The present invention relates generally to compounds comprising a hydrocarbon chain portion and more particular to compounds comprising chemical derivatizations of the hydrocarbon chain which are useful therapeutic and prophylactic molecules. The present invention further provides compounds where the hydrocarbon chain portion is a carrier molecule for functional groups, moieties or agents. The compounds of the present invention are particularly useful in the treatment and prophylaxis of a range of conditions including cancers, protein kinase c (PKC)- or NFkB-related- or -associated conditions, cardiovascular conditions, pain, inflammatory conditions, vascular or immunological conditions such as diabetes, neurological conditions and infection by a range of viruses or prokaryotic or eukaryotic organisms. The present invention further provides pharmaceutical compositions and methods of medical treatment.
THERAPEUTIC AND CARRIER MOLECULES

BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

The present invention relates generally to compounds comprising a hydrocarbon chain portion and more particular to compounds comprising chemical derivatizations of the hydrocarbon chain which are useful therapeutic and prophylactic molecules. The present invention further provides compounds where the hydrocarbon chain portion is a carrier molecule for functional groups, moieties or agents. The compounds of the present invention are particularly useful in the treatment and prophylaxis of a range of conditions including cancers, protein kinase c(PKC)- or NFkB-related- or -associated conditions, cardiovascular conditions, pain, inflammatory conditions, vascular or immunological conditions such as diabetes, neurological conditions and infection by a range of viruses or prokaryotic or eukaryotic organisms. The present invention further provides pharmaceutical compositions and methods of medical treatment.

DESCRIPTION OF THE PRIOR ART

Reference to any prior art in this specification is not, and should not be taken as, an acknowledgment or any form of suggestion that that prior art forms part of the common general knowledge in any country.

Fatty acids are one of the most extensively studied classes of compounds due to their important role in biological systems (Ferrante et al., In The Neutrophils: New outlook for the old cells [Ed Garblovich] Imperial College Press 4:79-150, 1999; Sinclair and Gibson (Eds) Invited papers from the Third International Congress, American Oil Chemists'
Society, Champaign, Illinois, 1-482, 1992). Fatty acids consist of saturated, monosaturated and polyunsaturated fatty acids having a chain length from 4 to 30 carbon atoms. Polyunsaturated fatty acids (PUFAs) contain 16 to 30 carbon atoms with two or more methylene-interrupted cis-double bonds.

PUFA nomenclature includes recitation of the number of carbon atoms in the hydrocarbon chain, the number of double bonds and the position of the first double bond from the terminal methyl group (the ω-carbon atom). For example, the PUFA, arachidonic acid, contains 20 carbon atoms and four methylene-interrupted cis-double bonds commencing six carbons from the ω-carbon, viz: this PUFA is referred to as “arachidonic acid (20:6 n-6)”.

PUFAs can be divided into four families based on the fatty acids from which they are derived: linoleic acid (18:2 n-6), α-linolenic acid (18:3 n-3), oleic acid (18:1 n-9) and palmitoleic acid (16:1 n-7). The n-6 and n-3 PUFAs cannot be synthesized by mammals and are known as essential fatty acids (EFAs). They are acquired by mammalian bodies indirectly through desaturation or elongation of linoleic and α-linolenic acids, which must be supplied in the diet.

It is now well appreciated that ω-3 fatty acids confer some protection against a range of diseases. Synthetic fats have been synthesized which are useful in the treatment of a variety of conditions.

International Patent Publication Nos. WO 96/11908, WO 96/13507, WO 97/38688, WO 01/21172 and WO 01/21575 describe a range of PUFAs referred to as the MP Series, PT Series, Lx Series and MP-PT hybrid series. Some of these PUFAs, such as those of the MP Series, have reduced susceptibility to breakdown and, hence, are far less likely to cause the production of oxygen radicals which is the consequence of the metabolism of the natural ω-3 fatty acids. PT Series' PUFAs also have this property of resisting breakdown but in addition are more soluble. MP-PT hybrids are particularly useful anti-inflammatory agents.
As indicated above, naturally occurring ω-3 fatty acids have been found to be useful in treating a range of conditions including rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease and systemic lupus. The PUFAs of the MP, PT, Lx and MP-PT hybrid series have also been proposed for the treatment of malaria, to stimulate or inhibit neutrophil activity, to treat T-cell diseases and in the treatment of cancer.

There is a need to determine the full range of activities of the PUFAs and to identify naturally occurring members or to generate synthetic derivatives which have therapeutic potential.
SUMMARY OF THE INVENTION

Throughout this specification, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated element or integer or group of elements or integers but not the exclusion of any other element or integer or group of elements or integers.

In accordance with the present invention, it is proposed that the PUFAs are useful in the treatment inter alia of conditions associated with or involving protein kinase Cβ (PKCβ) and/or NFκB and in the treatment of pain, inflammation, vascular or immunological conditions such as diabetes, cardiovascular conditions, atherosclerosis, neurological conditions and infection by a range of viruses, prokaryotes or eukaryotes.

In particular, the present invention contemplates a method for the treatment or prophylaxis of a condition selected from the list consisting of an NFκB-related or -associated condition, a PKCβ-related or associated condition, vascular or immunological conditions such as diabetes, inflammation, neurological conditions, cardiovascular disease and pain in a subject, said method comprising administering to said subject an effective amount of a compound having the structure of Formula (I):

\[
\begin{align*}
[R_6]_g - [R_7]_h \\
R_1 - ([R_2]_a - [R_3]_b) \\
([R_4]_d - [R_5]_e) \\
\end{align*}
\]

wherein

\( R_1 \) is a saturated or unsaturated hydrocarbon chain of from about 9 to about 26
carbon atoms and which optionally carries one or more of a oxa, thia, hydroxy, hydroperoxy, epoxy and peroxy substitution;

\[ R_2, R_4 \text{ and } R_6 \text{ may be the same or different and each is selected from } \text{O}_2, \text{NO}, \text{NO}_2, \]

\[ \text{S(O)}_x \text{C(H)}_y \text{H, COOH, P(X)}_6 \text{(Y), N(H)}_z \text{ C}=\text{O, OH, } \text{C}–\text{NH–, C}_1-6 \text{ alkyl, C}_1-6 \]

\[ \text{alkoxy, amino, mono-acid di-C}_1-6 \text{ alkylamino, C}_1-6 \text{ alkylthio, S(O)}_x \text{C}_1-3 \text{ alkyl, C}_1-6 \]

\[ \text{alkoxycarbonyl, halo selected from fluoro, chloro, bromo and iodo, oxo, amidino and } \]

\[ \text{guanidino, C}_2-12 \text{ alkenyl, C}_2-12 \text{ alkynyl, aryl, heteroaryl and cyano, wherein } x \text{ and } z \text{ are } 0, 1 \]

\[ \text{or } 2 \text{ and } y \text{ is } 0, 1, 2 \text{ or } 3 \text{ and } X \text{ is } O, S \text{ or } \text{NR}_8, Y \text{ is OR}_9, \text{SR}_{10} \text{ or } \text{NR}_{11} \text{R}_{12} \text{ and } R_8, R_9, R_{10}, \]

\[ R_{11} \text{ and } R_{12} \text{ are selected from H, alkyl, alkenyl, alkynyl, aryl and heteroaryl, } \delta \text{ is } 0 \text{ or } 1; \]

\[ \text{each of } R_3, R_5 \text{ and } R_7 \text{ is respectively } [(\text{CH}_2)_j (\text{COOH})_l]_0, [(\text{CH}_2)_m (\text{COOH})_n]_0 \text{ and } [(\text{CH}_2)_p (\text{COOH})_q]_r, \text{ wherein each of } j, m \text{ and } p \text{ is } 0, 1, 2, 3, 4, 5 \text{ or } 6, \text{ each of } k, n \text{ and } q \text{ is } 0, 1 \text{ or } 2, \text{ and each of } l, o \text{ and } r \text{ is } 0 \text{ or } 1, \]

\[ \text{each of } c \text{ and } f \text{ is } 0 \text{ or } 1 \text{ or } 2; \]

\[ \text{each of } a, d \text{ and } g \text{ is } 0 \text{ or } 1 \text{ or } 2; \]

\[ \text{each of } b, e \text{ and } h \text{ is } 0 \text{ or } 1 \text{ or } 2; \]

\[ \text{said administration being for a time and under conditions sufficient to prevent the } \]

\[ \text{condition or to ameliorate one or more symptoms of the condition.} \]

\[ \text{The present invention extends to isolated naturally occurring PUFAs as well as synthetic or } \]

\[ \text{modified molecules. The subject molecules also include a range of hybrids in which the } \]

\[ \text{PUFA is conjugated to an L- or D-amino acid or a chemical analog of an amino acid.} \]

\[ \text{The present invention further extends to compounds of general Formula (I) as defined } \]

\[ \text{above in isolated form or in a composition such as a pharmaceutical composition or} \]
formulation.

The present invention further provides for the use of a compound of general Formula (I) as defined above in the manufacture of a medicament for the treatment of a condition selected from the list consisting of a condition associated with or involving NFκB, PKCβ, pain, vascular or immunological conditions such as diabetes and cardiovascular disease, atherosclerosis, neurological conditions, inflammation and infection by a range of viruses, prokaryotes and eukaryotes.

The present invention also provides a compound of Formula (I):

\[
\left[ R_6 \right]_g \left[ R_7 \right]_h \\
R_1 \left[ R_2 \right]_a \left[ R_3 \right]_b \\
\left[ R_4 \right]_d \left[ R_5 \right]_e
\]  

(I)

wherein

- \( R_1 \) is a saturated or unsaturated hydrocarbon chain of from about 9 to about 26 carbon atoms and which is optionally carries one or more of a oxa, thia, hydroxy, hydroperoxy, epoxy and peroxy substitution;
- \( R_2, R_4 \) and \( R_6 \) may be the same or different and each is selected from \( O_2, NO, NO_2, S(O)\x, C(H)\y, H, COOH, P(X)\x(Y), N(H)\z, C=O, OH, \)  
  \( \text{-NH-}, C_{1-6} \text{ alkyl}, C_{1-6} \text{ alkoxy}, \)  
  amino, mono-acid \( C_{1-6} \text{ alkylamino}, \)  
  alkylthio, \( S(O)\x-C_{1-3} \text{ alkyl}, C_{1-6} \text{ alkoxy carbonyl}, \)  
  halo selected from fluoro, chloro, bromo and iodo, oxo, amidino and guanidino, \( C_{2-12} \text{ alkenyl}, C_{2-12} \text{ alkynyl, aryl, heteroaryl and cyano,} \)  
  wherein \( x \) and \( z \) are 0, 1
or 2 and y is 0, 1, 2 or 3 and X is O, S or NR, Y is OR or NR, R, R, R, R, R, R, R, R are selected from H, alkyl, alkenyl, alkynyl, aryl and heteroaryl, δ is 0 or 1;

each of R, R, and R is respectively [(CH) (COOH)]j, [(CH) (COOH)]o and [(CH) (COOH)]r, wherein each of j, m and p is 0, 1, 2, 3, 4, 5 or 6, each of k, n and q is 0, 1 or 2, and each of l, o and r is 0 or 1,

each of c, i and f is 0 or 1 or 2; and

each of a, d and g is 0 or 1 or 2;

each of b, e and h is 0 or 1 or 2.
BRIEF DESCRIPTION OF THE FIGURES

Figure 1 is a diagrammatic representation showing the principle mechanism involving T-lymphocytes, leukocytes, macrophages and other cells of the immune system.

Figure 2 is a graphical representation of the activation of neutrophil NADPH oxidase in the presence of 20 μM fatty acid as determined by lucigenin-dependent chemiluminescence.

Figure 3 is a graphical representation showing the analgesic effects of PT2 in PQ writhing test.

Figure 4 is a graphical representation showing the analgesic effects of PT2 in the formalin test.

Figure 5 is a diagrammatic representation of a structure of MP3 (β-oxa-23:4n-6).

Figure 6 is a diagrammatic representation showing the suppression of TNF-stimulated endothelial cell adhesion molecule expression by cells were pre-treated with MP3 (1h) before being stimulated with TNF for the times indicated. Adhesion molecule expression was determined by ELISA.

Figure 7 is a diagrammatic representation showing the suppression of LPS-stimulated leukocyte infiltration into the peritoneal cavity (a) and suppression of E-selectin expression by aortic endothelium (b) by MP3.

Figure 8 is a diagrammatic representation showing the prevention of TNF-stimulated loss of IκBα in HUVEC by MP3 or 22:6n-3 cells were pre-treated with MP3 or 22:6n-3 (1 hr), stimulated with TNF (15 min) lysed and the lysate subjected to Western blot analysis using anti-IκBα antibody.
Figure 9 is a diagrammatic representation showing the suppression of PKCβ1 translocation in glucose-stimulated mesangial cells (a) and in the glomeruli of a diabetic rat (b). Mesangial cells were pre-treated with MP5 or vehicle (ethanol) for 1 hr before being incubated with 25 mM glucose for 5 days. Male rats were rendered diabetic with streptozotocin and MP5 or vehicle (ethanol) was administered for 7 days after confirmation of diabetes. The cells and glomeruli were sonicated and particulate fraction-associated PKCβ1 was determined by Western blot analysis. High glucose and diabetes increased PKCβ1 in the particulate fraction. MP5 inhibited this effect.

Figure 10 is a representation showing comparison of the ability of MP3 (β-oxa-23:4n-6) PMA (100 nmol/l) and 22:6n-3 to stimulate the neutrophil respiratory burst. Neutrophils were treated with DPC (Control), 23:4n-6, PMA or 22:6n-3 and then tested for chemiluminescence activity. The fatty acids were used at 20 µmol/l. The results are the mean ± SEM of quadruplicates and is representative of two other experimental runs.

Figure 11 is a representation showing effect of β-oxa, β-thia and natural PUFA on TNF-enhanced neutrophil adherence to HUVEC. HUVEC were pre-treated with the fatty acids (20 µmol/l) for 60 min at 37°C before being stimulated with TNF (125 U/200 µl medium) for 4 hr at 37°C. The cells were then co-incubated with neutrophils (5x10⁵ cells/well) at 37°C for 30 min and the degree of neutrophil adherence quantitated. The results are expressed as % of control and represent the mean ± SEM of three separate experiments each performed in triplicate. *p < 0.05, ***p < 0.001, for significant differences between pre-treatment with fatty acid and control (one-way analysis of variance followed by the Dunnett test for multiple comparisons).

Figure 12 is a representation showing effect of MP3 derivatives on TNF-enhanced neutrophil adherence to HUVEC. HUVEC were pre-treated with MP3 (20 µmol/l), β-oxa-23:4n-6 derivatives (20 µmol/l) or diluent (control) for 60 min and then challenged with TNF (125 U/200 µl medium) for a further 4 hr. The ability of HUVEC to adhere neutrophils was then assessed. The results are expressed as % of control and represent the
mean ± SEM of three separate experiments each performed in triplicate. ***p < 0.001, for significant differences between pre-treatment with MP3 (β-oxa-23:4n-6) or derivative and control (one-way analysis of variance followed by the Dunnett test for multiple comparisons). Abbreviations used: β-oxa-23:4n-6ME, β-oxa-23:4n-6 methyl ester; β-oxa-23:0, saturated form of β-oxa-23:4n-6; β-oxa-23:4n-6OH, 18-monohydroxy-β-oxa-23:4n-6; β-oxa-23:4n-6OOH, 18-monohydroperoxy-β-oxa-23:4n-6.

**Figure 13** is a representation showing effect of MP3 (β-oxa-23:4n-6) and 20:4n-6 on time-related changes in TNF-α-induced E-selectin, ICAM-1 and VCAM-1 expression on HUVEC. HUVEC were pre-treated with 20 µmol/l β-oxa-23:4n-6 (closed triangles), 20 µmol/l 20:4n-6 (open squares), or DPC (control) for 60 min and then further incubated with TNF-α (125 U/200 µl medium) for up to 24 hr. The expression of E-selectin, ICAM-1 and VCAM-1 adhesion molecules was determined by ELISA. The results are expressed as % of control and represent the mean ± SEM of three separate experiments each performed in triplicate. *p < 0.05, **p < 0.01, ***p < 0.001, for significant differences between pre-treatment with fatty acid and corresponding control at a particular time point (one-way analysis of variance followed by the Dunnett test for multiple comparisons).

**Inset:** The effect of β-oxa-23:4n-6 on TNF-α-induced expression of E-selectin mRNA in HUVEC. HUVEC were pre-incubated with β-oxa-23:4n-6 (20 µmol/l) or DPC (control) in 1 ml of medium at 37°C for 60 min. After the addition of TNF-α, the cells were further incubated at 37°C for 2 hr. E-selectin mRNA expression was then determined and the results expressed as relative %. Results are the mean ± SEM of three separate experiments each performed in quadruplicate. *p < 0.0001, for significant differences between pre-treatment with β-oxa-23:4n-6, and control (two-tailed Student’s t-test for unpaired data).

**Figure 14** is a representation showing (A) effect of MP3 on in vivo inflammatory response measured as delayed type hypersensitivity (DTH) to sheep erythrocytes and LPS-induced influx of neutrophils and mononuclear cells in the peritoneal cavity in BALB/c mice. In the DTH experiments mice were injected with sheep erythrocytes subcutaneously, challenged with the antigen in the hind foot pad 6 days later and the amount of foot pad
swelling measured 48 hr later. One hour prior to challenge mice were given 10 mg/kg body weight of \( \beta \)-oxa fatty acid in 7% w/v DMSO as vehicle intraperitoneally. For the peritoneal cavity inflammation, mice were given intravenously 40 mg/kg MP3 intravencously and 6 hr later injected with LPS intraperitoneally. The cellular infiltrates were examined 24 and 72 hr later. The data, expressed as % of control, are presented as mean ± SEM of 10 and 5 mice for DTH and peritoneal inflammation, respectively. Analysis of data by two-tailed student's t-test: **p<0.01, ***p<0.001. (B) Shows the effect of \( \beta \)-oxa-23:4n-6 on LPS-induced expression of E-selectin in aortic endothelium of BALB/C mice. Mice were treated intravenously with the fatty acid and 2 hr later injected intraperitoneally with LPS. After 5 hr the aortas were isolated, cut into small pieces and incubated with a monoclonal antibody to mouse E-selection (or isotype matched control) (Becton Dickinson, California) followed by an HRP-conjugated secondary antibody and then with the substrate ABTS (ELISA method). The data, expressed as % of control, are presented as mean ± SEM of ten mice per group and is representative of two experimental runs. Analysis of the data by the two-tailed student's t-test: **p<0.01.

**Figure 15** is a representation showing the chemical structure of MP3 (\( \beta \)-oxa-23:4n-6) and of the monohydroxylated derivatives of \( \beta \)-oxa-23:4n-6 formed via the lipoyxgenase pathway in HUVECs (15-monohydroperoxy- \( \beta \)-oxa-23:4n-6 was the predominant product).

**Figure 16** is a representation showing the effects of lipoyxgenase/cyclooxygenase inhibitors and antioxidants on the modulation of E-selectin expression on HUVEC by \( \beta \)-oxa-23:4n-6. HUVEC were pre-treated with NDGA, baicalein, MK886, indomethacin, Vitamin E, or diluent (control) for 15 min. The cells were then further incubated with 20 \( \mu \)mol/1 \( \beta \)-oxa-23:4n-6 or diluent (control) for 60 min followed by TNF-\( \alpha \) (125 U/200 \( \mu \)l medium) for 4 hr and the expression of E-selectin adhesion molecule was determined. The results are expressed as % inhibition of the suppressive effect of \( \beta \)-oxa-23:4n-6 and represent the mean ± SEM of three separate experiments each performed in quadruplicate. * p<0.01, for significant differences between pre-treatment with inhibitor and
corresponding control (one-way analysis of variance followed by the Dunnett test for multiple comparisons).

**Figure 17** is a representation showing (A) the effect of MP3 (β-oxa 23:4n-6) and DHA on TNF-induced degradation of IκBα in HUVEC. Cells were pre-treated with the fatty acids (20 μmol/l) for 30 min and then stimulated with TNF (125 U/ml) for 10 min. After cell lysis the proteins were analyzed by Western blots using anti-IκBα antibodies. (B) The effects of β-oxa-23:4n-6 on TNF-induced activation of transcriptional factor, NFκB in HUVEC. Cells were pre-treated with β-oxa-23:4n-6 (20 μmol/l) for 30 min and then stimulated with TNF for 2 hr. After cell lysis, nuclear fractions were prepared, nuclear proteins separated by SDS PAGE (12% w/v gel), transferred to nitrocellulose and probed with an anti-NFκB p65 antibody (Santa Cruz). Densitometric analysis of data from three experiments showed that β-oxa 23:4n-6 reduced TNF-stimulated nuclear accumulation of NFκB by 66± 2% (mean ± SEM) (p<0.001, two-tailed student’s t-test). (C) The effect of β-oxa 23:4n-6 on TNF-stimulated activation of IKK. Cells were pre-treated with β-oxa 23:4n-6 (20 μmol/l) for 30 min and then stimulated with TNF for 5 min. After cell lysis IKK was immunoprecipitated with anti-IKKα antibody and kinase activity determined.
DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention provides compounds of general Formula (I):

\[
\begin{align*}
\text{R}_1 \left[ \text{R}_2 \right]_a & \left[ \text{R}_3 \right]_b \left[ \text{R}_4 \right]_d \left[ \text{R}_5 \right]_e \\
\text{R}_1 & \left[ \text{R}_2 \right]_a \left[ \text{R}_3 \right]_b \\
\text{R}_1 & \left[ \text{R}_4 \right]_d \left[ \text{R}_5 \right]_e
\end{align*}
\]

\[(I)\]

wherein

R\(_1\) is a saturated or unsaturated hydrocarbon chain of from about 9 to about 26 carbon atoms and which is optionally carries one or more of a oxa, thia, hydroxy, hydroperoxy, epoxy and peroxy substitution;

R\(_2\), R\(_4\) and R\(_6\) may be the same or different and each is selected from O\(_2\), NO, NO\(_2\), S(O)\(_x\), C(H)\(_y\), H, COOH, P(X)\(_6\)(Y), N(H)\(_z\), C=O, OH, C\(_{1-6}\) alkyl, C\(_{1-6}\) alkoxy, amino, mono-acid di-C\(_{1-6}\) alkylamino, C\(_{1-6}\) alkylthio, S(O)\(_x\)-C\(_{1-3}\) alkyl, C\(_{1-6}\) alkoxy carbonyl, halo selected from fluoro, chloro, bromo and iodo, o xo, amidino and guanidino, C\(_{2-12}\) alkenyl, C\(_{2-12}\) alkynyl, aryl, heteroaryl and cyano, wherein x and z are 0, 1 or 2 and y is 0, 1, 2 or 3 and X is O, S or NR\(_8\), Y is OR\(_9\), SR\(_{10}\) or NR\(_{11}\)R\(_{12}\) and R\(_8\), R\(_9\), R\(_{10}\), R\(_{11}\) and R\(_{12}\) are selected from H, alkyl, alkenyl, alkynyl, aryl and heteroaryl, \(\delta\) is 0 or 1;

each of R\(_3\), R\(_5\) and R\(_7\) is respectively \([\text{CH}_2]_j (\text{COOH})_k\)_l, \([\text{CH}_2]_m (\text{COOH})_n\)_o and \([\text{CH}_2]_p (\text{COOH})_q\)_r, wherein each of j, m and p is 0, 1, 2, 3, 4, 5 or 6, each of k, n and q is 0, 1 or 2, and each of l, o and r is 0 or 1;

each of c, i and f is 0 or 1 or 2; and
each of a, d and g is 0 or 1 or 2;

each of b, e and h is 0 or 1 or 2.

More particularly, the present invention contemplates a method for the treatment or prophylaxis of a condition selected from the list consisting of an NFKB-related or associated condition, a PKCβ related or associated condition, vascular or immunological conditions such as diabetes, inflammation, neurological conditions, cardiovascular disease and pain in a subject, said method comprising administering to said subject an effective amount of a compound having the structure of Formula (I):

\[
\begin{align*}
&[R_5]_g-[R_7]_h]_i \\
&[R_1]-([R_2]_a-[R_3]_b]_e \quad \text{(I)} \\
&[R_4]_d-[R_5]_f \\
\end{align*}
\]

wherein

R₁ is a saturated or unsaturated hydrocarbon chain of from about 9 to about 26 carbon atoms and which is optionally carries one or more of a oxa, thia, hydroxy, hydroperoxy, epoxy and peroxo substitution;

R₂, R₄ and R₆ may be the same or different and each is selected from O₂, NO, NO₂, S(O)ₓ₂, C(H)ₓ, H, COOH, P(X)ₙ(Y), N(H)ₓ, C=O, OH, \( \text{NH} \), C₁₋₆ alkyl, C₁₋₆ alkoxy, amino, mono-acid di-C₁₋₆ alkylamino, C₁₋₆ alkythio, S(O)ₓ-C₁₋₆ alkyl, C₁₋₆ alkoxy carbonyl, halo selected from fluoro, chloro, bromo and iodo, oxo, amidino and guanidino, C₂₋₁₂ alkenyl, C₂₋₁₂ alkynyl, aryl, heteroaryl and cyano, wherein x and z are 0, 1
or 2 and y is 0, 1, 2 or 3 and X is O, S or NR₈, Y is OR₀, SR₁₀ or NR₁₁R₁₂ and R₈, R₉, R₁₀, R₁₁ and R₁₂ are selected from H, alkyl, alkenyl, alkynyl, aryl and heteroaryl, δ is 0 or 1;

each of R₃, R₅ and R₇ is respectively \([(\text{CH}_2)_j (\text{COOH})_k]_l\), \([(\text{CH}_2)_m (\text{COOH})_n]_o\) and \([(\text{CH}_2)_p (\text{COOH})_q]_r\), wherein each of j, m and p is 0, 1, 2, 3, 4, 5 or 6, each of k, n and q is 0, 1 or 2, and each of l, o and r is 0 or 1,

each of c, i and f is 0 or 1 or 2;

each of a, d and g is 0 or 1 or 2;

each of b, e and h is 0 or 1 or 2;

said administration being for a time and under conditions sufficient to prevent the condition or to ameliorate one or more symptoms of the condition.

The compound of Formula (I) may comprise, when i, c and f are 0, a straight hydrocarbon chain such as that shown in Formula (II):

\[
\left[(\text{H})_{a'}\right]_{a''}
\]  \hspace{1cm} (II)

which represents a hydrocarbon chain of \(a''\) carbons in length from about 9 to about 26 carbon atoms, which hydrocarbon chain is saturated or unsaturated and which carries one or more of a oxa, thia, hydroxy, hydroperoxy, epoxy and/or peroxy substitution; \(a'\) may be 0, 1, 2 or 3.

The compound of Formula I may also comprise two of i, c or f being 0 and one of the remaining i, c or f being 1. For example, where i and f are each 0, the resulting compound has the structure of Formula (III):

\[
R_1-[R_2]_a-[R_3]_b
\]  \hspace{1cm} (III)
wherein $R_1$, $R_2$, $R_3$, $a$ and $b$ are as defined above.

When the compound of Formula (III) comprises each of, $a$, $o$ and $b$ being 1, the resulting compound has the structure of Formula (IV):

$$R_1-R_3$$

(IV)

wherein $R_1$ and $R_3$ are as defined above.

Given that $R_3$ is $[(\text{CH}_2)_j(\text{COOH})_k]_l$, Formula (IV) can be represented as a compound of Formula (V):

$$R_1-[(\text{CH}_2)_j(\text{COOH})_k]_l$$

(V)

wherein $R_1$, $j$, $k$ and $l$ are as represented above.

In a preferred embodiment, $l$ is a saturated or unsaturated fatty acid. In another preferred embodiment, the saturated or unsaturated fatty acid carries one or more of a $\beta$-oxa, $\alpha$-oxa, $\gamma$-oxa, $\beta$-thia, $\alpha$-thia, $\gamma$-thia, hydroxy, hydroperoxy, epoxy, peroxy, peracetyl or other protected hydroperoxy substitution. Substitutions may be at the level of a carbon atom or hydrogen atom.
Examples of compounds of Formula (V) include:

- 18:3n-3
- 22:6n-3
- 20:4n-6
- 23:4n-6
- 20:5n-3

Examples of compounds where R₁ comprises a substitution include:

- 15-OOH-20:4n-6
- 18 -

\[ \text{[Diagram: Chemical structures and labels] } \]

- \( \beta\text{-oxa-23:4n-6 (MP3)} \)
- \( \beta\text{-oxa-21:4n-3 (MP7)} \)
- \( \beta\text{-oxa-21:3n-6 (MP4)} \)
- \( 16\text{-OH-} \beta\text{ ox-a-21:3n-6 (TR1)} \)
- \( \beta\text{-oxa-21:3n-3 (MP5)} \)
- \( 16\text{-OH-} \beta\text{-oxa-21:3n-3 (TR2)} \)
- \( \beta\text{-oxa-25:6n-3 (MP6)} \)

- \( \beta\text{-thia-21:0 (MP2)} \)
- \( \beta\text{-thia-25:6n-3 (MP14)} \)
- \( \beta\text{-thia-21:3n-6 (MP9)} \)
- \( \beta\text{-thia-23:4n-6 (MP8)} \)
- \( \beta\text{-thia-21:3n-3 (MP10)} \)
- \( \alpha\text{carbocarboxymethyl-thia-23:4n-6 (MP15)} \)
When each of \([R_6]_g[R_7]_h\), \([R_2]_a[R_3]_b\) and/or \([R_4]_d[R_5]_e\) are presented in multiple forms, then the multiple forms may be represented linearly. For example, if \(i\) and \(f\) are each 0, \(a\) is 3, \(b\) is 1 and \(c\) is 1, then the compound may be represented as in Formula (VI):

\[
R_1-R_2-R_2-R_2-R_3
\]  

(VI)

If, on the other hand, \(c\) is 2, then the compound is represented as Formula (VII):

\[
\begin{align*}
R_1 & \quad R_2 \quad R_2 \quad R_2 \quad R_3 \\
R_2 & \\
R_2 & \\
R_3 &
\end{align*}
\]  

(VII)

In one non-limiting example, in the case when the compound is a carboxymethyl derivative, then the values in Formula (I) are as follows:

\[
i = 0, \text{ each of } c \text{ and } f = 1, \text{ each of } a \text{ and } d = 0 \text{ and each of } R_3 \text{ and } R_5 \text{ is } [(\text{CH}_2)_j \text{ (COOH)}_k]_l \text{ and } [(\text{CH}_2)_m \text{ (COOH)}_n]_o, \text{ respectively where, in one example,}
\]


\[
\begin{align*}
each of j \text{ and } m \text{ is } 0, \\
each of l \text{ and } o \text{ is } 1; \text{ and}
\end{align*}
\]

\[
each of k \text{ and } n \text{ is } 1,
\]

resulting in a compound of Formula (VIII):
More commonly, however, $j$ may be 1, and $m$ may be 2 resulting a compound of Formula (IX):

$$\begin{align*}
R_1 & \quad \text{COOH} \\
\text{COOH} & 
\end{align*}$$

Reference to "from about 9 to about 26 carbon atoms" herein includes 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25 and 26 carbon atoms.

The compound of Formula (I) may have each of $i$, $c$ and $f$ as 0 (zero), two of $i$, $c$ and $f$ as 0 (zero) or one of $i$, $c$ and $f$ as 0 (zero); or each of $i$, $c$ and $f$ as 1; two of $i$, $c$ and $f$ as 1 or one of $i$, $c$ and $f$ as 1; or each of $i$, $c$ and $f$ as two, two of $i$, $c$ and $f$ as two, or one of $i$, $c$ and $f$ as two.

The compound of Formula (I) may have each of $g$, $a$ and $d$ as 0 (zero), two of $g$, $a$ and $d$ as 0 (zero) or one of $g$, $a$ and $d$ as 0 (zero); or each of $g$, $a$ and $d$ as 1; two of $g$, $a$ and $d$ as 1 or one of $g$, $a$ and $d$ as 1; or each of $g$, $a$ and $d$ as two, two of $g$, $a$ and $d$ as two, or one of $g$, $a$ and $d$ as two.

The compound of Formula (I) may have each of $h$, $b$ and $e$ as 0 (zero), two of $h$, $b$ and $e$ as 0 (zero) or one of $h$, $b$ and $e$ as 0 (zero); or each of $h$, $b$ and $e$ as 1; two of $h$, $b$ and $e$ as 1 or one of $h$, $b$ and $e$ as 1; or each of $h$, $b$ and $e$ as two, two of $h$, $b$ and $e$ as two, or one of $h$, $b$ and $e$ as two.

These aspects of the present invention cover naturally occurring PUFAs as well as synthetic, modified or derivitized PUFAs. Furthermore, modified PUFAs encompassed by
Formulae (I) through (VIII) include naturally occurring or synthetic, derivatized or modified PUFAs conjugated to an L- or D-amino acid or amino acid analog or a sequence of amino acids such as in peptide, polypeptide or a protein. The latter aspect includes proteins in the form of cytokines, growth factors, proteases, enzymes, apoptotic proteins and pro-survival proteins.

Examples of L-amino acids include alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine and valine.

methylnorvaline, L-α-methylphenylalanine, L-α-methylserine, L-α-methyltryptophan, L-α-methylvaline, N-(N-(2,2-diphenylethyl)carbamylmethyl)glycine and 1-carboxy-1-(2,2-diphenyl-ethylamino)cyclopropane.

Examples of cytokines include but are not limited to BDNF, CNTF, EGF, EPO, FGF1, FGF2, FGF3, FGF4, FGF5, FGF6, FGF7, FGF8, FGF9, FGF10, FGF11, FGF12, FGF13, FGF14, FGF15, FGF16, FGF17, FGF18, FGF19, FGF20, FGF21, FGF22, FGF23, G-CSF, GM-CSF, IFNα, IFNβ, IFNγ, IL1, IL2, IL3, IL4, IL5, IL6, IL7, IL8, IL9, IL10, IL11, IL12, IL13, IL14, IL15, LIF, MCP1, MCP2, MCP3, MCP4, MCP5, M-CSF, MIP1, MIP2, NGF, NT3, NT4, NT5, NT6, NT7, OSM, PBP, PBSF, PDGF, PF4, RANTES, SCF, TGFα, TGFβ, TNFα, TNFβ, TPO, VEGF, GH, insulin and the like.

Examples of apoptotic proteins include but are not limited to A1, A9, A20, A46R, A52R, A53, A238L, Aac11, AATF, AATYK, ABIN1, ABIN-1, ABIN2, acidic sphigomyelinase, Acinus, Act1, Act2, activin, AD3LP, AD5, ADAR, adrenomedullin, aggrecan, AMAM17, 33, A1l, AIF, AILIM, AIM2, AIR, AITR, Akt, ALCAM, ALG2, ALG3, ALG4, ALP, Alix, Armadillo, AMAC1, AMH, AMID, Amida, angiotensinogen, Ankyrin, ANT1, AO7, AP1, Apaf-1, APC, APC2, APCL, APE1820, AP1, APO-1, APO-2, APO-3, Apopain, APP1, APP2, Apr, APRIL, ARA54, ARC, ARF, arkadia, ARHI1, 2, ASC, Ash2, Ask1, Ask2, ASPP1, ASPP2, AT2R1, AT2R2, ATAR, ATF1, ATF2, ATF3, ATF4, ATM, atona, ATRI, AUF1, Aven, AVP, AvrA, AvrBsT, Axam, Axin, Axin 2, Axin, b-catenin, b-TrCP, B28R, B7-1, B7-2, B7h2, B7RP1, Bach2, Bad, BAFF, BAG-1, -2, -3, -4, -5, Bak, BALF1, Bam32, BAP-1, BAP31, BAP29, BAR, BARD1, BAT3, Bax, Bbc3, BCA1, BCAN, Bel-2, BCL2, Bcl-3, Bcl-10, BCL10, Bcl-G, Bcl-Rambo, Bcl-w, Bcl-x, beclin, BEHAB, BERP, Bfl-1, BFL1, BG1, BG2, BG4, BG5, BHP1, BHRF1, BI-1, Bid, Bif-1, Bik, Bis, Bim, Bimp-1, Bimp1, Bimp2, Bimp3, BIR1, BIRP, BL-CAM, BLC, Blik, BLNK, BLR1, BLyS, BMI-1, BmP109, BNIP3, BNIP3a, BNIP3L, Bok, bone sialoprotein, bonus, Boo, BPI, BRAL1, BRAG-1, BRAP, Bravo, BRCA1, BRN3a, BRN3b, BRN3c, brevican, BPR, BSAC, BUFFY, C1q, C1r, C1s, C2, C3, C4a, C4b, C5, C6, C7, C8a, C8b, C8g, C9, C1qBP, C3ar, C4BPa,b, C5R1, CR2, CIITA, C5L, c-E10, c-FLIP, c-Fms, c-Fos, c-IAP1, cIAP1, c-IAP-1, c-IAP2, cIAP2, c-IAP-2, c-Jun, c-Myc, c-Rel, cactus, CAD, cadherin, E,
N, P, VE, calcineurin, CARD4, CARD7, CARD9, CARD10, CARD11, CARD12, CARD14, CARDIAK, Carma1, CARMA-1, CARMA2, CARMA3, CARMA, CARMEN, CAP1, CAR1, CART1, CAS, CAS-L, caspase-1, -2, -3, -4, -5, -6, -7, -8, -9, -11, -12, -13, -14, Casper-1, -2, -3, -4, -5, -6, -7, -8, -9, -10, -11, -12, -13, -14, -15, -16, -17, -18, -19, -20, -21, -22, -23, -24, -25, -26, -27, -28, CASH, CBL, CBL-B, CBL-C, CC-CKR-6, CCF, CCL, CCPI, CCRs, CD2, CD3, CD4, CD5, CD6, CD7, CD8, CD9, CD11, CD14, CD18, CD19, CD20, CD21 (CR2), CD22, CD23, CD25, CD27, CD27L, CD28, CD28LG1, CD28LG2, CD29, CD30, CD31, CD32, CD33, CD34, CD35, CD36, CD40, CD40L, CD41, CD43, CD44, CD45, CD46, CD47, CD48, CD49, CD50, CD53, CD54, CD55, CD56, CD58, CD59, CD61, CD62E, L, H, CD66, CD63, CD64, CD66a-e, CD67, CD70, CD72, CD74, CD79a, b, CD80, CD84, CD85a-m, CD86, CD88, CD89, CD90, CD92, CD94, CD95, CD96, CD97, CD99, CD100, CD101, CD102, CD104, CD105, CD106, CD108, CD112, CD115, CD116, CD117, CD119, CD120a-b, CD121a-b, CD122, CD123, CD124, CD125, CD126, CD127, CD128a-b, CD130, CD131, CD132, CD134, CD135, CD136, CD137, CD140a, CD140b, CD143, CD144, CD146, CD147, CD148, CD150, CD151, CD152, CD153, CD154, CD155, CD158a-z, CD159, CD160, CD161, CD162, CD166, CD178, CD180, CD183, CD184, CD195, CD197, CD207, CD229, CD244, CDC2, CDC25, CDC42, CDK1, CDK2, CDK5, CDM, CEA, CEAL, CEACAM1, 6, C/EBP, CED1, CED2, CED3, CED4, CED5, CED6, CED7, CED8, CED9, CED-9, CED10, CED11, CED12, CED, CEP-1, CES1, CES2, CES3, CETP, CeTraf, Cezanne, CGR19, CGRP, Che1, Che-1, CHFR, chemokines, CHOP, CHUK, cIAP1, cIAP2, c-IAP1, c-IAP2, c-IAP-1, c-IAP-2, CIDE-A, CIDE-B, CIKS, CIN85, CIP-1, CIPER, CIK, Ckb, 8, CKR1, 2, 3, 4, 5, CKRL1, Clan, CLAP, CLARP, CMD1, CMH1, CMKBR1, 2, 3,, 4, 5, 6, CMPD1, conductin, Cop9 subunit 3, COP11, COP53, COP55, COT, COX-1, COX-2, 25 CPAN, CPP32, CPZ, CRADD, CRAF1, CR8, CREB, CREM, Crk-II, crinkled, crmA, crmB, CSBP1, CSMF, CSN3, Csp-1, Csp-2, Csp-3, CSPG2, 3, Csx, CTACK, CTAP3, CTGF, CTLA4, cytochrome c, cytotoxic PL A2, CXCLs, CXC-R3, DAAM1, Dad1, DAD-1, Damm, DAP1, DAP3, DAP5, DAP12, DAP kinase 1, DAPP1, DAXX, Dborg1, dCAD, DCCK1, DCP1, Dcp-1, Dcp-2, DcR-1, DcR-2, DD2, Decay, DED, DEDAF, DEDD, DEDD2, dedprod, defensin, DEFT, dFADD, DFF, DFF35, DFF40, DFF45, DG17, Diablo, DIAP1, DIAP2, Dickkopf, DIF, DIF2, DIHA, DIK, Drosophila IKK, PKC8-
interacting protein kinase, DIO1, DIP, dishevelled, diubiquitin, DKK-1, DKK-2, DKK-3, DKK-4, DLAK, DLK, DMDL, DNase II, Diva, DONG1, Dorsal, DP1, DP2, DP5, Drob1, DRP-1, DocA, dock188, Dok1, Doom, dorf11, DR3,4,5,6, DRAK 1-2, DREAM, DREP -1, DREP-2, DREP-3, DREP-4, DrICE, DRONC, DRP1, DTR, DTS, DUSP, E1.1, EIB 19K, E10, E2Fs, E4BP4, E4ORF4, E8, E4, E48, E3RS, eae7, Ear7, EBAF, EBI1, EBP1, EBI6, ECSIT, EDA, EDAR, Edradd, EFP, EGL1, Egr1-2-3, EHF, eIF-2aK, Eiger, ELAM, ELF2, ELK1-4, EMR1, ENA78, Encofin, Endoglin, Endophilin B1, endothelin, ENG, eNOS, eosin, E10, ER1, ERICE, ES18, Ets-1-2, ER81, ErbAa, ERG, ERM, ESE2, Eskine, ETV1, 2,3,4,5,6, exondu-1, exondu-2, exondu-3, FADD, Fas associated via death domain.

FAF1, FA4M, FAN, FANCC, Fas, FAST, FAT10, fb1, FCAR, FELL, FEM-1, FEM-2, FHR1-2, FHR-3, FHR-4, FHR-5, FKBP4, FIFG, FIL1d, E, eta, zeta, FIP1, FIP2, FKSG2, FIST, FKHL12, FKHR, FKHRL1, FLAME-1, FLAME-3, FLAME3, FLASH, FLDED-1, FLI-1, FLII, FLICE, FLICE2, FLICE-2, FLIP, FLT3L, Fliz1, Fln29, Fms, Fnk, fortillin, Fos, FOXO1A, FOXO3A, FOXE3, FPV039, Fra1, Fra2, Fractalkine, FRAP, FREAC8, Frizzled, Fzd, Fz, FRING, FRP1-2-3, FRP1(ATTR), frpHE, FRZB-PEN, Fsp27, FUS, FUS6, Fusin, FXY, FY, G-coupled receptors, G10P1, G25K, G4R, G6C, G6E, GADD34, GADD45, GADD153, GATA1,2,3,4,5,6, GBP2, GCP2, GDFs, gelsolin, Gfi-1, Gfi1, GFRP1, GILZ, gingipain, GITR, GL50, glycoeserin A, GM2A, gp34, GPR5, GPR9, GPR-9-6, Granzyme B, Grim, GRMP, Groa, Grob, GRS, GSKβ, H2TF1, H731-like, Hakai, HB-EGF, Hek, HF1, HFB30, HFL3, HHARI, hIAP-1, hIAP1, Hid, HIF1 α, HIP1, HIP116, HIPPI, HIK1,2,3, histamine receptors, HIVEP1-3, HIV-EP1, HLT1, HM85, HM89, HM145, HMR, HNRPD, HRD1, Hnk, HtrA2, Huntingtin, HVEM, HVEM1, HYP, IAP-1, IAP1, IAP2, IAP, iAPP, ICAD, ICBP90, ICE, ICEBERG, ICE-LAP3, ICE-LAP6, ICErel-IL, ICErel-III , Ichi1, ICH-1, Ich2, ICH-2, Ich3, ICH-3, ICOS, I-TRAFl, FLICE, IEX-1m

IFI, IFIT-1, IFIT-2, IFIT-3, IFIT-4, IFP35, IgE Fc receptor, IGF1 and its receptor, IGFBP3, IKAP, Ikaros, IKB-1, Ikb-a, Ikb-b, Ikb-e, IKKAP, IKK-1, IKK-2, IKK-a, IKK-b, IKK-g, interleukins, interleukin receptors, IL1 antagonist, anti-IL1, IL1RacP, IL8R1, ILA, ILC, ILP, ILP-1, ILP-2, ILT1-11, ING1, ING2, ING3, Inhibin, INK4, INK4A, integrin, IP10, IPN10, Ipaf, IRAK, IRAK2, IRAM-M, IRE1, RE1p, IRE, IRF, IRTA1-5, ISGF3g, ITA, It, Jab1, Jak1, 2, 3, JDP2, JIK, JN, K, K13, KARAP, KBF-1, KBF-2, KBF-3, KDS, KE05, KET, kf-1, KIAP, Killer, KIR2DL1-5, KIR2DS1-6, KROX2, L-Myc,
lactalbumin α, LAG1, LAIR1, LALBA, LAM, LAP1, LAP3, LAR, LARD, LARC, LATS1, 2, LBP, Lck, LCP2, LD78b, LEFTY, LESTR, Leu1, Leu8, Leu14, leukotactin, LFA3, LFG, LICE, LICE2, LIF, LIGHT, LIR1, LIR-2, LIR-3, LIR-4, LIR-5, LIR-6, LIR-7, LIR-8, Livin, LMP1, LMW5-HL, LOK, Lot1, LRDD, LRP, Low affinity NGFR, LTa, LTb, LTbR, LTP2, Ly63, lymphotactin, Ly1, Lyf1, Lysozyme, Lyt-10, LYVE1, LZR, M11, M159L, M160L, MA-3, MACH, Mad, Mad3, MADD, Maf, c-Maf, makorin, MAL, MALT, MAP-1, MAPKKKs, MAPKKks, MAPKs, MAPKs, Math1, Max, MBD4, MBLR, MBP1, MCL1, Mch2, Mch3, Mch4, Mch5, Mch6, MCP1, MCP2, MCP3, Mda-7, MD-1, MD-2, Mdm2, Mdm4, MdmX, MDP62, mE10, MEF2a, MEKKs, Mel-18, MEKD, Meprin, metacaspase, MIC1, MID1, MIF, MIG, MIHC, MIP1-2-2a-2b, MIP-T3, MIR, MIS, MITF, MKK6, MKL1, MKP1, ML-1, ML-IAP, MLN64, MLX, MMP-1, MMP-2, MMP-3, MMP-4, MMP-5, MMP-6, MMP-7, MMP-8, MMP-9, MMP-10, MMP-11, MMP-12, MMP-13, MMP-14, MMP-15, MMP-16, MNDA, MNT, Mob1, mod (mdg4), MORT1, MIFI1, MRF, MRIT, Msx1, Msx2, MTAP44, Mtd, mTOR, MUC1, MUC2, MUL, MURF-1-2-3, mup-nop30, Mxa, MexB, Mxi1, Mxi2, MYAK, Myc, MyD88, MyD118, MYLK, myoblast city, N-Myc, NAF1, NAIP, NALP1, NALP2, NAP2, NAK3, Nrk, NBS1, NCA, NCAM, NCC-1, NCC-2, NCC-3, NCC-4, NGD1, neural sphingomyelinase, neuralin, NEMO, neogenin, neurotactin, neurocan, NF-kB, NF-X1, NFATs, NFIL3, NFIL6, NFkB1, 2, NIP1, NIP2, NIP3, NIPK, Nik, Nix, NKAT1-9, NKX2-5, nNOS, Notch, NOD-1, NOD-2, nop30, Nor-1, NOS2, NOS2B, NOS3, Nov, Noxa, NP10, Np95, Npc2, NPY3R, Nr-CAM, NR3, NR3, NR3, NR-13, NRAGE, NRIF1, nucleolin, Nur77, NY-REN-64, OCIF, ODF, ODFR, OIAS, ORF16, posteprotegerin, OSX, OX40, OX40L, OPG, OPGL, Osi, osteonectin, osteopontin, p14, p16, p33ING1, p35, p38, p49, p49, p55, p52, p53, p53AIP1, p53DINP1, p55, p60, p62, p62Dok, p63, p65, p73, p75NTR, p84, p100, p105, p193, p202, PAC1, PACAP, PACT, PAF400, PAG-3, PAG608, PAK1, PAK2, PAK3, PAP1, PAR4, paracaspase, PARC, Park2, parkin, PARP, PAX-2, PAX-3, PAX-5, PAX-8, PBEF, PBP, PD1, PDGF, PEA15, Pellino, PERK, PERP, PEK, Pelle, PEX10, PF4, PGRP, PI3K, Pidd, PIK-1, PLAB, Pik, Pik3, PKC, PKR, PKY, PLAG1, PLAIDD, PLA2, PLC, PLD, Pli, Pml, PMP41, POSH, PP1A, PP14, PP2Ca, PRKR, PRSS25, polycystin 1, porimin, PRG1, Prk, PRL, prolactin receptor, PS-1, PS-2, PSCA, PSMD-11, PSMD-12, PSMD-13, PSP-C, PSK, PSSALRE, PTEN, PTK1, PTPs,
PTP1C, PTP2C, PTP1G, PTPL1, PU.1, puckered, Pum, Q2/2, Rac, RAI, RANTES, RAX, Rb, Relish, RELT, Raf, RANK, RANKL, RAIDD, RBBP6, RBQ1, Rcm, Reaper, RelA, relaxin H1, H2, H3, RelB, Requiem, RFP, RFPL-1-2-3, RGS, RhoA, RICK, RIG-G, Ro52, Ro 60kDa, ROC-1, ROC-2, RORgamma, ROX, RIFF, RIP, RIP2, RIP3, RNM561, RNF, RP-8, RP8, RP105, Rpr, RRP5, RYBP, S9, S152, SAG, Salvador, SAP1, SAPK2A, Sara, SARP 1,2,3, Sav, Sca2, SCA-2, SCC-S2, SCF, SCDGF, SCM1-1a, Scythe, SDF1, selectin L-E-P, SENP1, SENP2, sentrin/SUMO-specific protease, SETA, SFRP1-2-3-4-5, SFTP2, SFTPC, SGK, SGL, SGN5, SH2D1A, SHP1, 2, Siah, SIMPL, SIP27, SIP18, SIR2, SIVA, SLC, SLK, SLP-65, SLP-76, SLUG, Smac, SMADs, SMARDs, SMARCA3, SMN, SMT 3A, B, 3C, SNAI1, SNAI2, SOD2, somatostatin, Son3, SOX9, SP5, SP-C, SPARC, sphigomyelinase, Smase, SPOP, SPP1, SPRK, Spatzle, SFRP1-2, S5-56, SSA, SSA1, SSA2, ST2L, stabilin 1-2, STATs, STCP1, STG6, STEP, STM-2, Stra3, STRICA, Substance P, SUMO1, survivin, SYK, SY, T cell receptor, T2BP, T6BP, TAB1, Tab2, Tabby, TACI, TACTILE, Tag7, tachykinin, TAJ, TAK1, Tak1, TALL-1, TANK, TAO1, TAO2, TARC, TBX1, TBX-2, TBX-3, TBX-4, TBX-10, TBX-18, TBX-19, TBX-20, TBX-21, TBX-22, TCA3, TCA-3, TC1, TC2, TCR, TCTP, TDAG51, TEAP, TECK, TEGT, TEL, (TEL1), TEL2 (TELb), telokin, TERF, TFT, TGB, TGFβ-1, TGFβ-2, TGFβ-3, THG1, THRa, Thy-1, TIA1, TIAP, TIEG, TIF1, TIFγ, TIL6, TIMP1-2-3, Tip49, Tip60, TIRAP, TIS, TLRs, TLS, TMS1, TNFa, TNFAIP3, A20, TNFAIP6, TNFb, TNF-C, TNFR1, TNFR2, TNFR-2, TNFRSF1-19, Toll, Tollo, Tollip, TONEBP, Toso, Tp44, TPL-2, TR3, TR2L, TRABID, TRADD, TRADEC, TRAF1, TRAF1(Dm), TRAF2, TRAF2(Dm), TRAF3, TRAF4, TRAF5, TRAF6, TRAF6(Dm), TRAFamn, TRAIL, TRAIL-R2, TRAMP, TRANCE, TRC8, TRIAD1-3, TRIF, TRIM, TRIP15, TRF-1, TRF2, TRF1, TRF2, traube, TRDL-1, TRG, TRH, TRICK2, TRIP, Tristetraproline, TROY, TRRAP, TSC-22, TSC-22R, TTRAP, Tube, TUCAN, TWEAK, TX, TXBP151, TY, Tyk, UBCH7BP, UL36, UL37, Ulp, Unc5, UNC5h3, Urinary, stone protein (SPP1), USP7, usurpin, urophil, vaspressin, vav, vav1, vav2, vav3, vav-1, vav-2, vav-3, versican, viCA, VIAF1, vBcl-2, VEGI, VEGF, Ventroptin, VG-1, VG71, VHR, v-IAPs, VI, warts, Wengen, WIG1, WISP-1, 2, 3, Wnt, WSL-1, WT1, WW45, WWOX, XAF1, XAP4, XCL1, 2, XEDAR, XIAP1, xRI, xRII, XICE, XICEa, XICE, Yama, Yop1, YY1AF, Zac, Zac1, ZAP70, ZBP89, zfβ, ZFP26, ZFP127, ZH-DR, ZNF-40, ZNF-124, ZNF-148, as TFs,
ZNF-144, ZNF-147, ZNF-179, ZNF-313, ZNF-364 as RING, ZIP-kinase, ZPR, 18 wheeler, 24.6K Glu/Pro-rich, 4-1BB, 4-1BBL, 4-1BB ligand and 53BP2, 7TM.

Examples of pro-survival proteins include, but are not limited to Bcl-2, Bcl-XL, Mcl-1 and A1.

Examples of PUFAs contemplated by the present invention include:

18:3\textit{n-3} \hspace{1cm} 22:6\textit{n-3}

20:4\textit{n-6} \hspace{1cm} 23:4\textit{n-6}

20:5\textit{n-3} \hspace{1cm} 15-OOH-20:4\textit{n-6}

Natural PUFA and hydroperoxy derivative
MP series, β-oxa compounds

β-oxa-23:4n-6 (MP3)  β-oxa-21:4n-3 (MP7)

β-oxa-21:3n-6 (MP4)  16-OH-β-oxa-21:3n-6 (TR1)

β-oxa-21:3n-3 (MP5)  16-OH-β-oxa-21:3n-3 (TR2)

β-oxa-25:6n-3 (MP6)

MP series, β-thia compounds

β-thia-21:0 (MP2)  β-thia-25:6n-3 (MP14)

β-thia-21:3n-6 (MP9)  β-thia-23:4n-6 (MP8)

β-thia-21:3n-3 (MP10)  α-carboxymethyl-β-thia-23:4n-6 (MP15)
\[
\begin{align*}
\text{\(\gamma\text{-thia-22:3 (n-6)}\)} & \quad \text{\(\gamma\text{-thia-24:4 (n-6)}\)} \\
\text{\(\gamma\text{-thia-22:3 (n-3)}\)} & \quad \text{\(\gamma\text{-thia-25:6 (n-3)}\)} \\
\text{MP series, \(\gamma\text{-thia compounds}\)} \\
\text{15-OOC(CH\text{\(_3\text{)}\text{2OCH\text{\(_3\text{)}}\text{20:4n-6 (MP16)}}\)} & \quad \text{15-OOC(CH\text{\(_3\text{)}\text{2OCH\text{\(_3\text{)}}\text{\(\beta\)-oxa 23:4n-6 (MP17)}}\)} \\
\text{MP series, protected hydroperoxy compounds}
\end{align*}
\]
PT series: PUFA-amino acid conjugates
The present invention is directed *inter alia* to the treatment of pain, cancers, PKC- and/or NFκB-associated or -related conditions, vascular and/or immunological conditions, inflammatory conditions, neurological conditions and infection.

Other compounds contemplated by the present invention include β-oxa 23:0, β-thia 23:0, β-oxa 23:4 (n-6), β-oxa 21:3 (n-6); β-oxa 21:3 (n-3), β-oxa 25:6 (n-3), β-oxa 21:4 (n-3), β-thia 23:4 (n-6), β-thia 21:3 (n-6), β-thia 21:3 (n-3), γ-thia 24:4 (n-6), γ-thia 22:3 (n-6), γ-thia 22:3 (n-3), β-thia 25:6 (n-3), α-CH₂CO₂H-β-thia 23:4 (n-6), 15-OOCMe₂OMe 20:4 (n-6), 15-OOCMe₂OMe β-oxa 23:4 (n-6), 13-OH-β-oxa 21:3 (n-6), 13-OH-β-oxa 21:3 (n-3), 20:4 (n-6)-gly, 20:4 (n-6)-asp, 20:5 (n-3)-gly, 20:5 (n-3)-asp, 22:6 (n-3)-gly, 22:6 (n-3)-asp, 18:3 (n-6)-gly, 18:3 (n-6)-asp, 18:3 (n-3)-gly, 18:3 (n-3)-asp, 19:0-NO₂, 19:3
(n-3)-NO$_2$, 19:3 (n-6)-NO$_2$, 21:4 (n-6)-NO$_2$, 23:6 (n-3)-NO$_2$, $\gamma$-NO$_2$ 21:0, $\gamma$-NO$_2$ 23:4 (n-6) and $\gamma,\gamma'$ (COOH), 21:4 (n-6)NO$_2$.

The present invention is particularly directed to the treatment of pain including *inter alia* neuropathic or neurological pain, chronic pain, acute pain, migraine, headache inflammatory pain, post-operative pain, pain due to multiple sclerosis, Parkinson's disease or other neurological or autoimmune disorder or following or during periods of anxiety, delayed onset muscle soreness, burns or during or following infection or a convulsion, post-poliomyelitic pain, bipolar disorder, panic attack or epilepsy.

Neurological disease states which can be treated in accordance with the present invention include depression, including major depression (single episode, recurrent, melancholic), atypical, dysthnia, sub-syndromal, agitated, retarded, co-morbid with cancer, diabetes, or post-myocardial infarction, involutional, bipolar disorder, psychotic depression, endogenous and reactive, obsessive-compulsive disorder, or bulimia. In addition, NAALADase inhibitors can be used to treat patients suffering from pain (given alone or in combination with morphine, codeine, or dextropropoxyphene), obsessive-compulsive personality disorder, post-traumatic stress disorder, hypertension, atherosclerosis, anxiety, anorexia nervosa, panic, social phobia, stuttering, sleep disorders, chronic fatigue, cognition deficit associated with Alzheimer's disease, alcohol abuse, appetite disorders, weight loss, agoraphobia, improving memory, amnesia, smoking cessation, nicotine withdrawal syndrome symptoms, disturbances of mood and/or appetite associated with pre-menstrual syndrome, depressed mood and/or carbohydrate craving associated with pre-menstrual syndrome, disturbances of mood, disturbances of appetite or disturbances which contribute to recidivism associated with nicotine withdrawal, circadian rhythm disorder, borderline personality disorder, hypochondriasis, pre-menstrual syndrome (PMS), late luteal phase dysphoric disorder, pre-menstrual dysphoric disorder, trichotillomania, symptoms following discontinuation of other anti-depressants, aggressive/intermittent explosive disorder, compulsive gambling, compulsive spending, compulsive sex, psychoactive substance use disorder, sexual disorder, schizophrenia, premature ejaculation,
or psychiatric symptoms selected from stress, worry, anger, rejection sensitivity, and lack of mental or physical energy.

Other examples of pathological or psychological conditions which may be treated in accordance with this invention include, but are not limited to: Moderate Mental Retardation, Severe Mental Retardation, Profound Mental Retardation, Unspecified Mental Retardation, Autistic Disorder, Pervasive Development Disorder NOS, Attention-Deficit Hyperactivity Disorder, Conduct Disorder, Group Type, Conduct Disorder, Solitary Aggressive Type, Conduct Disorder, Undifferentiated Type, Tourette's Disorder, Chronic Motor or Vocal Tic Disorder, Transient Tic Disorder, Tic Disorder NOS, Primary Degenerative Dementia of the Alzheimer Type, Senile Onset, Uncomplicated, Primary Degenerative Dementia of the Alzheimer Type, Senile Onset, with Delirium, Primary Degenerative Dementia of the Alzheimer Type, Senile Onset, with Delusions, Primary Degenerative Dementia of the Alzheimer Type, Senile Onset, with Depression, Primary Degenerative Dementia of the Alzheimer Type, Presenile Onset, Uncomplicated, Primary Degenerative Dementia of the Alzheimer Type, Presenile Onset, with Delirium, Primary Degenerative Dementia of the Alzheimer Type, Presenile Onset, with Delusions, Primary Degenerative Dementia of the Alzheimer Type, Presenile Onset, with Depression, Multi-infarct dementia, Uncomplicated, Multi-infarct dementia, with Delirium, Multi-infarct Dementia, with Delusions, Multi-infarct Dementia, with Depression, Senile Dementia NOS, Presenile Dementia NOS, Alcohol Withdrawal Delirium, Alcohol Hallucinosis, Alcohol Dementia Associated with Alcoholism, Amphetamine or Similarly Acting Sympathomimetic Intoxication, Amphetamine or Similarly Acting Sympathomimetic Delusional Disorder, Cannabis Delusional Disorder, Cocaine Intoxication, Cocaine Delirium, Cocaine Delusional Disorder, Hallucinogen Hallucinosis, Hallucinogen Delusional Disorder, Hallucinogen Mood Disorder, Hallucinogen Posthallucinogen Perception Disorder, Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Intoxication, Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Delirium, Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Delusional Disorder, Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Hood Disorder, Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Organic Mental Disorder
NOS, Other or unspecified Psychoactive Substance Intoxication, Other or Unspecified Psychoactive Substance Delirium, Other or Unspecified Psychoactive Substance Dementia, Other or Unspecified Psychoactive Substance Delusional Disorder, Other or Unspecified Psychoactive Substance Hallucinosis, Other or Unspecified Psychoactive Substance Mood Disorder, Other or Unspecified Psychoactive Substance Anxiety Disorder, Other or Unspecified Psychoactive Substance Personality Disorder, Other or Unspecified Psychoactive Substance Organic Mental Disorder NOS, Delirium, Dementia, Organic Delusional Disorder, Organic Hallucinosis, Organic Mood Disorder, Organic Anxiety Disorder, Organic Personality Disorder, Organic Mental Disorder, Obsessive Compulsive Disorder, Post-traumatic Stress Disorder, Generalized Anxiety Disorder, Anxiety Disorder NOS, Body Dysmorphic Disorder, Hypochondriasis (or Hypochondriacal Neurosis), Somatization Disorder, Undifferentiated Somatoform Disorder, Somatoform Disorder NOS, Intermittent Explosive Disorder, Kleptomania, Pathological Gambling, Pyromania, Trichotillomania and Impulse Control Disorder NOS.

Additional examples of pathological or psychological conditions which may be treated as described in this invention include Schizophrenia, Catatonic, Sub-chronic, Schizophrenia, Catatonic, Chronic, Schizophrenia, Catatonic, Sub-chronic with Acute Exacerbation, Schizophrenia, Catatonic, Chronic with Acute Exacerbation, Schizophrenia, Catatonic, in Remission, Schizophrenia, Catatonic, Unspecified, Schizophrenia, Disorganized, Chronic, Schizophrenia, Disorganized, Subchronic with Acute Exacerbation, Schizophrenia, Disorganized, Chronic with Acute Exacerbation, Schizophrenia, Disorganized, in Remission, Schizophrenia, Disorganized, Unspecified, Schizophrenia, Paranoid, Subchronic, Schizophrenia, Paranoid, Chronic, Schizophrenia, Paranoid, Sub-chronic with Acute Exacerbation, Schizophrenia, Paranoid, Chronic with Acute Exacerbation, Schizophrenia, Paranoid, in Remission, Schizophrenia, Paranoid, Unspecified, Schizophrenia, Undifferentiated, Sub-chronic, Schizophrenia, Undifferentiated, Chronic, Schizophrenia, Undifferentiated, Sub-chronic with Acute Exacerbation, Schizophrenia, Undifferentiated, Chronic with Acute Exacerbation, Schizophrenia, Undifferentiated, in Remission, Schizophrenia, Undifferentiated, Unspecified, Schizophrenia, Residual, Sub-chronic, Schizophrenia, Residual, Chronic, Schizophrenia, Residual, Subchronic with
Acute Exacerbation, Schizophrenia, Residual, Chronic with Acute Exacerbation, Schizophrenia, Residual, in Remission, Schizophrenia, Residual, unspecified, Delusional (Paranoid) Disorder, Brief Reactive Psychosis, Schizophreniform Disorder, Schizoaffective Disorder, induced Psychotic Disorder, Psychotic Disorder NOS (Atypical Psychosis), Bipolar Disorder, Mixed, Severe, without Psychotic Features, Bipolar Disorder, Manic, Severe, without Psychotic Features, Bipolar Disorder, Depressed, Severe, without Psychotic Features, Bipolar Disorder, Mixed, with Psychotic Features, Bipolar Disorder, Manic, with Psychotic Features, Bipolar Disorder, Depressed, with Psychotic Features, Bipolar Disorder NOS, Major Depression, Single Episode, with Psychotic Features, Major Depression, Recurrent with Psychotic Features Personality Disorders, Paranoid Personality Disorders, Schizoid, Personality Disorders, Schizotypal, Personality Disorders, Anti-social, Personality Disorders and Borderline.

Anxiety disorders which may be treated in accordance with this invention include, but are not limited to Anxiety Disorders, Panic Disorder, Panic Disorder with Agoraphobia, Panic Disorder without Agoraphobia, Agoraphobia without History of Panic Disorders, Social Phobia, Simple Phobia, Organic Anxiety Disorder, Psychoactive Substance Anxiety Disorder, Separation Anxiety Disorder, Avoidant Disorder of Childhood or Adolescence, and Overanxious Disorder.

Reference to cardiovascular disease includes strokes and any condition of the systemic vasculature and includes atherosclerosis, chronic heart failure and general heart disease.

Syndrome, Basedow Disease, Bassen-Kornzweig Syndrome, Batten Disease, Batten-Mayou Syndrome, Batten-Spielmeyer-Vogt’s Disease, Batten Turner Syndrome, Batten Turner Type Congenital myopathy, Batten-Vogt Syndrome, BBB Syndrome, BBB Syndrome (Opitz), BBB Syndrome, BBBG Syndrome, BCKD Deficiency, BD, BDLS, BE, Beals Syndrome, Beals Syndrome, Beals-Hecht Syndrome, Bean Syndrome, BEB, Bechterew Syndrome, Becker Disease, Becker Muscular Dystrophy, Becker Nevus, Beckwith Wiedemann Syndrome, Beckwith-Syndrome, Begez-Cesar’s Syndrome, Behcet’s syndrome, Behcet’s Disease, Behr 1, Behr 2, Bell’s Palsy, Benign Acanthosis Nigricans, Benign Astrocytoma, Benign Cranial Nerve Tumors, Benign Cystinosis, Benign Essential Blepharospasm, Benign Essential Tremor, Benign Familial Hematuria, Benign Focal Amyotrophy, Benign Focal Amyotrophy of ALS, Benign Hydrocephalus, Benign Hypermobility Syndrome, Benign Keratosis Nigricans, Benign Paroxysmal Peritonitis, Benign Recurrent Hematuria, Benign Recurrent Intrahepatic Cholestasis, Benign Spinal Muscular Atrophy with Hypertrophy of the Calves, Benign Symmetrical Lipomatosis, Benign Tumors of the Central Nervous System, Berardinelli-Seip Syndrome, Berger’s Disease, Beriberi, Berman Syndrome, Bernard-Horner Syndrome, Bernard-Soulier Syndrome, Besnier Prurigo, Best Disease, β-Alanine-Pyruvate Aminotransferase, β-Galactosidase Deficiency Morquio Syndrome, β-Glucuronidase Deficiency, β Oxidation Defects, β Thalassemia Major, β Thalassemia Minor, β-lipoprotein Deficiency, Bethlem myopathy, Beuren Syndrome, BH4 Deficiency, Biber-Haab-Dimmer Corneal Dystrophy, Bicuspid Aortic Valve, Biedl-Bardet, Bifid Cranium, Bifunctional Enzyme Deficiency, Bilateral Acoustic Neurofibromatosis, Bilateral Acoustic Neuroma, Bilateral Right-Sidedness Sequence, Bilateral Renal Agenesis, Bilateral Temporal Lobe Disorder, Bilious Attacks, Bilirubin Glucuronosyltransferase Deficiency Type I, Binder Syndrome, Binswanger’s Disease, Binswanger’s Encephalopathy, Biotinidase deficiency, Bird-Headed Dwarfism Seckel Type, Birth Defects, Birthmark, Bitemporal Forceps Marks Syndrome, Biventricular Fibrosis, Bjornstad Syndrome, B-K Mole Syndrome, Black Locks-Albinism-Deafness of Sensoneural Type (BADS), Blackfan-Diamond Anemia, Blennorrheal Idiopathic Arthritis, Blepharophimosis, Ptosis, Epicantthus Inversus Syndrome, Blepharospasm, Blepharospasm Benign Essential, Blepharospasm Oromandibular Dystonia, Blessig Cysts, BLFS, Blindness, Bloch-Siemens Incontinentia
Pigmenti Melanoblastosis Cutis Linearis, Bloch-Siemens-Sulzberger Syndrome, Bloch-Sulzberger Syndrome, Blood types, Blood type A, Blood type B, Blood type AB, Blood type O, Bloom Syndrome, Bloom-Torre-Mackacek Syndrome, Blue Rubber Bleb Nevus, Blue Baby, Blue Diaper Syndrome, BMD, BOD, BOFS, Bone Tumor-Epidermoid Cyst-Polyposis, Bonnet-Dechaume-Blanc Syndrome, Bonnevie-Ulrich Syndrome, Book Syndrome, BOR Syndrome, BORJ, Borjeson Syndrome, Borjeson-Forssman-Lehmann Syndrome, Bowen Syndrome, Bowen-Conradi Syndrome, Bowen-Conradi Hutterite, Bowen-Conradi Type Hutterite Syndrome, Bowman’s Layer, BPEI, BPES, Brachial Neuritis, Brachial Neuritis Syndrome, Brachial Plexus Neuritis, Brachial-Plexus-Neuropathy, Brachiocephalic Ischemia, Brachmann-de Lange Syndrome, Brachycephaly, Brachymorphic Type Congenital, Bradycardia, Brain Tumors, Brain Tumors Benign, Brain Tumors Malignant, Branched Chain a-Ketoacid Dehydrogenase Deficiency, Branched Chain Ketonuria I, Brancher Deficiency, Branchio-Oculo-Facial Syndrome, Branchio-Oto-Renal Dysplasia, Branchio-Oto-Renal Syndrome, Branchiooculofacial Syndrome, Branchiootic Syndrome, Brandt Syndrome, Brandywine Type Dentinogenesis Imperfecta, Brandywine type Dentinogenesis Imperfecta, Breast Cancer, BRIC Syndrome, Brittle Bone Disease, Broad β Disease, Broad Thumb Syndrome, Broad Thumbs and Great Toes Characteristic Facies and Mental Retardation, Broad Thumb-Hallux, Broca’s Aphasia, Brocq-Duhring Disease, Bronze Diabetes, Bronze Schilder’s Disease, Brown Albinism, Brown Enamel Hereditary, Brown-Sequard Syndrome, Brown Syndrome, BRRS, Brueghel Syndrome, Bruton’s A γ-globulinemia Common, BS, BSS, Buchanan’s Syndrome, Budd’s Syndrome, Budd-Chiari Syndrome, Buerger-Gruetz Syndrome, Bulbospinal Muscular Atrophy-X-linked, Bulldog Syndrome, Bullosa Hereditaria, Bullous CIE, Bullous Congenital Ichthyosiform Erythroderma, Bullous Ichthyosis, Bullous Pemphigoid, Burkitt’s Lymphoma, Burkitt’s Lymphoma African type, Burkitt’s Lymphoma Non-african type, BWS, Byler’s Disease, C Syndrome, C1 Esterase Inhibitor Dysfunction Type II Angioedema, C1-INH, C1 Esterase Inhibitor Deficiency Type I Angioedema, C1NH, Cacchi-Ricci Disease, CAD, CADASIL, CAH, Calcaneal Valgus, Calcaneovalgus, Calcium Pyrophosphate Dihydrate Deposits, Callosal Agenesis and Ocular Abnormalities, Calves-Hypertrophy of Spinal Muscular Atrophy, Campomelic Dysplasia, Campomelic Dwarfism, Campomelic Syndrome, Camptodactyly-Cleft Palate-Clubfoot, Camptodactyly-
Limited Jaw Excursion, Camptomelic Dwarfism, Camptomelic Syndrome, Camptomelic Syndrome Long-Limb Type, Camurati-Engelmann Disease, Canada-Cronkhite Disease, Canavan disease, Canavan’s Disease Included, Canavan’s Leukodystrophy, Cancer, Cancer Family Syndrome Lynch Type, Cantrell Syndrome, Cantrell-Haller-Ravich Syndrome, Cantrell Pentalogy, Carbamyl Phosphate Synthetase Deficiency, Carbohydrate Deficient Glycoprotein Syndrome, Carbohydrate-Deficient Glycoprotein Syndrome Type Ia, Carbohydrate-Induced Hyperlipemia, Carbohydrate Intolerance of Glucose Galactose, Carbon Dioxide Acidosis, Carboxylase Deficiency Multiple, Cardiac-Limb Syndrome, Cardio-auditory Syndrome, Cardioauditory Syndrome of Jervell and and Lange-Nielsen, Cardiocutaneous Syndrome, Cardio-facial-cutaneous syndrome, Cardiofacial Syndrome Cayler Type, Cardiomegalia Glycogenica Diffusa, Cardiomyopathic Lentiginosis, Cardiomyopathy, Cardiomyopathy Associated with Desmin Storage myopathy, Cardiomyopathy Due to Desmin Defect, Cardiomyopathy-Neutropenia Syndrome, Cardiomyopathy-Neutropenia Syndrome Lethal Infantile Cardio myopathy, Cardiopathic Amyloidosis, Cardiospasm, Cardiocardiac Syndrome, Carnitine-Acylcarnitine Translocase Deficiency, Carnitine Deficiency and Disorders, Carnitine Deficiency Primary, Carnitine Deficiency Secondary, Carnitine Deficiency Secondary to MCAD Deficiency, Carnitine Deficiency Syndrome, Carnitine Palmitoyl Transferase I & II (CPT I & II), Carnitine Palmitoyltransferase Deficiency, Carnitine Palmitoyltransferase Deficiency Type 1, Carnitine Palmitoyltransferase Deficiency Type 2 benign classical muscular form included severe infantile form included, Carnitine Transport Defect (Primary Carnitine Deficiency), Carnosinase Deficiency, Carnosinemia, Caroli Disease, Carpenter syndrome, Carpenter’s, Cartilage-Hair Hypoplasia, Castleman’s Disease, Castleman’s Disease Hyaline Vascular Type, Castleman’s Disease Plasma Cell Type, Castleman Tumor, Cat Eye Syndrome, Cat’s Cry Syndrome, Catalayse deficiency, Cataract-Dental Syndrome, Cataract X-Linked with Hutchinsonian Teeth, Catecholamine hormones, Catel-Manzke Syndrome, Catel-Manzke Type Palatodigital Syndrome, Caudal Dysplasia, Caudal Dysplasia Sequence, Caudal Regression Syndrome, Causalgia Syndrome Major, Cavernomas, Cavernous Angioma, Cavernous Hemangioma, Cavernous Lymphangioma, Cavernous Malformations, Cayler Syndrome, Cazenave’s Vitiligo, CBGD, CBPS, CCA, CCD, CCHS, CCM Syndrome, CCMS, CCO, CD, CDG1a, CDG1A, CDGS Type Ia, CDGS, CDI, CdLS, Celiac Disease,
Celiac sprue, Celiac Sprue-Dermatitis, Cellular Immunodeficiency with Purine Nucleoside Phosphorylase Deficiency, Celsus’ Vitiligo, Central Apnea, Central Core Disease, Central Diabetes Insipidus, Central Form Neurofibromatosis, Central Hypoventilation, Central Sleep Apnea, Centrifugal Lipodystrophy, Centronuclear myopathy, CEP, Cephalocele, Cephalothoracic Lipodystrophy, Ceramide Trihexosidase Deficiency, Cerebellar Agenesis, Cerebellar Aplasia, Cerebellar Hemiagenesis, Cerebellar Hypoplasia, Cerebellar Vermis Aplasia, Cerebellar Vermis Agenesis-Hypernea-Episodic Eye Moves-Ataxia-Retardation, Cerebellar Syndrome, Cerebellarparenchymal Disorder IV, Cerebellomedullary Malformation Syndrome, Cerebello-Oculocutaneous Telangiectasia, Cerebelloparenchymal Disorder IV Familial, Cerebellopontine Angle Tumor, Cerebral Arachnoiditis, Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukodystrophy, Cerebral Beriberi, Cerebral Diplegia, Cerebral Gigantism, Cerebral Malformations Vascular, Cerebral Palsy, Cerebro-Oculorenal Dystrophy, Cerebro-Oculo-Facio-Skeletal Syndrome, Cerebrocostomandibular syndrome, Cerebrohepatorenal Syndrome, Cerebromacular Degeneration, Cerebromuscular Dystrophy Fukuyama Type, Cerebroocular Dysgenesis, Cerebroocular Dysplasia-Muscular Dystrophy Syndrome, Cerebrooculofacioskeletal Syndrome, Cerebroside Lipidosis, Cerebrosidosis, Cerebrotendinous Xanthomatosis, Cerebrovascular Ferrocalcinosis, Ceroid-Lipofuscinosis Adult form, Cervical Dystonia, Cervical Dystonia, Cervico-Oculo-Acoustic Syndrome, Cervical Spinal Stenosis, Cervical Vertebral Fusion, CES, CF, CFC syndrome, CFIDS, CFND, CGD, CGF, Chalasdermia Generalized, Chanarin Dorfman Disease, Chanarin Dorfman Syndrome, Chanarin Dorfman Ichthyosis Syndrome, Chandler’s Syndrome, Charcot’s Syndrome, Charcot-Marie-Tooth, Charcot-Marie-Tooth Disease, Charcot-Marie-Tooth Disease Variant, Charcot-Marie-Tooth-Roussy-Levy Disease, CHARGE Association, Charge Syndrome, CHARGE Syndrome, Chaund’s Ectodermal Dysplasias, Chediak-Higashi Syndrome, Chediak-Steinbrinck-Higashi Syndrome, Cheilitis Granulomatosa, Cheiloschisis, Chemke Syndrome, Cheney Syndrome, Cherry Red Spot and Myoclonus Syndrome, CHF, CHH, Chiari’s Disease, Chiari Malformation I, Chiari Malformation, Chiari Type I (Chiari Malformation I), Chiari Type II (Chiari Malformation II), Chiari I Syndrome, Chiari-Budd Syndrome, Chiari-Frommel Syndrome, Chiari Malformation II, CHILD Syndrome, CHILD Ichthyosis
Arachnoiditis, Chronic Adrenocortical Insufficiency, Chronic Cavernositis, Chronic Congenital Aregenerative Anemia, Chronic Dysphagocytosis, Chronic Familial Granulomatosis, Chronic Familial Icterus, Chronic Fatigue Immune Dysfunction Syndrome (CFIDS), Chronic Granulomatous Disease, Chronic Guillain-Barre Syndrome, Chronic Idiopathic Jaundice, Chronic Idiopathic Polyneuritis (CIP), Chronic Inflammatory Demyelinating Polyneuropathy, Chronic Inflammatory Demyelinating Polyradiculoneuropathy, Chronic Motor Tic, Chronic Mucocutaneous Candidiasis, Chronic Multiple Tics, Chronic Non-Specific Ulcerative Colitis, Chronic Obliterative Cholangitis, Chronic Peptic Ulcer and Esophagitis Syndrome, Chronic Progressive Chorea, Chronic Progressive External Ophthalmoplegia Syndrome, Chronic Progressive External Ophthalmoplegia and myopathy, Chronic Progressive External Ophthalmoplegia with Ragged Red Fibers, Chronic Relapsing Polyneuropathy, Chronic Sarcoïdosis, Chronic Spasmodic Dysphonía, Chronic Vomiting in Childhood, CHS, Churg-Strauss Syndrome, Cicatricial Pemphigoid, CIP, Cirrhosis Congenital Pigmentary, Cirrhosis, Cistinuria, Citrullinemia, CJD, Classic Schindler Disease, Classic Type Pfeiffer Syndrome, Classical Maple Syrup Urine Disease, Classical Hemophilia, Classical Form Cockayne Syndrome Type I (Type A), Classical Leigh's Disease, Classical Phenylketonuria, Classical X-Linked Pelizaeus-Merzbacher Brain Sclerosis, CLE, Cleft Lip/Palate Mucous Cysts Lower Lip PP Digital and Genital Anomalies, Cleft Lip-Palate Blepharophimosis Lagophthalmos and Hypertelorism, Cleft Lip/Palate with Abnormal Thumbs and Microcephaly, Cleft palate-joint contractures-dandy walker malformations, Cleft Palate and Cleft Lip, Cleidocranial Dysplasia w/ Micrognathia, Absent Thumbs, & Distal Aphalangia, Cleidocranial Dysostosis, Cleidocranial Dysplasia, Click murmur syndrome, CLN1, Clonic Spasmodic, Clouston Syndrome, Clubfoot, CMDI, CMM, CMT, CMTC, CMTX, COA Syndrome, Coarctation of the aorta, Coats' Disease, Cobblestone dysplasia, Cochin Jewish Disorder, Cockayne Syndrome, COD-MD Syndrome, COD, Coffin Lowry Syndrome, Coffin Syndrome, Coffin Siris Syndrome, COFS Syndrome, Cogan Corneal Dystrophy, Cogan Reese Syndrome, Cohen Syndrome, Cold Agglutinin Disease, Cold Antibody Disease, Cold Antibody Hemolytic Anemia, Colitis Ulcerative, Colitis Gravis, Colitis Ulcerative Polyneuritis.
and Ear Anomalies, Coloboma, Colonic Neurosis, Color blindness, Colour blindness, Colpocephaly, Columnar-Like Esophagus, Combined Cone-Rod Degeneration, Combined Immunodeficiency with Immunoglobulins, Combined Mesoectodermal Dysplasia, Common Variable Hypogammaglobulinemia, Common Variable Immunodeficiency, Common Ventricle, Communicating Hydrocephalus, Complete Absence of Hypoxanthine-Guanine Phosphoribosyltransferase, Complete Atroventricular Septal Defect, Complement Component 1 Inhibitor Deficiency, Complement Component C1 Regulatory Component Deficiency, Complete Heart Block, Complex Carbohydrate Intolerance, Complex Regional Pain Syndrome, Complex V ATP Synthase Deficiency, Complex I, Complex I NADH dehydrogenase deficiency, Complex II, Complex II Succinate dehydrogenase deficiency, Complex III, Complex III Ubiquinone-cytochrome c oxidoreductase deficiency, Complex IV, Complex IV Cytochrome C Oxidase Deficiency, Complex IV Deficiency, Complex V, Cone-Rod Degeneration, Cone-Rod Degeneration Progressive, Cone Dystrophy, Cone-Rod Dystrophy, Confluent Reticular Papillomatosis, Congenital with low PK Kinetics, Congenital Absence of Abdominal Muscles, Congenital Absence of the Thymus and Parathyroids, Congenital Achromia, Congenital Addison’s Disease, Congenital Adrenal Hyperplasia, Congenital Adrenneal Hyperplasia, Congenital Afibrinogenemia, Congenital Alveolar Hypoventilation, Congenital Anemia of Newborn, Congenital Bilateral Persylvian Syndrome, Congenital Brown Syndrome, Congenital Cardiovascular Defects, Congenital Central Hypoventilation Syndrome, Congenital Cerebral Palsy, Congenital Cervical Synostosis, Congenital Clasped Thumb with Mental Retardation, Congenital Contractural Arachnodactyly, Congenital Contractures Multiple with Arachnodactyly, Congenital Cyanosis, Congenital Defect of the Skull and Scalp, Congenital Dilatation of Intrahepatic Bile Duct, Congenital Dysmyelinating Neuropathy, Congenital Dysphagocytosis, Congenital Dysplastic Angiectasia, Congenital Erythropoietic Porphyria, Congenital Factor XIII Deficiency, Congenital Failure of Autonomic Control of Respiration, Congenital Familial Nonhemolytic Jaundice Type I, Congenital Familial Protracted Diarrhea, Congenital Form Cockayne Syndrome Type II (Type B), Congenital Generalized Fibromatosis, Congenital German Measles, Congenital Giant Axonal Neuropathy, Congenital Heart Block, Congenital Heart Defects, Congenital Hemidysplasia with Ichthyosis Erythroderma and Limb Defects, Congenital Hemolytic Jaundice,
Convulsions, Cooley’s anemia, Copper Transport Disease, Coproporphyria Porphyria Hepatica, Cor Triatriatum, Cor Triatriatum Sinistrum, Cor Triloculare Biaatriatum, Cor Biloculare, Cori Disease, Cornea Dystrophy, Corneal Amyloidosis, Corneal Clouding-Cutis Laxa-Mental Retardation, Corneal Dystrophy, Cornelia de Lange Syndrome, Coronal Dentine Dysplasia, Coronary Artery Disease, Coronary Heart Disease, Corpus Callosum Agenesis, Cortical-Basal Ganglionic Degeneration, Corticalis Deformaris, Cortico-Basal Ganglionic Degeneration (CBGD), Corticobasal Degeneration, Corticosterone Methloxidase Deficiency Type I, Corticosterone Methyloxidase Deficiency Type II, Cortisol, Costello Syndrome, Cot Death, COVESDEM Syndrome, COX, COX Deficiency, COX Deficiency French-Canadian Type, COX Deficiency Infantile Mitochondrial myopathy de Toni-Fanconi-Debre included, COX Deficiency Type Benign Infantile Mitochondrial Myopathy, CP, CPEO, CPEO with myopathy, CPEO with Ragged-Red Fibers, CPPD Familial Form, CPT Deficiency, CPTD, Cranial Arteritis, Cranial Meningoencephalocele, Cranio-Oro-Digital Syndrome, Craniocarpotarsal dystrophy, Craniocele, Craniodigital Syndrome-Mental Retardation Scott Type, Craniofacial Dysostosis, Craniofacial Dysostosis-PD Arteriosus-Hypertrichosis-Hypoplasia of Labia, Craniofrontonasal Dysplasia, Cranioetaphyseal Dysplasia, Cranioorodigital Syndrome, Cranioorodigital Syndrome Type II, Craniostenosis Crouzon Type, Craniostenosis, Craniosynostosis-Choanal Atresia-Radial Humeral Synostosis, Craniosynostosis-Hypertrichosis-Facial and Other Anomalies, Craniosynostosis Midfacial Hypoplasia and Foot Abnormalities, Craniosynostosis Primary, Craniosynostosis-Radial Aplasia Syndrome, Craniosynostosis with Radial Defects, Cranium Bifidum, CREST Syndrome, Creutzfeldt Jakob Disease, Cri du Chat Syndrome, Crib Death, Crigler Najjar Syndrome Type I, Crohn’s Disease, Cronkhite-Canada Syndrome, Cross Syndrome, Cross’ Syndrome, Cross-McKusick-Breen Syndrome, Crouzon, Crouzon Syndrome, Crouzon Craniofacial Dysostosis, Cryoglobulinemia Essential Mixed, Cryptophthalmos-Syndactyly Syndrome, Cryptorchidism-Dwarfism-Subnormal Mentality, Crystalline Corneal Dystrophy of Schnyder, CS, CSD, CSID, CSO, CST Syndrome, Curly Hair-Ankyloblephanon-Nail Dysplasia, Curschmann-Batten-Steinert Syndrome, Curth Macklin Type Ichthyosis Hystric, Curth-Macklin Type, Cushing’s, Cushing Syndrome, Cushing’s III, Cutaneous Malignant Melanoma Hereditary, Cutaneous Porphyrias, Cutis Laxa, Cutis
Laxa-Growth Deficiency Syndrome, Cutis Marmorata Telangiectatica Congenita, CVI, CVID, CVS, Cystic vomiting syndrome, Cystic Disease of the Renal Medulla, Cystic Hygroma, Cystic Fibrosis, Cystic Lymphangioma, Cystine-Lysine-Arginine-Ornithinuria, Cystine Storage Disease, Cystinosis, Cystinuria, Cystinuria with Dibasic Aminoaciduria, Cystinuria Type I, Cystinuria Type II, Cystinuria Type III, Cysts of the Renal Medulla Congenital, Cytochrome C Oxidase Deficiency, Dacryosialoadenopathia, Dacryosialoadenopathia, Dalpro, Dalton, Daltonism, Danbolt-Cross Syndrome, Dancing Eyes-Dancing Feet Syndrome, Dandy-Walker Syndrome, Dandy-Walker Cyst, Dandy-Walker Deformity, Dandy Walker Malformation, Danish Cardiac Type Amyloidosis (Type III), Darier Disease, Davidson’s Disease, Davies’ Disease, DBA, DBS, DC, DD, De Barsy Syndrome, De Barsy-Moenes-Diercks Syndrome, de Lange Syndrome, De Morsier Syndrome, De Santis Cacchione Syndrome, de Toni-Fanconi Syndrome, Deafness Congenital and Functional Heart Disease, Deafness-Dwarfism-Retinal Atrophy, Deafness-Functional Heart Disease, Deafness Onychodystrophy Osteodystrophy and Mental Retardation, Deafness and Pili Torti Bjornstad Type, Deafness Sensorineural with Imperforate Anus and Hypoplastic Thumbs, Debrancher Deficiency, Deciduous Skin, Defect of Enterocyte Intrinsic Factor Receptor, Defect in Natural Killer Lymphocytes, Defect of Renal Reabsorption of Carnitine, Deficiency of Glycoprotein Neuraminidase, Deficiency of Mitochondrial Respiratory Chain Complex IV, Deficiency of Platelet Glycoprotein Ib, Deficiency of Von Willebrand Factor Receptor, Deficiency of Short-Chain Acyl-CoA Dehydrogenase (ACADS), Deformity with Mesomelic Dwarfism, Degenerative Chorea, Degenerative Lumbar Spinal Stenosis, Degos Disease, Degos-Kohlmeier Disease, Degos Syndrome, DEH, Dejerine-Roussy Syndrome, Dejerine Sottas Disease, Deletion 9p Syndrome Partial, Deletion 11q Syndrome Partial, Deletion 13q Syndrome Partial, Dellemann-Oorthuys Syndrome, Dellemann Syndrome, Dementia with Lobar Atrophy and Neuronal Cytoplasmic Inclusions, Demyelinating Disease, DeMyer Syndrome, Dentin Dysplasia Coronal, Dentin Dysplasia Radicular, Dentin Dysplasia Type I, Dentin Dysplasia Type II, Dentinogenesis Imperfecta Brandywine type, Dentinogenesis Imperfecta Shields Type, Dentinogenesis Imperfecta Type III, Dento-Oculo-Osseous Dysplasia, Dentooculocutaneous Syndrome, Denys-Drash Syndrome, Depakene, DepakeneTM exposure, Depakote, Depakote Sprinkle, Depigmentation-Gingival
Fibromatosis-Microphthalmia, Dercum Disease, Dermatitis Atopic, Dermatitis Exfoliativa, Dermatitis Herpetiformis, Dermatitis Multiformis, Dermatochalasia Generalized, Dermatolysis Generalized, Dermatomegaly, Dermatomyositis sine myositis, Dermatomyositis, Dermatosparaxis, Dermatostomatitis Stevens Johnson Type, Desbuquois Syndrome, Desmin Storage myopathy, Desquamation of Newborn, Deuteranomaly, Developmental Reading Disorder, Developmental Gerstmann Syndrome, Devergie Disease, Devic Disease, Devic Syndrome, Dextrocardia-Bronchiectasis and Sinusitis, Dextrocardia with Situs Inversus, DGS, DGSX Golabi-Rosen Syndrome Included, DH, DHAP alkyl transferase deficiency, DHBS Deficiency, DHOF, DHPR Deficiency, Diabetes Insipidus, Diabetes Insipidus Diabetes Mellitus Optic Atrophy and Deafness, Diabetes Insipidus Neurohypophyseal, Diabetes Insulin Dependent, Diabetes Mellitus, Diabetes Mellitus Addison’s Disease Myxedema, Diabetic Acidosis, Diabetic Bearded Woman Syndrome, Diamond-Blackfan Anemia, Diaphragmatic Apnea, Diaphysseal Aclasis, Diastrophic Dwarfism, Diastrophic Dysplasia, Diastrophic Nanism Syndrome, Dicarboxylic Aminoaciduria, Dicarboxylicaciduria Caused by Defect in β-Oxidation of Fatty Acids, Dicarboxylicaciduria due to Defect in β-Oxidation of Fatty Acids, Dicarboxylicaciduria due to MCADH Deficiency, Dichromasy, Dicker-Opitz, DIDMOAD, Diencephalic Syndrome, Diencephalic Syndrome of Childhood, Diencephalic Syndrome of Emaciation, Dienoyl-CoA Reductase Deficiency, Diffuse Cerebral Degeneration in Infancy, Diffuse Degenerative Cerebral Disease, Diffuse Idiopathic Skeletal Hyperostosis, Diffusum-Glycopeptiduria, DiGeorge Syndrome, Digital-Oro-Cranio Syndrome, Digitoto-Oto-Palatal Syndrome, Digitoto-Oto-Palatal Syndrome Type I, Digitoto-Oto-Palatal Syndrome Type II, Dihydrobiopterin Synthetase Deficiency, Dihydropteridine Reductase Deficiency, Dihydroxyacetonephosphate synthase, Dilated (Congestive) Cardiomyopathy, Dimitri Disease, Diplegia of Cerebral Palsy, Diplo-Y Syndrome, Disaccharidase Deficiency, Disaccharide Intolerance I, Discoid Lupus, Discoid Lupus Erythematosus, DISH, Disorder of Cornification, Disorder of Cornification Type I, Disorder of Cornification Type 4, Disorder of Cornification 6, Disorder of Cornification 8, Disorder of Cornification 9 Netherton’s Type, Disorder of Cornification 11 Phytanic Acid Type, Disorder of Cornification 12 (Neutral Lipid Storage Type), Disorder of Cornification 13, Disorder of Cornification 14, Disorder of Cornification 14 Trichothiodystrophy Type, Disorder of Cornification 15 (Keratitis
Deafness Type), Disorder of Cornification 16, Disorder of Cornification 18
Erythrokeratodermia Variabilis Type, Disorder of Cornification 19, Disorder of
Cornification 20, Disorder of Cornification 24, Displaced Spleen, Disseminated Lupus
Erythematosus, Disseminated Neurodermatitis, Disseminated Sclerosis, Distal 11q
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Monosomy, Distal 11q- Syndrome, Distal Arthrogryposis Multiplex Congenita Type IIA,
Distal Arthrogryposis Multiplex Congenita Type IIA, Distal Arthrogryposis Type IIA,
Distal Arthrogryposis Type 2A, Distal Duplication 6q, Distal Duplication 10q, Dup(10q)
Syndrome, Distal Duplication 15q, Distal Monosomy 9p, Distal Trisomy 6q, Distal
Trisomy 10q Syndrome, Distal Trisomy 11q, Divalproex, DJS, DKC, DLE, DLP III, DM,
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DMC Syndrome, DMC Disease, DMD, DNS Hereditary, DOC I, DOC 2, DOC 4, DOC 6
(Harlequin Type), DOC 8 Curth-Macklin Type, DOC 11 Phytic Acid Type, DOC 12
(Neutral Lipid Storage Type), DOC 13, DOC 14, DOC 14 Trichoiodystrophy Type,
DOC 15 (Keratitis Deafness Type), DOC 16, DOC 16 Unilateral Hemidysplasia Type,
DOC 18, DOC 19, DOC 20, DOC 24, Dohle’s Bodies-Myelopathy, Dolichospondylic
Dysplasia, Dolichostenomelia, Dolichostenomelia Syndrome, Dominant Type Kenny-
Caffe Syndrome, Dominant Type Myotonia Congenita, Donahue Syndrome, Donath-
Landsteiner Hemolytic Anemia, Donath-Landsteiner Syndrome, DOOR Syndrome,
DOORS Syndrome, Dopa-responsive Dystonia (DRD), Dorfman Chanarin Syndrome,
Dowling-Meara Syndrome, Down Syndrome, DR Syndrome, Drash Syndrome, DRD,
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Dreifuss-Emery Type Muscular Dystrophy with Contractures, Dressler Syndrome, Drifting
Spleen, Drug-induced Acanthosis Nigricans, Drug-induced Lupus Erythematosus, Drug-
related Adrenal Insufficiency, Drummond’s Syndrome, Dry Beriberi, Dry Eye, DTD,
Duane’s Retraction Syndrome, Duane Syndrome, Duane Syndrome Type 1A 1B and 1C,
Duane Syndrome Type 2A 2B and 2C, Duane Syndrome Type 3A 3B and 3C, Dubin
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Johnson Syndrome, Dubowitz Syndrome, Duchenne, Duchenne Muscular Dystrophy,
Duchenne’s Paralysis, Duhring’s Disease, Duncan Disease, Duncan’s Disease, Duodenal
Atresia, Duodenal Stenosis, Duodenitis, Duplication 4p Syndrome, Duplication 6q Partial,
Dupuy’s Syndrome, Dupuyten’s Contracture, Dutch-Kennedy Syndrome, Dwarfism,
Dwarfism Camptomelic, Dwarfism Cortical Thickening of the Tubular Bones & Transient
Hypocalcemia, Dwarfism Levi’s Type, Dwarfism Metatropic, Dwarfism-Onychodysplasia,
Dwarfism-Pericarditis, Dwarfism with Renal Atrophy and Deafness, Dwarfism with
Varicella Zoster Syndrome, FFDD Type II, FG Syndrome, FGDY, FHS, Fibrin Stabilizing Factor Deficiency, Fibrinase Deficiency, Fibrinoid Degeneration of Astrocytes, Fibrinoid Leukodystrophy, Fibrinoligase Deficiency, Fibroblastoma Perineural, Fibrocystic Disease of Pancreas, Fibrodysplasia Ossificans Progressiva, Fibroelastic Endocarditis, Fibromyalgia, Fibromyalgia-Fibromyositis, Fibromyositis, Fibroin Cholangitis, Fibrosis, Fibrous Ankylosis of Multiple Joints, Fibrous Cavernositis, Fibrous Dysplasia, Fibrous Plaques of the Penis, Fibrous Sclerosis of the Penis, Fickler-Winkler Type, Fiedler Disease, Fifth Digit Syndrome, Filippi Syndrome, Finnish Type Amyloidosis (Type V), First Degree Congenital Heart Block, First and Second Branchial Arch Syndrome, Fischer's Syndrome, Fish Odor Syndrome, Fissured Tongue, Flat Adenoma Syndrome, Flatau-Schilder Disease, Flavin Containing Monooxygenase 2, Floating β Disease, Floating-Harbor Syndrome, Floating Spleen, Floppy Infant Syndrome, Floppy Valve Syndrome, Fluent Aphasia, FMD, FMF, FMO Adult Liver Form, FMO2, FND, Focal Dermal Dysplasia Syndrome, Focal Dermal Hypoplasia, Focal Dermato-Phalangeal Dysplasia, Focal Dystonia, Focal Epilepsy, Focal Facial Dermal Dysplasia Type II, Focal Neuromyotonia, FODH, Folling Syndrome, Fong Disease, FOP, Forbes Disease, Forbes-Albright Syndrome, Forestier's Disease, Forsius-Eriksson Syndrome (X-Linked), Fothergill Disease, Fountain Syndrome, Foveal Dystrophy Progressive, FPO Syndrome Type II, FPO, Fraccaro Type Achondrogenesis (Type IB), Fragile X syndrome, Franceschetti-Zwalen-Klein Syndrome, Francois Dyscephaly Syndrome, Francois-Neetens Speckled Dystrophy, Flecked Corneal Dystrophy, Fraser Syndrome, FRAXA, FRDA, Fredrickson Type I Hyperlipoproteinemia, Freeman-Sheldon Syndrome, Freire-Maia Syndrome, Frey’s Syndrome, Friedreich’s Ataxia, Friedreich’s Disease, Friedreich’s Tabes, FRNS, Froelich’s Syndrome, Frommel-Chiari Syndrome, Frommel-Chiari Syndrome Lactation-Uterus Atrophy, Frontodigital Syndrome, Frontofacialnasal Dysostosis, Frontofacialnasal Dysplasia, Frontonasal Dysplasia, Frontonasal Dysplasia with Coronal Craniosynostosis, Fructose-1-Phosphate Aldolase Deficiency, Fructosemia, Fructosuria, Fryns Syndrome, FSH, FSHD, FSS, Fuchs Dystrophy, Fucosidosis Type 1, Fucosidosis Type 2, Fucosidosis Type 3, Fukuhara Syndrome, Fukuyama Disease, Fukuyama Type Muscular Dystrophy, Fumarylacetoacetase Deficiency, Furrowed Tongue, G Syndrome, G6PD Deficiency, G6PD, GA I, GA IIB, GA IIA, GA II, GAII & MADD,
Galactorrhea-Amenorrhea Syndrome Nonpuerperal, Galactorrhea-Amenorrhea without Pregnancy, Galactosamine-6-Sulfatase Deficiency, Galactose-1-Phosphate Uridyl Transferase Deficiency, Galactosemia, GALB Deficiency, Galloway-Mowat Syndrome, Galloway Syndrome, GALT Deficiency, Gammaglobulin Deficiency, GAN, Ganglioside Neuraminidase Deficiency, Ganglioside Sialidase Deficiency, Gangliosidosis GM1 Type 1, Gangliosidosis GM2 Type 2, Gangliosidosis β Hexosaminidase B Defeciency, Gardner Syndrome, Gargoilism, Garies-Mason Syndrome, Gasser Syndrome, Gastric Intrinsic Factor Failure of Secretion, Enterocyte Cobalamin, Gastrinoma, Gastritis, Gastroesophageal Laceration-Hemorrhage, Gastrointestinal Polyposis and Ectodermal Changes, Gastrochisis, Gaucher Disease, Gaucher-Schlagenhaufer, Gayet-Wernicke Syndrome, GBS, GCA, GCM Syndrome, GCPS, Gee-Herter Disease, Gee-Thaysen Disease, Gehrig's Disease, Gelineau's Syndrome, Gence-Wiedemann Syndrome, Generalized Dystonia, Generalized Familial Neuromyotonia, Generalized Fibromatosis, Generalized Flexion Epilepsy, Generalized Glycogenosis, Generalized Hyperhidrosis, Generalized Lipofuscinosis, Generalized Myasthenia Gravis, Generalized Myotonia, Generalized Sporadic Neuromyotonia, Genetic Disorders, Genital Defects, Genital and Urinary Tract Defects, Gerstmann Syndrome, Gerstmann Tetrad, GHBP, GHD, GHR, Giant Axonal Disease, Giant Axonal Neuropathy, Giant Benign Lymphoma, Giant Cell Glioblastoma Astrocytoma, Giant Cell Arteritis, Giant Cell Disease of the Liver, Giant Cell Hepatitis, Giant Cell of Newborns Cirrhosis, Giant Cyst of the Retina, Giant Lymph Node Hyperplasia, Giant Platelet Syndrome Hereditary, Giant Tongue, Macular Dystrophy, Gilbert's Disease, Gilbert Syndrome, Gilbert-Dreyfus Syndrome, Gilbert-Lereboullet Syndrome, Gilford Syndrome, Gilles de la Tourette's syndrome, Gillespie Syndrome, Gingival Fibromatosis-Abnormal Fingers Nails Nose Ear Splenomegaly, GLA Deficiency, GLA, GLB1, Glioma Retina, Global Aphasia, Globoid Leukodystrophy, Glossoptosis Micrognathia and Cleft Palate, Glucocerebrosidase Deficiency, Glucocerebrosidosis, Glucose-6-Phosphate Dehydrogenase Deficiency, Glucose-6-Phosphate Transport Defect, Glucose-6-Phosphatase Translocase Deficiency, Glucose-G-Phosphatase Deficiency, Glucose-Galactose Malabsorption, Glucosyl Ceramide Lipidosis, Glutaric Aciduria I, Glutaric Acidemia I, Glutaric Acidemia II, Glutaric Aciduria Type II, Glutaric Aciduria Type III, Glutaricacidemia I,
Glutaricacidemia II, Glutaricaciduria I, Glutaricaciduria Type IIA, Glutaricaciduria Type IIB, Glutaryl-CoA Dehydrogenase Deficiency, Glutaurate-Aspartate Transport Defect, Gluten-Sensitive Enteropathy, Glycogen Disease of Muscle Type VII, Glycogen Storage Disease I, Glycogen Storage Disease III, Glycogen Storage Disease IV, Glycogen Storage Disease Type V, Glycogen Storage Disease VI, Glycogen Storage Disease VII, Glycogen Storage Disease VIII, Glycogen Storage Disease Type II, Glycogen Storage Disease-Type II, Glycogenosis, Glycogenosis Type I, Glycogenosis Type IA, Glycogenosis Type IB, Glycogenosis Type II, Glycogenosis Type II, Glycogenosis Type III, Glycogenosis Type IV, Glycogenosis Type V, Glycogenosis Type VI, Glycogenosis Type VII, Glycogenosis Type VIII, Glycolic Aciduria, Glycolipid Lipidosis, GM2 Gangliosidosis Type 1, GM2 Gangliosidosis Type 1, GNPTA, Goitrous Autoimmune Thyroiditis, Goldenhar Syndrome, Goldenhar-Gorlin Syndrome, Goldscheider’s Disease, Goltz Syndrome, Goltz-Gorlin Syndrome, Gonadal Dysgenesis 45 X, Gonadal Dysgenesis XO, Goniodysgenesis-Hypodontia, Goodman Syndrome, Goodman, Goodpasture Syndrome, Gordon Syndrome, Gorlin’s Syndrome, Gorlin-Chaudhry-Moss Syndrome, Gottron Erythrokeratodermia Congenitalis Progressiva Symmetrica, Gottron’s Syndrome, Gougerot-Carteaud Syndrome, Graft versus Host Disease, Grand Mal Epilepsy, Granular Type Corneal Dystrophy, Granulomatous Arteritis, Granulomatous Colitis, Granulomatous Dermatitis with Eosinophilia, Granulomatous Ileitis, Graves Disease, Graves’ Hyperthyroidism, Graves’ Disease, Greig Cephalopolysyndactyly Syndrome, Groenouw Type I Corneal Dystrophy, Groenouw Type II Corneal Dystrophy, Gronblad-Strandberg Syndrome, Grotton Syndrome, Growth Hormone Receptor Deficiency, Growth Hormone Binding Protein Deficiency, Growth Hormone Deficiency, Growth-Mental Deficiency Syndrome of Myhre, Growth Retardation-Rieger Anomaly, GRS, Gruber Syndrome, GS, GSD6, GSD8, GTS, Guanosine Triphosphate-Cyclohydrolase Deficiency, Guanosine Triphosphate-Cyclohydrolase Deficiency, Guenther Porphyria, Guerin-Stern Syndrome, Guillain-Barré, Guillain-Barré Syndrome, Gunther Disease, H Disease, H. Gottron’s Syndrome, Habit Spasms, HAE, Hageman Factor Deficiency, Hageman factor, Haim-Munk Syndrome, Hajdu-Cheney Syndrome, Hajdu Cheney, HAL Deficiency, Hall-Pallister Syndrome, Hallermann-Streiff-Francois Syndrome, Hallermann-Streiff Syndrome, Hallervorden-Spatz Disease, Hallervorden-Spatz Syndrome, Hallopeau-
Type III, Hyperlipoproteinemia Type IV, Hyperoxaluria, Hyperphalangy-Clinodactyly of
Index Finger with Pierre Robin Syndrome, Hyperphenylalanemia, Hyperplastic
Epidermolysis Bullosa, Hyperpnea, Hyperpotassemia, Hyperprebeta-Lipoproteinemia,
Hyperprolinemia Type I, Hyperprolinemia Type II, Hypersplenism, Hypertelorism with
Esophageal Abnormalities and Hydrospadias, Hypertelorism-Hydrospadias Syndrome,
Hypertrophic Cardiomyopathy, Hypertrophic Interstitial Neuropathy, Hypertrophic
Interstitial Neuritis, Hypertrophic Interstitial Radiculoneuropathy, Hypertrophic
Neuropathy of Refsum, Hypertrophic Obstructive Cardiomyopathy, Hyperuricemia
Choreoathetosis Self-multilation Syndrome, Hyperuricemia-Oligophrenia,
Hypervalinemia, Hypocalcified (Hypomineralized) Type, Hypochondrogenesis,
Hypochondroplasia, Hypo-γ-globulinemia, Hypo-γ-globulinemia Transient of Infancy,
Hypogenital Dystrophy with Diabetic Tendency, Hypoglossia-Hypodactylia Syndrome,
Hypoglycemia, Exogenous Hypoglycemia, Hypoglycemia with Macroglossia,
Hypoglycosylation Syndrome Type 1a, Hypoglycosylation Syndrome Type 1a,
Hypogonadism with Anosmia, Hypogonadotropic Hypogonadism and Anosmia,
Hypohydrotic Ectodermal Dysplasia, Hypohydrotic Ectodermal Dysplasia Autosomal
Dominant type, Hypohydrotic Ectodermal Dysplasias Auto-recessive, Hypokalemia,
Hypokalemic Alkalosis with Hypercalciuria, Hypokalemic Syndrome, Hypolactasia,
Hypomaturative Type (Snow-Capped Teeth), Hypomelanosis of Ito, Hypomelia-
Hypotrichosis-Facial Hemangioma Syndrome, Hypomyelination Neuropathy,
Hypoparathyroidism, Hypophosphatasia, Hypophosphatemic Rickets with Hypercalcemia,
Hypopigmentation, Hypopigmented macular lesion, Hypoplasia of the Depressor Anguli
Oris Muscle with Cardiac Defects, Hypoplastic Anemia, Hypoplastic Congenital Anemia,
Hypoplastic Chondrodystrophy, Hypoplastic Enamel-Onycholysis-Hypohidrosis,
Hypoplastic (Hypoplastic-Explanic) Type, Hypoplastic Left Heart Syndrome,
Hypoplastic-Triphalangeal Thumbs, Hypopotassemia Syndrome, Hydrospadias-Dysphagia
Syndrome, Hyposmia, Hypothalamic Hamartoblastoma Hypopituitarism Imperforate Anus
Polydactyly, Hypothalamic Infantilism-Obesity, Hypothyroidism, Hypoponcia-Hypometia-
Hypogonadism-Obesity Syndrome, Hypoxanthine-Guanine Phosphoribosyltransferase
Defect (Complete Absence of), I-Cell Disease, Iatrogenic Hypoglycemia, IBGC, IBIDS
Syndrome, IBM, IBS, IC, I-Cell Disease, ICD, ICE Syndrome Cogan-Reese Type,
Degeneration Disciform, Macular Degeneration Senile, Macular Dystrophy, Macular Type
Corneal Dystrophy, MAD, Madelung's Disease, Maffucci Syndrome, Major Epilepsy,
Malabsorption, Malabsorption-Ectodermal Dysplasia-Nasal Alar Hypoplasia, Maladie de
Roger, Maladie de Tics, Male Malformation of Limbs and Kidneys, Male Turner
Syndrome, Malignant Acanthosis, Malignant Acanthosis Nigricans, Malignant
Astrocytoma, Malignant Atrophic Papulosis, Malignant Fever, Malignant
Hyperphenylalaninemia, Malignant Hyperpyrexia, Malignant Hyperthermia, Malignant
Melanoma, Malignant Tumors of the Central Nervous System, Mallory-Weiss Laceration,
Mallory-Weiss Tear, Mallory-Weiss Syndrome, Mammary Paget's Disease, Mandibular
Ameloblastoma, Mandibulofacial Dysostosis, Manic Depression Illness Disease,
Mannosidosis, Map-Dot-Fingerprint Type Corneal Dystrophy, Maple Syrup Urine Disease,
Marble Bones, Marchiafava-Micheli Syndrome, Marcus Gunn Jaw-Winking Syndrome,
Marcus Gunn Phenomenon, Marcus Gunn Ptosis with Jaw-Winking, Marcus Gunn
Syndrome, Marcus Gunn (Jaw-Winking) Syndrome, Marcus Gunn Ptosis (with Jaw-
Winking), Marden-Walker Syndrome, Marden-Walker Type Connective Tissue Disorder,
Marfan's Abiotrophy, Marfan-Achard Syndrome, Marfan Syndrome, Marfan's Syndrome
I, Marfan's Variant, Marfanoid Hypermobility Syndrome, Marginal Corneal Dystrophy,
Marie's Ataxia, Marie Disease, Marie-Sainton Disease, Marie Strumpell Disease, Marie-
Strumpell Spondylitis, Marinesco-Sjogren Syndrome, Marinesco-Sjogren-Gorland
Syndrome, Marker X Syndrome, Maroteaux Lamy Syndrome, Maroteaux Type
Acromesomelic Dysplasia, Marshall's Ectodermal Dysplasias With Ocular and Hearing
Defects, Marshall-Smith Syndrome, Marshall Syndrome, Marshall Type Deafness-
Myopia-Cataract-Saddle Nose, Martin-Albright Syndrome, Martin-Bell Syndrome,
Martorell Syndrome, MASA Syndrome, Massive Myoclonia, Mast Cell Leukemia,
Mastocytosis, Mastocytosis With an Associated Hematologic Disorder, Maumenee
Corneal Dystrophy, Maxillary Ameloblastoma, Maxillofacial Dysostosis, Maxillonasal
Dysplasia, Maxillonasal Dysplasia Binder Type, Maxillopalpebral Synkinesis, May-
Hegglin Anomaly, MCAD Deficiency, MCAD, McArdle Disease, McCune-Albright,
MCD, McKusick Type Metaphyseal Chondrodysplasia, MCR, MCTD, Meckel Syndrome,
Meckel-Gruber Syndrome, Median Cleft Face Syndrome, Mediterranean Anemia,
Medium-Chain Acyl-CoA Dehydrogenase (ACADM), Medium Chain Acyl-CoA
Dehydrogenase (MCAD) Deficiency, Medium-Chain Acyl-CoA Dehydrogenase Deficiency, Medullary Cystic Disease, Medullary Sponge Kidney, MEF, Megaesophagus, Megalencephaly, Megalencephaly with Hyaline Inclusion, Megalencephaly with Hyaline Panneuropathy, Megaloblastic Anemia, Megaloblastic Anemia of Pregnancy, Megalocornea-Mental Retardation Syndrome, Meier-Gorlin Syndrome, Meige's Lymphedema, Meige's Syndrome, Melanodermic Leukodystrophy, Melanodermic Intestinal Polyposis, Melanodermic-Intestinal Polyposis, MELAS Syndrome, MELAS, Melkerson Syndrome, Melnick-Fraser Syndrome, Melnick-Needles Osteodysplasty, Melnick-Needles Syndrome, Membranous Lipodystrophy, Mendes Da Costa Syndrome, Meniere Disease, Ménière's Disease, Meningeal Capillary Angiomatosis, Menkes Disease, Menke's Syndrome I, Mental Retardation Aphasia Shuffling Gait Adducted Thumbs (MASA), Mental Retardation-Deafness-Skeletal Abnormalities-Coarse Face with Full Lips, Mental Retardation with Hypoplastic 5th Fingernails and Toenails, Mental Retardation with Osteocartilaginous Abnormalities, Mental Retardation-X-linked with Growth Delay-Deafness-Microgenitalism, Menzel Type OPCA, Mermaid Syndrome, MERRF, MERRF Syndrome, Merten-Singleton Syndrome, MES, Mesangial IGA Nephropathy, Mesenteric Lipodystrophy, Mesiodens-Cataract Syndrome, Mesodermal Dysmorphodystrophy, Mesomelic Dwarfism-Madelung Deformity, Metabolic Acidosis, Metachromatic Leukodystrophy, Metatarsus Varus, Metatropic Dwarfism Syndrome, Metatropic Dysplasia, Metatropic Dysplasia I, Metatropic Dysplasia II, Methylmalonic Acidemia, Methylmalonic Aciduria, Meulengracht's Disease, MFD1, MG, MH, MHA, Micrencephaly, Microcephalic Primordial Dwarfism I, Microcephaly, Microcephaly-Hiatal Hernia-Nephrosis Galloway Type, Microcephaly-Hiatal Hernia-Nephrotic Syndrome, Microcystic Corneal Dystrophy, Microcythemia, Microlissencephaly, Microphthalmia, Microphthalmia or Anophthalmos with Associated Anomalies, Micropolygyria With Muscular Dystrophy, Microtia Absent Patellae Micrognathia Syndrome, Microvillus Inclusion Disease, MID, Midsystolic-Click-Late Systolic Murmur Syndrome, Miescher's Type I Syndrome, Mikulicz Syndrome, Mikulicz-Radecki Syndrome, Mikulicz-Sjogren Syndrome, Mild Autosomal Recessive, Mild Intermediate Maple Syrup Urine Disease, Mild Maple Syrup Urine Disease, Miller Syndrome, Miller-Dieker Syndrome, Miller-Fisher Syndrome, Milroy Disease, Minkowski-Chauffard Syndrome, Minor Epilepsy,
Minot-Von Willebrand Disease, Mirror-Image Dextrocardia, Mitochondrial β-Oxidation Disorders, Mitochondrial and Cytosolic, Mitochondrial Cytopathy, Mitochondrial Cytopathy, Kearns-Sayre Type, Mitochondrial Encephalopathy, Mitochondrial Encephalo Myopathy Lactic Acidosis and Strokelike Episodes, Mitochondrial Myopathy, Mitochondrial Myopathy Encephalopathy Lactic Acidosis Stroke-Like Episode, Mitochondrial PEPCK Deficiency, Mitral-valve prolapse, Mixed Apnea, Mixed Connective Tissue Disease, Mixed Hepatic Porphyria, Mixed Non-Fluent Aphasia, Mixed Sleep Apnea, Mixed Tonic and Clonic Torticollis, MJD, MKS, ML I, ML II, ML III, ML IV, ML Disorder Type I, ML Disorder Type II, ML Disorder Type III, ML Disorder Type IV, MLNS, MMR Syndrome, MND, MNGIE, MNS, Mobitz I, Mobitz II, Mobius Syndrome, Moebius Syndrome, Moersch-Woltmann Syndrome, Mohr Syndrome, Monilethrix, Monomodal Visual Amnesia, Mononeuritis Multiplex, Mononeuritis Peripheral, Mononeuropathy Peripheral, Monosomy 3p2, Monosomy 9p Partial, Monosomy 11q Partial, Monosomy 13q Partial, Monosomy 18q Syndrome, Monosomy X, Monostotic Fibrous Dysplasia, Morgagni-Turner-Albright Syndrome, Morphea, Morquio Disease, Morquio Syndrome A, Morquio Syndrome B, Morquio-Brailsford Syndrome, Morvan Disease, Mosaic Tetrasomy 9p, Motor Neuron Disease, Motor Neuron Syndrome, Motor Neurone Disease, Motoneuron Disease, Motor-System Disease (Focal and Slow), Moya-Moya Disease, MPS, MPS I, MPS I H, MPS I H/S Hurler/Scheie Syndrome, MPS I S Scheie Syndrome, MPS II, MPS IIA, MPS IIB, MPS II-AR Autosomal Recessive Hunter Syndrome, MPS II-XR, MPS II-XR Severe Autosomal Recessive, MPS III, MPS III A, B, C and D, Sanfilippo A, MPS IV, MPS IV A and B Morquio A, MPS V, MPS VI Severe Intermediate Mild Maroteaux-Lamy, MPS VII Sly Syndrome, MPS VIII, MPS Disorder, MPS Disorder VI, MRS, MS, MSA, MSD, MSL, MSS, MSUD, MSUD, MSUD Type Ib, MSUD Type II, Mucocutaneous Lymph Node Syndrome, Mucolipidosis I, Mucolipidosis II, Mucolipidosis III, Mucolipidosis IV, Mucopolysaccharidosis, Mucopolysaccharidosis I-H, Mucopolysaccharidosis I-S, Mucopolysaccharidosis II, Mucopolysaccharidosis III, Mucopolysaccharidosis IV, Mucopolysaccharidosis VI, Mucopolysaccharidosis VII, Mucopolysaccharidosis Type I, Mucopolysaccharidosis Type II, Mucopolysaccharidosis Type III, Mucopolysaccharidosis Type VII, Mucosis, Mucosulfatidosis, Mucous Colitis,
Mucoviscidosis, Mulibrey Dwarfism, Mulibrey Nanism Syndrome, Mullerian Duct Aplasia-Renal Aplasia-Cervicothoracic Somite Dysplasia, Mullerian Duct-Renal-Cervicothoracic-Upper Limb Defects, Mullerian Duct and Renal Agenesis with Upper Limb and Rib Anomalies, Mullerian-Renal-Cervicothoracic Somite Abnormalities, Multi-Infarct Dementia Binswanger's Type, Multicentric Castleman's Disease, Multifocal Eosinophilic Granuloma, Multiple Acyl-CoA Dehydrogenase Deficiency, Multiple Acyl-CoA Dehydrogenase Deficiency / Glutaric Aciduria Type II, Multiple Angiomas and Endochondromas, Multiple Carboxylase Deficiency, Multiple Cartilaginous Enchondromatosis, Multiple Cartilaginous Exostoses, Multiple Enchondromatosis, Multiple Endocrine Deficiency Syndrome Type II, Multiple Epiphyseal Dysplasia, Multiple Exostoses, Multiple Exostoses Syndrome, Multiple Familial Polyposis, Multiple Lentigines Syndrome, Multiple Myeloma, Multiple Neuritis of the Shoulder Girdle, Multiple Osteochondromatosis, Multiple Peripheral Neuritis, Multiple Polyposis of the Colon, Multiple Pterygium Syndrome, Multiple Sclerosis, Multiple Sulfatase Deficiency, Multiple Symmetric Lipomatosis, Multiple System Atrophy, Multi-synostotic Osteodysgenesis, Multi-synostotic Osteodysgenesis with Long Bone Fractures, Mulvihill-Smith Syndrome, MURCS Association, Murk Jansen Type Metaphyseal Chondrodysplasia, Muscle Carnitine Deficiency, Muscle Core Disease, Muscle Phosphofructokinase Deficiency, Muscular Central Core Disease, Muscular Dystrophy, Muscular Dystrophy Classic X-linked Recessive, Muscular Dystrophy Congenital With Central Nervous System Involvement, Muscular Dystrophy Congenital Progressive with Mental Retardation, Muscular Dystrophy Facioscapulohumeral, Muscular Rheumatism, Muscular Rigidity - Progressive Spasm, Musculoskeletal Pain Syndrome, Myalgia, MVP, MVP, MWS, Myasthenia Gravis, Myasthenic Syndrome of Lambert-Eaton, Myeloclastoclastic Diffuse Sclerosis, Myelomatosis, Myhre Syndrome, Myoclonic Astatic Petit Mal Epilepsy, Myoclonic Dystonia, Myoclonic Encephalopathy of Infants, Myoclonic Epilepsy, Myoclonic Epilepsy Hartung Type, Myoclonus Epilepsy Associated with Ragged Red Fibers, Myoclonic Epilepsy and Ragged-Red Fiber Disease, Myoclonic Progressive Familial Epilepsy, Myoclonic Progressive Familial Epilepsy, Myoclonic Seizure, Myoclonus, Myoclonus Epilepsy, Myocencephalopathy Ragged-Red Fiber Disease, Myofibromatosis, Myofibromatosis Congenital, Myogenic Facio-Scapulo-Peroneal
Syndrome Ichthyosis, Nettleship Falls Syndrome (X-Linked), Neu-Laxova Syndrome, Neuhauser Syndrome, Neural-Tube Defects, Neuralgic Amyotrophy, Neuraminidase Deficiency, Neuraocutaneous Melanosis, Neurinoma of the Acoustic Nerve, Neurinoma, Neuroacanthocytosis, Neuroaxonal Dystrophy Schindler Type, Neurodegeneration with Brain Iron Accumulation Type 1 (NBIA1), Neurofibroma of the Acoustic Nerve, Neurogenic Arthrogryposis Multiplex Congenita, Neuromyelitis Optica, Neuromyotonia, Focal, Neuromyotonia, Generalized, Familial, Neuromyotonia, Generalized, Sporadic, Neuronal Axonal Dystrophy Schindler Type, Neuronal Ceroid Lipofuscinosis Adult Type, Neuronal Ceroid Lipofuscinosis Juvenile Type, Neuronal Ceroid Lipofuscinosis Type 1, Neuronopathic Acute Gaucher Disease, Neuropathic Amyloidosis, Neuropathic Beriberi, Neuropathy Ataxia and Retinitis Pigmentosa, Neuropathy of Brachialpexus Syndrome, Neuropathy Hereditary Sensory Type I, Neuropathy Hereditary Sensory Type II, Neutral Lipid Storage Disease, Nevii, Nevus Depigmentosus, Nevus Sebaceous of Jadassohn, Nezelof’s Syndrome, Nezelof’s Thymic Aplasia, Nezelof Type Severe Combined Immunodeficiency, NF, NF1, NF2, NF-1, NF-2, NHS, Niemann Pick Disease, Nieman Pick Disease Type A (acute neuronopathic form), Nieman Pick disease Type B, Nieman Pick Disease Type C (chronic neuronopathic form), Nieman Pick Disease Type D (Nova Scotia variant), Nieman Pick Disease Type E, Nieman Pick Disease Type F (sea-blue histiocyte disease), Night Blindness, Nigrospinodentatal Degeneration, Niikawakuroki Syndrome, NLS, NM, Noack Syndrome Type I, Nocturnal Myoclonus Hereditary Essential Myoclonus, Nodular Cornea Degeneration, Non-Bullous CIE, Non-Bullous Congenital Ichthyosiform Erythroderma, Non-Communicating Hydrocephalus, Non-Deletion Type α-Thalassemia / Mental Retardation syndrome, Non-Ketonic Hyperglycinemia Type I (NKHI), Non-Ketotic Hyperglycinemia, Non-Lipid Reticuloendotheliosis, Non-Neuronopathic Chronic Adult Gaucher Disease, Non-Scarring Epidermolysis Bullosa, Non-arteriosclerotic Cerebral Calcifications, Non-articular Rheumatism, Non-cerebral, Juvenile Gaucher Disease, Non-diabetic Glycosuria, Non-ischemic Cardiomyopathy, Non-ketotic Hypoglycemia and Carnitine Deficiency due to MCAD Deficiency, Non-ketotic Hypoglycemia Caused by Deficiency of Acyl-CoA Dehydrogenase, Non-ketotic Glycinemia, Nonne’s Syndrome, Nonne-Milroy-Meige
Component Deficiency, Plasma Transglutaminase Deficiency, Plastic Induration Corpora Cavernosa, Plastic Induration of the Penis, PLD, Plicated Tongue, PLS, PMD, Pneumorenal Syndrome, PNH, PNM, PNP Deficiency, POD, POH, Poikiloderma Atrophicans and Cataract, Poikiloderma Congenitale, Poland Anomaly, Poland Sequence, Poland Syndactyly, Poland Syndrome, Poliodystrophia Cerebri Progressiva, Polyarthritis Enterica, Polyarteritis Nodosa, Polyarticular-Onset Juvenile Arthritis Type I, Polyarticular-Onset Juvenile Arthritis Type II, Polychondritis, Polycystic Kidney Disease, Polycystic Kidney Disease Medullary Type, Polycystic Liver Disease, Polycystic Ovary Disease, Polycystic Renal Diseases, Polydactyly-Joubert Syndrome, Polydysplastic Epidermolysis Bullosa, Polydystrophia Oligophrenia, Polydystrophic Dwarfism, Polyglandular Autoimmune Syndrome Type III, Polyglandular Autoimmune Syndrome Type II, Polyglandular Autoimmune Syndrome Type I, Polyglandular Autoimmune Syndrome Type II, Polyglandular Syndromes, Polymorphic Macula Lutea Degeneration, Polymorphic Macular Degeneration, Polymorphism of Platelet Glycoprotein Ib, Polymorphous Corneal Dystrophy Hereditary, Polymyalgia Rheumatica, Polymyositis and Dermatomyositis, Primary A γ-globulinemia, Polyneuritis Peripheral, Polyneuropathy-Deafness-Optic Atrophy, Polyneuropathy Peripheral, Polyneuropathy and Polyradiculoneuropathy, Polystotic Fibrous Dysplasia, Polystotic Sclerosing Histiocytosis, Polyposis Familial, Polyposis Gardner Type, Polyposis Hamartomatous Intestinal, Polyposis-Osteomatos- Epidermoid Cyst Syndrome, Polyposis Skin Pigmentation Alopecia and Fingernail Changes, Polyps and Spots Syndrome, Polyserositis Recurrent, Polysomy Y, Polysyndactyly with Peculiar Skull Shape, Polysyndactyly-Dysmorphic Craniofacies Greig Type, Pompe Disease, Pompe Disease, Popliteal Pterygium Syndrome, Porcupine Man, Porencephaly, Porencephaly, Porphobilinogen deaminase (PBG-D), Porphyria, Porphyria Acute Intermittent, Porphyria ALA-D, Porphyria Cutanea Tarda, Porphyria Cutanea Tarda Hereditaria, Porphyria Cutanea Tarda Symptomatica, Porphyria Hepatica Variegate, Porphyria Swedish Type, Porphyria Variegate, Porphyriam Acute Intermittent, Porphyris, Porrigo Decalvans, Port Wine Stains, Portuguese Type Amyloidosis, Post-Infective Polyneuritis, Postanoxic Intention Myoclonus, Postaxial Acrofacial Dysostosis, Postaxial Polydactyly, Postencephalitic Intention Myoclonus, Posterior Corneal Dystrophy Hereditary, Posterior Thalamic Syndrome, Post-myelographic Arachnoiditis, Post-natal
Cerebral Palsy, Post-operative Cholestasis, Postpartum Galactorrhea-Amenorrhea Syndrome, Postpartum Hypopituitarism, Postpartum Panhypopituitary Syndrome, Postpartum Panhypopituitarism, Postpartum Pituitary Necrosis, Postural Hypotension, Potassium-Losing Nephritis, Potassium Loss Syndrome, Potter Type I Infantile Polycystic Kidney Diseases, Potter Type III Polycystic Kidney Disease, PPH, PPS, Prader-Willi Syndrome, Prader-Labhart-Willi Fancone Syndrome, Prealbumin Tyr-77 Amyloidosis, Pre-excitation Syndrome, Pregnenolone Deficiency, Premature Atrial Contractions, Premature Senility Syndrome, Premature Supraventricular Contractions, Premature Ventricular Complexes, Pre-natal or Con-natal Neuroaxonal Dystrophy, Pre-senile Dementia, Pre-senile Macula Lutea Retinae Degeneration, Primary Adrenal Insufficiency, Primary A γ-globulinemias, Primary Aldosteronism, Primary Alveolar Hypoventilation, Primary Amyloidosis, Primary Anemia, Primary Beriberi, Primary Biliary, Primary Biliary Cirrhosis, Primary Brown Syndrome, Primary Carnitine Deficiency, Primary Central Hypoventilation Syndrome, Primary Ciliary Dyskinesia Kartagener Type, Primary Cutaneous Amyloidosis, Primary Dystonia, Primary Failure Adrenocortical Insufficiency, Primary Familial Hypoplasia of the Maxilla, Primary Hemochromatosis, Primary Hyperhidrosis, Primary Hyperoxaluria [Type I], Primary Hyperoxaluria Type I (PH1), Primary Hyperoxaluria Type II, Primary Hyperoxaluria Type III, Primary Hypogonadism, Primary Intestinal Lymphangiectasia, Primary Lateral Sclerosis, Primary Non-hereditary Amyloidosis, Primary Obliterative Pulmonary Vascular Disease, Primary Progressive Multiple Sclerosis, Primary Pulmonary Hypertension, Primary Reading Disability, Primary Renal Glycosuria, Primary Sclerosing Cholangitis, Primary Thrombocythemia, Primary Tumors of Central Nervous System, Primary Visual Agnosia, Proctocolitis Idiopathic, Proctocolitis Idiopathic, Progeria of Adulthood, Progeria of Childhood, Progeroid Nanism, Progeriod Short Stature with Pigmented Nevi, Progeroid Syndrome of De Barsy, Progressive Autonomic Failure with Multiple System Atrophy, Progressive Bulbar Palsy, Progressive Bulbar Palsy Included, Progressive Cardiomyopathic Lentiginosis, Progressive Cerebellar Ataxia Familial, Progressive Cerebral Poliodystrophy, Progressive Choroidal Atrophy, Progressive Diaphyseal Dysplasia, Progressive Facial Hemiatrophy, Progressive Familial Myoclonic Epilepsy, Progressive Hemifacial Atrophy, Progressive Hypoerythemia, Progressive Infantile
Sensory, Radicular Neuropathy Sensory Recessive, Radicular Dentin Dysplasia, Rapid-Onset Dystonia-Parkinsonism, Rapp-Hodgkin Syndrome, Rapp-Hodgkin (hypohidrotic) Ectodermal Dysplasia syndrome, Rapp-Hodgkin Hypohidrotic Ectodermal Dysplasias, Rare Hereditary Ataxia With Polyneuritic Changes and Deafness Caused by a Defect in the Enzyme Phytanic Acid Hydroxylase, Rautenstrauch-Wiedemann Syndrome, Rautenstrauch-Wiedemann Type Neonatal Progeria, Raynaud’s Phenomenon, RDP, Reactive Functional Hypoglycemia, Reactive Hypoglycemia Secondary to Mild Diabetes, Recessive Type Kenny-Caffè Syndrome, Recklin Recessive Type Myotonia Congenita, Recklinghausen Disease, Rectoperineal Fistula, Recurrent Vomiting, Reflex Neurovascular Dystrophy, Reflex Sympathetic Dystrophy Syndrome, Refractive Errors, Refractory Anemia, Refrigeration Palsy, Refsum Disease, Refsum’s Disease, Regional Enteritis, Reid-Barlow’s syndrome, Reifenstein Syndrome, Reiger Anomaly-Growth Retardation, Reiger Syndrome, Reimann Periodic Disease, Reimann’s Syndrome, Reis-Bucklers Corneal Dystrophy, Reiter’s Syndrome, Relapsing Guillon-Barre Syndrome, Relapsing-Remitting Multiple Sclerosis, Renal Agenesis, Renal Dysplasia-Blindness Hereditary, Renal Dysplasia-Retinal Aplasia Loken-Senior Type, Renal Glycosuria, Renal Glycosuria Type A, Renal Glycosuria Type B, Renal Glycosuria Type O, Renal-Oculocerebrodystrophy, Renal-Retinal Dysplasia with Medullary Cystic Disease, Renal-Retinal Dystrophy Familial, Renal-Retinal Syndrome, Rendu-Osler-Weber Syndrome, Respiratory Acidosis, Respiratory Chain Disorders, Respiratory Myoclonus, Restless Legs Syndrome, Restrictive Cardiomyopathy, Retention Hyperlipemia, Rethore Syndrome (obsolete), Reticular Dysgenesis, Retinal Aplastic-Cystic Kidneys-Joubert Syndrome, Retinal Cone Degeneration, Retinal Cone Dystrophy, Retinal Cone-Rod Dystrophy, Retinitis Pigmentosa, Retinitis Pigmentosa and Congenital Deafness, Retinoblastoma, Retinol Deficiency, Retinoschisis, Retinoschisis Juvenile, Retraction Syndrome, Rctrobulbar Neuropathy, Retrolenticular Syndrome, Rett Syndrome, Reverse Coarction, Reye’s Syndrome, RGS, Rh Blood Factors, Rh Disease, Rh Factor Incompatibility, Rh Incompatibility, Rhesus Incompatibility, Rheumatic Fever, Rheumatoid Arthritis, Rheumatoid Myositis, Rhinosinusogenic Cerebral Arachnoiditis, Rhizomelic Chondrodysplasia Punctata (RCDP), Acatalasemia, Classical Refsum Disease, RHS, Rhythmic Myoclonus, Rib Gap Defects with Micrognathia, Ribbing Disease (obsolete),
Ribbing Disease, Richner-Hanhart Syndrome, Rieger Syndrome, Rieter's Syndrome, Right Ventricular Fibrosis, Riley-Day Syndrome, Riley-Smith Syndrome, Ring Chromosome 14, Ring Chromosome 18, Ring 4, Ring 4 Chromosome, Ring 6, Ring 6 Chromosome, Ring 9, Ring 9 Chromosome R9, Ring 14, Ring 15, Ring 15 Chromosome (mosaic pattern), Ring 18, Ring Chromosome 18, Ring 21, Ring 21 Chromosome, Ring 22, Ring 22 Chromosome, Ritter Disease, Ritter-Lyell Syndrome, RLS, RMSS, Roberts SC-Phocomelia Syndrome, Roberts Syndrome, Roberts Tetraphocomelia Syndrome, Robertson's Ectodermal Dysplasias, Robin Anomalad, Robin Sequence, Robin Syndrome, Robinow Dwarfism, Robinow Syndrome, Robinow Syndrome Dominant Form, Robinow Syndrome Recessive Form, Rod Myopathy, Roger Disease, Rokitansky's Disease, Romano-Ward Syndrome, Romberg Syndrome, Rootless Teeth, Rosenberg-Chutorian Syndrome, Rosewater Syndrome, Rosselli-Guilenatti Syndrome, Rothmund-Thomson Syndrome, Roussy-Levy Syndrome, RP, RS X-Linked, RS, RSDS, RSH Syndrome, RSS, RSTS, RTS, Rubella Congenital, Rubinstein Syndrome, Rubinstein-Taybi Syndrome, Rubinstein Taybi Broad Thumb-Hallux Syndrome, Rufous Albinism, Ruhr's Syndrome, Russell's Diencephalic Cachexia, Russell's Syndrome, Russell-Silver Dwarfism, Russell-Silver Syndrome, Russell-Silver Syndrome X-linked, Ruvalcaba-Myhre-Smith syndrome (RMSS), Ruvalcaba Syndrome, Ruvalcaba Type Osseous Dysplasia with Mental Retardation, Sacral Regression, Sacral Agenesis Congenital, SAE, Saethre-Chotzen Syndrome, Sakati, Sakati Syndrome, Sakati-Nyhan Syndrome, Salaam Spasms, Salivosudoriparous Syndrome, Salzman Nodular Corneal Dystrophy, Sandhoff Disease, Sanfilippo Syndrome, Sanfilippo Type A, Sanfilippo Type B, Santavuori Disease, Santavuori-Haltia Disease, Sarcoïd of Boeck, Sarcoïdosis, Sathre-chotzen, Saturday Night Palsy, SBMA, SC Phocomelia Syndrome, SC Syndrome, SCA 3, SCAD Deficiency, SCAD Deficiency Adult-Onset Localized, SCAD Deficiency Congenital Generalized, SCAD, SCADH Deficiency, Scalded Skin Syndrome, Scalp Defect Congenital, Scaphocephaly, Scapula Elevata, Scapuloperoneal Myopathy, Scapuloperoneal Muscular Dystrophy, Scapuloperoneal Syndrome Myopathic Type, Scarring Bullosa, SCHAD, Schaumann's Disease, Schei Syndrome, Schereshevki-Turner Syndrome, Schilder Disease, Schilder Encephalitis, Schilder's Disease, Schindler Disease Type I (Infantile Onset), Schindler Disease Infantile Onset, Schindler Disease, Schindler Disease Type II
Minor, Thalassemia Major, Thiamine Deficiency, Thiamine-Responsive Maple Syrup Urine Disease, Thin-Basement-Membrane Nephropathy, Thiolase Deficiency, RCDP, Acyl-CoA Dihydroxyacetonephosphate Acyltransferase, Third and Fourth Pharyngeal Pouch Syndrome, Third Degree Congenital (Complete) Heart Block, Thomsen Disease, Thoracic-Pelvic-Phalangeal Dystrophy, Thoracic Spinal Canal, Thoracoabdominal Syndrome, Thoracoabdominal Ectopia Cordis Syndrome, Three M Syndrome, Three-M Slender-Boned Nanism, Thrombasthenia of Glanzmann and Naegeli, Thrombocytopenia-Absent Radius Syndrome, Thrombocytopenia-Hemangioma Syndrome, Thrombocytopenia-Absent Radii Syndrome, Thrombophilia Hereditary Due to AT III, Thrombotic Thrombocytopenic Purpura, Thromboulcerative Colitis, Thymic Dysplasia with Normal Immunoglobulins, Thymic Agenesis, Thymic Aplasia DiGeorge Type, Thymic Hypoplasia A γ-globulinemias Primary Included, Thymic Hypoplasia DiGeorge Type, Thymus Congenital Aplasia, Tic Douloureux, Tics, Tinel’s Syndrome, Tolosa Hunt Syndrome, Tonic Spasmodic Torticollis, Tonic Pupil Syndrome, Tooth and Nail Syndrome, Torch Infection, TORCH Syndrome, Torsion Dystonia, Torticollis, Total Lipodystrophy, Total Anomalous Pulmonary Venous Connection, Touraine’s Aphthosis, Tourette Syndrome, Tourette’s Disorder, Townes-Brocks Syndrome, Townes Syndrome, Toxic Paralytic Anemia, Toxic Epidermal Necrolysis, Toxopachyosteose Diaphysaire Tibio-Peroniere, Toxopachyosteose, Toxoplasmosis Other Agents Rubella Cytomegalovirus Herpes Simplex, Tracheoesophageal Fistula with or without Esophageal Atresia, Tracheoesophageal Fistula, Transient Neonatal Myasthenia Gravis, Transitional Atrioventricular Septal Defect, Transposition of the Great Arteries, Transtelephonic Monitoring, Transthyretin Methionine-30 Amyloidosis (Type I), Trapeziocephaly-Multiple Synostosis Syndrome, Treacher Collins Syndrome, Treacher Collins-Franceschetti Syndrome 1, Trevor Disease, Triatrial Heart, Tricho-Dento-Osseous Syndrome, Trichopoliodystrophy, Trichorhinophalangeal Syndrome, Tricuspid atresia, Trifunctional Protein Deficiency, Trigeminal Neuralgia, Triglyceride Storage Disease Impaired Long-Chain Fatty Acid Oxidation, Trigonitis, Trigonocephaly, Trigonocephaly Syndrome, Trigonocephaly “C” Syndrome, Trimethylaminuria, Triphalangeal Thumbs- Hypoplastic Distal Phalanges-Onychodystrophy, Triphalangeal Thumb Syndrome, Triple Symptom Complex of Behcet, Triple X Syndrome, Triplo X Syndrome, Triploid
Syndrome, Triploidy, Triploidy Syndrome, Trismus-Pseudocamptodactyly Syndrome, Trisomy, Trisomy G Syndrome, Trisomy X, Trisomy 6q Partial, Trisomy 6q Syndrome Partial, Trisomy 9 Mosaic, Trisomy 9P Syndrome (Partial) Included, Trisomy 11q Partial, Trisomy 14 Mosaic, Trisomy 14 Mosaicism Syndrome, Trisomy 21 Syndrome, Trisomy 22 Mosaic, Trisomy 22 Mosaicism Syndrome, TRPS, TRPS1, TRPS2, TRPS3, True Hermaphroditism, Truncus arteriosus, Tryptophan Malabsorption, Tryptophan Pyrrolase Deficiency, TS, TTP, TTTS, Tuberous Sclerosis, Tubular Ectasia, Turcot Syndrome, Turner Syndrome, Turner-Kieser Syndrome, Turner Phenotype with Normal Chromosomes (Karyotype), Turner-Varny Syndrome, Turricephaly, Twin-Twin Transfusion Syndrome, Twin-to-Twin Transfusion Syndrome, Type A, Type B, Type AB, Type O, Type I Diabetes, Type I Familial Incomplete Male, Type I Familial Incomplete Male Pseudohermaphroditism, Type I Gaucher Disease, Type I (PCCA Deficiency), Type I Tyrosinemia, Type II Gaucher Disease, Type II Histiocytosis, Type II (PCCB Deficiency), Type II Tyrosinnemia, Type IIA Distal Arthrogryposis Multiplex Congenita, Type III Gaucher Disease, Type III Tyrosinemia, Type III Dentinogenesis Imperfecta, Typical Retinoschisis, Tyrosinase Negative Albinism (Type I), Tyrosinase Positive Albinism (Type II), Tyrosinemia Type I Acute Form, Tyrosinemia Type I Chronic Form, Tyrosinosis, UCE, Ulcerative Colitis, Ulcerative Colitis Chronic Non-Specific, Ulnar-Mammary Syndrome, Ulnar-Mammary Syndrome of Pallister, Ulnar Nerve Palsy, UMS, Unclassified FODs, Unconjugated Benign Bilirubinemiav, Underactivity of Parathyroid, Unilateral Ichthyosiform Erythroderma with Ipsilateral Malformations Limb, Unilateral Chondromatosis, Unilateral Defect of Pectoralis Muscle and Syndactyly of the Hand, Unilateral Hemidisplasia Type, Unilateral Megalencephaly, Unilateral Partial Lipodystrophy, Unilateral Renal Agenesis, Unstable Colon, Unverricht Disease, Unverricht-Lundborg Disease, Unverricht-Lundborg-Laf Disease, Unverricht Syndrome, Upper Limb - Cardiovascular Syndrome (Holt-Oram), Upper Motor Neuron Disease, Upper Airway Apnea, Urea Cycle Defects or Disorders, Urea Cycle Disorder Arginase Type, Urea Cycle Disorder Arginino Succinase Type, Urea Cycle Disorders Carbamyl Phosphate Synthetase Type, Urea Cycle Disorder Citrullinemia Type, Urea Cycle Disorders N-Acetyl Glutamate Synthetase Typ, Urea Cycle Disorder OTC Type, Urethral Syndrome, Urethro-Oculo-Articular Syndrome, Uridine Diphosphate
It is to be understood that unless otherwise indicated, the subject invention is not limited to specific formulations of components, manufacturing methods, dosage regimens or the like, as such may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting.

The singular forms “a”, “an” and “the” include plural aspects unless the context clearly dictates otherwise. Thus, for example, reference to a PUFA includes reference to a single PUFA as well as two or more PUFAs or families of PUFAs, an agent includes a single agent, as well as two or more agents.

In describing and claiming the present invention, the following terminology is used in accordance with the definitions set forth below.

The terms “compound”, “active agent”, “chemical agent”, “pharmacologically active agent”, “medicament”, “active” and “drug” are used interchangeably herein to refer to a chemical compound that induces a desired pharmacological and/or physiological effect. All such terms also cover naturally occurring PUFAs and derivatives or modified forms thereof. The terms also encompass pharmaceutically acceptable and pharmacologically active ingredients of those active agents specifically mentioned herein including but not limited to salts, esters, amides, prodrugs, active metabolites, analogs and the like. When the terms “compound”, “active agent”, “chemical agent” “pharmacologically active agent”, “medicament”, “active” and “drug” are used, then it is to be understood that this includes the active agent per se as well as pharmaceutically acceptable, pharmacologically active salts, esters, amides, prodrugs, metabolites, analogs, etc.

Reference to a “compound”, “active agent”, “chemical agent” “pharmacologically active agent”, “medicament”, “active” or “drug” includes combinations of two or more actives such as two or more PUFAs or families of PUFAs. A “combination” also includes multi-part such as a two-part composition where the agents are provided separately and given or dispensed separately or admixed together prior to dispensation. For example, a multi-part pharmaceutical pack may have two or more agents separately maintained.
The term "combination" in addition, encompasses multivalent PUFAs such as two or more PUFAs linked via chemical bond formation.

In addition, the PUFAs may be co-administered with a range of other therapeutic agents including pain relievers such as opiates, preferably morphine, buprenorphine, levomethadone, codeine, tramadol or tilidine, non-steroidal analgesics, for example, acetylsalicylic acid, paracetamol, diclofenac, meloxicam, ibuprofen, ibuprofen lysinate, ibuprofen in extruded form (as described in WO 99/06038), gabapentine or anti-depressants, preferably imipramine, maprotiline, mianserin, fluoxetine, viloxazine, tranylcypromine and/or moclobemide.

The terms “effective amount” and “therapeutically effective amount” of an agent as used herein mean a sufficient amount of the agent (e.g. an agent such as a PUFA or a derivative thereof) to provide the desired therapeutic or physiological effect or outcome. Undesirable effects, e.g. side effects, are sometimes manifested along with the desired therapeutic effect; hence, a practitioner balances the potential benefits against the potential risks in determining what is an appropriate “effective amount”. The exact amount required will vary from subject to subject, depending on the species, age and general condition of the subject, mode of administration and the like. Thus, it may not be possible to specify an exact “effective amount”. However, an appropriate “effective amount” in any individual case may be determined by one of ordinary skill in the art using only routine experimentation.

By “pharmaceutically acceptable” carrier, excipient or diluent is meant a pharmaceutical vehicle comprised of a material that is not biologically or otherwise undesirable, i.e. the material may be administered to a subject along with the selected active agent without causing any or a substantial adverse reaction. Carriers may include excipients and other additives such as diluents, detergents, coloring agents, wetting or emulsifying agents, pH buffering agents, preservatives, and the like.
Similarly, a “pharmacologically acceptable” salt, ester, amide, prodrug or derivative of a compound as provided herein is a salt, ester, amide, prodrug or derivative that is not biologically or otherwise undesirable.

“Treating” a subject may involve prevention of a condition or other adverse physiological event in a susceptible individual as well as treatment of a clinically symptomatic individual by ameliorating the symptoms of the condition.

A “subject” as used herein refers to an animal, preferably a mammal and more preferably a human who can benefit from the pharmaceutical formulations and methods of the present invention. There is no limitation on the type of animal that could benefit from the presently described pharmaceutical formulations and methods. A subject regardless of whether a human or non-human animal may be referred to as an individual, patient, animal, host or recipient. The compounds and methods of the present invention have applications in human medicine, veterinary medicine as well as in general, domestic or wild animal husbandry. Non-human animals contemplated herein include livestock animals (e.g. sheep, pigs, cows, horses, donkeys), laboratory test animals (e.g. mice, rabbits, rats, guinea pigs), companion animals (e.g. dogs, cats) and captive wild animals.

The term “animals” include avian species such as poultry birds (e.g. chickens, ducks, turkeys, geese) and wild and game birds (e.g. wild ducks, pheasants, emus) and aviary birds.

The present invention is further described by the following non-limiting Examples.
EXAMPLE 1

Chemical Engineering of Fats

Compounds were generated by the method described in WO 96/11908, WO 96/13507, WO 97/38688, WO 01/21172 and WO 01/21575 and are designated MP series, PT series and MP-PT hybrids. Molecules of the MP series possess the property of increased stability to oxidative breakdown. This reduced susceptibility to breakdown means that they are far less likely to cause the production of oxygen radicals which is the consequence of the metabolism of the natural omega-3 fatty acids. Molecules of the PT series also have this property but in addition are more soluble. The hybrid MP-PT series possess the above properties and demonstrate an expected outcome of higher antiinflammatory activity.

The structure of a natural fish oil fatty acid, ecosapentaenoic acid, is shown in structure (a). The features of these types of fatty acids is a long carbon chain, unsaturation (double bonds) and a carboxyl group (acid group) at one end of the chain.

![Fish oil fatty acid](a)

The chemical engineering takes the form of *inter alia* substituting an oxygen atom (or sulphur) for the carbon, second from the carboxyl group end (b). This is called the β-position. It is this area on the molecule to which the enzyme involved in the metabolism of the fats binds. Due to this change, the enzyme cannot act on this group as efficiently as in the unsubstituted molecule. Thus, the fat is handled differently by body tissues.

![β-oxa-21:3n-3](b)
EXAMPLE 2

Treating Inflammatory Disease

The naturally occurring ω-3 polyunsaturates (such as fish oil) have found use in the treatment of inflammatory diseases. These include the highly debilitating chronic forms such as rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease and systemic lupus erythrocytosis. These are life-long diseases which are managed but cannot be cured. The principle mechanisms involve the T-lymphocyte and macrophage and other white blood cells of the immune system (see Figure 1). These inappropriately attach to either joint tissue (in arthritis), blood vessel (in lupus), brain (multiple sclerosis) and gut tissue (inflammatory bowel disease) and then damage the tissue.

The PUFAs of the present invention target T-lymphocytes. When T-lymphocytes are exposed to MP5, for example, the cell takes up the fat as a nutritional requirement like any other fat but in this case the MP5 has a slight but vital change in its structure. MP5 stops the flow of a signal inside this cell preventing T-lymphocyte activation.

EXAMPLE 3

Transplantation

Management of patients with transplants involves the use of immunosuppressive medications, e.g. cyclosporin which stops T-lymphocyte activation. Rejection of transplanted tissues involves T-lymphocytes and macrophages in a similar manner to the delayed-type hypersensitivity (DTH) reaction. Thus, MP5 has the potential to be used as a suitable immunosuppressive agent in transplantation especially because of the advantages it confers regarding safety compared to presently used immunosuppressants.
EXAMPLE 4

Treating Asthma and Allergy

Tissues can be stimulated to produce fatty acid derived hormone like molecules called “eicosanoids” such as the leukotrienes. Production of these in an uncontrolled manner is known to lead to the appearance of serious diseases. These include asthma and allergic conditions. For example, some leukotrienes act on the smooth muscle of the broncus of the airway preventing its relaxation leading to breathing difficulties as in asthma. In accordance with the present invention, a new form of polyunsaturates is provided as inhibitors of eicosanoid production and hence as potential medication to treat asthma and allergic conditions.

EXAMPLE 5

Treating Pain

Some evidence has suggested that the novel fats may act on pathways involved in generating pain. As a consequence, some have been screened in two animal models of pain. The engineered polyunsaturates of the present invention were found to act in a similar manner to aspirin but by a different pathway, providing major advantages over toxicity problems associated with long term use of aspirin. One particular useful compound is PT2 (c). This is a polyunsaturated fatty acid which contains an amino acid covalently bound to its carboxyl group:

\[
\text{20:4n-6 Asp (PT2)}
\]
The chemical nature of these novel molecules suggests that they are easily delivered by skin application or oral administration. Investigations have demonstrated that after ingestion, they soon appear in target organs (brain, kidney, lungs or skin). In preliminary studies in rats, active anti-inflammatory levels of these molecules do not display any toxic side effects. The significant anti-inflammatory property as well as the analgesic value of these molecules and their benign non-toxic nature makes the compounds ideal pharmaceuticals.

EXAMPLE 6

Analgesic Properties of PT2

Screening of PT2 on neutrophil activation in vitro

The structure of PT2 is shown in (c) above. In this screening assay, neutrophils were prepared from the blood of healthy volunteers. Freshly collected blood was layered onto a Hypaque-Ficoll medium of density 1.114 and centrifuged at 400 g for 30 mins at room temperature. After centrifugation, the leukocytes resolved into two distinct bands, with neutrophils being present in the second band (Ferrante and Thong, J. Immun. Methods 48:81-85, 1982).

Activation of the neutrophil NADPH oxidase was measured by lucigenin-dependent chemiluminescence following a 10 min incubation of PT2 (20 μM, final concentration) with 1 x 10^6 neutrophils from different donors (Power et al, J. Immunol. 159:2952-2959, 1997). Arachidonic acid (20:4,n-6) was used as a positive stimulator of the oxidase.

It can be seen that PT2 lacks the ability to stimulate the neutrophil respiratory burst. In contrast, arachidonic acid (and other natural PUFAs) are able to elicit a strong respiratory burst (Figure 2).
Analgesic properties of PT2

Investigations of the effects of PT2 on pain induced by phenylquinolic acid (PQ writhing) and formalin have been made. In both the PQ writhing test (Figure 3) and the formalin algesia test (Figure 4), PT2 administered by intraperitoneal inoculation reduced pain and compared favourably with pain reduction by aspirin (oral, 100 mg/kg). In these tests, the EPUFA was administered 30 min before the pain stimulus and effects recorded over the following 20 min.

Investigations of PT2 in the formalin-induced analgesia model looking specifically at the biphasic response have also been undertaken and are shown in Table 1. It is well documented that in this model, aspirin suppresses only pain related to the inflammatory process (15-20 mins post-administration of formalin), while morphine suppresses pain in both phases of the response (0-5 min and 15-20 min). From Table 1, it can be seen that PT2 acts similarly to aspirin in having its major effect on the later phase of the pain response. MP5 was much less effective in inhibiting pain in this model.

Table 1

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Phase I (0-5 mins)</th>
<th>Phase II (15-20 mins)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBS</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PT2 (30 mg/kg)</td>
<td>0</td>
<td>41</td>
</tr>
<tr>
<td>PT2 (100 mg/kg)</td>
<td>30</td>
<td>97</td>
</tr>
<tr>
<td>MP5 (100 mg/kg)</td>
<td>34</td>
<td>37</td>
</tr>
<tr>
<td>Aspirin (300 mg/kg)</td>
<td>30</td>
<td>91</td>
</tr>
<tr>
<td>Morphine (10 mg/kg)</td>
<td>85</td>
<td>100</td>
</tr>
</tbody>
</table>
Compounds were administered intraperationedly (ip) 30 min prior to the administration of formalin (0.02 ml, 1% solution) via subplantar injection into the right hind paw. Reduction of the induced hind paw licking time recorded during the following 0-5 min period (Phase I response) or 15-20 min period (Phase II response) was determined. The data in Table 1 are the mean responses of 5 animals in each group.

EXAMPLE 7

*Effects of Nitroanalog (Lx) of PUFA on PKC Activation*

The effects of nitroanalogs of PUFAs on PKC activation were determined. Lx compounds at a concentration of 20 µM were incubated with the HL-60 cell line (final condition 10⁶ cells/ml) for 60 min. PKC activation was then attempted to be induced by PMA. PKC enzyme translocation was quantitated by Western blot. The results are shown in Table 2.

<table>
<thead>
<tr>
<th>PKC isozyme</th>
<th>Lx1</th>
<th>Lx2</th>
<th>Lx3</th>
<th>Lx4</th>
<th>Lx5</th>
<th>Lx6</th>
<th>Lx7</th>
<th>Lx8</th>
<th>Lx9</th>
</tr>
</thead>
<tbody>
<tr>
<td>α</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>++</td>
<td>-</td>
<td>ND</td>
<td>+++</td>
<td>+++</td>
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</tr>
<tr>
<td>β1</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+++</td>
<td>+</td>
<td>ND</td>
<td>+++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>β2</td>
<td>-</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>-</td>
<td>ND</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>δ</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+++</td>
<td>-</td>
<td>ND</td>
<td>+</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>ε</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>ND</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
</tr>
</tbody>
</table>

+++ = strong inhibition of PKC activation, - = no inhibition of PKC activation, ND = not determined

It is evident that there are substantial differences in ability to inhibit the spectrum of five PKC isozymes by the different Lx compounds. For anti-cancer effect, δ and ε are of interest. These have been clearly associated with cell survival (ε) and cell death (δ). In the examples of Lx7 and Lx8, Lx7 kills cancer cells very effectively, yet Lx8 kills cells very poorly. The data in Table 2 show that the activation of apoptopic protective isozyme ε is markedly inhibited by Lx7 without much inhibition of the activation of δ which promotes apoptosis. Therefore, the cell dies. In contrast with Lx8 both isozymes are inhibited. The net effect is survival.
With Lx9, the compound is also strong in killing cancer cells and there is balanced (+) inhibition of both δ and ε.

EXAMPLE 8

Treatment of Systemic Vasculature

The aim of the experiment was to establish conditions for optimal activity of β-oxa 23:4n-6 (MP3) in relation to inhibition of up-regulation of adhesion molecular expression on the endothelium in vivo and to determine whether or not MP3 possesses anti-atherosclerotic properties in experimental models.

It is proposed that β-oxa 23:4n-6 (MP3), through its ability to selectively inhibit the IκB kinase - NFκB signalling pathway, inhibits the expression cell adhesion molecules on and the adherence of monocytes to the aortic endothelium, thus preventing the development of atherosclerosis in vivo.

Atherosclerosis is a chronic inflammatory vascular disease which is characterized by a thickening of the vascular wall (atheroma) due to lipid accumulation and infiltration of circulating monocytes and T-lymphocytes. The recruitment of monocytes into the intima in lesion prone-sites is a key event in early atherogenesis. For this to occur, monocytes must first adhere to the endothelium at sites of endothelial injury or dysfunction caused by factors such as oxidized LDL, chylomicron remnants and/or advanced glycation end products (AGE) (Koya et al, Diabetes 47:859-866, 1998). Leukocyte adhesion to the endothelium and the subsequent emigration into the intima is mediated by leukocyte-endothelial cell adhesion molecules (CAMs). These CAMs include the leukocyte L-selectin and the endothelial E-selectin, P-selectin, intercellular adhesion molecule (ICAM)-1 which binds neutrophils and vascular cell adhesion molecule (VCAM)-1 which binds monocytes and T cells. The process begins by E-, L-, and P-selectin-mediated rolling of the leukocytes along the endothelial surface. This is followed by firm adhesion involving the β1 and β2 integrins and immunoglobulin adhesion superfamily members such as
ICAM-1 and VCAM-1. The leukocytes then migrate into the intima in response to hypercholesterolemia-induced production of chemokines (Koya et al., 1998 supra) and other activating molecules produced by the underlying vascular smooth muscle cells (Chou et al., Curr Biol. 8:1069-77, 1998). The monocytes differentiate into macrophages and ingest modified forms of LDL to become foam cells which give rise to fatty streaks. Activated macrophages release inflammatory cytokines and growth factors that may recruit additional blood monocytes into the developing lesion and stimulate smooth muscle cell migration and proliferation. These processes set the scene for the development of more advanced lesions which include a fibrofatty matrix of connective tissue, smooth muscle and foam cells, followed by the formation of dense fibrous plaques (Koya et al., 1998 supra).

There is overwhelming evidence that CAMs play key roles in atherogenesis. Many atherogenic factors, e.g. hypercholesterolemia, lysophosphatidylcholine and AGE have been reported to increase ICAM-1 and VCAM-1 expression on endothelial cells (Jaken et al., Bioessays 22:245-254, 2000). While oxidized LDL enhances VCAM-1 expression, it only does so in endothelial cells stimulated with cytokines such as tumour necrosis factor α (TNF) and interleukin 1β (Jaken et al., 2000 supra), which are produced at sites of inflammation. In vivo, increases in CAM expression is localized to human arteries with atherosclerotic lesions and in lesion-prone sites on the aorta of mice and rabbits (Koya et al., 1998 supra; Xia et al., J. Clin. Invest. 98:2018-2026, 1996). Studies in animal models have also demonstrated that preventing the expression of CAMs through inactivating mutations caused by homologous recombination (Jaken et al., 2000 supra; Koya et al., J. Clin. Invest. 100:115-126, 1997; Scivittaro et al, Am. J. Physiol. 278:F676-F683, 2000; Way et al, Diabetic Medicine 18:945-959, 2001), and antibody neutralization of CAMs reduce the recruitment of monocytes to atherosclerotic plaques and reduce lesion size (Jaken et al., 2000 supra; Ferrante et al, J. Clin. Invest. 99:1445-1452, 1997). Consequently, strategies to reduce CAM expression are attractive approaches to reduce or impede the development of atherosclerosis and this forms the focus of this application.
One of the essential factors that is required for the up-regulation of CAM expression on the endothelium is the transcription factor, NFκB. The activity of NFκB is tightly regulated by cytokines and other stimuli. In the resting cells, NFκB dimers are sequestered in the cytoplasm by IκB proteins. Upon activation, IκB is phosphorylated by a signalosome complex of IκB kinases. The phosphorylated IκB dissociates from NFκB and undergoes proteosome-mediated degradation, permitting the nuclear translocation of NFκB. Inhibition of NFκB activation results in the suppression of CAM expression. Thus, the NFκB signalling pathway is an attractive target for the development of drugs to suppress inflammatory diseases (Huang et al, Circ. Res. 80:149-158, 1997), including atherosclerosis.

The n-3 fatty acids and fish oil are currently believed to possess cardioprotective actions and one well-studied action is the suppression of CAM expression (Pitt et al, Chem. Phys. Lipids. 92:63-39, 1998). In accordance with the present invention, a novel engineered polyunsaturated fatty acid, β-oxa-23:4n-6 (MP3) (Figure 5) is identified which has the hall-marks of a new class of pharmaceuticals based on polyunsaturated fatty acids and which can be used to prevent and/or treat cardiovascular disease. MP3 suppresses the expression of CAM and hence leukocyte-endothelium interaction (Figure 6). This molecule, containing an oxygen atom in the β position of the carbon backbone, is better than docosahexaenoic acid (22:6n-3) at suppressing tumour necrosis factor (TNF)-, lipopolysaccharide (LPS)- or phorbol 12-myristate 13-acetate (PMA)-induced expression of E-selectin, ICAM-1 and VCAM-1 in vitro. However, unlike 22:6n-3 which is a strong stimulator of the phagocyte respiratory burst (AF30) and hence is a promoter of neutrophil-mediated tissue damage, MP3 is relatively poor at stimulating this response. Preliminary studies have found MP3 to be effective in vivo at suppressing LPS-stimulated up-regulation of E-selectin expression in the aortae of mice and prevents the infiltration of leukocytes, including monocytes, into sites of inflammation (Figure 7). Given at 50 mg/kg intravenously (i.v.), MP3 did not cause any observable signs of distress to the animals for the duration of the experiments (4 days). Preliminary data have also demonstrated that MP3 inhibits the ability of TNF to activate IκB kinase-NFκB signalling pathway (Figure
5). Docosahexaenoic acid (22:6 n-3) was less effective than MP3 at antagonizing the action of TNF on this pathway, consistent with its weaker ability than MP3 at suppressing CAM expression. The focus of this embodiment of the subject invention is, therefore, the efficacy of MP3 at suppressing adhesion molecule expression in vivo and the development of atherosclerosis.

**EXAMPLE 9**

**Animal Models and MP3**

The animal model used comprised the apolipoprotein E-deficient (ApoE"−") mice on a C57BL/6J background. Another model comprised using NZ white rabbits. The ability of MP3 to protect against atherogenesis in two different models, each displaying a different degree of atherosclerosis development, will be a better indicator of MP3's efficacy in protecting against atherogenesis.

ApoE, a 34 kDa glycoprotein that is synthesized predominantly in the liver, is a structural component of all lipoproteins other than LDL. One of its most important functions is to mediate the clearance via the liver of very low density lipoprotein (VLDL) and intermediate density lipoprotein (IDL) via the LDL receptor and of chylomicron remnants via both the LDL receptors and chylomicron remnant receptors (Pitt et al, 1997 supra). Humans with ApoE deficiency have type III hyperlipoproteinemia with elevated plasma cholesterol, early development of atherosclerosis and yellow lipid-laden xanthomatous skin nodules, although triglyceride levels are near normal (Pitt et al, 1997 supra). The ApoE"−" mouse has marked hypercholesterolemia and spontaneously develop lesion patterns characteristics of human atherosclerosis. Extensive fatty streak formation and advanced plaques are observed in many regions of the arterial tree, e.g. aortic root, curvature of the aortic arch, principal branches of the aorta and in the pulmonary and carotid arteries of 30-40 week old ApoE"−" mice (Costabile et al, J. Immunol. 167:2980-2987, 2001; Jirousek et al, J. Med. Chem. 39:2664-2671, 1996). However, signs of early atherosclerotic development is evident in lesion-prone sites, e.g. aortic arch, orifice of the bronchiocephalic artery, and branching sites of the abdominal aorta can be detected as
early as 5-6 weeks of age (Dekker et al, Biochem J. 347:285-289, 2000). If fed a Western-type diet, lesion development is accelerated and are more advanced than mice fed a normal chow diet (Costabile et al, J. Immunol. 167:2980-2987; Dekker et al, 2000 supra; Couper et al, Diabetologia 37:533-535, 1994). This mouse is being regarded as an excellent model for histological studies. Of particular relevance to this study is the demonstration in the ApoE^{−/−} mouse that increased expression of CAM at atherosclerosis-prone sites on the aortic endothelium has been observed (Dekker et al, 2000 supra; Couper et al, 1994 supra). More importantly, the concept that blocking CAM expression blocks leukocyte adherence to the endothelium at relevant lesion-prone sites of the aorta and consequently reduces atherogenesis has been validated in the ApoE^{−/−} model, using both genetic approaches and blocking antibodies of various CAM (Koya et al, 1998 supra; Scivittaro et al, 2000 supra, Way et al, 2001 supra, Ferrante et al, 1997 supra).

Furthermore, the experiments proposed to be conducted using the ApoE^{−/−} mouse.

The NZ white rabbit develops atherosclerotic lesions when given a high fat-high cholesterol Western-type diet. By 16 weeks, the animals are overtly hypercholesterolemic, and histological studies at this time reveal that 50-80% of aortic intima is covered by atherosclerotic lesions, including fatty streaks and plaques (Kikawa et al, Diabetologia 37:838-841, 1994). Cell proliferation, foam cell and T cell accumulation and lipid deposition are normal in the intima of these animals (Kikawa et al, 1994 supra).

A colony of ApoE^{−/−} mice (Animal Resource Centre, Perth) has been established at the Women's and Children's Hospital, Adelaide, South Australia and in preliminary studies, have confirmed the presence of atherosclerotic lesions in the aortic arch of 16 week old mice fed on standard chow. All ApoE^{−/−} animals for experimentation will be kept on standard chow (4.5% fat, 0.02 % cholesterol, w/w) to start with. When appropriate, their diets will be changed to high fat/high cholesterol Western-type diet (w/w) (21% fat - polyunsaturated:saturated = 0.07, 0.15% cholesterol).
EXAMPLE 10

Effects of MP3 administration on the adhesiveness of the endothelium in mice

Adhesion molecule expression

It is evident from the data that MP3 inhibits the activation of the IκB-NFκB pathway and the up-regulation of endothelial CAM expression in vitro and LPS-stimulated E-selectin expression in vivo. The aim of this application was to determine whether MP3 also inhibits the expression of VCAM-1 and ICAM-1. For this, C57BL/6J mice (6-8 animals per group, a number which was sufficient in the Balb/c experiments to give statistically significant differences) were pre-treated for 1 day (one dose) or 1 week (one dose/day) with either 40 mg/kg or 80 mg/kg of MP3 intravenously. These concentrations and the route of administration were used previously to demonstrate the suppression of LPS-stimulated E-selectin expression by MP3 in the aorta of Balb/c mice. The fatty acid were presented in DPC (dipalmitoylcholine) micelles (1:4, MP3:DPC, w/w), prepared by sonication. Control mice receive an equivalent amount of DPC. After the pre-treatment period, the mice were injected intraperitoneally with LPS (50 µg), an agent which induces the expression of E-selectin, ICAM-1 and VCAM-1. 24 hr after LPS administration, the animals were sacrificed by CO₂ asphyxiation and the aortae encompassing the ascending part of the aortic arch through to the bifurcation to the common iliac arteries were isolated. Each aorta was then separated into two pieces of equal length and minced. The tissue were fixed in 0.25% v/v glutaraldehyde and processed for enzyme immunoassay. One half of the aorta was stained with monoclonal antibody to mouse VCAM-1 and the other half stained with isotype-matched control IgG. In addition, adhesion molecule expression were assessed by immunohistochemistry using gold-conjugated reagents (Dekker et al, 2000 supra). Once conditions have been optimized with respect to pre-treatment time and the dose of MP3 to be used, the experiments were repeated to examine the effects of MP3 on ICAM-1 expression. As a negative control, MP1 (β-oxa-23:0), a novel fatty acid that is biologically inactive in in vitro assays, was also tested.
Next, the ability of MP3 to reduce the expression of CAM, e.g. VCAM-1, in ApoE<sup>−/−</sup> mice was investigated. Expression of E-selectin and ICAM-1 was investigated. A previous study found slightly increased expression of VCAM-1 at lesion-prone sites in ApoE<sup>−/−</sup> mice compared to control mice as early as 5 weeks of age (Dekker et al, 2000 supra). By 8 weeks of age, VCAM-1 staining was more intense and this was further increased in mice fed a Western-type diet. For experiments, the mice were weaned at 4 weeks of age (Dekker et al, 2000 supra). It is proposed to use 12 ApoE<sup>−/−</sup> mice/group (α = 0.5, β = 0.1) and these were housed in groups of 6-7 per cage. Some animals have been excluded owing to the presence of severe non-xanthomatous skin lesions or murine urological syndrome (Lallena et al, Mol. Cell. Biol. 19:2180-2188, 1999). At 5 weeks, one group of mice were fed a Western-type diet while the other were maintained on standard chow. The fifth week was chosen to start treatment in order to maximize the difference between control and MP3-treated groups. Two regimes of MP3 treatment were tested. In the first, mice were treated with MP3, DPC or MP1 by intraperitoneal injection a day prior to diet modification. Other studies have demonstrated the engineered fatty acids are effective at suppressing footpad inflammation when administered intraperitoneally (AF45). Treatment continued once daily for 5 or 15 weeks. The mice were sacrificed and adhesion molecule expression were determined as described above. To gauge the degree of suppression of adhesion molecule expression by MP3, the results were compared with those obtained in age-matched ApoE<sup>−/−</sup> and C57BL/6J mice fed normal chow and treated with DPC. It was expected that chow-fed C57BL/6J mice woulds have very low levels of CAM expression, chow-fed ApoE<sup>−/−</sup> mice would have intermediate levels of expression and ApoE<sup>−/−</sup> mice on Western-type diet would have the highest level of expression. If MP3 is efficacious, the levels of CAM expression would be less than that in DPC- or MP1-treated ApoE<sup>−/−</sup> mice on Western-type diet. In the second regime, mice were treated with MP3 or MP1, commencing at 8 weeks after diet modification and CAM expression would be determined after 10 weeks of MP3 treatment. This allowed the inventors to determine whether MP3 stopped or reversed atherogenesis.
Adherence of macrophages to the endothelium

To confirm that MP3 reduces the adhesiveness of the endothelium for leukocytes in vivo, an assay based on that described by Ferrante et al (J. Clin. Invest. 99:1445-1452, 1997) would be adopted. Peritoneal macrophages (from C57BL/6J mice) loaded with fluorescent microspheres (Molecular Probes) were injected intravenously into ApoE\(^{-}\) mice and 48 hr later, the number adhering to the aortic root at the level of the sinus of Valsalva would be scored. Although unprimed blood monocytes would also adhere to the endothelium under identical conditions, the level of adherence was found to be higher with peritoneal macrophages than monocytes and hence peritoneal macrophages were chosen (Ferrante et al, 1997 supra). In ApoE\(^{-}\) mice, the most advanced lesions were found over the aortic cusps at the level of the sinus of Valsalva (Couper et al, Diabetologia 37:533-535, 1994). Fed on normal chow, increased adherence of monocytes to the endothelium was observable by 6 weeks of age (Couper et al, 1994 supra). Again, 5 week old ApoE\(^{-}\) mice, in groups of 12 animals, were fed a Western-type diet (optimal period on this diet would be based on the results obtained above). Mice were treated with MP3, MP1 or DPC. On the last day of treatment, mice were injected intravenously with microsphere-loaded macrophages (1x10\(^7\) in 0.2 ml). After 48h, the mice were sacrificed, perfused with heparinized saline by injection through the apex of the left ventricle, and the base of the hearts and ascending aortae isolated, mounted in Tissue Tex freezing media and frozen in liquid N\(_2\). Hematoxylin-stained sections (200 consecutive 5 \(\mu\)m sections) covering the proximal 1 mm of the aortic root were analyzed by light and fluorescent microscopy, and the number of adherent fluorescent monocytes be counted in a blinded fashion. As a positive control, mice which had not been treated with a fatty acid were administered anti-\(\alpha_4\) integrin or ICAM-1 antibody (positive control) prior to the injection of microsphere-loaded macrophages (Ferrante et al, 1997 supra).

To provide another comparison for the degree of suppression of macrophage-endothelium interaction by MP3, macrophage adhesion were also determined in DPC-treated age-matched C57BL/6J mice fed a chow diet. It was envisaged that very few or no macrophages would adhere to the endothelium of these mice.
EXAMPLE 11

Effect of MP3 on the development of atherosclerosis

The anti-atherosclerotic effect of MP3 were examined first in ApoE−/− mice fed a Western diet. In these mice fed a normal chow diet, foam cell lesions were evident as early as 8 weeks of age and advanced lesions were observable by 15 weeks (Couper et al, 1994 supra). Mice fed a Western diet has more advanced lesions than those on normal chow (Couper et al, 1994 supra).

Mice (12 per group), weaned at 4 weeks of age, were switched from a chow diet to a Western-type diet at 5 weeks of age and maintained on this diet for up to 20 weeks. Daily treatment with MP3 (40 mg/kg), MP1 or DPC commenced at the time of the switch. As a positive control, another group of mice were treated with probucol which suppresses atherogenesis (Suzuma et al, J. Biol. Chem. 277:1047-1057, 2002). At various times, e.g. 5 and 20 weeks after the switch, mice are sacrificed and the degree of atherosclerosis assessed as previously described (Costabile et al, 2001 supra, Jirousek et al, 1996 supra) but with modifications. Briefly, the vascular tree were perfused via the heart with paraformaldehyde (4% w/v) and the heart and aortae down to the bifurcation at the common iliac arteries were isolated intact. The heart and an approximately 5 mm length of ascending aorta were removed from the remainder of the aorta and fixed in formalin. After embedding in paraffin, 4 µm-thick sections at 25 µm intervals were made beginning with the ascending aorta and proceeding through the entire aortic sinus until the ventricular chamber was reached. The sections are stained with Hematoxylin and Eosin and assessed using an Olympus BX51 microscope for foam cell infiltration, cellular proliferation and the presence of fibrous plaques or atheromatous lesions complicated by ulcerations or thrombosis. Images are captured using an Olympus DP12 digital camera. Lesion size (mean cross sectional area) and the percentage of the lumen area occupied by lesion were determined by using a computer assisted image measurement program (Measure Master, Leading Edge, Australia). Where appropriate, sections were stained with elastic Van Gieson and Masson’s trichrome to detect collagen. Some sections were also immunostained for macrophages using the anti-mouse macrophage antibody, MAC 3.
(Sigma Aldrich). It was also possible to grade these lesions according to the classification described by Stary and co-workers (Lallena et al, Mol. Cell. Biol. 19:2180-2188, 1999). The remaining section of the aorta were pinned on to a board, sectioned longitudinally, one half fixed in formalin, stained with Oil red O/Sudan IV and counter-stained with Hematoxylin Eosin to detect lipid laden cells. The other half were fixed and 12 μm frozen sections in the abdominal aorta around the renal arteries were stained to detect the lipid laden cells. Lesion size were determined as described above and results expressed as the percentage of lesion area relative to the total internal surface. Older mice (30 weeks) known to have advanced lesions were also treated with MP3 over a period of 15 weeks to determine whether atherosclerosis could be halted or reversed.

The experiments above were then repeated but with MP3 or control agents given orally. Being a fatty acid, it was expected for MP3 to be absorbed across the intestinal wall into the blood stream. Indeed, previous studies with another engineered fatty acid, MP5, have demonstrated that this fatty acid is present in the blood and various organs after oral administration. Studies in dogs have shown that a saturated β-oxa fatty acid is readily absorbed when given orally (Hii et al, J. Biol. Chem. 266:20238-20243, 1991). Thus, it was investigated whether MP3 is efficacious at suppressing atherosclerosis when given orally. The experiment essentially followed the schedule outlined above to determine whether MP3 prevented the development of atherosclerosis. Mice were administered MP3 or a control compound daily by gavage for the appropriate length of time (see above) and the degree of atherosclerosis assessed. Finally, the anti-atherosclerotic effects of MP3 were tested using NZ white rabbits. After 16 weeks on a high cholesterol diet, these animals were shown to be overtly hypercholesterolemic and histological studies at this time show that 50-80% of aortic intima was covered by atherosclerotic lesions, including fatty streaks and plaques. For the experiments, rabbits fed on standard chow, weighing 1.8-2.2 kg and with serum cholesterol of less than 100 mg/dl, were selected. They were divided into five groups of eight animals each: standard chow + DPC, standard chow + MP3, high cholesterol (2% w/w) diet + DPC, high cholesterol diet + MP3 and high cholesterol diet + probucol (0.25%). Treatment with MP3 (40 mg/kg) would coincide with the switch to a high cholesterol diet. The animals were kept on their diets and treated with MP3 for 16
weeks. At the end of this period, the animals were sacrificed by heart puncture under ketamine. The thoracic aortae were removed, sectioned longitudinally, one half pinned on to boards, fixed and stained with Oil red O. The sections were photographed as described above and the extent of Oil red O positive area between the first and fifth intercostal aortic branches were determined in a blinded fashion and expressed as a percentage of the total internal surface. The other half were processed for light microscopy and 4 μm sections were taken from a 5 mm segment around the first intercostal branch. After mounting on slides, lesion area was assessed as described above. These sections were also immunostained for macrophages using the rabbit macrophage antibody, RAM 11 (Dako, CA).

Statistical analysis of the results were performed by one way ANOVA followed by an appropriate post test, e.g. Bonferroni test for multiple comparison or Mann-Whitney U-test. Results were considered statistically significant when P<0.05.

**EXAMPLE 12**

*Effects of PUFAs on diabetes*

The overall aim of this Example was to evaluate the potential for a chemically engineered polyunsaturated fatty acid, MP5 (β-oxa-21:3n-3), to treat pathogenesis associated with diabetes by targeting the protein kinase C (PKC) system. The specific aims were to:

1. characterize the effects of MP5 on glucose or advanced glycosylation end product-stimulated activation of PKC, e.g. prevent agonist-stimulated association of PKCβ with a particulate fraction in mesangial cells;
2. determine whether esterification of MP5 into diacylglycerol was essential for the action of MP5;
3. investigate whether MP5 is efficacious at preventing glucose-induced responses *in vitro*, e.g. glucose-stimulated TGFβ production in mesangial cells, and *in vivo* in streptozotocin diabetic rats.
MP5, by virtue of its incorporation into membrane phospholipids and diacylglycerol, selectively targets the protein kinase Cβ isoforms in mesangial cells by preventing PKC translocation. This prevents glucose and advanced glycosylation end products from causing functional changes in mesangial cells in culture and in the kidneys of streptozotocin diabetic rats.

The majority of diabetic patients were not able to attain near normal glycaemia. This predisposed them to the development of diabetic microvascular and macrovascular complications. Therefore, novel approaches to prevent the effects of hyperglycemia were essential to the future management of diabetes. Recent focus centred on identifying the hyperglycemia-induced biochemical changes that were significant in causing vascular and neurological dysfunction. One consistent observation was that glucose stimulated the activity and expression of protein kinase C (PKC) in tissues at risk of developing diabetic complications (Koya et al., 1998 supra). This raises the likelihood that PKC may be an important mediator of the actions of glucose in these tissues.

PKC is a ubiquitous phospholipid-activated Ser/Thr kinase. Consisting of at least 11 isoforms, PKC is divided into classical (α, βI, βII and γ), novel (δ, ε, θ, η and δPKD) and atypical (ζ and ι/λ) isoforms (Chou et al, 1998 supra). The activity of the classical PKC isoforms is stimulated when diacylglycerol (DAG) and Ca\(^{2+}\) accumulate in appropriately stimulated cells while activation of the novel PKC isoforms requires only DAG. Both the classical and novel PKC can also be activated directly by phorbol esters such as phorbol 12-myristate 13-acetate (PMA). Activation of the atypical isoforms is regulated by other means, e.g. ceramide and phosphorylation (Chou et al, 1998 supra). In unstimulated cells, PKC is generally found in the cytoplasm and it translocates to particulate fractions upon stimulation where it associates with binding partners such as RACKs (receptor for activated C kinase) (Jaken et al, 2000 supra).

PKC regulates a diverse range of cellular processes in an isozyme(s)-specific manner. There is very strong evidence to implicate PKC, especially PKCβ, in mediating the actions of glucose in diabetes. This includes the activation of PKCβ in renal glomeruli, retina,
aorta and heart of diabetic animals and in glucose-stimulated cells (Koya et al., 1998 supra). More importantly, inhibition of PKCβ with the PKCβ-specific inhibitor, LY333531, reverses/blocks the actions of glucose in these tissues. For example, in the retinas of diabetic patients and animals with a short history of the disease, retinal blood flow is decreased due to glucose-induced vasoconstriction (Koya et al., 1998 supra). While direct stimulation of PKC with a phorbol ester causes retinal vasoconstriction, inhibition of PKC activity normalizes retinal blood flow in diabetic dogs (Koya et al., 1998 supra). Hyperglycemia-induced increase in endothelial cell permeability to macromolecules, another characteristic systemic vascular abnormality in diabetes, can be reproduced by the addition PMA and PKCβ has been implicated in causing this change in permeability (Koya et al., 1998 supra). In the microvessels and macrovessels, hyperglycemia-induced vasodilation and increase in contractility, respectively, can be reversed by inhibitors of PKC (Koya et al., 1998 supra). One of the factors that cause these changes in renal tissues is the glucose-induced increase in the activity of the renin-angiotensin system, and PKC has been implicated in the actions of angiotensin (Koya et al., 1998 supra). Increased angiogenesis, neovascularization and over-expression of the extracellular matrix proteins are also hallmarks of diabetes, and these are believed to be due to glucose-induced production of vascular-endothelial cell growth factor (VEGF) and TGFβ. While inhibition of PKC inhibits the actions of VEGF on endothelial cell proliferation (Xia et al., J. Clin. Invest. 98:2018-2026, 1996), inhibition of PKCβ effectively blocks hyperglycemia-induced production of TGFβ in mesangial cells and renal glomeruli (Koya et al, 1997 supra) and the associated expansion of the extracellular matrix. Furthermore, decreases in the activity of the Na⁺-K⁺-ATPase in vascular and neuronal tissues are widely reported in diabetic patients, and glucose-induced reduction in the Na⁺-K⁺ ATPase activity in mesangial cells and aortic smooth muscle cells has been found to be dependent on PKCβ. Current evidence also suggests that arachidonic acid, produced by the sequential activation of PKC and cytosolic phospholipase A₂, is responsible for the action of glucose on the sodium pump.

When the engineered polyunsaturates were examined for biological activity in human umbilical vein endothelial cells (HUVEC) and other cell-types, several were found to
display a more selective range of actions than their natural counterparts. One of these, MP5 (β-oxa-21:3n-3), inhibited PMA-stimulated translocation of PKCβI and βII to the particulate fraction in these cell-types. MP5 had minimal effects (<15%) on PKCε translocation and no effects on the translocation of the other PKC isoymes in Jurkat cells.

Preliminary data from glucose-stimulated mesangial cells (Figure 9a) and the glomeruli of diabetic rats (Figure 9b) have confirmed the ability of MP5 to prevent the translocation of PKCβI, the main β isoform in mesangial cells, to a particulate fraction. Long term in vivo experiments (up to three months) showed that treatment with MP5 (up to 100 mg/kg) had no visible adverse effects on the well-being of the animals, e.g. coat appearance and activity/mobility, and exerted no adverse effects on liver and kidney function and electrolyte levels. These data indicate that MP5 has the hallmarks of a lead compound for blocking the actions of glucose.

While LY33531 inhibits PKCβ by binding to the ATP-binding site of the kinase (Jirousek et al, 1996 supra), MP5 acts by reducing the association of PKCβ with the particulate fraction. Because of this unique mode of action, i.e. MP5 is not a kinase inhibitor, the likelihood of MP5 directly affecting the activity of any kinase is extremely remote. The potential for a kinase inhibitor such as LY333531 and derivatives to affect the activity of other kinases has been recently voiced (Jirousek et al, 1996 supra). Depending on the concentrations used, the preliminary data in HUVEC have demonstrated that MP5 is able to distinguish between PKCβI and PKCβII.

The objective of this Example was to determine whether EPUFA such as MP5 could be developed into novel therapeutics to prevent the severe and life-threatening pathology associated with diabetes using the kidney as a model. This is achieved by testing the ability of MP5 to block glucose- or AGE-stimulated activation of PKCβ and whether this requires esterification of MP5 into membrane phospholipids. Finally, MP5 is tested for efficaciously at inhibiting glucose-stimulated responses in mesangial cells in vitro and hyperglycemia-induced renal damage in an experimental animal model of diabetes.
EXAMPLE 13

Effects of MP5 (β-oxa 21:3n-3) on the activation/translocation of different PKC isozymes

Since glucose has been demonstrated to stimulate the translocation of PKCα and βI in mesangial cells (Koya et al, 1997 supra), the effects of MP5 on the association of PKCα and βI with the particulate fraction in glucose-stimulated mesangial cells is determined. Preliminary studies in glucose-stimulated mesangial cells have indicated that MP5 can prevent PKCβI from translocating the particulate fraction (Figure 9). Mesangial cells are prepared as previously described (Couper et al, 1994 supra).

Four groups of cells were set up: 5.5 mM glucose+ethanol (0.1% w/v or v/v), 5.5 mM glucose+MP5 (20 μM which is effective in the studies), 25 mM glucose+ethanol and 25 mM glucose+MP5. In some experiments, an additional group of cells are treated with MP1 (β-oxa 23:0) (20 μM), an inactive fatty acid. Cells were pre-incubated (30 min-24h) with MP5 before being challenged with glucose for 4 days. The kinetics studies have found that glucose-stimulated PKC translocation in mesangial cells reaches a maximum at day 4 of treatment, consistent with findings from previous reports (Koya et al 1997 supra). Cells are then be washed, sonicated and the amount of each PKC isozyme in the particulate fraction determined by Western blot analysis. The soluble fractions were kept for estimation of soluble PKC (non-particulate fraction-associated). The inventors' studies demonstrated that a 30 min pre-treatment period with MP5 was sufficient to inhibit agonist-stimulated increase in the association of PKC with the particulate fraction and block agonist-stimulated functional responses, but the IC₅₀ decreased with increasing time of pre-treatment. The cells remained viable throughout the period of study as judged by the trypan blue exclusion test. The studies were repeated with cells stimulated with AGE-human serum albumin (HSA) since AGE-HSA was demonstrated to stimulate PKCβII translocation without affecting PKCα translocation (Scivittaro et al, 2000 supra). AGE-HSA (pyrogen-free) were prepared by incubating the protein in the presence of glucose essentially as previously described (Scivittaro et al, 2000 supra). Control HSA were incubated in the absence of glucose. Analysis of the extent of AGE-HSA formation and
AGE-HSA purification were carried out as described (Scivittaro et al, 2000 supra). After removal of remaining glucose (centricon, 10 kDa cut-off), AGE-HSA were tested at 0.1-10 μM.

The effects of MP5 on glucose-stimulated PKC expression were investigated since glucose increased the expression of PKCβ in mesangial cells (Koya et al, 1997 supra). This was achieved by determining the level of PKCβ mRNA by slot blot analysis (Ferrante et al, 1997 supra). All classical and novel PKC isozymes were probed. The level of PKC mRNA are normalized by comparison with the level of glyceraldehyde 3-phosphate dehydrogenase mRNA in the same sample.

Mesangial cells express PKCα, βI, ε, δ and ζ (Koya et al, 1997 supra, Kikkawa et al, 1994 supra), and βII at lower levels (Koya et al, 1997 supra). To examine the effect of MP5 on the ability of other PKC isozymes in mesangial cells to translocate to the particulate fraction, the cells were pre-treated with MP5 before being stimulated with PMA (1-100 nM). This agent stimulated the translocation of all the classical and novel isozymes. The studies in HUVEC have demonstrated that MP5 suppressed PMA-stimulated association of PKCβI and βII with the particulate fraction. The studies were extended to other isozymes. For PKCγ (expressed mainly by neuronal cells), the effect of MP5 are tested using PMA-stimulated PC12 rat pheochromocytoma cells. To assess the effect of MP5 on the activation of atypical PKC isozymes such as PKCζ NIH3T3 cells were pre-treated with MP5 before being stimulated with tumour necrosis factor α (1000 U/ml) which stimulates PKCζ activity in these cells (Lallena et al, 1999 supra). The isozyme were immunoprecipitated (antibody from Santa Cruz) and kinase activity was determined using a PKCζ pseudosubstrate peptide or myelin basic protein as a substrate (Suzuma et al, 2002 supra).
EXAMPLE 14

_Incorporation of MP5 into diacylglycerol_

In MP5-treated HUVEC, the ratio of non-esterified MP5 to non-esterified arachidonic acid is as high as 5:1. Thus, incubation of mesangial cells with glucose and MP5 is likely to result in the formation of DAG that contains MP5. The formation of a more polar and conformationally different MP5-containing DAG can conceivably interfere with the ability of natural DAG to stimulate PKC translocation. The hypothesis is first tested that MP5 does not inhibit glucose-stimulated accumulation of DAG but leads to the formation of MP5-containing DAG. Mesangial cells were incubated with MP5 (30 μM, 1h) before increasing the glucose concentration to 25 mM. After 4 days, lipids were extracted (CHCl₃:CH₃OH=2:1), DAG isolated by thin layer chromatography (TLC), eluted from the silica and the presence of MP5 in DAG were determined and quantitated by GC/GCMS after hydrolysis of the esterified fatty acids (Hii et al., 1991 _supra_). DAG and conversion of the liberated MP5 to its methyl ester derivative. 19:0 methyl ester were used as a standard (Robinson et al, _Biochem J_. 336:611-617, 1998) and this method is used successfully to determine the content of EPUFA in DAG and phospholipids. To quantitate DAG, an assay developed and validated in mesangial cells were used (Musial et al, _J Biol Chem_. 270:21632-21638, 1995). DAG that is extracted from the TLC plates were acetylated with ¹⁴C-acetic anhydride and pyridine. After rechromatography by TLC, the DAG-acetate, after autoradiography, were subjected to liquid scintillation counting. Some cultures were incubated with the inactive MP1. If MP1 was also incorporated, it would imply that the biological activity of an EPUFA was governed by its structural elements. The rationale for the synthesis of EPUFA was based on this concept. The esterification of MP5 into DAG was next determined as to whether this was required for the inhibition of glucose-stimulated PKCβI-particulate fraction association. It is mandatory that fatty acids were converted to their coenzyme A derivatives for metabolism, including esterification into DAG. Cells were pre-incubated with DMSO (control) or triacin C₂, a commonly used inhibitor of long chain acyl coenzyme A synthetase (Korchak _et al_, _J Biol Chem_. 269:30281-30287, 1994), for 10 min before being incubated with MP5 (20 μM) for 1 hr since this pre-treatment time was sufficient to block PMA-stimulated PKCβ translocation.
in glucose stimulated HUVEC and mesangial cells. The cells were then stimulated with PMA (100 nM, 0.5-3 min) or vehicle (DMSO) instead of glucose to shorten the time required for PKC activation and to minimize the effect of triacin C on normal fatty acid metabolism. The amount of PKCβI and βII in particulate fraction were determined. Triacin C-mediated inhibition of $^3$H-palmitic acid incorporation into DAG and phosphatidylcholine (PC) (Hii et al, 1991 supra) serves to confirm that the triacin C is active.

**EXAMPLE 15**

**Effects of MP5 on glucose- or diabetes-induced functional changes associated with pathogenesis**

Once it was confirmed that MP5 inhibited the association of PKCβ with the particulate fraction in mesangial cells, MP5 were examined for its ability to inhibit *in vitro* parameters of glucose-induced functional changes. The data were normalised for cellular protein content. These investigations were followed by an examination of the efficacy of MP5 in protecting against hyperglycemia-induced functional changes in the kidneys of diabetic rats.

**In vitro studies**

*Suppression of glucose-stimulated production of TGFβ*

Glucose-induced expansion of the extracellular matrix via the production of TGFβ by mesangial cells was a major contributor to diabetic nephropathy and this action of glucose could be blocked by inhibitors of PKCβ (Koya et al, 1998 *supra*, Koya et al, 1997 *supra*). Thus, the ability of MP5 to inhibit glucose-stimulated TGFβ production were investigated. Cells were pre-treated with MP5 (see above) in DMEM (5.5 mM glucose) before being stimulated with glucose (25 mM) for 4 days. The amount of TGFβ present in the incubation medium was determined using a commercially available ELISA kit (Biosource, USA). MP1 was used as a negative control. LY333531 was tested as a positive control.
Suppression of phospholipase A\(_2\) activity

Hyperglycemia-induced production of prostaglandin E\(_2\) and I\(_2\) have been implicated as contributing factors to glomerular hyperfiltration in diabetes (Koya et al, 1998 supra). These vasodilatory prostanoids were derived from arachidonic acid via the action of the cytosolic phospholipase A\(_2\) (cPLA\(_2\)), and glucose stimulates the activity of cPLA\(_2\) in mesangial cells in a PKC-dependent manner (Koya et al, 1997 supra). Cells were pre-treated with MP5 before being stimulated with glucose. At the end of the incubation period, the cells were harvested, lysed and the activity of cPLA\(_2\) determined (Robinson et al, 1998 supra) using a commercial kit (Cayman Chemical, USA). The ability of MP5 to inhibit PKC-independent activation of cPLA\(_2\) by ionomycin (0.1 \(\mu\)M, 15 min) was also determined. If the fatty acid acted by specifically inhibiting PKC\(\beta\) translocation, ionomycin-stimulated cPLA\(_2\) activity would not be affected by the fatty acid.

Na\(^+\)K\(^+\) ATPase:

In addition to its central role in nerve function, the Na\(^+\)-K\(^+\) ATPase may also regulate barrier permeability and cellular integrity in the glomeruli. Glucose and diabetes have been widely reported to inhibit the activity of the Na\(^+\)-K\(^+\)-ATPase in the glomeruli/mesangial cells and aortic smooth muscle cells (Koya et al, 1998 supra, Koya et al, 1997 supra). This effect was believed to be due to glucose-stimulated accumulation of arachidonic acid, and inhibition of PKC\(\beta\) prevented the inhibition of the Na\(^+\)-K\(^+\)ATPase by glucose in aortic smooth muscle cells and mesangial cells (Koya et al, 1998 supra, Koya et al, 1997 supra). To determine whether MP5 blocked the action of glucose on the activity of the Na\(^+\)-K\(^+\) ATPase, the cells were pre-incubated with MP5 (see above) and then incubated in the presence of 25 mM glucose for 4 days. \(^{86}\)Rb\(^+\) uptake, a standard assay for Na\(^+\)-K\(^+\) ATPase, was determined as described (Koya et al, 1997 supra).
**In vivo studies**

The ability of MP5 to inhibit renal TGFβ production and albuminuria in streptozotocin-induced diabetic Sprague-Dawley rats were investigated. MP5 is non toxic to rats given at up to 100 mg/kg chronically as determined by liver and kidney biochemical and electrolyte markers. It is taken up by tissues, including kidneys, and incorporated into phospholipids following oral administration. Animals (130-150g) were placed randomly in one of five groups: control, MP5-treated, diabetic, diabetic + MP5 and diabetic + MP1. Power analysis ($\alpha = 0.5, \beta = 0.1$) (expecting at least a 50% reduction and an SD of 30% of mean) indicate that 7-8 animals/group were needed. The rats were rendered diabetic using streptozotocin (65 mg/kg. I.P) and blood glucose levels were measured 48 hr later to confirm the onset of diabetes (glucose>15 mM). Control and diabetic groups were administered vehicle (ethanol) or an EPUFA by gavage. Two doses were tested, 20 mg/kg and 50 mg/kg. The studies on the actions of EPUFA in vivo have demonstrated that the fatty acids were effective when given orally. Treatment was once daily for a period of 12 weeks (Koya et al, 1997 supra). Blood glucose was measured every week. The animals were treated with 2U of long acting insulin daily to maintain body weight and to prevent ketoacidosis but without normalizing hyperglycemia. At the end of the MP5 treatment period, rats were sacrificed and the level of TGFβ mRNA (Kikkawa et al 1994 supra) in the glomeruli were determined by slot blot analysis (Ferrante et al, 1997 supra) and normalized by comparison with the level of GAPDH (glyceraldehyde 3-phosphate dehydrogenase) mRNA in the same sample (Ferrante et al, 1997 supra). The amount of albumin in the urine were measured by using a commercial kit (EXOCCELL Inc. Philadelphia, PA). It was determined whether MP5 could halt/reverse complications in animals with more advanced (e.g. 15 weeks) diabetes. The diabetic animals were treated with MP5 (20 or 50 mg/kg, depending on the above results) once daily together with insulin (as above) for 12 weeks. Other parameters such as the production of hepatocyte growth factor by the glomeruli (Couper et al, 1994 supra) may also be examined if time permits.
EXAMPLE 16

Polyunsaturated fatty acid (PUFA) regulation of the activation of the IκB pathway

The objective of this Example is to make agents which are PUFA based, with many of the properties of PUFA, such as absorption following oral administration and incorporation into membrane phospholipids, but with more selective biological activities skewed towards anti-inflammatory effects.

Materials and Methods

10 Fatty acids

The fatty acids, arachidonic acid (20:4n-6), ecosapentaenoic acid 20:5n-3(EPA) and docosahexaenoic acid 22:6n-3(DHA) were purchased from Sigma Chemical Co, St Louis, Mo. The β-oxa and β-thia compounds were synthesized using published techniques. β-oxa-23:4n-6 methyl ester was formed by the treatment of β-oxa-23:4n-6 with diazomethane in diethyl ether, β-oxa-23:0 was prepared by hydrogenation of β-oxa-23:4n-6 in the presence of platinum oxide (Huang et al, 1997 supra), and 18-monohydroperoxy-β-oxa-23:4n-6 was prepared by incubation of β-oxa-23:4n-6 with soybean lipoxidase (Huang et al, 1997 supra). 18-monohydroxy-β-oxa-23:4n-6 was obtained by reduction of the 18-monohydroperoxy product with sodium borohydride (Huang et al, 1997 supra).

The products were not individually purified, but were separated by 1D TLC (Et2O/hexane/acetic acid ; 60:40:1). The appropriate lipid zones were visualized under UV light with dichlorofluoroscein (0.2% v/v) in ethanol and identified by comparison of RFs with those of similar structured analogs. No other mono-hydroxylated materials were evident, but more polar polyhydroxylated compounds would have been present in the polar fractions of the chromatogram (at the baseline).

Fatty acids and derivatives were dissolved in ethanol (0.1% final, v/v) (in vitro), dipalmitoylphosphatidylcholine (DPC) (Ferrante et al, 1997 supra) or DMSO (7 % v/v) (in vivo). At these concentrations these diluents did not affect cellular functions. Thin-layer
chromatography and gas-liquid chromatography-mass spectrometry showed that the lipids were at least 98% pure.

Neutrophil respiratory burst

Neutrophil respiratory burst was determined as previously described (Li et al, J. Clin. Invest. 97:1605-1609, 1996).

Neutrophil adhesion to human umbilical vein endothelial cells (HUVEC)

Adhesion of neutrophils, prepared by the rapid-single-step method (Ferrante et al, J. Immun. Methods 36:109-117, 1980), to HUVEC isolated from umbilical cords was carried out essentially as described (Huang et al, 1997 supra).

Measurement of endothelial cell adhesion molecules

HUVEC were stimulated with TNF, bacterial lipopolysaccharide (LPS) or PMA for 24 hr. Expression of E-selectin, ICAM-1 and VCAM-1 was determined by an enzyme-linked immunosorbent assay (ELISA) or as mRNA using a slot blot technique (Huang et al 1997 supra).

The LPS-induced expression of E-selectin in the aortic endothelium of BALB/c mice was determined following injection of 50 μg LPS intraperitoneally and aortas encompassing the ascending part of the aortic arch through to the bifurcation to the common iliac arteries isolated after 5 hr. Each was cut into two pieces of equal length, minced, fixed in 0.25% v/v glutaraldehyde, incubated with a monoclonal antibody to mouse E-selectin (one half) or isotype matched control (other half) (Becton Dickinson, Ca) followed by an HRP-conjugated secondary antibody and then with the substrate ABTS (ELISA method).

Measurements of lipoxygenase products

Lipids were extracted from the HUVEC culture medium and oxygenated fatty acid derivatives were isolated by thin-layer chromatography. The recovered oxygenated derivatives of β-oxa-23:4n-6 were characterized by electrospray mass spectrometry according to Pitt et al (Pitt et al, 1998 supra). Electrospray ionisation mass spectra (ESI-
were recorded on a Finnigan LCQ spectrometer, operating at a spray voltage of 5.20 kV, capillary temperature of 200°C and capillary voltage of 35V. Analyses were performed in methanol, and ions were reported as their M+H+, M+Na+, or M+K+ ions.

5 Preparation of cell lysates

Cell lysates were prepared as previously described for IκB kinase (IKK) activity (Lee et al., Proc. Natl. Acad. Sci. USA 95:9319-9324, 1998), IκBα degradation, MAP kinase activity (Hii et al, 1998 supra) and nuclear translocation of NFκB (p65 rel) (Jersmann et al, Infect. Immun. 69:1273-1279, 2001).

10 Western blot analysis to detect NFκB and IκBα

Proteins (50 μg) were separated by SDS PAGE (12% w/v gel), transferred to nitrocellulose and probed with an anti-NFκB p65 or anti-IκBα antibody (Santa Cruz Biotech, Santa Cruz, Ca). Immunocomplexes were detected by enhanced chemiluminescence (Hii et al, 1998 supra).

IKB kinase kinase (IKK) assay

IKK was immunoprecipitated with anti-IKKα (M-280) antibody (sc-7182, Santa Cruz, Biotech) and kinase activity determined using GST-IκBα (residues 5-55) as previously described (Lee et al, 1998 supra). Proteins were fractionated by SDS PAGE and radioactivity associated with GST-IκBα (residues 5-55) determined using an instant imager.

Measurement of the activity of p38, ERK and JNK

ERK and p38 were precipitated with anti-ERK2 (C-14, sc-154) and anti-p38 (C-20, sc-535) antibody, respectively (Santa Cruz Biotech) and the activity determined using myelin basic protein as a substrate (Hii et al, 1995 supra, Hii et al, 1998 supra). JNK activity was determined in a solid phase assay using GST c-Jun (residues 1-79) as a substrate (Hii et al, 1995 supra, Hii et al, 1998 supra).
Inflammatory reactions

Effect of MP3 (β-oxa-23:4n-6) on the in vivo inflammatory response was measured as a delayed type hypersensitivity (DTH) reaction and LPS-induced influx of neutrophils and mononuclear cells in the peritoneal cavity in BALB/c mice. For DTH experiments, mice were injected subcutaneously with 100 μl of 10% hematocrit sheep erythrocytes, challenged with the antigen (25 μl of 40%) in the hind foot pad 6 days later and the degree of foot pad swelling measured 48 hr later (Ferrante et al, Clin. & Exp. Immunol. 38:70-76, 1979). One hour prior to challenge mice were given 10 mg/kg body weight of the fatty acid, intraperitoneally. For peritoneal inflammation, mice were injected with 50 μg of LPS intraperitoneally 6 hr after intravenous fatty acid treatment. At 24 hr and 72 hr the peritoneal exudate was harvested and the number and proportion of neutrophils and macrophages determined microscopically from Giemsa stained smears.

Results

Effects on the neutrophil respiratory burst

Unlike natural PUFA, the β-oxa and β-thia compounds are not readily β-oxidized and hence show high levels of intracellular stability (Pitt et al, 1998 supra). Compared with 20:4n-6 and 22:6n-3, β-substituted PUFA were found to be weak at stimulating the oxygen radical production in human neutrophils. In the case of MP3 (β-oxa 23:4n-6), a concentration of up to 30 μmol/l failed to cause any significant respiratory burst (chemiluminescence response), while the same concentration of 22:6n-3 produced marked responses, similar to the strong neutrophil activator, PMA (Figure 10).

Effects on TNF-induced up-regulation of neutrophil adherence to HUVEC

Data in Figure 11 show that pre-treatment of HUVEC for 1 hr with β-oxa-PUFA (β-oxa-23:4n-6, β-oxa-21:3n-6, β-oxa-21:3n-3) or β-thia-PUFA (β-thia-23:4n-6, β-thia-21:3n-6 β-thia-21:3n-3) inhibited their ability to be stimulated by tumour necrosis factor-α (TNF-α) for enhanced neutrophil adhesion. In contrast, pre-treatment with the naturally-occurring PUFA, 20:4n-6, octadecadienoic acid (linoleic acid, 18:2n-6) and 22:6n-3, had no
significant effect on the cytokine-induced adhesion of leukocytes to HUVEC. Although
the fatty acids were presented to the cells with ethanol as diluent (0.1% v/v final
concentration), similar results were obtained using mixed fatty acid - DPC micelles.
Trypan blue exclusion and lack of [{\textsuperscript{51}}Cr] chromate release from labeled cells showed that
the cells remained viable under these experimental conditions. Furthermore, the
engineered fatty acids did not affect DNA synthesis, glucose metabolism and G3PDH
mRNA expression in HUVEC. MP3 caused the greatest suppression of TNF-\(\alpha\)-induced
neutrophil adhesion to HUVEC (Figure 11) and was, therefore, employed in further
studies. The magnitude of the suppressive effect of -MP3 was dependent on pre-treatment
time and concentration with significant effects observed with a pre-treatment time of 1 hr
and a concentration of \(\geq 5\) \(\mu\)mol/l. In addition, \(\beta\)-oxa 23:4n-6 inhibited the increase in
neutrophil adhesion to HUVEC induced by bacterial lipopolysaccharide (LPS) or PMA.

Effects of derivatives of MP3 (\(\beta\)-oxa-23:4n-6)

Derivatization of MP3 to methylated, saturated and 18-monohydroxy- and hydroperoxy-
forms abolished its inhibitory effect on TNF-\(\alpha\)-stimulated neutrophil adhesion to HUVEC
(Figure 12), demonstrating not only the specificity of the parent molecule but also that the
structure of the parent molecule is critical for activity.

Effects on TNF-induced expression of adhesion molecules on EC.
The inhibitory effect of \(\beta\)-oxa-23:4n-6 on adhesion was consistent with the ability of \(\beta\)-
oxa-PUFA to suppress the TNF-\(\alpha\)-induced expression of E-selectin (CD62E), intercellular
adhesion molecule-1 (ICAM-1; CD54) and vascular cell adhesion molecule-1 (VCAM-1;
CD106) adhesion molecules on HUVEC. As shown in Figure 13, maximum inhibition of
TNF-\(\alpha\)-stimulated E-selectin, ICAM-1 and VCAM-1 expression was observed after 4, 6
and 12 hr of cytokine treatment respectively, after which there was recovery (particularly
in the case of E-selectin and ICAM-1) up to 24 hr. The ability of the cells to regain their
capacity to express adhesion molecules confirms that the synthetic fatty acid did not affect
their viability. \(\beta\)-oxa-23:4n-6 inhibited the expression of E-selectin, ICAM-1 and VCAM-
1 molecules in a concentration-dependent manner, which corresponded with the levels
required to reduce neutrophil adherence. 20:4n-6 had no significant effect on HUVEC
adhesion molecule expression compared with β-oxa-23:4n-6. TNF-α-induced increase in expression of E-selectin mRNA was found to be substantially depressed by β-oxa-23:4n-6 treatment (Figure 13). β-oxa-23:4n-6 also inhibited LPS and PMA-induced, up-regulation of E-selectin, ICAM-1 and VCAM-1 induced by these agonists.

In vivo activity of β-oxa-23:4n-6 (MP3).
The β-oxa fatty acid was also found to be active in vivo. Mice sensitized with sheep erythrocytes were inhibited in ability to manifest a delayed type hypersensitivity reaction to this antigen if given an injection of β-oxa 23:4n-6 1 day prior to antigen challenge (Figure 14A). This illustrated an effect on chronic inflammation probably through the inhibition of T cells and monocytes binding to the endothelium. When an acute inflammatory reaction (24 hr) was induced in mice by intraperitoneal injection of LPS, treatment with β-oxa 23:4n-6 inhibited the neutrophil influx (Figure 11A). A similar inhibition of chronic inflammation was seen in terms of the inhibition of the mononuclear cell infiltrate after 72 hr (Figure 14A).

The in vitro effects of β-oxa-23:4n-6 on adhesion molecule expression on endothelial cells was confirmed in mice treated with LPS (Figure 14B). Mice treated with β-oxa-23:4n-6 showed a significant reduction in LPS-induced E-selectin expression in aortic endothelium.

Metabolism of β-oxa 23:4n-6 in HUVEC.
After incubation of HUVEC with β-oxa-23:4n-6 for 60 min, small amounts of three oxygenated fatty acids products were observed. The total ion chromatogram produced by electrospray MS of the combined products showed a molecular ion at m/z 365 (M+ + 1) (expected for mono-hydroxylated analogs of β-oxa-23:4n-6). Three daughter ions were found at m/z 264, 224 and 132 corresponding to loss of a C₆H₁₃O, C₉H₁₇O and C₁₆H₂₅O fragment, resulting from C₁₇-C₁₈, C₁₄-C₁₅ and C₇-C₈ bond cleavage, respectively. These fragments unambiguously confirm the identification of the three oxygenated products with mono hydroxyl group at carbons 18, 15, and 8 (Figure 15). The 15-hydroxylated derivative was the major component (>90%). Pre-treatment of HUVEC with
nordihydroguaiaretic acid (NDGA; a non-selective lipoxygenase inhibitor) markedly suppressed the formation of the oxygenated fatty acid products of β-oxa 23:4n-6, whereas indomethacin (a cyclooxygenase inhibitor) had no effect. Together, these results provide evidence that HUVEC converted β-oxa-23:4n-6 to 18-, 15- and 8- mono-hydroxylated derivatives (Figure 15) by the lipoxygenase enzyme pathway, i.e. an enzymatic process rather than by auto-oxidation. Isomeric forms of monohydroxylated 20:4n-6 are synthesized from 20:4n-6 by cells via the action of stereo-specific lipoxygenase enzymes (Spector et al, Prog. Lipid. Res. 27:271-323, 1988). In HUVEC the lipoxygenase activity is mainly attributed to the 15-lipoxygenase (Buchanan et al, Haemostasis 18:360-375, 1988). The lipoxygenase positional isomer specificity is determined by the carbon chain length from the methyl end of the fatty acid substrates. Since β-oxa-23:4n-6 has three additional carbon atoms in its chain compared to 20:4n-6, it is likely that the 18-, 15- and 8- monohydroxylated derivatives of β-oxa-23:4n-6 are formed by the 15-, 12- and 5-lipoxygenases respectively in HUVEC.

The importance of the 12-LO in the action of β-oxa 23:4n-6

Confluent second-passage HUVEC in 96-well tissue culture plates were pre-treated with 10 μmol/l NDGA (non-selective lipoxygenase inhibitor); 10 μmol/l baicalein (a specific 12-lipoxygenase inhibitor); 500 nM MK886 (an inhibitor of the 5-lipoxygenase activating protein), 10 μmol/l indomethacin (a cyclooxygenase inhibitor); 10 μmol/l Vitamin E (an antioxidant); or diluent (control) for 15 min. The cells were then further incubated with 20 μmol/l β-oxa-23:4n-6 or diluent (control) for 60 min followed by TNF-α (125U) for 4h. The expression of E-selectin adhesion molecule was determined by ELISA. While none of the inhibitors/antioxidants affected the ability of TNF to enhance E-selectin expression on HUVEC, the ability of β-oxa 23:4n-6 to suppress the action of TNF was reduced when the cells were pre-treated with either NDGA or baicalein but not with indomethacin, Vitamin E or MK886 (Figure 16). This indicated that conversion of β-oxa-23:4n-6 to an oxygenated product(s) via the 12-lipoxygenase pathway was important for the inhibitory activity of the fatty acid. It is unlikely that oxygenated products formed by the 15-
lipoygenase are involved in the inhibitory action of β-oxa-23:4n-6 because the 18-monohydroxy/hydroperoxy derivatives were inactive (Figure 12).

**Effects of β-oxa 23:4n-6 (MP3) on TNF-induced activation of intracellular signalling molecules.**

Examination of the effects of β-oxa 23:4n-6 on intracellular signalling molecules involved in TNF-induced expression of these adhesion molecules, showed that pre-treatment of HUVECs with the fatty acid did not affect the ability of TNF to stimulate p38, ERK and JNK.

The effects of the β-oxa PUFA on the IKK-NFκB pathway were also examined which is important in the stimulation of expression of adhesion molecules on endothelial cells (Read et al, J. Biol. Chem. 272:2753-61, 1997). In this pathway, IκB, which ordinarily sequesters NFκB in the cytoplasm, is phosphorylated by IKK. This phosphorylation targets IκB for degradation, thereby allowing the nuclear translocation of NFκB. HUVEC pre-treated with β-oxa 23:4n-6 showed marked inhibition of IκBα degradation (>92%) induced by TNF (Figure 17A). In comparison, the same concentration of DHA caused less than 50% inhibition of TNF-stimulated IκB degradation (Figure 17A).

The effects of β-oxa 23:4n-6 on TNF induced activation of NFκB was confirmed by examining the translocation of the NFκB to the nucleus. The data showed inhibition of translocation of NFκB to the nucleus (Figure 17B).

To see whether the effects of β-oxa 23:4n-6 on IκBα degradation could be due to inhibition of IKK activation, cells were pre-treated with β-oxa 23:4n-6, then stimulated with TNF and assayed for IKK activation. The results showed that β-oxa 23:4n-6 significantly inhibited the activation IKK (Figure 17C).

The data demonstrate that by placing an oxygen or sulphur atom in the β-position of a PUFA, molecules can be generated which vary in biological activities from the natural n-3.
PUFA. An important characteristic of the β-oxa/β-thia-compounds was their greatly reduced ability to stimulate the neutrophils respiratory burst but which retained or increased anti-inflammatory properties displayed by the n-3 PUFA. The β-oxa and β-thia PUFA significantly decreased the agonist-induced increase of neutrophil adhesion to the endothelium, while 20:4n-6 and 22:6n-3 showed no inhibition of this response under these conditions. However, longer term exposure of HUVEC to 22:6n-3 had previously been shown to decrease up-regulation of adhesion properties of these cells (De Caterina et al, Arterioscler Thromb. 14:1929-1936, 1994, Weber et al, Arterioscler Thromb. Vasc. Biol. 15:622-628, 1995). The most active of these newly synthesized compounds was β-oxa 23:4n-6. The corresponding β-thia 23:4n-6 was less active than this β-oxa compound.

This illustrates how fatty acids bearing the same structural elements can vary dramatically in activity depending on whether these contain an oxygen or sulphur atom in the β-position. The novel PUFA and in particular β-oxa 23:4n-6, are therefore, similar in biological properties to the 15-HPETE which was shown to lack the ability to stimulate oxygen radicals in neutrophils but inhibited leukocyte adhesion to endothelial cells (Huang et al, 1997 supra, Sethi et al, J. Lab. Clin. Med. 128:27-38, 1996) and TNF production by macrophages (Ferrante et al, 1997 supra).

Those skilled in the art will appreciate that the invention described herein is susceptible to variations and modifications other than those specifically described. It is to be understood that the invention includes all such variations and modifications. The invention also includes all of the steps, features, compositions and compounds referred to or indicated in this specification, individually or collectively, and any and all combinations of any two or more of said steps or features.
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CLAIMS

1. A method for the treatment or prophylaxis of a condition selected from a NFκB related or associated condition, a PKCβ related or associated condition, vascular or immunological conditions such as diabetes, inflammation, neurological conditions, cardiovascular disease and pain in a subject, said method comprising administering to said subject an effective amount of a compound having the structure of Formula (I):

\[
\begin{align*}
&\left[R_4\right]_d\left[R_5\right]_g \quad (I) \\
&\left[R_6\right]_e\left[R_7\right]_h \\
&\left[R_1\right]_i
\end{align*}
\]

wherein

- \( R_1 \) is a saturated or unsaturated hydrocarbon chain of from about 9 to about 26 carbon atoms and which is optionally carries one or more of a oxa, thia, hydroxy, hydroperoxy, epoxy and peroxy substitution;

- \( R_2, R_4 \) and \( R_6 \) may be the same and each is selected from \( \text{O}_2, \text{NO}, \text{NO}_2, \text{S(O)}_x, \text{C(H)}_y, \text{H}, \text{COOH}, \text{P(X)}_b(Y), \text{N(H)}_b, \text{C}=\text{O}, \text{OH}, \text{C}=\text{N}-\text{H}, \text{C}_{1-6} \text{ alkyl}, \text{C}_{1-6} \text{ alkoxy}, \text{amino}, \text{mono-acid di-C}_{1-6} \text{ alkylamino}, \text{C}_{1-6} \text{ alkylthio}, \text{S(O)}_x\text{C}_{1-3} \text{ alkyl}, \text{C}_{1-6} \text{ alkoxy carbonyl}, \text{halo selected from fluoro, chloro, bromo and iodo, oxo, amidino and guanidino, C}_{2-12} \text{ alkenyl, C}_{2-12} \text{ alkynyl, aryl, heteroaryl and cyano, wherein x and z are 0, 1 or 2 and y is 0, 1, 2 or 3 and X is O, S or NR}_{8}, \text{Y is OR}_{9}, \text{SR}_{10} \text{ or NR}_{11}\text{R}_{12} \text{ and R}_8, \text{R}_9, \text{R}_{10}, \text{R}_{11} \text{ and R}_{12} \text{ are selected from H, alkyl, alkenyl, alkynyl, aryl and heteroaryl, } \delta \text{ is 0 or 1;} \)
each of R₃, R₅ and R₇ is respectively \[(\text{CH}_2)_j \text{(COOH)}_k\], \[(\text{CH}_2)_m \text{(COOH)}_n\] and \[(\text{CH}_2)_p \text{(COOH)}_q\], wherein each of j, m and p is 0, 1, 2, 3, 4, 5 or 6, each of k, n and q is 0, 1 or 2, and each of l, o and r is 0 or 1,

each of c i and f is 0 or 1 or 2;

each of a, d and g is 0 or 1 or 2;

each of b, e and h is 0 or 1 or 2;

said administration being for a time and under conditions sufficient to prevent the condition or to ameliorate one or more symptoms of the condition.

2. The method of Claim 1 wherein the subject is a mammal.

3. The method of Claim 2 wherein the mammal is a human.

4. The method of Claim 1 wherein in Formula (I) each of i, c and f is 0 (zero), two of i, c and f is 0 (zero) or one of i, c and f is 0 (zero); or each of i, c and f is 1; two of i, c and f is 1 or one of i, c and f is 1; or each of i, c and f is two, two of i, c and f is two, or one of i, c and f is two.

5. The method of Claim 1 or 4 wherein in Formula (I) each of g, a and d is 0 (zero), two of g, a and d is 0 (zero) or one of g, a and d is 0 (zero); or each of g, a and d is 1; two of g, a and d is 1 or one of g, a and d is 1; or each of g, a and d is two, two of g, a and d is two, or one of g, a and d is two.

6. The method of Claim 1 or 4 or 5 wherein in Formula (I) each of h, b and e is 0 (zero), two of h, b and e is 0 (zero) or one of h, b and e is 0 (zero); or each of h, b and e is 1; two of h, b and e is 1 or one of h, b and e is 1; or each of h, b and e is two, two of h, b and e is two, or one of h, b and e is two.
7. The method of Claim 1 or 4 or 5 or 6 wherein the L-amino acid is selected from alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine and valine.

8. The method of Claim 1 or 4 or 5 or 6 wherein a chemical analog of an amino acid is selected from α-aminobutyric acid, α-amino-α-methylbutyrate, aminocyclopropane-, carboxylate, aminosobutyric acid, aminonorbornyl-, carboxylate, cyclohexylalanine, cyclopentylalanine, D-alanine, D-arginine, D-aspartic acid, methylmethionine, D-cysteine, N-methylnorleucine, D-glutamine, D-glutamic acid, methylornithine, D-histidine, N-methylphenylalanine, D-isoleucine, D-leucine, D-lysine, D-methionine, D-ornithine, D-phenylalanine, D-proline, D-serine, D-threonine, D-tryptophan, D-tyrosine, D-valine, D-α-methylalanine, D-α-methylarginine, D-α-methylasparagine, D-α-methyaspartate, D-α-methylcysteine, D-α-methylglutamine, D-α-methylhistidine, D-α-methylisoleucine, D-α-methyleneleucine, D-α-methyllysine, D-α-methylmethionine, D-α-methylornithine, D-α-methylphenylalanine, D-α-methylproline, D-α-methylserine, D-α-methylthreonine, D-α-methyltryptophan, D-α-methyltyrosine, D-α-methylvaline, D-N-methylalanine, D-N-methylarginine, D-N-methylasparagine, D-N-methylaspartate, D-N-methylcysteine, D-N-methylglutamine, D-N-methylglutamate, D-N-methylhistidine, D-N-methylisoleucine, D-N-methyleneleucine, D-N-methyllysine, N-methylcyclohexylalanine, D-N-methylornithine, N-methylglycine, N-methylaminobutyrate, N-(1-methylpropyl)glycine, N-(2-methylpropyl)glycine, D-N-methyltryptophan, D-N-methyltyrosine, D-N-methylvaline, γ-aminobutyric acid, L-t-butylglycine, L-ethylglycine, L-homophenylalanine, L-α-methylarginine, L-α-methylaspartate, L-α-methylcysteine, L-α-methylglutamine, L-α-methylhistidine, L-α-methlysleucine, L-α-methylisoleucine, L-α-methylmethionine, L-α-methylnorvaline, L-α-methylphenylalanine, L-α-methylserine, L-α-methyltryptophan, L-α-methylvaline, N-(N-(2,2-diphenylethyl)carbamylmethyl)glycine and 1-carboxy-1-(2,2-diphenyl-ethylamino)cyclopropane.

9. The method of Claim 1 or 4 or 5 or 6 wherein the cytokine is selected from BDNF, CNTF, EGF, EPO, FGF1, FGF2, FGF3, FGF4, FGF5, FGF6, FGF7, FGF8, FGF9, FGF10,
FGF11, FGF12, FGF13, FGF14, FGF15, FGF16, FGF17, FGF18, FGF19, FGF20, FGF21, FGF22, FGF23, G-CSF, GM-CSF, IFNα, IFNβ, IFNγ, IL1, IL2, IL3, IL4, IL5, IL6, IL7, IL8, IL9, IL10, IL11, IL12, IL13, IL14, IL15, LIF, MCP1, MCP2, MCP3, MCP4, MCP5, M-CSF, MIP1, MIP2, NGF, NT 3, NT4, NT5, NT6, NT7, OSM, PBP, PBSF, PDGF, PF4, RANTES, SCF, TGFα, TGFβ, TNFα, TNFβ, TPO, VEGF, GH and insulin.

10. The method of Claim 1 or 4 or 5 or 6 wherein the apoptotic proteins is selected from A1, A9, A20, A46R, A52R, A53, A238L, Aac11, AATF, AATYK, ABIN1, ABIN-1, ABIN2, acidic sphingomyelinase, Acinus, Act1, Act2, activin, AD3LP, AD5, ADAR, adrenomedullin, aggrecan, AMAM17, 33, AI1, AIF, AILIM, AIM2, AIR, AITR, Akt, ALCAM, ALG2, ALG3, ALG4, ALP, Alix, Armadillo, AMAC1, AMH, AMID, Amida, angiotensinogen, Ankyrin, ANT1, AO7, AP1, Apaf-1, APC, APC2, APCL, APE1820, APJ, APO-1, APO-2, APO-3, Apopain, APP1, APP2, Apr, APRIL, ARA54, ARC, ARF, arakdia, ARH1, 2, ASC, Ash2, Ask1, Ask2, ASPP1, ASPP2, AT2R1, AT2R2, ATAR, ATF1, ATF2, ATF3, ATF4, ATM, atona, ATR1, AUF1, Aven, AVP, AvrA, AvrBsT, Axam, Axin, Axin 2, Axi, b-catenin, b-TrCP, B28R, B7-1, B7-2, B7h2, B7RP1, Bach2, Bad, BAFF, BAG -1,-2, -3, -4, -5, Bak, BALF1, Bam32, BAP-1, BAP31, BAP29, BAR, BARD1, BAT3, Bax, BBe3, BCA1, BCAN, Bel-2, BCL2, Bcl-3, Bcl-10, BCL10, Bcl-G, Bcl-Rambo, Bcl-w, Bcl-x, beclin, BEHAB, BERP, Bfl-1, BFL1, BG1, BG2, BG4, BG5, BHP1, BHRF1, BI-1, Bid, Bif-1, Bik, Bis, Bim, Bimp-1, Bimp1, Bimp2, Bimp3, BIR1, BIRP, BL-CAM, BLC, Blk, BLNK, BLR1, BLyS, BMI-1, BmP109, BNIP3, BNIP3a, BNIP3L, Bok, bone sialoprotein, bonus, Boo, BPI, BRAL1, BRAG-1, BRAP, Bravo, BRCA1, BRN3a, BRN3b, BRN3c, brevican, BPR, BSAC, BUFFY, C1q, C1r, C1s, C2, C3, C4a, C4b, C5, C6, C7, C8a, C8b, C8g, C9, C1qBP, C3aR, C4BPa,b, C5R1, CR2, CIITA, C5L, c-E10, c-FLIP, c-Fms, c-Fos, c-IAP1, c-IAP1, c-IAP-1, c-IAP2, c-IAP2, c-IAP-2, c-Jun, c-Myc, c-Rel, cactus, CAD, cadherin, E, N, P, VE, calcineurin, CARD4, CARD7, CARD9, CARD10, CARD11, CARD12, CARD14, CARDIAK, Carma1, CARMA-1, CARMA2, CARMA3, CARMA, CARMEN, CAP1, CAR1, CART1, CAS, CAS-L, caspase -1,-2, -3, -4, -5, -6, -7, -8, -9, -11, -12, -13, -14, Casper -1, -2, -3, -4, -5, -6, -7, -8, -9, -10, -11, -12, -13, -14, -15, -16, -17, -18, -19, -20, -21, -22, -23, -24, -25, -26,
27, -28, CASH, CBL, CBL-B, CBL-C, CC-CKR-6, CCF, CCL, CCP, CCRs, CD2, CD3, CD4, CD5, CD6, CD7, CD8, CD9, CD11, CD14, CD18, CD19, CD20, CD21 (CR2), CD22, CD23, CD25, CD27, CD27L, CD28, CD28LG1, CD28LG2, CD29, CD30, CD31, CD32, CD33, CD34, CD35, CD36, CD40, CD40L, CD41, CD43, CD44, CD45, CD46, CD47, CD48, CD49, CD50, CD53, CD54, CD55, CD56, CD58, CD59, CD61, CD62E, L, H, CD66, CD63, CD64, CD66a-e, CD67, CD70, CD72, CD74, CD79a, b, CD80, CD84, CD85a-m, CD86, CD88, CD89, CD90, CD92, CD94, CD95, CD96, CD97, CD99, CD100, CD101, CD102, CD104, CD105, CD106, CD108, CD112, CD115, CD116, CD117, CD119, CD120a-b, CD121a-b, CD122, CD123, CD124, CD125, CD126, CD127, CD128a-b, CD130, CD131, CD132, CD134, CD135, CD136, CD137, CD140a, CD140b, CD143, CD144, CD146, CD147, CD148, CD150, CD151, CD152, CD153, CD154, CD155, CD158a-z, CD159, CD160, CD161, CD162, CD166, CD178, CD180, CD183, CD184, CD195, CD207, CD229, CD244, CDC2, CDC25, CDC42, CDK1, CDK2, CDK5, CDM, CEA, CEAL, CEACAM1, 6, C/EBP, CED1, CED2, CED3, CED4, CED5, CED6, CED7, CED8, Ced-9, CED10, CED11, CED12, CED, CEP-1, CES1, CES2, CES3, CETP, CeTRAf, Ceza1ne, CRGR19, CGRP, Che1, Che-1, CHFR, chemokines, CHOP, CHUK, cIAP1, cIAP2, c-IAP1, c-IAP2, c-IAP-1, c-IAP-2, CIDE -A, CIDE-B, CIKS, CIN85, CIP-1, CIPER, CISK, Ckb-8, CRK1, 2, 3, 4, 5, CRKL1, Clan, CLAP, CLARP, CMD1, CMH1, CMKBR1, 2, 3, 4, 5, 6, CMPD1, conductin, Cop9 subunit 3, COP11, COP53, COP55, COT, COX-1, COX-2, CPAN, CPP32, CPZ, CRADD, CRAW, CR8, CREB, CREM, Crk-II, crinkled, crrmA, crrmB, CSBP1, CSMF, CSN3, Csp-1, Csp-2, Csp-3, CSPPG2, 3, Csx, CTAck, CTAP3, CTGF, CTLA4, cytochrome c, cytosolic PL A2, CXCLs, CXC-R3, DAAM1, Dad1, DAD-1, Damm, DAP1, DAP2, DAP4, DAP5, DAP12, DAP kinase 1, DAPP1, DAXX, Dborg1, dCAD, DCCK1, DCP1, Dep-1, Dep-2, DeR-1, DeR-2, DeR-3, DD2, Decay, DED, DEDAF, DEDD, DEDD2, dedp101, defensin, DEFT, dFADD, DFF, DFF35, DFF40, DFF45, DG17, Diabo, DIAP1, DIAP2, Dickkopf, DIF, DIF2, DIHA, DIK, Drosophila IKK, PKCS8-interacting protein kinase, DIO1, DIP, dishevelled, diubiquitin, DKK1, 2, 3, 4, DLAK, DLK, DMDL, DNase II, Diva, DONG1, Dorsal, DP1, DP2, DP5, Drobl, DRP-1, DocA, dock188, Dok1, Doom, dorf1, DR3,4,5,6, DRAK 1-2, DREAM, DREP -1, -2, -3, CD, DrICE, DRONC, DRP1, DTR, DTS, DUSP, E1.1, E1B 19K, E10, E2Fs, E4BP4, E4ORF4, E8, E4, E48, E3RS, eae7, Ear7, EBAF, EBI1, EBP1, EBI6,
ECSIT, EDA, EDAR, Edradd, EFP, EGL1, Egr1-2-3, EHF, eIF-2aK, Eiger, ELAM, ELF2, ELK1-4, EMR1, ENA78, Endofin, Endoglin, Endophilin B1, endothelin, ENG, eNOS, eotaxin 1,2, ERN1, ERICE, ES18, Ets-1-2, ER81, ErbAa, ERG, ERM, ESE2, Eskine, ETV1, 2,3,4,5,6, exodus-1, exodus-2, exodus-3, FADD, Fas associated via death domain, FAF1, FAIM, FAN, FANCC, Fas, FAST, FAT10, fb1, FCAR, FELL, FEM-1, FEM-2, FHR1-2, FHR-3, FHR-4, TKP4, FKBPs, FIGF, FIL1d, e, eta, zeta, FIP2, FIP3, FKSG2, FIST, FKHL12, FKHR, FKHL11, FLAME-1, FLAME-3, FLAME3, FLASH, FLDED-1, FNI-1, FNI, FLICE, FLICE2, FLICE-2, FLIP, FLT3L, Fliz1, Fln29, Fms, Fnk, fortilin, Fos, FOXO1A, FOXO3A, FOXE3, FPV039, Fra1, Fra2, Fractalkine, FRAP, FREAC8, Frizzled, Fzd, Fz, FRING, FRP1-2-3, FRP1(ATR), frpHE, FRZB-PEN, Fsp27, FUS, FUS6, Fusin, FXY, FY, G-coupled receptors, G10P1, G25K, G4R, G6C, G6E, GADD34, GADD45, GADD153, GATA1,2,3,4,5,6, GBP2, GCP2, GDFs, gelsoin, Gfi-1, Gfi1, GFRP1, Gilz, gingipain, GITR, GL50, glycodelin A, GM2A, gp34, GPR5, GPR9, GPR9-6, Granzyme B, Grim, GRMP, Groa, Grob, GRS, GSK3, H2TF1, H731-like, Hakai, HB-EGF, Hck, HF1, HFB30, HFL3, HHARI, hIAP-1, hIAP1, Hid, HIF1 3, HIP1, HIP116, HIPPI, HIPK1,2,3, histamine receptors, HIVEP1,-3, HIV-EP1, HLTF, HM85, HM89, HM145, HMR, HNRPD, HRD1, Hrk, HtrA2, Huntingtin, HVEM, HVEML, HYP, IAP-1, IAP1, IAP2, IAP, iAPP, ICAD, ICBP90, ICE, ICEBERG, ICE-LAP3, ICE-LAP6, ICErel-II, ICErel-III, Ich1, ICH-1, Ich2, ICH-2, Ich3, ICH-3, ICOS, I-TRAFF, I-LICLE, IEX1m IFI, IFIT-1, IFIT-2, IFIT-3, IFIT-4, IFP35, IgE Fc receptor, IGF1 and its receptor, IGFBP-3, IKAP, Ikaros, IKB-1, Ilk-b-a, Ilk-b-b, Ilk-b-e, I KKAP1, IKK-1, IKK-2, IKK-a, IKK-b, IKKg, interleukins, interleukin receptors, IL1 antagonist, anti-IL1, IL1RacP, IL8R1, ILA, ILC, ILP, ILP-1, ILP-2, ILT1-11, ING1, ING2, ING3, Inhibin, INK4, INK4A, integrin, IP10, INP10, IP30, Ipaf, IRAK, IRAK2, IRAM-M, IRE1, RE1p, IRE, IRF, IRTAI-5, ISGF3g, ITA, It, JAB1, Jak1, 2, 3, JDP2, JIK, JN, K, K13, KARAP, KBF-1, KBF-2, KBF3, KDS, KE05, KET, lcf-1, KIAA, Killer, KIR2DL1-5, KIR2DS1-6, KROX2, L-Myc, lactalbumin 3, LAG1, LAIR1, LALBA, LAM, LAP1, LAP3, LAR, LARD, LARC, LATS1, 2, LBP, Lck, LCP2, LD78b, LEFTY, LESTR, Leu1, Leu8, Leu14, leukotactin, LFA3, LFG, LICE, LICE2, LIF, LIGHT, LIR1, LIR-2, LIR-3, LIR-4, LIR-5, LIR-6, LIR-7, LIR-8, Livin, LMP1, LMW5-4, LOK, Lot1, LRDD, LRP, Low affinity NGFR, LTA, LTb, LTbR, LTP2, Ly63, lymphotactin, Ly1, Lyf1, Lysozyme, Lyt-10, LYVE1, LZK...
M11, M159L, M160L, MA-3, MACH, Mad, Mad3, MADD, Maf, c-Maf, makorin, MAL, MALT, MAP-1, MAPKKKs, MAPKKs, MAPKs, Math1, Max, MBD4, MBLR, MBP1, MCL1, Mch2, Mch3, Mch4, Mch5, Mch6, MCP1, MCP2, MCP3, Mda-7, MD-1, MD-2, Mdm2, Mdm4, Mdp62, mE10, MEF2a, MEKKs, Mel-18, MEMD, Meprin, metacaspase, MIC1, MID1, MIF, MIG, MIHC, MIP1-2-a-2b, MIP-T3, MIR, MIS, MITF, MKK6, Mkl1, MKP1, ML-1, ML-IAP, MLN64, MLX, MMP-1, MMP-2, MMP-3, MMP-4, MMP-5, MMP-6, MMP-7, MMP-8, MMP-9, MMP-10, MMP-11, MMP-12, MMP-13, MMP-14, MMP-15, MMP-16, Mnda, Mnt, Mob1, mod (mdg4), MORT1, MIF1, 2, MRFP, MRIT, Mxx1, Mxx2, MTAP44, Mtd, mTOR, Muc1, MUC2, MUL, MURF-1-2-3, myp-nop30, Mxa, Mxb, Mxi1, Mxi2, MYAK, Myc, MyD88, MyD118, MyLk, myoblast city, N-Myc, Naf1, NAIP, Nalp1, Nalp2, NAP2, Nbk, NBS1, NCA, NCAM, Ncc-1, Ncc-2, Ncc-3, NCC-4, Nd1, neural sphingomyelinase, neuralin, Nemo, Neoegenin, neuroactin, Neurocan, NF-kB, NF-X1, NFATs, NFIL3, NFIL6, NFkB1, 2, Nip1, Nip2, Nip3, NipK, NIK, Nix, NKAT1-9, NKX2-5, nNOS, Notch, Nod-1, Nod-2, nop30, Nor-1, Nos2, Nos2B, Nos3, Nov, Noxa, Np10, Np95, Npc2, Npy3R, Nr-CAM, Nr3, Nr13, Nr-13, Nrage, NRIF1, nucleolin, Nur77, NY-REN-64, OCIF, ODF, ODFR, Oias, Orf16, posteprotein, OSX, Ox40, Ox40L, Opg, Opgl, Osi, osteoconectin, osteoponti, p14, p16, p33ing1, P35, P38, P49, P49, P55, P52, P53AIP1, P53DINP1, P55, P60, P62, P62Dok, P63, P65, P73, P75NTr, P84, P100, P105, P193, P202, Pac1, Pacap, PacT, Paf400, PAG-3, PAG608, Pak1, Pak2, Pak3, Pap1, Par4, paracaspase, PARC, Park2, parkin, PARP, Pax-2, Pax-3, Pax-5, PAX-8, PBEF, PBP, PD1, PDGF, Pea15, Pellino, Perk, Perp, Pek, Pelle, Pex10, Pf4, Pgrp, PI3k, Pidd, Pik-1, Plab, Pik, Pik3, Pkc, Pkr, PKY, Plagl1, Plaidd, Pla2, Plc, PLD, Pli, Pml, Pmp41, Posh, Ppp1A, PP14, PP2Ca, PrKR, PrSS25, polycystin 1, polimin, PrGI, PrK, PRl, prolatin receptor, Ps-1, Ps-2, Psca, Psmd-11, Psmd-12, Psmd-13, Psmd-14, Psp-c, PsK, Pssalre, Pten, PtK1, PTPs, PTP1C, PTP2C, PTP1G, PtPL1, Pu.1, puckered, Pum, Q2/2, Rac, Rai, Rantes, Rax, Rb, Relish, RelT, Raf, RANK, RANKL, RAIDD, RBBP6, RBQ1, Rem, Reaper, RelA, relaxin H1, H2, H3, RelB, Requiem, Rfp, Rfpl-1-2-3, Rgs, RhoA, Ricks, Rigs-G, Ro52, Ro 60kDa, ROC-1, ROC-2, RORgamma, ROX, Riff, Rip, Rip2, Rip3, RnM561, Rnf, RP-8, RP8, R105, Rpr, RRP5, RyBP, S9, S152, SAG, Salvador, Sap1, Sapk2A, Sara,
SARP 1,2,3, Sav, Sco2, SCA-2, SCC-S2, SCF, SCDGF, SCM1-1a, Scythe, SDF1, selectin L-E-P, SENP1, SENP2, sentrin/SUMO-specific protease, SETA, SFRP1-2-3-4-5, SFTP2, SFTPC, SGK, SGL, SGN5, SH2D1A, SHP1, 2, Siah, SIMPL, SIP27, SIP18, SIR2, SIVA, SLC, SLK, SLP-65, SLP-76, SLUG, Smac, SMADs, SMARCA3, SMN, SMT 3 A, B, 3C, SNAIL, SNF2L3, SODD, somatostatin, Son3, SOX9, SP5, SP-C, SPARC, sphingomyelinase, Smase, SPOP, SPP1, SPRK, Spatzle, SFRP1,2,5, SS-56, SSA, SSA1, SSA2, ST2L, stabilin 1-2, STATs, STCP1, STG6, STEP, STM-2, Stra3, STRICA, Substance P, SUMO1, survivin, SYK, SY, T cell receptor, T2BP, T6BP, TAB1, Tab2, Tabby, TACI, TACTILE, Tag7, tachykinin, TAJ, TAK1, Tak1, TALL-1, TANK, TAO1, TAO2, TARC, TBX1, TBX-2, TBX-3, TBX-4, TBX-10, TBX-18, TBX-19, TBX-20, TBX-21, TBX-22, TCA3, TCA-3, TC1, TC2, TCR, TCTP, TDAG51, TEAP, TECK, TEGT, TEL, (TEL1), TEL2 (TELb), telokin, TERF, TFF, TGb, TGFβ-1, TGFβ-2, TGFβ-3, THG1, THRa, Thy-1, TIA1, TIAP, TIEG, TIF1, TIFγ, TIL6, TIMP1-2-3, TIP49, Tip60, TIRAP, TIS, TLRs, TLS, TMS1, TNFa, TNFAIP3, A20, TNFAIP6, TNFb, TNF-C, TNFR1, TNFR2, TNFR-II, TNFRSF1-19, Toll, Tollo, Tollip, TONEBP, Tos5, Tp44, TPL-2, TR3, TR2L, TRABID, TRADD, TRAF, TRAF1, TRAF1(Dm), TRAF2, TRAF2(Dm), TRAF3, TRAF4, TRAF5, TRAF6, TRAF6(Dm), TRAFamn, TRAIL, TRAIL-R2, TRAMP, TRANCE, TRC8, TRIAD1-3, TRIF, TRIM, TRIP15, TRF-1, TRF-2, TRF1, TRF2, traube, TRDL-1, TRG, TRH, TRICK2, TRIP, Tristetraproline, TROY, TRRAP, TSC-22, TSC-22R, TTRAP, Tube, TUCAN, TWEAK, TX, TXBP151, TY, Tyk, UBC7BP, UL36, UL37, Ulp, Unc5, UNC5h3, Urinary, stone protein (SPP1), USP7, usurpin, uterophi, vasopressin, vav, vav1, vav2, vav3, vav-1, vav-2, vav-3, versican, vICA, VIAF1, vBcl-2, VEG1, VEGF, Ventroptin, VG-1, VG71, VHR, v-IAPs, VI, warts, Wengen, WIG1, WISP-1, 2, 3, Wnt, WSL-1, WT1, WW45, WWOX, XAF1, XAP4, XCL1, 2, XEDAR, XIAP1, xRl, xRll, XICE, XICEa, XICE, Yama, YopJ, YY1AF, Zac, Zac1, ZAP70, ZBP89, zf3, ZFP26, ZFP127, ZH-DR, ZNF-40, ZNF-124, ZNF-148, as TFs, ZNF-144, ZNF-147, ZNF-179, ZNF-313, ZNF-364 as RING, ZIP-kinase, ZPR, 18 wheeler, 24.6K Glu/Pro-rich, 4-1BB, 4-1BBL, 4-1BB ligand and 53BP2, 7TM.

11. The methods of Claim 1 or 4 or 5 or 6 wherein the pro-survival protein is selected from Bcl-2, Bcl-XL, Mcl-1 and A1.
12. The method of Claim 1 or 4 or 5 or 6 wherein the compound is selected from

- 18:3n-3  
- 20:4n-6  
- 20:5n-3

- 22:6n-3  
- 23:4n-6  
- 15-OOH-20:4n-6

- β-oxa-23:4n-6 (MP3)  
- β-oxa-21:4n-6 (MP4)  
- β-oxa-21:3n-6 (MP5)  
- β-oxa-25:6n-3 (MP6)

- β-oxa-21:3n-3 (MP5)  
- 16-OH-β-oxa-21:3n-3 (TR2)
\[ \begin{align*}
\beta\text{-}\text{thia-21:0 (MP2)} & \quad \beta\text{-}\text{thia-25:6n-3 (MP14)} \\
\beta\text{-}\text{thia-21:3n-6 (MP9)} & \quad \beta\text{-}\text{thia-23:4n-6 (MP8)} \\
\beta\text{-}\text{thia-21:3n-3 (MP10)} & \quad \alpha\text{-}\text{carboxymethyl- \beta\text{-}thia-23:4n-6 (MP15)} \\
\gamma\text{-}\text{thia-22:3 (n-6)} & \quad \gamma\text{-}\text{thia-24:4 (n-6)} \\
\gamma\text{-}\text{thia-22:3 (n-3)} & \quad \gamma\text{-}\text{thia-25:6 (n-3)} \\
15\text{-OOC(CH}_3)_2\text{OCH}_3\text{-20:4n-6 (MP16)} & \quad 15\text{-OOC(CH}_3)_2\text{OCH}_3\beta\text{-}\text{oxa 23:4n-6 (MP17)}
\end{align*} \]
20:4n-6 Gly (PT1) 22:6n-3 Asp (PT6)

20:4n-6 Asp (PT2)

20:5n-3 Gly (PT3) 18:3n-6 Gly (PT7)

20:5n-3 Asp (PT4) 18:3n-6 Asp (PT8)

22:6n-3 Gly (PT5) 18:3n-3 Asp (PT10)
13. The method of Claim 1 wherein the treatment is for pain including *inter alia* neuropathic or neurological pain, chronic pain, acute pain, migraine, headache inflammatory pain, postoperative pain, pain due to multiple sclerosis, Parkinson's disease or other neurological or autoimmune disorder or following or during periods of anxiety, delayed onset muscle soreness, burns or during or following infection or a convulsion, post-poliomyelitic pain, bipolar disorder, panic attack or epilepsy.

14. The method of Claim 1 wherein the treatment is for depression, including major depression (single episode, recurrent, melancholic), atypical, dysthymia, subsyndromal, agitated, retarded, co-morbid with cancer, diabetes, or post-myocardial infarction, involutinal, bipolar disorder, psychotic depression, endogenous and reactive, obsessive-compulsive disorder, or bulimia. In addition, NAALADase inhibitors can be used to treat patients suffering from pain (given alone or in combination with morphine, codeine, or
dextroproposyphene), obsessive-compulsive personality disorder, post-traumatic stress disorder, hypertension, atherosclerosis, anxiety, anorexia nervosa, panic, social phobia, stuttering, sleep disorders, chronic fatigue, cognition deficit associated with Alzheimer's disease, alcohol abuse, appetite disorders, weight loss, agoraphobia, improving memory, amnesia, smoking cessation, nicotine withdrawal syndrome symptoms, disturbances of mood and/or appetite associated with pre-menstrual syndrome, depressed mood and/or carbohydrate craving associated with pre-menstrual syndrome, disturbances of mood, disturbances of appetite or disturbances which contribute to recidivism associated with nicotine withdrawal, circadian rhythm disorder, borderline personality disorder, hypochondriasis, pre-menstrual syndrome (PMS), late luteal phase dysphoric disorder, pre-menstrual dysphoric disorder, trichotillomania, symptoms following discontinuation of other antidepressants, aggressive/intermittent explosive disorder, compulsive gambling, compulsive spending, compulsive sex, psychoactive substance use disorder, sexual disorder, schizophrenia, premature ejaculation, or psychiatric symptoms selected from stress, worry, anger, rejection sensitivity and lack of mental or physical energy.

15. The method of Claim 1 wherein the treatment is for Moderate Mental Retardation, Severe Mental Retardation, Profound Mental Retardation, Unspecified Mental Retardation, Autistic Disorder, Pervasive Development Disorder NOS, Attention-Deficit Hyperactivity Disorder, Conduct Disorder, Group Type, Conduct Disorder, Solitary Aggressive Type, Conduct Disorder, Undifferentiated Type, Tourette's Disorder, Chronic Motor or Vocal Tic Disorder, Transient Tic Disorder, Tic Disorder NOS, Primary Degenerative Dementia of the Alzheimer Type, Senile Onset, Uncomplicated, Primary Degenerative Dementia of The Alzheimer Type, Senile Onset, with Delirium, Primary Degenerative Dementia of the Alzheimer Type, Senile Onset, with Delusions, Primary Degenerative Dementia of the Alzheimer Type, Senile Onset, with Depression, Primary Degenerative Dementia of the Alzheimer Type, Presenile Onset, Uncomplicated, Primary Degenerative Dementia of the Alzheimer Type, Presenile Onset, with Delirium, Primary Degenerative Dementia of the Alzheimer Type, Presenile Onset, with Delusions, Primary Degenerative Dementia of the Alzheimer Type, Presenile Onset, with Depression, Multi-infarct dementia, Uncomplicated, Multi-infarct dementia, with Delirium, Multi-infarct Dementia, with
Delusions, Multi-infarct Dementia, with Depression, Senile Dementia NOS, Presenile Dementia NOS, Alcohol Withdrawal Delirium, Alcohol Hallucinosis, Alcohol Dementia Associated with Alcoholism, Amphetamine or Similarly Acting Sympathomimetic Intoxication, Amphetamine or Similarly Acting Sympathomimetic Delusional Disorder, Cannabis Delusional Disorder, Cocaine Intoxication, Cocaine Delirium, Cocaine Delusional Disorder, Hallucinogen Hallucinosis, Hallucinogen Delusional Disorder, Hallucinogen Mood Disorder, Hallucinogen Posthallucinogen Perception Disorder, Phencyclidine (PCP or Similarly Acting Arylcyclohexylamine Intoxication, Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Delirium, Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Delusional Disorder, Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Hood Disorder, Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Organic Mental Disorder NOS, Other or unspecified Psychoactive Substance Intoxication, Other or Unspecified Psychoactive Substance Delirium, Other or Unspecified Psychoactive Substance Dementia, Other or Unspecified Psychoactive Substance Delusional Disorder, Other or Unspecified Psychoactive Substance Hallucinosis, Other or Unspecified Psychoactive Substance Mood Disorder, Other or Unspecified Psychoactive Substance Anxiety Disorder, Other or Unspecified Psychoactive Substance Personality Disorder, Other or Unspecified Psychoactive Substance Organic Mental Disorder NOS, Delirium, Dementia, Organic Delusional Disorder, Organic Hallucinosis, Organic Mood Disorder, Organic Anxiety Disorder, Organic Personality Disorder, Organic Mental Disorder, Obsessive Compulsive Disorder, Post-traumatic Stress Disorder, Generalized Anxiety Disorder, Anxiety Disorder NOS, Body Dysmorphic Disorder, Hypochondriasis (or Hypochondriacal Neurosis), Somatization Disorder, Undifferentiated Somatoform Disorder, Somatoform Disorder NOS, Intermittent Explosive Disorder, Kleptomania, Pathological Gambling, Pyromania, Trichotillomania and Impulse Control Disorder NOS.

16. The method of Claim 1 wherein the treatment is for Schizophrenia, Catatonic, Sub-chronic, Schizophrenia, Catatonic, Chronic, Schizophrenia, Catatonic, Sub-chronic with Acute Exacerbation, Schizophrenia, Catatonic, Chronic with Acute Exacerbation, Schizophrenia, Catatonic, in Remission, Schizophrenia, Catatonic, Unspecified,
Schizophrenia, Disorganized, Chronic, Schizophrenia, Disorganized, Subchronic with Acute Exacerbation, Schizophrenia, Disorganized, Chronic with Acute Exacerbation, Schizophrenia, Disorganized, in Remission, Schizophrenia, Disorganized, Unspecified, Schizophrenia, Paranoid, Subchronic, Schizophrenia, Paranoid, Chronic, Schizophrenia, Paranoid, Sub-chronic with Acute Exacerbation, Schizophrenia, Paranoid, Chronic with Acute Exacerbation, Schizophrenia, Paranoid, in Remission, Schizophrenia, Paranoid, Unspecified, Schizophrenia, Undifferentiated, Sub-chronic, Schizophrenia, Undifferentiated, Chronic, Schizophrenia, Undifferentiated, Sub-chronic with Acute Exacerbation, Schizophrenia, Undifferentiated, Chronic with Acute Exacerbation, Schizophrenia, Undifferentiated, in Remission, Schizophrenia, Undifferentiated, Unspecified, Schizophrenia, Residual, Sub-chronic, Schizophrenia, Residual, Chronic, Schizophrenia, Residual, Subchronic with Acute Exacerbation, Schizophrenia, Residual, Chronic with Acute Exacerbation, Schizophrenia, Residual, unspecified, Delusional (Paranoid) Disorder, Brief Reactive Psychosis, Schizophreniform Disorder, Schizoaffective Disorder, induced Psychotic Disorder, Psychotic Disorder NOS (Atypical Psychosis), Bipolar Disorder, Mixed, Severe, without Psychotic Features, Bipolar Disorder, Manic, Severe, without Psychotic Features, Bipolar Disorder, Depressed, Severe, without Psychotic Features, Bipolar Disorder, Mixed, with Psychotic Features, Bipolar Disorder, Manic, with Psychotic Features, Bipolar Disorder, Depressed, with Psychotic Features, Bipolar Disorder NOS, Major Depression, Single Episode, with Psychotic Features, Major Depression, Recurrent with Psychotic Features Personality Disorders, Paranoid Personality Disorders, Schizoid, Personality Disorders, Schizotypal, Personality Disorders, Anti-social, Personality Disorders and Borderline.

17. The method of Claim 1 wherein the treatment is for Anxiety Disorders, Panic Disorder, Panic Disorder with Agoraphobia, Panic Disorder without Agoraphobia, Agoraphobia without History of Panic Disorders, Social Phobia, Simple Phobia, Organic Anxiety Disorder, Psychoactive Substance Anxiety Disorder, Separation Anxiety Disorder, Avoidant Disorder of Childhood or Adolescence, and Overanxious Disorder.
18. The method of Claim 1 wherein the treatment is for cardiovascular disease includes strokes and any condition of the systemic vasculature and includes atherosclerosis, chronic heart failure and general heart disease.

19. A compound of general Formula (I)

\[
\left[\begin{array}{c}
[R_6]_{h-g} \cdot [R_7]_{h}
\end{array}\right]_i \\
R_1 \cdot \left[\begin{array}{c}
[R_2]_{a-b} \cdot [R_3]_{b}
\end{array}\right]_c \\
\left[\begin{array}{c}
[R_4]_{d-e} \cdot [R_5]_{e}
\end{array}\right]_f
\]

wherein

- \( R_1 \) is a saturated or unsaturated hydrocarbon chain of from about 9 to about 26 carbon atoms and which is optionally carries one or more of a oxa, thia, hydroxy, hydroperoxy, epoxy and peroxy substitution;

- \( R_2, R_4 \) and \( R_6 \) may be the same or different and each is selected from \( O_2, NO, NO_2, S(O)_x, C(H)_y, H, COOH, P(X)_0(Y), N(H)_z, C=O, OH, \) each of \( j, m \) and \( p \) is 0, 1, 2, 3, 4, 5 or 6, each of \( k, n \) and \( q \) is 0, 1 or 2, and each of \( l, o \) and \( r \) is 0 or 1;
each of c, i and f is 0 or 1 or 2;

each of a, d and g is 0 or 1 or 2; and

each of b, e and h is 0 or 1 or 2.
Figure 1
Effect of EPUFA on oxygen radical production

![Graph showing the effect of EPUFA on oxygen radical production.]

**Figure 2**
Figure 3
Figure 4
Figure 7
Figure 8
<table>
<thead>
<tr>
<th></th>
<th>Low Glucose</th>
<th>Low Glucose +MP5</th>
<th>High Glucose</th>
<th>High Glucose +MP5</th>
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</thead>
<tbody>
<tr>
<td>Control rat</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetic rat</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetic rat +MP5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Figure 9**
Figure 10
Figure 11
Figure 12
Figure 13
**Figure 14**

**A**

<table>
<thead>
<tr>
<th></th>
<th>% of control</th>
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</thead>
<tbody>
<tr>
<td>DTH</td>
<td>***</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>**</td>
</tr>
<tr>
<td>Mononuclear cells</td>
<td>**</td>
</tr>
</tbody>
</table>

Inflammatory response:

- Footpad reaction
- Peritoneal inflammation

**B**

<table>
<thead>
<tr>
<th>% of control</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-oxa-23:4n-6</td>
</tr>
</tbody>
</table>

E-selectin in aortic endothelium
\[ \beta\text{-}\text{oxa-23:4 ( n-6)} \]

8-monohydro- \( \beta\text{-}\text{ox-23:4 n-6) xy} \)

15-monohydro- \( \beta\text{-}\text{ox-23:4 n-6) xy} \)

18-monohydro- \( \beta\text{-}\text{ox-23:4 n-7) xy} \)

**Figure 15**
Figure 16

% loss of the inhibitory effect of β-oxa 23:4n-6 on TNF-induced E-selectin expression

Inhibitor

- Vitamin E
- NDGA
- Baicalin
- MK886
- Indomethacin
Figure 17