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(54) **DERIVES DE MERCAPTOACETYLAMIDES
HYPOCHOLESTEROLEMIQUES, ANTIATHEROSCLEREAUX
ET HYPOTRIGLYCERIDEMIQUES**
**HYPOCHOLESTEROLEMIC, ANTIATHEROSCLEROTIC AND
HYPOTRIGLYCERIDEMIC MERCAPTOACETYLAMIDE
DERIVATIVES**

(57) La présente invention concerne l'utilisation de certains dérivés de mercaptoacétylamides pour le traitement de patients atteints d'hypertriglycéridémie, athérosclérose et d'hypercholestérolémie.

(57) The present invention relates to the use of certain mercaptoacetyl amide derivatives in treating patients suffering from hypertriglyceridemia, atherosclerosis and hypercholesterolemia.



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(54) Title: HYPOCHOLESTEROLEMIC, ANTIATHEROSCLEROTIC AND HYPOTRIGLYCERIDEMIC MERCAPTOACETYLAMIDE DERIVATIVES					
(57) Abstract					
<p>The present invention relates to the use of certain mercaptoacetylamide derivatives in treating patients suffering from hypertriglyceridemia, atherosclerosis and hypercholesterolemia.</p>					

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10 HYPOCHOLESTEROLEMIC, ANTIATHEROSCLEROTIC AND
 HYPOTRIGLYCERIDEMIC MERCAPTOACETYLAMIDE DERIVATIVES

BACKGROUND OF THE INVENTION

15 Coronary heart disease (CHD) remains the leading cause of death in the industrialized countries. Despite recent declines in CHD mortality, CHD is still responsible for more than 500,000 deaths in the U.S. annually. It is estimated that CHD, directly and indirectly, costs the U.S. more than 20 \$100 billion a year. The primary cause of CHD is atherosclerosis, a disease characterized by the deposition of lipid (cholesterol and triglycerides) in the arterial vessel wall, resulting in a narrowing of the arterial lumen and ultimately hardening of the arteries.

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Atherosclerosis as manifested in its major clinical complication, coronary heart disease (CHD) or ischaemic heart disease, continues to be a major cause of death in industrialized countries. It is now well accepted that 30 atherosclerosis can begin with local injury to the arterial endothelium followed by the penetration of circulatory monocytes into the intima of the arterial wall where they become loaded with lipoprotein derived lipids. At about the same time there seems to be a migration of arterial smooth 35 muscle cells from the medial layer to the intimal layer and their proliferation there along with the deposition of lipid and accumulation of foam cells in the lesion. As the atherosclerotic plaque develops it progressively occludes

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more and more of the affected blood vessel and can eventually lead to ischaemia, thrombosis or infarction. Therefore, it is desirable to provide methods of inhibiting 5 the progression of atherosclerosis in patients in need thereof.

National Institutes of Health Consensus Development Conference Panel concluded that lowering plasma cholesterol 10 levels (specifically blood levels of low-density lipoprotein cholesterol) will definitely reduce the risk of heart attacks due to CHD. Serum lipoproteins are the carriers for lipids in the circulation. They are classified according to their density; i.e., chylomicrons, very low-density 15 lipoproteins (VLDL), intermediate density lipoproteins (IDL), low density lipoproteins (LDL) and high-density lipoproteins (HDL). About 50% to 70% of the cholesterol circulating in the blood is carried as LDL. In contrast, about 25% of total cholesterol is found in HDL, while VLDL 20 carries most of the plasma triglycerides and only about 10% to 15% of the total cholesterol.

Chylomicrons are assembled in the intestinal wall from products of lipid digestion and are then transported into 25 the peripheral circulation via the thoracicolymphatic system. In the circulation, they are broken down by lipoprotein lipase (LPL) into free fatty acids and triglycerides which are primarily used by muscles for energy or stored in adipose tissue. The other serum lipoproteins 30 are involved in the transport of endogenously synthesized lipid. Endogenous lipid transport begins when the liver secretes triglycerides and cholesterol into the plasma as VLDL. The triglycerides of VLDL are cleaved in the capillaries by LPL to IDL and finally LDL. Some of these 35 particles are cleared rapidly by the liver by receptor-mediated endocytosis. The remainder circulate mainly as LDL.

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As cells die and cell membranes turn over, cholesterol is continuously released into the plasma and becomes HDL. HDL promotes the removal of cholesterol from peripheral 5 cells and facilitates its transport back to the liver.

Arterial wall cholesterol is derived almost exclusively from LDL [Brown and Goldstein, Ann. Rev. Biochem. 52, 223 (1983); Miller, Ann. Rev. Med. 31, 97 (1980)]. Framingham 10 investigators found the higher the levels of LDL, the higher the risk of developing CHD [Am. J. Med. 80 (Suppl. 2A) 23-32, 1986]. In patients with low levels of LDL, the development of atherosclerosis is rare [Patton et. al, Clin. Chem. 29, 1890 (1983)]. Accordingly, it is desirable to provide a 15 method for reducing plasma cholesterol in patients with hypercholesterolemia or at risk of developing hypercholesterolemia.

Elevated cholesterol levels are also associated with a 20 number of disease states, including coronary artery disease, angina pectoris, carotid artery disease, strokes, cerebral arteriosclerosis, and xanthoma. It is desirable to provide a method for reducing plasma cholesterol in patients with, or at risk of developing disease states associated with 25 elevated cholesterol levels.

Hypertriglyceridemia is a condition in which there is an excessive amount of triglyceride (>500mg/dl) in the plasma. It may play a role in atherogenesis and the development of 30 coronary heart disease [Vega and Grundy, Adv. Exp. Med. 243, 311 (1989)]. In addition, severe hypertriglyceridemia (>1000mg/dl) is associated with chylomicronemia and causes acute pancreatitis [See K. Soergel, ACUTE PANCREATITIS, in *Gastrointestinal Disease* 91, 3rd ed. (Sleisenger, M. H., and 35 Fordtran, J. S., eds.), W. B. Saunders Company, Philadelphia, Pa., 1983, pp. 1462-1485; and See Brown, M. S., and Goldstein, J. L., DRUGS USED IN THE TREATMENT OF HYPERLIPOPROTEINEMIAS, in *Goodman and Gillman's, The*

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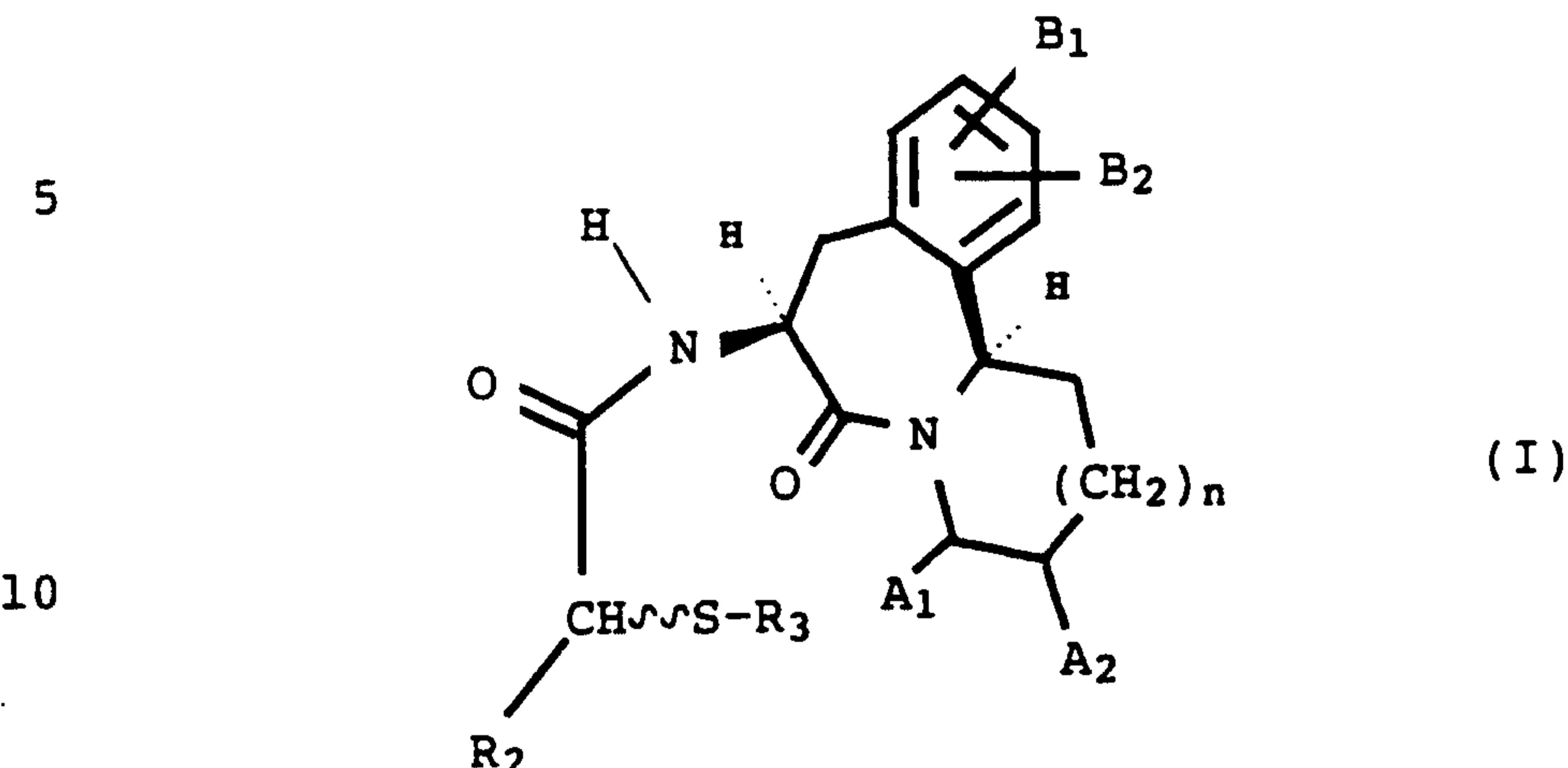
Pharmacological Basis of Therapeutics 34, 7th edition, (Macmillan Publishing Co., New York, 1985, pp. 827-845]. Severe elevations in chylomicrons directly induce pancreatitis, and 5 it can be prevented by triglyceride reduction [U.S. Department of Health and Human Services, NIH Publication No. 89-2925, pp. 74-77, January 1989, "Report of the Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults"] It is therefore desirable to 10 provide a method for reducing plasma triglycerides in patients with hypertriglyceridemia.

The present invention relates to the use of certain mercaptoacetylamide derivatives known to be useful for the 15 inhibition of Enkephalinase (EC 3.4.24.1) and ACE (EC 3.4.15.1) [Flynn, Warshawsky, Mehdi, Bey, Beight, Giroux and Burkholder, European Patent Application, Publication Number 0 481 522 A1, published April 22, 1992] in treating patients suffering from hypercholesterolemia and atherosclerosis or 20 hypertriglyceridemia.

SUMMARY OF THE INVENTION

25 The present invention provides a method of treating hypercholesterolemia, atherosclerosis and hypertriglyceridemia in a patient in need thereof comprising administering to said patient an effective hypcholesterolemic, antiatherosclerotic or 30 hypotriglyceridemic amount of a compound of the Formula (I)

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wherein

A₁ and A₂ are each independently hydrogen or -COOR₄ wherein R₄ is hydrogen; -CH₂O-C(O)C(CH₃)₃; a C₁-C₄ alkyl; an Ar-Y- group wherein Ar is aryl and Y is a C₀-C₄ alkyl; or diphenylmethyl; with the proviso that where A₁ is hydrogen, A₂ is -COOR₄, and where A₁ is -COOR₄, A₂ is hydrogen;

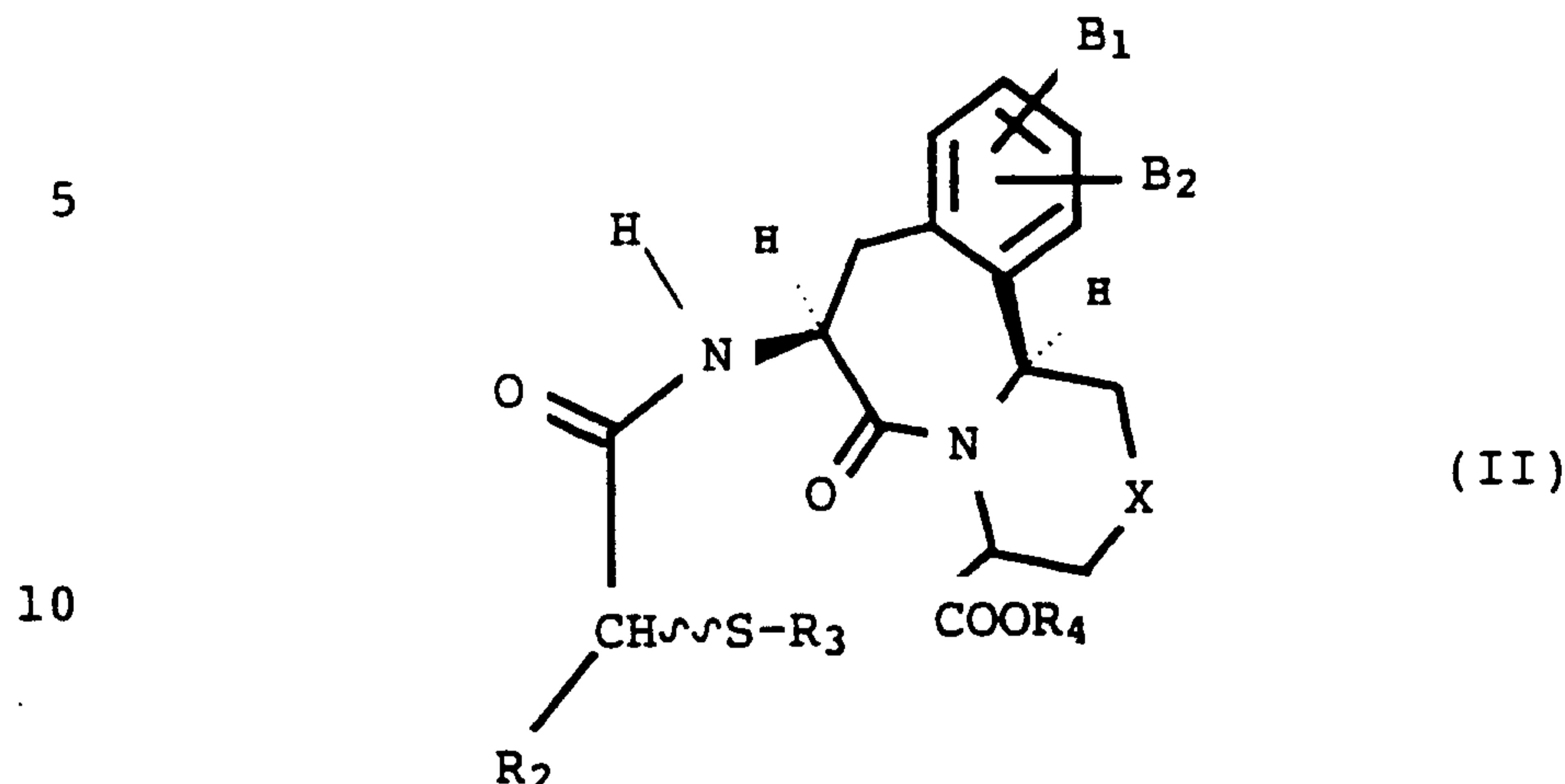
B₁ and B₂ are each independently hydrogen; hydroxy; -OR₅ wherein R₅ is a C₁-C₄ alkyl or an Ar-Y- group; or, where B₁ and B₂ are attached to adjacent carbon atoms, B₁ and B₂ can be taken together with said adjacent carbons to form a benzene ring or methylenedioxy;

R₂ is hydrogen, C₁-C₈ alkyl, -CH₂OCH₂CH₂OCH₃ or an Ar-Y- group;

R₃ is hydrogen, acetyl, -CH₂O-C(O)C(CH₃)₃ or benzoyl; and n is an integer 0 or 1.

The present invention further provides a method of treating hypercholesterolemia, atherosclerosis and hypertriglyceridemia in a patient in need thereof comprising administering to said patient an effective hypocholesterolemic, antiatherosclerotic or hypotriglyceridemic amount of a compound of the Formula (II) wherein

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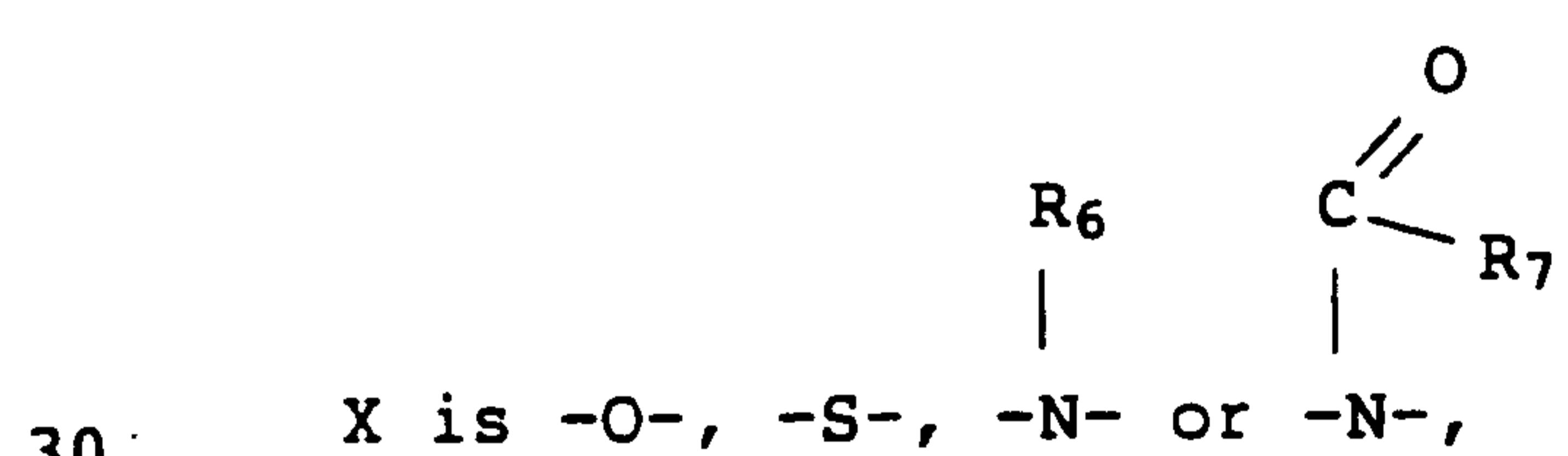
15 B_1 and B_2 are each independently hydrogen; hydroxy; -OR₅ wherein R₅ is a C₁-C₄ alkyl or an Ar-Y- group wherein Ar is aryl and Y is a C₀-C₄ alkyl; or, where B_1 and B_2 are attached together with said adjacent carbons to form a benzene ring or methylenedioxy;

20 R₂ is hydrogen, C₁-C₈ alkyl, -CH₂OCH₂CH₂OCH₃ or an Ar-Y- group;

R₃ is hydrogen, acetyl, -CH₂O-C(O)C(CH₃)₃ or benzoyl;

R₄ is hydrogen, a C₁-C₄ alkyl or an Ar-Y- group, -CH₂O-C(O)C(CH₃)₃ or diphenylmethyl; and

25



wherein R₆ is hydrogen, a C₁-C₄ alkyl or an Ar-Y- group and R₇ is -CF₃, C₁-C₁₀ alkyl or an Ar-Y- group.

35 DETAILED DESCRIPTION OF THE INVENTION

As used herein, the term "C₁-C₄ alkyl" refers to a saturated straight or branched chain hydrocarbyl radical of

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one to four carbon atoms and includes methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tertiary butyl and the like. The terms "C₁-C₈ alkyl" and "C₁-C₁₀ alkyl" refer to saturated 5 straight or branched chain hydrocarbyl radicals of one to eight and one to ten carbon atoms, respectively, including methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tertiary butyl, pentyl, isopentyl, hexyl, 2,3-dimethyl-2-butyl, heptyl, 2,2-dimethyl-3-pentyl, 2-methyl-2-hexyl, 10 octyl, 4-methyl-3-heptyl and the like.

As used herein, the term "Ar-Y-" refers to a radical wherein Ar is an aryl group and Y is a C₀-C₄ alkyl. The term "Ar" refers to a phenyl or naphthyl group unsubstituted or 15 substituted with from one to three substituents selected from the group consisting of methylenedioxy, hydroxy, C₁-C₄ alkoxy, fluoro and chloro. The term "C₀-C₄ alkyl" refers to a saturated straight or branched chain hydrocarbyl radical of zero to four carbon atoms and includes a bond, methyl, 20 ethyl, propyl, isopropyl, n-butyl, isobutyl, tertiary butyl and the like. Specifically included within the scope of the term "Ar-Y-" are phenyl, naphthyl, phenylmethyl or benzyl, phenylethyl, p-methoxybenzyl, 3,4-methylenedioxy, p-fluorobenzyl and p-chlorobenzyl.

25

As used herein, the designation "ss" refers to a bond to a chiral atom for which the stereochemistry is not designated.

30 As used herein, the term "patient" refers to warm-blooded animals or mammals, including rabbits, rodents, monkeys and humans, who are in need of treatment for hypertriglyceridemia atherosclerosis or hypercholesterolemia, such as, for example, in the case of 35 a patient suffering from familial hyperlipidemia. Patients are in need of treatment for hypertriglyceridemia, for example, in the case of a patient suffering from Type IV Hyperlipoproteinemia (indicating elevated VLDL) according

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to the Fredrickson classification [Fredrickson and Levy, FAMILIAL HYPERLIPOPROTEINEMIA, in *The Metabolic Basis of Inherited Disease*, 3rd ed. (Stanbury, J. B.; Wyngaarden, J. B.; and 5 Fredrickson, D. S.; eds.) McGraw-Hill Book Co., New York, 1972, pp. 545-614].

Hypercholesterolemia is a disease state characterized by levels of serum cholesterol or of LDL cholesterol which 10 are elevated by a clinically significant amount over that considered normal by those of ordinary skill in the art. The identification of those patients who are in need of treatment for hypercholesterolemia is well within the ability and knowledge of one skilled in the art. For 15 example, individuals who have serum cholesterol levels or LDL cholesterol levels, as determined by clinical laboratory tests, which are substantially and chronically elevated over that considered normal by those of ordinary skill in the art, are patients in need of treatment for 20 hypercholesterolemia. By way of further example, individuals who are at risk of developing hypercholesterolemia can also be patients in need of treatment for hypercholesterolemia. A clinician skilled in the art can readily identify, by the use of clinical tests, 25 physical examination and medical/family history, those patients who are suffering from hypercholesterolemia and those who are at risk of developing hypercholesterolemia and thus readily determine if an individual is a patient in need of treatment for hypercholesterolemia.

30

An effective hypocholesterolemic amount of a compound of Formula (I) or (II) is an amount which is effective in reducing serum cholesterol levels or LDL cholesterol levels in a patient in need thereof. As such, successful treatment 35 of a patient for hypercholesterolemia is understood to include reducing a patient's serum cholesterol or LDL cholesterol levels. Successful treatment for hypercholesterolemia is also understood to include

prophylaxis in preventing clinically significant elevations in serum cholesterol or in LDL cholesterol levels in a patient who is at risk of the development of 5 hypercholesterolemia.

Atherosclerosis is a disease state characterized by the development and growth of atherosclerotic lesions or plaque. The identification of those patients who are in need of 10 treatment for atherosclerosis is well within the ability and knowledge of one skilled in the art. For example, individuals who are either suffering from clinically significant atherosclerosis or who are at risk of developing clinically significant atherosclerosis are patients in need 15 of treatment for atherosclerosis. A clinician skilled in the art can readily determine, by the use of clinical tests, physical examination and medical/family history, if an individual is a patient in need of treatment for atherosclerosis.

20

An effective antiatherosclerotic amount of a compound of Formula (I) or (II) is an amount which is effective in inhibiting development or growth of atherosclerosis in a patient in need thereof. As such, successful treatment of a 25 patient for atherosclerosis is understood to include effectively slowing, interrupting, arresting, or stopping atherosclerotic lesion or plaque development or growth and does not necessarily indicate a total elimination of the atherosclerosis. It is further understood and appreciated 30 by those skilled in the art that successful treatment for atherosclerosis can include prophylaxis in preventing atherosclerotic lesion or plaque formation.

An effective antiatherosclerotic or hypcholesterolemic 35 dose can be readily determined by the use of conventional techniques and by observing results obtained under analogous circumstances. In determining the effective dose, a number of factors are considered including, but not limited to:

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the species of patient; its size, age, and general health; the specific disease involved; the degree of or involvement or the severity of the disease; the response of the 5 individual patient; the particular compound administered; the mode of administration; the bioavailability characteristics of the preparation administered; the dose regimen selected; and the use of concomitant medication.

10 An effective antiatherosclerotic or hypocholesterolemic amount of a compound of Formula (I) or (II) will generally vary from about 1 milligram per kilogram of body weight per day (mg/kg/day) to about 1000 milligrams per kilogram of body weight per day (1 gm/kg/day). A daily dose of from 15 about 2 mg/kg to about 200 mg/kg is preferred.

In effecting treatment of a patient, a compound of Formula (I) or (II) can be administered in any form or mode which makes the compound bioavailable in effective amounts, 20 including oral and parenteral routes. For example, the compound can be administered orally, subcutaneously, intramuscularly, intravenously, transdermally, intranasally, rectally, and the like. Oral administration is generally preferred. One skilled in the art of preparing formulations 25 can readily select the proper form and mode of administration depending upon the disease state to be treated, the stage of the disease, and other relevant circumstances.

30 Compounds of Formula (I) or (II) can be administered in the form of pharmaceutical compositions or medicaments which are made by combining the compound of Formula (I) or (II) with pharmaceutically acceptable carriers or excipients, the proportion and nature of which are determined by the chosen 35 route of administration, and standard pharmaceutical practice.

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Hypertriglyceridemia is a disease state characterized by levels of plasma triglycerides which are elevated by a clinically significant amount over that considered normal by 5 those of ordinary skill in the art. The identification of those patients who are in need of treatment for hypertriglyceridemia is well within the ability and knowledge of one skilled in the art. For example, individuals who have plasma triglyceride levels, as 10 determined by clinical laboratory tests, which are substantially and chronically elevated over that considered normal by those of ordinary skill in the art, are patients in need of treatment for hypertriglyceridemia. By way of further example, individuals who are at risk of developing 15 hypertriglyceridemia can also represent patients in need of treatment for hypertriglyceridemia. A clinician skilled in the art can readily identify, by the use of clinical tests, physical examination and medical/family history, those patients who are suffering from hypertriglyceridemia and 20 those who are at risk of developing hypertriglyceridemia and thus readily determine if an individual is a patient in need of treatment for hypertriglyceridemia.

An effective hypotriglyceridemic amount of a compound of 25 Formula (I) or (II) is an amount which is effective in reducing plasma triglyceride levels in a patient in need thereof. As such, successful treatment of a patient for hypertriglyceridemia is understood to include reducing a patient's plasma triglyceride levels. Successful treatment 30 for hypertriglyceridemia is also understood to include prophylaxis in preventing clinically significant elevations in plasma triglyceride levels in a patient who is at risk of the development of hypertriglyceridemia.

35 An effective hypotriglyceridemic dose can be readily determined by the use of conventional techniques and by observing results obtained under analogous circumstances. In determining the effective dose, a number of factors are

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considered including, but not limited to: the species of patient; its size, age, and general health; the specific disease involved; the degree of or involvement or the 5 severity of the disease; the response of the individual patient; the particular compound administered; the mode of administration; the bioavailability characteristics of the preparation administered; the dose regimen selected; and the use of concomitant medication.

10

An effective hypotriglyceridemic amount of a compound of Formula (I) or (II) will generally vary from about 1 milligram per kilogram of body weight per day (mg/kg/day) to about 1000 milligrams per kilogram of body weight per day 15 (1.0 gm/kg/day). A daily dose of from about 1 mg/kg to about 200 mg/kg is preferred.

In effecting treatment of a patient, a compound of Formula (I) or (II) can be administered in any form or mode 20 which makes the compound bioavailable in effective amounts, including oral and parenteral routes. For example, the compound can be administered orally, subcutaneously, intramuscularly, intravenously, transdermally, intranasally, rectally, and the like. Oral administration is generally 25 preferred. One skilled in the art of preparing formulations can readily select the proper form and mode of administration depending upon the disease state to be treated, the stage of the disease, and other relevant circumstances.

30

A compound of Formula (I) or (II) can be administered in the form of pharmaceutical compositions or medicaments which are made by combining a compound of Formula (I) or (II) with pharmaceutically acceptable carriers or excipients, the 35 proportion and nature of which are determined by the chosen route of administration, and standard pharmaceutical practice.

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The pharmaceutical compositions or medicaments are prepared in a manner well known in the pharmaceutical art. The carrier or excipient may be a solid, semi-solid, or 5 liquid material which can serve as a vehicle or medium for the active ingredient. Suitable carriers or excipients are well known in the art. The pharmaceutical composition may be adapted for oral or parenteral use and may be administered to the patient in the form of tablets, 10 capsules, suppositories, solution, suspensions, or the like.

The pharmaceutical compositions may be administered orally, for example, with an inert diluent or with an edible carrier. They may be enclosed in gelatin capsules or 15 compressed into tablets. For the purpose of oral therapeutic administration, a compound Formula (I) or (II) may be incorporated with excipients and used in the form of tablets, troches, capsules, elixirs, suspensions, syrups, wafers, chewing gums and the like. These preparations 20 should contain at least 4% of the compound of formula (I) or (II), the active ingredient, but may be varied depending upon the particular form and may conveniently be between 4% to about 70% of the weight of the unit. The amount of the active ingredient present in compositions is such that a 25 unit dosage form suitable for administration will be obtained.

The tablets, pills, capsules, troches and the like may also contain one or more of the following adjuvants: 30 binders, such as microcrystalline cellulose, gum tragacanth or gelatin; excipients, such as starch or lactose, disintegrating agents such as alginic acid, Primogel™, corn starch and the like; lubricants, such as magnesium stearate or Sterotex; glidants, such as colloidal silicon dioxide; 35 and sweetening agents, such as sucrose or saccharin may be added or flavoring agents, such as peppermint, methyl salicylate or orange flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of

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the above type, a liquid carrier such as polyethylene glycol or a fatty oil. Other dosage unit forms may contain other various materials which modify the physical form of the 5 dosage unit, for example, as coatings. Thus, tablets or pills may be coated with sugar, shellac, or other enteric coating agents. A syrup may contain, in addition to the active ingredient, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors. Materials 10 used in preparing these various compositions should be pharmaceutically pure and non-toxic in the amounts used.

For the purpose of parenteral administration, a compound of Formula (I) or (II) may be incorporated into a solution 15 or suspension. These preparations should contain at least 0.1% of a compound of the invention, but may be varied to be between 0.1 and about 50% of the weight thereof. The amount of the active ingredient present in such compositions is such that a suitable dosage will be obtained.

20

The solutions or suspensions may also include one or more of the following adjuvants: sterile diluents such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other 25 synthetic solvents; antibacterial agents such as benzyl alcohol or methyl paraben; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylene diaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of toxicity such 30 as sodium chloride or dextrose. The parenteral preparation can be enclosed in ampules, disposable syringes or multiple dose vials made of glass or plastic.

The compounds of Formula (I) and (II) can be prepared as 35 described in European Patent Application, Publication Number 0 481 522 A1, published April 22, 1992.

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The following example illustrates the utility of the mercaptoacetylamide derivatives of the present invention as hypocholesterolemic, antiatherosclerotic and 5 hypocholesterolemic agents. This example is understood to be illustrative only and is not intended to limit the scope of the present invention in any way.

Example 1

10 Rabbit Test for Hypocholesterolemic, Antiatherosclerotic and Hypotriglyceridemic Activities

Feed rabbits a high cholesterol (1%) diet for eight weeks, supplementing the diets of certain rabbits with the agent of interest. At the end of eight weeks, sacrifice the rabbits, 15 collect the serum and determine cholesterol and triglyceride levels by standard methods [Hypertension 15:327-331, 1990].

Dissect the aorta of each rabbit from the ascending arch to the iliac bifurcation, clean and prepare for staining with 20 Sudan IV to determine areas of atherosclerotic lesion with the use of image analysis.

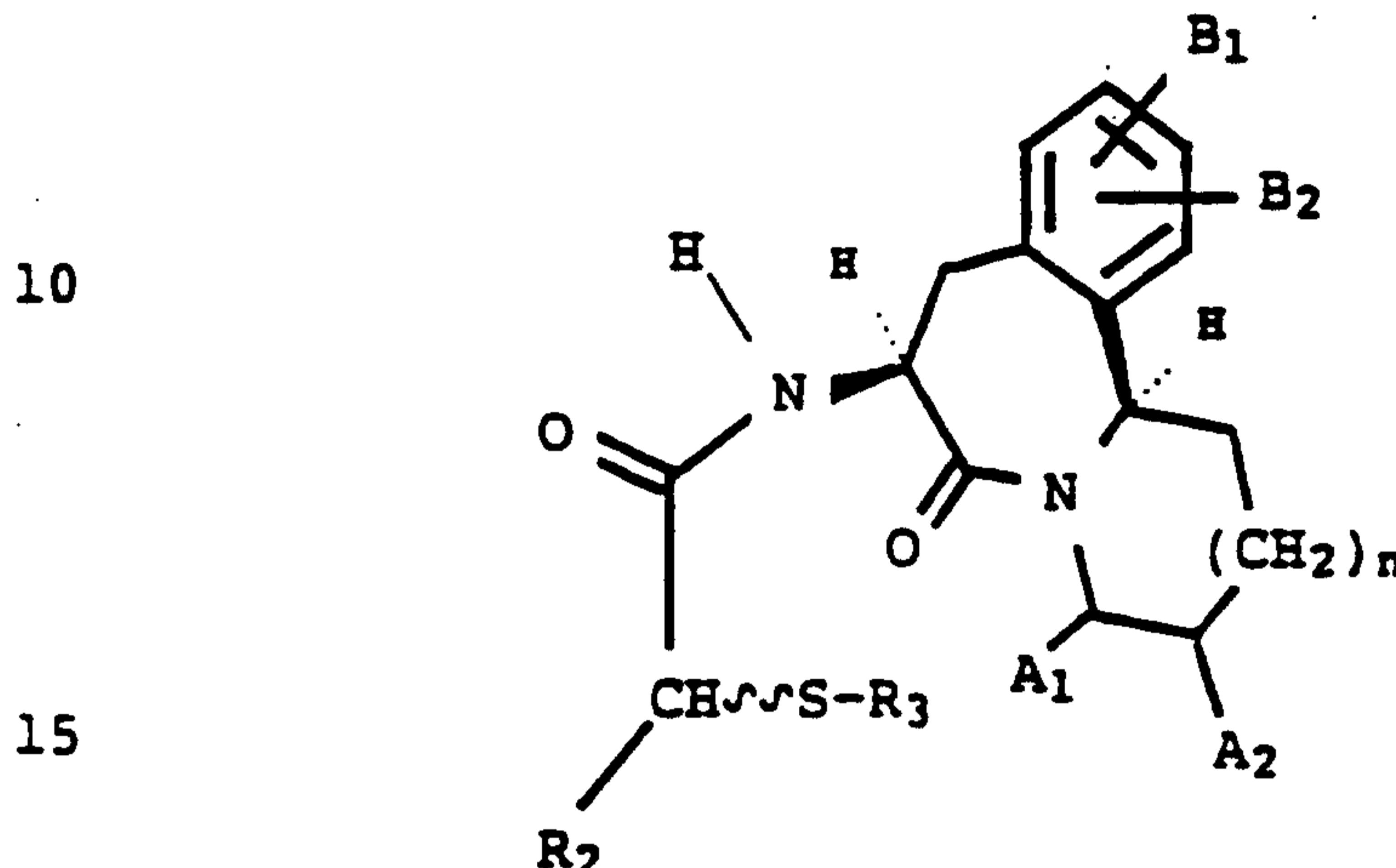
Make statistical comparisons between the control and drug-treated groups to determine the activity of the agent of 25 interest.

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WHAT IS CLAIMED IS:

1. Use of a therapeutically effective
 5 hypocholesterolemic amount of a compound of the Formula



wherein

20 A_1 and A_2 are each independently hydrogen or $-COOR_4$
 wherein R_4 is hydrogen; $-CH_2O-C(O)C(CH_3)_3$; a C_1-C_4
 alkyl; an $Ar-Y-$ group wherein Ar is aryl and Y is a
 C_0-C_4 alkyl; or diphenylmethyl; with the proviso
 that where A_1 is hydrogen, A_2 is $-COOR_4$, and where A_1
 25 is $-COOR_4$, A_2 is hydrogen;

B_1 and B_2 are each independently hydrogen; hydroxy;
 $-OR_5$ wherein R_5 is a C_1-C_4 alkyl or an $Ar-Y-$ group;
 or, where B_1 and B_2 are attached to adjacent carbon
 atoms, B_1 and B_2 can be taken together with said
 30 adjacent carbons to form a benzene ring or
 methylenedioxy;

R_2 is hydrogen, C_1-C_8 alkyl, $-CH_2OCH_2CH_2OCH_3$ or an $Ar-Y-$
 group;

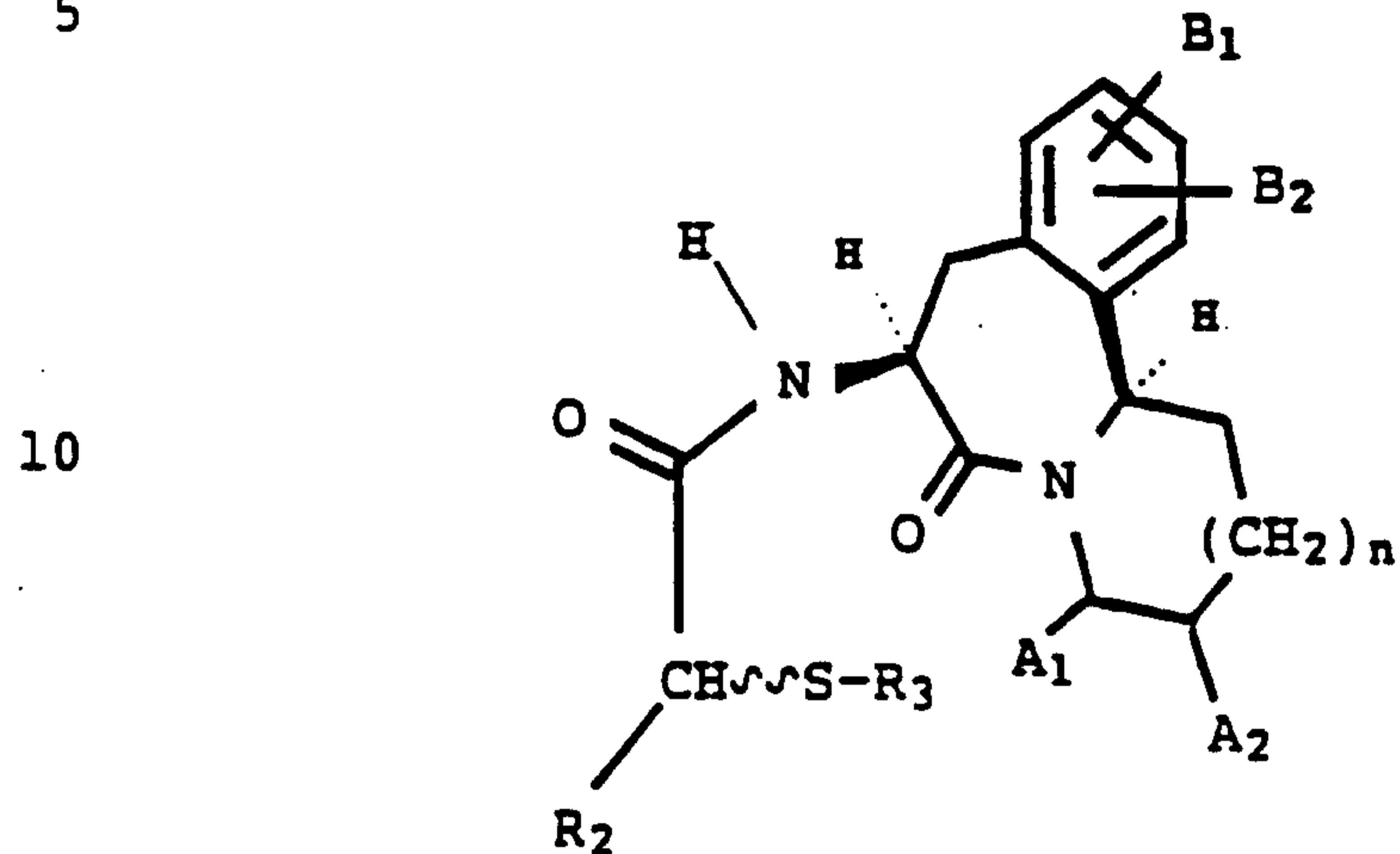
R_3 is hydrogen, acetyl, $-CH_2O-C(O)C(CH_3)_3$ or benzoyl; and
 35 n is an integer 0 or 1,
 for lowering total serum cholesterol in a patient in
 need thereof.

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2. Use of a therapeutically effective hypocholesterolemic amount of a compound of the Formula

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10

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wherein

A₁ and A₂ are each independently hydrogen or -COOR₄ wherein R₄ is hydrogen; -CH₂O-C(O)C(CH₃)₃; a C₁-C₄ alkyl; an Ar-Y- group wherein Ar is aryl and Y is a C₀-C₄ alkyl; or diphenylmethyl; with the proviso that where A₁ is hydrogen, A₂ is -COOR₄, and where A₁ is -COOR₄, A₂ is hydrogen;

B₁ and B₂ are each independently hydrogen; hydroxy; -OR₅ wherein R₅ is a C₁-C₄ alkyl or an Ar-Y- group; or, where B₁ and B₂ are attached to adjacent carbon atoms, B₁ and B₂ can be taken together with said adjacent carbons to form a benzene ring or methylenedioxy;

R₂ is hydrogen, C₁-C₈ alkyl, -CH₂OCH₂CH₂OCH₃ or an Ar-Y- group;

R₃ is hydrogen, acetyl, -CH₂O-C(O)C(CH₃)₃ or benzoyl; and n is an integer 0 or 1,

for treating a patient for hypercholesterolemia.

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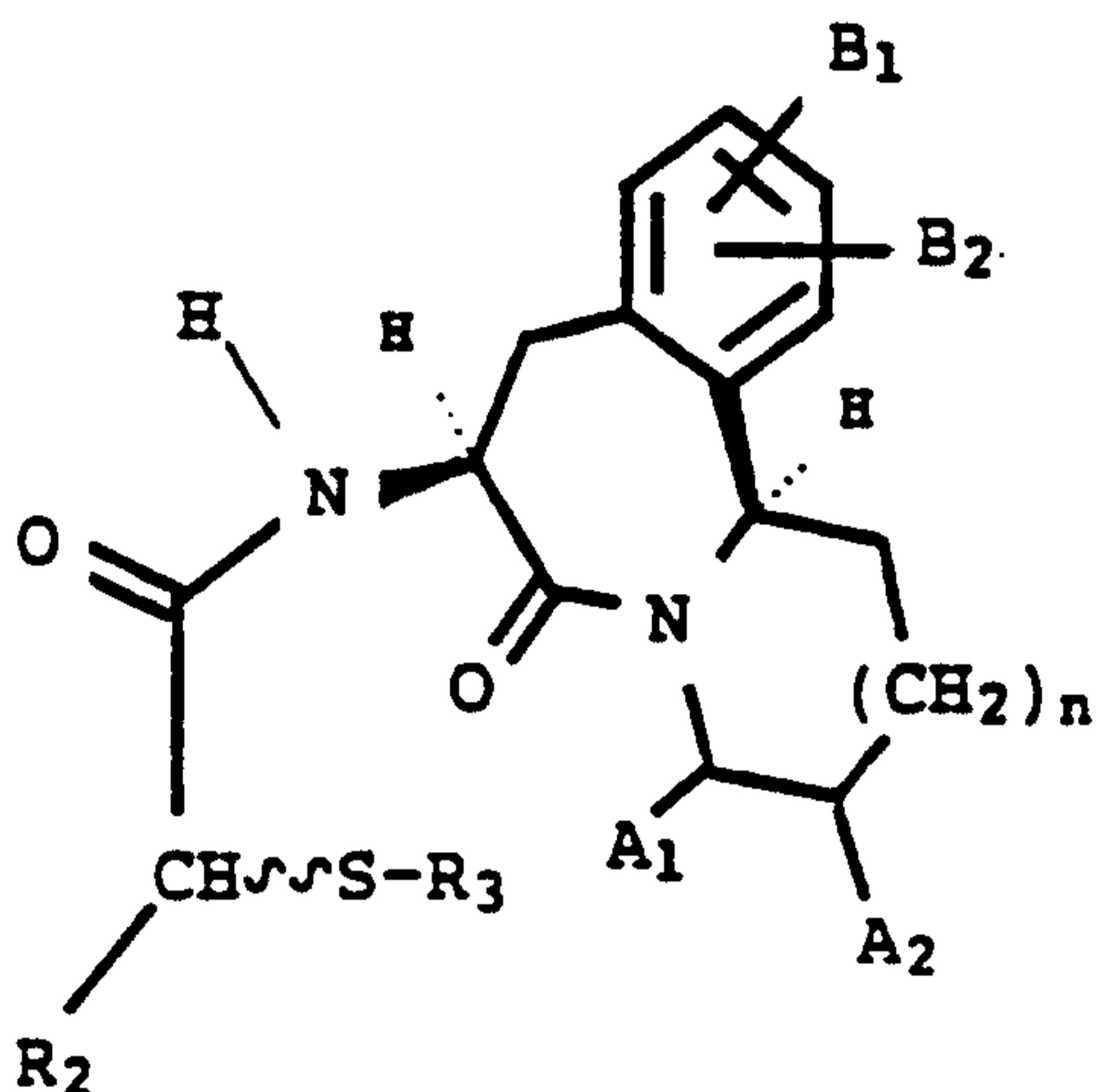
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3. Use of a therapeutically effective
hypotriglyceridemic amount of a compound of the Formula

5

10

15



wherein

20

A₁ and A₂ are each independently hydrogen or -COOR₄
wherein R₄ is hydrogen; -CH₂O-C(O)C(CH₃)₃; a C₁-C₄
alkyl; an Ar-Y- group wherein Ar is aryl and Y is a
C₀-C₄ alkyl; or diphenylmethyl; with the proviso
that where A₁ is hydrogen, A₂ is -COOR₄, and where A₁
is -COOR₄, A₂ is hydrogen;

25

B₁ and B₂ are each independently hydrogen; hydroxy;
-OR₅ wherein R₅ is a C₁-C₄ alkyl or an Ar-Y- group;
or, where B₁ and B₂ are attached to adjacent carbon
atoms, B₁ and B₂ can be taken together with said
adjacent carbons to form a benzene ring or
methylenedioxy;

30

R₂ is hydrogen, C₁-C₈ alkyl, -CH₂OCH₂CH₂OCH₃ or an Ar-Y-
group;

35

R₃ is hydrogen, acetyl, -CH₂O-C(O)C(CH₃)₃ or benzoyl; and
n is an integer 0 or 1,
for lowering plasma triglycerides in a patient in
need thereof.

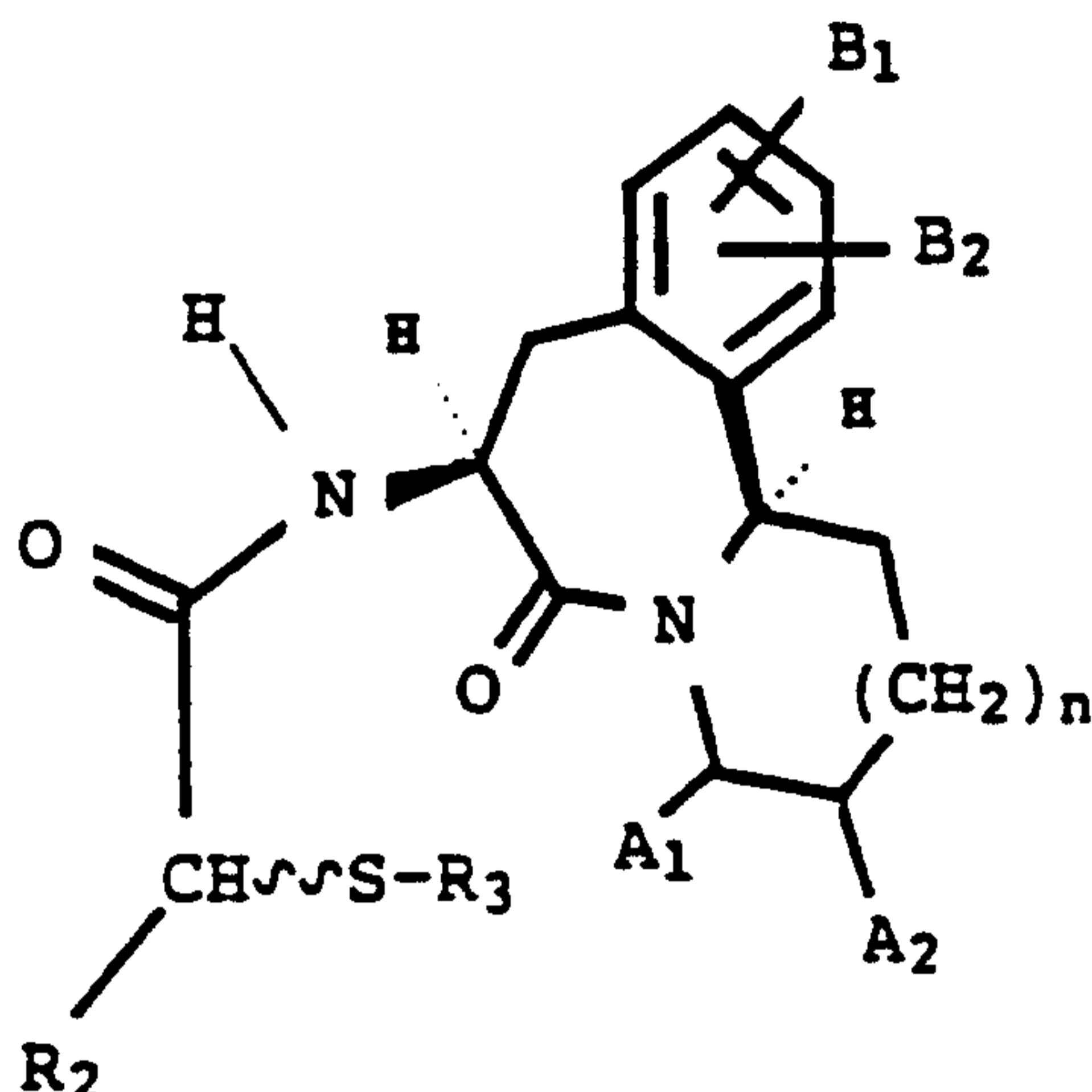
A

4. Use of a therapeutically effective hypotriglyceridemic amount of a compound of the Formula

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10

15



wherein

20 A₁ and A₂ are each independently hydrogen or -COOR₄ wherein R₄ is hydrogen; -CH₂O-C(O)C(CH₃)₃; a C₁-C₄ alkyl; an Ar-Y- group wherein Ar is aryl and Y is a C₀-C₄ alkyl; or diphenylmethyl; with the proviso that where A₁ is hydrogen, A₂ is -COOR₄, and where A₁ is -COOR₄, A₂ is hydrogen;

25 B₁ and B₂ are each independently hydrogen; hydroxy; -OR₅ wherein R₅ is a C₁-C₄ alkyl or an Ar-Y- group; or, where B₁ and B₂ are attached to adjacent carbon atoms, B₁ and B₂ can be taken together with said adjacent carbons to form a benzene ring or methylenedioxy;

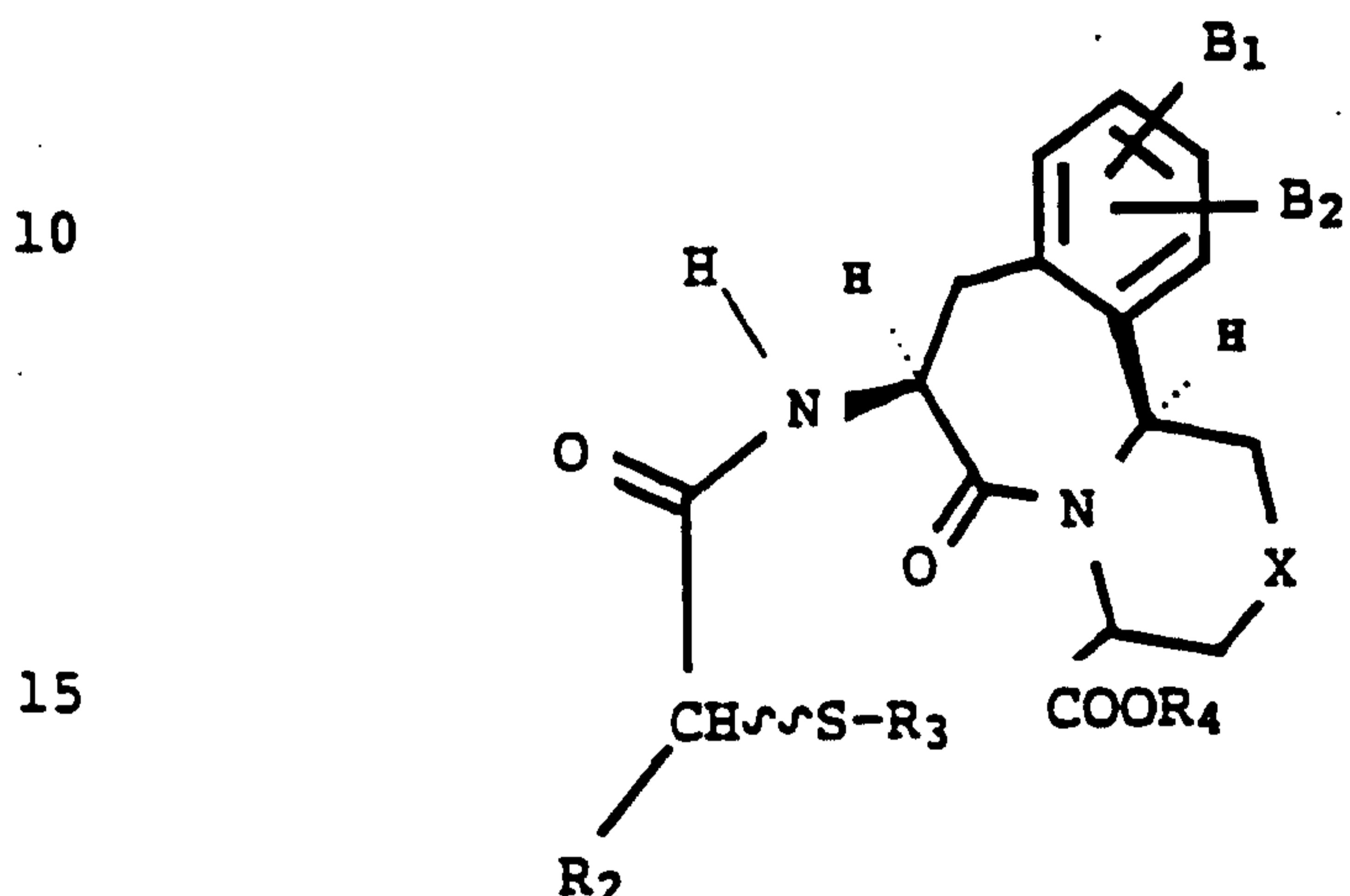
30 R₂ is hydrogen, C₁-C₈ alkyl, -CH₂OCH₂CH₂OCH₃ or an Ar-Y- group;

35 R₃ is hydrogen, acetyl, -CH₂O-C(O)C(CH₃)₃ or benzoyl; and n is an integer 0 or 1,
for treating a patient suffering from hypertriglyceridemia.

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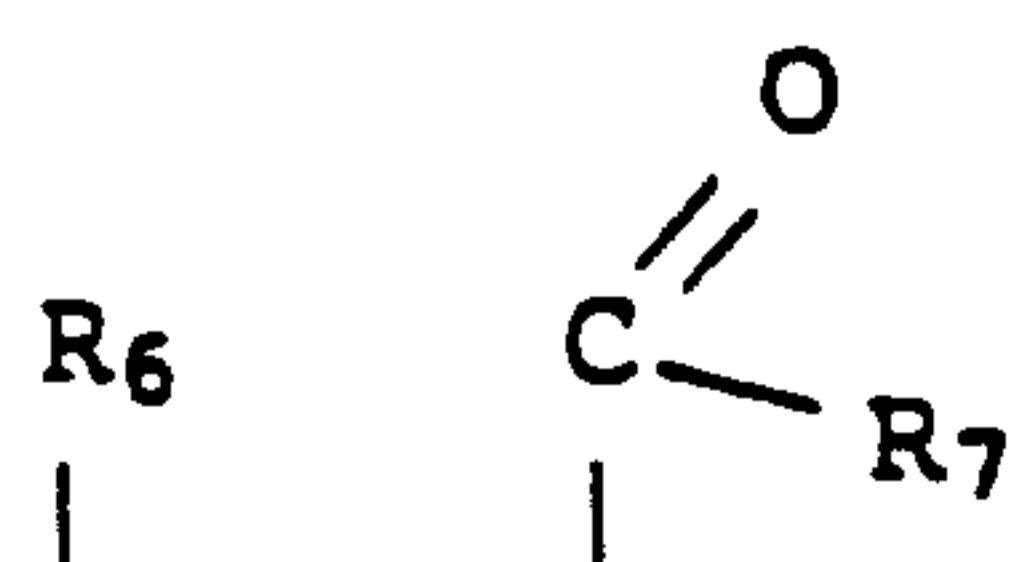
5. Use of a therapeutically effective hypcholesterolemic amount of a compound of the Formula

5



wherein

20 B₁ and B₂ are each independently hydrogen; hydroxy;
-OR₅ wherein R₅ is a C₁-C₄ alkyl or an Ar-Y- group
wherein Ar is aryl and Y is a C₀-C₄ alkyl; or, where
B₁ and B₂ are attached to adjacent carbon atoms, B₁
and B₂ can be taken together with said adjacent
25 carbons to form a benzene ring or methylenedioxy;
R₂ is hydrogen, C₁-C₈ alkyl, -CH₂OCH₂CH₂OCH₃ or an Ar-Y-
group;
R₃ is hydrogen, acetyl, -CH₂O-C(O)C(CH₃)₃ or benzoyl;
30 R₄ is hydrogen, a C₁-C₄ alkyl or an Ar-Y- group,
-CH₂O-C(O)C(CH₃)₃ or diphenylmethyl; and



35 X is -O-, -S-, -N- or -N-,

A

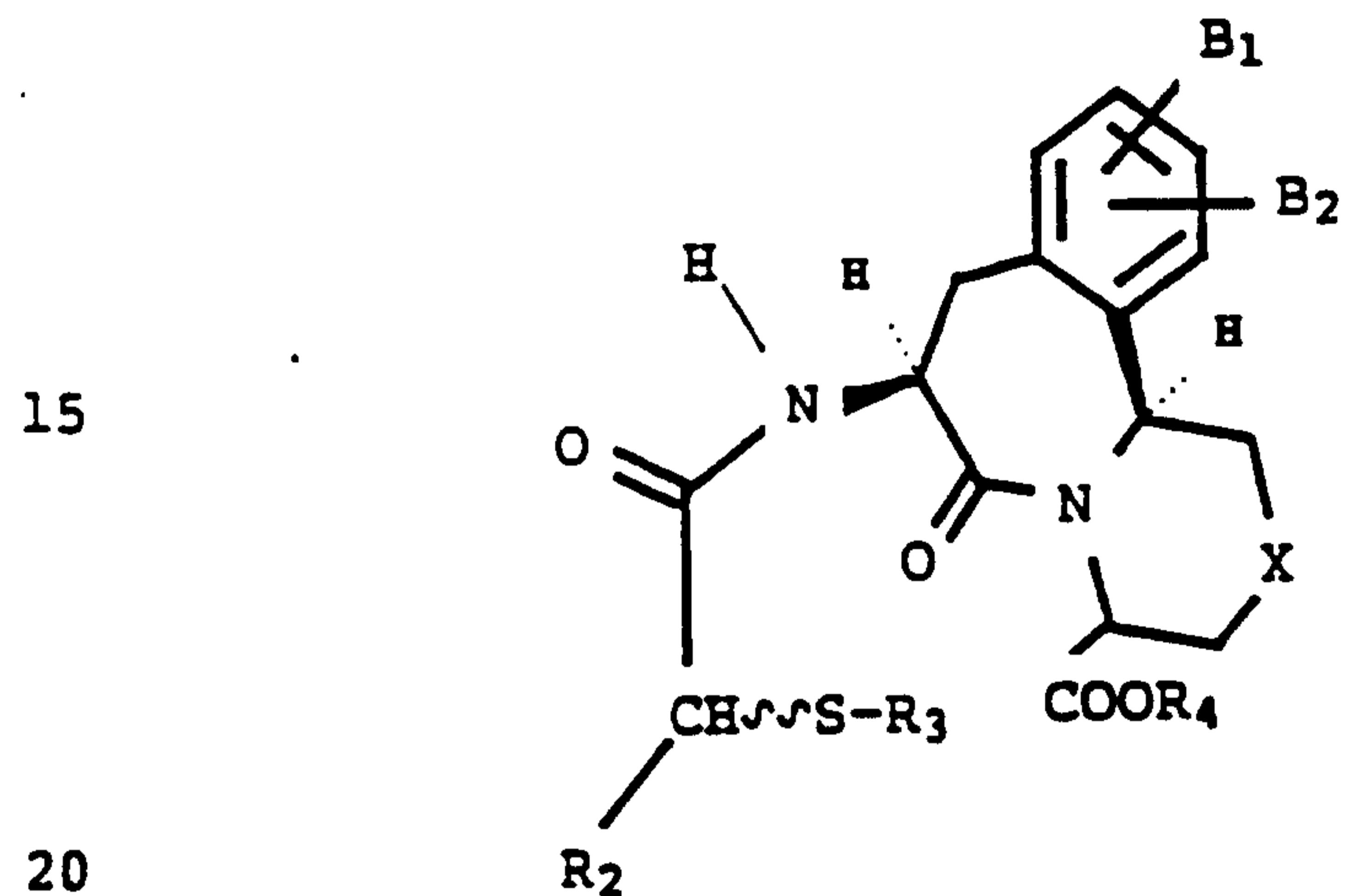
-21-

wherein R_6 is hydrogen, a C_1-C_4 alkyl or an $Ar-Y-$ group and R_7 is $-CF_3$, a C_1-C_{10} alkyl or an $Ar-Y-$ group,

5 for lowering total serum cholesterol in a patient in need thereof.

6. Use of therapeutically effective hypocholesterolemic amount of a compound of the Formula

10



wherein

25 B_1 and B_2 are each independently hydrogen; hydroxy; $-OR_5$ wherein R_5 is a C_1-C_4 alkyl or an $Ar-Y-$ group wherein Ar is aryl and Y is a C_0-C_4 alkyl; or, where B_1 and B_2 are attached to adjacent carbon atoms, B_1 and B_2 can be taken together with said adjacent carbons to form a benzene ring or methylenedioxy;

30 R_2 is hydrogen, C_1-C_8 alkyl, $-CH_2OCH_2CH_2OCH_3$ or an $Ar-Y-$ group;

R_3 is hydrogen, acetyl, $-CH_2O-C(O)C(CH_3)_3$ or benzoyl;

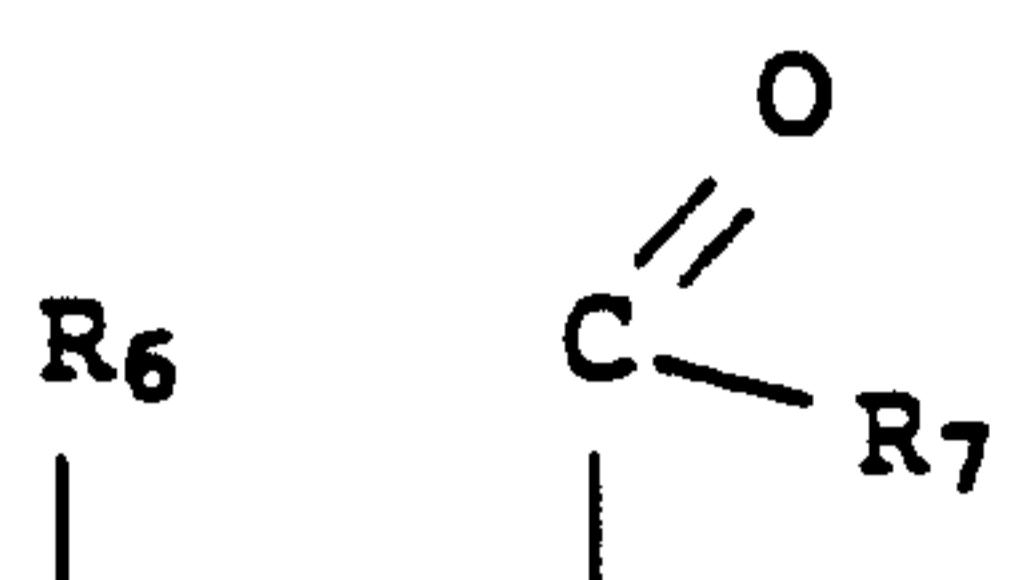
R_4 is hydrogen, a C_1-C_4 alkyl or an $Ar-Y-$ group,

$-CH_2O-C(O)C(CH_3)_3$ or diphenylmethyl; and

35

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5



X is -O-, -S-, -N- or -N-,

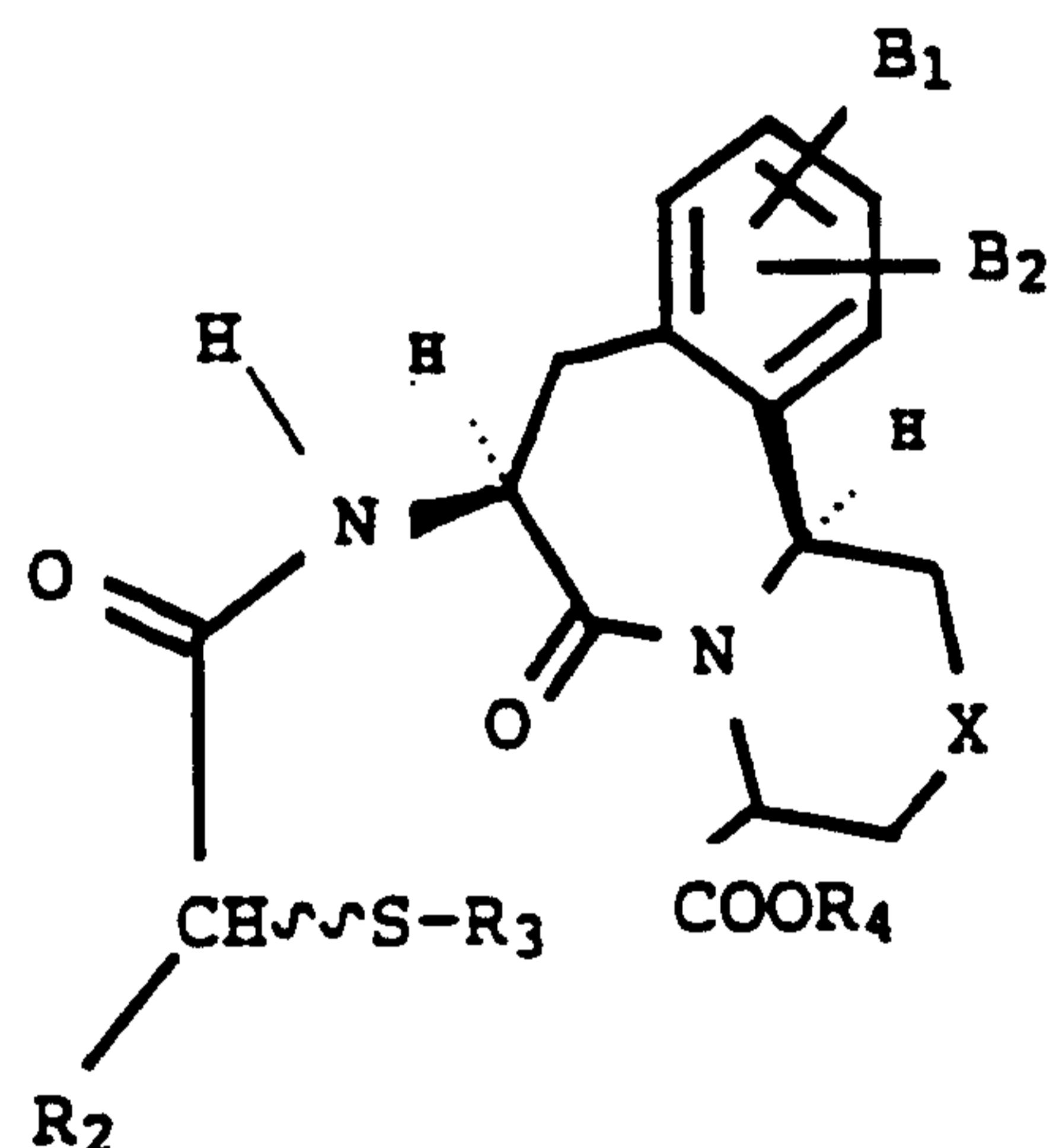
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wherein R₆ is hydrogen, a C₁-C₄ alkyl or an Ar-Y-group and R₇ is -CF₃, a C₁-C₁₀ alkyl or an Ar-Y-group,

for treating a patient for hypercholesterolemia.

15

7. Use of a therapeutically effective hypotriglyceridemic amount of a compound of the Formula

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25

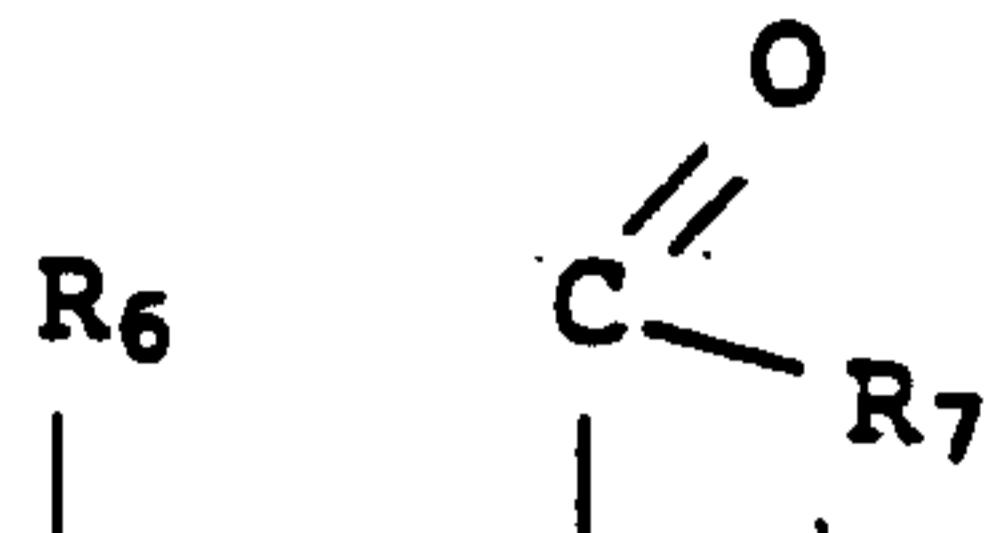
wherein

30 B₁ and B₂ are each independently hydrogen; hydroxy; -OR₅ wherein R₅ is a C₁-C₄ alkyl or an Ar-Y-group wherein Ar is aryl and Y is a C₀-C₄ alkyl; or, where B₁ and B₂ are attached to adjacent carbon atoms, B₁ and B₂ can be taken together with said adjacent carbons to form a benzene ring or methylenedioxy;
35 R₂ is hydrogen, C₁-C₈ alkyl, -CH₂OCH₂CH₂OCH₃ or an Ar-Y-group;
R₃ is hydrogen, acetyl, -CH₂O-C(O)C(CH₃)₃ or benzoyl;

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R₄ is hydrogen, a C₁-C₄ alkyl or an Ar-Y- group, -CH₂O-C(O)C(CH₃)₃ or diphenylmethyl; and

5



X is -O-, -S-, -N- or -N-,

10

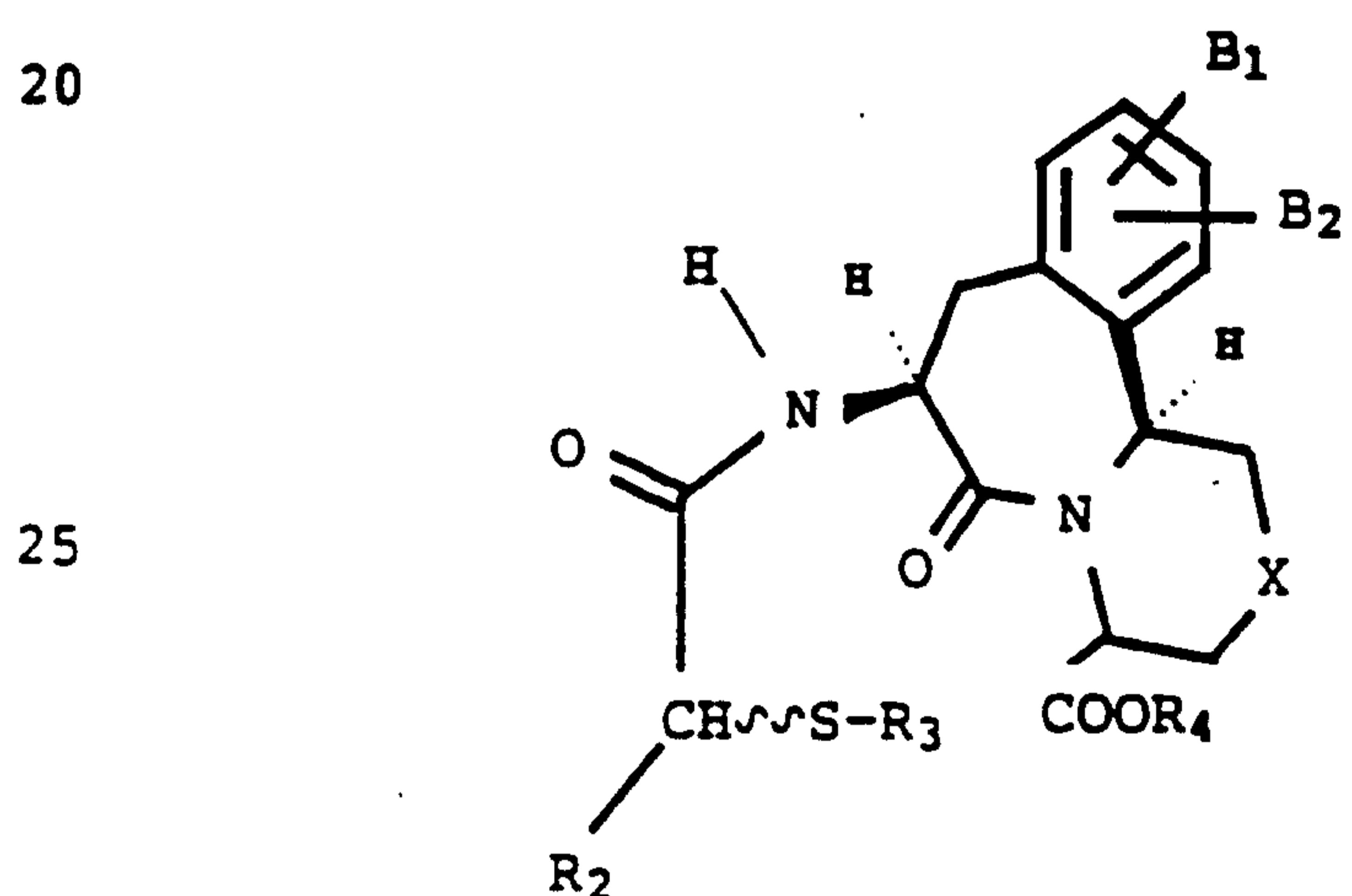
wherein R₆ is hydrogen, a C₁-C₄ alkyl or an Ar-Y- group and R₇ is -CF₃, a C₁-C₁₀ alkyl or an Ar-Y- group,

for lowering plasma triglycerides in a patient in need thereof.

15

8. Use of a therapeutically effective hypotriglyceridemic amount a compound of the Formula

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25

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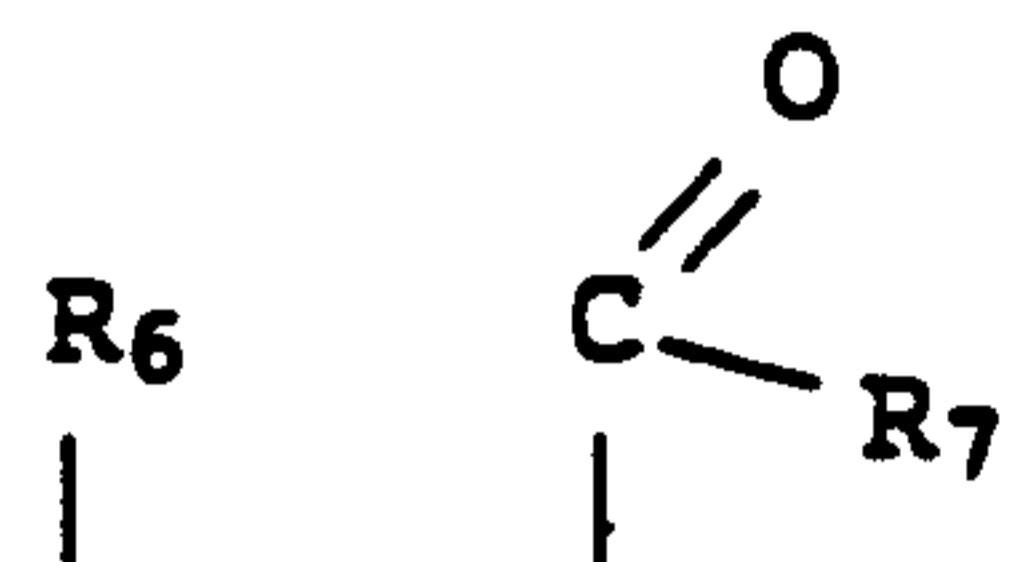
wherein

B₁ and B₂ are each independently hydrogen; hydroxy; -OR₅ wherein R₅ is a C₁-C₄ alkyl or an Ar-Y- group wherein Ar is aryl and Y is a C₀-C₄ alkyl; or, where B₁ and B₂ are attached to adjacent carbon atoms, B₁ and B₂ can be taken together with said adjacent carbons to form a benzene ring or methylenedioxy; R₂ is hydrogen, C₁-C₈ alkyl, -CH₂OCH₂CH₂OCH₃ or an Ar-Y-

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group;

R₃ is hydrogen, acetyl, -CH₂O-C(O)C(CH₃)₃ or benzoyl;R₄ is hydrogen, a C₁-C₄ alkyl or an Ar-Y- group,5 -CH₂O-C(O)C(CH₃)₃ or diphenylmethyl; and

10 X is -O-, -S-, -N- or -N-,

wherein R₆ is hydrogen, a C₁-C₄ alkyl or an Ar-Y-group and R₇ is -CF₃, a C₁-C₁₀ alkyl or an Ar-Y-group,

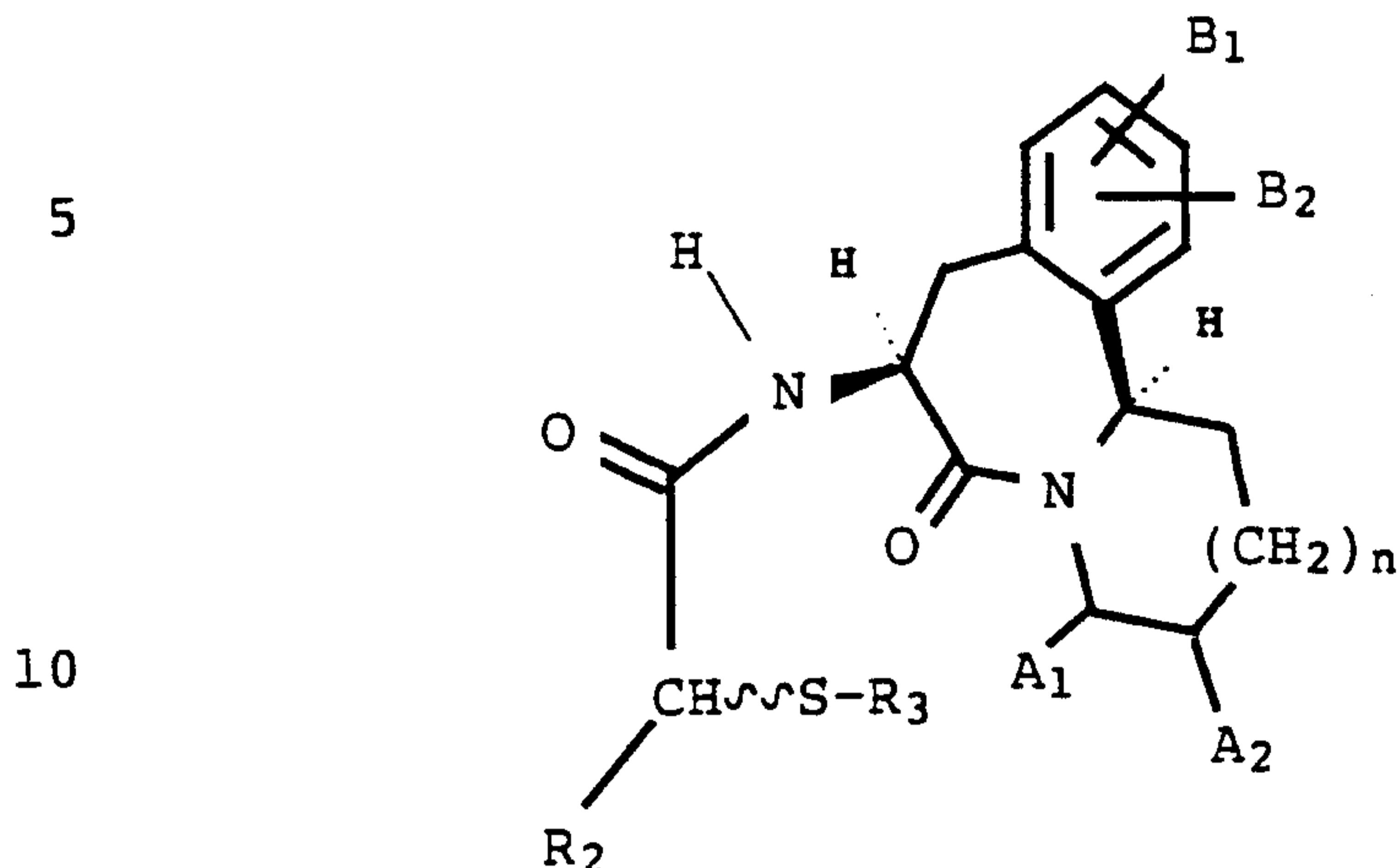
15

for treating a patient suffering from hypertriglyceridemia.

9. A use according to any of Claims 1-8 wherein the 20 compound is [4S-[4a, 7a(R*), 12b8]]-7-[(1-oxo-2(S)-acetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid.

25 10. A use according to any of Claims 1-8 wherein the compound is [4S-[4a, 7a(R*), 12b8]]-7-[(1-oxo-2(S)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid.

30 11. The use of a compound of the formula



wherein

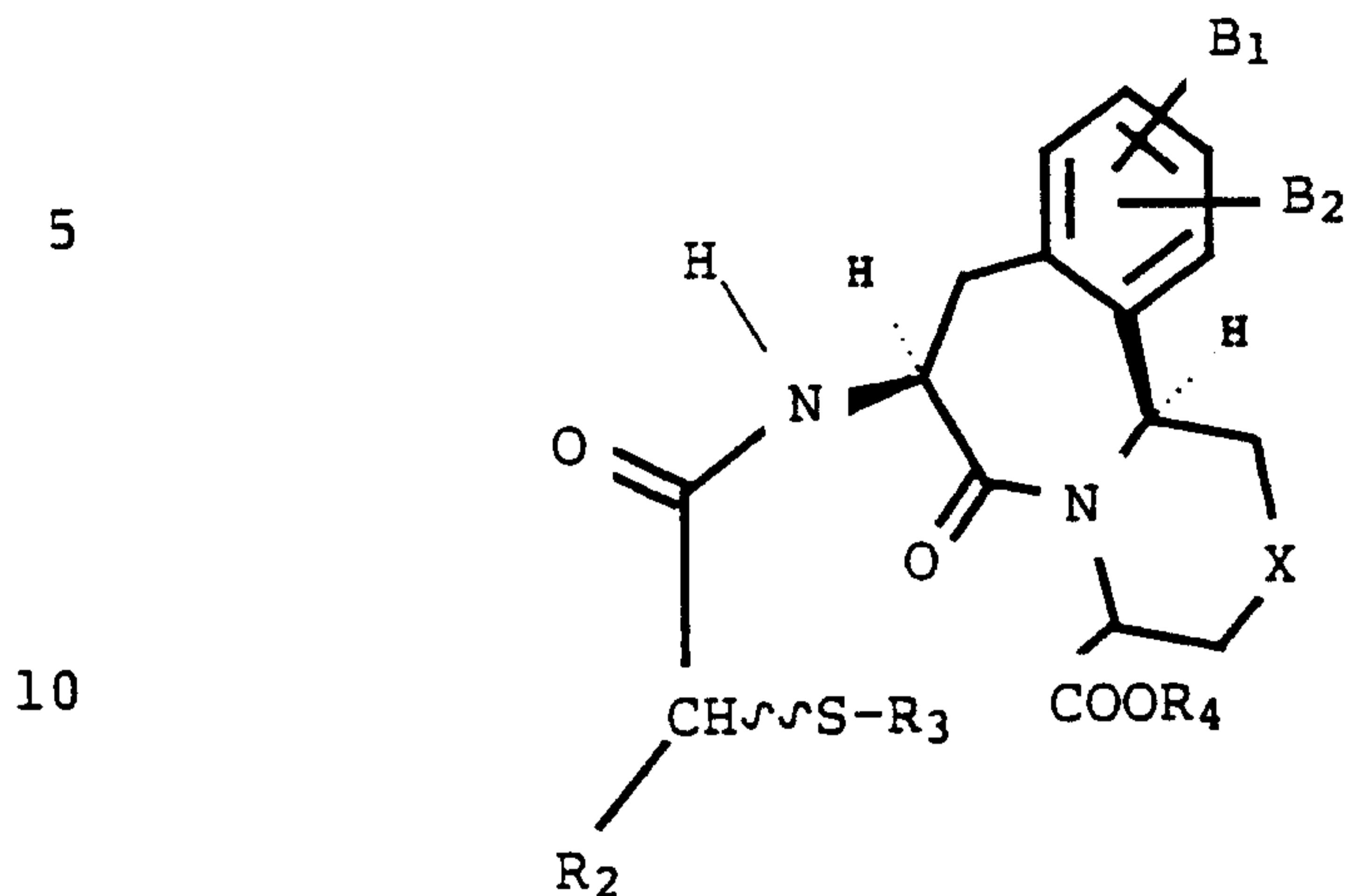
A₁ and A₂ are each independently hydrogen or -COOR₄ wherein R₄ is hydrogen; -CH₂O-C(O)C(CH₃)₃; a C₁-C₄ alkyl; an Ar-Y- group wherein Ar is aryl and Y is a C₀-C₄ alkyl; or diphenylmethyl; with the proviso that where A₁ is hydrogen, A₂ is -COOR₄, and where A₁ is -COOR₄, A₂ is hydrogen;

B₁ and B₂ are each independently hydrogen; hydroxy; -OR₅ wherein R₅ is a C₁-C₄ alkyl or an Ar-Y- group; or, where B₁ and B₂ are attached to adjacent carbon atoms, B₁ and B₂ can be taken together with said adjacent carbons to form a benzene ring or methylenedioxy;

R₂ is hydrogen, C₁-C₈ alkyl, -CH₂OCH₂CH₂OCH₃ or an Ar-Y- group;

R₃ is hydrogen, acetyl, -CH₂O-C(O)C(CH₃)₃ or benzoyl; and n is an integer 0 or 1, optionally in combination with a pharmaceutically acceptable carrier, for the preparation of a pharmaceutical composition for the treatment of hypercholesterolemia or hypertriglyceridemia, or atherosclerosis by virtue of the lowering of cholesterol and/or triglycerides.

12. The use of a compound of the formula

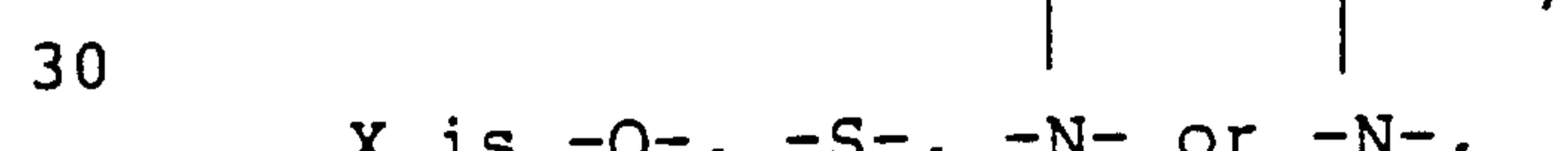


wherein

15 B₁ and B₂ are each independently hydrogen; hydroxy; -OR₅ wherein R₅ is a C₁-C₄ alkyl or an Ar-Y- group wherein Ar is aryl and Y is a C₀-C₄ alkyl; or, where B₁ and B₂ are attached to adjacent carbon atoms, B₁ and B₂ can be taken together with said adjacent carbons to form a benzene ring or methylenedioxy;

20 R₂ is hydrogen, C₁-C₈ alkyl, -CH₂OCH₂CH₂OCH₃ or an Ar-Y- group;

25 R₃ is hydrogen, acetyl, -CH₂O-C(O)C(CH₃)₃ or benzoyl; R₄ is hydrogen, a C₁-C₄ alkyl or an Ar-Y- group, -CH₂O-C(O)C(CH₃)₃ or diphenylmethyl; and



X is -O-, -S-, -N- or -N-,

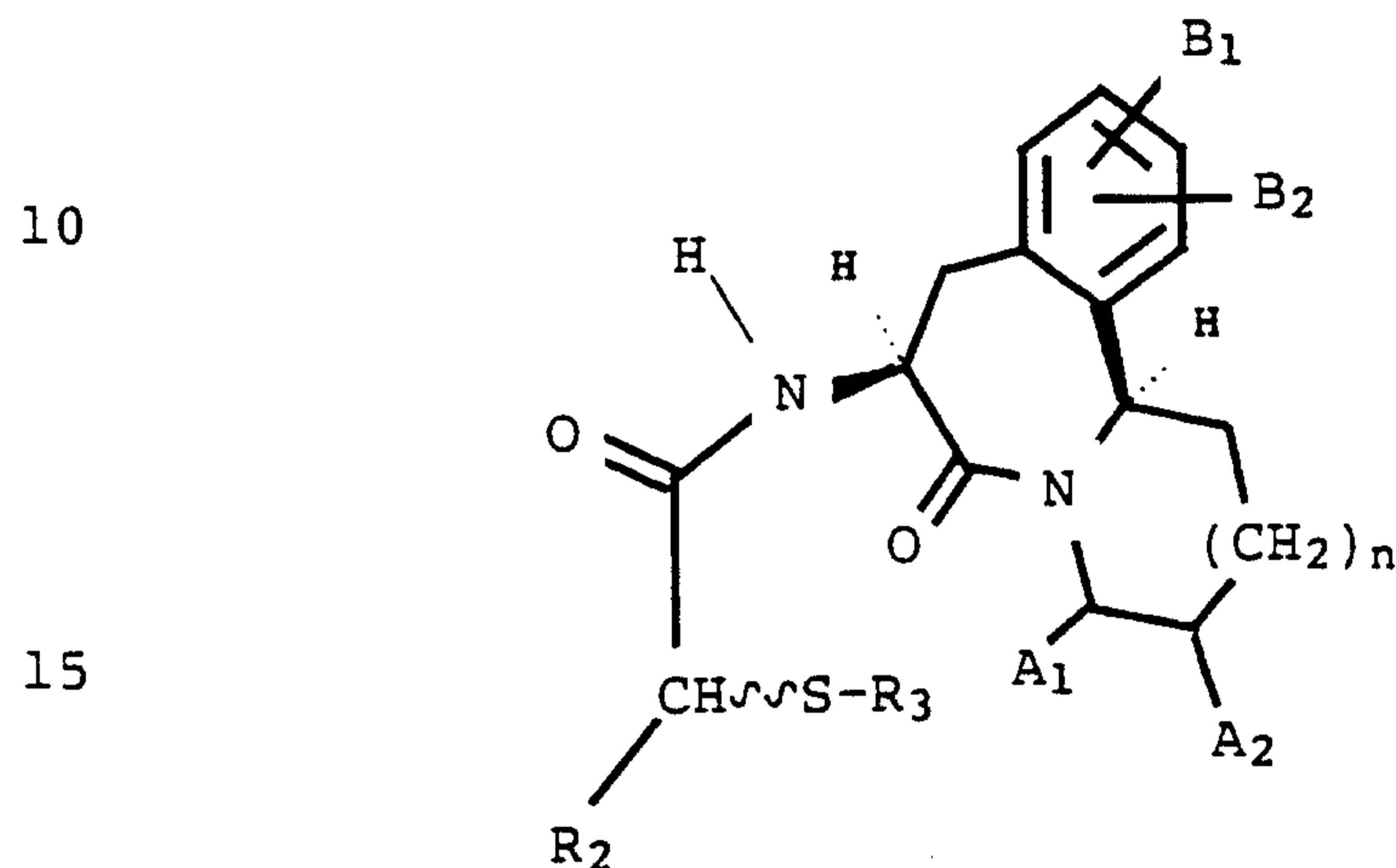
35 wherein R₆ is hydrogen, a C₁-C₄ alkyl or an Ar-Y- group and R₇ is -CF₃, a C₁-C₁₀ alkyl or an Ar-Y- group,

optionally in combination with a pharmaceutically acceptable carrier, for the preparation of a pharmaceutical composition for the treatment of hypercholesterolemia or

hypertriglyceridemia or hypertriglyceridemia, or atherosclerosis by virtue of the lowering of cholesterol and/or triglycerides.

5

13. The use of a compound of the formula



wherein

A₁ and A₂ are each independently hydrogen or -COOR₄ wherein R₄ is hydrogen; -CH₂O-C(O)C(CH₃)₃; a C₁-C₄ alkyl; an Ar-Y- group wherein Ar is aryl and Y is a C₀-C₄ alkyl; or diphenylmethyl; with the proviso that where A₁ is hydrogen, A₂ is -COOR₄, and where A₁ is -COOR₄, A₂ is hydrogen;

B₁ and B₂ are each independently hydrogen; hydroxy; -OR₅ wherein R₅ is a C₁-C₄ alkyl or an Ar-Y- group; or, where B₁ and B₂ are attached to adjacent carbon atoms, B₁ and B₂ can be taken together with said adjacent carbons to form a benzene ring or methylenedioxy;

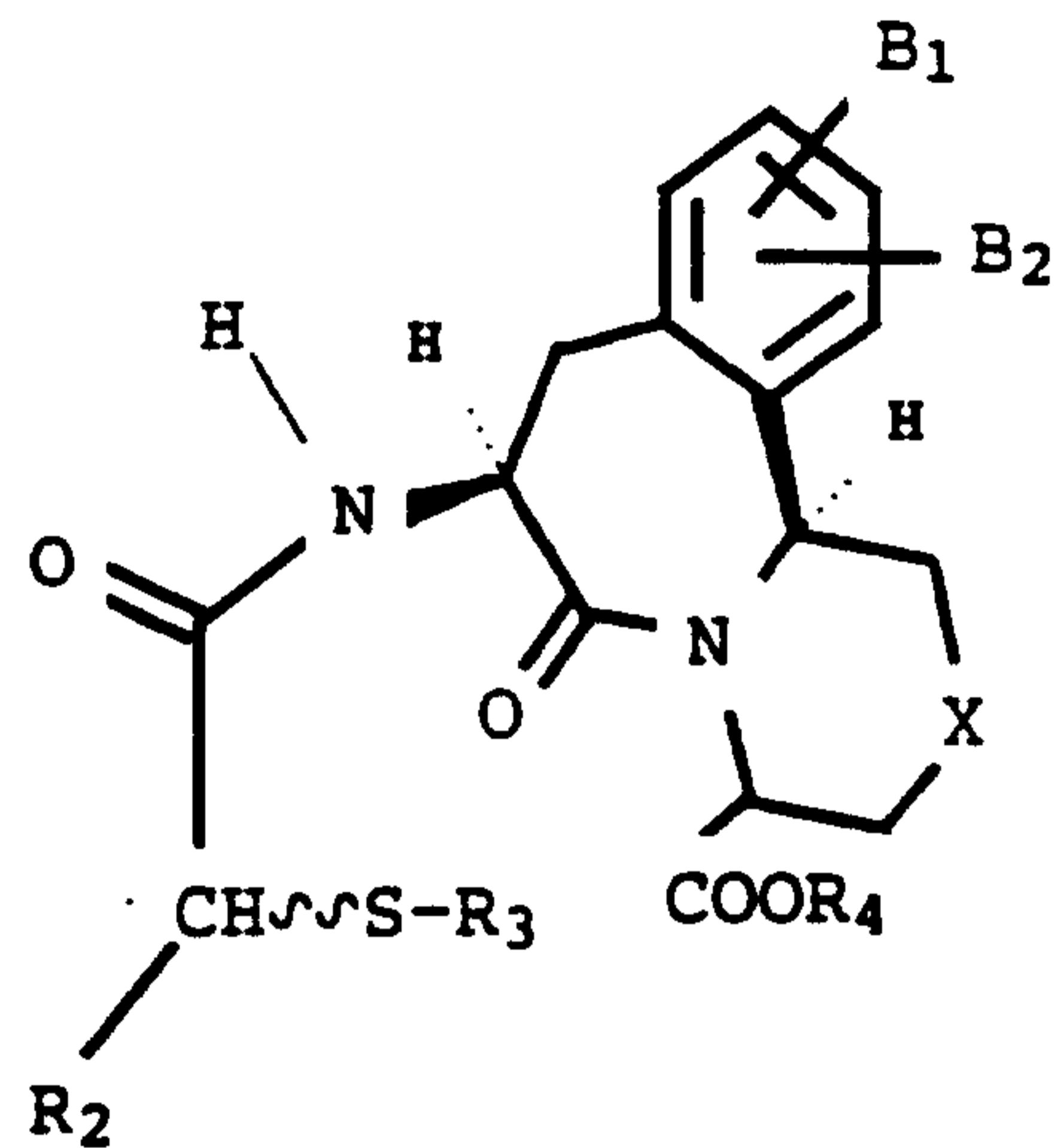
R₂ is hydrogen, C₁-C₈ alkyl, -CH₂OCH₂CH₂OCH₃ or an Ar-Y- group;

R₃ is hydrogen, acetyl, -CH₂O-C(O)C(CH₃)₃ or benzoyl; and n is an integer 0 or 1,

optionally in combination with a pharmaceutically acceptable carrier, for the preparation of a plasma triglyceride lowering agent.

14. The use of a compound of the formula

5



10

15

wherein

B₁ and B₂ are each independently hydrogen; hydroxy; -OR₅ wherein R₅ is a C₁-C₄ alkyl or an Ar-Y- group wherein Ar is aryl and Y is a C₀-C₄ alkyl; or, where B₁ and B₂ are attached to adjacent carbon atoms, B₁ and B₂ can be taken together with said adjacent carbons to form a benzene ring or methylenedioxy;

20

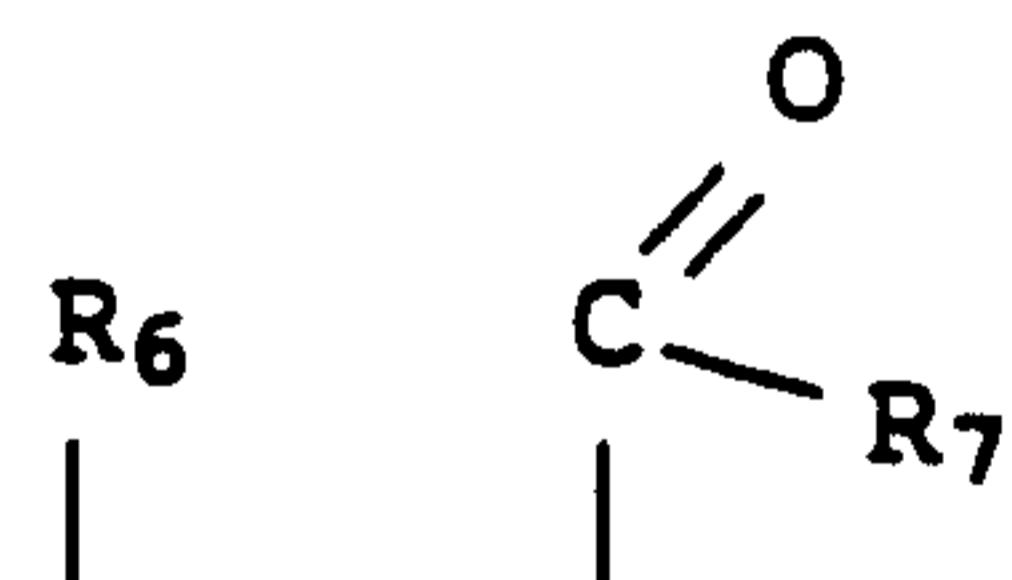
R₂ is hydrogen, C₁-C₈ alkyl, -CH₂OCH₂CH₂OCH₃ or an Ar-Y-group;

25

R₃ is hydrogen, acetyl, -CH₂O-C(O)C(CH₃)₃ or benzoyl;

R₄ is hydrogen, a C₁-C₄ alkyl or an Ar-Y- group, -CH₂O-C(O)C(CH₃)₃ or diphenylmethyl; and

30



X is -O-, -S-, -N- or -N-,

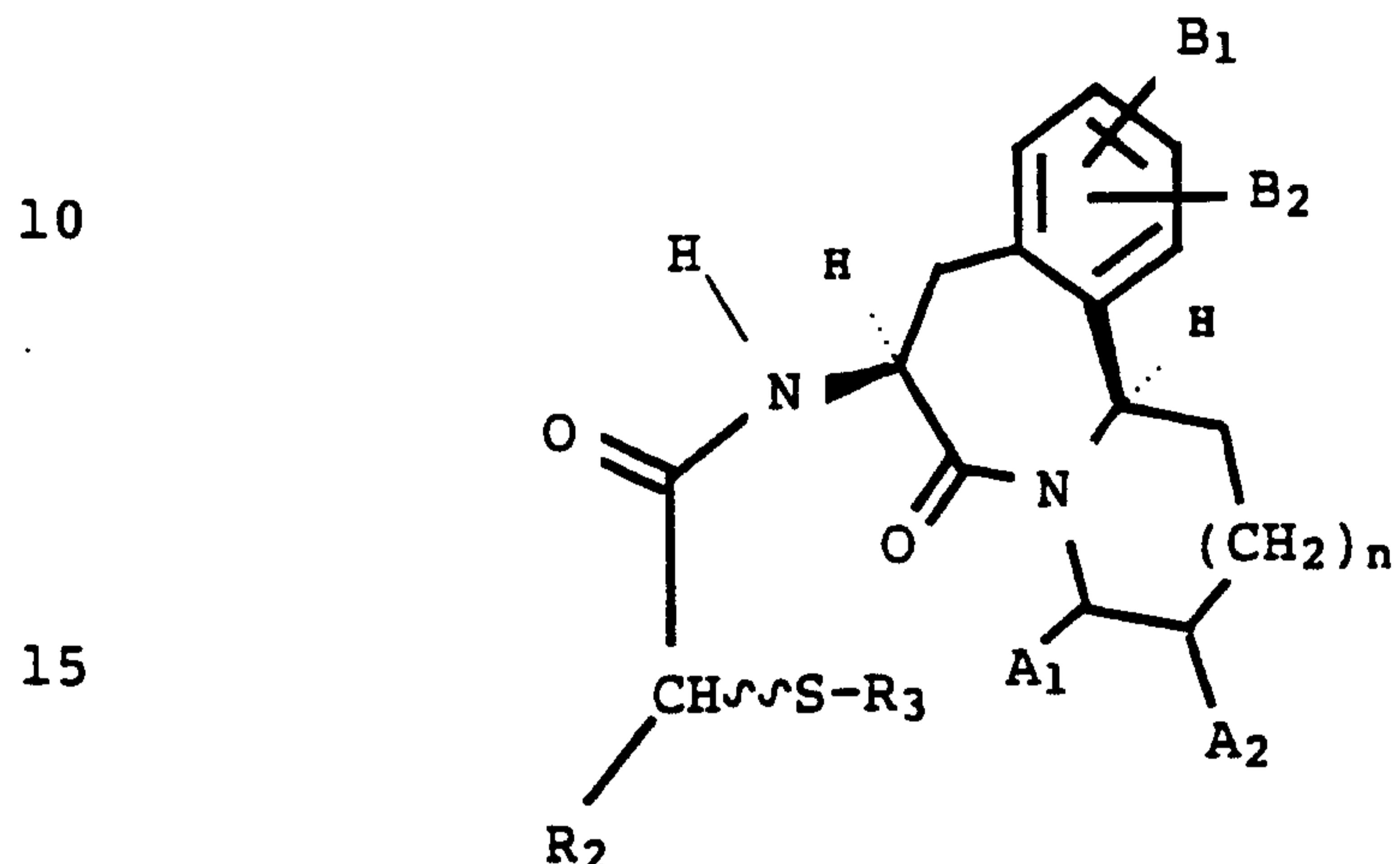
35

wherein R₆ is hydrogen, a C₁-C₄ alkyl or an Ar-Y-group and R₇ is -CF₃, a C₁-C₁₀ alkyl or an Ar-Y-group,

optionally in combination with a pharmaceutically acceptable carrier, for the preparation of a plasma triglyceride lowering agent.

5

15. The use of a compound of the formula



wherein

A₁ and A₂ are each independently hydrogen or -COOR₄ wherein R₄ is hydrogen; -CH₂O-C(O)C(CH₃)₃; a C₁-C₄ alkyl; an Ar-Y- group wherein Ar is aryl and Y is a C₀-C₄ alkyl; or diphenylmethyl; with the proviso that where A₁ is hydrogen, A₂ is -COOR₄, and where A₁ is -COOR₄, A₂ is hydrogen;

B₁ and B₂ are each independently hydrogen; hydroxy; -OR₅ wherein R₅ is a C₁-C₄ alkyl or an Ar-Y- group; or, where B₁ and B₂ are attached to adjacent carbon atoms, B₁ and B₂ can be taken together with said adjacent carbons to form a benzene ring or methylenedioxy;

R₂ is hydrogen, C₁-C₈ alkyl, -CH₂OCH₂CH₂OCH₃ or an Ar-Y- group;

R₃ is hydrogen, acetyl, -CH₂O-C(O)C(CH₃)₃ or benzoyl; and n is an integer 0 or 1,

optionally in combination with a pharmaceutically acceptable carrier, for the preparation of a serum cholesterol lowering agent.

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16. The use of a compound of the formula

5

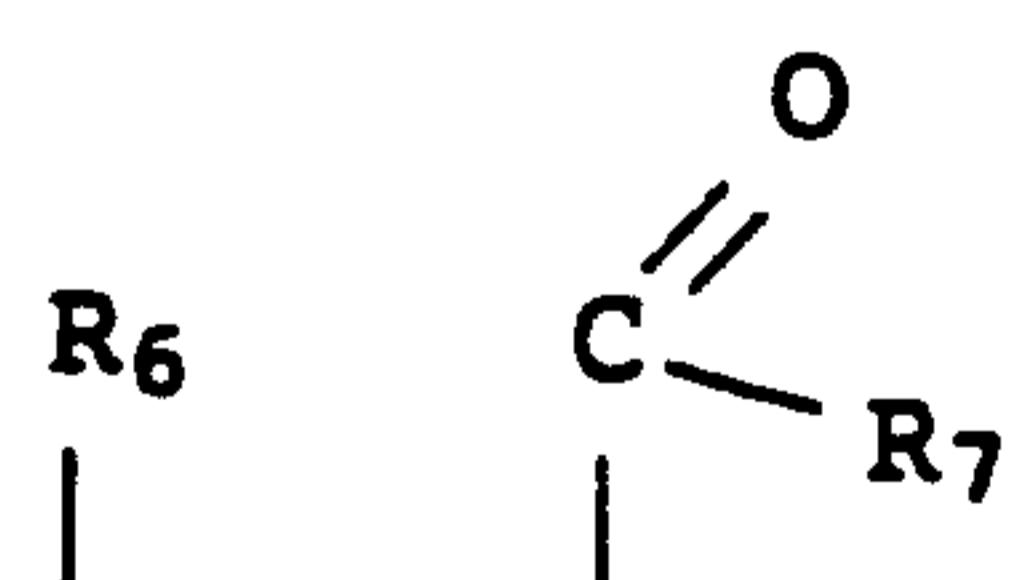
10

15

wherein

B₁ and B₂ are each independently hydrogen; hydroxy; -OR₅ wherein R₅ is a C₁-C₄ alkyl or an Ar-Y- group wherein Ar is aryl and Y is a C₀-C₄ alkyl; or, where B₁ and B₂ are attached to adjacent carbon atoms, B₁ and B₂ can be taken together with said adjacent carbons to form a benzene ring or methylenedioxy; R₂ is hydrogen, C₁-C₈ alkyl, -CH₂OCH₂CH₂OCH₃ or an Ar-Y-group; R₃ is hydrogen, acetyl, -CH₂O-C(O)C(CH₃)₃ or benzoyl; R₄ is hydrogen, a C₁-C₄ alkyl or an Ar-Y- group, -CH₂O-C(O)C(CH₃)₃ or diphenylmethyl; and

30



X is -O-, -S-, -N- or -N-,

35

wherein R₆ is hydrogen, a C₁-C₄ alkyl or an Ar-Y- group and R₇ is -CF₃, a C₁-C₁₀ alkyl or an Ar-Y- group,

optionally in combination with a pharmaceutically acceptable carrier, for the preparation of a serum cholesterol lowering agent.

5

17. The use of a compound [4S-[4 α , 7 α (R*), 12b β]]-7-[(1-oxo-2(S)-acetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid, optionally in combination with a pharmaceutically acceptable carrier, for the preparation of a pharmaceutical composition for the treatment of hypercholesterolemia or hypertriglyceridemia or hypertriglyceridemia, or atherosclerosis by virtue of the lowering of cholesterol and/or triglycerides.

15

18. The use of a compound [4S-[4 α , 7 α (R*), 12b β]]-7-[(1-oxo-2(S)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid, optionally in combination with a pharmaceutically acceptable carrier, for the preparation of a pharmaceutical composition for the treatment of hypercholesterolemia or hypertriglyceridemia or hypertriglyceridemia, or atherosclerosis by virtue of the lowering of cholesterol and/or triglycerides.

25

19. The use of a compound [4S-[4 α , 7 α (R*), 12b β]]-7-[(1-oxo-2(S)-acetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid, optionally in combination with a pharmaceutically acceptable carrier, for the preparation of a plasma triglyceride lowering agent.

20. The use of a compound [4S-[4 α , 7 α (R*), 12b β]]-7-[(1-oxo-2(S)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid, optionally in combination with a pharmaceutically acceptable carrier, for the preparation of a plasma triglyceride lowering agent.

21. The use of a compound [4S-[4 α , 7 α (R*), 12b β]]-7-
[(1-oxo-2(S)-acetylthio-3-phenylpropyl)amino]-
5 1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-
a][2]benzazepine-4-carboxylic acid, optionally in
combination with a pharmaceutically acceptable carrier, for
the preparation of a serum cholesterol lowering agent.

10 22. The use of a compound [4S-[4 α , 7 α (R*), 12b β]]-7-
[(1-oxo-2(S)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-
octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic
acid, optionally in combination with a pharmaceutically
acceptable carrier, for the preparation of a serum
15 cholesterol lowering agent.

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