(57) Abstract: The present invention relates to certain novel compounds of the Formula (I) to processes for preparing such compounds, to their utility in modulation of nuclear hormone receptors Liver X Receptor (LXR) α (NR1H3) and/or β (NR1H2) and in treating clinical conditions including cardiovascular diseases such as atherosclerosis; inflammatory diseases, Alzheimer’s disease, lipid disorders (dyslipidemias) whether or not associated with insulin resistance, type 2 diabetes and other manifestations of the metabolic syndrome, to methods for their therapeutic use and to pharmaceutical compositions containing them.
5-THIOXO-1,5-DIHYDRO-2H-PYRROL-2-ONE DERIVATIVES AS LIVER X RECEPTOR MODULATORS

Field of the invention

The present invention relates to certain novel, substituted 5-thioxo-1,5-dihydro-2H-pyrrol-2-one, to processes for preparing such compounds, to their the utility in modulation of nuclear hormone receptors Liver X Receptor (LXR) α (NR1H3) and/or β (NR1H2) and in treating clinical conditions including cardiovascular diseases such as atherosclerosis; inflammatory diseases, Alzheimer’s disease, lipid disorders (dyslipidemias) whether or not associated with insulin resistance, type 2 diabetes and other manifestations of the metabolic syndrome, to methods for their therapeutic use and to pharmaceutical compositions containing them.

Background of the invention

Abnormalities of cholesterol and fatty acid homeostasis, that are reflected as diverse dyslipidemias, are causal of atherosclerosis and consequently cardiovascular disease (CVD). This disease is one of the major health problems in industrialized countries and is reaching the same prevalence in adults in developing nations. Most studies show that statins reduce low density lipoproteins (LDL) cholesterol by 25-30% and the relative risk of coronary events by approximately 30%. While this beneficial effect is significant, effectively 70% of the treated cohort remains with unchanged risk. This has prompted intense research in order to identify other common abnormalities of lipid metabolism that if efficiently treated could improve the results of current CVD therapy.

The nuclear hormone receptors LXR α and β use oxysterols as natural ligands. They appear to act as cholesterol sensors with target genes that are required for cholesterol efflux from macrophages, like ATP binding cassette transporter A1 (ABCA1) and apoE as well as gene products, like cholesterol ester transferase protein (CETP) and phospholipid transport protein (PLTP), that are required for the function of high density lipoprotein (HDL) in the reverse cholesterol transport. In addition, LXR upregulates lipoprotein lipase in liver and macrophages, a function that may stimulate fatty acid uptake and very low density
lipoprotein (VLDL) remodeling. In the liver, LXR ligands seem to stimulate the hepatobiliary secretion of cholesterol, a pathway controlled by the ABCG5 and ABCG8. The same cholesterol transporters appear to reduce cholesterol absorption in enterocytes, therefore influencing total body cholesterol balance. These effects of LXR stimulation could explain its remarkable anti-atherosclerotic properties observed in several animal models.

Recently the synthetic LXR ligands GW3965 (Glaxo) and T-0901317 (Tularik) were reported to increase glucose tolerance in fat fed obese mouse which was interpreted to result from reduced hepatic gluconeogenesis and increased glucose uptake in adipocytes (Lafitte BA et al. (Proc Natl Acad Sci U S A. 2003 Apr 29;100(9):5419-24). Activation of LXR's improves glucose tolerance through coordinated regulation of glucose metabolism in liver and adipose tissue.

WO00/21927 discloses pyrrole-2,5-diones which are GSK-3 inhibitors and claimed to be useful in the treatment of dementias such as Alzheimer's disease, manic depression and diabetes. There is no suggestion that these compounds have activity as LXR modulators.

The term "LXR modulator" as used herein, means a small molecule that modulates the biological activities of LXR α and/or LXR β. More specifically, such an LXR modulator either enhances or inhibits the biological activities of LXR. If such a modulator partially or completely enhances the biological activities of LXR, it is a partial or full LXR agonist, respectively. It is the object of the present invention to provide LXR modulators. Another object of this invention is to provide LXR modulator compounds being LXR agonists.

Description of the invention

According to a first aspect of the present invention there is provided a compound of Formula I

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R²NH
O
N
S
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R¹
R²
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Formula I

wherein:

R¹ is selected from phenyl(1-4C)alkyl wherein the phenyl is optionally substituted by (1-4C)alkoxy carbonyl or a group of formula NRᵃRᵇ in which Rᵃ and Rᵇ independently represent H or (1-4C)alkyl; heteroaryl(1-4C)alkyl wherein the heteroaryl is optionally substituted by (1-4C)alkyl or a group of formula NRᵃRᵇ in which Rᵃ and Rᵇ independently represent H or (1-4C)alkyl; or a (1-6C)alkyl group which is optionally substituted by one or more of the following: fluoro, (1-4C)alkoxy carbonyl, (1-3C)alkylthio or (1-3C)alkoxy optionally substituted by one or more fluoro;
R² is phenyl;
R³ is selected from phenyl, indolyl or benzofuranyl each optionally substituted by one or more of the following: (1-3C)alkanoyl, (1-4C)alkoxy optionally substituted by one or more fluoro; (1-3C)alkylthio; or a group of formula NRᵃRᵇ in which Rᵃ and Rᵇ independently represent H, (1-3C)alkyl or (1-3C)alkanoyl or Rᵃ and Rᵇ together with the nitrogen atom to which they are attached represent morpholino;
or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt.

The term heteroaryl means pyridyl, furyl or isoxazolyl each of which is optionally substituted by one or more of the following: (1-4C)alkyl or a group of formula NRᵃRᵇ in which Rᵃ and Rᵇ independently represent H or (1-4C)alkyl.

Further values of R¹, R², and R³ in compounds of formula I now follow. It will be understood that such values may be used where appropriate with any of the definitions, claims or embodiments defined hereinbefore or hereinafter.

In a first group of compounds of formula I
R1 is selected from methyl, ethyl, propyl, butyl, 2,2,2-trifluoroethyl, benzyl, 2-
methoxyethyl, 3-pyridylmethyl, 4-pyridylmethyl or 6-amino-3-pyridylmethyl;
R2 is phenyl;
R3 is selected from 4-methoxyphenyl, 4-difluoromethoxyphenyl or 4-morpholinophenyl;

In a second group of compounds of formula I
R1 is selected from methyl, ethyl, 2,2,2-trifluoroethyl, benzyl, 3-pyridylmethyl or 6-amino-
3-pyridylmethyl;
R2 is phenyl;
R3 is selected from 4-methoxyphenyl, 4-difluoromethoxyphenyl or 4-morpholinophenyl;

In a fourth group of compounds of formula I
R1 is selected from ethyl, 2,2,2-trifluoroethyl, benzyl, 3-pyridylmethyl, 6-amino-3-
pyridylmethyl;
R2 is phenyl;
R3 is selected from 4-methoxyphenyl, 4-difluoromethoxyphenyl or 4-morpholinophenyl;

In a fifth group of compounds of formula I
R1 is selected from methyl, ethyl, 2,2,2-trifluoroethyl, 2-pyridylmethyl, 3-pyridylmethyl,
4-pyridylmethyl;
R2 is phenyl;
R3 is selected from 4-methoxyphenyl;

In a sixth group of compounds of formula I
R1 is selected from 2-methoxyethyl or 6-amino-3-pyridylmethyl;
R2 is phenyl;
R3 is selected from 4-methoxyphenyl or 4-difluoromethoxyphenyl;

The compounds of formula I have activity as medicaments. In particular the compounds of
formula I are LXR agonists.
A specific compound of the invention is 1-[(6-aminopyridin-3-yl)methyl]-3-[(4-(difluoromethoxy)phenyl)amino]-4-phenyl-5-thioxo-1,5-dihydro-2H-pyrrol-2-one or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt.

Certain compounds of the present invention may exist as tautomers. It is to be understood that the present invention encompasses all such tautomers.

Methods of preparation

The compounds of the invention may be prepared as outlined below. However, the invention is not limited to these methods. The compounds may also be prepared as described for structurally related compounds in the prior art. The reactions can be carried out according to standard procedures or as described in the experimental section.

Compounds of formula I may be prepared by reacting a compound of formula II

![Chemical structure](image)

in which R¹, R² and R³ are as previously defined with a sulphurating agent, for example Lawesson’s reagent, optionally in the presence of an inert organic liquid for example an aromatic hydrocarbon, e.g. toluene, or an organic liquid for example an ether, e.g. dioxane at a temperature in the range of 0°C to 200°C. Compounds of formula I may be prepared using an approximately molar equivalent of the sulphurating agent.

Compounds of formula II may be prepared by reacting a compound of formula III
in which $R^2$ and $R^3$ are as previously defined with a compound of formula IV

$$R^1\text{OH}$$

IV

in which $R^1$ is as previously defined in the presence of a dialkyl azodicarboxylate, for example diethyl azodicarboxylate, and a phosphine, for example triphenylphosphine, optionally in the presence of an inert organic liquid for example an ether e.g. tetrahydrofuran at a temperature in the range of 0°C to 200°C.

Compounds of formula II may also be prepared by reacting a compound of formula V

$$Y - R^2$$

V

in which $R^1$ and $R^2$ are as previously defined and $Y$ is a leaving group for example halo e.g. Cl, Br or I with a compound of formula VI

$$R^3\text{NH}_2$$

VI

in which $R^3$ is as previously defined optionally in the presence of an inert organic liquid for example dimethylformamide and optionally in the presence of a base for example potassium carbonate at a temperature in the range of 0°C to 250°C.
Compounds of formula III may be prepared by reacting a compound of formula VII

\[
\begin{array}{c}
Y \\
\hline
\text{III} \\
\hline
\text{VII} \\
\hline
\text{VI} \\
\end{array}
\]

in which \( R^2 \) is as previously defined and \( Y \) is a leaving group for example halo eg Cl, Br or I with a compound of formula VI

\[
R^3\text{NH}_2
\]

in which \( R^3 \) is as previously defined optionally in the presence of an inert organic liquid for example dimethylformamide and optionally in the presence of a base for example triethylamine at a temperature in the range of 0°C to 250°C.

Compounds of formula IV and VI are commercially available or may be prepared by methods known to those skilled in the art.

Compounds of formula V may be prepared by reacting a compound of formula VIII

\[
\begin{array}{c}
Y \\
\hline
\text{VIII} \\
\end{array}
\]

in which \( R^2 \) is as previously defined and \( Y \) is a leaving group for example halo eg Cl, Br or I with a compound of formula IX.
in which R¹ is as previously defined optionally in the presence of an organic liquid, for example glacial acetic acid at a temperature in the range of 0°C to 200°C.

Compounds of formula V may also be prepared by reacting a compound of formula VII with a compound of formula XII

R¹L

XII

in which R¹ is as previously defined and L is a leaving group for example halo eg bromo in the presence of an inert organic liquid for example dimethylformamide and optionally in the presence of a base for example potassium carbonate at a temperature in the range of -78°C to 200°C.

Compounds of formula VII may be prepared by reacting a compound of formula X

in which R² is as previously defined with a halogenating agent for example oxalyl chloride optionally in the presence of an inert organic liquid for example dichloromethane and optionally in the presence of a catalytic amount of dimethylformamide at a temperature in the range of 0°C to 200°C.

Compounds of formula VIII may be prepared by reacting a compound of formula XI
in which R² is as previously defined with a halogenating agent for example thionyl chloride optionally in the presence of an inert organic liquid for example dichloromethane and optionally in the presence of a base for example pyridine at a temperature in the range of 0°C to 200°C.

Compounds of formula IX, X, XI, and XII are commercially available or may be prepared by methods known to those skilled in the art.

Certain compounds of formula III and V are useful intermediates in the preparation of compounds of formula I and are believed to be novel and are claimed herein as useful intermediates in the preparation of compounds of formula I.

The compounds of the invention may be isolated from their reaction mixtures using conventional techniques.

Persons skilled in the art will appreciate that, in order to obtain compounds of the invention in an alternative and in some occasions, more convenient manner, the individual process steps mentioned hereinbefore may be performed in different order, and/or the individual reactions may be performed at different stage in the overall route (i.e. chemical transformations may be performed upon different intermediates to those associated hereinbefore with a particular reaction).

The expression “inert organic liquid” refers to a liquid that does not react with the starting materials, reagents, intermediates or products in a manner that adversely affects the yield of the desired product.
Pharmaceutical preparations

The compounds of the invention will normally be administered via the oral, parenteral, intravenous, intramuscular, subcutaneous or in other injectable ways, buccal, rectal, vaginal, transdermal and/or nasal route and/or via inhalation, in the form of pharmaceutical preparations comprising the active ingredient or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, in a pharmaceutically acceptable dosage form. Depending upon the disorder and patient to be treated and the route of administration, the compositions may be administered at varying doses.

Suitable daily doses of the compounds of the invention in therapeutical treatment of humans are about 0.0001-100 mg/kg body weight, preferably 0.01-10 mg/kg body weight.

Oral formulations are preferred particularly tablets or capsules which may be formulated by methods known to those skilled in the art to provide doses of the active compound in the range of 0.007 mg to 700 mg for example 1 mg, 3 mg, 5 mg, 10 mg, 25 mg, 50 mg, 100 mg and 250 mg.

According to a further aspect of the invention there is thus provided a pharmaceutical formulation including any of the compounds of the invention, or pharmaceutically acceptable derivatives thereof, in admixture with pharmaceutically acceptable adjuvants, diluents and/or carriers.

Pharmacological properties

The compounds of formula I are useful for normalization of cholesterol homeostasis, decreasing intestinal cholesterol absorption, improving reverse cholesterol transport, improving HDL functionality, increasing HDL-cholesterol levels, decreasing LDL-cholesterol levels, decreasing cholesterol content of apoB-containing lipoproteins, stimulating cholesterol efflux from vascular cells and/or decreasing the inflammatory response of vascular cells. As a consequence of these properties the compounds of formula I are expected to have anti-atherosclerotic effects.
The compounds of formula I are useful in the prevention or treatment of cardiovascular disease in a mammal, particularly a human. The compounds of formula I are useful in the prevention or treatment of atherosclerosis in a mammal, particularly a human.

Cardiovascular disease includes but is not limited to conditions associated with atherosclerosis, arteriosclerosis, hypercholesterolemia, and other kinds of dyslipidemia that increase the risk for cardiovascular disease. In particular the compounds of formula I are useful in the treatment or prevention of cardiovascular disease, especially those involving atherosclerosis and hypercholesterolemia.

The compounds of formula I also serve to prevent lipid accumulation in, or remove lipids from, tissue deposits such as atherosclerotic plaques or xanthomas in a patient with atherosclerotic disease manifest by clinical signs such as angina, claudication, bruits, one that has suffered a myocardial infarction or transient ischemic attack, or one diagnosed by angiography, sonography or MRI.

The compounds of formula I also serve to prevent or reduce the risk of developing atherosclerosis, as well as for halting or slowing the progression of atherosclerotic disease once it has become clinically evident, comprising the administration of a prophylactically or therapeutically effective amount, as appropriate, of a compound of formula I to a mammal, including a human, who is at risk of developing atherosclerosis or who already has atherosclerotic disease.

Atherosclerosis encompasses vascular diseases and conditions that are recognized and understood by physicians practicing in the relevant fields of medicine. Atherosclerotic cardiovascular disease including restenosis following revascularization procedures, coronary heart disease (also known as coronary artery disease or ischemic heart disease), cerebrovascular disease including multi-infarct dementia, and peripheral vessel disease including erectile dysfunction are all clinical manifestations of atherosclerosis and are therefore encompassed by the terms “atherosclerosis” and “atherosclerotic disease”.

The present compounds of formula I are also useful for the prophylaxis and/or treatment of clinical conditions associated with atherosclerosis such as inherent or induced hypercholesterolemia as well as inherent or induced reduced sensitivity to insulin (insulin
resistance syndrome also known as metabolic syndrome) and associated metabolic
disorders. These clinical conditions will include, but will not be limited to, general obesity,
abdominal obesity, arterial hypertension, hyperinsulinaemia, hyperglycaemia, type 2
diabetes and the dyslipidaemia characteristically appearing with insulin resistance. This
dyslipidaemia, also known as the atherogenic lipoprotein profile, is characterised by
moderately elevated non-esterified fatty acids, elevated VLDL triglyceride rich particles,
high Apo B levels, low HDL levels associated with low apoAI levels in the presence of
small, dense, LDL particles, phenotype B.

The compounds of formula I are expected to be useful in treating patients with combined
or mixed hyperlipidemias and dyslipidemias, especially low HDL levels with or without
other manifestations of the metabolic syndrome.

Treatment with the compounds of formula I are expected to lower the cardiovascular
morbidity and mortality associated with atherosclerosis due to their antidyslipidaemic as
well as antiinflammatory properties. The cardiovascular disease conditions include macro-
angiopathies of various internal organs causing myocardial infarction, congestive heart
failure, cerebrovascular disease and peripheral arterial insufficiency of the lower
extremities. The insulin sensitizing effect of the compounds of formula I is also expected
to prevent or delay the development of type 2 diabetes from the metabolic syndrome and
diabetes of pregnancy. Therefore the development of long-term complications associated
with chronic hyperglycaemia in diabetes mellitus such as the micro-angiopathies causing
renal disease, retinal damage and peripheral vascular disease of the lower limbs are
expected to be delayed.

The compounds of formula I may also be useful for the prevention or treatment of
inflammation and neurodegenerative diseases or neurological disorders. Accordingly, this
invention also provides a method for preventing or treating inflammation in the CNS, and a
method for preventing or treating neurodegenerative diseases or disorders characterized by
neuron degeneration, neuron injury or impaired plasticity or inflammation in the CNS. The
neurodegenerative diseases or conditions characterized by neuron degeneration and
inflammation will include but will not be limited to stroke, Alzheimer’s disease, fronto-
temporal dementias (tauopathies), peripheral neuropathy, Parkinson’s disease, dementia with Lewy bodies, Huntington’s disease, amyotrophic lateral sclerosis and multiple sclerosis.

The compounds of formula I are useful in preventing or treating inflammatory conditions or diseases. These diseases or conditions will include but will not be limited to atherosclerotic diseases such as angina pectoris and myocardial infarction as well as inflammatory bowel diseases or conditions such as Crohn’s disease, ulcerative colitis and distal proctitis. Compounds of formula I may also be used in other inflammatory conditions of the lung including asthma, adult respiratory distress syndrome, chronic obstructive pulmonary disease and pneumonia bronchitis.

Furthermore the compounds of formula I may be useful in treatment of various conditions outside the cardiovascular system whether or not associated with insulin resistance, like polycystic ovarian syndrome, obesity and cancer.

The present invention provides a method of treating and/or preventing dyslipidemias, the insulin resistance syndrome and/or metabolic disorders (as defined above) comprising the administration of a compound of formula I to a mammal (particularly a human) in need thereof.

The present invention provides a method of treating and/or preventing type 2 diabetes comprising the administration of an effective amount of a compound of formula I to a mammal (particularly a human) in need thereof.

The present invention provides a method of treating and/or preventing cardiovascular disease comprising the administration of an effective amount of a compound of formula I to a mammal (particularly a human) in need thereof.

The present invention provides a method of treating and/or preventing atherosclerosis comprising the administration of an effective amount of a compound of formula I to a mammal (particularly a human) in need thereof.
The present invention provides a method of treating and/or preventing hypercholesterolemia comprising the administration of an effective amount of a compound of formula I to a mammal (particularly a human) in need thereof.

The present invention provides a method of treating and/or preventing conditions associated with a need for improving reverse cholesterol transport comprising the administration of an effective amount of a compound of formula I to a mammal (particularly a human) in need thereof.

The present invention provides a method of treating and/or preventing conditions associated with a need for decreasing intestinal cholesterol absorption comprising the administration of an effective amount of a compound of formula I to a mammal (particularly a human) in need thereof.

The present invention provides a method of treating and/or preventing conditions associated with a need for increasing HDL-cholesterol levels comprising the administration of an effective amount of a compound of formula I to a mammal (particularly a human) in need thereof.

The present invention provides a method of treating and/or preventing inflammatory conditions comprising the administration of an effective amount of a compound of formula I to a mammal (particularly a human) in need thereof.

The present invention provides a method of treating and/or preventing Alzheimer’s disease comprising the administration of an effective amount of a compound of formula I to a mammal (particularly a human) in need thereof.
The present invention provides a method of treating and/or preventing arteriosclerosis comprising the administration of an effective amount of a compound of formula I to a mammal (particularly a human) in need thereof.

The present invention provides a method of treating and/or preventing conditions associated with a need for improving HDL function comprising the administration of an effective amount of a compound of formula I to a mammal (particularly a human) in need thereof.

The present invention provides a method of treating and/or preventing hyperlipidemic conditions comprising the administration of an effective amount of a compound of formula I to a mammal (particularly a human) in need thereof.

In a further aspect the present invention provides the use of a compound of formula I as a medicament.

In a further aspect the present invention provides the use of a compound of formula I in the manufacture of a medicament for the treatment and/or prophylaxis of dyslipidemic conditions.

In a further aspect the present invention provides the use of a compound of formula I in the manufacture of a medicament for the treatment and/or prophylaxis of insulin resistance syndrome and/or metabolic disorders.

In a further aspect the present invention provides the use of a compound of formula I in the manufacture of a medicament for the treatment and/or prophylaxis of cardiovascular disease.

In a further aspect the present invention provides the use of a compound of formula I in the manufacture of a medicament for the treatment and/or prophylaxis of atherosclerosis.
In a further aspect the present invention provides the use of a compound of formula I in the manufacture of a medicament for the treatment and/or prophylaxis of hypercholesterolemia.

In a further aspect the present invention provides the use of a compound of formula I in the manufacture of a medicament for the treatment and/or prophylaxis of conditions associated with a need for improving reverse cholesterol transport.

In a further aspect the present invention provides the use of a compound of formula I in the manufacture of a medicament for the treatment and/or prophylaxis of conditions associated with a need for decreasing intestinal cholesterol absorption.

In a further aspect the present invention provides the use of a compound of formula I in the manufacture of a medicament for the treatment and/or prophylaxis of conditions associated with a need for increasing HDL-cholesterol levels.

In a further aspect the present invention provides the use of a compound of formula I in the manufacture of a medicament for the treatment and/or prophylaxis of conditions associated with a need for decreasing LDL-cholesterol levels.

In a further aspect the present invention provides the use of a compound of formula I in the manufacture of a medicament for the treatment and/or prophylaxis of inflammatory conditions.

In a further aspect the present invention provides the use of a compound of formula I in the manufacture of a medicament for the treatment and/or prophylaxis of Alzheimer´s disease.

In a further aspect the present invention provides the use of a compound of formula I in the manufacture of a medicament for the treatment and/or prophylaxis of arteriosclerosis.

In a further aspect the present invention provides the use of a compound of formula I in the manufacture of a medicament for the treatment and/or prophylaxis of type 2 diabetes.
In a further aspect the present invention provides the use of a compound of formula I in the manufacture of a medicament for the treatment and/or prophylaxis of conditions associated with a need for improving HDL function.

In a further aspect the present invention provides the use of a compound of formula I in the manufacture of a medicament for the treatment and/or prophylaxis of hyperlipidemic conditions.

**Combination Therapy**

The compounds of the invention may be combined with another therapeutic agent that is useful in the treatment of disorders associated with the development and progress of atherosclerosis such as hypertension, hyperlipidaemias, dyslipidaemias, diabetes, inflammation and obesity. The compounds of the invention may be combined with another therapeutic agent that decreases the ratio of LDL:HDL or an agent that causes a decrease in circulating levels of LDL-cholesterol. In patients with diabetes mellitus the compounds of the invention may also be combined with therapeutic agents used to treat complications related to micro-angiopathies.

In another aspect of the present invention, the compound of formula I, or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, may be administered in association with cholesterol biosynthesis inhibitors, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof. Suitable cholesterol biosynthesis inhibitors include HMG CoA reductase inhibitors, squalene synthesis inhibitors and squalene epoxidase inhibitors. A suitable squalene synthesis inhibitor is squalestatin 1 and a suitable squalene epoxidase inhibitor is NB-598.

In this aspect of the invention, the compound of formula I, or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, may be administrated in association with an HMG CoA reductase inhibitor, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof. Suitably the HMG CoA reductase inhibitor, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs
thereof are statins well known in the art. Particular statins are selected from the group consisting of atorvastatin, fluvastatin, pitavastatin, lovastatin, mevastatin, nicostatin, nivastatin, pravastatin and simvastatin, or a pharmaceutically acceptable salt, especially sodium or calcium, solvate, solvate of such a salt or a prodrug thereof. A particular statin is atorvastatin, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof. A more particular statin is atorvastatin calcium salt. A particularly preferred statin is, however, rosvastatin, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof. A preferable particular statin is rosvastatin calcium salt.

In the present application, the term “cholesterol biosynthesis inhibitors” also includes chemical modifications of the HMG CoA reductase inhibitors, squalene synthesis inhibitors and squalene epoxidase inhibitors, such as esters, prodrugs and metabolites, whether active or inactive.

In another aspect of the present invention, the compound of formula I, or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, may be administered in association with an inhibitor of the ileal bile acid transport system (IBAT inhibitor), or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof.


Further suitable compounds possessing IBAT inhibitory activity have been described in WO 94/24087, WO 98/56757, WO 00/20392, WO 00/20393, WO 00/20410, WO 00/20437, WO 01/34570, WO 00/35889, WO 01/68637, WO 02/08211, WO 03/020710,
WO 03/022825, WO 03/022830, WO 03/022826, WO 03/091232, WO 03/106482, JP 10072371, US 5070103, EP 251 315, EP 417 725, EP 869 121, EP 1 070 703 and EP 597 107 and the contents of these patent applications are incorporated herein by reference. Particular classes of IBAT inhibitors suitable for use in the present invention are benzothiazepines, and the compounds described in the claims, particularly claim 1, of WO 00/01687, WO 96/08484 and WO 97/33882 are incorporated herein by reference. Other suitable classes of IBAT inhibitors are the 1,2-benzothiazepines, 1,4-benzothiazepines and 1,5-benzothiazepines. A further suitable class of IBAT inhibitors is the 1,2,5-benzothiadiazepines.

One particular suitable compound possessing IBAT inhibitory activity is (3R,5R)-3-butyl-3-ethyl-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydro-1,4-benzothiazepin-8-yl β-D-glucopyranosiduronic acid (EP 864 582). A further suitable compound possessing IBAT inhibitory activity is S-8921 (EP 597 107).

In another aspect of the present invention, the compound of formula I, or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, may be administered in association with a cholesterol absorption antagonist, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof, for example azetidinones such as ezetrol (zetia, ezetimibe) and those described in US 5,767,115 which are incorporated herein by reference. Suitable compounds possessing cholesterol absorption antagonist activity have been described, see for instance the compounds described in WO 02/50027, WO 02/66464, WO 04/005247, WO 04/000803, WO 04/000804 and WO 04/000805 which are incorporated herein by reference. In another aspect of the present invention, the compound of formula I, or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, may be administered in association with a bile acid sequestrant or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof. Suitable bile acid sequestrants include cholestyramine, cholestipol and cosevelam hydrochloride.

In another aspect of the invention, the compound of formula I, or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, may be administered in association with a peroxisome proliferator-activated receptor (PPAR) modulating agent. PPAR modulating agents include but are not limited to a PPAR alpha and/or gamma and/or
delta agonist, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof. Suitable PPAR alpha and/or gamma and/or delta agonists, pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof are well known in the art. These include the compounds described in WO 01/12187, WO 01/12612, WO 99/62870, WO 99/62872, WO 99/62871, WO 98/57941, WO 01/40170, WO 04/000790, WO 04/000295, WO 04/000294, WO 03/051822, WO 03/051821, WO 02/096863, WO 03/051826, WO 02/085844, WO 01/40172, J Med Chem, 1996, 39, 665, Expert Opinion on Therapeutic Patents, 10 (5), 623-634 (in particular the compounds described in the patent applications listed on page 634) and J Med Chem, 2000, 43, 527 which are all incorporated herein by reference. Particularly a PPAR alpha and/or gamma and/or delta agonist refers to muraglitazar (BMS 298585), rivoglitazone (CS-011), netoglitazone (MCC-555), balaglitazone (DRF-2593, NN-2344), clofibrate, fenofibrate, bezafibrate, gemfibrozil, ciprofibrate, pioglitazone, AVE-0847, AVE-8134, CLX-0921, DRF-10945, DRF-4832, LY-518674, LY-818, LY-929, 641597, GW-590735, GW-677954, GW-501516, MBX-102, ONO-5129, KRP-101, R-483 (BM131258), TAK-559 or TAK-654. Particularly a PPAR alpha and/or gamma and/or delta agonist refers to tesaglitazar ((S)-2-ethoxy-3-[4-(2-(4-methanesulphonyl-oxypyphenyl)ethoxy)phenyl]propanoic acid) and pharmaceutically acceptable salts thereof. In yet another aspect of the invention, the compound of formula I, or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, may be administered in association with a pyruvate dehydrogenase kinase (PDK) inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, or modulators of nuclear receptors such as retenoid X receptor (RXR), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

In another aspect of the invention, the compound of formula I, or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, may be administered in association with a choleseryl ester transfer protein (CETP) inhibitor, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof, for example those referenced and described in WO 00/38725 page 7 line 22 - page 10, line 17 which are incorporated herein by reference.
In another aspect of the invention, the compound of formula I, or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, may be administered in association with a microsomal transfer protein (MTP) inhibitor, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof, for example implipitide and those described in WO 03/004020, WO 03/002533, WO 02/083658 and WO 00/242291, and the contents of these patent applications are incorporated herein by reference, or those described in Science, 282, 751-54, 1998 which are incorporated herein by reference.

In another aspect of the invention, the compound of formula I, or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, may be administered in association with a nicotinic acid derivative, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof, including slow release and combination products, for example, nicotinic acid (niacin), acipimox, ni cofuranose, NIASPAN® and niceritrol.

In another aspect of the invention, the compound of formula I; or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, may be administered in association with a acyl coenzymA: cholesterol O-acyltransferase (ACAT) inhibitor, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof, for example CS-505, efucimibe (F-12511) and SMP-797.

In yet another aspect of the invention, the compound of formula I, or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, may be administered in association with modulators of nuclear receptors such as farnesoid X receptor (FXR), or pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

In another aspect of the invention, the compound of formula I, or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, may be administered in association with a phytosterol compound, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof, for example stanols.

In another aspect of the invention, the compound of formula I, or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, may be administered in association with other therapies for the treatment of metabolic syndrome or type 2 diabetes and its associated complications, these include biguanide drugs, for example metformin,
phenformin and buformin, insulin (synthetic insulin analogues, amylin) and oral antihyperglycemics (these are divided into prandial glucose regulators and alpha-glucosidase inhibitors). An example of an alpha-glucosidase inhibitor is acarbose or voglibose or miglitol. An example of a prandial glucose regulator is repaglinide or nateglinide.

In another aspect of the invention, the compound of formula I, or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, may be administered in association with a sulfonylurea for example: glimepiride, glibenclamide (glyburide), gliclazide, glipizide, gliquidone, chloropropamide, tolbutamide, acetohexamide, glycopyramide, carbamamide, glibonuride, glisoxepid, glybuthiazole, glibuzole, glyhexamide, glymidine, glypinamide, phenbutamide, tolcyamide and tolazamide. Preferably the sulfonylurea is glimepiride or glibenclamide (glyburide). More preferably the sulfonylurea is glimepiride. Therefore the present invention includes administration of a compound of the present invention in conjunction with one, two or more existing therapies described in this paragraph. The doses of the other existing therapies for the treatment of type 2 diabetes and its associated complications will be those known in the art and approved for use by regulatory bodies for example the FDA and may be found in the Orange Book published by the FDA. Alternatively smaller doses may be used as a result of the benefits derived from the combination.

In another aspect of the invention, the compound of formula I, or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, may be administered in association with an antihypertensive compound for example an angiotensin converting enzyme (ACE) inhibitor, an angiotensin II receptor antagonist, an andrenergic blocker, an alpha andrenergic blocker, a beta andrenergic blocker, a mixed alpha/beta andrenergic blocker, an andrenergic stimulant, calcium channel blocker, an AT-1 blocker, a saluretic, a diuretic or a vasodilator, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof. Particular ACE inhibitors or pharmaceutically acceptable salts, solvates, solvate of such salts or prodrugs thereof, including active metabolites, which can be used in combination with a compound of formula I include but are not limited to, the following compounds: alacepril, alatriopril, ancovenin, benazepril, benazepril hydrochloride, benazeprilat, benzyolcaptopril, captopril, captopril-cysteine, captopril-
glutathione, ceranopril, cilazapril, cilazaprilat, delapril, delapril-diacid, enalapril, enalaprilat, enapril, epicaptopril, foroxymithine, fosfenopril, fosenopril, fosenopril sodium, fosinopril, fosinopril sodium, fosinoprilat, fosinoprilic acid, hemorphin-4, imidapril, indapril, indaprilat, lisinopril, lyciumin A, lyciumin B, moexipril, moexiprilat, muracein A, muracein B, muracein C, pentopril, perindopril, perindoprilat, pivalopril, pivopril, quinapril, quinapril hydrochloride, quinaprilat, ramipril, ramiprilat, spirapril, spirapril hydrochloride, spiraprilat, spropril, spropril hydrochloride, temocapril, temocapril hydrochloride, teprotide, trandolapril, trandolaprilat, zofenopril and zofenoprilat. Preferred ACE inhibitors for use in the present invention are ramipril, ramiprilat, lisinopril, enalapril and enalaprilat. More preferred ACE inhibitors for use in the present invention are ramipril and ramiprilat. Preferred angiotensin II receptor antagonists, pharmaceutically acceptable salts, solvates, solvate of such salts or a prodrugs thereof for use in combination with a compound of formula I include, but are not limited to, compounds: candesartan, candesartan cilexetil, losartan, valsartan, irbesartan, telmisartan and eprosartan. Particularly preferred angiotensin II receptor antagonists or pharmaceutically acceptable derivatives thereof for use in the present invention are candesartan and candesartan cilexetil.

In another aspect of the invention, the compound of formula I, or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, may be administered in association with an anti-obesity compound, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof, for example a pancreatic lipase inhibitor e.g. orlistat (EP 129,748) or an appetite (satiety) controlling substance for example sibutramine (GB 2,184,122 and US 4,929,629), a cannabinoid 1 (CB1) antagonist or inverse agonist, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof, for example rimonabant (EP 656354 ) and as described in WO01/70700 or a melanin concentrating hormone (MCH) antagonist, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof, for example as described in WO 04/004726.

In another aspect of the invention, the compounds of formula I, or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, may be administrated in association with an anti-inflammatory agent such as glucocorticoids, non-steroidal anti-
inflammatory agents (NSAID) or intestinal anti-inflammatory agents, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof. Suitable glucocorticoids will include, but will not be limited to betametason, dexametason, methyl prednisolon, prednisolon, prednison, triamcinolon, hydrocortison, cortison and budesonid. Suitable non-steroidal anti-inflammatory agents will include, but will not be limited to indometacin, diklofenak, ibuprofen as well as acetylsalicylic acid. Suitable intestinal anti-inflammatory agents will include, but will not be limited to amino salicylates such as sulfasalazin, mesalazin, olsalazin and balsalazid.

In another aspect of the invention, the compounds of formula I, or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, may be administrated in association with a cholinesterase inhibitor or an N-methyl-D-aspartate (NMDA) receptor antagonist, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof, such as donepezil, rivastigmin or galantamin or memantin.

In an additional feature of the invention, there is provided a method for the treatment and/or prophylaxis of metabolic disorders in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula I, or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, in simultaneous, sequential or separate administration with an effective amount of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

In an additional feature of the invention, there is provided a method for the treatment and/or prophylaxis of dyslipidemia in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula I, or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, in simultaneous, sequential or separate administration with an effective amount of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.
In an additional feature of the invention, there is provided a method for the treatment and/or prophylaxis of the insulin resistance syndrome in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula I, or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, in simultaneous, sequential or separate administration with an effective amount of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

Therefore in an additional feature of the invention, there is provided a method for the treatment and/or prophylaxis of type 2 diabetes and its associated complications in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula I, or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt in simultaneous, sequential or separate administration with an effective amount of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

Therefore in an additional feature of the invention, there is provided a method of treating and/or preventing hyperlipidemic conditions in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula I, or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt in simultaneous, sequential or separate administration with an effective amount of one of the other compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

In an additional feature of the invention, there is provided a method for the treatment and/or prophylaxis of cardiovascular disease in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula I, or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt in simultaneous, sequential or separate administration with an
effective amount of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

In an additional feature of the invention, there is provided a method for the treatment and/or prophylaxis of atherosclerosis in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula I, or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt in simultaneous, sequential or separate administration with an effective amount of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

In an additional feature of the invention, there is provided a method for the treatment and/or prophylaxis of hypercholesterolemia in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula I, or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt in simultaneous, sequential or separate administration with an effective amount of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

In an additional feature of the invention, there is provided a method for treating and/or preventing conditions associated with a need for improving reverse cholesterol transport in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula I, or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt in simultaneous, sequential or separate administration with an effective amount of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

In an additional feature of the invention, there is provided a method for treating and/or preventing conditions associated with a need for decreasing intestinal cholesterol absorption in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula I, or
a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt in simultaneous, sequential or separate administration with an effective amount of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

In an additional feature of the invention, there is provided a method for treating and/or preventing conditions associated with a need for increasing HDL-cholesterol levels in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula I, or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt in simultaneous, sequential or separate administration with an effective amount of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

In an additional feature of the invention, there is provided a method for treating and/or preventing conditions associated with a need for decreasing LDL-cholesterol levels in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula I, or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt in simultaneous, sequential or separate administration with an effective amount of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

In an additional feature of the invention, there is provided a method for the treatment and/or prophylaxis of inflammatory conditions in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula I, or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt in simultaneous, sequential or separate administration with an effective amount of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.
In an additional feature of the invention, there is provided a method for the treatment and/or prophylaxis of Alzheimer's disease in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula I, or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt in simultaneous, sequential or separate administration with an effective amount of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

In an additional feature of the invention, there is provided a method for the treatment and/or prophylaxis of arteriosclerosis a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula I, or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt in simultaneous, sequential or separate administration with an effective amount of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

In an additional feature of the invention, there is provided a method for treating and/or preventing conditions associated with a need for improving HDL function in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula I, or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt in simultaneous, sequential or separate administration with an effective amount of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula I, or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, and one of the other compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in association with a pharmaceutically acceptable diluent or carrier.
According to a further aspect of the present invention there is provided a kit comprising a compound of formula I, or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, and one of the other compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further aspect of the present invention there is provided a kit comprising:

a) a compound of formula I, or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, in a first unit dosage form;

b) one of the other compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof; in a second unit dosage form; and

c) container means for containing said first and second dosage forms.

According to a further aspect of the present invention there is provided a kit comprising:

a) a compound of formula I, or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, together with a pharmaceutically acceptable diluent or carrier, in a first unit dosage form;

b) one of the other compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a second unit dosage form; and

c) container means for containing said first and second dosage forms.

According to another feature of the invention there is provided the use of a compound of the formula I, or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment and/or prophylaxis of metabolic disorders in a warm-blooded animal, such as man.
According to another feature of the invention there is provided the use of a compound of the formula I, or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment and/or prophylaxis of dyslipidemia in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula I, or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment and/or prophylaxis of metabolic syndrome or type 2 diabetes and its associated complications in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula I, or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment and/or prophylaxis of hyperlipidaemic conditions in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula I, or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment and/or prophylaxis of cardiovascular disease in a warm-blooded animal, such as man.
pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment and/or prophylaxis of atherosclerosis in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula I, or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment and/or prophylaxis of hypercholesterolemia in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula I, or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment and/or prophylaxis of a conditions associated with a need for improving reverse cholesterol transport in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula I, or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment and/or prophylaxis of a conditions associated with a need for decreasing intestinal cholesterol absorption in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula I, or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment and/or prophylaxis of a conditions
associated with a need for increasing HDL-cholesterol levels in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula I, or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment and/or prophylaxis of a conditions associated with a need for decreasing LDL-cholesterol levels in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula I, or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment and/or prophylaxis of inflammatory conditions in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula I, or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment and/or prophylaxis of Alzheimer’s disease in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula I, or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment and/or prophylaxis of arteriosclerosis in a warm-blooded animal, such as man.
According to another feature of the invention there is provided the use of a compound of the formula I, or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment and/or prophylaxis of a conditions associated with a need for improving HDL function in a warm-blooded animal, such as man.

According to a further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of a compound of the formula I, or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration of an effective amount of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man in need of such therapeutic treatment.

**Examples**

**Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>DCM</td>
<td>Dichloromethane</td>
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<tr>
<td>DMF</td>
<td>N, N-dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
</tr>
<tr>
<td>EtOAc</td>
<td>ethyl acetate</td>
</tr>
<tr>
<td>EtOH</td>
<td>ethanol</td>
</tr>
<tr>
<td>HPLC</td>
<td>high performance liquid chromatography</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>UV</td>
<td>ultra violet</td>
</tr>
<tr>
<td>h</td>
<td>hour</td>
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<td>min.</td>
<td>minutes</td>
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</table>
rt  room temperature
br  broad
bs  broad singlet
bt  broad triplet
d  doublet
dd  doublet of doublets
m  multiplet
q  quartet
s  singlet
t  triplet

**General Experimental Procedures**

Flash column chromatography employed normal phase silica gel 60 (0.040-0.063 mm, Merck) or IST Isolute® SPE columns normal phase silica gel. Purifications were performed on either a Gilson preparative HPLC system with a UV triggered fraction collector, equipped with a ACE C8 5 μm 250 mm x 20 mm column, or on a Waters preparative HPLC system equipped with an ACE C8 5 μm 250 mm x 50 mm column or an ACE C8 5 μm 250 mm x 20 mm column. ^1H NMR spectra were obtained on a Varian Unity Plus, 400 MHz, operating at 9.3 T, equipped with a 5 mm switchable probe with an inner X-coil, for solutions in CDCl3 (residual CHCl3 (δH 7.23 ppm) as internal standard), or DMSO-<sup>d6</sup> (residual DMSO (δH 2.50 ppm) as internal standard) at 300K. Chemical shifts are given in ppm. Microwave heating was performed using single node heating in a Smith Creator from Personal Chemistry, Uppsala, Sweden. Lawesson’s reagent is 2,4-Bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide.

**Synthesis of Starting Materials and Intermediates**

3-Hydroxy-4-phenyl-1H-pyrrole-2,5-dione

3-Chloro-4-phenyl-1H-pyrrole-2,5-dione
To a suspension of 3-hydroxy-4-phenyl-1H-pyrrole-2,5-dione (25.0g, 0.13mol) in dichloromethane (600mL) under an atmosphere of nitrogen was added DMF (36mL). The suspension was cooled to ice temperature and treated with oxalyl chloride (40.0g, 0.32mol). The reaction mixture was subsequently refluxed overnight. After cooling to rt, silica gel was added and the reaction mixture evaporated to dryness and subjected to flash chromatography (hexane:EtOAc, 80:20). Trituration with dichloromethane, filtration and drying gave (17.6g, 64%) of the title compound; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.96-7.89 (m, 2H), 7.88-7.77 (bs, 1H), 7.55-7.45 (m, 3H).

tert-butyl [5-(bromomethyl)pyridin-2-yl]carbamate

tert-Butyl [5-{[(3-chloro-2,5-dioxo-4-phenyl-2,5-dihydro-1H-pyrrol-1-yl)methyl]pyridin-2-yl}carbamate
3-Chloro-4-phenyl-1H-pyrrole-2,5-dione (1.55g, 7.47mmol) was dissolved in DMF (25 mL) under nitrogen atmosphere and cooled in an ice-bath. tert-Butyl [5-(bromomethyl)pyridin-2-yl]carbamate (2.14g, 7.47mmol) was added followed by anhydrous potassium carbonate (1.03g, 7.47mmol). The mixture was stirred for 1.5h whereafter the cooling-bath was removed and the mixture was stirred for another two h and then neutralized with 1%HCl. Water (100mL) was added and the mixture was extracted with CH$_2$Cl$_2$ (50mL x 3). The extracts were combined, washed with water (100mL x 2), dried with magnesium sulphate, filtered and evaporated. The crude product (3.41g) was used in the next step without further purification; $^1$H NMR (400 MHz, CDCl$_3$) δ 8.32 (d, J=2 Hz, 1H), 7.92-7.89 (m, 3H), 7.83 (bs, 1H), 7.72 (dd, J =9, 2 Hz, 1H), 7.49-7.47 (m, 3H), 4.71 (s, 2H) and 1.52 (s, 9H).

1-[(6-Aminopyridin-3-yl)methyl]-3-{[4-(difluoromethoxy)phenyl]amino}-4-phenyl-1H-pyrrole-2,5-dione
A mixture of tert-butyl [5-{[(3-chloro-2,5-dioxo-4-phenyl-2,5-dihydro-1H-pyrrol-1-yl)methyl]pyridin-2-yl}carbamate (0.70g, 1.7mmol) and 4-(difluoromethoxy)aniline (0.54g, 3.4mmol) in DMF (4mL) was heated in a microwave reactor at 150°C for 8
minutes. The solvent was evaporated and the residue was purified on a pre-packed SiO₂ column (Isolute® SI, 10g/70 mL) using CH₂Cl₂ and then CH₃OH/CH₂Cl₂ (1:99, 2:98 and then 5:95) as eluant to give 0.4g (54%) of the title compound; ¹H NMR (400 MHz, CDCl₃) δ 7.99 (bs, 1H), 7.67-7.62 (m, 2H), 7.14-7.04 (m, 3H), 6.91 (d, J=8 Hz, 2H), 6.78 (d, J=8 Hz, 1H), 6.72 (d, J=9 Hz, 2H), 6.63 (d, J=9 Hz, 2H), 6.33 (t, J=74 Hz, 1H) and 4.60 (s, 2H).

Examples

Example 1

1-[(6-aminopyridin-3-yl)methyl]-3-[(4-(difluoromethoxy)phenyl)amino]-4-phenyl-5-thioxo-1,5-dihydro-2H-pyrrol-2-one

Phosphorus pentasulfide (1.6g, 3.6mmol) was added into 1-[(6-aminopyridin-3-yl)methyl]-3-[(4-(difluoromethoxy)phenyl)amino]-4-phenyl-1H-pyrrrole-2,3-dione (2.83g, 6.5mmol) in dioxane (100mL). It was dipped into a preheated oil bath at 120°C. The reaction mixture was refluxed for 15 minutes, cooled to room temperature and concentrated. The residue was purified by preparative HPLC using acetonitrile/water (0.1% TFA) system. The acetonitrile was removed in vacuo at room temperature and it was then freeze dried. The obtained material was dissolved in DCM (10mL). It was then shaken with a mixture of NaHCO₃ (2mL, sat.) and brine (1mL) in a separatory funnel. The two phases were separated and the organic phase was dried (Na₂SO₄) and evaporated. It was further purified by column chromatography (ISOLUTE SI, 5 g/25 mL), eluting with DCM, MeOH:DCM (0.5: 99.5, then 1:99), to give the (2mg) of the title compound; ¹H NMR (400 MHz, CDCl₃): δ 4.59 (br, 2H), 5.04 (s, 2H), 6.32 (t, 1H), 6.46 (d, 1H), 6.60 (d, 2H), 6.69 (d, 2H), 6.93-6.96 (m, 3H), 7.06-7.14 (m, 3H), 7.60 (dd, 1H), 8.19 (d, 2H); MS: M-H⁺ 451.

BIOLGICAL ACTIVITY

CO-ACTIVATOR RECRUITEMENT ASSAY

The Ligand Binding Domain (LBD) of human LXRalpha (amino acid 205-447) and LXRbeta (amino acid 216-461) was produced by recombinant techniques in E coli. A fragment of the human Steroid Receptor Co-Activator-1 (SRC-1) was produced as a
synthetic peptide. An anti-6His-antibody coupled with Europium (Eu$^{3+}$) was used to recognize the His-tag on the LXR-LBD and Allophycocyanin (APC) coupled to streptavidin was used to recognize the biotinylated SRC-1. Agonist binding to LXRRa or LXRRb enhances the affinity of LXR towards SRC-1 and thereby brings Eu$^{3+}$ and APC in close proximity. Eu$^{3+}$ is excited at 337 nm and emits light at 620 nm. This emission, when in close proximity, excites APC to emit light at 665 nm.

Dilution plates with compounds in DMSO were further diluted in buffer {20mM [Tris(hydroxymethyl)aminomethane] pH 7.5, 0.125% CHAPS {3-[(3-Cholamidopropyl)dimethylammonio]-1-propanesulfonate}, 2mM DTT (Dithiothreitol) and 0.05% BSA (Bovine Serum Albumin)} in order to reduce DMSO concentration, 0.5 μl to 13.5 μl. To this, 6 μl assay mix was added and the plates (384-well V-groove plates) were incubated at room temperature for 60 to 80 min. The assay mix has the following final concentrations; LXRRa mix: 0.06 μg/ mL Eu-labelled anti-6x His Ab, 1.15μg/ mL Streptavidin APC, 30 nM SRC-1 peptide and 0.9 μg/ mL LXRRa mix; 0.06 μg/ mL Eu-labelled anti-6x His Ab, 1.15μg/ mL Streptavidin APC, 90 nM SRC-1 peptide and 0.2 μg/ mL LXRRb in buffer. Time-resolved fluorescence readings were done in a Wallac Victor reader at 665 nm followed by reading at 615 nm. The LXR ligand, 22-R Hydroxycholesterol at 50μM was used as the 100% control.

TRANSACTIVATION ASSAY

Expression vectors were prepared by inserting the ligand binding domain cDNA (complementary DNA) of human LXRRa (amino acid 205-447) and LXRRb (amino acid 216-461) in frame with, 3' to the yeast GAL4 transcription factor DNA binding domain and the nuclear localization signal from the T-antigen of Polyoma Virus in the eucaryotic expression vector pSG5 (Stratagene). The resulting expression vectors pSGGAL-LXRRa and pSGGAL-LXRRb were used in cotransfection experiments together with the pGL3 luciferase reporter plasmid containing a minimal SV40 promoter and five copies of the UAS GAL4 recognition site. 2.5 μg pSGGAL-LXRRa or beta were mixed with 25 μg pGL3 5xUAS and 22.5 μg pBluscript in 0.95 mL ice cold PBS containing approx. 4-9 milij. U2/OS osteosarcoma cells. After a five minute incubation on ice the cell/DNA mixture was electroporated in 0.4 cm cuvettes at 960 μF, 230 V using a
BioRad electroporator and diluted to 0.32 milj cells/mL in complete DMEM (Dulbecco’s Modified Eagle Medium) medium (Gibco 31966-021). Cells from at least two electroporations were pooled in order to avoid variations between different electroporations. 25 µl diluted, electroporated cells, were seeded onto 384-well plates (0.8 x 10^4 cells/well) and the cells were allowed to adhere for 2 h at 37°C, 5% CO₂ in a cell culture incubator. Dilution plates with compounds in DMSO were further diluted in DMEM w/o phenol red (Gibco 11880-028) including 10% FBS (Foetal Bovine Serum), 1% PEST (Penicillin Streptomycin), 20mM Hepes, 2mM L-Glutamine and 0.36% Glucose (2.5 µl to 97.5 µl) in order to reduce DMSO concentration. 7 µl of this was added to the electroporated cells in 384-well plates and incubation was continued for 48 h in a cell culture incubator, after which cells were lysed by adding 32 µl/well LucLite luciferase substrate. Luciferase activity was measured using the “Luminescence 384 protocol” in the Wallac Victor reader after 15 min. incubation at room temperature. The LXR ligand, Tularik T0901317, at 1µM was used as the 100% control.

The compounds of formula I have an EC₅₀ of less than 50µmol/l for LXRalpha and/or beta in coactivator recruitment assays and/or reporter gene assays. For example, the compound of Example 1 was EC₅₀’s of 0.28 µmol/l and 0.32 µmol/l in reporter gene assays, respectively.

In addition the compounds of the present invention exhibit improved physical and/or chemical and/or DMPK (Drug Metabolism and Pharmacokinetic) properties, for example they exhibit improved metabolic stability in vitro, and/or exhibit favourable pharmacological effects in vivo. The compounds also have a promising toxicological profile.
CLAIMS

1. A compound of Formula I

Formula I

wherein:

- $R^1$ is selected from phenyl(1-4C)alkyl wherein the phenyl is optionally substituted by (1-4C)alkoxycarbonyl or a group of formula NR$^a$R$^b$ in which R$^a$ and R$^b$ independently represent H or (1-4C)alkyl; heteroaryl(1-4C)alkyl wherein the heteroaryl is optionally substituted by (1-4C)alkyl or a group of formula NR$^a$R$^b$ in which R$^a$ and R$^b$ independently represent H or (1-4C)alkyl; or a (1-6C)alkyl group which is optionally substituted by one or more of the following: fluoro, (1-4C)alkoxycarbonyl, (1-3C)alkylthio or (1-3C)alkoxy optionally substituted by one or more fluoro;
- $R^2$ is phenyl;
- $R^3$ is selected from phenyl, indolyl or benzofuranyl each optionally substituted by one or more of the following: (1-3C)alkanoyl, (1-4C)alkoxy optionally substituted by one or more fluoro; (1-3C)alkylthio; or a group of formula NR$^a$R$^b$ in which R$^a$ and R$^b$ independently represent H, (1-3C)alkyl or (1-3C)alkanoyl or R$^a$ and R$^b$ together with the nitrogen atom to which they are attached represent morpholino; or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt.

2. A compound according to claim 1 in which $R^1$ is selected from methyl, ethyl, propyl, butyl, 2-methoxyethyl, 2,2,2-trifluoroethyl, benzyl, 4-pyridylmethyl, 3-pyridylmethyl or 6-amino-3-pyridylmethyl.
3. A compound according to any previous claim in which R³ is 4-methoxyphenyl, 4-difluoromethoxyphenyl or 4-morpholinophenyl.

4. A compound according to claim 1 wherein R¹ is selected from methyl, ethyl, 2,2,2-trifluoroethyl, benzyl, 3-pyridylmethyl or 6-amino-3-pyridylmethyl;
   R² is phenyl;
   R³ is selected from 4-methoxyphenyl, 4-difluoromethoxyphenyl or 4-morpholinophenyl.

5. A compound according to claim 1 wherein R¹ is selected from ethyl, 2,2,2-trifluoroethyl, benzyl, 3-pyridylmethyl or 6-amino-3-pyridylmethyl;
   R² is phenyl;
   R³ is selected from 4-methoxyphenyl, 4-difluoromethoxyphenyl or 4-morpholinophenyl.

6. A compound according to claim 1 wherein R¹ is selected from methyl, ethyl, 2,2,2-trifluoroethyl, 2-pyridylmethyl, 3-pyridylmethyl or 4-pyridylmethyl;
   R² is phenyl;
   R³ is selected from 4-methoxyphenyl.

7. A compound according to claim 1 wherein R¹ is selected from 2-methoxyethyl or 6-amino-3-pyridylmethyl;
   R² is phenyl;
   R³ is selected from 4-methoxyphenyl or 4-difluoromethoxyphenyl.

8. 1-[(6-Aminopyridin-3-yl)methyl]-3-[(4-(difluoromethoxy)phenyl)amino]-4-phenyl-5-thioxo-1,5-dihydro-2H-pyrrol-2-one or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt.

9. A process for the preparation of a compound according to any one of claims 1-8,
   wherein R¹, R² and R³ are as defined in claim 1, comprising the step of reacting a compound of formula II,
wherein $R^2$ and $R^3$ are as defined in claim 1, with a sulphurating agent, for example Lawesson’s reagent, optionally in the presence of an inert organic liquid for example an aromatic hydrocarbon, e.g. toluene, at a temperature in the range of 0°C to 200°C.

10. A pharmaceutical formulation comprising a compound according to any one of claims 1-8 in admixture with pharmaceutically acceptable adjuvants, diluents and/or carriers.

11. The use of a compound according to any one of claims 1-8 in therapy.

12. The use of a compound according to any one of claims 1-8 for the manufacture of a medicament for the modulation of the nuclear hormone receptors LXR $\alpha$ and/or $\beta$.

13. The use of a compound according to any one of claims 1-8 in the manufacture of a medicament for the treatment and/or prophylaxis of cardiovascular disease.

14. The use of a compound according to any one of claims 1-8 in the manufacture of a medicament for the treatment and/or prophylaxis of atherosclerosis.

15. The use of a compound according to any one of claims 1-8 in the manufacture of a medicament for the treatment and/or prophylaxis of hypercholesterolemia.

16. The use of a compound according to any one of claims 1-8 in the manufacture of a medicament for the treatment and/or prophylaxis of conditions associated with a need for improving reverse cholesterol transport.
17. The use of a compound according to any one of claims 1-8 in the manufacture of a medicament for the treatment and/or prophylaxis of conditions associated with a need for decreasing intestinal cholesterol absorption.

18. The use of a compound according to any one of claims 1-8 in the manufacture of a medicament for the treatment and/or prophylaxis of conditions associated with a need for increasing HDL-cholesterol levels.

19. The use of a compound according to any one of claims 1-8 in the manufacture of a medicament for the treatment and/or prophylaxis of conditions associated with a need for decreasing LDL-cholesterol levels.

20. The use of a compound according to any one of claims 1-8 in the manufacture of a medicament for the treatment and/or prophylaxis of inflammatory conditions.

21. The use of a compound according to any one of claims 1-8 in the manufacture of a medicament for the treatment and/or prophylaxis of Alzheimer’s disease.

22. The use of a compound according to any one of claims 1-8 in the manufacture of a medicament for the treatment and/or prophylaxis of arteriosclerosis.

23. The use of a compound according to any one of claims 1-8 in the manufacture of a medicament for the treatment and/or prophylaxis of type 2 diabetes.

24. The use of a compound according to any one of claims 1-8 in the manufacture of a medicament the treatment and/or prophylaxis of conditions associated with a need for improving HDL function.

25. The use of a compound according to any one of claims 1-8 in the manufacture of a medicament for the treatment and/or prophylaxis of lipid disorders (dyslipidemia) whether or not associated with insulin resistance.
26. A method of treating and/or preventing lipid disorders (dyslipidemia) whether or not associated with insulin resistance comprising the administration of a compound according to any one of claims 1-8 to a mammal in need thereof.

27. A method for treatment and/or prophylaxis of cardiovascular disease comprising administering to a mammal, including man, in need of such a treatment an effective amount of a compound as defined in any of claims 1-8.

28. A method of treating and/or preventing atherosclerosis comprising the administration of an effective amount of a compound of formula I according to any one of claims 1-8 to a mammal in need thereof.

29. A method for treatment and/or prophylaxis of hypercholesterolemia comprising administering to a mammal, including man, in need of such a treatment an effective amount of a compound as defined in any of claims 1-8.

30. A method for treatment and/or prophylaxis of conditions associated with a need for improving reverse cholesterol transport comprising administering to a mammal, including man, in need of such a treatment an effective amount of a compound as defined in any of claims 1-8.

31. A method for treatment and/or prophylaxis of conditions associated with a need for decreasing intestinal cholesterol absorption comprising administering to a mammal, including man, in need of such a treatment an effective amount of a compound as defined in any of claims 1-8.

32. A method for treatment and/or prophylaxis of conditions associated with a need for increasing HDL-cholesterol levels comprising administering to a mammal, including man, in need of such a treatment an effective amount of a compound as defined in any of claims 1-8.
33. A method for treatment and/or prophylaxis of conditions associated with a need for decreasing LDL-cholesterol levels comprising administering to a mammal, including man, in need of such a treatment an effective amount of a compound as defined in any of claims 1-8.

34. A method for treatment and/or prophylaxis of inflammatory conditions comprising administering to a mammal, including man, in need of such a treatment an effective amount of a compound as defined in any of claims 1-8.

35. A method for treatment and/or prophylaxis of Alzheimer’s disease comprising administering to a mammal, including man, in need of such a treatment an effective amount of a compound as defined in any of claims 1-8.

36. A method for treatment and/or prophylaxis of arteriosclerosis comprising administering to a mammal, including man, in need of such a treatment an effective amount of a compound as defined in any of claims 1-8.

37. A method for treatment and/or prophylaxis of type 2 diabetes comprising administering to a mammal, including man, in need of such a treatment an effective amount of a compound as defined in any of claims 1-8.

38. A method for treatment and/or prophylaxis of conditions associated with a need for improving HDL function comprising administering to a mammal, including man, in need of such a treatment an effective amount of a compound as defined in any of claims 1-8.

39. A pharmaceutical formulation for use in the treatment or prophylaxis of conditions associated with a need for modulation of the nuclear hormone receptors LXR α and/or β, comprising a compound according to any one of claims 1-8 as active ingredient in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

40. A pharmaceutical composition comprising a compound as claimed in any one of claims 1-8 combined with another therapeutic agent that is useful in the treatment of conditions or
disorders associated with the development and progress of atherosclerosis such as hypertension, dyslipidemias, hyperlipidaemias, hypercholesterolemias, type 2 diabetes, inflammation, obesity as well as conditions associated with a need for improving reverse cholesterol transport and/or decreasing intestinal cholesterol absorption.
PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT
(PCT Article 18 and Rules 43 and 44)

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<td>see Form PCT/ISA/220 as well as, where applicable, item 5 below.</td>
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<td>10 January 2005</td>
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Applicant

AstraZeneca AB et al

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 6 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report
   a. With regard to the language, the international search was carried out on the basis of:
      ☑ the international application in the language in which it was filed
      ☐ a translation of the international application into
      ☐ a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

   b. ☑ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2. ☑ Certain claims were found unsearchable (see Box No. II)

3. ☐ Unity of invention is lacking (see Box No. III)

4. With regard to the title,
   ☑ the text is approved as submitted by the applicant.
   ☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,
   ☑ the text is approved as submitted by the applicant.
   ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the drawings,
   a. the figure of the drawings to be published with the abstract is Figure No. __________
      ☑ as suggested by the applicant.
      ☑ as selected by this Authority, because the applicant failed to suggest a figure.
      ☑ as selected by this Authority, because this figure better characterizes the invention.
   b. ☐ none of the figures is to be published with the abstract.

Form PCT/ISA/210 (first sheet) (April 2005)
## INTERNATIONAL SEARCH REPORT

**International application No.**
PCT/SE2006/000030

### A. CLASSIFICATION OF SUBJECT MATTER

**IPC:** see extra sheet
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:** C07D

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

SE, DK, FI, NO classes as above

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

**EPO-INTERNAL, WPI DATA, PAJ, CHEM ABS DATA**

### C. DOCUMENTS CONSIDERED TO BE RELEVANT

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

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

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

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of 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

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"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

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**Date of the actual completion of the international search** 7 April 2006

**Date of mailing of the international search report** 10-04-2006

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Name and mailing address of the ISA/
Swedish Patent Office
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Authorized officer
Eva Johansson/EB
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A61P 25/28 (2006.01)
A61P 29/00 (2006.01)
A61P 3/04 (2006.01)
A61P 3/06 (2006.01)
A61P 3/10 (2006.01)
A61P 9/00 (2006.01)
A61P 9/10 (2006.01)
C07D 207/456 (2006.01)

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Paper copies can be ordered at a cost of 50 SEK per copy from PRV InterPat (telephone number 08-782 28 85).

Cited literature, if any, will be enclosed in paper form.
INTERNATIONAL SEARCH REPORT

Box No. 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. ☑ Claims Nos.: 11, 26-38
   because they relate to subject matter not required to be searched by this Authority, namely:
   Claims 11, 26-38 relate to a method of treatment of the human or animal body by surgery or by therapy, as well as diagnostic

2. ☐ 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:

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 No. 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 and, where applicable, the payment of a protest fee.
☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (2)) (April 2005)
methods /Rule 39.1(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds.
### INTERNATIONAL SEARCH REPORT

**Information on patent family members**

**31/12/2005**

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