CLAIMS

1. A compound of the formula (I):

$$G^1—L—G^2$$

(I)

wherein:

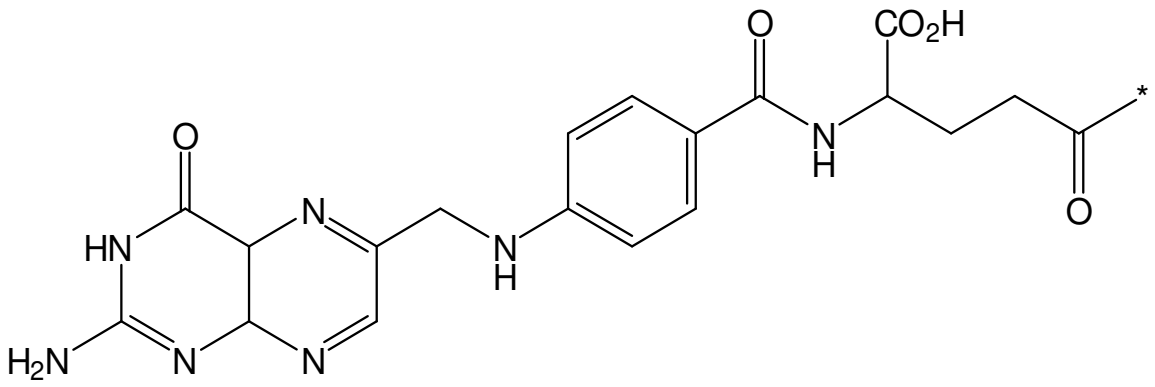
G^1 is a folate radical, an antifolate radical, or a folate analog radical;

L is a linker; and

G^2 is a radical of a steroid;

or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, wherein the folate radical has the formula:



wherein the asterisk denotes the point of attachment of the carbonyl carbon to the linker L.

3. The compound of claim 1 or 2, where G^1 is a pteroyl-amino acid radical where the amino acid is selected from the group consisting of aspartic acid, lysine, tyrosine, cysteine, threonine, serine, histidine, arginine, and an unnatural amino acid with a derivatizable moiety in the side chain and/or wherein G^1 is an antifolate radical or a folate analog radical comprising an amino acid selected from the group consisting of aspartic acid, lysine, tyrosine, cysteine, threonine, serine, histidine, and arginine.

4. The compound of any one of claims 1-3, wherein G^2 is a radical of a steroid selected from the group consisting of a radical of dexamethasone, a radical of prednisone, a radical of prednisolone, a radical of methylprednisolone, a radical of budesonide, a radical of triamcinolone; and a radical of betamethasone; and/or wherein G^2 is selected from:betamethasone, cortisone, cortivazol, difluprednate, hydrocortisone, prednisolone, methylprednisolone, prednisone, dexamethasone, hydrocortisone-17-valerate, budesonide, flumethazone, fluticasone proprionate, fluorocortisone, fludrocortisone, paramethasone, eplerenone, and an ester of any of the foregoing.

5. The compound of any one of claims 1-4, wherein the linker is releasable or wherein the linker is non-releasable, and/or

wherein the linker comprises one or more of an amino acid, an alkyl chain, a polyethylene glycol (PEG) monomer, a PEG oligomer, a PEG polymer, or a combination of any of the foregoing, and/or

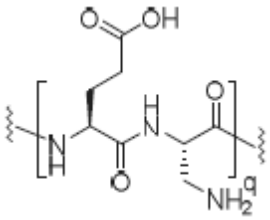
wherein the linker increases the water solubility of the compound, and/or

wherein the linker comprises an oligomer of peptidoglycans, glycans, anions, or a combination of any of the foregoing, and/or

wherein the linker comprises at least one 2,3-diaminopropionic acid group, at least one glutamic acid group, and at least one cysteine group, and/or

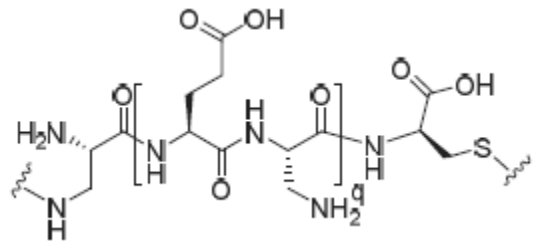
wherein the linker is selected from:

a linker comprising a repeating unit of the formula:



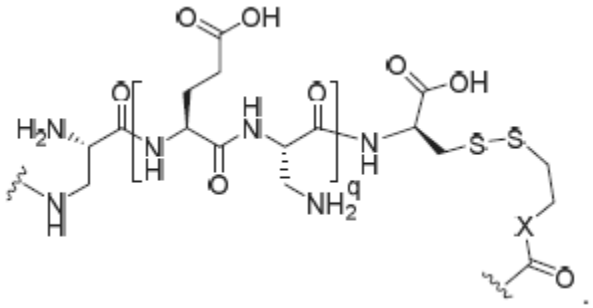
wherein q is an integer from 1 to 10;

a linker comprising the formula:



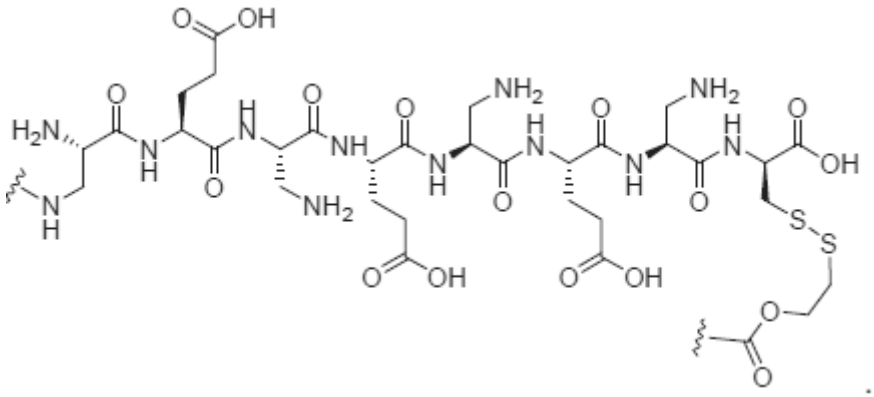
wherein q is an integer from 1 to 10;

a linker comprising the formula:



wherein X can be O, NH, NR, or S, and q is an integer from 1 to 10; and

a linker comprising the formula:



, and/or

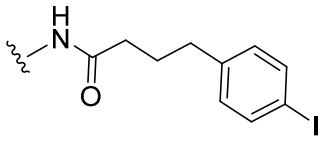
wherein the linker is a bivalent linker or

wherein the linker is polyvalent and has multiple attachment points for one or more additional chemical groups, and/or

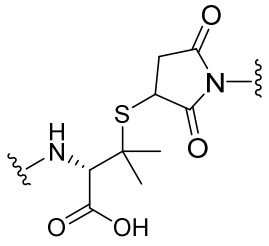
wherein the linker is polyvalent and has multiple attachment points for one or more additional chemical groups and the additional chemical groups comprise one or more additional G^1 groups, and/or

wherein the linker is polyvalent and has multiple attachment points for one or more additional chemical groups and the additional chemical groups comprise one or more binding ligands that are not G^1 groups, and/or

wherein the linker comprises a PEG oligomer with 2-16 PEG units, for example wherein the linker comprises a PEG oligomer with 12 PEG units, and/or

wherein the linker comprises an albumin ligand, for example wherein the albumin ligand comprises , and/or

wherein the linker comprises a dimethylcysteine group, for example wherein the dimethylcysteine group is linked to a succinimide to form:

, and/or

wherein the linker comprises a phosphate or pyrophosphate group, and/or

wherein the linker comprises a cathepsin B cleavable group, for example wherein the cathepsin B cleavable group is Valine-Citrulline, and/or

wherein the linker comprises a carbamate moiety; or wherein the linker comprises a β-glucuronide; or wherein the linker comprises an ester, phosphate, oxime, acetal, pyrophosphate, polyphosphate, disulfide, sulfate, hydrazide, imine, carbonate, carbamate or enzyme-cleavable amino acid sequence, and/or

wherein the linker comprises a self-immolative moiety.

6. The compound of any one of claims 1-4, wherein the linker comprises a self-immolative moiety selected from:

a self-immolative disulfide and or sterically protected disulfide bond;

a self-immolative cathepsin-cleavable amino acid sequence;

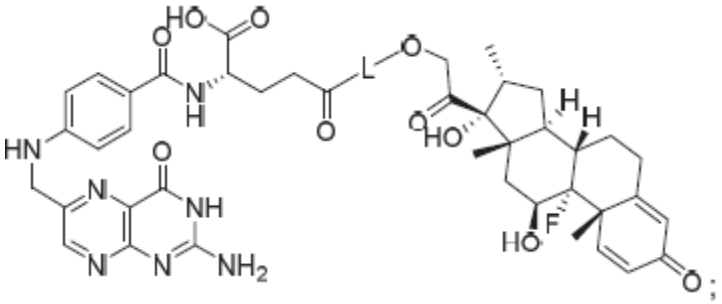
a self-immolative furin-cleavable amino acid sequence;

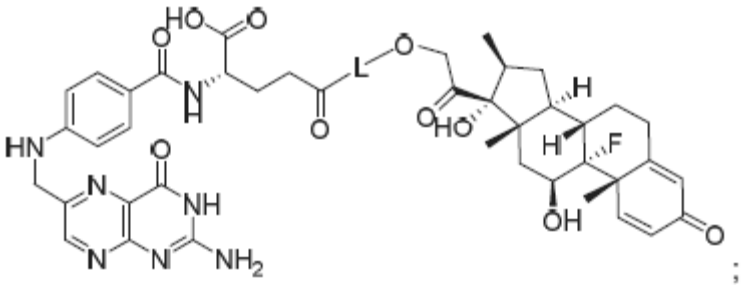
a self-immolative β-glucuronidase-cleavable moiety;

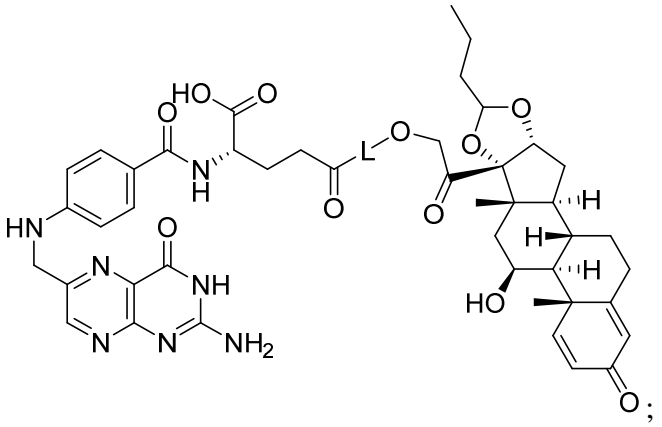
a self-immolative phosphatase-cleavable moiety; and

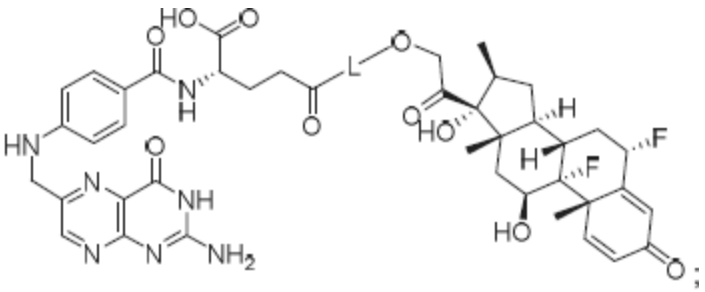
a self-immolative sulfatase-cleavable moiety.

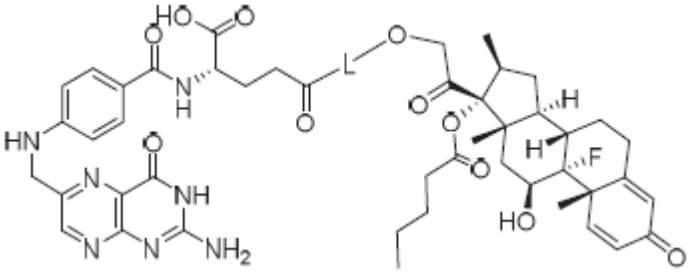
7. The compound of any one of claims 1-6, wherein the compound has the formula:

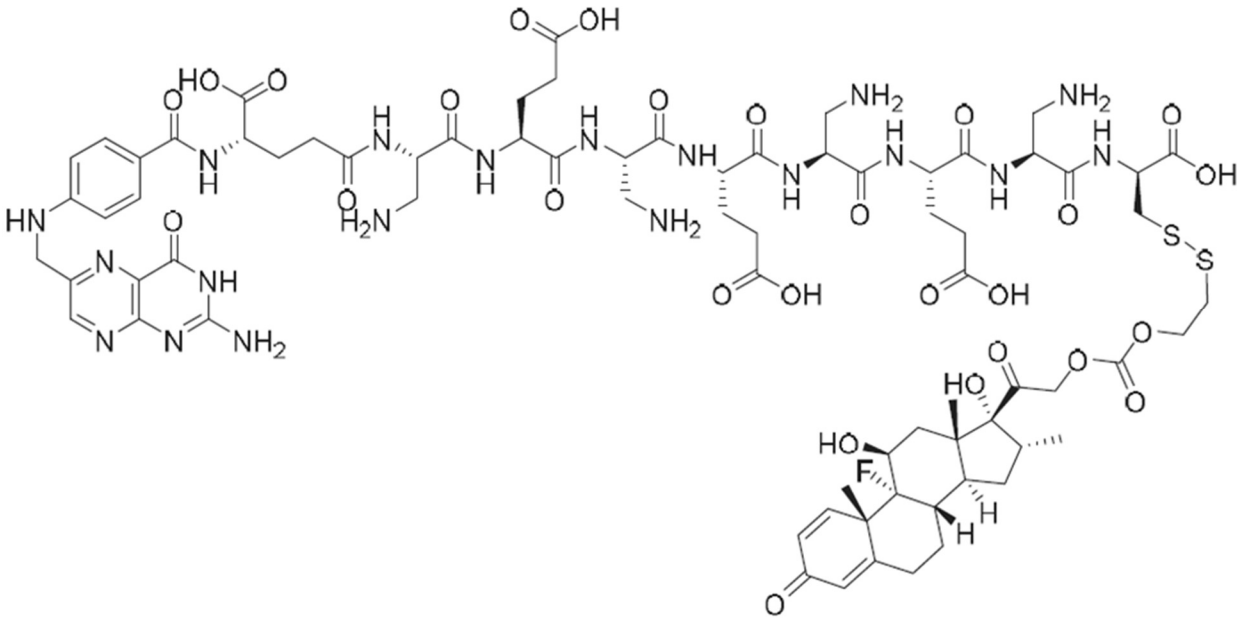


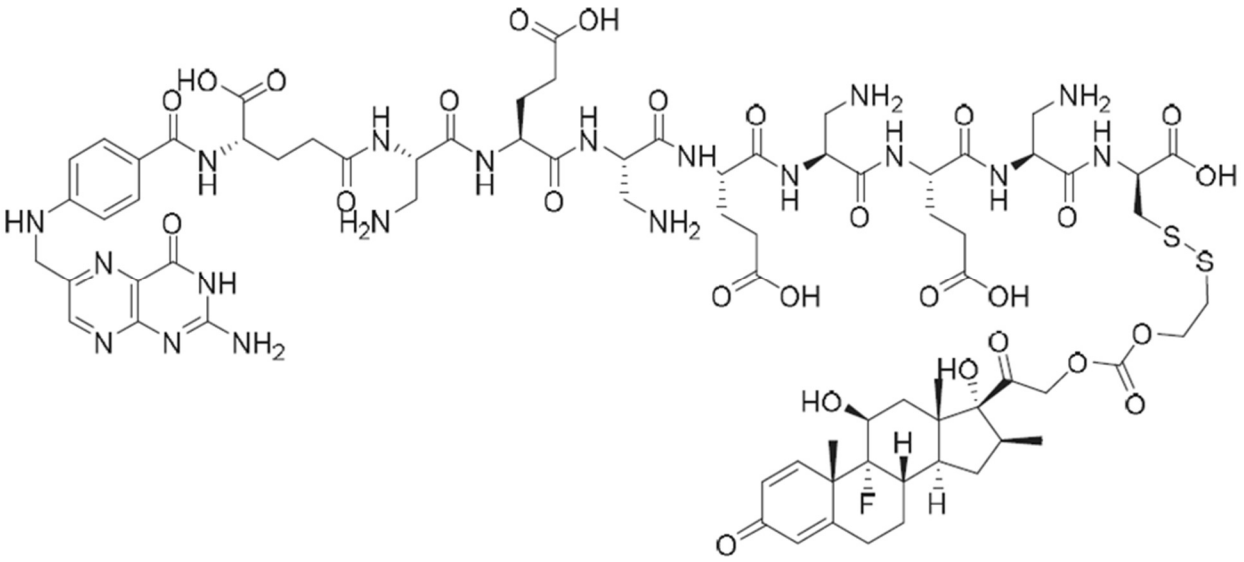


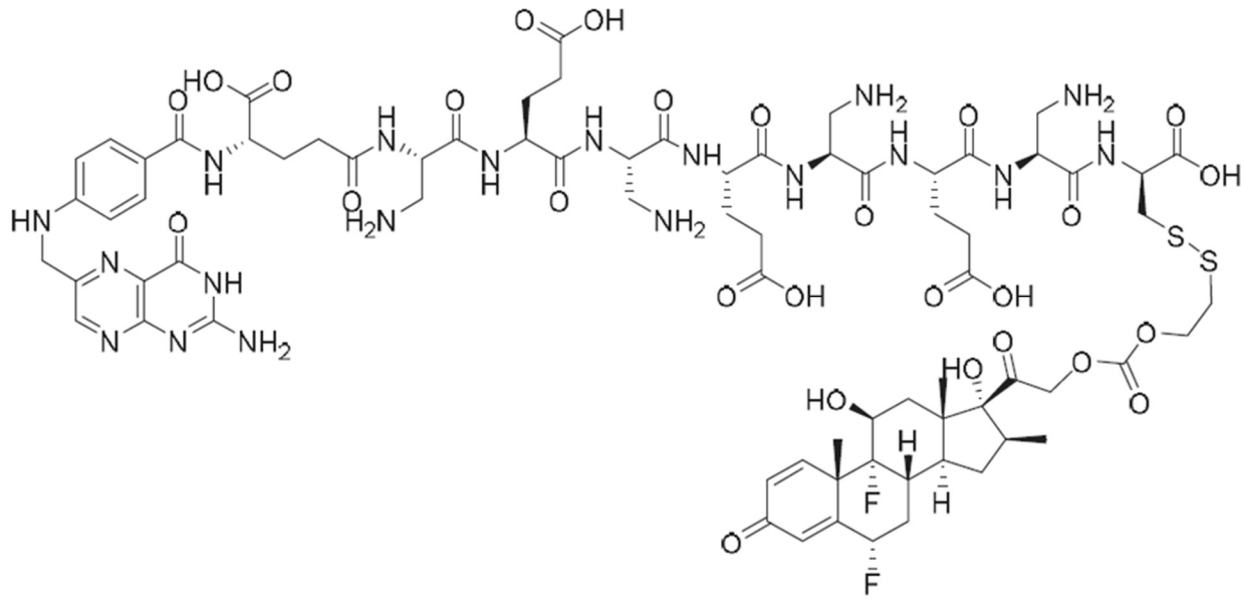


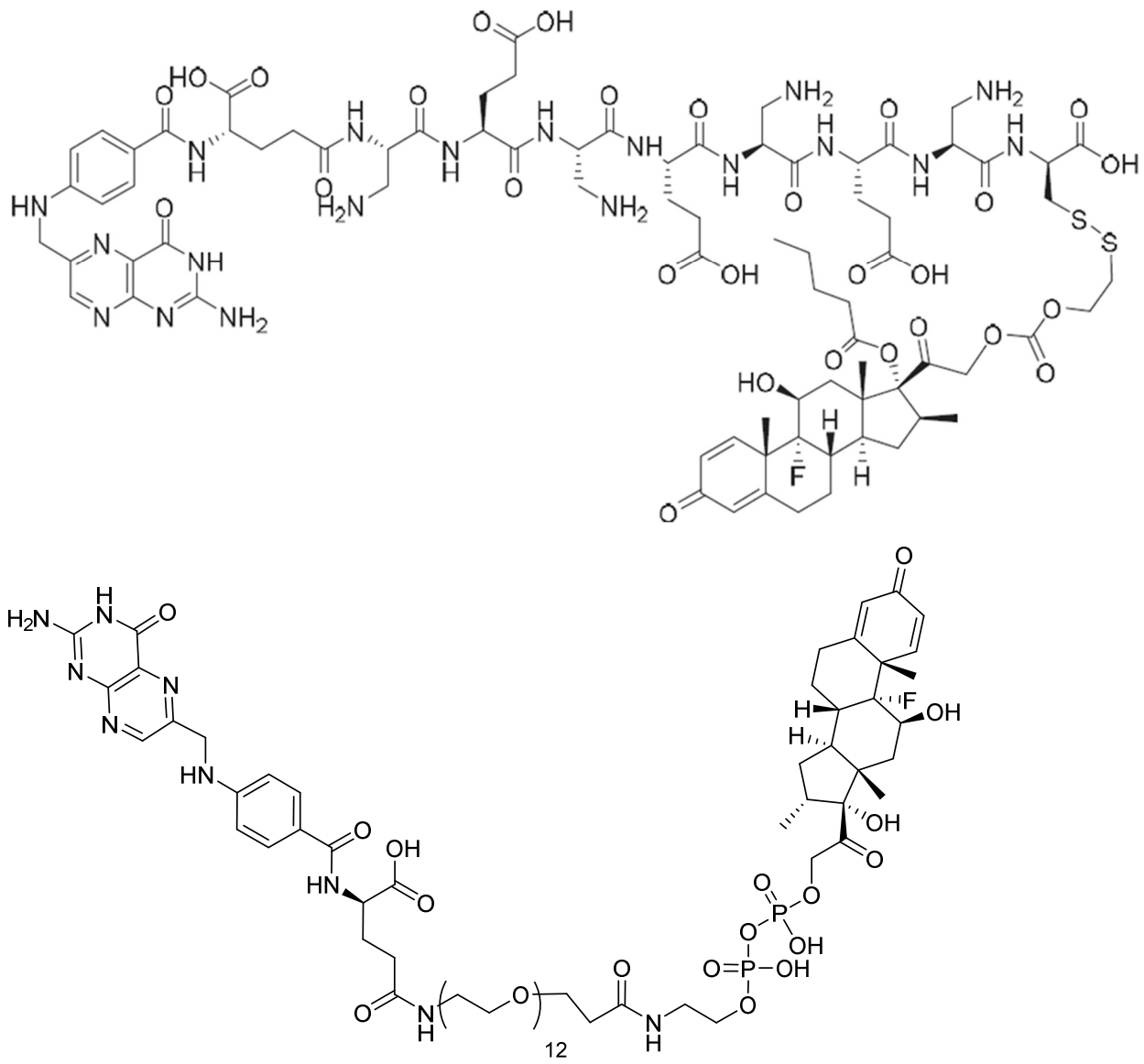


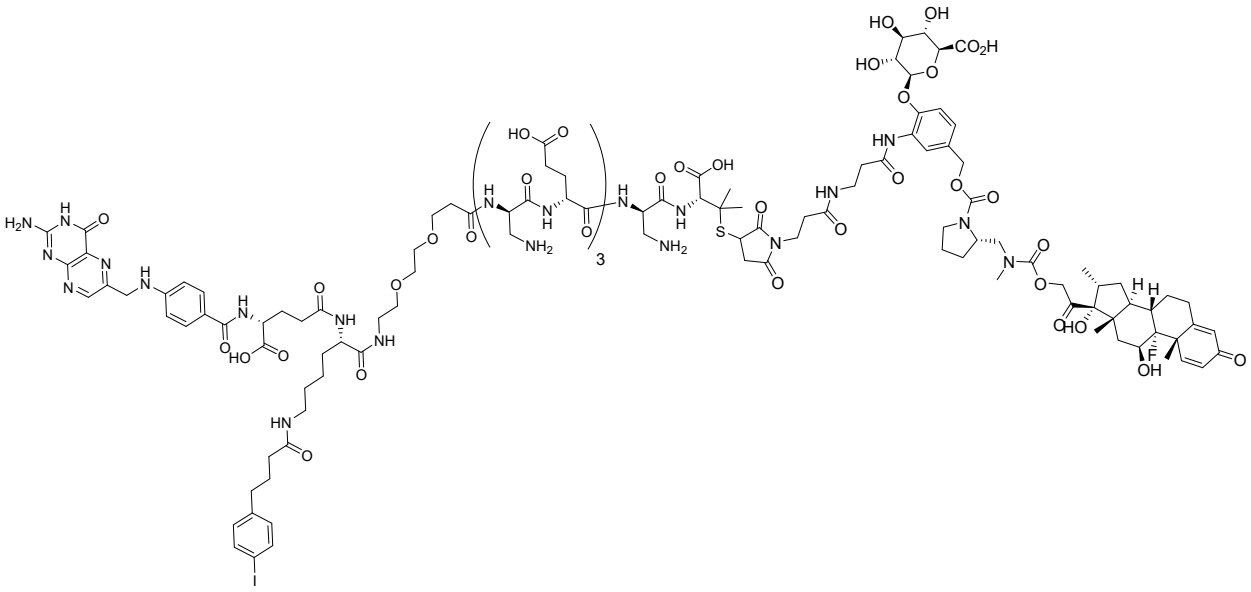


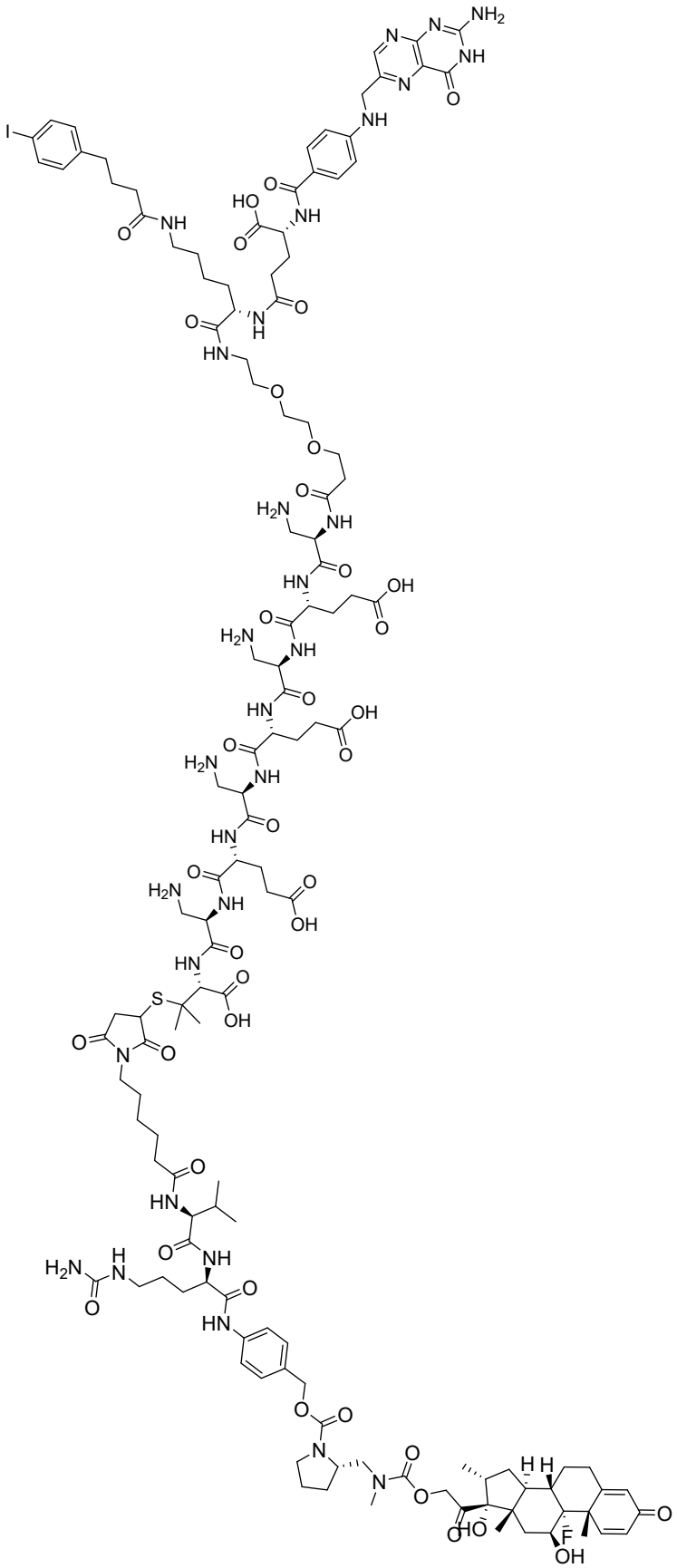












or a pharmaceutically acceptable salt thereof.

8. A pharmaceutical composition, comprising:
   a. a compound of any one of claims 1-7; and
   b. a pharmaceutically acceptable excipient.

9. The pharmaceutical composition of claim 8, wherein a pharmaceutically acceptable excipient is part of a nanoparticle, a liposomal formulation or an exosomal formulation.

10. Use of a therapeutically effective amount of the compound of any one of claims 1-7 or a composition of claim 8 or 9 in the manufacture of a medicament for the treatment of shifting macrophages from M1 to M2 in a subject in need thereof.

11. Use of a therapeutically effective amount of a compound of any one of claims 1-7 or a composition of claim 8 or 9 in the manufacture of a medicament for the treatment of an inflammatory disorder in a subject in need thereof.

12. The use of claim 11, wherein the inflammatory disorder is Crohn's disease, lupus, inflammatory bowel disease (IBS), Addison's disease, Grave's disease, Sjogren's syndrome, celiac disease, Hashimoto' s thyroiditis, myasthenia gravis, autoimmune vasculitis, reactive arthritis, psoriatic arthritis, pernicious anemia, ulcerative colitis, rheumatoid arthritis, type 1 diabetes, multiple sclerosis, or fibrotic disease, graft vs. host disease (GVHD), fatty liver disease, asthma, osteoporosis, sarcoidosis, ischemia-reperfusion injury, prosthesis osteolysis, glomerulonephritis, scleroderma, psoriasis, with autoimmune myocarditis, spinal cord injury, central nervous system, viral infection, influenza, coronavirus infection, cytokine storm syndrome, bone damage, inflammatory brain disease, atherosclerosis, cancer, or a tumor.

13. Use of a therapeutically effective amount of a compound of any one of claims 1-7 or a composition of claim 8 or 9 in the manufacture of a medicament for the treatment of an autoimmune disease in a subject in need thereof.

14. Use of a therapeutically effective amount of a compound of any one of claims 1-7 or a composition of claim 8 or 9 in the manufacture of a medicament for the treatment of inflammation in a subject in need thereof.

15. The use of claim 14, wherein the inflammation is associated with an autoimmune disease.

16. The use of claim 14, wherein G^2 is a radical of a steroid selected from the group consisting of dexamethasone, betamethasone, budesonide, fludrocortisone, beclomethasone, fluticasone, mometasone, ciclesonide, cortisone, cortivazol, hydrocortisone, 21-hydroxypregnenolone, meprednisone, dexamethasone, triamcinolone, betamethasone, prednisone, prednisolone, and methylprednisolone.

17. The use of claim 14, wherein the inflammation is associated with an immune disorder or disease, with a neuromuscular disorder or disease, with a hormonal disorder or disease, with a gastrointestinal disorder or disease, with a connective tissue disease or disorder, with a liver disease or disorder, with a musculoskeletal disease or disorder, with a blood disease of disorder, with a metabolic disease or disorder, with a metabolic disease or disorder, with an endocrine disease or disorder, with an infection, with a neurological disease or disorder, with a renal disease or disorder, with a pulmonary disease or disorder, or with a tissue disease or disorder.

18. The use of claim 14, wherein the inflammation is associated with Crohn's disease, lupus, inflammatory bowel disease (IBS), Addison's disease, Grave's disease, Sjogren's syndrome, celiac disease, Hashimoto's thyroiditis, myasthenia gravis, autoimmune vasculitis, reactive arthritis, psoriatic arthritis, pernicious anemia, ulcerative colitis, rheumatoid arthritis, type 1 diabetes, multiple sclerosis, or fibrotic disease, graft vs. host disease (GVHD), fatty liver disease, asthma, osteoporosis, sarcoidosis, ischemia-reperfusion injury, prosthesis osteolysis, glomerulonephritis, scleroderma, psoriasis, with autoimmune myocarditis, spinal cord injury, central nervous system, viral infection, influenza, coronavirus infection, cytokine storm syndrome, bone damage, inflammatory brain disease, atherosclerosis, cancer, or a tumor.

19. The use of claim 14, wherein the:

inflammation is associated with Crohn's disease, and G^2 is a radical of a steroid selected from the group consisting of dexamethasone, hydrocortisone, budesonide, betamethasone, prednisone, prednisolone, and methylprednisolone;

inflammation associated with lupus, and G^2 is a radical of a steroid selected from the group consisting of dexamethasone, hydrocortisone, betamethasone, budesonide, prednisone, prednisolone, and methylprednisolone;

inflammation associated with inflammatory bowel disease, and wherein G^2 is a radical of a steroid selected from the group consisting of dexamethasone, betamethasone, hydrocortisone, budesonide, prednisone, prednisolone, and methylprednisolone;

inflammation associated with Addison's disease, and G^2 is a radical of a steroid selected from the group consisting of dexamethasone, betamethasone, hydrocortisone, fludrocortisone, prednisone, prednisolone, and methylprednisolone;

inflammation associated with Grave's disease, and G^2 is a radical of a steroid selected from the group consisting of dexamethasone, betamethasone, budesonide, prednisone, prednisolone, and methylprednisolone;

inflammation associated with Sjogren's syndrome, and G^2 is a radical of a steroid selected from the group consisting of dexamethasone, betamethasone, budesonide, prednisone, prednisolone, and methylprednisolone;

inflammation associated with celiac disease, and G^2 is a radical of a steroid selected from the group consisting of dexamethasone, betamethasone, budesonide, prednisone, prednisolone, and methylprednisolone;

inflammation associated with Hashimoto's thyroiditis, and wherein G^2 is a radical of a steroid selected from the group consisting of dexamethasone, betamethasone, budesonide, prednisone, prednisolone, and methylprednisolone;

inflammation associated with myasthenia gravis, and G^2 is a radical of a steroid selected from the group consisting of dexamethasone, betamethasone, budesonide, prednisone, prednisolone, and methylprednisolone;

inflammation associated with autoimmune vasculitis, and G^2 is a radical of a steroid selected from the group consisting of dexamethasone, betamethasone, budesonide, prednisone, prednisolone, and methylprednisolone;

inflammation associated with reactive arthritis, and G^2 is a radical of a steroid selected from the group consisting of cortisone, hydrocortisone, dexamethasone, betamethasone, budesonide, prednisone, prednisolone, and methylprednisolone;

inflammation associated with psoriatic arthritis, and G^2 is a radical of a steroid selected from the group consisting of cortisone, hydrocortisone, dexamethasone, betamethasone, budesonide, prednisone, prednisolone, and methylprednisolone;

inflammation associated with pernicious anemia, and G^2 is a radical of a steroid selected from the group consisting of dexamethasone, betamethasone, prednisone, prednisolone, and methylprednisolone;

inflammation associated with ulcerative colitis, and G^2 is a radical of a steroid selected from the group consisting of cortisone, hydrocortisone, triamcinolone, beclomethasone, betamethasone, dexamethasone, budesonide, prednisone, prednisolone, and methylprednisolone;

inflammation associated with rheumatoid arthritis, and G^2 is a radical of a steroid selected from the group consisting of cortisone, hydrocortisone, triamcinolone, beclomethasone, betamethasone, dexamethasone, budesonide, prednisone, prednisolone, and methylprednisolone;

inflammation associated with type 1 diabetes, and G^2 is a radical of a steroid selected from the group consisting of dexamethasone, betamethasone, prednisone, prednisolone, and methylprednisolone;

inflammation associated with multiple sclerosis, and G^2 is a radical of a steroid selected from the group consisting of dexamethasone, betamethasone, prednisone, prednisolone, and methylprednisolone;

inflammation associated with asthma, and G^2 is a radical of a steroid selected from the group consisting of triamcinolone, fluticasone, budesonide, mometasone, beclomethasone, ciclesonide, dexamethasone, betamethasone, budesonide, prednisone, prednisolone, and methylprednisolone;

inflammation associated with osteoporosis, and G^2 is a radical of a steroid selected from the group consisting of dexamethasone, betamethasone, prednisone, prednisolone, and methylprednisolone;

inflammation associated with sarcoidosis, and G^2 is a radical of a steroid selected from the group consisting of dexamethasone, betamethasone, prednisone, prednisolone, and methylprednisolone;

inflammation associated with glomerulonephritis, and G^2 is a radical of a steroid selected from the group consisting of dexamethasone, betamethasone, budesonide, prednisone, prednisolone, and methylprednisolone;

inflammation associated with autoimmune myocarditis, and G^2 is a radical of a steroid selected from the group consisting of dexamethasone, betamethasone, budesonide, prednisone, prednisolone, and methylprednisolone;

inflammation associated with a fibrotic disease, and G^2 is a radical of a steroid selected from the group consisting of dexamethasone, betamethasone, budesonide, and prednisone;

inflammation associated with graft vs. host disease (GVHD), and G^2 is a radical of a steroid selected from the group consisting of dexamethasone, betamethasone, budesonide, prednisone, prednisolone, and methylprednisolone;

inflammation associated with fatty liver disease, and G^2 is a radical of a steroid selected from the group consisting of dexamethasone, betamethasone, budesonide, prednisone, prednisolone, and methylprednisolone;

inflammation associated with ischemia-reperfusion injury, and G^2 is a radical of a steroid selected from the group consisting of dexamethasone, betamethasone, budesonide, prednisone, prednisolone, and methylprednisolone;

inflammation associated with prosthesis osteolysis, and G^2 is a radical of a steroid selected from the group consisting of dexamethasone, betamethasone, budesonide, prednisone, prednisolone, and methylprednisolone;

inflammation associated with scleroderma, and G^2 is a radical of a steroid selected from the group consisting of dexamethasone, budesonide, betamethasone, triamcinolone, prednisone, prednisolone, and methylprednisolone;

inflammation associated with psoriasis, and G^2 is a radical of a steroid selected from the group consisting of budesonide, betamethasone, triamcinolone, prednisone, prednisolone, methylprednisolone, hydrocortisone, dexamethasone, hydrocortisone-17-valerate, diflorasone, meprednisone, halobetacol, tixocortol, amcinonide, desonide, fluocinolone acetonide, fluocinonide, halcinonide, beclomethasone, and halometasone;

inflammation associated with spinal cord injury, and G^2 is a radical of a steroid selected from the group consisting of dexamethasone, betamethasone, budesonide, prednisone, prednisolone, and methylprednisolone;

inflammation of the central nervous system, and G^2 is a radical of a steroid selected from the group consisting of dexamethasone, betamethasone, budesonide, prednisone, prednisolone, and methylprednisolone;

inflammation associated with a viral infection, and G^2 is a radical of a steroid selected from the group consisting of hydrocortisone, dexamethasone, betamethasone, budesonide, prednisone, prednisolone, and methylprednisolone;

inflammation associated with influenza, and G^2 is a radical of a steroid selected from the group consisting of hydrocortisone, dexamethasone, betamethasone, budesonide, prednisone, prednisolone, and methylprednisolone;

inflammation associated with SARS-CoV-2 (COVID-19), and G^2 is a radical of a steroid selected from the group consisting of hydrocortisone, dexamethasone, betamethasone, budesonide, and prednisone, prednisolone, and methylprednisolone;

inflammation associated with cytokine storm syndrome, and G^2 is a radical of a steroid selected from the group consisting of hydrocortisone, dexamethasone, betamethasone, budesonide, prednisone, prednisolone, and methylprednisolone;

inflammation associated with damage to bone, and G^2 is a radical of a steroid selected from the group consisting of cortisone, cortivazol, hydrocortisone, 21-hydroxypregnenolone, meprednisone, dexamethasone, triamcinolone, betamethasone, budesonide, prednisone, prednisolone, and methylprednisolone;

inflammation associated with inflammatory brain disease, and G^2 is a radical of a steroid selected from the group consisting of dexamethasone, betamethasone, budesonide, prednisone, prednisolone, and methylprednisolone;

inflammation associated with atherosclerosis, and G^2 is a radical of a steroid selected from the group consisting of fluticasone, budesonide, beclomethasone, ciclesonide, dexamethasone, betamethasone, prednisone, prednisolone, and methylprednisolone;

inflammation associated with a tumor, and wherein G^2 is a radical of a steroid selected from the group consisting of cortisone, hydrocortisone, clobetasol, dexamethasone, betamethasone, budesonide, meprednisone, prednisone, prednisolone, and methylprednisolone; and

inflammation associated with cancer, and G^2 is a radical of a steroid selected from the group consisting of cortisone, hydrocortisone, clobetasol, dexamethasone, betamethasone, budesonide, meprednisone, prednisone, prednisolone, and methylprednisolone.

20. Use of a therapeutically effective amount of a compound of any one of claims 1-7 or a composition of claim 8 or 9 in the manufacture of a medicament for the treatment of a disease or disorder that involves polarizing macrophages from M1 to M2 in a subject in need thereof.