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(54) Title: COMBINATIONS OF CORROLES AND STATINS

CHOLESTEROL BIOSYNTHESIS IN MACROPHAGE MODEL IN PRESENCE OF
STATINS, CORROLES AND COMBINATIONS THEREOF AS INHIBITORS

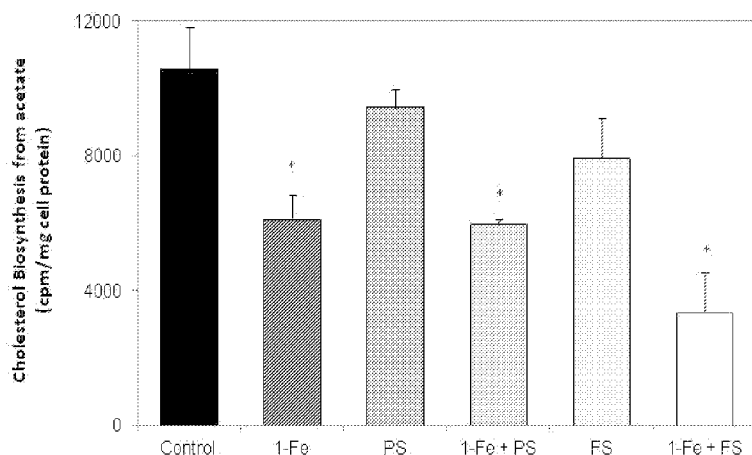


Fig. 1B

(57) **Abstract:** Embodiments of the invention relate to methods of treatment a cardiovascular disease in a patient comprising administering an effective amount of a statin or a pharmaceutically acceptable salt thereof in combination with an effective amount of a transition metal complex of a corrole, an optically active isomer thereof or a pharmaceutically acceptable salt thereof. Further embodiments refer to pharmaceutical compositions comprising a statin and a corrole.



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COMBINATIONS OF CORROLES AND STATINS

RELATED APPLICATIONS

[0001] The present application claims the benefit under 35 U.S.C. 119(e) of U.S. Provisional Application 61/523,476 filed on 15 August 2011, the disclosure of which is incorporated herein by reference.

TECHNICAL FIELD

[0002] Embodiments of the invention relate to a drug combination comprising a corrole and a statin.

BACKGROUND

[0003] Cardiovascular disease (CVD) is a class of diseases that involves the heart and/or blood vessels. This class of diseases is a leading cause of morbidity and mortality worldwide. The most prominent CVD is atherosclerosis, a condition in which an artery wall thickens as a result of accumulation of fatty materials therein. As atherosclerotic plaques develop they may cause complete closure of the artery lumen, resulting in insufficient blood supply to downstream tissues. Such blockage commonly occurs in coronary arteries or in the arteries of the brain, resulting in myocardial infarction or stroke, respectively.

[0004] Lipidic materials, including cholesterol, are transported in the circulatory system by lipoproteins, of which two major classes are high density lipoproteins (HDL) and low density lipoproteins (LDL). HDL is commonly referred to as “good cholesterol” as it operates to remove excess cholesterol from the arteries and transport it to the liver. LDL is commonly referred to as “bad cholesterol”, as it delivers cholesterol to the tissues, thus contributing to cholesterol accumulation in arterial macrophages, a first step in the development of atherosclerotic plaques. Patients with cholesterol levels higher than normal, in particular LDL cholesterol, a condition commonly referred to as hypercholesterolemia, are at high risk of developing atherosclerosis. One of the ways to control hypercholesterolemia is to limit dietary cholesterol intake. However, in many patients, controlling dietary cholesterol intake is not sufficient in reducing cholesterol levels. Medications such as statins are commonly administered to patients with hypercholesterolemia in order to lower the risk of CVD.

[0005] Statins are compounds which inhibit the enzyme HMG-CoA reductase, a key enzyme in the de novo synthesis of cholesterol, thereby lowering the production of cholesterol within the

cells (A. Rosanoff 2004). This causes increased cholesterol uptake from the bloodstream to the cells, thus lowering serum cholesterol and the risk of CVD. The first statin marketed was lovastatin, which was isolated from the fungus *Aspergillus terreus* and marketed by Merck & Co. Other statins were identified in naturally occurring fungi such as oyster mushrooms and red yeast rice. After lovastatin, other statins were developed and their use became common among hypercholesterolemia patients and patients at high risk of CVD. Additional statins include atorvastatin, cerivastatin, fluvastatin, mevastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin. Statins are now the most prescribed drugs worldwide.

[0006] In addition to lipoprotein concentration in the blood, lipoprotein oxidation also plays a major role in the development of atherosclerosis. Oxidized LDL (oxLDL) is taken up by arterial macrophages in a non-controlled fashion, thus leading to accumulation of cholesterol in the arteries (B. Fuhrman 2002). In addition, beneficial anti-atherogenic effects of HDL are impaired upon its oxidation (Smith 2010). Antioxidants that reduce oxidation of LDL and HDL were found to have an in vivo effect in reducing atherosclerosis. For example, a mixture of antioxidants lycopene, resveratrol, catechin and vitamins E and C reduced atherosclerosis in transgenic mice (L. Verschuren 2011).

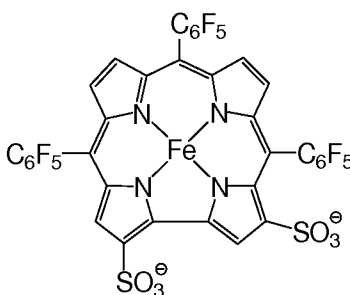
[0007] Although statins and antioxidants were shown to have a beneficial effect on atherosclerosis and on coronary heart disease, when statins were administered in combination with some antioxidants, not only did there appear to be an absence of benefit from the combinations relative to the use of each component alone, but the components of the combinations appeared to interfere with each other. The combinations appeared less effective as anti-atherosclerotic agents than the statins and the antioxidants when not administered in combination. For example, in patients with low HDL, beneficial effects of simvastatin and niacin were blunted when compared to a group of patients receiving simvastatin/niacin in combination with the antioxidants beta-carotene, vitamin C, vitamin E, and selenium (M.C. Cheung 2001). Another study showed that patients receiving atorvastatin in combination with the antioxidant vitamin E experienced less of a reduction in the expression of pro-inflammatory cytokines than patients receiving atorvastatin alone (D. Tousoulis 2005).

SUMMARY

[0008] An embodiment of the invention provides a method for treating a CVD in a subject comprising administering an effective amount of a statin or a pharmaceutically acceptable salt

thereof in combination with an effective amount of a transition metal complex of a corrole, an optically active isomer thereof, or a pharmaceutically acceptable salt thereof.

[0009] Corroles are organic molecules having a contracted porphyrin ring comprising nineteen carbon atoms and 4 nitrogen atoms, and are capable of binding transition metals. Transition metal complexes of corroles were found to have an antioxidant effect. The iron(III) complex of a corrole whose structural formula is depicted below, also known as 1-Fe, is a potent catalytic antioxidant (I. Aviv-Harel 2009).



[00010] It has been shown that 1-Fe spontaneously conjugates to HDL and LDL to protect them against oxidation and nitration (A. Haber 2008)(A. Haber 2011). Unlike other antioxidants which seem to interfere with the action of statins, corroles have been shown by the inventors to synergistically lower cholesterol levels when used in combination with statins.

[00011] “In combination” refers to both drugs being substantially effective in the body at a same time. Both drugs can be administered substantially at the same time, or both drugs can be administered at different times but have effect on the body at the same time. For example, “in combination” includes administering a corrole before the administration of the statin, and subsequently administering the statin while functioning of the corrole in the body is substantially extant.

[00012] An embodiment of the invention provides a pharmaceutical composition for delivering a statin and a corrole in combination. The composition optionally comprises: a transition metal complex of a corrole, an optically active isomer thereof, or a pharmaceutically acceptable salt thereof; a statin or a pharmaceutically acceptable salt thereof; and at least one pharmaceutically acceptable carrier.

[00013] A method for treating CVD using a combination of a statin and a corrole in accordance with an embodiment of the invention appears more effective than treatment of CVD with either a statin without a corrole or with a corrole without a statin. It appears that methods in accordance

with an embodiment of the invention can provide beneficial therapeutic effects in treating CVD using relatively reduced dosages of statins, potentially ameliorating side effects associated with statins.

[00014] In the discussion unless otherwise stated, adjectives such as “substantially” and “about” modifying a condition or relationship characteristic of a feature or features of an embodiment of the invention, are understood to mean that the condition or characteristic is defined to within tolerances that are acceptable for operation of the embodiment for an application for which it is intended.

[00015] This summary is provided to introduce a selection of concepts in a simplified form that are further described below in the detailed description. This summary is not intended to identify key features or essential features of the claimed subject matter, nor is it intended to be used to limit the scope of the claimed subject matter.

BRIEF DESCRIPTION OF FIGURES

[00016] Fig. 1A shows a graph depicting cholesterol biosynthesis relative to corrole dosage and corrole intracellular concentration in J774.A1 macrophages;

[00017] Fig. 1B shows a histogram depicting cholesterol biosynthesis in J774.A1 macrophages in absence of a pharmaceutical agent and in the presence of a corrole (1-Fe), a statin (fluvastatin [FS] or pravastatin [PS]) and combinations of a corrole and a statin (FS or PS); and

[00018] Fig. 2A and 2B show histograms depicting effect of 20 micromolar 1-Fe (2A), 15 micromolar 1-Fe (2B), FS, PS and combinations of 1-Fe and FS or PS on inhibition of an HMG-CoA reductase- catalyzed reaction, an enzyme induced biochemical reaction through which a precursor to cholesterol is formed in humans.

DETAILED DESCRIPTION

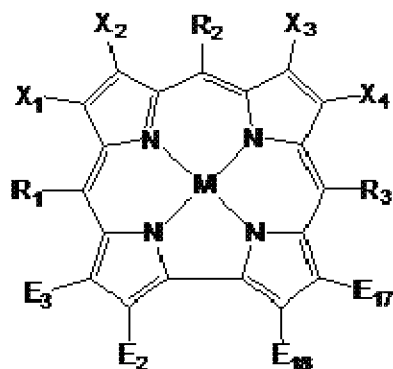
[00019] The administration of two drugs to treat a given condition raises a number of potential problems. When two drugs are introduced into the body, each drug can affect the absorption, distribution, and elimination of the other and hence, alter the effects of the other. Thus, when two drugs are administered to treat the same condition, it may be unpredictable whether each will complement, have no effect on, or interfere with, the therapeutic activity of the other in a human subject. For example, as noted above, even though both statins and antioxidants when administered independently of each other appeared beneficial in combating atherosclerosis, when administered in combination they reduced each other's beneficial effects.

[00020] Statins are currently approved for use in many dosages. It is recommended for patients to start statin therapy at lower dosages, for example, 10-20 milligrams (mg) daily of simvastatin, and increase dosage if the lower dosages are ineffective after being administered for a time. Certain patients having a high risk of CVD are recommended to start therapy at a moderate dose, for example, 40 mg of simvastatin daily. Statins as monotherapy, although approved for treatment of CVDs, are associated with health risks and potential side effects. The US Food and Drug Administration recently issued a safety announcement warning the public about an increased risk of muscle injury in patients taking the highest approved dose (80 mg) of simvastatin (FDA n.d.). In addition, taking high doses of 80 mg of simvastatin or atorvastatin increases the chance of developing Type 2 diabetes by 12 percent over five years compared to taking moderate dose statins (D.D. Waters 2011) (D. Preiss 2011).

[00021] When treating CVD with a combination of a statin or a pharmaceutically acceptable salt thereof in combination with an effective amount of a transition metal complex of a corrole, an optically active isomer thereof or a pharmaceutically acceptable salt thereof according to an embodiment of the invention, a smaller dosage of the statin may be needed to obtain a same therapeutic effect than when the statin is administered without the corrole. Therefore, the side effects associated with statin treatment when treating according to an embodiment of the invention may be reduced. For example, the beneficial effects of high dosage statin therapy may be obtained without the associated side effects by administering a moderate or low dose of a statin in combination with a transition metal complex of a corrole. In an embodiment of the invention the statin is selected from the group consisting of: atorvastatin, cerivastatin, fluvastatin, lovastatin, mevastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin.

[00022] Pharmaceutical compositions comprising corroles have been disclosed in US 6,730,666, incorporated herein by reference. Methods of manufacture of corroles are described in US 6,541,628, incorporated herein by reference.

[00023] In an embodiment of the invention the transition metal complex of a corrole has the formula:



wherein R_1 , R_2 and R_3 are each independently a carbocyclic aryl ring or a heterocyclic aryl ring, each ring comprising 5 or 6 atoms;

M is a transition metal selected from the group consisting of Mn, Fe, Ru, Co, V, Cr, and Cu;

X_1 , X_2 , X_3 and X_4 are each independently H or a halogen;

E_2 , E_3 , E_{17} and E_{18} are each independently H, halogen, SO_2Cl , SO_3H , $SO_2NR_4R_5$, CO_2H , CO_2R , $COCl$, $CONR_4R_5$, CHO , $CH=C(CO_2H)_2$, $CH=C(CN)CO_2H$, or NO_2 , R is alkyl or aryl and R_4 and R_5 are each independently H, alkyl, aryl or together with the N atom to which they are attached form a saturated 5-6 membered ring optionally containing an additional heteroatom selected from the group consisting of O, S and N.

[00024] In an embodiment of the invention, the transition metal is Fe;

R_1 , R_2 and R_3 are each pentafluorophenyl; E_2 and E_{17} are SO_3H ; X_1 , X_2 , X_3 and X_4 are each H; and E_3 and E_{18} are H.

[00025] In an embodiment of the invention, the transition metal is Fe;

R_1 , R_2 and R_3 are each 4-nitrophenyl; E_2 and E_{17} are SO_3H ; X_1 , X_2 , X_3 and X_4 are each H; and E_3 and E_{18} are H.

[00026] In an embodiment of the invention, the transition metal is Mn;

R_1 , R_2 and R_3 are each pentafluorophenyl; E_2 and E_{17} are SO_3H ; X_1 , X_2 , X_3 and X_4 are each H; and E_3 and E_{18} are H.

[00027] In an embodiment of the invention, the transition metal is Mn;

R_1 , R_2 and R_3 are each 4-nitrophenyl; E_2 and E_{17} are SO_3H ; X_1 , X_2 , X_3 and X_4 are each H; and E_3 and E_{18} are H.

[00028] In an embodiment of the invention a transition metal complex of a corrole, an optically active isomer thereof or a pharmaceutically acceptable salt thereof is administered in the same dosage form as a statin or a pharmaceutically acceptable salt thereof.

[00029] In an embodiment of the invention a transition metal complex of a corrole, an optically active isomer thereof or a pharmaceutically acceptable salt thereof is administered in a different dosage form than a statin or a pharmaceutically acceptable salt thereof. In an embodiment of the invention, the statin or pharmaceutically acceptable salt thereof is administered at the same time as the transition metal complex of a corrole, an optically active isomer thereof or a pharmaceutically acceptable salt thereof. In an embodiment of the invention, the statin or pharmaceutically acceptable salt thereof is administered before the transition metal complex of a corrole, an optically active isomer thereof or a pharmaceutically acceptable salt thereof. In an embodiment of the invention, the statin or pharmaceutically acceptable salt thereof is administered after the transition metal complex of a corrole, an optically active isomer thereof or a pharmaceutically acceptable salt thereof.

[00030] In an embodiment of the invention, the transition metal complex of a corrole, an optically active isomer thereof or a pharmaceutically acceptable salt thereof and a statin or a pharmaceutically acceptable salt thereof are each administered via oral, rectal, vaginal, topical, nasal, ophthalmic, transdermal, subcutaneous, intramuscular, intraperitoneal or intravenous routes of administration.

[00031] The pharmaceutical compositions according to an embodiment of the invention are conveniently presented in unit dosage form and are prepared by any of the methods well known in the art of pharmacy. In an embodiment of the invention, the unit dosage form is in the form of a tablet, capsule, lozenge, wafer, patch, ampoule, vial or pre-filled syringe.

[00032] The compositions of the present invention are generally administered in the form of a pharmaceutical composition comprising at least one of the active components (corrole or statin) of this invention together with a pharmaceutically acceptable carrier or diluent. Thus, the compositions of this invention can be administered either individually or together in any conventional oral, parenteral or transdermal dosage form.

[00033] For oral administration a pharmaceutical composition can take the form of solutions, suspensions, tablets, pills, capsules, powders, and the like. Tablets containing various excipients such as sodium citrate, calcium carbonate and calcium phosphate are employed along with various disintegrants such as starch and preferably potato or tapioca starch and certain complex

silicates, together with binding agents such as polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tableting purposes. Solid compositions of a similar type are also employed as fillers in soft and hard-filled gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the components of this invention can be combined with various sweetening agents, flavoring agents, coloring agents, emulsifying agents and/or suspending agents, as well as such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

[00034] The combinations according to embodiments of this invention may also be administered in a controlled release formulation such as a slow release or a fast release formulation. Such controlled release dosage formulations of the combinations of this invention may be prepared using methods well known to those skilled in the art.

[00035] For purposes of parenteral administration, solutions in sesame or peanut oil or in aqueous propylene glycol can be employed, as well as sterile aqueous solutions of the corresponding water-soluble salts. Such aqueous solutions may be suitably buffered, if necessary, and the liquid diluent first rendered isotonic with sufficient saline or glucose. These aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal injection purposes.

[00036] Pharmaceutical compositions according to embodiments of the invention may contain 0.1%-95% of the active component(s) of this invention, preferably 1%-70%. In any event, the composition or formulation to be administered may contain a quantity of active components according to embodiments of the invention in an amount effective to treat the condition or disease of the subject being treated.

[00037] Since embodiments of the present invention relate to the treatment of diseases and conditions with a combination of active ingredients which may be administered separately, separate pharmaceutical compositions may be packaged in kit form. The kit may comprise two separate pharmaceutical compositions, a corrole and a statin. The kit form is particularly advantageous when the separate components are preferably administered in different dosage forms (e.g., oral and parenteral), are administered at different dosage intervals, or when titration of the individual components of the combination is desired by the prescribing physician.

[00038] In an embodiment of the invention, the daily dosage of the transition metal complex of a corrole, an optically active isomer thereof or a pharmaceutically acceptable salt thereof is between 0.1 mg and 1500 mg (expressed in terms of active corrole equivalent in the case of a salt). In embodiments of the invention, the daily dosage of the statin is administered in accordance with table 1 below:

[00039] Table 1:

Statin	Salt	Daily dosage (in mg statin or statin equivalent in the case of a salt)
Atorvastatin	Calcium	10, 20, 40 or 80
Cerivastatin	Sodium	0.05, 0.1, 0.2, 0.3, 0.4 or 0.8
Fluvastatin	Sodium	20, 40 or 80
Lovastatin	(none)	10, 20, 40, 60
Mevastatin	(none)	10-50
Pitavastatin	Calcium	1, 2 or 4
Pravastatin	Sodium	10, 20, 30, 40 or 80
Rosuvastatin	Calcium	5, 10, 20 or 40
Simvastatin	(none)	10, 20, 40 or 80

[00040] In embodiments of the invention, the daily dosage of the statin is administered in dosages lower than the dosages listed in Table 1.

[00041] In an embodiment of the invention, the statin is administered before bedtime.

[00042] An embodiment of the invention provides a method for treating a CVD in a patient comprising administering an effective amount of a statin or a pharmaceutically acceptable salt thereof in combination with an effective amount of an anti-oxidant that is a transition metal complex of a corrole, an optically active isomer thereof or a pharmaceutically acceptable salt thereof, in combination with niacin.

[00043] An embodiment of the invention provides a method for treatment of a CVD in a subject comprising administering an effective amount of a transition metal complex of a corrole, an optically active isomer thereof or a pharmaceutically acceptable salt thereof in combination with

a statin or a pharmaceutically acceptable salt thereof, wherein the CVD is selected from the group consisting of: coronary heart disease, primary hyperlipidemia, mixed dyslipidemia, hypertriglyceridemia, dysbetalipoproteinemia, homozygous familial hypercholesterolemia, heterozygous familial hypercholesterolemia, atherosclerosis, congestive heart failure, myocardial infarction, myocardial ischemia and reperfusion.

[00044] An embodiment of the invention provides a method for treatment of a CVD in a subject having a risk factor associated with CVD comprising administering an effective amount of a transition metal complex of a corrole, an optically active isomer thereof or a pharmaceutically acceptable salt thereof in combination with a statin or a pharmaceutically acceptable salt thereof, wherein the risk factor associated with CVD is selected from the group consisting of: elevated total cholesterol, elevated LDL cholesterol, elevated VLDL cholesterol, elevated apolipoprotein B, elevated triglycerides, decreased HDL cholesterol, elevated oxidized HDL, elevated oxidized LDL, obesity, smoking, type 2 diabetes, type 1 diabetes, history of myocardial infarction, history of revascularization procedures, history of stroke and history of angina.

[00045] Example 1: Cholesterol Biosynthesis Model

[00046] Accumulation of cholesterol within arterial macrophages is a step in the development of atherosclerosis (M. Aviram 2004). Statins can lower the levels of cholesterol biosynthesis in arterial macrophages. The cholesterol biosynthesis model which was employed determined the effect of various agents (pravastatin alone, fluvastatin alone, 1-Fe alone in various concentrations, 1-Fe in combination with pravastatin and 1-Fe in combination with fluvastatin) on reduction of cholesterol biosynthesis in macrophages.

[00047] Murine J774.A1 macrophages were cultured in DMEM (Dulbecco's Modified Eagle Medium) containing 5% FCS (fetal calf serum) in a humidified incubator. 1-Fe was prepared in accordance with known procedures (A. Mahammed 2005) (I. Saltsman 2002). The effect of different concentrations of 1-Fe on cholesterol biosynthesis from acetate and on 1-Fe cellular uptake were determined by incubating J774.A1 macrophages for 24 h (hours) with 0, 5, 20 or 50 μ M (micromolar) of 1-Fe. Intracellular corrole concentrations were then determined by a chemiluminescent method, and cholesterol biosynthesis was assayed by measuring acetate incorporation into cholesterol. The chemiluminescent method involved rupturing cells and checking emission at 430 nm (nanometers) after the addition of 1 mM (millimolar) luminol and 10 mM H_2O_2 (pH = 13) to the ruptured cells. Acetate incorporation into cholesterol was performed by incubating cells overnight with DMEM containing 2% BSA (bovine serum

albumin), followed by incubation with isotopically labeled [^3H]acetate (1 millicurie/milliliter) (Amersham International, Bucks, UK) in DMEM containing 2% BSA for 3 h at 37°C (degrees Celsius). Cellular lipids were then extracted in hexane:isopropanol (3:2, volume ratio), and the upper phase separated by thin layer chromatography (TLC) on silica gel plates with hexane:ether:acetic acid (80:20:1.5, volume ratio). Unesterified cholesterol spots were visualized by iodine vapor (using appropriate standard), scraped into scintillation vials and counted in a β -counter. 0.1 M (molar) NaOH (sodium hydroxide) was added to the remains of the cells, and cellular proteins were measured the following day by the Lowry method.

[00048] As seen in the solid line in Figure 1A, the amounts of cholesterol synthesized from acetate by the macrophages (expressed in counts per minute/mg of cell protein) decreased as the dosage of 1-Fe increased, in parallel with the increase in 1-Fe cellular uptake (indicated by broken line, measured in terms of picomoles of 1-Fe per 10^5 cells,) indicating a dose dependent effect of 1-Fe on inhibition of cholesterol biosynthesis. This is in sharp contrast with studies of metalloporphyrins, the most closely related class of compounds (in terms of structure and activity), which actually increase hepatic cholesterol levels in treated rats (Chandra 2000).

[00049] In order to determine the combined effects of statins and 1-Fe on cholesterol biosynthesis, J774.A1 macrophages (2×10^6 cells/well) were incubated for 24 h in the absence of a corrole and a statin (control) or with the following agents: 20 μM 1-Fe alone, 200 μM pravastatin (PS), 20 μM 1-Fe with 200 μM PS, 20 μM fluvastatin (FS), or 20 μM 1-Fe with 20 μM FS. After removal of the non-internalized fraction of the test compounds, cholesterol biosynthesis from acetate was determined as described above.

[00050] The reduction of macrophage biosynthesis of cholesterol was determined to be 35% for 1-Fe alone, 10% for PS alone, 45% for 1-Fe and PS, 25% for FS alone and 70% for 1-Fe and FS. The results are depicted in Figure 1B. The results show the combined positive effect of 1-Fe with either one of the statins, and suggest that as opposed to other antioxidants that hinder the activity of statins, the combination of corroles and statins may reduce cholesterol biosynthesis much beyond the level feasible by statins alone.

[00051] As corrole treatment addresses the problem of oxidation of cholesterol, its administration may improve not only cholesterol quantities, but also may improve the quality of lipoproteins by reducing the amount of oxLDL and oxHDL due to the pronounced catalytic antioxidant activity of the corrole.

[00052] Example 2: Corrole-statin synergism

[00053] Mevalonic acid serves as one of the precursors to cholesterol biosynthesis in humans. Mevalonic acid is synthesized from 3-hydroxy-3methylglutaryl-CoA (HMG-CoA) and nicotineamide adenine dinucleotide phosphate (NADPH) in a reaction catalyzed by the enzyme HMG-CoA reductase (HMGCR). It is suggested by the inventors that both statins and corroles have an inhibitory effect on the reaction catalyzed by the enzyme HMGCR, thereby reducing mevalonic acid synthesis which in turn reduces cholesterol biosynthesis.

[00054] The effects of 1-Fe and statins fluvastatin and pravastatin alone and in combination on mevalonic acid production were tested using the following in vitro method.

[00055] Substrates of the HMGCR catalyzed reaction, NADPH (400 μ M] and HMGCR (200 μ M) were mixed in activity buffer comprising 100 mM sodium phosphate buffer, 1 mM ethylenediaminetetraacetic acid (EDTA), 10 mM dithiothreitol , 2% dimethyl sulfoxide, and 1 mM magnesium sulphate, the mixture having a pH of 6.8. 1-Fe, PS, or FS (alone or as a corrole statin combination) were added to the substrate mixture at various concentrations, followed by addition of HMGCR (0.48 μ M). Reactions were then incubated at 37 °C for 15 minutes, followed by injection of 80 μ l (microliter) to a reverse phase GraceSmart RP18 high performance liquid chromatography column (HPLC). The column was eluted with 10 mM ammonium acetate buffer with a pH of 5.8-6 containing 10 mM tetrabutyl ammonium acetate and acetonitrile in varying concentrations. As mevalonate concentration is difficult to identify in reaction mixture because it has no absorbance in the UV range, the yield of each reaction was calculated from the amount of CoA byproduct formed in the reaction after subtracting the baseline amount of CoA present as an impurity in the commercial HMG-CoA determined by injecting the substrate mixture alone. The inhibition percentage was calculated from the yield of each reaction relative to the yield of the enzymatic reaction without the addition of inhibitor. Table 2 lists average inhibition percentages for each inhibitor in two separate tests that were each performed in triplicate. The results are also shown in Figures 2A and 2B.

[00056] Table 2

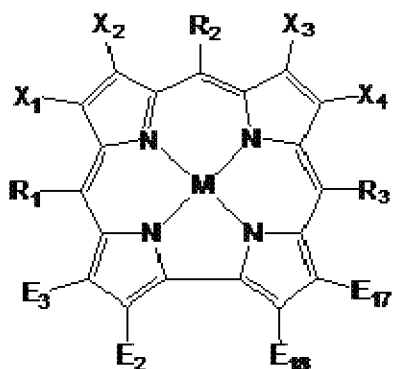
Inhibitor concentrations in micromolar			Inhibition Percent
1-Fe	PS	FS	
20	0	0	32
0	5	0	17
0	0	1	9
20	5	0	>98
20	0	1	>98
15	0	0	8
0	5	0	17
0	0	1	9
15	5	0	96
15	0	1	91

[00057] 1-Fe, PS and FS inhibited the formation of CoA in the HMGCR catalyzed reaction. For analysis of the combined effect of 1-Fe and statins, the statins were used at low concentrations that provide low reaction inhibition, 5 μ M of PS and 1 μ M of FS that provided 17% and 9% inhibition, respectively. The combinations of 1-Fe with a statin were highly synergistic. For example, 20 μ M 1-Fe produced 32% reaction inhibition alone, but in combination with either statin provided more than 98% inhibition. Even when using 1-Fe at a low concentration of 15 μ M, that alone provided only 8% reaction inhibition, the combined effect with either statin was still higher than 90%.

[00058] This example indicates that statins can be used in combination with corroles such as 1-Fe to provide high levels of HMGCR inhibition, thereby treating CVD and lowering risks of CVD through controlling cholesterol levels. The example further indicates that lower dosages of statins and of 1-Fe may be used in combination to achieve high HMGCR inhibitory effects while limiting risks associated with high concentrations of statin administration.

[00059] There is further provided, in accordance with an embodiment of the invention, a method for treatment of a CVD in a subject comprising administering an effective amount of a transition metal complex of a corrole, an optically active isomer thereof or a pharmaceutically acceptable

salt thereof in combination with a statin or a pharmaceutically acceptable salt thereof. Optionally, the CVD is selected from the group consisting of: coronary heart disease, primary hyperlipidemia, mixed dyslipidemia, hypertriglyceridemia, dysbetalipoproteinemia, homozygous familial hypercholesterolemia, heterozygous familial hypercholesterolemia, atherosclerosis, congestive heart failure, myocardial infarction, myocardial ischemia and reperfusion. Optionally, the subject suffers from a risk factor associated with CVD selected from the group consisting of: elevated total cholesterol, elevated LDL cholesterol, elevated VLDL cholesterol, elevated apolipoprotein B, elevated triglycerides, decreased HDL cholesterol, elevated oxidized HDL, elevated oxidized LDL, obesity, smoking, type 2 diabetes, type 1 diabetes, history of myocardial infarction, history of revascularization procedures, history of stroke and history of angina. Optionally, the transition metal complex of a corrole has a structure:



wherein R_1 , R_2 and R_3 are each independently a carbocyclic aryl ring or a heterocyclic aryl ring, each ring comprising 5 or 6 atoms; M is a transition metal selected from the group consisting of Mn, Fe, Ru, Co, V, Cr, and Cu; X_1 , X_2 , X_3 and X_4 are each independently H or a halogen; E_2 , E_3 , E_{17} and E_{18} are each independently H, halogen, SO_2Cl , SO_3H , $SO_2NR_4R_5$, CO_2H , CO_2R , $COCl$, $CONR_4R_5$, CHO , $CH=C(CO_2H)_2$, $CH=C(CN)CO_2H$, or NO_2 , R is alkyl or aryl and R_4 and R_5 are each independently H, alkyl, aryl or together with the N atom to which they are attached form a saturated 5-6 membered ring optionally containing an additional heteroatom selected from the group consisting of O, S and N. Optionally, M is Fe or Mn.

[00060] Optionally, R_1 , R_2 and R_3 are each pentafluorophenyl; E_2 and E_{17} are SO_3H ; X_1 , X_2 , X_3 and X_4 are each H; and E_3 and E_{18} are H. Optionally, R_1 , R_2 and R_3 are each 4-nitrophenyl; E_2 and E_{17} are SO_3H ; X_1 , X_2 , X_3 and X_4 are each H; and E_3 and E_{18} are H.

[00061] Optionally, the statin is selected from the group consisting of: atorvastatin, cerivastatin, fluvastatin, lovastatin, mevastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin.

Optionally the daily corrole dosage is between 0.1 mg and 1500 mg, optionally between 1 mg and 100 mg. Optionally, the transition metal complex of a corrole, an optically active isomer thereof or a pharmaceutically acceptable salt thereof and the statin or a pharmaceutically acceptable salt thereof are administered at the same time. Optionally, the transition metal complex of a corrole, an optically active isomer thereof or a pharmaceutically acceptable salt thereof and the statin or a pharmaceutically acceptable salt thereof are administered in the same dosage form. Optionally, the daily dosage of the statin is a low dose. Optionally, the transition metal complex of a corrole, an optically active isomer thereof or a pharmaceutically acceptable salt thereof the statin or a pharmaceutically acceptable salt thereof are administered through the oral route.

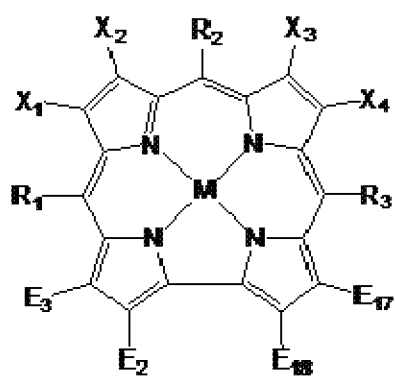
[00062] Optionally, the subject suffers from a risk factor after a prolonged treatment regimen of a statin. Optionally, the prolonged treatment is longer than three months, optionally longer than one year. Optionally, the subject was treated with a high dose statin. Optionally, the risk factor is selected from the group consisting of: elevated total cholesterol, elevated LDL cholesterol, elevated VLDL cholesterol, elevated apolipoprotein B, elevated triglycerides, decreased HDL cholesterol, elevated oxidized HDL and elevated oxidized LDL. Optionally, the administration of an effective amount of a transition metal complex of a corrole, an optically active isomer thereof or a pharmaceutically acceptable salt thereof in combination with a statin or a pharmaceutically acceptable salt thereof is effective in lowering at least one risk factor in the subject.

[00063] There is further provided in accordance with an embodiment of the invention a method for treatment of a CVD in a subject undergoing treatment using a statin comprising: administering an effective amount of a transition metal complex of a corrole, an optically active isomer thereof or a pharmaceutically acceptable salt thereof; and continuing his statin treatment at a lower dose than the dose administered before corrole administration. Optionally, the statin dose administered after the corrole treatment was initiated is a low dose. Optionally, the subject suffered from an undesirable side effect of statin treatment before initiation of corrole administration. Optionally, the undesirable side effect is selected from the group consisting of: raised liver enzymes, muscle pain, muscle cramps, myalgia, myositis, myopathy, rhabdomyolysis and renal failure.

[00064] There is further provided in accordance with an embodiment of the invention a method for lowering cholesterol levels in a subject comprising administering to the subject: an effective

amount of a transition metal complex of a corrole, an optically active isomer thereof or a pharmaceutically acceptable salt thereof in combination with a statin or a pharmaceutically acceptable salt thereof. Optionally, the cholesterol level is the total cholesterol level, the LDL level, the oxidized LDL level, the oxidized HDL level, or high triglycerides.

[00065] There is further provided in accordance with an embodiment of the invention a pharmaceutical composition comprising: a transition metal complex of a corrole, an optically active isomer thereof or a pharmaceutically acceptable salt thereof; a statin or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier. Optionally, the pharmaceutical composition is in the form of a tablet or a capsule. Optionally, transition metal complex of a corrole has a structure:



wherein R₁, R₂ and R₃ are each independently a carbocyclic aryl

ring or a heterocyclic aryl ring, each ring comprising 5 or 6 atoms; M is a transition metal selected from the group consisting of Mn, Fe, Ru, Co, V, Cr, and Cu; X₁, X₂, X₃ and X₄ are each independently H or a halogen; E₂, E₃, E₁₇ and E₁₈ are each independently H, halogen, SO₂Cl, SO₃H, SO₂NR₄R₅, CO₂H, CO₂R, COCl, CONR₄R₅, CHO, CH=C(CO₂H)₂, CH=C(CN)CO₂H, or NO₂, R is alkyl or aryl and R₄ and R₅ are each independently H, alkyl, aryl or together with the N atom to which they are attached form a saturated 5-6 membered ring optionally containing an additional heteroatom selected from the group consisting of O, S and N. Optionally, M is Fe or Mn. Optionally, R₁, R₂ and R₃ are each pentafluorophenyl; E₂ and E₁₇ are SO₃H; X₁, X₂, X₃ and X₄ are each H; and E₃ and E₁₈ are H. Optionally, R₁, R₂ and R₃ are each 4-nitrophenyl; E₂ and E₁₇ are SO₃H; X₁, X₂, X₃ and X₄ are each H; and E₃ and E₁₈ are H. Optionally, the statin is selected from the group consisting of: atorvastatin, cerivastatin, fluvastatin, lovastatin, mevastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin. Optionally, the percentage by weight of active ingredients relative to total weight of pharmaceutical composition is between 1% and 70%.

[00066] In the description and claims of the present application, each of the verbs, “comprise,” “include” and “have,” and conjugates thereof, are used to indicate that the object or objects of the verb are not necessarily a complete listing of components, elements or parts of the subject or subjects of the verb.

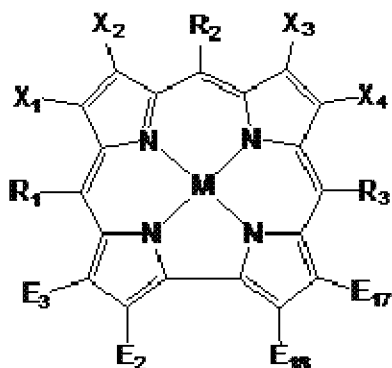
[00067] Descriptions of embodiments of the invention in the present application are provided by way of example and are not intended to limit the scope of the invention. The described embodiments comprise different features, not all of which are required in all embodiments of the invention. Some embodiments utilize only some of the features or possible combinations of the features. Variations of embodiments of the invention that are described, and embodiments of the invention comprising different combinations of features noted in the described embodiments, will occur to persons of the art. The scope of the invention is limited only by the claims.

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CLAIMS

1. A method for treatment of a cardiovascular disease in a subject comprising administering an effective amount of a transition metal complex of a corrole, an optically active isomer thereof or a pharmaceutically acceptable salt thereof in combination with a statin or a pharmaceutically acceptable salt thereof.
2. The method according to claim 1 wherein the cardiovascular disease is selected from the group consisting of: coronary heart disease, primary hyperlipidemia, mixed dyslipidemia, hypertriglyceridemia, dysbetalipoproteinemia, homozygous familial hypercholesterolemia, heterozygous familial hypercholesterolemia, atherosclerosis, congestive heart failure, myocardial infarction, myocardial ischemia and reperfusion.
3. The method according to claim 1 wherein the subject suffers from a risk factor associated with cardiovascular disease selected from the group consisting of: elevated total cholesterol, elevated LDL cholesterol, elevated VLDL cholesterol, elevated apolipoprotein B, elevated triglycerides, decreased HDL cholesterol, elevated oxidized HDL, elevated oxidized LDL, obesity, smoking, type 2 diabetes, type 1 diabetes, history of myocardial infarction, history of revascularization procedures, history of stroke and history of angina.
4. The method according to any one of the previous claims wherein the transition metal complex of a corrole has a structure:



wherein R_1 , R_2 and R_3 are each independently a carbocyclic aryl ring or a heterocyclic aryl ring, each ring comprising 5 or 6 atoms;

M is a transition metal selected from the group consisting of Mn, Fe, Ru, Co, V, Cr, and Cu;

X_1 , X_2 , X_3 and X_4 are each independently H or a halogen;

E_2 , E_3 , E_{17} and E_{18} are each independently H, halogen, SO_2Cl , SO_3H , $SO_2NR_4R_5$, CO_2H , CO_2R , $COCl$, $CONR_4R_5$, CHO , $CH=C(CO_2H)_2$, $CH=C(CN)CO_2H$, or NO_2 ,

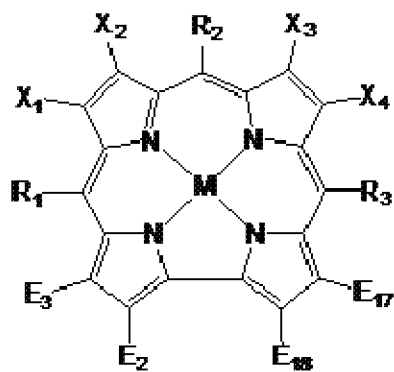
R is alkyl or aryl and R₄ and R₅ are each independently H, alkyl, aryl or together with the N atom to which they are attached form a saturated 5-6 membered ring optionally containing an additional heteroatom selected from the group consisting of O, S and N.

5. The method according to claim 4 wherein M is Fe or Mn.
6. The method according to claim 4 or 5 wherein R₁, R₂ and R₃ are each pentafluorophenyl; E₂ and E₁₇ are SO₃H; X₁, X₂, X₃ and X₄ are each H; and E₃ and E₁₈ are H.
7. The method according to claim 4 or 5 wherein R₁, R₂ and R₃ are each 4-nitrophenyl; E₂ and E₁₇ are SO₃H; X₁, X₂, X₃ and X₄ are each H; and E₃ and E₁₈ are H.
8. The method according to any one of the previous claims wherein the statin is selected from the group consisting of: atorvastatin, cerivastatin, fluvastatin, lovastatin, mevastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin.
9. The method according to any one of the previous claims wherein the daily corrole dosage is between 0.1 mg and 1500 mg.
10. The method according any one of the previous claims wherein the daily corrole dosage is between 1 mg and 100 mg.
11. The method according any one of the previous claims wherein the transition metal complex of a corrole, an optically active isomer thereof or a pharmaceutically acceptable salt thereof and the statin or a pharmaceutically acceptable salt thereof are administered at the same time.
12. The method according to claim 11 wherein the transition metal complex of a corrole, an optically active isomer thereof or a pharmaceutically acceptable salt thereof and the statin or a pharmaceutically acceptable salt thereof are administered in the same dosage form.
13. The method according to any one of the previous claims wherein the daily dosage of the statin is a low dose.
14. The method according to any one of the previous claims wherein the transition metal complex of a corrole, an optically active isomer thereof or a pharmaceutically

acceptable salt thereof, the statin or a pharmaceutically acceptable salt thereof, are administered through the oral route.

15. The method according to claim 1 wherein the subject suffers from a risk factor after a prolonged treatment regimen of a statin.
16. The method according to claim 15 wherein the prolonged treatment is longer than three months.
17. The method according to claim 15 wherein the prolonged treatment is longer than one year.
18. The method according to any one of claims 15 to 17 wherein the subject was treated with a high dose statin.
19. The method according to any one of claims 15 to 18 wherein the risk factor is selected from the group consisting of: elevated total cholesterol, elevated LDL cholesterol, elevated VLDL cholesterol, elevated apolipoprotein B, elevated triglycerides, decreased HDL cholesterol, elevated oxidized HDL, elevated oxidized LDL.
20. The method according to claim 19 wherein the administration of an effective amount of a transition metal complex of a corrole, an optically active isomer thereof or a pharmaceutically acceptable salt thereof in combination with a statin or a pharmaceutically acceptable salt thereof is effective in lowering at least one risk factor in the subject.
21. A method for treatment or of a cardiovascular disease in a subject undergoing treatment using a statin comprising:
administering an effective amount of a transition metal complex of a corrole, an optically active isomer thereof or a pharmaceutically acceptable salt thereof; and
continuing his or her statin treatment at a lower dose than the dose administered before corrole administration.
22. The method according to claim 21 wherein the statin dose administered after the corrole treatment was initiated is a low dose.
23. The method according to claim 21 or 22 wherein the subject suffered from an undesirable side effect of statin treatment before initiation of corrole administration.

24. The method according to claim 23 wherein the undesirable side effect is selected from the group consisting of: raised liver enzymes, muscle pain, muscle cramps, myalgia, myositis, myopathy, rhabdomyolysis and renal failure.
25. A method for lowering cholesterol levels in a subject comprising administering to the subject:
an effective amount of a transition metal complex of a corrole, an optically active isomer thereof or a pharmaceutically acceptable salt thereof in combination with a statin or a pharmaceutically acceptable salt thereof.
26. The method according to claim 25 wherein the cholesterol level is the total cholesterol level, the LDL level, the oxidized LDL level, the oxidized HDL level, or high triglycerides.
27. A pharmaceutical composition comprising:
a transition metal complex of a corrole, an optically active isomer thereof or a pharmaceutically acceptable salt thereof;
a statin or a pharmaceutically acceptable salt thereof; and
a pharmaceutically acceptable carrier.
28. The pharmaceutical composition according to claim 27 in the form of a tablet or a capsule.
29. The pharmaceutical composition according to claim 27 or 28 wherein the transition metal complex of a corrole has a structure:



wherein R_1 , R_2 and R_3 are each independently a carbocyclic aryl ring or a heterocyclic aryl ring, each ring comprising 5 or 6 atoms;

M is a transition metal selected from the group consisting of Mn, Fe, Ru, Co, V, Cr, and Cu;

X_1 , X_2 , X_3 and X_4 are each independently H or a halogen;

E₂, E₃, E₁₇ and E₁₈ are each independently H, halogen, SO₂Cl, SO₃H, SO₂NR₄R₅, CO₂H, CO₂R, COCl, CONR₄R₅, CHO, CH=C(CO₂H)₂, CH=C(CN)CO₂H), or NO₂, R is alkyl or aryl and R₄ and R₅ are each independently H, alkyl, aryl or together with the N atom to which they are attached form a saturated 5-6 membered ring optionally containing an additional heteroatom selected from the group consisting of O, S and N.

30. The pharmaceutical composition according to claim 29 wherein M is Fe or Mn.
31. The pharmaceutical composition according to claim 29 or 30 wherein R₁, R₂ and R₃ are each pentafluorophenyl; E₂ and E₁₇ are SO₃H; X₁, X₂, X₃ and X₄ are each H; and E₃ and E₁₈ are H.
32. The pharmaceutical composition according to claim 29 or 30 wherein R₁, R₂ and R₃ are each 4-nitrophenyl; E₂ and E₁₇ are SO₃H; X₁, X₂, X₃ and X₄ are each H; and E₃ and E₁₈ are H.
33. The pharmaceutical composition according to any one of claims 27 to 32 wherein the statin is selected from the group consisting of: atorvastatin, cerivastatin, fluvastatin, lovastatin, mevastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin.
34. The pharmaceutical composition according to any one of claims 27 to 33 wherein the percentage by weight of active ingredients relative to total weight of pharmaceutical composition is between 1% and 70%.

CHOLESTEROL BIOSYNTHESIS IN MACROPHAGE MODEL IN
PRESENCE OF VARYING LEVELS OF CORROLE AS AN INHIBITOR

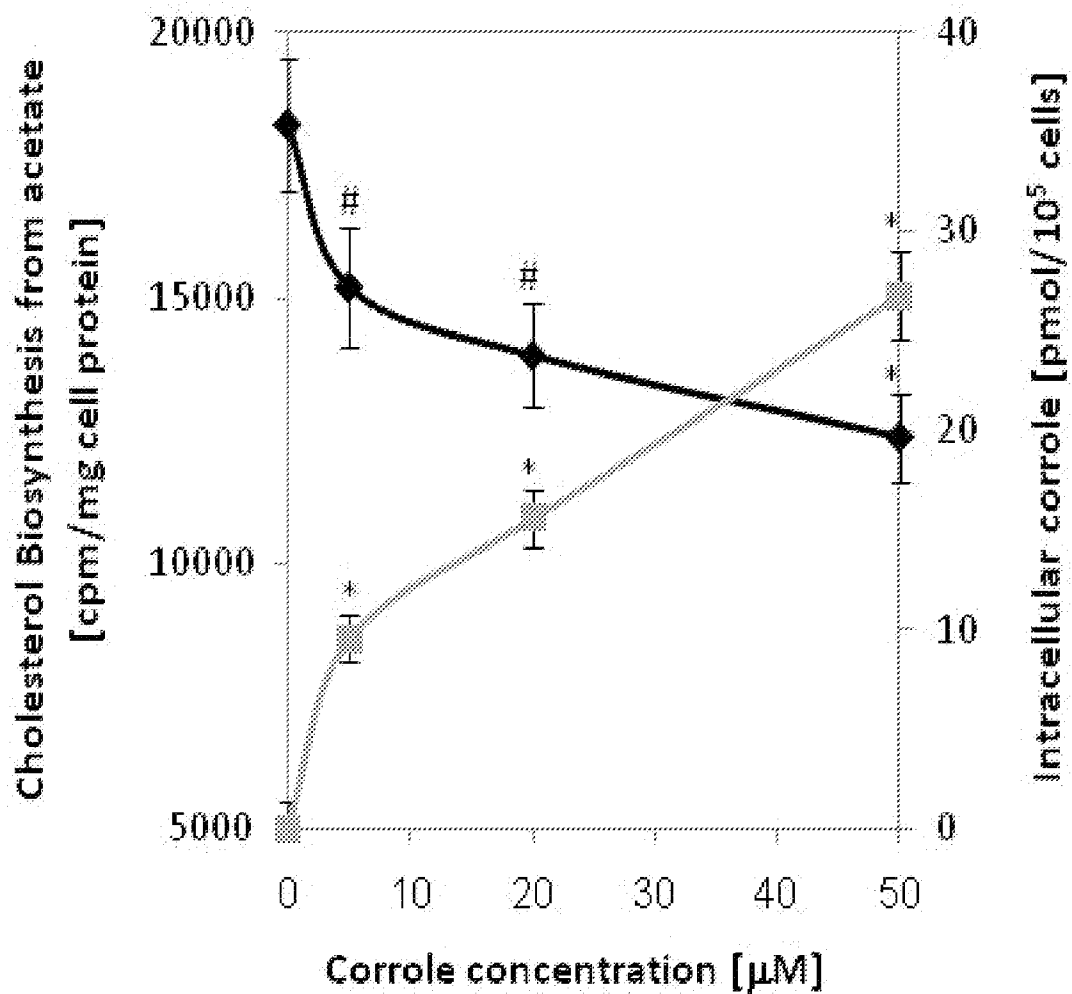


Fig. 1A

CHOLESTEROL BIOSYNTHESIS IN MACROPHAGE MODEL IN PRESENCE OF
STATINS, CORROLES AND COMBINATIONS THEREOF AS INHIBITORS

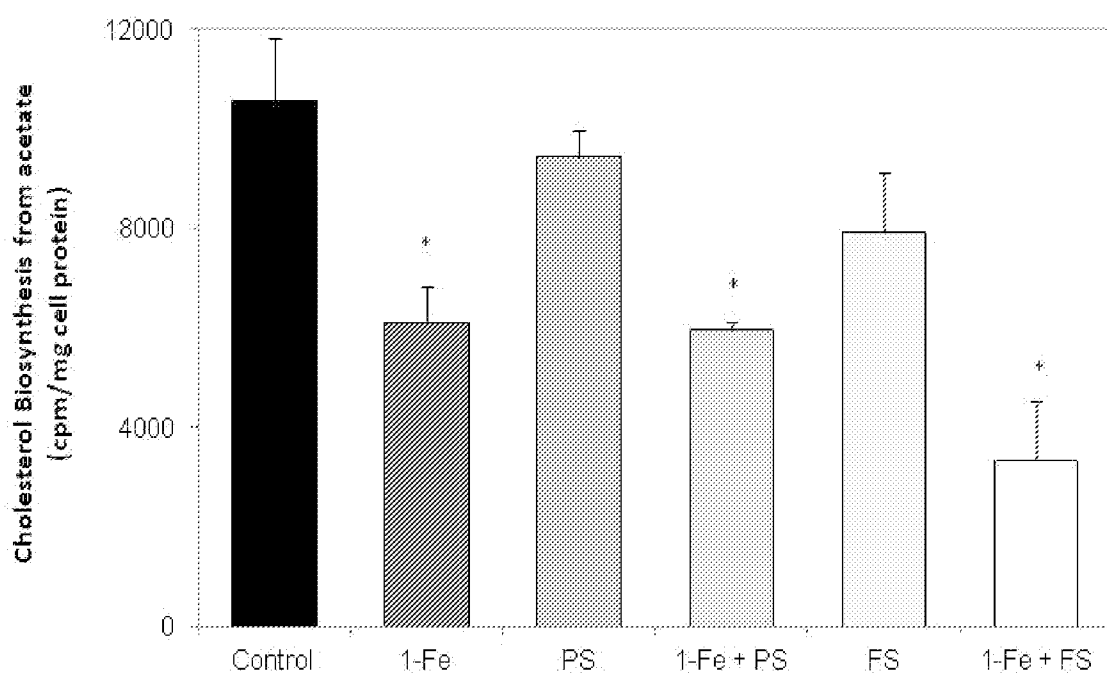


Fig. 1B

EFFECT OF STATINS, CORROLE (20
MICROMOLAR) AND
COMBINATIONS THEREOF ON
HMGCR CATALYZED REACTION

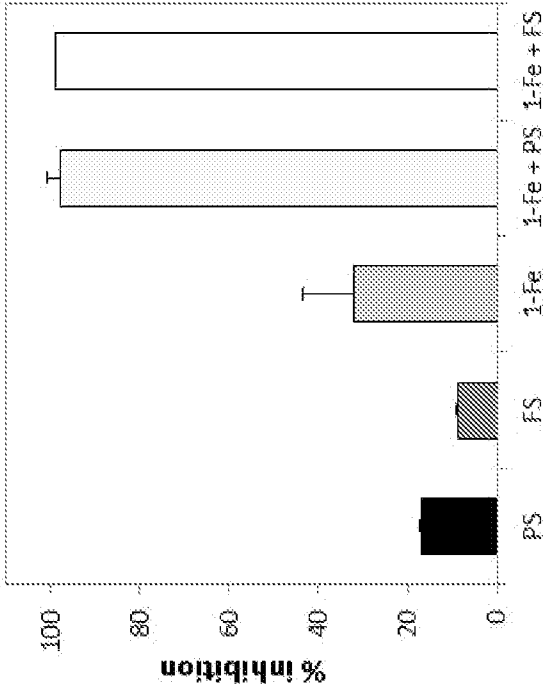


Fig. 2A

EFFECT OF STATINS, CORROLE (15
MICROMOLAR) AND
COMBINATIONS THEREOF ON
HMGCR CATALYZED REACTION

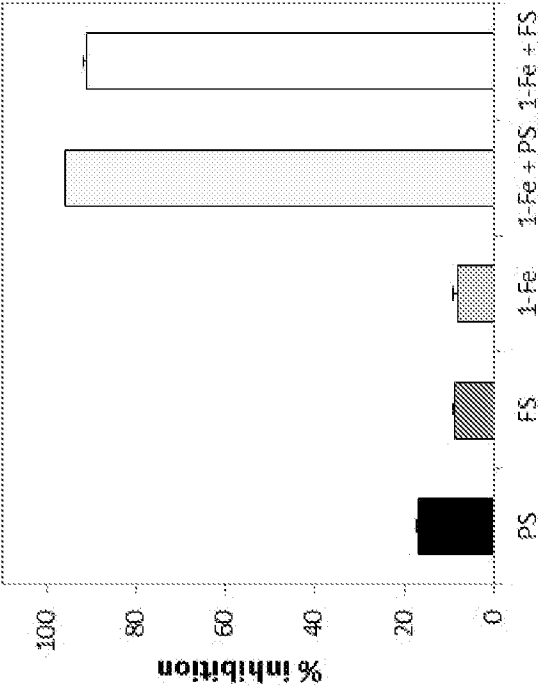


Fig. 2B

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2012/054124

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/22 A61K31/351 A61K31/40 A61K31/405 A61K31/409
A61K31/4418 A61K31/47 A61K31/505 A61K33/24 A61K33/26
A61K33/32 A61K33/34 A61K9/00 A61K9/20 A61K9/48

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, BIOSIS, WPI Data, EMBASE, FSTA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2009/027965 A1 (TECHNION RES & DEV FOUNDATION [IL]; GROSS ZEEV [IL]; AVIRAM MICHAEL [I] 5 March 2009 (2009-03-05) page 5, line 6 - page 7, line 26 page 12, line 11 - page 16, line 24 -----	1-34
Y	Jennifer Newton: "Iron complex could prevent cardiovascular disease", RSCPublishing 2 November 2010 (2010-11-02), XP002688244, Retrieved from the Internet: URL:http://www.rsc.org/Publishing/ChemScience/Volume/2010/12/iron_complex.asp [retrieved on 2012-11-23] the whole document ----- -/--	1-34



Further documents are listed in the continuation of Box C.



See patent family annex.

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"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

29 November 2012

Date of mailing of the international search report

12/12/2012

Name and mailing address of the ISA/

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Fax: (+31-70) 340-3016

Authorized officer

Houyvet-Landriscina

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2012/054124

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>Karin Kloosterman: "Israel-US Team Kills Breast Cancer in the Dark", Arutz Sheva News</p> <p>12 June 2009 (2009-06-12), XP002688245, Retrieved from the Internet: URL:http://www.israelnationalnews.com/Controls/SendFriend.ashx?print=1&type=0&item=131839 [retrieved on 2012-11-23] the whole document</p>	1-34
Y	<p>-----</p> <p>KR 2008 0107129 A (IAC IN NAT UNIV CHUNGNAM [KR]) 10 December 2008 (2008-12-10) abstract</p>	1-34
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A	<p>-----</p> <p>US 2010/305335 A1 (PALMER JOSHUA H [US] ET AL) 2 December 2010 (2010-12-02) paragraphs [0003], [0007], [0063] - [0065]</p> <p>-----</p>	1-34

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2012/054124

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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US 2010305335 A1	02-12-2010	NONE	
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