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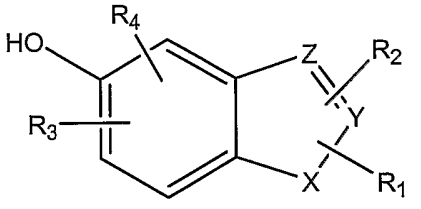
(54) Title: HETEROCYCLIC COMPOUNDS USEFUL AS MALONYL-COA DECARBOXYLASE INHIBITORS



(I)

(57) Abstract: The present invention provides methods for the use of compounds as depicted by structure I, pharmaceutical compositions containing the same, and methods for the prophylaxis, management and treatment of metabolic diseases and diseases modulated by MCD inhibition. The compounds disclosed in this invention are useful for the prophylaxis, management and treatment of diseases involving in malonyl-CoA regulated glucose/fatty acid metabolism pathway. In particular, these compounds and pharmaceutical composition containing the same are indicated in the prophylaxis, management and treatment of cardiovascular diseases, diabetes, cancer and obesity.

HETEROCYCLIC COMPOUNDS USEFUL AS MALONYL-COA DECARBOXYLASE INHIBITORS

FIELD OF THE INVENTION

The present invention relates to methods of treatment of certain metabolic diseases and the use of compounds and their prodrugs, and/or pharmaceutically acceptable salts, pharmaceutical compositions containing such compounds useful in treating such diseases. In particular, the invention relates to the use of compounds and compositions for the prophylaxis, management or treatment of cardiovascular diseases, diabetes, cancers, and obesity through the inhibition of malonyl-coenzyme A decarboxylase (malonyl-CoA decarboxylase, MCD).

BACKGROUND OF THE INVENTION

Malonyl-CoA is an important metabolic intermediary produced by the enzyme Acetyl-CoA Carboxylase (ACC) in the body. In the liver, adipocytes, and other tissues, malonyl-CoA is a substrate for fatty acid synthase (FAS). ACC and malonyl-CoA are found in skeletal muscle and cardiac muscle tissue, where fatty acid synthase levels are low. The enzyme malonyl-CoA decarboxylase (MCD, EC 4.1.1.9) catalyzes the conversion of malonyl-CoA to acetyl-CoA and thereby regulates malonyl-CoA levels. MCD activity has been described in a wide array of organisms, including prokaryotes, birds, and mammals. It has been purified from the bacteria *Rhizobium trifolii* (An et al., *J. Biochem. Mol. Biol.* 32:414-418(1999)), the uropygial glands of waterfowl (Buckner, et al., *Arch. Biochem. Biophys* 177:539(1976); Kim and Kolattukudy *Arch. Biochem. Biophys* 190:585(1978)), rat liver mitochondria (Kim and Kolattukudy, *Arch. Biochem. Biophys.* 190:234(1978)), rat mammary glands (Kim and Kolattukudy, *Biochim. Biophys, Acta* 531:187(1978)), rat pancreatic β-cell (Voilley et al., *Biochem. J.* 340:213 (1999)) and goose (*Anser anser*) (Jang et al., *J. Biol. Chem.* 264:3500 (1989)). Identification of patients with MCD deficiency lead to the cloning of a human gene homologous to goose and rat MCD genes (Gao et al., *J. Lipid. Res.* 40:178 (1999); Sacksteder et al., *J. Biol. Chem.* 274:24461(1999); FitzPatrick et al., *Am. J. Hum. Genet.* 65:318(1999)). A single human MCD mRNA is observed by Northern Blot analysis. The highest mRNA

expression levels are found in muscle and heart tissues, followed by liver, kidney and pancreas, with detectable amounts in all other tissues examined.

Malonyl-CoA is a potent endogenous inhibitor of carnitine palmitoyltransferase-I (CPT-I), an enzyme essential for the metabolism of long-chain fatty acids. CPT-I is the rate-limiting enzyme in fatty acid oxidation and catalyzes the formation of acyl-carnitine, which is transported from the cytosol across the mitochondrial membranes by acyl carnitine translocase. Inside of the mitochondria the long-chain fatty acids are transferred back to CoA form by a complementary enzyme, CPT-II, and, in the mitochondria, acyl-CoA enters the β-oxidation pathway generating acetyl-CoA. In the liver, high levels of acetyl-CoA occurs for example following a meal, leading to elevated malonyl-CoA levels, which inhibit CPT-I, thereby preventing fat metabolism and favoring fat synthesis. Conversely, low malonyl-CoA levels favor fatty acid metabolism by allowing the transport of long-chain fatty acids into the mitochondria. Hence, malonyl-CoA is a central metabolite that plays a key role in balancing fatty acid synthesis and fatty acid oxidation (Zammit, *Biochem. J.* 343:5050-515(1999)). Recent work indicates that MCD is able to regulate cytoplasmic as well as mitochondrial malonyl-CoA levels [Alam and Saggerson, *Biochem J.* 334:233-241(1998); Dyck et al., *Am J Physiology* 275:H2122-2129(1998)].

Although malonyl-CoA is present in muscle and cardiac tissues, only low levels of FAS have been detected in these tissues. It is believed that the role of malonyl-CoA and MCD in these tissues is to regulate fatty acid metabolism. This is achieved *via* malonyl-CoA inhibition of muscle (M) and liver (L) isoforms of CPT-I, which are encoded by distinct genes (McGarry and Brown, *Eur. J. Biochem.* 244:1-14(1997)). The muscle isoform is more sensitive to malonyl-CoA inhibition (IC50 0.03 μM) than the liver isoform (IC_{50} 2.5 μM). Malonyl-CoA regulation of CPT-I has been described in the liver, heart, skeletal muscle and pancreatic β-cells. In addition, malonyl-CoA sensitive acyl-CoA transferase activity present in microsomes, perhaps part of a system that delivers acyl groups into the endoplasmic reticulum, has also been described (Fraser et al., *FEBS Lett.* 446: 69-74 (1999)).

Cardiovascular Diseases

The healthy human heart utilizes available metabolic substrates. When blood glucose levels are high, uptake and metabolism of glucose provide the major source of fuel for the heart. In the fasting state, lipids are provided by adipose tissues, and fatty acid uptake and metabolism in the heart down regulate glucose metabolism. The regulation of intermediary metabolism by serum levels of fatty acid and glucose comprises the glucose-fatty acid cycle (Randle et al., *Lancet*, 1:785-789(1963)). Under ischemic conditions, limited oxygen supply reduces both fatty acid and glucose oxidation and reduces the amount of ATP produced by oxidative phosphorylation in the cardiac tissues. In the absence of sufficient oxygen, glycolysis increases in an attempt to maintain ATP levels and a buildup of lactate and a drop in intracellular pH results. Energy is spent maintaining ion homeostasis, and myocyte cell death occurs as a result of abnormally low ATP levels and disrupted cellular osmolarity. Additionally, AMPK, activated during ischemia, phosphorylates and thus inactivates ACC. Total cardiac malonyl-CoA levels drop, CPT-I activity therefore is increased and fatty acid oxidation is favored over glucose oxidation. The beneficial effects of metabolic modulators in cardiac tissue are the increased efficiency of ATP/mole oxygen for glucose as compared to fatty acids and more importantly the increased coupling of glycolysis to glucose oxidation resulting in the net reduction of the proton burden in the ischemic tissue.

A number of clinical and experimental studies indicate that shifting energy metabolism in the heart towards glucose oxidation is an effective approach to decreasing the symptoms associated with cardiovascular diseases, such as but not limited, to myocardial ischemia (Hearse, *"Metabolic approaches to ischemic heart disease and its management"*, Science Press). Several clinically proven anti-angina drugs including perhexiline and amiodarone inhibit fatty acid oxidation *via* inhibition of CPT-I (Kennedy et al., *Biochem. Pharmacology*, 52: 273 (1996)). The antianginal drugs ranolazine, currently in Phase III clinical trials, and trimetazidine are shown to inhibit fatty acid β-oxidation (McCormack et al., *Genet. Pharmac.* 30:639(1998), Pepine et al., *Am. J. Cardiology* 84:46 (1999)). Trimetazidine has been shown to specifically inhibit the long-chain 3-ketoactyl CoA thiolase, an essential step in fatty acid oxidation. (Kantor et al.,

Circ. Res. 86:580-588 (2000)). Dichloroacetate increases glucose oxidation by stimulating the pyruvate dehydrogenase complex and improves cardiac function in those patients with coronary artery diseases (Wargovich et al., *Am. J. Cardiol.* 61:65-70 (1996)). Inhibiting CPT-I activity through the increased malonyl-CoA levels with MCD inhibitors would result in not only a novel, but also a much safer method, as compared to other known small molecule CPT-I inhibitors, to the prophylaxis and treatment of cardiovascular diseases.

Most of the steps involved in glycerol-lipid synthesis occur on the cytosolic side of liver endoplasmic reticulum (ER) membrane. The synthesis of triacyl glycerol (TAG) targeted for secretion inside the ER from diacyl gycerol (DAG) and acyl CoA is dependent upon acyl CoA transport across the ER membrane. This transport is dependent upon a malonyl-CoA sensitive acyl-CoA transferase activity (Zammit, *Biochem. J.* 343: 505(1999) Abo-Hashema, *Biochem.* 38: 15840 (1999) and Abo-Hashema, *J. Biol. Chem.* 274:35577 (1999)). Inhibition of TAG biosynthesis by a MCD inhibitor may improve the blood lipid profile and therefore reduce the risk factor for coronary artery disease of patients.

Diabetes

Two metabolic complications most commonly associated with diabetes are hepatic overproduction of ketone bodies (in NIDDM) and organ toxicity associated with sustained elevated levels of glucose. Inhibition of fatty acid oxidation can regulate blood-glucose levels and ameliorate some symptoms of type II diabetes. Malonyl-CoA inhibition of CPT-I is the most important regulatory mechanism that controls the rate of fatty acid oxidation during the onset of the hypoinsulinemic-hyperglucagonemic state. Several irreversible and reversible CPT-I inhibitors have been evaluated for their ability to control blood glucose levels and they are all invariably hypoglycemic (Anderson, *Current Pharmaceutical Design* 4:1(1998)). A liver specific and reversible CPT-inhibitor, SDZ-CPI-975, significantly lowers glucose levels in normal 18-hour-fasted nonhuman primates and rats without inducing cardiac hypertrophy (Deems et al., *Am. J. Physiology* 274:R524 (1998)). Malonyl-CoA plays a significant role as a sensor of the relative availability of glucose and fatty acid in pancreatic β-cells, and thus links glucose metabolism to cellular energy status and insulin secretion.

It has been shown that insulin secretagogues elevate malonyl-CoA concentration in β-cells (Prentki et al., *Diabetes* 45: 273 (1996)). Treating diabetes directly with CPT-I inhibitors has, however, resulted in mechanism-based hepatic and myocardial toxicities. MCD inhibitors that inhibit CPT-I through the increase of its endogenous inhibitor, malonyl-CoA, are thus safer and superior as compared to CPT-I inhibitors for treatment of diabetic diseases.

Cancers

Malonyl-CoA has been suggested to be a potential mediator of cytotoxicity induced by fatty-acid synthase inhibition in human breast cancer cells and xenografts (Pizer et al., *Cancer Res.* 60:213 (2000)). It is found that inhibition of fatty acid synthase using antitumor antibiotic cerulenin or a synthetic analog C75 markedly increase the malonyl-CoA levels in breast carcinoma cells. On the other hand, the fatty acid synthesis inhibitor, TOFA (5-(tetradecyloxy)-2-furoic acid), which only inhibits at the acetyl-CoA carboxylase (ACC) level, does not show any antitumor activity, while at the same time the malonyl-CoA level is decreased to 60% of the control. It is believed that the increased malonyl-CoA level is responsible for the antitumor activity of these fatty acid synthase inhibitors. Regulating malonyl-CoA levels using MCD inhibitors thus constitutes a valuable therapeutic strategy for the treatment of cancer diseases.

Obesity

It is suggested that malonyl-CoA may play a key role in appetite signaling in the brain *via* the inhibition of the neuropepetide Y pathway (Loftus et al., *Science* 288: 2379(2000)). Systemic or intracerebroventricular treatment of mice with fatty acid synthase (FAS) inhibitor cerulenin or C75 led to inhibition of feeding and dramatic weight loss. It is found that C75 inhibited expression of the prophagic signal neuropeptide Y in the hypothalamus and acted in a leptin-independent manner that appears to be mediated by malonyl-CoA. Therefore control of malonyl-CoA levels through inhibition of MCD provides a novel approach to the prophylaxis and treatment of obesity.

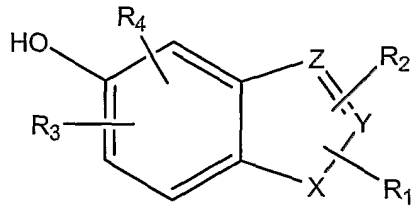
Additionally, these compounds are also useful as a diagnostic tool for diseases associated with MCD deficiency or malfunctions.

SUMMARY OF THE INVENTION

The present invention provides methods for the use of compounds as depicted by structure I, pharmaceutical compositions containing the same, and methods for the prophylaxis, management and treatment of metabolic diseases and diseases modulated by MCD inhibition. The compounds disclosed in this invention are useful for the prophylaxis, management and treatment of diseases involving in malonyl-CoA regulated glucose/fatty acid metabolism pathway. In particular, these compounds and pharmaceutical composition containing the same are indicated in the prophylaxis, management and treatment of cardiovascular diseases, diabetes, cancer and obesity.

The present invention also includes within its scope diagnostic methods for the detection of diseases associated with MCD deficiency or malfunctions.

The compounds useful in the present invention are represented by the following structures:



I

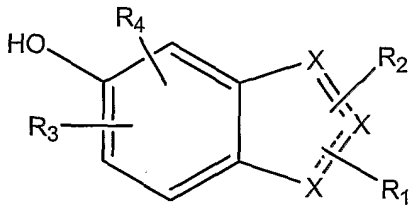
Wherein R_1, R_2, R_3, R4, X, Y and Z are as defined below. Also included within the scope of these compounds are the corresponding enantiomers, diastereoisomers, prodrugs, and pharmaceutically acceptable salts. Other aspects of this invention will become apparent as the description of this invention continues. Hence, the foregoing merely summarizes certain aspects of the invention and is not intended, nor should it be construed, as limiting the invention in any way.

DETAILED DESCRIPTION OF THE INVENTION

The detailed description of the invention that follows is not intended to be exhaustive or to limit the invention to the precise details disclosed. It has been

chosen and described to best explain the details of the invention to others skilled in the art.

The compounds useful in the present invention are represented by the following formulae (I):



(I)

wherein

R_1 and R_2 are independently selected from hydrogen, halogen, C_1-C_6 substituted alkyl, C_1-C_6 substituted alkenyl, C_1-C_6 substituted alkynyl, alkoxyl, phenyl, substituted phenyl, aryl, heteroaryl, substituted heteroaryl, -$NHCONR_5R_6$, -COR_5, -$CONR_5R_6$, -$S(O)_nR_5$, or -$SO_2NR_5R_6$,;

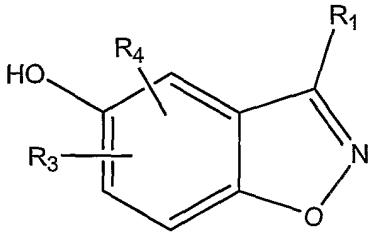
R_3 and R4 are independently selected from hydrogen, bromo, chloro, fluoro, iodo, hydroxyl, methoxyl, -COOH, -$COOR_5$, -$NHCONR_5R_6$, -COR_5, -$CONR_5R_6$, -$S(O)_nR_5$, or -$SO_2NR_5R_6$, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, C_1-C_6 alkoxyl, phenyl, substituted phenyl, aryl or heteroaryl;

R_5 and R_6 are independently selected from hydrogen, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, phenyl, substituted phenyl, aryl or heteroaryl;

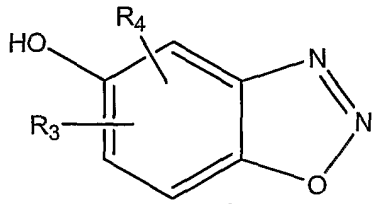
X is chosen form O, N, NH, NR_5, S, or C;

its corresponding enantiomers, diastereoisomers or tautomers, or a pharmaceutically acceptable salt, or a prodrug thereof in an pharmaceutically-acceptable carrier.

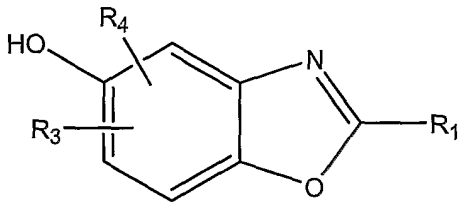
Preferably, the compounds in the present invention are represented by the following formulae (Ia - If):



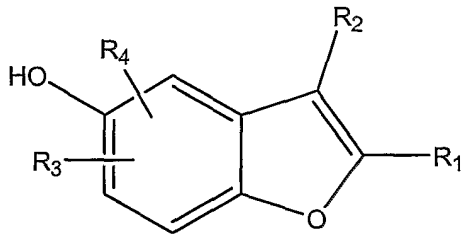
Ib



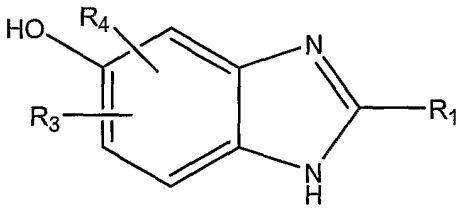
Ic



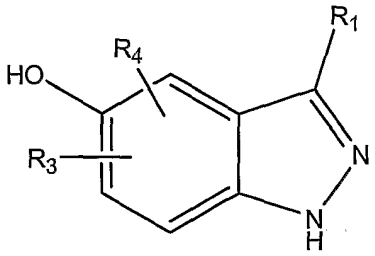
Id



Ie



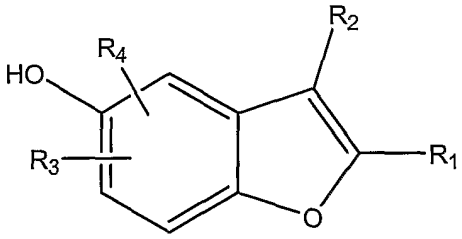
If



Ig

wherein R_1, R_2, R_3 and R_4 are as defined above.

More preferably, the compounds in the present invention are represented by the general formulae Ie



Ie

wherein R_1, R_2, R_3 and R_4 are as defined above.

COMPOSITIONS

The compositions of the present invention comprise:

(a) a safe and therapeutically effective amount of an MCD inhibiting compound I or II, its corresponding enantiomer, diastereoisomer or tautomer, or pharmaceutically acceptable salt, or a prodrug thereof; and

(b) a pharmaceutically-acceptable carrier.

As discussed above, numerous diseases can be mediated by MCD related therapy.

Accordingly, the compounds useful in this invention can be formulated into pharmaceutical compositions for use in prophylaxis, management and treatment of these conditions. Standard pharmaceutical formulation techniques are used, such as those disclosed in Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, PA.

A "safe and therapeutically effective amount" of a compound useful in the present invention is an amount that is effective, to inhibit MCD at the site(s) of activity, in a subject, a tissue, or a cell, and preferably in an animal, more preferably in a mammal, without undue adverse side effects (such as toxicity, irritation, or allergic response), commensurate with a reasonable benefit/risk ratio, when used in the manner of this invention. The specific "safe and therapeutically effective amount" will, obviously, vary with such factors as the particular condition being treated, the physical condition of the patient, the duration of treatment, the nature of concurrent therapy (if any), the specific dosage form to be used, the carrier employed, the solubility of the compound therein, and the dosage regimen desired for the composition.

In addition to the selected compound useful for the present invention, the compositions of the present invention contain a pharmaceutically-acceptable carrier. The term "pharmaceutically-acceptable carrier", as used herein, means one or more compatible solid or liquid filler diluents or encapsulating substances which are suitable for administration to a mammal. The term "compatible", as used herein, means that the components of the composition are capable of being commingled with the subject compound, and with each other, in a manner such that there is no interaction which would substantially reduce the pharmaceutical efficacy of the composition under ordinary use situations. Pharmaceutically-acceptable carriers must, of course, be of sufficiently high

purity and sufficiently low toxicity to render them suitable for administration preferably to an animal, preferably mammal being treated.

Some examples of substances, which can serve as pharmaceutically-acceptable carriers or components thereof, are sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose, and methyl cellulose; powdered tragacanth; malt; gelatin; talc; solid lubricants, such as stearic acid and magnesium stearate; calcium sulfate; vegetable oils, such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil and oil of theobroma; polyols such as propylene glycol, glycerine, sorbitol, mannitol, and polyethylene glycol; alginic acid; emulsifiers, such as the TWEENS; wetting agents, such sodium lauryl sulfate; coloring agents; flavoring agents; tableting agents, stabilizers; antioxidants; preservatives; pyrogen-free water; isotonic saline; and phosphate buffer solutions.

The choice of a pharmaceutically-acceptable carrier to be used in conjunction with the subject compound is basically determined by the way the compound is to be administered.

If the subject compound is to be injected, the preferred pharmaceutically-acceptable carrier is sterile, physiological saline, with blood-compatible suspending agent, the pH of which has been adjusted to about 7.4. In particular, pharmaceutically-acceptable carriers for systemic administration include sugars, starches, cellulose and its derivatives, malt, gelatin, talc, calcium sulfate, vegetable oils, synthetic oils, polyols, alginic acid, phosphate buffer solutions, emulsifiers, isotonic saline, and pyrogen-free water. Preferred carriers for parenteral administration include propylene glycol, ethyl oleate, pyrrolidone, ethanol, and sesame oil. Preferably, the pharmaceutically-acceptable carrier, in compositions for parenteral administration, comprises at least about 90% by weight of the total composition.

The compositions of this invention are preferably provided in unit dosage form. As used herein, a "unit dosage form" is a composition of this invention containing an amount of a compound that is suitable for administration to an animal, preferably mammal subject, in a single dose, according to good medical practice. (The preparation of a single or unit dosage form however, does not

imply that the dosage form is administered once per day or once per course of therapy. Such dosage forms are contemplated to be administered once, twice, thrice or more per day, and are expected to be given more than once during a course of therapy, though a single administration is not specifically excluded. The skilled artisan will recognize that the formulation does not specifically contemplate the entire course of therapy and such decisions are left for those skilled in the art of treatment rather than formulation.) These compositions preferably contain from about 5 mg (milligrams), more preferably from about 10 mg to about 1000 mg, more preferably to about 500 mg, most preferably to about 300 mg, of the selected compound.

The compositions useful for this invention may be in any of a variety of forms, suitable (for example) for oral, nasal, rectal, topical (including transdermal), ocular, intracereberally, intravenous, intramuscular, or parenteral administration. (The skilled artisan will appreciate that oral and nasal compositions comprise compositions that are administered by inhalation, and made using available methodologies.) Depending upon the particular route of administration desired, a variety of pharmaceutically-acceptable carriers well-known in the art may be used. These include solid or liquid fillers, diluents, hydrotropies, surface-active agents, and encapsulating substances. Optional pharmaceutically-active materials may be included, which do not substantially interfere with the inhibitory activity of the compound. The amount of carrier employed in conjunction with the compound is sufficient to provide a practical quantity of material for administration per unit dose of the compound. Techniques and compositions for making dosage forms useful in the methods of this invention are described in the following references, all incorporated by reference herein: Modern Pharmaceutics, Chapters 9 and 10 (Banker & Rhodes, editors, 1979); Lieberman et al., Pharmaceutical Dosage Forms: Tablets (1981); and Ansel, Introduction to Pharmaceutical Dosage Forms 2d Edition (1976).

Various oral dosage forms can be used, including such solid forms as tablets, capsules, granules and bulk powders. These oral forms comprise a safe and effective amount, usually at least about 5%, and preferably from about 25% to about 50%, of the compound. Tablets can be compressed, tablet triturates, enteric-coated, sugar-coated, film-coated, or multiple-compressed, containing

suitable binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, flow-inducing agents, and melting agents. Liquid oral dosage forms include aqueous solutions, emulsions, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules, and effervescent preparations reconstituted from effervescent granules, containing suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, melting agents, coloring agents and flavoring agents.

The pharmaceutically-acceptable carrier suitable for the preparation of unit dosage forms for peroral administration are well-known in the art. Tablets typically comprise conventional pharmaceutically-compatible adjuvants as inert diluents, such as calcium carbonate, sodium carbonate, mannitol, lactose and cellulose; binders such as starch, gelatin and sucrose; disintegrants such as starch, alginic acid and croscarmelose; lubricants such as magnesium stearate, stearic acid and talc. Glidants such as silicon dioxide can be used to improve flow characteristics of the powder mixture. Coloring agents, such as the FD&C dyes, can be added for appearance. Sweeteners and flavoring agents, such as aspartame, saccharin, menthol, peppermint, and fruit flavors, are useful adjuvants for chewable tablets. Capsules typically comprise one or more solid diluents disclosed above. The selection of carrier components depends on secondary considerations like taste, cost, and shelf stability, which are not critical for the purposes of the subject invention, and can be readily made by a person skilled in the art.

Peroral compositions also include liquid solutions, emulsions, suspensions, and the like. The pharmaceutically-acceptable carriers suitable for preparation of such compositions are well known in the art. Typical components of carriers for syrups, elixirs, emulsions and suspensions include ethanol, glycerol, propylene glycol, polyethylene glycol, liquid sucrose, sorbitol and water. For a suspension, typical suspending agents include methyl cellulose, sodium carboxymethyl cellulose, AVICEL RC-591, tragacanth and sodium alginate; typical wetting agents include lecithin and polysorbate 80; and typical preservatives include methyl paraben and sodium benzoate. Peroral liquid compositions may also contain one or more components such as sweeteners, flavoring agents and colorants disclosed above.

Such compositions may also be coated by conventional methods, typically with pH or time-dependent coatings, such that the subject compound is released in the gastrointestinal tract in the vicinity of the desired topical application, or at various times to extend the desired action. Such dosage forms typically include, but are not limited to, one or more of cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropyl methyl cellulose phthalate, ethyl cellulose, Eudragit coatings, waxes and shellac.

Compositions of the subject invention may optionally include other drug actives.

Other compositions useful for attaining systemic delivery of the subject compounds include sublingual, buccal and nasal dosage forms. Such compositions typically comprise one or more of soluble filler substances such as sucrose, sorbitol and mannitol; and binders such as acacia, microcrystalline cellulose, carboxymethyl cellulose and hydroxypropyl methyl cellulose. Glidants, lubricants, sweeteners, colorants, antioxidants and flavoring agents disclosed above may also be included.

The compositions of this invention can also be administered topically to a subject, e.g., by the direct application or spreading of the composition on the epidermal or epithelial tissue of the subject, or transdermally via a "patch". Such compositions include, for example, lotions, creams, solutions, gels and solids. These topical compositions preferably comprise a safe and effective amount, usually at least about 0.1%, and preferably from about 1% to about 5%, of the compound. Suitable carriers for topical administration preferably remain in place on the skin as a continuous film, and resist being removed by perspiration or immersion in water. Generally, the carrier is organic in nature and capable of having dispersed or dissolved therein the compound. The carrier may include pharmaceutically-acceptable emollient, emulsifiers, thickening agents, solvents and the like.

METHODS OF ADMINISTRATION

The compounds and compositions useful in this invention can be administered topically or systemically. Systemic application includes any method of introducing compound into the tissues of the body, e.g., intra-articular,

intrathecal, epidural, intramuscular, transdermal, intravenous, intraperitoneal, subcutaneous, sublingual administration, inhalation, rectal, or oral administration. The compounds useful in the present invention are preferably administered orally.

The specific dosage of the compound to be administered, as well as the duration of treatment is to be individualised by the treating clinicians. Typically, for a human adult (weighing approximately 70 kilograms), from about 5 mg, preferably from about 10 mg to about 3000 mg, more preferably to about 1000 mg, more preferably to about 300 mg, of the selected compound is administered per day. It is understood that these dosage ranges are by way of example only, and that daily administration can be adjusted depending on the factors listed above.

In all of the foregoing, of course, the compounds useful in the present invention can be administered alone or as mixtures, and the compositions may further include additional drugs or excipients as appropriate for the indication. For example, in the treatment of cardiovascular diseases, it is clearly contemplated that the invention may be used in conjunction with beta-blockers, calcium antagonists, ACE inhibitors, diuretics, angiotensin receptor inhibitors, or known cardiovascular drugs or therapies. Hence, in this example, compounds or compositions useful in this invention are useful when dosed together with another active and can be combined in a single dosage form or composition.

These compositions can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines.

DEFINITIONS

As used herein, "alkyl" means a straight chain alkane, alkene, or alkyne substituent containing only carbon and hydrogen, such as methyl, ethyl, butyl, pentyl, heptyl and the like. Alkyl groups can be saturated or unsaturated (i.e., containing -C=C- or -C≡C- linkages), at one or several positions. When a specific degree of unsaturation is preferred, said substituent is referred to as either

"alkenyl" or "alkynyl", denoting substituents containing -C=C- or -C≡C- linkages, respectively. The number of carbons may be denoted as "C_i-C_j-alkyl" wherein I and j refer to the minimum and maximum number of carbon atoms, respectively. Typically, alkyl groups will comprise 1 to 12 carbon atoms, preferably 1 to 10, and more preferably 2 to 8 carbon atoms.

As used herein, "substituted alkyl" means a hydrocarbon substituent, which is linear, cyclic or branched, in which one or more hydrogen atoms are substituted by carboxy, hydroxy, alkoxy, cyano, nitro, carbonyl, aryl, carboxyalkyl, mercapto, amino, amido, ureido, carbamoyl, sulfonamido, sulfamido, or halogen. Preferred substituted alkyls have their alkyl spacers (i.e., portion which is alkyl) of 1 to about 5 carbons, and may be branched or linear, and may include cyclic substituents, either as part or all of their structure. Preferred examples of "substituted alkyls" include 4-carboxybutyl, pyridin-2-ylmethyl, and 1,3-thiazol-2-ylmethyl, benzyl, phenethyl, and trifluoromethyl. The term "substituted alkyl" may be combined with other art accepted terms. For example "substituted alkoxy" means alkoxy as understood in the art, wherein the alkyl portion of the substituent is substituted.

As used herein, "branched alkyl" means a subset of "alkyl", and thus is a hydrocarbon substituent, which is branched. Preferred branched alkyls are of 3 to about 12 carbons, and may include cycloalkyl within their structure. Examples of branched alkyl include isopropyl, isobutyl, 1,2-dimethyl-propyl, cyclopentylmethyl and the like. The term "branched alkyl" may be combined with other art accepted terms. For example "branched alkoxy" means alkoxy as understood in the art, wherein the alkyl portion of the substituent is branched.

As used herein, "cycloalkyl" is a hydrocarbon substituent that is cyclic, and can be substituted or unsubstituted. Where it is substituted, one or more hydrogen atoms are substituted by carboxy, hydroxy, alkoxy, cyano, nitro, carbonyl, aryl, carboxyalkyl, mercapto, amino, amido, ureido, carbamoyl, sulfonamido, sulfamido, or halogen. Preferred cyclic alkyls are of 3 to about 7 carbons. Examples of cycloalkyl include cyclopropyl, cyclopentyl, 4-fluoro-cyclohexyl, 2,3-dihydroxy-cyclopentyl, and the like.

As used herein, "alkylene" is an alkyl diradical, i.e., an alkyl that has open valences on two different carbon atoms. Hence "(alkylene)R_i" is an alkyl diradical

attached at one carbon and having substituent R_i attached at another carbon, which may be one or more carbons away from the point of attachment. Alkylene can be linear, branched, or cyclic. Examples of alkylene include $-CH_2-$, CH_2CH_2-, $-(CH_2)_4-$, -(cyclohexyl)-, and the like.

As used herein, "aryl" is a substituted or unsubstituted aromatic, i.e., Hückel 4n + 2 rule applies, radical having a single-ring (e.g., phenyl) or multiple condensed rings (e.g., naphthyl or anthryl), which may contain zero to 4 heteroatoms. Hence the term "heteroaryl" is clearly contemplated in the term "aryl". Preferred carbocyclic aryl, is phenyl. Preferred monocyclic heterocycles, i.e., heteroaryls, are 5 or 6 membered rings. Preferably, where the term "aryl" represents an aromatic heterocycle, it is referred to as "heteroaryl" or "heteroaromatic", and has one or more heteroatom(s). Preferred numbers of such heteroatoms are from one to three N atoms, and preferably when "heteroaryl" is a heterocycle of five members, it has one or two heteroatoms selected from O, N, or S. Hence, preferred heterocycles have up to three, more preferably two or less, heteroatoms present in the aromatic ring. The skilled artisan will recognize that among heteroaryl, there are both five and six membered rings. Examples of "heteroaryl" include; thienyl, pyridyl, pyrimidyl, pyridazyl, furyl, oxazolyl, imidazolyl, thiazolyl, oxadiazilyl, triazinyl, triazolyl, thiadiazolyl, and others, which the skilled artisan will recognize. In this definition it is clearly contemplated that substitution on the aryl ring is within the scope of this invention. Where substitution occurs, the radical is referred to as "substituted aryl". Preferably one to three, more preferably one or two, and most preferably one substituent is attached to the aryl ring. Although many substituents will be useful, preferred substituents include those commonly found in aryl compounds, such as alkyl, hydroxy, alkoxy, cyano, nitro, halo, haloalkyl, mercapto and the like. Such substituents are prepared using known methodologies. These substituents may be attached at various positions of the aryl ring, and wherein a given placement is preferred, such placement is indicated by "*o,m,p*-R_i-aryl". Thus, if substituent R_i is attached at the para position of the aryl, then this is indicated as "*p*-R_i-substituted aryl".

As used herein, "amide" includes both RNR'CO- (in the case of R = alkyl, alkaminocarbonyl-) and RCONR'- (in the case of R = alkyl, alkyl

carbonylamino-).

As used herein, "ester" includes both ROCO- (in the case of R = alkyl, alkoxycarbonyl-) and RCOO- (in the case of R = alkyl, alkylcarbonyloxy-).

As used herein, "halogen" is a chloro, bromo, fluoro or iodo atom radical. Chloro, bromo and fluoro are preferred halogens. The term "halogen" also contemplates terms sometimes referred to as "halo" or "halide".

As used herein, "alkylamino" is an amine radical in which at least one hydrogen atom on the nitrogen has been replaced with alkyl. Preferred examples include ethylamino, butylamino, isopropylamino, and the like. The alkyl component may be linear, branched, cyclic, substituted, saturated, or unsaturated.

As used herein, "alkylsulfanyl" is a thiol radical in which the hydrogen atom on sulfur has been replaced with alkyl. Preferred examples include ethylsulfanyl, butylsulfanyl, isopropylsulfanyl, and the like. The alkyl component may be linear, branched, cyclic, substituted, saturated, or unsaturated.

As used herein, "alkoxy" is a hydoxyl radical in which the hydrogen atom on oxygen has been replaced with alkyl. Preferred examples include ethoxy, butoxy, benzyloxy, and the like. The alkyl component may be linear, branched, cyclic, substituted, saturated, or unsaturated.

As used herein, "heterocycle(s)" means ring systems, preferably of 3-7 members, which are saturated or unsaturated, and non-aromatic. These may be substituted or unsubstituted, and are attached to other parts of the molecule via any available valence, preferably any available carbon or nitrogen. More preferred heterocycles are of 5 or 6 members. In six-membered monocyclic heterocycles, the heteroatom(s) are from one to three of O, S, or N, and wherein when the heterocycle is five-membered, preferably it has one or two heteroatoms selected from O, N, or S.

As used herein, "heterocyclyl" means radical heterocycles. These may be substituted or unsubstituted, and are attached to other via any available valence, preferably any available carbon or nitrogen.

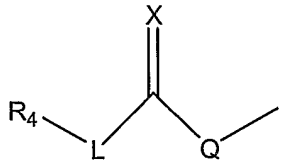
As used herein, "sulfamido" means an alkyl-N-$S(O)_2N$-, aryl-$NS(O)_2N$- or heterocyclyl-$NS(O)_2N$- group wherein the alkyl, aryl or heterocyclyl group is as defined herein above.

As used herein, "sulfonamido" means an alkyl-$S(O)_2N$-, aryl-$S(O)_2N$- or heterocyclyl- $S(O)_2N$- group wherein the alkyl, aryl or heterocyclcyl group is as herein described.

As used herein, "ureido" means an alkyl-NCON-, aryl-NCON- or heterocyclyl-NCON- group wherein the alkyl, aryl or heterocyclyl group is as herein described.

A substituent referred to as a radical in this specification may form a ring with another radical as described herein. When such radicals are combined, the skilled artisan will understand that there are no unsatisfied valences in such a case, but that specific substitutions, for example a bond for a hydrogen, is made. Hence certain radicals can be described as forming rings together. The skilled artisan will recognize that such rings can and are readily formed by routine chemical reactions, and it is within the purview of the skilled artisan to both envision such rings and the methods of their formations. Preferred are rings having from 3-7 members, more preferably 5 or 6 members. Compounds described herein may have cyclic structures therein, such as a ring R_1 and R_2. In that regard the skilled artisan recognizes that this method of description is routine in medicinal chemistry, though such may not rigorously reflect the chemical synthetic route. As used herein the term “ring” or “rings” when formed by the combination of two radicals refers to heterocyclic or carbocyclic radicals, and such radicals may be saturated, unsaturated, or aromatic. For example, preferred heterocyclic ring systems include heterocyclic rings, such as morpholinyl, piperdinyl, imidazolyl, pyrrolidinyl, and pyridyl.

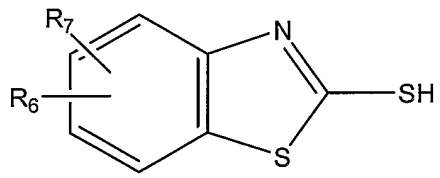
The skilled artisan will recognize that the radical of formula:

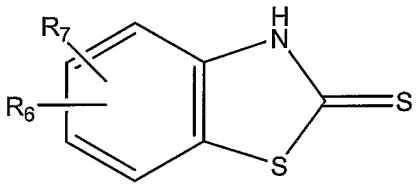


represents a number of different functionalities. Preferred functionalities represented by this structure include amides, ureas, thioureas, carbamates,

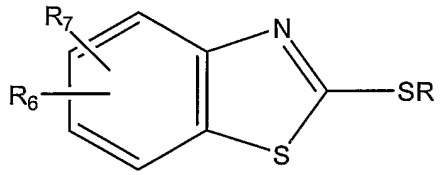
esters, thioesters, amidines, ketones, oximes, nitroolefines, hydroxyguanidines and guanidines. More preferred functionalities include ureas, thioureas, amides, and carbamates.

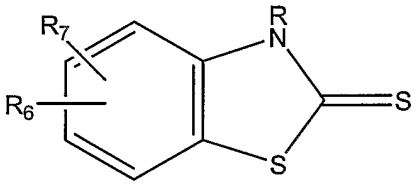
The skilled artisan will recognize that some structures described herein may be resonance forms or tautomers of compounds that may be fairly represented by other chemical structures. The artisan recognizes that such structures are clearly contemplated within the scope of this invention, although such resonance forms or tautomers are not represented herein. For example, the structures:





clearly represent the same compound(s), and reference to either clearly contemplates the other. In addition, the compounds useful in this invention can be provided as prodrugs, the following of which serve as examples:





wherein R is a group (or linkage) removed by biological processes. Hence, clearly contemplated in this invention is the use compounds provided as biohydrolyzable prodrugs, as they are understood in the art. “Prodrug”, as used herein is any compound wherein when it is exposed to the biological processes in an organism, is hydrolyzed, metabolized, derivatized or the like, to yield an active substance having the desired activity. The skilled artisan will recognize that prodrugs may or may not have any activity as prodrugs. It is the intent that the prodrugs described herein have no deleterious effect on the subject to be treated when dosed in safe and effective amounts. These include for example, biohydrolyzable amides and esters. A "biohydrolyzable amide" is an amide compound which does not essentially interfere with the activity of the compound, or that is readily converted *in vivo* by a cell, tissue, or human, mammal, or animal subject to yield an active compound. A "biohydrolyzable ester" refers to an ester compound that does not interfere

with the activity of these compounds or that is readily converted by an animal to yield an active compound. Such biohydrolyzable prodrugs are understood by the skilled artisan and are embodied in regulatory guidelines.

Compounds and compositions herein also specifically contemplate pharmaceutically acceptable salts, whether cationic or anionic. A "pharmaceutically-acceptable salt" is an anionic salt formed at any acidic (e.g., carboxyl) group, or a cationic salt formed at any basic (e.g., amino) group. Many such salts are known in the art, as described in World Patent Publication 87/05297, Johnston et al., published September 11, 1987 (incorporated by reference herein). Preferred counter-ions of salts formable at acidic groups can include cations of salts, such as the alkali metal salts (such as sodium and potassium), and alkaline earth metal salts (such as magnesium and calcium) and organic salts. Preferred salts formable at basic sites include anions such as the halides (such as chloride salts). Of course, the skilled artisan is aware that a great number and variation of salts may be used, and examples exist in the literature of either organic or inorganic salts useful in this manner.

Inasmuch as the compounds useful in this invention may contain one or more stereogenic centers, "Optical isomer", "stereoisomer", "enantiomer," "diastereomer," as referred to herein have the standard art recognized meanings (cf. *Hawleys Condensed Chemical Dictionary*, 11th Ed.) and are included in these compounds, whether as racemates, or their optical isomers, stereoisomers, enantiomers, and diastereomers.

As used herein, the term "metabolic disease", means a group of identified disorders in which errors of metabolism, imbalances in metabolism, or sub-optimal metabolism occur. The metabolic diseases as used herein also contemplate a disease that can be treated through the modulation of metabolism, although the disease itself may or may not be caused by specific metabolism blockage. Preferably, such metabolic disease involves glucose and fatty acid oxidation pathway. More preferably, such metabolic disease involves MCD or is modulated by levels of Malonyl CoA, and is referred to herein as an "MCD or MCA related disorder."

PREPARATION OF COMPOUNDS

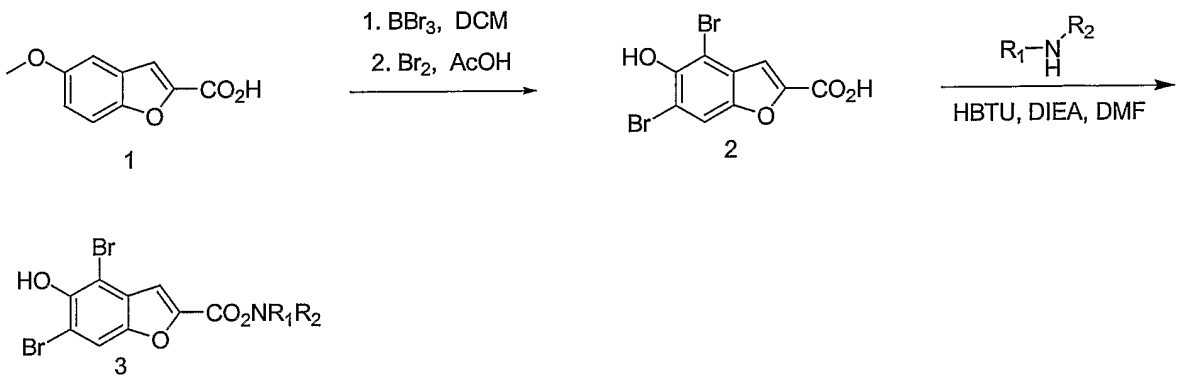
The starting materials used in preparing the compounds useful in this invention are known, made by known methods, or are commercially available. It will be apparent to the skilled artisan that methods for preparing precursors and functionality related to the compounds claimed herein are generally described in the literature. The skilled artisan given the literature and this disclosure is well equipped to prepare any of these compounds.

It is recognized that the skilled artisan in the art of organic chemistry can readily carry out manipulations without further direction, that is, it is well within the scope and practice of the skilled artisan to carry out these manipulations. These include reduction of carbonyl compounds to their corresponding alcohols, reductive alkylation of amines, oxidations, acylations, aromatic substitutions, both electrophilic and nucleophilic, etherifications, esterification, saponification and the like. These manipulations are discussed in standard texts such as March *Advanced Organic Chemistry* (Wiley), Carey and Sundberg, *Advanced Organic Chemistry* and the like.

The skilled artisan will readily appreciate that certain reactions are best carried out when other functionality is masked or protected in the molecule, thus avoiding any undesirable side reactions and/or increasing the yield of the reaction. Often the skilled artisan utilizes protecting groups to accomplish such increased yields or to avoid the undesired reactions. These reactions are found in the literature and are also well within the scope of the skilled artisan. Examples of many of these manipulations can be found for example in T. Greene and P. Wuts *Protecting Groups in Organic Synthesis*, 2nd Ed., John Wiley & Sons (1991).

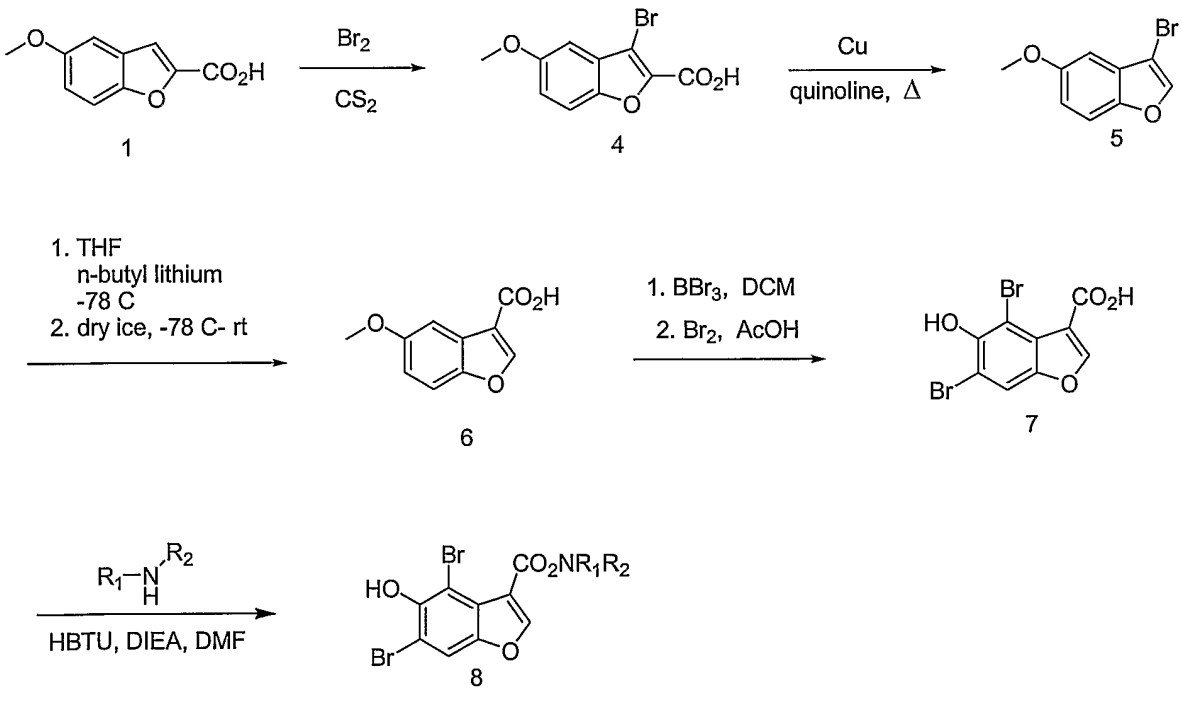
The following example schemes are provided for the guidance of the reader, and represent preferred methods for making the compounds exemplified herein. These methods are not limiting, and it will be apparent that other routes may be employed to prepare these compounds. Such methods specifically include solid phase based chemistries, including combinatorial chemistry. The skilled artisan is thoroughly equipped to prepare these compounds by those methods given the literature and this disclosure.

Scheme 1



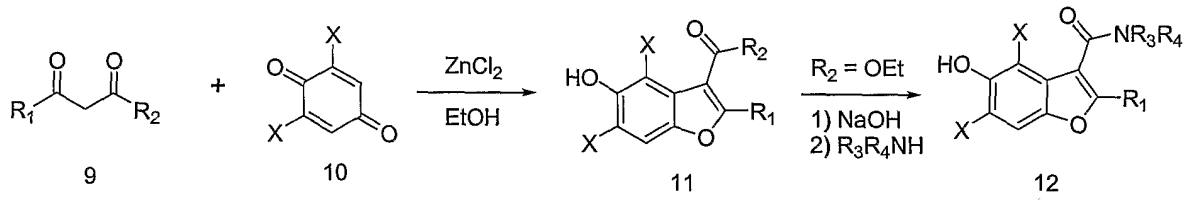
As shown in the above scheme, treatment of benzofuran O-methyl ether (1) with tribromoboron in dichloromethane provided the free 5-hydroxylbenzofuran compound 2 which coupled to primary or secondary amine under conventional peptide coupling conditions gave rise to the desired 2-carboxamide derivatives 3.

Scheme 2



Scheme 2 illustrated the synthesis of C-3 carboxamides. Starting from the same starting material 1, bromination occurred at C-3 position in the presence of bromine and using CS_2 as solvent. Decarboxylation of C-2 carboxylic acid group was achieved under conventional condition (Cu-Quinoline) to provide 3-bromo-5-methoxy-benzofuran 5 in good yields. Compound 5 was subsequently treated with n-butyllithium followed by dry ice to furnish C-3 carboxylic acid compound 6. Following the sequence in Scheme 1, the intermediate compound 6 was converted into its corresponding C-3 carboxamides 8.

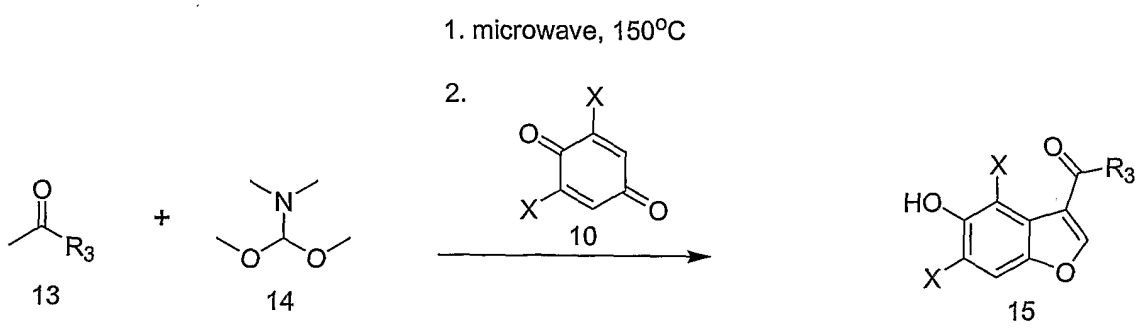
Scheme 3



9 10 11 12

Alternatively, C-2 substituted C-3 carboxamides compounds 12 could be prepared by the procedure shown in the Scheme 3 (Giza; Hinman; *J.Org.Chem.*; 1964, 29:1453). In the presence of Lewis acid (e.g. ZnCl2), b-diketone or b-ketoester 9 was coupled with quinone derivatives 10 to provide the desired C2 substituted C-3 ketone derivatives in one step. Or when R_2 =OEt, the C-3 carboxylate was sponified to give rise to the corresponding carboxylic acid which was subsequently converted into its corresponding amide derivatives 12.

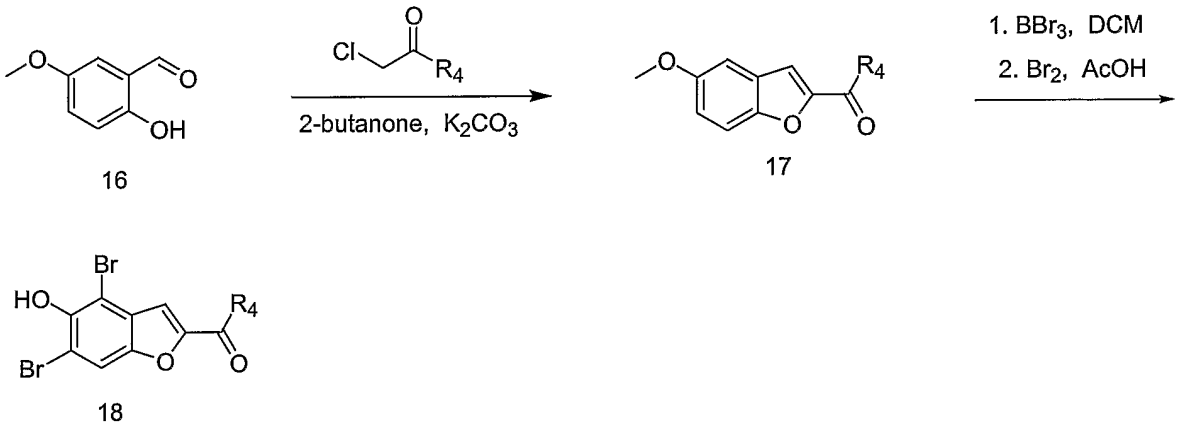
Scheme 4



13 14 10 15

A similar method was employed to prepare C-2 unsubstituted C-3 keto derivatives. Methyl ketone 13 was easily converted into its corresponding enamine intermediate under heating with microwave. The intermediate then was coupled with quinone derivative 10 to provide the desired C-3 ketone compounds.

Scheme 5



On the other hand, C-2 ketone derivatives were prepared via the procedure illustrated in Scheme 5. Ring formation of o-hydroxybenzaldehyde 16 with a-chloromethylketone in the presence of weak base such as K2CO3 led to the C-2 ketone benzofuran intermediate 17. Subsequent removal of methoxy protecting group and bromination at C-4 and C-6 position resulted in the final product 18

In vitro MCD Inhibitory Assay

The conversion of acetyl-CoA from malonyl-CoA was assayed using a modified protocol as previously described by Kim, Y. S. and Kolattukudy, P. E. in 1978 (*Arch. Biochem. Biophys* 190:585 (1978)). As shown in eq. 1 – 3, the establishment of the kinetic equilibrium between malate / NAD and oxaloacetate / NADH was catalyzed by malic dehydrogenase (eq. 2). The enzymatic reaction product of MCD, acetyl-CoA, shifted the equilibrium by condensing with oxaloacetate in the presence of citrate synthase (eq. 3), which resulted in a continuous generation of NADH from NAD. The accumulation of NADH can be

continuously followed by monitoring the increase of fluorescence emission at 460 nm on a fluorescence plate reader. The fluorescence plate reader was calibrated using the authentic acetyl-CoA from Sigma. For a typical 96-well plate assay, the increase in the fluorescence emission (λ_{ex} = 360 nm, λ_{em} = 460 nm, for NADH) in each well was used to calculate the initial velocity of hMCD. Each 50 μL assay contained 10 mM phosphate buffered saline (Sigma), pH 7.4, 0.05% Tween-20, 25mM K_2HPO_4 - KH_2PO_4 (Sigma), 2 mM Malate (Sigma), 2 mM NAD (Boehringer Mannheim), 0.786 units of MD (Roche Chemicals), 0.028 unit of CS (Roche Chemicals), 5 – 10 nM hMCD, and varying amounts of MCA substrate. Assays were initiated by the addition of MCA, and the rates were corrected for the background rate determined in the absence of hMCD.

Isolated Working Rat Heart Assay Protocol

Isolated working hearts from male Sprague-Dawley rats (300-350 g) are subjected to a 60-minute aerobic perfusion period. The working hearts are perfused with 95% O_2, 5% CO_2 with a modified Krebs-Henseleit solution containing 5 mM glucose; 100 μU/mL insulin; 3% fatty acid-free BSA; 2.5 mM free Ca^{2+}, and 0.4 to 1.2 mmol/L palmitate (Kantor et al., *Circulation Research* 86:580-588(2000)). The test compound is added 5 minutes before the perfusion period. DMSO (0.05%) is used as control.

Measurement of Glucose Oxidation Rates

Samples were taken at 10-minute intervals for measurements of experimental parameters. Glucose oxidation rates are determined by the quantitative collection of $^{14}CO_2$ produced by hearts perfused with buffer containing [U14]-Glucose (R. Barr and G. Lopaschuk, in *"Measurement of cardiovascular function"*, McNeill, J. H. ed., Chapter 2, CRC press, New York (1997)). After the perfusion, the $^{14}CO_2$ from the perfusae is subsequently released by injecting 1 mL of perfusate into sealed test tube containing 1 mL of 9N H_2SO4. The tube was sealed with a rubber stopper attached to a scintillation vial containing a piece of filter papers saturated with 300 μl of hyamine hydroxide. The scintillation vials with filter papers were then removed and Ecolite Scintillation Fluid added.

Samples were counted by standard procedures as described above. Average rates of glucose oxidation for each phase of perfusion are expressed as μmol /min/g dry wt as described above.

Measurement of Fatty Acid Oxidation Rates

Rates of fatty acid oxidation are determined using the same method as described above for glucose oxidation rate measurement using [^{14}C]palmitate or by the quantitative collection of ^3H_2O produced by hearts perfused with buffer containing [5-^{3}H]palmitate (R. Barr and G. Lopaschuk, in *"Measurement of cardiovascular function"*, McNeill, J. H. ed., Chapter 2, CRC press, New York (1997)). ^3H_2O was separated from [5-^{3}H]palmitate by treating 0.5 mL buffer samples with 1.88 mL of a mixture of chloroform/methanol (1:2 v:v) and then adding 0.625 mL of chloroform and 0.625 mL of a 2 M KCl/HCl solution. The sample is centrifuged for 10 min and aqueous phase was removed and treated with a mixture of 1 mL of chloroform, 1 mL of methanol and 0.9 mL KCl/HCl with a ration of 1:1:0.9. The aqueous layer was then counted for total ^3H_2O determination. This process resulted in greater than 99.7% extraction and separation of ^3H_2O from the pamiltate. Average rates of fatty acid oxidation for each phase of perfusion are expressed as nmol/min/g dry wt after taking consideration the dilution factor.

Active compounds are characterized by an increase in glucose oxidation and/or decrease in fatty acid oxidation as compared to the control experiments (DMSO). The compounds that caused statistically significant increases in glucose oxidation and/or decrease in fatty acid oxidation are considered to be active. Statistical significance was calculated using the Student's t test for paired or unpaired samples, as appropriate. The results with $P < 0.05$ are considered to be statistically significant.

Table I. In vitro Enzymatic Inhibitory Activities

Examples	Ki (nM)
CBP-000022880	33.5
CBP-000022880	35.7
CBP-000022902	998.1
CBM-000302109	450
CBM-000302150	121
CBM-000302151	1296.9
CBM-000302164	3293.8
CBM-000302272	3692.3
CBM-000302300	1653.1
CBM-000302301	315.1
CBM-000302323	1561.7
CBM-000302324	2326.1
CBM-000302325	4392.9
CBM-000302331	299.2
CBM-000302332	3696.2
CBM-000302333	3433.1
CBM-000302335	919.4
CBM-000302336	2808.2
CBM-000302349	1704.9
CBM-000302351	2911.3
CBM-000302352	3821
CBM-000302364	4512
CBM-000302366	2499.9
CBM-000302381	94.4
CBM-000302382	1431.1
CBM-000302383	1753.6
CBM-000302401	224.5
CBM-000302402	195.7
CBM-000302403	4655.1
CBM-000302416	2477.1
CBM-000302417	1649.1
CBM-000302418	2158.9
CBM-000302420	50.6
CBM-000302421	3208.8
CBM-000302423	1590.5
CBM-000302437	3804.3
CBM-000302441	31.6
CBM-000302448	3425.2
CBM-000302450	3338.2
CBM-000302452	4671.2
CBM-000302453	5326.3
CBM-000302454	1990.1
CBM-000302455	4144.3
CBM-000302456	1116.7
CBM-000302457	2343.3
CBM-000302477	2094.7

Table I. In vitro Enzymatic Inhibitory Activities (continued)

CBM-000302478	208.9
CBM-000302494	755.9
CBM-000302496	1982.6
CBM-000302497	2080.8
CBM-000302498	616.2
CBM-000302499	1664.8
CBM-000302501	4812
CBM-000302502	3666.6
CBM-000302503	269.1
CBM-000302505	4750.2
CBM-000302507	681.1
CBM-000302508	26.7
CBM-000302512	1149.9
CBM-000302513	3318.8
CBM-000302528	3630.3
CBM-000302529	1965.7

EXAMPLES

To further illustrate this invention, the following examples are included. The examples should not be construed as specifically limiting the invention. Variations of these examples within the scope of the claims are within the purview of one skilled in the art are considered to fall within the scope of the invention as described, and claimed herein. The reader will recognize that the skilled artisan, armed with the present disclosure, and skill in the art is able to prepare and use the invention without exhaustive examples.

Trademarks used herein are examples only and reflect illustrative materials used at the time of the invention. The skilled artisan will recognize that variations in lot, manufacturing processes, and the like, are expected. Hence the examples, and the trademarks used in them are non-limiting, and they are not intended to be limiting, but are merely an illustration of how a skilled artisan may choose to perform one or more of the embodiments of the invention.

^{1}H nuclear magnetic resonance spectra (NMR) is measured in $CDCl_3$ or other solvents as indicated by a Varian NMR spectrometer (Unity Plus 400, 400 MHz for ^{1}H) unless otherwise indicated and peak positions are expressed in parts per million (ppm) downfield from tetramethylsilane. The peak shapes are denoted as follows, s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet.

The following abbreviations have the indicated meanings:

Ac = acetyl

Bn = benzyl

Bz= benzoyl

CDI = carbonyl diimidazole

CH_2Cl_2 = dichloromethane

DIBAL= diisobutylaluminum hydride

DMAP = 4-(dimethylamino)-pyridine

DMF= N,N-dimethylformamide

DMSO = dimethylsulfoxide

EDCI or ECAC =1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloric acid

ESIMS = electron spray mass spectrometry

Et_3N = triethylamine

EtOAc = ethyl acetate

HMTA = hexamethylenetetramine

LDA = lithium diisopropylamide

LHDMS = lithium bis(trimethylsilyl)amide

$MgSO_4$ = magnesium sulfate

NaH = sodium hydride

NBS = N-bromosuccinimide

NCS = N-chlorosuccinimide

NH_4Cl= ammonium chloride

Ph = phenyl

Py = pyridinyl

r.t.= room temperature

TFA = trifluoroacetic acid

THF = tetrahydrofuran

TLC = thin layer chromatography

Tf_2O = triflic anhydride

Alkyl group abbreviations

Me = methyl

Et = ethyl

n-Pr = normal propyl

i-Pr = isopropyl

n-Bu = normal butyl

i-Bu = isobutyl

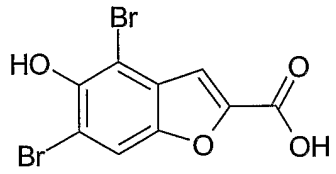
t-Bu = tertiary butyl

s-Bu = seconday butyl

c-Hex = cyclohexyl

Example 1

Preparation of 4,6-dibromo-2-carboxy-5-hydroxybenzofuran:



Step 1: Preparation of 2-carboxy-5-hydroxybenzofuran.

2-Carboxy-5-methoxybenzofuran (1.0 g, 5.2 mmol) was dissolved in anhydrous dichloromethane (25 ml) and cooled to –78°C. A 1 M solution of borontribromide (15.6 ml) in dichloromethane was added slowly. The reaction mixture was allowed to warm to ambient temperature under an atmosphere of nitrogen, and stirred 4 hours. The solution was quenched with aqueous ammonium chloride (20 ml) and extracted with ethyl acetate. The aqueous layer was washed with water and dried over sodium sulfate. 0.9 g (100%) of crude product was obtained. ^{1}H NMR (CD_3OD) δ = 6.84 (dd, 1H), 6.95 (d, 1H), 7.17 (s, 1H), 7.32 (d, 1H).

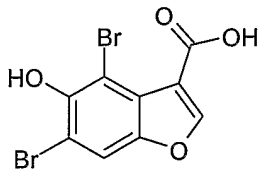
Step 2: Preparation of 4,6-dibromo-2-carboxy-5-hydroxybenzofuran.

2-carboxy-5-hydroxybenzofuran (980 mg, 5.50 mmol) and potassium acetate (1.10 g, 11.21 mmol) were dissolved in acetic acid (30 ml) and cooled to 0°C. Bromine (845 µl, 16.50 mmol) was dissolved in acetic acid (2 ml) and added slowly to the above solution. The reaction mixture was allowed to warm to ambient temperature under an atmosphere of nitrogen, and stirred 2.5 hours. Water (20 ml) was then added to the solution and the reaction quenched upon the addition of $Na_2S_2O_3$-$5H_2O$ (260 mg). The aqueous solution was extracted with diethyl ether, and the organic layer washed with aqueous sodium thiosulfate

and dried over sodium sulfate. Concentration *in vacuo* yielded a tan solid which was washed with hexanes to yield 1.04 g (56%). ^{1}H NMR (CD_3OD) δ = 7.39 (s, 1H), 7.82 (s, 1H).

Example 2

Preparation of 4,6-dibromo-3-carboxy-5-hydroxybenzofuran



Step 1: Preparation of 3-bromo-2-carboxy-5-methoxybenzofuran.
2-Carboxy-5-methoxybenzofuran (2.00 g, 10.41 mmol) was suspended in carbon disulfide (70 ml) and bromine (1.18 ml, 22.96 mmol) was added. The mixture was refluxed 48 hours. The crude product was isolated by evaporation of solvent *in vacuo.* 2.64 g (96%). ^{1}H NMR (CD_3OD) δ3.94 (s, 3H), 7.28 (d, 1H), 7.48 (s, 1H), 7.57 (d, 1H).

Step 2: Preparation of 3-bromo-5-methoxybenzofuran.
3-Bromo-2-carboxy-5-methoxybenzofuran (1.36 g, 5.02 mmol), powdered copper (371 mg, 5.84 mmol), and quinoline (16 ml) were combined and heated to 210°C for 0.5 hours. After the mixture cooled to ambient temperature the solids were removed by filtration through celite. The filtrate was diluted with dichloromethane and washed three times with 1 M aqueous hydrochloric acid, once with aqueous sodium bicarbonate, and once with brine. The organic phase was dried over sodium sulfate, concentrated *in vacuo*, and purified by column chromatography (SiO_2 gel, 6:1 hexanes/ethyl acetate) to yield 708 mg (62%). ^{1}H NMR ($CDCl_3$) δ3.94 (s, 3H), 6.79 (d, 1H), 6.96 (s, 1H), 7.34 (dd, 1H), 7.64 (d, 1H).

Step 3: Preparation of 3-carboxy-5-methoxybenzofuran.

A 2.5 M solution of n-butyl lithium (5.6 ml, 2.24 mmol) in hexanes was added dropwise to a solution of 3-bromo-5-methoxybenzofuran (483 mg, 2.13 mmol) in anhydrous THF at –78°C. the cooled reaction mixture was stirred for 0.5 hours under an atmosphere of nitrogen. Powdered CO_2(s) was added and the mixture stirred an additional 0.5 hours before allowing it to warm to ambient temperature. After 0.5 hours the reaction was quenched with 2 M aqueous hydrochloric acid, concentrated *in vacuo*, and extracted with ethyl acetate. The organic layer was washed with water and dried over sodium sulfate. Purification by preparative TLC (3:2 hexanes/ethyl acetate) yielded 113 mg (9%). ^{1}H NMR (CD_3OD) δ3.84 (s, 3H), 6.94 (dd, 1H), 7.42 (d, 1H), 7.49 (d, 1H), 8.35 (s, 1H).

Step 4: Preparation of 3-carboxy-5-hydroxybenzofuran

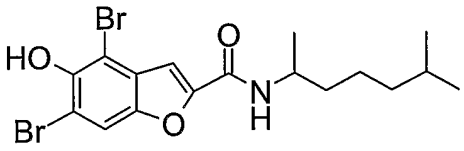
3-carboxy-5-methoxybenzofuran (128 mg, 0.666 mmol) was dissolved in anhydrous dichloromethane (25 ml) and cooled to –78°C. A 1 M solution of borontribromide (15.6 ml) in dichloromethane was added slowly. The reaction mixture was allowed to warm to ambient temperature under an atmosphere of nitrogen, and stirred 3 hours. The solution was quenched with aqueous ammonium chloride (20 ml) and extracted with ethyl acetate. The aqueous layer was washed with water and dried over sodium sulfate. 106 mg (89%) of crude product was obtained. ^{1}H NMR (CD_3OD) δ6.84 (dd, 1H), 7.36 (d, 1H), 7.39 (d, 1H), 8.32 (s, 1H).

Step 5: Preparation of 4,6-dibromo-3-carboxy-5-hydroxybenzofuran.

3-carboxy-5-hydroxybenzofuran (100 mg, 0.561 mmol) and potassium acetate (83 mg, 0.842 mmol) were dissolved in acetic acid (10 ml) and cooled to 0°C. Bromine (86 µl, 1.680 mmol) was and added slowly to the above solution and the reaction mixture was allowed to warm to ambient temperature under an atmosphere of nitrogen, stirring 3 hours. The reaction was quenched with aqueous sodium thiosulfate, extracted with ethyl acetate, washed with water and dried over sodium sulfate. Concentration *in vacuo* yielded a tan solid which was washed with hexanes to yield 155 mg (82%). ^{1}H NMR (CD_3OD) δ 7.83 (s, 1H), 8.37 (s, 1H).

Example 3

Preparation of N-alkyl-4,6-dibromo-5-hydroxybenzofuran-2-carboxamides



Step 1: Preparation of N-1,5-dimethylhexyl-4,6-dibromo-5-hydroxybenzofuran-2-carboxamide.

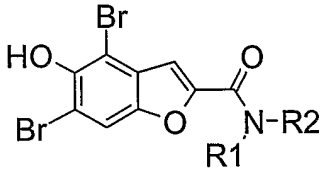
Combined 4,6-dibromo-2-carboxy-5-hydroxybenzofuran (16 mg, 0.048 mmol), 1,5-dimethylhexylamine (9 mg, 0.052 mmol), HBTU (33 mg, 0.062 mmol), and N,N-diisopropylethylamine (26 μl, 0.144 mmol) in DMF (2 ml) at 0°C. The mixture was stirred 2 hours, concentrated *in vacuo* and purified by preparative TLC (50% ethyl acetate, 50% hexanes) to yield 3.5 mg (16%). ^{1}H NMR ($CDCl_3$) δ 0.84 (m, 6H), 1.09 - 1.36 (m, 5H), 1.50 – 1.60 (m, 5H), 4.09 (m, 1H), 6.29 (d, 1H), 7.38 (s, 1H), 7.64 (s, 1H).

Example 4

Preparation of N-alkyl-4,6-dibromo-5-hydroxybenzofuran-2-carboxamides

All the compounds listed in Table 1 were prepared according to the procedure described in the above examples.

Table 1. *N*-alkyl-4,6-dibromo-5-hydroxybenzofuran-2-carboxamides.



Examples	R1	R2
4-1	1-Me-2-(CO2tBu)-ethyl	H
4-2	1,5-dimethylhexyl	H
4-3	cyclohexylmethyl	H
4-4	4-(3-Me-pentyl)-Ph	H
4-5	4-(4,4,4-trifluorobutyl)-Ph	H
4-6	OMe	Me

Table 1. *N*-alkyl-4,6-dibromo-5-hydroxybenzofuran-2-carboxamides. (continued)

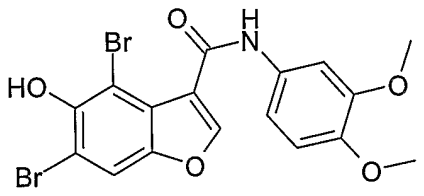
4-7	4-[CH2(CO2Et)]-Ph	H
4-8	2-(CO2tBu)-ethyl	H
4-9	1-iPr-2-(CO2tBu)-ethyl	H
4-10	2,5-diMeO-PhCH2	H
4-11	2,5-diMeO-PhCH2CH2	H
4-12	4-nBuO-Ph	H
4-13	furan-2-ylmethyl	H
4-14	2,5-diMeO-PhCONH	H
4-15	Ph	Me
4-16	4-(CO2Me)-Ph	Me
4-17	(CO2tBu)CH2	Me
4-18	cyclohexyl	H
4-19	3,4,5-triMeO-Ph	H
4-20	4-Me-Ph	H
4-21	Ph	H
4-22	4-(NCCH2)-Ph	H
4-23	3,5-diBr-4-OH-Ph	H
4-24	PhCH2CH2	Me
4-25	Ph	iPr
4-26	PhCH2	Me
4-27	iBu	Me
4-28	(CO2Et)CH2	Me
4-29	(CO2tBu)CH2	H
4-30	4-MeO-Ph	Me
4-31	4-CF3-PhCH2	Me
4-32	4-CF3O-PhCH2	Me
4-33	4-(CO2Me)-PhCH2	Me
4-34	(CO2tBu)CH2	tBu
4-35	3,5-diMeO-Ph	H
4-36	(CO2tBu)CH2	iPr
4-37	2,5-diMeO-Ph	H
4-38	2,3-diMeO-Ph	H
4-39	4-tBu-Ph	H
4-40	3,4-diMeO-Ph	H
4-41	1,3-dioxolanylmethyl	Me
4-42	n-pentyl	Me
4-43	2-(N,N-dimethyl)-ethyl	Me
4-44	2-(N,N-diethyl)-ethyl	Me
4-45	2-(N,N-dimethyl)-propyl	Me
4-46	2-Cl-Ph	Me
4-47	4-Cl-Ph	Me
4-48	2-Me-Ph	Me
4-49	4-Me-Ph	Me
4-50	furan-2-ylmethyl	Me
4-51	napthalyl	Me
4-52	4-MeO-Ph	Me

Table 1. *N*-alkyl-4,6-dibromo-5-hydroxybenzofuran-2-carboxamides. (continued)

4-53	3,4-diMeO-PhCH2CH2	Me
4-54	3,4-diCl-Ph	Me
4-55	3,4,5-triMeO-PhCH2	Me
4-56	3-Me-Ph	Me
4-57	2-(6-MeO)-pyridinyl	Me
4-58	1,1-dimethyl-2-(CO2tBu)ethyl	H

Example 5

Preparation of N-alkyl-4,6-dibromo-5-hydroxybenzofuran-3-carboxamides



Step 1: Preparation of N-(3,4-dimethoxyphenyl)-4,6-dibromo-5-hydroxybenzofuran-3-carboxamide.

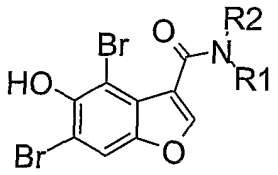
Combined 4,6-dibromo-3-carboxy-5-hydroxybenzofuran (60 mg, 0.179 mmol), 3,4-dimethoxyaniline (27 mg, 0.179 mmol), and EDC (41 mg, 0.215 mmol in THF (5 ml) and stirred overnight. The mixture was diluted with water, extracted with ethyl acetate, dried over sodium sulfate, and concentrated *in vacuo*. The crude material was purified by preparative TLC (2:1 hexanes/ethyl acetate) to yield 9 mg (23%). ^{1}H NMR ($CDCl_3$) δ 3.87 (s, 3H), 3.90 (s, 3H), 5.96 (s, 1H), 6.83 (d, 1H), 6.99 (d, 1H), 7.44 (d, 1H), 7.72 (m, 2H), 8.05 (s, 1H); ESIMS: *m/z* 470 (M-H).

Example 6

Preparation of *N*-alkyl-4,6-dibromo-5-hydroxybenzofuran-3-carboxamides

All compounds listed in Table 2 were prepared according to the procedure described in the above examples.

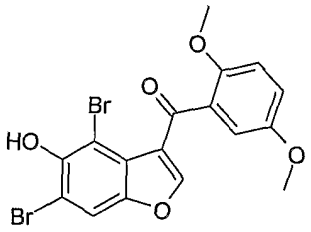
Table 2. *N*-alkyl-4,6-dibromo-5-hydroxybenzofuran-3-carboxamides.



Examples	R1	R2
6-1	(CO2tBu)-methyl	Me
6-2	Ph	H
6-3	4-(CO2Me)-Ph	Me
6-4	3,4,5-triMeO-Ph	H
6-5	3,5-diMeO-Ph	H
6-6	3,4-diMeO-Ph	H
6-7	4-CF3O-Ph	Me
6-8	4-CF3O-PhCH2	H
6-9	3,4,5-triMeO-PhCH2	Me
6-10		H
6-11	(CO2tBu)-methyl	iPr
6-12	2-[2-Me-(CO2tBu)]-ethyl	H
6-13	2-(CO2tBu)-ethyl	H
6-14	3-(iPrO)-propyl	H

Example 7

Preparation of 4,6-dibromo-5-hydroxybenzofuran-3-ketones



Step 1: Preparation of 4,6-dibromo-3-(2,5-dimethoxybenzoyl)-5-hydroxybenzofuran.

N,N-dimethylformamide dimethyl acetal (141 μl, 1.06 mmol) and 2,5-dimethoxyacetophenone (161 μl, 1.01 mmol) were microwaved together at 150°C for two hours. 2,6-dibromo-p-benzoquinone (266 mg, 1.00 mmol) was added in acetic acid (0.5 ml) and the mixture stirred overnight. The reaction was concentrated *in vacuo* and purified by preparative TLC (50% ethyl acetate, 50% hexanes) to yield 37 mg (8%). ^{1}H NMR (CD_3OD) δ3.55 (s, 3H), 3.77 (s, 3H), 6.90 (s, 1H), 7.03 (d, 1H), 7.16 (m, 2H), 7.81 (s, 1H), 8.01 (s, 1H); ESIMS: *m/z* 455 (M-H).

Example 8

Preparation of 4,6-dibromo-5-hydroxybenzofuran-3-ketones

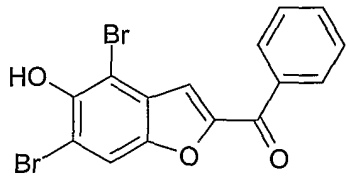
All compounds listed in Table 3 were prepared according to the procedure described in the above examples.

Table 3. 4,6-dibromo-5-hydroxybenzofuran-3-ketones.

Example	R1
8-1	2,5-diMeO-Ph
8-2	Ph
8-3	2-F-5-CF3-Ph
8-4	2-OH-5-Br-Ph
8-5	3,4,5-triMeO-Ph
8-6	1-napthyl
8-7	3,5-diMeO-Ph
8-8	1,4-benzodioxan-6-yl
8-9	4-Me-Ph
8-10	4-MeO-Ph
8-11	4-tBu-Ph
8-12	3-MeO-Ph
8-13	2-pyridinyl
8-14	2-(4-MeO-PhO)-Et
8-15	Me
8-16	3-NO2-Ph
8-17	2-Br-Ph
8-18	3,5-di(PhCH2O)-Ph
8-19	4-CF3-Ph
8-20	4-F-Ph
8-21	4-(PhSO2)-Ph
8-22	4-pyridinyl
8-23	3-pyridinyl
8-24	4-Cl-Ph
8-25	3-Cl-Ph
8-26	6-[1,3-thiazolo(3,2-A)pyrimidinone]
8-27	2-(3-Me-benzothiophene)
8-28	2-(1,2,4-triazol-1-yl)-ethyl
8-29	indol-3-yl
8-30	N-Me-1,3-thiazol-2-amine

Example 9

Preparation of 4,6-dibromo-5-hydroxybenzofuran-2-ketones



Step 1: Preparation of 2-benzoyl-5-methoxybenzofuran.

2-hydroxy-5-methoxybenzaldehyde (164 μl, 1.31 mmol), α-chloroacetophenone (203 mg, 1.31 mmol), and potassium carbonate (217 mg, 1.57 mmol) were heated in 2-butanone (10ml) at 80°C for 7 hours. The solvent was removed *in vacuo* and the residue was dissolved in ethyl acetate. The organic solution was washed twice with 2 M aqueous sodium hydroxide, once with brine, and dried over sodium sulfate to yield 315 mg (95%) of crude product. ^{1}H NMR ($CDCl_3$) δ3.87 (s, 3H), 7.12 (s, 1H), 7.14 (d, 1H), 7.53 – 7.56 (m, 3H), 7.65 (m, 1H), 8.04 (d, 2H).

Step 2: Preparation of 2-benzoyl-5-hydroxybenzofuran.

2-benzoyl-5-methoxybenzofuran (100 mg, 0.396 mmol) was dissolved in anhydrous dichloromethane (10 ml) and cooled to –78°C. A 1 M solution of borontribromide (1.2 ml) in dichloromethane was added slowly. The reaction mixture was allowed to warm to ambient temperature under an atmosphere of nitrogen, and stirred 3 hours. The solution was quenched with aqueous ammonium chloride (10 ml) and extracted with ethyl acetate. The aqueous layer was washed with water and dried over sodium sulfate. 69 mg (73%) of crude product was obtained. ^{1}H NMR (CD_3OD) δ 7.04 (dd, 1H), 7.09 (d, 1H), 7.45 (d, 1H), 7.52 (s, 1H), 7.55 (m, 2H), 7.67 (m, 1H), 8.01 (m, 2H).

Step 3: Preparation of 2-benzoyl-4,6-dibromo-5-hydroxybenzofuran.

2-benzoyl-5-hydroxybenzofuran (60 mg, 0.252 mmol) and potassium acetate (37 mg, 0.378 mmol) were dissolved in acetic acid (10 ml) and cooled to 0°C. Bromine (39 μl, 0.756 mmol) was and added slowly to the above solution and the reaction mixture was allowed to warm to ambient temperature under an atmosphere of nitrogen, stirring 3 hours. The reaction was quenched with aqueous sodium thiosulfate, extracted with ethyl acetate, washed with water and

dried over sodium sulfate. Concentration *in vacuo* yielded a tan solid which was washed with hexanes to yield 7 mg (7%). ^{1}H NMR ($CDCl_3$) δ5.91 (s, 1H), 7.44 (s, 1H), 7.57 (app t, 2H), 7.68 (app t, 1H), 7.81 (s, 1H), 8.03 (m, 2H). ESIMS: *m/z* 395 (M-H).

5

Example 10.

Preparation of 4,6-dibromo-5-hydroxybenzofuran-2-ketones

All the compounds listed in Table 4 were prepared according to the procedure described in the above examples.

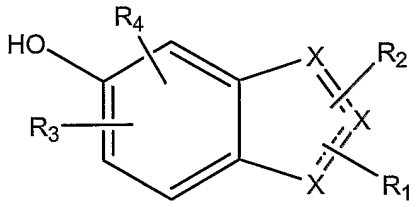
10

Table 4. 4,6-dibromo-5-hydroxybenzofuran-2-ketones.

Examples	R1
10-1	4-Me-Ph
10-2	Ph
10-3	3-NO2-Ph

We claim:

1. A pharmaceutical composition useful for inhibiting the enzyme malonyl-CoA decarboxylase which comprises a member selected from the group consisting of compounds of the formula (I):



(I)

wherein

R_1 and R_2 are independently selected from hydrogen, halogen, C_1-C_6 substituted alkyl, C_1-C_6 substituted alkenyl, C_1-C_6 substituted alkynyl, alkoxyl, phenyl, substituted phenyl, aryl, heteroaryl, substituted heteroaryl, $-NHCONR_5R_6$, $-COR_5$, $-CONR_5R_6$, $-S(O)_nR_5$, or $-SO_2NR_5R_6$,;

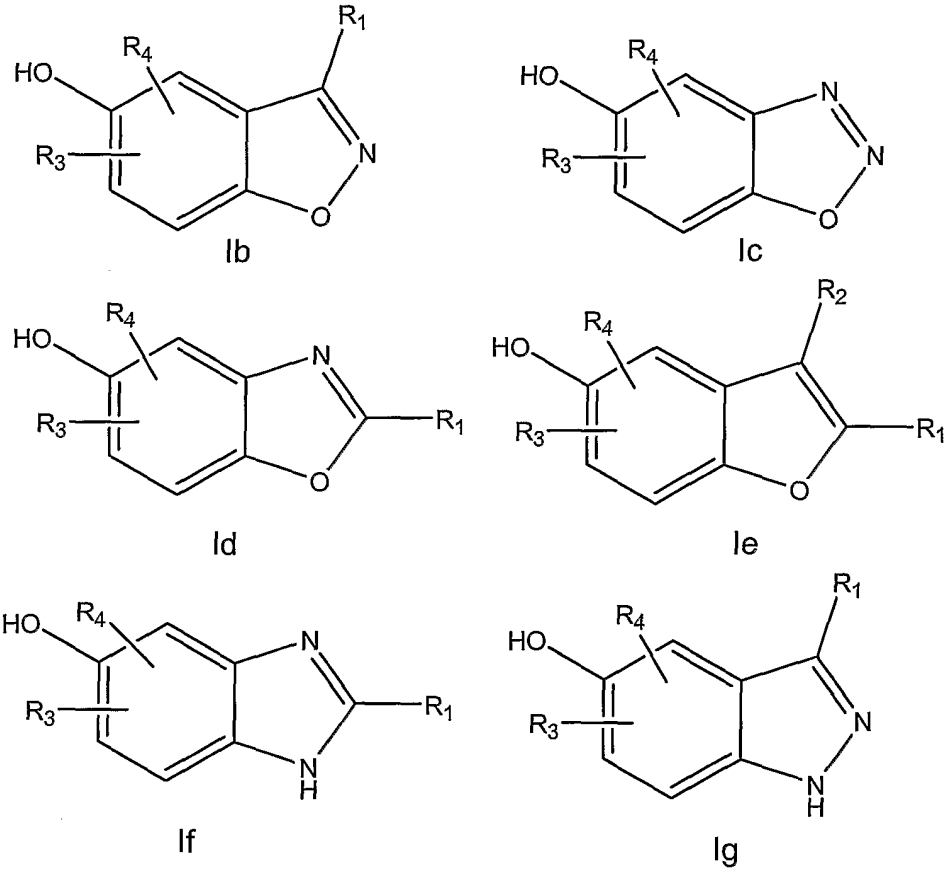
R_3 and R4 are independently selected from hydrogen, bromo, chloro, fluoro, iodo, hydroxyl, methoxyl, -COOH, $-COOR_5$, $-NHCONR_5R_6$, $-COR_5$, $-CONR_5R_6$, $-S(O)_nR_5$, or $-SO_2NR_5R_6$, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, C_1-C_6 alkoxyl, phenyl, substituted phenyl, aryl or heteroaryl;

R_5 and R_6 are independently selected from hydrogen, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, phenyl, substituted phenyl, aryl or heteroaryl;

X is independently chosen from O, N, NH, NR_5, S, or C;

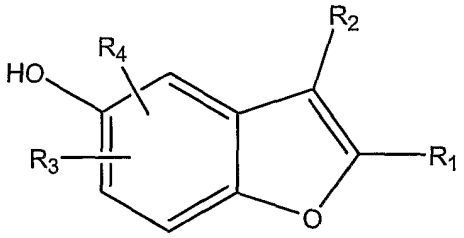
its corresponding enantiomers, diastereoisomers or tautomers, or a pharmaceutically acceptable salt, or a prodrug thereof in an pharmaceutically-acceptable carrier.

2. A compound according to Claim 1 having the general structure formula (Ia-Ig):



wherein R_1, R_2, R_3 and R_4 are as defined in claim 1.

3. A compound according to Claims 1 or 2 having the general structure formulae (Ie)



Ie

wherein R_1, R_2, R_3 and R_4 are as defined in claim 1.

4. A compound according to Claims 1, 2 or 3 selected from the group consisting of:

(4,6-dibromo-5-hydroxy-1-benzofuran-2-yl)(phenyl)methanone;

4,6-dibromo-N-(4-tert-butylphenyl)-5-hydroxy-1-benzofuran-2-carboxamide;

4,6-dibromo-N-(3,4-dimethoxyphenyl)-5-hydroxy-1-benzofuran-2-carboxamide;
4,6-dibromo-N-(1,3-dioxolan-2-ylmethyl)-5-hydroxy-N-methyl-1-benzofuran-2-carboxamide;
4,6-dibromo-5-hydroxy-N-methyl-N-pentyl-1-benzofuran-2-carboxamide;
4,6-dibromo-N-[2-(dimethylamino)ethyl]-5-hydroxy-N-methyl-1-benzofuran-2-carboxamide;
4,6-dibromo-N-[2-(diethylamino)ethyl]-5-hydroxy-N-methyl-1-benzofuran-2-carboxamide;
4,6-dibromo-N-[3-(dimethylamino)propyl]-5-hydroxy-N-methyl-1-benzofuran-2-carboxamide;
4,6-dibromo-5-hydroxy-N-methyl-N-(2-methylphenyl)-1-benzofuran-2-carboxamide;
4,6-dibromo-5-hydroxy-N-methyl-N-(4-methylphenyl)-1-benzofuran-2-carboxamide;
4,6-dibromo-N-(2-furylmethyl)-5-hydroxy-N-methyl-1-benzofuran-2-carboxamide;
4,6-dibromo-N-(2-chlorophenyl)-5-hydroxy-N-methyl-1-benzofuran-2-carboxamide;
4,6-dibromo-N-(4-chlorophenyl)-5-hydroxy-N-methyl-1-benzofuran-2-carboxamide;
4,6-dibromo-5-hydroxy-N-methyl-N-(1-naphthylmethyl)-1-benzofuran-2-carboxamide;
4,6-dibromo-5-hydroxy-N-(4-methoxyphenyl)-N-methyl-1-benzofuran-2-carboxamide;
4,6-dibromo-N-[2-(3,4-dimethoxyphenyl)ethyl]-5-hydroxy-N-methyl-1-benzofuran-2-carboxamide;
4,6-dibromo-N-(3,4-dichlorophenyl)-5-hydroxy-N-methyl-1-benzofuran-2-carboxamide;
4,6-dibromo-5-hydroxy-N-methyl-N-(3,4,5-trimethoxybenzyl)-1-benzofuran-2-carboxamide;
4,6-dibromo-5-hydroxy-N-methyl-N-(3-methylphenyl)-1-benzofuran-2-carboxamide;

4,6-dibromo-5-hydroxy-N-(6-methoxypyridin-2-yl)-N-methyl-1-benzofuran-2-carboxamide;
tert-butyl 3-{[(4,6-dibromo-5-hydroxy-1-benzofuran-2-yl)carbonyl]amino}-3-methylbutanoate;
(5-methoxy-1-benzofuran-2-yl)(3-nitrophenyl)methanone;
(5-methoxy-1-benzofuran-2-yl)(4-methylphenyl)methanone;
(5-hydroxy-1-benzofuran-2-yl)(3-nitrophenyl)methanone;
(5-hydroxy-1-benzofuran-2-yl)(4-methylphenyl)methanone;
4,6-dibromo-N-(3,4-dimethoxyphenyl)-5-hydroxy-1-benzofuran-3-carboxamide;
4,6-dibromo-5-hydroxy-N-methyl-N-[4-(trifluoromethoxy)phenyl]-1-benzofuran-3-carboxamide;
4,6-dibromo-5-hydroxy-N-(4-methoxybenzyl)-1-benzofuran-3-carboxamide;
4,6-dibromo-5-hydroxy-N-methyl-N-(3,4,5-trimethoxybenzyl)-1-benzofuran-3-carboxamide;
4,6-dibromo-5-hydroxy-N-[4-(trifluoromethoxy)phenyl]-1-benzofuran-3-carboxamide;
tert-butyl N-[(4,6-dibromo-5-hydroxy-1-benzofuran-3-yl)carbonyl]-N-isopropylglycinate;
tert-butyl 3-{[(4,6-dibromo-5-hydroxy-1-benzofuran-3-yl)carbonyl]amino}-3-methylbutanoate;
(4,6-dibromo-5-hydroxy-1-benzofuran-3-yl)carbonyl N-[3-(dimethylamino)propyl]-N'-ethylimidocarbamate;
(4,6-dibromo-5-hydroxy-1-benzofuran-2-yl)(3-nitrophenyl)methanone;
(4,6-dibromo-5-hydroxy-1-benzofuran-2-yl)(4-methylphenyl)methanone;
tert-butyl 3-{[(4,6-dibromo-5-hydroxy-1-benzofuran-3-yl)carbonyl]amino}butanoate; and
4,6-dibromo-5-hydroxy-N-(3-isopropoxypropyl)-1-benzofuran-3-carboxamide.

5. A method for inhibiting malonyl-CoA decarboxylase in a patient which comprises the administration of a therapeutically effective amount of a composition according to Claim 1.

6. A method for shifting fatty acid metabolism to carbohydrate metabolism in a patient by increasing malonyl-CoA concentration which comprises the administration of a therapeutically effective amount of a composition according to Claim 1.

7. A method for treating diseases associated with fatty acid and glucose metabolism mediated by malonyl-CoA decarboxylase in a patient which comprises the administration of a therapeutically effective amount of a composition according to Claim 1.

8. A method according to claim 7 wherein said disease is a cardiovascular disease.

9. A method according to Claim 8 wherein said cardiovascular disease is congestive heart failure.

10. A method according to Claim 9 wherein said cardiovascular disease is an ischemic cardiovascular disease.

11. A method according to Claim 10 wherein said ischemic cardiovascular disease is angina pectoris.

12. A method according to claim 7 wherein said disease is diabetes.

13. A method according to claim 7 wherein said disease is obesity.

14. A method according to claim 7 wherein said disease is acidosis.

15. A method according to claim 7 wherein said disease is cancer.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/343 A61P3/04 A61P9/00 A61P9/10 A61P3/10
A61P3/00 A61P35/00 C07D307/80 C07D307/85

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 7 A61P A61K C07D

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 practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/051860 A (WYETH CORP) 26 June 2003 (2003-06-26) abstract page 4, line 5 - page 5, line 5; table 1 page 26, line 18 - page 29, line 31 page 31, line 22 - page 32, line 26 page 38, lines 1-21 page 40, line 27 - page 41, line 34; examples 4-16,20-22,24,25,27,30,32,35-39,42,43,48,49,57-65 examples 67-73,77,80,100,102-105,108,110-113,118-120,123 examples 124,126,128,129,132,135,137,138,141 -/--	1-3, 5-13,15

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in 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 document 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 another 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	Date of mailing of the international search report
17 December 2004	05/01/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	A. Jakobs

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PCT/US2004/024285

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 165 810 A (MERCK FROSST CANADA INC) 27 December 1985 (1985-12-27) abstract page 4, line 15 - page 5, line 3 page 50, lines 5-10; table 1; compounds 42-44,66,76,79,80,102,156,161	1-3, 5-11,15
X	CARNEIRO DO NASCIMENTO S ET AL: "IN VITRO ANTITUMOR ACTIVITY OF FUSED 2-CARBOXALDEHYDE N,N-DIMETHYLHYDRAZONE-3-METHYLFURAN DERIVATIVES" PHARMAZIE, VEB VERLAG VOLK UND GESUNDHEIT. BERLIN, DD, vol. 49, no. 4, 1994, pages 296-297, XP008036264 ISSN: 0031-7144 table 1; compound 2	1-3,5-7, 15
X	BRAVO P ET AL: "THE REACTION OF O.HYDROXYBENZALDEHYDES WITH KETO-STABILIZED SULPHONIUM YLIDES: SYNTHESIS OF BENZOFURANES" GAZZETTA CHIMICA ITALIANA, SOCIETA CHIMICA ITALIANA, ROME, IT, vol. 103, no. 1/2, 1973, pages 95-103, XP008036246 ISSN: 0016-5603 page 96, paragraph 3 page 101, paragraph 5 - page 102, paragraph 1	2-4
X	WO 97/08145 A (DESAI BIPINCHANDRA NANUBHAI ; LINDMARK RICHARD JOHN (US); RUSSELL MARK) 6 March 1997 (1997-03-06) abstract page 12, line 22 - page 13, line 6 page 29, lines 12-34; examples 223,259	1-3,5-7, 12,15
X	BANSKOTA A H ET AL: "TWO NOVEL CYTOTOXIC BENZOFURAN DERIVATIVES FROM BRAZILIAN PROPOLIS" JOURNAL OF NATURAL PRODUCTS, XX, XX, vol. 63, no. 9, 2000, pages 1277-1279, XP008036243 ISSN: 0163-3864 abstract; compound 1 page 1279, column 1, paragraph 3	1-3,5-7, 15
X	WO 00/38687 A (MARQUIS ROBERT WELLS JR ; SMITHKLINE BEECHAM CORP (US); RU YU (US); CU) 6 July 2000 (2000-07-06) page 54, line 1 - page 55, line 4; example 81	1-3,5-7, 15

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 674 876 A (GILBERT JOHN C ET AL) 7 October 1997 (1997-10-07) abstract; examples 37,57,59 column 4, lines 6-18	1-3,5-7, 15
X	WO 01/95911 A (MARQUIS ROBERT W JR ; SMITHKLINE BEECHAM CORP (US); RU YU (US); VEBER) 20 December 2001 (2001-12-20) abstract page 74, lines 10-20; example 81	1-3,5-7, 15
X	EP 1 215 203 A (ONO PHARMACEUTICAL CO) 19 June 2002 (2002-06-19) abstract page 61, lines 1-22	1-3,5-7, 12,15
X	WO 02/074296 A (ONO PHARMACEUTICAL CO ; NAKA MASAO (JP); TAKAHASHI KANJI (JP)) 26 September 2002 (2002-09-26) abstract page 96, lines 8-17	1-3,5-7, 15
X	DATABASE WPI Section Ch, Week 200034 Derwent Publications Ltd., London, GB; Class B02, AN 2000-390106 XP002311132 & JP 2000 128878 A (TEIJIN LTD) 9 May 2000 (2000-05-09) abstract	1-3,5-7
X	DATABASE WPI Section Ch, Week 199730 Derwent Publications Ltd., London, GB; Class B02, AN 1997-323149 XP002311133 & JP 09 124632 A (SANKYO CO LTD) 13 May 1997 (1997-05-13) abstract	1-3,5-7, 15
X	DATABASE WPI Section Ch, Week 199538 Derwent Publications Ltd., London, GB; Class B03, AN 1995-290402 XP002311134 & JP 07 188227 A (JAPAN TOBACCO INC) 25 July 1995 (1995-07-25) abstract; example 8	1-3,5-7, 12

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INTERNATIONAL SEARCH REPORT

International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE WPI Section Ch, Week 199517 Derwent Publications Ltd., London, GB; Class B02, AN 1995-129576 XP002311135 & SU 1 681 502 A1 (A MED CARDIOLOGY RES CENTRE) 15 June 1994 (1994-06-15) abstract	1-3,5-8
X	CHEN C-C ET AL: "CONJUGATED POLYHYDROXYBENZENE DERIVATIVES BLOCK TUMOR NECROSIS FACTOR-ALPHA-MEDIATED NUCLEAR FACTOR-KAPPAB ACTIVATION AND CYCLOOXYGENASE-2 GENE TRANSCRIPTION BY TARGETING IKAPPAB KINASE ACTIVITY" MOLECULAR PHARMACOLOGY, BALTIMORE, MD, US, vol. 60, no. 6, 2001, pages 1439-1448, XP008036242 ISSN: 0026-895X the whole document	1-3,5-7, 15
P,X	WO 03/066618 A (GALILEO LAB INC) 14 August 2003 (2003-08-14) the whole document	1-3, 5-13,15

INTERNATIONAL SEARCH REPORT

national application No.
PCT/US2004/024285

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 5-15 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Although claims 5-15 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box II.2

Remark: (5-methoxy-1-benzofuran-2-yl)(3-nitrophenyl)methanone and (5-methoxy-1-benzofuran-2-yl)(4-methylphenyl)methanone of claim 4 are not compounds according to formula 1

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

INTERNATIONAL SEARCH REPORT

formation on patent family members

International Application No
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03051860 A	26-06-2003	CA 2470352 A1	26-06-2003
		EP 1458700 A2	22-09-2004
		WO 03051860 A2	26-06-2003
		US 2003171428 A1	11-09-2003
EP 0165810 A	27-12-1985	AT 45736 T	15-09-1989
		AU 4377585 A	02-01-1986
		CA 1281325 C	12-03-1991
		DE 3572486 D1	28-09-1989
		DK 276985 A	21-12-1985
		EP 0165810 A2	27-12-1985
		ES 8800190 A1	01-01-1988
		GR 851493 A1	25-11-1985
		JP 61017579 A	25-01-1986
		PT 80660 A ,B	01-07-1985
		US 4863958 A	05-09-1989
		US 5087638 A	11-02-1992
		ZA 8504652 A	30-04-1986
WO 9708145 A	06-03-1997	AT 203234 T	15-08-2001
		AU 702487 B2	25-02-1999
		AU 7103996 A	19-03-1997
		BR 9610422 A	13-07-1999
		CA 2230209 A1	06-03-1997
		CN 1201454 A ,B	09-12-1998
		CZ 9800341 A3	16-09-1998
		DE 69613985 D1	23-08-2001
		DE 69613985 T2	13-06-2002
		DK 850221 T3	24-09-2001
		EP 0850221 A1	01-07-1998
		ES 2161373 T3	01-12-2001
		GR 3036751 T3	31-12-2001
		IL 123164 A	19-03-2001
		JP 11510814 T	21-09-1999
		NO 980817 A	24-04-1998
		NZ 318926 A	29-04-1999
		PL 325312 A1	20-07-1998
		PT 850221 T	30-11-2001
		RO 118289 B1	30-04-2003
		RO 118290 B1	30-04-2003
		RU 2196769 C2	20-01-2003
		US 6013651 A	11-01-2000
		WO 9708145 A1	06-03-1997
		US 6831199 B1	14-12-2004
		US 6100423 A	08-08-2000
		US 6028223 A	22-02-2000
		ZA 9607379 A	30-03-1998
WO 0038687 A	06-07-2000	AU 768565 B2	18-12-2003
		AU 1941100 A	31-07-2000
		BR 9916488 A	09-10-2001
		CA 2356671 A1	06-07-2000
		CN 1350458 T	22-05-2002
		CZ 20012277 A3	14-11-2001
		EP 1384713 A1	28-01-2004
		EP 1158986 A1	05-12-2001
		HU 0104768 A2	29-04-2002
		JP 2002533397 T	08-10-2002

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US2004/024285

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0038687 A		NO 20013124 A	22-06-2001
		NZ 511710 A	19-12-2003
		PL 350132 A1	04-11-2002
		TR 200101869 T2	21-01-2002
		US 2003044399 A1	06-03-2003
		US 2002147188 A1	10-10-2002
		WO 0038687 A1	06-07-2000
		US 2003225061 A1	04-12-2003
		US 2004002487 A1	01-01-2004
		US 2003144175 A1	31-07-2003
		ZA 200104208 A	23-05-2002
US 5674876 A	07-10-1997	AU 4899096 A	07-08-1996
		WO 9622089 A1	25-07-1996
		ZA 9600428 A	21-07-1997
WO 0195911 A	20-12-2001	AU 6840701 A	24-12-2001
		BG 107327 A	31-07-2003
		BR 0111693 A	06-04-2004
		CA 2412353 A1	20-12-2001
		CN 1444481 T	24-09-2003
		CZ 20024086 A3	14-05-2003
		EP 1307204 A1	07-05-2003
		HU 0301231 A2	28-08-2003
		JP 2004503502 T	05-02-2004
		MA 25758 A1	01-04-2003
		NO 20025786 A	12-02-2003
		NZ 522965 A	25-06-2004
		PL 360508 A1	06-09-2004
		SK 17592002 A3	02-05-2003
		WO 0195911 A1	20-12-2001
		US 2003044399 A1	06-03-2003
		US 2002147188 A1	10-10-2002
		US 2003225061 A1	04-12-2003
		US 2004002487 A1	01-01-2004
		US 2003144175 A1	31-07-2003
EP 1215203 A	19-06-2002	AU 7320100 A	24-04-2001
		EP 1215203 A1	19-06-2002
		US 6770644 B1	03-08-2004
		WO 0121583 A1	29-03-2001
		JP 2002080445 A	19-03-2002
		US 2004214896 A1	28-10-2004
WO 02074296 A	26-09-2002	WO 02074296 A1	26-09-2002
JP 2000128878 A	09-05-2000	NONE	
JP 9124632 A	13-05-1997	NONE	
JP 7188227 A	25-07-1995	NONE	
SU 1681502 A1	15-06-1994	NONE	
WO 03066618 A	14-08-2003	CA 2474974 A1	14-08-2003
		EP 1472241 A1	03-11-2004
		WO 03066618 A1	14-08-2003
		US 6653346 B1	25-11-2003

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US2004/024285

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03066618 A		US 2004063975 A1	01-04-2004