or ethyl; R^3 represents alkyl having 1 to 3 carbon atoms; W represents $(CH_2)_x$ where x is 3 to 5, alkenylene having 3 to 5 carbon atoms, alkynylene having 3 to 5 carbon atoms, or cyclopentylene; R^4 represents alkyl having 2 to 4 carbon atoms, acetyl or benzoyl; R^5 represents hydrogen, or alkyl having 1 to 4 carbon atoms; and A represents - Z - CO_2R^7, wherein R^7 represents hydrogen or alkyl having 1 to 4 carbon atoms, and wherein Z is absent or represents alkylene having up to 2 carbon atoms; or a stereoisomer or pharmaceutically acceptable salt thereof of this subgroup. Particularly useful are compounds represented by Formula (I) wherein R^1 is n-propyl; R^2 and R^3 each is methyl; W is $(CH_2)_x$, where x is 3,4 or 5; R^4 is n-propyl; R^5 represents hydrogen or alkyl of 1 to 4 carbon atoms; and A represents - Z - CO_2R^7 wherein R^7 represents hydrogen or alkyl having 1 to 4 carbon atoms and Z is absent or represents alkylene having up to 2 carbon atoms; or a stereoisomer or a pharmaceutically acceptable salt thereof. Particularly preferred is a

leukotriene receptor antagonist as represented by Formula (I) wherein R^1 is n-propyl, R^2 and R^3 each is methyl, R^4 is n-propyl at the 8 - position. W is $(CH_2)_3$; R^5 is H; and A is $(CH_2)_p$ - COOH, where p is 0,1 or 2, especially 0 or a stereoisomer or a pharmaceutically acceptable salt thereof.

Other compounds useful in this invention are set forth in U.S. Patent 4,788,214.

The compounds represented by Formula (I) in which position 2 of the benzopyran ring is a chiral center exist in racemic form as a mixture of individual enantiomers (i.e., racemate), or as the pure individual enantiomers. Formula (I) is intended to cover the racemic mixture containing equal quantities of dextrorotatory (+) and levorotatory (-) enantiomers as well as the individual dextroratory enantiomer, the levorotatory enantiomer and other non-equal mixtures of enantiomers. The formula is to be interpreted as covering any stereoisomer of the compound.

Representative compounds include the following (or the corresponding pharmaceutically acceptable salts thereof or the stereoisomers):

7-[3-(4-acetyl-3-methoxy-2-propylphenoxy)propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid;

7-[[5-(4-acetyl-3-methoxy-2-propylphenoxy)pentyl]oxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid, ethyl ester;

7-[3-(4-acetyl-3-methoxy-2-propylphenoxy)propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-propanoic acid;

7-[3-(4-acetyl-3-methoxy-2-propylphenoxy)propoxy]-3,4-dihydro-2-methyl-8-propyl-2H-1-benzopyran-2-propanoic acid;

7-[3-(4-acetyl-3-methoxy-2-propylphenoxy)propoxy]-3,4-dihydro-2-methyl-8-propyl-2H-1-benzopyran-2-propanoic acid, methyl ester;

7-[3-(4-acetyl-2-(cyclopropylmethyl)-3-methoxyphenoxy) propoxy]-3,4dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid;

7-[[5-(4-acetyl-3-methoxy-2-propylphenoxy)pentyl]oxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid;

7-[5-(4-acetyl-3-hydroxy-2-propylphenoxy)-pentyloxy]-6-acetyl-3, 4-dihydro-2H-1-benzopyran-2-carboxylic acid; and

7-[5-(4-acetyl-3-hydroxy-2-propylphenoxy)-pentyloxy]-6-benzoyl-3, 4-dihydro-2H-1-benzopyran-2-carboxylic acid.

Preparation of Compounds Useful in this Invention

These compounds are prepared by processes set forth in U.S. Patent 4,889,871 issued December 26, 1989 to Djuric, et al. and U.S. Patent 4,788,214 issued November 29, 1988 to Cohen et al. These patents are incorporated herein by reference in their entirety. The compounds useful in this invention are prepared by methods that result in the racemic compound or by stereospecific methods that result in the individual stereoisomers.

U.S. Pat. No. 4,665,203 issued May 12, 1987 discloses methods for making some of the intermediates used in making compounds of the present invention. The patent is incorporated herein by reference.

Preferred compounds useful in this invention, where R^2 is methyl or ethyl, are generally prepared by alkylating the prior art phenol hydroxy (R^2 is H) compounds to form compounds of Formula (I) by conventional techniques. Thus, the reaction of the phenol hydroxy (R^2 is H) with methyl iodide in potassium carbonate provides the ether. Dimethyl sulfate in acetone and base is also useful in preparing ethers. Alternatively, intermediates can be alkylated prior to forming the $-O-(CH_2)_x-O-$ bridge. Hydrolysis of the ester compounds in the presence of lithium hydroxide and methanol gives the acid compounds.

The compounds of Formula (I) and those of U.S. Patent 4,788,214 that contain an asymmetric carbon atom at position 2 of the benzopyran ring are normally obtained from the synthesis as racemic mixtures. Resolution of the racemates into the corresponding

optically active isomers (enantiomers) can be carried out by persons skilled in the art using known procedures.

Compounds of Formula (I) when R^7 is hydrogen are carboxylic acids. A racemic mixture of a carboxylic acid may be resolved by first treating the racemate with an optically active amine base to form a mixture of diastereomeric salts. Examples of optically active amine bases that may be used for this purpose are (R)-(+)-∝-methylbenzylamine, (S)-(-)- ∝-methylbenzylamine, (1R,2S)-(-)-ephedrine, quinine, and quinidine. The thusly formed diastereomeric salts have different properties, such as solubility, and the diastereomers may therefore be separated by selective recrystallization from a suitable solvent. The optically active carboxylic acids may then be obtained by re-acidification of the separated diastereomeric salts.

Alternatively, a racemic mixture of a carboxylic acid may be treated with an optically active alcohol to form a mixture of diastereomeric esters. Examples of optically active alcohols that may be used for this purpose are (1R,2S,5R)-(-)-menthol, (1S,2R,5S)-(+)- menthol, (R)-(-)-2-octanol, and (S)-(+)-2-octanol. The thusly-formed mixture of diastereomeric esters may then be separated by chromatography. The optically active carboxylic acids may then be obtained from the separated diastereomeric esters by conventional techniques, such as treatment of the esters with sodium hydroxide or lithium hydroxide followed by reacidification.

Compounds of Formula (I) when R^7 is alkyl are esters. A racemate of the esters may be resolved into the enantiomers by first resolving a racemic mixture of the corresponding carboxylic acid using one of the methods described above. The optically active ester may be obtained by esterification of the corresponding optically active carboxylic acid by procedures similar to those used to prepare a racemic ester.

Alternatively, a racemic mixture of a carboxylic acid of Formula (I) or a racemic mixture of an ester of Formula (I), may be separated into the individual enantiomers by high performance liquid chromatography using a suitable chiral stationary phase and a suitable eluent.

Administration of Compounds Useful in this Invention

An aspect of this invention is a method of mitigating an adverse pharmacological effect of IL-2 in a subject at risk of, or in fact exhibiting, such effect. The method comprises administering to a subject receiving IL-2 an amount of a leukotriene receptor antagonist that is sufficient to mitigate the adverse effects of the IL-2. Generally the excess IL-2 is a result of IL-2 (e.g., PROLEUKIN®) administration to treat a malignancy, acquired immunodeficiency syndrome (AIDS) or other malady.

To mitigate the adverse effects induced by IL-2 administration, a compound is delivered at a level sufficient to reduce those effects. That amount will vary somewhat from subject to subject but generally will be in the range of about 0.1 mg to about 10.0 mg per kilogram of body weight per day. The preferred range is from 0.1 to 5.0 mg/kg/day while the most preferred range is from 1.0 to 5.0 mg/kg/day. Thus, for a 50 kg person, about 5.0 to 500 mg/day would be administered. For a 70 kg person about 7.0 to 700 mg/day.

In general, the adverse pharmacological effect of IL-2 in a subject will occur during the treatment of the subject for an IL-2-responsive disease state. Thus, the method, along with other aspects of the invention, is useful in treating a subject having a leukotriene receptor in its system. This generally includes mammals, such as livestock and pets, and particularly humans. Thus, this invention will find use in treating humans of all ages as well as in treating animals, i.e., in veterinary uses. The invention may be used for treating livestock such as cattle, sheep, pigs, goats, and the like or for treating household pets such as dogs, cats, rabbits, hamsters, mice, rats, and the like. The primary utility is for treating humans. IL-2 is administered to a human as part of the treatment of a malignant tumor, i.e., cancer, or a viral disease such as AIDS. The adverse pharmacological effect often seen in such treatment is increased vascular permeability, e.g., VLS. The signs and symptoms of the adverse pharmacological effect are, for example, cardiovascular (hypotension requiring pressors; arrhythmias, pericardial effusion); pulmonary (congestion, dyspnea, pulmonary edema); hepatic (increased bilirubin, jaundice, ascites); hematologic (anemia, thrombocytopenia, leukopenia);

gastrointestinal (nausea, emesis, diarrhea, gastrointestinal bleeding); renal (oliguria/anuria, decreased excretory function); dermatologic (pruritus, erythema, rash); musculoskeletal (arthralgia, myalgia); general (fever, pain, fatigue, weakness, edema, infection, weight gain, headache).

Thus, another aspect of this invention is a method of treating a malignancy or viral disease in a mammal, which method comprises administering a therapeutically effective amount of IL-2 in conjunction with the LA, as described herein, in an amount sufficient to mitigate IL-2-induced adverse physiological effects. The method may be performed by administering the IL-2 and the LA in combination as a unit dosage or the IL-2 and the LA may be administered individually, with the LA being administered before, during or after the administration of the IL-2. The LA may be administered orally before, during or after the IL-2 is administered.

Viewed another way, this invention may be seen as an improvement in a method of treating a malignancy, or other malady requiring IL-2 treatment. The subject method comprises administering a therapeutically effective amount of IL-2. Because this treatment induces adverse pharmacological effects in the mammal, the improvement of this invention comprises administering the LA in an amount sufficient to mitigate IL-2 induced adverse pharmacological effects.

Human recombinant interleukin-2 is a well-studied, well-characterized and effective antineoplastic drug with well documented, often severe, and sometimes life-threatening or fatal side effects. One of the most serious is VLS, which can affect the entire body, but is often most serious when affecting the lungs.

According to the "package insert" provided by Chiron Therapeutics, IL-2 (PROLEUKIN®) is a highly purified protein with a molecular weight of approximately 15,300 Daltons. The chemical name is des-alanyl-1, serine-125 human interleukin-2. IL-2, a lymphokine, is produced by recombinant DNA technology using a genetically engineered E. coli strain containing an analogue of the human interleukin-2 gene. Genetic engineering techniques were used to modify the human IL-2 gene, and the resulting expression clone encodes a modified human interleukin-2. This recombinant

form differs from the native interleukin-2 in the follow ways: a) IL-2 is not glycosylated because it is derived from E. coli; b) the molecule has no N-terminal alanine; the codon for this amino acid was deleted during the genetic engineering procedure; c) the molecule has serine substituted for cysteine at amino acid position 125; this was accomplished by site specific manipulation during the genetic engineering procedure; and d) the aggregation state of PROLEUKIN® is likely to be different from that of native interleukin-2.

In addition, Chiron Therapeutics indicates that certain *in vitro* studies were performed to determine the properties of PROLEUKIN® and that these include: a) enhancement of lymphocyte mitogenesis and stimulation of long-term growth of human interleukin-2 dependent cell lines; b) enhancement of lymphocyte cytotoxicity; c) induction of killer cell (lymphokine-activated [LAK] and natural [NK] activity; and d) induction of interferon-gamma production. In *in vivo* studies, IL-2 produces multiple immunological effects in murine models in a dose-dependent manner. These include: a) activation of cellular immunity with profound lymphocytosis, eosinophilia, and thrombocytopenia; b) the production of other cytokines such as tumor necrosis factor, interleukin-1, and gamma interferon; c) inhibition of tumor growth. In addition, as noted previously, interleukin-2 has now been shown to stimulate the production of potentially toxic and inflammatory leukotrienes. Despite the large amount of knowledge concerning the effects of IL-2, the exact mechanism by which IL-2 mediates its antitumor (and toxic) effects in humans is unknown.

A compound useful in this invention is administered to an appropriate subject in need of these compounds by a medically acceptable route of administration such as orally, parenterally (e.g., intramuscularly, intravenously, subcutaneously, interperitoneally), transdermally, rectally, by inhalation and the like.

Unit doses or multiple dose forms are contemplated, each offering advantages in certain clinical settings. The unit dose would contain a predetermined quantity of active compound calculated to produce the desired effect(s) in the setting of IL-2 coadministration. The multiple dose form may be particularly useful when multiples of

single doses, or fractional doses, are required to achieve the desired ends. Either of these dosing forms may have specifications that are dictated by or directly dependent upon the unique characteristic of the particular compound, the particular therapeutic effect to be achieved (e.g., the attenuation of IL-2 toxicity, especially VLS), and any limitations inherent in the art of preparing the particular compound for treatment of IL-2 toxicity or VLS in living subjects.

A unit dose will contain an amount sufficient to mitigate the adverse effects induced by excess IL-2 in a subject and may contain from about 5.0 to 1000 mg of compound with the preferred range being 50 to 350 mg. The multiple dose form could contain from 0.2 to 4,000 mg with the preferred range being 100 to 500 mg.

The compound will preferably be administered orally in a suitable formulation as an ingestible tablet, a buccal tablet, capsule, caplet, elixir, suspension, syrup, trouche, wafer, lozenge, and the like. Generally, the most straightforward formulation is a tablet or capsule (individually or collectively designated as an "oral dosage unit"). Suitable formulations are prepared in accordance with a standard formulating techniques available that match the characteristics of the compound to the excipients available for formulating an appropriate composition. A tablet or capsule will contain about 25 to about 500mg of a compound of Formula (I), preferably about 50-250mg, and most preferably about 100-200mg.

The form may deliver the LA rapidly or may be a sustained-release preparation. The LA may be enclosed in a hard or soft capsule, may be compressed into tablets, or may be incorporated with beverages, food or otherwise into the diet. The percentage of the final composition and the preparations may, of course, be varied and may conveniently range between 1 and 70% of the weight of the final form, e.g., tablet. The amount of LA in such therapeutically useful compositions is such that a suitable dosage will be obtained. Preferred compositions according to the current invention are prepared so that an oral dosage unit form contains between about 2.5 to about 50 LA by weight (%w) in dosage units weighing between 50 and 1000 mg.

The suitable formulation of an oral dosage unit may also contain: a binder, such as gum tragacanth, acacia, corn starch, gelatin; sweetening agents such as lactose or sucrose; disintegrating agents such as corn starch, alginic acid and the like; a lubricant such as magnesium stearate; or flavoring such a peppermint, oil of wintergreen or the like. Various other material may be present as coating or to otherwise modify the physical form of the oral dosage unit. The oral dosage unit may be coated with shellac, a sugar or both. Syrup or elixir may contain the LA, sucrose as a sweetening agent, methyl and propylparabens as a preservative, a dye and flavoring. Any material utilized should be pharmaceutically-acceptable and substantially non-toxic. Details of the types of excipients useful may be found in the nineteenth edition of "Remington: The Science and Practice of Pharmacy," Mack Printing Company, Easton, PA. See particularly chapters 91-93 for a fuller discussion.

A compound may be administered parenterally, e.g., intravenously, intramuscularly, intravenously, subcutaneously, or interperitonieally. The carrier or excipient or excipient mixture can be a solvent or a dispersive medium containing, for example, various polar or non-polar solvents, suitable mixtures thereof, or oils. As used herein "carrier" or "excipient" means a pharmaceutically acceptable carrier or excipient and includes any and all solvents, dispersive agents or media, coating(s), antimicrobial agents, iso/hypo/hypertonic agents, absorption-modifying agents, and the like. The use of such substances and the agents for pharmaceutically active substances is well known in the art. Except in so far as any conventional media or agent is incompatible with the active ingredient, use in therapeutic compositions is contemplated. Moreover, other or supplementary active ingredients can also be incorporated into the final composition.

Solutions of the inhibitor may be prepared in suitable diluents such as water, ethanol, glycerol, liquid polyethylene glycol(s), various oils, and/or mixtures thereof, and others known to those skilled in the art.

The pharmaceutical forms suitable for injectable use include sterile solutions, dispersions, emulsions, and sterile powders. The final form must be stable under conditions of manufacture and storage. Furthermore, the final pharmaceutical form must

be protected against contamination and must, therefore, be able to inhibit the growth of microorganisms such as bacteria or fungi. A single intravenous or intraperitoneal dose can be administered. Alternatively, a slow long term infusion or multiple short term daily infusions may be utilized, typically lasting from 1 to 8 days. Alternate day or dosing once every several days may also be utilized.

Sterile, injectable solutions are prepared by incorporating a compound in the required amount into one or more appropriate solvents to which other ingredients, listed above or known to those skilled in the art, may be added as required. Sterile injectable solutions are prepared by incorporating the compound in the required amount in the appropriate solvent with various other ingredients as required. Sterilizing procedures, such as filtration, then follow. Typically, dispersions are made by incorporating the compound into a sterile vehicle which also contains the dispersion medium and the required other ingredients as indicated above. In the case of a sterile powder, the preferred methods include vacuum drying or freeze drying to which any required ingredients are added.

In all cases the final form, as noted, must be sterile and must also be able to pass readily through an injection device such as a hollow needle. The proper viscosity may be achieved and maintained by the proper choice of solvents or excipients. Moreover, the use of molecular or particulate coatings such as lecithin, the proper selection of particle size in dispersions, or the use of materials with surfactant properties may be utilized.

Prevention or inhibition of growth of microorganisms may be achieved through the addition of one or more antimicrobial agents such as chlorobutanol, ascorbic acid, parabens, thermerosal, or the like. It may also be preferable to include agents that alter the tonicity such as sugars or salts.

Another aspect of this invention is an article of manufacture that comprises a pharmaceutical composition comprising a leukotriene receptor antagonist (as described herein) as a unit dosage in combination with printed labeling instructions for administering the composition to a mammal undergoing treatment of a malignancy or

viral disease with IL-2, wherein the amount of the composition administered is sufficient to reduce IL-induced adverse pharmacological effects in the mammal being treated.

An advantage of this invention is that it obviates the need to place patients into intensive care units and onto respirators in the case of severe pulmonary edema, or to place patients into cardiac or coronary care units in the case of severe arrhythmias or congestive heart failure or onto dialysis protocols in the case of renal compromise. A further advantage is the reduction of intensive nursing care or supportive care or need of ICUs or CCUs.

Moreover, the mitigation of IL-2-related adverse events enables the safe administration of higher doses of IL-2 such that the antitumor efficacy of the combined regimen (LA+IL-2) is superior to IL-2 alone.

A compound of particular value in this invention is (±)7-[3-(4-acetyl-3-methoxy-2-propylphenoxy)propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid. The compound is a potent, highly selective leukotriene B4 receptor antagonist. A summary of its properties appears below.

***In Vitro* Pharmacology**

Inhibition of LTB4 binding to human neutrophils

IC50 = 0.3 micromolar

Inhibition of LTB4 chemotaxis

range = 0.3 - 3.0 micromolar

Inhibition of human neutrophil adhesion to LTB4-stimulated umbilical vein endothelial cells

range = 0.3 - 1.0 micromolar

Inhibition of LTB4-induced neutrophil granulation

range = 1 – 3 micromolar

Inhibition of LTB4 synthesis

IC50 = 2.1 micromolar

Inhibition of LTA4 conversion into LTB4

IC50 = 20 micromolar

***In Vivo* Pharmacology**

Inhibition of LTB4 chemotaxis in guinea pigs

ED50 = 0.6 mg/kg i.g.

Inhibition of 12 (R) - HETE in guinea pigs

ED50 = 20 mg/kg i.g.

Inhibition of acetic acid colonic inflammation in rats and guinea pig

ED50 = 20 mg/kg i.g.

Inhibition of calcium ionophore dermal inflammation in the guinea pig ear

ED50 = 0.7 mg/ear

These *in vitro* and *in vivo* data establish the potency and selectivity of the preferred compound and are particularly relevant to diminishing, *i.e.*, mitigating the unwanted effects of IL-2. These data are also particularly relevant to establishing that leukotriene B4 mediated responses, including VLS, whether induced initially by administration of IL-2 or by other means, are blunted by the preferred compound.

All publications and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

The invention now being fully described, it will be apparent to one of ordinary skill in the art that many changes and modifications can be made thereto without departing from the spirit or scope of the appended claims.

Example 1

This example is a reproduction (without formulae) of Example 1 from U.S. Patent 4,889,871 and sets forth a method for making a preferred compound useful in this invention,7-[3-(4-acetyl-3-methoxy-2-propylphenoxy)propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid.

(a) 493 mg of methyl 7-[3-(4-acetyl-3-hydroxy-2-propylphenoxy)propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylate was added to 25 ml of acetone containing 276 mg of anhydrous potassium carbonate and 282 mg of methyl iodide. The mixture was refluxed for about 24 hours and water was added and the mixture was then extracted with ethyl acetate. The extract was dried, the solvent removed under vacuum, and the residual oil was chromatographed over silica gel with a 40/60 mixture of ethyl acetate/hexane to provide pure-methyl ether, methyl 7-[3[(4-acetyl-3-methoxy-2-propylphenoxy)propoxy]-3,4-dihydro-8- propy-2H-1-benzopyran-2-carboxylate.

(b) The methyl ether (340 mg) was dissolved in methanol (5 ml) containing lithium hydroxide (0.7 ml of a 2N LiOH solution in water). The mixture was stirred at room temperature overnight and the solvent removed in vacuo. The residue was partitioned between ethyl acetate and 2N HCl and the organic layer separated and washed with brine. Evaporation of the volatiles in vacuo afforded crude acid. This material was purified by silica gel chromatography using ethyl acetate/hexane/acetic acid (40:60:0.5) as eluant. The pure product was recrystallized from ethyl acetate/hexane to afford 200 mg of product, 7-[3-(4-acetyl-3-methoxy-2-propylphenoxy)propoxy]- 3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid, m.p. 65°-68° C.

Microanalysis: Found: C 69.22, H 7.53. Theory: C 69.40, H 7.49.

The NMR ($CDCl_3$) shows a $-OCH_3$ at δ3.75.

Example 2

This example explains how compound of Formula (I) is administered to sheep to mitigate the adverse effect of excess IL-2.

Preparation of Sheep

Yearling male or female interbred sheep (N Å 24) and weighing approximately 20 to 40 kg are prepared with chronic lung lymph fistulae essentially according to a modification of the technique described by Staub et al (see "Relevant Literature," supra at 6 and as further described within reference 2 herein and other references cited within reference 2). Through a thoracotomy, the efferent duct of the caudal mediastinal lymph node is cannulated, the distal portion of the lymph node below the level of the inferior pulmonary ligament is ligated, and the diaphragm around the lymph node is circumferentially cauterized or otherwise securely closed. All visible systemic lymph tributaries to the proximal portion are cauterized or ligated to minimize extra-pulmonary contamination of collected lymph. A suitable thermistor-tipped pulmonary arterial and central venous catheter are introduced through the right internal jugular vein. The aorta is then cannulated via the adjacent carotid artery. After a recovery period of a variable number of days, preferably 4-5, when the animals appear vigorous again, are afebrile, and have a steady flow of blood-free lymph, the experiment is conducted.

Measurement of Cardiopulmonary Function

To measure cardiopulmonary function, suitable strain-gauge transducers are used to measure the following pressures: mean arterial pressure (MAP); mean pulmonary wedge pressure (MPAP, and the pulmonary arterial wedge pressure (PAWP). The pulmonary microvascular pressure (Pmv) is calculated from the Gaar equation where Pmv = PAWP + 0.4 ¥ (MPAP-PAWP). Pulse rate is determined from the arterial pressure tracings. Cardiac output is measured serially by thermodilution or dye techniques using suitable, standard equipment. Arterial blood gases, pH, oxygen saturation, and hemoglobin levels are also measured with suitable, standard laboratory equipment and by spectrophotometry using extinction coefficients determined for the species being tested.

Hematology

Circulating platelets and leukocytes are counted by means of standard laboratory equipment or by phase microscopy while leukocyte differential counts are determined by counting microscopically on ruled stages of Wright's stained blood smears.

Biochemical Assays

Concentrations of leukotrienes and thromboxanes are measured using standard radioimmunoassays. Such measurements are or can be made on lung lymph as well. In addition, lymphatic (LY) and plasma (PL) total protein concentrations are determined by using standard spectrophotometric techniques. The LY/PL protein ratio is calculated and multiplied by lymph flow (QL) to obtain the lymphatic protein clearance rate.

IL-2

The recombinant interleukin-2 (PROLEUKIN®) is utilized. The dose of IL-2 can be varied as desired. The preferred range is 1,000 to 1,000,000 IU/kg while the most preferred range is 400,000 to 800,000 IU/kg.

Protocol

Experiments are or can be performed on conscious, instrumented sheep having free access to food and water. Sheep are allowed to stand or recline as desired. Transducers are re-leveled as necessary to accommodate the sheep stance or posture. Baseline measurements are obtained for variable lengths of time with the preferred period being at least one hour.

Certain animals receive IL-2 alone, 400,000 to 800,000 IU/kg, given either as a bolus injection over one to several minutes or as a slower infusion over several minutes to several hours. Other animals receive the same IL-2 treatment but also receive, for example, the compound. The compound may be given by any of the routes identified previously. For simplicity in the animal laboratory, intravenous dosing is preferred although oral dosing is also acceptable. Effective doses of the LA range from 0.1 mg/kg/day to 10 mg/kg/day, while the preferred dose range is 0.1 to 2.0 mg/kg/day and the most preferred dose range is 0.5 to 1.0 mg/kg/day. When given intravenously, the LA may be dosed either as a bolus injection over one to several minutes or as a slower infusion over several minutes to several hours. Maintaining continuous but not necessarily invariant levels of LA during IL-2 exposure is preferred but is not necessary. LA dosing may begin before, during, or after the IL-2 administration. It is preferred to begin LA before IL-2 administration and is most preferred to begin dosing at least one hour prior to the start of IL-2 administration. The purpose of this prophylactic regimen is to establish effective blockade of the leukotriene receptors prior to IL-2- induced increases in plasma levels of leukotrienes.

Cardiopulmonary function, lymph flows and protein content, hematology and other chemical laboratory tests are assessed during and for several hours after IL-2 administration begins. In this model it is preferred to monitor animals as described for a period of 4-6 hours.

Results

The *in vitro* and *in vivo* results demonstrate the effectiveness of the referenced compound in mitigating, reducing or eliminating leukotriene B4 induced biological responses. Appropriate analysis of the data from the ovine experiment described herein extend the beneficial effects of LA's, LA's preferably, and the referenced LA most preferably, to the setting of preventing IL-2-induced VLS and adverse alterations in cardiopulmonary function and laboratory testing.

Example 3

This example explains how a compound of Formula (I) is administered to rats to mitigate the adverse effect of excess IL-2 in rats.

Test Material

A preferred LA compound, (±) 7 – [3-(4-acetyl-3-methoxy-2-propylphenoxy) propoxy]-3, 4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid, (Lot Number 101-8802) was supplied as a white crystalline solid by BioMedicines, Inc. For intraperitoneal (i.p.) injection, the LA was freshly dissolved in a mixture of 0.1 M potassium phosphate buffer (pH 6.8), ethanol, and propylene glycol (65:20:15 by volume). The concentration of the LA solution was adjusted so that the volume for each injection was 3 ml/kg for all groups.

IL-2

Proleukin® for Injection (Chiron Therapeutics) recombinant human interleukin-2 (IL-2), is supplied as a lyophilized powder in vials containing 22 million international units (MIU). For intravenous (i.v.) injection, Proleukin was reconstituted with Sterile Water for Injection, USP, to provide a solution of 18 million IU/ml. The reconstituted solution was further diluted with 5% Dextrose Injection, USP as needed so that the volume for each injection was 0.208 ml/rat. The dose can be varied as usual. The preferred range for purposes of this example is 6 – 24 MIU/kg while the most preferred range is 10-15 MIU/kg. Any of the previously mentioned routes of administration may be used. The preferred route is i.v. or intraperitoneal (i.p.) while the most preferred, for purposes of this example, is i.v.

Animals

Male Sprague Dawley rats were obtained from Harlan Sprague Dawley, Inc., Indianapolis, Indiana. All rats were six to eight weeks old and weighed approximately 250 to 300 g when used in the experiments. Each animal was numbered on the tail with indelible ink. The animals were housed in groups of up to three per cage and were allowed access to standard chow and water ad libitum. The study was conducted at an AAALAC accredited facility in compliance with the National Institutes of Health "Guide for the Care and Use of Laboratory Animals," Publication No. 86-23 and the USDA Laboratory Animal Welfare Act, Publication L. 89-544.

Experimental Protocol

Six groups of animals were studied (total N = 57) in a modification of the technique of Edwards et al (Edwards MJ, Miller FN, Simms DE et al. Interleukin-2 Acutely Induces Platelet and neutrophil-Endothelial Adherence and Macromolecular Leakage. Cancer Research 52: 1992:3425-31). Animals were weighed on the day of dosing and the appropriate doses of IL-2 and/or LA were calculated. The animals remained conscious throughout the experiment until an anesthetic was administered approximately 10 minutes before exsanguination. The anesthetic consisted of a mixture of ketamine (45 mg/ml) xylazine (2.5 mg/ml), and acepromazine (0.37 mg/ml) diluted with water and administered subcutaneously at a dose of 2.0 ml/kg.

Group 1 (n=14) consisted of control animals that received both i.v. and i.p. injections of vehicle. The other five groups received i.v. injections of IL-2 via the tail vein. Groups 2 (n = 8), 3 (n = 4), and 4 (n = 10) received IL-2 in doses of 1.5, 6.0, and 12.5 million IU(MIU)/kg, respectively. In addition to 12.5 million IU/kg of IL-2, Groups 5 (n = 8) and 6 (n = 13) received i.p. injections of the LA. The LA was administered in two equal, divided doses; the first dose of LA was given 20 minutes before administration of IL-2 and the second dose was given 50 minutes after administration of IL-2. Group 5 was administered 2 x 10 mg/kg of the LA. Group 6 was administered 2 x 30 mg/kg of the LA.

Two hours after the IL-2 injection, the animals were exsanguinated via the abdominal aorta and the arterial blood was collected for measurement of PaO2.

Measurement of Blood Oxygen Levels

Whole arterial blood was collected into heparinized blood arterial gas syringes. Immediately after collection, the blood sample was analyzed using PaO2 electrode model DO-166FT. Sample blood was pre-oxygenated and used as a standard before and after each test sample.

Analysis of Data

Data are shown as mean ± SEM. Data were analyzed using the Tukey-Kramer test (JMP® statistical software from SAS, Inc.) Significance was defined as a p-value less than 0.05.

Results of *In vivo* Study

Progressively higher doses of interleukin-2 progressively reduced arterial oxygen levels in the rodent. With a dose of 12.5 MIU IL-2, oxygen levels in the rat declined from a control value of 93.0±2.2 mm Hg to 77.5 ± 2.5 mm Hg ($p<0.001$). When LA was administered as described the reduction in oxygenation induced by IL-2 was mitigated ($p>.0.5$ vs control and $p< 0.001$ vs IL-2 alone for both LA-treated groups; see Figure 1).

Discussion

Interleukin-2 predictably lowers arterial oxygenation in humans when administered in a sufficiently high dose. This is an adverse pharmacological effect. This reduction in oxygenation is attributable to impaired ventilatory responses that occur, at least in part, because of the VLS induced by IL-2. The current *in vitro* findings demonstrate that the LA utilized in this example blocks leukotriene B4 receptors and thereby reduces leukotriene B4 activity. Furthermore, the *in vivo* findings demonstrate that the administration of an LA prevents the clinically important adverse event of hypoxemia associated with exposure to IL-2 and thereby demonstrating a beneficial effect in preventing the VLS caused by IL-2.

The subject matter claimed is:

1. A method of mitigating an adverse pharmacological effect of IL-2 in a subject, which method comprises administering to a subject at risk of, or in fact exhibiting, such adverse effect an amount of a leukotriene receptor antagonist that is sufficient to mitigate the adverse effect.

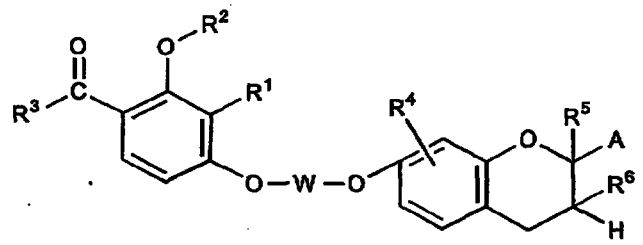
2. The method of Claim 1 wherein IL-2 is administered to a human as part of the treatment of a malignancy or a viral disease.

3. The method of Claim 1 wherein the adverse pharmacological effect is increased vascular permeability.

4. The method of Claim 3 wherein the signs and symptoms of the adverse pharmacological effect include edema, systemic hypotension, reduced organ perfusion, or dysfunction of one or more organs, tissues or cells of the subject body.

5. The method of Claim 1 wherein the leukotriene receptor antagonist is represented by the formula

(I)



or a stereoisomer or a pharmaceutically acceptable salt thereof, wherein

R^1 represents hydrogen, alkyl having 2 to 6 carbon atoms, alkenyl having 2 to 6 carbon atoms, alkynyl having 2 to 6 carbon atoms, or $(CH_2)_nR$ wherein R represents cycloalkyl of 3 to 5 carbon atoms and n is 1 or 2;

* C L M S *

R^2 represents hydrogen, methyl or ethyl;

R^3 represents alkyl having 1 to 5 carbon atoms;

W represents $(CH_2)_x$ where x is 2 to 7, alkenylene having 3 to 7 carbon atoms, alkynylene having 3 to 7 carbon atoms or cyclopentylene;

R^4 represents hydrogen, alkyl having 2 to 5 carbon atoms, alkynyl having 2 to 5 carbon atoms, alkenyl having 2 to 5 carbon atoms, alkanoyl of 2 to 5 carbon atoms or aralkanoyl of 7 to 9 carbon atoms;

R^5 represents hydrogen, alkyl having 1 to 6 carbon atoms, or R^5 represents alkanoyl having 2 to 4 carbon atoms, or $(CH_2)_Y - CO_2R^8$ wherein Y is 0 to 4 and R^8 is hydrogen or alkyl having 1 to 6 carbon atoms;

R^6 represents hydrogen or together with R^5 represents a carbon to carbon bond; and

A represents - Z - CO_2R^7 wherein R^7 represents hydrogen or alkyl having 1 to 6 carbon atoms, and wherein Z is absent or represents straight or branched chain alkylene or alkenylene having up to 6 carbon atoms.

6. The method of Claim 5 wherein the leukotriene receptor antagonist is represented by Formula (I) and

R^1 represents alkyl having 2 to 4 carbon atoms;

R^2 represents hydrogen, methyl or ethyl;

R^3 represents alkyl having 1 to 3 carbon atoms;

W represents $(CH_2)_x$ where x is 3 to 5, alkenylene having 3 to 5 carbon atoms, alkynylene having 3 to 5 carbon atoms, or cyclopentylene;

R^4 represents alkyl having 2 to 4 carbon atoms, acetyl or benzoyl;

R^5 represents hydrogen or alkyl having 1 to 4 carbon atoms;

* C L M S *

R^6 represents hydrogen; and

A represents - Z - CO_2R^7, wherein R^7 represents hydrogen or alkyl having 1 to 4 carbon atoms, and wherein Z is absent or represents alkylene having up to 2 carbon atoms.

7. The method of Claim 6 wherein the leukotriene receptor antagonist is represented by Formula (I) and

R^1 is n-propyl;

R^2 and R^3 each is methyl;

W is $(CH_2)_x$, where x is 3,4 or 5;

R^4 is 8-n-propyl;

R^5 represents hydrogen or alkyl of 1 to 4 carbon atoms; and

A represents - Z - CO_2R^7 wherein R^7 represents hydrogen or alkyl having 1 to 4 carbon atoms and Z is absent or represents alkylene having up to 2 carbon atoms.

8. The method of Claim 7 wherein the leukotriene receptor antagonist is represented by Formula (I) and W is $(CH_2)_3$, R^5 is H and A is $(CH_2)_p$ - COOH where p is 0,1 or 2.

9. The method of Claim 8 wherein the leukotriene antagonist is represented by Formula (I) and A is -CO_2H.

10. The method of Claim 6 wherein R^1 is n-propyl, R^2 is hydrogen, R^3 is methyl, W is $(CH_2)_5$, R^4 is 6-acetyl, R^5 is hydrogen, and A is COOH.

11. A method of treating a malignancy or a viral disease in a subject, which method comprises administering a therapeutically effective amount of IL-2 in conjunction with a leukotriene receptor antagonist in an amount sufficient to reduce IL-2-induced adverse pharmacological effects.

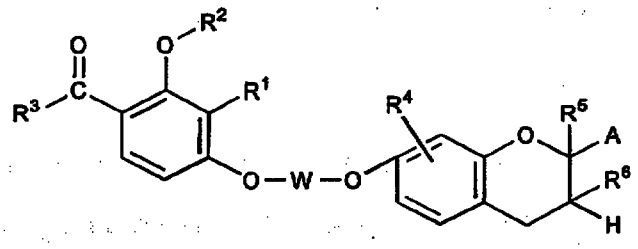
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12. The method of Claim 11 wherein the adverse pharmacological effect is increased vascular permeability.

13. The method of Claim 12, wherein the signs and symptoms of the adverse pharmacological effect include one or more of edema, systemic hypotension, reduced organ perfusion, or dysfunction of one or more organs, tissues or cells of the subject's body.

14. The method of Claim 11, wherein the leukotriene receptor antagonist is represented by the formula

(I)



or a stereoisomer or a pharmaceutically acceptable salt thereof wherein

R^1 represents alkyl having 2 to 6 carbon atoms, alkenyl having 2 to 6 carbon atoms, alkynyl having 2 to 6 carbon atoms, or $(CH_2)_nR$ wherein R represents cycloalkyl of 3 to 5 carbon atoms and n is 1 or 2;

R^2 represents hydrogen, methyl or ethyl;

R^3 represents alkyl having 1 to 5 carbon atoms;

W represents $(CH_2)_x$ where x is 2 to 7, alkenylene having 3 to 7 carbon atoms, alkynylene having 3 to 7, or cyclopentylene;

R^4 represents hydrogen, alkyl having 2 to 5 carbon atoms, alkenyl having 2 to 5 carbon atoms, alkenyl having 2 to 5 carbon atoms, alkanoyl of 2 to 5 carbon atoms, or aralkanoyl of 7-9 carbon atoms;

* C L M S *

R^5 represents hydrogen, alkyl having 1 to 6 carbon atoms, or R^5 represents alkanoyl having 2 to 4 carbon atoms, or $(CH_2)_y$ - CO^2R^8 wherein y is 0 to 4 and R^8 is hydrogen or alkyl having 1 to 6 carbon atoms;

R^6 represents hydrogen or together with R^5 represents a carbon to carbon bond; and

A represents - Z - CO_2R^7 wherein R^7 represents hydrogen or alkyl having 1 to 6 carbon atoms, and wherein Z is absent or represents straight or branched chain alkylene or alkenylene having up to 6 carbon atoms.

15. The method of Claim 14 wherein the leukotriene receptor antagonist is represented by Formula (I) and

R^1 represents alkyl having 2 to 4 carbon atoms;

R^2 represents hydrogen, methyl or ethyl;

R^3 represents alkyl having 1 to 3 carbon atoms;

W represents $(CH_2)_x$ where x is 3 to 5, alkenylene having 3 to 5 carbon atoms, alkynylene having 3 to 5 carbon atoms, or cyclopentylene;

R^4 represents alkyl having 2 to 4 carbon atoms, acetyl or benzoyl;

R^5 represents hydrogen or alkyl having 1 to 4 carbon atoms;

R^6 represents hydrogen; and

A represents -Z-CO_2R^7, wherein R^7 represents hydrogen or alkyl having 1 to 4 carbon atoms, and wherein Z is absent or represents alkylene having up to 2 carbon atoms.

16. The method of Claim 15 wherein the leukotriene receptor antagonist is represented by Formula (I) and

R^1 is n-propyl;

* C L M S *

R^2 and R^3 each is methyl;

W is $(CH_2)_x$, where x is 3,4 or 5;

R_4 is 8-n-propyl;

R_5 represents hydrogen or alkyl of 1 to 4 carbon atoms; and

A represents $-Z-CO_2R^7$ wherein R^7 represents hydrogen or alkyl having 1 to 4 carbon atoms and Z is absent or represents alkylene having up to 2 carbon atoms.

17. The method of Claim 16 wherein the leukotriene receptor antagonist is represented by Formula (I) and W is $(CH_2)_3$, R^5 is H and A is $(CH_2)_p$ - COOH where p is 0,1 or 2.

18. The method of Claim 17 wherein the leukotriene antagonist is represented by Formula (I) and A is -COOH.

19. The method of Claim 15 wherein R^1 is n-propyl, R^2 is hydrogen, R^3 is methyl, W is $(CH_2)_5$, R^4 is 6-acetyl, R^5 is hydrogen, and A is COOH.

20. The method of Claim 11 wherein the IL-2 and the leukotriene receptor antagonist are administered in combination as a unit dosage.

21. The method of Claim 11 wherein the IL-2 and the leukotriene receptor antagonist are administered individually.

22. The method of Claim 21 wherein the leukotriene receptor antagonist is administered orally before, during or after the IL-2 is administered.

23. An article of manufacture that comprises a pharmaceutical composition comprising a leukotriene receptor antagonist as a unit or multiple dosage in combination with printed labeling instructions for administering the dosage to a subject undergoing treatment of a malignancy or viral disease with IL-2, wherein the amount of the composition administered is sufficient to mitigate IL-induced adverse pharmacological effects in the mammal being treated.

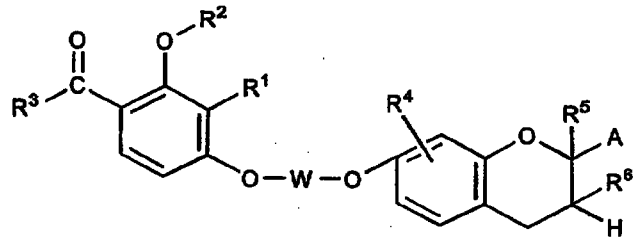
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24. The article of manufacture of Claim 23 wherein the adverse pharmacological effect is increased vascular permeability.

25. The article of manufacture of Claim 24 wherein the signs and symptoms of the adverse pharmacological effect include one or more of edema, systemic hypotension, reduced organ perfusion, or dysfunction of one or more organs of the mammal's body.

26. The article of manufacture of Claim 23 wherein the leukotriene receptor antagonist is represented by the formula

(I)



or a stereoisomer or a pharmaceutically acceptable salt thereof wherein

R^1 represents alkyl having 2 to 6 carbon atoms, alkenyl having 2 to 6 carbon atoms, alkynyl having 2 to 6 carbon atoms, or $(CH_2)_nR$ wherein R represents cycloalkyl of 3 to 5 carbon atoms and n is 1 or 2;

R^2 represents hydrogen, methyl or ethyl;

R^3 represents alkyl having 1 to 5 carbon atoms;

W represents $(CH_2)_x$ where x is 2 to 7, alkenylene having 3 to 7 carbon atoms, alkynylene having 3 to 7 carbon atoms, or cyclopentyl;

* C L M S *

R^4 represents hydrogen, alkyl having 2 to 5 carbon atoms, alkenyl having 2 to 5 carbon atoms, alkenyl having 2 to 5 carbon atoms, alkanoyl of 2 to 5 carbon atoms, or aralkanoyl of 7 to 9 carbon atoms;

R^5 represents hydrogen, alkyl having 1 to 6 carbon atoms, or R^5 represents alkanoyl having 2 to 4 carbon atoms, or $(CH_2)_y$ - CO_2R^8 wherein Y is 0 to 4 and R^8 is hydrogen or alkyl having 1 to 6 carbon atoms;

R^6 represents hydrogen or, together with R^5, represents a carbon to carbon bond; andA represents - Z - CO_2R^7 wherein R^7 represents hydrogen or alkyl having 1 to 6 carbon atoms, and wherein Z is absent or represents straight or branched chain alkylene or alkenylene having up to 6 carbon atoms.

27. The article of manufacture of Claim 26 wherein the leukotriene receptor antagonist is represented by Formula (I) and

R^1 represents alkyl having 2 to 4 carbon atoms;

R^2 represents hydrogen, methyl or ethyl;

R^3 represents alkyl having 1 to 3 carbon atoms;

W represents $(CH_2)_x$ where x is 3 to 5, alkenylene having 3 to 5 carbon atoms, alkynylene having 3 to 5 carbon atoms, or cyclopentylene;

R^4 represents alkyl having 2 to 4 carbon atoms, acetyl or benzoyl;

R^5 represents hydrogen, alkyl having 1 to 4 carbon atoms;

R^6 represents hydrogen; and

A represents - Z - CO_2R^7, wherein R^7 represents hydrogen or alkyl having 1 to 4 carbon atoms, and wherein Z is absent or represents alkylene having up to 2 carbon atoms.

* C L M S *

28. The article of manufacture of Claim 27 wherein the leukotriene receptor antagonist is represented by Formula (I) and

R^1 is n-propyl;

R^2 and R^3 each is methyl;

W is (CH2)x, where x is 3,4 or 5;

R^4 is 8-n-propyl;

R^5 represents hydrogen or alkyl of 1 to 4 carbon atoms; and

A represents $-Z-CO_2R^7$ wherein R^7 represents hydrogen or alkyl having 1 to 4 carbon atoms and Z is absent or represents alkylene having up to 2 carbon atoms.

29. The article of manufacture of Claim 27 wherein the leukotriene receptor antagonist is represented by Formula (I) and W is $(CH_2)_3$, R^5 is H and A is $(CH_2)_p$ - COOH where p is 0,1 or 2.

30. The article of manufacture of Claim 29 wherein the leukotriene antagonist is represented by Formula (I) and A is –COOH.

31. The article of manufacture of Claim 27 wherein R^1 is n-propyl, R^2 is hydrogen, R^3 is methyl, W is $(CH_2)_5$, R^4 is 6-acetyl, R^5 is hydrogen, and A is COOH.

32. The article of manufacture of Claim 23 wherein the composition comprises IL-2 and the leukotriene receptor antagonist in combination as a unit dosage.

33. The article of manufacture of Claim 23 wherein the labeling instructions indicate that the IL-2 and the leukotriene receptor antagonist are administered individually.

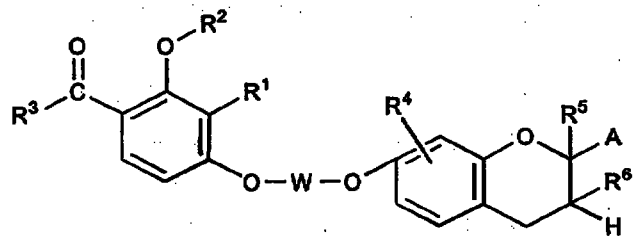
34. The article of manufacture of Claim 23 wherein the labeling instructions indicate that the leukotriene receptor antagonist is administered orally before, during or after the IL-2 is administered.

* C L M S *

35. A process for preparing a pharmaceutical composition useful for mitigating an adverse pharmacological effect of IL-2 in a subject, which process comprises combining a leukotriene receptor inhibitor with a pharmaceutically acceptable excipient.

36. The process of Claim 35 wherein the leukotriene receptor antagonist is represented by the formula

(I)



or a stereoisomer or a pharmaceutically acceptable salt thereof, wherein

R^1 represents hydrogen, alkyl having 2 to 6 carbon atoms, alkenyl having 2 to 6 carbon atoms, alkynyl having 2 to 6 carbon atoms, or $(CH_2)_nR$ wherein R represents cycloalkyl of 3 to 5 carbon atoms and n is 1 or 2;

R^2 represents hydrogen, methyl or ethyl;

R^3 represents alkyl having 1 to 5 carbon atoms;

W represents $(CH_2)_x$ where x is 2 to 7, alkenylene having 3 to 7 carbon atoms, alkynylene having 3 to 7 carbon atoms or cyclopentylene;

R^4 represents hydrogen, alkyl having 2 to 5 carbon atoms, alkynyl having 2 to 5 carbon atoms, alkenyl having 2 to 5 carbon atoms, alkanoyl of 2 to 5 carbon atoms or aralkanoyl of 7-9 carbon atoms;

* C L M S *

R^5 represents hydrogen, alkyl having 1 to 6 carbon atoms, or R^5 represents alkanoyl having 2 to 4 carbon atoms, or $(CH_2)_Y$ - CO_2R^8 wherein Y is 0 to 4 and R^8 is hydrogen or alkyl having 1 to 6 carbon atoms;

R^6 represents hydrogen or, together with R^5, represents a carbon to carbon bond; and

A represents - Z - CO_2R^7 wherein R^7 represents hydrogen or alkyl having 1 to 6 carbon atoms, and wherein Z is absent or represents straight or branched chain alkylene or alkenylene having up to 6 carbon atoms.

37. The process of Claim 36 wherein the leukotriene receptor antagonist is represented by Formula (I) and

R^1 represents alkyl having 2 to 4 carbon atoms;

R^2 represents hydrogen, methyl or ethyl;

R^3 represents alkyl having 1 to 3 carbon atoms;

W represents $(CH_2)_x$ where x is 3 to 5, alkenylene having 3 to 5 carbon atoms, alkynylene having 3 to 5 carbon atoms, or cyclopentylene;

R^4 represents alkyl having 2 to 4 carbon atoms, acetyl or benzoyl;

R^5 represents hydrogen or alkyl having 1 to 4 carbon atoms;

R^6 represents hydrogen; and

A represents - Z - CO_2R^7, wherein R^7 represents hydrogen or alkyl having 1 to 4 carbon atoms, and wherein Z is absent or represents alkylene having up to 2 carbon atoms.

38. The process of Claim 37 wherein the leukotriene receptor antagonist is represented by Formula (I) and

R^1 is n-propyl;

* C L M S *

R^2 and R^3 each is methyl;

W is $(CH_2)_x$, where x is 3,4 or 5;

R^4 is 8-n-propyl;

R^5 represents hydrogen or alkyl of 1 to 4 carbon atoms; and

A represents - Z - CO_2R^7 wherein R^7 represents hydrogen or alkyl having 1 to 4 carbon atoms and Z is absent or represents alkylene having up to 2 carbon atoms.

39. The process of Claim 38 wherein the leukotriene receptor antagonist is represented by Formula (I) and W is $(CH_2)_3$, R^5 is H and A is $(CH_2)_p$ - COOH where p is 0,1 or 2.

40. The process of Claim 39 wherein the leukotriene antagonist is represented by Formula (I) and A is -CO_2H.

41. The process of Claim 37 wherein R^1 is n-propyl, R^2 is hydrogen, R^3 is methyl, W is $(CH_2)_5$, R^4 is 6-acetyl, R^5 is hydrogen, and A is COOH.

* C L M S *