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Substituted 1,3,4-oxadiazoles for use in the treatment or prophylaxis of diseases

Substituierte 1,3,4-Oxadiazole zur Behandlung oder Prophylaxe von Krankheiten

1,3,4-Oxadiazoles substituées pour le traitement et la prophylaxie de maladies

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The present invention relates to the use of substituted 1,3,4-oxadiazole compounds for the manufacture of a medicament for the prophylaxis of atopic dermatitis, psoriasis, lupus, a viral infection, or viral conjunctivitis wherein the medicament is adapted for topical administration or for the manufacture of a medicament for the treatment of ulcerative colitis or systemic lupus erythematosus, or the topical treatment of atopic dermatitis, psoriasis, lupus, a viral infection, or viral conjunctivitis.

Tumor necrosis factor-α (TNFα) is a cytokine which is released primarily by cells of immune systems in response to certain immunostimulators. When administered to animals or humans, it causes inflammation, fever, cardiovascular effects, hemorrhage, coagulation, cachexia, and acute phase responses similar to those seen during acute infections, inflammatory diseases, and shock states. Excessive or unregulated TNFα production 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)], rheumatoid arthritis, inflammatory bowel disease, cachexia [Dezube, et al., Lancet, 335 (8690), 662 (1990)], and lupus. TNFα concentration in excess of 12,000 pg/mL have been detected in pulmonary aspirates from Adult Respiratory Distress Syndrome (ARDS) patients [Millar, et al., Lancet 2 (8665), 712-714 (1989)]. Systemic infusion of recombinant TNFα resulted in changes typically seen in ARDS [Ferrai-Baliviera, et al., Arch. Surg. 124(12), 1400-1405 (1989)].

TNFα appears to be involved in a number of bone resorption diseases, including arthritis. When activated, leukocytes will produce bone-resorption. TNFα apparently contributes to this mechanism. [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 functions. Another 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 Reactions, increased serum TNFα levels have been associated with major complications following acute allogenic bone marrow transplants [Holler, et al., Blood, 75(4), 1011-1016 (1990)].

Validation of TNF-α inhibition as a clinical therapy has been demonstrated by the therapeutic use of TNF-α antibodies and soluble TNF-α receptors. TNFα blockade 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]. High levels of TNFα are associated with Crohn’s disease [von Dullemen, et al., Gastroenterology, 1995 109(1), 129-135] treatment with soluble TNFα receptor treatment gave clinical benefits.

Cerebral malaria is a lethal hyperacute neurological syndrome associated with high blood levels of TNFα and the most severe complication occurring in malaria patients. Elevated 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)].

TNFα 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. Antibodies 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)].

Elevated levels of TNFα are implicated in reperfusion injury, the inflammatory response which follows reperfusion, and is a major cause of tissue damage after blood flow loss [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, suppressing the anticoagulant protein C pathway, and 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. TNFα-induced expression of adhesion molecules, such as intercellular adhesion molecules (ICAM) or endothelial leukocyte adhesion molecules (ELAM) on endothelial cells may be especially important [Munro, et al., Am. J. Path. 135(1), 121-132 (1989)].

It has been reported 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)]. At least three types or strains of HIV (i.e., HIV-1, HIV-2 and HIV-3) have been identified. 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. This virus protein expression and/or replication is mediated or regulated by cytokines including but not limited to TNF-α. Cytokines, specifically TNF-α, 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 prevention or inhibition of cytokine production, notably TNF-α, 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 TNF-α, 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 TNF-α as a common factor in the activation of HIV in vitro and have 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 reducing TNF-α synthesis may have an antiviral effect in HIV infections, by reducing transcription and thus virus production.

AIDS viral replication of latent HIV in T-cell and macrophage lines can be induced by TNF-α [Folks, et al., PNAS 86, 2365-2368 (1989)]. A molecular mechanism for the virus inducing activity is suggested by TNF-α’s ability to activate a gene regulatory protein (transcription factor, NF-κB) 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)]. TNF-α in AIDS associated cachexia is suggested by elevated serum TNF and high levels of spontaneous TNF-α production in peripheral blood monocytes from patients [Wright, et al., J. Immunol. 141(1), 99-104 (1988)]. TNF-α 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.


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 TNF-α and NF-κB. Increased levels of cAMP also lead to the relaxation of airway smooth muscle.

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 ten known members of the family of PDEs. It is well documented that the inhibition of PDE type IV (PDE 4) enzyme is particularly effective in both the inhibition of inflammatory mediator release and the relaxation of airway smooth muscle [Vergheese, et al., Journal of Pharmacology and Experimental Therapeutics, 272(3), 1313-1320, 1995].

Decreasing TNF-α 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 and other dermal diseases, congestive heart failure, fibrotic disease, cachexia, graft rejection, cancer, tumor growth, undesirable angiogenesis, autoimmune disease, opportunistic infections in AIDS, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, other arthritic conditions, inflammatory bowel disease, Crohn’s disease, ulcerative colitis, multiple sclerosis, systemic lupus erythematosus, ENL in leprosy, radiation damage, and hyperoxic alveolar injury. Prior efforts directed to the suppression of the effects of TNF-α 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].

Angiogenesis, the process of new blood vessel development and formation, plays an important role in numerous normal and pathological physiological events. Angiogenesis occurs in response to specific signals and involves a complex
process characterized by infiltration of the basal lamina by vascular endothelial cells in response to angiogenic growth signals), migration of the endothelial cells toward the source of the signal(s), and subsequent proliferation and formation of the capillary tube. Blood flow through the newly formed capillary is initiated after the endothelial cells come into contact and connect with a preexisting capillary. Angiogenesis is required for tumor growth beyond a certain size.

**[0016]** Inhibitory influences predominate in the naturally occurring balance between endogenous stimulators and inhibitors of angiogenesis [Rastinejad, et al., 1989, Cell 56:345-355]. In those rare instances in which neovascularization occurs under normal physiological conditions, such as wound healing, organ regeneration, embryonic development and female reproductive processes, angiogenesis is stringently regulated and spatially and temporally delimited. Under conditions of pathological angiogenesis such as that characterizing solid tumor growth, these regulatory controls fail.


**[0018]** The maintenance of the avascularity of the cornea, lens, and trabecular meshwork is crucial for vision as well as for ocular physiology. See, e.g., reviews by Waltman, et al., 1978, Am. J. Ophthal. 85:704-710 and Gartner, et al., 1978, Surv. Ophthal. 22:291-312. Currently, the treatment of these diseases, especially once neovascularization has occurred, is inadequate and blindness often results.

**[0019]** An inhibitor of angiogenesis could have an important therapeutic role in limiting the contributions of this process to pathological progression of the underlying disease states as well as providing a valuable means of studying their etiology. For example, agents that inhibit tumor neovascularization could play an important role in inhibiting metastatic and solid tumor growth.

**[0020]** Several kinds of compounds have been used to prevent angiogenesis. Taylor, et al. used protamine to inhibit angiogenesis, [Taylor, et al., Nature 297:307 (1982)]. The toxicity of protamine limits its practical use as a therapeutic. Folkman, et al. used heparin and steroids to control angiogenesis. [Folkman, et al., Science 221:719 (1983) and U.S. Pat. Nos. 5,001,116 and 4,994,443]. Steroids, such as tetrahydrocortisol, which lack gluco and mineral corticoid activity, are angiogenic inhibitors. Interferon β is also a potent inhibitor of angiogenesis induced by allogeneic spleen cells [Sidky, et al., Cancer Research 47:5155-5161 (1987)]. Human recombinant interferon-α was reported to be successfully used in the treatment of pulmonary hemangiomatosis, an angiogenesis-induced disease [White, et al., New England J. Med. 320:1197-1200 (1989)].

**[0021]** Other agents which have been used to inhibit angiogenesis include ascorbic acid ethers and related compounds [Japanese Kokai Tokkyo Koho No. 58-131978]. Sulfated polysaccharide DS 4152 also shows angiogenic inhibition [Japanese Kokai Tokkyo Koho No. 63-119500]. A fungal product, fumagillin, is a potent angiostatic agent in vitro. The compound is toxic in vivo, but a synthetic derivative, AGM 12470, has been used in vivo to treat collagen II arthritis. Fumagillin and o-substituted fumagillin derivatives are disclosed in EPO Publication Nos. 0325199A2 and 0357061A1.

**[0022]** In U.S. Pat. No. 5,874,081, Parish teaches use of monoclonal antibodies to inhibit angiogenesis. In WO92/12717, Brem, et al. teach that some tetracyclines, particularly Minocycline, Chlortetracycline, Demeclocycline and Lymecycline are useful as inhibitors of angiogenesis. Brem, et al. teach that Minocycline inhibits angiogenesis to an extent comparable to that of the combination therapy of heparin and cortisone [Cancer Research, 51, 672-675, Jan. 15, 1991]. Teicher, et al. teach that tumor growth is decreased and the number of metastases is reduced when the anti-angiogenic agent of metastases is reduced when the anti-angiogenic agent Minocycline is used in conjunction with cancer chemotherapy or radiation therapy [Cancer Research, 52, 6702-6704, Dec. 1, 1992].

**[0023]** Macrophage-induced angiogenesis is known to be stimulated by TNFα. Leibovich, et al. reported that TNFα induces in vivo capillary blood vessel formation in the rat cornea and the developing chick choioallantoic membranes at very low doses and suggested TNFα is a candidate for inducing angiogenesis in inflammation, wound repair, and tumor growth [Nature, 329, 630-632 (1987)].

**[0024]** All of the various cell types of the body can be transformed into benign or malignant tumor cells. The most frequent tumor site is lung, followed by colorectal, breast, prostate, bladder, pancreas, and then ovary. Other prevalent types of cancer include leukemia, central nervous system cancers, brain cancer, melanoma, lymphoma, erythrolymphemkia, uterine cancer, bone cancer, and head and neck cancer.

**[0025]** Cancer is now primarily treated with one or a combination of three types of therapies: surgery, radiation, and chemotherapy. Surgery involves the bulk removal of diseased tissue. While surgery is sometimes effective in removing tumors located at certain sites (e.g., in the breast, colon, and skin) surgery cannot be used in the treatment of tumors located in other areas (e.g., the backbone) nor in the treatment of disseminated neoplastic conditions (e.g., leukemia). Chemotherapy involves the disruption of cell replication or cell metabolism. Chemotherapy is used most often in the
Chemotherapeutic agents are often referred to as antineoplastic agents. The alkylating agents are believed to act by alkylating and cross-linking guanine and possibly other bases in DNA, arresting cell division. Typical alkylating agents include nitrogen mustards, ethyleneimine compounds, alkyl sulfates, cisplatin, and various nitrosoureas. A disadvantage with these compounds is that they not only attack malignant cells, but also other cells which are naturally dividing, such as those of bone marrow, skin, gastro-intestinal mucosa, and fetal tissue. Antimetabolites are typically reversible or irreversible enzyme inhibitors, or compounds that otherwise interfere with the replication, translation or transcription of nucleic acids. Thus, it would be preferable to find less toxic compounds for cancer treatment.

Matrix metalloproteinase (MMP) inhibition has been associated with several activities including inhibition of TNFα [Mohler, et al., Nature, 370, 218-220 (1994)] and inhibition of angiogenesis. MMPs are a family of secreted and membrane-bound zinc endopeptidases that play a key role in both physiological and pathological tissue degradation [Yu, et al., Drugs & Aging, 1997, (3):229-244; Wojtowicz-Praga, et al., Int. New Drugs, 16:61-75 (1997)]. These enzymes are capable of degrading the components of the extracellular matrix, including fibrillar and non-fibrillar collagens, fibronectin, laminin, and membrane glycoproteins. Ordinarily, there is a delicate balance between cell division, matrix synthesis, matrix degradation (under the control of cytokines), growth factors, and cell matrix interactions. Under pathological conditions, however, this balance can be disrupted. Conditions and diseases associated with undesired MMP levels include, but are not limited to: tumor metastasis invasion and growth, angiogenesis, rheumatoid arthritis, osteoarthritis, osteopenias such as osteoporosis, periodontitis, gingivitis, Crohn’s disease, inflammatory bowel disease, and corneal epidermal or gastric ulceration.

Increased MMP activity has been detected in a wide range of cancers [Denis, et al., Invest. New Drugs, 15: 175-185 (1987)]. As with TNFα, MMPs are believed to be involved in the invasive processes of angiogenesis and tumor metastasis.

US5968945 discloses novel amides and imides which are inhibitors of TNFα and phosphodiesterase and can be used to combat cachexia, endotoxic shock, retrovirus replication, asthma and inflammatory conditions.
the carbon atom designated * constitutes a center of chirality;
Y is C=O, CH₂, SO₂ or CH₃C=O;
X is hydrogen, or alkyl of 1 to 4 carbon atoms;
each of R¹, R², R³, and R⁴, independently of the others, is hydrogen, halo, trifluoromethyl, acetyl, alkyl of 1 to 8 carbon atoms, alkylx of 1 to 4 carbon atoms, nitro, cyano, hydroxy, tert-butyl, -CH₂NR⁸R⁹, -(CH₂)₂NR⁸R⁹, or -NR⁸R⁹; or
any two of R¹, R², R³, and R⁴ on adjacent carbon atoms, together with the depicted phenylene ring are naphthylidene, quinoline, quinoxaline, benzimidazole, benzodioxole or 2-hydroxybenzimidazole;
each of R⁵ and R⁶, independently of the other, is hydrogen, alkyl of 1 to 4 carbon atoms, alkyl of 1 to 6 carbon atoms, cyano, benzyloxyalkoxy, cycloalkoxy of up to 18 carbon atoms, bicycloalkoxy of up to 18 carbon atoms, tricycloalkoxy of up to 18 carbon atoms, or cycloalkylalkoxy of up to 18 carbon atoms;
each of R⁸ and R⁹ taken independently of the other is hydrogen, straight alkyl of 1 to 8 carbon atoms, branched alkyl of 1 to 8 carbon atoms, phenyl, benzyl, pyridyl, pyridymethyl, or one of R⁸ and R⁹ is hydrogen and the other is -COR¹⁰, or
SO₂R¹⁰, or
R⁸ and R⁹ taken together are tetramethylene, pentamethylene, -CH₂CH₂X¹₂CH₂CH₂-, in which X¹ is -O-, -S-, or -NH-;
R¹⁰ is hydrogen, alkyl of 1 to 8 carbon atoms, cycloalkyl, cycloalkylmethyl of up to 6 carbon atoms, phenyl, pyridyl, benzyl, imidazolymethyl, pyridymethyl, NR¹¹R¹², CH₂NR*R⁰, or NR¹¹R¹² wherein R⁸ and R¹⁰, independently of each other, are hydrogen, methyl, ethyl, or propyl, and wherein R¹¹ and R¹², independently of each other, are hydrogen, alkyl of 1 to 8 carbon atoms, phenyl, or benzyl; and

[0033] (b) the acid addition salts of said compounds which contain a nitrogen atom susceptible of protonation for the manufacture of a medicament for the prophylaxis of atopic dermatitis, psoriasis, lupus, a viral infection, or viral conjunctivitis wherein the medicament is adapted for topical administration or for the manufacture of a medicament for the treatment of ulcerative colitis or systemic lupus erythematosus, or the topical treatment of atopic dermatitis, psoriasis, lupus, a viral infection, or viral conjunctivitis.

[0034] It will be appreciated that while for convenience the compounds of Formula I are identified as 1,3,4-oxadiazoles. The term alkyl denotes a univalent saturated or unsaturated branched, or straight, cyclic or mixture thereof hydrocarbon chain containing from 1 to 8 carbon atoms. Representative of such alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, cyclopentyl, and cyclopropymethyl. Alkylx refers to an alkyl group bound to the remainder of the molecule through an ethereal oxygen atom. Representative of such alkoxyl groups are methoxy, ethoxy, propoxy, isoproxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, cyclohexylmethoxy, and cyclopentylmethoxy.

[0035] The term cycloalkyl as used herein denotes a univalent cyclic hydrocarbon chain which may be saturated or unsaturated. Unless otherwise stated, such chains can contain up to 18 carbon atoms and include monocyloalkyl, dicycloalkyl, polyalkylalkyl, and benzocyloalkyl structures. Monocyloalkyl refers to groups having a single ring group.

[0036] Polycycloalkyl denotes hydrocarbon systems containing two or more ring systems with one or more ring carbon atoms in common; i.e., a spiro, fused, or bridged structure. Benzocyloalkyl signifies a monocyclic alkyl group fused to a benzo group. Representative of monocyclicalkyl groups are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, cycloundecyl, cyclooctadecyl, cyclohexadecyl, cycloheptadecyl, and cyclooctadecyl. Representative of polycycloalkyl include decahydronaphthalene, spiro[4.5]decyl, bicyclo[2.2.1]heptyl, bicyclo[3.2.1]octyl, pinanyl, norbornyl, and bicyclo[2.2.2]octyl. Benzocyloalkyl is typified by tetrahydroanaphthalenyl, indanyl, and 1,2-benzocycloheptanyl. Cycloalkoxy refers to a cycloalkyl group as just described, and that is a monocycloalkyl, polycycloalkyl, or benzocyloalkyl structure, bound to the remainder of the molecule through an ethereal oxygen atom.

[0037] A first preferred group of compounds are those of Formula I in which Y is C=O.
[0038] A further preferred group of compounds are those of Formula I in which Y is CH₂.
[0039] A further preferred group of compounds are those of Formula I in which each of R¹, R², R³, and R⁴ independently of the others, is hydrogen, halo, methyl, ethyl, methoxy, ethoxy, nitro, cyano, hydroxy, or -NR⁸R⁹ in which each of R⁸ and R⁹ taken independently of the other is hydrogen or methyl or one of R⁸ and R⁹ is hydrogen and the other is -COCH₃, or COR, where R is alkyl, benzyl, pyridyl, or pyridymethyl.
[0040] A further preferred group of compounds are those of Formula I in which one of R¹, R², R³ and R⁴ is -NH₂ or -CH₃ and the remaining of R¹, R², R³ and R⁴ are hydrogen.
[0041] A further preferred group of compounds are those of Formula I in which one of R¹, R², R³, and R⁴ is -NHCOCH₃, NHSO₂R¹⁰, or NHCOR¹⁰, and the remaining of R¹, R², R³ and R⁴ are hydrogen.
[0042] A further preferred group of compounds are those of Formula I in which one of R¹, R², R³, and R⁴ is -N(CH₃)₂.
and the remaining of R1, R2, R3 and R4 are hydrogen.

[0043] A further preferred group of compounds are those of Formula I in which one of R1, R2, R3, and R4 is methyl or ethyl and the remaining of R1, R2, R3, and R4 are hydrogen.

[0044] A further preferred group of compounds are those of Formula I in which each of R5 and R6, independently of the other, is methoxy, ethoxy, propoxy, cyclopent oxy, or cyclohexoxy.

[0045] A further preferred group of compounds are those of Formula I in which R5 is methoxy and R6 is alkoxy, monocy cloalkoxy, polycycloalkoxy, and benzocycloalkoxy.

[0046] A further preferred group of compounds are those of Formula I in which each of R5 and R6, independently of the other, is methoxy, ethoxy, propoxy, cyclopent oxy, or cyclohexoxy.

[0047] The compounds of Formula I are used, under the supervision of qualified professionals, to inhibit the undesirable effects of TNFα and PDE 4. The compounds may also be given to treat cancer conditions, undesirable angiogenesis, inflammation, skin conditions, etc. 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. Use of the terms PDE IV and PDE 4 are deemed equivalent.

[0048] The compounds are used topically in the treatment or prophylaxis of topical disease states including atopic dermatitis, psoriasis, lupus, viral infections, such as those caused by the herpes viruses, or viral conjunctivitis, psoriasis, cancer, etc. PDE 4 inhibition is a preferred embodiment, though inhibition of other phosphodiesterases is envisioned.

[0049] The compounds also can be used in the veterinary treatment of mammals other than humans in need of prevention or inhibition of TNFα production or PDE 4 inhibition.

[0050] TNFα mediated diseases for treatment, therapeutically or prophylactically, in animals which include disease states such as those noted above. Viral infection examples include feline immunodeficiency virus, equine infectious anemia virus, caprine arthritis virus, visna virus, and maedi virus, as well as other lentiviruses.

[0051] Methods of preparation of acids (I) are described in U.S. Patent No. 5,605,914 which is incorporated by reference herein. The preparation of the oxadiazoles (III) can be done in a two-step fashion or in a single-pot fashion. Reaction of acid (I) with carbonyldiimidazole (CDI) or another activating agent, followed by addition of an acyl hydrazide (NH2NHCXO, wherein X is a hydrogen or alkyl) provides a compound of Formula (II). Preferred solvents for this reaction ("a") are aprotic polar solvent that include acetonitrile (CH3CN), tetrahydrofuran (THF), and ethyl acetate (EtOAc). Compounds of Formula (II) can be isolated at this point. Alternatively, a compound of Formula (II) can be used in the next reaction "b" without isolation (a preferred solvent is then acetonitrile). In reaction "b" dehydration of a compound of Formula (II) with dehydrating reagents such as phosphorous oxychloride (POCl3) or phosphorous pentoxide (P2O5) provides a compound of Formula (III). Heat may be used in reaction "b".
When one of R₁, R₂, R₃, and R₄ is to be amino in the final 1,3,4-oxadiazole, it often is desirable to utilize the corresponding nitro compound (I) and then reduce the resulting nitroisoindolinone to an aminoisooindolinone after formation. Alternatively, amino groups and other groups which may react can be converted to an appropriately protected group.

Protecting groups utilized herein denote groups which generally are not found in the final therapeutic compounds but which are intentionally introduced at some stage of the synthesis in order to protect groups which otherwise might be altered in the course of chemical manipulations. Such protecting groups are removed at a later stage of the synthesis and compounds bearing such protecting groups thus are of importance primarily as chemical intermediates (although some derivatives also exhibit biological activity). Accordingly the precise structure of the protecting group is not critical. Numerous reactions for the formation and removal of such protecting groups are described in a number of standard works including, for example, "Protective Groups in Organic Chemistry", Plenum Press, London and New York, 1973; Greene, Th. W. "Protective Groups in Organic Synthesis", Wiley, New York, 1981; "The Peptides", Vol. 1, Schröder and Lubke, Academic Press, London and New York, 1965; "Methoden der organischen Chemie", Houben-Weyl, 4th Edition, Vol. 15/1, Georg Thieme Verlag, Stuttgart 1974, the disclosures of which are incorporated herein by reference.

The compounds of Formula I possess a center of chirality and thus can exist as optical isomers. Both the racemates of these isomers and the individual isomers themselves, as well as diastereomers when there are two chiral centers, are within the scope of the present invention. The racemates can be used as such or can be separated into their individual isomers mechanically as by chromatography using a chiral absorbent. Alternatively, the individual isomers can be prepared in chiral form or separated chemically from a mixture by forming salts with a chiral acid or base, or have such as the individual enantiomers of 10-camphorsulfonic acid, camphoric acid, α-bromocamphoric acid, methoxyacetic acid, tartaric acid, diacetyltartaric acid, malic acid, pyrrolidone-5-carboxylic acid, and the like, and then freeing one or both of the resolved bases, optionally repeating the process, so as obtain either or both substantially free of the other; i.e., in a form having an optical purity of >95%.

Preferred examples include substantially chirally pure (R)-isomer, a substantially chirally pure (S)-isomer, or a mixture thereof, wherein the isomer is 2-[1-(3-ethoxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)ethyl]isoindoline-1,3-dione, 2-[1-(3-ethoxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)ethyl]benzo[e]isoindoline-1,3-dione, 2-[1-(3-ethoxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)ethyl]benzo[e]isoindoline-1,3-dione, 2-[1-(3-ethoxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)ethyl]benzo[e]isoindoline-1,3-dione.
(POCl3, 0.54 mL, 5.8 mmol) in acetonitrile (20 mL) was heated to reflux for 2 hours. This solution was poured into water for 1 hour. The suspension was filtered and washed with water and ether to give crude 3-(1,3-dioxoisoindolin-2-yl)-N-carbonylamino-3-(3-ethoxy-4-methoxyphenyl)-propanamide (600 mg, 1.46 mmol) and phosphorus oxychloride ethyl(1,3-dioxoisindolin-4-yl)-acetamide, 5-(tert-butyl)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)ethyl]isoindoline-1,3-dione, 2-[1-(3,4-dimethoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)ethyl]isoindoline-1,3-dione, N-[1-(3-ethoxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)ethyl]-1,3-dioxoisindolin-4-yl]acetamide, N-[1-(3-ethoxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)ethyl]isoindoline-1,3-dione, 2-[1-(3,4-oxadiazol-2-yl)ethyl]isoindoline-1,3-dione, 2-[1-(3-ethoxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)ethyl]isoindoline-1,3-dione, 2-[1-(3-ethoxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)ethyl]isoindoline-1,3-dione, 2-[1-(3,4-oxadiazol-2-yl)ethyl]isoindoline-1,3-dione, and 2-[1-(3-ethoxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)ethyl]-3-pyrrolino[3,4-]quinoline-1,3-dione.

[0056] The present invention also pertains to the use of physiologically acceptable non-toxic acid addition salts of the compounds of Formula I. Such salts include those derived from organic and inorganic acids such as, without limitation, hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, acetic acid, tartaric acid, lactic acid, succinic acid, citric acid, maleic acid, sorbic acid, acetic acid, salicylic acid, phthalic acid, embonic acid, and the like.

[0057] Oral dosage forms include tablets, capsules, drages, and similar shaped, compressed pharmaceutical forms containing from 1 to 100 mg of drug per unit dosage. Mixtures containing from 20 to 100 mg/mL can be formulated for parenteral administration which includes intramuscular, intrathecal, intravenous and intra-arterial routes of administration. Rectal administration can be effected through the use of suppositories formulated from conventional carriers such as cocoa butter.

[0058] Pharmaceutical compositions thus comprise one or more compounds of the present invention associated with at least one pharmaceutically acceptable carrier, diluent or excipient. In preparing such compositions, the active ingredients are usually mixed with or diluted by an excipient or enclosed within such a carrier which can be in the form of a capsule or sachet. When the excipient serves as a diluent, it may be a solid, semi-solid, or liquid material which acts as a vehicle, carrier, or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, elixirs, suspensions, emulsions, solutions, syrups, soft and hard gelatin capsules, suppositories, sterile injectable solutions and sterile packaged powders.

[0059] The compositions preferably are formulated in unit dosage form, meaning physically discrete units suitable as a unitary dosage, or a predetermined fraction of a unitary dose to be administered in a single or multiple dosage regimen to human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect in association with a suitable pharmaceutical excipient. The compositions can be formulated so as to provide an immediate, sustained or delayed release of active ingredient after administration to the patient by employing procedures well known in the art.

[0060] The following examples will serve to further typify the nature of this invention but should not be construed as a limitation in the scope thereof, which scope is defined solely by the appended claims.

Example 1

2-[1-(3-Ethoxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)ethyl] isoindoline-1,3-dione

[0061] A mixture of 3-(1,3-dioxoisindolin-2-yl)-3-(3-ethoxy-4-methoxyphenyl)propanoic acid (3.0 g, 8.1 mmol) and carbonyldimidazole (1.45 g, 8.94 mmol) in tetrahydrofuran (15 mL) was stirred at room temperature for 2 hours. To the solution was added formic hydrazide (125 mg, 1.6 mmol). The mixture was stirred for 18 hours. The resulting suspension was filtered and washed with ether. The isolated solid was stirred in a mixture of ethyl acetate (40 mL) and water (10 mL) for 1 hour. The suspension was filtered and washed with ether. The isolated solid was stirred in a mixture of ethyl acetate (40 mL) and water (10 mL) for 1 hour. The suspension was filtered and washed with water and ether to give crude 3-(1,3-dioxoisindolin-2-yl)-N-carbonylamino-3-(3-ethoxy-4-methoxyphenyl)propanamide (1.3 g, 39% yield). A solution of 3-(1,3-dioxoisindolin-2-yl)-N-carbonylamino-3-(3-ethoxy-4-methoxyphenyl)propanamide (600 mg, 1.46 mmol) and phosphorus oxychloride (POCl3, 0.54 mL, 5.8 mmol) in acetonitrile (20 mL) was heated to reflux for 2 hours. This solution was poured into water (10 mL). The aqueous layer was extracted with ethyl acetate (2 X 50 mL). The combined organic layers were washed with sodium hydrogen carbonate (50 mL, sat), brine (50 mL) and dried over magnesium sulfate. Removal of solvent and chromatography gave an oil. The oil was slurried in ether (10 mL). The resulting suspension was filtered to yield 2-[1-(3-ethoxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)ethyl]isoindoline-1,3-dione (1.3 g, 72% yield), mp 132.0-134.0 °C; 1H NMR (CDCl3), δ 1.46 (t, J = 6.9 Hz, 2H, CH3), 2.82 (dd, J = 6.0, 15.6 Hz, 1H, CHH), 3.84 (s, 3H, CH3), 4.11 (q, J = 7.0 Hz, 2H, CH2), 4.37 (dd, J = 10.3, 15.7 Hz, 1H, CHH), 5.81 (dd, J = 6.0, 15.3 Hz, 1H, CHH), 6.62 (d, J = 7.9 Hz, 1H, Ar), 7.13-7.17 (m, 2H, Ar), 7.67-7.72 (m, 2H, Ar), 7.75-7.82 (m, 2H, Ar), 8.29 (s, 1H, Ar); 13C NMR
Example 2

2-[1-(3-Ethoxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)ethyl]benzo[e]isoindoline-1,3-dione

[0062] 2-[1-(3-Ethoxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)ethyl]benzo[e]isoindoline-1,3-dione was prepared by the procedure used in Example 1. Thus, reaction of 3-(1,3-dioxobenzo[e]isoindolin-2-yl)-3-(3-ethoxy-4-methoxyphenyl)propanoic acid (1.50 g, 3.58 mmol), carbonyldiimidazole (0.70 g, 4.3 mmol) and formic hydrazide (310 mg, 5.16 mmol) in tetrahydrofuran (20 mL) gave crude 3-(1,3-dioxobenzo[e]isoindolin-2-yl)-N-carbonylamino-3-(3-ethoxy-4-methoxy-phenyl)propanamide (1.0 g, 2.2 mmol), which was then treated with phosphorus oxychloride (POCl$_3$, 0.4 mL, 4.3 mmol) in acetonitrile (10 mL). The product was obtained as a yellow solid (135 mg, 8% overall yield): mp, 139.0-141.5 °C; $^1$H NMR (CDCl$_3$) $\delta$ 1.47 (t, J = 7.2 Hz, 3H, CH$_3$), 3.85 (s, 3H, CH$_3$), 3.87 (dd, J = 6.0, 15.6 Hz, 1H, CHH), 4.13 (q, J = 6.9 Hz, 2H, CH$_2$), 4.42 (dd, J = 5.9, 10.4 Hz, 1H, NCH), 6.84 (d, J = 8.7 Hz, 1H, Ar), 7.18-7.27 (m, 2H, Ar), 7.64-7.75 (m, 2H, Ar), 7.81 (d, J = 8.3 Hz, 1H, Ar), 8.14 (d, J = 8.2 Hz, 1H, Ar), 8.29 (s, 1H, CH); $^{13}$C NMR (CDCl$_3$) $\delta$ 14.69, 27.70, 51.85, 55.90, 64.42, 111.32, 112.51, 120.32, 123.44, 130.14, 131.63, 134.13, 143.43, 153.03, 163.99, 167.93; Anal Calcd for C$_{21}$H$_{29}$N$_3$O$_5$: C, 64.12; H, 4.87; N, 10.68. Found: C, 63.84; H, 4.90; N, 10.48.

Example 3

2-[1-(3-Ethoxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)ethyl]-4-methylisoindoline-1,3-dione

[0063] 2-[1-(3-Ethoxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)ethyl]-4-methylisoindoline-1,3-dione was prepared by the procedure of Example 1. Reaction of 3-(3-ethoxy-4-methoxyphenyl)-3-(4-methyl-1,3-dioxoisoindolin-2-yl)propanoic acid (2.03 g, 5.29 mmol), carbonyldiimidazole (1.03 g, 6.35 mmol) and formic hydrazide (420 mg, 6.99 mmol) in tetrahydrofuran (20 mL) gave crude N-carbonylamino-3-(3-ethoxy-4-methoxyphenyl)-3-(4-methyl-1,3-dioxoisoindolin-2-yl)propanamide (610 mg, 1.43 mmol), which was then treated with phosphorus oxychloride (0.4 mL, 4.3 mmol) in acetonitrile (6 mL). The product was obtained as a white solid (311 mg, 14% overall yield): mp, 96.0-98.0 °C; $^1$H NMR (CDCl$_3$) $\delta$ 1.47 (t, J = 6.9 Hz, 2H, CH$_2$), 2.67 (s, 3H, CH$_3$), 3.81 (dd, J = 6.0, 15.7 Hz, 1H, CHH), 3.85 (s, 3H, CH$_3$), 4.12 (q, J = 6.9 Hz, 2H, CH$_2$), 4.37 (dd, J = 10.2, 15.6 Hz, 1H, CHH), 5.81 (t, J = 6.0, 10.3 Hz, 1H, NCH), 6.83 (d, J = 8.7 Hz, 1H, Ar), 7.14-7.17 (m, 2H, Ar), 7.43 (d, J = 7.6 Hz, 1H, Ar), 7.54 (t, J = 7.3 Hz, 1H, Ar), 7.63 (d, J = 7.1 Hz, 1H, Ar), 8.30 (s, 1H, CH); $^{13}$C NMR (CDCl$_3$) $\delta$ 14.69, 17.52, 27.71, 51.62, 55.92, 64.46, 111.37, 112.63, 120.33, 121.06, 123.27, 123.88, 128.97, 130.23, 131.95, 134.58, 145.39, 146.33, 149.42, 153.02, 164-04, 168.04, 168.53; Anal Calcd for C$_{25}$H$_{21}$N$_3$O$_5$ + 0.2 H$_2$O: C, 64.29; H, 5.25; N, 10.22; H$_2$O, 0.90. Found: C, 64.62; H, 5.30; N, 9.83; H$_2$O, 0.71.

Example 4

2-[1-(3-Ethoxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)ethyl]-5-methylisoindoline-1,3-dione

[0064] 2-[1-(3-Ethoxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)ethyl]-5-methylisoindoline-1,3-dione was prepared by the procedure of Example 1. Reaction of 3-(3-ethoxy-4-methoxyphenyl)-3-(5-methyl-1,3-dioxoisoindolin-2-yl)propanoic acid (1.81 g, 4.72 mmol), carbonyldiimidazole (0.92 g, 5.7 mmol) and formic hydrazide (375 mg, 6.2 mmol) in ethyl acetate (20 mL) gave crude N-carbonylamino-3-(3-ethoxy-4-methoxyphenyl)-3-(5-methyl-1,3-dioxoisoindolin-2-yl)propanamide (0.93 g, 2.2 mmol), which was then treated with phosphorus oxychloride (0.4 mL, 4.3 mmol) in acetonitrile (12 mL). The product was obtained as a white solid (371 mg, 19% overall yield): mp, 122.0-124.0 °C; $^1$H NMR (CDCl$_3$) $\delta$ 1.45 (t, J = 6.9 Hz, 2H, CH$_2$), 2.48 (s, 3H, CH$_3$), 3.80 (dd, J = 6.0, 15.6 Hz, 1H, CHH), 3.84 (s, 3H, CH$_3$), 4.10 (q, J = 6.9 Hz, 2H, CH$_2$), 4.35 (dd, J = 10.3, 15.6 Hz, 1H, CHH), 5.79 (dd, J = 6.0, 10.2 Hz, 1H, NCH), 6.82 (d, J = 8.1 Hz, 1H, Ar), 7.12-7.17 (m, 2H, Ar), 7.47 (d, J = 7.5 Hz, 1H, Ar), 7.59 (s, 1H, Ar), 7.68 (d, J = 7.6 Hz, 1H, Ar), 8.08 (s, 1H, Ar); $^{13}$C NMR (CDCl$_3$) $\delta$ 14.61, 21.86, 27.67, 51.71, 55.83, 64.36, 111.29, 114.49, 120.22, 123.27, 123.88, 128.97, 130.23, 131.95, 134.58, 145.39, 146.33, 149.34, 152.93, 163.97, 167.91, 168.04; Anal Calcd for C$_{22}$H$_{21}$N$_3$O$_5$: C, 64.86; H, 5.20; N, 9.30. Found: C, 64.77; H, 5.07; N, 10.30.
Example 5

2-[1-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)ethyl]-5-methylisoindoline-1,3-dione

[0065] 2-[1-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)ethyl]-5-methylisoindoline-1,3-dione was prepared by the procedure of Example 1. Reaction of 3-[3-cyclopentyloxy-4-methoxyphenyl-3-(5-methyl-1,3-dioxoisindolin-2-yl)propanoic acid (2.33 g, 5.5 mmol), carbonyldiimidazole (1.07 g, 6.59 mmol) and formic hydrazide (436 mg, 7.26 mmol) in ethyl acetate (20 mL) gave crude N-carbonylamino-3-[3-cyclopentyloxy-4-methoxyphenyl]-3-(5-methyl-1,3-dioxoisindolin-2-yl)propanamide (2.24 g, 4.8 mmol), which was then treated with phosphorus oxychloride (0.9 mL, 9.6 mmol) in acetonitrile (10 mL). The product was obtained as a white solid (728 mg, 32% overall yield): mp, 184.0-186.5 °C; 1H NMR (CDCl3) δ 1.55-2.00 (m, 8H, C5H8), 2.48 (s, 3H, CH3), 3.81 (s, 3H, CH3), 3.82 (dd, J = 6.1, 15.7 Hz, 1H, CHH), 4.36 (dd, J = 10.3, 15.7 Hz, 1H, -CHH), 4.74-4.81 (m, 1H, OCH), 5.79 (dd, J = 5.9, 10.3 Hz, 1H, NCH), 6.80 (d, J = 8.4 Hz, 1H, Ar), 7.10 (dd, J = 2.0 Hz, 1H, Ar), 7.18 (d, J = 2.0 Hz, 1H, Ar), 7.47 (d, J = 7.5 Hz, 1H, Ar), 7.59 (s, 1H, Ar), 7.67 (d, J = 7.6 Hz, 1H, Ar), 8.28 (s, 1H, CH); 13C NMR (CDCl3) δ 21.95, 24.09, 27.75, 32.77, 51.79, 56.00, 80.48, 111.73, 114.51, 120.16, 123.34, 123.95, 129.05, 130.22, 132.03, 134.65, 145.44, 147.75, 150.03, 153.00, 164.08, 167.98, 168.11; Anal Calcd for C25H25N3O5 + 0.13 Et2O: C, 67.05; H, 5.80; N, 9.19. Found: C, 66.95; H, 5.88; N, 8.97. (HNMR showed the sample contained 0.13 equiv. of ether).

Example 6

2-[1-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)ethyl]-4-methylisoindoline-1,3-dione

[0066] 2-[1-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)ethyl]-4-methylisoindoline-1,3-dione was prepared by the procedure of Example 1. Reaction of 3-(3-cyclopentyloxy-4-methoxyphenyl)-3-(4-methyl-1,3-dioxoisindolin-2-yl)propanoic acid (2.23 g, 5.27 mmol), carbonyldiimidazole (0.94 g, 5.8 mmol) and formic hydrazide (382 mg, 6.36 mmol) in ethyl acetate (20 mL) gave crude N-carbonylamino-3-(3-cyclopentyloxy-4-methoxyphenyl)-3-(4-methyl-1,3-dioxoisoindolin-2-yl)propanamide (1.71 g, 3.67 mmol), which was then treated with phosphorus oxychloride (0.8 mL, 8.6 mmol) in acetonitrile (10 mL). The product was obtained as a white solid (368 mg, 16% overall yield): mp, 126.0-128.5 °C; 1H NMR (CDCl3) δ 1.21-1.99 (m, 8H, C5H8), 2.66 (s, 3H, CH3), 3.81 (s, 3H, CH3), 3.82 (dd, J = 6.1, 15.8 Hz, 1H, CHH), 4.37 (dd, J = 10.3, 15.6 Hz, 1H, CHH), 4.76-4.83 (m, 1H, OCH), 5.80 (dd, J = 5.9, 10.3 Hz, 1H, NCH), 6.81 (d, J = 8.4 Hz, 1H, Ar), 7.09-7.18 (m, 2H, Ar), 7.43 (d, J = 7.6 Hz, 1H, Ar), 7.47 (d, J = 7.6 Hz, 1H, Ar), 8.28 (s, 1H, CH); 13C NMR (CDCl3) δ 17.45, 24.00, 27.67, 32.68, 51.57, 55.94, 80.44, 111.69, 114.55, 120.13, 120.98, 128.25, 130.22, 132.01, 133.51, 135.94, 136.44, 138.08, 147.68, 149.99, 152.93, 164.04, 167.95, 168.56; Anal Calcd for C25H25N3O5: C, 67.10; H, 5.63; N, 9.39. Found: C, 67.14; H, 5.55; N, 9.19.

Example 7

N-[2-[1-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(1,3-dioxoisindolin-4-yl)acetamide

[0067] N-[2-[1-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)ethyl]-1,3-dioxoisindolin-4-yl]acetamide was prepared by the procedure of Example 1. Reaction of 3-[4-(acetylamino)-1,3-dioxoisindolin-2-yl]propanoic acid (2.23 g, 5.5 mmol), carbonyldiimidazole (0.94 g, 5.8 mmol) and formic hydrazide (382 mg, 6.36 mmol) in ethyl acetate (20 mL) gave crude 3-[4-(acetylamino)-1,3-dioxoisindolin-2-yl]propanamide, which was then reacted with phosphorus oxychloride (1.0 mL, 10.7 mmol) in acetonitrile (15 mL). The product was isolated as a yellow solid (555 mg, 28% overall yield): mp, 115.0-117.0 °C; 1H NMR (CDCl3) δ 1.62-1.97 (m, 8H, C5H8), 2.27 (s, 3H, CH3), 3.76 (dd, J = 5.6, 15.9 Hz, 1H, CHH), 3.83 (s, 3H, CH3), 4.40 (dd, J = 10.7, 15.8 Hz, 1H, CHH), 4.76-4.82 (m, 1H, OCH), 5.78 (dd, J = 5.5, 10.7 Hz, 1H, NCH), 6.84 (d, J = 8.1 Hz, 1H, Ar), 7.09-7.15 (m, 2H, Ar), 7.47 (d, J = 7.2 Hz, 1H, Ar), 7.65 (t, J = 7.5 Hz, 1H, Ar), 8.32 (s, 1H, CH), 8.76 (d, J = 8.4 Hz, 1H, Ar), 9.48 (s, 1H, NH); 13C NMR (CDCl3) δ 23.99, 24.85, 27.58, 32.68, 51.71, 55.95, 80.53, 111.75, 114.46, 115.10, 118.03, 119.88, 124.82, 129.77, 130.95, 135.94, 137.48, 147.77, 150.21, 152.99, 163.85, 167.36, 168.07, 167.71; Anal Calcd for C25H25N3O5 + 0.1 hexane: C, 64.01; H, 5.53; N, 11.22. Found: C, 64.01; H, 5.58; N, 10.97. (HNMR showed the product contained 10% of hexane).

Example 8

N-[2-[1-(3-Ethoxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)ethyl]-1,3-dioxoisindolin-4-yl]acetamide

[0068] A mixture of 3-[4-(acetylamino)-1,3-dioxoisindolin-2-yl]-3-(3-ethoxy-4-methoxyphenyl)propanoic acid (1.69 g,
The product was obtained as a white solid (250 mg, 16% overall yield): mp, 143.5-144.5 °C; 1H NMR (CDCl3)
then reacted with phosphorus pentoxide (2.32 g, 16.3 mmol) in chloroform (30 mL) at room temperature for 18 hours.
N-carbonylamino-3-(3-ethoxy-4-methoxyphenyl)-3-(1-oxoisoindotin-2-yl)-propanamide (1.0 g, 2.2 mmol), which was
bonyldiimidazole (0.80 g, 4.9 mmol) and formic hydrazide (310 mg, 5.16 mmol) in tetrahydrofuran (10 mL) yielded crude
136.0-138.5 °C; 1H NMR (CDCl3) chloride (1.0 mL, 10.7 mmol) in acetonitrile (20 mL). The product was isolated as a white solid (800 mg, 38% yield): mp, 83.0-85.0 °C; 1H NMR (CDCl3)
5-(t Butyl)-2-[1-(3-ethoxy-4-methoacyphenyl)-2-(1,3,4-oxadiazol-2-yl)ethyl]isoindoline-1,3-dione was prepared
[0069] Example 1. Reaction of 3-(3-ethoxy-4-methoxyphenyl)-3-(1-oxoisoindolin-2-yl)propanoic acid (1.50 g, 4.22 mmol), carbonyldiimidazole (1.0 g, 6.2 mmol), formic hydrazide (0.41 g, 6.8 mmol), and phosphorus oxychloride (1.3 mL, 14 mmol) in acetonitrile (20 mL). The product was obtained as a white solid (730 mg, 34% yield): mp, 83.0-85.0 °C; 1H NMR (CDCl3)
66.51; H, 6.08; N, 9.31; H2O, 0.43. Found: C, 66.42; H, 5.83; N, 9.18; H2O, 0.43.

Example 9

5-(tert-Butyl)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)ethyl]isoindoline-1,3-dione

[0069] 5-(t-Butyl)-2-[1-(3-ethoxy-4-methacry phenyl)-2-(1,3,4-oxadiazol-2-yl)ethyl]isoindoline-1,3-dione was prepared as described for Example 8 from 3-[5-(tert-butyl)-1,3-dioxoisoindolin-2-yl]-3-(3-ethoxy-4-methoxyphenyl)propanoic acid (2.0 g, 4.7 mmol), carbonyldiimidazole (1.0 g, 8.1 mm, 5.0 mmol), formic hydrazide (0.35 g, 5.8 mmol), and phosphorus oxychloride (1.0 mL, 10.7 mmol) in acetonitrile (20 mL). The product was isolated as a white solid (478 mg, 27% yield): mp, 141.0-143.0 °C; 1H NMR (CDCl3)

Example 10

2-[1-(3,4-Dimethoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)ethyl]isoindoline-1,3-dione

[0070] 2-[1-(3,4-Dimethoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)ethyl]isoindoline-1,3-dione was prepared by the procedure of Example 8 from 3-(3,4-dimethoxyphenyl)-3-(1,3-dioxoisoindolin-2-yl)-propanoic acid (2.0 g, 3.6 mmol), carbonyldimidazole (1.0 g, 6.2 mmol), formic hydrazide (0.41 g, 6.8 mmol), and phosphorus oxychloride (1.3 mL, 14 mmol) in acetonitrile (20 mL). The product was obtained as a white solid (730 mg, 34% yield): mp, 83.0-85.0 °C; 1H NMR (CDCl3)

Example 11

2-[1-(3-Ethoxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)ethyl]isoindolin-1-one

[0071] 2-[1-(3-Ethoxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)ethyl]isoindolin-1-one was prepared as described in Example 1. Reaction of 3-(3-ethoxy-4-methoxyphenyl)-3-(1-oxoisoindolin-2-yl)propanoic acid (1.50 g, 4.22 mmol), carbonyldimidazole (0.80 g, 4.9 mmol) and formic hydrazide (310 mg, 5.16 mmol) in tetrahydrofuran (10 mL) yielded crude N-carbonylamino-3-(3-ethoxy-4-methoxyphenyl)-3-(1-oxoisoindolin-2-yl)-propanamide (1.0 g, 2.2 mmol), which was then reacted with phosphorus pentoxide (2.32 g, 16.3 mmol) in chloroform (30 mL) at room temperature for 18 hours. The product was obtained as a white solid (250 mg, 16% overall yield): mp, 143.5-144.5 °C; 1H NMR (CDCl3)
Example 12

2-[1-(3-Ethoxy-4-methoxyphenyl)-2-(5-methyl(1,3,4-oxadiazol-2-yl))ethyl]isoindolin-1-one

[0072] 2-[1-(3-Ethoxy-4-methoxyphenyl)-2-(5-methyl(1,3,4-oxadiazol-2-yl))ethyl]isoindolin-1-one was prepared by the procedure of Example 1. Reaction 3-(3-ethoxy-4-methoxyphenyl)-3-(1-oxoisoinolin-2-yl)propanoic acid (1.50 g, 4.22 mmol), carbonyldiimidazole (0.76 g, 4.7 mmol) and acetic hydrazide (381 mg, 5.16 mmol) in tetrahydrofuran (15 mL) gave crude N-carbonylamino-3-(3-ethoxy-4-methoxyphenyl)-3-(1-oxoisoinolin-2-yl)propanamide (1.22 g, 3.06 mmol), which (650 mg, 1.47 mmol) was then reacted with phosphorus pentoxide (2.0 g, 14 mmol) in chloroform (30 mL) at room temperature for 18 hours. The product was obtained as a white solid (250 mg, 32% overall yield): mp, 125.5-128.0 °C; 1H NMR (CDCl3) δ 1.43 (t, J = 7.0 Hz, 3H, CH3), 2.46 (s, 3H, CH3), 3.56 (dd, J = 6.3, 15.1 Hz, 1H, CHH), 3.76 (dd, J = 10.0, 15.0 Hz, 1H, CHH), 3.86 (s, 3H, CH3), 4.02-4.11 (m, 3H, NCHH, CH2), 4.46 (d, J = 16.6 Hz, 1H, NCHH), 5.97 (dd, J = 6.3, 9.9 Hz, 1H, NCH), 6.83-6.87 (m, 1H, Ar), 6.95-7.01 (m, 2H, Ar), 7.35-7.53 (m, 3H, Ar), 7.77-7.81 (m, 1H, Ar); 13C NMR (CDCl3) δ 10.89, 14.64, 28.04, 46.18, 52.08, 55.89, 64.47, 111.32, 112.51, 119.03, 122.81, 123.74, 127.95, 130.13, 131.48, 132.11, 141.17, 148.66, 149.31, 163.86, 164.23, 168.30, Anal Calcd for C22H23N3O4 + 0.28 EtOAc: C, 66.42; H, 6.08; N, 10.05. Found: C, 66.47; H, 5.98; N, 10.04. (1H NMR showed that the sample contained 28% of ethyl acetate).

Example 13

2-[1-(3-Ethoxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)ethyl]-3-pyrrolino[3,4]quinoline-1,3-dione

[0073] 2-[1-(3-Ethoxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)ethyl]-3-pyrrolino[3,4-h]-quinoline-1,3-dione was prepared by the procedure of Example 1. Reaction of 3-(1,3-dioxo(3-pyrrolino[3,4-h]quinolin-2-yl))-3-(3-ethoxy-4-methoxyphenyl)propanoic acid (1.0 g, 2.4 mmol), CDI (0.46 g, 2.8 mmol) and formic hydrazide (0.20 g, 3.4 mmol) in THF (10 mL) gave crude 3-(1,3-dioxo(3-pyrrolino[3,4-h]quinolin-2-yl))-N-carbonylamino-3-(3-ethoxy-4-methoxyphenyl)propanamide (1.12 g), which was then reacted with phosphorus oxychloride (0.8 mL, 8.6 mmol) in acetonitrile (30 mL). The product was obtained as a white solid (350 mg, 33% overall yield): mp, 166-168 °C; 1H NMR (CDCl3) δ 1.47 (t, J = 6.8 Hz, 3H, CH3), 3.85 (dd, J = 5.9, 15.8 Hz, 1H, CHH), 3.85 (s, 3H, CH3), 4.13 (q, J = 6.9 Hz, 2H, CH2), 4.48 (dd, J = 10.4, 15.8 Hz, 1H, CHH), 5.91 (dd, J = 5.8, 10.4 Hz, 1H, NCH), 6.82-6.85 (m, 1H, Ar), 7.21-7.25 (m, 2H, Ar), 7.58 (dd, J = 4.2, 8.4 Hz, 1H, Ar), 7.94 (d, J = 8.0 Hz, 1H, Ar), 8.19 (d, J = 8.2 Hz, 1H, Ar), 8.27 (dd, J = 1.7, 8.4 Hz, 1H, Ar), 8.28 (s, 1H, CH), 9.24 (dd, J = 1.7, 4.2 Hz, 1H); 13C NMR (CDCl3) δ 14.63, 27.60, 51.83, 55.85, 64.39, 111.29, 112.58, 119.52, 120.43, 123.16, 126.81, 130.08, 132.14, 134.44, 135.57, 136.68, 142.77, 148.34, 149.36, 152.97, 154.27, 163.99, 170.07, 167.80, Anal Calcd for C24H20N4O5 + 0.05 CH2Cl2: C, 64.38; H, 5.42; N, 12.49. Found: C, 64.33; H, 4.58; N, 12.12. (H NMR showed the sample contained ~5% of CH2Cl2).

Example 14

[0074] Tablets, each containing 50 mg of 2-[1-(3-cyclopentyloxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)ethyl]-methylisoindoline-1,3-dione are prepared in the following manner:

Constituents (for 1000 tablets)
2-[1-(3-cyclopentyloxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)ethyl]-methylisoindoline-1,3-dione 50.0 g
lactose 50.7 g
wheat starch 7.5 g
polyethylene glycol 6000 5.0 g
talc 5.0 g
magnesium stearate 1.8 g
demineralized water q.s.

The solid ingredients are first forced through a sieve of 0.6 mm mesh width. The active ingredient, lactose, talc, magnesium stearate and half of the starch then are mixed. The other half of the starch is suspended in 40 mL of water and this suspension is added to a boiling solution of the polyethylene glycol in 100 mL of water. The resulting paste is added to...
the pulverulent substances and the mixture is granulated, if necessary with the addition of water. The granulate is dried overnight at 35°C, forced through a sieve of 1.2 mm mesh width and compressed to form tablets of approximately 6 mm diameter which are concave on both sides.

**Example 15**

[0075] Tablets, each containing 100 mg of 2-[1-(3-cyclopentyl oxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)ethyl]-5-methylisoindoline-1,3-dione, can be prepared in the following manner

<table>
<thead>
<tr>
<th>Constituents (for 1000 tablets)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>2-[1-(3-cyclopentyl oxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)ethyl]-5-methylisoindoline-1,3-dione</td>
<td>100.0 g</td>
</tr>
<tr>
<td>lactose</td>
<td>100.0 g</td>
</tr>
<tr>
<td>wheat starch</td>
<td>47.0 g</td>
</tr>
<tr>
<td>magnesium stearate</td>
<td>3.0 g</td>
</tr>
</tbody>
</table>

All the solid ingredients are first forced through a sieve of 0.6 mm mesh width. The active ingredient, lactose, magnesium stearate and half of the starch then are mixed. The other half of the starch is suspended in 40 mL of water and this suspension is added to 100 mL of boiling water. The resulting paste is added to the pulverulent substances and the mixture is granulated, if necessary with the addition of water. The granulate is dried overnight at 35°C, forced through a sieve of 1.2 mm mesh width and compressed to form tablets of approximately 6 mm diameter which are concave on both sides.

**Example 16**

[0076] Tablets for chewing, each containing 75 mg of 2-[1-(3-cyclopentyl oxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)ethyl]-5-methylisoindoline-1,3-dione, can be prepared in the following manner:

<table>
<thead>
<tr>
<th>Composition (for 1000 tablets)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>2-[1-(3-cyclopentyl oxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)ethyl]-5-methylisoindoline-1,3-dione</td>
<td>75.0 g</td>
</tr>
<tr>
<td>mannitol</td>
<td>230.0 g</td>
</tr>
<tr>
<td>lactose</td>
<td>150.0 g</td>
</tr>
<tr>
<td>talc</td>
<td>21.0 g</td>
</tr>
<tr>
<td>glycine</td>
<td>12.5 g</td>
</tr>
<tr>
<td>stearic acid</td>
<td>10.0 g</td>
</tr>
<tr>
<td>saccharin</td>
<td>1.5 g</td>
</tr>
<tr>
<td>5% gelatin solution</td>
<td>q.s.</td>
</tr>
</tbody>
</table>

All the solid ingredients are first forced through a sieve of 0.25 mm mesh width. The active ingredient, lactose, magnesium stearate and half of the starch then are mixed. The other half of the starch is suspended in 40 mL of water and this suspension is added to 100 mL of boiling water. The resulting paste is added to the pulverulent substances and the mixture is granulated, if necessary with the addition of water. The granulate is dried overnight at 35°C, forced through a sieve of 1.2 mm mesh width and compressed to form tablets of approximately 6 mm diameter which are concave on both sides and have a breaking groove on the upper side.

**Example 17**

[0077] Tablets, each containing 10 mg 2-[1-(3-cyclopentyl oxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)ethyl]-5-methylisoindoline-1,3-dione, can be prepared in the following manner:

<table>
<thead>
<tr>
<th>Composition (for 1000 tablets)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>2-[1-(3-cyclopentyl oxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)ethyl]-5-methylisoindoline-1,3-dione</td>
<td>10.0 g</td>
</tr>
<tr>
<td>lactose</td>
<td>328.5 g</td>
</tr>
<tr>
<td>corn starch</td>
<td>17.5 g</td>
</tr>
<tr>
<td>polyethylene glycol 6000</td>
<td>5.0 g</td>
</tr>
<tr>
<td>talc</td>
<td>25.0 g</td>
</tr>
</tbody>
</table>
The solid ingredients are first forced through a sieve of 0.6 mm mesh width. Then the active imide ingredient, lactose, talc, magnesium stearate and half of the starch are intimately mixed. The other half of the starch is suspended in 65 mL of water and this suspension is added to a boiling solution of the polyethylene glycol in 260 mL of water. The resulting paste is added to the pulverulent substances, and the whole is mixed and granulated, if necessary with the addition of water. The granulate is dried overnight at 35°C, forced through a sieve of 1.2 mm mesh width and compressed to form tablets of approximately 10 mm diameter which are concave on both sides and have a breaking notch on the upper side.

Example 18

Gelatin dry-filled capsules, each containing 100 mg of 2-(1-(3-cyclopentyloxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)ethyl]-5-methylisoindoline-1,3-dione, can be prepared in the following manner:

Composition (for 1000 capsules)

<table>
<thead>
<tr>
<th>Component</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-(1-(3-cyclopentyloxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)ethyl]-5-methylisoindoline-1,3-dione</td>
<td>100.0 g</td>
</tr>
<tr>
<td>microcrystalline cellulose</td>
<td>30.0 g</td>
</tr>
<tr>
<td>sodium lauryl sulfate</td>
<td>2.0 g</td>
</tr>
<tr>
<td>magnesium stearate</td>
<td>8.0 g</td>
</tr>
</tbody>
</table>

The sodium lauryl sulfate is sieved into the 2-(1-(3-cyclopentyloxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)ethyl]-5-methylisoindoline-1,3-dione through a sieve of 0.2 mm mesh width and the two components are intimately mixed for 10 minutes. The microcrystalline cellulose is then added through a sieve of 0.9 mm mesh width and the whole is again intimately mixed for 10 minutes. Finally, the magnesium stearate is added through a sieve of 0.8 mm width and, after mixing for a further 3 minutes, the mixture is introduced in portions of 140 mg each into size 0 (elongated) gelatin dry-fill capsules.

Example 19

Gelatin dry-filled capsules, each containing 100 mg of 2-(1-(3-cyclopentyloxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)ethyl]-5-methylisoindoline-1,3-dione, can be prepared in the following manner:

Composition (for 1000 capsules)

<table>
<thead>
<tr>
<th>Component</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-(1-(3-cyclopentyloxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)ethyl]-5-methylisoindoline-1,3-dione</td>
<td>5.0 g</td>
</tr>
<tr>
<td>microcrystalline cellulose</td>
<td>30.0 g</td>
</tr>
<tr>
<td>sodium lauryl sulfate</td>
<td>2.0 g</td>
</tr>
<tr>
<td>magnesium stearate</td>
<td>8.0 g</td>
</tr>
</tbody>
</table>

The sodium lauryl sulfate is sieved into the 2-(1-(3-cyclopentyloxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)ethyl]-5-methylisoindoline-1,3-dione through a sieve of 0.2 mm mesh width and the two components are intimately mixed for 10 minutes. The microcrystalline cellulose is then added through a sieve of 0.9 mm mesh width and the whole is again intimately mixed for 10 minutes. Finally, the magnesium stearate is added through a sieve of 0.8 mm width and, after mixing for a further 3 minutes, the mixture is introduced in portions of 140 mg each into size 0 (elongated) gelatin dry-fill capsules.

Claims

1. Use of a 1,3,4-oxadiazole compound of formula I,
or a physiologically acceptable non-toxic acid addition salt thereof, for the manufacture of a medicament for the treatment of ulcerative colitis or systemic lupus erythematosi s, or the topical treatment of atopic dermatitis, psoriasis, lupus, a viral infection, or viral conjunctivitis:

wherein:

- the carbon atom designated * constitutes a center of chirality;
- Y is C=O, CH₂, SO₂ or CH₂C=O;
- X is hydrogen or alkyl of 1 to 4 carbon atoms;
- each of R₁, R₂, R₃ and R₄, independently of the others, is hydrogen, halo, trifluoromethyl, acetyl, alkyl of 1 to 8 carbon atoms, alkoxy of 1 to 4 carbon atoms, nitro, cyano, hydroxy, tert-butyl, -CH₂NR₈R₉, -CH₂CH₂NR₈R₉ or -NR₈R₉, or any two of R₁, R₂, R₃ and R₄ on adjacent carbon atoms, together with the depicted phenylene ring, are naphthylidene, quinoline, quinoxaline, benzimidazole, benzodioxole or 2-hydroxybenzimidazole;
- each of R₅ and R₆, independently of the other, is hydrogen, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 6 carbon atoms, cyano, benzocycloalkoxy, cycloalkoxy of up to 18 carbon atoms, bicycloalkoxy of up to 18 carbon atoms, tricycloalkoxy of up to 18 carbon atoms, or cycloalkylalkoxy of up to 18 carbon atoms;
- each of R₈ and R₉, taken independently of the other, is hydrogen, straight alkyl of 1 to 8 carbon atoms, branched alkyl of 1 to 8 carbon atoms, phenyl, benzyl, pyridyl, pyridylimethyl, or one of R₈ and R₉ is hydrogen and the other is -COR₁₀ or -SO₂R₁₀; or R₈ and R₉, taken together, are tetramethylene, pentamethylene, -CHNCH₂-, hexamethylene, -CH₂CH₂X₁CH₂CH₂- in which X₁ is -O-, -S-, or -NH-; and R₁₀ is hydroxy, alkyl of 1 to 8 carbon atoms, cycloalkyl, cycloalkylimethyl of up to 6 carbon atoms, phenyl, pyridyl, benzyl, imidazolylmethyl, pyridylimethyl, NR₁₁R₁₂ or CH₂NR*R₀, wherein R₁₁ and R₁₂, independently of each other, are hydrogen, alkyl of 1 to 8 carbon atoms, phenyl, or benzyl, and wherein R* and R₀, independently of each other, are hydrogen, methyl, ethyl, or propyl.

2. The use of claim 1, wherein the compound is substantially chirally pure.

3. The use of claim 1, wherein the medicament is for the treatment of ulcerative colitis or systemic lupus erythematosi s and is adapted for oral, rectal, parenteral, or topical administration.

4. The use of claim 1, wherein the compound of formula I is:

   2-[1-(3-ethoxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)]ethylisoindoline-1,3-dione;
   2-[1-(3-ethoxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)]ethylbenz[e]isoindoline-1,3-dione;
   2-[1-(3-ethoxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)]ethyl-4-methylisoindoline-1,3-dione;
   2-[1-(3-ethoxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)]ethyl-5-methylisoindoline-1,3-dione;
   2-[1-(3-cyclopentyloxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)]ethyl-5-methylisoindoline-1,3-dione;
   2-[1-(3-cyclopentyloxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)]ethyl-4-methylisoindoline-1,3-dione;
   2-[1-(3-cyclopentyloxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)]ethyl-4-methylisoindoline-1,3-dione;
   N-[2-[1-(3-cyclopentyloxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)]ethyl]-1,3-dioxoisooxindolin-4-yl]acetamide;
   N-[2-[1-(3-ethoxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)]ethyl]-1,3-dioxoisooxindolin-4-yl]acetamide;
   5-(tert-butyl)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)]ethyl]isoindoline-1,3-dione;
   2-[1-(3,4-dimethoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)]ethyl]isoindoline-1,3-dione;
   2-[1-(3-ethoxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)]ethyl]isoindolin-1-one;
   2-[1-(3-ethoxy-4-methoxyphenyl)-2-(5-methyl(1,3,4-Oxadiazol-2-yl)]ethyl]isoindolin-1-one; or
   2-[1-(3-ethoxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)]ethyl]-3-pyrroline[3,4-]quinoline-1,3-dione.

5. The use of claim 4, wherein the compound is substantially chirally pure.
6. Use of a 1,3,4-oxadiazole compound of formula I, or a physiologically acceptable non-toxic acid addition salt thereof, for the manufacture of a medicament for the prophylaxis of atopic dermatitis, psoriasis, lupus, a viral infection, or viral conjunctivitis wherein the medicament is adapted for topical administration: where:

- the carbon atom designated * constitutes a center of chirality;
- Y is C=O, CH₂, SO₂ or CH₂C=O;
- X is hydrogen or alkyl of 1 to 4 carbon atoms;
- each of R¹, R², R³ and R⁴, independently of the others, is hydrogen, halo, trifluoromethyl, acetyl, alkyl of 1 to 8 carbon atoms, alkoxyl of 1 to 4 carbon atoms, nitro, cyano, hydroxy, tert-butyl, -(CH₂)₂NR₈R₉, -(CH₂)₃NR₈R₉ or -NR₈R₉; or any two of R¹, R², R³ and R⁴ on adjacent carbon atoms, together with the depicted phenylene ring, are naphthylidene, quinoline, quinoxaline, benzimidazole, benzodioxole or 2-hydroxybenzimidazole;
- each of R⁵ and R⁶, independently of the other, is hydrogen, alkyl of 1 to 4 carbon atoms, alkoxyl of 1 to 6 carbon atoms, cyano, benzocycloalkoxyl, cycloalkoxy of up to 18 carbon atoms, tricycloalkoxy of up to 18 carbon atoms, tricycloalkoxy of up to 18 carbon atoms, or cycloalkylalkoxyl of up to 18 carbon atoms;
- each of R⁸ and R⁹, taken independently of the other, is hydrogen, straight alkyl of 1 to 8 carbon atoms, branched alkyl of 1 to 8 carbon atoms, phenyl, benzyl, pyridyl, pyridylmethyl, or one of R⁸ and R⁹ is hydrogen and the other is -COR¹⁰ or -SO₂R¹⁰; or R⁸ and R⁹, taken together, are tetramethylene, pentamethylene, -CHNCHCH-, hexamethylene, or -(CH₂)₄X¹CH₂CH₂- in which X¹ is -O-, -S-, or -NH-; and
- R¹⁰ is hydrogen, alkyl of 1 to 8 carbon atoms, cyano, cycloalkyl, cycloalkylalkoxyl of up to 6 carbon atoms, phenyl, pyridyl, benzyl, imidazolylmethyl, pyridylmethyl, NR₁₁R₁₂ or CH₂NR*, wherein R₁₁ and R₁₂, independently of each other, are hydrogen, alkyl of 1 to 8 carbon atoms, phenyl, or benzyl, and wherein R* and R₀, independently of each other, are hydrogen, methyl, ethyl, or propyl.

7. The use of claim 6, wherein the compound is substantially chirally pure.

8. The use of claim 6, wherein the viral infection is herpes infection.

9. The use of claim 6, wherein the compound of formula I is:

- 2-[1-(3-ethoxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)ethyl]isoindoline-1,3-dione;
- 2-[1-(3-ethoxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)ethyl]benzo[1]isoindoline-1,3-dione;
- 2-[1-(3-ethoxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)ethyl]-4-methylisoindoline-1,3-dione;
- 2-[1-(3-ethoxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)ethyl]-5-methylisoindoline-1,3-dione;
- 2-[1-(3-cyclopentyloxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)ethyl]-5-methylisoindoline-1,3-dione;
- 2-[1-(3-cyclopentyloxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)ethyl]-4-methylisoindoline-1,3-dione;
- N-[2-[1-(3-cyclopentoyxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)ethyl]-1,3-dioxoisooindol-4-yl]acetamide;
- N-[2-[1-(3-cyclopentoyxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)ethyl]-1,3-dioxoisooindol-4-yl]acetamide;
- 5-(tert-butyl)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)ethyl]isoindoline-1,3-dione;
- 2-[1-(3,4-dimethoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)ethyl]isoindoline-1,3-dione;
- 2-[1-(3-ethoxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)ethyl]isoindolin-1-one;
- 2-[1-(3-ethoxy-4-methoxyphenyl)-2-(5-methyl(1,3,4-Oxadiazol-2-yl))ethyl] isoindolin-1-one; or
EP 1 510 518 B1
2-[1-(3-ethoxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)ethyl]-3-pyrrolino[3,4-]quinoline-1,3-dione.

10. The use of claim 9, wherein the compound is substantially chirally pure.

**Patentansprüche**

1. Verwendung einer 1,3,5-Oxadiazolverbindung der Formel I,

![Chemical Structure](image)

oder eines physiologisch verträglichen nicht-toxischen Säureadditionssalzes davon, zur Herstellung eines Medikaments zur Behandlung von Colitis ulcerosa oder systemischem Lupus erythematoses, oder zur topischen Behandlung von atopischer Dermatitis, Psoriasis, Lupus, einer viralen Infektion oder viraler Konjunktivitis:

wobei:

- das mit * gekennzeichnete Kohlenstoffatom ein Chiralitätszentrum darstellt;
- Y C=O, CH₂, SO₂ oder CH₂C=O ist;
- X Wasserstoff oder Alkyl mit 1 bis 4 Kohlenstoffatomen ist;
- jedes R¹, R², R³ und R⁴ unabhängig von den anderen Wasserstoff, Halogen, Trifluormethyl, Acetyl, Alkyl mit 1 bis 8 Kohlenstoffatomen, Alkoxy mit 1 bis 4 Kohlenstoffatomen, Nitro, Cyan, Hydroxy, tert-Butyl, -CH₂NR₈R₉, -(CH₂)₂NR₈R₉ oder -NR₈R₉ ist; oder beliebige zwei von R¹, R², R³ und R⁴ an benachbarten Kohlenstoffatomen zusammen mit dem dargestellten Phenylethenring Naphthyliden, Chinolin, Chinoxalin, Benzimidazol, Benzidin oder 2-Hydroxybenzimidazol sind;
- jedes R⁵ und R⁶ unabhängig von dem anderen Wasserstoff, Alkyl mit 1 bis 4 Kohlenstoffatomen, Alkoxy mit 1 bis 6 Kohlenstoffatomen, Cyano, Benzocycloalkoxy, Cycloalkoxy mit bis zu 18 Kohlenstoffatomen, Bicycloalkoxy mit bis zu 18 Kohlenstoffatomen, Tricycloalkoxy mit bis zu 18 Kohlenstoffatomen oder Cycloalkylalkoxy mit bis zu 18 Kohlenstoffatomen ist;
- jedes R⁷ und R⁸ unabhängig von dem anderen Wasserstoff, geradkettiges Alkyl mit 1 bis 8 Kohlenstoffatomen, verzweigtes Alkyl mit bis zu 8 Kohlenstoffatomen, Phenyl, Benzyl, Pyridyl, Pyridylmethyl ist, oder eines von R⁸ und R⁹ Wasserstoff ist und das andere -COR¹⁰ oder -SO₂R¹⁰ ist; oder R⁷ und R⁸ zusammengenommen Tetramethylen, Pentamethylen, -CH(NH)CH₂-, Hexamethylen oder -CH₂CH₂X¹CH₂CH₂- sind, wobei X¹-O-, -S- oder -NH- ist; und
- R¹⁰ Wasserstoff, Alkyl mit 1 bis 8 Kohlenstoffatomen, Cycloalkyl, Cycloalkylalkylmethyl mit bis zu 6 Kohlenstoffatomen, Phenyl, Pyridyl, Benzyl, Imidazolylalkylmethyl, Pyridylalkylmethyl, NR¹¹R¹² oder CH₂NR¹⁰R¹⁰ ist, wobei R¹¹ und R¹² unabhängig voneinander Wasserstoff, Alkyl mit 1 bis 8 Kohlenstoffatomen, Phenyl oder Benzyl sind, und wobei R⁸ und R⁹ unabhängig voneinander Wasserstoff, Methyl, Ethyl oder Propyl sind.

2. Verwendung gemäß Anspruch 1, wobei die Verbindung im Wesentlichen chiral rein ist.

3. Verwendung gemäß Anspruch 1, wobei das Medikament zur Behandlung von Colitis ulcerosa oder systemischem Lupus erythematoses ist und für orale, rektale, parenterale oder topische Verabreichung hergerichtet ist.

4. Verwendung gemäß Anspruch 1, wobei die Verbindung der Formel I ist:
2-[1-(3-Ethoxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)ethyl]isoindolin-1,3-dion; 2-[1-(3-Ethoxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)ethyl]benzo[e]isoindolin-1,3-dion; 2-[1-(3-Ethoxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)ethyl]4-methylisoindolin-1,3-dion; 2-[1-(3-Ethoxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)ethyl]-5-methylisoindolin-1,3-dion; 2-[1-(3-Cyclopentylxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)ethyl]-4-methylisoindolin-1,3-dion; N-[2-[1-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)ethyl]-1,3-dioxoisoindolin-4-yl] acetamid; 2-[1-(3-Ethoxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-yl)ethyl]isoindolin-1,3-dion; 2-[1-(3,4-Dimethoxyphenyl)-2-(1,3,4-oxadiazol-2-y1)ethyl]isoindolin-1,3-dion; 2-[1-(3-Ethoxy-4-methoxyphenyl)-2-(1,3,4-oxadiazol-2-y1)ethyl]-3-pyrrolino[3,4-]chinolin-1,3-dion.

5. Verwendung gemäß Anspruch 4, wobei die Verbindung im Wesentlichen chiral rein ist.

6. Verwendung einer 1,3,4-Oxadiazolverbindung der Formel I,

\[
\text{I}
\]

oder eines physiologisch verträglichen nicht-toxischen Säureadditionssalzes davon, zur Herstellung eines Medikaments zur Vorbeugung von atopischer Dermatitis, Psoriasis, Lupus, einer viralen Infektion oder viraler Konjunktivitis, wobei das Medikament zur topischen Verabreichung hergerichtet ist:

wobei:

das mit * gekennzeichnete Kohlenstoffatom ein Chiralitätszentrum darstellt;

Y C=O, CH2, SO2 oder CH2C=O ist;

X Wasserstoff oder Alkyl mit 1 bis 4 Kohlenstoffatomen ist;

jedes R1, R2, R3 und R4 unabhängig von den anderen Wasserstoff, Halogen, Trifluormethyl, Acetyl, Alkyl mit 1 bis 8 Kohlenstoffatomen, Alkoxy mit 1 bis 4 Kohlenstoffatomen, Nitro, Cyano, Hydroxy, tert-Butyl, -CH2NR8R9, -(CH2)2NR8R9 oder -NR8R9 ist; oder beliebige zwei R1, R2, R3 und R4 an benachbarten Kohlenstoffatomen zusammen mit dem dargestellten Phenyleinring Naphthyliden, Chinolin, Chinoxalin, Benzimidazol, Benzodioxol oder 2-Hydroxybenzimidazol sind;

jedes R5 und R6 unabhängig von dem anderen Wasserstoff, Alkyl mit 1 bis 4 Kohlenstoffatomen, Alkoxy mit 1 bis 6 Kohlenstoffatomen, Cyano, Benzyloxyalkoxy, Cycloalkoxy mit bis zu 18 Kohlenstoffatomen, Bicycloalkoxy mit bis zu 18 Kohlenstoffatomen, Tricycloalkoxy mit bis zu 18 Kohlenstoffatomen oder Cycloalkylalkoxy mit bis zu 18 Kohlenstoffatomen ist;

jedes R6 und R8 unabhängig von dem anderen Wasserstoff, geradkettiges Alkyl mit 1 bis 8 Kohlenstoffatomen, verzweigtes Alkyl mit 1 bis 8 Kohlenstoffatomen, Phenyl, Benzyl, Pyridyl, Pyridymethyl ist, oder eines von R8 und R9 Wasserstoff ist und das andere -COR10 oder SO2R10 ist; oder R6 und R8 zusammengenommen Tetramethyl, Pentamethyliden, - CHNCHCH-, Hexamethylen oder -CH2CH2X1CH2CH2- sind, wobei X1 -O-, -S- oder -NH ist; und

R10 Wasserstoff, Alkyl mit 1 bis 8 Kohlenstoffatomen, Cycloalkyl, Cycloalkylalkoxy mit bis zu 6 Kohlenstoffatomen, Phenyl, Pyridyl, Benzyl, Imidazolylmethyl, Pyridymethyl, NR11R12 oder CH2NR10R12 ist, wobei R11 und R12 unabhängig voneinander Wasserstoff, Alkyl mit 1 bis 8 Kohlenstoffatomen, Phenyl oder Benzyl sind, und wobei R* und R0 unabhängig voneinander Wasserstoff, Methyl, Ethyl oder Propyl sind.
7. Verwendung gemäß Anspruch 6, wobei die Verbindung im Wesentlichen chiral rein ist.

8. Verwendung gemäß Anspruch 6, wobei die virale Infektion eine Herpesinfektion ist.

9. Verwendung gemäß Anspruch 6, wobei die Verbindung der Formel I ist:

\[
\begin{align*}
2(1-(3\text{-Ethoxy}-4\text{-methoxyphenyl})\text{-2-(1,3,4-oxadiazol-2-yl)ethyl}]isoindolin-1,3-dion; \\
2(1-(3\text{-Ethoxy}-4\text{-methoxyphenyl})\text{-2-(1,3,4-oxadiazol-2-yl)ethyl}]benzo[e]isoindolin-1,3-dion; \\
2(1-(3\text{-Ethoxy}-4\text{-methoxyphenyl})\text{-2-(1,3,4-oxadiazol-2-yl)ethyl}]4\text{-methylisoindolin-1,3-dion}; \\
2(1-(3\text{-Ethoxy-4-methoxyphenyl})\text{-2-(1,3,4-oxadiazol-2-yl)ethyl}]5\text{-methylisoindolin-1,3-dion}; \\
2(1-(3\text{-Ethoxy-4-methoxyphenyl})\text{-2-(1,3,4-oxadiazol-2-yl)ethyl}]2\text{-methylisoindolin-1,3-dion}; \\
2(1-(3\text{-Cyclopentyloxy-4-methoxyphenyl})\text{-2-(1,3,4-oxadiazol-2-yl)ethyl}]4\text{-methylisoindolin-1,3-dion}; \\
N\text{-}[2(1-(3\text{-Cyclopentyloxy-4-methoxyphenyl})\text{-2-(1,3,4-oxadiazol-2-yl)ethyl}]1,3\text{-dioxoisindolin-4-yl]acetamid}; \\
N\text{-}[2(1-(3\text{-Ethoxy-4-methoxyphenyl})\text{-2-(1,3,4-oxadiazol-2-yl)ethyl}]1,3\text{-dioxoisindolin-4-yl]acetamid}; \\
5\text{-}(\text{tert-Butyl})\text{-}[2(1-(3\text{-Ethoxy-4-methoxyphenyl})\text{-2-(1,3,4-oxadiazol-2-yl)ethyl}]1,3\text{-dioxoisindolin-1,3-dion}; \\
2(1-(3\text{-Ethoxy-4-methoxyphenyl})\text{-2-(1,3,4-oxadiazol-2-yl)ethyl}]4\text{-methylisoindolin-1,3-dion}; \\
2(1-(3\text{-Ethoxy-4-methoxyphenyl})\text{-2-(1,3,4-oxadiazol-2-yl)ethyl}]5\text{-methylisoindolin-1,3-dion}; \\
oder 2(1-(3\text{-Ethoxy-4-methoxyphenyl})\text{-2-(1,3,4-oxadiazol-2-yl)ethyl}]3\text{-pyrrolo[3,4-]chinolin-1,3-dion}.
\end{align*}
\]

10. Verwendung gemäß Anspruch 10, wobei die Verbindung im Wesentlichen chiral rein ist.

**Revendications**

1. Utilisation d’un composé 1,3,4-oxadiazole de formule I,

ou d’un sel d’addition acide non toxique physiologiquement acceptable de celui-ci, pour la fabrication d’un médicamente pour le traitement de la rectocolite hémorragique ou du lupus érythémateux systémique ou le traitement topique de la dermatite atopique, du psoriasis, du lupus, d’une infection virale ou d’une conjonctivite virale :

dans laquelle :

l’atome de carbone désigné par * constitue un centre de chiralité ;
Y est C=O, CH₂, SO₂ ou CH₂C=O ;
X est un atome d’hydrogène ou un groupe alkyle de 1 à 4 atome(s) de carbone ;
chacun parmi R¹, R², R³ et R⁴, indépendamment des autres, est un atome d’hydrogène, un groupe halogéno, trifluorométhyle, acétyle, alkyle de 1 à 4 atome(s) de carbone, alcoxy de 1 à 4 atome(s) de carbone, nitro, cyano, hydroxy, tert-butyle, -(CH₂)NR₈R₉, -(CH₂)₂NR₈R₉ ou -(CH₂)₃NR₈R₉ ; ou n’importe quel groupe de deux parmi R¹, R², R³ et R⁴ sur des atomes de carbone adjacents, conjointement au cycle phényléine illustré, sont un groupe naphthylidène, quinoléine, quinoxaline, benzimidazole, benzodioxole ou 2-hydroxybenzimidazole ;
chacun parmi R⁵ et R⁶ indépendamment de l’autre, est un atome d’hydrogène, un groupe alkyle de 1 à 4 atome(s) de carbone, alcoxy de 1 à 6 atome(s) de carbone, cyano, benzyloxy, cycloalkylalcoxy, cycloalkyloxy allant jusqu’à 18 atomes de carbone, bicycloalkyloxy allant jusqu’à 18 atomes de carbone, tricycloalkyloxy allant jusqu’à 18 atomes de carbone, de cycloalkyloxy allant jusqu’à 18 atomes de carbone ;
chacun parmi \( R^8 \) et \( R^9 \), pris indépendamment de l’autre, est un atome d’hydrogène, un groupe alkyle linéaire de 1 à 8 atome(s) de carbone, alkyle ramifié de 1 à 8 atome(s) de carbone, phényle, benzyle, pyridyle, pyridylméthyle ou l’un parmi \( R^8 \) et \( R^9 \) est un atome d’hydrogène et l’autre est -COR\(^{10} \) ou -SO\(_2\)R\(^{10} \); ou \( R^8 \) et \( R^9 \), pris conjointement, sont un groupe tétraméthylène, pentaméthylène, -CH\(2\)NCH\(2\)CH\(2\)-, dans lequel \( X^1 \) est -O-, -S- ou -NH-; et \( R^{10} \) est un atome d’hydrogène, un groupe alkyle de 1 à 8 atome(s) de carbone, cycloalkyle, cycloalkylméthyle allant jusqu’à 6 atomes de carbone, phényle, pyridyle, benzyle, imidazolylméthyle, pyridylméthyle, NR\(^{11}\)R\(^{12} \) ou CH\(_2\)N\(R^*\)R\(^0\), dans lequel le R\(^{11}\) et le R\(^{12}\), indépendamment l’un de l’autre, sont un atome d’hydrogène, un groupe alkyle de 1 à 8 atome(s) de carbone, phényle ou benzyle et dans lequel R\(^*\) et R\(^0\), indépendamment l’un de l’autre, sont un atome d’hydrogène, un groupe méthyle, éthyle ou propyle.

2. Utilisation selon la revendication 1, dans laquelle le composé est substantiellement chiralement pur.

3. Utilisation selon la revendication 1, dans laquelle le médicament sert au traitement de la rectocolite hémorragique ou du lupus érythémateux systémique et est adapté à l’administration par voie orale, rectale, parentérale ou topique.

4. Utilisation selon la revendication 1, dans laquelle le composé de formule I est :

- la 2-[1-(3-éthoxy-4-méthoxyphényl)-2-(1,3,4-oxadiazol-2-yl)éthyl]isoindoline-1,3-dione ;
- la 2-[1-(3-éthoxy-4-méthoxyphényl)-2-(1,3,4-oxadiazol-2-yl)éthyl]benzo[e]isoindoline-1,3-dione ;
- la 2-[1-(3-éthoxy-4-méthoxyphényl)-2-(1,3,4-oxadiazol-2-yl)éthyl]-4-méthylisoindoline-1,3-dione ;
- la 2-[1-(3-éthoxy-4-méthoxyphényl)-2-(1,3,4-oxadiazol-2-yl)éthyl]-5-méthylisoindoline-1,3-dione ;
- la 2-[1-(3-cyclopentyloxy-4-méthoxyphényl)-2-(1,3,4-oxadiazol-2-yl)éthyl]-5-méthylisoindoline-1,3-dione ;
- la 2-[1-(3-cyclopentyloxy-4-méthoxyphényl)-2-(1,3,4-oxadiazol-2-yl)éthyl]-4-méthylisoindoline-1,3-dione ;
- le N-[2-(1-(3-cyclopentyloxy-4-méthoxyphényl)-2-(1,3,4-oxadiazol-2-yl)éthyl]-1,3-dioxoisoindolin-4-yl]acétamide ;
- le N-[2-(1-(3-éthoxy-4-méthoxyphényl)-2-(1,3,4-oxadiazol-2-yl)éthyl]-1,3-dioxoisoindolin-4-yl]acétamide ;
- la 5-(tert-butyl)-2-[1-(3-éthoxy-4-méthoxyphényl)-2-(1,3,4-oxadiazol-2-yl)éthyl]isoindoline-1,3-dione ;
- la 2-[1-(3,4-diméthoxyphényl)-2-(1,3,4-oxadiazol-2-yl)éthyl]isoindoline-1,3-dione ;
- la 2-[1-(3-éthoxy-4-méthoxyphényl)-2-(1,3,4-oxadiazol-2-yl)éthyl]isoindolin-1-one ;
- la 2-[1-(3-éthoxy-4-méthoxyphényl)-2-(5-méthyl(1,3,4-oxadiazol-2-yl))éthyl]isoindolin-1-one ; ou
- la 2-[1-(3-éthoxy-4-méthoxyphényl)-3-pyrrolo[3,4-]quinoléine-1,3-dione.

5. Utilisation selon la revendication 4, dans laquelle le composé est substantiellement chiralement pur.

6. Utilisation d’un composé 1,3,4-oxadiazole de formule I,

\[
\text{I}
\]

ou d’un sel d’addition acide non toxique physiologiquement acceptable de celui-ci, pour la fabrication d’un médicament pour la prophylaxie de la dermatite atopique, du psoriasis, ou d’une infection virale et d’une conjonctivite virale dans laquelle le médicament est adapté à l’administration par voie topique :

dans laquelle :

- l’atome de carbone désigné par constitue un centre de chiralité ;
- Y est C=O, CH\(_2\), SO\(_2\) ou CH\(_2\)C=O ;

\( R^8 \) et \( R^9 \) ;

\( R^{10} \) ;

\( X^1 \) est -O-, -S- ou -NH- ;

\( R^* \) et \( R^0 \) ;
X est un atome d'hydrogène ou un groupe alkyle de 1 à 4 atome(s) de carbone ;
chacun parmi R1, R2, R3 et R4, indépendamment des autres, est un atome d'hydrogène, un groupe halogéné,
trifluorométhyle, acétyle, alkyle de 1 à 8 atome(s) de carbone, alcoxy de 1 à 4 atome(s) de carbone, nitro, cyano,
hydroxy, tert-butylo, -CH2NR8R9, -CH2NR8R9 ou -NR8R9 ; ou n’importe quel groupe de deux parmi R1, R2,
R3 et R4 sur des atomes de carbone adjacents, conjointement au cycle phényléne illustré, sont un groupe
naphtyléne, quinoléine, quinoxaline, benzimidazole, benzodioxole ou 2-hydroxybenzimidazole ;
chacun parmi R5 et R6 indépendamment de l’autre, est un atome d’hydrogène, un groupe alkyle de 1 à 4 atome(s)
de carbone, alcoxy de 1 à 6 atome(s) de carbone, cyano, benzylocycloacétyle, cycloacétyle allant jusqu’à 18
atomes de carbone, bicycloacétyle allant jusqu’à 18 atomes de carbone, tricycloacétyle allant jusqu’à 18 atomes
de carbone ou cycloalkylacétyle allant jusqu’à 18 atomes de carbone ;
chacun parmi R8 et R9, pris indépendamment de l’autre, est un atome d’hydrogène, un groupe alkyle linéaire
de 1 à 8 atome(s) de carbone, alkyle ramifié de 1 à 8 atome(s) de carbone, phényle, benzyle, pyridyle, pyridyl-
méthyle ou l’un de R8 et R9 est un atome d’hydrogène et l’autre est -COR10 ou -SO2R10 ; où R8 et R9, pris
conjointement, sont un groupe tétraméthyléne, pentaméthyléne, -CHNCHCH- ; hexaméthyléne ou
\[-CH2CH2X1CH2CH2-\] dans lequel X1 est -O-, -S- ou -NH- ; et
R10 est un atome d’hydrogène, un groupe alkyle de 1 à 8 atome(s) de carbone, cycloalkyle, cycloalkylméthyle
allant jusqu’à 6 atome(s) de carbone, phényle, benzyle, imidazolylméthyle, pyridylméthyle, NR11R12 dans lequel R11 et R12, indépendamment l’un de l’autre, sont un atome d’hydrogène, un groupe
alkyle de 1 à 8 atome(s) de carbone, phényle ou benzyle et dans lequel R* et R0, indépendamment l’un de
l’autre, sont un atome d’hydrogène, un groupe méthyle, éthyle ou propyle.

7. Utilisation selon la revendication 6, dans laquelle le composé est substantiellement chiralement pur.
8. Utilisation selon la revendication 6, dans laquelle l’infection virale est l’infection de type herpès.
9. Utilisation selon la revendication 6, dans laquelle le composé de formule I est :

la 2-[1-(3-éthoxy-4-méthoxyphényl)-2-(1,3,4-oxadiazol-2-yl)éthyl]isoindoline-1,3-dione ;
la 2-[1-(3-éthoxy-4-méthoxyphényl)-2-(1,3,4-oxadiazol-2-yl)éthyl]benzo[e]isoindoline-1,3-dione ;
la 2-[1-(3-éthoxy-4-méthoxyphényl)-2-(1,3,4-oxadiazol-2-yl)éthyl]4-méthylisoindoline-1,3-dione ;
la 2-[1-(3-éthoxy-4-méthoxyphényl)-2-(1,3,4-oxadiazol-2-yl)éthyl]5-méthylisoindoline-1,3-dione ;
la 2-[1-(3-cyclopentyloxy-4-méthoxy-phényl)-2-(1,3,4-oxadiazol-2-yl)éthyl]5-méthylisoindoline-1,3-dione ;
la 2-[1-(3-cyclopentyloxy-4-méthoxy-phényl)-2-(1,3,4-oxadiazol-2-yl)éthyl]4-méthylisoindoline-1,3-dione ;
le N-[2-[1-(3-cyclopentyloxy-4-méthoxyphényl)-2-(1,3,4-oxadiazol-2-yl)éthyl]1,3-dioxoisoinol-4-yl]acétami-de ;
le N-[2-[1-(3-éthoxy-4-méthoxyphényl)-2-(1,3,4-oxadiazol-2-yl)éthyl]1,3-dioxoisoinol-4-yl]acétamide ;
la 5-(tert-butyl)-2-[1-(3-éthoxy-4-méthoxyphényl)-2-(1,3,4-oxadiazol-2-yl)éthyl]isoindoline-1,3-dione ;
la 2-[1-(3,4-diméthoxyphényl)-2-(1,3,4-oxadiazol-2-yl)éthyl]isoindoline-1,3-dione ;
la 2-[1-(3-éthoxy-4-méthoxyphényl)-2-(1,3,4-oxadiazol-2-yl)éthyl]isoindoline-1,3-dione ;
la 2-[1-(3-éthoxy-4-méthoxyphényl)-2-(1,3,4-oxadiazol-2-yl)éthyl]isoindoline-1,3-dione ;
la 2-[1-(3-éthoxy-4-méthoxyphényl)-2-(5-méthyl(1,3,4-oxadiazol-2-yl))éthyl]isoindoline-1,3-dione ;
on la 2-[1-(3-éthoxy-4-méthoxyphényl)-2-(1,3,4-oxadiazol-2-yl)éthyl]-3-pyrrolino[3,4-]quinoléine-1,3-dione.

10. Utilisation selon la revendication 9, dans laquelle le composé est substantiellement chiralement pur.
REFERENCES CITED IN THE DESCRIPTION

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