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(54) Title: NAPHTHOQUINONE-BASED PHARMACEUTICAL COMPOSITION FOR TREATMENT OR PREVENTION OF DISEASES INVOLVING OBESITY, DIABETES, METABOLIC SYNDROME, NEURO-DEGENERATIVE DISEASES AND MITOCHONDRIA DYSFUNCTION DISEASES

(57) Abstract: Provided is a pharmaceutical composition for the treatment and/or prevention of disease syndromes by including (a) a therapeutically effective amount of a specific naphthoquinone-based compound, or a pharmaceutically acceptable salt, prodrug, solvate or isomer thereof, and (b) a pharmaceutically acceptable carrier, a diluent or an excipient, or any combination thereof.

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**NAPHTHOQUINONE-BASED PHARMACEUTICAL
COMPOSITION FOR TREATMENT OR PREVENTION OF
DISEASES INVOLVING OBESITY, DIABETES, METABOLIC
5 SYNDROME, NEURO-DEGENERATIVE DISEASES, AND
 MITOCHONDRIA DYSFUNCTION DISEASES**

FIELD OF THE INVENTION

The present invention relates to a pharmaceutical composition for treatment or
10 prevention of various diseases involving obesity, diabetes, metabolic syndrome, neuro-
degenerative diseases, and mitochondria dysfunction diseases.

BACKGROUND OF THE INVENTION

Obesity, a condition in which an amount of body fat is abnormally higher than
15 standard body weight, refers to a disease resulting from accumulation of surplus calories
in adipose tissues of the body when calorie intake is greater than calorie expenditure.
Complications caused from obesity include, for example hypertension, myocardial
infarction, varicosis, pulmonary embolism, coronary artery diseases, cerebral
hemorrhage, senile dementia, Parkinson's disease, type 2 diabetes, hyperlipidemia,
20 cerebral apoplexy, various cancers (such as uterine cancer, breast cancer, prostate
cancer, colon cancer and the like), heart diseases, gall bladder diseases, sleep apnea
syndrome, arthritis, infertility, venous ulcer, sudden death, fatty liver, hypertrophic

cardiomyopathy (HCM), thromboembolism, esophagitis, abdominal wall hernia (Ventral Hernia), urinary incontinence, cardiovascular diseases, endocrine diseases and the like (Obesity Research Vol. 12(8), 2004, 1197-1211).

Diabetes is a systemic metabolic disorder resulting from multiple
5 environmental and genetic factors, and refers to a condition characterized by abnormally elevated blood glucose levels due to absolute or relative deficiency of insulin in the body. Complications of diabetes includes, for example hypoglycemia, ketoacidosis, hyperosmolar coma, macrovascular complications, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy and the like.

10 Metabolic syndromes refer to syndromes accompanied by health risk factors such as hypertriglyceridemia, hypertension, glycometabolism disorders, blood coagulation disorders and obesity. According to the ATP III criteria of the National Cholesterol Education Program (NCEP) published in 2001, individuals are diagnosed
15 with the metabolic syndrome by the presence of three or more of the following components: 1) A waistline of 40 inches (102 cm) or more for men and 35 inches (88 cm) or more for women (central obesity as measured by waist circumference), 2) A triglyceride level of above 150 mg/dl, 3) A high density lipoprotein level (HDL) less than 40 mg/dl (men), or under 50 mg/dl (women), 4) A blood pressure of 130/85 mmHg or higher and 5) A fasting blood glucose level 110 mg/dl or more.

20 Insulin resistance refers to a phenomenon wherein, even though insulin is normally secreted in the body, "supply of glucose into cells" performed by insulin does not work properly. Therefore, glucose in the blood cannot enter cells, thus causing hyperglycemia, and further, cells themselves cannot perform normal functions thereof due to a shortage of glucose, leading to the manifestation of metabolic syndrome.

The degenerative disease is the term derived from pathological findings, thus meaning the condition which is accompanied by “decreases in consumption of oxygen”, and refers to a degenerative disease wherein dysfunction of mitochondria, which is an organelle that generates energy using oxygen within the cell, is related to senescence. As
5 examples of the degenerative disease, mention may be made of neurodegenerative disease such as Alzheimer's disease, Parkinson's disease and Huntington's disease (Korean Society of Medical Biochemistry and Molecular Biology News, 2004, 11(2), 16-22).

Diseases arising from mitochondrial dysfunction may include for example,
10 mitochondrial swelling due to mitochondrial membrane potential malfunction, functional disorders due to oxidative stress such as by the action of reactive oxygen species (ROS) or free radicals, functional disorders due to genetic factors, and diseases due to functional deficiency of oxidative phosphorylation mechanisms for energy production of mitochondria. Specific examples of diseases, developed by the above-
15 mentioned pathological causes, may include multiple sclerosis, encephalomyelitis, cerebral radiculitis, peripheral neuropathy, Reye's syndrome, Friedrich's ataxia, Alpers syndrome, MELAS, migraine, psychosis, depression, seizure and dementia, paralytic episode, optic atrophy, optic neuropathy, retinitis pigmentosa, cataract, hyperaldosteronemia, hypoparathyroidism, myopathy, amyotrophy, myoglobinuria,
20 hypotonia, myalgia, the decrease of exercise tolerance, renal tubulopathy, renal failure, hepatic failure, liver function failure, hepatomegaly, red blood cell anemia (iron-deficiency anemia), neutropenia, thrombocytopenia, diarrhea, villous atrophy, multiple vomiting, dysphagia, constipation, sensorineural hearing loss (SNHL), epilepsy, mental retardation, Alzheimer's disease, Parkinson's disease and Huntington's disease (see, for

example US Patent No. 6,183,948, Journal of clinical investigation 111, 303-312, 2003, Mitochondria 74, 1188-1199, 2003, Biochimica et Biophysica acta 1658 (2004) 80-88).

The above-mentioned obesity, diabetes, metabolic syndromes, degenerative diseases and mitochondrial dysfunction-related diseases will be collectively referred to
5 as “disease syndromes” hereinafter.

At present, the most effective way to ameliorate or fight against the conditions associated with such disease syndromes is known to be getting more exercise and dietary control, and losing weight. All of the currently effective ways of fighting against the disease syndromes have in common the fact that they facilitate energy metabolism,
10 thus resulting in promoted expenditure of surplus energy in the body leading to prevention of energy accumulation. Effective expenditure of such surplus energy is considered a method for treating the disease syndromes. Promoting energy metabolism is most important for effective elimination of surplus energy. For this purpose, it is essential to achieve inhibition of lipogenesis, inhibition of gluconeogenesis, facilitation
15 of glucose consumption, facilitation of fat oxidation, facilitation of biogenesis of mitochondria which is a central apparatus of energy metabolism and collective activation of factors involved in metabolic activation.

There is yet little known about targets to treat the disease-syndromes, whereas numerous target proteins or genes are known only for treating individual diseases and
20 therefore there have been proposed some methods for the prevention or treatment of such diseases via use of the above-mentioned corresponding target proteins or genes. However, there is still a room for further significant improvement even in treatment of individual diseases such as metabolic syndromes including obesity, diabetes and the like. In spite of the fact that a great deal of studies has been conducted on treatment of

diseases, there are yet no drugs available for the treatment of various diseases resulting from excess energy intake and aging.

Most of diseases including obesity, diabetes, metabolic syndromes, degenerative diseases and mitochondrial dysfunction-related diseases, i.e., large numbers of diseases including disease syndromes, stem from imbalance of energy metabolism and oxidation-reduction state. For this reason, the present invention has also employed a method of confirming the presence/absence of activation effects on AMP-activated protein kinase (AMPK), as the most fundamental primary test to confirm biological efficacy of compounds of interest on disease syndromes.

Meanwhile, once AMPK is activated, a variety of physiological events are consequently affected in the downstream of the mechanism thereof. In this regard, factors to be regulated and expression phenomena are provided as follows.

1. Glycometabolism

In muscle tissues and myocardium, AMPK promotes muscle contraction and thereby facilitates intake of glucose. That is, AMPK activates GLUT 1, or induces migration of GLUT 4 to a plasma membrane, regardless of insulin action, resulting in increased glucose uptake into cells (Arch. Biochem. Biophys. 380, 347-352, 2000, J. Appl. Physiol. 91, 1073-1083, 2001). After increasing glucose uptake into cells, AMPK activates hexokinase, thereby increasing flux of glycometabolism processes and simultaneously inhibiting glycogen synthesis. It is known that in myocardial tissues under ischemic conditions, AMPK activates a phosphorylation process of 6-phosphofructo-2-kinase (PFK-2), with consequent activation of a metabolic cascade

leading to increased flux of glycometabolism (Curr. Biol. 10, 1247-1255, 2000). In addition, it was confirmed that activation of AMPK in the liver inhibits release of glucose from hepatocytes, and activity of phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase, which are gluconeogenesis enzymes, is inhibited by AMPK
5 (Diabetes 49, 896-903, 2000). This is because AMPK independently takes part in regulation of a blood glucose level via inhibition of release of glucose from the liver, irrespective of insulin.

2. Mitochondrial Biogenesis

10 One important function of mitochondria is to carry out an oxidative phosphorylation process, which converts energy produced from fuel metabolites such as glucose and fatty acids into ATP. It is known that the incidence of disorders in mitochondrial functions is involved in a pathogenic mechanism of various degenerative diseases associated with senescence, such as diabetes, cardiovascular diseases,
15 Parkinson's disease and senile dementia (Curr. Opin. Cell Biol. 15, 706-716, 2003). Peterson, et al (Science 300, 1140-1142, 2003) have suggested the possibility that deteriorated mitochondrial function is a probable pathogenic cause of insulin resistance syndrome, with reporting that oxidative phosphorylation functions of mitochondria were weakened by about 40% in the elderly. Lee, et al (Diabetes Res. Clin. Pract. 42,
20 161-167, 1998) have confirmed that a decrease in the content of mitochondrial DNA in the peripheral blood is initiated from before the incidence of diabetes. Biogenesis of mitochondria in muscles is known to be promoted by an adaptive reaction in which metabolic activity of oxidative phosphorylation of muscle cells is increased by chronic energy depletion and exercise. Zong, et al (Proc Natl. Acad. Sci. USA 99: 15983-15987,

2002) have revealed that, using a transgenic mouse in which AMPK was genetically inactivated, AMPK is required for mitochondrial biogenesis in skeletal muscle under conditions in which chronic energy deprivation was induced. Further, Putman, et al (J. Physiol. 551, 169-178, 2003) have demonstrated the hypothesis that AMPK in association with continuous exercise is involved in an increase of mitochondrial volume.

Meanwhile, it was confirmed that AMPK increases gene expression of a peroxisome proliferator-activated receptor gamma coactivator 1 α (PGC-1 α) which is known to play an important role in mitochondrial biogenesis (Endocr. Rev. 24, 78-90, 2003). Raynald, et al (Am. J. Physiol. Endocrinol. Metab. 281, 1340, 2001) have suggested that a nuclear respiratory factor-1 (NRF-1), which is a gene essential for transcription of proteins associated with a mitochondrial respiratory system as well as mitochondrial transcription and replication, plays an important role to increase oxidation capability in muscle cells in response to chronic energy stress. Therefore, NRF-1 consequently participates in an increase of mitochondrial biogenesis. In addition, it is known that enzymatic activity of citrate synthase and 3-hydroxyacyl-CoA dehydrogenase, known as being increased in conjunction with increased amounts of UCP-3 protein and mRNA thereof and increased mitochondrial volume, is increased by activation of AMPK (J. Physiol. 551, 169-178, 2003).

20

3. Fat metabolism regulation and AMPK

Upon reviewing a mechanism of AMPK participating in fat metabolism, AMPK induces phosphorylation of acetyl-CoA carboxylase, thereby resulting in inhibition of fatty acid synthesis. Therefore, AMPK is known to facilitate fatty acid

oxidation, by the action of decreasing an intracellular concentration of malonyl-CoA that is an intermediate of fatty acid synthesis and is an inhibitor of carnitine palmitoyl-CoA transferase I (CPT I). CPT I is an enzyme essential for a fatty acid oxidation process wherein fatty acids enter mitochondria and are oxidized, and is known under the control of malonyl-CoA. In addition, AMPK is known to inhibit activity of HMG-CoA reductase and glycerol phosphate acyl transferase (GPAT), involved in synthesis of cholesterol and triacylglycerol, through phosphorylation (J. Biol. Chem. 277, 32571-32577, 2002, J. Appl. Physiol. 92, 2475-2482, 2002).

Meanwhile, it was found that activation of AMPK in the liver inhibits the activity of pyruvate kinase, fatty acid synthase and ACC through phosphorylation of carbohydrate-response-element-binding protein (ChREBP) (J. Biol. Chem. 277, 3829-3835, 2002). In addition, activity of sterol-regulatory-element binding protein-1 (SREBP-1), which plays an important role in differentiation of adipocytes, is also inhibited by the action of AMPK, which results then in inhibition of adipocyte differentiation.

4. Protein synthesis regulation and AMPK

In the protein synthesis process, AMPK inhibits synthesis of proteins via inhibition of mTOR and p70S6K by activating TSC, or AMPK inhibits translation elongation via activation of elongation factor-2 (eEF2) kinase and inactivation of eEF2 through phosphorylation thereof. It was found that eEF2 kinase is a direct substrate for AMPK (J. Biol. Chem. 278, 41970-41976, 2003).

As discussed above, AMPK is known to play a central role in energy metabolism of glucose, protein, fat and the like, *in vitro* and *in vivo*. Neil, et al (Nature drug discovery, 3(April), 340, 2004) has asserted that AMPK and Malonyl-CoA are possible targets for the treatment of metabolic syndromes, and they have also stated that

5 patients suffering from metabolic syndromes can be characterized by insulin resistance, obesity, hypertension, dyslipidemia, and dysfunction of pancreatic beta cells, type II diabetes and manifestation of arteriosclerosis. It was hypothesized that a common feature linking these multiple abnormalities is dysregulation of AMPK/Malonyl-CoA energy level-sensing and signaling network. It was proposed that such dysregulation

10 leads to alterations in cellular fatty-acid metabolism that in turn cause abnormal fat accumulation, cellular dysfunction and ultimately disease. Evidence is also presented that factors activating AMPK and/or reducing malonyl-CoA levels might reverse these abnormalities and syndromes or prevent incidence of these diseases.

Roger, et al (Cell, 117, 145-151, 2004) have suggested that AMPK may be a

15 possible target to control obesity by lowering activity of hypothalamic AMPK, thereby increasing a content of malonyl-CoA and then regulating appetite for food intake.

Lee, et al (Nature medicine, 13(June), 2004) have suggested that alpha-lipoic acid can exert anti-obesity effects by suppressing hypothalamic AMPK activity, thus controlling appetite. They have also reported that alpha-lipoic acid promotes fat

20 metabolism via activation of AMPK in muscle tissues, not hypothalamus, and alpha-lipoic acid is therapeutically effective for the treatment of obesity because it facilitates energy expenditure by activating UCP-1, particularly in adipocytes.

Diraison, et al (Diabetes 53, S84-91, 2004) have reported that activation of AMPK in pancreatic cells leads to four-fold increases in expression of the gut hormone

peptide YY responsible for appetite control and thus appetite can be regulated by the action of AMPK in other tissues other than hypothalamus.

Nandakumar, et al (Progress in lipid research 42, 238-256, 2003) have proposed that, in ischemic heart diseases, AMPK would be a target to treat ischemia
5 reperfusion injuries via regulation of fat and glucose metabolism.

Min, et al (Am. J. Physiol. Gastrointest Liver Physiol 287, G1-6, 2004) have reported that AMPK is effective for regulation of alcoholic fatty liver.

Genevieve, et al (J. Biol. Chem. 279, 20767-74, 2004) have reported that activation of AMPK inhibits activity of an iNOS enzyme that is an inflammation
10 mediator in chronic inflammatory conditions or endotoxin shock, including obesity-related diabetes and thus AMPK will be effective for developing new medicines having a mechanism capable of enhancing insulin sensitivity. In addition, they have reported that inhibition of iNOS activity is effected by activation of AMPK, and thus this finding is clinically applicable to diseases such as septicemia, multiple sclerosis, myocardial
15 infarction, inflammatory bowel diseases and pancreatic beta-cell dysfunction.

Zhi-ping et al (FEBS Letters 443, 285-289, 1999) have reported that endothelial NO synthase (eNOS) is phosphorylated by AMPK, in the presence of Ca-calmodulin in murine muscle cells and myocardial cells. This represents that AMPK is implicated in heart diseases including angina pectoris.

20 Javier, et al (Genes & Develop. 2004) have reported that a lifespan can be extended by limiting utilization of energy and such a prolonged lifespan is achieved in a manner that an *in vivo* AMP/ATP ratio is increased and therefore the $\alpha 2$ subunit of AMPK is activated by AMP. Therefore, they have suggested that AMPK may function

as a sensor to detect the relationship between lifespan extension and energy level and insulin-like signal information.

SUMMARY OF THE INVENTION

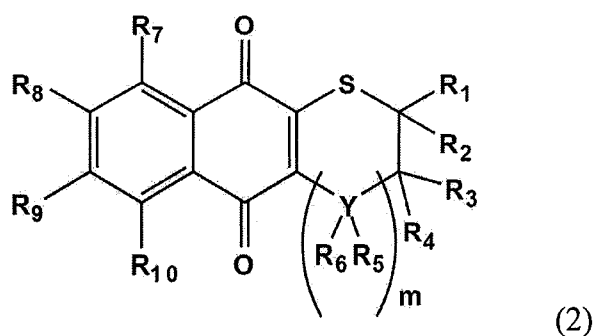
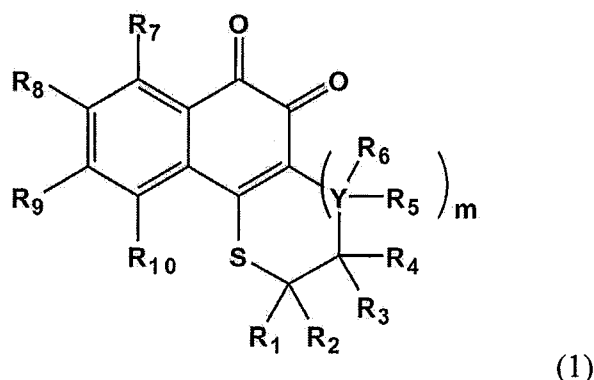
5 The inventors of the present invention have newly confirmed that furano-1,2-naphthoquinone-based or pyrano-1,2-naphthoquinone-based compounds such as β -lapachone (2,2-dimethyl-3,4-dihydro-2*H*-naphtho[2,3-*b*]pyran-5,6-dione), dunnione (2,3,3-trimethyl-2,3-dihydro-naphtho[2,3-*b*]furan-4,5-dione), α -dunnione (2,2,3-trimethyl-2,3-dihydro-naphtho[2,3-*b*]furan-4,5-dione), nocardinone A, nocardinone B,
10 lantalucratin A, lantalucratin B and lantalucratin C can be used in the prevention or treatment of various diseases such as obesity, diabetes, metabolic syndromes, degenerative diseases and diseases associated with mitochondrial dysfunction. Based on these facts, the inventors have readily filed for patents.

In furtherance, the inventors of the present invention have newly confirmed
15 that sulfur derivative compounds of furano-1,2-naphthoquinone-based or pyrano-1,2-naphthoquinone-based compounds such as thiophene-1,2-naphthoquinone or thiopyran-1,2-naphthoquinone and thioxane-1,2-naphthoquinone can also be used in the prevention or treatment of various diseases such as obesity, diabetes, metabolic syndromes, degenerative diseases and diseases associated with mitochondrial
20 dysfunction. Such pharmaceutical effects are very new and have been unknown to the present.

Therefore, an object of the present invention is to provide a pharmaceutical composition comprising, as an active ingredient, a specific naphthoquinone-based

compound which is effective for the treatment and prevention of disease syndromes such as obesity, diabetes, metabolic syndromes, degenerative diseases and mitochondrial dysfunction-related diseases.

In accordance with an aspect of the present invention, the above and other
 5 objects can be accomplished by the provision of a pharmaceutical composition for the treatment and/or prevention of disease syndromes such as obesity, diabetes, metabolic syndromes, degenerative diseases and mitochondrial dysfunction-related diseases, comprising: (a) a therapeutically effective amount of one or more selected from the naphthoquinone-based compounds represented by Formula 1 and Formula 2 below, or
 10 a pharmaceutically acceptable salt, prodrug, solvate or isomer thereof:



wherein

R₁ to R₆ are each independently selected from the group consisting of hydrogen
 15 (H), hydroxy (OH), substituted or unsubstituted C₁-C₁₀ alkyl, substituted or

In another preferred example, in the compound of Formula 1 or 2, R₁ to R₄ may be hydrogen; R₅ and R₆ may be methyl; and R₇ to R₁₀ may be hydrogen.

In order to confirm therapeutic and prophylactic effects of the naphthoquinone-based compound on disease syndromes, the present inventors, as will be illustrated in
5 Experimental Examples hereinafter, have measured activity of the naphthoquinone-based compound on AMPK activity in Colon cells and suppression of cellular differentiation in preadipocytes (3T3-L1 and F442A cells) and as a result, have confirmed that such a compound exhibits superior AMPK activation effects and inhibitory effects of adipocyte differentiation.

10 In addition, the present inventors have further confirmed that therapeutic and prophylactic effects of disease syndromes by the naphthoquinone-based compound were examined through *in vivo* experiments using ob/ob mice, a model of obesity, db/db mice, a model of obesity/diabetes, DIO (diet-induced obesity) mice, caused by high fat dietary conditions, and Zucker fa/fa mice, a model of obesity/diabetes, and as a result,
15 the naphthoquinone-based compound was highly therapeutically effective.

Therefore, it is expected that the pharmaceutical composition of the present invention, comprising the naphthoquinone-based compound as an active ingredient, can treat and prevent a variety of disease syndromes as defined in the present invention via activation of AMPK.

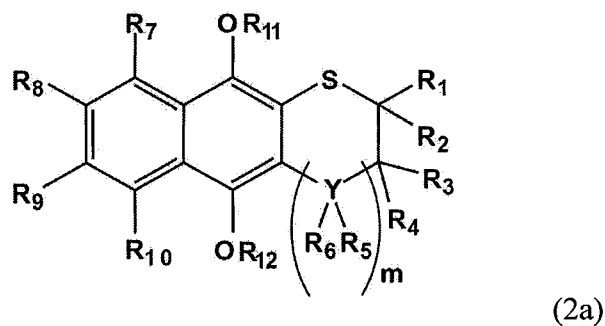
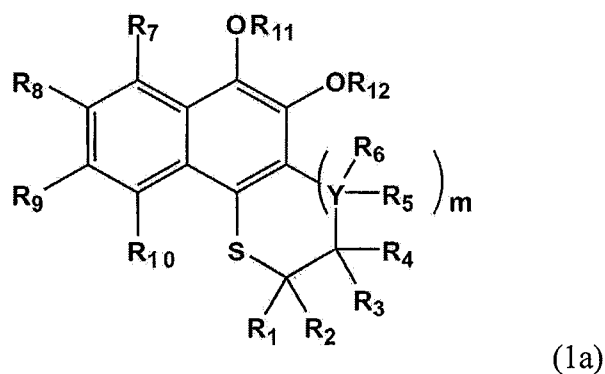
20 As used the present disclosure, the term “pharmaceutically acceptable salt” means a formulation of a compound that does not cause significant irritation to an organism to which it is administered and does not abrogate the biological activity and properties of the compound. Examples of the pharmaceutical salt may include acid addition salts of the compound with acids capable of forming a non-toxic acid addition

salt containing pharmaceutically acceptable anions, for example, inorganic acids such as hydrochloric acid, sulfuric acid, nitric acid, phosphoric acid, hydrobromic acid and hydroiodic acid; organic carbonic acids such as tartaric acid, formic acid, citric acid, acetic acid, trichloroacetic acid, trifluoroacetic acid, gluconic acid, benzoic acid, lactic acid, fumaric acid, maleic acid and salicylic acid; or sulfonic acids such as methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid and p-toluenesulfonic acid. Specifically, examples of pharmaceutically acceptable carboxylic acid salts include salts with alkali metals or alkaline earth metals such as lithium, sodium, potassium, calcium and magnesium, salts with amino acids such as lysine, arginine, and guanidine, salts with organic bases such as dicyclohexylamine, N-methyl-D-glucamine, tris(hydroxymethyl)methylamine, diethanolamine, choline and triethylamine. The compound in accordance with the present invention may be converted into salts thereof, by conventional methods well-known in the art.

As used herein, the term "prodrug" means an agent that is converted into the parent drug *in vivo*. Prodrugs are often useful because, in some situations, they may be easier to administer than the parent drug. They may, for instance, be bioavailable by oral administration, whereas the parent may be not. The prodrugs may also have improved solubility in pharmaceutical compositions over the parent drug. An example of a prodrug, without limitation, would be a compound of the present invention which is administered as an ester (the "prodrug") to facilitate transport across a cell membrane where water-solubility is detrimental to mobility, but which then is metabolically hydrolyzed to the carboxylic acid, the active entity, once inside the cell where water solubility is beneficial. A further example of the prodrug might be a short peptide

(polyamino acid) bonded to an acidic group, where the peptide is metabolized to reveal the active moiety.

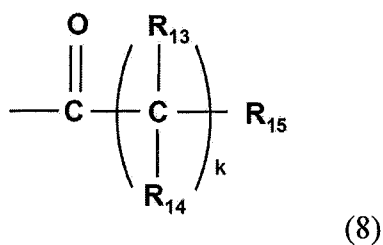
As an example of such prodrug, the pharmaceutical compounds in accordance with the present invention can include one or more prodrugs selected from compounds
5 represented by Formulas 1a and 2a below as an active material:



wherein,

$R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, Y$ and m are as defined in Formula 1;

10 R_{11} and R_{12} are each independently $-\text{SO}_3\text{Na}^+$ or substituent represented by Formula 8 below or a salt thereof,



wherein,

R₁₃ and R₁₄ are each independently hydrogen or substituted or unsubstituted C₁-C₂₀ linear alkyl or C₁-C₂₀ branched alkyl,

5 R₁₅ is selected from the group consisting of substituents i) to viii) below:

i) hydrogen;

ii) substituted or unsubstituted C₁-C₂₀ linear alkyl or C₁-C₂₀ branched alkyl;

10 iii) substituted or unsubstituted amine;

iv) substituted or unsubstituted C₃-C₁₀ cycloalkyl or C₃-C₁₀ heterocycloalkyl;

v) substituted or unsubstituted C₄-C₁₀ aryl or C₄-C₁₀ heteroaryl;

15 vi) -(CRR'-NR''CO)_l-R₁₄, wherein R, R' and R'' are each independently hydrogen, or substituted or unsubstituted C₁-C₂₀ linear alkyl or C₁-C₂₀ branched alkyl, R₁₄ is selected from the group consisting of hydrogen, substituted or unsubstituted amine, C₃-C₁₀ cycloalkyl, C₃-C₁₀ heterocycloalkyl, C₄-C₁₀ aryl and C₄-C₁₀ heteroaryl, l is selected from the 1~5;

vii) substituted or unsubstituted carboxyl;

viii) $-\text{OSO}_3\text{Na}^+$;

k is selected from the 0~20, with proviso that when k is 0, R_{13} and R_{14} are not anything, and R_{15} is directly bond to a carbonyl group and,

wherein hetero atom(s) in the heterocycloalkyl or heteroaryl is(are) one or
5 more selected from O, N and S.

As used herein, the term “solvate” means a compound of the present invention or a salt thereof, which further includes a stoichiometric or non-stoichiometric amount of a solvent bound thereto by non-covalent intermolecular forces. Preferred solvents are volatile, non-toxic, and/or acceptable for administration to humans. Where the solvent is
10 water, the solvate refers to a hydrate.

As used herein, the term “isomer” means a compound of the present invention or a salt thereof that has the same chemical formula or molecular formula but is optically or sterically different therefrom. D type optical isomer and L type optical isomer can be present in the Formula 1 or 2, depending on the $R_1\sim R_6$ types of
15 substituents selected.

Unless otherwise specified, the term “naphthoquinone-based compound” or “compound of Formula 1 or 2” is intended to encompass a compound *per se*, and a pharmaceutically acceptable salt, prodrug, solvate and isomer thereof.

As used herein, the term “alkyl” refers to a radical which contains carbon and
20 hydrogen, without unsaturation. The alkyl radical may be linear or branched. Examples of alkyl radical include, but are not limited to, methyl, ethyl, propyl, isopropyl, hexyl, t-butyl and sec-butyl. Lower alkyl is $C_1\text{-}C_{10}$ alkyl (for example, the alkyl which has 1~10 carbon atoms in its linear or branched alkyl mainchain). The alkyl can be substituted

optionally. When substituted, the alkyl can be substituted as 4 and less substituents specified below at any specific bonding point (at any carbon atom); can be substituted as one or more components such as hydroxyl, carboxylate, oxo, halogen (for example, F, Cl, Br, I), haloalkyl (for example, CCl_3 or CF_3), alkyloxycarbonyl ($-\text{C}(\text{O})\text{R}$),
5 alkylocarbonyloxy ($-\text{OCOR}$), carbamoyl ($-\text{NHCOOR}-$ or $-\text{OCONHR}-$), urea ($-\text{NHCONHR}-$), thiol, cyano, nitro, amino, acylamino, C_1 - C_6 alkylthio, arylthio, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, aryloxy, alkylocarbonyloxy, arylcarbonyloxy, C_3 - C_6 cycloalkyl, C_3 - C_6 cycloalkyloxy, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, aryl, aminocarbonyl, C_1 - C_6 alkylocarbonyl, C_3 - C_6 cycloalkylcarbonyl, heterocyclycarbonyl, arylcarbonyl,
10 aryloxycarbonyl, C_1 - C_6 alkoxy carbonyl, C_3 - C_6 cycloalkyloxycarbonyl, heterocyclyloxycarbonyl, C_1 - C_6 alkylsufonyl, arylsufonyl, heterocyclyl.

Meanwhile, when the alkyl is substituted by another alkyl group, it may be used as the same meaning of "branched alkyl".

Preferred alkyl includes 1~6 carbon atoms. Alkylene, as used herein, means a
15 cross linked alkyl group whose chemical formula is C_nH_{2n} . For example, it includes CH_2 , $-\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{CH}_2-$.

As used herein, the term "cycloalkyl" means an alkyl group which includes 3~15 carbon atoms without any shift or resonance double bond. The cycloalkyl may include 1~4 rings. Examples of the cycloalkyl include cyclopropyl, cyclobutyl,
20 cyclopentyl, cyclohexyl and adamantyl. An example substituent for cycloalkyl includes one or more groups from halogen, alkyl, alkoxy, alkylhydroxy, amino, nitro, cyano, thiol and/or alkylthio.

As used herein, the term "heterocycloalkyl", "heterocyclyl", or "heterocyclic" means saturated or unsaturated 7~11 membered bicyclic heterocyclic rings or

chemically stable non-aromatic 3~7 membered monocyclic heterocyclic rings, and may form an additional ring via fusion, spiro, cross-linking. Each heterocyclic ring is composed of 1~4 hetero atoms selected from the group which is consisted of at least one carbon atom, nitrogen, oxygen and sulfur. Heterocyclyl radical is bound with any endocyclic ring which creates a stable structure. Preferred heterocyclic ring includes 3~7 membered monocyclic heterocyclic rings (more preferably 5~7 membered monocyclic heterocyclic rings) such as, but not limited to, piperidinyl, pyranyl, piperazinyl, morpholinyl, thiamorpholinyl and tetrahydrofuranlyl.

As used herein, the term "alkenyl" means an unsaturated aliphatic group that is similar to alkyl mentioned above such as length and substitutability but contains one or more carbon-carbon double bonds. For example, the term "alkenyl includes linear alkenyl (for example, ethenyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl, decenyl), branched alkenyl, cycloalkenyl (alicyclic compound, for example, cyclopropenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl), cycloalkenyl which is substituted by alkyl or alkenyl and alkenyl which is substituted by cycloalkyl or cycloalkenyl. The term "alkenyl" also includes an additional alkenyl group which has one or more carbon atoms substituted by oxygen, nitrogen, sulfur or phosphorus. For specific example, a linear or branched alkenyl group has 6 and less carbon atoms at its mainchain (for example, C₂-C₆ for linear, C₃-C₆ for branched). Similarly, cycloalkenyl may have 3~8 carbon atoms in the ring system; more preferably, have 5~6 carbon atoms. The term "C₂-C₆ alkenyl" includes an alkenyl group which contains 2~6 carbon atoms.

As used herein, the term "alkynyl" means an unsaturated aliphatic group that is similar to alkyl mentioned above such as length and substitutability but contains one or

more carbon-carbon triple bonds. For example, the term “alkynyl” includes linear alkynyl (for example, ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl, decynyl), branched alkynyl (including alkynyl which is substituted by alkyl or alkenyl) and alkynyl which is substituted by cycloalkyl or cycloalkenyl. The term
5 “alkynyl” also includes an additional alkynyl group which has one or more carbohydrogen mainchain carbon atoms substituted by oxygen, nitrogen, sulfur or phosphorus. For specific example, a linear or branched alkynyl group has 6 and less carbon atoms at its mainchain (for example, C₂-C₆ for linear, C₃-C₆ for branched). The term “C₂-C₆ alkynyl” includes an alkynyl group which contains 2~6 carbon atoms.

10 As used herein, the term “acyl” includes compound and component which contain acyl radical (CH₃CO-) or carbonyl. The “substituted acyl” includes a acyl group which has one or more substituted hydrogen substituted by, for example, alkyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxy carbonyloxy, aryloxy carbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxy carbonyl,
15 aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxy, phosphate, phosphonato, phosphinato, cyano, amino (including alkylamino, dialkylamino, arylamino, diarylamino and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfate, alkylsulfinyl, sulfonato,
20 sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl or by aromatic or heteroaromatic component.

As used herein, the term “aryl” means an aromatic carbocyclic compounds or heteroaromatic components which have 1, 2 or 3 rings. The aryl may be a carbocyclic

compound or may have 1~4 hetero atoms (for example, nitrogen (N), sulfur (S) or oxygen (O)) in its aromatic ring system optionally.

Examples of aryl include, but are not limited to, phenyl, naftyl, pyridyl, pyrimidyl, pyrrolyl, isothiazolyl, triazolyl, tetrazolyl, pyrazolyl, oxazolyl, isooxazolyl, pyrazinyl, pyridazinyl, triazinyl, quinazolinyl, thiazolyl, benzothiophenyl, furanyl, imidazolyl and thiophenyl. The aryl may be optionally substituted by one or more substituents, for example, hydroxyl, halogen, thiol, cyano, nitro, amino, acylamino, C₁-C₆ alkylthio, arylthio, C₁-C₆ alkyl, C₁-C₆ alkoxy, aryloxy, alkylcarbonyloxy, arylcarbonyloxy, C₃-C₆ cycloalkyl, C₃-C₆ cycloalkyloxy, C₂-C₆ alkenyl, C₂-C₆ alkynyl, aryl, carboxylate, aminocarbonyl, C₁-C₆ alkylcarbonyl, C₃-C₆ cycloalkylcarbonyl, heterocyclylcarbonyl, arylcarbonyl, aryloxycarbonyl, C₁-C₆ alkoxycarbonyl, C₃-C₆ cycloalkyloxycarbonyl, heterocyclyloxycarbonyl, aryloxycarbonyl, C₁-C₆ alkylsulfonyl, arylsulfonyl, and heterocyclyl.

As used herein, the term "alkoxy" means -O- alkyl (wherein, alkyl is defined as the above). The alkoxy bind to mainchain, aryl or heteroaryl via oxo-bridge. The alkoxy may be linear or branched, but linear is preferred. For example, methoxy, ethyloxy, propoxy, butyloxy, t-butyloxy or i-propoxy is included. Preferred alkoxy includes 1~4 carbon atoms; particularly preferred alkoxy includes 1~3 carbon atoms. The most preferred alkoxy is methoxy.

As used herein, the term "halogen" or "halo" includes VIIa group elements, for example, chlorine (Cl), bromine (Br), fluorine (F), iodine (I).

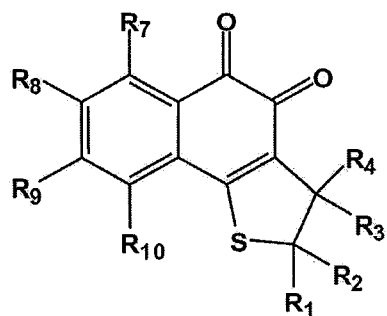
As used herein, the term "amine" or "amino" includes compound which has a covalent coupled nitrogen atom with one or more carbon or hetero atoms.

As used herein, the term “alkylamino” includes compound or group which has nitrogen combined with one or more additional alkyl groups. As used herein, the term “dialkylamino” includes a group which has nitrogen combined with two or more additional alkyl groups. As used herein, the term “arylamino” and “diarylamino” include a group which has nitrogen combined with one, two or more additional alkyl groups. As used herein, the term “alkylarylamino”, “alkylaminoaryl” or “arylaminoalkyl” means amino group combined with one or more alkyl groups and with one or more aryl groups. As used herein, the term “alkylaminoalkyl” means alkyl, alkenyl and alkynyl group combined with nitrogen atom that is also combined with another alkyl group.

As used herein, the term “carbonyl” or “carboxy” includes compound and component which have carbon atom double bonded to oxygen atom. Examples of component containing carbonyl include aldehyde, ketone, carboxylic acid, amide, ester, and anhydride.

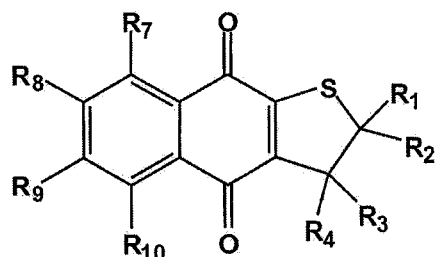
Among compounds of Formula 1 or 2, preferred are compounds represented by Formula 3 to Formula 7 below.

Compounds of Formula 3 are compounds wherein m is 0, and adjacent carbon atoms form a cyclic structure (furan ring) via a direct bond therebetween in Formula 1, are often referred to as “Thiophen-1,2-naphthoquinone derivatives” hereinafter.



(3)

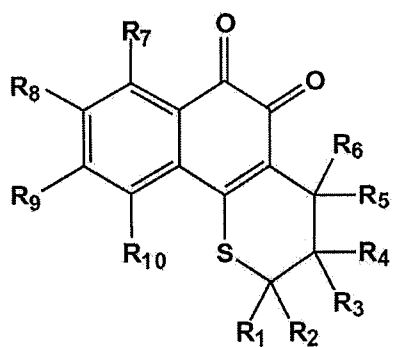
Compounds of Formula 4 are compounds wherein m is 0, and adjacent carbon atoms form a cyclic structure (furan ring) via a direct bond therebetween in Formula 2, are often referred to as “Thiophen-1,4-naphthoquinone derivatives” hereinafter.



(4)

5

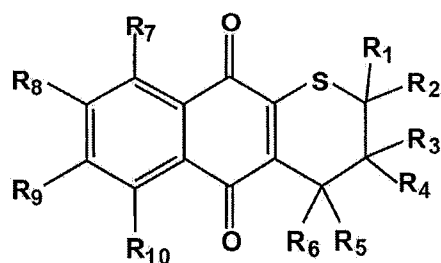
Compounds of Formula 5 are compounds wherein m is 1 and Y is C in Formula 1 are often referred to as “Thiopyrano-1,2-naphthoquinone derivatives” hereinafter.



(5)

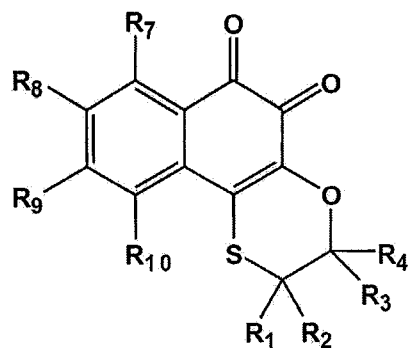
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Compounds of Formula 6 are compounds wherein m is 1 and Y is C in Formula 2 are often referred to as “Thiopyrano-1,4-naphthoquinone derivatives” hereinafter.



(6)

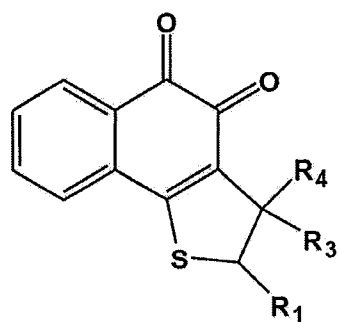
Compounds of Formula 7 are compounds wherein m is 1 and Y is O in Formula 1 are often referred to as “Thioxane-1,2-naphthoquinone derivatives” hereinafter.



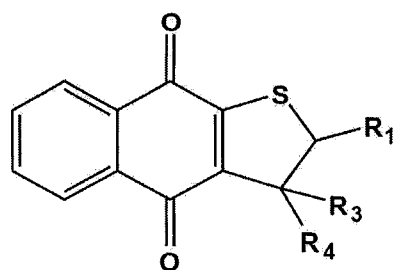
5

(7)

Among the furan derivatives of Formula 3 or 4, particularly preferred are compounds of Formulae 3a and 4a, wherein R₂, R₇, R₈, R₉ and R₁₀ are hydrogen, and compounds of Formulae 3b and 4b wherein R₄, R₇, R₈, R₉ and R₁₀ are hydrogen.

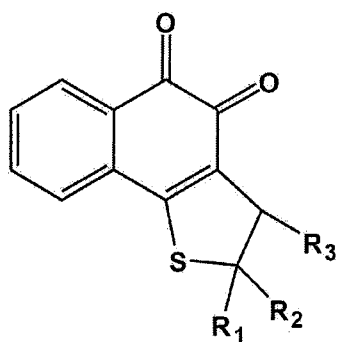


(3a)

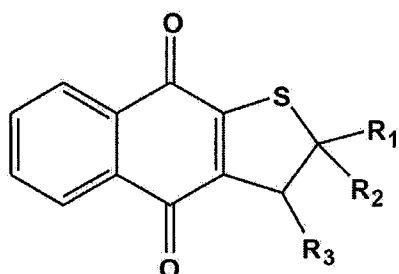


(4a)

wherein, R₁, R₃ and R₄ are defined as in the Formula 1.



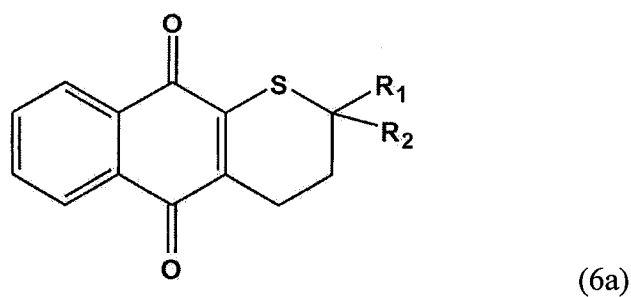
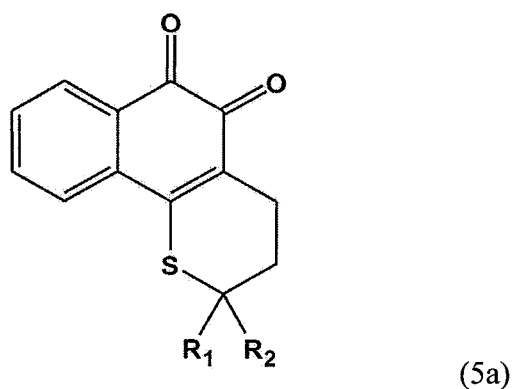
(3b)



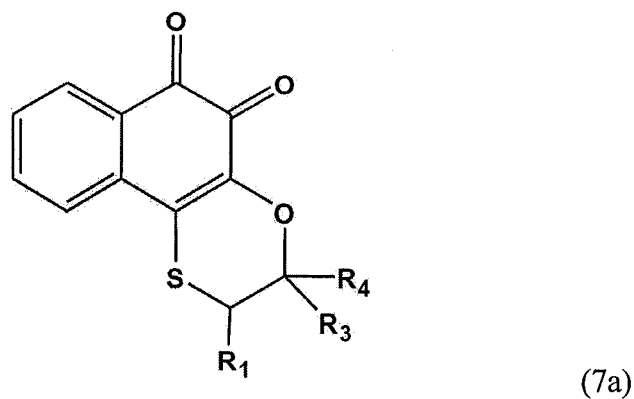
(4b)

5 wherein, R₁, R₂ and R₃ are defined as in the Formula 1.

Among the pyran compounds of Formulae 5 and 6, particularly preferred are compounds of Formulae 5a and 6a wherein R₃, R₄, R₅, R₆, R₇, R₈, R₉ and R₁₀ are hydrogen, and Y is C.



Further, among the thioxane-1,2-naphthoquinone derivatives of Formula 7, particularly preferred is compounds of Formula 7a wherein R₂, R₇, R₈, R₉ and R₁₀ are hydrogen.



The term “pharmaceutical composition” as used herein means a mixture of a compound of Formula 1 or 2 with other chemical components, such as diluents or carriers. The pharmaceutical composition facilitates administration of the compound to an organism. Various techniques of administering a compound are known in the art and include, but are not limited to oral, injection, aerosol, parenteral and topical

administrations. Pharmaceutical compositions can also be obtained by reacting compounds of interest with acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, methanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like.

5 The term “therapeutically effective amount” means an amount of an active ingredient that is effective to relieve or reduce to some extent one or more of the symptoms of the disease in need of treatment, or to retard initiation of clinical markers or symptoms of a disease in need of prevention, when the compound is administered. Thus, a therapeutically effective amount refers to an amount of the active ingredient
10 which exhibit effects of (i) reversing the rate of progress of a disease; (ii) inhibiting to some extent further progress of the disease; and/or, (iii) relieving to some extent (or, preferably, eliminating) one or more symptoms associated with the disease. The therapeutically effective amount may be empirically determined by experimenting with the compounds concerned in known *in vivo* and *in vitro* model systems for a disease in
15 need of treatment.

Effective substance which exerts therapeutic effect on the treatment and/or prevention of disease syndromes in the present invention is often referred to as “active ingredient” hereinafter.

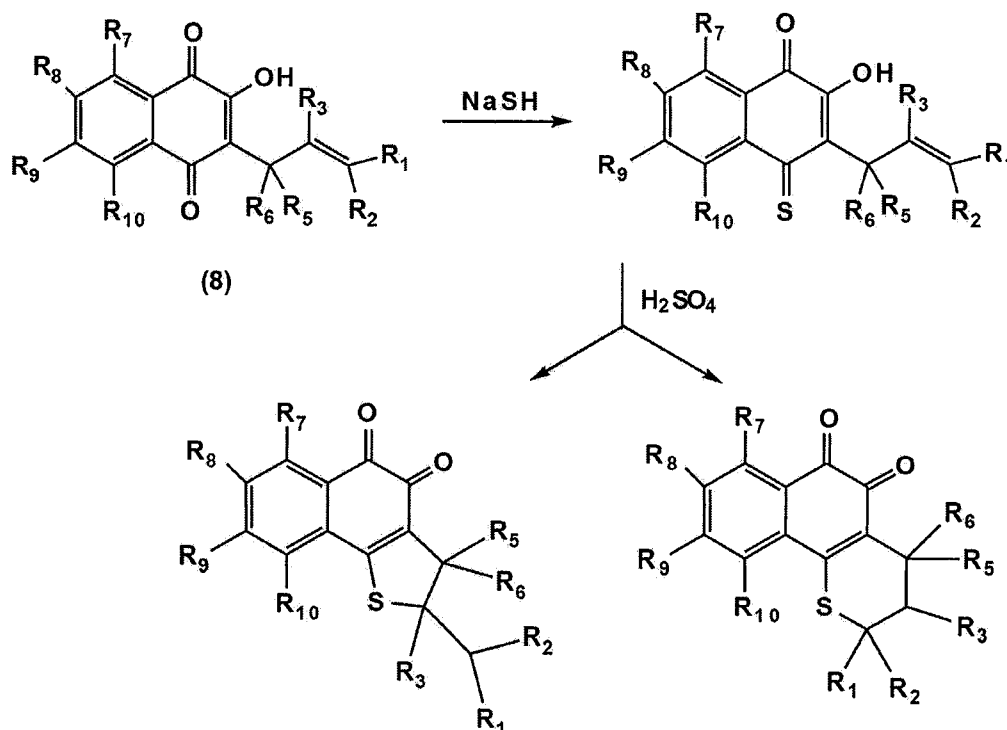
In the pharmaceutical composition in accordance with the present invention,
20 compounds of Formula 1 or 2 which are active ingredients, as will be illustrated hereinafter, can be prepared by conventional methods known in the art and/or various processes which are based upon the general technologies and practices in the organic chemistry synthesis field. The preparation processes described below are only

exemplary ones and other processes can also be employed. As such, the scope of the instant invention is not limited to the following processes.

Preparation method 1: Acid-catalyzed cyclization of lapachol derivatives

5 The compound of Formula 1 according to present invention can be obtained by reacting lapachol derivatives, 2-hydroxy-3-allyl-1,4-naphthoquinone derivatives such as the following compound of Formula 8, with NaSH to prepare thioquinone thereof, and then by deriving cyclization reaction in the strong acid condition. The above synthesis process may be summarized as follows.

10 [Synthesis process 1]



In this case, 5 or 6-cyclic cyclization occurs depending on the types of R₁, R₂, and R₃ via a cationic cyclization. That is, when R₁ and R₂ are H, C5 cyclic ring is formed, and when R₁, R₂ are alkyl and R₃ is H, C6 cyclic ring is formed. Further, when

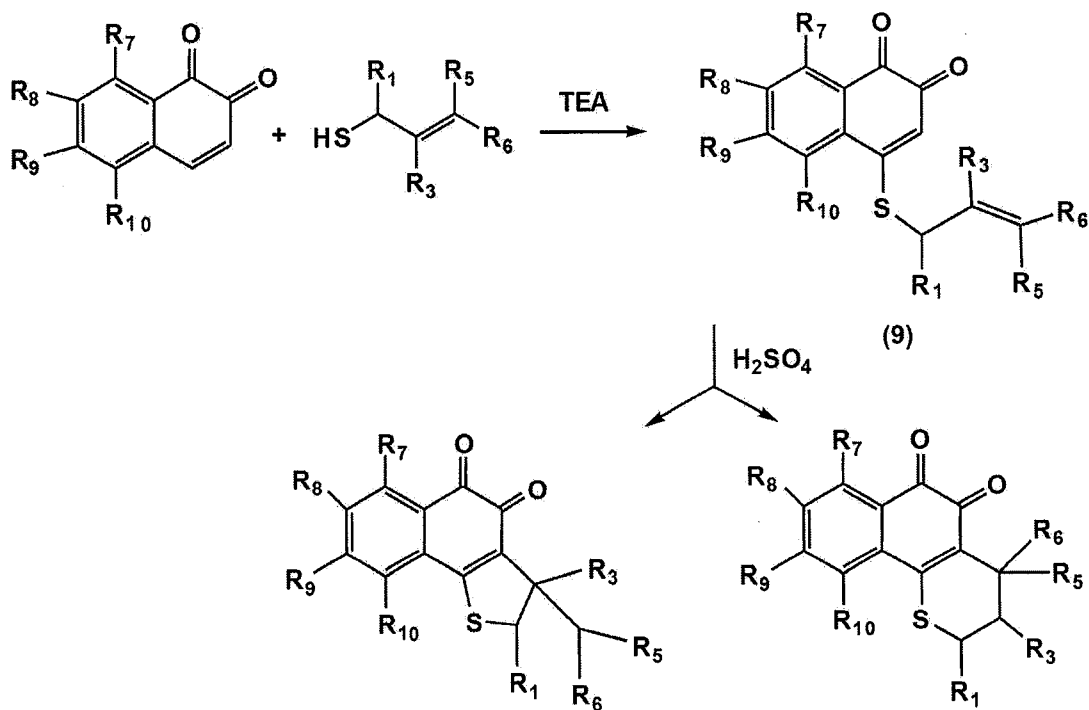
R₂ and R₃ are H, a mixture of C5 cyclic ring and C6 cyclic ring is made. Generally, most of thiopyrano-1,2-naphthoquinone and thiophen-1,2-naphthoquinone derivatives, as a tricyclic naphthoquinone compound having simple structure, can be synthesized by two-step reactions from lapachol derivatives such as the compound of Formula 8 above.

5

Preparation method 2: Acid-catalyzed cyclization of 4-thioalkoxy-1,2-naphthoquinone derivatives

As another method, as summarized by Synthesis process 2 below, the compound of Formula 1 can be prepared by reacting 1,2-naphthoquinone with allyl thiol in the presence of base to obtain 4-allylthio-1,2-naphthoquinone as the compound of Formula 9 below, and then by deriving cyclization reaction in the strong acid condition. The above synthesis process may be summarized as follows.

[Synthesis process 2]

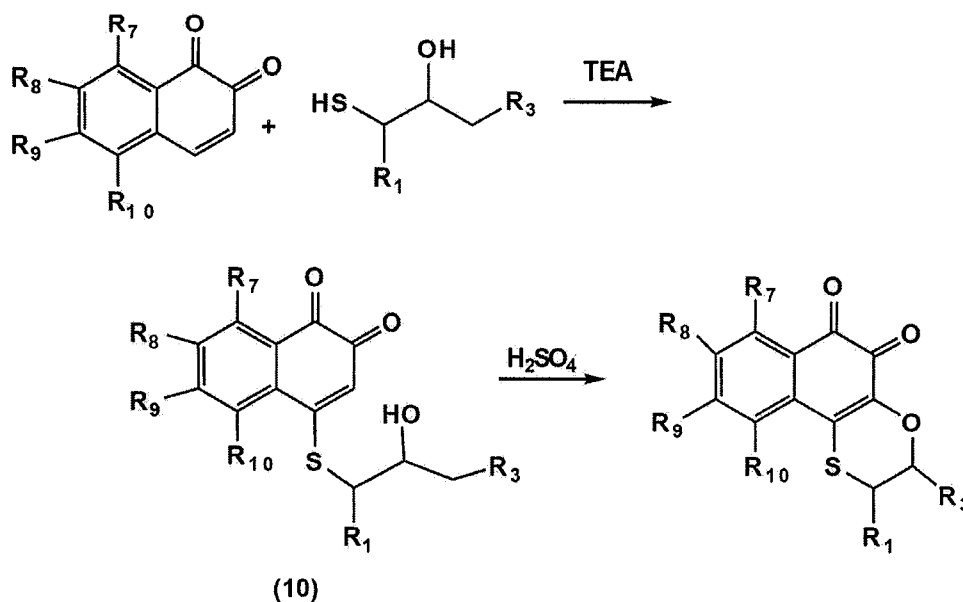


In this case, 5 or 6-cyclic cyclization occurs depending on the types of R₁, R₃, R₅ and R₆. That is, when R₃ is H and R₅ and R₆ are alkyl or aryl, C6 cyclic ring is formed, and when R₃ is alkyl and R₅ and R₆ are H, C5 cyclic ring is formed. In addition, when all of R₃, R₅ and R₆ are alkyl, a mixture of C5 cyclic ring and C6 cyclic ring is made. Generally, most of thiopyrano-1,2-naphthoquinone and thiophen-1,2-naphthoquinone derivatives, as a tricyclic naphthoquinon compound having the simple structure, can be synthesized by the strong acid-catalyzed reaction from 4-allylthio-1,2-naphthoquinone as the compound of Formula 9 above.

10 Preparation method 3: cyclization reaction of 4-(2-hydroxyethyl-1-thio)-1,2-naphthoquinone derivatives

As summarized by Synthesis process 3 below, 1,2-naphthoquinone can be reacted with 2-hydroxyethyl-1-thiol in the presence of base to synthesize 4-(2-hydroxyethylthio)-1,2-naphthoquinone as the compound of Formula 10 below, which is then subjected to cyclization under the strong acid condition to synthesize thioxan-1,2-naphthoquinone. The above synthesis process may be summarized as follows.

[Synthesis process 3]

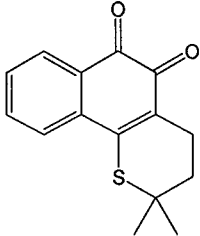
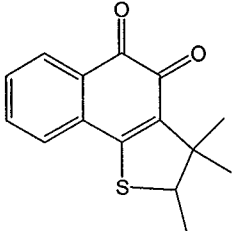
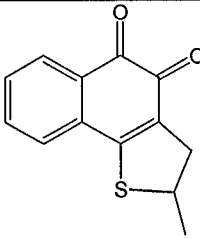
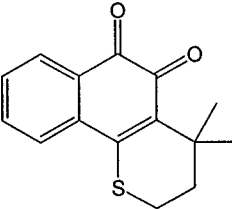
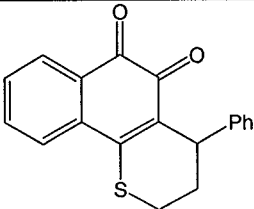
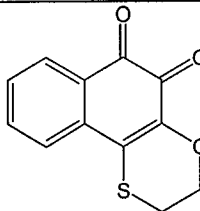


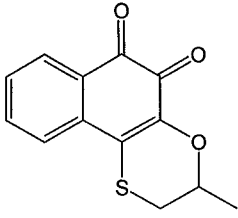
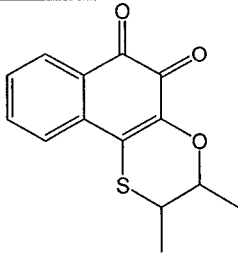
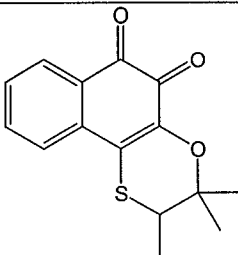
In this case, it can be understood that a cationic cyclization reaction occurs by oxidation of oxygen present in the air, while a strong acid serves as a catalyst. The above reaction was at first intended to synthesize thiopyrano naphthoquinone derivatives or thiophen naphthoquinone derivatives; however, unlike such intention, thioxan-1,2-naphthoquinone and 2,3-dihydro-naphtho[2,1-*b*][1,4]oxathiine-5,6-dione derivatives were synthesized, which was confirmed to exhibit the identical pharmacological actions to the other compounds according to the present invention by physiologic activity experiments.

Based on the above-mentioned preparation methods, various derivatives may be synthesized using relevant synthesis methods, depending upon kinds of substituents.

Among compounds of according to the present invention, particularly preferred are the compounds in Table 1 below, but are not limited thereto.

[Table 1]

Compound 1		$C_{15}H_{14}O_2S$	258.34	Method 1
Compound 2		$C_{15}H_{14}O_2S$	258.34	Method 1
Compound 3		$C_{13}H_{10}O_2S$	230.28	Method 1
Compound 4		$C_{15}H_{14}O_2S$	258.34	Method 2
Compound 5		$C_{19}H_{14}O_2S$	306.38	Method 2
Compound 6		$C_{12}H_8O_3S$	232.26	Method 3

Compound 7		$C_{13}H_{10}O_3S$	246.28	Method 3
Compound 8		$C_{14}H_{12}O_3S$	260.31	Method 3
Compound 9		$C_{15}H_{14}O_3S$	274.34	Method 3

The pharmaceutical composition of the present invention may be manufactured in a manner that is itself known, *e.g.*, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes.

- 5 The pharmaceutical composition of the present invention may include additionally a pharmaceutically acceptable carrier, a diluent or an excipient, or any combination thereof. That may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used
- 10 pharmaceutically. The pharmaceutical composition facilitates administration of the compound to an organism.

The term “carrier” means a chemical compound that facilitates the incorporation of a compound into cells or tissues. For example, dimethyl sulfoxide

(DMSO) is a commonly utilized carrier as it facilitates the uptake of many organic compounds into the cells or tissues of an organism.

The term "diluent" defines chemical compounds diluted in water that will dissolve the compound of interest as well as stabilize the biologically active form of the compound. Salts dissolved in buffered solutions are utilized as diluents in the art. One
5 commonly used buffer solution is phosphate buffered saline (PBS) because it mimics the ionic strength conditions of human body fluid. Since buffer salts can control the pH of a solution at low concentrations, a buffer diluent rarely modifies the biological activity of a compound.

10 The compounds described herein may be administered to a human patient *per se*, or in the form of pharmaceutical compositions in which they are mixed with other active ingredients, as in combination therapy, or suitable carriers or excipient(s). Techniques for formulation and administration of the compounds may be found in "Remington's Pharmaceutical Sciences," Mack Publishing Co., Easton, PA, 18th
15 edition, 1990.

Various techniques of administering a compound are known in the art and include, but are not limited to oral, injection, aerosol, parenteral and topical administrations. Pharmaceutical compositions can also be obtained by reacting
20 compounds of interest with acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, methanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like.

The compounds may be formulated by a variety of methods known in the art, preferably formulated into pharmaceutically acceptable oral, external, transmucosal and

injectable preparation which is pharmaceutically acceptable, more preferably formulated into oral preparation.

For injection, the agents of the present invention may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks's solution, Ringer's solution, or physiological saline. For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

The pharmaceutical compounds in accordance with the present invention, may be particularly preferably an oral pharmaceutical composition which is prepared into an intestine-targeted formulation.

Generally, an oral pharmaceutical composition passes through the stomach upon oral administration, is largely absorbed by the small intestine and then diffused into all the tissues of the body, thereby exerting therapeutic effects on the target tissues.

In this connection, the oral pharmaceutical composition according to the present invention enhances bioabsorption and bioavailability of compound of Formula 1 or 2 as active ingredient via intestine-targeted formulation of the active ingredient. More specifically, when the active ingredient in the pharmaceutical composition according to the present invention is primarily absorbed in the stomach, and upper parts of the small intestine, the active ingredient absorbed into the body directly undergoes liver metabolism which is then accompanied by substantial degradation of the active ingredient, so it is impossible to exert a desired level of therapeutic effects. On the other hand, it is expected that when the active ingredient is largely absorbed around and downstream of the lower small intestine, the absorbed active ingredient migrates via lymph vessels to the target tissues to thereby exert high therapeutic effects.

Further, as it is constructed in such a way that the pharmaceutical composition according to the present invention targets up to the colon which is a final destination of the digestion process, it is possible to increase the *in vivo* retention time of the drug and it is also possible to minimize decomposition of the drug which may take place due to the body metabolism upon administration of the drug into the body. As a result, it is possible to improve pharmacokinetic properties of the drug, to significantly lower a critical effective dose of the active ingredient necessary for the treatment of the disease, and to obtain desired therapeutic effects even with administration of a trace amount of the active ingredient. Further, in the oral pharmaceutical composition, it is also possible to minimize the absorption variation of the drug by reducing the between- and within-individual variation of the bioavailability which may result from intragastric pH changes and dietary uptake patterns.

Therefore, the intestine-targeted formulation according to the present invention is configured such that the active ingredient is largely absorbed in the small and large intestines, more preferably in the jejunum, and the ileum and colon corresponding to the lower small intestine, particularly preferably in the ileum or colon.

The intestine-targeted formulation may be designed by taking advantage of numerous physiological parameters of the digestive tract, through a variety of methods. In one preferred embodiment of the present invention, the intestine-targeted formulation may be prepared by (1) a formulation method based on a pH-sensitive polymer, (2) a formulation method based on a biodegradable polymer which is decomposable by an intestine-specific bacterial enzyme, (3) a formulation method based on a biodegradable matrix which is decomposable by an intestine-specific bacterial enzyme, or (4) a

formulation method which allows release of a drug after a given lag time, and any combination thereof.

Specifically, the intestine-targeted formulation (1) using the pH-sensitive polymer is a drug delivery system which is based on pH changes of the digestive tract.

5 The pH of the stomach is in a range of 1 to 3, whereas the pH of the small and large intestines has a value of 7 or more, which is higher as compared to that of the stomach. Based on this fact, the pH-sensitive polymer may be used in order to ensure that the pharmaceutical composition reaches the lower intestinal parts without being affected by pH fluctuations of the digestive tract. Examples of the pH-sensitive polymer may
10 include, but are not limited to, at least one selected from the group consisting of methacrylic acid-ethyl acrylate copolymer (Eudragit: Registered Trademark of Rohm Pharma GmbH), hydroxypropylmethyl cellulose phthalate (HPMCP) and a mixture thereof.

Preferably, the pH-sensitive polymer may be added by a coating process. For
15 example, addition of the polymer may be carried out by mixing the polymer in a solvent to form an aqueous coating suspension, spraying the resulting coating suspension to form a film coating, and drying the film coating.

The intestine-targeted formulation (2) using the biodegradable polymer which is decomposable by the intestine-specific bacterial enzyme is based on the utilization of
20 a degradative ability of a specific enzyme that can be produced by enteric bacteria. Examples of the specific enzyme may include azoreductase, bacterial hydrolase glycosidase, esterase, polysaccharidase, and the like.

When it is desired to design the intestine-targeted formulation using azoreductase as a target, the biodegradable polymer may be a polymer containing an

azoaromatic linkage, for example, a copolymer of styrene and hydroxyethylmethacrylate (HEMA). When the polymer is added to the formulation containing the active ingredient, the active ingredient may be liberated into the intestine by reduction of an azo group of the polymer via the action of the azoreductase which is specifically secreted by enteric bacteria, for example, *Bacteroides fragilis* and *Eubacterium limosum*.

When it is desired to design the intestine-targeted formulation using glycosidase, esterase, or polysaccharidase as a target, the biodegradable polymer may be a naturally-occurring polysaccharide or a substituted derivative thereof. For example, the biodegradable polymer may be at least one selected from the group consisting of dextran ester, pectin, amylose, ethyl cellulose and a pharmaceutically acceptable salt thereof. When the polymer is added to the active ingredient, the active ingredient may be liberated into the intestine by hydrolysis of the polymer via the action of each enzyme which is specifically secreted by enteric bacteria, for example, *Bifidobacteria* and *Bacteroides* spp. These polymers are natural materials, and have an advantage of low risk of *in vivo* toxicity.

The intestine-targeted formulation (3) using the biodegradable matrix which is decomposable by an intestine-specific bacterial enzyme may be a form in which the biodegradable polymers are cross-linked to each other and are added to the active ingredient or the active ingredient-containing formulation. Examples of the biodegradable polymer may include naturally-occurring polymers such as chondroitin sulfate, guar gum, chitosan, pectin, and the like. The degree of drug release may vary depending upon the degree of cross-linking of the matrix-constituting polymer.

In addition to the naturally-occurring polymers, the biodegradable matrix may be a synthetic hydrogel based on N-substituted acrylamide. For example, there may be used a hydrogel synthesized by cross-linking of N-tert-butylacryl amide with acrylic acid or copolymerization of 2-hydroxyethyl methacrylate and 4-methacryloyloxyazobenzene, as the matrix. The cross-linking may be, for example an azo linkage as mentioned above, and the formulation may be a form where the density of cross-linking is maintained to provide the optimal conditions for intestinal drug delivery and the linkage is degraded to interact with the intestinal mucous membrane when the drug is delivered to the intestine.

Further, the intestine-targeted formulation (4) with time-course release of the drug after a lag time is a drug delivery system utilizing a mechanism that is allowed to release the active ingredient after a predetermined time irrespective of pH changes. In order to achieve enteric release of the active drug, the formulation should be resistant to the gastric pH environment, and should be in a silent phase for 5 to 6 hours corresponding to a time period taken for delivery of the drug from the body to the intestine, prior to release of the active ingredient into the intestine. The time-specific delayed-release formulation may be prepared by addition of the hydrogel prepared from copolymerization of polyethylene oxide with polyurethane.

Specifically, the delayed-release formulation may have a configuration in which the formulation absorbs water and then swells while it stays within the stomach and the upper digestive tract of the small intestine, upon addition of a hydrogel having the above-mentioned composition after applying the drug to an insoluble polymer, and then migrates to the lower part of the small intestine which is the lower digestive tract

and liberates the drug, and the lag time of drug is determined depending upon a length of the hydrogel.

As another example of the polymer, ethyl cellulose (EC) may be used in the delayed-release dosage formulation. EC is an insoluble polymer, and may serve as a factor to delay a drug release time, in response to swelling of a swelling medium due to water penetration or changes in the internal pressure of the intestines due to a peristaltic motion. The lag time may be controlled by the thickness of EC. As an additional example, hydroxypropylmethyl cellulose (HPMC) may also be used as a retarding agent that allows drug release after a given period of time by thickness control of the polymer, and may have a lag time of 5 to 10 hours.

In the oral pharmaceutical composition according to the present invention, the active ingredient may have a crystalline structure with a high degree of crystallinity, or a crystalline structure with a low degree of crystallinity.

As used herein, the term "degree of crystallinity" is defined as the weight fraction of the crystalline portion of the total compound and may be determined by a conventional method known in the art. For example, measurement of the degree of crystallinity may be carried out by a density method or precipitation method which calculates the crystallinity degree by previous assumption of a preset value obtained by addition and/or reduction of appropriate values to/from each density of the crystalline portion and the amorphous portion, a method involving measurement of the heat of fusion, an X-ray method in which the crystallinity degree is calculated by separation of the crystalline diffraction fraction and the noncrystalline diffraction fraction from X-ray diffraction intensity distribution upon X-ray diffraction analysis, or an infrared method

which calculates the crystallinity degree from a peak of the width between crystalline bands of the infrared absorption spectrum.

In the oral pharmaceutical composition according to the present invention, the crystallinity degree of the active ingredient is preferably 50% or less. More preferably, the active ingredient may have an amorphous structure from which the intrinsic crystallinity of the material was completely lost. The amorphous naphthoquinone-based compound exhibits a relatively high solubility, as compared to the crystalline naphthoquinone-based compound, and can significantly improve a dissolution rate and *in vivo* absorption rate of the drug.

In one preferred embodiment of the present invention, the amorphous structure may be formed during preparation of the active ingredient into microparticles or fine particles (micronization of the active ingredient). The microparticles may be prepared, for example by spray drying of active ingredients, melting methods involving formation of melts of active ingredients with polymers, co-precipitation involving formation of coprecipitates of active ingredients with polymers after dissolution of active ingredients in solvents, inclusion body formation, solvent volatilization, and the like. Preferred is spray drying. Even when the active ingredient is not of an amorphous structure, that is has a crystalline structure or semi-crystalline structure, micronization of the active ingredient into fine particles via mechanical milling contributes to improvement of solubility, due to a large specific surface area of the particles, consequently resulting in improved dissolution rate and bioabsorption rate of the active drug.

The spray drying is a method of making fine particles by dissolving the active ingredient in a certain solvent and the spray-drying the resulting solution. During the spray-drying process, a high percent of the crystallinity of the naphthoquinone

compound is lost to thereby result in an amorphous state, and therefore the spray-dried product in the form of a fine powder is obtained.

The mechanical milling is a method of grinding the active ingredient into fine particles by applying strong physical force to active ingredient particles. The
5 mechanical milling may be carried out by using a variety of milling processes such as jet milling, ball milling, vibration milling, hammer milling, and the like. Particularly preferred is jet milling which can be carried out using an air pressure, at a temperature of 40 °C or less.

Meanwhile, irrespective of the crystalline structure, a decreasing particle
10 diameter of the particulate active ingredient leads to an increasing specific surface area, thereby increasing the dissolution rate and solubility. However, an excessively small particle diameter makes it difficult to prepare fine particles having such a size and also brings about agglomeration or aggregation of particles which may result in deterioration of the solubility. Therefore, in one preferred embodiment, the particle diameter of the
15 active ingredient may be in a range of 5 nm to 500 μm . In this range, the particle agglomeration or aggregation can be maximally inhibited, and the dissolution rate and solubility can be maximized due to a high specific surface area of the particles.

Preferably, a surfactant may be additionally added to prevent the particle
agglomeration or aggregation which may occur during formation of the fine particles,
20 and/or an antistatic agent may be additionally added to prevent the occurrence of static electricity.

If necessary, a moisture-absorbent material may be further added during the milling process. The naphthoquinone-based compound of Formula 1 or 2 has a tendency to be crystallized by water, so incorporation of the moisture-absorbent material inhibits

recrystallization of the naphthoquinone-based compound over time and enables maintenance of increased solubility of compound particles due to micronization. Further, the moisture-absorbent material serves to suppress coagulation and aggregation of the pharmaceutical composition while not adversely affecting therapeutic effects of
5 the active ingredient.

Examples of the surfactant may include, but are not limited to, anionic surfactants such as docusate sodium and sodium lauryl sulfate; cationic surfactants such as benzalkonium chloride, benzethonium chloride and cetrimide; nonionic surfactants such as glyceryl monooleate, polyoxyethylene sorbitan fatty acid ester, and sorbitan
10 ester; amphiphilic polymers such as polyethylene-polypropylene polymer and polyoxyethylene-polyoxypropylene polymer (Poloxamer), and Gelucire™ series (Gattefosse Corporation, USA); propylene glycol monocaprylate, oleoyl macrogol-6-glyceride, linoleoyl macrogol-6-glyceride, caprylocaproyl macrogol-8-glyceride, propylene glycol monolaurate, and polyglyceryl-6-dioleate. These materials may be
15 used alone or in any combination thereof.

Examples of the moisture-absorbent material may include, but are not limited to, colloidal silica, light anhydrous silicic acid, heavy anhydrous silicic acid, sodium chloride, calcium silicate, potassium aluminosilicate, calcium aluminosilicate, and the like. These materials may be used alone or in any combination thereof.

20 Some of the above-mentioned moisture absorbents may also be used as the antistatic agent.

The surfactant, antistatic agent, and moisture absorbent are added in a certain amount that is capable of achieving the above-mentioned effects, and such an amount may be appropriately adjusted depending upon micronization conditions. Preferably, the

additives may be used in a range of 0.05 to 20% by weight, based on the total weight of the active ingredient.

In one preferred embodiment, during formulation of the pharmaceutical composition according to the present invention into preparations for oral administration, 5 water-soluble polymers, solubilizers and disintegration-promoting agents may be further added. Preferably, formulation of the composition into a desired dosage form may be made by mixing the additives and the particulate active ingredient in a solvent and spray-drying the mixture.

The water-soluble polymer is of help to prevent aggregation of the particulate 10 active ingredients, by rendering surroundings of naphthoquinone-based compound molecules or particles hydrophilic to consequently enhance water solubility, and preferably to maintain the amorphous state of the compound of Formula 1 or 2 as an active ingredient.

Preferably, the water-soluble polymer is a pH-independent polymer, and can 15 bring about crystallinity loss and enhanced hydrophilicity of the active ingredient, even under the between- and within-individual variation of the gastrointestinal pH.

Preferred examples of the water-soluble polymers may include at least one selected from the group consisting of cellulose derivatives such as methyl cellulose, hydroxymethyl cellulose, hydroxyethyl cellulose, ethyl cellulose, hydroxyethylmethyl 20 cellulose, carboxymethyl cellulose, hydroxypropylmethyl cellulose, hydroxypropylmethyl cellulose phthalate, sodium carboxymethyl cellulose, and carboxymethylethyl cellulose; polyvinyl alcohols; polyvinyl acetate, polyvinyl acetate phthalate, polyvinylpyrrolidone (PVP), and polymers containing the same; polyalkene

oxide or polyalkene glycol, and polymers containing the same. Preferred is hydroxypropylmethyl cellulose.

In the pharmaceutical composition of the present invention, an excessive content of the water-soluble polymer which is higher than a given level provides no further increased solubility, but disadvantageously brings about various problems such as overall increases in the hardness of the formulation, and non-penetration of an eluent into the formulation, by formation of films around the formulation due to excessive swelling of water-soluble polymers upon exposure to the eluent. Accordingly, the solubilizer is preferably added to maximize the solubility of the formulation by modifying physical properties of the compound of Formula 1 or 2.

In this respect, the solubilizer serves to enhance solubilization and wettability of the sparingly-soluble compound of Formula 1 or 2, and can significantly reduce the bioavailability variation of the naphthoquinone-based compound originating from diets and the time difference of drug administration after dietary uptake. The solubilizer may be selected from conventionally widely used surfactants or amphiphiles, and specific examples of the solubilizer may refer to the surfactants as defined above.

The disintegration-promoting agent serves to improve the drug release rate, and enables rapid release of the drug at the target site to thereby increase bioavailability of the drug.

Preferred examples of the disintegration-promoting agent may include, but are not limited to, at least one selected from the group consisting of Croscarmellose sodium, Crospovidone, calcium carboxymethylcellulose, starch glycolate sodium and lower substituted hydroxypropyl cellulose. Preferred is Croscarmellose sodium.

Upon taking into consideration various factors as described above, it is preferred to add 10 to 1000 parts by weight of the water-soluble polymer, 1 to 30 parts by weight of the disintegration-promoting agent and 0.1 to 20 parts by weight of the solubilizer, based on 100 parts by weight of the active ingredient.

5 In addition to the above-mentioned ingredients, other materials known in the art in connection with formulation may be optionally added, if necessary.

The solvent for spray drying is a material exhibiting a high solubility without modification of physical properties thereof and easy volatility during the spray drying process. Preferred examples of such a solvent may include, but are not limited to,
10 dichloromethane, chloroform, methanol, and ethanol. These materials may be used alone or in any combination thereof. Preferably, a content of solids in the spray solution is in a range of 5 to 50% by weight, based on the total weight of the spray solution.

The above-mentioned intestine-targeted formulation process may be preferably carried out for formulation particles prepared as above.

15 In one preferred embodiment, the oral pharmaceutical composition according to the present invention may be formulated by a process comprising the following steps:

(a) adding the compound of Formula 1 or 2 alone or in combination with a surfactant and a moisture-absorbent material, and grinding the compound of Formula 1 or 2 with a jet mill to prepare active ingredient microparticles;

20 (b) dissolving the active ingredient microparticles in conjunction with a water-soluble polymer, a solubilizer and a disintegration-promoting agent in a solvent and spray-drying the resulting solution to prepare formulation particles; and

(c) dissolving the formulation particles in conjunction with a pH-sensitive polymer and a plasticizer in a solvent and spray-drying the resulting solution to carry out intestine-targeted coating on the formulation particles.

The surfactant, moisture-absorbent material, water-soluble polymer, solubilizer
5 and disintegration-promoting agent are as defined above. The plasticizer is an additive added to prevent hardening of the coating, and may include, for example polymers such as polyethylene glycol.

Alternatively, formulation of the active ingredient may be carried out by sequential or concurrent spraying of vehicles of Step (b) and intestine-targeted coating
10 materials of Step (c) onto jet-milled active ingredient particles of Step (a) as a seed.

Pharmaceutical compositions suitable for use in the present invention include compositions in which the active ingredients are contained in an amount effective to achieve its intended purpose. More specifically, a therapeutically effective amount means an amount of compound effective to prevent, alleviate or ameliorate symptoms
15 of disease or prolong the survival of the subject being treated. Determination of a therapeutically effective amount is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

When the pharmaceutical composition of the present invention is formulated into a unit dosage form, the naphthoquinone-based compound as an active ingredient is
20 preferably contained in a unit dose of about 0.1 to 1,000 mg. The amount of the compound of Formula 1 or 2 administered will be determined by the attending physician, depending upon body weight and age of patients being treated, characteristic nature and the severity of diseases.

In accordance with another aspect of the present invention, there is provided a use of naphthoquinone-based compound in preparing pharmaceutical composition for preventing and treating disease syndrome. As used herein, the term “disease syndromes” includes obesity, diabetes, metabolic syndromes, degenerative diseases and
5 mitochondrial dysfunction-related diseases or the like, and the term “treatment” refers to stopping or delaying of the disease progress, when the drug is used in the subject exhibiting symptoms of disease onset. The term “prevention” refers to stopping or delaying of symptoms of disease onset, when the drug is used in the subject exhibiting no symptoms of disease onset but having high risk of disease onset.

10 Complications caused from obesity include, for example hypertension, myocardial infarction, varicosis, pulmonary embolism, coronary artery diseases, cerebral hemorrhage, senile dementia, Parkinson’s disease, type 2 diabetes, hyperlipidemia, cerebral apoplexy, various cancers (such as uterine cancer, breast cancer, prostate cancer, colon cancer and the like), heart diseases, gall bladder diseases,
15 sleep apnea syndrome, arthritis, infertility, venous ulcer, sudden death, fatty liver, hypertrophic cardiomyopathy (HCM), thromboembolism, esophagitis, abdominal wall hernia (Ventral Hernia), urinary incontinence, cardiovascular diseases, endocrine diseases and the like.

Complications of diabetes include hypoglycemia, ketoacidosis, hyperosmolar
20 coma, macrovascular complications, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy and the like.

Metabolic syndromes refer to syndromes accompanied by health risk factors such as hypertriglyceridemia, hypertension, glycometabolism disorders, blood coagulation disorders and obesity.

Therefore, the metabolic syndrome includes various diseases such as obesity, an obesity complication, a liver disease, arteriosclerosis, cerebral apoplexy, myocardial infarction, a cardiovascular disease, an ischemic disease, diabetes, a diabetes-related complication or an inflammatory disease.

5 As examples of the degenerative disease, may include Alzheimer's disease, Parkinson's disease and Huntington's disease and the like.

Examples of diseases may include multiple sclerosis, encephalomyelitis, cerebral radiculitis, peripheral neuropathy, Reye's syndrome, Friedrich's ataxia, Alpers syndrome, MELAS, migraine, psychosis, depression, seizure and dementia, paralytic
10 episode, optic atrophy, optic neuropathy, retinitis pigmentosa, cataract, hyperaldosteronemia, hypoparathyroidism, myopathy, amyotrophy, myoglobinuria, hypotonia, myalgia, the decrease of exercise tolerance, renal tubulopathy, renal failure, hepatic failure, liver function failure, hepatomegaly, red blood cell anemia (iron-deficiency anemia), neutropenia, thrombocytopenia, diarrhea, villous atrophy, multiple
15 vomiting, dysphagia, constipation, sensorineural hearing loss (SNHL), epilepsy, mental retardation, Alzheimer's disease, Parkinson's disease and Huntington's disease.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

Now, the present invention will be described in more detail with reference to
20 the following Examples. These examples are provided only for illustrating the present invention and should not be construed as limiting the scope and spirit of the present invention.

Example 1: Synthesis of Compound 1 (2,2-dimethyl-3,4-dihydro-2H-naphtho[1,2-b]thiopyran-5,6-dione)

2.43 g (10 mmol) of lapachol was dissolved in anhydrous THF, and 1.2 g (20 mmol) of sodium hydrogen sulfide was added thereto. The reaction mixture was stirred
5 vigorously for 3 hours at room temperature, followed by vacuum evaporation to concentrate exhaustively. The reaction mixture was cooled to 0°C without the additional purification processes followed by reacting with 10 ml of concentrated sulfuric acid. Then, the reaction mixture was stirred vigorously for 30 minutes. To terminate the reaction, 50 g of ice water was added to the reaction mixture which was
10 then extracted twice (50 ml × 2) with CH₂Cl₂. The extracted organic layer was concentrated. The concentrated solution was purified by a silica gel, thereby obtaining Compound 1 (0.18 g).

¹H-NMR (CDCl₃, δ): 8.11 (1H, dd, J=1, 8Hz), 7.79 (1H, dd, J=1, 8 Hz), 7.64 (1H, dt, J=1, 8 Hz), 7.49 (1H, dt, J=1, 8 Hz), 2.83 (2H, t, J=6.5 Hz), 1.91 (2H, t, J=6.5 Hz) 1.45
15 (6H, s)

Example 2: Synthesis of Compound 2 (2,3,3-trimethyl-2,3-dihydronaphtho[1,2-b]thiophene-4,5-dione)

2.43 g (10 mmol) of 2-hydroxy-3-(2-methyl-3-buten-2-yl)-1,4-naphthoquinone,
20 which is one of lapachol derivatives, was dissolved in anhydrous THF, and 1.2 g (20 mmol) of sodium hydrogen sulfide was added thereto. The reaction mixture was stirred vigorously for 3 hours at room temperature, followed by vacuum evaporation to concentrate completely. The reaction mixture was cooled to 0°C without the additional

purification processes followed by reacting with 10 ml of concentrated sulfuric acid. Then, the reaction mixture was stirred vigorously for 30 minutes. To terminate the reaction, 50 g of ice water was added to the reaction mixture which was then extracted twice (50 ml × 2) with CH₂Cl₂. The extracted organic layer was concentrated. The
5 concentrated solution was purified by a silica gel, thereby obtaining Compound 2 (0.13 g).

¹H-NMR (CDCl₃, δ): 8.09 (1H, d, J=8Hz), 7.64 (1H, t, J=8Hz), 7.56 (1H, t, J=8Hz), 7.47 (1H, d, J=8Hz), 3.98 (1H, q, J=7Hz), 1.59 (3H, s), 1.39 (3H, s), 1.21 (3H, d, J=7Hz)

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Example 3: Synthesis of Compound 3 (2-methyl-2,3-dihydro-naphtho[1,2-*b*]thiophene-4,5-dione)

Compound 3 was obtained in the same manner as in Example 2, except that 2-hydroxy-3-(2-propenyl)-1,4-naphthoquinone, which is one of lapachol derivatives, was
15 used.

Example 4: Synthesis of Compound 4 (4,4-dimethyl-2,3-dihydro-4*H*-naphtho[1,2-*b*]thiopyran-5,6-dione)

6.33 g (40.0 mmol) of 1,2-naphthoquinone was dissolved in 300 ml of well-
20 dried acetonitrile, followed by adding 2.0 ml of triethylamine. Then, 4.10 g (40.0 mmol) of 3-methyl-1-mercapto-2-butene was gradually added to the reaction solution over 1 hour while stirring the reaction solution at room temperature. The reaction solution was additionally stirred vigorously for 1 hour, followed by vacuum evaporation to

completely remove the acetonitrile solvent. In order to even more completely remove acetonitrile from the concentrated solution, 200 ml of toluene was added to the concentrated solution which was again vacuum evaporated. Thusly obtained reaction mixture was reacted with 50 ml of concentrated sulfuric acid at room temperature
5 without the additional purification processes and stirred vigorously for 30 minutes. To terminate the reaction, 200 g of ice was added to the reaction mixture which was then extracted twice (100 ml × 2) with CH₂Cl₂. The extracted organic layer was concentrated. The concentrated solution was purified by a silica gel, thereby obtaining Compound 4 (0.11 g).

10 ¹H-NMR (CDCl₃, δ): 8.07 (1H, d, J=8Hz), 7.88 (2H, t, J=8Hz), 7.65 (1H, t, J=8Hz), 7.47 (1H, t, J=8Hz), 3.10 (2H, t, J=7Hz), 1.98 (2H, t, J=7Hz), 1.43 (6H, s)

Example 5: Synthesis of Compound 5 (4-phenyl-2,3-dihydro-4*H*-naphtho[1,2-*b*]thiopyran-5,6-dione)

15 Compound 5 was obtained in the same manner as in Example 4, except that cinnamyl thiol was used instead of 3-methyl-1-mercapto-2-butene.

Example 6: Synthesis of Compound 6 (2,3-dihydro-naphtho[2,1-*b*][1,4]oxathiine-5,6-dione)

20 6.33 g (40.0 mmol) of 1,2-naphthoquinone was dissolved in 300 ml of well-dried acetonitrile, followed by adding 2.0 ml of triethylamine. Then, 3.12 g (40.0 mmol) of 2-mercaptoethanol was gradually added to the reaction solution over 1 hour while stirring the reaction solution at room temperature. The reaction solution was stirred

vigorously overnight, followed by vacuum evaporation to completely remove the acetonitrile solvent. In order to even more completely remove acetonitrile from the concentrated solution, 200 ml of toluene was added to the concentrated solution which was again vacuum evaporated. Thusly obtained reaction mixture was reacted with 30 ml
5 of concentrated sulfuric acid at room temperature without the additional purification processes and stirred vigorously for 1 hour. To terminate the reaction, 200 g of ice was added to the reaction mixture which was then extracted twice (100 ml × 2) with CH₂Cl₂. The extracted organic layer was concentrated. The concentrated solution was purified by a silica gel, thereby obtaining Compound 6 (0.08 g).

10 ¹H-NMR (CDCl₃, δ): 8.04 (1H, d, J=8Hz), 7.72 (2H, t, , J=8Hz), 7.64 (1H, t, J=8Hz), 7.48 (1H, t, J=8Hz), 4.69 (2H, t, J=5Hz), 3.16 (2H, t, J=5Hz)

Example 7: Synthesis of Compound 7 (3-methyl-2,3-dihydro-naphtho[2,1-b][1,4]oxathiine-5,6-dione)

15 Compound 7 was obtained in the same manner as in Example 6, except that 1-mercapto-2-propanol was used instead of 2-mercaptoethanol.

Example 8: Synthesis of Compound 8 (2,3-dimethyl-2,3-dihydro-naphtho[2,1-b][1,4]oxathiine-5,6-dione)

20 Compound 8 was obtained in the same manner as in Example 6, except that 3-mercapto-2-butanol was used instead of 2-mercaptoethanol.

Example 9: Synthesis of Compound 9 (2,3-dimethyl-2,3-dihydro-naphtho[2,1-b][1,4]oxathiine-5,6-dione)

Compound 9 was obtained in the same manner as in Example 6, except that 3-mercapto-2-methyl-2-butanol was used instead of 2-mercaptoethanol.

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Experimental Example 1: Determination of AMPK activation

Mouse colon adenocarcinoma Colon 26 cells were cultured in MEM containing 10% Fetal Bovine Serum. 3×10^5 cell was added to 12 well plate and reacted for 24 hours, and then the culture medium was replaced with a medium containing 5mM glucose, kreb's buffer (118 mM NaCl, 4.8 mM KCl, 1.3 mM CaCl₂, 1.2 mM KH₂PO₄, 1.3 mM MgSO₄, 5 mM NaHCO₃, 25 mM HEPES), to induce starvation. The synthesized samples were treated at a concentration of 5 or 10 μ M for 30minutes, and compared with a control group. Enzymatic activity of AMPK was determined as follows. Firstly, colon cells were lysed with Digitonin buffer (50 mM Tris-HCl, pH 7.5, 1 mM EDTA, 0.25 % Sucrose, 0.4 mg/ml Digitonin, 1.5 mM PMSF) to obtain protein extracts, and the extracts were diluted to a final concentration of 0.2 μ g/ μ l. 50 μ l of the extracts was added to the avidine coated 96 well plate. This was followed by putting the plate into the 4°C refrigerator during o/n, and as a result, the protein was attached to the plate. It was washed with TBST buffer (20 mM Tris-HCl, pH 7.6, 150 mM NaCl, 0.05 % Tween 20) 5 times and antibodies specific for Acetyl-CoA carboxylase (ACC) were diluted with TBST buffer to 1:500. Thereafter, 50 μ l of protein was added to each well of 96 well plate, and then reacted at normal temperature for 2 hours. It was washed with TBST buffer 5 times. Antibodys bound with Horse radish peroxidase and specific for igG of rabbit were diluted with TBST buffer to 1:1250, reacted at normal

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temperature for one hour, and washed with TBST buffer 5 times again. 50 μ l TMB (#T8665, Sigma) was added to 96 well, reacted at normal temperature for 10 minutes, and terminated with addition of 100 μ l 1N hydrochloric acid. Thereafter, absorbencies thereof were measured at 450 nm.

- 5 The experimental results showed that Compound 1 exhibits a 3.17-fold increase of AMPK activation compared to Control group, and the compounds of the present invention generally exhibit at least an about 1.1-fold increase of AMPK activation.

[Table 2]

	AMPK Fold
Control	1
Compound 5	1.23
Compound 1	3.17

- 10 As seen from Table 2, when compounds according to the present invention were treated on Colon cells, this treatment leads to increased enzymatic activity of AMPK.

Experimental Example 2: Weight loss effects in obese mice (ob/ob)

- 15 8-week-old C57BL/6J Lep ob/ob male mice of Charls River Inc., having obesity characteristics were purchased from Orient bio Inc. Animals were raised in a breeding room maintained at a temperature of 23 °C, 55% humidity, illumination of 300 to 500 lux, a 12-h light/dark (L/D) cycle, and ventilation of 10 to 18 times/hr. Animals were fed *ad libitum* pellets of 11.9 Kcal% fat P5053(purchased from Labdiet Inc., USA,

imported by Orient bio Inc.) as a solid feed for experimental animals and tap water as drinking water. Mice were allowed to acclimate to new environment of the breeding room for four weeks, then Compound 1 synthesized according to the present invention was orally administered to the mice at doses of 200 mg/kg SLS vehicle (10 mg/kg) for 5 14 days. Observations were made on changes in body weight, blood glucose and food intake, with respect to a time course of administration. After administration was complete, changes in glucose, lipid and enzyme levels in blood and liver were observed.

Table 3 below shows results of changes over time in body weight of C57BL/6JL Lep ob/ob mice to which Compounds of the present invention were 10 administered.

[Table 3]

Sample	Initial BW (g)	Final BW (g)	Increase in BW (%)
Control	56.0	59.6	6.4%
Compound 1	55.0	55.4	0.7%

As seen from Table 3 above, administration of the compounds according to the present invention leads to a significant reduction in body weight, as compared to the control group.

15 Table 4 below shows changes in blood lipid and glucose levels of C57BL/6JL Lep ob/Lep ob mice to which Compounds of the present invention were administered.

[Table 4]

Sample	GOT	GPT	Creatinine (UL)	T. chol (mg/dL)	HDL Chol (mg/dL)	LDL Chol (mg/dL)	TG (mg/dL)	Glucose (mg/dL)
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Control	29.5	51.0	40.0	5.3	11.80	1.96	0.06	174.3
Compound 1	21.0	32.5	38.5	5.6	10.61	1.89	0.04	89.3

As seen from Table 4 above, the groups to which Compounds according to the present invention were administered exhibited a significant reduction in triglyceride, cholesterol and glucose levels in the blood, as compared to the control group.

Hereinafter, Formulation Examples of the pharmaceutical composition in accordance with the present invention and Application Examples thereof to cosmetics will be described. These examples are provided only for illustrating the present invention and should not be construed as limiting the scope and spirit of the present invention.

10 Experimental Example 3: Preparation of Tablet

- Compound 1 -----20 g
- Milk serum protein ----- 820 g
- Crystalline cellulose ----- 140 g
- Magnesium stearate ----- 10 g
- 15 Hydroxypropylmethylcellulose ----- 10 g

Experimental Example 4: Preparation of Powder

- Compound 1 ----- 2 g
- Soybean protein ----- 58 g
- 20 Carboxycellulose ----- 40 g

Total ----- 100 g

Experimental Example 5: Application of Inventive compound to cosmetic lotion

	1,3-butylene glycol -----	5%
5	Glycerine -----	5%
	EDTA-2Na -----	0.02%
	Trimethylglycine -----	2.0%
	Cetanol -----	1.0%
	Glyceryl monostearate emulsifier -----	1.0%
10	Polysorbate 60 -----	1.2%
	Sorbitan sesquioleate -----	0.3%
	Cetyl 2-ethyl-hexaoate -----	4.0%
	Squalane -----	5.0%
	Dimethicone -----	0.3%
15	Glyceryl stearate -----	0.5%
	Carbomer -----	0.15%
	Triethanolamine -----	0.5%
	Imidazolidinyl urea -----	0.2%
	Compound 1-----	0.2%
20	Purified water -----	73.6%

Experimental Example 6: Application of Inventive compound to cosmetic skin care

	1,3-butylene glycol -----	4.0%
	Dipropylene glycol -----	5.0%
5	EDTA-2Na -----	0.02%
	Octyldodeceth-16 -----	0.3%
	PEG60 hydrogenated castor oil -----	0.25%
	Compound 1 -----	0.03%
	Purified water -----	90%

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INDUSTRIAL APPLICABILITY

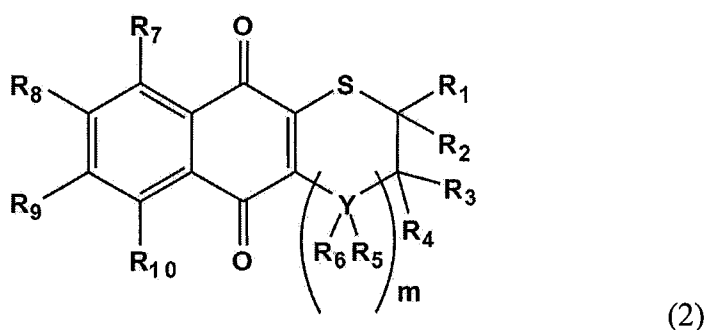
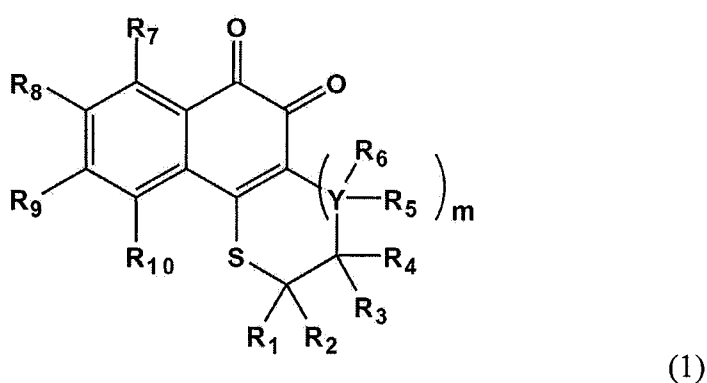
As apparent from the foregoing, it is expected that compounds in accordance with the present invention are compounds modulating activity of various genes and proteins, and therefore will be therapeutically effective for the treatment of various diseases and disorders via regulation of energy levels *in vivo*. Pharmaceuticals using the above-mentioned compounds as an active ingredient exhibit superior effects on the treatment and/or prevention of various diseases such as obesity, diabetes, metabolic syndromes, degenerative diseases and mitochondrial dysfunction-related diseases.

Although the preferred embodiments of the present invention have been disclosed for illustrative purposes, those skilled in the art will appreciate that various modifications, additions and substitutions are possible, without departing from the scope and spirit of the invention as disclosed in the accompanying claims.

WHAT IS CLAIMED IS

1. A pharmaceutical composition for the treatment and/or prevention of disease syndromes, comprising:

(a) a therapeutically effective amount of one or more selected from the naphthoquinone-based compounds represented by Formula 1 and Formula 2 below, or a pharmaceutically acceptable salt, prodrug, solvate or isomer thereof:



wherein

10 R_1 to R_6 are each independently selected from the group consisting of hydrogen (H), hydroxy (OH), substituted or unsubstituted C_1 - C_{10} alkyl, substituted or unsubstituted C_1 - C_{10} alkenyl, substituted or unsubstituted C_1 - C_{10} alkoxy, substituted or unsubstituted C_1 - C_{10} alkoxycarbonyl, substituted or unsubstituted C_1 - C_{10} acyl, $-(CH_2)_n$ -amino, $-(CH_2)_n$ -aryl, $-(CH_2)_n$ -heterocyclic and $-(CH_2)_n$ -phenyl; or any one of R_1 or R_2

and any one of R₃ or R₄ form a 4~8-membered fused ring, or any one of R₃ or R₄ and any one of R₅ or R₆ form a 4~8-membered fused ring;

R₇ to R₁₀ are each independently hydrogen, hydroxyl, halogen, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₁-C₁₀ alkoxy, nitro, cyano or
5 amide;

m is 0 or 1, with proviso that when m is 0, carbon atoms adjacent to m form a cyclic structure via a direct bond, and n is 0~10 integer,

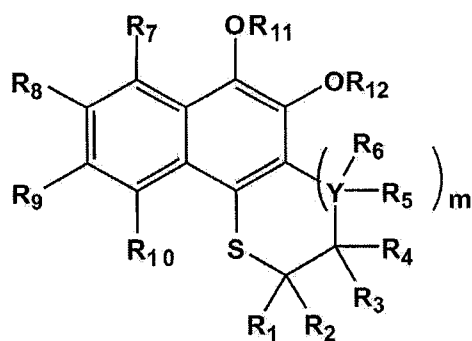
Y is carbon (C), sulfur (S), nitrogen (N), or oxygen (O), with proviso that when Y is S or O, R₅ and R₆ are nothing and when Y is N, R₅ is hydrogen or C₁-C₁₀ alkyl and
10 R₆ is nothing,

wherein heteroatom(s) in the heterocyclic is(are) one or more selected from O, N and S; and

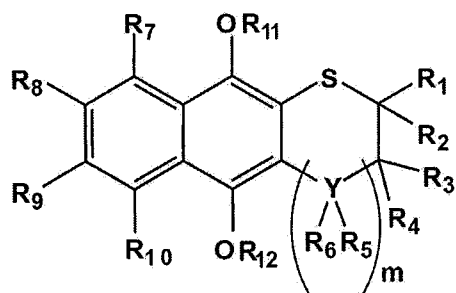
(b) a pharmaceutically acceptable carrier, a diluent or an excipient, or any combination thereof.

15 2. The composition according to claim 1, wherein Y is C or O; R₁ and R₂ are each independently H or alkyl; R₃ to R₆ are each independently selected from the group consisting of -H, -OH, halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, substituted or unsubstituted C₁-C₆ acyl, substituted C₁-C₆ alkenyl, substituted C₁-C₆ alkyl carbonyl and C₄-C₁₁ aryl; and R₇ to R₁₀ are hydrogen.

20 3. The composition according to claim 1, wherein the prodrug is/are one or more selected from the compounds represented by Formulas 1a and 2a below:



(1a)

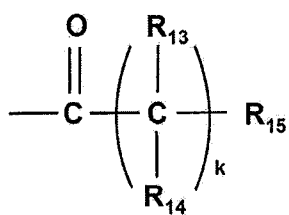


(2a)

wherein,

R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, R₉, R₁₀, Y and m are as defined in Formula 1;

5 R₁₁ and R₁₂ are each independently -SO₃⁻Na⁺ or substituent represented by Formula 8 below or a salt thereof,



(8)

wherein,

R₁₃ and R₁₄ are each independently hydrogen, or substituted or unsubstituted

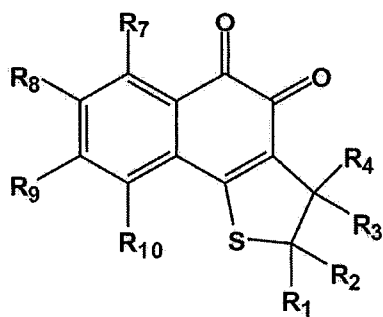
10 C₁-C₂₀ linear alkyl or C₁-C₂₀ branched alkyl;

R₁₅ is selected from the group consisting of substituents i) to viii) below:

- i) hydrogen;
- ii) substituted or unsubstituted C₁-C₂₀ linear alkyl or C₁-C₂₀ branched alkyl;
- iii) substituted or unsubstituted amine;
- 5 iv) substituted or unsubstituted C₃-C₁₀ cycloalkyl or C₃-C₁₀ heterocycloalkyl;
- v) substituted or unsubstituted C₄-C₁₁ aryl or C₄-C₁₁ heteroaryl;
- vi) -(CRR'-NR''CO)_l-R₁₄, wherein, R, R' and R'' are each independently hydrogen, or substituted or unsubstituted C₁-C₂₀ linear alkyl or C₁-C₂₀ branched
- 10 alkyl, R₁₄ is selected from the group consisting of hydrogen, substituted or unsubstituted amine, C₃-C₁₀ cycloalkyl, C₃-C₁₀ heterocycloalkyl, C₄-C₁₁ aryl and C₄-C₁₁ heteroaryl, and l is selected from the 1~5;
- vii) substituted or unsubstituted carboxyl;
- viii) -OSO₃⁻Na⁺;
- 15 k is selected from the 0~20, with proviso that when k is 0, R₁₃ and R₁₄ are not anything, and R₁₅ is directly bond to a carbonyl group; and

wherein hetero atom(s) in the heterocycloalkyl and heteroaryl is(are) one or more selected from O, N and S.

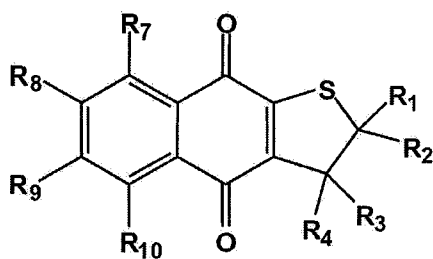
4. The composition according to claim 1, wherein the naphthoquinone-based
- 20 compound is the compound of Formula 3 below in which m is 0 and adjacent carbon atoms form a cyclic structure via a direct bond therebetween in Formula 1:



(3)

wherein R₁, R₂, R₃, R₄, R₇, R₈, R₉ and R₁₀ are defined as in the claim 1.

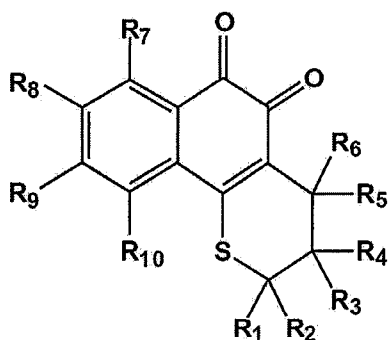
5. The composition according to claim 1, wherein the naphthoquinone-based compound is the compound of Formula 4 below in which m is 0 and adjacent carbon atoms form a cyclic structure via a direct bond therebetween in Formula 2:



(4)

wherein R₁, R₂, R₃, R₄, R₇, R₈, R₉ and R₁₀ are defined as in the claim 1.

6. The composition according to claim 1, wherein the naphthoquinone-based compound is a compound of Formula 5 below in which m is 1 and Y is C in Formula 1:

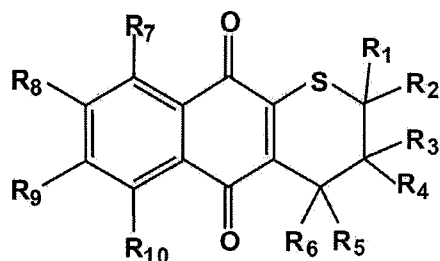


(5)

wherein R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, R₉ and R₁₀ are defined as in the claim 1.

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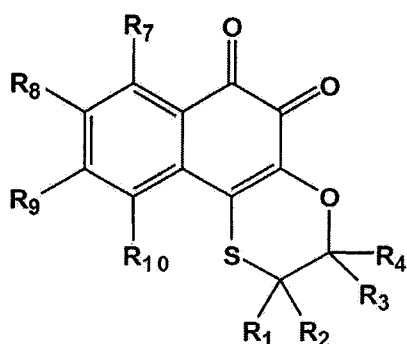
7. The composition according to claim 1, wherein the naphthoquinone-based compound is a compound of Formula 6 below in which m is 1 and Y is C in Formula 2:



(6)

wherein, R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, R₉ and R₁₀ are defined as in the claim 1.

5 8. The composition according to claim 1, wherein the naphthoquinone-based compound is a compound of Formula 7 below in which m is 1 and Y is O in Formula 1:

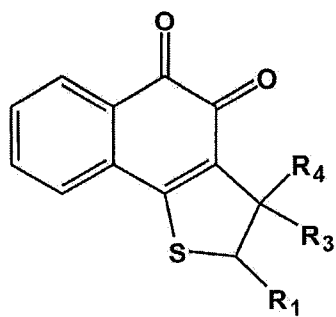


(7)

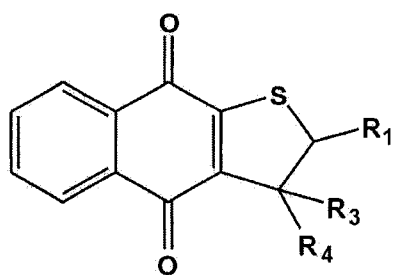
wherein, R₁, R₂, R₃, R₄, R₇, R₈, R₉ and R₁₀ are defined as in the claim 1.

9. The composition according to claim 1, wherein R₇, R₈, R₉ and R₁₀ in Formula 1
10 or 2 are respectively hydrogen.

10. The composition according to claim 4 or 5, wherein the compound of Formula 3 or Formula 4 is the compound of Formula 3a or Formula 4a below in which R₂, R₇, R₈, R₉ and R₁₀ are respectively hydrogen in Formula 3 or Formula 4, or the compound of Formula 3b or Formula 4b below in which R₄, R₇, R₈, R₉ and R₁₀ are respectively
15 hydrogen in Formula 3 or Formula 4:

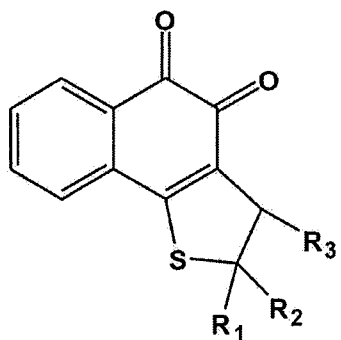


(3a)

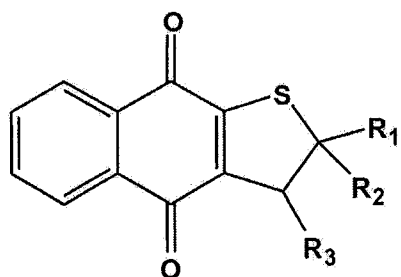


(4a)

wherein, R₁, R₃ and R₄ are defined as in the claim 1.



(3b)

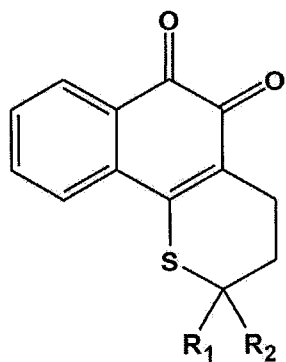


(4b)

5

wherein, R₁, R₂ and R₃ are defined as in the claim 1.

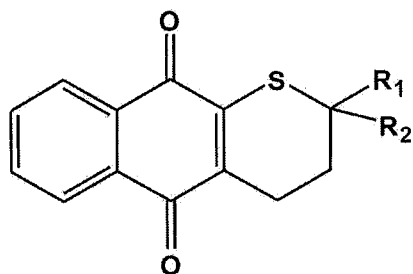
11. The composition according to claim 6, wherein the compound of Formula 5 is the compound of Formula 5a in which R₃, R₄, R₅, R₆, R₇, R₈, R₉ and R₁₀ are respectively hydrogen and Y is C in Formula 5:



(5a)

5 wherein, R₁ and R₂ are defined as in the claim 1.

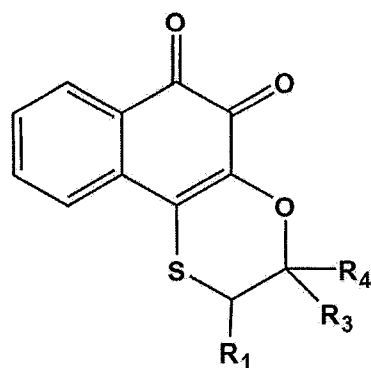
12. The composition according to claim 7, wherein the compound of Formula 6 is the compound of Formula 6a below in which R₃, R₄, R₅, R₆, R₇, R₈, R₉ and R₁₀ are respectively hydrogen and Y is C in Formula 6:



(6a)

10 wherein R₁ and R₂ are defined as in the claim 1.

13. The composition according to claim 8, wherein the compound of Formula 7 is the compound of Formula 7a below in which R₂, R₇, R₈, R₉ and R₁₀ are respectively hydrogen and Y is O in Formula 7:



(7a)

wherein R₁, R₃ and R₄ are defined as in the claim 1.

14. The composition according to claim 1, wherein the disease syndrome includes obesity, diabetes, a metabolic syndrome, a degenerative disease and a mitochondrial
5 dysfunction-related disease.

15. The composition according to claim 14, wherein the metabolic syndrome is one or more selected from the group consisting of obesity, an obesity complication, a liver disease, arteriosclerosis, cerebral apoplexy, myocardial infarction, a cardiovascular disease, an ischemic disease, diabetes, a diabetes-related complication and an
10 inflammatory disease.

16. Use of the compound according to claim 1 in the preparation of a drug for preventing and treating disease syndrome.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2008/002569**A. CLASSIFICATION OF SUBJECT MATTER***A61K 31/122(2006.01)i*

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)

IPC 8 as above

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)

eKIPASS(KIPO internal), STN(CA)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2004/0253730 A1 (LI C.), 16 Dec 2004 See theTable 1	1-2,6,9,11,16
X	VISHNU K. TANDON, "Synthesis and biological evaluation of novel 1,4-naphthoquinone derivatives as antibacterial and antiviral agents", Bioorganic & Medicinal Chemistry Letters, 15 July 2005, Volume 15, Issue 14, , Pages 3463-3466 See the Scheme 1	1-2,6,9,11,16
A	KR 10-2006-0092106 A (KT & G CORPORATION), 22 Aug 2006 See the Table 1	1-16

 Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

20 AUGUST 2008 (20.08.2008)

Date of mailing of the international search report

20 AUGUST 2008 (20.08.2008)

Name and mailing address of the ISA/KR

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Telephone No. 82-42-481-5612



INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/KR2008/002569

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		US 2008-0146655 A1	19. 06. 2008
		WO 2006-088315 A1	24. 08. 2006