# USE OF JAK INHIBITORS 3-[4-(7H-PYRROLO[2,3-D]PYRIMIDIN-4-YL)-1H-PYRAZOL-1-YL]OCTANE- OR HEPTANE-NITRILE

This application claims the benefit of priority of U.S. Prov. Appl. No. 61/180,582, filed May 22, 2009 and is a divisional of Singaporean Patent Application No. 201108457-1, both of which are incorporated herein by reference in their entirety.

## FIELD OF THE INVENTION

The present invention relates to the Janus kinase (JAK) inhibitors 3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile or 3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile, as well as its uses for the preparation of medicaments for use in the treatment of JAK-associated diseases including, for example, inflammatory and autoimmune disorders, skin disorders, cancer, and other diseases.

## BACKGROUND OF THE INVENTION

Protein kinases (PKs) regulate diverse biological processes including cell growth, survival, differentiation, organ formation, morphogenesis, neovascularization, tissue repair, and regeneration, among others. Protein kinases also play specialized roles in a host of human diseases including cancer. Cytokines, low-molecular weight polypeptides or glycoproteins, regulate many pathways involved in the host inflammatory response to sepsis. Cytokines influence cell differentiation, proliferation and activation, and can modulate both pro-inflammatory and anti-inflammatory responses to allow the host to react appropriately to pathogens. Signaling of a wide range of cytokines involves the Janus kinase family (JAKs) of protein tyrosine kinases and Signal Transducers and Activators of Transcription (STATs). There are four known mammalian JAKs: JAK1 (Janus kinase-1), JAK2, JAK3 (also known as Janus kinase, leukocyte; JAKL; and L-JAK), and TYK2 (protein-tyrosine kinase 2).

Cytokine-stimulated immune and inflammatory responses contribute to pathogenesis of diseases: pathologies such as severe combined immunodeficiency (SCID) arise from suppression of the immune system, while a hyperactive or inappropriate immune/inflammatory response contributes to the pathology of autoimmune diseases (*e.g.*, asthma, systemic lupus

erythematosus, thyroiditis, myocarditis), and illnesses such as scleroderma and osteoarthritis (Ortmann, R. A., T. Cheng, *et al*. (2000) *Arthritis Res* 2(1): 16-32).

Deficiencies in expression of JAKs are associated with many disease states. For example, Jak1-/- mice are runted at birth, fail to nurse, and die perinatally (Rodig, S. J., M. A. Meraz, *et al.* (1998) *Cell* 93(3): 373-83). Jak2-/- mouse embryos are anemic and die around day 12.5 postcoitum due to the absence of definitive erythropoiesis.

The JAK/STAT pathway, and in particular all four JAKs, are believed to play a role in the pathogenesis of asthmatic response, chronic obstructive pulmonary disease, bronchitis, and other related inflammatory diseases of the lower respiratory tract. Multiple cytokines that signal through JAKs have been linked to inflammatory diseases/conditions of the upper respiratory tract, such as those affecting the nose and sinuses (*e.g.*, rhinitis and sinusitis) whether classically allergic reactions or not. The JAK/STAT pathway has also been implicated in inflammatory diseases/conditions of the eye and chronic allergic responses.

Activation of JAK/STAT in cancers may occur by cytokine stimulation (*e.g.* IL-6 or GM-CSF) or by a reduction in the endogenous suppressors of JAK signaling such as SOCS (suppressor or cytokine signaling) or PIAS (protein inhibitor of activated STAT) (Boudny, V., and Kovarik, J., *Neoplasm*. 49:349-355, 2002). Activation of STAT signaling, as well as other pathways downstream of JAKs (*e.g.*, Akt), has been correlated with poor prognosis in many cancer types (Bowman, T., *et al. Oncogene* 19:2474-2488, 2000). Elevated levels of circulating cytokines that signal through JAK/STAT play a causal role in cachexia and/or chronic fatigue. As such, JAK inhibition may be beneficial to cancer patients for reasons that extend beyond potential anti-tumor activity.

JAK2 tyrosine kinase can be beneficial for patients with myeloproliferative disorders, *e.g.*, polycythemia vera (PV), essential thrombocythemia (ET), myeloid metaplasia with myelofibrosis (MMM) (Levin, *et al.*, *Cancer Cell*, vol. 7, 2005: 387-397). Inhibition of the JAK2V617F kinase decreases proliferation of hematopoietic cells, suggesting JAK2 as a potential target for pharmacologic inhibition in patients with PV, ET, and MMM.

Inhibition of the JAKs may benefit patients suffering from skin immune disorders such as psoriasis, and skin sensitization. The maintenance of psoriasis is believed to depend on a number of inflammatory cytokines in addition to various chemokines and growth factors (JCI, 113:1664-1675), many of which signal through JAKs (*Adv Pharmacol.* 2000;47:113-74).

Accordingly, inhibitors of Janus kinases or related kinases are widely sought. For example, certain JAK inhibitors, including pyrrolopyridine and pyrrolopyrimidines, are reported in U.S. Ser. No. 11/637,545, filed December 12, 2006.

Thus, new or improved agents which inhibit kinases such as JAKs are continually needed for developing new and more effective pharmaceuticals that are aimed at augmentation or suppression of the immune and inflammatory pathways (such as immunosuppressive agents for organ transplants), as well as agents for the prevention and treatment of autoimmune diseases, diseases involving a hyperactive inflammatory response (*e.g.*, eczema), allergies, cancer (*e.g.*, prostate, leukemia, multiple myeloma), and some immune reactions (*e.g.*, skin rash or contact dermatitis or diarrhea) caused by other therapeutics. The compounds, as well as their compositions and uses described herein are directed toward these needs and other ends.

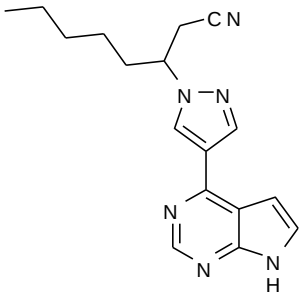
## SUMMARY OF THE INVENTION

The present invention provides, *inter alia* , the use of a compound selected from 3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile and 3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile, or a pharmaceutically acceptable salt thereof, for preparation of a medicament for use in treatment of a disease in a patient, wherein said disease is associated with JAK activity.

Methods of treating autoimmune diseases, cancers, myeloproliferative disorders, inflammatory diseases, viral diseases, and skin disorders in a patient by topically administering a therapeutically effective amount of 3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile or 3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile, or pharmaceutically acceptable salt thereof.

## DETAILED DESCRIPTION

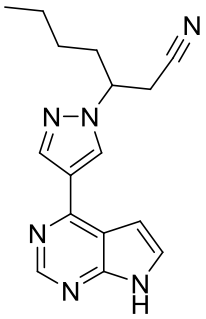
The present invention is in relation to the JAK inhibitor 3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile (Formula I):



I

or a pharmaceutically acceptable salt thereof and

the JAK inhibitor 3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile (Formula II):



**II**

or a pharmaceutically acceptable salt thereof.

The compounds described herein can be asymmetric (*e.g.*, having one or more stereocenters). Both R/S enantiomers are intended unless otherwise indicated. The compounds discussed in relation to the invention can be isolated in optically active or racemic forms. Methods on how to prepare optically active forms from optically inactive starting materials are known in the art, such as by resolution of racemic mixtures or by stereoselective synthesis. In some embodiments, the compound of Formula I or II is the R enantiomer, optionally substantially isolated from the S enantiomer. In some embodiments, the compound of Formula I or II is the S enantiomer, optionally substantially isolated from the R enantiomer.

Resolution of racemic mixtures of compounds can be carried out by any of numerous methods known in the art. An example method includes fractional recrystallization using a chiral resolving acid which is an optically active, salt-forming organic acid. Suitable resolving agents for fractional recrystallization methods are, for example, optically active acids, such as the D and L forms of tartaric acid, diacetyltartaric acid, dibenzoyltartaric acid, mandelic acid, malic acid, lactic acid or the various optically active camphorsulfonic acids such as β-camphorsulfonic acid.

Resolution of racemic mixtures can also be carried out by elution on a column packed with an optically active resolving agent (*e.g.*, dinitrobenzoylphenylglycine). Suitable elution solvent composition can be determined by one skilled in the art.

The term, "compound," as used herein is meant to include, unless otherwise specified, all stereoisomers and isotopes of the structures depicted.

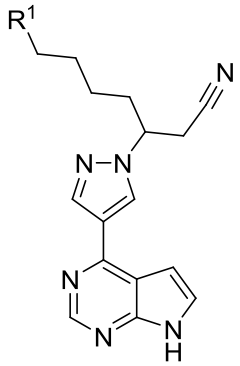
All compounds, and pharmaceutically acceptable salts thereof, can be found together with other substances such as water and solvents (e.g. hydrates and solvates) or can be isolated.

In some embodiments, the compounds or a salt thereof, is substantially isolated. By "substantially isolated" is meant that the compound is at least partially or substantially separated from the environment in which it was formed or detected. Partial separation can include, for example, a composition enriched in a compound. Substantial separation can include compositions containing at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 97%, or at least about 99% by weight of a compound or salt thereof. Methods for isolating compounds and their salts are routine in the art.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

The expressions, "ambient temperature" and "room temperature," as used herein, are understood in the art, and refer generally to a temperature, *e.g.* a reaction temperature, that is about the temperature of the room in which the reaction is carried out, for example, a temperature from about 20 ºC to about 30 ºC.

The compounds can be prepared according to the synthetic procedures described below in the Example section. In another aspect, the present invention provides a process for preparing a phosphoric acid salt of a compound of Formula III:



**III**

wherein $R^1$ is H or methyl, comprising combining a compound of Formula III with phosphoric acid. In some embodiments, the combining is performed in the presence of an organic solvent (such as an alcohol) at a temperature of greater than about 20 °C (e.g., greater than about 40 °C, greater than about 60 °C, greater than about 80 °C, or greater than about 100 °C). In some embodiments, the combining can be performed at about 60 °C. In some embodiments, the alcohol can be methanol, ethanol, isopropanol, or butanol. In some embodiments, the alcohol is isopropanol.

In some embodiments, the process for preparing 3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile phosphoric acid salt includes combining 3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile with phosphoric acid, optionally in the presence of an organic solvent (such as an alcohol) at a temperature of greater than about 20 °C (e.g., greater than about 40 °C, greater than about 60 °C, greater than about 80 °C, or greater than about 100 °C). In some embodiments, the combining can be performed at about 60 °C. In some embodiments, the alcohol can be methanol, ethanol, isopropanol, or butanol.

In some embodiments, the process for preparing 3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile phosphoric acid salt includes combining 3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile with phosphoric acid, optionally in the presence of an organic solvent (such as an alcohol) at a temperature of greater than about 20 °C (e.g., greater than about 40 °C, greater than about 60 °C, greater than about 80 °C, or greater than about 100 °C). In some embodiments, the combining can be performed at about 60 °C. In some embodiments, the alcohol can be methanol, ethanol, isopropanol, or butanol.

As used herein, "pharmaceutically acceptable salts" refers to derivatives of the disclosed compounds wherein the parent compound is modified by converting an existing acid or base

moiety to its salt form. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. The pharmaceutically acceptable salts can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, non-aqueous media like ether, ethyl acetate, alcohols (e.g., methanol, ethanol, iso-propanol, or butanol) or acetonitrile (ACN) are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, Pa., 1985, p. 1418 and *Journal of Pharmaceutical Science*, 66, 2 (1977), each of which is incorporated herein by reference in its entirety.

*Methods*

The compounds can modulate activity of one or more Janus kinases (JAKs). The term "modulate" is meant to refer to an ability to increase or decrease the activity of one or more members of the JAK family of kinases. Accordingly, the compounds can be used in methods of modulating a JAK by contacting the JAK with any one or more of the compounds or compositions described herein. In some embodiments, compounds can act as inhibitors of one or more JAKs. In further embodiments, the compounds can be used to modulate activity of a JAK in an individual in need of modulation of the receptor by administering a modulating amount of a compound, or a pharmaceutically acceptable salt thereof.

Methods of treating a JAK-associated disease or disorder in an individual (*e.g.*, patient) can be achieved by administering to the individual in need of such treatment a therapeutically effective amount or dose of the compound or a pharmaceutical composition thereof. A JAK-associated disease can include any disease, disorder or condition that is directly or indirectly linked to expression or activity of the JAK, including overexpression and/or abnormal activity levels. A JAK-associated disease can also include any disease, disorder or condition that can be prevented, ameliorated, or cured by modulating JAK activity.

Examples of JAK-associated diseases include diseases involving the immune system including, for example, organ transplant rejection (*e.g.*, allograft rejection and graft versus host disease).

Further examples of JAK-associated diseases include autoimmune diseases such as multiple sclerosis, rheumatoid arthritis, juvenile arthritis, psoriatic arthritis, type I diabetes, lupus, psoriasis, inflammatory bowel disease, ulcerative colitis, Crohn's disease, myasthenia gravis, immunoglobulin nephropathies, autoimmune thyroid disorders, and the like. In some embodiments, the autoimmune disease is an autoimmune bullous skin disorder such as pemphigus vulgaris (PV) or bullous pemphigoid (BP).

Further examples of JAK-associated diseases include allergic conditions such as asthma, food allergies, atopic dermatitis and rhinitis. Further examples of JAK-associated diseases include viral diseases such as Epstein Barr Virus (EBV), Hepatitis B, Hepatitis C, HIV, HTLV 1, Varicella-Zoster Virus (VZV) and Human Papilloma Virus (HPV).

Further examples of JAK-associated diseases or conditions include skin disorders such as psoriasis (for example, psoriasis vulgaris), atopic dermatitis, skin rash, skin irritation, skin sensitization (*e.g.*, contact dermatitis or allergic contact dermatitis). For example, certain substances including some pharmaceuticals when topically applied can cause skin sensitization. In some embodiments, co-administration or sequential administration of at least one JAK inhibitor together with the agent causing unwanted sensitization can be helpful in treating such unwanted sensitization or dermatitis. In some embodiments, the skin disorder is treated by topical administration of at least one JAK inhibitor.

In further embodiments, the JAK-associated disease is cancer including those characterized by solid tumors (*e.g.*, prostate cancer, renal cancer, hepatic cancer, pancreatic cancer, gastric cancer, breast cancer, lung cancer, cancers of the head and neck, thyroid cancer, glioblastoma, Kaposi's sarcoma, Castleman's disease, melanoma etc.), hematological cancers (*e.g.*, lymphoma, leukemia such as acute lymphoblastic leukemia, acute myelogenous leukemia (AML) or multiple myeloma), and skin cancer such as cutaneous T-cell lymphoma (CTCL) and cutaneous B-cell lymphoma. Example CTCLs include Sezary syndrome and mycosis fungoides.

In some embodiments, the JAK inhibitors described herein, as well as other JAK inhibitors, such as those reported in U.S. Ser. No. 11/637,545, can be used to treat inflammation-associated cancers. In some embodiments, the cancer is associated with inflammatory bowel

disease. In some embodiments, the inflammatory bowel disease is ulcerative colitis. In some embodiments, the inflammatory bowel disease is Crohn's disease. In some embodiments, the inflammation-associated cancer is colitis-associated cancer. In some embodiments, the inflammation-associated cancer is colon cancer or colorectal cancer. In some embodiments, the cancer is gastric cancer, gastrointestinal carcinoid tumor, gastrointestinal stromal tumor (GIST), adenocarcinoma, small intestine cancer, or rectal cancer.

JAK-associated diseases can further include those characterized by expression of a mutant JAK2 such as those having at least one mutation in the pseudo-kinase domain (*e.g.*, JAK2V617F).

JAK-associated diseases can further include myeloproliferative disorders (MPDs) such as polycythemia vera (PV), essential thrombocythemia (ET), myelofibrosis with myeloid metaplasia (MMM), primary myelofibrosis (PMF), chronic myelogenous leukemia (CML), chronic myelomonocytic leukemia (CMML), hypereosinophilic syndrome (HES), systemic mast cell disease (SMCD), and the like. In some embodiments, the myeloproliferative disorder is primary myelofibrosis (PMF) or post polycythemia vera/essential thrombocythemia myelofibrosis (Post-PV/ET MF).

Methods of treating psoriasis or other skin disorders can be achieved by administration of a topical formulation containing the described compounds.

Method of treating dermatological side effects of other pharmaceuticals can be achieved by administration of the described compounds. For example, numerous pharmaceutical agents result in unwanted allergic reactions which can manifest as acneiform rash or related dermatitis. Example pharmaceutical agents that have such undesirable side effects include anti-cancer drugs such as gefitinib, cetuximab, erlotinib, and the like. The compounds can be administered systemically or topically (e.g., localized to the vicinity of the dermatitis) in combination with (e.g., simultaneously or sequentially) the pharmaceutical agent having the undesirable dermatological side effect. In some embodiments, a compound can be administered topically together with one or more other pharmaceuticals, where the other pharmaceuticals when topically applied in the absence of a compound of the invention cause contact dermatitis, allergic contact sensitization, or similar skin disorder. Accordingly, compositions include topical formulations containing the described compounds and a further pharmaceutical agent which can cause dermatitis, skin disorders, or related side effects.

Further JAK-associated diseases include inflammation and inflammatory diseases. Example inflammatory diseases include inflammatory diseases of the eye (*e.g.*, iritis, uveitis, scleritis, conjunctivitis, or related disease), inflammatory diseases of the respiratory tract (*e.g.*, the upper respiratory tract including the nose and sinuses such as rhinitis or sinusitis or the lower respiratory tract including bronchitis, chronic obstructive pulmonary disease, and the like), inflammatory myopathy such as myocarditis, and other inflammatory diseases.

The JAK inhibitors described herein can further be used to treat ischemia reperfusion injuries or a disease or condition related to an inflammatory ischemic event such as stroke or cardiac arrest. The JAK inhibitors described herein can further be used to treat anorexia, cachexia, or fatigue such as that resulting from or associated with cancer. The JAK inhibitors described herein can further be used to treat restenosis, sclerodermitis, or fibrosis. The JAK inhibitors described herein can further be used to treat conditions associated with hypoxia or astrogliosis such as, for example, diabetic retinopathy, cancer, or neurodegeneration. See, e.g., Dudley, A.C. *et al. Biochem. J.* 2005, 390(Pt 2):427-36 and Sriram, K. *et al. J. Biol. Chem.* 2004, 279(19):19936-47. Epub 2004 Mar 2. The JAK inhibitors described herein can be used to treat Alzheimer's disease.

The JAK inhibitors described herein can further be used to treat other inflammatory diseases such as systemic inflammatory response syndrome (SIRS) and septic shock.

The JAK inhibitors described herein can further be used to treat gout and increased prostate size due to, e.g., benign prostatic hypertrophy or benign prostatic hyperplasia.

In some embodiments, JAK inhibitors described herein can further be used to treat a dry eye disorder. As used herein, "dry eye disorder" is intended to encompass the disease states summarized in a recent official report of the Dry Eye Workshop (DEWS), which defined dry eye as "a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface." Lemp, "The Definition and Classification of Dry Eye Disease: Report of the Definition and Classification Subcommittee of the International Dry Eye Workshop", *The Ocular Surface*, 5(2), 75-92 April 2007. In some embodiments, the dry eye disorder is selected from aqueous tear-deficient dry eye (ADDE) or evaporative dry eye disorder, or appropriate combinations thereof.

A method of treating conjunctivitis, uveitis (including chronic uveitis), chorioditis, retinitis, cyclitis, sclieritis, episcleritis, or iritis; treating inflammation or pain related to corneal transplant, LASIK (laser assisted in situ keratomileusis), photorefractive keratectomy, or LASEK (laser assisted sub-epithelial keratomileusis); inhibiting loss of visual acuity related to corneal transplant, LASIK, photorefractive keratectomy, or LASEK; or inhibiting transplant rejection in a patient in need thereof, can comprise administering to the patient a therapeutically effective amount of the described compound/s, or a pharmaceutically acceptable salt thereof.

Additionally, the described compound/s, as well as other JAK inhibitors such as those reported in U.S. Ser. No. 11/637,545, can be used to treat respiratory dysfunction or failure associated with viral infection, such as influenza and SARS.

As used herein, the term "contacting" refers to the bringing together of indicated moieties in an *in vitro* system or an *in vivo* system. For example, "contacting" a JAK with the described compound/s includes the administration of the compound to an individual or patient, such as a human, having a JAK, as well as, for example, introducing the compound into a sample containing a cellular or purified preparation containing the JAK.

As used herein, the term "individual" or "patient," used interchangeably, refers to any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates, and most preferably humans.

As used herein, the phrase "therapeutically effective amount" refers to the amount of active compound or pharmaceutical agent that elicits the biological or medicinal response that is being sought in a tissue, system, animal, individual or human by a researcher, veterinarian, medical doctor or other clinician.

As used herein, the term "treating" or "treatment" refers to one or more of (1) preventing the disease; for example, preventing a disease, condition or disorder in an individual who may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease; (2) inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., arresting further development of the pathology and/or symptomatology); and (3) ameliorating the disease; for example, ameliorating a disease, condition or disorder in an individual who is experiencing or displaying the pathology or

symptomatology of the disease, condition or disorder (i.e., reversing the pathology and/or symptomatology) such as decreasing the severity of disease.

*Combination Therapies*

One or more additional pharmaceutical agents such as, for example, chemotherapeutics, anti-inflammatory agents, steroids, immunosuppressants, as well as Bcr-Abl, Flt-3, RAF and FAK kinase inhibitors such as, for example, those described in WO 2006/056399, or other agents can be used in combination with the described compound/s for treatment of JAK-associated diseases, disorders or conditions. The one or more additional pharmaceutical agents can be administered to a patient simultaneously or sequentially.

Example chemotherapeutic include proteosome inhibitors (*e.g.*, bortezomib), thalidomide, revlimid, and DNA-damaging agents such as melphalan, doxorubicin, cyclophosphamide, vincristine, etoposide, carmustine, and the like.

Example steroids include coriticosteroids such as dexamethasone or prednisone.

Example Bcr-Abl inhibitors include the compounds, and pharmaceutically acceptable salts thereof, of the genera and species disclosed in U.S. Pat. No. 5,521,184, WO 04/005281, EP2005/009967, EP2005/010408, and U.S. Ser. No. 60/578,491.

Example suitable Flt-3 inhibitors include compounds, and their pharmaceutically acceptable salts, as disclosed in WO 03/037347, WO 03/099771, and WO 04/046120.

Example suitable RAF inhibitors include compounds, and their pharmaceutically acceptable salts, as disclosed in WO 00/09495 and WO 05/028444.

Example suitable FAK inhibitors include compounds, and their pharmaceutically acceptable salts, as disclosed in WO 04/080980, WO 04/056786, WO 03/024967, WO 01/064655, WO 00/053595, and WO 01/014402.

In some embodiments, the described compound/s can be used in combination with one or more other kinase inhibitors including imatinib, particularly for treating patients resistant to imatinib or other kinase inhibitors.

In some embodiments, the described compound/s can be used in combination with a chemotherapeutic in the treatment of cancer, such as multiple myeloma, and may improve the treatment response as compared to the response to the chemotherapeutic agent alone, without exacerbation of its toxic effects. Examples of additional pharmaceutical agents used in the

treatment of multiple myeloma, for example, can include, without limitation, melphalan, melphalan plus prednisone [MP], doxorubicin, dexamethasone, and Velcade (bortezomib). Further additional agents used in the treatment of multiple myeloma include Bcr-Abl, Flt-3, RAF and FAK kinase inhibitors. Additive or synergistic effects are desirable outcomes of combining a JAK inhibitor with an additional agent. Furthermore, resistance of multiple myeloma cells to agents such as dexamethasone may be reversible upon treatment with the JAK inhibitor. The agents can be combined with the present compound in a single or continuous dosage form, or the agents can be administered simultaneously or sequentially as separate dosage forms.

In some embodiments, a corticosteroid such as dexamethasone is administered to a patient in combination with the described compound/s where the dexamethasone is administered intermittently as opposed to continuously.

In some further embodiments, combinations of the described compound/s with other therapeutic agents can be administered to a patient prior to, during, and/or after a bone marrow transplant or stem cell transplant.

*Pharmaceutical Formulations and Dosage Forms*

When employed as pharmaceuticals, the described compounds can be administered in the form of pharmaceutical compositions. These compositions can be prepared in a manner well known in the pharmaceutical art, and can be administered by a variety of routes, depending upon whether local or systemic treatment is desired and upon the area to be treated. Administration may be topical (including transdermal, epidermal, ophthalmic and to mucous membranes including intranasal, vaginal and rectal delivery), pulmonary (*e.g.*, by inhalation or insufflation of powders or aerosols, including by nebulizer; intratracheal or intranasal), oral or parenteral. Parenteral administration includes intravenous, intraarterial, subcutaneous, intraperitoneal intramuscular or injection or infusion; or intracranial, *e.g.*, intrathecal or intraventricular, administration. Parenteral administration can be in the form of a single bolus dose, or may be, for example, by a continuous perfusion pump. Pharmaceutical compositions and formulations for topical administration may include transdermal patches, ointments, lotions, creams, gels, drops, suppositories, sprays, liquids and powders. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like may be necessary or desirable. Coated condoms, gloves and the like may also be useful.

Pharmaceutical compositions may contain, as the active ingredient, the described compound/s or a pharmaceutically acceptable salt thereof, in combination with one or more pharmaceutically acceptable carriers (excipients). In some embodiments, the composition is suitable for topical administration. In making the compositions, the active ingredient is typically mixed with an excipient, diluted by an excipient or enclosed within such a carrier in the form of, for example, a capsule, sachet, paper, or other container. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders.

In preparing a formulation, the active compound can be milled to provide the appropriate particle size prior to combining with the other ingredients. If the active compound is substantially insoluble, it can be milled to a particle size of less than 200 mesh. If the active compound is substantially water soluble, the particle size can be adjusted by milling to provide a substantially uniform distribution in the formulation, *e.g.* about 40 mesh.

The described compound/s may be milled using known milling procedures such as wet milling to obtain a particle size appropriate for tablet formation and for other formulation types. Finely divided (nanoparticulate) preparations of the compound can be prepared by processes known in the art, e.g., see International App. No. WO 2002/000196.

Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water, syrup, and methyl cellulose. The formulations can additionally include: lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl- and propylhydroxy-benzoates; sweetening agents; and flavoring agents. The compositions can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures known in the art.

The compositions can be formulated in a unit dosage form, each dosage containing from about 5 to about 1000 mg (1 g), more usually about 100 to about 500 mg, of the active

ingredient. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient.

The active compound can be effective over a wide dosage range and is generally administered in a pharmaceutically effective amount. It will be understood, however, that the amount of the compound actually administered will usually be determined by a physician, according to the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical excipient to form a solid preformulation composition containing a homogeneous mixture of the described compound/s. When referring to these preformulation compositions as homogeneous, the active ingredient is typically dispersed evenly throughout the composition so that the composition can be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation is then subdivided into unit dosage forms of the type described above containing from, for example, about 0.1 to about 1000 mg of the active ingredient.

The tablets or pills can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permit the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol, and cellulose acetate.

The liquid forms in which the compound and compositions can be incorporated for administration orally or by injection include aqueous solutions, suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil, or peanut oil, as well as elixirs and similar pharmaceutical vehicles.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described *supra*. In some embodiments, the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in can be nebulized by use of inert gases. Nebulized solutions may be breathed directly from the nebulizing device or the nebulizing device can be attached to a face masks tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder compositions can be administered orally or nasally from devices which deliver the formulation in an appropriate manner.

Topical formulations can contain one or more conventional carriers. In some embodiments, ointments can contain water and one or more hydrophobic carriers selected from, for example, liquid paraffin, polyoxyethylene alkyl ether, propylene glycol, white Vaseline, and the like. Carrier compositions of creams can be based on water in combination with glycerol and one or more other components, e.g. glycerinemonostearate, PEG-glycerinemonostearate and cetylstearyl alcohol. Gels can be formulated using isopropyl alcohol and water, suitably in combination with other components such as, for example, glycerol, hydroxyethyl cellulose, and the like. In some embodiments, topical formulations contain at least about 0.1, at least about 0.25, at least about 0.5, at least about 1, at least about 2, or at least about 5 wt % of the described compound. The topical formulations can be suitably packaged in tubes of, for example, 100 g which are optionally associated with instructions for the treatment of the select indication, e.g., psoriasis or other skin condition.

A pharmaceutical formulation for topical skin application, may comprise a therapeutically effective amount of the described compound/s, or a pharmaceutically acceptable salt thereof.

In some embodiments, the pharmaceutical formulation comprises:

an oil-in-water emulsion; and

a therapeutically effective amount of the described compound/s, or a pharmaceutically acceptable salt thereof.

In some embodiments, the emulsion comprises water, an oil component, and an emulsifier component.

As used herein, the term “emulsifier component” refers, in one aspect, to a substance, or mixtures of substances that maintains an element or particle in suspension within a fluid medium. In some embodiments, the emulsifier component allows an oil phase to form an emulsion when combined with water. In some embodiments, the emulsifier component refers to one or more non-ionic surfactants.

In some embodiments, the oil component is present in an amount of about 10% to about 40% by weight of the formulation.

In some embodiments, the oil component comprises one or more substances independently selected from petrolatums, fatty alcohols, mineral oils, triglycerides, and silicone oils.

In some embodiments, the oil component comprises one or more substances independently selected from white petrolatum, cetyl alcohol, stearyl alcohol, light mineral oil, medium chain triglycerides, and dimethicone.

In some embodiments, the oil component comprises an occlusive agent component.

In some embodiments, the occlusive agent component is present in an amount of about 2% to about 15% by weight of the formulation.

As used herein, the term “occlusive agent component” refers to a hydrophobic agent or mixtures of hydrophobic agents that form an occlusive film on skin that reduces transepidermal water loss (TEWL) by preventing evaporation of water from the stratum corneum.

In some embodiments, the occlusive agent component comprises one or more substances selected from fatty acids (e.g., lanolin acid), fatty alcohols (e.g., lanolin alcohol), hydrocarbon oils & waxes (e.g., petrolatum), polyhydric alcohols (e.g., propylene glycol), silicones (e.g., dimethicone), sterols (e.g., cholesterol). vegetable or animal fat (e.g., cocoa butter), vegetable wax (e.g., Carnauba wax), and wax ester (e.g., bees wax).

In some embodiments, the occlusive agent component comprises one or more substances selected from lanolin acid fatty alcohols, lanolin alcohol, petrolatum, propylene glycol, dimethicone, cholesterol, cocoa butter, Carnauba wax, and bees wax.

In some embodiments, the occlusive agent component comprises petrolatum.

In some embodiments, the occlusive agent component comprises white petrolatum.

In some embodiments, the oil component comprises a stiffening agent component.

In some embodiments, the stiffening agent component is present in an amount of about 2% to about 8% by weight of the formulation.

As used herein, the term "stiffening agent component" refers to a substance or mixture of substances that increases the viscosity and/or consistency of the formulation or improves the rheology of the formulation.

In some embodiments, the stiffening agent component comprises one or more substances independently selected from fatty alcohols.

In some embodiments, the stiffening agent component comprises one or more substances independently selected from $C_{12-20}$ fatty alcohols.

In some embodiments, the stiffening agent component comprises one or more substances independently selected from $C_{16-18}$ fatty alcohols.

In some embodiments, the stiffening agent component comprises one or more substances independently selected from cetyl alcohol and stearyl alcohol.

In some embodiments, the oil component comprises an emollient component.

In some embodiments, the emollient component is present in an amount of about 5% to about 15% by weight of the formulation.

As used herein, the term "emollient component" refers to an agent that softens or soothes the skin or soothes an irritated internal surface.

In some embodiments, the emollient component comprises one or more substances independently selected from mineral oils and triglycerides.

In some embodiments, the emollient component comprises one or more substances independently selected from light mineral oil and medium chain triglycerides.

In some embodiments, the emollient component comprises one or more substances independently selected from light mineral oil, medium chain triglycerides, and dimethicone.

In some embodiments, the water is present in an amount of about 35% to about 65% by weight of the formulation.

In some embodiments, the emulsifier component is present in an amount of about 1% to about 9% by weight of the formulation.

In some embodiments, the emulsifier component comprises one or more substances independently selected from glyceryl fatty esters and sorbitan fatty esters.

In some embodiments, the emulsifier component comprises one or more substances independently selected from glyceryl stearate, and polysorbate 20.

In some embodiments, the pharmaceutical formulation further comprises a stabilizing agent component.

In some embodiments, the stabilizing agent component is present in an amount of about 0.05% to about 5% by weight of the formulation.

As used herein, the term "stabilizing agent component" refers to a substance or mixture of substances that improves the stability of the pharmaceutical formulation and/or the compatibility of the components in the formulation. In some embodiments, the stabilizing agent component prevents agglomeration of the emulsion and stabilizes the droplets in the oil-in-water emulsion.

In some embodiments, the stabilizing agent component comprises one or more substances independently selected from polysaccharides.

In some embodiments, the stabilizing agent component comprises xanthan gum.

In some embodiments, the pharmaceutical formulation further comprises a solvent component.

In some embodiments, the solvent component is present in an amount of about 10% to about 35% by weight of the formulation.

As used herein, the term "solvent component" is a liquid substance or mixture of liquid substances capable of dissolving the described compound/s or other substances in the formulation. In some embodiments, the solvent component is a liquid substance or mixture of liquid substances in which the described compound/s, or a pharmaceutically acceptable salt thereof, has reasonable solubility.

In some embodiments, the solvent component comprises one or more substances independently selected from alkylene glycols and polyalkylene glycols.

In some embodiments, the solvent component comprises one or more substances independently selected from propylene glycol and polyethylene glycol.

In some embodiments, the compound is present in an amount of about 0.5% to about 2.0% by weight of the formulation on a free base basis.

In some embodiments, the compound is present in an amount of about 0.5% by weight of the formulation on a free base basis.

In some embodiments, the compound is present in an amount of about 1% by weight of the formulation on a free base basis.

In some embodiments, the compound is present in an amount of about 1.5% by weight of the formulation on a free base basis.

In some embodiments, the compound is present in an amount selected from about 0.5, 0.6, 0.7, 0.8, 09, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, and 2.0% by weight of the formulation on a free base basis.

In some embodiments, the pharmaceutical formulation comprises: water; an oil component; an emulsifier component; a solvent component; a stabilizing agent component; and from about 0.5% to about 2.0% of the described compound/s, or a pharmaceutically acceptable salt thereof, by weight of the formulation on a free base basis.

In some embodiments, the pharmaceutical formulation comprises:

from about 35% to about 65% of water by weight of the formulation;

from about 10% to about 40% of an oil component by weight of the formulation;

from about 1% to about 9% of an emulsifier component by weight of the formulation;

from about 10% to about 35% of a solvent component by weight of the formulation;

from about 0.05% to about 5% of a stabilizing agent component by weight of the formulation; and

from about 0.5% to about 2.0% of the compound, or a pharmaceutically acceptable salt thereof, by weight of the formulation on a free base basis.

In some embodiments:

the oil component comprises one or more substances independently selected from petrolatums, fatty alcohols, mineral oils, triglycerides, and dimethicones;

the emulsifier component comprises one or more substances independently selected from glyceryl fatty esters and sorbitan fatty esters;

the solvent component comprises one or more substances independently selected from alkylene glycols and polyalkylene glycols; and

the stabilizing agent component comprises one or more substances independently selected from polysaccharides.

In some embodiments:

the oil component comprises one or more substances independently selected from white petrolatum, cetyl alcohol, stearyl alcohol, light mineral oil, medium chain triglycerides, and dimethicone;

the emulsifier component comprises one or more substances independently selected from glyceryl stearate and polysorbate 20;

the solvent component comprises one or more substances independently selected from propylene glycol and polyethylene glycol; and

the stabilizing agent component comprises xanthan gum.

In some embodiments, the pharmaceutical formulation comprises:

from about 35% to about 65% of water by weight of the formulation;

from about 2% to about 15% of an occlusive agent component by weight of the formulation;

from about 2% to about 8% of a stiffening agent component by weight of the formulation;

from about 5% to about 15% of an emollient component by weight of the formulation;

from about 1% to about 9% of an emulsifier component by weight of the formulation;

from about 0.05% to about 5% of a stabilizing agent component by weight of the formulation;

from about 10% to about 35% of a solvent component by weight of the formulation; and

from about 0.5% to about 2.0% of a compound, or a pharmaceutically acceptable salt thereof, by weight of the formulation on a free base basis.

In some embodiments:

the occlusive agent component comprises a petrolatum;

the stiffening agent component comprises one or more substances independently selected from one or more fatty alcohols;

the emollient component comprises one or more substances independently selected from mineral oils and triglycerides;

the emulsifier component comprises one or more substances independently selected from glyceryl fatty esters and sorbitan fatty esters;

the stabilizing agent component comprises one or more substances independently selected from polysaccharides; and

the solvent component comprises one or more substances independently selected from alkylene glycols and polyalkylene glycols.

In some embodiments:

the occlusive agent component comprises white petrolatum;

the stiffening agent component comprises one or more substances independently selected from cetyl alcohol and stearyl alcohol;

the emollient component comprises one or more substances independently selected from light mineral oil, medium chain triglycerides, and dimethicone;

the emulsifier component comprises one or more substances independently selected from glyceryl stearate and polysorbate 20;

the stabilizing agent component comprises xanthan gum; and

the solvent component comprises one or more substances independently selected from propylene glycol and polyethylene glycol.

In some embodiments, the pharmaceutical formulation further comprises an antimicrobial preservative component.

In some embodiments, the antimicrobial preservative component is present in an amount of about 0.05% to about 3% by weight of the formulation.

As used herein, the phrase "antimicrobial preservative component" is a substance or mixtures of substances which inhibits microbial growth in the formulation.

In some embodiments, the antimicrobial preservative component comprises one or more substances independently selected from alkyl parabens and phenoxyethanol.

In some embodiments, the antimicrobial preservative component comprises one or more substances independently selected from methyl paraben, propyl paraben, and phenoxyethanol.

In some embodiments, the pharmaceutical formulation further comprises a chelating agent component.

As used herein, the phrase "chelating agent component" refers to a compound or mixtures of compounds that has the ability to bind strongly with metal ions.

In some embodiments, the chelating agent component comprises edetate disodium.

As used herein, "% by weight of the formulation" means the percent concentration of the component in the formulation is on weight/weight basis. For example, 1% w/w of component A = [(mass of component A) / (total mass of the formulation)] x 100.

As used herein, "% by weight of the formulation on a free base basis" of the described compound/s, or a pharmaceutically acceptable salt thereof" means that the % w/w is calculated based on the weight of the free base of the compound in the total formulation.

In some embodiments, the components are present in exactly the ranges specified (e.g., the term "about" is not present). In some embodiments, "about" means plus or minus 10% of the value.

As will be appreciated, some components of the pharmaceutical formulations described herein can possess multiple functions. For example, a given substance may act as both an emulsifying agent component and a stabilizing agent. In some such cases, the function of a given component can be considered singular, even though its properties may allow multiple functionality. In some embodiments, each component of the formulation comprises a different substance or mixture of substances.

As used herein, the term "component" can mean one substance or a mixture of substances.

As used herein, the term "fatty acid" refers to an aliphatic acid that is saturated or unsaturated. In some embodiments, the fatty acid is a mixture of different fatty acids. In some embodiments, the fatty acid has between about eight to about thirty carbons on average. In some embodiments, the fatty acid has about 12 to 20, 14-20, or 16-18 carbons on average. Suitable fatty acids include, but are not limited to, cetyl acid, stearic acid, lauric acid, myristic acid, erucic acid, palmitic acid, palmitoleic acid, capric acid, caprylic acid, oleic acid, linoleic acid, linolenic acid, hydroxystearic acid, 12-hydroxystearic acid, cetostearic acid, isostearic acid, sesquioleic acid, sesqui-9-octadecanoic acid, sesquiisooctadecanoic acid, behenic acid, isobehenic acid, and arachidonic acid, or mixtures thereof.

As used herein, the term "fatty alcohol" refers to an aliphatic alcohol that is saturated or unsaturated. In some embodiments, the fatty alcohol is a mixture of different fatty alcohols. In some embodiments, the fatty alcohol has between about 12 to about 20, about 14 to about 20, or about 16 to about 18 carbons on average. Suitable fatty alcohols include, but are not limited to, stearyl alcohol, lauryl alcohol, palmityl alcohol, cetyl alcohol, capryl alcohol, caprylyl alcohol, oleyl alcohol, linolenyl alcohol, arachidonic alcohol, behenyl alcohol, isobehenyl alcohol, selachyl alcohol, chimyl alcohol, and linoleyl alcohol, or mixtures thereof.

As used herein, the term "polyalkylene glycol", employed alone or in combination with other terms, refers to a polymer containing oxyalkylene monomer units, or copolymer of different oxyalkylene monomer units, wherein the alkylene group has 2 to 6, 2 to 4, or 2 to 3 carbon atoms. As used herein, the term "oxyalkylene", employed alone or in combination with other terms, refers to a group of formula –O-alkylene-. In some embodiments, the polyalkylene glycol is polyethylene glycol.

As used herein, the term, "sorbitan fatty ester" includes products derived from sorbitan or sorbitol and fatty acids and, optionally, poly(ethylene glycol) units, including sorbitan esters and polyethoxylated sorbitan esters. In some embodiments, the sorbitan fatty ester is a polyethoxylated sorbitan ester.

As used herein, the term "sorbitan ester" refers to a compound, or mixture of compounds, derived from the esterification of sorbitol and at least one fatty acid. Fatty acids useful for deriving the sorbitan esters include, but are not limited to, those described herein. Suitable sorbitan esters include, but are not limited to, the Span™ series (available from Uniqema), which includes Span 20 (sorbitan monolaurate), 40 (sorbitan monopalmitate), 60 (sorbitan monostearate), 65 (sorbitan tristearate), 80 (sorbitan monooleate), and 85 (sorbitan trioleate). Other suitable sorbitan esters include those listed in R. C. Rowe and P. J. Shesky, Handbook of pharmaceutical excipients, (2006), 5th ed., which is incorporated herein by reference in its entirety.

As used herein, the term "polyethoxylated sorbitan ester" refers to a compound, or mixture thereof, derived from the ethoxylation of a sorbitan ester. The polyoxethylene portion of the compound can be between the fatty ester and the sorbitan moiety. As used herein, the term "sorbitan ester" refers to a compound, or mixture of compounds, derived from the esterification of sorbitol and at least one fatty acid. Fatty acids useful for deriving the polyethoyxlated sorbitan esters include, but are not limited to, those described herein. In some embodiments, the polyoxyethylene portion of the compound or mixture has about 2 to about 200 oxyethylene units. In some embodiments, the polyoxyethylene portion of the compound or mixture has about 2 to about 100 oxyethylene units. In some embodiments, the polyoxyethylene portion of the compound or mixture has about 4 to about 80 oxyethylene units. In some embodiments, the polyoxyethylene portion of the compound or mixture has about 4 to about 40 oxyethylene units. In some embodiments, the polyoxyethylene portion of the compound or mixture has about 4 to

about 20 oxyethylene units. Suitable polyethoxylated sorbitan esters include, but are not limited to the Tween™ series (available from Uniqema), which includes Tween 20 (POE(20) sorbitan monolaurate), 21 (POE(4) sorbitan monolaurate), 40 (POE(20) sorbitan monopalmitate), 60 (POE(20) sorbitan monostearate), 60K (POE(20) sorbitan monostearate), 61 (POE(4) sorbitan monostearate), 65 (POE(20) sorbitan tristearate), 80 (POE(20) sorbitan monooleate), 80K (POE(20) sorbitan monooleate), 81 (POE(5) sorbitan monooleate), and 85 (POE(20) sorbitan trioleate). As used herein, the abbreviation "POE" refers to polyoxyethylene. The number following the POE abbreviation refers to the number of oxyethylene repeat units in the compound. Other suitable polyethoxylated sorbitan esters include the polyoxyethylene sorbitan fatty acid esters listed in R. C. Rowe and P. J. Shesky, Handbook of pharmaceutical excipients, (2006), 5th ed., which is incorporated herein by reference in its entirety. In some embodiments, the polyethoxylated sorbitan ester is a polysorbate. In some embodiments, the polyethoxylated sorbitan ester is polysorbate 20.

As used herein, the term "glyceryl fatty esters" refers to mono-, di- or triglycerides of fatty acids. The glyceryl fatty esters may be optionally substituted with sulfonic acid groups, or pharmaceutically acceptable salts thereof. Suitable fatty acids for deriving glycerides of fatty acids include, but are not limited to, those described herein. In some embodiments, the glyceryl fatty ester is a mono-glyceride of a fatty acid having 12 to 18 carbon atoms. In some embodiments, the glyceryl fatty ester is glyceryl stearate.

As used herein, the term "triglycerides" refers to a triglyceride of a fatty acid. In some embodiments, the triglyceride is medium chain triglycerides.

As used herein, the term "alkylene glycol" refers to a group of formula –O-alkylene-, wherein the alkylene group has 2 to 6, 2 to 4, or 2 to 3 carbon atoms. In some embodiments, the alkylene glycol is propylene glycol (1,2-propanediol).

As used herein, the term "polyethylene glycol" refers to a polymer containing ethylene glycol monomer units of formula -O-$CH_2$-$CH_2$-. Suitable polyethylene glycols may have a free hydroxyl group at each end of the polymer molecule, or may have one or more hydroxyl groups etherified with a lower alkyl, e.g., a methyl group. Also suitable are derivatives of polyethylene glycols having esterifiable carboxy groups. Polyethylene glycols can be polymers of any chain length or molecular weight, and can include branching. In some embodiments, the average molecular weight of the polyethylene glycol is from about 200 to about 9000. In some

embodiments, the average molecular weight of the polyethylene glycol is from about 200 to about 5000. In some embodiments, the average molecular weight of the polyethylene glycol is from about 200 to about 900. In some embodiments, the average molecular weight of the polyethylene glycol is about 400. Suitable polyethylene glycols include, but are not limited to polyethylene glycol-200, polyethylene glycol-300, polyethylene glycol-400, polyethylene glycol-600, and polyethylene glycol-900. The number following the dash in the name refers to the average molecular weight of the polymer.

The oil-in-water cream formulations can be synthesized according using an overhead mixer with high and low shear mixing blades. For example, in some embodiments, the formulation can be synthesized by the following procedure.

1. An antimicrobial preservative phase can be prepared by mixing at least a portion of the antimicrobial preservative component with a portion of a solvent component.

2. Next, a stabilizing agent phase is prepared by mixing a stabilizing agent component with a portion of the solvent component.

3. An oil phase is then prepared by mixing an emollient component, an emulsifier component, an occlusive agent component, and a stiffening agent component. The oil phase is heated to 70-80 °C to melt and form a uniform mixture.

4. An aqueous phase is next prepared by mixing purified water, the remainder of the solvent component, and a chelating agent component. The phase is heated to 70-80 °C.

5. The aqueous phase of step 4, antimicrobial preservative phase of step 1, and the described compound/s, or a pharmaceutically acceptable salt thereof, are combined to form a mixture.

6. The stabilizing agent phase from step 2 was then added to the mixture from step 5.

7. The oil phase from step 3 is then combined under high shear mixing with the mixture from step 6 to form an emulsion.

8. Finally, additional antimicrobial preservative component may be then added to the emulsion from step 7. Mixing is continued, and then the product is cooled under low shear mixing.

The amount of compound or composition administered to a patient will vary depending upon what is being administered, the purpose of the administration, such as prophylaxis or therapy, the state of the patient, the manner of administration, and the like. In therapeutic applications, compositions can be administered to a patient already suffering from a disease in an

amount sufficient to cure or at least partially arrest the symptoms of the disease and its complications. Effective doses will depend on the disease condition being treated as well as by the judgment of the attending clinician depending upon factors such as the severity of the disease, the age, weight and general condition of the patient, and the like.

The compositions administered to a patient can be in the form of pharmaceutical compositions described above. These compositions can be sterilized by conventional sterilization techniques, or may be sterile filtered. Aqueous solutions can be packaged for use as is, or lyophilized, the lyophilized preparation being combined with a sterile aqueous carrier prior to administration. The pH of the compound preparations typically will be between 3 and 11, more preferably from 5 to 9 and most preferably from 7 to 8. It will be understood that use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of pharmaceutical salts.

The therapeutic dosage of the compound can vary according to, for example, the particular use for which the treatment is made, the manner of administration of the compound, the health and condition of the patient, and the judgment of the prescribing physician. The proportion or concentration of a compound in a pharmaceutical composition can vary depending upon a number of factors including dosage, chemical characteristics (*e.g.*, hydrophobicity), and the route of administration. For example, a compound can be provided in an aqueous physiological buffer solution containing about 0.1 to about 10% w/v of the compound for parenteral administration. Some typical dose ranges are from about 1 μg/kg to about 1 g/kg of body weight per day. In some embodiments, the dose range is from about 0.01 mg/kg to about 100 mg/kg of body weight per day. The dosage is likely to depend on such variables as the type and extent of progression of the disease or disorder, the overall health status of the particular patient, the relative biological efficacy of the compound selected, formulation of the excipient, and its route of administration. Effective doses can be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

The compositions can further include one or more additional pharmaceutical agents such as a chemotherapeutic, steroid, anti-inflammatory compound, or immunosuppressant, examples of which are listed hereinabove.

*Labeled Compounds and Assay Methods*

The described compound/s can be labeled (radio-labeled, fluorescent-labeled, etc.) and thus would be useful not only in imaging techniques but also in assays, both *in vitro* and *in vivo*, for localizing and quantitating JAK in tissue samples, including human, and for identifying JAK ligands by inhibition binding of a labeled compound. Accordingly, JAK assays may contain such labeled compounds.

The present invention further includes isotopically-labeled compounds of the invention. An "isotopically" or "radio-labeled" compound is a described compound where one or more atoms are replaced or substituted by an atom having an atomic mass or mass number different from the atomic mass or mass number typically found in nature (*i.e.*, naturally occurring). Suitable radionuclides that may be incorporated in compounds include but are not limited to $^{2}H$ (also written as D for deuterium), $^{3}H$ (also written as T for tritium), $^{11}C$, $^{13}C$, $^{14}C$, $^{13}N$, $^{15}N$, $^{15}O$, $^{17}O$, $^{18}O$, $^{18}F$, $^{35}S$, $^{36}Cl$, $^{82}Br$, $^{75}Br$, $^{76}Br$, $^{77}Br$, $^{123}I$, $^{124}I$, $^{125}I$ and $^{131}I$. The radionuclide that is incorporated in the instant radio-labeled compounds will depend on the specific application of that radio-labeled compound. For example, for *in vitro* JAK labeling and competition assays, compounds that incorporate $^{3}H$, $^{14}C$, $^{82}Br$, $^{125}I$ , $^{131}I$, $^{35}S$ or will generally be most useful. For radio-imaging applications $^{11}C$, $^{18}F$, $^{125}I$, $^{123}I$, $^{124}I$, $^{131}I$, $^{75}Br$, $^{76}Br$ or $^{77}Br$ will generally be most useful.

It is understood that a "radio-labeled " or "labeled compound" is a compound that has incorporated at least one radionuclide. In some embodiments the radionuclide is selected from the group consisting of $^{3}H$, $^{14}C$, $^{125}I$ , $^{35}S$ and $^{82}Br$.

Synthetic methods for incorporating radio-isotopes into the described compounds can be used. Synthetic methods for incorporating radio-isotopes into organic compounds are well known in the art, and an ordinary skill in the art will readily recognize the methods applicable for the described compounds.

A labeled described compound/s can be used in a screening assay to identify/evaluate compounds. For example, a newly synthesized or identified compound (*i.e.*, test compound) which is labeled can be evaluated for its ability to bind a JAK by monitoring its concentration variation when contacting with the JAK, through tracking of the labeling. For example, a test compound (labeled) can be evaluated for its ability to reduce binding of another compound which is known to bind to a JAK (*i.e.*, standard compound). Accordingly, the ability of a test compound to compete with the standard compound for binding to the JAK directly correlates to

its binding affinity. Conversely, in some other screening assays, the standard compound is labeled and test compounds are unlabeled. Accordingly, the concentration of the labeled standard compound is monitored in order to evaluate the competition between the standard compound and the test compound, and the relative binding affinity of the test compound is thus ascertained.

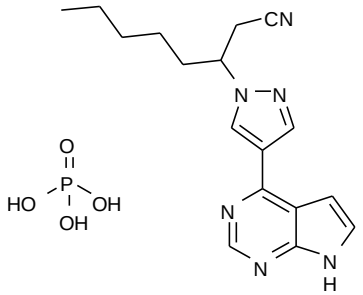
*Kits*

Pharmaceutical kits are useful, for example, in the treatment or prevention of JAK-associated diseases or disorders, such as cancer, which include one or more containers containing a pharmaceutical composition comprising a therapeutically effective amount of the described compound/s. Such kits can further include, if desired, one or more of various conventional pharmaceutical kit components, such as, for example, containers with one or more pharmaceutically acceptable carriers, additional containers, etc., as will be readily apparent to those skilled in the art. Instructions, either as inserts or as labels, indicating quantities of the components to be administered, guidelines for administration, and/or guidelines for mixing the components, can also be included in the kit.

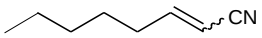
The invention will be described in greater detail by way of specific examples. The following examples are offered for illustrative purposes, and are not intended to limit the invention in any manner. Those of skill in the art will readily recognize a variety of non-critical parameters which can be changed or modified to yield essentially the same results.

**EXAMPLES**

**Example 1. 3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile phosphoric acid salt**

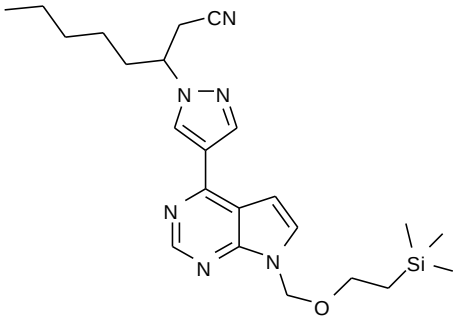



*Step 1: Oct-2-enenitrile*




To a solution of 1.0 M of potassium tert-butoxide in tetrahydrofuran (165 mL, 0.165 mol) at 0 °C was added dropwise a solution of diethyl cyanomethylphosphonate (27 mL, 0.17 mol) in tetrahydrofuran (100 mL). The reaction was warmed to room temperature and then cooled to 0 °C again after stirring for 30 min. To the reaction mixture was added a solution of hexanal (18 mL, 0.15 mol) in tetrahydrofuran (150 mL). The reaction was stirred overnight, allowed to warm up to room temperature. The reaction was quenched with water and extracted with ethyl acetate (EtOAc). The combined organic layers were washed with brine, dried over $MgSO_4$, concentrated, and purified on silica gel (eluting with 0 to15% EtOAc in hexanes) to provide the desired product (~17 g, 92%) as a mixture of cis and trans isomers. MS calculated for $C_8H_{14}N(M+H)^+$: m/z = 124.113; Found: 124.3.

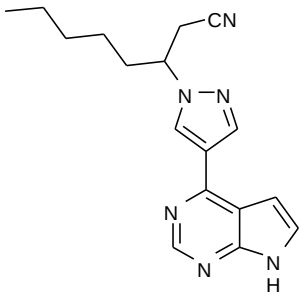
*Step 2: 3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile*




A mixture of 4-(1H-pyrazol-4-yl)-7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidine (prepared substantially as described in Example 65 of U.S. Pat. App. Pub. No. 2007/0135461 or International App. No. PCT/US2006/047369 (published as WO 2007/070514); 12 g, 0.038 mol), oct-2-enenitrile (6.0 g, 0.049 mol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 4.6 mL, 0.030 mol) in acetonitrile (120 mL, 2.3 mol) was stirred at room temperature overnight. After being concentrated in vacuo, the resultant residue was purified on silica gel (eluting with 0 to 40% EtOAc in hexanes) to give the desired product (15 g, 89.89%). The enantiomers (first peak retention time 11.02 min, second peak retention time 14.10 min) were separated on a ChiralCel OD-H column (30×250 mm, 5μM), eluting with mobile phase of 15% ethanol and 85% hexane at 25 mL/min. MS calculated for $C_{23}H_{35}N_6OSi(M+H)^+$: m/z = 439.264; Found: 439.4. $^1H$ NMR (300 MHz, $CDCl_3$) δ 8.91 (1H, s), 8.38 (1H, s), 8.37 (1H, s), 7.46 (1H,

d, J = 3.8 Hz), 6.86 (1H, d, J = 3.8 Hz), 5.73 (2H, s), 4.59 (1H, m), 3.60 (2H, t, J = 8.3 Hz), 3.06 (2H, td, J = 16.8 and 7.5 Hz), 2.21 (1H, m), 2.01 (1H, m), 1.40-1.21 (6H, m), 0.98 (2H, t, J = 8.3 Hz), 0.91 (3H, t, J = 6.3 Hz), 0.00 (9H, s) ppm.

*Step 3: 3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile*



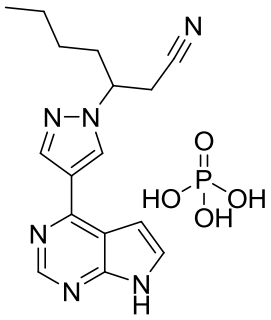

To a solution of 3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile (13 g, 0.030 mol) (peak 2 from chiral separation in Step 2) in acetonitrile (200.0 mL, 3.829 mol) and water (16.0 mL, 0.888 mol, ~8% acetonitrile/water) was added lithium tetrafluoroborate (28.4 g, 0.297 mol). The reaction was refluxed at 100 °C overnight. The mixture was cooled down and 7.2 M of ammonium hydroxide in water (17 mL, 0.12 mol) was added in portions over a period of 5 minutes at room temperature, adjusting pH to 9-10 with stirring for 2 h. The solid was removed by filtration and the filtrate was diluted with acetonitrile, water and MeOH for purification by preparative LCMS (XBridge C18 Column, eluting with a gradient of acetonitrile/water containing 0.15% $NH_4OH$) to give the desired product (5.9 g, 64%). MS calculated for $C_{17}H_{21}N_6(M+H)^+$: m/z = 309.183; Found: 309.3. $^1H$ NMR (300 MHz, DMSO-$D_6$) δ 12.10 (1H, s), 8.78 (1H, s), 8.66 (1H, s), 8.36 (1H, s), 7.58 (1H, m), 6.97 (1H, m), 4.71 (1H, m), 3.18 (1H, m), 3.16 (1H, br s), 1.93 (1H, m), 1.81 (1H, m), 1.19 (5H, m), 0.97 (1H, m), 0.78 (3H, t, J = 6.3 Hz) ppm.

*Step 4. 3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile phosphoric acid salt*

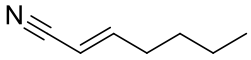
To a solution of 3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile (from step 3, 4.50 g, 0.0146 mol) in isopropyl alcohol (80 mL, 1 mol) was added a mixture of phosphoric acid (1.43 g, 0.0146 mol) in isopropanol (5.0 mL) while solution was kept at 60 °C. The phosphoric acid salt precipitated. The heating was continued but did not affect dissolution.

After being cooled to room temperature, the phosphoric acid salts were filtered off, air dried, then rinsed with some diethyl ether, and air dried. MS calculated for the base, $C_{17}H_{21}N_6(M+H)^+$: m/z = 309.183; Found: 309.3. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 12.10 ( 1H, s), 8.79 (1H, s), 8.66 (1H, s), 8.36 (1H, s), 7.58 (1H, d, J = 3.6 Hz), 6.97 (1H, d, J = 3.6 Hz), 4.71 (1H, m), 3.17 (2H, m), 1.94 (1H, m), 1.81 (1H, m), 1.18 (5H, m), 0.97 (1H, m), 0.78 (3H, t, J = 6.8 Hz). The product was confirmed to be 99.9% pure by three different runs on reverse phase HPLC column, and having 99.7% enantiomeric excess by six different runs on chiral HPLC column.

**Example 2. 3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile phosphoric acid salt**

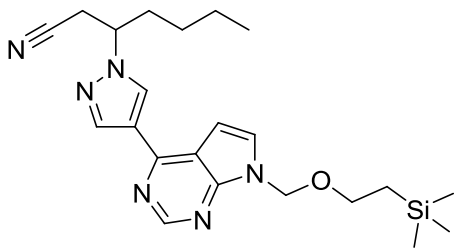


*Step 1. Hept-2-enenitrile*



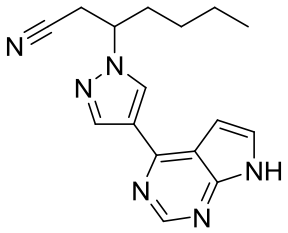
To a solution of 1.00 M of potassium *tert*-butoxide in tetrahydrofuran (49.3 mL, 49.3 mmol) at 0 °C was added dropwise a solution of diethyl cyanomethylphosphonate (8.37 mL, 51.7 mmol) in tetrahydrofuran (63 mL). The reaction was warmed to room temperature and then cooled at 0 °C again. To the reaction mixture was added a solution of pentanal (5.0 mL, 47 mmol) in tetrahydrofuran (12.6 mL). The reaction was allowed to warm up to room temperature and stirred overnight. After quenched with water, the mixture was extracted with ether. The combined organic layers were washed with brine, dried, and evaporated to dryness. The crude mixture was used directly in next step. LCMS calculated for $C_7H_{12}N(M+H)^+$: m/z = 110.1; Found: 110.3.

*Step 2. 3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile*



To a solution of 4-(1H-pyrazol-4-yl)-7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidine (6.1 g, 19 mmol) in acetonitrile (58 mL) was added crude hept-2-enenitrile (2.6 g, 23 mmol), followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (3.49 mL, 23.4 mmol). The resulting mixture was stirred at room temperature over the weekend and then evaporated to dryness. The residue was purified on silica gel, eluting with 0 to 50% of ethyl acetate in hexane, to give the desired product (6.90 g, 84%). LCMS calculated for $C_{22}H_{33}N_6OSi(M+H)^+$: m/z = 425.2; Found: 425.4. The racemic mixture was applied on an OD-H column (3x25cm, 5 μM), eluting with 15% ethanol and 85% hexane mixture at a flow rate of 28 mL/min to give the two desired enantiomers. First peak retention time of 9.46 min; second peak (3.45 g) retention time of 12.35 min.

*Step 3. 3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile*



Into a 500 mL round bottom flask fitted with stir bar, condenser and nitrogen inlet was charged acetonitrile (58 mL), water (5.0 mL), 3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile ($2^{nd}$ peak from chiral separation in step 2, 3.50 g, 8.24 mmol), and lithium tetrafluoroborate (7.88 g, 82.4 mmol). The mixture was warmed to reflux overnight. To the reaction mixture was charged 7.2 M of ammonium hydroxide in water (4.3 mL, 31 mmol) in portions over a period of 5 minutes at room temperature adjusting pH to 9-10. The resulting reaction mixture was stirred for 2 hours at room temperature. Solid was removed by filtration and the filtrate was purified on RP-HPLC (XBridge column C18, 30 x 100 mm 5 μM; with injection volume 5 mL and flow rate 60 mL/min; at a gradient of water and acetonitrile and 0.15% $NH_4OH$) to give desired product (1.79

g, 74%). LCMS calculated for $C_{16}H_{19}N_6(M+H)^+$: m/z = 295.2; Found: 295.2.

*Step 4. 3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile phosphate*

To a solution of 3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile (0.363 g, 1.23 mmol) in isopropyl alcohol (8.0 mL) was added phosphoric acid (0.133 g, 1.36 mmol) in 1.0 mL isopropyl alcohol at 60 °C. The mixture was heated at 60 °C for 1 hour, then cooled to room temperature. The precipitate was filtered off and air dried, rinsed with ethyl ether, and then air dried further to provide the desired phosphoric acid salt (418 mg, 86.5%). $^1$H NMR (DMSO-$d_6$, 400 MHz) δ 12.10 (1H, s), 8.78 (1H, s), 8.66 (1H, s), 8.36 (1H, s), 7.58 (1H, m), 6.97 (1H, m), 4.71 (1H, m), 3.18 (1H, m), 3.17 (1H, m), 1.93 (1H, m), 1.82 (1H, m), 1.21 (3H, m), 0.95 (1H, m), 0.78 (3H, t, J = 7.2 Hz) ppm.

**Example A: *In vitro* JAK Kinase Assay**

The described compounds were tested for inhibitory activity of JAK targets according to the following *in vitro* assay described in Park *et al.*, *Analytical Biochemistry* **1999**, *269*, 94-104. The catalytic domains of human JAK1 (a.a. 837-1142), JAK2 (a.a. 828-1132) and JAK3 (a.a. 781-1124) with an N-terminal His tag were expressed using baculovirus in insect cells and purified. The catalytic activity of JAK1, JAK2 or JAK3 was assayed by measuring the phosphorylation of a biotinylated peptide. The phosphorylated peptide was detected by homogenous time resolved fluorescence (HTRF). $IC_{50}$ was measured for each kinase in the 40 μL reactions that contain the enzyme, ATP and 500 nM peptide in 50 mM Tris (pH 7.8) buffer with 100 mM NaCl, 5 mM DTT, and 0.1 mg/mL (0.01%) BSA. The ATP concentration in the reactions was 90 μM for Jak1, 30 μM for Jak2 and 3 μM for Jak3. Reactions were carried out at room temperature for 1 hr and then stopped with 20 μL 45 mM EDTA, 300 nM SA-APC, 6 nM Eu-Py20 in assay buffer (Perkin Elmer, Boston, MA). Binding to the Europium labeled antibody took place for 40 minutes and HTRF signal was measured on a Fusion plate reader (Perkin Elmer, Boston, MA).

The described compounds were found to be potent JAK inhibitors. For Example 1, the enantiomer deriving from peak 2 of the chiral separation step was found to have an $IC_{50}$ value less than 10 nM for JAK2. The phosphoric salt form of the same enantiomer was similarly active. Also for Example 1, the enantiomer deriving from peak 1 of the chiral separation step

was also found to have an $IC_{50}$ value less than 10 nM for JAK2, though it was not as potent as the other enantiomer.

**Table 1**

| Example | JAK1 $IC_{50}$ (nM) at Km ATP | JAK2 $IC_{50}$ (nM) at Km ATP |
|---|---|---|
| 1, first peak (free base) | 3.9 | 2.2 |
| 1, second peak (free base) | 0.34 | 0.26 |
| 1, second peak (phosphate salt) | 0.63 | 0.29 |
| 2, first peak (free base) | 1.8 | 1.4 |
| 2, second peak (free base) | 0.57 | 0.3 |
| 2, second peak (phosphate salt) | 2 | 0.65 |

**Example B: Cellular Assays**

Cancer cell lines dependent on cytokines and hence JAK/STAT signal transduction, for growth (e.g., INA-6), are plated at 6000 cells per well (96 well plate format) in RPMI 1640, 10% FBS, and 1 ng/mL of appropriate cytokine. Compounds are added to the cells in DMSO/media (final concentration 0.2% DMSO) and incubated for 72 hours at 37 °C, 5% $CO_2$. The effect of compound on cell viability is assessed using the CellTiter-Glo Luminescent Cell Viability Assay (Promega) followed by TopCount (Perkin Elmer, Boston, MA) quantitation. Potential off-target effects of compounds are measured in parallel using a non-JAK driven cell line with the same assay readout. All experiments are typically performed in duplicate.

The above cell lines are used to examine the effects of compounds on phosphorylation of JAK kinases or potential downstream substrates such as STAT proteins, Akt, Shp2, or Erk. These experiments are performed following an overnight cytokine starvation, followed by a brief pre-incubation with compound (2 hours or less) and cytokine stimulation of approximately 1 hour or less. Proteins are then extracted from cells and analyzed by techniques familiar to those schooled in the art including Western blotting or ELISAs using antibodies that can differentiate between phosphorylated and total protein. These experiments utilize normal or cancer cells to investigate the activity of compounds on tumor cell survival biology or on mediators of

inflammatory disease. For example, with regards to the latter, cytokines such as IL-6, IL-12, IL-23, or IFN are used to stimulate JAK activation resulting in phosphorylation of STAT protein(s) and potentially in transcriptional profiles (assessed by array or qPCR technology) or production and/or secretion of proteins, such as IL-17. The ability of compounds to inhibit these cytokine mediated effects are measured using techniques common to those schooled in the art.

The described compounds can be tested in cellular models designed to evaluate their potency and activity against mutant JAKs, for example, the JAK2V617F mutation found in myeloid proliferative disorders. These experiments often utilize cytokine dependent cells of hematological lineage (*e.g.* BaF/3) into which the wild-type or mutant JAK kinases are ectopically expressed (James, C., *et al. Nature* 434:1144-1148; Staerk, J., *et al.* JBC 280:41893-41899). Endpoints include the effects of compounds on cell survival, proliferation, and phosphorylated JAK, STAT, Akt, or Erk proteins.

The described compounds can be evaluated for its activity inhibiting T-cell proliferation. Such an assay can be considered a second cytokine (*i.e.* JAK) driven proliferation assay and also a simplistic assay of immune suppression or inhibition of immune activation. The following is a brief outline of how such experiments is performed. Peripheral blood mononuclear cells (PBMCs) are prepared from human whole blood samples using Ficoll Hypaque separation method and T-cells (fraction 2000) are obtained from PBMCs by elutriation. Freshly isolated human T-cells are maintained in culture medium (RPMI 1640 supplemented with 10% fetal bovine serum, 100 U/ml penicillin, 100 μg/ml streptomycin) at a density of 2 x $10^6$ cells/ml at 37 °C for up to 2 days. For IL-2 stimulated cell proliferation analysis, T-cells are first treated with Phytohemagglutinin (PHA) at a final concentration of 10 μg/mL for 72h. After washing once with PBS, 6000 cells/well are plated in 96-well plates and treated with compounds at different concentrations in the culture medium in the presence of 100 U/mL human IL-2 (ProSpec-Tany TechnoGene; Rehovot, Israel). The plates are incubated at 37 °C for 72h and the proliferation index is assessed using CellTiter-Glo Luminescent reagents following the manufactory suggested protocol (Promega; Madison, WI).

**Example C: *In vivo* anti-tumor efficacy**

The described compounds can be evaluated in human tumor xenograft models in immune compromised mice. For example, a tumorigenic variant of the INA-6 plasmacytoma cell line can

be used to inoculate SCID mice subcutaneously (Burger, R., *et al. Hematol J.* 2:42-53, 2001). Tumor bearing animals were then randomized into drug or vehicle treatment groups and different doses of compounds can be administered by any number of the usual routes including oral, i.p., or continuous infusion using implantable pumps. Tumor growth can be followed over time using calipers. Further, tumor samples can be harvested at any time after the initiation of treatment for analysis as described above (Example B) to evaluate compound effects on JAK activity and downstream signaling pathways. In addition, selectivity of the compound can be assessed using xenograft tumor models that are driven by other known kinases (*e.g.* Bcr-Abl) such as the K562 tumor model.

**Example D: Murine Skin Contact Delayed Hypersensitivity Response Test**

The described compounds can also be tested for efficacy (of inhibiting JAK targets) in the T-cell driven murine delayed hypersensitivity test model. The murine skin contact delayed-type hypersensitivity (DTH) response is considered to be a valid model of clinical contact dermatitis, and other T-lymphocyte mediated immune disorders of the skin, such as psoriasis (*Immunol Today*. 1998 Jan;19(1):37-44). Murine DTH shares multiple characteristics with psoriasis, including the immune infiltrate, the accompanying increase in inflammatory cytokines, and keratinocyte hyperproliferation. Furthermore, many classes of agents that are efficacious in treating psoriasis in the clinic are also effective inhibitors of the DTH response in mice (*Agents Actions.* 1993 Jan;38(1-2):116-21).

On Day 0 and 1, Balb/c mice are sensitized with a topical application, to their shaved abdomen with the antigen 2,4,dinitro-fluorobenzene (DNFB). On day 5, ears are measured for thickness using an engineer's micrometer. This measurement is recorded and used as a baseline. Both of the animals' ears are then challenged by a topical application of DNFB in a total of 20 μL (10 μL on the internal pinna and 10 μL on the external pinna) at a concentration of 0.2%. Twenty-four to seventy-two hours after the challenge, ears are measured again. Treatment with the test compound was given throughout the sensitization and challenge phases (day -1 to day 7) or prior to and throughout the challenge phase (usually afternoon of day 4 to day 7). Treatment of the test compound (in different concentration) was administered either systemically or topically (topical application of the treatment to the ears). Efficacy of the test compound is indicated by a reduction in ear swelling comparing to the situation without the treatment. If the

compound causes a reduction of 20% or more it is considered efficacious. In some experiments, the mice are challenged but not sensitized (negative control).

The inhibitive effect (inhibiting activation of the JAK-STAT pathways) of the test compounds can be confirmed by immunohistochemical analysis. Activation of the JAK-STAT pathway(s) results in the formation and translocation of functional transcription factors. Further, the influx of immune cells and the increased proliferation of keratinocytes should also provide unique expression profile changes in the ear that can be investigated and quantified. Formalin fixed and paraffin embedded ear sections (harvested after the challenge phase in the DTH model) are subjected to immunohistochemical analysis using an antibody that specifically interacts with phosphorylated STAT3 (clone 58E12, Cell Signaling Technologies). The mouse ears are treated with test compound, vehicle, or dexamethasone (a clinically efficacious treatment for psoriasis), or without any treatment, in the DTH model for comparisons. Test compound and the dexamethasone can produce similar transcriptional changes both qualitatively and quantitatively, and both the test compound and dexamethasone can reduce the number of infiltrating cells. Both systemic and topical administration of the test compound can produce inhibitive effects, *i.e.*, reduction in the number of infiltrating cells and inhibition of the transcriptional changes.

**Example E: *In vivo* anti-inflammatory activity**

The described compounds can be evaluated in rodent or non-rodent models designed to replicate a single or complex inflammation response. For instance, rodent models of arthritis can be used to evaluate the therapeutic potential of compounds dosed preventatively or therapeutically. These models include but are not limited to mouse or rat collagen-induced arthritis, rat adjuvant-induced arthritis, and collagen antibody-induced arthritis. Autoimmune diseases including, but not limited to, multiple sclerosis, type I-diabetes mellitus, uveoretinitis, thyroditis, myasthenia gravis, immunoglobulin nephropathies, myocarditis, airway sensitization (asthma), lupus, or colitis may also be used to evaluate the therapeutic potential of compounds herein. These models are well established in the research community and are familiar to those schooled in the art (*Current Protocols in Immunology*, Vol 3., Coligan, J.E. *et al*, Wiley Press.; *Methods in Molecular Biology*: Vol. 225, Inflammation Protocols., Winyard, P.G. and Willoughby, D.A., Humana Press, 2003.).

**Example F: Animal Models for the Treatment of Dry Eye, Uveitis, and Conjunctivitis**

Agents may be evaluated in one or more preclinical models of dry eye known to those schooled in the art including, but not limited to, the rabbit concanavalin A (ConA) lacrimal gland model, the scopolamine mouse model (subcutaneous or transdermal), the Botulinumn mouse lacrimal gland model, or any of a number of spontaneous rodent auto-immune models that result in ocular gland dysfunction (e.g. NOD-SCID, MRL/lpr, or NZB/NZW) (Barabino *et al.*, *Experimental Eye Research* 2004, 79, 613-621 and Schrader *et al.*, *Developmental Opthalmology*, Karger 2008, 41, 298-312). Endpoints in these models may include histopathology of the ocular glands and eye (cornea, etc.) and possibly the classic Schirmer test or modified versions thereof (Barabino *et al.*) which measure tear production. Activity may be assessed by dosing via multiple routes of administration (e.g. systemic or topical) which may begin prior to or after measurable disease exists.

Agents may be evaluated in one or more preclinical models of uveitis known to those schooled in the art. These include, but are not limited to, models of experimental autoimmune uveitis (EAU) and endotoxin induced uveitis (EIU). EAU experiments may be performed in the rabbit, rat, or mouse and may involve passive or activate immunization. For instance, any of a number or retinal antigens may be used to sensitize animals to a relevant immunogen after which animals may be challenged ocularly with the same antigen. The EIU model is more acute and involves local or systemic administration of lipopolysaccaride at sublethal doses. Endpoints for both the EIU and EAU models may include fundoscopic exam, histopathology amongst others. These models are reviewed by Smith *et al.* (*Immunology and Cell Biology* 1998, 76, 497-512). Activity is assessed by dosing via multiple routes of administration (e.g. systemic or topical) which may begin prior to or after measurable disease exists. Some models listed above may also develop scleritis/episcleritis, chorioditis, cyclitis, or iritis and are therefore useful in investigating the potential activity of compounds for the therapeutic treatment of these diseases.

Agents may also be evaluated in one or more preclinical models of conjunctivitis known those schooled in the art. These include, but are not limited to, rodent models utilizing guinea-pig, rat, or mouse. The guinea-pig models include those utilizing active or passive immunization and/or immune challenge protocols with antigens such as ovalbumin or ragweed (reviewed in Groneberg, D.A., *et al.*, *Allergy* 2003, 58, 1101-1113). Rat and mouse models are similar in general design to those in the guinea-pig (also reviewed by Groneberg). Activity may be

assessed by dosing via multiple routes of administration (e.g. systemic or topical) which may begin prior to or after measurable disease exists. Endpoints for such studies may include, for example, histological, immunological, biochemical, or molecular analysis of ocular tissues such as the conjunctiva.

Various modifications of the invention, in addition to those described herein, will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims. Each reference, including all patent, patent applications, and publications, cited in the present application is incorporated herein by reference in its entirety.

**The Claims defining the invention are as follows:**

1. Use of a compound or salt of a compound, which is selected from:

3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile, a pharmaceutically acceptable salt thereof;

(3R)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile, a pharmaceutically acceptable salt thereof;

(3S)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile, a pharmaceutically acceptable salt thereof;

3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile, a pharmaceutically acceptable salt thereof;

(3R)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile, a pharmaceutically acceptable salt thereof;

(3S)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile, a pharmaceutically acceptable salt thereof;

3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile phosphoric acid salt;

(3R)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile phosphoric acid salt;

(3S)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile phosphoric acid salt;

3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile phosphoric acid salt;

(3R)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile phosphoric acid salt; and

(3S)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile phosphoric acid salt;

for the manufacture of a medicament for the treatment of an autoimmune disease.

2. The use of claim 1, wherein said autoimmune disease is a skin disorder, multiple sclerosis, rheumatoid arthritis, psoriatic arthritis, juvenile arthritis, type I diabetes, lupus, psoriasis, inflammatory bowel disease, Crohn's disease, myasthenia gravis, immunoglobulin nephropathies, myocarditis, or autoimmune thyroid disorder.

3. The use of claim 1, wherein said autoimmune disease is a bullous skin disorder.

4. The use of claim 3, wherein said bullous skin disorder is pemphigus vulgaris (PV) or bullous pemphigoid (BP).

5. The use of claim 1, wherein said autoimmune disease is rheumatoid arthritis.

6. The use of claim 1, wherein said autoimmune disease is a skin disorder.

7. The use of claim 6, wherein said skin disorder is atopic dermatitis or psoriasis.

8. The use of claim 6, wherein said skin disorder is skin sensitization, skin irritation, skin rash, contact dermatitis or allergic contact sensitization.

9. Use of a compound or salt of a compound, which is selected from:

3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile, a pharmaceutically acceptable salt thereof;

(3R)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile, a pharmaceutically acceptable salt thereof;

(3S)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile, a pharmaceutically acceptable salt thereof;

3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile, a pharmaceutically acceptable salt thereof;

(3R)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile, a pharmaceutically acceptable salt thereof;

(3S)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile, a pharmaceutically acceptable salt thereof;

3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile phosphoric acid salt;

(3R)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile phosphoric acid salt;

(3S)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile phosphoric acid salt;

3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile phosphoric acid salt;

(3R)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile phosphoric acid salt; and

(3S)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile phosphoric acid salt;

for the manufacture of a medicament for the treatment of cancer.

10. The use of claim 9, wherein said cancer is a solid tumor.

11. The use of claim 9, wherein said cancer is prostate cancer, renal cancer, hepatic cancer, breast cancer, lung cancer, thyroid cancer, Kaposi's sarcoma, Castleman's disease or pancreatic cancer.

12. The use of claim 9, wherein said cancer is lymphoma, leukemia, or multiple myeloma.

13. The use of claim 9, wherein said cancer is cutaneous T-cell lymphoma or cutaneous B-cell lymphoma.

14. Use of a compound or salt of a compound, which is selected from:

3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile, a pharmaceutically acceptable salt thereof;

(3R)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile, a pharmaceutically acceptable salt thereof;

(3S)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile, a pharmaceutically acceptable salt thereof;

3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile, a pharmaceutically acceptable salt thereof;

(3R)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile, a pharmaceutically acceptable salt thereof;

(3S)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile, a pharmaceutically acceptable salt thereof;

3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile phosphoric acid salt;

(3R)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile phosphoric acid salt;

(3S)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile phosphoric acid salt;

3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile phosphoric acid salt;

(3R)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile phosphoric acid salt; and

(3S)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile phosphoric acid salt;

for the manufacture of a medicament for the treatment of a myeloproliferative disorder.

15. The use of claim 14, wherein said myeloproliferative disorder is polycythemia vera (PV), essential thrombocythemia (ET), primary myelofibrosis (PMF), chronic myelogenous leukemia (CML), chronic myelomonocytic leukemia (CMML), hypereosinophilic syndrome (HES), idiopathic myelofibrosis (IMF), or systemic mast cell disease (SMCD).

16. Use of a compound or salt of a compound, which is selected from:

3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile, a pharmaceutically acceptable salt thereof;

(3R)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile, a pharmaceutically acceptable salt thereof;

(3S)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile, a pharmaceutically acceptable salt thereof;

3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile, a pharmaceutically acceptable salt thereof;

(3R)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile, a pharmaceutically acceptable salt thereof;

(3S)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile, a pharmaceutically acceptable salt thereof;

3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile phosphoric acid salt;

(3R)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile phosphoric acid salt;

(3S)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile phosphoric acid salt;

3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile phosphoric acid salt;

(3R)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile phosphoric acid salt; and

(3S)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile phosphoric acid salt;

for the manufacture of a medicament for the treatment of an inflammatory disease.

17. The use of claim 16, wherein said inflammatory disease is iritis, uveitis, scleritis, conjunctivitis, inflammatory disease of the respiratory tract, inflammatory myopathy, or myocarditis.

18. Use of a compound or salt of a compound, which is selected from:

3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile, a pharmaceutically acceptable salt thereof;

(3R)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile, a pharmaceutically acceptable salt thereof;

(3S)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile, a pharmaceutically acceptable salt thereof;

3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile, a pharmaceutically acceptable salt thereof;

(3R)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile, a pharmaceutically acceptable salt thereof;

(3S)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile, a pharmaceutically acceptable salt thereof;

3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile phosphoric acid salt;

(3R)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile phosphoric acid salt;

(3S)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile phosphoric acid salt;

3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile phosphoric acid salt;

(3R)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile phosphoric acid salt; and

(3S)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile phosphoric acid salt;

for the manufacture of a medicament for the treatment of organ transplant rejection.

19. Use of a compound or salt of a compound, which is selected from:

3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile, a pharmaceutically acceptable salt thereof;

(3R)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile, a pharmaceutically acceptable salt thereof;

(3S)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile, a pharmaceutically acceptable salt thereof;

3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile, a pharmaceutically acceptable salt thereof;

(3R)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile, a pharmaceutically acceptable salt thereof;

(3S)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile, a pharmaceutically acceptable salt thereof;

3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile phosphoric acid salt;

(3R)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile phosphoric acid salt;

(3S)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile phosphoric acid salt;

3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile phosphoric acid salt;

(3R)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile phosphoric acid salt; and

(3S)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile phosphoric acid salt;

for the manufacture of a medicament for the treatment of ischemia reperfusion or a disease related to an ischemic event.

20. Use of a compound or salt of a compound, which is selected from:

3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile, a pharmaceutically acceptable salt thereof;

(3R)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile, a pharmaceutically acceptable salt thereof;

(3S)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile, a pharmaceutically acceptable salt thereof;

3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile, a pharmaceutically acceptable salt thereof;

(3R)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile, a pharmaceutically acceptable salt thereof;

(3S)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile, a pharmaceutically acceptable salt thereof;

3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile phosphoric acid salt;

(3R)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile phosphoric acid salt;

(3S)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile phosphoric acid salt;

3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile phosphoric acid salt;

(3R)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile phosphoric acid salt; and

(3S)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile phosphoric acid salt;

for the manufacture of a medicament for the treatment of anorexia or cachexia, wherein the anorexia or cachexia is resulting from or associated with cancer.

21. Use of a compound or salt of a compound, which is selected from:

3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile, a pharmaceutically acceptable salt thereof;

(3R)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile, a pharmaceutically acceptable salt thereof;

(3S)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile, a pharmaceutically acceptable salt thereof;

3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile, a pharmaceutically acceptable salt thereof;

(3R)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile, a pharmaceutically acceptable salt thereof;

(3S)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile, a pharmaceutically acceptable salt thereof;

3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile phosphoric acid salt;

(3R)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile phosphoric acid salt;

(3S)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile phosphoric acid salt;

3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile phosphoric acid salt;

(3R)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile phosphoric acid salt; and

(3S)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile phosphoric acid salt;

for the manufacture of a medicament for the treatment of fatigue, wherein the fatigue is resulting from or associated with cancer.

22. Use of a compound or salt of a compound, which is selected from:

3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile, a pharmaceutically acceptable salt thereof;

(3R)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile, a pharmaceutically acceptable salt thereof;

(3S)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile, a pharmaceutically acceptable salt thereof;

3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile, a pharmaceutically acceptable salt thereof;

(3R)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile, a pharmaceutically acceptable salt thereof;

(3S)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile, a pharmaceutically acceptable salt thereof;

3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile phosphoric acid salt;

(3R)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile phosphoric acid salt;

(3S)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile phosphoric acid salt;

3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile phosphoric acid salt;

(3R)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile phosphoric acid salt; and

(3S)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile phosphoric acid salt;

for the manufacture of a medicament for the treatment of allograft rejection or graft versus host disease.

23. Use of a compound or salt of a compound, which is selected from:

3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile, a pharmaceutically acceptable salt thereof;

(3R)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile, a pharmaceutically acceptable salt thereof;

(3S)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile, a pharmaceutically acceptable salt thereof;

3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile, a pharmaceutically acceptable salt thereof;

(3R)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile, a pharmaceutically acceptable salt thereof;

(3S)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile, a pharmaceutically acceptable salt thereof;

3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile phosphoric acid salt;

(3R)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile phosphoric acid salt;

(3S)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile phosphoric acid salt;

3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile phosphoric acid salt;

(3R)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile phosphoric acid salt; and

(3S)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile phosphoric acid salt;

for the manufacture of a medicament for the treatment of rheumatoid arthritis.

24. Use of a compound or salt of a compound, which is selected from:

3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile, a

pharmaceutically acceptable salt thereof;

(3R)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile, a pharmaceutically acceptable salt thereof;

(3S)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile, a pharmaceutically acceptable salt thereof;

3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile, a pharmaceutically acceptable salt thereof;

(3R)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile, a pharmaceutically acceptable salt thereof;

(3S)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile, a pharmaceutically acceptable salt thereof;

3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile phosphoric acid salt;

(3R)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile phosphoric acid salt;

(3S)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile phosphoric acid salt;

3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile phosphoric acid salt;

(3R)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile phosphoric acid salt; and

(3S)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile phosphoric acid salt;

for the manufacture of a medicament for the treatment of psoriasis.

25. Use of a compound or salt of a compound, which is selected from:

3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile, a pharmaceutically acceptable salt thereof;

(3R)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile, a

pharmaceutically acceptable salt thereof;

(3S)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile, a pharmaceutically acceptable salt thereof;

3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile, a pharmaceutically acceptable salt thereof;

(3R)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile, a pharmaceutically acceptable salt thereof;

(3S)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile, a pharmaceutically acceptable salt thereof;

3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile phosphoric acid salt;

(3R)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile phosphoric acid salt;

(3S)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile phosphoric acid salt;

3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile phosphoric acid salt;

(3R)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile phosphoric acid salt; and

(3S)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile phosphoric acid salt;

for the manufacture of a medicament for the treatment of dermatitis.

26. Use of a compound or salt of a compound, which is selected from:

3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile, a pharmaceutically acceptable salt thereof;

(3R)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile, a pharmaceutically acceptable salt thereof;

(3S)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile, a

pharmaceutically acceptable salt thereof;

3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile, a pharmaceutically acceptable salt thereof;

(3R)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile, a pharmaceutically acceptable salt thereof;

(3S)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile, a pharmaceutically acceptable salt thereof;

3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile phosphoric acid salt;

(3R)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile phosphoric acid salt;

(3S)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile phosphoric acid salt;

3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile phosphoric acid salt;

(3R)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile phosphoric acid salt; and

(3S)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile phosphoric acid salt;

for the manufacture of a medicament for the treatment of iritis.

27. Use of a compound or salt of a compound, which is selected from:

3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile, a pharmaceutically acceptable salt thereof;

(3R)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile, a pharmaceutically acceptable salt thereof;

(3S)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile, a pharmaceutically acceptable salt thereof;

3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile, a

pharmaceutically acceptable salt thereof;
(3R)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile, a pharmaceutically acceptable salt thereof;
(3S)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile, a pharmaceutically acceptable salt thereof;
3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile phosphoric acid salt;
(3R)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile phosphoric acid salt;
(3S)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile phosphoric acid salt;
3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile phosphoric acid salt;
(3R)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile phosphoric acid salt; and
(3S)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile phosphoric acid salt;

for the manufacture of a medicament for the treatment of uveitis.

28. Use of a compound or salt of a compound, which is selected from:
3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile, a pharmaceutically acceptable salt thereof;
(3R)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile, a pharmaceutically acceptable salt thereof;
(3S)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile, a pharmaceutically acceptable salt thereof;
3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile, a pharmaceutically acceptable salt thereof;
(3R)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile, a

pharmaceutically acceptable salt thereof;

(3S)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile, a pharmaceutically acceptable salt thereof;

3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile phosphoric acid salt;

(3R)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile phosphoric acid salt;

(3S)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile phosphoric acid salt;

3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile phosphoric acid salt;

(3R)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile phosphoric acid salt; and

(3S)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile phosphoric acid salt;

for the manufacture of a medicament for the treatment of scleritis.

29. Use of a compound or salt of a compound, which is selected from:

3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile, a pharmaceutically acceptable salt thereof;

(3R)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile, a pharmaceutically acceptable salt thereof;

(3S)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile, a pharmaceutically acceptable salt thereof;

3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile, a pharmaceutically acceptable salt thereof;

(3R)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile, a pharmaceutically acceptable salt thereof;

(3S)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile, a

pharmaceutically acceptable salt thereof;

3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile phosphoric acid salt;

(3R)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile phosphoric acid salt;

(3S)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile phosphoric acid salt;

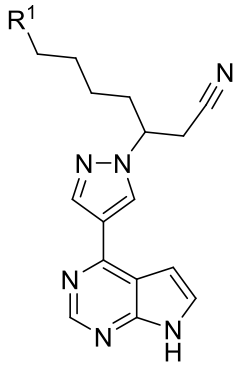
3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile phosphoric acid salt;

(3R)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile phosphoric acid salt; and

(3S)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile phosphoric acid salt;

for the manufacture of a medicament for the treatment of conjunctivitis.

30. A process for preparing a phosphoric acid salt of a compound of Formula III:




**III**

wherein $R^1$ is H or methyl, comprising combining a compound of Formula III with phosphoric acid.

31. The process of claim 30, wherein said process is a process of preparing 3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile phosphoric acid salt.

32. The process of claim 30, wherein said process is a process of preparing 3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]heptanenitrile phosphoric acid salt.

33. The process of any one of claims 30 to 32, wherein said combining is carried out in the presence of an organic solvent.

34. The process of claim 33, wherein the organic solvent is an alcohol.

35. The process of claim 34, wherein the alcohol is selected from the group consisting of methanol, ethanol, isopropanol, and butanol.

36. The process of any one of claims 30 to 32, wherein the combining is performed at a temperature of greater than about 20 °C.

37. The process of any one of claims 30 to 32, wherein the combining is performed at a temperature of about 60 °C.