acute phase and/or at onset and duration of an acute flare) and for a limited amount of time so as to maximixe short term relief, minimize long term progression of the disease, and minimize long term toxicological and other adverse effects.

In one aspect, there is provided the use of a compound selected from (E) isomer, (Z) isomer, and a mixture of (E) and (Z) isomer of 2-[(3R)-3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile, or a pharmaceutically acceptable salt of any of the foregoing compounds in the manufacture of a medicament for treating thrombotic thrombocytopenic purpura, polyarteritis nodosa, cutaneous lupus, cutaneous form of systemic sclerosis (CREST), mixed connective tissue disease, cryoglobulinemia, primary biliary sclerosis, sclerosing cholangitis, AI urticaria, IgA nephropathy, lupus nephritis, granulomatosis with polyangiitis, or pemphigus vulgaris in a mammal.

In another aspect, there is provided the use of a compound selected from (E) isomer, (Z) isomer, and a mixture of (E) and (Z) isomer of 2-[(3R)-3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile, or a pharmaceutically acceptable salt of any of the foregoing compounds, in the manufacture of a medicament for treating thrombotic thrombocytopenic purpura, polyarteritis nodosa, cutaneous lupus, cutaneous form of systemic sclerosis (CREST), systemic sclerosis, mixed connective tissue disease, cryoglobulinemia, primary biliary sclerosis, sclerosing cholangitis, AI urticaria, IgA nephropathy, lupus nephritis, autoimmune hemolytic anemia, granulomatosis with polyangiitis, or pemphigus vulgaris in a mammal.

In another aspect, there is provided the use of a compound selected from (E) isomer, (Z) isomer, and a mixture of (E) and (Z) isomer of 2-[(3R)-3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile, or a pharmaceutically acceptable salt of any of the foregoing compounds, in the manufacture of a medicament for treating an acute inflammatory and/or autoimmune disease in a mammal in need thereof in place of or in combination with a corticosteroid therapy, wherein said (E) isomer, (Z) isomer, or mixture of (E) and (Z) isomer of 2-[(3R)-3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile, or
a pharmaceutically acceptable salt of any of the foregoing compounds is to be optionally administered in combination with a noncorticosteroidal immunosupressive and/or antiinflammatory agent.

In another aspect, there is provided the use of a compound selected from (E) isomer, (Z) isomer, and a mixture of (E) and (Z) isomer of 2-[(3R)-3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile, or a pharmaceutically acceptable salt of any of the foregoing compounds, in the manufacture of a medicament for treating an inflammatory and/or autoimmune disease in a mammal in need thereof in place of or in combination with a corticosteroid therapy,

wherein: said (E) isomer, (Z) isomer, or mixture of (E) and (Z) isomer of 2-[(3R)-3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile, or a pharmaceutically acceptable salt of any of the foregoing compounds, is to be optionally administered in combination with a noncorticosteroidal immunosupressive and/or antiinflammatory agent.

In another aspect, there is provided a sulfonic acid or carboxylic acid salt of a compound selected from (E) isomer, (Z) isomer, and a mixture of (E) and (Z) isomer of 2-[(3R)-3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]-pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile.

In another aspect, there is provided an amorphous form of a pharmaceutically acceptable salt of a compound selected from (E) isomer, (Z) isomer, and a mixture of (E) and (Z) isomer of 2-[(3R)-3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]-pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile.

In a further aspect, there is provided a pharmaceutical composition comprising: a pharmaceutically acceptable excipient; and the sulfonic acid or carboxylic acid salt of compound disclosed herein or the amorphous form of a pharmaceutically acceptable salt of a compound selected from (E) isomer, (Z) isomer, and a mixture of (E) and (Z) isomer of 2-[(3R)-3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]-pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile.

In yet another aspect, there is provided the use of a pharmaceutical composition disclosed herein in the manufacture of a medicament for treating an autoimmune disease, an inflammatory disease, or cancer in a mammal in need thereof.

Accordingly, in a first aspect disclosed herein is a sulfonic acid or a carboxylic acid salt of compound (I).

Embodiment (1a)

In one embodiment (embodiment (Ia)) of the first aspect, the salt is a sulfonic acid salt of compound (I).

What is Claimed:

1. The use of a compound selected from (E) isomer, (Z) isomer, and a mixture of (E) and (Z) isomer of 2-[(3R)-3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile, or a pharmaceutically acceptable salt of any of the foregoing compounds, in the manufacture of a medicament for treating thrombotic thrombocytopenic purpura, polyarteritis nodosa, cutaneous lupus, cutaneous form of systemic sclerosis (CREST), mixed connective tissue disease, cryoglobulinemia, primary biliary sclerosis, sclerosing cholangitis, AI urticaria, IgA nephropathy, lupus nephritis, granulomatosis with polyangiitis, or pemphigus vulgaris in a mammal.

2. The use of a compound selected from (E) isomer, (Z) isomer, and a mixture of (E) and (Z) isomer of 2-[(3R)-3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile, or a pharmaceutically acceptable salt of any of the foregoing compounds, in the manufacture of a medicament for treating an acute inflammatory and/or autoimmune disease in a mammal in need thereof in place of or in combination with a corticosteroid therapy, wherein:

said (E) isomer, (Z) isomer, or a mixture of (E) and (Z) isomer of 2-[(3R)-3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile, or a pharmaceutically acceptable salt of any of the foregoing compounds, is to be optionally administered in combination with a noncorticosteroidal immunosupressive and/or antiinflammatory agent.

3. The use of a compound selected from (E) isomer, (Z) isomer, and a mixture of (E) and (Z) isomer of 2-[(3R)-3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile, or a pharmaceutically acceptable salt of any of the foregoing compounds, in the manufacture of a medicament for treating an inflammatory and/or autoimmune disease in a mammal in need thereof in place of or in combination with a corticosteroid therapy, wherein:

said (E) isomer, (Z) isomer, or mixture of (E) and (Z) isomer of 2-[(3R)-3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile, or a pharmaceutically acceptable salt of any of the foregoing compounds,

is to be optionally administered in combination with a noncorticosteroidal immunosupressive and/or antiinflammatory agent.

4. The use of any of Claims 1-3, wherein: the compound is a substantially pure (E) or (Z) isomer of 2-[(3R)-3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile, or a pharmaceutically acceptable salt of the compound; and the mammal is a human.

5. The use of Claim 4, wherein at least 85% w/w of 2-[(3R)-3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile or at least 85% w/w of a pharmaceutically acceptable salt of 2-[(3R)-3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile is the (E) isomer.

6. The use of Claim 4, wherein at least 90% w/w of 2-[(3R)-3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile or at least 90% w/w of a pharmaceutically acceptable salt of 2-[(3R)-3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile is the (E) isomer.

7. The use of any of Claims 3-6, wherein: the compound is 2-[(3R)-3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile; and the disease to be treated is pemphigus vulgaris.

8. The use of any of Claims 1-7, wherein the compound or a pharmaceutically acceptable salt thereof is to be optionally administered in combination with an immunosuppressive agent selected from interferon alpha, interferon gamma, cyclophosphamide, tacrolimus, mycophenolate mofetil, methotrexate, dapsone, sulfasalazine, azathioprine, an anti-CD20 agent, anti-TNFalpha agent, anti-IL6 agent toward ligand or its receptors, anti-IL17 agent to ligand or its receptors, anti-IL1 agent to ligand or its receptors, anti-IL2 agent to ligand or its receptors, anti-CD2 agent, anti-CD3 agent, anti-CD80/86 agent, anti-sphingosine-1-phosphate receptor agent, anti-C5 agent, anti-mTOR agent, anti-calcineurin agent, anti-BAFF/BlyS agent, leflunomide and teriflunomide.

9. The use of any of Claims 1-7, wherein the compound or a pharmaceutically acceptable salt thereof is to be optionally administered in combination with rituximab, ofatumumab, obinutuzumab, or veltuzumab.

10. A sulfonic acid or carboxylic acid salt of a compound selected from (E) isomer, (Z) isomer, and a mixture of (E) and (Z) isomer of 2-[(3R)-3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]-pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile.

11. The sulfonic acid or carboxylic acid salt of the compound of Claim 10, wherein the salt is a sulfonic acid salt selected from mono- or di-methanesulfonic acid salt.

12. An amorphous form of a pharmaceutically acceptable salt of a compound selected from (E) isomer, (Z) isomer, and a mixture of (E) and (Z) isomer of 2-[(3R)-3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]-pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile.

13. The amorphous form of the pharmaceutically acceptable salt of the compound of Claim 12, wherein the pharmaceutically acceptable salt is a sulfonic acid or a carboxylic acid salt.

14. The amorphous form of the pharmaceutically acceptable salt of the compound of Claim 12, wherein the pharmaceutically acceptable salt is a sulfonic acid salt selected from mono- or di-methanesulfonic acid salt.

15. The amorphous form of the pharmaceutically acceptable salt of the compound of any of Claims 12-14, wherein the amorphous form is substantially free of any crystalline form(s) of the pharmaceutically acceptable salt of said compound.

16. The amorphous form of the pharmaceutically acceptable salt of the compound of any of Claims 12-15, wherein at least 90% w/w of the pharmaceutically acceptable salt of said compound is in amorphous form.

17. The sulfonic acid or carboxylic acid salt of the compound of any of Claims 10-11, wherein the salt of said compound is a substantially pure (E) or (Z) isomer.

18. The amorphous form of the pharmaceutically acceptable salt of the compound of any of Claims 12-16, wherein the salt of said compound is a substantially pure (E) or (Z) isomer.

19. The sulfonic acid or carboxylic acid salt of the compound of Claim 17, wherein at least 80% w/w of the salt of the compound is the (E) isomer.

20. The amorphous form of the pharmaceutically acceptable salt of the compound of Claim 18, wherein at least 80% w/w of the pharmaceutically acceptable salt of the compound is the (E) isomer.

21. A pharmaceutical composition comprising:
a pharmaceutically acceptable excipient; and the sulfonic acid or carboxylic acid salt of compound of any of Claims 10-11, 17, and 19; or the amorphous form of a pharmaceutically acceptable salt of a compound selected from (E) isomer, (Z) isomer, and a mixture of (E) and (Z) isomer of 2-[(3R)-3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]-pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile of any of Claims 12-16, 18, and 20.

22. The use of a pharmaceutical composition of Claim 21 in the manufacture of a medicament for treating an autoimmune disease, an inflammatory disease, or cancer in a mammal in need thereof.

23. The use of Claim 22, wherein the mammal is a human.

24. The use of Claim 22, wherein the autoimmune disease is lupus, pemphigus vulgaris, granulomatosis with polyangiitis, or rheumatoid arthritis.

25. The use of a compound selected from (E) isomer, (Z) isomer, and a mixture of (E) and (Z) isomer of 2-[(3R)-3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile, or a pharmaceutically acceptable salt of any of the foregoing compounds, in the manufacture of a medicament for treating thrombotic thrombocytopenic purpura, polyarteritis nodosa, cutaneous lupus, cutaneous form of systemic sclerosis (CREST), systemic sclerosis, mixed connective tissue disease, cryoglobulinemia, primary biliary sclerosis, sclerosing cholangitis, AI urticaria, IgA nephropathy, lupus nephritis, autoimmune hemolytic anemia, granulomatosis with polyangiitis, or pemphigus vulgaris in a mammal.