Claims

1. A water soluble fatty acid derivative comprising a fatty acid or fatty acid ester attached to a water soluble linker, said fatty acid derivative stably attached to a therapeutic protein, wherein the water soluble linker comprises a water soluble polymer and at least one functional group attached to the therapeutic protein, wherein the functional group is an aminooxy group.

2. The fatty acid derivative according to claim 1 that binds human serum albumin (HSA) in vitro or in vivo.

~~3. The fatty acid derivative according to any of claims 1-2 that~~ has increased half-life relative to a native therapeutic protein, and.

~~4. The fatty acid derivative according to any of claims 1-3~~ wherein the fatty acid is a saturated fatty acid or unsaturated fatty acid.

~~5. The fatty acid derivative of claim 4 wherein the fatty acid is a saturated fatty acid.~~

3~~6~~. The fatty acid derivative of claim 2 ~~4~~ wherein the fatty acid is a branched chain fatty acid.

4~~7~~. The fatty acid derivative according to any of claims 1-3~~6~~ wherein the fatty acid comprises a chain length selected from the group consisting of C10, C12, C14, C16, C18, C20, C22, and C24.

~~8. The fatty acid derivative of claim 7 wherein the fatty acid has a chain length selected from the group consisting of C14, C16 and C18.~~

59. The fatty acid derivative according to any of claims 1-48 wherein the fatty acid is attached to the water soluble linker at a group on the fatty acid selected from the group consisting of: terminal carboxyl group and ω-group.

~~10. The fatty acid derivative of claim 9 wherein the fatty acid is attached to the water soluble linker at the ω-group.~~

~~11. The fatty acid derivative of claim 10~~ wherein the ω-group is selected from the group consisting of: hydroxyl, amino, thio, and carboxyl.

612. The fatty acid derivative according to claim 1 or 2 ~~any of claims 1-3~~ wherein the fatty acid is 16-hydroxyhexadecanoic acid or the fatty acid ester is 16-hydroxyhexadecanoic acid methyl ester.

713. The fatty acid derivative according to claim 1 or 2 ~~any of claims 1-3~~ wherein the fatty acid ester is selected from the group consisting of: methyl ester and ethyl ester.

~~14. The fatty acid derivative of claim 13 wherein the fatty acid ester is 16-hydroxyhexadecanoic acid methyl ester.~~

~~15. The fatty acid derivative according to any of claims 1-14 wherein the water soluble linker comprises a water-soluble polymer and at least one functional group attached to the therapeutic protein.~~

~~16. The fatty acid derivative of claim 15 wherein the functional group is selected from the group consisting of a sulfo group, carboxyl group, hydroxyl group, amino group, amido group, maleimido group, aminooxy group and hydrazide group.~~

~~17. The fatty acid derivative according to claim 16 wherein the functional group is an aminooxy group.~~

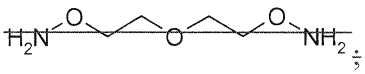
18. The fatty acid derivative according to any one of claims 15-17 wherein the water soluble polymer is selected from the group consisting of: polyethylene glycol (PEG), branched PEG, polysialic acid (PSA), hydroxyalkyl starch (HAS), hydroxyethyl starch (HES), carbohydrate, polysaccharides, pullulane, chitosan, hyaluronic acid, chondroitin sulfate, dermatan sulfate, starch, dextran, carboxymethyl-dextran, polyalkylene oxide (PAO), polyalkylene glycol (PAG), polypropylene glycol (PPG), polyoxazoline, polyacryloylmorpholine, polyvinyl alcohol (PVA), polycarboxylate, polyvinylpyrrolidone, polyphosphazene, polyoxazoline, polyethylene-co-maleic acid anhydride, polystyrene-co-maleic acid anhydride, poly(1-hydroxymethylethylene hydroxymethylformal) (PHF), and 2-methacryloyloxy-2'-ethyltrimethylammoniumphosphate (MPC).

19. The fatty acid derivative of claim 18 wherein the water soluble polymer is PEG.

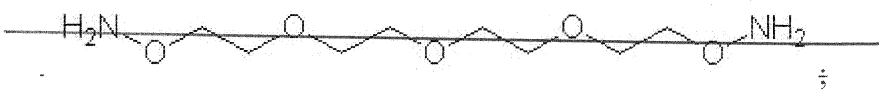
20. The fatty acid derivative according to any one of claims 15-17 and 19 wherein the water soluble polymer comprises a chain length selected from the group consisting of O3, O5, O7, O9, O11, O13 and O15.

21. The fatty acid derivative according to claim 17 wherein the water soluble linker is selected from the group consisting of:

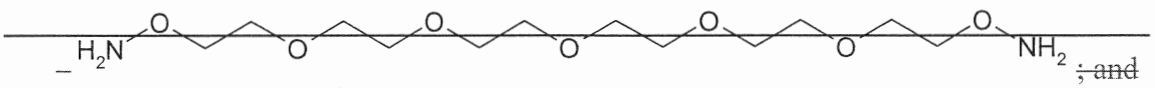
a) 3-oxapentane-1,5-dioxyamine of the formula:



b) 3,6,9-triaoxaundecane-1,11-dioxyamine of the formula:

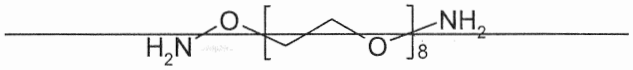


c) 3,6,9,12,15-penatoxaheptadecane-1,17-dioxyamine of the formula:

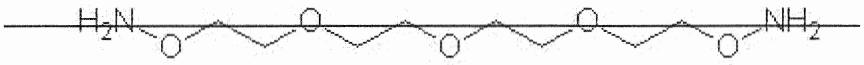


; and

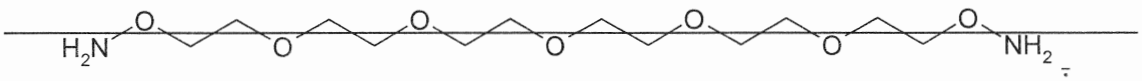
d) 3,6,9,12,15,18,21-heptaoxatricosane-1,23-dioxyamine of the formula:



22. The fatty acid derivative of claim 21 wherein the water soluble linker is 3,6,9-triaoxaundecane-1,11-dioxyamine of the formula:



23. The fatty acid derivative of claim 21 wherein the water soluble linker is 3,6,9,12,15-penatoxaheptadecane-1,17-dioxyamine of the formula:



8~~2~~4. The fatty acid derivative according to any one of claims 1-3 wherein the fatty acid derivative is stably attached to the therapeutic protein by an oxime linkage~~,~~.

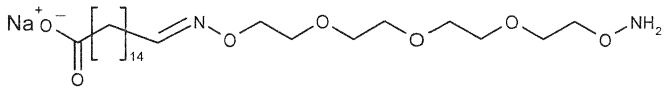
25. The fatty acid derivative of claim 24 wherein the oxime linkage is formed between an aminooxy-~~oxime~~ group on the water soluble linker and an aldehyde group of an oxidized carbohydrate on the therapeutic protein.

26. The fatty acid derivative according to any one of claims 1-3 wherein the fatty acid derivative is stably attached to the therapeutic protein by a maleimide group on the water soluble linker to a free sulfhydryl group on the therapeutic protein.

~~27. The fatty acid derivative according to any one of claims 1-3 wherein the fatty acid derivative is stably attached to the therapeutic protein by an N-hydroxysuccinimide ester on the water soluble linker to a free amino group on the therapeutic protein.~~

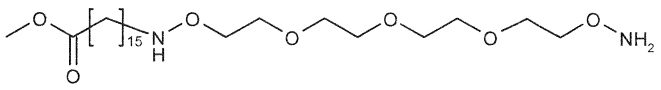
~~9~~28. The fatty acid derivative according to any one of claims 1-3 wherein the fatty acid derivative is selected from the group consisting of:

a) 16-(2-(2-(2-(2-aminooxyethoxy)-ethoxy)-ethoxy)-ethoxyimino)-hexadecanoic acid sodium salt of the formula:



; and

b) 16-(2-(2-(2-(2-aminooxyethoxy)-ethoxy)-ethoxy)-ethoxyamino)-hexadecanoic acid methyl ester,



.

~~29. The fatty acid derivative according to any one of claims 1-28 wherein the therapeutic protein is selected from the group consisting of: Factor IX (FIX), Factor VIII (FVIII), Factor VIIa (FVIIa), von Willebrand Factor (VWF), Factor FV (FV), Factor X (FX), Factor XI (FXI), Factor XII (FXII), thrombin (FII), protein C, protein S, tPA, PAI-1, tissue factor (TF),ADAMTS-13 protease, IL-1 alpha, IL-1 beta, IL-2, IL-3, IL-4, IL-5, IL-6, IL-11, colony stimulating factor-1 (CSF-1), M-CSF, SCF, GM-CSF, granulocyte colony stimulating factor (G-CSF), EPO, interferon-alpha (IFN-alpha), consensus interferon, IFN-beta, IFN-gamma, IFN-omega, IL-7, IL-8, IL-9, IL-10, IL-12, IL-13, IL-14, IL-15, IL-16, IL-17, IL-18, IL-19, IL-20, IL-21, IL-22, IL-23, IL-24, IL-31, IL-32 alpha, IL-33, thrombopoietin (TPO), Ang-1, Ang-2, Ang-4, Ang-Y, angiopoietin-like polypeptide 1 (ANGPTL1), angiopoietin-like polypeptide 2 (ANGPTL2), angiopoietin-like polypeptide 3 (ANGPTL3), angiopoietin-like polypeptide 4 (ANGPTL4), angiopoietin-like polypeptide 5 (ANGPTL5), angiopoietin-like polypeptide 6 (ANGPTL6), angiopoietin-like polypeptide 7 (ANGPTL7), vitronectin, vascular endothelial growth factor (VEGF), angiogenin, activin A, activin B, activin C, bone~~

morphogenic protein-1, bone morphogenic protein-2, bone morphogenic protein-3, bone morphogenic protein-4, bone morphogenic protein-5, bone morphogenic protein-6, bone morphogenic protein-7, bone morphogenic protein-8, bone morphogenic protein-9, bone morphogenic protein-10, bone morphogenic protein-11, bone morphogenic protein-12, bone morphogenic protein-13, bone morphogenic protein-14, bone morphogenic protein-15, bone morphogenic protein receptor IA, bone morphogenic protein receptor IB, bone morphogenic protein receptor II, brain derived neurotrophic factor, cardiotrophin-1, ciliary neutrophic factor, ciliary neutrophic factor receptor, cripto, cryptic, cytokine-induced neutrophil chemotactic factor 1, cytokine-induced neutrophil, chemotactic factor 2α, cytokine-induced neutrophil chemotactic factor 2β, β endothelial cell growth factor, endothelin 1, epidermal growth factor, epigen, epiregulin, epithelial-derived neutrophil attractant, fibroblast growth factor 4, fibroblast growth factor 5, fibroblast growth factor 6, fibroblast growth factor 7, fibroblast growth factor 8, fibroblast growth factor 8b, fibroblast growth factor 8c, fibroblast growth factor 9, fibroblast growth factor 10, fibroblast growth factor 11, fibroblast growth factor 12, fibroblast growth factor 13, fibroblast growth factor 16, fibroblast growth factor 17, fibroblast growth factor 19, fibroblast growth factor 20, fibroblast growth factor 21, fibroblast growth factor acidic, fibroblast growth factor basic, glial cell line-derived neutrophic factor receptor α1, glial cell line-derived neutrophic factor receptor α2, growth related protein, growth related protein α, growth related protein β, growth related protein γ, heparin binding epidermal growth factor, hepatocyte growth factor, hepatocyte growth factor receptor, hepatoma-derived growth factor, insulin-like growth factor I, insulin-like growth factor receptor, insulin-like growth factor II, insulin-like growth factor binding protein, keratinocyte growth factor, leukemia inhibitory factor, leukemia inhibitory factor receptor α, nerve growth factor nerve growth factor receptor, neuropoietin,neurotrophin-3, neurotrophin-4, oncostatin M (OSM), placenta growth factor, placenta growth factor 2, platelet-derived endothelial cell growth factor, platelet derived growth factor, platelet derived growth factor A chain, platelet derived growth factor AA, platelet derived growth factor AB, platelet derived growth factor B chain, platelet derived growth factor BB, platelet derived growth factor receptor α, platelet derived growth factor receptor β, pre-B cell growth stimulating factor, stem cell factor (SCF), stem cell factor receptor, TNF, TNF0, TNF1, TNF2, transforming growth factor α, transforming growth factor β, transforming growth factor β1, transforming growth factor β1.2, transforming growth factor β2, transforming growth factor β3, transforming growth factor β5, latent transforming growth factor β1, transforming growth factor β binding protein I, transforming growth factor β binding protein II, transforming growth factor β binding

~~protein III, thymic stromal lymphopoietin (TSLP), tumor necrosis factor receptor type I, tumor necrosis factor receptor type II, urokinase-type plasminogen activator receptor, phospholipase-activating protein (PUP), insulin, lectin ricin, prolactin, chorionic gonadotropin, follicle-stimulating hormone, thyroid-stimulating hormone, tissue plasminogen activator, IgG, IgE, IgM, IgA, and IgD, α-galactosidase, β-galactosidase, DNAse, fetuin, leutinizing hormone, estrogen, insulin, albumin, lipoproteins, fetoprotein, transferrin, thrombopoietin, urokinase, integrin, thrombin, leptin, Humira (adalimumab), Prolia (denosumab), Enbrel (etanercept), a protein in Table 1, or a biologically active fragment, derivative or variant thereof.~~

~~30. The fatty acid derivative of claim 29 wherein the therapeutic protein is FVIIa.~~

~~31. The fatty acid derivative of claim 29 wherein the therapeutic protein is FVIII.~~

~~32. The fatty acid derivative of claim 29 wherein the therapeutic protein is FIX.~~

10~~33~~. A method of preparing a fatty acid derivative according to claim 1 comprising:

a) oxidizing an ω-hydroxy group on a fatty acid to generate an aldehyde group on the fatty acid; and

b) coupling a water soluble linker comprising an active aminooxy group to the aldehyde group to form a stable oxime linkage;

wherein said fatty acid derivative is water soluble;~~.~~

~~34. The method according to claim 33~~ wherein the ω-hydroxy group is oxidized by an oxidation reagent selected from the group consisting of: Dess Martin periodinane reagent, Tempo reagent, oxalyl chloride/DMSO, tetrapropylammoniumperruthenate (TPAP) and crome VI reagents (Collins reagent, pyridinium chloro chromate (PCC) and pyridinium dichromate);~~.~~

~~35. The method according to claim 34 wherein the oxidation reagent is Dess Martin periodinane.~~

~~36. The method according to any one of claims 33-35~~ wherein the fatty acid is a saturated fatty acid or unsaturated fatty acid.

~~37. The method of claim 36 wherein the fatty acid is a saturated fatty acid.~~

~~38. The method of claim 36 wherein the fatty acid is a branched chain fatty acid.~~

~~39. The method according to any of claims 33-37 wherein the fatty acid comprises a chain length selected from the group consisting of C10, C12, C14, C16, C18, C20, C22, and C24.~~

~~40. The method of claim 39 wherein the fatty acid has a chain length selected from the group consisting of C14, C16 and C18.~~

~~41. The method according to claim 40 wherein the fatty acid is 16-hydroxyhexadecanoic acid.~~

~~42. The method according to any one of claims 33-41 wherein the water soluble linker comprises a water-soluble polymer and at least one aminooxy group.~~

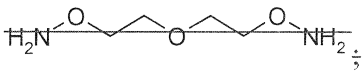
43. The method according to claim 42 wherein the water soluble polymer is selected from the group consisting of: polyethylene glycol (PEG), branched PEG, polysialic acid (PSA), hydroxyalkyl starch (HAS), hydroxyethyl starch (HES), carbohydrate, polysaccharides, pullulane, chitosan, hyaluronic acid, chondroitin sulfate, dermatan sulfate, starch, dextran, carboxymethyl-dextran, polyalkylene oxide (PAO), polyalkylene glycol (PAG), polypropylene glycol (PPG), polyoxazoline, polyacryloylmorpholine, polyvinyl alcohol (PVA), polycarboxylate, polyvinylpyrrolidone, polyphosphazene, polyoxazoline, polyethylene-co-maleic acid anhydride, polystyrene-co-maleic acid anhydride, poly(1-hydroxymethylethylene hydroxymethylformal) (PHF), and 2-methacryloyloxy-2'-ethyltrimethylammoniumphosphate (MPC).

44. The method of claim 43 wherein the water soluble polymer is PEG.

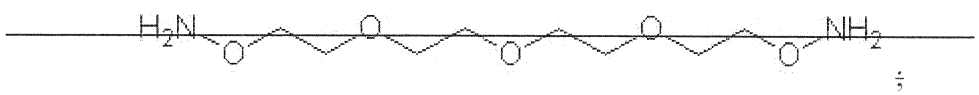
45. The method according to any one of claims 42 or 44 wherein the water soluble polymer comprises a chain length selected from the group consisting of O5, O7, O9, O11, O13 and O15.

46. The method of claim 45 wherein the water soluble linker is selected from the group consisting of:

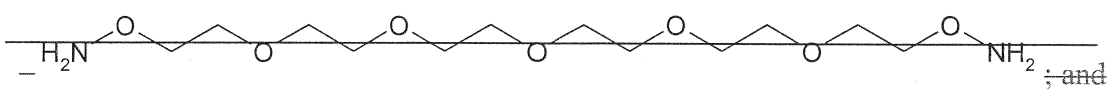
a) 3-oxapentane-1,5-dioxyamine of the formula:



b) 3,6,9-triaoxaundecane-1,11-dioxyamine of the formula:

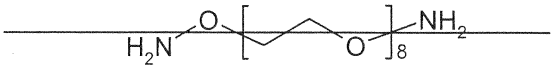


c) 3,6,9,12,15-penatoxaheptadecane-1,17-dioxyamine of the formula:

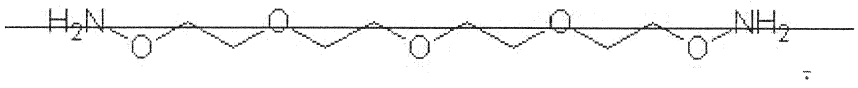


; and

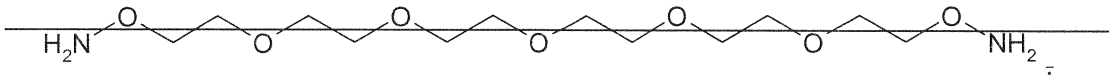
~~d) 3,6,9,12,15,18,21-heptaoxatricosane-1,23-dioxyamine of the formula:~~



~~47. The fatty acid derivative of claim 46 wherein the water soluble linker is 3,6,9-triaoxaundecane-1,11-dioxyamine of the formula:~~



~~48. The fatty acid derivative of claim 46 wherein the water soluble linker is 3,6,9,12,15-pentaoxaheptadecane-1,17-dioxyamine of the formula:~~



1149. A method of preparing a fatty acid derivative according to claim 1 comprising:

a) esterifying a carboxyl group on a fatty acid to generate an ester on the fatty acid;

b) activating an ω-hydroxy group on a fatty acid to generate a mesyl group on the fatty acid of step a); and

c) coupling a water soluble linker comprising an active aminooxy group by substituting the mesyl group of step b) thereby forming a stable oxyimine-methylene bond;

wherein said fatty acid derivative is water soluble;

~~50. The method according to claim 49~~ wherein the carboxyl group is esterified by an esterifying agent selected from the group consisting of: acetyl chloride, methanol in the presence of acid, ethanol in the presence of acid, diazomethane, and methyliodide;

~~51. The method according to claim 50 wherein the esterifying agent is acetyl chloride.~~

~~52. The method according to any one of claims 49-51~~ wherein the ω-hydroxy group is activated by an activating agent selected from the group consisting of: mesyl chloride, tosyl chloride and nosyl chloride; and~~.~~

~~53. The method according to claim 52 wherein the activating agent is mesyl chloride.~~

~~54. The method according to any one of claims 49-53~~ wherein the fatty acid is a saturated fatty acid or unsaturated fatty acid.

~~55. The method of claim 54 wherein the fatty acid is a saturated fatty acid.~~

12~~56~~. The method of claim 10 or 11 ~~54~~ wherein the fatty acid is a branched chain fatty acid.

13~~57~~. The method according to claim 10 or 11~~any of claims 49-54~~ wherein the fatty acid comprises a chain length selected from the group consisting of C10, C12, C14, C16, C18, C20, C22, and C24, optionally~~.~~

~~58. The method of claim 57 wherein the fatty acid has a chain length selected from the group consisting of: C14, C16 and C18.~~

~~59. The method according to claim 58~~ wherein the fatty acid is 16-hydroxyhexadecanoic acid.

~~60. The method according to any one of claims 49-59 wherein the water soluble linker comprises a water soluble polymer and at least one aminooxy group.~~

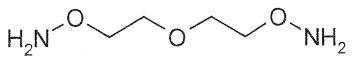
1461. The fatty acid derivative according to claim 1 or the method according to claim 10 or 1160 wherein the water soluble polymer is selected from the group consisting of: polyethylene glycol (PEG), branched PEG, polysialic acid (PSA), hydroxyalkyl starch (HAS), hydroxyethyl starch (HES), carbohydrate, polysaccharides, pullulane, chitosan, hyaluronic acid, chondroitin sulfate, dermatan sulfate, starch, dextran, carboxymethyl-dextran, polyalkylene oxide (PAO), polyalkylene glycol (PAG), polypropylene glycol (PPG), polyoxazoline, polyacryloylmorpholine, polyvinyl alcohol (PVA), polycarboxylate, polyvinylpyrrolidone, polyphosphazene, polyoxazoline, polyethylene-co-maleic acid anhydride, polystyrene-co-maleic acid anhydride, poly(1-hydroxymethylethylene hydroxymethylformal) (PHF), and 2-methacryloyloxy-2'-ethyltrimethylammoniumphosphate (MPC).

~~62. The method of claim 61 wherein the water soluble polymer is PEG.~~

1563. The fatty acid derivative or method according to claim 14 ~~any one of claims 60 or 62~~ wherein the water soluble polymer is PEG and comprises a chain length selected from the group consisting of O3, O5, O7, O9, O11, O13 and O15.

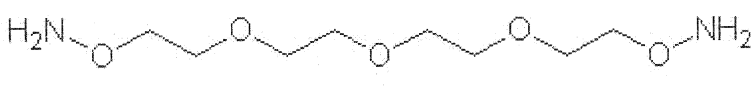
1664. The fatty acid derivative or method of claim 1563 wherein the water soluble linker is selected from the group consisting of:

a) 3-oxapentane-1,5-dioxyamine of the formula:



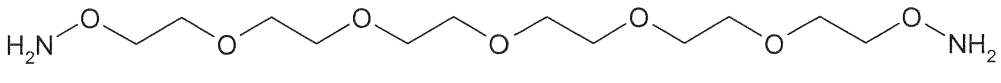
;

b) 3,6,9-triaoxaundecane-1,11-dioxyamine of the formula:



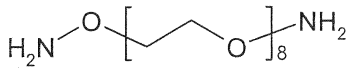
;

c) 3,6,9,12,15-penatoxaheptadecane-1,17-dioxyamine of the formula:



; and

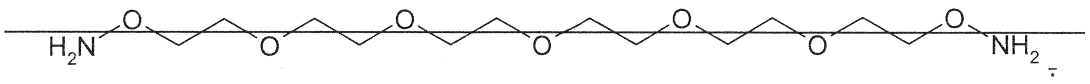
d) 3,6,9,12,15,18,21-heptaoxatricosane-1,23-dioxyamine of the formula:



~~65. The fatty acid derivative of claim 64 wherein the water soluble linker is 3,6,9-triaoxaundecane-1,11-dioxyamine of the formula:~~



~~66. The fatty acid derivative of claim 64 wherein the water soluble linker is 3,6,9,12,15-penatoxaheptadecane-1,17-dioxyamine of the formula:~~



1767. A method of preparing a conjugated therapeutic protein comprising contacting an oxidized carbohydrate moiety on the therapeutic protein with a fatty acid derivative according to claim 1 under conditions that allow conjugation;

said carbohydrate moiety oxidized by incubation with a buffer comprising an oxidizing agent selected from the group consisting of sodium periodate (NaIO4), lead tetraacetate (Pb(OAc)4) and potassium peruthenate (KRuO4);

wherein an oxime linkage is formed between the oxidized carbohydrate moiety and the active aminooxy group on the fatty acid derivative;

and wherein said oxime linkage formation is catalyzed by a nucleophilic catalyst selected from the group consisting of aniline, o-amino benzoic acid, m-amino benzoic acid, p-amino benzoic acid, sulfanilic acid, o-aminobenzamide, o-toluidine, m-toluidine, p-toluidine, o-anisidine, m-anisidine, and p-anisidine.

1868. The fatty acid derivative according to any of claims 1 to 9 or the method according to claim 17-67 wherein the therapeutic protein is selected from the group consisting of: Factor IX (FIX), Factor VIII (FVIII), Factor VIIa (FVIIa), von Willebrand Factor (VWF), Factor FV (FV), Factor X (FX), Factor XI (FXI), Factor XII (FXII), thrombin (FII), protein C, protein S, tPA, PAI-1, tissue factor (TF),ADAMTS 13 protease, IL-1 alpha, IL-1 beta, IL-2, IL-3, IL-4, IL-5, IL-6, IL-11, colony stimulating factor-1 (CSF-1), M-CSF, SCF, GM-CSF, granulocyte colony stimulating factor (G-CSF), EPO, interferon-alpha (IFN-alpha), consensus interferon, IFN-beta, IFN-gamma, IFN-omega, IL-7, IL-8, IL-9, IL-10, IL-12, IL-13, IL-14, IL-15, IL-16, IL-17, IL-18, IL-19, IL-20, IL-21, IL-22, IL-23, IL-24, IL-31, IL-32 alpha, IL-33, thrombopoietin (TPO), Ang-1, Ang-2, Ang-4, Ang-Y, angiopoietin-like polypeptide 1 (ANGPTL1), angiopoietin-like polypeptide 2 (ANGPTL2), angiopoietin-like polypeptide 3 (ANGPTL3), angiopoietin-like polypeptide 4 (ANGPTL4), angiopoietin-like polypeptide 5 (ANGPTL5), angiopoietin-like polypeptide 6 (ANGPTL6), angiopoietin-like polypeptide 7 (ANGPTL7), vitronectin, vascular endothelial growth factor (VEGF), angiogenin, activin A, activin B, activin C, bone morphogenic protein-1, bone morphogenic protein-2, bone morphogenic protein-3, bone morphogenic protein-4, bone morphogenic protein-5, bone morphogenic protein-6, bone morphogenic protein-7, bone morphogenic protein-8, bone morphogenic protein-9, bone morphogenic protein-10, bone morphogenic protein-11, bone morphogenic protein-12, bone morphogenic protein-13, bone morphogenic protein-14, bone morphogenic protein-15, bone morphogenic protein receptor IA, bone morphogenic protein receptor IB, bone morphogenic protein receptor II, brain derived neurotrophic factor, cardiotrophin-1, ciliary neutrophic factor, ciliary neutrophic factor receptor, cripto, cryptic, cytokine-induced neutrophil chemotactic factor 1, cytokine-induced neutrophil, chemotactic factor 2α, cytokine-induced neutrophil chemotactic factor 2β, β endothelial cell growth factor, endothelin 1, epidermal growth factor, epigen, epiregulin, epithelial-derived neutrophil attractant, fibroblast growth factor 4, fibroblast growth factor 5, fibroblast growth factor 6, fibroblast growth factor 7, fibroblast growth factor 8, fibroblast growth factor 8b, fibroblast growth factor 8c, fibroblast growth factor 9, fibroblast growth factor 10, fibroblast growth factor 11, fibroblast growth factor 12, fibroblast growth factor 13, fibroblast growth factor 16, fibroblast growth factor 17, fibroblast growth factor 19, fibroblast growth factor 20, fibroblast growth factor 21, fibroblast growth factor acidic, fibroblast growth factor basic, glial cell line-derived neutrophic factor receptor α1, glial cell line-derived neutrophic factor receptor α2, growth related protein,

growth related protein α, growth related protein β, growth related protein γ, heparin binding epidermal growth factor, hepatocyte growth factor, hepatocyte growth factor receptor, hepatoma-derived growth factor, insulin-like growth factor I, insulin-like growth factor receptor, insulin-like growth factor II, insulin-like growth factor binding protein, keratinocyte growth factor, leukemia inhibitory factor, leukemia inhibitory factor receptor α, nerve growth factor nerve growth factor receptor, neuropoietin,neurotrophin-3, neurotrophin-4, oncostatin M (OSM), placenta growth factor, placenta growth factor 2, platelet-derived endothelial cell growth factor, platelet derived growth factor, platelet derived growth factor A chain, platelet derived growth factor AA, platelet derived growth factor AB, platelet derived growth factor B chain, platelet derived growth factor BB, platelet derived growth factor receptor α, platelet derived growth factor receptor β, pre-B cell growth stimulating factor, stem cell factor (SCF), stem cell factor receptor, TNF, TNF0, TNF1, TNF2, transforming growth factor α, transforming growth factor β, transforming growth factor β1, transforming growth factor β1.2, transforming growth factor β2, transforming growth factor β3, transforming growth factor β5, latent transforming growth factor β1, transforming growth factor β binding protein I, transforming growth factor β binding protein II, transforming growth factor β binding protein III, thymic stromal lymphopoietin (TSLP), tumor necrosis factor receptor type I, tumor necrosis factor receptor type II, urokinase-type plasminogen activator receptor, phospholipase-activating protein (PUP), insulin, lectin ricin, prolactin, chorionic gonadotropin, follicle-stimulating hormone, thyroid-stimulating hormone, tissue plasminogen activator, IgG, IgE, IgM, IgA, and IgD, α-galactosidase, β-galactosidase, DNAse, fetuin, leutinizing hormone, estrogen, insulin, albumin, lipoproteins, fetoprotein, transferrin, thrombopoietin, urokinase, integrin, thrombin, leptin, Humira (adalimumab), Prolia (denosumab), Enbrel (etanercept), a protein in Table 1, or a biologically active fragment, derivative or variant thereof.

~~69. The method according to any one of claims 67-68.~~

~~70. The method according to any one of claims 67-69 wherein the therapeutic protein is FVIIa.~~

71. The method according to any one of claims 67-69 wherein the therapeutic protein is FVIII.

72. The method according to any one of claims 67-69 wherein the therapeutic protein is FIX.

73. The method according to any one of claims 67-72 wherein the oxidizing agent is sodium periodate (NaIO4).

74. The method according to any one of claims 67-73 wherein the nucleophilic catalyst is m-toluidine.

75. The method according to any one of claims 67-74 further comprising purifying the conjugated therapeutic protein.

76. The method according to any one of claims 67-75 wherein the fatty acid derivative is prepared by a method according to any one of claims 33-47.

77. The method according to any one of claims 67-75 wherein the fatty acid derivative is prepared by a method according to any one of claims 49-66.

78. A method of preparing a fatty acid derivative according to claim 1 comprising:

a) esterifying a carboxyl group on a fatty acid to generate an ester on the fatty acid; and

b) coupling a water soluble linker comprising an active maleimide group to a free sulfhydryl (SH) group, thereby forming a stable thioether bond;

wherein said fatty acid derivative is water soluble.

~~79. A method of preparing a fatty acid derivative according to claim 1 comprising:~~

~~a) esterifying a carboxyl group on a fatty acid to generate fatty acid ester;~~

~~b) reacting the fatty acid resulting from step a) with an azide reagent thereby producing a corresponding fatty acid azide;~~

~~c) hydrogenating the fatty acid azide of step b) to produce a corresponding fatty acid amine; and~~

~~d) coupling a water soluble linker comprising an active NHS group to a free amine group, thereby forming a stable bond;~~

~~wherein said fatty acid derivative is water soluble.~~