GLUCOCORTICOID RECEPTOR AGONIST AND IMMUNOCONJUGATES THEREOF

Related Applications

[0001] This application claims priority to U.S. Provisional Application No. 62/344,948, filed June 2, 2016, and U.S. Provisional Application No. 62/371,134, filed August 4, 2016, each of which is herein incorporated by reference in its entirety.

Field of the Invention

[0002] The field of the invention generally relates to glucocorticoid receptor agonist immunoconjugates, and methods of making and using the same, e.g., to treat autoimmune or inflammatory diseases.

Background of the Invention

[0003] Tumor Necrosis Factor alpha (TNFa) plays a central role in the pathophysiology of several human disorders, and anti-TNFa agents (e.g., adalimumab, etanercept, and infliximab) have clinically validated therapeutic utility in the treatment of autoimmune and inflammatory disorders, such as rheumatoid arthritis, psoriasis and inflammatory bowel disease. Despite their success in the clinic, anti-TNFa biologics are still limited in the maximal efficacy they can achieve in patients, necessitating the identification and development of more potent and effective therapeutics. Patients treated with anti-TNFa biologics may also develop an immunogenic response to the therapeutic thus limiting its effectiveness. Therefore anti-TNFa therapies with lower immunogenicity and high efficacy would be useful for further controlling disease.

[0004] Synthetic glucocorticoid receptor agonists (e.g., dexamethasone, prednisolone, and budesonide) are a potent class of small molecules used in the treatment of inflammatory disorders, but their utility in the chronic treatment of disease is limited due to severe side effects. Several approaches to retain the anti-inflammatory efficacy of synthetic glucocorticoids while sparing the unwanted toxicities have been described (Rosen, J and Miner, JN *Endocrine Reviews* 26: 452-64 (2005)). However these methodologies have met with little success. There is a need in the field of autoimmune and inflammatory disease therapeutics to develop therapeutics with enhanced efficacy and longer duration of action compared to anti-TNF antibodies and with minimal unwanted effects.

SUMMARY

[0005] In one embodiment, the present disclosure provides a glucocorticoid receptor agonist immunoconjugate represented by Formulae **I-a** and **I-b**, below, and the pharmaceutically acceptable salts, solvates, or prodrugs thereof. In another embodiment, the present disclosure provides a glucocorticoid receptor

agonist immunoconjugate represented by Formulae **I-a** and **I-b**, below. Glucocorticoid receptor agonist immunoconjugates having Formulae **I-a** and **I-b** are useful for treating autoimmune diseases such as, but not limited to, rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, adult Crohn's disease, pediatric Crohn's disease, ulcerative colitis, plaque psoriasis, hidradenitis suppurativa, uveitis, Behcets disease, a spondyloarthropathy, or psoriasis. In one embodiment, glucocorticoid receptor agonist immunoconjugates having Formulae **I-a** and **I-b** are useful for treating rheumatoid arthritis. In one embodiment, glucocorticoid receptor agonist immunoconjugates having Formulae **I-a** and **I-b** are useful for treating juvenile idiopathic arthritis. In one embodiment, glucocorticoid receptor agonist immunoconjugates having Formulae **I-a** and **I-b** are useful for treating psoriatic arthritis. In one embodiment, glucocorticoid receptor agonist immunoconjugates having Formulae **I-a** and **I-b** are useful for treating ankylosing spondylitis. In one embodiment, glucocorticoid receptor agonist immunoconjugates having Formulae **I-a** and **I-b** are useful for treating adult Crohn's disease. In one embodiment, glucocorticoid receptor agonist immunoconjugates having Formulae **I-a** and **I-b** are useful for treating pediatric Crohn's disease. In one embodiment, glucocorticoid receptor agonist immunoconjugates having Formulae **I-a** and **I-b** are useful for treating ulcerative colitis. In one embodiment, glucocorticoid receptor agonist immunoconjugates having Formulae **I-a** and **I-b** are useful for treating plaque psoriasis. In one embodiment, glucocorticoid receptor agonist immunoconjugates having Formulae **I-a** and **I-b** are useful for treating hidradenitis suppurativa. In one embodiment, glucocorticoid receptor agonist immunoconjugates having Formulae **I-a** and **I-b** are useful for treating uveitis. In one embodiment, glucocorticoid receptor agonist immunoconjugates having Formulae **I-a** and **I-b** are useful for treating Behcets disease. In one embodiment, glucocorticoid receptor agonist immunoconjugates having Formulae **I-a** and **I-b** are useful for treating a spondyloarthropathy. In one embodiment, glucocorticoid receptor agonist immunoconjugates having Formulae **I-a** and **I-b** are useful for treating psoriasis.

[0006] In another embodiment, the present disclosure provides a glucocorticoid receptor agonist represented by Formulae **VII**, **VII-A**, **VII-B**, **VIII**, **VIII-a**, **VIII-b**, **IX**, **IX-a**, and **IX-b**, or by Formulae **VII'**, **VII-A'**, **VII-B'**, **VIII'**, **VIII-a'**, **VIII-b'**, **IX'**, **IX-a'**, **IX-b'**, **VII"**, **VII-A"**, **VII-B"**, **VIII"**, **VIII-a"**, **VIII-b"**, **IX"**, **IX-a"**, and **IX-b"**, below, (wherein R^{7b} is hydrogen) and the pharmaceutically acceptable salts, solvates, or prodrugs thereof. In another embodiment, the present disclosure provides a glucocorticoid receptor agonist represented by Formulae **VII**, **VII-A**, **VII-B**, **VIII**, **VIII-a**, **VIII-b**, **IX**, **IX-a**, and **IX-b**, or by Formulae **VII'**, **VII-A'**, **VII-B'**, **VIII'**, **VIII-a'**, **VIII-b'**, **IX'**, **IX-a'**, **IX-b'**, **VII"**, **VII-A"**, **VII-B"**, **VIII"**, **VIII-a"**, **VIII-b"**, **IX"**, **IX-a"**, and **IX-b"**, below, (wherein R^{7b} is hydrogen). Compounds having Formulae **VII**, **VII-A**, **VII-B**, **VIII**, **VIII-a**, **VIII-b**, **IX**, **IX-a**, and **IX-b**, or Formulae **VII'**, **VII-A'**, **VII-B'**, **VIII'**, **VIII-a'**, **VIII-b'**, **IX'**, **IX-a'**, **IX-b'**, **VII"**, **VII-A"**, **VII-B"**, **VIII"**, **VIII-a"**, **VIII-b"**, **IX"**, **IX-a"**, and **IX-b"**, are useful for treating autoimmune diseases such as, but not limited to, rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, adult Crohn's disease,

pediatric Crohn's disease, ulcerative colitis, plaque psoriasis, hidradenitis suppurativa, uveitis, Behcets disease, a spondyloarthropathy, or psoriasis. In one embodiment, compounds having Formulae **VII**, **VII-A**, **VII-B**, **VIII**, **VIII-a**, **VIII-b**, **IX**, **IX-a**, and **IX-b**, or Formulae **VII'**, **VII-A'**, **VII-B'**, **VIII'**, **VIII-a'**, **VIII-b'**, **IX'**, **IX-a'**, **IX-b'**, **VII"**, **VII-A"**, **VII-B"**, **VIII"**, **VIII-a"**, **VIII-b"**, **IX"**, **IX-a"**, and **IX-b"**, are useful for treating rheumatoid arthritis. In one embodiment, compounds having Formulae **VII**, **VII-A**, **VII-B**, **VIII**, **VIII-a**, **VIII-b**, **IX**, **IX-a**, and **IX-b**, or Formulae **VII'**, **VII-A'**, **VII-B'**, **VIII'**, **VIII-a'**, **VIII-b'**, **IX'**, **IX-a'**, **IX-b'**, **VII"**, **VII-A"**, **VII-B"**, **VIII"**, **VIII-a"**, **VIII-b"**, **IX"**, **IX-a"**, and **IX-b"**, are useful for treating juvenile idiopathic arthritis. In one embodiment, compounds having Formulae **VII**, **VII-A**, **VII-B**, **VIII**, **VIII-a**, **VIII-b**, **IX**, **IX-a**, and **IX-b**, or Formulae **VII'**, **VII-A'**, **VII-B'**, **VIII'**, **VIII-a'**, **VIII-b'**, **IX'**, **IX-a'**, **IX-b'**, **VII"**, **VII-A"**, **VII-B"**, **VIII"**, **VIII-a"**, **VIII-b"**, **IX"**, **IX-a"**, and **IX-b"**, are useful for treating psoriatic arthritis. In one embodiment, compounds having Formulae **VII**, **VII-A**, **VII-B**, **VIII**, **VIII-a**, **VIII-b**, **IX**, **IX-a**, and **IX-b**, or Formulae **VII'**, **VII-A'**, **VII-B'**, **VIII'**, **VIII-a'**, **VIII-b'**, **IX'**, **IX-a'**, **IX-b'**, **VII"**, **VII-A"**, **VII-B"**, **VIII"**, **VIII-a"**, **VIII-b"**, **IX"**, **IX-a"**, and **IX-b"**, are useful for treating ankylosing spondylitis. In one embodiment, compounds having Formulae **VII**, **VII-A**, **VII-B**, **VIII**, **VIII-a**, **VIII-b**, **IX**, **IX-a**, and **IX-b**, or Formulae **VII'**, **VII-A'**, **VII-B'**, **VIII'**, **VIII-a'**, **VIII-b'**, **IX'**, **IX-a'**, **IX-b'**, **VII"**, **VII-A"**, **VII-B"**, **VIII"**, **VIII-a"**, **VIII-b"**, **IX"**, **IX-a"**, and **IX-b"**, are useful for treating adult Crohn's disease. In one embodiment, compounds having Formulae **VII**, **VII-A**, **VII-B**, **VIII**, **VIII-a**, **VIII-b**, **IX**, **IX-a**, and **IX-b**, or Formulae **VII'**, **VII-A'**, **VII-B'**, **VIII'**, **VIII-a'**, **VIII-b'**, **IX'**, **IX-a'**, **IX-b'**, **VII"**, **VII-A"**, **VII-B"**, **VIII"**, **VIII-a"**, **VIII-b"**, **IX"**, **IX-a"**, and **IX-b"**, are useful for treating pediatric Crohn's disease. In one embodiment, compounds having Formulae **VII**, **VII-A**, **VII-B**, **VIII**, **VIII-a**, **VIII-b**, **IX**, **IX-a**, and **IX-b**, or Formulae **VII'**, **VII-A'**, **VII-B'**, **VIII'**, **VIII-a'**, **VIII-b'**, **IX'**, **IX-a'**, **IX-b'**, **VII"**, **VII-A"**, **VII-B"**, **VIII"**, **VIII-a"**, **VIII-b"**, **IX"**, **IX-a"**, and **IX-b"**, are useful for treating ulcerative colitis. In one embodiment, compounds having Formulae **VII**, **VII-A**, **VII-B**, **VIII**, **VIII-a**, **VIII-b**, **IX**, **IX-a**, and **IX-b**, or Formulae **VII'**, **VII-A'**, **VII-B'**, **VIII'**, **VIII-a'**, **VIII-b'**, **IX'**, **IX-a'**, **IX-b'**, **VII"**, **VII-A"**, **VII-B"**, **VIII"**, **VIII-a"**, **VIII-b"**, **IX"**, **IX-a"**, and **IX-b"**, are useful for treating plaque psoriasis. In one embodiment, compounds having Formulae **VII**, **VII-A**, **VII-B**, **VIII**, **VIII-a**, **VIII-b**, **IX**, **IX-a**, and **IX-b**, or Formulae **VII'**, **VII-A'**, **VII-B'**, **VIII'**, **VIII-a'**, **VIII-b'**, **IX'**, **IX-a'**, **IX-b'**, **VII"**, **VII-A"**, **VII-B"**, **VIII"**, **VIII-a"**, **VIII-b"**, **IX"**, **IX-a"**, and **IX-b"**, are useful for treating hidradenitis suppurativa. In one embodiment, compounds having Formulae **VII**, **VII-A**, **VII-B**, **VIII**, **VIII-a**, **VIII-b**, **IX**, **IX-a**, and **IX-b**, or Formulae **VII'**, **VII-A'**, **VII-B'**, **VIII'**, **VIII-a'**, **VIII-b'**, **IX'**, **IX-a'**, **IX-b'**, **VII"**, **VII-A"**, **VII-B"**, **VIII"**, **VIII-a"**, **VIII-b"**, **IX"**, **IX-a"**, and **IX-b"**, are useful for treating uveitis. In one embodiment, compounds having Formulae **VII**, **VII-A**, **VII-B**, **VIII**, **VIII-a**, **VIII-b**, **IX**, **IX-a**, and **IX-b**, or Formulae **VII'**, **VII-A'**, **VII-B'**, **VIII'**, **VIII-a'**, **VIII-b'**, **IX'**, **IX-a'**, **IX-b'**, **VII"**, **VII-A"**, **VII-B"**, **VIII"**, **VIII-a"**, **VIII-b"**, **IX"**, **IX-a"**, and **IX-b"**, are useful for treating Behcets disease. In one embodiment, compounds having Formulae **VII**, **VII-A**, **VII-B**, **VIII**, **VIII-a**, **VIII-b**, **IX**, **IX-a**, and **IX-b**, or Formulae **VII'**, **VII-A'**, **VII-B'**, **VIII'**,

VIII-a', **VIII-b'**, **IX'**, **IX-a'**, **IX-b'**, **VII"**, **VII-A"**, **VII-B"**, **VIII"**, **VIII-a"**, **VIII-b"**, **IX"**, **IX-a"**, and **IX-b"**, are useful for treating a spondyloarthropathy. In one embodiment, compounds having Formulae **VII**, **VII-A**, **VII-B**, **VIII**, **VIII-a**, **VIII-b**, **IX**, **IX-a**, and **IX-b**, or Formulae **VII'**, **VII-A'**, **VII-B'**, **VIII'**, **VIII-a'**, **VIII-b'**, **IX'**, **IX-a'**, **IX-b'**, **VII"**, **VII-A"**, **VII-B"**, **VIII"**, **VIII-a"**, **VIII-b"**, **IX"**, **IX-a"**, and **IX-b"**, are useful for treating psoriasis.

[0007] In another embodiment, the present disclosure provides compounds represented by Formulae **VII**, **VII-A**, **VII-B**, **VIII**, **VIII-a**, **VIII-b**, **IX**, **IX-a**, and **IX-b**, or by Formulae **VII'**, **VII-A'**, **VII-B'**, **VIII'**, **VIII-a'**, **VIII-b'**, **IX'**, **IX-a'**, **IX-b'**, **VII"**, **VII-A"**, **VII-B"**, **VIII"**, **VIII-a"**, **VIII-b"**, **IX"**, **IX-a"**, and **IX-b"**, as synthetic intermediates that can be used to prepare glucocorticoid receptor agonist immunoconjugates having Formulae **I-a** and **I-b.**

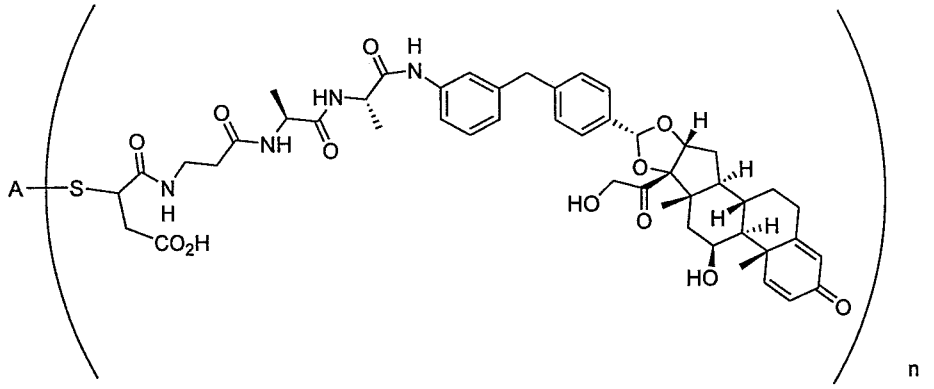
[0008] In another embodiment, the present disclosure provides a pharmaceutical composition comprising a glucocorticoid receptor agonist immunoconjugate represented by Formulae **I-a** and **I-b**, or a glucocorticoid receptor agonist represented by Formulae **VII**, **VII-A**, **VII-B**, **VIII**, **VIII-a**, **VIII-b**, **IX**, **IX-a**, and **IX-b**, or by Formulae **VII'**, **VII-A'**, **VII-B'**, **VIII'**, **VIII-a'**, **VIII-b'**, **IX'**, **IX-a'**, **IX-b'**, **VII"**, **VII-A"**, **VII-B"**, **VIII"**, **VIII-a"**, **VIII-b"**, **IX"**, **IX-a"**, and **IX-b"**, and an excipient and/or a pharmaceutically acceptable carrier.

[0009] In another embodiment, the present disclosure provides a glucocorticoid receptor agonist immunoconjugate represented by Formulae **I-a** and **I-b**, or a glucocorticoid receptor agonist represented by Formulae **VII**, **VII-A**, **VII-B**, **VIII**, **VIII-a**, **VIII-b**, **IX**, **IX-a**, and **IX-b** or by Formulae **VII'**, **VII-A'**, **VII-B'**, **VIII'**, **VIII-a'**, **VIII-b'**, **IX'**, **IX-a'**, **IX-b'**, **VII"**, **VII-A"**, **VII-B"**, **VIII"**, **VIII-a"**, **VIII-b"**, **IX"**, **IX-a"**, and **IX-b"**, for use in treatment of autoimmune diseases.

[0010] In another embodiment, the present disclosure provides a use of a glucocorticoid receptor agonist immunoconjugates represented by Formulae **I-a** and **I-b**, or a glucocorticoid receptor agonist represented by Formulae **VII**, **VII-A**, **VII-B**, **VIII**, **VIII-a**, **VIII-b**, **IX**, **IX-a**, and **IX-b**, or by Formulae **VII'**, **VII-A'**, **VII-B'**, **VIII'**, **VIII-a'**, **VIII-b'**, **IX'**, **IX-a'**, **IX-b'**, **VII"**, **VII-A"**, **VII-B"**, **VIII"**, **VIII-a"**, **VIII-b"**, **IX"**, **IX-a"**, and **IX-b"**, for the manufacture of a medicament for treating autoimmune diseases.

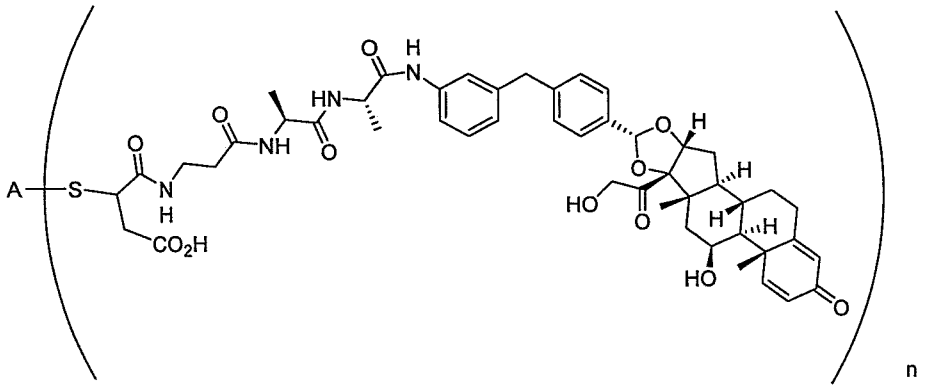
[0011] In another embodiment, the present disclosure provides methods of preparing glucocorticoid receptor agonist immunoconjugates represented by Formulae **I-a** and **I-b.**

[0011a] In one aspect, there is provided a compound:



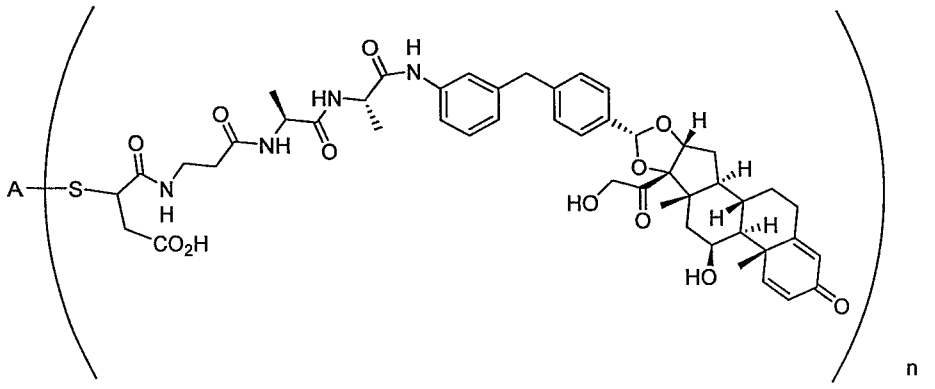
wherein n is 4, and A is an antibody comprising SEQ ID NO: 66 and SEQ ID NO:73.

[0011b] In another aspect, there is provided a compound:



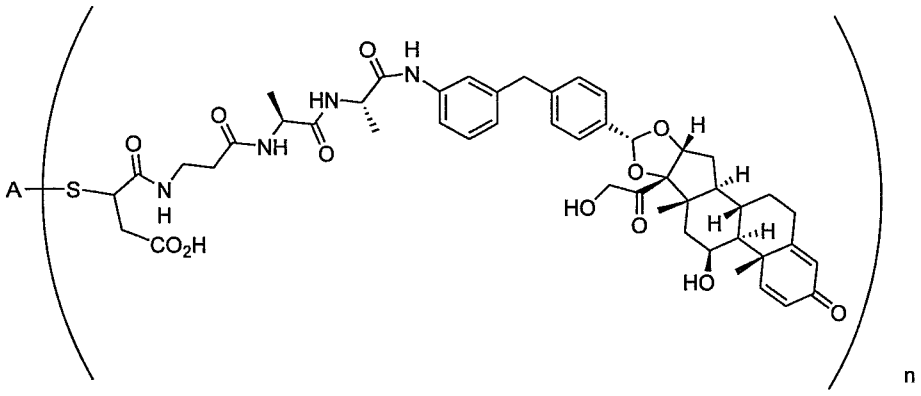
wherein n is 2, and A is an antibody comprising SEQ ID NO: 66 and SEQ ID NO:73.

[0011c] In another aspect, there is provided a compound:



wherein n is 4, and A is adalimumab.

[0011d] In another aspect, there is provided a compound:



wherein n is 2, and A is adalimumab.

[0011e] In another aspect, there is provided a pharmaceutical composition comprising the compound disclosed herein, and a pharmaceutically acceptable carrier.

BRIEF DESCRIPTION OF THE DRAWINGS/FIGURES

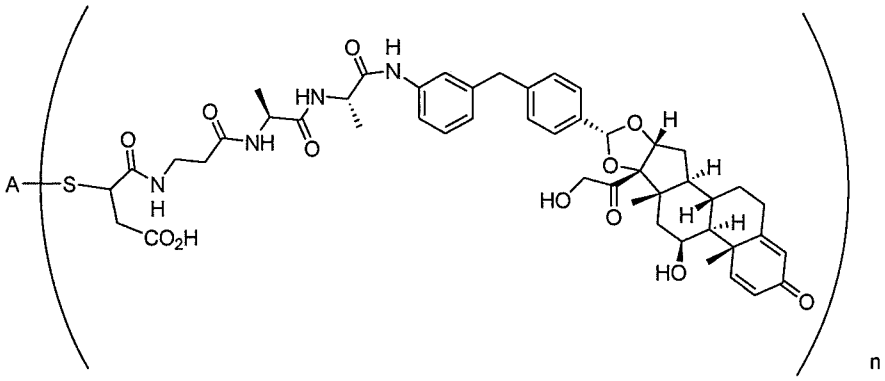
[0012] Figure 1 shows the proteolytic stability of an ADC containing a steroid and an ADC containing MMAE (monomethyl auristatin E). (See Example 76.)

[0013] Figure 2 shows the kinetics of drug linker loss of steroid ADC in mice. (See Example 77.)

[0014] Figure 3 shows the activity of a single therapeutic dose response of anti-mTNFa steroid ADC in a mouse model of arthritis. (See Example 85.)

What is claimed is:

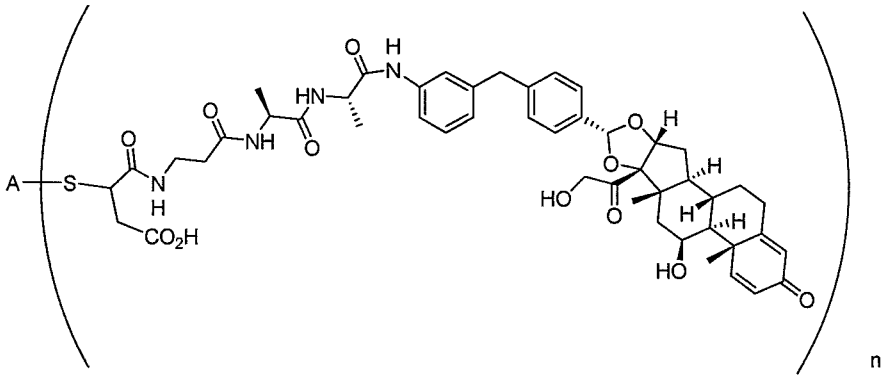
1. A compound:



wherein n is 4, and A is an antibody comprising SEQ ID NO: 66 and SEQ ID NO:73.

2. A pharmaceutical composition comprising the compound according to claim 1, and a pharmaceutically acceptable carrier.

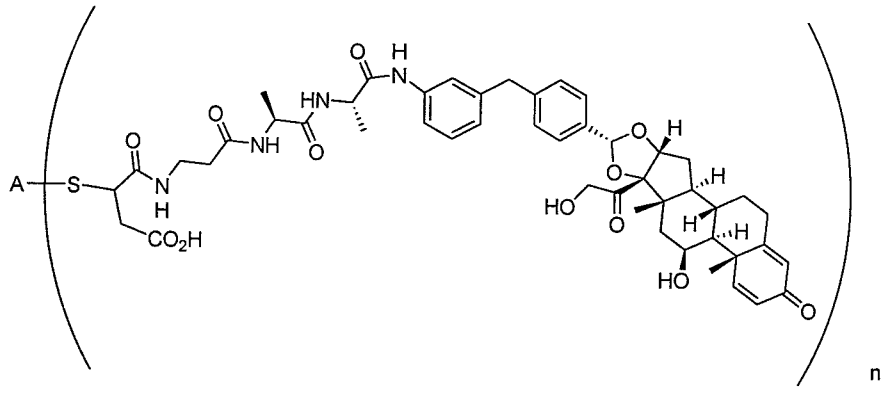
3. A compound:



wherein n is 2, and A is an antibody comprising SEQ ID NO: 66 and SEQ ID NO:73.

4. A pharmaceutical composition comprising the compound according to claim 3, and a pharmaceutically acceptable carrier.

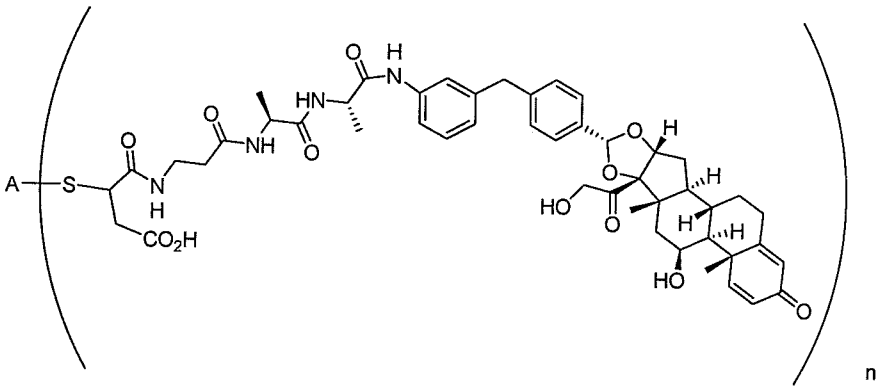
5. A compound:



wherein n is 4, and A is adalimumab.

6. A pharmaceutical composition comprising the compound according to claim 5, and a pharmaceutically acceptable carrier.

7. A compound:



wherein n is 2, and A is adalimumab.

8. A pharmaceutical composition comprising the compound according to claim 7, and a pharmaceutically acceptable carrier.