METHODS OF TREATING ARTHRITIC CONDITIONS USING (+)-2-[1-(3-ETHOXY-4-METHOXYPHENYL)-2-METHYLSULFONYLETHYL]-4-ACETYLAMINOISOINDOLINE 1,3-DIONE

This application is a continuation application of U.S. patent application Ser. No. 12/630,788, filed Dec. 3, 2009, which is a continuation application of U.S. patent application Ser. No. 12/098,379, filed Apr. 4, 2008, which issued as U.S. Pat. No. 7,659,303, which is a divisional application of U.S. patent application Ser. No. 11/170,308, filed Jun. 28, 2005, which issued as U.S. Pat. No. 7,358,272, which is a divisional application of U.S. patent application Ser. No. 10/392,195, filed Mar. 19, 2003, which issued as U.S. Pat. No. 6,962,940, which claims the benefit of U.S. Provisional Application No. 60/366,515 filed Mar. 20, 2002 and U.S. Provisional Application No. 60/438,450 filed Jan. 7, 2003, all of which are incorporated herein by reference in their entireties.

1. FIELD OF INVENTION

The invention relates to methods of using and compositions comprising the (+) enantiomer of 2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione.

2. BACKGROUND OF THE INVENTION

Tumor necrosis factor alpha, (TNF-α) is a cytokine that is released primarily by mononuclear phagocytes in response to immunostimulators. TNF-α is capable of enhancing most cellular processes, such as differentiation, recruitment, proliferation, and proteolytic degradation. At low levels, TNF-α confers protection against infective agents, tumors, and tissue damage. But TNF-α also has a role in many diseases. When administered to mammals or humans, TNF-α causes or aggravates inflammation, fever, cardiovascular effects, hemorrhage, coagulation, and acute phase responses similar to those seen during acute infections and shock states. Enhanced or unregulated TNF-α production has been implicated in a number of diseases and medical conditions, for example, cancers, such as solid tumors and blood-born tumors; heart disease, such as congestive heart failure; and viral, genetic, inflammatory, allergic, and autoimmune diseases.

Adenosine 3',5'-cyclic monophosphate (cAMP) also plays a role in many diseases and conditions, such as but not limited to asthma and inflammation, and other conditions (Lowe and Cheng. *Drugs of the Future,* 17(9), 799-807, 1992). It has been shown that the elevation of cAMP in inflammatory leukocytes inhibits their activation and the subsequent release of inflammatory mediators, including TNF-α and NF-κB. Increased levels of cAMP also leads to the relaxation of airway smooth muscle.

It is believed that the primary cellular mechanism for the inactivation of cAMP is the breakdown of cAMP by a family of isoenzymes referred to as cyclic nucleotide phosphodiesterases (PDE) (Beavo and Reitsnyder, *Trends in Pharm.,* 11, 150-155, 1990). There are eleven known PDE families. It is recognized, for example, that the inhibition of PDE type IV is particularly effective in both the inhibition of inflammatory mediator release and the relaxation of airway smooth muscle (Verghese, at al., *Journal of Pharmacology and Experimental Therapeutics,* 272(3), 1313-1320, 1995). Thus, compounds that inhibit PDE4 (PDE IV) specifically, may inhibit inflammation and aid the relaxation of airway smooth muscle with a minimum of unwanted side effects, such as cardiovascular or anti-platelet effects. Currently used PDE4 inhibitors lack the selective action at acceptable therapeutic doses.

Cancer is a particularly devastating disease, and increases in blood TNF-α levels are implicated in the risk of and the spreading of cancer. Normally, in healthy subjects, cancer cells fail to survive in the circulatory system, one of the reasons being that the lining of blood vessels acts as a barrier to tumor-cell extravasation. But increased levels of cytokines have been shown to substantially increase the adhesion of cancer cells to endothelium in vitro. One explanation is that cytokines, such as TNF-α, stimulate the biosynthesis and expression of a cell surface receptors called ELAM-1 (endothelial leukocyte adhesion molecule). ELAM-1 is a member of a family of calcium-dependent cell adhesion receptors, known as LEC-CAMs, which includes LECAM-1 and GMP-140. During an inflammatory response, ELAM-1 on endothelial cells functions as a "homing receptor" for leukocytes. Recently, ELAM-1 on endothelial cells was shown to mediate the increased adhesion of colon cancer cells to endothelium treated with cytokines (Rice at al., 1989, *Science* 246:1303-1306).

Inflammatory diseases such as arthritis, related arthritic conditions (e.g., osteoarthritis and rheumatoid arthritis), inflammatory bowel disease (e.g., Crohn's disease and ulcerative colitis), sepsis, psoriasis, atopic dermatitis, contact dermatitis, and chronic obstructive pulmonary disease, chronic inflammatory pulmonary diseases are also prevalent and problematic ailments. TNF-α plays a central role in the inflammatory response and the administration of their antagonists block chronic and acute responses in animal models of inflammatory disease.

Enhanced or unregulated TNF-α production has been implicated in viral, genetic, inflammatory, allergic, and autoimmune diseases. Examples of such diseases include but are not limited to: HIV; hepatitis; adult respiratory distress syndrome; bone-resorption diseases; chronic obstructive pulmonary diseases; chronic pulmonary inflammatory diseases; asthma, dermatitis; cystic fibrosis; septic shock; sepsis; endotoxic shock; hemodynamic shock; sepsis syndrome; post ischemic reperfusion injury; meningitis; psoriasis; fibrotic disease; cachexia; graft rejection; auto-immune disease; rheumatoid spondylitis; arthritic conditions, such as rheumatoid arthritis and osteoarthritis; osteoporosis; Crohn's disease; ulcerative colitis; inflammatory-bowel disease; multiple sclerosis; systemic lupus erythrematosus; ENL in leprosy, radiation damage; asthma; and hyperoxic alveolar injury. Tracey et al., 1987, *Nature* 330:662.664 and Hinshaw et al., 1990, *Circ. Shock* 30:279-292 (endotoxic shock); Dezube et al., 1990, *Lancet,* 335:662 (cachexia); Millar et al., 1989, *Lancet* 2:712-714 and Ferrai-Baliviera et al., 1989, *Arch. Surg.* 124:1400-1405 (adult respiratory distress syndrome); Bertolini et al., 1986, *Nature* 319:516-518, Johnson et al., 1989, *Endocrinology* 124:1424-1427, Holler et al., 1990, *Blood* 75:1011-1016, and Grau et al., 1989, *N. Engl. J. Med.* 320:1586-1591 (bone resorption diseases); Pignet at al., 1990, *Nature,* 344:245.247, Bissonnette et al., 1989, *Inflammation* 13:329-339 and Baughman et al., 1990, *J. Lab. Clin. Med.* 115:36-42 (chronic pulmonary inflammatory diseases); Elliot et al., 1995, *Int. J. Pharmac.* 17:141-145 (rheumatoid arthritis); von Dullemen et al., 1995, *Gastroenterology,* 109: 129-135 (Crohn's disease); Duh et al., 1989, *Proc. Nat. Acad. Sci.* 86:5974-5978, Poll a al, 1990, *Proc. Nat. Acad Sci.* 87:782-785, Monto et al., 1990, *Blood* 79:2670, Clouse et al., 1989, *J. Immunol.* 142, 431-438, Poll et al., 1992, *AIDS Res. Hum. Retrovirus,* 191-197, Poll et al. 1990, *Proc. Natl. Acad. Sci.* 87:782-784, Folks et al., 1989, PNAS 86:2365-2368 (HIV and opportunistic infections resulting from HIV).