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(54) **ISOINDOLINES, METHOD OF USE, AND PHARMACEUTICAL COMPOSITIONS**

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(60) Provisional application No. 60/048,278, filed on May 30, 1997.

(51) **Int. Cl.**[7] **A61K 31/445**; C07D 401/04

(52) **U.S. Cl.** **514/323**; 546/201

(58) **Field of Search** 514/323; 546/201

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(57) **ABSTRACT**

Substituted 1-oxo-2-(2,6-dioxopiperidin-3-yl)isoindolines are useful in treating inflammation, inflammatory disease, autoimmune disease, and oncogenic or cancerous conditions in a mammal. Typical embodiments are 1-oxo-2-(2,6-dioxopiperidin-3-yl)-4-aminoisoindoline and 1-oxo-2-(2,6-dioxo-3-methylpiperidin-3-yl)-4-aminoisoindoline.

26 Claims, No Drawings

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ISOINDOLINES, METHOD OF USE, AND PHARMACEUTICAL COMPOSITIONS

CROSS-REFERENCE TO RELATED APPLICATIONS

This is a divisional of Ser. No. 09/230,389, now abandoned, which is based on PCT/US97/13375 filed Jul. 24, 1997, which is a continuation of Ser. No. 08/690,258 filed Jul. 24, 1996, now U.S. Pat. No. 5,635,517, which is a continuation of Ser. No. 08/701,494 filed Aug. 22, 1996 now U.S. Pat. No. 5,798,368, and provisional application Ser. No. 60/048,278 filed May 30, 1997.

DETAILED DESCRIPTION

The present invention relates to substituted 2-(2,6-dioxopiperidin-3-yl)phthalimides and substituted 2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolines, the method of reducing levels of tumor necrosis factor α in a mammal through the administration thereof, and pharmaceutical compositions of such derivatives.

BACKGROUND OF THE INVENTION

Tumor necrosis factor α, or TNFα, is a cytokine which is released primarily by mononuclear phagocytes in response to a number immunostimulators. When administered to animals or humans, it causes inflammation, fever, cardiovascular effects, hemorrhage, coagulation, and acute phase responses similar to those seen during acute infections and shock states. Excessive or unregulated TNFα production thus has been implicated in a number of disease conditions. These include endotoxemia and/or toxic shock syndrome {Tracey et al., *Nature* 330, 662–664 (1987) and Hinshaw et al., Circ. Shock 30, 279–292 (1990)}; cachexia {Dezube et al., *Lancet,* 335 (8690), 662 (1990)} and Adult Respiratory Distress Svndrome where TNFα concentration in excess of 12,000 pg/mL have been detected in pulmonary aspirates from ARDS patients {Millar et al., *Lancet* 2(8665), 712–714 (1989)}. Systemic infusion of recombinant TNFα also resulted in changes typically seen in ARDS {Ferrai-Baliviera et al., *Arch. Surg.* 124(12), 1400–1405 (1989)}.

TNFα appears to be involved in bone resorption diseases, including arthritis. When activated, leukocytes will produce bone-resorption, an activity to which the data suggest TNFα contributes. {Bertolini et al., *Nature* 319, 516–518 (1986) and Johnson et al., *Endocrinology* 124(3), 1424–1427 (1989).} TNFα also has been shown to stimulate bone resorption and inhibit bone formation in vitro and in vivo through stimulation of osteoclast formation and activation combined with inhibition of osteoblast function. Although TNFα may be involved in many bone resorption diseases, including arthritis, the most compelling link with disease is the association between production of TNFα by tumor or host tissues and malignancy associated hypercalcemia {*Calci. Tissue Int. (US)* 46(Suppl.), S3-10 (1990)}. In Graft versus Host Reaction, increased serum TNFα levels have been associated with major complication following acute allogenic bone marrow transplants {Holler et al., *Blood,* 75(4), 1011–1016 (1990)}.

Cerebral malaria is a lethal hyperacute neurological syndrome associated with high blood levels of TNFα and the most severe complication occurring in malaria patients. Levels of serum TNFα correlated directly with the severity of disease and the prognosis in patients with acute malaria attacks {Grau et al., *N. Engl. J. Med.* 320(24), 1586–1591 (1989)}.

Macrophage-induced angiogenesis TNFα is known to be mediated by TNFα. Leibovich et al. {*Nature,* 329, 630–632 (1987)} showed TNFα induces in vivo capillary blood vessel formation in the rat cornea and the developing chick chorloallantoic membranes at very low doses and suggest TNFα is a candidate for inducing angiogenesis in inflammation, wound repair, and tumor growth. TNFα production also has been associated with cancerous conditions, particularly induced tumors {Ching et al., *Brit. J. Cancer,* (1955) 72, 339–343, and Koch, *Progress in Medicinal Chemistry,* 22, 166–242 (1985)}.

TNFα also plays a role in the area of chronic pulmonary inflammatory diseases. The deposition of silica particles leads to silicosis, a disease of progressive respiratory failure caused by a fibrotic reaction. Antibody to TNFα completely blocked the silica-induced lung fibrosis in mice {Pignet et al., *Nature,* 344:245–247 (1990)}. High levels of TNFα production (in the serum and in isolated macrophages) have been demonstrated in animal models of silica and asbestos induced fibrosis {Bissonnette et al., *Inflammation* 13(3), 329–339 (1989)}. Alveolar macrophages from pulmonary sarcoidosis patients have also been found to spontaneously release massive quantities of TNFα as compared with macrophages from normal donors {Baughman et al., *J. Lab. Clin. Med.* 115(1), 36–42 (1990)}.

TNFα is also implicated in the inflammatory response which follows reperfusion, called reperfusion injury, and is a major cause of tissue damage after loss of blood flow {Vedder et al., *PNAS* 87, 2643–2646 (1990)}. TNFα also alters the properties of endothelial cells and has various pro-coagulant activities, such as producing an increase in tissue factor pro-coagulant activity and suppression of the anticoagulant protein C pathway as well as down-regulating the expression of thrombomodulin {Sherry et al., *J. Cell Biol.* 107, 1269–1277 (1988)}. TNFα has pro-inflammatory activities which together with its early production (during the initial stage of an inflammatory event) make it a likely mediator of tissue injury in several important disorders including but not limited to, myocardial infarction, stroke and circulatory shock. Of specific importance may be TNFα-induced expression of adhesion molecules, such as intercellular adhesion molecule (ICAM) or endothelial leukocyte adhesion molecule (ELAM) on endothelial cells {Munro et al., *Am. J. Path.* 135(1), 121–132 (1989)}.

TNFα blockage with monoclonal anti-TNFα antibodies has been shown to be beneficial in rheumatoid arthritis {Elliot et al., *Int. J. Pharmac.* 1995 17(2), 141–145} and Crohn's disease {von Dullemen et al., *Gastroenterology,* 1995 109(1), 129–135}

Moreover, it now is known that TNFα is a potent activator of retrovirus replication including activation of HIV-1. {Duh et al., *Proc. Nat. Acad. Sci.* 86, 5974–5978 (1989); Poll et al., *Proc. Nat. Acad. Sci.* 87, 782–785 (1990); Monto et al., *Blood* 79, 2670 (1990); Clouse et al., *J. Immunol.* 142, 431–438 (1989); Poll et al., *AIDS Res. Hum. Retrovirus,* 191–197 (1992)}. AIDS results from the infection of T lymphocytes with Human Immunodeficiency Virus (HIV). At least three types or strains of HIV have been identified, i.e., HIV-1, HIV-2 and HIV-3. As a consequence of HIV infection, T-cell mediated immunity is impaired and infected individuals manifest severe opportunistic infections and/or unusual neoplasms. HIV entry into the T lymphocyte requires T lymphocyte activation. Other viruses, such as HIV-1, HIV-2 infect T lymphocytes after T cell activation and such virus protein expression and/or replication is mediated or maintained by such T cell activation. Once an activated T lymphocyte is infected with HIV, the T lympho-

cyte must continue to be maintained in an activated state to permit HIV gene expression and/or HIV replication. Cytokines, specifically TNFα, are implicated in activated T-cell mediated HIV protein expression and/or virus replication by playing a role in maintaining T lymphocyte activation. Therefore, interference with cytokine activity such as by prevention or inhibition of cytokine production, notably TNFα, in an HIV-infected individual assists in limiting the maintenance of T lymphocyte caused by HIV infection.

Monocytes, macrophages, and related cells, such as kupffer and glial cells, also have been implicated in maintenance of the HIV infection. These cells, like T cells, are targets for viral replication and the level of viral replication is dependent upon the activation state of the cells. {Rosenberg et al., *The Immunopathogenesis of HIV Infection,* Advances in Immunology, 57 (1989)}. Cytokines, such as TNFα, have been shown to activate HIV replication in monocytes and/or macrophages {Poli et al., *Proc. Natl. Acad. Sci.,* 87, 782–784 (1990)}, therefore, prevention or inhibition of cytokine production or activity aids in limiting HIV progression for T cells. Additional studies have identified TNFα as a common factor in the activation of HIV in vitro and has provided a clear mechanism of action via a nuclear regulatory protein found in the cytoplasm of cells (Osborn, et al., *PNAS* 86 2336–2340). This evidence suggests that a reduction of TNFα synthesis may have an antiviral effect in HIV infections, by reducing the transcription and thus virus production.

AIDS viral replication of latent HIV in T cell and macrophage lines can be induced by TNFα {Folks el al., *PNAS* 86, 2365–2368 (1989)}. A molecular mechanism for the virus inducing activity is suggested by TNFα's ability to activate a gene regulatory protein (NFκB) found in the cytoplasm of cells, which promotes HIV replication through binding to a viral regulatory gene sequence (LTR) {Osborn et al., *PNAS* 86, 2336–2340 (1989)}. TNFα in AIDS associated cachexia is suggested by elevated serum TNFα and high levels of spontaneous TNFα production in peripheral blood monocytes from patients {Wright et al., *J. Immunol.* 141(1), 99–104 (1988)}. TNFα has been implicated in various roles with other viral infections, such as the cytomegalia virus (CMV), influenza virus, adenovirus, and the herpes family of viruses for similar reasons as those noted.

The nuclear factor κB (NFκB) is a pleiotropic transcriptional activator (Lenardo, et al., *Cell* 1989, 58, 227–29). NFκB has been implicated as a transcriptional activator in a variety of disease and inflammatory states and is thought to regulate cytokine levels including but not limited to TNFα and also to be an activator of HIV transcription (Dbaibo, et al., *J. Biol. Chem.* 1993, 17762–66; Duh et al., *Proc. Natl. Acad. Sci.* 1989, 86, 5974–78; Bachelerie et al., *Nature* 1991, 350, 709–12; Boswas et al., *J. Acquired Immune Deficiency Syndrome* 1993, 6, 778–786; Suzuki el al., *Biochem. And Biophys. Res. Comm.* 1993, 193, 277–83; Suzuki et al., *Biochem. And Biophys. Res Comm.* 1992, 189, 1709–15; Suzuki et al., *Biochem. Mol. Bio. Int.* 1993, 31(4), 693– 700; Shakhov et al., *Proc. Natl. Acad. Sci. USA* 1990, 171, 35–47; and Staal et al., *Proc. Natl. Acad. Sci. USA* 1990, 87, 9943–47). Thus, inhibition of NFκB binding can regulate transcription of cytokine gene(s) and through this modulation and other mechanisms be useful in the inhibition of a multitude of disease states. The compounds described herein can inhibit the action of NFκB in the nucleus and thus are useful in the treatment of a variety of diseases including but not limited to rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, other arthritic conditions, septic shock, septis, endotoxic shock, graft versus host disease, wasting, Crohn's disease, ulcerative colitis, multiple sclerosis, systemic lupus erythrematosis, ENL in leprosy, HIV, AIDS, and opportunistic infections in AIDS. TNFα and NFκB levels are influenced by a reciprocal feedback loop. As noted above, the compounds of the present invention affect the levels of both TNFα and NFκB.

Many cellular functions are mediated by levels of adenosine 3',5'-cyclic monophosphate (cAMP). Such cellular functions can contribute to inflammatory conditions and diseases including asthma, 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 TNFα and NFκB. Increased levels of cAMP also leads to the relaxation of airway smooth muscle.

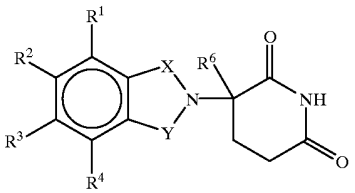
Decreasing TNFα levels and/or increasing cAMP levels thus constitutes a valuable therapeutic strategy for the treatment of many inflammatory, infectious, immunological, and malignant diseases. These include but are not restricted to septic shock, sepsis, endotoxic shock, hemodynamic shock and sepsis syndrome, post ischemic reperfusion injury, malaria, mycobacterial infection, meningitis, psoriasis, congestive heart failure, fibrotic disease, cachexia, graft rejection, oncogenic or cancerous conditions, asthma, autoimmune disease, opportunistic infections in AIDS, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, other arthritic conditions, Crohn's disease, ulcerative colitis, multiple sclerosis, systemic lupus erythrematosis, ENL in leprosy, radiation damage, oncogenic conditions, and hyperoxic alveolar injury. Prior efforts directed to the suppression of the effects of TNFα have ranged from the utilization of steroids such as dexamethasone and prednisolone to the use of both polyclonal and monoclonal antibodies {Beutler et al., *Science* 234, 470–474 (1985); WO 92/11383}.

DETAILED DESCRIPTION

The present invention is based on the discovery that certain classes of non-polypeptide compounds more fully described herein decrease the levels of TNFα.

In particular, the invention pertains to (i) compounds of the formula:

I



in which:

one of X and Y is C═O and the other of X and Y is C═O or CH_2;

(i) each of R^1, R^2, R^3, and R^4, independently of the others, is halo, alkyl of 1 to 4 carbon atoms, or alkoxy of 1 to 4 carbon atoms or (ii) one of R^1, R^2, R^3, and R^4 is —NHR^5 and the remaining of R^1, R^2, R^3, and R^4 are hydrogen;

R^5 is hydrogen or alkyl of 1 to 8 carbon atoms;

R^6 is hydrogen, alkyl of 1 to 8 carbon atoms, benzyl, or halo;

provided that R^6 is other than hydrogen if X and Y are C═O and (i) each of R^1, R^2, R^3, and R^4 is fluoro or (ii) one of R^1, R^2, R^3, or R^4 is amino; and

(b) the acid addition salts of said compounds which contain a nitrogen atom capable of being protonated.

A preferred group of compounds are those of Formula I in which each of R^1, R^2, R^3, and R^4, independently of the others, is halo, alkyl of 1 to 4 carbon atoms, or alkoxy of 1 to 4 carbon atoms, and R^6 is hydrogen, methyl, ethyl, or propyl. A second preferred group of compounds are those of Formula I in which one of R^1, R^2, R^3, and R^4 is —NH_2, the remaining of R^1, R^2, R^3, and R^4 are hydrogen, and R^6 is hydrogen, methyl, ethyl, or propyl.

Unless otherwise defined, the term alkyl denotes a univalent saturated branched or straight hydrocarbon chain containing from 1 to 8 carbon atoms. Representative of such alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, and tert-butyl. Alkoxy refers to an alkyl group bound to the remainder of the molecule through an ethereal oxygen atom. Representative of such alkoxy groups are methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, and tert-butoxy. Preferably R^1, R^2, R^3, and R^4 are chloro, fluoro, methyl or methoxy.

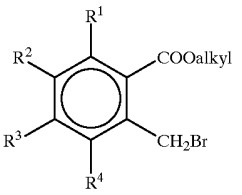
The compounds of Formula I are used, under the supervision of qualified professionals, to inhibit the undesirable effects of TNFα. The compounds can be administered orally, rectally, or parenterally, alone or in combination with other therapeutic agents including antibiotics, steroids, etc., to a mammal in need of treatment.

The compounds of the present invention also can be used topically in the treatment or prophylaxis of topical disease states mediated or exacerbated by excessive TNFα production, respectively, such as viral infections, such as those caused by the herpes viruses, or viral conjunctivitis, psoriasis, atopic dermatitis, etc.

The compounds also can be used in the veterinary treatment of mammals other than humans in need of prevention or inhibition of TNFα production. TNFα mediated diseases for treatment, therapeutically or prophylactically, in animals include disease states such as those noted above, but in particular viral infections. Examples include feline immunodeficiency virus, equine infectious anaemia virus, caprine arthritis virus, visna virus, and maedi virus, as well as other lentiviruses.

Compounds in which one of R^1, R^2, R^3, R^4 is amino and R^5 and R^6, as well as the remainder of R^1, R^2, R^3, R^4, are hydrogen, as for example, 1,3-dioxo-2-(2,6-dioxopiperidin-3-yl)-4-aminoisoindoline or 1,3-dioxo-2-(2,6-dioxopiperidin-3-yl)-5-aminoisoindoline are known. See, e.g. Jönsson, *Acta Pharma. Succica,* 9, 521–542 (1972).

The compounds can be prepared using methods which are known in general. In particular, the compounds can be prepared through the reaction of 2,6-dioxopiperidin-3-ammonium chloride, and a lower alkyl ester of 2-bromomethylbenzoic acid in the presence of an acid acceptor such as dimethylaminopyridine or triethylamine.



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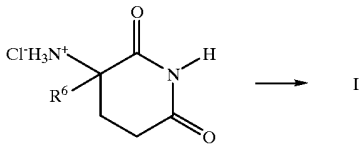
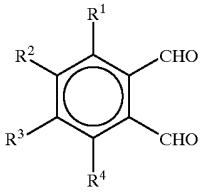


The substituted benzoate intermediates are known or can be obtained though conventional processes. For example, a lower alkyl ester of an ortho-toluic acid is brominated with N-bromosuccinimide under the influence of light to yield the lower alkyl 2-bromomethylbenzoate.

Alternatively, a dialdehyde is allowed to react with 2,6-dioxopiperidin-3-ammonium chloride:



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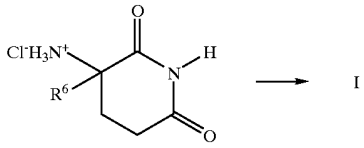
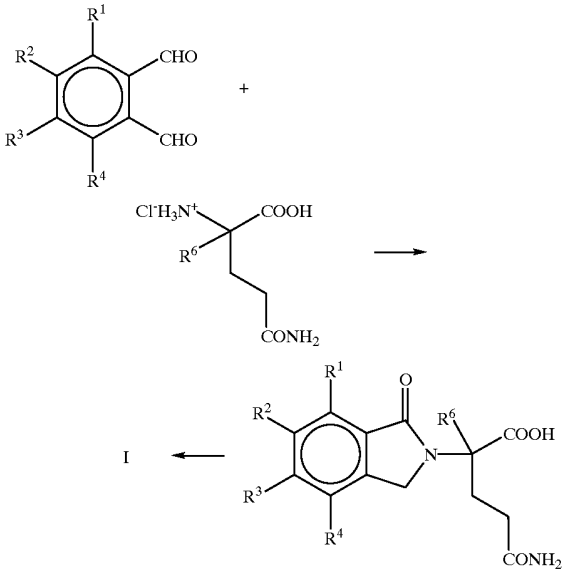


In a further method, a dialdehyde is allowed to react with glutamine and the resulting 2-(1-oxoisoindoiln-2-yl)glutaric acid then cyclized to yield a 1-oxo-2-(2,6-dioxopiperidin-3-yl)-isoindoline of Formula I:



Finally, an appropriately substituted phthalidimide intermediate is selectively reduced:

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