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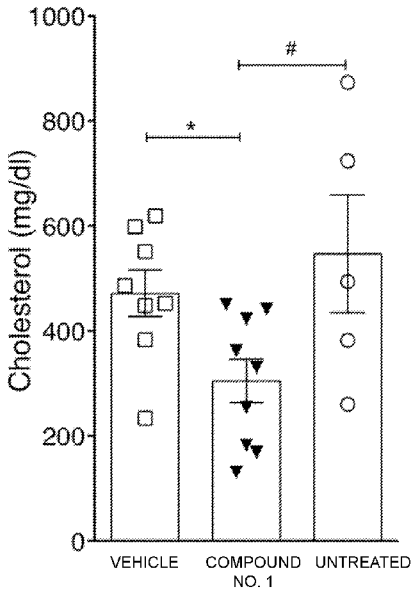
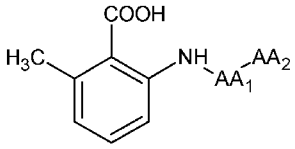


Fig. 1



(I)

(57) Abstract: The present invention relates to novel antiatherosclerotic compounds of formula (I), their pharmaceutically acceptable salts, their isomers, and processes for preparing them. The present invention further provides pharmaceutical compositions comprising compounds of formula (I).

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ANTIATHEROSCLEROTIC AGENTS

TECHNICAL FIELD

The present invention relates to novel antiatherosclerotic compounds, methods for preparing them, and medical uses thereof.

BACKGROUND

Cardiovascular diseases (CVDs), largely caused by formation of atherosclerotic plaques in the arteries, are the main cause of death in the Western world and also increasingly in developing countries.

CVDs account for >17 million deaths globally each year (30% of all deaths), 80% of which occur in low-income and middle-income countries, and this figure is expected to grow to 23.6 million by 2030 (Global Atlas on Cardiovascular Disease Prevention and Control (WHO, 2011)).

Hyperlipidemia is the most important risk factor for atherosclerosis. Atherosclerosis is a chronic inflammatory condition in the artery wall. It is initiated by retention and accumulation of apolipoprotein B100 (ApoB100), particularly in low density lipoprotein (LDL), in the artery wall, which triggers a maladaptive set of responses of macrophages, T cells and vascular cells that in turn cause the formation of atherosclerotic plaques in the arteries.

Atherosclerosis can lead to blockage of blood flow in medium- and large-sized arteries, leading to organ ischemia and its consequences, such as myocardial infarction and stroke. This blockage occurs upon plaque rupture, which allows blood to make contact with the prothrombotic molecules of the plaque core. Thrombosis can also be triggered by plaque erosion, another cause of the inflammatory process in the artery. Notably, lipid deposition in the artery is a natural process with aging, but it can be accelerated in some individuals, leading to its pathological consequences.

There are two main approaches for the management of atherosclerosis: (1) invasive techniques; and (2) non-invasive techniques. Among the non-invasive approaches, the most commonly used one is to lower blood lipids, especially cholesterol and triglycerides. In this approach, the enzyme β-hydroxy β-methylglutaryl coenzyme A reductase (HMG-CoA reductase or HMGCoAR) in the cholesterol synthesis

pathway is a major target. Drugs that inhibit HMGCoAR are called statins. They can reduce LDL cholesterol levels in most individuals but have only minor effects on high density lipoprotein (HDL).

Yet another potential approach to combat atherosclerosis is to increase HDL cholesterol levels in the blood. Unfortunately, attempts at elevating HDL pharmacologically have not been successful in cardiovascular prevention. Therefore, physical exercise and dietary changes may be the only way to achieve this goal.

Since atherosclerosis is a multifactorial disease, clinical guidelines recommend a combination of several medicines to manage this disease. However, there is a lack of compounds that can target several etiological factors and be given in one formulation. The patient is supposed to take several medicines in a day, which is inconvenient and a source of concern for most patients.

Although cardiovascular prevention has been successful in a large number of patients, the overall success rate is still modest. Myocardial infarction and ischemic stroke can be prevented in less than 50% of all patients even when offered state-of-the-art treatment of risk factors. Furthermore, a small but significant proportion of patients do not tolerate statins or other conventional lipid-lowering agents.

Experimental and clinical research has identified inflammation as a major pathogenetic mechanism in atherosclerosis. A large secondary prevention trial showed that an antibody that neutralized the proinflammatory cytokine, interleukin-1β, significantly reduced the incidence of myocardial infarction, stroke and cardiovascular death. However, the use of such antibodies is limited because of the need for parenteral injections, the risk for immune reactions to the antibody, the increased risk for infections as a side effect, and the high cost of recombinant antibodies.

Due to the deficiencies in the current treatments of hyperlipidemia, there remains a need for compounds that are effective in treatment or prevention of hyperlipidemia, vascular inflammation, and cardiovascular complications thereof.

WO 2013/019156 relates to the use of a tryptophan metabolite, 3-hydroxyanthranilic acid (3-HAA) or a functional analogue thereof, for prophylactic and/or therapeutic treatment of mammals, in special humans, against hyperlipidemia and its cardiovascular complications, i.e., atheroma formation,

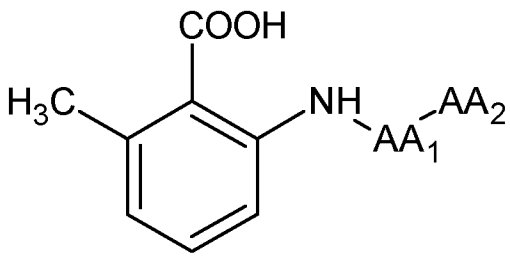
myocardial infarction and heart failure, ischemic stroke and transient ischemic attacks, renal impairment, aortic aneurysms and critical limb ischemia caused by atherosclerosis.

SUMMARY

It is a general objective to provide novel lipid lowering and antiatherosclerotic compounds.

It is a particular objective to provide such compounds useful for treatment, prevention and/or inhibition of hyperlipidemia, vascular inflammation, and/or cardiovascular complications thereof.

An aspect of the invention relates to a compound of formula (I),

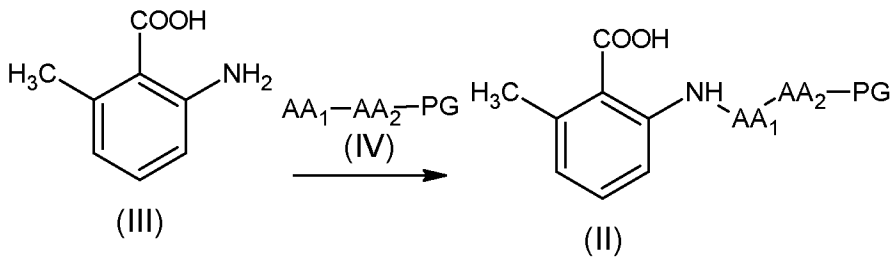


(I)

or an isomer thereof, or a pharmaceutically acceptable salt thereof. AA_1 is an amino acid selected from proline or alanine and AA_2 is an amino acid selected from leucine, valine or phenylalanine.

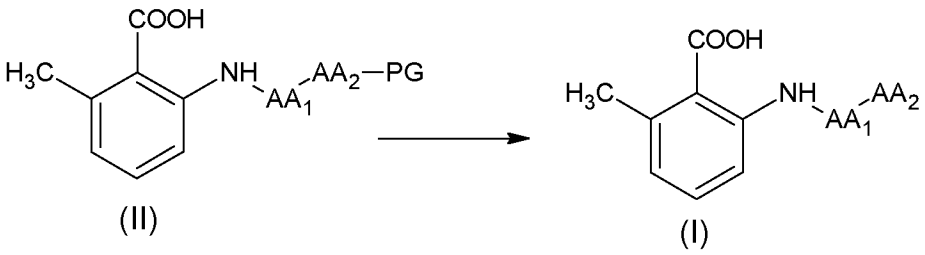
Another aspect of the invention relates to a method for preparation of a compound of formula (I).

In an embodiment, the method comprises reacting a compound of formula (III) with a compound of formula (IV) in an amide formation reaction to obtain a compound of formula (II).

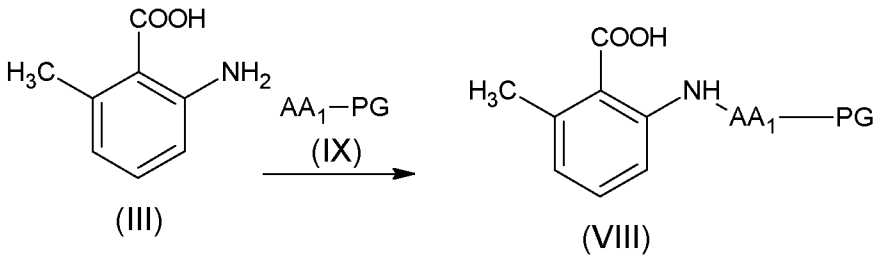


(III) (II)

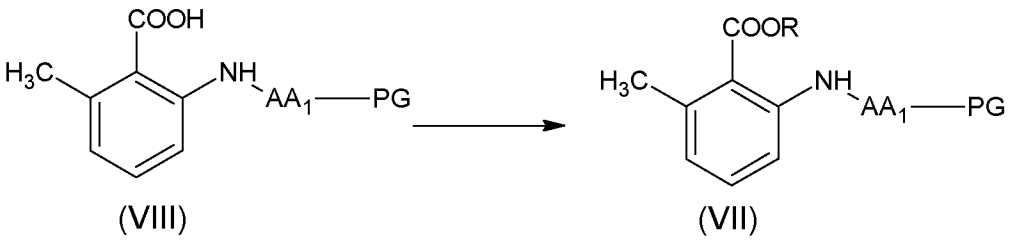
In this embodiment, AA_1 is an amino acid selected from the group consisting of proline and alanine, AA_2 is an amino acid selected from the group consisting of leucine, valine and phenylalanine, and PG is an amine protecting group. The method also comprises deprotecting the amine protecting group in the compound of formula (II) to obtain the compound of formula (I)



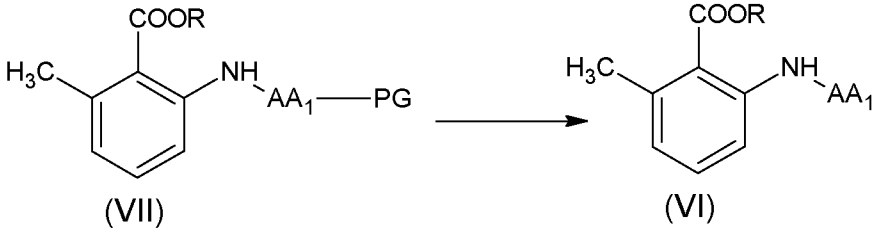
In another embodiment, the method comprises reacting a compound of formula (III) with a compound of formula (IX) in an amide formation reaction to obtain a compound of formula (VIII).



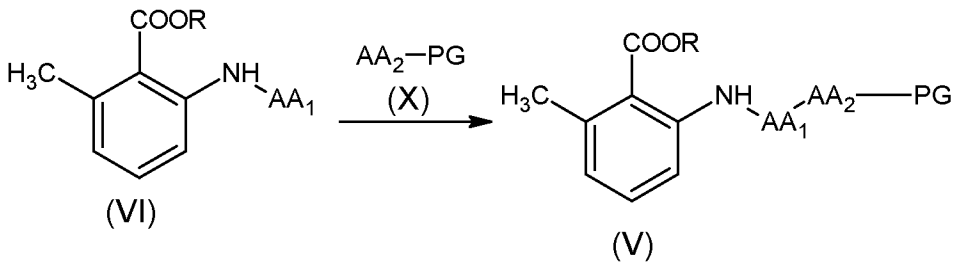
In this embodiment, AA_1 is an amino acid selected from the group consisting of proline and alanine, and PG is an amine protecting group. The method also comprises introducing a carboxy protecting group R in the compound of formula (VIII) in an esterification reaction to obtain a compound of formula (VII).



The method further comprises deprotecting the amine protecting group in the compound of formula (VII) to obtain a compound of formula (VI).

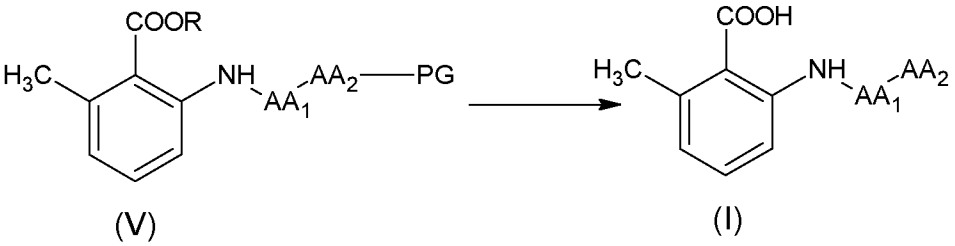


The method additionally comprises reacting the compound of formula (VI) with a compound of formula (X) in an amide formation reaction to obtain a compound of formula (V).



(VI) (V)

In this embodiment, AA_2 is an amino acid selected from the group consisting of leucine, valine and phenylalanine, and PG is an amine protecting group. The method also comprises deprotecting the amine protecting group and the carboxy protecting group in the compound of formula (V) to obtain the compound of formula (I)



(V) (I)

A further aspect of the invention relates to a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (I).

Additional aspects of the invention relate to a compound of formula (I) or a pharmaceutical composition according to above for use as medicament or for use in treatment, prevention and/or inhibition of a disease selected from the group consisting of hyperlipidemia, vascular inflammation and cardiovascular complications thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

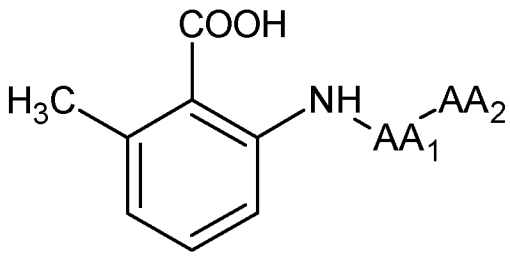
The embodiments, together with further objects and advantages thereof, may best be understood by making reference to the following description taken together with the accompanying drawings, in which:

Fig. 1 illustrates the effects of compound no. 1 on plasma cholesterol levels. Eleven-week-old *Ldlr*$^{-/-}$ mice were daily treated with compound no. 1 (140 mg/kg, n=9) or corn oil vehicle (n=8) by oral gavage (8 weeks of treatment). An untreated group was used for reference (n=5). Graphs show mean ± SEM of plasma cholesterol levels. *P<0.05, #P=0.054.

DETAILED DESCRIPTION

The present invention relates to novel antiatherosclerotic compounds, methods for preparing them, and medical uses thereof.

In one embodiment, the present invention provides compounds of formula (I),



(I)

or isomers thereof, or pharmaceutically acceptable salts thereof, wherein

AA_1 is an amino acid selected from proline or alanine; and

AA_2 is an amino acid selected from leucine, valine or phenylalanine.

In an embodiment, AA_1 is proline and AA_2 is an amino acid selected from leucine, valine or phenylalanine.

In a particular embodiment, AA_1 is proline and AA_2 is leucine.

In another particular embodiment, AA_1 is proline and AA_2 is valine.

In a further particular embodiment, AA_1 is proline and AA_2 is phenylalanine.

In another embodiment, AA_1 is alanine and AA_2 is an amino acid selected from leucine, valine or phenylalanine.

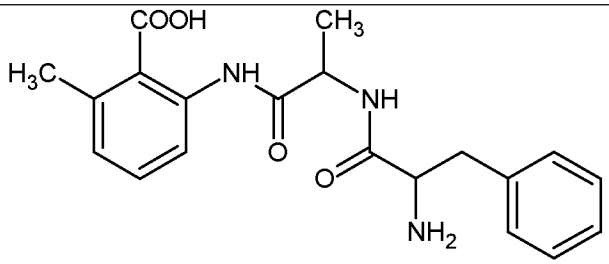
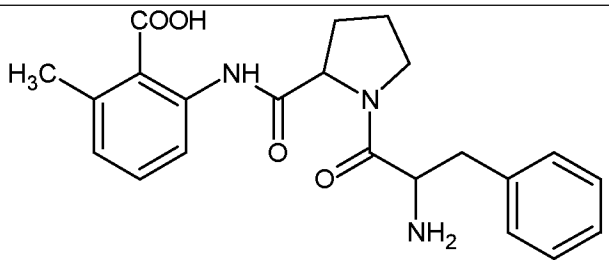
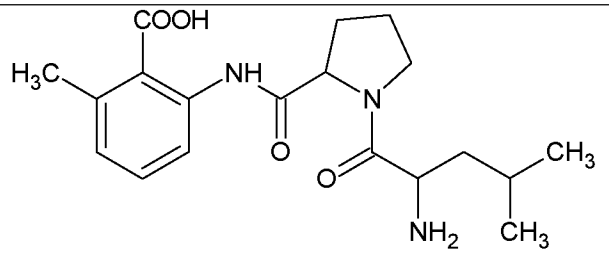
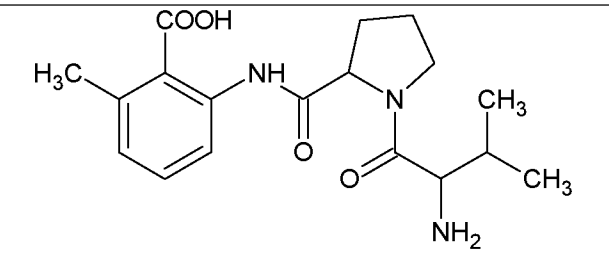
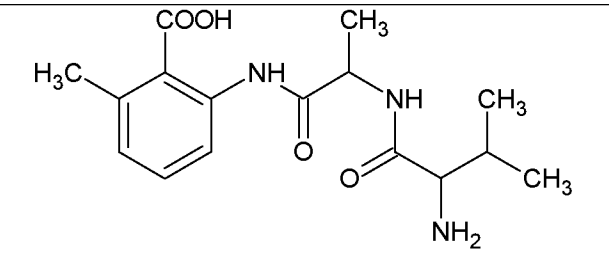
In a particular embodiment, AA_1 is alanine and AA_2 is leucine.

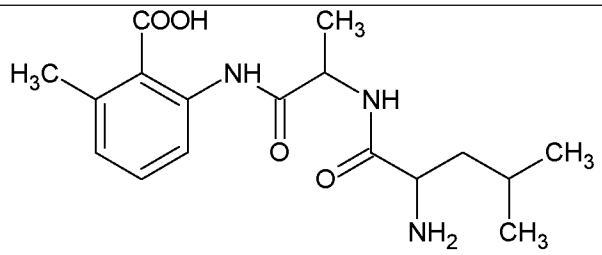
In another particular embodiment, AA_1 is alanine and AA_2 is valine.

In a further particular embodiment, AA_1 is alanine and AA_2 is phenylalanine.

Compounds within the scope of present invention and pharmaceutically acceptable salts thereof are presented in the following Table 1.

Table 1 – antiatherosclerotic compounds

No.	Chemical structure	Chemical name
1		2-({2-[(2-amino-3-phenylpropanoyl)amino]propanoyl}amino)-6-methylbenzoic acid
2		2-{[1-(2-amino-3-phenyl-propionyl)-pyrrolidine-2-carbonyl]-amino}-6-methyl-benzoic acid
3		2-{[1-(2-amino-4-methyl-pentanoyl)-pyrrolidine-2-carbonyl]-amino}-6-methyl-benzoic acid
4		2-({[1-(2-amino-3-methylbutanoyl)pyrrolidin-2-yl]carbonyl}amino)-6-methylbenzoic acid
5		2-({2-[(2-amino-3-methylbutanoyl)amino]propanoyl}amino)-6-methylbenzoic acid

6		2-({2-[(2-amino-4-methylpentanoyl)amino]propanoyl}amino)-6-methylbenzoic acid

The nomenclature of compounds of the present invention as indicated herein is according to Chemdraw (version 7.0).

In an embodiment, the compound of formula (I) is selected from the group consisting of compound nos. 1 to 6 in Table 1.

A non-limiting, but illustrative, example of a salt of the compounds of formula (I) is a trifluoroacetate (TFA) salt.

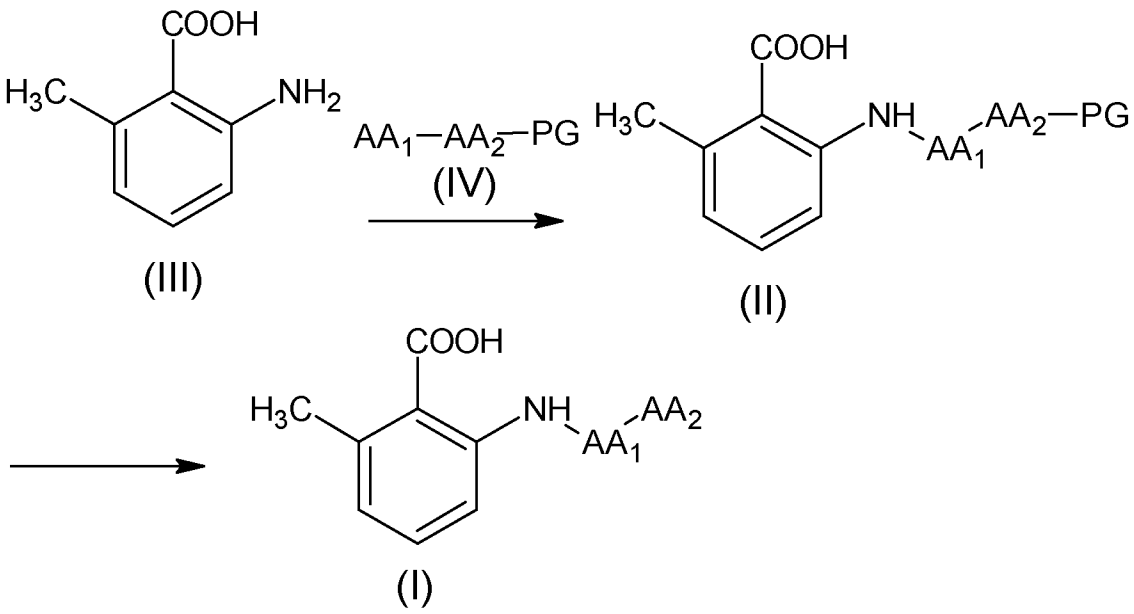
The term "protecting group" as used herein refers to a carboxy protecting group or an amino protecting group.

The term "carboxy protecting group" as used herein refers to one of the ester derivatives of the carboxylic acid group commonly employed to block or protect the carboxylic acid group while reactions are carried out on other functional groups on the compound. Examples of such carboxy protecting groups include, but are not limited to, methyl, ethyl, propyl, butyl, tert-butyl, benzyl, diphenylmethyl, trityl, p-nitrobenzyl, tetrahydropyranyl, dimethylaminoethyl, dimethylchlorosilyl, trichlorosilyl, and the like.

The term "amino protecting group" as used herein refers to substituents of the amino group commonly employed to block or protect the amino functionality while reacting other functional groups on the compound. Examples of such amino protecting groups include, but are not limited to, benzyl, benzylidene, formyl, trityl, phthalimido, acetyl, trifluoroacetyl, trichloroacetyl, chloroacetyl, bromoacetyl, iodoacetyl, t-butyloxycarbonyl, benzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, 9-fluorenylmethoxycarbonyl (FMOC), 2-(trimethysilyl)ethoxycarbonyl, allyloxycarbonyl and the like; the benzoylmethylsulfonyl group, the 2-(nitro)phenysulfenyl group, the diphenylphosphine oxide group and the like.

Compounds of formula (I) can be prepared by the following methods described in schemes A and B.

Scheme A



Compounds of formula (I) can be prepared from compounds of formula (III) as shown in scheme A, wherein PG is an amino protecting group as defined in the foregoing. In a preferred embodiment, the amino protecting group is selected from the group consisting of benzyl, benzyloxycarbonyl and t-butyloxycarbonyl. AA_1 and AA_2 are as defined in the foregoing.

In general, compounds of formula (I) can be prepared by deprotecting compounds of formula (II), i.e., deprotecting the amine protecting group in the compound of formula (II). The reagents used for the deprotection of compounds of formula (II) include, but are not limited to, acids, such as trifluoroacetic acid, hydrochloric acid, phosphoric acid and p-toluenesulphonic acid; bases, such as piperidine; or hydrogenation reagents, such as Pd/C.

In general, compounds of formula (II) can be prepared by reacting compounds of formula (III) with compounds of formula (IV) in an amide formation reaction.

Coupling reagents used for preparing compounds of formula (II) are selected from a group consisting of a carbodiimide, such as 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC), EDC hydrochloride (EDC.HCl) or N,N'-dicyclohexylcarbodimide (DCC); a phosphonium, such as (benzotriazol-1-yloxy)tris(dimethylamino) phosphonium hexafluorophosphate (BOP) or benzotriazol-1-yl-oxytripyrrolidino phosphonium hexafluorophosphate (PyBOP); an imidazolium, such as 1,1'-carbonyldiimidazole (CDI); an

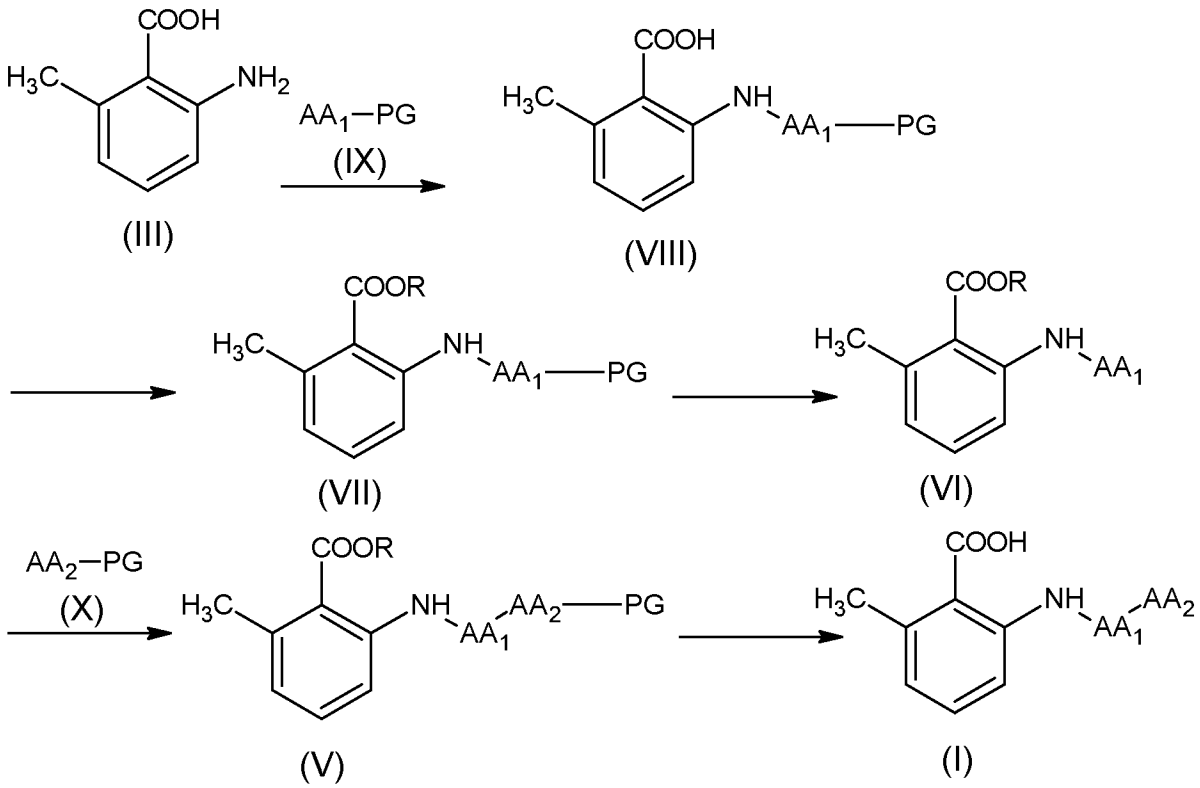
organophosphorus; an acid chloride, such as pivaloyl chloride; a chloroformate, such as ethylchloroformate; and a pyridinium. Hence, in an embodiment, the reacting step comprises adding at least one coupling reagent to the reaction mixture.

The coupling reaction can optionally be performed in the presence of a coupling additive selected from a group consisting of benzotriazoles, such as 1-hydroxybenzotriazole (HOBt), 6-chloro-1-hydroxybenzotriazole (Cl-HOBt), or 1-hydroxy-7-azabenzotriazole (HOAt); dicarboximides, such as N-hydroxy-5-norbornene-2,3-dicarboximide (HONB); and succinimides, such as N-hydroxysuccinimide (HOSu). Hence, in an embodiment, the reacting step comprises adding at least one coupling additive to the reaction mixture.

Solvents are preferably selected from a group consisting of ether solvents, such as tetrahydrofuran (THF); ester solvents, such as ethylacetate; alcohol solvents, such as methanol; halogenated solvents, such as dichloromethane; aprotic solvents, such as dimethylformamide (DMF); and mixtures thereof.

Bases are preferably selected from a group consisting of organic bases, such as triethylamine, diisopropyl amine, diisopropylethyl amine; inorganic bases, including hydroxides, such as sodium hydroxide, potassium hydroxide; carbonates, such as sodium carbonate, sodium bicarbonate, potassium carbonate; hydrides, such as sodium hydride and suitable mixtures of one or more from those described above. Hence, in an embodiment, the reacting step comprises adding at least one base to the reaction mixture.

Scheme B



Compounds of formula (I) can be prepared from compounds of formula (III) as shown in scheme B, wherein PG is an amino protecting group and R is a carboxy protecting group. AA_1 and AA_2 are as defined in the foregoing.

In general, compounds of formula (I) can be prepared by deprotecting compounds of formula (V), i.e., deprotecting the amine protecting group and the carboxy protecting group in the compound of formula (V) to obtain the compound of formula (I). The reagents used for the deprotection of compounds of formula (V) include, but are not limited to, acids, such as trifluoroacetic acid, hydrochloric acid, phosphoric acid and p-toluenesulphonic acid; bases, such as piperidine; or hydrogenation reagents, such as Pd/C.

Compounds of formula (V) can be prepared by reacting compounds of formula (VI) with compounds of formula (X) through an amide formation reaction.

Compounds of formula (VI) can be prepared by deprotecting the amine protecting group in compounds of formula (VII). The reagents used for the deprotection can be selected among the above described examples.

Compounds of formula (VII) can be prepared by introducing a carboxy protecting group in compounds of formula (VIII) through an esterification reaction.

Compounds of formula (VIII) can be prepared by reacting compounds of formula (III) with compounds of formula (IX) through an amide formation reaction.

The reacting steps may optionally include adding at least one coupling reagent, at least one coupling additive and/or at least one base as described above in connection with scheme A. The illustrative examples of solvents presented above for scheme A can also be used for scheme B.

In another embodiment, the present invention provides a pharmaceutical composition comprising a therapeutically effective amount of one or more compounds of formula (I). While it is possible to administer a therapeutically effective quantity of compounds of formula (I) either individually or in combination, directly without any formulation, it is common practice to administer the compounds in the form of pharmaceutical dosage forms comprising pharmaceutically acceptable excipient(s), adjuvant(s) and/or carrier and at least one active ingredient. These dosage forms may be administered by a variety of routes including oral, topical, transdermal, subcutaneous, intramuscular, intravenous, intraperitoneal, intranasal, pulmonary etc. In a particular embodiment, the compounds or pharmaceutical compositions of the invention are provided in a formula or form suitable for oral administration, intravenous administration or subcutaneous administration, such as oral administration.

Compositions may be in the form of solid or liquid dosage form in dosage units.

In particular for oral administration, the dosage units may be powder mixtures to be dissolved in water or another drinkable liquid, tablets, pills, lozenges, capsules, drops, liquid syrups, oral sprays, gels, etc.

Non-limiting examples of excipients include anti-adherents, binders, coatings, disintegrants, filers, flavours, colors, lubricants, glidants, sorbents, preservatives and sweeteners.

Non-limiting examples of carriers include liquid carriers, such as saline, water, an aqueous solution and a buffer solution, and solid carriers, such as nanoparticles, liposomes, microspheres and polymeric micelles.

Adjuvants can be selected among adjuvants used in medicine and in particular used in connection with treatment of hyperlipidemia, vascular inflammation, or cardiovascular complications thereof. Illustrative, but non-limiting, examples of such adjuvants include guggulipid, plant sterols, fish oils, soluble dietary fibers, etc.

In another embodiment, the present invention provides a method for treatment of hyperlipidemia, inflammation, or cardiovascular complications of both by administering a therapeutically effective amount of at least one compound of formula (I) or the pharmaceutical composition to a mammal, including human being, in need thereof.

In another embodiment, the present invention provides the use of at least one compound of formula (I) for the preparation of a medicament for the treatment of hyperlipidemia, vascular inflammation, or cardiovascular complications thereof.

Hyperlipidemia is the condition of abnormally elevated levels of blood lipids, in particular cholesterol and triglycerides transported in the plasma lipoproteins LDL and VLDL. High lipid levels are followed by sub-endothelial retention and accumulation of LDL in the artery wall. This leads to a chronic maladaptive inflammatory response of macrophages and T cells and to atheroma formation.

Cardiovascular complications of hyperlipidemia and/or vascular inflammation include atheroma formation, myocardial infarction, heart failure, angina pectoris, ischemic stroke, transient ischemic attacks, peripheral ischemia, gangrene, renal impairment, aortic aneurysms and critical limb ischemia caused by atherosclerosis.

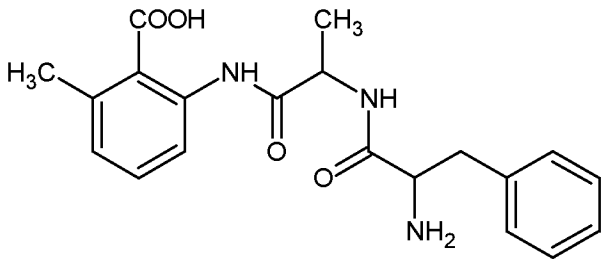
In an embodiment, the hyperlipidemia is selected from the group consisting of hypercholesterolemia, hypertriglyceridemia and combined forms of hyperlipidemia. In an embodiment, the hyperlipidemia is associated with low levels of HDL in plasma.

Treating or inhibiting a disease as used herein also encompass reducing the severity of and/or slowing progression of the disease.

The invention is now illustrated with non-limiting examples.

EXAMPLES

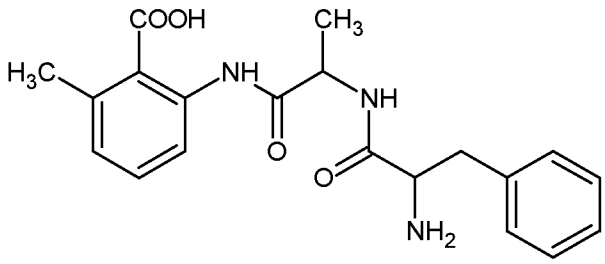
Example 1: Preparation of 2-({2-[(2-amino-3-phenylpropanoyl)amino]propanoyl}amino)-6-methylbenzoic acid trifluoroacetate salt



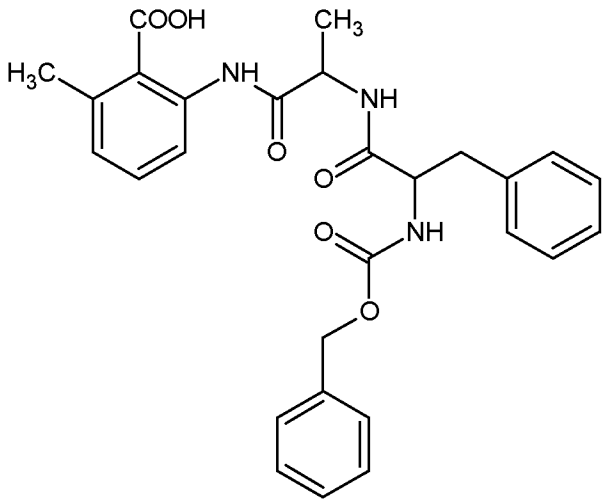
.CF_3COOH

A solution of triethylamine (1.97 ml) in tetrahydofuran was added to a stirred solution of 2-(2-tert-butoxycarbonylamino-3-phenyl-propionylamino)-propionic acid (2 g) in tetrahydrofuran at 0-5°C followed by addition of ethylchloroformate (1.16 g) and then stirred for 30 minutes. A solution of 2-amino-6-methyl-benzoic acid (1.34 g) in tetrahydrofuran was added drop-wise to the reaction mixture and the reaction mixture was stirred at 0-5°C for 30 minutes and it was brought to room temperature (20-25°C) and stirred for 12-15 hours. The reaction progress was monitored by thin layer chromatography (TLC) (solvent system: 30% ethylacetate in n-hexane). After completion of the reaction, the reaction mixture was quenched in cold water, stirred for 15 minutes and extracted with ethyl acetate (250 ml × 2). The separated organic layer was washed with aqueous 1 N HCl solution, brine, dried over sodium sulfate and concentrated under vacuum at 45°C. The concentrated mass was purified with column chromatography (dichloromethane : methanol : acetic acid). Electrospray ionization mass spectrometry (ESMS): 468.50 (M^+-1). The pure compound was dissolved in dichloromethane and the reaction mixture was cooled to 0-5°C under stirring. A solution of trifluoroacetic acid in dichloromethane was added to the reaction mixture. The reaction mixture was stirred for 2 hours and the reaction progress was monitored by TLC (solvent system: 5% methanol in dichloromethane). After completion of the reaction, the reaction mass was concentrated and degassed under vacuum to get the 1.1 g title compound. Yield: 37%; ESMS: 370.44 (M^++1).

Example 2: Preparation of 2-({2-[(2-amino-3-phenylpropanoyl)amino]propanoyl}amino)-6-methylbenzoic acid



Step 1: Synthesis of 2-[2-(2-benzyloxycarbonylamino-3-phenyl-propionylamino)-propionylamino]-6-methyl-benzoic acid



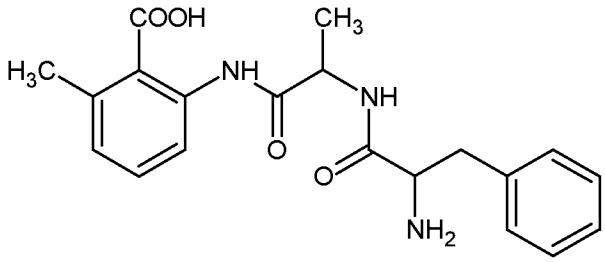
A solution of EDC.HCl (44.50 g) in tetrahydrofuran (300 ml) was added to a stirred solution of 2-(2-benzyloxycarbonylamino-3-phenyl-propionylamino)-propionic acid (66.08 g), diisopropylethylamine (74 ml), HOBt (35.55 g) at 0-10°C. A solution of 2-amino-6-methyl-benzoic acid (30 g) in tetrahydrofuran was added dropwise to the reaction mixture and the reaction mixture was brought to room temperature and stirred for 12-15 hours. The reaction progress was monitored by TLC (solvent system: 30% ethylacetate : n-hexane). After the completion of the reaction, the reaction mixture was quenched into cold aqueous 1N HCl, stirred for 15 minutes, extracted with ethyl acetate (250 ml × 2), dried over sodium sulfate and concentrated under vacuum at 45°C. 10% acetic acid was added to the concentrated mass and the reaction mixture was stirred for 15 minutes and filtered. The material was washed with n-hexane and dried to give 65 g title compound. Yield: 72.31%, ESMS: 502.37 (M^+-1).

Step 2: Synthesis of 2-[2-(2-amino-3-phenyl-propionylamino)-propionylamino]-6-methyl-benzoic acid

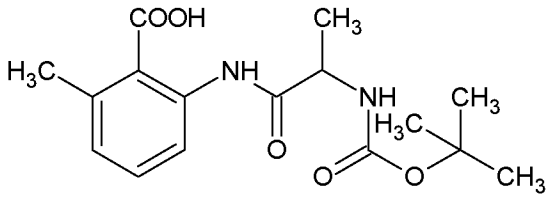
A solution of benzyloxycarbonyl derivative as obtained in step 1 (60 g) in methanol (600 ml) and acetic acid (30 ml) was charged to a 1 liter hydrogenator assembly and the reaction mixture was stirred for 15 minutes

at room temperature. Palladium on carbon (Pd/C) (6 g) was added to the reaction mixture and the reaction mixture was stirred at room temperature under hydrogen atmosphere at a pressure of 1-2 kg for 12-15 hours. The reaction progress was monitored by TLC (solvent system: dichloromethane : methanol : acetic acid). After the completion of the reaction, the reaction mixture was filtered through hyflow bed and washed a mixture of tetrahydrofuran and acetic acid. The filtrate was then concentrated under vacuum followed by azeotropic distillation of acetic acid using toluene under vacuum. The concentrated mass was degassed at 40-45°C under vacuum. The degassed material was purified by column chromatography (solvent system: dichloromethane : methanol : acetic acid) followed by crystallization in methanol. The reaction mixture was filtered and the residue was dried at 50-60°C to give 15 g of title compound. Yield: 28%, Purity: > 98%.

Example 3: Preparation of 2-({2-[(2-amino-3-phenylpropanoyl)amino]propanoyl}amino)-6-methylbenzoic acid

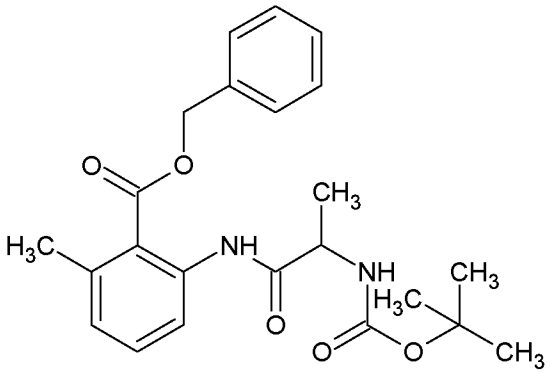


Step 1: Synthesis of 2-(2-tert-butoxycarbonylamino-propionylamino)-6-methyl- benzoic acid



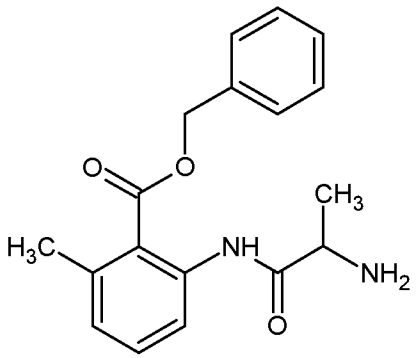
A solution of EDC.HCl (31.60 g) in tetrahydrofuran (250 ml) was added to a stirred solution of 2-tert-butoxycarbonylamino-propionic acid (24 g), diisopropylethylamine (76 ml), HOBt (25.26 g) and the reaction mixture was stirred at 0-10°C for 15 minutes. A solution of 2-amino-6-methyl-benzoic acid (21.11 g) in tetrahydrofuran was added dropwise to the reaction mixture and the reaction mixture was brought to room temperature and stirred for 12-15 hrs. The reaction progress was monitored by TLC (solvent system: 30% ethylacetate : n-hexane). After the completion of the reaction, the reaction mixture was quenched into cooled aqueous 1N HCl and stirred for 15 minutes. The reaction mixture was extracted with ethyl acetate (250 ml × 2), dried over sodium sulfate and concentrated under vacuum at 45°C to give 36 g of title compound. Yield: 80.53%.

Step 2: Synthesis of 2-(2-tert-butoxycarbonylamino-propionylamino)-6-methyl-benzoic acid benzyl ester



Benzyl chloride (78 ml) was added to a stirred solution of tert-butoxycarbonyl derivative as obtained in step 1 (36 g) and sodium carbonate (36 g) in dimethylformamide (108 ml) at room temperature and the reaction mixture was stirred for 15 minutes. The reaction mixture was heated to 60-65°C and stirred for 3 hrs. The reaction progress was monitored by TLC (solvent system: 30% ethylacetate : n-hexane). After the completion of the reaction, the reaction mixture was quenched into cooled water and stirred for 15 minutes. The reaction mixture was extracted with ethyl acetate (250 ml × 2), dried over sodium sulfate and concentrated under vacuum at 45°C to give 40 g of title compound. Yield: 86.95%.

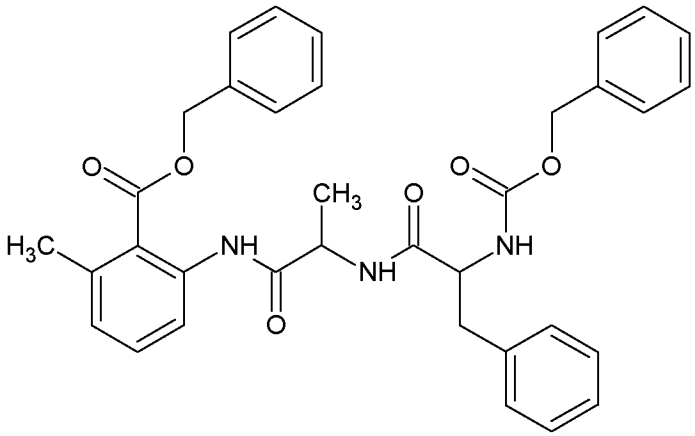
Step 3: Synthesis of 2-(2-amino-propionylamino)-6-methyl-benzoic acid benzyl ester



Ethylacetate HCl (150 ml) was added to the ester derivative as obtained in step 2 (40 g) and was stirred at room temperature for 1 hr and the reaction progress was monitored by TLC (solvent system: 30% ethylacetate : n-hexane). After the reaction completion, the reaction mixture was concentrated at 40-45°C under vacuum and n-hexane was added to the concentrated mass. The reaction mixture was stirred vigorously for 30 min, filtered and dried at 40-45°C. The filtered compound was dissolved in water at room temperature and washed with n-hexane. The separated aqueous layer was basified with sodium carbonate,

extracted with ethylacetate (250 ml × 2), dried over sodium sulfate and concentrated under vacuum at 45°C to give 30 g of title compound. Yield: 99%; ESMS: 313.39 (M^++1).

Step 4: Synthesis of 2-[2-(2-benzyloxycarbonylamino-3-phenyl-propionylamino)-propionylamino]-6-methyl-benzoic acid benzyl ester



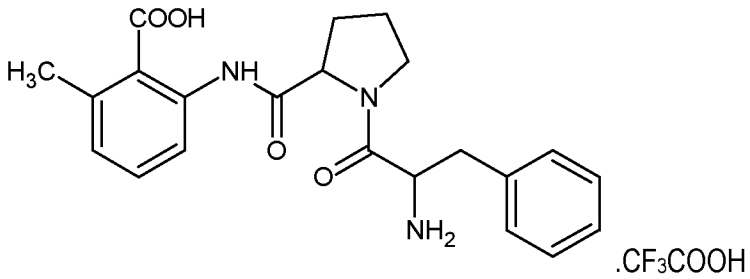
A solution of EDC.HCl (26.34 g) in tetrahydrofuran was added to a stirred solution of 2-benzyloxycarbonylamino-3-phenyl-propionic acid (31.6 g), HOBt (21.08 g) and diisopropylethylamine (27.23 ml). The reaction mixture was cooled to 0-10°C and stirred for 15 minutes. A solution of an amino derivative as obtained in step 3 (30 g) in tetrahydrofuran was added dropwise to the reaction mixture and the reaction mixture was brought to room temperature and stirred for 12-15 hrs. The reaction progress was monitored by TLC (solvent system: 30% ethylacetate : n-hexane). After the completion of reaction, the reaction mixture was quenched into cooled aqueous 10% sodium bicarbonate solution and stirred for 30 minutes. The reaction mixture was filtered and the residue was washed with 1 N HCl followed by washing with water till the pH of residue becomes neutral. The residue was dried at 50-60°C to give 48 g of title compound. Yield: 84%.

Step 5: Synthesis of 2-[2-(2-amino-3-phenyl-propionylamino)-propionylamino]-6-methyl-benzoic acid

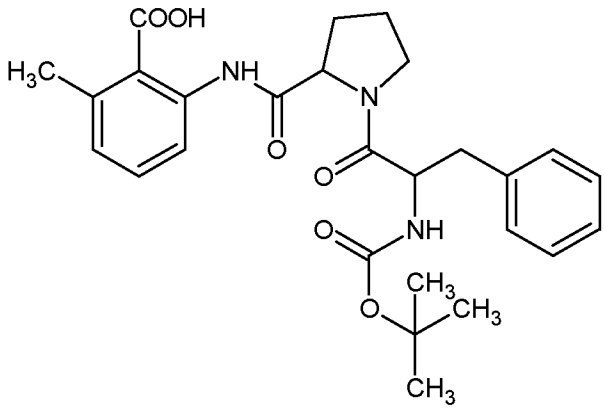
Pd/C (9 g) was added to benzyloxycarbonyl derivative as obtained in step 4 (45 g), acetic acid (45 ml) and tetrahydrofuran (450 ml) in a 1 liter hydrogenator assembly and the reaction mixture was stirred at room temperature under hydrogen atmosphere at a pressure of 1-2 kg for 12-15 hrs. The reaction progress was monitored by TLC (solvent system: 30% ethylacetate : n-hexane). After the completion of the reaction, the reaction mixture was filtered through hyflow bed and washed with mixture of tetrahydrofuran and acetic acid. The filtrate was then concentrated under vacuum followed by azeotropic distillation of acetic acid using

toluene under vacuum. The concentrated mass was degassed at 40-45°C under vacuum. The degassed material was purified by column chromatography followed by crystallization in methanol and dried at 50-60°C to give title 10 g of title compound. Yield: 31%, Purity: ≥99%, ESMS: 370.30 (M^++1).

Example 4: Preparation of 2-{[1-(2-amino-3-phenyl-propionyl)-pyrrolidine-2-carbonyl]-amino}-6-methyl-benzoic acid trifluoroacetic acid salt



Step 1: Synthesis of 2-{[1-(2-tert-butoxycarbonylamino-3-phenyl-propionyl)-pyrrolidine-2-carbonyl]-amino}-6-methyl-benzoic acid

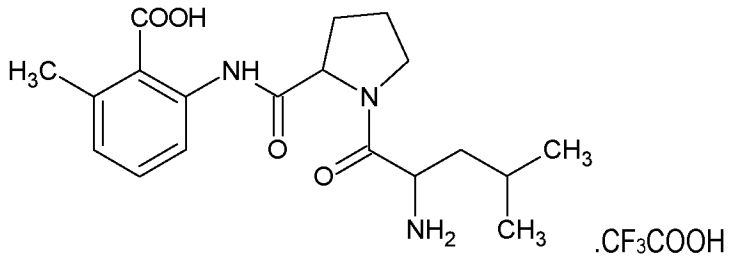


A solution of EDC.HCl (2.24 g) in tetrahydrofuran (32 ml) was added to a stirred solution of 1-(2-tert-butoxycarbonylamino-3-phenyl-propionyl)-pyrrolidine-2-carboxylic acid (3.27 g), diisopropylethylamine (1.51 ml) and HOBt (1.79 g) and the reaction mixture cooled to 0-10°C. A solution of 2-amino-6-methyl-benzoic acid (1.50 g) in tetrahydrofuran was added drop wise to the reaction mixture. The reaction mixture was brought to room temperature and stirred for 12-15 hours. The reaction progress was monitored by TLC (solvent system: 30% ethylacetate : n-hexane) and after the completion of reaction, the reaction mixture was quenched into cooled aqueous 1N HCl and stirred for 15 minutes. The reaction mixture was extracted with ethyl acetate (250 ml × 2), dried over sodium sulfate and concentrated under vacuum at 45°C. 10% acetic acid was added to the concentrated mass and the reaction mixture was stirred for 15 minutes followed by filtration to obtain crude. ESMS: 494.43 (M+-1). The crude residue was purified by column chromatography (methanol : dichloromethane) to give 2.1 g title compound. Yield: 46.97%; ESMS: 494.50 (M^+-1).

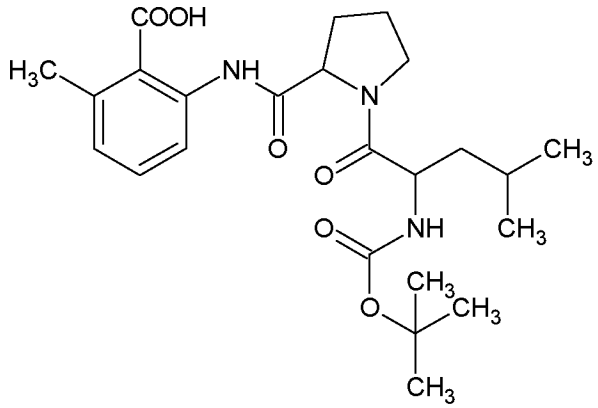
Step 2: Synthesis of 2-{[1-(2-amino-3-phenyl-propionyl)-pyrrolidine-2-carbonyl]-amino}-6-methyl-benzoic acid trifluoroacetic acid salt

A solution of 20% trifluoroacetic acid in dichloromethane (30 ml) was added slowly to tert-butoxycarbonyl derivative as obtained in step 1 (2.1 g) at 0-10°C. The reaction mixture was brought to room temperature and stirred for 3 hours and the reaction progress was monitored by TLC (solvent system: 5% methanol : dichloromethane). After completion of the reaction, the reaction mixture was concentrated under vacuum at 40-45°C and degassed for 3 hours. Di-isopropylether was added to the concentrated mass. The reaction mixture was stirred well followed by decanting di-isopropylether from the reaction mixture. Vacuum was applied to the reaction mixture for 3 hours to get the 1.5 g title compound. Yield: 69.76%; ESMS: 396.39 (M^++1), 394.27 (M^+-1).

Example 5: Preparation of 2-{[1-(2-amino-4-methyl-pentanoyl)-pyrrolidine-2-carbonyl]-amino}-6-methyl-benzoic acid trifluoroacetate



Step 1: Synthesis of 2-{[1-(2-tert-butoxycarbonylamino-4-methyl-pentanoyl)-pyrrolidine-2-carbonyl]-amino}-6-methyl-benzoic acid



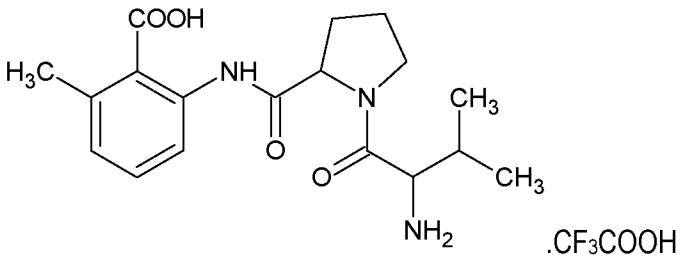
A solution of EDC.HCl (2.02 g) in tetrahydrofuran (15 ml) was added to a stirred solution of 1-(2-tert-butoxycarbonylamino-4-methyl-pentanoyl)-pyrrolidine-2-carboxylic acid (3.0 g), diisopropylethylamine (1.36 g) and HOBt (1.61 g) and the reaction mixture cooled to 0-10°C. A solution of 2-amino-6-methyl-benzoic acid (1.90 g) in tetrahydrofuran was added drop wise to the reaction mixture. The reaction mixture was brought

to room temperature and stirred for 12-15 hours. The reaction progress was monitored by TLC (solvent system: 30% ethylacetate : n-hexane) and after the completion of reaction, the reaction mixture was quenched into cooled aqueous 1N HCl and stirred for 15 minutes. The reaction mixture was extracted with ethyl acetate (250 ml × 2), dried over sodium sulfate and concentrated under vacuum at 45°C. 10% acetic acid was added to the concentrated mass and the reaction mixture was stirred for 15 minutes followed by filtration. The residue was washed with n-hexane to give 3.5 g title compound. Yield: 83.13%; ESMS: 460.54 (M^+-1).

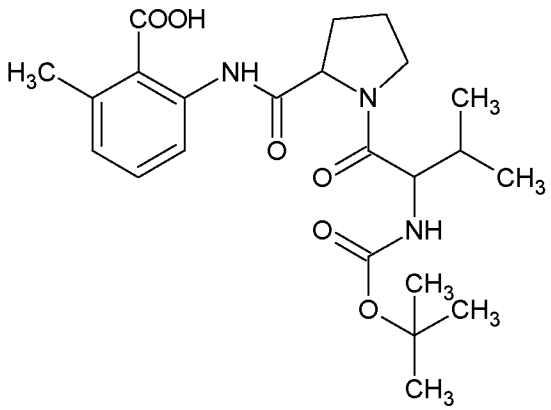
Step 2: Synthesis of 2-{[1-(2-amino-4-methyl-pentanoyl)-pyrrolidine-2-carbonyl]-amino}-6-methyl-benzoic acid trifluoroacetic acid salt

A solution of 20% trifluoroacetic acid in dichloromethane (30 ml) was added slowly to tert-butoxycarbonyl derivative as obtained in step 1 (3.2 g) at 0-10°C. The reaction mixture was brought to room temperature and stirred for 3 hours and the reaction progress was monitored by TLC (solvent system: 5% methanol : dichloromethane). After completion of the reaction, the reaction mixture was concentrated under vacuum at 40-45°C and degassed for 3 hours. Di-isopropylether was added to the concentrated mass. The reaction mixture was stirred well followed by decanting di-isopropylether from the reaction mixture. Vacuum was applied to the reaction mixture for 3 hours to get the 1.8 g title compound. Yield: 54.17%; ESMS: 362.29 (M^++1).

Example 6: Preparation of 2-{[1-(2-amino-3-methyl-butyryl)-pyrrolidine-2-carbonyl]-amino}-6-methyl-benzoic acid trifluoroacetic acid salt



Step 1: Synthesis of 2-{[1-(2-tert-butoxycarbonylamino-3-methyl-butyryl)-pyrrolidine-2-carbonyl]-amino}-6-methyl-benzoic acid

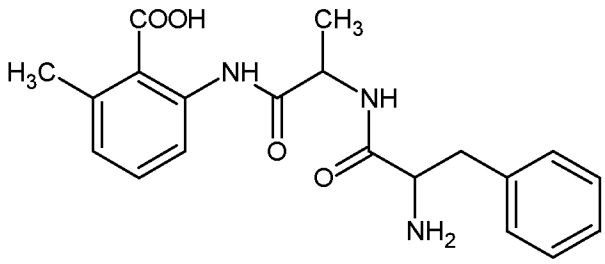


Ethylchloroformate (2.05 g) was added to a stirred solution of 1-(2-tert-butoxycarbonylamino-3-methyl-butyryl)-pyrrolidine-2-carboxylic acid (3.0 g), triethylamine (2.39 g) in tetrahydrofuran (30 ml) at 0-10°C and the reaction mixture was stirred for 15 minutes. A solution of 2-amino-6-methyl-benzoic acid (2.14 g) in tetrahydrofuran was added drop wise to the reaction mixture. The reaction mixture was brought to room temperature and stirred for 12-15 hours. The reaction progress was monitored by TLC (solvent system: 30% ethylacetate : n-hexane) and after the completion of reaction, the reaction mixture was quenched into cooled aqueous 1N HCl and stirred for 15 minutes. The reaction mixture was extracted with ethyl acetate (250 ml × 2), dried over sodium sulfate and concentrated under vacuum at 45°C to obtain crude 3.2 g of title compound. The crude was purified by column chromatography to give 2.3 g title compound. Yield: 53.99%; ESMS: 446.36 (M^+-1).

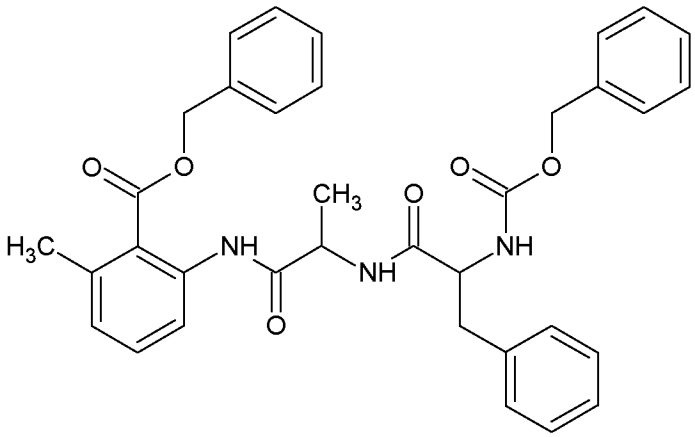
Step 2: Synthesis of 2-{[1-(2-amino-3-methyl-butyryl)-pyrrolidine-2-carbonyl]-amino}-6-methyl-benzoic acid trifluoroacetic acid salt

A solution of 20% trifluoroacetic acid in dichloromethane (30 ml) was slowly added to tert-butoxycarbonyl derivative as obtained in step 1 (2.3 g) at 0-10°C. The reaction mixture was brought to room temperature and stirred for 3 hours and the reaction progress was monitored by TLC (solvent system: 5% methanol : dichloromethane). After completion of the reaction, the reaction mixture was concentrated under vacuum at 40-45°C and degassed for 3 hours. Di-isopropylether was added to the concentrated mass. The reaction mixture was stirred well followed by decanting di-isopropylether from the reaction mixture. Vacuum was applied to the reaction mixture for 3 hours to get the 1.03 g title compound. Yield: 43.45%; ESMS: 346.36 (M^+-1).

Example 7: Preparation of 2-({2-[(2-amino-3-phenylpropanoyl)amino]propanoyl}amino)-6-methylbenzoic acid



Step 1: Synthesis of 2-[2-(2-benzyloxycarbonylamino-3-phenyl-propionyl amino)-propionylamino]-6-methyl-benzoic acid benzyl ester



N,N'-Diisopropylcarbodiimide (93.24 g) was added to a stirred solution of 2-benzyloxycarbonylamino-3-phenyl-propionic acid (210 g), hydroxybenzotriazole (113.28 g) and dimethylformamide (800 ml) at 10-15°C and stirred the reaction mixture for 20 minutes. A solution of 2-(2-amino-propionylamino)-6-methyl-benzoic acid benzyl ester (210 g) in dimethylformamide was added drop wise to the reaction mixture at 10-15°C and the reaction mixture was stirred for 2-3 hrs. The reaction progress was monitored by TLC (solvent system: 5% methanol : dichloromethane). After the completion of reaction, the reaction mixture was quenched into 1N aqueous HCl solution and stirred for 10-20 minutes at 10-15°C. The reaction mixture was filtered and solid was slurry washed with 10% sodium bicarbonate solution followed by washing with water till the pH of filtrate became neutral. The material was dried at 50-60°C. The dried solid was added in mixture of isopropyl alcohol (855 ml) and ethyl acetate (45 ml) and the reaction mixture was refluxed for 1 hour. The reaction mixture was then cooled up to 55-60°C and filtered to give 350 g of title compound as white solid material. Yield: 88%.

Step 2: Synthesis of 2-[2-(2-amino-3-phenyl-propionylamino)-propionylamino]-6-methyl-benzoic acid

Pd/C (18 g) was added to benzyloxycarbonyl derivative as obtained in step 1 (65 g), methanol (600 ml) and tetrahydrofuran (600 ml) in a 3 liter hydrogenator assembly and the reaction mixture was stirred at room

temperature under hydrogen atmosphere at a pressure of 1-2 kg for 20-24 hrs. The reaction progress was monitored by TLC (solvent system: 30% ethyl acetate : n-hexane). After the completion of reaction, the reaction mixture was dissolved in methanol, filtered through hyflow bed and washed with methanol. The filtrate was then concentrated under vacuum followed by degassing at 40-45°C under vacuum. The degassed material was crystallized in methanol and dried at 50-60°C to give title 32 g of title compound. Yield: 86%, Purity: ≥98%, ESMS: 370.30 (M^++1).

1H-NMR (400 MHz, DMSO): δ 7.2 (5H, m), 7.17 (1H, t), 3.06 (2H, m), 3.99 (1H, t), 8.6 (1H, d), 6.85 (1H, d), 1.26 (3H, s), 3.84 (1H, m), 7.9 (1H, d), 11.6 (1H, s), 2.4 (3H, s).

Evaluation of therapeutic effect of compound no. 1 (2-({2-[(2-amino-3-phenylpropanoyl)amino]propanoyl}amino)-6-methylbenzoic acid)

Four to five weeks old male Wistar rats were fed high fat high cholesterol diet to induce hyperlipidemia. Animals were given compound no. 1 in Table 1 daily at 250 mg/kg and blood was taken for evaluation of its effects on total plasma cholesterol and triglyceride (TG) levels. Results are summarized in Table 2.

Table 2 – plasma cholesterol and TG levels

Group	Cholesterol			TG		
	Day 1	Day 31	Day 61	Day 1	Day 31	Day 61
Normal control	65.24	58.76	59.1	75.26	66.58	86.7
HFHC	62.39	163.8	123.7	115.28	80.1	93.3
HFHC + compound no. 1	72.33	122.43	93	100.11	65.00	65.1

HFHC: High Fat High Cholesterol (diet); TG: Triglycerides.

There was an increase in plasma lipids in animals fed high cholesterol diet. However, this increase in plasma lipids was significantly lower when animals received compound no. 1. The effect was seen to persist at two months when animals continued to receive same treatment.

Evaluation of therapeutic effect of compound no. 1 (2-({2-[(2-amino-3-phenylpropanoyl)amino]propanoyl}amino)-6-methylbenzoic acid)

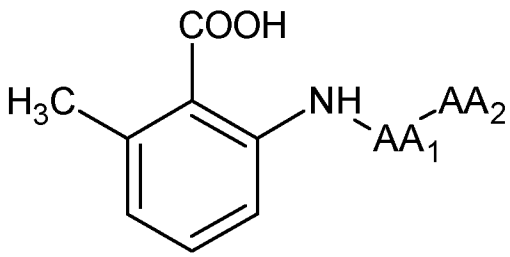
The efficacy of compound no. 1 in Table 1 on lowering plasma lipids was evaluated using a *Ldlr*$^{-/-}$ hypercholesterolemic mouse model. Mice were orally treated with compound no. 1 in corn oil vehicle for

8 weeks. During treatment, the mice were also fed a high-fat diet (corn starch, cocoa butter, casein, glucose, sucrose, cellulose flour, minerals and vitamins; 17.2% protein, 21% fat, 0.15% cholesterol, 43% carbohydrates, 10% H_2O and 3.9% cellulose fibers) (R638 Lantmännen, Sweden). As is shown in Fig. 1, compared to vehicle control, plasma levels of cholesterol were significantly reduced upon treatment with compound no. 1.

The embodiments described above are to be understood as a few illustrative examples of the present invention. It will be understood by those skilled in the art that various modifications, combinations and changes may be made to the embodiments without departing from the scope of the present invention. In particular, different part solutions in the different embodiments can be combined in other configurations, where technically possible. The scope of the present invention is, however, defined by the appended claims.

CLAIMS

1. A compound of formula (I),



(I)

or an isomer thereof, or a pharmaceutically acceptable salt thereof, wherein

AA1 is an amino acid selected from the group consisting of proline and alanine; and

AA2 is an amino acid selected from the group consisting of leucine, valine and phenylalanine.

2. The compound according to claim 1, wherein the compound is selected from the group consisting of:

2-({2-[(2-amino-3-phenylpropanoyl)amino]propanoyl}amino)-6-methylbenzoic acid;

2-{[1-(2-amino-3-phenyl-propionyl)-pyrrolidine-2-carbonyl]-amino}-6-methylbenzoic acid;

2-{[1-(2-amino-4-methyl-pentanoyl)-pyrrolidine-2-carbonyl]-amino}-6-methylbenzoic acid;

2-({[1-(2-amino-3-methyl-butanoyl)-pyrrolidine-2-yl]carbonyl}-amino}-6-methylbenzoic acid;

2-({2-[(2-amino-3-methyl-butanoyl)amino]propanoyl}amino)-6-methylbenzoic acid; and

2-({2-[(2-amino-4-methylpentanoyl)amino]propanoyl}amino)-6-methylbenzoic acid.

3. The compound according to claim 1 or 2, wherein AA1 is proline.

4. The compound according to claim 3, wherein AA2 is leucine.

5. The compound according to claim 1 or 2, wherein AA1 is alanine.

6. The compound according to claim 5, wherein AA2 is phenylalanine.

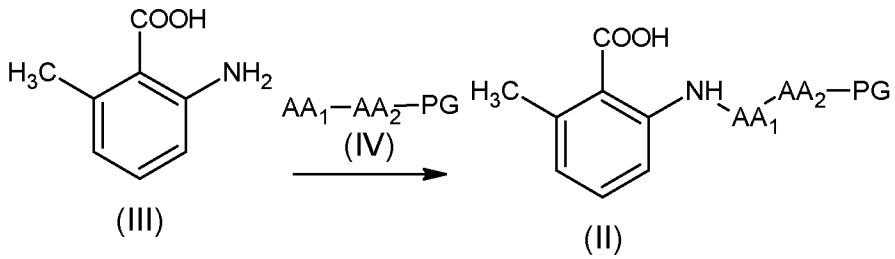
7. A pharmaceutical composition comprising a therapeutically effective amount of at least one compound of formula (I) according to any of the claims 1 to 6.

8. The pharmaceutical composition according to claim 7, further comprising:
at least one pharmaceutically acceptable excipient; and/or
at least one pharmaceutically acceptable adjuvant; and/or
a pharmaceutically acceptable carrier.

9. A compound of formula (I) according to any of the claims 1 to 6 or a pharmaceutical composition according to claim 7 or 8 for use as medicament.

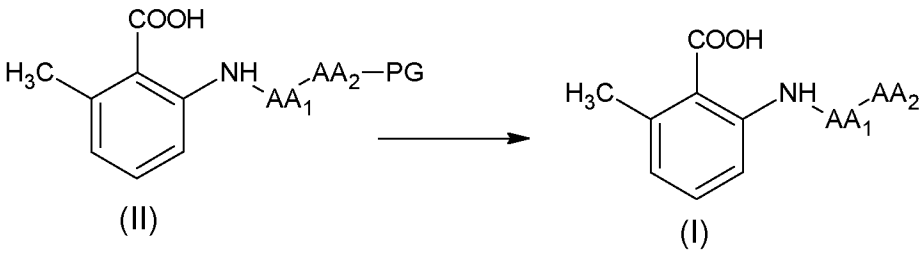
10. A compound of formula (I) according to any of the claims 1 to 6 or a pharmaceutical composition according to claim 7 or 8 for use in treatment, prevention and/or inhibition of a disease selected from the group consisting of hyperlipidemia, vascular inflammation and cardiovascular complications thereof.

11. A method for preparation of a compound of formula (I) according to any of the claims 1 to 6 comprising the steps of:
reacting a compound of formula (III) with a compound of formula (IV) in an amide formation reaction to obtain a compound of formula (II),



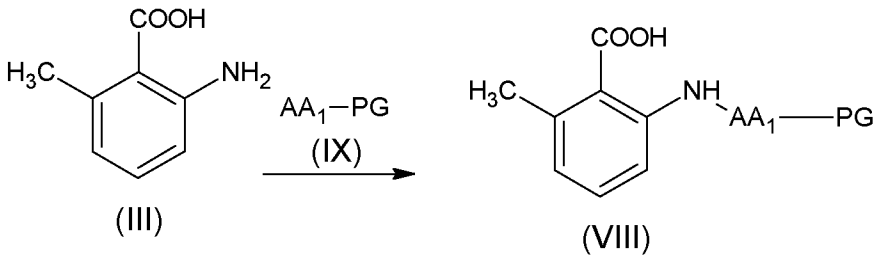
(III) (II)

wherein
AA1 is an amino acid selected from the group consisting of proline and alanine;
AA2 is an amino acid selected from the group consisting of leucine, valine and phenylalanine; and
PG is an amine protecting group; and
deprotecting the amine protecting group in the compound of formula (II) to obtain the compound of formula (I)



12. A method for preparation of a compound of formula (I) according to any of the claims 1 to 6 comprising the steps of:

reacting a compound of formula (III) with a compound of formula (IX) in an amide formation reaction to obtain a compound of formula (VIII),

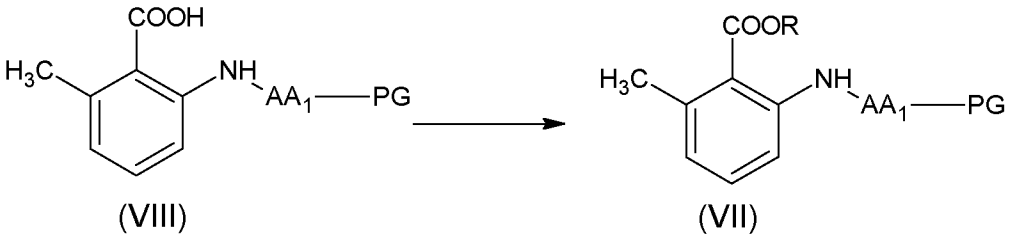


wherein

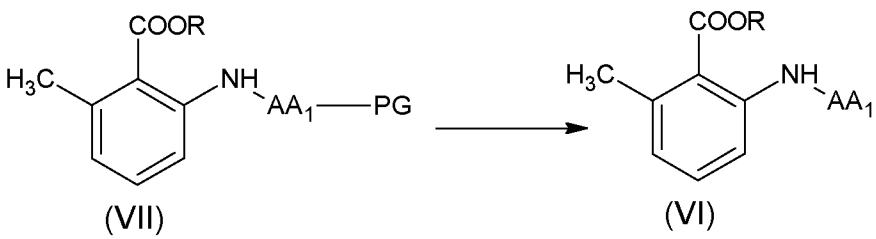
AA1 is an amino acid selected from the group consisting of proline and alanine; and

PG is an amine protecting group;

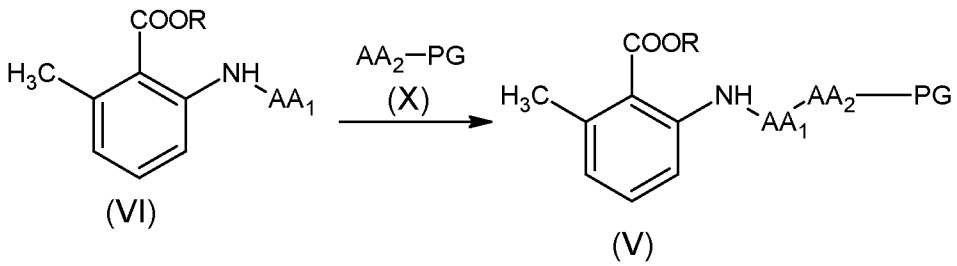
introducing a carboxy protecting group R in the compound of formula (VIII) in an esterification reaction to obtain a compound of formula (VII);



deprotecting the amine protecting group in the compound of formula (VII) to obtain a compound of formula (VI);



reacting the compound of formula (VI) with a compound of formula (X) in an amide formation reaction to obtain a compound of formula (V),



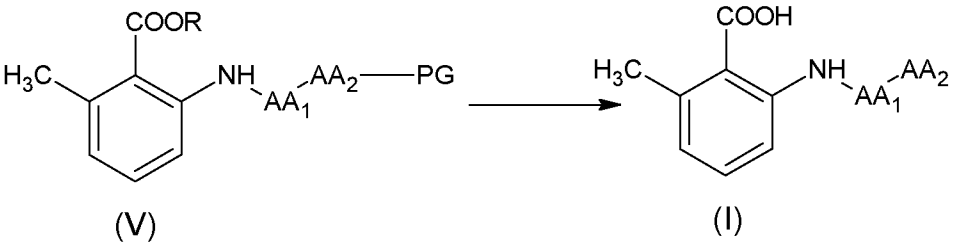
(VI) (V)

wherein

AA2 is an amino acid selected from the group consisting of leucine, valine and phenylalanine; and

PG is an amine protecting group; and

deprotecting the amine protecting group and the carboxy protecting group in the compound of formula (V) to obtain the compound of formula (I)



(V) (I)

.

13. The method according to claim 12, wherein the carboxy protecting group is selected from the group consisting of methyl, ethyl, propyl, butyl, tert-butyl, benzyl, diphenylmethyl, trityl, p-nitrobenzyl, tetrahydropyranyl, dimethylaminoethyl, dimethylchlorosilyl, and trichlorosilyl.

14. The method according to any of the claims 11 to 13, wherein the reacting step comprises adding a coupling reagent selected from the group consisting of a carbodiimide, preferably 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC), EDC hydrochloride (EDC.HCl) or N,N'-dicyclohexylcarbodimide (DCC); a phosphonium, preferably (benzotriazol-1-yloxy)tris(dimethylamino) phosphonium hexafluorophosphate (BOP) or benzotriazol-1-yl-oxytripyrrolidino phosphonium hexafluorophosphate (PyBOP); an imidazolium, preferably 1,1'-carbonyldiimidazole (CDI); an organophosphorus; an acid chloride, preferably pivaloyl chloride; a chloroformate, preferably ethylchloroformate; a pyridinium; and a mixture thereof.

15. The method according to any of the claims 11 to 14, wherein the reacting step comprises adding a coupling additive selected from the group comprising a benzotriazole, preferably 1-hydroxybenzotriazole (HOBt), 6-chloro-1-hydroxybenzotriazole (Cl-HOBt), or 1-hydroxy-7-azabenzotriazole (HOAt); a dicarboximide, preferably N-hydroxy-5-norbornene-2,3-dicarboximide (HONB); a succinimide, preferably N-hydroxysuccinimide (HOSu); and a mixture thereof.

16. The method according to any of the claims 11 to 15, wherein the reacting step comprises adding a base selected from the group consisting of an organic base, preferably triethylamine, diisopropyl amine, or diisopropylethyl amine; an inorganic base, preferably a hydroxide, such as sodium hydroxide, potassium hydroxide; a carbonate, such as sodium carbonate, sodium bicarbonate, potassium carbonate; a hydride, such as sodium hydride; and a mixture thereof.

17. The method according to any of the claims 11 to 16, wherein the deprotecting step comprises adding a deprotecting reagent selected from the group consisting of an acid, preferably trifluoroacetic acid, hydrochloric acid, phosphoric acid or p-toluenesulphonic acid; a base, preferably piperidine; and a hydrogenation reagent, preferably Pd/C.

18. The method according to any of the claims 11 or 17, wherein the amine protecting group is selected from the group consisting of benzyl, benzylidene, formyl, trityl, phtalimido, acetyl, trifluoroacetyl, trichloroacetyl, chloroacetyl, bromoacetyl, iodoacetyl, t-butyloxycarbonyl, benzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, 9-fluorenylmethoxycarbonyl (FMOC), 2-(trimethylsilyl)ethoxycarbonyl, allyloxycarbonyl, benzoylmethylsulfonyl, 2-(nitro)pheysulfenyl, and diphenylphosphine oxide, preferably selected from the group consisting of benzyl, benzyloxycarbonyl and t-butyloxycarbonyl.

19. The method according to any of the claims 11 to 18, wherein the steps are performed in a solvent selected from the group consisting of an ether solvent, preferably tetrahydrofuran (THF); an ester solvent, preferably ethylacetate; an alcohol solvent, preferably methanol; a halogenated solvent, preferably dichloromethane; an aprotic solvent, preferably dimethylformamide (DMF); and a mixture thereof.

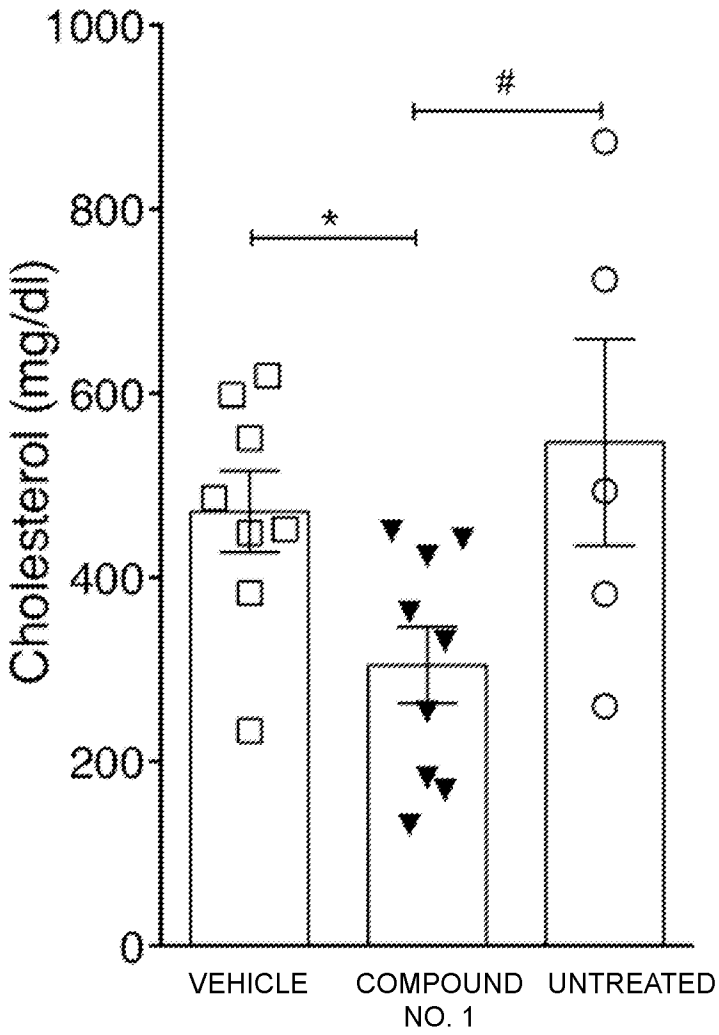

1000
800
600
400
200
0
Cholesterol (mg/dl)
#
*
VEHICLE
COMPOUND NO. 1
UNTREATED

Fig. 1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2019/050060

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: C07K

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, PAJ, WPI data, BIOSIS, CHEM ABS Data, EMBASE, MEDLINE, PUBCHEM

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0466944 A1 (TEIJIN LTD), 22 January 1992 (1992-01-22); abstract --	1-19
A	EP 2736505 A1 (HANSSON GÖRAN K), 4 June 2014 (2014-06-04); abstract; claims --	1-19
A	WO 0027800 A1 (SMITHKLINE BEECHAM CORP ET AL), 18 May 2000 (2000-05-18); abstract --	1-19

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

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
09-04-2019	09-04-2019

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2019/050060

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Palus et al. "Bis(2-amidophenyl) Diselenides Derived from Amino Acids and Dipeptides: Synthesis, Antiviral and Antimicrobial Activity" In: Polish J. Chem., 2008, Vol. 82, pp. 1015-1022.; abstract --	1-19
A	Zhang et al. "The tryptophan metabolite 3-hydroxyanthranilic acid lowers plasma lipids and decreases atherosclerosis in hypercholesterolaemic mice" In: Eur. Heart J., 2012, Vol. 33, pp. 2025-2034.; whole document --	1-19
A	Senten et al. "Polymer-assisted solution-phase parallel synthesis of dipeptide p-nitroanilides and dipeptide diphenyl phosphonates" In: Tet. Lett., 2001, Vol. 42, pp. 9135-9138.; whole document -- --------	1-19

International application No.
PCT/SE2019/050060

Continuation of: second sheet

International Patent Classification (IPC)

C07K 5/06 (2006.01)
C07K 1/06 (2006.01)
C07K 1/10 (2006.01)

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				CA	2051115	A1 16/08/1991
				JP	2685648	B2 03/12/1997
				WO	9112245	A1 22/08/1991
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				EA	023954	B1 29/07/2016
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				MX	343138	B 25/10/2016
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				ZA	201400695	B 28/10/2015
WO	0027800	A1	18/05/2000	NONE		