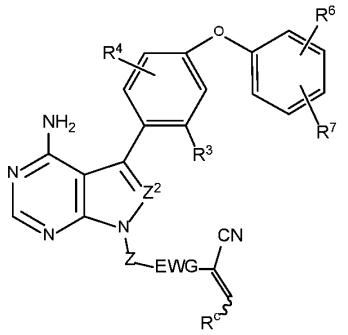
What is Claimed:

1. A method of treating a disease chosen from acute respiratory distress syndrome, sepsis, sepsis induced acute lung injury, diffuse alveolar damage, macrophage activation syndrome, secondary hemophagocytic lymphohistiocytosis, cytokine release syndrome, and systemic inflammatory response syndrome comprising administering to a mammal in need of such treatment a pharmaceutical composition comprising a Bruton's tyrosine kinase (BTK) inhibitor and a pharmaceutically acceptable carrier or excipient, wherein the BTK inhibitor is a small molecule.

2. The method according to claim 1, wherein the BTK inhibitor is a compound of Formula (**I**) or a pharmaceutically acceptable salt thereof:



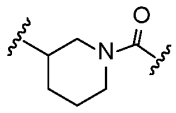
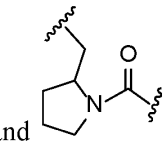
(**I**)

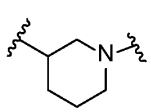
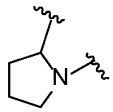
wherein:

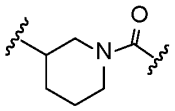
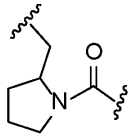
Z^2 is –N- or CR^2, wherein R^2 is chosen from hydrogen and alkyl;

R^3 and R^4 are independently chosen from hydrogen, methyl, chloro, fluoro, cyclopropyl, hydroxy, methoxy, cyano, trifluoromethyl, and trifluoromethoxy;

R^6 and R^7 are independently chosen from hydrogen, methyl, methoxy, fluoro, chloro, trifluoromethyl, trifluoromethoxy, and cyano;

-Z-EWG- is chosen from –alkylene-NR'CO-, -alkylene-NR'SO_2-, , and , wherein:

each of  and  is independently substituted with 0, 1, or 2 substituents independently chosen from alkyl, hydroxy, and halo;

the carbonyl or the sulfonyl group in –alkylene-NR'CO-, -alkylene-NR'SO_2-,  , and  is attached to -C(CN)=CHR^c; and

R' is independently chosen from hydrogen and alkyl;

R^c is chosen from alkyl, haloalkoxy, substituted alkyl, cycloalkyl, cycloalkylene-NR^{d}R^e, and cycloalkylene-alkylene-NR^{d}R^e; and

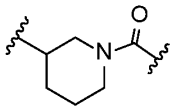
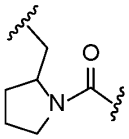
R^d and R^e are independently chosen from hydrogen, alkyl, cycloalkyl, and 3 to 6 membered saturated monocyclic heterocyclyls, wherein:

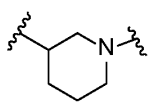
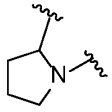
the heterocyclyls comprise one or two heteroatoms independently chosen from N, O, and S; and

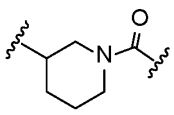
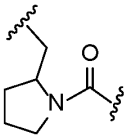
the heterocyclyls are substituted with 0, 1, or 2 substituents independently chosen from hydroxy, alkyl and fluoro.

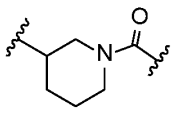
3. The method according to any one of claims 1-2, wherein Z^2 is -N-.

4. The method according to any one of claims 1-3, wherein:

-Z-EWG- is  or  , wherein:

 and  are independently substituted with 0, 1, or 2 substituents independently chosen from alkyl, hydroxy, and halo, and

the carbonyl group in  and  is attached to -C(CN)=CHR^c.

5. The method according to any one of claims 1-4, wherein -Z-EWG- is .

6. The method according to claim 5, wherein the BTK inhibitor is chosen from (E) isomer, (Z) isomer, and a mixture of (E) and (Z) isomers of:

(R)-2-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-3-cyclopropylacrylonitrile;

2-((R)-3-(4-amino-3-(4-(3,4-dichlorophenoxy)-3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-3-cyclopropylacrylonitrile;

(R)-2-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-4,4-dimethylpent-2-enenitrile;

(R)-2-(3-(4-amino-3-(4-(3,4-dichlorophenoxy)-3-methoxyphenyl)-1H-pyrazolo-[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-4,4-dimethylpent-2-enenitrile;

(R)-2-(3-(4-amino-3-(4-(2-fluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-3-cyclopropylacrylonitrile;

(R)-2-(3-(4-amino-3-(4-(3-fluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-3-cyclopropylacrylonitrile;

(R)-2-(3-(4-amino-3-(4-(2,3-difluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-3-cyclopropylacrylonitrile;

(R)-2-(3-(4-amino-3-(4-(2,6-difluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-3-cyclopropylacrylonitrile;

(R)-2-(3-(4-amino-3-(4-(3,5-difluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-3-cyclopropylacrylonitrile;

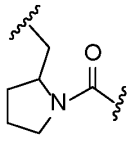
(R)-2-(3-(4-amino-3-(4-(2,5-difluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-3-cyclopropylacrylonitrile;

(R)-2-(3-(4-amino-3-(2-fluoro-4-(phenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-3-cyclopropylacrylonitrile;

(R)-2-(3-(4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)piperidine-1-carbonyl)-3-cyclopropylacrylonitrile; and

(R)-2-(3-(4-amino-3-(4-(2,3-difluorophenoxy)-2-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-4-methylpent-2-enenitrile;

or a pharmaceutically acceptable salt of any of the foregoing compounds.

7. The method according to any one of claims 1-4, wherein -Z-EWG- is .

8. The method according to claim 7, wherein the BTK inhibitor is chosen from (E) isomer, (Z) isomer, and a mixture of (E) and (Z) isomers of:

2-(2-((4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)pyrrolidine-1-carbonyl)-4,4-dimethylpent-2-enenitrile;

(R)-2-(2-((4-amino-3-(4-(3-fluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)pyrrolidine-1-carbonyl)-3-cyclopropylacrylonitrile;

(R)-2-(2-((4-amino-3-(4-(2,6-difluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)pyrrolidine-1-carbonyl)-3-cyclopropylacrylonitrile;

(R)-2-(2-((4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)pyrrolidine-1-carbonyl)-3-cyclopropylacrylonitrile;

(R)-2-(2-((4-amino-3-(4-(2,3-difluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)pyrrolidine-1-carbonyl)-3-cyclopropylacrylonitrile;

(R)-2-(2-((4-amino-3-(4-(3,5-difluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)pyrrolidine-1-carbonyl)-3-cyclopropylacrylonitrile;

(R)-2-(2-((4-amino-3-(4-(2-fluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)pyrrolidine-1-carbonyl)-3-cyclopropylacrylonitrile;

(S)-2-{2-[4-amino-5-(4-phenoxy-phenyl)-pyrrolo[2,3-d]pyrimidin-7-ylmethyl]-pyrrolidine-1-carbonyl}-3-cyclopropyl-acrylonitrile;

(S)-2-(2-((4-amino-6-methyl-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)methyl)pyrrolidine-1-carbonyl)-3-cyclopropylacrylonitrile;

(S)-2-(2-((4-amino-6-methyl-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)methyl)pyrrolidine-1-carbonyl)-4-(dimethylamino)-4-methylpent-2-enenitrile;

(S)-2-(2-((4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)pyrrolidine-1-carbonyl)-3-cyclopropylacrylonitrile;

(R)-2-(2-((4-amino-3-(4-(2,3-difluorophenoxy)-2-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)pyrrolidine-1-carbonyl)-3-cyclopropylacrylonitrile;

(S)-2-(2-((4-amino-3-(4-(2,3-difluorophenoxy)-2-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)pyrrolidine-1-carbonyl)-3-cyclopropylacrylonitrile;

2-((S)-2-((4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)pyrrolidine-1-carbonyl)-4-(ethylamino)-4-methylpent-2-enenitrile;

2-((R)-2-((4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)pyrrolidine-1-carbonyl)-4-(ethylamino)-4-methylpent-2-enenitrile;

2-((S)-2-((4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)pyrrolidine-1-carbonyl)-4-(cyclopropylamino)-4-methylpent-2-enenitrile;

2-((S)-2-((4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)pyrrolidine-1-carbonyl)-4-(2-methoxyethylamino)-4-methylpent-2-enenitrile;

(R)-2-(2-((4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)pyrrolidine-1-carbonyl)-3-(1-aminocyclopropyl)acrylonitrile;

2-[(2S)-2-[[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]methyl]pyrrolidine-1-carbonyl]-4-methyl-4-morpholino-pent-2-enenitrile;

2-[(2R)-2-[[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]methyl]pyrrolidine-1-carbonyl]-4-methyl-4-morpholino-pent-2-enenitrile;

2-[(2R)-2-[[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]methyl]pyrrolidine-1-carbonyl]-4-methyl-4-(1-piperidyl)pent-2-enenitrile;

2-[(2S)-2-[[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]methyl]pyrrolidine-1-carbonyl]-4-methyl-4-(1-piperidyl)pent-2-enenitrile; and

2-[(2S)-2-[[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]methyl]- pyrrolidine-1-carbonyl]-3-(3-methyloxetan-3-yl)prop-2-enenitrile;

or a pharmaceutically acceptable salt of any of the foregoing compounds.

9. The method according to any one of claims 1-5, wherein R^c is alkyl.

10. The method according to claim 9, wherein R^c is *t*-butyl.

11. The method according to claim 10, wherein the BTK inhibitor is chosen from (E) isomer, (Z) isomer, and a mixture of (E) and (Z) isomers of (R)-2-(3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-4,4-dimethylpent-2-enenitrile (Compound (**IA**)), and/or a pharmaceutically acceptable salt any of the foregoing compounds.

12. The method according to claim 10, wherein the compound is a substantially pure (E) or (Z) isomer of (R)-2-(3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-

d]pyrimidin-1-yl)piperidine-1-carbonyl)-4,4-dimethylpent-2-enenitrile (Compound (**IA**)), and/or a pharmaceutically acceptable salt thereof.

13. The method according to claim12, wherein at least about 85% w/w of (R)-2-(3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-4,4-dimethylpent-2-enenitrile or at least about 85% w/w of a pharmaceutically acceptable salt of (R)-2-(3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-4,4-dimethylpent-2-enenitrile is the (E) isomer.

14. The method according to claim 5, wherein R^c is substituted alkyl.

15. The method according to claim 14, wherein:

R^c is $-C(CH_3)_2$-(4-R^8-piperazin-1-yl);

R^8 is chosen from hydrogen, alkyl, alkoxyalkyl, haloalkyl, alkylsulfonyl, alkoxycarbonyl, acyl, and oxetan-3-yl; and

the piperazinyl ring is additionally optionally and independently substituted with one or two alkyls.

16. The method according to claim 15, wherein the BTK inhibitor is chosen from (E) isomer, (Z) isomer, and a mixture of (E) and (Z) isomers of:

2-[[(3R)-3-[4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]-pyrimidin-1-yl]-piperidin-1-yl]carbonyl]-4-methyl-4-(4-methylpiperazin-1-yl)pent-2-enenitrile;

2-((R)-3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-4-methyl-4-(piperazin-1-yl)pent-2-enenitrile;

2-[(3R)-3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]-pyrimidin-1-yl]piperidine-1-carbonyl]-4-(4-ethylpiperazin-1-yl)-4-methyl-pent-2-enenitrile;

(R)-2-(3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-4-(4-isopropylpiperazin-1-yl)-4-methylpent-2-enenitrile;

(R)-2-(3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-4-(4-(tert-butyl)piperazin-1-yl)-4-methylpent-2-enenitrile;

(R)-2-(3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-4-(4-(2-methoxyethyl)piperazin-1-yl)-4-methylpent-2-enenitrile;

(R)-2-(3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-4-methyl-4-(4-(methylsulfonyl)piperazin-1-yl)pent-2-enenitrile;

(R)-2-(3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-4-methyl-4-(4-(2,2,2-trifluoroethyl)piperazin-1-yl)pent-2-enenitrile;

2-((R)-3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-4-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)pent-2-enenitrile;

2-((R)-3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-4-((3S,5R)-3,5-dimethylpiperazin-1-yl)-4-methylpent-2-enenitrile;

(R)-2-(3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-4-methyl-4-(4-(oxetan-3-yl)piperazin-1-yl)pent-2-enenitrile;

(R)-4-(4-acetylpiperazin-1-yl)-2-(3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-4-methylpent-2-enenitrile; and

(R)-methyl-4-(5-(3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-4-cyano-2-methyl-5-oxopent-3-en-2-yl)piperazine-1-carboxylate;

or a pharmaceutically acceptable salt of any of the foregoing compounds.

17. The method according to claim 15, wherein R^8 is oxetan-3-yl.

18. The method according to claim 17, wherein the BTK inhibitor is chosen from (E) isomer, (Z) isomer, and a mixture of (E) and (Z) isomers 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 (Compound (**IB**)); and/or a pharmaceutically acceptable salt of any of the foregoing compounds.

19. The method according to claim 17, wherein the BTK inhibitor 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 (Compound (**IB**)), or a pharmaceutically acceptable salt thereof.

20. The method according to claim 19, wherein at least about 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 about 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.

21. The method according to any one of claims 1-20, wherein the pharmaceutical composition is administered in place of a corticosteroid therapy.

22. The method according to any one of claims 1-20, wherein the pharmaceutical composition is administered in combination with a corticosteroid therapy.

23. The method according to any one of claims 1-20, wherein the pharmaceutical composition is administered in combination with a noncorticosteroidal immunosuppressive and/or anti-inflammatory agent.

24. The method according to any one of claims 1-20, wherein the pharmaceutical composition is administered in combination with a corticosteroid maintenance therapy.

25. The method according to any one of claims 1-24, wherein the mammal is a human.

26. The method according to any one of claims 1-25, wherein the pharmaceutical composition is administered in combination with an active pharmaceutical ingredient chosen from interferon alpha, interferon gamma, cyclophosphamide, tacrolimus, mycophenolate mofetil, methotrexate, dapsone, sulfasalazine, azathioprine, an anti-CD20 agent, an anti-TN alpha agent, an anti-IL6 agent toward ligand or its receptors, an anti-IL17 agent to ligand or its receptors, an anti-IL1 agent to ligand or its receptors, an anti-IL2 agent to ligand or its receptors, an anti-CD2 agent, an anti-CD3 agent, an anti-CD80/86 agent, an anti-sphingosine-1-phosphate receptor agent, an anti-C5 agent, an anti-mTOR agent, an anti-calcineurin agent, an anti-BAFF/BlyS agent, leflunomide, and teriflunomide.

27. The method according to any one of claims 1-26, wherein the pharmaceutical composition is administered in combination with rituximab, ofatumumab, obinutuzumab, or veltuzumab, or a biosimilar version of any of the foregoing.

28. The method according to any one of claims 1-26, wherein the pharmaceutical composition is administered in combination with at least one antiviral agent.

29. The method according to claim 28, wherein the antiviral agent comprises at least one agent chosen from entry inhibitors, uncoating inhibitors, reverse transcriptase inhibitors, integrase inhibitors, transcription inhibitors, and protease inhibitors.

30. The method according to claim 28 or 29, wherein the antiviral agent comprises remdesivir.