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(54) **Pharmaceutical combination of an aldosterone synthase inhibitor and a glucocorticoid receptor antagonist or a cortisol synthesis inhibitor or a corticotropin releasing factor antagonist**

(57) The invention relates to a pharmaceutical combination comprising (a) an aldosterone synthase inhibitor or a pharmaceutically acceptable salt thereof, and (b) a glucocorticoid receptor antagonist or a cortisol synthesis inhibitor or a cortisol re-synthesis inhibitor or a corticotrophin-releasing hormone receptor antagonist or combinations thereof or in each case a pharmaceutically acceptable salt thereof. Said composition is useful for the manufacture of a medicament, in particular for the manufacture of a medicament for the prevention of, delay of progression of treatment of a disease or condition characterized by the metabolic syndrome.

EP 1 886 695 A1

Description

FIELD OF THE INVENTION

[0001] The invention relates to pharmaceutical compositions and methods for achieving a therapeutic effect including, but not limited to, the treatment of the metabolic syndrome, including obesity, insulin resistance, hypertension, dyslipidemia and atherosclerosis, in an animal, preferably a mammal including a human subject or a companion animal, using (i) an aldosterone synthase inhibitor or a pharmaceutically acceptable salt thereof in combination with (ii) a glucocorticoid receptor antagonist or a pharmaceutically acceptable salt thereof and/or (iii) a cortisol synthesis inhibitor or a pharmaceutically acceptable salt thereof, (iv) and/or a cortisol re-synthesis inhibitor or a pharmaceutically acceptable salt thereof, (v) and/or a corticotrophin-releasing hormone receptor antagonist or a pharmaceutically acceptable salt thereof and (vi) a pharmaceutically acceptable carrier.

BACKGROUND OF THE INVENTION

[0002] An aggregate of signs and symptoms that constitute together the picture of a disease is commonly named a syndrome. The metabolic syndrome is often defined as a state of metabolic dysregulation characterized by insulin resistance and a predisposition to type 2 diabetes, central and visceral obesity, hypertension and dyslipidemia. Thus, the metabolic syndrome is associated with a marked increased incidence of coronary, cerebral and peripheral artery disease. A combination of overnutrition, physical inactivity, endocrine imbalance as well as genetic and environmental factors interacts to produce a state of metabolic dysregulation that leads to obesity, insulin resistance and hypertension.

[0003] An endocrine imbalance underlying the state of metabolic dysregulation can be mediated by the adrenal gland steroid hormones cortisol and aldosterone. Disorders of the adrenal cortex and medulla can result in glucose intolerance or overt diabetes as well as in water retention and hypertension. Cushing's syndrome, characterized by excessive secretion of glucocorticoids, impairs glucose tolerance primarily by causing insulin resistance and enhancing hepatic glucose production. On the other hand, phaeochromocytoma and hyperaldosteronism, via the respective actions of catecholamines and hypokalemia on the pancreatic beta-cell, impair glucose tolerance primarily by inhibiting insulin release. In addition, plasma aldosterone levels determine vascular stiffness, regulate the salt balance and thus blood pressure.

[0004] The primary biological function of the glucocorticoid cortisol is to regulate the production and the availability of carbohydrates for the brain and other metabolically active tissues. Increased cortisol production and secretion is a normal physiological response to stress and leads to the essential mobilization of fats, proteins and carbohydrates to meet an increased demand for energy by the body. Glucocorticoids are potent antagonists of insulin and when in excess can promote insulin resistance and obesity. Chronically excessive cortisol release describes the condition of Cushing's syndrome. Cushing syndrome may be produced on one hand by hypersynthesis of cortisol, which may be generated by an adrenocortical tumor, or be produced on the other hand as the consequence of excessive stimulation of the adrenal cortex by adrenocorticotropic hormone (ACTH) whose secretion is mainly controlled by the hypothalamic corticotrophin-releasing hormone (CRH). The first form is referred to as primary hypercortisolism, and the second form as secondary hypercortisolism. An excessive and persistent cortisol secretion may also accompany a stress response, which may lead to depression, hyperglycemia and to suppression of the immune system. Thus, metabolic and Cushing's syndromes share many features, suggesting that abnormalities of glucocorticoid hormone action may contribute to the pathogenesis by promoting lipolysis and triglyceride storage, inducing gluconeogenesis, hypertension and fat cell differentiation.

[0005] Aldosterone regulates electrolyte excretion and intravascular volume mainly through its effects on the distal tubules and cortical collecting ducts of the kidney by increasing sodium (Na+) reabsorption and potassium (K+) excretion. The state of excessive aldosterone secretion may lead to sodium and water retention, high blood pressure, hypokalemia, alkalosis, muscle weakness, polyuria, edemas, vasculitits, increased collagen formation, vascular remodeling, tissue fibrosis and endothelial dysfunction. Recent clinical evaluations indicate that primary hyperaldosteronism is common in subjects with resistant hypertension. Resistant hypertension has been conventionally defined as persistently elevated blood pressure in spite of use of three or more antihypertensive agents of different classes, one of which is a diuretic.

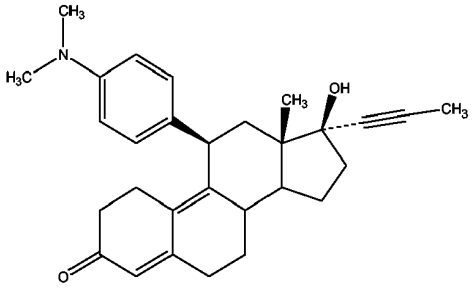
[0006] Cortisol and aldosterone exert most of their biological effects by binding to their respective intracellular nuclear receptors. In the hormone-bound state, these receptors specifically bind to and modulate the activity of target gene promoters thus eleciting hormone specific genomic responses. The glucocorticoid receptor is ubiquitously expressed and regulates, either directly or indirectly, target genes involved in glucose homeostasis and cell differentiation. The mineralcorticoid receptor is found in epithelial tissues (e.g. kidney, gastrointestinal tract, salivary and sweat glands) as well as in non-epithelial cells (heart, hippocampus, vasculature, mammary gland or leukocytes) and regulates genes involved in salt and tissue homeostasis. Recently, also non-genomic responses to these steroids have been postulated.

[0007] Cortisol is a steroidal hormone which is synthesized almost exclusively in the zona fasciculata of the adrenal cortex by the cytochrome P450 enzyme 11-β-hydroxylase (CYP11B1). Cortisol production is controlled by ACTH and

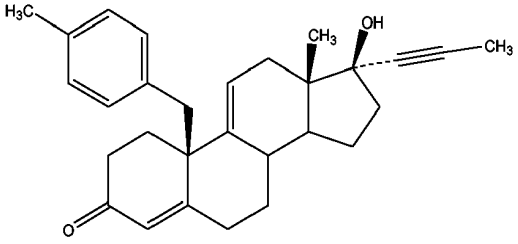
a negative feedback loop via the hypothalamic-pituitary-adrenal axis. The main regulators of intracellular glucocorticoid levels are 11β-hydroxysteroid dehydrogenase (HSD) enzymes. 11β-HSD type 1 is an NADP(H)-dependent enzyme that acts primarily as a reductase, converting the inactive 11-keto metabolites cortisone (in humans) or 11-dehydrocorticosterone (in rodents) into the active glucocorticoids cortisol or corticosterone, respectively. 11β-HSD type 1 is expressed in most tissue types and potentiates the action of endogenous glucocortocids by increasing their local concentration due to re-synthesis. 11β-HSD type 2 is an NAD(H)-dependent enzyme that catalyzes the reverse reaction, oxidizing active glucocorticoids to their inactive 11-keto forms. Although 11β-HSD type 1 is widely expressed, 11β-HSD type 2 expression is limited to tissues that express the mineralocorticoid receptor. By inactivating cortisol, 11β-HSD type 2 prevents it from binding to the mineralcorticoid receptor, thus conferring aldosterone specificity on the receptor.

[0008] Against this background, it has been reasoned that subtle abnormalities of steroid biosynthesis or metabolism may contribute to the pathophysiology of the metabolic syndrome. Four pharmacological strategies have been proposed to block excessive cortisol actions: A) the administration of a glucocorticoid receptor antagonist; B) the application of a cortisol synthesis inhibitor, C) the development of a cortisol re-synthesis inhibitor by blocking 11β-hydroxysteroid dehydrogenase type I and D) the use of a corticotrophin-releasing hormone receptor antagonist.

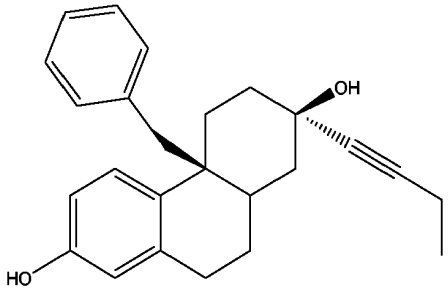
A) Steroidal glucocorticoid receptor antagonist had been derived from the glucocorticoid scaffold. For instance, RU 38486 (mifepristone, 11 β-(4-dimethylaminophenyl)-17β-hydroxy-17α-(1-propylynyl)estra-4,9-dien-3-one), formula (I) is described as an unselective glucocorticoid and progesterone receptor antagonist whereas the derivative RU-43044, formula (II) is reported as a selective glucocorticoid receptor antagonist. Selective, nonsteroidal glucocorticoid receptor antagonists have been derived from RU 38486 and for instance described by Morgan et al. (2002) in J. Med. Chem. 45, 2417-2424, as CP-394531, formula (III) and CP-409069, formula (IV) Other nonsteroidal glucocorticoid receptor antagonist compounds are described for example in following patents and patent applications: US 6,380,223 B1, US 6,436,986 B1, US 6,468,975 B1, US 2002/0147336 A1, US 2002/0107235 A1, US 2004/0014741 A1, US 2004/0176595 A1, WO 2004/009017 A2, WO 2004/110385 A2, WO 2004/111015 A1, US 2004/0266758 A1, US 2004/0266831 A1, WO 2001/16128 A1.



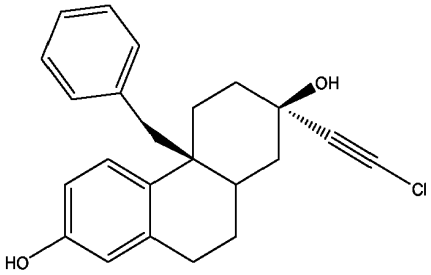
RU-38486 (I)



RU-43044 (II)

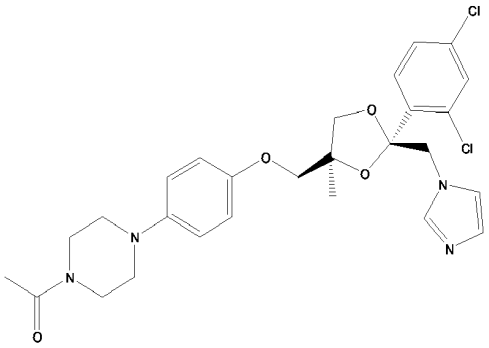


CP-409069 (III)

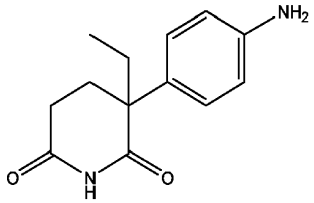


CP-394531 (IV)

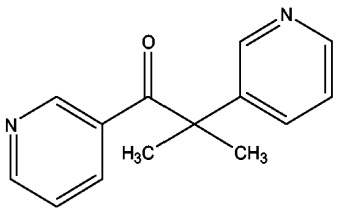
B) Cortisol synthesis inhibitory properties have been ascribed to several drugs. For instance, ketoconazol, formula (V) was initially developed as an anti-fungal therapy. The drug inhibits unselectively the synthesis corticosteroids and at higher doses the synthesis of testosterone as observed by Pont et al., (1982) Ann. Intern. Med 97, 370-372; Engelhardt et al. (1983) Klin. Wochenschr. 61, 373-375; Van Tyle (1984) Pharmacotherapy 4, 343-373. Recently, the use of ketoconazole in cardiovascular and metabolic diseases has been claimed by e.g. US 6,274582 B1, US 6,642,236 B1, US 2006/0014758 A1. Aminogluthetimide, formula (VI) inhibits side-chain cleavage to produce medical adrenalectomy and furthermore several steroidogenic hydroxylation steps as described by Schteingart and Conn (1967) J. Clin. Endocrinol. Metab. 27, 1657-1666; Wipple et al. Steroids (1981) 37, 673-679; Lambert et al. (1984) Mol. Cell. Endocrinol 37, 115-120;. Therefore, aminogluthetimide induces adrenal insufficiency of both, glucocorticoids and mineralocorticoids in patients. Metyrapone, formula (VII) is an unselective 11 β-hydroxylase inhibitor and also used as a diagnostic tool for adrenal function. Trilostane, formula (VIII) is a steroidal 3β-hydroxysteroid dehydrogenase / delta 5-4 isomerase inhibitor in the adrenal cortex. The administration of trilostane results in the inhibition of the synthesis of both, mineralocorticoids and glucocorticods. A similar profile had been observed with CGS-16949A as noted by Lamberts et al. (1989) J. Clin. Endocrinol. Metab. 69, 896-901. Other drugs shown to inhibited cortisol output such as etomidate, epostane, thiopentone, ketotrilostane were described by Lambert et al. (1986) Ann. Clin. Biochem. 23, 225-229. Finally, mitotane, formula (IX) is a chemotherapeutic agent which is cytotoxic to the adrenal gland as studied by Touitou et al. (1979) J. Endocrinol. 82, 87-94. Several other analogous compounds were identified as 11-β-hydroxylase inhibitors such as 4-phenylimidazole, 1-benzylimidazole, 17-β-ureido-1,4-androstadien-3-one, SU-8000, 4-methyl-aminoglutethimide and 20-α-hydroxycholesterol as diescribed by Whipple et al. (1981) Steroids 37, 673-679. Recently, Ulmschneider et al. (2005) J. Med. Chem. 48, 1563-1575, described selective 11-β-hydroxylase (CYP11 B1) inhibitors that are derived from formula (X).



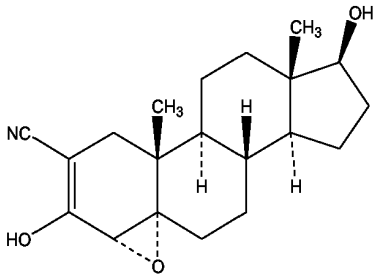
Ketoconazole (V)



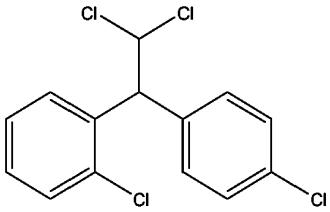
Aminogluthetimide (VI)



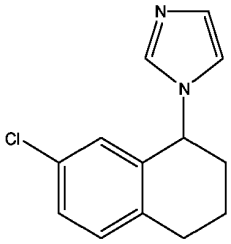
Metyrapone (VII)



Trilostane (VIII)



Mitotane (IX)



HB6 (X)

C) The selective inhibition of cortisol re-synthesis by blockade of 11β-hydroxysteroid dehydrogenase type I to prevent the conversion of inactive glucocorticoid metabolites into active glucocorticoids in metabolically active tissues is a novel approach that is being investigated. The potential to inhibit 11β-hydroxysteroid dehydrogenase type I has been shown with liquorice extracts, glycyrrhetinic acid and carbenoxolone, formula (XI) as described by Andrews et al. (2003) J. Clin. Endocrinol. Metab. 88, 285-291; Li eta l. (2004) 53, 600-606. Chenodeoxycholic acid and metyrapone have also been described as enzyme inhibitors by Morris et al. (2004) 53, 811-816; Sampath-Kumar et al. (1997) 62, 195-199. Other structures such as perhydoquinolylbenzamides and flavanones have been characterized as 11β-hydroxysteroid dehydrogenase type I inhibitors by Coppola et al. (2005) Metabolism 48, 6696-6712 and Schweizer at al. (2003) Mol. Cell. Endocrinol. 212, 41-49. Compound 544, formula (XII) is described in the literature as a potent and enzyme selective inhibitor.

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