GLUCOCORTICOID RECEPTOR AGONIST AND IMMUNOCONJUGATES THEREOF

RELATED APPLICATIONS

[0001] This application claims priority to US Provisional Application Number 62/593,776, filed December 1, 2017 and US Provisional Application Number 62/595,054, filed December 5, 2017, each of which is incorporated by reference in its entirety.

SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on November 28, 2018, is named A103017_1490WO_SL.txt and is 14,758 bytes in size.

TECHNICAL FIELD

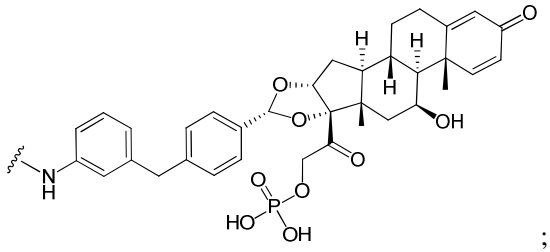
[0003] Tumor Necrosis Factor α (TNFα) plays a central role in the pathophysiology of several human disorders, and anti-TNFα agents have clinically validated therapeutic utility in the treatment of autoimmune and inflammatory disorders, such as rheumatoid arthritis, psoriasis and inflammatory bowel disease. Despite their success in the clinic, anti-TNFα 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-TNFα biologics may also develop an immunogenic response to the therapeutic thus limiting its effectiveness. Therefore anti-TNFα therapies with lower immunogenicity and high efficacy would be useful for further controlling disease.

[0004] Synthetic glucocorticoid receptor agonists 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. There is a need to develop therapeutics with enhanced efficacy and longer duration of action compared to anti-TNF antibodies and with minimal unwanted effects.

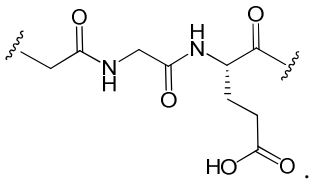
SUMMARY

[0005] The present disclosure provides glucocorticoid receptor agonist immunoconjugates useful for treating autoimmune diseases.

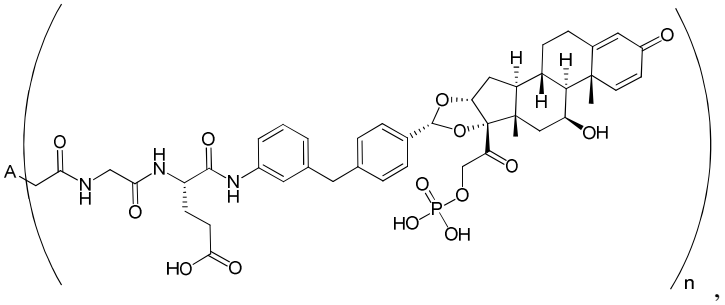
[0006] In one aspect, the present disclosure provides an antibody drug conjugate comprising:
(a) an anti-TNFα antibody comprising a heavy chain set forth as SEQ ID NO: 3 and a light chain set forth as SEQ ID NO: 4; and (b) a glucocorticoid receptor agonist comprising a radical represented by the formula:


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and wherein the antibody is conjugated to the glucocorticoid receptor agonist via a linker represented by the formula:

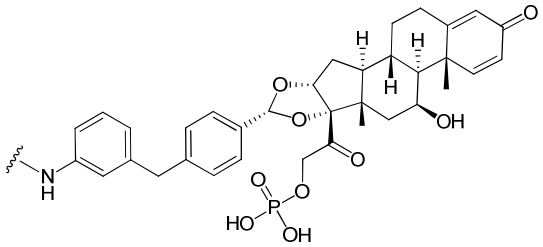

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[0007] In one example, the present disclosure provides an antibody drug conjugate according to the formula:

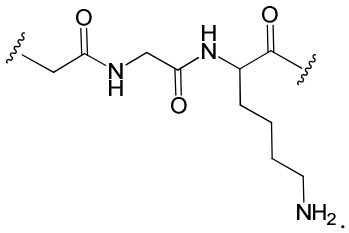

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wherein A is the antibody and n is an integer from 1-10.

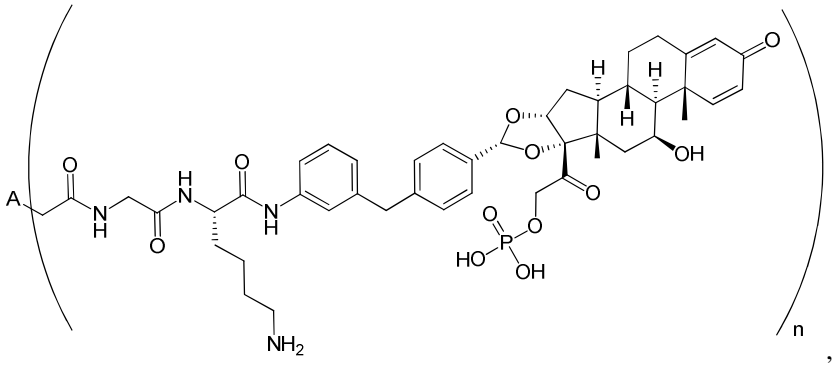
[0008] In one example, the present disclosure provides an antibody drug conjugate comprising:
(a) an anti-TNFα antibody comprising a heavy chain set forth as SEQ ID NO: 3 and a light chain set forth as SEQ ID NO: 4; and (b) a glucocorticoid receptor agonist comprising a radical represented by the formula:


;

and wherein the antibody is conjugated to the glucocorticoid receptor agonist via a linker represented by the formula:


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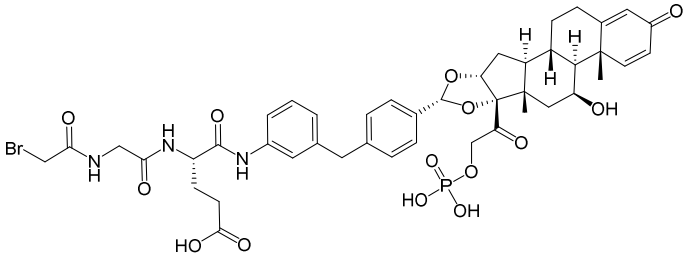
[0009] In one example, the present disclosure provides an antibody drug conjugate according to the formula:



wherein A is the antibody and n is an integer from 1-10.

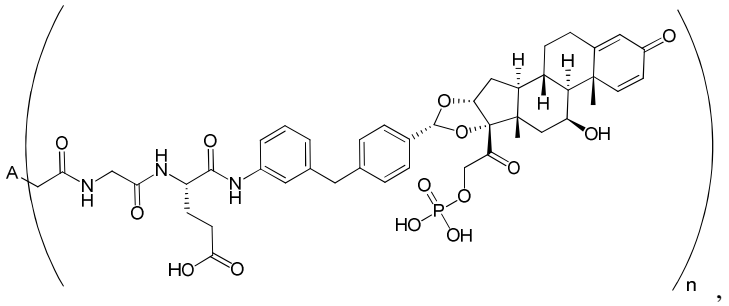
[0010] In one example, the present disclosure provides the antibody drug conjugate of any preceding example, wherein the drug loading is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10. In one example, the present disclosure provides the antibody drug conjugate of any preceding example, wherein the drug loading is 4, for example, n in the foregoing antibody drug conjugate formula equals 4. In one example, the present disclosure provides the antibody drug conjugate of any preceding example, wherein the drug loading is 2, for example, n in the foregoing antibody drug conjugate formula equals 2.

[0011] In one example, the present disclosure provides a method of making the antibody drug conjugate of any preceding example, comprising the step of conjugating the antibody to the glucocorticoid receptor agonist. In one example, the present disclosure provides the method of the preceding example, further comprising the step of introducing a PO_4 moiety on the glucocorticoid receptor agonist before conjugating the antibody to the glucocorticoid receptor agonist. In one example, the present disclosure provides the method of any preceding example, wherein the conjugating comprises partially reducing the antibody, and alkylating the partially reduced antibody with a compound according to the formula:



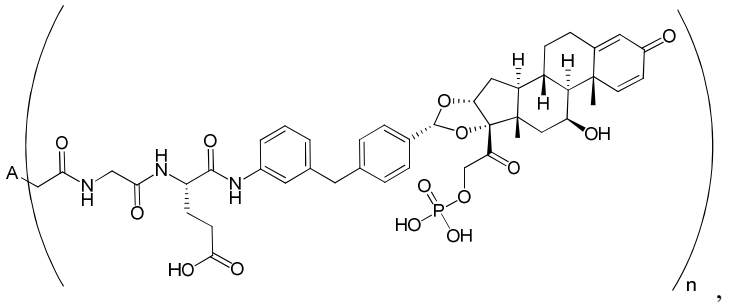
[0012] In one example, the present disclosure provides a pharmaceutical composition comprising the antibody drug conjugate of any preceding example and a pharmaceutically acceptable carrier. In one example, the present disclosure provides the pharmaceutical composition of any of the preceding examples, comprising a drug to antibody ratio (DAR) of 1-10.

[0013] In one aspect, the present disclosure provides an antibody drug conjugate according to the formula:



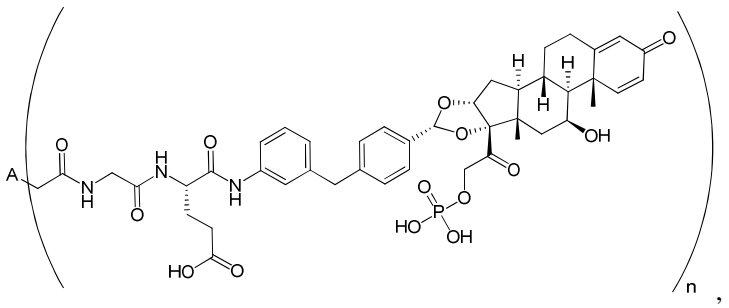
wherein A is adalimumab and n is 4.

[0014] In one preferred example, the present disclosure provides an antibody drug conjugate according to the formula:

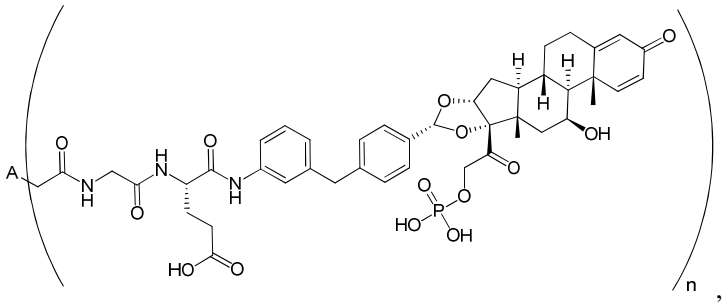


wherein A is an anti-TNFα antibody comprising a heavy chain set forth as SEQ ID NO: 3 and a light chain set forth as SEQ ID NO: 4, and n is 4.

[0015] In another aspect, the present disclosure provides an antibody drug conjugate according to the formula:



[0016] wherein A is adalimumab and n is 2. In another preferred example, the present disclosure provides an antibody drug conjugate according to the formula:



wherein A is an anti-TNFα antibody comprising a heavy chain set forth as SEQ ID NO: 3 and a light chain set forth as SEQ ID NO: 4, and n is 2.

[0017] In one preferred example, the present disclosure provides the pharmaceutical composition of any preceding example, comprising a drug to antibody ratio (DAR) of 2.0.

[0018] In one preferred example, the present disclosure provides the pharmaceutical composition of any preceding example, comprising a drug to antibody ratio (DAR) of 4.0.

[0019] In one example, the present disclosure provides a method of treating a condition selected from rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, ulcerative colitis, adult Crohn's disease, pediatric Crohn's disease, uveitis, hidradenitis suppurativa, and juvenile idiopathic arthritis in a subject, comprising administering an effective amount of the antibody drug conjugate of any preceding example or the pharmaceutical composition of any preceding example to the subject.

[0020] In one example, the present disclosure provides the antibody drug conjugate of any preceding example or the pharmaceutical composition of any preceding example for use in the treatment of a condition selected from rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, ulcerative colitis, adult Crohn's disease, pediatric Crohn's disease, uveitis, hidradenitis suppurativa, and juvenile idiopathic arthritis.

[0021] In one example, the present disclosure provides use of the antibody drug conjugate of any preceding example or the pharmaceutical composition of any preceding example for preparation of a medicament for treating a condition selected from rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, ulcerative colitis, adult Crohn's disease, pediatric Crohn's disease, uveitis, hidradenitis suppurativa, and juvenile idiopathic arthritis.

[0022] In one example, the present disclosure provides a kit comprising: (a) a container comprising the antibody drug conjugate of any preceding example or the pharmaceutical composition of any preceding example; and (b) a label or package insert on or associated with the one or more containers, wherein the label or package insert indicates that the antibody drug conjugate or pharmaceutical composition is used for treating a condition selected from rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, plaque

psoriasis, ulcerative colitis, adult Crohn's disease, pediatric Crohn's disease, uveitis, hidradenitis suppurativa, and juvenile idiopathic arthritis.

[0023] In one example, the present disclosure provides a method of delivering a glucocorticoid receptor agonist to a TNFα-expressing cell, comprising the step of contacting the cell with the antibody drug conjugate of any preceding example. In one example, the present disclosure provides a method of determining anti-inflammatory activity of an antibody drug conjugate comprising: (a) contacting a TNFα-expressing cell with the antibody drug conjugate of any preceding example; and (b) determining release of pro-inflammatory cytokines from the cell as compared to a control cell.

BRIEF DESCRIPTION OF THE DRAWINGS

[0024] Fig. 1 provides a chromatographic resolution of BrAc-Gly-Glu-glucocorticoid receptor modulator (GRM)-PO_4, as performed and described in Example 7. As shown, the ADC is a heterogeneous ADC mixture containing ADCs with two drug linker molecules attached, and ADCs with four drug linker molecules attached.

[0025] Fig. 2 sets forth deconvoluted MS data of adalimumab conjugated with BrAc-Gly-Glu-glucocorticosteroid-PO_4. As shown, conjugation was achieved.

[0026] Fig. 3 provides a graph demonstrating the efficacy of a high and low dose of ADC1 compared to anti-TNFα mAb (high dose) or vehicle in a mouse collagen-induced arthritis (CIA) model of arthritis, as performed and described in Example 7. As shown, a single dose of anti-TNFa glucocorticosteroid ADC1 exhibited an extended duration of action through amelioration of paw swelling for ~28 days compared to anti-TNFa mAb or vehicles alone.

[0027] Fig. 4 is a graph of concentration (ug/ml) for closed and open ring ADC in cynomolgus monkeys over time, as performed and described in Example 7. As shown, the ring closed form is susceptible to the reverse Michael reaction and subsequent loss of linker-drug *in vivo*.

DETAILED DESCRIPTION

[0028] Provided herein are glucocorticoid receptor agonist immunoconjugates, glucocorticoid receptor agonists, and methods of making and using the same.

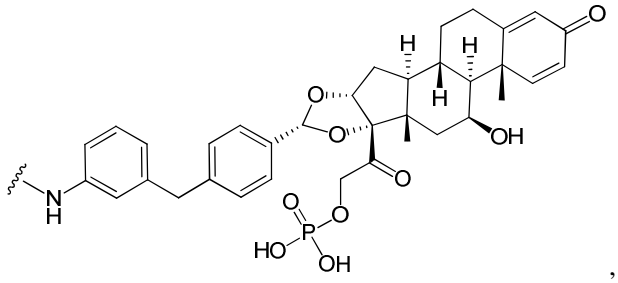
[0029] Provided herein is an antibody drug conjugate according to the formula:

WHAT IS CLAIMED IS:

1. An antibody drug conjugate comprising:

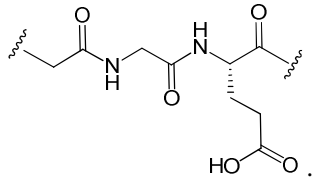
(a) an anti-TNFα antibody comprising a heavy chain set forth as SEQ ID NO: 3 and a light chain set forth as SEQ ID NO: 4; and

(b) a glucocorticoid receptor agonist comprising a radical represented by the formula:



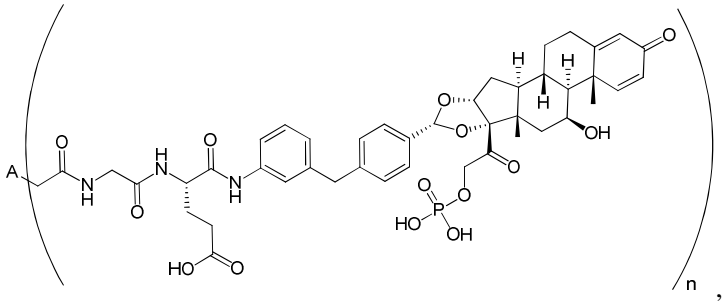
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wherein the antibody is conjugated to the glucocorticoid receptor agonist via a linker represented by the formula:



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2. The antibody drug conjugate of claim 1, according to the formula:



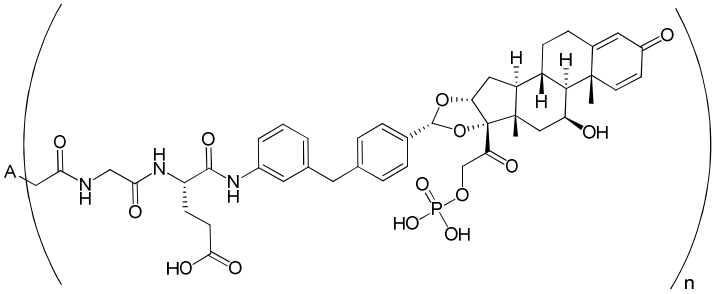
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wherein A is the antibody and n is an integer from 1-10.

3. The antibody drug conjugate of claim 2, wherein n is 4.

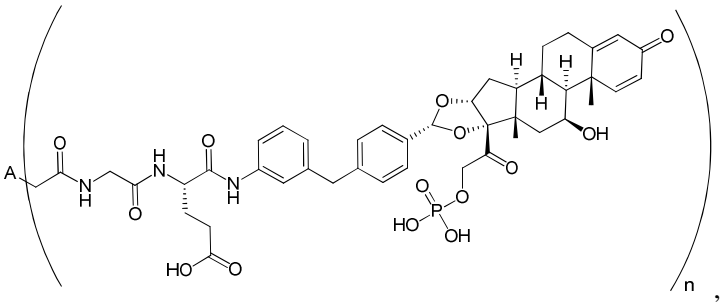
4. The antibody drug conjugate of claim 2, wherein n is 2.

5. An antibody drug conjugate according to the formula:



wherein A is adalimumab and n is 4.

6. An antibody drug conjugate according to the formula:



wherein A is adalimumab and n is 2.