TREATMENT OF PEMPHIGUS

This application claims the benefit of priority to United States provisional patent application serial number 62/093,891, filed December 18, 2014; the contents of which are incorporated by referenece herein.

The present disclosure provides methods of treating a blistering disease, in particular pemphigus vulgaris or pemphigus foliaceous 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, and pharmaceutical formulations comprising the same.

Pemphigus vulgaris (PV) is a tissue-specific autoimmune blistering disease of the skin and mucous membranes in humans (Scully C, Challacombe S.J. Pemphigus vulgaris: update on etiopathogenesis, oral manifestations, and management. Crit Rev Oral Biol Med 2002; 13: 397-408) and is associated with considerable risks of morbidity and mortality. PV patients exhibit severe mucosal erosions and epidermal blistering that rupture easily, leading to erosions and crusts.

The disease is characterized by deposition of immunoglobulin G (IgG) and blister formation just above the basal cell layer of the epidermis. PV is associated with and thought to be driven by autoantibodies against the adhesion molecules desmoglein 3 (Dsg3) and desmoglein 1 (Dsg1), transmembrane proteins belonging to the cadherin family. Dsg3 and Dsg1 play a role connecting cells in the stratified squamous epithelium. Antibodies against Dsg3 and Dsg1 as well as PV patient sera have been associated with disruption of desmosomal function and keratinocyte adhesion (Ugajin T, Yahara H, Moriyama Y, et al. Two siblings with neonatal pemphigus vulgaris associated with mild maternal disease. Br J Dermatol 2007; 157 (1): 192-4). Anti-Dsg3 titres are correlated with the disease activity, and reactivity to certain epitopes on Dsg3 are correlated with clinical phenotype or severity (Campo-Voegeli A. Neonatal pemphigus vulgaris with extensive mucocutaneous lesions from a mother with oral pemphigus vulgaris. Br J Dermatol 2002; 147: 801-5).

At present the mainstay treatment for PV includes high doses of oral or parenteral corticosteroids either alone or in combination with immunosuppressive drugs such as cyclophosphamide, mycophenolate mofetil, methotrexate, dapsone, sulfasalazine or azathioprine (Murrell DF, Autoimmune blistering diseases: Part II – diagnosis and

management. Dermatol Clinics Vol 29, No 4, October 2011, Ribeiro AM, Alvarez RR, Friedman H, et al. The profile of fogo selvagem (endemic pemphigus foliaceus) at the University Hospital of Brasilia-Brazil: epidemiological and clinical considerations. Int J Dermatol 2005 Apr; 44 (4): 293-8). Optimization of these therapies is difficult and significant side effects of corticosteroids, such as weight gain with Cushingoid features, hypertension, disturbances of glucose and calcium metabolism, myopathy, mood disorder, and sepsis, are experienced by patients and contribute to the relatively high mortality in the first year of approximately 5% (Murrell D.F, AutoImmune Blistering Disease Part I, An Issue of Dermatologic Clinics, 1st Edition, ISBN 9781455710331).

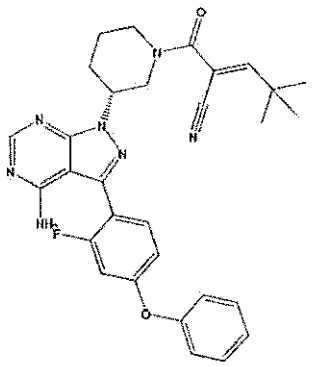
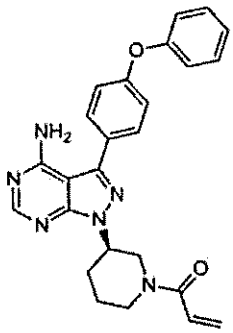
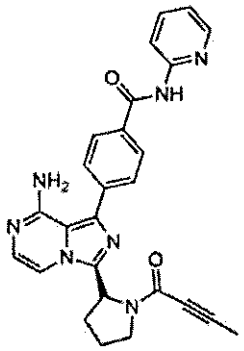
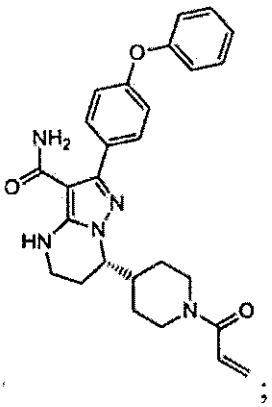
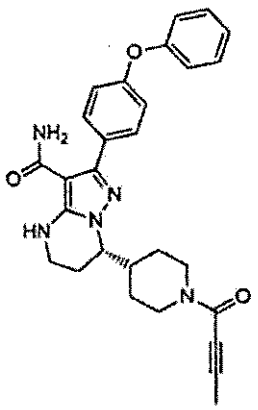
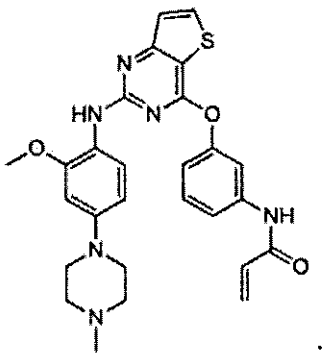
Due to severe side effects associated with use of corticosteroid, alternative therapies to corticosteroids for the treatment in PV have been explored and some of them include use of (i) high dose intravenous immunoglobulin (IVIG) administration when conventional immunosuppressive therapies are not effective and (ii) anti-CD20 antibody rituximab, which is approved for treatment of B cell malignancies and is increasing being used to treat automimmune diseases (Esmaili N, Chams-Davatchi C, Valikhani M, et al. Pemphigus vulgaris in Iran: a clinical study of 140 cases. Int J Dermatol 2007; 46: 1166-70; Mahoney M, Wang Z, Rothenberger K, et al. Explanations for the clinical and microscopic localization of lesions in pemphigus foliaceus and vulgaris. J Clin Invest 1999; 103: 461-8).

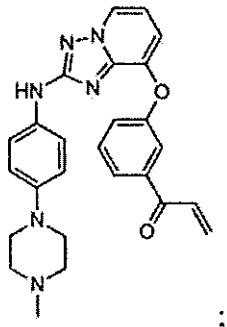
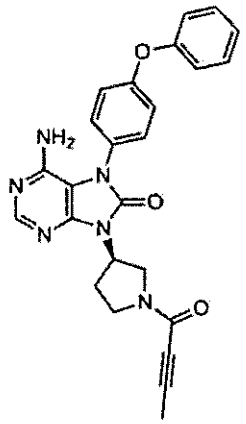
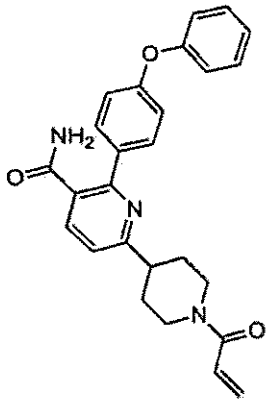
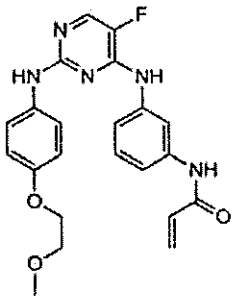
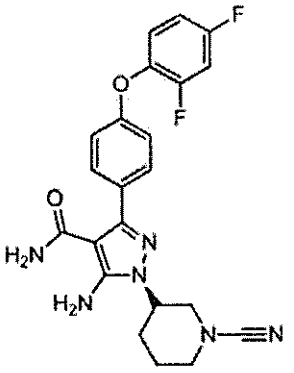
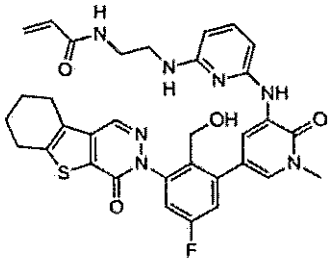
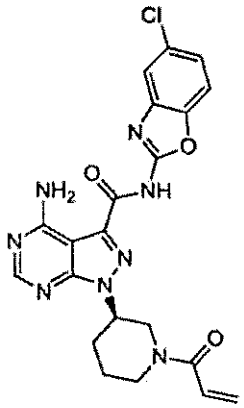
The drawbacks of the above therapies is that the IVIG therapy is expensive and has adverse effects such as headache, backache, flushing, fever, nausea and vomiting, anaphylaxis, aseptic meningitis, renal failure, and hypertension (see Product Label) and rituximab has significant delay in clinical response (maximal effect at 8-12 weeks see Lundardon L & Payne AS G Ital Dermatol Venereol 2012;147(3):269-276) requiring continued corticosteroid therapy for some months and furthermore the durability of the response as measured by anti-keritinocyte antibodies are varied ranging between no relapse to multiple relapses. In addition, patients treated with rituximab suffered serious side effects such as pneumonia (see Morrison L. H. Therapy of refractory pemphigus vulgaris with monoclonal anti-CD20 antibody (rituximab) J Am Acad Dermatol 2004;51:817-819 and Dupuy A, et. al. Treatment of refractory pemphigus vulgaris with rituximab (anti-CD20 monoclonal antibody) Arch Dermatol. 2004;140:91-96), neutropenia (see Rios-Fernandez R. et al. Late-onset neutropenia following rituximab treatment in patients with autoimmune disease Br J. Detmatol. 2007;157:1271-1273 and Goh M. S et al. Rituximab in the adjuvant treatment of pemphigus vulgaris: a prospective open-label pilot study in five patients. Br J.

(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.

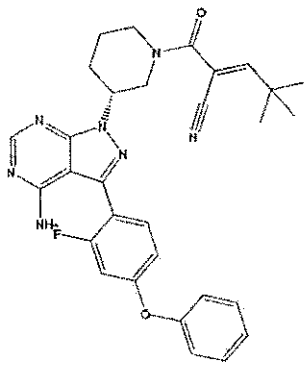
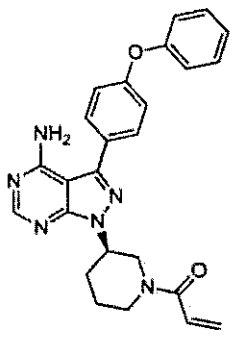
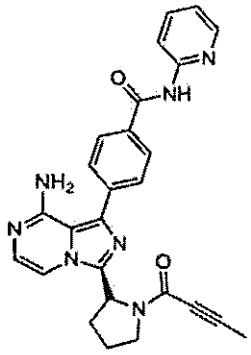
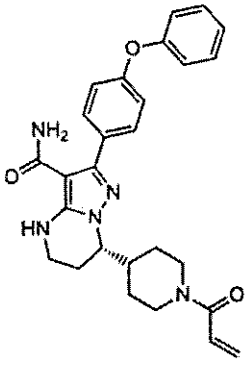
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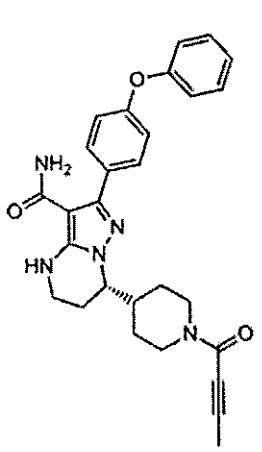
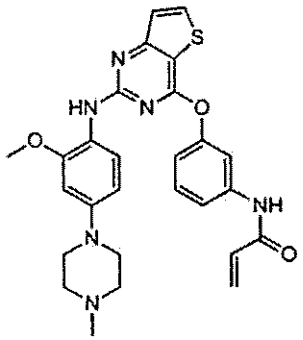
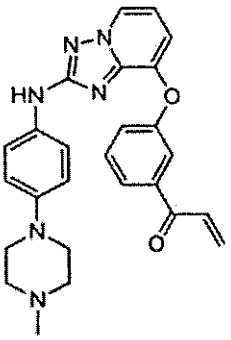
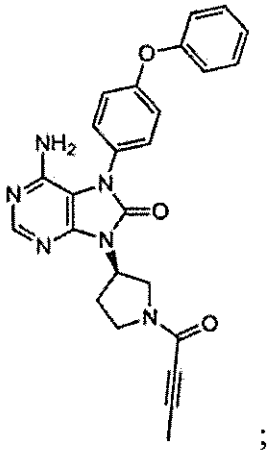
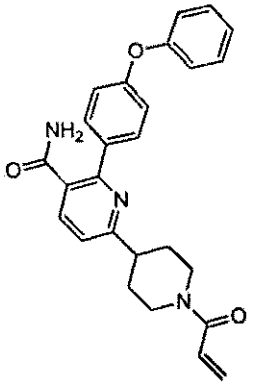
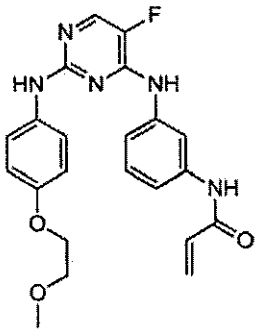
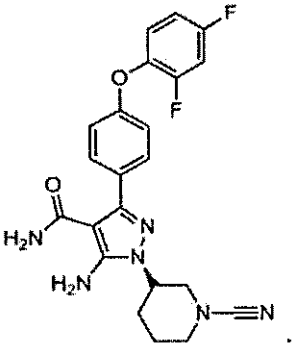
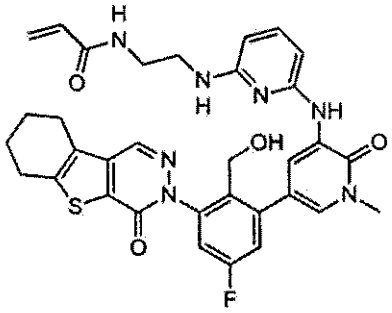
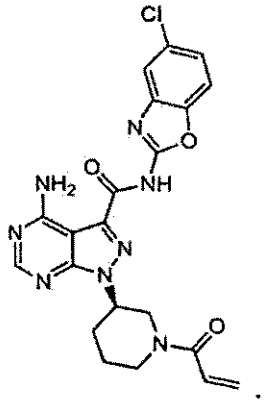
In one aspect, the present disclosure provides a use of a therapeutically effective amount of a BTK inhibitor in the manufacture of a medicament for the treatment of pemphigus vulgaris or pemphigus foliaceus in a mammal in need thereof, wherein said BTK inhibitor is used in place of, or in combination 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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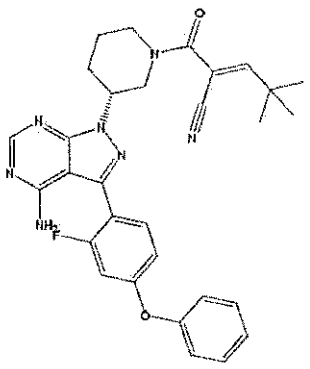
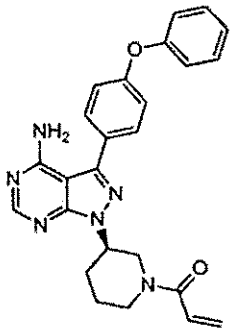
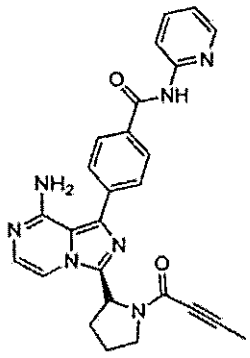
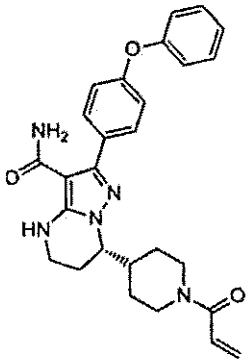
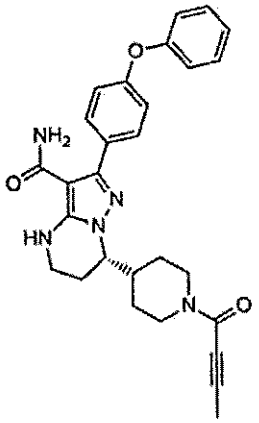
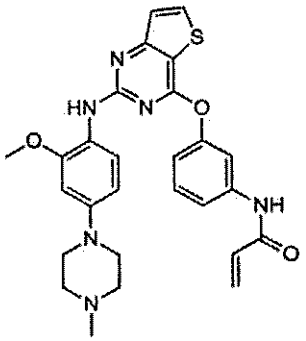
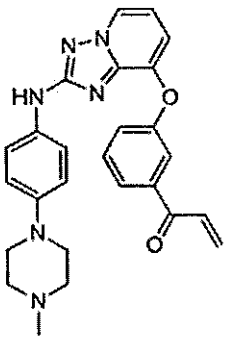
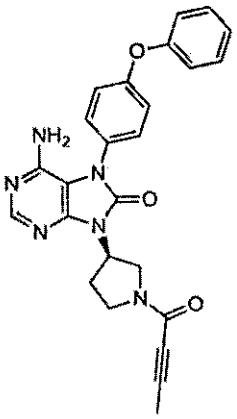
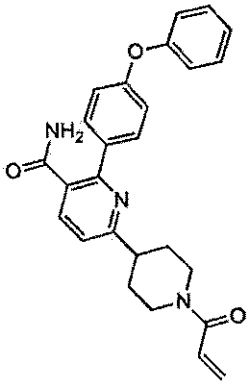
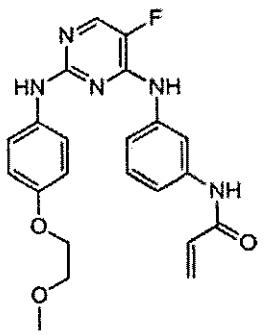
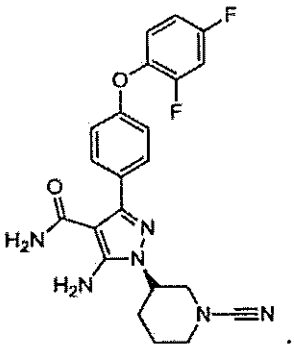
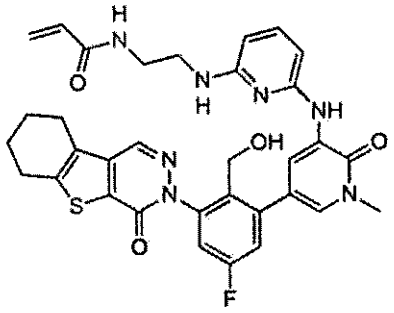
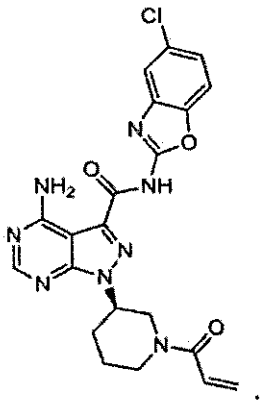

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In another aspect, the present disclosure provides the use of a therapeutically effective amount of a BTK inhibitor in the manufacture of a medicament, for eliminating or reducing therapeutic dose of the corticosteroid to be used in the treatment of 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.

In a second aspect, provided is a method of treating an acute inflammatory and/or autoimmune disease in a mammal in need thereof where corticosteroid therapy is used as the first or second line therapy comprising administering to said mammal in need of said treatment a therapeutically effective amount of a BTK inhibitor in place of or in combination with said corticosteroid therapy; and

optionally administering said BTK inhibitor in combination with a noncorticosteroidal immunosupressive and/or antiinflammatory agents.

In a third aspect, provided is a method of treating an inflammatory and/or autoimmune disease in a mammal in need thereof where corticosteroid therapy is used as the first or second line maintenance therapy comprising administering to said mammal in need of said treatment a therapeutically effective amount of a BTK inhibitor in place of or in combination with said corticosteroid therapy; and

optionally administering said BTK inhibitor in combination with a noncorticosteroidal immunosupressive and/or antiinflammatory agent.

In a fourth aspect, provided is a method of eliminating or reducing a therapeutic dose of corticosteroid used in chronic maintenance therapy of an inflammatory and/or autoimmune disease in a mammal in need thereof where corticosteroid therapy is used as the first or second line comprising administering to said mammal in need of said treatment a therapeutically effective amount of a BTK inhibitor in place of or in combination with said corticosteroid chronic maintenance therapy; and

optionally administering said BTK inhibitor in combination with a noncorticosteroidal, immunosupressive, and/or antiinflammatory agents.

In a fifth aspect, provided is a method of treating acute flares of an autoimmune and/or inflammatory 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 for a treatment period sufficient to treat acute flares of the autoimmune disease. In one embodiment of the fifith aspect,the BTK inhibitor is used instead of corticosteroid therapy where corticosteroid therapy is normally used as the first or second line to treat flares.

In a first embodiment of the secondand fifth aspects, the autoimmune and/or inflammatory disease is chosen from Table (I):

Table (I)

Acute indications for corticosteroid therapy	**Effects of B cell therapy if known**

Initial presentations or flares of rheumatic disorders such as psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis, bursitis, tenosynovitis, gout, synovitis of osteoarthritis, epicondylitis	Rituximab takes 4-12 weeks to take effect in rheumatoid arthritis (ref Rituxan US label)
Initial presentation or flares of collagen disease such as systemic lupus erythematosus (SLE), dermato/polymyositis, rheumatic carditis, vasculitis	Rituximab has delayed effect in ANCA-associated vasculitis and achieves remission in only 64% of cases despite concomitant use of corticosteroids for 5 months (Stone et al. 2010). Belimumab, an anti-Blys antibody, has a modest and delayed effect on improvement of chronic SLE including the ability to reduce corticosteroid use to <7.5mg of prednisone at week 40-52 in no more than 21% of patients (Benlysta US Product Information).
Initial presentations or flares of dermatologic diseases such as pemphigus, Stevens-Johnson syndrome, exfoliative dermatitis, mycosis fungoides, severe psoriasis, severe seborrheic dermatitis	Rituximab has delayed effect in pemphigus vulgaris with maximal effect at 8-12 weeks (Lundardon & Payne 2012)
Control of incapacitating allergic reactions including asthma, contact or atopic dermatitis, serum sickness, drug hypersensitivity	
Initial presentations or flares of ophthalmic diseases including allergic corneal ulcers, herpes zoster of the eye, anterior or posterior inflammation/uveitis or choroiditis, sympathetic ophthalmia, allergic conjunctivitis, keratitis, chorioretinitis, optic neuritis, iritis, iridocyclitis	
Initial presentations or flares of respiratory diseases including symptomatic sarcoidosis, Loeffler's syndrome, berylliosis, fulminating or disseminated tuberculosis, aspiration pneumonitis	
Initial presentations or flares of hematologic disorders including idiopathic thrombocytopenic purpura, secondary thrombocytopenia, autoimmune hemolytic anemia, erythroblastopenia, congential hypoplastic anemia	
Acute nephrotic syndrome of SLE	
Initial presentations or flares of gastrointestinal disease such as ulcerative colitis, Crohn's disease	

Acute neurological trauma to reduce swelling	

In a second embodiment of the first, second, third, fourth, and fifth aspects, the autoimmune and/or inflammatory disease is chosen from Table (II) below:

Table (II)

Indications for Prednisone tablets
Endocrine disorders: • Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone is the first choice: synthetic analogs may be used in conjunction with mineralocorticoids where applicable; in infancy mineralocorticoid supplementation is of particular importance). • Congenital adrenal hyperplasia • Nonsuppurative thyroiditis • Hypercalcemia associated with cancer
Rheumatic disorders: As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in: • Psoriatic arthritis • Rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy) • Ankylosing spondylitis • Acute and subacute bursitis • Acute nonspecific tenosynovitis • Acute gouty arthritis • Post-traumatic osteoarthritis • Synovitis of osteoarthritis • Epicondylitis
Collagen diseases: During an exacerbation or as maintenance therapy in selected cases of: • Systemic lupus erythematosus • Systemic dermatomyositis (polymyositis) • Acute rheumatic carditis
Dermatologic diseases: • Pemphigus • Bullous dermatitis herpetiformis • Severe erythema multiforme (Stevens-Johnson syndrome) • Exfoliative dermatitis • Mycosis fungoides

• Severe psoriasis • Severe seborrheic dermatitis
Allergic states: Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment: • Seasonal or perennial allergic rhinitis • Serum sickness • Bronchial asthma • Contact dermatitis • Atopic dermatitis • Drug hypersensitivity reactions
Ophthalmic diseases: Severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa, such as: • Allergic conjunctivitis • Keratitis • Allergic corneal marginal ulcers • Herpes zoster ophthalmicus • Iritis and iridocyclitis • Chorioretinitis • Anterior segment inflammation • Diffuse posterior uveitis and choroiditis • Optic neuritis • Sympathetic ophthalmia
Respiratory diseases: • Symptomatic sarcoidosis • Loeffler's syndrome not manageable by other means • Berylliosis • Fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy. • Aspiration pneumonitis
Hematologic disorders: • Idiopathic thrombocytopenic purpura in adults • Secondary thrombocytopenia in adults • Acquired (autoimmune) hemolytic anemia • Eythroblastopenia (RBC anemia) • Congenital (erythroid) hypoplastic anemia
Neoplastic diseases: For palliative management of: • Leukemias and lymphomas in adults

• Acute leukemia of childhood
Edematous states: To induce a diuresis or remission of proteinuria in the nephrotic syndrome, without uremia, of the idiopathic type or that due to lupus erythematosus.
Gastrointestinal diseases: To tide the patient over a critical period of the disease in: • Ulcerative colitis • Regional enteritis
Nervous system: Acute exacerbations of multiple sclerosis
Miscellaneous: Tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate antituberculous chemotherapy. Trichinosis with neurologic or myocardial involvement.

In a third embodiment of the first, second, third, fourth, and fifth aspects, the disease is pemphigus vulgaris (PG) or pemphigus foliaceus (PF). In a fourth embodiment of the first, second, third, fourth, and fifth aspects, and the first and second embodiments contained therein, the BTK inhibitor is administered as a monotherapy. In a fifth embodiment of the first, second, third, fourth, and fifth aspects, and the first, second and third embodiments contained therein, the BTK inhibitor is administered in acute PG or acute PF in place of or in combination with cortisterods and optionally in combination with an immunosuppressive agent chosen from interferon alpha, interferon gamma, cyclophosphamide, tacrolimus, mycophenolate mofetil, methotrexate, dapsone, sulfasalazine, azathioprine, an anti-CD20 agent (such as rituximab, ofatumumab, obinutuzumab, or veltuzumab, or a biosimilar version thereof), anti-TNFalpha agent (such as entanercept, infliximab, golilumab, adalimumab, or certolizumab pegol or a biosimilar version thereof), anti-IL6 agent toward ligand or its receptors (such as tocilizumab, sarilumab, olokizumab, elsililumab, or siltuximab), anti-IL17 agent to ligand or its receptors (such as secukinumab, ustekinumab, brodalumab, or ixekizumab), anti-IL1 agent to ligand or its receptors (such as with rilonacept, canakinumab, or anakinra), anti-IL2 agent to ligand or its receptors (such as basiliximab or daclizumab), anti-CD2 agent such as alefacept, anti-CD3 agent such as muromonab-cd3, anti-CD80/86 agent such as abatacept or belatacept, anti-sphingosine-1-phosphate receptor agent such as fingolimod, anti-C5 agent such as eculizumab, anti-integrin alpha4 agent such as natalizumab, anti- $\alpha_4\beta_7$ agent such as vedolizumab, anti-mTOR agent such as sirolimus or

everolimus, anti-calcineurin agent such as tacrolimus, or anti-BAFF/BlyS agent (such as belimumab, VAY736, or blisibimod), leflunomide and teriflunomide. Preferably, rituximab, ofatumumab, obinutuzumab, or veltuzumab, or a biosimilar version thereof .

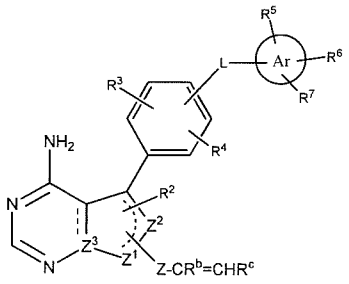
In a sixth embodiment of the first, second, third, fourth, and fifth aspects, and the first second, and third embodiments contained therein, the BTK inhibitor is administered in acute pemphigus vulgaris or acute pemphigus foliaceus in place of corticosteroids and optionally in combinations with an immunosuppressive agent chosen from interferon alpha, interferon gamma, cyclophosphamide, tacrolimus, mycophenolate mofetil, methotrexate, dapsone, sulfasalazine, azathioprine, an anti-CD20 agent (such as rituximab, ofatumumab, obinutuzumab, or veltuzumab, or a biosimilar version thereof), anti-TNFalpha agent (such as entanercept, infliximab, golilumab, adalimumab, or certolizumab pegol or a biosimilar version thereof), anti-IL6 agent toward ligand or its receptors (such as tocilizumab, sarilumab, olokizumab, elsililumab, or siltuximab), anti-IL17 agent to ligand or its receptors (such as secukinumab, ustekinumab, brodalumab, or ixekizumab), anti-IL1 agent to ligand or its receptors (such as with rilonacept, canakinumab, or anakinra), anti-IL2 agent to ligand or its receptors (such as basiliximab or daclizumab), anti-CD2 agent such as alefacept, anti-CD3 agent such as muromonab-cd3, anti-CD80/86 agent such as abatacept or belatacept, anti-sphingosine-1-phosphate receptor agent such as fingolimod, anti-C5 agent such as eculizumab, anti-integrin alpha4 agent such as natalizumab, anti- $\alpha_4\beta_7$ agent such as vedolizumab, anti-mTOR agent such as sirolimus or everolimus, anti-calcineurin agent such as tacrolimus, or anti-BAFF/BlyS agent (such as belimumab, VAY736, or blisibimod), leflunomide and teriflunomide. Preferably, rituximab, ofatumumab, obinutuzumab, or veltuzumab, or a biosimilar version thereof. In yet another embodiment of any of the above aspects, the BTK inhibitor is injected locally into the patient to treat the condition of small areas of the body. Examples of conditions for which local injections can be used include inflammation of a bursa (bursitis of the hip, knee, elbow, or shoulder), a tendon (tendinitis, such as tennis elbow), and a joint (arthritis). Knee osteoarthritis, hip bursitis, painful foot conditions such as plantar fasciitis, and rotator cuff tendinitis may be treated by local injection of a BTK inhibitor.

In a sixth aspect, provided is a method of treating an autoimmune disease and/or inflammatory disease in a mammal which method comprises administering to the mammal in need thereof a therapeutically effective amount of a BTK inhibitor in combination with an immunosuppressive agent having slow manifestions of clinical effect. In one embodiment,

the immunosuppressive agent is a biologic chosen from as interferon alpha, interferon gamma, an anti-CD20 agent (such as rituximab, ofatumumab, obinutuzumab, veltuzumab, or a biosimilar version thereof), anti-TNFalpha agent (such as entanercept, infliximab, golilumab, adalimumab, certolizumab pegol or a biosimilar version thereof), anti-IL6 agent toward ligand or its receptors (such as tocilizumab, sarilumab, olokizumab, elsililumab, or siltuximab), anti-IL17 agent to ligand or its receptors (such as secukinumab, ustekinumab, brodalumab, or ixekizumab), anti-IL1 agent to ligand or its receptors (such as with rilonacept, canakinumab, or anakinra), anti-IL2 agent to ligand or its receptors such as with basiliximab or daclizumab, anti-CD2 agent such as alefacept, anti-CD3 agent such as muromonab-cd3, anti-CD80/86 agent such as with abatacept orbelatacept, anti-C5 agent such as eculizumab, anti-integrin alpha4 agent such as natalizumab, anti- $\alpha_4\beta_7$ agent such as vedolizumab, and anti-BAFF/BlyS agent (such as belimumab, VAY736, or blisibimod). Preferably, rituximab, ofatumumab, obinutuzumab, or veltuzumab, or a biosimilar version thereof..

Representative advantages of the above methods, include sparing the patient of disease activity without immunosuppression for prolonged periods that can lead to serious side effects. Additionally, the longer the acute flares and acute phases persist the more likely the disease process will progress and cause serious complications. Thus prompt remission of acute phases and acute flares will have a beneficial effect on the course of the disease, even without continued administration or maintenance of the active agents.

In another embodiment of the first, second, third, fourth, fifth, or sixth aspects and embodiments contained therein, the BTK inbibitor is a compound of Formula (I):



(I)

wherein:

dashed lines are an optional bond;

Z^1, Z^2, and Z^3 are –N- or –CH-, provided that one or two of Z^1, Z^2, and Z^3 are simultaneously –N-;

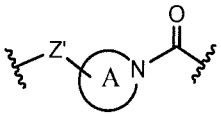
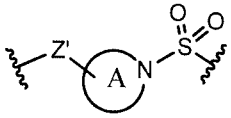
L is O, NR, NRCO, CONR, or NR'CONR where each R and R' is independently hydrogen or alkyl;

Ar is aryl, heteroaryl, cycloalkyl or heterocyclyl;

R^2 is hydrogen, alkyl, hydroxy, alkoxy, cyano, halo or haloalkyl;

R^3 and R^4 are independently hydrogen, alkyl, cyclopropyl, hydroxy, alkoxy, cyano, halo, haloalkyl or haloalkoxy;

R^5, R^6 and R^7 are independently hydrogen, alkyl, hydroxy, alkoxy, halo, haloalkyl, haloalkoxy, carboxy, alkoxycarbonyl, cyano, $-CONH_2$, amino, alkylamino, or dialkylamino;

Z is –alkyleneCO-, –alkyleneOCO-, –alkyleneSO_2-, ,  (where Z' is bond or alkylene, and ring A is heterocycloamino optionally substituted with one or two substituents independently selected from alkyl, hydroxy and fluoro, –(alkylene)-NR^aCO- or –(alkylene)-NR^aSO_2- (where each R^a is hydrogen, alkyl or cycloalkyl);

R^b is hydrogen, cyano, nitro, halo, haloalkyl, haloalkoxy, alkylthio, or alkylsulfonyl;

R^c is hydrogen, alkyl, haloalkoxy, substituted alkyl, cycloalkyl, cycloalkyleneNR^dR^e (where R^d and R^e are independently hydrogen, alkyl, or cycloalkyl), or 3 to 6 membered saturated monocyclic heterocyclyl containing one or two heteroatoms selected from N, O, or S and optionally substituted with one or two substituents independently selected from hydroxy, alkyl or fluoro;

and/or a pharmaceutically acceptable salt thereof;

wherein the terms are as defined below.

"Alkyl" means a linear saturated monovalent hydrocarbon radical of one to six carbon atoms or a branched saturated monovalent hydrocarbon radical of three to six carbon atoms, e.g., methyl, ethyl, propyl, 2-propyl, butyl (including all isomeric forms), pentyl (including all isomeric forms), and the like.

"Alkylene" means a linear saturated divalent hydrocarbon radical of one to six carbon atoms or a branched saturated divalent hydrocarbon radical of three to six carbon atoms unless otherwise stated e.g., methylene, ethylene, propylene, 1-methylpropylene, 2-methylpropylene, butylene, pentylene, and the like.

"Alkylthio" means an -SR radical where R is alkyl as defined above, e.g., methylthio, ethylthio, and the like.

"Alkylsulfonyl" means an $-SO_2R$ radical where R is alkyl as defined above, e.g., methylsulfonyl, ethylsulfonyl, and the like.

"Amino" means an $-NH_2$.

"Alkylamino" means an -NHR radical where R is alkyl as defined above, e.g., methylamino, ethylamino, propylamino, or 2-propylamino, and the like.

"Alkoxy" means an -OR radical where R is alkyl as defined above, e.g., methoxy, ethoxy, propoxy, or 2-propoxy, *n*-, *iso*-, or *tert*-butoxy, and the like.

"Alkoxyalkyl" means a linear monovalent hydrocarbon radical of one to six carbon atoms or a branched monovalent hydrocarbon radical of three to six carbons substituted with an alkoxy group, or one or two alkoxy groups, as defined above, e.g., 2-methoxyethyl, 1-, 2-, or 3-methoxypropyl, 2-ethoxyethyl, and the like.

"Alkoxycarbonyl" means a -C(O)OR radical where R is alkyl as defined above, e.g., methoxycarbonyl, ethoxycarbonyl, and the like.

"Aryl" means a monovalent monocyclic or bicyclic aromatic hydrocarbon radical of 6 to 10 ring atoms e.g., phenyl or naphthyl.

"Cycloalkyl" means a cyclic saturated monovalent hydrocarbon radical of three to ten carbon atoms wherein one or two carbon atoms may be replaced by an oxo group, e.g., cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl, and the like.

"Cycloalkylene" means a cyclic saturated divalent hydrocarbon radical of three to ten carbon atoms wherein one or two carbon atoms may be replaced by an oxo group, e.g., cyclopropylene, cyclobutylene, cyclopentylene, or cyclohexylene, and the like.

"Carboxy" means –COOH.

"Dialkylamino" means an –NRR' radical where R and R' are independently alkyl, as defined above.

"Halo" means fluoro, chloro, bromo, or iodo. In one embodiment halo is fluoro or chloro.

"Haloalkyl" means alkyl radical as defined above, which is substituted with a halogen atoms or one to five halogen atoms (in one embodiment fluorine or chlorine), including those substituted with different halogens, e.g., $-CH_2Cl$, $-CF_3$, $-CHF_2$, $-CH_2CF_3$, $-CF_2CF_3$, $-CF(CH_3)_2$, and the like. When the alkyl is substituted with only fluoro, it is referred to in this Application as fluoroalkyl.

"Haloalkoxy" means a –OR radical where R is haloalkyl as defined above e.g., $-OCF_3$,

$-OCHF_2$, and the like. When R is haloalkyl where the alkyl is substituted with only fluoro, it is referred to in this Application as fluoroalkoxy.

"Hydroxyalkyl" means an alkyl, as defined above, substituted with one or two hydroxy groups, provided that if two hydroxy groups are present they are not both on the same carbon atom. Representative examples include, but are not limited to, hydroxymethyl, 2-hydroxyethyl, 2-hydroxypropyl, 3-hydroxypropyl, 1-(hydroxymethyl)-2-methylpropyl, 2-hydroxybutyl, 3-hydroxybutyl, 4-hydroxybutyl, 2,3-dihydroxypropyl, 1-(hydroxymethyl)-2-hydroxyethyl, 2,3-dihydroxybutyl, 3,4-dihydroxybutyl and 2-(hydroxymethyl)-3-hydroxypropyl. In one embodiment, 2-hydroxyethyl, 2,3-dihydroxypropyl, and 1-(hydroxymethyl)-2-hydroxyethyl.

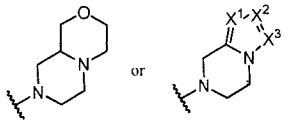
"Heterocyclyl" means a saturated or unsaturated monovalent monocyclic group of 4 to 8 ring atoms in which one or two ring atoms are heteroatoms selected from N, O, or $S(O)_n$, where n is an integer from 0 to 2, the remaining ring atoms being C. The heterocyclyl ring is optionally fused to an (one) aryl or heteroaryl ring as defined herein provided the aryl and heteroaryl rings are monocyclic. The heterocyclyl ring fused to monocyclic aryl or heteroaryl ring is also referred to in this Application as "bicyclic heterocyclyl" ring, even though a portion of the bicycle is aromatic. Additionally, one or two ring carbon atoms in the heterocyclyl ring can optionally be replaced by a –CO- group. More specifically the term heterocyclyl includes, but is not limited to, pyrrolidino, piperidino, homopiperidino, 2-oxopyrrolidinyl, 2-oxopiperidinyl, morpholino, piperazino, tetrahydropyranyl, thiomorpholino, and the like. When the heterocyclyl ring is unsaturated it can contain one or two ring double bonds provided that the ring is not aromatic. When the heterocyclyl group contains a nitrogen atom, it is also referred to herein as heterocycloamino and is a subset of the heterocyclyl group. When the heterocyclyl group is a saturated ring and is not fused to aryl or heteroaryl ring as stated above, it is also referred to herein as saturated monocyclic heterocyclyl.

"Heterocycloamino" means a saturated or unsaturated monovalent monocyclic group of 4 to 8 ring atoms in which one or two ring atoms are heteroatom selected from N, O, or $S(O)_n$, where n is an integer from 0 to 2, the remaining ring atoms being C provided that a ring atom is N. Additionally, one or two ring carbon atoms in the heterocycloamino ring can optionally be replaced by a –CO- group. When the heterocycloamino ring is unsaturated it can contain one or two ring double bonds provided that the ring is not aromatic.

"Heteroaryl" means a monovalent monocyclic or bicyclic aromatic radical of 5 to 10 ring atoms where one or more, or one, two, or three, ring atoms are heteroatom selected from N, O, or S, the remaining ring atoms being carbon. Representative examples include, but are not limited to, pyrrolyl, thienyl, thiazolyl, imidazolyl, furanyl, indolyl, isoindolyl, oxazolyl, isoxazolyl, benzothiazolyl, benzoxazolyl, quinolinyl, isoquinolinyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazolyl, tetrazolyl, and the like.

"Oxo" or "carbonyl" means C=(O) group.

"Substituted alkyl" means alkyl group as defined herein which is substituted with one, two, or three substituents independently selected from hydroxyl, alkoxy, carboxy, cyano, carboxy, alkoxycarbonyl, alkylthio, alkylsulfonyl, halo, -CONRR' or –NRR' (where each R is hydrogen, alkyl, cycloalkyl, hydroxyalkyl, or alkoxyalkyl, and each R' is hydrogen, alkyl, or cycloalkyl), heterocyclyl (in one embodiment heterocycloamino as defined herein) which is optionally substituted with one or two groups independently selected from alkyl, hydroxyl, alkoxy, alkylthio, alkylsulfonyl, halo, or -CONRR' where R and R' are as defined above,



where one or two of X^1, X^2 and X^3 are nitrogen and the rest are carbon and the ring is optionally substituted with one or two substituents independently selected from alkyl, haloalkyl, or halo.

"Optional" or "optionally" means that the subsequently described event or circumstance may but need not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, "heterocyclyl group optionally substituted with an alkyl group" means that the alkyl may but need not be present, and the description includes situations where the heterocyclyl group is substituted with an alkyl group and situations where the heterocyclyl group is not substituted with alkyl.

In one embodiment,the compound of Formula (I) is:

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

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

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

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

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

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

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

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

2-(4-(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;

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

N-((1s,4s)-4-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexyl)-2-cyano-3-cyclopropylacrylamide;

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

N-((1r,4r)-4-(4-amino-3-(4-(3,4-dichlorophenoxy)-3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexyl)-2-cyano-3-cyclopropylacrylamide;

N-((1s,4s)-4-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexyl)-2-cyano-4,4-dimethylpent-2-enamide;

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

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

N-((1r,4r)-4-(4-amino-3-(4-(3,4-dichlorophenoxy)-3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexyl)-2-cyano-4,4-dimethylpent-2-enamide;

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

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

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

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;

N-((1s,4s)-4-(4-amino-3-(4-(3,4-dichlorophenoxy)-3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexyl)-2-cyano-3-cyclopropylacrylamide;

N-((1s,4s)-4-(4-amino-3-(4-(3,4-dichlorophenoxy)-3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexyl)-2-cyano-4,4-dimethylpent-2-enamide;

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

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

(S)-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;

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

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

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

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

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

(S)-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-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-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;

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

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

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

N-(2-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-2-cyano-3-cyclopropylacrylamide;

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

(S)-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;

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

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

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

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

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

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

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

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

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

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

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

N-(2-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-2-cyano-3-cyclopropylacrylamide;

N-(2-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-2-methylpropyl)-2-cyano-3-cyclopropylacrylamide;

N-(1-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-2-methylpropan-2-yl)-2-cyano-3-cyclopropylacrylamide;

N-(2-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-1-cyano-2-cyclopropylethenesulfonamide;

N-(2-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-1-cyano-2-cyclopropyl-N-methylethenesulfonamide;

2-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl 2-cyano-3-cyclopropylacrylate;

1-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-2-methylpropan-2-yl 2-cyano-3-cyclopropylacrylate;

2-((2-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)sulfonyl)-3-cyclopropylacrylonitrile;

2-(5-((4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)oxazol-2-yl)-3-cyclopropylacrylonitrile;

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

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

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

(S)-2-(3-(4-amino-5-(4-(3,5-difluorophenoxy)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)piperidine-1-carbonyl)-3-cyclopropylacrylonitrile;

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

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

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

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

(R)-2-(2-((4-amino-5-(4-(3,5-difluorophenoxy)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)methyl)pyrrolidine-1-carbonyl)-3-cyclopropylacrylonitrile;

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

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

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

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

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

(R)-2-(3-(4-amino-5-(4-(3,5-difluorophenoxy)phenyl)-6-methyl-7H-pyrrolo[2,3-d]pyrimidin-7-yl)piperidine-1-carbonyl)-3-cyclopropylacrylonitrile;

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

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

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

(R)- (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)-3-cyclopropylacrylonitrile;

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

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

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

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

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

N-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-2,2-dimethylpropyl)-2-cyano-3-cyclopropylacrylamide;

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

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

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

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

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

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

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

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

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

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

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

(S)-2-(2-((4-amino-3-(2-fluoro-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-(2,6-difluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)pyrrolidine-1-carbonyl)-4-methylpent-2-enenitrile;

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

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

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

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

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

(S)-2-(2-((4-amino-3-(4-(2,6-difluorophenoxy)-2-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)pyrrolidine-1-carbonyl)-4-methylpent-2-enenitrile;

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

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

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

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

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

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

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

(S)-2-(2-((4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)pyrrolidine-1-carbonyl)-4-(dimethylamino)-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)-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)-4-(ethylamino)-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)-4-(ethylamino)-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)-4-(isopropylamino)-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)-4-(isopropylamino)-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)-4-(cyclopropylamino)-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)-4-(cyclopropylamino)-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)-4-((2-methoxyethyl)amino)-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)-4-((2-methoxyethyl)amino)-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)-4-ethoxy-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)-4-ethoxy-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-(1-aminocyclopropyl)acrylonitrile;

(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;

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

(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-(1-aminocyclopropyl)acrylonitrile;

(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-(1-aminocyclopropyl)acrylonitrile;

(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-(1-(methylamino)cyclopropyl)-acrylonitrile;

(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-(1-(methylamino)cyclopropyl)-acrylonitrile;

(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-(1-(ethylamino)cyclopropyl)acrylonitrile;

(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-(1-(ethylamino)cyclopropyl)acrylonitrile;

(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-(1-(isopropylamino)cyclopropyl)-acrylonitrile;

(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-(1-(isopropylamino)cyclopropyl)-acrylonitrile;

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

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

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

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

(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-(1-((diethylamino)methyl)cyclopentyl)-acrylonitrile;

(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-(1-((diethylamino)methyl)cyclopentyl)-acrylonitrile;

(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-(1-((dimethylamino)methyl)-cyclopentyl)acrylonitrile;

(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-(1-((dimethylamino)-methyl)-cyclopentyl)acrylonitrile;

(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-(1-methylpiperidin-4-yl)acrylonitrile;

(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-(1-methylpiperidin-4-yl)acrylonitrile;

(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-(tetrahydro-2H-pyran-4-yl)acrylonitrile;

(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-(tetrahydro-2H-pyran-4-yl)acrylonitrile;

(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-(piperidin-4-yl)acrylonitrile;

(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-(piperidin-4-yl)acrylonitrile;

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

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

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

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

(S)-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;

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

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

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

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

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

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

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

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

(S)-2-(3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-4-ethoxy-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)-3-(1-aminocyclopropyl)acrylonitrile;

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

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

(S)-2-(3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-3-(1-(methylamino)cyclopropyl)acrylonitrile;

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

(S)-2-(3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-3-(1-(ethylamino)cyclopropyl)acrylonitrile;

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

(S)-2-(3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-3-(1-(isopropylamino)cyclopropyl)acrylonitrile;

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

2-((S)-3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-3-(pyrrolidin-2-yl)acrylonitrile;

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

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

(S)-2-(3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-3-(1-((diethylamino)methyl)-cyclopentyl)acrylonitrile;

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

(S)-2-(3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-3-(1-((dimethylamino)methyl)cyclopentyl)-acrylonitrile;

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

(S)-2-(3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-3-(1-methylpiperidin-4-yl)acrylonitrile;

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

(S)-2-(3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-3-(tetrahydro-2H-pyran-4-yl)acrylonitrile;

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

(S)-2-(3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-3-(piperidin-4-yl)acrylonitrile;

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

2-((S)-3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-3-(piperidin-3-yl)acrylonitrile;

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

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

(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;

(S)-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;

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

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

(R)-4-amino-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;

(S)-4-amino-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;

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

(S)-2-(3-(4-amino-3-(4-(2,3-difluorophenoxy)-2-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-4-methyl-4-(methylamino)pent-2-enenitrile;

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

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

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

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

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

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

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

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

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

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

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

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

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

(S)-2-(3-(4-amino-3-(4-(2,3-difluorophenoxy)-2-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-3-(1-aminocyclopropyl)-acrylonitrile;

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

(S)-2-(3-(4-amino-3-(4-(2,3-difluorophenoxy)-2-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-3-(1-(methylamino)cyclopropyl)-acrylonitrile;

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

(S)-2-(3-(4-amino-3-(4-(2,3-difluorophenoxy)-2-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-3-(1-(ethylamino)cyclopropyl)-acrylonitrile;

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

(S)-2-(3-(4-amino-3-(4-(2,3-difluorophenoxy)-2-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-3-(1-(isopropylamino)-cyclopropyl)acrylonitrile;

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

2-((S)-3-(4-amino-3-(4-(2,3-difluorophenoxy)-2-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-3-(pyrrolidin-2-yl)acrylonitrile;

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

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

(R)-2-(3-(4-amino-3-(4-(2,3-difluorophenoxy)-2-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-3-(1-((diethylamino)methyl)-cyclopentyl)-acrylonitrile;

(S)-2-(3-(4-amino-3-(4-(2,3-difluorophenoxy)-2-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-3-(1-((diethylamino)methyl)-cyclopentyl)-acrylonitrile;

(R)-2-(3-(4-amino-3-(4-(2,3-difluorophenoxy)-2-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-3-(1-((dimethylamino)-methyl)cyclopentyl)-acrylonitrile;

(S)-2-(3-(4-amino-3-(4-(2,3-difluorophenoxy)-2-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-3-(1-((dimethylamino)-methyl)cyclopentyl)-acrylonitrile;

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

(S)-2-(3-(4-amino-3-(4-(2,3-difluorophenoxy)-2-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-3-(1-methylpiperidin-4-yl)acrylonitrile;

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

(S)-2-(3-(4-amino-3-(4-(2,3-difluorophenoxy)-2-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-3-(tetrahydro-2H-pyran-4-yl)acrylonitrile;

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

(S)-2-(3-(4-amino-3-(4-(2,3-difluorophenoxy)-2-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-3-(piperidin-4-yl)acrylonitrile;

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

2-((S)-3-(4-amino-3-(4-(2,3-difluorophenoxy)-2-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-3-(piperidin-3-yl)acrylonitrile;

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

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

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

(R)-2-(2-((4-amino-5-(4-(2,3-difluorophenoxy)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)methyl)pyrrolidine-1-carbonyl)-3-cyclopropylacrylonitrile;

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

(R)-2-(2-((4-amino-5-(4-(2,3-difluorophenoxy)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)methyl)pyrrolidine-1-carbonyl)-4-methylpent-2-enenitrile;

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

(R)-2-(2-((4-amino-5-(4-(2,3-difluorophenoxy)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)methyl)pyrrolidine-1-carbonyl)-4,4-dimethylpent-2-enenitrile;

(S)-2-(2-((4-amino-5-(4-(2,3-difluorophenoxy)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)methyl)pyrrolidine-1-carbonyl)-4,4-dimethylpent-2-enenitrile;

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

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

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

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

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

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

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

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

(R)-2-(2-((4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-methyl)pyrrolidine-1-carbonyl)-4-methyl-4-morpholinopent-2-enenitrile

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

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

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

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

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

(R)-N-(1-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-propan-2-yl)-2-cyano-4,4-dimethylpent-2-enamide;

(S)-N-(1-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)propan-2-yl)-2-cyano-4,4-dimethylpent-2-enamide;

(R)-N-(1-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)propan-2-yl)-2-cyano-4-methylpent-2-enamide;

(S)-N-(1-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)propan-2-yl)-2-cyano-4-methylpent-2-enamide;

(R)-N-(1-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)propan-2-yl)-2-cyano-4-ethoxy-4-methylpent-2-enamide;

(S)-N-(1-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)propan-2-yl)-2-cyano-4-ethoxy-4-methylpent-2-enamide;

(R)-N-(1-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)propan-2-yl)-2-cyano-4-(dimethylamino)-4-methylpent-2-enamide;

(S)-N-(1-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)propan-2-yl)-2-cyano-4-(dimethylamino)-4-methylpent-2-enamide;

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

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

(R)-4-amino-N-(1-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]-pyrimidin-1-yl)propan-2-yl)-2-cyano-4-methylpent-2-enamide;

(S)-4-amino-N-(1-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]-pyrimidin-1-yl)propan-2-yl)-2-cyano-4-methylpent-2-enamide;

N-(2-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-2-cyano-3-cyclopropyl-N-methylacrylamide;

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

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

(S)-N-(1-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)propan-2-yl)-2-cyano-4,4-dimethylpent-2-enamide;

(S)-N-(1-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)propan-2-yl)-2-cyano-4-methylpent-2-enamide;

(S)-N-(1-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)propan-2-yl)-2-cyano-4-(dimethylamino)-4-methylpent-2-enamide;

(S)-N-(1-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)propan-2-yl)-2-cyano-4-ethoxy-4-methylpent-2-enamide;

(S)-4-amino-N-(1-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]-pyrimidin-1-yl)propan-2-yl)-2-cyano-4-methylpent-2-enamide;

(S)-N-(1-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)propan-2-yl)-2-cyano-3-cyclopropylacrylamide;

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

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

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

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-[[(3S)-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-((S)-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;

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

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

(S)-2-(3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-4-methyl-4-(2-oxa-6-azaspiro[3.3]heptan-6-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-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pent-2-enenitrile;

(S)-2-(2-((4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)pyrrolidine-1-carbonyl)-4-methyl-4-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pent-2-enenitrile;

(R)-2-(2-((4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)pyrrolidine-1-carbonyl)-4-methyl-4-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pent-2-enenitrile;

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

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

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-ethylpiperazin-1-yl)pent-2-enenitrile;

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

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

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

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

(S)-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;

(S)-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;

(S)-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;

2-((R)-3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-4-((R)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)-4-methylpent-2-enenitrile;

2-((S)-3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-4-((R)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)-4-methylpent-2-enenitrile;

2-((R)-3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-4-((S)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)-4-methylpent-2-enenitrile;

2-((S)-3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-4-((S)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-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-(2,2,2-trifluoroethyl)piperazin-1-yl)pent-2-enenitrile;

(S)-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-((S)-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;

2-((S)-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;

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

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

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

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

2-((S)-3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-4-methyl-4-((2S,5R)-2,4,5-trimethylpiperazin-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-(5,6-dihydroimidazo[1,2-a]pyrazin-7(8H)-yl)-4-methylpent-2-enenitrile;

(S)-2-(3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-4-(5,6-dihydroimidazo[1,2-a]pyrazin-7(8H)-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;

(S)-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-methyl-3-oxopiperazin-1-yl)pent-2-enenitrile;

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

(S)-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;

(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;

(S)-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;

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

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

or a mixture of R and S isomers thereof;

or an individual E or Z isomer of any of the above compounds; and/or

a pharmaceutically acceptable salt of any of the above compounds.

In another embodiment of the first, second, third, fourth, fifth, or sixth aspects and embodiments contained therein, the BTK inhibitor is a compound of formula (Ia) or (Ib) disclosed on pages 4-6, and specific compounds disclosed on pages 57-94, of PCT application publication no. WO 2009/158571, the disclosure of those pages relating to the BTK inhibitor is incorporated herein by reference in their entirety. The scope of the terms in compound for formula (Ia) and (Ib) are disclosed on pages 4-6 are as defined on pages 6-14 of WO 2009/158571, the disclosure of those pages relating to definitions is incorporated herein by reference in their entirety. In one embodiment, the compound is N-(3-((5-fluoro-2-((4-(2-methoxyethoxy)phenyl)amino)-pyrimidin-4-yl)amino)phenyl)acrylamide and/or a pharmaceutically acceptable salt thereof.

In another embodiment of the first, second, third, fourth, fifth, or sixth aspects and embodiments contained therein, the BTK inhibitors are compounds of formula (I) disclosed on pages 1 and 2, paragraph [0005] and the specific compound disclosed on page 3, paragraph [0008] of PCT application publication no. WO 2013/173518, the disclosure of those pages relating to the BTK inhibitor is incorporated herein by reference in their entirety. The scope of the terms in formula (I) is disclosed on pages 1 and 2 as defined on pages 4-7, paragraphs [0013]-[0031] of WO 2013/173518 and the disclosure of those pages relating to scope of the terms is incorporated herein by reference in their entirety.

In another embodiment of the first, second, third, fourth, fifth, or sixth aspects and embodiments contained therein, the BTK inhibitors are compounds of formula (I) disclosed on pages 2 and 3, paragraph [0007], formula (Ia), paragraph [0014] disclosed on pages 5 and 6, formula (Ib), paragraph [0021] disclosed on pages 7 -9, formula (II) on pages 12-13, paragraph [0043], formula (III) on pages 65-66, paragraph [00250], and formula (IV) disclosed on pages 75-76, paragraph [00272], and the specific compound disclosed on pages 80-85 and pages 165-175 of PCT application publication no. WO 2013/102059, the disclosure of those pages relating to BTK inhibitors is incorporated herein by reference in their entirety. The scope of the terms used to define the compounds of formulae (I), (Ia), (II), (III) and (IV) are as defined on pages 26-35, paragraphs [00104]-[00163], [00167], [00177] of WO 2013/102059 and the disclosure of those pages relating to scope is incorporated herein by reference in their entirety.

In another embodiment of the first, second, third, fourth, fifth, or sixth aspects and embodiments contained therein, the BTK inhibitors are compounds of formula (I) disclosed

on pages 2 and 3, paragraph [0007], formula (Ia) disclosed on pages 46 - 48, paragraph [00207], formula (Ib) disclosed on pages 51 -53, paragraph [00218], formula (III) on pages 4-5, paragraph [0009], formula (II) on pages 57 and 58, paragraph [00229], and formula (IV) disclosed on pages 63-65, paragraph [00249], and the specific compound disclosed on pages 66-75 of PCT application publication no. WO 2014/078578, the disclosure of those pages relating to BTK inhibitors is incorporated herein by reference in their entirety. The scope of the terms used to define the compounds of formulae (I), (Ia), (II), (III) and (IV) are as defined on pages 18-28, paragraphs [0066]-[00133], [00137], [00147] of WO 2014/078578 and the disclosure of those pages relating to scope is incorporated herein by reference in their entirety.

In another embodiment of the first, second, third, fourth, fifth, or sixth aspects and embodiments contained therein, the BTK inhibitor is a compound of formula (I) disclosed on pages 2 and 3, paragraph [0007], formula (II) disclosed on pages 6 and 7, paragraph [0014], formula (III) on pages 8-10, paragraph [0019], formula (Ia) disclosed on pages 50 -52, paragaraph [00219], formula (Ib) disclosed on pages 54 -56, paragaraph [00228], formula (II), page 58-60, paragaraph [00237], formula (IIa) disclosed on pages 63-65, paragaraph [00247], formula (IIb) disclosed on pages 67-69, paragaraph [00255], formula (III), page 71-73, paragaraph [00263], formula (IIIa) disclosed on pages 77-79, paragaraph [00277], formula (IIIb) disclosed on pages 82-83, paragaraph [00286], formula (IIIc) disclosed on pages 86-87, paragaraph [00295], and the specific compound disclosed on pages 91-102 of PCT application publication no. WO 2013/116382, the disclosure of those pages relating to BTK inhibitor is incorporated herein by reference in their entirety. The scope of the terms used to define the compounds of formulae (I), (Ia), (Ib), (II), (IIa), (IIb), (III), (IIIa), (IIIb) and (IIIc) are as defined on pages 25-36, paragraphs [0088]-[00155], [00164], of WO 2013/116382 and the disclosure of those pages relating to scope is incorporated herein by reference in their entirety.

In another embodiment of the first, second, third, fourth, fifth, or sixth aspects and embodiments contained therein, the BTK inhibitor is a compound of formula (A) disclosed on pages 25 and 26, paragraph [00185], formula (B) disclosed on pages 26 and 27, paragraph [00186], formula (C) on pages 27-28, paragraph [00189], formula (D) disclosed on page 28-29, paragraph [00196], and the specific compound disclosed on pages 30-31, of PCT application publication no. WO 2008/039218, the disclosure of those pages relating to BTK inhibitor is incorporated herein by reference in their entirety. The scope of the terms in

compounds of formulae (A), (B), (C), and (D) are as defined on pages 11-17 of WO 2008/039218, paragraph [0061]-[00119], [00123], [00133], and the disclosure of those pages relating to scope is incorporated herein by reference in their entirety. In one embodiment, the compound is BTK inhibitor Ibrutinib.

In another embodiment of the first, second, and third aspects and embodiments contained therein, the BTK inhibitor is a compound of formula (I) disclosed on pages 2 and 3, paragraph [0007], formula (II), pages 4-7, paragraph [0013], formula (Ia), paragraph [00216], formula (Ib), paragraph [00227], formula (Ic), paragraph [00237], formula (Id), paragraph [00247], formula (IIa), paragraph [00271], formula (III), paragraph [00283], formula (IIIa), paragraph [00293], formula (IV), paragraph [00304], formula (IVa), paragraph [00315], and the specific compounds no. 6, 13, 17, 23, 29, 35, 43, 48, 54 and 60 of PCT application publication no. WO 2014/130693 the disclosure of those pages relating to BTK inhibitor is incorporated herein by reference in their entirety. The scope of the terms in compounds of formula (I) are defined on pages 22-32, paragraph [0079]-[00146], [00160], of WO 2014/130693 and the disclosure of those pages relating to scope is incorporated herein by reference in their entirety.

In another embodiment of the first, second, third, fourth, fifth, or sixth aspects and embodiments contained therein, the BTK inbibitor is a compound of formula (I) disclosed on pages 22 -24, lines 21-11 and specific compounds disclosed in table 1 page 28-34 of PCT application publication no. WO 2013/067277, the disclosure of those pages relating to BTK inhibitor is incorporated herein by reference in their entirety. The scope of the terms used to define the compounds of formula (I) are as defined on pages 6-11, lines 25 to 28 of WO 2013/067277 and the disclosure of those pages relating to scope is incorporated herein by reference in their entirety.

In another embodiment of the first, second, third, fourth, fifth, or sixth aspects and embodiments contained therein, the BTK inhibitor is a compound of formula (I) disclosed on pages 24 -26, lines 1 to 15, and specific compounds disclosed in table 1 page 34-78 of PCT application publication no. WO 2013/067274, the disclosure of those pages relating to BTK inhibitor is incorporated herein by reference in their entirety. The scope of the terms used to define the compounds of formula (I) are as defined on pages 8-13, lines 1 to 5 of WO 2013/067274 are the disclosure of those pages relating to scope is incorporated herein by reference in their entirety.

In another embodiment of the first, second, third, fourth, fifth, or sixth aspects and embodiments contained therein, the BTK inhibitor is a compound of formula (I) disclosed on pages 19 -20, lines 1 to 5 and specific compounds disclosed in table 1 page 32-94 of PCT application publication no. WO 2011/140488, the disclosure of those pages relating to BTK inhibitor is incorporated herein by reference in their entirety. The scope of the terms used to define the compounds of formula (I) are as defined on pages 4-8, lines 30 to 25 of WO 2011/140488 and the disclosure of those pages relating to scope is incorporated herein by reference in their entirety.

In another embodiment of the first, second, third, fourth, fifth, or sixth aspects and embodiments contained therein, the BTK inhibitor is a compound of formula (I) disclosed on page 3, paragraph [0022] and specific compounds disclosed in table 1 pages 34-78 of US application publication no. US 2013/0217880 and specific compounds disclosed therein the disclosure of those pages relating to BTK inhibitor is incorporated herein by reference in their entirety. The scope of the terms used to define the compounds of formula (I) are as defined on pages 4-5 of US 2013/0217880 are the disclosure of those pages relating to scope is incorporated herein by reference in their entirety. In one embodiment the compound is 6-amino-9-[(3R)-1-(2-butynoyl)-3-pyrrolidinyl]-7-(4-phenylphenyl)-7,9-dihydro-8H-purin-8-one and/or a salt thereof.

In another embodiment of the first, second, third, fourth, fifth, or sixth aspects and embodiments contained therein, the BTK inhibitor is a compound of formula (I) disclosed on pages 4-14, lines 1 to 11 and specific compounds disclosed in table 1 page 33-77 of PCT application publication no. WO 2013/010380 and specific compounds disclosed therein the disclosure of those pages relating to BTK inhibitor is incorporated herein by reference in their entirety. The scope of the terms used to define the compounds of formula (I) are as defined on pages 14-23, lines 13 to 4 of WO 2013/010380 and the disclosure of those pages relating to scope is incorporated herein by reference in their entirety.

In another embodiment of the first, second, third, fourth, fifth, or sixth aspects and embodiments contained therein, the BTK inhibitor is a compound of formula (I) disclosed on pages 3-4, lines 4-28 and specific compounds disclosed in table 1 page 10-16 of PCT application publication no. WO 2013/010868 and specific compounds disclosed therein the disclosure of those pages relating to BTK inhibitor is incorporated herein by reference in their entirety. The scope of the terms used to define the compounds of formula (I) are as defined

on pages 4-6, lines 30-37 of WO 2013/010868 and the disclosure of those pages relating to scope is incorporated herein by reference in their entirety.

In another embodiment of the first, second, third, fourth, fifth, or sixth aspects and embodiments contained therein, the BTK inhibitor is a compound of formula (I) disclosed on pages 3-4, lines 5 to 31 and specific compounds disclosed in table 1 page 43-47 of PCT application publication no. WO 2013/010869 and specific compounds disclosed therein the disclosure of those pages relating to BTK inhibitor is incorporated herein by reference in their entirety. The scope of the terms used to define the compounds of formula (I) are as defined on pages 4-7, lines 34 to 37 of WO 2013/010869 and the disclosure of those pages relating to scope is incorporated herein by reference in their entirety.

In another embodiment of the first, second, third, fourth, fifth, or sixth aspects and embodiments contained therein, the BTK inhibitors are those disclosed in WO2014/025976, WO2014/151620, and WO2014/152114, the disclosures of which related to BTK inhibitors are incorporated herein by reference in their entirety.

In another embodiment of the first, second, third, fourth, fifth, or sixth aspects and embodiments contained therein, the BTK inbibitor is (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 or an (E), or (Z) isomer thereof, Ibrutinib (Pharmacyclics/Johnson and Johnson) AVL 263 and 293 (Avila Therapeutics, Celgene Corporation), GDC-0834 (Genentech), GDC0853 (Genentech), BMS-488516 and 509744 (Bristol Myers Squibb), CGI-1746 (Gilead Sciences), CTA-056 (Genentech), HY-11066 (also CTK417891), ONO-4059 (Ono Pharmaceutical Co. Ltd), ONO-WG37 (Ono Pharmaceutical Co. Ltd), PLS-123 (Peking Univ.), RN486 (Hoffmann Las Roche), HM71224 (Hanmi Pharmceutical Co. Ltd.), or ACP-196 (Acerta Pharma BV).

In another embodiment of the first, second, third, fourth, fifth, or sixth aspects and embodiments contained therein, the BTK inhibitor is ABT-105 or ABBV-105 (AbbVie), AC0025 (ACEA Biosciences), BGB3111(BeiGene), CC-292 (Celgene), EBI-1266 (Eternity Bioscience), MSC-2364447 (Merck Biopharma), PF-06250112 and PF-303 (Pfizer), RG7625 and RG7880 (Hoffmann La Roche), SNS-062 (Sunesis), TP-4207 (Tolero Pharmaceuticals), or X-022 (X-Chem).

In another embodiment of the first, second, third, fourth, fifth, or sixth aspects and embodiments contained therein, the BTK inhibitor is

(R)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one,

(R)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide,

(S)-7-(1-acryloylpiperidin-4-yl)-2-(4-phenoxyphenyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-3-carboxamide,

(S)-7-(1-(but-2-ynoyl)piperidin-4-yl)-2-(4-phenoxyphenyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-3-carboxamide,

N-(3-((2-((2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)amino)thieno[3,2-d]pyrimidin-4-yl)oxy)phenyl)acrylamide,

1-(3-((2-((4-(4-methylpiperazin-1-yl)phenyl)amino)-[1,2,4]triazolo[1,5-a]pyridin-8-yl)oxy)phenyl)prop-2-en-1-one,

(R)-6-amino-9-(1-(but-2-ynoyl)pyrrolidin-3-yl)-7-(4-phenoxyphenyl)-7H-purin-8(9H)-one,

N-(2-((6-((5-(5-fluoro-2-(hydroxymethyl)-3-(4-oxo-6,7,8,9-tetrahydrobenzo[4,5]thieno[2,3-d]pyridazin-3(4H)-yl)phenyl)-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)amino)pyridin-2-yl)amino)ethyl)acrylamide,

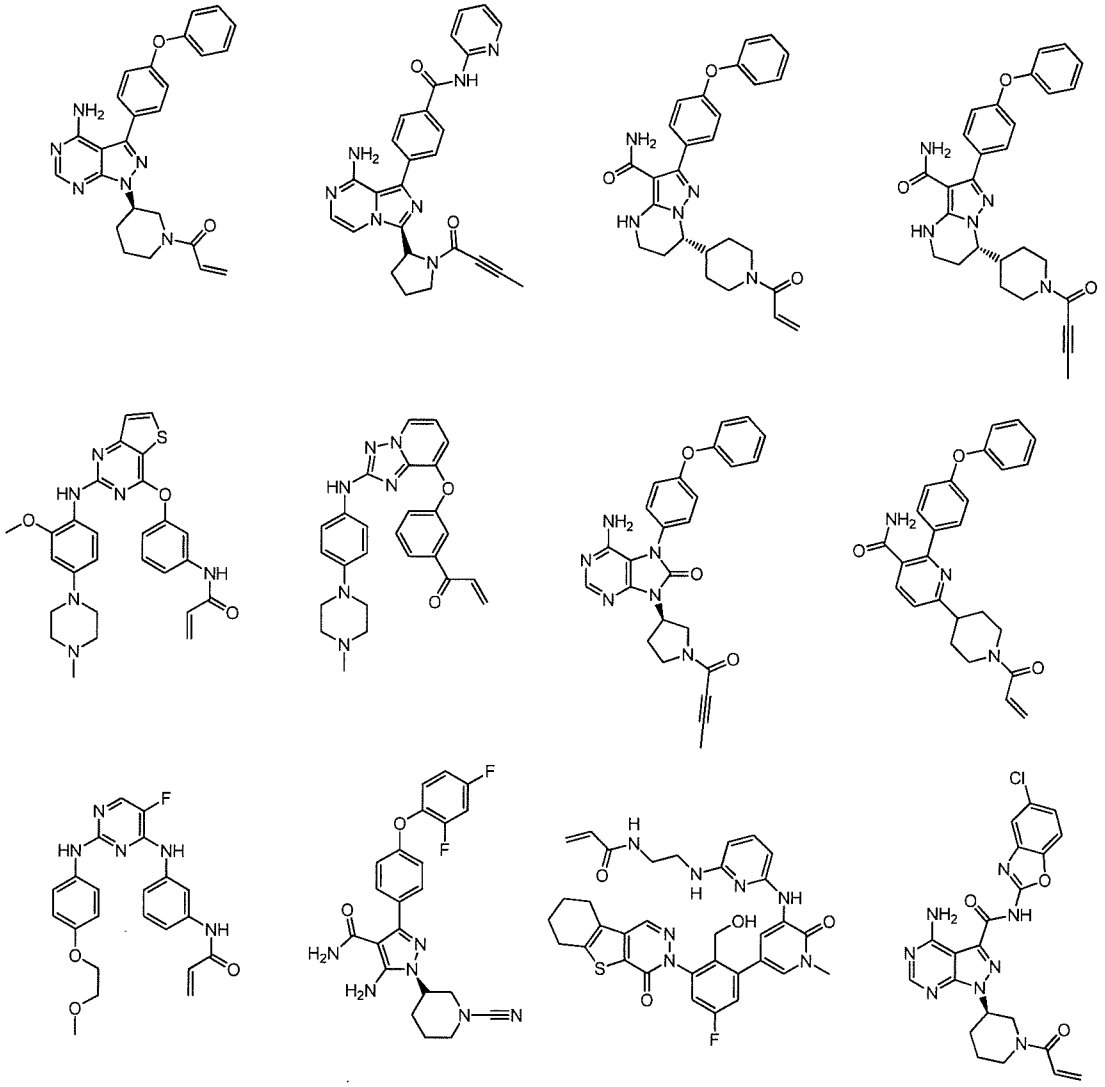
N-(3-((5-fluoro-2-((4-(2-methoxyethoxy)phenyl)amino)pyrimidin-4-yl)amino)phenyl)acrylamide,

(S)-5-amino-1-(1-cyanopiperidin-3-yl)-3-(4-(2,4-difluorophenoxy)phenyl)-1H-pyrazole-4-carboxamide,

6-(1-acryloylpiperidin-4-yl)-2-(4-phenoxyphenyl)nicotinamide, or

(R)-1-(1-acryloylpiperidin-3-yl)-4-amino-N-(5-chlorobenzo[d]oxazol-2-yl)-1H-pyrazolo[3,4-d]pyrimidine-3-carboxamide.

In another embodiment of the first, second, third, fourth, fifth, or sixth aspects and embodiments contained therein, the BTK inhibitor is chosen from:



Other terms used herein have the following meaning unless stated otherwise:

"Acute" as used herein means a disease with a rapid onset and/or a short course.

A "pharmaceutically acceptable salt" of a compound means a salt that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. Such salts include:

acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as formic acid, acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-

hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, glucoheptonic acid, 4,4'-methylenebis-(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like; or

salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, tromethamine, *N*-methylglucamine, and the like. It is understood that the pharmaceutically acceptable salts are non-toxic. Additional information on suitable pharmaceutically acceptable salts can be found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, PA, 1985, portions of which relate to suitable pharmaceutically acceptable salts are incorporated herein by reference. See also Berge at al., Pharmaceutical Salts, Journal of Pharmaceutical Sciences, 1, Volume 66, Number 1, January 1997.

Treatment decisions often follow formal or informal algorithmic guidelines. Treatment options can often be ranked or prioritized into lines of therapy: first-line therapy, second-line therapy, third-line therapy, and so on. First-line therapy is the first therapy that will be tried. Its priority over other options is usually either (1) formally recommended on the basis of clinical trial evidence for its best-available combination of efficacy, safety, and tolerability or (2) chosen based on the clinical experience of the physician. If a first-line therapy either fails to resolve the issue or produces intolerable side effects, additional (second-line) therapies may be substituted or added to the treatment regimen, followed by third-line therapies, and so on. Accordingly, "first-line" therapy as used herein means therapy usually given when someone is diagnosed with a particular disease or condition and can be categorized as standard of care.

"Maintenance therapy" as used herein means a therapy, therapeutic regimen, or course of therapy which is administered subsequent to an initial course of therapy administered to a patient with a disease. Maintenance therapy can be used to halt, slow down, or even reverse the progression of the disease, to maintain the improvement in health achieved by the initial treatment and/or enhance the gains achieved by the initial therapy.

"Flares" as used herein means an exacerbation of a chronic disease. Sometimes referred to as a flare-up, a flare occurs when symptoms of a disease that has been present for a time suddenly worsen.. For example, in many arthritis conditions the joints can flare with worsening of stiffness, pain, and swelling.

The compounds of the present disclosure may have stereocenter, i.e., assymetric centers, also referenced as chiral centers. Compounds of the present disclosure containing an asymmetrically substituted atom may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of materials. All chiral, diastereomeric, and racemic forms are within the scope of this disclosure, unless the specific stereochemistry or isomeric form is specifically indicated.

The compounds of the present disclosure can exist as tautomers and/or geometric isomers. All possible tautomers and *cis* and *trans* isomers, as individual forms and mixtures thereof are within the scope of this disclosure. Additionally, as used herein the term alkyl includes all the possible isomeric forms of said alkyl group albeit only a few examples are set forth. Furthermore, when the cyclic groups such as aryl, heteroaryl, heterocyclyl are substituted, they include all the positional isomers albeit only a few examples are set forth. Furthermore, all polymorphic forms and hydrates of a compound of Formula (I) (or any of the embodiments thereof described herein), are within the scope of this disclosure and claims appended hereto.

It will be understood by a person of ordinary skill in the art that when a compound is denoted as (R), it may contain the corresponding (S) stereoiomer as an impurity i.e., the (S) stereoisomer in less than about 1% by wt and vice versa. Accordingly, when thecompound herein is denotes as a mixture of (R) and (S) stereoisomers, it means that the amount of (R) or (S) enantiomer in the mixture is greater than about 1% by wt. Similar analysis applies with when a compound is denoted as the (E) isomer, (Z) isomer or a mixture of (E) and (Z) isomers. And herein, where the term 'about' is used with a numerical value, the numerical value may vary by ±10%." Therefore, "about 1" denotes a range from 0.9 to 1.1.

A "pharmaceutically acceptable carrier or excipient" means a carrier or an excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes a carrier or an excipient that is acceptable for veterinary use as well as human pharmaceutical use. And in the specification, including the documents incorporated herein by reference, and in the claims, unless the

context clearly dictates otherwise, the term "a" has its customary meaning of "one or more." Hence, "a pharmaceutically acceptable carrier/excipient,"as used in the specification and claims means one or more pharmaceutically acceptable carrier/excipient.

"Treating," "treat," or "treatment" of a disease includes:

(1) inhibiting the disease, i.e., arresting or reducing the development of the disease or its clinical symptoms; or

(2) relieving the disease, i.e., causing regression of the disease or its clinical symptoms. A "therapeutically effective amount" means the amount of a compound of the present disclosure that, when administered to a mammal, such as a human, for treating a disease, is sufficient to effect such treatment for the disease. The "therapeutically effective amount" will vary depending on the compound, the disease and its severity and the age, weight, etc., of the mammal to be treated.

"Mammal" as used herein means animals such as dogs, cats, and humans, preferably humans.

Formulations and Administration

In general, the compounds of this disclosure will be administered in a therapeutically effective amount by any of the accepted modes of administration, such as oral, for agents that serve similar utilities. Therapeutically effective amounts of compounds this disclosure may range from about 0.01 to about 500 mg per kg patient body weight per day, which can be administered in single or multiple doses. A suitable dosage level may be from about 0.1 to about 250 mg/kg per day, such as about 0.5 to about 100 mg/kg per day.

A suitable dosage level may also be about 0.01 to about 250 mg/kg per day, such as about 0.05 to about 100 mg/kg per day, and further such as about 0.1 to about 50 mg/kg per day. Within this range the dosage can be about 0.05 to about 0.5, such as about 0.5 to about 5, and further such as about 5 to about 50 mg/kg per day. For oral administration, the compositions can be provided in the form of tablets containing about 1 to about 1000 milligrams of the active ingredient, particularly about 1, 5, 10, 15, 20, 25, 50, 75, 100, 150, 200, 250, 300, 400, 500, 600, 750, 800, 900, and 1000 milligrams of the active ingredient. The actual amount to be administered of the compound of this disclosure, i.e., the active ingredient, will depend upon numerous factors such as the severity of the disease to be treated, the age and relative health of the patient, the potency of the compound being utilized, the route and form of administration, and other factors.

In general, compounds of this disclosure will be administered as pharmaceutical compositions by any one of the following routes: oral, systemic (e.g., transdermal, intranasal or by suppository), or parenteral (e.g., intramuscular, intravenous or subcutaneous) administration. The preferred manner of administration is oral using a convenient daily dosage regimen, which can be adjusted according to the degree of affliction. Compositions can take the form of tablets, pills, capsules, semisolids, powders, sustained release formulations, solutions, suspensions, elixirs, aerosols, or any other appropriate compositions.

The choice of formulation depends on various factors such as the mode of drug administration (e.g., for oral administration, formulations in the form of tablets, pills or capsules, including enteric coated or delayed release tablets, pills or capsules are preferred) and the bioavailability of the drug substance. Recently, pharmaceutical formulations have been developed especially for drugs that show poor bioavailability based upon the principle that bioavailability can be increased by increasing the surface area i.e., decreasing particle size. For example, U.S. Pat. No. 4,107,288 describes a pharmaceutical formulation having particles in the size range from 10 to 1,000 nm in which the active material is supported on a cross-linked matrix of macromolecules. U.S. Pat. No. 5,145,684 describes the production of a pharmaceutical formulation in which the drug substance is pulverized to nanoparticles (average particle size of 400 nm) in the presence of a surface modifier and then dispersed in a liquid medium to give a pharmaceutical formulation that exhibits remarkably high bioavailability. The disclosures of those two patents are incorporated by reference with respect to those portions relating to pharmaceutical formulations.

The compositions comprise, in general, a compound of this disclosure) in combination with a pharmaceutically acceptable excipient. Pharmaceutically acceptable excipients are non-toxic, aid administration, and do not adversely affect the therapeutic benefit of the compound of this disclosure. Such excipient may be any solid, liquid, semi-solid or, in the case of an aerosol composition, gaseous excipient that is generally available to one of skill in the art.

Solid pharmaceutical excipients include starch, cellulose, talc, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, magnesium stearate, sodium stearate, glycerol monostearate, sodium chloride, dried skim milk and the like. Liquid and semisolid excipients may be selected from glycerol, propylene glycol, water, ethanol and various oils, including those of petroleum, animal, vegetable or synthetic origin, e.g., peanut oil, soybean

oil, mineral oil, sesame oil, etc. Preferred liquid carriers, particularly for injectable solutions, include water, saline, aqueous dextrose, and glycols.

Compressed gases may be used to disperse a compound of this disclosure in aerosol form. Inert gases suitable for this purpose are nitrogen, carbon dioxide, etc.

Other suitable pharmaceutical excipients and their formulations are described in Remington's Pharmaceutical Sciences, edited by E. W. Martin (Mack Publishing Company, 20th ed., 2000), incorporated by reference herein with respect to the portions relating to pharmaceutical excipients and their formulations.

The level of the compound in a formulation can vary within the full range employed by those skilled in the art. Typically, the formulation will contain, on a weight percent (wt. %) basis, from about 0.01-99.99 wt. % of a compound of this disclosure based on the total formulation, with the balance being a suitable pharmaceutical excipients. For example, the compound is present at a level of about 1-80 wt. %. With respect to the numerical range 0.01-99.99 "about" denotes less than 0.01%. With respect to the numerical range 1 to 80, "about" denotes 0.05 with respect to 1 and 10 with respect to 80, thus covering a range from 0.05 to 90 wt. %.

The compounds of this disclosure may be used in combination with one or more other drugs in the treatment of diseases or conditions for which compounds of this disclosure or the other drugs may have utility. Such other drug(s) may be administered, by a route and in an amount commonly used therefore, contemporaneously, such as fixed dose combination, or sequentially with a compound of the present disclosure. When a compound of this disclosure is used contemporaneously with one or more other drugs, a pharmaceutical composition in unit dosage form containing such other drugs and the compound of the present disclosure, i.e., a fixed dose compound, is preferred. However, the combination therapy may also include therapies in which the compound of this disclosure and one or more other drugs are administered on different overlapping schedules or even non-overlapping schedules. It is also contemplated that situations will arise that when used in combination with one or more other active ingredients, the compounds of the present disclosure and the other active ingredients may be used in lower doses than when each is used singly.

Dog Pemphigus Foliaceus Study

A 30 kg Doberman dog with a characteristic first presentation of pemphigus folliaceus on the nose and paws was administered an oral dose of 500 mg daily of the BTK inhibitor

(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 instead of the usual treatment for pemphigus of high dose corticosteroids (typically 1-2 mg/kg). This dose resulted in a level of BTK occupancy 24 hours after each dose of approximately 70% as confirmed by blood taken 24 hours after the first dose.

The dog responded clinically to the drug as a monotherapy within three days, with improved eating and ambulation noted by the owner. At the one week follow up visit both owner and observing veterinarian reported improved general health and commencement of pemphigus lesion healing. The observing veterinarian commented that the improvement was "just like with corticosteroids" and recommended that corticosteroid therapy did not need to be commenced. No well-known corticosteroid-like adverse effects in canines, such as polyuria, polydipsia, polyphagia or weight gain, were noted.

After two weeks of treatment, the general health of the dog was excellent and skin lesions continued to improve. By four weeks, skin lesions had completely healed (see Figures 1 and 2).

The surprising conclusion of this experiment is that adequate doses of a BTK inhibitor are effective and safe as the acute treatment for pemphigus folliaceus in a dog, replacing the need for corticosteroid therapy.

As shown in Table 3, dog PF and human PV share many similar characteristics that make generalization of treatment effects for human disease from observations of the dog disease credible.

Table 3

Comparison of dog pemphigus foliaceus (PF) and human pemphigus vulgaris (PV)

Naturally occurring autoimmune blistering disease	Dog PF	Human PV
Autoantigens to epidermal proteins	√	√
Never resolves spontaneously	√	√
Mainstay of treatment high dose corticosteroids	√	√
Early disease response to corticosteroids 1-2 weeks	√	√
Full disease control with corticosteroids takes 4-12 weeks	√	√
Relapses without maintenance treatment	√	√
High mortality in first year, partly presumed due to high dose	√	√

corticosteroids		

In addition, the ability of (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 to rapidly control dog PF suggests that adequate doses of a BTK inhibitor can replace corticosteroids not just in human PV but in other diseases where corticosteroids are used acutely.

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 (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.

2. The use according to claim 1, wherein said mammal is a human.

3. The use according to claim 1, wherein said mammal is an animal.

4. The use according to claim 1, wherein said mammal is a canine.

5. The use according to claim 1, wherein said BTK inhibitor is to be used in place of a corticosteriod therapy.

6. The use according to claim 1, wherein said BTK inhibitor is to be used in combination with a corticosteriod therapy.

7. The use according to claim 1, wherein said BTK inhibitor is to be administered in combination with a noncorticosteroidal immunosuppressive and/or anti-inflammatory agent.

8. The use according to claim 7, 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.

9. The use according to claim 7, wherein said noncorticosteroidal immunosuppressive and/or anti-inflammatory agent is chosen from rituximab, tositumomab, veltuzumab, obinutuzumab, Enbrel, and ofatumumab, or a biosimilar version thereof.

10. 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 (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.

11. The use according to claim 10, wherein said mammal is a human.

12. The use according to claim 10, wherein said mammal is an animal.

13. The use according to claim 10, wherien said mammal is a canine.

14. The use according to claim 10, wherein said BTK inhibitor is to be used in place of a corticosteriod therapy.

15. The use according to claim 10, wherein said BTK inhibitor is to be used in combination with a corticosteriod therapy.

16. The use according to claim 10, wherein said BTK inhibitor is to be administered in combination with a noncorticosteroidal immunosuppressive and/or anti-inflammatory agent.

17. The use according to claim 16, 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.

18. The use according to claim 16, wherein said noncorticosteroidal immunosuppressive and/or anti-inflammatory agent is chosen from rituximab, tositumomab, veltuzumab, obinutuzumab, Enbrel, and ofatumumab, or a biosimilar version thereof.

19. 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 (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.

20. The use according to claim 19, wherein said mammal is a human.

21. The use according to claim 19, wherein said mammal is an animal.

22. The use according to claim 19, wherein said mammal is a canine.

23. The use according to claim 19, wherein said BTK inhibitor is to be used in place of a corticosteriod therapy.

24. The use according to claim 19, wherein said BTK inhibitor is to be used in combination with a corticosteriod therapy.

25. The use according to claim 19, wherein said BTK inhibitor is to be administered in combination with a noncorticosteroidal immunosuppressive and/or anti-inflammatory agent.

26. The use according to claim 25, 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.

27. The use according to claim 25, wherein said noncorticosteroidal immunosuppressive and/or anti-inflammatory agent is chosen from rituximab, tositumomab, veltuzumab, obinutuzumab, Enbrel, and ofatumumab, or a biosimilar version thereof.