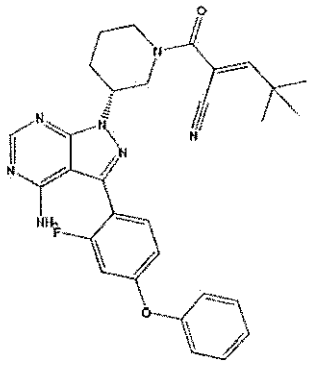
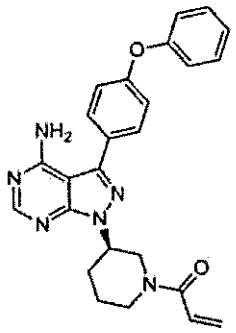
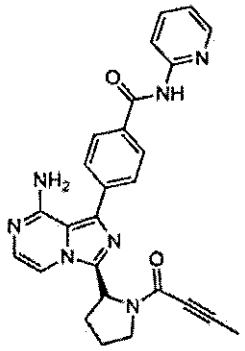
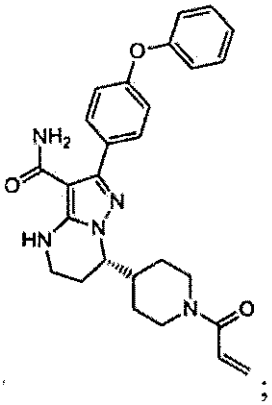
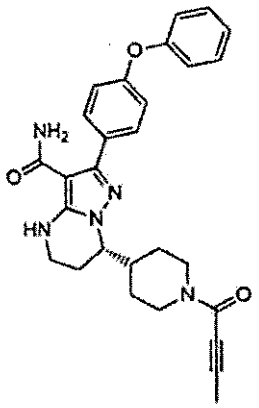
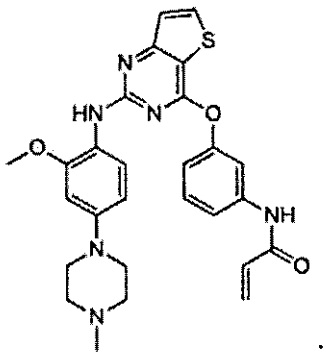
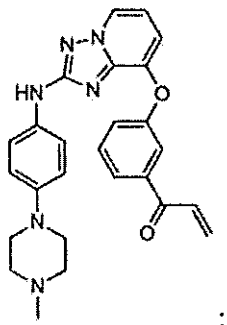
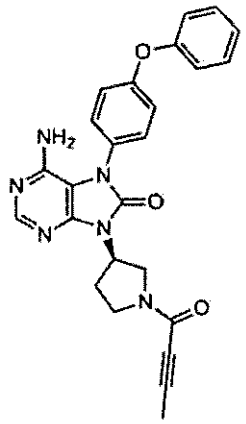
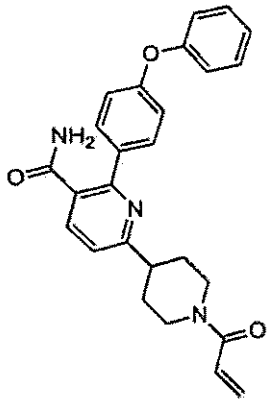
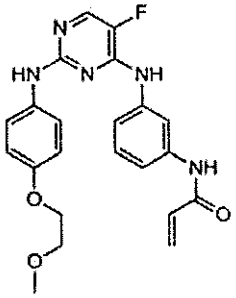
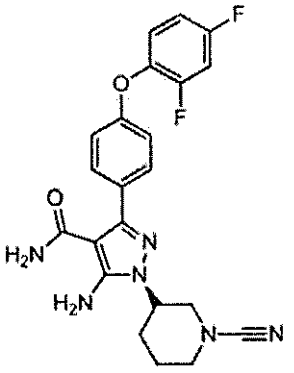
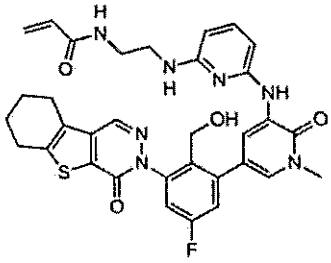
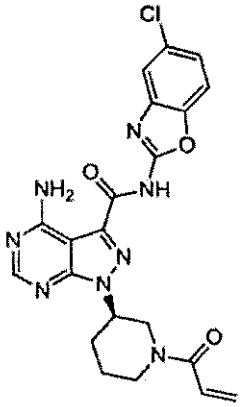
(Tournadre A, et al. Polymyositis and pemphigus vulgaris in a patient successful treatment with rituximab Jt Bone Spine 2008;75:728-729). Accordingly, there is a need for new therapies that can treat PV effectively and related diseases without causing or at least reducing serious side effects compared to the standard of care in treating pemphigus.

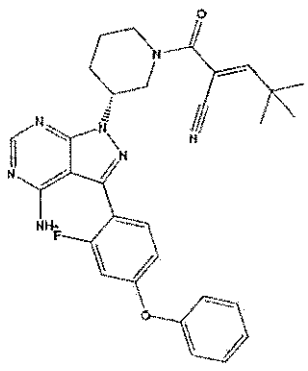
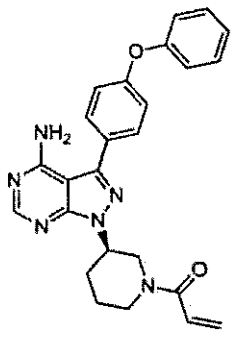
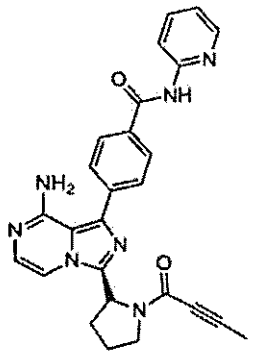
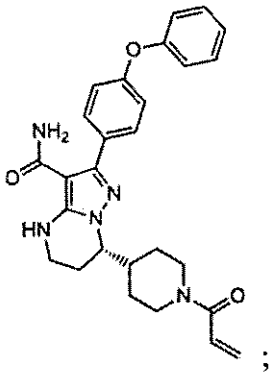
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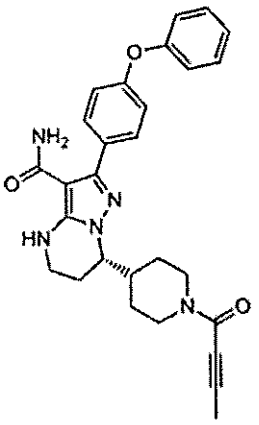
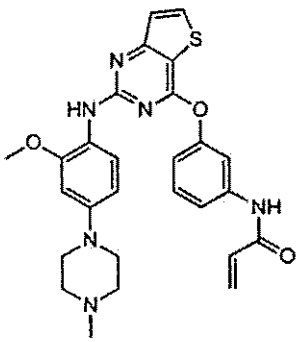
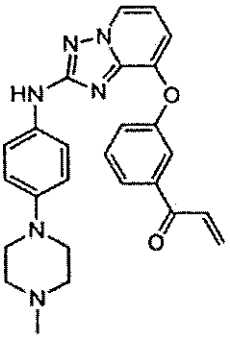
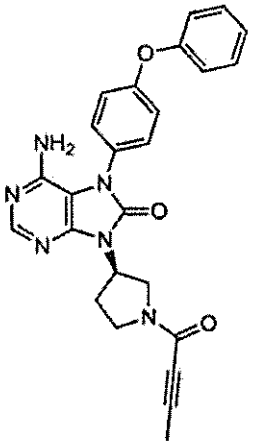
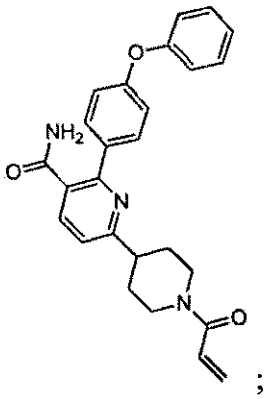
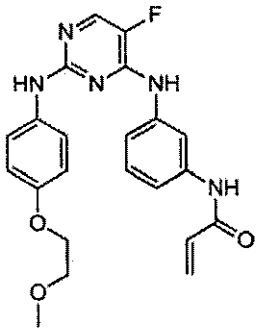
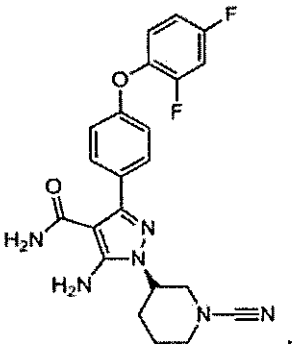
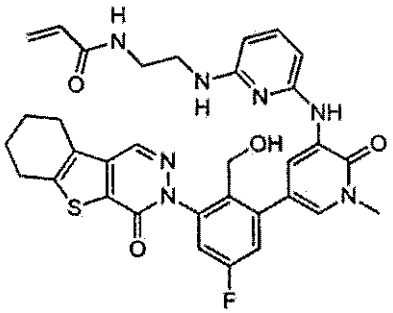
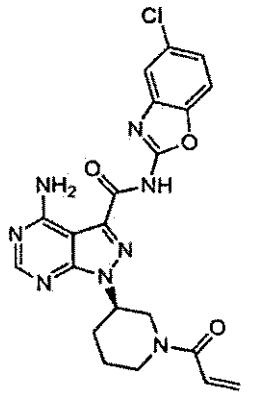
In one aspect, the present disclosure provides a use of a therapeutically effective amount of a BTK inhibitor in the manufacture of a medicament for the treatment of pemphigus vulgaris or pemphigus foliaceus in a mammal in need thereof, wherein said BTK inhibitor is used in place of, or in combination with, a corticosteroid therapy; optionally, said BTK inhibitor is to be administered in combination with a noncorticosteroidal immunosupressive and/or antiinflammatory agent; and wherein said BTK inhibitor is chosen from : AVL 263 and 293; GDC-0834; GDC0853; BMS-488516; BMS-509744; CGI-1746; CTA-056; HY-11066; ONO-WG37; PLS-123; RN486; HM71224; ABT-105/ABBV-105; AC0025; EBI-1266; MSC-2364447; PF-06250112; PF-303; RG7625; RG7880; SNS-062; TP-4207; X-022;


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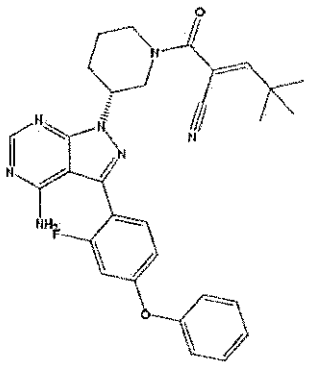
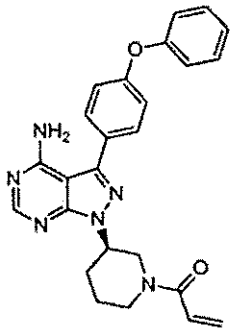
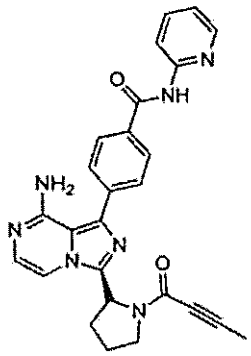
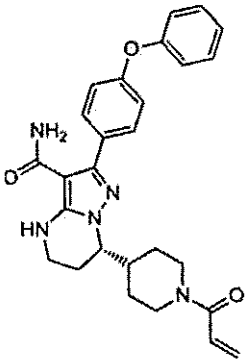
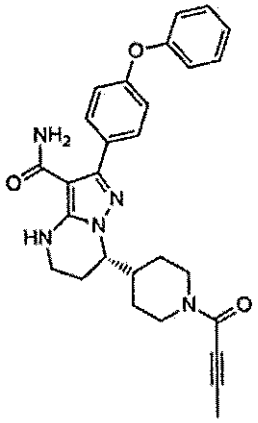
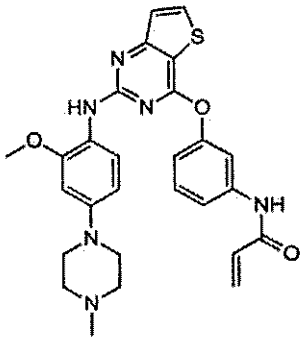
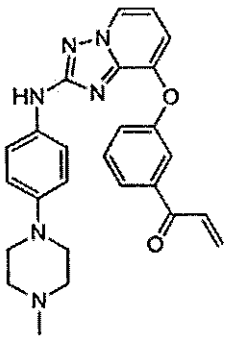
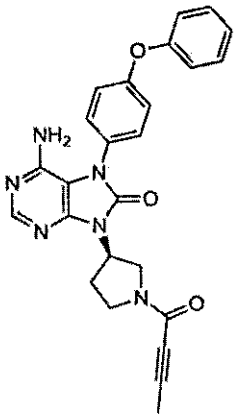
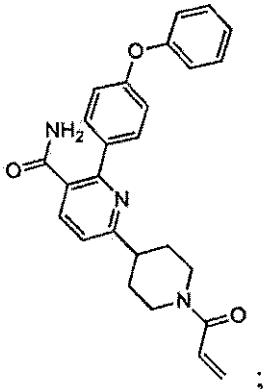
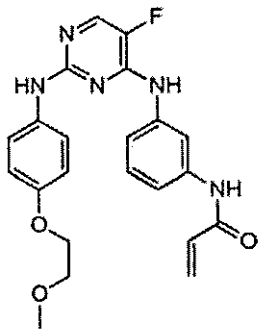
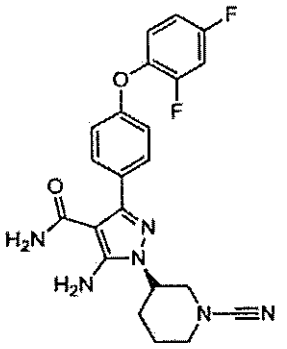
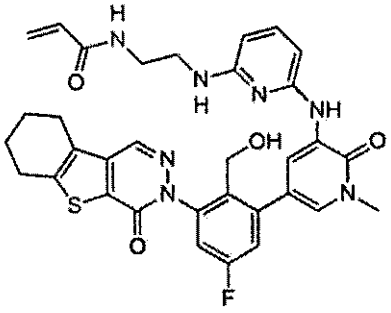
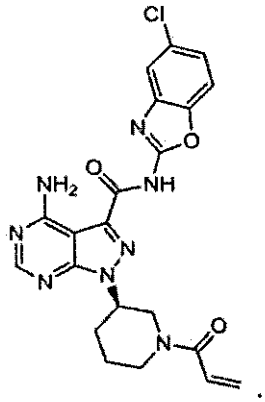

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In another aspect, the present disclosure provides the use of a therapeutically effective amount of a BTK inhibitor in the manufacture of a medicament, for eliminating or reducing therapeutic dose of the corticosteroid to be used in the treatment of pemphigus vulgaris or pemphigus foliaceus in a mammal in need thereof, said BTK inhibitor is to be used in place of or in combination with said corticosteroid therapy;; and optionally, said BTK inhibitor is to be used in combination with a noncorticosteroidal immunosupressive and/or antiinflammatory agent, , wherein said BTK inhibitor is chosen from: AVL 263 and 293; GDC-0834; GDC0853; BMS-488516; BMS-509744; CGI-1746; CTA-056; HY-11066; ONO-WG37; PLS-123; RN486; HM71224; ABT-105/ABBV-105; AC0025; EBI-1266; MSC-2364447; PF-06250112; PF-303; RG7625; RG7880; SNS-062; TP-4207; X-022;


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In a further aspect, the present disclosure provides the use of a therapeutically effective amount of a BTK inhibitor in the manufacture of a medicament, for the treatment of pemphigus vulgaris or pemphigus foliaceus in a mammal in need thereof, wherein said BTK inhibitor is chosen from: AVL 263 and 293; GDC-0834; GDC0853; BMS-488516; BMS-509744; CGI-1746; CTA-056; HY-11066; ONO-WG37; PLS-123; RN486; HM71224; ABT-105/ABBV-105; AC0025; EBI-1266; MSC-2364447; PF-06250112; PF-303; RG7625; RG7880; SNS-062; TP-4207; X-022;


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5 **Detailed Disclosure of Embodiments**

In a recent study conducted by the Applicant in which a dog suffering from pemphigus foliaceus (PF) was administered (R,E)-2-(3-(4-amino-3-(2-fluoro-4-phenoxy-

phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-4,4-dimethylpent-2-enenitrile, a Bruton Tyrosine Kinase (BTK) inhibitor, as a single agent, it was surprisingly discovered that inhibition of BTK is effective and safe for the treatment of PF.

In addition, it was surprisingly discoved that the manifestation of clinical response with (R,E)-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, was as rapid and comparable to that observed with systemic corticosteroid therapy. Additionally, none of the well-known corticosteroid-like adverse effects in canines, such as polyuria, polydipsia, polyphagia or weight gain, was observed.

Accordingly, the present disclosure provides methods of treating a blistering disease, such as pemphigus vulgaris (PV) or pemphigus foliaceous (PF) with a BTK inbibitor in a mammal, use of a BTK inhibitor as a replacement therapy for corticosteroid therapy for diseases treatable with a corticosteroid (such as autoimmune or inflammatory disease and in particular where corticosteroids are used as first or second line therapy), where a rapid clinical response is desirable. Also, disclosed are methods of treating automimmune and/or inflammatory diseases with a BTK inhibitor at a specific phase of the disease process (such as 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.

Accordingly, in a first aspect, provided is a method of treating an autoimmune blistering disease in a mammal in need thereof which method comprises administering to the mammal in need of said treatment a therapeutically effective amount of a BTK inhibitor.

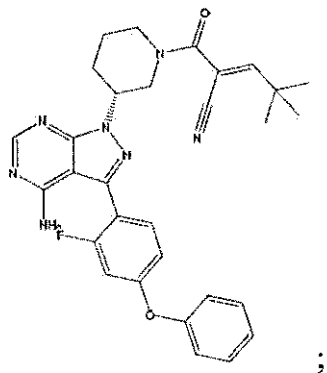
Claims

1. Use of a therapeutically effective amount of a BTK inhibitor in the manufacture of a medicament for the treatment of pemphigus vulgaris or pemphigus foliaceus in a mammal in need thereof, wherein:

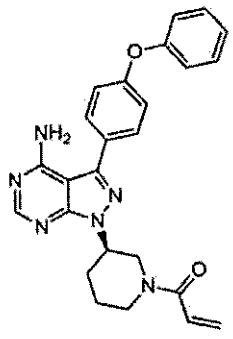
said BTK inhibitor is to be used in place of, or in combination with, a corticosteroid therapy; and

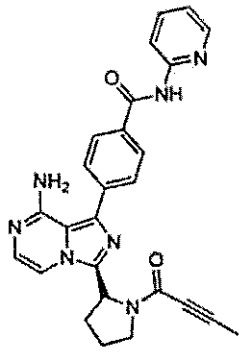
optionally, said BTK inhibitor is to be used in combination with a noncorticosteroidal immunosupressive and/or anti-inflammatory agent,

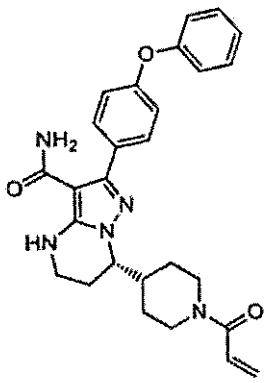
wherein said BTK inhibitor is chosen from: AVL 263 and 293; GDC-0834; GDC0853; BMS-488516; BMS-509744; CGI-1746; CTA-056; HY-11066; ONO-WG37; PLS-123; RN486; HM71224; ABT-105/ABBV-105; AC0025; EBI-1266; MSC-2364447; PF-

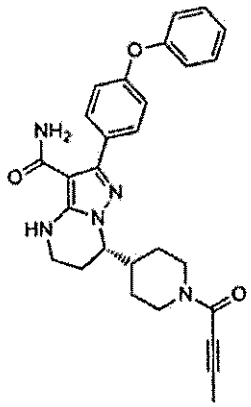


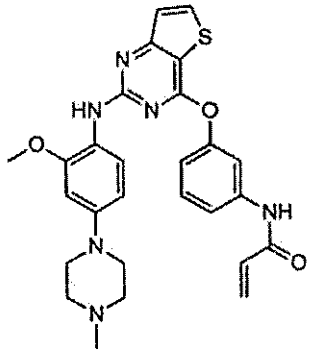
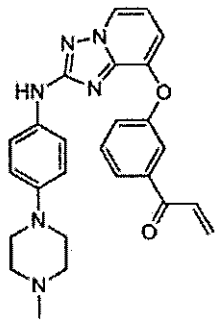
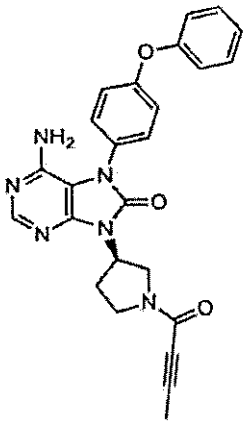
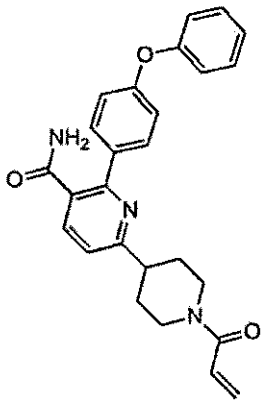
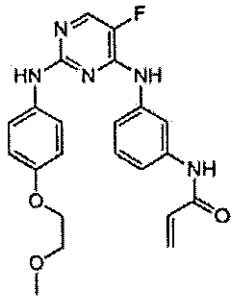
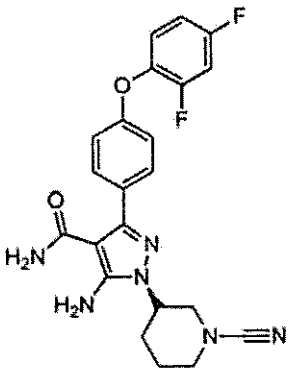
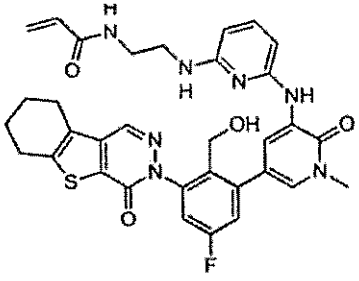
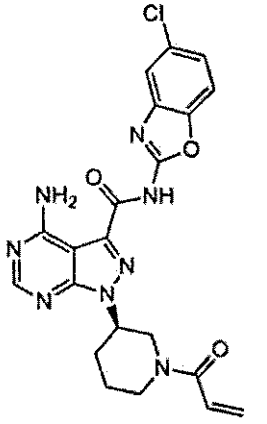
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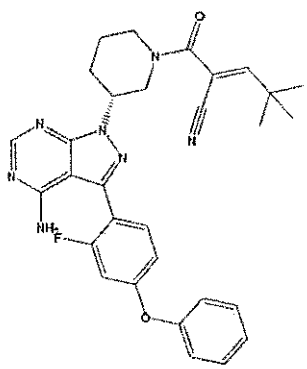
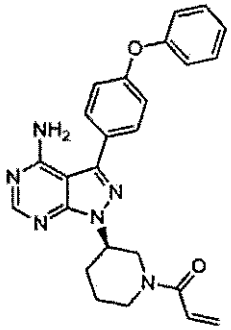
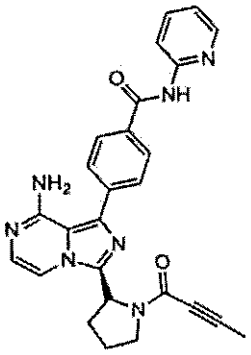
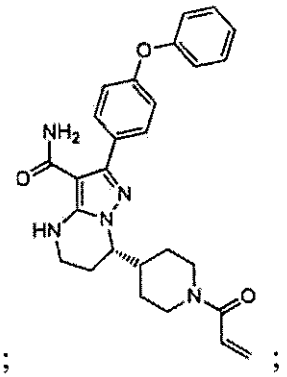
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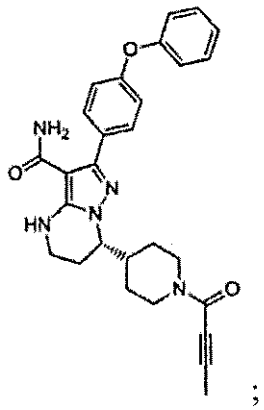
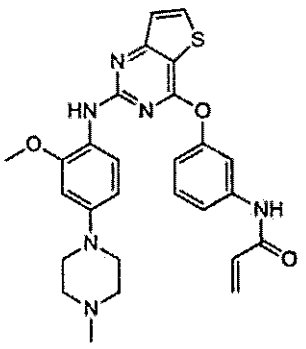
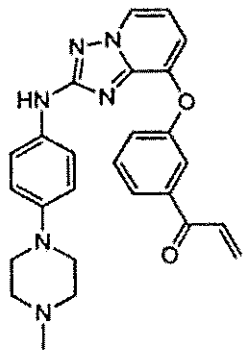
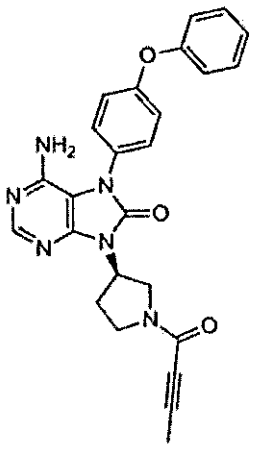
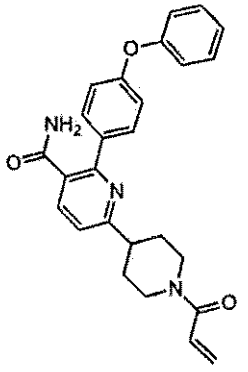
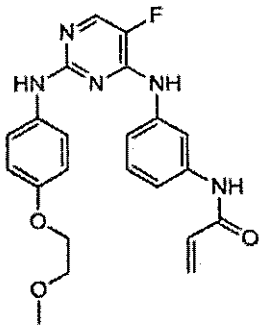
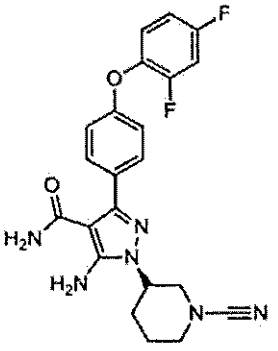
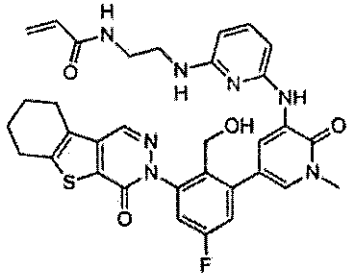
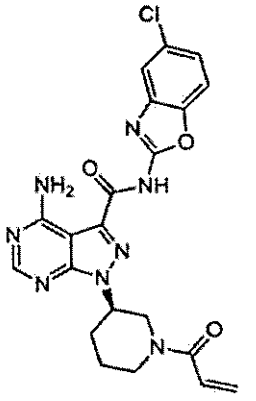
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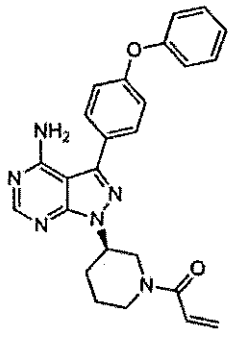
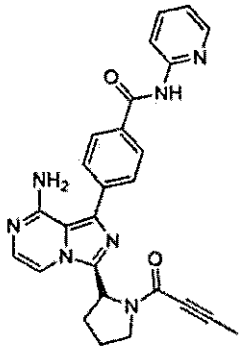
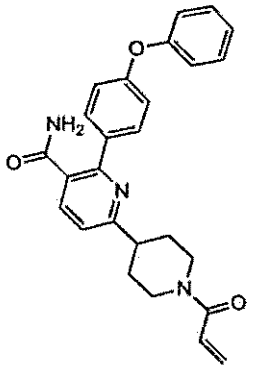
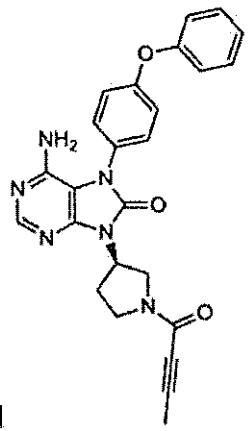

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2. The use of claim 1, wherein said BTK inhibitor is chosen from:


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3. The use of claim 1 or 2, wherein said BTK inhibitor is chosen from :

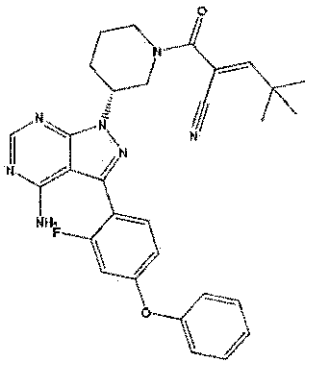

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4. Use of a therapeutically effective amount of a BTK inhibitor in the manufacture of a medicament for eliminating or reducing a therapeutic dose of corticosteroid to be used in the treatment of pemphigus vulgaris or pemphigus foliaceus in a mammal in need thereof, wherein:

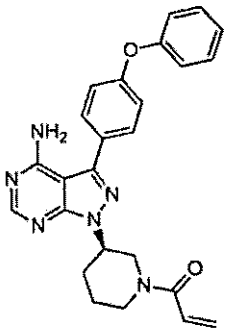
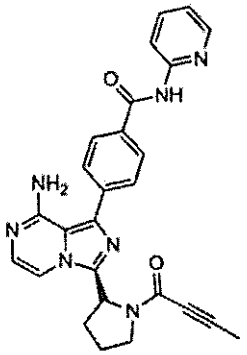
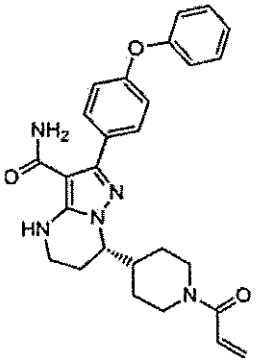
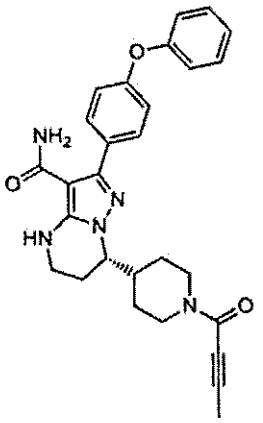
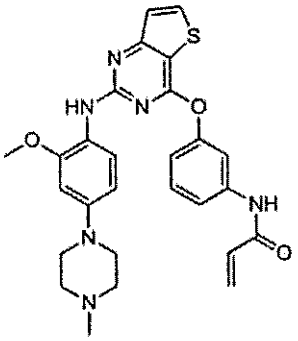
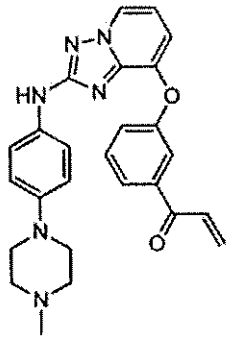
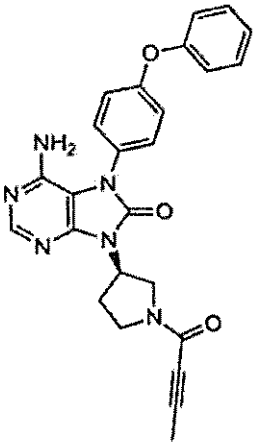
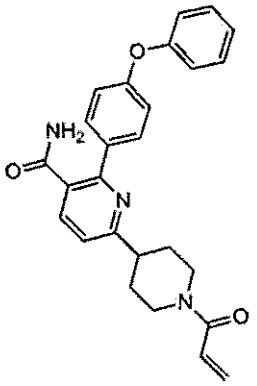
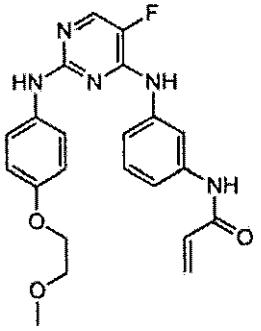
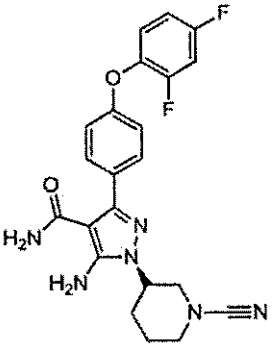
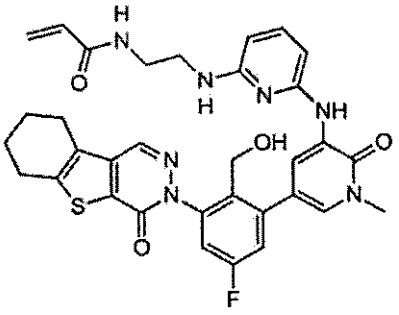
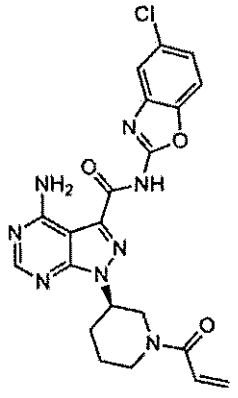
said BTK inhibitor is to be used in place of or in combination with said corticosteroid therapy; and

optionally, said BTK inhibitor is to be used in combination with a noncorticosteroidal immunosupressive and/or anti-inflammatory agent,

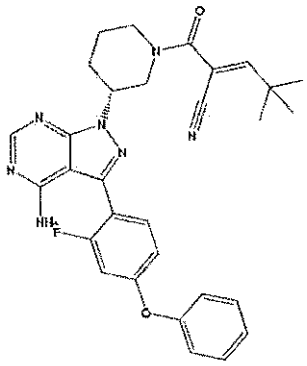
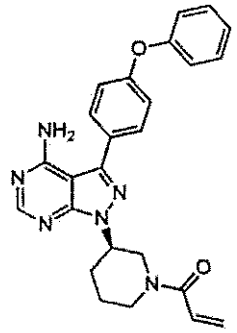
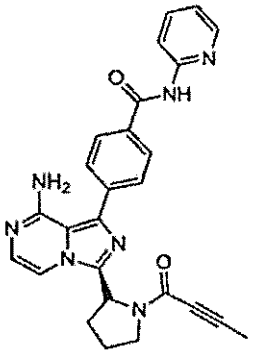
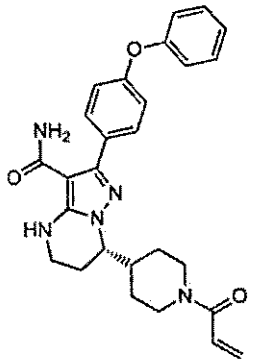
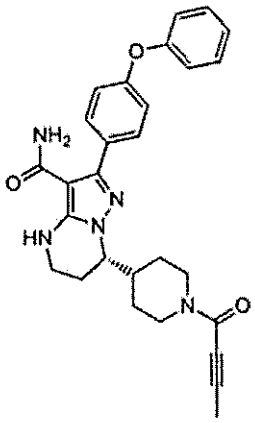
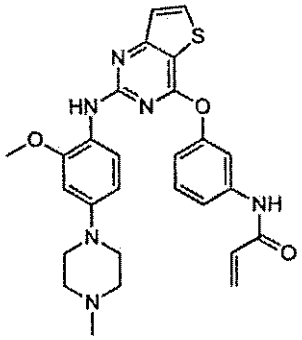
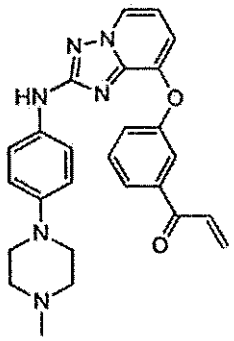
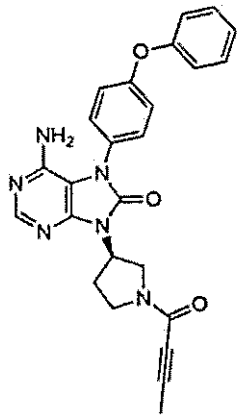
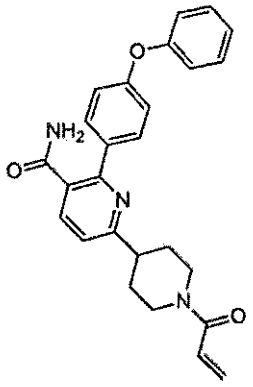
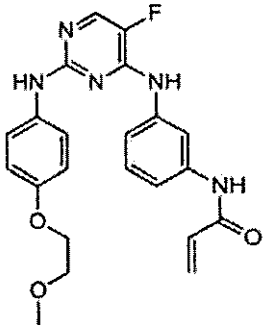
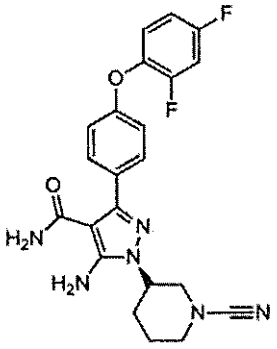
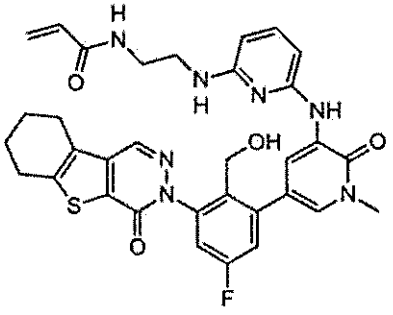
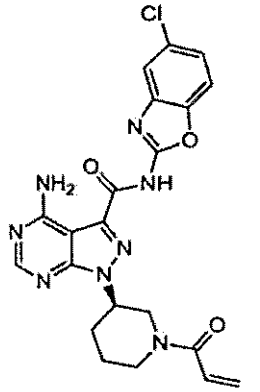
wherein said BTK inhibitor is chosen from: AVL 263 and 293; GDC-0834; GDC0853; BMS-488516; BMS-509744; CGI-1746; CTA-056; HY-11066; ONO-WG37; PLS-123; RN486; HM71224; ABT-105/ABBV-105; AC0025; EBI-1266; MSC-2364447; PF-



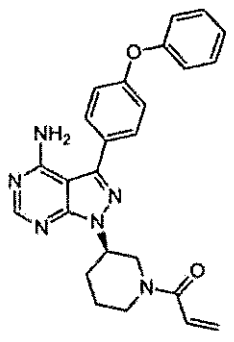
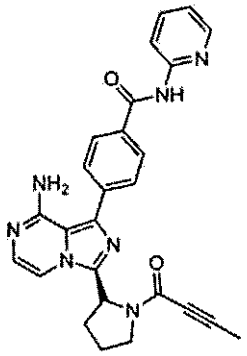
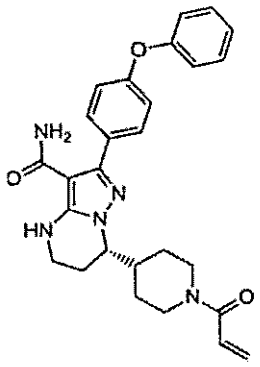
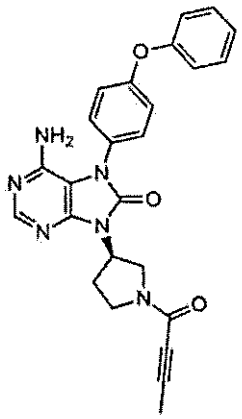
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5. The use of claim 4, wherein said BTK inhibitor is chosen from:


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6. The use of claim 4 or 5, wherein said BTK inhibitor is chosen from:

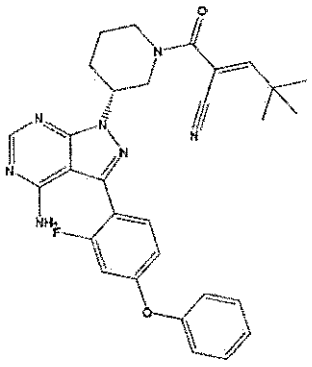

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7. Use of a therapeutically effective amount of a BTK inhibitor in the manufacture of a medicament for the treatment of acute flares of pemphigus vulgaris or pemphigus foliaceus in a mammal in need thereof, wherein:

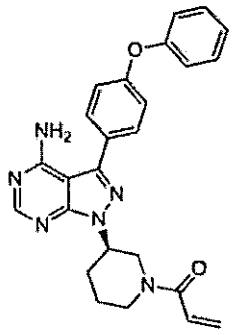
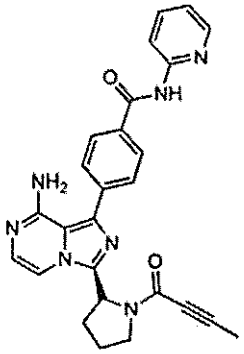
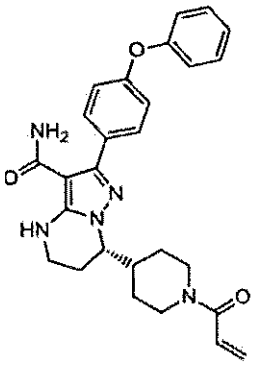
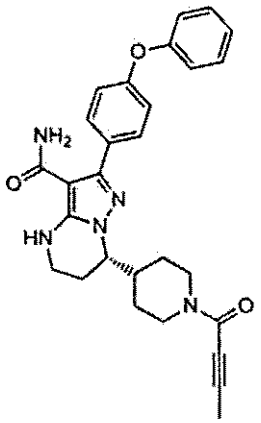
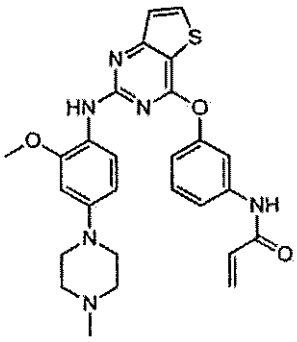
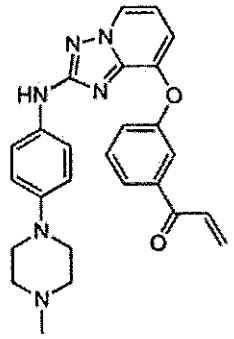
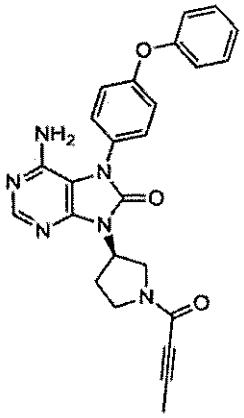
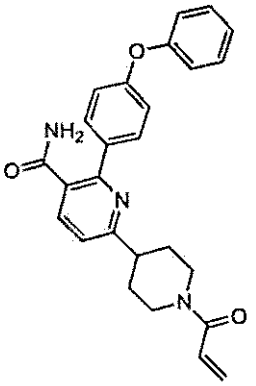
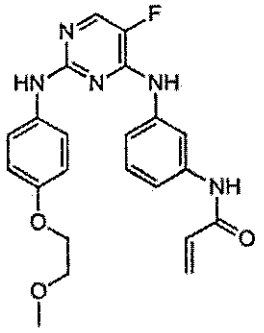
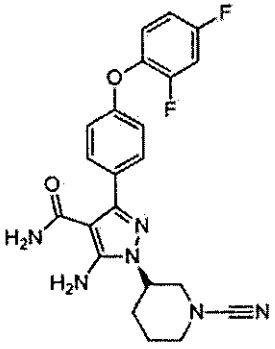
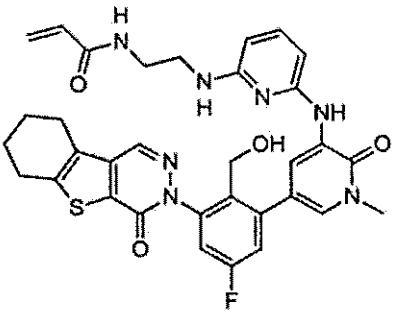
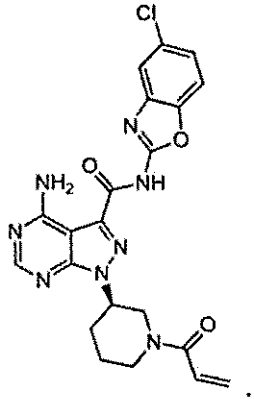
said BTK inhibitor is to be used in place of, or in combination with, a corticosteroid therapy; and

optionally, said BTK inhibitor is to be used in combination with a noncorticosteroidal immunosupressive and/or anti-inflammatory agent,

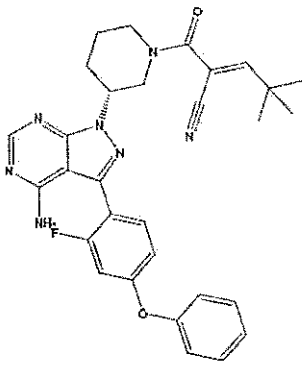
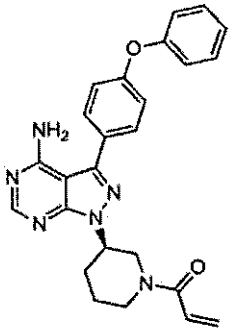
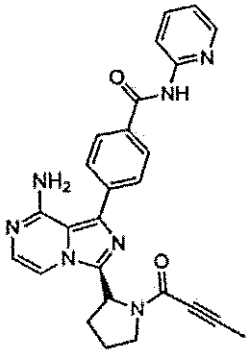
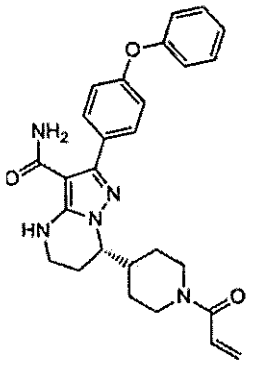
wherein said BTK inhibitor is chosen from: AVL 263 and 293; GDC-0834; GDC0853; BMS-488516; BMS-509744; CGI-1746; CTA-056; HY-11066; ONO-WG37; PLS-123; RN486; HM71224; ABT-105/ABBV-105; AC0025; EBI-1266; MSC-2364447; PF-

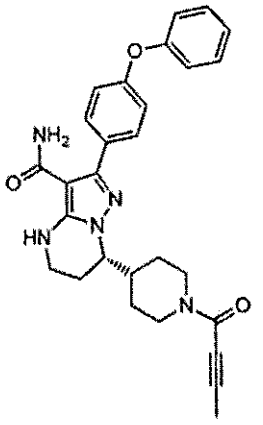
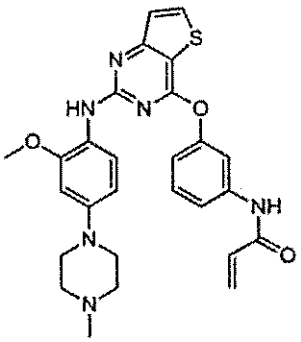
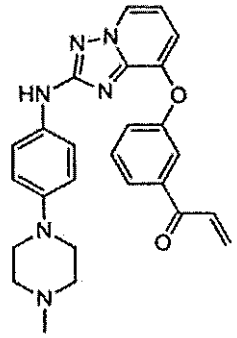
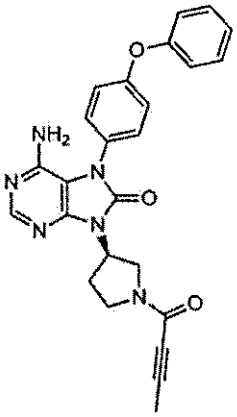


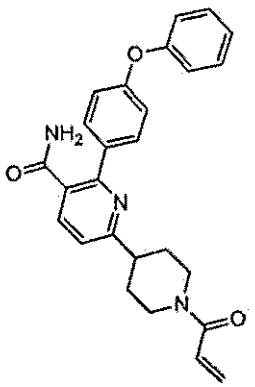
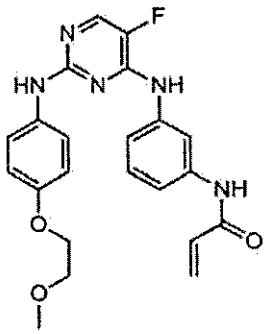
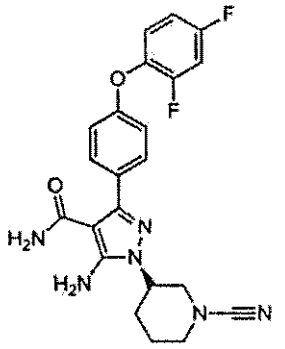
06250112; PF-303; RG7625; RG7880; SNS-062; TP-4207; X-022; ;

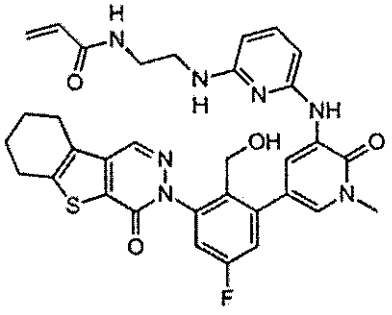
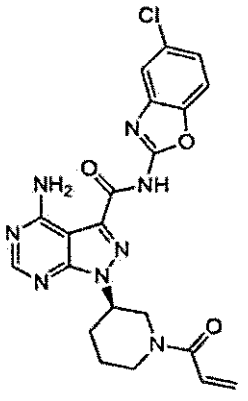

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8. The use of claim 7, wherein said BTK inhibitor is chosen from:

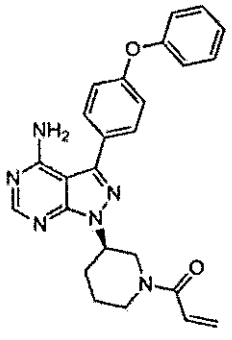

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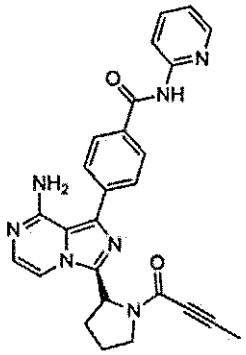

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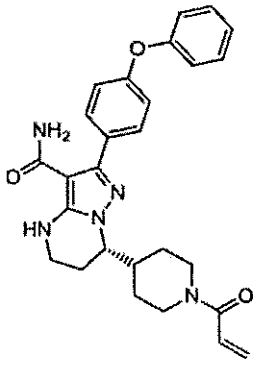

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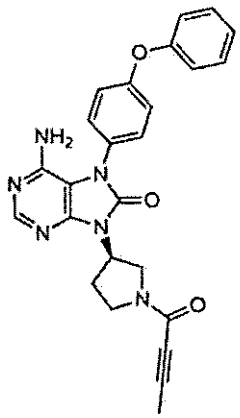


; and .

9. The use of claim 7 or 8, wherein said BTK inhibitor is chosen from:



;


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; and


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10. The use of any one of claims 1 to 9, wherein said BTK inhibitor is used in the treatment of pemphigus vulgaris

11. The use of any one of claims 1 to 9, wherein said BTK inhibitor is used in the treatment of pemphigus foliaceus.

12. The use of any one of claims 1 to 11, wherein said BTK inhibitor is to be administered as a monotherapy.

13. The use of any one of claims 1 to 11, wherein said BTK inhibitor is to be administered in combination with a noncorticosteroidal immunosuppressive and/or anti-inflammatory agent.

14. The use of claim 13, wherein said noncorticosteroidal immunosuppressive and/or anti-inflammatory agent is chosen from anti-CD20 antibody, anti-TNF antibody, anti-IL6 agent, anti-IL17 agent, and abatacept.

15. The use of any one of claims 1 to 11, wherein said noncorticosteroidal immunosuppressive and/or anti-inflammatory agent is chosen from rituximab, tositumomab, veltuzumab, obinutuzumab, Enbrel, and ofatumumab, or a biosimilar version thereof.