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(54) Title: PHARMACEUTICAL COMPOSITIONS COMPRISING GLITAZONES AND NRF2 ACTIVATORS

(57) Abstract: The invention relates to pharmaceutical compositions comprising PPAR agonists and Nrf2 activators and methods of using combinations of PPAR agonists and Nrf2 activators for treating diseases such as psoriasis, asthma, multiple sclerosis, inflammatory bowel disease, and arthritis.

# PHARMACEUTICAL COMPOSITIONS COMPRISING GLITAZONES AND NRF2 ACTIVATORS

Disclosed herein are pharmaceutical compositions comprising PPAR agonists and Nrf2 activators (each an "agent" and together "agents"), and methods of using combinations of PPAR agonists and Nrf2 activators for treating diseases such as psoriasis, asthma, multiple sclerosis, inflammatory bowel disease, and arthritis.

Perixome Proliferator Activated Receptors (PPARs) activate transcription by binding to elements of DNA sequences, known as peroxisome proliferator response elements (PPRE), in the form of a heterodimer with retinoid X receptors (known as RXRs). Three subtypes of human PPARs have been identified and described: PPARα, PPARγ (PPAR gamma) and PPARδ (or NUC1). PPARα is mainly expressed in the liver, while PPARδ is ubiquitous. PPARγ is the most extensively studied of the three subtypes. See e.g. "Differential Expression of Peroxisome Proliferator-Activated Receptor Subtypes During the Differentiation of Human Keratinocytes", Michel Rivier et al., J. Invest. Dermatol., 111, 1998, pp. 1116-1121, in which is listed a large number of bibliographic references relating to receptors of PPAR type. Mention may also be made of the report entitled "The PPARs: From orphan receptors to Drug Discovery", Timothy M. Willson, Peter J. Brown, Daniel D. Sternbach and Brad R. Henke, J. Med. Chem., 2000, Vol. 43, pp. 527-550. It is suggested that PPARγ play a critical role in regulating the differentiation of adipocytes, where it is greatly expressed. It also has a key role in systemic lipid homeostasis.

It has been reported that the thiazolidinedione class of compounds (the group of so-called glitazones) including rosiglitazone, rosiglitazone maleate, pioglitazone, pioglitazone hydrochloride, troglitazone and ciglitazone and or its salt forms are potent and selective activators of PPAR-gamma (so-called PPAR gamma agonists) and bind directly to the PPAR-gamma receptor (J. M. Lehmann et al., J. Biol. Chem. 12953-12956, 270 (1995)), providing evidence that PPAR-gamma is a possible target for the therapeutic actions of the thiazolidinediones. Since this observation, activation of this nuclear hormone receptor has been shown to have

pleiotropic metabolic and nonhypoglycemic effects. Clinical use of the agents in the treatment of Type 2 diabetes mellitus (or non insulin dependent diabetes mellitus (NIDDM)) is associated with sensitization to the glucose lowering effects of insulin as well as potentiation of other biological actions of insulin in target tissues. When used as monotherapy, there are reports of fluid retention resulting in volume expansion and, in some patients, clinical edema. The incidence of edema appears to be increased when both these agents are used in combination with insulin (Nesto R. W. et al, 2003, Circulation, 108, 2941-2948). However, the mechanisms involved in these effects have not been well described but the nature of the presentation suggests an integrated physiological response which includes an effect on renal salt and water balance. PPAR gamma receptors have been found in the renal collecting duct (Guan Y. et al; 2001, Kidney Int. 60, 14-30) and, therefore, the PPAR gamma agonists might be involved directly in renal tubular metabolism or could have secondary effects on salt and water homeostasis. The PPAR gamma agonist pioglitazone has been suggested as a treatment of psoriasis in e.g. British Journal of Dermatology 2005 152, pp176–198.

Nuclear factor erythroid-2 related factor 2 or Nuclear Factor E2p45-Related Factor (Nrf2) is a cap-and-collar basic leucine zipper transcription factor, regulates a transcriptional program that maintains cellular redox homeostasis and protects cells from oxidative insult (Rangasamy T, et al., J Clin Invest 114, 1248 (2004); Thimmulappa R K, et al. Cancer Res 62, 5196 (2002); So H S, et al. Cell Death Differ (2006)). NRF2 activates transcription of its target genes through binding specifically to the antioxidant-response element (ARE) found in those gene promoters. The NRF2-regulated transcriptional program includes a broad spectrum of genes, including antioxidants, such as γ-glutamyl cysteine synthetase modifier subunit (GCLm), γ-glutamyl cysteine synthetase catalytic subunit (GCLc), heme oxygenase-1, superoxide dismutase, glutathione reductase (GSR), glutathione peroxidase, thioredoxin, thioredoxin reductase, peroxiredoxins (PRDX), cysteine/glutamate transporter (SLC7A11) (7, 8)], phase II detoxification enzymes [NADP(H) quinone oxidoreductase 1 (NQO1), GST, UDP-glucuronosyltransferase (Rangasamy T, et al. J Clin Invest 114: 1248 (2004); Thimmulappa R K, et al. Cancer Res 62: 5196 (2002)), and several ATP-dependent drug efflux pumps, including MRP1, MRP2 (Hayashi A, et al. Biochem Biophy Res Commun 310: 824

(2003)); Vollrath V, et al. Biochem J (2006)); Nguyen T, et al. Annu Rev Pharmacol Toxicol 43: 233 (2003)).

Interlinked with Nrf2 is KEAP1, which is a cytoplasmic anchor of Nrf2 that also functions as a substrate adaptor protein for a Cul3-dependent E3 ubiquitin ligase complex to maintain steady-state levels of NRF2 and NRF2-dependent transcription (Kobayashi et al., Mol Cell Biol 24: 7130 (2004); Zhang D, et al. Mol Cell Biol 24: 10491 (2004)). The Keap1 gene is located at human chromosomal locus 19p13.2. The KEAP1 polypeptide has three major domains: (1) an N-terminal Broad complex, Tramtrack, and Bric-a-brac (BTB) domain; (2) a central intervening region (IVR); and (3) a series of six C-terminal Kelch repeats (Adams J, et al. Trends Cell Biol 10:17 (2000)). The Kelch repeats of KEAP1 bind the Neh2 domain of Nrf2, whereas the IVR and BTB domains are required for the redox-sensitive regulation of Nrf2 through a series of reactive cysteines present throughout this region (Wakabayashi N, et al. Proc Natl Acad Sci USA 101: 2040 (2004)). KEAP1 constitutively suppresses Nrf2 activity in the absence of stress. Oxidants, xenobiotics and electrophiles hamper KEAP1-mediated proteasomal degradation of Nrf2, which results in increased nuclear accumulation and, in turn, the transcriptional induction of target genes that ensure cell survival (Wakabayashi N, et al. Nat Genet. 35: 238 (2003)). Prothymosin α, a novel binding partner of KEAP1, has been shown to be an intranuclear dissociator of NRF2-KEAP1 complex and can upregulate the expression of Nrf2 target genes (Karapetian R N, et al. Mol Cell Biol 25: 1089 (2005)). Certain interactions between Nrf2 and PPAR gamma have been suggested, e.g. Am J Respir Crit Care Med 2010; 182:170–182.

Nrf2 activators according to the present invention are agents that after administration result in a stimulated and/or increased nuclear translocation of Nrf2 protein and causes the subsequent increases in gene products that detoxify and eliminate cytotoxic metabolites. Nrf2 activators according to the present invention may act directly on Nrf2, KEAP1, the NRF2-KEAP1 complex and/or otherwise. Nrf2 activators of the present invention may comprise a Michael addition acceptor, one or more fumaric acid esters, i.e. fumaric acid mono- and/or diesters which are preferably selected from the group of monoalkyl hydrogen fumarate and dialkyl fumarate, such as monomethyl hydrogen fumarate, dimethyl fumarate, monoethyl hydrogen fumarate, and diethyl fumarate, furthermore ethacrynic acid, bardoxolone

methyl (methyl 2-cyano-3,12-dioxooleana-1,9(11)dien-28-oate), isothiocyanate such as sulforaphane, 1,2-dithiole-3-thione such as oltipraz, 3,5-di-tert-butyl-4-hydroxytoluene, 3-hydroxycoumarin, or a pharmacologically active derivative or analog of the aforementioned agents.

Very preferred Nrf2 activators for use in combination with PPAR gamma agonists according to the present invention are bardoxolone methyl and fumaric acid esters.

Fumaric acid esters are approved in Germany for the treatment of psoriasis, are being evaluated in the United States for the treatment of psoriasis and multiple sclerosis, and have been proposed for use in treating a wide range of immunological, autoimmune, and inflammatory diseases and conditions. FAEs and other fumaric acid derivatives have been proposed for use in treating a wide-variety of diseases and conditions involving immunological, autoimmune, and/or inflammatory processes including psoriasis (Joshi and Strebel, WO 1999/49858; US 6,277,882; Mrowietz and Asadullah, Trends Mol Med 2005, 111(1), 43-48; and Yazdi and Mrowietz, Clinics Dermatology 2008, 26, 522-526); asthma and chronic obstructive pulmonary diseases (Joshi et al., WO 2005/023241 and US 2007/0027076); cardiac insufficiency including left ventricular insufficiency, myocardial infarction and angina pectoris (Joshi et al., WO 2005/023241; Joshi et al., US 2007/0027076); mitochondrial and neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, Huntington's disease, retinopathia pigmentosa and mitochondrial encephalomyopathy (Joshi and Strebel, WO 2002/055063, US 2006/0205659, US 6,509,376, US 6,858,750, and US 7,157,423); transplantation (Joshi and Strebel, WO 2002/055063, US 2006/0205659, US 6,359,003, US 6,509,376, and US 7,157,423; and Lehmann et al, Arch Dermatol Res 2002, 294, 399-404); autoimmune diseases (Joshi and Strebel, WO 2002/055063, US 6,509,376, US 7,157,423, and US 2006/0205659) including multiple sclerosis (MS) (Joshi and Strebel, WO 1998/52549 and US 6,436,992; Went and Lieberburg, US 2008/0089896; Schimrigk et al., Eur J Neurology 2006, 13, 604-610; and Schilling et al., Clin Experimental Immunology 2006, 145, 101-107); ischemia and reperfusion injury (Joshi et al., US 2007/0027076); AGE-induced genome damage (Heidland, WO 2005/027899); inflammatory bowel diseases such as Crohn's disease and ulcerative colitis; arthritis; and others (Nilsson

et al., WO 2006/037342 and Nilsson and Muller, WO 2007/042034). All these indications and diseases can be treated or prevented with the combination treatment of the present invention.

Fumaderm®, an enteric coated tablet containing a salt mixture of monoethyl fumarate and dimethylfumarate, which is rapidly hydrolyzed to monomethyl fumarate, was approved in Germany in 1994 for the treatment of psoriasis. Fumaderm® is dosed TID with 1-2 grams/day administered for the treatment of psoriasis.

Biogen Idec Inc. is presently evaluating dimethyl fumarate under the product name BG-12 in the treatment of relapsing-remitting multiple sclerosis. The drug is under review with U.S. and European regulators.

Fumaric acid derivatives (Joshi and Strebel, WO 2002/055063, US 2006/0205659, and US 7,157,423 (amide compounds and protein-fumarate conjugates); Joshi et al., WO 2002/055066 and Joshi and Strebel, US 6,355,676 (mono and dialkyl esters); Joshi and Strebel, WO 2003/087174 (carbocyclic and oxacarbocylic compounds); Joshi et al., WO 2006/122652 (thiosuccinates); Joshi et al., US 2008/0233185 (dialkyl and diaryl esters) and salts (Nilsson et al., US 2008/0004344) have been developed in an effort to overcome the deficiencies of current therapy with fumaric acid esters. Controlled release pharmaceutical compositions comprising fumaric acid esters are disclosed by Nilsson and Möller, WO 2007/042034. Prodrugs are described by Nielsen and Bundgaard, J Pharm Sci 1988, 77(4), 285-298 and in WO2010/022177.

**Detailed Description**

Preferably, the term "alkyl" is specifically intended to include groups having any degree or level of saturation, i.e., groups having exclusively single carbon-carbon bonds, groups having one or more double carbon-carbon bonds, groups having one or more triple carbon-carbon bonds, and groups having combinations of single, double, and triple carbon-carbon bonds. Where a specific level of saturation is intended, the terms alkanyl, alkenyl, and alkynyl are used. In certain embodiments, an alkyl group can have from 1 to 20 carbon atoms (Ci-20) in certain embodiments, from 1 to 10 carbon atoms (Ci-I0), in certain embodiments from 1 to 8 carbon atoms (C]-8), in certain embodiments, from 1 to 6 carbon atoms

(C1-6), in certain embodiments from 1 to 4 carbon atoms (C1 -4), and in certain embodiments, from 1 to 3 carbon atoms (Ci-3). The term "alkoxy" refers to a group O-alkyl, wherein alkyl has the meaning indicated above. The term "perfluoroalkyl" refers to an alkyl group wherein all hydrogen atoms have been replaced by fluoro.

"Treating" or "treatment" of any disease refers to reversing, alleviating, arresting, or ameliorating a disease or at least one of the clinical symptoms of a disease, reducing the risk of acquiring a disease or at least one of the clinical symptoms of a disease, inhibiting the progress of a disease or at least one of the clinical symptoms of the disease or reducing the risk of developing a disease or at least one of the clinical symptoms of a disease. "Treating" or "treatment" also refers to inhibiting the disease, either physically, (e.g., stabilization of a discernible symptom), physiologically, (e.g., stabilization of a physical parameter), or both, and to inhibiting at least one physical parameter that may or may not be discernible to the patient. In certain embodiments, "treating" or "treatment" refers to delaying the onset of the disease or at least one or more symptoms thereof in a patient which may be exposed to or predisposed to a disease even though that patient does not yet experience or display symptoms of the disease.

"Therapeutically effective amount" refers to the amount of a compound that, when administered to a subject for treating a disease, or at least one of the clinical symptoms of a disease, is sufficient to affect such treatment of the disease or symptom thereof. The "therapeutically effective amount" may vary depending, for example, on the compound, the disease and/or symptoms of the disease, severity of the disease and/or symptoms of the disease or disorder, the age, weight, and/or health of the patient to be treated, and the judgment of the prescribing physician. An appropriate amount in any given instance may be ascertained by those skilled in the art or capable of determination by routine experimentation.

"Therapeutically effective dose" refers to a dose that provides effective treatment of a disease or disorder in a patient. A therapeutically effective dose may vary from compound to compound, and from patient to patient, and may depend upon factors such as the condition of the patient and the route of delivery. A therapeutically effective dose may be determined in accordance with routine pharmacological procedures known to those skilled in the art.

Throughout the specification, the term "isolated Nrf2 activator" preferably refers to an Nrf2 activator which, if naturally occurring, is substantially separated from other components and other molecules which naturally accompany the respective Nrf2 activator. The term embraces an Nrf2 activator, which has been removed from its naturally occurring environment or its natural state through purifying steps that separate other molecules naturally associated with it, e.g. by known conventional methods, such as chromatography, crystallization and distillation. The term "isolated Nrf2 activator" preferably still allows for the Nrf2 activator to be in admixture with various amounts of water, such as up to about 20 weight %. The term "isolated Nrf2 activator" preferably excludes such Nrf2 activators which are still in their natural state, e.g. which are still contained in their source of origin or parts thereof, such as a plant, irrespective of whether or not this source of origin has been dried. Moreover, the term "isolated Nrf2 activator" preferably refers to a natural or synthetically prepared molecule, which has a purity of above 70 weight %, preferably of above 80 weight % and more preferably of above 90 weight %, such as about 95 weight %, about 97 weight % or about 99 weight % before being formulated in a pharmaceutical composition, if so desired. In case the Nrf2 activator is naturally occurring, e.g. as a natural product, it is preferably an isolated Nrf2 activator, i.e. not in form of an e.g. herbal preparation.

In case the PPAR gamma agonist is naturally occurring, e.g. as a natural product, it is preferably an isolated PPAR gamma agonist, i.e. not in form of an e.g. herbal preparation.

Reference is now made in detail to certain embodiments of compounds, compositions, and methods. The disclosed embodiments are not intended to be limiting of the claims.

According to the present invention, strongly improved treatment results are obtained in the treatment of autoimmune and/or inflammatory diseases, when a PPAR agonist and preferably a PPAR gamma agonist and an Nrf2 activator are used in the treatment of the disease in combination as compared to the treatment with a PPAR gamma agonist or an Nrf2 activator, alone. Co-administration of a PPAR gamma agonist and an Nrf2 activator or an administration of a fixed dose combination of a PPAR gamma agonist and an Nrf2 activator results in a improved therapeutic effect, which may be a more than additive effect, compared to the

administration of a PPAR gamma agonist or Nrf2 activators, respectively, administered as mono-therapy.

In particular, it has been found that the advantageous therapeutic results in inflammatory and/or autoimmune diseases resulting from use of compounds such as dexamethasone, having both PPAR gamma agonistic and Nrf2 activating effects, can be matched or even surpassed by the combination treatment of the present invention, wherein at least two individual and different compounds having each either PPAR gamma agonistic or Nrf2 activating effects, are employed. Thus, a combination treatment comprising at least one PPAR gamma agonist, which may have no significant or only a minor modulating or activating effect on Nrf2, and at least one Nrf2, which may have no significant or only a minor modulating or activating effect on PPAR gamma, result in improved and synergistic therapeutic effects, as compared to the administration of such PPAR gamma agonist or such Nrf2 activator, respectively, administered as mono-therapy. The synergistic effect is often more pronounced with such combinations, where the agents employed are predominantly either PPAR gamma agonists or Nrf2 activators, which each have no significant activity on the respective other target. Nevertheless, even in those cases where one or both of the agents display significant PPAR gamma agonistic and Nrf2 activating effects at the same time, such as in the case of dexamethasone and 15-deoxy-delta(12,14)-prostaglandin J(2) (15d-PGJ(2)), the combination treatment according to the present invention can lead to improved treatment results over the mono-therapy. A compound having dual effects on the targets PPAR gamma and Nrf2, is unlikely to show an ideally distributed effect on both targets for therapeutic use. By applying the present invention each target can be addressed individually and activated with suitable and appropriate concentrations of the respective agents.

Thus, embodiments are preferred, wherein at least one agent is not both, PPAR gamma agonist and Nrf2 activator at the same time.

Combination treatments and fixed dose combinations according to the present invention are preferred, which comprise at least two different agents having either PPAR gamma agonistic or Nrf2 activating effects at the concentration used in the combination.

The present invention relates to combination treatments, compositions containing the inventive combination of agents and related fixed-dose

combinations, wherein the PPAR agonist, such as the PPAR gamma agonist and the Nrf2 activator are different compounds which are preferably having a different chemical structure, e.g. having a difference in carbon atoms of at least 3 carbon atoms, preferably at least 5 or at least 10 carbon atoms, and are not belonging to the same chemical class. Throughout this specification, the use of a singular includes also the plural, if not indicated otherwise.

Preferred PPAR agonists are compounds having a PPAR gamma agonistic effect without significantly activating Nrf2. These are preferably compounds having no ability to form covalent bonds with organic thiol groups under physiological conditions, such as with glutathione. Thus, preferred PPAR gamma agonists are compounds that, contrary to e.g. 15-deoxy-delta(12,14)-prostaglandin J(2) (15d-PGJ(2)), cannot bind covalently through e.g. Michael addition reaction to the PPA receptor. Most preferred PPAR agonists are glitazones, glitazars and sartans.

PPAR agonists are PPAR activators (e.g PPAR gamma agonist are PPAR gamma activators). The definition "PPAR agonist" and "PPAR gamma agonist" according to the present invention preferably includes such agonists, i.e compounds, that directly bind to the PPA receptor and have an agonistic, i.e. activating effect, as well as so-called physiological PPAR agonists and physiological PPAR gamma agonists, which do not necessarily bind to the PPAR receptor, but result in an activation of PPAR through other pathways, such as by increasing the concentration of endogenous PPAR gamma agonist 15-deoxy-Delta(12,14)-prostaglandin J(2) (15d-PGJ(2).

A large number of natural and synthetic PPAR agonists are known (e.g. see Michalik et al. (2006) Pharmacological Reviews 58:726-725; Gilde et al. (2003) Circulation Research 92(5):5 18-524; Peraza et al. (2005) Toxicological Sciences 90(2):269-295; and Desvergne & Wahli (1999) Endocrine Reviews 20(5):649-688). Some of these known agonists are specific for a single PPAR isotype, whilst others target multiple PPAR subtypes. PPAR agonists are preferred, if the PPAR agonist stronger activate PPAR gamma or PPAR gamma and PPAR alpha simultaneously, than other isoforms.

In one embodiment, the PPAR agonist may be selected from the group consisting of PPAR gamma agonists, such as glitazones and dual PPAR

alpha/gamma agonists, such as glitazars. In yet further embodiments, the glitazone may be selected from the group consisting of troglitazone, pioglitazone, rosiglitazone, ciglitazone, englitazone, darglitazone, netoglitazone, isaglitazone, MC-555, balaglitazone, rivoglitazone, and the like. In yet further embodiments, the glitazar may be selected from the group consisting of muraglitazar, naveglitazar, tesaglitazar, ragaglitazar, reglitazar and farglitazar. In yet further embodiments, PPAR agonists are selected from berberine, K-111, INT-131, MBX-102 (metaglidisen), MBX-2044, FK614, GSK-376501, GW 1929, S26948, psi-baptigenin and the like, such as those disclosed in US5002953, US4687777 and US5965584. Pioglitazone and rosiglitazone are very preferred and most preferred are pioglitazone hydrochloride and rosiglitazone maleate.

In a further preferred embodiment of the present inventions, PPAR gamma agonists are selected from the class of statins or HMG-CoA reductase inhibitors, preferably selected from atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin, mevastatin and pitavastatin. Statins are a class of drugs used to lower cholesterol levels by inhibiting the enzyme HMG-CoA reductase, which plays a central role in the production of cholesterol in the liver. Increased cholesterol levels have been associated with cardiovascular diseases, and statins are therefore used in the prevention of these diseases. Statins have also been suggested for the treatment of multiple sclerosis (e.g. US 2004/0013643). Although statins are believed to activate PPAR gamma only indirectly (Circ Res. 2007; 100:1442-1451), as physiological PPAR gamma agonists they are included in the definition of PPAR gamma agonists for the purposes of the present invention.

In a further preferred embodiment of the present inventions, PPAR gamma agonists are selected from the chemical classes of sartans, also known as angiotensin II receptor antagonists, angiotensin receptor blockers (ARBs) or AT1-receptor antagonists. Sartans, such as valsartan, losartan, azilsartan, irbesartan, olmesartan, telmisartan, candesartan and eprosartan are a group of pharmaceuticals which modulate the renin-angiotensin-aldosterone system. Preferred sartans used in the present invention are selected from losartan, irbesartan, telmisartan and candesartan, which have shown to bind to and activate PPAR gamma (Drug Development Research 67:579–581, 2006). Treatment with sartans has been suggested to improve multiple sclerosis. The sartanes are predominantly used in the

treatment of hypertension, diabetic nephropathy (kidney damage due to diabetes) and chronic kidney disease as well as congestive heart failure and are also preferably employed for these diseases and conditions when combined with Nrf2 activators according to the present invention.

In a further preferred embodiment of the present inventions, PPAR gamma agonists are selected from nonsteroidal anti-inflammatory drugs (NSAIDs) having PPAR gamma activating properties, preferably indomethacin, flufenamic acid, fenoprofen and ibuprofen (The Journal of Biological Chemistry, vol. 272, no. 6, issue 7, pp. 3406–3410, 1997). NSAIDs are included in the definition of PPAR gamma agonists for the purposes of the present invention as they may bind directly to the PPAR or act as a physiological PPAR gamma agonist. In one embodiment, NSAIDs other than aspirin are preferred.

The group of NSAIDs comprises the following compounds: Salicylates, such as aspirin (acetylsalicylic acid), diflunisal, salsalate, propionic acid derivatives such as ibuprofen, dexibuprofen, naproxen, fenoprofen, ketoprofen, dexketoprofen, flurbiprofen, oxaprozin, loxoprofen, acetic acid derivatives such asindomethacin, sulindac, etodolac, ketorolac, diclofenac, nabumetone, enolic acid (oxicam) derivatives such as piroxicam, meloxicam, tenoxicam, droxicam, lornoxicam, isoxicam, fenamic acid derivatives (fenamates) such as mefenamic acid, meclofenamic acid, flufenamic acid, tolfenamic acid, selective cox-2 inhibitors (coxibs) such as celecoxib, rofecoxib, valdecoxib, parecoxib, lumiracoxib, etoricoxib, firocoxib, sulphonanilides such as nimesulide and others such as licofelone, lysine clonixinate.

Nrf2-activating compounds can be classified based on their chemical structures: Diphenols, Michael reaction acceptors, isothiocyanates, thiocarbamates, trivalent arsenicals, 1,2-dithiole-3- thiones, hydroperoxides, vicinal dimercaptans, heavy metals, and polyenes. Moreover, Nrf2 activators (i) all are chemically reactive; (ii) nearly all are electrophiles; (iii) most are substrates for glutathione transferases; and (iv) all can modify sulfhydryl groups by alkylation, oxidation, or reduction (PNAS February 17, 2004 vol. 101 no. 7 2040-2045, Mol. Cell. Biol. 2009, 29(2):493). The activity of the compounds can be identified by known methods.

Preferred Nrf2 activators are compounds without significant PPAR gamma agonistic effect. These are preferably compounds, which may or may not bind covalently to the PPA receptor, but are not able to change the conformation of the PPAR and preferably the PPA gamma receptor to an extent that this would result in an activation of the PPA receptor. According to the present invention these preferred Nrf2 activators are small and of low molecular weight. These compounds are preferably lacking the structural elements to bind to the PPA receptor non-covalently with the result of a change of conformation and activation of the PPA receptor. In a preferred embodiment, the Nrf2 activators may be able to bind covalently to the PPA receptor, e.g. via a Michael reaction with a thiol group of the PPA receptor, without resulting in a conformation change of the PPA receptor. Due to their limited size however, these preferred Nrf2 activators may not prevent PPAR agonists, and in particular PPAR gamma agonists, especially glitazones such as pioglitazone or rosiglitazone from binding non-covalently to the PPA receptor with the result of a conformation change.

In a very preferred example, the covalent binding of a Nrf2 activator such as monomethyl hydrogen fumarate or dimethyl fumarate and the non-covalent binding of a PPAR gamma agonist such as a glitazone, like pioglitazone or rosiglitazone leads to synergistic and strongly improved therapeutic results.

In one embodiment, the preferred are Nrf2 activators selected from organic compounds having not more than one or two 5- or 6-membered carbocyclic rings or 5- or 6-membered heterocyclic rings having 1, 2 or 3 N-, O or S-atoms as ring atoms which may be fused to each other or preferably no or only one carbocyclic or heterocyclic ring and/or less than 35, preferably less than 30, more preferably less than 25 and most preferably less than 20 or even less than 15 or less than 10 carbon atoms and/or have a molecular weight of less than 400, preferably less than 300 and most preferably less than 200 g/mol or less than 170 g/mol and are selected from the chemical classes of Michael reaction acceptors, phenols, diphenols, chalcones, isothiocyanates, thiocarbamates, quinones, naphtoquinones and 1,2 dithiole-3-thiones, wherein one or more, preferably up to seven H-atoms may be substituted by linear or branched alkyl and perfluoroalkyl, such as methyl, ethyl, trifluoromethyl, halogen such as Br, Cl F or I, hydroxy, alkoxy and perfluoroalkoxy, such as methoxy, ethoxy, trifluoromethoxy, cyano and nitro.

In cases where compounds of the chemical class of quinones are employed as Nrf2 activator, the respective hydroquinones can be used alternatively. However the respective oxidized form, i.e. the respective quinone, is preferred. The Nrf2 activity can be determined according to e.g. JALA 2008; 13: 243-248. Bardoxolone methyl and derivatives are described in patents US8129429, US7435755 and US2009/0060873. Amorphous Bardoxolone methyl and suitable formulations are disclosed in WO2010/093944.

Very preferred Nrf2 activators are capable of provoking or inducing a stimulated and/or increased nuclear translocation of Nrf2 protein and are:

a) selected from the group of Michael reaction acceptors, phenols, diphenols, chalcones, isothiocyanates, thiocarbamates, quinones, naphtoquinones and 1,2 dithiole-3-thiones; and

b) contain less than 35 carbon atoms; and/or

c) have a molecular weight of less than 600 g/mol; and/or

d) contain no or not more than one or two fused or monocyclic 5- or 6-membered carbocyclic or heterocyclic rings, having 1, 2 or 3 ring atoms selected from N, O or S.

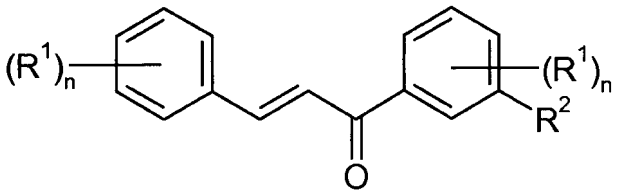
In these preferred Nrf2 activators, one or more, preferably up to seven H-atoms may be substituted preferably by linear or branched alkyl and perfluoroalkyl, such as methyl, ethyl, trifluoromethyl, halogen such as Br, Cl, F or I, hydroxy, alkoxy and perfluoroalkoxy, such as methoxy, ethoxy, trifluoromethoxy, cyano and nitro.

More preferred embodiments of these Nrf2 activators contain no ring system or only one or two rings, which may be carbocyclic and/or heterocyclic rings. Even more preferred Nrf2 activators contain less than 30, more preferably less than 25 and most preferably less than 20 or even less than 15 or less than 10 carbon atoms and/or have a molecular weight of less than 400 g/mol and more preferably less than 300 g/mol and most preferably less than 200 g/mol or less than 170 g/mol. Further preferred Nrf2 activators bind covalently to Keap1 protein, preferably via an S-atom of the proteins amino acids.

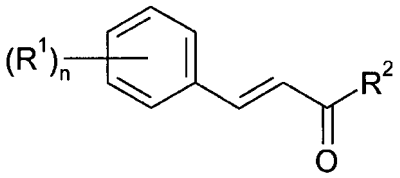
Preferred Michael reaction acceptors are ketones, aldehydes, carboxylic acid esters and carboxylic acid amides all of which being alpha, beta unsaturated.

More preferred Nrf2 activators are the compounds A to Z given below,

including their tautomers and stereoisomers:



A



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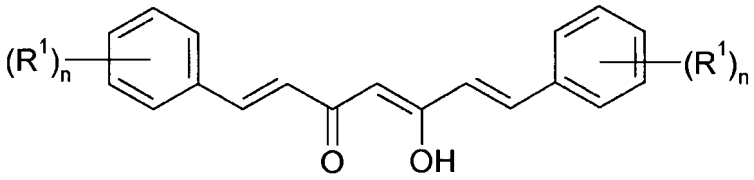
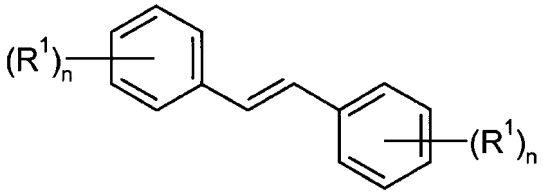


C



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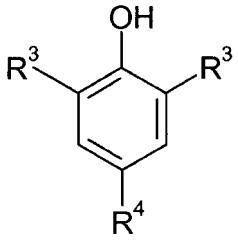

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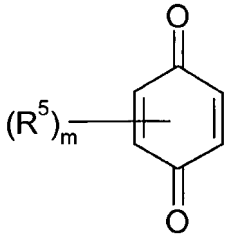
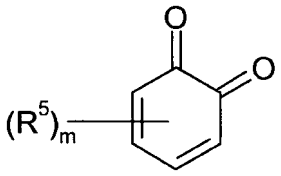
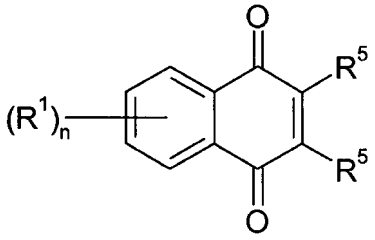


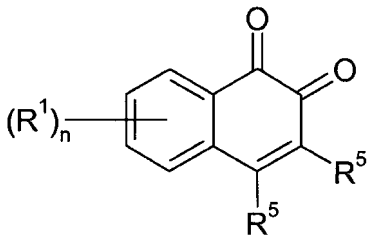
F



G



H



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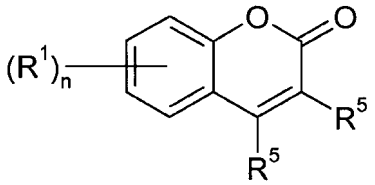

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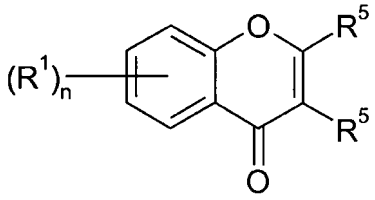

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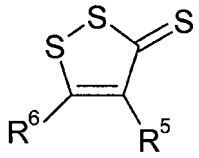
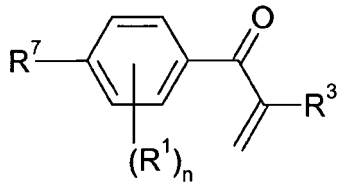
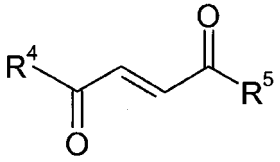


L



M

SCN-$R^8$ N



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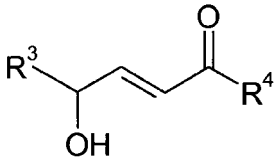

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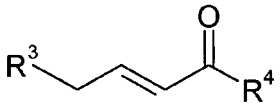

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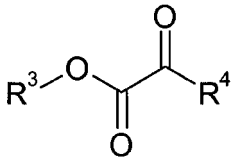

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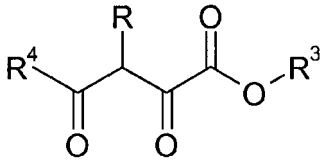

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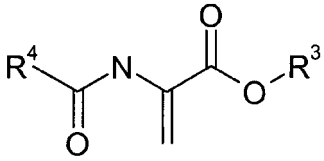

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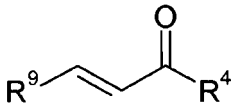

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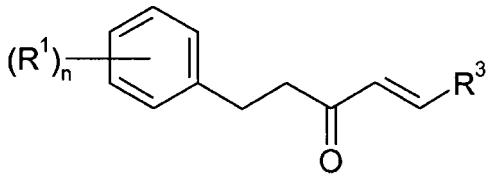

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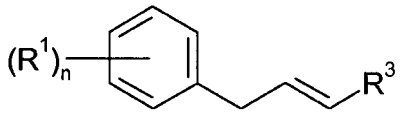

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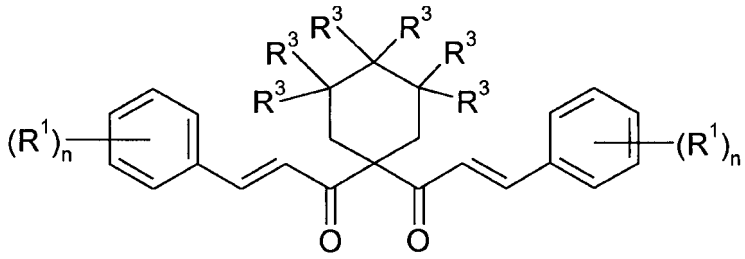
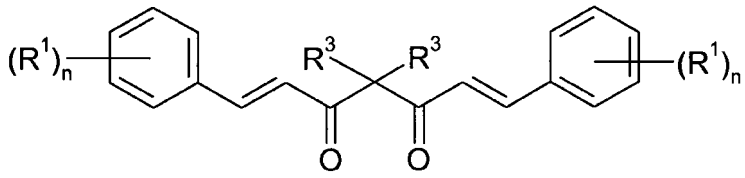
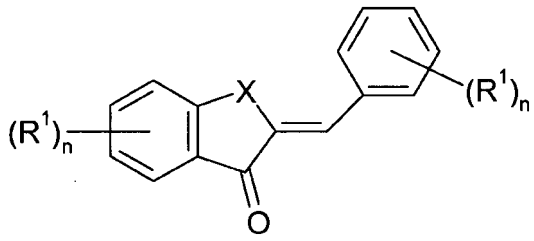


X



Y



Z

Wherein the individual radicals have the meaning given below:

| | |
|---|---|
| $R^1$ | H, OH, Hal, CN, A, perfluoroalkyl, perfluoroalkoxy |
| $R^2$ | H, OH, A, alkoxy, amino |
| $R^3$ | H, alkyl |
| $R^4$ | H, OH, alkyl, alkoxy |
| $R^5$ | H, OH, A, alkoxy |
| $R^6$ | H, A, alkoxy, aryl, het |

| | |
|---|---|
| $R^7$ | H, OH, A, alkoxy |
| $R^8$ | A |
| X | O, NH, S |
| $R^9$ | Het |
| m | 1, 2 |
| n | 1, 2, 3 |

Hal is F, Cl, Br or I, preferably F or Cl.

A is preferably alkyl which denotes a straight or branched carbon chain having 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 carbon atoms. Alkyl preferably denotes methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl or tert-butyl, furthermore also pentyl, 1-, 2- or 3-methylbutyl, 1,1-, 1,2- or 2,2-dimethylpropyl, 1-ethylpropyl, hexyl, 1-, 2-, 3- or 4-methylpentyl, 1,1-, 1,2-, 1,3-, 2,2-, 2,3- or 3,3-dimethylbutyl, 1- or 2-ethylbutyl, 1-ethyl-1-methylpropyl, 1-ethyl-2-methylpropyl, 1,1,2- or 1,2,2-trimethylpropyl. Alternatively, A denotes cycloalkyl having 3 ,4, 5, 6 or 7 carbon atoms or branched or linear alkyl having 2 to 12 C-atoms, wherein one or more, preferably 1 to 7 H-atoms may be replaced by Hal, alkyl, alkoxy, cycloalkyl, phenyl, p-, m- o- hydroxyphenyl, , p-, m- o- alkoxyphenyl, $N(R^3)_2$, OH, $CO_2H$, $CF_3$ and/or wherein one or more, preferably 1 to 7 non-adjacent $CH_2$-groups may be replaced by –O-, -S-, -SO-, $-NR^3-$, -CO-, $-CO_2-$, -CH=CH-S- and/ or -CH=CH-. Cycloalkyl preferably denotes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl.

Alkoxy is preferably a group O-alkyl, wherein alkyl is defined as above. Preferably, alkoxy denotes a group $-O-(CH_2)_n-CH_3$,wherein n is 0, 1, 2, 3 or 4, more preferably methoxy or ethoxy.

Perfluoroalkyl preferably denotes a straight or branched alkyl chain having 1 to 8 carbon atoms, preferably 1 to 6 carbon atoms, and wherein all hydrogen atoms are replaced by F atoms, preferably, for example, trifluoromethyl or pentafluoroethyl.

Perfluoroalkoxy is preferably a group O-perfluoroalkyl, wherein perfluoroalkyl is defined as above. Perfluoroalkoxy preferably denotes $OCF_3$.

Amino denotes preferably the group –NR'R'' where each R', R'' is independently hydrogen or alkyl. The group –NR'R'' can also form a cyclic group selected from piperidinyl, piperazinyl, pyrrolyl or morpholinyl, wherein one, two or three H atoms may be substituted by alkyl, such as methyl. In one embodiment, amino denotes dialkylamino, wherein alkyl has the meaning given above and is preferably dimethylamino.

Aryl preferably denotes a monocyclic or bicyclic, aromatic carbocyclic ring having 6 to 14 carbon atoms, which is unsubstituted or monosubstituted, disubstituted or trisubstituted by F, Cl, Br, $CF_3$, $OCF_3$, $NO_2$, CN, alkyl, alkoxy, OH, amino, CO-amino, NHCO-alkyl, CO-alkyl, CO-alkoxy, $SO_2$-alkyl, $SO_2$-amino. Most preferably, aryl denotes unsubstituted or monosubstituted phenyl.

Het preferably denotes, not withstanding further substitutions, a 6 to 14 membered monocyclic or bicyclic saturated, unsaturated or aromatic heterocyclic ring system containing 1 or 2 heteroatoms selected from N, O and S, which is unsubstituted or monosubstituted, disubstituted or trisubstituted by F, Cl, Br, $CF_3$, $OCF_3$, $NO_2$, CN, alkyl, alkoxy, OH, amino, CO-amino, NHCO-alkyl, CO-alkyl, CO-alkoxy, $SO_2$-alkyl, $SO_2$-amino. More preferably, Het is 2- or 3-furyl, 2- or 3-thienyl, 1-, 2- or 3-pyrrolyl, 1-, 2-, 4- or 5-imidazolyl, 1-, 3-, 4- or 5-pyrazolyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isoxazolyl, 2-, 4- or 5-thiazolyl, 3-, 4- or 5-isothiazolyl, 2-, 3- or 4-pyridyl, 2-, 4-, 5- or 6-pyrimidinyl, furthermore preferably 1,2,3-triazol-1-, -4- or -5-yl, 1,2,4-triazol-1-, -3- or -5-yl, 1- or 5-tetrazolyl, 1,2,3-oxadiazol-4- or -5-yl, 1,2,4-oxadiazol-3- or -5-yl, 1,3,4-thiadiazol-2- or -5-yl, 1,2,4-thiadiazol-3- or -5-yl, 1,2,3-thiadiazol-4- or -5-yl, 3- or 4-pyridazinyl, pyrazinyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl, indazolyl, 4- or 5-isoindolyl, 1-, 2-, 4- or 5-benzimidazolyl, 1-, 3-, 4-, 5-, 6- or 7-benzopyrazolyl, 2-, 4-, 5-, 6- or 7-benzoxazolyl, 3-, 4-, 5-, 6- or 7-benzisoxazolyl, 2-, 4-, 5-, 6- or 7-benzothiazolyl, 2-, 4-, 5-, 6- or 7-benzisothiazolyl, 4-, 5-, 6- or 7-benz-2,1,3-oxadiazolyl, 2-, 3-, 4-, 5-, 6-, 7- or 8-quinolyl, 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolyl, 3-, 4-, 5-, 6-, 7- or 8-cinnolinyl, 2-, 4-, 5-, 6-, 7- or 8-quinazolinyl, 5- or 6-quinoxalinyl, 2-, 3-, 5-, 6-, 7- or 8-2H-benzo-1,4-oxazinyl, furthermore preferably 1,3-benzodioxol-5-yl, 1,4-benzodioxane-6-yl, 2,1,3-benzothiadiazol-4-

or -5-yl or 2,1,3-benzoxadiazol-5-yl. The heterocyclic radicals may also be partially or fully hydrogenated. Het can thus also denote, for example, 2,3-dihydro-2-, -3-, -4- or -5-furyl, 2,5-dihydro-2-, -3-, -4- or -5-furyl, tetrahydro-2- or -3-furyl, 1,3-dioxolan-4-yl, tetrahydro-2- or -3-thienyl, 2,3-dihydro-1-, -2-, -3-, -4- or -5-pyrrolyl, 2,5-dihydro-1-, -2-, -3-, -4- or -5-pyrrolyl, 1-, 2- or 3-pyrrolidinyl, tetrahydro-1-, -2- or -4-imidazolyl, 2,3-dihydro-1-, -2-, -3-, -4- or -5-pyrazolyl, tetrahydro-1-, -3- or -4-pyrazolyl, 1,4-dihydro-1-, -2-, -3- or -4-pyridyl, 1,2,3,4-tetrahydro-1-, -2-, -3-, -4-, -5- or -6-pyridyl, 1-, 2-, 3- or 4-piperidinyl, 2-, 3- or 4-morpholinyl, tetrahydro-2-, -3- or -4-pyranyl, 1,4-dioxaneyl, 1,3-dioxane-2-, -4- or -5-yl, hexahydro-1-, -3- or -4-pyridazinyl, hexahydro-1-, -2-, -4- or -5-pyrimidinyl, 1-, 2- or 3-piperazinyl, 1,2,3,4-tetrahydro-1-, -2-, -3-, -4-, -5-, -6-, -7- or -8-quinolyl, 1,2,3,4-tetrahydro-1-, -2-, -3-, -4-, -5-, -6-, -7- or -8-isoquinolyl, 2-, 3-, 5-, 6-, 7- or 8-3,4-dihydro-2H-benzo-1,4-oxazinyl, furthermore preferably 2,3-methylenedioxyphenyl, 3,4-methylenedioxyphenyl, 2,3-ethylenedioxyphenyl, 3,4-ethylenedioxyphenyl, 3,4-(difluoromethylenedioxy)phenyl, 2,3-dihydrobenzofuran-5- or -6-yl, 2,3-(2-oxomethylenedioxy)phenyl or also 3,4-dihydro-2H-1,5-benzodioxepin-6- or -7-yl, furthermore preferably 2,3-dihydrobenzofuranyl or 2,3-dihydro-2-oxofuranyl. Very preferably, Heteroaryl is unsubstituted or monosubstituted 2-pyridyl, pyrimidyl or imidazolyl.

$R^1$ is preferably H, OH, F, methyl, methoxy, trifluoromethoxy.

$R^2$ is preferably H, OH, alkoxy, such as methoxy, $OCH_2CH_2$-phenyl.

$R^3$ is preferably H or alkyl, preferably H, methyl or tert-butyl.

$R^4$ is preferably H, OH, alkoxy, such as methoxy.

$R^5$ is preferably H or A.

$R^6$ is preferably H or Het.

$R^7$ is preferably $(CH_2)_mCOR^2$, $(CH_2)_mCOR^2$, $O(CH_2)_mCOR^2$ or $O(CH_2)_mCOR^2$.

$R^8$ is preferably allyl or a group selected from $(C(R^3)_2)_qS$-alkyl or $(C(R^3)_2)_qSO$-alkyl, wherein q is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12.

Preferred Nrf2 activators are selected from: Chalcone derivatives as disclosed in J. Med. Chem., 2011, 54 (12), pp 4147–4159, such as 2-trifluoromethyl-2′-methoxychalcone, auranofin (as contained in FDA approved drug Ridaura), ebselen, 1,2-naphthoquinone, cynnamic aldehyde, caffeic acid and

its esters, curcumin, reservatrol, artesunate, tert-butylhydroquinone, and –quinone, (tBHQ, tBQ), vitamins K1, K2 and K3, preferably menadione, fumaric acid esters, i.e. fumaric acid mono- and/or diester which is preferably selected from the group of monoalkyl hydrogen fumarate and dialkyl fumarate, such as monomethyl hydrogen fumarate, dimethyl fumarate, monoethyl hydrogen fumarate, and diethyl fumarate, 2-cyclopentenones, , ethacrynic acid and its alkyl esters, bardoxolone methyl (methyl 2-cyano-3,12-dioxooleana-1,9(11)dien-28-oate) (CDDO-Me, RTA 402), ethyl 2-cyano-3,12-dioxooleana-1,9(11)dien-28-oate, 2-cyano-3,12-dioxooleana-1,9(11)dien-28-oic acid (CDDO), 1[2-Cyano-3,12-dioxooleana-1,9(11)-dien-28-oyl]imidazole (CDDO-Im), (2-cyano-N-methyl-3,12-dioxooleana-1,9(11)-dien-28 amide (CDDO-methyl amide, CDDO-MA), isothiocyanate such as sulforaphane, 1,2-dithiole-3-thione such as oltipraz, capsaicin, 3,5-di-tert-butyl-4-hydroxytoluene, 3-hydroxycoumarin, cromolyn sodium or any other salt therof or nedocromil or its salt such as the sodium salt, 4-hydroxynonenal, 4-oxononenal, malondialdehyde, (E)-2-hexenal, capsaicin, allicin, allylisothiocyanate, 6-methylthiohexyl isothiocyanate, 7-methylthioheptyl isothiocyanate, sulforaphane, 8-methylthiooctyl isothiocyanate, corticosteroids, such as dexamethasone, 8-iso prostaglandin A2, alkyl pyruvate, such as methyl and ethyl pyruvate, diethyl or dimethyl oxaloproprionate, 2-acetamidoacrylate, methyl or ethyl-2-acetamidoacrylate, hypoestoxide, parthenolide, eriodictyol, 4-Hydroxy-2-nonenal, 4-oxo-2nonenal, geranial, zerumbone, aurone, isoliquiritigenin, xanthohumol, [10]-Shogaol, eugenol, 1′-acetoxychavicol acetate, allyl isothiocyanate, benzyl isothiocyanate, phenethyl isothiocyanate, 4-(Methylthio)-3-butenyl isothiocyanate and 6-Methylsulfinylhexyl isothiocyanate, ferulic acid and its esters, such as ferulic acid ethyl ester, and ferulic acid methyl ester, sofalcone, 4-methyl daphnetin, imperatorin, auraptene, poncimarin, bis[2-hydroxybenzylidene]acetones, alicylcurcuminoid, 4 -bromo flavone, β-naphthoflavone, sappanone A, aurones and its corresponding indole derivatives such as benzylidene-indolin-2-ones, perillaldehyde, quercetin, fisetin, koparin, genistein, tanshinone IIA, BHA, BHT, PMX-290, AL-1, avicin D, gedunin, fisetin, andrographolide, [(±)-(4bS,8aR,10aS)-10a-ethynyl-4b,8,8-trimethyl-3,7-dioxo-3,4b,7,8,8a,9,10,10a-octahydrophenanthrene-2,6-dicarbonitrile] (TBE-31), 2-cyano-3,12-dioxooleana-1,9(11)-dien-28-onitrile (TP-225), [(±)-(4bS,8aR,10aS)-10a-ethynyl-4b,8,8-

trimethyl-3,7-dioxo-3,4b,7,8,8a,9,10,10a-octahydrophenanthrene-2,6-dicarbonitrile] (TBE-31), (TP-225), MCE-1, MCE5, ADT as referred to in in Medicinal Research Reviews, 32, No. 4, 687–726, 2012, gallic acid esters, such as alkyl esters, preferably ethyl gallate, n-propyl gallate and octyl gallate, or epigallocatechingallate, caffeic acid esters such as alkyl esters or its phenethyl ester, Coenzyme Q10 (Ubiquinone, Ubidecarenone), and the respective quinone or hydroquinone forms of the aforementioned quinone and hydroquinone derivatives and stereoisomers, tautomers or pharmacologically active derivatives of the aforementioned agents, such as the respective phenyl esters, alkyl esters, alkanoyl esters and benzoyl esters, phenyl ethers and alkyl ethers.

Very preferred Nrf2 activators are selected from: carnosic acid, 2-naphthoquinone, cynnamic aldehyde, caffeic acid and its esters, curcumin, reservatrol, artesunate, tert-butylhydroquinone, vitamins K1, K2 and K3, fumaric acid esters, i.e. fumaric acid mono- and/or diester which is preferably selected from the group of monoalkyl hydrogen fumarate and dialkyl fumarate, such as monomethyl hydrogen fumarate, dimethyl fumarate, monoethyl hydrogen fumarate, and diethyl fumarate, isothiocyanate such as sulforaphane, 1,2-dithiole-3-thione such as oltipraz, capsaicin, 3,5-di-tert-butyl-4-hydroxytoluene, 3-hydroxycoumarin, 4-hydroxynonenal, 4-oxononenal, malondialdehyde, (E)-2-hexenal, capsaicin, allicin, allylisothiocyanate, 6-methylthiohexyl isothiocyanate, 7-methylthioheptyl isothiocyanate, sulforaphane, 8-methylthiooctyl isothiocyanate, 8-iso prostaglandin A2, alkyl pyruvate, such as methyl and ethyl pyruvate, diethyl or dimethyl oxaloproprionate, 2-acetamidoacrylate, methyl or ethyl-2-acetamidoacrylate, hypoestoxide, parthenolide, eriodictyol, 4-Hydroxy-2-nonenal, 4-oxo-2nonenal, geranial, zerumbone, aurone, isoliquiritigenin, xanthohumol, [10]-Shogaol, eugenol, 1′-acetoxychavicol acetate, allyl isothiocyanate, benzyl isothiocyanate, phenethyl isothiocyanate, 4-(Methylthio)-3-butenyl isothiocyanate and 6-Methylsulfinylhexyl isothiocyanate and the respective quinone or hydroquinone forms of the aforementioned quinone and hydroquinone derivatives, and stereoisomers, tautomers or pharmacologically active derivatives of the aforementioned agents. Very preferred Nrf2 activators are Michael reaction acceptors such as dimethyl fumarate, monomethyl hydrogen fumarate isothiocyanates and 1,2-dithiole-3- thiones. In another embodiment, very preferred

Nrf2 activators are selected from monomethyl hydrogen fumarate, dimethyl fumarate, oltipraz, 1,2-naphthoquinone, tert-butylhydroquinone, methyl or ethyl pyruvate, 3,5-di-tert-butyl-4-hydroxytoluene, diethyl and dimethyl oxaloproprionate, hypoestoxide, parthenolide, eriodictyol, 4-Hydroxy-2-nonenal, 4-oxo-2nonenal, geranial, zerumbone, aurone, isoliquiritigenin, xanthohumol, [10]-Shogaol, eugenol, 1′-acetoxychavicol acetate, allyl isothiocyanate, benzyl isothiocyanate, phenethyl isothiocyanate, 4-(Methylthio)-3-butenyl isothiocyanate and 6-Methylsulfinylhexyl isothiocyanate.

Another group of preferred Nrf2 activators is comprising the preferred Nrf2 activators fumaric acid esters, bardoxolone methyl (methyl 2-cyano-3,12-dioxooleana-1,9(11)dien-28-oate, CDDO-Me, RTA 402), ethyl 2-cyano-3,12-dioxooleana-1,9(11)dien-28-oate, 2-cyano-3,12-dioxooleana-1,9(11)dien-28-oic acid (CDDO), 1[2-Cyano-3,12-dioxooleana-1,9(11)-dien-28-oyl]imidazole (CDDO-Im), 2-cyano-N-methyl-3,12-dioxooleana-1,9(11)-dien-28 amide (CDDO-methyl amide, CDDO-MA), [(±)-(4bS,8aR,10aS)-10a-ethynyl-4b,8,8-trimethyl-3,7-dioxo-3,4b,7,8,8a,9,10,10a-octahydrophenanthrene-2,6-dicarbonitrile] (TBE-31), 2-cyano-3,12-dioxooleana-1,9(11)-dien-28-onitrile (TP-225), 3-tert-butyl-4-hydroxyanisole, 2-tert-butyl-4-hydroxyanisole (BHA), tert-butylquinone (tBQ), tert-butylhydroquinone (tBHQ), 3,5-di-tert-butyl-4-hydroxytoluene (BHT), 2,6-Di-tert-butyl-4-methylene-2,5-cyclohexadien-1-one (2,6-Di-tert-butylquinone methide, BHT-quinone methide), ethoxyquin, gallic acid esters, alpha lipoic acid and its esters, such as alkyl esters, preferably lipoic acid etyl ester, curcumin, reservatrol, menadione, cinnamic aldehyde, cinnamic acid esters, caffeic acid esters, cafestol, kahweol, lycopene, carnosol, sulforaphane, oltipraz, capsaicin (8-Methyl-N-vanillyl-trans-6-nonenamide), 5-(4-methoxy-phenyl)-1,2-dithiole-3-thione (ADT), sulfasalazine, 5-aminosalicylic acid (mesalamine), 5-amino-2-hydroxy-benzoic acid 4-(5-thioxo-5H-[1,2]dithiol-3-yl)-phenyl ester (ATB-429), allicin, allylisothiocyanate, zerumbone, phenethyl isothiocyanate, benzyl isothiocyanate, 6-methylsulfinylhexyl isothiocyanate as well as alkyl and alkanoyl esters, alkyl ethers, stereoisomers, tautomers and salts of the aforementioned agents.

In an even more preferred embodiment of the present invention, the Nrf2 activator is selected from the group of fumaric acid esters, 3-tert-butyl-4-hydroxyanisole, 2-tert-butyl-4-hydroxyanisole (BHA), tert-butylquinone (tBQ),

tert-butylhydroquinone (tBHQ), 3,5-di-tert-butyl-4-hydroxytoluene (BHT), 2,6-Di-tert-butyl-4-methylene-2,5-cyclohexadien-1-one (2,6-Di-tert-butylquinone methide, BHT-quinone methide), ethoxyquin, gallic acid esters, curcumin, reservatrol, menadione, cinnamic aldehyde, cinnamic acid esters, caffeic acid esters, cafestol, kahweol, lycopene, carnosol, sulforaphane, oltipraz, 5-(4-methoxy-phenyl)-1,2-dithiole-3-thione (ADT), sulfasalazine, 5-aminosalicylic acid (mesalamine), 5-amino-2-hydroxy-benzoic acid 4-(5-thioxo-5H-[1,2]dithiol-3-yl)-phenyl ester (ATB-429), allicin, allylisothiocyanate, zerumbone, phenethyl isothiocyanate, benzyl isothiocyanate, 6-methylsulfinylhexyl isothiocyanate as well as alkyl and alkanoyl esters, alkyl ethers, stereoisomers, tautomers and salts of the aforementioned agents. These preferred aforementioned Nrf2 activators have no or no significant agonistic activity or significant effect on PPAR gamma.

In a further embodiment of the present invention, the Nrf2 activator is auranofin. Auranofin is preferably used according to the invention with a glitazone, more preferably pioglitazone or rosiglitazone.

In a further embodiment of the present invention, the Nrf2 activator is selected from sulfasalazine or 5-aminosalicylic acid (mesalamine). Sulfasalazine or 5-aminosalicylic acid (mesalamine) is preferably used according to the invention with a glitazone, more preferably pioglitazone or rosiglitazone.

It is particularly advantageous that the use of the PPAR gamma agonist and the Nrf2 activator according to the present invention may allow for the maximum dosage of each agent when used in mono-therapy, which result in maximal therapeutic effect. No or only very limited increase in adverse side effects known for the individual PPAR gamma agonist or the Nrf2 activator can be observed. It may also be advantageous to reduce the dose of one or both of the agents employed in the combination treatment of the present invention. Thus, side effects that may be observed in mono-therapy with the agents may be avoided or reduced. Throughout the specification, the term "pharmacologically active derivatives" denotes preferably salts, amides and esters, such as alkylesters including methyl and ethyl esters, of phamacologically active acids and alkanoic acid esters and ethers of pharmocologically active alcohols, such as acetic acid esters and methyl

ethers as well as alkanoic acid amides of pharmocologically active amines, such as the respective acetic acid amide.

The combination treatment of the present invention can be further combined with treatments and medicaments that are generally used in the various indications as a standard treatment. In the treatment of multiple sclerosis for example, the combination treatment of the present invention can be further combined with interferon, such as interfernon beta 1b or interferon beta 1a (Rebif, Avonex) or glatiramer acetate (Copaxone), a sphingosine 1-phosphate receptor modulator, such as Fingolimod (Gilenya) and/or methotrexate. The combination treatment of the present invention can be further combined with RXR specific ligands, such as 9-cis- retinoic acid (RA) in order to obtain even further improved results, particularly in the treatment of psoriasis.

The combination therapy of the present invention can, especially for the treatment of Parkinson's disease be further combined with established therapeutic agents well known in the art for the disease, such as levodopa, usually combined with a dopa decarboxylase inhibitor such as carbidopa or benserazide or a COMT inhibitor, such as entacapone, tolcapone or nitecapone. Moreover, the combination therapy of the present invention can be further combined with dopamine agonists, such as bromocriptine, pergolide, pramipexole, ropinirole, piribedil, cabergoline, apomorphine or lisuride or rotigotine and MAO-B inhibitors such as selegiline or rasagiline.

The combination therapy according to the present invention may be administered as a simultaneous or sequential regimen, also referred to as co-administration. When administered sequentially, the combination may be administered in two or more administrations. It is also possible to combine any PPAR gamma agonist with an Nrf2 activator in a unitary dosage form for simultaneous or sequential administration to a patient.

In general, for compositions containing fumaric acid esters, an administration twice daily (BID) or thrice daily (TID) is preferred. The dosages of the individual agents are adjusted accordingly.

Co-administration of a PPAR gamma agonist with an Nrf2 activator according to the invention generally and preferably refers to simultaneous or sequential administration of a PPAR gamma agonist and an Nrf2 activator, such

that therapeutically effective amounts of the PPAR gamma agonist and the Nrf2 activator are both present at the same time in the body of the patient.

Co-administration includes simultaneous administration and administration of the an agent according to the invention before or after administration of the other agent, for example, administration of both agents according to the invention within seconds, minutes, or hours. In one embodiment, the first agent is administered, followed, after a period of hours, e.g., 0.25-12 hours, preferably 0.5 to 3 hours most preferably 1 to 2 hours), by administration of the second agent.

The combination therapy and co-administration according to the invention frequently provides "synergy" and "synergistic effect", i.e. the therapeutic effect achieved when the PPAR gamma agonist and the Nrf2 activator are used together is more than additive, i.e. greater than the sum of the effects that result from using each agent alone.

An appropriate dose of a PPAR agonist and an Nrf2 activator or pharmaceutical composition comprising a PPAR agonist and an Nrf2 activator for use in the present invention, may be determined according to any one of several well-established protocols. For example, animal studies such as studies using mice, rats, dogs, and/or monkeys may be used to determine an appropriate dose of a pharmaceutical compound. Results from animal studies may be extrapolated to determine doses for use in other species, such as for example, humans.

In general, a preferred PPAR gamma agonist is administered in combination with a preferred Nrf2 activator according to the invention, preferably orally, in daily dosages of 0.01 mg to 50 mg per kg body weight, dependent on the activity and safety of the respective PPAR gamma agonist. If not indicated otherwise, the dosages given above and below reflect the amount of free base of the PPAR gamma agonist, even if used in form of the maleate or another acid addition salt.

Preferred Nrf 2 activators are bardoxolone methyl and dialkyl fumarate such as dimethyl fumarate and diethyl fumarate.

The dialkyl fumarates to be used according to the invention are prepared by processes known in the art (see, for example, EP 0 312 697).

Preferably, the active ingredients, i.e. the agents, are used for preparing oral preparations in the form of tablets, micro-tablets, pellets or granulates, optionally in capsules or sachets. Preparations in the form of micro-tablets or pellets, optionally

filled in capsules or sachets are preferred and are also a subject matter of the invention. According to a preferred embodiment, the size or the mean diameter, respectively, of the pellets or micro-tablets is in the range from 300 to 2,000 μm, especially in the range of 500 or 1,000 μm.

The oral preparations may be provided with an enteric coating. Capsules may be soft or hard gelatine capsules.

The dialkyl fumarates used according to the invention may be used alone or as a mixture of several compounds, optionally in combination with the customary carriers and excipients. The amounts to be used are selected in such a manner that the preparations, such as tablets, obtained contain the active ingredient in an amount corresponding to 10 to 300 mg of fumaric acid per dosage unit.

Preferred preparations according to the invention contain a total amount of 10 to 300 mg of dimethyl fumarate and/or diethyl fumarate.

Fixed-dose combinations of a PPAR agonist and preferably a PPAR gamma agonist with an Nrf2 activator are preferred. Fixed-dose combinations of rosiglitazone with dimethyl fumarate and rosiglitazone with bardoxolone methyl are particularly preferred. Fixed-dose combinations of pioglitazone with dimethyl fumarate and rosiglitazone with bardoxolone methyl are particularly preferred.

In particular, rosiglitazone is preferably administered according to the invention in form of its maleate in daily dosages of 0.01 to 0.2 mg per kg body weight, more preferably in daily dosages of 0.02 to 0.16 mg per kg body weight and most preferably in daily dosages of 0.025 mg to 0.14 mg per kg body weight, such as in daily dosages of 0.03 mg, 0.06 mg or 0.12 mg per kg body weight. Daily oral dosages of 2 mg, 4 mg and 8 mg rosiglitazone per patient are particularly preferred.

In particular, pioglitazone is preferably administered according to the invention in form of its hydrochloride in daily dosages of 0.05 to 1 mg per kg body weight, more preferably in daily dosages of 0.1 to 0.8 mg per kg body weight and most preferably in daily dosages of 0.15 mg to 0.7 mg per kg body weight, such as in daily dosages of about 0.2 mg, about 0.4 mg or about 0.6 mg per kg body weight. Daily oral dosages of about 15 mg, about 30 mg and about 45 mg pioglitazone per patient are particularly preferred.

In particular, ciglitazone or troglitazone are preferably administered according to the invention in daily dosages of 1 to 20 mg per kg body weight, more preferably in daily dosages of 2 to 15 mg per kg body weight and most preferably in daily dosages of 3 mg to 10 mg per kg body weight. Oral dosages are particularly preferred.

In general, a preferred Nrf2 activator is administered in combination with a preferred PPAR gamma agonist, preferably orally, in daily dosages of 0.1 mg to 20 mg per kg body weight, dependent on the activity and safety of the respective Nrf2 activator.

In particular, bardoxolone methyl is preferably administered according to the invention in daily dosages of 0.1 to 3 mg per kg body weight, more preferably in daily dosages of 0.2 to 2.5 mg per kg body weight and most preferably in daily dosages of 0.3 mg to 2.2 mg per kg body weight, such as in daily dosages of about 0.35 mg, about 1.1 mg or about 2 mg per kg body weight. Daily oral dosages of about 25 mg, about 75 mg and about 150 mg bardoxolone methyl per patient are particularly preferred.

In particular, dimethyl fumarate is preferably administered according to the invention in daily dosages of 1 to 20 mg per kg body weight, more preferably in daily dosages of 2 to 15 mg per kg body weight and most preferably in daily dosages of 3 mg to 12 mg per kg body weight, such as in daily dosages of about 3.4 mg, about 7 mg or about 10 mg per kg body weight. Daily oral dosages of about 240 mg, about 480 mg and about 720 mg dimethyl fumarate per patient are particularly preferred.

The ratio between the dosages of the PPAR gamma agonist and the Nrf2 activator used in the combinations according to the present invention, depends on the activity of the particular PPAR gamma agonist and Nrf2 activator selected.

Daily oral dosages of 2 mg, 4 mg and 8 mg rosiglitazone per patient are particularly preferred.

Daily oral dosages of about 20 mg, about 25 mg, about 75 mg and about 150 mg bardoxolone methyl per patient are particularly preferred. In case bardoxolone methyl is employed in amorphous form, daily dosages of about 20 mg per patient are most preferred.

Daily oral dosages of about 120 mg, about 240 mg, about 360 mg, about 480 mg, about 600 mg and about 720 mg dimethyl fumarate per patient are particularly preferred.

If the Nrf2 activator is dimethyl fumarate, once or twice daily dosing is preferred.

Preferred dosage forms and in particular oral dosage forms such as tablets or capsules may contain:

For daily administration, dosage forms such as tablets or capsules may contain preferably about 2 mg rosiglitazone and about 25 mg bardoxolone methyl or about 2 mg rosiglitazone and about 75 mg bardoxolone methyl or about 2 mg rosiglitazone and about 150 mg bardoxolone methyl or about 4 mg rosiglitazone and about 25 mg bardoxolone methyl or about 4 mg rosiglitazone and about 75 mg bardoxolone methyl or about 4 mg rosiglitazone and about 150 mg bardoxolone methyl or about 8 mg rosiglitazone and about 25 mg bardoxolone methyl or about 8 mg rosiglitazone and about 75 mg bardoxolone methyl or about 8 mg rosiglitazone and about 150 mg bardoxolone methyl. Most preferably, a dosage form may contain about 8 mg rosiglitazone and about 150 mg bardoxolone methyl.

For administration three times daily, preferred dosage forms such as tablets or capsules may contain about 0.7 mg, preferably about 0.67 mg, rosiglitazone and 240 mg dimethyl fumarate or about 1.3 mg, preferably about 1.33 mg, rosiglitazone and about 240 mg dimethyl fumarate or about 2.7 mg preferably about 2.67 mg, rosiglitazone and about 240 mg dimethyl fumarate or about 0.7 mg, preferably about 0.67 mg, rosiglitazone and 120 mg dimethyl fumarate or about 1.3 mg, preferably about 1.33 mg, rosiglitazone and about 120 mg dimethyl fumarate or about 2.7 mg preferably about 2.67 mg, rosiglitazone and about 120 mg dimethyl fumarate. Most preferably, a dosage form may contain about 2.7 mg preferably about 2.67 mg, rosiglitazone and about 240 mg dimethyl fumarate.

For administration two times daily, preferred dosage forms such as tablets or capsules may contain about 1 mg rosiglitazone and about 240 mg dimethyl fumarate or about 2 mg rosiglitazone and about 240 mg dimethyl fumarate or about 4 mg rosiglitazone and about 240 mg dimethyl fumarate.

For daily administration, dosage forms such as tablets or capsules may contain preferably about 15 mg pioglitazone and about 25 mg bardoxolone methyl

or about 15 mg pioglitazone and about 75 mg bardoxolone methyl or about 15 mg pioglitazone and about 150 mg bardoxolone methyl or about 30 mg pioglitazone and about 25 mg bardoxolone methyl or about 30 mg pioglitazone and about 75 mg bardoxolone methyl or about 30 mg pioglitazone and about 150 mg bardoxolone methyl or about 45 mg pioglitazone and about 25 mg bardoxolone methyl or about 45 mg pioglitazone and about 75 mg bardoxolone methyl or about 45 mg pioglitazone and about 150 mg bardoxolone methyl. Most preferably, a dosage form may contain about 45 mg pioglitazone and about 150 mg bardoxolone methyl.

For administration three times daily, preferred dosage forms such as tablets or capsules may contain about 5 mg pioglitazone and 240 mg dimethyl fumarate or about 10 mg pioglitazone and about 240 mg dimethyl fumarate or about 15 mg pioglitazone and about 240 mg dimethyl fumarate or about 5 mg pioglitazone and 120 mg dimethyl fumarate or about 10 mg pioglitazone and about 120 mg dimethyl fumarate or about 15 mg pioglitazone and about 120 mg dimethyl fumarate, Most preferably, a dosage form may contain about 15 mg pioglitazone and about 240 mg dimethyl fumarate.

For administration two times daily, preferred dosage forms such as tablets or capsules may contain about 7.5 mg pioglitazone and about 240 mg dimethyl fumarate or about 15 mg pioglitazone and about 240 mg dimethyl fumarate or about 22.5 mg pioglitazone and about 240 mg dimethyl fumarate.

Moreover, pharmaceutical compositions according to the present invention are preferred which comprise as a PPAR gamma agonist about 5 mg, about 7.5 mg, about 10 mg, about 15 mg, about 20 mg, about 22.5 mg or about 25 mg of pioglitazone. Also, pharmaceutical compositions according to the present invention are preferred which comprise as a PPAR gamma agonist about 0.7 mg, about 1 mg, about 1.3 mg, about 2 mg, about 2.7 mg, about 3 mg, about 3.5 mg, about 4 or about 5 mg of rosiglitazone.

Pharmaceutical compositions according to the present invention are preferred which comprise about 120 mg, about 200 mg or about 240 mg of dimethyl fumarate.

In particular, atorvastatin is preferably administered according to the invention in form of its calcium salt in daily oral dosages of about 10, about 20, about 40 or about 80 mg per patient. Preferably, atorvastatin is combined in the

above dosages with dimethylfumarate in dosages of about 120, about 240 or about 360, about 480 or about 720 mg per day. Most preferred are combinations containing about 20 mg or about 40 mg of atorvastatin in form of its calcium salt, and about 240 mg dimethyl fumarate.

In a further embodiment, atorvastatin is combined in the above dosages with bardoxolone methyl in its amorphous form in dosages of about 20 mg per day. Most preferred are combinations containing about 40 mg or about 80 mg of atorvastatin in form of its calcium salt, and about 20 mg bardoxolone methyl in its amorphous form.

In particular, losartan is preferably administered according to the invention in daily oral dosages of about 25, about 50, about 75 or about 100 mg per patient. Preferably, losartan is combined in the above dosages with dimethylfumarate in dosages of about 120, about 240 or about 360, about 480 or about 720 mg per day. Most preferred are combinations containing about 25 mg or about 50 mg of losartan, and about 240 mg dimethyl fumarate. The combination is preferably administered twice daily. The combination treatments of sartanes and preferably losartan, irbesartan, telmisartan and candesartan with Nrf2 activators such as dimehtyl fumarate and bardoxolone methyl are particularly effective for the treatment of diabetic nephropathy (kidney damage due to diabetes) and chronic kidney disease, but also for the treatment of multiple sclerosis.

In a further example, losartan is combined in the above dosages with bardoxolone methyl in its amorphous form in dosages of about 20 mg per day. Most preferred are combinations containing about 25 mg or about 50 mg of losartan, and about 20 mg bardoxolone methyl in its amorphous form. The combination is preferably administered once daily.

In particular, ibuprofen is preferably administered according to the invention in daily dosages that are applicable to the monotherapy with ibuprofen, such as about 600 mg, about 800 mg or about 1200 mg or about 2400 mg per patient. Most preferred are combinations containing about 600 mg of ibuprofen and about 240 mg dimethyl fumarate. The combination is preferably administered twice daily.

In a further example, ibuprofen is combined in the above dosages with bardoxolone methyl in its amorphous form in dosages of about 20 mg per day.

Most preferred are combinations containing about 800 mg of ibuprofen, and about 20 mg bardoxolone methyl in its amorphous form. The combination is preferably administered once daily.

Preferred ratios between rosiglitazone and dimethyl fumarate are selected from 1/20 to 1/400 (w/w, rosiglitazone/dimethyl fumarate), preferably from 1/25 to 380, more preferably from 1/28 to 1/360. Most preferably the ratios are about 1/30, about 1/45, such as about 1/44.4, about 1/60, about 1/90, such as about 1/88.9 or about 1/92.3, about 1/120, about 1/180, such as 1/171.4 or 1/184.6, about 1/240, about 1/340, such as about 1/342.9.

Preferred ratios between pioglitazone and dimethyl fumarate are selected from 1/3 to 1/60 (w/w, pioglitazone/dimethyl fumarate), preferably from 1/4 to 1/55, more preferably from 1/5 to 1/52. Most preferably the ratios are about 1/5.3, about 1/8, about 1/10, such as 1/10.7, about 1/12, about 1/16, about 1/24, about 1/32, about 1 to 48.

In general, ratios between rosiglitazone and bardoxolone methyl are selected from 1/1 to 1/100 (w/w, rosiglitazone/bardoxolone methyl), preferably from 1/1.5 to 1/80, more preferably from 1/2 to 1/75. Most preferably the ratios are about 1/2.5, such as about 1/3.1 or about 1/5, such as 1/6.3, about 1/10, such as about 1/9.4 or about 1/12.5, about 1/20, such as 1/18.8, about 1/40, such as about 1/37.5, about 1/70, such as about 1/75.

In general, ratios between pioglitazone and bardoxolone methyl are selected from 1/0.1 to 1/20 (w/w, pioglitazone/bardoxolone methyl), preferably from 1/0.3 to 1/15, more preferably from 1/0.4 to 1/12. Most preferably the ratios are about 1/0.5, such as about 1/0.4 or about 1/0.6 or about 1/0.7, or about 1/0.8, about 1/2, such as about 1/1.7 or about 1/2.5, about 1/3, such as about 1/3.3, about 1/5 or about 1/10.

In preferred embodiments of the present invention, amorphic bardoxolone methyl is employed more preferably in a pharmaceutical formulation comprising amorphous bardoxolone methyl, preferably obtained as spray-dried dispersion with a glass-forming excipient, such as methacrylic acid copolymer Type C, USP, e.g. in a 4/6 weight ratio of bardoxolone methyl to methacrylic acid copolymer Type C, USP (Eurdagit), more preferably admixed with particles comprised of at least one hydrophilic binder, such as hydroxypropylmethylcellulose, according to

US2012/022156. Preferred compositions of bardoxolone methyl according to the present invention, also contain a surface active ingredient, such as sodium lauryl sulfate, preferably in amounts of about 1 to 5 weight %, preferably about 3%, such as 2.73%, of the total composition.

In preferred embodiments, amorphous bardoxolone methyl is administered according to the invention in daily dosages of 0.05 to 1 mg per kg body weight, more preferably in dosages of 0.1 to 0.8 mg per kg body weight and most preferably in dosages of 0.2 mg to 0.6 mg per kg body weight, such as in daily dosages of about 0.15 mg, about 0.25 mg or about 0.35 mg per kg body weight. Daily oral dosages of about 10 mg, about 20 mg, and about 30 mg bardoxolone methyl per patient are particularly preferred.

For daily administration of amorphous bardoxolone methyl, the following dosages are employed per patient: About 2 mg rosiglitazone and about 10 mg bardoxolone methyl or about 2 mg rosiglitazone and about 20 mg bardoxolone methyl or about 2 mg rosiglitazone and about 30 mg bardoxolone methyl or about 4 mg rosiglitazone and about 10 mg bardoxolone methyl or about 4 mg rosiglitazone and about 20 mg bardoxolone methyl or about 4 mg rosiglitazone and about 30 mg bardoxolone methyl or about 8 mg rosiglitazone and about 10 mg bardoxolone methyl or about 8 mg rosiglitazone and about 20 mg bardoxolone methyl or about 8 mg rosiglitazone and about 30 mg bardoxolone methyl. Most preferably, about 8 mg rosiglitazone and about 20 mg bardoxolone methyl are employed. In particular it is preferred if the above amounts are used in a fixed dose combination, i.e. in a solid oral dosage form.

Alternatively, for daily administration or amorphous bardoxolone methyl, the following dosages are employed per patient: About 15 mg pioglitazone and about 10 mg bardoxolone methyl or about 15 mg pioglitazone and about 20 mg bardoxolone methyl or about 15 mg pioglitazone and about 30 mg bardoxolone methyl or about 30 mg pioglitazone and about 10 mg bardoxolone methyl or about 30 mg pioglitazone and about 20 mg bardoxolone methyl or about 30 mg pioglitazone and about 30 mg bardoxolone methyl or about 45 mg pioglitazone and about 10 mg bardoxolone methyl or about 45 mg pioglitazone and about 20 mg bardoxolone methyl or about 45 mg pioglitazone and about 30 mg bardoxolone methyl. Most preferably, about 45 mg pioglitazone and about 20 mg bardoxolone

methyl are employed. Most preferably, about 8 mg rosiglitazone and about 20 mg bardoxolone methyl are employed. In particular it is preferred if the above amounts are used in a fixed dose combination, i.e. in a solid oral dosage form.

In preferred embodiments of the present invention, where bardoxolone methyl is employed in amorphic form, preferred ratios between rosiglitazone and bardoxolone methyl are from 1/1 to 1/20 ("/" indicates "to" throughout this application, when a ratio is concerned, w/w, rosiglitazone/bardoxolone methyl), preferably from 1/1.1 to 1/17 , more preferably from 1/1.2 to 1/16. Most preferably the ratios are about 1/1.3, such as about 1/1.25, about 1/2.5, about 1/3.5, such as 1/3.75, about 1/5, about 7.5, about 1/10.

In further In preferred embodiments of the present invention, where bardoxolone methyl is employed in amorphic form, preferred ratios between pioglitazone and bardoxolone methyl are from 1/0.1 to 1/3 (w/w, pioglitazone/bardoxolone methyl), preferably from 1/0.15 to 1/2.5, more preferably from 1/0.2 to 1/2.2. Most preferably the ratios are about 1/0.2, such as about 1/0.22, about 1/0.3, such as about 1/0.33, about 1/0.4, such as about 1/0.44, about 1/0.7, such as about 1/0.67, about 1/1 or about 1/2.

Dosage forms and in particular oral dosage forms such as tablets or capsules containing both a PPAR gamma agonist and a Nrf2 activator in a fixed dose combination comprising the above compositions in the given ratios and especially those containing amorphic bardoxolone methyl, are preferred.

Fixed dose combinations, such as tablets containing the active ingredients in the above amounts and ratios, are most preferred.

Pharmaceutical compositions provided by the present disclosure may comprise a therapeutically effective amount of a PPAR gamma agonist and an Nrf2 activator together with a suitable amount of one or more pharmaceutically acceptable vehicles so as to provide a composition for proper administration to a patient. Suitable pharmaceutical vehicles are described in the art.

In certain embodiments, a PPAR gamma agonist and an Nrf2 activator may together be incorporated into pharmaceutical compositions to be administered orally. Oral administration of such pharmaceutical compositions may result in uptake of the PPAR gamma agonist and the Nrf2 activator throughout the intestine and entry into the systemic circulation. Such oral compositions may be prepared in

a manner known in the pharmaceutical art and comprise a PPAR gamma agonist and an Nrf2 activator and at least one pharmaceutically acceptable vehicle. Oral pharmaceutical compositions may include a therapeutically effective amount of a PPAR gamma agonist and an Nrf2 activator and a suitable amount of a pharmaceutically acceptable vehicle, so as to provide an appropriate form for administration to a patient.

A PPAR gamma agonist and an Nrf2 activator may together be incorporated into pharmaceutical compositions to be administered by any other appropriate route of administration including intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, oral, sublingual, intracerebral, intravaginal, transdermal, rectal, inhalation, or topical.

In one embodiment of the present invention, a topical formulation is provided, containing a PPAR agonist, such as a glitazone like pioglitazone or rosiglitazone and an Nrft2 activator, preferably Nrf2 activator that does not or only rarely cause a allergic skin reaction, such as bardoxolone methyl, CDDO, CDDO-IM, CDDO-MA, TP-225, menadione, vitamin K1, BHA, BHT, tBHQ, tBQ, curcumin, reservatrol, cynnamic aldehyde or oltipraz. The topical formulation is preferably used in the treatment of psoriasis, acne, rosacea and skin rash such as skin rash caused by EGFR inhibitors like cetuximab,zalutumumab, nimotuzumab, and matuzumab. gefitinib, erlotinib, and lapatinib. The formulations are prepared with customary ingredients and processes known in the art and/or disclosed herein.

Pharmaceutical compositions comprising a PPAR gamma agonist and an Nrf2 activator may be manufactured by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, or lyophilizing processes. Pharmaceutical compositions may be formulated in a conventional manner using one or more physiologically acceptable carriers, diluents, excipients, or auxiliaries, which facilitate processing of the PPAR gamma agonist and the Nrf2 activator or crystalline forms thereof and one or more pharmaceutically acceptable vehicles into formulations that can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. Pharmaceutical compositions provided by the present disclosure may take the form of solutions, suspensions, emulsion, tablets, pills, pellets, capsules, capsules containing liquids, powders, sustained-release formulations, suppositories,

emulsions, aerosols, sprays, suspensions, or any other form suitable for administration to a patient. Pharmaceutical compositions provided by the present disclosure may be formulated in a unit dosage form. A unit dosage form refers to a physically discrete unit suitable as a unitary dose for patients undergoing treatment, with each unit containing a predetermined quantity of a PPAR gamma agonist and an Nrf2 activator calculated to produce an intended therapeutic effect. A unit dosage form may be for a single daily dose, for administration 2 times per day, or one of multiple daily doses, e.g., 3 or more times per day. When multiple daily doses are used, a unit dosage form may be the same or different for each dose. One or more dosage forms may comprise a dose, which may be administered to a patient at a single point in time or during a time interval.

Pharmaceutical compositions comprising a PPAR gamma agonist and an Nrf2 activator may be formulated for immediate release or controlled or sustained or delayed release.

In certain embodiments, an oral dosage form provided by the present disclosure may be a controlled release dosage form. Controlled delivery technologies can improve the absorption of a drug in a particular region or regions of the gastrointestinal tract. Controlled drug delivery systems may be designed to deliver a drug in such a way that the drug level is maintained within a therapeutically effective window and effective and safe blood levels are maintained for a period as long as the system continues to deliver the drug with a particular release profile in the gastrointestinal tract. Controlled drug delivery may produce substantially constant blood levels of the PPAR gamma agonist and the Nrf2 activator over a period of time as compared to fluctuations observed with immediate release dosage forms. For some PPAR gamma agonists and Nrf2 activators, maintaining a constant blood and tissue concentration throughout the course of therapy is the most desirable mode of treatment. Immediate release of the PPAR gamma agonist and the Nrf2 activator may cause blood levels to peak above the level required to elicit a desired response, which may waste the agents and may cause or exacerbate toxic side effects. Controlled drug delivery can result in optimum therapy, and not only can reduce the frequency of dosing, but may also reduce the severity of side effects. Examples of controlled release dosage forms include dissolution controlled systems, diffusion controlled systems, ion exchange

resins, osmotically controlled systems, erodable matrix systems, pH independent formulations, gastric retention systems, and the like.

An appropriate oral dosage form for a particular pharmaceutical composition provided by the present disclosure may depend, at least in part, on the gastrointestinal absorption properties of the PPAR gamma agonist and the Nrf2 activator and the stability of these agents in the gastrointestinal tract, the pharmacokinetics thereof and the intended therapeutic profile. An appropriate controlled release oral dosage form may be selected for a particular a PPAR gamma agonist and Nrf2 activator. For example, gastric retention oral dosage forms may be appropriate for agents absorbed primarily from the upper gastrointestinal tract, and sustained release oral dosage forms may be appropriate for agents absorbed primarily from the lower gastrointestinal tract.

In certain embodiments, pharmaceutical compositions provided by the present disclosure may be practiced with dosage forms adapted to provide sustained release of a PPAR gamma agonist and an Nrf2 activator upon oral administration. Sustained release oral dosage forms may be used to release the PPAR gamma agonist and/or the Nrf2 activator over a prolonged time period and are useful when it is desired that an agent be delivered to the lower gastrointestinal tract. Sustained release oral dosage forms include any oral dosage form that maintains therapeutic concentrations of the agents in a biological fluid such as the plasma, blood, cerebrospinal fluid, or in a tissue or organ for a prolonged time period. Sustained release oral dosage forms include diffusion-controlled systems such as reservoir devices and matrix devices, dissolution-controlled systems, osmotic systems, and erosion-controlled systems. Sustained release oral dosage forms and methods of preparing the same are well known in the art.

In each of the above dosage forms, the PPAR gamma agonist may be formulated together in admixture or preferably separately from the Nrf2 activator. Each of the PPAR gamma agonist and Nrf2 activator may preferably be contained in separate form within the dosage form, such as an oral dosage form, which is preferably a tablet or capsule. In such oral dosage form, wherein the PPAR gamma agonist and the Nrf2 activator are separated, each agent may be formulated with different excipients. The PPAR gamma agonist and the Nrf2 activator may also be

each contained in formulations with different release profiles, i.e. with immediate, controlled or delayed release.

The formulations and in particular the solid oral dosage forms containing a PPAR gamma agonist and/or an Nrf2 activator may contain a conventional additive in the field of pharmaceutical preparation and can be also produced according to a known method. As the additive, for example, excipient, disintegrant, binder, lubricant, coloring agent, pH regulator, surfactant, release-sustaining agent, stabilizer, sour agent, flavor, glidant and the like can be mentioned. These additives are used in an amount conventionally employed in the field of pharmaceutical preparation.

As the excipient, for example, starches such as corn starch, potato starch, wheat starch, rice starch, partly pregelatinized starch, pregelatinized starch, porous starch and the like; sugars and sugar alcohols such as lactose, fructose, glucose, D-mannitol, sorbitol and the like; anhydrous calcium phosphate, crystalline cellulose, precipitated calcium carbonate, calcium silicate and the like can be mentioned.

As the disintegrant, for example, carboxymethyl cellulose, calcium carboxymethyl cellulose, sodium carboxymethyl starch, croscarmellose sodium, crospovidone, low-substituted hydroxypropyl cellulose, hydroxypropyl starch and the like are used. The amount of the disintegrant to be used is preferably 0.5-25 parts by weight, more preferably 1-15 parts by weight, per 100 parts by weight of the solid preparation.

As the binder, for example, crystalline cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, polyvinylpyrrolidone, gum arabic powder and the like can be mentioned. The amount of the binder to be used is preferably 0.1-50 parts by weight, more preferably 0.5-40 parts by weight, per 100 parts by weight of the solid preparation.

Preferable examples of the lubricant include magnesium stearate, calcium stearate, talc, sucrose esters of fatty acids, sodium stearyl fumarate and the like. As the coloring agent, for example, food colors such as Food Yellow No. 5, Food Red No. 2, Food Blue No. 2 and the like, food lake colors, ferric oxide and the like can be mentioned. As the pH regulator, citrate, phosphate, carbonate, tartrate, fumarate, acetate, amino acid salt and the like can be mentioned. As the surfactant, sodium

lauryl sulfate, polysorbate 80, polyoxyethylene (160) polyoxypropylene (30) glycol and the like can be mentioned.

As the release-sustaining agent, for example, cellulose polymers such as hydroxypropyl cellulose, hydroxypropylmethyl cellulose (preferably hydroxypropylmethyl cellulose 2910, hydroxypropylmethyl cellulose 2208 and the like), cellulose acetate (preferably cellulose acetate having an acetyl content of 39.3-40%), cellulose diacetate, cellulose triacetate, cellulose acetate propionate, ethyl cellulose, sodium carboxymethyl cellulose, crystalline cellulose sodium carboxymethyl cellulose and the like; sodium alginate, carboxyvinyl polymer; acrylic acid polymers such as aminoalkylmethacrylate copolymer RS [Eudragit RS (trademark), Rohm Pharma], ethyl acrylate-methyl methacrylate copolymer suspension [Eudragit NE (trademark), Rohm Pharma] and the like; and the like can be mentioned. The release-sustaining agent may contain, for example, flux enhancers (e.g., sodium chloride, potassium chloride, sucrose, sorbitol, D-mannitol, polyethylene glycol (preferably polyethylene glycol 400 and the like), propylene glycol, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, hydroxypropylmethyl cellulose phthalate, cellulose acetate phthalate, polyvinyl alcohol, methacrylic acid polymer), plasticizers (e.g., triacetin, acetylated monoglyceride, grape seed oil, olive oil, sesame oil, acetyltributyl citrate, acetyltriethyl citrate, glycerin sorbitol, diethyl oxalate, diethyl maleate, diethyl fumarate, dibutyl succinate, diethyl malonate, dioctyl phthalate, dibutyl sebacate, triethyl citrate, tributyl citrate, glycerol tributyrate) and the like. Preferable examples of the release-sustaining agent include (1) a semipermeable membrane coating containing cellulose acetate (preferably cellulose acetate having an acetyl content of 39.3-40%), polyethylene glycol (preferably polyethylene glycol 400 and the like) and triacetin; (2) a release-sustaining composition containing sodium carboxymethyl cellulose, hydroxypropylmethyl cellulose 2910, hydroxypropylmethyl cellulose 2208 and microcrystalline cellulose; and the like.

As the stabilizer, for example, tocopherol, tetrasodium edetate, nicotinamide, cyclodextrins and the like can be mentioned. As the sour agent, for example, ascorbic acid, citric acid, tartaric acid, malic acid and the like can be mentioned. As the flavor, for example, menthol, peppermint oil, lemon oil, vanillin

and the like can be mentioned. As the glidant, for example, light anhydrous silicic acid, hydrated silicon dioxide and the like can be mentioned.

The above-mentioned additives may be used in a mixture of two or more kinds thereof in an appropriate ratio.

**Use**

An appropriate dose of each a PPAR gamma agonist and Nrf2 activator may be determined based on several factors, including, for example, the body weight and/or condition of the patient being treated, the severity of the disease being treated, the incidence and/or severity of side effects, the manner of administration, and the judgment of the prescribing physician. Appropriate dose ranges may be determined by methods known to those skilled in the art.

In one embodiment the invention provides a combination of an Nrf2 activator and a PPAR gamma agonist for use in the treatment of inflammatory and autoimmune diseases.

In another embodiment, the invention provides a PPAR gamma agonist for use in combination with a fumaric acid mono- and/or diester, characterized in that the PPAR gamma agonist is selective and has no substantial activity on PPAR alpha or delta.

A therapeutically effective amount of a combination of a PPAR gamma agonist and an Nrf2 activator may be administered as a treatment or preventative measure to a patient having a predisposition for and/or history of immunological, autoimmune, and/or inflammatory diseases including psoriasis, asthma and chronic obstructive pulmonary diseases, cardiac insufficiency including left ventricular insufficiency, myocardial infarction and angina pectoris, mitochondrial and neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, Huntington's disease, dementia, retinopathia pigmentosa and mitochondrial encephalomyopathy, transplantation rejection, autoimmune diseases including multiple sclerosis, ischemia and reperfusion injury, advanced glycation endproducts (AGE)-induced genome and protein damage, inflammatory bowel diseases such as Crohn's disease and ulcerative colitis, thyroid eye disease-related inflammation, fibrosis, such as lung fibrosis, chronic lymphocytic leukemia, aphthous stomatitis, such as recurrent aphthous stomatitis, acute lung injury, non-alcoholic

steatohepatitis acute renal injury and aging-related progressive renal injury, diabetic cardiomyopathy and nephropathy. Chronic kidney disease (CKD), Atherosclerosis, hypercholesterolemia, hyperlipidemia, aortic stenosis, acute kidney injury (AKI) after surgery. The present invention can also be used in the prevention of cardiovascular disease, for plaque stabilization, reduction of inflammation, reversal of endothelial dysfunction, and decreased thrombogenicity and wound healing in diabetes. Moreover, the combination treatment of the present invention can be used in the treatment and prevention of atopic dermatitis, dementia, gastritis, fibrosis, insulin resistance, type I and type II diabetes and Syndrome X.

In a preferred embodiment of the present invention the Nrf2 activatior is selected from sulfasalazine(2-Hydroxy-5-[4-(2-pyridylsulfamoyl)-phenyldiazenyl]-benzoesäure, 5-[4-(2-Pyridylsulfamoyl)-phenylazo]salicylsäure), mesalamine, 5-amino-2-hydroxy-benzoic acid 4-(5-thioxo-5H-[1,2]dithiol-3-yl)-phenyl ester hydrochloride (ATB-429). According to the present invention, these Nrf2 activators are preferably combined with a glitazone, such as pioglitazone or rosiglitazone. More preferably, these combinations are preferably used for the treatment of IBS and arthritic diseases.

In a preferred embodiment of the present invention a fumaric acid ester, such as dimethyl fumarate is combined with a glitzone, such as pioglitazone or rosiglitazone for the treatment of chronic kidney disease (CKD).

In one embodiment of the present invention, the combination treatment is preferably used in the prophylaxis or treatment of polycystic ovary syndrome (PCOS). It can also be found that compounds being both, PPAR gamma agonists and Nrf2 activators, show suitable effects as a monotherapeutic agent. Preferred compounds which can be used in the prophylaxis and treatment of PCOS as a single active ingredient in a dosage form such as a tablet, are bardoxolone methyl, CDDO, CDDO-IM, CDDO-MA or TP-225. Thus, another object of the present invention is the use of bardoxolone methyl, CDDO, CDDO-IM, CDDO-MA or TP-225 in the prophylaxis and treatment of PCOS and a method of treating PCOS by administration of a pharmacologically effective amount of bardoxolone methyl, CDDO, CDDO-IM, CDDO-MA, TBE-31 or TP-225 or another Nrf2 activator to a patient in need thereof. In many instances, the mono-therapy with the

aforementioned Nrf2 activators can be further improved with co-administration of a PPAR agonist, such as a glitazone like pioglitazone or rosiglitazone.

NF-κB mediated and/or other diseases are described in the following.

According to another embodiment of the invention, the administration or co-administration of a combination of a PPAR gamma agonist and an Nrf2 activator is effective for treating a member of the group of diseases consisting of a neurological disorder, an opthalmological disorder, in a mammal, including, without limitation, a human. According to another embodiment the neurological disorder, an opthalmological disorder, or a combination thereof results from at least one member of the group consisting of trauma, ischemia, and hypoxia. According to another embodiment the neurological disorder, opthalmological disorder, or combination thereof is selected from the group consisting of painful neuropathy, neuropathic pain, diabetic neuropathy, drug dependence, drug addition, drug withdrawal, nicotine withdrawal, opiate tolerance, opiate withdrawal, depression, anxiety, a movement disorder, tardive dyskinesia, a cerebral infection that disrupts the blood-brain barrier, meningitis, meningoencephalitis, stroke, hypoglycemia, cardiac arrest, spinal cord trauma, head trauma, perinatal hypoxia, cardiac arrest, hypoglycemic neuronal damage, glaucoma, retinal ischemia, ischemic optic neuropathy, macular degeneration, multiple sclerosis, sequalae of hyperhomocystinemia, convulsion, pain, schizophrenia, muscle spasm, migraine headache, urinary incontinence, emesis, brain edema, tardive dyskinesia, AIDS-induced dementia, ocular damage, retinopathy, a cognitive disorder, and a neuronal injury associated with HIV infection. According to another embodiment the neurological disorder, opthalmological disorder, or combination thereof is selected from the group consisting of epilepsy, Alzheimer's disease, vascular (multi-infarct) dementia, Huntington's disease, Parkinsonism, multiple sclerosis, amyotrophic lateral sclerosis, and minimal cognitive impairment (MCI).

Psoriasis is characterized by hyperkeratosis and thickening of the epidermis as well as by increased vascularity and infiltration of inflammatory cells in the dermis. Psoriasis vulgaris manifests as silvery, scaly, erythematous plaques on typically the scalp, elbows, knees, and buttocks. Guttate psoriasis occurs as tear-drop size lesions. Fumaric acid esters are recognized for the treatment of psoriasis and dimethyl fumarate is approved for the systemic treatment of psoriasis in

Germany (Mrowietz and Asadullah, Trends Mol Med 2005, 11(1), 43-48; and Mrowietz et al, Br J Dermatology 1999, 141, 424-429). Efficacy for treating psoriasis can be determined using animal models and in clinical trials. Contrary to fumaric acid esters, it has been found that PPAR gamma agonists are not advantageous in the treatment of psoriasis (Placebo response in two long-term randomized psoriasis studies that are negative for rosiglitazone. Am J Clin Dermatol. 2007;8(2):93-102). Contrary to this result, it can be found that PPAR gamma agonist provide therapeutic benefit in a combined treatment of psoriasis according to the present invention.

Inflammatory arthritis includes diseases such as rheumatoid arthritis, juvenile rheumatoid arthritis (juvenile idiopathic arthritis), psoriatic arthritis, and ankylosing spondylitis produce joint inflammation. The pathogenesis of immune-mediated inflammatory diseases including inflammatory arthritis is believed to involve TNF and NK-κB signaling pathways (Tracey et al., Pharmacology & Therapeutics 2008, 117, 244-279). Dimethyl fumarate has been shown to inhibit TNF and inflammatory diseases including inflammatory arthritis are believed to involve TNF and NK-κB signaling and therefore may be useful in treating inflammatory arthritis (Lowewe et al., J Immunology 2002, 168, 4781-4787).

Preferably the inventive method of treatment and combinations can be used in the prophylaxis and treatment of neurodegernative diseases, such as multiple sclerosis, clinically isolated syndrome (CIS) leading to multiple sclerosis, Parkinson's disease, Alzheimer's disease, Huntington's disease, dementia, mitochondrial encephalomyopathy and amyotrophic lateral sclerosis (ALS).

Multiple sclerosis (MS) is an inflammatory autoimmune disease of the central nervous system caused by an autoimmune attack against the isolating axonal myelin sheets of the central nervous system. Demyelination leads to the breakdown of conduction and to severe disease with destruction of local axons and irreversible neuronal cell death. The symptoms of MS are highly varied with each individual patient exhibiting a particular pattern of motor, sensible, and sensory disturbances. MS is typified pathologically by multiple inflammatory foci, plaques of demyelination, gliosis, and axonal pathology within the brain and spinal cord, all of which contribute to the clinical manifestations of neurological disability (see e.g., Wingerchuk, Lab Invest 2001, 81, 263-281; and Virley, NeuroRx 2005, 2(4),

638-649). Although the causal events that precipitate MS are not fully understood, evidence implicates an autoimmune etiology together with environmental factors, as well as specific genetic predispositions. Functional impairment, disability, and handicap are expressed as paralysis, sensory and octintive disturbances spasticity, tremor, a lack of coordination, and visual impairment, which impact on the quality of life of the individual. The clinical course of MS can vary from individual to individual, but invariably the disease can be categorized in three forms: relapsing-remitting, secondary progressive, and primary progressive.

Studies support the efficacy of fumaric acid esters for treating MS and have undergone phase II clinical testing (Schimrigk et ah, Eur J Neurology 2006, 13, 604-610; and Wakkee and Thio, Current Opinion Investigational Drugs 2007, 8(11), 955-962). Assessment of MS treatment efficacy in clinical trials can be accomplished using tools such as the Expanded Disability Status Scale and the MS Functional as well as magnetic resonance imaging lesion load, biomarkers, and self-reported quality of life. Animal models of MS shown to be useful to identify and validate potential therapeutics include experimental autoimmune/allergic encephalomyelitis (EAE) rodent models that simulate the clinical and pathological manifestations of MS and nonhuman primate EAE models.

Inflammatory Bowel Disease (Crohn 's Disease, Ulcerative Colitis) Inflammatory bowel disease (IBD) is a group of inflammatory conditions of the large intestine and in some cases, the small intestine that includes Crohn's disease and ulcerative colitis. Crohn's disease, which is characterized by areas of inflammation with areas of normal lining in between, can affect any part of the gastrointestinal tract from the mouth to the anus. The main gastrointestinal symptoms are abdominal pain, diarrhea, constipation, vomiting, weight loss, and/or weight gain. Crohn's disease can also cause skin rashes, arthritis, and inflammation of the eye. Ulcerative colitis is characterized by ulcers or open sores in the large intestine or colon. The main symptom of ulcerative colitis is typically constant diarrhea with mixed blood of gradual onset. Other types of intestinal bowel disease include collagenous colitis, lymphocytic colitis, ischaemic colitis, diversion colitis, Behcet's colitis, and indeterminate colitis.

Asthma is reversible airway obstruction in which the airway occasionally constricts, becomes inflamed, and is lined with an excessive amount of mucus.

Symptoms of asthma include dyspnea, wheezing, chest tightness, and cough. Asthma episodes may be induced by airborne allergens, food allergies, medications, inhaled irritants, physical exercise, respiratory infection, psychological stress, hormonal changes, cold weather, or other factors.

As shown in animal studies (Joshi et ah, US 2007/0027076) fumaric acid esters may be useful in treating pulmonary diseases such as asthma and chronic obstructive pulmonary disorder.

Chronic obstructive pulmonary disease (COPD), also known as chronic obstructive airway disease, is a group of diseases characterized by the pathological limitation of airflow in the airway that is not fully reversible, and includes conditions such as chronic bronchitis, emphysema, as well as other lung disorders such as asbestosis, pneumoconiosis, and pulmonary neoplasms {see, e.g., Barnes, Pharmacological Reviews 2004, 56(4), 515-548). The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lungs to noxious particles and gases. COPD is characterized by a shortness of breath the last for months or years, possibly accompanied by wheezing, and a persistent cough with sputum production. COPD is most often caused by tobacco smoking, although it can also be caused by other airborne irritants such as coal dust, asbestos, urban pollution, or solvents. COPD encompasses chronic obstructive bronchiolitis with fibrosis and obstruction of small airways, and emphysema with enlargement of airspaces and destruction of lung parenchyma, loss of lung elasticity, and closure of small airways.

Neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, Huntington's disease and amyoptrophic lateral sclerosis are characterized by progressive dysfunction and neuronal death.

Parkinson's disease is a slowly progressive degenerative disorder of the nervous system characterized by tremor when muscles are at rest (resting tremor), slowness of voluntary movements, and increased muscle tone (rigidity). In Parkinson's disease, nerve cells in the basal ganglia, e.g., substantia nigra, degenerate, and thereby reduce the production of dopamine and the number of connections between nerve cells in the basal ganglia. As a result, the basal ganglia are unable to smooth muscle movements and coordinate changes in posture as

normal, leading to tremor, incoordination, and slowed, reduced movement (bradykinesia) (Blandini, et ah, MoI. Neurobiol. 1996, 12, 73-94).

Alzheimer's disease is a progressive loss of mental function characterized by degeneration of brain tissue, including loss of nerve cells and the development of senile plaques and neurofibrillary tangles. In Alzheimer's disease, parts of the brain degenerate, destroying nerve cells and reducing the responsiveness of the maintaining neurons to neurotransmitters. Abnormalities in brain tissue consist of senile or neuritic plaques, e.g., clumps of dead nerve cells containing an abnormal, insoluble protein called amyloid, and neurofibrillary tangles, twisted strands of insoluble proteins in the nerve cell.

Huntington's disease is an autosomal dominant neurodegenerative disorder in which specific cell death occurs in the neostriatum and cortex (Martin, N Engl J Med 1999, 340, 1970-80). Onset usually occurs during the fourth or fifth decade of life, with a mean survival at age of onset of 14 to 20 years. Huntington's disease is universally fatal, and there is no effective treatment. Symptoms include a characteristic movement disorder (Huntington's chorea), cognitive dysfunction, and psychiatric symptoms. The disease is caused by a mutation encoding an abnormal expansion of CAG-encoded polyglutamine repeats in the protein, huntingtin.

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder characterized by the progressive and specific loss of motor neurons in the brain, brain stem, and spinal cord (Rowland and Schneider, N Engl J Med 2001, 344, 1688-1700). ALS begins with weakness, often in the hands and less frequently in the feet that generally progresses up an arm or leg. Over time, weakness increases and spasticity develops characterized by muscle twitching and tightening, followed by muscle spasms and possibly tremors. The average age of onset is 55 years, and the average life expectancy after the clinical onset is 4 years. The only recognized treatment for ALS is riluzole, which can extend survival by only about three months.

Myasthenia gravis (MG) is a classic autoimmune disease affecting neuromuscular junctions of striated muscle. Immunization of different animal species with acetylcholine receptor (AChR) and complete Freund's adjuvant (CFA) results in an animal model of MG named experimental autoimmune myasthenia gravis (EAMG).

Alopecia areata is a common disease, but for ethical reasons it seems difficult to perform large-scale studies to elucidate the pathogenesis and to develop new therapeutic approaches in man. It is therefore helpful to develop appropriate animal models. The Dundee experimental bald rat (DEBR) and the C3H/HeJ mouse are well-established animal models for alopecia areata and can be used for the study of genetic aspects, pathogenesis and therapy of the disease (J Dtsch Dermatol Ges. 2004 Apr;2(4):260-73).

A mouse model for diabetic nephropathy can be utilized according to Kidney International 77, 749-750 (May 2010), in order to prove the effect of the combination according to the present invention.

Thus, diseases and conditions for which treatment with the combination of a PPAR gamma agonist and an Nrf2 activator can be useful, include rheumatica, granuloma annulare, lupus, autoimmune carditis, eczema, sarcoidosis, and autoimmune diseases including acute disseminated encephalomyelitis, Addison's disease, alopecia areata, ankylosing spondylitis, antiphospholipid antibody syndrome, autoimmune hemolytic anemia, autoimmune hepatitis, autoimmune inner ear disease, bullous pemphigoid, Behcet's disease, celiac disease, Chagas disease, chronic obstructive pulmonary disease, Crohn's disease, dermatomyositis, diabetes mellitus type I, endometriosis, Goodpasture's syndrome, Graves' disease, Guillain-Barre syndrome, Hashimoto's disease, hidradenitis suppurativea, Kawasaki disease, IgA neuropathy, idiopathic thrombocytopenic purpura, interstitial cystitis, lupus erythematosus, mixed connective tissue disease, morphea, multiple sclerosis, myasthenia gravis, narcolepsy, neuromyotonia, pemphigus vulgaris, pernicious anaemia, psoriasis, psoriatic arthritis, polymyositis, primary biliary cirrhosis, rheumatoid arthritis, schizophrena, scleroderma, Sjogren's syndrome, stiff person syndrome, temporal arteritis, ulcerative colitis, vasculitis, vitiligo, and Wegener's granulomatosis.

**Administration**

The combination of an Nrf2 activator and a PPAR gamma agonist and pharmaceutical compositions thereof may be administered orally or by any other appropriate route, for example, by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (e.g., oral mucosa, rectal, and intestinal

mucosa, etc.). Other suitable routes of administration include, but are not limited to, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, oral, sublingual, intracerebral, intravaginal, transdermal, rectal, inhalation, or topical.

Administration may be systemic or local. Various delivery systems are known, e.g., encapsulation in liposomes, microparticles, microcapsules, capsules, etc.) that may be used to administer a compound and/or pharmaceutical composition.

For systemic administration, a therapeutically effective dose may be estimated initially from in vitro assays. For example, a dose may be formulated in animal models to achieve a beneficial circulating composition concentration range. Initial doses may also be estimated from in vivo data, e.g., animal models, using techniques that are known in the art. Such information may be used to more accurately determine useful doses in humans. One having ordinary skill in the art may optimize administration to humans based on animal data.

The embodiment "PPAR gamma agonist for use in combination with a fumaric acid mono- and/or diester in the treatment of an autoimmune and/or inflammatory disease" relates to a method of use of at least one PPAR gamma agonist in combination with a fumaric acid mono- and/or diester in the treatment of an autoimmune and/or inflammatory disease.

Preferred embodiments of the invention are described in the following:

1. PPAR gamma agonist for use in combination with a fumaric acid mono- and/or diester in the treatment of an autoimmune and/or inflammatory disease.

2. PPAR gamma agonist such as rosiglitazone, for use in combination with a fumaric acid mono- and/or diester according to one or more of the foregoing embodiment and/or embodiment 1, characterized in that the autoimmune and/or inflammatory disease is psoriasis.

3. PPAR gamma agonist for use in combination with a fumaric acid mono- and/or diester according to one or more of the foregoing embodiments and/or embodiment 1, characterized in that the autoimmune and/or inflammatory disease is selected from the group of psoriatic arthritis, multiple sclerosis, inflammatory

bowel disease (IBS), colitis ulcerosa, Crohn's disease, hepatitis, effluvium, allopecia areata, cicatricial alopecia, diabetic nephrophathy, CKD and myasthenia gravis.

4. PPAR gamma agonist for use in combination with a fumaric acid mono- and/or diester, according to the aforementioned embodiments, characterized in that the PPAR gamma agonist is selected from the group of rosiglitazone, pioglitazone, troglitazone and ciglitazone.

5. PPAR gamma agonist for use in combination with a fumaric acid mono- and/or diester, according to the aforementioned embodiments, characterized in that the fumaric acid mono- and/or diester is selected from the group of monomethyl hydrogen fumarate, dimethyl fumarate, monoethyl hydrogen fumarate and diethyl fumarate.

6. A pharmaceutical composition comprising a PPAR gamma agonist and a fumaric acid mono- and/or diester and optionally one or more excipients.

7. A pharmaceutical composition comprising rosiglitazone, pioglitazone, troglitazone or ciglitazone and a fumaric acid mono- and/or diester and optionally one or more excipients.

8. A pharmaceutical composition according to one or more of the foregoing embodiments and/or embodiments 6 or 7, characterized in that the fumaric acid mono- and/or diester is selected from the group of monomethyl hydrogen fumarate, dimethyl fumarate, monoethyl hydrogen fumarate, and diethyl fumarate.

9. A solid oral dosage form comprising a PPAR gamma agonist and a fumaric acid mono- and/or diester.

10. A solid oral dosage form comprising rosiglitazone, pioglitazone, troglitazone or ciglitazone as a PPAR gamma agonist and a fumaric acid mono- and/or diester.

11. A solid oral dosage form according to one or more of the foregoing embodiments and/or embodiments 9 or 10, characterized in that the fumaric acid mono- and/or diester is selected from the group of monomethyl hydrogen fumarate, dimethyl fumarate, monoethyl hydrogen fumarate, and diethyl fumarate.

12. A solid oral dosage form according to one or more of the foregoing embodiments and/or embodiments 9 to 10, characterized in that the PPAR gamma agonist and the fumaric acid mono- and/or diester are each contained in the dosage form in a separate composition optionally containing one or more excipients.

13. Kit of parts comprising a) a PPAR gamma agonist and b) a fumaric acid mono- and/or diester and optionally c) instructions for a dosing regime.

14. Kit of parts comprising a) rosiglitazone, pioglitazone, troglitazone or ciglitazone b) a fumaric acid mono- and/or diester and optionally c) instructions for a dosing regime.

15. Kit of parts according to one or more of the foregoing embodiments and/or embodiments 13 or 14, characterized in that the fumaric acid mono- and/or diester is selected from the group of monomethyl hydrogen fumarate, dimethyl fumarate, monoethyl hydrogen fumarate, and diethyl fumarate.

16. PPAR gamma agonist for use in combination with an Nrf2 activator selected from the group of monoalkyl hydrogen fumarate, dialkyl fumarate and bardoxolone alkyl in the treatment of multiple sclerosis.

17. PPAR gamma agonist for use in combination with an Nrf2 activator according to the foregoing embodiments, characterized in that multiple sclerosis includes relapsing-remitting (RR), secondary progressive (SP), primary progressive (PP) and progressive relapsing (PR) multiple sclerosis and the first demyelinating event suggestive of MS or clinically isolated syndrome (CIS).

18. PPAR gamma agonist for use in combination with an Nrf2 activator according to the foregoing embodiments, characterized in that the PPAR gamma agonist is a glitazone.

19. PPAR gamma agonist for use in combination with an Nrf2 activator according to the foregoing embodiments, characterized in that the PPAR gamma agonist is a glitazone selected from the group of pioglitazone and rosiglitazone.

20. PPAR gamma agonist for use in combination with an Nrf2 activator according to the foregoing embodiments, characterized in that Nrf2 activator selected from the group of monomethyl hydrogen fumarate, dimethyl fumarate and bardoxolone methyl.

21. PPAR gamma agonist for use in combination with an Nrf2 activator according to the foregoing embodiments, characterized in that ratios between rosiglitazone and dimethyl fumarate are selected from 1/20 to 1/400 (w/w, rosiglitazone/dimethyl fumarate).

22. PPAR gamma agonist for use in combination with an Nrf2 activator according to the foregoing embodiments, characterized in that ratios between pioglitazone and dimethyl fumarate are selected from 1/3 to 1/60 (w/w, pioglitazone/dimethyl fumarate).

23. PPAR gamma agonist for use in combination with an Nrf2 activator according to the foregoing embodiments, characterized in that ratios between rosiglitazone and bardoxolone methyl are selected from 1/1 to 1/100 (w/w, rosiglitazone/bardoxolone methyl).

24. PPAR gamma agonist for use in combination with an Nrf2 activator according to the foregoing embodiments, characterized in that bardoxolone methyl is employed in amorphic form and ratios between rosiglitazone and bardoxolone methyl are from 1/1 to 1/20 (w/w, rosiglitazone/bardoxolone methyl).

25. PPAR gamma agonist for use in combination with an Nrf2 activator according to the foregoing embodiments, characterized in that ratios between pioglitazone and bardoxolone methyl are selected from 1/0.1 to 1/20 (w/w, pioglitazone/bardoxolone methyl).

26. PPAR gamma agonist for use in combination with an Nrf2 activator according to the foregoing embodiments, characterized in that bardoxolone methyl is employed in amorphic form and ratios between pioglitazone and bardoxolone methyl are from 1/0.1 to 1/3 (w/w, pioglitazone/bardoxolone methyl).

27. A pharmaceutical composition comprising a PPAR gamma agonist and an Nrf2 activator selected from the group of monoalkyl hydrogen fumarate, dialkyl fumarate and bardoxolone alkyl and optionally one or more excipients.

28. A pharmaceutical composition according to one or more of the foregoing embodiments and/or embodiment 27, characterized in that the PPAR gamma agonist is a glitazone.

29. A pharmaceutical composition according to one or more of the foregoing embodiments and/or embodiment 28, characterized in that the glitazone is selected from the group of pioglitazone and rosiglitazone.

30. A pharmaceutical composition according to one or more of the foregoing embodiments and/or embodiments 28 to 30, characterized in that Nrf2 activator selected from the group of monomethyl hydrogen fumarate, dimethyl fumarate and bardoxolone methyl.

31. A pharmaceutical composition according to one or more of the foregoing embodiments and/or embodiments 28 to 30, characterized in that ratios between rosiglitazone and dimethyl fumarate are selected from 1/20 to 1/400 (w/w, rosiglitazone/dimethyl fumarate).

32. A pharmaceutical composition according to one or more of the foregoing embodiments and/or embodiments 28 to 30, characterized in that ratios between pioglitazone and dimethyl fumarate are selected from 1/3 to 1/60 (w/w, pioglitazone/dimethyl fumarate).

33. A pharmaceutical composition according to one or more of the foregoing embodiments and/or embodiments 28 to 30, characterized in that ratios between rosiglitazone and bardoxolone methyl are selected from 1/1 to 1/100 (w/w, rosiglitazone/bardoxolone methyl).

34. A pharmaceutical composition according to one or more of the foregoing embodiments and/or embodiments 28 to 30, characterized in that bardoxolone methyl is employed in amorphic form and ratios between rosiglitazone and bardoxolone methyl are from 1/1 to 1/20 (w/w, rosiglitazone/bardoxolone methyl).

35. A pharmaceutical composition according to one or more of the foregoing embodiments and/or embodiments 28 to 30, characterized in that ratios between pioglitazone and bardoxolone methyl are selected from 1/0.1 to 1/20 (w/w, pioglitazone/bardoxolone methyl).

36. A pharmaceutical composition according to one or more of the foregoing embodiments and/or embodiments 28 to 30, characterized in bardoxolone methyl is employed in amorphic form and ratios between pioglitazone and bardoxolone methyl are from 1/0.1 to 1/3 (w/w, pioglitazone/bardoxolone methyl).

37. A solid oral dosage form comprising the pharmaceutical composition according to one or more of the foregoing embodiments and/or embodiments 27 to 36.

38. A solid oral dosage form comprising a PPAR gamma agonist and an Nrf2 activator selected from the group of monoalkyl hydrogen fumarate, dialkyl fumarate and bardoxolone alkyl and optionally one or more excipients, wherein the

PPAR gamma agonist and the Nrf2 activator are each contained in a separate pharmaceutical formulation.

39. A solid oral dosage form according to one or more of the foregoing embodiments and/or embodiment 38, wherein the PPAR gamma agonist is a glitazone and the Nrf2 activator is selected from the group of of monomethyl hydrogen fumarate, dimethyl fumarate and bardoxolone methyl.

40. A solid oral dosage form according to the aforementioned embodiments, wherein the Nrf2 activator is bardoxolone methyl contained in an amorphous form.

41. A solid oral dosage form according to the aforementioned embodiments, wherein the Nrf2 activator is bardoxolone methyl contained in an amorphous dispersion formulation.

42. A solid oral dosage form according to the aforementioned embodiments, wherein the Nrf2 activator is bardoxolone methyl contained in an amorphous dispersion formulation obtained by spray drying or freeze drying.

43. A solid oral dosage form according to the aforementioned embodiments, wherein the Nrf2 activator is bardoxolone methyl contained in an amorphous dispersion formulation with methacrylic acid copolymer Type C, USP.

44. A solid oral dosage form according to the aforementioned embodiments, wherein the Nrf2 activator is bardoxolone methyl contained in an amorphous dispersion formulation with methacrylic acid copolymer Type C, USP in a weight ratio of 4/6.

45. A solid oral dosage form according to the aforementioned embodiments, wherein the Nrf2 activator is bardoxolone methyl contained in an amorphous dispersion formulation comprising at least one hydrophilic binder.

46. A solid oral dosage form according to the aforementioned embodiments, wherein the hydrophilic binder is employed in an amount of between about 1 and about 40% (weight % of the total pharmaceutical composition used for the dosage form), preferably between about 2 to about 20%, more preferably between about 4 and about 10% even more preferably between about 5 and about 7.5% and most preferred between about 7 and 7.5%, such as about 7%.

47. A solid oral dosage form according to the aforementioned embodiments, wherein the hydrophilic binder is hydroxypropylmethylcellulose.

48. A solid oral dosage form according to the aforementioned embodiments, wherein the Nrf2 activator is bardoxolone methyl contained in an amorphous dispersion formulation and wherein the dosage form also contains a surface active agent, such as sodium lauryl sulfate, preferably in an amount of about 3% of the total weight of the dosage form.

49. Kit of parts comprising a) a PPAR gamma agonist and b) an Nrf2 activator selected from the group of monoalkyl hydrogen fumarate, dialkyl fumarate and bardoxolone alkyl and optionally c) instructions for a dosing regime.

50. Kit of parts comprising a) a PPAR agonist and b) an Nrf2 activator selected from the group of monoalkyl hydrogen fumarate, dialkyl fumarate and bardoxolone alkyl and optionally c) instructions for a dosing regime.

51. Kit of parts according to the foregoing embodiment, characterized in that the PPAR gamma agonist is rosiglitazone or pioglitazone.

52. Kit of parts according to the foregoing embodiment, characterized in that the Nrf2 activator is dimethyl fumarate or bardoxolone methyl.

53. PPAR gamma agonist for use in combination with an Nrf2 activator for the treatment of multiple sclerosis according to the foregoing embodiments, wherein said PPAR agonist is administered to a patient simultaneously with or up

to 2 days before or after an Nrf2 activator, such as those selected from the group of monoalkyl hydrogen fumarate, dialkyl fumarate and bardoxolone alkyl, is administered to said patient.

54. PPAR gamma agonist for use in combination with an Nrf2 activator for the treatment of multiple sclerosis according to the foregoing embodiments, wherein said PPAR agonist is administered once or twice daily.

55. PPAR gamma agonist for use in combination with an Nrf2 activator for the treatment of multiple sclerosis according to the foregoing embodiments, wherein said Nrf2 activator is administered once or twice daily.

56. PPAR gamma agonist for use in combination with an Nrf2 activator in the treatment of autoimmune and/or inflammatory diseases other than psoriasis.

57. PPAR gamma agonist, preferably other than pioglitazone, for use in combination with an Nrf2 activator belonging to a different chemical class, in the treatment of autoimmune and/or inflammatory diseases, such as multiple sclerosis, psoriasis or chronic kidney disease.

58. PPAR gamma agonist, preferably other than pioglitazone, for use according to the aforementioned embodiment, wherein the Nrf2 activator having no significant PPAR gamma agonistic effect.

59. PPAR gamma agonist, preferably other than pioglitazone, having no significant activating effect on Nrf2, for use in combination with an Nrf2 activator having no significant PPAR gamma agonistic effect, in the treatment of autoimmune and/or inflammatory diseases, such as multiple sclerosis, psoriasis or chronic kidney disease.

60. PPAR gamma agonist, preferably other than pioglitazone, for use in combination with an Nrf2 activator belonging to different chemical class, wherein the Nrf2 activator is other than bardoxolone methyl and its derivatives, in the

treatment of autoimmune and/or inflammatory diseases, such as multiple sclerosis, psoriasis or chronic kidney disease.

61. Composition comprising a PPAR gamma agonist and an Nrf2 activator belonging to a different chemical class, for use in the treatment of autoimmune and/or inflammatory diseases, such as multiple sclerosis, psoriasis or chronic kidney disease.

62. Composition according to the aforementioned embodiment, comprising a PPAR gamma agonist having no significant activating effect on Nrf2, and an Nrf2 activator having no significant PPAR gamma agonistic effect, for use in the treatment of autoimmune and/or inflammatory diseases, such as multiple sclerosis, psoriasis or chronic kidney disease.

63. Composition comprising a PPAR gamma agonist, such as pioglitazone and an Nrf2 activator.

64. Composition comprising a PPAR gamma agonist, such as pioglitazone and an Nrf2 activator having no significant PPAR gamma agonistic effect.

65. Composition comprising pioglitazone and an Nrf2 activator having no significant PPAR gamma agonistic effect, for use in the treatment of psoriasis and other autoimmune and/or inflammatory diseases, such as multiple sclerosis, psoriasis or chronic kidney disease.

66. PPAR gamma agonist for use in combination with an Nrf2 activator having no significant PPAR gamma agonistic effect, in the treatment of multiple sclerosis.

67. PPAR gamma agonist for use in combination with an Nrf2 activator other than bardoxolone methyl, in the treatment of CKD or multiple sclerosis.

68. PPAR gamma agonist for use in combination with an Nrf2 activator according to the foregoing embodiment, characterized in that multiple sclerosis includes relapsing-remitting (RR), secondary progressive (SP), primary progressive (PP) and progressive relapsing (PR) multiple sclerosis and the first demyelinating event suggestive of MS or clinically isolated syndrome (CIS).

69. PPAR gamma agonist for use in combination with an Nrf2 activator according to the foregoing embodiments, characterized in that the PPAR gamma agonist is a glitazone.

70. PPAR gamma agonist for use in combination with an Nrf2 activator according to any of the foregoing embodiments, characterized in that the PPAR gamma agonist is a glitazone selected from the group of pioglitazone and rosiglitazone.

71. PPAR gamma agonist for use in combination with an Nrf2 activator according to any of the foregoing embodiments, characterized in that the Nrf2 activator is selected chemical compounds belonging to the group of Michael reaction acceptors, phenols, diphenols, chalcones, isothiocyanates, thiocarbamates, quinones, naphtoquinones and 1,2 dithiole-3-thiones, wherein one or more, preferably 1, 2, 3, 4 , 5 , 6 or 7 H-atoms may be substituted by linear or branched alkyl and perfluoroalkyl, such as methyl, ethyl, trifluoromethyl, halogen such as Br, Cl F or I, hydroxy, alkoxy and perfluoroalkoxy, such as methoxy, ethoxy, trifluoromethoxy, cyano and nitro, which chemical compounds have not more than one or two 5- or 6-membered carbocyclic rings or 5- or 6-membered heterocyclic rings having 1, 2 or 3 N-, O or S-atoms as ring atoms which rings may be fused to each other or preferably no or only one carbocyclic or heterocyclic ring. Compositions containing these Nrf2 activators are preferred.

Preferred Nrf2 activators for use in combination according to the invention and particularly according to embodiment 71 above, are chemical compounds, containing less than 35, preferably less than 30, more preferably less than 25 and most preferably less than 20 or even less than 15 or less than 10 carbon atoms and/or having a molecular weight of less than 400, preferably less than 300 and

most preferably less than 200 g/mol or less than 170 g/mol and/or having no significant PPAR gamma agonistic activity. Compositions containing these Nrf2 activators are preferred.

72. PPAR gamma agonist for use in combination with an Nrf2 activator and compositions according to any of the foregoing embodiments, characterized in that the Nrf2 activator is selected from 2-naphthoquinone, cynnamic aldehyde, caffeic acid and its esters, curcumin, reservatrol, artesunate, tert-butylhydroquinone, vitamins K1, K2 and K3 and the respective quinone or hydroquinone forms of the aforementioned quinone and hydroquinone derivatives, fumaric acid esters, i.e. fumaric acid mono- and/or diester which is preferably selected from the group of monoalkyl hydrogen fumarate and dialkyl fumarate, such as monomethyl hydrogen fumarate, dimethyl fumarate, monoethyl hydrogen fumarate, and diethyl fumarate, isothiocyanate such as sulforaphane, 1,2-dithiole-3-thione such as oltipraz, 3,5-di-tert-butyl-4-hydroxytoluene, 3-hydroxycoumarin, 4-hydroxynonenal, 4-oxononenal, malondialdehyde, (E)-2-hexenal, capsaicin, allicin, allylisothiocyanate, 6-methylthiohexyl isothiocyanate, 7-methylthioheptyl isothiocyanate, sulforaphane, 8-methylthiooctyl isothiocyanate, 8-iso prostaglandin A2, alkyl pyruvate, such as methyl and ethyl pyruvate, diethyl or dimethyl oxaloproprionate, 2-acetamidoacrylate, and methyl or ethyl-2-acetamidoacrylate, and a pharmacologically active stereoisomer or derivative of the aforementioned agents.

73. PPAR gamma agonist for use in combination with an Nrf2 activator and compositons according to any the foregoing embodiments, characterized in that the nrf2 activator is selected from monomethyl hydrogen fumarate, dimethyl fumarate, oltipraz, 1,2-naphthoquinone, tert-butylhydroquinone, methyl or ethyl pyruvate, 3,5-di-tert-butyl-4-hydroxytoluene, diethyl and dimethyl oxaloproprionate.

74. Kit of parts comprising a) a PPAR gamma agonist other than pioglitazone and b) an Nrf2 activator selected from the group of monoalkyl hydrogen fumarate, dialkyl fumarate and bardoxolone alkyl and optionally c) instructions for a dosing regime.

75. Kit of parts comprising a) a PPAR gamma agonist having no significant activating effect on Nrf2, b) an Nrf2 activator selected from the group of monoalkyl hydrogen fumarate, dialkyl fumarate and bardoxolone and optionally c) instructions for a dosing regime.

76. Kit of parts comprising a) a PPAR gamma agonist having no significant activating effect on Nrf2, b) an Nrf2 activator having no significant PPAR gamma agonistic effect and optionally c) instructions for a dosing regime.

77. Kit of parts comprising a) a PPAR gamma agonist having no significant activating effect on Nrf2, b) an Nrf2 activator selected chemical compounds belonging to the group of Michael reaction acceptors, phenols, diphenols, chalcones, isothiocyanates, thiocarbamates, quinones, naphtoquinones and 1,2 dithiole-3-thiones, wherein one or more, preferably 1, 2, 3, 4, 5, 6 or 7 H-atoms may be substituted by linear or branched alkyl and perfluoroalkyl, such as methyl, ethyl, trifluoromethyl, halogen such as Br, Cl F or I, hydroxy, alkoxy and perfluoroalkoxy, such as methoxy, ethoxy, trifluoromethoxy, cyano and nitro, which chemical compounds have not more than one or two 5- or 6-membered carbocyclic rings or 5- or 6-membered heterocyclic rings having 1, 2 or 3 N-, O or S-atoms as ring atoms which rings may be fused to each other or preferably no or only one carbocyclic or heterocyclic ring and optionally c) instructions for a dosing regime.

78. Composition comprising a) a PPAR gamma agonist, preferably other than pioglitazone and b) an Nrf2 activator selected from the group of monoalkyl hydrogen fumarate, dialkyl fumarate and bardoxolone alkyl.

79. Composition comprising a) a PPAR gamma agonist having no significant activating effect on Nrf2, b) an Nrf2 activator selected from the group of monoalkyl hydrogen fumarate, dialkyl fumarate and bardoxolone.

80. Composition comprising a) a PPAR gamma agonist having no significant activating effect on Nrf2, b) an Nrf2 activator having no significant PPAR gamma agonistic effect.

81. Composition comprising a) a PPAR gamma agonist having no significant activating effect on Nrf2, b) an Nrf2 activator selected chemical compounds belonging to the group of Michael reaction acceptors, phenols, diphenols, chalcones, isothiocyanates, thiocarbamates, quinones, naphtoquinones and 1,2 dithiole-3-thiones, wherein one or more, preferably 1, 2, 3, 4, 5, 6 or 7 H-atoms may be substituted by linear or branched alkyl and perfluoroalkyl, such as methyl, ethyl, trifluoromethyl, halogen such as Br, Cl F or I, hydroxy, alkoxy and perfluoroalkoxy, such as methoxy, ethoxy, trifluoromethoxy, cyano and nitro, which chemical compounds have not more than one or two 5- or 6-membered carbocyclic rings or 5- or 6-membered heterocyclic rings having 1, 2 or 3 N-, O or S-atoms as ring atoms which rings may be fused to each other or preferably no or only one carbocyclic or heterocyclic ring.

82. Method of treating or preventing cancer, preferably heamatological cancer such as leukemia such as acute myeloid leukaemia (AML), comprising administration of a PPAR gamma agonist and an Nrf2 activator to a patient in need thereof, wherein said Nrf2 activator is capable of provoking or inducing a stimulated and/or increased nuclear translocation of Nrf2 protein and is

a) selected from the group of Michael reaction acceptors, phenols, diphenols, chalcones, isothiocyanates, thiocarbamates, quinones, naphtoquinones and 1,2 dithiole-3-thiones; and

b) contains less than 35 carbon atoms; and/or

c) has a molecular weight of less than 600 g/mol; and/or

d) contains no or not more than one or two fused or monocyclic 5- or 6-membered carbocyclic or heterocyclic rings, having 1, 2 or 3 ring atoms selected from N, O or S.

In one embodiment of the foregoing method, the Nrf2 activator is preferably other than arsenic trioxide. Preferably, the Nrf2 activator is dimethyl fumarate, monomethyl hydrogen fumarate or bardoloxolone methyl.

83. Method of treating or preventing diabetes such as type II diabetes and its complications, such as arthritis, chronic kidney disease and syndrome x, comprising administration of a PPAR gamma agonist and an Nrf2 activator to a patient in need thereof, wherein said Nrf2 activator is capable of provoking or inducing a stimulated and/or increased nuclear translocation of Nrf2 protein and is

a) selected from the group of Michael reaction acceptors, phenols, diphenols, chalcones, isothiocyanates, thiocarbamates, quinones, naphtoquinones and 1,2 dithiole-3-thiones; and

b) contains less than 35 carbon atoms; and/or

c) has a molecular weight of less than 600 g/mol; and/or

d) contains no or not more than one or two fused or monocyclic 5- or 6-membered carbocyclic or heterocyclic rings, having 1, 2 or 3 ring atoms selected from N, O or S.

In one embodiment of the foregoing method, the Nrf2 activator is preferably other than bardoxolone methyl and/or a corticosteroide. Preferably, the Nrf2 activator is dimethyl fumarate or monomethyl hydrogen fumarate.

84. Method of treating or preventing cardiovascular diseases, comprising administration of a PPAR gamma agonist and an Nrf2 activator to a patient in need thereof, wherein said Nrf2 activator is capable of provoking or inducing a stimulated and/or increased nuclear translocation of Nrf2 protein and is

a) selected from the group of Michael reaction acceptors, phenols, diphenols, chalcones, isothiocyanates, thiocarbamates, quinones, naphtoquinones and 1,2 dithiole-3-thiones; and

b) contains less than 35 carbon atoms; and/or

c) has a molecular weight of less than 600 g/mol; and/or

d) contains no or not more than one or two fused or monocyclic 5- or 6-membered carbocyclic or heterocyclic rings, having 1, 2 or 3 ring atoms selected from N, O or S.

85. Method of treating or preventing respiratory diseases, such as asthma, chronic obstructive pulmonary disorder and fibrosis, comprising administration of a

PPAR gamma agonist and an Nrf2 activator to a patient in need thereof, wherein said Nrf2 activator is capable of provoking or inducing a stimulated and/or increased nuclear translocation of Nrf2 protein and is

a) selected from the group of Michael reaction acceptors, phenols, diphenols, chalcones, isothiocyanates, thiocarbamates, quinones, naphtoquinones and 1,2 dithiole-3-thiones; and

b) contains less than 35 carbon atoms; and/or

c) has a molecular weight of less than 600 g/mol; and/or

d) contains no or not more than one or two fused or monocyclic 5- or 6-membered carbocyclic or heterocyclic rings, having 1, 2 or 3 ring atoms selected from N, O or S.

In one embodiment of the foregoing method, the Nrf2 activator is preferably other than a corticosteroide. Preferably, the Nrf2 activator is dimethyl fumarate, monomethyl hydrogen fumarate or bardoloxolone methyl.

86. Method of treating or preventing graft rejection and/or necrosis, comprising administration of a PPAR gamma agonist and an Nrf2 activator to a patient in need thereof, wherein said Nrf2 activator is capable of provoking or inducing a stimulated and/or increased nuclear translocation of Nrf2 protein and is

a) selected from the group of Michael reaction acceptors, phenols, diphenols, chalcones, isothiocyanates, thiocarbamates, quinones, naphtoquinones and 1,2 dithiole-3-thiones; and

b) contains less than 35 carbon atoms; and/or

c) has a molecular weight of less than 600 g/mol; and/or

d) contains no or not more than one or two fused or monocyclic 5- or 6-membered carbocyclic or heterocyclic rings, having 1, 2 or 3 ring atoms selected from N, O or S.

87. Method of treating or preventing psoriasis, comprising administration of a PPAR agonist and an Nrf2 activator to a patient in need thereof, wherein said Nrf2 activator is capable of provoking or inducing a stimulated and/or increased nuclear translocation of Nrf2 protein and is

a) selected from the group of Michael reaction acceptors, phenols, diphenols, chalcones, isothiocyanates, thiocarbamates, quinones, naphtoquinones and 1,2 dithiole-3-thiones; and

b) contains less than 35 carbon atoms; and/or

c) has a molecular weight of less than 600 g/mol; and/or

d) contains no or not more than one or two fused or monocyclic 5- or 6-membered carbocyclic or heterocyclic rings, having 1, 2 or 3 ring atoms selected from N, O or S.

In one embodiment of the foregoing method, no therapeutic amounts of hydroxurea are co-administrated to the patient. In another embodiment of the foregoing method, no therapeutic amounts of monomethyl hydrogen fumarate are co-administrated to the patient. In another embodiment of the foregoing method, no therapeutic amounts of dimethyl fumarate are co-administrated to the patient. In another embodiment of the foregoing method, the Nrf2 activator is bardoloxolone methyl. In another embodiment of the foregoing method, the PPAR agonist is other than pioglitazone, such as rosiglitazone.

88. Method of treating or preventing autoimmune and/or inflammatory diseases other than psoriasis, comprising administration of a PPAR agonist and dialkyl fumarate and/or monoalkyl hydrogen fumarate to a patient in need thereof.

89. Method of treating or preventing autoimmune and/or inflammatory diseases other than chronic kidney disease, comprising administration of a PPAR agonist and bardoxolone methyl to a patient in need thereof.

90. Method of treating or preventing cardiovascular diseases, respiratory disorders, graft rejection, cancer and diabetes and its complications, comprising administration of a PPAR agonist and dimethyl fumarate and/or monomethyl hydrogen fumarate to a patient in need thereof.

91. Method of treating or preventing autoimmune/inflammatory and cardiovascular diseases, respiratory disorders, graft rejection, cancer and diabetes and its complications, comprising administration of a PPAR agonist other than

pioglitazone, and dimethyl fumarate and/or monomethyl hydrogen fumarate to a patient in need thereof.

92. PPAR gamma agonist for use in combination with an Nrf2 activator in the treatment of an autoimmune and/or inflammatory disease.

93. PPAR gamma agonist for use in combination with an Nrf2 activator according to one or more of the foregoing embodiments and/or embodiment 92, characterized in that the Nrf2 activator is dimethyl fumarate.

94. PPAR gamma agonist for use in combination with an Nrf2 activator according to one or more of the foregoing embodiments and/or embodiment 92, characterized in that the Nrf2 activator is bardoxolone methyl.

95. PPAR gamma agonist for use in combination with an Nrf2 activator according to one of the foregoing embodiments, characterized in that the PPAR gamma agonist is pioglitazone.

96. PPAR gamma agonist for use in combination with an Nrf2 activator according to one of the foregoing embodiments, characterized in that the PPAR gamma agonist is selected from the group of rosiglitazone, troglitazone and ciglitazone.

97. PPAR gamma agonist for use in combination with an Nrf2 activator according to one of the foregoing embodiments, characterized in that the autoimmune and/or inflammatory disease is psoriasis.

98. PPAR gamma agonist for use in combination with an Nrf2 activator according to one of the foregoing embodiments, characterized in that the autoimmune and/or inflammatory disease is multiple sclerosis.

99. PPAR gamma agonist for use in combination with an Nrf2 activator according to one of the foregoing embodiments, characterized in that the autoimmune and/or inflammatory disease is colitis ulcerosa.

100. PPAR gamma agonist for use in combination with an Nrf2 activator according to one of the foregoing embodiments, characterized in that the autoimmune and/or inflammatory disease is Crohn's disease.

101. PPAR gamma agonist for use in combination with an Nrf2 activator according to one of the foregoing embodiments, characterized in that the autoimmune and/or inflammatory disease is allopecia areata or cicatricial alopecia.

102. PPAR gamma agonist for use in combination with an Nrf2 activator according to one of the foregoing embodiments, characterized in that the autoimmune and/or inflammatory disease is diabetic nephrophathy.

103. PPAR gamma agonist for use in combination with an Nrf2 activator according to one of the foregoing embodiments, characterized in that the autoimmune and/or inflammatory disease is myasthenia gravis.

104. A pharmaceutical composition comprising pioglitazone, dimethyl fumarate and optionally one or more excipients.

105. A pharmaceutical composition comprising dimethyl fumarate and a PPAR gamma agonist selected from rosiglitazone, troglitazone and ciglitazone, and optionally one or more excipients.

106. A pharmaceutical composition comprising bardoxolone methyl and a PPAR gamma agonist selected from pioglitazone, rosiglitazone, troglitazone and ciglitazone, and optionally one or more excipients.

107. Method of treating or preventing neurodegenerative diseases, comprising administration of a PPAR gamma agonist selected from the group of

glitazones and a fumaric acid monoalkyl and/or dialkyl ester to a patient in need thereof.

108. Method according to one or more of the foregoing embodiments and/or embodiment 107, wherein the fumaric acid dialkyl ester is selected from dimethyl fumarate and diethyl fumarate and the fumaric acid monoalkyl ester is selected from monomethyl hydrogen fumarate and monoethyl hydrogen fumarate.

109. Method according to one or more of the foregoing embodiments and/or embodiment 107 or 108, wherein the PPAR gamma agonist glitazone is selected from pioglitazone and rosiglitazone.

110. Method according to one or more of the foregoing embodiments and/or embodiment 107, 108 or 109, wherein the neurodegenerative disease is multiple sclerosis.

111. A pharmaceutical composition comprising a PPAR gamma agonist selected from the group of glitazones and a fumaric acid monoalkyl and/or dialkyl ester and optionally one or more excipients.

112. A pharmaceutical composition according to one or more of the foregoing embodiments and/or embodiment 111, wherein the fumaric acid dialkyl ester is selected from dimethyl fumarate and diethyl fumarate and the fumaric acid monoalkyl ester is selected from monomethyl hydrogen fumarate and monoethyl hydrogen fumarate.

113. A pharmaceutical composition according to one or more of the foregoing embodiments and/or embodiment 111 or 112, wherein the PPAR gamma agonist glitazone is selected from pioglitazone and rosiglitazone.

114. Method of treating or preventing neurodegenerative diseases, comprising administration of a pharmaceutical composition according to one or

more of the foregoing embodiments and/or embodiments 111, 112 or 113 to a patient in need thereof.

115. Method according to one or more of the foregoing embodiments and/or embodiment 114, wherein the neurodegenerative disease is multiple sclerosis.

116. A solid oral dosage form comprising a PPAR gamma agonist selected from the group of glitazones and a fumaric acid monoalkyl and/or dialkyl ester and optionally one or more excipients.

117. A solid oral dosage form according to one or more of the foregoing embodiments and/or embodiment 116, wherein the fumaric acid dialkyl ester is selected from dimethyl fumarate and diethyl fumarate and the fumaric acid monoalkyl ester is selected from monomethyl hydrogen fumarate and monoethyl hydrogen fumarate.

118. A solid oral dosage form according to one or more of the foregoing embodiments and/or embodiment 116 or 117, wherein the PPAR gamma agonist glitazone is selected from pioglitazone and rosiglitazone.

119. Method of treating or preventing neurodegenerative diseases, comprising oral administration of a solid oral dosage form according to one or more of the foregoing embodiments and/or embodiments 116, 117 or 118 to a patient in need thereof.

120. Method according to one or more of the foregoing embodiments and/or embodiment 119, wherein the neurodegenerative disease is multiple sclerosis.

121. Kit of parts comprising a) a PPAR gamma agonist selected from the group of glitazones and b) a fumaric acid monoalkyl and/or dialkyl ester and optionally c) instructions for a dosage regime.

122. Kit of parts according to one or more of the foregoing embodiments and/or embodiment 121, wherein the fumaric acid dialkyl ester is selected from dimethyl fumarate and diethyl fumarate and the fumaric acid monoalkyl ester is selected from monomethyl hydrogen fumarate and monoethyl hydrogen fumarate.

123. Kit of parts according to one or more of the foregoing embodiments and/or embodiment 121 or 122, wherein the PPAR gamma agonist glitazone is selected from pioglitazone and rosiglitazone.

124. A method of treatment of an autoimmune and/or inflammatory disorder comprising administration of a combination of a PPAR gamma agonist selected from the group of glitazones and a) an isolated Nrf2 activator, selected from the group of fumaric acid esters, bardoxolone methyl (methyl 2-cyano-3,12-dioxooleana-1,9(11)dien-28-oate, CDDO-Me, RTA 402), ethyl 2-cyano-3,12-dioxooleana-1,9(11)dien-28-oate, 2-cyano-3,12-dioxooleana-1,9(11)dien-28-oic acid (CDDO), 1[2-Cyano-3,12-dioxooleana-1,9(11)-dien-28-oyl]imidazole (CDDO-Im), 2-cyano-N-methyl-3,12-dioxooleana-1,9(11)-dien-28 amide (CDDO-methyl amide, CDDO-MA), [(±)-(4bS,8aR,10aS)-10a-ethynyl-4b,8,8-trimethyl-3,7-dioxo-3,4b,7,8,8a,9,10,10a-octahydrophenanthrene-2,6-dicarbonitrile] (TBE-31), 2-cyano-3,12-dioxooleana-1,9(11)-dien-28-onitrile (TP-225), 3-tert-butyl-4-hydroxyanisole, 2-tert-butyl-4-hydroxyanisole (BHA), tert-butylquinone (tBQ), tert-butylhydroquinone (tBHQ), 3,5-di-tert-butyl-4-hydroxytoluene (BHT), 2,6-Di-tert-butyl-4-methylene-2,5-cyclohexadien-1-one (2,6-Di-tert-butylquinone methide, BHT-quinone methide), ethoxyquin, gallic acid esters, auranofin, curcumin, reservatrol, menadione, cinnamic aldehyde, cinnamic acid esters, caffeic acid esters, cafestol, kahweol, lycopene, carnosol, sulforaphane, oltipraz, 5-(4-methoxy-phenyl)-1,2-dithiole-3-thione (ADT), sulfasalazine, 5-aminosalicylic acid (mesalamine), 5-amino-2-hydroxy-benzoic acid 4-(5-thioxo-5H-[1,2]dithiol-3-yl)-phenyl ester (ATB-429), allicin, allylisothiocyanate, zerumbone, phenethyl isothiocyanate, benzyl isothiocyanate, 6-methylsulfinylhexyl isothiocyanate as well as alkyl and alkanoyl esters, alkyl ethers, stereoisomers, tautomers and salts of the aforementioned agents, or b) a pharmaceutical composition comprising said isolated Nrf2 activator,

provided that

if the autoimmune and/or inflammatory disorder is psoriasis and the PPAR agonist is pioglitazone and the Nrf2 activator is a fumaric acid ester, the treatment is not combined with hydroxyurea.

125. A method of treatment of an autoimmune and/or inflammatory disorder comprising administration of a combination of a PPAR gamma agonist selected from the group of glitazones and a) an isolated Nrf2 activator, selected from the group of fumaric acid esters, 3-tert-butyl-4-hydroxyanisole, 2-tert-butyl-4-hydroxyanisole (BHA), tert-butylquinone (tBQ), tert-butylhydroquinone (tBHQ), 3,5-di-tert-butyl-4-hydroxytoluene (BHT), 2,6-Di-tert-butyl-4-methylene-2,5-cyclohexadien-1-one (2,6-Di-tert-butylquinone methide, BHT-quinone methide), ethoxyquin, gallic acid esters, auranofin, curcumin, reservatrol, menadione, cinnamic aldehyde, cinnamic acid esters, caffeic acid esters, cafestol, kahweol, lycopene, carnosol, sulforaphane, oltipraz, 5-(4-methoxy-phenyl)-1,2-dithiole-3-thione (ADT), sulfasalazine, 5-aminosalicylic acid (mesalamine), 5-amino-2-hydroxy-benzoic acid 4-(5-thioxo-5H-[1,2]dithiol-3-yl)-phenyl ester (ATB-429), allicin, allylisothiocyanate, zerumbone, phenethyl isothiocyanate, benzyl isothiocyanate, 6-methylsulfinylhexyl isothiocyanate as well as alkyl and alkanoyl esters, alkyl ethers, stereoisomers, tautomers and salts of the aforementioned agents, or b) a pharmaceutical composition comprising said isolated Nrf2 activator,

provided that

if the autoimmune and/or inflammatory disorder is psoriasis and the PPAR agonist is pioglitazone and the Nrf2 activator is a fumaric acid ester, the treatment is not combined with hydroxyurea.

126. A method of treatment according to the aforementioned embodiments, wherein the autoimmune and/or inflammatory disorder is selected from psoriasis, scleroderma, chronic kidney disease (CKD), neurodegenerative diseases, asthma, chronic obstructive pulmonary disorder (COPD), fibrosis, inflammatory arthritis disease and inflammatory bowel disease (IBD).

127. A method of treatment according to the aforementioned embodiment, wherein the autoimmune and/or inflammatory disorder is a neurodegenerative disease selected from multiple sclerosis, clinically isolated syndrome (CIS), amyotrophic lateral sclerosis, Alzheimer's disease, Huntington's disease, and Parkinson's disease.

128. A method for the reduction of inflammation in a patient, comprising administration of a combination of a PPAR gamma agonist selected from the group of glitazones and a) an isolated Nrf2 activator selected from the group of fumaric acid esters, bardoxolone methyl (methyl 2-cyano-3,12-dioxooleana-1,9(11)dien-28-oate, CDDO-Me, RTA 402), ethyl 2-cyano-3,12-dioxooleana-1,9(11)dien-28-oate, 2-cyano-3,12-dioxooleana-1,9(11)dien-28-oic acid (CDDO), 1[2-Cyano-3,12-dioxooleana-1,9(11)-dien-28-oyl]imidazole (CDDO-Im), 2-cyano-N-methyl-3,12-dioxooleana-1,9(11)-dien-28 amide (CDDO-methyl amide, CDDO-MA), [(±)-(4bS,8aR,10aS)-10a-ethynyl-4b,8,8-trimethyl-3,7-dioxo-3,4b,7,8,8a,9,10,10a-octahydrophenanthrene-2,6-dicarbonitrile] (TBE-31), 2-cyano-3,12-dioxooleana-1,9(11)-dien-28-onitrile (TP-225), 3-tert-butyl-4-hydroxyanisole, 2-tert-butyl-4-hydroxyanisole (BHA), tert-butylquinone (tBQ), tert-butylhydroquinone (tBHQ), 3,5-di-tert-butyl-4-hydroxytoluene (BHT), 2,6-Di-tert-butyl-4-methylene-2,5-cyclohexadien-1-one (2,6-Di-tert-butylquinone methide, BHT-quinone methide), ethoxyquin, gallic acid esters, auranofin, curcumin, reservatrol, menadione, cinnamic aldehyde, cinnamic acid esters, caffeic acid esters, cafestol, kahweol, lycopene, carnosol, sulforaphane, oltipraz, 5-(4-methoxy-phenyl)-1,2-dithiole-3-thione (ADT), sulfasalazine, 5-aminosalicylic acid (mesalamine), 5-amino-2-hydroxy-benzoic acid 4-(5-thioxo-5H-[1,2]dithiol-3-yl)-phenyl ester (ATB-429), allicin, allylisothiocyanate, zerumbone, phenethyl isothiocyanate, benzyl isothiocyanate, 6-methylsulfinylhexyl isothiocyanate as well as alkyl and alkanoyl esters, alkyl ethers, stereoisomers, tautomers and salts of the aforementioned agents, or b) a pharmaceutical composition comprising said isolated Nrf2 activator,

provided that

if the inflammation is occurring with and/or is resulting from psoriasis and the PPAR agonist is pioglitazone and the Nrf2 activator is a fumaric acid ester, the treatment is not combined with hydroxyurea.

129. A method for the reduction of inflammation in a patient, comprising administration of a combination of a PPAR gamma agonist selected from the group of glitazones and a) an isolated Nrf2 activator selected from the group of fumaric acid esters, 3-tert-butyl-4-hydroxyanisole, 2-tert-butyl-4-hydroxyanisole (BHA), tert-butylquinone (tBQ), tert-butylhydroquinone (tBHQ), 3,5-di-tert-butyl-4-hydroxytoluene (BHT), 2,6-Di-tert-butyl-4-methylene-2,5-cyclohexadien-1-one (2,6-Di-tert-butylquinone methide, BHT-quinone methide), ethoxyquin, gallic acid esters, auranofin, curcumin, reservatrol, menadione, cinnamic aldehyde, cinnamic acid esters, caffeic acid esters, cafestol, kahweol, lycopene, carnosol, sulforaphane, oltipraz, 5-(4-methoxy-phenyl)-1,2-dithiole-3-thione (ADT), sulfasalazine, 5-aminosalicylic acid (mesalamine), 5-amino-2-hydroxy-benzoic acid 4-(5-thioxo-5H-[1,2]dithiol-3-yl)-phenyl ester (ATB-429), allicin, allylisothiocyanate, zerumbone, phenethyl isothiocyanate, benzyl isothiocyanate, 6-methylsulfinylhexyl isothiocyanate as well as alkyl and alkanoyl esters, alkyl ethers, stereoisomers, tautomers and salts of the aforementioned agents, or b) a pharmaceutical composition comprising said isolated Nrf2 activator,

provided that

if the inflammation is occurring with and/or is resulting from psoriasis and the PPAR agonist is pioglitazone and the Nrf2 activator is a fumaric acid ester, the treatment is not combined with hydroxyurea.

130. A method according to the aforementioned embodiments, wherein the inflammation is a chronic inflammation.

131. A method according to the aforementioned embodiments, wherein the PPAR gamma agonist glitazone is selected from pioglitazone and rosiglitazone.

132. A method according to the aforementioned embodiments, wherein the Nrf2 activator is a fumaric acid ester selected from dialkyl fumarate and monoalkyl fumarate.

133. A method according to the aforementioned embodiment, wherein the Nrf2 activator is dimethyl fumarate.

134. A pharmaceutical composition comprising a PPAR gamma agonist selected from the group of glitazones and an Nrf2 activator selected from the group of fumaric acid esters, bardoxolone methyl (methyl 2-cyano-3,12-dioxooleana-1,9(11)dien-28-oate, CDDO-Me, RTA 402), ethyl 2-cyano-3,12-dioxooleana-1,9(11)dien-28-oate, 2-cyano-3,12-dioxooleana-1,9(11)dien-28-oic acid (CDDO), 1[2-Cyano-3,12-dioxooleana-1,9(11)-dien-28-oyl]imidazole (CDDO-Im), 2-cyano-N-methyl-3,12-dioxooleana-1,9(11)-dien-28 amide (CDDO-methyl amide, CDDO-MA), [(±)-(4bS,8aR,10aS)-10a-ethynyl-4b,8,8-trimethyl-3,7-dioxo-3,4b,7,8,8a,9,10,10a-octahydrophenanthrene-2,6-dicarbonitrile] (TBE-31), 2-cyano-3,12-dioxooleana-1,9(11)-dien-28-onitrile (TP-225), 3-tert-butyl-4-hydroxyanisole, 2-tert-butyl-4-hydroxyanisole (BHA), tert-butylquinone (tBQ), tert-butylhydroquinone (tBHQ), 3,5-di-tert-butyl-4-hydroxytoluene (BHT), 2,6-Di-tert-butyl-4-methylene-2,5-cyclohexadien-1-one (2,6-Di-tert-butylquinone methide, BHT-quinone methide), ethoxyquin, gallic acid esters, auranofin, curcumin, reservatrol, menadione, cinnamic aldehyde, cinnamic acid esters, caffeic acid esters, cafestol, kahweol, lycopene, carnosol, sulforaphane, oltipraz, 5-(4-methoxy-phenyl)-1,2-dithiole-3-thione (ADT), sulfasalazine, 5-aminosalicylic acid (mesalamine), 5-amino-2-hydroxy-benzoic acid 4-(5-thioxo-5H-[1,2]dithiol-3-yl)-phenyl ester (ATB-429), allicin, allylisothiocyanate, zerumbone, phenethyl isothiocyanate, benzyl isothiocyanate, 6-methylsulfinylhexyl isothiocyanate as well as alkyl and alkanoyl esters, alkyl ethers, stereoisomers, tautomers and salts of the aforementioned agents, and optionally one or more excipients.

135. A pharmaceutical composition comprising a PPAR gamma agonist selected from the group of glitazones and an Nrf2 activator selected from the group of fumaric acid esters, 3-tert-butyl-4-hydroxyanisole, 2-tert-butyl-4-hydroxyanisole

(BHA), tert-butylquinone (tBQ), tert-butylhydroquinone (tBHQ), 3,5-di-tert-butyl-4-hydroxytoluene (BHT), 2,6-Di-tert-butyl-4-methylene-2,5-cyclohexadien-1-one (2,6-Di-tert-butylquinone methide, BHT-quinone methide), ethoxyquin, gallic acid esters, auranofin, curcumin, reservatrol, menadione, cinnamic aldehyde, cinnamic acid esters, caffeic acid esters, cafestol, kahweol, lycopene, carnosol, sulforaphane, oltipraz, 5-(4-methoxy-phenyl)-1,2-dithiole-3-thione (ADT), sulfasalazine, 5-aminosalicylic acid (mesalamine), 5-amino-2-hydroxy-benzoic acid 4-(5-thioxo-5H-[1,2]dithiol-3-yl)-phenyl ester (ATB-429), allicin, allylisothiocyanate, zerumbone, phenethyl isothiocyanate, benzyl isothiocyanate, 6-methylsulfinylhexyl isothiocyanate as well as alkyl and alkanoyl esters, alkyl ethers, stereoisomers, tautomers and salts of the aforementioned agents, and optionally one or more excipients.

136. A pharmaceutical composition according to the aforementioned embodiments, wherein the PPAR gamma agonist glitazone is selected from pioglitazone and rosiglitazone.

137. A pharmaceutical composition according to the aforementioned embodiments, wherein the Nrf2 activator is a fumaric acid ester selected from dialkyl fumarate and monoalkyl fumarate.

138. A pharmaceutical composition according to the aforementioned embodiment, wherein the Nrf2 activator is dimethyl fumarate.

139. A solid oral dosage form comprising the pharmaceutical composition according to the aforementioned embodiments.

140. A method of treatment of an autoimmune and/or inflammatory disorder comprising administration of a pharmaceutical composition according to one or more of the foregoing embodiments and/or embodiments 134 135, 136, 137 or 138.

141. A method of treatment according to the aforementioned embodiment, wherein the autoimmune and/or inflammatory disorder is selected from psoriasis, scleroderma, chronic kidney disease (CKD), neurodegenerative diseases, asthma,

chronic obstructive pulmonary disorder (COPD), fibrosis, inflammatory arthritis disease and inflammatory bowel disease (IBD).

142. A method of treatment according to the aforementioned embodiment, wherein the autoimmune and/or inflammatory disorder is a neurodegenerative disease selected from multiple sclerosis, clinically isolated syndrome (CIS), amyotrophic lateral sclerosis, Alzheimer's disease, Huntington's disease, and Parkinson's disease.

143. A method for the reduction of inflammation in a patient comprising administration of a pharmaceutical composition according to one or more of the foregoing embodiments and/or embodiments 134 135, 136, 137 or 138.

144. A method according to the aforementioned embodiment, wherein the inflammation is a chronic inflammation.

145. A kit of parts comprising a) a PPAR gamma agonist selected from the group of glitazones and b) an Nrf2 activator selected from the group of fumaric acid esters, bardoxolone methyl (methyl 2-cyano-3,12-dioxooleana-1,9(11)dien-28-oate, CDDO-Me, RTA 402), ethyl 2-cyano-3,12-dioxooleana-1,9(11)dien-28-oate, 2-cyano-3,12-dioxooleana-1,9(11)dien-28-oic acid (CDDO), 1[2-Cyano-3,12-dioxooleana-1,9(11)-dien-28-oyl]imidazole (CDDO-Im), 2-cyano-N-methyl-3,12-dioxooleana-1,9(11)-dien-28 amide (CDDO-methyl amide, CDDO-MA), [(±)-(4bS,8aR,10aS)-10a-ethynyl-4b,8,8-trimethyl-3,7-dioxo-3,4b,7,8,8a,9,10,10a-octahydrophenanthrene-2,6-dicarbonitrile] (TBE-31), 2-cyano-3,12-dioxooleana-1,9(11)-dien-28-onitrile (TP-225), 3-tert-butyl-4-hydroxyanisole, 2-tert-butyl-4-hydroxyanisole (BHA), tert-butylquinone (tBQ), tert-butylhydroquinone (tBHQ), 3,5-di-tert-butyl-4-hydroxytoluene (BHT), 2,6-Di-tert-butyl-4-methylene-2,5-cyclohexadien-1-one (2,6-Di-tert-butylquinone methide, BHT-quinone methide), ethoxyquin, gallic acid esters, auranofin, curcumin, reservatrol, menadione, cinnamic aldehyde, cinnamic acid esters, caffeic acid esters, cafestol, kahweol, lycopene, carnosol, sulforaphane, oltipraz, 5-(4-methoxy-phenyl)-1,2-dithiole-3-thione (ADT), sulfasalazine, 5-aminosalicylic acid (mesalamine), 5-amino-2-

hydroxy-benzoic acid 4-(5-thioxo-5H-[1,2]dithiol-3-yl)-phenyl ester (ATB-429), allicin, allylisothiocyanate, zerumbone, phenethyl isothiocyanate, benzyl isothiocyanate, 6-methylsulfinylhexyl isothiocyanate as well as alkyl and alkanoyl esters, alkyl ethers, stereoisomers, tautomers and salts of the aforementioned agents, and optionally c) instructions for a dosing regimen.

146. A kit of parts comprising a) a PPAR gamma agonist selected from the group of glitazones and b) an Nrf2 activator selected from the group of fumaric acid esters, 3-tert-butyl-4-hydroxyanisole, 2-tert-butyl-4-hydroxyanisole (BHA), tert-butylquinone (tBQ), tert-butylhydroquinone (tBHQ), 3,5-di-tert-butyl-4-hydroxytoluene (BHT), 2,6-Di-tert-butyl-4-methylene-2,5-cyclohexadien-1-one (2,6-Di-tert-butylquinone methide, BHT-quinone methide), ethoxyquin, gallic acid esters, auranofin, curcumin, reservatrol, menadione, cinnamic aldehyde, cinnamic acid esters, caffeic acid esters, cafestol, kahweol, lycopene, carnosol, sulforaphane, oltipraz, 5-(4-methoxy-phenyl)-1,2-dithiole-3-thione (ADT), sulfasalazine, 5-aminosalicylic acid (mesalamine), 5-amino-2-hydroxy-benzoic acid 4-(5-thioxo-5H-[1,2]dithiol-3-yl)-phenyl ester (ATB-429), allicin, allylisothiocyanate, zerumbone, phenethyl isothiocyanate, benzyl isothiocyanate, 6-methylsulfinylhexyl isothiocyanate as well as alkyl and alkanoyl esters, alkyl ethers, stereoisomers, tautomers and salts of the aforementioned agents, and optionally c) instructions for a dosing regimen.

147. A kit of parts according to the aforementioned embodiments, wherein the PPAR gamma agonist glitazone is selected from pioglitazone and rosiglitazone.

148. A kit of parts according to the aforementioned embodiments, wherein the Nrf2 activator is a fumaric acid ester selected from dialkyl fumarate and monoalkyl fumarate.

149. A kit of parts according to the aforementioned embodiment, wherein the Nrf2 activator is dimethyl fumarate.

150. A method of treating multiple sclerosis or clinically isolated syndrome (CIS) comprising the administration of a pharmaceutical composition comprising a glitazone and a fumaric acid monoalkyl ester and/or fumaric acid dialkyl ester to a patient having multiple sclerosis or clinically isolated syndrome.

151. The method according to one or more of the foregoing embodiments and/or embodiment 150, wherein the fumaric acid dialkyl ester is selected from dimethyl fumarate or diethyl fumarate and the fumaric acid monoalkyl ester is selected from monomethyl hydrogen fumarate or monoethyl hydrogen fumarate.

152. The method according to one or more of the foregoing embodiments and/or embodiment 151, wherein the fumaric acid dialkyl ester is dimethyl fumarate.

153. The method according to one or more of the foregoing embodiments and/or embodiment 150, wherein the glitazone is pioglitazone or rosiglitazone.

154. The method according to one or more of the foregoing embodiments and/or embodiment 150, wherein said composition comprises a fumaric acid dialkyl ester selected from dimethyl fumarate or diethyl fumarate, the glitazone is pioglitazone or rosiglitazone and said pharmaceutical composition is a solid oral dosage form.

155. The method according to one or more of the foregoing embodiments and/or embodiment 154, wherein said fumaric acid dialkyl ester is dimethyl fumarate.

156. A pharmaceutical composition comprising a glitazone and a fumaric acid monoalkyl ester and/or fumaric acid dialkyl ester and, optionally, one or more excipients.

157. The pharmaceutical composition according to one or more of the foregoing embodiments and/or embodiment 156, wherein the fumaric acid dialkyl

ester is selected from dimethyl fumarate or diethyl fumarate and the fumaric acid monoalkyl ester is selected from monomethyl hydrogen fumarate or monoethyl hydrogen fumarate.

158. The pharmaceutical composition according to one or more of the foregoing embodiments and/or embodiment 156, wherein the glitazone is pioglitazone or rosiglitazone.

159. The pharmaceutical composition according to one or more of the foregoing embodiments and/or embodiment 157, wherein the fumaric acid dialkyl ester is dimethyl fumarate.

160. The pharmaceutical composition according to one or more of the foregoing embodiments and/or embodiment 156, wherein said pharmaceutical composition comprises a solid oral dosage form.

161. The pharmaceutical composition according to one or more of the foregoing embodiments and/or embodiment 156, wherein the fumaric acid dialkyl ester is selected from dimethyl fumarate or diethyl fumarate and the fumaric acid monoalkyl ester is selected from monomethyl hydrogen fumarate or monoethyl hydrogen fumarate, the glitazone is pioglitazone or rosiglitazone and said pharmaceutical composition is an oral dosage form.

162. The pharmaceutical composition according to one or more of the foregoing embodiments and/or embodiment 161, wherein said fumaric acid dialkyl ester is dimethyl fumarate.

163. The method according to one or more of the foregoing embodiments and/or embodiment 150, wherein said patient has multiple sclerosis.

164. The method according to one or more of the foregoing embodiments and/or embodiment 150, wherein said patient has clinically isolated syndrome.

165. Method of treating or preventing an autoimmune and/or inflammatory disorder, comprising administration of a PPAR gamma agonist selected from the group of glitazones and a bardoxolone alkyl to a patient in need thereof.

166. Method according to one or more of the foregoing embodiments and/or embodiment 165, wherein the bardoxolone alkyl is bardoxolone methyl.

167. Method according to one or more of the foregoing embodiments and/or embodiment 165 or 166, wherein the PPAR gamma agonist glitazone is selected from pioglitazone and rosiglitazone.

168. Method according to one or more of the foregoing embodiments and/or embodiment 165, 166 or 167, wherein the autoimmune and/or inflammatory disorder is chronic kidney disease.

169. Method according to one or more of the foregoing embodiments and/or embodiment 165, 166 or 167, wherein the autoimmune and/or inflammatory disorder is multiple sclerosis.

170. A composition comprising a) a compound selected from auranofin, sulfasalazine or 5-aminosalicylic acid (mesalamine) and b) a glitazone.

171. A composition comprising a) a compound selected from auranofin, sulfasalazine or 5-aminosalicylic acid (mesalamine) and b) pioglitazone.

172. A composition comprising a) a compound selected from auranofin, sulfasalazine or 5-aminosalicylic acid (mesalamine) and b) rosiglitazone.

173. A pharmaceutical composition comprising a) a compound selected from auranofin, sulfasalazine or 5-aminosalicylic acid (mesalamine) and b) a glitazone, such as pioglitazone or rosiglitazone, and optionally c) one or more excipients.

174. Method of treating rheumatoid arthritis comprising administering the composition according to embodiments 170 to 173, preferably a composition comprising a) auranofin or sulfasalazine and b) a glitazone, to a patient.

175. Method of treating a condition selected from inflammatory bowel disease, such as ulcerative colitis and Crohn's disease, comprising administering a composition according to embodiments 170 to 173, preferably a composition comprising sulfasalazine or 5-aminosalicylic acid (mesalamine) and a glitazone to a patient.

In another embodiment of the present invention, the autoimmune and/or inflammatory disease is an oral cavity inflammation or throat inflammation, such as gingivitis, peridontitis or tonsillitis. In a preferred embodiment, such diseases are preferably treated by rinsing the oral cavity and/or throat with a solution or applying a gel or a cream comprising a PPAR gamma agonist, such as a glitazone, preferably pioglitazone or rosiglitazone, and an Nrf2 activator, such as sulforaphane, tert-butylhydroquinone and/or butylated hydroxyanisole or others mentioned herein, preferably 3-tert-butyl-4-hydroxyanisole, 2-tert-butyl-4-hydroxyanisole (BHA), tert-butylquinone (tBQ), tert-butylhydroquinone (tBHQ), 3,5-di-tert-butyl-4-hydroxytoluene (BHT), 2,6-Di-tert-butyl-4-methylene-2,5-cyclohexadien-1-one (2,6-Di-tert-butylquinone methide, BHT-quinone methide), ethoxyquin, gallic acid esters, curcumin, reservatrol, menadione, cinnamic aldehyde, cinnamic acid esters, caffeic acid esters, cafestol, kahweol, lycopene, carnosol, sulforaphane, oltipraz, 5-(4-methoxy-phenyl)-1,2-dithiole-3-thione (ADT), 5-amino-2-hydroxy-benzoic acid 4-(5-thioxo-5H-[1,2]dithiol-3-yl)-phenyl ester (ATB-429), allicin, allylisothiocyanate, zerumbone, phenethyl isothiocyanate, benzyl isothiocyanate, 6-methylsulfinylhexyl isothiocyanate as well as alkyl and alkanoyl esters, alkyl ethers, stereoisomers, tautomers and salts of the aforementioned agents. The above solution or the gel can be based on known conventional excipient formulations, such as aqueous formulation of the agents containing polyvinylpyrrolidone as an excipient. Moreover, the solutions or gels may contain in addition to the agents also antibacterials such as chlorohexidine, such as chlorhexidine gluconate, cetylpyridinium chloride, tin fluoride, hexetidine,

benzoic acid and its sals, such as sodium benzoate, salicylates, such as methyl salicylate, benzalkonium chloride, methylparaben and/or domiphen bromide.

Therefore, preferred embodiments of the present invention are solutions and gels or creams containing a PPAR agonist and preferably a PPAR gamma agonist, such as a glitazone, preferably pioglitazone or rosiglitazone, and an Nrf2 activator, such as sulforaphane, tert-butylhydroquinone and/or butylated hydroxyanisole or others mentioned herein, in particular 3-tert-butyl-4-hydroxyanisole, 2-tert-butyl-4-hydroxyanisole (BHA), tert-butylquinone (tBQ), tert-butylhydroquinone (tBHQ), 3,5-di-tert-butyl-4-hydroxytoluene (BHT), 2,6-Di-tert-butyl-4-methylene-2,5-cyclohexadien-1-one (2,6-Di-tert-butylquinone methide, BHT-quinone methide), ethoxyquin, gallic acid esters, curcumin, reservatrol, menadione, cinnamic aldehyde, cinnamic acid esters, caffeic acid esters, cafestol, kahweol, lycopene, carnosol, sulforaphane, oltipraz, 5-(4-methoxy-phenyl)-1,2-dithiole-3-thione (ADT), 5-amino-2-hydroxy-benzoic acid 4-(5-thioxo-5H-[1,2]dithiol-3-yl)-phenyl ester (ATB-429), allicin, allylisothiocyanate, zerumbone, phenethyl isothiocyanate, benzyl isothiocyanate, 6-methylsulfinylhexyl isothiocyanate as well as alkyl and alkanoyl esters, alkyl ethers, stereoisomers, tautomers and salts of the aforementioned agents. In a further preferred embodiment, each of the agent is employed in these solutions, gels or creams in an amount of at least 0.1 %, preferably at least 0.5 % or at least 1, 2 or 3 % (w/w) of the total weight of the solution, cream or gel.

The role of reactive oxygen species and antioxidants in inflammatory diseases has been described in the Journal of Clinical Periodontology Volume 24, Issue 5, 1997, Pages 287-296.

Animal models for peridontitis and gingivitis are well known in the art, e.g. Journal of Biomedicine and Biotechnology Volume 2011, Article ID 754857, 8 pages doi:10.1155/2011/754857

In another preferrd embodiment of the present invention, the PPAR gamma agonist, such as pioglitazone or rosiglitazone is administered with the Nrf2

activator capsaicin fort he treatment of an autoimmune and/or inflammatory disorder such as psoriasis, psoriatic arthritis, and arthritis, such as rheumatoid arthritis. The combination can also be used for the treatment of pain, such as neuropathic pain. Combinations with capsaicin are preferably applied topically in form of a cream or a gel or patch. More preferably the invention relates to a cream or a gel or patch comprising capsaicin and a PPAR gamma agonist, such as a glitazone, preferably pioglitazone or rosiglitazone.

The cream, gel or patch comprising capsaicin accoriding to the invention, provides advantagous results when topically applied in the animal models for psoriasis and rheumatoid arthritis as described herein. In these animal models, the cream, gel or patch comprising capsaicin and a PPAR gamma agonist, such as a glitazone, preferably pioglitazone or rosiglitazone are applied to the joints or other areas of the skin where symptoms are presented.

In another preferred embodiment, the Nrf2 activators cromolyn sodium or nedocromil are combined with a PPAR gamma agonist, such as a glitazone, preferably pioglitazone or rosiglitazone in order to treat or prevent an autoimmune and/or inflammatory disease, such as asthma, allergies such as season allergy or hay fever, COPD or allergic rhinitis. Preferably, combinations containing cromolyn sodium or any other salt therof or nedocromil or its salt such as the sodium salt, as an Nrf2 activator are combined with the PPAR agonist in a solution or gel or a cream or patch, specifically a solution for inhalation or an eye-drop solution, which comprise conventional excipients.

Pioglitazone can be used in enantiomerically pure or enriched form such as disclosed in WO 2011015868 and WO2011098746, which is particularly advantagous for oral mouth rinses, or oral gels, inhalation solutions eye-drops and topic creams or gels or patches for the treatment of the skin.

Preferably, the PPAR agonist and the Nrf2 activator used in the present invention do not belong to the same chemical class of compounds, i.e. the Nrf2 activator preferably belongs to a different class of compounds as the PPAR agonist.

Solid oral dosage forms comprising the inventive combinations for use in treatment of inflammatory and/or autoimmune diseases are preferred. Solid oral dosage forms are well known in the art and comprise powders, granules, lozenges, capsules and tablets, such as compressed tablets (CT), sugar-coated tablets (SCT), film-coated tablets (FCT), enteric-coated tablets (ECT), multiple compressed tablets (MCT), which are compressed tablets made by more than one compression cycle, layered tablets, prepared by compressing an additional tablet granulation on a previously compressed granulation, press-coated tablets, controlled-release tablets, effervescent tablets, compressed suppositories, buccal and sublingual tablets, molded tablets (tablet triturates, TT) and hypodermic tablets (HT). Most preferred are solid oral dosage forms that contain both agents togehter in a single pharmaceutical composition.

Preferred is also a composition comprising dimethyl fumarate, monomethyl fumarate, optionally in form of its zinc, magnesium and/or calcium salts and a PPAR agonist. The use of this composition in the treatment of psoriasis is particularly preferred.

Preferred is also a PPAR gamma agonist for use in combination with an Nrf2 activator in the treatment of an autoimmune and/or inflammatory disease, according to any of the foregoing embodiments, characterized in that the treatment excludes or does not comprise the administration of hydroxyurea (hydroxycarbamid), in particular, if the PPAR gamma agonist and the Nrf2 activator is not used or administered in admixture or in a single pharmaceutical formulation containing both agents together.

In one embodiment of the present invention, the autoimmune and/or inflammatory disorder treated according to the present invention is psoriasis and/or inflammation resulting from or occurring with psoriasis. Preferably, the inventive treatment combines a glitazone with dimethyl fumarate for treating psoriasis and/or inflammation resulting from or occurring with psoriasis. If in this case the glitazone is pioglitazone, in particular, if it is not used or administered in admixture with the Nrf2 activator or in a single pharmaceutical formulation containing both agents together, the patient to be treated has preferably not received therapeutic amounts of hydroxyurea before the treatment according to the present invention, is not receiving hydroxyurea concomitantly with the treatment according to the present

invention and preferably neither thereafter, while pioglitazone, dimethyl fumarate or their metabolites are still present in the body. Thus, if the autoimmune and/or inflammatory disorder is psoriasis and the PPAR agonist is pioglitazone and the Nrf2 activator is a fumaric acid ester, the treatment is preferably not combined with hydroxyurea, in particular, if the PPAR gamma agonist and the Nrf2 activator is not used or administered in admixture or in a single pharmaceutical formulation containing both agents together.

If the autoimmune and/or inflammatory disorder treated according to the present invention is psoriasis and/or inflammation resulting from or occurring with psoriasis the glitazone is in one embodiment preferably other than pioglitzaone, such as rosiglitazone, or the Nrf2 activator is other than a fumaric acid ester.

Pioglitazone and rosiglitazone tablets are commercially available and can be used as such for the combination therapy according to the invention.

In one embodiment, preferred tablets are film-coated tablets containing rosiglitazone maleate equivalent to rosiglitazone, 2 mg, 4 mg, or 8 mg, for oral administration, with the following inactive ingredients: Hypromellose 2910, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol 3000, sodium starch glycolate, titanium dioxide, triacetin, and 1 or more of the following: Synthetic red and yellow iron oxides and talc.

In one embodiment, preferred tablet for oral administration contain 15 mg, 30 mg, or 45 mg of pioglitazone (as the base) formulated with the following excipients: lactose monohydrate NF, hydroxypropylcellulose NF, carboxymethylcellulose calcium NF, and magnesium stearate NF.

Other formulations can be obtained in analogy to US6355676, US7976853 and 6403121.

Throughout the specification, the term "no significant PPAR gamma agonistic activity" or "no significant PPAR gamma agonistic effect" means that at the therapeutically useful concentration of the Nrf2 activator, no therapeutically useful PPAR gamma activation can be obtained or measured.

Throughout the specification, the term "no significant effect on Nrf2" or "no significantly activating effect on Nrf2" or "no significant effect on Nrf2 activity" means that at the therapeutically useful concentration of the PPAR gamma agonist, no therapeutically useful Nrf2 activation can be obtained or measured.

The term monoalkyl fumarate and monoalkyl hydrogen fumarate are used synonymously, such as monomethyl fumarate and monomethyl hydrogen fumarate.

## EXAMPLES

**Example 1**

*Preparation of Enteric-coated micro-tablets in capsules containing 120.0 mg of dimethyl fumarate*

Following patent US7320999, 12.000 kg of dimethyl fumarate are crushed, mixed and homogenized by means of a sieve 800. Then an excipient mixture with the following composition is prepared: 17.50 kg of starch derivative (STA-RX® 1500), 0.30 kg of microcrystalline cellulose (Avicel® PH 101), 0.75 kg of PVP (Kollidon® 120), 4.00 kg of Primogel®, 0.25 kg of colloidal silicic acid (Aerosil®). Dimethyl fumarate is added to the entire powder mixture, mixed, homogenized by means of a sieve 200, processed in the usual manner with a 2% aqueous solution of polyvidon pyrrolidone (Kollidon® K25) to obtain a binder granulate and then mixed in the dry state with the outer phase. Said outer phase consists of 0.50 kg of Mg stearate and 1.50 kg of talcum.

The powder mixture is compressed in the usual manner into 10 mg-micro tablet cores.

To achieve resistance to gastric acid a solution of 2.250 kg of hydroxy propyl methyl cellulose phthalate (HPMCP, Pharmacoat® HP 50) is dissolved in portions in a mixture of the following solvents: 13.00 L of acetone, 13.50 L of ethanol (94 wt.-%, denatured with 2% of ketone) and 1.50 L of demineralised water. As a plasticiser, castor oil (0.240 kg) is added to the finished solution, which is applied in portions onto the micro tablet cores in the customary manner.

After drying is completed, a suspension of the following composition is applied as a film coat in the same apparatus: 0.340 kg of talcum, 0.400 kg of titanium(VI) oxide Cronus RN 56, 0.324 kg of coloured lacquer L-Rot-lack 86837, 4.800 kg of Eudragit E 12.5% and 0.120 kg of polyethylene glycol 6000, pH 11 XI in a solvent mixture of the following composition: 8.170 kg of 2-propanol, 0.200 kg of demineralised water and 0.600 kg of glycerine triacetate (Triacetin). This procedure resulted in enteric-coated micro-tablets.

Subsequently, the enteric-coated micro-tablets are filled into hard gelatine capsules and are sealed for use according to the invention.

Micro pellets can be obtained similarly according to US7320999.

**Example 2**

*Preparation of tablets containing pioglitazone and dimethyl fumarate in separate tablet layers*

According to US807113, a mixture of pioglitazone hydrochloride (99.2 g), croscarmellose sodium (13.2 g) and lactose (184.9 g) is granulated by spraying thereon 136.2 g of an aqueous solution of hydroxypropylcellulose (6.81 g), in a fluid bed granulator (manufactured by Powrex Corp., Model: LAB-1). The resulting granulated powder is then granulated by spraying a suspension obtained by dispersing lactose (36 g) in 148.6 g of an aqueous solution of hydroxypropylcellulose (7.59 g) thereon in a fluid bed granulator (manufactured by Powrex Corp., Model: LAB-1) to obtain pioglitazone hydrochloride-containing granulated powder coated with lactose. To a part (23.18 g) of the granulated powder thus obtained, croscarmellose sodium (0.728 g) and magnesium stearate (0.096 g) are added and mixed to obtain pioglitazone hydrochloride-containing mixed powder. The pioglitazone hydrochloride-containing mixed powder is compressed in the form of laminate with a powder obtained according to example 1, containing dimethyl fumarate, a starch derivative (STA-RX® 1500), microcrystalline cellulose (Avicel® PH 101), PVP (Kollidon® 120), Primogel®, and colloidal silicic acid (Aerosil®).

**Example 3**

According to US7976853, hydroxypropyl cellulose (26.4 g, Grade SSL, Nippon Soda Co., Ltd.) (viscosity of 5% aqueous solution at 20° C.: 8 mPa·s), polyethylene glycol 6000 (1.32 g), titanium oxide (2.64 g) and pioglitazone hydrochloride (16.5 g) are dispersed in water (297 g) to give a coating solution. The enteric coated micro-tablets obtained in example 1 are fed in a film coating equipment (Hicoater-Mini, Freund Industrial Co. Ltd.) and coated with the aforementioned coating solution to give a coated preparation. Subsequently, these enteric-coated micro-tablets, which are coated with pioglitazone hydrochloride, are

filled into hard gelatine capsules and are sealed for use according to the present invention.

Alternatively, according to example 1, an enteric-coated tablet containing the desired amount of dimethyl fumarate can be obtained, followed by a coating with a pioglitazone formulation as described above. The tablets can be used as such for the combination treatment according to the invention.

**Example 4**

A mixture of pioglitazone hydrochloride (99.2 g), croscarmellose sodium (13.2 g) and lactose (184.9 g) which is granulated by spraying thereon 136.2 g of an aqueous solution of hydroxypropylcellulose (6.81 g), in a fluid bed granulator (manufactured by Powrex Corp., Model: LAB-1). The resulting granulated powder is then granulated by spraying a suspension obtained by dispersing lactose (36 g) in 148.6 g of an aqueous solution of hydroxypropylcellulose (7.59 g) thereon in a fluid bed granulator (manufactured by Powrex Corp., Model: LAB-1) to obtain pioglitazone hydrochloride-containing granulated powder coated with lactose. A desired amount of the granulated powder thus obtained, is filled in a capsules containing dimethyl fumarate enteric-coated micro tablets obtained according to example 1, which are thereafter sealed.

**Example 5**

A capsule is filled a dispersion of 20 mg of amorphous bardoxolone methyl in methacrylic acid copolymer Type C, USP in a 4/6 weight ratio of bardoxolone methyl to methacrylic acid copolymer Type C, USP having the following composition is prepared according to US2012/022156:

Amorphous bardoxolone methyl as 40% dispersion: 11.36%

SMCC (90LM, silicified microcrystalline cellusose, as listed in the FDA Inactive Ingredients Guide): 36.36%

lactose monohydrate: 40.91%

hydroxypropyl methylcellulose: 6.82%

colloidal silicon dioxide: 0.91%

magnesium Stearate: 0.91%

sodium lauryl sulphate: 2.73%.

In addition, the capsule is filled with an equivalent of 45 mg of pioglitazone in form of its hydrochloride as a granulated powder coated with lactose obtained according to the first part of example 4. The capsule is thereafter sealed for use.

Alternatively, the bardoxolone methyl containing mixture and the pioglitazone containing mixture can be compressed into a tablet, preferably a layered tablet, wherein the formulations are arranged in a laminar manner. In one embodiment, an enteric coat is applied to the tablet.

**General Experimental Protocols**

If not mentioned otherwise, treatment in the following animal models consists of, or animals are treated with, dimethyl fumarate and pioglitazone in form of its hydrochloride, which are dissolved or dispersed in 0.5% methocellulose/0.1% Tween80 in distilled water and administered by oral gavage twice daily. Treatment groups are generally as follows: vehicle alone, dimethyl fumarate alone, pioglitazone alone or the combination of dimethyl fumarate and pioglitazone. The combination according to the invention results in an improved response to treatment over the vehicle and the respective agents alone.

The effect of the combinations according to the present invention in the treatment of cancer and preferably hematologic cancers such as CLL and AML can be found according to Blood. 2006 Nov 15;108(10):3530-7 and Cancer Res June 15, 2010 70; 4949.

*Animal Model for Assessing the Therapeutic and Preventive Effect of the combination of a PPAR gamma agonist and an Nrf2 activator in oral cavity inflammation and throat inflammation including gingivitis, peridontitis, tonsillites*

Specific pathogen-free C3H/HeN mice are infected according to J. Periodontol. 2000 Jul; 71(7):1167-73 and are treated daily by oral gavage according to the general example with pioglitatzone hydrochloride, sulforaphane or tert-butylhydroquinone or the combination of pioglitatzone hydrochloride and sulforaphane or pioglitazone hydrochloride and tert-butylhydroquinone. The treatment with the combinations results in prevention or delayed onset and reduced signs of inflammation compared to the individual agents and compared to non-

treated animals. Similar qualitative results are obtained by applying the treatment by daily rinsing the mouth of the animals for 2 minutes with a solution of the agents.

*Animal Model for Assessing the Therapeutic and Preventive Effect of the combination of a PPAR gamma agonist and an Nrf2 activator in Rheumatoid Arthritis*

Animals are prepared according to Wilder, R. L. 2001 (Streptococcal Cell Wall Arthritis) Current Protocols in Immunology. 26:15.10.1–15.10.12 and treated daily by oral gavage according to the general example with pioglitatzone hydrochloride, dimethyl fumarate or the combination of the agents. The treatment with the combination results in prevention or delayed onset and reduced signs of arthritis and inflammation compared to the individual agents and compared to non-treated animals.

*Use of an Animal Model to Assess Effect in Treating Psoriasis*

The severe, combined immunodeficient (SCID) mouse model can be used to evaluate the efficacy of compounds for treating psoriasis in humans (Boehncke, Ernst Schering Res Found Workshop 2005, 50, 213-34; and Bhagavathula et ah, J Pharmacol Expt 7 Therapeutics 2008, 324(3), 938-947).

SCID mice are used as tissue recipients. One biopsy for each normal or psoriatic volunteer is transplanted onto the dorsal surface of a recipient mouse. Treatment is initiated 1 to 2 weeks after transplantation. Animals with the human skin transplants are divided into treatment groups. Animals are treated twice daily for 14 days. At the end of treatment, animals are photographed and then euthanized. The transplanted human tissue along with the surrounding mouse skin is surgically removed and fixed in 10% formalin and samples obtained for microscopy. Epidermal thickness is measured. Tissue sections are stained with an antibody to the proliferation-associated antigen Ki-67 and with an anti -human CD3+ monoclonal antibody to detect human T lymphocytes in the transplanted tissue. Sections are also probed with antibodies to c-myc and β-catenin. A positive response to treatment is reflected by a reduction in the average epiderma thickness

of the psoriatic skin transplants. A positive response is also associated with reduced expression of Ki-67 in keratinocytes.

*General EAE Animal Model for Assessing Therapeutic Effect of the combination of a PPAR gamma agonist and an Nrf2 activator for Treating Multiple Sclerosis*

Animals and EAE Induction Female C57BL/6 mice, 8-10 weeks old (Harlan Laboratories, Livermore, CA), are immunized subcutaneously in the flanks and mid-scapular region with 200µg of myelin oligodendrocyte glycoprotein peptide (MOG3S-Ss) (synthesized by Invitrogen) emulsified (1: 1 volume ratio) with complete Freund's adjuvant (CFA) (containing 4 mg/nL Mycobacterium tuberculosis). Emulsion is prepared by the syringe-extrusion method with two glass Luer-Lock syringes connected by a 3 -way stopcock. Mice are also given an intraperitoneal injection of 200 ng pertussis toxin (List Biological Laboratories, Inc, Campbell, CA) on the day of immunization and on day two post immunization. Mice are weighed and examined daily for clinical signs of experimental autoimmune encephalomyelitis (EAE). Food and water is provided ad libitum and once animals start to show disease, food is provided on the cage bottom.

Clinical Evaluation

Mice are scored daily beginning on day 7 post immunization. The clinical scoring scale is as follows (Miller and Karplus, Current Protocols in Immunology 2007, 15.1.1-15.1.18): 0 = normal; 1 = limp tail or hind limb weakness (defined by foot slips between bars of cage top while walking); 2 = limp tail and hind limb weakness; 3 = partial hind limb paralysis (defined as no weight bearing on hind limbs but can still move one or both hind limbs to some extent); 4 = complete hind limb paralysis; 5 = moribund state (includes forelimb paralysis) or death.

*Animal Model for Assessing Therapeutic Effect of the combination of a PPAR gamma agonist and an Nrf2 activator for treating Multiple Sclerosis*

Experiments are conducted on female mice aged 4-6 weeks belong to the C57BL/6 strain weighing 17-20 g. Experimental autoimmune encephalomyelitis (EAE) is actively induced using >95% pure synthetic myelin oligodendrocyte glycoprotein peptide 35-55 (MOG35-55, MEVGWYRSPFSRVVHLYRNGK). Each mouse is anesthetized and receives 200 μg of MOG peptide and 15 μg of Saponin extract from Quilija bark emulsified in 100 μL of phosphate-buffered saline. A 25 μL volume is injected subcutaneously over four flank areas. Mice are also intraperitoneally injected with 200 ng of pertussis toxin in 200 μL of PBS. A second, identical injection of pertussis toxin is given after 48 h.

Daily treatment extends from day 26 to day 36 post-immunization. Clinical scores are obtained daily from day 0 post-immunization until day 60. Clinical signs are scored using the following protocol: 0, no detectable signs; 0.5, distal tail limpness, hunched appearance and quiet demeanor; 1, completely limp tail; 1.5, limp tail and hindlimb weakness (unsteady gait and poor grip with hindlimbs); 2, unilateral partial hindlimb paralysis; 2.5, bilateral hindlimb paralysis; 3, complete bilateral hindlimb paralysis; 3.5, complete hindlimb paralysis and unilateral forelimb paralysis; 4, total paralysis of hindlimbs and forelimbs (Eugster et al., Eur J Immunol 2001, 31, 2302-2312).

Inflammation and demyelination are assessed by histology on sections from the CNS of EAE mice. Mice are sacrificed after 30 or 60 days and whole spinal cords are removed and placed in 0.32 M sucrose solution at 40C overnight. Tissues are prepared and sectioned. Luxol fast blue stain is used to observe areas of demyelination. Haematoxylin and eosin staining is used to highlight areas of inflammation by darkly staining the nuclei of mononuclear cells. Immune cells stained with H&E are counted in a blinded manner under a light microscope. Sections are separated into gray and white matter and each sector is counted manually before being combined to give a total for the section. T cells are immunolabeled with anti-CD3+ monoclonal antibody. After washing, sections are incubated with goat anti-rat HRP secondary antibody. Sections are then washed and counterstained with methyl green. Splenocytes isolated from mice at 30 and 60 days post-immunization are treated with lysis buffer to remove red blood cells. Cells are then resuspended in PBS and counted. Cells at a density of about 3 x 106 cells/mL are incubated overnight with 20 μg/mL of MOG peptide. Supernatants

from stimulated cells are assayed for IFN-γ protein levels using an appropriate mouse IFN-γ immunoassay system.

*Use of an Animal Model to Assess Effect in Treating Inflammatory Bowel Disease*

Animal models of inflammatory bowel disease are described by Jurjus et al, J Pharmaocol Toxicol Methods 2004, 50, 81-92; Villegas et al, Int'l lmmunopharmacol 2003, 3, 1731-1741; and Murakami et al, Biochemical Pharmacol 2003, 66, 1253-1261. For example, the following protocol can be used to assess the effect of the combination according to the present invention for treating inflammatory bowel disease, morbus Crohn und colitis.

Female ICR mice are used. Mice are divided into treatment groups. Groups are given either water (control), 5% DSS in tap water is given at the beginning of the experiment to induce colitis, or treatment is given. After administering the treatment for 1 week, 5% DSS in tap water is also administered to the groups receiving treatment for 1 week. At the end of the experiment, all mice are killed and the large intestine is removed. Colonic mucosa samples are obtained and homogenized. Proinflammatory mediators (e.g., IL-lα, IL-lβ, TNF-α, PGE2, and PGF2α) and protein concentrations are quantified. Each excised large intestine is histologically examined and the damage to the colon scored.

*Clinical Trial for Assessing Effect in Treating Asthma*

Adult subjects (nonsmokers) with stable mild-to-moderate asthma are enrolled (see, e.g., Van Schoor and Pauwels, Eur Respir J 2002, 19, 997-1002). A randomized, double-blind, placebo-controlled, two-period crossover design is used. Placebo, dimethyl fumarate alone, pioglitazone alone and a combination of dimethyl fumarate and pioglitazone is administered orally in different arms. The combination according to the invention results in an improved response to treatment over the vehicle and the agents alone.

*Use of an Animal Model to Assess Effect in Treating Chronic Obstructive PulmonaryDisease*

An animal model using mice chronically exposed to cigarette smoke can be used for assessing efficacy in treating emphysema (see, e.g., Martorana et al., Am J

Respir Crit Care Med 2005, 172, 848-835; and Cavarra et al., Am J Respir Crit Care Med 2001, 164, 886-890). Six-week old C57B1/6J male mice are used. In the acute study, the mice are exposed either to room air or to the smoke of five cigarettes for 20 minutes. In the chronic study, the mice are exposed to either room air or to the smoke of three cigarettes/day for 5 days/week for 7 months.

In the acute study, mice are divided into three groups. These groups are then divided into four subgroups of 10 mice each as follows: (1) no treatment/air-exposed; (2) no treatment/smoke-exposed; (3) the combination of dimethyl fumarate and pioglitazone plus smoke-exposed; and (4) pioglitazone plus smoke-exposed; and (5) dimethyl fumarate plus smoke-exposed. In the first group, trolox equivalent antioxidant capacity is assessed at the end of the exposure in bronchoalveolar lavage fluid. In the second group, cytokines and chemokines are determined in bronchoalveolar lavage fluid using a commercial cytokine panel at 4 hours; and in the third group bronchoalveolar lavage fluid cell count is assessed at 24 hours.

*Animal Models for Assessing Therapeutic Effect of the combination of a PPAR gamma agonist and an Nrf2 activator for Treating Parkinson's Disease*

*MPTP Induced Neurotoxicity*

MPTP, or l-methyl-4-phenyl-l,2,3,6-tetrahydropyridine is a neurotoxin that produces a Parkinsonian syndrome in both man and experimental animals. Studies of the mechanism of MPTP neurotoxicity show that it involves the generation of a major metabolite, MPP+, formed by the activity of monoamine oxidase on MPTP. Inhibitors of monoamine oxidase block the neurotoxicity of MPTP in both mice and primates. The specificity of the neurotoxic effects of MPP+ for dopaminergic neurons appears to be due to the uptake of MPP+ by the synaptic dopamine transporter. Blockers of this transporter prevent MPP+ neurotoxicity. MPP+ has been shown to be a relatively specific inhibitor of mitochondrial complex I activity, binding to complex I at the retenone binding site and impairing oxidative phosphorylation. In vivo studies have shown that MPTP can deplete striatal ATP concentrations in mice. It has been demonstrated that MPP+ administered intrastriatally to rats produces significant depletion of ATP as well as increased lactate concentration confined to the striatum at the site of the injections.

Compounds that enhance ATP production can protect against MPTP toxicity in mice.

Mice or rats are treated either with vehicle alone, dimethyl fumarate alone pioglitazone alone or the combination of dimethyl fumarate and pioglitazone for three weeks before treatment with MPTP. MPTP is administered at an appropriate dose, dosing interval, and mode of administration for 1 week before sacrifice. Control groups receive either normal saline or MPTP hydrochloride alone. Following sacrifice the two striate are rapidly dissected and placed in chilled 0.1 M perchloric acid. Tissue is subsequently sonicated and aliquots analyzed for protein content using a fiuorometer assay. Dopamine, 3,4-dihydroxyphenylacetic acid (DOPAC), and homovanillic acid (HVA) are also quantified. Concentrations of dopamine and metabolites are expressed as nmol/mg protein.

*Haloperidol-Induced Hypolocomotion*

The ability of a compound to reverse the behavioral depressant effects of dopamine antagonists such as haloperidol, in rodents and is considered a valid method for screening drags with potential antiparkinsonian effects (Mandhane, et al., Eur. J. Pharmacol 1997, 328, 135-141). Hence, the ability of the treatment to block haloperidol-induced deficits in locomotor activity in mice can be used to assess both in vivo and potential anti-Parkinsonian efficacy.

Mice used in the experiments are housed in a controlled environment and allowed to acclimatize before experimental use. One and one-half (1.5) hours before testing, mice are administered 0.2 mg/kg haloperidol, a dose that reduces baseline locomotor activity by at least 50%. Treatment is administered a suitably long prior to testing. The animals are then placed individually into clean, clear polycarbonate cages with a flat perforated lid.

Horizontal locomotor activity is determined by placing the cages within a frame containing a 3x6 array of photocells interfaced to a computer to tabulate beam interrupts. Mice are left undisturbed to explore for 1 h, and the number of beam interruptions made during this period serves as an indicator of locomotor activity, which is compared with data for control animals for statistically significant differences.

*6-Hydroxydopamine Animal Model*

The neurochemical deficits seen in Parkinson's disease can be reproduced by local injection of the dopaminergic neurotoxin, 6-hydroxydopamine (6-OHDA) into brain regions containing either the cell bodies or axonal fibers of the nigrostriatal neurons. By unilaterally lesioning the nigrostriatal pathway on only one-side of the brain, a behavioral asymmetry in movement inhibition is observed. Although unilaterally-lesioned animals are still mobile and capable of self maintenance, the remaining dopamine-sensitive neurons on the lesioned side become supersensitive to stimulation. This is demonstrated by the observation that following systemic administration of dopamine agonists, such as apomorphine, animals show a pronounced rotation in a direction contralateral to the side of lesioning. The ability of compounds to induce contralateral rotations in 6-OHDA lesioned rats has been shown to be a sensitive model to predict drug efficacy in the treatment of Parkinson's disease.

Male Sprague-Dawley rats are housed in a controlled environment and allowed to acclimatize before experimental use. Fifteen minutes prior to surgery, animals are given an intraperitoneal injection of the noradrenergic uptake inhibitor desipramine (25 mg/kg) to prevent damage to nondopamine neurons. Animals are then placed in an anesthetic chamber and anesthetized using a mixture of oxygen and isoflurane. Once unconscious, the animals are transferred to a stereotaxic frame, where anesthesia is maintained through a mask. The top of the head is shaved and sterilized using an iodine solution. Once dry, a 2 cm long incision is made along the midline of the scalp and the skin retracted and clipped back to expose the skull. A small hole is then drilled through the skull above the injection site. In order to lesion the nigrostriatal pathway, the injection cannula is slowly lowered to position above the right medial forebrain bundle at -3.2 mm anterior posterior, -1.5 mm medial lateral from the bregma, and to a depth of 7.2 mm below the duramater. Two minutes after lowering the cannula, 6-OHDA is infused at a rate of 0.5 μL/min over 4 min, to provide a final dose of 8 μg. The cannula is left in place for an additional 5 min to facilitate diffusion before being slowly withdrawn. The skin is then sutured shut, the animal removed from the sterereotaxic frame, and returned to its housing. The rats are allowed to recover from surgery for two weeks before behavioral testing.

Rotational behavior is measured using a rotameter system having stainless steel bowls (45 cm dia x 15 cm high) enclosed in a transparent Plexiglas cover around the edge of the bowl and extending to a height of 29 cm. To assess rotation, rats are placed in a cloth jacket attached to a spring tether connected to an optical rotameter positioned above the bowl, which assesses movement to the left or right either as partial (45°) or full (360°) rotations.

Treatment is given for a suitable period prior to testing. Animals are given a subcutaneous injection of a subthreshold dose of apomorphine, and are then placed in the harness. The number of rotations are recorded for one hour. The total number of full contralatral rotations during the hour test period serves as an index of antiparkinsonian drug efficacy.

*Animal Model for Assessing Therapeutic Effect for Treating Alzheimer's Disease*

Heterozygous transgenic mice expressing the Swedish AD mutant gene, hAPPK670N, M671L (Tg2576; Hsiao, Learning & Memory 2001, 8, 301-308) are used as an animal model of Alzheimer's disease. Animals are housed under standard conditions with a 12:12 light/dark cycle and food and water available ad libitum. Beginning at 9 months of age, mice are divided into two groups. The groups of animals receive treatment over six weeks.

Behavioral testing is performed at each drug dose using the same sequence over two weeks in all experimental groups: (1) spatial reversal learning, (2) locomotion, (3) fear conditioning, and (4) shock sensitivity.

Acquisition of the spatial learning paradigm and reversal learning are tested during the first five days of test compound administration using a water T-maze as described in Bardgett et al., Brain Res Bull 2003, 60, 131-142. Mice are habituated to the water T-maze during days 1-3, and task acquisition begins on day 4. On day 4, mice are trained to find the escape platform in one choice arm of the maze until 6 to 8 correct choices are made on consecutive trails. The reversal learning phase is then conducted on day 5. During the reversal learning phase, mice are trained to find the escape platform in the choice arm opposite from the location of the escape platform on day 4. The same performance criteria and inter-trial interval are used as during task acquisition.

Large ambulatory movements are assessed to determine that the results of the spatial reversal learning paradigm are not influenced by the capacity for ambulation. After a rest period of two days, horizontal ambulatory movements, excluding vertical and fine motor movements, are assessed in a chamber equipped with a grid of motion-sensitive detectors on day 8. The number of movements accompanied by simultaneous blocking and unblocking of a detector in the horizontal dimension are measured during a one-hour period.

The capacity of an animal for contextual and cued memory is tested using a fear conditioning paradigm beginning on day 9. Testing takes place in a chamber that contains a piece of absorbent cotton soaked in an odor-emitting solution such as mint extract placed below the grid floor. A 5-min, 3 trial 80 db, 2800 Hz tone-foot shock sequence is administered to train the animals on day 9. On day 10, memory for context is tested by returning each mouse to the chamber without exposure to the tone and foot shock, and recording the presence or absence of freezing behavior every 10 seconds for 8 minutes. Freezing is defined as no movement, such as ambulation, sniffing or stereotypy, other than respiration.

On day 11, the response of the animal to an alternate context and to the auditory cue is tested. Coconut extract is placed in a cup and the 80 dB tone is presented, but no foot shock is delivered. The presence or absence of freezing in response to the alternate context is then determined during the first 2 minutes of the trial. The tone is then presented continuously for the remaining 8 minutes of the trial, and the presence or absence of freezing in response to the tone is determined.

On day 12, the animals are tested to assess their sensitivity to the conditioning stimulus, i.e., foot shock. Following the last day of behavioral testing, animals are anesthetized and the brains removed, post-fixed overnight, and sections cut through the hippocampus. The sections are stained to image β-amyloid plaques.

Data is analyzed using appropriate statistical methods.

*Animal Model for Assessing Therapeutic Effect for Treating Huntington's Disease*

Neuroprotective Effects in a Transgenic Mouse Model of Huntington 's Disease Transgenic HD mice of the N171-82Q strain and non-transgenic littermates are treated from 10 weeks of age. The mice are placed on a rotating rod ("rotarod"). The length of time at which a mouse falls from the rotarod is recorded as a measure

of motor coordination. The total distance traveled by a mouse is also recorded as a measure of overall locomotion. Mice showing improved response to treatment with the combination of dimethyl fumarate and pioglitazone remain on the rotarod for a longer period of time and travel farther than mice administered vehicle or either agent alone.

*Malonate Model of Huntington's Disease*

A series of reversible and irreversible inhibitors of enzymes involved in energy generating pathways has been used to generate animal models for neurodegenerative diseases such as Parkinson's and Huntington's diseases. In particular, inhibitors of succinate dehydrogenase, an enzyme that impacts cellular energy homeostasis, has been used to generate a model for Huntington's disease.

In this malonate model for Huntington's disease, treatment is administered at an appropriate dose, dosing interval, and route, to male Sprague-Dawley rats. Treatment is administered for two weeks prior to the administration of malonate and then for an additional week prior to sacrifice. Malonate is dissolved in distilled deionized water and the pH adjusted to 7.4 with 0.1 M HCl. Intrastriatal injections of 1.5 μL of 3 μmol malonate are made into the left striatum at the level of the Bregma 2.4 mm lateral to the midline and 4.5 mm ventral to the dura. Animals are sacrificed at 7 days by decapitation and the brains quickly removed and placed in ice cold 0.9% saline solution. Brains are sectioned at 2 mm intervals in a brain mold. Slices are then placed posterior side down in 2% 2,3,5-tiphenyltetrazolium chloride. Slices are stained in the dark at room temperature for 30 min and then removed and placed in 4% paraformaldehyde pH 7.3. Lesions, noted by pale staining, are evaluated on the posterior surface of each section. The measurements are validated by comparison with measurements obtained on adjacent Nissl stain sections.

*Animal Model for Assessing Therapeutic Effect for Treating Amyotrophic Lateral Sclerosis*

A murine model of SOD1 mutation-associated ALS has been developed in which mice express the human superoxide dismutase (SOD) mutation glycine—alanine at residue 93 (SOD1). These SOD1 mice exhibit a dominant gain of the

adverse property of SOD, and develop motor neuron degeneration and dysfunction similar to that of human ALS. The SOD1 transgenic mice show signs of posterior limb weakness at about 3 months of age and die at 4 months. Features common to human ALS include astrocytosis, microgliosis, oxidative stress, increased levels of cyclooxygenase/prostaglandin, and, as the disease progresses, profound motor neuron loss. Studies are performed on transgenic mice overexpressing human Cu/Zn-SOD G93A mutations (B6S JL-TgN (SOD1-G93A) 1 Gur) and non-transgenic B6/SJL mice and their wild litter mates. Mice are housed on a 12-hr day/light cycle and (beginning at 45 d of age) allowed ad libitum access to either test compound-supplemented chow, or, as a control, regular formula cold press chow processed into identical pellets. Genotyping can be conducted at 21 days of age as described in Gurney et ah, Science 1994, 264(5166), 1772-1775. The SOD1 mice are separated into groups and treatment is administered for a suitable period.

The mice are observed daily and weighed weekly. To assess health status mice are weighed weekly and examined for changes in lacrimation/salivation, palpebral closure, ear twitch and pupillary responses, whisker orienting, postural and righting reflexes and overall body condition score. A general pathological examination is conducted at the time of sacrifice.

Motor coordination performance of the animals can be assessed by one or more methods known to those skilled in the art. For example, motor coordination can be assessed using a neurological scoring method. In neurological scoring, the neurological score of each limb is monitored and recorded according to a defined 4-point scale: 0 - normal reflex on the hind limbs (animal will splay its hind limbs when lifted by its tail); 1 - abnormal reflex of hind limbs (lack of splaying of hind limbs weight animal is lifted by the tail); 2 - abnormal reflex of limbs and evidence of paralysis; 3 - lack of reflex and complete paralysis; and 4 -inability to right when placed on the side in 30 seconds or found dead. The primary end point is survival with secondary end points of neurological score and body weight. Neurological score observations and body weight are made and recorded five days per week. Data analysis is performed using appropriate statistical methods. The rotarod test evaluates the ability of an animal to stay on a rotating dowel allowing evaluation of motor coordination and proprioceptive sensitivity. The apparatus is a 3 cm diameter automated rod turning at, for example, 12 rounds per min. The rotarod test

measures how long the mouse can maintain itself on the rod without falling. The test can be stopped after an arbitrary limit of 120 sec. Should the animal fall down before 120 sec, the performance is recorded and two additional trials are performed. The mean time of 3 trials is calculated. A motor deficit is indicated by a decrease of walking time.

In the grid test, mice are placed on a grid (length: 37 cm, width: 10.5 cm, mesh size: 1 x 1 cm2) situated above a plane support. The number of times the mice put their paws through the grid is counted and serves as a measure for motor coordination. The hanging test evaluates the ability of an animal to hang on a wire. The apparatus is a wire stretched horizontally 40 cm above a table. The animal is attached to the wire by its forepaws. The time needed by the animal to catch the string with its hind paws is recorded (60 sec max) during three consecutive trials.

Electrophysiological measurements (EMG) can also be used to assess motor activity condition. Electromyographic recordings are performed using an electromyography apparatus. During EMG monitoring mice are anesthetized. The measured parameters are the amplitude and the latency of the compound muscle action potential (CMAP). CMAP is measured in gastrocnemius muscle after stimulation of the sciatic nerve. A reference electrode is inserted near the Achilles tendon and an active needle placed at the base of the tail. A ground needle is inserted on the lower back of the mice. The sciatic nerve is stimulated with a single 0.2 msec pulse at supramaximal intensity (12.9 mA). The amplitude (mV) and the latency of the response (ms) are measured. The amplitude is indicative of the number of active motor units, while distal latency reflects motor nerve conduction velocity. The effect of the combinations according to the present invention can also be evaluated using biomarker analysis. To assess the regulation of protein biomarkers in SOD1 mice during the onset of motor impairment, samples of lumbar spinal cord (protein extracts) are applied to ProteinChip Arrays with varying surface chemical/biochemical properties and analyzed, for example, by surface enhanced laser desorption ionization time of flight mass spectrometry. Then, using integrated protein mass profile analysis methods, data is used to compare protein expression profiles of the various treatment groups. Analysis can be performed using appropriate statistical methods.

*Animal Model for Assessing Therapeutic Effect in myasthenia gravis*

Induction and clinical evaluation of EAMG according to International Immunology, Vol. 10, No. 9, pp. 1359–1365

B6 and μMT mice are immunized s.c. along the shoulders and back with 20 μg AChR with CFA in a total volume of 100 μl, and boosted twice at monthly intervals with 20 μg of AChR in CFA s.c. at four sites on the shoulders and thighs. The mice are observed every other day in a blinded fashion for signs of muscle weakness characteristic of EAMG. The clinical symptoms are graded between 0 and 3 (4): 0, no definite muscle weakness; 1, normal strength at rest but weak with chin on the floor and inability to raise the head after exercise consisting of 20 consecutive paw grips; 2, as grade 1 and weakness at rest; and 3, moribund, dehydrated and paralyzed. Clinical EAMG is confirmed by injection of neostigmine bromide and atropine sulfate. The mice are grouped and treatment is administered for a suitable period before testing.

*Animal model for assessing the therapeutic effect in alopecia*

The Dundee experimental bald rat (DEBR) and the C3H/HeJ mouse are well-established animal models for alopecia areata and can be used for the study of genetic aspects, pathogenesis and therapy of the disease. In C3H/HeJ mice alopecia areata can be experimentally induced by grafting lesional skin from an affected mouse to a histocompatible recipient which offers the possibility to study the influence of various factors on the development of the disease. The mice are grouped and treatment is administered for a suitable period before testing.

*General Experimental Protocol*

Treatment in the following animal models consists of, dimethyl fumarate dissolved or dispersed in 0.5% Hydroxypropyl methylcellulose (HPMC) K4 M/0.25% Tween 20 and pioglitazone dissolved or dispersed in kleptose in distilled water. Treatments were administered by oral gavage once or twice daily. Treatment groups were generally as follows: appropriate vehicles, dimethyl fumarate, pioglitazone or the combination of dimethyl fumarate and pioglitazone. The combination according to the invention results in an improved response to treatment over the vehicle and the respective agents alone.

*EAE Animal Model for Assessing Therapeutic Effect of the Combination of the PPAR gamma agonist and Nrf2 activator for treating Multiple Sclerosis*

Female C57BL/6 mice are ordered (Janvier France or Charles River) between 7-8 weeks old and used between 9-11 weeks after an acclimatization period. Experimental autoimmune encephalomyelitis (EAE) is actively induced using >95% pure synthetic myelin oligodendrocyte glycoprotein peptide 35-55 (MOG35-55), Met-Glu-Val-Gly-Trp-Tyr-Arg-Ser-Pro-Phe-Ser-Arg-Val-Val-His-Leu-Tyr-Arg-Asn-Gly-Lys, Ref SC1272, NeoMPS). Each mouse is anesthetized and receives a subcutaneous injection of 100 µl of a Complete Freunds Adjuvant (Ref 263810, Difco) emulsion containing 200 µg of MOG35-55 and 250 µg of dried and killed M. Tuberculosis H37 Ra, Ref 231141 Difco) into the lower back. The emulsion is prepared by the syringe method with two syringes connected through a Luer-lock tube. Mice also receive an intra-peritoneal injection of 300 ng of Pertussis Toxin (Ref BML-G100, Enzo Lifescience) diluted in 200 µl PBS. Pertussis Toxin injection is repeated 48 hours later. Mice are weighed and examined daily for clinical signs of EAE. Food and water are provided ad libitum.

Clinical Evaluation

Animals were assessed for neurological deficits (clinical score) and weighed daily. The clinical scoring scale is as follows; 0 = no signs; 0.5 = distal limp tail; 1 = complete tail paralysis; 1.5 = hind limb weakness; 2 = unilateral partial hind limb paralysis; 2.5 = bilateral partial hind limb paralysis; 3 = complete bilateral hind limb paralysis; 3.5 = fore limb weakness and complete bilateral hind limb paralysis; 4 = quadriplegia / moribund; 5 = death from EAE.

Results: Assessment of Treatment with dimethyl fumarate in combination with pioglitazone in form of its hydrochloride

Forty female C57BL/6 mice aged 8-9 weeks were immunized according to the EAE protocol described in the methods section. Mice were assorted into 4 different treatment groups (n=10) and received treatment with HPMC 0.5%/Tween20 0.25% (vehicle for dimethyl fumarate) b.i.d. plus Kleptose 20% (vehicle for pioglitazone) q.d., dimethyl fumarate 60 mg/kg b.i.d. plus Kleptose

20% q.d., pioglitazone 10 mg/kg q.d. plus HPMC 0.5%/Tween20 0.25% b.i.d. or dimethyl fumarate 60 mg/kg b.i.d plus pioglitazone 10 mg/kg q.d. For simplicity, the vehicle treatments were not mentioned in graph legends and the groups above were named as control, dimethyl fumarate 60 mg/kg bid, pioglitazone 10 mg/kg q.d or dimethyl fumarate + pioglitazone, respectively. Drug treatment started at day 0 post-immunisation. As shown in Fig 1A, immunization of C57BL/6 mice with MOG35-55 induces locomotor disability with the clinical signs arising around day 9 post-immunisation.

The effect of the combination (dimethyl fumarate + pioglitazone) treatment significantly reduced average daily clinical scores (Fig. 1A). The combination efficacy was more pronounced and statistically different from the effect of individual treatments. Suppression of inflammation-induced cachexia acts as a reliable marker of treatment benefit. Combination treatment (dimethyl fumarate + pioglitazone) treatment significantly improved body weight in comparison to vehicle or single drug treatments (Fig. 1B).

The effect of drug treatment on the prevalence of disease is analysed on Fig 2. The onset of disease is defined at the point each mouse first exhibit a clinical score $\geq 1$. Fig 2A depicts a Kaplan Meier analysis showing that control group mice start developing EAE from day 9 with complete susceptibility by day 14 post-immunisation. The combination treatment with dimethyl fumarate + pioglitazone shifted the EAE onset curve. Not all animals treated with the drug combination developed signs of disease until the termination of the experiment i.e. day 22 post-immunisation. The effect of the combination treatment was statistically different not only in comparison with the control group, but also in comparison with each of the drugs dosed alone. Fig 2B is a different representation of the same data. On average, mice treated with vehicle, dimethyl fumarate or pioglitazone alone indistinctly exhibited first clinical signs of disease around day 12-13 post-immunisation, whereas in the combination group the average onset of EAE was around day 17 post-immunisation. The effect of the combination treatment was again statistically different from and more potent than the other treated groups. This data shows that combination treatment results in a synergistic treatment effect which is not observed by individual treatments.

Gastrointestinal changes including haemorrhage are known side-effects of dimethyl fumarate treatment. Combination treatment and dimethyl fumarate alone treatment resulted in similar hyperplasia of the macrovilosity of the stomach. There was no worsening of symptoms with combination treatment. Representative images of the stomach of mice chronically treated for 22 days with dimethyl fumarate, pioglitazone or their vehicles are shown in Fig 3 to demonstrate some of these observations. Importantly, the synergistic efficacy discussed in the previous paragraphs was not associated with increased gastrointestinal adverse events.

## BRIEF DESCRIPTION OF THE FIGURES

**Figure 1**: Combination treatment with dimethyl fumarate + pioglitazone is significantly more efficacious than each individual drug as stand-alone treatments or treatment with vehicle on mean clinical scores and also on body weight changes associated with disease. Average clinical scores (A) and percentual body weight changes (B) of MOG35-55 mice treated with vehicle, dimethyl fumarate, pioglitazone or a combination of both drugs from day 0-post immunisation. Kruskal-Wallis (non-parametric ANOVA) with Dunn's multiple test correction was applied in A and Student's t-test in B. Horizontal bars represent $P<0.05$ where $\lambda$ compares combination treatment *versus* vehicle; $\Psi$ combination treatment *versus* dimethyl fumarate and $\Phi$ combination treatment *versus* pioglitazone.

**Figure 2**: Combination treatment with dimethyl fumarate + pioglitazone causes a delay on the onset of disease in comparison with each individual drug as stand-alone treatments or treatment with vehicle. Kaplan Meier analysis of the disease prevalence curves (A) and average day of onset of disease (B) of MOG35-55 mice treated with vehicle, dimethyl fumarate, pioglitazone or a combination of both drugs from day 0-post immunisation. The onset of disease was defined as the day mice first exhibit a clinical score $\geq 1$. Gehan-Breslow-Wilcoxon test was applied in A and Kruskal-Wallis followed by Dunn's multiple test correction in B. Horizontal bars represent $P<0.05$ where $\lambda$ compares combination treatment *versus* vehicle; $\Psi$ combination treatment *versus* dimethyl fumarate and $\Phi$ combination treatment *versus* pioglitazone.

**Figure 3:** Alteration in the macroscopical appearance of the stomach of mice chronically treated with dimethyl fumarate, but not with pioglitazone or vehicle. Forty C57BL/6 mice immunized with MOG35-55 and treated by oral gavage for 22 days with a combination of HPMC0.5%/Tween20 0.25% b.i.d. plus Kleptose 20% q.d. (A, Figure 3A), dimethyl fumarate 60 mg/kg b.i.d. plus Kleptose 20% q.d (B), pioglitazone 10 mg/kg q.d. plus HPMC 0.5%/Tween20 0.25% b.i.d. (C, Figure C) or dimethyl fumarate 60 mg/kg b.i.d plus pioglitazone 10 mg/kg q.d. (D, Figure 3D). An additional group of five mice were sham-immunized (emulsion without MOG35-55) and treated with HPMC0.5%/Tween20 0.25% b.i.d. plus Kleptose 20% q.d. (E, Figure 3E). Throughout the length of the experiment three mice were either sacrificed due to humane end-points or succumbed to disease. The forty-two remaining animals were euthanized under pentobarbital terminal anesthesia, the right atrium of the heart was incised and mice were perfused with 4% paraformaldehyde through the left ventricle. The stomach of each mouse was dissected by a transection of the proximal segment of the oesophagus and the duodenum then cut open via a longitudinal incision through the longest possible axis linking the remaining stretch of duodenum and the *Fundus*. Each piece was washed with phosphate buffered saline and open-mounted. The images shown are from one representative mouse from each group. Note the normal appearance of stomachs of all groups of mice that were not exposed to dimethyl fumarate (A, C, E, Figures 3A, 3C, 3E, respectively) and the seemingly pathological increase in macrovilosity of the stomachs of groups B and D that were treated with dimethyl fumarate as stand-alone or combination treatment with pioglitazone, respectively, giving them a thickened and rugous appearance (Figures 3B, 3D, respectively).

## CLAIMS

1. A PPAR gamma agonist selected from the group of glitazones for use in the treatment of an autoimmune and/or inflammatory disorder, wherein said PPAR gamma agonist is administered simultaneously, separately or sequentially with a) an isolated Nrf2 activator, selected from the group of fumaric acid esters, bardoxolone methyl (methyl 2-cyano-3,12-dioxooleana-1,9(11)dien-28-oate, CDDO-Me, RTA 402), ethyl 2-cyano-3,12-dioxooleana-1,9(11)dien-28-oate, 2-cyano-3,12-dioxooleana-1,9(11)dien-28-oic acid (CDDO), 1[2-Cyano-3,12-dioxooleana-1,9(11)-dien-28-oyl]imidazole (CDDO-Im), 2-cyano-N-methyl-3,12-dioxooleana-1,9(11)-dien-28 amide (CDDO-methyl amide, CDDO-MA), [(±)-(4bS,8aR,10aS)-10a-ethynyl-4b,8,8-trimethyl-3,7-dioxo-3,4b,7,8,8a,9,10,10a-octahydrophenanthrene-2,6-dicarbonitrile] (TBE-31), 2-cyano-3,12-dioxooleana-1,9(11)-dien-28-onitrile (TP-225), 3-tert-butyl-4-hydroxyanisole, 2-tert-butyl-4-hydroxyanisole (BHA), tert-butylquinone (tBQ), tert-butylhydroquinone (tBHQ), 3,5-di-tert-butyl-4-hydroxytoluene (BHT), 2,6-Di-tert-butyl-4-methylene-2,5-cyclohexadien-1-one (2,6-Di-tert-butylquinone methide, BHT-quinone methide), ethoxyquin, gallic acid esters, curcumin, reservatrol, menadione, cinnamic aldehyde, cinnamic acid esters, caffeic acid esters, cafestol, kahweol, lycopene, carnosol, sulforaphane, oltipraz, 5-(4-methoxy-phenyl)-1,2-dithiole-3-thione (ADT), 5-amino-2-hydroxy-benzoic acid 4-(5-thioxo-5H-[1,2]dithiol-3-yl)-phenyl ester (ATB-429), allicin, allylisothiocyanate, zerumbone, phenethyl isothiocyanate, benzyl isothiocyanate, alkylsulfinylalkyl isothiocyanate, such as 6-methylsulfinylhexyl isothiocyanate as well as alkyl and alkanoyl esters, alkyl ethers, stereoisomers, tautomers and salts of the aforementioned agents, or b) a pharmaceutical composition comprising said isolated Nrf2 activator,

provided that

no hydroxyurea is administered with the PPAR gamma agonist pioglitazone for use in the treatment of psoriasis wherein pioglitazone is administered simultaneously, separately or sequentially with a fumaric acid ester.

2. A PPAR gamma agonist for use according to the aforementioned claim, wherein the autoimmune and/or inflammatory disorder is selected from psoriasis,

scleroderma, chronic kidney disease (CKD), neurodegenerative diseases, asthma, chronic obstructive pulmonary disorder (COPD), fibrosis, inflammatory arthritis disease and inflammatory bowel disease (IBD).

3. A PPAR gamma agonist for use according to the aforementioned claim, wherein the autoimmune and/or inflammatory disorder is a neurodegenerative disease selected from multiple sclerosis, clinically isolated syndrome (CIS), amyotrophic lateral sclerosis, Alzheimer's disease, dementia, Huntington's disease, and Parkinson's disease.

4. A PPAR gamma agonist selected from the group of glitazones for use in the reduction of inflammation in a patient, wherein said PPAR gamma agonist is administered simultaneously, separately or sequentially with a) an isolated Nrf2 activator, selected from the group of fumaric acid esters, bardoxolone methyl (methyl 2-cyano-3,12-dioxooleana-1,9(11)dien-28-oate, CDDO-Me, RTA 402), ethyl 2-cyano-3,12-dioxooleana-1,9(11)dien-28-oate, 2-cyano-3,12-dioxooleana-1,9(11)dien-28-oic acid (CDDO), 1[2-Cyano-3,12-dioxooleana-1,9(11)-dien-28-oyl]imidazole (CDDO-Im), 2-cyano-N-methyl-3,12-dioxooleana-1,9(11)-dien-28 amide (CDDO-methyl amide, CDDO-MA), [(±)-(4bS,8aR,10aS)-10a-ethynyl-4b,8,8-trimethyl-3,7-dioxo-3,4b,7,8,8a,9,10,10a-octahydrophenanthrene-2,6-dicarbonitrile] (TBE-31), 2-cyano-3,12-dioxooleana-1,9(11)-dien-28-onitrile (TP-225), 3-tert-butyl-4-hydroxyanisole, 2-tert-butyl-4-hydroxyanisole (BHA), tert-butylquinone (tBQ), tert-butylhydroquinone (tBHQ), 3,5-di-tert-butyl-4-hydroxytoluene (BHT), 2,6-Di-tert-butyl-4-methylene-2,5-cyclohexadien-1-one (2,6-Di-tert-butylquinone methide, BHT-quinone methide), ethoxyquin, gallic acid esters, curcumin, reservatrol, menadione, cinnamic aldehyde, cinnamic acid esters, caffeic acid esters, cafestol, kahweol, lycopene, carnosol, sulforaphane, oltipraz, 5-(4-methoxy-phenyl)-1,2-dithiole-3-thione (ADT), 5-amino-2-hydroxy-benzoic acid 4-(5-thioxo-5H-[1,2]dithiol-3-yl)-phenyl ester (ATB-429), allicin, allylisothiocyanate, zerumbone, phenethyl isothiocyanate, benzyl isothiocyanate, alkylsulfinylalkyl isothiocyanate, such as 6-methylsulfinylhexyl isothiocyanate as well as alkyl and alkanoyl esters, alkyl ethers, stereoisomers, tautomers and salts of

the aforementioned agents, or b) a pharmaceutical composition comprising said isolated Nrf2 activator,

provided that

no hydroxyurea is administered with the PPAR gamma agonist pioglitazone for use in the reduction of inflammation in a patient, which is occurring with and/or is resulting from psoriasis, wherein pioglitazone is administered simultaneously, separately or sequentially with a fumaric acid ester.

5. A PPAR gamma agonist for use according to the aforementioned claim, wherein the inflammation is a chronic inflammation.

6. A PPAR gamma agonist for use according to the aforementioned claims, wherein the PPAR gamma agonist is selected from pioglitazone and rosiglitazone.

7. A PPAR gamma agonist for use according to the aforementioned claims, wherein the PPAR gamma agonist is pioglitazone in a daily dose of about 45 mg.

8. A PPAR gamma agonist for use according to the aforementioned claims, wherein the PPAR gamma agonist is rosiglitazone in a daily dose of about 8 mg.

9. A PPAR gamma agonist for use according to the aforementioned claims, wherein the Nrf2 activator is a fumaric acid ester selected from dialkyl fumarate and monoalkyl fumarate.

10. A PPAR gamma agonist for use according to the aforementioned claims, wherein the Nrf2 activator is dimethyl fumarate.

11. A PPAR gamma agonist for use according to the aforementioned claims, wherein the Nrf2 activator is dimethyl fumarate in a daily dose of about 480 mg or about 720 mg.

12. A pharmaceutical composition comprising a PPAR gamma agonist selected from the group of glitazones and an Nrf2 activator selected from the group

of fumaric acid esters, bardoxolone methyl (methyl 2-cyano-3,12-dioxooleana-1,9(11)dien-28-oate, CDDO-Me, RTA 402), ethyl 2-cyano-3,12-dioxooleana-1,9(11)dien-28-oate, 2-cyano-3,12-dioxooleana-1,9(11)dien-28-oic acid (CDDO), 1[2-Cyano-3,12-dioxooleana-1,9(11)-dien-28-oyl]imidazole (CDDO-Im), 2-cyano-N-methyl-3,12-dioxooleana-1,9(11)-dien-28 amide (CDDO-methyl amide, CDDO-MA), [(±)-(4bS,8aR,10aS)-10a-ethynyl-4b,8,8-trimethyl-3,7-dioxo-3,4b,7,8,8a,9,10,10a-octahydrophenanthrene-2,6-dicarbonitrile] (TBE-31), 2-cyano-3,12-dioxooleana-1,9(11)-dien-28-onitrile (TP-225), 3-tert-butyl-4-hydroxyanisole, 2-tert-butyl-4-hydroxyanisole (BHA), tert-butylquinone (tBQ), tert-butylhydroquinone (tBHQ), 3,5-di-tert-butyl-4-hydroxytoluene (BHT), 2,6-Di-tert-butyl-4-methylene-2,5-cyclohexadien-1-one (2,6-Di-tert-butylquinone methide, BHT-quinone methide), ethoxyquin, gallic acid esters, curcumin, reservatrol, menadione, cinnamic aldehyde, cinnamic acid esters, caffeic acid esters, cafestol, kahweol, lycopene, carnosol, sulforaphane, oltipraz, 5-(4-methoxy-phenyl)-1,2-dithiole-3-thione (ADT), 5-amino-2-hydroxy-benzoic acid 4-(5-thioxo-5H-[1,2]dithiol-3-yl)-phenyl ester (ATB-429), allicin, allylisothiocyanate, zerumbone, phenethyl isothiocyanate, benzyl isothiocyanate, alkylsulfinylalkyl isothiocyanate, such as 6-methylsulfinylhexyl isothiocyanate, as well as alkyl and alkanoyl esters, alkyl ethers, stereoisomers, tautomers and salts of the aforementioned agents, and optionally one or more excipients.

13. A pharmaceutical composition according to the aforementioned claim, wherein the PPAR gamma agonist is selected from pioglitazone and rosiglitazone.

14. A pharmaceutical composition according to the aforementioned claim, comprising about 5 mg, about 7.5 mg, about 10 mg, about 15 mg, about 20 mg, about 22.5 mg or about 25 mg of pioglitazone.

15. A pharmaceutical composition according to the aforementioned claim, comprising about 0.7 mg, about 1 mg, about 1.3 mg, about 2 mg, about 2.7 mg, about 3 mg, about 3.5 mg, about 4 or about 5 mg of rosiglitazone.

16. A pharmaceutical composition according to the aforementioned claims, wherein the Nrf2 activator is a fumaric acid ester selected from dialkyl fumarate and monoalkyl fumarate.

17. A pharmaceutical composition according to the aforementioned claims, wherein the Nrf2 activator is dimethyl fumarate.

18. A pharmaceutical composition according to the aforementioned claims, comprising about 240 mg of dimethyl fumarate.

19. A solid oral dosage form comprising the pharmaceutical composition according to the aforementioned claims.

20. A pharmaceutical composition according to claims 12, 13, 14, 15, 16, 17 or 18 for use in the treatment of an autoimmune and/or inflammatory disorder.

21. A pharmaceutical composition for use according to the aforementioned claim, wherein the autoimmune and/or inflammatory disorder is selected from psoriasis, scleroderma, chronic kidney disease (CKD), neurodegenerative diseases, asthma, chronic obstructive pulmonary disorder (COPD), fibrosis, inflammatory arthritis disease and inflammatory bowel disease (IBD).

22. A pharmaceutical composition for use according to the aforementioned claim, wherein the autoimmune and/or inflammatory disorder is a neurodegenerative disease selected from multiple sclerosis, clinically isolated syndrome (CIS), amyotrophic lateral sclerosis, Alzheimer's disease, dementia, Huntington's disease, and Parkinson's disease.

23. A pharmaceutical composition according to claims 12, 13, 14, 15, 16, 17 or 18 for use in the reduction of inflammation in a patient.

24. A pharmaceutical composition for use according to the aforementioned claim, wherein the inflammation is a chronic inflammation.

25. A kit of parts comprising a) a PPAR gamma agonist selected from the group of glitazones and b) an Nrf2 activator selected from the group of fumaric acid esters, bardoxolone methyl (methyl 2-cyano-3,12-dioxooleana-1,9(11)dien-28-oate, CDDO-Me, RTA 402), ethyl 2-cyano-3,12-dioxooleana-1,9(11)dien-28-oate, 2-cyano-3,12-dioxooleana-1,9(11)dien-28-oic acid (CDDO), 1[2-Cyano-3,12-dioxooleana-1,9(11)-dien-28-oyl]imidazole (CDDO-Im), 2-cyano-N-methyl-3,12-dioxooleana-1,9(11)-dien-28 amide (CDDO-methyl amide, CDDO-MA), [(±)-(4bS,8aR,10aS)-10a-ethynyl-4b,8,8-trimethyl-3,7-dioxo-3,4b,7,8,8a,9,10,10a-octahydrophenanthrene-2,6-dicarbonitrile] (TBE-31), 2-cyano-3,12-dioxooleana-1,9(11)-dien-28-onitrile (TP-225), 3-tert-butyl-4-hydroxyanisole, 2-tert-butyl-4-hydroxyanisole (BHA), tert-butylquinone (tBQ), tert-butylhydroquinone (tBHQ), 3,5-di-tert-butyl-4-hydroxytoluene (BHT), 2,6-Di-tert-butyl-4-methylene-2,5-cyclohexadien-1-one (2,6-Di-tert-butylquinone methide, BHT-quinone methide), ethoxyquin, gallic acid esters, curcumin, reservatrol, menadione, cinnamic aldehyde, cinnamic acid esters, caffeic acid esters, cafestol, kahweol, lycopene, carnosol, sulforaphane, oltipraz, 5-(4-methoxy-phenyl)-1,2-dithiole-3-thione (ADT), 5-amino-2-hydroxy-benzoic acid 4-(5-thioxo-5H-[1,2]dithiol-3-yl)-phenyl ester (ATB-429), allicin, allylisothiocyanate, zerumbone, phenethyl isothiocyanate, benzyl isothiocyanate, alkylsulfinylalkyl isothiocyanate, such as 6-methylsulfinylhexyl isothiocyanate as well as alkyl and alkanoyl esters, alkyl ethers, stereoisomers, tautomers and salts of the aforementioned agents, and optionally c) instructions for a dosing regimen.

26. A kit of parts according to the aforementioned claims, wherein the PPAR gamma agonist is selected from pioglitazone and rosiglitazone.

27. A kit of parts according to the aforementioned claims, wherein the Nrf2 activator is a fumaric acid ester selected from dialkyl fumarate and monoalkyl fumarate.

28. A kit of parts according to the aforementioned claim, wherein the Nrf2 activator is dimethyl fumarate.

**Figure 1**

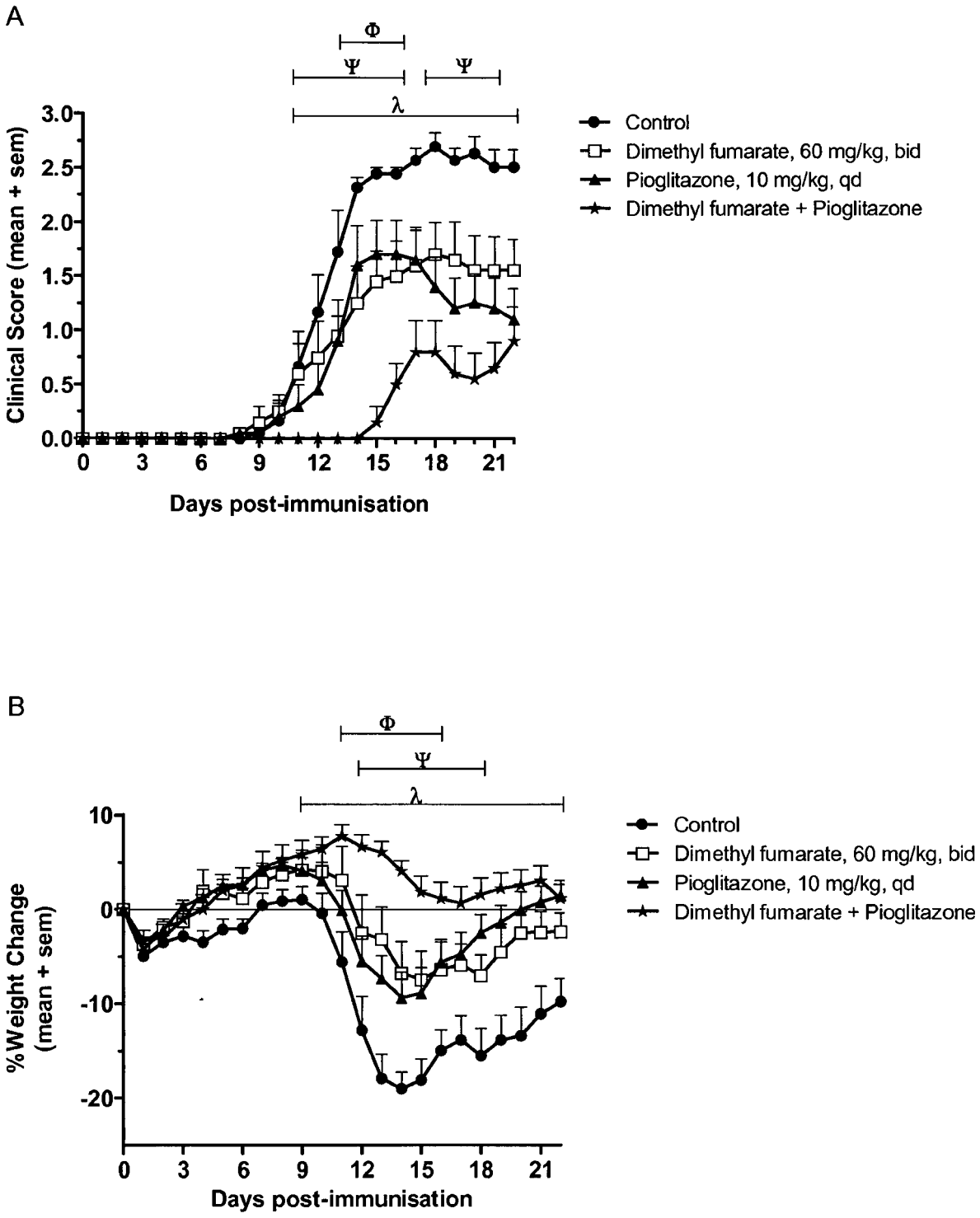
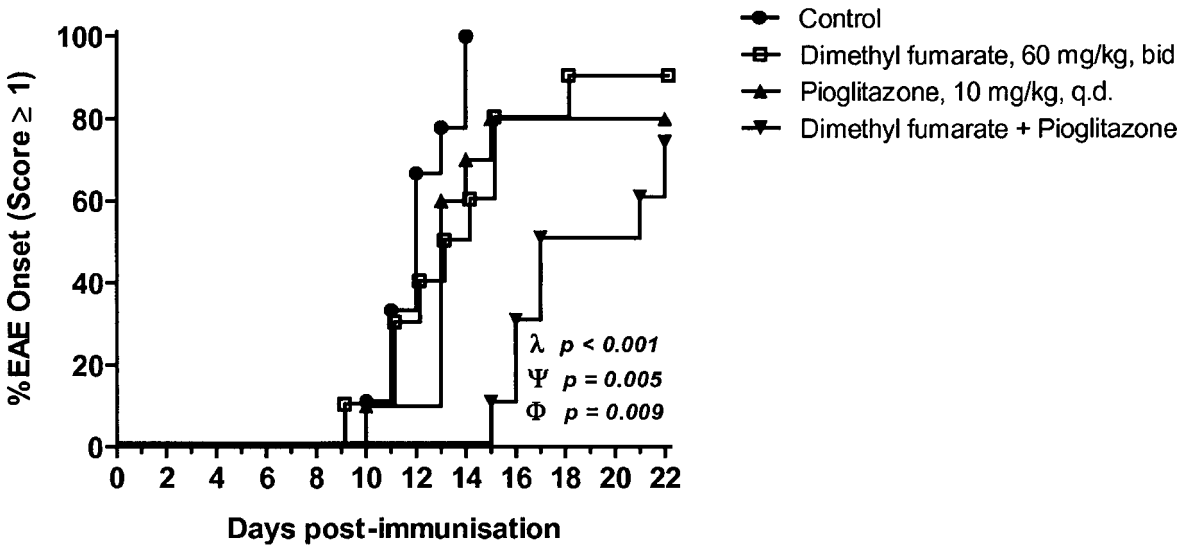

A
Φ
Ψ
Ψ
λ
Clinical Score (mean + sem)
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0
3
6
9
12
15
18
21
Days post-immunisation
Control
Dimethyl fumarate, 60 mg/kg, bid
Pioglitazone, 10 mg/kg, qd
Dimethyl fumarate + Pioglitazone
B
Φ
Ψ
λ
%Weight Change (mean + sem)
10
0
-10
-20
0
3
6
9
12
15
18
21
Days post-immunisation
Control
Dimethyl fumarate, 60 mg/kg, bid
Pioglitazone, 10 mg/kg, qd
Dimethyl fumarate + Pioglitazone

**Figure 2**

A


% EAE Onset (Score ≥ 1)
100
80
60
40
20
0
0 2 4 6 8 10 12 14 16 18 20 22
Days post-immunisation
λ p < 0.001
Ψ p = 0.005
Φ p = 0.009
Control
Dimethyl fumarate, 60 mg/kg, bid
Pioglitazone, 10 mg/kg, q.d.
Dimethyl fumarate + Pioglitazone

B

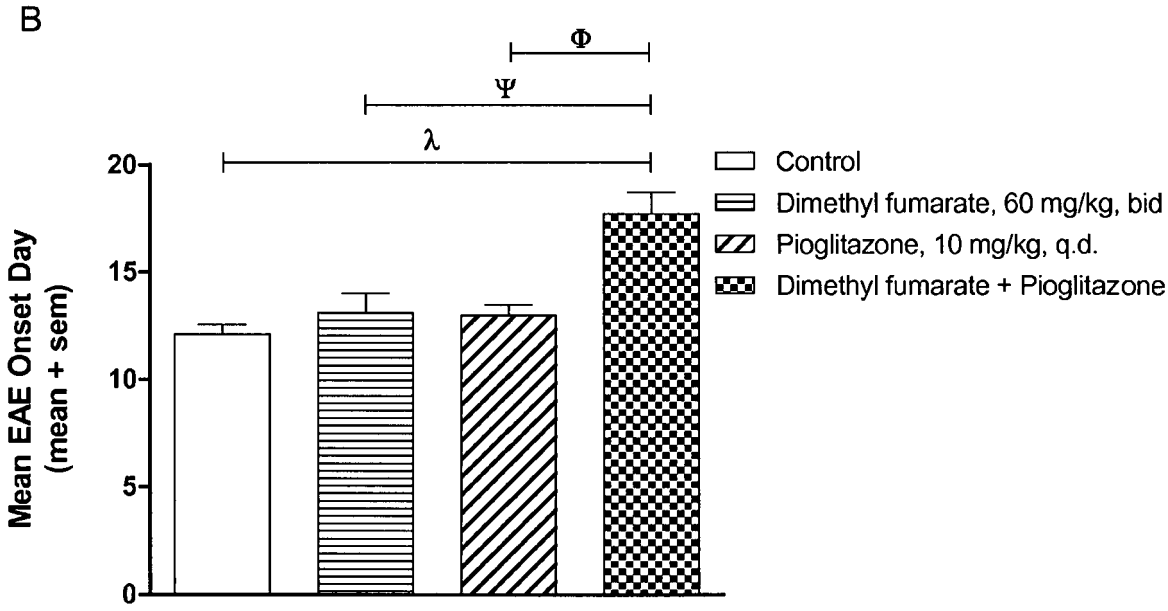

Φ
Ψ
λ
Mean EAE Onset Day
(mean + sem)
20
15
10
5
0
Control
Dimethyl fumarate, 60 mg/kg, bid
Pioglitazone, 10 mg/kg, q.d.
Dimethyl fumarate + Pioglitazone

**Figure 3**

**Figure 3A**

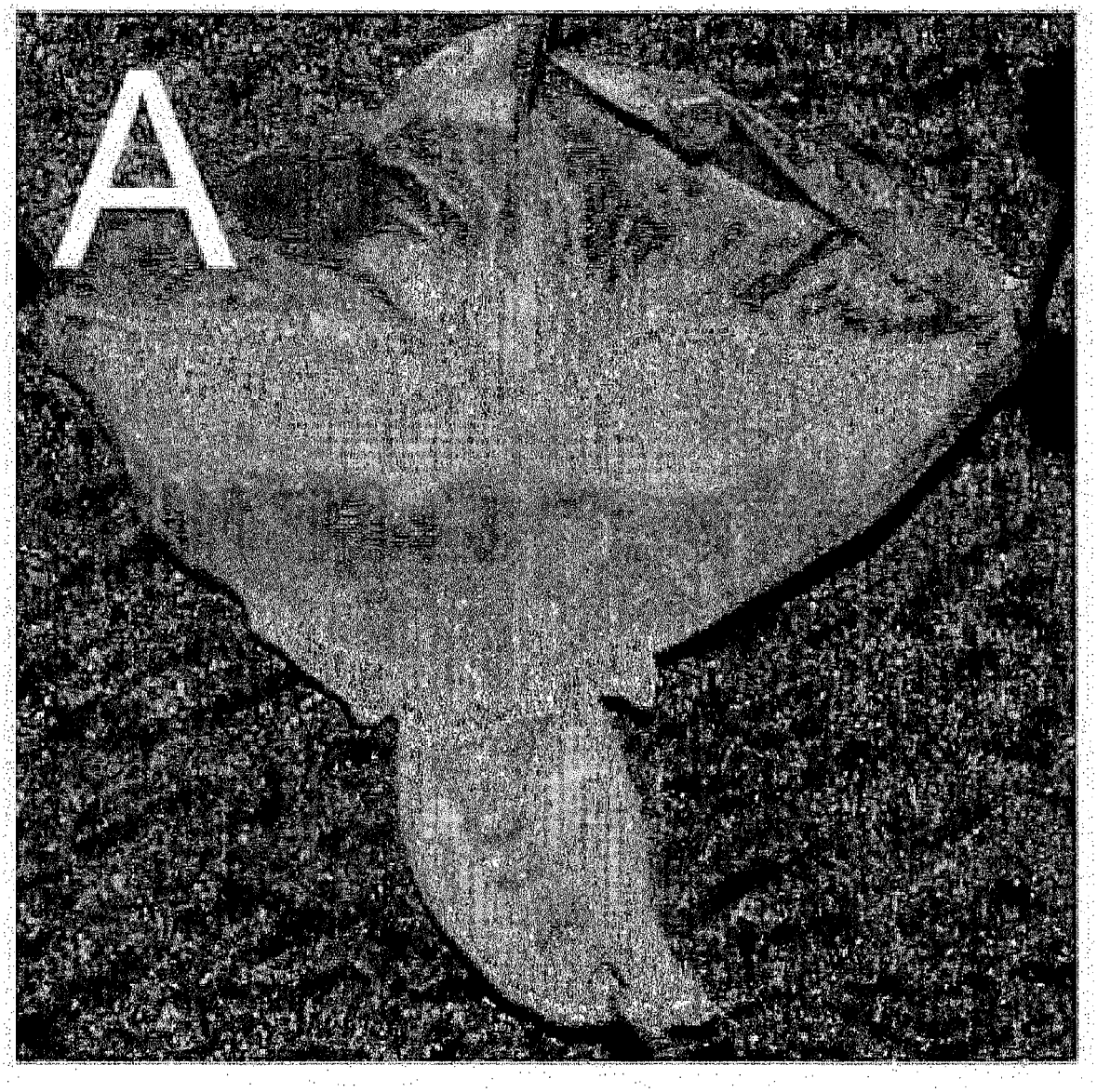


**Figure 3B**

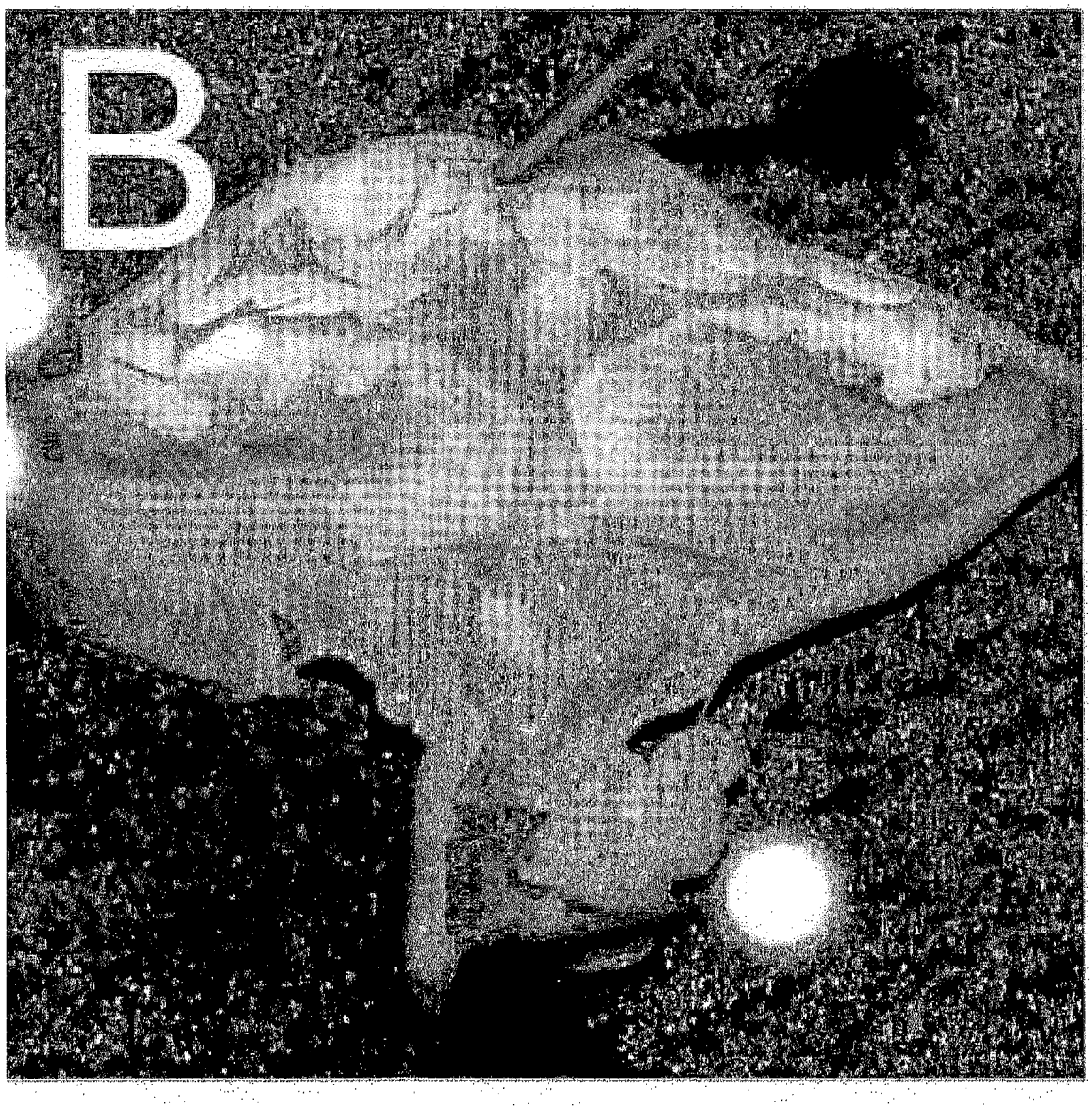


Figure 3C

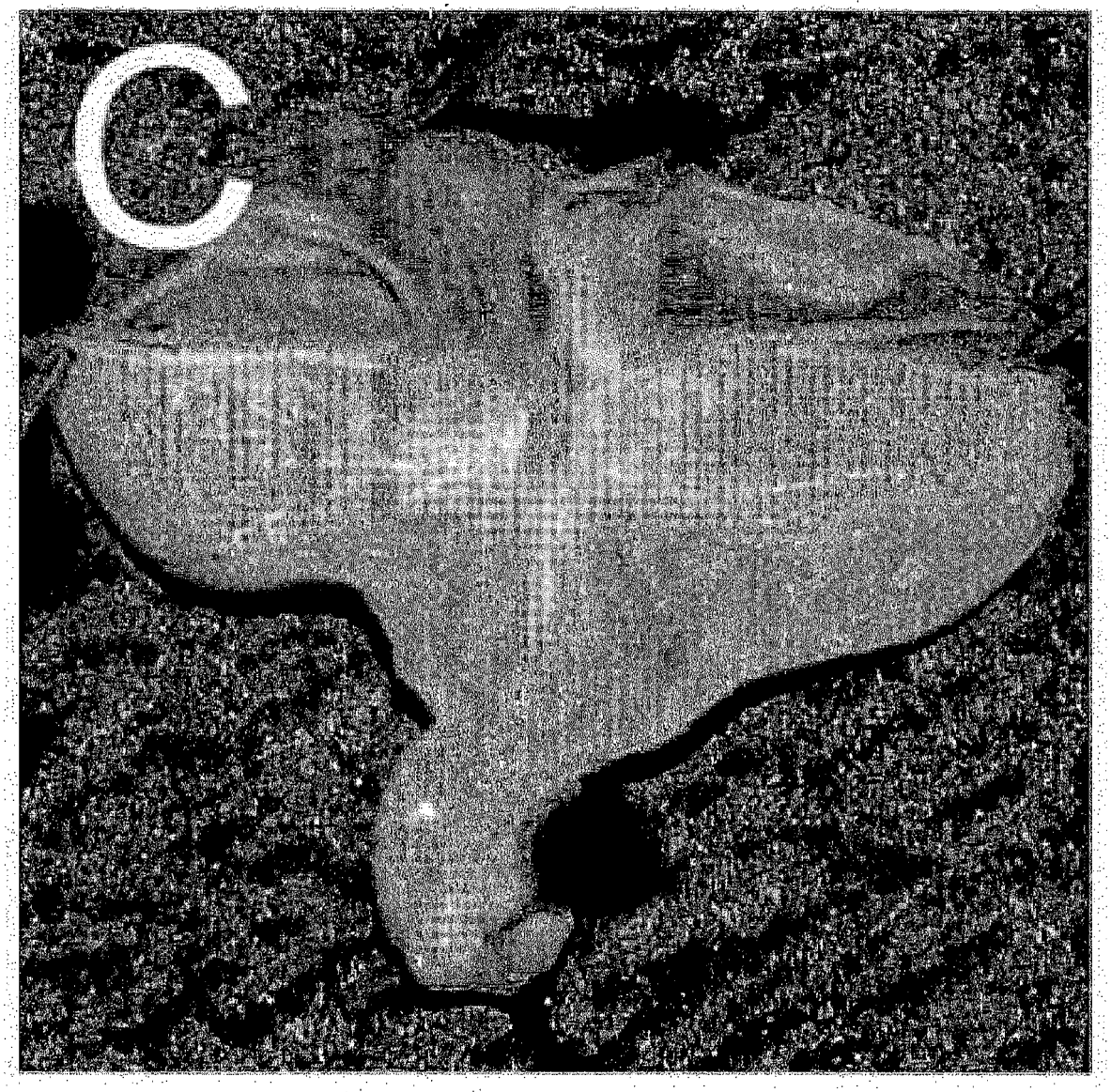


Figure 3D

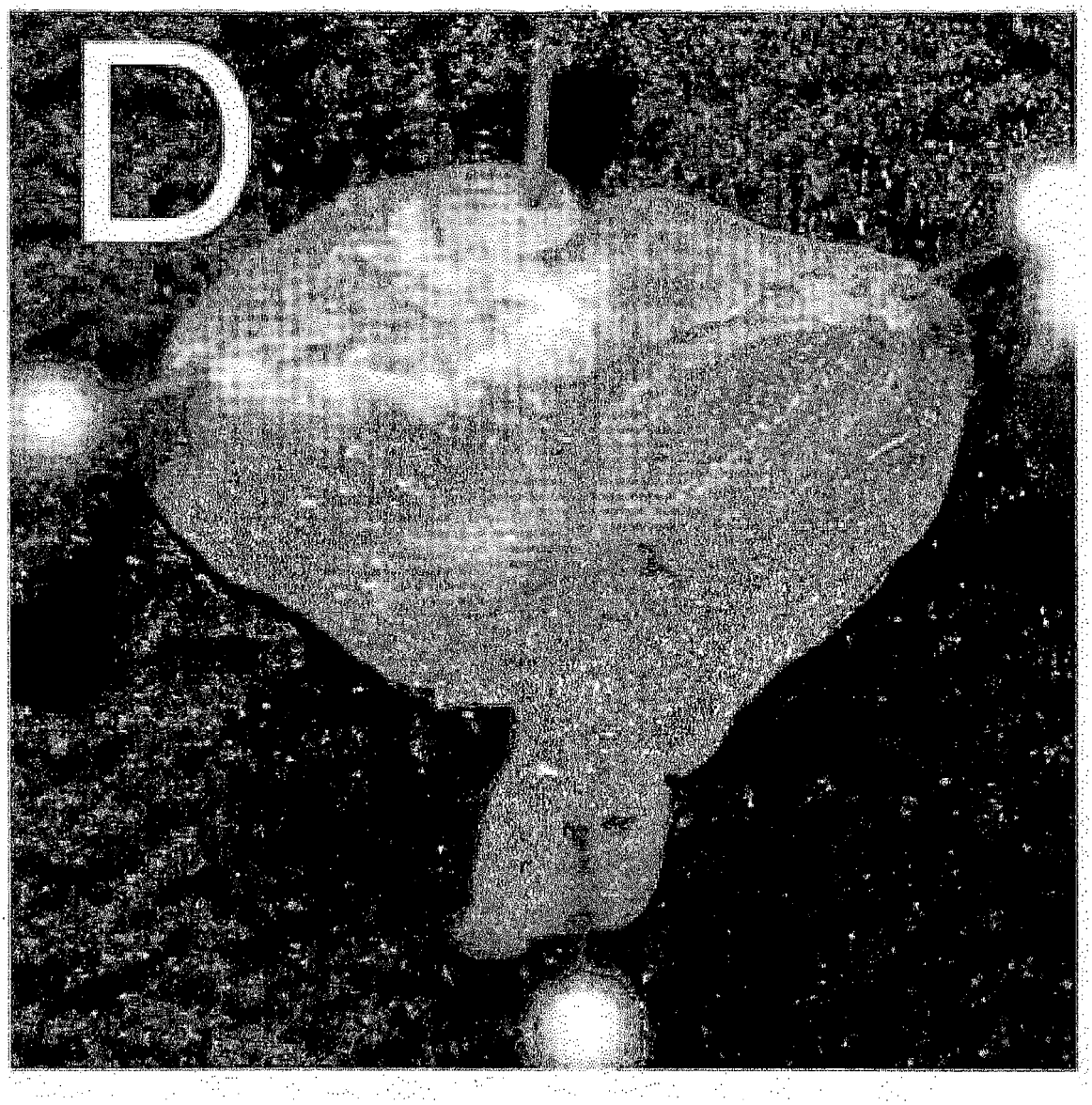
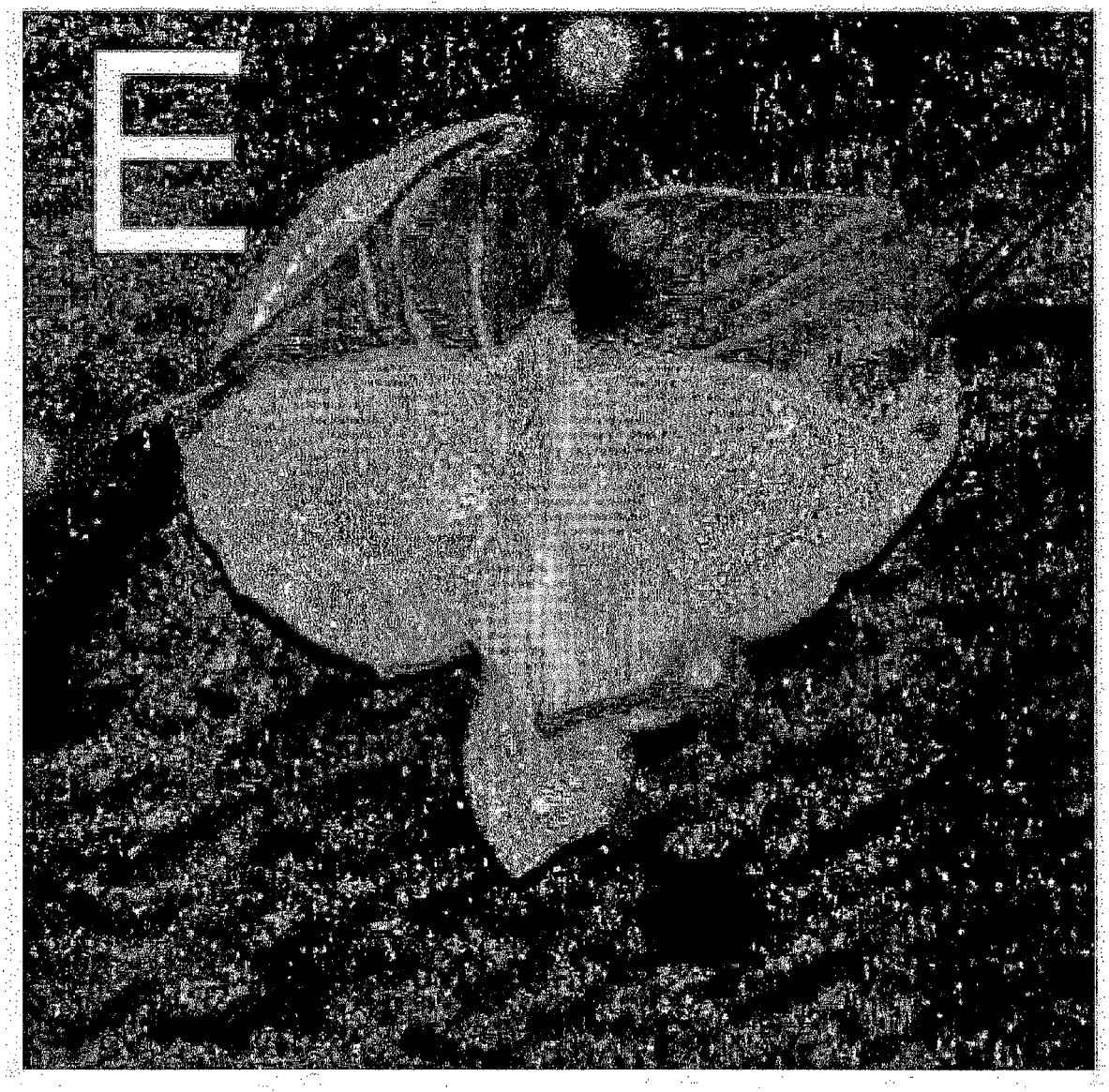


**Figure 3E**



# INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2012/074915

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/225 A61K31/4439 A61K31/70 A61K45/06 A61P17/06
A61P1/04 A61P17/14 A61P5/48 A61P21/04 A61K31/05
A61K31/12 A61K31/16 A61K31/19 A61K31/216 A61K31/26

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, EMBASE, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 10 April 2013 | 18/04/2013 |

| Name and mailing address of the ISA/ | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040,<br>Fax: (+31-70) 340-3016 | Jakobs, Andreas |

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| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
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Information on patent family members

International application No
PCT/EP2012/074915

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(71)申请人 阿雷斯贸易股份有限公司
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代理人 沈晓书 黄革生

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*A61K 31/4439*(2006.01)
*A61K 31/70*(2006.01)
*A61K 45/06*(2006.01)
*A61P 17/06*(2006.01)
*A61P 1/04*(2006.01)
*A61P 17/14*(2006.01)
*A61P 5/48*(2006.01)
*A61P 21/04*(2006.01)
*A61K 31/05*(2006.01)
*A61K 31/12*(2006.01)
*A61K 31/16*(2006.01)
*A61K 31/19*(2006.01)
*A61K 31/216*(2006.01)
*A61K 31/26*(2006.01)
*A61K 31/385*(2006.01)
*A61K 31/47*(2006.01)

权利要求书4页 说明书55页 附图7页

(54)发明名称

包含格列酮和NRF2激活剂的药物组合物

(57)摘要

本发明涉及包含PPAR激动剂和Nrf2激活剂的药物组合物和使用的PPAR激动剂和Nrf2激活剂的组合治疗疾病例如银屑病、哮喘、多发性硬化、炎性肠病和关节炎的方法。

CN 103998035 A

1. 选自格列酮的 PPARγ 激动剂，其用于治疗自身免疫障碍和 / 或炎性障碍，其中所述 PPARγ 激动剂与如下成分同时、分别或依次施用 :a) 分离的 Nrf2 激活剂，其选自富马酸酯、甲基巴多索隆 (2- 氰基 -3,12- 二氧代齐墩果 -1,9(11) 二烯 -28- 酸甲酯，CDDO-Me，RTA 402)、2- 氰基 -3,12- 二氧代齐墩果 -1,9(11) 二烯 -28- 酸乙酯、2- 氰基 -3,12- 二氧代齐墩果 -1,9(11) 二烯 -28- 酸 (CDDO)、1[2- 氰基 -3,12- 二氧代齐墩果 -1,9(11)- 二烯 -28- 酰基 ] 咪唑 (CDDO-Im)、2- 氰基 -N- 甲基 -3,12- 二氧代齐墩果 -1,9(11)- 二烯 -28 酰胺 (CDDO- 甲基酰胺，CDDO-MA)、[(±)-(4bS,8aR,10aS)-10a- 乙炔基 -4b,8,8- 三甲基 -3,7- 二氧代 -3,4b,7,8,8a,9,10,10a- 八氢菲 -2,6- 二腈 ](TBE-31)、2- 氰基 -3,12- 二氧代齐墩果 -1,9(11)- 二烯 -28- 腈 (TP-225)、3- 叔丁基 -4- 羟基苯甲醚、2- 叔丁基 -4- 羟基苯甲醚 (BHA)、叔丁基醌 (tBQ)、叔丁基氢醌 (tBHQ)、3,5- 二 - 叔丁基 -4- 羟基甲苯 (BHT)、2,6- 二 - 叔丁基 -4- 亚甲基 -2,5- 环己二烯 -1- 酮 (2,6- 二 - 叔丁基醌甲基化物，BHT- 醌甲基化物 )、乙氧喹、没食子酸酯、姜黄素、白藜芦醇、甲萘醌、肉桂醛、肉桂酸酯、咖啡酸酯、咖啡醇、咖啡白脂、番茄红素、鼠尾草酚、莱菔硫烷、奥替普拉、5-(4- 甲氧基 - 苯基 )-1,2- 二硫杂环戊二烯 -3- 硫酮 (ADT)、5- 氨基 -2- 羟基 - 苯甲酸 4-(5- 硫代 -5H-[1,2] 二硫杂环戊二烯 -3- 基 )- 苯基酯 (ATB-429)、大蒜素、异硫氰酸烯丙酯、花姜酮、异硫氰酸苯乙酯、异硫氰酸苄酯、异硫氰酸烷基亚磺酰基烷基酯，例如异硫氰酸 6- 甲基亚磺酰基己酯以及上述提及的活性剂的烷基和烷酰基酯、烷基醚、立体异构体、互变异构体和盐 ；或 b) 包含所述分离的 Nrf2 激活剂的药物组合物，

条件是 :

不将羟基脲与 PPARγ 激动剂吡格列酮一起施用用于治疗银屑病，其中将吡格列酮与富马酸酯同时、分别或依次施用。

2. 根据上述权利要求应用的 PPARγ 激动剂，其中自身免疫障碍和 / 或炎性障碍选自银屑病、硬皮病、慢性肾疾病 (CKD)、神经变性疾病、哮喘、慢性阻塞性肺障碍 (COPD)、纤维化、炎性关节炎疾病和炎性肠病 (IBD)。

3. 根据上述权利要求应用的 PPARγ 激动剂，其中自身免疫障碍和 / 或炎性障碍是神经变性疾病，其选自多发性硬化、临床孤立综合征 (CIS)、肌萎缩侧索硬化、阿尔茨海默病、痴呆、亨廷顿病和帕金森病。

4. 选自格列酮的 PPARγ 激动剂，其用于减轻患者炎症，其中所述 PPARγ 激动剂与如下成分同时、分别或依次施用 :a) 分离的 Nrf2 激活剂，其选自富马酸酯、甲基巴多索隆 (2- 氰基 -3,12- 二氧代齐墩果 -1,9(11) 二烯 -28- 酸甲酯，CDDO-Me，RTA 402)、2- 氰基 -3,12- 二氧代齐墩果 -1,9(11) 二烯 -28- 酸乙酯、2- 氰基 -3,12- 二氧代齐墩果 -1,9(11) 二烯 -28- 酸 (CDDO)、1[2- 氰基 -3,12- 二氧代齐墩果 -1,9(11)- 二烯 -28- 酰基 ] 咪唑 (CDDO-Im)、2- 氰基 -N- 甲基 -3,12- 二氧代齐墩果 -1,9(11)- 二烯 -28 酰胺 (CDDO- 甲基酰胺、CDDO-MA)、[(±)-(4bS,8aR,10aS)-10a- 乙炔基 -4b,8,8- 三甲基 -3,7- 二氧代 -3,4b,7,8,8a,9,10,10a- 八氢菲 -2,6- 二腈 ](TBE-31)、2- 氰基 -3,12- 二氧代齐墩果 -1,9(11)- 二烯 -28- 腈 (TP-225)、3- 叔丁基 -4- 羟基苯甲醚、2- 叔丁基 -4- 羟基苯甲醚 (BHA)、叔丁基醌 (tBQ)、叔丁基氢醌 (tBHQ)、3,5- 二 - 叔丁基 -4- 羟基甲苯 (BHT)、2,6- 二 - 叔丁基 -4- 亚甲基 -2,5- 环己二烯 -1- 酮 (2,6- 二 - 叔丁基醌甲基化物，BHT- 醌甲基化物 )、乙氧喹、没食子酸酯、姜黄素、白藜芦醇、甲萘醌、肉桂醛、肉桂酸酯、咖啡酸酯、

咖啡醇、咖啡白脂、番茄红素、鼠尾草酚、莱菔硫烷、奥替普拉、5-(4-甲氧基-苯基)-1,2-二硫杂环戊二烯-3-硫酮(ADT)、5-氨基-2-羟基-苯甲酸4-(5-硫代-5H-[1,2]二硫杂环戊二烯-3-基)-苯基酯(ATB-429)、大蒜素、异硫氰酸烯丙酯、花姜酮、异硫氰酸苯乙酯、异硫氰酸苄酯、异硫氰酸烷基亚磺酰基烷基酯，例如异硫氰酸6-甲基亚磺酰基己酯以及上述提及的活性剂的烷基和烷酰基酯、烷基醚、立体异构体、互变异构体和盐；或b)包含所述分离的Nrf2激活剂的药物组合物，

条件是：

不将羟基脲与PPARγ激动剂吡格列酮一起施用用于减轻患者炎症，所述炎症与银屑病一起存在和/或因银屑病导致，其中将吡格列酮与富马酸酯同时、分别或依次施用。

5. 根据上述权利要求应用的PPARγ激动剂，其中所述炎症是慢性炎症。

6. 根据上述权利要求应用的PPARγ激动剂，其中PPARγ激动剂选自吡格列酮和罗格列酮。

7. 根据上述权利要求应用的PPARγ激动剂，其中PPARγ激动剂是每日剂量约45mg的吡格列酮。

8. 根据上述权利要求应用的PPARγ激动剂，其中PPARγ激动剂是每日剂量约8mg的罗格列酮。

9. 根据上述权利要求应用的PPARγ激动剂，其中Nrf2激活剂是富马酸酯，其选自富马酸二烷基酯和富马酸一烷基酯。

10. 根据上述权利要求应用的PPARγ激动剂，其中Nrf2激活剂是富马酸二甲酯。

11. 根据上述权利要求应用的PPARγ激动剂，其中Nrf2激活剂是每日剂量约480mg或约720mg的富马酸二甲酯。

12. 药物组合物，其包含：PPARγ激动剂，其选自格列酮；和Nrf2激活剂，其选自富马酸酯、甲基巴多索隆(2-氰基-3,12-二氧代齐墩果-1,9(11)二烯-28-酸甲酯，CDDO-Me，RTA 402)、2-氰基-3,12-二氧代齐墩果-1,9(11)二烯-28-酸乙酯、2-氰基-3,12-二氧代齐墩果-1,9(11)二烯-28-酸(CDDO)、1[2-氰基-3,12-二氧代齐墩果-1,9(11)-二烯-28-酰基]咪唑(CDDO-Im)、2-氰基-N-甲基-3,12-二氧代齐墩果-1,9(11)-二烯-28酰胺(CDDO-甲基酰胺，CDDO-MA)、[(±)-(4bS,8aR,10aS)-10a-乙炔基-4b,8,8-三甲基-3,7-二氧代-3,4b,7,8,8a,9,10,10a-八氢菲-2,6-二腈](TBE-31)、2-氰基-3,12-二氧代齐墩果-1,9(11)-二烯-28-腈(TP-225)、3-叔丁基-4-羟基苯甲醚、2-叔丁基-4-羟基苯甲醚(BHA)、叔丁基醌(tBQ)、叔丁基氢醌(tBHQ)、3,5-二-叔丁基-4-羟基甲苯(BHT)、2,6-二-叔丁基-4-亚甲基-2,5-环己二烯-1-酮(2,6-二-叔丁基醌甲基化物，BHT-醌甲基化物)、乙氧喹、没食子酸酯、姜黄素、白藜芦醇、甲萘醌、肉桂醛、肉桂酸酯、咖啡酸酯、咖啡醇、咖啡白脂、番茄红素、鼠尾草酚、莱菔硫烷、奥替普拉、5-(4-甲氧基-苯基)-1,2-二硫杂环戊二烯-3-硫酮(ADT)、5-氨基-2-羟基-苯甲酸4-(5-硫代-5H-[1,2]二硫杂环戊二烯-3-基)-苯基酯(ATB-429)、大蒜素、异硫氰酸烯丙酯、花姜酮、异硫氰酸苯乙酯、异硫氰酸苄酯、异硫氰酸烷基亚磺酰基烷基酯，例如异硫氰酸6-甲基亚磺酰基己酯以及上述提及的活性剂的烷基和烷酰基酯、烷基醚、立体异构体、互变异构体和盐；和任选的一种或多种赋形剂。

13. 根据上述权利要求的药物组合物，其中PPARγ激动剂选自吡格列酮和罗格列酮。

14. 根据上述权利要求的药物组合物，其包含约 5mg、约 7.5mg、约 10mg、约 15mg、约 20mg、约 22.5mg 或约 25mg 的吡格列酮。

15. 根据上述权利要求的药物组合物，其包含约 0.7mg、约 1mg、约 1.3mg、约 2mg、约 2.7mg、约 3mg、约 3.5mg、约 4 或约 5mg 的罗格列酮。

16. 根据上述权利要求的药物组合物，其中 Nrf2 激活剂是富马酸酯，其选自富马酸二烷基酯和富马酸一烷基酯。

17. 根据上述权利要求的药物组合物，其中 Nrf2 激活剂是富马酸二甲酯。

18. 根据上述权利要求的药物组合物，其包含约 240mg 的富马酸二甲酯。

19. 固体口服剂型，其包含上述权利要求的药物组合物。

20. 根据权利要求 12、13、14、15、16、17 或 18 的药物组合物，其用于治疗自身免疫障碍和 / 或炎性障碍。

21. 根据上述权利要求应用的药物组合物，其中自身免疫障碍和 / 或炎性障碍选自银屑病、硬皮病、慢性肾疾病 (CKD)、神经变性疾病、哮喘、慢性阻塞性肺障碍 (COPD)、纤维化、炎性关节炎疾病和炎性肠病 (IBD)。

22. 根据上述权利要求应用的药物组合物，其中自身免疫障碍和 / 或炎性障碍是神经变性疾病，其选自多发性硬化、临床孤立综合征 (CIS)、肌萎缩侧索硬化、阿尔茨海默病、痴呆、亨廷顿病和帕金森病。

23. 根据权利要求 12、13、14、15、16、17 或 18 的药物组合物，其用于减轻患者炎症。

24. 根据上述权利要求应用的药物组合物，其中所述炎症是慢性炎症。

25. 成套药盒，其包含 :a)PPAR γ 激动剂，其选自格列酮 ;和 b)Nrf2 激活剂，其选自富马酸酯、甲基巴多索隆 (2- 氰基 -3,12- 二氧代齐墩果 -1,9(11) 二烯 -28- 酸甲酯，CDDO-Me，RTA 402)、2- 氰基 -3,12- 二氧代齐墩果 -1,9(11) 二烯 -28- 酸乙酯、2- 氰基 -3,12- 二氧代齐墩果 -1,9(11) 二烯 -28- 酸 (CDDO)、1[2- 氰基 -3,12- 二氧代齐墩果 -1,9(11)- 二烯 -28- 酰基 ] 咪唑 (CDDO-Im)、2- 氰基 -N- 甲基 -3,12- 二氧代齐墩果 -1,9(11)- 二烯 -28 酰胺 (CDDO- 甲基酰胺，CDDO-MA)、[(±)-(4bS,8aR,10aS)-10a- 乙炔基 -4b,8,8- 三甲基 -3,7- 二氧代 -3,4b,7,8,8a,9,10,10a- 八氢菲 -2,6- 二腈 ](TBE-31)、2- 氰基 -3,12- 二氧代齐墩果 -1,9(11)- 二烯 -28- 腈 (TP-225)、3- 叔丁基 -4- 羟基苯甲醚、2- 叔丁基 -4- 羟基苯甲醚 (BHA)、叔丁基醌 (tBQ)、叔丁基氢醌 (tBHQ)、3,5- 二 - 叔丁基 -4- 羟基甲苯 (BHT)、2,6- 二 - 叔丁基 -4- 亚甲基 -2,5- 环己二烯 -1- 酮 (2,6- 二 - 叔丁基醌甲基化物，BHT- 醌甲基化物 )、乙氧喹、没食子酸酯、姜黄素、白藜芦醇、甲萘醌、肉桂醛、肉桂酸酯、咖啡酸酯、咖啡醇、咖啡白脂、番茄红素、鼠尾草酚、莱菔硫烷、奥替普拉、5-(4- 甲氧基 - 苯基 )-1,2- 二硫杂环戊二烯 -3- 硫酮 (ADT)、5- 氨基 -2- 羟基 - 苯甲酸 4-(5- 硫代 -5H-[1,2] 二硫杂环戊二烯 -3- 基 )- 苯基酯 (ATB-429)、大蒜素、异硫氰酸烯丙酯、花姜酮、异硫氰酸苯乙酯、异硫氰酸苄酯、异硫氰酸烷基亚磺酰基烷基酯，例如异硫氰酸 6- 甲基亚磺酰基己酯以及上述提及的活性剂的烷基和烷酰基酯、烷基醚、立体异构体、互变异构体和盐 ;和任选的 c) 给药方案说明书。

26. 根据上述权利要求的成套药盒，其中 PPAR γ 激动剂选自吡格列酮和罗格列酮。

27. 根据上述权利要求的成套药盒，其中 Nrf2 激活剂是富马酸酯，其选自富马酸二烷基酯和富马酸一烷基酯。

28. 根据上述权利要求的成套药盒，其中 Nrf2 激活剂是富马酸二甲酯。

# 包含格列酮和 NRF2 激活剂的药物组合物

[0001] 本文公开了包含 PPAR 激动剂和 Nrf2 激活剂（各自为“活性剂”和一起为“活性剂”）的药物组合物和使用 PPAR 激动剂和 Nrf2 激活剂的组合治疗疾病例如银屑病、哮喘、多发性硬化、炎性肠病和关节炎的方法。

[0002] 过氧化物酶体增殖物激活受体 (PPAR) 通过结合 DNA 序列元件激活转录，所述 DNA 序列元件称作过氧化物酶体增殖物反应元件 (PPRE)，为与类视黄醇 X 受体（称作 RXR）的异二聚体形式。已经鉴定了人 PPAR 的 3 种亚型并且描述为 :PPARα、PPARγ (PPARγ) 和 PPARδ（或 NUC1）。PPARα 主要在肝中表达，而 PPARδ 是普遍存在的。PPARγ 是 3 种亚型中研究最深入的。例如，参见“Differential Expression of Peroxisome Proliferator-Activated Receptor Subtypes During the Differentiation of Human Keratinocytes”, Michel Rivier 等人，J. Invest. Dermatol, 111, 1998, 第 1116-1121 页，其中举出了大量涉及 PPAR 型受体的文献参考。还可以在如下标题为“The PPARs: From orphan receptors to Drug Discovery”的报告中提及 :Timothy M. Willson, Peter J. Brown, Daniel D. Sternbach 和 Brad R. Henke, J. Med. Chem., 2000, 第 43 卷，第 527-550 页。启示 PPARγ 在调节脂肪细胞分化方面起至关重要的作用，其中它得到广泛表达。它还在全身脂质体内稳定中起关键作用。

[0003] 已经报道噻唑烷二酮类化合物（所谓的格列酮类）包括罗格列酮、马来酸罗格列酮、吡格列酮、盐酸吡格列酮、曲格列酮和环格列酮和或其盐形式是有效的和选择性的 PPAR-γ 激活剂（所谓的 PPARγ 激动剂），并且直接结合 PPAR-γ 受体 (J. M. Lehmann 等人，J. Biol. Chem. 12953-12956, 270(1995))，从而提供了 PPAR-γ 是可能的噻唑烷二酮类的治疗作用靶标的证据。由于这一观察结果，所以证实激活这种核激素受体具有多向性代谢和非降血糖作用。这些活性剂在治疗 2 型糖尿病（或非胰岛素依赖性糖尿病 (NIDDM)）中的应用与对胰岛素的降血糖作用敏感和胰岛素在靶组织中的其它生物作用增强相关。当作为单一疗法使用时，有导致容积扩张的液体潴留的报道，并且在一些患者中，存在临床水肿。水肿的发生率在这些活性剂与胰岛素组合应用时显示增加 (Nesto R. W. 等人，2003, Circulation, 108, 2941-2948)。然而，尚未描述涉及这些作用的机制，而呈现的性质启示包括对肾盐和水平衡的作用的生理学应答整合。已经在肾集合管中发现了 PPARγ 受体 (Guan Y. 等人 ;2001, Kidney Int. 60, 14-30)，因此，PPARγ 激动剂可能直接涉及肾导管代谢或可能对盐和水的体内稳态具有继发作用。已经启示 PPARγ 激动剂吡格列酮作为治疗银屑病的方法，例如 British Journal of Dermatology 2005 152, 第 176-198 页。

[0004] 核因子红色 -2 相关因子 2 或核因子 E2p45- 相关因子 (Nrf2) 是帽和环 (cap-and-collar) 基础亮氨酸拉链转录因子，其调节维持细胞氧化还原体内稳态的转录程序并且防止细胞氧化性损伤 (Rangasamy T 等人，J Clin Invest 114, 1248(2004) ; Thimmulappa R K 等人 Cancer Res 62, 5196(2002) ; So H S 等人 Cell Death Differ(2006))。NRF2 通过特异性结合在那些基因启动子中发现的抗氧化剂应答元件 (ARE) 激活其靶基因转录。NRF2- 调节的转录程序包括广谱基因，包括抗氧化剂，例如 γ- 谷氨酰半胱氨酸合成酶修饰亚单位 (GCLm)、γ- 谷氨酰半胱氨酸合成酶催化亚单位 (GCLc)、血红素加氧酶 -1、

超氧化物歧化酶、谷胱甘肽还原酶 (GSR)、谷胱甘肽过氧化物酶、硫氧还蛋白、硫氧还蛋白还原酶、过氧化氧化还原蛋白 (PRDX)、半胱氨酸 / 谷氨酸转运蛋白 (SLC7A11)(7,8)]、II 期代谢解毒酶 [NADP(H) 醌氧化还原酶 1(NQO1)、GST、UDP- 葡糖醛酸基转移酶 (Rangasamy T 等人 J Clin Invest 114:1248(2004) ;Thimmulappa R K 等人 Cancer Res 62:5196(2002)) 和几种 ATP- 依赖性药物流出泵,包括 MRP1、MRP2(Hayashi A, 等人 Biochem Biophy Res Commun 310:824(2003)) ;Vollrath V 等人 Biochem J(2006)) ;Nguyen T 等人, Annu Rev Pharmacol Toxicol 43:233(2003)]。

[0005] 与 Nrf2 互连的是 KEAP1,其为 Nrf2 的胞质锚定物,该锚定物也作为 Cul3- 依赖性 E3 遍在蛋白连接酶复合物的底物衔接蛋白起作用以维持稳态水平的 NRF2 和 NRF2- 依赖性转录 (Kobayashi 等人 ,Mol Cell Biol 24:7130(2004) ;Zhang D 等人 Mol Cell Biol 24:10491(2004))。Keap1 基因位于人染色体基因座 19p13.2 上。KEAP1 多肽具有 3 个主要结构域 :(1)N- 末端 Broad 复合物、Tramtrack 和 Bric-a-brac(BTB) 结构域 ;(2) 中心介入区 (IVR) ;和 (3) 一系列 6 个 C- 末端 Kelch 重复单元 (Adams J 等人 Trends Cell Biol 10:17(2000))。KEAP1 的 Kelch 重复单元结合 Nrf2 的 Neh2 结构域,而 IVR 和 BTB 结构域是通过该区中自始至终存在的一系列反应性半胱氨酸对 Nrf2 的氧化还原 - 敏感性进行调节所需的 (Wakabayashi N 等人 Proc Natl Acad Sci USA 101:2040(2004))。KEAP1 以组成型方式在无应激的存在下抑制 Nrf2 活性。氧化剂、异生物质和亲电体阻碍 KEAP1- 介导的 Nrf2 蛋白酶体降解,导致核蓄积增加且由此转录诱导确保细胞存活的靶基因 (Wakabayashi N 等人 Nat Genet. 35:238(2003))。已经证实 KEAP1 的一种新的结合伴侣前胸腺素 α 是 NRF2-KEAP1 复合物的核内解离因子并且可以上调 Nrf2 靶基因的表达 (Karapetian R N 等人 Mol Cell Biol 25:1089(2005))。已经启示了 Nrf2 与 PPARγ 之间的一些相互作用,例如 Am J Respir Crit Care Med 2010 ;182:170-182。

[0006] 本发明的 Nrf2 激活剂是在施用后导致 Nrf2 蛋白核易位受到刺激和 / 或增加并且导致随后基因产物增加的活性剂,所述的基因产物使细胞毒性代谢物解毒并且消除它们。本发明的 Nrf2 激活剂可以直接对 Nrf2、KEAP1、NRF2-KEAP1 复合物和 / 或其它起作用。本发明的 Nrf2 激活剂可以包括 :迈克尔加成受体 ;一种或多种富马酸酯,即富马酸一 - 和 / 或二酯,其优选选自富马酸一烷基酯和富马酸二烷基酯,例如富马酸一甲酯、富马酸二甲酯、富马酸一乙酯和富马酸二乙酯,还有依他尼酸 ;甲基巴多索隆 (2- 氰基 -3,12- 二氧代齐墩果 -1,9(11) 二烯 -28- 酸甲酯 ) ;异硫氰酸酯,例如莱菔硫烷 ;1,2- 二硫杂环戊二烯 -3- 硫酮,例如奥替普拉 ;3,5- 二 - 叔丁基 -4- 羟基甲苯、3- 羟基香豆素或上述活性剂的药理学活性衍生物或类似物。

[0007] 用于与本发明的 PPARγ 激动剂组合应用的极为优选的 Nrf2 激活剂是甲基巴多索隆和富马酸酯。

[0008] 富马酸酯在德国经批准用于治疗银屑病,其正在美国评价用于治疗银屑病和多发性硬化,并且已经提出用于治疗广泛的免疫学、自身免疫和炎性疾病和病症。已经提出 FAE 和其它富马酸衍生物用于治疗各种疾病和病症,包括免疫学、自身免疫和 / 或炎性过程,包括银屑病 (Joshi 和 Strebel, WO1999/49858 ;US 6,277,882 ;Mrowietz 和 Asadullah, Trends Mol Med 2005, 111(1), 43-48 ; 以及 Yazdi 和 Mrowietz, Clinics Dermatology 2008, 26, 522-526) ;哮喘和慢性阻塞性肺疾病 (Joshi 等人 , WO 2005/023241

和 US2007/0027076)；心功能不全，包括左心室功能不全、心肌梗死和心绞痛 (Joshi 等人，WO 2005/023241；Joshi 等人，US 2007/0027076)；线粒体和神经变性疾病，例如帕金森病、阿尔茨海默病、亨廷顿病、色素性视网膜病变 (retinopathia pigmentosa) 和线粒体脑肌病 (Joshi 和 Strebel, WO2002/055063、US 2006/0205659、US 6,509,376、US 6,858,750 和 US7,157,423)；移植 (Joshi 和 Strebel, WO 2002/055063、US 2006/0205659、US 6,359,003、US 6,509,376 和 US 7,157,423；和 Lehmann 等人，Arch Dermatol Res 2002,294,399-404)；自身免疫疾病 (Joshi 和 Strebel, WO2002/055063、US 6,509,376、US 7,157,423 和 US 2006/0205659)，包括多发性硬化 (MS)(Joshi 和 Strebel, WO 1998/52549 和 US 6,436,992；Went 和 Lieberburg, US 2008/0089896；Schimrigk 等人，Eur J Neurology 2006,13,604-610；和 Schilling 等人，Clin Experimental Immunology 2006,145,101-107)；局部缺血和再灌注损伤 (Joshi 等人，US 2007/0027076)；AGE-诱导的基因组损伤 (Heidland, WO 2005/027899)；炎性肠病，例如克罗恩氏病和溃疡性结肠炎；关节炎等 (Nilsson 等人，WO 2006/037342 和 Nilsson 和 Muller, WO 2007/042034)。可以使用本发明的组合治疗治疗或预防所有这些适应证和疾病。

[0009] **Fumaderm®**，即包含富马酸一乙酯和富马酸二甲酯的盐混合物的肠溶包衣片，其可快速地水解成富马酸一甲酯，该片剂在德国在 1994 年批准用于治疗银屑病。以 1-2 克 / 天 TID 施用 **Fumaderm®**，用于治疗银屑病。

[0010] Biogen Idee Inc. 是目前评价的产品名称为 BG-12 的富马酸二甲酯，其用于治疗复发 - 缓解性多发性硬化。该药物在美国和欧洲管理机构进行评审。

[0011] 已经尝试研发：富马酸衍生物 (Joshi 和 Strebel, WO 2002/055063、US2006/0205659 和 US 7,157,423(酰胺化合物和蛋白质 - 富马酸酯结合物)；Joshi 等人，WO 2002/055066 以及 Joshi 和 Strebel, US 6,355,676(一和二烷基酯)；Joshi 和 Strebel, WO 2003/087174(碳环和氧杂碳环化合物)；Joshi 等人，WO 2006/122652(硫代琥珀酸酯)；Joshi 等人，US 2008/0233185(二烷基和二芳基酯) 和盐 (Nilsson 等人，US 2008/0004344)，以克服目前使用富马酸酯治疗的缺陷。Nilsson 和 **Müller** 在 WO 2007/042034 中公开了包含富马酸酯的控释药物组合物。Nielsen 和 Bundgaard, J Pharm Sci 1988,77(4),285-298 和 WO2010/022177 描述了前药。

[0012] 详细描述

[0013] 优选地，术语“烷基”特别地旨在包括具有任意饱和度或水平的基团，即仅具有碳 - 碳单键的基团、具有一个或多个碳 - 碳双键的基团、具有一个或多个碳 - 碳三键的基团和具有碳 - 碳单键、双键和三键的组合的基团。如果预期特定的饱和水平，则使用术语烷基、烯基和炔基。在一些实施方案中，烷基可以具有 1-20 个碳原子 (C1-20)，在一些实施方案中，具有 1-10 个碳原子 (C1-10)，在一些实施方案中，具有 1-8 个碳原子 (C1-8)，在一些实施方案中，具有 1-6 个碳原子 (C1-6)，在一些实施方案中，具有 1-4 个碳原子 (C1-4)，以及在一些实施方案中，具有 1-3 个碳原子 (C1-3)。术语“烷氧基”是指基团 O- 烷基，其中烷基具有上述含义。术语“全氟烷基”是指烷基，其中全部氢原子被氟代替。

[0014] 任意疾病的“治疗”是指逆转、缓解、阻止或改善疾病或至少一种疾病的临床症状，降低获得疾病或至少一种疾病的临床症状的风险，抑制疾病或至少一种疾病的临床症状进

展或降低发生疾病或至少一种疾病的临床症状的风险。“治疗”还指在身体（例如稳定可辨别的症状）、生理学（例如稳定身体参数）方面或以上两方面抑制疾病和抑制至少一种在患者中可以分辨或不能分辨的身体参数。在一些实施方案中，“治疗”是指延迟患者疾病或至少一种或多种其症状发作，所述患者接触或易感疾病，尽管，该患者未经历或展示出疾病症状。

[0015] “治疗有效量”是指在对个体施用以治疗疾病或至少一种疾病的临床症状时足以影响疾病或其症状的这种治疗的化合物的量。“治疗有效量”可以根据例如化合物、疾病和/或疾病症状、疾病和/或疾病或障碍的症状的严重性、所治疗患者的年龄、体重和/或健康状况以及开据处方的临床医师的判断的不同而改变。在任意指定情况中的适合的量可以由本领域技术人员确定或能够通过常规试验确定。

[0016] “治疗有效剂量”是指提供患者有效治疗疾病或障碍的剂量。治疗有效剂量可以根据化合物与化合物和患者与患者的不同而改变并且可以取决于因素例如患者的病症和递送途径。治疗有效剂量可以根据本领域技术人员已知的常规药理学方法确定。

[0017] 在本说明书上下文中，术语“分离的 Nrf2 激活剂”优选是指 Nrf2 激活剂，如果天然存在，其基本上与天然伴随相应的 Nrf2 激活剂的其它组分和其它分子分离。该术语包括 Nrf2 激活剂，将它通过纯化步骤从其天然存在环境或其天然状态中取出，所述纯化步骤分离与之天然结合的其它分子，例如通过已知的常规方法，例如色谱法、结晶和蒸馏。术语“分离的 Nrf2 激活剂”优选允许 Nrf2 激活剂是与不同量水的混合物，例如至多约 20 重量%。术语“分离的 Nrf2 激活剂”优选不包括这样的 Nrf2 激活剂，仍然在其天然状态下，例如，仍然包含在其原始来源或其部分中，例如植物，与这种原始的来源是否干燥无关。此外，术语“分离的 Nrf2 激活剂”优选是指天然或合成制备的分子，其具有的纯度高于 70 重量%，优选高于 80 重量%，并且更优选高于 90 重量%，例如约 95 重量%、约 97 重量%或约 99 重量%，然后配制成药物组合物，只要有这样的期望。在 Nrf2 激活剂是天然存在的情况中，例如作为天然产物，它优选是分离的 Nrf2 激活剂，即不是例如草药制剂的形式。

[0018] 在 PPAR γ 激动剂是天然存在的情况中，例如作为天然产物，它优选是分离的 PPAR γ 激动剂，即不是例如草药制剂的形式。

[0019] 现在详细地涉及一些化合物、组合物和方法的实施方案。所公开的实施方案不预以限制权利要求。

[0020] 根据本发明，当 PPAR 激动剂且优选 PPAR γ 激动剂和 Nrf2 激活剂以组合用于治疗疾病时，与用单独的 PPAR γ 激动剂或 Nrf2 激活剂治疗相比，在治疗自身免疫和/或炎性疾病中得到强有力改善的治疗效果。共同施用 PPAR γ 激动剂和 Nrf2 激活剂或施用固定剂量的 PPAR γ 激动剂和 Nrf2 激活剂的组合与分别施用作为单一疗法施用的 PPAR γ 激动剂和 Nrf2 激活剂相比导致治疗作用改善，可以高于累加的效果。

[0021] 特别地，已经发现在因使用具有 PPAR γ 激动和 Nrf2 激活作用的化合物例如地塞米松在炎性和/或自身免疫疾病中导致的有利治疗效果可以匹配乃至超过本发明的组合治疗，其中使用各自具有 PPAR γ 激动或 Nrf2 激活作用的至少两种单独和不同的化合物。因此，包含至少一种 PPAR γ 激动剂和至少一种 Nrf2 激活剂的组合治疗与分别施用作为单一疗法施用的这样的 PPAR γ 激动剂和这样的 Nrf2 激活剂相比产生改善和协同的治疗作用，所述至少一种 PPAR γ 激动剂可能对 Nrf2 不具有显著的或仅有最小的调节或激活作用，所

述至少一种 Nrf2 激活剂可能对 PPARγ 不具有显著的或仅有最小的调节或激活作用。使用这种组合通常使协同作用更显著，其中所用的活性剂主要是 PPARγ 激动剂或 Nrf2 激活剂，它们各自对相应的另一种靶标不具有显著的活性。尽管如此，但是甚至在一种或两种活性剂同时展示出显著的 PPARγ 激动和 Nrf2 激活作用的情况中，例如在地塞米松和 15- 脱氧 -δ(12,14)- 前列腺素 J(2)(15d-PGJ(2)) 的情况中，本发明的组合治疗可以导致治疗效果比单一疗法改善。对靶标 PPARγ 和 Nrf2 具有双重作用的化合物不能显示对两种靶标的治疗用途的理想分布效果。通过应用本发明，可以分别解决每种靶标并且使用适合和合适浓度的相应活性剂激活它们。

[0022] 因此，优选这样的实施方案，其中至少一种活性剂不同时是 PPARγ 激动剂和 Nrf2 激活剂。

[0023] 优选本发明的组合治疗和固定剂量组合，其包含至少两种不同的活性剂，其在用于该组合中的浓度下具有 PPARγ 激动或 Nrf2 激活作用。

[0024] 本发明涉及组合治疗，包含本发明活性剂组合和相关固定剂量组合的组合物，其中 PPAR 激动剂例如 PPARγ 激动剂和 Nrf2 激活剂是不同的化合物，它们优选具有不同的化学结构，例如在碳原子方面具有至少 3 个碳原子、优选至少 5 个或至少 10 个碳原子的差别并且不属于相同的化学类型。在本说明书上下文中，如果不另外指示，则单数的应用也包括复数。

[0025] 优选的 PPAR 激动剂是具有 PPARγ 激动作用、而不显著激活 Nrf2 的化合物。它们优选是在生理条件下不能与有机硫醇基团例如与谷胱甘肽形成共价键的化合物。因此，优选的 PPARγ 激动剂是这样的化合物，它们与例如 15- 脱氧 -δ(12,14)- 前列腺素 J(2)(15d-PGJ(2)) 相反，不能通过例如迈克尔加成反应与 PPA 受体共价结合。最优选的 PPAR 激动剂是格列酮、格列扎和沙坦。

[0026] PPAR 激动剂是 PPAR 激活剂（例如 PPARγ 激动剂是 PPARγ 激活剂）。本发明的定义“PPAR 激动剂”和“PPARγ 激动剂”优选包括这样的激动剂，即直接结合 PPA 受体并且具有激动即激活作用的化合物，以及所谓的生理学 PPAR 激动剂和生理学 PPARγ 激动剂，它们不一定结合 PPAR 受体，但通过其它途径导致 PPAR 激活，例如通过增加内源性 PPARγ 激动剂 15- 脱氧 -δ(12,14)- 前列腺素 J(2)(15d-PGJ(2)) 的浓度。

[0027] 已知大量天然和合成的 PPAR 激动剂（例如，参见 Michalik 等人 (2006) Pharmacological Reviews 58:726-725 ;Gilde 等人 (2003)Circulation Research 92(5):518-524 ;Peraza 等人 (2005)Toxicological Sciences 90(2):269-295 ; 和 Desvergne & Wahli(1999)Endocrine Reviews20(5):649-688)。这些已知的激动剂的一些对单一 PPAR 同种型具有特异性，同时其它的靶向多种 PPAR 亚型。优选 PPAR 激动剂，条件是 PPAR 激动剂对 PPARγ 或同时对 PPARγ 和 PPARα 的激活强于对其它同种型。

[0028] 在一个实施方案中，PPAR 激动剂可以选自 PPARγ 激动剂，例如格列酮；和双重 PPARα/γ 激动剂，例如格列扎。在另外的实施方案中，格列酮可以选自曲格列酮、吡格列酮、罗格列酮、环格列酮、恩格列酮、达格列酮、萘格列酮、伊沙列酮 (isaglitazone)、MC-555、巴格列酮、利格列酮等。在另外的实施方案中，格列扎可以选自莫格列他、那格列扎、替格列扎、拉格列扎、瑞格列扎和法格列扎。在另外的实施方案中，PPAR 激动剂选自小檗碱、K-111、INT-131、MBX-102(metaglidisen)、MBX-2044、FK614、GSK-376501、GW 1929、

S26948、psi- 膦靛素等，例如公开在 US5002953、US4687777 和 US5965584 中的那些。极为优选吡格列酮和罗格列酮，并且最优选盐酸吡格列酮和马来酸罗格列酮。

[0029] 在本发明的另一个优选的实施方案中，PPAR γ 激动剂选自他汀类或 HMG-CoA 还原酶抑制剂，优选选自阿托伐他汀、氟伐他汀、洛伐他汀、普伐他汀、瑞舒伐他汀、辛伐他汀、美伐他汀和匹伐他汀。他汀是用于通过抑制酶 HMG-CoA 还原酶降低胆固醇水平的药物类型，所述 HMG-CoA 还原酶在肝中胆固醇产生中起重要作用。胆固醇水平增加与心血管疾病相关，并且他汀由此用于预防这些疾病。还启示他汀用于治疗多发性硬化（例如 US 2004/0013643）。尽管认为他汀仅间接激活 PPAR γ (Circ Res. 2007 ;100:1442-1451)，但是作为生理学 PPAR γ 激动剂，它们包括在用于本发明目的的 PPAR γ 激动剂的定义中。

[0030] 在本发明的另一个优选的实施方案中，PPAR γ 激动剂选自如下化学类型 :沙坦，也称作血管紧张素 II 受体拮抗剂、血管紧张素受体阻滞剂 (ARB) 或 AT1- 受体拮抗剂。沙坦，例如缬沙坦、氯沙坦、阿齐沙坦、厄贝沙坦、奥美沙坦、替米沙坦、坎地沙坦和依普罗沙坦是调节肾素 - 血管紧张素 - 醛固酮系统的药物类型。用于本发明的优选的沙坦选自氯沙坦、厄贝沙坦、替米沙坦和坎地沙坦，已经证实它们结合并且激活 PPAR γ (Drug Development Research 67:579-581, 2006)。已经启示使用沙坦治疗改善了多发性硬化。沙坦主要用于治疗高血压、糖尿病肾病（因糖尿病导致的肾损伤）和慢性肾疾病以及充血性心力衰竭，并且在与本发明的 Nrf2 激活剂组合时，也优选用于这些疾病和病症。

[0031] 在本发明的另一个优选的实施方案中，PPAR γ 激动剂选自具有 PPAR γ 激活特性的非甾体抗炎药 (NSAID)，优选吲哚美辛、氟芬那酸、非诺洛芬和布洛芬 (The Journal of Biological Chemistry, 第 272 卷，第 6 期，第 7 号，第 3406-3410 页，1997)。就本发明的目的而言，NSAID 包括在 PPAR γ 激动剂定义中，因为它们可以直接结合 PPAR 或作为生理学 PPAR γ 激动剂起作用。在一个实施方案中，优选非阿司匹林的 NSAID。

[0032] NSAID 的类型包括如下化合物 :水杨酸化合物，例如阿司匹林（乙酰水杨酸）、二氟尼柳、双水杨酯、丙酸衍生物例如布洛芬、右布洛芬、萘普生、非诺洛芬、酮洛芬、右酮洛芬、氟比洛芬、奥沙普秦、洛索洛芬、乙酸衍生物例如吲哚美辛、舒林酸、依托度酸、酮咯酸、双氯芬酸、萘丁美酮、烯醇酸（昔康）衍生物例如吡罗昔康、美洛昔康、替诺昔康、屈昔康、氯诺昔康、伊索昔康、灭酸衍生物（芬那酸）例如甲芬那酸、甲氯芬那酸、氟芬那酸、托芬那酸、选择性 cox-2 抑制剂（昔布）例如塞来昔布、罗非昔布、伐地考昔、帕瑞考昔、芦米考昔、依托考昔、非罗考昔、硫酰替苯胺例如尼美舒利等例如利考非隆、赖氨酸氯尼辛。

[0033] Nrf2- 激活化合物可以基于其化学结构分类 :联苯酚、迈克尔反应受体、异硫氰酸酯、硫代氨基甲酸酯、三价砷剂、1,2- 二硫杂环戊二烯 -3- 硫酮、氢过氧化物、邻位二硫醇、重金属和聚烯。此外，Nrf2 激活剂 (i) 均为化学反应性的 ;(ii) 几乎均为亲电体 ;(iii) 大部分是谷胱甘肽转移酶的底物 ;和 (iv) 均可以通过烷基化、氧化或还原修饰巯基 (PNAS 2004 年 2 月 17 日，第 101 卷，第 7 期，2040-2045, Mol. Cell. Biol. 2009, 29(2):493)。可以通过已知方法鉴别化合物的活性。

[0034] 优选的 Nrf2 激活剂是没有显著 PPAR γ 激动作用的化合物。这些是优选的化合物，它们可以与 PPA 受体共价结合，也可以不与 PPA 受体共价结合，但不能将 PPAR 且优选 PPA γ 受体的构象改变至可以导致 PPA 受体激活的程度。根据本发明，这些优选的 Nrf2 激活剂是小的和低分子量的。这些化合物优选缺乏非共价结合 PPA 受体的结构元件，结果是 PPA 受

体构象改变和激活。在优选的实施方案中，Nrf2 激活剂可能能够与 PPA 受体共价结合，例如通过与 PPA 受体硫醇基团的迈克尔反应，但不会导致 PPA 受体构象改变。然而，这些优选的 Nrf2 激活剂因其有限的大小而可能不能防止 PPAR 激动剂且特别是 PPAR γ 激动剂、尤其是格列酮、例如吡格列酮或罗格列酮与 PPA 受体非共价结合，结果是构象改变。

[0035] 在一个极为优选的实例中，Nrf2 激活剂例如富马酸一甲酯或富马酸二甲酯的共价结合和 PPAR γ 激动剂例如格列酮如吡格列酮或罗格列酮的非共价结合导致协同和强有力改善的治疗结果。

[0036] 在一个实施方案中，优选 Nrf2 激活剂，其选自具有不超过 1 个或 2 个 5- 或 6- 元碳环或带有 1、2 或 3 个 N-、O 或 S- 原子作为环原子的 5- 或 6- 元杂环的有机化合物，所述环可以彼此稠合或优选无或仅有 1 个碳环或杂环和 / 或小于 35、优选小于 30、更优选小于 25 并且最优选小于 20 或甚至小于 15 或小于 10 个碳原子和 / 或具有小于 400、优选小于 300 并且最优选小于 200g/mol 或小于 170g/mol 的分子量，并且选自迈克尔反应受体、酚、联苯酚、查耳酮、异硫氰酸酯、硫代氨基甲酸酯、醌、萘醌和 1,2 二硫杂环戊二烯 -3- 硫酮的化学类型，其中一个或多个、优选至多 7 个 H- 原子可以被直链或支链烷基和全氟烷基例如甲基、乙基、三氟甲基、卤素例如 Br、Cl、F 或 I、羟基、烷氧基和全氟烷氧基例如甲氧基、乙氧基、三氟甲氧基、氰基和硝基取代。

[0037] 在醌化学类型的化合物用作 Nrf2 激活剂的情况中，可以代替地使用相应的氢醌。然而，优选相应的氧化形式，即相应的醌。可以根据例如 JALA2008 ;13:243-248 测定 Nrf2 活性。甲基巴多索隆和衍生物描述在专利 US8129429、US7435755 和 US2009/0060873 中。无定形甲基巴多索隆和适合的制剂公开在 WO2010/093944 中。

[0038] 极为优选的 Nrf2 激活剂能够引起或诱导刺激和 / 或增加的 Nrf2 蛋白核易位并且：

[0039] a) 选自迈克尔反应受体、酚、联苯酚、查耳酮、异硫氰酸酯、硫代氨基甲酸酯、醌、萘醌和 1,2 二硫杂环戊二烯 -3- 硫酮 ;和

[0040] b) 包含小于 35 个碳原子 ;和 / 或

[0041] c) 具有小于 600g/mol 的分子量 ;和 / 或

[0042] d) 不含或包含不超过 1 个或 2 个稠合或单环 5- 或 6- 元碳环或杂环，其具有 1、2 或 3 个选自 N、O 或 S 的环原子。

[0043] 在这些优选的 Nrf2 激活剂中，一个或多个、优选至多 7 个 H- 原子可以被直链或支链烷基和全氟烷基例如甲基、乙基、三氟甲基、卤素例如 Br、Cl、F 或 I、羟基、烷氧基和全氟烷氧基例如甲氧基、乙氧基、三氟甲氧基、氰基和硝基取代。

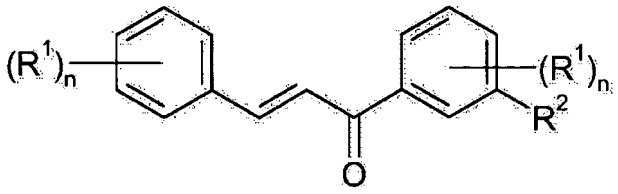
[0044] 这些 Nrf2 激活剂的更优选的实施方案不含环系或仅包含 1 个或 2 个环，其可以是碳环和 / 或杂环。甚至更优选的 Nrf2 激活剂包含小于 30、更优选小于 25 并且最优选小于 20 或甚至小于 15 或小于 10 个碳原子和 / 或具有小于 400g/mol 并且更优选小于 300g/mol 并且最优选小于 200g/mol 或小于 170g/mol 的分子量。另外优选的 Nrf2 激活剂与 Keap1 蛋白优选通过蛋白质氨基酸的 S- 原子共价结合。

[0045] 优选的迈克尔反应受体是酮、醛、羧酸酯和羧酸酰胺，它们全部是 α，β 不饱和的。

[0046] 更优选的 Nrf2 激活剂是如下所示的化合物 A 至 Z，包括其互变异构体和立体异构

体：

[0047]



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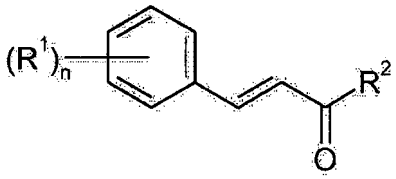

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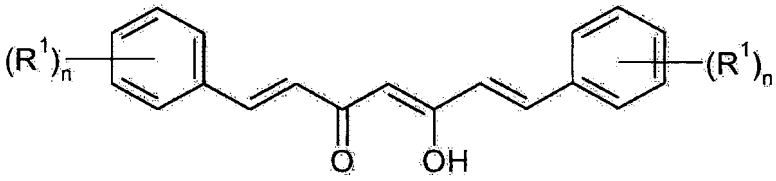

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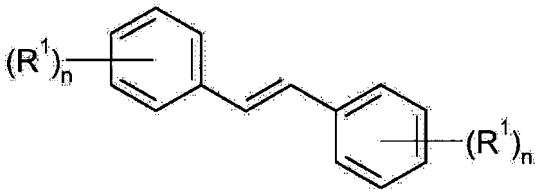

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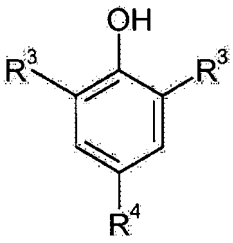

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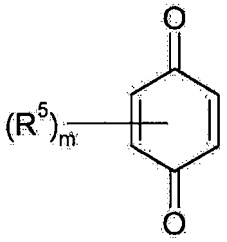
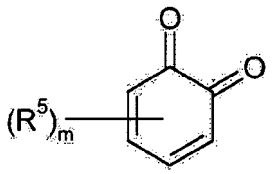


F

[0048]



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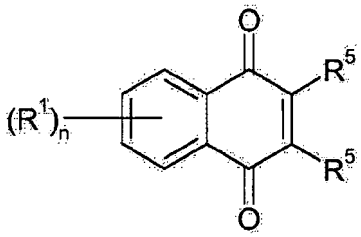

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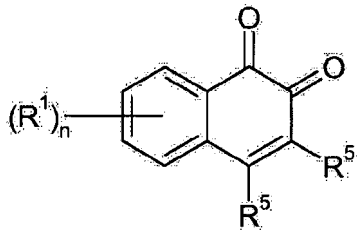

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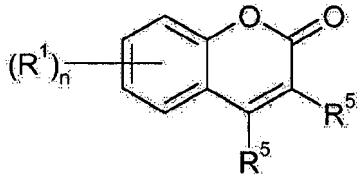

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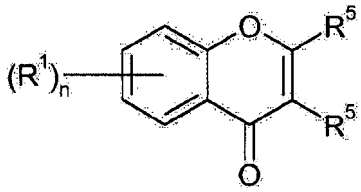

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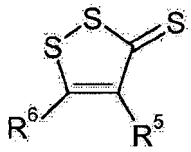

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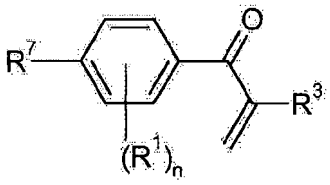

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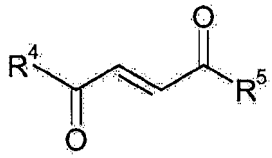

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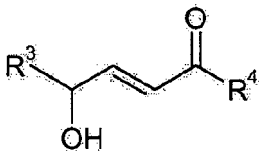
[0049]



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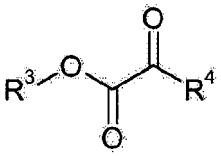

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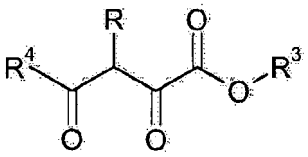

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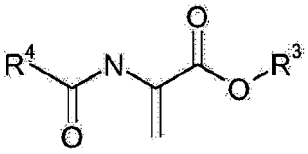

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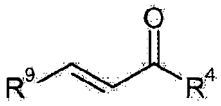

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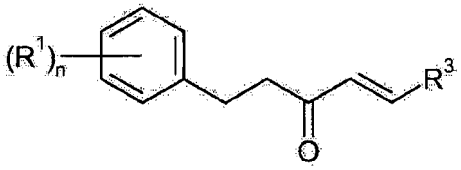

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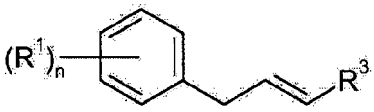

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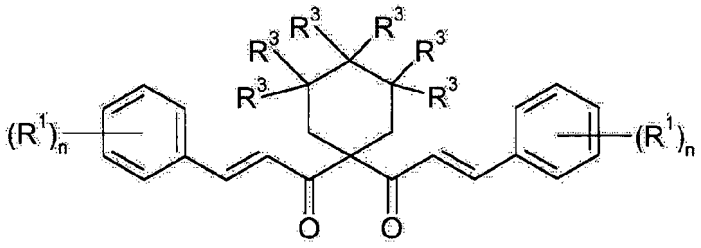
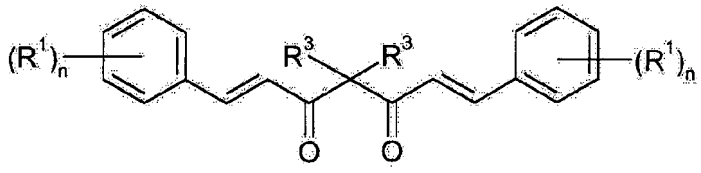
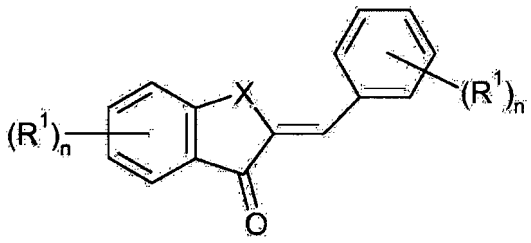


X



Y

[0050]



Z

[0051] 其中各个基团具有如下所示的含义：

[0052] $R^1$ 是 H、OH、Hal、CN、A、全氟烷基、全氟烷氧基；

[0053] $R^2$ 是 H、OH、A、烷氧基、氨基；

[0054] $R^3$ 是 H、烷基；

[0055] $R^4$ 是 H、OH、烷基、烷氧基；

[0056] $R^5$ 是 H、OH、A、烷氧基；

[0057] $R^6$ 是 H、A、烷氧基、芳基、het；

[0058] $R^7$ 是 H、OH、A、烷氧基；

[0059] $R^8$ 是 A；

[0060] X 是 O、NH、S；

[0061] $R^9$ 是 Het；

[0062] m 是 1、2；

[0063] n 是 1、2、3；

[0064] Hal 是 F、Cl、Br 或 I，优选 F 或 Cl。

[0065] A 优选是表示直链或支链碳链的具有 1、2、3、4、5、6、7、8、9、10、11 或 12 个碳原子的烷基。烷基优选表示甲基、乙基、丙基、异丙基、丁基、异丁基、仲丁基或叔丁基，另外还优选戊基、1-、2- 或 3- 甲基丁基、1,1-、1,2- 或 2,2- 二甲基丙基、1- 乙基丙基、己基、1-、2-、3- 或 4- 甲基戊基、1,1-、1,2-、1,3-、2,2-、2,3- 或 3,3- 二甲基丁基、1- 或 2- 乙基丁基、1- 乙基 -1- 甲基丙基、1- 乙基 -2- 甲基丙基、1,1,2- 或 1,2,2- 三甲基丙基。或者，A 表示具有 3、4、5、6 或 7 个碳原子的环烷基或具有 2-12 个 C- 原子的支链或直链烷基，其中一个或多个优选 1-7 个 H- 原子可以被 Hal、烷基、烷氧基、环烷基、苯基、p-、m-、o- 羟基苯基、p-、m-、o- 烷氧基苯基、$N(R^3)_2$、OH、$CO_2H$、$CF_3$ 代替和 / 或其中一个或多个优选 1-7 个不相邻 $CH_2$- 基团可以被 -O-、-S-、-SO-、$-NR^3-$、-CO-、$-CO_2-$、-CH = CH-S- 和 / 或 -CH = CH- 代替。环烷基优选表示环丙基、环丁基、环戊基、环己基或环庚基。

[0066] 烷氧基优选是基团 O- 烷基，其中烷基如上述所定义为。优选地，烷氧基表示基团 $-O-(CH_2)_n-CH_3$，其中 n 是 0、1、2、3 或 4，更优选甲氧基或乙氧基。

[0067] 全氟烷基优选表示具有 1-8 个碳原子、优选 1-6 个碳原子的直链或支链烷基，并且其中全部氢原子被 F 原子代替，优选地，例如三氟甲基或五氟乙基。

[0068] 全氟烷氧基优选是基团 O- 全氟烷基，其中全氟烷基如上述所定义。全氟烷氧基优选表示 $OCF_3$。

[0069] 氨基优选表示基团 -NR' R"，其中 R'、R" 各自独立地是氢或烷基。基团 -NR' R" 还可以形成选自环状基团，其选自哌啶基、哌嗪基、吡咯基或吗啉基，其中 1、2 或 3 个 H 原子可以被烷基、例如甲基取代。在一个实施方案中，氨基表示二烷基氨基，其中烷基具有上述给

出的含义，并且优选是二甲基氨基。

[0070] 芳基优选表示具有 6-14 个碳原子的单环或二环芳族碳环，其是未取代的或者被 F、Cl、Br、$CF_3$、$OCF_3$、$NO_2$、CN、烷基、烷氧基、OH、氨基、CO- 氨基、NHCO- 烷基、CO- 烷基、CO- 烷氧基、$SO_2$- 烷基、$SO_2$- 氨基单取代、二取代或三取代。最优选芳基表示未取代或单取代的苯基。

[0071] Het 优选表示不一定进一步取代的包含 1 或 2 个选自 N、O 和 S 的杂原子的 6-14 元单环或二环饱和、不饱和或芳族杂环系，其是未取代的或者被 F、Cl、Br、$CF_3$、$OCF_3$、$NO_2$、CN、烷基、烷氧基、OH、氨基、CO- 氨基、NHCO- 烷基、CO- 烷基、CO- 烷氧基、$SO_2$- 烷基、$SO_2$- 氨基单取代、二取代或三取代。更优选 Het 是 2- 或 3- 呋喃基、2- 或 3- 噻吩基、1-、2- 或 3- 吡咯基、1-、2-、4- 或 5- 咪唑基、1-、3-、4- 或 5- 吡唑基、2-、4- 或 5- 噁唑基、3-、4- 或 5- 异噁唑基、2-、4- 或 5- 噻唑基、3-、4- 或 5- 异噻唑基、2-、3- 或 4- 吡啶基、2-、4-、5- 或 6- 嘧啶基、还优选 1,2,3- 三唑 -1-、-4- 或 -5- 基、1,2,4- 三唑 -1-、-3- 或 -5- 基、1- 或 5- 四唑基、1,2,3- 噁二唑 -4- 或 -5- 基、1,2,4- 噁二唑 -3- 或 -5- 基、1,3,4- 噻二唑 -2- 或 -5- 基、1,2,4- 噻二唑 -3- 或 -5- 基、1,2,3- 噻二唑 -4- 或 -5- 基、3- 或 4- 哒嗪基、吡嗪基、1-、2-、3-、4-、5-、6- 或 7- 吲哚基、吲唑基、4- 或 5- 异吲哚基、1-、2-、4- 或 5- 苯并咪唑基、1-、3-、4-、5-、6- 或 7- 苯并吡唑基、2-、4-、5-、6- 或 7- 苯并噁唑基、3-、4-、5-、6- 或 7- 苯并异噁唑基、2-、4-、5-、6- 或 7- 苯并噻唑基、2-、4-、5-、6- 或 7- 苯并异噻唑基、4-、5-、6- 或 7- 苯并 -2,1,3- 噁二唑基、2-、3-、4-、5-、6-、7- 或 8- 喹啉基、1-、3-、4-、5-、6-、7- 或 8- 异喹啉基、3-、4-、5-、6-、7- 或 8- 噌啉基、2-、4-、5-、6-、7- 或 8- 喹唑啉基、5- 或 6- 喹喔啉基、2-、3-、5-、6-、7- 或 8-2H- 苯并 -1,4- 噁嗪基，还优选 1,3- 苯并间二氧杂环戊烯 -5- 基、1,4- 苯并二噁烷 -6- 基、2,1,3- 苯并噻二唑 -4- 或 -5- 基或 2,1,3- 苯并噁二唑 -5- 基。杂环基还可以是部分或完全氢化的。Het 由此还可以表示，例如 2,3- 二氢 -2-、-3-、-4- 或 -5- 呋喃基、2,5- 二氢 -2-、-3-、-4- 或 -5- 呋喃基、四氢 -2- 或 -3- 呋喃基、1,3- 二氧戊环 -4- 基、四氢 -2- 或 -3- 噻吩基、2,3- 二氢 -1-、-2-、-3-、-4- 或 -5- 吡咯基、2,5- 二氢 -1-、-2-、-3-、-4- 或 -5- 吡咯基、1-、2- 或 3- 吡咯烷基、四氢 -1-、-2- 或 -4- 咪唑基、2,3- 二氢 -1-、-2-、-3-、-4- 或 -5- 吡唑基、四氢 -1-、-3- 或 -4- 吡唑基、1,4- 二氢 -1-、-2-、-3- 或 -4- 吡啶基、1,2,3,4- 四氢 -1-、-2-、-3-、-4-、-5- 或 -6- 吡啶基、1-、2-、3- 或 4- 哌啶基、2-、3- 或 4- 吗啉基、四氢 -2-、-3- 或 -4- 吡喃基、1,4- 二噁烷基、1,3- 二噁烷 -2-、-4- 或 -5- 基、六氢 -1-、-3- 或 -4- 哒嗪基、六氢 -1-、-2-、-4- 或 -5- 嘧啶基、1-、2- 或 3- 哌嗪基、1,2,3,4- 四氢 -1-、-2-、-3-、-4-、-5-、-6-、-7- 或 -8- 喹啉基、1,2,3,4- 四氢 -1-、-2-、-3-、-4-、-5-、-6-、-7- 或 -8- 异喹啉基、2-、3-、5-、6-、7- 或 8-3,4- 二氢 -2H- 苯并 -1,4- 噁嗪基，还优选 2,3- 亚甲基二氧基苯基、3,4- 亚甲基二氧基苯基、2,3- 亚乙基二氧基苯基、3,4- 亚乙基二氧基苯基、3,4-( 二氟亚甲基二氧基 ) 苯基、2,3- 二氢苯并呋喃 -5- 或 -6- 基、2,3-(2- 氧代亚甲基二氧基 ) 苯基或还有 3,4- 二氢 -2H-1,5- 苯并二氧杂环庚烯 -6- 或 -7- 基，还优选 2,3- 二氢苯并呋喃基或 2,3- 二氢 -2- 氧代呋喃基。极为优选杂芳基是未取代的或是单取代的 2- 吡啶基、嘧啶基或咪唑基。

[0072] $R^1$ 优选是 H、OH、F、甲基、甲氧基、三氟甲氧基。

[0073] $R^2$ 优选是 H、OH、烷氧基，例如甲氧基、$OCH_2CH_2$- 苯基。

[0074] $R^3$ 优选是 H 或烷基，优选 H、甲基或叔丁基。

[0075] $R^4$ 优选是 H、OH、烷氧基，例如甲氧基。

[0076] $R^5$ 优选是 H 或 A。

[0077] $R^6$ 优选是 H 或 Het。

[0078] $R^7$ 优选是 $(CH_2)_mCOR^2$、$(CH_2)_mCOR^2$、$O(CH_2)_mCOR^2$ 或 $O(CH_2)_mCOR^2$。

[0079] $R^8$ 优选是烯丙基或基团选自 $(C(R^3)_2)_qS$- 烷基或 $(C(R^3)_2)_qSO$- 烷基，其中 q 是 1、2、3、4、5、6、7、8、9、10、11 或 12。

[0080] 优选的 Nrf2 激活剂选自：如 J. Med. Chem., 2011, 54(12), 第 4147-4159 页中公开的查耳酮衍生物，例如 2- 三氟甲基 -2' - 甲氧基查耳酮、金诺芬（作为 FDA 批准的药物瑞得中包含的）、依布硒、1, 2- 萘醌、肉桂醛、咖啡酸及其酯、姜黄素、白藜芦醇、青蒿琥酯、叔丁基氢醌和 - 醌 (tBHQ、tBQ)、维生素 K1、K2 和 K3，优选甲萘醌、富马酸酯即富马酸一 - 和 / 或二酯，其优选选自富马酸一烷基酯和富马酸二烷基酯，例如富马酸一甲酯、富马酸二甲酯、富马酸一乙酯和富马酸二乙酯、2- 环戊烯酮、依他尼酸及其烷基酯、甲基巴多索隆 (2- 氰基 -3, 12- 二氧代齐墩果 -1, 9(11) 二烯 -28- 酸甲酯）(CDDO-Me，RTA 402)、2- 氰基 -3, 12- 二氧代齐墩果 -1, 9(11) 二烯 -28- 酸乙酯、2- 氰基 -3, 12- 二氧代齐墩果 -1, 9(11) 二烯 -28- 酸 (CDDO)、1[2- 氰基 -3, 12- 二氧代齐墩果 -1, 9(11)- 二烯 -28- 酰基 ] 咪唑 (CDDO-Im)、(2- 氰基 -N- 甲基 -3, 12- 二氧代齐墩果 -1, 9(11)- 二烯 -28 酰胺 (CDDO- 甲基酰胺，CDDO-MA)、异硫氰酸酯例如莱菔硫烷、1, 2- 二硫杂环戊二烯 -3- 硫酮例如奥替普拉、辣椒辣素、3, 5- 二 - 叔丁基 -4- 羟基甲苯、3- 羟基香豆素、色甘酸钠或其任意其它盐或奈多罗米或其盐例如钠盐、4- 羟基丙烯醛、4- 氧代丙烯醛、丙二醛、(E)-2- 依维派钠、辣椒辣素、大蒜素、异硫氰酸烯丙酯、异硫氰酸 6- 甲硫基己酯、异硫氰酸 7- 甲硫基庚酯、莱菔硫烷、异硫氰酸 8- 甲硫基辛酯、皮质类固醇例如地塞米松、8- 异前列腺素 A2、丙酮酸烷基酯例如丙酮酸甲酯和丙酮酸乙酯、草酰丙酸二乙酯或草酰丙酸二甲酯、2- 乙酰氨基丙烯酸酯、甲基或乙基 -2- 乙酰氨基丙烯酸酯、hypoestoxide、欧苷菊、圣草酚、4- 羟基 -2- 丙烯醛、4- 氧代 -2 丙烯醛、牛龙牛儿醛、花姜酮、橙酮、异甘草根亭配基、黄腐醇、[10]- 姜烯粉、丁香酚、1' - 乙酰氧基胡椒酚乙酸酯、异硫氰酸酯烯丙酯、异硫氰酸苄酯、异硫氰酸苯乙酯、异硫氰酸 4-( 甲硫基 )-3- 丁烯酯和异硫氰酸 6- 甲基亚磺酰基己酯、阿魏酸及其酯例如阿魏酸乙酯和阿魏酸甲酯、索法酮、4- 甲基瑞香素、白茅苷、葡萄内酯、枸橼苦素、双 [2- 羟基亚苄基 ] 丙酮、脂环族类姜黄色素、4- 溴黄酮、β - 萘黄酮、苏木黄酮 A、橙酮及其相应的吲哚衍生物例如亚苄基 - 二氢吲哚 -2- 酮、紫苏醛、槲皮素、非瑟酮、koparin、染料木黄酮、丹参酮 IIA、BHA、BHT、PMX-290、AL-1、avicin D、葛杜宁、非瑟酮、穿心莲内酯、[(±)-(4bS, 8aR, 10aS)-10a- 乙炔基 -4b, 8, 8- 三甲基 -3, 7- 二氧代 -3, 4b, 7, 8, 8a, 9, 10, 10a- 八氢菲 -2, 6- 二腈 ](TBE-31)、2- 氰基 -3, 12- 二氧代齐墩果 -1, 9(11)- 二烯 -28- 腈 (TP-225)、[(±)-(4bS, 8aR, 10aS)-10a- 乙炔基 -4b, 8, 8- 三甲基 -3, 7- 二氧代 -3, 4b, 7, 8, 8a, 9, 10, 10a- 八氢菲 -2, 6- 二腈 ](TBE-31)、(TP-225)、MCE-1、MCE5、Medicinal Research Reviews, 32, No. 4, 687-726, 2012 中涉及的 ADT、没食子酸酯例如烷基酯优选棓酸乙酯、棓酸正丙酯和棓酸辛酯或表没食子儿茶素没食子酸酯、咖啡酸酯例

如烷基酯或其苯乙酯、辅酶 Q10（泛醌，泛癸利酮）和上述举出的醌和氢醌衍生物的相应的醌或氢醌形式和上述举出的活性剂的立体异构体、互变异构体或药理学活性衍生物例如相应的苯基酯、烷基酯、烷酰基酯和苯甲酰基酯、苯基醚和烷基醚。

[0081] 极为优选的 Nrf2 激活剂选自：鼠尾草酸、2- 萘醌、肉桂醛、咖啡酸及其酯、姜黄素、白藜芦醇、青蒿琥酯、叔丁基氢醌、维生素 K1、K2 和 K3、富马酸酯即富马酸一 - 和 / 或二酯，其优选选自富马酸一烷基酯和富马酸二烷基酯，例如富马酸一甲酯、富马酸二甲酯、富马酸一乙酯和富马酸二乙酯，异硫氰酸酯例如莱菔硫烷、1,2- 二硫杂环戊二烯 -3- 硫酮例如奥替普拉、辣椒辣素、3,5- 二 - 叔丁基 -4- 羟基甲苯、3- 羟基香豆素、4- 羟基丙烯醛、4- 氧代丙烯醛、丙二醛、(E)-2- 依维派钠、辣椒辣素、大蒜素、异硫氰酸烯丙酯、异硫氰酸 6- 甲硫基己酯、异硫氰酸 7- 甲硫基庚酯、莱菔硫烷、异硫氰酸 8- 甲硫基辛酯、8- 异前列腺素 A2、丙酮酸烷基酯例如丙酮酸甲酯和丙酮酸乙酯、草酰丙酸二乙酯或草酰丙酸二甲酯、2- 乙酰氨基丙烯酸酯、甲基或乙基 -2- 乙酰氨基丙烯酸酯、hypoestoxide、欧苷菊、圣草酚、4- 羟基 -2- 丙烯醛、4- 氧代 -2 丙烯醛、牛龙牛儿醛、花姜酮、橙酮、异甘草根亭配基、黄腐醇、[10]- 姜烯酚、丁香酚、1'- 乙酰氧基胡椒酚乙酸酯、异硫氰酸烯丙酯、异硫氰酸苄酯、异硫氰酸苯乙酯、异硫氰酸 4-（甲硫基）-3- 丁烯酯和异硫氰酸 6- 甲基亚磺酰基己酯和上述举出的醌和氢醌衍生物的相应的醌或氢醌形式和上述举出的活性剂的立体异构体、互变异构体或药理学活性衍生物。极为优选的 Nrf2 激活剂是迈克尔反应受体例如富马酸二甲酯、富马酸一甲酯、异硫氰酸酯和 1,2- 二硫杂环戊二烯 -3- 硫酮。在另一个实施方案中，极为优选的 Nrf2 激活剂选自富马酸一甲酯、富马酸二甲酯、奥替普拉、1,2- 萘醌、叔丁基氢醌、丙酮酸甲酯或丙酮酸乙酯、3,5- 二 - 叔丁基 -4- 羟基甲苯、草酰丙酸二乙酯或草酰丙酸二甲酯、hypoestoxide、欧苷菊、圣草酚、4- 羟基 -2- 丙烯醛、4- 氧代 -2 丙烯醛、牛龙牛儿醛、花姜酮、橙酮、异甘草根亭配基、黄腐醇、[10]- 姜烯酚、丁香酚、1' - 乙酰氧基胡椒酚乙酸酯、异硫氰酸烯丙酯、异硫氰酸苄酯、异硫氰酸苯乙酯、异硫氰酸 4-（甲硫基）-3- 丁烯酯和异硫氰酸 6- 甲基亚磺酰基己酯。

[0082] 另一组优选的 Nrf2 激活剂包含优选的 Nrf2 激活剂富马酸酯、甲基巴多索隆 (2- 氰基 -3,12- 二氧代齐墩果 -1,9(11) 二烯 -28- 酸甲酯，CDDO-Me，RTA 402)、2- 氰基 -3,12- 二氧代齐墩果 -1,9(11) 二烯 -28- 酸乙酯、2- 氰基 -3,12- 二氧代齐墩果 -1,9(11) 二烯 -28- 酸 (CDDO)、1[2- 氰基 -3,12- 二氧代齐墩果 -1,9(11)- 二烯 -28- 酰基 ] 咪唑 (CDDO-Im)、2- 氰基 -N- 甲基 -3,12- 二氧代齐墩果 -1,9(11)- 二烯 -28 酰胺 (CDDO- 甲基酰胺、CDDO-MA)、[(±)-(4bS,8aR,10aS)-10a- 乙炔基 -4b,8,8- 三甲基 -3,7- 二氧代 -3,4b,7,8,8a,9,10,10a- 八氢菲 -2,6- 二腈 ](TBE-31)、2- 氰基 -3,12- 二氧代齐墩果 -1,9(11)- 二烯 -28- 腈 (TP-225)、3- 叔丁基 -4- 羟基苯甲醚、2- 叔丁基 -4- 羟基苯甲醚 (BHA)、叔丁基醌 (tBQ)、叔丁基氢醌 (tBHQ)、3,5- 二 - 叔丁基 -4- 羟基甲苯 (BHT)、2,6- 二 - 叔丁基 -4- 亚甲基 -2,5- 环己二烯 -1- 酮 (2,6- 二 - 叔丁基醌甲基化物，BHT- 醌甲基化物 )、乙氧喹、没食子酸酯、α 硫辛酸及其酯例如烷基酯优选硫辛酸乙酯、姜黄素、白藜芦醇、甲萘醌、肉桂醛、肉桂酸酯、咖啡酸酯、咖啡醇、咖啡白脂、番茄红素、鼠尾草酚、莱菔硫烷、奥替普拉、辣椒辣素 (8- 甲基 -N- 香草基 - 反式 -6- 壬烯酰胺 )、5-(4- 甲氧基 - 苯基 )-1,2- 二硫杂环戊二烯 -3- 硫酮 (ADT)、柳氮磺吡啶、5- 氨基水杨酸 ( 美沙拉秦 )、5- 氨基 -2- 羟基 - 苯甲酸 4-(5- 硫代 -5H-[1,2] 二硫杂环戊二烯 -3- 基 )- 苯基酯 (ATB-429)、大

蒜素、异硫氰酸烯丙酯、花姜酮、异硫氰酸苯乙酯、异硫氰酸苄酯、异硫氰酸 6- 甲基亚磺酰基己酯以及上述举出的活性剂的烷基和烷酰基酯、烷基醚、立体异构体、互变异构体和盐。

[0083] 在本发明的甚至更优选的实施方案中，Nrf2 激活剂选自富马酸酯、3- 叔丁基 -4- 羟基苯甲醚、2- 叔丁基 -4- 羟基苯甲醚 (BHA)、叔丁基醌 (tBQ)、叔丁基氢醌 (tBHQ)、3,5- 二 - 叔丁基 -4- 羟基甲苯 (BHT)、2,6- 二 - 叔丁基 -4- 亚甲基 -2,5- 环己二烯 -1- 酮 (2,6- 二 - 叔丁基醌甲基化物、BHT- 醌甲基化物 )、乙氧喹、没食子酸酯、姜黄素、白藜芦醇、甲萘醌、肉桂醛、肉桂酸酯、咖啡酸酯、咖啡醇、咖啡白脂、番茄红素、鼠尾草酚、莱菔硫烷、奥替普拉、5-(4- 甲氧基 - 苯基 )-1,2- 二硫杂环戊二烯 -3- 硫酮 (ADT)、柳氮磺吡啶、5- 氨基水杨酸 ( 美沙拉秦 )、5- 氨基 -2- 羟基 - 苯甲酸 4-(5- 硫代 -5H-[1,2] 二硫杂环戊二烯 -3- 基 )- 苯基酯 (ATB-429)、大蒜素、异硫氰酸烯丙酯、花姜酮、异硫氰酸苯乙酯、异硫氰酸苄酯、异硫氰酸 6- 甲酯亚磺酰基己酯以及上述举出的活性剂的烷基和烷酰基酯、烷基醚、立体异构体、互变异构体和盐。这些优选的上述举出的 Nrf2 激活剂对 PPAR γ 不具有或没有显著的激动活性或显著作用。

[0084] 在本发明的另一个实施方案中，Nrf2 激活剂是金诺芬。根据本发明优选将金诺芬与格列酮、更优选吡格列酮或罗格列酮联用。

[0085] 在本发明的另一个实施方案中，Nrf2 激活剂选自柳氮磺吡啶或 5- 氨基水杨酸 ( 美沙拉秦 )。根据本发明优选将柳氮磺吡啶或 5- 氨基水杨酸 ( 美沙拉秦 ) 与格列酮、更优选吡格列酮或罗格列酮联用。

[0086] 特别有利的是本发明 PPAR γ 激动剂和 Nrf2 激活剂的应用能够使得活性剂各自在单一疗法中使用时的剂量最大化，从而产生最大的治疗效果。对 PPAR γ 激动剂或 Nrf2 激活剂各自未观察到已知的不良副作用增加或仅有极为有限的不良副作用增加。另外有利的是在本发明的组合治疗中降低了所用活性剂之一或它们两者的剂量。因此，可以避免或减少在使用所述活性剂的单一疗法中观察到的副作用。在本说明书的上下文中，术语“药理学活性衍生物”优选表示药理活性酸的盐、酰胺和酯，例如烷基酯，包括甲酯和乙酯；和药理活性醇的链烷酸酯和醚，例如乙酸酯和甲基醚以及药理活性胺的链烷酸酰胺，例如相应的乙酰胺。

[0087] 本发明的组合治疗还可以与一般用于作为标准疗法的多种适应证的治疗和药物组合。例如，在治疗多发性硬化的过程中，本发明的组合治疗还可以与干扰素例如干扰素 β 1b 或干扰素 β 1a(Rebif，Avonex) 或醋酸格拉替雷 ( 考帕松 )、鞘氨醇 1- 磷酸受体调节剂例如芬戈莫德 (Gilenya) 和 / 或甲氨蝶呤组合。本发明的组合治疗还可以与 RXR 特异性配体例如 9- 顺式 - 视黄酸 (RA) 组合以得到甚至更为改善的结果，特别是是在治疗银屑病的过程中。

[0088] 本发明的组合治疗尤其还可以与治疗帕金森病领域众所周知的确立治疗剂进一步组合用于治疗帕金森病，治疗帕金森病领域众所周知的确立治疗剂例如左旋多巴，通常与多巴脱羧酶抑制剂例如卡比多巴或苄丝肼或 COMT 抑制剂例如恩他卡朋、托卡朋或硝替卡朋组合。此外，本发明的组合治疗还可以与多巴胺激动剂，例如溴隐亭、培高利特、普拉克索、罗匹尼罗、吡贝地尔、卡麦角林、阿扑吗啡或利舒脲或罗替高汀，和 MAO-B 抑制剂，例如司来吉兰或雷沙吉兰组合。

[0089] 本发明的组合治疗可以作为同时或依次方案施用，也称作共同施用。当依次施用

时，组合可以两次或多次施用进行施用。可能将任何 PPARγ 激动剂与 Nrf2 激活剂组合在单位剂型中用于同时或依次给患者施用。

[0090] 一般而言，对于包含富马酸酯的组合物，优选每日 2 次 (BID) 或每日 3 次 (TID) 施用。因此，调整各活性剂的剂量。

[0091] 根据本发明共同施用 PPARγ 激动剂与 Nrf2 激活剂一般且优选是指同时或依次施用 PPARγ 激动剂与 Nrf2 激活剂，使得 PPARγ 激动剂与 Nrf2 激活剂的治疗有效量同时出现在患者体内。

[0092] 共同施用包括同时施用本发明的一种活性剂和另一种活性剂和在施用本发明的一种活性剂之前或之后施用另一种活性剂，例如在数秒、数分钟或数小时内施用本发明的两种活性剂。在一个实施方案中，在施用第一种活性剂之后数小时期限、例如 0.25-12 小时、优选 0.5-3 小时、最优选 1-2 小时施用第二种活性剂。

[0093] 本发明的组合治疗和共同施用通常提供了“协同作用”和“协同效果”，即当一起使用 PPARγ 激动剂与 Nrf2 激活剂时获得的治疗效果高于累加的效果，即大于因使用每种单独的活性剂产生的效果的总和。

[0094] 可以根据几种充分建立的方案的任意一种确定用于本发明的 PPARγ 激动剂和 Nrf2 激活剂或包含 PPARγ 激动剂与 Nrf2 激活剂的药物组合物的适合剂量。例如，动物研究例如使用小鼠、大鼠、狗和 / 或猴子的研究可以用于确定药物化合物的适合剂量。从动物研究的结果可以推算以确定用于其它种类的剂量，例如用于人的剂量。

[0095] 一般而言，根据本发明，将优选的 PPARγ 激动剂与优选的 Nrf2 激活剂组合施用，优选口服，每日剂量为 0.01mg-50mg/kg 体重，取决于相应的 PPARγ 激动剂的活性和安全性。如果没有另外指明，则尽管以马来酸盐或另一种酸加成盐的形式使用，但是上下文给出的剂量反映 PPARγ 激动剂的游离碱的量。

[0096] 优选的 Nrf 2 激活剂是甲基巴多索隆和富马酸二烷基酯，例如富马酸二甲酯和富马酸二乙酯。

[0097] 本发明使用的富马酸二烷基酯通过本领域已知的方法制备（例如，参见 EP 0 312 697）。

[0098] 优选地，活性成分，即活性剂用于制备片剂、微型片剂、小丸剂或颗粒形式，任选胶囊剂或小药囊形式的口服制剂。优选微型片剂或小丸剂，任选填充入胶囊或小药囊形式的制剂，并且它们也是本发明的主题。根据优选的实施方案，小丸剂或微型片剂的大小或平均直径范围分别为 300-2,000μm，特别是 500 或 1,000μm。

[0099] 可以给口服制剂包肠溶衣。胶囊剂可以是软或硬明胶胶囊剂。

[0100] 本发明使用的富马酸二烷基酯可以单独使用或作为几种化合物的混合物使用，任选地组合常用载体和赋形剂。按照这样的方式选择所用的量，使得得到的制剂、例如片剂包含相当于 10-300mg 富马酸 / 剂量单位的量的活性成分。

[0101] 本发明优选的制剂包含总量为 10-300mg 的富马酸二甲酯和 / 或富马酸二乙酯。

[0102] 优选 PPAR 激动剂且优选 PPARγ 激动剂与 Nrf2 激活剂的固定剂量组合。特别优选罗格列酮与富马酸二甲酯以及罗格列酮与甲基巴多索隆的固定剂量组合。特别优选吡格列酮与富马酸二甲酯以及罗格列酮与甲基巴多索隆的固定剂量组合。

[0103] 特别地，本发明优选以其马来酸盐的形式施用罗格列酮，每日剂量为

0.01-0.2mg/kg 体重，更优选每日剂量为 0.02-0.16mg/kg 体重，并且最优选每日剂量为 0.025mg-0.14mg/kg 体重，例如每日剂量为 0.03mg、0.06mg 或 0.12mg/kg 体重。特别优选每日口服剂量为 2mg、4mg 和 8mg 罗格列酮 / 患者。

[0104] 特别地，本发明优选以其盐酸盐的形式施用吡格列酮，每日剂量为 0.05-1mg/kg 体重，更优选每日剂量为 0.1-0.8mg/kg 体重，并且最优选每日剂量为 0.15mg-0.7mg/kg 体重，例如每日剂量为约 0.2mg、约 0.4mg 或约 0.6mg/kg 体重。特别优选每日口服剂量为约 15mg、约 30mg 和约 45mg 吡格列酮 / 患者。

[0105] 特别地，本发明优选施用噻格列酮或曲格列酮，每日剂量为 1-20mg/kg 体重，更优选每日剂量为 2-15mg/kg 体重，并且最优选每日剂量为 3mg-10mg/kg 体重。特别优选口服剂量。

[0106] 一般而言，将优选的 Nrf2 激活剂与优选的 PPAR γ 激动剂组合施用，优选口服，每日剂量为 0.1mg-20mg/kg 体重，取决于相应的 Nrf2 激活剂的活性和安全性。

[0107] 特别地，本发明优选施用甲基巴多索隆，每日剂量为 0.1-3mg/kg 体重，更优选每日剂量为 0.2-2.5mg/kg 体重，并且最优选每日剂量为 0.3mg-2.2mg/kg 体重，例如每日剂量为约 0.35mg、约 1.1mg 或约 2mg/kg 体重。特别优选每日口服剂量为约 25mg、约 75mg 和约 150mg 甲基巴多索隆 / 患者。

[0108] 特别地，本发明优选施用富马酸二甲酯，每日剂量为 1-20mg/kg 体重，更优选每日剂量为 2-15mg/kg 体重，并且最优选每日剂量为 3mg-12mg/kg 体重，例如每日剂量为约 3.4mg、约 7mg 或约 10mg/kg 体重。特别优选每日口服剂量为约 240mg、约 480mg 和约 720mg 富马酸二甲酯 / 患者。

[0109] 用于本发明组合中的 PPAR γ 激动剂与 Nrf2 激活剂的剂量之比取决于选择的具体 PPAR γ 激动剂与 Nrf2 激活剂的活性。

[0110] 特别优选的每日口服剂量为 2mg、4mg 和 8mg 罗格列酮 / 患者。

[0111] 特别优选的每日口服剂量为约 20mg、约 25mg、约 75mg 和约 150mg 甲基巴多索隆 / 患者。就以无定形形式使用甲基巴多索隆而言，最优选每日剂量为约 20mg/ 患者。

[0112] 特别优选每日口服剂量为约 120mg、约 240mg、约 360mg、约 480mg、约 600mg 和约 720mg 富马酸二甲酯 / 患者。

[0113] 如果 Nrf2 激活剂是富马酸二甲酯，则优选每日施用 1 次或 2 次。

[0114] 优选的剂型且特别是口服剂型例如片剂或胶囊剂可以包含 ：

[0115] 对于口服施用，剂型例如片剂或胶囊剂可以优选包含约 2mg 罗格列酮和约 25mg 甲基巴多索隆或约 2mg 罗格列酮和约 75mg 甲基巴多索隆或约 2mg 罗格列酮和约 150mg 甲基巴多索隆或约 4mg 罗格列酮和约 25mg 甲基巴多索隆或约 4mg 罗格列酮和约 75mg 甲基巴多索隆或约 4mg 罗格列酮和约 150mg 甲基巴多索隆或约 8mg 罗格列酮和约 25mg 甲基巴多索隆或约 8mg 罗格列酮和约 75mg 甲基巴多索隆或约 8mg 罗格列酮和约 150mg 甲基巴多索隆。最优选剂型可以包含约 8mg 罗格列酮和约 150mg 甲基巴多索隆。

[0116] 对于每日施用 3 次，优选的剂型例如片剂或胶囊剂可以包含约 0.7mg、优选约 0.67mg 罗格列酮和 240mg 富马酸二甲酯或约 1.3mg、优选约 1.33mg 罗格列酮和约 240mg 富马酸二甲酯或约 2.7mg、优选约 2.67mg 罗格列酮和约 240mg 富马酸二甲酯或约 0.7mg、优选约 0.67mg 罗格列酮和 120mg 富马酸二甲酯或约 1.3mg、优选约 1.33mg 罗格列酮和约 120mg

富马酸二甲酯或约 2.7mg、优选约 2.67mg 罗格列酮和约 120mg 富马酸二甲酯。最优选剂型可以包含约 2.7mg、优选约 2.67mg 罗格列酮和约 240mg 富马酸二甲酯。

[0117] 对于每日施用 2 次，优选的剂型例如片剂或胶囊剂可以包含约 1mg 罗格列酮和约 240mg 富马酸二甲酯或约 2mg 罗格列酮和约 240mg 富马酸二甲酯或约 4mg 罗格列酮和约 240mg 富马酸二甲酯。

[0118] 对于每日施用，剂型例如片剂或胶囊剂可以优选包含约 15mg 吡格列酮和约 25mg 甲基巴多索隆或约 15mg 吡格列酮和约 75mg 甲基巴多索隆或约 15mg 吡格列酮和约 150mg 甲基巴多索隆或约 30mg 吡格列酮和约 25mg 甲基巴多索隆或约 30mg 吡格列酮和约 75mg 甲基巴多索隆或约 30mg 吡格列酮和约 150mg 甲基巴多索隆或约 45mg 吡格列酮和约 25mg 甲基巴多索隆或约 45mg 吡格列酮和约 75mg 甲基巴多索隆或约 45mg 吡格列酮和约 150mg 甲基巴多索隆。最优选剂型可以包含约 45mg 吡格列酮和约 150mg 甲基巴多索隆。

[0119] 对于每日施用 3 次，优选的剂型例如片剂或胶囊剂可以包含约 5mg 吡格列酮和 240mg 富马酸二甲酯或约 10mg 吡格列酮和约 240mg 富马酸二甲酯或约 15mg 吡格列酮和约 240mg 富马酸二甲酯或约 5mg 吡格列酮和 120mg 富马酸二甲酯或约 10mg 吡格列酮和约 120mg 富马酸二甲酯或约 15mg 吡格列酮和约 120mg 富马酸二甲酯。最优选剂型可以包含约 15mg 吡格列酮和约 240mg 富马酸二甲酯。

[0120] 对于每日施用 2 次，优选的剂型例如片剂或胶囊剂可以包含约 7.5mg 吡格列酮和约 240mg 富马酸二甲酯或约 15mg 吡格列酮和约 240mg 富马酸二甲酯或约 22.5mg 吡格列酮和约 240mg 富马酸二甲酯。

[0121] 此外，本发明的药物组合物优选包含约 5mg、约 7.5mg、约 10mg、约 15mg、约 20mg、约 22.5mg 或约 25mg 吡格列酮作为 PPAR γ 激动剂。此外，本发明的药物组合物优选包含约 0.7mg、约 1mg、约 1.3mg、约 2mg、约 2.7mg、约 3mg、约 3.5mg、约 4 或约 5mg 罗格列酮作为 PPAR γ 激动剂。

[0122] 本发明的药物组合物优选包含约 120mg、约 200mg 或约 240mg 富马酸二甲酯。

[0123] 特别地，本发明优选以其钙盐的形式施用阿托伐他汀，每日口服剂量为约 10、约 20、约 40 或约 80mg/ 患者。优选地，将阿托伐他汀以上述剂量与约 120、约 240 或约 360、约 480 或约 720mg/ 天的剂量的富马酸二甲酯组合。最优选包含约 20mg 或约 40mg 钙盐形式的阿托伐他汀和约 240mg 富马酸二甲酯的组合。

[0124] 在进一步的实施方案中，将阿托伐他汀以上述剂量与无定形形式的约 20mg/ 天剂量的甲基巴多索隆组合。最优选包含约 40mg 或约 80mg 钙盐形式的阿托伐他汀和约 20mg 无定形形式的甲基巴多索隆的组合。

[0125] 特别地，本发明优选施用洛沙坦，每日口服剂量为约 25、约 50、约 75 或约 100mg/ 患者。将上述剂量的洛沙坦与约 120、约 240 或约 360、约 480 或约 720mg/ 天的剂量的富马酸二甲酯组合。最优选包含约 25mg 或约 50mg 洛沙坦和约 240mg 富马酸二甲酯的组合。优选将该组合每日施用 2 次。沙坦且优选洛沙坦、厄贝沙坦、替米沙坦和坎地沙坦与 Nrf2 激活剂例如富马酸二甲酯和甲基巴多索隆的组合治疗对治疗糖尿病肾病（因糖尿病导致的肾损伤）和慢性肾疾病特别有效，而且可以用于治疗多发性硬化。

[0126] 在进一步的实例中，将洛沙坦以上述剂量与无定形形式的约 20mg/ 天剂量的甲基巴多索隆组合。最优选包含约 25mg 或约 50mg 洛沙坦和约 20mg 无定形形式的甲基巴多索

隆的组合。优选将该组合每日施用 1 次。

[0127] 特别地，本发明优选施用布洛芬，其每日剂量适用于使用布洛芬的单一疗法，例如约 600mg、约 800mg 或约 1200mg 或约 2400mg/ 患者。最优选包含约 600mg 布洛芬和约 240mg 富马酸二甲酯的组合。优选将该组合物每日施用 2 次。

[0128] 在进一步的实例中，将布洛芬以上述剂量与无定形形式的约 20mg/ 天剂量的甲基巴多索隆组合。最优选包含约 800mg 布洛芬和约 20mg 无定形形式的甲基巴多索隆的组合。优选将该组合每日施用 1 次。

[0129] 罗格列酮与富马酸二甲酯的优选比选自 1/20-1/400(w/w，罗格列酮 / 富马酸二甲酯)、优选 1/25-380，更优选 1/28-1/360。最优选该比例为约 1/30、约 1/45、例如约 1/44.4、约 1/60、约 1/90、例如约 1/88.9 或约 1/92.3、约 1/120、约 1/180，例如 1/171.4 或 1/184.6、约 1/240、约 1/340，例如约 1/342.9。

[0130] 吡格列酮与富马酸二甲酯的优选比选自 1/3-1/60(w/w，吡格列酮 / 富马酸二甲酯)、优选 1/4-1/55，更优选 1/5-1/52。最优选该比例为约 1/5.3、约 1/8、约 1/10、例如 1/10.7、约 1/12、约 1/16、约 1/24、约 1/32、约 1-48。

[0131] 一般而言，罗格列酮与甲基巴多索隆之比选自 1/1-1/100(w/w，罗格列酮 / 甲基巴多索隆 )、优选 1/1.5-1/80，更优选 1/2-1/75。最优选该比例为约 1/2.5、例如约 1/3.1 或约 1/5，例如 1/6.3、约 1/10、例如约 1/9.4 或约 1/12.5、约 1/20、例如 1/18.8、约 1/40、例如约 1/37.5、约 1/70、例如约 1/75。

[0132] 一般而言，吡格列酮和甲基巴多索隆之比选自 1/0.1-1/20(w/w，吡格列酮 / 甲基巴多索隆 )、优选 1/0.3-1/15，更优选 1/0.4-1/12。最优选该比例为约 1/0.5 例如约 1/0.4 或约 1/0.6 或约 1/0.7 或约 1/0.8、约 1/2，例如约 1/1.7 或约 1/2.5、约 1/3、例如约 1/3.3、约 1/5 或约 1/10。

[0133] 在本发明优选的实施方案中，根据 US2012/022156，更优选在包含无定形甲基巴多索隆的药物制剂中使用无定形甲基巴多索隆，其作为使用玻璃成形赋形剂 (glass-forming excipient) 喷雾干燥的分散体得到，所述玻璃成形赋形剂例如甲基丙烯酸共聚物 Type C，USP，例如 4/6 重量比的甲基巴多索隆和甲基丙烯酸共聚物 Type C，USP(Eurdagit)，更优选与由至少一种亲水性粘合剂例如羟丙基甲基纤维素组成的颗粒混合。本发明优选的甲基巴多索隆组合物还包含表面活性剂，例如十二烷基硫酸钠，优选量占总组合物的约 1-5 重量%，优选约 3%，例如 2.73%。

[0134] 在优选的实施方案中，根据本发明施用无定形甲基巴多索隆，其每日剂量为 0.05-1mg/kg 体重，更优选剂量为 0.1-0.8mg/kg 体重，并且最优选剂量为 0.2mg-0.6mg/kg 体重，例如每日剂量为约 0.15mg、约 0.25mg 或约 0.35mg/kg 体重。特别优选每日剂量为约 10mg、约 20mg 和约 30mg 甲基巴多索隆 / 患者。

[0135] 对于每日施用无定形甲基巴多索隆，使用如下剂量 / 患者 :约 2mg 罗格列酮和约 10mg 甲基巴多索隆或约 2mg 罗格列酮和约 20mg 甲基巴多索隆或约 2mg 罗格列酮和约 30mg 甲基巴多索隆或约 4mg 罗格列酮和约 10mg 甲基巴多索隆或约 4mg 罗格列酮和约 20mg 甲基巴多索隆或约 4mg 罗格列酮和约 30mg 甲基巴多索隆或约 8mg 罗格列酮和约 10mg 甲基巴多索隆或约 8mg 罗格列酮和约 20mg 甲基巴多索隆或约 8mg 罗格列酮和约 30mg 甲基巴多索隆。最优选使用约 8mg 罗格列酮和约 20mg 甲基巴多索隆。特别地，优选如果以固定剂量组合使

用上述量，即为固体口服剂型。

[0136] 或者，对于每日施用无定形甲基巴多索隆，则使用如下剂量 / 患者 :约 15mg 吡格列酮和约 10mg 甲基巴多索隆或约 15mg 吡格列酮和约 20mg 甲基巴多索隆或约 15mg 吡格列酮和约 30mg 甲基巴多索隆或约 30mg 吡格列酮和约 10mg 甲基巴多索隆或约 30mg 吡格列酮和约 20mg 甲基巴多索隆或约 30mg 吡格列酮和约 30mg 甲基巴多索隆或约 45mg 吡格列酮和约 10mg 甲基巴多索隆或约 45mg 吡格列酮和约 20mg 甲基巴多索隆或约 45mg 吡格列酮和约 30mg 甲基巴多索隆。最优选使用约 45mg 吡格列酮和约 20mg 甲基巴多索隆。最优选使用约 8mg 罗格列酮和约 20mg 甲基巴多索隆。特别地，优选如果以固定剂量组合使用上述量，即为固体口服剂型。

[0137] 在本发明优选的实施方案中，如果使用无定形形式的甲基巴多索隆，则罗格列酮与甲基巴多索隆之间的优选比为 1/1-1/20（在本申请上下文中，当涉及比例时，“/”表示“:”，w/w，罗格列酮 / 甲基巴多索隆），优选 1/1.1-1/17，更优选 1/1.2-1/16。最优选该比例为约 1/1.3 例如约 1/1.25、约 1/2.5、约 1/3.5 例如 1/3.75、约 1/5、约 7.5、约 1/10。

[0138] 在本发明进一步优选的实施方案中，如果使用无定形形式的甲基巴多索隆，则吡格列酮与甲基巴多索隆之间的优选比为 1/0.1-1/3(w/w，吡格列酮 / 甲基巴多索隆），优选 1/0.15-1/2.5，更优选 1/0.2-1/2.2。最优选该比例为约 1/0.2、例如约 1/0.22、约 1/0.3、例如约 1/0.33、约 1/0.4、例如约 1/0.44、约 1/0.7、例如约 1/0.67、约 1/1 或约 1/2。

[0139] 优选包含以固定剂量组合的 PPAR γ 激动剂和 Nrf2 激活剂的剂型且特别是口服剂型，例如片剂或胶囊剂，所述固定剂量组合包含上述给出比例的组合物且尤其是包含无定形甲基巴多索隆的那些。

[0140] 最优选包含上述量和比例的活性成分的固定剂量组合，例如片剂。

[0141] 本公开提供的药物组合物可以包含治疗有效量的 PPAR γ 激动剂和 Nrf2 激活剂以及适量的一种或多种可药用介质，以提供适合于对患者施用的组合物。适合的药物介质在本领域中有描述。

[0142] 在一些实施方案中，可以将 PPAR γ 激动剂和 Nrf2 激活剂一起掺入口服施用的药物组合物。这种药物组合物的口服施用可以导致 PPAR γ 激动剂和 Nrf2 激活剂自始至终在肠中吸收并且进入全身循环。可以按照制药领域公知的方式制备这种口服组合物并且其包含 PPAR γ 激动剂和 Nrf2 激活剂和至少一种可药用介质。口服药物组合物可以包含治疗有效量的 PPAR γ 激动剂和 Nrf2 激活剂和适合量的可药用介质，以提供施用于患者的适当形式。

[0143] 可以将 PPAR γ 激动剂和 Nrf2 激活剂一起掺入通过任意其它适合的施用途径施用的药物组合物，所述施用途径包括真皮内、肌内、腹膜内、静脉内、皮下、鼻内、硬膜外、口服、舌下、脑内、阴道内、透皮、直肠、吸入或局部。

[0144] 在本发明的一个实施方案中，提供了局部制剂，其包含 PPAR 激动剂，例如格列酮，如吡格列酮或罗格列酮 ;和 Nrft2 激活剂，优选不会导致或仅罕见地导致过敏性皮肤反应的 Nrf2 激活剂，例如甲基巴多索隆、CDDO、CDDO-IM、CDDO-MA、TP-225、甲萘醌、维生素 K1、BHA、BHT、tBHQ、tBQ、姜黄素、白藜芦醇、肉桂醛或奥替普拉。局部制剂优选用于治疗银屑病、痤疮、玫瑰痤疮和皮疹例如因 EGFR 抑制剂如西妥昔单抗、扎鲁木单抗、尼妥珠单抗和马妥珠单抗、吉非替尼、厄洛替尼和拉帕替尼导致的皮疹。使用常规成分和本领域公知和 / 或

本文公开的方法制备制剂。

[0145] 可以通过常规的混合、溶解、制粒、制糖锭、水飞、乳化、包囊、俘获或冻干方法制备包含 PPARγ 激动剂和 Nrf2 激活剂的药物组合物。可以使用一种或多种有利于 PPARγ 激动剂和 Nrf2 激活剂或其晶体形式加工的生理学可接受的载体、稀释剂、赋形剂或助剂和一种和多种可药用介质按照常规方式将药物组合物配制成药学上使用的制剂。适合的制剂取决于所选择的施用途径。本公开提供的药物组合物可以采用溶液剂、混悬剂、乳剂、片剂、丸剂、小丸剂、胶囊剂、包含液体的胶囊剂、散剂、缓释制剂、栓剂、乳剂、气雾剂、喷雾剂、混悬剂或任意其它适合于施用于患者的形式。可以将本公开提供的药物组合物配制成单位剂型。单位剂型是指适合于作为进行治疗的患者的单位剂量的物理分散单位，每个单位包含预定量的 PPARγ 激动剂和 Nrf2 激活剂，经计算，其可产生预期的治疗效果。单位剂型可以用于单一每日剂量，每日施用 2 次；或多个每日剂量之一，例如每日 3 次或以上。当使用多个每日剂量时，单位剂型对每个剂量而言可以是相同或不同的。一种或多种剂型可以包含可以在单一时间点及时或在定时间隔期间施用于患者的剂量。

[0146] 可以为速释或控释或缓释或延迟释放配制包含 PPARγ 激动剂和 Nrf2 激活剂的药物组合物。

[0147] 在一些实施方案中，本公开提供的口服剂型可以为控释剂型。控制递送技术可以改善药物在特定区域或胃肠道区域中的吸收。可以设计控制递药系统以便以这样的方式递药：将药物水平维持在治疗有效窗内并且将有效或安全血液水平维持所述系统在胃肠道中持续以特定释放特性递药同样长的期限。控制递药与使用立即释放剂型观察到的波动相比可以在一定时间期限内产生基本上恒定血液水平的 PPARγ 激动剂和 Nrf2 激活剂。对于一些 PPARγ 激动剂和 Nrf2 激活剂，在治疗期间自始至终维持恒定血液和组织浓度是最期望的治疗模式。PPARγ 激动剂和 Nrf2 激活剂的立即释放可以导致达到峰值的血液水平高于引起期望响应所需的水平，这可能导致消耗了活性剂并且可能导致或加剧毒性副作用。控制递药可以产生最佳疗法，且不仅可以降低给药频率，而且可以减轻副作用的严重性。控释剂型的实例包括溶出控制系统、扩散控制系统、离子交换树脂、渗透控制系统、可浸蚀基质系统、不依赖于 pH 的制剂、胃潴留系统等。

[0148] 本公开提供的特定药物组合物的适合的口服剂型至少部分可以取决于 PPARγ 激动剂和 Nrf2 激活剂的胃肠吸收特性和这些活性剂在胃肠道中的稳定性、其药代动力学和预期的治疗特性。对具体的 PPARγ 激动剂和 Nrf2 激活剂可以选择适合的控释口服剂型。例如，胃潴留口服剂型可以适合于主要从上胃肠道吸收的活性剂且缓释口服剂型可以适合于主要从下胃肠道吸收的活性剂。

[0149] 在一些实施方案中，本公开提供的药物组合物可以使用适合于在口服施用时提供 PPARγ 激动剂和 Nrf2 激活剂缓释的剂型实施。缓释口服剂型可以用于在延长时间期限内释放 PPARγ 激动剂和 / 或 Nrf2 激活剂并且在期望将活性剂递送至下胃肠道时是有用的。缓释口服剂型包括将活性剂在生物流体例如血浆、血液、脑脊髓液或组织或器官中的治疗浓度维持延长时间期限的任意口服剂型。缓释口服剂型包括扩散控制系统，例如贮器装置和基质装置；溶出控制系统、渗透系统或浸蚀控制系统。缓释口服剂型及其制备方法是本领域众所周知的。

[0150] 在上述各剂型中，可以将 PPARγ 激动剂与 Nrf2 激活剂一起混合配制或优选将它

们彼此单独配制。PPARγ 激动剂和 Nrf2 激活剂各自可以优选以单独的形式包含在剂型中，例如口服剂型，优选是片剂或胶凝剂。在这种口服剂型中，如果 PPARγ 激动剂和 Nrf2 激活剂是分离的，则可以用不同的赋形剂配制每种活性剂。还可以使 PPARγ 激动剂和 Nrf2 激活剂各自包含在具有不同释放特性即立即释放、控释或延迟释放的制剂中。

[0151] 包含 PPARγ 激动剂和 / 或 Nrf2 激活剂的制剂且特别是固体口服剂型可以包含药物制剂领域中常用的添加剂且还可以根据已知的方法制备。作为添加剂，例如，可以提及赋形剂、崩解剂、粘合剂、润滑剂、着色剂、pH 调节剂、表面活性剂、缓释剂、稳定剂、酸味剂、矫味剂、助流剂等。以常用于药物制剂领域的量使用这些添加剂。

[0152] 作为赋形剂，例如，可以提及：淀粉，例如玉米淀粉、马铃薯淀粉、小麦淀粉、稻米淀粉、部分预胶化淀粉、预胶化地方、多孔淀粉等；糖和糖醇，例如乳糖、果糖、葡萄糖、D- 甘露糖醇、山梨醇等；无水磷酸钙、结晶纤维素、沉淀碳酸钙、硅酸钙等。

[0153] 作为崩解剂，例如，使用羧甲基纤维素、羧甲基纤维素钙、羧甲基淀粉钠、交联羧甲基纤维素钠、交联聚维酮、低取代的羟丙基纤维素、羟丙基淀粉等。每 100 重量份固体制剂中所用的崩解剂的量优选是 0.5-25 重量份，更优选 1-15 重量份。

[0154] 作为粘合剂，例如，可以提及结晶纤维素、羟丙基纤维素、羟丙基甲基纤维素、聚乙烯吡咯烷酮、阿拉伯胶粉等。每 100 重量份固体制剂中所用的粘合剂的量优选是 0.1-50 重量份，更优选 0.5-40 重量份。

[0155] 润滑剂的优选实例包括硬脂酸镁、硬脂酸钙、滑石粉、脂肪酸的蔗糖酯、硬脂富马酸钠等。作为着色剂，例如，可以提及食用色素，例如 Food Yellow No. 5、Food Red No. 2、Food Blue No. 2 等；食品色淀、氧化铁等。作为 pH 调节剂，可以提及柠檬酸盐、磷酸盐、酒石酸盐、富马酸盐、乙酸盐、氨基酸盐等。作为表面活性剂，可以提及十二烷基硫酸钠、聚山梨醇酯 80、聚氧乙烯 (160) 聚氧丙烯 (30) 二醇等。

[0156] 作为缓释剂，例如，可以提及纤维素聚合物，例如羟丙基纤维素、羟丙基甲基纤维素（优选羟丙基甲基纤维素 2910、羟丙基甲基纤维素 2208 等）、醋酸纤维素（优选具有 39.3-40％乙酰基含量的醋酸纤维素）、二乙酸纤维素、三乙酸纤维素、乙酸丙酸纤维素、乙基纤维素、羧甲基纤维素钠、结晶纤维素羧甲基纤维素钠等；藻酸钠、羧乙烯基聚合物；丙烯酸聚合物，例如氨基烷基甲基丙烯酸酯共聚物 RS[Eudragit RS（商标）、Rohm Pharma]、丙烯酸乙酯 - 甲基丙烯酸甲酯共聚物混悬液 [Eudragit NE（商标）、Rohm Pharma] 等。缓释剂可以包含，例如，流量促进剂（例如氯化钠、氯化钾、蔗糖、山梨醇、D- 甘露醇、聚乙二醇（优选聚乙二醇 400 等）、丙二醇、羟丙基纤维素、羟丙基甲基纤维素、邻苯二甲酸羟丙基甲基纤维素、醋酸邻苯二甲酸纤维素、聚乙烯醇、甲基丙烯酸聚合物）、增塑剂（例如三醋精、乙酰化单甘油酯、葡萄籽油、橄榄油、芝麻油、柠檬酸乙酰基三丁酯、柠檬酸乙酰基三乙酯、甘油山梨醇、草酸二乙酯、马来酸二乙酯、富马酸二乙酯、琥珀酸二丁酯、丙二酸二乙酯、邻苯二甲酸二辛酯、癸二酸二丁酯、柠檬酸三乙酯、柠檬酸三丁酯、三丁酸甘油酯）等。缓释剂的优选实例包括：(1) 包含醋酸纤维素（优选具有 39.3-40％乙酰基含量的醋酸纤维素）、聚乙二醇（优选聚乙二醇 400 等）和三醋精的半透膜涂层；(2) 包含羧甲基纤维素钠、羟丙基甲基纤维素 2910、羟丙基甲基纤维素 2208 和微晶纤维素等的缓释组合物。

[0157] 作为稳定剂，例如，可以提及生育酚、依地酸四钠、烟酰胺、环糊精等。作为酸味剂，例如，可以提及抗坏血酸、柠檬酸、酒石酸、苹果酸等。作为矫味剂，例如，可以提及薄荷醇、

薄荷油、柠檬油、香草醛等。作为助流剂，例如，可以提及轻无水硅酸、水化二氧化硅等。

[0158] 以上提及的添加剂可以以适当比例的其两种或多种的混合物使用。

[0159] 用途

[0160] PPAR γ 激动剂和 Nrf2 激活剂各自的适合剂量可以基于几个因素确定，包括，例如，所治疗患者的体重和 / 或病症、所治疗疾病的严重性、副作用的发生率和 / 或严重性、施用方式和开据处方的临床医师的判断。可以提高本领域技术人员公知的方法确定适合的剂量范围。

[0161] 在一个实施方案中，本发明提供了 Nrf2 激活剂和 PPAR γ 激动剂的组合，其用于治疗炎性疾病和自身免疫疾病。

[0162] 在另一个实施方案中，本发明提供了 PPAR γ 激动剂与富马酸一 - 和 / 或二酯组合应用，其特征在于所述 PPAR γ 激动剂是选择性的且对 PPAR α 或 δ 基本上没有活性。

[0163] 可以施用治疗有效量的 PPAR γ 激动剂和 Nrf2 激活剂的组合作为具有易感免疫、自身免疫和 / 或炎性疾病和 / 或具有上述疾病病史的患者的治疗和预防措施，所述免疫、自身免疫和 / 或炎性疾病包括：银屑病、哮喘和慢性阻塞性肺疾病；心功能不全，包括左心室功能不全、心肌梗死和心绞痛；线粒体和神经变性疾病，例如帕金森病、阿尔茨海默病、亨廷顿病、痴呆、色素性视网膜病变和线粒体脑肌病、移植排斥；自身免疫疾病，包括多发性硬化、局部缺血和再灌注损伤、高级糖化终产物 (AGE)- 诱导的基因组和蛋白质损伤；炎性肠病，例如克隆病和溃疡性结肠炎、甲状腺眼疾病相关的炎症；纤维化，例如肺纤维化；慢性淋巴细胞白血病；阿弗他口炎，例如复发性阿弗他口炎；急性肺损伤、非酒精性脂肪性肝炎、急性肾损伤和与年龄相关的进行性肾损伤、糖尿病心肌病和肾病、慢性肾疾病 (CKD)、动脉粥样硬化、高胆固醇血症、高脂血症、主动脉狭窄、术后急性肾损伤 (AKI)。本发明还可以用于预防心血管疾病，用于斑块稳定，减轻炎症，逆转内皮功能障碍和糖尿病中的促凝性和伤口愈合下降。此外，本发明的组合治疗可以用于治疗和预防特应性皮炎、痴呆、胃炎、纤维化、胰岛素抵抗、I 型和 II 型糖尿病和 X 综合征。

[0164] 在本发明的优选的实施方案中，Nrf2 激活剂选自柳氮磺吡啶 (2- 羟基 -5-[4-(2- 吡啶基氨磺酰基 )- 苯基二氮烯基 ]- **benzoesäure**、5-[4-(2- 吡啶基氨磺酰基 )- 苯基偶氮 ] **salicylsäure**)、美沙拉秦、5- 氨基 -2- 羟基 - 苯甲酸 4-(5- 硫代 -5H-[1,2] 二硫杂环戊二烯 -3- 基 )- 苯基酯盐酸盐 (ATB-429)。根据本发明，这些 Nrf2 激活剂优选与格列酮例如吡格列酮或罗格列酮组合。更优选这些组合优选用于治疗 IBS 和关节炎疾病。

[0165] 在本发明优选的实施方案中，富马酸酯例如富马酸二甲酯与格列酮例如吡格列酮或罗格列酮组合用于治疗慢性肾疾病 (CKD)。

[0166] 在本发明的一个实施方案中，所述组合治疗优选用于预防或治疗多囊性卵巢综合征 (PCOS)。还发现同时是 PPAR γ 激动剂和 Nrf2 激活剂的化合物显示作为单一治疗剂的适合作用。可以用于预防和治疗 PCOS 的作为剂型例如片剂中的单一活性成分的优选化合物是甲基巴多索隆、CDDO、CDDO-IM、CDDO-MA 或 TP-225。因此，本发明的另一个主题是甲基巴多索隆、CDDO、CDDO-IM、CDDO-MA 或 TP-225 在预防和治疗 PCOS 中的用途和治疗 PCOS 的方法，通过对需要的患者施用药理学有效量的甲基巴多索隆、CDDO、CDDO-IM、CDDO-MA、TBE-31 或 TP-225 或另一种 Nrf2 激活剂来进行。在许多情况中，通过共同施用 PPAR 激动剂例如格

列酮如吡格列酮或罗格列酮可以进一步改善使用上述 Nrf2 激活剂的单一疗法。

[0167] NF-κB 介导的疾病和 / 或其它疾病描述如下。

[0168] 根据本发明的另一个实施方案，施用或共同施用 PPARγ 激动剂和 Nrf2 激活剂的组合有效地治疗许多类型的由神经性疾病、眼科障碍组成的哺乳动物疾病，所述哺乳动物包括但不限于人。根据本发明的另一个实施方案，所述神经性障碍、眼科障碍或其组合因选自创伤、局部缺血和缺氧的至少一个成员导致。根据本发明的另一个实施方案，所述神经性障碍、眼科障碍或其组合选自痛性神经病、神经性疼痛、糖尿病神经病、药物依赖、药物成瘾、药物戒断、烟碱戒断、阿片耐受、阿片戒断、抑郁症、焦虑、运动障碍、迟发性运动障碍、破坏血脑屏障的脑感染、脑膜炎、脑膜脑炎、中风、低血糖症、心脏停搏、脊髓损伤、头损伤、围产期缺氧、心脏停搏、低血糖性神经元损伤、青光眼、视网膜缺血、缺血性视神经病变、黄斑变性、多发性硬化、高同型半胱氨酸血症后遗症、惊厥、疼痛、精神分裂症、肌肉痉挛、偏头痛、尿失禁、呕吐、脑水肿、迟发性运动障碍、AIDS- 诱导的痴呆、眼损伤、视网膜病、认知障碍和与 HIV 感染相关的神经元损伤。根据另一个实施方案，所述神经性障碍、眼科障碍或其组合选自癫痫症、阿尔茨海默病、血管性（多发梗塞性）痴呆、亨廷顿病、帕金森综合征、多发性硬化、肌萎缩侧索硬化和最轻度认知缺损 (MCI)。

[0169] 银屑病的特征在于角化过度和表皮增厚以及血管供应增加和真皮中炎性细胞浸润。寻常型银屑病表现为典型地在头皮、肘、膝和臀部上的银色、鳞片、红斑。点滴状银屑病作为泪珠状大小损害出现。认为富马酸酯用于治疗银屑病且在德国富马酸二甲酯经批准用于全身性治疗银屑病 (Mrowietz 和 Asadullah, Trends Mol Med 2005, 11(1)、43-48 ;和 Mrowietz 等人，Br J Dermatology 1999, 141, 424-429)。可以使用动物模型并且在临床试验中测定治疗银屑病的效力。与富马酸酯相反，已经发现 PPARγ 激动剂在治疗银屑病方面并不有利 (Placebo response in two long-term randomized psoriasis studies that are negative for rosiglitazone Am J Clin Dermatol. 2007 ;8(2):93-102)。与这一结果相反，发现根据本发明，PPARγ 激动剂在银屑病组合治疗中提供了治疗有益性。

[0170] 炎性关节炎包括这样的疾病，例如类风湿性关节炎、青少年类风湿性关节炎（青少年特发性关节炎）、银屑病关节炎，且强直性脊柱炎产生关节炎症。认为免疫介导的炎性疾病包括炎性关节炎的发病机制涉及 TNF 和 NF-κB 信号传导途径 (Tracey 等人，Pharmacology & Therapeutics 2008, 117, 244-279)。已经证实富马酸二甲酯抑制 TNF 且认为炎性疾病包括炎性关节炎涉及 TNF 和 NF-κB 信号传导途径，且由此可以用于治疗炎性关节炎 (Lowewe 等人，J Immunology 2002, 168, 4781-4787)。

[0171] 优选本发明的治疗方法和组合可以用于预防和治疗神经变性疾病，例如多发性硬化、导致多发性硬化的临床孤立综合征 (CIS)、帕金森病、阿尔茨海默病、亨廷顿病、痴呆、线粒体脑肌病和肌萎缩侧索硬化 (ALS)。

[0172] 多发性硬化 (MS) 是自身免疫疾病攻击中枢神经系统孤立性轴突髓磷脂片导致的中枢神经系统炎性自身免疫疾病。脱髓鞘导致传导破坏和具有局部轴突破坏和不可逆的神经元细胞死亡的严重性疾病。MS 的症状随每个显示特定模式运动、感觉和感觉障碍的个体患者的不同高度可变。MS 典型的发病机制在于脑和脊髓内的多炎性病灶、脱髓鞘斑块、神经胶质增生和轴突病理学情况，所有的它们促成神经失能的临床表现（例如，参见 Wingerchuk, Lab Invest 2001, 81, 263-281 ;和 Virley, NeuroRx 2005, 2(4), 638-649)。尽管

涉及 MS 的原因情况尚未得到完全理解，但是有证据涉及自身免疫疾病病因学与环境因素以及特异性遗传诱因。将功能损伤、残疾失能和障碍表现为麻痹、感觉和 octintive 紊乱、痉挛状态、颤动、缺乏协调和视觉损伤，它们影响个体的生活质量。MS 的临床过程可以因个体间差异而不同，但一定不变的是该病可以被分类为三种形式：复发 - 缓解型、继发进行型和原发进行型。

[0173] 研究支持了富马酸酯在治疗 MS 中的效力且已经进行了 II 期临床试验 (Schimrigk 等人，Eur J Neurology 2006, 13, 604-610；和 Wakkee 和 Thio, Current Opinion Investigational Drugs 2007, 8(11), 955-962)。可以使用例如工具扩展的失能状态量表 (Expanded Disability Status Scale) 和 MS 功能性磁共振成像损害负荷、生物标记和自我报告的生活质量对临床试验中 MS 的治疗效力进行评价。显示可用于鉴定和验证潜在治疗剂的 MS 动物模型包括模拟 MS 临床和病理学表现的试验性自身免疫 / 变应性脑脊髓炎 (EAE) 啮齿动物模型和非人的灵长类 EAE 模型。

[0174] 炎性肠病 ( 克隆病、溃疡性结肠炎 )。炎性肠病 (IBD) 是一组大肠的炎性病症，在一些情况中，是包括克隆病和溃疡性结肠炎的小肠的炎性病症。克隆病的特征在于具有正常内层之间的区域的炎症区域，该病可以侵害从入口到肛门的胃肠道的任意部分。主要的胃肠症状是腹痛、腹泻、便秘、呕吐、体重减轻和 / 或体重增长。克隆病还可以导致皮疹、关节炎和眼部炎症。溃疡性结肠炎的特征在于大肠或结肠中的溃疡或开放式溃疡。溃疡性结肠炎的主要症状典型地为持续性腹泻伴有逐渐发生的混合有血液。其它类型的肠病包括胶原性结肠炎、淋巴细胞性结肠炎、缺血性结肠炎、改道性结肠炎、贝赫切特结肠炎和不确定性结肠炎。

[0175] 哮喘是可逆的气道阻塞，其中气道偶然收缩、发炎和散布过量的粘液。哮喘的症状包括呼吸困难、喘鸣、胸部紧迫感和咳嗽。哮喘发作可以因空气变应原、食物过敏、药物、吸入刺激物、体育运动、呼吸道感染、心理学应激、激素改变、寒冷气候或其它因素诱导。

[0176] 正如动物研究中所示 (Joshi 等人，US 2007/0027076)，富马酸酯可以用于治疗肺部疾病，例如哮喘和慢性阻塞性肺障碍。

[0177] 慢性阻塞性肺疾病 (COPD)、也称作慢性阻塞性气道疾病是一组这样的疾病，其特征在于气道中的气流病理性地不完全可逆地受限，且包括这样的疾病，例如慢性支气管炎、肺气肿以及其它肺障碍，例如石棉肺、肺尘症和肺部肿瘤 { 例如，参见 Barnes, Pharmacological Reviews 2004, 56(4)、515-548}。气流受限通常是进行性的且伴随肺对有害颗粒和气体的异常炎性应答。COPD 的特征在于呼吸短促持续数月或数年，可能伴随哮鸣和持续性咳嗽与生痰。COPD 最常见的是因吸烟导致，不过，也可以由其它空气中播散的刺激物导致，例如煤尘、石棉、污染源或溶剂。COPD 包括具有纤维化和小气道阻塞的慢性阻塞性毛细支气管炎和具有空隙扩大和肺实质破坏、肺弹性缺失和小气道关闭的肺气肿。

[0178] 神经变性疾病例如帕金森病、阿尔茨海默病、亨廷顿病和肌萎缩侧索硬化的特征在于进行性功能障碍和神经元死亡。

[0179] 帕金森病是缓慢的中枢系统进行性变性障碍，其特征在于当肌肉静止时颤动 ( 休息性震颤 )、随意运动迟钝和肌张力增加 ( 僵硬 )。在帕金森病中，基底神经节例如黑质中的神经细胞变性且由此减少了多巴胺产生和基底神经节中神经细胞之间连接的数量。作为

结果，基底神经节不能使肌肉运动平稳和协同作为正常的姿势改变，从而导致颤动、动作失调和迟缓、运动减少（运动迟缓）(Blandini 等人，Mol. Neurobiol. 1996, 12, 73-94)。

[0180] 阿尔茨海默病是精神功能进行性缺失，其特征在于脑组织变性，包括神经细胞缺失和衰老斑和神经原纤维缠结发展。在阿尔茨海默病中，部分脑变性，从而破坏了神经细胞并且减少了维持神经元对神经递质的应答性。脑组织中的异常由衰老或神经炎性斑块组成，例如包含异常的称作淀粉样蛋白的不溶蛋白和神经原纤维缠结的死亡神经细胞簇，即神经细胞中不溶蛋白的扭曲条。

[0181] 亨廷顿病是常染色体显性神经变性障碍，其中特异性细胞死亡发生在新纹状体和皮质中 (Martin, N Engl J Med 1999, 340, 1970-80)。发作通常发生在生命的第四十或第五十年期间，在发作年龄时的平均存活期限为 14-20 年。亨廷顿病普遍是致命性的且没有有效的治疗方法。症状包括特征性运动障碍（亨廷顿舞蹈病）、认知功能障碍和精神症状。该病的原因在于编码蛋白质亨廷丁中 CAG- 编码的聚谷氨酰胺重复单元的异常伸展的突变。

[0182] 肌萎缩侧索硬化 (ALS) 是进行性神经变性障碍，其特征在于脑、脑干和脊髓中进行性和特异性运动神经元缺失 (Rowland 和 Schneider, N Engl J Med 2001, 344, 1688-1700)。ALS 从通常在手中的虚弱开始且在足中频繁地下降，一般进行至臂或腿，虚弱随时间增加且痉挛状态发生，特征在于肌肉颤搐和紧固，随后发生肌痉挛和可能发生颤动。发作的平均年龄为 55 岁且临床发作后的平均预期寿命为 4 年。唯一公认的 ALS 治疗方法为利鲁唑，其仅可以将存活延长约 3 个月。

[0183] 重症肌无力 (MG) 是侵害横纹肌神经肌肉连接的典型的自身免疫疾病。给不同的动物种类免疫接种乙酰胆碱受体 (AChR) 和弗氏完全佐剂 (CFA) 产生称作试验性自身免疫重症肌无力 (EAMG) 的 MG 动物模型。

[0184] 斑秃是常见病，但因伦理原因，显然难以进行大规模研究以根除其发病机制和研发用于人体的新治疗方法。因此，有帮助的是研发适合的动物模型。Dundee 试验性秃头大鼠 (DEBR) 和 C3H/HeJ 小鼠是充分建立的斑秃动物模型并且可以用于研究该病的遗传方面、发病机制和疗法 (J Dtsch Dermatol Ges. 2004 年 4 月 ;2(4):260-73)。

[0185] 根据 Kidney International 77, 749-750(2010 年 5 月）使用糖尿病肾病的小鼠模型，以证实本发明组合的效果。

[0186] 因此，使用可能是有用的 PPAR γ 激动剂和 Nrf2 激活剂的组合治疗的疾病和病症包括风湿病 (rheumatica)、环形肉芽肿、狼疮、自身免疫心脏炎、湿疹、结节病和自身免疫疾病，包括急性播散性脑脊髓炎、阿狄森病、斑秃、强直性脊柱炎、抗磷脂抗体综合征、自身免疫溶血性贫血、自身免疫肝炎、自身免疫内耳病、大疱性类天疱疮、贝切特病、乳糜泻、Chagas 病、慢性阻塞性肺疾病、克隆病、皮肌炎、I 型糖尿病、子宫内膜异位症、古德帕斯彻氏综合征、格雷夫斯病、格 - 巴二氏综合征、桥本病、化脓性汗腺炎 (hidradenitis suppurativea)、川崎病、IgA 神经病、特发性血小板减少性紫癜、间质性膀胱炎、红斑狼疮、混合性结缔组织病、硬斑病、多发性硬化、重症肌无力、发作性睡病、神经性肌强直、寻常型天疱疮、恶性贫血、银屑病、银屑病关节炎、多肌炎、原发性胆汁性肝硬变、类风湿性关节炎、精神分裂症、硬皮病、舍格伦综合征、僵人综合征、颞动脉炎、溃疡性结肠炎、脉管炎、白癜风和韦格纳肉芽肿。

[0187] 施用

[0188] Nrf2 激活剂和 PPAR γ 激动剂的组合及其药物组合物可以通过口服或通过任意其它适合的途径施用，例如通过输注或推注，通过经上皮或皮肤粘膜内层吸收（例如口腔粘膜、直肠和肠粘膜等）。其它适合的施用途径包括但不限于真皮内、肌内、腹膜内、静脉内、皮下、鼻内、硬膜外、口服、舌下、大脑内、阴道内、透皮、直肠、吸入或局部。

[0189] 施用可以是全身或局部的。已知各种递送系统，例如脂质体、微粒、微囊、胶囊等中包囊），其可以用于施用化合物和 / 或药物组合物。

[0190] 对于全身施用，最初可以根据体外试验评估治疗有效剂量。例如，可以在动物模型中配制剂量以得到有益的循环组合物浓度范围。还可以根据体内数据例如动物模型、使用本领域公知的技术评估初始剂量。这种信息可以用于更精确地确定在人体中的有用剂量。本领域普通技术人员可以基于动物数据优化对人体的施用。

[0191] 实施方案“PPAR γ 激动剂与富马酸一 - 和 / 或二酯的组合用于治疗自身免疫疾病和 / 或炎性疾病”涉及至少一种 PPAR γ 激动剂与富马酸一 - 和 / 或二酯的组合在治疗自身免疫疾病和 / 或炎性疾病中的使用方法。

[0192] 本发明的优选实施方案描述如下：

[0193] 1. PPAR γ 激动剂与富马酸一 - 和 / 或二酯的组合用于治疗自身免疫疾病和 / 或炎性疾病。

[0194] 2. 根据上述实施方案和 / 或实施方案 1 的一种或多种的 PPAR γ 激动剂例如罗格列酮与富马酸一 - 和 / 或二酯组合应用，其特征在于所述自身免疫疾病和 / 或炎性疾病是银屑病。

[0195] 3. 根据上述实施方案和 / 或实施方案 1 的一种或多种的 PPAR γ 激动剂与富马酸一 - 和 / 或二酯组合应用，其特征在于所述自身免疫疾病和 / 或炎性疾病选自银屑病关节炎、多发性硬化、炎性肠病 (IBS)、溃疡性结肠炎、克隆病、肝炎、脱发、斑秃、瘢痕性脱发、糖尿病肾病、CKD 和重症肌无力。

[0196] 4. 根据上述提及的实施方案的 PPAR γ 激动剂与富马酸一 - 和 / 或二酯组合应用，其特征在于所述 PPAR γ 激动剂选自罗格列酮、吡格列酮、曲格列酮和环格列酮。

[0197] 5. 根据上述提及的实施方案的 PPAR γ 激动剂与富马酸一 - 和 / 或二酯组合应用，其特征在于所述富马酸一 - 和 / 或二酯选自富马酸一甲酯、富马酸二甲酯、富马酸一乙酯和富马酸二乙酯。

[0198] 6. 药物组合物，其包含 PPAR γ 激动剂和富马酸一 - 和 / 或二酯和任选的一种或多种赋形剂。

[0199] 7. 药物组合物，其包含罗格列酮、吡格列酮、曲格列酮或环格列酮和富马酸一 - 和 / 或二酯和任选的一种或多种赋形剂。

[0200] 8. 根据上述实施方案和 / 或实施方案 6 或 7 的一种或多种的药物组合物，其特征在于所述富马酸一 - 和 / 或二酯选自富马酸一甲酯、富马酸二甲酯、富马酸一乙酯和富马酸二乙酯。

[0201] 9. 固体口服剂型，其包含 PPAR γ 激动剂和富马酸一 - 和 / 或二酯。

[0202] 10. 固体口服剂型，其包含作为 PPAR γ 激动剂的罗格列酮、吡格列酮、曲格列酮或环格列酮和富马酸一 - 和 / 或二酯。

[0203] 11. 根据上述实施方案和 / 或实施方案 9 或 10 的一种或多种的固体口服剂型，其

特征在于所述富马酸一-和/或二酯选自富马酸一甲酯、富马酸二甲酯、富马酸一乙酯和富马酸二乙酯。

[0204] 12. 根据上述实施方案和/或实施方案 9 或 10 的一种或多种的固体口服剂型，其特征在于所述 PPARγ 激动剂和所述富马酸一-和/或二酯各自以单独组合物的形式包含在所述剂型中，所述单独的组合物任选包含一种或多种赋形剂。

[0205] 13. 成套药盒，其包含：a) PPARγ 激动剂；和 b) 富马酸一-和/或二酯；和任选的 c) 用于给药方案的说明书。

[0206] 14. 成套药盒，其包含：a) 罗格列酮、吡格列酮、曲格列酮或环格列酮；b) 富马酸一-和/或二酯；和任选的 c) 用于给药方案的说明书。

[0207] 15. 根据上述实施方案和/或实施方案 13 或 14 的一种或多种的成套药盒，其特征在于所述富马酸一-和/或二酯选自富马酸一甲酯、富马酸二甲酯、富马酸一乙酯和富马酸二乙酯。

[0208] 16. PPARγ 激动剂与选自富马酸一烷基酯、富马酸二烷基酯和烷基巴多索隆的 Nrf2 激活剂组合用于治疗多发性硬化。

[0209] 17. 根据上述实施方案的 PPARγ 激动剂与 Nrf2 激活剂组合应用，其特征在于多发性硬化包括复发-缓解型 (RR)、继发进行型 (SP)、原发进行型 (PP) 和进行复发型 (PR) 多发性硬化和 MS 或临床孤立综合征 (CIS) 的首次脱髓鞘事件启示。

[0210] 18. 根据上述实施方案的 PPARγ 激动剂与 Nrf2 激活剂组合应用，其特征在于所述 PPARγ 激动剂是格列酮。

[0211] 19. 根据上述实施方案的 PPARγ 激动剂与 Nrf2 激活剂组合应用，其特征在于所述 PPARγ 激动剂是选自吡格列酮和罗格列酮的格列酮。

[0212] 20. 根据上述实施方案的 PPARγ 激动剂与 Nrf2 激活剂组合应用，其特征在于所述 Nrf2 激活剂选自富马酸一甲酯、富马酸二甲酯和甲基巴多索隆。

[0213] 21. 根据上述实施方案的 PPARγ 激动剂与 Nrf2 激活剂组合应用，其特征在于罗格列酮和富马酸二甲酯之比选自 1/20-1/400(w/w，罗格列酮/富马酸二甲酯)。

[0214] 22. 根据上述实施方案的 PPARγ 激动剂与 Nrf2 激活剂组合应用，其特征在于吡格列酮和富马酸二甲酯之比选自 1/3-1/60(w/w，吡格列酮/富马酸二甲酯)。

[0215] 23. 根据上述实施方案的 PPARγ 激动剂与 Nrf2 激活剂组合应用，其特征在于罗格列酮与甲基巴多索隆之比选自 1/1-1/100(w/w，罗格列酮/甲基巴多索隆)。

[0216] 24. 根据上述实施方案的 PPARγ 激动剂与 Nrf2 激活剂组合应用，其特征在于使用无定形形式的甲基巴多索隆且罗格列酮与甲基巴多索隆之比为 1/1-1/20(w/w，罗格列酮/甲基巴多索隆)。

[0217] 25. 根据上述实施方案的 PPARγ 激动剂与 Nrf2 激活剂组合应用，其特征在于吡格列酮与甲基巴多索隆之比选自 1/0.1-1/20(w/w，吡格列酮/甲基巴多索隆)。

[0218] 26. 根据上述实施方案的 PPARγ 激动剂与 Nrf2 激活剂组合应用，其特征在于使用无定形形式的甲基巴多索隆且吡格列酮与甲基巴多索隆之比为 1/0.1-1/3(w/w，吡格列酮/甲基巴多索隆)。

[0219] 27. 药物组合物，其包含 PPARγ 激动剂和选自富马酸一烷基酯、富马酸二烷基酯和烷基巴多索隆的 Nrf2 激活剂和任选的一种或多种赋形剂。

[0220] 28. 根据上述实施方案和 / 或实施方案 27 的一种或多种的药物组合物，其特征在于所述 PPAR γ 激动剂是格列酮。

[0221] 29. 根据上述实施方案和 / 或实施方案 28 的一种或多种的药物组合物，其特征在于所述格列酮选自吡格列酮和罗格列酮。

[0222] 30. 根据上述实施方案和 / 或实施方案 28-30 的一种或多种的药物组合物，其特征在于 Nrf2 激活剂选自富马酸一甲酯、富马酸二甲酯和甲基巴多索隆。

[0223] 31. 根据上述实施方案和 / 或实施方案 28-30 的一种或多种的药物组合物，其特征在于罗格列酮与富马酸二甲酯之比选自 1/20-1/400(w/w，罗格列酮 / 富马酸二甲酯 )。

[0224] 32. 根据上述实施方案和 / 或实施方案 28-30 的一种或多种的药物组合物，其特征在于吡格列酮与富马酸二甲酯之比选自 1/3-1/60(w/w，吡格列酮 / 富马酸二甲酯 )。

[0225] 33. 根据上述实施方案和 / 或实施方案 28-30 的一种或多种的药物组合物，其特征在于罗格列酮与甲基巴多索隆之比选自 1/1-1/100(w/w，罗格列酮 / 甲基巴多索隆 )。

[0226] 34. 根据上述实施方案和 / 或实施方案 28-30 的一种或多种的药物组合物，其特征在于使用无定形形式的甲基巴多索隆且罗格列酮与甲基巴多索隆之比为 1/1-1/20(w/w，罗格列酮 / 甲基巴多索隆 )。

[0227] 35. 根据上述实施方案和 / 或实施方案 28-30 的一种或多种的药物组合物，其特征在于吡格列酮与甲基巴多索隆之比选自 1/0.1-1/20(w/w，吡格列酮 / 甲基巴多索隆 )。

[0228] 36. 根据上述实施方案和 / 或实施方案 28-30 的一种或多种的药物组合物，其特征在于使用无定形形式的甲基巴多索隆且吡格列酮与甲基巴多索隆之比为 1/0.1-1/3(w/w，吡格列酮 / 甲基巴多索隆 )。

[0229] 37. 固体口服剂型，其包含根据上述实施方案和 / 或实施方案 27-36 的一种或多种的药物组合物。

[0230] 38. 固体口服剂型，其包含 PPAR γ 激动剂和选自富马酸一烷基酯、富马酸二烷基酯和烷基巴多索隆的 Nrf2 激活剂和任选的一种或多种赋形剂，其中所述 PPAR γ 激动剂和所述 Nrf2 激活剂各自包含在单独的药物制剂中。

[0231] 39. 根据上述实施方案和 / 或实施方案 38 的一种或多种的固体口服剂型，其中所述 PPAR γ 激动剂是格列酮且所述 Nrf2 激活剂选自富马酸一甲酯、富马酸二甲酯和甲基巴多索隆。

[0232] 40. 根据上述提及的实施方案的固体口服剂型，其中所述 Nrf2 激活剂是以无定形形式包含的甲基巴多索隆。

[0233] 41. 根据上述提及的实施方案的固体口服剂型，其中所述 Nrf2 激活剂是包含在无定形分散体制剂中的甲基巴多索隆。

[0234] 42. 根据上述提及的实施方案的固体口服剂型，其中所述 Nrf2 激活剂是通过喷雾干燥或冷冻干燥得到的包含在无定形分散体制剂中的甲基巴多索隆。

[0235] 43. 根据上述提及的实施方案的固体口服剂型，其中所述 Nrf2 激活剂是与甲基丙烯酸共聚物 Type C, USP 一起包含在无定形分散体制剂中的甲基巴多索隆。

[0236] 44. 根据上述提及的实施方案的固体口服剂型，其中所述 Nrf2 激活剂是与甲基丙烯酸共聚物 Type C, USP 一起包含在无定形分散体制剂中的甲基巴多索隆，它们的重量比为 4/6。

[0237] 45. 根据上述提及的实施方案的固体口服剂型，其中所述 Nrf2 激活剂是包含在无定形分散体制剂中的甲基巴多索隆，该制剂包含至少一种亲水性粘合剂。

[0238] 46. 根据上述提及的实施方案的固体口服剂型，其中所述亲水性粘合剂的使用量为约 1- 约 40％（占用于该剂型的药物组合物总重的％）、优选约 2- 约 20％、更优选约 4- 约 10％、甚至更优选约 5- 约 7.5％且最优选约 7-7.5％，例如约 7％。

[0239] 47. 根据上述提及的实施方案的固体口服剂型，其中所述亲水性粘合剂是羟丙基甲基纤维素。

[0240] 48. 根据上述提及的实施方案的固体口服剂型，其中所述 Nrf2 激活剂是包含在无定形分散体制剂中的甲基巴多索隆，且其中该剂型还包含表面活性剂，例如十二烷基硫酸钠，优选其量占该剂型总重的约 3％。

[0241] 49. 成套药盒，其包含 a)PPAR γ 激动剂；和 b) 选自富马酸一烷基酯、富马酸二烷基酯和烷基巴多索隆的 Nrf2 激活剂；和任选的 c) 用于给药方案的说明书。

[0242] 50. 成套药盒，其包含 a)PPAR 激动剂；和 b) 选自富马酸一烷基酯、富马酸二烷基酯和烷基巴多索隆的 Nrf2 激活剂；和任选的 c) 用于给药方案的说明书。

[0243] 51. 根据上述实施方案的成套药盒，其特征在于所述 PPAR γ 激动剂是罗格列酮或吡格列酮。

[0244] 52. 根据上述实施方案的成套药盒，其特征在于所述 Nrf2 激活剂是富马酸二甲酯或甲基巴多索隆。

[0245] 53. 根据上述实施方案的 PPAR γ 激动剂与 Nrf2 激活剂组合用于治疗多发性硬化，其中将所述 PPAR 激动剂与例如选自富马酸一烷基酯、富马酸二烷基酯和烷基巴多索隆的 Nrf2 激活剂同时或在其施用于患者之前至多 2 天或之后至多 2 天施用于患者。

[0246] 54. 根据上述实施方案的 PPAR γ 激动剂与 Nrf2 激活剂组合用于治疗多发性硬化，其中将所述 PPAR 激动剂每日施用 1 次或 2 次。

[0247] 55. 根据上述实施方案的 PPAR γ 激动剂与 Nrf2 激活剂组合用于治疗多发性硬化，其中将所述 Nrf2 激活剂每日施用 1 次或 2 次。

[0248] 56. PPAR γ 激动剂与 Nrf2 激活剂组合用于治疗非银屑病的自身免疫疾病和 / 或炎性疾病。

[0249] 57. PPAR γ 激动剂、优选不是吡格列酮与属于不同化学类型的 Nrf2 激活剂组合用于治疗自身免疫疾病和 / 或炎性疾病例如多发性硬化、银屑病或慢性肾病。

[0250] 58. 根据上述提及的实施方案所用的 PPAR γ 激动剂、优选不是吡格列酮，其中所述 Nrf2 激活剂没有显著的 PPAR γ 激动作用。

[0251] 59. 对 Nrf2 没有显著的激活作用的 PPAR γ 激动剂、优选不是吡格列酮与没有显著的 PPAR γ 激动作用的 Nrf2 激活剂组合用于治疗自身免疫疾病和 / 或炎性疾病例如多发性硬化、银屑病或慢性肾病。

[0252] 60. PPAR γ 激动剂、优选不是吡格列酮与属于不同化学类型的 Nrf2 激活剂组合用于治疗自身免疫疾病和 / 或炎性疾病例如多发性硬化、银屑病或慢性肾病，其中 Nrf2 激活剂不是甲基巴多索隆及其衍生物。

[0253] 61. 组合物，其包含 PPAR γ 激动剂和属于不同化学类型的 Nrf2 激活剂，该组合物用于治疗自身免疫疾病和 / 或炎性疾病，例如多发性硬化、银屑病或慢性肾病。

[0254] 62. 根据上述提及的实施方案的组合物，其包含对 Nrf2 没有显著的激活作用的 PPAR γ 激动剂和没有显著的 PPAR γ 激动作用的 Nrf2 激活剂，该组合物用于治疗自身免疫疾病和 / 或炎性疾病，例如多发性硬化、银屑病或慢性肾病。

[0255] 63. 组合物，其包含 PPAR γ 激动剂，例如吡格列酮和 Nrf2 激活剂。

[0256] 64. 组合物，其包含 PPAR γ 激动剂，例如吡格列酮和没有显著的 PPAR γ 激动作用的 Nrf2 激活剂。

[0257] 65. 组合物，其包含吡格列酮和没有显著的 PPAR γ 激动作用的 Nrf2 激活剂，该组合物用于治疗银屑病和其它自身免疫疾病和 / 或炎性疾病，例如多发性硬化、银屑病或慢性肾病。

[0258] 66. PPAR γ 激动剂与没有显著的 PPAR γ 激动作用的 Nrf2 激活剂组合用于治疗多发性硬化。

[0259] 67. PPAR γ 激动剂与不是甲基巴多索隆的 Nrf2 激活剂组合用于治疗 CKD 或多发性硬化。

[0260] 68. 根据上述实施方案的 PPAR γ 激动剂与 Nrf2 激活剂组合应用，其特征在于多发性硬化包括复发 - 缓解型 (RR)、继发进行型 (SP)、原发进行型 (PP) 和进行复发型 (PR) 多发性硬化和 MS 或临床孤立综合征 (CIS) 的首次脱髓鞘事件启示。

[0261] 69. 根据上述实施方案的 PPAR γ 激动剂与 Nrf2 激活剂组合应用，其特征在于所述 PPAR γ 激动剂是格列酮。

[0262] 70. 根据任意上述实施方案的 PPAR γ 激动剂与 Nrf2 激活剂组合应用，其特征在于所述 PPAR γ 激动剂是选自吡格列酮和罗格列酮的格列酮。

[0263] 71. 根据任意上述实施方案的 PPAR γ 激动剂与 Nrf2 激活剂组合应用，其特征在于所述 Nrf2 激活剂选自属于如下类型的化学化合物 :迈克尔反应受体、酚、联苯酚、查耳酮、异硫氰酸酯、硫代氨基甲酸酯、醌、萘醌和 1,2 二硫杂环戊二烯 -3- 硫酮，其中一个或多个、优选 1、2、3、4、5、6 或 7 个 H- 原子可以被直链或支链烷基和全氟烷基例如甲基、乙基、三氟甲基、卤素例如 Br、Cl、F 或 I、羟基、烷氧基和全氟烷氧基例如甲氧基、乙氧基、三氟甲氧基、氰基和硝基取代，所述化学化合物具有不超过 1 个或 2 个 5- 或 6- 元碳环或具有 1、2 或 3 个 N-、O 或 S- 原子作为环原子的 5- 或 6- 元杂环，所述环可以彼此稠合，或优选没有或仅有 1 个碳环或杂环。优选包含这些 Nrf2 激活剂的组合物。

[0264] 根据本发明且特别是根据上述实施方案 71 的优选的 Nrf2 激活剂的组合应用，所述 Nrf2 激活剂是化学化合物，其包含小于 35、优选小于 30、更优选小于 25 且最优选小于 20 或甚至小于 15 或小于 10 个碳原子和 / 或具有小于 400、优选小于 300 且最优选小于 200g/mol 或小于 170g/mol 的分子量和 / 或没有显著的 PPAR γ 激动活性。优选包含这些 Nrf2 激活剂的组合物。

[0265] 72. 根据任意上述实施方案的 PPAR γ 激动剂与 Nrf2 激活剂组合应用，其特征在于所述 Nrf2 激活剂选自 2- 萘醌、肉桂醛、咖啡酸及其酯类、姜黄素、白藜芦醇、青蒿琥酯、叔丁基氢醌、维生素 K1、K2 和 K3 和上述提及的醌和氢醌衍生物相应的醌或氢醌形式、富马酸酯即富马酸一 - 和 / 或二酯优选自富马酸一烷基酯和富马酸二烷基酯例如富马酸一甲酯、富马酸二甲酯、富马酸一乙酯和富马酸二乙酯、异硫氰酸酯例如莱菔硫烷、1,2- 二硫杂环戊二烯 -3- 硫酮例如奥替普拉、3,5- 二 - 叔丁基 -4- 羟基甲苯、3- 羟基香豆素、4- 羟基丙烯醛、

4- 氧代丙烯醛、丙二醛、(E)-2- 己烯醛、辣椒辣素、大蒜素、异硫氰酸烯丙酯、异硫氰酸 6- 甲硫基己酯、异硫氰酸 7- 甲硫基庚酯、莱菔硫烷、异硫氰酸 8- 甲硫基辛酯、8- 异前列腺素 A2、丙酮酸烷基酯例如丙酮酸甲酯和丙酮酸乙酯、草酰丙酸二乙酯或草酰丙酸二甲酯、2- 乙酰氨基丙烯酸酯和甲基或乙基 -2- 乙酰氨基丙烯酸酯和上述提及的活性剂的药理学活性立体异构体或衍生物。

[0266] 73. 根据任意上述实施方案的 PPAR γ 激动剂与 Nrf2 激活剂组合应用，其特征在于所述 nrf2 激活剂选自富马酸一甲酯、富马酸二甲酯、奥替普拉、1,2- 萘醌、叔丁基氢醌、丙酮酸甲酯和丙酮酸乙酯、3,5- 二 - 叔丁基 -4- 羟基甲苯、草酰丙酸二乙酯和草酰丙酸二甲酯。

[0267] 74. 成套药盒，包含 a) 非吡格列酮的 PPAR γ 激动剂；和 b) 选自富马酸一烷基酯、富马酸二烷基酯和烷基巴多索隆的 Nrf2 激活剂；和任选的 c) 用于给药方案的说明书。

[0268] 75. 成套药盒，其包含 a) 对 Nrf2 没有显著的激活作用的 PPAR γ 激动剂；b) 选自富马酸一烷基酯、富马酸二烷基酯和巴多索隆的 Nrf2 激活剂；和任选的 c) 用于给药方案的说明书。

[0269] 76. 成套药盒，其包含 a) 对 Nrf2 没有显著的激活作用的 PPAR γ 激动剂；b) 没有显著的 PPAR γ 激动作用的 Nrf2 激活剂；和任选的 c) 用于给药方案的说明书。

[0270] 77. 成套药盒，其包含 a) 对 Nrf2 没有显著的激活作用的 PPAR γ 激动剂；b) 选自属于如下类型的化学化合物的 Nrf2 激活剂：迈克尔反应受体、酚、联苯酚、查耳酮、异硫氰酸酯、硫代氨基甲酸酯、醌、萘醌和 1,2 二硫杂环戊二烯 -3- 硫酮，其中一个或多个、优选 1、2、3、4、5、6 或 7 个 H- 原子可以被直链或支链烷基和全氟烷基例如甲基、乙基、三氟甲基、卤素例如 Br、Cl、F 或 I、羟基、烷氧基和全氟烷氧基例如甲氧基、乙氧基、三氟甲氧基、氰基和硝基取代，所述化学化合物具有不超过 1 个或 2 个 5- 或 6- 元碳环或具有 1、2 或 3 个 N-、O 或 S- 原子作为环原子的 5- 或 6- 元杂环，所述环可以彼此稠合，或优选没有或仅有 1 个碳环或杂环；和任选的 c) 用于给药方案的说明书。

[0271] 78. 组合物，其包含 a)PPAR γ 激动剂，优选不是吡格列酮；和 b) 选自富马酸一烷基酯、富马酸二烷基酯和烷基巴多索隆的 Nrf2 激活剂。

[0272] 79. 组合物，其包含 a) 对 Nrf2 没有显著的激活作用的 PPAR γ 激动剂；b) 选自富马酸一烷基酯、富马酸二烷基酯和巴多索隆的 Nrf2 激活剂。

[0273] 80. 组合物，其包含 a) 对 Nrf2 没有显著的激活作用的 PPAR γ 激动剂；b) 没有显著的 PPAR γ 激动作用的 Nrf2 激活剂。

[0274] 81. 组合物，其包含 a) 对 Nrf2 没有显著的激活作用的 PPAR γ 激动剂；b) 选自属于如下类型的化学化合物 Nrf2 激活剂：迈克尔反应受体、酚、联苯酚、查耳酮、异硫氰酸酯、硫代氨基甲酸酯、醌、萘醌和 1,2 二硫杂环戊二烯 -3- 硫酮，其中一个或多个、优选 1、2、3、4、5、6 或 7 个 H- 原子可以被直链或支链烷基和全氟烷基例如甲基、乙基、三氟甲基、卤素例如 Br、Cl、F 或 I、羟基、烷氧基和全氟烷氧基例如甲氧基、乙氧基、三氟甲氧基、氰基和硝基取代，所述化学化合物具有不超过 1 个或 2 个 5- 或 6- 元碳环或具有 1、2 或 3 个 N-、O 或 S- 原子作为环原子的 5- 或 6- 元杂环，所述环可以彼此稠合，或优选没有或仅有 1 个碳环或杂环。

[0275] 82. 治疗或预防癌症、优选血癌例如白血病例如急性髓性白血病 (AML) 的方法，该

方法包括给需要的患者施用 PPAR γ 激动剂和 Nrf2 激活剂，其中所述 Nrf2 激活剂能够引起或诱导刺激和 / 或增加的 Nrf2 蛋白核易位并且 ：

[0276] a) 选自迈克尔反应受体、酚、联苯酚、查耳酮、异硫氰酸酯、硫代氨基甲酸酯、醌、萘醌和 1,2 二硫杂环戊二烯 -3- 硫酮 ；和

[0277] b) 包含小于 35 个碳原子 ；和 / 或

[0278] c) 具有小于 600g/mol 的分子量 ；和 / 或

[0279] d) 不包含或包含不超过 1 个或 2 个稠合或单环 5- 或 6- 元碳环或杂环，其具有 1、2 或 3 个选自 N、O 或 S 的环原子。

[0280] 在上述方法的一个实施方案中，所述 Nrf2 激活剂优选不是三氧化二砷。优选地，所述 Nrf2 激活剂是富马酸二甲酯、富马酸一甲酯或甲基巴多索隆。

[0281] 83. 治疗或预防糖尿病、例如 II 型糖尿病及其并发症例如关节炎、慢性肾病和 x 综合征的方法，该方法包括给需要的患者施用 PPAR γ 激动剂和 Nrf2 激活剂，其中所述 Nrf2 激活剂能够引起或诱导刺激和 / 或增加的 Nrf2 蛋白核易位并且

[0282] a) 选自迈克尔反应受体、酚、联苯酚、查耳酮、异硫氰酸酯、硫代氨基甲酸酯、醌、萘醌和 1,2 二硫杂环戊二烯 -3- 硫酮 ；和

[0283] b) 包含小于 35 个碳原子 ；和 / 或

[0284] c) 具有小于 600g/mol 的分子量 ；和 / 或

[0285] d) 不包含或包含不超过 1 个或 2 个稠合或单环 5- 或 6- 元碳环或杂环，其具有 1、2 或 3 个选自 N、O 或 S 的环原子。

[0286] 在上述方法的一个实施方案中，所述 Nrf2 激活剂优选不是甲基巴多索隆和 / 或皮质类固醇。优选地，所述 Nrf2 激活剂是富马酸二甲酯或富马酸一甲酯。

[0287] 84. 治疗或预防心血管疾病的方法，该方法包括给需要的患者施用 PPAR γ 激动剂和 Nrf2 激活剂，其中所述 Nrf2 激活剂能够引起或诱导刺激和 / 或增加的 Nrf2 蛋白核易位并且

[0288] a) 选自迈克尔反应受体、酚、联苯酚、查耳酮、异硫氰酸酯、硫代氨基甲酸酯、醌、萘醌和 1,2 二硫杂环戊二烯 -3- 硫酮 ；和

[0289] b) 包含小于 35 个碳原子 ；和 / 或

[0290] c) 具有小于 600g/mol 的分子量 ；和 / 或

[0291] d) 不包含或包含不超过 1 个或 2 个稠合或单环 5- 或 6- 元碳环或杂环，其具有 1、2 或 3 个选自 N、O 或 S 的环原子。

[0292] 85. 治疗或预防呼吸疾病例如哮喘、慢性阻塞性肺障碍和纤维化的方法，该方法包括给需要的患者施用 PPAR γ 激动剂和 Nrf2 激活剂，其中所述 Nrf2 激活剂能够引起或诱导刺激和 / 或增加的 Nrf2 蛋白核易位并且

[0293] a) 选自迈克尔反应受体、酚、联苯酚、查耳酮、异硫氰酸酯、硫代氨基甲酸酯、醌、萘醌和 1,2 二硫杂环戊二烯 -3- 硫酮 ；和

[0294] b) 包含小于 35 个碳原子 ；和 / 或

[0295] c) 具有小于 600g/mol 的分子量 ；和 / 或

[0296] d) 不包含或包含不超过 1 个或 2 个稠合或单环 5- 或 6- 元碳环或杂环，其具有 1、2 或 3 个选自 N、O 或 S 的环原子。

[0297] 在上述方法的一个实施方案中，所述 Nrf2 激活剂优选不是皮质类固醇。优选地，所述 Nrf2 激活剂是富马酸二甲酯、富马酸一甲酯或甲基巴多索隆。

[0298] 86. 治疗或预防移植物排斥和 / 或坏死的方法，该方法包括给需要的患者施用 PPAR γ 激动剂和 Nrf2 激活剂，其中所述 Nrf2 激活剂能够引起或诱导刺激和 / 或增加的 Nrf2 蛋白核易位并且

[0299] a) 选自迈克尔反应受体、酚、联苯酚、查耳酮、异硫氰酸酯、硫代氨基甲酸酯、醌、萘醌和 1,2 二硫杂环戊二烯 -3- 硫酮 ;和

[0300] b) 包含小于 35 个碳原子 ;和 / 或

[0301] c) 具有小于 600g/mol 的分子量 ;和 / 或

[0302] d) 不包含或包含不超过 1 个或 2 个稠合或单环 5- 或 6- 元碳环或杂环，其具有 1、2 或 3 个选自 N、O 或 S 的环原子。

[0303] 87. 治疗或预防银屑病的方法，该方法包括给需要的患者施用 PPAR γ 激动剂和 Nrf2 激活剂，其中所述 Nrf2 激活剂能够引起或诱导刺激和 / 或增加的 Nrf2 蛋白核易位并且

[0304] a) 选自迈克尔反应受体、酚、联苯酚、查耳酮、异硫氰酸酯、硫代氨基甲酸酯、醌、萘醌和 1,2 二硫杂环戊二烯 -3- 硫酮 ;和

[0305] b) 包含小于 35 个碳原子 ;和 / 或

[0306] c) 具有小于 600g/mol 的分子量 ;和 / 或

[0307] d) 不包含或包含不超过 1 个或 2 个稠合或单环 5- 或 6- 元碳环或杂环，其具有 1、2 或 3 个选自 N、O 或 S 的环原子。

[0308] 在上述方法的一个实施方案中，将非治疗量的羟基脲共同施用于患者。在上述方法的另一个实施方案中，将非治疗量的富马酸一甲酯共同施用于患者。在上述方法的另一个实施方案中，将非治疗量的富马酸二甲酯共同施用于患者。在上述方法的另一个实施方案中，所述 Nrf2 激活剂是甲基巴多索隆。在上述方法的另一个实施方案中，所述 PPAR 激动剂不是吡格列酮，例如罗格列酮。

[0309] 88. 治疗或预防非银屑病的自身免疫疾病和 / 或炎性疾病的方法，该方法包括给需要的患者施用 PPAR 激动剂和富马酸二烷基酯和 / 或富马酸一烷基酯。

[0310] 89. 治疗或预防非慢性肾病的自身免疫疾病和 / 或炎性疾病的方法，该方法包括给需要的患者施用 PPAR 激动剂和甲基巴多索隆。

[0311] 90. 治疗或预防心血管疾病、呼吸障碍、移植物排斥、癌症和糖尿病及其并发症的方法，该方法包括给需要的患者施用 PPAR 激动剂和富马酸二甲酯和 / 或富马酸一甲酯。

[0312] 91. 治疗或预防自身免疫疾病 / 炎性疾病和心血管疾病、呼吸障碍、移植物排斥、癌症和糖尿病及其并发症的方法，该方法包括给需要的患者施用非吡格列酮的 PPAR 激动剂和富马酸二甲酯和 / 或富马酸一甲酯。

[0313] 92. PPAR γ 激动剂和 Nrf2 激活剂组合用于治疗自身免疫疾病和 / 或炎性疾病。

[0314] 93. 根据上述实施方案和 / 或实施方案 92 的一种或多种的 PPAR γ 激动剂和 Nrf2 激活剂组合应用，其特征在于所述 Nrf2 激活剂是富马酸二甲酯。

[0315] 94. 根据上述实施方案和 / 或实施方案 92 的一种或多种的 PPAR γ 激动剂和 Nrf2 激活剂组合应用，其特征在于所述 Nrf2 激活剂是甲基巴多索隆。

[0316] 95. 根据上述实施方案之一的PPAR γ 激动剂和Nrf2激活剂组合应用，其特征在于所述 PPAR γ 激动剂是吡格列酮。

[0317] 96. 根据上述实施方案之一的PPAR γ 激动剂和Nrf2激活剂组合应用，其特征在于所述 PPAR γ 激动剂选自罗格列酮、曲格列酮和环格列酮。

[0318] 97. 根据上述实施方案之一的PPAR γ 激动剂和Nrf2激活剂组合应用，其特征在于所述自身免疫疾病和 / 或炎性疾病是银屑病。

[0319] 98. 根据上述实施方案之一的PPAR γ 激动剂和Nrf2激活剂组合应用，其特征在于所述自身免疫疾病和 / 或炎性疾病是多发性硬化。

[0320] 99. 根据上述实施方案之一的PPAR γ 激动剂和Nrf2激活剂组合应用，其特征在于所述自身免疫疾病和 / 或炎性疾病是溃疡性结肠炎。

[0321] 100. 根据上述实施方案之一的 PPAR γ 激动剂和 Nrf2 激活剂组合应用，其特征在于所述自身免疫疾病和 / 或炎性疾病是克隆病。

[0322] 101. 根据上述实施方案之一的 PPAR γ 激动剂和 Nrf2 激活剂组合应用，其特征在于所述自身免疫疾病和 / 或炎性疾病是斑秃或瘢痕性脱发。

[0323] 102. 根据上述实施方案之一的 PPAR γ 激动剂和 Nrf2 激活剂组合应用，其特征在于所述自身免疫疾病和 / 或炎性疾病是糖尿病肾病。

[0324] 103. 根据上述实施方案之一的 PPAR γ 激动剂和 Nrf2 激活剂组合应用，其特征在于所述自身免疫疾病和 / 或炎性疾病是重症肌无力。

[0325] 104. 药物组合物，其包含吡格列酮、富马酸二甲酯和任选的一种或多种赋形剂。

[0326] 105. 药物组合物，其包含富马酸二甲酯和选自罗格列酮、曲格列酮和环格列酮的 PPAR γ 激动剂和任选的一种或多种赋形剂。

[0327] 106. 药物组合物，其包含甲基巴多索隆和选自吡格列酮、罗格列酮、曲格列酮和环格列酮的 PPAR γ 激动剂和任选的一种或多种赋形剂。

[0328] 107. 治疗或预防神经变性疾病的方法，该方法包括给需要的患者施用选自格列酮的 PPAR γ 激动剂和富马酸一烷基酯和 / 或二烷基酯。

[0329] 108. 根据上述实施方案和 / 或实施方案 107 的一种或多种的方法，其中所述富马酸二烷基酯选自富马酸二甲酯和富马酸二乙酯且所述富马酸一烷基酯选自富马酸一甲酯和富马酸一乙酯。

[0330] 109. 根据上述实施方案和 / 或实施方案 107 或 108 的一种或多种的方法，其中所述 PPAR γ 激动剂格列酮选自吡格列酮和罗格列酮。

[0331] 110. 根据上述实施方案和 / 或实施方案 107、108 或 109 的一种或多种的方法，其中所述神经变性疾病是多发性硬化。

[0332] 111. 药物组合物，其包含选自格列酮的PPAR γ 激动剂和富马酸一烷基酯和 / 或二烷基酯和任选的一种或多种赋形剂。

[0333] 112. 根据上述实施方案和 / 或实施方案 111 的一种或多种的药物组合物，其中所述富马酸二烷基酯选自富马酸二甲酯和富马酸二乙酯且所述富马酸一烷基酯选自富马酸一甲酯和富马酸一乙酯。

[0334] 113. 根据上述实施方案和 / 或实施方案 111 或 112 的一种或多种的药物组合物，其中 PPAR γ 激动剂格列酮选自吡格列酮和罗格列酮。

[0335] 114. 治疗或预防神经变性疾病的方法，该方法包括给需要的患者施用根据上述实施方案和 / 或实施方案 111、112 或 113 的一种或多种的药物组合物。

[0336] 115. 根据上述实施方案和 / 或实施方案 114 的一种或多种的方法，其中神经变性疾病是多发性硬化。

[0337] 116. 固体口服剂型，其包含选自格列酮的 PPAR γ 激动剂和富马酸一烷基酯和 / 或二烷基酯和任选的一种或多种赋形剂。

[0338] 117. 根据上述实施方案和 / 或实施方案 116 的一种或多种的固体口服剂型，其中所述富马酸二烷基酯选自富马酸二甲酯和富马酸二乙酯且所述富马酸一烷基酯选自富马酸一甲酯和富马酸一乙酯。

[0339] 118. 根据上述实施方案和 / 或实施方案 116 或 117 的一种或多种的固体口服剂型，其中 PPAR γ 激动剂格列酮选自吡格列酮和罗格列酮。

[0340] 119. 治疗或预防神经变性疾病的方法，该方法包括给需要的患者口服施用根据上述实施方案和 / 或实施方案 116、117 或 118 的一种或多种的固体口服剂型。

[0341] 120. 根据上述实施方案和 / 或实施方案 119 的一种或多种的方法，其中神经变性疾病是多发性硬化。

[0342] 121. 成套药盒，其包含 a) 选自格列酮的 PPAR γ 激动剂 ；和 b) 富马酸一烷基酯和 / 或二烷基酯 ；和任选的 c) 剂量方案说明书。

[0343] 122. 根据上述实施方案和 / 或实施方案 121 的一种或多种的成套药盒，其中所述富马酸二烷基酯选自富马酸二甲酯和富马酸二乙酯且所述富马酸一烷基酯选自富马酸一甲酯和富马酸一乙酯。

[0344] 123. 根据上述实施方案和 / 或实施方案 121 或 122 的一种或多种的成套药盒，其中 PPAR γ 激动剂格列酮选自吡格列酮和罗格列酮。

[0345] 124. 治疗自身免疫障碍和 / 或炎性障碍的方法，该方法包括组合施用选自格列酮的 PPAR γ 激动剂 ；和 a) 分离的 Nrf2 激活剂，其选自富马酸酯、甲基巴多索隆 (2- 氰基 -3, 12- 二氧代齐墩果 -1, 9(11) 二烯 -28- 酸甲酯、CDDO-Me、RTA 402)、2- 氰基 -3, 12- 二氧代齐墩果 -1, 9(11) 二烯 -28- 酸乙酯、2- 氰基 -3, 12- 二氧代齐墩果 -1, 9(11) 二烯 -28- 酸 (CDDO)、1[2- 氰基 -3, 12- 二氧代齐墩果 -1, 9(11)- 二烯 -28- 酰基 ] 咪唑 (CDDO-Im)、2- 氰基 -N- 甲基 -3, 12- 二氧代齐墩果 -1, 9(11)- 二烯 -28 酰胺 (CDDO- 甲基酰胺、CDDO-MA)、[(±)-(4bS, 8aR, 10aS)-10a- 乙炔基 -4b, 8, 8- 三甲基 -3, 7- 二氧代 -3, 4b, 7, 8, 8a, 9, 10, 10a- 八氢菲 -2, 6- 二腈 ](TBE-31)、2- 氰基 -3, 12- 二氧代齐墩果 -1, 9(11)- 二烯 -28- 腈 (TP-225)、3- 叔丁基 -4- 羟基苯甲醚、2- 叔丁基 -4- 羟基苯甲醚 (BHA)、叔丁基醌 (tBQ)、叔丁基氢醌 (tBHQ)、3, 5- 二 - 叔丁基 -4- 羟基甲苯 (BHT)、2, 6- 二 - 叔丁基 -4- 亚甲基 -2, 5- 环己二烯 -1- 酮 (2, 6- 二 - 叔丁基醌甲基化物、BHT- 醌甲基化物 )、乙氧喹、没食子酸酯、金诺芬、姜黄素、白藜芦醇、甲萘醌、肉桂醛、肉桂酸酯、咖啡酸酯、咖啡醇、咖啡白脂、番茄红素、鼠尾草酚、莱菔硫烷、奥替普拉、5-(4- 甲氧基 - 苯基 )-1, 2- 二硫杂环戊二烯 -3- 硫酮 (ADT)、柳氮磺吡啶、5- 氨基水杨酸 ( 美沙拉秦 )、5- 氨基 -2- 羟基 - 苯甲酸 4-(5- 硫代 -5H-[1, 2] 二硫杂环戊二烯 -3- 基 )- 苯基酯 (ATB-429)、大蒜素、异硫氰酸烯丙酯、花姜酮、异硫氰酸苯乙酯、异硫氰酸苄酯、异硫氰酸 6- 甲基亚磺酰基己酯以及上述提及的活性剂的烷基和烷酰基酯、烷基醚、立体异构体、互变异构体和盐 ；

或 b) 包含所述分离的 Nrf2 激活剂的药物组合物，

[0346] 条件是：

[0347] 如果所述自身免疫障碍和 / 或炎性障碍是银屑病且所述 PPAR 激动剂是吡格列酮且所述 Nrf2 激活剂是富马酸酯，则该治疗不与羟基脲组合。

[0348] 125. 治疗自身免疫障碍和 / 或炎性障碍的方法，该方法包括组合施用选自格列酮类的 PPAR γ 激动剂；和 a) 分离的 Nrf2 激活剂，其选自富马酸酯类、3- 叔丁基 -4- 羟基苯甲醚、2- 叔丁基 -4- 羟基苯甲醚 (BHA)、叔丁基醌 (tBQ)、叔丁基氢醌 (tBHQ)、3,5- 二 - 叔丁基 -4- 羟基甲苯 (BHT)、2,6- 二 - 叔丁基 -4- 亚甲基 -2,5- 环己二烯 -1- 酮 (2,6- 二 - 叔丁基醌甲基化物、BHT- 醌甲基化物 )、乙氧喹、没食子酸酯、金诺芬、姜黄素、白藜芦醇、甲萘醌、肉桂醛、肉桂酸酯、咖啡酸酯、咖啡醇、咖啡白脂、番茄红素、鼠尾草酚、莱菔硫烷、奥替普拉、5-(4- 甲氧基 - 苯基 )-1,2- 二硫杂环戊二烯 -3- 硫酮 (ADT)、柳氮磺吡啶、5- 氨基水杨酸 ( 美沙拉秦 )、5- 氨基 -2- 羟基 - 苯甲酸 4-(5- 硫代 -5H-[1,2] 二硫杂环戊二烯 -3- 基 )- 苯基酯 (ATB-429)、大蒜素、异硫氰酸烯丙酯、花姜酮、异硫氰酸苯乙酯、异硫氰酸苄酯、异硫氰酸 6- 甲基亚磺酰基己酯以及上述提及的活性剂的烷基和烷酰基酯、烷基醚、立体异构体、互变异构体和盐；或 b) 包含所述分离的 Nrf2 激活剂的药物组合物，

[0349] 条件是

[0350] 如果所述自身免疫障碍和 / 或炎性障碍是银屑病且所述 PPAR 激动剂是吡格列酮且所述 Nrf2 激活剂是富马酸酯，则该治疗不与羟基脲组合。

[0351] 126. 根据上述提及的实施方案的治疗方法，其中自身免疫障碍和 / 或炎性障碍选自银屑病、硬皮病、慢性肾疾病 (CKD)、神经变性疾病、哮喘、慢性阻塞性肺障碍 (COPD)、纤维化、炎性关节炎疾病和炎性肠病 (IBD)。

[0352] 127. 根据上述提及的实施方案的治疗方法，其中自身免疫障碍和 / 或炎性障碍是神经变性疾病，其选自多发性硬化、临床孤立综合征 (CIS)、肌萎缩侧索硬化、阿尔茨海默病、亨廷顿病和帕金森病。

[0353] 128. 减轻患者炎症的方法，该方法包括组合施用选自格列酮的 PPAR γ 激动剂；和 a) 分离的 Nrf2 激活剂，其选自富马酸酯、甲基巴多索隆 (2- 氰基 -3,12- 二氧代齐墩果 -1,9(11) 二烯 -28- 酸甲酯、CDDO-Me、RTA 402)、2- 氰基 -3,12- 二氧代齐墩果 -1,9(11) 二烯 -28- 酸乙酯、2- 氰基 -3,12- 二氧代齐墩果 -1,9(11) 二烯 -28- 酸 (CDDO)、1[2- 氰基 -3,12- 二氧代齐墩果 -1,9(11)- 二烯 -28- 酰基 ] 咪唑 (CDDO-Im)、2- 氰基 -N- 甲基 -3,12- 二氧代齐墩果 -1,9(11)- 二烯 -28 酰胺 (CDDO- 甲基酰胺，CDDO-MA)、[(±)-(4bS,8aR,10aS)-10a- 乙炔基 -4b,8,8- 三甲基 -3,7- 二氧代 -3,4b,7,8,8a,9,10,10a- 八氢菲 -2,6- 二腈 ](TBE-31)、2- 氰基 -3,12- 二氧代齐墩果 -1,9(11)- 二烯 -28- 腈 (TP-225)、3- 叔丁基 -4- 羟基苯甲醚、2- 叔丁基 -4- 羟基苯甲醚 (BHA)、叔丁基醌 (tBQ)、叔丁基氢醌 (tBHQ)、3,5- 二 - 叔丁基 -4- 羟基甲苯 (BHT)、2,6- 二 - 叔丁基 -4- 亚甲基 -2,5- 环己二烯 -1- 酮 (2,6- 二 - 叔丁基醌甲基化物、BHT- 醌甲基化物 )、乙氧喹、没食子酸酯、金诺芬、姜黄素、白藜芦醇、甲萘醌、肉桂醛、肉桂酸酯、咖啡酸酯、咖啡醇、咖啡白脂、番茄红素、鼠尾草酚、莱菔硫烷、奥替普拉、5-(4- 甲氧基 - 苯基 )-1,2- 二硫杂环戊二烯 -3- 硫酮 (ADT)、柳氮磺吡啶、5- 氨基水杨酸 ( 美沙拉秦 )、5- 氨基 -2- 羟基 - 苯甲酸 4-(5- 硫代 -5H-[1,2] 二硫杂环戊二烯 -3- 基 )- 苯基酯 (ATB-429)、大

蒜素、异硫氰酸烯丙酯、花姜酮、异硫氰酸苯乙酯、异硫氰酸苄酯、异硫氰酸 6- 甲基亚磺酰基己酯以及上述提及的活性剂的烷基和烷酰基酯、烷基醚、立体异构体、互变异构体和盐；或 b) 包含所述分离的 Nrf2 激活剂的药物组合物，

[0354] 条件是：

[0355] 如果所述炎症与银屑病一起发生和 / 或因银屑病导致且所述 PPAR 激动剂是吡格列酮且所述 Nrf2 激活剂是富马酸酯，则该治疗不与羟基脲组合。

[0356] 129. 减轻患者炎症的方法，该方法包括组合施用选自格列酮的 PPAR γ 激动剂；和 a) 分离的 Nrf2 激活剂，其选自富马酸酯、3- 叔丁基 -4- 羟基苯甲醚、2- 叔丁基 -4- 羟基苯甲醚 (BHA)、叔丁基醌 (tBQ)、叔丁基氢醌 (tBHQ)、3,5- 二 - 叔丁基 -4- 羟基甲苯 (BHT)、2,6- 二 - 叔丁基 -4- 亚甲基 -2,5- 环己二烯 -1- 酮 (2,6- 二 - 叔丁基醌甲基化物、BHT- 醌甲基化物 )、乙氧喹、没食子酸酯、金诺芬、姜黄素、白藜芦醇、甲萘醌、肉桂醛、肉桂酸酯、咖啡酸酯、咖啡醇、咖啡白脂、番茄红素、鼠尾草酚、莱菔硫烷、奥替普拉、5-(4- 甲氧基 - 苯基 )-1,2- 二硫杂环戊二烯 -3- 硫酮 (ADT)、柳氮磺吡啶、5- 氨基水杨酸 ( 美沙拉秦 )、5- 氨基 -2- 羟基 - 苯甲酸 4-(5- 硫代 -5H-[1,2] 二硫杂环戊二烯 -3- 基 )- 苯基酯 (ATB-429)、大蒜素、异硫氰酸烯丙酯、花姜酮、异硫氰酸苯乙酯、异硫氰酸苄酯、异硫氰酸 6- 甲基亚磺酰基己酯以及上述提及的活性剂的烷基和烷酰基酯、烷基醚、立体异构体、互变异构体和盐；或 b) 包含所述分离的 Nrf2 激活剂的药物组合物，

[0357] 条件是

[0358] 如果所述炎症与银屑病一起发生和 / 或因银屑病导致且所述 PPAR 激动剂是吡格列酮且所述 Nrf2 激活剂是富马酸酯，则该治疗不与羟基脲组合。

[0359] 130. 根据上述提及的实施方案的方法，其中所述炎症是慢性炎症。

[0360] 131. 根据上述提及的实施方案的方法，其中 PPAR γ 激动剂格列酮选自吡格列酮和罗格列酮。

[0361] 132. 根据上述提及的实施方案的方法，其中 Nrf2 激活剂是选自富马酸二烷基酯和富马酸一烷基酯的富马酸酯。

[0362] 133. 根据上述实施方案的方法，其中所述 Nrf2 激活剂是富马酸二甲酯。

[0363] 134. 药物组合物，其包含：选自格列酮的 PPAR γ 激动剂；和 Nrf2 激活剂，其选自富马酸酯、甲基巴多索隆 (2- 氰基 -3,12- 二氧代齐墩果 -1,9(11) 二烯 -28- 酸甲酯、CDDO-Me、RTA 402)、2- 氰基 -3,12- 二氧代齐墩果 -1,9(11) 二烯 -28- 酸乙酯、2- 氰基 -3,12- 二氧代齐墩果 -1,9(11) 二烯 -28- 酸 (CDDO)、1[2- 氰基 -3,12- 二氧代齐墩果 -1,9(11)- 二烯 -28- 酰基 ] 咪唑 (CDDO-Im)、2- 氰基 -N- 甲基 -3,12- 二氧代齐墩果 -1,9(11)- 二烯 -28 酰胺 (CDDO- 甲基酰胺、CDDO-MA)、[(±)-(4bS,8aR,10aS)-10a- 乙炔基 -4b,8,8- 三甲基 -3,7- 二氧代 -3,4b,7,8,8a,9,10,10a- 八氢菲 -2,6- 二腈 ](TBE-31)、2- 氰基 -3,12- 二氧代齐墩果 -1,9(11)- 二烯 -28- 腈 (TP-225)、3- 叔丁基 -4- 羟基苯甲醚、2- 叔丁基 -4- 羟基苯甲醚 (BHA)、叔丁基醌 (tBQ)、叔丁基氢醌 (tBHQ)、3,5- 二 - 叔丁基 -4- 羟基甲苯 (BHT)、2,6- 二 - 叔丁基 -4- 亚甲基 -2,5- 环己二烯 -1- 酮 (2,6- 二 - 叔丁基醌甲基化物、BHT- 醌甲基化物 )、乙氧喹、没食子酸酯、金诺芬、姜黄素、白藜芦醇、甲萘醌、肉桂醛、肉桂酸酯、咖啡酸酯、咖啡醇、咖啡白脂、番茄红素、鼠尾草酚、莱菔硫烷、奥替普拉、5-(4- 甲氧基 - 苯基 )-1,2- 二硫杂环戊二烯 -3- 硫酮 (ADT)、柳氮磺吡啶、5- 氨基水杨酸

(美沙拉秦)、5-氨基-2-羟基-苯甲酸4-(5-硫代-5H-[1,2]二硫杂环戊二烯-3-基)-苯基酯(ATB-429)、大蒜素、异硫氰酸烯丙酯、花姜酮、异硫氰酸苯乙酯、异硫氰酸苄酯、异硫氰酸6-甲基亚磺酰基己酯以及上述提及的活性剂的烷基和烷酰基酯、烷基醚、立体异构体、互变异构体和盐;和任选的一种或多种赋形剂。

[0364] 135. 药物组合物,其包含:选自格列酮的PPARγ激动剂;和Nrf2激活剂,其选自富马酸酯、3-叔丁基-4-羟基苯甲醚、2-叔丁基-4-羟基苯甲醚(BHA)、叔丁基醌(tBQ)、叔丁基氢醌(tBHQ)、3,5-二-叔丁基-4-羟基甲苯(BHT)、2,6-二-叔丁基-4-亚甲基-2,5-环己二烯-1-酮(2,6-二-叔丁基醌甲基化物、BHT-醌甲基化物)、乙氧喹、没食子酸酯、金诺芬、姜黄素、白藜芦醇、甲萘醌、肉桂醛、肉桂酸酯、咖啡酸酯、咖啡醇、咖啡白脂、番茄红素、鼠尾草酚、莱菔硫烷、奥替普拉、5-(4-甲氧基-苯基)-1,2-二硫杂环戊二烯-3-硫酮(ADT)、柳氮磺吡啶、5-氨基水杨酸(美沙拉秦)、5-氨基-2-羟基-苯甲酸4-(5-硫代-5H-[1,2]二硫杂环戊二烯-3-基)-苯基酯(ATB-429)、大蒜素、异硫氰酸烯丙酯、花姜酮、异硫氰酸苯乙酯、异硫氰酸苄酯、异硫氰酸6-甲基亚磺酰基己酯以及上述提及的活性剂的烷基和烷酰基酯、烷基醚、立体异构体、互变异构体和盐;和任选的一种或多种赋形剂。

[0365] 136. 根据上述提及的实施方案的药物组合物,其中PPARγ激动剂格列酮选自吡格列酮和罗格列酮。

[0366] 137. 根据上述提及的实施方案的药物组合物,其中所述Nrf2激活剂是选自富马酸二烷基酯和富马酸一烷基酯的富马酸酯。

[0367] 138. 根据上述提及的实施方案的药物组合物,其中所述Nrf2激活剂是富马酸二甲酯。

[0368] 139. 固体口服剂型,其包含根据上述提及的实施方案的药物组合物。

[0369] 140. 治疗自身免疫障碍和/或炎性障碍的方法,该方法包括施用根据上述实施方案和/或实施方案134、135、136、137或138的一种或多种的药物组合物。

[0370] 141. 根据上述提及的实施方案的治疗方法,其中自身免疫障碍和/或炎性障碍选自银屑病、硬皮病、慢性肾疾病(CKD)、神经变性疾病、哮喘、慢性阻塞性肺疾病(COPD)、纤维化、炎性关节炎疾病和炎性肠病(IBD)。

[0371] 142. 根据上述提及的实施方案的治疗方法,其中自身免疫障碍和/或炎性障碍是神经变性疾病,其选自多发性硬化、临床孤立综合征(CIS)、肌萎缩侧索硬化、阿尔茨海默病、亨廷顿病和帕金森病。

[0372] 143. 减轻患者炎症的方法,该方法包括施用根据的上述实施方案和/或实施方案134、135、136、137或138一种或多种的药物组合物。

[0373] 144. 根据上述实施方案的方法,其中所述炎症是慢性炎症。

[0374] 145. 成套药盒,其包含:a)选自格列酮的PPARγ激动剂;和b)Nrf2激活剂,其选自富马酸酯、甲基巴多索隆(2-氰基-3,12-二氧代齐墩果-1,9(11)二烯-28-酸甲酯、CDDO-Me、RTA 402)、2-氰基-3,12-二氧代齐墩果-1,9(11)二烯-28-酸乙酯、2-氰基-3,12-二氧代齐墩果-1,9(11)二烯-28-酸(CDDO)、1[2-氰基-3,12-二氧代齐墩果-1,9(11)-二烯-28-酰基]咪唑(CDDO-Im)、2-氰基-N-甲基-3,12-二氧代齐墩果-1,9(11)-二烯-28酰胺(CDDO-甲基酰胺、CDDO-MA)、[(±)-(4bS,8aR,10aS)-10a-乙炔

基-4b,8,8-三甲基-3,7-二氧代-3,4b,7,8,8a,9,10,10a-八氢菲-2,6-二腈](TBE-31)、2-氰基-3,12-二氧代齐墩果-1,9(11)-二烯-28-腈(TP-225)、3-叔丁基-4-羟基苯甲醚、2-叔丁基-4-羟基苯甲醚(BHA)、叔丁基醌(tBQ)、叔丁基氢醌(tBHQ)、3,5-二-叔丁基-4-羟基甲苯(BHT)、2,6-二-叔丁基-4-亚甲基-2,5-环己二烯-1-酮(2,6-二-叔丁基醌甲基化物、BHT-醌甲基化物)、乙氧喹、没食子酸酯、金诺芬、姜黄素、白藜芦醇、甲萘醌、肉桂醛、肉桂酸酯、咖啡酸酯、咖啡醇、咖啡白脂、番茄红素、鼠尾草酚、莱菔硫烷、奥替普拉、5-(4-甲氧基-苯基)-1,2-二硫杂环戊二烯-3-硫酮(ADT)、柳氮磺吡啶、5-氨基水杨酸(美沙拉秦)、5-氨基-2-羟基-苯甲酸4-(5-硫代-5H-[1,2]二硫杂环戊二烯-3-基)-苯基酯(ATB-429)、大蒜素、异硫氰酸烯丙酯、花姜酮、异硫氰酸苯乙酯、异硫氰酸苄酯、异硫氰酸6-甲基亚磺酰基己酯以及上述提及的活性剂的烷基和烷酰基酯、烷基醚类、立体异构体、互变异构体和盐;和任选的c)用于给药方案的说明书。

[0375] 146. 成套药盒,其包含a)选自格列酮的PPARγ激动剂;和b)Nrf2激活剂,其选自富马酸酯、3-叔丁基-4-羟基苯甲醚、2-叔丁基-4-羟基苯甲醚(BHA)、叔丁基醌(tBQ)、叔丁基氢醌(tBHQ)、3,5-二-叔丁基-4-羟基甲苯(BHT)、2,6-二-叔丁基-4-亚甲基-2,5-环己二烯-1-酮(2,6-二-叔丁基醌甲基化物、BHT-醌甲基化物)、乙氧喹、没食子酸酯、金诺芬、姜黄素、白藜芦醇、甲萘醌、肉桂醛、肉桂酸酯、咖啡酸酯、咖啡醇、咖啡白脂、番茄红素、鼠尾草酚、莱菔硫烷、奥替普拉、5-(4-甲氧基-苯基)-1,2-二硫杂环戊二烯-3-硫酮(ADT)、柳氮磺吡啶、5-氨基水杨酸(美沙拉秦)、5-氨基-2-羟基-苯甲酸4-(5-硫代-5H-[1,2]二硫杂环戊二烯-3-基)-苯基酯(ATB-429)、大蒜素、异硫氰酸烯丙酯、花姜酮、异硫氰酸苯乙酯、异硫氰酸苄酯、异硫氰酸6-甲基亚磺酰基己酯以及上述提及的活性剂的烷基和烷酰基酯、烷基醚、立体异构体、互变异构体和盐;和任选的c)用于给药方案的说明书。

[0376] 147. 根据上述提及的实施方案的成套药盒,其中PPARγ激动剂格列酮选自吡格列酮和罗格列酮。

[0377] 148. 根据上述提及的实施方案的成套药盒,其中所述Nrf2激活剂是选自富马酸二烷基酯和富马酸一烷基酯的富马酸酯。

[0378] 149. 根据上述提及的实施方案的成套药盒,其中所述Nrf2激活剂是富马酸二甲酯。

[0379] 150. 治疗多发性硬化或临床孤立综合征(CIS)的方法,该方法包括给具有多发性硬化或临床孤立综合征的患者施用包含格列酮和富马酸一烷基酯和/或富马酸二烷基酯的药物组合物。

[0380] 151. 根据上述实施方案和/或实施方案150的一种或多种的方法,其中所述富马酸二烷基酯选自富马酸二甲酯或富马酸二乙酯且所述富马酸一烷基酯选自富马酸一甲酯或富马酸一乙酯。

[0381] 152. 根据上述实施方案和/或实施方案151的一种或多种的方法,其中所述富马酸二烷基酯是富马酸二甲酯。

[0382] 153. 根据上述实施方案和/或实施方案150的一种或多种的方法,其中所述格列酮是吡格列酮或罗格列酮。

[0383] 154. 根据上述实施方案和/或实施方案150的一种或多种的方法,其中所述组合

物包含富马酸二烷基酯选自富马酸二甲酯或富马酸二乙酯，所述格列酮是吡格列酮或罗格列酮且所述药物组合物是固体口服剂型。

[0384] 155. 根据上述实施方案和 / 或实施方案 154 的一种或多种的方法，其中所述富马酸二烷基酯是富马酸二甲酯。

[0385] 156. 药物组合物，其包含格列酮和富马酸一烷基酯和 / 或富马酸二烷基酯和任选的一种或多种赋形剂。

[0386] 157. 根据上述实施方案和 / 或实施方案 156 的一种或多种的药物组合物，其中所述富马酸二烷基酯选自富马酸二甲酯或富马酸二乙酯且所述富马酸一烷基酯选自富马酸一甲酯或富马酸一乙酯。

[0387] 158. 根据上述实施方案和 / 或实施方案 156 的一种或多种的药物组合物，其中所述格列酮是吡格列酮或罗格列酮。

[0388] 159. 根据上述实施方案和 / 或实施方案 157 的一种或多种的药物组合物，其中所述富马酸二烷基酯是富马酸二甲酯。

[0389] 160. 根据上述实施方案和 / 或实施方案 156 的一种或多种的药物组合物，其中所述药物组合物包含固体口服剂型。

[0390] 161. 根据上述实施方案和 / 或实施方案 156 的一种或多种的药物组合物，其中所述富马酸二烷基酯选自富马酸二甲酯或富马酸二乙酯且所述富马酸一烷基酯选自富马酸一甲酯或富马酸一乙酯，所述格列酮是吡格列酮或罗格列酮，且所述药物组合物是口服剂型。

[0391] 162. 根据上述实施方案和 / 或实施方案 161 的一种或多种的药物组合物，其中所述富马酸二烷基酯是富马酸二甲酯。

[0392] 163. 根据上述实施方案和 / 或实施方案 150 的一种或多种的方法，其中所述患者具有多发性硬化。

[0393] 164. 根据上述实施方案和 / 或实施方案 150 的一种或多种的方法，其中所述患者具有临床孤立综合征。

[0394] 165. 治疗或预防自身免疫障碍和 / 或炎性障碍的方法，该方法包括给需要的患者施用选自格列酮的 PPAR γ 激动剂和烷基巴多索隆。

[0395] 166. 根据上述实施方案和 / 或实施方案 165 的一种或多种的方法，其中烷基巴多索隆是甲基巴多索隆。

[0396] 167. 根据上述实施方案和 / 或实施方案 165 或 166 的一种或多种的方法，其中 PPAR γ 激动剂格列酮选自吡格列酮和罗格列酮。

[0397] 168. 根据上述实施方案和 / 或实施方案 165、166 或 167 的一种或多种的方法，其中所述自身免疫障碍和 / 或炎性障碍是慢性肾病。

[0398] 169. 根据上述实施方案和 / 或实施方案 165、166 或 167 的一种或多种的方法，其中自身免疫障碍和 / 或炎性障碍是多发性硬化。

[0399] 170. 组合物，其包含 a) 选自金诺芬、柳氮磺吡啶或 5- 氨基水杨酸（美沙拉秦）的化合物和 b) 格列酮。

[0400] 171. 组合物，其包含 a) 选自金诺芬、柳氮磺吡啶或 5- 氨基水杨酸（美沙拉秦）的化合物和 b) 吡格列酮。

[0401] 172. 组合物，其包含 a) 选自金诺芬、柳氮磺吡啶或 5- 氨基水杨酸（美沙拉秦）的化合物和 b) 罗格列酮。

[0402] 173. 药物组合物，其包含 a) 选自金诺芬、柳氮磺吡啶或 5- 氨基水杨酸（美沙拉秦）的化合物；和 b) 格列酮，例如吡格列酮或罗格列酮；和任选的 c) 一种或多种赋形剂。

[0403] 174. 治疗类风湿性关节炎的方法，该方法包括给患者施用根据实施方案 170-173 的组合物，优选包含 a) 金诺芬或柳氮磺吡啶和 b) 格列酮的组合物。

[0404] 175. 治疗选自炎性肠病的疾病、例如溃疡性结肠炎和克隆病的病症的方法，该方法包括给患者施用根据实施方案 170-173 的组合物，优选包含柳氮磺吡啶或 5- 氨基水杨酸（美沙拉秦）和格列酮的组合物。

[0405] 在本发明的另一个实施方案中，所述自身免疫疾病和 / 或炎性疾病是口腔炎症或咽喉炎症，例如牙龈炎、牙周炎或扁桃体炎。在优选的实施方案中，优选通过用溶液冲洗口腔和 / 或咽喉或应用凝胶剂或乳膏剂治疗这样的疾病，所述溶液剂或凝胶剂或乳膏剂包含：PPAR γ 激动剂，例如格列酮，优选吡格列酮或罗格列酮；和 Nrf2 激活剂，例如莱菔硫烷、叔丁基氢醌和 / 或丁基化羟基苯甲醚或本文提及的其它活性剂，优选 3- 叔丁基 -4- 羟基苯甲醚、2- 叔丁基 -4- 羟基苯甲醚 (BHA)、叔丁基醌 (tBQ)、叔丁基氢醌 (tBHQ)、3,5- 二 - 叔丁基 -4- 羟基甲苯 (BHT)、2,6- 二 - 叔丁基 -4- 亚甲基 -2,5- 环己二烯 -1- 酮 (2,6- 二 - 叔丁基醌甲基化物、BHT- 醌甲基化物）、乙氧喹、没食子酸酯、姜黄素、白藜芦醇、甲萘醌、肉桂醛、肉桂酸酯、咖啡酸酯、咖啡醇、咖啡白脂、番茄红素、鼠尾草酚、莱菔硫烷、奥替普拉、5-(4- 甲氧基 - 苯基 )-1,2- 二硫杂环戊二烯 -3- 硫酮 (ADT)、5- 氨基 -2- 羟基 - 苯甲酸 4-(5- 硫代 -5H-[1,2] 二硫杂环戊二烯 -3- 基 )- 苯基酯 (ATB-429)、大蒜素、异硫氰酸烯丙酯、花姜酮、异硫氰酸苯乙酯、异硫氰酸苄酯、异硫氰酸 6- 甲基亚磺酰基己酯以及上述提及的活性剂的烷基和烷酰基酯、烷基醚、立体异构体、互变异构体和盐。上述溶液或凝胶可以基于已知的常规赋形剂制剂，例如包含聚乙烯吡咯烷酮作为赋形剂的活性剂的水性制剂。此外，所述溶液剂或凝胶剂除所述活性剂外还可以包含抗菌剂，例如氯己定，例如葡糖酸氯己定、西吡氯铵、氟化锡、海克替啶、苯甲酸及其盐例如苯甲酸钠、水杨酸酯例如水杨酸甲酯、苯扎氯铵、对羟基苯甲酸甲酯和 / 或度米芬。

[0406] 因此，本发明优选的实施方案是溶液剂和凝胶剂或乳膏剂，其包含：PPAR 激动剂，且优选 PPAR γ 激动剂，例如格列酮，优选吡格列酮或罗格列酮；和 Nrf2 激活剂，例如莱菔硫烷、叔丁基氢醌和 / 或丁基化羟基苯甲醚或本文提及的其它活性剂，特别是 3- 叔丁基 -4- 羟基苯甲醚、2- 叔丁基 -4- 羟基苯甲醚 (BHA)、叔丁基醌 (tBQ)、叔丁基氢醌 (tBHQ)、3,5- 二 - 叔丁基 -4- 羟基甲苯 (BHT)、2,6- 二 - 叔丁基 -4- 亚甲基 -2,5- 环己二烯 -1- 酮 (2,6- 二 - 叔丁基醌甲基化物、BHT- 醌甲基化物）、乙氧喹、没食子酸酯、姜黄素、白藜芦醇、甲萘醌、肉桂醛、肉桂酸酯、咖啡酸酯、咖啡醇、咖啡白脂、番茄红素、鼠尾草酚、莱菔硫烷、奥替普拉、5-(4- 甲氧基 - 苯基 )-1,2- 二硫杂环戊二烯 -3- 硫酮 (ADT)、5- 氨基 -2- 羟基 - 苯甲酸 4-(5- 硫代 -5H-[1,2] 二硫杂环戊二烯 -3- 基 )- 苯基酯 (ATB-429)、大蒜素、异硫氰酸烯丙酯、花姜酮、异硫氰酸苯乙酯、异硫氰酸苄酯、异硫氰酸 6- 甲基亚磺酰基己酯以及上述提及的活性剂的烷基和烷酰基酯、烷基醚、立体异构体、互变异构体和盐。在进一步优选的实施方案中，所述活性剂各自在这些溶液剂、凝胶剂或乳膏剂中的使用量占该溶液剂、乳膏剂或凝胶剂总重的至少 0.1%，优选至少 0.5% 或至少 1、2 或 3% (w/w)。

[0407] 活性氧类别和抗氧化剂在炎性疾病中的作用描述在 Journal of Clinical Periodontology 第 24 卷第 5 期，1997，第 287-296 页中。

[0408] 牙周炎和牙龈炎的动物模型是本领域众所周知的，例如 Journal of Biomedicine and Biotechnology Volume 2011, Article ID 754857, 8 pages doi:10.1155/2011/754857。

[0409] 在本发明的另一个优选的实施方案中，将所述 PPAR γ 激动剂例如吡格列酮或罗格列酮与 Nrf2 激活剂辣椒辣素一起施用用于治疗自身免疫障碍和 / 或炎性障碍，例如银屑病、银屑病关节炎和关节炎，例如类风湿性关节炎。还可以将该组合用于治疗疼痛，例如神经性疼痛。与辣椒辣素的组合优选以乳膏剂或凝胶剂或贴剂的形式局部应用。更优选本发明涉及包含辣椒辣素和 PPAR γ 激动剂例如格列酮、优选吡格列酮或罗格列酮的霜剂乳膏剂或凝胶剂或贴剂。

[0410] 本发明包含辣椒辣素的乳膏剂、凝胶剂或贴剂在局部施用于本文所述的银屑病和类风湿性关节炎的动物模型时提供了有利的结果。在这些动物模型中，将包含辣椒辣素和 PPAR γ 激动剂例如格列酮、优选吡格列酮或罗格列酮的乳膏剂、凝胶剂或贴剂施用于其中出现症状的关节或其它皮肤区域。

[0411] 在另一个优选的实施方案中，将 Nrf2 激活剂色甘酸钠或奈多罗米与 PPAR γ 激动剂例如格列酮、优选吡格列酮或罗格列酮组合，以便治疗或预防自身免疫疾病和 / 或炎性疾病，例如哮喘、过敏反应例如季节性过敏反应或花粉热、COPD 或过敏性鼻炎。优选地，将包含作为 Nrf2 激活剂的色甘酸钠或其任意的其它盐或奈多罗米或其盐例如钠盐的组合与 PPAR 激动剂组合在溶液剂或凝胶剂或乳膏剂或贴剂中，特别是吸入用溶液剂或滴眼液，其包含常用赋形剂。

[0412] 吡格列酮可以以例如公开在 WO 2011015868 和 WO2011098746 中的对映异构体纯或富含对映异构体形式使用，其特别有利于口腔冲洗液或口腔用凝胶剂、吸入溶液剂、滴眼剂和用于治疗皮肤的局部用乳膏剂或凝胶剂或贴剂。

[0413] 优选地，本发明中使用的 PPAR 激动剂和 Nrf2 激活剂不属于相同化学类型的化合物，即 Nrf2 激活剂优选属于与 PPAR 激动剂不同类型的化合物。

[0414] 优选包含用于治疗炎性疾病和 / 或自身免疫疾病的本发明组合的固体口服剂型。固体口服剂型是本领域众所周知的且包含散剂、颗粒剂、锭剂、胶囊剂和片剂，例如压制片 (CT)、包糖衣片 (SCT)、薄膜包衣片 (FCT)、肠溶衣片 (ECT)、多次压制片 (MCT)（其是通过一个以上压制循环制备的压制片）、通过在预先压制的颗粒上压制另外的片剂颗粒制备的分层片、压制包衣片、控释片、泡腾片、压制栓剂、口含片和舌下片、模制片（模印片，TT）和皮下片 (HT)。最优选共同包含在单一药物组合物中的两种活性剂的固体口服剂型。

[0415] 还优选包含富马酸二甲酯、富马酸一甲酯、任选其锌、镁和 / 或钙盐的形式和 PPAR 激动剂的组合物。特别优选该组合物在治疗银屑病中的用途。

[0416] 根据任意上述实施方案，还优选 PPAR γ 激动剂与 Nrf2 激活剂组合用于治疗自身免疫疾病和 / 或炎性疾病，其特征在于该治疗排除或不包含施用羟基脲（羟基脲），特别地，条件是不以混合物或包含共同的两种活性剂的单一药物制剂的形式使用或施用 PPAR γ 激动剂和 Nrf2 激活剂。

[0417] 在本发明的一个实施方案中，根据本发明治疗的自身免疫障碍和 / 或炎性障碍是银屑病和 / 或因银屑病导致或与之一起发生的炎症。优选地，本发明的治疗组合了格列酮

与富马酸二甲酯治疗银屑病和/或因银屑病导致或与之一起发生的炎症。如果在这种情况中，所述格列酮是吡格列酮，特别地，如果不以与 Nrf2 激活剂的混合物或包含共同的两种活性剂的单一药物制剂的形式使用或施用，则优选所治疗的患者在本发明治疗前不接受治疗量的羟基脲，在根据本发明治疗的同时不接受羟基脲且优选在其之后也不接受羟基脲，而吡格列酮、富马酸二甲酯或其代谢物仍然存在于体内。因此，如果所述自身免疫障碍和/或炎性障碍是银屑病且所述 PPAR 激动是吡格列酮且所述 Nrf2 激活剂是富马酸酯，则优选不将所述治疗与羟基脲组合，特别地，条件是不以混合物或包含共同的两种活性剂的单一药物制剂的形式使用或施用 PPARγ 激动剂和 Nrf2 激活剂。

[0418] 如果根据本发明治疗的自身免疫障碍和/或炎性障碍是银屑病和/或因银屑病导致或与之一起发生的炎症，则在一个实施方案中，所述格列酮优选不是吡格列酮，例如罗格列酮；或所述 Nrf2 激活剂不是富马酸酯。

[0419] 吡格列酮和罗格列酮片剂是可商购获得的且可以以本身用于本发明的组合治疗。

[0420] 在一个实施方案中，优选的片剂是薄膜包衣片，其包含相当于罗格列酮 2mg、4mg 或 8mg 的马来酸罗格列酮，用于口服施用，具有如下非活性成分：羟丙甲纤维素 2910、一水合乳糖、硬脂酸镁、微晶纤维素、聚乙二醇 3000、淀粉羟乙酸钠、二氧化钛、三醋精和 1 种或多种如下成分：合成红色或黄色氧化铁和滑石粉。

[0421] 在一个实施方案中，用于口服施用的优选片剂包含用如下赋形剂配制的 15mg、30mg 或 45mg 吡格列酮（作为碱）：一水合乳糖 NF、羟丙基纤维素 NF、羧甲基纤维素钙 NF 和硬脂酸镁 NF。

[0422] 可以按照与 US6355676、US7976853 和 6403121 类似的方式得到其它制剂。

[0423] 在本说明书的上下文中，术语“没有显著的 PPARγ 激动活性”或“没有显著的 PPARγ 激动作用”是指在 Nrf2 激活剂的治疗有用浓度下，未得到或测定治疗有用的 PPARγ 激活。

[0424] 在本说明书的上下文中，术语“对 Nrf2 没有显著的作用”或“对 Nrf2 没有显著的激活作用”或“对 Nrf2 活性没有显著的作用”是指在 PPARγ 激动剂的治疗有用浓度下，未得到或测定治疗有用的 Nrf2 激活。术语富马酸一烷基酯 (monoalkyl fumarate) 和富马酸一烷基酯 (monoalkyl hydrogen fumarate) 是同义词，例如富马酸一甲酯 (monomethyl fumarate) 和富马酸一甲酯 (monomethyl hydrogen fumarate)。

## 实施例

[0425] 实施例 1

[0426] 包含 120.0mg 富马酸二甲酯的在胶囊中的肠溶衣微型片剂的制备

[0427] 按照专利 US7320999，粉碎 12.000kg 富马酸二甲酯，通过筛 800 混合并且匀化。然后制备具有如下组成的赋形剂混合物：17.50kg 淀粉衍生物（**STA-RX®** 1500）、0.30kg 微晶纤维素（**Avicel®** PH 101）、0.75kg PVP（**Kollidon®** 120）、4.00kg **Primogel®**、0.25kg 胶体硅酸（**Aerosil®**）。将富马酸二甲酯加入到全部粉末混合物中，通过筛 200 混合、匀化，按照常用方式使用聚乙烯吡咯烷酮（**Kollidon®** K25）的 2%水溶液加工，得到

粘合剂颗粒，然后以干燥态与外相混合。所述外相由 0.50kg 硬脂酸镁和 1.50kg 滑石粉组成。

[0428] 按照常规方式将粉末混合物压制成 10mg- 微型片芯。

[0429] 为了实现耐受胃酸，将 2.250kg 邻苯二甲酸羟丙基甲基纤维素 (HPMCP, **Pharmacoat®** HP 50) 溶液分批溶于如下溶剂的混合物：13.00L 丙酮、13.50L 乙醇 (94wt.-%，用 2% 酮变性) 和 1.50L 软化水。作为增塑剂，将蓖麻油 (0.240kg) 加入到最终溶液中，按照常规方式将其分批应用于微型片芯上。

[0430] 在干燥完成后，用相同装置将如下组成的混悬液应用成薄膜衣：0.340kg 滑石粉、0.400kg 氧化钛 (VI) Cronus R 56、0.324kg 着色涂漆 L-Rot-lack86837、4.800kg Eudragit E 12.5% 和 0.120kg 聚乙二醇 6000、pH 11 XI，在如下组成的溶剂混合物中：8.170kg2- 丙醇、0.200kg 软化水和 0.600kg 三乙酸甘油酯 ( 三醋精 )。该方法产生肠溶衣微型片剂。

[0431] 随后将肠溶衣微型片剂填充入硬明胶胶囊中并且密封，根据本发明应用。

[0432] 可以根据 US7320999 类似地得到微丸。

[0433] 实施例 2

[0434] 不同的片层中包含吡格列酮和富马酸二甲酯的片剂的制备

[0435] 根据 US807113，将盐酸吡格列酮 (99.2g)、交联羧甲基纤维素钠 (13.2g) 和乳糖 (184.9g) 的混合物通过用流化床制粒机 ( 由 Powrex Corp. 制造，Model:LAB-1) 在其上喷雾 136.2g 羟丙基纤维素 (6.81g) 水溶液制粒。然后将得到的颗粒化粉末通过用流化床制粒机 ( 由 Powrex Corp. 制造，Model:LAB-1) 在其上喷雾通过将乳糖 (36g) 分散于 148.6g 羟丙基纤维素 (7.59g) 水溶液中得到的混悬液制粒，得到包含盐酸吡格列酮的用乳糖包衣的颗粒化粉末。向部分 (23.18g) 由此得到的颗粒化粉末中加入交联羧甲基纤维素钠 (0.728g) 和硬脂酸镁 (0.096g)，并且混合，得到包含盐酸吡格列酮的混合粉末。用根据实施例 1 得到的包含富马酸二甲酯、淀粉衍生物 (STA-**RX®** 1500)、微晶纤维素 ( **Avicel®** PH 101)、PVP(Kollidon(R)120)、**Primogel®** 和胶体硅酸 ( **Aerosil®** ) 的粉末将包含盐酸吡格列酮的混合粉末压制成层状物形式。

[0436] 实施例 3

[0437] 根据 US7976853，将羟丙基纤维素 (26.4g, Grade SSL, Nippon Soda Co., Ltd.) (5% 水溶液在 20℃的粘度：8mPa-s)、聚乙二醇 6000(1.32g)、氧化钛 (2.64g) 和盐酸吡格列酮 (16.5g) 分散于水 (297g) 中，得到包衣溶液。使实施例 1 中得到的肠溶衣微型片剂进料入薄膜包衣设备 (Hicoater-Mini, Freund Industrial Co. Ltd.) 并且用上述提及的包衣溶液包衣，得到包衣制剂。随后将这些用盐酸吡格列酮包衣的肠溶衣微型片剂填充入硬明胶胶囊中并且密封，根据本发明应用。

[0438] 或者，根据实施例 1，可以得到包含期望量的富马酸二甲酯的肠溶衣片，随后用如上所述的吡格列酮制剂包衣。该片剂可以以本身用于本发明的组合治疗。

[0439] 实施例 4

[0440] 将盐酸吡格列酮 (99.2g)、交联羧甲基纤维素钠 (13.2g) 和乳糖 (184.9g) 的混合物通过用流化床制粒机 ( 由 Powrex Corp. 制造，Model:LAB-1) 在其上喷雾 136.2g 羟丙基纤维素 (6.81g) 水溶液制粒。然后将得到的颗粒化粉末通过用流化床制粒机 ( 由 Powrex

Corp. 制造，Model:LAB-1）在其上喷雾通过将乳糖（36g）分散于 148.6g 羟丙基纤维素（7.59g）水溶液中得到的混悬液制粒，得到包含盐酸吡格列酮的用乳糖包衣的颗粒化粉末。将由此得到的期望量的颗粒化粉末填充入包含根据实施例 1 中得到的富马酸二甲酯肠溶衣微型片剂的胶囊中，然后密封。

[0441] 实施例 5

[0442] 向胶囊中填充 20mg 无水甲基巴多索隆在甲基丙烯酸共聚物 Type C, USP 中的分散体，甲基巴多索隆与甲基丙烯酸共聚物 Type C, USP 的重量比为 4/6，根据 US2012/022156 制备如下组合物：

[0443] 作为 40％分散体的无水甲基巴多索隆：11.36％

[0444] SMCC（90LM，硅化微晶纤维素，如 FDA Inactive Ingredients Guide 中列出的）：36.36％

[0445] 一水合乳糖：40.91％

[0446] 羟丙基甲基纤维素：6.82％

[0447] 胶体二氧化硅：0.91％

[0448] 硬脂酸镁：0.91％

[0449] 十二烷基硫酸钠：2.73％。

[0450] 此外，向胶囊中填充与根据实施例 4 第一部分得到的乳糖包衣的颗粒化粉末等量的盐酸盐形式的 45mg 吡格列酮。此后密封胶囊，用于应用。

[0451] 或者，可以将包含甲基巴多索隆的混合物和包含吡格列酮的混合物压制成片剂，优选分层片，其中制剂以分层的方式排列。在一个实施方案中，将肠溶衣应用在片剂上。

[0452] 通用试验方案

[0453] 如果没有另外提及，则在下列动物模型中的治疗由富马酸二甲酯和盐酸盐形式的吡格列酮组成或用它们治疗动物，将它们溶于或分散于在蒸馏水中的 0.5％甲基纤维素/0.1％ Tween80 并且通过口服管饲每日 2 次施用。治疗组通常如下：单独的介质；单独的富马酸二甲酯；单独的吡格列酮；或富马酸二甲酯和吡格列酮的组合。本发明的组合比介质和相应的单独的活性剂对治疗产生了改善的响应。

[0454] 本发明组合在治疗癌症且优选血癌例如 CLL 和 AML 中的效果可以在 Blood. 2006 年 11 月 15 日；108(10):3530-7 和 Cancer Res, 2010 年 6 月 15 日，70；4949 中找到。

[0455] 用于评价 PPARγ 激动剂和 Nrf2 激活剂的组合在口腔炎症和咽喉炎症包括牙龈炎、牙周炎、扁桃体炎中的治疗和预防作用的动物模型

[0456] 根据 J. Periodontol. 2000 年 7 月；71(7):1167-73 感染不含特异性病原体的 C3H/HeN 小鼠，并且根据通用实施例每日通过口服管饲用盐酸吡格列酮、莱菔硫烷或叔丁基氢醌或盐酸吡格列酮和莱菔硫烷或盐酸吡格列酮和叔丁基氢醌的组合治疗。使用所述组合治疗与单个活性剂对比和与未治疗动物对比导致预防或延迟发作以及炎症征候的减轻。通过应用治疗，用所述活性剂的溶液将动物口腔每日冲洗 2 分钟，得到类似的定性结果。

[0457] 用于评价 PPARγ 激动剂和 Nrf2 激活剂的组合在类风湿性关节炎中的治疗和预防作用的动物模型

[0458] 根据 Wilder, R. L. 2001 (Streptococcal Cell Wall Arthritis) Current Protocols in Immunology. 26:15.10.1-15.10.12 准备动物并且根据通用实施例每日使用盐酸吡格列

酮、富马酸二甲酯或所述活性剂的组合通过口服管饲治疗。使用所述组合治疗与单个活性剂对比和与未治疗动物对比导致预防或延迟发作和关节炎征候的减轻。

[0459] 动物模型在评价治疗银屑病中的作用中的应用

[0460] 严重性合并免疫缺陷 (SCID) 小鼠模型可以用于评价化合物在治疗人银屑病中的效力 (Boehncke, Ernst Schering Res Found Workshop 2005, 50, 213-34 ;和 Bhagavathula 等人 , J Pharmacol Expt 7 Therapeutics 2008, 324(3), 938-947)。

[0461] SCID 小鼠用作组织接受者。将一种正常或银屑病志愿者各自的活检组织植入接受小鼠的背侧表面。治疗从植入后 1-2 周开始。将具有人体皮肤植入物的动物分入治疗组。将动物每日 2 次治疗 14 天。在治疗结束时,给动物拍照,然后实施安乐死。手术取出沿周围小鼠皮肤的植入人体组织,并且固定在 10% 福尔马林中,得到样品用于显微镜检查。测定表皮厚度。用针对增殖相关抗原 Ki-67 的抗体和抗人 CD3+ 单克隆抗体染色组织切片,以检测植入组织中的人 T 淋巴细胞。另外,用针对 c-myc 和 β - 连环蛋白的抗体探测切片。对治疗的阳性响应是通过银屑病皮肤植入物平均表皮厚度的减小反应的。阳性响应还与角质细胞中 Ki-67 表达减少相关。

[0462] 用于评价 PPAR γ 激动剂和 Nrf2 激活剂的组合在治疗多发性硬化中的治疗作用的通用 EAE 动物模型

[0463] 给动物和 8-10 周龄 EAE 诱导雌性 C57BL/6 小鼠 (Harlan Laboratories, Livermore, CA) 经皮下在侧腹和肩胛间区域免疫接种用弗氏完全佐剂 (CFA)( 包含 4mg/nL 结核分枝杆菌 (Mycobacterium tuberculosis)) 乳化的 200μg 髓磷脂少突胶质细胞糖蛋白肽 (MOG3S-Ss)( 由 Invitrogen 合成 )(1 :1 体积比 )。通过注射器 - 挤出法用经三通连接的两支玻璃路厄粗头旋口注射器制备乳剂。另外,在免疫接种的当天和免疫接种后第 2 天,对小鼠给予腹膜内注射 200ng 百日咳毒素 (List Biological Laboratories, Inc, Campbell, CA)。给小鼠称重,并且每日检查试验性自身免疫脑脊髓炎 (EAE) 的临床病征。提供随意的取食和饮水,并且一旦动物开始表现出疾病,则在笼子底部提供食物。

[0464] 临床评价

[0465] 从免疫接种后第 7 天开始每日给小鼠评分。临床评分等级如下 (Miller 和 Karplus, Current Protocols in Immunology 2007, 15.1.1-15.1.18) :0 = 正常 ;1 = 跛行尾或后肢软弱 ( 定义为在行走的同时足从笼顶部的杆之间滑落 ) ;2 = 跛行尾和后肢软弱 ;3 = 部分后肢麻痹 ( 定义为后肢上不能承重,但仍然可以移动一侧或两侧后肢至一定程度 ) ;4 = 后肢完全麻痹 ;5 = 垂死状态 ( 包括前肢麻痹 ) 或死亡。

[0466] 用于评价 PPAR γ 激动剂和 Nrf2 激活剂的组合在治疗多发性硬化中的治疗作用的动物模型

[0467] 对属于 C57BL/6 品系的体重为 17-20g 的年龄为 4-6 周的雌性小鼠进行试验。使用 >95% 纯的合成髓磷脂少突胶质细胞糖蛋白肽 35-55(MOG35-55, MEVGWYRSPFSRVVHLYRGK ) 主动诱导试验性自身免疫脑脊髓炎 (EAE)。麻醉每只小鼠并且使其接受在 100μL 磷酸盐缓冲盐水中乳化的 200μg MOG 肽和 15μg 来自皂树 (Quilija) 树皮的皂苷提取物。在 4 个侧腹区域皮下注射 25μL 体积。还经腹膜内给小鼠注射 200μL PBS 中的 200ng 百日咳毒素。48 小时后给予第二次相同的百日咳毒素注射。

[0468] 每日治疗从第 26 天延伸至免疫接种后第 36 天。从免疫接种后第 0 天到第 60 天每日获得临床评分。使用如下方案对临床病征进行评分 :0，没有可检测到的病征 ; 0.5，远端尾虚弱、弓形外观和安静行为 ;1，完全跛行尾 ;1.5，跛行尾和后肢软弱（不稳定步态和后肢难以抓紧）;2，单侧部分后肢麻痹 ;2.5，双侧后肢麻痹 ;3，双侧后肢完全麻痹 ;3.5，后肢完全麻痹和单侧前肢麻痹 ;4，后肢和前肢完全麻痹 (Eugster 等人，Eur J Immunol2001, 31, 2302-2312)。

[0469] 根据来自 EAE 小鼠 CNS 的切片上的组织学情况评价炎症和脱髓鞘。30 或 60 天后处死小鼠，并且取出完整的脊髓，并且在 40℃放入 0.32M 蔗糖溶液中过夜。制备组织并且切片。勒克司坚牢蓝染色剂用于观察脱髓鞘区域。苏木精和曙红用于通过深度染色单核细胞的细胞核高亮显示炎症区域。在光学显微镜下以双盲方式计数用 H&E 染色的免疫细胞。将切片分成灰质和白质，并且手动计数每个扇区，然后合并得到切片的总和。用抗 -CD3+ 单克隆抗体免疫标记 T 细胞。洗涤后，将切片与山羊抗 - 大鼠 HRP 二级抗体一起温育。然后洗涤切片，并且用甲基绿复染。用裂解缓冲液处理在免疫接种后 30 和 60 天从小鼠中分离的脾细胞以取出红细胞。然后将细胞重新混悬于 PBS 并且计数。将细胞以约 $3\times10^6$ 个细胞 / mL 的密度与 20μg/mL MOG 肽一起温育过夜。使用适合的小鼠 IFN-γ 免疫测定系统测定来自刺激的细胞的上清液的 IFN-γ 蛋白质水平。

[0470] 动物模型在评价在治疗炎性肠病中的作用中的用途

[0471] 炎性肠病的动物模型由 Jurjus 等人，J Pharmaocol Toxicol Methods2004, 50, 81-92 ;Villegas 等人，Int' l Immunopharmacol 2003, 3, 1731-1741 ; 和 Murakami 等人，Biochemical Pharmacol 2003, 66, 1253-1261 中描述。例如，如下方案可以用于评价本发明的组合在治疗炎性肠病、克隆病和结肠炎中的作用。

[0472] 使用雌性 ICR 小鼠。将小鼠分入治疗组。对各组给予水（对照组）、在试验开始时给予在自来水中的 5% DSS 以诱导结肠炎，或给予治疗。施用治疗 1 周后，还对接受治疗 1 周的组施用在自来水中的 5% DSS。在试验结束时，处死全部小鼠并且取出大肠。得到结肠粘膜样品并且匀化。定量促炎介体（例如 IL-1α、IL-1β、TNF-α、PGE2 和 PGF2α）和蛋白质浓度。对每个切下的大肠进行组织学检查并且对结肠损害评分。

[0473] 用于评价在治疗哮喘中的作用的临床试验

[0474] 登记具有稳定的轻度至中度哮喘的成年个体（不吸烟者）（例如，参见 Van Schoor 和 Pauwels, Eur Respir J 2002, 19, 997-1002)。使用随机化、双盲、安慰剂对照、两期交叉设计。在不同的臂中口服施用安慰剂、单独的富马酸二甲酯、单独的吡格列酮以及富马酸二甲酯和吡格列酮的组合。本发明的组合与介质或单独的活性剂相比对治疗的响应改善。

[0475] 动物模型在评价治疗慢性阻塞性肺疾病中作用中的用途

[0476] 使用长期接触吸香烟的小鼠的动物模型可以用于评价在治疗肺气肿中的效力（例如，参见 Martorana 等人，Am J Respir Crit Care Med 2005, 172, 848-835 ; 和 Cavarra 等人，Am J Respir Crit Care Med 2001, 164, 886-890)。使用 6 周龄 C57B1/6J 雄性小鼠。在急性研究中，使小鼠暴露于室内空气或 5 支香烟的烟雾中 20 分钟。在长期研究中，使小鼠暴露于室内空气或 3 支香烟的烟雾 / 天，5 天 / 周，达 7 个月。

[0477] 在急性研究中，将小鼠分成 3 个组。然后将这些组分成各 10 只小鼠的 4 个亚组，如下 :(1) 无治疗 / 暴露于空气 ;(2) 无治疗 / 暴露于烟雾 ;(3) 富马酸二甲酯和吡格列酮的

组合 + 暴露于烟雾 ;和 (4) 吡格列酮 + 暴露于烟雾 ;和 (5) 富马酸二甲酯 + 暴露于烟雾。在第一组中,在支气管肺泡灌洗液接触结束时评价 trolox 等效抗氧化剂能力。在第二组中,在 4 小时时使用商购细胞因子组测定支气管肺泡灌洗液中的细胞因子和趋化因子 ;并且在第三组中在 24 小时时评价支气管肺泡灌洗液的细胞计数。

[0478] 用于评价 PPAR γ 激动剂和 Nrf2 激活剂的组合在治疗帕金森病中的治疗作用的动物模型

[0479] MPTP 诱导的神经毒性

[0480] MPTP 或 1- 甲基 -4- 苯基 -1,2,3,6- 四氢吡啶是在男性人体和试验动物中产生帕金森综合征的神经毒素。对 MPTP 神经毒性机理的研究显示它涉及单胺氧化酶对 MPTP 的活性形成的主要代谢物 MPP+ 的生成。单胺氧化酶抑制剂阻断小鼠和灵长类中的 MPTP 的神经毒性。MPP+ 对多巴胺能神经元的神经毒性作用的特异性似乎归因于突触多巴胺转运蛋白摄取 MPP+。这种转运蛋白的阻断剂防止了 MPP+ 的神经毒性。已经显示 MPP+ 为线粒体复合物 I 活性的相对特异性抑制剂,其在鱼藤酮 (retenone) 结合位点结合复合物 I 并且损害氧化磷酸化。在体内研究中,已经显示 MPTP 可以耗尽小鼠中的纹状体 ATP 浓度。已经显示在纹状体内施用的 MPP+ 使大鼠产生显著的 ATP 耗尽以及注射部位上限于纹状体的乳酸盐浓度增加。促进 ATP 产生的化合物可以防止小鼠中的 MPTP 毒性。

[0481] 用单独的介质、单独的富马酸二甲酯、单独的吡格列酮或富马酸二甲酯和吡格列酮的组合将小鼠或大鼠治疗 3 周,然后用 MPTP 治疗。以适当的剂量、施药间隔和施用方式施用 MPTP 达 1 周,然后处死。对照组接受生理盐水或单独的盐酸 MPTP。在处死后,快速地剖离两个纹状体并且放入冷冻的 0.1M 高氯酸。随后超声处理组织,并且使用荧光计测定法分析等份部分的蛋白质含量。还定量了多巴胺、3,4- 二羟基苯基乙酸 (DOPAC) 和高草香酸 (HVA)。将多巴胺和代谢物的浓度表示为 nmol/mg 蛋白质。

[0482] 氟哌啶醇 - 诱导的运动不足症

[0483] 化合物逆转多巴胺拮抗剂例如氟哌啶醇在啮齿动物中的行为抑制作用的能力被视为筛选具有潜在抗帕金森作用的药物 (drags) 的有效方法 (Mandhane 等人 ,Eur. J. Pharmacol 1997,328,135-141)。因此,阻断氟哌啶醇诱导的小鼠运动行为缺乏的治疗能力可以用于评价体内和潜在的抗帕金森效力。

[0484] 使用于本试验的小鼠寄居在受控环境中并且使其适应,然后用于试验。测试前 1 和 1 个半小时 (1.5),给小鼠施用 0.2mg/kg 氟哌啶醇,施用剂量为将基线运动行为减少至少 50% 的剂量。在测试前将治疗施用适当的长度。然后将动物各自放入具有平面多孔的盖的干净透明的聚碳酸酯笼中。

[0485] 通过将笼子放在框架内测定水平的运动行为,所述框架包含 3×6 阵列的光电池,其界面上连接计算机以便将光束阻断列表。使小鼠保持安静状态探查 1 小时并且将在该期间形成的光束阻断数用作运动行为指示物,将其与对照组动物的数据比较统计学显著性差异。

[0486] 6- 羟基多巴胺动物模型

[0487] 通过将多巴胺能神经毒素 6- 羟基多巴胺 (6-OHDA) 局部注入包含黑质纹状体神经元细胞体或轴突纤维的脑区域再现帕金森病中观察到的神经化学缺陷。通过仅单侧损害脑一侧上的黑质纹状体途径,观察到运动抑制的行为不对称性。尽管单侧损害的动物仍然可

以活动且能够自我维护，但是在受损一侧上的其余多巴胺－敏感性神经元变成对刺激过度敏感。通过如下观察结果证实了这一情况：在全身施用多巴胺激动剂例如阿扑吗啡后，动物在损害侧相对的方向上显示明显的旋转。化合物诱导 6-OHDA 受损大鼠中对侧旋转的能力已经显示为预测药物在治疗帕金森病中的效力的敏感性模型。

[0488] 使雄性 Sprague-Dawley 大鼠寄居在受控环境中并且使适应，然后用于试验。在手术前 15 分钟，给予大鼠腹膜内注射去甲肾上腺素能摄取抑制剂地昔帕明 (25mg/kg) 以防止损害非多巴胺神经元。然后将动物放入麻醉室并且使用氧和异氟烷的混合物麻醉。一旦失去意识，则将动物转入立体定位架，其中通过面罩维持麻醉。剃刮头顶部并且使用碘溶液消毒。一旦干燥，则沿头皮中线做 2cm 长切口并且除去皮肤，反向夹住以暴露颅骨。然后在注射部位以上通过颅骨钻小孔。为了损害黑质纹状体途径，将注射套管缓慢地降低至定位于高于右侧内侧前脑束前后 -3.2mm、距离前囟点 -1.5mm 内侧和至低于硬脑脊膜 7.2mm 深度。降低套管后 2 分钟，历经 4 分钟以 0.5μL/ 分钟的速率输注 6-OHDA，得到最终剂量 8μg。将套管保持就位再经过 5 分钟以促进扩散，然后缓慢地取出。然后缝合皮肤，从立体定位架中取出动物，放回到其居室中。使大鼠从手术中恢复 2 周，然后进行行为测试。使用具有用透明 Plexiglas 盖包封（在球的周围）的不锈钢球并且伸长至 29cm 高度的旋转系统 (45cm 直径 ×15cm 高）测定旋转行为。为了评价旋转，将大鼠放入连接弹簧系链的布罩中，所述弹簧系链连接位于球上部的光学旋转器，其用于评价作为部分 (45° ) 或整体 (360° ) 旋转的向左或向右的运动。

[0489] 将治疗给予适当的期限，然后进行测试。给予动物皮下注射亚阈值剂量的阿扑吗啡，然后放入带状装置 (harness) 中。将旋转次数记录 1 小时。在该小时测试期间的整体对侧旋转的总次数用作抗帕金森药物效力的指数。

[0490] 用于评价在治疗阿尔茨海默病中的治疗作用的动物模型

[0491] 表达瑞典 AD 突变基因 hAPPK670N 的杂合转基因小鼠 M671L(Tg2576；Hsiao, Learning & Memory 2001, 8, 301-308) 用作阿尔茨海默病的动物模型。使动物寄居在具有 12:12 光照 / 黑暗周期和可随意取食和饮水的标准条件下。从 9 个月龄开始，将小鼠分成 2 组。历经 6 周，动物组接受治疗。

[0492] 在全部试验组中在每个药物剂量下使用相同的顺序历经 2 周进行行为测试：(1) 空间反转学习；(2) 运动；(3) 恐惧条件；和 (4) 电击敏感性。

[0493] 在试验化合物施用的前 5 天期间使用如 Bardgett 等人在 Brain Res Bull 2003, 60, 131-142 中所述的水 T- 型迷宫测试对空间学习方式和反转学习的获取。在第 1-3 天期间使小鼠习惯于水 T- 型迷宫并且在第 4 天开始任务获取。在第 4 天时，训练小鼠发现在迷宫的一个选择臂上的逃逸平台，直到在连续的路径上进行了 6-8 个正确选择为止。然后在第 5 天时进行反转学习期。在反转学习期间，训练小鼠在第 4 天时找到与逃逸平台位置相对的选择臂上的逃逸平台。将相同的行为标准和试验间隔用作任务期间的获取。

[0494] 评价大量能走动的运动以确定空间反转学习方式的结果没有受到活动能力影响。在 2 天休息期后，在第 8 天时在安装网格运动敏感性检测器的室内评价水平移动活动，不包括垂直和精细运动活动。在 1 小时期间测定伴随同时阻断和不阻断水平方向的检测器的运动次数。

[0495] 从第 9 天开始使用恐惧条件方式测试动物对环境和线索记忆的能力。测试在包含

浸入置于栅格地板下发射气味的溶液例如薄荷提取物的 1 片脱脂棉的室内进行。在第 9 天时施用 5 分钟、3 次试验 80db、2800Hz 音调 - 足电击顺序以训练动物。在第 10 天时，通过将每只小鼠放回到不接触音调和足电击的室内并且每隔 10 秒记录存在或不存在僵硬行为达 8 分钟测试对环境的记忆。将僵硬定义为不活动，例如移动、嗅气味或刻板而不是呼吸。

[0496] 在第 11 天时，测试动物对交替环境和听觉线索的响应。将椰子提取液放入杯中并且提供 80dB 音调，但不递送足电击。然后在本试验的前 2 分钟期间测定对交替环境存在或不存在僵硬响应。然后在本试验的其余 8 分钟连续提供音调并且测定存在或不存在对该音调的响应。

[0497] 在第 12 天时，测试动物以评价它们对条件刺激即足电击的敏感性。在行为测试的最后一天，麻醉动物并且取出脑，固定后过夜，并且通过海马切下切片。染色切片以便对 β - 淀粉质斑块成像。

[0498] 使用适合的统计学方法分析数据。

[0499] 用于评价在治疗亨廷顿病中的治疗作用的动物模型

[0500] 从 10 周龄开始处理 N171-82Q 品系的亨廷顿病转基因 HD 小鼠和非转基因同窝出生的转基因小鼠模型中的神经保护作用。将小鼠放在旋转杆（“转棒 (rotarod)”）上。将小鼠从转棒上跌落时的时间长短记录为运动协调测量值。另外，将小鼠经过的总距离记录为总运动测量值。显示对富马酸二甲酯和吡格列酮的组合治疗具有改善的响应的小鼠保持在转棒上更长的时间期限并且移动了比施用介质或单独的活性剂更远的距离。

[0501] 亨廷顿病的丙二酸盐模型

[0502] 涉及酶生成途径的酶的一系列可逆和不可逆抑制剂已经用于生成神经变性疾病的动物模型，例如帕金森病和亨廷顿病。特别地，琥珀酸脱氢酶（即影响细胞能量体内稳态的酶）的抑制剂已经用于生成亨廷顿病模型。

[0503] 在这种亨廷顿病的丙二酸盐模型中，以适当的剂量、给药间隔和途径对雄性 Sprague-Dawley 大鼠施用治疗。将治疗施用 2 周，然后施用丙二酸盐，然后再经过 1 周，随后处死。将丙二酸盐溶于去离子蒸馏水，用 0.1M HCl 将 pH 调整至 7.4。将 1.5μL3μmol 丙二酸盐以侧面距中线前囟点 2.4mm 和腹侧距硬脑膜 4.5mm 经纹状体内注入左侧纹状体。在 7 天时通过断头术处死动物，并且快速取出脑，并且放入冰冷 0.9％盐水溶液。在脑模具中将脑切成 2mm 间隔的切片。然后将切片后侧放入 2％ 2,3,5- 三苯基四唑鎓氯化物。将切片在室温在黑暗中染色 30 分钟，然后取出，并且放入 4％ pH7.3 低聚甲醛。对每一切片背侧表面上通过青白色染色注意到的损害进行评价。通过与使用相邻尼斯尔染色切片得到的测量值对比验证测量值。

[0504] 用于评价在治疗肌萎缩侧索硬化中的治疗作用的动物模型

[0505] 研发了 SOD1 突变 - 相关 ALS 的鼠模型，其中表达残基 93 上人超氧化物岐化酶 (SOD) 突变甘氨酸 - 丙氨酸的小鼠 (SOD1)。这些 SOD1 小鼠显示 SOD 的不良特性显著增加并且发生与人 ALS 类似的运动神经元变性和功能障碍。SOD1 转基因小鼠在约 3 个月龄时显示后肢虚弱病征并且在 4 个月时死亡。与人 ALS 共同的特征包括星形细胞增生、小胶质细胞增生 (microgliosis)、氧化性应激、环加氧酶 / 前列腺素水平增加，且当疾病发展时，出现显著的运动神经元缺失。对超表达人 Cu/Zn-SOD G93A 突变的转基因小鼠 (B6SJL-TgN(SOD1-G93A)1Gur) 和非转基因 B6/SJL 小鼠及其野生型同窝出生的进行研究。使小

鼠寄居在 12-hr 日 / 光照周期并且（在 45 日龄开始）使其可随意得到试验化合物 - 补充的食物，或者，作为对照组，将规定配方的冷压食物加工成相同的颗粒。如 Gurney 等人在 Science 1994, 264(5166), 1772-1775 中所述在 21 日龄时进行基因分型。将 SOD1 小鼠分组并且施用治疗适当的期限。

[0506] 每日观察小鼠并且每周称重。为了评价健康状况，每周称重小鼠并且检查流泪 / 流涎、眼脸闭合、耳颤搐和瞳孔反应、颈须方向、姿势和翻正反射和总体身体状况评分的改变。在处死时进行通用病理学检查。

[0507] 通过本领域技术人员公知的一种或多种方法可以评价动物的运动协调性能。例如，可以使用神经学评分方法评价运动协调性。在神经学评分中，根据确定的 4- 点量表监测和记录每条肢体的神经学评分 :0- 后肢上的正常反射（动物被举起其尾时张开其后肢）；1- 后肢异常反射（动物被举起其尾时后肢展开重量缺乏）;2- 肢体异常反射和麻痹证据；3- 无反射和完全麻痹 ;和 4- 当置于一侧时在 30 秒内不能恢复平稳或发现死亡。初步终点在于存活，而二次终点在于神经学评分和体重。每周进行 5 天的神经学评分观察和体重称量并且记录。使用适当的统计学方法进行数据分析。转杆试验评价了动物在旋转杆上停留的能力，从而能够评价运动协调性和本体感受敏感性。该仪器是 3cm 直径的自动化旋转杆，例如，12 转 / 分钟。转杆试验测定了小鼠需要多长时间可以维持其在该杆上而不跌落。在任意 120 秒的限制后可以停止本试验。动物应在 120 秒前跌落，记录该行为并且进行另外两次试验。计算 3 次试验的平均时间。根据行走时间的减少指示运动缺陷。

[0508] 在栅格试验中，将小鼠放在位于平面支持物上部的栅格上（长 :37cm，宽 :10.5cm，筛目 :1×1cm$^2$）。计数小鼠将其爪通过栅格放置的次数并且用作运动协调性的测量值。悬挂试验评价动物紧握不放金属丝的能力。该仪器是高于桌面 40cm 的水平拉伸的金属丝。动物通过其前爪拉住金属丝。在 3 次连续试验期间记录动物用其后爪抓住该丝所需的时间（最长 60 秒）。

[0509] 电生理测量值 (EMG) 也可以用于评价运动活动情况。使用肌电描记仪器进行肌电图记录。在 EMG 监测期间，麻醉动物。测量的参数是化合物复合肌活动电位 (CMAP) 的振幅和潜伏期。在刺激坐骨神经后测定腓肠肌中的 CMAP。将参比电极插入跟腱附近并且将活动针头置于尾底部。将磨光的针头插在小鼠腰部上。用单一 0.2msec 脉冲在超极限强度 (12.9mA) 刺激坐骨神经。测定振幅 (mV) 和响应的潜伏期 (ms)。振幅表示活动运动单位的数量，而远端潜伏期反映出运动神经传导速度。本发明的组合的作用也可以使用生物标记分析评价。为了评价运动受损发作期间 SOD1 小鼠中的蛋白质生物标记调节，将腰脊髓样品（蛋白质提取物）施用于具有可变表面化学 / 生物化学特性的蛋白质阵列分析 (ProteinChip Arrays) 并且例如通过表面增强的激光解析电离飞行时间质谱进行分析。然后使用整合蛋白质量特性分析方法，将数据用于比较不同治疗组的蛋白质表达特性。可以使用适合的统计学方法进行分析。

[0510] 用于评价在重症肌无力中的治疗作用的动物模型

[0511] 根据 International Immunology, 第 10 卷，第 9 期，第 1359-1365 页对 EAMG 进行诱导和临床评估

[0512] 沿双肩和背给 B6 和 μMT 小鼠进行皮下免疫接种总体积为 100μL 的在 CFA 中的 20μg AChR 并且在月间隔在双肩和双腿上的 4 个部位皮下加强注射 2 次在 CFA 中的 20μg

AChR。以双盲方式隔天观察小鼠的EAMG的肌肉虚弱特征病征。将临床症状在0-3(4)之间分级:0,无确定的肌肉虚弱;1,在静止时正常强度,但在地板上使用下颚的力量虚弱并且在20次连续的爪紧握组成的练习后不能抬起头;2,为1级和在静止时虚弱;和3,垂死,脱水和麻痹。通过注射溴新斯的明和硫酸阿托品证实临床EAMG。将小鼠分组并且施用治疗适当的期限,然后测试。

[0513] 用于评价在脱发中的治疗作用的动物模型

[0514] Dundee试验性秃头大鼠(DEBR)和C3H/HeJ小鼠是充分建立的斑秃动物模型并且可以用于研究该病的遗传方面、发病机制和疗法。在C3H/HeJ小鼠中,可以通过试验方式诱导斑秃,通过下列步骤进行:将来自受侵害小鼠的损害皮肤移植入组织相容性接受者,其提供研究不同因素对发生该病的影响的可能性。将小鼠分组并且施用治疗适当的期限,然后测试。

[0515] 通用试验方案

[0516] 在如下动物模型中的治疗由溶于或分散于0.5%羟丙基甲基纤维素(HPMC)K4M/0.25% Tween 20的富马酸二甲酯和溶于或分散于kleptose(在蒸馏水中)的吡格列酮组成。通过每日口服管饲1次或2次施用治疗。治疗组通常如下:适合的介质;富马酸二甲酯;吡格列酮;或富马酸二甲酯和吡格列酮的组合。本发明的该组合导致比介质和相应的单独的活性剂对治疗的响应改善。

[0517] 用于评价PPARγ激动剂和Nrf2激活剂的组合在治疗多发性硬化中的治疗作用的EAE动物模型

[0518] 排序7-8周龄的雌性C57BL/6小鼠(Janvier France或Charles River)并且在适应期后9-11周使用。使用>95%纯的合成髓磷脂少突胶质细胞糖蛋白肽35-55(MOG35-55)、Met-Glu-Val-Gly-Trp-Tyr-Arg-Ser-Pro-Phe-Ser-Arg-Val-Val-His-Leu-Tyr-Arg-Asn-Gly-Lys,Ref SCI 272,NeoMPS)主动诱导试验性自身免疫脑脊髓炎(EAE)。麻醉每只小鼠并且使其接受皮下注入腰部的100μL完全弗氏佐剂(Ref263810,Difco)乳剂,其包含200μg MOG35-55和250μg干燥且灭活的结核分支杆菌H37 Ra,Ref 231141 Difco)。该乳剂通过使用两支通过Luer锁紧接口连接的注射器的注射器法制备。小鼠还接受腹膜内注射用200μL PBS稀释的300ng百日咳毒素(Ref BML-G100,Enzo Lifescience)。48小时后重复百日咳毒素注射。每日称重小鼠并且检查EAE临床病征。提供随意的取食和饮水。

[0519] 临床评价

[0520] 每日评价动物的神经性缺陷(临床评分)和体重。临床评分量表如下:0=无病征;0.5=远端跛行尾;1=完全尾麻痹;1.5=后肢虚弱;2=单侧部分后肢麻痹;2.5=双侧部分后肢麻痹;3=完全双侧后肢麻痹;3.5=前肢虚弱和完全双侧后肢麻痹;4=四肢麻痹/垂死;5=死于EAE。

[0521] 结果:使用富马酸二甲酯与盐酸盐形式的吡格列酮的组合的治疗评价

[0522] 根据方法部分中所述的EAE方案给40只雌性8-9周的C57BL/6小鼠免疫接种。将小鼠分成4个不同的治疗组(n=10)并且接受用HPMC0.5%/Tween20 0.25%(富马酸二甲酯的介质)b.i.d.+Kleptose 20%(吡格列酮的介质)q.d.、富马酸二甲酯60mg/kg b.i.d.+Kleptose 20% q.d.、吡格列酮10mg/kg q.d.+HPMC 0.5%/Tween20 0.25% b.i.d.或富马酸二甲酯60mg/kg b.i.d+吡格列酮10mg/kg q.d.治疗。为简便起见,在图

例中未提及介质治疗并且将上述组分别称作对照组、富马酸二甲酯 60mg/kg bid、吡格列酮 10mg/kg q.d 或富马酸二甲酯 + 吡格列酮。药物治疗从免疫接种后第 0 天开始。如图 1A 中所示，给 C57BL/6 小鼠免疫接种 MOG35-55 诱导运动失能，其临床病征在免疫接种后第 9 天左右增加。

[0523] 组合（富马酸二甲酯 + 吡格列酮）治疗的效果显著地降低了每日平均临床评分（图 1A）。组合效力与单个治疗的效果相比更为显著并且具有统计学差异。抑制炎症诱导的恶病质作为治疗有益性的可靠标记起作用。组合治疗（富马酸二甲酯 + 吡格列酮）的疗法比介质或单一药物治疗显著地改善了体重（图 1B）。

[0524] 在图 2 中分析了药物治疗对疾病发生率的作用。将疾病发展定义为每只小鼠首次显示临床评分≥ 1 的时间点。图 2A 描述了 Kaplan Meier 分析，其显示对照组小鼠从第 9 天时开始发生 EAE，并且在免疫接种后第 14 天完全易感。使用富马酸二甲酯 + 吡格列酮的组合治疗移动了 EAE 发作曲线。不是所有用药物组合治疗的动物直到本试验终止为止即免疫接种后第 22 天发生疾病病征。组合治疗的效果不仅比对照组、而且比单独施用药物的各组具有统计学差异。图 2B 是相同数据的不同表现。平均而言，用介质、单独的富马酸二甲酯或吡格列酮治疗的小鼠在免疫接种后大约第 12-13 天时未明显地显示首次临床病征，而在组合组中，平均 EAE 发作是在免疫接种后大约第 17 天时。组合治疗的作用比其它治疗组再次显示了统计学差异并且更为有效。这种数据显示组合治疗产生协同治疗作用，这一结果在单个治疗中未观察到。

[0525] 胃肠道改变包括出血是已知的富马酸二甲酯治疗的副作用。组合治疗和单独的富马酸二甲酯治疗导致类似的胃巨大速度 (macrovilosity) 增生。使用组合治疗无症状恶化。使用富马酸二甲酯、吡格列酮或其介质长期治疗 22 天的小鼠胃的有代表性的影像如图 3 中所示，其显示了一些观察结果。重要的是，在上述段落中讨论的协同作用效力与胃肠道不良反应事件增加无关。

[0526] 附图简述

[0527] 图 1：使用富马酸二甲酯 + 吡格列酮的组合治疗比作为独立治疗的各单个药物或使用介质治疗在平均临床评分方面且还在与疾病相关的体重改变方面显著更为有效。在免疫接种后第 0 天开始使用介质、富马酸二甲酯、吡格列酮或两种药物组合治疗的 MOG35-55 小鼠的平均临床评分 (A) 和体重改变百分比 (B)。Kruskal-Wallis（非参数 ANOVA）与 Dunn 多重检验校正应用于 A 和 B 中的 Student's t- 检验。水平条代表 $P<0.05$，其中 λ 比较组合治疗与介质；ψ 组合治疗与富马酸二甲酯；和φ组合治疗与吡格列酮。

[0528] 图 2：使用富马酸二甲酯 + 吡格列酮的组合治疗导致比作为独立治疗的各单个药物或使用介质治疗在疾病发作方面延迟。在免疫接种后第 0 天开始使用介质、富马酸二甲酯、吡格列酮或两种药物组合治疗的 MOG35-55 小鼠的疾病发生率曲线 (A) 和疾病发作的平均天数 (B) 的 Kaplan Meier 分析。将疾病发作定义为小鼠首次显示临床评分≥ 1 的天数。Gehan-Breslow-Wilcoxon 检验应用于 A 且 Kruskal-Wallis、随后 Dunn 多重检验校正应用于 B。水平条代表 $P<0.05$，其中 λ 比较组合治疗与介质；ψ 组合治疗与富马酸二甲酯；和φ组合治疗与吡格列酮。

[0529] 图 3：使用富马酸二甲酯、但不使用吡格列酮或介质长期治疗的小鼠胃的目视外观改变。给 40 只 C57BL/6 小鼠免疫接种 MOG35-55 并且通过使用 HPMC 0.5％ /Tween20

0.25％ b.i.d.+Kleptose 20％ q.d.(A，图 3A)、富马酸二甲酯 60mg/kg b.i.d.+Kleptose 20％ q.d(B)、吡格列酮 10mg/kg q.d.+HPMC 0.5％ /Tween20 0.25％ b.i.d.(C，图 C) 或富马酸二甲酯 60mg/kg b.i.d+ 吡格列酮 10mg/kg q.d.(D，图 3D) 的组合口服管饲治疗 22 天。给另外 1 组 5 只小鼠假拟免疫接种（不含 MOG35-55 的乳剂）并且用 HPMC0.5％ /Tween20 0.25％ b.i.d.+Kleptose 20％ q.d.(E，图 3E) 治疗。在本试验的至始至终期间，因人道终点或因疾病死亡的原因处死 3 只小鼠。在戊巴比妥最终麻醉下对其余 42 只动物实施安乐死，切下心脏右心房并且给小鼠左心室灌注 4％低聚甲醛。通过横切食道近端节段剖离每只小鼠的胃，然后通过纵切口经连接其余的十二指肠伸长部分和胃底的最长可能的轴切开十二指肠。用磷酸缓冲盐水洗涤每一切片并且开放固定。所示的影像是来自每个组的 1 只有代表性的小鼠。注意未暴露于富马酸二甲酯 (A、C、E；分别为图 3A、3C、3E) 的所有组的小鼠的胃的外观均正常，且分别用作为独立的富马酸二甲酯或与吡格列酮组合治疗的 B 和 D 组的胃显然以巨大速率呈病理性的增加，导致它们增厚和有皱纹的外观（分别为图 3B、3D)。

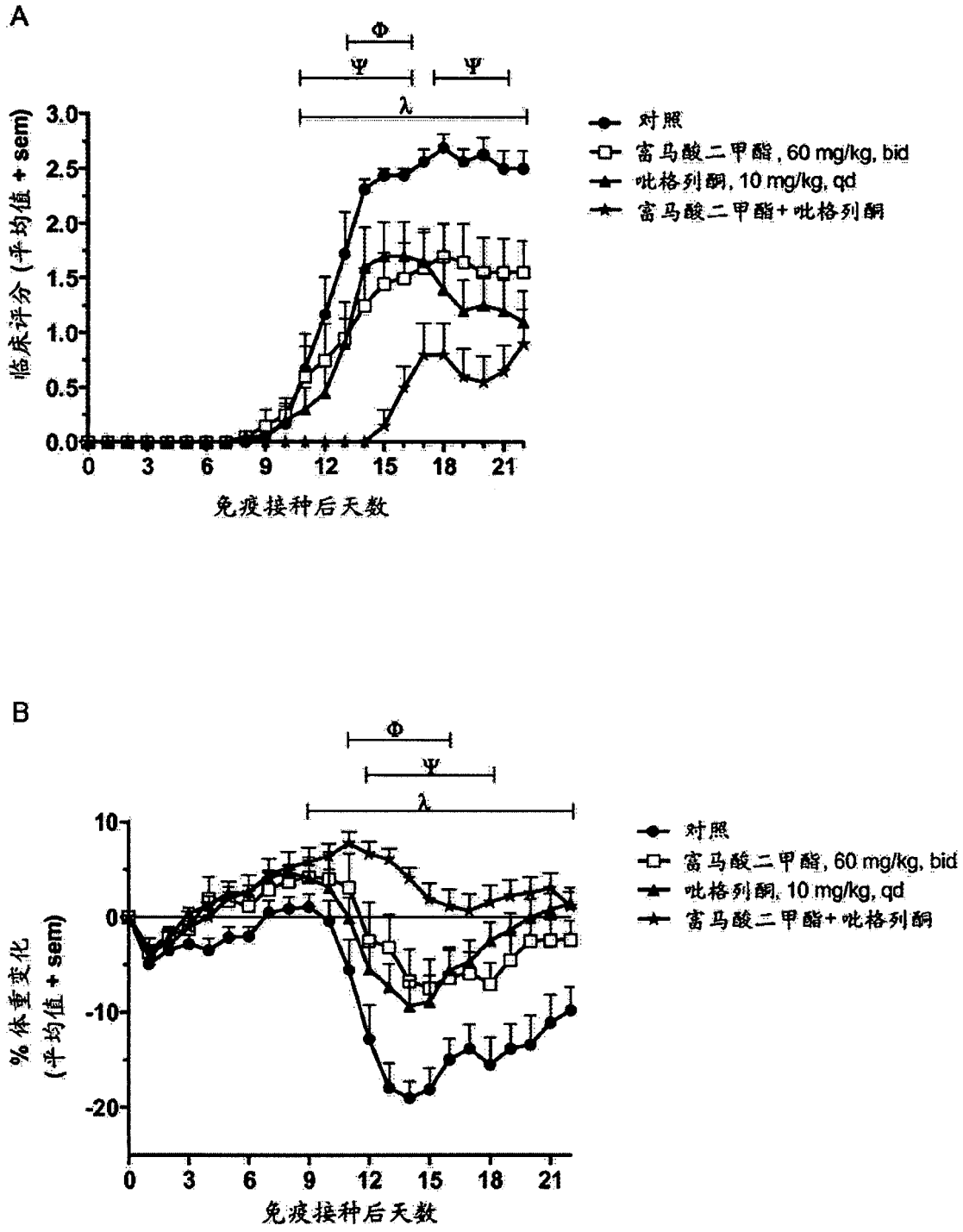

A
Φ
Ψ
Ψ
λ
临床评分 (平均值 + sem)
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0 3 6 9 12 15 18 21
免疫接种后天数
对照
富马酸二甲酯, 60 mg/kg, bid
吡格列酮, 10 mg/kg, qd
富马酸二甲酯+吡格列酮
B
Φ
Ψ
λ
% 体重变化
(平均值 + sem)
10
0
-10
-20
0 3 6 9 12 15 18 21
免疫接种后天数
对照
富马酸二甲酯, 60 mg/kg, bid
吡格列酮, 10 mg/kg, qd
富马酸二甲酯+吡格列酮

图 1

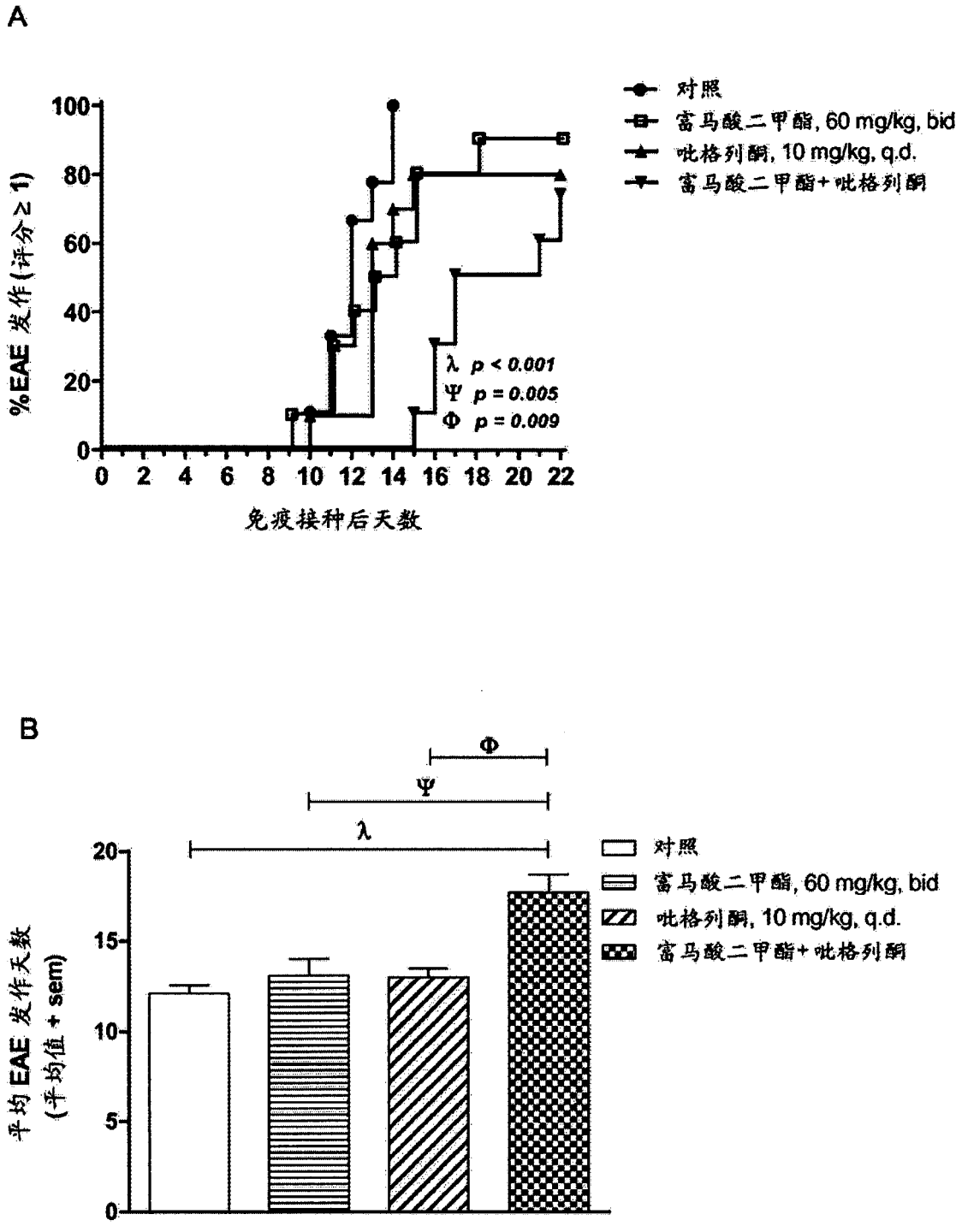

A
%EAE 发作(评分≥1)
100
80
60
40
20
0
0 2 4 6 8 10 12 14 16 18 20 22
免疫接种后天数
λ p < 0.001
Ψ p = 0.005
Φ p = 0.009
对照
富马酸二甲酯, 60 mg/kg, bid
吡格列酮, 10 mg/kg, q.d.
富马酸二甲酯+吡格列酮
B
Φ
Ψ
λ
平均 EAE 发作天数
(平均值 + sem)
20
15
10
5
0
对照
富马酸二甲酯, 60 mg/kg, bid
吡格列酮, 10 mg/kg, q.d.
富马酸二甲酯+吡格列酮

图 2


图 3A

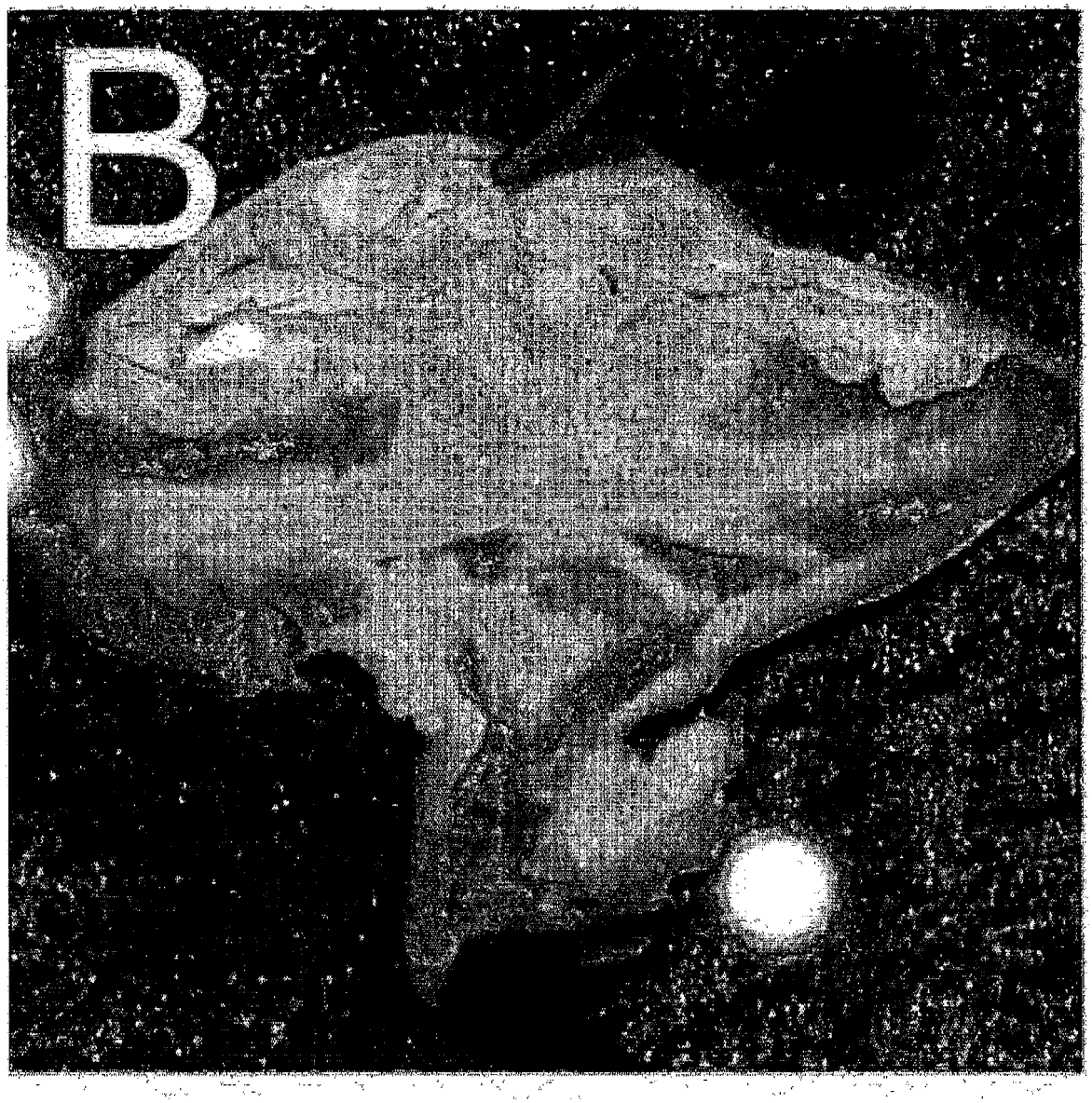



图 3B

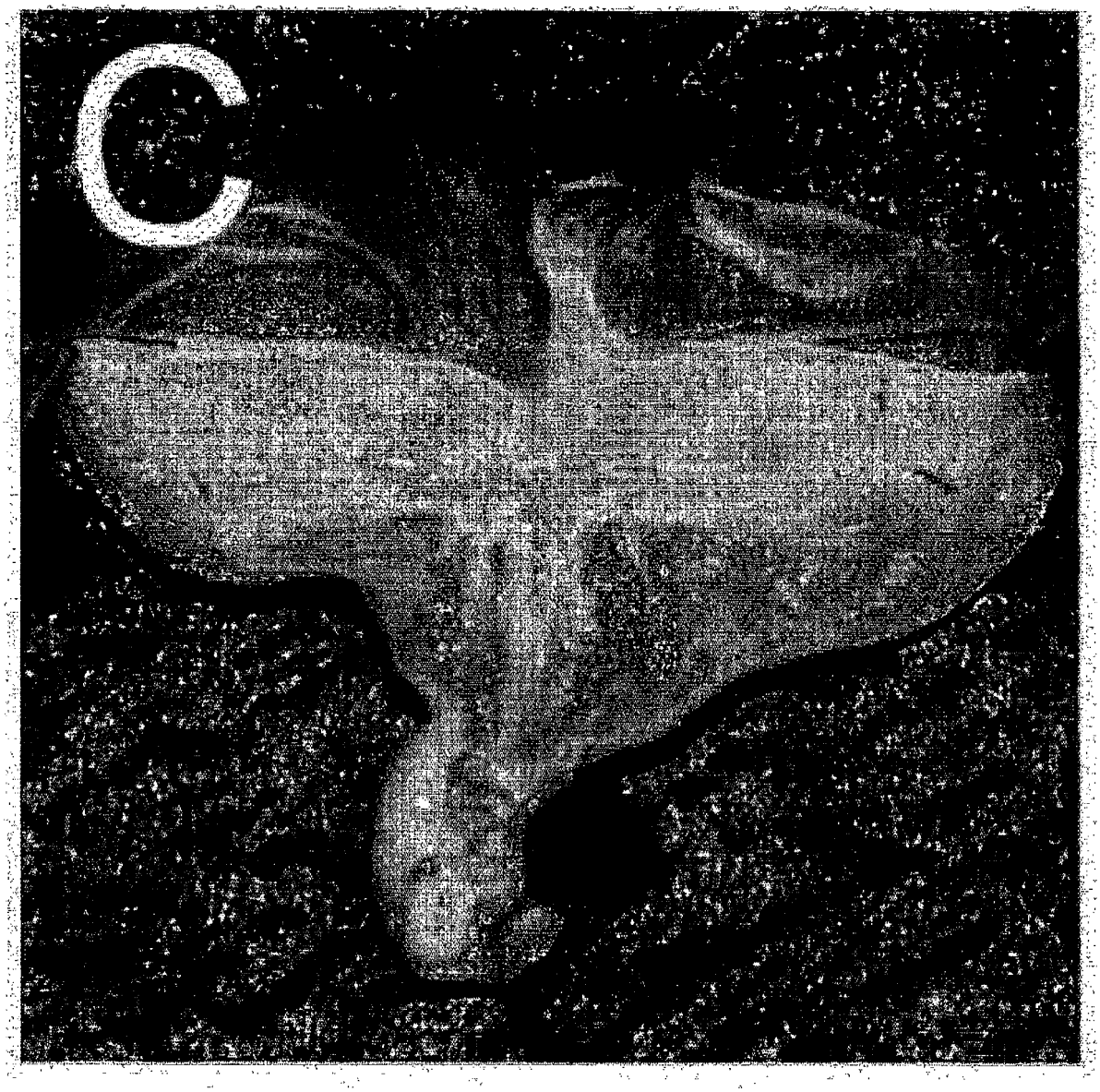



图 3C

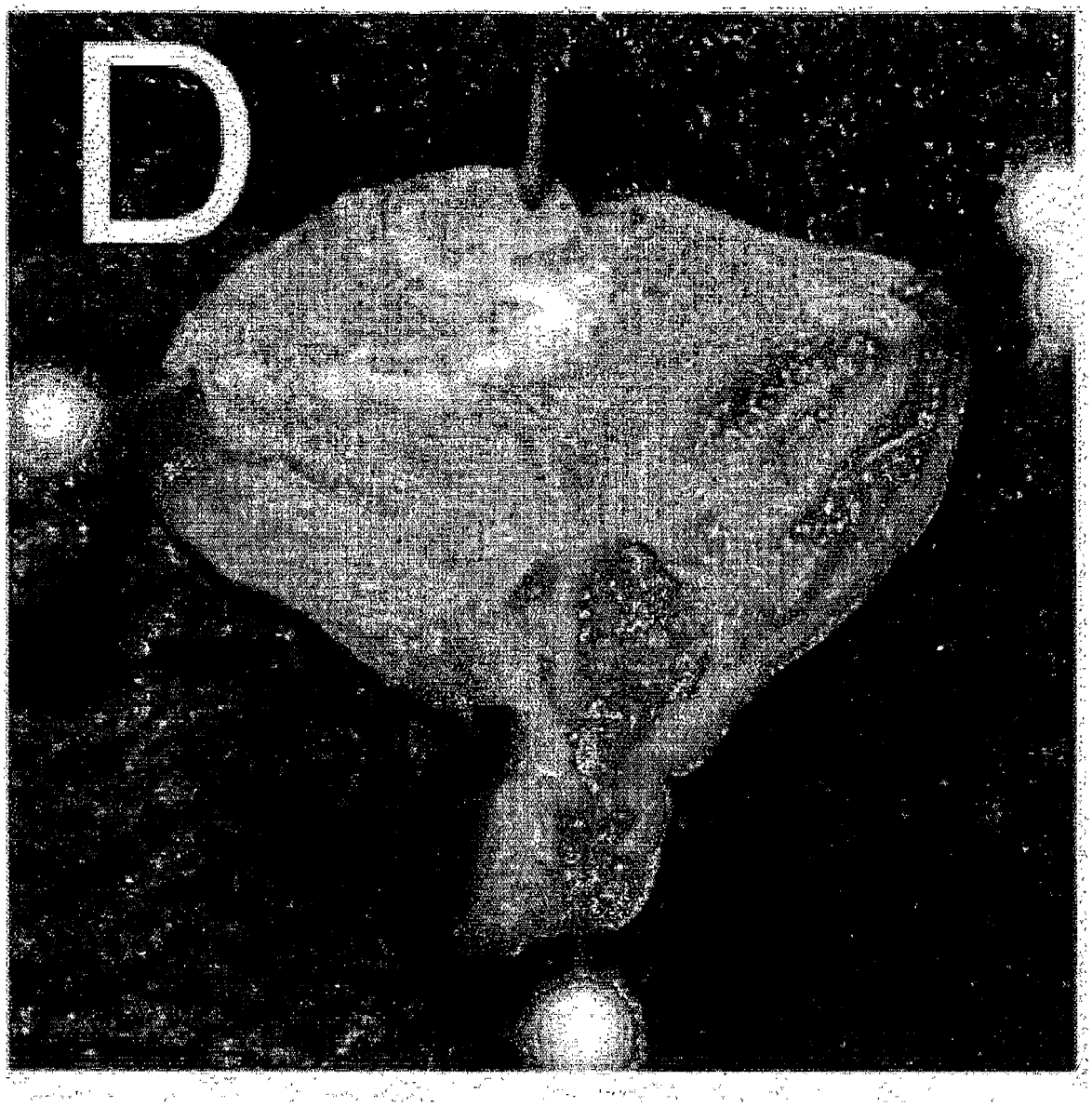



图 3D

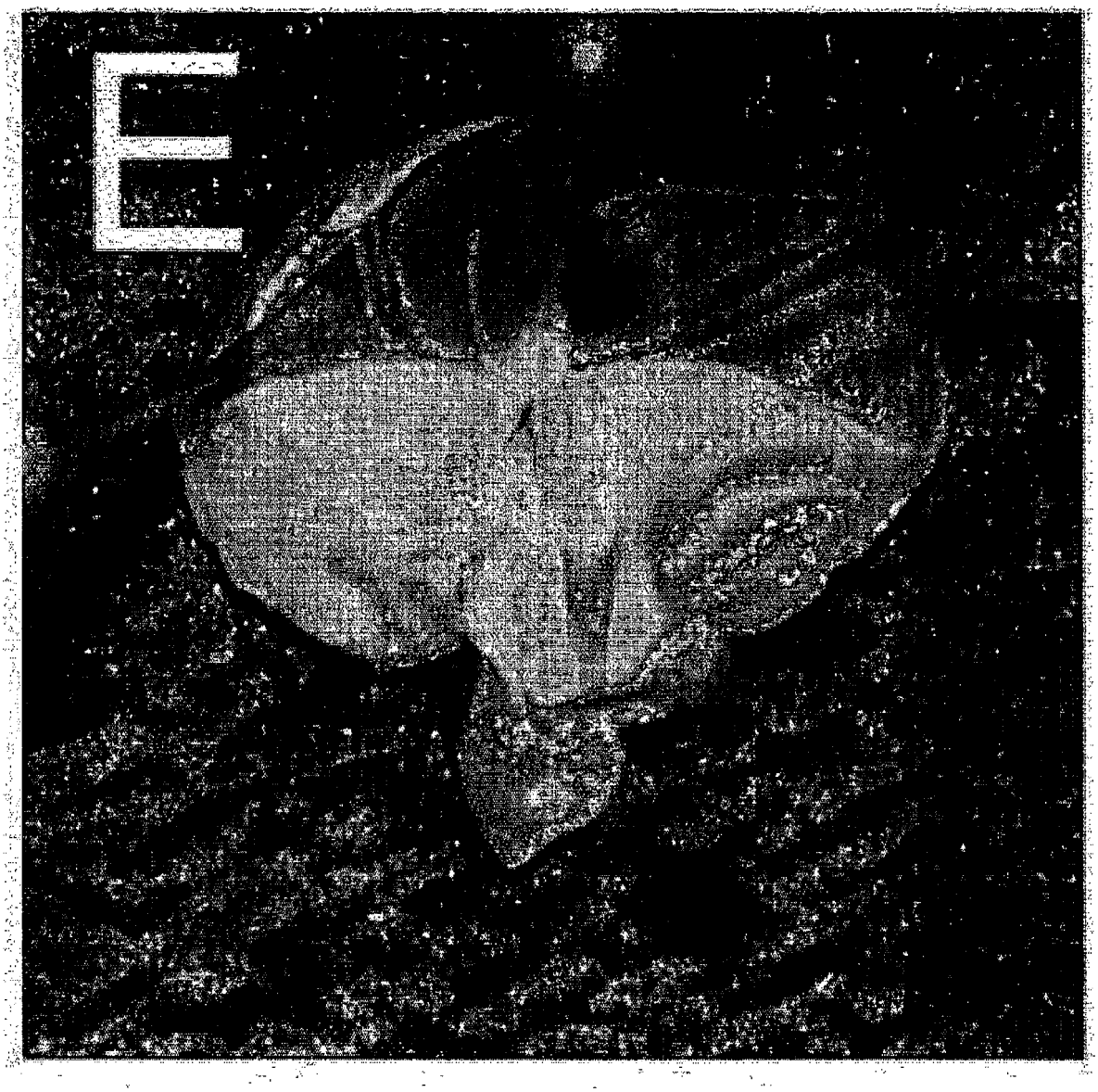



图 3E

# Abstract

The invention relates to pharmaceutical compositions comprising PPAR agonists and Nrf2 activators and methods of using combinations of PPAR agonists and Nrf2 activators for treating diseases such as psoriasis, asthma, multiple sclerosis, inflammatory bowel disease, and arthritis.