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(54) **COMBINATION OF ORGANIC COMPOUNDS**

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(57) **ABSTRACT**

The invention relates to a combination, such as a combined preparation or a pharmaceutical composition, respectively comprising

a renin inhibitor, or a pharmaceutically acceptable salt thereof, and

at least one therapeutic agent selected from the group consisting of

(a) a specific anti-dyslipidemic agent and

(b) a specific anti-obesity agent

or, in each case, a pharmaceutically acceptable salt thereof.

COMBINATION OF ORGANIC COMPOUNDS

BACKGROUND AND RELATED PRIOR ART

[0001] Disorders of lipid metabolism, or dyslipidemias, include various conditions characterized by abnormal concentrations of one or more lipids (i.e. cholesterol and triglycerides), and/or apolipoproteins (i.e., apolipoproteins A, B. C and E), and/or lipoproteins (i.e., the macromolecular complexes formed by the lipid and the apolipoprotein that allow lipids to circulate in blood, such as LDL, VLDL and IDL).

[0002] Hyperlipidemia is associated with abnormally high levels of lipids, LDL and VLDL cholesterol, and/or triglycerides. Cholesterol is mostly carried in Low Density Lipoproteins (LDL), and this component is commonly known as the "bad" cholesterol because it has been shown that elevations in LDL—cholesterol correlate closely to the risk of coronary heart disease. A smaller component of cholesterol is carried in the High Density Lipoproteins and is commonly known as the "good" cholesterol. In fact, it is known that the primary function of HDL is to accept cholesterol deposited in the arterial wall and to transport it back to the liver for disposal through the intestine. Although it is desirable to lower elevated levels of LDL cholesterol, it is also desirable to increase levels of HDL cholesterol. Generally, it has been found that increased levels of HDL are associated with lower risk for coronary heart disease (CW)). See, for example, Gordon, et al., Am. J. Med., 62, 707-714 (1977); Stampfer, et al., N. England J. Med., 325, 373 381 (1991); and Kannel, et al., Ann. Internal Med., 90, 85-91 (1979). An example of an HDL raising agent is nicotinic acid, a drug with limited utility because doses that achieve HDL raising are associated with undesirable effects, such as flushing.

[0003] Dyslipidemias were originally classified by Fredrickson according to the combination of alterations mentioned above. The Fredrickson classification includes 6 phenotypes (i.e., I, IIa, IIb, III, IV and V) with the most common being the isolated hypercholesterolemia (or type IIa) which is usually accompained by elevated concentrations of total and LDL cholesterol. The initial treatment for hypercholesterolemia is often aimed at avoiding risk factors such as obesity, and at modifying the diet to one low in fat and cholesterol, coupled with appropriate physical exercise, followed by drug therapy when LDL-lowering goals are not met by diet and exercise alone.

[0004] A second common form of dyslipidemia is the mixed or combined hyperlipidemia or type IIb and III of the Fredrickson classification. This dyslipidemia is often prevalent in patients with type 2 diabetes, obesity and metabolic syndrome. In this dyslipidemia there are modest elevations of LDL-cholesterol, accompanied by more pronounced elevations of small dense LDL-cholesterol particles, VLDL and/or IDL (i.e., triglyceride rich lipoproteins), and total triglycerides. In addition, concentrations of HDL are often low.

[0005] The risk of atherosclerosis and coronary artery or carotid artery disease, and therefore the risk of having a heart attack or stroke, increases as the total cholesterol level increases. Atherosclerosis refers to a disease in which the wall of an artery becomes thicker and less elastic. In atherosclerosis, fatty material accumulates under the inner lining of the arterial wall. Atherosclerosis can affect the arteries of the brain, heart, kidneys, other vital organs, and the arms and legs. When atherosclerosis develops in the arteries that supply heart attack may occur. Arteries affected with atherosclerosis lose their elasticity, an as the atheromas (patchy thickening in the inner lining of the artery) grow, the arteries narrow. With time, the atheromas collect calcium deposits, may become brittle, and may rupture. Blood may then enter a ruptured atheroma, making it larger, so that it narrows the artery even more. A ruptured atheroma also may spill its fatty contents and trigger the formation of a blood clot (thrombus). The clot may further narrow or even occlude the artery, or it may detach and float downstream where it causes an occlusion (embolism).

[0006] Causes of high cholesterol levels include a diet high in saturated fats and cholesterol; cirrhosis, poorly controlled diabetes, underactive thyroid gland, overactive pituitary gland, kidney failure, porphyria, and heredity. Causes of high triglyceride levels include excess calories in diet, severe uncontrolled diabetes, kidney failure, acute alcohol abuse, certain drugs, and heredity.

[0007] Obesity is one of the factors contributing to high levels of certain lipids, such as VLDL and LDL, as a result, the initial treatment for overweight patients with high cholesterol or triglyceride levels is to lose weight. Levels of fatty material such as cholesterol and triglycerides may also be controlled with a variety of drugs. Hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors block the synthesis of cholesterol and enhance the removal of low density lipoproteins from the bloodstream.

[0008] Obesity is a common and chronic condition whose prevalence has increased steadily in advanced nations. Though the molecular pathways regulating energy balance are beginning to be illuminated, the causes of obesity remain elusive. In part, this reflects the fact that obesity is a heterogeneous group of disorders. At one level, the pathophysiology of obesity seems simple: a chronic excess of nutrient intake relative to the level of energy expenditure. However, due to the complexity of the neuroendocrine and metabolic systems that regulate energy intake, storage, and expenditure, it has been difficult to quantitate all the relevant parameters (e.g., food intake and energy expenditure) over time in human subjects. Obesity contributes to a myriad of health problems, including type 2 diabetes mellitus, hypertension, congestive heart failure, lipid disorders, arthritis, and some cancers. Obesity and related conditions contribute to nearly 300 000 annual deaths in the United States. Unfortunately, obesity is not well understood.

[0009] Obesity is important as a risk factor of the onset of diseases represented by geriatric diseases from hygienic and cosmetic viewpoints. Harmful influences of obesity have been recognized for a long time in advanced nations. Agents for preventing and/or treating obesity which have been developed until: now have side effects or produce unsatisfactory effects. Despite short-term benefits, medication-induced weight loss is often associated with rebound weight gain after the cessation of drug use, side effects from the medications, and the potential for drug abuse. Given the need for effective therapies, many possible compounds and combinations have been evaluated. For instance when fenfluramine was administered together with phentermine, as "fen-phen," the combination was widely used based on controlled trials that demonstrated modest but definite efficacy. However, the risk of

approval of the fen-phen combination in 1997 when reports suggested an association with right- and left-sided valvular heart disease.

[0010] Thus there still exists a need for more effective anti-dyslipidemic and anti-obesity combinations with less or no side effects such as described herein and lower toxicity.

[0011] Besides genetic predisposition, obesity and dyslipidemia are the most important risk factors for the development cardiovascular disorders. Even modest weight reduction can improve e.g. blood pressure control in overweight subjects. Thus, there is furthermore a need for a combination which is also effective for treating or preventing certain cardiovascular disorders with less or no side effects such as described herein e.g. weight gain and lower toxicity.

[0012] Particularly, there is a need of new combinations for the treatment and/or prevention of cardiovascular disorders, dyslipidemia or obesity and showing furthermore beneficial effects on diseases and conditions associated with cardiovascular disorders, dyslipidemia or obesity.

[0013] High blood pressure becomes increasingly difficult to treat when patients present with additional co-morbidities such as diabetes, obesity, dyslipidemia or metabolic disturbances. To achieve target blood pressure goals in patients with coexistent risk factors or conditions, multi-drug therapy is often required. If blood pressure or other co-morbidities are inadequately modified, the patient is at greater risk of serious adverse events such as myocardial infarction, stroke and progressive organ damage.

[0014] Moreover, while renin angiotensin system (RAS) blockade, either with the use of angiotensin converting enzyme inhibitors (ACEi) or with angiotensin receptor blbckers (ARBs) has proven to be a very effective means of lowering elevated blood pressure, many patients, for example, obese or overweight individuals or dyslipidemic patients, may require additional therapeutic interventions to achieve specific target blood pressure goals. Furthermore, obese or overweight patients or dyslipidemic patients may need treatment with drugs designed specifically to interrupt key pathways contributing to this metabolic phenotype.

[0015] There is accumulating evidence that obese subjects have an increased risk of cardiovascular and metabolic diseases (Montani J P, Antic V, Yang Z. Pathways from obesity to hypertension: from the perspective of a vicious triangle. *Internat J Obesity* 26(Suppl 2):S28-S38, 2002). Also, a strong correlation between body weight and blood pressure has been demonstrated in humans (Jones D W, Kim J S, Andrew M E, Kim S J, Hong Y P. Body mass index and blood pressure in Korean men and women: the Korean National Blood Pressure Survey. *J Hypertens* 12:1433-1437, 1994). In short-term studies, it has been shown that weight loss in overweight or obese human subjects leads to a reduction in both systolic and diastolic blood pressure (Aucott L, Poobalan A, Smith W C S, Avenell A, Jung R, Broom J. Effects of weight loss in overweight/obese individuals and long-term hypertension outcomes. *Hypertension* 45:1035-1041, 2005). The precise mechanisms underlying this relationship are not known, however, a clear association between weight gain and activation of the sympathetic nervous system has been shown (Masuo K, Mikami H, Ogihara T, Tuck M L. Weight gain-induced blood pressure elevation. *Hypertension* 35:1135-1140, 2000). Increased sympathetic activity results in vasoconstriction and sodium retention, two factors that directly contribute to a rise blood pressure, heart rate, and plasma insulin (Hall J E, Brands M W, Dixon W N, Smith M J Jr. Obesity-induced hypertension. Renal function and systemic hemodynamics. *Hypertension* 22:292-299, 1993). These results suggest that a similar cause and effect relationship may exist in animals and in humans and thus allows for the study of this set of conditions in appropriate animal species. Several additional factors also may contribute to the linkage seen between weight gain and blood pressure in animals and in man including leptin, free fatty acids, and insulin. Leptin and free fatty acids rise progressively with increasing adiposity and are released by visceral adipocytes. These mediators may act alone or in concert to increase sympathetic tone and vasoconstriction, thereby leading to an increase in blood pressure (Montani et al., 2002). Adipose tissue can be considered an endocrine organ, whereby release of leptin can have profound effects within the central nervous system to induce satiety and activate the sympathetic nervous system (Pantanetti P, Garrapa G G M, Mantero F, Boscaro M, Faloia E, Venarucci D. Adipose tissue as an endocrine organ? A review of recent data related to cardiovascular complications of endocrine dysfunctions. *Clin Exper Hypertens* 26(4):387-398, 2004). In obese humans, leptin is elevated in plasma yet these individuals do not appear to have a normal satiety response to this hormone. The concept of selective leptin resistance has been introduced to explain the phenomenon whereby the hypothalamus becomes unresponsive to the satiety effects of leptin but the central nervous system retains full reactivity to the stimulation of the sympathetic nervous system (SNS). Consequently, the obese or overweight phenotype lingers due to the inability of leptin to invoke a satiety response. Additionally, chronic over-activity of the SNS persists and leads to an increase in systemic blood pressure (Mark A L, Correia M L G, Rahmouni K, Haynes W G. Selective leptin resistance: a new concept in leptin physiology with cardiovascular implications. *J Hypertens* 20:1245-1250, 2002). Thus, human obesity is considered by some to be a leptin-resistant state. The model of the Agouti yellow obese mouse may mimic this phenotype (Correia M L G, Haynes W G, Rahmouni K, Morgan D A, Sivitz W I, Mark A L. The concept of selective leptin resistance. *Diabetes* 51:439-442, 2002).

[0016] Recently, it has been demonstrated that adipose tissue contains all of the components of the RAS (Goossens G H, Blaak E E, van Baak M A. Possible involvement of the adipose tissue renin-angiotensin system in the pathophysiology of obesity and obesity-related disorders. *Obesity Reviews* 4:43-55, 2003). Thus, the RAS contained in its entirety within the adipocyte may provide an important link between a major cardiovascular control system and obesity and obesity-related diseases. A high fat diet in rodents leads to increased generation of angiotensinogen and angiotensin II in adipocytes. Angiotensin II promotes adipocyte growth. Angiotensin II, either adipocyte-derived or formed in the plasma can have profound effects on fat cells directly or in distal cell types accessible from the circulation. Clearly, angiotensin II can result in a potent vasoconstrictor effect and sodium retention to increase arterial blood pressure. The findings relating components of the RAS within and/or released from adipocytes, have been equivocal in animal models and in humans (Engeli S, Schling P, Gorzelniak K, Boschmann M, Janke J, Ailhaud G, Teboul M, Massiera F, Sharma A M. The adipose-tissue renin-angiotensin-aldosterone system: role in the meta-

[0017] Although the association between body weight, dyslipidemia and blood pressure is closely linked, the assignment of specific mechanisms underlying this relationship have been more difficult to prove since investigations have relied on several species, including man and the use of various animal models, cell systems and assay conditions.

[0018] Therefore, an object of the present invention is to provide more effective anti-dyslipidemic, anti-obesity and/or compositions to treat cardiovascular disorders and new therapeutic methods with less or no side effects and lower toxicity for treating or preventing cardiovascular disorders, dyslipidemia or obesity, and conditions associated therewith.

SUMMARY OF THE PRESENT INVENTION

[0019] In this application, the following effects were surprisingly found:

[0020] A potentiation of the blood pressure lowering and weight loss with the use of a renin inhibitor when given in combination with a drug used for weight loss (also known as an anti-obesity agent).

[0021] A potentiation of the blood pressure lowering and lowering of the lipid levels with the use of a renin inhibitor when given in combination with a drug used for lowering lipid levels (also known as an anti-dyslipidemic agent)

This is an unexpected finding in that the components of the combination interact in a complementary manner to elicit effects that can not be achieved by any single agent when given alone.

[0022] The present invention relates to a combination, such as a combined preparation or a pharmaceutical composition, respectively, comprising a renin inhibitor, or a pharmaceutically acceptable salt thereof, and at least one therapeutic agent selected from the group consisting of

(a) an anti-dyslipidemic agent selected from the group consisting of a bile acid sequesterant, a cholesterol absorption inhibitor, an acyl coenzyme A-cholesterol acyl transferase (ACAT) inhibitor, a squalene synthetase inhibitor, an antioxidant, a FXR receptor modulator, a LXR receptor agonist, a lipoprotein synthesis inhibitor, a microsomal triglyceride transport inhibitor, a bile acid reabsorption inhibitor, a triglyceride synthesis inhibitor, a transcription modulator, a squalene epoxidase inhibitor, a low density lipoprotein (LDL) receptor inducer, a 5-LO or FLAP inhibitor, and niacin or a niacin receptor agonist, or a pharmaceutically acceptable salt thereof; and

(b) an anti-obesity agent selected from the group consisting of a 5HT (serotonin) transporter inhibitor, a NE (norepinephrine) transporter inhibitor, a ghrelin antibody, a ghrelin antagonist, a H3 (histamine H3) antagonist/inverse agonist, a MCH1R (melanin concentrating hormone 1R) antagonist, a MCH2R (melanin concentrating hormone 2R) agonist/antagonist, a NPY1 (neuropeptide Y Y1) antagonist, a NPY2 (neuropeptide Y Y2) agonist, a NPY5 (neuropeptide Y Y5) antagonist, leptin, a leptin derivative, an opioid antagonist, an orexin antagonist, a BRS3 (bombesin receptor subtype 3) agonist, a CCK-A (cholecystokinin-A) agonist, a CNTF (ciliary neurotrophic factor), a CNTF derivative, a GHS (growth hormone secretagogue receptor) agonist, 5HT2c (serotonin receptor 2c) agonist, a Mc3r (melanocortin 3 receptor) agonist, a Mc4r (melanocortin 4 receptor) agonist, a monoamine reuptake inhibitor, a serotonin reuptake inhibitor, topiramate, FAS (fatty acid synthase) inhibitor, a PDE (phosphodiesterase) inhibitor, a thyroid hormone, B agonist, an UCP-1 (uncoupling protein 1), 2, or 3 activator, an acyl-estrogen, a glucocorticoid antagonist, an 110 HSD-1 (11-beta hydroxy steroid dehydrogenase type 1) inhibitor, a lipase inhibitor, a fatty acid transporter inhibitor, a dicarboxylate transporter inhibitor, a glucose transporter inhibitor, and a phosphate transporter inhibitor,

or a pharmaceutically acceptable salt thereof.

[0023] Another example of an anti-dyslipidemic agent mentioned abovew under (a) is a cholesteryl ester transfer protein inhibitor. Consequently, the present invention is also related to a combination of at least two components selected from the group consisting of:

(i) a renin inhibitor or a renin inhibitor combined with a diuretic a pharmaceutically acceptable salt thereof; and

(ii) a cholesteryl ester transfer protein inhibitor or a pharmaceutically acceptable salt thereof.

[0024] Furthermore, the present invention provides pharmaceutical compositions comprising a renin inhibitor, or a pharmaceutically acceptable salt thereof, and at least one therapeutic agent selected from the group consisting of

(a) an anti-dyslipidemic agent selected from the group consisting of a bile acid sequesterant, a cholesterol absorption inhibitor, an acyl coenzyme A-cholesterol acyl transferase (ACAT) inhibitor, a squalene synthetase inhibitor, an antioxidant, a FXR receptor modulator, a LXR receptor agonist, a lipoprotein synthesis inhibitor, a microsomal triglyceride transport inhibitor, a bile acid reabsorption inhibitor, a triglyceride synthesis inhibitor, a transcription modulator, a squalene epoxidase inhibitor, a low density lipoprotein (LDL) receptor inducer, a 5-LO or FLAP inhibitor, and niacin or a niacin receptor agonist, or a pharmaceutically acceptable salt thereof; and

(b) an anti-obesity agent selected from the group consisting of a 5HT (serotonin) transporter inhibitor, a NE (norepinephrine) transporter inhibitor, a ghrelin antibody, a ghrelin antagonist, a H3 (histamine H3) antagonist/inverse agonist, a MCH1R (melanin concentrating hormone 1R) antagonist, a MCH2R (melanin concentrating hormone 2R) agonist/antagonist, a NPY1 (neuropeptide Y Y1) antagonist, a NPY2 (neuropeptide Y Y2) agonist, a NPY5 (neuropeptide Y Y5) antagonist, leptin, a leptin derivative, an opioid antagonist, an orexin antagonist, a BRS3 (bombesin receptor subtype 3) agonist, a CCK-A (cholecystokinin-A) agonist, a CNTF (ciliary neurotrophic factor), a CNTF derivative, a GHS (growth hormone secretagogue receptor) agonist, 5HT2c (serotonin receptor 2c) agonist, a Mc3r (melanocortin 3 receptor) agonist, a Mc4r (melanocortin 4 receptor) agonist, a monoamine reuptake inhibitor, a serotonin reuptake inhibitor, topiramate, phytopharm compound 57, an ACC2 (acetyl-CoA carboxylase-2) inhibitor, a β3 (beta adrenergic receptor 3) agonist, a FAS (fatty acid synthase) inhibitor, a PDE (phosphodiesterase) inhibitor, a thyroid hormone, B agonist, an UCP-1 (uncoupling protein 1), 2, or 3 activator, an acyl-estrogen, a glucocorticoid antagonist, an 110 HSD-1 (11-beta hydroxy steroid dehydrogenase type 1) inhibitor, a lipase inhibitor, a fatty acid transporter inhibitor, a dicarboxylate transporter inhibitor, a glucose transporter inhibitor, and a phosphate transporter inhibitor,

or a pharmaceutically acceptable salt thereof;

and a pharmaceutically acceptable carrier.

a pharmaceutically acceptable salt thereof, and a cholesteryl ester transfer protein inhibitor or a pharmaceutically acceptable salt thereof.

[0026] Furthermore, the present invention provides a method for the prevention of, delay the onset of or treatment of dyslipidemia, dyslipidemia associated with obesity, dyslipidemia-related disorders, obesity, obesity-related disorders and/or a disease or a condition modulated by the inhibition of renin activity, which method comprises administering to a warm-blooded animal, including man, in need thereof, a therapeutically effective amount of a combination comprising a renin inhibitor, or a pharmaceutically acceptable salt thereof, and at least one therapeutic agent selected from the group consisting of

(a) an anti-dyslipidemic agent selected from the group consisting of a bile acid sequesterant, a cholesterol absorption inhibitor, an acyl coenzyme A-cholesterol acyl transferase (ACAT) inhibitor, a squalene synthetase inhibitor, an antioxidant, a FXR receptor modulator, a LXR receptor agonist, a lipoprotein synthesis inhibitor, a microsomal triglyceride transport inhibitor, a bile acid reabsorption inhibitor, a triglyceride synthesis inhibitor, a transcription modulator, a squalene epoxidase inhibitor, a low density lipoprotein (LDL) receptor inducer, a 5-LO or FLAP inhibitor, and niacin or a niacin receptor agonist, or a pharmaceutically acceptable salt thereof; and

(b) an anti-obesity agent selected from the group consisting of a 5HT (serotonin) transporter inhibitor, a NE (norepinephrine) transporter inhibitor, a ghrelin antibody, a ghrelin antagonist, a H3 (histamine H3) antagonist/inverse agonist, a MCH1R (melanin concentrating hormone 1R) antagonist, a MCH2R (melanin concentrating hormone 2R) agonist/antagonist, a NPY1 (neuropeptide Y Y1) antagonist, a NPY2 (neuropeptide Y Y2) agonist, a NPY5 (neuropeptide Y Y5) antagonist, leptin, a leptin derivative, an opioid antagonist, an orexin antagonist, a BRS3 (bombesin receptor subtype 3) agonist, a CCK-A (cholecystokinin-A) agonist, a CNTF (ciliary neurotrophic factor), a CNTF derivative, a GHS (growth hormone secretagogue receptor) agonist, 5HT2c (serotonin receptor 2c) agonist, a Mc3r (melanocortin 3 receptor) agonist, a Mc4r (melanocortin 4 receptor) agonist, a monoamine reuptake inhibitor, a serotonin reuptake inhibitor, topiramate, phytopharm compound 57, an ACC2 (acetyl-CoA carboxylase-2) inhibitor, a β3 (beta adrenergic receptor 3) agonist, a FAS (fatty acid synthase) inhibitor, a PDE (phosphodiesterase) inhibitor, a thyroid hormone, B agonist, an UCP-1 (uncoupling protein 1), 2, or 3 activator, an acyl-estrogen, a glucocorticoid antagonist, an 110 HSD-1 (11-beta hydroxy steroid dehydrogenase type 1) inhibitor, a lipase inhibitor, a fatty acid transporter inhibitor, a dicarboxylate transporter inhibitor, a glucose transporter inhibitor, and a phosphate transporter inhibitor,

or a pharmaceutically acceptable salt thereof.

[0027] Furthermore, the present invention provides a method for the prevention of, delay the onset of or treatment of dyslipidemia, dyslipidemia associated with obesity, dyslipidemia-related disorders, obesity, obesity-related disorders and/or a disease or a condition modulated by the inhibition of renin activity, which method comprises administering to a warm-blooded animal, including man, in need thereof, a

thereof, and a cholesteryl ester transfer protein inhibitor or a pharmaceutically acceptable salt thereof.

DEFINITIONS

[0028] The term "at least one therapeutic agent" shall mean that in addition to a renin inhibitor one or more, for example, two, furthermore three, active ingredients as specified according to the present invention can be combined. This means in particular that beside the renin inhibitor one or more, e.g. two or three, anti-obesity agents can be present. Likewise, this means in particular that beside the renin inhibitor one or more, e.g. two or three, anti-dyslipidemic agents can be present. Furthermore, one or more of both the anti-dyslipidemic and the anti-obesity agents can be present.

[0029] The term "combination" of a renin inhibitor, or a pharmaceutically acceptable salt thereof, and at least one therapeutic agent selected from the group consisting of (a) and (b) as defined above, means that the components can be administered together as a pharmaceutical composition or as part of the same, unitary dosage form. A combination also includes administering a renin inhibitor, or a pharmaceutically acceptable salt thereof, and at least one therapeutic agent selected from the group consisting of (a) and (b) as defined above, each separately but as part of the same therapeutic regimen. The components, if administered separately, need not necessarily be administered at essentially the same time, although they can if so desired. Thus, a combination also refers, for example, administering a renin inhibitor, or a pharmaceutically acceptable salt thereof, and at least one therapeutic agent selected from the group consisting of (a) and (b) as defined above, as separate dosages or dosage forms, but at the same time. A combination also includes separate administration at different times and in any order.

[0030] The term "prevention" refers to prophylactic administration to healthy patients to prevent the development of the conditions mentioned herein. Moreover, the term "prevention" means prophylactic administration to patients being in a pre-stage of the conditions to be treated.

[0031] The term "delay the onset of", as used herein, refers to administration to patients being in a pre-stage of the condition to be treated in which patients with a pre-form of the corresponding condition is diagnosed.

[0032] The term "treatment" is understood the management and care of a patient for the purpose of combating the disease, condition or disorder.

[0033] The term "therapeutically effective amount" refers to an amount of a drug or a therapeutic agent that will elicit the desired biological or medical response of a tissue, system or an animal (including man) that is being sought by a researcher or clinician.

[0034] The term "warm-blooded animal or patient" are used interchangeably herein and include, but are not limited to, humans, dogs, cats, horses, pigs, cows, monkeys, rabbits, mice and laboratory animals. The preferred mammals are humans.

[0035] The term "pharmaceutically acceptable salt" refers to a non-toxic salt commonly used in the pharmaceutical industry which may be prepared according to methods well-known in the art.

[0036] Diseases or a conditions modulated by the inhibition of renin activity as defined in the present invention include, but are not limited to, hypertension, congestive heart failure,

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