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(71) Applicants *(for all designated States except US)*: **THE REGENTS OF THE UNIVERSITY OF CALIFORNINA** [US/US]; 1111 Franklin Street, 12th Floor, Oakland, CA 94607-5200 (US). **FOGELMAN, Alan, M.** [US/US]; 481 Hillgreen Drive, Beverly Hills, CA 90212-4107 (US).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **NAVAB, Mohamad** [US/US]; 1135 North Bundy Drive, Los Angeles, CA 90049-1512 (US).

(74) Agents: **HUNTER, Tom** et al.; Beyer Weaver LLP, P.O. Box 70250, Oakland, CA 94612-0250 (US).

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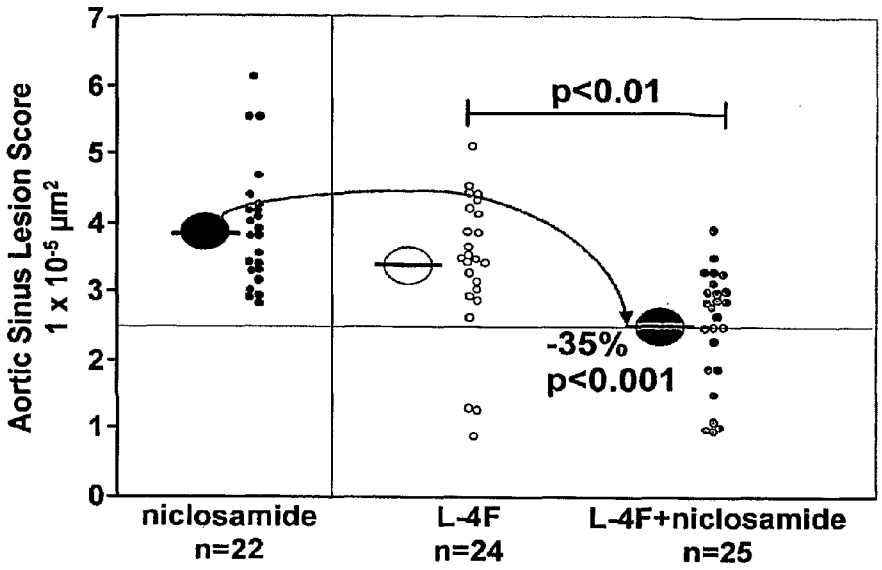
(54) **Title:** SALICYLANILIDES ENHANCE ORAL DELIVERY OF THERAPEUTIC PEPTIDES



(57) **Abstract:** This invention pertains to the surprising discovery that salicylanilides, e.g., niclosamide and/or niclosamide analogues when orally administered in conjunction with a peptide pharmaceutical (e.g., a class A amphipathic helical peptide as described herein) significantly increases the bioavailability of that peptide. Methods of peptide delivery using such "delivery agents" and pharmaceutical formulations are provided.

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SALICYLANILIDES ENHANCE ORAL DELIVERY OF THERAPEUTIC PEPTIDES

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to and benefit of USSN 60/836,501, filed on August 8, 2006, and USSN 60/868,845, filed on December 6, 2006, both of which are incorporated herein by reference in their entirety for all purposes.

STATEMENT AS TO RIGHTS TO INVENTIONS MADE UNDER FEDERALLY SPONSORED RESEARCH AND DEVELOPMENT

[0002] This work was supported, in part, by USPHS Grant 2 P01 HL-030568. The government of the United States of America may possess certain rights in this invention.

FIELD OF THE INVENTION

[0003] The present invention relates to oral peptide pharmaceuticals where the active compounds include a plurality of amino acids and at least one peptide bond in their molecular structures, and to methods of enhancing bioavailability of such peptide compounds when administered orally.

BACKGROUND OF THE INVENTION

[0004] Numerous human hormones, neurotransmitters, or therapeutic antibodies are peptides or comprise peptides as a substantial part of their molecular structures. Therapeutically effective amounts of such biologically relevant peptides may be administered to patients in a variety of ways. Oral delivery of pharmacologically active agents is generally the delivery route of choice since it is convenient, self administration is relatively easy and generally painless, resulting in greater patient compliance as compared to other modes of delivery.

[0005] Biological, chemical and physical barriers such as varying pH in the gastrointestinal tract, powerful digestive enzymes in the stomach and intestine, and active agent impermeable gastrointestinal membranes, however, often makes the effective delivery of peptide pharmaceuticals problematic. For example, the oral delivery of calcitonins, has proven difficult due, at least in part, to the insufficient stability of calcitonin in the

gastrointestinal tract as well as the inability of calcitonin to be readily transported through the intestinal walls into the blood stream.

[0006] Consequently, peptide pharmaceuticals used in the prior art frequently have been administered by injection or by nasal administration. Insulin is one example of a peptide pharmaceutical frequently administered by injection. Injection and nasal administration, however, are significantly less convenient than, and involve more patient discomfort than, oral administration. Often this inconvenience or discomfort results in substantial patient noncompliance with a treatment regimen. Thus, there is a need in the art for more effective and reproducible oral administration of peptide pharmaceuticals like insulin, calcitonin and others discussed in more detail herein.

SUMMARY OF THE INVENTION

[0007] This invention pertains to the surprising discovery that salicylanilides, e.g., niclosamide and/or niclosamide analogues when orally administered in conjunction with a peptide pharmaceutical (*e.g.*, a class A amphipathic helical peptide as described herein) significantly increase the bioavailability of that peptide. Methods of peptide delivery using such "delivery agents" and pharmaceutical formulations are provided.

[0008] Thus, in certain embodiments, compositions (*e.g.*, pharmaceutical formulations) are provided that comprise a therapeutic agent (*e.g.*, a therapeutic peptide) in combination with a salicylanilide (*e.g.*, niclosamide and/or a niclosamide analogue). In certain embodiments the salicylanilide comprises niclosamide or niclosamide analogue such as 2'5-dichloro-4'-nitrosalicylanilide, 5-chloro-salicyl-(2-chloro-4-nitro) anilide 2-aminoethanol salt, 5-chloro-salicyl-(2-chloro-4-nitro) anilide piperazine salt, and 5-chloro-salicyl-(2-chloro-4-nitro) anilide monohydrate. In certain embodiments the niclosamide analogue is a compound in Figures 2, 3, 4, 5, 6, 7, and/or Table 1. In various embodiments the peptide ranges in length from 3 amino acids to 300 amino acids, preferably from about 5 to about 200 amino acids, more preferably from about 5, 10, 15, 18, 20, 25, or 30 amino acids to about 200, 150, 100, 90, 70, or 50 amino acids. In various embodiments the peptide comprises an amphipathic helix. In certain embodiments the peptide is an ApoJ peptide, ApoA-I, ApoA-I milano, or 18A. In certain embodiments the peptide comprises a class A amphipathic helix. In various embodiments the peptide consists of all "L" amino acids, or one or more "D" amino acids, or all "D" amino acids. In certain embodiments the

peptide is a D or L peptide whose sequence is shown in any of Tables 2-11 and/or SEQ ID Nos:1-1176. In certain embodiments the peptide comprises a protecting group at the amino and/or carboxyl terminus. In certain embodiments the protecting group is a protecting group selected from the group consisting of acetyl, amide, and 3 to 20 carbon alkyl groups, Fmoc, Tboc, 9-fluoreneacetyl group, 1-fluorenecarboxylic group, 9-florenecarboxylic group, 9-fluorenone-1-carboxylic group, benzyloxycarbonyl, Xanthyl (Xan), Trityl (Trt), 4-methyltrityl (Mtt), 4-methoxytrityl (Mmt), 4-methoxy-2,3,6-trimethyl-benzenesulphonyl (Mtr), Mesitylene-2-sulphonyl (Mts), 4,4-dimethoxybenzhydryl (Mbh), Tosyl (Tos), 2,2,5,7,8-pentamethyl chroman-6-sulphonyl (Pmc), 4-methylbenzyl (MeBzl), 4-methoxybenzyl (MeOBzl), Benzyloxy (BzlO), Benzyl (Bzl), Benzoyl (Bz), 3-nitro-2-pyridinesulphenyl (Npys), 1-(4,4-dimentyl-2,6-diaxocyclohexylidene)ethyl (Dde), 2,6-dichlorobenzyl (2,6-DiCl-Bzl), 2-chlorobenzyloxycarbonyl (2-Cl-Z), 2-bromobenzyloxycarbonyl (2-Br-Z), Benzyloxymethyl (Bom), t-butoxycarbonyl (Boc), cyclohexyloxy (cHxO),t-butoxymethyl (Bum), t-butoxy (tBuO), t-Butyl (tBu), Acetyl (Ac), and Trifluoroacetyl (TFA). In certain embodiments the amino protecting group is a protecting group selected from the group consisting of acetyl, propeonyl, and a 3 to 20 carbon alkyl and/or the carboxyl said second protecting group is an amide. In certain embodiments the salyclanalide (*e.g.*, niclosamide or niclosamide analogue) and the therapeutic peptide are intermixed. in certain embodiments the salicylanilide (*e.g.* niclosamide or niclosamide analogue) and the therapeutic peptide are combined (*e.g.*, under acidic conditions) to form an adduct. In certain embodiments the composition is a unit dosage formulation. In certain embodiments the peptide and the salicylanilide are segregated from each other. In certain embodiments the composition is formulated so that the niclosamide or niclosamide analogue is released or solubilized before the peptide.

[0009] In certain embodiments said salicylanilide is niclosamide or a niclosamide analogue; and the peptide is a D or L peptide comprising the amino acid sequence DWFKAFYDKVAEKFKEAF (SEQ ID NO:5) or the amino acid sequence FAEKFKEAVKDYFAKFWD (SEQ ID NO:104). In certain embodiments the peptide comprises a carboxyl terminal protecting group (*e.g.*, an amide) and/or an amino terminal protecting group (*e.g.*, acetyl). In certain embodiments the niclosamide or niclosamide analogue is niclosamide. In certain embodiments the niclosamide forms an adduct with the peptide.

[0010] In various embodiments methods are provided for enhancing the *in vivo* activity of a therapeutic peptide orally administered to a mammal *(e.g.,* a human or a non-human mammal). The methods typically involve orally administering the peptide in conjunction with an amount of niclosamide or a niclosamide analogue sufficient to enhance the *in vivo activity* of the peptide. In various embodiments the peptide ranges in length from 3 amino acids to 300 amino acids, preferably from about 5 to about 200 amino acids, more preferably from about 5, 10, 15, 18, 20, 25, or 30 amino acids to about 200, 150, 100, 90, 70, or 50 amino acids. In various embodiments the peptide comprises an amphipathic helix. In certain embodiments the peptide is an ApoJ peptide, ApoA-I, ApoA-I milano (Apolipoprotein M), or 18A. In certain embodiments the peptide comprises a class A amphipathic helix. In various embodiments the peptide consists of all "L" amino acids, or one or more "D" amino acids, or all "D" amino acids. In certain embodiments the peptide is a D or L peptide whose sequence is shown in any of Tables 2-11 and/or SEQ ID Nos:1-1175. In certain embodiments the peptide is a D or L peptide comprising the amino acid sequence DWFKAFYDKVAEKFKEAF (SEQ ID NO:5) or the amino acid sequence FAEKFKEAVKDYFAKFWD (SEQ ID NO:104). In certain embodiments the peptide comprises a carboxyl terminal protecting group (*e.g.,* an amide) and/or an amino terminal protecting group (*e.g.,* acetyl). In various embodiments the peptide used in this method are protected with a carboxyl and/or an amino protecting group as described herein (*e.g.,* a protecting group selected from the group consisting of acetyl, amide, and 3 to 20 carbon alkyl groups, Fmoc, Tboc, 9-fluoreneacetyl group, 1-fluorenecarboxylic group, 9-florenecarboxylic group, 9-fluorenone-1-carboxylic group, benzyloxycarbonyl, Xanthyl (Xan), Trityl (Trt), 4-methyltrityl (Mtt), 4-methoxytrityl (Mmt), 4-methoxy-2,3,6-trimethyl-benzenesulphonyl (Mtr), Mesitylene-2-sulphonyl (Mts), 4,4-dimethoxybenzhydryl (Mbh),Tosyl (Tos), 2,2,5,7,8-pentamethyl chroman-6-sulphonyl (Pmc), 4-methylbenzyl (MeBzl), 4-methoxybenzyl (MeOBzl), Benzyloxy (BzlO), Benzyl (Bzl), Benzoyl (Bz), 3-nitro-2-pyridinesulphenyl (Npys), 1-(4,4-dimentyl-2,6-diaxocyclohexylidene)ethyl (Dde), 2,6-dichlorobenzyl (2,6-DiCl-Bzl), 2-chlorobenzyloxycarbonyl (2-Cl-Z), 2-bromobenzyloxycarbonyl (2-Br-Z), Benzyloxymethyl (Bom), t-butoxycarbonyl (Boc), cyclohexyloxy (cHxO),t-butoxymethyl (Bum), t-butoxy (tBuO), t-Butyl (tBu), Acetyl (Ac), and Trifluoroacetyl (TFA)). In various embodiments the niclosamide or niclosamide analogue is administered before administration of said peptide. In various embodiments the

niclosamide or niclosamide analogue is administered at the same time as said peptide. In certain embodiments the niclosamide or niclosamide analogue is combined with the peptide to form an adduct. In certain embodiments the niclosamide analogue is a compound in Figures 2, 3, 4, 5, 6, 7, and/or Table 1.

[0011] In another embodiment pharmaceutical formulations are provided. The formulations typically comprise an orally administered pharmacologically active agent (*e.g.*, a therapeutic peptide); and a salicylanilide (*e.g.*, niclosamide and/or a niclosamide analogue). In certain embodiments the pharmacologically active agent is a therapeutic peptide and the peptide and the salicylanilide form an adduct. In certain embodiments the pharmaceutically active agent is not a non-peptide antiproliferative agent and/or not a non-peptide anti-cancer drug. In certain embodiments the pharmaceutically active agent is a peptide antiproliferative agent. In certain embodiments the formulation comprises a therapeutic amphipathic helical peptide; and niclosamide and/or a niclosamide analogue, where the niclosamide and/or niclosamide analogue in the formulation shows substantially greater solubility in an aqueous solution than the niclosamide and/or niclosamide analogue in an aqueous solution absent the amphipathic helical peptide. In certain embodiments the peptide is selected from the group consisting of ApoJ, ApoA-I, ApoA-I milano, or 18A. In certain embodiments the peptide forms a class A amphipathic helix. In certain embodiments the peptide consists of all "L" amino acids, or at least one "D" amino acid, or all "D" amino acids. In various embodiments the peptide consists of all "L" amino acids, or one or more "D" amino acids, or all "D" amino acids. In certain embodiments the peptide is a D or L peptide whose sequence is shown in any of Tables 2-11 and/or SEQ ID Nos:1-1175. In certain embodiments the peptide is a D or L peptide comprising the amino acid sequence DWFKAFYDKVAEKFKEAF (SEQ ID NO:5) or the amino acid sequence FAEKFKEAVKDYFAKFWD (SEQ ID NO:104). In certain embodiments the peptide comprises a carboxyl terminal protecting group (*e.g.*, an amide) and/or an amino terminal protecting group (*e.g.*, acetyl). In various embodiments the peptides used in this method are protected with a carboxyl and/or an amino protecting group as described herein (*e.g.*, a protecting group selected from the group consisting of acetyl, amide, and 3 to 20 carbon alkyl groups, Fmoc, Tboc, 9-fluoreneacetyl group, 1-fluorenecarboxylic group, 9-florenecarboxylic group, 9-fluorenone-1-carboxylic group, benzyloxycarbonyl, Xanthyl (Xan), Trityl (Trt), 4-methyltrityl (Mtt), 4-methoxytrityl (Mmt), 4-methoxy-2,3,6-trimethyl-

benzenesulphonyl (Mtr), Mesitylene-2-sulphonyl (Mts), 4,4-dimethoxybenzhydryl (Mbh),Tosyl (Tos), 2,2,5,7,8-pentamethyl chroman-6-sulphonyl (Pmc), 4-methylbenzyl (MeBzl), 4-methoxybenzyl (MeOBzl), Benzyloxy (BzlO), Benzyl (Bzl), Benzoyl (Bz), 3-nitro-2-pyridinesulphenyl (Npys), 1-(4,4-dimentyl-2,6-diaxocyclohexylidene)ethyl (Dde), 2,6-dichlorobenzyl (2,6-DiCl-Bzl), 2-chlorobenzyloxycarbonyl (2-Cl-Z), 2-bromobenzyloxycarbonyl (2-Br-Z), Benzyloxymethyl (Bom), t-butoxycarbonyl (Boc), cyclohexyloxy (cHxO),t-butoxymethyl (Bum), t-butoxy (tBuO), t-Butyl (tBu), Acetyl (Ac), and Trifluoroacetyl (TFA)). In various embodiments the niclosamide or niclosamide analogue is administered before administration of said peptide. In various embodiments the niclosamide or niclosamide analogue is administered at the same time as said peptide. In certain embodiments the niclosamide or niclosamide analogue is combined with the peptide to form an adduct. In certain embodiments the niclosamide or niclosamide analogue is a compound in Figures 2, 3, 4, 5, 6, 7, and/or Table 1.

[0012] Also provided are methods of mitigating one or more symptoms of a pathology characterized by an inflammatory response in a mammal (*e.g.*, a human, a non-human primate, a feline, an equine, a porcine, a bovine, a rodent, *etc.*). The methods typically involve orally administering to the mammal an amphipathic helical peptide that mitigates one or more symptoms of atherosclerosis or other pathology characterized by an inflammatory response in conjunction with niclosamide or a niclosamide analogue, whereby the oral delivery provides *in vivo* activity of the peptide to mitigate one or more symptoms of the pathology. In certain embodiments the niclosamide or niclosamide analogue is administered before the peptide, or administered simultaneously with peptide. In certain embodiments the niclosamide or niclosamide analogue and the peptide are administered as a single formulation. In certain embodiments the niclosamide or niclosamide analogue and the peptide are combined to form an adduct prior to administration. In certain embodiments the niclosamide or niclosamide analogue is selected from the group consisting of 2'5-dichloro-4'-nitrosalicylanilide, 5-chloro-salicyl-(2-chloro-4-nitro) anilide 2-aminoethanol salt, 5-chloro-salicyl-(2-chloro-4-nitro) anilide piperazine salt, and 5-chloro-salicyl-(2-chloro-4-nitro) anilide monohydrate. In certain embodiments the niclosamide or niclosamide analogue is a compound in Figures 2, 3, 4, 5, 6, 7, and/or Table 1. In certain embodiments the niclosamide or niclosamide analogue and/or the peptide are administered as a unit dosage formulation. In certain embodiments the niclosamide or niclosamide

analogue and the peptide are administered as a unit dosage formulation formulated so that the niclosamide or niclosamide analogue is released or solubilized simultaneously with, or before the peptide. In certain embodiments the pathology is selected from the group consisting of atherosclerosis, rheumatoid arthritis, lupus erythematous, polyarteritis nodosa, osteoporosis, Altzheimer's disease, multiple sclerosis, chronic obstructive pulmonary disease, asthma, diabetes, and a viral illnesses. . In various embodiments the peptide ranges in length from 3 amino acids to 300 amino acids, preferably from about 5 to about 200 amino acids, more preferably from about 5, 10, 15, 18, 20, 25, or 30 amino acids to about 200, 150, 100, 90, 70, or 50 amino acids. In various embodiments the peptide comprises an amphipathic helix. In certain embodiments the peptide is an ApoJ peptide, ApoA-I, ApoA-I milano (Apolipoprotein M), or 18A. In certain embodiments the peptide comprises a class A amphipathic helix. In various embodiments the peptide consists of all "L" amino acids, or one or more "D" amino acids, or all "D" amino acids. In certain embodiments the peptide is a D or L peptide whose sequence is shown in any of Tables 2-11 and/or SEQ ID Nos:1-1175. In certain embodiments the peptide is a D or L peptide comprising the amino acid sequence DWFKAFYDKVAEKFKEAF (SEQ ID NO:5) or the amino acid sequence FAEKFKEAVKDYFAKFWD (SEQ ID NO:104). In certain embodiments the peptide comprises a carboxyl terminal protecting group (*e.g.*, an amide) and/or an amino terminal protecting group (*e.g.*, acetyl). In various embodiments the peptide used in this method are protected with a carboxyl and/or an amino protecting group as described herein (*e.g.*, a protecting group selected from the group consisting of acetyl, amide, and 3 to 20 carbon alkyl groups, Fmoc, Tboc, 9-fluoreneacetyl group, 1-fluorenecarboxylic group, 9-florenecarboxylic group, 9-fluorenone-1-carboxylic group, benzyloxycarbonyl, Xanthyl (Xan), Trityl (Trt), 4-methyltrityl (Mtt), 4-methoxytrityl (Mmt), 4-methoxy-2,3,6-trimethyl-benzenesulphonyl (Mtr), Mesitylene-2-sulphonyl (Mts), 4,4-dimethoxybenzhydryl (Mbh),Tosyl (Tos), 2,2,5,7,8-pentamethyl chroman-6-sulphonyl (Pmc), 4-methylbenzyl (MeBzl), 4-methoxybenzyl (MeOBzl), Benzyloxy (BzlO), Benzyl (Bzl), Benzoyl (Bz), 3-nitro-2-pyridinesulphenyl (Npys), 1-(4,4-dimentyl-2,6-diaxocyclohexylidene)ethyl (Dde), 2,6-dichlorobenzyl (2,6-DiCl-Bzl), 2-chlorobenzyloxycarbonyl (2-Cl-Z), 2-bromobenzyloxycarbonyl (2-Br-Z), Benzyloxymethyl (Bom), t-butoxycarbonyl (Boc), cyclohexyloxy (cHxO),t-butoxymethyl (Bum), t-butoxy (tBuO), t-Butyl (tBu), Acetyl (Ac), and Trifluoroacetyl (TFA)).

[0013] In various embodiments kits are provided. In certain embodiments the kits comprise a container containing a salicylanilide and a therapeutic peptide. The salicylanilide and the peptide can be in separate containers or combined in a single container. In certain embodiments the salicylanilide and the peptide are combined to form an adduct. In various embodiments the salicylanilide is niclosamide or a niclosamide analogue as described herein. In certain embodiments the peptide is a therapeutic peptide as described herein (*e.g.*, ApoJ, ApoA-I, ApoA-I milano, and 18A, D-4F, L-4F, retro D-4F, retro L-4F, *etc.*).

[0014] In certain embodiments this invention also contemplates formulations and methods where the salicylanilide (*e.g.*, niclosamide and/or a niclosamide analogue) is replaced or used in combination with any one or more of the other "delivery agents" described herein (*e.g.*, N-(5-chlorosalicyloyl)-8-aminocaprylic acid (5-CNAC), N-(10-[2-hydroxybenzoyl]aminodecanoic acid (SNAD), and N-(8-[2-hydroxybenzoyl]amino)caprylic acid (SNAC) and various salts thereof (*e.g.*, disodium salts), any one or more of the delivery agents disclosed in U.S. Patent 5,866,536, U.S. Patent 5,773,647, and WO 00/059863, and the like).

[0015] In certain embodiments this invention excludes formulations and/or methods utilizing any one or more of the delivery agents disclosed in U.S. Patent 5,866,536, U.S. Patent 5,773,647, WO 00/059863.

[0016] In certain embodiments niclosamide analogs used in the methods and compositions described herein include, but are not limited to those defined by Formula I, where substituents R^1, R^2, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11} and R^{12} are as described herein. In certain embodiments these substituents do not comprise one or more of the following moieties: carboxylic acid, and/or alkyl carboxylates, and/or hydroxamic acid and/or alkyl hydroxamates, and/or sulfonic acid and/or alkyl sulfones, and/or phosphoric acid and/or alkyl phosphates, and/or tetrazole.

DEFINITIONS

[0017] The phrase "enhancing the *in vivo* activity" or "enhancing the apparent activity" when referring to the agents described herein indicates that the agents, when administered in conjunction with an orally delivered pharmaceutical produce a greater

biological response in the organism than the same dosage orally administered without the agent. Without being bound to a particular theory, the *in vivo* activity can be enhanced by any of a number of mechanisms including, but not limited to increased absorption, decreased degradation, a combination of increased absorption and decreased degradation, enhanced active transport, and the like.

[0018] The terms "coadministration" or "administration in conjunction with" when used in reference to the use of a delivery agent (*e.g.*, niclosamide, niclosamide analogue or other delivery agent described herein) in conjunction with an orally administered pharmaceutical (*e.g.*, a therapeutic peptide such as L-4F) indicates that the delivery agent and the orally administered pharmaceutical are administered so that there is at least some chronological overlap in the activity of the delivery agent and administration of the pharmaceutical such that the delivery agent enhances *in vivo* activity (*e.g.*, via increased uptake and/or bioavailability) of the pharmaceutical. In sequential administration there may even be some substantial delay (*e.g.*, minutes or even hours) between administration of the delivery agent and the pharmaceutical as long as the delivery agent is present in a manner that enhances *in vivo* activity of the pharmaceutical.

[0019] The term mammal includes essentially any mammal including, but not limited to dogs, cats, sheep, cattle, horses, goats, mice, rabbits, hamsters, pigs, monkeys and other non-human primates, and humans. Thus, veterinary as well as medical applications of this invention are contemplated.

[0020] The term "oral bioavailability" refers to the bioavailablity (*e.g.*, plasma concentration) of an active agent when administered orally (*e.g.*, in an oral formulation).

[0021] The term "L form peptide" refers to a peptide comprising all L form amino acids.

[0022] The term "D form peptide" refers to a peptide comprising at least one D amino acid. In certain embodiments at least half, and preferably all of the amino acids are D amino acids.

[0023] The term "treat" when used with reference to treating, *e.g.*, a pathology or disease refers to the mitigation and/or elimination of one or more symptoms of that

pathology or disease, and/or a reduction in the rate of onset or severity of one or more symptoms of that pathology or disease, and/or the prevention of that pathology or disease.

[0024] The terms "isolated", "purified", or "biologically pure" when referring to an isolated polypeptide refer to material that is substantially or essentially free from components that normally accompany it as found in its native state. With respect to nucleic acids and/or polypeptides the term can refer to nucleic acids or polypeptides that are no longer flanked by the sequences typically flanking them in nature. Chemically synthesized polypeptides are "isolated" because they are not found in a native state (*e.g.*, in blood, serum, *etc.*). In certain embodiments, the term "isolated" indicates that the polypeptide is not found in nature.

[0025] The terms "polypeptide", "peptide" and "protein" are used interchangeably herein to refer to a polymer of amino acid residues. The terms apply to amino acid polymers in which one or more amino acid residues is an artificial chemical analogue of a corresponding naturally occurring amino acid, as well as to naturally occurring amino acid polymers. Where the amino acid sequence of a peptide is provided the description of that peptide includes L peptides, D peptides, inverse peptides, retro peptides, and retroinverse peptides.

[0026] The term "an amphipathic helical peptide" refers to a peptide comprising at least one amphipathic helix (amphipathic helical domain). Certain amphipathic helical peptides of this invention can comprise two or more (*e.g.*, 3, 4, 5, *etc.*) amphipathic helices.

[0027] The term "class A amphipathic helix" refers to a protein structure that forms an α-helix producing a segregation of a polar and nonpolar faces with the positively charged residues residing at the polar-nonpolar interface and the negatively charged residues residing at the center of the polar face (*see, e.g.*, Segrest *et al.* (1990) *Proteins: Structure, Function, and Genetics* 8: 103-117).

[0028] "Apolipoprotein J" (apo J) is known by a variety of names including clusterin, TRPM2, GP80, and SP 40 (*see, e.g.*, Fritz (1995) Pp 112 In: *Clusterin: Role in Vertebrate Development, Function, and Adaptation* (Harmony JAK Ed.), R.G. Landes, Georgetown, TX,). It was first described as a heterodimeric glycoprotein and a component of the secreted proteins of cultured rat Sertoli cells (*see, e.g.*, Kissinger *et al.* (1982) *Biol. Reprod.*; 27: 233240). The translated product is a single-chain precursor protein that

undergoes intracellular cleavage into a disulfide-linked 34kDa α subunit and a 47 kDa β subunit (*see, e.g.,* Collard and Griswold (1987) *Biochem.*, 26: 3297-3303). It has been associated with cellular injury, lipid transport, apoptosis and it may be involved in clearance of cellular debris caused by cell injury or death. Clusterin has been shown to bind to a variety of molecules with high affinity including lipids, peptides, and proteins and the hydrophobic probe 1-anilino-8-naphthalenesulfonate (Bailey *et al.* (2001) *Biochem.*, 40: 11828-11840).

[0029] The class G amphipathic helix is found in globular proteins, and thus, the name class G. The feature of this class of amphipathic helix is that it possesses a random distribution of positively charged and negatively charged residues on the polar face with a narrow nonpolar face. Because of the narrow nonpolar face this class does not readily associate with phospholipid (*see, e.g.,* Segrest *et al.* (1990) *Proteins: Structure, Function, and Genetics*. 8: 103-117; Erratum (1991) *Proteins: Structure, Function and Genetics*, 9: 79). Several exchangeable apolipoproteins possess similar but not identical characteristics to the G amphipathic helix. Similar to the class G amphipathic helix, this other class possesses a random distribution of positively and negatively charged residues on the polar face. However, in contrast to the class G amphipathic helix which has a narrow nonpolar face, this class has a wide nonpolar face that allows this class to readily bind phospholipid and the class is termed G* to differentiate it from the G class of amphipathic helix (*see, e.g.,* Segrest *et al.* (1992) *J. Lipid Res.*, 33: 141-166; Anantharamaiah *et al.* (1993) Pp. 109-142 In: *The Amphipathic Helix,* Epand, R.M. Ed CRC Press, Boca Raton, Florida). Computer programs to identify and classify amphipathic helical domains have been described by Jones *et al.*(1992) *J. Lipid Res.* 33: 287-296) and include, but are not limited to the helical wheel program (WHEEL or WHEEL/SNORKEL), helical net program (HELNET, HELNET/SNORKEL, HELNET/Angle), program for addition of helical wheels (COMBO or COMBO/SNORKEL), program for addition of helical nets (COMNET, COMNET/SNORKEL, COMBO/SELECT, COMBO/NET), consensus wheel program (CONSENSUS, CONSENSUS/SNORKEL), and the like.

[0030] The term "ameliorating" when used with respect to "ameliorating one or more symptoms of atherosclerosis" refers to a reduction, prevention, or elimination of one or more symptoms characteristic of atherosclerosis and/or associated pathologies. Such a reduction includes, but is not limited to a reduction or elimination of oxidized

phospholipids, a reduction in atherosclerotic plaque formation and rupture, a reduction in clinical events such as heart attack, angina, or stroke, a decrease in hypertension, a decrease in inflammatory protein biosynthesis, reduction in plasma cholesterol, and the like.

[0031] The term "enantiomeric amino acids" refers to amino acids that can exist in at least two forms that are nonsuperimposable mirror images of each other. Most amino acids (except glycine) are enantiomeric and exist in a so-called L-form (L amino acid) or D-form (D amino acid). Most naturally occurring amino acids are "L" amino acids. The terms "D amino acid" and "L amino acid" are used to refer to absolute configuration of the amino acid, rather than a particular direction of rotation of plane-polarized light. The usage herein is consistent with standard usage by those of skill in the art. Amino acids are designated herein using standard 1-letter or three-letter codes, *e.g.*, as designated in Standard ST.25 in the Handbook On Industrial Property Information and Documentation.

[0032] The term "protecting group" refers to a chemical group that, when attached to a functional group in an amino acid (*e.g.*, a side chain, an alpha amino group, an alpha carboxyl group, *etc.*) blocks or masks the properties of that functional group. In certain embodiments amino-terminal protecting groups include, but are not limited to acetyl, or amino groups. Other amino-terminal protecting groups include, but are not limited to alkyl chains as in fatty acids, propeonyl, formyl and others. In certain embodiments, preferred carboxyl terminal protecting groups include, but are not limited to, groups that form amides or esters.

[0033] The phrase "protect a phospholipid from oxidation by an oxidizing agent" refers to the ability of a compound to reduce the rate of oxidation of a phospholipid (or the amount of oxidized phospholipid produced) when that phospholipid is contacted with an oxidizing agent (*e.g.*, hydrogen peroxide, 13-(S)-HPODE, 15-(S)-HPETE, HPODE, HPETE, HODE, HETE, *etc.*).

[0034] The terms "low density lipoprotein" or "LDL" is defined in accordance with common usage of those of skill in the art. Generally, LDL refers to the lipid-protein complex which when isolated by ultracentrifugation is found in the density range d = 1.019 to d = 1.063.

[0035] The terms "high density lipoprotein" or "HDL" is defined in accordance with common usage of those of skill in the art. Generally "HDL" refers to a lipid-protein

complex which when isolated by ultracentrifugation is found in the density range of d = 1.063 to d = 1.21.

[0036] The term "Group I HDL" refers to a high density lipoprotein or components thereof (*e.g.*, apo A-I, paraoxonase, platelet activating factor acetylhydrolase, *etc.*) that reduce oxidized lipids (*e.g.*, in low density lipoproteins) or that protect oxidized lipids from oxidation by oxidizing agents.

[0037] The term "Group II HDL" refers to an HDL that offers reduced activity or no activity in protecting lipids from oxidation or in repairing (*e.g.*, reducing) oxidized lipids.

[0038] The term "HDL component" refers to a component (*e.g.*, molecules) that comprises a high density lipoprotein (HDL). Assays for HDL that protect lipids from oxidation or that repair (*e.g.*, reduce oxidized lipids) also include assays for components of HDL (*e.g.*, apo A-I, paraoxonase, platelet activating factor acetylhydrolase, *etc.*) that display such activity.

[0039] The terms "human apo A-I peptide" or "human apo A-I protein" can refer to a full-length human apo A-I peptide or to a fragment or domain thereof comprising a class A amphipathic helix.

[0040] A "monocytic reaction" as used herein refers to monocyte activity characteristic of the "inflammatory response" associated with atherosclerotic plaque formation. The monocytic reaction is characterized by monocyte adhesion to cells of the vascular wall (*e.g.*, cells of the vascular endothelium), and/or chemotaxis into the subendothelial space, and/or differentiation of monocytes into macrophages.

[0041] The following abbreviations may be used herein: PAPC: L-α-1-palmitoyl-2-arachidonoyl-*sn*-glycero-3-phosphocholine; POVPC: 1-palmitoyl-2-(5-oxovaleryl)-*sn*-glycero-3-phosphocholine; PGPC: 1-palmitoyl-2-glutaryl-*sn*-glycero-3-phosphocholine; PEIPC: 1-palmitoyl-2-(5,6-epoxyisoprostane E_2)-*sn*-glycero-3-phosphocholine; ChC18:2: cholesteryl linoleate; ChC18:2-OOH: cholesteryl linoleate hydroperoxide; DMPC: 1,2-ditetradecanoyl-rac-glycerol-3-phosphocholine; PON: paraoxonase; HPF: Standardized high power field; PAPC: L-α-1-palmitoyl-2-arachidonoyl-*sn*-glycero-3-phosphocholine; BL/6: C57BL/6J; C3H:C3H/HeJ.

[0042] The term "conservative substitution" is used in reference to proteins or peptides to reflect amino acid substitutions that do not substantially alter the activity (specificity (*e.g.*, for lipoproteins)) or binding affinity (*e.g.*, for lipids or lipoproteins)) of the molecule. Typically conservative amino acid substitutions involve substitution one amino acid for another amino acid with similar chemical properties (*e.g.*, charge or hydrophobicity). The following six groups each contain amino acids that are typical conservative substitutions for one another: 1) Alanine (A), Serine (S), Threonine (T); 2) Aspartic acid (D), Glutamic acid (E); 3) Asparagine (N), Glutamine (Q); 4) Arginine (R), Lysine (K); 5) Isoleucine (I), Leucine (L), Methionine (M), Valine (V); and 6) Phenylalanine (F), Tyrosine (Y), Tryptophan (W).

[0043] The terms "identical" or percent "identity," in the context of two or more nucleic acids or polypeptide sequences, refer to two or more sequences or subsequences that are the same or have a specified percentage of amino acid residues or nucleotides that are the same, when compared and aligned for maximum correspondence, as measured using one of the following sequence comparison algorithms or by visual inspection. With respect to the peptides of this invention sequence identity is determined over the full length of the peptide.

[0044] One example of algorithm that is suitable for determining percent sequence identity and sequence similarity is the BLAST algorithm, which is described in Altschul *et al.* (1990) *J. Mol. Biol.* 215: 403-410. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information (http://www.ncbi.nlm.nih.gov/). This algorithm involves first identifying high scoring sequence pairs (HSPs) by identifying short words of length W in the query sequence, which either match or satisfy some positive-valued threshold score T when aligned with a word of the same length in a database sequence. T is referred to as the neighborhood word score threshold (Altschul *et al, supra*). These initial neighborhood word hits act as seeds for initiating searches to find longer HSPs containing them. The word hits are then extended in both directions along each sequence for as far as the cumulative alignment score can be increased. Cumulative scores are calculated using, for nucleotide sequences, the parameters M (reward score for a pair of matching residues; always > 0) and N (penalty score for mismatching residues; always < 0). For amino acid sequences, a scoring matrix is used to calculate the cumulative score. Extension of the word hits in each direction are halted

when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T, and X determine the sensitivity and speed of the alignment. The BLASTN program (for nucleotide sequences) uses as defaults a word length (W) of 11, an expectation (E) of 10, M=5, N=-4, and a comparison of both strands. For amino acid sequences, the BLASTP program uses as defaults a word length (W) of 3, an expectation (E) of 10, and the BLOSUM62 scoring matrix (*see* Henikoff & Henikoff (1989) *Proc. Natl. Acad. Sci. USA* 89:10915).

[0045] In addition to calculating percent sequence identity, the BLAST algorithm also performs a statistical analysis of the similarity between two sequences (*see, e.g.*, Karlin & Altschul (1993) *Proc. Natl. Acad. Sci. USA* ,90: 5873-5787). One measure of similarity provided by the BLAST algorithm is the smallest sum probability (P(N)), which provides an indication of the probability by which a match between two nucleotide or amino acid sequences would occur by chance. For example, a nucleic acid is considered similar to a reference sequence if the smallest sum probability in a comparison of the test nucleic acid to the reference nucleic acid is less than about 0.1, more preferably less than about 0.01, and most preferably less than about 0.001.

[0046] The phrases "adjacent to each other in a helical wheel diagram of a peptide" or "contiguous in a helical wheel diagram of a peptide" when referring to residues in a helical peptide indicates that in the helical wheel representation the residues appear adjacent or contiguous even though they may not be adjacent or contiguous in the linear peptide.

[0047] As used herein, the terms "alkyl" and the prefix "alk-" are inclusive of both straight chain and branched chain groups and of cyclic groups, i.e., cycloalkyl. Cyclic groups can be monocyclic or polycyclic and preferably have from 3 to 6 ring carbon atoms, inclusive. Illustrative cyclic groups include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl groups. The C_{1-10} alkyl group can be substituted or unsubstituted. Illustrative substituents include alkoxy, aryloxy, sulfhydryl, alkylthio, arylthio, halide, hydroxyl, fluoroalkyl, perfluoralkyl, amino, aminoalkyl, disubstituted amino, quaternary amino, hydroxyalkyl, carboxyalkyl, and carboxyl groups. C_{1-10} alkyls include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, cyclopropyl, cyclopropylmethyl, cyclopropylethyl, n-

butyl, iso-butyl, sec-butyl, tert-butyl, cyclobutyl, cyclobutylmethyl, cyclobutylethyl, n-pentyl, cyclopentyl, cyclopentylmethyl, cyclopentylethyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 2,2-dimethylpropyl, 1-ethylpropyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl, 1-ethylbutyl, 2-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-timethylpropyl, 1-ethyl-l-methylpropyl, 1-ethyl-2-methylpropyl, cyclohexyl, and the like.

[0048] A "C_{2-10} alkenyl" refers to a branched or unbranched hydrocarbon group containing one or more double bonds and having from 2 to 10 carbon atoms. A C_{2-10} alkenyl can optionally include monocyclic or polycyclic rings, in which each ring has from three to six members. The C_{2-10} alkenyl group can be substituted or unsubstituted. Illustrative substituents include alkoxy, aryloxy, sulfhydryl, alkylthio, arylthio, halide, hydroxyl, fluoroalkyl, perfluoralkyl, amino, aminoalkyl, disubstituted amino, quaternary amino, hydroxyalkyl, carboxyalkyl, and carboxyl groups. C_{2-10} alkenyls include, but are not limited to, vinyl; allyl; 2-cyclopropyl-1-ethenyl; 1-propenyl; 1 -butenyl; 2-butenyl; 3-butenyl; 2-methyl-1 - propenyl; 2-methyl-2-propenyl; 1-pentenyl; 2-pentenyl; 3-pentenyl; 4-pentenyl; 3-methyl-l-butenyl; 3-methyl-2-butenyl; 3-methyl-3-butenyl; 2-methyl-l-butenyl; 2-methyl-2-butenyl; 2-methyl-3-butenyl; 2-ethyl-2-propenyl; 1-methyl-1-butenyl; 1-methyl-2-butenyl; 1-methyl-3-butenyl; 2-methyl-2-pentenyl; 3-methyl-2-pentenyl; 4-methyl-2-pentenyl; 2-methyl-3-pentenyl; 3-methyl-3-pentenyl; 4-methyl-3-pentenyl; 2-methyl-4-pentenyl; 3-methyl-4-pentenyl; 1,2-dimethyl-1-propenyl; 1,2-dimethyl-1-butenyl; 1,3-dimethyl-l-butenyl; 1,2-dimethyl-2-butenyl; 1,1-dimethyl-2-butenyl; 2,3-dimethyl-2-butenyl; 2,3-dimethyl-3-butenyl; 1,3-dimethyl-3-butenyl; 1,1-dimethyl-3-butenyl, 2,2-dimethyl-3-butenyl, and the like.

[0049] A "C_{2-10} alkynyl" refers to a branched or unbranched hydrocarbon group containing one or more triple bonds and having from 2 to 10 carbon atoms. A C_{2-10} alkynyl can optionally include monocyclic, bicyclic, or tricyclic rings, in which each ring has five or six members. The C_{2-10} alkynyl group can be substituted or unsubstituted. Illustrative substituents include alkoxy, aryloxy, sulfhydryl, alkylthio, arylthio, halide, hydroxy, fluoroalkyl, perfluoralkyl, amino, aminoalkyl, disubstituted amino, quaternary amino, hydroxyalkyl, carboxyalkyl, and carboxyl groups. C_{2-10} alkynyls include, but are not limited to, ethynyl, 1- propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butenyl, 1-

pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 5-hexene-1-ynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl; 1-methyl-2-propynyl; 1-methyl-2-butenyl; 1-methyl-3-butynyl; 2-methyl-3-butynyl; 1,2-dimethyl-3-butynyl; 2,2-dimethyl-3-butynyl; 1-methyl-2-pentynyl; 2-methyl-3-pentynyl; 1-methyl-4-pentynyl; 2-methyl-4-pentynyl, 3-methyl-4-pentynyl, and the like.

[0050] A "C_{2-6} heterocyclyl" refers to a stable 5- to 7-membered monocyclic or 7- to 14-membered bicyclic heterocyclic ring that is saturated, partially unsaturated or unsaturated (aromatic), and that consists of 2 to 6 carbon atoms and 1, 2, 3 or 4 heteroatoms independently selected from the group consisting of N, 0, and S and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclyl group can be substituted or unsubstituted. Illustrative substituents include, but are not limited to alkoxy, aryloxy, sulfhydryl, alkylthio, arylthio, halide, hydroxy, fluoroalkyl, perfluoralkyl, amino, aminoalkyl, disubstituted amino, quaternary amino, hydroxyalkyl, carboxyalkyl, and carboxyl groups. The nitrogen and sulfur heteroatoms can optionally be oxidized. The heterocyclic ring can be covalently attached via any heteroatom or carbon atom that results in a stable structure, e.g., an imidazolinyl ring can be linked at either of the ring-carbon atom positions or at the nitrogen atom. A nitrogen atom in the heterocycle can optionally be quaternized. In certain embodiments, when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another. Heterocycles include, but are not limited to, 1H-indazole, 2-pyrrolidonyl, 2H,6H-1,5,2-dithiazinyl, 2H-pyrrolyl, 3H-indolyl, 4-piperidonyl, 4aH-carbazole, 4H-quinolizinyl, 6H-1,2,5-thiadiazinyl, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazalonyl, carbazolyl, 4aH-carbazolyl, b-carbolinyl, chromanyl, chromenyl, cinolinyl, decahydroquinolinyl, 2H,6H-1,5,2-dithiazinyl, dihydrofuro[2,3-bjtetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinylperimidinyl, phenanthridinyl, phenanthrolinyl, phenarsazinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl,

piperidinyl, pteridinyl, piperidonyl, 4-piperidonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, pyrrolyl, quinolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, carbolinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, xanthenyl. Preferred 5 to 10 membered heterocycles include, but are not limited to, pyridinyl, pyrimidinyl, triazinyl, furanyl, thienyl, thiazolyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, tetrazolyl, benzofuranyl, benzothiofuranyl, indolyl, benzimidazolyl, 1H-indazolyl, oxazolidinyl, isoxazolidinyl, benzotriazolyl, benzisoxazolyl, oxindolyl, benzoxazolinyl, quinolinyl, and isoquinolinyl. In certain embodiments, 5 to 6 membered heterocycles include, but are not limited to, pyridinyl, pyrimidinyl, triazinyl, furanyl, thienyl, thiazolyl, pyrrolyl, piperazinyl, piperidinyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, tetrazolyl, and the like.

[0051] A "C_{6-12} aryl" refers to an aromatic group having a ring system comprised of carbon atoms with conjugated electrons (e.g., phenyl). The aryl group typically has from 6 to 12 carbon atoms. Aryl groups can optionally include monocyclic, bicyclic, or tricyclic rings, in which each ring has five or six members. The aryl group can be substituted or unsubstituted. Illustrative substituents include, but are not limited to, alkyl, hydroxy, alkoxy, aryloxy, sulflhydryl, alkylthio, arylthio, halide, fluoroalkyl, carboxyl, hydroxyalkyl, carboxyalkyl, amino, aminoalkyl, monosubstituted amino, disubstituted amino, quaternary amino groups, and the like.

[0052] A "C_{7-14} alkaryl" refers to an alkyl substituted by an aryl group (e.g., benzyl, phenethyl, or 3,4-dichlorophenethyl) having from 7 to 14 carbon atoms.

[0053] A "C_{3-10} alkheterocyclyl" refers to an alkyl substituted heterocyclic group having from 3 to 10 carbon atoms in addition to one or more heteroatoms (e.g., 3-furanylmethyl, 2-furanylmethyl, 3-tetrahydrofuranylmethyl, 2-tetrahydrofuranylmethyl, and the like).

[0054] A "C_{1-10} heteroalkyl" refers to a branched or unbranched alkyl, alkenyl, or alkynyl group having from 1 to 10 carbon atoms in addition to one or more heteroatoms, where one or more methylenes (CH_2) or methines (CH) are replaced by nitrogen, oxygen, sulfur, carbonyl, thiocarbonyl, phosphoryl, or sulfonyl. Heteroalkyls include, but are not limited to, tertiary amines, secondary amines, ethers, thioethers, amides, thioamides, carbamates, thiocarbamates, phosphoramidates, sulfonamides, and disulfides. A heteroalkyl can optionally include monocyclic, bicyclic, or tricyclic rings, in which each ring has three to six members. The heteroalkyl group can be substituted or unsubstituted. Illustrative substituents include, but are not limited to alkoxy, aryloxy, sulfhydryl, allcylthio, arylthio, halide, hydroxyl, fluoroalkyl, perfluoralkyl, amino, amino alkyl, disubstituted amino, quaternary amino, hydroxyalkyl, hydroxyalkyl, carboxyalkyl, and carboxyl groups.

[0055] The term "acyl" refers to a chemical moiety with the formula R-C(O)-, where R is selected from C_{1-10} alkyl, C_{1-10} alkenyl, C_{1-10} alkynyl, C_{2-6} heterocyclyl, C_{6-12} aryl, C_{7-14} alkaryl, C_{3-10} alkheterocyclyl, C_{1-10} heteroalkyl, and the like.

[0056] A "halide" refers to meant bromine, chlorine, iodine, or fluorine.

BRIEF DESCRIPTION OF THE DRAWINGS

[0057] Figure 1, panels A-D, shows various forms of niclosamide. A: 2'5-dichloro-4'-nitrosalicylanilide; B: 5-chloro-salicyl-(2-chloro-4-nitro) anilide 2-aminoethanol salt; C: 5-chloro-salicyl-(2-chloro-4-nitro) anilide piperazine salt; and D: 5-chloro-salicyl-(2-chloro-4-nitro)anilide monohydrate.

[0058] Figure 2 illustrates various niclosamide analogues. A: Oxyclozanide (3,3',5,5',6-pentachloro-2'-hydroxy salicylanilide; 2,3,5-trichloro-N-(3,5-dichloro-2-hydroxyphenyl)-6-hydroxybenzamide); B: Closantel (5'-Chloro-alpha4-(p-chlorophenyl)-alpha4-cyano-3,5-diiodo-2',4'-salicyloxylidide; N-[5-Choloro-4- [(4-Chlorophenyl) Cyanomethyl]-2-Methylpheny]- 2-Hydroxy-3-5- Diiodobenzamide); C: Rafoxanide (also known as Disalan; Flukanide; N-(3-chloro-4-(4-chlorophenoxy)phenyl)-2-hydroxy-3,5-diiodobenzamide; 3'-Chloro-4'-(p-chlorophenoxy)-3,5-diiodosalicylanilide); D: Flusalan (3,5-Dibromo-2-hydroxy-N-(3-trifluoromethyl-phenyl)-benzamide); E: Tribromsalan (3,5-Dibromo-N-(4-bromo-phenyl)-2-hydroxy-benzamide) ; F: Resorantel (N-(4-Bromo-

phenyl)-2,6-dihydroxy-benzamide); G: Clioxanide (Acetic acid 2-(4-chloro-phenylcarbamoyl)-4,6-diiodo-phenyl ester).

[0059] Figure 3 illustrates various niclosamide analogues and salts thereof.

[0060] Figure 4 illustrates niclosamide analogues in which one halogen group is relocated within the same ring (*see, e.g.,* compounds A-D) or both halogen groups are relocated within the same ring (*see, e.g.,* compounds E-G).

[0061] Figure 5 illustrates niclosamides in which the nitro group is relocated within the same ring (*see, e.g.,* compounds A-C) and niclosamide analogues where the hydroxyl group is relocated within the same ring (*see, e.g.,* compounds D-F).

[0062] Figure 6 illustrates niclosamide analogues where both halogen and hydroxy and/or nitro groups are relocated while keeping the substituents within the aromatic ring (*see, e.g.,* compounds A-F) and niclosamide analogues having a nitro- and a hydroxyl group relocation (*see, e.g.,* compounds G-I).

[0063] Figure 7 illustrates niclosamide analogues comprising a single halogen exchange (*see, e.g.,* compounds A-D), niclosamide analogues comprising a double halogen exchange (*see, e.g.,* compounds E-F), niclosamide analogues comprising an exchange of Cl- to Br- (*see, e.g.,* compound G), and niclosamide analogs comprising an exchange of Cl- to F- (*see, e.g.,* compound H).

[0064] Figure 8 shows HDL inflammatory index for apoE null mice fed chow containing or not containing additions. C: Mice were given chow alone; D: Mice given chow supplemented with 8.0 micrograms of niclosamide; E: Mice given chow supplemented with 2.0 micrograms of L-4F; F: Mice given chow supplemented with 8.0 micrograms of Niclosamide together with 2.0 micrograms of L-4F (free base) per gram of chow. The mouse HDL (C – J) was also compared to a standard human HDL (B) that was added at the same concentrations as the mouse HDL. The resulting monocyte chemotactic activity was normalized to the standard control LDL added alone (A). The results are plotted as the HDL-inflammatory index, which is the result of dividing the monocyte chemotactic activity measured for each condition by the monocyte chemotactic activity obtained by the standard control LDL added alone, which was normalized to 1.0. G-I: A second experiment. G: Chow alone; H: chow supplemented with 100 micrograms of

Niclosamide per gram of chow; I: Chow supplemented with 10 micrograms of L-4F (free base) per gram of mouse chow; J: Chow supplemented with 10 micrograms of L-4F (free base) together with 100 micrograms of Niclosamide per gram of chow. The data shown are the Mean ± S.D.

[0065] Figure 9 shows that administration of niclosamide as an oral bolus by gastric gavage (stomach tube) immediately followed by administration of L-4F as an oral bolus by stomach tube rendered apoE null mouse HDL anti-inflammatory. the HDL-containing fractions were tested for their ability to inhibit the induction of monocyte chemotactic activity by a standard control human LDL, which was added to cultures of human aortic endothelial cells. The values obtained after the addition of the standard control HDL or the mouse HDL were compared to the values obtained by the standard control LDL alone to give the HDL Inflammatory Index. The values shown are the Mean ± S.D.

[0066] Figure 10 shows that administration of Niclosamide as an oral bolus by stomach tube immediately followed by administration of L-4F as an oral bolus by stomach tube significantly reduced the ability of apoE null mouse LDL to induce monocyte chemotactic activity in cultures of human aortic endothelial cells. The LDL fractions from the mice described in Figure 9 were tested for their ability to induce monocyte chemotactic activity in cultures of human aortic endothelial cells and compared to a standard control human LDL whose values were normalized to 1.0 for the LDL-inflammatory index. The data shown are the Mean ± S.D.

[0067] Figure 11 shows that oral administration of niclosamide (5.0 mg/kg body weight) immediately followed by oral administration of L-4F (0.5 mg/kg/body weight) renders monkey HDL anti-inflammatory. The data shown are the Mean ± S.D. for the HDL

[0068] Figure 12 shows that oral administration of niclosamide (5.0 mg/kg body weight) immediately followed by oral administration of L-4F (0.5 mg/kg/body weight) significantly reduced the ability of monkey LDL to induce monocyte chemotactic activity in cultures of human aortic endothelial cells. The LDL fractions from the monkey plasma described in Figure 11 were tested as described in Figure 10. The data shown are the Mean ± S.D.

[0069] Figure 13 shows that an amphipathic helical peptide (L-4F) increases the solubility of niclosamide in an aqueous system. Niclosamide at 10 mg per mL was added to

water, or to water containing 1.0 mg/mL L-4F (free base) and was homogenized in a glass-glass homogenizer. The solutions were stored at 4°C for ten days and photographed

[0070] Figure 14 shows the HDL inflammatory index for female apoE null mice that were given by gastric gavage (stomach tube) 100 μL water alone or 100 μL water containing niclosamide or containing niclosamide in combination with L-4F at the doses shown on the X-axis. The solutions of niclosamide with or without L-4F shown in Figure 13 were serially diluted and given by gastric gavage (stomach tube) to fasting seven month old female apoE null mice in a volume of 100 microliters per mouse (n = 8 per group). Blood was collected 6 hours following treatment while the mice were still fasting and the plasma was separated by FPLC and the HDL fractions were tested as described in Figure 8. The data shown are the Mean ± S.D, h = human, m = mouse.

[0071] Figure 15 LDL from the mice described in Figure 14 was tested for its ability to induce human aortic endothelial cells to produce monocyte chemotactic activity. The data are plotted as the LDL-inflammatory index as described for Figure 10. The values shown are the Mean ± S.D.

[0072] Figure 16 shows the HDL from mice that were given niclosamide in mouse chow at 250 μg per day per mouse with or without L-4F (free base). Seven month old female apoE null mice (n=8 per treatment group) were given niclosamide in mouse chow at 250 micrograms per day per mouse with or without L-4F (free base) at 25 micrograms per day per mouse in the drinking water or in mouse chow (food) with the niclosamide. After three days the mice were bled, their plasma was fractionated by FPLC and the ability of the mouse HDL (m) to inhibit LDL-induced monocyte chemotactic activity was determined in cultures of human aortic endothelial cells and calculated as the HDL-inflammatory index as described in Figure 8. Normal anti-inflammatory human (h) HDL was included in the assays as a positive control. The values shown are the Mean ± S.D..

[0073] Figure 17 shows the results of LDL from the mice (m) in Figure 16 tested for its ability to induce monocyte chemotactic activity in cultures of human aortic endothelial cells. The data is expressed as the LDL-inflammatory index by comparing the results to the monocyte chemotactic activity induced by a standard control human (h) LDL alone, which was normalized to 1.0. The values shown are the Mean ± S.D; h = human, m = mouse.

[0074] Figure 18 shows pre-beta HDL formation in mice administered niclosamide with L-4F compared to D-4F.

[0075] Figure 19 shows the HDL-inflammatory index after oral administration of D-4F or L-4F. Niclosamide was homogenized with or without D-4F or L-4F (both as the free-base) in a ratio of 10:1 (nicolsamide:peptipde; wt:wt) in ABCT buffer pH 7.0 and incubated at 37°C for 1 hour. The buffer without peptide or with the peptides at 2.5, 5.0, or 10 μg was administered to 3 month old fasting female apoE null mice (n = 8 per group) in 100 μL by stomach tube. Six hours later the mice were bled and their plasma separated by FPLC and the HDL fractions from the mice were tested in cultures of human aortic endothelial cells exposed to normal human LDL to determine the HDL-inflammatory index as described in Figure 8. In the absence of added HDL (0) the monocyte chemotactic activity obtained after addition of the normal control LDL was normalized to 1.0. The monocyte chemotactic activity after addition of the human LDL plus a normal control human HDL (h) or mouse HDL (m) was divided by the monocyte chemotactic activity obtained following addition of the human LDL without HDL to give the HDL-inflammatory index. The data shown are the Mean ± S.D; h = human, m = mouse.

[0076] Figure 20 shows the results of a cell-free assay of HDL taken from mice receiving oral D-4F or L-4F. The HDL from the mice described in Figure 19 was tested in the cell-free assay. The data shown are the Mean ± S.D.

[0077] Figure 21 shows plasma paraoxonase activity from the mice described in Figure 19. The data shown are the Mean ± S.D.

[0078] Figure 22 shows that co-administration of niclosamide with L-4F renders apoE null mouse HDL anti-inflammatory to a degree that is similar to normal human HDL. Free base D-4F or L-4F were homogenized with or without niclosamide in a ratio of 10:1 (niclosamide:peptide; wt:wt) in ABCT buffer adjusted to pH 8.0 using 0.1 NaOH. The buffer without the peptide or with the peptides at 10 μg in 100 μL was administered to 4-month-old fasting apoE null female mice (n = 8 per group) by stomach tube. Seven hours later the mice were bled and their plasma separated by FPLC and the HDL fractions from the mice were tested in cultures of human aortic endothelial cells exposed to normal human LDL to determine the HDL-inflammatory index as described in Figure 8. The data shown are the Mean ± S.D; h = human, m = mouse.

[0079] Figure 23. The LDL-inflammatory index from the mice described in Figure 22 was determined. The data shown are the Mean ± S.D; h = human, m = mouse.

[0080] Figure 24 shows that new salicylanilides (BP-1001 and BP-1012) are more potent than niclosamide in improving the HDL-inflammatory index. Niclosamide (BP-124) or BP-1001, or BP-1012 were homogenized with or without D-4F or L-4F (both as the free base) in a ratio of 10:1 (wt:wt) in ABCT buffer. The buffer without peptide or with peptide at 5 μg in 100 μL was administered to 4-month-old fasting apoE null mice (n = 4 per group) by stomach tube. Six hours later the mice were bled and their plasma separated by FPLC and the HDL fractions from the mice were tested in cultures of human aortic endothelial cells exposed to normal human LDL to determine the HDL-inflammatory index as described in Figure 8. The data shown are the Mean ± S.D; h = human, m = mouse..

[0081] Figure 25. The LDL-inflammatory index for LDL taken from the mice described in Figure 24 was determined as described in Figure 10. The data shown are the Mean ± S.D; h = human, m = mouse.

[0082] Figure 26 shows a comparison of niclosamide (BP-124) with other salicylanilides. Niclosamide (BP-124) or the salicylanilides whose numbers (BP#) are shown on the X-axis were homogenized with L-4F (as the free base) in a ratio of 10:1 (salicylanilide: L-4F; wt:wt) in ABCT buffer which was adjusted to pH 8.0 with 0.1N NaOH. The buffer without peptide or salicylanilide or with salicylanilide at 100 μg together with L-4F at 10 μg in 100 μL was administered to 5-month-old fasting male apoE null mice (n = 4 per group) by stomach tube. Eight hours later the mice were bled and their plasma separated by FPLC and the HDL fractions from the mice were tested in cultures of human aortic endothelial cells exposed to normal human LDL to determine the HDL-inflammatory index as described in Figure 8. The data shown are the Mean ± S.D; h = human, m = mouse.

[0083] Figure 27 shows that niclosamide increases L-4F absorption in apoE null mice. Fasted apoE null mice 6-months of age (n=4 per group) were administered by stomach tube ^{14}C-L-4F (21,000 dpm containing 10 micrograms of L-4F per mouse) with or without 100 micrograms of niclosamide in 200 microliters. Fasting was continued and the mice were bled at the time points shown on the X-axis and the dpm per mL plasma determined.

[0084] Figure 28 demonstrates that the ^{14}C-L-4F used in Figure 27 was biologically active. The HDL inflammatory index was determined as described in Figure 8 after administration of the compounds shown in Figure 27.

[0085] Figure 29 shows aortic sinus lesion score in apoE null mice receiving oral doses of niclosamide, L-4F, or niclosamide together with L-4F. Seventeen week old female apoE null mice who were on chow were divided into three groups and the following additions were made to the chow for each group: Group I: Niclosamide at 250 micrograms/mouse/day; Group II: L-4F at 25 micrograms/mouse/day; Group III: L-4F at 25 micrograms/mouse/day plus Niclosamide at 250 micrograms/mouse/day. All groups received 50 micrograms/mouse/day of pravastatin in their drinking water. After 14 weeks the mice were sacrificed and aortic sinus lesion area was determined as described previously (Navab *et al.* (2005) *Arterioscler. Thromb. Vasc. Biol.*, 25: 1426-1432).

[0086] Figure 30 shows the percent aortic surface area determined by en face analysis for the mice described in Figure 29.

[0087] Figure 31 shows the percent macrophage lesion area for the mice described in Figure 29.

[0088] Figure 32 shows that oral administration of L-4F together with niclosamide causes lesion regression in old apoE null mice. Ninety-five female apoE null mice age 9.5 months from the UCLA breeding colony were identified. Twenty-three were sacrificed at time Zero (Group I) to establish lesion area at the start of the experiment. The remainder of the mice were divided into three groups of 24 mice each and the following additions were made to the chow for each group: Group II: Niclosamide at 2,000 micrograms/mouse/day; Group III: L-4F at 200 micrograms/mouse/day; Group IV: L-4F at 200 micrograms/mouse/day plus Niclosamide at 2,000 micrograms/mouse/day. All groups received 50 micrograms/mouse/day of pravastatin in their drinking water. At the veterinarian's request because of fighting and/or ulcerative dermatitis mice were euthanized prior to the end of the experiment as follows: 6 mice from Group II; 5 mice from Group III; 4 mice from Group IV. After six months the remaining mice were sacrificed and aortic sinus lesion area was determined as described previously (*Id.*).

[0089] Figure 33 shows the percent aortic surface lesion area determined by en face analysis for the mice described in Figure 32.

[0090] Figure 34 shows the percent macrophage lesion area for the mice described in Figure 32.

[0091] Figure 35 shows the HDL-inflammatory index determined for apoE-null mice administered L-[113-122]apoJ or L-4F with and without niclosamide. Ten month old apoE null mice (n=4 per group) were administered by stomach tube 2 mg of niclosamide or 200 micrograms of L-[113-122]apoJ or 2 mg of niclosamide plus 200 micrograms of L-[113-122]apoJ. Eight hours later the mice were bled, their plasma separted by FPLC and the HDL-inflammatory index determined as described in Figure 8. The data shown are Mean ± S.D.

DETAILED DESCRIPTION

[0092] This invention pertains to the surprising discovery that salicylanilides, including, but not limited to niclosamide and/or niclosamide analogues when orally administered in conjunction with a pharmaceutical (*e.g.*, a peptide pharmaceutical such as a helical peptide (*e.g.*, a class A amphipathic helical peptide, a G* helical peptide, etc.) as described herein) significantly increases the bioavailability and/or apparent *in vivo* activity of that peptide. Moreover, the increase in bioavailability or apparent activity is sufficient so that peptide pharmaceuticals previously formulated as "D" amino acid isomers and protected at both termini to permit oral administration can readily be formulated utilizing all L form amino acids with optionally protected termini for oral administration. This significantly reduces the cost to manufacture such peptides and increases the predictability of the peptide's behavior in mammalian systems since the biological activity of L peptides is generally better characterized and understood.

[0093] Moreover, it was a surprising discovery that when salicylanilides, including, but not limited to niclosamide and/or niclosamide analogues, are combined (*e.g.*, under acidic conditions) with peptide or protein therapeutics (*e.g.*, amphipathic helical peptides, *e.g.*, apolipoprotein A-I [apoA-I] or portions of apoA-I, or ApoJ, *etc.*) the salicylanilide and the peptide form an adduct that increases the apparent solubility of the bioactive agent(s) and/or the bioavailablity of the agent(s).

[0094] Thus, in certain embodiments, this invention contemplates methods of enhancing the uptake and *in vivo* activity of a peptide orally administered to a mammal by

orally administering the peptide in conjunction with an amount of niclosamide or a niclosamide analogue sufficient to enhance *in vivo* activity (*e.g.*, via enhanced uptake and/or bioavailability) of the peptide. To facilitate such methods, in certain embodiments, pharmaceutical formulations are contemplated that comprise both the peptide pharmaceutical(s) along with niclosamide and/or a niclosamide analogue. In certain embodiments the result of the reaction between the salicylanilide (*e.g.*, niclosamide or niclosamides analogue) with the peptide or protein will be achieved by chemical synthesis prior to administration of the peptide/protein comprising the salicylanilide-derived adduct.

[0095] It was also a surprising discovery that the amphipathic helical peptides described herein can increase the solubility of niclosamide and/or niclosamide analogues in aqueous systems thereby enhancing/facilitating the incorporation of niclosamide in a pharmaceutical formulation. Thus, in certain embodiments, this invention contemplates pharmaceutical formulations comprising a combination of a therapeutic amphipathic helical peptide (*e.g.*, D-4F, L-4F, L-5F, *etc.*) and niclosamide or a niclosamide analogue, wherein said niclosamide in the formulation shows substantially greater solubility in an aqueous solution than niclosamide in an aqueous solution absent the amphipathic helical peptide.

[0096] In certain embodiments, this invention also pertains to the surprising discovery that agents such as N-(5-chlorosalicyloyl)-8-aminocaprylic acid (5-CNAC), N-(10-[2-hydroxybenzoyl]aminodecanoic acid (SNAD), and N-(8-[2-hydroxybenzoyl]amino)caprylic acid (SNAC), and the like, can increase the oral bioavailability and/or apparent activity of L form peptides to therapeutically relevant levels. This permits the use of such L form peptides as orally delivered therapeutics where previously D form peptides were preferred. In certain preferred embodiments the L form peptides are the amphipathic helical peptides described herein (*e.g.*, L-4F, L-5F, *etc.*).

[0097] In certain embodiments, when administered in conjunction niclosamide and/or niclosamide analogues as described herein (including, but not necessarily limited to those shown in Formula I and/or Table 1), L-form peptides, *e.g.*, as described herein, do not even require amino or carboxyl terminal blocking/protecting groups. Peptides lacking such blocking groups can easily be synthesized using recombinant expression systems rather than chemical peptide synthesis methods. Bioreactors can thus readily be used to prepare such unprotected peptides at very low cost (as compared to chemically synthesized peptides).

[0098] In various embodiments formulations comprising one or more therapeutic peptides in combination with niclosamide and/or niclosamide analogues as described herein, are contemplated. The formulations are typically suitable for oral administration. In certain embodiments the formulations can provide for release of niclosamide and/or niclosamide analogues and/or permeability enhancer(s) before the peptide.

[0099] While niclosamide and niclosamide analogues and/or other "permeability" enhancers described herein are particularly useful for enhancing the oral bioavailability of L peptides as described herein, the uses of these agents is not so limited. Thus, in certain embodiments the use of such agents with protected L peptides and or protected or unprotected peptides comprising one or more D amino acid residues is also contemplated.

I. Salicylanilides to enhance pharmaceutical *in vivo* activity.

[0100] As indicated above, it is a surprising discovery that various salicylanilides including, but not limited to niclosamide and niclosamide analogues are effective to substantially increase the *in vivo* activity (*e.g.*, bioavailability, bioactivity, *etc.*) of a pharmaceutical (*e.g.*, a therapeutic peptide) orally administered to a mammal.

A) Niclosamide and niclosamide analogues

[0101] Niclosamide is a chloronitrophenol derivative (*see* compound A in Figure 1) principally used against aquatic snails but also as an antiparasitic drug in human and veterinary medicine. Niclosamide is known by the IUPAC designation: 2'5-dichloro-4'-nitrosalicylanilide and by the CAS designation: CAS: 5-chloro-N-(2-chloro-4-nitrophenyl)-2-hydroxybenzamide.

[0102] Niclosamide is not very water soluble, 5-8 mg/L at 20°C, sparingly soluble in ether, ethanol and chloroform, and soluble in acetone; the ethanolamine salt dissolves in distilled water 180-280 mg/L at 20°C. It was a surprising discovery, however, that the inclusion of an amphipathic helical peptide, *e.g.*, as described herein, significantly increases the solubility of niclosamide and facilitates the preparation of pharmaceutical formulations.

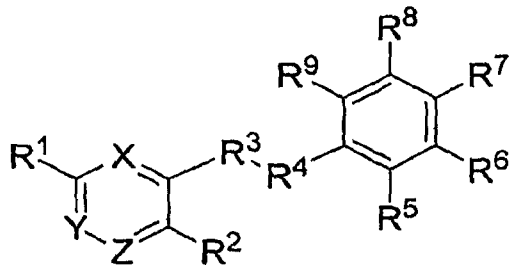
[0103] In tablets niclosamide undergoes a biodegradation in moist environments but niclosamide itself is stable in an aqueous solution for several months. The ethanolamine salt

is stable to heat, hydrolyzed by concentrated acid or alkali, and stable in aquatic environments.

[0104] Niclosamide is readily available in a number of formulations. These include, but are not limited to, the ethanolamine salt (*see* compound C in Figure 1) known by the IUPAC designation 5-chloro-salicyl-(2-chloro-4-nitro) anilide 2-aminoethanol salt or the CAS designation 5-chloro-N-(2-chloro-4-nitrophenyl)-2-hydroxybenzamide with 2-aminoethanol (1:1), the piperazine salt (*see* compound B in Figure 1) known by the IUPAC designation 5-chloro-salicyl-(2-chloro-4-nitro) anilide piperazine salt or the CAS designation 5-chloro-N-(2-chloro-4-nitrophenyl)-2-hydroxybenzamide with piperazine (2:1), and niclosamide monohydrate (*see* compound D in Figure 1) known by the IUPAC designation 5-chloro-salicyl-(2-chloro-4-nitro) anilide monohydrate or the CAS designation 5-chloro-N-(2-chloro-4-nitrophenyl)-2-hydroxybenzamide with monohydrate (1:1).

[0105] Niclosamide is commercially available in a number of formulations including, but not limited to BAYER 73®, BAYER 2353®, BAYER 25 648®, BAYLUSCID®, BAYLUSCIDE®, CESTOCID®, CLONITRALID, DICHLOSALE®, FENASAL®, HL 2447®, IOMESAN®, IOMEZAN®, LINTEX®, MANOSIL®, NASEMO®, NICLOSAMID®, PHENASAL®, TREDEMINE®, SULQUI®, VERMITID®, VERMITIN®, YOMESAN®, and the like.

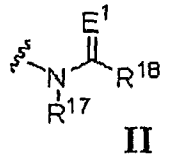
[0106] This invention also contemplates the use of various niclosamide analogues to enhance the *in vivo* of orally administered pharmaceuticals (*e.g.*, therapeutic peptides). Such analogues include, but are not limited to, compounds according to Formula I:



I

where X is N or CR^{10}; Y is N or CR^{11}; Z is N or CR^{12}; and each of R^1, R^2, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11} and R^{12} is independently selected from H, halide (F, Cl, Br, or I), NO_2, OH, OR^{13}, SR^{14}, $NR^{15}R^{16}$, CN, CF_3, $C_{1\text{-}10}$ alkyl, $C_{2\text{-}10}$ alkenyl, $C_{2\text{-}10}$ alkynyl, $C_{2\text{-}6}$ heterocyclyl,

C_{6-12} aryl, C_{7-14} alkaryl, C_{3-10} alkheterocyclyl, C_{1-10} heteroalkyl, or is described by one of the Formulas II-XIV:



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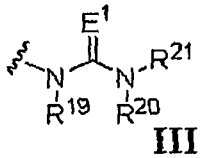

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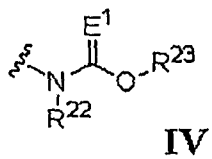

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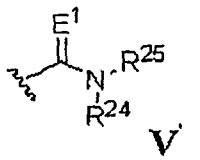

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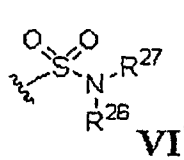

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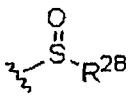

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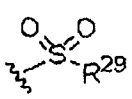

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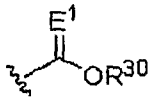

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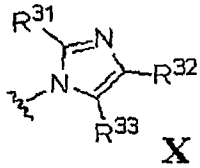

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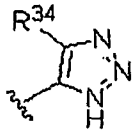

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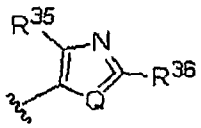

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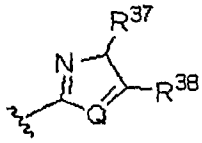
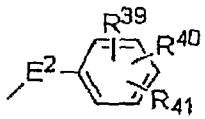


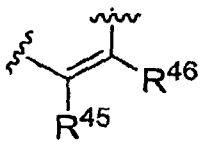
XIII

or



XIV

[0107] In compounds of formula I, R^3 and R^4 are independently selected from the group consisting of C=O, C=S, C=NR^{42}, NH, NR^{43}, $CHOR^{44}$, CH_2, and the like. Groups R^2 and R^4; X and R^4; R^5 and R^3; R^9 and R^3 may combine to form a six-membered ring, using connections described by one of the groups:



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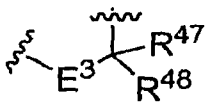

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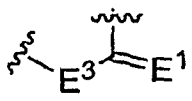
or

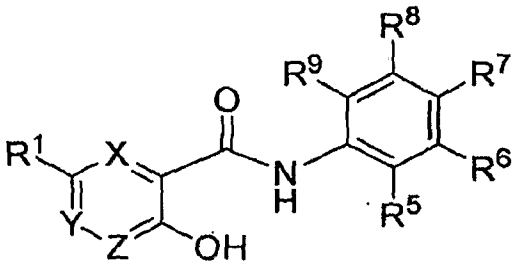


XVII

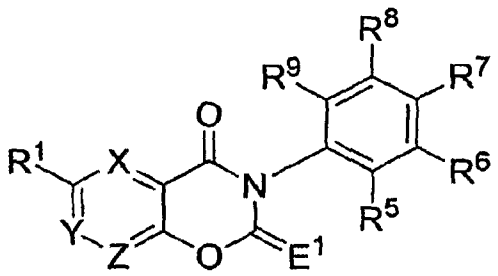
For compounds of formula I, each E^1 is independently O, S, or NR^{42}; each E^2 is independently $CR^{49}R^{50}$, O or S; each E^3 is independently $CR^{51}R^{52}$, O, S, or NR^{53}; each Q is, independently, O, S, or NR^{54}. R^{13} and R^{14} are each independently, acyl, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{2-6} heterocyclyl, C_{6-12} aryl, C_{7-14} alkaryl, C_{3-10} alkheterocyclyl, C_{1-10} heteroalkyl; R^{18}, R^{23}, R^{28}, R^{29}, R^{30}, R^{42}, R^{54} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{2-6} heterocyclyl, C_{6-12} aryl, C_{7-14} alkaryl, C_{3-10} alkheterocyclyl, C_{1-10} heteroalkyl; R^{15}, R^{16}, R^{17}, R^{19}, R^{20}, R^{21}, R^{22}, R^{24}, R^{25}, R^{26}, R^{27}, R^{43}, R^{44}, R^{45}, R^{46}, R^{47}, R^{48}, R^{51}, R^{52}, and R^{53} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{2-6} heterocyclyl, C_{6-12} aryl, C_{7-14} alkaryl, C_{3-10} alkheterocyclyl, C_{1-10} heteroalkyl; R^{31}, R^{32}, R^{33},

R^{34}, R^{35}, R^{36}, R^{37}, R^{38}, R^{39}, R^{40}, R^{41}, R^{49}, and R^{50} are each, independently, H, halide, NO_2, CN, CF_3, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{2-6} heterocyclyl, C_{6-12} aryl, C_{7-14} alkaryl, C_{3-10} alkheterocyclyl, or C_{1-10} heteroalkyl.

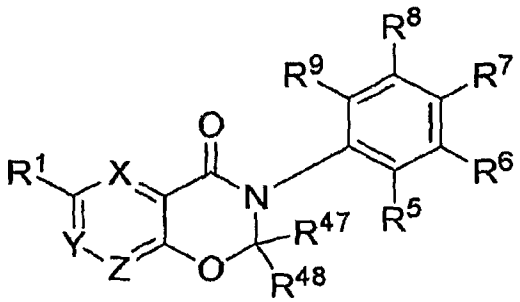
[0108] In certain embodiments, compounds of formula I are further described by any of formulas XVIII-**XXI**:



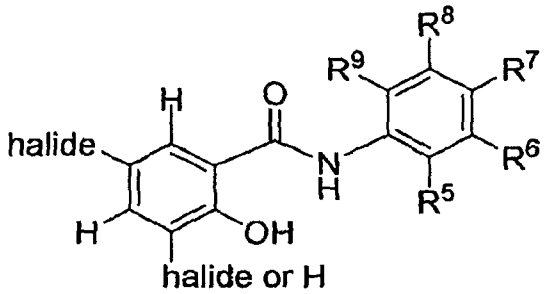
XVIII



XIX



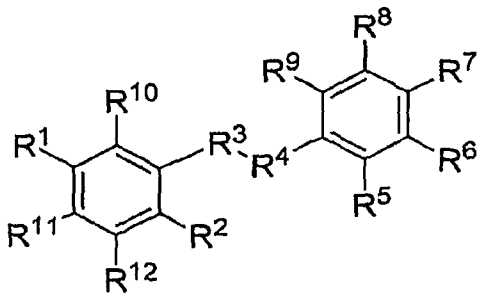
XX



XXI

where X, Y, Z, E^1, R^1, R^5, R^6, R^7, R^8, R^9, R^{47}, and R^{48} are as defined above.

[0109] In certain embodiments compounds include compounds described by Formula **XXII**:



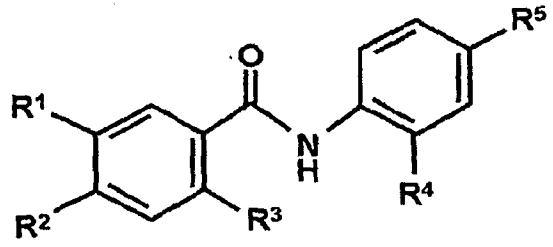
XXII

where R^1, R^2, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11} and R^{12} are independently selected from the group consisting of H, halide, NO_2, CF_3, OH, acyl, CN, C_1-C_{10} alkyl (preferably C_1-C_3 alkyl), C_1-C_{10} heteroalkyl (preferably C_1-C_3 heteroalkyl) ; and wherein R^3 and R^4 are as defined above. In certain embodiments, R^3 is C=O, while R^4 is NH or R^3 is NH while R^4 is C=O. In these and certain other embodiments, only two of R^1, R^2, R^{10}, R^{11}, and R^{12} are present, and one is H or OH, while the other is halogen (*e.g.*, Cl, Br, or F).

[0110] In these and certain other embodiments, only two of R^5, R^6, R^7, R^8, and R^9 are present and these are NO_2 and halogen (*e.g.*, Cl, Br, or F).

[0111] In certain embodiments niclosamide analogues include, but are not limited to niclosamide analogues in which one halogen group is relocated within the same ring (*see, e.g.*, compounds A-D in Figure 4) or both halogen groups are relocated within the same ring (*see, e.g.*, compounds E-G in Figure 4), niclosamides in which the nitro group is relocated within the same ring (*see, e.g.*, compounds A-C in Figure 5), niclosamide analogues where the hydroxyl group is relocated within the same ring (*see, e.g.*, compounds D-F in Figure 5), niclosamide analogues where both halogen and hydroxy and/or nitro groups are relocated while keeping the substituents within the aromatic ring (*see, e.g.*, compounds A-F in Figure 6), compounds like A-F in Figure 6, except having except (3-chloro-4-nitrophenyl) in place of (2-chloro-4-nitrophenyl), niclosamide analogues having a nitro- and a hydroxyl group relocation (*see, e.g.*, compounds G-I in Figure 6), niclosamide analogues comprising a single halogen exchange (*see, e.g.*, compounds A-D in Figure 7), niclosamide analogues comprising a double halogen exchange (*see, e.g.*, compounds E-F in Figure 7), niclosamide analogs comprising an exchange of Cl- to Br- (*see, e.g.*, compound G in Figure 7), niclosamide analogs comprising an exchange of Cl- to F- (*see, e.g.*, compound H in Figure 7), and the like.

[0112] In certain embodiments the niclosamide analogues include, but are not limited to compounds according to Formula **XXIII**:

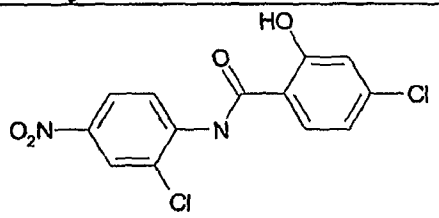
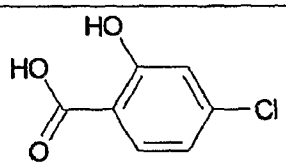
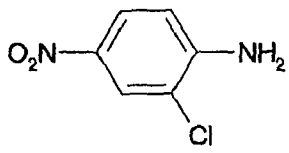
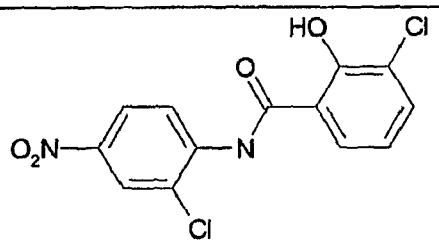
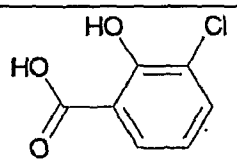
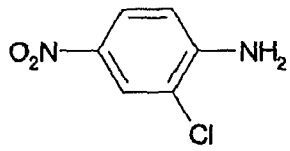
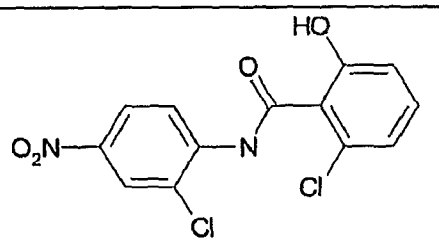
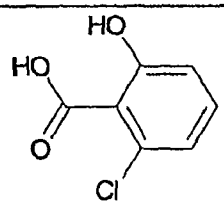
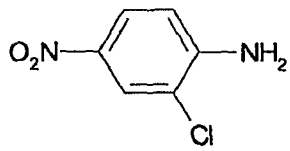


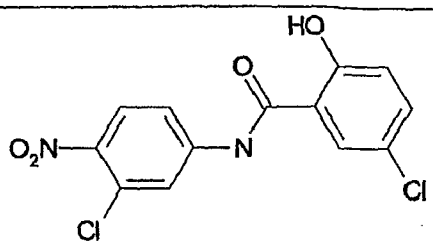
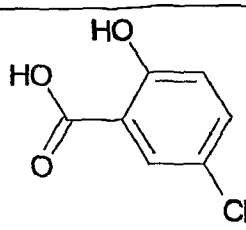
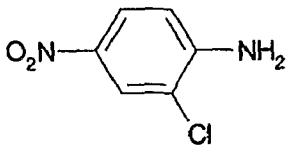
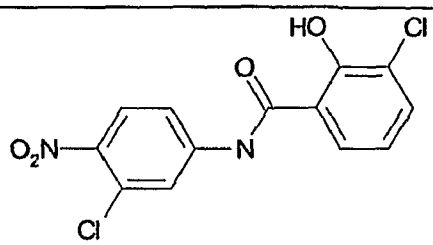
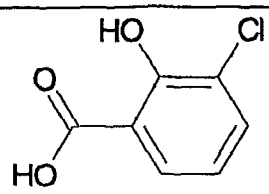
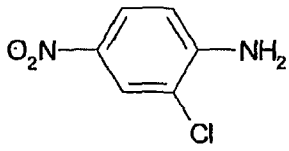
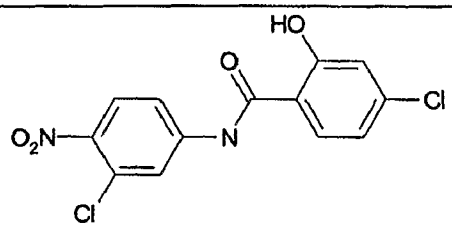
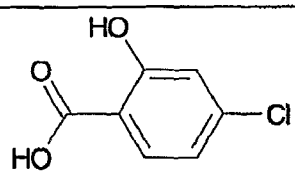
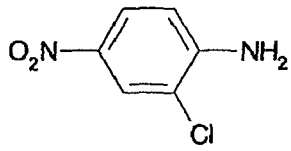
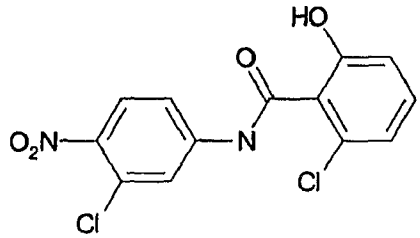
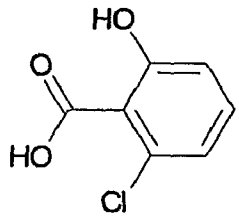
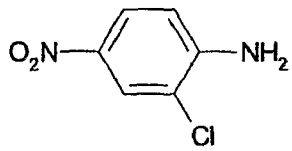
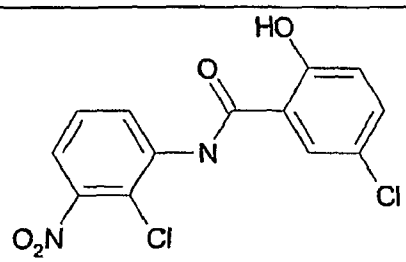
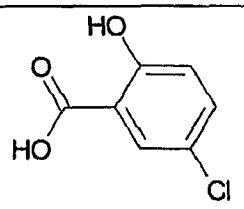
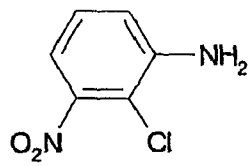
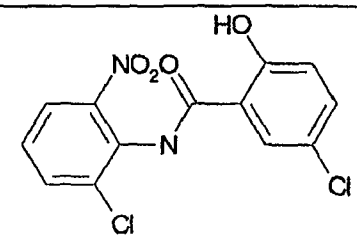
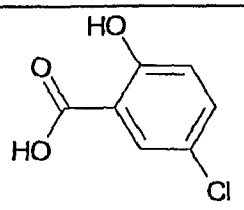
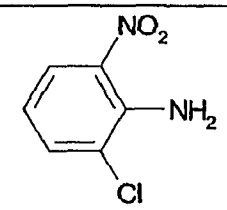
XXIII

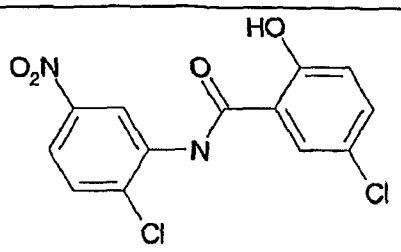
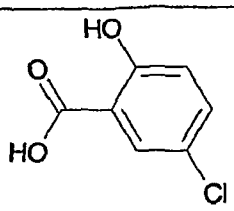
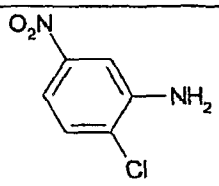
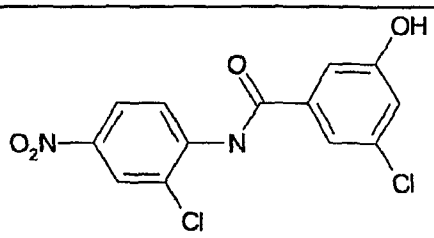
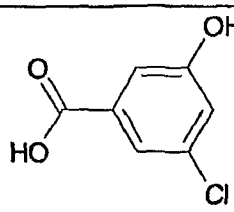
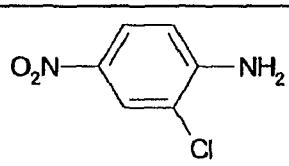
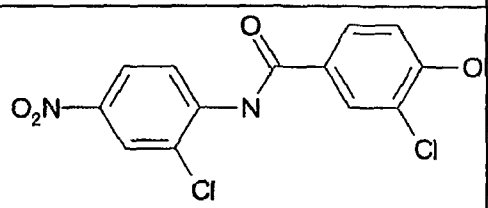
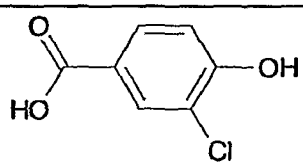
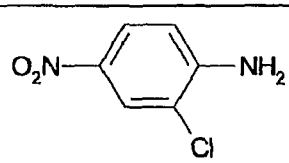
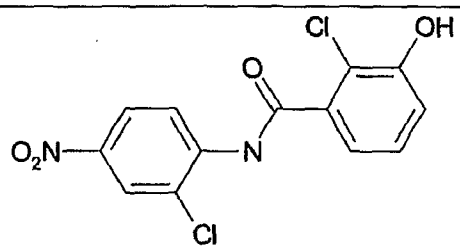
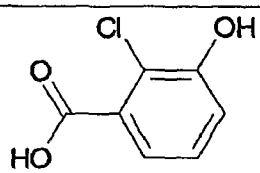
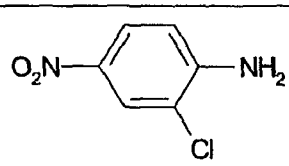
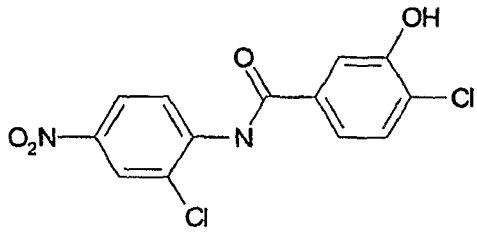
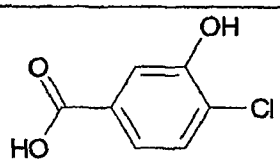
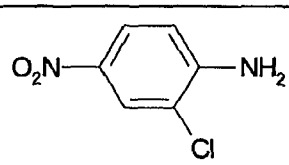
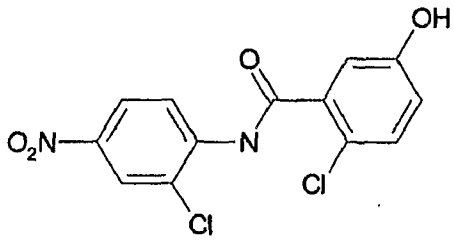
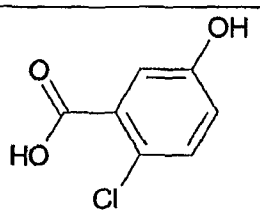
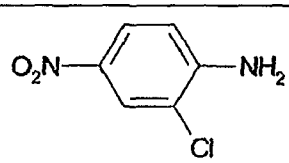
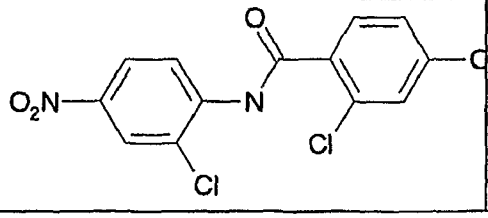
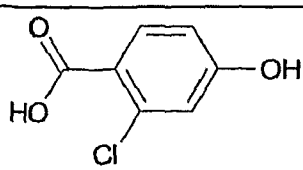
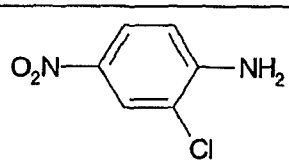
where R^1, R^2, R^3, R^4, and R^5, are independently present or absent, and when present are independently selected from the group consisting of Cl, Br, alkyl, methyl, hydroxyalkyl, and the like. These analogues are meant to be illustrative and not limiting. Using the teaching provided herein, other suitable niclosamide analogs will be recognized by one of skill in the art.

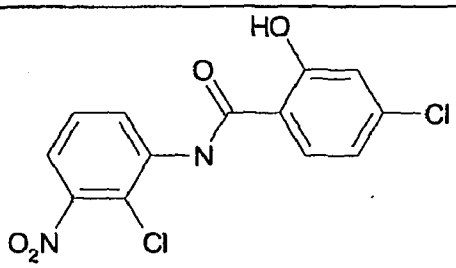
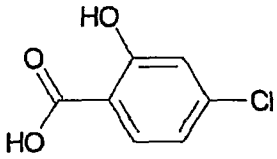
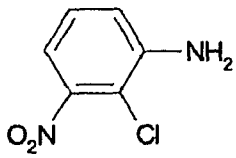
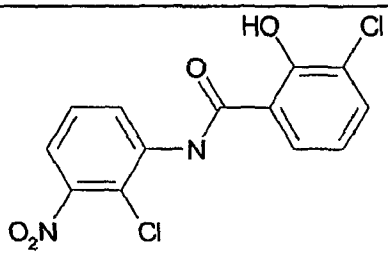
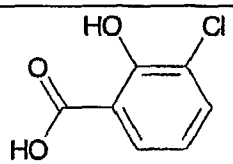
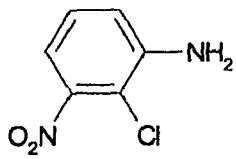
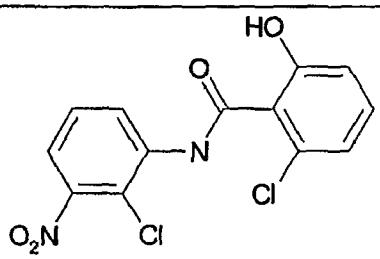
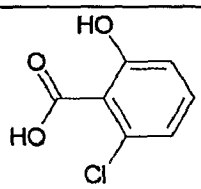
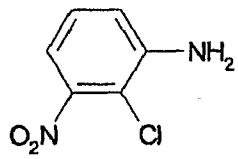
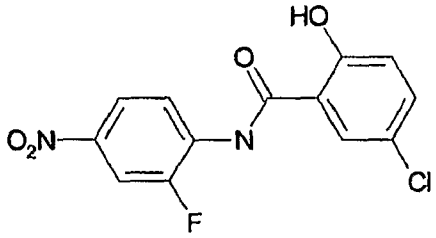
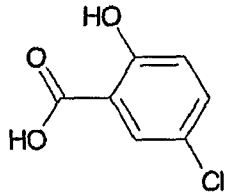
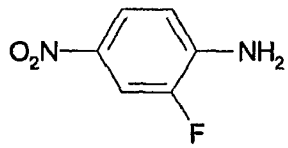
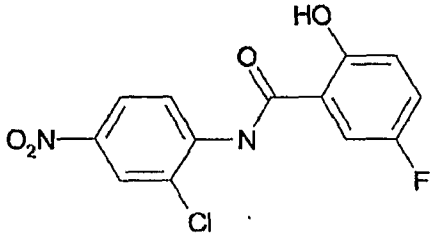
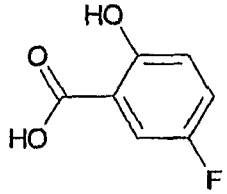
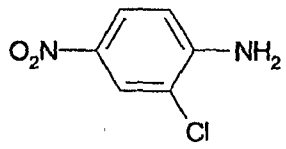
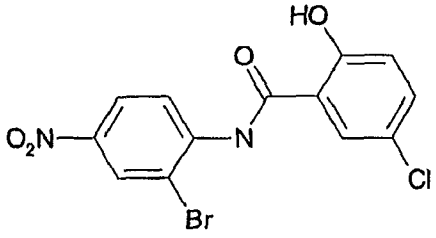
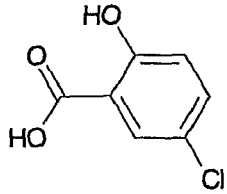
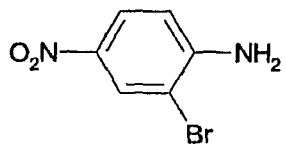
[0113] In certain embodiments the salicylanilides include, but are not limited to salicylanilides shown in Table 1.

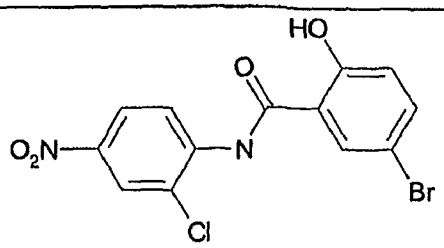
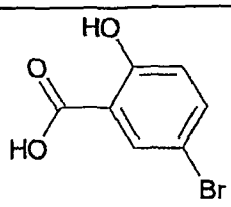
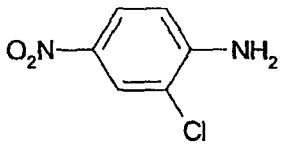
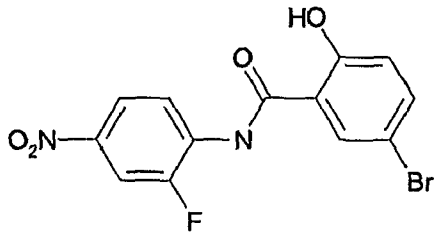
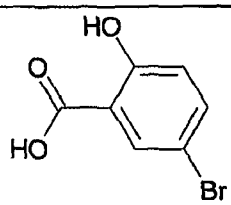
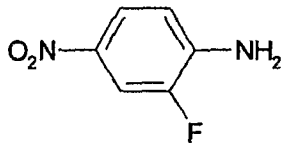
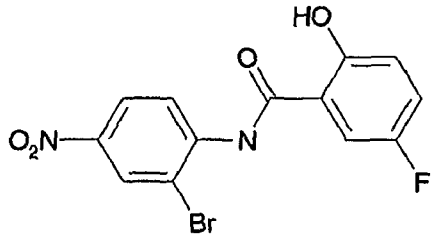
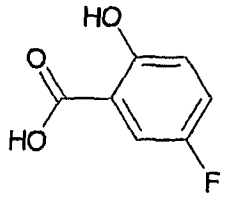
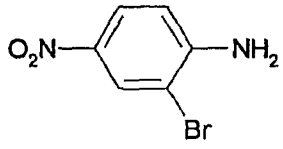
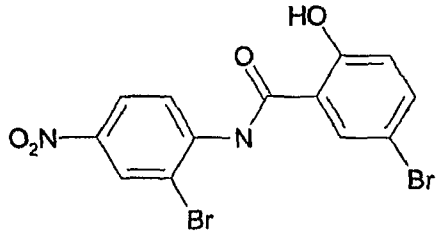
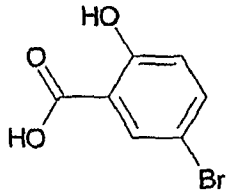
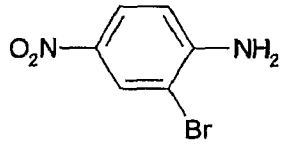
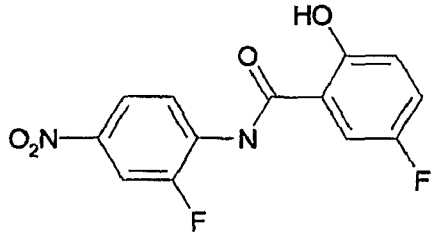
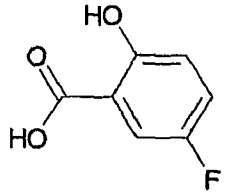
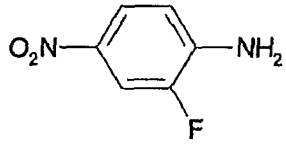
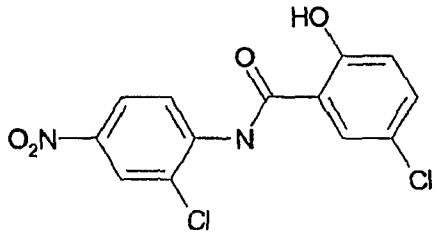
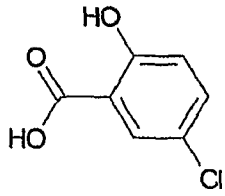
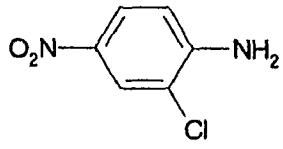
[0114] **Table** 1. Illustrative salicylanilides.

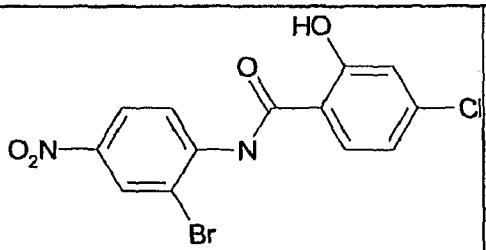
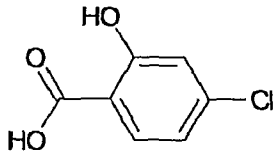
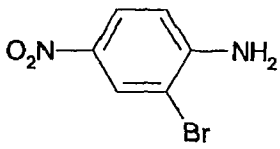
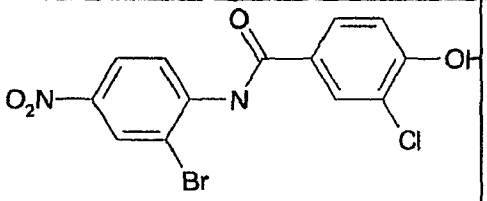
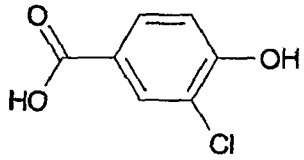
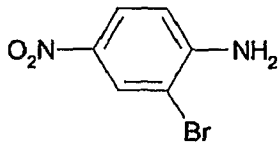
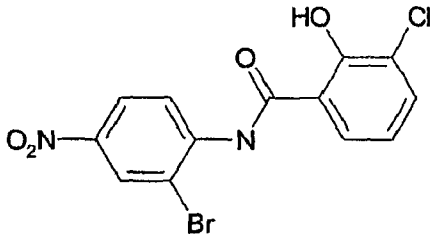
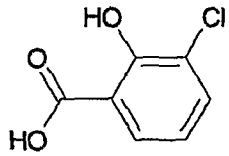
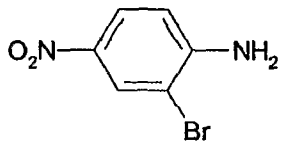
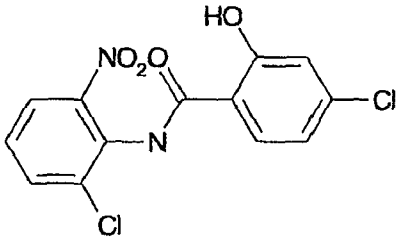
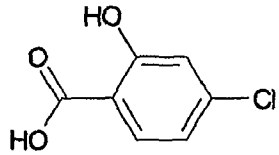
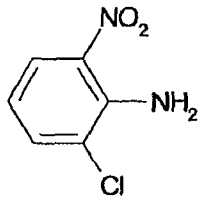
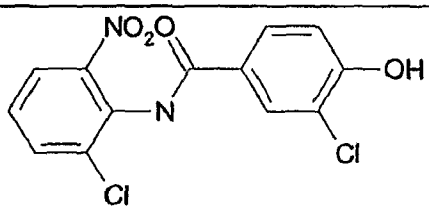
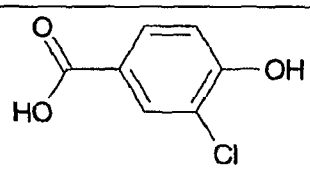
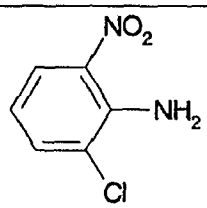
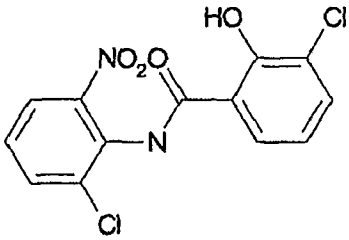
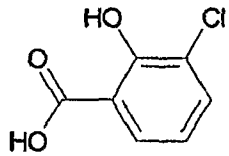
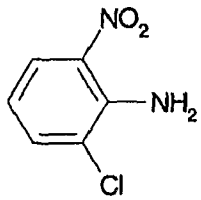
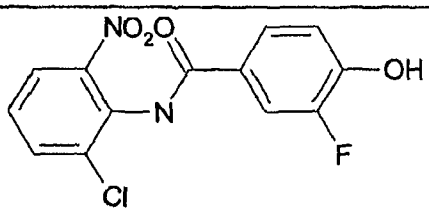
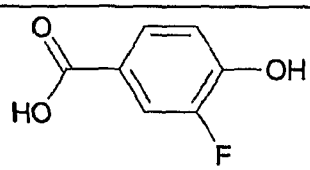
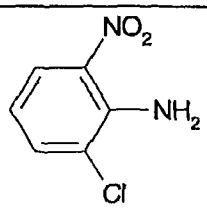
Cmpd	Salicylanilide	Parent Acid	Parent Amine
BP 1001			
BP 1002			
BP 1003			

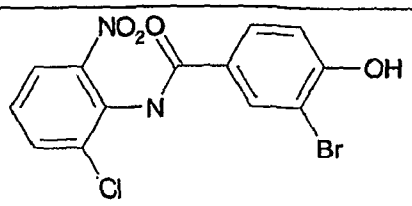
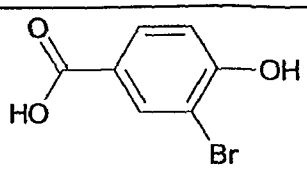
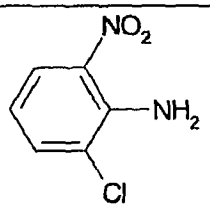
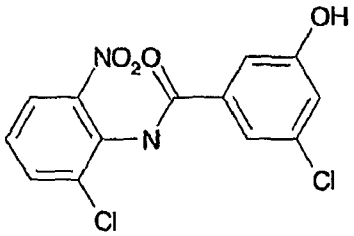
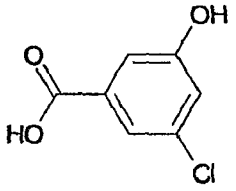
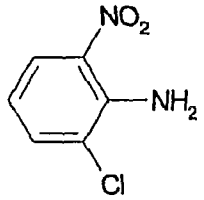
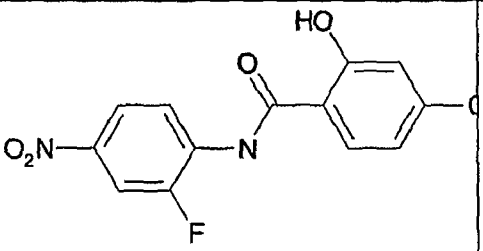
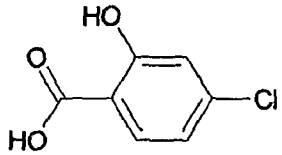
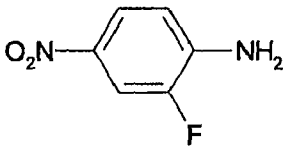
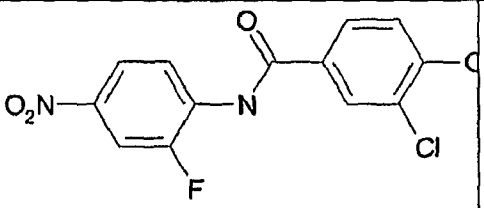
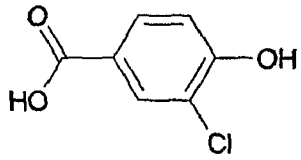
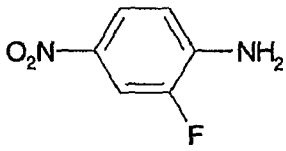
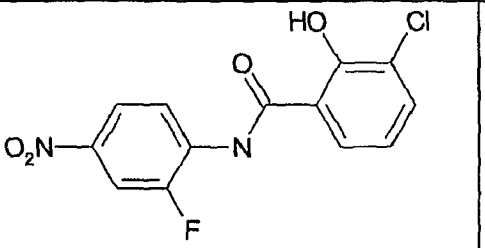
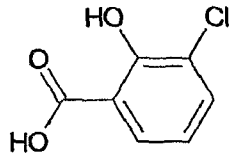
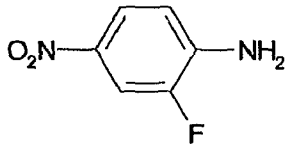
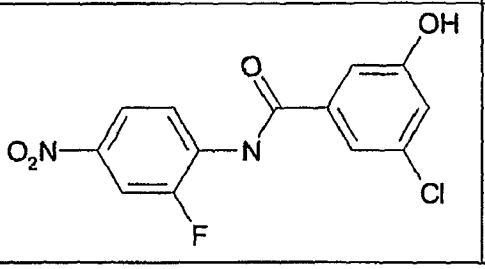
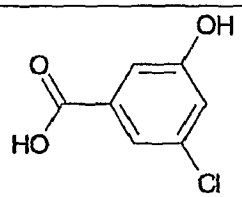
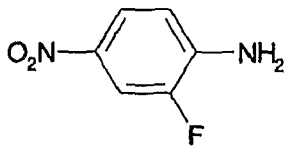
BP 1004			
BP 1005			
BP 1006			
BP 1007			
BP 1008			
BP 1009			

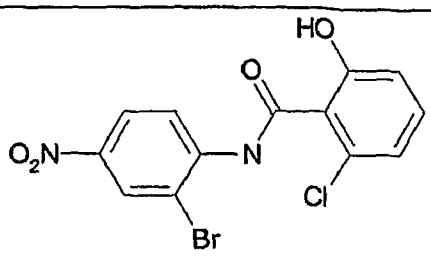
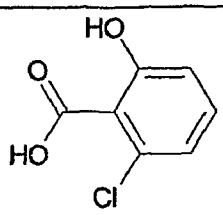
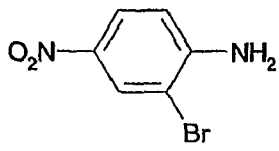
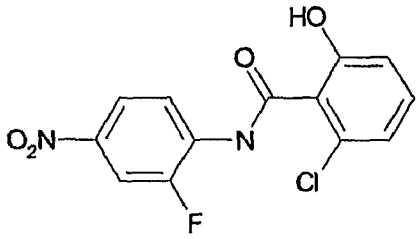
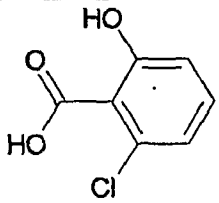
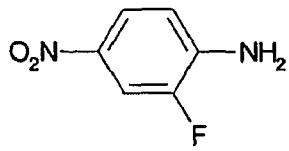
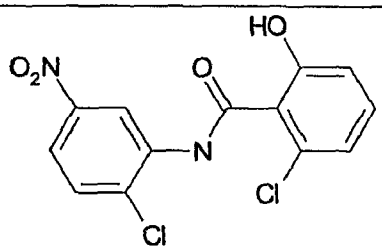
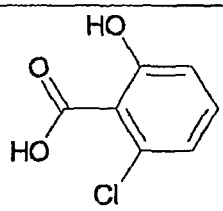
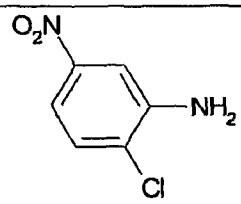
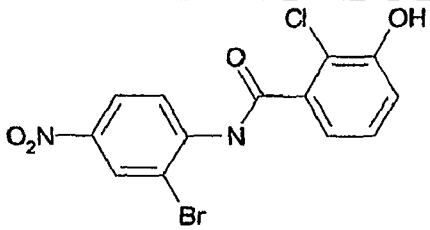
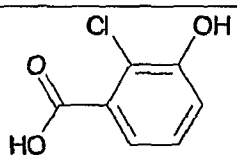
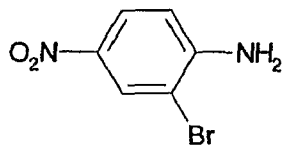
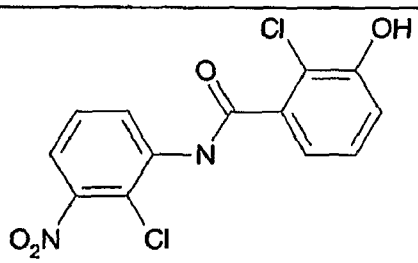
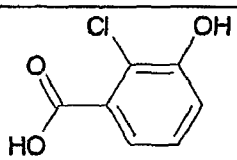
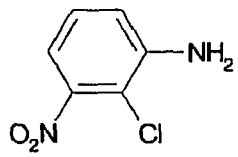
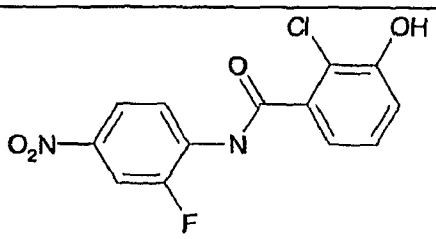
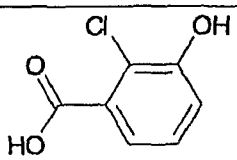
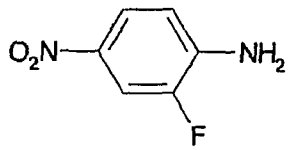
BP 1010			
BP 1011			
BP 1012			
BP 1013			
BP 1014			
BP 1015			
BP 1016			

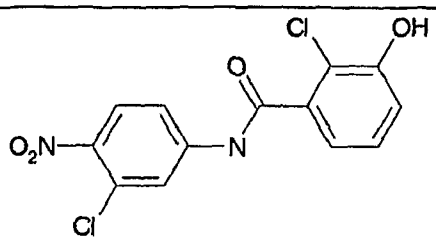
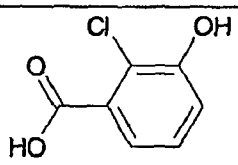
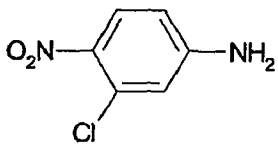
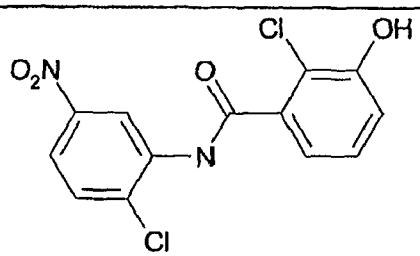
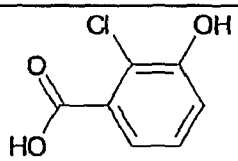
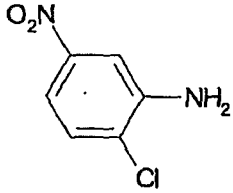
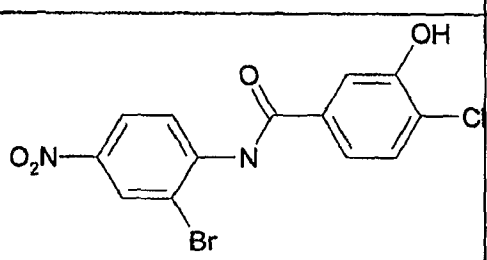
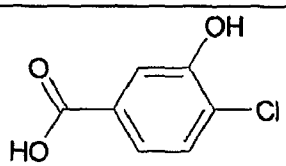
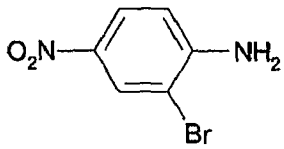
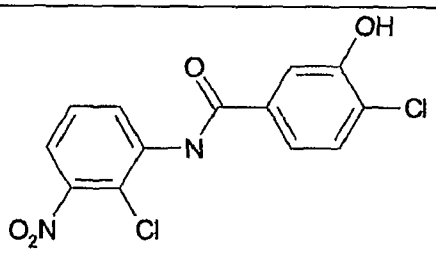
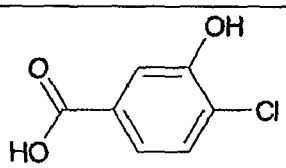
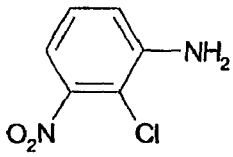
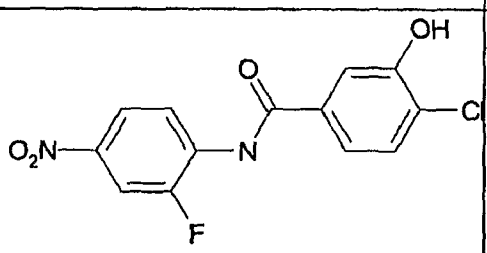
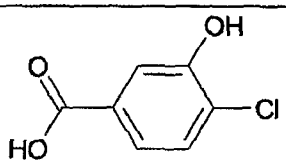
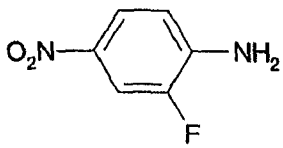
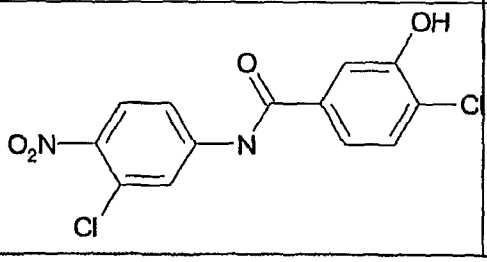
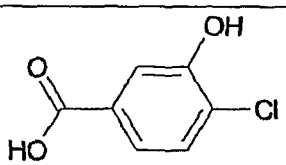
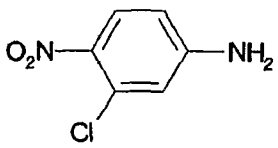
BP 1017			
BP 1018			
BP 1019			
BP 1020			
BP 1021			
BP 1022			

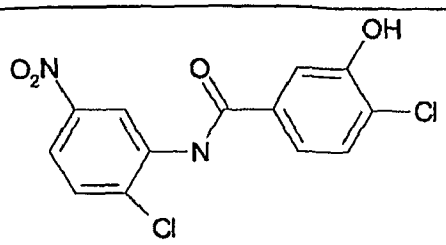
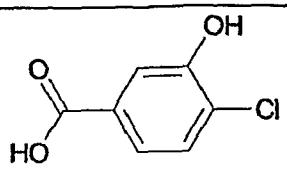
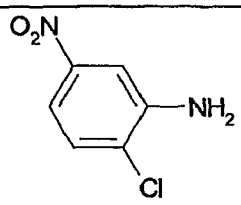
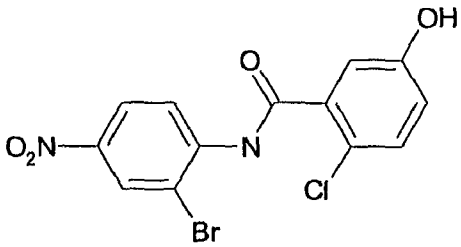
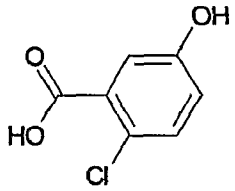
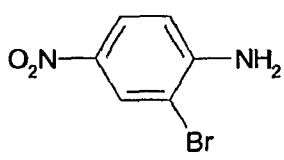
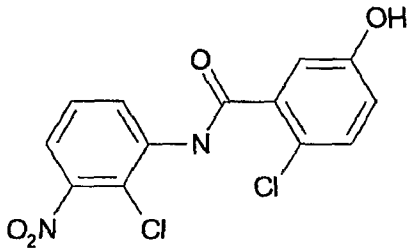
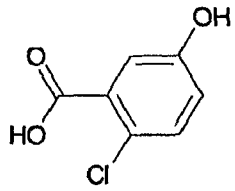
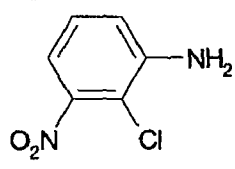
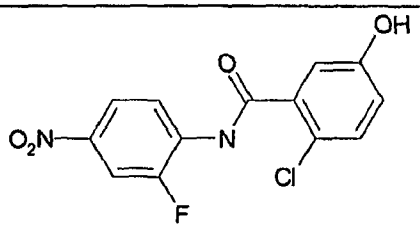
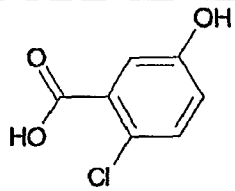
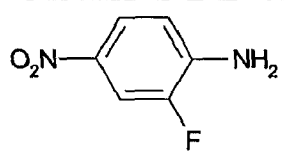
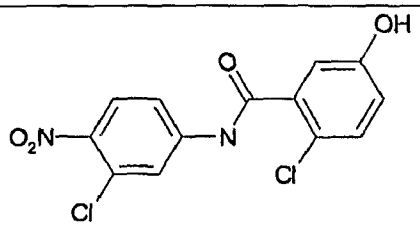
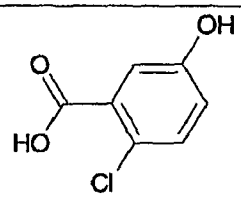
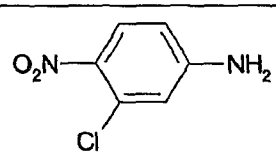
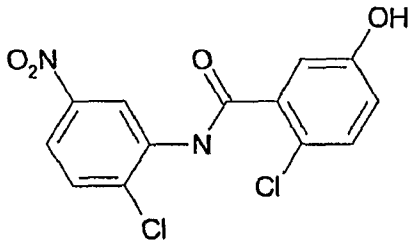
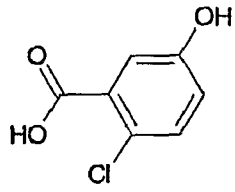
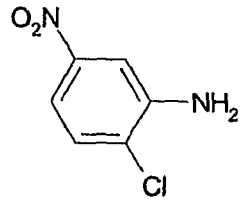
BP 1023			
BP 1024			
BP 1025			
BP 1026			
BP 1027			
BP 1028			

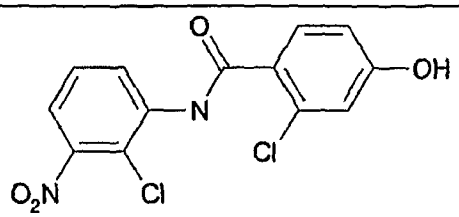
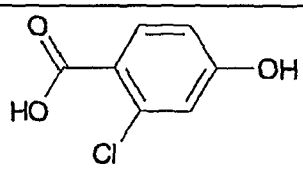
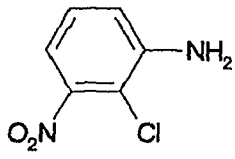
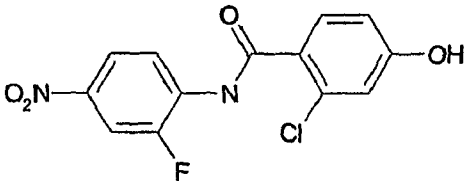
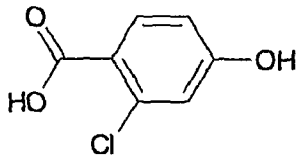
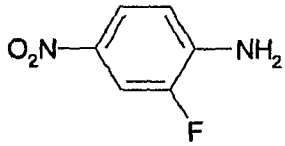
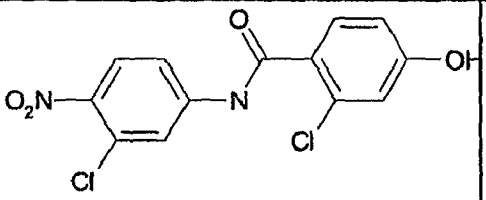
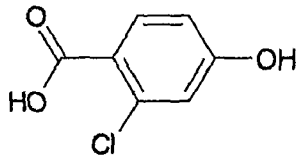
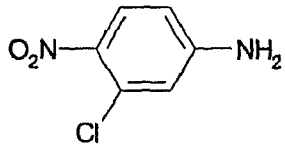
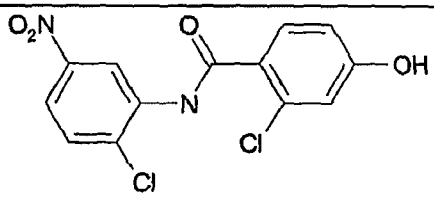
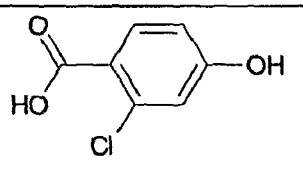
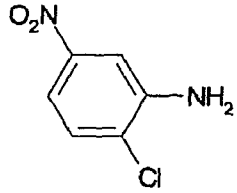
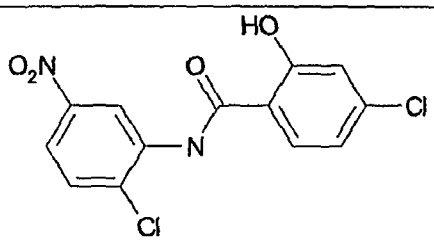
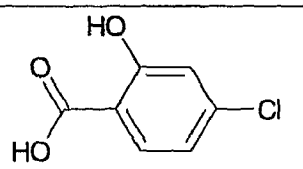
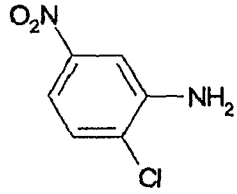
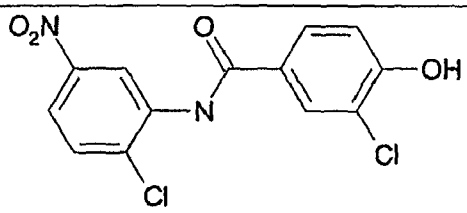
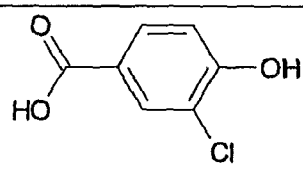
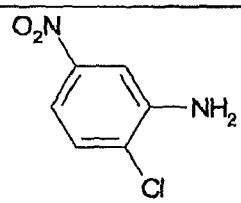
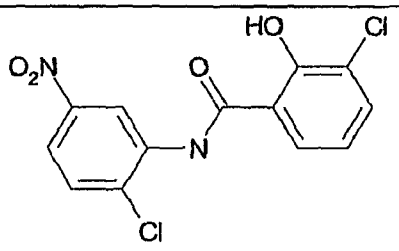
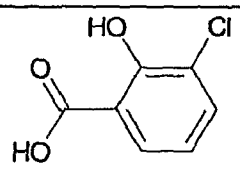
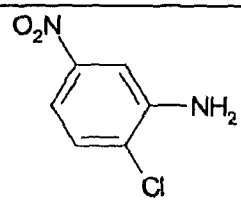
BP 1029			
BP 1030			
BP 1031			
BP 1032			
BP 1033			
BP 1034			
BP 1035			

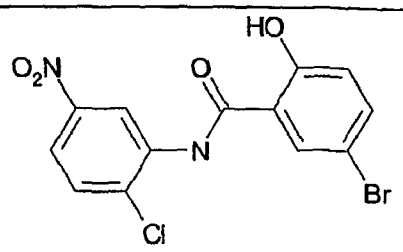
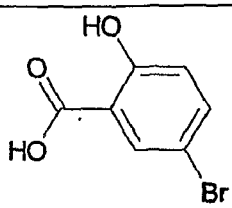
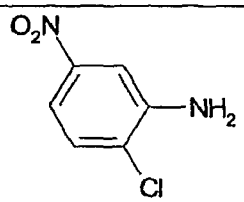
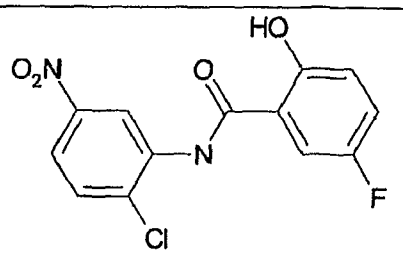
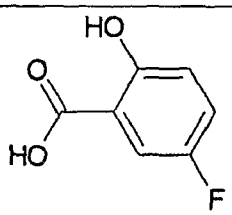
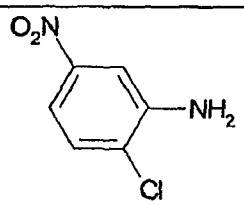
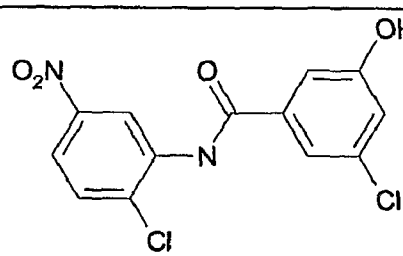
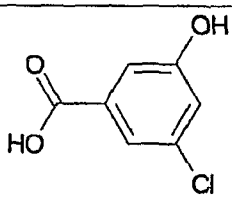
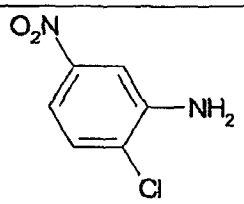
BP 1036			
BP 1037			
BP 1038			
BP 1039			
BP 1040			
BP 1041			

BP 1042			
BP 1043			
BP 1044			
BP 1045			
BP 1046			
BP 1047			

BP 1048			
BP 1049			
BP 1050			
BP 1051			
BP 1052			
BP 1053			

BP 1055			
BP 1056			
BP 1057			
BP 1058			
BP 1059			
BP 1061			

BP 1063			
BP 1064			
BP 1065			
BP 1067			
BP 1068			
BP 1069			
BP 1070			

BP 1071			
BP 1072			
BP 1073			

B) Other Salicylanilides

[0115] Without being bound by a particular theory, it is believed that a number of other salicylanilides can act in a manner similar to niclosamide to enhance *in vivo* activity of orally administered pharmaceuticals (*e.g.*, therapeutic peptides). Illustrative salicylanilides include, but are not limited to Closantel (CAS #: 57808-65-8, *see, e.g.*, Figure 2, compound A), Oxyclozanide (CAS #: 2277-92-1, *see, e.g.*, Figure 2, compound B), Rafoxanide (CAS #: 22662-39-1, *see, e.g.*, Figure 2, compound C), Flusalan (CAS #: 4776-06-1, *see, e.g.*, Figure 2, compound D), Tribromsalan (CAS #: 87-10-5, *see, e.g.*, Figure 2, compound E), Resorantel (CAS #: 20788-07-2, *see, e.g.*, Figure 2, compound F), Clioxanide (CAS #: 14437-41-3, *see, e.g.*, Figure 2, compound G)Other suitable salicylanilides include Brotianide (CAS #: 23233-88-7), 4'-chloro-3-nitrosalicylanilide, 4'-chloro-5-nitrosalicylanilide, 2'-chloro-5'-methoxy-3-nitrosalicylanilide, 2'-methoxy-3,4'-dinitrosalicylanilide, 2',4'-dimethyl-3-nitrosalicylanilide, 4',5-dibromo-3-nitrosalicylanilide, 2'-chloro-3,4'-dinitrosalicylanilide, 2'-ethyl-3-nitrosalicylanilide, 2'-

bromo-3-nitrosalicylanilide, and the like. In certain embodiments the salicylanilides include one or more of the compounds shown in Figure 3.

[0116] It is noted that these salicylanilides are intended to be illustrative and not limiting. Methods of making salicylanilides are well known to those of skill in the art (*see, e.g.*, PCT/US2003/022026 (WO 2004/006906) which is herein incorporated by reference for all purposes).

C) Identifying effective salicylanilides.

[0117] Using the teaching provided herein, other suitable salicylanilides can readily be identified using only routine experimentation. Various salicylanilides can be purchased from commercial vendors (*e.g.*, Sigma Chemical, Aldrich, *etc.*) and then screened for their ability to enhance the apparent *in vivo* activity of an orally administered pharmaceutical (*e.g.*, a peptide such as L-4F). Such screening methods can include for example, administering the salicylanilide in question in conjunction with L-4F (SEQ ID NO:5) to an apoE null mouse with appropriate controls and evaluating HDL-containing blood fractions for their ability to inhibit monocyte chemotactic activity induced by a standard control human LDL in cultures of human aortic endothelial cells. Salicylanilides that, when administered with L-4F produce more protective HDL than L-4F alone are compounds that enhance the *in vivo* activity (apparent activity) of that peptide. Such assays are illustrated herein in Example 1.

II. Other delivery agents.

[0118] Without being bound to a particular theory, in view of the niclosamide data presented herein, it is also believed that number of other delivery agents are also capable of enhancing the *in vivo* activity (apparent activity) of therapeutic orally administered pharmaceuticals, including, but not limited to amphipathic helical peptides (*e.g.*, ApoA-I, ApoA-I milano, 4F, D18A, *etc.*) such that the L form of the peptide achieves therapeutically relevant levels of bioavailability when administered with the delivery agent(s).

[0119] Such delivery agents include, but are not limited to agents such N-(5-chlorosalicyloyl)-8-aminocaprylic acid (5-CNAC), N-(10-[2-hydroxybenzoyl]aminodecanoic acid (SNAD), and N-(8-[2-hydroxybenzoyl]amino)caprylic acid (SNAC) and various salts (*e.g.*, disodium salts) thereof. In certain embodiments such

delivery agents include any one or more of the modified amino acids disclosed in aforementioned U.S. Patent 5,866,536 or any one of the modified amino acids described in U.S. Patent 5,773,647, which are incorporated herein by reference. Also included are various salts of such agents including, but not limited to the disodium salts described in WO 00/059863 which is incorporated herein by reference.

[0120] In certain embodiments the delivery agents comprise a compound selected from the group consisting of 4-{4-{N-(4-bromobenzoyl)aminophenyl]}butyric acid, 4-{4-N-(2-iodobenzoyl)aminophenyl]}butyric acid, 3-(4-(2,5-dimethoxybenzoyl)aminophenyl)propionic acid, 4-{n-[4-(3-iodobenzoyl)aminophenyl]}butyric acid, 4-(o-anisoyl)aminophenylacetic acid, 3-[4-(2,4-dimethoxybenzoyl)aminophenyl]prioionic acid, 4-{4-[N-(4-iodobenzoyl)]aminophenyl}butyric acid, 3-4-(2,3-dimethoxybenzoyl)aminophenyl]pripionic acid, 4-{N-2[N-2-bromobenzoyl)]aminophenyl}butyric acid, 4-{N-2[N-3-bromobenzoyl]aminophenyl}butyric acid, 4-{4-[N-(4-bromobenzoyl)aminophenyl]}butyric acid, 4-{N-[4-(2-methoxy-4-nitrobenzoyl)aminophenyl]}butyric acid, 4-(4-(2,3-dimethoxybenzoyl)aminophenyl)butyric acid, 4-[4-N-(4-methoxy-3-nitrobenzoyl)aminophenyl]butyric acid, and the like.

III. Therapeutic peptides.

[0121] This invention pertains to the use of salicylanilides (*e.g.*, niclosamide) as well as other delivery agents to facilitate/permit the oral delivery of therapeutic peptides even when the peptides are L-form peptides and/or are unprotected. A therapeutic peptide is a peptide that is used to mitigate one or more symptoms of a disease or pathology.

[0122] A wide variety of therapeutic peptides are known to those of skill in the art and can be use in the formulations and methods of this invention. Such peptides include, for example, growth hormone (*e.g.*, isolated and/or human, porcine, or bovine growth hormones), natural, synthetic, or recombinant growth hormone releasing hormones (GHRH), interferons (*e.g.*, alpha, beta, and gamma interferon), interleukins (*e.g.*, interleukin-1, interleukin, 2, *etc.*), natural, synthetic or recombinant insulin (*e.g.*, porcine, bovine, human insulins), insulin-like growth factor-1 (IGF-1), insulin-like growth factor-2 (IGF2, somatostatin), heparin, heparinoids, dermatans, chondroitins, calcitonin (*e.g.*,

natural, synthetic, or recombinant salmon, procine, eel, chicken, and human calcitonin), antigens (*e.g.*, influenza antigen, hepatitis A, B, C antigen, HPV antigen, *etc*), antibodies (polyclonal and monoclonal) (*e.g.*, HERCEPTIN®, RITUXAN®, AVASTIN®, ERBITUX®, *etc.*), oxytocin, leutinizing-hormone-releasing hormone (LHRH), follicle stimulating hormone (FSH); glucocerebrosidase, thrombopoietin; filgrastim; prostaglandins; vasopressin; cromolyn sodium (*e.g.*, sodium or disodium chromoglycate), vancomycin, desferrioxamine (DFO); parathyroid hormone (PTH) including its fragments, antimicrobials (*e.g.*, anti-bacterial agents, including anti-fungal agents, *etc.*), and the like. In addition, the therapeutic peptides include analogs, fragments, mimetics or modified derivatives of these compounds (*e.g.*, polyethylene glycol (PEG)-modified derivatives, glycosylated derivatives, *etc.*), or any combination thereof.

[0123] In certain preferred embodiments, the therapeutic peptides are peptides that ameliorate one or more symptoms of a pathology associated with an inflammatory response (*e.g.*, atherosclerosis). Such peptides include, but are not limited to ApoA-I (natural, synthetic, recombinant), ApoA-I milano, (natural, synthetic, recombinant), apolipoprotein M, 18A, and related peptides (*see, e.g.*, U.S. Patent 4,643,988, U.S. Patent 6,037,323, and PCT Publication WO 97/36927 all of which are incorporated herein by reference).

[0124] In certain particularly preferred embodiments, the therapeutic peptides used in the methods and formulations described herein include one or more of the peptides described below.

A) Class A amphipathic helical peptides.

[0125] In certain embodiments, the peptides for use in the method of this invention include class A amphipathic helical peptides, *e.g.*, as described in U.S. Patent 6,664,230, and PCT Publications WO 02/15923 and WO 2004/034977. It was discovered that peptides comprising a class A amphipathic helix ("class A peptides"), in addition to being capable of mitigating one or more symptoms of atherosclerosis are also useful in the treatment of one or more of the other indications described herein.

[0126] Class A peptides are characterized by formation of an α-helix that produces a segregation of polar and non-polar residues thereby forming a polar and a nonpolar face with the positively charged residues residing at the polar-nonpolar interface and the

negatively charged residues residing at the center of the polar face (*see, e.g.,* Anantharamaiah (1986) *Meth. Enzymol.*, 128: 626-668). It is noted that the fourth exon of apo A-I, when folded into 3.667 residues/turn produces a class A amphipathic helical structure.

[0127] One class A peptide, designated 18A (*see, e.g.,* Anantharamaiah (1986) *Meth. Enzymol.*, 128: 626-668) was modified as described herein to produce peptides orally administrable and highly effective at inhibiting or preventing one or more symptoms of atherosclerosis and/or other indications described herein.. Without being bound by a particular theory, it is believed that the peptides of this invention may act *in vivo* by picking up/sequestering seeding molecule(s) that mitigate oxidation of LDL.

[0128] We determined that increasing the number of Phe residues on the hydrophobic face of 18A would theoretically increase lipid affinity as determined by the computation described by Palgunachari *et al.* (1996) *Arteriosclerosis, Thrombosis, & Vascular Biol.* 16: 328-338. Theoretically, a systematic substitution of residues in the nonpolar face of 18A with Phe could yield six peptides. Peptides with an additional 2, 3 and 4 Phe would have theoretical lipid affinity (λ) values of 13, 14 and 15 units, respectively. However, the λ values jumped four units if the additional Phe were increased from 4 to 5 (to 19 λ units). Increasing to 6 or 7 Phe would produce a less dramatic increase (to 20 and 21 λ units, respectively).

[0129] A number of these class A peptides were made including, the peptide designated 4F (L-4F), D-4F, 5F (L-5F), and D-5F, and the like. Various class A peptides inhibited lesion development in atherosclerosis-susceptible mice. In addition, the peptides show varying, but significant degrees of efficacy in mitigating one or more symptoms of the various pathologies described herein. A number of such peptides are illustrated in Table 2.

[0130] Table 2. Illustrative class A amphipathic helical peptides for use in this invention.

Peptide Name	Amino Acid Sequence	SEQ ID NO.
18A	D-W-L-K-A-F-Y-D-K-V-A-E-K-L-K-E-A-F	1
2F	Ac-D-W-L-K-A-F-Y-D-K-V-A-E-K-L-K-E-A-F-NH_2	2
3F	Ac-D-W-F-K-A-F-Y-D-K-V-A-E-K-L-K-E-A-F-NH_2	3

3F14	Ac-D-W-L-K-A-F-Y-D-K-V-A-E-K-F-K-E-A-F-NH_2	4
4F	Ac-D-W-F-K-A-F-Y-D-K-V-A-E-K-F-K-E-A-F-NH_2	5
5F	Ac-D-W-L-K-A-F-Y-D-K-V-F-E-K-F-K-E-F-F-NH_2	6
6F	Ac-D-W-L-K-A-F-Y-D-K-F-F-E-K-F-K-E-F-F-NH_2	7
7F	Ac-D-W-F-K-A-F-Y-D-K-F-F-E-K-F-K-E-F-F-NH_2	8
	Ac-D-W-L-K-A-F-Y-D-K-V-A-E-K-L-K-E-F-F-NH_2	9
	Ac-D-W-L-K-A-F-Y-D-K-V-F-E-K-F-K-E-A-F-NH_2	10
	Ac-D-W-L-K-A-F-Y-D-K-V-F-E-K-L-K-E-F-F-NH_2	11
	Ac-D-W-L-K-A-F-Y-D-K-V-A-E-K-F-K-E-F-F-NH_2	12
	Ac-D-W-L-K-A-F-Y-D-K-V-F-E-K-F-K-E-F-F-NH_2	13
	Ac-E-W-L-K-L-F-Y-E-K-V-L-E-K-F-K-E-A-F-NH_2	14
	Ac-E-W-L-K-A-F-Y-D-K-V-A-E-K-F-K-E-A-F-NH_2	15
	Ac-E-W-L-K-A-F-Y-D-K-V-A-E-K-L-K-E-F-F-NH_2	16
	Ac-E-W-L-K-A-F-Y-D-K-V-F-E-K-F-K-E-A-F-NH_2	17
	Ac-E-W-L-K-A-F-Y-D-K-V-F-E-K-L-K-E-F-F-NH_2	18
	Ac-E-W-L-K-A-F-Y-D-K-V-A-E-K-F-K-E-F-F-NH_2	19
	Ac-E-W-L-K-A-F-Y-D-K-V-F-E-K-F-K-E-F-F-NH_2	20
	AC-A-F-Y-D-K-V-A-E-K-L-K-E-A-F-NH_2	21
	Ac-A-F-Y-D-K-V-A-E-K-F-K-E-A-F-NH_2	22
	Ac-A-F-Y-D-K-V-A-E-K-F-K-E-A-F-NH_2	23
	Ac-A-F-Y-D-K-F-F-E-K-F-K-E-F-F-NH_2	24
	Ac-A-F-Y-D-K-F-F-E-K-F-K-E-F-F-NH_2	25
	Ac-A-F-Y-D-K-V-A-E-K-F-K-E-A-F-NH_2	26
	Ac-A-F-Y-D-K-V-A-E-K-L-K-E-F-F-NH_2	27
	Ac-A-F-Y-D-K-V-F-E-K-F-K-E-A-F-NH_2	28
	Ac-A-F-Y-D-K-V-F-E-K-L-K-E-F-F-NH_2	29
	Ac-A-F-Y-D-K-V-A-E-K-F-K-E-F-F-NH_2	30
	Ac-K-A-F-Y-D-K-V-F-E-K-F-K-E-F-NH_2	31
	Ac-L-F-Y-E-K-V-L-E-K-F-K-E-A-F-NH_2	32
	Ac-A-F-Y-D-K-V-A-E-K-F-K-E-A-F-NH_2	33
	Ac-A-F-Y-D-K-V-A-E-K-L-K-E-F-F-NH_2	34
	Ac-A-F-Y-D-K-V-F-E-K-F-K-E-A-F-NH_2	35
	Ac-A-F-Y-D-K-V-F-E-K-L-K-E-F-F-NH_2	36
	Ac-A-F-Y-D-K-V-A-E-K-F-K-E-F-F-NH_2	37
	Ac-A-F-Y-D-K-V-F-E-K-F-K-E-F-F-NH_2	38
	Ac-D-W-L-K-A-L-Y-D-K-V-A-E-K-L-K-E-A-L-NH_2	39
	Ac-D-W-F-K-A-F-Y-E-K-V-A-E-K-L-K-E-F-F-NH_2	40
	Ac-D-W-F-K-A-F-Y-E-K-F-F-E-K-F-K-E-F-F-NH_2	41
	Ac-E-W-L-K-A-L-Y-E-K-V-A-E-K-L-K-E-A-L-NH_2	42

Ac-E-W-L-K-A-F-Y-E-K-V-A-E-K-L-K-E-A-F-NH_2 43

Ac-E-W-F-K-A-F-Y-E-K-V-A-E-K-L-K-E-F-F-NH_2 44

Ac-E-W-L-K-A-F-Y-E-K-V-F-E-K-F-K-E-F-F-NH_2 45

Ac-E-W-L-K-A-F-Y-E-K-F-F-E-K-F-K-E-F-F-NH_2 46

Ac-E-W-F-K-A-F-Y-E-K-F-F-E-K-F-K-E-F-F-NH_2 47

Ac-D-F-L-K-A-W-Y-D-K-V-A-E-K-L-K-E-A-W-NH_2 48

Ac-E-F-L-K-A-W-Y-E-K-V-A-E-K-L-K-E-A-W-NH_2 49

Ac-D-F-W-K-A-W-Y-D-K-V-A-E-K-L-K-E-W-W-NH_2 50

Ac-E-F-W-K-A-W-Y-E-K-V-A-E-K-L-K-E-W-W-NH_2 51

Ac-D-K-L-K-A-F-Y-D-K-V-F-E-W-A-K-E-A-F-NH_2 52

Ac-D-K-W-K-A-V-Y-D-K-F-A-E-A-F-K-E-F-L-NH_2 53

Ac-E-K-L-K-A-F-Y-E-K-V-F-E-W-A-K-E-A-F-NH_2 54

Ac-E-K-W-K-A-V-Y-E-K-F-A-E-A-F-K-E-F-L-NH_2 55

Ac-D-W-L-K-A-F-V-D-K-F-A-E-K-F-K-E-A-Y-NH_2 56

Ac-E-K-W-K-A-V-Y-E-K-F-A-E-A-F-K-E-F-L-NH_2 57

Ac-D-W-L-K-A-F-V-Y-D-K-V-F-K-L-K-E-F-F-NH_2 58

Ac-E-W-L-K-A-F-V-Y-E-K-V-F-K-L-K-E-F-F-NH_2 59

Ac-D-W-L-R-A-F-Y-D-K-V-A-E-K-L-K-E-A-F-NH_2 60

Ac-E-W-L-R-A-F-Y-E-K-V-A-E-K-L-K-E-A-F-NH_2 61

Ac-D-W-L-K-A-F-Y-D-R-V-A-E-K-L-K-E-A-F-NH_2 62

Ac-E-W-L-K-A-F-Y-E-R-V-A-E-K-L-K-E-A-F-NH_2 63

Ac-D-W-L-K-A-F-Y-D-K-V-A-E-R-L-K-E-A-F-NH_2 64

Ac-E-W-L-K-A-F-Y-E-K-V-A-E-R-L-K-E-A-F-NH_2 65

Ac-D-W-L-K-A-F-Y-D-K-V-A-E-K-L-R-E-A-F-NH_2 66

Ac-E-W-L-K-A-F-Y-E-K-V-A-E-K-L-R-E-A-F-NH_2 67

Ac-D-W-L-K-A-F-Y-D-R-V-A-E-R-L-K-E-A-F-NH_2 68

Ac-E-W-L-K-A-F-Y-E-R-V-A-E-R-L-K-E-A-F-NH_2 69

Ac-D-W-L-R-A-F-Y-D-K-V-A-E-K-L-R-E-A-F-NH_2 70

Ac-E-W-L-R-A-F-Y-E-K-V-A-E-K-L-R-E-A-F-NH_2 71

Ac-D-W-L-R-A-F-Y-D-R-V-A-E-K-L-K-E-A-F-NH_2 72

Ac-E-W-L-R-A-F-Y-E-R-V-A-E-K-L-K-E-A-F-NH_2 73

Ac-D-W-L-K-A-F-Y-D-K-V-A-E-R-L-R-E-A-F-NH_2 74

Ac-E-W-L-K-A-F-Y-E-K-V-A-E-R-L-R-E-A-F-NH_2 75

Ac-D-W-L-R-A-F-Y-D-K-V-A-E-R-L-K-E-A-F-NH_2 76

Ac-E-W-L-R-A-F-Y-E-K-V-A-E-R-L-K-E-A-F-NH2 77

D-W-L-K-A-F-Y-D-K-V-A-E-K-L-K-E-A-F-**P**-D-W-L-K-A-F-Y-D-K-V-A-E-K-L-K-E-A-F 78

D-W-L-K-A-F-Y-D-K-V-A-E-K-L-K-E-F-F-**P**-D-W-L-K-A-F-Y-D-K-V-A-E-K-L-K-E-F-F 79

D-W-F-K-A-F-Y-D-K-V-A-E-K-L-K-E-A-F-**P**-D-W- 80

F-K-A-F-Y-D-K-V-A-E-K-L-K-E-A-F	
D-K-L-K-A-F-Y-D-K-V-F-E-W-A-K-E-A-F-**P**-D-K-L-K-A-F-Y-D-K-V-F-E-W-L-K-E-A-F	81
D-K-W-K-A-V-Y-D-K-F-A-E-A-F-K-E-F-L-**P**-D-K-W-K-A-V-Y-D-K-F-A-E-A-F-K-E-F-L	82
D-W-F-K-A-F-Y-D-K-V-A-E-K-F-K-E-A-F-**P**-D-W-F-K-A-F-Y-D-K-V-A-E-K-F-K-E-A-F	83
D-W-L-K-A-F-V-Y-D-K-V-F-K-L-K-E-F-F-**P**-D-W-L-K-A-F-V-Y-D-K-V-F-K-L-K-E-F-F	84
D-W-L-K-A-F-Y-D-K-F-A-E-K-F-K-E-F-F-**P**-D-W-L-K-A-F-Y-D-K-F-A-E-K-F-K-E-F-F	85
Ac-E-W-F-K-A-F-Y-E-K-V-A-E-K-F-K-E-A-F-NH_2	86
Ac-D-W-F-K-A-F-Y-D-K-V-A-E-K-F-NH_2	87
Ac-F-K-A-F-Y-D-K-V-A-E-K-F-K-E-NH_2	88
Ac-F-K-A-F-Y-E-K-V-A-E-K-F-K-E-NH_2	89
NMA-F-K-A-F-Y-D-K-V-A-E-K-F-K-E-NH_2	90
NMA-F-K-A-F-Y-E-K-V-A-E-K-F-K-E-NH_2	91
NMA-D-W-F-K-A-F-Y-D-K-V-A-E-K-F-K-E-A-F-NH_2	92
NMA-E-W-F-K-A-F-Y-E-K-V-A-E-K-F-K-E-A-F-NH_2	93
NMA-A-F-Y-D-K-V-A-E-K-F-K-E-A-F-NH_2	94
NMA-D-W-F-K-A-F-Y-D-K-V-A-E-K-F-NH_2	95
Ac-D-W-L-K-A-F-Y-D-K-V-F-E-K-F-K-E-F-F-NH_2	96
NMA-D-W-L-K-A-F-Y-D-K-V-F-E-K-F-K-E-F-F-NH_2	
Ac-E-W-L-K-A-F-Y-E-K-V-F-E-K-F-K-E-F-F-NH_2	97
NMA-E-W-L-K-A-F-Y-E-K-V-F-E-K-F-K-E-F-F-NH_2	
Ac-A-F-Y-D-K-V-F-E-K-F-K-E-F-F-NH_2	98
NMA-A-F-Y-D-K-V-F-E-K-F-K-E-F-F-NH_2	
Ac-A-F-Y-E-K-V-F-E-K-F-K-E-F-F-NH_2	99
NMA-A-F-Y-E-K-V-F-E-K-F-K-E-F-F-NH_2	
Ac-D-W-L-K-A-F-Y-D-K-V-F-E-K-F-NH_2	100
NMA-D-W-L-K-A-F-Y-D-K-V-F-E-K-F-NH_2	
Ac-E-W-L-K-A-F-Y-E-K-V-F-E-K-F-NH_2	101
NMA-E-W-L-K-A-F-Y-E-K-V-F-E-K-F-NH_2	
Ac-L-K-A-F-Y-D-K-V-F-E-K-F-K-E-NH_2	102
NMA-L-K-A-F-Y-D-K-V-F-E-K-F-K-E-NH_2	
Ac-L-K-A-F-Y-E-K-V-F-E-K-F-K-E-NH_2	103
NMA-L-K-A-F-Y-E-K-V-F-E-K-F-K-E-NH_2	

[T]Linkers are underlined.

NMA is N-Methyl Anthranilyl.

[0131] In certain preferred embodiments, the peptides include variations of 4F ((SEQ ID NO:5 in Table 2), also known as L-4F, where all residues are L form amino acids) or D-4F where one or more residues are D form amino acids). In any of the peptides described herein, the C-terminus, and/or N-terminus, and/or internal residues can be blocked with one or more blocking groups as described herein. Also, with respect to any of the peptides disclosed herein this invention contemplates L-form peptides as well as D form peptides, retro- sequences, inverse- sequences, and retro-inverse sequences.

[0132] In addition, while various peptides of Table 2, are illustrated with an acetyl group or an N-methylanthranilyl group protecting the amino terminus and an amide group protecting the carboxyl terminus, any of these protecting groups may be eliminated and/or substituted with another protecting group as described herein. In particularly preferred embodiments, the peptides comprise one or more D-form amino acids as described herein. In certain embodiments, every amino acid (*e.g.*, every enantiomeric amino acid) of the peptides of Table 2 is a D-form amino acid.

[0133] It is also noted that Table 2 is not fully inclusive. Using the teachings provided herein, other suitable class A amphipathic helical peptides can routinely be produced (*e.g.*, by conservative or semi-conservative substitutions (*e.g.*, D replaced by E), extensions, deletions, and the like). Thus, for example, one embodiment utilizes truncations of any one or more of peptides shown herein (*e.g.*, peptides identified by SEQ ID Nos:2-20 and 39- in Table 2). Thus, for example, SEQ ID NO:21 illustrates a peptide comprising 14 amino acids from the C-terminus of 18A comprising one or more D amino acids, while SEQ ID NOS:22-38 illustrate other truncations.

[0134] Longer peptides are also suitable. Such longer peptides may entirely form a class A amphipathic helix, or the class A amphipathic helix (helices) can form one or more domains of the peptide. In addition, this invention contemplates multimeric versions of the peptides (*e.g.*, concatamers). Thus, for example, the peptides illustrated herein can be coupled together (directly or through a linker (*e.g.*, a carbon linker, or one or more amino acids) with one or more intervening amino acids). Illustrative polymeric peptides include 18A-Pro-18A and the peptides of SEQ ID NOs:78-85, in certain embodiments comprising one or more D amino acids, more preferably with every amino acid a D amino acid as described herein and/or having one or both termini protected.

[0135] It will also be appreciated in addition to the D-form and L-form peptide sequences expressly illustrated herein, this invention also contemplates retro and retro-inverso forms of each of these peptides. In retro forms, the direction of the sequence is reversed. In inverse forms, the chirality of the constituent amino acids is reversed (*i.e.*, L form amino acids become D form amino acids and D form amino acids become L form amino acids). In the retro-inverso form, both the order and the chirality of the amino acids is reversed. Thus, for example, a retro form of the 4F peptide (DWFKAFYDKVAEKFKEAF, SEQ ID NO:5), where the amino terminus is at the aspartate (D) and the carboxyl terminus is at the phenylalanine (F), has the same sequence, but the amino terminus is at the phenylalanine and the carboxy terminus is at the aspartate (*i.e.*, FAEKFKEAVKDYFAKFWD, SEQ ID NO:104). Where the 4F peptide comprises all L amino acids, the retro-inverso form will have the sequence shown above (SEQ ID NO:104) and comprise all D form amino acids. As illustrated in the helical wheel diagrams shown in related application USSN 11/407,390 and PCT/US2006/014389, which are incorporated herein by reference, 4F and retroinverso (Rev-4F) are mirror images of each other with identical segregation of the polar and nonpolar faces with the positively charged residues residing at the polar-nonpolar interface and the negatively charged residues residing at the center of the polar face. These mirror images of the same polymer of amino acids are identical in terms of the segregation of the polar and nonpolar faces with the positively charged residues residing at the polar-nonpolar interface and the negatively charged residues residing at the center of the polar face. Thus, 4F and Rev-4F are enantiomers of each other. For a discussion of retro- and retro-inverso peptides *see, e.g.*, Chorev and Goodman, (1995) *TibTech*, 13: 439-445.

[0136] Where reference is made to a sequence and orientation is not expressly indicated, the sequence can be viewed as representing the amino acid sequence in the amino to carboxyl orientation, the retro form (*i.e.*, the amino acid sequence in the carboxyl to amino orientation), the retro form where L amino acids are replaced with D amino acids or D amino acids are replaced with L amino acids, and the retro-inverso form where both the order is reversed and the amino acid chirality is reversed.

B) Class A amphipathic helical peptide mimetics of apoA-I having Aromatic or aliphatic residues in the non-polar face.

[0137] In certain embodiments, this invention also provides modified class A amphipathic helix peptides. Certain preferred peptides incorporate one or more aromatic residues at the center of the nonpolar face, *e.g.*, $3F^{C\pi}$, (as present in 4F), or with one or more aliphatic residues at the center of the nonpolar face, *e.g.*, $3F^{I\pi}$, *see, e.g.,* Table 3. Without being bound to a particular theory, we believe the central aromatic residues on the nonpolar face of the peptide $3F^{C\pi}$, due to the presence of π electrons at the center of the nonpolar face, allow water molecules to penetrate near the hydrophobic lipid alkyl chains of the peptide-lipid complex, which in turn would enable the entry of reactive oxygen species (such as lipid hydroperoxides) shielding them from the cell surface. Similarly, we also believe the peptides with aliphatic residues at the center of the nonpolar face, *e.g.*, $3F^{I\pi}$, will act similarly but not quite as effectively as $3F^{C\pi}$.

[0138] Preferred peptides will convert pro-inflammatory HDL to anti-inflammatory HDL or make anti-inflammatory HDL more anti-inflammatory, and/or decrease LDL-induced monocyte chemotactic activity generated by artery wall cells equal to or greater than D-4F or other peptides shown in Table 2.

[0139] Table 3. Examples of certain preferred peptides.

Name	Sequence	SEQ ID NO
($3F^{C\pi}$)	Ac-DKWKAVYDKFAEAFKEFL-NH_2	105
($3F^{I\pi}$)	Ac-DKLKAFYDKVFEWAKEAF-NH_2	106

C) Other class A and some class Y amphipathic helical peptides.

[0140] In certain embodiments this invention also contemplates class a amphipathic helical peptides that have an amino acid composition identical to one or more of the class a amphipathic helical peptides described above. Thus, for example, in certain embodiments this invention contemplates peptides having an amino acid composition identical to 4F. Thus, in certain embodiments, this invention includes peptides that comprise 18 amino acids, where the 18 amino acids consist of 3 alanines (A), 2 aspartates (D), 2 glutamates (E), 4 phenylalanines (F), 4 lysines (K), 1 valine (V), 1 tryptophan (W), and 1 tyrosine (Y); and where the peptide forms a class A amphipathic helix; and protects a phospholipid against

oxidation by an oxidizing agent. In various embodiments, the peptides comprise least one "D" amino acid residue; and in certain embodimemtns, the peptides comprise all "D: form amino acid residues. A variety of such peptides are illustrated in Table 4. Reverse (retro-), inverse, retro-inverso-, and circularly permuted forms of these peptides are also contemplated.

[0141] Table 4. Illustrative 18 amino acid length class A amphipathic helical peptides with the amino acid composition 3 alanines (A), 2 aspartates (D), 2 glutamates (E), 4 phenylalanines (F), 4 lysines (K), 1 valine (V), 1 tryptophan (W), and 1 tyrosine (Y).

Name	Sequence	SEQ ID NO
[Switch D-E]-4F analogs		107
[Switch D-E]-1-4F	Ac-**E**WFKAFY**E**KVA**D**KFK**D**AF-NH2	108
[Switch D-E]-2-4F	Ac-**E**WFKAFYDKVADKFK**E**AF-NH2	109
[Switch D-E]-3-4F	Ac-DWFKAFY**E**KVA**D**KFKEAF-NH2	110
[Switch D-E]-4-4F	Ac-DWFKAFY**E**KVAEKFK**D**AF-NH2	111
[W-2,F-3 positions reversed]		112
4F-2	Ac-D**FW**KAFYDKVAEKFKEAF-NH_2	113
[Switch D-E]-1-4F-2	Ac-**E**FWKAFY**E**KVA**D**KFK**D**AF-NH2	114
[Switch D-E]-2-4F-2	Ac-**E**FWKAFYDKVADKFK**E**AF-NH2	115
[Switch D-E]-3-4F-2	Ac-DFWKAFY**E**KVA**D**KFKEAF-NH2	116
[Switch D-E]-4-4F-2	Ac-DFWKAFY**E**KVAEKFK**D**AF-NH2	117
[F-6 and Y-7 positions switched]		118
4F-3	Ac-DWFKA**YF**DKVAEKFKEAF-NH_2	119
[Switch D-E]-1-4F-5	Ac-**E**WFKAYF**E**KVA**D**KFK**D**AF-NH2	120
[Switch D-E]-2-4F-5	Ac-**E**WFKAYFDKVADKFK**E**AF-NH2	121
[Switch D-E]-3-4F-5	Ac-DWFKAYF**E**KVA**D**KFKEAF-NH2	122
[Switch D-E]-4-4F-5	Ac-DWFKAYF**E**KVAEKFK**D**AF-NH2	123
[Y-7and 10V positions switched]		124
4F-4	Ac-DWFKAF**V**DK**Y**AEKFKEAF-NH_2	125
[Switch D-E]-1-4F-4	Ac-**E**WFKAFV**E**KYA**D**KFK**D**AF-NH2	126
[Switch D-E]-2-4F-4	Ac-**E**WFKAFVDKYADKFK**E**AF-NH2	127
[Switch D-E]-3-4F-4	Ac-DWFKAFV**E**KYA**D**KFKEAF-NH2	128
[Switch D-E]-4-4F	Ac-DWFKAFV**E**KYAEKFK**D**AF-NH2	129
[V-10 and A-11 switched]		130
4-F-5	Ac-DWFKAFYDK**AV**EKFKEAF-NH_2	131
[Switch D-E]-1-4F-5	Ac-**E**WFKAFY**E**KAV**D**KFK**D**AF-NH2	132
[Switch D-E]-2-4F-5	Ac-**E**WFKAFYDKAVDKFK**E**AF-NH2	133
[Switch D-E]-3-4F-5	Ac-DWFKAFY**E**KAV**D**KFKEAF-NH2	134

[Switch D-E]-4-4F-5	Ac-DWFKAFY**E**KAVEKFK**D**AF-NH2	135
[A-11 and F-14 switched]		136
4F-6	Ac-DWFKAFYDKV**F**EK**A**KEAF-NH_2	137
[Switch D-E]-1-4F-6	Ac-**E**WFKAFY**E**KVF**D**KAK**D**AF-NH2	138
[Switch D-E]-2-4F-6	Ac-**E**WFKAFYDKVFDKAK**E**AF-NH2	139
[Switch D-E]-3-4F-6	Ac-DWFKAFY**E**KVF**D**KAKEAF-NH2	140
[Switch D-E]-4-4F-6	Ac-DWFKAFY**E**KVFEKAK**D**AF-NH2	141
[F-14 and A-17 switched]		142
4F-7	Ac-DWFKAFYDKVAEK**A**KE**F**F-NH_2	143
[Switch D-E]-1-4F-7	Ac-**E**WFKAFY**E**KVA**D**KAK**D**FF-NH2	144
[Switch D-E]-2-4F-7	Ac-**E**WFKAFYDKVADKAK**E**FF-NH2	145
[Switch D-E]-3-4F-7	Ac-DWFKAFY**E**KVA**D**KAKEFF-NH2	146
[Switch D-E]-4-4F-7	Ac-DWFKAFY**E**KVAEKAK**D**FF-NH2	147
[A-17 and F-18 switched]		148
4F-8	Ac-DWFKAFYDKVAEKFKE**F**A-NH_2	149
[Switch D-E]-1-4F-8	Ac-**E**WFKAFY**E**KVA**D**KFK**D**FA-NH2	150
[Switch D-E]-2-4F-8	Ac-**E**WFKAFYDKVADKFK**E**FA-NH2	151
[Switch D-E]-3-4F-8	Ac-DWFKAFY**E**KVA**D**KFKEFA-NH2	152
[Switch D-E]-4-4F-8	Ac-DWFKAFY**E**KVAEKFK**D**FA-NH2	153
[W-2 and A-17 switched]		154
4F-9	Ac-D**A**FKAFYDKVAEKFKE**W**F-NH_2	155
[Switch D-E]-1-4F-9	Ac-**E**AFKAFY**E**KVA**D**KFK**D**WF-NH2	156
[Switch D-E]-2-4F-9	Ac-**E**AFKAFYDKVADKFK**E**WF-NH2	157
[Switch D-E]-3-4F-9	Ac-DAFKAFY**E**KVA**D**KFKEWF-NH2	158
[Switch D-E]-4-4F-9	Ac-DAFKAFY**E**KVAEKFK**D**WF-NH2	159
[W-2 and A-11 switched]		160
4F-10	Ac-D**A**FKAFYDKV**W**EKFKEAF-NH_2	161
[Switch D-E]-1-4F-10	Ac-**E**AFKAFY**E**KVW**D**KFK**D**AF-NH2	162
[Switch D-E]-2-4F-10	Ac-**E**AFKAFYDKVWDKFK**E**AF-NH2	163
[Switch D-E]-3-4F-10	Ac-DAFKAFY**E**KVW**D**KFKEAF-NH2	164
[Switch D-E]-4-4F-10	Ac-DAFKAFY**E**KVWEKFK**D**AF-NH2	165
[W-2 and Y-7 switched]		166
4F-11	Ac-D**Y**FKAF**W**DKVAEKFKEAF-NH_2	167
[Switch D-E]-1-4F-11	Ac-**E**YFKAFW**E**KVA**D**KFK**D**AF-NH2	168
[Switch D-E]-2-4F-11	Ac-**E**YFKAFWDKVADKFK**E**AF-NH2	169
[Switch D-E]-3-4F-11	Ac-DYFKAFW**E**KVA**D**KFKEAF-NH2	170
[Switch D-E]-4-4F-11	Ac-DYFKAFW**E**KVAEKFK**D**AF-NH2	171
[F-3 and A-17 switched]		172
4F-12	Ac-DW**A**KAFYDKVAEKFKE**F**F-NH_2	173
[Switch D-E]-1-4F-12	Ac-**E**WAKAFY**E**KVA**D**KFK**D**FF-NH2	174
[Switch D-E]-2-4F-12	Ac-**E**WAKAFYDKVADKFK**E**FF-NH2	175
[Switch D-E]-3-4F-12	Ac-DWAKAFY**E**KVA**D**KFKEFF-NH2	176
[Switch D-E]-4-4F-12	Ac-DWAKAFY**E**KVAEKFK**D**FF-NH2	177
[F-6 and A-17 switched]		178
4F-13	Ac-DWFKA**A**YDKVAEKFKE**F**F-NH_2	179
[Switch D-E]-1-4F-13	Ac-**E**WFKAAY**E**KVA**D**KFK**D**FF-NH2	180

[Switch D-E]-2-4F-13	Ac-**E**WFKAAYDKVADKFK**E**FF-NH2	181
[Switch D-E]-3-4F-13	Ac-DWFKAAY**E**KVA**D**KFKEFF-NH2	182
[Switch D-E]-4-4F-13	Ac-DWFKAAY**E**KVAEKFK**D**FF-NH2	183
[Y-7 and A-17 switched		184
4F-14	Ac-DWFKAF**A**DKVAEKFKE**Y**F-NH_2	185
[Switch D-E]-1-4F-14	Ac-**E**WFKAFA**E**KVA**D**KFK**D**YF-NH2	186
[Switch D-E]-2-4F-14	Ac-**E**WFKAFADKVADKFK**E**YF-NH2	187
[Switch D-E]-3-4F-14	Ac-DWFKAFA**E**KVA**D**KFKEYF-NH2	188
[Switch D-E]-4-4F	Ac-DWFKAFA**E**KVAEKFK**D**YF-NH2	189
[V-10 and A-17 switched]		190
4F-15	Ac-DWFKAFYDK**A**AEKFKE**V**F-NH_2	191
[Switch D-E]-1-4F-15	Ac-**E**WFKAFY**E**KAA**D**KFK**D**VF-NH2	192
[Switch D-E]-2-4F-15	Ac-**E**WFKAFYDKAADKFK**E**VF-NH2	193
[Switch D-E]-3-4F-15	Ac-DWFKAFY**E**KAA**D**KFKEVF-NH2	194
[Switch D-E]-4-4F-15	Ac-DWFKAFY**E**KAAEKFK**D**VF-NH2	195
[F3 and Y-7 switched]		196
4F-16	Ac-DW**Y**KAF**F**DKVAEKFKEAF-NH_2	197
[Switch D-E]-1-4F-16	Ac-**E**WYKAFF**E**KVA**D**KFK**D**AF-NH2	198
[Switch D-E]-2-4F-16	Ac-**E**WYKAFFDKVADKFK**E**AF-NH2	199
[Switch D-E]-3-4F-16	Ac-DWYKAFF**E**KVA**D**KFKEAF-NH2	200
[Switch D-E]-4-4F-16	Ac-DWYKAFF**E**KVAEKFK**D**AF-NH2	201
[F-3 and V-10 switched]		202
4F-17	Ac-DW**V**KAFYDK**F**AEKFKEAF-NH_2	203
[Switch D-E]-1-4F-17	Ac-**E**WVKAFY**E**KFA**D**KFK**D**AF-NH2	204
[Switch D-E]-2-4F-17	Ac-**E**WVKAFYDKFADKFK**E**AF-NH2	205
[Switch D-E]-3-4F-17	Ac-DWVKAFY**E**KFA**D**KFKEAF-NH2	206
[Switch D-E]-4-4F-17	Ac-DWVKAFY**E**KFAEKFK**D**AF-NH2	207
[Y-7 and F-14 switched]		208
4F-18	Ac-DWFKAF**F**DKVAEK**Y**KEAF-NH_2	209
[Switch D-E]-1-4F-18	Ac-**E**WFKAFF**E**KVA**D**KYK**D**AF-NH2	210
[Switch D-E]-2-4F-18	Ac-**E**WFKAFFDKVADKYK**E**AF-NH2	211
[Switch D-E]-3-4F-18	Ac-DWFKAFF**E**KVA**D**KYKEAF-NH2	212
[Switch D-E]-3-4F-18	Ac-DWFKAFF**E**KVA**D**KYKEAF-NH2	213
[Y-7 and F-18 switched]		214
4F-19	Ac-DWFKAF**F**DKVAEKFKEA**Y**-NH_2	215
[Switch D-E]-1-4F-19	Ac-**E**WFKAFF**E**KVA**D**KFK**D**AY-NH2	216
[Switch D-E]-2-4F-19	Ac-**E**WFKAFFDKVADKFK**E**AY-NH2	217
[Switch D-E]-3-4F-19	Ac-DWFKAFF**E**KVA**D**KFKEAY-NH2	218
[Switch D-E]-4-4F-19	Ac-DWFKAFF**E**KVAEKFK**D**AY-NH2	219
[V-10 and F-18 switched		220
4F-20	Ac-DWFKAFYDK**F**AEKFKEA**V**-NH_2	221
[Switch D-E]-1-4F-20	Ac-**E**WFKAFY**E**KFA**D**KFK**D**AV-NH2	222
[Switch D-E]-2-4F-20	Ac-**E**WFKAFYDKFADKFK**E**AV-NH2	223
[Switch D-E]-3-4F-20	Ac-DWFKAFY**E**KFA**D**KFKEAV-NH2	224
[Switch D-E]-4-4F-20	Ac-DWFKAFY**E**KFAEKFK**D**AV-NH2	225
[W-2 and K13 switched]		226

4F-21	Ac-D**K**FKAFYDKVAEKF**W**EAF-NH_2	227
[Switch D-E]-1-4F-21	Ac-**E**KFKAFY**E**KVA**D**KFW**D**AF-NH2	228
[Switch D-E]-2-4F-21	Ac-**E**KFKAFYDKVADKFW**E**AF-NH2	229
[Switch D-E]-3-4F-21	Ac-DKFKAFY**E**KVA**D**KFWEAF-NH2	230
[Switch D-E]-4-4F-21	Ac-DKFKAFY**E**KVAEKFW**D**AF-NH2	231
[W-3, F-13 and K-2 4F]		232
4F-22	Ac-D**KW**KAFYDKVAEKF**F**EAF-NH_2	233
[Switch D-E]-1-4F-22	Ac-**E**KWKAFY**E**KVA**D**KFF**D**AF-NH2	234
[Switch D-E]-2-4F-22	Ac-**E**KWKAFYDKVADKFF**E**AF-NH2	235
[Switch D-E]-3-4F-22	Ac-DKWKAFY**E**KVA**D**KFFEAF-NH2	236
[Switch D-E]-4-4F-22	Ac-DKWKAFY**E**KVAEKFF**D**AF-NH2	237
[K-2, W10, V-13]		238
4F-23	Ac-D**K**FKAFYDK**W**AE**V**FKEAF-NH_2	239
[Switch D-E]-4F analogs		240
[Switch D-E]-1-4F-23	Ac-**E**KFKAFY**E**KWA**D**VFK**D**AF-NH2	241
[Switch D-E]-2-4F-23	Ac-**E**KFKAFYDKWADVFK**E**AF-NH2	242
[Switch D-E]-3-4F-23	Ac-DKFKAFY**E**KWA**D**VFKEAF-NH2	243
[Switch D-E]-4-4F-23	Ac-DKFKAFY**E**KWAEVFK**D**AF-NH2	244
[K-2, F-13, W-14 4F]		245
4F-24	Ac-D**K**FKAFYDKVAE**FW**KEAF-NH_2	246
[Switch D-E]-4F analogs		247
[Switch D-E]-1-4F-24	Ac-**E**KFKAFY**E**KVA**D**FWK**D**AF-NH2	248
[Switch D-E]-2-4F-24	Ac-**E**KFKAFYDKVADFWK**E**AF-NH2	249
[Switch D-E]-3-4F-24	Ac-DKFKAFY**E**KVA**D**FWKEAF-NH2	250
[Switch D-E]-4-4F-24	Ac-DKFKAFY**E**KVAEFWK**D**AF-NH2	251
Reverse 4F analogs		252
Rev-4F	Ac-FAEKFKEAVKDYFAKFWD-NH2	253
[Switch D-E]-1-Rev-4F	Ac-FA**D**KFK**D**AVK**E**YFAKFW**E**-NH2	254
[Switch D-E]-2-Rev-4F	Ac-FA**D**KFKEAVKDYFAKFW**E**-NH2	255
[Switch D-E]-3-Rev-4F	Ac-FAEKFK**D**AVK**E**YFAKFWD-NH2	256
[Switch D-E]-4-Rev-4F	Ac-FAEKFK**D**AVKDYFAKFW**E**-NH2	257
[A-2 and W-17 switched]		258
Rev-4F-1	Ac-F**W**EKFKEAVKDYFAKF**A**D-NH2	259
[Switch D-E]-1-Rev-4F-1	Ac-FW**D**KFK**D**AVK**E**YFAKFA**E**-NH2	260
[Switch D-E]-2-Rev-4F-1	Ac-FA**D**KFKEAVKDYFAKFW**E**-NH2	261
[Switch D-E]-3-Rev-4F-1	Ac-FAEKFK**D**AVK**E**YFAKFWD-NH2	262
[Switch D-E]-4-Rev-4F-1	Ac-FAEKFK**D**AVKDYFAKFW**E**-NH2	263
[Switch A-2 and F-16]		264
Rev-4F-2	Ac-F**F**EKFKEAVKDYFAK**A**WD-NH2	265
[Switch D-E]-1-Rev-4F-2	Ac-FF**D**KFK**D**AVK**E**YFAKAW**E**-NH2	266
[Switch D-E]-2-Rev-4F-2	Ac-FF**D**KFKEAVKDYFAKAW**E**-NH2	267
[Switch D-E]-3-Rev-4F-2	Ac-FFEKFK**D**AVK**E**YFAKAWD-NH2	268
[Switch D-E]-4-Rev-4F-2	Ac-FFEKFK**D**AVKDYFAKAW**E**-NH2	269
[switch F-5 and A-8]		270
Rev-4F-3	Ac-FAEK**A**KE**F**VKDYFAKFWD-NH2	271
[Switch D-E]-1-Rev-4F-3	Ac-FA**D**KAK**D**FVK**E**YFAKFW**E**-NH2	272

[Switch D-E]-2-Rev-4F-3	Ac-FA**D**KAKEFVKDYFAKFW**E**-NH2	273
[Switch D-E]-3-Rev-4F-3	Ac-FAEKAK**D**FVK**E**YFAKFWD-NH2	274
[Switch D-E]-4-Rev-4F-3	Ac-FAEKAK**D**FVKDYFAKFW**E**-NH2	275
[Switch A-8 and V9]		276
Rev-4F-4	Ac-FAEKFKE**V**A**A**KDYFAKFWD-NH2	277
[Switch D-E]-1-Rev-4F-4	Ac-FA**D**KFK**D**VAK**E**YFAKFW**E**-NH2	278
[Switch D-E]-2-Rev-4F-4	Ac-FA**D**KFKEVAKDYFAKFW**E**-NH2	279
[Switch D-E]-3-Rev-4F-4	Ac-FAEKFK**D**VAK**E**YFAKFWD-NH2	280
[Switch D-E]-4-Rev-4F-4	Ac-FAEKFK**D**VAKDYFAKFW**E**-NH2	281
[Switch V-9 to Y-12]		282
Rev-4F-5	Ac-FAEKFKEA**Y**KD**V**FAKFWD-NH2	283
[Switch D-E]-1-Rev-4F-5	Ac-FA**D**KFK**D**AYK**E**VFAKFW**E**-NH2	284
[Switch D-E]-2-Rev-4F-5	Ac-FA**D**KFKEAYKDVFAKFW**E**-NH2	285
[Switch D-E]-3-Rev-4F-5	Ac-FAEKFK**D**AYK**E**VFAKFWD-NH2	286
[Switch D-E]-4-Rev-4F-5	Ac-FAEKFK**D**AYKDVFAKFW**E**-NH2	287
[Switch Y-12 and F-13]		288
Rev-4F-6	Ac-FAEKFKEAVKD**FY**AKFWD-NH2	289
[Switch D-E]-1-Rev-4F-6	Ac-FA**D**KFK**D**AVK**E**FYAKFW**E**-NH2	290
[Switch D-E]-2-Rev-4F-6	Ac-FA**D**KFKEAVKDFYAKFW**E**-NH2	291
[Switch D-E]-3-Rev-4F-6	Ac-FAEKFK**D**AVK**E**FYAKFWD-NH2	292
[Switch D-E]-4-Rev-4F-6	Ac-FAEKFK**D**AVKDFYAKFW**E**-NH2	293
[Switch K-6 and W-17]		294
Rev-4F-7	Ac-FAEKF**W**EAVKDYFAKF**K**D-NH2	295
[Switch D-E]-1-Rev-4F-7	Ac-FA**D**KFW**D**AVK**E**YFAKFK**E**-NH2	296
[Switch D-E]-2-Rev-4F-7	Ac-FA**D**KFWEAVKDYFAKFK**E**-NH2	297
[Switch D-E]-3-Rev-4F-7	Ac-FAEKFW**D**AVK**E**YFAKFKD-NH2	298
[Switch D-E]-4-Rev-4F-7	Ac-FAEKFW**D**AVKDYFAKFK**E**-NH2	299
[Switch F-1 and A-2]		300
Rev-4F-8	Ac-**A**FEKFKEAVKDYFAKFWD-NH2	301
[Switch D-E]-1-Rev-4F-8	Ac-AF**D**KFK**D**AVK**E**YFAKFW**E**-NH2	302
[Switch D-E]-2-Rev-4F-8	Ac-AF**D**KFKEAVKDYFAKFW**E**-NH2	303
[Switch D-E]-3-Rev-4F-8	Ac-AFEKFK**D**AVK**E**YFAKFWD-NH2	304
[Switch D-E]-4-Rev-4F-8	Ac-AFEKFK**D**AVKDYFAKFW**E**-NH2	305
[F-1 and V-9 are switched]		306
Rev-F-9	Ac-**V**AEKFKEA**F**KDYFAKFWD-NH2	307
[Switch D-E]-1-Rev-4F-9	Ac-VA**D**KFK**D**AFK**E**YFAKFW**E**-NH2	308
[Switch D-E]-2-Rev-4F-9	Ac-VA**D**KFKEAFKDYFAKFW**E**-NH2	309
[Switch D-E]-3-Rev-4F-9	Ac-VAEKFK**D**AFK**E**YFAKFWD-NH2	310
[Switch D-E]-4-Rev-4F-9	Ac-VAEKFK**D**AFKDYFAKFW**E**-NH2	311
[F-1 and Y-12 are switched]		312
Rev-4F-10	Ac-**Y**AEKFKEAVKD**F**FAKFWD-NH2	313
[Switch D-E]-1-Rev-4F-10	Ac-YA**D**KFK**D**AVK**E**FFAKFW**E**-NH2	314
[Switch D-E]-2-Rev-4F-10	Ac-YA**D**KFKEAVKDFFAKFW**E**-NH2	315
[Switch D-E]-3-Rev-4F-10	Ac-YAEKFK**D**AVK**E**FFAKFWD-NH2	316
[Switch D-E]-4-Rev-4F-10	Ac-YAEKFK**D**AVKDFFAKFW**E**-NH2	317
[F-1 and A-8 are switched]		318

Rev-4F-11	Ac-**A**AEKFKE**F**VKDYFAKFWD-NH2	319
[Switch D-E]-1-Rev-4F-11	Ac-AA**D**KFK**D**FVK**E**YFAKFW**E**-NH2	320
[Switch D-E]-2-Rev-4F-11	Ac-AA**D**KFKEFVKDYFAKFW**E**-NH2	321
[Switch D-E]-3-Rev-4F-11	Ac-AAEKFK**D**FVK**E**YFAKFWD-NH2	322
Switch D-E]-4-Rev-4F-11	Ac-AAEKFK**D**FVKDYFAKFW**E**-NH2	323
[A-2 and F-5 are switched]		324
Rev-4F-12	Ac-F**F**EK**A**KEAVKDYFAKFWD-NH2	325
[Switch D-E]-1-Rev-4F-12	Ac-FF**D**KAK**D**AVK**E**YFAKFW**E**-NH2	326
[Switch D-E]-2-Rev-4F-12	Ac-FF**D**KAKEAVKDYFAKFW**E**-NH2	327
[Switch D-E]-3-Rev-4F-12	Ac-FFEKAK**D**AVK**E**YFAKFWD-NH2	328
[Switch D-E]-4-Rev-4F-12	Ac-FFEKAK**D**AVKDYFAKFW**E**-NH2	329
[A-2 and Y12 are switched		330
Rev-4F-13	Ac-F**Y**EKFKEAVKD**A**FAKFWD-NH2	331
[Switch D-E]-1-Rev-4F-13	Ac-FY**D**KFK**D**AVK**E**AFAKFW**E**-NH2	332
[Switch D-E]-2-Rev-4F-13	Ac-FY**D**KFKEAVKDAFAKFW**E**-NH2	333
[Switch D-E]-3-Rev-4F-13	Ac-FYEKFK**D**AVK**E**AFAKFWD-NH2	334
[Switch D-E]-4-Rev-4F-13	Ac-FYEKFK**D**AVKDAFAKFW**E**-NH2	335
[A-2 and V-9 are switched]		336
Rev-4F-14	Ac-F**V**EKFKEA**A**KDYFAKFWD-NH2	337
[Switch D-E]-1-Rev-4F-14	Ac-FV**D**KFK**D**AAK**E**YFAKFW**E**-NH2	338
[Switch D-E]-2-Rev-4F-14	Ac-FV**D**KFKEAAKDYFAKFW**E**-NH2	339
[Switch D-E]-3-Rev-4F-14	Ac-FVEKFK**D**AAK**E**YFAKFWD-NH2	340
[Switch D-E]-4-Rev-4F-14	Ac-FVEKFK**D**AAKDYFAKFW**E**-NH2	341
[F-5 and Y-12 are switched]		342
Rev-4F-15	Ac-FAEK**Y**KEAVKD**F**FAKFWD-NH2	343
[Switch D-E]-1-Rev-4F-15	Ac-FA**D**KYK**D**AVK**E**FFAKFW**E**-NH2	344
[Switch D-E]-2-Rev-4F-15	Ac-FA**D**KYKEAVKDFFAKFW**E**-NH2	345
[Switch D-E]-3-Rev-4F-15	Ac-FAEKYK**D**AVK**E**FFAKFWD-NH2	346
[Switch D-E]-4-Rev-4F-15	Ac-FAEKYK**D**AVKDFFAKFW**E**-NH2	347
[F-5 and V-9 are switched]		348
Rev-4F-16	Ac-FAEK**V**KEA**F**KDYFAKFWD-NH2	349
[Switch D-E]-1-Rev-4F-16	Ac-FA**D**KVK**D**AFK**E**YFAKFW**E**-NH2	350
[Switch D-E]-2-Rev-4F-16	Ac-FA**D**KVKEAFKDYFAKFW**E**-NH2	351
[Switch D-E]-3-Rev-4F-16	Ac-FAEKVK**D**AFK**E**YFAKFWD-NH2	352
[Switch D-E]-4-Rev-4F-16	Ac-FAEKVK**D**AFKDYFAKFW**E**-NH2	353
[A-8 and Y-12 switched]		354
Rev-4F-17	Ac-FAEKFKE**Y**VKD**A**FAKFWD-NH2	355
[Switch D-E]-1-Rev-4F-17	Ac-FA**D**KFK**D**YVK**E**AFAKFW**E**-NH2	356
[Switch D-E]-2-Rev-4F-17	Ac-FA**D**KFKEYVKDAFAKFW**E**-NH2	357
[Switch D-E]-3-Rev-4F-17	Ac-FAEKFK**D**YVK**E**AFAKFWD-NH2	358
[Switch D-E]-4-Rev-4F-17	Ac-FAEKFK**D**YVKDAFAKFW**E**-NH2	359
[V-9 and F-13 are switched]		360
Rev-4F-18	Ac-FAEKFKEA**F**K**D**Y**V**AKFWD-NH2	361
[Switch D-E]-1-Rev-4F-18	Ac-FA**D**KFK**D**AFK**E**YVAKFW**E**-NH2	362
[Switch D-E]-2-Rev-4F-18	Ac-FA**D**KFKEAFKDYVAKFW**E**-NH2	363
[Switch D-E]-3-Rev-4F-18	Ac-FAEKFK**D**AFK**E**YVAKFWD-NH2	364

[Switch D-E]-4-Rev-4F-18	Ac-FAEKFK**D**AFKDYVAKFW**E**-NH2	365
[V-9 and F-16 switched]		366
Rev-4F-19	Ac-FAEKFKEA**F**KDYFAK**V**WD-NH2	367
[Switch D-E]-1-Rev-4F-19	Ac-FA**D**KFK**D**AFK**E**YFAKVW**E**-NH2	368
[Switch D-E]-2-Rev-4F-19	Ac-FA**D**KFKEAFKDYFAKVW**E**-NH2	369
[Switch D-E]-3-Rev-4F-19	Ac-FAEKFK**D**AFK**E**YFAKVWD-NH2	370
Switch D-E]-4-Rev-4F-19	Ac-FAEKFK**D**AFKDYFAKVW**E**-NH2	371
[Y-12 and F-16 are switched		372
Rev-4F-20	Ac-FAEKFKEAVKD**F**FAK**Y**WD-NH2	373
[Switch D-E]-1-Rev-4F-20	Ac-FA**D**KFK**D**AVK**E**FFAKYW**E**-NH2	374
[Switch D-E]-2-Rev-4F-20	Ac-FA**D**KFKEAVKDFFAKYW**E**-NH2	375
[Switch D-E]-3-Rev-4F-20	Ac-FAEKFK**D**AVK**E**FFAKYWD-NH2	376
[Switch D-E]-4-Rev-4F-20	Ac-FAEKFK**D**AVKDFFAKYW**E**-NH2	377
[W-1, F-6 and K-17 Rev 4F]		378
Rev-4F-21	Ac-**W**AEKF**F**EAVKDYFAKF**K**D-NH2	379
[Switch D-E]-1-Rev-4F-7	Ac-WA**D**KFF**D**AVK**E**YFAKFK**E**-NH2	380
[Switch D-E]-2-Rev-4F-7	Ac-WA**D**KFFEAVKDYFAKFK**E**-NH2	381
[Switch D-E]-3-Rev-4F-7	Ac-WAEKFF**D**AVK**E**YFAKFKD-NH2	382
Switch D-E]-4-Rev-4F-7	Ac-WAEKFF**D**AVKDYFAKFK**E**-NH2	383
[W-5, F-6 and K-17 Rev-4F]		384
Rev-4F-22	Ac-FAEK**W**F**F**EAVKDYFAKF**K**D-NH2	385
[Switch D-E]-1-Rev-4F-22	Ac-FA**D**KWF**D**AVK**E**YFAKFK**E**-NH2	386
[Switch D-E]-2-Rev-4F-22	Ac-FA**D**KWFEAVKDYFAKFK**E**-NH2	387
[Switch D-E]-3-Rev-4F-22	Ac-FAEKWF**D**AVK**E**YFAKFKD-NH2	388
[Switch D-E]-4-Rev-4F-22	Ac-FAEKWF**D**AVKDYFAKFK**E**-NH2	389
[V-6, W-9, K-17 Rev-4F]		390
Rev-4F-23	Ac-FAEKF**V**EA**W**KDYFAKF**K**D-NH2	391
[Switch D-E]-1-Rev-4F-23	Ac-FA**D**KFV**D**AWK**E**YFAKFK**E**-NH2	392
[Switch D-E]-2-Rev-4F-23	Ac-FA**D**KFVEAWKDYFAKFK**E**-NH2	393
[Switch D-E]-3-Rev-4F-23	Ac-FAEKFV**D**AWK**E**YFAKFKD-NH2	394
[Switch D-E]-4-Rev-4F-23	Ac-FAEKFV**D**AWKDYFAKFK**E**-NH2	395
[Y-2, A-4, W-12, K-17 Rev-4F]		396
Rev-4F-24	Ac-F**Y**EKF**A**EAVKD**W**FAKF**K**D-NH2	397
[Switch D-E]-1-Rev-4F-24	Ac-FY**D**KFA**D**AVK**E**WFAKFK**E**-NH2	398
[Switch D-E]-2-Rev-4F-24	Ac-FY**D**KFAEAVKDWFAKFK**E**-NH2	399
[Switch D-E]-3-Rev-4F-24	Ac-FYEKFA**D**AVK**E**WFAKFKD-NH2	400
[Switch D-E]-4-Rev-4F-24	Ac-FYEKFA**D**AVKDWFAKFK**E**-NH2	401

[0142] Based on helical wheel diagrams, it is possible to readily identify biologically active and useful peptides. Thus, for example, the following peptides have been accurately identified as active: 3F1; 3F2; 4F the inverse forms thereof, the reverse (retro) forms thereof and the retro-inverso forms thereof. Thus, in certain embodiments, this invention contemplates active agents comprising a peptide that is 18 amino acids in

length and forms a class A amphipathic helix where the peptide has the amino acid composition 2 aspartates, 2 glutamates, 4 lysines, 1 tryptophan, 1 tyrosine, no more than one leucine, no more than 1 valine, no less than 1 and no more than 3 alanines, and with 3 to 6 amino acids from the group: phenylalanine, alpha-naphthalanine, beta-naphthalanine, histidine, and contains either 9 or 10 amino acids on the polar face in a helical wheel representation of the class A amphipathic helix including 4 amino acids with positive charge at neutral pH with two of the positively charged residues residing at the interface between the polar and non-polar faces and with two of the four positively charged residues on the polar face that are contiguous and on the non-polar face two of the amino acid residues from the group: phenylalanine, alpha-naphthalanine, beta-naphthalanine, histidine are also contiguous and if there are 4 or more amino acids from this group on the non-polar face there are also at least 2 residues from this group that are not contiguous.

[0143] In certain embodiments, this invention also contemplates certain class Y as well as class A amphipathic helical peptides. Class Y amphipathic helical peptides are known to those of skill in the art (*see, e.g.*, Segrest *et al.* (1992) *J. Lipid Res.* 33: 141-166; Oram and Heinecke (2005) *Physiol Rev.* 85: 1343-1372, and the like). In various embodiments these peptides include, but are not limited to an 18 amino acid peptide that forms a class A amphipathic helix or a class Y amphipathic helix described by Formula XXIV (SEQ ID NO:402):

D X X K Y X X D K X Y D KX K D Y X XXIV

where the D's are independently Asp or Glu; the Ks are independently Lys or Arg; the Xs are independently Leu, norLeu, Val, Ile, Trp, Phe, Tyr, β–Nal, or α–Nal and all X residues are on the non-polar face (*e.g.*, when viewed in a helical wheel diagram) except for one that can be on the polar face between two K residues; the Y's are independently Ala, His, Ser, Gln, Asn, or Thr non-polar face (*e.g.*, when viewed in a helical wheel diagram) and the Y's are independently one Ala on the polar face, one His, one Ser, one Gln one Asn, or one Thr on the polar face (*e.g.*, when viewed in a helical wheel diagram), where no more than two K are be contiguous (*e.g.*, when viewed in a helical wheel diagram); and where no more than 3 D's are contiguous (*e.g.*, when viewed in a helical wheel diagram) and the fourth D is be separated from the other D's by a Y. Illustrative peptides of this kind which include peptides with histidine, and/or alpha- and/or beta-napthalanine are shown in Table 5.

Reverse (retro-), inverse, retro-inverso-, and circularly permuted forms of these peptides are also contemplated.

[0144] Table 5. Illustrates various class A and/or class Y peptide analogs with His incorporated into the sequence.

Short name	Peptide sequence	SEQ ID NO
[A-5>H] 4F	Ac-DWFK**H**FYDKVAEKFKEAF-NH_2	403
[A-5>H, D-E switched]4F	Ac-**E**WFK**H**FY**E**KVA**D**KFK**D**AF-NH_2	404
[A-5>H, D-1>E]4F	Ac-**E**WFK**H**FYDKVAEKFKEAF-NH_2	405
[A-5>H, D-8>E]4-F	Ac-DWFK**H**FY**E**KVAEKFKEAF-NH_2	406
[A-5>H, E-12>D] 4F	Ac-DWFK**H**FYDKVA**D**KFKEAF-NH_2	407
[A-5>H, E-16>D] 4F	Ac-DWFK**H**FYDKVAEKFK**D**AF-NH_2	408
[F-3>H,A-5>F] -4F	Ac-DW**H**K**F**FYDKVAEKFKEAF-NH_2	409
[F-3>H,A-5>F, D-E switched] -4F	Ac-**E**W**H**K**F**FY**E**KVA**D**KFK**D**AF-NH_2	410
[F-3>H,A-5>F,D-1>E] -4F	Ac-**E**W**H**K**F**FYDKVAEKFKEAF-NH_2	411
[F-3>H,A-5>F,D-8>E] -4F	Ac-DW**H**K**F**FY**E**KVAEKFKEAF-NH_2	412
[F-3>H,A-5>F,E-12>D] -4F	Ac-DW**H**K**F**FYDKVA**D**KFKEAF-NH_2	413
[F-3>H,A-5>F, E-16>D] -4F	Ac-DW**H**K**F**FYDKVAEKFK**D**AF-NH_2	414
[A-5>F,F-6>H]4F	Ac-DWFK**FH**YDKVAEKFKEAF-NH_2	415
[A-5>F,F-6>H,D-E switched]4F	Ac-**E**WFK**FH**Y**E**KVA**D**KFK**D**AF-NH_2	416
[[A-5>F,F-6>H, D-1>E]4F	Ac-**E**WFK**FH**YDKVAEKFKEAF-NH_2	417
[A-5>F,F-6>H, D-8>E]4F	Ac-DWFK**FH**Y**E**KVAEKFKEAF-NH_2	418
[A-5>F,F-6>H, E-12>D]4F	Ac-DWFK**FH**YDKVA**D**KFKEAF-NH_2	419
[A-5>F,F-6>H,E-16>D]4F	Ac-DWFK**FH**YDKVAEKFK**D**AF-NH_2	420
[A-5>V, V-10>H]4F	Ac-DWFK**V**FYDK**H**AEKFKEAF-NH_2	421
[A-5>V, V-10>H,D-E switched]4F	Ac-**E**WFK**V**FY**E**K**H**A**D**KFK**D**AF-NH_2	422
[A-5>V, V-10>H,D-1>E]4F	Ac-**E**WFK**V**FYDK**H**AEKFKEAF-NH_2	423
[A-5>V, V-10>H, D-8>E] 4F	Ac-DWFK**V**FY**E**K**H**AEKFKEAF-NH_2	424
[A-5>V, V-10>H,E-12>D] 4F	Ac-DWFK**V**FYDK**H**A**D**KFKEAF-NH_2	425
[A-5>V, V-10>H,E16>D] 4F	Ac-DWFK**V**FYDK**H**AEKFK**D**AF-NH_2	426
[[A-17>H]4F	Ac-DWFKAFYDKVAEKFKE**H**F-NH_2	427

[A-17>H, D-E switched] 4F	Ac-**E**WFKAFY**E**KVA**D**KFK**DH**F-NH_2	428
[[A-17>H,D-1>E]4F	Ac-**E**WFKAFYDKVAEKFKE**H**F-NH_2	429
[[A-17>H, D-8>E]4F	Ac-DWFKAFY**E**KVAEKFKE**H**F-NH_2	430
[[A-17>H,E-12>D]4F	Ac-DWFKAFYDKVA**D**KFKE**H**F-NH_2	431
[[A-17>H, E16>D]4F	Ac-DWFKAFYDKVAEKFK**DH**F-NH_2	432
[A-17>F, F-18>H] 4F	Ac-DWFKAFYDKVAEKFKE**FH**-NH_2	433
[A-17>F, F-18>H,D-E switched] 4F	Ac-**E**WFKAFY**E**KVA**D**KFK**DFH**-NH_2	434
[A-17>F, F-18>H,D-1>E] -4F	Ac-**E**WFKAFYDKVAEKFKE**FH**-NH_2	435
[A-17>F, F-18>H] 4F	Ac-DWFKAFYDKVAEKFKE**FH**-NH_2	436
[A-17>F, F-18>H,D-8>E] -4F	Ac-DWFKAFY**E**KVAEKFKE**FH**-NH_2	437
[A-17>F, F-18>H,E-12>D] 4F	Ac-DWFKAFYDKVAEKFKE**FH**-NH_2	438
[A-17>F, F-18>H],E-16>D]-4F	Ac-DWFKAFYDKVAEKFK**DFH**-NH_2	439
Rev-4F	Ac-FAEKFKEAVKDYFAKFWD-NH_2	440
[A-2>H]Rev4F	Ac-F**H**EKFKEAVKDYFAKFWD-NH_2	441
Rev-[A-2>H, D>E]-4F	Ac-F**H**EKFKEAVK**E**YFAKFW**E**-NH_2	442
Rev-[A-2>H, E>D]4F	Ac-F**HD**KFK**D**AVKDYFAKFWD-NH_2	443
[A-2>H, D-E switched] Rev-4F	Ac-F**HD**KFK**D**AVK**E**YFAKFW**E**-NH_2	444
[A-2>H, E-3>D]Rev-4F	Ac-F**HD**KFKEAVKDYFAKFWD-NH_2	445
[A-2>H, E-7>D]Rev-4F	Ac-F**H**EKFK**D**AVKDYFAKFWD-NH_2	446
[A-2>H, D-11>E]Rev-4F	Ac-F**H**EKFKEAVK**E**YFAKFWD-NH_2	447
[A-2>H, D-18>E]Rev-4F	Ac-F**H**EKFKEAVKDYFAKFW**E**-NH_2	448
[F-1>H, A-2>F]Rev-4F	Ac-**HF**EKFKEAVKDYFAKFWD-NH_2	449
[F-1>H, A-2>F,D-E switched]Rev-4F	Ac-**HFD**KFK**D**AVK**E**YFAKFW**E**-NH_2	450
[F-1>H, A-2>F, D>E]Rev-4F	Ac-**HF**EKFKEAVK**E**YFAKFW**E**-NH_2	451
[F-1>H, A-2>F,E-3>D]Rev-4F	Ac-**HFD**KFKEAVKDYFAKFWD-NH_2	452
[F-1>H, A-2>F,E-7>D]Rev-4F	Ac-**HF**EKFK**D**AVKDYFAKFWD-NH_2	453
[F-1>H, A-2>F,D-11>E]Rev-4F	Ac-**HF**EKFKEAVK**E**YFAKFWD-NH_2	454
[F-1>H, A-2>F, D-18>E]Rev-4F	Ac-**HF**EKFKEAVKDYFAKFW**E**-NH_2	455
[A-2>F, F-5>H] Rev D-4F	Ac-F**F**EK**H**KEAVKDYFAKFWD-NH_2	456
[A-2>F, F-5>H,D-E switched] Rev D-4F	Ac-F**FD**K**H**K**D**AVK**E**YFAKFW**E**-NH_2	457

[A-2>F, F-5>H, D>E] Rev D-4F	Ac-F**F**EK**H**KEAVK**E**YFAKFW**E**-NH_2	458
[A-2>F, F-5>H,E>D] Rev D-4F	Ac-F**F****D**K**H**K**D**AVKDYFAKFWD-NH_2	459
[A-2>F, F-5>H,E-3>D] Rev D-4F	Ac-F**F****D**K**H**KEAVKDYFAKFWD-NH_2	460
[A-2>F, F-5>H,D-11>E] Rev D-4F	Ac-F**F**EK**H**K**E**AVK**E**YFAKFWD-NH_2	461
[A-2>F, F-5>H,D-18>E] Rev D-4F	Ac-F**F**EK**H**KEAVKDYFAKFW**E**-NH_2	462
[A-2>V, V-9>H] Rev D-4F	Ac-F**V**EKFKEA**H**KDYFAKFWD-NH_2	463
[A-2>V, V-9>H,D-E switched] Rev D-4F	Ac-F**V****D**KFK**D**A**H**K**E**YFAKFW**E**-NH_2	464
[A-2>V, V-9>H,D>E] Rev D-4F	Ac-F**V**EKFKEA**H**K**E**YFAKFW**E**-NH_2	465
[A-2>V, V-9>H,E>D] Rev D-4F	Ac-F**V****D**KFK**D**A**H**KDYFAKFWD-NH_2	466
[A-2>V, V-9>H,E-3>D] Rev D-4F	Ac-F**V****D**KFKEA**H**KDYFAKFWD-NH_2	467
[A-2>V, V-9>H,E-7>D] Rev D-4F	Ac-F**V**EKFK**D**A**H**KDYFAKFWD-NH_2	468
[A-2>V, V-9>H,D-11>E] Rev D-4F	Ac-F**V**EKFKEA**H**K**E**YFAKFWD-NH_2	469
[A-2>V, V-9>H,D-18>E] Rev D-4F	Ac-F**V**EKFKEA**H**KDYFAKFW**E**-NH_2	470
[A-8>H]Rev-4F	Ac-FAEKFKE**H**VKDYFAKFWD-NH_2	471
[A-8>H,D-E switched]Rev-4F	Ac-FA**D**KFK**DH**VK**E**YFAKFW**E**-NH_2	472
[A-8>H,D>E]Rev-4F	Ac-FAEKFKE**H**VK**E**YFAKFWE-NH_2	473
[A-8>H,E>D]Rev-4F	Ac-FA**D**KFK**DH**VKDYFAKFWD-NH_2	474
[A-8>H,E-3>D]Rev-4F	Ac-FA**D**KFKE**H**VKDYFAKFWD-NH_2	475
[A-8>H, E-7>D]Rev-4F	Ac-FAEKFK**DH**VKDYFAKFWD-NH_2	476
[A-8>H, D-11>E]Rev-4F	Ac-FAEKFKE**H**VK**E**YFAKFWD-NH_2	477
[A-8>H, D-18>E]Rev-4F	Ac-FAEKFKE**H**VKDYFAKFW**E**-NH_2	478
[A-8>F,F-13>H]Rev-4F	Ac-FAEKFKE**F**VKDY**H**AKFWD-NH_2	479
[A-8>F,F-13>H,D-E switched]Rev-4F	Ac-FA**D**KFK**DF**VK**E**Y**H**AKFW**E**-NH_2	480
[A-8>F,F-13>H, E-3>D]Rev-4F	Ac-FA**D**KFKE**F**VKDY**H**AKFWD-NH_2	481
[A-8>F,F-13>H, E-7>D]Rev-4F	Ac-FAEKFK**DF**VKDY**H**AKFWD-NH_2	482
[A-8>F,F-13>H, E>D]Rev-4F	Ac-FA**D**KFK**DF**VKDY**H**AKFWD-NH_2	483
[A-8>F,F-13>H,D>E]Rev-4F	Ac-FAEKFKE**F**VK**E**Y**H**AKFW**E**-NH_2	484
[A-8>F,F-13>H,D-11>E]Rev-4F	Ac-FAEKFKE**F**VK**E**Y**H**AKFWD-NH_2	485
[A-8>F,F-13>H, D-18>E]Rev-4F	Ac-FAEKFKE**F**VKDY**H**AKFW**E**-NH_2	486
[A-8>F, F16>H]Rev.-4F	Ac-FAEKFKE**F**VKDYFAK**H**WD-NH_2	487

[A-8>F, F16>H,D-E switched]Rev.-4F	Ac-FA**D**KFK**DF**VK**E**YFAK**H**W**E**-NH_2	488
[A-8>F, F16>H,D>E]Rev.-4F	Ac-FAEKFKE**F**VK**E**YFAK**H**W**E**-NH_2	489
[A-8>F, F16>H, E>D]Rev.-4F	Ac-FA**D**KFK**DF**VKDYFAK**H**WD-NH_2	490
[A-8>F, F16>H,E-3>D]Rev.-4F	Ac-FA**D**KFKE**F**VKDYFAK**H**WD-NH_2	491
[A-8>F, F16>H,E-7>D]Rev.-4F	Ac-FAEKFK**DF**VKDYFAK**H**WD-NH_2	492
[A-8>F, F16>H,D-11>E]Rev.-4F	Ac-FAEKFKE**F**VK**E**YFAK**H**WD-NH_2	493
[A-8>F, F16>H,D-18>E]Rev.-4F	Ac-FAEKFKE**F**VKDYFAK**H**W**E**-NH_2	494

Examples of class A 4F and Rev 4F analogs with beta-Nph. Similarly, alpha-Nph analogs can be designed. Similarly to the above analogs, His can be incorporated to Nph analogs. D>E analogs, E>D analogs and D-E switch analogs are additional possibilities similarly to the above described analogs.

4Nph	Ac-DW**Nph**KA**Nph**YDKVAEK**Nph**KEA**Nph**-NH_2	495
[D-E switched]4Nph	Ac-**E**W**Nph**KA**Nph**Y**E**KVA**D**K**Nph**K**D**A**Nph**-NH_2	496
[D>E]4Nph	Ac-**E**W**Nph**KA**Nph**Y**E**KVAEK**Nph**KEA**Nph**-NH_2	497
[E>D]4Nph	Ac-DW**Nph**KA**Nph**YDKVA**D**K**Nph**K**D**A**Nph**-NH_2	498
[D-1>E] 4Nph	Ac-**E**W**Nph**KA**Nph**YDKVAEK**Nph**KEA**Nph**-NH_2	499
[D-8>E]4Nph	Ac-DW**Nph**KA**Nph**Y**E**KVAEK**Nph**KEA**Nph**-NH_2	500
[E-12>D]4Nph	Ac-DW**Nph**KA**Nph**YDKVA**D**K**Nph**KEA**Nph**-NH_2	501
[E-16>D]4Nph	Ac-DW**Nph**KA**Nph**YDKVAEK**Nph**K**D**A**Nph**-NH_2	502

As described above for 4Nph, a minimum of 7 additional analogs for each of the analogs given below.

[F-3,6,>Nph]4F	Ac-DW**Nph**KA**Nph**YDKVAEKFKEAF-NH_2	503
[F-14,18>Nph]4F	Ac-DWFKAFYDKVAEK**Nph**KEA**Nph**-NH_2	504
[[F-3>Nph]4F	Ac-DW**Nph**KAFYDKVAEKFKEAF-NH_2	505
[F-6>Nph]4F	Ac-DWFKA**Nph**YDKVAEKFKEAF-NH_2	506
[F-14>Nph]4F	Ac-DWFKAFYDKVAEK**Nph**KEAF-NH_2	507
[F-18>Nph]4F	Ac-DWFKAFYDKVAEKFKEA**Nph**-NH_2	508

For each of the analog described below, a minimum of 7 additional analogs are possible as described above by switching D-E, D>E and E>D and single D or E analogs.

Rev-4Nph	Ac-**Nph**AEK**Nph**KEAVKDY**Nph**AK**Nph**WD-NH_2	509
[F-3,6>Nph]Rev 4F	Ac-**Nph**AEK**Nph**KEAVKDYFAKFWD-NH_2	510
[F-13,16]Rev-4F	Ac-FAEKFKEAVKDY**Nph**AK**Nph**WD-NH_2	511

[F-3>Nph]Rev-4F	Ac-**Nph**AEKFKEAVKDYFAKFWD-NH_2	512
[F-6>Nph]Rev-4F	Ac-FAEK**Nph**KEAVKDYFAKFWD-NH_2	513
[F-13>Nph]Rev-4F	Ac-FAEKFKEAVKDY**Nph**AKFWD-NH_2	514
[F-16>Nph]Rev-4F	Ac-FAEKFKEAVKDYFAK**Nph**WD-NH_2	515

For the analogs described below, additional analogs are possible by incorporating His or alpha-Nph and beta-Nph

Rev-[D>E]-4F	Ac-FAEKFKEAVK**E**YFAKFW**E**-NH_2	516
Rev-[E>D]4F	Ac-FA**D**KFK**D**AVKDYFAKFWD-NH_2	517
Rev-R4-4F	Ac-FAE**R**FREAVKDYFAKFWD-NH_2	518
Rev-R6-4F	Ac-FAEKF**R**EAVKDYFAKFWD-NH_2	519
Rev-R10-4F	Ac-FAEKFKEAV**R**DYFAKFWD-NH_2	520
Rev-R14 -4F	Ac-FAEKFKEAVKDYFA**R**FWD-NH_2	521
Rev-[D>E]-4F	Ac-FAEKFKEAVK**E**YFAKFW**E**-NH_2	522
Rev-[E>D]4F	Ac-FA**D**KFK**D**AVKDYFAKFWD-NH_2	523
Rev-R4-4F	Ac-FAE**R**FREAVKDYFAKFWD-NH_2	524
Rev-R6-4F	Ac-FAEKF**R**EAVKDYFAKFWD-NH_2	525
Rev-R10-4F	Ac-FAEKFKEAV**R**DYFAKFWD-NH_2	526
Rev-R14 -4F	Ac-FAEKFKEAVKDYFA**R**FWD-NH_2	527
Rev-[D>E]-4F	Ac-FAEKFKEAVK**E**YFAKFW**E**-NH_2	528
Rev-[E>D]4F	Ac-FA**D**KFK**D**AVKDYFAKFWD-NH_2	529
Rev-R4-4F	Ac-FAE**R**FREAVKDYFAKFWD-NH_2	530
Rev-R6-4F	Ac-FAEKF**R**EAVKDYFAKFWD-NH_2	531
Rev-R10-4F	Ac-FAEKFKEAV**R**DYFAKFWD-NH_2	532
Rev-R14 -4F	Ac-FAEKFKEAVKDYFA**R**FWD-NH_2	533
Rev-R4-4F	Ac-FAE**R**FREAVKDYFAKFWD-NH_2	534
Rev-R6-4F	Ac-FAEKF**R**EAVKDYFAKFWD-NH_2	535
Rev-R10-4F	Ac-FAEKFKEAV**R**DYFAKFWD-NH_2	536
Rev-R14 -4F	Ac-FAEKFKEAVKDYFA**R**FWD-NH_2	537
Rev-[D>E]-4F	Ac-FAEKFKEAVK**E**YFAKFW**E**-NH_2	538
Rev-[E>D]4F	Ac-FA**D**KFK**D**AVKDYFAKFWD-NH_2	539
Rev-R4-4F	Ac-FAE**R**FREAVKDYFAKFWD-NH_2	540
Rev-R6-4F	Ac-FAEKF**R**EAVKDYFAKFWD-NH_2	541

Rev-R10-4F	Ac-FAEKFKEAVRDYFAKFWD-NH_2	542
Rev-R14 -4F	Ac-FAEKFKEAVKDYFARFWD-NH_2	543

For each of the analogs below, additional H and Nph analogs are possible using the examples described above. Each analog can yield 7 analogs with the changes described in the examples given above.

Rev3F-2	Ac-LFEKFAEAFKDYVAKWKD-NH_2	544
RevR4-3F-2	Ac-LFERFAEAFKDYVAKWKD-NH_2	545
RevR10-3F2	Ac-LFEKFAEAFRDYVAKWKD-NH_2	546
RevR15-3F-2	Ac-LFEKFAEAFKDYVARWKD-NH_2	547
Rev R17-3F-2	Ac-LFEKFAEAFKDYVAKWRD-NH_2	548
Rev[D>E]3F2	Ac-LFEKFAEAFKEYVAKWKE-NH_2	549
Rev[E>D]3F-2	Ac-LFDKFADAFKDYVAKWKD-NH_2	550
Rev-[E3>D]-3F-2	Ac-LFDKFAEAFKDYVAKWKD-NH_2	551
Rev-[E7>D]-3F-2	Ac-LFEKFADAFKDYVAKWKD-NH_2	552
Rev[D11>E]3F-2	Ac-LFEKFAEAFKEYVAKWKD-NH_2	553
Rev-[D18>E]3F-2	Ac-LFEKFAEAFKDYVAKWKE-NH_2	554
Rev3F-1	Ac-FAEKAWEFVKDYFAKLKD-NH_2	555
RevR4-3F-1	Ac-FAERAWEFVKDYFAKLKD-NH_2	556
RevR10-3F-1	Ac-FAEKAWEFVKDYFAKLKD-NH_2	557
RevR15-3F-1	Ac- FAEKAWEFVKDYFAKLKD-NH_2	558
RevR17-3F-1	Ac-FAEKAWEFVKDYFAKLRD-NH_2	559
Rev[D>E]3F-1	Ac- FAEKAWEFVKEYFAKLKE-NH_2	560
Rev[E>D}3F-1	Ac-FADKAWDFVKDYFAKLKD-NH_2	561
Rev[E3>D]-3F-1	Ac- FADKAWEFVKDYFAKLKD-NH_2	562
Rev[E7>D]3F-1	Ac- FAEKAWDFVKDYFAKLKD-NH_2	563
Rev-[D11>E]3F-1	Ac- FAEKAWEFVKEYFAKLKD-NH_2	564
Rev-[D18>E]3F-1	Ac- FAEKAWEFVKDYFAKLKE-NH_2	565
Rev-5F	Ac-FFEKFKEFVKDYFAKLWD-NH_2	566
Rev-[D>E]5F	Ac-FFEKFKEFVKEYFAKLWE-NH_2	567
Rev-[E>D]5F	Ac-FFDKFKDFVKDYFAKLWD-NH_2	568
Rev-R4-5F	Ac-FFERFKEFVKDYFAKLWD-NH_2	569
Rev-R6-5F	Ac-FFEKFREFVKDYFAKLWD-NH_2	570
Rev-R10-5F	Ac-FFEKFKEFVRDYFAKLWD-NH_2	571

Rev-R15-5F	Ac-FFEKFKEFVKDYFARLWD-NH_2	572
Rev-[E3>D]-5F	Ac-FFDKFKEFVKDYFAKLWD-NH_2	573
Rev-[E7>D]5F	Ac-FFEKFKDFVKDYFAKLWD-NH_2	574
Rev-[D11>E]-5F	Ac-FFEKFKEFVKEYFAKLWD-NH_2	575
Rev-[D18>E]-5F	Ac-FFEKFKEFVKDYFAKLWE-NH_2	576
Rev-5F-2	Ac-FLEKFKEFVKDYFAKFWD-NH_2	577
Rev-[D>E]-5F-2	Ac-FLEKFKEFVKEYFAKFWE-NH_2	578
Rev-[E>D]-5F-2	Ac-FLDKFKEFVKDYFAKFWD-NH_2	579
Rev-[E3>D]-5F-2	Ac-FLDKFKEFVKDYFAKFWD-NH_2	580
Rev-[E7>D]-5F-2	Ac-FLEKFKDFVKDYFAKFWD-NH_2	581
Rev-[D11>E]-5F-2	Ac-FLEKFKEFVKEYFAKFWD-NH_2	582
Rev-[D18>E]-5F-2	Ac-FLEKFKEFVKDYFAKFWE-NH_2	583
Rev-R4-5F-2	Ac-FLERFKEFVKDYFAKFWD-NH_2	584
Rev-R6-5F-2	Ac-FLEKFREFVKDYFAKFWD-NH_2	585
RevR10-5F-2	Ac-FLEKFKEFVRDYFAKFWD-NH_2	586
Rev-R16-5F-2	Ac-FLEKFKEFVKDYFARFWD-NH_2	587
Rev-6F	Ac-FFEKFKEFFKDYFAKLWD-NH_2	588
Rev-[D>E]-6F	Ac-FFEKFKEFFKEYFAKLWE-NH_2	589
Rev-[E>D]-6F	Ac-FFDKFKDFFKDYFAKLWD-NH_2	590
Rev-R4-6F	Ac-FFERFKEFFKDYFAKLWD-NH_2	591
Rev-R6-6F	Ac-FFEKFREFFKDYFAKLWD-NH_2	592
Rev-R10-6F	Ac-FFEKFKEFFRDYFAKLWD-NH_2	593
Rev-R14-6F	Ac-FFERFKEFFKDYFARLWD-NH_2	594
Rev-[E3>D]-6F	Ac-FFDKFKEFFKDYFAKLWD-NH_2	595
Rev-[E7>D]-6F	Ac-FFEKFKDFFKDYFAKLWD-NH_2	596
Rev-[D11>E]-6F	Ac-FFEKFKEFFKEYFAKLWD-NH_2	597
Rev-[D18>E]-6F	Ac-FFEKFKEFFKDYFAKLWE-NH_2	598
Rev-4F	Ac-FAEKFKEAVKDYFAKFWD-NH_2	599
Rev-[D>E]-4F	Ac-FAEKFKEAVKEYFAKFWE-NH_2	600
Rev-[E>D]4F	Ac-FADKFKDAVKDYFAKFWD-NH_2	601
Rev-R4-4F	Ac-FAERFREAVKDYFAKFWD-NH_2	602
Rev-R6-4F	Ac-FAEKFREAVKDYFAKFWD-NH_2	603

Rev-R10-4F	Ac-FAEKFKEAVRDYFAKFWD-NH_2	604
Rev-R14 -4F	Ac-FAEKFKEAVKDYFARFWD-NH_2	605
4F-2	Ac-DKWKAVYDKFAEAFKEFF-NH_2	606
[D>E]-4F-2	Ac-EKWKAVYEKFAEAFKEFF-NH_2	607
[E>D]-4F-2	Ac-DKWKAVYDKFADAFKDFF-NH_2	608
R2-4F-2	Ac-DRWKAVYDKFAEAFKEFF-NH_2	609
R4-4F-2	Ac-DKWRAVYDKFAEAFKEFF-NH_2	610
R9-4F-2	Ac-DKWKAVYDRFAEAFKEFF-NH_2	611
R14-4F-2	Ac-DKWKAVYDKFAEAFREFF-NH_2	612
Rev4F-2	Ac-FFEKFAEAFKDYVAKWKD-NH_2	613
Rev-[D>E]-4F-2	Ac-FFEKFAEAFKEYVAKWKE-NH_2	614
Rev-[E>D]-3F-2	Ac-FFDKFADAFKDYVAKWKD-NH_2	615
Rev-R4-4F-2	Ac-FFERFAEAFKDYVAKWKD-NH_2	616
Rev-R10-4F-2	Ac-FFERFAEAFRDYVAKWKD-NH_2	617
Rev-R15-4F-2	Ac-FFEKFAEAFKDYVARWKD-NH_2	618
Rev-R17-4F-2	Ac-FFERFAEAFKDYVAKWRD-NH_2	619
Rev-[E3>D]-4F-2	Ac-FFDKFAEAFKDYVAKWKD-NH_2	620
Rev-[E7>D]-4F-2	Ac-FFEKFADAFKDYVAKWKD-NH_2	621
Rev-[D11>E]-4F-2	Ac-FFERFAEAFKEYVAKWKD-NH_2	622
Rev-[D18>E]-4F-2	Ac-FFERFAEAFKDYVAKWKE-NH_2	623
Rev-7F	Ac-FFEKFKEFFKDYFAKFWD-NH_2	624
Rev-[E>D]-7F	Ac-FFDKFKDFFKDYFAKFWD-NH_2	625
Rev-[D>E]-7F	Ac-FFEKFKEFFKEYFAKFWE-NH_2	626
Rev-R4-7F	Ac-FFERFKEFFKDYFAKFWD-NH_2	627
Rev-R6-7F	Ac-FFEKFREFFKDYFAKFWD-NH_2	628
Rev-R10-7F	Ac-FFEKFKEFFRDYFAKFWD-NH_2	629
Rev-R14-7F	Ac-FFEKFKEFFKDYFARFWD-NH_2	630
Rev-[E3>D]-7F	Ac-FFDKFKEFFKDYFAKFWD-NH_2	631
Rev-[E7>D]7F	Ac-FFEKFKDFFKDYFAKFWD-NH_2	632
Rev-[D11>E]-7F	Ac-FFEKFKEFFKEYFAKFWD-NH_2	633
Rev-[D18>E]-7F	Ac-FFEKFKEFFKDYFAKFWE-NH_2	634

[0145] It is also noted that any of the pepides described herein can comprise non-natural amino acids in addition to or instead of the corresponding natural amino acids identified herien. Such modifications include, but are not limited to acetylation, amidation, formylation, methylation, sulfation, and the like. Illustrative non-natural amino acids include, but are not limited to Ornithine, norleucine, norvaline, N-methylvaline, 6-N-methyllysine, N-methylisoleucine, N-methylglycine, sarcosine, inosine, allo-isoleucine, isodesmolysine, 4-hydroxyproline, 3-hydroxyproline, allo-hydroxylysine, hydoxylisine, N-ethylasparagine, N-ethylglycine, 2,3-diaminopropionic acid, 2,2'-diaminopropionic acid, desmosine, 2,4-diaminobutyric acid, 2-aminopimelic acid, 3-aminoisobutyric acid, 2-aminoisobutyric acid, 2-aminoheptanoic acid, 6-aminocaproic acid, 4-aminobutyric acid, 2-aminobutyric acid, beta-alanine, 3-aminoadipic acid, 2-aminoadipic acid, and the like. In certain embodiments andy one or more of the "natural" amino acids of the peptides described herein, can be substituted with the correspondign non-natural amino acid (*e.g.*, as describe above).

[0146] In certain embodiments, this invention contemplates particularly the use of modified lysines. Such modifications include, but are not limited to, biotin modification of epsilon lysines and/or methylation of the epsilon lysines. Illustative peptide comprising epsilon methylated lysines include, but are not limited to: Ac-D-W-F-K(eCH_3)$_2$-A-F-Y-D-K(eCH_3)$_2$-V-A-E-K(eCH_3)$_2$-F-K(eCH_3)$_2$-E-A-F-NH(CH_3)$_2$ (SEQ ID NO:635) and : Ac-DWFK(eCH_3)$_2$AFYDK(eCH_3)$_2$VAEK(eCH_3)$_2$FK(eCH_3)$_2$EAF-NH(CH_3) (SEQ ID NO:636). Other modified amino acids include but are not limited to ornithine analogs and homoaminoalanine analogs (instead of $(CH_2)_4$-NH_2 for Lys it can be -$(CH_2)_2$-NH_2 for Haa and -$(CH_2)_3$-NH_2 for Orn] and the like. It is noted that these modifications are illustrative and not intended to be limiting. Illustrative 4F analogues that possess modified amino acids are shown in Table 6.

[0147] Table 6. Illustrative 4F analogs that comprise modified amino acids.

Peptide	SEQ ID NO
εN-Dimethyl-Lys derivative of 4F (εN-Dime):	
Ac-D-W-F-K(εN-Dime)-A-F-Y-D-K(εN-Dime)-V-A-E-K(εN-Dime)-F-K(εN-Dime)-E-A-F-NH_2	637
Ac-D-W-F-K-(εN-Dime)-A-F-Y-D-K(εN-Dime)-V-A-E-K(εN-Dime)-F-	638

K((εN-Dime)-E-A-F-NH-Me	
Ac-D-W-F-K-(εN-Dime)-A-F-Y-D-K(εN-Dime)-V-A-E-K(εN-Dime)-F-K(εN-Dime)-E-A-F-N-$(Me)_2$	639
εN-Diethyl-Lys derivatives of 4F (εN-Diet)	
Ac-D-W-F-K(εN-Diet)-A-F-Y-D-K(εN-Diet)-V-A-E-K(εN-Diet)-F-K(εN-Diet)-E-A-F-NH_2	640
Ac-D-W-F-K(εN-Diet)-A-F-Y-D-K(εN-Diet)-V-A-E-K(εN-Diet)-F-K(εN-Diet)-E-A-F-NH-Et	641
Ac-D-W-F-K(εN-Diet)-A-F-Y-D-K(εN-Diet)-V-A-E-K(εN-Diet)-F-K(εN-Diet)-E-A-F-NH-$(Et)_2$	642
εN-Monomethyl-Lys derivative of 4F (εN–Me)	
Ac-D-W-F-K(εN–Me)-A-F-Y-D-K(εN–Me)-V-A-E-K(εN–Me)-F-K(εN–Me)-E-A-F-NH_2	643
Ac-D-W-F-K(εN–Me)-A-F-Y-D-K(εN–Me)-V-A-E-K(εN–Me)-F-K(εN–Me)-E-A-F-NH-Me	644
Ac-D-W-F-K(εN–Me)-A-F-Y-D-K(εN–Me)-V-A-E-K(εN–Me)-F-K(εN–Me)-E-A-F-N-$(Me)_2$	645
εN-ethylLys derivative of 4F (εN–Et)	
Ac—D-W-F-K(εN–Et)-A-F-Y-D-K(εN–Et)-V-A-E-K(εN–Et)-F-K(εN–Et)-E-A-F-NH_2	646
Ac—D-W-F-K(εN–Et)-A-F-Y-D-K(εN–Et)-V-A-E-K(εN–Et)-F-K(εN–Et)-E-A-F-NH-Et	647
Ac—D-W-F-K(εN–Et)-A-F-Y-D-K(εN–Et)-V-A-E-K(εN–Et)-F-K(εN–Et)-E-A-F-NH-$(Et)_2$	648
HomoLys analogs of 4F (hK) $(-CH_2)_5-NH_2$:	
Ac—D-W-F-hK-A-F-Y-D-hK-V-A-E-hK-F-hK-E-A-F-NH_2	649
Ac—D-W-F-hK(εN-Dime)-A-F-Y-D-hK(εN-Dime)-V-A-E-hK(εN-Dime)-F-hK(εN-Dime)-E-A-F-NH_2	650
Ac—D-W-F-hK(εN-Dime)-A-F-Y-D-hK(εN-Dime)-V-A-E-hK(εN-Dime)-F-hK(εN-Dime)-E-A-F-N-$(Me)_2$	651
Ac—D-W-F-hK(εN-Dime)-A-F-Y-D-hK(εN-Dime)-V-A-E-hK(εN-Dime)-F-hK(εN-Dime)-E-A-F-NH-Me	652
Ac—D-W-F-hK(εN-Diet)-A-F-Y-D-hK(εN-Diet)-V-A-E-hK(εN-Diet)-F-hK(εN-Diet)-E-A-F-NH-Et	653
Ac-D-W-F-hK(εN–Me)-A-F-Y-D-hK(εN–Me)-V-A-E-hK(εN–Me)-F-hK(εN–Me)-E-A-F-NH_2	654
Ac-D-W-F-hK(εN–Me)-A-F-Y-D-hK(εN–Me)-V-A-E-hK(εN–Me)-F-hK(εN–Me)-E-A-F-NH-Me	655
Ac-D-W-F-hK(εN–Me)-A-F-Y-D-hK(εN–Me)-V-A-E-hK(εN–Me)-F-hK(εN–Me)-E-A-F-N-$(Me)_2$	656
Ac—D-W-F-hK(εN–Et)-A-F-Y-D-hK(εN–Et)-V-A-E-hK(εN–Et)-F-hK(εN–Et)-E-A-F-NH_2	657
Ac—D-W-F-hK(εN–Et)-A-F-Y-D-hK(εN–Et)-V-A-E-hK(εN–Et)-F-	658

hK(εN–Et)-E-A-F-NH-Et	
Ac—D-W-F-hK(εN–Et)-A-F-Y-D-hK(εN–Et)-V-A-E-hK(εN–Et)-F-hK(εN–Et)-E-A-F-NH-$(Et)_2$	659
4F analogs in which K is replaced O (O=Ornithine, -$(CH_2)_3$-NH_2):	660
Ac—D-W-F-O-A-F-Y-D-O-V-A-E-O-F-O-E-A-F-NH_2	661
Ac—D-W-F-O(δN-Dime)-A-F-Y-D-O(δN-Dime)-V-A-E-O(δN-Dime)-F-O(δN-Dime)-E-A-F-NH_2	662
Ac—D-W-F-O(δN-Dime)-A-F-Y-D-)(δN-Dime)-V-A-E-O(δN-Dime)-F-O(δN-Dime)-E-A-F-N-$(Me)_2$	663
Ac—D-W-F-O(δN-Dime)-A-F-Y-D-O(δN-Dime)-V-A-E-O(δN-Dime)-F-O(δN-Dime)-E-A-F-NH-Me	664
Ac—D-W-F-O(δN-Diet)-A-F-Y-D-O(δN-Diet)-V-A-E-O(δN-Diet)-F-O(δN-Diet)-E-A-F-NH-Et	665
Ac-D-W-F-O(δN–Me)-A-F-Y-D-O(δN–Me)-V-A-E-O(δN–Me)-F-O(δN–Me)-E-A-F-NH_2	666
Ac-D-W-F-O(δN–Me)-A-F-Y-D-O(δN–Me)-V-A-E-O(δN–Me)-F-O(δN–Me)-E-A-F-NH-Me	667
Ac-D-W-F-O(δN–Me)-A-F-Y-D-O(δN–Me)-V-A-E-O(δN–Me)-F-O(δN–Me)-E-A-F-N-$(Me)_2$	668
Ac—D-W-F-O(δN–Et)-A-F-Y-D-O(δN–Et)-V-A-E-O(δN–Et)-F-O(δN–Et)-E-A-F-NH_2	669
Ac—D-W-F-O(δN–Et)-A-F-Y-D-O(δN–Et)-V-A-E-O(δN–Et)-F-O(δN–Et)-E-A-F-NH-Et	670
Ac—D-W-F-O(δN–Et)-A-F-Y-D-O(δN–Et)-V-A-E-OdεN–Et)-F-O(δN–Et)-E-A-F-NH-$(Et)_2$	671

[0148] The peptides and modifications shown above are intended to be illustrative and not limiting.

D) Smaller peptides.

[0149] It was also a surprising discovery that certain small peptides consisting of a minimum of three amino acids preferentially (but not necessarily) with one or more of the amino acids being the D-stereoisomer of the amino acid, and possessing hydrophobic domains to permit lipid protein interactions, and hydrophilic domains to permit a degree of water solubility also possess significant anti-inflammatory properties and are useful in treating one ore more of the pathologies described herein. The "small peptides" typically range in length from 2 amino acids to about 15 amino acids, more preferably from about 3 amino acids to about 10 or 11 amino acids, and most preferably from about 4 to about 8 or

10 amino acids. In various embodiments the peptides are typically characterized by having hydrophobic terminal amino acids or terminal amino acids rendered hydrophobic by the attachment of one or more hydrophobic "protecting" groups. Various "small peptides" are described in copending applications USSN 10/649,378, filed August 26, 2003, and in USSN 10/913,800, filed on August 6, 2004, and in PCT Application PCT/US2004/026288.

[0150] In certain embodiments, the peptides can be characterized by Formula XXV, below:

$$X^1\text{-}X^2\text{-}X^3{}_n\text{-}X^4 \qquad \textbf{XXV}$$

where, n is 0 or 1, X^1 is a hydrophobic amino acid and/or bears a hydrophobic protecting group, X^4 is a hydrophobic amino acid and/or bears a hydrophobic protecting group; and when n is 0 X^2 is an acidic or a basic amino acid; when n is 1: X^2 and X^3 are independently an acidic amino acid, a basic amino acid, an aliphatic amino acid, or an aromatic amino acid such that when X^2 is an acidic amino acid; X^3 is a basic amino acid, an aliphatic amino acid, or an aromatic amino acid; when X^2 is a basic amino acid; X^3 is an acidic amino acid, an aliphatic amino acid, or an aromatic amino acid; and when X^2 is an aliphatic or aromatic amino acid, X^3 is an acidic amino acid, or a basic amino acid.

[0151] Longer peptides (*e.g.*, up to 10, 11, or 15 amino acids) are also contemplated within the scope of this invention. Typically where the shorter peptides (*e.g.*, peptides according to Formula XXV) are characterized by an acidic, basic, aliphatic, or aromatic amino acid, the longer peptides are characterized by acidic, basic, aliphatic, or aromatic domains comprising two or more amino acids of that type.

1) Functional properties of active small peptides.

[0152] It was a surprising finding of this invention that a number of physical properties predict the ability of small peptides (*e.g.*, less than 10 amino acids, preferably less than 8 amino acids, more preferably from about 3 to about 5 or 6 amino acids) of this invention to render HDL more anti-inflammatory and to mitigate atherosclerosis and/or other pathologies characterized by an inflammatory response in a mammal. The physical properties include high solubility in ethyl acetate (*e.g.*, greater than about 4 mg/mL), and solubility in aqueous buffer at pH 7.0. Upon contacting phospholipids such as 1,2-Dimyristoyl-*sn*-glycero-3-phosphocholine (DMPC), in an aqueous environment, the

particularly effective small peptides induce or participate in the formation of particles with a diameter of approximately 7.5 nm (± 0.1 nm), and/or induce or participate in the formation of stacked bilayers with a bilayer dimension on the order of 3.4 to 4.1 nm with spacing between the bilayers in the stack of approximately 2 nm, and/or also induce or participate in the formation of vesicular structures of approximately 38 nm). In certain preferred embodiments, the small peptides have a molecular weight of less than about 900 Da.

[0153] Thus, in certain embodiments, this invention contemplates small peptides that ameliorate one or more symptoms of an indication/pathology described herein, *e.g.*, an inflammatory condition, where the peptide(s): ranges in length from about 3 to about 8 amino acids, preferably from about 3 to about 6, or 7 amino acids, and more preferably from about 3 to about 5 amino acids; are soluble in ethyl acetate at a concentration greater than about 4mg/mL; are soluble in aqueous buffer at pH 7.0; when contacted with a phospholipid in an aqueous environment, form particles with a diameter of approximately 7.5 nm and/or form stacked bilayers with a bilayer dimension on the order of 3.4 to 4.1 nm with spacing between the bilayers in the stack of approximately 2 nm; have a molecular weight less than about 900 daltons; convert pro-inflammatory HDL to anti-inflammatory HDL or make anti-inflammatory HDL more anti-inflammatory. In certain embodiments the peptides include, but are not limited to peptides having the amino acid sequence Lys-Arg-Asp-Ser (SEQ ID NO:801), especially in which Lys-Arg-Asp and Ser are all L amino acids. In certain embodiments, these small peptides protect a phospholipid against oxidation by an oxidizing agent. In certain embodiments the compositions and methods described herein exclude the amino acid sequence Lys-Arg-Asp-Ser (SEQ ID NO:801), especially in which Lys-Arg-Asp and Ser are all L amino acids.

[0154] While these small peptides need not be so limited, in certain embodiments, these small peptides can include the small peptides described below.

2) Tripeptides.

[0155] It was discovered that certain tripeptides (3 amino acid peptides) can be synthesized that show desirable properties as described herein (*e.g.*, the ability to convert pro-inflammatory HDL to anti-inflammatory HDL, the ability to decrease LDL-induced monocyte chemotactic activity generated by artery wall cells. In certain embodiments, the

peptides are characterized by Formula XXV, wherein N is zero, shown below as Formula XXVI:

$$X^1\text{-}X^2\text{-}X^4 \qquad \textbf{XXVI}$$

where the end amino acids (X^1 and X^4) are hydrophobic either because of a hydrophobic side chain or because the side chain or the C and/or N terminus is blocked with one or more hydrophobic protecting group(s) (*e.g.*, the N-terminus is blocked with Boc-, Fmoc-, nicotinyl-, *etc.*, and the C-terminus blocked with (*t*Bu)-O*t*Bu, *etc.*). In certain embodiments, the X^2 amino acid is either acidic (*e.g.*, aspartic acid, glutamic acid, *etc.*) or basic (*e.g.*, histidine, arginine, lysine, *etc.*). The peptide can be all L- amino acids or include one or more or all D-amino acids.

[0156] Certain tripeptides of this invention include, but are not limited to the peptides shown in Table 7.

[0157] Table 7. Examples of certain preferred tripeptides bearing hydrophobic blocking groups and acidic, basic, or histidine central amino acids.

X^1	X^2	X^3	X^4	SEQ ID NO
Boc-Lys(εBoc)	Arg		Ser(*t*Bu)-O*t*Bu	672
Boc-Lys(εBoc)	Arg		Thr(*t*Bu)-O*t*Bu	673
Boc-Trp	Arg		Ile-O*t*Bu	674
Boc-Trp	Arg		Leu-O*t*Bu	675
Boc-Phe	Arg		Ile –O*t*Bu	676
Boc-Phe	Arg		Leu-O*t*Bu	677
Boc-Lys(εBoc)	Glu		Ser(*t*Bu)-O*t*Bu	678
Boc-Lys(εBoc)	Glu		Thr(*t*Bu)-O*t*Bu	679
Boc-Lys(εBoc)	Asp		Ser(*t*Bu)-O*t*Bu	680
Boc-Lys(εBoc)	Asp		Thr(*t*Bu)-O*t*Bu	681
Boc-Lys(εBoc)	Arg		Ser(*t*Bu)-O*t*Bu	682
Boc-Lys(εBoc)	Arg		Thr(*t*Bu)-O*t*Bu	683
Boc-Leu	Glu		Ser(*t*Bu)-O*t*Bu	684
Boc-Leu	Glu		Thr(*t*Bu)-O*t*Bu	685
Fmoc-Trp	Arg		Ser(*t*Bu)-O*t*Bu	686
Fmoc-Trp	Asp		Ser(*t*Bu)-O*t*Bu	687
Fmoc-Trp	Glu		Ser(*t*Bu)-O*t*Bu	688
Fmoc-Trp	Arg		Ser(*t*Bu)-O*t*Bu	689
Boc-Lys(εBoc)	Glu		Leu-O*t*Bu	690
Fmoc-Leu	Arg		Ser(*t*Bu)-O*t*Bu	691

Fmoc-Leu	Asp	Ser(*t*Bu)-O*t*Bu	692
Fmoc-Leu	Glu	Ser(*t*Bu)-O*t*Bu	693
Fmoc-Leu	Arg	Ser(*t*Bu)-O*t*Bu	694
Fmoc-Leu	Arg	Thr(*t*Bu)-O*t*Bu	695
Boc-Glu	Asp	Tyr(*t*Bu)-O*t*Bu	696
Fmoc-Lys(εFmoc)	Arg	Ser(*t*Bu)-O*t*Bu	697
Fmoc-Trp	Arg	Ile-O*t*Bu	698
Fmoc-Trp	Arg	Leu-O*t*Bu	699
Fmoc-Phe	Arg	Ile-O*t*Bu	700
Fmoc-Phe	Arg	Leu-O*t*Bu	701
Boc-Trp	Arg	Phe-O*t*Bu	702
Boc-Trp	Arg	Tyr-O*t*Bu	703
Fmoc-Trp	Arg	Phe-O*t*Bu	704
Fmoc-Trp	Arg	Tyr-O*t*Bu	705
Boc-Orn(δBoc)	Arg	Ser(*t*Bu)-O*t*Bu	706
Nicotinyl Lys(εBoc)	Arg	Ser(*t*Bu)-O*t*Bu	707
Nicotinyl Lys(εBoc)	Arg	Thr(*t*Bu)-O*t*Bu	708
Fmoc-Leu	Asp	Thr(*t*Bu)-OtBu	709
Fmoc-Leu	Glu	Thr(*t*Bu)-OtBu	710
Fmoc-Leu	Arg	Thr(*t*Bu)-OtBu	711
Fmoc-norLeu	Arg	Ser(*t*Bu)-OtBu	712
Fmoc-norLeu	Asp	Ser(*t*Bu)-OtBu	713
Fmoc-norLeu	Glu	Ser(*t*Bu)-OtBu	714
Fmoc-Lys(εBoc)	Arg	Ser(*t*Bu)-OtBu	715
Fmoc-Lys(εBoc)	Arg	Thr(*t*Bu)-OtBu	716
Fmoc-Lys(εBoc)	Glu	Ser(*t*Bu)-OtBu	717
Fmoc-Lys(εBoc)	Glu	Thr(*t*Bu)-OtBu	718
Fmoc-Lys(εBoc)	Asp	Ser(*t*Bu)-OtBu	719
Fmoc-Lys(εBoc)	Asp	Thr(*t*Bu)-OtBu	720
Fmoc-Lys(εBoc)	Glu	Leu-*OtBu*	721
Fmoc-Lys(εBoc)	Arg	Leu-*OtBu*	722
Fmoc-Lys(εFmoc)	Arg	Thr(*t*Bu)-OtBu	723
Fmoc- Lys(εFmoc)	Glu	Ser(*t*Bu)-OtBu	724
Fmoc- Lys(εFmoc)	Glu	Thr(*t*Bu)-OtBu	725
Fmoc- Lys(εFmoc)	Asp	Ser(*t*Bu)-OtBu	726
Fmoc- Lys(εFmoc)	Asp	Thr(*t*Bu)-OtBu	727
Fmoc- Lys(εFmoc)	Arg	Ser(*t*Bu)-OtBu	728
Fmoc- Lys(εFmoc))	Glu	Leu-*OtBu*	729
Boc-Lys(εFmoc)	Asp	Ser(*t*Bu)-OtBu	730
Boc-Lys(εFmoc)	Asp	Thr(*t*Bu)-OtBu	731
Boc-Lys(εFmoc)	Arg	Thr(*t*Bu)-OtBu	732

Boc-Lys(εFmoc)	Glu	Leu-*OtBu*	733
Boc-Orn(δFmoc)	Glu	Ser(*t*Bu)-OtBu	734
Boc-Orn(δFmoc)	Asp	Ser(*t*Bu)-OtBu	735
Boc-Orn(δFmoc)	Asp	Thr(*t*Bu)-OtBu	736
Boc-Orn(δFmoc)	Arg	Thr(*t*Bu)-OtBu	737
Boc-Orn(δFmoc)	Glu	Thr(*t*Bu)-OtBu	738
Fmoc-Trp	Asp	Ile-OtBu	739
Fmoc-Trp	Arg	Ile-OtBu	740
Fmoc-Trp	Glu	Ile-OtBu	741
Fmoc-Trp	Asp	Leu-OtBu	742
Fmoc-Trp	Glu	Leu-OtBu	743
Fmoc-Phe	Asp	Ile-OtBu	744
Fmoc-Phe	Asp	Leu-OtBu	745
Fmoc-Phe	Glu	Leu-OtBu	746
Fmoc-Trp	Arg	Phe-OtBu	747
Fmoc-Trp	Glu	Phe-OtBu	748
Fmoc-Trp	Asp	Phe-OtBu	749
Fmoc-Trp	Asp	Tyr-OtBu	750
Fmoc-Trp	Arg	Tyr-OtBu	751
Fmoc-Trp	Glu	Tyr-OtBu	752
Fmoc-Trp	Arg	Thr(*t*Bu)-OtBu	753
Fmoc-Trp	Asp	Thr(*t*Bu)-OtBu	754
Fmoc-Trp	Glu	Thr(*t*Bu)-OtBu	755
Boc-Phe	Arg	norLeu-OtBu	756
Boc-Phe	Glu	norLeu-OtBu	757
Fmoc-Phe	Asp	norLeu-OtBu	758
Boc-Glu	His	Tyr(*t*Bu)-O*t*Bu	759
Boc-Leu	His	Ser(*t*Bu)-O*t*Bu	760
Boc-Leu	His	Thr(*t*Bu)-O*t*Bu	761
Boc-Lys(εBoc)	His	Ser(*t*Bu)-O*t*Bu	762
Boc-Lys(εBoc)	His	Thr(*t*Bu)-O*t*Bu	763
Boc-Lys(εBoc)	His	Leu-*OtBu*	764
Boc-Lys(εFmoc)	His	Ser(*t*Bu)-OtBu	765
Boc-Lys(εFmoc)	His	Thr(*t*Bu)-OtBu	766
Boc-Lys(εFmoc)	His	Leu-*OtBu*	767
Boc-Orn(δBoc)	His	Ser(*t*Bu)-O*t*Bu	768
Boc-Orn(δFmoc)	His	Thr(*t*Bu)-OtBu	769
Boc-Phe	His	Ile –O*t*Bu	770

Boc-Phe	His	Leu-O*t*Bu	771
Boc-Phe	His	norLeu-OtBu	772
Boc-Phe	Lys	Leu-O*t*Bu	773
Boc-Trp	His	Ile-O*t*Bu	774
Boc-Trp	His	Leu-O*t*Bu	775
Boc-Trp	His	Phe-O*t*Bu	776
Boc-Trp	His	Tyr-O*t*Bu	777
Boc-Phe	Lys	Leu-O*t*Bu	778
Fmoc- Lys(εFmoc)	His	Ser(*t*Bu)-OtBu	779
Fmoc- Lys(εFmoc)	His	Thr(*t*Bu)-OtBu	780
Fmoc- Lys(εFmoc)	His	Leu-O*t*Bu	781
Fmoc-Leu	His	Ser(*t*Bu)-O*t*Bu	782
Fmoc-Leu	His	Thr(*t*Bu)-OtBu	783
Fmoc-Lys(εBoc)	His	Ser(*t*Bu)-OtBu	784
Fmoc-Lys(εBoc)	His	Thr(*t*Bu)-OtBu	785
Fmoc-Lys(εBoc)	His	Leu-*OtBu*	786
Fmoc-Lys(εFmoc)	His	Ser(*t*Bu)-O*t*Bu	787
Fmoc-Lys(εFmoc)	His	Thr(*t*Bu)-OtBu	788
Fmoc-norLeu	His	Ser(*t*Bu)-OtBu	789
Fmoc-Phe	His	Ile-O*t*Bu	790
Fmoc-Phe	His	Leu-O*t*Bu	791
Fmoc-Phe	His	norLeu-OtBu	792
Fmoc-Trp	His	Ser(*t*Bu)-O*t*Bu	793
Fmoc-Trp	His	Ile-O*t*Bu	794
Fmoc-Trp	His	Leu-O*t*Bu	795
Fmoc-Trp	His	Phe-O*t*Bu	796
Fmoc-Trp	His	Tyr-O*t*Bu	797
Fmoc-Trp	His	Thr(*t*Bu)-OtBu	798
Nicotinyl Lys(εBoc)	His	Ser(*t*Bu)-O*t*Bu	799
Nicotinyl Lys(εBoc)	His	Thr(*t*Bu)-O*t*Bu	800

[0158] While the peptides of Table 7 are illustrated with particular protecting groups, it is noted that any of these groups may be eliminated and/or substituted with other protecting groups as described herein.

3) Small peptides with central acidic and basic amino acids.

[0159] In certain embodiments, the peptides of this invention range from four amino acids to about ten amino acids. The terminal amino acids are typically hydrophobic either because of a hydrophobic side chain or because the terminal amino acids bear one or more hydrophobic protecting groups end amino acids (X^1 and X^4) are hydrophobic either because of a hydrophobic side chain or because the side chain or the C and/or N terminus is blocked with one or more hydrophobic protecting group(s) (*e.g.*, the N-terminus is blocked with Boc-, Fmoc-, Nicotinyl-, *etc.*, and the C-terminus blocked with (*t*Bu)-O*t*Bu, *etc.*). Typically, the central portion of the peptide comprises a basic amino acid and an acidic amino acid (*e.g.*, in a 4 mer) or a basic domain and/or an acidic domain in a longer molecule.

[0160] These four-mers can be represented by Formula XXV in which X^1 and X^4 are hydrophobic and/or bear hydrophobic protecting group(s) as described herein and X^2 is acidic while X^3 is basic or X^2 is basic while X^3 is acidic. The peptide can be all L- amino acids or include one or more or all D-amino acids.

[0161] Certain preferred of this invention include, but are not limited to the peptides shown in Table 8.

[0162] Table 8. Illustrative examples of small peptides with central acidic and basic amino acids.

X^1	X^2	X^3	X^4	SEQ ID NO
Boc-Lys(εBoc)	Arg	Asp	Ser(*t*Bu)-O*t*Bu	801
Boc-Lys(εBoc)	Arg	Asp	Thr(*t*Bu)-O*t*Bu	802
Boc-Trp	Arg	Asp	Ile-O*t*Bu	803
Boc-Trp	Arg	Asp	Leu-O*t*Bu	804
Boc-Phe	Arg	Asp	Leu-O*t*Bu	805
Boc-Phe	Arg	Asp	Ile-O*t*Bu	806
Boc-Phe	Arg	Asp	norLeu-O*t*Bu	807
Boc-Phe	Arg	Glu	norLeu-O*t*Bu	808

Boc-Phe	Arg	Glu	Ile-*O*t*B*u	809
Boc-Phe	Asp	Arg	Ile-O*t*Bu	810
Boc-Phe	Glu	Arg	Ile-O*t*Bu	811
Boc-Phe	Asp	Arg	Leu-O*t*Bu	812
Boc-Phe	Arg	Glu	Leu-O*t*Bu	813
Boc-Phe	Glu	Arg	Leu-O*t*Bu	814
Boc-Phe	Asp	Arg	norLeu-O*t*Bu	815
Boc-Phe	Glu	Arg	norLeu-O*t*Bu	816
Boc-Lys(εBoc)	Glu	Arg	Ser(*t*Bu)-O*t*Bu	817
Boc-Lys(εBoc)	Glu	Arg	Thr(*t*Bu)-O*t*Bu	818
Boc-Lys(εBoc)	Asp	Arg	Ser(*t*Bu)-O*t*Bu	819
Boc-Lys(εBoc)	Asp	Arg	Thr(*t*Bu)-O*t*Bu	820
Boc-Lys(εBoc)	Arg	Glu	Ser(*t*Bu)-O*t*Bu	821
Boc-Lys(εBoc)	Arg	Glu	Thr(*t*Bu)-O*t*Bu	822
Boc-Leu	Glu	Arg	Ser(*t*Bu)-O*t*Bu	823
Boc-Leu	Glu	Arg	Thr(*t*Bu)-O*t*Bu	824
Fmoc-Trp	Arg	Asp	Ser(*t*Bu)-O*t*Bu	825
Fmoc-Trp	Asp	Arg	Ser(*t*Bu)-O*t*Bu	826
Fmoc-Trp	Glu	Arg	Ser(*t*Bu)-O*t*Bu	827
Fmoc-Trp	Arg	Glu	Ser(*t*Bu)-O*t*Bu	828
Boc-Lys(εBoc)	Glu	Arg	Leu-*O*t*B*u	829
Fmoc-Leu	Arg	Asp	Ser(*t*Bu)-O*t*Bu	830
Fmoc-Leu	Asp	Arg	Ser(*t*Bu)-O*t*Bu	831
Fmoc-Leu	Glu	Arg	Ser(*t*Bu)-O*t*Bu	832
Fmoc-Leu	Arg	Glu	Ser(*t*Bu)-O*t*Bu	833
Fmoc-Leu	Arg	Asp	Thr(*t*Bu)-O*t*Bu	834
Boc-Glu	Asp	Arg	Tyr(*t*Bu)-O*t*Bu	835
Fmoc-Lys(εFmoc)	Arg	Asp	Ser(*t*Bu)-O*t*Bu	836
Fmoc-Trp	Arg	Asp	Ile-O*t*Bu	837
Fmoc-Trp	Arg	Asp	Leu-O*t*Bu	838
Fmoc-Phe	Arg	Asp	Ile-O*t*Bu	839
Fmoc-Phe	Arg	Asp	Leu-O*t*Bu	840
Boc-Trp	Arg	Asp	Phe-O*t*Bu	841
Boc-Trp	Arg	Asp	Tyr-O*t*Bu	842
Fmoc-Trp	Arg	Asp	Phe-O*t*Bu	843
Fmoc-Trp	Arg	Asp	Tyr-O*t*Bu	844
Boc-Orn(δBoc)	Arg	Glu	Ser(*t*Bu)-O*t*Bu	845
Nicotinyl Lys(εBoc)	Arg	Asp	Ser(*t*Bu)-O*t*Bu	846
Nicotinyl Lys(εBoc)	Arg	Asp	Thr(*t*Bu)-O*t*Bu	847

Fmoc-Leu	Asp	Arg	Thr(*t*Bu)-OtBu	848
Fmoc-Leu	Glu	Arg	Thr(*t*Bu)-OtBu	849
Fmoc-Leu	Arg	Glu	Thr(*t*Bu)-OtBu	850
Fmoc-norLeu	Arg	Asp	Ser(*t*Bu)-OtBu	851
Fmoc-norLeu	Asp	Arg	Ser(*t*Bu)-OtBu	852
Fmoc-norLeu	Glu	Arg	Ser(*t*Bu)-OtBu	853
Fmoc-norLeu	Arg	Glu	Ser(*t*Bu)-OtBu	854
Fmoc-Lys(εBoc)	Arg	Asp	Ser(*t*Bu)-OtBu	855
Fmoc-Lys(εBoc)	Arg	Asp	Thr(*t*Bu)-OtBu	856
Fmoc-Lys(εBoc)	Glu	Arg	Ser(*t*Bu)-OtBu	857
Fmoc-Lys(εBoc)	Glu	Arg	Thr(*t*Bu)-OtBu	858
Fmoc-Lys(εBoc)	Asp	Arg	Ser(*t*Bu)-OtBu	859
Fmoc-Lys(εBoc)	Asp	Arg	Thr(*t*Bu)-OtBu	860
Fmoc-Lys(εBoc)	Arg	Glu	Ser(*t*Bu)-OtBu	861
Fmoc-Lys(εBoc)	Arg	Glu	Thr(*t*Bu)-OtBu	862
Fmoc-Lys(εBoc)	Glu	Arg	Leu-*OtBu*	863
Fmoc-Lys(εBoc)	Arg	Glu	Leu-*OtBu*	864
Fmoc-Lys(εFmoc)	Arg	Asp	Thr(*t*Bu)-OtBu	865
Fmoc- Lys(εFmoc)	Glu	Arg	Ser(*t*Bu)-OtBu	866
Fmoc- Lys(εFmoc)	Glu	Arg	Thr(*t*Bu)-OtBu	867
Fmoc- Lys(εFmoc)	Asp	Arg	Ser(*t*Bu)-OtBu	868
Fmoc- Lys(εFmoc)	Asp	Arg	Thr(*t*Bu)-OtBu	869
Fmoc- Lys(εFmoc)	Arg	Glu	Ser(*t*Bu)-OtBu	870
Fmoc- Lys(εFmoc)	Arg	Glu	Thr(*t*Bu)-OtBu	871
Fmoc- Lys(εFmoc))	Glu	Arg	Leu-*OtBu*	872
Boc-Lys(εFmoc)	Arg	Asp	Ser(*t*Bu)-OtBu	873
Boc-Lys(εFmoc)	Arg	Asp	Thr(*t*Bu)-OtBu	874
Boc-Lys(εFmoc)	Glu	Arg	Ser(*t*Bu)-OtBu	875
Boc-Lys(εFmoc)	Glu	Arg	Thr(*t*Bu)-OtBu	876
Boc-Lys(εFmoc)	Asp	Arg	Ser(*t*Bu)-OtBu	877
Boc-Lys(εFmoc)	Asp	Arg	Thr(*t*Bu)-OtBu	878
Boc-Lys(εFmoc)	Arg	Glu	Ser(*t*Bu)-OtBu	879
Boc-Lys(εFmoc)	Arg	Glu	Thr(*t*Bu)-OtBu	880
Boc-Lys(εFmoc)	Glu	Arg	Leu-*OtBu*	881
Boc-Orn(δFmoc)	Arg	Glu	Ser(*t*Bu)-OtBu	882
Boc-Orn(δFmoc)	Glu	Arg	Ser(*t*Bu)-OtBu	883
Boc-Orn(δFmoc)	Arg	Asp	Ser(*t*Bu)-OtBu	884
Boc-Orn(δFmoc)	Asp	Arg	Ser(*t*Bu)-OtBu	885

Boc-Orn(δFmoc)	Asp	Arg	Thr(*t*Bu)-OtBu	886
Boc-Orn(δFmoc)	Arg	Asp	Thr(*t*Bu)-OtBu	887
Boc-Orn(δFmoc)	Glu	Arg	Thr(*t*Bu)-OtBu	888
Boc-Orn(δFmoc)	Arg	Glu	Thr(*t*Bu)-OtBu	889
Fmoc-Trp	Asp	Arg	Ile-OtBu	890
Fmoc-Trp	Arg	Glu	Ile-OtBu	891
Fmoc-Trp	Glu	Arg	Ile-OtBu	892
Fmoc-Trp	Asp	Arg	Leu-OtBu	893
Fmoc-Trp	Arg	Glu	Leu-OtBu	894
Fmoc-Trp	Glu	Arg	Leu-OtBu	895
Fmoc-Phe	Asp	Arg	Ile-OtBu	896
Fmoc-Phe	Arg	Glu	Ile-OtBu	897
Fmoc-Phe	Glu	Arg	Ile-OtBu	898
Fmoc-Phe	Asp	Arg	Leu-OtBu	899
Fmoc-Phe	Arg	Glu	Leu-OtBu	900
Fmoc-Phe	Glu	Arg	Leu-OtBu	901
Fmoc-Trp	Arg	Asp	Phe-OtBu	902
Fmoc-Trp	Arg	Glu	Phe-OtBu	903
Fmoc-Trp	Glu	Arg	Phe-OtBu	904
Fmoc-Trp	Asp	Arg	Tyr-OtBu	905
Fmoc-Trp	Arg	Glu	Tyr-OtBu	906
Fmoc-Trp	Glu	Arg	Tyr-OtBu	907
Fmoc-Trp	Arg	Asp	Thr(*t*Bu)-OtBu	908
Fmoc-Trp	Asp	Arg	Thr(*t*Bu)-OtBu	909
Fmoc-Trp	Arg	Glu	Thr(*t*Bu)-OtBu	910
Fmoc-Trp	Glu	Arg	Thr(*t*Bu)-OtBu	911
Fmoc-Phe	Arg	Asp	norLeu-OtBu	912
Fmoc-Phe	Arg	Glu	norLeu-OtBu	913
Boc-Phe	Lys	Asp	Leu-OtBu	914
Boc-Phe	Asp	Lys	Leu-OtBu	915
Boc-Phe	Lys	Glu	Leu-OtBu	916
Boc-Phe	Glu	Lys	Leu-OtBu	917
Boc-Phe	Lys	Asp	Ile-OtBu	918
Boc-Phe	Asp	Lys	Ile-OtBu	919
Boc-Phe	Lys	Glu	Ile-OtBu	920
Boc-Phe	Glu	Lys	Ile-OtBu	921
Boc-Phe	Lys	Asp	norLeu-OtBu	922
Boc-Phe	Asp	Lys	norLeu-OtBu	923
Boc-Phe	Lys	Glu	norLeu-OtBu	924

Boc-Phe	Glu	Lys	norLeu-OtBu	925
Boc-Phe	His	Asp	Leu-OtBu	926
Boc-Phe	Asp	His	Leu-OtBu	927
Boc-Phe	His	Glu	Leu-OtBu	928
Boc-Phe	Glu	His	Leu-OtBu	929
Boc-Phe	His	Asp	Ile-OtBu	930
Boc-Phe	Asp	His	Ile-OtBu	931
Boc-Phe	His	Glu	Ile-OtBu	932
Boc-Phe	Glu	His	Ile-OtBu	933
Boc-Phe	His	Asp	norLeu-OtBu	934
Boc-Phe	Asp	His	norLeu-OtBu	935
Boc-Phe	His	Glu	norLeu-OtBu	936
Boc-Phe	Glu	His	norLeu-OtBu	937
Boc-Lys(εBoc)	Lys	Asp	Ser(*t*Bu)-OtBu	938
Boc-Lys(εBoc)	Asp	Lys	Ser(*t*Bu)-OtBu	939
Boc-Lys(εBoc)	Lys	Glu	Ser(*t*Bu)-OtBu	940
Boc-Lys(εBoc)	Glu	Lys	Ser(*t*Bu)-OtBu	941
Boc-Lys(εBoc)	His	Asp	Ser(*t*Bu)-OtBu	942
Boc-Lys(εBoc)	Asp	His	Ser(*t*Bu)-OtBu	943
Boc-Lys(εBoc)	His	Glu	Ser(*t*Bu)-OtBu	944
Boc-Lys(εBoc)	Glu	His	Ser(*t*Bu)-OtBu	945

[0163] While the peptides of Table 8 are illustrated with particular protecting groups, it is noted that these groups may be substituted with other protecting groups as described herein and/or one or more of the shown protecting group can be eliminated.

4) Small peptides having either an acidic or basic amino acid in the center together with a central aliphatic amino acid.

[0164] In certain embodiments, the peptides of this invention range from four amino acids to about ten amino acids. The terminal amino acids are typically hydrophobic either because of a hydrophobic side chain or because the terminal amino acids bear one or more hydrophobic protecting groups. End amino acids (X^1 and X^4) are hydrophobic either because of a hydrophobic side chain or because the side chain or the C and/or N terminus is blocked with one or more hydrophobic protecting group(s) (*e.g.*, the N-terminus is blocked with Boc-, Fmoc-, Nicotinyl-, *etc.*, and the C-terminus blocked with (*t*Bu)-O*t*Bu, *etc.*).

Typically, the central portion of the peptide comprises a basic or acidic amino acid and an aliphatic amino acid (*e.g.*, in a 4 mer) or a basic domain or an acidic domain and an aliphatic domain in a longer molecule.

[0165] These four-mers can be represented by Formula XXV in which X^1 and X^4 are hydrophobic and/or bear hydrophobic protecting group(s) as described herein and X^2 is acidic or basic while X^3 is aliphatic or X^2 is aliphatic while X^3 is acidic or basic. The peptide can be all L- amino acids or include one, or more, or all D-amino acids.

[0166] Certain preferred peptides of this invention include, but are not limited to the peptides shown in Table 9.

[0167] Table 9. Examples of certain preferred peptides having either an acidic or basic amino acid in the center together with a central aliphatic amino acid.

X^1	X^2	X^3	X^4	SEQ ID NO
Fmoc-Lys(εBoc)	Leu	Arg	Ser(*t*Bu)-OtBu	946
Fmoc-Lys(εBoc)	Arg	Leu	Ser(*t*Bu)-OtBu	947
Fmoc-Lys(εBoc)	Leu	Arg	Thr(*t*Bu)-OtBu	948
Fmoc-Lys(εBoc)	Arg	Leu	Thr(*t*Bu)-OtBu	949
Fmoc-Lys(εBoc)	Glu	Leu	Ser(*t*Bu)-OtBu	950
Fmoc-Lys(εBoc)	Leu	Glu	Ser(*t*Bu)-OtBu	951
Fmoc-Lys(εBoc)	Glu	Leu	Thr(*t*Bu)-OtBu	952
Fmoc- Lys(εFmoc)	Leu	Arg	Ser(*t*Bu)-OtBu	953
Fmoc- Lys(εFmoc)	Leu	Arg	Thr(*t*Bu)-OtBu	954
Fmoc- Lys(εFmoc)	Glu	Leu	Ser(*t*Bu)-OtBu	955
Fmoc- Lys(εFmoc)	Glu	Leu	Thr(*t*Bu)-OtBu	956
Boc-Lys(Fmoc)	Glu	Ile	Thr(*t*Bu)-OtBu	957
Boc-Lys(εFmoc)	Leu	Arg	Ser(*t*Bu)-OtBu	958
Boc-Lys(εFmoc)	Leu	Arg	Thr(*t*Bu)-OtBu	959
Boc-Lys(εFmoc)	Glu	Leu	Ser(*t*Bu)-OtBu	960
Boc-Lys(εFmoc)	Glu	Leu	Thr(*t*Bu)-OtBu	961
Boc-Lys(εBoc)	Leu	Arg	Ser(*t*Bu)-OtBu	962
Boc-Lys(εBoc)	Arg	Phe	Thr(*t*Bu)-OtBu	963
Boc-Lys(εBoc)	Leu	Arg	Thr(*t*Bu)-OtBu	964
Boc-Lys(εBoc)	Glu	Ile	Thr(*t*Bu)	965
Boc-Lys(εBoc)	Glu	Val	Thr(*t*Bu)	966

Boc-Lys(εBoc)	Glu	Ala	Thr(*t*Bu)	967
Boc-Lys(εBoc)	Glu	Gly	Thr(*t*Bu)	968
Boc--Lys(εBoc)	Glu	Leu	Ser(*t*Bu)-OtBu	969
Boc-Lys(εBoc)	Glu	Leu	Thr(*t*Bu)-OtBu	970

[0168] While the peptides of Table 9 are illustrated with particular protecting groups, it is noted that these groups may be substituted with other protecting groups as described herein and/or one or more of the shown protecting group can be eliminated.

5) Small peptides having either an acidic or basic amino acid in the center together with a central aromatic amino acid.

[0169] In certain embodiments, the "small" peptides of this invention range from four amino acids to about ten amino acids. The terminal amino acids are typically hydrophobic either because of a hydrophobic side chain or because the terminal amino acids bear one or more hydrophobic protecting groups end amino acids (X^1 and X^4) are hydrophobic either because of a hydrophobic side chain or because the side chain or the C and/or N terminus is blocked with one or more hydrophobic protecting group(s) (*e.g.*, the N-terminus is blocked with Boc-, Fmoc-, Nicotinyl-, *etc.*, and the C-terminus blocked with (*t*Bu)-O*t*Bu, *etc.*). Typically, the central portion of the peptide comprises a basic or acidic amino acid and an aromatic amino acid (*e.g.*, in a 4 mer) or a basic domain or an acidic domain and an aromatic domain in a longer molecule.

[0170] These four-mers can be represented by Formula XXV in which X^1 and X^4 are hydrophobic and/or bear hydrophobic protecting group(s) as described herein and X^2 is acidic or basic while X^3 is aromatic or X^2 is aromatic while X^3 is acidic or basic. The peptide can be all L- amino acids or include one, or more, or all D-amino acids. Five-mers can be represented by a minor modification of Formula XXV in which X^5 is inserted as shown in Table 10 and in which X^5 is typically an aromatic amino acid, *e.g.*,

$$X^1\text{-}X^2\text{-}X^3{}_n\text{-}\ X^5{}_p\text{-}X^4 \qquad \text{XXVII}$$

where X^1, X^2, X^3, and X^4 are as described above, p is 0 or 1 and X^5 is typically an aromatic amino acid.

[0171] Certain preferred peptides of this invention include, but are not limited to the peptides shown in Table 10.

[0172] Table 10. Examples of certain preferred peptides having either an acidic or basic amino acid in the center together with a central aromatic amino acid.

X^1	X^2	X^3	X^5	X^4	SEQ ID NO
Fmoc-Lys(εBoc)	Arg	Trp		Tyr(*t*Bu)-OtBu	971
Fmoc-Lys(εBoc)	Trp	Arg		Tyr(*t*Bu)-OtBu	972
Fmoc-Lys(εBoc)	Arg	Tyr		Trp-OtBu	973
Fmoc-Lys(εBoc)	Tyr	Arg		Trp-OtBu	974
Fmoc-Lys(εBoc)	Arg	Tyr	Trp	Thr(*t*Bu)-OtBu	975
Fmoc-Lys(εBoc)	Arg	Tyr		Thr(*t*Bu)-OtBu	976
Fmoc-Lys(εBoc)	Arg	Trp		Thr(*t*Bu)-OtBu	977
Fmoc- Lys(εFmoc)	Arg	Trp		Tyr(*t*Bu)-OtBu	978
Fmoc- Lys(εFmoc)	Arg	Tyr		Trp-OtBu	979
Fmoc- Lys(εFmoc)	Arg	Tyr	Trp	Thr(*t*Bu)-OtBu	980
Fmoc- Lys(εFmoc)	Arg	Tyr		Thr(*t*Bu)-OtBu	981
Fmoc- Lys(εFmoc)	Arg	Trp		Thr(*t*Bu)-OtBu	982
Boc-Lys(εFmoc)	Arg	Trp		Tyr(*t*Bu)-OtBu	983
Boc-Lys(εFmoc)	Arg	Tyr		Trp-OtBu	984
Boc-Lys(εFmoc)	Arg	Tyr	Trp	Thr(*t*Bu)-OtBu	985
Boc-Lys(εFmoc)	Arg	Tyr		Thr(*t*Bu)-OtBu	986
Boc-Lys(εFmoc)	Arg	Trp		Thr(*t*Bu)-OtBu	987
Boc-Glu	Lys(εFmoc)	Arg		Tyr(*t*Bu)-OtBu	988
Boc-Lys(εBoc)	Arg	Trp		Tyr(*t*Bu)-OtBu	989
Boc-Lys(εBoc)	Arg	Tyr		Trp-OtBu	990
Boc-Lys(εBoc)	Arg	Tyr	Trp	Thr(*t*Bu)-OtBu	991
Boc-Lys(εBoc)	Arg	Tyr		Thr(*t*Bu)-OtBu	992
Boc-Lys(εBoc)	Arg	Phe		Thr(*t*Bu)-OtBu	993
Boc-Lys(εBoc)	Arg	Trp		Thr(*t*Bu)-OtBu	994

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[0173] While the peptides of Table 10 are illustrated with particular protecting groups, it is noted that these groups may be substituted with other protecting groups as described herein and/or one or more of the shown protecting groups can be eliminated.

6) Small peptides having aromatic amino acids or aromatic amino acids separated by histidine(s) at the center.

[0174] In certain embodiments, the peptides of this invention are characterized by π electrons that are exposed in the center of the molecule which allow hydration of the particle and that allow the peptide particles to trap pro-inflammatory oxidized lipids such as fatty acid hydroperoxides and phospholipids that contain an oxidation product of arachidonic acid at the sn-2 position.

[0175] In certain embodiments, these peptides consist of a minimum of 4 amino acids and a maximum of about 10 amino acids, preferentially (but not necessarily) with one or more of the amino acids being the D-sterioisomer of the amino acid, with the end amino acids being hydrophobic either because of a hydrophobic side chain or because the terminal amino acid(s) bear one or more hydrophobic blocking group(s), (*e.g.*, an N-terminus blocked with Boc-, Fmoc-, Nicotinyl-, and the like, and a C-terminus blocked with (*t*Bu)-O*t*Bu groups and the like). Instead of having an acidic or basic amino acid in the center, these peptides generally have an aromatic amino acid at the center or have aromatic amino acids separated by histidine in the center of the peptide.

[0176] Certain preferred peptides of this invention include, but are not limited to the peptides shown in Table 11.

[0177] Table 11. Examples of peptides having aromatic amino acids in the center or aromatic amino acids or aromatic domains separated by one or more histidines.

X^1	X^2	X^3	X^4	X^5	SEQ ID NO
Boc-Lys(εBoc)	Phe	Trp	Phe	Ser(*t*Bu)-OtBu	995
Boc-Lys(εBoc)	Phe	Trp	Phe	Thr(*t*Bu)-OtBu	996
Boc-Lys(εBoc)	Phe	Tyr	Phe	Ser(*t*Bu)-OtBu	997
Boc-Lys(εBoc)	Phe	Tyr	Phe	Thr(*t*Bu)-OtBu	998
Boc-Lys(εBoc)	Phe	His	Phe	Ser(*t*Bu)-OtBu	999
Boc-Lys(εBoc)	Phe	His	Phe	Thr(*t*Bu)-OtBu	1000
Boc-Lys(εBoc)	Val	Phe	Phe-Tyr	Ser(*t*Bu)-OtBu	1001
Nicotinyl-Lys(εBoc)	Phe	Trp	Phe	Ser(*t*Bu)-OtBu	1002
Nicotinyl-Lys(εBoc)	Phe	Trp	Phe	Thr(*t*Bu)-OtBu	1003
Nicotinyl-Lys(εBoc)	Phe	Tyr	Phe	Ser(*t*Bu)-OtBu	1004

Nicotinyl-Lys(εBoc)	Phe	Tyr	Phe	Thr(*t*Bu)-OtBu	1005
Nicotinyl-Lys(εBoc)	Phe	His	Phe	Ser(*t*Bu)-OtBu	1006
Nicotinyl-Lys(εBoc)	Phe	His	Phe	Thr(*t*Bu)-OtBu	1007
Boc-Leu	Phe	Trp	Phe	Thr(*t*Bu)-OtBu	1008
Boc-Leu	Phe	Trp	Phe	Ser(*t*Bu)-OtBu	1009

[0178] While the peptides of Table 11 are illustrated with particular protecting groups, it is noted that these groups may be substituted with other protecting groups as described herein and/or one or more of the shown protecting group can be eliminated.

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7) Summary of tripeptides and tetrapeptides.

[0179] For the sake of clarity, a number of tripeptides and tetrapeptides of this invention are generally summarized below in Table 12.

[0180] Table 12. General structure of certain peptides of this invention.

X^1	X^2	X^3	X^4
hydrophobic side chain or hydrophobic protecting group(s)	Acidic or Basic	----	hydrophobic side chain or hydrophobic protecting group(s)
hydrophobic side chain or hydrophobic protecting group(s)	Basic	Acidic	hydrophobic side chain or hydrophobic protecting group(s)
hydrophobic side chain or hydrophobic protecting group(s)	Acidic	Basic	hydrophobic side chain or hydrophobic protecting group(s)
hydrophobic side chain or hydrophobic protecting group(s)	Acidic or Basic	Aliphatic	hydrophobic side chain or hydrophobic protecting group(s)
hydrophobic side chain or hydrophobic protecting group(s)	Aliphatic	Acidic or Basic	hydrophobic side chain or hydrophobic protecting group(s)
hydrophobic side chain or hydrophobic protecting group(s)	Acidic or Basic	Aromatic	hydrophobic side chain or hydrophobic protecting group(s)
hydrophobic side chain or hydrophobic protecting group(s)	Aromatic	Acidic or Basic	hydrophobic side chain or hydrophobic

hydrophobic side chain or hydrophobic protecting group(s)	Aromatic	His	Aromatic	protecting group(s) hydrophobic side chain or hydrophobic protecting group(s)

[0181] Where longer peptides are desired, X^2 and X^3 can represent domains (*e.g.*, regions of two or more amino acids of the specified type) rather than individual amino acids. Table 12 is intended to be illustrative and not limiting. Using the teaching provided herein, other suitable peptides can readily be identified.

8) Paired amino acids and dipeptides.

[0182] In certain embodiments, this invention pertains to the discovery that certain pairs of amino acids, administered in conjunction with each other or linked to form a dipeptide have one or more of the properties described herein. Thus, without being bound to a particular theory, it is believed that when the pairs of amino acids are administered in conjunction with each other, as described herein, they are capable participating in or inducing the formation of micelles *in vivo*.

[0183] Similar to the other small peptides described herein, it is believed that the pairs of peptides will associate *in vivo*, and demonstrate physical properties including high solubility in ethyl acetate (*e.g.*, greater than about 4 mg/mL), solubility in aqueous buffer at pH 7.0. Upon contacting phospholipids such as 1,2-Dimyristoyl-*sn*-glycero-3-phosphocholine (DMPC), in an aqueous environment, it is believed the pairs of amino acids induce or participate in the formation of particles with a diameter of approximately 7.5 nm (± 0.1 nm), and/or induce or participate in the formation of stacked bilayers with a bilayer dimension on the order of 3.4 to 4.1 nm with spacing between the bilayers in the stack of approximately 2 nm, and/or also induce or participate in the formation of vesicular structures of approximately 38 nm).

[0184] Moreover, it is further believed that the pairs of amino acids can display one or more of the following physiologically relevant properties:

[0185] 1. They convert pro-inflammatory HDL to anti-inflammatory HDL or make anti-inflammatory HDL more anti-inflammatory;

[0186] 2. They decrease LDL-induced monocyte chemotactic activity generated by artery wall cells;

[0187] 3. They stimulate the formation and cycling of pre-β HDL;

[0188] 4. They raise HDL cholesterol; and/or

[0189] 5. They increase HDL paraoxonase activity.

[0190] The pairs of amino acids can be administered as separate amino acids (administered sequentially or simultaneously, *e.g.*, in a combined formulation) or they can be covalently coupled directly or through a linker (*e.g.*, a PEG linker, a carbon linker, a branched linker, a straight chain linker, a heterocyclic linker, a linker formed of derivatized lipid, *etc.*). In certain embodiments, the pairs of amino acids are covalently linked through a peptide bond to form a dipeptide. In various embodiments while the dipeptides will typically comprise two amino acids each bearing an attached protecting group, this invention also contemplates dipeptides wherein only one of the amino acids bears one or more protecting groups.

[0191] The pairs of amino acids typically comprise amino acids where each amino acid is attached to at least one protecting group (*e.g.*, a hydrophobic protecting group as described herein). The amino acids can be in the D or the L form. In certain embodiments, where the amino acids comprising the pairs are not attached to each other, each amino acid bears two protecting groups (*e.g.*, such as molecules 1 and 2 in Table 13).

[0192] Table 13. Illustrative amino acid pairs of this invention.

	Amino Acid Pair/dipeptide
1.	Boc-Arg-OtBu*
2.	Boc-Glu-OtBu*
3.	Boc-Phe-Arg-OtBu**
4.	Boc-Glu-Leu-OtBu**
5.	Boc-Arg-Glu-OtBu***

*This would typically be administered in conjunction with a second amino acid.

**In certain embodiments, these dipeptides would be administered in conjunction with each other.

*** In certain embodiments, this peptide would be administered either alone or in combination with one of the other peptides described herein..

[0193] Suitable pairs of amino acids can readily be identified by providing the pair of protected amino acids and/or a dipeptide and then screening the pair of amino acids/dipeptide for one or more of the physical and/or physiological properties described above. In certain embodiments, this invention excludes pairs of amino acids and/or dipeptides comprising aspartic acid and phenylalanine. In certain embodiments, this invention excludes pairs of amino acids and/or dipeptides in which one amino acid is (-)-N-[(trans-4-isopropylcyclohexane)carbonyl]-D-phenylalanine (nateglinide).

[0194] In certain embodiments, the amino acids comprising the pair are independently selected from the group consisting of an acidic amino acid (*e.g.*, aspartic acid, glutamic acid, *etc.*), a basic amino acid (*e.g.*, lysine, arginine, histidine, *etc.*), and a non-polar amino acid (*e.g.*, alanine, valine, leucine, isoleucine, proline, phenylalanine, tryptophan, methionine, *etc.*). In certain embodiments, where the first amino acid is acidic or basic, the second amino acid is non-polar and where the second amino acid is acidic or basic, the first amino acid is non-polar. In certain embodiments, where the first amino acid is acidic, the second amino acid is basic, and vice versa. (*see, e.g.,* Table 14).

[0195] Similar combinations can be obtained by administering pairs of dipeptides. Thus, for example in certain embodiments, molecules 3 and 4 in Table 13 would be administered in conjunction with each other.

Table 14. Certain generalized amino acid pairs/dipeptides.

	First Amino acid	Second Amino acid
1.	Acidic	Basic
2.	Basic	Acidic
3.	Acidic	Non-polar
4.	Non-polar	Acidic
5.	Basic	Non-polar
6.	Non-polar	Basic

[0196] It is noted that these amino acid pairs/dipeptides are intended to be illustrative and not limiting. Using the teaching provided herein other suitable amino acid pairs/dipeptides can readily be determined.

[0197] In certain embodiments, however, dipeptides and/or amino acid pairs comprising L-Glu-L-Trp, e.g., as described in U.S. Patent 5,807,830 and/or any other peptides disclosed in this patent, are expressly excluded from the methods and/or formulations described herein.

E) Apo-J (G* peptides).

[0198] It was also a discovery of this invention that peptides that mimicking the amphipathic helical domains of apo J are capable of mitigating one or more symptoms of atherosclerosis and/or other pathologies described herein. Apolipoprotein J possesses a wide nonpolar face termed globular protein-like, or G* amphipathic helical domains. The class G amphipathic helix is found in globular proteins, and thus, the name class G. This class of amphipathic helix is characterized by a random distribution of positively charged and negatively charged residues on the polar face with a narrow nonpolar face. Because of the narrow nonpolar face this class does not readily associate with phospholipids. The G* of amphipathic helix possesses similar, but not identical, characteristics to the G amphipathic helix. Similar to the class G amphipathic helix, the G* class peptides possesses a random distribution of positively and negatively charged residues on the polar face. However, in contrast to the class G amphipathic helix which has a narrow nonpolar face, this class has a wide nonpolar face that allows this class to readily bind phospholipid and the class is termed G* to differentiate it from the G class of amphipathic helix.

[0199] A number of suitable G* amphipathic peptides are described in copending applications USSN 10/120,508, filed April 5, 2002, USSN 10/520,207, filed April 1, 2003, and PCT Application PCT/US03/09988, filed April 1, 2003. In addition, a variety of suitable peptides of this invention that are related to G* amphipathic helical domains of apo J are illustrated in Table 15.

[0200] Table 15. Certain peptides for use in this invention related to G* amphipathic helical domains of apo J.

Amino Acid Sequence	SEQ ID NO
LLEQLNEQFNWVSRLANLTQGE	1010
LLEQLNEQFNWVSRLANL	1011
NELQEMSNQGSKYVNKEIQNAVNGV	1012
IQNAVNGVKQIKTLIEKTNEE	1013
RKTLLSNLEEAKKKKEDALNETRESETKLKEL	1014
PGVCNETMMALWEECK	1015
PCLKQTCMKFYARVCR	1016
ECKPCLKQTCMKFYARVCR	1017
LVGRQLEEFL	1018
MNGDRIDSLLEN	1019
QQTHMLDVMQD	1020
FSRASSIIDELFQD	1021
PFLEMIHEAQQAMDI	1022
PTEFIREGDDD	1023
RMKDQCDKCREILSV	1024
PSQAKLRRELDESLQVAERLTRKYNELLKSYQ	1025
LLEQLNEQFNWVSRLANLTEGE	1026
DQYYLRVTTVA	1027
PSGVTEVVVKLFDS	1028
PKFMETVAEKALQEYRKKHRE	1029

[0201] The peptides of this invention, however, are not limited to G* variants of apo J. Generally speaking G* domains from essentially any other protein preferably apo proteins are also suitable. The particular suitability of such proteins can readily be determined using assays for protective activity (*e.g.*, protecting LDL from oxidation, and the like), *e.g.*, as illustrated herein in the Examples. Some particularly preferred proteins include G* amphipathic helical domains or variants thereof (*e.g.*, conservative substitutions, and the like) of proteins including, but not limited to apo AI, apo AIV, apo E, apo CII, apo CIII, and the like.

[0202] Certain preferred peptides for related to G* amphipathic helical domains related to apoproteins other than apo J are illustrated in Table 16.

[0203] Table 16. Certain peptides for use in this invention related to G* amphipathic helical domains related to apoproteins other than apo J.

Amino Acid Sequence	SEQ ID NO
WDRVKDLATVYVDVLKDSGRDYVSQF (Related to the 8 to 33 region of apo AI)	1030
VATVMWDYFSQLSNNAKEAVEHLQK (Related to the 7 to 31 region of apo AIV)	1031
RWELALGRFWDYLRWVQTLSEQVQEEL (Related to the 25 to 51 region of apo E)	1032
LSSQVTQELRALMDETMKELKELKAYKSELEEQLT (Related to the 52 to 83 region of apo E)	1033
ARLSKELQAAQARLGADMEDVCGRLV (Related to the 91 to 116 region of apo E)	1034
VRLASHLRKLRKRLLRDADDLQKRLA (Related to the135 to 160 region of apo E)	1035
PLVEDMQRQWAGLVEKVQA (267 to 285 of apo E.27)	1036
MSTYTGIFTDQVLSVLK (Related to the 60 to 76 region of apo CII)	1037
LLSFMQGYMKHATKTAKDALSS (Related to the 8 to 29 region of apo CIII)	1038

[0204] Additional illustrative G* peptides are shown in Table 17.

[0205] Table 17. Additional illustrative G* peptides.

Peptide	SEQ ID NO
Ac-Lys-Trp-Ile-Tyr-His-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Leu-Arg-Thr-Glu-Gly-NH_2	1039
Ac-Lys-Trp-Phe-Tyr-His-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Leu-Arg-Thr-Glu-Gly-NH_2	1040
Ac-Lys-Trp-Leu-Tyr-His-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Leu-Arg-Thr-Glu-Gly-NH_2	1041
Ac-Lys-Trp-Val-Tyr-His-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Leu-Arg-Thr-Glu-Gly-NH_2	1042
Ac-Lys-Tyr-Ile-Trp-His-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Leu-Arg-Thr-Glu-Gly-NH_2	1043
Ac-Lys-Trp-Ile-Tyr-His-Phe-Thr-Glu-Gly-Ser-Thr-Asp-Leu-Arg-Thr-Glu-Gly-NH_2	1044
Ac-Lys-Trp-Phe-Tyr-His-Ile-Thr-Glu-Gly-Ser-Thr-Asp-Leu-Arg-Thr-Glu-Gly-NH_2	1045
Ac-Lys-Trp-Leu-Tyr-His-Val-Thr-Glu-Gly-Ser-Thr-Asp-Leu-Arg-Thr-Glu-Gly-NH_2	1046

Ac-Lys-Trp-Val-Tyr-His-Tyr-Thr-Glu-Gly-Ser-Thr-Asp-Leu-Arg-Thr-Glu-Gly-NH_2	1047
Ac-Lys-Tyr-Ile-Trp-His-Phe-Thr-Glu-Gly-Ser-Thr-Asp-Leu-Arg-Thr-Glu-Gly-NH_2	1048
Ac-Lys-Tyr-Ile-Trp-His-Ile-Thr-Glu-Gly-Ser-Thr-Asp-Leu-Arg-Thr-Glu-Gly-NH_2	1049
Ac-Lys-Tyr-Ile-Trp-His-Val-Thr-Glu-Gly-Ser-Thr-Asp-Leu-Arg-Thr-Glu-Gly-NH_2	1050
Ac-Lys-Tyr-Ile-Trp-His-Tyr-Thr-Glu-Gly-Ser-Thr-Asp-Leu-Arg-Thr-Glu-Gly-NH_2	1051
Ac-Lys-Phe-Ile-Trp-His-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Leu-Arg-Thr-Glu-Gly-NH_2	1052
Ac-Lys-Leu-Ile-Trp-His-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Leu-Arg-Thr-Glu-Gly-NH_2	1053
Ac-Lys-Ile-Ile-Trp-His-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Leu-Arg-Thr-Glu-Gly-NH_2	1054
Ac-Lys-Tyr-Ile-Trp-Phe-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Leu-Arg-Thr-Glu-Gly-NH_2	1055
Ac-Lys-Trp-Ile-Tyr-Phe-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Leu-Arg-Thr-Glu-Gly-NH_2	1056
Ac-Lys-Trp-Ile-Tyr-Leu-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Leu-Arg-Thr-Glu-Gly-NH_2	1057
Ac-Lys-Trp-Ile-Tyr-His-Phe-Thr-Glu-Gly-Ser-Thr-Asp-Leu-Arg-Thr-Glu-Gly-NH_2	1058
Ac-Lys-Trp-Ile-Tyr-His-Tyr-Thr-Glu-Gly-Ser-Thr-Asp-Leu-Arg-Thr-Glu-Gly-NH_2	1059
Ac-Lys-Trp-Ile-Tyr-His-Ile-Thr-Glu-Gly-Ser-Thr-Asp-Leu-Arg-Thr-Glu-Gly-NH_2	1060
Ac-Lys-Trp-Ile-Tyr-His-Leu-Ser-Glu-Gly-Ser-Thr-Asp-Leu-Arg-Thr-Glu-Gly-NH_2	1061
Ac-Lys-Trp-Ile-Tyr-His-Leu-Thr-Asp-Gly-Ser-Thr-Asp-Leu-Arg-Thr-Glu-Gly-NH_2	1062
Ac-Lys-Trp-Ile-Tyr-His-Leu-Thr-Glu-Gly-Thr-Ser-Asp-Leu-Arg-Thr-Glu-Gly-NH_2	1063
Ac-Lys-Trp-Ile-Tyr-His-Leu-Thr-Glu-Gly-Ser-Thr-Glu-Leu-Arg-Thr-Glu-Gly-NH_2	1064
Ac-Lys-Trp-Ile-Tyr-His-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Phe-Arg-Thr-Glu-Gly-NH_2	1065
Ac-Lys-Trp-Ile-Tyr-His-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Tyr-Arg-Thr-Glu-Gly-NH_2	1066
Ac-Lys-Trp-Ile-Tyr-His-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Ile-Arg-Thr-Glu-Gly-NH_2	1067
Ac-Lys-Trp-Ile-Tyr-His-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Val-Arg-Thr-Glu-Gly-NH_2	1068
Ac-Lys-Trp-Ile-Tyr-His-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Leu-Lys-Thr-Glu-Gly-NH_2	1069
Ac-Lys-Trp-Ile-Tyr-His-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Leu-Arg-	1070

Ser-Glu-Gly-NH_2	
Ac-Lys-Trp-Ile-Tyr-His-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Leu-Arg-Thr-Asp-Gly-NH_2	1071
Ac-Lys-Trp-Ile-Tyr-His-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Ile-Lys-Thr-Glu-Gly-NH_2	1072
Ac-Lys-Trp-Ile-Tyr-His-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Ile-Arg-Ser-Glu-Gly-NH_2	1073
Ac-Lys-Trp-Ile-Tyr-His-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Ile-Lys-Ser-Glu-Gly-NH_2	1074
Ac-Lys-Trp-Ile-Tyr-His-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Ile-Lys-Ser-Asp-Gly-NH_2	1075
Ac-Arg-Trp-Ile-Tyr-His-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Leu-Arg-Thr-Glu-Gly-NH_2	1076
Ac-Arg-Tyr-Ile-Trp-His-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Ile-Arg-Thr-Glu-Gly-NH_2	1077
Ac-Arg-Trp-Ile-Tyr-His-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Ile-Arg-Thr-Asp-Gly-NH_2	1078
Ac-Arg-Trp-Ile-Phe-His-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Ile-Arg-Thr-Glu-Gly-NH_2	1079
Ac-Arg-Trp-Ile-Tyr-His-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Leu-Lys-Thr-Glu-Gly-NH_2	1080
Ac-Arg-Trp-Ile-Tyr-His-Leu-Thr-Asp-Gly-Ser-Thr-Asp-Ile-Arg-Thr-Glu-Gly-NH_2	1081
Ac-Arg-Trp-Ile-Tyr-His-Leu-Thr-Asp-Gly-Ser-Thr-Asp-Leu-Arg-Thr-Glu-Gly-NH_2	1082
Ac-Arg-Trp-Ile-Tyr-Phe-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Ile-Arg-Thr-Glu-Gly-NH_2	1083
Ac-Arg-Trp-Ile-Tyr-Phe-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Leu-Arg-Thr-Glu-Gly-NH_2	1084
Ac-Lys-Trp-Phe-Tyr-His-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Phe-Arg-Thr-Glu-Gly-NH_2	1085
Ac-Arg-Trp-Phe-Tyr-His-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Leu-Arg-Thr-Glu-Gly-NH_2	1086
Ac-Lys-Trp-Ile-Phe-His-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Ile-Arg-Thr-Asp-Gly-NH_2	1087
Ac-Arg-Trp-Ile-Tyr-His-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Ile-Arg-Thr-Asp-Gly-NH_2	1088
Ac-Arg-Trp-Ile-Tyr-His-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Leu-Arg-Thr-Asp-Gly-NH_2	1089
Ac-Lys-Trp-Ile-Tyr-His-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Ile-Lys-Thr-Glu-Gly-NH_2	1090
Ac-Lys-Trp-Ile-Tyr-His-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Ile-Lys-Thr-Asp-Gly-NH_2	1091
Ac-Lys-Trp-Ile-Tyr-His-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Phe-Lys-Thr-Glu-Gly-NH_2	1092
Ac-Lys-Trp-Ile-Tyr-His-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Tyr-Lys-Thr-Glu-Gly-NH_2	1093

Ac-Lys-Trp-Ile-Tyr-His-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Ile-Arg-Thr-Glu-Gly-NH_2	1094
Ac-Lys-Trp-Phe-Tyr-His-Phe-Thr-Glu-Gly-Ser-Thr-Asp-Leu-Arg-Thr-Glu-Gly-NH_2	1095
Ac-Arg-Trp-Phe-Tyr-His-Phe-Thr-Glu-Gly-Ser-Thr-Asp-Leu-Arg-Thr-Glu-Gly-NH_2	1096
Ac-Lys-Trp-Phe-Tyr-His-Phe-Thr-Glu-Gly-Ser-Thr-Asp-Phe-Arg-Thr-Glu-Gly-NH_2	1097
Ac-Lys-Trp-Phe-Tyr-His-Phe-Thr-Asp-Gly-Ser-Thr-Asp-Ile-Arg-Thr-Glu-Gly-NH_2	1098
Ac-Arg-Trp-Phe-Tyr-His-Phe-Thr-Glu-Gly-Ser-Thr-Asp-Leu-Arg-Thr-Glu-Gly-NH_2	1099
Ac-Arg-Trp-Phe-Tyr-His-Phe-Thr-Glu-Gly-Ser-Thr-Asp-Phe-Arg-Thr-Glu-Gly-NH_2	1100
Ac-Arg-Trp-Phe-Tyr-His-Phe-Thr-Glu-Gly-Ser-Thr-Asp-Phe-Arg-Thr-Asp-Gly-NH_2	1101
Ac-Glu-Lys-Cys-Val-Glu-Glu-Phe-Lys-Ser-Leu-Thr-Ser-Cys-Leu-Asp-Ser-Lys-Ala-Phe-NH_2	1102
Ac-Asp-Lys-Cys-Val-Glu-Glu-Phe-Lys-Ser-Leu-Thr-Ser-Cys-Leu-Asp-Ser-Lys-Ala-Phe-NH_2	1103
Ac-Glu-Lys-Cys-Val-Asp-Glu-Phe-Lys-Ser-Leu-Thr-Ser-Cys-Leu-Asp-Ser-Lys-Ala-Phe-NH_2	1104
Ac-Glu-Lys-Cys-Val-Glu-Asp-Phe-Lys-Ser-Leu-Thr-Ser-Cys-Leu-Asp-Ser-Lys-Ala-Phe-NH_2	1105
Ac-Glu-Arg-Cys-Val-Glu-Glu-Phe-Lys-Ser-Leu-Thr-Ser-Cys-Leu-Asp-Ser-Lys-Ala-Phe-NH_2	1106
Ac-Asp-Lys-Cys-Val-Asp-Asp-Phe-Lys-Ser-Leu-Thr-Ser-Cys-Leu-Asp-Ser-Lys-Ala-Phe-NH_2	1107
Ac-Asp-Arg-Cys-Val-Glu-Glu-Phe-Lys-Ser-Leu-Thr-Ser-Cys-Leu-Asp-Ser-Lys-Ala-Phe-NH_2	1108
Ac-Glu-Arg-Cys-Val-Asp-Asp-Phe-Lys-Ser-Leu-Thr-Ser-Cys-Leu-Asp-Ser-Lys-Ala-Phe-NH_2	1109
Ac-Glu-Lys-Cys-Val-Glu-Glu-Phe-Lys-Ser-Phe-Thr-Ser-Cys-Leu-Asp-Ser-Lys-Ala-Phe-NH_2	1110
Ac-Glu-Lys-Cys-Val-Glu-Glu-Phe-Lys-Ser-Ile-Thr-Ser-Cys-Leu-Asp-Ser-Lys-Ala-Phe-NH_2	1111
Ac-Glu-Lys-Cys-Val-Glu-Glu-Phe-Lys-Ser-Val-Thr-Ser-Cys-Leu-Asp-Ser-Lys-Ala-Phe-NH_2	1112
Ac-Glu-Arg-Cys-Val-Glu-Glu-Phe-Lys-Ser-Tyr-Thr-Ser-Cys-Leu-Asp-Ser-Lys-Ala-Phe-NH_2	1113
Ac-Glu-Arg-Cys-Val-Glu-Glu-Phe-Lys-Ser-Phe-Thr-Ser-Cys-Leu-Asp-Ser-Lys-Ala-Phe-NH_2	1114
Ac-Glu-Arg-Cys-Val-Glu-Glu-Phe-Lys-Ser-Ile-Thr-Ser-Cys-Leu-Asp-Ser-Lys-Ala-Phe-NH_2	1115
Ac-Glu-Arg-Cys-Val-Glu-Glu-Phe-Lys-Ser-Val-Thr-Ser-Cys-Leu-Asp-Ser-Lys-Ala-Phe-NH_2	1116
Ac-Glu-Arg-Cys-Val-Glu-Glu-Phe-Lys-Ser-Tyr-Thr-Ser-Cys-Leu-	1117

Asp-Ser-Lys-Ala-Phe-NH_2	
Ac-Glu-Lys-Cys-Val-Glu-Glu-Phe-Lys-Ser-Phe-Thr-Thr-Cys-Leu-Asp-Ser-Lys-Ala-Phe-NH_2	1118
Ac-Glu-Lys-Cys-Val-Glu-Glu-Phe-Lys-Ser-Ile-Ser-Ser-Cys-Leu-Asp-Ser-Lys-Ala-Phe-NH_2	1119
Ac-Glu-Lys-Cys-Val-Glu-Glu-Phe-Lys-Ser-Val-Ser-Thr-Cys-Leu-Asp-Ser-Lys-Ala-Phe-NH_2	1120
Ac-Glu-Lys-Cys-Val-Glu-Glu-Phe-Lys-Ser-Tyr-Thr-Ser-Cys-Leu-Asp-Ser-Lys-Ala-Phe-NH_2	1121
Ac-Glu-Lys-Cys-Val-Glu-Glu-Phe-Lys-Ser-Phe-Thr-Thr-Cys-Leu-Asp-Ser-Lys-Ala-Phe-NH_2	1122
Ac-Glu-Lys-Cys-Val-Glu-Glu-Phe-Lys-Ser-Phe-Ser-Ser-Cys-Leu-Asp-Ser-Lys-Ala-Phe-NH_2	1123
Ac-Glu-Lys-Cys-Val-Glu-Glu-Phe-Lys-Ser-Phe-Thr-Ser-Cys-Leu-Asp-Ser-Lys-Ala-Phe-NH_2	1124
Ac-Glu-Lys-Cys-Val-Glu-Glu-Phe-Lys-Ser-Phe-Thr-Ser-Cys-Leu-Asp-Ser-Lys-Ala-Phe-NH_2	1125
Ac-Glu-Lys-Cys-Val-Glu-Glu-Phe-Lys-Ser-Phe-Thr-Ser-Cys-Leu-Asp-Ser-Lys-Ala-Phe-NH_2	1126
Ac-Glu-Lys-Cys-Val-Glu-Glu-Phe-Lys-Ser-Phe-Thr-Ser-Cys-Phe-Asp-Ser-Lys-Ala-Phe-NH_2	1127
Ac-Glu-Lys-Cys-Val-Glu-Glu-Phe-Lys-Ser-Phe-Thr-Ser-Cys-Phe-Glu-Ser-Lys-Ala-Phe-NH_2	1128
Ac-Glu-Lys-Cys-Val-Glu-Glu-Phe-Lys-Ser-Phe-Thr-Ser-Cys-Leu-Glu-Ser-Lys-Ala-Phe-NH_2	1129
Ac-Glu-Lys-Cys-Val-Glu-Glu-Phe-Lys-Ser-Phe-Thr-Ser-Cys-Ile-Asp-Ser-Lys-Ala-Phe-NH_2	1130
Ac-Glu-Lys-Cys-Val-Glu-Glu-Leu-Lys-Ser-Phe-Thr-Ser-Cys-Phe-Asp-Ser-Lys-Ala-Phe-NH_2	1131
Ac-Asp-Lys-Cys-Val-Glu-Glu-Phe-Lys-Ser-Phe-Thr-Ser-Cys-Phe-Asp-Ser-Lys-Ala-Phe-NH_2	1132
Ac-Asp-Lys-Cys-Val-Glu-Glu-Phe-Lys-Ser-Phe-Thr-Ser-Cys-Phe-Glu-Ser-Lys-Ala-Phe-NH_2	1133
Ac-Glu-Arg-Cys-Val-Glu-Glu-Phe-Lys-Ser-Phe-Thr-Ser-Cys-Phe-Asp-Ser-Lys-Ala-Phe-NH_2	1134
Ac-Glu-Lys-Cys-Phe-Glu-Glu-Phe-Lys-Ser-Phe-Thr-Ser-Cys-Phe-Asp-Ser-Lys-Ala-Phe-NH_2	1135
Ac-Glu-Lys-Cys-Phe-Glu-Glu-Phe-Lys-Ser-Phe-Thr-Ser-Cys-Phe-Glu-Ser-Lys-Ala-Phe-NH_2	1136
Ac-Glu-Lys-Cys-Val-Glu-Glu-Phe-Lys-Ser-Phe-Ser-Ser-Cys-Phe-Glu-Ser-Lys-Ala-Phe-NH_2	1137
Ac-Glu-Lys-Cys-Val-Glu-Glu-Phe-Lys-Ser-Phe-Gln-Ser-Cys-Phe-Asp-Ser-Lys-Ala-Phe-NH_2	1138
Ac-Glu-Lys-Cys-Phe-Glu-Glu-Phe-Lys-Ser-Phe-Gln-Ser-Cys-Phe-Asp-Ser-Lys-Ala-Phe-NH_2	1139
Ac-Glu-Lys-Cys-Val-Glu-Glu-Phe-Lys-Gln-Phe-Thr-Ser-Cys-Phe-Asp-Ser-Lys-Ala-Phe-NH_2	1140

Ac-Glu-Lys-Cys-Val-Glu-Glu-Phe-Lys-Gln-Leu-Thr-Ser-Cys-Leu-Asp-Ser-Lys-Ala-Phe-NH_2	1141
Ac-Glu-Lys-Cys-Phe-Glu-Glu-Phe-Lys-Ser-Phe-Gln-Ser-Cys-Leu-Asp-Ser-Lys-Ala-Phe-NH_2	1142
Ac-Glu-Lys-Cys-Val-Glu-Glu-Phe-Lys-Gln-Phe-Thr-Ser-Cys-Phe-Asp-Ser-Lys-Ala-Phe-NH_2	1143
Ac-Glu-Lys-Cys-Val-Glu-Glu-Phe-Lys-Ser-Phe-Thr-Ser-Cys-Phe-Glu-Ser-Lys-Ala-Phe-NH_2	1144
Ac-Glu-Arg-Cys-Phe-Glu-Glu-Phe-Lys-Ser-Phe-Thr-Ser-Cys-Phe-Asp-Ser-Lys-Ala-Phe-NH_2	1145
Ac-Asp-Lys-Cys-Phe-Glu-Glu-Phe-Lys-Ser-Phe-Thr-Ser-Cys-Phe-Asp-Ser-Lys-Ala-Phe-NH_2	1146
Ac-Glu-Arg-Cys-Val-Glu-Glu-Phe-Lys-Ser-Leu-Thr-Ser-Cys-Leu-Glu-Ser-Lys-Ala-Phe-NH_2	1147
Ac-Glu-Lys-Cys-Val-Glu-Glu-Phe-Lys-Ser-Leu-Thr-Ser-Cys-Leu-Asp-Ser-Lys-Phe-Phe-NH_2	1148
Ac-Glu-Lys-Cys-Phe-Glu-Glu-Phe-Lys-Ser-Phe-Thr-Ser-Cys-Phe-Asp-Ser-Lys-Phe-Phe-NH_2	1149
Ac-Asp-Lys-Cys-Phe-Glu-Glu-Phe-Lys-Ser-Phe-Thr-Ser-Cys-Leu-Asp-Ser-Lys-Phe-Phe-NH_2	1150
Ac-Asp-Lys-Cys-Phe-Glu-Glu-Phe-Lys-Ser-Phe-Thr-Ser-Cys-Leu-Glu-Ser-Lys-Phe-Phe-NH_2	1151
Ac-Asp-Lys-Cys-Phe-Glu-Glu-Leu-Lys-Ser-Phe-Thr-Ser-Cys-Leu-Asp-Ser-Lys-Phe-Phe-NH_2	1152
Ac-Glu-Arg-Cys-Phe-Glu-Glu-Phe-Lys-Ser-Phe-Thr-Ser-Cys-Leu-Asp-Ser-Lys-Phe-Phe-NH_2	1153
Ac-Glu-Lys-Ala-Val-Glu-Glu-Phe-Lys-Ser-Phe-Thr-Ser-Cys-Leu-Asp-Ser-Lys-Ala-Phe-NH_2	1154
Ac-Asp-Lys-Ala-Val-Glu-Glu-Phe-Lys-Ser-Phe-Thr-Ser-Cys-Leu-Asp-Ser-Lys-Phe-Phe-NH_2	1155
Ac-Glu-Lys-Ala-Val-Glu-Glu-Phe-Lys-Ser-Phe-Thr-Ser-Ala-Leu-Asp-Ser-Lys-Ala-Phe-NH_2	1156
Ac-Asp-Lys-Ala-Val-Glu-Glu-Phe-Lys-Ser-Phe-Thr-Ser-Ala-Leu-Asp-Ser-Lys-Ala-Phe-NH_2	1157
Ac-Asp-Arg-Ala-Phe-Glu-Glu-Phe-Lys-Ser-Phe-Thr-Ser-Cys-Leu-Asp-Ser-Lys-Phe-Phe-NH_2	1158
Ac-Asp-Arg-Ala-Phe-Glu-Glu-Phe-Lys-Ser-Phe-Thr-Ser-Ala-Leu-Asp-Ser-Lys-Phe-Phe-NH_2	1159
Ac-Asp-Lys-Cys-Phe-Glu-Glu-Phe-Lys-Ser-Phe-Thr-Ser-Cys-Phe-Glu-Ser-Lys-Phe-Phe-NH_2	1160
Ac-Glu-Lys-Cys-Tyr-Glu-Glu-Phe-Lys-Ser-Phe-Thr-Ser-Cys-Leu-Asp-Ser-Lys-Phe-Phe-NH_2	1161
Ac-Asp-Lys-Cys-Trp-Glu-Glu-Phe-Lys-Ser-Phe-Thr-Ser-Cys-Leu-Asp-Ser-Lys-Phe-Phe-NH_2	1162
Ac-Glu-Lys-Cys-Phe-Glu-Glu-Phe-Lys-Ser-Tyr-Thr-Ser-Cys-Leu-Asp-Ser-Lys-Phe-Phe-NH_2	1163
Ac-Glu-Lys-Cys-Phe-Glu-Glu-Phe-Lys-Ser-Trp-Thr-Ser-Cys-Leu-	1164

Asp-Ser-Lys-Phe-Phe-NH_2	
Ac-Glu-Lys-Cys-Val-Glu-Glu-Phe-Lys-Ser-Trp-Thr-Ser-Cys-Leu-Asp-Ser-Lys-Ala-Phe-NH_2	1165
Ac-Asp-Lys-Cys-Phe-Glu-Glu-Phe-Lys-Ser-Trp-Thr-Ser-Cys-Leu-Asp-Ser-Lys-Ala-Phe-NH_2	1166

[0206] Other suitable peptides include, but are not limited to the peptides of Table 18.

[0207] Table 18. Illustrative peptides having an improved hydrophobic phase.

Name	Sequence	SEQ ID NO
V2W3A5F1017-D-4F	Ac-Asp-Val-Trp-Lys-Ala-Ala-Tyr-Asp-Lys-Phe-Ala-Glu-Lys-Phe-Lys-Glu-Phe-Phe-NH2	1167
V2W3F10-D-4F	Ac-Asp-Val-Trp-Lys-Ala-Phe-Tyr-Asp-Lys-Phe-Ala-Glu-Lys-Phe-Lys-Glu-Ala-Phe-NH2	1168
W3-D-4F	Ac-Asp-Phe-Trp-Lys-Ala-Phe-Tyr-Asp-Lys-Val-Ala-Glu-Lys-Phe-Lys-Glu-Ala-Phe-NH2	1169

[0208] The peptides described here (V2W3A5F10,17-D-4F; V2W3F10-D-4F; W3-D-4F) may be more potent than the original D-4F.

[0209] Still other suitable peptides include, but are not limited to: P^1-Dimethyltyrosine-D-Arg-Phe-Lys-P^2 (SEQ ID NO:1170) and P^1-Dimethyltyrosine-Arg-Glu-Leu-P^2 where P1 and P2 are protecting groups as described herein. In certain embodiments, these peptides include, but are not limited to BocDimethyltyrosine-D-Arg-Phe-Lys(OtBu) and BocDimethyltyrosine-Arg-Glu-Leu(OtBu).

[0210] In certain embodiments, the peptides of this invention include peptides comprising or consisting of the amino acid sequence LAEYHAK (SEQ ID NO:1171) comprising at least one D amino acid and/or at least one or two terminal protecting groups. In certain embodiments, this invention includes a peptide that ameliorates one or more symptoms of an inflammatory condition, wherein the peptide: ranges in length from about 3 to about 10 amino acids; comprises an amino acid sequence where the sequence comprises acidic or basic amino acids alternating with aromatic or hydrophobic amino acids; comprises hydrophobic terminal amino acids or terminal amino acids bearing a hydrophobic protecting group. In certain embodiments, the peptide is not the sequence LAEYHAK (SEQ ID NO:1172) comprising all L amino acids; where the peptide converts pro-

inflammatory HDL to anti-inflammatory HDL and/or makes anti-inflammatory HDL more anti-inflammatory.

[0211] It is also noted that the peptides listed in the Tables herein are not fully inclusive. Using the teaching provided herein, other suitable peptides can routinely be produced (*e.g.*, by conservative or semi-conservative substitutions (*e.g.*, D replaced by E), extensions, deletions, and the like). Thus, for example, one embodiment utilizes truncations of any one or more of peptides identified by SEQ ID Nos:1010-1038.

[0212] Longer peptides are also suitable. Such longer peptides may entirely form a class G or G* amphipathic helix, or the G amphipathic helix (helices) can form one or more domains of the peptide. In addition, this invention contemplates multimeric versions of the peptides. Thus, for example, the peptides illustrated in the tables herein can be coupled together (directly or through a linker (*e.g.*, a carbon linker, or one or more amino acids) with one or more intervening amino acids). Suitable linkers include, but are not limited to Proline (-Pro-), Gly_4Ser_3 (SEQ ID NO: 1173), and the like. Thus, one illustrative multimeric peptide according to this invention is (D-J336)-P-(D-J336) (*i.e.* Ac-L-L-E-Q-L-N-E-Q-F-N-W-V-S-R-L-A-N-L-T- Q-G-E-**P**-L-L-E-Q-L-N-E-Q-F-N-W-V-S-R-L-A-N-L-T-Q-G-E-NH_2, SEQ ID NO: 1174).

[0213] This invention also contemplates the use of "hybrid" peptides comprising a one or more G or G* amphipathic helical domains and one or more class A amphipathic helices. Suitable class A amphipathic helical peptides are described in PCT publication WO 02/15923. Thus, by way of illustration, one such "hybrid" peptide is (D-J336)-Pro-(4F) (*i.e.* Ac-L-L-E-Q-L-N-E-Q-F-N-W-V-S-R-L-A-N-L-T-Q-G-E-**P**-D-W-F-K-A-F-Y-D-K-V-A-E-K-F-K-E-A-F-NH_2, SEQ ID NO: 1175), and the like.

[0214] Using the teaching provided herein, one of skill can routinely modify the illustrated amphipathic helical peptides to produce other suitable apo J variants and/or amphipathic G and/or A helical peptides of this invention. For example, routine conservative or semi-conservative substitutions (*e.g.*, E for D) can be made of the existing amino acids. The effect of various substitutions on lipid affinity of the resulting peptide can be predicted using the computational method described by Palgunachari *et al.* (1996) *Arteriosclerosis, Thrombosis, & Vascular Biology* 16: 328-338. The peptides can be lengthened or shortened as long as the class helix structure(s) are preserved. In addition,

substitutions can be made to render the resulting peptide more similar to peptide(s) endogenously produced by the subject species.

[0215] While, in preferred embodiments, the peptides of this invention utilize naturally-occurring amino acids or D forms of naturally occurring amino acids, substitutions with non-naturally occurring amino acids (*e.g.*, methionine sulfoxide, methionine methylsulfonium, norleucine, episilon-aminocaproic acid, 4-aminobutanoic acid, tetrahydroisoquinoline-3-carboxylic acid, 8-aminocaprylic acid, 4-aminobutyric acid, Lys(N(epsilon)-trifluoroacetyl), α-aminoisobutyric acid, and the like) are also contemplated.

[0216] New peptides can be designed and/or evaluated using computational methods. Computer programs to identify and classify amphipathic helical domains are well known to those of skill in the art and many have been described by Jones *et al.*(1992) *J. Lipid Res.* 33: 287-296). Such programs include, but are not limited to the helical wheel program (WHEEL or WHEEL/SNORKEL), helical net program (HELNET, HELNET/SNORKEL, HELNET/Angle), program for addition of helical wheels (COMBO or COMBO/SNORKEL), program for addition of helical nets (COMNET, COMNET/SNORKEL, COMBO/SELECT, COMBO/NET), consensus wheel program (CONSENSUS, CONSENSUS/SNORKEL), and the like.

F) Blocking groups and D residues.

[0217] While the various peptides and/or amino acid pairs described herein may be shown with no protecting groups, in certain embodiments (*e.g.*, for oral administration), they can bear one, two, three, four, or more protecting groups. The protecting groups can be coupled to the C- and/or N-terminus of the peptide(s) and/or to one or more internal residues comprising the peptide(s) (*e.g.*, one or more R-groups on the constituent amino acids can be blocked). Thus, for example, in certain embodiments, any of the peptides described herein can bear, *e.g.*, an acetyl group protecting the amino terminus and/or an amide group protecting the carboxyl terminus. One example of such a "dual protected peptide is Ac-L-L-E-Q-L-N-E-Q-F-N-W-V-S-R-L-A-N-L-T-Q-G-E-NH_2 (SEQ ID NO:1010 with blocking groups), either or both of these protecting groups can be eliminated and/or substituted with another protecting group as described herein.

[0218] Without being bound by a particular theory, it was a discovery of this invention that blockage, particularly of the amino and/or carboxyl termini of the subject peptides of this invention greatly improves oral delivery and significantly increases serum half-life. It was also a surprising discovery, however, that in certain embodiments, particular when used in conjunction with the salicylanilides (*e.g.*, niclosamide) and other delivery agents described herein, any or all of the protecting groups can be omitted and the peptides are still orally administrable. Nevertheless, in certain embodiments the peptides, even when formulated with and/or administered in conjunction with a salicylanilide or other delivery agent as described herein bears one or more protecting groups (*e.g.*, terminal protecting groups).

[0219] A wide number of protecting groups are suitable for this purpose. Such groups include, but are not limited to acetyl, amide, and alkyl groups with acetyl and alkyl groups being particularly preferred for N-terminal protection and amide groups being preferred for carboxyl terminal protection. In certain particularly preferred embodiments, the protecting groups include, but are not limited to alkyl chains as in fatty acids, propeonyl, formyl, and others. Particularly preferred carboxyl protecting groups include amides, esters, and ether-forming protecting groups. In one preferred embodiment, an acetyl group is used to protect the amino terminus and an amide group is used to protect the carboxyl terminus. These blocking groups enhance the helix-forming tendencies of the peptides. Certain particularly preferred blocking groups include alkyl groups of various lengths, *e.g.*, groups having the formula: CH_3-$(CH_2)_n$-CO- where n ranges from about 1 to about 20, preferably from about 1 to about 16 or 18, more preferably from about 3 to about 13, and most preferably from about 3 to about 10.

[0220] In certain particularly preferred embodiments, the protecting groups include, but are not limited to alkyl chains as in fatty acids, propeonyl, formyl, and others. Particularly preferred carboxyl protecting groups include amides, esters, and ether-forming protecting groups. In one preferred embodiment, an acetyl group is used to protect the amino terminus and an amide group is used to protect the carboxyl terminus. These blocking groups enhance the helix-forming tendencies of the peptides. Certain particularly preferred blocking groups include alkyl groups of various lengths, *e.g.*, groups having the formula: CH_3-$(CH_2)_n$-CO- where n ranges from about 3 to about 20, preferably from about 3

to about 16, more preferably from about 3 to about 13, and most preferably from about 3 to about 10.

[0221] Other protecting groups include, but are not limited to Fmoc, t-butoxycarbonyl (*t*-BOC), 9-fluoreneacetyl group, 1-fluorenecarboxylic group, 9-florenecarboxylic group, 9-fluorenone-1-carboxylic group, benzyloxycarbonyl, Xanthyl (Xan), Trityl (Trt), 4-methyltrityl (Mtt), 4-methoxytrityl (Mmt), 4-methoxy-2,3,6-trimethyl-benzenesulphonyl (Mtr), Mesitylene-2-sulphonyl (Mts), 4,4-dimethoxybenzhydryl (Mbh),Tosyl (Tos), 2,2,5,7,8-pentamethyl chroman-6-sulphonyl (Pmc), 4-methylbenzyl (MeBzl), 4-methoxybenzyl (MeOBzl), Benzyloxy (BzlO), Benzyl (Bzl), Benzoyl (Bz), 3-nitro-2-pyridinesulphenyl (Npys), 1-(4,4-dimentyl-2,6-diaxocyclohexylidene)ethyl (Dde), 2,6-dichlorobenzyl (2,6-DiCl-Bzl), 2-chlorobenzyloxycarbonyl (2-Cl-Z), 2-bromobenzyloxycarbonyl (2-Br-Z), Benzyloxymethyl (Bom), cyclohexyloxy (cHxO),t-butoxymethyl (Bum), t-butoxy (tBuO), t-Butyl (tBu), Acetyl (Ac), and Trifluoroacetyl (TFA).

[0222] Protecting/blocking groups are well known to those of skill as are methods of coupling such groups to the appropriate residue(s) comprising the peptides of this invention (*see, e.g.*, Greene *et al.*, (1991) *Protective Groups in Organic Synthesis, 2nd ed.*, John Wiley & Sons, Inc. Somerset, N.J.). In one preferred embodiment, for example, acetylation is accomplished during the synthesis when the peptide is on the resin using acetic anhydride. Amide protection can be achieved by the selection of a proper resin for the synthesis. During the synthesis of the peptides described herein in the examples, rink amide resin was used. After the completion of the synthesis, the semipermanent protecting groups on acidic bifunctional amino acids such as Asp and Glu and basic amino acid Lys, hydroxyl of Tyr are all simultaneously removed. The peptides released from such a resin using acidic treatment comes out with the n-terminal protected as acetyl and the carboxyl protected as NH_2 and with the simultaneous removal of all of the other protecting groups.

[0223] In certain particularly preferred embodiments, the peptides comprise one or more D-form (dextro rather than levo) amino acids as described herein. In certain embodiments at least two enantiomeric amino acids, more preferably at least 4 enantiomeric amino acids and most preferably at least 8 or 10 enantiomeric amino acids are "D" form

amino acids. In certain embodiments every other, ore even every amino acid (*e.g.*, every enantiomeric amino acid) of the peptides described herein is a D-form amino acid.

[0224] In certain embodiments at least 50% of the enantiomeric amino acids are "D" form, more preferably at least 80% of the enantiomeric amino acids are "D" form, and most preferably at least 90% or even all of the enantiomeric amino acids are "D" form amino acids.

G) Peptide Mimetics.

[0225] In addition to the peptides described herein, it is believed that the salicylanilides (*e.g.*, niclosamide) and other delivery agents described herein are also useful to improve *in vivo* activity of orally delivered peptide mimetics. Peptide analogs are commonly used in the pharmaceutical industry as non-peptide drugs with properties analogous to those of the template peptide. These types of non-peptide compound are termed "peptide mimetics" or "peptidomimetics" (Fauchere (1986) *Adv. Drug Res.* 15: 29; Veber and Freidinger (1985) *TINS* p.392; and Evans *et al.* (1987) *J. Med. Chem.* 30: 1229) and are usually developed with the aid of computerized molecular modeling. Peptide mimetics that are structurally similar to therapeutically useful peptides may be used to produce an equivalent therapeutic or prophylactic effect.

[0226] Generally, peptidomimetics are structurally similar to a paradigm polypeptide (*e.g.*, SEQ ID NO:5 shown in Table 1), but have one or more peptide linkages optionally replaced by a linkage selected from the group consisting of: $-CH_2NH-$, $-CH_2S-$, $-CH_2-CH_2-$, -CH=CH- (cis and trans), $-COCH_2-$, $-CH(OH)CH_2-$, $-CH_2SO-$, *etc.* by methods known in the art and further described in the following references: Spatola (1983) p. 267 in *Chemistry and Biochemistry of Amino Acids, Peptides, and Proteins*, B. Weinstein, eds., Marcel Dekker, New York,; Spatola (1983) *Vega Data* 1(3) *Peptide Backbone Modifications*. (general review); Morley (1980) *Trends Pharm Sci* pp. 463-468 (general review); Hudson *et al.* (1979) *Int J Pept Prot Res* 14:177-185 ($-CH_2NH-$, CH_2CH_2-); Spatola et al. (1986) *Life Sci* 38:1243-1249 ($-CH_2-S$); Hann, (1982) *J Chem Soc Perkin Trans* I 307-314 (-CH-CH-, cis and trans); Almquist *et al.* (1980) *J Med Chem.* 23:1392-1398 ($-COCH_2-$); Jennings-White *et al.* (1982) *Tetrahedron Lett.* 23:2533 ($-COCH_2-$); Szelke et al., European Appln. EP 45665 (1982) CA: 97:39405 (1982) (-CH(OH)CH2-);

Holladay *et al.* (1983) *Tetrahedron Lett* 24:4401-4404 (-C(OH)CH_2-); and Hruby (1982) *Life Sci.*, 31:189-199 (-CH_2-S-)).

[0227] One particularly preferred non-peptide linkage is -CH_2NH-. Such peptide mimetics may have significant advantages over polypeptide embodiments, including, for example: more economical production, greater chemical stability, enhanced pharmacological properties (half-life, absorption, potency, efficacy, *etc.*), reduced antigenicity, and others.

[0228] In addition, circularly permutations of the peptides described herein or constrained peptides (including cyclized peptides) comprising a consensus sequence or a substantially identical consensus sequence variation may be generated by methods known in the art (Rizo and Gierasch (1992) *Ann. Rev. Biochem.* 61: 387); for example, by adding internal cysteine residues capable of forming intramolecular disulfide bridges which cyclize the peptide.

H) Small organic molecules.

[0229] In addition to the peptides described herein, it is believed that the salicylanilides (*e.g.*, niclosamide) and other delivery agents described herein are also useful to improve *in vivo* activity (apparent activity) of orally delivered small organic molecules, *e.g.*, as described in copending application USSN 60/600,925, filed August 11, 2004. In various embodiments the small organic molecules are similar to, and in certain cases, mimetics of the tetra- and penta-peptides described in copending application USSN 10/649,378, filed on August 26, 2003 and USSN 60/494,449, filed on August 11.

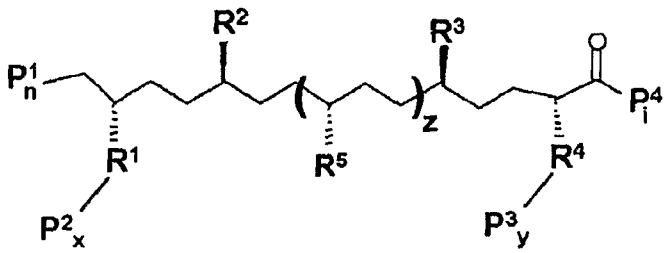
[0230] The small organic molecules of this invention typically have molecular weights less than about 900 Daltons. Typically the molecules are highly soluble in ethyl acetate (*e.g.*, at concentrations equal to or greater than 4 mg/mL), and also are soluble in aqueous buffer at pH 7.0.

[0231] Contacting phospholipids such as 1,2-dimyristoyl-*sn*-glycero-3-phosphocholine (DMPC), with the small organic molecules of this invention in an aqueous environment typically results in the formation of particles with a diameter of approximately 7.5 nm (± 0.1 nm). In addition, stacked bilayers are often formed with a bilayer dimension on the order of 3.4 to 4.1 nm with spacing between the bilayers in the stack of

approximately 2 nm. Vesicular structures of approximately 38 nm are also often formed. Moreover, when the molecules of this invention are administered to a mammal they render HDL more anti-inflammatory and mitigate one or more symptoms of atherosclerosis and/or other conditions characterized by an inflammatory response.

[0232] Thus, in certain embodiments, the small organic molecule is one that ameliorates one or more symptoms of a pathology characterized by an inflammatory response in a mammal (*e.g.*, atherosclerosis), where the small molecule is soluble in ethyl acetate at a concentration greater than 4mg/mL, is soluble in aqueous buffer at pH 7.0, and, when contacted with a phospholipid in an aqueous environment, forms particles with a diameter of approximately 7.5 nm and forms stacked bilayers with a bilayer dimension on the order of 3.4 to 4.1 nm with spacing between the bilayers in the stack of approximately 2 nm, and has a molecular weight les than 900 daltons.

[0233] In certain embodiment, the molecule has the formula:



I.

where P^1, P^2, P^3, and P^4 are independently selected hydrophobic protecting groups; R^1 and $R^4$are independently selected amino acid R groups; n, i, x, y, and z are independently zero or 1 such that when n and x are both zero, R^1 is a hydrophobic group and when y and i are both zero, R^4 is a hydrophobic group; R^2 and R^3 are acidic or basic groups at pH 7.0 such that when R^2 is acidic, R^3 is basic and when R^2 is basic, R^3 is acidic; and R^5, when present is selected from the group consisting of an aromatic group, an aliphatic group, a positively charged group, or a negatively charged group. In certain embodiments, R^2 or R^3 is $-(CH_2)j-COOH$ where j=1, 2, 3, or 4 and/or $-(CH_2)j-NH_2$ where j = 1, 2, 3, 4, or 5, or $-(CH_2)j-NH-C(=NH)-NH_2$ where n= 1, 2, 3 or 4. In certain embodiments, R^2, R^3, and R^5, when present, are amino acid R groups. Thus, for example, In various embodiments R^2 and R^3 are

independently an aspartic acid R group, a glutamic acid R group, a lysine R group, a histidine R group, or an arginine R group (*e.g.*, as illustrated in Table 1).

[0234] In certain embodiments, R^1 is selected from the group consisting of a Lys R group, a Trp R group, a Phe R group, a Leu R group, an Orn R group, pr a norLeu R group. In certain embodiments, R^4 is selected from the group consisting of a Ser R group, a Thr R group, an Ile R group, a Leu R group, a norLeu R group, a Phe R group, or a Tyr R group.

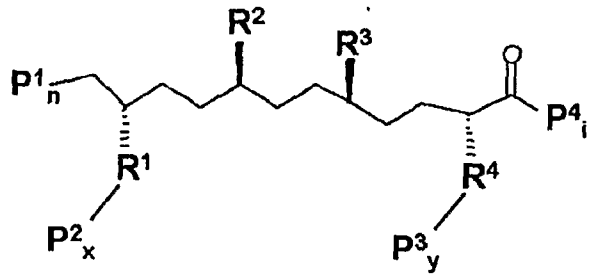
[0235] In various embodiments x is 1, and R^5 is an aromatic group (*e.g.*, a Trp R group).

[0236] In various embodiments at least one of n, x, y, and i is 1 and P^1, P^2, P^3, and P^4 when present, are independently selected from the group consisting of polyethylene glycol (PEG), an acetyl, amide, a 3 to 20 carbon alkyl group, fmoc, 9-fluoreneacetyl group, 1-fluorenecarboxylic group, 9-fluorenecarboxylic, 9-fluorenone-1-carboxylic group, benzyloxycarbonyl, xanthyl (Xan), Trityl (Trt), 4-methyltrityl (Mtt), 4-methoxytrityl (Mmt), 4-methoxy-2,3,6-trimethyl-benzenesulphonyl (Mtr), Mesitylene-2-sulphonyl (Mts),-4,4-dimethoxybenzhydryl (Mbh),Tosyl (Tos), 2,2,5,7,8-pentamethyl chroman-6-sulphonyl (Pmc), 4-methylbenzyl (MeBzl), 4-methoxybenzyl (MeOBzl), benzyloxy (BzlO), benzyl (Bzl), benzoyl (Bz), 3-nitro-2-pyridinesulphenyl (Npys), 1-(4,4-dimethyl-2,6-dioxocyclohexylidene)ethyl (Dde), 2,6-dichlorobenzyl (2,6-DiCl-Bzl), 2-chlorobenzyloxycarbonyl (2-Cl-Z), 2-bromobenzyloxycarbonyl (2-Br-Z), benzyloxymethyl (Bom), t-butoxycarbonyl (Boc), cyclohexyloxy (cHxO),t-butoxymethyl (Bum), t-butoxy (tBuO), t-Butyl (tBu), a propyl group, a butyl group, a pentyl group, a hexyl group, and trifluoroacetyl (TFA). In certain embodiments, P^1 when present and/or P^2 when present are independently selected from the group consisting of Boc-, Fmoc-, and Nicotinyl- and/or P^3 when present and/or P^4 when present are independently selected from the group consisting of *t*Bu, and O*t*Bu.

[0237] While a number of protecting groups (P^1, P^2, P^3, P^4) are illustrated above, this list is intended to be illustrative and not limiting. In view of the teachings provided herein, a number of other protecting/blocking groups will also be known to one of skill in the art. Such blocking groups can be selected to minimize digestion (*e.g.*, for oral pharmaceutical delivery), and/or to increase uptake/bioavailability (*e.g.*, through mucosal surfaces in nasal delivery, inhalation therapy, rectal administration), and/or to increase

serum/plasma half-life. In certain embodiments, the protecting groups can be provided as an excipient or as a component of an excipient.

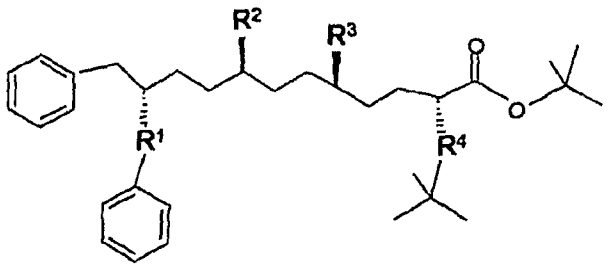
[0238] In certain embodiments, z is zero and the molecule has the formula:



II.

where P^1, P^2, P^3, P^4, R^1, R^2, R^3, R^4, n, x, y, and i are as described above.

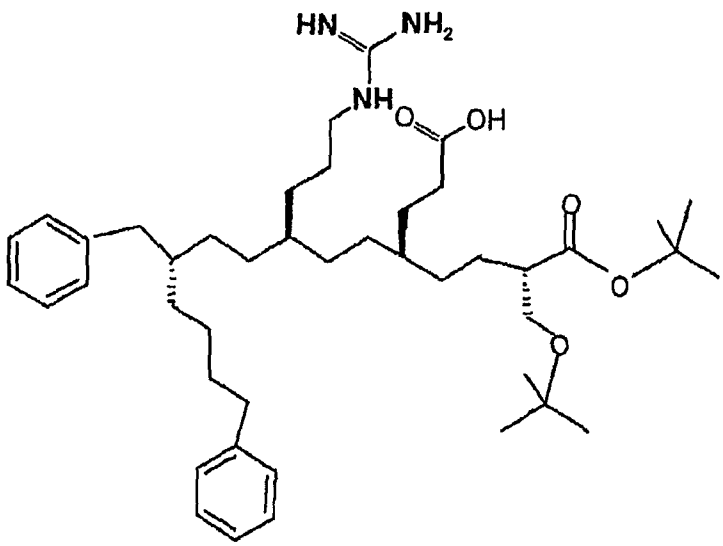
[0239] In certain embodiments, z is zero and the molecule has the formula:



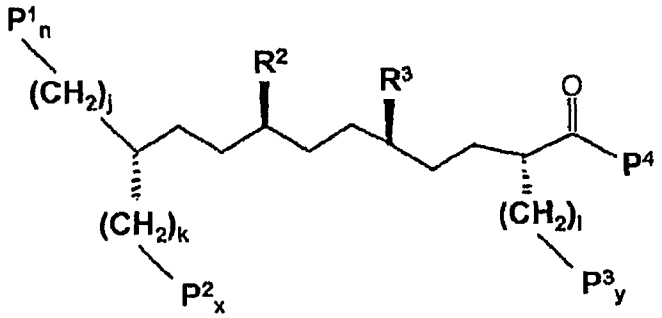
III.

where R^1, R^2, R^3, and R^4 are as described above .

[0240] In one embodiment, the molecule has the formula:



[0241] In certain embodiments, this invention contemplates small molecules having one or more of the physical and/or functional properties described herein and having the formula:



where P^1, P^2, P^3, and P^4 are independently selected hydrophobic protecting groups as described above, n, x, and y are independently zero or 1; j, k, and l are independently zero, 1, 2, 3, 4, or 5; and R^2 and R^3 are acidic or basic groups at pH 7.0 such that when R^2 is acidic, R^3 is basic and when R^2 is basic, R^3 is acidic. In certain preferred embodiments, the small molecule is soluble in water; and the small molecule has a molecular weight less than about 900 Daltons. In certain embodiments, n, x, y, j, and l are 1; and k is 4.

[0242] In certain embodiments, P^1 and/or P^2 are aromatic protecting groups. In certain embodiments, R^2 and R^3 are amino acid R groups, *e.g.*, as described above. In various embodiments least one of n, x, and y, is 1 and P^1, P^2, P^3 and P^4 when present, are independently protecting groups, *e.g.*, as described above. In certain embodiments the protecting groups, when present, are independently selected from the group consisting of polyethylene glycol (PEG), an acetyl, amide, 3 to 20 carbon alkyl groups, Fmoc, 9-fluoreneacetyl group, 1-fluorenecarboxylic group, 9-fluorenecarboxylic, 9-fluorenone-1-carboxylic group, benzyloxycarbonyl, Xanthyl (Xan), Trityl (Trt), 4-methyltrityl (Mtt), 4-methoxytrityl (Mmt), 4-methoxy-2,3,6-trimethyl-benzenesulphonyl (Mtr), Mesitylene-2-sulphonyl (Mts),-4,4-dimethoxybenzhydryl (Mbh),Tosyl (Tos), 2,2,5,7,8-pentamethyl chroman-6-sulphonyl (Pmc), 4-methylbenzyl (MeBzl), 4-methoxybenzyl (MeOBzl), benzyloxy (BzlO), benzyl (Bzl), benzoyl (Bz), 3-nitro-2-pyridinesulphenyl (Npys), 1-(4,4-dimethyl-2,6-dioxocyclohexylidene)ethyl (Dde), 2,6-dichlorobenzyl (2,6-DiCl-Bzl), 2-chlorobenzyloxycarbonyl (2-Cl-Z), 2-bromobenzyloxycarbonyl (2-Br-Z), benzyloxymethyl (Bom), t-butoxycarbonyl (Boc), cyclohexyloxy (cHxO),t-butoxymethyl (Bum), t-butoxy (tBuO), t-Butyl (tBu), a propyl group, a butyl group, a pentyl group, a hexyl group, and

trifluoroacetyl (TFA). In certain embodiments, P^1 when present and/or P^2 when present are independently selected from the group consisting of Boc-, Fmoc-, and Nicotinyl- and/or P^3 when present and/or P^4 when present are independently selected from the group consisting of *t*Bu, and O*t*Bu.

IV. Pharmaceutical formulations.

A) Pharmaceutical formulations.

[0243] In order to carry out the methods of the invention, one or more therapeutic peptides, mimetics, or small organic molecules described herein are administered in conjunction with a salicylanilide (*e.g.*, niclosamide or niclosamide analogue) or one of the other delivery agents described herein to a mammal, *e.g.*, to an individual diagnosed as having one or more symptoms of atherosclerosis, or as being at risk for atherosclerosis and or the various other pathologies described herein.

[0244] In various embodiments the "active agent(s)", therapeutic peptides, mimetics, or small organic molecules described herein, are formulated in combination with one or more of the salicylanilides (*e.g.*, niclosamide or niclosamide analogue) or one of the other delivery agents described herein. In certain embodiments one or more active agent(s) are combined with one or more salicylanilides (*e.g.*, niclosamide or niclosamide analogs) to form an adduct. The active agent(s) can be administered in the "native" form or, if desired, in the form of salts, esters, amides, prodrugs, derivatives, and the like, provided the salt, ester, amide, prodrug or derivative is suitable pharmacologically, *i.e.*, effective in the present method. Salts, esters, amides, prodrugs and other derivatives of the active agents can be prepared using standard procedures known to those skilled in the art of synthetic organic chemistry and described, for example, by March (1992) *Advanced Organic Chemistry; Reactions, Mechanisms and Structure*, 4th Ed. N.Y. Wiley-Interscience.

[0245] Similarly, the delivery agent(s) can also be formulated as salts, esters, amides, and the like.

[0246] Methods of formulating such derivatives are known to those of skill in the art. For example, the disulfide salts of a number of delivery agents are described in PCT Publication WO 00/059863 which is incorporated herein by reference. Similarly, acid salts of therapeutic peptides, mimetics, and small organic molecules can be prepared from the

free base using conventional methodology, that typically involves reaction with a suitable acid. Generally, the base form of the drug is dissolved in a polar organic solvent such as methanol or ethanol and the acid is added thereto. The resulting salt either precipitates or can be brought out of solution by addition of a less polar solvent. Suitable acids for preparing acid addition salts include both organic acids, *e.g.*, acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like, as well as inorganic acids, *e.g.*, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. An acid addition salt may be reconverted to the free base by treatment with a suitable base. Particularly preferred acid addition salts of the active agents herein are halide salts, such as may be prepared using hydrochloric or hydrobromic acids. Conversely, preparation of basic salts of the active agents of this invention are prepared in a similar manner using a pharmaceutically acceptable base such as sodium hydroxide, potassium hydroxide, ammonium hydroxide, calcium hydroxide, trimethylamine, or the like. Particularly preferred basic salts include alkali metal salts, *e.g.*, the sodium salt, and copper salts.

[0247] Preparation of esters typically involves functionalization of hydroxyl and/or carboxyl groups which may be present within the molecular structure of the drug. The esters are typically acyl-substituted derivatives of free alcohol groups, *i.e.*, moieties that are derived from carboxylic acids of the formula RCOOH where R is alky, and preferably is lower alkyl. Esters can be reconverted to the free acids, if desired, by using conventional hydrogenolysis or hydrolysis procedures.

[0248] Amides and prodrugs can also be prepared using techniques known to those skilled in the art or described in the pertinent literature. For example, amides may be prepared from esters, using suitable amine reactants, or they may be prepared from an anhydride or an acid chloride by reaction with ammonia or a lower alkyl amine. Prodrugs are typically prepared by covalent attachment of a moiety that results in a compound that is therapeutically inactive until modified by an individual's metabolic system.

[0249] The active agents identified herein are useful for parenteral, topical, oral, nasal (or otherwise inhaled), rectal, or local administration, such as by aerosol or

transdermally, for prophylactic and/or therapeutic treatment of one or more of the pathologies/indications described herein (*e.g.*, atherosclerosis and/or symptoms thereof). The pharmaceutical compositions can be administered in a variety of unit dosage forms depending upon the method of administration. Suitable unit dosage forms, include, but are not limited to powders, tablets, pills, capsules, lozenges, suppositories, patches, nasal sprays, injectibles, implantable sustained-release formulations, lipid complexes, *etc.*

[0250] In addition to administration in conjunction with or formulation with one or more delivery agents, the active agents of this invention can also be combined with a pharmaceutically acceptable carrier (excipient) to form a pharmacological composition. Pharmaceutically acceptable carriers can contain one or more physiologically acceptable compound(s) that act, for example, to stabilize the composition or to increase or decrease the absorption of the active agent(s). Physiologically acceptable compounds can include, for example, carbohydrates, such as glucose, sucrose, or dextrans, antioxidants, such as ascorbic acid or glutathione, chelating agents, low molecular weight proteins, protection and uptake enhancers such as lipids, compositions that reduce the clearance or hydrolysis of the active agents, or excipients or other stabilizers and/or buffers.

[0251] Other physiologically acceptable compounds, particularly of use in the preparation of tablets, capsules, gel caps, and the like include, but are not limited to binders, diluent/fillers, disentegrants, lubricants, susupending agents, and the like.

[0252] In certain embodiments, to manufacture an oral dosage form (*e.g.*, a tablet), an excipient (e.g., lactose, sucrose, starch, mannitol, etc.), an optional disintegrator (e.g. calcium carbonate, carboxymethylcellulose calcium, sodium starch glycollate, crospovidone etc.), a binder (e.g. alpha-starch, gum arabic, microcrystalline cellulose, carboxymethylcellulose, polyvinylpyrrolidone, hydroxypropylcellulose, cyclodextrin, *etc.*), and an optional lubricant (e.g., talc, magnesium stearate, polyethylene glycol 6000, etc.), for instance, are added to the active component or components (*e.g.*, active peptide and salicylanilide) and the resulting composition is compressed. Where necessary, the compressed product is coated, *e.g.*, known methods for masking the taste or for enteric dissolution or sustained release. Suitable coating materials include, but are not limited to ethyl-cellulose, hydroxymethylcellulose, polyoxyethylene glycol, cellulose acetate

phthalate, hydroxypropylmethylcellulose phthalate, and Eudragit (Rohm & Haas, Germany; methacrylic-acrylic copolymer).

[0253] Other physiologically acceptable compounds include wetting agents, emulsifying agents, dispersing agents or preservatives that are particularly useful for preventing the growth or action of microorganisms. Various preservatives are well known and include, for example, phenol and ascorbic acid. One skilled in the art would appreciate that the choice of pharmaceutically acceptable carrier(s), including a physiologically acceptable compound depends, for example, on the route of administration of the active agent(s) and on the particular physio-chemical characteristics of the active agent(s).

[0254] In certain embodiments the excipients are sterile and generally free of undesirable matter. These compositions can be sterilized by conventional, well-known sterilization techniques. For various oral dosage form excipients such as tablets and capsules sterility is not required. The USP/NF standard is usually sufficient.

[0255] In therapeutic applications, the compositions of this invention are administered, *e.g.*, orally administered, to a patient suffering from one or more symptoms of the one or more pathologies described herein, or at risk for one or more of the pathologies described herein in an amount sufficient to prevent and/or cure and/or or at least partially prevent or arrest the disease and/or its complications. An amount adequate to accomplish this is defined as a "therapeutically effective dose." Amounts effective for this use will depend upon the severity of the disease and the general state of the patient's health. Single or multiple administrations of the compositions may be administered depending on the dosage and frequency as required and tolerated by the patient. In any event, the composition should provide a sufficient quantity of the active agents of the formulations of this invention to effectively treat (ameliorate one or more symptoms) the patient.

[0256] The concentration of active agent(s) can vary widely, and will be selected primarily based on activity of the active ingredient(s), body weight and the like in accordance with the particular mode of administration selected and the patient's needs. Concentrations, however, will typically be selected to provide dosages ranging from about 0.1 or 1 mg/kg/day to about 50 mg/kg/day and sometimes higher. Typical dosages range from about 3 mg/kg/day to about 3.5 mg/kg/day, preferably from about 3.5 mg/kg/day to about 7.2 mg/kg/day, more preferably from about 7.2 mg/kg/day to about 11.0 mg/kg/day,

and most preferably from about 11.0 mg/kg/day to about 15.0 mg/kg/day. In certain preferred embodiments, dosages range from about 10 mg/kg/day to about 50 mg/kg/day. In certain embodiments, dosages range from about 20 mg to about 50 mg given orally twice daily. It will be appreciated that such dosages may be varied to optimize a therapeutic regimen in a particular subject or group of subjects.

[0257] In certain embodiments, the active agents of this invention are administered orally (*e.g.*, via a tablet, capsule, caplet, gel cap, *etc.*). It was a surprising discovery that therapeutic peptides can be orally administered and achieve therapeutically effective levels, particularly when administered with a salicylanilide (*e.g.*, niclosamide or a niclosamide analogue) or one of the other delivery agents described herein. It was particularly surprising that when so administered, the therapeutic peptide can be an L-form peptide and need not bear protecting groups. The combination of therapeutic peptide with a salicylanilide or other delivery agent is not limited to unprotected L-form peptides. To the contrary, the use salicylanilides and/or other delivery agent(s) with L-form peptides bearing one or more protecting groups, D-form peptides, and D-form peptides bearing one or more protecting groups is also contemplated.

[0258] In certain embodiments the active agents of this invention are administered as an injectable in accordance with standard methods well known to those of skill in the art. In other preferred embodiments, the agents, can also be delivered through the skin using conventional transdermal drug delivery systems, *i.e.*, transdermal "patches" wherein the active agent(s) are typically contained within a laminated structure that serves as a drug delivery device to be affixed to the skin. In such a structure, the drug composition is typically contained in a layer, or "reservoir," underlying an upper backing layer. It will be appreciated that the term "reservoir" in this context refers to a quantity of "active ingredient(s)" that is ultimately available for delivery to the surface of the skin. Thus, for example, the "reservoir" may include the active ingredient(s) in an adhesive on a backing layer of the patch, or in any of a variety of different matrix formulations known to those of skill in the art. The patch may contain a single reservoir, or it may contain multiple reservoirs.

[0259] In one embodiment, the reservoir comprises a polymeric matrix of a pharmaceutically acceptable contact adhesive material that serves to affix the system to the

skin during drug delivery. Examples of suitable skin contact adhesive materials include, but are not limited to, polyethylenes, polysiloxanes, polyisobutylenes, polyacrylates, polyurethanes, and the like. Alternatively, the drug-containing reservoir and skin contact adhesive are present as separate and distinct layers, with the adhesive underlying the reservoir which, in this case, may be either a polymeric matrix as described above, or it may be a liquid or hydrogel reservoir, or may take some other form. The backing layer in these laminates, which serves as the upper surface of the device, preferably functions as a primary structural element of the "patch" and provides the device with much of its flexibility. The material selected for the backing layer is preferably substantially impermeable to the active agent(s) and any other materials that are present.

[0260] Other formulations for topical drug delivery include, but are not limited to, ointments and creams. Ointments are semisolid preparations that are typically based on petrolatum or other petroleum derivatives. Creams containing the selected active agent are typically viscous liquid or semisolid emulsions, often either oil-in-water or water-in-oil. Cream bases are typically water-washable, and contain an oil phase, an emulsifier and an aqueous phase. The oil phase, also sometimes called the "internal" phase, is generally comprised of petrolatum and a fatty alcohol such as cetyl or stearyl alcohol; the aqueous phase usually, although not necessarily, exceeds the oil phase in volume, and generally contains a humectant. The emulsifier in a cream formulation is generally a nonionic, anionic, cationic or amphoteric surfactant. The specific ointment or cream base to be used, as will be appreciated by those skilled in the art, is one that will provide for optimum drug delivery. As with other carriers or vehicles, an ointment base should be inert, stable, nonirritating and nonsensitizing.

[0261] As indicated above, various buccal, and sublingual formulations are also contemplated.

[0262] The use of salicylanilide or other delivery agents as described herein need not be limited to oral delivery. In certain embodiments the use of such delivery agents is also contemplated in formulations intended for transdermal delivery, injectable delivery, surgical implantation, nasal delivery, rectal delivery, and the like.

[0263] In another embodiment, one or more components of the formulation (*e.g.*, delivery agent and/or active agent) can be provided as a "concentrate", *e.g.*, in a storage

container (*e.g.*, in a premature volume) ready for dilution, or in a soluble capsule ready for addition to a volume of water. In certain embodiments the salicylanilide or other delivery agent and the therapeutic agent are provided separately. Thus for example, salicylanilide or other delivery agent is provided as a solution that is administered immediately or some time prior to administration of the therapeutic agent (*e.g.*, therapeutic peptide), or the salicylanilide or other delivery agent is provided as a solution used while swallowing the active agent(s) formulated as a capsule, tablet, gel cap, *etc.*

[0264] The foregoing formulations and administration methods are intended to be illustrative and not limiting. It will be appreciated that, using the teaching provided herein, other suitable formulations and modes of administration can be readily devised.

B) Lipid-based formulations.

[0265] In certain embodiments, the active agents and/or salicylanilide or other delivery agent(s) of this invention are administered in conjunction with one or more lipids. The lipids can be formulated as an excipient to protect and/or enhance transport/uptake of the active agents or they can be administered separately.

[0266] Without being bound by a particular theory, it was discovered of this invention that administration (*e.g.*,. oral administration) of certain phospholipids can significantly increase HDL/LDL ratios. In addition, it is believed that certain medium-length phospholipids are transported by a process different than that involved in general lipid transport. Thus, co-administration of certain medium-length phospholipids with the active agents of this invention confer a number of advantages: They protect the active agents from digestion or hydrolysis, they improve uptake, and they improve HDL/LDL ratios.

[0267] The lipids can be formed into liposomes that encapsulate the active agents of this invention and/or they can be complexed/admixed with the active agents and/or they can be covalently coupled to the active agents. Methods of making liposomes and encapsulating reagents are well known to those of skill in the art (*see, e.g.*, Martin and Papahadjopoulos (1982) *J. Biol. Chem.*, 257: 286-288; Papahadjopoulos *et al.* (1991) *Proc. Natl. Acad. Sci. USA*, 88: 11460-11464; Huang *et al.* (1992) *Cancer Res.*, 52:6774-6781; Lasic *et al.* (1992) *FEBS Lett.*, 312: 255-258., and the like).

[0268] Preferred phospholipids for use in these methods have fatty acids ranging from about 4 carbons to about 24 carbons in the sn-1 and sn-2 positions. In certain preferred embodiments, the fatty acids are saturated. In other preferred embodiments, the fatty acids can be unsaturated. Various preferred fatty acids are illustrated in Table 19.

[0269] **Table** 19. Preferred fatty acids in the sn-1 and/or sn-2 position of the preferred phospholipids for administration of active agents described herein.

Carbon No.	Common Name	IUPAC Name
3:0	Propionoyl	Trianoic
4:0	Butanoyl	Tetranoic
5:0	Pentanoyl	Pentanoic
6:0	Caproyl	Hexanoic
7:0	Heptanoyl	Heptanoic
8:0	Capryloyl	Octanoic
9:0	Nonanoyl	Nonanoic
10:0	Capryl	Decanoic
11:0	Undcanoyl	Undecanoic
12:0	Lauroyl	Dodecanoic
13:0	Tridecanoyl	Tridecanoic
14:0	Myristoyl	Tetradecanoic
15:0	Pentadecanoyl	Pentadecanoic
16:0	Palmitoyl	Hexadecanoic
17:0	Heptadecanoyl	Heptadecanoic
18:0	Stearoyl	Octadecanoic
19:0	Nonadecanoyl	Nonadecanoic
20:0	Arachidoyl	Eicosanoic
21:0	Heniecosanoyl	Heniecosanoic
22:0	Behenoyl	Docosanoic
23:0	Trucisanoyl	Trocosanoic
24:0	Lignoceroyl	Tetracosanoic
14:1	Myristoleoyl (9-cis)	
14:1	Myristelaidoyl (9-trans)	
16:1	Palmitoleoyl (9-cis)	
16:1	Palmitelaidoyl (9-trans)	

[0270] The fatty acids in these positions can be the same or different. Particularly preferred phospholipids have phosphorylcholine at the sn-3 position.

V. Additional pharmacologically active agents.

A) Combined active agents

[0271] In various embodiments, the use of combinations of two or more active agents described is contemplated in the treatment of the various pathologies/indications described herein. The use of combinations of active agents can alter pharmacological activity, bioavailability, and the like.

[0272] By way of illustration, it is noted that D-4F and L-4Frapidly associates with pre-beta HDL and HDL and then are rapidly cleared from the circulation (it is essentially non-detectable 6 hours after an oral dose), while D-[113-122]apoJ slowly associates with pre-beta HDL and to a lesser extent with HDL but remains associated with these HDL fractions for at least 36 hours. FREL associates with HDL and only HDL but remains detectable in HDL for much longer than D-4F (*i.e.*, it is detectable in HDL 48 hours after a single oral dose in mice). In certain embodiments this invention thus contemplates combinations of, for example, these three peptides to reduce the amount to reduce production expense, and/or to optimize dosage regimen, therapeutic profile, and the like. In certain embodiments combinations of the active agents described herein can be simply coadministered and/or added together to form a single pharmaceutical formulation. In certain embodiments the various active agent(s) can be complexed together (*e.g.*, via hydrogen bonding) to form active agent complexes that are more effective than the parent agents.

B) Use with additional pharmacologically active materials.

[0273] Additional pharmacologically active materials (*i.e.*, drugs) can be delivered in conjunction with one or more of the active agents described herein. In certain embodiments, such agents include, but are not limited to agents that reduce the risk of atherosclerotic events and/or complications thereof. Such agents include, but are not limited to beta blockers, beta blockers and thiazide diuretic combinations, statins, aspirin, ace inhibitors, ace receptor inhibitors (ARBs), and the like.

[0274] It was discovered that, adding a low dosage active agent (*e.g.*, of D-4F) (1 μg/ml) to the drinking water of apoE null mice for 24 hours did not significantly improve HDL function (*see, e.g.*, related application USSN 10/423,830, filed on April 25, 2003,

which is incorporated herein by reference). In addition, adding 0.05 mg/ml of atorvastatin or pravastatin alone to the drinking water of the apoE null mice for 24 hours did not improve HDL function. However, when D-4F 1 μg/ml was added to the drinking water together with 0.05 mg/ml of atorvastatin or pravastatin there was a significant improvement in HDL function). Indeed the pro-inflammatory apoE null HDL became as anti-inflammatory as 350 μg/ml of normal human HDL (h, HDL see, *e.g.*, related application USSN 10/423,830).

[0275] Thus, doses of D-4F alone, or statins alone, which by themselves had no effect on HDL function when given together acted synergistically. When D-4F and a statin were given together to apo E null mice, their pro-inflammatory HDL at 50 μg/ml of HDL-cholesterol became as effective as normal human HDL at 350 μg/ml of HDL-cholesterol in preventing the inflammatory response induced by the action of HPODE oxidizing PAPC in cocultures of human artery wall cells.

[0276] Thus, in certain embodiments this invention provides methods for enhancing the activity of statins. The methods generally involve administering one or more of the active agents described herein, as described herein in conjunction with one or more statins. The active agents achieve synergistic action between the statin and the agent(s) to ameliorate one or more symptoms of atherosclerosis. In this context statins can be administered at significantly lower dosages thereby avoiding various harmful side effects (*e.g.*, muscle wasting) associated with high dosage statin use and/or the anti-inflammatory properties of statins at any given dose are significantly enhanced.

[0277] Suitable statins include, but are not limited to pravastatin (Pravachol/Bristol-Myers Squibb), simvastatin (Zocor/Merck), lovastatin (Mevacor/Merck), and the like.

[0278] In various embodiments the active agent(s) described herein are administered in conjunction with one or more beta blockers. Suitable beta blockers include, but are not limited to cardioselective (selective beta 1 blockers), *e.g.*, acebutolol (Sectral™), atenolol (Tenormin™), betaxolol (Kerlone™), bisoprolol (Zebeta™), metoprolol (Lopressor™), and the like. Suitable non-selective blockers (block beta 1 and beta 2 equally) include, but are not limited to carteolol (Cartrol™), nadolol (Corgard™), penbutolol (Levatol™), pindolol (Visken™), propranolol (Inderal™), timolol (Blockadren™), labetalol (Normodyne™, Trandate™), and the like.

[0279] Suitable beta blocker thiazide diuretic combinations include, but are not limited to Lopressor HCT, ZIAC, Tenoretic, Corzide, Timolide, Inderal LA 40/25, Inderide, Normozide, and the like.

[0280] Suitable ace inhibitors include, but are not limited to captopril (*e.g.*, Capoten™ by Squibb), benazepril (*e.g.*, Lotensin™ by Novartis), enalapril (*e.g.*, Vasotec™ by Merck), fosinopril (*e.g.*, Monopril™ by Bristol-Myers), lisinopril (*e.g.*, Prinivil™ by Merck or Zestril™ by Astra-Zeneca), quinapril (*e.g.*, Accupril™ by Parke-Davis), ramipril (*e.g.*, Altace™ by Hoechst Marion Roussel, King Pharmaceuticals), imidapril, perindopril erbumine (*e.g.*, Aceon™ by Rhone-Polenc Rorer), trandolapril (*e.g.*, Mavik™ by Knoll Pharmaceutical), and the like. Suitable ARBS (Ace Receptor Blockers) include but are not limited to losartan (*e.g.*, Cozaar™ by Merck), irbesartan (*e.g.*, Avapro™ by Sanofi), candesartan (*e.g.*, Atacand™ by Astra Merck), valsartan (*e.g.*, Diovan™ by Novartis), and the like.

[0281] In various embodiments, one or more agents described herein are administered with one or more of the drugs identified below.

[0282] Thus, in certain embodiments one or more active agents are administered in conjunction with cholesteryl ester transfer protein (CETP) inhibitors (*e.g.*, torcetrapib, JTT-705. CP-529414) and/or acyl-CoA:cholesterol O-acyltransferase (ACAT) inhibitors (*e.g.*, Avasimibe (CI-1011), CP 113818, F-1394, and the like), and/or immunomodulators (*e.g.*, FTY720 (sphingosine-1-phosphate receptor agonist), Thalomid (thalidomide), Imuran (azathioprine), Copaxone (glatiramer acetate), Certican® (everolimus), Neoral® (cyclosporine), antd the like), and/or dipeptidyl-peptidase-4 (DPP4) inhibitors (*e.g.*, 2-Pyrrolidinecarbonitrile, 1-[[[2-[(5-cyano-2-pyridinyl) amino]ethyl]amino]acetyl], *see also* U.S. Patent Publication 2005-0070530), and/or calcium channel blockers (*e.g.*, Adalat, Adalat CC, Calan, Calan SR, Cardene, Cardizem, Cardizem CD, Cardizem SR, Dilacor-XR, DynaCirc, Isoptin, Isoptin SR, Nimotop, Norvasc, Plendil, Procardia, Procardia XL, Vascor, Verelan), and/or peroxisome proliferator-activated receptor (PPAR) agonists for, *e.g.*, α, γ; δ receptors (*e.g.*, Azelaoyl PAF, 2-Bromohexadecanoic acid, Ciglitizone, Clofibrate, 15-Deoxy-$\delta^{12,14}$-prostaglandin J_2, Fenofibrate, Fmoc-Leu-OH, GW1929, GW7647, 8(S)-Hydroxy-(5Z,9E,11Z,14Z)-eicosatetraenoic acid (8(S)-HETE), Leukotriene B_4, LY-171,883

(Tomelukast), Prostaglandin A_2, Prostaglandin J_2, Tetradecylthioacetic acid (TTA), Troglitazone (CS-045), WY-14643 (Pirinixic acid)), and the like.

[0283] In certain embodiments one or more of the active agents are administered in conjunction with fibrates (*e.g.*, clofibrate (atromid), gemfibrozil (lopid), fenofibrate (tricor), *etc.*), bile acid sequestrants (*e.g.*, cholestyramine, colestipol, *etc.*), cholesterol absorption blockers (*e.g.*, ezetimibe (Zetia), *etc.*), Vytorin ((ezetimibe/simvastatin combination), and/or steroids, warfarin, and/or aspirin, and/or Bcr-Abl inhibitors/antagonists (*e.g.*, Gleevec (Imatinib Mesylate), AMN107, STI571 (CGP57148B), ON 012380, PLX225, and the like), and/or renin angiotensin pathway blockers (*e.g.*, Losartan (Cozaar®), Valsartan (Diovan®), Irbesartan (Avapro®), Candesartan (Atacand®), and the like), and/or angiotensin II receptor antagonists (*e.g.*. losartan (Cozaar), valsartan (Diovan), irbesartan (Avapro), candesartan (Atacand) and telmisartan (Micardis), *etc.*), and/or PKC inhibitors (*e.g.*, Calphostin C, Chelerythrine chloride, Chelerythrine . chloride, Copper bis-3,5-diisopropylsalicylate, Ebselen, EGF Receptor (human) (651-658) (N-Myristoylated), Gö 6976, H-7 . dihydrochloride, 1-O-Hexadecyl-2-O-methyl-*rac*-glycerol, Hexadecyl-phosphocholine ($C_{16:0}$); Miltefosine, Hypericin, Melittin (natural), Melittin (synthetic), ML-7 . hydrochloride, ML-9 . hydrochloride, Palmitoyl-DL-carnitine . hydrochloride, Protein Kinase C (19-31), Protein Kinase C (19-36), Quercetin . dihydrate, Quercetin . dihydrate, D-*erythro*-Sphingosine (isolated), D-*erythro*-Sphingosine (synthetic), Sphingosine, N,N-dimethyl, D-*erythro*-Sphingosine, Dihydro-, D-*erythro*-Sphingosine, N,N-Dimethyl-, D-*erythro*-Sphingosine chloride, N,N,N-Trimethyl-, Staurosporine, Bisindolylmaleimide I, G-6203, and the like).

[0284] In certain embodiments, one or more of the active agents are administered in conjunction with ApoAI, Apo A-I derivatives and/or agonists (*e.g.*, ApoAI milano, see, *e.g.*, U.S. Patent Publications 20050004082, 20040224011, 20040198662, 20040181034, 20040122091, 20040082548, 20040029807, 20030149094, 20030125559, 20030109442, 20030065195, 20030008827, and 20020071862, and U.S. Patents 6,831,105, 6,790,953, 6,773,719, 6,713,507, 6,703,422, 6,699,910, 6,680,203, 6,673,780, 6,646,170, 6,617,134, 6,559,284, 6,506,879, 6,506,799, 6,459,003, 6,423,830, 6,410,802, 6,376,464, 6,367,479, 6,329,341, 6,287,590, 6,090,921, 5,990,081, and the like), renin inhibitors (*e.g.*, SPP630 and SPP635, SPP100, Aliskiren, and the like), and/or MR antagonist (*e.g.*, spironolactone, aldosterone glucuronide, and the like), and/or aldosterone synthase inhibitors, and/or alpha-

adrenergic antagonists (*e.g.*, Aldomet® (Methyldopa), Cardura® (Doxazosin), Catapres®; Catapres-TTS®; Duraclon™ (Clonidine), Dibenzyline® (Phenoxybenzamine), Hylorel® (Guanadrel), Hytrin® (Terazosin), Minipress® (Prazosin), Tenex® (Guanfacine), Guanabenz, Phentolamine, Reserpine, and the like), and/or liver X receptor (LXR) agonists (*e.g.*, T0901317, GW3965, ATI-829, acetyl-podocarpic dimer (APD), and the like), and/or farnesoid X receptor (FXR) agonists (*e.g.*, GW4064, 6alpha-ethyl-chenodeoxycholic acid (6-ECDCA), T0901317, and the like), and/or plasminogen activator-1 (PAI-1) inhibitors (*see, e.g.*, oxime-based PAI-1 inhibitors, see also U.S. Patent 5,639,726, and the like), and/or low molecular weight heparin, and/or AGE inhibitors/breakers (*e.g.*, Benfotiamine, aminoguanidine, pyridoxamine, Tenilsetam, Pimagedine, and the like) and/or ADP receptor blockers (*e.g.*, Clopidigrel, AZD6140, and the like), and/or ABCA1 agonists, and/or scavenger receptor B1 agonists, and/or Adiponectic receptor agonist or adiponectin inducers, and/or stearoyl-CoA Desaturase I (SCD1) inhibitors, and/or Cholesterol synthesis inhibitors (non-statins), and/or Diacylglycerol Acyltransferase I (DGAT1) inhibitors, and/or Acetyl CoA Carboxylase 2 inhibitors, and/or LP-PLA2 inhibitors, and/or GLP-1, and/or glucokinase activator, and/or CB-1 agonists, and/or anti-thrombotic/coagulants, and/or Factor Xa inhibitors, and/or GPIIb/IIIa inhibitors, and/or Factor VIIa inhibitors, and/or Tissue factor inhibitors, and/or anti-inflammatory drugs, and/or Probucol and derivatives (*e.g.*, AGI-1067, etc.), and/or CCR2 antagonists, and/or CX3CR1 antagonists, and/or IL-1 antagonists, and/or nitrates and NO donors, and/or phosphodiesterase inhibitors, and the like.

C) Administration.

[0285] Typically the active agent(s) described hereinwill be administered (typically in conjunction with a salicylanilide (*e.g.*, niclosamide or niclosamide analogue) or other delivery agent as described herein) to a mammal (*e.g.*,. a human) in need thereof. Such a mammal will typically include a mammal (*e.g.*, a human) having or at risk for one or more of the pathologies described herein.

[0286] The active agent(s) can be administered, as described herein, according to any of a number of standard methods including, but not limited to injection, suppository, nasal spray, time-release implant, transdermal patch, and the like. In one particularly

preferred embodiment, the peptide(s) are administered orally (*e.g.*, as a syrup, capsule, or tablet).

[0287] The methods involve the administration of a single active agent of this invention or the administration of two or more different active agents, typically in conjunction with a salicylanilide (*e.g.*, niclosamide or niclosamide analogue) or other delivery agent as described herein. The active agents can be provided as monomers (*e.g.*, in separate or combined formulations), or in dimeric, oligomeric or polymeric forms. In certain embodiments, the multimeric forms may comprise associated monomers (*e.g.*, ionically or hydrophobically linked) while certain other multimeric forms comprise covalently linked monomers (directly linked or through a linker).

[0288] While the invention is described with respect to use in humans, it is also suitable for animal, *e.g.*, veterinary use. Thus certain preferred organisms include, but are not limited to humans, non-human primates, canines, equines, felines, porcines, ungulates, largomorphs, and the like.

[0289] The methods of this invention are not limited to humans or non-human animals showing one or more symptom(s) of the pathologies described herein, but are also useful in a prophylactic context. Thus, the active agents of this invention can be administered to organisms to prevent the onset/development of one or more symptoms of the pathologies described herein (*e.g.*, atherosclerosis, stroke, *etc.*). Particularly preferred subjects in this context are subjects showing one or more risk factors for the pathology. Thus, for example, in the case of atherosclerosis risk factors include family history, hypertension, obesity, high alcohol consumption, smoking, high blood cholesterol, high blood triglycerides, elevated blood LDL, VLDL, IDL, or low HDL, diabetes, or a family history of diabetes, high blood lipids, heart attack, angina or stroke, *etc.*

VI. Kits for the treatment of one or more indications.

[0290] In another embodiment this invention provides kits for amelioration of one or more symptoms of atherosclerosis or for the prophylactic treatment of a subject (human or animal) at risk for atherosclerosis and/or the treatment or prophylaxis of one or more of the conditions described herein. The kits preferably comprise a container containing one or more of the active agents described herein. The active agent(s) can be provided in a unit

dosage formulation (*e.g.*, suppository, tablet, caplet, patch, *etc.*) and/or may be optionally combined with one or more pharmaceutically acceptable excipients.

[0291] In various embodiments the kits typically additionally comprise a salicylanilide or other delivery agent described herein. The salicylanilide or other delivery agent can be formulated as a compound formulation with one or more of the active agents described herein. Alternatively, the salicylanilide or other delivery agent can be provided separately, *e.g.*, in a separate container.

[0292] The kit can, optionally, further comprise one or more other agents used in the treatment of the condition/pathology of interest. Such agents include, but are not limited to, beta blockers, vasodilators, aspirin, statins, ace inhibitors or ace receptor inhibitors (ARBs) and the like, *e.g.*, as described above.

[0293] In addition, the kits optionally include labeling and/or instructional materials providing directions (*i.e.*, protocols) for the practice of the methods or use of the "therapeutics" or "prophylactics" of this invention. Preferred instructional materials describe the use of one or more active agent(s) of this invention to mitigate one or more symptoms of atherosclerosis (or other pathologies described herein) and/or to prevent the onset or increase of one or more of such symptoms in an individual at risk for atherosclerosis (or other pathologies described herein). The instructional materials may also, optionally, teach preferred dosages/therapeutic regiment, counter indications and the like.

[0294] While the instructional materials typically comprise written or printed materials they are not limited to such. Any medium capable of storing such instructions and communicating them to an end user is contemplated by this invention. Such media include, but are not limited to electronic storage media (*e.g.*, magnetic discs, tapes, cartridges, chips), optical media (*e.g.*, CD ROM), and the like. Such media may include addresses to internet sites that provide such instructional materials.

VII. Indications.

[0295] The active agents (*e.g.*, peptides, small organic molecules, amino acid pairs, *etc.*) described herein are effective for mitigating one or more symptoms and/or reducing the rate of onset and/or severity of one or more indications described herein. In particular,

the active agents (*e.g.*, peptides, small organic molecules, amino acid pairs, *etc.*) described herein are effective for mitigating one or more symptoms of atherosclerosis. Without being bound to a particular theory, it is believed that the peptides bind the "seeding molecules" required for the formation of pro-inflammatory oxidized phospholipids such as Ox-PAPC, POVPC, PGPC, and PEIPC.

[0296] In addition, since many inflammatory conditions and/or other pathologies are mediated at least in part by oxidized lipids, we believe that the peptides of this invention are effective in ameliorating conditions that are characterized by the formation of biologically active oxidized lipids. In addition, there are a number of other conditions for which the active agents described herein appear to be efficacious.

[0297] A number of pathologies for which the active agents described herein appear to be a palliative and/or a preventative are shown in Table Table 20.

[0298] Table 20. Summary of conditions in which the active agents (*e.g.*, D-4F) have been shown to be or are believed to be effective.

atherosclerosis/symptoms/consequences thereof
plaque formation
lesion formation
myocardial infarction
stroke
congestive heart failure
vascular function:
arteriole function
arteriolar disease
associated with aging
associated with Alzheimer's disease
associated with chronic kidney disease
associated with hypertension
associated with multi-infarct dementia
associated with subarachnoid hemorrhage
peripheral vascular disease
pulmonary disease:
chronic obstructive pulmonary disease (COPD),
emphysema
asthma
idiopathic pulmonary fibrosis
Pulmonary fibrosis

adult respiratory distress syndrome
osteoporosis
Paget's disease
coronary calcification
autoimmune:
rheumatoid arthritis
polyarteritis nodosa
polymyalgia rheumatica
lupus erythematosus
multiple sclerosis
Wegener's granulomatosis
central nervous system vasculitis (CNSV)
Sjögren's syndrome
Scleroderma
polymyositis.
AIDS inflammatory response
infections:
bacterial
fungal
viral
parasitic
influenza
avian flu
viral pneumonia
endotoxic shock syndrome
sepsis
sepsis syndrome
(clinical syndrome where it appears that the patient is septic but no organisms are recovered from the blood)
trauma/wound:
organ transplant
transplant atherosclerosis
transplant rejection
corneal ulcer
chronic/non-healing wound
ulcerative colitis
reperfusion injury (prevent and/or treat)
ischemic reperfusion injury (prevent and/or treat)
spinal cord injuries (mitigating effects)
cancers
myeloma/multiple myeloma
ovarian cancer

breast cancer colon cancer bone cancer
osteoarthritis
inflammatory bowel disease
allergic rhinitis
cachexia
diabetes
Alzheimer's disease
implanted prosthesis
biofilm formation
Crohns' disease
dermatitis, acute and chronic eczema psoriasis contact dermatitis scleroderma
diabetes and related conditions Type I Diabetes Type II Diabetes Juvenile Onset Diabetes Prevention of the onset of diabetes Diabetic Nephropathy Diabetic Neuropathy Diabetic Retinopathy
erectile dysfunction
macular degeneration
multiple sclerosis
nephropathy
neuropathy
Parkinson's Disease
peripheral Vascular Disease
meningitis
Specific biological activities: increase Heme Oxygenase 1 increase extracellular superoxide dismutase prevent endothelial sloughing prevent the association of myeloperoxidase with ApoA-I prevent the nitrosylation of tyrosine in ApoA-I render HDL anti-inflammatory improve vasoreactivity

increase the formation of pre-beta HDL
promote reverse cholesterol transport
promote reverse cholesterol transport from macrophages
synergize the action of statins

[0299] It is noted that the conditions listed in Table 20 are intended to be illustrative and not limiting.

EXAMPLES

[0300] The following examples are offered to illustrate, but not to limit the claimed invention.

Example 1

Niclosamide Enhances Uptake/Bioavailability of Orally Administered Peptides

[0301] We previously reported that the amino acid sequence D-W-F-K-A-F-Y-D-K-V-A-E-KF-K-E-A-F(SEQ-ID-NO:5) bearing at least one protecting group (*see, e.g.,* U.S. Patent 6,933,279) when synthesized from all L-amino acids (L-4F) and administered orally to mice was rapidly degraded and did not significantly alter the protective capacity of HDL to inhibit LDL-induced monocyte chemotactic activity in cultures of human artery wall cells (Navab *et al.* (2002) *Circulation* 105: 290-292).

[0302] It was a surprising finding of this invention that administering L-4F with niclosamide orally to mice resulted in significant improvement in the ability of HDL from these mice to inhibit LDL-induced monocyte chemotactic activity. In contrast orally administering either agent alone was ineffective or significantly less effective.

[0303] As shown in Figure 8, the combination of oral Niclosamide and L-4F was potent in a mouse model of atherosclerosis. 11-month-old female apoE null mice were fasted during the day. At night the mice were provided chow containing or not containing additions. In the first experiment the mice were given chow alone (C) or chow supplemented with 8.0 micrograms of Niclosamide (2',5-Dichloro-4'-nitrosalicylanilide; Niclosamide, Sigma catalog number N-3510 Page 1711 2006 - 2007 catalog Empirical Formula (Hill Notation): $C_{13}H_8C_{l2}N_2O_4$ Formula Weight: 327.12, CAS Number: 50-65-7 Batch 105K0666 EC 200-056-8) per gram of chow (D) or chow supplemented with 2.0 micrograms of L-4F (free base) per gram of chow (E), or chow supplemented with 8.0

micrograms of Niclosamide together with 2.0 micrograms of L-4F (free base) per gram of chow (F). The mice were only given one gram of chow per mouse (n = 8 mice per group) so that they would consume all of the chow. In the morning after the chow was consumed the mice were bled and their plasma was sucrose cryopreserved and fractionated by FPLC and the HDL-containing fractions were tested for their ability to inhibit monocyte chemotactic activity induced by a standard control human LDL (A) in cultures of human aortic endothelial cells. The mouse HDL (C – J) was also compared to a standard human HDL (B) that was added at the same concentrations as the mouse HDL. The resulting monocyte chemotactic activity was normalized to the standard control LDL added alone (A). The results are plotted as the HDL-inflammatory index, which is the result of dividing the monocyte chemotactic activity measured for each condition by the monocyte chemotactic activity obtained by the standard control LDL added alone, which was normalized to 1.0 as described previously (Navab et al. (2004) *J Lipid Res*, 45: 993-1007).

[0304] A second experiment was performed as described for the first experiment with 8 mice in each group except that the additions to the chow were different. Chow alone in the second experiment (G) was compared to chow supplemented with 100 micrograms of Niclosamide per gram of chow (H), or supplemented with 10 micrograms of L-4F (free base) per gram of mouse chow (I), or supplemented with 10 micrograms of L-4F (free base) together with 100 micrograms of Niclosamide per gram of chow (J). As in the first experiment the mice were only given one gram of chow per mouse so that they would consume all of the chow. In the morning this second group of mice were bled and their HDL tested in the human artery wall cell culture together with the HDL from the first experiment.

[0305] The data indicate that addition of either 2 (E) or 10 (I) micrograms of L-4F to the chow slightly but significantly improved the HDL-inflammatory index and the difference between these two doses in the absence of Niclosamide was not significant confirming our previous report (Navab *et al.* (2002) *Circulation*, 105: 290-292). As shown in Figure 1 (D) and (H), administering Niclosamide by itself was ineffective. Surprisingly the oral combination of Niclosamide with L-4F in each case resulted in dramatic statistically significant improvement in the HDL-inflammatory index. The use of 10 micrograms of L-4F together with 100 micrograms of Niclosamide (J) was significantly better than 2 micrograms of L-4F together with 8 micrograms of Niclosamide (F).

[0306] As shown in Figure 9, administration of Niclosamide as an oral bolus by gastric gavage (stomach tube) immediately followed by administration of L-4F as an oral bolus by stomach tube rendered apoE null mouse HDL anti-inflammatory. Ten mg of Niclosamide was placed in a glass-glass homogenizer with mortar and round bottom pestle (Kontes Dounce Tissue grinder, K885300-0015 available from Fisher, VWR) and 200 μL of ethanol was added. The Niclosamide ethanol mixture was homogenized using 2 – 3 strokes and distilled water was added and the mixture further homogenized using 5 – 10 strokes and the volume was adjusted to 10 mL with distilled water. Serial dilutions of this mixture were made using distilled water to give the micrograms of Niclosamide shown on the x-axis, which were contained in 100 μL. L-4F (free base) was diluted with water to give 10 μg per 100 μL of water. One hundred microliters of the Niclosamide solution was given by stomach tube to each mouse in each group of twelve-month-old non-fasting female apoE null mice (n = 4 per group) and immediately followed by 100 μL containing 10 μg of L-4F (free base) in water. The mice were fasted and after 7 hours they were bled and their plasma was sucrose cryopreserved. The plasma was fractionated by FPLC and the HDL-containing fractions were tested for their ability to inhibit the induction of monocyte chemotactic activity by a standard control human LDL, which was added to cultures of human aortic endothelial cells. The standard control human LDL was also added by itself or with a standard control human HDL. The values obtained by the standard control human LDL alone were normalized to 1.0. The values obtained after the addition of the standard control HDL or the mouse HDL were compared to the values obtained by the standard control LDL alone to give the HDL Inflammatory Index.

[0307] Figure 10 shows that Administration of Niclosamide as an oral bolus by stomach tube immediately followed by administration of L-4F as an oral bolus by stomach tube significantly reduced the ability of apoE null mouse LDL to induce monocyte chemotactic activity in cultures of human aortic endothelial cells. The LDL fractions from the mice described in Figure 9 were tested for their ability to induce monocyte chemotactic activity in cultures of human aortic endothelial cells and compared to a standard control human LDL whose values were normalized to 1.0 for the LDL-inflammatory index.

[0308] Figure 11 shows that oral administration of niclosamide (5.0 mg/kg body weight) immediately followed by oral administration of L-4F (0.5 mg/kg/body weight)

renders monkey HDL anti-inflammatory. One hundred mg of niclosamide was placed in a glass-glass homogenizer with mortar and round bottom pestle (Kontes Dounce Tissue grinder, K885300-0015 available from Fisher, VWR) and 200 μL of ethanol was added. The Niclosamide ethanol mixture was homogenized using 2 – 3 strokes and distilled water was added and the mixture further homogenized using 5 – 10 strokes and the volume was adjusted to 10 mL with distilled water. The niclosamide mixture was again mixed immediately before the dose was removed as the Niclosamide tends to settle out. Each of 4 monkeys (2 Female and 2 Male) were given 5.0 mg/kg body weight of Niclosamide contained in 2.5 mL of the mixture by stomach tube. L-4F (free base) was added to 10 mL of distilled water in the glass-glass homogenizer and homogenized using 5 – 10 strokes. Immediately after administration of the Niclosamide mixture each monkey was given 0.5 mg/kg body weight of L-4F (free base) contained in 2.5 mL water by stomach tube. Blood was obtained 5 hours later and the plasma was separated by FPLC and the lipoproteins tested as described in Figure 8 for the HDL-inflammatory index and Figure 10 for the LDL-inflammatory index. The data shown are the Mean ± S.D. for the HDL Inflammatory Index for monkey HDL before and 5 hours after treatment (the data for the standard control human LDL alone and the standard control human LDL plus the standard control human HDL are not shown in the figure).

[0309] Oral administration of niclosamide (5.0 mg/kg body weight) immediately followed by oral administration of L-4F (0.5 mg/kg/body weight) significantly reduced the ability of monkey LDL to induce monocyte chemotactic activity in cultures of human aortic endothelial cells (*see, e.g.*, Figure 12). The LDL fractions from the monkey plasma described in Figure 11 were tested as described in Figure 10.

[0310] Niclosamide is relatively insoluble in aqueous solutions even when added in ethanol and homogenized. It was a surprising finding of this invention that L-4F solubilized niclosamide in aqueous solution as shown in Figure 13. Niclosamide at 10 mg per mL was added to water, or to water containing 1.0 mg/mL L-4F (free base) and was homogenized in a glass-glass homogenizer. The solutions were stored at 4°C for ten days and photographed (*see* Figure 13).

[0311] The solutions of Niclosamide with or without L-4F shown above in Figure 13 were serially diluted and given by gastric gavage (stomach tube) to fasting seven month

old female apoE null mice in a volume of 100 μL per mouse (n = 8 per group). Blood was collected 6 hrs following treatment while the mice were still fasting and the plasma was separated by FPLC and the HDL fractions were tested as described in Figure 8 and the data are shown in Figure 14.

[0312] The micrograms of L-4F and/or niclosamides are shown on the X-axis. Six hours after administration the mice were bled and the ability of mouse HDL (m) or human HDL (h) to inhibit LDL-induced monocyte chemotactic activity in cultures of human aortic endothelial cells was determined and plotted as the HDL-inflammatory index as described for Figure 8.

[0313] As shown in Figure 15, administration of the L-4F together with the solubilized niclosamide resulted in a significant reduction in the ability of mouse LDL to induce monocyte chemotactic activity in cultures of human aortic endothelial cells.

[0314] The data in Figures 14 and 15 demonstrate the remarkable, novel, and unexpected findings that the peptide L-4F solubilizes niclosamide and results in a therapeutic combination that renders HDL anti-inflammatory and significantly reduces the inflammatory properties of LDL in a mouse model of atherosclerosis.

[0315] It was also a surprising finding of this invention that administration of Niclosamide in mouse chow greatly enhanced the ability of L-4F to render HDL anti-inflammatory and to decrease the ability of LDL to induce monocyte chemotactic activity in cultures of human aortic endothelial cells even when the L-4F was administered in the drinking water (*see, e.g.*, Figures 16 and 17).

[0316] L-4F was previously thought to be ineffective in rendering HDL anti-inflammatory and ineffective in reducing the ability of LDL to induce monocyte chemotactic activity in cultures of human aortic endothelial cells if the peptide was given orally (*see, e.g.*, Navab *et al.* (2002) *Circulation,* 105: 290-292). The data in Figures 8-17 demonstrate the surprising and unexpected finding that if L-4F is given orally with niclosamide it is highly effective in rendering HDL anti-inflammatory and highly effective in reducing the inflammatory properties of LDL. This invention also demonstrates the surprising and unexpected finding that L-4F solubilizes niclosamide.

Example 2

Salicylanilides Combined with L-4F Enhance Formation of Pre-Beta HDL

[0317] Niclosamide plus L-4F causes the formation of pre-β HDL in apoE null mice after oral administration (*see, e.g.*, Figure 18). D-4F (free base) was dissolved in 0.1% Tween20 in ammonium bicarbonate buffer (ABCT) pH 7.0. L-4F (free base) plus niclosamide were dissolved in ABCT in a ratio of 1:10 (L-4F:Niclosamide; wt:wt). ABCT alone or ABCT containing the micrograms of L-4F or D-4F with or without the micrograms of niclosamide shown in Figure 18 on the X-axis were administered in 100 μL by stomach tube to 8 month old female apoE null mice that were fasted overnight (n = 8 per group). Thirty to forty minutes later the mice were bled and the percent of apolipoprotein A-I contained in pre-β–1 HDL was determined in triplicate 2-dimensional gels by scanning. The data shown are the Mean ± S.D.

[0318] It was also a surprising discovery that oral co-administration of niclosamide and L-4F improved the inflammatory properties of apoE null mouse HDL (as measured in a cell-based assay) to a degree similar to that seen when niclosamide was administered with D-4F (*see, e.g.*, Figure 19).

[0319] Similar results were obtained when the inflammatory properties of HDL were measured by a cell-free assay (*see, e.g.*, Figure 20).

[0320] It was also a surprising discovery that when niclosamide and L-4F were co-administered orally to apoE null mice the increase in paraoxonase activity was similar to that seen when niclosamide was co-administered with D-4F (*see, e.g*, Figure 21).

[0321] Oral co-administration of niclosamide with either D-4F or L-4F enhanced the ability of both peptides to improve HDL inflammatory properties in apoE null mice. In the absence of niclosamide, however, D-4F was able to render apoE null mouse HDL anti-inflammatory to a degree comparable to normal human HDL while L-4F was only able to achieve this degree of efficacy when co-administered with niclosamide (*see, e.g.*, Figure 22).

[0322] As shown in Figure 23 the inflammatory properties of LDL from apoE null mice were reduced by the co-administration orally of niclosamide and L-4F.

[0323] It was a surprising discovery of this invention that some of the salicylanilides described in Figures 24-26 were even more potent than niclosamide in rendering apoE null

mouse HDL anti-inflammatory when administered orally together with either D-4F or L-4F. As shown in Figure 24 neither niclosamide nor the new salicylanilides were anti-inflammatory when administered without the peptides.

[0324] As shown in Figure 25 the new salicylanilides (BP-1001 and BP-1012) were also more potent in reducing the inflammatory properties of LDL than niclosamide when co-administered with D-4F or L-4F.

[0325] As shown in Figure 26, other salicylanilides were similar to niclosamide (BP-124) in bioactivity while still others were more potent.

Example 3

Niclosamide Increases L-4F Absorption In Apoe Null Mice.

[0326] L-4F absorption was determined with and without niclosamide (BP-124) using ^{14}C-L-4F. Fasted female apoE null mice 6-months of age (n=4 per group) were administered by stomach tube L-4F (21,000 dpm containing 10 micrograms of L-4F per mouse) with or without 100 micrograms of niclosamide in 200 μL 0.1% Tween20 in ammonium bicarbonate at pH·7.0. Fasting was continued and the mice were bled at the time points shown on the X-axis in Figure 27 and the dpm per mL plasma determined. The area under the curve (AUC) in Figure 27 for the mice receiving L-4F + niclosamide was 4.4 times greater than the AUC for the mice receiving L-4F without niclosamide.

[0327] The data indicate that one of the mechanisms by which niclosamide enhances the *in vivo* bioactivity of L-4F is by increasing the absorption of L-4F.

[0328] The foregoing data (Examples 1, 2, and 3) show that the combination of niclosamide or other salicylanilides with L-4F, and presumably other therapeutic peptides, appears to have great potential for oral therapy. Based on these data it is believed that the use of niclosamide or other salicylanilides with other peptides or proteins will make new oral therapeutics possible.

[0329] The data in Figure 27 indicate that without niclosamide administration of ^{14}C-L-4F by stomach tube resulted in low plasma levels that lasted no more than 5 minutes. In contrast, when ^{14}C-L-4F was administered with niclosamide a C_{max} of approximately 150 nanograms/mL was achieved which persisted for more than an hour and at a lower level for up to four hours.

[0330] The data in Figure 28 demonstrate that the ^{14}C-L-4F used in Figure 28 was biologically active when given with niclosamide. Fasted apoE null mice 5-months of age (n = 4 per group) were administered by stomach tube ^{14}C-L-4F (21,000 dpm containing 10 μg of L-4F per mouse) with or without 100 μg of niclosamide (Niclos.) in 200 μL. Fasting was continued and the mice were bled 5 hours later and the HDL inflammatory index determined in cultures of human aortic endothelial cells as described in Figure 8. Briefly, To determine the HDL-inflammatory index lipoproteins were added to human aortic endothelial cell cultures as described previously (Navab *et al.*(2005) *Circulation Research* 97: 524-532). A normal control human LDL was added to each well in triplicate at a final concentration of 100 μg/mL of LDL-cholesterol. A normal human HDL was added to three wells containing human LDL at a final concentration of 50 μg/mL HDL-cholesterol as a positive control. HDL from the mice at a final concentration of 50 μg/mL HDL-cholesterol was added in triplicate to other wells containing human LDL. After 8 hours of culture the supernatants were removed and monocyte chemotactic activity was determined as previously described (Navab *et al.* (2001) *J. Lipid Res.*, 42: 1308-1317; Danciger *et al.* (2004) *J. Immunol. Meth.*, 288: 123-124). The values obtained from wells containing the human LDL but no HDL were normalized to 1.0. The values obtained from wells containing the human LDL with either human or mouse HDL were divided by the values obtained from wells with human LDL without added HDL to give the HDL-inflammatory index as previously described (Ansell *et al.* (2003) *Circulation* 108: 2751-2756). The data in Figure 28 demonstrate that the ^{14}C-L-4F used in the experiments described in Figure 27 was biologically active.

Example 4

Niclosamide Plus L-4F Administered Orally (But Not L-4F Alone) Reduces Lesions In Mouse Models Of Atherosclerosis.

[0331] In another experiment, seventeen week old female apoE null mice were divided into three groups: Group I received niclosamide 250 μg/mouse/day in rodent chow. Group II received L-4F at 25 μg/mouse/day in rodent chow. Group III received niclosamide at 250 μg/mouse/day together with L-4F 25 μg/mouse/day in rodent chow. All three groups received pravastatin 50 μg/mouse/day in drinking water. After 14 weeks the mice were sacrificed and aortic sinus lesion area was determined. As shown in Figures 29-

31 oral administration of L-4F together with niclosamide but not without niclosamide significantly inhibits atherosclerosis in apoE Null mice.

[0332] In still another experiments, nine and half months-old female apoE null mice were divided into four groups: Group I was sacrificed to establish base line lesion area (Time Zero). Group II received niclosamide at 2 mg/mouse/day in rodent chow. Group III received L-4F at 200 μg/mouse/day in rodent chow. Group IV received niclosamide (Niclos.) at 2 mg/mouse/day together with L-4F 200 μg/mouse/day in rodent chow. Groups II – IV received pravastatin 50 μg/mouse/day in drinking water. After 26 weeks the mice were sacrificed and aortic sinus lesion area was determined. The data in Figures 32-34 demonstrate that the combination of L-4F plus niclosamide caused lesion regression in old apoE null mice. In contrast, neither niclosamide nor L-4F without niclosamide significantly reduced lesions.

[0333] L-4F forms a class A amphipathic helix. The sequence comprising residues 113-122 in apolipoprotein J (apoJ) comprises a potential G* helix. Administration of this peptide synthesized from all D-amino acids, D-[113-122]apoJ, dramatically improved HDL inflammatory properties and reduced atherosclerosis in apoE null mice (Navab *et al.* (2005) *Arterioscler. Thromb. Vasc. Biol.* 25: 1932-1937).

[0334] To determine whether niclosamide could improve activity of the L- form of apoJ, ten month old apoE null mice (n = 4 per group) were administered by stomach tube 2 mg of niclosamide or 200 μg of L-[113-122]apoJ or 2 mg of niclosamide together with 100 or 200 μg of L-[113-122]apoJ or were administered 2 mg of niclosamide together with 100 or 200 μg of L-4F. Eight hours later the mice were bled and the HDL inflammatory index was determined in cultures of human aortic endothelial cells as described in Figure 8. As shown in Figure 35 oral administration of the same peptide but synthesized from all L-amino acids and administered with niclosamide rendered apoE null mouse HDL anti-inflammatory to the same degree as normal human HDL, but when the peptide was administered orally without niclosamide this was not the case.

[0335] It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims. All publications, patents, and patent

applications cited herein are hereby incorporated by reference in their entirety for all purposes.

CLAIMS

What is claimed is:

1. A composition comprising a therapeutic peptide in combination with a salicylanilide.

2. The composition of claim 1, wherein said composition comprises a therapeutic peptide in combination with niclosamide or a niclosamide analogue.

3. The composition of claim 2, wherein said niclosamide or niclosamide analogue is selected from the group consisting of 2'5-dichloro-4'-nitrosalicylanilide, 5-chloro-salicyl-(2-chloro-4-nitro) anilide 2-aminoethanol salt, 5-chloro-salicyl-(2-chloro-4-nitro) anilide piperazine salt, and 5-chloro-salicyl-(2-chloro-4-nitro) anilide monohydrate.

4. The composition of claim 2, wherein said niclosamide analogue is a compound in Figure 2, 3, 4, 5, 6, 7, and/or Table 1.

5. The composition of claim 2, wherein said peptide ranges in length from 3 amino acids to 300 amino acids.

6. The composition of claim 2, wherein said peptide forms an amphipathic helix.

7. The composition of claim 2, wherein said peptide is selected from the group consisting of ApoJ, ApoA-I, ApoA-I milano, and 18A.

8. The formulation of claim 2, wherein said peptide is an Apo-J peptide.

9. The composition of claim 2, wherein said peptide forms a class A amphipathic helix.

10. The composition of any one of claims 2, 7, or 9, wherein said peptide consists of all "L" amino acids.

11. The composition of any one of claims 2, 7, or 9, wherein said peptide comprises at least one "D" amino acid.

12. The composition of any one of claims 2, 7, or 9, wherein said peptide consists of all "D" amino acids.

13. The composition of claim 2, wherein said peptide is a D or L peptide whose sequence is shown in any of Tables 2-11 and/or SEQ ID Nos:1-1175.

14. The composition of claim 13, wherein said peptide consists of all L amino acids.

15. The composition of claims 13, or 14, wherein said peptide comprises a protecting group at the amino or carboxyl terminus.

16. The composition of claims 13, or 14, wherein said peptide comprises a first protecting group coupled to the amino terminus and a second protecting group coupled to the carboxyl terminus.

17. The composition of claim 16, wherein said protecting group is a protecting group selected from the group consisting of acetyl, amide, and 3 to 20 carbon alkyl groups, Fmoc, Tboc, 9-fluoreneacetyl group, 1-fluorenecarboxylic group, 9-florenecarboxylic group, 9-fluorenone-1-carboxylic group, benzyloxycarbonyl, Xanthyl (Xan), Trityl (Trt), 4-methyltrityl (Mtt), 4-methoxytrityl (Mmt), 4-methoxy-2,3,6-trimethyl-benzenesulphonyl (Mtr), Mesitylene-2-sulphonyl (Mts), 4,4-dimethoxybenzhydryl (Mbh),Tosyl (Tos), 2,2,5,7,8-pentamethyl chroman-6-sulphonyl (Pmc), 4-methylbenzyl (MeBzl), 4-methoxybenzyl (MeOBzl), Benzyloxy (BzlO), Benzyl (Bzl), Benzoyl (Bz), 3-nitro-2-pyridinesulphenyl (Npys), 1-(4,4-dimentyl-2,6-diaxocyclohexylidene)ethyl (Dde), 2,6-dichlorobenzyl (2,6-DiCl-Bzl), 2-chlorobenzyloxycarbonyl (2-Cl-Z), 2-bromobenzyloxycarbonyl (2-Br-Z), Benzyloxymethyl (Bom), t-butoxycarbonyl (Boc), cyclohexyloxy (cHxO),t-butoxymethyl (Bum), t-butoxy (tBuO), t-Butyl (tBu), Acetyl (Ac), and Trifluoroacetyl (TFA).

18. The composition of claim 16, wherein said first protecting group is a protecting group selected from the group consisting of acetyl, propeonyl, and a 3 to 20 carbon alkyl.

19. The composition of claim 18, wherein said second protecting group is an amide.

20. The composition of claim 2, wherein said niclosamide or niclosamide analogue and said therapeutic peptide are intermixed.

21. The composition of claim 2, wherein said niclosamide or niclosamide analogue and said therapeutic peptide form an adduct.

22. The composition of claim 2, wherein said composition is a unit dosage formulation.

23. The composition of claim 2, wherein said composition is formulated so that the niclosamide or niclosamide analogue is released or solubilized before the peptide.

24. The composition of claim 2, wherein:
said salicylanilide is niclosamide or a niclosamide analogue; and
said peptide is a D or L peptide comprising the amino acid sequence DWFKAFYDKVAEKFKEAF (SEQ ID NO:5) or the amino acid sequence FAEKFKEAVKDYFAKFWD (SEQ ID NO:104).

25. The composition of claim 24, wherein said peptide comprises a carboxyl terminal protecting group and an amino terminal protecting group.

26. The composition of claim 25, wherein:
said peptide comprises a protecting group coupled to the carboxyl terminus and said carboxyl terminal protecting group is an amide; and
said peptide comprises a protecting group coupled to the amino terminus and said amino terminal protecting group is an acetyl.

27. The composition of claim 26, wherein said niclosamide or niclosamide analogue is niclosamide.

28. The composition of claim 26, wherein said niclosamide or niclosamide analogue form an adduct with said peptide.

29. A method of enhancing the *in vivo* activity of a therapeutic peptide orally administered to a mammal, said method comprising orally administering said peptide in conjunction with an amount of niclosamide or a niclosamide analogue sufficient to enhance the *in vivo activity* of said peptide.

30. The method of claim 29, wherein said peptide ranges in length from 3 amino acids to 300 amino acids.

31. The method of claim 29, wherein said peptide forms an amphipathic helix.

32. The method of claim 31, wherein said peptide forms a class A amphipathic helix.

33. The method of claim 31, wherein said peptide is selected from the group consisting of ApoJ, ApoA-I, ApoA-I milano, and 18A.

34. The method of claim 31, wherein said peptide is an Apo-J peptide.

35. The method of any one of claims 29-33, wherein said peptide consists of all "L" amino acids.

36. The method of any one of claims 29-33, wherein said peptide comprises at least one "D" amino acid.

37. The method of any one of claims 29-33, wherein said peptide consists of all "D" amino acids.

38. The method of claim 31, wherein said peptide is a D or L peptide whose sequence is shown in any of Tables 2-11 and/or SEQ ID Nos:1-1175.

39. The method of claim 31, wherein said peptide is a D or L peptide comprising the amino acid sequence DWFKAFYDKVAEKFKEAF (SEQ ID NO:5) or the retro amino acid sequence FAEKFKEAVKDYFAKFWD (SEQ ID NO:104).

40. The method of claim 39, wherein said peptide consists of all L amino acids.

41. The method of claims 38, 39 or 47, wherein said peptide comprises a protecting group at the amino or carboxyl terminus.

42. The method of claims 38, 39 or 47, wherein said peptide comprises a first protecting group coupled to the amino terminus and a second protecting group coupled to the carboxyl terminus.

43. The method of claim 42, wherein said protecting group is a protecting group selected from the group consisting of acetyl, amide, and 3 to 20 carbon alkyl groups, Fmoc, Tboc, 9-fluoreneacetyl group, 1-fluorenecarboxylic group, 9-florenecarboxylic group, 9-fluorenone-1-carboxylic group, benzyloxycarbonyl, Xanthyl (Xan), Trityl (Trt), 4-methyltrityl (Mtt), 4-methoxytrityl (Mmt), 4-methoxy-2,3,6-trimethyl-benzenesulphonyl (Mtr), Mesitylene-2-sulphonyl (Mts), 4,4-dimethoxybenzhydryl (Mbh),Tosyl (Tos), 2,2,5,7,8-pentamethyl chroman-6-sulphonyl (Pmc), 4-methylbenzyl (MeBzl), 4-methoxybenzyl (MeOBzl), Benzyloxy (BzlO), Benzyl (Bzl), Benzoyl (Bz), 3-nitro-2-pyridinesulphenyl (Npys), 1-(4,4-dimentyl-2,6-diaxocyclohexylidene)ethyl (Dde), 2,6-dichlorobenzyl (2,6-DiCl-Bzl), 2-chlorobenzyloxycarbonyl (2-Cl-Z), 2-bromobenzyloxycarbonyl (2-Br-Z), Benzyloxymethyl (Bom), t-butoxycarbonyl (Boc), cyclohexyloxy (cHxO),t-butoxymethyl (Bum), t-butoxy (tBuO), t-Butyl (tBu), Acetyl (Ac), and Trifluoroacetyl (TFA).

44. The method of claim 42, wherein said peptide comprises a protecting group coupled to the amino terminal and said amino terminal protecting group is a protecting group selected from the group consisting of acetyl, propeonyl, and a 3 to 20 carbon alkyl.

45. The method of claim 44, wherein said peptide comprises a protecting group coupled to the carboxyl terminal and said carboxyl terminal protecting group is an amide.

46. The method of claim 29, wherein said niclosamide is administered before administration of said peptide.

47. The method of claim 29, wherein said niclosamide is administered at the same time as said peptide.

48. The method of claim 29, wherein said niclosamide is combined with said peptide to form an adduct.

49. The method of claim 29, wherein said niclosamide is selected from the group consisting of 2'5-dichloro-4'-nitrosalicylanilide, 5-chloro-salicyl-(2-chloro-4-nitro) anilide 2-aminoethanol salt, 5-chloro-salicyl-(2-chloro-4-nitro) anilide piperazine salt, and 5-chloro-salicyl-(2-chloro-4-nitro) anilide monohydrate.

50. The method of claim 29, wherein said niclosamide analogue is a compound in Figure 2, 4, 5, 6, or 7.

51. A pharmaceutical formulation comprising:
an orally administered pharmacologically active agent; and
a salicylanilide.

52. The formulation of claim 51, wherein said salicylanilide comprises niclosamide and/or a niclosamide analogue.

53. The formulation of claims 51 or 52, wherein said orally administered pharmacologically active agent is a therapeutic peptide.

54. The formulation of claim 53, wherein said therapeutic peptide and said salicylanilide form an adduct.

55. The formulation of claim 51 wherein pharmaceutically active agent is not a non-peptide antiproliferative agent.

56. The formulation of claim 51 wherein pharmaceutically active agent is not a non-peptide anti-cancer drug.

57. The formulation of claim 51 wherein pharmaceutically active agent is a peptide antiproliferative agent.

58. The formulation of claim 51 comprising:
a therapeutic amphipathic helical peptide; and

niclosamide and/or a niclosamide analogue, wherein said niclosamide and/or niclosamide analogue in said formulation shows substantially greater solubility in an aqueous solution than the niclosamide and/or niclosamide analogue in an aqueous solution absent said amphipathic helical peptide.

59. The formulation of claim 58, wherein said peptide is selected from the group consisting of ApoJ, ApoA-I, ApoA-I milano, or 18A.

60. The formulation of claim 58, wherein said peptide forms a class A amphipathic helix.

61. The formulation of claim 58, wherein said peptide is an Apo-J peptide.

62. The formulation of claim 58, wherein said peptide consists of all "L" amino acids.

63. The formulation of claim 58, wherein said peptide comprises at least one "D" amino acid.

64. The formulation of claim 58, wherein said peptide consists of all "D" amino acids.

65. The formulation of claim 58, wherein said peptide is a D or L peptide whose sequence is shown in any of Tables 2-11 and/or SEQ ID Nos:1-1175.

66. The formulation of claim 58, wherein said peptide is a D or L peptide having the amino acid sequence DWFKAFYDKVAEKFKEAF (SEQ ID NO:5) or the retro amino acid sequence FAEKFKEAVKDYFAKFWD (SEQ ID NO: 104).

67. The formulation of claim 66, wherein said peptide consists of all L amino acids.

68. The formulation of claims 58 or 66, wherein said peptide comprises a protecting group at the amino or carboxyl terminus.

69. The formulation of claims 58 or 66, wherein said peptide comprises a first protecting group coupled to the amino terminus and a second protecting group coupled to the carboxyl terminus.

70. The formulation of claim 69, wherein said protecting group is a protecting group selected from the group consisting of acetyl, amide, and 3 to 20 carbon alkyl groups, Fmoc, Tboc, 9-fluoreneacetyl group, 1-fluorenecarboxylic group, 9-florenecarboxylic group, 9-fluorenone-1-carboxylic group, benzyloxycarbonyl, Xanthyl (Xan), Trityl (Trt), 4-methyltrityl (Mtt), 4-methoxytrityl (Mmt), 4-methoxy-2,3,6-trimethyl-benzenesulphonyl (Mtr), Mesitylene-2-sulphonyl (Mts), 4,4-dimethoxybenzhydryl (Mbh),Tosyl (Tos), 2,2,5,7,8-pentamethyl chroman-6-sulphonyl (Pmc), 4-methylbenzyl (MeBzl), 4-methoxybenzyl (MeOBzl), Benzyloxy (BzlO), Benzyl (Bzl), Benzoyl (Bz), 3-nitro-2-pyridinesulphenyl (Npys), 1-(4,4-dimentyl-2,6-diaxocyclohexylidene)ethyl (Dde), 2,6-dichlorobenzyl (2,6-DiCl-Bzl), 2-chlorobenzyloxycarbonyl (2-Cl-Z), 2-bromobenzyloxycarbonyl (2-Br-Z), Benzyloxymethyl (Bom), t-butoxycarbonyl (Boc), cyclohexyloxy (cHxO),t-butoxymethyl (Bum), t-butoxy (tBuO), t-Butyl (tBu), Acetyl (Ac), and Trifluoroacetyl (TFA).

71. The formulation of claim 69, wherein said first protecting group is a protecting group selected from the group consisting of acetyl, propeonyl, and a 3 to 20 carbon alkyl.

72. The formulation of claim 71, wherein said second protecting group is an amide.

73. A method of mitigating one or more symptoms of a pathology characterized by an inflammatory response in a mammal, said method comprising:

orally administering to said mammal an amphipathic helical peptide that mitigates one or more symptoms of atherosclerosis or other pathology characterized by an inflammatory response in conjunction with niclosamide or a niclosamide analogue, whereby said oral delivery provides *in vivo* activity of said peptide to mitigate one or more symptoms of said pathology.

74. The method of claim 73, wherein said niclosamide or niclosamide analogue is administered before said peptide.

75. The method of claim 73, wherein said niclosamide or niclosamide analogue is administered simultaneously with peptide.

76. The method of claim 73, wherein said niclosamide or niclosamide analogue and said peptide are administered as a single formulation.

77. The method of claim 73, wherein said niclosamide or niclosamide analogue and said peptide are combined to form an adduct prior to administration.

78. The method of claim 73, wherein said niclosamide is selected from the group consisting of 2'5-dichloro-4'-nitrosalicylanilide, 5-chloro-salicyl-(2-chloro-4-nitro) anilide 2-aminoethanol salt, 5-chloro-salicyl-(2-chloro-4-nitro) anilide piperazine salt, and 5-chloro-salicyl-(2-chloro-4-nitro) anilide monohydrate.

79. The method of claim 73, wherein said niclosamide analogue is a compound in Figure 2, 3, 4, 5, 6, 7, and Table 1.

80. The method of claim 73, wherein said niclosamide or niclosamide analogue and said peptide are administered as a unit dosage formulation.

81. The method of claim 73, wherein said niclosamide or niclosamide analogue and said peptide are administered as a unit dosage formulation formulated so that the niclosamide or niclosamide analogue is released or solubilized before the peptide.

82. The method of claim 73, wherein said pathology is selected from the group consisting of atherosclerosis, rheumatoid arthritis, lupus erythematous, polyarteritis nodosa, osteoporosis, Altzheimer's disease, multiple sclerosis, chronic obstructive pulmonary disease, asthma, diabetes, chronic renal disease, and a viral illnesses.

83. The method of claim 73, wherein said pathology is atherosclerosis.

84. The method of claim 73, wherein said peptide is ApoA-I milano.

85. The method of claim 73, wherein said peptide forms a class A amphipathic helix.

86. The method of claim 73, wherein said peptide is an Apo-J peptide.

87. The method of claim 73, wherein said peptide consists of all "L" amino acids.

88. The method of claim 73, wherein said peptide comprises at least one "D" amino acid.

89. The method of claim 73, wherein said peptide consists of all "D" amino acids.

90. The method of claim 73, wherein said peptide is a D or L peptide shown in Tables 2-11 and/or SEQ ID Nos:1-1175.

91. The method of claim 73, wherein said peptide is a D or L peptide having the amino acid sequence DWFKAFYDKVAEKFKEAF (SEQ ID NO:5) or the retro amino acid sequence FAEKFKEAVKDYFAKFWD (SEQ ID NO: 104).

92. The method of claim 91, wherein said peptide consists of all L amino acids.

93. The method of claims 73 or 91, wherein said peptide comprises a protecting group at the amino or carboxyl terminus.

94. The method of claim 93, wherein said protecting group is a protecting group selected from the group consisting of acetyl, amide, and 3 to 20 carbon alkyl groups, Fmoc, Tboc, 9-fluoreneacetyl group, 1-fluorenecarboxylic group, 9-florenecarboxylic group, 9-fluorenone-1-carboxylic group, benzyloxycarbonyl, Xanthyl (Xan), Trityl (Trt), 4-methyltrityl (Mtt), 4-methoxytrityl (Mmt), 4-methoxy-2,3,6-trimethyl-benzenesulphonyl (Mtr), Mesitylene-2-sulphonyl (Mts), 4,4-dimethoxybenzhydryl (Mbh),Tosyl (Tos), 2,2,5,7,8-pentamethyl chroman-6-sulphonyl (Pmc), 4-methylbenzyl (MeBzl), 4-methoxybenzyl (MeOBzl), Benzyloxy (BzlO), Benzyl (Bzl), Benzoyl (Bz), 3-nitro-2-pyridinesulphenyl (Npys), 1-(4,4-dimentyl-2,6-diaxocyclohexylidene)ethyl (Dde), 2,6-

dichlorobenzyl (2,6-DiCl-Bzl), 2-chlorobenzyloxycarbonyl (2-Cl-Z), 2-bromobenzyloxycarbonyl (2-Br-Z), Benzyloxymethyl (Bom), t-butoxycarbonyl (Boc), cyclohexyloxy (cHxO),t-butoxymethyl (Bum), t-butoxy (tBuO), t-Butyl (tBu), Acetyl (Ac), and Trifluoroacetyl (TFA).

95. The method of claim 93, wherein said first protecting group is a protecting group selected from the group consisting of acetyl, propeonyl, and a 3 to 20 carbon alkyl.

96. The method of claim 95, wherein said second protecting group is an amide.

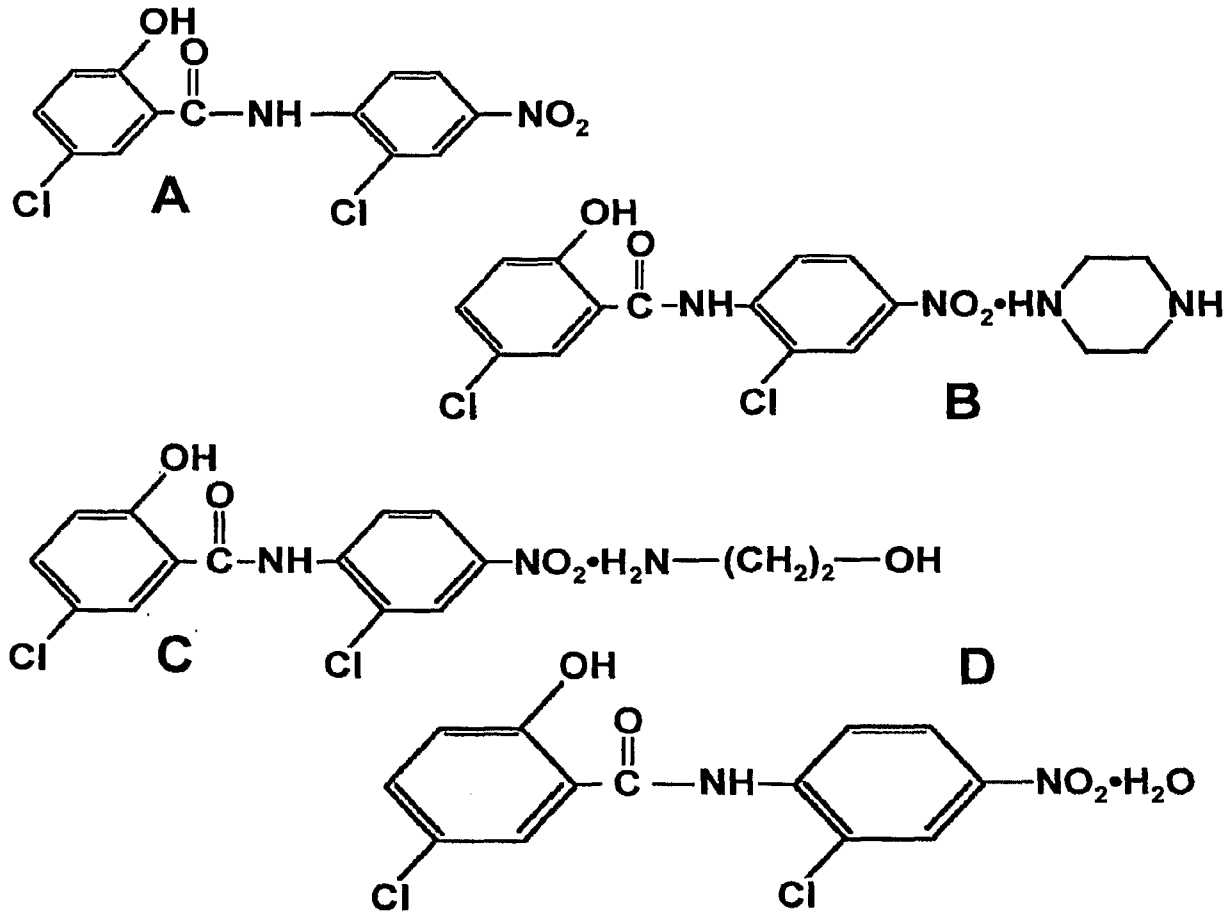
97. A kit comprising a container containing a salicylanilide and a therapeutic peptide.

98. The kit of claim 97, wherein said salicylanilide is niclosamide or a niclosamide analogue.

99. The kit of claim 97, wherein said peptide is selected from the group consisting of ApoJ, ApoA-I, ApoA-I milano, and 18A.

100. The kit of claim 97, wherein said peptide forms a class A amphipathic helix.

101. The kit of claim 97, wherein said peptide is a D or L peptide having the amino acid sequence DWFKAFYDKVAEKFKEAF (SEQ ID NO:5) or the retro amino acid sequence FAEKFKEAVKDYFAKFWD (SEQ ID NO: 104).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O
C
NH
NO2
Cl
A
Cl
OH
O
C
NH
NO2•HN
NH
Cl
Cl
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O
C
NH
NO2•H2N—(CH2)2—OH
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C
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D
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C
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NO2•H2O
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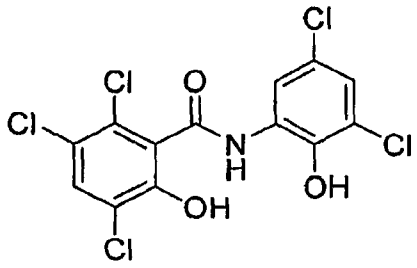
Cl

Fig. 1



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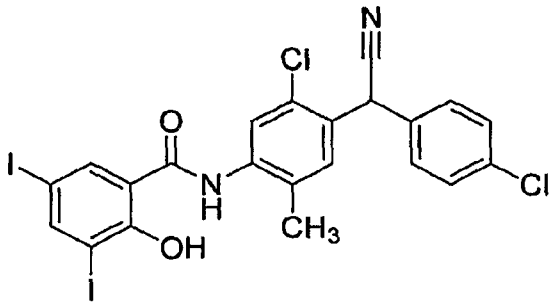

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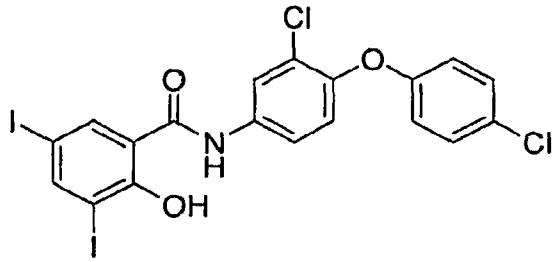

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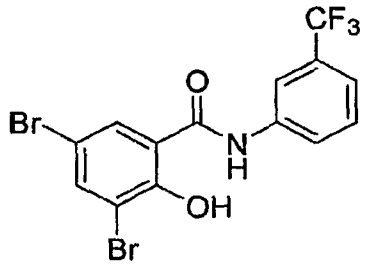

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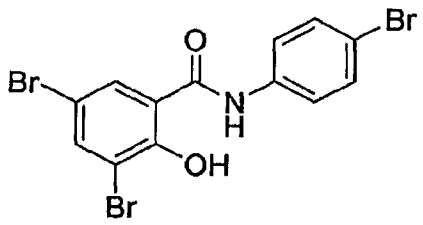

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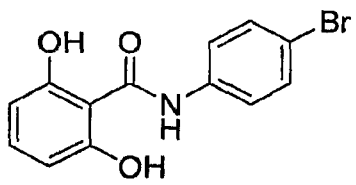

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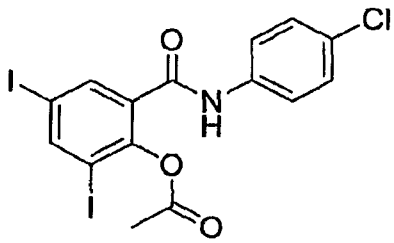
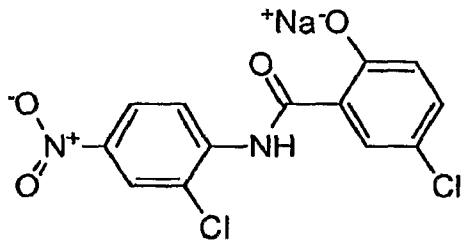


G

Fig. 2



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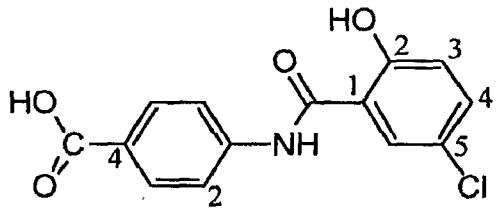

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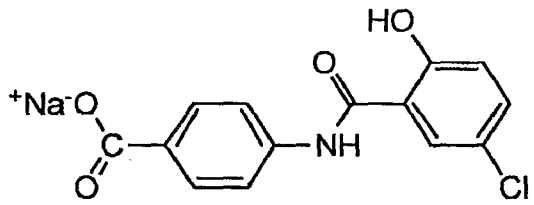

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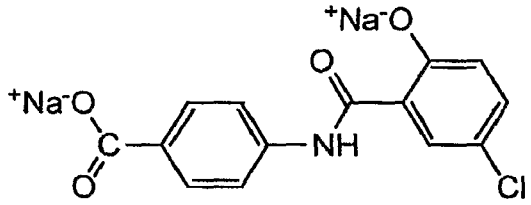

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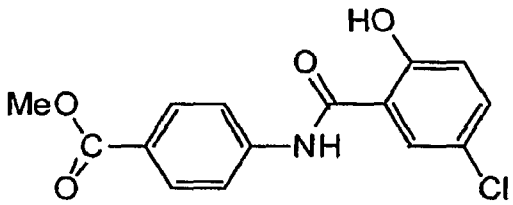

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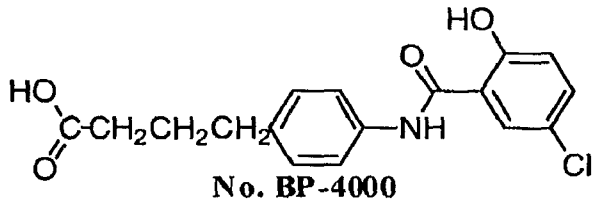

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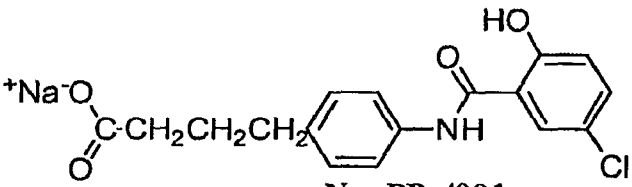
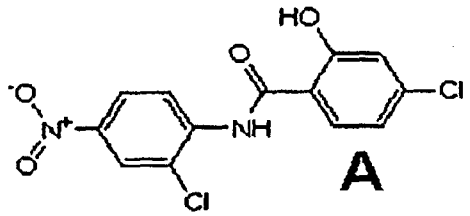
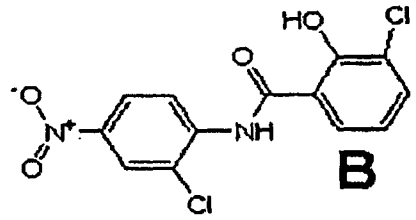


No. BP-4001

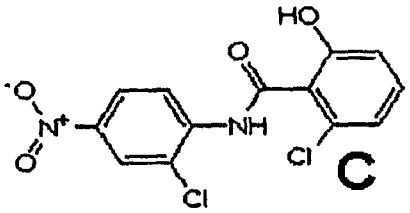
Fig. 3



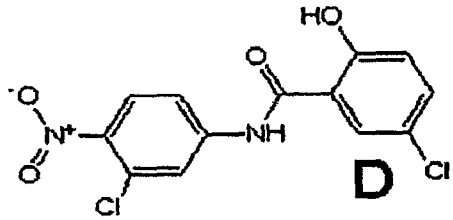
4-chloro-*N*-(2-chloro-4-nitrophenyl)-2-hydroxybenzamide



3-chloro-*N*-(2-chloro-4-nitrophenyl)-2-hydroxybenzamide



2-chloro-*N*-(2-chloro-4-nitrophenyl)-6-hydroxybenzamide



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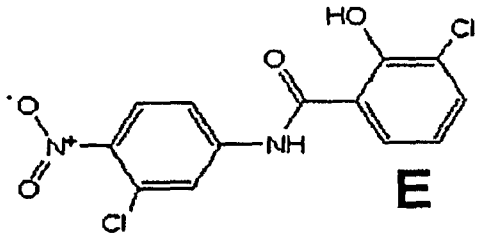

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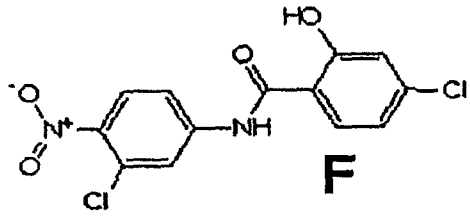

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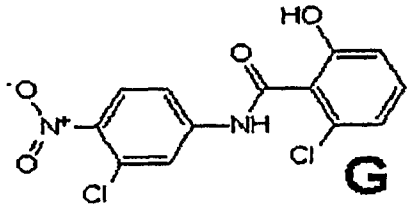
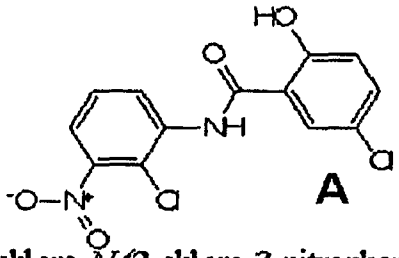


2-chloro-*N*-(3-chloro-4-nitrophenyl)-6-hydroxybenzamide

Fig. 4



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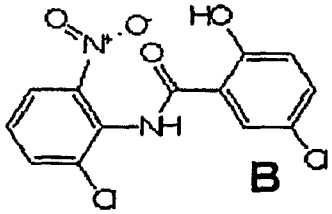

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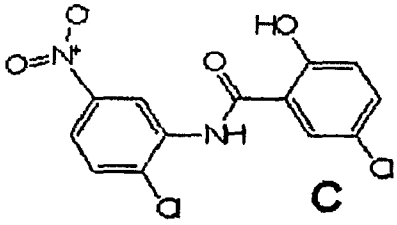

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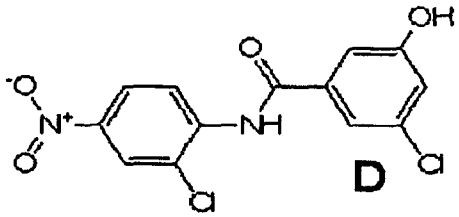

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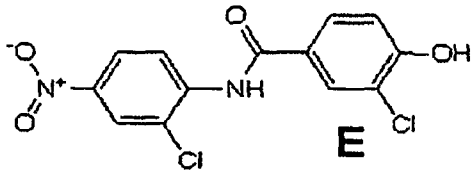

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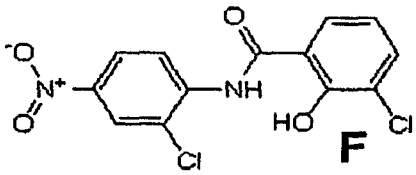
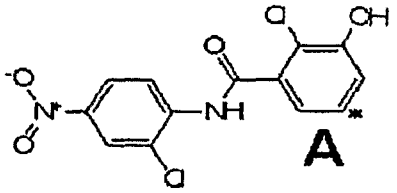


3-chloro-*N*-(2-chloro-4-nitrophenyl)-2-hydroxybenzamide

Fig. 5



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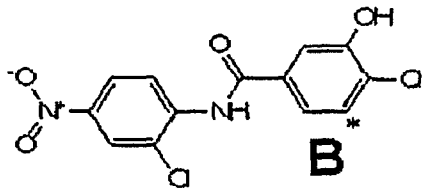
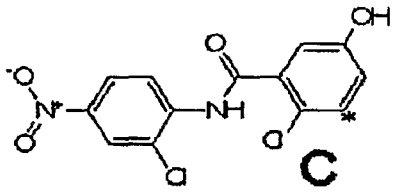
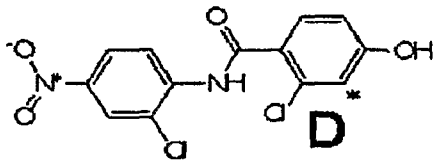


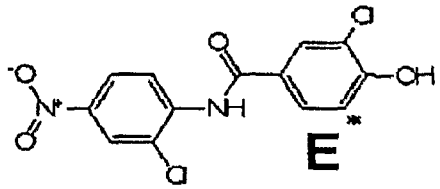
4-chloro-*N*-(2-chloro-4-nitrophenyl)-3-hydroxybenzamide



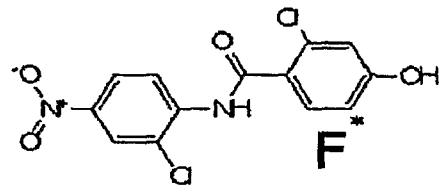
2-chloro-*N*-(2-chloro-4-nitrophenyl)-5-hydroxybenzamide



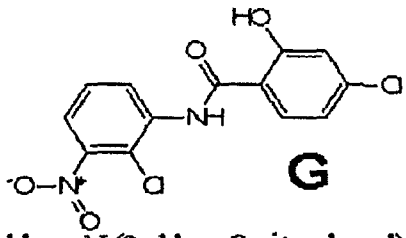
2-chloro-*N*-(2-chloro-4-nitrophenyl)-4-hydroxybenzamide



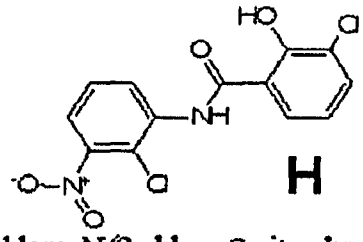
3-chloro-*N*-(2-chloro-4-nitrophenyl)-4-hydroxybenzamide



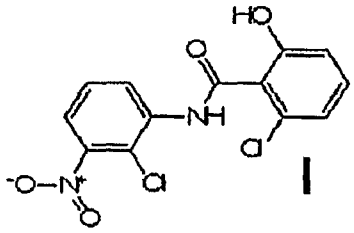
2-chloro-*N*-(2-chloro-4-nitrophenyl)-4-hydroxybenzamide



4-chloro-*N*-(2-chloro-3-nitrophenyl)-2-hydroxybenzamide

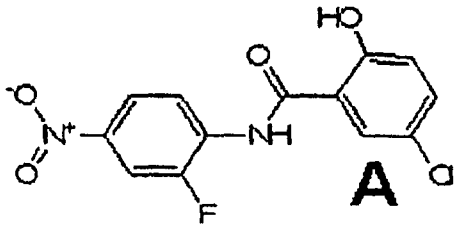


3-chloro-*N*-(2-chloro-3-nitrophenyl)-2-hydroxybenzamide

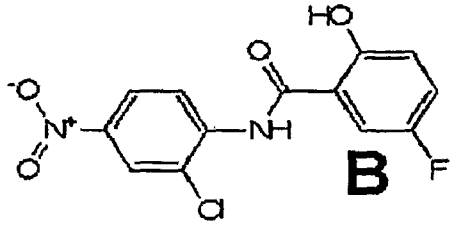


2-chloro-*N*-(2-chloro-3-nitrophenyl)-6-hydroxybenzamide

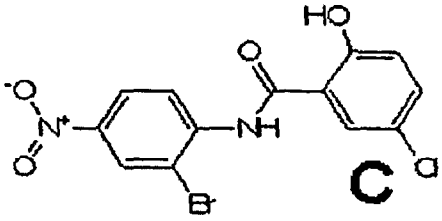
Fig. 6



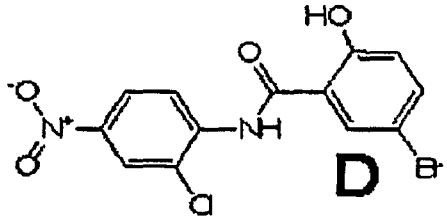
5-chloro-*N*-(2-fluoro-4-nitrophenyl)-2-hydroxybenzamide



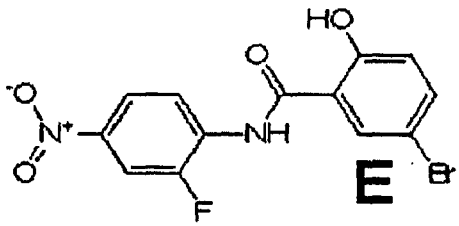
N-(2-chloro-4-nitrophenyl)-5-fluoro-2-hydroxybenzamide



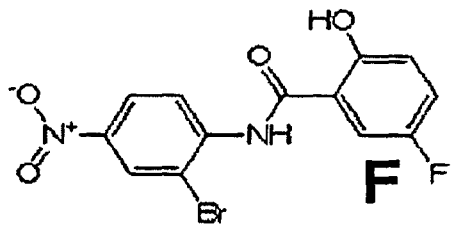
N-(2-bromo-4-nitrophenyl)-5-chloro-2-hydroxybenzamide



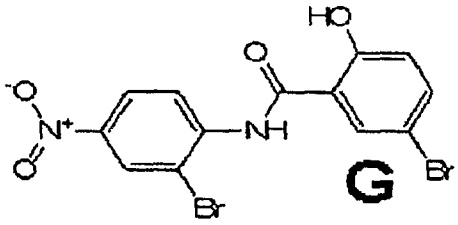
5-bromo-*N*-(2-chloro-4-nitrophenyl)-2-hydroxybenzamide



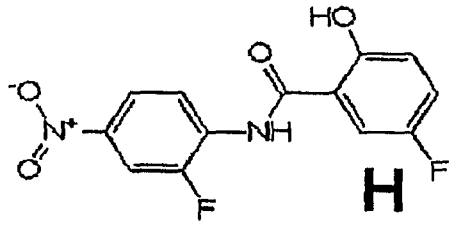
5-bromo-*N*-(2-fluoro-4-nitrophenyl)-2-hydroxybenzamide



N-(2-bromo-4-nitrophenyl)-5-fluoro-2-hydroxybenzamide



5-bromo-*N*-(2-bromo-4-nitrophenyl)-2-hydroxybenzamide



5-fluoro-*N*-(2-fluoro-4-nitrophenyl)-2-hydroxybenzamide

Fig. 7

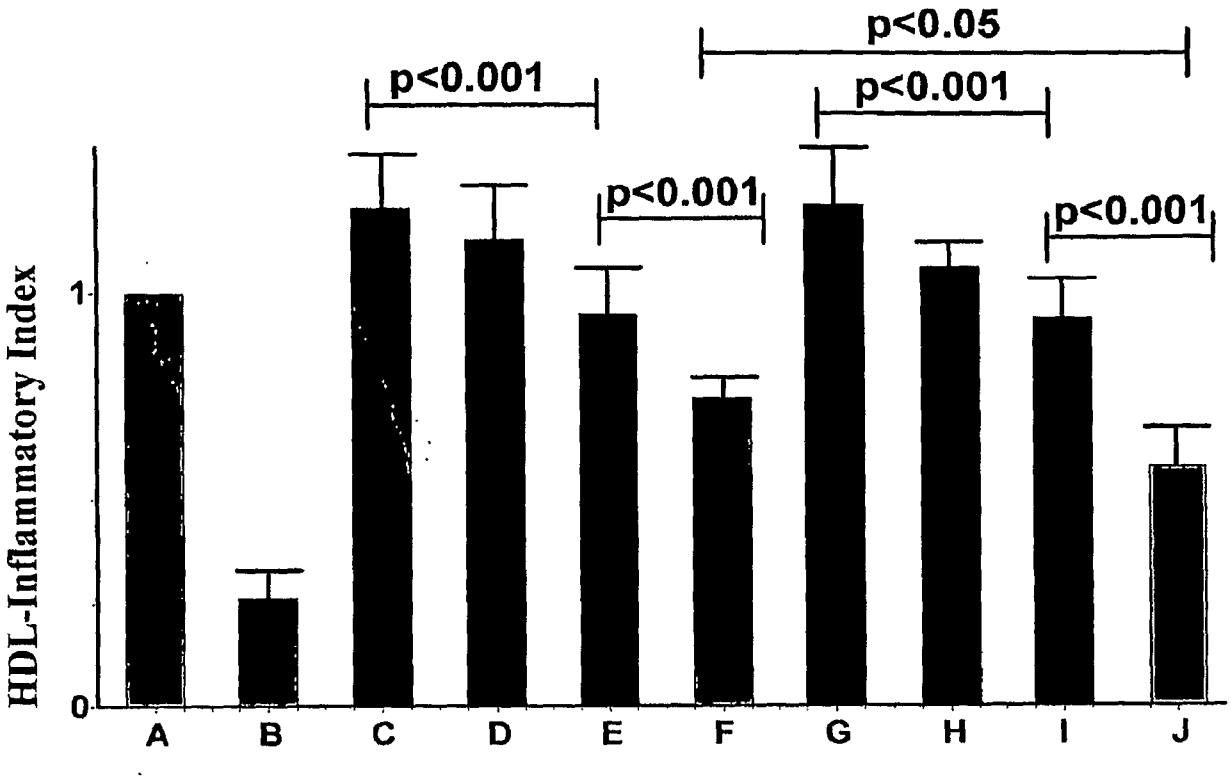

p<0.05
p<0.001
p<0.001
p<0.001
p<0.001
HDL-Inflammatory Index
1
0
A
B
C
D
E
F
G
H
I
J

Fig. 8

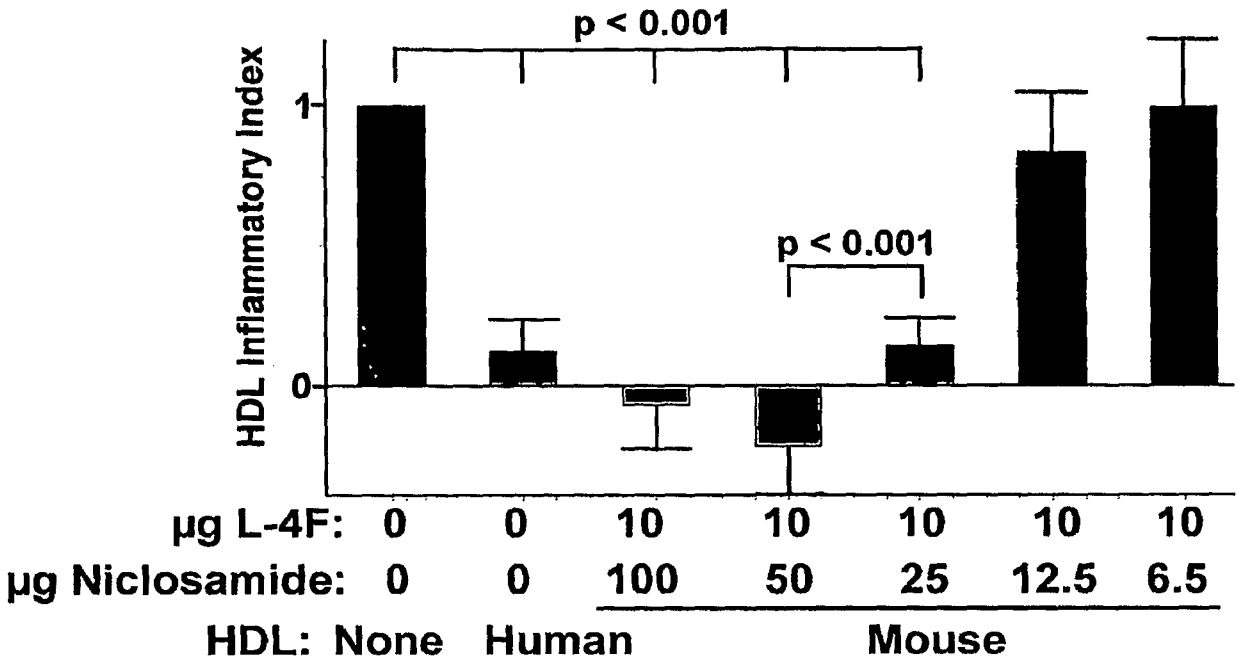

p < 0.001
p < 0.001
HDL Inflammatory Index
1
0
µg L-4F: 0 0 10 10 10 10 10
µg Niclosamide: 0 0 100 50 25 12.5 6.5
HDL: None Human Mouse

Fig. 9

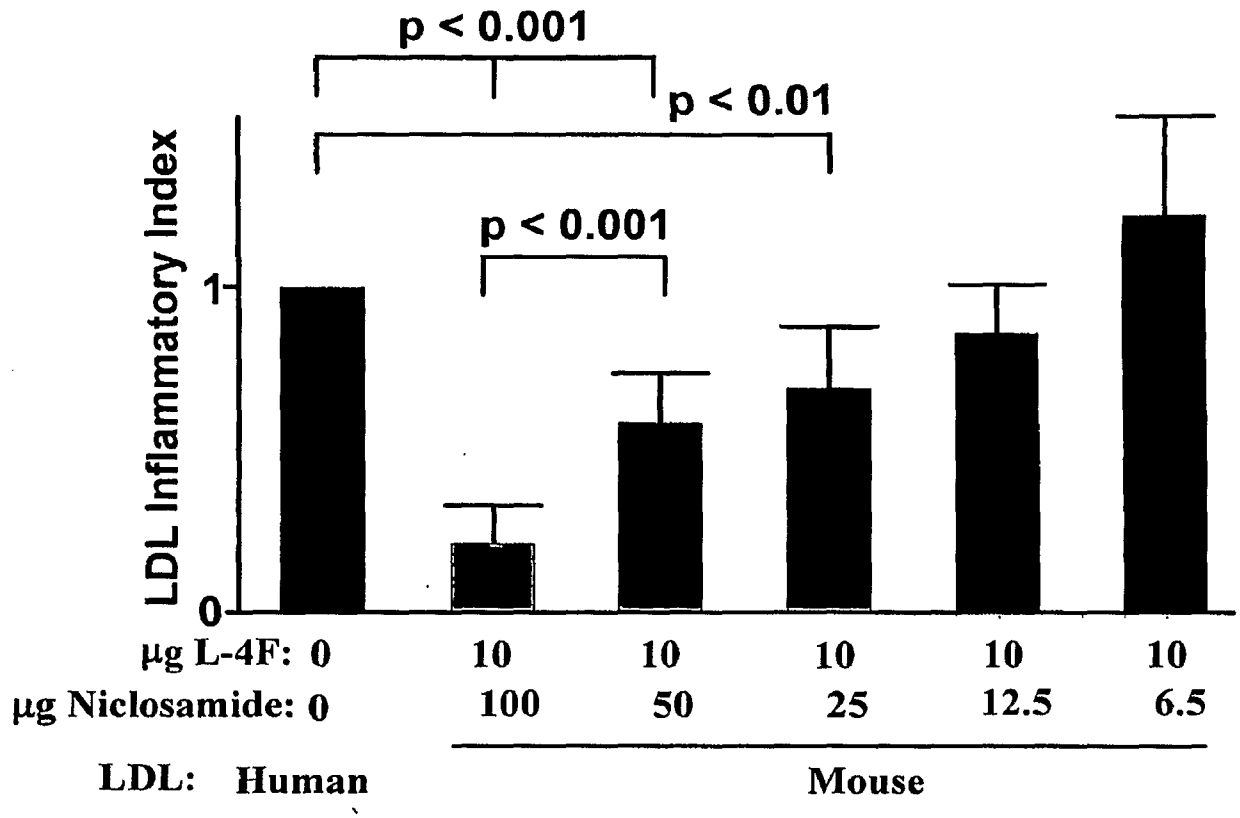

p < 0.001
p < 0.01
p < 0.001
LDL Inflammatory Index
1
0
µg L-4F: 0 10 10 10 10 10
µg Niclosamide: 0 100 50 25 12.5 6.5
LDL: Human Mouse

Fig.10

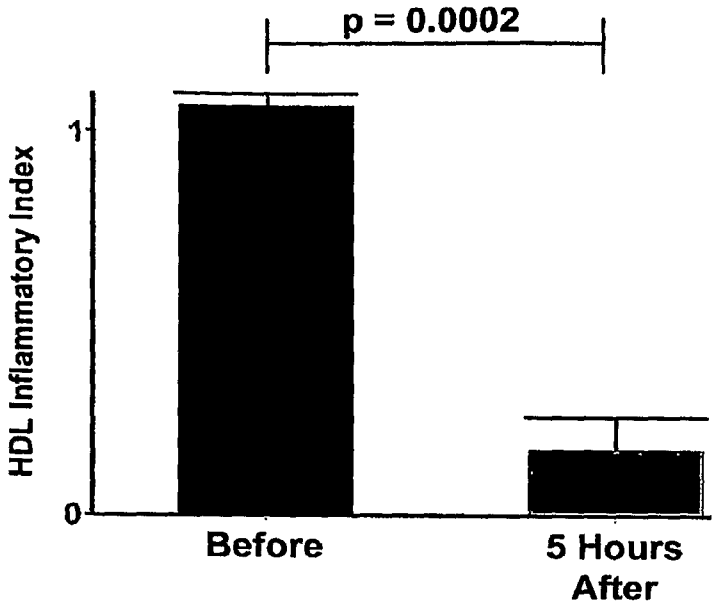

p = 0.0002
HDL Inflammatory Index
1
0
Before
5 Hours After

Fig.11

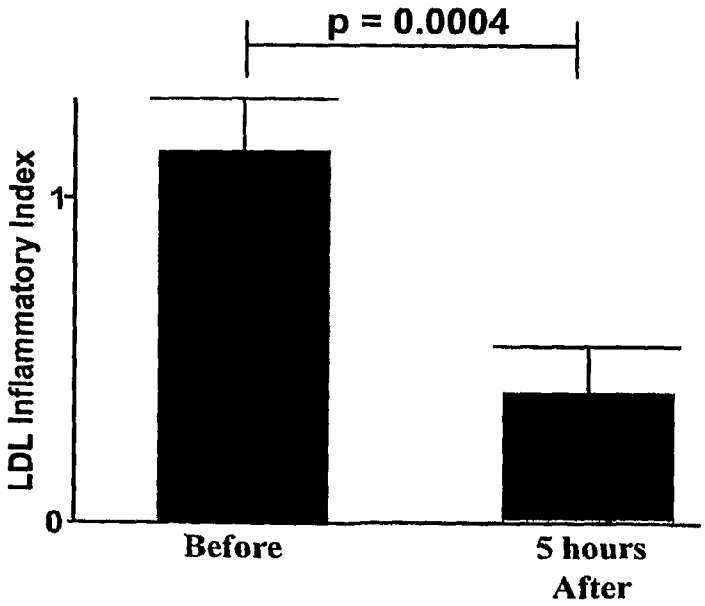
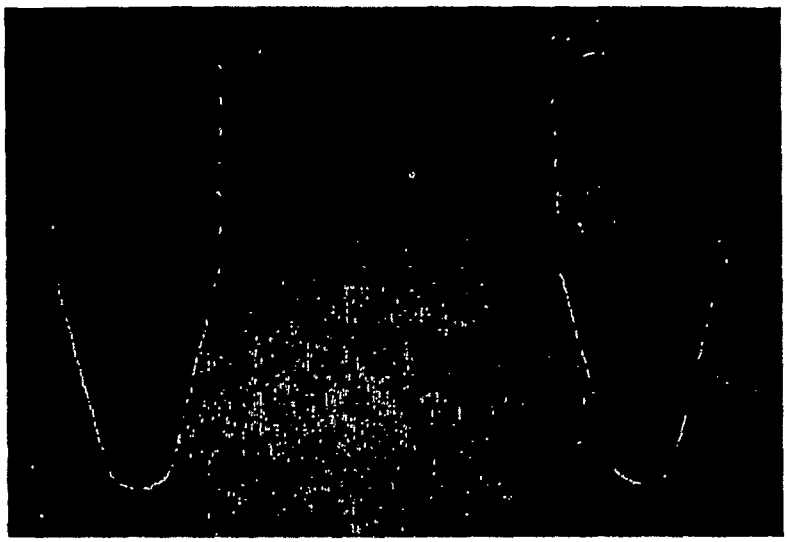

p = 0.0004
LDL Inflammatory Index
1
0
Before
5 hours After

Fig. 12



Niclosamide in Water

Niclosamide + L-4F in Water

Fig. 13

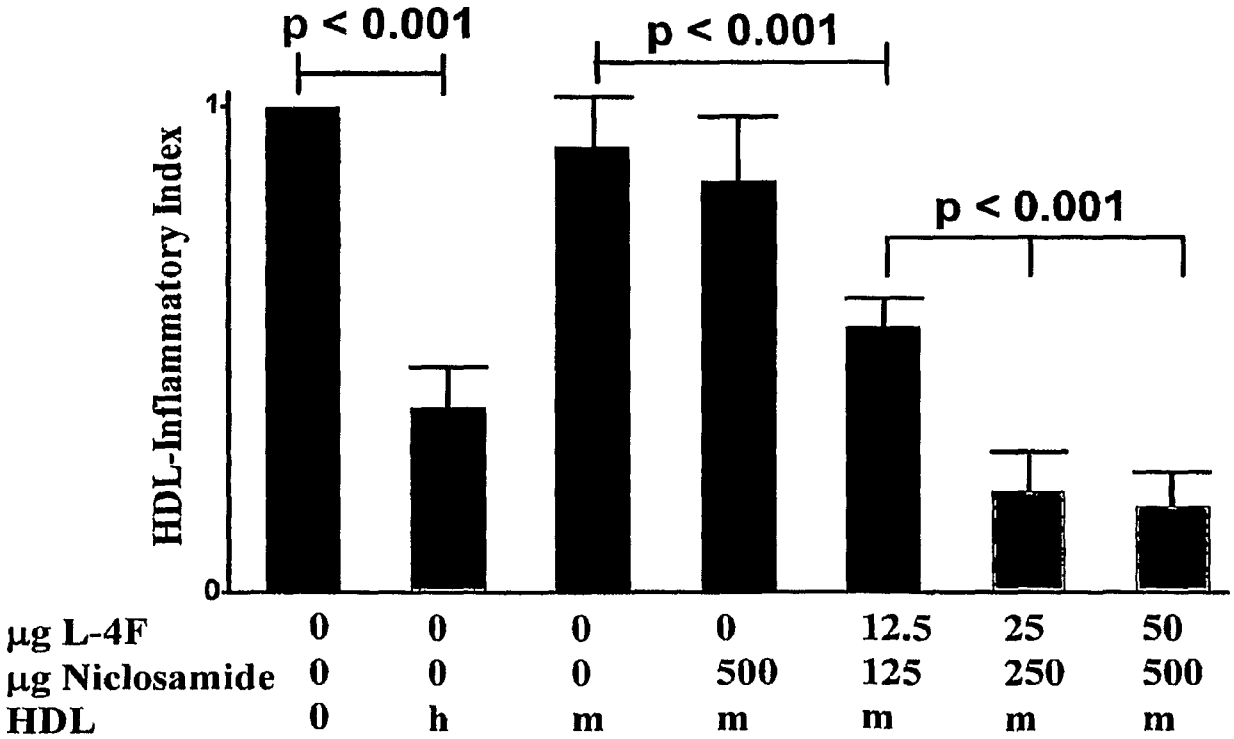


Fig. 14

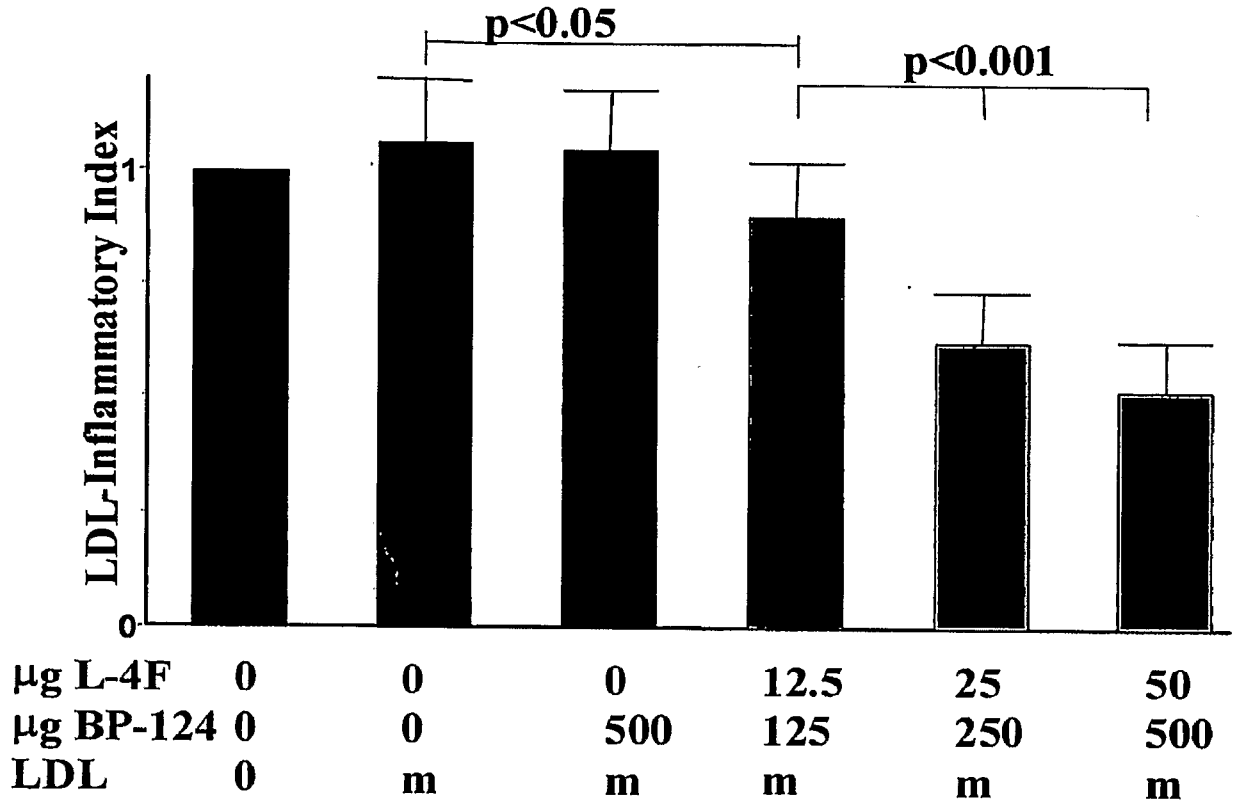
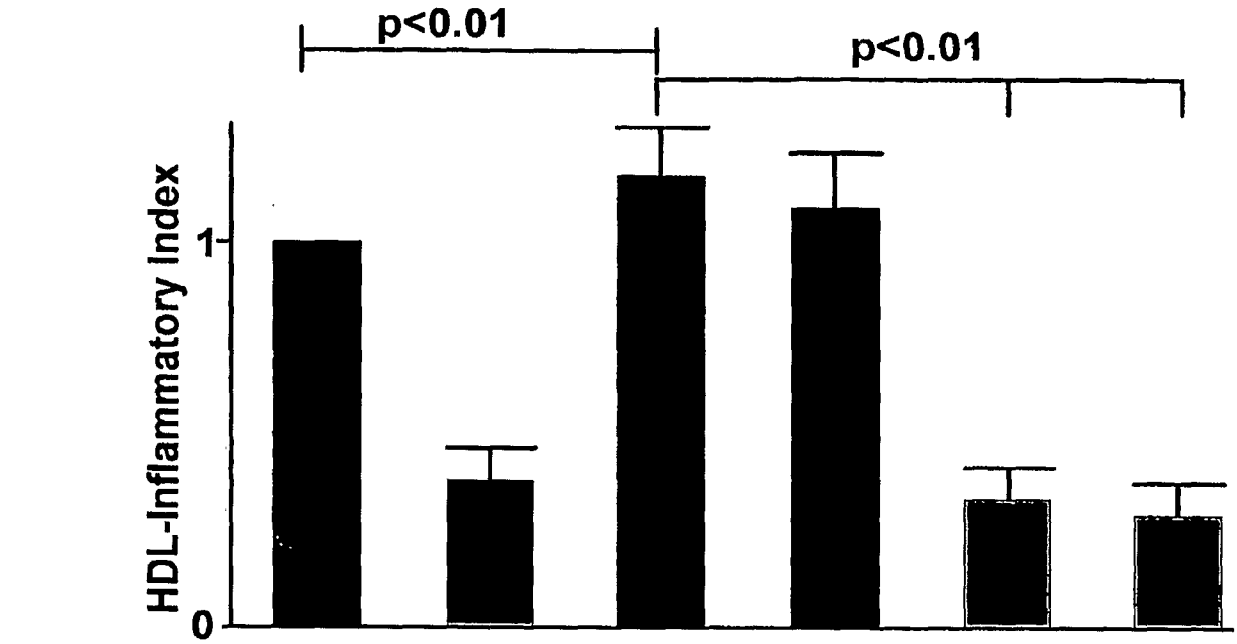
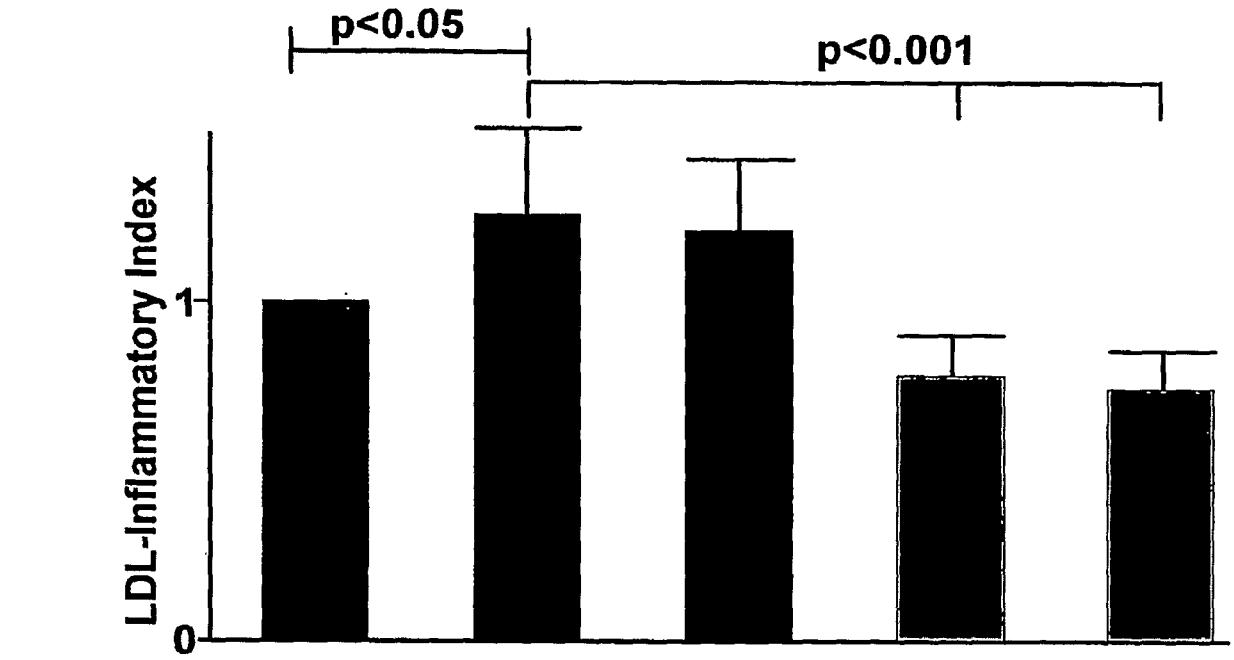

p<0.05
p<0.001
LDL-Inflammatory Index
1
0
µg L-4F 0 0 0 12.5 25 50
µg BP-124 0 0 500 125 250 500
LDL 0 m m m m m

Fig. 15



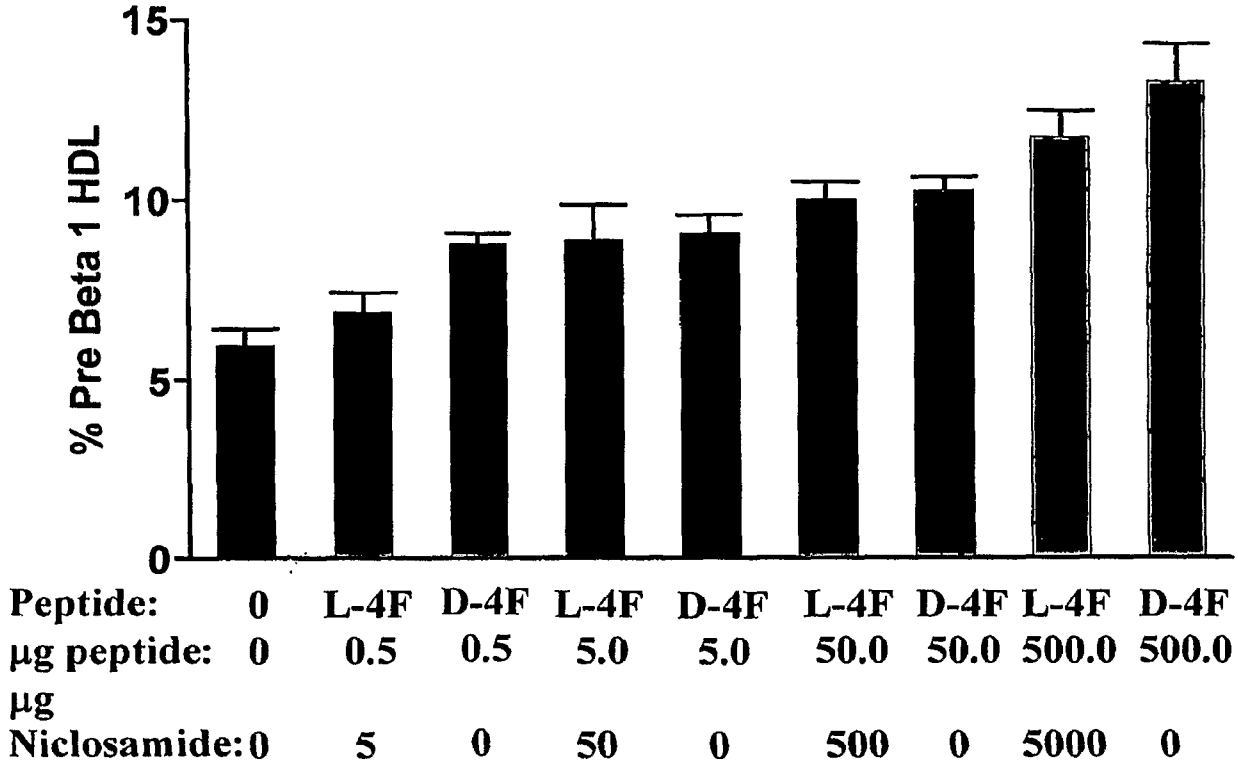
µg L-4F water	0	0	0	0	25	0
µg L-4F food	0	0	0	0	0	25
µg Niclosamide	0	0	0	250	250	250
HDL	0	h	m	m	m	m

Fig. 16



µg L-4F water	0	0	0	25	0
µg L-4F food	0	0	0	0	25
µg Niclosamide	0	0	250	250	250
LDL	h	m	m	m	m

Fig. 17



Peptide:	0	L-4F	D-4F	L-4F	D-4F	L-4F	D-4F	L-4F	D-4F
µg peptide:	0	0.5	0.5	5.0	5.0	50.0	50.0	500.0	500.0
µg Niclosamide:	0	5	0	50	0	500	0	5000	0

Fig. 18

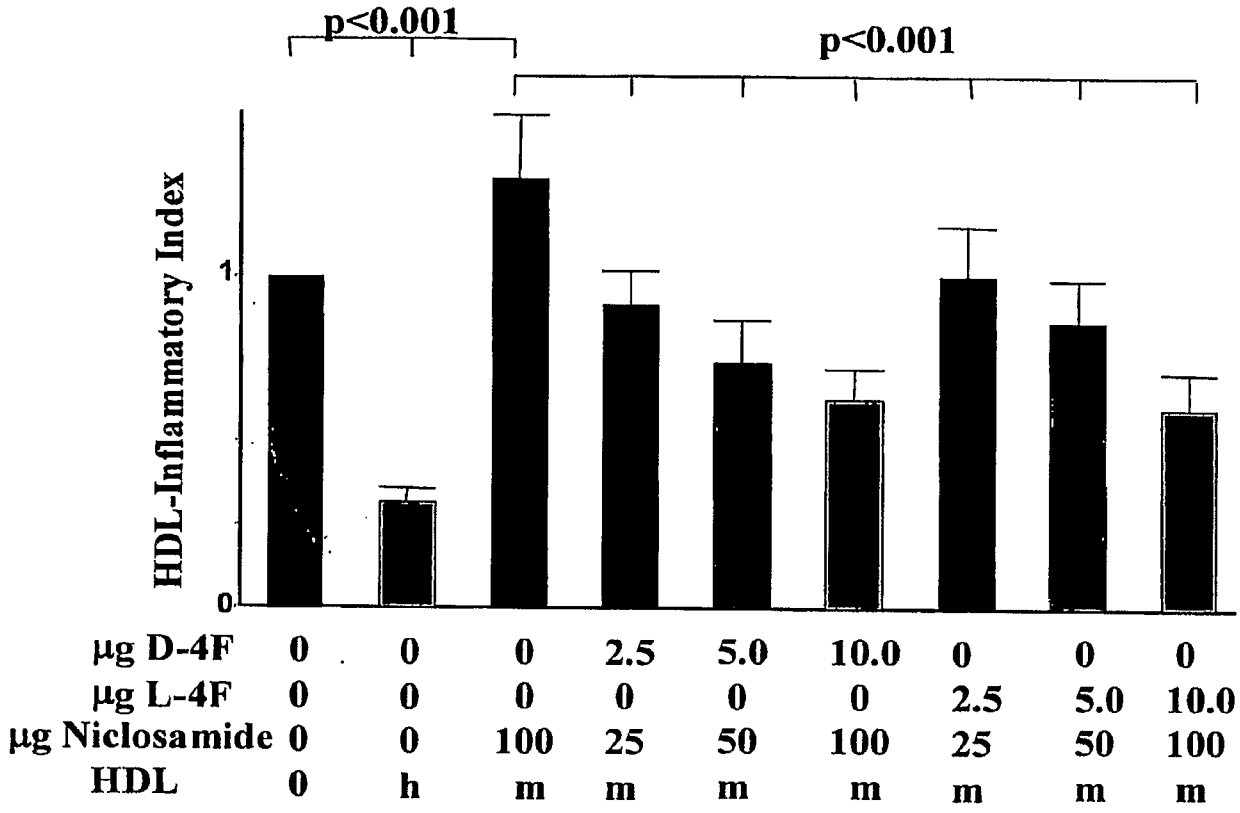
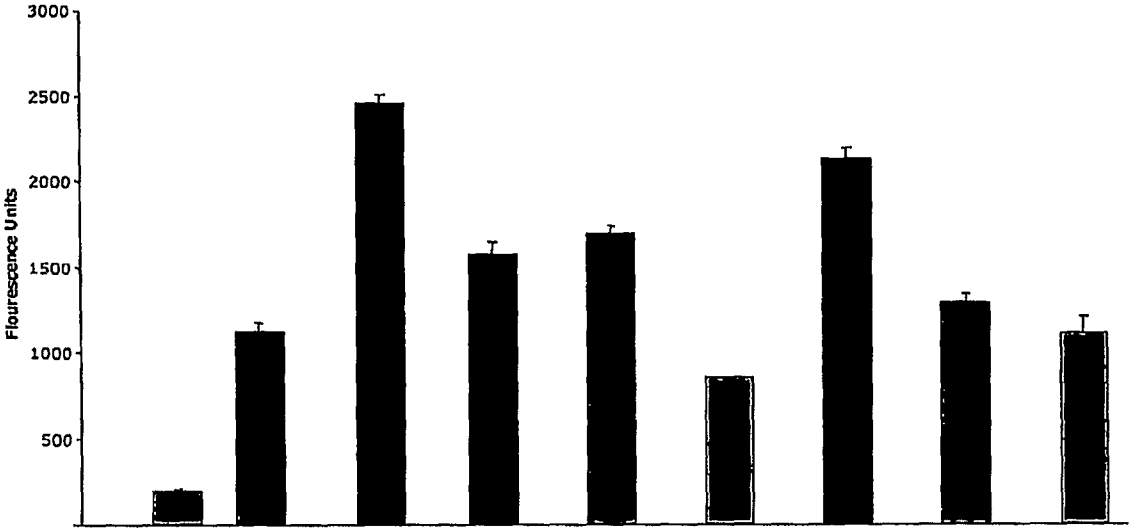

p<0.001
p<0.001
HDL-Inflammatory Index
1
0
µg D-4F 0 0 0 2.5 5.0 10.0 0 0 0
µg L-4F 0 0 0 0 0 0 2.5 5.0 10.0
µg Niclosamide 0 0 100 25 50 100 25 50 100
HDL 0 h m m m m m m m

Fig. 19



µg D-4F	0	0	0	2.5	5.0	10.0	0	0	0
µg L-4F	0	0	0	0	0	0	2.5	5.0	10.0
µg Niclosamide	0	0	100	25	50	100	25	50	100
LDL	0	h	h	h	h	h	h	h	h
HDL	0	0	m	m	m	m	m	m	m

Fig. 20

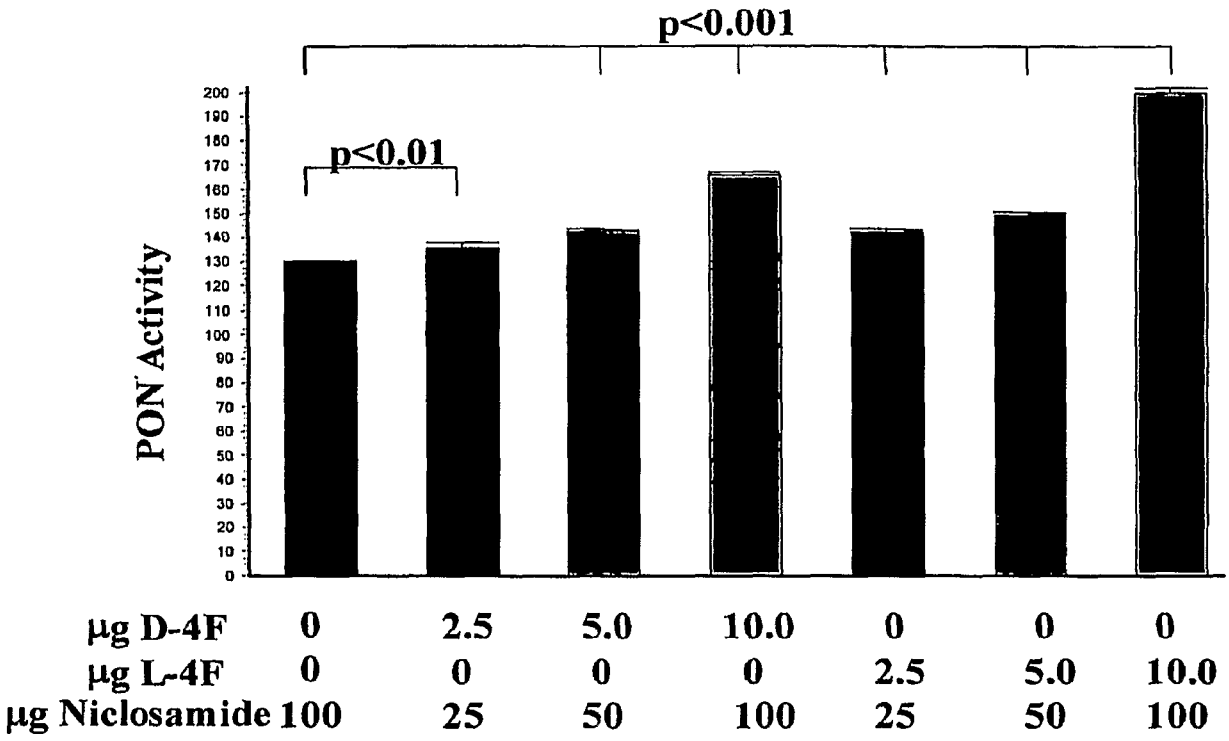

p<0.001
p<0.01
PON Activity
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
µg D-4F 0 2.5 5.0 10.0 0 0 0
µg L-4F 0 0 0 0 2.5 5.0 10.0
µg Niclosamide 100 25 50 100 25 50 100

Fig. 21

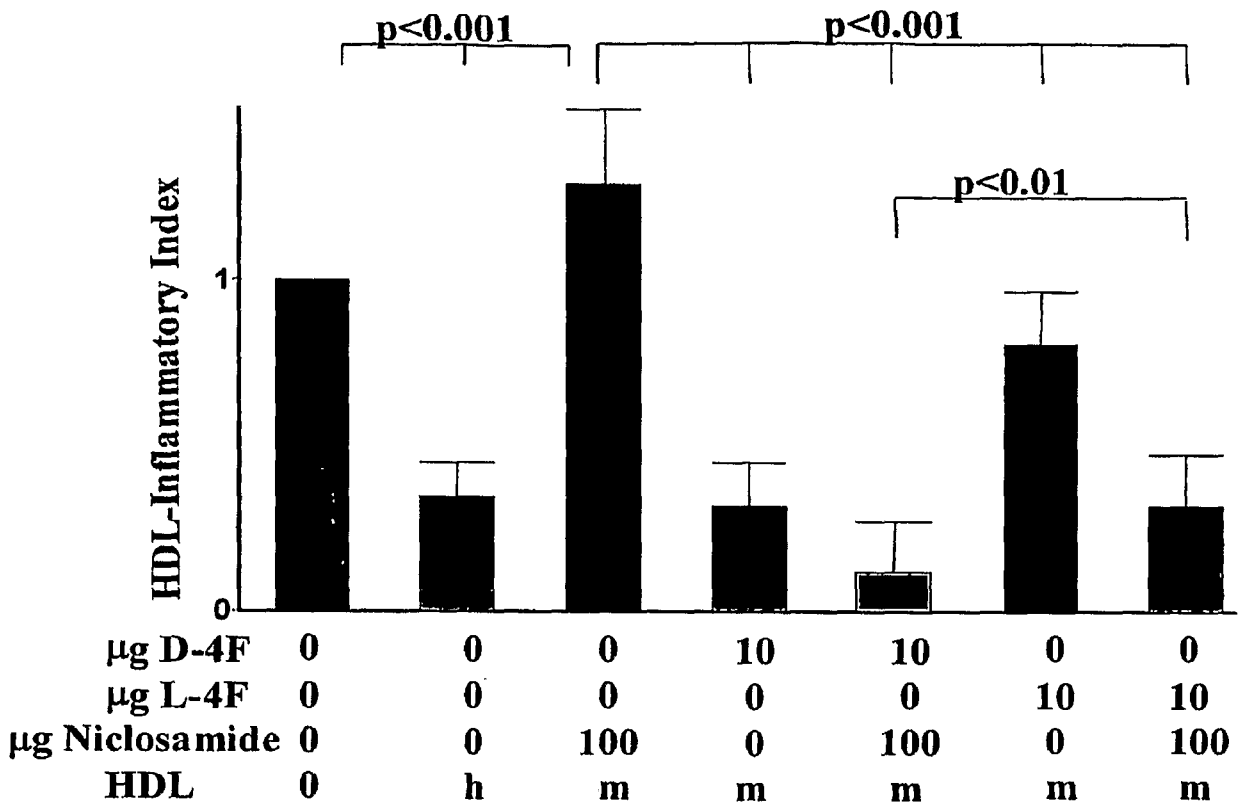

p<0.001
p<0.001
p<0.01
HDL-Inflammatory Index
1
0
µg D-4F 0 0 0 10 10 0 0
µg L-4F 0 0 0 0 0 10 10
µg Niclosamide 0 0 100 0 100 0 100
HDL 0 h m m m m m

Fig. 22

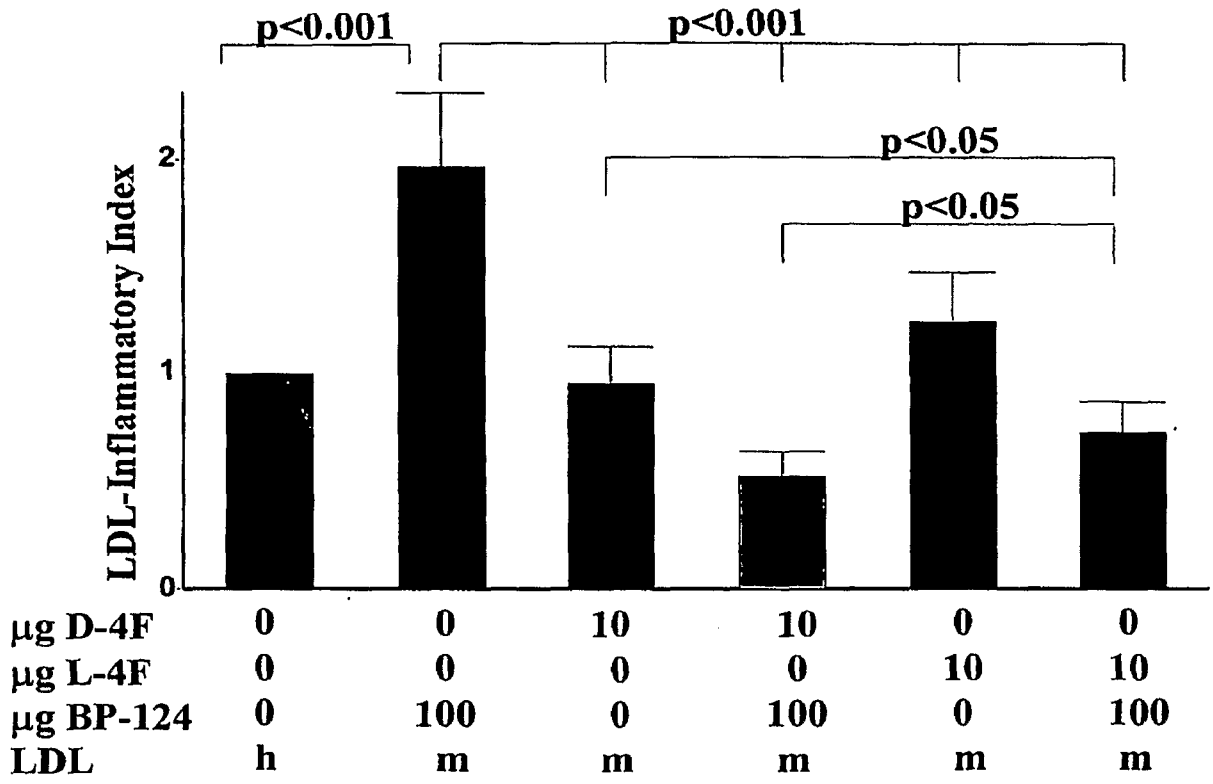

p<0.001
p<0.001
p<0.05
p<0.05
LDL-Inflammatory Index
2
1
0
µg D-4F 0 0 10 10 0 0
µg L-4F 0 0 0 0 10 10
µg BP-124 0 100 0 100 0 100
LDL h m m m m m

Fig. 23

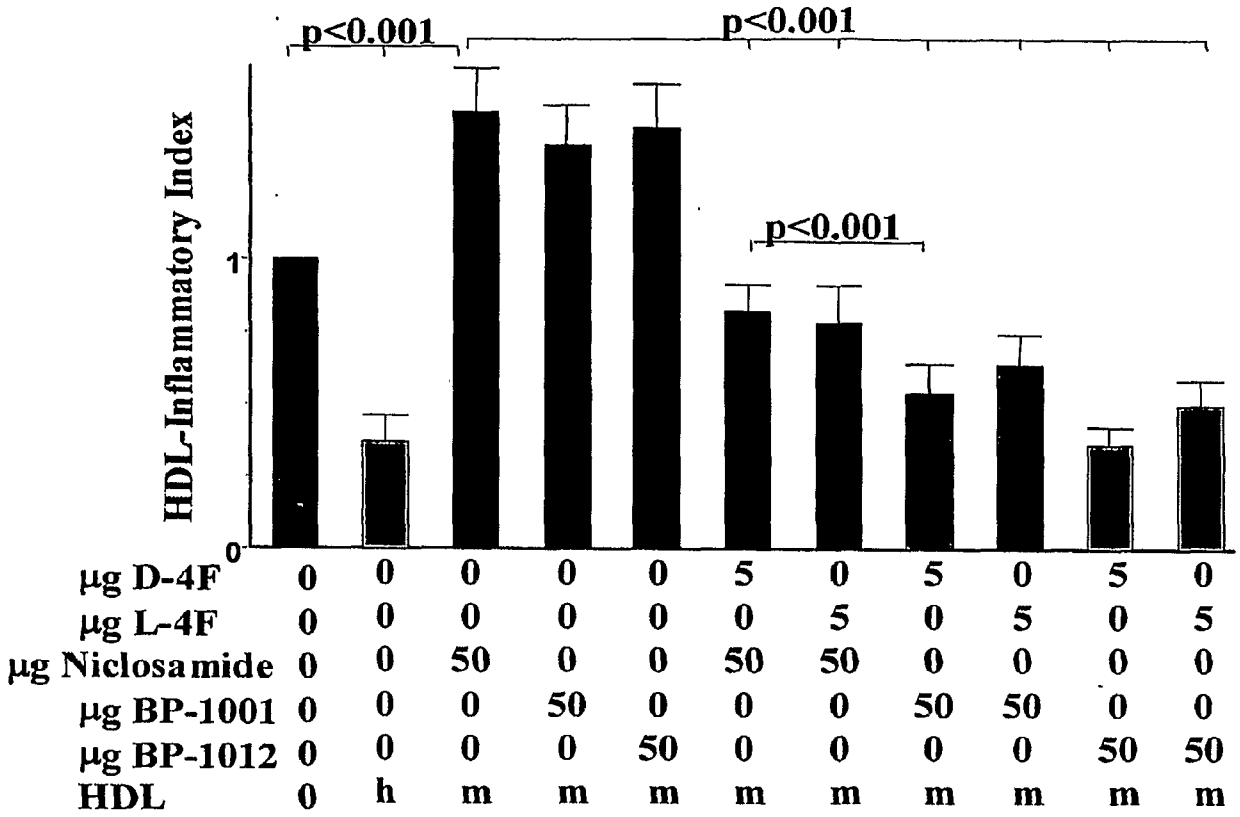

p<0.001
p<0.001
p<0.001
HDL-Inflammatory Index
1
0
µg D-4F 0 0 0 0 0 5 0 5 0 5 0
µg L-4F 0 0 0 0 0 0 5 0 5 0 5
µg Niclosamide 0 0 50 0 0 50 50 0 0 0 0
µg BP-1001 0 0 0 50 0 0 0 50 50 0 0
µg BP-1012 0 0 0 0 50 0 0 0 0 50 50
HDL 0 h m m m m m m m m m

Fig. 24

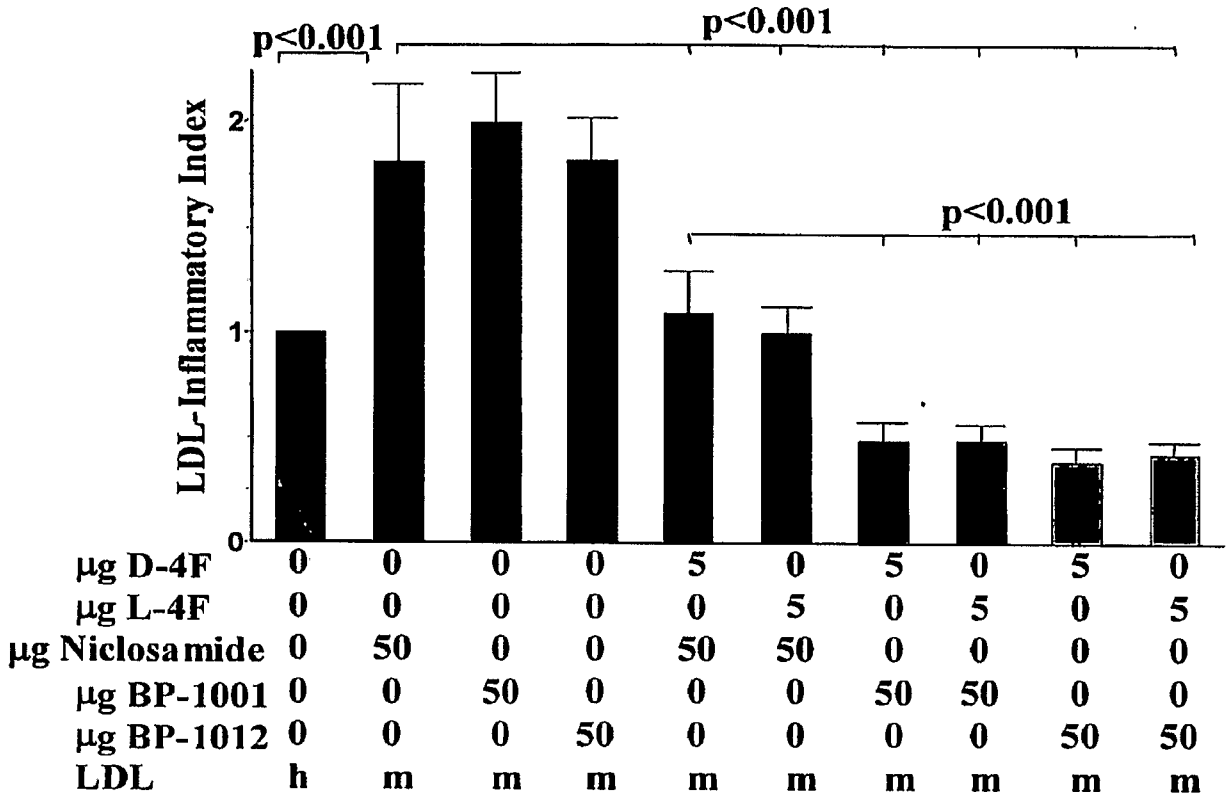

p<0.001
p<0.001
p<0.001
LDL-Inflammatory Index
2
1
0
µg D-4F 0 0 0 0 5 0 5 0 5 0
µg L-4F 0 0 0 0 0 5 0 5 0 5
µg Niclosamide 0 50 0 0 50 50 0 0 0 0
µg BP-1001 0 0 50 0 0 0 50 50 0 0
µg BP-1012 0 0 0 50 0 0 0 0 50 50
LDL h m m m m m m m m m

Fig. 25

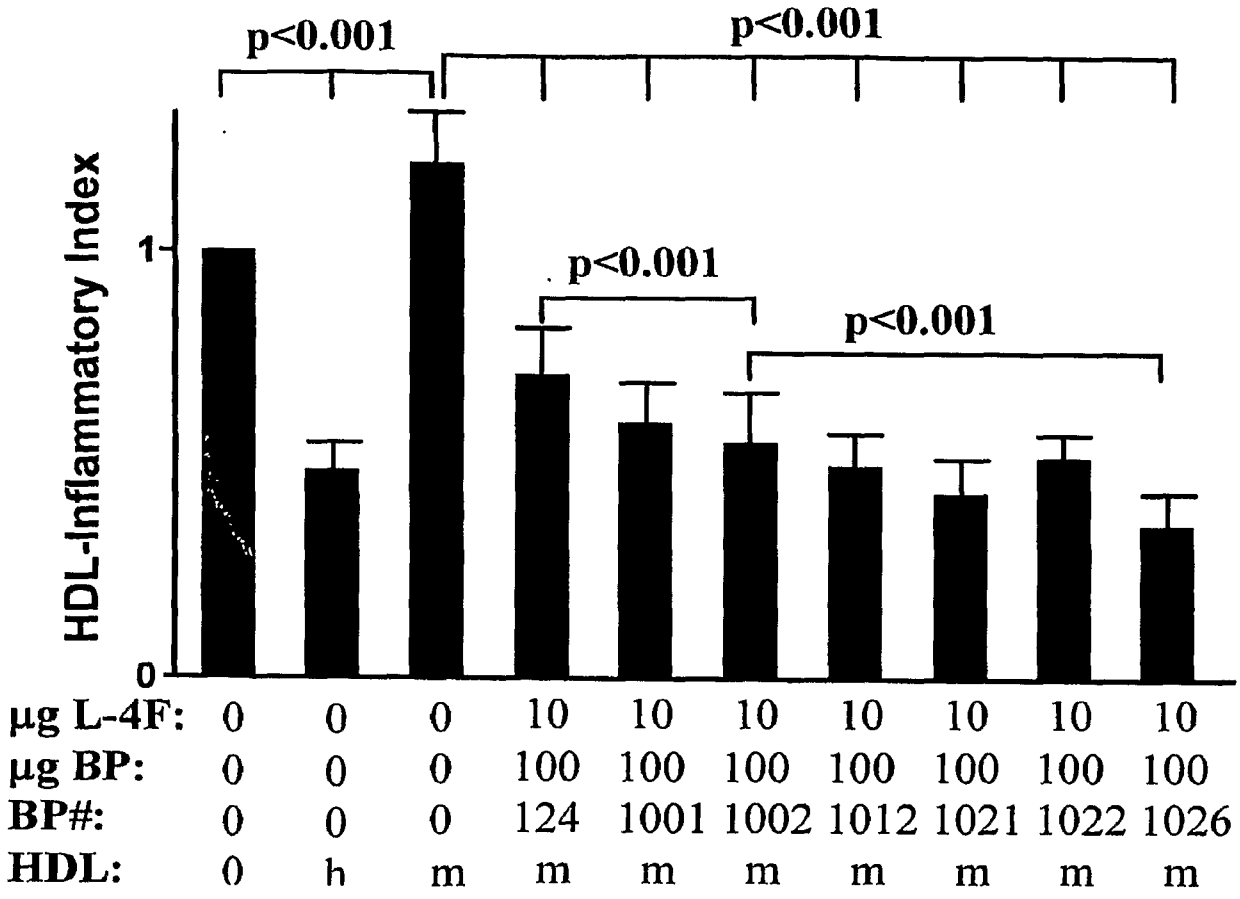

p<0.001
p<0.001
p<0.001
p<0.001
HDL-Inflammatory Index
1
0
µg L-4F: 0 0 0 10 10 10 10 10 10 10
µg BP: 0 0 0 100 100 100 100 100 100 100
BP#: 0 0 0 124 1001 1002 1012 1021 1022 1026
HDL: 0 h m m m m m m m m

Fig. 26

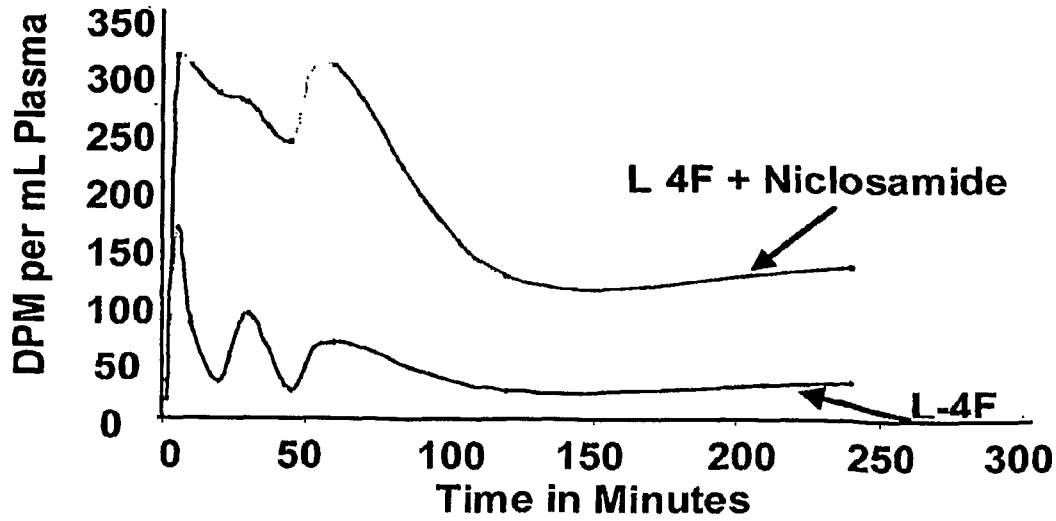

DPM per mL Plasma
350
300
250
200
150
100
50
0
L 4F + Niclosamide
L-4F
0 50 100 150 200 250 300
Time in Minutes

Fig. 27

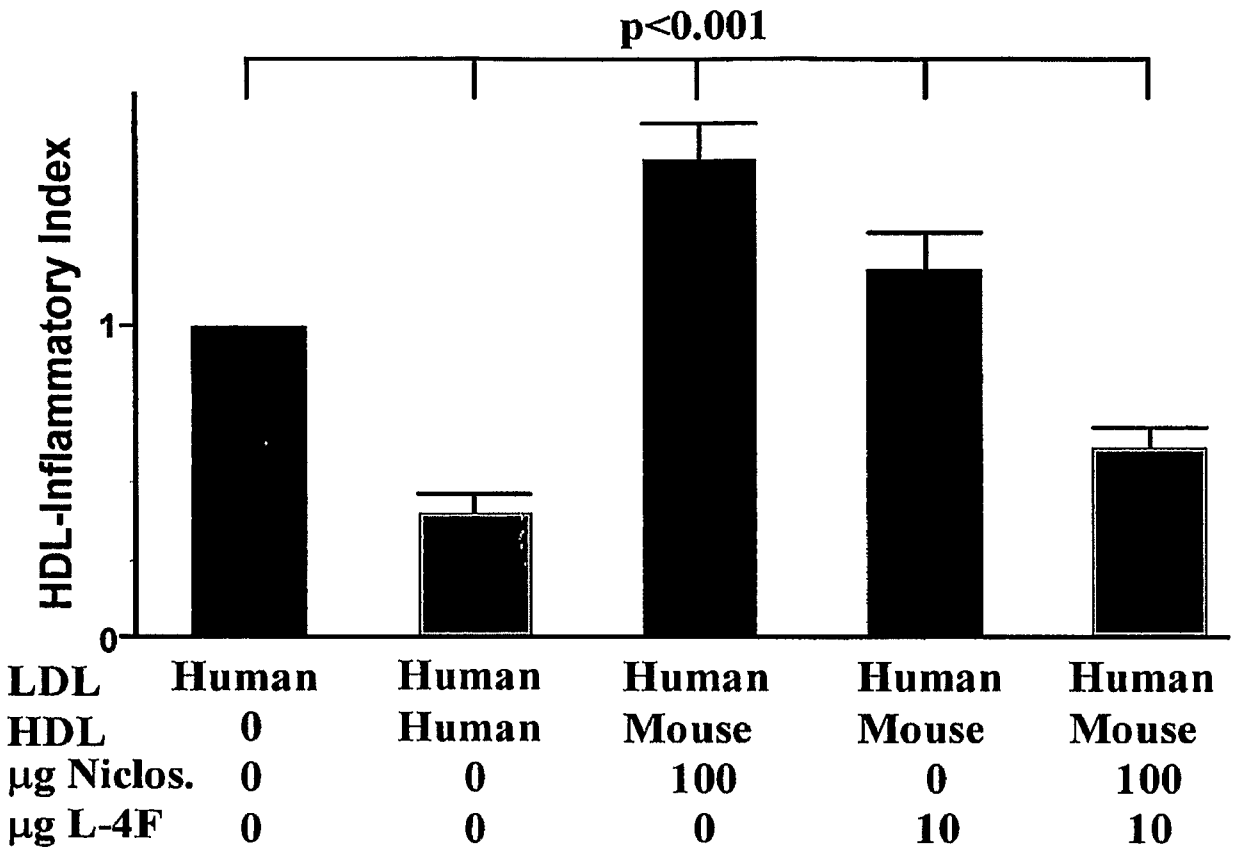

p<0.001
HDL-Inflammatory Index
1
0
LDL Human Human Human Human Human
HDL 0 Human Mouse Mouse Mouse
µg Niclos. 0 0 100 0 100
µg L-4F 0 0 0 10 10

Fig. 28

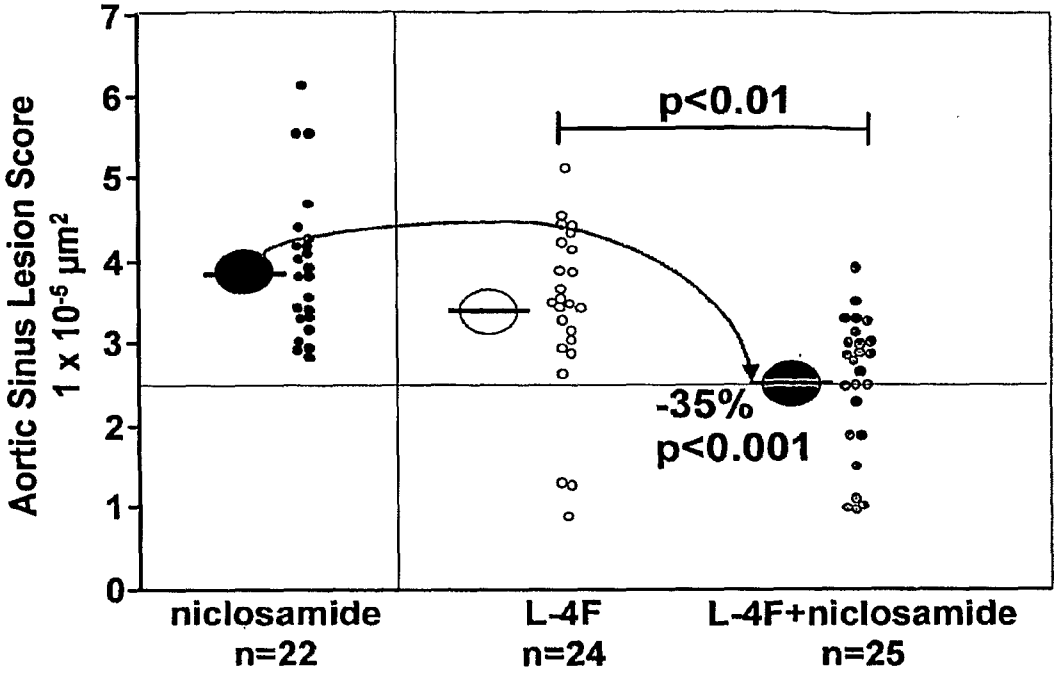

Aortic Sinus Lesion Score
1 x 10-5 µm2
7
6
5
4
3
2
1
0
p<0.01
-35%
p<0.001
niclosamide
n=22
L-4F
n=24
L-4F+niclosamide
n=25

Fig. 29

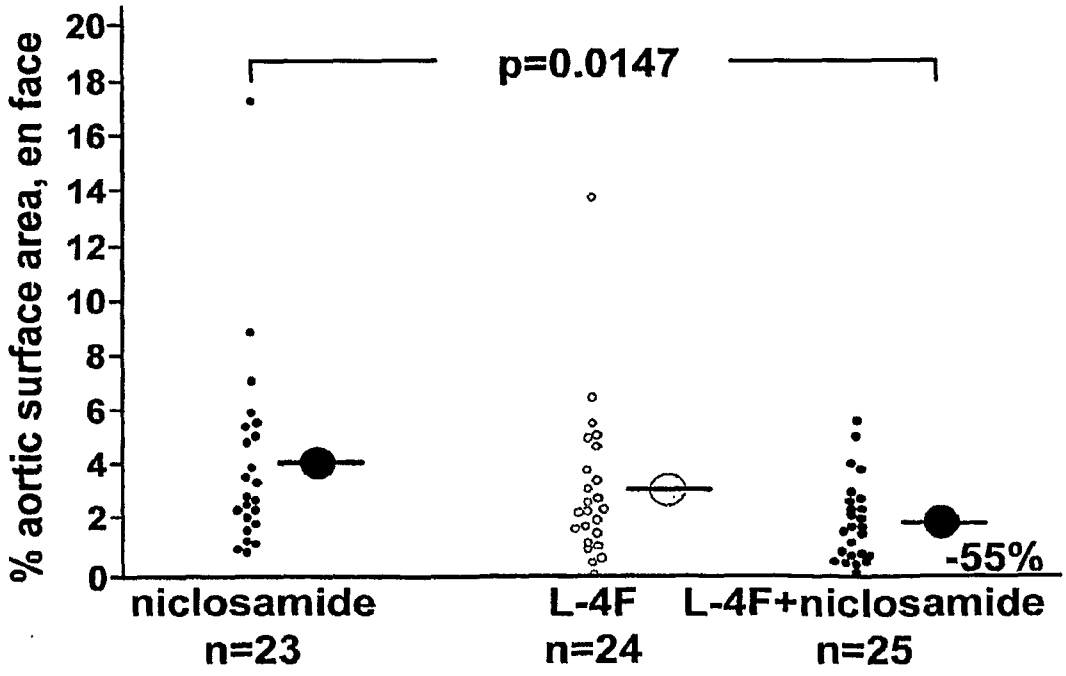

% aortic surface area, en face
20
18
16
14
12
10
8
6
4
2
0
p=0.0147
-55%
niclosamide
n=23
L-4F
n=24
L-4F+niclosamide
n=25

Fig. 30

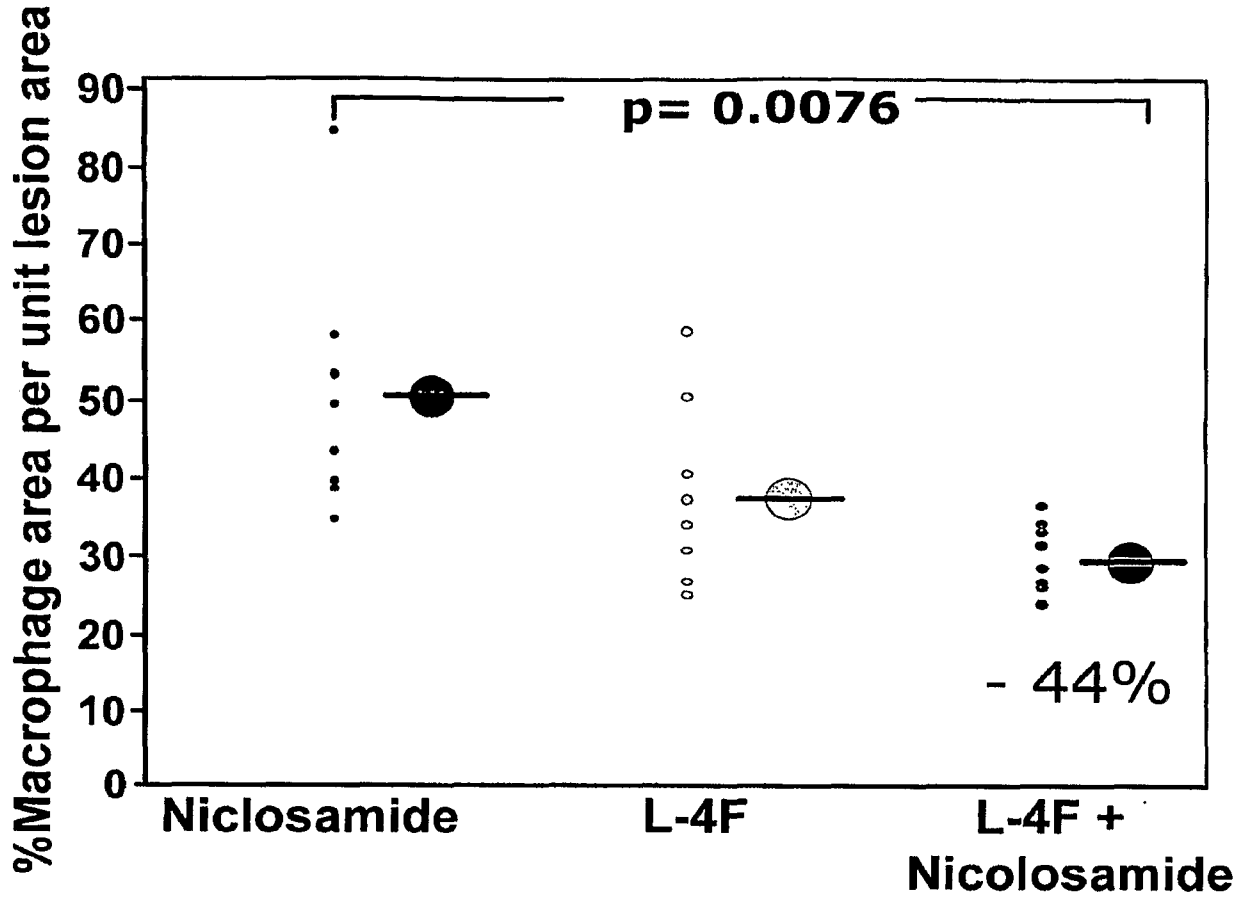

%Macrophage area per unit lesion area
90
80
70
60
50
40
30
20
10
0
p= 0.0076
- 44%
Niclosamide
L-4F
L-4F +
Nicolosamide

Fig. 31

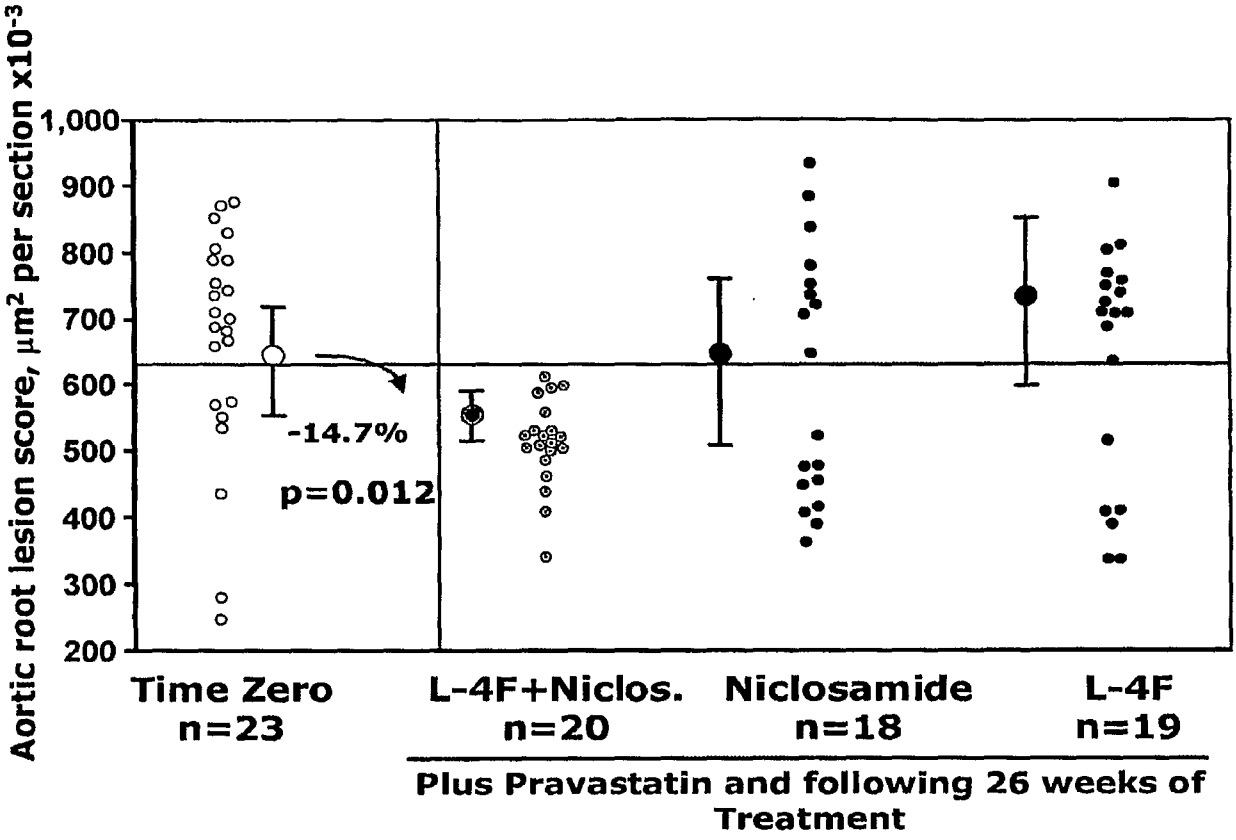

Aortic root lesion score, μm² per section x10⁻³
1,000
900
800
700
600
500
400
300
200
-14.7%
p=0.012
Time Zero
n=23
L-4F+Niclos.
n=20
Niclosamide
n=18
L-4F
n=19
Plus Pravastatin and following 26 weeks of Treatment

Fig. 32

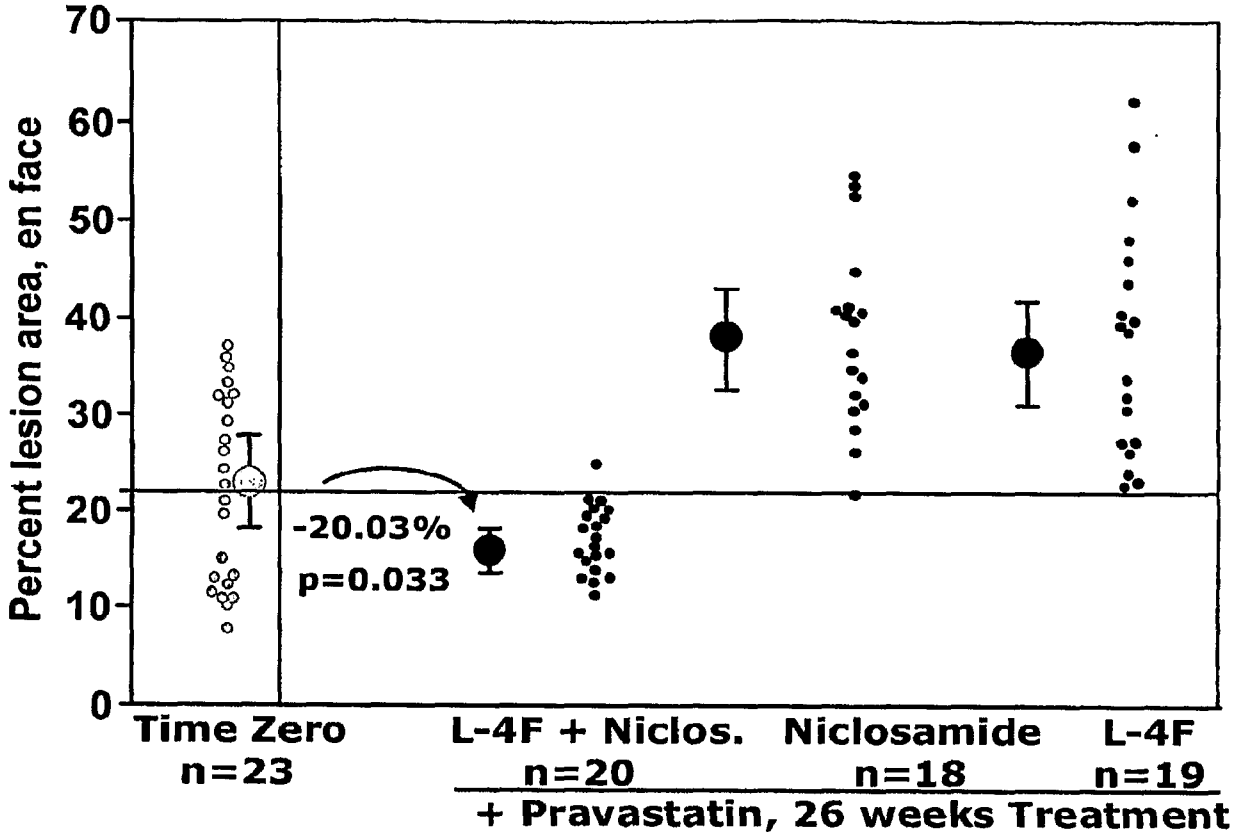

Percent lesion area, en face
70
60
50
40
30
20
10
0
-20.03%
p=0.033
Time Zero
n=23
L-4F + Niclos.
n=20
Niclosamide
n=18
L-4F
n=19
+ Pravastatin, 26 weeks Treatment

Fig. 33

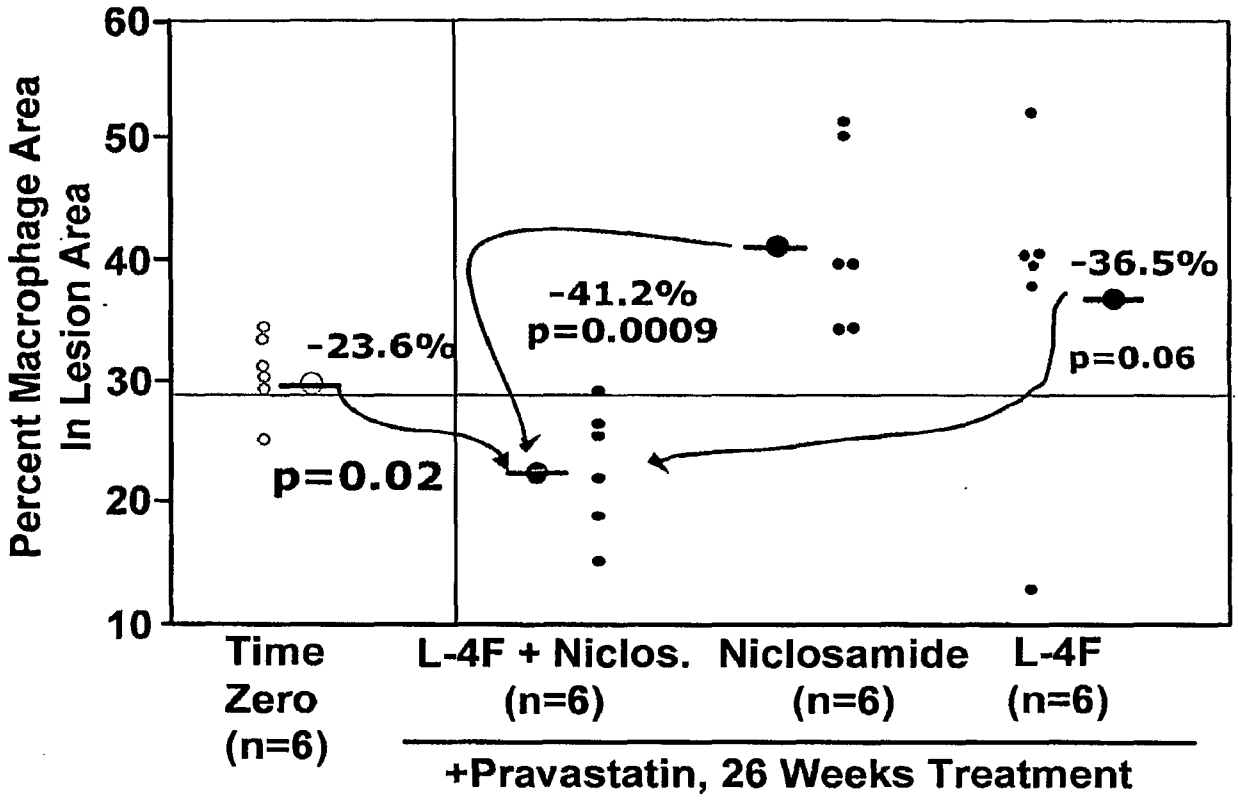

Percent Macrophage Area In Lesion Area
60
50
40
30
20
10
-23.6%
p=0.02
-41.2%
p=0.0009
-36.5%
p=0.06
Time Zero (n=6)
L-4F + Niclos. (n=6)
Niclosamide (n=6)
L-4F (n=6)
+Pravastatin, 26 Weeks Treatment

Fig. 34

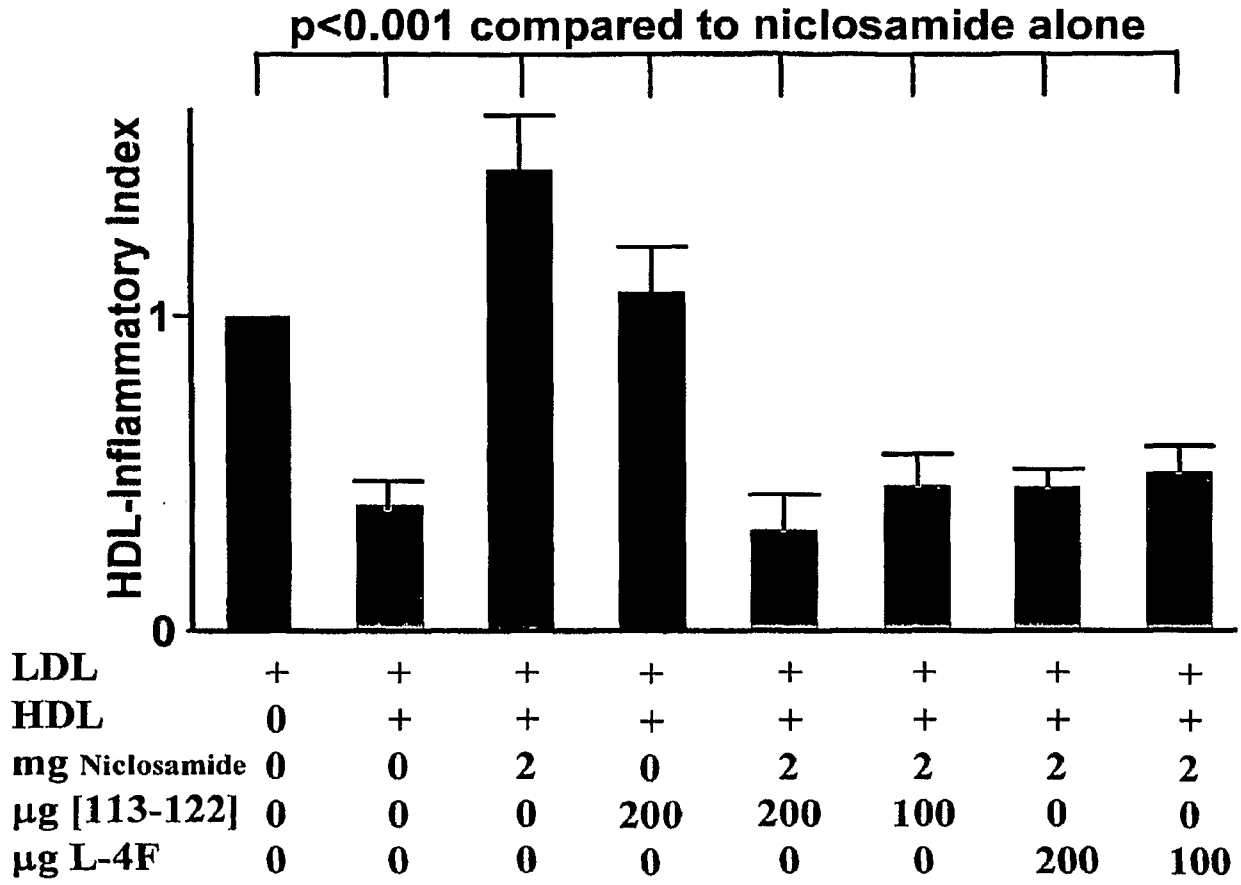

p<0.001 compared to niclosamide alone
HDL-Inflammatory Index
1
0
LDL + + + + + + + +
HDL 0 + + + + + + +
mg Niclosamide 0 0 2 0 2 2 2 2
µg [113-122] 0 0 0 200 200 100 0 0
µg L-4F 0 0 0 0 0 0 200 100

Fig. 35