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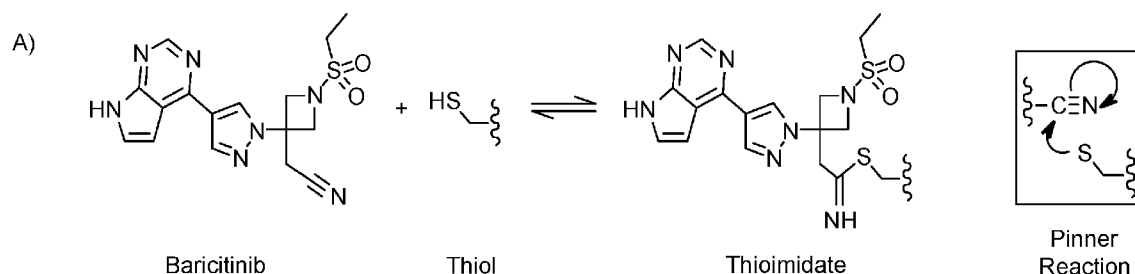
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(54) Title: SUSTAINED DELIVERY OF NITRILE-CONTAINING JAK INHIBITORS FROM A HYDROGEL THROUGH REVERSIBLE THIOIMIDATE ADDUCTS

FIG. 1



(57) Abstract: The invention provides sustained delivery JAK inhibitor hydrogels for treatment of an inflammatory disorder, autoimmune disease, an autoimmune and inflammatory hair loss, and/or a non-inflammatory disorder hair loss, the JAK inhibitor hydrogel comprising a JAK inhibitor having a nitrile group reversibly conjugated to a thiol group of a thiolated polymer to form a thioimide adduct. The invention also provides injectable pharmaceutical compositions for treatment of an inflammatory disorder, an autoimmune disease, an autoimmune and inflammatory hair loss, and/or a non-inflammatory disorder hair loss, the injectable pharmaceutical compositions comprising a nitrile-containing JAK inhibitor and a pharmaceutically acceptable carrier.

SUSTAINED DELIVERY OF NITRILE-CONTAINING JAK INHIBITORS FROM A HYDROGEL THROUGH REVERSIBLE THIOIMIDATE ADDUCTS

FIELD OF THE INVENTION

[001] The invention relates to sustained delivery JAK inhibitor hydrogels comprising JAK inhibitors having a nitrile group reversibly conjugated to a thiol group of a thiolated polymer, such as hyaluronic acid, to form a thioimide adduct for the treatment of an inflammatory disorder such as inflammatory skin disorders and autoimmune diseases such as rheumatoid arthritis, psoriatic arthritis or reactive arthritis, as well as autoimmune and inflammatory hair loss, such as alopecia areata, and/or non-inflammatory disorder hair loss, such as androgenetic alopecia. The invention also relates to methods for treating inflammatory disorders, including skin disorders such as atopic dermatitis, alopecia areata, central centrifugal cicatricial alopecia, lichen planopilaris; hidradenitis suppurativa, lichen planus, mucosal lichen planus, psoriasis, pemphigus or vitiligo, and other autoimmune diseases such as rheumatoid arthritis, psoriatic arthritis or reactive arthritis by administering to a subject in need thereof a JAK inhibitor having a nitrile group reversibly conjugated to a thiol group of a thiolated hyaluronic acid to form a thioimide adduct. The invention further relates to methods for treating such inflammatory disorders and autoimmune diseases by administering to a subject in need thereof a composition comprising an injectable nitrile-containing JAK inhibitor, for example, baricitinib or any other nitrile-containing JAK inhibitors, as described *infra* in the absence of a thiolated polymer that forms a hydrogel, wherein the JAK inhibitor crystallizes or precipitates out of the composition and sustains its own release.

BACKGROUND OF THE INVENTION

[002] The Janus kinase and signal transducer and activator of transcription JAK (Janus kinase)/STAT pathway has emerged as a disease target for many inflammatory disorders in the skin. To date, several small molecule inhibitors of JAK-STAT signaling have been FDA approved and are highly effective in dermatology, including in atopic dermatitis (e.g., ruxolitinib, abrocitinib, upadacitinib), vitiligo (ruxolitinib), alopecia areata (e.g., ritlecitinib, baricitinib), psoriasis/psoriatic arthritis (e.g., deucravacitinib, tofacitinib), while many others are currently under investigation for other dermatologic diseases. Despite their broad clinical efficacy in dermatology, systemic use of JAK inhibitors is associated with serious risks of infections, major adverse cardiovascular events, thromboses, malignancy, and death leading to a black box warning

for all FDA approved JAK inhibitors. As a result, providers and patients are forced to exercise caution in their use while patients at high risk for cardiovascular events and malignancy are excluded altogether. As a result, patients are unable to clinically benefit from the effectiveness of these medications without taking on high levels of risk. To overcome limitations of systemic JAK inhibitors, biomaterial-based drug delivery systems can be utilized to retain payloads at a particular target tissue of interest, maximizing bioavailability while minimizing systemic absorption and off-target toxicities. In this regard, hydrogels are desirable as they are often biocompatible due to their high-water content and they can be engineered to be injectable for minimally invasive delivery. Although hydrogel systems have been attempted for drug delivery, their use for local and sustained drug release in dermatology remains difficult. For example, small molecules such as JAK inhibitors are challenging to deliver from hydrogels due to their small size and rapid diffusion. Previous research delivering JAK inhibitors from hydrogels showed release over days but were unable to achieve longer-term release profiles. A notable and similar dermatologic example showed metalloprotease-triggered delivery of tofacitinib for atopic dermatitis *in vitro* from a polyethylene glycol hydrogel but with release of ~40% at 48 hours. Further, the need for repeated administrations either as a topical or injectable limits compliance and is a major barrier to use and clinical translation.

[003] Accordingly, there remains a need for developing improved compositions to deliver JAK inhibitors to the skin that could be readily administered in dermatology clinics and methods for treatment of inflammatory disorders of the skin and autoimmune diseases affecting the skin with enhanced compositions.

SUMMARY OF THE INVENTION

[004] In one aspect, provided herein are sustained delivery hydrogels for treatment of a disorder or a disease comprising a small molecule drug having a nitrile group reversibly conjugated to a thiol group of a thiolated polymer, such as hyaluronic acid, to form a thioimide adduct. Also provided herein are injectable pharmaceutical compositions for treatment of a disorder or a disease, comprising the foregoing sustained delivery hydrogels and a pharmaceutically acceptable carrier. Also provided herein are methods for treating a disorder or a disease in a subject in need thereof, the method comprising administering the foregoing sustained delivery hydrogels to the subject.

[005] In one aspect, provided herein are sustained delivery JAK inhibitor hydrogels for treatment of an inflammatory disorder, an autoimmune disease, an autoimmune and inflammatory hair loss, and/or a non-inflammatory disorder hair loss, the JAK inhibitor hydrogel comprising a JAK inhibitor having a nitrile group reversibly conjugated to a thiol group of a thiolated polymer to form a thioimide adduct.

[006] In another aspect, provided herein are sustained delivery baricitinib hydrogels comprising baricitinib having a nitrile group reversibly conjugated to a thiol group of a thiolated polymer to form a thioimide adduct for treatment of an inflammatory disorder, an autoimmune disease, an autoimmune and inflammatory hair loss, and/or a non-inflammatory disorder hair loss.

[007] In one aspect, the invention provides injectable pharmaceutical compositions for treatment of an inflammatory disorder, an autoimmune disease, an autoimmune and inflammatory hair loss, and/or a non-inflammatory disorder hair loss, the injectable pharmaceutical composition comprising a nitrile-containing JAK inhibitor, e.g., baricitinib, and a pharmaceutically acceptable carrier. In another aspect, the invention provides sustained delivery pharmaceutical compositions for treatment of an inflammatory disorder, an autoimmune disease, an autoimmune and inflammatory hair loss, and/or a non-inflammatory disorder hair loss, the sustained delivery pharmaceutical composition comprising a nitrile-containing JAK inhibitor, e.g., baricitinib, and a pharmaceutically acceptable carrier. In an embodiment, the sustained delivery pharmaceutical composition is an injectable pharmaceutical composition.

[008] In another aspect, the invention provides injectable pharmaceutical compositions for treatment of an inflammatory disorder, an autoimmune disease, an autoimmune and inflammatory hair loss, and/or a non-inflammatory disorder hair loss, the injectable pharmaceutical composition comprising a low concentration of thiolated hydrogel, a nitrile-containing JAK inhibitor and a pharmaceutically acceptable carrier.

[009] In another aspect, the invention provides methods for treating an inflammatory disorder, an autoimmune disease, an autoimmune and inflammatory hair loss, and/or a non-inflammatory disorder hair loss in a subject in need thereof, the method comprising administering a sustained delivery nitrile-containing JAK inhibitor hydrogel to a body part of the subject affected by the inflammatory disorder, the autoimmune disease, the autoimmune and inflammatory hair loss, and/or the non-inflammatory disorder hair loss, wherein the JAK inhibitor hydrogel comprises a

JAK inhibitor having a nitrile group reversibly conjugated to a thiol group of a thiolated polymer by a thioimide adduct.

[0010] In still another aspect, the invention provides methods for treating an inflammatory disorder, an autoimmune disease, an autoimmune and inflammatory hair loss, and/or a non-inflammatory disorder hair loss in a subject in need thereof, the method comprising administering a sustained delivery baricitinib hydrogel to a body part of the subject affected by the inflammatory disorder, autoimmune disease, the autoimmune and inflammatory hair loss, and/or the non-inflammatory disorder hair loss, wherein the sustained delivery baricitinib hydrogel comprises baricitinib reversibly conjugated at a nitrile group to a thiol group of a thiolated polymer by a thioimide adduct.

[0011] In one aspect, the invention provides methods for treating an inflammatory disorder, an autoimmune disease, an autoimmune and inflammatory hair loss, and/or a non-inflammatory disorder hair loss in a subject in need thereof, the method comprising administering an injectable pharmaceutical composition to a body part of the subject affected by the inflammatory disorder, the autoimmune disease, the autoimmune and inflammatory hair loss, and/or the non-inflammatory disorder hair loss, wherein the injectable pharmaceutical composition comprises a nitrile-containing JAK inhibitor, e.g., baricitinib, and a pharmaceutically acceptable carrier. In an embodiment, the injectable pharmaceutical composition is administered with hollow microneedles that allow delivery of the injectable pharmaceutical composition comprising the therapeutic agent (the JAK inhibitor) in a upon application of pressure.

[0012] In another aspect, the invention provides methods for treating an inflammatory disorder, an autoimmune disease, an autoimmune and inflammatory hair loss, and/or a non-inflammatory disorder hair loss in a subject in need thereof, the method comprising administering a sustained delivery pharmaceutical composition to a body part of the subject affected by the inflammatory disorder, the autoimmune disease, the autoimmune and inflammatory hair loss, and/or the non-inflammatory disorder hair loss, wherein the sustained delivery pharmaceutical composition comprises a nitrile-containing JAK inhibitor, e.g., baricitinib, and a pharmaceutically acceptable carrier. In an embodiment, the sustained delivery pharmaceutical composition is an injectable pharmaceutical composition.

[0013] In another aspect, the invention provides methods for producing a sustained delivery JAK inhibitor hydrogel for treatment of an inflammatory disorder, an autoimmune disease, an

autoimmune and inflammatory hair loss, and/or a non-inflammatory disorder hair loss in a subject in need thereof, wherein the JAK inhibitor hydrogel comprises a nitrile-containing JAK inhibitor and the nitrile group is reversibly conjugated to a thiol group of a thiolated polymer to form thioimide adduct, the method comprising: (a) mixing a thiolated polymer with the nitrile-containing JAK inhibitor having a nitrile group to a desired weight percent concentration (w/v) of from about 0.5 to 10 wt.% for 24 hours to form a crosslinked JAK inhibitor hydrogel, wherein the thiolated polymer and the JAK inhibitor are each dissolved in a respective solvent; (b) centrifuging the crosslinked JAK inhibitor hydrogel; and (c) washing the centrifuged crosslinked JAK inhibitor hydrogel to remove the solvent.

[0014] Other features and advantages of the present invention will become apparent from the following detailed description examples and figures. It should be understood, however, that the detailed description and the specific examples while indicating preferred embodiments of the invention are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

[0015] The following drawings form part of the present specification and are included to further demonstrate certain aspects of the present disclosure, the inventions of which can be better understood by reference to one or more of these drawings in combination with the detailed description of specific embodiments presented herein.

[0016] **Figures 1A-1B** show baricitinib and cysteamine thioimide formation. **Fig. 1A** shows baricitinib nitrile ($\text{—C}\equiv\text{N}$, also called a cyano group) interacts with thiols (—SH functional group) to form thioimides (—S—CR=NH , R is C or N). The reaction forms through a modified Pinner reaction in which a free, nucleophilic thiol attacks the electrophilic nitrile on baricitinib. **Fig. 1B** shows liquid chromatography-mass spectrometry demonstrates product formation between baricitinib (373 Da), cysteamine (77 Da), and baricitinib-cysteamine (449 Da), resolving with three distinct retention time peaks (0.3 s, 1.5 s, 1.4 s, respectively).

[0017] **Figures 2A-2D** show polymer design, thioimide bonding, and hydrogel disulfide crosslinking. **Fig. 2A** shows hyaluronic acid (100 kDa) is amidated at its carboxyl position with cysteamine to yield a thiolated product where x is the fraction of disaccharides with thiol modification and 1-x is the fraction of unmodified disaccharides. **Fig. 2B** shows baricitinib nitrile

($\text{—C} \equiv \text{N}$) interacts with the thiolated hyaluronic acid polymer (—SH) to yield thioimides (—S—CR=NH , R is C), where y represents the fraction of disaccharides with bound baricitinib. Simultaneously, unmodified thiols oxidize and form disulfide crosslinks between polymer chains under physiologic conditions to yield a dynamically crosslinked hydrogel. The degree of unbound thiols which form disulfides is represented by x-y, and unmodified disaccharides are represented as 1-x. **Figs. 2C-2E** show the structures of three iterations of disaccharide modifications that form during thioimide bonding between baricitinib and hyaluronic acid, namely the thioimide, free thiol, and disulfide.

[0018] Figures 3A-3B show quantification of hyaluronic acid thiolation and consumption of thiols by baricitinib. **Fig. 3A** shows the validation of the presence of thiols on hyaluronic acid using a commercially available assay. Fluorescence excitation at 494 and emission at 517 nm was performed using glutathione (GSH) standards and compared to thiolated hyaluronic acid (10 μM , yellow bar), n=3 per group. **Fig. 3B** shows thiolated hyaluronic acid (25 μM) was incubated with varying doses of baricitinib (0-400 μM), n=3 per group. Free thiols were subsequently quantified using the thiol quantification assay demonstrating consumption of free thiols on hyaluronic acid with increasing concentrations of baricitinib. *p<0.05 compared to $[\text{CN}]/[\text{SH}]$ of 1, n=3 per group. C) Comparison of nitrile to thiol ratio demonstrates incomplete bond formation and reversibility. K_{eq} measurements at tested concentrations of $[\text{CN}]/[\text{SH}]$ of 1, 2, 4, 8, and 16.

[0019] Figures 4A-4B show that ^{13}C and ^1H NMR validate thioimide formation between baricitinib and thiolated hyaluronic acid. **Fig. 4A** shows ^{13}C NMR of baricitinib, thiolated hyaluronic acid, and the product baricitinib-thiolated hyaluronic acid demonstrate the unique spectra of each individual reactant and a new peak at 170 ppm corresponding to the predicted chemical shift of the double-bonded sp^2 thioimide carbon (R—N=C(SR)R). **Fig. 4B** shows ^1H NMR of baricitinib, thiolated hyaluronic acid, and the product baricitinib-thiolated hyaluronic acid demonstrate the unique spectra of each individual reactant with distinct aromatic protons in the baricitinib-hyaluronic acid group that is chemically shifted from the aromatic protons of baricitinib alone, suggesting the presence of a modified product in solution consistent with the thioimide adduct.

[0020] Figures 5A-5C show hydrogel formation and shear oscillatory rheometry. **Fig. 5A** shows hydrogels are formed between thiolated hyaluronic acid and baricitinib, where thioimide adducts and disulfide crosslinks form simultaneously. Upon material deposition, thioimide bonds reverse

to release baricitinib into the surrounding environment. **Fig. 5B** shows shear oscillatory rheometry over 24 hours demonstrating crosslinking of polymers into hydrogels (~100 Pa) with and without baricitinib (2 mg/mL) which occur over the course of 24 hours. Frequency sweeps demonstrate classic viscoelastic behavior of materials. **Fig. 5C** shows mechanical properties of hydrogels (n=3) and baricitinib hydrogels (n=3) measured by shear oscillatory rheometry (0.5% strain, 10 Hz) demonstrate comparable properties.

[0021] **Figures 6A-6C** show baricitinib release and ultraviolet spectrometry. **Fig. 6A** shows quantification of baricitinib aromatic absorption in ultraviolet A and B range (280-400 nm) demonstrating highest absorption in the ultraviolet B range. Subsequent plotting of absorbance against dose demonstrates linear absorption at 300 nm. **Fig. 6B** shows measuring baricitinib release at 300 nm against a standard curve allows quantification of baricitinib release from hydrogel formulations. Tunable release is exhibited over the course of six weeks with release dependent on material formulation. *p<0.05 between groups at each timepoint, n=3 per group. **Fig. 6C** shows release curves for hydrogels assembled at 0.2 mg/mL or 2 mg/mL baricitinib loaded (2 wt% hydrogel, 30% thiol modification).

[0022] **Figures 7A-7E** show validation of baricitinib activity on JAK/STAT signaling using a HEK293 luciferase reporter. **Fig. 7A** shows HEK293 cell line with the firefly luciferase gene under the control of Interferon Stimulated Response Element (ISRE) where type I interferon-induced JAK/STAT signaling pathway in the target cells can be monitored by measuring luciferase activity. IFN α (EC₅₀ 15 U/mL) leads to induction of luminescence, n=3 per group. **Fig. 7B** shows that After stimulation with 100 U/mL IFN α , baricitinib leads to near complete silencing of luciferase activity, n=3 per group. **Fig. 7C** shows a schematic of experimental design demonstrating hydrogel incubation in saline with collection and replacement of releasate performed at regular intervals and then added directly to cells. **Fig. 7D** shows incubation of cells with 5 μ L releasates demonstrates sustained JAK/STAT inhibition but only from the 2 mg/mL formulation. *p<0.05 between 0.2 mg/mL and 2 mg/mL. Incubation of cells with 20 μ L of releasates demonstrates near complete inhibition of JAK/STAT signaling at all tested timepoints, n=3 per group. **Fig. 7E** shows proliferative activity after incubation with hydrogels (2 wt%, 30% thiol mod) in a transwell insert was determined in immortalized human keratinocytes (HaCaT cells) using an MTS cell proliferation assay at 24 hours, 72 hours, and 96 hours by measuring absorbance at 490 nm.

Representative images demonstrate confluent monolayers of keratinocytes at 96 hours without evidence of cytotoxicity. Scale = 1 mm, n=3 per group.

[0023] **Figures 8A-8D** show *in vivo* injections of baricitinib hydrogel in an imiquimod model of psoriasiform dermatitis. **Fig. 8A** shows four 25 uL injections of baricitinib hydrogel (n=7) or PBS, hydrogel alone, or baricitinib alone controls (n=6 per group) are injected into four spots in dorsal mouse skin. After injection, imiquimod is applied daily for five days to induce psoriasiform inflammation before sacrifice. Imiquimod treated mice are compared to mice without imiquimod (n=6). **Fig. 8B** shows images of skin changes at five days and seven days. **Fig. 8C** shows H&E sections demonstrating skin thickening in response to imiquimod application with reduced thickening seen in treatment groups at seven days. Scale = 100 μ m. **Fig. 8D** shows quantification of epidermal thickness at seven days by quantifying epidermal ROI divided by length. *p<0.05 by one-way ANOVA.

[0024] **Figure 9** shows LCMS between sulfur-containing small molecules and baricitinib. L-cysteine (122 Da), a thiol, forms a product with baricitinib (372 Da) at 494 Da, indicating formation of a thioimide. Levamisole (205 Da), a thiazole, does not form a product with baricitinib.

[0025] **Figure 10** shows ^1H NMR with shifted aromatic peaks on baricitinib. Individual aromatic protons are highlighted. Shifted protons (yellow, green, red, orange) are highlighted relative to thioimide (purple). One proton (blue) is unshifted.

[0026] **Figure 11** shows hydrogel formation and shear oscillatory rheometry frequency sweeps. Frequency sweeps (0.5% strain) between hydrogels and baricitinib hydrogels demonstrate frequency dependent properties to suggest viscoelastic behavior.

[0027] **Figure 12** shows ROI selection in FIJI accurately highlights the epidermis for quantification of total thickness.

[0028] **Figure 13** shows representative H&E images of skin sections demonstrating changes in epidermal thickness in response to baricitinib hydrogel treatments. Sections represent tissue examined directly over injection sites.

[0029] **Figures 14A-14B** shows weight loss trends in response to treatment with PBS (n=3), hydrogel (n=3), baricitinib (n=3), or baricitinib hydrogel (n=4). **Fig. 14A** shows absolute weight at five days. **Fig. 14B** shows weight loss as percentage of untreated controls that did not receive imiquimod.

[0030] **Figure 15** shows a representative section of hydrogel in subcutaneous tissue in imiquimod mouse model. Hydrogels in the dermis are typically lost in processing but can be observed in few sections in the subcutaneous space, where they are stable one week after injection.

[0031] **Figure 16** shows using ^1H NMR that an aromatic nitrile containing molecule, CHIR 99021, and thiolated hyaluronic acid react in a reversible manner to form a thioimide. The ^1H NMR data shows the formation of a new set of peaks in the aromatic region downfield from those in CHIR99021 alone. Thiolated hyaluronic acid alone shows no peaks in this region.

DETAILED DESCRIPTION OF THE INVENTION

[0032] The present subject matter may be understood more readily by reference to the following detailed description which forms a part of this disclosure. It is to be understood that this invention is not limited to the specific products, methods, conditions or parameters described and/or shown herein, and that the terminology used herein is for the purpose of describing particular embodiments by way of example only and is not intended to be limiting of the claimed invention.

[0033] The small size and rapid diffusion of small molecules such as JAK inhibitors not only render their delivery from hydrogels difficult but also limit their ability to attain longer-term release profiles. These drawbacks necessitate recurring topical or injectable administrations of the small molecules, thus constraining patient use and clinical application.

[0034] Nitriles react with thiols to form thioimide adducts, which possess reversible and dynamic S-C covalent bonds that form through a Pinner-like mechanism between a thiol nucleophile and an electrophilic carbon of a nitrile group. The thioimide can be further stabilized through other mechanisms. This was first demonstrated through a reversible interaction between benzoylamidoacetonitrile and a cysteine of papain, a papaya cysteine protease; yet, it is now widely accepted that thioimides form under a range of conditions and also with aliphatic nitriles, where nitrile groups are frequently employed as reversible inhibitors of cysteine proteases (e.g., Cathepsin C inhibitors) to form thioimides. However, the biologic function of the nitrile group is unknown and is not well understood.

[0035] Based on this body of research, a hydrogel comprising a small molecule drug having an electrophilic aliphatic nitrile to reversibly conjugate a nucleophilic thiol of a thiolated polymer as a thioimide adduct was sought to achieve a pharmacologic goal of a slow drug release over a period of about 12 weeks to treat various dermatologic indications. Previously formulated hydrogels comprising small molecules demonstrated a rapid release of the small molecules from

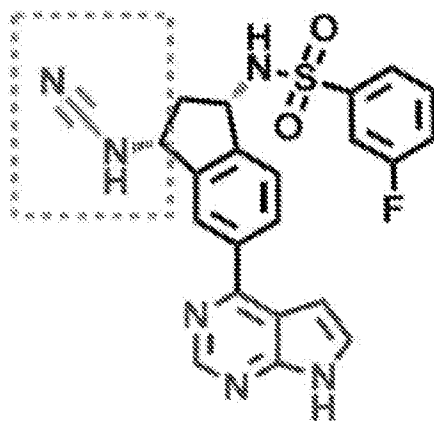
the hydrogels during four to six weeks. A 12-week release period would enable a patient to make quarterly visits for routine intradermal or subcutaneous injections of the small molecule-containing thiolated hydrogels under already well-established and well-accepted protocols that are used, for example, for hydrogel dermal filler treatments, and avoid systemic exposure to the small molecule.

[0036] An aliphatic nitrile that is present on numerous clinically approved JAK inhibitors was identified as a potential reactive electrophile that can be leveraged to reversibly and covalently bind the drug, i.e., the JAK inhibitor, within a thiolated hydrogel for controlled and tunable release for local delivery, e.g., in the skin or a joint.

[0037] The sustained release of JAK inhibitors from hydrogels that present thiols to form thioimide bonds with aliphatic nitriles of JAK inhibitors was pursued to leverage the dynamic and reversible bonds that are needed to bind and then later release drugs in unmodified forms. To this end, an injectable JAK inhibitor eluting hyaluronic acid hydrogel with a high degree of thiol modification was engineered. In this system, thiols on a thiolated polymer, such as hyaluronic acid, are available to (i) bind a nitrile-containing JAK inhibitor, such as baricitinib, which is a representative JAK1/2 inhibitor, and (ii) react with themselves to form disulfide crosslinks to form a hydrogel. Hyaluronic acid, which is a naturally occurring glycosaminoglycan that is biocompatible, widely investigated for drug delivery applications, and already used in dermal injectables clinically, was selected. However, any thiol-containing polymer may be used according to the present invention. Using rational design, the formation of thioimides with baricitinib was investigated and tuned baricitinib release from thiolated hydrogels was demonstrated, as described in **Example 1**, the JAK inhibitor drug-hydrogel material for JAK-STAT inhibition *in vitro* was tested, as described in **Example 2**, and an injectable therapeutic comprising a JAK inhibitor hydrogel was tested *in vivo* in a mouse model of psoriasis, as described in **Example 3**.

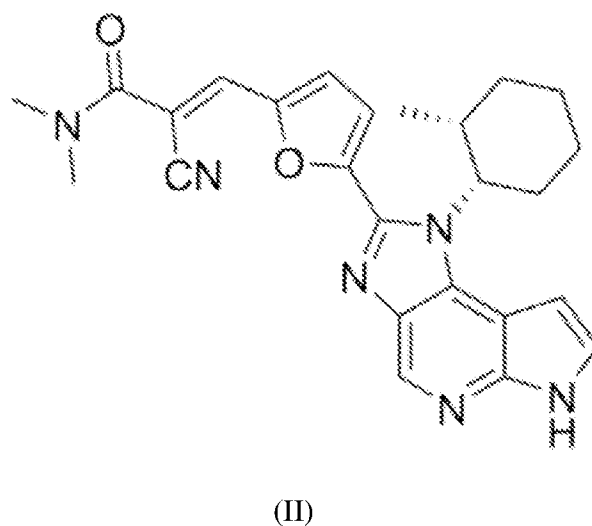
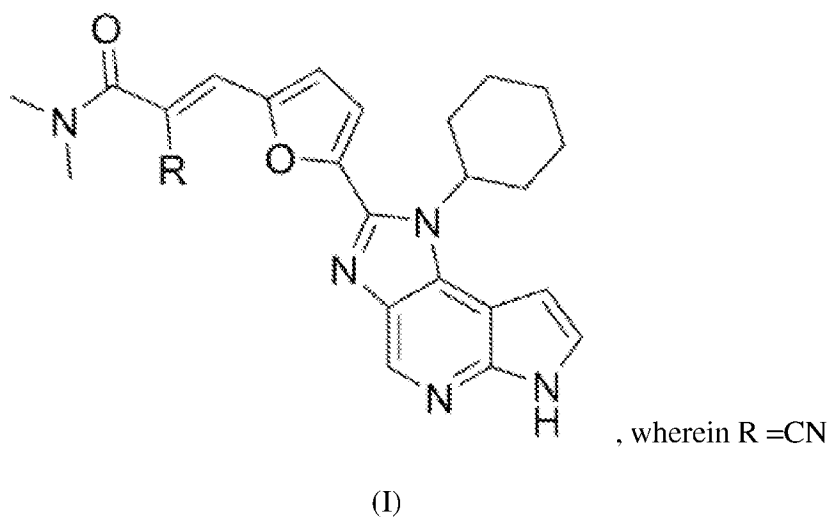
[0038] In one aspect, the invention provides sustained delivery JAK inhibitor hydrogels for treatment of an inflammatory disorder, an autoimmune disease, an autoimmune and inflammatory hair loss, and/or a non-inflammatory disorder hair loss, the JAK inhibitor hydrogel comprising a JAK inhibitor having a nitrile group reversibly conjugated to a thiol group of a thiolated polymer to form a thioimide adduct. In an embodiment of the sustained delivery JAK inhibitor hydrogel, the thiolated polymer is a thiolated hyaluronic acid, a thiolated chitosan, a thiolated cyclodextrin, a thiolated poly(ethylene glycol), a thiolated polyvinyl alcohol, a thiolated polyacrylamide, a thiolated polyethylene oxide, a thiolated polymethacrylate, a thiolated dextran, a thiolated alginate,

a thiolated cellulose, a thiolated gelatin, a thiolated collagen, a thiolated silk, a thiolated keratin or a thiolated elastin. In some embodiments, the thiolated polymer is a thiolated hyaluronic acid. In various embodiments, the thiolated hyaluronic acid has an average molecular weight of from 1 KD to 1,000,000 KD when the hyaluronic acid is polydispersed in solution. In an embodiment of the sustained delivery JAK inhibitor hydrogel, the thiolated hyaluronic acid has an average molecular weight of from 10,000 KD to 1,000,000 KD when the hyaluronic acid is polydispersed in solution. In a particular embodiment, the thiolated hyaluronic acid has an average molecular weight of 100,000 KD when the hyaluronic acid is polydispersed in solution. In an embodiment of the sustained delivery JAK inhibitor hydrogel, the nitrile-containing JAK inhibitor is baricitinib, delgocitinib, ruxolitinib, deuruxolitinib, tofacitinib, momelotinib, gusacitinib, itacitinib, izencitinib, lorpucitinib, povorcitinib or a nitrile-containing metabolite thereof. In some embodiments, the nitrile-containing JAK inhibitor is a compound having chemical structure (A):



(A)

[0039] In another embodiment, the nitrile-containing JAK inhibitor is a compound having structure (I) or (II):

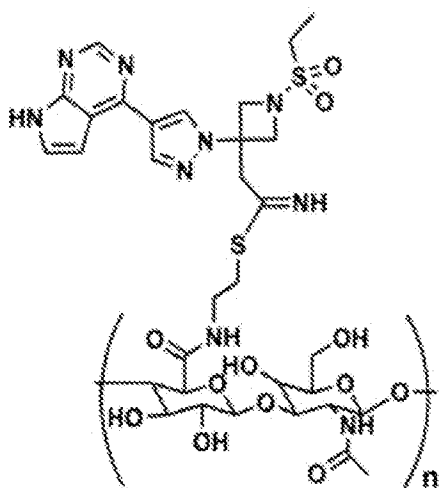


[0040] In certain embodiments of the sustained delivery JAK inhibitor hydrogel, the sustained delivery JAK inhibitor hydrogel is formulated for local administration. In some embodiments, the local administration comprises transdermal administration, intradermal injection, intramuscular injection, subcutaneous injection or intra-articular injection. In an embodiment, the local administration comprises transdermal administration. In a particular embodiment, the transdermal administration comprises transdermal delivery via microneedles coated with the JAK inhibitor, a solid polymer matrix having the JAK inhibitor incorporated therein, dissolving polymer microneedles having the JAK inhibitor incorporated therein, hydrogel-forming microneedles comprising the JAK inhibitor in the hydrogel, or a transdermal patch. In some embodiments, the inflammatory disorder is an inflammatory skin disorder. In certain embodiments, the inflammatory

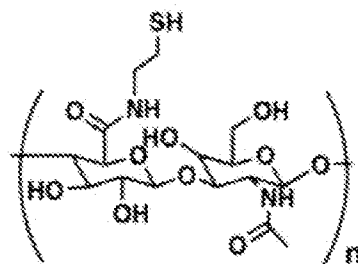
skin disorder is atopic dermatitis, cicatricial alopecia, central centrifugal cicatricial alopecia, hidradenitis suppurativa, lichen planopilaris, frontal fibrosing alopecia, alopecia areata, lichen planus, mucosal lichen planus, psoriasis, pemphigus or vitiligo. In various embodiments, the autoimmune disease is alopecia areata, persistent patchy alopecia areata, alopecia totalis, alopecia universalis, ophiasis alopecia, alopecia barbae, rheumatoid arthritis, psoriatic arthritis or reactive arthritis. In a particular embodiment, the autoimmune and inflammatory hair loss is alopecia areata. In some embodiments, the hair loss is a non-inflammatory disorder hair loss, wherein the non-inflammatory disorder hair loss is male or female androgenetic alopecia (male pattern baldness or female pattern baldness) or telogen effluvium.

[0041] In another aspect, the invention provides sustained delivery baricitinib hydrogels comprising baricitinib having a nitrile group reversibly conjugated to a thiol group of a thiolated polymer to form a thioimide adduct for treatment of an inflammatory disorder, an autoimmune disease, an autoimmune and inflammatory hair loss, and/or a non-inflammatory disorder hair loss. In an embodiment of the sustained delivery baricitinib hydrogel, the thiolated polymer is a thiolated hyaluronic acid, a thiolated chitosan, a thiolated cyclodextrin, a thiolated poly(ethylene glycol), a thiolated polyvinyl alcohol, a thiolated polyacrylamide, a thiolated polyethylene oxide, a thiolated polymethacrylate, a thiolated dextran, a thiolated alginate, a thiolated cellulose, a thiolated gelatin, a thiolated collagen, a thiolated silk, a thiolated keratin or a thiolated elastin. In some embodiments, the thiolated polymer is a thiolated hyaluronic acid. In an embodiment, the thiolated hyaluronic acid has an average molecular weight of from 1 KD to 1,000,000 KD when the hyaluronic acid is polydispersed in solution. In some embodiments, the thiolated hyaluronic acid has an average molecular weight of from 10,000 KD to 1,000,000 KD when the hyaluronic acid is polydispersed in solution. In a particular embodiment, the thiolated hyaluronic acid has an average molecular weight of 100,000 KD when the hyaluronic acid is polydispersed in solution. In some embodiments, the sustained delivery baricitinib hydrogel is formulated for local administration, wherein the local administration comprises intradermal injection, intramuscular injection, subcutaneous injection or intra-articular injection. In an embodiment, the local administration comprises transdermal administration. In various embodiments, the inflammatory disorder is an inflammatory skin disorder. In a particular embodiment, the inflammatory skin disorder is atopic dermatitis, cicatricial alopecia, central centrifugal cicatricial alopecia, hidradenitis suppurativa, lichen planopilaris, frontal fibrosing alopecia, alopecia areata, lichen

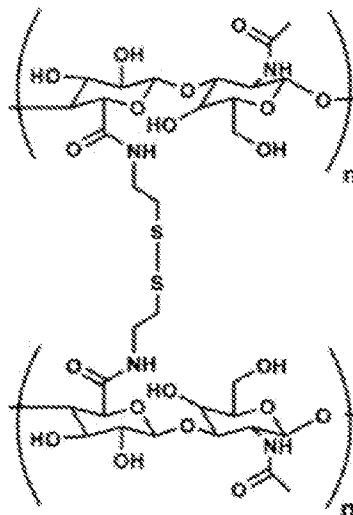
planus, mucosal lichen planus, psoriasis, pemphigus or vitiligo. In some embodiments, the autoimmune disease is alopecia areata, persistent patchy alopecia areata, alopecia totalis, alopecia universalis, ophiasis alopecia, alopecia barbae, rheumatoid arthritis, psoriatic arthritis or reactive arthritis. In some embodiments, the autoimmune and inflammatory hair loss is alopecia areata. In certain embodiments, the hair loss is a non-inflammatory disorder hair loss, wherein the non-inflammatory disorder hair loss is male or female androgenetic alopecia (male pattern baldness or female pattern baldness) or telogen effluvium. In an embodiment, the sustained delivery baricitinib hydrogel comprises chemical substructures (a) together with (b) and (c):



(a)

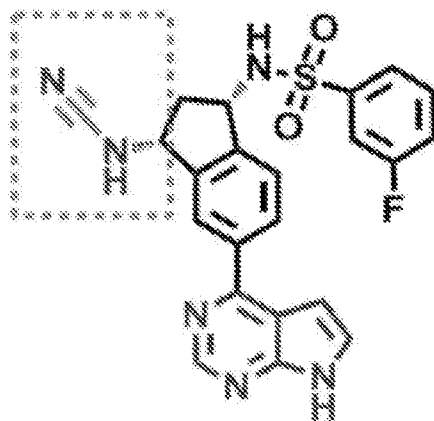


(b)



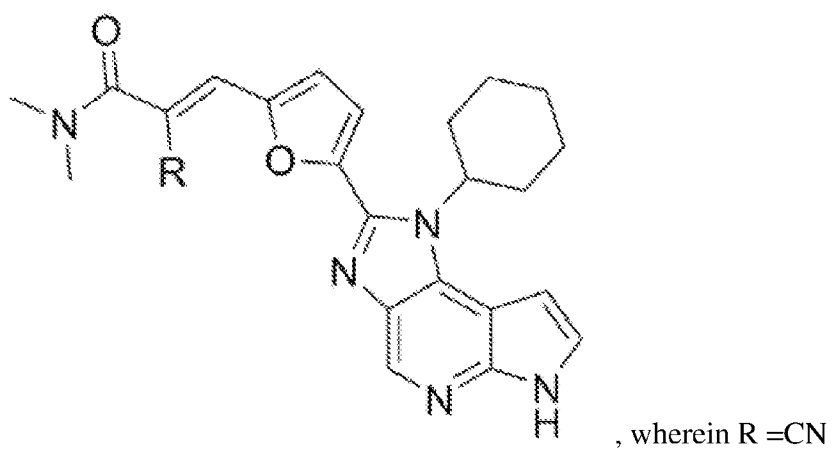
(c).

[0042] In one aspect, the invention provides injectable pharmaceutical compositions for treatment of an inflammatory disorder, an autoimmune disease, an autoimmune and inflammatory hair loss, and/or a non-inflammatory disorder hair loss, the injectable pharmaceutical composition comprising a nitrile-containing JAK inhibitor and a pharmaceutically acceptable carrier. In particular embodiments of the injectable pharmaceutical composition, the nitrile-containing JAK inhibitor JAK inhibitor is baricitinib, delgocitinib, ruxolitinib, deuruxolitinib, tofacitinib, momelotinib, gusacitinib, itacitinib, izencitinib, lorpucitinib, povorcitinib or a nitrile-containing metabolite thereof. In an embodiment, the nitrile-containing JAK inhibitor is a compound having chemical structure (A):

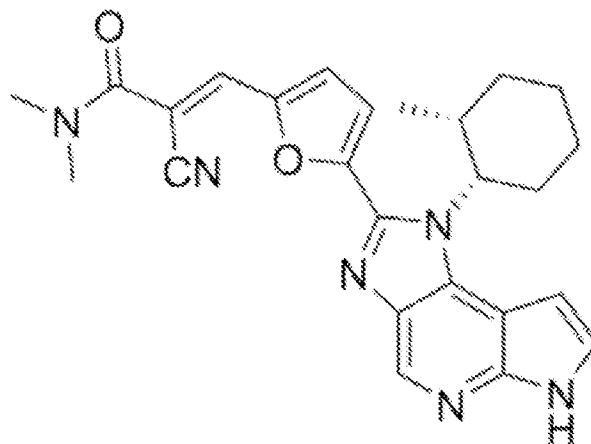


(A)

[0043] In some embodiments of the injectable pharmaceutical composition, the nitrile-containing JAK inhibitor is a compound having structure (I) or (II):



(I)



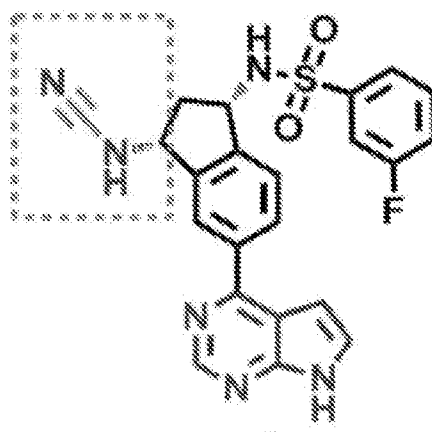
(II).

[0044] In an embodiment of the injectable pharmaceutical composition, the pharmaceutical composition is formulated for local administration. In another embodiment, the local administration comprises intradermal injection, intramuscular injection, subcutaneous injection or intra-articular injection. In an embodiment, the local administration comprises transdermal administration. In an embodiment, the injectable pharmaceutical composition is administered with hollow microneedles that allow delivery of the injectable pharmaceutical composition comprising the therapeutic agent (the JAK inhibitor) in a upon application of pressure. In a particular embodiment of the injectable pharmaceutical composition, the transdermal administration comprises transdermal delivery via microneedles coated with the JAK inhibitor, a solid polymer matrix having the JAK inhibitor incorporated therein, dissolving polymer microneedles having the JAK inhibitor incorporated therein, hydrogel-forming microneedles comprising the JAK inhibitor in the hydrogel, or a transdermal patch. In some embodiments, the local administration comprises intradermal injection, intramuscular injection, subcutaneous injection, or intra-articular injection. In an embodiment, the local administration comprises transdermal administration. In a particular embodiment, the inflammatory disorder is an inflammatory skin disorder. In certain embodiments of the injectable pharmaceutical composition, the inflammatory skin disorder is atopic dermatitis, cicatricial alopecia, central centrifugal cicatricial alopecia, hidradenitis suppurativa, lichen planopilaris, frontal fibrosing alopecia, alopecia areata, lichen planus, mucosal lichen planus, psoriasis, pemphigus or vitiligo. In some embodiments, the autoimmune disease is alopecia areata, persistent patchy alopecia areata, alopecia totalis, alopecia universalis, ophiasis alopecia, alopecia barbae, rheumatoid arthritis, psoriatic arthritis or reactive arthritis. In an embodiment of the

injectable pharmaceutical composition, the autoimmune and inflammatory hair loss is alopecia areata. In another embodiment of the injectable pharmaceutical composition, the hair loss is a non-inflammatory disorder hair loss, wherein the non-inflammatory disorder hair loss is male or female androgenetic alopecia (male pattern baldness or female pattern baldness) or telogen effluvium.

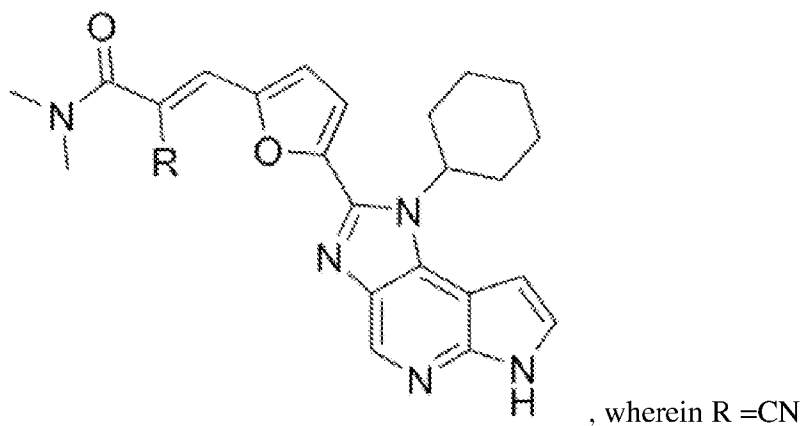
[0045] In another aspect, the invention provides methods for treating an inflammatory disorder, an autoimmune disease, an autoimmune and inflammatory hair loss, and/or a non-inflammatory disorder hair loss in a subject in need thereof, the method comprising administering a sustained delivery nitrile-containing JAK inhibitor hydrogel to a body part of the subject affected by the inflammatory disorder, the autoimmune disease, the autoimmune and inflammatory hair loss, and/or the non-inflammatory disorder hair loss, wherein the JAK inhibitor hydrogel comprises a JAK inhibitor having a nitrile group reversibly conjugated to a thiol group of a thiolated polymer to form a thioimide adduct. In an embodiment of said method, the thiolated polymer is a thiolated hyaluronic acid, a thiolated chitosan, a thiolated cyclodextrin, a thiolated poly(ethylene glycol), a thiolated polyvinyl alcohol, a thiolated polyacrylamide, a thiolated polyethylene oxide, a thiolated polymethacrylate, a thiolated dextran, a thiolated alginate, a thiolated cellulose, a thiolated gelatin, a thiolated collagen, a thiolated silk, a thiolated keratin or a thiolated elastin. In particular embodiments, the thiolated polymer is a thiolated hyaluronic acid. In an embodiment, the thiolated hyaluronic acid has an average molecular weight of from 1 KD to 1,000,000 KD when the hyaluronic acid is polydispersed in solution. In some embodiments, the thiolated hyaluronic acid has an average molecular weight of from 10,000 KD to 1,000,000 KD when the hyaluronic acid is polydispersed in solution. In a particular embodiment, the thiolated hyaluronic acid has an average molecular weight of 100,000 KD when the hyaluronic acid is polydispersed in solution. In some embodiments of said methods, only a single dose of the hydrogel is administered. In some embodiments of said methods, multiple doses (for example, two, three, four or more doses) of the hydrogel are administered (for example, weekly or monthly). In an embodiment, the nitrile-containing JAK inhibitor hydrogel is formulated for local administration. In some embodiments, the local administration comprises intradermal injection, intramuscular injection, subcutaneous injection or intra-articular injection. In an embodiment, the local administration comprises transdermal administration. In certain embodiments of said methods, the transdermal administration comprises transdermal delivery via microneedles coated with the JAK inhibitor, a solid polymer matrix having the JAK inhibitor incorporated therein, dissolving polymer

microneedles having the JAK inhibitor incorporated therein, hydrogel-forming microneedles comprising the JAK inhibitor in the hydrogel, or a transdermal patch. In some embodiments, the local administration comprises transdermal injection, intradermal injection intramuscular injection, or intra-articular injection. In an embodiment, the inflammatory disorder is an inflammatory skin disorder. In various embodiments, the inflammatory skin disorder is atopic dermatitis, cicatricial alopecia, central centrifugal cicatricial alopecia, hidradenitis suppurativa, lichen planopilaris, frontal fibrosing alopecia, alopecia areata, lichen planus, mucosal lichen planus, psoriasis, pemphigus or vitiligo. In certain embodiments, the autoimmune disease is alopecia areata, persistent patchy alopecia areata, alopecia totalis, alopecia universalis, ophiasis alopecia, alopecia barbae, rheumatoid arthritis, psoriatic arthritis or reactive arthritis. In a particular embodiment, the autoimmune and inflammatory hair loss is alopecia areata. In some embodiments of said methods, the hair loss is a non-inflammatory disorder hair loss, wherein the non-inflammatory disorder hair loss is male or female androgenetic alopecia (male pattern baldness or female pattern baldness) or telogen effluvium. In a particular embodiment of said methods, the nitrile-containing JAK inhibitor is baricitinib, delgocitinib, ruxolitinib, deuruxolitinib, tofacitinib, momelotinib, gusacitinib, itacitinib, izencitinib, lorpucitinib, povorcitinib or a nitrile-containing metabolite thereof. In some embodiments of said methods, the nitrile-containing JAK inhibitor is a compound having chemical structure (A):

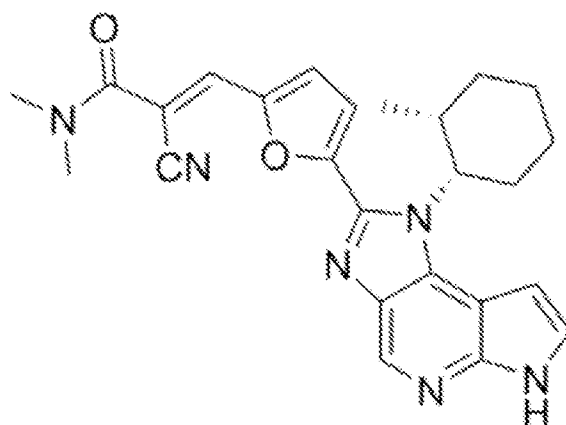


(A)

[0046] In an embodiment of said methods, wherein the nitrile-containing JAK inhibitor is a compound having structure (I) or (II):



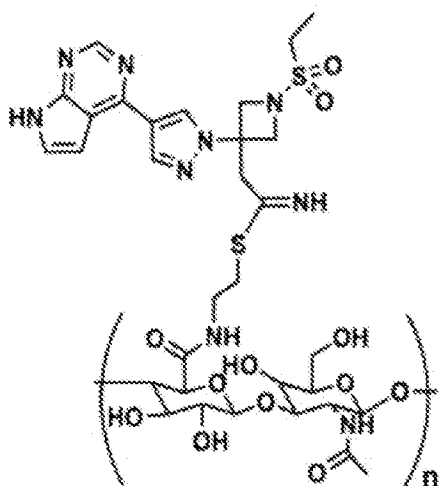
(I)



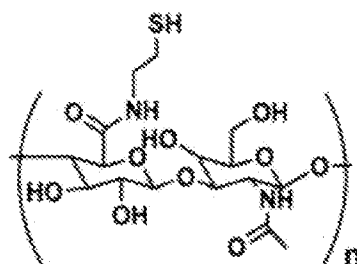
(II)

[0047] In still another aspect, the invention provides methods for treating an inflammatory disorder, an autoimmune disease, an autoimmune and inflammatory hair loss, and/or a non-inflammatory disorder hair loss in a subject in need thereof, the method comprising administering a sustained delivery baricitinib hydrogel to a body part of the subject affected by the inflammatory disorder, autoimmune disease, the autoimmune and inflammatory hair loss, and/or the non-inflammatory disorder hair loss, wherein the sustained delivery baricitinib hydrogel comprises baricitinib reversibly conjugated at a nitrile group to a thiol group of a thiolated polymer to form a thioimide adduct. In some embodiments of said method, the thiolated polymer is a thiolated hyaluronic acid, a thiolated chitosan, a thiolated cyclodextrin, a thiolated poly(ethylene glycol), a

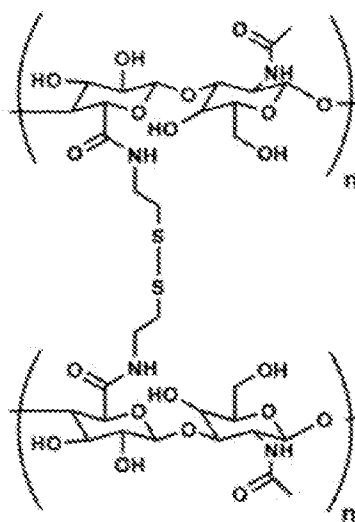
thiolated polyvinyl alcohol, a thiolated polyacrylamide, a thiolated polyethylene oxide, a thiolated polymethacrylate, a thiolated dextran, a thiolated alginate, a thiolated cellulose, a thiolated gelatin, a thiolated collagen, a thiolated silk, a thiolated keratin or a thiolated elastin. In a particular embodiment, the thiolated polymer is a thiolated hyaluronic acid. In various embodiments, the thiolated hyaluronic acid has an average molecular weight of from 1 KD to 1,000,000 KD when the hyaluronic acid is polydispersed in solution. In certain embodiments of said methods, the thiolated hyaluronic acid has an average molecular weight of from 10,000 KD to 1,000,000 KD when the hyaluronic acid is polydispersed in solution. In particular embodiments of said methods, the thiolated hyaluronic acid has an average molecular weight of 100,000 KD when the hyaluronic acid is polydispersed in solution. In some embodiments, the sustained delivery baricitinib hydrogel is formulated for local administration, wherein the local administration comprises intradermal injection, intramuscular injection, subcutaneous injection or intra-articular injection. In an embodiment, the local administration comprises transdermal administration. In an embodiment, the inflammatory disorder is an inflammatory skin disorder. In some embodiments of said methods, the inflammatory skin disorder is atopic dermatitis, cicatricial alopecia, central centrifugal cicatricial alopecia, hidradenitis suppurativa, lichen planopilaris, frontal fibrosing alopecia, alopecia areata, lichen planus, mucosal lichen planus, psoriasis, pemphigus or vitiligo. In various embodiments, the autoimmune disease is alopecia areata, persistent patchy alopecia areata, alopecia totalis, alopecia universalis, ophiasis alopecia, alopecia barbae, rheumatoid arthritis, psoriatic arthritis or reactive arthritis. In an embodiment, the autoimmune and inflammatory hair loss is alopecia areata. In some embodiments of said methods, the hair loss is a non-inflammatory disorder hair loss, wherein the non-inflammatory disorder hair loss is male or female androgenetic alopecia (male pattern baldness or female pattern baldness), or telogen effluvium. In an embodiment, the sustained delivery baricitinib hydrogel comprises chemical substructures (a), (b) and (c):



(a)

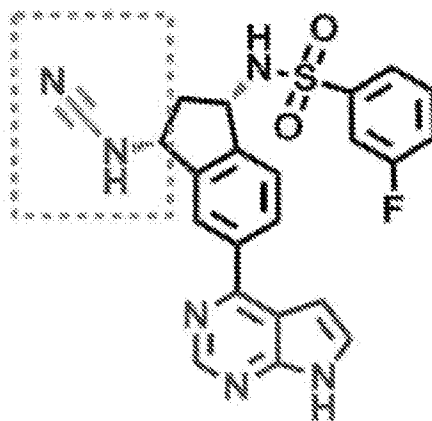


(b)



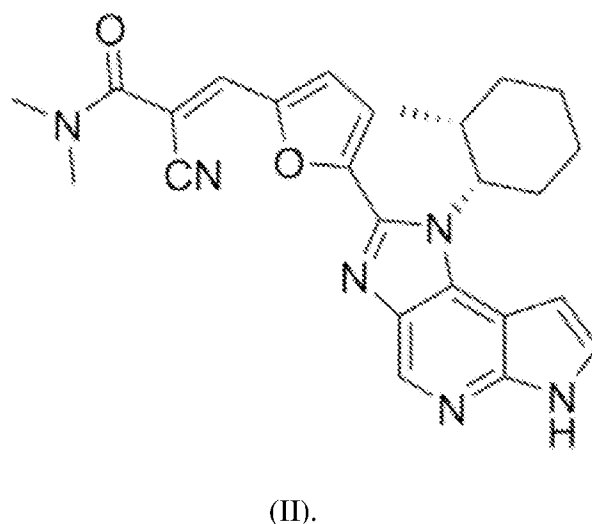
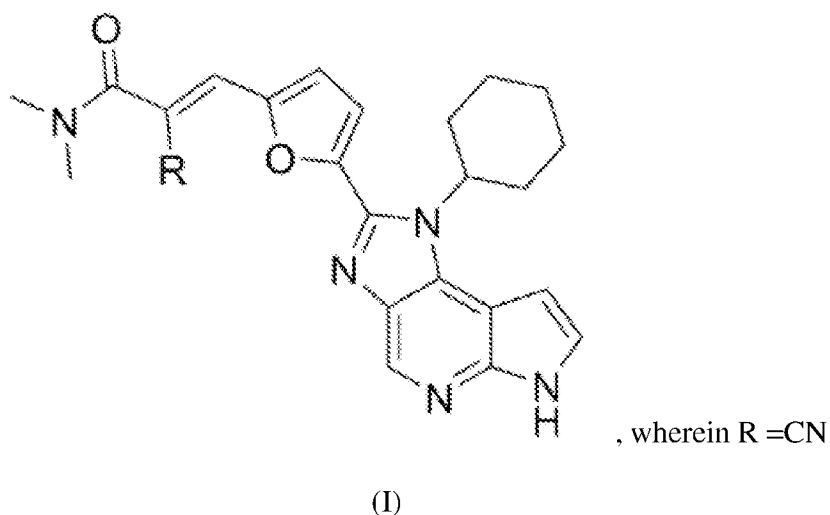
(c).

[0048] In one aspect, the invention provides methods for treating an inflammatory disorder, an autoimmune disease, an autoimmune and inflammatory hair loss, and/or a non-inflammatory disorder hair loss in a subject in need thereof, the method comprising administering an injectable pharmaceutical composition to a body part of the subject affected by the inflammatory disorder, the autoimmune disease, the autoimmune and inflammatory hair loss, and/or the non-inflammatory disorder hair loss, wherein the injectable pharmaceutical composition comprises a nitrile-containing JAK inhibitor and a pharmaceutically acceptable carrier. In a particular embodiment of said method, the nitrile-containing JAK inhibitor JAK inhibitor is baricitinib, delgocitinib, ruxolitinib, deuruxolitinib, tofacitinib, momelotinib, gusacitinib, itacitinib, izencitinib, lorpucitinib, povorcitinib or a nitrile-containing metabolite thereof. In an embodiment, the nitrile-containing JAK inhibitor JAK inhibitor is a compound having chemical structure (A):



(A)

[0049] In some embodiments of said methods, the nitrile-containing JAK inhibitor is a compound having structure (I) or (II):

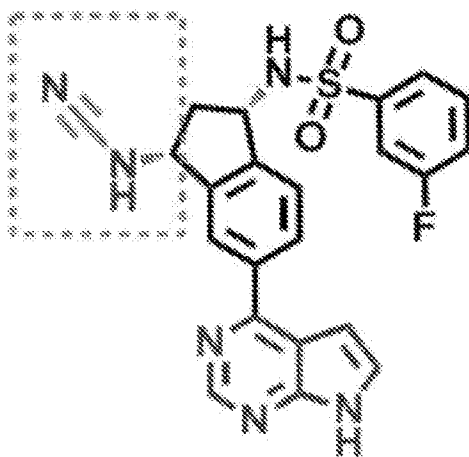


[0050] In an embodiment of said methods, the injectable pharmaceutical composition is formulated for local administration. In some embodiments, the local administration comprises intradermal injection, intramuscular injection, subcutaneous injection or intra-articular injection. In an embodiment, the local administration comprises transdermal administration. In an embodiment, the injectable pharmaceutical composition is administered with hollow microneedles that allow delivery of a therapeutic agent (the JAK inhibitor) upon application of pressure. In particular embodiments of said methods, the transdermal administration comprises transdermal delivery via microneedles coated with the JAK inhibitor, a solid polymer matrix having the JAK inhibitor incorporated therein, dissolving polymer microneedles having the JAK inhibitor incorporated therein, hydrogel-forming microneedles comprising the JAK inhibitor in the

hydrogel, or a transdermal patch. In some embodiments, the local administration comprises intradermal injection, intramuscular injection, or intra-articular injection. In an embodiment, the inflammatory disorder is an inflammatory skin disorder. In an embodiment, the local administration comprises transdermal injection. In a particular embodiment, the inflammatory skin disorder is atopic dermatitis, cicatricial alopecia, central centrifugal cicatricial alopecia, hidradenitis suppurativa, lichen planopilaris, frontal fibrosing alopecia, alopecia areata, lichen planus, mucosal lichen planus, psoriasis, pemphigus or vitiligo. In some embodiments, the autoimmune disease is alopecia areata, persistent patchy alopecia areata, alopecia totalis, alopecia universalis, ophiasis alopecia, alopecia barbae, rheumatoid arthritis, psoriatic arthritis or reactive arthritis. In a particular embodiment, the autoimmune and inflammatory hair loss is alopecia areata. In certain embodiments of said methods, the hair loss is a non-inflammatory disorder hair loss, wherein the non-inflammatory disorder hair loss is male or female androgenetic alopecia (male pattern baldness or female pattern baldness) or telogen effluvium.

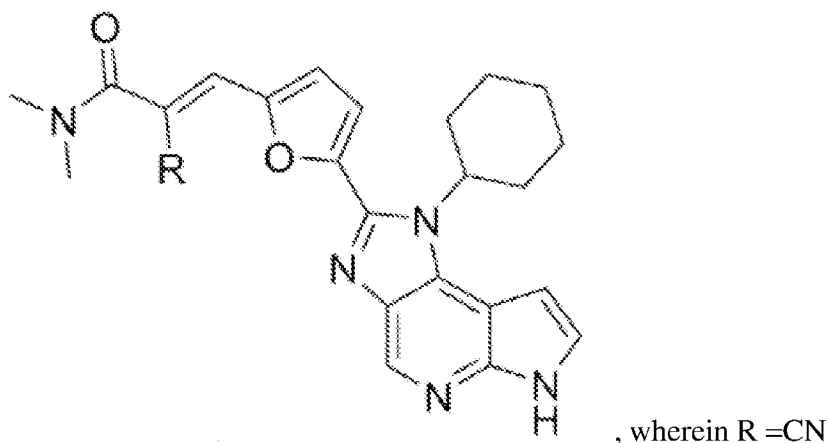
[0051] In another aspect, the invention provides methods for producing a sustained delivery JAK inhibitor hydrogel for treatment of an inflammatory disorder, an autoimmune disease, an autoimmune and inflammatory hair loss, and/or a non-inflammatory disorder hair loss in a subject in need thereof, wherein the JAK inhibitor hydrogel comprises a nitrile-containing JAK inhibitor and the nitrile group is reversibly conjugated to a thiol group of a thiolated polymer to form a thioimide adduct, the method comprising: (a) mixing a thiolated polymer with the nitrile-containing JAK inhibitor having a nitrile group to a desired weight percent concentration (w/v) of from 0.5 to 10 wt.% for 24 hours to form a crosslinked JAK inhibitor hydrogel, wherein the thiolated polymer and the JAK inhibitor are each dissolved in a respective solvent; (b) centrifuging the crosslinked JAK inhibitor hydrogel; and (c) washing the centrifuged crosslinked JAK inhibitor hydrogel to remove the solvent. In an embodiment of said method, the thiolated polymer is a thiolated hyaluronic acid, a thiolated chitosan, a thiolated cyclodextrin, a thiolated poly(ethylene glycol), a thiolated polyvinyl alcohol, a thiolated polyacrylamide, a thiolated polyethylene oxide, a thiolated polymethacrylate, a thiolated dextran, a thiolated alginate, a thiolated cellulose, a thiolated gelatin, a thiolated collagen, a thiolated silk, a thiolated keratin or a thiolated elastin. In a particular embodiment, the thiolated polymer is a thiolated hyaluronic acid. In some embodiments of said methods, the thiolated hyaluronic acid has an average molecular weight of from 1 KD to 1,000,000 KD when polydispersed in solution. In an embodiment, the thiolated

hyaluronic acid has an average molecular weight of from 10,000 KD to 1,000,000 KD when polydispersed in solution. In certain embodiments, the thiolated hyaluronic acid has an average molecular weight of 100,000 KD when polydispersed in solution. In a particular embodiment of said methods, the nitrile-containing JAK inhibitor is baricitinib, delgocitinib, ruxolitinib, deuruxolitinib, tofacitinib, momelotinib, gusacitinib, itacitinib, izencitinib, lorpucitinib, povorcitinib or a nitrile-containing metabolite thereof. In an embodiment, the nitrile-containing JAK inhibitor is a compound having chemical structure (A):

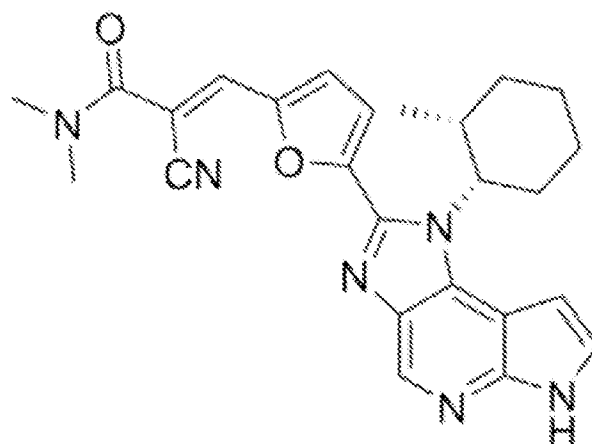


(A)

[0052] In another embodiment of said methods, the nitrile-containing JAK inhibitor is a compound having structure (I) or (II):



(I)



(II).

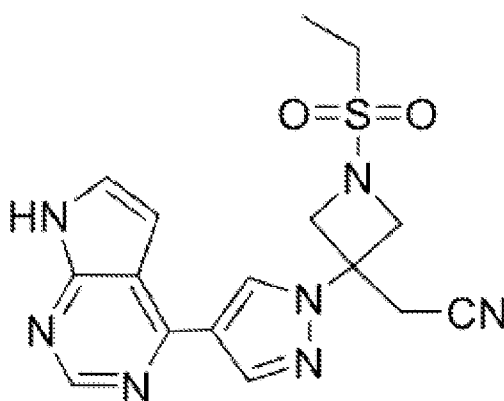
[0053] In some embodiments, the method further comprises formulating the sustained delivery JAK inhibitor hydrogel for local administration. In an embodiment, the local administration comprises intradermal injection, intramuscular injection, subcutaneous injection or intra-articular injection. In an embodiment, the local administration comprises transdermal administration. In certain embodiments, the transdermal administration comprises transdermal delivery via microneedles coated with the JAK inhibitor, a solid polymer matrix having the JAK inhibitor incorporated therein, dissolving polymer microneedles having the JAK inhibitor incorporated therein, hydrogel-forming microneedles comprising the JAK inhibitor in the hydrogel, or a transdermal patch. In various embodiments, the local administration comprises intradermal injection, intramuscular injection, or intra-articular injection. In an embodiment, the local administration comprises transdermal administration. In some embodiments of said methods, the inflammatory disorder is an inflammatory skin disorder. In a particular embodiments, the inflammatory skin disorder is atopic dermatitis, cicatricial alopecia, central centrifugal cicatricial alopecia, hidradenitis suppurativa, lichen planopilaris, frontal fibrosing alopecia, alopecia areata, lichen planus, mucosal lichen planus, psoriasis, pemphigus or vitiligo. In certain embodiments, the autoimmune disease is alopecia areata, persistent patchy alopecia areata, alopecia totalis, alopecia universalis, ophiasis alopecia, alopecia barbae, rheumatoid arthritis, psoriatic arthritis or reactive arthritis. In an embodiment, the autoimmune and inflammatory hair loss is alopecia areata. In some embodiments, the hair loss is a non-inflammatory disorder hair loss, wherein the non-inflammatory

disorder hair loss is male or female androgenetic alopecia (male pattern baldness or female pattern baldness) or telogen effluvium.

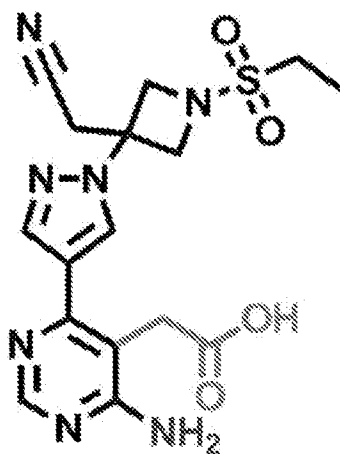
Nitrile-Containing JAK Inhibitors

[0054] The JAK inhibitors according to embodiments of the present invention may be any JAK inhibitors having a nitrile group that is capable of being reversibly conjugated to a thiol group of any thiolated polymer to form a thioimide adduct, thereby forming an administrable JAK inhibitor hydrogel or the nitrile-containing JAK inhibitor may be administered as an injectable pharmaceutical composition in the absence of conjugation to a thiolated polymer. Nitrile-containing JAK inhibitors that are capable of being reversibly conjugated to a thiol group of a thiolated hyaluronic acid to form a thioimide adduct that are amenable for sustained delivery in hydrogel according to embodiments of the invention include, but are not limited to, baricitinib, delgocitinib, ruxolitinib, deuruxolitinib, tofacitinib, momelotinib, gusacitinib, itacitinib, izencitinib, lorpucitinib, povorcitinib and nitrile-containing metabolites or derivatives thereof.

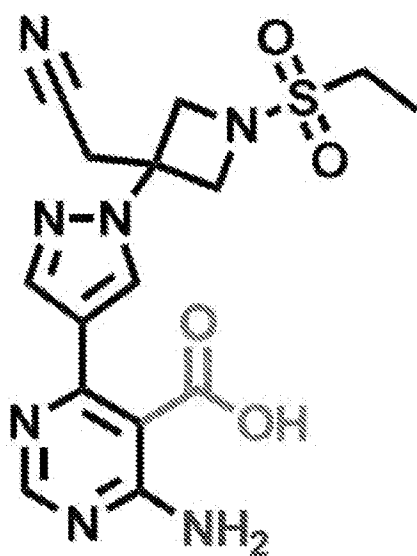
[0055] Baricitinib has the following chemical structure:



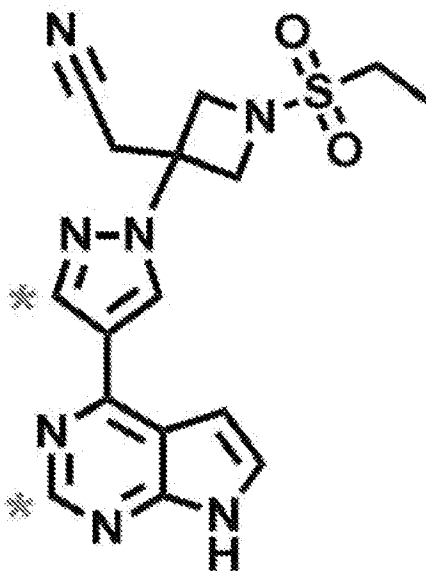
[0056] In an embodiment, a nitrile-containing metabolite compound of baricitinib has the following structures, M3, M12, M10 or M22, as shown in Shawky A.M., et al. *Pharmaceutics*, 2022, 14(5): 1001, which is incorporated herein in its entirety:



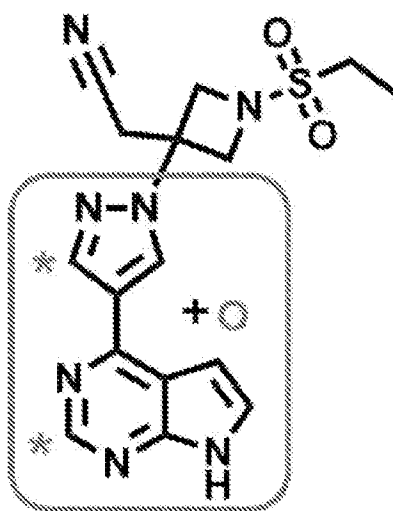
M3



M12,



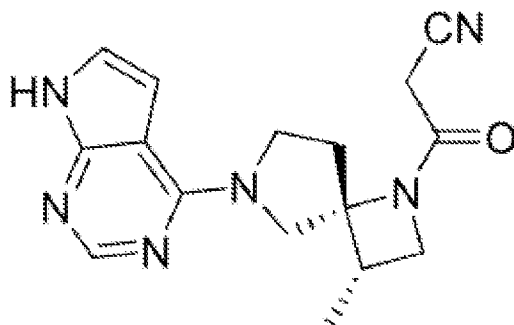
M10 or



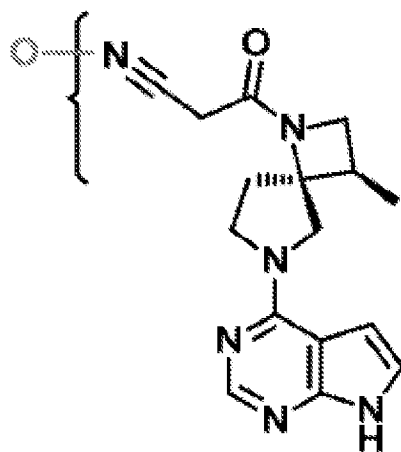
M22.

[0057] These nitrile- and nitrile oxide-containing metabolite compounds of baricitinib reversibly may be conjugated to a thiol group of a thiolated polymer, such as hyaluronic acid or other thiolated polymers, as described herein, to form a thioimide adduct or thioimide oxide adduct for the treatment of the diseases and disorders described herein.

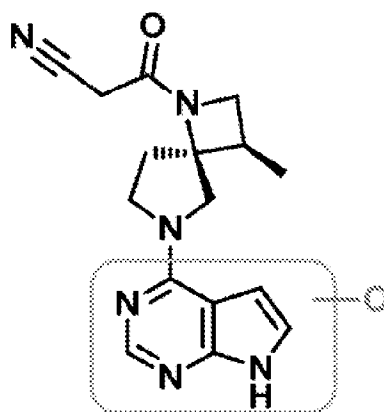
[0058] Delgocitinib has the following chemical structure:



[0059] In an embodiment, a nitrile-containing metabolite compound of delgocitinib has the following structures, M1, M2 and M3, as shown in Shawky A.M., et al. Pharmaceutics, 2022, 14(5): 1001, which is incorporated herein in its entirety:



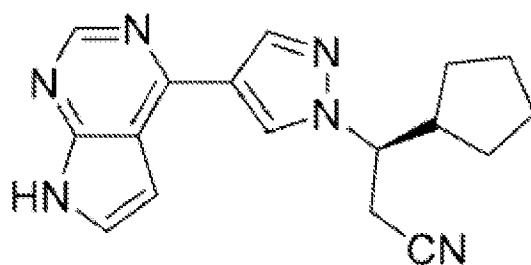
M1



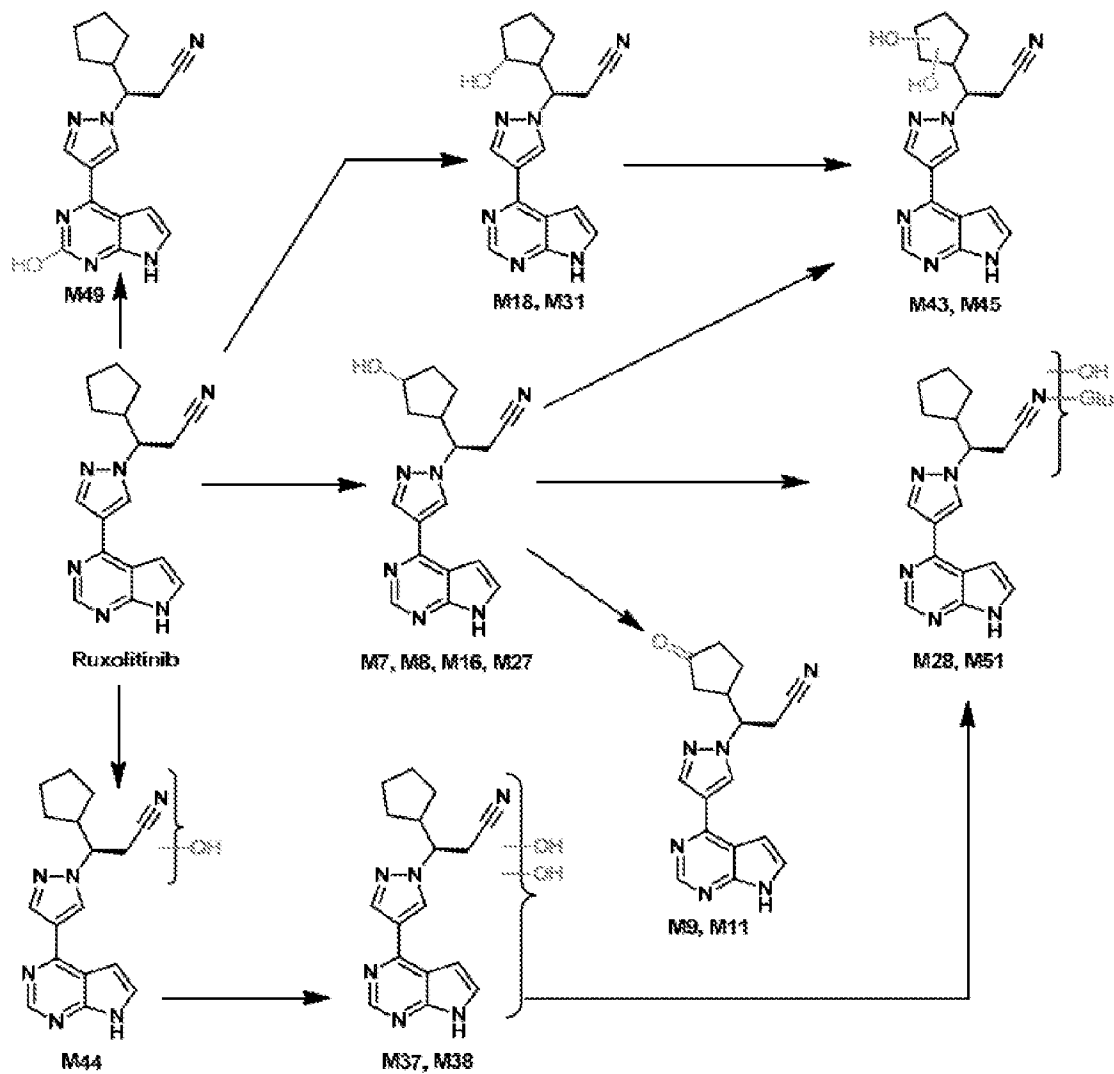
M2 and M3

[0060] These nitrile-containing metabolite compounds of delgocitinib may be reversibly conjugated to a thiol group of a thiolated polymer, such as hyaluronic acid or other thiolated polymers, as described herein, to form a thioimide adduct for the treatment of the diseases and disorders described herein.

[0061] Ruxolitinib has the following chemical structure:

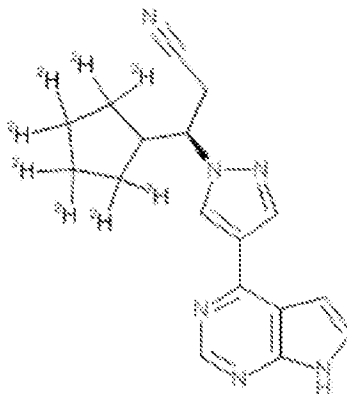


[0062] In an embodiment, a nitrile-containing metabolite compound of ruxolitinib has the following structures, M49, M18/M31, M43/M45, M7/M8/M16/M27, M44/M37/M38 and M28/M51, M44, M9/M11, and M37/M38, as shown in Shawky A.M., et al. *Pharmaceutics*, 2022, 14(5): 1001, which is incorporated herein in its entirety:

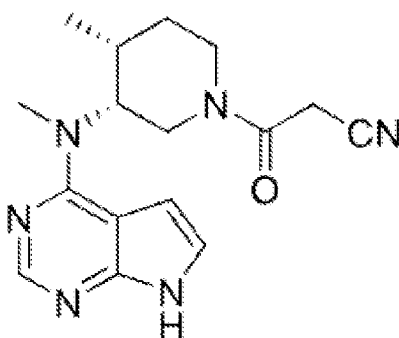


[0063] These nitrile-containing metabolite compounds of ruxolitinib may be reversibly conjugated to a thiol group of a thiolated polymer, such as hyaluronic acid or other thiolated polymers, as described herein, to form a thioimide adduct for the treatment of the diseases and disorders described herein.

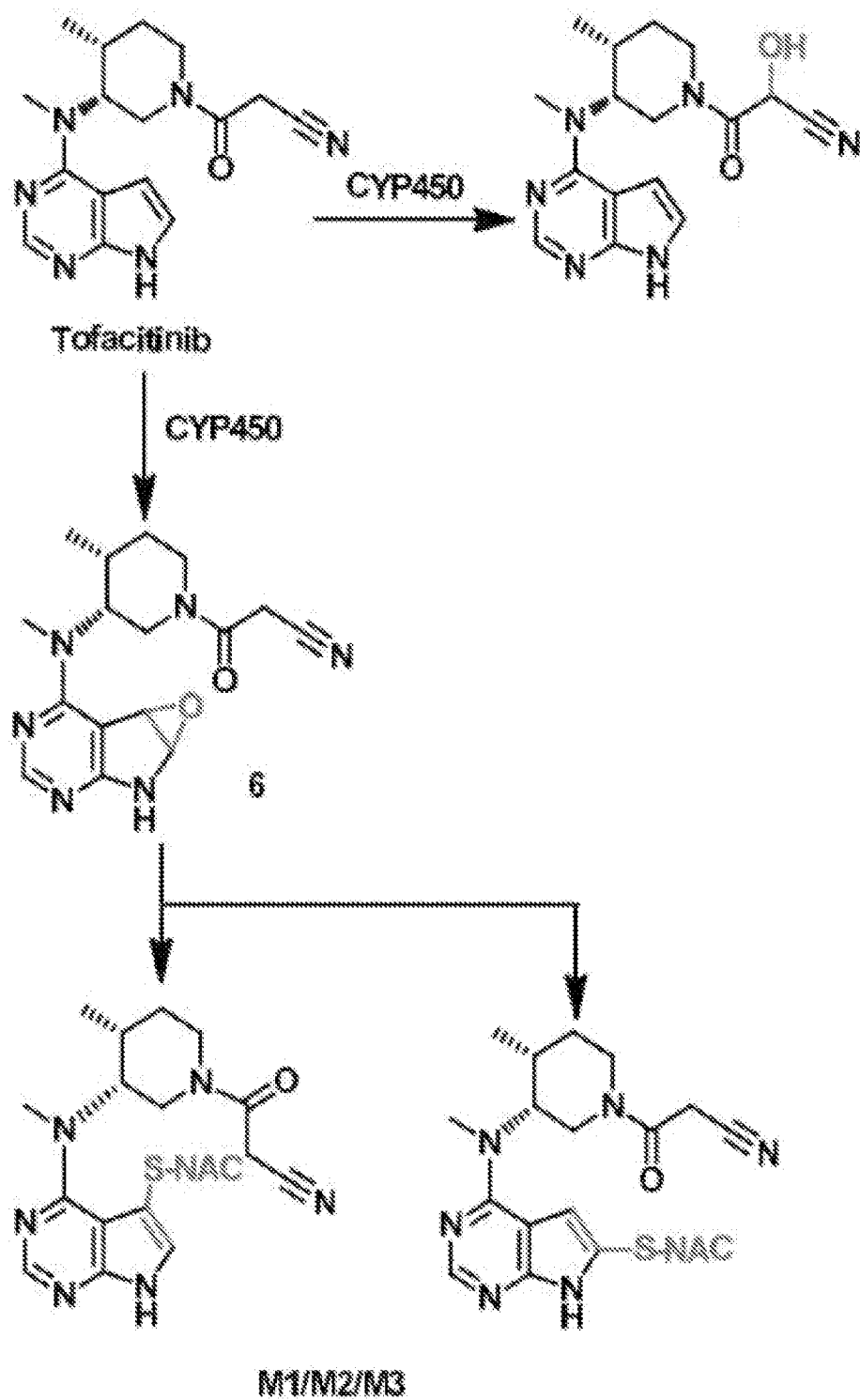
[0064] In an embodiment, the nitrile-containing JAK inhibitor is deuruxolitinib (CAS 1513883-39-0) having the following chemical structure:



[0065] Tofacitinib has the following chemical structure:

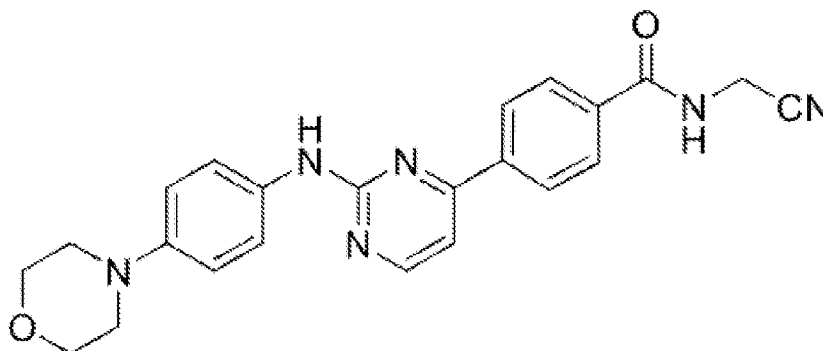


[0066] In an embodiment, a nitrile-containing metabolite compound of tofacitinib has the following structures, M1/M2/M3, as shown in Shawky A.M., et al. *Pharmaceutics*, 2022, 14(5): 1001, which is incorporated herein in its entirety:

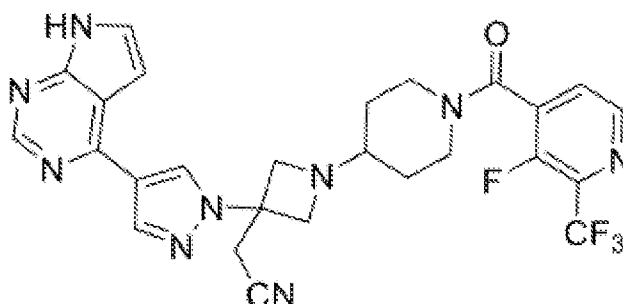


[0067] These nitrile-containing metabolite compounds of tofacitinib may be reversibly conjugated to a thiol group of a thiolated polymer, such as hyaluronic acid or other thiolated polymers, as described herein, to form a thioimide adduct for the treatment of the diseases and disorders described herein.

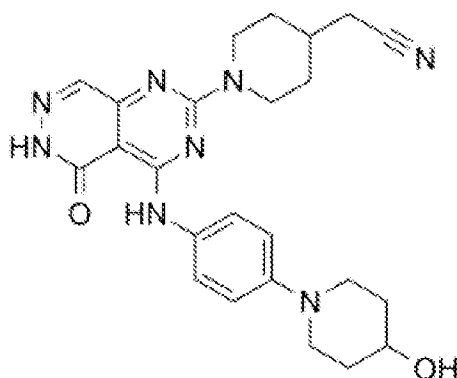
[0068] Momelotinib has the following chemical structure:



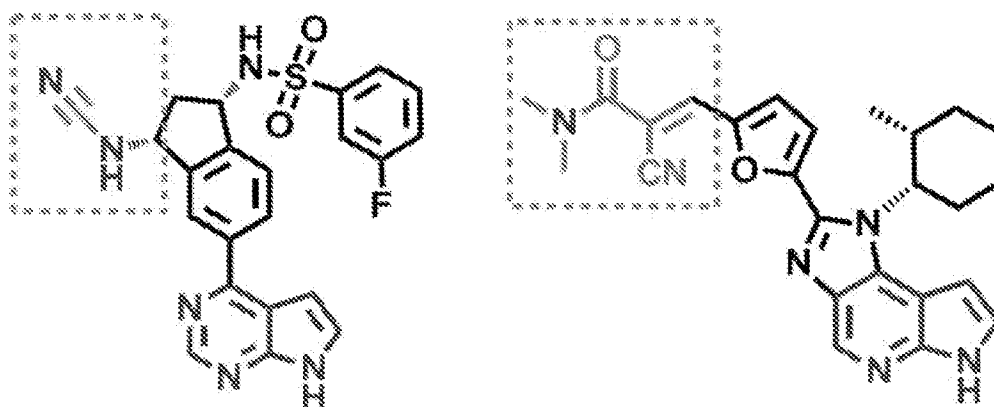
[0069] Itacitinib has the following chemical structure:



[0070] Gusacitinib has the following chemical structure:

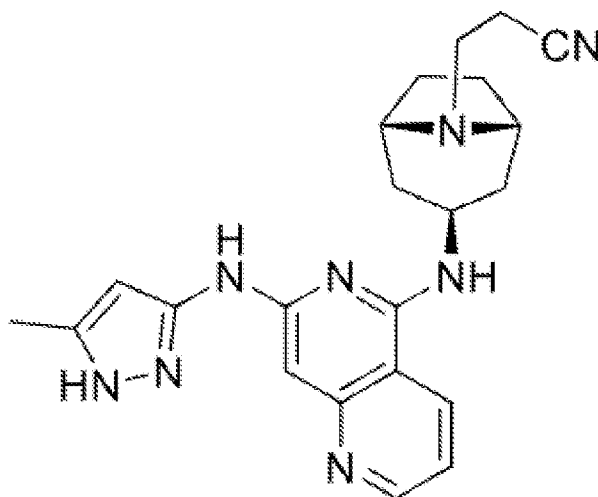


as described by Shawky A.M., et al. *Pharmaceutics*, 2022, 14(5): 1001, which is incorporated herein in its entirety. Shawky et al. also describe the following nitrile-containing JAK inhibitors, Compounds 1 (referred to as “compound A” herein) and 3 (referred to as “compound II” herein), respectively:

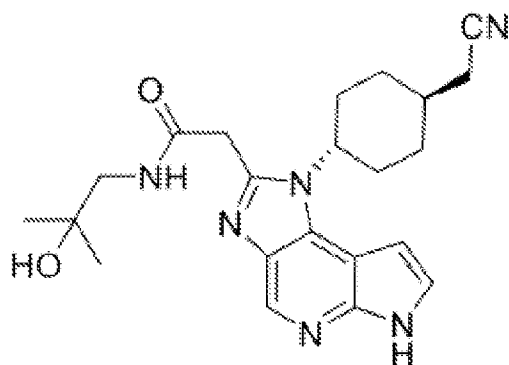


[0071] In some embodiments, the nitrile-containing JAK inhibitor is izencitinib, lorpucitinib or povorcitinib, whose structure is described by Zhang et al., *European Journal of Medicinal Chemistry* 261 (2023) 115848, which is incorporated herein in its entirety.

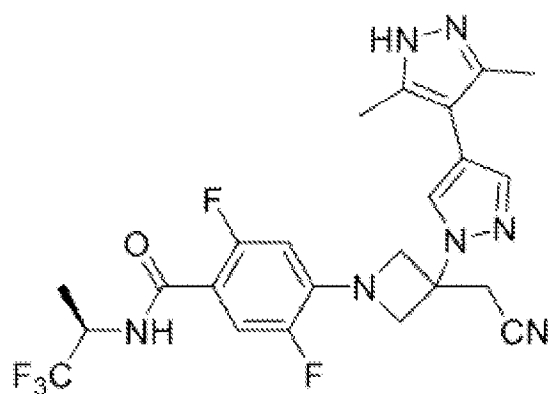
[0072] Izencitinib has the following chemical structure:



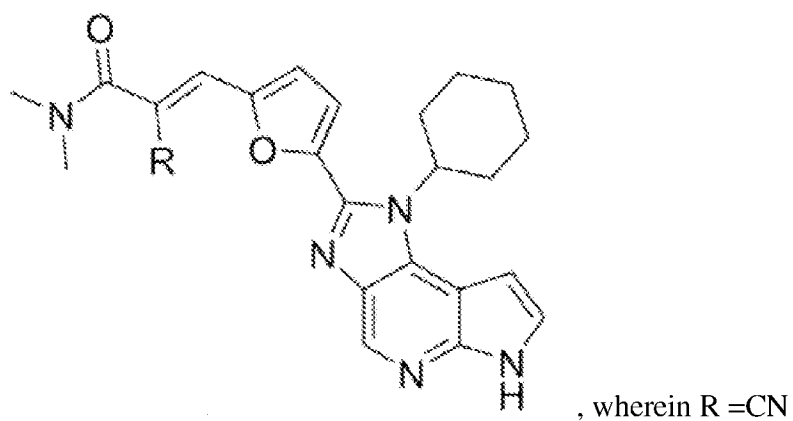
[0073] Lorpucitinib has the following chemical structure:



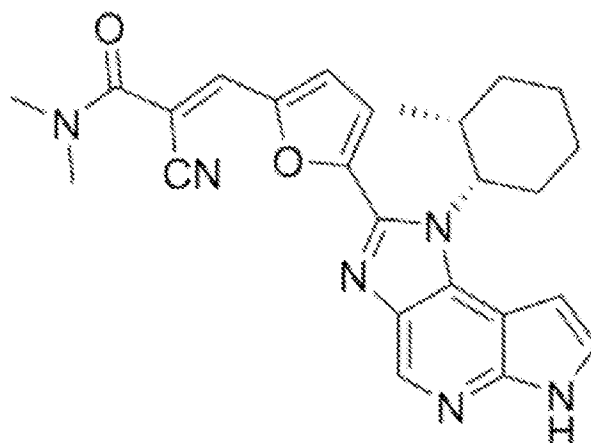
[0074] Povorcitinib has the following chemical structure:



[0075] In an embodiment, the nitrile-containing JAK inhibitor is a compound having chemical structure (I) or (II):



(I)



(II)

as described by Forster *et al.*, 2016, *Cell Chemical Biology* 23, 1335–1340, which is incorporated herein in its entirety.

Thiolated Polymeric Hydrogels

[0076] The term “hydrogel” is well-known in the art and means a crosslinked polymer network in water. Hydrogels may be used to encapsulate and release a therapeutic agent for local and sustained delivery. As used herein a “sustained delivery JAK inhibitor hydrogel” is a crosslinked polymer network comprising a JAK inhibitor having a nitrile group that is reversibly conjugated to a thiol group of a thiolated polymer to form a thioimide adduct.

[0077] The thiolated polymers according to embodiments of the present invention may be any polymer having a thiol group that is capable of being reversibly conjugated to a nitrile group of any nitrile-containing JAK inhibitor to form a thioimide adduct, thereby forming an administrable JAK inhibitor hydrogel. Thiol-containing polymers that are capable of being reversibly conjugated to a nitrile group of a nitrile-containing JAK inhibitor to form a thioimide adduct that are amenable for sustained delivery in hydrogel according to embodiments of the invention include, but are not limited to a thiolated hyaluronic acid, a thiolated chitosan, a thiolated cyclodextrin, a thiolated poly(ethylene glycol), a thiolated polyvinyl alcohol, a thiolated polyacrylamide, a thiolated polyethylene oxide, a thiolated polymethacrylate, a thiolated dextran, a thiolated alginate, a thiolated cellulose, a thiolated gelatin, a thiolated collagen, a thiolated silk, a thiolated keratin and a thiolated elastin, which crosslink via their thiol groups. These thiol group-containing polymers also form intra- and inter-chain disulfide bonds which contribute to their

gelling properties. The ability to cross-link via disulfide binds within their own structure results in formation of stable three-dimensional hydrophilic networks.

[0078] Polymers may be thiolated by methods that are well-known in the art. As used herein, a “thiolating agent” is an organic compound that contains a thiol functional group and is used to conjugate the thiol group to a polymer to form a thiolated polymer. Thiolating agents, include but are not limited to cystine, cysteamine, and 3,3'-dithiodipropionic acid. Any of the aforementioned thiolating agents are capable of conjugating a thiol group to a polymer, e.g., to a hyaluronic acid, to thiolate the polymer.

[0079] At low concentrations of thiolated polymer, the thiolated hydrogel is a viscous solution. Accordingly, in some embodiments, such low concentration-hydrogels may be delivered locally as an injectable composition comprising a JAK inhibitor for non-sustained release from the hydrogel. In an embodiment, a low concentration thiolated polymer hydrogel comprises about 0.5 wt% of a thiolated polymer. Whereas high concentrations of the thiolated polymer form a composition that is neither a hydrogel nor a solid, rendering it unusable for local delivery. In an embodiment, a high concentration thiolated polymer hydrogel comprises about 20 wt% of a thiolated polymer.

[0080] Unless otherwise defined herein, scientific and technical terms used in connection with the present application shall have the meanings that are commonly understood by those of ordinary skill in the art. Further, unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular.

[0081] As employed above and throughout the disclosure, the following terms and abbreviations, unless otherwise indicated, shall be understood to have the following meanings.

[0082] In the present disclosure the singular forms “a,” “an,” and “the” include the plural reference, and reference to a particular numerical value includes at least that particular value, unless the context clearly indicates otherwise. Thus, for example, a reference to “a compound” is a reference to one or more of such compounds and equivalents thereof known to those skilled in the art, and so forth. The term “plurality”, as used herein, means more than one. When a range of values is expressed, another embodiment includes from the one particular and/or to the other particular value. Similarly, when values are expressed as approximations, by use of the antecedent “about,” it is understood that the particular value forms another embodiment. All ranges are inclusive and combinable.

[0083] The term “about” or “approximately” means within an acceptable error range for the particular value as determined by one of ordinary skill in the art, which will depend in part on how the value is measured or determined, i.e., the limitations of the measurement system. For example, “about” can mean within 1 or more than 1 standard deviations, per practice in the art. Alternatively, when referring to a measurable value such as an amount, e.g., in mg, a temporal duration, a concentration, and the like, may encompass variations of $\pm 20\%$ or $\pm 10\%$, more preferably $\pm 5\%$, even more preferably $\pm 1\%$, and still more preferably $\pm 0.1\%$ from the specified value, as such variations are appropriate to perform the disclosed methods.

[0084] As used herein, the terms “component,” “composition,” “composition of compounds,” “compound,” “drug,” “pharmacologically active agent,” “active agent,” “therapeutic,” “therapy,” “treatment,” or “medicament” are used interchangeably herein to refer to a compound or compounds or composition of matter which, when administered to a subject (human or animal) induces a desired pharmacological and/or physiologic effect by local and/or systemic action.

[0085] The term “solvent” is well-known in the art and means any substance that is capable of dissolving one or several substances, thus creating a solution. A solvent typically is a liquid, but alternatively may be a solid or a gas.

[0086] The term “treatment” or “treating” as used herein refers to the administering of a therapeutically effective amount of the compound of the invention, i.e., a nitrile-containing small molecule such as a JAK inhibitor, to ameliorate undesired symptoms associated with a disease or disorder, to prevent the manifestation of such symptoms before they occur, to slow down the progression of the disorders described herein, slow down the deterioration of symptoms, to slow down the irreversible damage caused in the progressive chronic stage of the disease, to delay the onset of said progressive stage, to lessen the severity or cure the disease, to improve survival rate or more rapid recovery, or to prevent the disease from occurring or a combination of two or more of the above. As used herein, the terms “treatment” or “therapy” (as well as different forms thereof) include preventative (e.g., prophylactic), curative or palliative treatment.

[0087] In an embodiment the disorder is an inflammatory disorder. In some embodiments, the inflammatory disorder is an inflammatory skin disorder. The term “inflammatory skin disorder” is well-known in the art and means a disorder or disease of the skin involving different immune cells, in which the immune cells, e.g., white blood cells (lymphocytes, monocytes, neutrophils, eosinophils and basophils), release inflammatory mediators, which in turn cause small blood

vessels in tissues to dilate, resulting in the affected area of the skin to turn red, swell, feel hot, and be painful, i.e., to become inflamed. The dilated blood vessels and inflammatory mediators permit additional immune cells to enter the affected skin; the immune cells also cause fluid to enter the inflamed skin causing swelling. Additional inflammatory mediators, include but are not limited to, cytokines, arachidonic acid metabolites, e.g., prostaglandins and leukotrienes, nitric oxide, and oxygen free radicals, which are produced by epithelial cells, endothelial cells, and infiltrating inflammatory cells. JAK inhibitors have been shown to disrupt T cell-induced macrophage activation and to reduce downstream proinflammatory cytokine and chemokine responses, which suggests that suppressing the T cell-macrophage interaction contributes to the therapeutic effect of JAK inhibitors, as described by Nyirenda MH, Nijjar JS, Frleta-Gilchrist M, et al. JAK inhibitors disrupt T cell-induced proinflammatory macrophage activation. *RMD Open* 2023;9:e002671. doi:10.1136/rmdopen-2022-00267, which is incorporated by reference in its entirety.

[0088] In particular embodiments, the inflammatory skin disorder is atopic dermatitis, alopecia areata, central centrifugal cicatricial alopecia; hidradenitis suppurativa, lichen planus, lichen planopilaris, frontal fibrosing alopecia, mucosal lichen planus, psoriasis, pemphigus and/or vitiligo. In some embodiments, the inflammatory disorder is rheumatoid arthritis, psoriatic arthritis or reactive arthritis. As used herein, the term “treating” includes alleviating or reducing at least one adverse or negative effect or symptom of a condition, disease or disorder.

[0089] The term “autoimmune disease” is well-known in the art and means a disease in which the body's immune system attacks healthy cells and tissues. Over 100 autoimmune diseases have been identified that affect over 24 million people. Rheumatoid arthritis (RA) is an example of an autoimmune disease; in RA, the immune system produces antibodies that attach to the lining of joints and the immune system attacks this lining causing chronic inflammation and painful swelling that lead to bone erosion and joint deformity.

[0090] A “therapeutically effective amount” as used herein refers to that amount which provides a therapeutic effect for a given indication and administration regimen.

[0091] The term “sustained delivery” is well-known in the art and means a delivery of a drug in a human body (or in a non-human mammal, e.g., dog) at a predetermined and constant rate (zero-order drug release) to maintain a continuous level of the drug, usually over an extended period of time with the least possible side-effects after administration of a single dose. Zero-order drug release is a way to improve the therapeutic effect and avoid the side effects of the drug. The drug

is released from the carrier. In the context of the present invention, the hydrogel in which the nitrile-group of the JAK inhibitor is reversibly conjugated to a thiol group of a thiolated polymer to form a thioimide adduct, provides a “sustained delivery of the JAK inhibitor” at a constant rate after one administration, such as by intradermal or subcutaneous injection, such as over a 12-week period; thus, the drug concentration–time profile is flat.

[0092] The terms “subject,” “individual,” and “patient” are used interchangeably herein, and refer to an animal, for example a human, to whom treatment, including prophylactic treatment, with the pharmaceutical compositions according to the present invention, i.e., the herein described multifunctional branched therapeutic agents, respectively, is provided. The term “subject” as used herein refers to human and non-human animals. The terms “non-human animals” and “non-human mammals” are used interchangeably herein and include all vertebrates, e.g., mammals, such as non-human primates, (particularly higher primates), sheep, dog, rodent, (e.g., mouse or rat), guinea pig, goat, pig, cat, rabbits, cows, horses and non-mammals such as reptiles, amphibians, chickens, and turkeys.

[0093] As used herein, a “pharmaceutically acceptable carrier” is well known to those skilled in the art. The carrier may be a solid carrier for solid formulations, a liquid carrier or diluent for liquid formulations, or mixtures thereof. In addition, the pharmaceutical compositions of the invention may further include one or more ingredient selected from diluents, buffers, flavoring agents, binders, disintegrants, surface active agents, thickeners, lubricants, preservatives (including antioxidants), and the like. The formulations may be of immediate release, sustained release, delayed-onset release or any other release profile known to one skilled in the art.

[0094] In some embodiments, 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.

[0095] The present invention also includes “pharmaceutically acceptable salts” of the compounds, i.e., the nitrile-containing JAK inhibitors described herein, e.g., baricitinib. 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 of the compounds of the invention include the conventional non-toxic salts of the parent compounds formed, for example, from non-toxic inorganic or organic acids, including salts of baricitinib, delgocitinib, ruxolitinib, deuruxolitinib, tofacitinib, momelotinib, gusacitinib, itacitinib, izencitinib, lorpucitinib, povorcitinib or a nitrile-containing metabolite thereof. The pharmaceutically acceptable salts of the compounds of the invention 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. In some embodiments, the solvent is a nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile.

[0096] The pharmaceutically acceptable salts of the compounds of the invention can be formed by conventional means, such as by reacting the free base or free acid form of the product with one or more equivalents of the appropriate acid or base in a solvent or medium in which the salt is insoluble or in a solvent such as water, which is removed *in vacuo* or by freeze drying or by exchanging the ions of an existing salt for another ion or suitable ion-exchange resin.

[0097] Possible pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge, *et al.* describe pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences*, 66: 1-19, 1977; which is incorporated herein by reference in its entirety.

[0098] A pharmaceutically acceptable salt form of a compound of the invention can be prepared *in situ* during the final isolation and purification of the compound, or separately by reacting the free base functionality with a suitable organic or inorganic acid. Suitable acids for preparation of the pharmaceutically acceptable salts include, but are not limited to, inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, and perchloric acid, or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid, or malonic acid or by using other methods used in the art such as ion exchange.

[0099] Other pharmaceutically acceptable salts can include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, harnisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate,

methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like.

[00100] Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and quaternary ammonium salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, lower alkyl sulfonate and aryl sulfonate.

[00101] Suitable bases for use in the preparation of pharmaceutically acceptable salts, including, but not limited to, inorganic bases, such as magnesium hydroxide, calcium hydroxide, potassium hydroxide, zinc hydroxide, or sodium hydroxide; and organic bases, such as primary, secondary, tertiary, and quaternary, aliphatic and aromatic amines, including L-arginine, benethamine, benzathine, choline, deanol, diethanolamine, diethylamine, dimethylamine, dipropylamine, diisopropylamine, 2-(diethylamino)-ethanol, ethanolamine, ethylamine, ethylenediamine, isopropylamine, N-methyl-glucamine, hydrabamine, 1H-imidazole, L-lysine, morpholine, 4-(2-hydroxyethyl)-morpholine, methylamine, piperidine, piperazine, propylamine, pyrrolidine, 1-(2-hydroxyethyl)-pyrrolidine, pyridine, quinuclidine, quinoline, isoquinoline, secondary amines, triethanolamine, trimethylamine, triethylamine, N-methyl-D-glucamine, 2-amino-2-(hydroxymethyl)-1,3-propanediol, and tromethamine.

[00102] The invention further includes derivatives of the compounds of the invention, i.e., derivatives of the nitrile-containing JAK inhibitors which also contain a nitrile group. The term “derivatives” includes but is not limited to ether derivatives, acid derivatives, amide derivatives, ester derivatives and the like.

[00103] The invention further includes metabolites of the compounds of the invention, i.e., metabolites of the nitrile-containing JAK inhibitors which also contain a nitrile group. The term “metabolite” means any substance produced from another substance by metabolism or a metabolic process.

[00104] The invention further includes pharmaceutical products of the compounds of the invention. The term “pharmaceutical product” means a composition suitable for pharmaceutical use (pharmaceutical composition), as defined herein.

[00105] The invention further includes prodrugs of the compounds of the invention. The term “prodrug” means a substance which can be converted *in vivo* into a biologically active agent by such reactions as hydrolysis, esterification, de-esterification, activation, salt formation and the like.

[00106] This invention further includes crystals of the compounds of the invention. Further, this invention provides polymorphs of the compound of the invention. The term “crystal” means a substance in a crystalline state. The term “polymorph” refers to a particular crystalline state of a substance, having particular physical properties such as X-ray diffraction, IR spectra, melting point, and the like.

[00107] The invention further includes sustained delivery hydrogels comprising a small molecule drug having a nitrile group reversibly conjugated to a thiol group of a thiolated polymer, such as hyaluronic acid, to form a thioimide adduct. The small molecule drug may be selected from any of those drugs which treat any of diverse disease states, including respiratory, cardiovascular, metabolic, infectious, and rare diseases, as well as drugs that are useful in the therapeutic areas of oncology, immunology, inflammation, endocrinology, dermatology, neurology, ophthalmology, hematology, gastroenterology, and aesthetics. The nitrile group of the small molecule drug may adjoin an aliphatic carbon, a non-aromatic unsaturated carbon, an aromatic carbon, a nitrogen atom, or a sulfur atom within the small molecule drug.

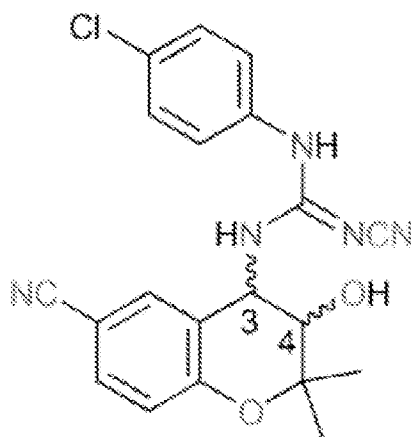
[00108] Examples of small molecule drugs having a nitrile group include, but are not limited to, the compounds listed in **Table 1** thru **Table 7** below. For example, the small molecule drug having a nitrile group is a dipeptidyl peptidase-4 (DPP-4) inhibitor (also known as gliptins). For example, the small molecule drug having a nitrile group is the DPP-4 inhibitor alogliptin.

[00109] In another example, the small molecule drug having a nitrile group is a Wnt signaling pathway agonist. For example, the small molecule drug having a nitrile group is the Wnt signaling pathway agonist CHIR 99021.

[00110] Also provided herein are processes of making the sustained delivery hydrogels comprising a small molecule drug having a nitrile group reversibly conjugated to a thiol group of a thiolated polymer to form a thioimide adduct. Persons skilled in the art will understand that the same general principles and concepts described here in conjunction with baricitinib and other nitrile-containing JAK inhibitors, including principles and concepts related to methods of making and using such hydrogels and pharmaceutical compositions thereof, apply with equal force to other small molecule drugs having a nitrile group.

[00111] Also provided herein are methods for treating a disorder or a disease in a subject in need thereof, the method comprising administering a sustained delivery hydrogel with a nitrile-containing small molecule drug hydrogel to the subject, wherein the sustained delivery hydrogel comprises the small molecule drug having a nitrile group reversibly conjugated to a thiol group of a thiolated polymer to form a thioimide adduct. The small molecule drugs having a nitrile group listed in **Table 1** thru **Table 7** below may, but is not limited to, be used to treat a disorder or disease indicated therein.

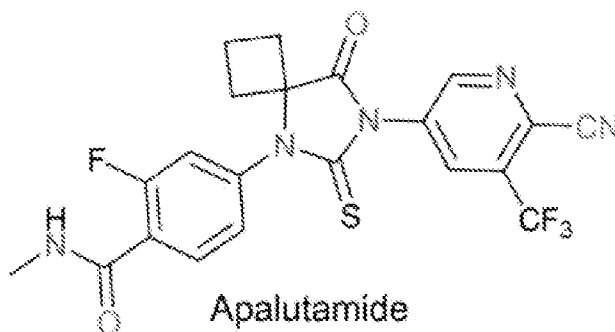
[00112] In some embodiments of the hydrogels, processes and methods provided herein, the small molecule drug having a nitrile group is BMS-180428 or BMS-180448, which have the structures depicted below.



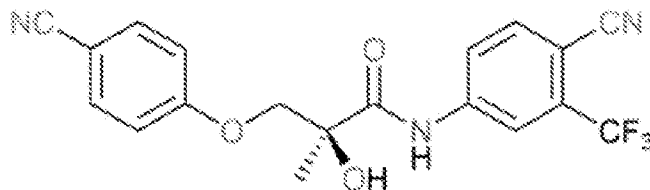
BMS-180428 (3*R*, 4*S*)

BMS-180448 (3*S*, 4*R*)

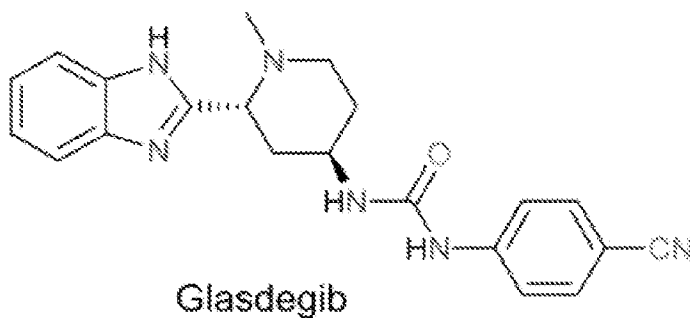
[00113] In some embodiments of the hydrogels, processes and methods provided herein, the small molecule drug having a nitrile group is apalutamide (ERLEADA®), which has the structure depicted below. Apalutamide, an androgen receptor (AR) antagonist, is a nonsteroidal antiandrogen used for the treatment of prostate cancer.



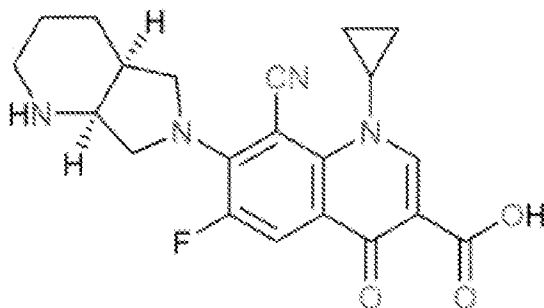
[00114] In some embodiments of the hydrogels, processes and methods provided herein, the small molecule drug having a nitrile group is enobosarm, which has the structure depicted below.



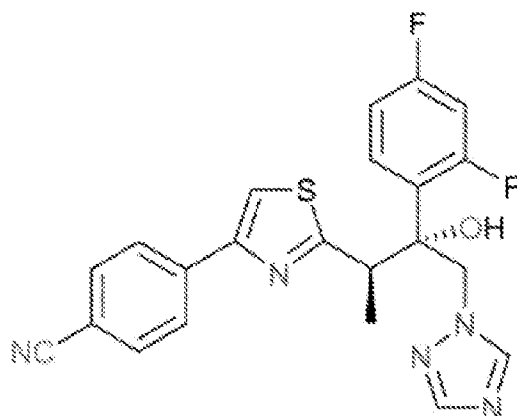
[00115] In some embodiments of the hydrogels, processes and methods provided herein, the small molecule drug having a nitrile group is glasdegib (DAURISMO™), which has the structure depicted below. Glasdegib, a hedgehog pathway inhibitor, is used for the treatment of acute myeloid leukemia (AML).



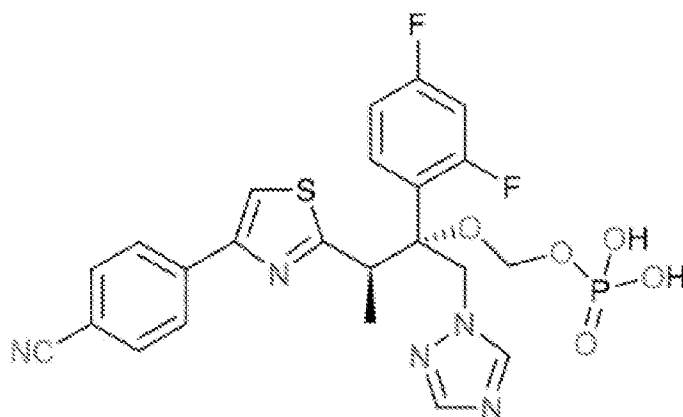
[00116] In some embodiments of the hydrogels, processes and methods provided herein, the small molecule drug having a nitrile group is pradofloxacin, which has the structure depicted below.



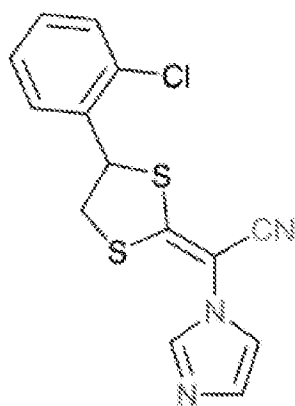
[00117] In some embodiments of the hydrogels, processes and methods provided herein, the small molecule drug having a nitrile group is ravuconazole, which has the structure depicted below.



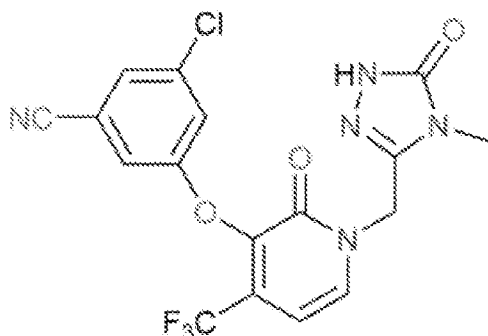
[00118] In some embodiments of the hydrogels, processes and methods provided herein, the small molecule drug having a nitrile group is fosravuconazole, which has the structure depicted below.



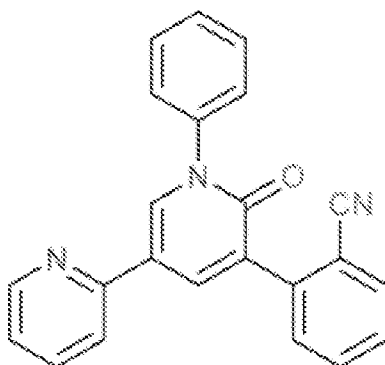
[00119] In some embodiments of the hydrogels, processes and methods provided herein, the small molecule drug having a nitrile group is lanoconazole, which has the structure depicted below.



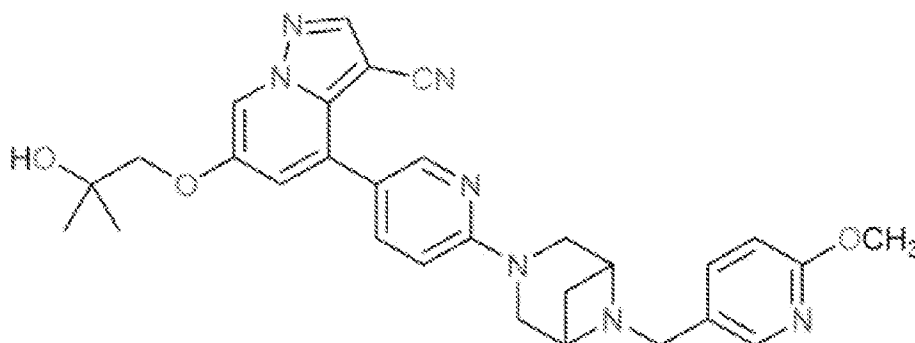
[00120] In some embodiments of the hydrogels, processes and methods provided herein, the small molecule drug having a nitrile group is doravirine (PIFELTRO®), which has the structure depicted below. Doravirine, a non-nucleoside reverse transcriptase inhibitor, is used in the treatment of HIV/AIDS.



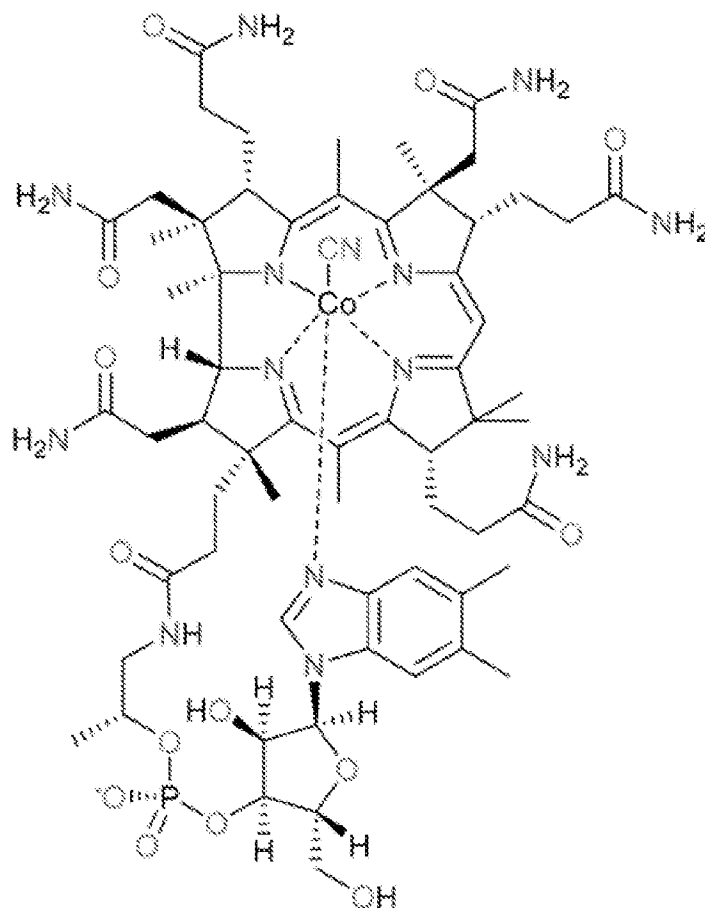
[00121] In some embodiments of the hydrogels, processes and methods provided herein, the small molecule drug having a nitrile group is perampanel (FYCOMPA™), which has the structure depicted below and is used as an anti-epileptic medication.



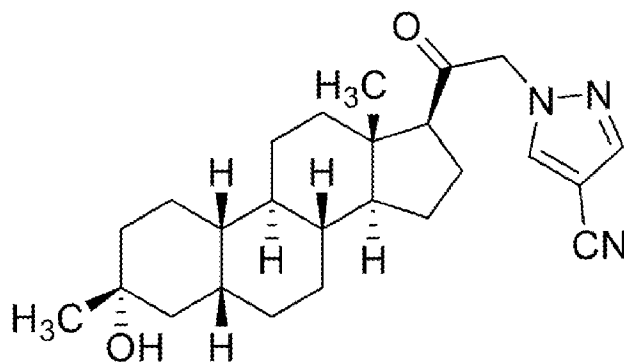
[00122] In some embodiments of the hydrogels, processes and methods provided herein, the small molecule drug having a nitrile group is selpercatinib (RETEVMO®), which has the structure depicted below; it is a kinase inhibitor and used in the treatment of cancer.



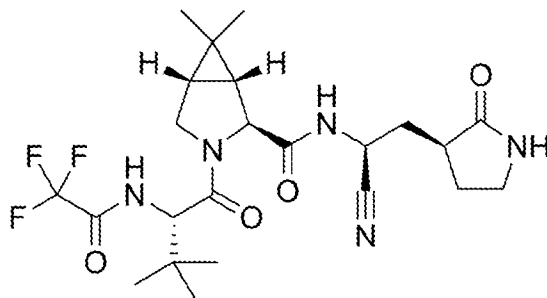
[00123] In some embodiments of the hydrogels, processes and methods provided herein, the small molecule drug having a nitrile group is cyanocobalamin (Vitamin B12), which has the structure depicted below.



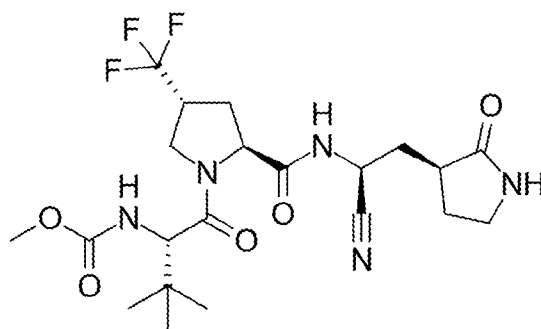
[00124] In some embodiments of the hydrogels, processes and methods provided herein, the small molecule drug having a nitrile group is zuranolone (ZURZUVAE™), which has the structure depicted below. Zuranolone, a neuroactive steroid gamma-aminobutyric acid (GABA) A receptor positive modulator, is used for the treatment of postpartum depression (PPD).



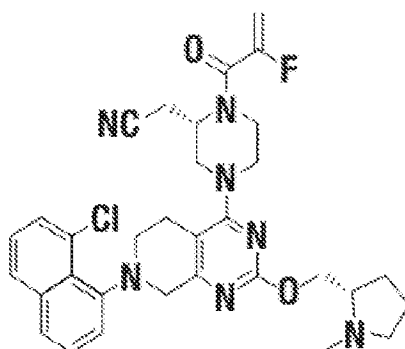
[00125] In some embodiments of the hydrogels, processes and methods provided herein, the small molecule drug having a nitrile group is nirmatrelvir, which has the structure depicted below. Nirmatrelvir, a 3C-like protease inhibitor, is part of a nirmatrelvir/ritonavir combination (PAXLOVID™) used to treat COVID-19.



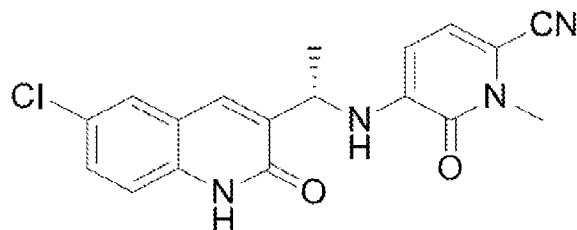
[00126] In some embodiments of the hydrogels, processes and methods provided herein, the small molecule drug having a nitrile group is ibuzatrelvir, which has the structure depicted below. Ibuzatrelvir is an antiviral being developed for the treatment of COVID-19.



[00127] In some embodiments of the hydrogels, processes and methods provided herein, the small molecule drug having a nitrile group is adagrasib (KRAZATI®), which has the structure depicted below. Adagrasib, an irreversible inhibitor of KRAS G12C, is used in the treatment of non-small cell lung and colorectal cancers.



[00128] In some embodiments of the hydrogels, processes and methods provided herein, the small molecule drug having a nitrile group is olutasidenib (REZLIDHIA®), which has the structure depicted below. Olutasidenib, an isocitrate dehydrogenase-1 (IDH1) inhibitor, is used for the treatment of acute myeloid leukemia (AML).



[00129] For treating a specific disorder or disease in a subject, particularly humans, with sustained delivery hydrogels comprising a small molecule drug having a nitrile group, it is expected that the physician will determine the actual dosage and duration of treatment, which will be most suitable for an individual with that disorder or disease and can vary with the age, weight, genetics and/or response of the particular individual, as well as be informed by the use of that small molecule drug having a nitrile group alone, i.e, in the absence of a hydrogel.

Table 1. Cyano-containing small molecule drugs that are FDA-approved.

IUPAC Name	CAS #	SMILES Notation	USAN Name / Trade Name	Representative Tx Class	Representative Disease
9-ethyl-6,6-dimethyl-8-(4-morpholin-4-yl)piperidin-1-yl)-11-oxo-5H-benzob[carbazole-3-carbonitrile	CAS 1256580-46-7	<chem>CCC1=CC2=C(C=C1N3CCCC(C3)N4CCOC4)C(C5=C(C2=O)C6=C(N5)C=C(C=C6)C#N)C(C</chem>	Alectinib		Lung cancer; Non-small-cell lung cancer
2-[[6-[(3R)-3-aminopiperidin-1-yl]-3-methyl-2,4-dioxypyrimidin-1-yl]methyl]benzonitrile	CAS 850649-61-5	<chem>CN1C(=O)C=C(N(C1=O)CC2=CC=CC=C2C#N)N3CCC[C@H](C3)N</chem>	Alogliptin		Type-2 diabetes
N-[2-[[2-[(2S)-2-cyanopyrrolidin-1-yl]-2-oxoethyl]amino]-2-methylpropyl]-2-methylpyrazolo[1,5-a]pyrimidine-6-carboxamide	CAS 739366-20-2	<chem>CC1=NN2C=C(C=NC2=C1)C(=O)NCC(C)(C)NCC(=O)N3CCC[C@H]3C#N</chem>	Anagliptin		Type-2 diabetes
2-[3-(2-cyanopropan-2-yl)-5-(1,2,4-triazol-1-ylmethyl)phenyl]-2-methylpropanenitrile	CAS 120511-73-1	<chem>CC(C)(C#N)C1=CC(=CC(=C1)CN2C=NC=N2)C(C)(C)C#N</chem>	Anastrozole	Anticancer Agents	Breast cancer
4-[7-[6-cyano-5-(trifluoromethyl)pyridin-3-yl]-8-oxo-6-sulfanylidene-5,7-diazaspiro[3.4]octan-5-yl]-2-fluoro-N-methylbenzamide	CAS 956104-40-8	<chem>CNC(=O)C1=C(C=C(C(C=C1)N2C(=S)N(C(=O)C23CCCC3)C4=CC(=C(N=C4)C#N)C(F)(F)F)F)C5=CC=CC(=C5)C#N</chem>	Arn-509		Acute myeloid leukaemia; Prostate cancer
2-[1-ethylsulfonyl-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)pyrazol-1-yl]azetidin-3-yl]acetoneitrile	CAS 1187594-09-7	<chem>CCS(=O)(=O)N1CC(C1)(C#N)N2C=C(C(=N2)C3=C4C=CN4=NC=N3</chem>	Baricitinib		Rheumatoid arthritis
2-[3-(aminomethyl)phenyl]-N-[5-[(R)-{(3-cyanophenyl)-(cyclopropylmethylamino)methyl]-2-fluorophenyl]-5-(trifluoromethyl)pyrazole-3-carboxamide	CAS 180910-50-1	<chem>C1CC1CN[C@@H](C2=CC(=C(C=C2)F)NC(=O)C3=CC(=NN3C4=CC=CC(=C4)CN)C(F)(F)F)C5=CC=CC(=C5)C#N</chem>	Berotrastat		Hereditary angioedema
N-[4-cyano-3-(trifluoromethyl)phenyl]-3-(4-fluorophenyl)sulfonyl-2-hydroxy-2-methylpropanamide	CAS 90357-06-5	<chem>CC(CS(=O)(=O)C1=C(C=C(C(C=C1)F)C(=O)N2=CC(=C(C=C2)C#N)C(F)(F)F)O</chem>	Bicalutamide	Anticancer Agents	Prostate cancer
4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinoline-3-carbonitrile	CAS 380843-75-4	<chem>CN1CCN(CC1)CCOC2=C(C=C3C(=C2)N=CC(=C3NC4=CC(=C(C=C4Cl)Cl)OC)C#N)O</chem>	Bosutinib	Anticancer Agents	Breast cancer
{6R,7R}-3-(acetyloxymethyl)-7-[(2-cyanoacetyl)amino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid	CAS 10206-21-0	<chem>CC(=O)OCC1=C(N2[C@H]([C@@H]([C@H]([C@H]2)O)NC(=O)CC#N)SC1)C(=O)O</chem>	Cefacetrile	Antibiotics	Bacterial infection
{6R,7S}-7-[(2-(cyanomethylsulfanyl)acetyl)amino]-7-methoxy-3-[(1-methyltetrazol-5-yl)sulfanylmethyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid	CAS 56796-20-4	<chem>CN1C(=NN=N1)SCC2=C(N3[C@H]([C@@H]([C@H]([C3=O)NC(=O)CSCC#N)OC)SC2)C(=O)O</chem>	Cefmetazole	Antibiotics	Bacterial infection
1-cyano-2-methyl-3-[2-[(5-methyl-1H-imidazol-4-yl)methylsulfanyl]ethyl]guanidine	CAS 51481-61-9	<chem>CC1=C(N=CN1)CSCCNC(=NC)NC#N</chem>	Cimetidine	Antiulcer Agents	Acid-reflux disorder
3-[7-chloro-5-(2-fluorophenyl)-3-hydroxy-2-oxo-3H-1,4-benzodiazepin-1-yl]propanenitrile	CAS 75696-02-5	<chem>C1=CC=C(C(C=C1)C2=NC(C(=O)N(C3=C2C=C(C=C3)Cl)CCC#N)O)F</chem>	Cinolazepam	Anticonvulsants	Muscle spasm

IUPAC Name	CAS #	SMILES Notation	USAN Name / Trade Name	Representative Tx Class	Representative Disease
1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-3H-2-benzofuran-5-carbonitrile	CAS 59729-33-8	<chem>CN(C)C(CCC1C2=C(C(CO1)C=C(C=C2)C#N)C3=CC=C(C=C3)F</chem>	Citalopram	Antidepressants	Depression
4-[(1-hydroxy-3H-2,1-benzoxaborol-5-yl)oxy]benzonitrile	CAS 906673-24-3	<chem>B1(C2=C(C(CO1)C=C(C=C2)OC3=CC=C(C=C3)C#N)O</chem>	Crisaborole		Atopic dermatitis
N-[(2S)-1-[3-(3-chloro-4-cyanophenyl)pyrazol-1-yl]propan-2-yl]-5-(1-hydroxyethyl)-1H-pyrazole-3-carboxamide	CAS 1297538-32-9	<chem>C[C@@H](CN1C=CC(=N1)C2=CC(=C(C=C2)C#N)C)NC(=O)C3=NNC(=C3)C(C)O</chem>	Darolutamide		Prostate cancer
ethyl 1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carboxylate	CAS 915-30-0	<chem>CCOC(=O)C1(CCN(C(C1)CCC(C#N)(C2=CC=CC=C2)C3=CC=CC=C3)C4=CC=CC=C4</chem>	Diphenoxylate	Analgesics	Diarrhea
2-(2-oxo-1-phenyl-5-pyridin-2-ylpyridin-3-yl)benzonitrile	CAS 380917-97-5	<chem>C1=CC=C(C=C1)N2C=C(C(C=C(C2=O)C3=C(C=CC=C3C#N)C4=CC=CC=N4</chem>	E-2007		Diabetic neuropathy; Parkinson disease
(E)-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)-N,N-diethylprop-2-enamide	CAS 130929-57-6	<chem>CCN(CC)C(=O)C(=C/C1=C(C(=C(C=C1)O)O)N+)(=O)O-)/C#N</chem>	Entacapone	Antiparkinson Agents	Parkinson disease
4-[3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl]-2-fluoro-N-methylbenzamide	CAS 915087-33-1	<chem>CC1(C(=O)N(C(=S)N1C2=CC(=C(C=C2)C(=O)NC(F)C3=CC(=C(C=C3)C#N)C(F)F)C</chem>	Enzalutamide		Prostate cancer
(1S)-1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-3H-2-benzofuran-5-carbonitrile	CAS 128196-01-0	<chem>CN(C)CCC[C@@H]1(C2=C(C(CO1)C=C(C=C2)C#N)C3=CC=C(C=C3)F</chem>	Escitalopram	Antidepressants	Major depressive disorder
[(8R,9S,13S,14S,17S)-3-hydroxy-13-methyl-6,7,8,9,11,12,14,15,16,17-decahydrocyclopenta[a]phenanthren-17-yl]pentanoate;2-[(8S,13S,14S,17R)-17-hydroxy-13-methyl-3-oxo-1,2,6,7,8,11,12,14,15,16-decahydrocyclopenta[a]phenanthren-17-yl]acetoneitrile	CAS 307334-58-3	<chem>CCCCC(=O)O[C@H]1CC[C@H]2[C@@H]2[C@@H]1(C[C@H]3[C@H]2CCC4=C3C=CC(=C4)O)C.[C@H]12CCC3=C4CCC(=O)C=C4CC[C@H]3[C@@H]1CC[C@H]2(CC#N)O</chem>	Estradiol valerate/dienogest		Discovery agent
4-[6-amino-5-bromo-2-(4-cyanoanilino)pyrimidin-4-yl]oxy-3,5-dimethylbenzonitrile	CAS 269055-15-4	<chem>CC1=CC(=CC(=C1OC2=NC(=NC(=C2Br)N)NC3=CC=C(C=C3)C#N)C(C#N</chem>	Etravirine		Human immunodeficiency virus-1 infection
4-(5,6,7,8-tetrahydroimidazo[1,5-a]pyridin-5-yl)benzonitrile	CAS 102676-47-1	<chem>C1CC(N2C=NC=C2C1)C3=CC=C(C=C3)C#N</chem>	FADROZOLE		Breast cancer
2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methyl-1,3-thiazole-5-carboxylic acid	CAS 144060-53-7	<chem>CC1=C(SC(=N1)C2=CC(=C(C=C2)OCC(C)C)C#N)C(=O)O</chem>	Febuxostat		Hyperuricaemia
7-[(4aS,7aS)-3,4,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazin-6-yl]-8-cyano-1-cyclopropyl-6-fluoro-4-oxoquinoline-3-carboxylic acid	CAS 209342-40-5	<chem>C1CC1N2C=C(C(C(=O)C3=CC(=C(C=C32)C#N)N4C[C@H]5[C@H](C4)OCCN5)F)C(=O)O</chem>	Finalexacin		Urinary tract infection
[2-[1-[1-[(2R,3R)-3-[4-(4-cyanophenyl)-1,3-thiazol-2-yl]-2-(2,5-difluorophenyl)-2-hydroxybutyl]-1,2,4-triazol-4-ium-4-yl]ethoxycarbonyl-	CAS 742049-41-8	<chem>CC(C1=NC(=CS1)C2=CC=C(C=C2)C#N)C(CN3C=[N+](C=N3)C(C)OC(=O)N(C)C4=C(C</chem>	Isavuconazonium		Allergic bronchopulmonary aspergillosis

IUPAC Name	CAS #	SMILES Notation	USAN Name / Trade Name	Representative Tx Class	Representative Disease
methylamino]pyridin-3-yl[methyl 2-(methylamino)acetate		<chem>C=CC(=N4)COC(=O)CNC(C)(C5=C(C=CC(=C5)F)F)O</chem>			
(2S)-N-[(1S)-1-(2-chlorophenyl)-2-[(3,3-difluorocyclobutyl)amino]-2-oxoethyl]-1-(4-cyanopyridin-2-yl)-N-(5-fluoropyridin-3-yl)-5-oxopyrrolidine-2-carboxamide	CAS 1448347-49-6	<chem>C1CC(=O)N([C@@H]1C(=O)N(C2=CC(=C(N=C2)F)C(=O)N(C3=CC=CC(=C3)C)C(=O)N4CC(C4)(F)C5=NC=CC(=C5)C#N</chem>	Ivosidenib		Haematological malignancy; Acute myeloid leukaemia; Cholangiocarcinoma
(2S)-N-[(1S)-1-(2-chlorophenyl)-2-[(3,3-difluorocyclobutyl)amino]-2-oxoethyl]-1-(4-cyanopyridin-2-yl)-N-(5-fluoropyridin-3-yl)-5-oxopyrrolidine-2-carboxamide	CAS 1448347-49-6	<chem>C1CC(=O)N(C1C(=O)N(C2=CC(=CN=C2)F)C(C3=CC=CC(=C3)C)C(=O)N4CC(C4)(F)F)C5=NC=CC(=C5)C#N</chem>	Ivosidenib	Anticancer Agents	Acute myeloid leukemia; Cholangiocarcinoma
(1R,3R)-2-[(2R)-2-amino-2-(3-hydroxy-1-adamantyl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile;3-(diaminomethylidene)-1,1-dimethylguanidine	CAS 1198772-17-6	<chem>CN(C)C(=N)N=C(N)N.C1[C@H]([N]([C@H]2C1C2)C(=O)[C@H]([C34CC5CC(C3)CC(C5)(C4)O)N)C#N</chem>	Kombiglyze XR/komboglyze FDC		Diabetic complication
4-[(4-cyanophenyl)-(1,2,4-triazol-1-yl)methyl]benzonitrile	CAS 112809-51-5	<chem>C1=CC(=CC=C1C#N)C(C2=CC=C(C=C2)C#N)N3C=NC=N3</chem>	Letrozole	Anticancer Agents	Hormonally-responsive breast cancer
(3S,4R)-1-[4-cyano-4-(4-fluorophenyl)cyclohexyl]-3-methyl-4-phenylpiperidine-4-carboxylic acid	CAS 79449-98-2	<chem>C[C@H]1CN(C[C@H]1C(=O)N(C2=CC=CC=C2)C(=O)O)C3CCC(CC3)(C#N)C4=CC=C(C=C4)F</chem>	Levocabastine	Antiallergic Agents	Allergic conjunctivitis
2-[[4-[(4R)-4-methyl-6-oxo-4,5-dihydro-1H-pyridazin-3-yl]phenyl]hydrazinylidene]propanedinitrile	CAS 141505-33-1	<chem>C[C@H]1CC(=O)NN=C1C2=CC=C(C=C2)N(C(C#N)N=C(C#N)C#N</chem>	Levosimendan	Cardiotonic Agents	Cardiac output syndrome; Pulmonary hypertension; Congestive heart failure; Heart failure
(16R)-19-amino-13-fluoro-4,8,16-trimethyl-9-oxo-17-oxa-4,5,8,20-tetrazatetracyclo[16.3.1.02.6.010.15]docosa-1(22),2,5,10(15),11,13,18,20-octaene-3-carbonitrile	CAS 1454846-35-5	<chem>C[C@H]1C2=C(C=CC(=C2)F)C(=O)N(C(C3=NN(C(=C3C4=CC(=C(N=C4)N)O1)C#N)C)C</chem>	Lorlatinib		Non-small-cell lung cancer
(2E)-2-[(4R)-4-(2,4-dichlorophenyl)-1,3-dithiolan-2-ylidene]-2-imidazol-1-ylacetoneitrile	CAS 187164-19-8	<chem>C1[C@H]([S]/C(=C([C@@H]1N2C=CN=C2)/S1)C3=C(C=C(C3)Cl)Cl</chem>	Luliconazole		Tinea pedis; Dry eye disease
6-methyl-2-oxo-5-pyridin-4-yl-1H-pyridine-3-carbonitrile	CAS 78415-72-2	<chem>CC1=C(C=C(C(=O)N1)C#N)C2=CC=CC=NC=C2</chem>	Milrinone	Cardiotonic Agents	Congestive heart failure
3-chloro-5-[1-[(4-methyl-5-oxo-1H-1,2,4-triazol-3-yl)methyl]-2-oxo-4-(trifluoromethyl)pyridin-3-yl]oxybenzonitrile	CAS 1338225-97-0	<chem>CN1C(=NNC1=O)CN2C=CC(=C(C2=O)OC3=CC(=CC(=C3)C#N)C)C(F)F</chem>	MK-1439		Human immunodeficiency virus infection

IUPAC Name	CAS #	SMILES Notation	USAN Name / Trade Name	Representative Tx Class	Representative Disease
(Z)-but-2-enedioic acid; (E)-N-[4-{3-chloro-4-(pyridin-2-ylmethoxy)anilino}-3-cyano-7-ethoxyquinolin-6-yl]-4-(dimethylamino)but-2-enamide	CAS 915942-22-2	<chem>CCOC1=C(C=C2C(=C1)N=CC(=C2NC3=CC(=C(C=C3)OCC4=CC=CC(=N4)C)C#N)NC(=O)/C=C/CN(C)C.C(=C)\C(=O)O)\C(=O)O</chem>	NERATINIB MALEATE		HER2/NEU overexpressing breast cancer
2-[(8S,13S,14S,17R)-17-hydroxy-13-methyl-3-oxo-1,2,6,7,8,11,12,14,15,16-decahydrocyclopenta[a]phenanthren-17-yl]acetoneitrile	CAS 65928-58-7	<chem>C[C@]12CCC3=C4CCC(=O)C=C4CC[C@H]3[C@@H]1CC[C@]2(CCC#N)O</chem>	Oestradiol valerate and dienogest		Endometriosis; Contraception
5-imidazo[1,2-a]pyridin-6-yl-6-methyl-2-oxo-1H-pyridine-3-carbonitrile	CAS 106730-54-5	<chem>CC1=C(C=C(C(=O)N1)C#N)C2=CN3C=CN=C3C=C2</chem>	Olprinone		Heart failure
4-[(5R)-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-5-yl]-3-fluorobenzonitrile	CAS 928134-65-0	<chem>C1CC2=CN=CN2[C@H]1C3=C(C=C(C=C3)C#N)F</chem>	Osilodrostat		Cushing disease
5-[3-{[(1S)-1-(2-hydroxyethylamino)-2,3-dihydro-1H-inden-4-yl]-1,2,4-oxadiazol-5-yl]-2-propan-2-yloxybenzonitrile	CAS 1306760-87-1	<chem>CC(C)OC1=C(C=C(C(=C1)C2=NC(=NO2)C3=C4CC[C@H](C4=CC=C3)NCCO)C#N</chem>	Ozanimod		Crohn disease; Ulcerative colitis; Non-small-cell lung cancer; Multiple sclerosis
1-[(2R,4R)-2-(1H-benzimidazol-2-yl)-1-methylpiperidin-4-yl]-3-(4-cyanophenyl)urea	CAS 1095173-27-5	<chem>CN1CC[C@H](C[C@H]1C2=NC3=CC=C(C=C3N2)NC(=O)NC4=CC=C(C=C4)C#N</chem>	PF-04449913		Chronic myelomonocytic leukaemia; Solid tumour/cancer
1-cyano-2-(3,3-dimethylbutan-2-yl)-3-pyridin-4-ylguanidine	CAS 60560-33-0	<chem>CC(C)(C)C(C)N=C(NC#N)NC1=CC=NC=C1</chem>	Pinacidil	Antihypertensive Agents	High blood pressure
10-[3-{(4-hydroxypiperidin-1-yl)propyl}phenothiazine-2-carbonitrile	CAS 2622-26-6	<chem>C1CN(CCC1O)CCCN2C3=CC=CC=C3SC4=C2C=C(C=C4)C#N</chem>	Propericiazine	Antipsychotic Agents	Psychiatric disorder
2-ethylbutyl (2S)-2-[[[(2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxyoxolan-2-yl]methoxy-phenoxyphosphoryl]amino]propanoate	CAS 1809249-37-3	<chem>CCC(CC)COC(=O)[C@H](C)N[P@]([O])(O)C[C@H]1[C@H]([C@H]([C@H]([C@]([O1])(C#N)C2=CC=C3N2N=CN=C3N)O)OC4=CC=CC=C4</chem>	Remdesivir		Ebola virus infection; Coronavirus Disease 2019 (COVID-19)
4-[[4-{(E)-2-cyanoethenyl}-2,6-dimethylanilino]pyrimidin-2-yl]amino]benzonitrile	CAS 500287-72-9	<chem>CC1=CC(=CC(=CC1=CN2=NC(=NC=C2)NC3=CC=C(C=C3)C#N)C)/C=C/C#N</chem>	Rilpivirine		Human immunodeficiency virus infection; Pain
(3R)-3-cyclopentyl-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)pyrazol-1-yl]propanenitrile	CAS 941678-49-5	<chem>C1CCC(C1)C@H[CC#N]N2C=C(C(=N2)C3=C4C=CN4=NC=N3</chem>	Ruxolitinib		High-risk myelofibrosis; Pancreatic cancer; Essential thrombocythemia; Atopic dermatitis; Vitiligo

IUPAC Name	CAS #	SMILES Notation	USAN Name / Trade Name	Representative Tx Class	Representative Disease
(1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxy-1-adamantyl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile	CAS 361442-04-8	<chem>C1[C@H]2C[C@H]2N1[C@@H]1C#N(C(=O)[C@H](C34CC5CC(C3)CC(C5)(C4)O)N</chem>	Saxagliptin		Type-2 diabetes
4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-7-[5-[(4-methylpiperazin-1-yl)methyl]furan-3-yl]quinoline-3-carbonitrile		<chem>CN1CCN(CC1)CC2=CC(=CO2)C3=C(C=C4C(=C3)N=CC(=C4NC5=CC(=C(C=C5C)Cl)OC)C#N)OC</chem>	SKI-758		Ischemia
3-[1-[3-[5-[(1-methylpiperidin-4-yl)methoxy]pyrimidin-2-yl]phenyl]methyl]-6-oxopyridazin-3-yl]benzonitrile	CAS 1100598-32-0	<chem>CN1CC(C(C1)COC2=CN=C(N=C2)C3=CC=CC(=C3)CN4C(=O)C=CC(=N4)C5=CC=CC(=C5)C#N</chem>	Tepotinib		Solid tumour/cancer; Hepatocellular carcinoma; Non-small cell lung cancer
(Z)-2-cyano-3-hydroxy-N-{4-(trifluoromethyl)phenyl}but-2-enamide	CAS 163451-81-8	<chem>C/C(=C(\C#N)/C(=O)N)C1=CC=CC(=C1)C(F)(F)F/O</chem>	Teriflunomide		Hyperlipidaemia; Multiple sclerosis; Hepatitis B virus infection; Rheumatoid arthritis
3-[(3R,4R)-4-methyl-3-[methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]piperidin-1-yl]-3-oxopropanenitrile	CAS 477600-75-2	<chem>C[C@H]1CCN(C[C@H]1N(C)C2=NC=NC3=C2C=CN3)C(=O)CC#N</chem>	Tofacitinib		Rheumatoid arthritis
(1S,2R,6R,8S,11S,12S,15S,16S)-5,15-dihydroxy-2,16-dimethyl-7-oxapentacyclo[9.7.0.02,8.06,8.012,16]octadec-4-ene-4-carbonitrile	CAS 13647-35-3	<chem>C[C@H]12CC[C@H]3[C@H]1[C@@H]1CC[C@@H]2O)CC[C@H]45[C@@]3(C)CC(=C([C@H]4O5)O)C#N)C</chem>	Trilostane		Cushing disease
2-(3,4-dimethoxyphenyl)-5-[2-(3,4-dimethoxyphenyl)ethyl-methylamino]-2-propan-2-ylpentanenitrile	CAS 52-53-9	<chem>CC(C)C(CCCN(C)CCC1=CC(=C(C=C1)OC)OC)C(C#N)C2=CC(=C(C=C2)OC)OC</chem>	Verapamil	Analgesics	Hypertension
5-[4-[4-(5-cyano-1H-indol-3-yl)butyl]piperazin-1-yl]-1-benzofuran-2-carboxamide	CAS 163521-12-8	<chem>C1CN(CCN1CCCCC2=CNC3=C2C=C(C(=C3)C#N)C4=CC5=C(C=C4)OC(=C5)C(=O)N</chem>	Vilazodone		Major depressive disorder
(2S)-1-[2-[(3-hydroxy-1-adamantyl)amino]acetyl]pyrrolidine-2-carbonitrile	CAS 274901-16-5	<chem>C1C[C@H](N(C1)C(=O)CNC23CC4CC(C2)CC(C4)(C3)O)C#N</chem>	Vildagliptin		Type-2 diabetes
N-[4-(1-cyanocyclopentyl)phenyl]-2-(pyridin-4-ylmethylamino)pyridine-3-carboxamide; methanesulfonic acid	CAS 1218779-75-9	<chem>CS(=O)(=O)O.C1CCC(C1)(C#N)C2=CC=C(C(=C2)N(C(=O)C3=C(N=CC=C3)NCC4=CC=CC=C4)C#N)C(=O)C</chem>	Yn-968D1		Breast cancer
N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-ethylacetamide	CAS 151319-34-5	<chem>CCN(C1=CC=CC(=C1)C2=CC=CC(=C2)C(=N)N23)C#N)C(=O)C</chem>	Zaleplon	Hypnotics and Sedatives	Insomnia

Table 2. Cyano-containing small molecule drugs that are in clinical trials.

IUPAC Name	CAS #	SMILES Notation	USAN Name / Trade Name	Representative Tx Class	Representative Disease
3-O-methyl 5-O-propan-2-yl 2-cyano-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate	CAS 75530-68-6	<chem>CC1=C(C(C(=C(N1)C#N)C(=O)OC)C2=CC(=CC=C2)[N+](=O)[O-])C(=O)OC(C)C</chem>	Arc029		Alzheimer disease
methyl (4aS,6aR,6bS,8aR,12aS,14aR,14bS)-11-cyano-2,2,6a,6b,9,9,12a-heptamethyl-10,14-dioxo-1,3,4,5,6,7,8a,14a,14b-decahydropicene-4a-carboxylate	CAS 218600-53-4	<chem>C[C@@]12CC[C@]3(CCC(C[C@H]3[C@H]1C(=O)C=C4[C@]2(CC[C@H]5[C@@]4(C(=C(=O)C5(C)C#N)C)C(C)C(=O)OC</chem>	Bardoxolone methyl		Mixed connective tissue disease; Pulmonary arterial hypertension; Pulmonary hypertension
7-[(4aS,7aS)-3,4,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazin-6-yl]-8-cyano-1-cyclopropyl-6-fluoro-4-oxoquinoline-3-carboxylic acid;hydrochloride	CAS 209342-41-6	<chem>C1CC1N2C=C(C(=O)C3=CC(=C(C(=C3)2)C#N)N4C[C@H]5[C@H]([C4]OCCN5)F)C(=O)O.Cl</chem>	BAY-35-3377		Otitis media
(2R,3S,4S,5R)-2-(4-amino-2-oxopyrimidin-1-yl)-4-hydroxy-5-(hydroxymethyl)oxolane-3-carbonitrile	CAS 135598-68-4	<chem>C1=CN(C(=O)N=C1N)[C@H]2[C@H]([C@@H]([C@H]([C@H]([O2]CO)O)C#N</chem>	DFP-10917		Acute lymphoblastic leukaemia; Solid tumour/cancer; Acute myeloid leukaemia
(4S)-4-(4-cyano-2-methoxyphenyl)-5-ethoxy-2,8-dimethyl-1,4-dihydro-1,6-naphthyridine-3-carboxamide	CAS 1050477-31-0	<chem>CCOC1=NC=C(C2=C1[C@@H]([C@H]([C@H]([C@H]([O2]C3=CC(=C(C(=C3)C#N)OC)C</chem>	Finerenone		Diabetic nephropathy
(2R,3R,4S,5R)-2-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-3,4-dihydroxy-5-(hydroxymethyl)oxolane-2-carbonitrile	CAS 1191237-69-0	<chem>C1=C2C(=NC=NN2C(=C1)[C@]3([C@@H]([C@@H]([C@H]([O3]CO)O)O)C#N)N</chem>	GS-441524	Antiviral Agents	Coronavirus Disease 2019 (COVID-19)
4-[3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl]-2-fluoro-N-(trideuteriomethyl)benzamide	CAS 1443331-82-5	<chem>[2H]C([2H])([2H])NC(=O)C1=C(C(=C(C=C1)N2C(=S)N(C(=O)C2(C)C)C3=CC(=C(C(=C3)C#N)C(F)F)F</chem>	HC-1119		Prostate cancer
(E)-N-[4-[3-chloro-4-(pyridin-2-ylmethoxy)anilino]-3-cyano-7-ethoxyquinolin-6-yl]-4-(dimethylamino)but-2-enamide	CAS 698387-09-6	<chem>CCOC1=C(C(=C2C(=C1)N=CC(=C2)NC3=CC(=C(C(=C3)OCC4=CC=CC(=C4)C)C#N)NC(=O)/C=C/CN(C)C</chem>	HKI-272	Anticancer Agents	Breast cancer

IUPAC Name	CAS #	SMILES Notation	USAN Name / Trade Name	Representative Tx Class	Representative Disease
4-[2-[(2R,3R)-3-(2,5-difluorophenyl)-3-hydroxy-4-(1,2,4-triazol-1-yl)butan-2-yl]-1,3-thiazol-4-yl]benzonitrile	CAS 241479-67-4	<chem>[C@H](c1cc(C#N)[C@@H](c2cc(=O)c(c1)=CC=C(F)F)O)</chem>	Isavuconazole		Invasive aspergillosis; Invasive candidiasis; Candidemia
(3R)-3-cyclopentyl-3-[4-{(7H-pyrrolo[2,3-d]pyrimidin-4-yl)pyrazol-1-yl}propanenitrile;phosphoric acid N-(cyanomethyl)-4-[2-(4-morpholin-4-ylanilino)pyrimidin-4-yl]benzamide	CAS 1092939-17-7 CAS 1056634-68-4	<chem>C1CCC(C1)[C@@H]([C@H]([C@H])NC2C=C(C(N2)=N)C3=C4C=C(CNC4=NC=N3.OP(=O)(O)O)</chem> <chem>C1COCCN1C2=CC=C(C(C=C2)NC3=NC=CC(=N3)C4=CC=C(C(C=C4)C(=O)NCC#N</chem>	Jakafi Mometotinib		Essential thrombocythemia Myelofibrosis; Polycythemia vera; Thrombocythemia
2-[(2S)-4-[7-(8-chloronaphthalen-1-yl)-2-[[{(2S)-1-methylpyrrolidin-2-yl)methoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]-1-(2-fluoroprop-2-enoyl)piperazin-2-yl]acetoneitrile	CAS 2326521-71-3	<chem>CN1CCCC[C@H]1COC2=NC3=C(CCN(C3)C4=CC=CC5=C4C(=CC=C5)Cl)C(=N2)N6CCN([C@H]([C@H])(C6)CC#N)C(=O)C(=O)CF</chem>	MRTX849		Non-small-cell lung cancer
(2S)-N-(1-cyanocyclopropyl)-4-fluoro-4-methyl-2-[[{1S}-2,2,2-trifluoro-1-[4-(4-methylsulfonylphenyl)phenyl]ethyl]amino]pentanamide	CAS 603139-19-1	<chem>CC(C)[C][C@H]([C](C(=O)NC1(CC1)C#NN)[C@@H]([C2=CC=C(C(C=C2))C3=CC=C(C=C3)S(=O)(=O)C(C(F)F)F)F</chem>	Odanacatib		Osteoporosis
3-[[{(1S,2S,3R)-2,3-difluoro-1-hydroxy-7-methylsulfonyl-2,3-dihydro-1H-inden-4-yl]oxy]-5-fluorobenzonitrile	CAS 1672668-24-4	<chem>CS(=O)(=O)C1=C2[C@@H]([C@H]([C@H]([C@@H]([C@@H](C2=C(C(C=C1)OC3=CC(=CC(=C3)C#N)F)F)F)O</chem>	PT2977		Solid tumour/cancer; Von hippel-lindau disease; Renal cell carcinoma
2-ethylbutyl [(2S)-2-[[[(2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxoxolan-2-yl]]methoxy-phenoxy]phosphoryl]amino]propanoate	CAS 1809249-37-3	<chem>CCC(CC)COC(=O)[C@H]([C@H]([C@H]([C@H]([C@@H](OC[C@@H]1[C@H]1[C@H]([C@H]([C@H]([C@H](O1)C#N)C2=CC=C(C3N2N=CN=C3N)O)O)OC4=CC=CC=C4</chem>	Remdesivir	Antiviral Agents	Ebola virus infection; COVID-19; MERS; SARS
4-[[{(2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-(2,2-dimethylpropyl)pyrrolidine-2-carbonyl]amino]-3-methoxybenzoic acid	CAS 1229705-06-9	<chem>CC(C)[C][C@H]1[C@H]([C@H]([C@H]([C@H]([C@H]([C@H]([C@H]1C(=O)NC2=C(C(C=C2)C(=O)OC)C3=C(C(=CC=C3)Cl)F)(C#N)C4=C(C(C=C(C=C4)Cl)F</chem>	RG7388		Haematological malignancy; Solid tumour/cancer; Polycythemia vera; Acute myeloid leukaemia

IUPAC Name	CAS #	SMILES Notation	USAN Name / Trade Name	Representative Tx Class	Representative Disease
1-[2-[(3R,5R,8R,9R,10S,13S,14S,17S)-3-hydroxy-3,13-dimethyl-2,4,5,6,7,8,9,10,11,12,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl]pyrazole-4-carbonitrile	CAS 1632051-40-1	<chem>C[C@]1(CC[C@H]2[C@@H]1CC[C@@H]3[C@@H]2CC[C@]4([C@H]3CC[C@H]4C(=O)CN5C=C(C(=N5)C#N)CO</chem>	SAGE-217		Essential tremor or related tremors; Major depressive disorder; Parkinson disease; Postpartum depression
2-[[6-[(3R)-3-aminopiperidin-1-yl]-3-methyl-2,4-dioxypyrimidin-1-yl]methyl]-4-fluorobenzonitrile	CAS 865759-25-7	<chem>CN1C(=O)C=C(N(C1=O)CC2=C(C=CC(=C2)F)C#N)N3CCCC[C@H]1(C3)N</chem>	SYR-472		Non-insulin dependent diabetes; Metabolic disorder
2-[2-hydroxy-3-[[1-(1H-indol-3-yl)-2-methylpropan-2-yl]amino]propoxy]benzonitrile	CAS 71119-11-4	<chem>CC(C)(CC1=CNC2=CC=CC=C21)NCC(COC3=CC=CC=C3C#N)O</chem>	Bucindolol		Hypertension; Atrial fibrillation
(2S,4S)-1-[[2S)-2-amino-3,3-bis(4-fluorophenyl)propanoyl]-4-fluoropyrrolidine-2-carbonitrile	CAS 483369-58-0	<chem>C1[C@@H](CN[C@@H]1C#N)C(=O)[C@H](C2=CC=C(C(=C2)F)C3=CC=C(C(=C3)FN)F</chem>	Denaglipatin		Type-2 diabetes
N-[3-[(4S)-2-amino-4-methyl-1,3-thiazin-4-yl]-4-fluorophenyl]-5-cyanopyridine-2-carboxamide	CAS 1200493-78-2	<chem>C[C@]1(C=CSC(=N1)N)C2=C(C=CC(=C2)NC(=O)C3=NC=C(C(=C3)C#N)F</chem>	JNJ-54861911		Alzheimer disease
4-cyano-N-[(2R)-2-[4-(2,3-dihydro-1,4-benzodioxin-5-yl)piperazin-1-yl]propyl]-N-pyridin-2-ylbenzamide;hydrochloride	CAS 433282-68-9	<chem>C[C@H](CN(C1=CC=CC=N1)C(=O)C2=CC=C(C(=C2)C#N)N3CCN(CC3)C4=C5C(=CC=C4)OCCO5.Cl</chem>	LECOZOTAN HYDROCHLORIDE		Cognitive impairment
2-(3,4-dimethoxyphenyl)-5-[2-(3,4-dimethoxyphenyl)ethyl-methylamino]-2-propan-2-ylpentanenitrile	CAS 52-53-9	<chem>CC(C)(CCCN(C)CCC1=CC(=C(C(=C1)OC)OC(C#N)C2=CC(=C(C(=C2)OC)OC</chem>	Verapamil	Antiviral Agents	Coronavirus Disease 2019 (COVID-19)
3-O-(2-methoxyethyl) 5-O-propan-2-yl 4-(2-chloro-3-cyanophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate		<chem>CC1=C(C(C(=C(N1)C(C(=O)OC(C)C)C2=CC=CC(=C2C)C#N)C(=O)OCCOC</chem>	MEM-1003		Dementia; Bipolar disorder
4-[[1-hydroxy-3H-2,1-benzoxaborol-5-yl]oxy]benzene-1,2-dicarbonitrile	CAS 906673-33-4	<chem>B1(C2=C(CO1)C=C(C(=C2)OC3=CC(=C(C=C3)C#N)C#N)O</chem>	AN-2898		Atopic dermatitis
(2R)-2-(3,4-dimethoxyphenyl)-5-[2-(3,4-dimethoxyphenyl)ethylamino]-2-propan-2-ylpentanenitrile	CAS 123932-43-4	<chem>CC(C)[C@@]([CCNCCC1=CC(=C(C(=C1)OC)OC(C#N)C2=CC(=C(C(=C2)OC)OC</chem>	Arverapamil		Irritable bowel syndrome

IUPAC Name	CAS #	SMILES Notation	USAN Name / Trade Name	Representative Tx Class	Representative Disease
2-[1-[4-[4-(4-hydroxypiperidin-1-yl)anilino]-5-oxo-6H-pyrimido[4,5-d]pyridazin-2-yl]piperidin-4-yl]acetoneitrile	CAS 1425381-60-7	<chem>C1CN(CCC1CC#N)C2=NC3=C(C(=O)N)N=C3)C(=N2)NC4=CC=C(C(=C4)N5CC(C(C5)O</chem>	gusacitinib, ASN002		Eczema; Lymphoma; Solid tumour/cancer
(4S)-4-(4-cyano-2-methylsulfonylphenyl)-3,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-4H-pyrimidine-5-carbonitrile	CAS 1161921-82-9	<chem>CC1=C([C@H](N(C(=O)N)C2=CC=CC(=C2)C(F)(F)F)C)C3=C(C(=C(C(=C3)C#N)S(=O)(=O)C)C#N</chem>	BAY 85-8501		Bronchiectasis
propan-2-yl (4R)-2-amino-5-cyano-6-methyl-4-(3-phenylquinolin-5-yl)-1,4-dihydropyridine-3-carboxylate	CAS 146136-94-9	<chem>CC1=C([C@H](C(=C(N1)N)C(=O)OC(C)C2=C3C=C(C(=NC3=CC=C2)C4=C(C=CC=C4)C#N</chem>	BAY-Y-5959		Cardiovascular disease
2-methyl-2-[4-(3-methyl-2-oxo-8-quinolin-3-ylimidazo[4,5-c]quinolin-1-yl)phenyl]propanenitrile	CAS 915019-65-7	<chem>CC(C)(C#N)C1=CC=C(C(=C1)N2C3=C4C=C(C(=CC4=NC=C3N(C2=O)C)C5=CC6=CC=CC=C6N=C5</chem>	BEZ235		Solid tumour/cancer
2,2-dimethyl-4-(2-oxopyridin-1-yl)chromene-6-carbonitrile	CAS 117545-11-6	<chem>CC1(C=C(C2=C(C(O1)C=CC(=C2)C#N)N3C=CC=CC3=O)C</chem>	Bimakalim		Angina pectoris
2-amino-6-[[2-(4-chlorophenyl)-1,3-thiazol-4-yl]methylsulfonyl]-4-[4-(2-hydroxyethoxy)phenyl]pyridine-3,5-dicarbonitrile	CAS 544417-40-5	<chem>C1=CC(=CC=C1C2=C(C(=NC(=C2C#N)SCC3=CSC(=N3)C4=CC=C(C(=C4)Cl)N)C#N)OCCO</chem>	Capadenoson		Atrial fibrillation
4-[2-(4-aminopiperidin-1-yl)-5-(3-fluoro-4-methoxyphenyl)-1-methyl-6-oxopyrimidin-4-yl]-2-fluorobenzonitrile	CAS 1821307-10-1	<chem>NC1CCN(CC1)C=1N(C(C(=C(N1)C1=C(C(=C(C#N)C=C1)F)C1=CC(=C(C(=C1)O)C(F)=O)C</chem>	Pulrodestat; CC-90011; UNII-W6F4FRQ5QC; W6F4FRQ5QC		Lymphoma; Non-hodgkin lymphoma
4-[2-(4-aminopiperidin-1-yl)-5-(3-fluoro-4-methoxyphenyl)-1-methyl-6-oxo-1,6-dihydropyrimidin-4-yl]-2-fluorobenzonitrile; Benzonitrile, 4-(2-(4-amino-1-piperidinyl)-5-(3-fluoro-4-methoxyphenyl)-1,6-dihydro-1-methyl-6-oxo-4-pyrimidinyl)-2-fluoro- Free base, besylate					

IUPAC Name	CAS #	SMILES Notation	USAN Name / Trade Name	Representative Tx Class	Representative Disease
4-[2-(4-aminopiperidin-1-yl)-5-(3-fluoro-4-methoxyphenyl)-1-methyl-6-oxopyrimidin-4-yl]-2-fluorobenzonitrile	CAS 1821307-10-1	<chem>CN1C(=O)C(=C(N=C1N2CCC(CC2)N)C3=CC(=C(C(=C3)C#N)F)C4=CC(=C(C=C4)OC)F</chem>	CC-90011		Lymphoma; Non-hodgkin lymphoma
(3R)-3-(2,2,3,3,4,4,5-octadeuteriocyclopentyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)pyrazol-1-yl]propanenitrile	CAS 1513883-39-0	<chem>[2H]C1(C(C(C(C1([2H]))[2H]))([2H]))[2H]C(=N2)C3=C4C=CNC4=NC(=N3)[2H]</chem>	deuruxolitinib, CTP-543		Alopecia
3-methylsulfonylpropanenitrile	CAS 54863-37-5	<chem>CS(=O)(=O)CCCN</chem>	Dapansutrole		Acute gout flare; Musculoskeletal pain
3-cyano-N-(3-cyano-4-methyl-1H-indol-7-yl)benzenesulfonamide	CAS 289483-69-8	<chem>CC1=C2C(=NC2=C(C(=C1)NS(=O)(=O)C3=CC=CC(=C3)C#N)C#N</chem>	E7820		Solid tumour/cancer; Colorectal cancer
5-[2-(3,4-dimethoxyphenyl)ethyl-methylamino]-2-propan-2-yl-2-(3,4,5-trimethoxyphenyl)pentanenitrile	CAS 16662-47-8	<chem>CC(C)C(CCCN(C)CCC1=CC(=C(C(=C1)OC)OC(C#N)C2=CC(=C(C(=C2)OC)OC)C)OC</chem>	Gallopamil		Hypertension; Asthma
N-(4-bromo-2-cyanophenyl)-4-(diethoxyphosphorylmethyl)benzamide	CAS 133208-93-2	<chem>CCOP(=O)(CC1=CC=C(C(=C1)C(=O)NC2=C(C(=C(C(=C2)Br)C#N)OCC</chem>	Ibrolipim		Hyperlipidaemia
5-chloro-3-[(3-[(E)-2-cyanoethenyl]-5-methylphenyl)-methoxyphosphoryl]-1H-indole-2-carboxamide		<chem>CC1=CC(=CC(=C1)P(=O)(C2=C(NC3=C2C=C(C(=C3)Cl)C(=O)N)OC)/C=C/C#N</chem>	IDX899		Human immunodeficiency virus infection
2-[1-[3-fluoro-2-(trifluoromethyl)pyridine-4-carbonyl]piperidin-4-yl]-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)pyrazol-1-yl]azetidin-3-yl]acetoneitrile	CAS 1334298-90-6	<chem>C1CN(CCC1N2CC(C2)(CC#N)N3C=C(C(=N3)C4=C5C=CN(C5=NC(=N4)C(=O)C6=C(C(=NC(=C6)C(F)(F)F</chem>	itacitinib, INCB039110		Malignant neoplasm; Non-small-cell lung cancer
5-cyano-N-[2-(4,4-dimethylcyclohexen-1-yl)-6-(2,2,6,6-tetramethyloxan-4-yl)pyridin-3-yl]-1H-imidazole-2-carboxamide	CAS 1142363-52-7	<chem>CC1(CCC(=CC1)C2=C(C(=CC(=N2)C3C(C(OC(C3)(C(C)(C)C)NC(=O)C4=NC=C(N4)C#N)C</chem>	INJ-40346527		Hodgkin lymphoma
3-cyanopropyl carbamidodithioate	CAS 500863-50-3	<chem>C(CC#N)CSC(=N)N</chem>	Kevetrin		Solid tumour/cancer; Ovarian cancer
3-[(3S,4R)-3-methyl-7-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1,7-diazaspiro[3.4]octan-1-yl]-3-oxopropanenitrile	CAS 1263774-59-9	<chem>C[C@H]1CN([C@112CCN(C2)C3=NC=NC4=C3C=CN4)C(=O)CC#N</chem>	delgocitinib, LEO 124249		Asthma; Eczema

IUPAC Name	CAS #	SMILES Notation	USAN Name / Trade Name	Representative Tx Class	Representative Disease
decahydropicen-4a-yl]-2,2-difluoropropanamide		<chem>[J5][C@@H]4(C=C(C(=O)C5(C)C#N)C)C(C)CNC(=O)C(C)(F)F</chem>			Psychiatric disorder
2-[4-cyano-4-(3-cyclopentyl-4-methoxyphenyl)piperidin-1-yl]-N-hydroxyacetamide	CAS 401519-28-6	<chem>CCOC1=C(C=C(C(=O)C2(CCN(CC2)CC(=O)NO)C#N)OC3CCCC3</chem>	ONO-6126		Chronic obstructive pulmonary disease
(E)-N-[4-(3-chloro-4-fluoroanilino)-3-cyano-7-ethoxyquinolin-6-yl]-4-(dimethylamino)but-2-enamide	CAS 257933-82-7	<chem>CCOC1=C(C=C(C2(C(=O)N=CC(C2)NCC3=CC(=C(C(=O)C(C)C)C#N)C(C)C</chem>	Pelitinib		Lymphoma
N-[(3S,4S)-4-[4-(5-cyanothiophen-2-yl)phenoxy]oxolan-3-yl]propane-2-sulfonamide	CAS 1258963-59-5	<chem>CC(C)S(=O)(=O)N(C(=O)N[C@H]1COC(C@H)1OC2=CC=C(C(=O)C(S3)C#N</chem>	PF-04958242		Schizophrenia
(16R)-19-amino-13-fluoro-4,8,16-trimethyl-9-oxo-17-oxa-4,5,8,20-tetrazatetracyclo[16.3.1.02,6.010,15]docosa-1(22),2,5,10(15),11,13,18,20-octaene-3-carbonitrile	CAS 1454846-35-5	<chem>C[C@H]1C2=C(C(=CC(=C2)F)C(=O)N(CC3=NN(C(=C3C4=CC(=C(N=C4)N)O1)C#N)C)C</chem>	PF-06463922		Solid tumour/cancer; Non-small-cell lung cancer
3-(cyanomethyl)-3-[4-[6-(1-methylpyrazol-4-yl)pyrazolo[1,5-a]pyrazin-4-yl]pyrazol-1-yl]cyclobutane-1-carbonitrile	CAS 2127109-84-4	<chem>CN1C=C(C(=N1)C2=CN3C(=CC=N3)C(=N2)C4=CN(N=C4)C5(CC(C5)C#N)CC#N</chem>	PF-06826647		Plaque psoriasis
2-[[4-[6-[(4-cyano-2-fluorophenyl)methoxy]pyridin-2-yl]piperidin-1-yl]methyl]-3-[[[(2S)-oxetan-2-yl]methyl]benzimidazole-5-carboxylic acid	CAS 2230198-02-2	<chem>C1CO[C@H]1CN2C3=C(C=CC(=C3)C(=O)O)N=C2CN4CCC(C4)C5=NC(=CC=C5)OCC6=C(C=C(C(=C6)C#N)F</chem>	PF-06882961		Type 2 diabetes
(E)-2-[[3R)-3-[4-amino-3-(2-fluoro-4-phenoxyphenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile	CAS 1575596-29-0	<chem>CC(C)/C=C(C(\C#N)/C(=O)N1CCCC[C@H]1C1N2C3=NC=NC(=C3C(=N2)C4=C(C(=C(C(=C4)OC5=CC=CC(=C5)F)N)N6CCN(CC6)C7COC7</chem>	PRN1008		Pemphigus vulgaris
7-[4-[2-(4-fluorophenyl)ethyl]piperazine-1-carbonyl]-1H-indole-3-carbonitrile	CAS 443144-26-1	<chem>C1CN(CCN1CCC2=CC=C(C(=C2)F)C(=O)C3=CC=CC4=C3NC=C4C#N</chem>	PRUVANSERIN		Sleep-wake disorder
5-[[4-[(6-chlorothieno[2,3-d]pyrimidin-4-yl)amino]piperidin-1-yl]methyl]-2-fluorobenzonitrile	CAS 866206-54-4	<chem>C1CN(CCC1NC2=C3C=C(C(SC3=NC=N2)C)CC4=CC(=C(C(=C4)F)C#N</chem>	PRX-08066		Pulmonary arterial hypertension
3-[[[(1S)-2,2-difluoro-1-hydroxy-7-methylsulfonyl-1,3-dihydroinden-4-yl]oxy]-5-fluorobenzonitrile	CAS 1672665-49-4	<chem>CS(=O)(=O)C1=C2[C@H]1C(CC2=C(C=C1)OC3=CC(=CC(=C3)C#N)F)(F)F</chem>	PT2385		Recurrent glioblastoma; Von hippel-lindau

IUPAC Name	CAS #	SMILES Notation	USAN Name / Trade Name	Representative Tx Class	Representative Disease
2-[3-(4-cyanonaphthalen-1-yl)pyridin-4-yl]sulfanyl-2-methylpropanoic acid	CAS 1352792-74-5	<chem>CC(C)(C(=O)O)SC1=C(C=NC=C1)C2=CC=C(C3=CC=CC=C3)C#N</chem>	RDEA3170		disease; Brain cancer
(2S,4R)-N-(1-cyanocyclopropyl)-4-[4-(1-methylpyrazol-4-yl)-2-(trifluoromethyl)phenyl]sulfonyl-1-[1-(trifluoromethyl)cyclopropanecarbonyl]pyrrolidine-2-carboxamide	CAS 1252637-35-6	<chem>CN1C=C(C=N1)C2=CC(=C(C=C2)S(=O)(=O)[C@@H]3C[C@H](N(C3)C(=O)C4(C4)C(F)(F)C(=O)NC5(C5)C#N)C(F)(F)F</chem>	RG7625		Autoimmune disease; Coeliac disease; Sjogren syndrome
1-(2-bromophenyl)-3-(7-cyano-2H-benzotriazol-4-yl)urea	CAS 211096-49-0	<chem>C1=CC=C(C(C=C1)NC(=O)NC2=CC=C(C3=NNN=C23)C#N)Br</chem>	SB-265610		Chronic obstructive pulmonary disease; Asthma
(3S,6S)-6-[[[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]methyl]-3-(5-oxo-1H-1,2,4-triazol-4-yl)-6-phenylpiperidine-3-carbonitrile	CAS 873947-10-5	<chem>C[C@H](C1=CC(=CC(=C1)C(F)(F)F)C(F)(F)F)OC[C@]12(CC[C@](CN2)(C#N)N3C=NNC3=O)C4=CC=CC=C4</chem>	SCH-900978		Cough
3-fluoro-5-[5-[2-(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridin-2-yl]benzonitrile	CAS 935685-90-8	<chem>CC1=NC(=CS1)C#CC2=CN=C(C=C2)C3=CC(=CC(=C3)C#N)F</chem>	STX-107		Autism spectrum disorder
4-(5-pyridin-4-yl-1H-1,2,4-triazol-3-yl)pyridine-2-carbonitrile	CAS 577778-58-6	<chem>C1=CN=CC=C1C2=NC(=NN2)C3=CC(=NC=C3)C#N</chem>	Topiroxostat		Gout
4-[1-[4-cyclobutyl-2-methyl-5-(5-methyl-1H-1,2,4-triazol-3-yl)benzoyl]piperidin-4-yl]benzonitrile		<chem>CC1=CC(=C(C=C1C(=O)N2CCC(CC2)C3=CC=C(C=C3)C#N)C4=NNC(=N4)C)C5CCCC5</chem>	TVB-2640		Non-alcoholic fatty liver disease
[(2R)-1-cyanobutan-2-yl] N-[[[(1S)-1-[3-(3-methoxy-4-(1,3-oxazol-5-yl)phenyl]carbamoylamino]phenyl]ethyl]carbamate	CAS 297730-17-7	<chem>CC[C@H]([C@H](CC#N)OC(=O)N[C@@H]([C]1=CC(=CC=C1)NC(=O)NC2=CC(=C(C=C2)C3=CN=C(C3)C#N)OC</chem>	VX-944		Solid tumour/cancer
3-[2-amino-6-[1-[[[6-(2-hydroxypropan-2-yl)pyridin-2-yl]methyl]triazol-4-yl]pyrimidin-4-yl]-2-methylbenzonitrile	CAS 2239273-34-6	<chem>CC1=C(C=CC=C1C2=CC(=NC(=N2)N)C3=CN(N=N3)CC4=NC(=CC=C4)C(C)(C)O)C#N</chem>	AB928		Solid tumour/cancer; Metastatic colorectal cancer
(2S)-2,6-diamino-N-[4-[2-[2-[4-(2-cyanoethylamino)-1,2,5-oxadiazol-3-	CAS 1263384-43-5	<chem>C1=CC=C2C(=C1)N=C(N2CC(=O)C3=CC=C(C=C3)NC(=O)[C@H]([CCCCN])C4=NON=C4NCCCC#N</chem>	BAL-101553		Solid tumour/cancer;

IUPAC Name	CAS #	SMILES Notation	USAN Name / Trade Name	Representative Tx Class	Representative Disease
v benzimidazol-1-v acetyl phenyl hexanamide					Recurrent glioblastoma
2-[6-(4-chlorophenoxy)hexyl]-1-cyano-3-pyridin-4-ylguanidine	CAS 200484-11-3	C1=CC(=CC=C1OCCCCCN=C(NC#N)NC2=CC=NC=C2)Cl	CHS-828		Solid tumour/cancer
4-[[4-(2,4,6-trimethylanilino)pyrimidin-2-yl]amino]benzonitrile	CAS 244767-67-7	CC1=CC(=C(C(=C1)C)NC2=NC(=NC=C2)NC3=CC=C(C(=C3)C#N)C	Dapivirine		Human immunodeficiency virus infection
4-[(2S,3R,4S,5S,6R)-4-[(dimethylamino)methyl]-2,3-dihydroxy-10,12-dimethoxy-5-phenyl-7-oxa-11-azatricyclo[6.4.0.02,6]dodeca-1(12),8,10-trien-6-yl]benzonitrile	CAS 2098191-53-6	CN(C)C[C@@H]1[C@H]([C@H]([C@]12[C@@]([C@H]1O)(C3=C(N=C(C(=C3O2)OC)OC)O)C4=CC=C(C(=C4)C#N)C5=C(C=CC=C5	eFT226		Solid tumour/cancer
(E)-N-[(2S)-1-[5-[2-(4-cyanoanilino)-4-(propylamino)pyrimidin-5-yl]pent-4-ynylamino]-1-oxopropan-2-yl]-4-(dimethylamino)-N-methylbut-2-enamide	CAS 1472797-69-5	CCCCNC1=NC(=NC=C1C#CCCCNC(=O)[C@H](CN(C)C(=O)/C=C/CN(C)C)NC2=CC=C(C(=C2)C#N	FF-10101		Acute myeloid leukaemia
N-[5-cyano-4-(2-methoxyethylamino)pyridin-2-yl]-7-formyl-6-[(4-methyl-2-oxopiperazin-1-yl)methyl]-3,4-dihydro-2H-1,8-naphthyridine-1-carboxamide	CAS 1708971-55-4	CN1CCN(C(=O)C1)CC2=C(N=C3C(=C2)CCCN3C(=O)NC4=NC=C(C(=C4)NC(COC)C#N)C=O	FGF401		Hepatocellular carcinoma; Solid tumour/cancer
4-[(3S,3aS)-3-cyclopentyl-7-(4-hydroxypiperidine-1-carbonyl)-3,3a,4,5-tetrahydropyrazolo[3,4-f]quinolin-2-yl]-2-chlorobenzonitrile		C1CCC(C1)[C@H]12[C@H]1[C@@H]13CCCC(=C(C3=NN2C5=CC(=C(C(=C5)C#N)Cl)C=CC(=N4)C(=O)N6CCCC(CCC6)O	KBP-5074		Hypertension
4-methyl-5-[[4-[2-(methylamino)-6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl]amino]piperidin-1-yl]methyl]-1-[(2S)-2-(4-methylsulfonyl)piperazin-1-yl]propyl]indole-2-carbonitrile	CAS 2134675-36-6	CC1=C(C(=CC2=C1C=C(N2C[C@H](C)N3CCN(CCC3)S(=O)(=O)C)C#N)CN4CC(C(C4)NC5=C6C=C(C5C6=NC(=N5)NC)CC(F)(F)F	KO-539		Acute myeloid leukaemia
4-[(5R)-3-[4-cyano-3-(trifluoromethyl)phenyl]-4-oxo-2-sulfanylidene-7-oxa-1,3-diazaspiro[4.4]nonan-1-yl]-2-fluoro-N-methylbenzamide		CNC(=O)C1=C(C(=C(C(=C1)N2C(=S)N(C(=O)[C@]23CCOC3)C4=CC(=C(C(=C4)C#N)C(F)(F)F	ONC1-13B		Prostate cancer

IUPAC Name	CAS #	SMILES Notation	USAN Name / Trade Name	Representative Tx Class	Representative Disease
5-[8-oxo-5-(6-piperidin-4-yloxy)pyridin-3-yl]-6-sulfanylidene-5,7-diazaspiro[3.4]octan-7-yl]-3-(trifluoromethyl)pyridine-2-carbonitrile		<chem>C1CC2(C1)C(=O)N(C(=S)N2C3=CN=C(C=C3)OC4CCNCC4)C5=CC(=C(N=C5)C#N)C(F)(F)F</chem>	TRC-253		Prostate cancer
(E)-3-(6-bromopyridin-2-yl)-2-cyano-N-[(1S)-1-phenylethyl]prop-2-enamide	CAS 857064-38-1	<chem>C[C@@H](C1=CC=CC=C1)NC(=O)/C(=C/C2=NC(=CC=C2)Br)/C#N</chem>	WP-1066		Solid tumour/cancer; Brain cancer; Recurrent glioblastoma
4-[2-[2-[(2R)-2-methylpyrrolidin-1-yl]ethyl]-1-benzofuran-5-yl]benzonitrile	CAS 460746-46-7	<chem>C[C@@H](C1CCCC1)CCC2=CC3=C(O2)C=CC(=C3)C4=CC=C(C(=C4)C#N</chem>	ABT-239		Cognitive impairment
6-[2-(4-cyanophenyl)pyrazol-3-yl]-N-ethyl-5-methyl-3-oxo-4-[3-(trifluoromethyl)phenyl]pyrazine-2-carboxamide	CAS 956907-23-6	<chem>CCNC(=O)C1=NC(=C(N(C1=O)C2=CC=CC(=C2)C(F)(F)F)C3=CC=NN3C4=CC=C(C(=C4)C#N</chem>	AZD-9819		Chronic obstructive pulmonary disease
(E)-6-[3-[(N'-tert-butyl-N-cyanocarbamimidoyl)amino]phenyl]-6-pyridin-3-ylhex-5-enoic acid	CAS 149979-74-8	<chem>CC(C)C(N)=C(NC#N)NC1=CC=CC(=C1)/C(=C\CCCC(=O)O)/C2=CN=CC=C2</chem>	BIBV 308		Peripheral vascular disease
(3R)-3-benzyl-1-(1H-imidazol-5-ylmethyl)-4-thiophen-2-ylsulfonfyl-3,5-dihydro-2H-1,4-benzodiazepine-7-carbonitrile	CAS 195987-41-8	<chem>C1[C@H](N(C2=C(N1CC3=CN=CN3)C=CC(=C2)C#N)S(=O)(=O)C4=CC=CS4)CC5=CC=CC=C5</chem>	BMS214662	Anticancer Agents	Non-small-cell lung cancer
4-[(1E,3E)-4-[5-[(2R,3R)-3-(2,4-difluorophenyl)-3-hydroxy-4-(1,2,4-triazol-1-yl)butan-2-yl]sulfanyl-1,3-dioxan-2-yl]buta-1,3-dienyl]-3-fluorobenzonitrile	CAS 329744-44-7	<chem>C[C@H]([C@]([CN1C=NC=N1])(C2=C(C=C(C=C2)F)O)SC3COC(OC3)/C=C/C=C/C4=C(C=C(C(=C4)C#N)F</chem>	Embeconazole		Fungal infection
3-(1-ethylpiperidin-4-yl)oxy-5,8,10-triazatricyclo[7.4.0.0.2,7]trideca-1(9),2,4,6,10,12-hexaene-4-carbonitrile	CAS 1627539-18-7	<chem>CCN1CCC(CC1)OC2=C3C4=C(NC3=C(N=C2C#N)N=CC=C4</chem>	GDC-0425		Lymphoma
[4-[[N'-[6-(4-chlorophenoxy)hexyl]-N-cyanocarbamimidoyl]amino]pyridin-1-ium-1-yl]methyl 2-[2-[2-(methoxyethoxy)ethoxy]ethoxy]ethyl carbonate;chloride	CAS 432037-57-5	<chem>COCOCOCOCOCOC(=O)OC[N+]=CC=C(C=C1)NC(=NCCCCCOC2=CC=C(C(=C2)Cl)NC#N.[Cl-]</chem>	GMX1777	Anticancer Agents	Solid tumour/cancer
[(2R,3R,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-4-hydroxy-4-methyl-2-[[[(2S)-1-oxo-1-propan-2-	CAS 1350735-70-4	<chem>C[C@@H](C(=O)OC(C)CNP(=O)OC[C@@H]1[C@H]([C@@]([C@]([O1])C</chem>	GS-6620		Hepatitis C virus infection

IUPAC Name	CAS #	SMILES Notation	USAN Name / Trade Name	Representative Tx Class	Representative Disease
yloxypropan-2-yl]amino]-phenoxyphosphoryl]oxymethyl]oxolan-3-yl] 2-methylpropanoate		<chem>#N)C2=CC=C3N2N=CN=C3N)(C)O)C(=O)C(C)OC4=CC=CC=C4</chem>			
2,4-diamino-6-[[[S)-(5-chloro-8-fluoro-4-oxo-3-pyridin-3-ylquinazolin-2-yl)-cyclopropylmethyl]amino]pyrimidine-5-carbonitrile	CAS 1640247-87-5	<chem>C1CC1[C@@H](C2=NC3=C(C=CC(=C3C(=O)N2C4=CN=CC(=C4)C)F)NC5=NC(=NC(=C5C#N)N)N</chem>	GS-9901		Haematological malignancy
(1R,3S)-N-[[4-cyano-2-(trifluoromethyl)phenyl]methyl]-3-[[4-methyl-6-(methylamino)-1,3,5-triazin-2-yl]amino]cyclohexane-1-carboxamide	CAS 1142090-23-0	<chem>CC1=NC(=NC(=N1)N[C@H]2CCC[C@H](C2)C(=O)NCC3=C(C=C(C(=C3)C#N)C(F)(F)F)NC</chem>	GSK2256294		Chronic obstructive pulmonary disease
N-[4-[[2-[4-chloro-2-(3-chloro-5-cyanobenzoyl)phenoxy]acetyl]amino]-3-methylphenyl]sulfonylpropanamide		<chem>CCC(=O)NS(=O)(=O)C1=CC(=C(C=C1)NC(=O)COC2=C(C(=C(C(=C2)C)C(=O)C3=CC(=CC(=C3)C#N)C)C</chem>	GW-695634		Human immunodeficiency virus infection
(E)-but-2-enedioic acid;2-[1-[2-[[5-(piperidin-1-ylmethyl)furan-2-yl]methylamino]ethyl]imidazolidin-2-ylidene]propanedinitrile	CAS 135017-85-5	<chem>C1CCN(CC1)CC2=CC=C(C(=O2)CNCCN3CCNC3=C(C#N)C#N.C(=C/C(=O)O)\)C(=O)O</chem>	KW-5092		Pain
4-[[5-[[4-(3-chlorophenyl)-3-oxopiperazin-1-yl]methyl]imidazol-1-yl]methyl]benzonitrile	CAS 183499-57-2	<chem>C1CN(C(=O)CN1CC2=CN=CN2CC3=C(C=C(C(=C3)C#N)C4=CC(=CC(=C4)C)C1=CC2=C(NN=C2N=C1)CN3C4=C(C(=N3)C(=C(C(=C4)C)OC5=CC(=CC(=C5)C#N)C)C</chem>	L-778123		Lymphoma
3-chloro-5-[5-chloro-1-(2H-pyrazolo[3,4-b]pyridin-3-ylmethyl]indazol-4-yl]oxybenzonitrile	CAS 1034474-19-5	<chem>CCC(=O)C1=C(C(=C(C(=C1)F)[C@H]2C[C@H]2NC(=O)NC3=NC=C(C(=C3)C#N)O</chem>	MK-6186		Human immunodeficiency virus infection
1-(5-cyanopyridin-2-yl)-3-[(1R,2R)-2-(6-fluoro-2-hydroxy-3-propanoylphenyl)cyclopropyl]urea		<chem>CCC(=O)C1=C(C(=C(C(=C1)F)[C@H]2C[C@H]2NC(=O)NC3=NC=C(C(=C3)C#N)O</chem>	MSH-372		Human immunodeficiency virus infection
2-amino-5-(2-fluorophenyl)-4-methyl-1H-pyrrole-3-carbonitrile		<chem>CC1=C(NC(=C1C#N)N)C2=CC=CC=C2F</chem>	NS-8		Urinary incontinence
4-[3-cyclopropyl-5-methyl-1-(methylsulfonylmethyl)pyrazol-4-yl]oxy-2,6-dimethylbenzonitrile	CAS 936345-35-6	<chem>CC1=CC(=CC(=CC(=C1C#N)C)OC2=C(N(N=C2C3CC3)C5(=O)(=O)C)C</chem>	PF-2413873		Endometriosis
(E)-N-[4-[3-chloro-4-(pyridin-2-ylmethoxy)anilino]-3-cyano-7-ethoxyquinolin-6-yl]-3-[(2R)-1-methylpyrrolidin-2-yl]prop-2-enamide	CAS 1269662-73-8	<chem>CCOC1=C(C(=C2C(=C1)N=CC(=C2NC3=CC(=C(C(=C3)OCC4=CC=CC(=N4)C)C#N)NC(=O)/C=C/[C@H]5CCCN5C</chem>	Pyrotinib		Solid tumour/cancer

IUPAC Name	CAS #	SMILES Notation	USAN Name / Trade Name	Representative Tx Class	Representative Disease
4-[2-[6-(4-methylpiperazine-1-carbonyl)naphthalen-2-yl]ethylamino]quinazoline-6-carbonitrile	CAS 1449228-40-3	<chem>CN1CCN(CC1)C(=O)C2=CC3=C(C(=C2)C(=C(C(=C3)CCNC4=NC=NC5=C4C=C(C=C5)C#N</chem>	Quinazoline derivative 9		Breast cancer
2-chloro-4-[[[(1R,2S)-1-[5-(4-cyanophenyl)-1,3,4-oxadiazol-2-yl]-2-hydroxypropyl]amino]-3-methylbenzonitrile	CAS 1182367-47-0	<chem>CC1=C(C(=CC(=C1C)C#N)N[C@@H](C2=NN=C(O2)C3=CC=C(C(=C3)C#N)[C@H](C)O</chem>	RAD-140		Osteoporosis; Breast cancer
N-[3-[[4(R)-2-amino-5,5-difluoro-4-methyl-6H-1,3-oxazin-4-yl]-4-fluorophenyl]-5-cyanopyridine-2-carboxamide	CAS 1310347-50-2	<chem>[C@]1(C(COC(=N1)N)(F)C2=C(C(=CC(=C2)NC(=O)C3=NC=C(C(=C3)C#N)F</chem>	RG7129		Alzheimer disease
2-[3-[[4-cyanophenyl]methyl]indolizin-1-yl]-N-(3-methyl-1,2-thiazol-5-yl)-2-oxoacetamide	CAS 501948-05-6	<chem>CC1=NSC(=C1)NC(=O)C(=O)C2=C3C=CC=CN3C(=C2)CC4=CC=C(C(=C4)C#N</chem>	STA-5312		Solid tumour/cancer
(Z,Z)-4-amino-2-[amino-(2-aminophenyl)sulfanyl(methylidene)]-4-(2-aminophenyl)sulfanyl-3-isocyanobut-3-enenitrile		<chem>[C-]#[N+]/C(=C(N))\SC1=CC=CC=C1N)/C(=C(\N)/SC2=CC=CC=C2N)/C#N</chem>	TAK-701		Advanced malignancy
(11S)-16-amino-2-ethyl-6-fluoro-11-methyl-14-oxo-10-oxa-2,13,17,18,21-pentazatetracyclo[13.5.2.04,9.018,22]docosa-1(21),4(9),5,7,15(22),16,19-heptaene-5-carbonitrile		<chem>CCN1CC2=C(C(=CC(=C2C#N)F)O[C@H](CNC(=O)C3=C4N=C1C=CN4N=C3N)C</chem>	TPX-0022		Solid tumour/cancer
(2E,4E)-5-(6-bromopyridin-2-yl)-2-cyano-N-[(1S)-1-phenylethyl]penta-2,4-dienamide	CAS 1204306-34-2	<chem>[C@]1(C)C(=CC(=C1)NC(=O)C)/C(=C/C(=C2)NC(=CC(=C2)Br)/C#N</chem>	WP1220		Cutaneous T-cell lymphoma
N-[3-[[4(S,6S)-2-amino-4-methyl-6-(trifluoromethyl)-5,6-dihydro-1,3-oxazin-4-yl]-4-fluorophenyl]-5-cyanopyridine-2-carboxamide		<chem>[C@]1(C[C@H](OC(=N1)N)C(F)F)C2=C(C(=CC(=C2)NC(=O)C3=NC=C(C(=C3)C#N)F</chem>	oxazine 89		Diabetic nephropathy

Table 3. Additional cyano-containing small molecule drugs that are patented.

IUPAC Name	CAS #	SMILES Notation	USAN Name / Trade Name	Representative Tx Class	Representative Disease
(2R)-2-[[5-chloro-2-[[5-cyanopyridin-3-yl)methoxy]-4-[[2-methyl-3-quinoxalin-2-yl]phenyl)methoxy]phenyl]methylamino]-3-hydroxy-2-methylpropanoic acid		<chem>CC1=C(C(=CC(=C1C2=NC3=CC=CC=C3N=C2)COC4=C(C(=C(C(=C4)OCC5=CC(=CN=C5)C#N)CN[C@]1(C)CO)C(=O)O)Cl</chem>	1,3-dihydroxy phenyl derivative 2		solid tumour / cancer; infectious disease; Human immunodeficiency virus infection; Hepatitis

IUPAC Name	CAS #	SMILES Notation	USAN Name / Trade Name	Representative Tx Class	Representative Disease
6-(2-quinolin-2-ylethynyl)pyridine-2-carbonitrile		<chem>C1=CC=C2C(=C1)C=CC(=N2)C#CC3=NC(=CC=C3)C#N</chem>	2-(substituted ethynyl)quinoline derivative 4		
6-[2-(4-cyanophenyl)pyrazol-3-yl]-5-methyl-3-oxo-4-[3-(trifluoromethyl)phenyl]pyrazine-2-carboxamide		<chem>CC1=C(N=C(C(=O)N1C2=CC=CC(=C2)C(F)(F)C(=O)N)C3=CC=CC=CC=C3C(=O)N)C(=O)N</chem>	2-pyrazinone derivative 2		
4-(3-cyanophenyl)-6-[2-(4-cyanophenyl)pyrazol-3-yl]-N-cyclopropyl-5-methyl-3-oxopyrazine-2-carboxamide		<chem>CC1=C(N=C(C(=O)N1C2=CC=CC(=C2)C#N)C(=O)N)C3CC3C4=CC=CC=C4C5=CC=C(C=C5)C#N</chem>	2-pyrazinone derivative 6		
6-[3-(4-cyanophenyl)-5,5-dimethyl-4H-imidazol-2-yl]-5-methyl-3-oxo-4-[3-(trifluoromethyl)phenyl]pyrazine-2-carboxamide		<chem>CC1=C(N=C(C(=O)N1C2=CC=CC(=C2)C(F)(F)C(=O)N)C3=CC=CC(=C3)C(=O)N)C(=O)N</chem>	2-pyrazinone derivative 7		
2-(3-hydroxyanilino)-4-[4-methyl-2-(methylamino)-1,3-thiazol-5-yl]pyrimidine-5-carbonitrile		<chem>CC1=C(C(=O)N)NC2=CC(=O)N(C2)C3=CC(=O)N(C3)C#N</chem>	4-(thiazol-5-yl)-pyrimidine derivative 1		
4-[[4-[3-cyano-4-(oxan-4-yloxy)phenyl]pyrimidin-2-yl]amino]-N-[2-(dimethylamino)ethyl]-2-methoxy-N-methylbenzamide		<chem>CN(C)CCN(C)C(=O)C1=C(C(=O)C(=C(C=C1)NC2=CC=CC(=N2)C3=CC(=O)N(C3)C(=O)N)C4=CC(=O)N(C4)C#N</chem>	Aminopyrimidine derivative 10		
N-[2-cyano-4-[2-(4-morpholin-4-yl)anilino]pyrimidin-4-yl]phenyl]-3-methylbutanamide		<chem>CC(C)CC(=O)NC1=C(C(=O)C(=C(C=C1)C2=NC(=NC=C2)NC3=CC(=O)N(C3)C#N</chem>	Aminopyrimidine derivative 6		
5-[2-(4-morpholin-4-ylanilino)pyrimidin-4-yl]-2-(oxan-4-yloxy)benzonitrile		<chem>C1COC(C)OC2=C(C(=O)C(=C(C=C2)C3=NC(=NC=C3)NC4=CC(=O)N(C4)C#N</chem>	Aminopyrimidine derivative 7		
5-[2-[4-[4-(2-hydroxyethyl)piperazin-1-yl]anilino]pyrimidin-4-yl]-3-methoxy-2-(oxan-4-yloxy)benzonitrile		<chem>COC1=CC(=CC(=C1OC2COC(C)C2)C#N)C3=NC(=NC=C3)NC4=CC(=O)N(C4)C#N</chem>	Aminopyrimidine derivative 8		
N-[[4-[4-[3-cyano-4-(oxan-4-yloxy)phenyl]pyrimidin-2-yl]amino]phenyl]methanacetamide		<chem>CC(=O)NCCC1=CC=C(C(=O)C(=C1)NC2=CC(=CC(=N2)C3=CC(=O)N(C3)C#N</chem>	Aminopyrimidine derivative 9		
1-[5-(4-cyanoanilino)-6-[ethyl(oxan-4-yl)amino]pyridin-3-yl]cyclobutane-1-carboxylic acid		<chem>CCN(C1COC(C)C1)C2=C(C(=O)C(=N2)C3(CCC3)C(=O)O)NC4=CC(=O)N(C4)C#N</chem>	Aryl 1,2-diamine derivative 1		

IUPAC Name	CAS #	SMILES Notation	USAN Name / Trade Name	Representative Tx Class	Representative Disease
3-[4-[4-[4-(1-oxoisoquinolin-2-yl)phenyl]piperazin-1-yl]butyl]-1H-indole-5-carbonitrile		<chem>C1CN(CCN1CCCCC2=C(CN(C3=CC(=O)C=C(C3)C#N)C4=CC=C(C(C=C4)N5C=CC6=CC=CC=C6C5=O</chem>	Aryl piperazine derivative 14		
3-[4-[4-[4-(5-oxo-1,6-naphthyridin-6-yl)phenyl]piperazin-1-yl]butyl]-1H-indole-5-carbonitrile		<chem>C1CN(CCN1CCCCC2=C(CN(C3=CC(=O)C=C(C3)C#N)C4=CC=C(C(C=C4)N5C=CC6=CC(=O)C=C(C5=O)C=CC=N6</chem>	Aryl piperazine derivative 15		
3-[3-[4-[4-(5-oxo-1,6-naphthyridin-6-yl)phenyl]piperazin-1-yl]propyl]-1H-indole-5-carbonitrile		<chem>C1CN(CCN1CCCCC2=C(CN(C3=CC(=O)C=C(C3)C#N)C4=CC=C(C(C=C4)N5C=CC6=CC(=O)C=CC=N6</chem>	Aryl piperazine derivative 16		
4-(7-cyano-2-methoxypyrrrolo[1,2-b]pyridazin-5-yl)-2-hydroxybenzoic acid		<chem>COC1=NN2C(=C(C=C2C#N)C3=CC(=C(C=C3)C(=O)O)O)C=C1</chem>	Azaindole derivative 3		
4-(5-cyanopyrrolo[1,2-b]pyridazin-7-yl)-2-hydroxybenzoic acid		<chem>C1=CC2=C(C(C=C(N2N=C1)C3=CC(=C(C=C3)C(=O)O)O)C#N</chem>	Azaindole derivative 5		
4-(7-cyano-2-methylpyrrolo[1,2-b]pyridazin-5-yl)-2-hydroxybenzoic acid		<chem>CC1=NN2C(=C(C=C2C#N)C3=CC(=C(C=C3)C(=O)O)O)C=C1</chem>	Azaindole derivative 6		
4-(7-cyanopyrrolo[1,2-b]pyridazin-5-yl)-2-hydroxybenzoic acid		<chem>C1=CC2=C(C(C=C(N2N=C1)C#N)C3=CC(=C(C=C3)C(=O)O)O)O</chem>	Azaindole derivative 7		
N-cyano-3-[[5-fluoro-1-(2-methylpropyl)indazol-3-yl]amino]pyridine-4-carboxamide		<chem>CC(C)CN1C2=C(C=C(C(C=C2)F)C(=N1)NC3=C(C=CN=C3)C(=O)NC#N</chem>	BDBM50158803		
N-[2-[(2S)-2-cyano-4,4-difluoropyrrolidin-1-yl]-2-oxoethyl]naphthalene-1-carboxamide		<chem>C1[C@H](N(CCN1(F)F)C(=O)CNC(=O)C2=CC=CC3=CC=CC=C(C32)C#N</chem>	BDBM50382283		
7-chloro-N-[2-[(2S)-2-cyanopyrrolidin-1-yl]-2-oxoethyl]quinoline-4-carboxamide		<chem>C1C[C@H](N(C1)C(=O)CNC(=O)C2=C3C=CC(=CC3=NC=C2)C)C#N</chem>	BDBM50434164		
N-[2-[(2S)-2-cyanopyrrolidin-1-yl]-2-oxoethyl]-6-methoxyquinoline-4-carboxamide		<chem>COC1=CC2=C(C(C=CN=C2C=C1)C(=O)NCC(=O)N3CCCC[C@H]3C#N</chem>	BDBM50434165		
2-[[4-[(2-bromo-3-phenylphenyl)methoxy]-5-chloro-2-[[3-cyanophenyl)methoxy]phenyl]methylamino]-3-hydroxypropanoic acid		<chem>C1=CC=C(C(C=C1)C2=CC=CC(=C2Br)COC3=C(C=C(C(=C3)OCC4=CC(=CC=C4)C#N)CNC(CO)C(=O)O)Cl</chem>	Benzyl phenyl ether derivative 1		Solid tumour/cancer; Infectious disease; Human immunodeficiency virus infection; Hepatitis

IUPAC Name	CAS #	SMILES Notation	USAN Name / Trade Name	Representative Tx Class	Representative Disease
3-[[5-[(2-bromo-3-phenylphenyl)methoxy]-4-chloro-2-[[2-hydroxyethylamino)methyl]phenoxy]methyl]benzonitrile		<chem>C1=CC=C(C=C1)C2=CC=CC(=C2Br)COC3=C(C=C(C(=C3)OCC4=CC(=CC=C4)C#N)CNC(CO)Cl</chem>	Benzyl phenyl ether derivative 2		Solid tumour/cancer; Infectious disease; Human immunodeficiency virus infection; Hepatitis
2-[[4-[[3-[[4-acetyl-2-chloro-5-[(5-cyanopyridin-3-yl)methoxy]phenoxy]methyl]-2-methylphenyl]-2-methylphenyl]methoxy]-5-chloro-2-[[5-cyanopyridin-3-yl)methoxy]phenyl]methylamino]-3-hydroxy-2-methylpropanoic acid		<chem>CC1=C(C=CC=C1C2=CC=CC(=C2C)CO C3=C(C=C(C(=C3)OCC4=CC(=CN=C4)C#N)C(=O)C)COC5=C(C=C(C(=C5) OCC6=CC(=CN=C6)C#N)CNC(C(CO)C(=O)O)Cl</chem>	Biaryl compound 1		Solid tumour/cancer; Infectious disease; Human immunodeficiency virus infection; Hepatitis
2-[[4-[[3-[[4-[[[(2-carboxy-1-hydroxypropan-2-yl)amino]methyl]-2-chloro-5-[(5-cyanopyridin-3-yl)methoxy]phenoxy]methyl]-2-methylphenyl]-2-methylphenyl]methoxy]-5-chloro-2-[[5-cyanopyridin-3-yl)methoxy]phenyl]methylamino]-3-hydroxy-2-methylpropanoic acid		<chem>CC1=C(C=CC=C1C2=CC=CC(=C2C)CO C3=C(C=C(C(=C3)OCC4=CC(=CN=C4)C#N)CNC(C(CO)C(=O)O)Cl</chem>	Biaryl compound 2		Solid tumour/cancer; Infectious disease; Human immunodeficiency virus infection; Hepatitis
6-[[2-[[4-(2,4-dichlorophenyl)-5-(5-methyl-1H-imidazol-2-yl)pyrimidin-2-yl]amino]ethylamino]pyridine-3-carbonitrile	CAS 252917-06-9	<chem>CC1=CN=C(N1)C2=CC=CC(N=C2C3=C(C=C(C(=C3)C)C)NCCNC4=NC=C(C(=C4)C#N</chem>	CHIR-99021		Graft rejection; Allergic inflammation
1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-3H-2-benzofuran-5-carbonitrile	CAS 59729-33-8	<chem>CN(C)CCCC1(C2=C(C(CO1)C=C(C(=C2)C#N)C3=CC=C(C(=C3)F</chem>	Citalopram derivative 1		
2-[[2-ethyl-8-fluoro-6-[4-[2-(3-hydroxyazetidin-1-yl)-2-oxoethyl]piperazin-1-yl]imidazo[1,2-a]pyridin-3-yl]methylamino]-4-(4-fluorophenyl)-1,3-thiazole-5-carbonitrile		<chem>CCC1=C(N2C=C(C(=C(C2=N1)F)N3CC N(CC3)CC(=O)N4CC(C4)O)N(C)C5=NC(=C(S5)C#N)C6=CC=C(C(=C6)F</chem>	Complex heterocyclic compound 1		Inflammation
N-[2-[(2S)-2-cyanopyrrolidin-1-yl]-2-oxoethyl]-6-fluoroquinoline-4-carboxamide		<chem>C1C[C@H](N(C1)C(=O)CNC(=O)C2=C3C=C(C(=CC3=NC=C2)F)C#N</chem>	CRWCYVOHVXAEM F-LBPRGKRZSA-N		

IUPAC Name	CAS #	SMILES Notation	USAN Name / Trade Name	Representative Tx Class	Representative Disease
N-[3-(2-cyanopropan-2-yl)-1,2-oxazol-5-yl]-2-methyl-2-[methyl(oxan-4-ylmethyl)amino]propanamide		<chem>CC(C)(C#N)C1=NOC(=C1)NC(=O)C(C)(C)N(C)CC2CCOCC2</chem>	Cyano(dimethyl)methyl isoxazoles and [1,3,4]-thiadiazoles derivative 1		
4-(4-chloro-2-cyclopropyl-5-methoxyanilino)-7-[3-[4-(deuteriomethyl)piperazin-1-yl]propoxy]-6-methoxyquinoline-3-carbonitrile		<chem>[2H]CN1CCN(CC1)CCOCOC2=C(C=C3C(=C2)N=CC(=C3)NC4=CC(=C(C=C4)C5CC5)C)OC(C#N)OC</chem>	Deuterated 3-cyanoquinoline derivative 1		
[ethyl-[[3-[[5-fluoro-4-(4-fluoro-2-methoxyphenyl)pyrimidin-2-yl]amino]phenyl]methyl]-oxo-lambda6-sulfanylidene]cyanamide		<chem>CCS(=NC#N)(=O)CC1=CC(=CC=C1)NC2=NC=C(C(=N2)C3=C(C=C(C=C3)F)OC)F</chem>	Diaryl amine derivative 1		
2-(7-cyano-1H-indol-5-yl)-4-methyl-1,3-thiazole-5-carboxylic acid		<chem>CC1=C(SC(=N1)C2=CC(=C3C(=C2)C=CN3)C#N)C(=O)O</chem>	Fused heterocyclic compound 4		
2-(7-cyano-1-methylindol-5-yl)-4-methyl-1,3-thiazole-5-carboxylic acid		<chem>CC1=C(SC(=N1)C2=CC(=C3C(=C2)C=CN3)C#N)C(=O)O</chem>	Fused heterocyclic compound 5		
3-[2-(3-cyanophenyl)ethynyl]-N,N-dimethyl-7,8-dihydro-5H-1,6-naphthyridine-6-carboxamide		<chem>CN(C)C(=O)N1CCC2=C(C1)C=C(C(=N2)C#CC3=CC(=CC=C3)C#N</chem>	Heterocyclic derivative 2		
3-[[4-chlorophenyl]-3-[[1S]-2-fluoro-1-[3-fluoro-5-(2-oxo-3H-1,3,4-oxadiazol-5-yl)phenyl]-2-methylpropyl]azetidin-1-yl]methyl]benzonitrile		<chem>CC(C)(C@H)(C1CN(C1)C(C2=CC=C(C=C2)C(C=C2)C)C3=CC=CC(=C3)C#N)C4=C(C(=CC(=C4)C5=NNC(=O)O5)F)F</chem>	Heterocyclic-substituted 3-alkyl azetidine derivative 1		Obesity
3-[1-[1-[3-(5-amino-1,3,4-oxadiazol-2-yl)phenyl]-{4-cyanophenyl}methyl]azetidin-3-yl]-2-fluoro-2-methylpropyl]-5-fluorobenzonitrile		<chem>CC(C)(C1CN(C1)C(C2=CC=C(C=C2)C#N)C3=CC=CC(=C3)C4=NN=C(O4)N)C5=CC(=CC(=C5)C#N)F</chem>	Heterocyclic-substituted 3-alkyl azetidine derivative 2		Obesity
3-[3-[1-(3,5-difluorophenyl)-2-fluoro-2-methylpropyl]azetidin-1-yl]-[4-(2-oxo-3H-1,3,4-oxadiazol-5-yl)phenyl]methyl]benzonitrile		<chem>CC(C)(C1CN(C1)C(C2=CC=C(C=C2)C3=NNC(=O)O3)C4=CC=CC(=C4)C#N)C5=CC(=CC(=C5)F)F</chem>	Heterocyclic-substituted 3-alkyl azetidine derivative 3		Obesity
4-[5-[4-(dimethylamino)piperidin-1-yl]-1H-imidazo[4,5-b]pyridine-2-carbonyl]-2-isoquinolin-4-ylbenzonitrile		<chem>CN(C)C1CCN(CC1)C2=NC3=C(C=C2)NC(=N3)C(=O)C4=CC(=C(C=C4)C#N)C5=CN=CC6=CC=CC=C6</chem>	Imidazo pyridine derivative 3		

IUPAC Name	CAS #	SMILES Notation	USAN Name / Trade Name	Representative Tx Class	Representative Disease
4-[[[(5R)-5-(4-phenoxyphenyl)-4,5-dihydro-1,2-oxazol-3-yl]oxy]benzonitrile		<chem>C1[C@@H](ON=C1OC2=CC=C(C=C2)C#N)C3=CC=C(C=C3)OC4=CC=CC=C4</chem>	Isoxazoline derivative 3		
4-[[[(5S)-5-(4-phenoxyphenyl)-4,5-dihydro-1,2-oxazol-3-yl]oxy]benzonitrile		<chem>C1[C@H](ON=C1OC2=CC=C(C=C2)C#N)C3=CC=C(C=C3)OC4=CC=CC=C4</chem>	Isoxazoline derivative 4		
20-amino-14-fluoro-4,17-dimethyl-7,10,18-trioxo-4,5,21-triazatetracyclo[17.3.1.02,6.011,16]tricoso-1(23),2,5,11(16),12,14,19,21-octaene-3-carbonitrile		<chem>CC1C2=C(C=CC(=C2)F)OCCOC3=NN(C(=C3C4=CC=C(N=C4)N)O1)C#N)C</chem>	Macrocyclic derivative 13		Cell proliferative disorder
[[3-[[4-(2,4-difluorophenyl)-5-fluoropyrimidin-2-yl]amino]-5-(pentafluoro-lambda6-sulfanyl)phenyl]methyl-methyl-oxo-lambda6-sulfanylidene]cyanamide		<chem>CS(=NC#N)(=O)CC1=CC(=CC(=C1)S(F)(F)(F)F)NC2=NC=C(C(=N2)C3=C(C(=C(C3)F)F)F</chem>	N-phenyl-pyrimidin-4-amine derivative 1		
(2S)-2-[[[(2S)-2-[(4-cyanobenzoyl)amino]-3-(4-phosphonoxyphenyl)propanoyl]amino]-4-methyl]pentanoic acid		<chem>CC(C)[C@C@@H]([C@H](C(=O)O)NC(=O)[C@H](CC1=CC=C(C=C1)OP(=O)(O)O)NC(=O)C2=CC=C(C=C2)C#N</chem>	Peptidomimetic analog 5		
(1R,11S,13S,18R,19R)-10,10-dimethyl-21-oxo-22-oxa-8,17,20-triazahehexacyclo[17.3.1.01,9.02,7.011,19.013,17]tricoso-2,4,6,8-tetraene-18-carbonitrile		<chem>CC1([C@H]2[C@H]3CCCN3[C@H]([C@@]24[C@]5(C1=NC6=C(C=CC=C65)OC(=O)N4)C#N)C</chem>	PMID25399762-Compound-Figure3-Aspeverin		
3-[2-oxo-8-(2-phenylethynyl)-1,3-dihydro-1,5-benzodiazepin-4-yl]benzonitrile		<chem>C1C(=NC2=C(C=C(C(=C2)C#CC3=CC=CC=C3)NC1=O)C4=CC=CC(=C4)C#N</chem>	PMID25435285-Compound-26		
(2S)-1-[2-[[[1-(1,2,4-triazol-1-ylmethyl)-3-tricyclo[3.3.1.03,7]nonanylamino]acetyl]pyrrolidine-2-carbonitrile		<chem>C1C[C@H](N(C1)C(=O)CNC23CC4CC2CC(C4)(C3)CN5C=NC=N5)C#N</chem>	PMID25482888-Compound-11		
1-[(2S)-2-amino-3-[4-[4-(pyridin-2-ylamino)phenoxy]phenyl]propanoyl]pyrrolidine-2-carbonitrile		<chem>C1CC(N(C1)C(=O)[C@H](CC2=CC=C(C=C2)OC3=CC=C(C(=C3)NC4=CC=CC=N4)N)C#N</chem>	PMID25482888-Compound-12		
(1S,3S,5S)-2-[2-amino-2-(3-hydroxy-1-adamantyl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile		<chem>C1[C@H]2[C@H]2N([C@H]1C#N)C(=O)C(C34CC5CC(C3)CC(C5)(C4)O)N</chem>	PMID25482888-Compound-13		
1-(2-amino-2-cyclohexylacetyl)pyrrolidine-2-carbonitrile		<chem>C1CCC(CC1)C(C(=O)N2CCCC2C#N)N</chem>	PMID25482888-Compound-15		

IUPAC Name	CAS #	SMILES Notation	USAN Name / Trade Name	Representative Tx Class	Representative Disease
2-[[7-(3-aminopiperidin-1-yl)-3,5-dimethyl-2-oxoimidazo[4,5-b]pyridin-1-yl]methyl]benzonitrile		<chem>CC1=CC(=C2C(=N1)N(C(=O)N2CC3=CC=CC=C3C#N)C)N4CCCC(C4)N</chem>	PMID25482888-Compound-34		
3-[[8-[(3R)-3-aminopiperidin-1-yl]-7-but-2-ynyl-1-[(2-cyanopyridin-3-yl)methyl]-2,6-dioxopurin-3-yl]methyl]pyridine-2-carbonitrile		<chem>CC#CCN1C2=C(N=C1N3CCCC(C@H)[C3]N)N(C(=O)N(C2=O)CC4=C(N=CC=C4)C#N)CC5=C(N=CC=C5)C#N</chem>	PMID25482888-Compound-56		
N-[2-[4-(3-acetamidophenyl)piperidin-1-yl]ethyl]-5-(4-cyanophenyl)-1-benzofuran-2-carboxamide		<chem>CC(=O)NC1=CC=CC(=C1)C2CCN(CC2)CCNC(=O)C3=CC4=C(O3)C=CC(=C4)C5=CC=C(C=C5)C#N</chem>	PMID25522065-Compound-35		
1-[[4-[2-(4-chlorophenyl)-4-oxofuro[3,2-c]pyridin-5-yl]-2-methoxyphenoxy]methyl]cyclopropane-1-carbonitrile		<chem>COC1=C(C=CC(=C1)N2C=CC3=C(C2=O)C=C(O3)C4=CC=C(C=C4)C)OCC5(C5)C#N</chem>	PMID25522065-Compound-47		
4-anilino-2-(cyclohexylamino)pyrimidine-5-carbonitrile		<chem>C1CCC(CC1)NC2=NC=C(C(=N2)NC3=CC=CC=C3)C#N</chem>	PMID25991433-Compound-H1		
N-[4-[4-[(2Z)-3H-1,3-benzothiazol-2-ylidene(cyano)methyl]pyrimidin-2-yl]amino]phenyl]-3-[[[(E)-4-(dimethylamino)but-2-enoyl]amino]benzamide		<chem>CN(C)/C=C/C(C(=O)NC1=CC=CC(=C1)C(=O)NC2=CC=C(C=C2)NC3=NC=CC(=N3)/C(=C/4\NC5=CC=CC=C5S4)/C#N</chem>	PMID25991433-Compound-J6		
6-[2-oxo-4-[2-(1-oxo-3H-2-benzofuran-5-yl)ethyl]piperazin-1-yl]-5,6,7,8-tetrahydronaphthalene-2-carbonitrile		<chem>C1CC2=C(C(CC1N3CCN(CC3=O)CCC4=CC5=C(C=C4)C(=O)OC5)C=CC(=C2)C#N</chem>	PMID26004420-Compound-WO2013062900C		
4-[[4-(3-cyano-4-pyrrolidin-1-ylphenyl)pyrimidin-2-yl]amino]-N-propan-2-ylbenzamide		<chem>CC(C)NC(=O)C1=CC=C(C(=C1)NC2=NCC=CC(=N2)C3=CC(=C(C=C3)N4CCCC4)C#N</chem>	PMID26293650-Compound-34		
5-[4-(4-methylphenyl)sulfonyl-2,3-dihydro-1,4-benzoxazin-6-yl]thiophene-2-carbonitrile		<chem>CC1=CC=C(C=C1)S(=O)(=O)N2CCOC3=C2C(C=C3)C4=CC=C(C4)C#N</chem>	PMID26882240-Compound-15		
2-[[5-(1,2-oxazole-5-carbonyl)-[1,2,4]triazino[5,6-b]indol-3-yl]sulfonylmethyl]benzonitrile		<chem>C1=CC=C(C(=C1)CSC2=NC3=C(C4=C(C=CC=C4N3C(=O)C5=CC=CC=C5)N=N2)C#N</chem>	PMID27215781-Compound-27		
4-(6-cyano-2-methylthieno[3,2-b]pyrrol-4-yl)-2-hydroxybenzoic acid		<chem>CC1=CC2=C(S1)C(=CN2C3=CC(=C(C=C3)C(=O)O)O)C#N</chem>	PMID27414413-Compound-Figure8right		

IUPAC Name	CAS #	SMILES Notation	USAN Name / Trade Name	Representative Tx Class	Representative Disease
3-(5-hydroxy-5,6,7,8-tetrahydroquinolin-2-yl)-2-oxo-1,3-dihydroindole-5-carbonitrile		<chem>C1CC(C2=C(C1)N=C(C=C2)C3C4=C(C=CC(=C4)C#N)NC3=O)O</chem>	PMID27828716-Compound-21		
3-(4,6-dimethoxypyrimidin-2-yl)-2-methyl-2-(6-oxo-7,8,9,10-tetrahydro-5H-phenanthridin-3-yl)propanenitrile		<chem>CC(CCC1=NC(=CC(=N1)OC)OC)(C#N)C2=CC3=C(C=C2)C4=C(C(CCC4)C(=O)N3</chem>	PMID27841036-Compound-23		
6-[2-cyano-2-(6-oxo-7,8,9,10-tetrahydro-5H-phenanthridin-3-yl)propyl]pyridine-2-carbonitrile		<chem>CC(CCC1=NC(=CC(=C1)C#N)(C#N)C2=C(C3=C(C=C2)C4=C(C(CCC4)C(=O)N3</chem>	PMID27841036-Compound-24		
4-[3-cyano-4-(furan-2-yl)pyrrol-1-yl]-2-hydroxybenzoic acid		<chem>C1=COC(=C1)C2=CN(C=C2C#N)C3=C(C(=C(C3)C(=O)O)O</chem>	PMID27841045-Compound-132		
2-(3-cyano-4-phenylpyrrol-1-yl)pyridine-4-carboxylic acid		<chem>C1=CC=C(C(C=C1)C2=CN(C=C2C#N)C3=NC=CC(=C3)C(=O)O</chem>	PMID27841045-Compound-133		
4-(3-cyano-4-thiophen-2-ylpyrrol-1-yl)-2-hydroxybenzoic acid		<chem>C1=CSC(=C1)C2=CN(C=C2C#N)C3=C(C(=C(C3)C(=O)O)O</chem>	PMID27841045-Compound-134		
4-(3-butyl-4-cyanopyrrol-1-yl)-2-hydroxybenzoic acid		<chem>CCCCC1=CN(C=C1C#N)C2=CC(=C(C(=C2)C(=O)O)O</chem>	PMID27841045-Compound-135		
4-(3-cyano-4-phenylpyrrol-1-yl)-2-hydroxybenzoic acid		<chem>C1=CC=C(C(C=C1)C2=CN(C=C2C#N)C3=CC(=C(C3)C(=O)O)O</chem>	PMID27841045-Compound-136		
4-(3-cyano-4-thiophen-3-ylpyrrol-1-yl)-2-hydroxybenzoic acid		<chem>C1=CC(=C(C=C1N2C=C(C(=C2)C3=CS(C=C3)C#N)O)C(=O)O</chem>	PMID27841045-Compound-137		
2-[3-cyano-1-(cyclopropylmethyl)indol-5-yl]pyridine-4-carboxylic acid		<chem>C1CC1CN2C=C(C3=C2C=C(C(=C3)C4=NC=CC(=C4)C(=O)O)C#N</chem>	PMID27841045-Compound-143		
1-[3-cyano-1-(cyclopropylmethyl)indol-5-yl]pyrazole-4-carboxylic acid		<chem>C1CC1CN2C=C(C3=C2C=C(C(=C3)N4C=C(C(C=N4)C(=O)O)C#N</chem>	PMID27841045-Compound-144		
1-(3-cyano-1-propan-2-ylindol-5-yl)pyrazole-4-carboxylic acid		<chem>CC(C1N1C=C(C2=C1C=CC(=C2)N3C=C(C(=N3)C(=O)O)C#N</chem>	PMID27841045-Compound-145		
methyl 2-[[4,6-bis(propan-2-ylamino)-1,3,5-triazin-2-yl]-cyanoamino]acetate		<chem>CC(C1NC1=NC(=NC(=N1)N(CC(=O)O)C(C#N)NC(C)C</chem>	PMID27998201-Compound-1		Coronavirus infection; Henipavirus Encephalitis
methyl-[methyl-4-methyl-2-[3-(4-phenylphenyl)phenyl]pentanoyl]amino]cyanamide		<chem>CC(C)CC(C1=CC=CC(=C1)C2=CC=C(C(=C2)C3=CC=CC(=C3)C(=O)N(C)N(C)C#N</chem>	PMID27998201-Compound-10		Osteoporosis

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(2R)-N-(1-cyanocyclopropyl)-3-(cyclopropylmethylsulfanyl)-2-[[[(2S)-1,1-difluoro-1-(4-methylsulfanylphenoxy)pent-3-yn-2-yl]amino]propanamide		CC#[C@@H](C(OC1=CC=C(C=C1)S O)(F)F)N[C@@H](CSCC2CC2)C(=O)N C3(CC3)C#N	PMID27998201-Compound-5		Cirrhosis; Chronic obstructive pulmonary disease; Psoriasis vulgaris; Multiple sclerosis; Gastrointestinal disease
(2S,4R)-N-(1-cyanocyclopropyl)-1-[1-(3-fluoro-5-iodopyridin-2-yl)cyclopropanecarbonyl]-4-(2-fluorophenyl)sulfonylpyrrolidine-2-carboxamide		C1CC1(C#N)NC(=O)[C@@H]2[C@H](CN2C(=O)C3(CC3)C4=C(C=C(C=N 4))F)S(=O)(=O)C5=CC=CC=C5F	PMID27998201-Compound-7		Abdominal aortic aneurysm
N-[1-[[cyano(methyl)amino]-methylamino]-4-methyl-1-oxopentan-2-yl]-3-(4-phenylphenyl)benzamide		CC(C)CC(C(=O)N(C)N(C)C#N)NC(=O) C1=CC=CC(=C1)C2=CC=C(C(=C2)C3= CC=CC=C3	PMID27998201-Compound-9		Rheumatoid arthritis
3-chloro-5-(6-pyrazol-1-ylpyrimidin-4-yl)benzonitrile		C1=CN(N=C1)C2=NC=NC(=C2)C3=CC (=CC(=C3)C#N)Cl	PMID28067079-Compound-98		
(16R)-19-amino-13-fluoro-4,8,16-trimethyl-9-oxo-17-oxa-4,5,8,20-tetrazatetracyclo[16.3.1.02,6.010,15]docosa-1(22),2,5,10(15),11,13,18,20-octaene-3-carbonitrile	CAS 1454846-35-5	C[C@@H]1C2=C(C(=CC(=C2)F)C(=O) N(CC3=NN(C(=C3C4=CC(=C(N=C4)N) O1)C#N)C)C	PMID28270010-Compound-Figure21-b		Brain metastases
2-[[4,6-dimethyl-2-oxo-1H-pyridin-3-yl)methyl]-7-methoxy-1-oxo-3,4-dihydroisoquinoline-8-carbonitrile		CC1=CC(=C(C(=O)N1)CN2CCC3=C(C 2=O)C(=C(C=C3)OC)C#N)C	PMID28394193-Compound-45		
N-[[4aS,6aR,6bS,8aR,12aS)-11-cyano-2,2,6a,6b,9,9,12a-heptamethyl-10,14-dioxo-1,3,4,5,6,7,8,8a,14a,14b-decahydropicen-4a-yl]propanamide		CCC(=O)N[C@@@]12CC[C@]3(C(C1 CC(CC2)(C)C(=O)C=C4[C@@]3(CC[C @H]5[C@@@]4(C=C(C(=O)C5(C)C) C#N)C)C)C	PMID28454500-Compound-10		
N-[[4aS,6aR,6bS,8aR,12aS)-11-cyano-2,2,6a,6b,9,9,12a-heptamethyl-10,14-dioxo-1,3,4,5,6,7,8,8a,14a,14b-decahydropicen-4a-yl]acetamide		CC(=O)N[C@@@]12CC[C@]3(C(C1C C(CC2)(C)C(=O)C=C4[C@@]3(CC[C @H]5[C@@@]4(C=C(C(=O)C5(C)C) C#N)C)C)C	PMID28454500-Compound-11		
methyl (4aS,6aS,6bR,8aR,12aS,14aS)-11-cyano-14a-hydroxy-2,2,6a,6b,9,9,12a-heptamethyl-10,14-dioxo-1,3,4,5,6,7,8,8a,14a,14b-decahydropicen-4a-yl]acetamide		C[C@@]12CC[C@H]3[C@@@]1(C1= CC(=O)C(C)C(=O)C=C4[C@@]3(CC[C @H]5[C@@@]4(C=C(C(=O)C5(C)C) C#N)C)C)C	PMID28454500-Compound-13		

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heptamethyl-10,14-dioxo-3,4,5,6,7,8,8a,14b-octahydro-1H-picene-4a-carboxylate		<chem>CC(C(C5)(C)C(=O)OC)C(O)(C=C(C(=O)C3(C)C)C#N)C</chem>			
methyl (4aS,6aR,6bS,8aS,9S,12aR)-11-cyano-2,2,6a,6b,9,12a-hexamethyl-10,14-dioxo-3,4,5,6,7,8,8a,9,14a,14b-decahydro-1H-picene-4a-carboxylate		<chem>C[C@H]1[C@@H]2CC[C@@]3(C(=C(C(=O)C4[C@]3(CC[C@@]5[C4CC(C(C5)C)C(=O)OC)C)[C@]2(C=C(C1=O)C#N)C)C</chem>	PMID28454500-Compound-8		
(4S,4aS,6aS,6bR,8aS,14bR)-8a-(hydroxymethyl)-4,6a,6b,11,11,14b-hexamethyl-3,13-dioxo-4a,5,6,6a,7,8,9,10,12,12a-decahydro-4H-picene-2-carbonitrile		<chem>C[C@H]1[C@@H]2CC[C@@]3(C(=C(C(=O)C4[C@]3(CC[C@@]5[C4CC(C(C5)C)C(=O)OC)C)[C@]2(C=C(C1=O)C#N)C)C</chem>	PMID28454500-Compound-9		
11H-pyrido[4,3-a]carbazole-6-carbonitrile		<chem>C1=CC=C2C(=C1)C3=C(C=C4C=NC=C4=C3N2)C#N</chem>	PMID28766366-Compound-Scheme24-11H-pyrido[4,3-a]carbazole		
(Z)-2-(1H-indol-3-yl)-3-pyridin-3-ylprop-2-enenitrile		<chem>C1=CC=C2C(=C1)C(=CN2)/C(=C/C3=CN=CC=C3)/C#N</chem>	PMID28766366-Compound-Scheme24Paprotai n		
9-methoxy-11H-pyrido[4,3-a]carbazole-6-carbonitrile		<chem>COC1=CC2=C(C=C1)C3=C(C=C4C=N=C=CC4=C3N2)C#N</chem>	PMID28766366-Compound-Scheme25-2		
1,9-dimethoxy-11H-pyrido[4,3-a]carbazole-6-carbonitrile		<chem>COC1=CC2=C(C=C1)C3=C(C=C4C=N=C=CC4=C3N2)OC)C#N</chem>	PMID28766366-Compound-Scheme25-3		
4-[4-(1-propan-2-ylpiperidin-4-yl)oxypiperidin-1-yl]benzonitrile		<chem>CC(C)N1CCC(CC1)OC2CCN(CC2)C3=CC=C(C=C3)C#N</chem>	PMID29334795-Compound-24		
2-[[[3-(3-cyanophenyl)methoxy]-4-[[3-(2,3-dihydro-1,4-benzodioxin-6-yl)-2-methylphenyl]methoxy]-5-methylphenyl]methoxy]-3-hydroxypropanoic acid		<chem>CC1=CC(=C(C=C1OCC2=C(C(=CC=C2)C3=CC4=C(C=C3)OCCO4)C)OCC5=CC(=CC=C5)C#N)CNC(CO)C(=O)O</chem>	PMID30107136-Compound-Example3		Solid tumour/cancer; Infectious disease; Human immunodeficiency virus infection; Hepatitis

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2-(2,3-dihydro-1,4-benzodioxin-6-yl)-6-[4-[2-(1-methylpyrazol-4-yl)ethylamino]piperidin-1-yl]benzonitrile		<chem>CN1C=C(C=C(N1)CCNC2CCN(CC2)C3=CC=CC(=C3C#N)C4=CC5=C(C=C4)OCCO5</chem>	PMID30107136-Compound-Example42		Solid tumour/cancer; Infectious disease; Human immunodeficiency virus infection; Hepatitis
N-[2-cyano-3-(2,3-dihydro-1,4-benzodioxin-6-yl)phenyl]-5-[(2-hydroxyethylamino)methyl]-1-methyl-2-oxopyridine-3-carboxamide		<chem>CN1C=C(C=C(C1=O)C(=O)NC2=CC=C(C=C2C#N)C3=CC4=C(C=C3)OCCO4)CNCCO</chem>	PMID30107136-Compound-Example50		Solid tumour/cancer; Infectious disease; Human immunodeficiency virus infection; Hepatitis
N-[2-cyano-3-(2,3-dihydro-1,4-benzodioxin-6-yl)phenyl]-4,5,6,7-tetrahydro-[1,3]thiazolo[5,4-c]pyridine-2-carboxamide		<chem>C1CNCC2=C1N=C(C(S2)C(=O)NC3=CC=CC(=C3C#N)C4=CC5=C(C=C4)OCCO5</chem>	PMID30107136-Compound-Example51		Solid tumour/cancer; Infectious disease; Human immunodeficiency virus infection; Hepatitis
N-[2-cyano-3-(1-methylindazol-4-yl)phenyl]-4,5,6,7-tetrahydro-[1,3]thiazolo[5,4-c]pyridine-2-carboxamide		<chem>CN1C2=CC=CC(=C2C=N1)C3=C(C(=C(C=C3)NC(=O)C4=NC5=C(C(S4)CNCC5)C#N</chem>	PMID30107136-Compound-Example52		Solid tumour/cancer; Infectious disease; Human immunodeficiency virus infection; Hepatitis
2-[[5-[(2-morpholin-4-ylethylamino)methyl]-4-(4-phenylphenyl)-1,3-oxazol-2-yl]methoxy]-4-phenylpyridine-3-carbonitrile		<chem>C1COCCN1CCNCC2=C(N=C(O2)COC3=NC=CC(=C3C#N)C4=CC=CC=C4)C5=CC=C(C=C5)C6=CC=CC=C6</chem>	PMID30107136-Compound-Example59		Solid tumour/cancer; Infectious disease; Human immunodeficiency virus infection; Hepatitis

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4-(2,3-dihydro-1,4-benzodioxin-6-yl)-2-[[1-(2-hydroxyethyl)-4-methyl-5-[[2-(methylamino)ethylamino]methyl]imidazol-2-yl]methoxy]pyridine-3-carbonitrile		<chem>CC1=C(N(C(=N1)COC2=NC=CC(=C2)C#N)C3=CC4=C(C(=C3)OCCO4)CCO)C</chem> NCCNC	PMID30107136-Compound-Example60		Solid tumour/cancer; Infectious disease; Human immunodeficiency virus infection; Hepatitis
1-[[5-chloro-2-[[5-cyanopyridin-3-yl)methoxy]-4-[[3-[3-(4-hydroxypiperidin-1-yl)propoxy]-2-methylphenyl]-2-methylphenyl]methoxy]phenyl]methyl]piperidine-2-carboxylic acid		<chem>CC1=C(C(=CC=C1)C2=C(C(=CC=C2)OC(CCN3CCC(CC3)O)C)COC4=C(C=C(C(=C4)OCC5=CC(=CN=C5)C#N)CN6CCC(CC6)C(=O)O)C)Cl</chem>	PMID30107136-Compound-Example7		Solid tumour/cancer; Infectious disease; Human immunodeficiency virus infection; Hepatitis
5-[[[4-chloro-5-[[3-[3-(3,3-difluoropyrrolidin-1-yl)propoxy]-2-methylphenyl]-2-methylphenyl]methoxy]-2-[[[1,3-dihydroxy-2-(hydroxymethyl)propan-2-yl]-methylamino]methyl]phenoxy]methyl]pyridine-3-carbonitrile		<chem>CC1=C(C(=CC=C1)C2=C(C(=CC=C2)OC(CCN3CCC(CC3)F)C)COC4=C(C=C(C(=C4)OCC5=CC(=CN=C5)C#N)CN(C)C(CO)(CO)C)C)Cl</chem>	PMID30107136-Compound-Example8		Solid tumour/cancer; Infectious disease; Human immunodeficiency virus infection; Hepatitis
propan-2-yl 2-cyano-6-(3,4-difluorobenzoyl)-4,4-dimethyl-1,5,7,8-tetrahydropyrrolo[2,3-d]azepine-8-carboxylate		<chem>CC(C)OC(=O)C1CN(CC(C2=C1NC(=C2)C#N)(C)C(=O)C3=CC(=C(C(=C3)F)F)C#N)C(C)C(=O)C3=CC(=C(C(=C3)F)F)C#N</chem>	PMID30259754-Compound-pyrrole[2,3-d]azepines		
4-(2-amino-2-oxoethyl)-1-(2-chlorophenyl)-5-(4-chlorophenyl)-N-[(4-cyanophenyl)methyl]pyrazole-3-carboxamide		<chem>C1=CC=C(C(=C1)N2C(=C(C(=N2)C(=O)N)CC3=CC=C(C(=C3)C#N)CC(=O)N)C4=CC=C(C(=C4)Cl)Cl</chem>	Pyrazole derivative 38		Obesity
5-[4-(4-cyanobut-1-ynyl)phenyl]-1-(2,4-dichlorophenyl)-4-(hydroxymethyl)-N-morpholin-4-ylpyrazole-3-carboxamide		<chem>C1COCCN1NC(=O)C2=NN(C(=C2CO)C3=CC=C(C(=C3)C#CCCC#N)C4=C(C(=C(C(=C4)Cl)Cl</chem>	Pyrazole derivative 54		Obesity
N-(2-cyanoethyl)-2-[[7S)-2-[4-cyano-2-[(2-fluoroacetyl)amino]phenyl]-7-methyl-4-oxo-		<chem>C[C@H]1CN(C(=O)C2=CC(=NN12)C3=C(C(=C(C(=C3)C#N)NC(=O)CF)CC(=O)N(C)CCCC#N</chem>	Pyrazole derivative 87		

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6,7-dihydropyrazolo[1,5-a]pyrazin-5-yl]-N-methylacetamide					
1-cyano-N-[5-[(2R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl]pyrazolo[1,5-a]pyrimidin-3-yl]cyclopropane-1-carboxamide		<chem>C1C[C@H](N(C1)C2=NC3=C(C=NN3C=C2)NC(=O)C4(CC4)C#N)C5=C(C=CC(=C5)F)F</chem>	Pyrazolo[1,5-a]pyrimidine derivative 25		
4-[(4-pyrimidin-5-yl)-6,7-dihydro-5H-cyclopenta[b]pyridin-2-yl]oxymethyl]benzonitrile		<chem>C1CC2=C(C1)N=C(C=C2C3=CN=CN=C3)OCC4=CC=C(C=C4)C#N</chem>	Pyridine derivative 14		
5-[2-(pyridin-2-ylmethoxy)-5,6,7,8-tetrahydroquinolin-4-yl]pyrimidine-2-carbonitrile		<chem>C1CCC2=C(C1)C(=CC(=N2)OCC3=CC=CC=N3)C4=CN=C(C(N=C4)C#N</chem>	Pyridine derivative 15		
4-[7-tert-butyl-12-(4-chlorophenyl)-5-oxo-3,4,6,8,10-pentazatricyclo[7.4.0.0.2,6]trideca-1(13),2,7,9,11-pentaen-11-yl]-3-chlorobenzonitrile		<chem>CC(C)(C)C1=NC2=NC(=C(C=C2C3=NNC(=O)N31)C4=CC=C(C(C=C4)C)C5=C(C=C(C(C=C5)C#N)Cl</chem>	Pyridotriazolopyrimidine derivative 3		Obesity
5-[2-(4-cyanophenyl)pyrazol-3-yl]-N-[3-[[5-[2-(4-cyanophenyl)pyrazol-3-yl]-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]pyridine-3-carbonyl]amino]-2-hydroxypropyl]-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]pyridine-3-carboxamide		<chem>CC1=C(C(C=C(C(=O)N1C2=CC=CC(=C2)C(F)(F)C(=O)NCC(CNC(=O)C3=CC(=C(N(C3=O)C4=CC=CC(=C4)C(F)(F)C)C5=CC=NN5C6=CC=C(C(C=C6)C#N)O)C7=CC=NN7C8=CC=C(C(C=C8)C#N</chem>	Pyrimidinone derivative 4		
3-[[4-(3-cyano-4-pyrrolidin-1-yl)phenyl]pyrimidin-2-yl]amino]benzamide		<chem>C1CCN(C1)C2=C(C=C(C(C=C2)C3=NC(=NC=C3)NC4=CC=CC(=C4)C(=O)N)C#N</chem>	Pyrimidinyl compound 1		
5-[2-[[2-oxo-1,3-dihydroindol-5-yl]amino]pyrimidin-4-yl]-2-pyrrolidin-1-ylbenzonitrile		<chem>C1CCN(C1)C2=C(C=C(C(C=C2)C3=NC(=NC=C3)NC4=CC5=C(C(C=C4)NC(=O)C5)C#N</chem>	Pyrimidinyl compound 4		
5-[2-[[6-morpholin-4-ylpyridin-3-yl]amino]pyrimidin-4-yl]-2-pyrrolidin-1-ylbenzonitrile		<chem>C1CCN(C1)C2=C(C=C(C(C=C2)C3=NC(=NC=C3)NC4=CN=C(C(C=C4)N5CCOCC5)C#N</chem>	Pyrimidinyl compound 5		
N-[5-[[4-[3-cyano-4-(3-hydroxyazetid-1-yl)phenyl]pyrimidin-2-yl]amino]pyridin-2-yl]acetamide		<chem>CC(=O)NC1=NC=C(C(C=C1)NC2=NC=C(C(=N2)C3=CC(=C(C(C=C3)N4CC(C4)O)C#N</chem>	Pyrimidinyl compound 6		

IUPAC Name	CAS #	SMILES Notation	USAN Name / Trade Name	Representative Tx Class	Representative Disease
5-[2-[[6-[2-(dimethylamino)ethylamino]pyridin-3-yl]amino]pyrimidin-4-yl]-2-(3-fluoropyrrolidin-1-yl)benzonitrile		<chem>CN(C)CCNC1=NC=C(C=C1)NC2=NC=CC(=N2)C3=CC(=C(C=C3)N4CCC(C4)F)C#N</chem>	Pyrimidinyl compound 7		
3-[3-fluoro-3-(2-pyridin-2-ylethynyl)pyrrolidin-1-yl]benzonitrile		<chem>C1CN(CC1(C#CC2=CC=CC=N2)F)C3=CC=CC(=C3)C#N</chem>	Pyrrolidine derivative 2		
N-[2-[(3R)-3-aminopiperidin-1-yl]-3-[(2-cyanophenyl)methyl]-4-oxopyrrolo[2,1-f][1,2,4]triazin-6-yl]-4-methylbenzenesulfonamide		<chem>CC1=CC=C(C(C=C1)S(=O)(=O)NC2=CN3C(=C2)C(=O)N(C(=N3)N4CCC(C@H)(C4)N)CC5=CC=CC=C5C#N</chem>	Pyrrolo[1,2-f]triazine derivative 2		
(Z)-2-[3-[4-amino-5-(4-phenoxyphenyl)pyrrolo[2,3-d]pyrimidin-7-yl]piperidine-1-carbonyl]-3-cyclopropylprop-2-enenitrile		<chem>C1CC(CN(C1)C(=O)/C(=C/C2CC2)/C#N)N3C=C(C4=C(C(N=CN=C43)N)C5=C(C=C(C=C5)OC6=CC=CC=C6</chem>	Pyrrolo[2,3-d]pyrimidine derivative 16		Solid tumour/cancer; Autoimmune disease
(E)-2-[2-[4-amino-5-(4-phenoxyphenyl)pyrrolo[2,3-d]pyrimidin-7-yl)methyl]pyrrolidine-1-carbonyl]-4-(dimethylamino)-4-methylpent-2-enenitrile		<chem>CC(C)/C(=C/C#N)/C(=O)N1CCCC1CN2C=C(C3=C(C(N=CN=C32)N)C4=CC=C(C=C4)OC5=CC=CC=C5)N(C)C</chem>	Pyrrolo[2,3-d]pyrimidine derivative 17		Solid tumour/cancer; Autoimmune disease
1-[(4-ethoxy-2,6-difluorophenyl)methyl]-3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-5-methylpyrazole-4-carbonitrile		<chem>CCOC1=CC(=C(C(=C1)F)CN2C(=C(C(=N2)C3=NC=C(C(=N3)NC4=CC=CC=C4)OC(C#N)C)F</chem>	SCHEMBL16322760		
4-(3-chloro-4-cyanophenoxy)-3-cyano-N-(1,3-thiazol-2-yl)benzenesulfonamide		<chem>C1=CC(=C(C(=C1OC2=C(C(=C(C=C2)S(=O)(=O)NC3=NC=C(C(=N3)NC4=CC=CC=C4)OC(C#N)C)F</chem>	Sulfonamide derivative 10		
4-(3-chloro-4-cyanophenoxy)-3-cyano-N-(1,3-thiazol-2-yl)benzenesulfonamide		<chem>C1=CC(=C(C(=C1OC2=C(C(=C(C=C2)S(=O)(=O)NC3=NC=C(C(=N3)NC4=CC=CC=C4)OC(C#N)C)F</chem>	Sulfonamide derivative 11		
5-[(6S)-1-(2,6-dimethylpyridin-4-yl)-6-(fluoromethyl)-5,6,9-tetrahydroimidazo[1,5-d][1,4]oxazepin-3-yl]-2-(trifluoromethoxy)benzonitrile		<chem>CC1=CC(=CC(=N1)C)C2=C3CCO[C@H](CN3C(=N2)C4=CC(=C(C(=C4)OC(F)(F)F)C#N)CF</chem>	Tetra-hydroimidazo[1,5-d][1,4]oxazepin-3-yl derivative 6		
ethyl 2-cyano-3-(9-ethylcarbazol-3-yl)iminopropanoate		<chem>CCN1C2=C(C(=C(C=C2)N=CC(C#N)C(=O)OCC)C3=CC=CC=C31</chem>	Tricyclic compound 6		
2-[3-[4-[4-[[[(2S)-2-(hydroxymethyl)pyrrolidin-1-yl]methyl]-6-(trifluoromethyl)pyridin-2-yl]oxy]piperidin-1-		<chem>C1C[C@H](N(C1)CC2=CC(=NC(=C2)OC3CCN(CC3)C4CC(C4)(CC#N)N5C=</chem>	US10053465, 12		

IUPAC Name	CAS #	SMILES Notation	USAN Name / Trade Name	Representative Tx Class	Representative Disease
y]-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)pyrazol-1-yl]cyclobutyl]acetoneitrile		<chem>C(C(=N5)C6=C7C=CN7C=NC(=N6)C(F)(F)F)CO</chem>			
4-[4-(2-fluoro-4-isocyanobenzoyl)piperazin-1-yl]-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)pyrazol-1-yl]butanenitrile		<chem>[C-]#N+ [C1=CC(=C(C=C1)C(=O)N2CCN(CC2)CC(C(C#N)N3C=C(C(=N3)C4=C5C=CNC5=NC=N4)F</chem>	US10053465, 5		
4-[3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)pyrazol-1-yl]azetidin-1-yl]-N-[4-fluoro-2-(trifluoromethyl)phenyl]piperidine-1-carboxamide		<chem>C1CN(CCC1N2CC(C2)(CC#N)N3C=C(C(=N3)C4=C5C=CN5=NC(=N4)C(=O)NC6=C(C(=C(C(=C6)F)C(F)F)F</chem>	US10053465, 8		
tert-butyl (3S)-3-cyano-4-[3-[6-[ethyl(methylsulfonyl)amino]-2-(4-fluorophenyl)-3-(methylcarbamoyl)-1-benzofuran-5-yl]benzoyl]piperazine-1-carboxylate		<chem>CCN(C1=C(C(=C2C(=C1)OC(=C2C(=O)NC)C3=CC=C(C(=C3)F)C4=CC(=CC=C4)C(=O)N5CCN(C(C@H)5C#N)C(=O)OC(C)(C)OS(=O)(=O)C</chem>	US10087167, Compound 3002		
5-[3-(3-cyano-4-methylsulfonyl)piperazine-1-carbonyl]phenyl]-6-[ethyl(methylsulfonyl)amino]-2-(4-fluorophenyl)-N-methyl-1-benzofuran-3-carboxamide		<chem>CCN(C1=C(C(=C2C(=C1)OC(=C2C(=O)NC)C3=CC=C(C(=C3)F)C4=CC(=CC=C4)C(=O)N5CCN(C(C5)C#N)S(=O)(=O)C)S(=O)(=O)C</chem>	US10087167, Compound 3003		
5-[[6-(1,3-difluoropropan-2-yloxy)-1-(1-formylpiperidin-4-yl)-2,4-dioxo-4a,5,6,7,8a-hexahydroquinazolin-3-yl]methyl]-2-phenylbenzonitrile		<chem>C1CC2C(CC1OC(CF)C(=O)N(C(=O)N2C3CCN(CC3)C=O)CC4=CC(=C(C(=C4)C5=CC=CC=C5)C#N</chem>	US8846654, 294		
[[[2S,3S,4S,5S)-5-cyano-5-(2,4-dioxo-1,3-diazinan-1-yl)-3,4-dihydroxy-4-methyloxolan-2-yl]methoxy-hydroxyphosphoryl] phosphono hydrogen phosphate		<chem>C[C@@]1([C@H]([C@@H]([O][C@]1)(C#N)N2CCC(=O)NC2=O)COP(=O)(O)OP(=O)(O)OP(=O)(O)O</chem>	US8877733, 27		
[[[2S,3S,4S,5S)-5-(4-amino-2-oxopyrimidin-1-yl)-5-cyano-3,4-dihydroxy-4-methyloxolan-2-yl]methoxy-hydroxyphosphoryl] phosphono hydrogen phosphate		<chem>C[C@@]1([C@H]([C@@H]([O][C@]1)(C#N)N2C=CC(=NC2=O)N)COP(=O)(O)OP(=O)(O)OP(=O)(O)O</chem>	US8877733, 28		

IUPAC Name	CAS #	SMILES Notation	USAN Name / Trade Name	Representative Tx Class	Representative Disease
2-[2-chloro-5-cyano-3-(6-methyl-2,6-diazaspiro[3.3]heptan-2-yl)anilino]-4-(cyclopropylamino)imidazo[2,1-f][1,2,4]triazine-7-carbonitrile		<chem>CN1CC2(C1)CN(C2)C3=CC(=CC(=C3C)N)NC4=NN5C(=CN=C5C(=N4)NC6CC6)C#N)C#N</chem>	US8940736, 23		
2-[(3-cyano-1-methylindazol-5-yl)amino]-4-(cyclopropylamino)imidazo[2,1-f][1,2,4]triazine-7-carbonitrile		<chem>CN1C2=C(C=C(C=C2)NC3=NN4C(=CN=C4C(=N3)NC5CC5)C#N)C(=N1)C#N</chem>	US8940736, 6		
2-[2-chloro-5-cyano-3-(3-hydroxypyrrolidin-1-yl)anilino]-4-(cyclopropylamino)imidazo[2,1-f][1,2,4]triazine-7-carbonitrile		<chem>C1CC1NC2=NC(=NN3C2=NC=C3C#N)NC4=C(C(=CC(=C4)C#N)N5CCC(C5)O)Cl</chem>	US8940736, 7		
N-(1-cyanocyclopropyl)-2-hydroxy-2-[3-[5-phenyl-4-(trifluoromethyl)-1,2-oxazol-3-yl]-4,5-dihydrobenzo[g][2,1]benzoxazol-7-yl]acetamide		<chem>C1CC2=C(ON=C2C3=C1C=C(C=C3)C(C(=O)NC4(CC4)C#N)O)C5=NOC(=C5C(F)(F)F)C6=CC=CC=C6</chem>	US9216972, 132		
1-[[[1-cyano-4-hydroxy-7-phenoxyisoquinoline-3-carbonyl]amino]methyl]cyclopentane-1-carboxylic acid		<chem>C1CCC(C1)(CNC(=O)C2=C(C3=C(C=C(C3)OC4=CC=CC=C4)C(=N2)C#N)O)C(=O)O</chem>	US9409892, 19		
3-[[1-cyano-4-hydroxy-7-naphthalen-2-yloxyisoquinoline-3-carbonyl]amino]-2,2-dimethylpropanoic acid		<chem>CC(C)(CNC(=O)C1=C(C2=C(C=C(C=C2)OC3=CC4=CC=CC=C4C=C3)C(=N1)C#N)O)C(=O)O</chem>	US9409892, 59		
3-[4-[3,4-difluoro-2-(trifluoromethyl)phenyl]piperidine-1-carbonyl]-1,4,5,7-tetrahydropyrazolo[3,4-c]pyridine-6-carbonitrile		<chem>C1CN(CCC1C2=C(C(=C(C=C2)F)C(F)(F)F)C(=O)C3=NNC4=C3CCN(C4)C#N</chem>	US9434727, 120		
1-cyanobutan-2-yl N-[(1S)-1-[3-[(4-cyano-3-methoxyphenyl)carbamoylethyl]ethoxyphenyl]carbamate		<chem>CCC(CC#N)OC(=O)N[C@@H](C)C1=CC(=CC=C1)NC(=O)NC2=CC(=C(C=C2)C#N)OC</chem>	VX-148		Psoriasis vulgaris
3-(6-cyanopyridin-3-yl)-N-cyclopropylimidazo[1,2-b]pyridazine-2-carboxamide		<chem>C1CC1NC(=O)C2=C(N3C(=N2)C=CC(=N3)C4=CN=C(C=C4)C#N</chem>	ZINC584606052		

Table 4. Cyano-containing small molecule drugs that are in the pre-clinical stage.

IUPAC Name	CAS #	SMILES Notation	USAN Name / Trade Name	Representative Tx Class	Representative Disease
9-ethoxyiminoindeno[1,2-b]pyrazine-2,3-dicarbonitrile		<chem>CCON=C1C2=CC=CC=C2C3=NC(=C(N=C31)C#N)C#N</chem>	9-(Ethoxyimino)-9H-indeno[1,2-b]pyrazine-2,3-dicarbonitrile		Solid tumour/cancer
5-[[1R,5S)-3,6-diazabicyclo[3.2.0]heptan-6-yl]pyridine-3-carbonitrile	CAS 370882-41-0	<chem>C1[C@@H]2CN([C@@H]2CN1)C3=CN=CC(=C3)C#N</chem>	A-366833		Pain
N-[(4S)-2-[N-cyano-N'-(3-(difluoromethoxy)phenyl]carbamidoyl]-5-(3,4-dichlorophenyl)-3,4-dihydropyrazol-4-yl]-N-ethyl-2-hydroxyacetamide		<chem>CCN([C@H]1CN(N=C1C2=CC(=C(C=C2)OC(F)F)NC#N)C(=O)CO</chem>	BAY 598		Discovery agent
2-[6-amino-3,5-dicyano-4-[4-(cyclopropylmethoxy)phenyl]pyridin-2-yl]sulfanylamide	CAS 910487-58-0	<chem>C1CC1COC2=CC=C(C(=C2)C3=C(C(=N)C(=C3C#N)SCC(=O)N)N)C#N</chem>	BAY 60-6583		Myocardial ischemia
3-aminopropanenitrile	CAS 151-18-8	<chem>C(CN)C#N</chem>	Beta-aminopropionitrile		Cardiac arrest
(2S)-N-[(1S)-1-cyano-2-[4-(3-methyl-2-oxo-1,3-benzoxazol-5-yl)phenyl]ethyl]-1,4-oxazepane-2-carboxamide	CAS 1802148-05-5	<chem>CN1C2=C(C=CC(=C2)C3=CC=C(C(=C3)C[C@@H]([C@H]4CNCCO4)OC1=O)C@H]4CN</chem>	Brensocatib	Antiviral Agents	Coronavirus Disease 2019 (COVID-19)
2-[3-(tert-butylamino)-2-hydroxypropoxy]benzonitrile	CAS 34915-68-9	<chem>CC(C)(C)NCCC(COC1=CC=CC=C1C#N)O</chem>	Bunitrolol		
4-[4-[2-[[3-(2-aminoethyl)-1H-indol-5-yl]oxy]acetyl]piperazin-1-yl]benzonitrile	CAS 170912-52-4	<chem>C1CN(CCN1C2=CC=C(C(=C2)C#N)C(=O)COC3=CC4=C(C(=C3)NC=C4CCN</chem>	Donitriptan		Migraine
4-[(4S)-4-(hydroxymethyl)-3-methyl-2,5-dioxo-4-phenylimidazolidin-1-yl]-2-(trifluoromethyl)benzonitrile	CAS 1215085-92-9	<chem>CN1C(=O)N(C(=O)[C@@H]1(CO)C2=C(C=CC=C2)C3=CC(=C(C(=C3)C#N)C(F)(F)F</chem>	GLPG-0492		Cachexia
2-amino-6-[(E)-2-(3-fluorophenyl)ethenyl]-1H-indole-3-carbonitrile		<chem>C1=CC(=CC(=C1)F)/C=C/C2=CC3=C(C=C2)C(=C(CN3)N)C#N</chem>	GSK2643943A		Solid tumour/cancer
N-[1-(cyanomethylcarbamoyle)cyclohexyl]-4-[2-(4-methylpiperazin-1-yl)-1,3-thiazol-4-yl]benzamide	CAS 294623-49-7	<chem>CN1CCN(CC1)C2=NC(=CS2)C3=CC=C(C(=C3)C(=O)NC4(CCCCC4)C(=O)NCC#N</chem>	L-006235-1		Osteoarthritis
3-cyano-5-[2-[4-[2-(3-methylindol-1-yl)ethyl]piperazin-1-yl]phenyl]-N-(3-pyrrolidin-1-ylpropyl)benzamide		<chem>CC1=CN(C2=CC=CC=C2)CCN3CCN(CC3)C4=CC=CC(=C4)C5=CC(=CC(=C5)C#N)C(=O)NCCCN6CCCCC6</chem>	LLY-507		Solid tumour/cancer

IUPAC Name	CAS #	SMILES Notation	USAN Name / Trade Name	Representative Tx Class	Representative Disease
4-[[[6-[5-chloro-2-[[4-[[[(2R)-1-methoxypropan-2-yl]amino]cyclohexyl]amino]pyridin-4-yl]pyridin-2-yl]amino]methyl]oxane-4-carbonitrile		<chem>C[C@H]([C@H]1CCCC(C1)NC2=NC(=C(C=C2)C3=NC(=CC=C3)NCC4(COCC4)C#N)C1</chem>	NVP-2		Solid tumour/cancer
N-[4-[(3aR,9bS)-8-cyano-3,3a,4,9b-tetrahydro-1H-chromeno[3,4-c]pyrrol-2-yl]butyl]-4-phenylbenzamide	CAS 273203-30-8	<chem>C1[C@H]2COC3=C([C@H]2CN1CCCN(C(=O)C4=CC=C(C(=C4)C5=CC=CC=C5)C=C(C(=C3)C#N</chem>	S-33084		Psychotic disorder
2-cyano-N-[(E)-(1,4-dioxidoquinoxaline-1,4-dium-2-yl)methylideneamino]acetamide	CAS 65884-46-0	<chem>C1=CC=C2C(=C1)[N+](=CC(=[N+][2[O-])C=NNC(=O)CC#N])[O-]</chem>	VUFB-11502		Amebiasis
2-cyano-2-[3-ethyl-4-oxo-5-[[3-(2-pyrrolidin-1-ylethyl)anilino]methyl]-1,3-thiazolidin-2-yl]-N-(2,2,2-trifluoroethyl)acetamide		<chem>CCN1C(SC(C1=O)CNC2=CC=CC(=C2)CCN3CCCC3)C(C#N)C(=O)NCC(F)(F)F</chem>	ZK thiazolidinone	Anticancer Agents	Solid tumour/cancer

Table 5. Cyano-containing small molecule drugs that are in the investigative stage.

IUPAC Name	CAS #	SMILES Notation	USAN Name / Trade Name	Representative Tx Class	Representative Disease
3-(1-propylpiperidin-3-yl)benzonitrile	CAS 150336-90-6	<chem>CCCN1CCCC(C1)C2=CC=CC(=C2)C#N</chem>	(-)-3-(1-Propylpiperidin-3-yl)-benzonitrile		Discovery agent
(1R,5R)-30-oxo-19-oxa-2,6,10,12-tetrazahehexacyclo[18.6.2.12.5.114,18.08,12.023,2,7]triaconta-8,10,14(29),15,17,20(28),21,23(27)-octaene-17-carbonitrile		<chem>C1C[C@@H]2C3=C(C1)C=CC(=C3)OC4=C(C=CC(=C4)CN5C=NC=C5CN[C@@H]6CCN2C6=O)C#N</chem>	(1R,5R)-30-Oxo-19-Oxa-2,6,10,12-Tetrazahehexacyclo[18.6.2.1^2,5}.1^14,18}.0^8,12}.0^23,27]]TRIACONTA-ACONTA-8,10,14(29),15,17,20(28),21,23(27)-OCTAENE-17-CARBONITRILE (STRUCTURAL MIX)		Discovery agent
N-[(3R,4S)-6-cyano-3-hydroxy-2,2-dimethyl-3,4-dihydrochromen-4-yl]-N-methylethanesulfonamide	CAS 163163-23-3	<chem>CCS(=O)(=O)N(C)[C@@H]1[C@H]([C@@H]2C=CC(=C2)C#N)(C)C1O</chem>	(3R,4S)-293B		Discovery agent

IUPAC Name	CAS #	SMILES Notation	USAN Name / Trade Name	Representative Tx Class	Representative Disease
2-[4-(dipropylamino)cyclohexylidene]acetone nitrile		<chem>CCCN(CCC)C1CCC(=CC#N)CC1</chem>	(4-Dipropylamino-cyclohexylidene)-acetone nitrile		Discovery agent
2-(2-oxo-7-phenylmethoxychromen-4-yl)acetone nitrile		<chem>C1=CC=C(C=C1)COC2=CC3=C(C=C2)C(=CC(=O)O3)CC#N</chem>	(7-Benzyl-oxo-2-oxo-2H-chromen-4-yl)acetone nitrile		Discovery agent
6-[[[(3R)-pyrrolidin-3-yl]methoxy]naphthalene-2-carbonitrile		<chem>C1CN[C@@H](C1)COC2=CC3=C(C=C2)C=C(C=C3)C#N</chem>	(R)-6-(pyrrolidin-3-ylmethoxy)-2-naphthonitrile		Discovery agent
2-amino-N-[(1S)-1-cyano-2-phenylethyl]acetamide		<chem>C1=CC=C(C=C1)C[C@H](C#N)NC(=O)CN</chem>	(S)-2-amino-N-(1-cyano-2-phenylethyl)acetamide		Discovery agent
6-[[[(3S)-pyrrolidin-3-yl]methoxy]naphthalene-2-carbonitrile		<chem>C1CN[C@H](C1)COC2=CC3=C(C=C2)C=C(C=C3)C#N</chem>	(S)-6-(pyrrolidin-3-ylmethoxy)-2-naphthonitrile		Discovery agent
4-[2-hydroxy-3-(propan-2-ylamino)propoxy]-3-[(12S)]iodanyl-1H-indole-2-carbonitrile		<chem>CC(C)NCC(COC1=CC=CC2=C1C(=C(N2)C#N)[12S])O</chem>	[12S]]ICYP		Discovery agent
4-amino-N-[2-[[[N-cyano-N'-[3-[3-(piperidin-1-ylmethyl)phenoxy]propyl]carbamiidoyl]amino]ethyl]-3-(12S)]iodanylbenzamide		<chem>C1CCN(CC1)CC2=CC(=CC=C2)OCCCN=C(NCCNC(=O)C3=CC(=C(C=C3)N)[12S])NC#N</chem>	[12S]]iodoaminopotentidine		Discovery agent
(2S)-2-[3,4-dimethoxyphenyl]-5-[2-(3-methoxyphenylethyl)-methylamino]-2-propan-2-ylpentanenitrile	CAS 93468-87-2	<chem>CC(C)[C@](CCCC(C)CCC1=CC(=CC=C1)OC)(C#N)C2=CC(=C(C=C2)OC)OC</chem>	[3H](-)devapamil		Discovery agent
7-nitro-2,3-dioxo-1,4-dihydroquinoline-6-carbonitrile	CAS 115066-14-3	<chem>C1=C(C(=CC2=C1NC(=O)C(=O)N2)[N+](=O)[O-])C#N</chem>	[3H]CNQX		Discovery agent
1-ethyl-2-methyl-6-oxo-4-(1,2,4,5-tetrahydro-3-benzazepin-3-yl)pyrimidine-5-carbonitrile		<chem>CCN1C(=NC(=C(C1=O)C#N)N2CC3=CC=CC=C3CC2)C</chem>	[3H]EM-TBPC		Discovery agent
1-(cyclopropylmethyl)-2-oxo-4-(4-phenylpiperidin-1-yl)pyridine-3-carbonitrile		<chem>C1CC1CN2C=CC(=C(C2=O)C#N)N3CCC(CC3)C4=CC=CC=C4</chem>	[3H]JNJ-40068782		Discovery agent
1-(2-bromophenyl)-3-(4-cyano-2-hydroxyphenyl)urea		<chem>C1=CC=C(C(=C1)NC(=O)NC2=C(C=C(C=C2)C#N)O)Br</chem>	1-(2-bromophenyl)-3-(4-cyano-2-hydroxyphenyl)urea		Discovery agent
1-(3-cyano-1-methylindol-6-yl)-3-phenylurea		<chem>CN1C=C(C2=C1C=C(C=C2)NC(=O)NC3=CC=CC=C3)C#N</chem>	1-(3-cyano-1-methyl-1H-indol-6-yl)-3-phenylurea		Discovery agent

IUPAC Name	CAS #	SMILES Notation	USAN Name / Trade Name	Representative Tx Class	Representative Disease
1-(3-cyano-2-hydroxyphenyl)-3-phenylurea		<chem>C1=CC=C(C(=C1)NC(=O)NC2=CC=CC(=C2O)C#N</chem>	1-(3-cyano-2-hydroxyphenyl)-3-phenylurea		Discovery agent
1-(3-cyanophenyl)pyrazole-4-carboxylic acid		<chem>C1=CC(=CC(=C1)N2C=C(C(=N2)C(=O)O)C#N</chem>	1-(3-Cyano-phenyl)-1H-pyrazole-4-carboxylic acid		Discovery agent
1-(4-cyano-2-hydroxyphenyl)-3-phenylurea		<chem>C1=CC=C(C(=C1)NC(=O)NC2=CC(=C(C=C2)C#N)O</chem>	1-(4-cyano-2-hydroxyphenyl)-3-phenylurea		Discovery agent
4-[[[5-(2-fluorophenyl)imidazol-1-yl]methyl]benzonitrile		<chem>C1=CC=C(C(=C1)C2=CN=CN2CC3=CC=C(C(=C3)C#N)F</chem>	1-(4-Cyanobenzyl)-5-(2-fluorophenyl)-1H-imidazole		Discovery agent
4-[[[5-(2-methylphenyl)imidazol-1-yl]methyl]benzonitrile		<chem>CC1=CC=CC=C1C2=CN=CN2CC3=CC=C(C(=C3)C#N</chem>	1-(4-Cyanobenzyl)-5-(2-methylphenyl)-1H-imidazole		Discovery agent
4-[[[5-(3-fluorophenyl)imidazol-1-yl]methyl]benzonitrile		<chem>C1=CC(=CC(=C1)F)C2=CN=CN2CC3=CC=C(C(=C3)C#N</chem>	1-(4-Cyanobenzyl)-5-(3-fluorophenyl)-1H-imidazole		Discovery agent
4-[[[5-(3-methylphenyl)imidazol-1-yl]methyl]benzonitrile		<chem>CC1=CC(=CC(=C1)C2=CN=CN2CC3=CC=C(C(=C3)C#N</chem>	1-(4-Cyanobenzyl)-5-(3-methylphenyl)-1H-imidazole		Discovery agent
4-[[[5-(4-fluorophenyl)imidazol-1-yl]methyl]benzonitrile		<chem>C1=CC(=CC=C1CN2C=NC=C2C3=CC=C(C(=C3)F)C#N</chem>	1-(4-Cyanobenzyl)-5-(4-fluorophenyl)-1H-imidazole		Discovery agent
4-[[[5-(4-methylphenyl)imidazol-1-yl]methyl]benzonitrile		<chem>CC1=CC=C(C(=C1)C2=CN=CN2CC3=CC=C(C(=C3)C#N</chem>	1-(4-Cyanobenzyl)-5-(4-methylphenyl)-1H-imidazole		Discovery agent
4-[[[5-pyridin-4-yl]imidazol-1-yl]methyl]benzonitrile		<chem>C1=CC(=CC=C1CN2C=NC=C2C3=CC=NC(=C3)C#N</chem>	1-(4-Cyanobenzyl)-5-(4-pyridyl)-1H-imidazole		Discovery agent
4-[[[5-bromoimidazol-1-yl]methyl]benzonitrile		<chem>C1=CC(=CC=C1CN2C=NC=C2Br)C#N</chem>	1-(4-Cyanobenzyl)-5-bromo-1H-imidazole		Discovery agent
4-[[[5-formylimidazol-1-yl]methyl]benzonitrile	CAS 183500-37-0	<chem>C1=CC(=CC=C1CN2C=NC=C2C=O)C#N</chem>	1-(4-Cyanobenzyl)-5-formyl-1H-imidazole		Discovery agent

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4-[[5-(hydroxymethyl)imidazol-1-yl]methyl]benzonitrile	CAS 183500-36-9	<chem>C1=CC(=CC=C1CN2C=NC=C2CO)C#N</chem>	1-(4-Cyanobenzyl)-5-hydroxymethyl-1H-imidazole		Discovery agent
4-[[5-methylimidazol-1-yl)methyl]benzonitrile		<chem>CC1=CN=CN1CC2=CC=C(C=C2)C#N</chem>	1-(4-Cyanobenzyl)-5-methyl-1H-imidazole		Discovery agent
4-[[5-phenylimidazol-1-yl)methyl]benzonitrile		<chem>C1=CC=C(C=C1)C2=CN=CN2CC3=CC=C(C=C3)C#N</chem>	1-(4-Cyanobenzyl)-5-phenyl-1H-imidazole		Discovery agent
1-(4-cyano-1,3-thiazol-2-yl)-3-(2-phenylethyl)thiourea		<chem>C1=CC=C(C=C1)CCNC(=S)NC2=NC(=CS2)C#N</chem>	1-(4-Cyano-thiazol-2-yl)-3-phenethyl-thiourea		Discovery agent
4-[(E)-[(13S,17S)-3,17-dihydroxy-13-methyl-7,8,9,11,12,14,15,17-octahydro-6H-cyclopenta[a]phenanthren-16-ylidene]methyl]benzonitrile		<chem>C1C@12CCC3C(C1C/C(C=C1)C4=CC=C(C=C4)C#N)/[C@@H]2O)C#CC5=C3C=CC(=C5)O</chem>	16-(4-cyanobenzylidene)-estradiol		Discovery agent
3-[[[(2R)-2-[[1-(1-benzothiophen-2-yl)-2-methylpropan-2-yl]amino]-1-hydroxyethyl]pyrrolidin-1-yl]methyl]benzonitrile		<chem>C1C@12CC[C@H]3[C@H]1([C@@H]1C[C@H]([C@H]([C@H]2O)C#N)CCC4=C3C=CC(=C4)O</chem>	16beta-cyano-estradiol		Discovery agent
1-methylindole-3-carbonitrile	CAS 24662-37-1	<chem>CC(C)(CC1=CC2=CC=CC=C2S1)NC[C@H]1([C@H]3CCCN3CC4=CC(=CC=C4)C#N)O</chem>	1-arylmethylpyrrolidin-2-yl ethanol amine		Discovery agent
1-methyl-4-(4-methylphenyl)piperidine-4-carbonitrile		<chem>CC1=CC=C(C2=CC=CC=C2)C#N</chem>	1-methyl-1H-indole-3-carbonitrile		Discovery agent
2-(2-methylquinolin-7-yl)benzonitrile		<chem>CC1=CC=C(C(C=C1)C2(CCN(CC2)C)C#N</chem>	1-Methyl-4-p-tolyl-piperidine-4-carbonitrile		Discovery agent
2-(2-phenyl-2-piperazin-1-ylethyl)benzonitrile		<chem>CC1=NC2=C(C=C1)C=CC(=C2)C3=CC=CC=C3C#N</chem>	2-(2-methylquinolin-7-yl)benzonitrile		Discovery agent
2-[3-(2-methylquinolin-7-yl)phenyl]acetoneitrile		<chem>C1CN(CCN1)C(CC2=CC=CC=C2C#N)C3=CC=CC=C3</chem>	2-(2-phenyl-2-piperazin-1-ylethyl)benzonitrile		Discovery agent
		<chem>CC1=NC2=C(C=C1)C=CC(=C2)C3=CC=CC(=C3)CC#N</chem>	2-(3-(2-methylquinolin-7-yl)phenyl)acetoneitrile		Discovery agent

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2-[(3,4,5-trihydroxyphenyl)methylidene]propanedinitrile	CAS 118409-58-8	<chem>C1=C(C(=C(C(=C1O)O)O)C(=C(C#N)C#N</chem>	2-(3,4,5-Trihydroxy-benzylidene)-malononitrile		Discovery agent
2-chloro-6-[(3-chlorophenyl)methoxy]pyridine-4-carbonitrile		<chem>C1=CC(=CC(=C(C1Cl)Cl)COC2=NC(=CC(=C2)C#N)Cl</chem>	2-(3-chlorobenzoyloxy)-6-chloroisonicotinonitrile		Discovery agent
2-[(3-cyanophenyl)methyl]-5-sulfanylpentanoic acid		<chem>C1=CC(=CC(=C(C1C#N)CC(CCCS)C(=O)O</chem>	2-(3-cyanobenzyl)-5-mercaptopentanoic acid		Discovery agent
2-(4,5-dihydroxy-2,3-dihydroinden-1-ylidene)propanedinitrile		<chem>C1CC(=C(C#N)C#N)C2=C1C(=C(C=C2)O)O</chem>	2-(4,5-Dihydroxy-indan-1-ylidene)-malononitrile		Discovery agent
2-(4-cyano-2-cyclohexylphenoxy)acetic acid		<chem>C1CCC(CC1)C2=C(C(=CC(=C2)C#N)OCC(=O)O</chem>	2-(4-cyano-2-cyclohexylphenoxy)acetic acid		Discovery agent
2-[4-(dipropylamino)cyclohexylidene]propanedinitrile		<chem>CCCN(CCC)C1CCC(=C(C#N)C#N)CC1</chem>	2-(4-Dipropylamino-cyclohexylidene)-malononitrile		Discovery agent
2-(4-hydroxyphenyl)-3,3-diphenylprop-2-enenitrile		<chem>C1=CC=C(C(=C1)C(=C(C#N)C2=C(C(=C(C2)O)C3=CC=CC=C3</chem>	2-(4-Hydroxy-phenyl)-3,3-diphenylacrylonitrile		Discovery agent
2-[4-(4-methylphenyl)sulfonyl]piperazin-1-yl]pyridine-3-carbonitrile		<chem>CC1=CC=C(C(=C1)S(=O)(=O)N2CN(CN(C2)C3=C(C(=CC=N3)C#N</chem>	2-(4-tosylpiperazin-1-yl)nicotinonitrile		Discovery agent
2-(5,6-dihydroxy-2,3-dihydroinden-1-ylidene)propanedinitrile	CAS 133550-11-5	<chem>C1CC(=C(C#N)C#N)C2=CC(=C(C(=C21)O)O</chem>	2-(5,6-Dihydroxy-indan-1-ylidene)-malononitrile		Discovery agent
6-[9-[(2R,3R,4S,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-(methoxyamino)purin-2-yl]hex-5-ynenitrile		<chem>CONC1=C2C(=NC(=N1)C#CCCCC#N)N(C=N2)[C@H]3[C@@H]([C@@H]([C@H](O3)CO)O</chem>	2-(5-cyano-1-pent-1-ynyl)-N6-methoxyadenosine		Discovery agent
2-[(5-phenyl-1,3-oxazol-2-yl)amino]benzonitrile		<chem>C1=CC=C(C(=C1)C2=CN=C(O2)NC3=CC=CC=C3C#N</chem>	2-(5-Phenyl-oxazol-2-ylamino)-benzonitrile		Discovery agent
2-(7-phenylheptanoyl)-1,3-oxazole-4-carbonitrile		<chem>C1=CC=C(C(=C1)CCCCCCC(=O)C2=NC(=CO2)C#N</chem>	2-(7-phenylheptanoyl)oxazole-4-carbonitrile		Discovery agent

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2-(7-phenylheptanoyl)-1,3-oxazole-5-carbonitrile		<chem>C1=CC=C(C=C1)CCCCCCC(=O)C2=NC=C(O2)C#N</chem>	2-(7-phenylheptanoyl)oxazole-5-carbonitrile		Discovery agent
2-(4-methylaniilino)-4-phenylpyrimidine-5-carbonitrile		<chem>CC1=CC=C(C=C1)NC2=NC=C(C(=N2)C3=CC=CC=C3)C#N</chem>	2-(p-toluidino)-4-phenylpyrimidine-5-carbonitrile		Discovery agent
2-(pyrimidin-4-ylamino)-1,3-thiazole-5-carbonitrile	CAS 436852-19-6	<chem>C1=CC=CC=C1NC2=NC=C(S2)C#N</chem>	2-(pyrimidin-4-ylamino)thiazole-5-carbonitrile		Discovery agent
2,3,3-triphenylprop-2-enenitrile	CAS 6304-33-2	<chem>C1=CC=C(C=C1)C(=C(C2=CC=CC=C2)C3=CC=CC=C3)C#N</chem>	2,3,3-Triphenylacrylonitrile		Discovery agent
[4-(2,4-dicyanophenyl)phenyl] sulfamate		<chem>C1=CC(=CC=C1C2=C(C(=C(C=C2)C#N)C#N)OS(=O)(=O)N</chem>	2',4'-dicyanobiphenyl-4-yl sulfamate		Discovery agent
2-amino-4,6-bis(furan-2-yl)pyridine-3-carbonitrile		<chem>C1=COC(=C1)C2=CC(=NC(=C2C#N)N)C3=CC=CO3</chem>	2-Amino-4,6-di-furan-2-yl-nicotinonitrile		Discovery agent
2-amino-4,6-diphenylpyridine-3-carbonitrile	CAS 4604-06-2	<chem>C1=CC=C(C=C1)C2=CC(=NC(=C2C#N)N)C3=CC=CC=C3</chem>	2-Amino-4,6-diphenyl-nicotinonitrile		Discovery agent
2-amino-4,6-diphenylpyrimidine-5-carbonitrile		<chem>C1=CC=C(C=C1)C2=C(C(=NC(=N2)N)C3=CC=CC=C3)C#N</chem>	2-Amino-4,6-diphenylpyrimidin-5-carbonitrile		Discovery agent
2-amino-4,6-dithiophen-2-ylpyridine-3-carbonitrile		<chem>C1=CSC(=C1)C2=CC(=NC(=C2C#N)N)C3=CC=CC=C3</chem>	2-Amino-4,6-di-thiophen-2-yl-nicotinonitrile		Discovery agent
2-amino-4-(furan-2-yl)-6-phenylpyridine-3-carbonitrile		<chem>C1=CC=C(C=C1)C2=NC(=C(C(=C2)C3=CC=CO3)C#N)N</chem>	2-Amino-4-furan-2-yl-6-phenyl-nicotinonitrile		Discovery agent
2-amino-4-phenyl-6-thiophen-2-ylpyridine-3-carbonitrile		<chem>C1=CC=C(C=C1)C2=CC(=NC(=C2C#N)N)C3=CC=CC=C3</chem>	2-Amino-4-phenyl-6-thiophen-2-yl-nicotinonitrile		Discovery agent
2-amino-6-(2-bromophenyl)sulfonylbenzonitrile		<chem>C1=CC=C(C(=C1)S(=O)(=O)C2=C(C=CC(=C2C#N)N)Br</chem>	2-Amino-6-(2-bromo-benzenesulfonyl)-benzonitrile		Discovery agent
2-amino-6-(2-chlorophenyl)sulfonylbenzonitrile		<chem>C1=CC=C(C(=C1)S(=O)(=O)C2=C(C=CC(=C2C#N)N)Cl</chem>	2-Amino-6-(2-chloro-benzenesulfonyl)-benzonitrile		Discovery agent

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2-amino-6-(2-chlorophenyl)sulfany/benzonitrile		<chem>C1=CC=C(C(=C1)SC2=CC=CC(=C2C#N)N)Cl</chem>	2-Amino-6-(2-chloro-phenylsulfanyl)-benzonitrile		Discovery agent
2-amino-6-(2-cyanophenyl)sulfany/benzonitrile		<chem>C1=CC=C(C(=C1)C#N)S(=O)C2=CC=CC(=C2C#N)N</chem>	2-Amino-6-(2-cyano-benzenesulfonyl)-benzonitrile		Discovery agent
2-amino-6-(2-cyanophenyl)sulfony/benzonitrile		<chem>C1=CC=C(C(=C1)C#N)S(=O)(=O)C2=CC=CC(=C2C#N)N</chem>	2-Amino-6-(2-cyano-benzenesulfonyl)-benzonitrile		Discovery agent
2-amino-6-(2-cyanophenyl)sulfany/benzonitrile		<chem>C1=CC=C(C(=C1)C#N)SC2=CC=CC(=C2C#N)N</chem>	2-Amino-6-(2-cyano-phenylsulfanyl)-benzonitrile		Discovery agent
2-amino-6-(2-fluorophenyl)sulfony/benzonitrile		<chem>C1=CC=C(C(=C1)F)S(=O)(=O)C2=CC=CC(=C2C#N)N</chem>	2-Amino-6-(2-fluoro-benzenesulfonyl)-benzonitrile		Discovery agent
2-amino-6-(2-methoxyphenyl)sulfany/benzonitrile		<chem>COC1=CC=CC=C1SC2=CC=CC(=C2C#N)N</chem>	2-Amino-6-(2-methoxy-phenylsulfanyl)-benzonitrile		Discovery agent
2-amino-6-(3-bromophenyl)sulfony/benzonitrile		<chem>C1=CC(=CC(=C1)Br)S(=O)C2=CC=CC(=C2C#N)N</chem>	2-Amino-6-(3-bromo-benzenesulfonyl)-benzonitrile		Discovery agent
2-amino-6-(3-bromophenyl)sulfony/benzonitrile		<chem>C1=CC(=CC(=C1)Br)S(=O)(=O)C2=CC=CC(=C2C#N)N</chem>	2-Amino-6-(3-bromo-benzenesulfonyl)-benzonitrile		Discovery agent
2-amino-6-(3-bromophenyl)sulfany/benzonitrile		<chem>C1=CC(=CC(=C1)Br)SC2=CC=CC(=C2C#N)N</chem>	2-Amino-6-(3-bromo-phenylsulfanyl)-benzonitrile		Discovery agent
2-amino-6-(3-chlorophenyl)sulfony/benzonitrile		<chem>C1=CC(=CC(=C1)Cl)S(=O)(=O)C2=CC=CC(=C2C#N)N</chem>	2-Amino-6-(3-chloro-benzenesulfonyl)-benzonitrile		Discovery agent
2-amino-6-(3-chlorophenyl)sulfany/benzonitrile		<chem>C1=CC(=CC(=C1)Cl)SC2=CC=CC(=C2C#N)N</chem>	2-Amino-6-(3-chloro-phenylsulfanyl)-benzonitrile		Discovery agent

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2-amino-6-(3-cyanophenyl)sulfonylbenzonitrile		<chem>C1=CC(=CC(=C1)S(=O)(=O)C2=C(C=CC(=C2C#N)N)C#N</chem>	2-Amino-6-(3-cyano-benzenesulfonyl)-benzonitrile		Discovery agent
2-amino-6-(3-cyanophenyl)sulfanylbenzonitrile		<chem>C1=CC(=CC(=C1)SC2=CC=CC(=C2C#N)N)C#N</chem>	2-Amino-6-(3-cyano-phenylsulfonyl)-benzonitrile		Discovery agent
2-amino-6-(3-fluorophenyl)sulfonylbenzonitrile		<chem>C1=CC(=CC(=C1)SC2=CC=CC(=C2C#N)N)F</chem>	2-Amino-6-(3-fluoro-phenylsulfonyl)-benzonitrile		Discovery agent
2-amino-6-(3-methoxyphenyl)sulfonylbenzonitrile		<chem>COC1=CC(=CC(=C1)SC2=CC=CC(=C2C#N)N</chem>	2-Amino-6-(3-methoxy-phenylsulfonyl)-benzonitrile		Discovery agent
2-amino-6-(4-chlorophenyl)sulfonylbenzonitrile		<chem>C1=CC(=C(C(=C1)SC2=CC=CC(=C2)C)C#N)N</chem>	2-Amino-6-(4-chloro-phenylsulfonyl)-benzonitrile		Discovery agent
2-amino-6-naphthalen-1-ylsulfonylbenzonitrile		<chem>C1=CC=C2C(C(=C1)C=CC=C2S(=O)(=O)C3=CC=CC(=C3C#N)N</chem>	2-Amino-6-(naphthalene-1-sulfonyl)-benzonitrile		Discovery agent
2-amino-6-naphthalen-2-ylsulfonylbenzonitrile		<chem>C1=CC=C2C(C(=C(C(=CC2=C1)S(=O)(=O)C3=CC=CC(=C3C#N)N</chem>	2-Amino-6-(naphthalene-2-sulfonyl)-benzonitrile		Discovery agent
2-amino-6-(2-methylphenyl)sulfonylbenzonitrile		<chem>CC1=CC=CC(=CC(=C1S(=O)(=O)C2=CC=CC(=C2C#N)N</chem>	2-Amino-6-(toluene-2-sulfonyl)-benzonitrile		Discovery agent
2-amino-6-(3-methylphenyl)sulfonylbenzonitrile		<chem>CC1=CC(=CC(=CC(=C1)S(=O)(=O)C2=CC=CC(=C2C#N)N</chem>	2-Amino-6-(toluene-3-sulfonyl)-benzonitrile		Discovery agent
2-amino-6-(3-methylphenyl)sulfonylbenzonitrile		<chem>CC1=CC(=CC(=CC(=C1)S(=O)(=O)C2=CC=CC(=C2C#N)N</chem>	2-Amino-6-(toluene-3-sulfonyl)-benzonitrile		Discovery agent
2-amino-6-(4-methylphenyl)sulfonylbenzonitrile		<chem>CC1=CC=C(C(=C1)S(=O)(=O)C2=CC=CC(=C2C#N)N</chem>	2-Amino-6-(toluene-4-sulfonyl)-benzonitrile		Discovery agent
2-amino-6-(benzenesulfonyl)benzonitrile		<chem>C1=CC=C(C(=C1)S(=O)(=O)C2=C(C=CC(=C2C#N)N</chem>	2-Amino-6-benzenesulfonyl-benzonitrile		Discovery agent
2-amino-6-(furan-2-yl)-4-phenylpyridine-3-carbonitrile		<chem>C1=CC=C(C(=C1)C2=CC(=NC(=C2C#N)N)C3=CC=CO3</chem>	2-Amino-6-furan-2-yl-4-phenyl-nicotinonitrile		Discovery agent

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2-amino-6-(3-methylphenyl)sulfany/benzonitrile		<chem>CC1=CC(=CC=C1)SC2=CC=CC(=C2C#N)N</chem>	2-Amino-6-m-tolylsulfanyl-benzonitrile		Discovery agent
2-amino-4-(4-methylphenyl)-6-phenylpyridine-3-carbonitrile		<chem>CC1=CC=C(C(=C1)C2=CC(=NC(=C2C#N)N)C3=CC=CC=C3</chem>	2-amino-6-phenyl-4-p-tolylNicotinonitrile		Discovery agent
2-amino-6-phenyl-4-thiophen-2-ylpyridine-3-carbonitrile		<chem>C1=CC=C(C(=C1)C2=NC(=C(C(=C2)C3=CC=CS3)C#N)N</chem>	2-Amino-6-phenyl-4-thiophen-2-yl-nicotinonitrile		Discovery agent
2-amino-6-phenylsulfany/benzonitrile	CAS 123241-49-6	<chem>C1=CC=C(C(=C1)SC2=CC=CC(=C2C#N)N</chem>	2-Amino-6-phenylsulfanyl-benzonitrile		Discovery agent
2-amino-6-(4-methylphenyl)sulfany/benzonitrile	CAS 168910-27-8	<chem>CC1=CC=C(C(=C1)SC2=CC=CC(=C2C#N)N</chem>	2-Amino-6-p-tolylsulfanyl-benzonitrile		Discovery agent
5-(2-methylquinolin-7-yl)-2-phenylmethoxybenzonitrile		<chem>CC1=NC2=C(C(=C1)C=CC(=C2)C3=CC(=C(C(=C3)OCC4=CC=CC=C4)C#N</chem>	2-Benzoxo-5-(2-methylquinolin-7-yl)benzonitrile		Discovery agent
(E)-2-benzoyl-3-(3,4-dihydroxyphenyl)prop-2-enenitrile		<chem>C1=CC=C(C(=C1)C(=O)/C(=C/C2=CC(=C(C(=C2)O)O)/C#N</chem>	2-benzoyl-3-(3,4-dihydroxyphenyl)acrylonitrile		Discovery agent
2-chloro-4-(2-methylphenoxy)benzonitrile		<chem>CC1=CC=CC=C(C1OC2=CC(=C(C(=C2)C#N)Cl</chem>	2-chloro-4-(o-tolyl)benzonitrile		Discovery agent
2-chloro-5-(2-methylquinolin-7-yl)pyridine-3-carbonitrile		<chem>CC1=NC2=C(C(=C1)C=CC(=C2)C3=CC(=C(C(=C3)Cl)C#N</chem>	2-Chloro-5-(2-methylquinolin-7-yl)nicotinonitrile		Discovery agent
2-chloro-N-(6-cyanopyridin-3-yl)propanamide		<chem>CC(C(=O)NC1=CN=C(C(=C1)C#N)Cl</chem>	2-chloro-N-(6-cyanopyridin-3-yl)propanamide		Discovery agent
(E)-2-cyano-3-(3,4-dihydroxyphenyl)prop-2-enamide	CAS 118409-59-9	<chem>C1=CC(=C(C(=C1)C(=O)O)O)/C(=C/C2=CC(=C(C(=C2)C#N)C(=O)N)O)O</chem>	2-cyano-3-(3,4-dihydroxyphenyl)acrylamide		Discovery agent
6-(cyclohexylamino)pyridine-2-carbonitrile		<chem>C1CCC(CC1)NC2=CC=CC(=N2)C#N</chem>	2-cyclohexylamino-pyridine-2-carbonitrile		Discovery agent

IUPAC Name	CAS #	SMILES Notation	USAN Name / Trade Name	Representative Tx Class	Representative Disease
2-(cyclohexylamino)pyrimidine-4-carbonitrile		<chem>C1CCC(CC1)NC2=NC=CC(=N2)C#N</chem>	2-cyclohexylamino-pyrimidine-4-carbonitrile		Discovery agent
4-(2-hydroxyphenyl)-2-methoxybenzonitrile		<chem>COC1=C(C=CC(=C1)OC2=CC=CC=C2O)C#N</chem>	2'-Hydroxy-3-methoxy-biphenyl-4-carbonitrile		Discovery agent
2-methoxy-4-(2-methoxyphenyl)sulfanybenzonitrile		<chem>COC1=CC=CC=C1SC2=CC(=C(C=C2)C#N)OC</chem>	2-methoxy-4-(2-methoxyphenylthio)benzonitrile		Discovery agent
2-methoxy-4-(3-methylphenoxy)benzonitrile		<chem>CC1=CC(=CC=C1)OC2=CC(=C(C=C2)C#N)OC</chem>	2-methoxy-4-(m-tolyl)benzonitrile		Discovery agent
2-methoxy-4-(2-methylphenoxy)benzonitrile		<chem>CC1=CC=CC=C1OC2=CC(=C(C=C2)C#N)OC</chem>	2-methoxy-4-(o-tolyl)benzonitrile		Discovery agent
2-methoxy-4-propylsulfanybenzonitrile		<chem>CCSC1=CC(=C(C=C1)C#N)OC</chem>	2-methoxy-4-(propylthio)benzonitrile		Discovery agent
2-methoxy-4-(4-methylphenoxy)benzonitrile		<chem>CC1=CC=C(C=C1)OC2=CC(=C(C=C2)C#N)OC</chem>	2-methoxy-4-(p-tolyl)benzonitrile		Discovery agent
2-piperazin-1-ylbenzonitrile	CAS 111373-03-6	<chem>C1CN(CCN1)C2=CC=CC=C2C#N</chem>	2-Piperazin-1-ylbenzonitrile		Discovery agent
3-(1,5-naphthyridin-3-yl)benzonitrile		<chem>C1=CC(=CC(=C1)C2=CC3=C(C=C(C=N3)N=C2)C#N</chem>	3-(1,5-naphthyridin-3-yl)benzonitrile		Discovery agent
3-(1,8-naphthyridin-2-yl)benzonitrile		<chem>C1=CC(=CC(=C1)C2=NC3=C(C=C(C=N3)C=C2)C#N</chem>	3-(1,8-naphthyridin-2-yl)benzonitrile		Discovery agent
3-(1-pyridin-2-ylpyrazol-3-yl)benzonitrile		<chem>C1=CC=NC(=C1)N2C=CC(=N2)C3=CC=CC(=C3)C#N</chem>	3-(1-Pyridin-2-yl-1H-pyrazol-3-yl)-benzonitrile		Discovery agent
3-(1-pyridin-2-ylpyrazol-4-yl)benzonitrile		<chem>C1=CC=NC(=C1)N2C=C(C(=N2)C3=CC=CC(=C3)C#N</chem>	3-(1-Pyridin-2-yl-1H-pyrazol-4-yl)-benzonitrile		Discovery agent
3-(1-pyridin-2-ylpyrrol-3-yl)benzonitrile	CAS 566931-83-7	<chem>C1=CC=NC(=C1)N2C=CC(=C2)C3=CC=CC(=C3)C#N</chem>	3-(1-Pyridin-2-yl-1H-pyrrol-3-yl)-benzonitrile		Discovery agent
3-(2-methyl-1,3-benzothiazol-5-yl)benzonitrile		<chem>CC1=NC2=C(S1)C=CC(=C2)C3=C(C=CC(=C3)C#N</chem>	3-(2-methylbenzo[d]thiazol-5-yl)benzonitrile		Discovery agent
3-(2-methylquinolin-7-yl)benzonitrile		<chem>CC1=NC2=C(C=C1)C=CC(=C2)C3=CC=CC(=C3)C#N</chem>	3-(2-methylquinolin-7-yl)benzonitrile		Discovery agent

IUPAC Name	CAS #	SMILES Notation	USAN Name / Trade Name	Representative Tx Class	Representative Disease
3-(2-phenyl-2-piperazin-1-ylethyl)benzonitrile		<chem>C1CN(CCN1)C(CC2=CC(=CC=C2)C#N)C3=CC=CC=C3</chem>	3-(2-phenyl-2-(piperazin-1-ylethyl)benzonitrile		Discovery agent
3-(2-pyridin-2-yltetrazol-5-yl)benzonitrile		<chem>C1=CC=NC(=C1)N2N=C(N=N2)C3=CC=CC(=C3)C#N</chem>	3-(2-Pyridin-2-yl-2H-tetrazol-5-yl)-benzonitrile		Discovery agent
3-(3,3-dimethyl-2-oxo-1H-indol-5-yl)benzonitrile		<chem>CC1(C2=C(C=CC(=C2)C3=CC=CC(=C3)C#N)NC1=O)C</chem>	3-(3,3-dimethyl-2-oxoindolin-5-yl)benzonitrile		Discovery agent
3-(3-aminocyclopentyl)-1H-indole-5-carbonitrile		<chem>C1CC(CCN1C2=CNC3=C2C=C(C(=C3)C#N)N</chem>	3-(3-aminocyclopentyl)-1H-indole-5-carbonitrile		Discovery agent
3-(3-cyano-1H-indol-6-yl)-1-methyl-1-phenylurea		<chem>CN(C1=CC=CC=C1)C(=O)NC2=C(C3=C(C(=C2)C(=CN3)C#N</chem>	3-(3-cyano-1H-indol-6-yl)-1-methyl-1-phenylurea		Discovery agent
3-(3-pyridin-2-ylpyrazol-1-yl)benzonitrile		<chem>C1=CC=NC(=C1)C2=NN(C(=C2)C3=CC=CC(=C3)C#N</chem>	3-(3-Pyridin-2-yl-pyrazol-1-yl)-benzonitrile		Discovery agent
3-(3-pyridin-2-ylpyrrol-1-yl)benzonitrile		<chem>C1=CC=NC(=C1)C2=CN(C(=C2)C3=CC=CC(=C3)C#N</chem>	3-(3-Pyridin-2-yl-pyrrol-1-yl)-benzonitrile		Discovery agent
3-(4-cyanophenyl)quinoxaline-5-carboxamide		<chem>C1=CC(=C2C(=C1)N=CC(=N2)C3=CC=C(C(=C3)C#N)C(=O)N</chem>	3-(4-cyanophenyl)quinoxaline-5-carboxamide		Discovery agent
(E)-3-(4-hydroxyphenyl)-2,3-diphenylprop-2-enenitrile		<chem>C1=CC=C(C(=C1)/C(=C/C2=CC=CC=C2)\\C3=CC=C(C(=C3)O)/C#N</chem>	3-(4-Hydroxy-phenyl)-2,3-diphenylacrylonitrile		Discovery agent
3-(4-pyridin-2-ylimidazol-1-yl)benzonitrile		<chem>C1=CC=NC(=C1)C2=CN(C(=N2)C3=CC=CC(=C3)C#N</chem>	3-(4-Pyridin-2-ylimidazol-1-yl)-benzonitrile		Discovery agent
3-(4-pyridin-2-ylpyrazol-1-yl)benzonitrile	CAS 546141-91-7	<chem>C1=CC=NC(=C1)C2=CN(N=C2)C3=CC=CC(=C3)C#N</chem>	3-(4-Pyridin-2-yl-pyrazol-1-yl)-benzonitrile		Discovery agent
3-[(5-phenyl-1,3-oxazol-2-yl)amino]benzonitrile		<chem>C1=CC=C(C(=C1)C2=CN=C(C(=O2)N)C3=CC=CC(=C3)C#N</chem>	3-(5-Phenyl-oxazol-2-ylamino)-benzonitrile		Discovery agent

IUPAC Name	CAS #	SMILES Notation	USAN Name / Trade Name	Representative Tx Class	Representative Disease
3-(5-pyridin-2-yltetrazol-2-yl)benzonitrile	CAS 507268-13-5	<chem>C1=CC=NC(=C1)C2=NN(N=N2)C3=CC=CC(=C3)C#N</chem>	3-(5-Pyridin-2-yl-tetrazol-2-yl)-benzonitrile		Discovery agent
3-(6-anilino-7H-purin-8-yl)benzonitrile		<chem>C1=CC=C(C=C1)NC2=NC=NC3=C2NC(=N3)C4=CC=CC(=C4)C#N</chem>	3-(6-(phenylamino)-9H-purin-8-yl)benzonitrile		Discovery agent
3-[(6-fluoroquinazolin-4-yl)amino]benzonitrile		<chem>C1=CC(=CC(=C1)NC2=NC=NC3=C2C=C(C(=C3)F)C#N</chem>	3-(6-fluoroquinazolin-4-ylamino)benzonitrile		Discovery agent
3-(6-morpholin-4-yl-4-oxopyran-2-yl)benzonitrile		<chem>C1COCNC1C2=CC(=O)C=C(C(O2)C3=CC=CC(=C3)C#N</chem>	3-(6-morpholino-4-oxo-4H-pyran-2-yl)benzonitrile		Discovery agent
3-(7-methyl-1,8-naphthyridin-2-yl)benzonitrile		<chem>CC1=NC2=C(C=C1)C=CC(=N2)C3=CC=CC(=C3)C#N</chem>	3-(7-methyl-1,8-naphthyridin-2-yl)benzonitrile		Discovery agent
2-(trifluoromethyl)-4-[2-(trifluoromethyl)phenyl]benzonitrile		<chem>C1=CC=C(C(=C1)C2=CC(=C(C=C2)C#N)C(F)(F)C(F)F</chem>	3,2'-bis-trifluoromethyl-biphenyl-4-carbonitrile		Discovery agent
3,3-bis(4-hydroxyphenyl)-2-phenylprop-2-enenitrile		<chem>C1=CC=C(C(=C1)C(=C(C2=CC=C(C=C2)O)C3=CC=C(C(=C3)O)C#N</chem>	3,3-Bis-(4-hydroxyphenyl)-2-phenylacrylonitrile		Discovery agent
3,3-bis(4-methoxyphenyl)-2-phenylprop-2-enenitrile		<chem>COC1=CC=C(C(=C1)C(=C(C#N)C2=CC=CC=C2)C3=CC=C(C(=C3)OC</chem>	3,3-Bis-(4-methoxyphenyl)-2-phenylacrylonitrile		Discovery agent
3-[2-(2-methyl-1,3-thiazol-4-yl)ethynyl]benzonitrile		<chem>CC1=NC(=CS1)C#CC2=CC(=CC=C2)C#N</chem>	3-[(2-methyl-4-thiazolyl)ethynyl]benzonitrile		Discovery agent
3-[2-(6-methylpyridin-2-yl)ethynyl]benzonitrile		<chem>CC1=NC(=CC=C1)C#CC2=CC(=CC=C2)C#N</chem>	3-[(6-Methylpyridin-2-yl)ethynyl]benzonitrile		Discovery agent
4-[[5-(3-hydroxypropyl)imidazol-1-yl]methyl]benzonitrile		<chem>C1=CC(=CC(=C1)CN2C=NC=C2CCO)C#N</chem>	3-[1-(4-Cyanobenzyl)-1H-imidazol-5-yl]-1-propanol		Discovery agent
2-amino-4-(furan-2-yl)-6-phenylbenzene-1,3-dicarbonitrile		<chem>C1=CC=C(C(=C1)C2=CC(=C(C(=C2C#N)N)C#N)C3=CC=CO3</chem>	3-amino-5-(furan-2-yl)biphenyl-2,4-dicarbonitrile		Discovery agent
3-bromo-2H-indazole-7-carbonitrile	CAS 945762-00-5	<chem>C1=CC2=C(NN=C2C(=C1)C#N)Br</chem>	3-Bromo-1H-indazole-7-carbonitrile		Discovery agent

IUPAC Name	CAS #	SMILES Notation	USAN Name / Trade Name	Representative Tx Class	Representative Disease
3-bromo-5-(2-methylquinolin-7-yl)benzonitrile		<chem>CC1=NC2=C(C=C1)C=CC(=C2)C3=CC(=CC(=C3)C#N)Br</chem>	3-bromo-5-(2-methylquinolin-7-yl)benzonitrile		Discovery agent
3-chloro-4-(2-methylphenoxy)benzonitrile		<chem>CC1=CC=CC=C1OC2=C(C=C(C=C2)C#N)Cl</chem>	3-chloro-4-(o-tolyl)benzonitrile		Discovery agent
3-chloro-4-(2-methylphenyl)sulfanybenzonitrile		<chem>CC1=CC=CC=C1SC2=C(C=C(C=C2)C#N)Cl</chem>	3-chloro-4-(o-tolylthio)benzonitrile		Discovery agent
3-chloro-5-(2-methylquinolin-7-yl)benzonitrile		<chem>CC1=NC2=C(C=C1)C=CC(=C2)C3=CC(=CC(=C3)C#N)Cl</chem>	3-chloro-5-(2-methylquinolin-7-yl)benzonitrile		Discovery agent
3-cyano-5-fluoro-N-(3-fluorophenyl)benzamide		<chem>C1=CC(=CC(=C1)F)NC(=O)C2=C(C=CC(=C2)C#N)F</chem>	3-cyano-5-fluoro-N-(3-fluorophenyl)benzamide		Discovery agent
3-cyano-5-fluoro-N-pyridin-2-ylbenzamide		<chem>C1=CC=NC(=C1)NC(=O)C2=CC(=CC(=C2)C#N)F</chem>	3-cyano-5-fluoro-N-(pyridin-2-yl)benzamide		Discovery agent
3-cyano-5-fluoro-N-(3-methylphenyl)benzamide		<chem>CC1=CC(=CC(=C1)NC(=O)C2=CC(=CC(=C2)C#N)F</chem>	3-cyano-5-fluoro-N-m-tolylbenzamide		Discovery agent
3-cyano-5-fluoro-N-phenylbenzamide		<chem>C1=CC=C(C(=C1)NC(=O)C2=CC(=CC(=C2)C#N)F</chem>	3-cyano-5-fluoro-N-phenylbenzamide		Discovery agent
3-cyano-N-(2,5-diphenylpyrazol-3-yl)benzamide	CAS 781652-57-1	<chem>C1=CC=C(C(=C1)C2=NN(C(=C2)NC(=O)C3=CC=CC(=C3)C#N)C4=C(C=CC=C4)C#N</chem>	3-cyano-N-(1,3-diphenyl-1H-pyrazol-5-yl)benzamide		Discovery agent
3-cyano-N-(2,4-diphenylpyrazol-3-yl)benzamide		<chem>C1=CC=C(C(=C1)C2=C(N(N=C2)C3=CC=CC(=C3)NC(=O)C4=CC=CC(=C4)C#N</chem>	3-cyano-N-(1,4-diphenyl-1H-pyrazol-5-yl)benzamide		Discovery agent
3-cyano-N-(3-cyanophenyl)-5-fluorobenzamide		<chem>C1=CC(=CC(=C1)NC(=O)C2=CC(=CC(=C2)C#N)F)C#N</chem>	3-cyano-N-(3-cyanophenyl)-5-fluorobenzamide		Discovery agent
3-cyano-N-(3-ethylphenyl)-5-fluorobenzamide		<chem>CCC1=CC(=CC(=C1)NC(=O)C2=C(C=CC(=C2)C#N)F</chem>	3-cyano-N-(3-ethylphenyl)-5-fluorobenzamide		Discovery agent
3-cyano-N-(3-ethynylphenyl)-5-fluorobenzamide		<chem>C#CC1=CC(=CC(=C1)NC(=O)C2=CC(=CC(=C2)C#N)F</chem>	3-cyano-N-(3-ethynylphenyl)-5-fluorobenzamide		Discovery agent

IUPAC Name	CAS #	SMILES Notation	USAN Name / Trade Name	Representative Tx Class	Representative Disease
3-cyano-N-(6-ethylpyridin-2-yl)-5-fluorobenzamide		<chem>CCC1=NC(=CC=C1)NC(=O)C2=C(C=CC(=C2)C#N)F</chem>	3-cyano-N-(6-ethylpyridin-2-yl)-5-fluorobenzamide		Discovery agent
3-cyano-N-(6-methylpyridin-2-yl)benzamide		<chem>CC1=NC(=CC=C1)NC(=O)C2=CC=CC(=C2)C#N</chem>	3-cyano-N-(6-methylpyridin-2-yl)benzamide		Discovery agent
(3-cyanophenyl)boronic acid	CAS 150255-96-2	<chem>B(C1=CC(=CC=C1)C#N)(O)O</chem>	3-cyanophenylboronic acid		Discovery agent
3-ethoxy-5-(2-methylquinolin-7-yl)benzonitrile		<chem>CCOC1=CC(=CC(=C1)C2=CC3=C(C=CC(=N3)C)C=C2)C#N</chem>	3-ethoxy-5-(2-methylquinolin-7-yl)benzonitrile		Discovery agent
3-fluoro-5-(1,6-naphthyridin-7-yl)benzonitrile		<chem>C1=CC2=CN=C(C=C2N=C1)C3=C(C=CC(=C3)C#N)F</chem>	3-fluoro-5-(1,6-naphthyridin-7-yl)benzonitrile		Discovery agent
3-fluoro-5-(2-methylquinolin-7-yl)benzonitrile		<chem>CC1=NC2=C(C=C1)C=CC(=C2)C3=CC(=CC(=C3)C#N)F</chem>	3-fluoro-5-(2-methylquinolin-7-yl)benzonitrile		Discovery agent
3-hydroxy-5-(2-methylquinolin-7-yl)benzonitrile		<chem>CC1=NC2=C(C=C1)C=CC(=C2)C3=CC(=CC(=C3)C#N)O</chem>	3-hydroxy-5-(2-methylquinolin-7-yl)benzonitrile		Discovery agent
3-hydroxy-7-(3-hydroxyphenyl)naphthalene-1-carbonitrile		<chem>C1=CC(=CC(=C1)O)C2=CC3=C(C=C(C=C3C=C2)O)C#N</chem>	3-Hydroxy-7-(3-hydroxyphenyl)-1-naphthonitrile		Discovery agent
3-(2-methylpropoxy)-5-(2-methylquinolin-7-yl)benzonitrile		<chem>CC1=NC2=C(C=C1)C=CC(=C2)C3=CC(=CC(=C3)C#N)OCC(C)C</chem>	3-isobutoxy-5-(2-methylquinolin-7-yl)benzonitrile		Discovery agent
3-methoxy-4-(3-methylphenoxy)benzonitrile		<chem>CC1=CC(=CC(=C1)OC2=C(C=C(C=C2)C#N)OC</chem>	3-methoxy-4-(m-tolyloxy)benzonitrile		Discovery agent
3-methoxy-4-(2-methylphenoxy)benzonitrile		<chem>CC1=CC=CC=C1OC2=C(C=C(C=C2)C#N)OC</chem>	3-methoxy-4-(o-tolyloxy)benzonitrile		Discovery agent
3-methoxy-4-(4-methylphenoxy)benzonitrile		<chem>CC1=CC=C(C=C1)OC2=C(C=C(C=C2)C#N)OC</chem>	3-methoxy-4-(p-tolyloxy)benzonitrile		Discovery agent
3-methoxy-5-(1,5-naphthyridin-3-yl)benzonitrile		<chem>COC1=CC(=CC(=C1)C2=CC3=C(C=CC(=N3)N=C2)C#N</chem>	3-methoxy-5-(1,5-naphthyridin-3-yl)benzonitrile		Discovery agent

IUPAC Name	CAS #	SMILES Notation	USAN Name / Trade Name	Representative Tx Class	Representative Disease
3-methoxy-5-(1,6-naphthyridin-7-yl)benzonitrile		<chem>COC1=CC(=CC(=C1)C2=NC=C3C=CC=NC3=C2)C#N</chem>	3-methoxy-5-(1,6-naphthyridin-7-yl)benzonitrile		Discovery agent
3-methoxy-5-(2-methylquinolin-7-yl)benzonitrile		<chem>CC1=NC2=C(C(=C1)C=CC(=C2)C3=CC(=CC(=C3)C#N)OC</chem>	3-methoxy-5-(2-methylquinolin-7-yl)benzonitrile		Discovery agent
3-methyl-5-(2-methylquinolin-7-yl)benzonitrile		<chem>CC1=NC2=C(C(=C1)C=CC(=C2)C3=CC(=CC(=C3)C#N)C</chem>	3-methyl-5-(2-methylquinolin-7-yl)benzonitrile		Discovery agent
N-[(3S,4R)-6-cyano-3-hydroxy-2,2-dimethyl-3,4-dihydrochromen-4-yl]-N-methylethanesulfonamide	CAS 163163-25-5	<chem>CCS(=O)(=O)N(C)[C@H]1[C@@H](C(OC2=C1C=C(C(=C2)C#N)(C)C)O</chem>	3S,4R-293B		Discovery agent
4-(imidazol-1-ylmethyl)benzonitrile	CAS 112809-54-8	<chem>C1=CC(=CC(=C1)CN2C=CN=C2)C#N</chem>	4-((1H-imidazol-1-yl)methyl)benzonitrile		Discovery agent
4-(1H-indol-5-ylamino)-5-[(E)-2-phenylethenyl]pyridine-3-carbonitrile		<chem>C1=CC=C(C(=C1)/C=C/C2=CN=C(C(=C2)NC3=CC4=C(C(=C3)NC=C4)C#N</chem>	4-(1H-indol-5-ylamino)-5-styrylnicotinonitrile		Discovery agent
4-(1H-indol-5-yloxy)-5-[(E)-2-phenylethenyl]pyridine-3-carbonitrile		<chem>C1=CC=C(C(=C1)/C=C/C2=CN=C(C(=C2)OC3=CC4=C(C(=C3)NC=C4)C#N</chem>	4-(1H-indol-5-yloxy)-5-styrylnicotinonitrile		Discovery agent
4-(1H-indol-6-ylamino)-5-[(E)-2-phenylethenyl]pyridine-3-carbonitrile		<chem>C1=CC=C(C(=C1)/C=C/C2=CN=C(C(=C2)NC3=CC4=C(C(=C3)C=CN4)C#N</chem>	4-(1H-indol-6-ylamino)-5-styrylnicotinonitrile		Discovery agent
4-(1-imidazol-1-ylethenyl)benzonitrile		<chem>C=C(C1=CC=C(C(=C1)C#N)N2C=CN=C2</chem>	4-(1-Imidazol-1-yl-vinyl)-benzonitrile		Discovery agent
4-[2-[(dimethylamino)methyl]phenoxy]benzonitrile		<chem>CN(C)CC1=CC=CC(=CC(=C1)OC2=CC=C(C(=C2)C#N</chem>	4-[2-((dimethylamino)methyl)phenoxy]benzonitrile		Discovery agent
4-(2,4-dichlorophenoxy)-3-hydroxybenzonitrile		<chem>C1=CC(=C(C(=C1C#N)O)OC2=C(C(=C(C(=C2)Cl)Cl</chem>	4-(2,4-dichlorophenoxy)-3-hydroxybenzonitrile		Discovery agent
4-[(2,4-diethyl-1H-pyrrol-3-yl)oxy]benzonitrile		<chem>CCC1=CC=C(C(=C1)OC2=CC=C(C(=C2)C#N)CC</chem>	4-(2,4-diethyl-1H-pyrrol-3-yloxy)benzonitrile		Discovery agent

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4-(2,6-dimethylphenyl)sulfanyl-2-methoxybenzonitrile		<chem>CC1=C(C(=CC=C1)C)SC2=CC(=C(C=C2)C#N)OC</chem>	4-(2,6-dimethylphenylthio)-2-methoxybenzonitrile		Discovery agent
2-amino-4-[(3-cyanophenyl)methylsulfanyl]butanoic acid		<chem>C1=CC=C(C(=C1)CSCCC(C(=O)O)N)C#N</chem>	4-(2-cyanobenzylthio)-2-aminobutanoic acid		Discovery agent
4-(2-pyrrolidin-1-ylpentanoyl)benzonitrile		<chem>CCCC(C(=O)C1=CC=C(C(=C1)C#N)N2CCCC2)C#N</chem>	4-(2-pyrrolidin-1-ylpentanoyl)benzonitrile		Discovery agent
2-amino-4-[(3-cyanophenyl)methylsulfanyl]butanoic acid		<chem>C1=CC(=CC(=C1)C#N)CSCCC(C(=O)O)N</chem>	4-(3-cyanobenzylthio)-2-aminobutanoic acid		Discovery agent
4-(1H-indol-4-ylamino)-5-[(E)-2-phenylethenyl]pyridine-3-carbonitrile		<chem>C1=CC=C(C(=C1)/C=C/C2=CN=C(C=C2)NC3=CC=CC4=C3C=C(CN4)C#N</chem>	4-(3H-indol-4-ylamino)-5-styrylnicotinonitrile		Discovery agent
5-(4-phenoxyphenyl)-2H-triazole-4-carbonitrile		<chem>C1=CC=C(C(=C1)OC2=CC=C(C(=C2)C3=NNN=C3C#N</chem>	4-(3-phenoxyphenyl)-5-cyano-2H-1,2,3-triazole		Discovery agent
5-(4-bromophenyl)-2H-triazole-4-carbonitrile		<chem>C1=CC(=CC=C1C2=NNN=C2C#N)Br</chem>	4-(4-bromophenyl)-5-cyano-2H-1,2,3-triazole		Discovery agent
5-(4-chlorophenyl)-2H-triazole-4-carbonitrile		<chem>C1=CC(=CC=C1C2=NNN=C2C#N)Cl</chem>	4-(4-chlorophenyl)-5-cyano-2H-1,2,3-triazole		Discovery agent
4-(4-cyanophenoxy)pyridine-3-sulfonamide		<chem>C1=CC(=CC=C1C#N)OC2=C(C(=N(C=C2)S(=O)(=O)N</chem>	4-(4-Cyanophenoxy)-3-pyridinesulfonamide		Discovery agent
5-(4-propan-2-ylphenyl)-2H-triazole-4-carbonitrile		<chem>CC(C)C1=CC=C(C(=C1)C2=NNN=C2C#N</chem>	4-(4-isopropylphenyl)-5-cyano-2H-1,2,3-triazole		Discovery agent
4-(5-tert-butyl-1,3-dithian-2-yl)benzonitrile		<chem>CC(C)(C)C1CSC(SC1)C2=CC=C(C(=C2)C#N</chem>	4-(5-tert-Butyl-[1,3]dithian-2-yl)benzonitrile		Discovery agent
4-(6-morpholin-4-yl-4-oxopyran-2-yl)benzonitrile		<chem>C1COC(CN1C2=CC(=O)C=C(C(=O)C3=CC=C(C(=C3)C#N</chem>	4-(6-morpholino-4-oxo-4H-pyran-2-yl)benzonitrile		Discovery agent
4-butylsulfanyl-2-(trifluoromethyl)benzonitrile		<chem>CCCCSC1=CC(=C(C(=C1)C#N)C(F)(F)F</chem>	4-(butylthio)-2-(trifluoromethyl)benzonitrile		Discovery agent
4-butylsulfanyl-2-methoxybenzonitrile		<chem>CCCCSC1=CC(=C(C(=C1)C#N)OC</chem>	4-(butylthio)-2-methoxybenzonitrile		Discovery agent

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4-(cyanomethylsulfanyl)pyridine-3-sulfonamide		<chem>C1=CN=CC(=C1SCC#N)S(=O)(=O)N</chem>	4-(Cyanomethylthio)pyridine-3-sulfonamide		Discovery agent
4-(cyclobutylmethylsulfanyl)-2-methoxybenzonitrile		<chem>COC1=C(C=CC(=C1)SCC2CCC2)C#N</chem>	4-(cyclobutylmethylthio)-2-methoxybenzonitrile		Discovery agent
4-(cyclopropylmethylsulfanyl)-2-methoxybenzonitrile		<chem>COC1=C(C=CC(=C1)SCC2CC2)C#N</chem>	4-(cyclopropylmethylthio)-2-methoxybenzonitrile		Discovery agent
4-(3-methylbutylsulfanyl)-2-(trifluoromethyl)benzonitrile		<chem>CC(C)CCSC1=CC(=C(C=C1)C#N)C(F)(F)F</chem>	4-(isopentylthio)-2-(trifluoromethyl)benzonitrile		Discovery agent
2-methoxy-4-(3-methylbutylsulfanyl)benzonitrile		<chem>CC(C)CCSC1=CC(=C(C=C1)C#N)OC</chem>	4-(isopentylthio)-2-methoxybenzonitrile		Discovery agent
4-propan-2-ylsulfanyl-2-(trifluoromethyl)benzonitrile		<chem>CC(C)SC1=CC(=C(C=C1)C#N)C(F)(F)F</chem>	4-(isopropylthio)-2-(trifluoromethyl)benzonitrile		Discovery agent
2-methoxy-4-propan-2-ylsulfanylbenzonitrile		<chem>CC(C)SC1=CC(=C(C=C1)C#N)OC</chem>	4-(isopropylthio)-2-methoxybenzonitrile		Discovery agent
2-(trifluoromethyl)-4-(2,4,6-trimethylphenoxy)benzonitrile		<chem>CC1=CC(=C(C(C(=C1)C)OC2=CC(=C(C=C2)C#N)C(F)(F)F)C</chem>	4-(mesityloxy)-2-(trifluoromethyl)benzonitrile		Discovery agent
2-(trifluoromethyl)-4-(2,4,6-trimethylphenyl)sulfanylbenzonitrile		<chem>CC1=CC(=C(C(C(=C1)C)SC2=CC(=C(C=C2)C#N)C(F)(F)F)C</chem>	4-(mesitylthio)-2-(trifluoromethyl)benzonitrile		Discovery agent
2-methoxy-4-(2,4,6-trimethylphenyl)sulfanylbenzonitrile		<chem>CC1=CC(=C(C(C(=C1)C)SC2=CC(=C(C=C2)C#N)OC)C</chem>	4-(mesitylthio)-2-methoxybenzonitrile		Discovery agent
4-(3-methylphenoxy)-2-(trifluoromethyl)benzonitrile		<chem>CC1=CC(=CC(=CC=C1)OC2=CC(=C(C=C2)C#N)C(F)(F)F</chem>	4-(m-tolyloxy)-2-(trifluoromethyl)benzonitrile		Discovery agent
4-(2-methylphenoxy)-2-(trifluoromethyl)benzonitrile		<chem>CC1=CC=CC=CC1OC2=CC(=C(C=C2)C#N)C(F)(F)F</chem>	4-(o-tolyloxy)-2-(trifluoromethyl)benzonitrile		Discovery agent

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4-(2-methylphenyl)sulfanyl-2-(trifluoromethyl)benzonitrile		<chem>CC1=CC=CC=C1SC2=CC(=C(C=C2)C#N)C(F)(F)F</chem>	4-(o-tolylthio)-2-(trifluoromethyl)benzonitrile		Discovery agent
4-propylsulfanyl-2-(trifluoromethyl)benzonitrile		<chem>CCCS1=CC(=C(C=C1)C#N)C(F)(F)F</chem>	4-(propylthio)-2-(trifluoromethyl)benzonitrile		Discovery agent
4-(4-methylphenoxy)-2-(trifluoromethyl)benzonitrile		<chem>CC1=CC=C(C=C1)OC2=CC(=C(C=C2)C#N)C(F)(F)F</chem>	4-(p-tolylloxy)-2-(trifluoromethyl)benzonitrile		Discovery agent
4-amino-2,6-diphenylpyrimidine-5-carbonitrile		<chem>C1=CC=C(C=C1)C2=C(C(=NC(=N2)C3=CC=CC=C3N)C#N</chem>	4-Amino-2,6-diphenylpyrimidine-5-carbonitrile		Discovery agent
4-[3-(imidazol-1-ylmethyl)-7-methoxy-4-oxochromen-2-yl]benzonitrile		<chem>COC1=CC2=C(C=C1)C(=O)C(=C(C(=O2)C3=CC=C(C(=C3)C#N)CN4C=CCN=C4</chem>	4'-cyano-3-(imidazolylmethyl)-7-methoxyflavone		Discovery agent
4-[3-(imidazol-1-ylmethyl)-4-oxochromen-2-yl]benzonitrile		<chem>C1=CC=C2C(=C1)C(=O)C(=C(C(=O2)C3=CC=C(C(=C3)C#N)CN4C=CCN=C4</chem>	4'-cyano-3-(imidazolylmethyl)flavone		Discovery agent
4-cyano-N-(2,5-diphenylpyrazol-3-yl)benzamide		<chem>C1=CC=C(C(=C1)C2=NN(C(=C2)N(C(=O)C3=CC=C(C(=C3)C#N)C4=C(C=CC=C4</chem>	4-cyano-N-(1,3-diphenyl-1H-pyrazol-5-yl)benzamide		Discovery agent
4-hydroxybenzonitrile	CAS 767-00-0	<chem>C1=CC(=CC=C1C#N)O</chem>	4-CYANOPHENOL		Discovery agent
4-[dodecyl(ethoxy)phosphoryl]oxybenzonitrile		<chem>CCCCCCCCCCCOP(=O)(OCC)OC1=CC=C(C=C1)C#N</chem>	4-cyanophenyl ethyl dodecylphosphonate		Discovery agent
(4-cyanophenyl)boronic acid	CAS 126747-14-6	<chem>B(C1=CC=C(C(=C1)C#N)(O)O</chem>	4-cyanophenylboronic acid		Discovery agent
4-cycloheptyl-6-propylpyrimidine-2-carbonitrile		<chem>CCCC1=CC(=NC(=N1)C#N)C2CC(CCCC2</chem>	4-cycloheptyl-6-propylpyrimidine-2-carbonitrile		Discovery agent
4-cyclohexyl-6-propylpyrimidine-2-carbonitrile		<chem>CCCC1=CC(=NC(=N1)C#N)C2CC(CCCC2</chem>	4-cyclohexyl-6-propylpyrimidine-2-carbonitrile		Discovery agent
4-(cyclohexylamino)pyrimidine-2-carbonitrile		<chem>C1CCC(CC1)NC2=NC(=NC=C2)C#N</chem>	4-cyclohexylamino-pyrimidine-2-carbonitrile		Discovery agent

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4-cyclooctyl-6-propylpyrimidine-2-carbonitrile		<chem>CCCC1=CC(=NC(=N1)C#N)C2CC CCCC2</chem>	4-cyclooctyl-6-propylpyrimidine-2-carbonitrile		Discovery agent
4-(dipropylamino)cyclohexene-1-carbonitrile		<chem>CCCN(CCC)C1CCC(=CC1)C#N</chem>	4-Dipropylamino-cyclohex-1-enecarbonitrile		Discovery agent
(2S)-1-[[[(2S)-2-amino-3-(4-iodophenyl)propanoyl]pyrrolidine-2-carbonitrile		<chem>C1C[C@H]([N](C1)C(=O)[C@H](C2=CC=C(C=C2)N)C#N</chem>	4-iodophenyl-alaninyl-(S)-2-cyano-pyrrolidine		Discovery agent
2-anilino-4-phenylpyrimidine-5-carbonitrile		<chem>C1=CC=C(C=C1)C2=NC(=NC=C2C#N)NC3=CC=CC=C3</chem>	4-phenyl-2-(phenylamino)pyrimidine-5-carbonitrile		Discovery agent
4-phenyl-6-propylpyrimidine-2-carbonitrile		<chem>CCCC1=CC(=NC(=N1)C#N)C2=C C=CC=C2</chem>	4-phenyl-6-propylpyrimidine-2-carbonitrile		Discovery agent
4-(3-methylphenyl)-6-propylpyrimidine-2-carbonitrile		<chem>CCCC1=CC(=NC(=N1)C#N)C2=C C=CC(=C2)C</chem>	4-propyl-6-m-tolylpyrimidine-2-carbonitrile		Discovery agent
(4-sulfamoylphenyl) thiocyanate		<chem>C1=CC(=CC=C1SC#N)S(=O)(=O)N</chem>	4-Thiocyanato-benzenesulfonamide		Discovery agent
5-[2-(6-methylpyridin-2-yl)ethynyl]pyridine-3-carbonitrile		<chem>CC1=NC(=CC=C1)C#CC2=CC(=C N=C2)C#N</chem>	5-[(6-Methylpyridin-2-yl)ethynyl]nicotinonitrile		Discovery agent
5-(2-methylquinolin-7-yl)-2-phenylbenzonitrile		<chem>CC1=NC2=C(C=C1)C=CC(=C2)C3 =CC(=C(C=C3)C4=CC=CC=C4)C# N</chem>	5-(2-Methylquinolin-7-yl)-2-phenylbenzonitrile		Discovery agent
5-(2-methylquinolin-7-yl)-2-phenylpyridine-3-carbonitrile		<chem>CC1=NC2=C(C=C1)C=CC(=C2)C3 =CC(=C(N=C3)C4=CC=CC=C4)C# N</chem>	5-(2-Methylquinolin-7-yl)-2-phenylnicotinonitrile		Discovery agent
5-(2-methylquinolin-7-yl)benzene-1,3-dicarbonitrile		<chem>CC1=NC2=C(C=C1)C=CC(=C2)C3 =CC(=C(C=C3)C#N)C#N</chem>	5-(2-methylquinolin-7-yl)isophthalonitrile		Discovery agent
5-(2-methylquinolin-7-yl)pyridine-3-carbonitrile		<chem>CC1=NC2=C(C=C1)C=CC(=C2)C3 =CN=CC(=C3)C#N</chem>	5-(2-methylquinolin-7-yl)nicotinonitrile		Discovery agent
5-(2-oxo-1,3-dihydroindol-5-yl)-1H-pyrrole-2-carbonitrile		<chem>C1C2=C(C=CC(=C2)C3=CC=C(N3)C#N)NC1=O</chem>	5-(2-oxoindolin-5-yl)-1H-pyrrole-2-carbonitrile		Discovery agent

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5-[4-(3-cyanophenyl)phenyl]-3-hydroxypentanoic acid		<chem>C1=CC(=CC(=C1)C2=CC(=C(C=C2)C)CC(C(=O)O)O)C#N</chem>	5-(3'-cyanobiphenyl-4-yl)-3-hydroxypentanoic acid		Discovery agent
5-[4-(4-cyanophenyl)phenyl]-3-hydroxypentanoic acid		<chem>C1=CC(=CC(=C1)CCC(C(=O)O)O)C2=CC(=C(C=C2)C)C#N</chem>	5-(4'-cyanobiphenyl-4-yl)-3-hydroxypentanoic acid		Discovery agent
5-chloro-2-(2-methylquinolin-7-yl)benzonitrile		<chem>CC1=NC2=C(C=C1)C=CC(=C2)C3=C(C=C(C(=C3)C)C)C#N</chem>	5-Chloro-2-(2'-methylquinolin-7-yl)benzonitrile		Discovery agent
5-anilino-3-oxo-1,2-thiazole-4-carbonitrile	CAS 1137-65-1	<chem>C1=CC(=C(C=C1)NC2=C(C(=O)N)S2)C#N</chem>	5-phenylamino-4-cyano-3-hydroxyisothiazole		Discovery agent
6-[3-(trifluoromethyl)phenyl]pyridine-2-carbonitrile	CAS 833457-45-7	<chem>C1=CC(=CC(=C1)C(F)(F)F)C2=CC=CC(=N2)C#N</chem>	6-(3-(trifluoromethyl)phenyl)picolinonitrile		Discovery agent
6-(4-methylpyridin-3-yl)naphthalene-2-carbonitrile		<chem>CC1=C(C(=NC=C1)C2=CC3=C(C=C2)C=C(C(=C3)C)C#N</chem>	6-(4-Methylpyridin-3-yl)-2-naphthonitrile		Discovery agent
6-(benzylamino)-9-buty-purine-2-carbonitrile		<chem>CCCCN1C=NC2=C(N=C(N=C21)C#N)NCC3=CC=CC=C3</chem>	6-(benzylamino)-9-buty-9H-purine-2-carbonitrile		Discovery agent
6-(piperidin-4-ylmethoxy)naphthalene-2-carbonitrile		<chem>C1CNCCC1COC2=CC3=C(C(=C2)C=C(C(=C3)C)C#N</chem>	6-(piperidin-4-ylmethoxy)-2-naphthonitrile		Discovery agent
6-pyridin-3-yl-naphthalene-2-carbonitrile		<chem>C1=CC(=CN=C1)C2=CC3=C(C(=C2)C=C(C(=C3)C)C#N</chem>	6-(pyridin-3-yl)-2-naphthonitrile		Discovery agent
7-(piperidin-4-ylmethoxy)naphthalene-2-carbonitrile		<chem>C1CNCCC1COC2=CC3=C(C(=CC(=C3)C#N)C=C2</chem>	7-(piperidin-4-ylmethoxy)-2-naphthonitrile		Discovery agent
7-hydroxy-3-(3-hydroxyphenyl)naphthalene-1-carbonitrile		<chem>C1=CC(=CC(=C1)O)C2=CC(=C3C=C(C(=CC3=C2)O)C)C#N</chem>	7-Hydroxy-3-(3-hydroxyphenyl)-1-naphthonitrile		Discovery agent
8-chloro-4-(3-chloro-4-fluoroanilino)-6-(1H-imidazol-5-ylmethylamino)quinoline-3-carbonitrile		<chem>C1=CC(=C(C(=C1NC2=C3C=C(C(=C2)C(C3=NC=C2C#N)C)NCC4=CN=CN4)Cl)F</chem>	8-chloro-quinoline-3-carbonitrile		Discovery agent

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9-benzyl-6-(benzylamino)purine-2-carbonitrile		<chem>C1=CC=C(C=C1)CNC2=C3C(=NC(=N2)C#N)N(C(=N3)CC4=CC=CC=C4)</chem>	9-benzyl-6-(benzylamino)-9H-purine-2-carbonitrile		Discovery agent
4-[(4-cyanophenyl)methoxy-(3-methylimidazol-4-yl)methyl]-2-naphthalen-1-ylbenzonitrile		<chem>CN1C=NC=C1C(C2=CC(=C(C=C2)C#N)C3=CC=CC4=CC=CC(=C43)OCC5=CC=C(C(=C5)C#N)</chem>	A-313326		Discovery agent
4-[4-[3-[(3R)-3-(dimethylamino)pyrrolidin-1-yl]propoxy]phenyl]benzonitrile	CAS 392338-13-5	<chem>CN(C)[C@@H]1CCN(C1)CCCC2=CC=C(C(=C2)C3=CC=C(C(=C3)C#N)</chem>	A-331440		Obesity
N-[1-[(E)-[(cyanoamino)-(quinolin-5-ylamino)methylidene]amino]-2,2-dimethylpropyl]-2-(3,4-dimethoxyphenyl)acetamide	CAS 861393-28-4	<chem>CC(C)(C)C(NC(=O)CC1=CC(=C(C(=C1)OC)OC)/N=C(/NC#N)\NC2=CC=CC3=C2C=CC=N3</chem>	A-740003		Discovery agent
1-cyano-2-[(1S)-1-phenylethyl]-3-quinolin-5-ylguanidine		<chem>C[C@@H](C1=CC=CC=C1)N=C(NC#N)NC2=CC=CC3=C2C=CC=N3</chem>	A804598		
4-[2-amino-6-(4-methylpiperazin-1-yl)pyrimidin-4-yl]benzonitrile		<chem>CN1CCN(CC1)C2=NC(=NC(=C2)C3=CC=C(C(=C3)C#N)N</chem>	A-846714		Discovery agent
N-(3-cyano-4,5,6,7-tetrahydro-1-benzothiophen-2-yl)naphthalene-1-carboxamide	CAS 312917-14-9	<chem>C1CCC2=C(C1)C(=C(S2)NC(=O)C3=CC=CC4=CC=CC(=C43)C#N</chem>	AC1LG8KT		Discovery agent
(2S)-2-[[[(2S)-2-[[[(2S)-2-[[[(2R)-2-acetamido-3-sulfanypropanoyl]amino]-3-methylpentanoyl]amino]-3-(4-hydroxyphenyl)propanoyl]amino]-6-aminohexanoyl]amino]-3-(4-cyanophenyl)propanoyl]amino]-3-(4-hydroxyphenyl)propanoic acid		<chem>CCC(C)[C@@H](C)[C@H](C(=O)N)[C@@H](CC1=CC=C(C(=C1)O)C(=O)N[C@@H](CCCCN)C(=O)N[C@@H](CC2=CC=C(C(=C2)C#N)C(=O)N[C@@H](CC3=CC=C(C(=C3)O)C(=O)N[C@@H](C#N)C(=O)C</chem>	Ac-Cys-Ile-Tyr-Lys-Phe(4-CN)-Tyr		Discovery agent
2-amino-6-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-4-piperidin-4-ylpyridine-3-carbonitrile		<chem>C1CC1COC2=CC=CC(=C2C3=NC(=C(C(=C3)C4CCNCC4)C#N)N)O</chem>	ACHP		Multiple myeloma
2-[[[3-bromo-5-tert-butyl-4-hydroxyphenyl]methylidene]propanedinitrile	CAS 65678-07-1	<chem>CC(C)(C)C1=C(C(=CC(=C1)C=C(C(=C1)C#N)Br)O</chem>	AG 1024		Discovery agent
(3Z)-2-amino-4-(4-hydroxyphenyl)buta-1,3-diene-1,1,3-tricarbonitrile	CAS 122520-87-0	<chem>C1=CC(=CC=C1/C=C(C(\C#N)/C(=C(C#N)C#N)N)O</chem>	AG 112		Discovery agent

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2-[(4-methoxyphenyl)methylidene]propanedinitrile	CAS 2826-26-8	<chem>COC1=CC=C(C=C1)C=C(C#N)C#N</chem>	AG 9		Discovery agent
(E)-2-cyano-3-(3,4-dihydroxyphenyl)prop-2-enethioamide	CAS 122520-86-9	<chem>C1=CC(=C(C=C1)/C=C(C#N)/C(=S)N)O</chem>	AG-213		Discovery agent
(E)-2-(3,4-dihydroxybenzoyl)-3-(3,4-dihydroxyphenyl)prop-2-enenitrile		<chem>C1=CC(=C(C=C1)/C=C(C#N)/C(=O)C2=CC(=C(C=C2)O)O)O</chem>	AG-538		Discovery agent
(E)-2-cyano-3-[5-(2,5-dichlorophenyl)furan-2-yl]-N-quinolin-5-ylprop-2-enamide	CAS 304896-28-4	<chem>C1=CC2=C(C=CC=N2)C(=C1)NC(=O)/C(=C/C3=CC=C(O3)C4=C(C=CC(=C4)Cl)Cl)/C#N</chem>	AGK2		Discovery agent
(2S)-1-[(2S)-2-amino-3-naphthalen-1-ylpropanoyl]pyrrolidine-2-carbonitrile		<chem>C1C[C@H](N(C1)C(=O)[C@H](C2=CC=CC3=CC=CC=C32)N)C#N</chem>	Ala(1-naph)-Pro-CN		Discovery agent
3-[9-nitro-6-oxo-7,12-dihydro-5H-indolo[3,2-d][1]benzazepin-2-yl]propanenitrile		<chem>C1C2=C(C3=C(C=CC(=C3)CCC#N)NC1=O)NC4=C2C=C(C=C4)[N+](=O)[O-]</chem>	alsterpaullone 2-cyanoethyl		Discovery agent
N-(4-amino-5-cyano-6-ethoxypyridin-2-yl)-2-(2,5-dimethoxyphenyl)acetamide	CAS 894804-07-0	<chem>CCOC1=C(C(=CC(=N1)NC(=O)CC2=C(C=CC(=C2)OC)OC)N)C#N</chem>	Aminopyridine deriv. 2		Discovery agent
(2R,3R)-2-cyano-3-hydroxy-N-[4-(trifluoromethyl)phenyl]butanamide		<chem>C[C@H]([C@H](C#N)C(=O)NC1=CC=C(C=C1)C(F)FO</chem>	Antiproliferative Agent A771726		Discovery agent
5-(4-amino-5,8-difluorospiro[1H-quinazoline-2,4'-piperidine]-1'-carbonyl)pyridine-2-carbonitrile		<chem>C1CN(CCC12NC3=C(C=CC(=C3C(=N2)N)F)C(=O)C4=CN=C(C=C4)C#N</chem>	AR-C102222		Discovery agent
4-[4-[(4-methoxypyridin-2-yl)amino]piperidine-1-carbonyl]benzonitrile	CAS 268730-08-1	<chem>COC1=CC(=NC=C1)NC2CCN(CC2)C(=O)C3=CC=C(C=C3)C#N</chem>	AR-C133057XX		Discovery agent
2-(1,3-benzothiazol-2-yl)-2-[2-(2-pyridin-3-ylethylamino)pyrimidin-4-yl]acetoneitrile	CAS 345987-15-7	<chem>C1=CC=C2C(=C1)N=C(S2)C(C#N)C3=NC(=NC=C3)NCCC4=CN=CC=C4</chem>	AS-601245		Discovery agent
N-(4-cyanophenyl)-2-[4-(2,6-dioxo-1,3-dipropyl-7H-purin-8-yl)phenoxy]acetamide	CAS 264622-58-4	<chem>CCCN1C2=C(C(=O)N(C1=O)CCC)NC(=N2)C3=CC=C(C=C3)OCC(=O)NC4=CC=C(C=C4)C#N</chem>	ATL-844		Asthma
3-(2-cyanopropan-2-yl)-N-[4-methyl-3-[(3-methyl-4-oxoquinazolin-6-yl)amino]phenyl]benzamide	CAS 878739-06-1	<chem>CC1=C(C=C(C=C1)NC(=O)C2=CC(=CC=C2)C(C)C)C#N)NC3=CC4=C(C=C3)N=CN(C4=O)C</chem>	AZ-628		Solid tumour/cancer
5-fluoro-2-[[[(1S)-1-(4-fluorophenyl)ethyl]amino]-6-[[[5-methyl-1H-pyrazol-3-yl]amino]pyridine-3-carbonitrile	CAS 905586-69-8	<chem>CC1=CC(=NN1)NC2=C(C=C(C(=N2)N[C@H](C)C3=CC=C(C=C3)F)C#N)F</chem>	AZ960		Discovery agent

IUPAC Name	CAS #	SMILES Notation	USAN Name / Trade Name	Representative Tx Class	Representative Disease
2-methyl-2-[4-[2-methyl-8-(2-pyridin-3-ylethynyl)imidazo[4,5-c]quinolin-1-yl]phenyl]propanenitrile	CAS 853910-02-8	<chem>CC1=NC2=CN=C(C3C=CC(=CC3=C2N1C4=CC=C(C=C4)C(C)(C)C#N)C#CC5=CN=CC=C5</chem>	BAG956		Haematological malignancy
(E)-3-(4-methylphenyl)sulfonylprop-2-enenitrile	CAS 19542-67-7	<chem>CC1=CC=C(C(C=C1)S(=O)(=O)/C=C/C#N</chem>	BAY11-7082		Multiple myeloma
4-[5-(1-methylpyrazol-4-yl)-3-[2-(1-methylpyrazol-4-yl)ethyl]imidazol-4-yl]benzonitrile		<chem>CN1C=C(C=C1)CCN2C=NC(=C2C3=CC=C(C=C3)C#N)C4=CN(N=C4)C</chem>	BAZ2-ICR		Discovery agent
(2S,4S)-1-[(2R)-3-benzoylsulfinyl-2-methylpropanoyl]-4-phenylsulfanylpyrrolidine-2-carboxylic acid;(3S,4R)-3-hydroxy-2,2-dimethyl-4-(2-oxopyrrolidin-1-yl)-3,4-dihydrochromene-6-carbonitrile		<chem>C[C@@H](CS(=O)C(=O)C1=CC=CC=C1)C(=O)N2C[C@H](C[C@H]1C[C@H](C=C1)O)SC3=CC=CC=C3.CC1([C@H]([C@@H](C2=C(O1)C=CC(=C2)C#N)N3CCCCC3=O)O)C</chem>	Benzofuran-3-yl-(indol-3-yl)maleimides		Discovery agent
dimethyl 4-[3-[[N-cyano-N'-[3-[4-(3-methoxyphenyl)piperazin-1-yl]propyl]carbamidoyl]amino]phenyl]-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate		<chem>CC1=C(C(C(C(=C(N1)C(C(=O)OC)C2=CC(=CC=C2)NC(=NCCCN3CCN(CC3)C4=CC(=CC=C4)OC)NC#N)C(=O)OC</chem>	BMS-245782		Discovery agent
1-cyano-3-(2-methyl-1-benzofuran-5-yl)-2-[(3S)-2-oxo-1-(2-oxo-2-pyrrolidin-1-ylethyl)azepan-3-yl]guanidine		<chem>CC1=CC2=C(C(O1)C=CC(=C2)NC(=N[C@H]3CCCCCN(C3=O)CC(=O)N4CCCC4)NC#N</chem>	BMS-269223		Discovery agent
N-[6-cyano-1-[(3-methylimidazol-4-yl)methyl]-3,4-dihydro-2H-quinolin-3-yl]-N-(thiophen-3-ylmethyl)pyridine-2-sulfonamide		<chem>CN1C=NC=C1CN2CC(CCC3=C2C=CC(=C3)C#N)N(CC4=CSC=C4)S(=O)(=O)C5=CC=CC=N5</chem>	BMS-316810		Discovery agent
N-tert-butyl-2-[[6-cyano-1-[(3-methylimidazol-4-yl)methyl]-3,4-dihydro-2H-quinolin-3-yl]-pyridin-2-ylsulfonamino]acetamide		<chem>CC(C)(C)NC(=O)CN(C1CC2=C(C(=CC(=C2)C#N)N(C1)CC3=CN=CN3C)S(=O)(=O)C4=CC=CC=N4</chem>	BMS-404683		Discovery agent
4-[(7R,7aS)-7-hydroxy-1,3-dioxo-5,6,7,7a-tetrahydropyrrolo[1,2-c]imidazol-2-yl]-2-chloro-3-methylbenzonitrile	CAS 627530-84-1	<chem>CC1=C(C=C(C(=C1C)C#N)N2C(=O)C[C@@H]3[C@H](CCN3C2=O)O</chem>	BMS-564929		Discovery agent
2-[4-(1,3-benzoxazol-2-yl)-2-methoxyphenyl]acetoneitrile		<chem>COC1=C(C=CC(=C1)C2=NC3=CC=CC(=C3O2)CC#N</chem>	BOMA		Discovery agent
(1R,2R)-2-[(2S,4E,6Z,8R,9S,11R,13S,15S,16S)-7-cyano-8,16-dihydroxy-9,11,13,15-tetramethyl-18-oxo-1-oxacyclooctadeca-4,6-dien-2-yl]cyclopentane-1-carboxylic acid	CAS 7184-60-3	<chem>C[C@H]1C[C@H](C[C@H]1[C@@H]([C@@H]/C(=C/C=C/C[C@H](OC(=O)C[C@H]([C@H]([C1]C)O)[C</chem>	Borrelidin		Discovery agent

IUPAC Name	CAS #	SMILES Notation	USAN Name / Trade Name	Representative Tx Class	Representative Disease
(3Z)-N-methoxy-1-azabicyclo[2.2.2]octane-3-carboximidoyl cyanide		@@H]2CCC[C@@H]2C(=O)/C#N)OC	BRL-55473		Discovery agent
[[(2R,3R,5R,7R,8S,9S)]-(1S,3S,4S,5R,6R,7E,9E,11E,13Z)]-[14-cyano-3,5-dihydroxy-1-methoxy-4,6,8,9,13-pentamethyltetradeca-7,9,11,13-tetraenyl]-9-[[E]-3-{2-[(2S)-4-[(2S,3S,4S)-4-(dimethylamino)-2,3-dihydroxy-5-methoxypentanoylamino]butan-2-yl]-1,3-oxazol-4-yl}prop-2-enyl]-7-hydroxy-4,4,8-trimethyl-1,10-dioxaspiro[4.5]decan-3-yl]]dihydrogen phosphate	CAS 101932-71-2	C[C@@H]1[C@@@H][C@H](C[C@@@]2(C([C@H]([C@H](O2)[C@H](C[C@@H]([C@H](C[C@H](C\C/C=C\ C)\C/O)(C(O)OC)OP(=O)O)O)(C)O[C@H]1C/C=C/C3=COC(=N3)[C@@H](C)CCNC(=O)[C@H]([C@H]([C@H](COCN(C(C)O)O)O	Calyculin-A		Discovery agent
N-[3-(4-cyanophenyl)phenyl]-N-(pyridin-3-ylmethyl)ethanesulfonamide	CAS 353235-01-5	CCS(=O)=(O)N(CC1=CN=CC=C1)C2=CC=CC(=C2)C3=CC=C(C(=C3)C#N	CBIPES		Discovery agent
3-[[[2(R)-1-(dimethylamino)propan-2-yl]loxy-5-[[4-methoxy-5-(1-methylpyrazol-4-yl)pyridin-2-yl]amino]pyrazine-2-carbonitrile]	CAS 218600-44-3	C[C@H](CN(C)OC1=NC(=CN=C1C#N)NC2=NC=C(C(=C2)OC)C3=CN(N=C3)C	CCT244747		Discovery agent
(4aS,6aR,6bS,8aR,12aS,14aR,14bS)-11-cyano-2,2,6a,6b,9,9,12a-heptamethyl-10,14-dioxo-1,3,4,5,6,7,8a,14a,14b-decahydropicene-4a-carboxylic acid	CAS 218600-44-3	C[C@H]12CC[C@H]3(CCC(C[C@H]3[C@H]1C(=O)C=C4[C@H]2(C[C@H]5[C@@@]4(C=C(C(=O)C5(C)C#N)C(C)C(=O)O)	CDDO		Discovery agent
4-[[[4-cyanophenyl]-imidazol-1-ylmethyl]benzonitrile]		C1=CC(=CC=C1C#N)C(C2=CC=C(C=C2)C#N)N3C=CN=C3	CGS-18320B		Discovery agent
3-[3-(3-chloro-4-cyanophenyl)-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl]propane-1-sulfonamide	CAS 875055-92-8	CC1(C(=O)N(C(=S)N1CCCC(S(=O)(=O)N)C2=CC(=C(C(=C2)C#N)Cl)C	CH-4933468		Prostate cancer
2-[(2-chlorophenyl)methylidene]propanedinitrile	CAS 2698-41-1	C1=CC=C(C(=C1)C=C(C(#N)C#N)Cl	chlorobenzylidene malonanitrile		Discovery agent
10-[3-(dimethylamino)-2-methylpropyl]phenothiazine-2-carbonitrile	CAS 3546-03-0	CC(CN1C2=CC=CC=C2SC3=C1C=C(C=C3)C#N)CN(C)C	Cyamemazine		Discovery agent
4-[3-(tert-butylamino)-2-hydroxypropoxy]-1H-indole-2-carbonitrile	CAS 69906-85-0	CC(C)[C]NCC(COC1=CC=CC2=C1C=C(N2)C#NO	Cyanopindolol		Discovery agent

IUPAC Name	CAS #	SMILES Notation	USAN Name / Trade Name	Representative Tx Class	Representative Disease
2-cyclohexyl-2-(3,4-dichlorophenyl)acetonitrile		<chem>C1CCC(CC1)C(C#N)C2=CC(=C(C=C2)Cl)Cl</chem>	Cyclohexyl-(3,4-dichloro-phenyl)-acetonitrile		Discovery agent
(2S)-1-[(2S)-2-amino-2-cyclohexylacetyl]pyrrolidine-2-carbonitrile		<chem>C1CCC(CC1)[C@@H](C(=O)N2CC[C@H]2C#N)N</chem>	Cyclohexylglycine-(2S)-cyanopyrrolidine		Discovery agent
2-cyclopentyl-2-(3,4-dichlorophenyl)acetonitrile		<chem>C1CCC(C1)C(C#N)C2=CC(=C(C=C2)Cl)Cl</chem>	Cyclopentyl-(3,4-dichloro-phenyl)-acetonitrile		Discovery agent
formonitrile oxide	CAS 506-85-4	Fulminic acid; formonitrile oxide; Knallsaeure; HCNO; Hydrogen cyanide N-oxide; H-C#NO; formonitrile-N-oxide; [C(H)NO]; [CH(NO)]; (methylidyneammonium)oxid anide; methylidyne(oxo)-lambda(5)-azane; hydrido(oxidonitrato-N)carbon; hydrido(nitrosyl-kappaN)carbon; CHEMBL185198; CHEBI:29813; 51060-05-0; Cynooxide anion; Formnitrile oxide; AC1LAVEA; CTK1G9581; DTXSID30334603; BDBM50152965; formonitrile oxideformonitrile-N-oxidehydrido(nitrosyl-kappaN)carbonhydrido(oxidonitrato-N)carbon	Cynooxide anion		Discovery agent
(2R)-2-(3,4-dimethoxyphenyl)-5-[2-(3,4-dimethoxyphenyl)ethyl-methylamino]-2-propan-2-ylpentanenitrile	CAS 38321-02-7	<chem>CC(C)(CCCN(C)CCCC1=CC(=C(C=C1)OC)OC)(C#N)C2=CC(=C(C=C2)OC)OC</chem>	Dexverapamil		Discovery agent
2,3-bis(4-hydroxyphenyl)propanenitrile	CAS 1428-67-7	<chem>C1=CC(=CC=C1CC(C#N)C2=CC=C(C=C2)O)O</chem>	diarylpropionitril		Discovery agent
2-(cyclopropanecarbonyl)-3-[2-methylsulfonyl-4-(trifluoromethyl)phenyl]-3-oxopropanenitrile	CAS 143701-75-1	<chem>CS(=O)(=O)C1=C(C=CC(=C1)C(F)(F)F)C(=O)C(C#N)C(=O)C2CC2</chem>	Diketoneitrile		Discovery agent

IUPAC Name	CAS #	SMILES Notation	USAN Name / Trade Name	Representative Tx Class	Representative Disease
[4-[4-[3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-2,4-dioximidazolidin-1-yl]but-2-ynoxymethyl]-2-[[[(2S,3S,4S)-3-hydroxy-2-methyl-6-[[[(3S)-3,5,12-trihydroxy-3-(2-hydroxyacetyl)-10-methoxy-6,11-dioxo-2,4-dihydro-1H-tetracen-1-yl]oxy]oxan-4-yl]amino]methylcarbamoyl]phenyl] butanoate	CAS 88594-78-9	<chem>CCCC(=O)OC1=C(C=C(C=C1)COCC#CCN2C(=O)N(C(=O)C2(C)C)C3=CC(=C(C=C3)C#N)C(F)(F)C(=O)NCN1C@H]4CC(O)C@H)[C@H]4O)C)OC5C[C@]([C@H]4O)C(=O)C8=C(C7=O)C(=CC=C8)OC)O)C(=O)CO)O</chem>	Doxorubicin-Formaldehyde Conjugate		Discovery agent
5-(4-cyanophenyl)-6-methyl-2-oxo-1H-pyridine-3-carbonitrile	CAS 88594-78-9	<chem>CC1=C(C=C(C(=O)N1)C#N)C2=C(C=C(C=C2)C#N</chem>	DPN-205-734		Cardiac disease
3-[3-[2-[2-[4-cyano-N-[(3-methylimidazol-4-yl)methyl]anilino]ethyl]-[1-[(2-methylpropan-2-yl)oxycarbonyl]piperidin-4-yl)methyl]sulfamoyl]phenyl]propanoic acid		<chem>CC(C)(C)OC(=O)N1CCC(CC1)CN(CCN(CCC2=CN=CN2C)C3=CC=C(C=C3)C#N)S(=O)(=O)C4=CC=CC=C4C5=CC=CC(=C5)CCC(=O)O</chem>	ED1		Acute respiratory distress syndrome; Myocardial reperfusion injury; Sepsis
6-cyano-N-[(4,6-dimethyl-2-oxo-1H-pyridin-3-yl)methyl]-1-pentan-3-ylindole-4-carboxamide	CAS 1418308-27-6	<chem>CCC(CC)N1C=CC2=C(C=C(C=C21)C#N)C(=O)NCC3=C(C=C(C(=O)NC3=O)C)C</chem>	El1		Discovery agent
(8R,9S,13S,14S,17R)-3-(2-methoxyethoxy)-5',5',13-trimethyl-6'-oxospiro[7,8,9,11,12,14,15,16-octahydro-6H-cyclopenta[a]phenanthrene-17,2'-oxane]-2-carbonitrile		<chem>C[C@]12CC[C@H]3[C@H]1[C@H]([C@H]1CC[C@]2(C)O)CC[C@]45[C@@]3(CC(C([C@]4(O5)C)O)C(C)CCC5=CC(=C(C=C35)C#N)OCCOC</chem>	EM1396		Discovery agent
(1S,2R,6R,8S,11S,12S,15S,16S)-5,15-dihydroxy-2,6,15,16-tetramethyl-7-oxapentacyclo[9.7.0.02,8.06,8.012,16]octadec-4-ene-4-carbonitrile	CAS 80471-63-2	<chem>C[C@]12CC[C@H]3[C@H]1[C@H]([C@H]1CC[C@]2(C)O)CC[C@]45[C@@]3(CC(C([C@]4(O5)C)O)C#N)C</chem>	Epostane		Abortion
(1Z)-2-[5-tert-butyl-1,2-oxazol-3-yl]-N-(3-chloroanilino)-2-oxoethanimidoyl cyanide		<chem>CC(O)(C)C1=CC(=NO1)C(=O)/C(=N)\NC2=CC(=CC=C2)C1/C#N</chem>	ESI-09		Discovery agent
ethyl 2-cyano-2-quinoxalin-2-ylacetate		<chem>CCOC(=O)C(C#N)C1=NC2=CC=C(C=C2N=C1</chem>	Ethyl 2-cyano-2-(quinoxalin-2(1H)-ylidene)acetate		Discovery agent
ethyl 2-cyano-3-(3-phenylphenyl)iminopropanoate		<chem>CCOC(=O)C(C=NC1=CC=CC(=C1)C2=CC=CC=C2)C#N</chem>	Ethyl 3-(biphenyl-3-ylamino)-2-cyanoacrylate		Discovery agent

IUPAC Name	CAS #	SMILES Notation	USAN Name / Trade Name	Representative Tx Class	Representative Disease
(1R,3S,5R)-2-N-[1-carbamoyl-5-(cyanomethoxy)indol-3-yl]-3-N-[(3-chloro-2-fluorophenyl)methyl]-2-azabicyclo[3.1.0]hexane-2,3-dicarboxamide		<chem>C1[C@H]2[C@@H]1N([C@@H](C2)C(=O)NCC3=C(C(=CC=C3)Cl)F)C(=O)NC4=CN(C5=C4C=C(C(=C5)OCC#N)C(=O)N</chem>	example 373 [WO2012093101]		Discovery agent
(2S)-1-[(2S)-2-amino-3,3-dimethylbutanoyl]pyrrolidine-2-carbonitrile	CAS 171092-64-1	<chem>CC(C)(C)[C@H]([C@@H](C(=O)N1CCCC[C@H]1C#N)N</chem>	FE 999011		Discovery agent
3-(23-methyl-14-oxo-3,13,23-triazahexacyclo[14.7.0.0.2,10.0.4,9.0.11,15.0.17,22]triosa-1,4,6,8,10,15,17,19,21-nonaen-3-yl)propanenitrile	CAS 136194-77-9	<chem>CN1C2=CC=CC=C2C3=C4C(=C5C6=CC=CC=C6N(C5=C31)CCCC#N)CNC4=O</chem>	G6976		Solid tumour/cancer
3-(4-bromophenyl)-8-(5-methylfuran-2-yl)-6-oxo-2,4,7,8-tetrahydropyrido[2,1-b][1,3,5]thiadiazine-9-carbonitrile		<chem>CC1=CC=C(C(O1)C2CC(=O)N3CN(CSC3=C2C#N)C4=CC=C(C(=C4)Br</chem>	GNF-PF-3464		Discovery agent
N-[3-cyano-6-(2-methylbutan-2-yl)-4,5,6,7-tetrahydro-1-benzothiophen-2-yl]-2-ethylbutanamide	CAS 438618-32-7	<chem>CCC(CC)C(=O)N(C1=C(C2=C(C(S1)C(C(C2)C(C)(C)CC)C#N</chem>	hGGR antagonist		Discovery agent
N-(12-cyanoindolizino[2,3-b]quinoxalin-2-yl)thiophene-2-carboxamide	CAS 799819-78-6	<chem>C1=CC=C2C(C(=C1)N=C3C(=C4C=C(C(=CN4C3=N2)NC(=O)C5=CC=CC5)C#N</chem>	HITOPK-032		Nasopharyngeal carcinoma
N-butyl-N-(6-cyano-2,2-dimethyl-3,4-dihydrochromen-4-yl)ethanesulfonamide		<chem>CCCCN(C1CC(OC2=C1C=C(C(=C2)C#N)(C)C)S(=O)(=O)CC</chem>	IKs124		Discovery agent
1-cyano-3-[3-(1H-imidazol-5-yl)propyl]-2-methylguanidine		<chem>CN=C(NCCCC1=CN=CN1)NC#N</chem>	improgan		Discovery agent
3-[[5-(6-methylpyridin-2-yl)-4-quinoxalin-6-yl]-1H-imidazol-2-yl]methylamino]benzonitrile	CAS 945244-71-3	<chem>CC1=NC(=CC=C1)C2=C(C(=N(C(N2)CNC3=CC=CC(=C3)C#N)C4=CC5=NC=CN=C5C=C4</chem>	IN-1166		Discovery agent
4-amino-N-[2-[[[N-cyano-N'-[3-[3-(piperidin-1-ylmethyl)phenoxy]propyl]carbamiimidoyl]amino]ethyl]-3-iodobenzamide	CAS 126632-01-7	<chem>C1CCN(CC1)CC2=CC(=CC=C2)OCCCN=C(NCCNC(=O)C3=CC(=C(C(=C3)N))NC#N</chem>	iodoaminopotentialine		Discovery agent
4-[2-hydroxy-3-(propan-2-ylamino)propoxy]-3-iodo-1H-indole-2-carbonitrile	CAS 83498-72-0	<chem>CC(C)NCC(COC1=CC=CC2=C1C(=C(N2)C#N))O</chem>	iodocyanopindolol		Discovery agent
5-cyano-N-[2-(cyclohexen-1-yl)-4-[1-[2-(dimethylamino)acetyl]piperidin-4-yl]phenyl]-1H-imidazole-2-carboxamide	CAS 885692-52-4	<chem>CN(C)CC(=O)N1CCCC(C(C1)C2=CC(=C(C(=C2)NC(=O)C3=NC=C(N3)C#N)C4=CCCCC4</chem>	JNJ-28312141		Discovery agent

IUPAC Name	CAS #	SMILES Notation	USAN Name / Trade Name	Representative Tx Class	Representative Disease
(E)-N-(1-acetyl-2,3-dihydroindol-6-yl)-3-(3-cyanophenyl)-N-[1-(2-cyclopentylethyl)piperidin-4-yl]prop-2-enamide	CAS 683746-68-1	<chem>CC(=O)N1CC2=C1C=C(C(=C2)N(C3CCN(CCC3)CCC4CCCC4)C(=O)/C=C/C5=CC(=CC=C5)C#N</chem>	JNJ-5207787		Discovery agent
ethyl 3-[(E)-2-amino-1-cyanoethenyl]-6,7-dichloro-1-methylindole-2-carboxylate		<chem>CCOC(=O)C1=C(C2=C(N1C)C(=C(C=C2)C)C)/C(=C\N)/C#N</chem>	KH-CB19		Discovery agent
2-carbazol-9-yl-N-(2-chloro-6-cyanophenyl)acetamide		<chem>C1=CC=C2C(=C1)C3=CC=CC=C3N2CC(=O)NC4=C(C(=CC=C4Cl)C#N</chem>	KL044		Discovery agent
6-[2-[[2-(3-cyano-3,4-dihdropyrazol-2-yl)-2-oxoethyl]amino]ethylamino]pyridine-3-carbonitrile	CAS 761414-79-3	<chem>C1C=NN(C1C#N)C(=O)CNCNC2=NC=C(C=C2)C#N</chem>	KR-62436		Non-insulin dependent diabetes
4-(furan-3-yl)-7-[[[3-(3-hydroxy-6,8-dioxabicyclo[3.2.1]octan-3-yl)phenyl]methoxy]naphthalene-2-carbonitrile		<chem>C1C2COC(O2)CC1(C3=CC=CC(=C3)COC4=CC5=C(C(=C4)C(=CC(=C5)C#N)C6=COC=C6)O</chem>	L-702-539		Discovery agent
7-[[[3-fluoro-5-[(1S,3S,5R)-3-hydroxy-6,8-dioxabicyclo[3.2.1]octan-3-yl]phenoxy]methyl]-4-(furan-3-yl)quinoline-2-carbonitrile		<chem>C1[C@H]2CO[C@H](O2)C[C@@]1(C3=CC(=CC(=C3)F)OCC4=C(C5=NC(=CC(=C5C=C4)C6=COC=C6)C#N)O</chem>	L-746530		Discovery agent
(2S)-N-(cyanomethyl)-4-methyl-2-[[[(1S)-2,2,2-trifluoro-1-[4-(4-methylsulfonylphenyl)phenyl]ethyl]amino]penta	CAS 603139-12-4	<chem>CC(C)[C@@H](C(=O)NCC#N)N[C@@H](C1=CC=C(C(=C1)C2=CC=C(C(=C2)S(=O)(=O)C)C(F)F</chem>	L-873724		Asthma
2-[[[6aR,9S,10aR)-5-chloro-7-methyl-6,6a,8,9,10,10a-hexahydro-4H-indolo[4,3-fg]quinolin-9-yl]acetanitrile	CAS 36945-03-6	<chem>CN1C[C@@H](C[C@H]2[C@H]1CC3=C(NC4=CC=CC2=C34)C)C#N</chem>	lergotril		Discovery agent
(Z)-2-cyano-N-(2,5-dibromophenyl)-3-hydroxybut-2-enamide		<chem>C/C(=C(\C#N)/C(=O)NC1=C(C(=CC(=C1)Br)Br)/O</chem>	LFM-A13		Discovery agent
1-[2-[[3-[2-cyano-4-[2-(cyclopropylmethoxy)ethoxy]phenoxy]-2-hydroxypropyl]amino]ethyl]-3-(4-hydroxyphenyl)urea		<chem>C1CC1COCCOC2=CC(=C(C=C2)OCC(CNCCN(C(=O)NC3=CC=C(C(=C3)O)C#N</chem>	LK 204-545		Discovery agent
N-[[[4-(cyanophenyl)methyl]-6-[4-(2-phenylphenyl)piperazin-1-yl]hexanamide	CAS 1052147-86-0	<chem>C1CN(CCN1CCCCC(C(=O)NCC2=CC=C(C(=C2)C#N)C3=CC=CC=C3C4=CC=CC=C4</chem>	LP-211		Discovery agent

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2-amino-6-(2-hydroxyethylsulfanyl)-4-(4-hydroxyphenyl)pyridine-3,5-dicarbonitrile		<chem>C1=CC(=CC=C1C2=C(C(=NC(=C2)C#N)SCCO)N)C#N</chem>	LUF5831		Discovery agent
2-amino-4-(1,3-benzodioxol-5-yl)-6-(2-hydroxyethylsulfanyl)pyridine-3,5-dicarbonitrile		<chem>C1OC2=C(O1)C=C(C(=C2)C3=C(C(=NC(=C3)C#N)SCCO)N)C#N</chem>	LUF-5853		Discovery agent
4-[6-methoxy-2-(4-methoxyphenyl)-1-benzofuran-3-carbonyl]benzonitrile	CAS 176977-56-3	<chem>COC1=CC=C(C(=C1)C2=C(C(=C3=C(C2)C(=C(C(=C3)OC)C(=O)C4=CC=CC(=C4)C#N</chem>	LY320135		Discovery agent
(Z)-3-amino-3-(2-aminophenyl)sulfanyl-2-[3-[hydroxy(pyridin-4-yl)methyl]phenyl]prop-2-enenitrile		<chem>C1=CC=C(C(=C1)N)S/C(=C(\C#N)/C2=CC=CC(=C2)C(C3=CC=NC=C3)O)/N</chem>	MEK inhibitor I		Discovery agent
(3S,4R)-3-hydroxy-4-[(2S)-2-(hydroxymethyl)-5-oxopyrrolidin-1-yl]-2,2-dimethyl-3,4-dihydrochromene-6-carbonitrile	CAS 129655-17-0	<chem>CC1([C@H]([C@@H](C2=C(O1)C=CC(=C2)C#N)N3[C@@H](CCC3=O)CO)O)C</chem>	MJ-451		Discovery agent
(2S)-2-[[[(2S,4R)-1-(3-cyanophenyl)sulfonyl-4-(cyclobutylamino)pyrrolidine-2-carbonyl]amino]-3-[4-[[3,5-dichloropyridine-4-carbonyl]amino]phenyl]propanoic acid	CAS 865110-07-2	<chem>C1CC(C1)N[C@@H](C@H)2C[C@H](N(C2)S(=O)(=O)C3=CC=CC(=C3)C#N)C(=O)N[C@H](CC4=CC=C(C=C4)NC(=O)C5=C(C(=NC(=C5)Cl)Cl)C(=O)O</chem>	MK-0668		Discovery agent
3-[5-(3,5-difluorophenyl)-3-[[[(1S,3R)-3-fluorocyclopentyl]amino]methyl]-4-methylpyrazol-1-yl]propanenitrile		<chem>CC1=C(N(C(=N1)C1CN[C@H](C2CC[C@H](C2)F)CCC#N)C3=CC(=CC(=C3)F)F</chem>	MK-1925		Discovery agent
3-(9-iodo-2-oxo-3,4-dihydro-1H-1,6-benzodiazocin-5-yl)benzonitrile		<chem>C1CC(=O)NC2=C(C(=CC(=C2))N=C1C3=CC=CC(=C3)C#N</chem>	MNI-135		Discovery agent
4-(9-bromo-2-oxo-3,4-dihydro-1H-1,6-benzodiazocin-5-yl)pyridine-2-carbonitrile		<chem>C1CC(=O)NC2=C(C(=CC(=C2)Br)N=C1C3=CC(=NC(=C3)C#N</chem>	MNI-137		Discovery agent
N-[1-(cyanomethylcarbamoyle)cyclohexyl]benzamide		<chem>C1CCC(CC1)(C(=O)NCC#N)NC(=O)C2=CC=CC=C2</chem>	N-(1-(cyanomethyl)carbamoyle)cyclohexylbenzamide		Discovery agent
N-(1H-benzimidazol-2-yl)-3-cyanobenzamide		<chem>C1=CC=C2C(C(=C1)NC(=N2)NC(=O)C3=CC=CC(=C3)C#N</chem>	N-(1H-benzimidazol-2-yl)-3-cyanobenzamide		Discovery agent
N-(cyanomethyl)-2-(naphthalen-2-ylsulfonylamino)acetamide		<chem>C1=CC=C2C=C(C(=CC2=C1)S(=O)(=O)NCC(=O)NCC#N</chem>	N-(2-naphthylsulfonyl)-glycyl-glycine-nitrile		Discovery agent

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N-[3-[(3-cyanobenzoyl)amino]phenyl]-2-methoxybenzamide		<chem>COC1=CC=CC(=CC=C1C(=O)NC2=CC=CC(=C2)NC(=O)C3=CC=CC(=C3)C#N</chem>	N-(3-(3-cyanobenzamido)phenyl)-2-methoxybenzamide		Discovery agent
N-(3-chlorophenyl)-3-cyano-5-fluorobenzamide		<chem>C1=CC(=CC(=C1Cl)NC(=O)C2=C(C=CC(=C2)C#N)F</chem>	N-(3-chlorophenyl)-3-cyano-5-fluorobenzamide		Discovery agent
N-(4-amino-5-cyano-6-ethoxypyridin-2-yl)acetamide		<chem>CCOC1=C(C(=CC(=N1)NC(=O)C)C#N</chem>	N-(4-amino-5-cyano-6-ethoxypyridin-2-yl)acetamide		Discovery agent
N-(4-amino-5-cyano-6-phenylpyridin-2-yl)acetamide		<chem>CC(=O)NC1=NC(=C(C(=C1N)C#N)C2=CC=CC=C2</chem>	N-(4-amino-5-cyano-6-phenylpyridin-2-yl)acetamide		Discovery agent
N-(4-amino-6-butoxy-5-cyanopyridin-2-yl)acetamide		<chem>CCCCOC1=C(C(=CC(=N1)NC(=O)C)C#N</chem>	N-(4-amino-6-butoxy-5-cyanopyridin-2-yl)acetamide		Discovery agent
4-cyano-N-(diaminomethylidene)-3-methylsulfonylbenzamide		<chem>CS(=O)(=O)C1=C(C(=CC(=C1)C(=O)N=C(N)C#N</chem>	N-(4-Cyano-3-methanesulfonylbenzoyl)-guanidine		Discovery agent
1-cyano-4-(sulfamoylamino)benzene	CAS 164648-70-8	<chem>C1=CC(=CC(=C1C#N)NS(=O)(=O)N</chem>	N-(4-cyanophenyl)sulfamide		Discovery agent
N-[(2S)-1-(cyanomethylamino)-1-oxo-3-phenylpropan-2-yl]-4-phenylbenzamide		<chem>C1=CC=C(C(=C1)C[C@H](C(=O)NCC#N)NC(=O)C2=CC=C(C(=C2)C3=CC=CC=C3</chem>	N-(4-phenylbenzoyl)-phenylalanyl-glycine nitrile		Discovery agent
N-[8-(3-cyanophenyl)-7H-purin-6-yl]pentanamide		<chem>CCCCC(=O)NC1=NC=NC2=C1NC(=N2)C3=CC=CC(=C3)C#N</chem>	N-(8-(3-cyanophenyl)-9H-purin-6-yl)pentanamide		Discovery agent
benzyl N-[(2S)-1-(cyanomethylamino)-4-methyl-1-oxopentan-2-yl]carbamate		<chem>CC(C)[C@H](C(=O)NCC#N)NC(=O)OCC1=CC=CC=C1</chem>	N-(benzyloxycarbonyl)-leucyl-glycine nitrile		Discovery agent
(Z)-2-cyano-3-hydroxy-N-(4-phenylphenyl)but-2-enamide		<chem>C/C(=C(\C#N)/C(=O)NC1=CC=C(C=C1)C2=CC=CC=C2)/O</chem>	N-(Biphenyl-4-yl)-2-cyano-3-hydroxybut-2-enamide		Discovery agent
N-(cyanomethyl)cyclohexene-1-carboxamide		<chem>C1CCC(=CC1)C(=O)NCC#N</chem>	N-(cyanomethyl)cyclohex-1-ene-1-carboxamide		Discovery agent

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tert-butyl N-[(2S,3R)-1-(cyanomethylamino)-3-methyl-1-oxopentan-2-yl]carbamate		<chem>CC(C)[C@@H](C)[C@@H](C(=O)NCC#N)NC(=O)OC(C)(C)C</chem>	N-(tert-butoxycarbonyl)-isoleucyl-glycine-nitrile		Discovery agent
tert-butyl N-[(2S)-1-(cyanomethylamino)-4-methyl-1-oxopentan-2-yl]carbamate		<chem>CC(C)C[C@@H](C)[C@@H](C(=O)NCC#N)NC(=O)OC(C)(C)C</chem>	N-(tert-butoxycarbonyl)-leucyl-glycine-nitrile		Discovery agent
tert-butyl N-[(2S)-1-(cyanomethylamino)-4-methylsulfanyl-1-oxobutan-2-yl]carbamate		<chem>CC(C)(C)OC(=O)N[C@@H](CCSC)C(=O)NCC#N</chem>	N-(tert-butoxycarbonyl)-methionyl-glycine-nitrile		Discovery agent
tert-butyl N-[(2S)-1-(cyanomethylamino)-1-oxohexan-2-yl]carbamate		<chem>CCCC[C@@H](C)[C@@H](C(=O)NCC#N)NC(=O)OC(C)(C)C</chem>	N-(tert-butoxycarbonyl)-norleucyl-glycine-nitrile		Discovery agent
tert-butyl N-[(2S)-1-(cyanomethylamino)-1-oxopentan-2-yl]carbamate		<chem>CCCC[C@@H](C)[C@@H](C(=O)NCC#N)NC(=O)OC(C)(C)C</chem>	N-(tert-butoxycarbonyl)-norvalyl-glycine-nitrile		Discovery agent
tert-butyl N-[(2S)-1-(cyanomethylamino)-3-(4-hydroxyphenyl)-1-oxopropan-2-yl]carbamate		<chem>CC(C)(C)OC(=O)N[C@@H](C)[C@@H](CC1=CC=C(C=C1)O)C(=O)NCC#N</chem>	N-(tert-butoxycarbonyl)-tyrosyl-glycine-nitrile		Discovery agent
tert-butyl N-[(2S)-1-(cyanomethylamino)-3-methyl-1-oxobutan-2-yl]carbamate		<chem>CC(C)[C@@H](C)[C@@H](C(=O)NCC#N)NC(=O)OC(C)(C)C</chem>	N-(tert-butoxycarbonyl)-valyl-glycine-nitrile		Discovery agent
N,N-bis(cyanomethyl)-3,4-dimethoxybenzamide		<chem>COC1=C(C=C(C=C1)C(=O)N(CC#N)OC)CC#N</chem>	N,N-bis(cyanomethyl)-3,4-dimethoxybenzamide		Discovery agent
(2S)-2-acetamido-N-(cyanomethyl)-3-phenylpropanamide		<chem>CC(=O)N[C@@H](C)[C@@H](CC1=CC=CC=C1)C(=O)NCC#N</chem>	N-acetyl-phenylalanyl-glycine-nitrile		Discovery agent
N-[(1-butylpyrrolidin-2-yl)methyl]-4-cyano-1-methoxynaphthalene-2-carboxamide	CAS 149649-22-9	<chem>CCCC1CCCC1CNC(=O)C2=C(C3=CC=CC=C3C(=C2)C#N)OC</chem>	nafadotride		Discovery agent
[amino-[[N'-[2-[amino(cyano)methylidene]amino]ethyl]carbamimidoyl]amino]methylidene]-[6-[amino-[[N'-(2-aminoethyl)carbamimidoyl]amino]methylidene]azanium]hexyl]azanium;dichloride		<chem>C(CCC[NH+]=C(N)NC(=NCCN=C(C#N)N)N)CC[NH+]=C(N)NC(=NCN)N.[Cl-].[Cl-]</chem>	NB-325		Human immunodeficiency virus infection

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N-[(2S)-1-(cyanomethylamino)-1-oxo-3-phenylpropan-2-yl]benzamide		<chem>C1=CC=C(C=C1)C[C@@H](C(=O)NCC#N)NC(=O)C2=CC=CC=C2</chem>	N-benzoyl-phenylalanyl-glycine-nitrile		Discovery agent
(E)-3-[4-(4-cyanophenyl)phenyl]-N-hydroxyprop-2-enamide		<chem>C1=CC(=CC=C1/C=C/C(=O)NO)C2=CC=C(C(=C2)C#N</chem>	N-Hydroxy-E-3-(4'-cyanobiphenyl-4-yl)-acrylamide		Discovery agent
4-cyano-N-(1,3-dimethyl-2-oxoquinolin-6-yl)-2-methoxybenzenesulfonamide		<chem>CC1=CC2=C(C=CC(=C2)NS(=O)(=O)C3=C(C(=C(C(=C3)C#N)OC)N(C1=O)C</chem>	NI-57		Discovery agent
3-(3-pyridin-3-yl-1,2,4-oxadiazol-5-yl)benzonitrile		<chem>C1=CC(=CC(=C1)C2=NC(=NO2)C3=CN=CC=C3)C#N</chem>	NS9283		Discovery agent
5-(4-chloroanilino)-2-methyl-9-nitro-5H-chromeno[4,3-b]pyridine-3-carbonitrile		<chem>CC1=NC2=C(C(=C1C#N)C(OC3=C2C=C(C(=C3)[N+](=[O])[O-])N)C4=CC=C(C(=C4)Cl</chem>	NSC-613604		Discovery agent
4-(6,11-dioxo-3H-naphtho[2,3-e]benzimidazol-2-yl)benzonitrile		<chem>C1=CC=C2C(=C1)C(=O)C3=C(C2=O)C4=C(C(=C3)NC(=N4)C5=CC=C(C(=C5)C#N</chem>	NSC-745883		Discovery agent
(5Z,8Z,11Z,14Z)-20-cyano-N-[(2R)-1-hydroxypropan-2-yl]-16,16-dimethylicosane-5,8,11,14-tetraenamide	CAS 342882-77-3	<chem>C[C@H](CO)NC(=O)CCC/C=C\C/C=C\C/C=C\C/C=C\C(C)(C)CCCC#N</chem>	O-1812		Discovery agent
(3Z)-N-methoxy-1-azabicyclo[2.2.2]octane-3-carboximidoyl cyanide;hydrochloride		<chem>CO/N=C(\C#N)/C1CN2CCC1CC2.Cl</chem>	Olterodine		Discovery agent
4-[4-cyano-2-[2-(4-fluoronaphthalen-1-yl)propanoylamino]phenyl]butanoic acid	CAS 402473-54-5	<chem>CC(C1=CC=C(C(=CC(=C21)F)C(=O)NC3=C(C=CC(=C3)C#N)CC(C(=O)O</chem>	ONO-AE3-208		Discovery agent
(1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxy-1-adamantyl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile;2,2,2-trifluoroacetic acid	CAS 361442-05-9	<chem>C1[C@@H]2C[C@H]2N([C@@H]1C#N)C(=O)[C@H](C34CC5CC(C3)CC(C5)(C4)O)N.C(=O)C(F)(F)F)O</chem>	Oximidine II		Discovery agent
N-[6-cyano-1-[(3-methylimidazol-4-yl)methyl]-3,4-dihydro-2H-quinolin-3-yl]-N-(pyridin-2-yl)methyl]pyridine-2-sulfonamide		<chem>CN1C=NC=C1CN2CC(CCC3=C2C=CC(=C3)C#N)N(CCC4=CC=CC=N4)S(=O)(=O)C5=CC=CC=N5</chem>	PB-27		Discovery agent
N-tert-butyl-2-[[6-cyano-1-[(3-methylimidazol-4-yl)methyl]-3,4-dihydro-2H-quinolin-3-yl]-pyridin-3-yl]sulfonamide;acetamide		<chem>CC(C)[C]NC(=O)CN(C1CC2=C(C(=CC(=C2)C#N)N(C1)CC3=CN=CN3)C(=O)N)C4=CC=CC=C4</chem>	PB-80		Discovery agent

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N-tert-butyl-2-[[6-cyano-1-[(3-methylimidazol-4-yl)methyl]-3,4-dihydro-2H-quinolin-3-yl]-pyridin-4-ylsulfonylamino]acetamide		<chem>CC(O)(C)NC(=O)CN(C1CC2=C(C=CC(=C2)C#N)N(C1)CC3=CN=CN3C)S(=O)(=O)C4=CC=NC=C4</chem>	PB-81		Discovery agent
N-[[4-(2-cyanophenyl)piperazin-1-yl]methyl]-3-methylbenzamide	CAS 190383-31-4	<chem>CC1=CC(=CC=C1)C(=O)NCN2CCN(CC2)C3=CC=CC=C3C#N</chem>	PD-168077		Discovery agent
3-[[4-(4-cyanophenyl)phenoxy]methyl]-1-(4-methoxybenzoyl)pyrrolidine-3-carboxylic acid		<chem>COC1=CC=C(C(=C1)C(=O)N2CCC(C2)(COC3=CC=C(C(=C3)C4=CC=C(C(=C4)C#N)C(=O)O</chem>	PF-00212062		Solid tumour/cancer
2-[4-(4-cyanophenoxy)-3,5-dicyclopentylpyrazol-1-yl]-N-methylacetamide	CAS 913344-84-0	<chem>CNC(=O)CN1C(=C(C(=N1)C2CC2)OC3=CC=C(C(=C3)C#N)C4CC4</chem>	PF-02367982		Endometriosis
3-(4-morpholin-4-yl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)benzonitrile		<chem>C1COCN1C2=NC=NC3=C2C(=C(N3)C4=CC=CC(=C4)C#N</chem>	PF-06447475		Discovery agent
4-[(1R,2R)-2-hydroxycyclohexyl]-2-(trifluoromethyl)benzonitrile	CAS 1076225-27-8	<chem>C1CC[C@H]([C@H](C1)C2=CC(=C(C(=C2)C#N)C(F)(F)F)O</chem>	PF-0998425		Discovery agent
4-(4-cyano-2-fluorophenyl)-2-morpholin-4-yl-5-(1H-1,2,4-triazol-5-yl)thiophene-3-carbonitrile		<chem>C1COCN1C2=C(C(=C(C(=C2)C3=N(C=NN3)C4=C(C(=C(C(=C4)C#N)F)C#N</chem>	PF-4989216		Solid tumour/cancer
3-fluoro-5-(5-pyridin-2-yltetrazol-2-yl)benzonitrile	CAS 507269-27-4	<chem>C1=CC=NC(=C1)C2=NN(N=N2)C3=CC(=CC(=C3)C#N)F</chem>	PMID15482908C8		Discovery agent
2-[(2R)-3-[(2S)-2-benzylpyrrolidin-1-yl]-2-hydroxypropoxy]-6-chlorobenzonitrile		<chem>C1C[C@H]([N(C1)C[C@H](COC2=C(C(=CC(=C2)C)C#N)O)CC3=CC=CC=C3</chem>	PMID15686947C(S)-3h		Discovery agent
6-[(3-chlorophenyl)methoxy]-4-methylpyridine-2-carbonitrile		<chem>CC1=CC(=NC(=C1)OCC2=CC(=C(C(=C2)C)C#N</chem>	PMID16439120C20		Discovery agent
2-chloro-6-[(2-methylpyridin-4-yl)methoxy]pyridine-4-carbonitrile		<chem>CC1=NC=CC(=C1)COC2=NC(=CC(=C2)C#N)Cl</chem>	PMID16439120C26		Discovery agent
(3R,5R)-7-[5-[[4-cyanophenyl]methylcarbamoyl]-3-(4-fluorophenyl)-4-phenyl-1-propan-2-ylpyrrol-2-yl]-3,5-dihydroxyheptanoate		<chem>CC(O)N1C(=C(C(=C1C(=O)NCC2=CC=C(C(=C2)C#N)C3=CC=CC=C3)C4=CC=C(C(=C4)F)CC[C@H]([C@H]1)CC(=O)[O-])O)O</chem>	PMID17574412C33		Discovery agent
3-methoxy-5-(7-methylpyrido[2,3-d]pyrimidin-2-yl)benzonitrile		<chem>CC1=NC2=NC(=N(C=C2C=C1)C3=CC(=CC(=C3)C#N)OC</chem>	PMID17723296C18		Discovery agent
7-chloro-3-oxo-8-(1,3-thiazol-5-ylmethylamino)-11,16-dioxo-2,4,19,21-		<chem>C1COC2=NC(=CN=C2C#N)NC(=O)NC3=CC(=C(C(=C3OC1)NCC4=CN=CS4)Cl</chem>	PMID17935989C25		Discovery agent

IUPAC Name	CAS #	SMILES Notation	USAN Name / Trade Name	Representative Tx Class	Representative Disease
tetrazatricyclo[15.3.1.05,10]henicosa-1(20),5,7,9,17(21),18-hexaene-18-carbonitrile		<chem>C[C@H]1CN(CCN1C(=NC2=CC(=CC=C2)Br)NC#N)C3=NC=NC4=C3C(=CN4)C</chem>	PMID19831390C14		
(2S)-N'-(3-bromophenyl)-N-cyano-2-methyl-4-(5-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperazine-1-carboximidamide		<chem>C[C@H]1CN(CCN1C(=NC2=CC(=CC(=C2)C(=O)NCCO)NC#N)C3=NC=NC4=C3C(=CN4)C</chem>	PMID19831390C22m		Discovery agent
3-[[[cyanoamino]-(2S)-2-methyl-4-(5-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperazin-1-yl]methylidene]amino]-N-(2-hydroxyethyl)benzamide		<chem>CC(C)(C)C1=CC=C(C(=C1)OC[C@H]2CN(C(=O)O2)C3=CC=CC(=C3)C#N</chem>	PMID20409708C34		Discovery agent
3-[(5S)-5-[(4-tert-butyloxy)methyl]-2-oxo-1,3-oxazolidin-3-yl]benzonitrile		<chem>CC1=CSC(=N1)NC(=O)C2=CC(=CC(=C2)C#N)F</chem>	PMID20598884C8		Discovery agent
3-cyano-5-fluoro-N-(4-methyl-1,3-thiazol-2-yl)benzamide		<chem>CC1=CC(=NN1)NC2=C(C=C(C(=N2)N[C@H](C)C3=NC=C(C(=C3)F)C#N)F</chem>	PMID21493067C1d		Discovery agent
5-fluoro-2-[[[(1S)-1-(5-fluoropyridin-2-ylethyl)amino]-6-[(5-methyl-1H-pyrazol-3-yl)amino]pyridine-3-carbonitrile		<chem>CC1=C(N=CN=C1OC2C[C@H]3CC[C@H](C2)N3S(=O)(=O)C4CC4)NC5=C(C=C(C(=C5)C#N)Cl</chem>	PMID21536438C36j		Discovery agent
3-chloro-4-[[6-[[[(1S,5S)-8-cyclopropylsulfonyl-8-azabicyclo[3.2.1]octan-3-yl]oxy]-5-methylpyrimidin-4-yl]amino]benzonitrile		<chem>CC(C)CC1=C2CCCC2=C(C(=O)N1)C#N</chem>	PMID21692504C8		Discovery agent
1-(2-methylpropyl)-3-oxo-2,5,6,7-tetrahydrocyclopenta[c]pyridine-4-carbonitrile		<chem>CC1NC2=C(S1)C=CC(=C2)C3=CC(=CC(=C3)C#N)F</chem>	PMID21927650C18		Discovery agent
3-fluoro-5-(2-methyl-2,3-dihydro-1,3-benzothiazol-5-yl)benzonitrile		<chem>CC(O)OC(=O)N1CCN(CC1)C2=C(C=C(C(=N2)C3=CC4=NC=CN=C4C=C3)C#N</chem>	PMID21939274C1		Discovery agent
propan-2-yl 4-(3-cyano-5-quinoxalin-6-yl)pyridin-2-yl)piperazine-1-carboxylate		<chem>CC1=C(C=CC(=C1)C2=CC(=C(N=C2)N3CCC(CC3)C4=NC(=NO4)C(C)C)C#N)C#N</chem>	PMID21939274C2		Discovery agent
5-(4-cyano-3-methylphenyl)-2-[4-(3-propan-2-yl-1,2,4-oxadiazol-5-yl)piperidin-1-yl]pyridine-3-carbonitrile		<chem>CN1C2=C(C(=CC(=C2)Cl)Cl)C3=C1C(=O)NC4(C3C#N)CCNCC4</chem>	PMID22136433C20		Discovery agent
7,8-dichloro-9-methyl-1-oxospiro[2.4-dihydropyrido[3,4-b]indole-3,4'-piperidine]-4-carbonitrile					

IUPAC Name	CAS #	SMILES Notation	USAN Name / Trade Name	Representative Tx Class	Representative Disease
1-butyl-4-[3-fluoro-4-(2-methylpyridin-4-yl)oxyphenyl]-2-oxopyridine-3-carbonitrile		CCCCN1C=CC(=C(C1=O)C#N)C2=CC(=C(C=C2)OC3=CC(=NC=C3)C)F	PMID22364337C48		Discovery agent
4-[[2-[(2S)-2-methyl-4-(5-propan-2-yl-1,2,4-oxadiazol-3-yl)piperazin-1-yl]pyrimidin-5-yl]oxymethyl]pyridine-3-carbonitrile		C[C@H]1CN(CCN1C2=NC=C(C(=N2)OCC3=C(C=NC=C3)C#N)C4=NOC(=N4)C(C)C	PMID22545772C42		Discovery agent
N-[(2R)-1-[[cyano(methyl)amino]-methylamino]-3-(2-methylpropylsulfonyl)-1-oxopropan-2-yl]benzamide		CC(C)CS(=O)(=O)C[C@H]([C](=O)N(C)N(C)C#N)NC(=O)C1=CC=CC=C1	PMID22686657C(R)-26		Discovery agent
4-methoxy-3-[2-[3-methoxy-4-(4-methylpiperazin-1-yl)anilino]pyridin-4-yl]benzonitrile		CN1CCN(CC1)C2=C(C=C(C(=C2)NC3=NC=CC(=C3)C4=C(C(=CC(=C4)C#N)OC)OC	PMID23232060C5		Discovery agent
[4-(3-ethoxyphenyl)phenyl]methyl (2S)-2-[[[(1S)-3-amino-1-cyano-3-oxopropyl]carbamoyl]pyrrolidine-1-carboxylate		CCOC1=CC=CC(=C1)C2=CC=C(C(=C2)COC(=O)N3CCCC[C@H]3C(=O)N[C@@H]([CC(=O)N)C#N	PMID24775305C7u		Discovery agent
6-[(2R)-4-(4-benzyl-7-chlorophthalazin-1-yl)-2-methylpiperazin-1-yl]pyridine-3-carbonitrile		C[C@H]1CN(CCN1C2=NC=C(C(=C2)C#N)C3=NN=C(C4=C3C=C(C(=C4)Cl)CC5=CC=CC=C5	PMID24809814C31		Discovery agent
6-[4-[(6-chloroimidazo[1,2-a]pyridin-2-yl)methyl]piperazin-1-yl]pyridine-3-carbonitrile		C1CN(CCN1CC2=CN3C=C(C(=CC(=N2)C)C4=NC=C(C(=C4)C#N	PMID24900608C1		Discovery agent
N-[5-[3-cyano-7-(cyclopropylamino)pyrazolo[1,5-a]pyrimidin-5-yl]amino]-2-methylphenyl]acetamide		CC1=C(C(=C(C(=C1)NC2=NC3=C(C(=NN3C(=C2)NC4CC4)C#N)NC(=O)C	PMID24900749C1a		Discovery agent
4-[3-[2-(4-methyltriazol-1-yl)ethyl]-5-phenylimidazol-4-yl]benzonitrile		CC1=CN(N=N1)CCN2C=NC(=C2C3=CC=C(C(=C3)C#N)C4=CC=CC=C4	PMID25719566C1		Discovery agent
4-[5-(1-methylpyrazol-4-yl)-3-[2-(4-methyltriazol-1-yl)ethyl]imidazol-4-yl]benzonitrile		CC1=CN(N=N1)CCN2C=NC(=C2C3=CC=C(C(=C3)C#N)C4=CN(N=C4)C	PMID25719566C7		Discovery agent
5-[4-(4-cyanobut-1-ynyl)phenyl]-1-(2,4-dichlorophenyl)-4-(hydroxymethyl)-N-morpholin-4-ylpyrazole-3-carboxamide		C1COCCN1NC(=O)C2=NN(C(=C2CO)C3=CC=C(C(=C3)C#CCCC#N)C4=C(C(=C(C(=C4)Cl)Cl	PMID26161824C70		Discovery agent
2-amino-N-(1-cyano-2-phenylethyl)acetamide		C1=CC=C(C(=C1)CC(C#N)NC(=O)CN	PMID39414053C3d		Discovery agent

IUPAC Name	CAS #	SMILES Notation	USAN Name / Trade Name	Representative Tx Class	Representative Disease
4-[[[3-[[[(E)-6,6-dimethylhept-2-en-4-ynyl]-ethylamino]methyl]phenoxy]methyl]-dimethylsilyl]benzonitrile		<chem>CCN(C/C=C/C#C(C)(C)CC1=CC(=CC=C1)OC[Si](C)(C)C2=CC=C(C=C2)C#N</chem>	PMID7650673C4q		Discovery agent
N-benzyl-2-(3-cyanophenyl)-1,3,6-trioxo-5H-[1,2,4]triazolo[1,2-a]pyridazine-8-carboxamide	CAS 550368-41-7	<chem>C1C(=O)C=C(N2N1C(=O)N(C2=O)C3=CC=CC(=C3)C#N)C(=O)NC4=CC=CC=C4</chem>	PNRI-299		Discovery agent
(3S,8S,9S,10R,13S,14S,16R,17S)-17-acetyl-3-hydroxy-10,13-dimethyl-2,3,4,7,8,9,11,12,14,15,16,17-dodecahydro-1H-cyclopenta[a]phenanthrene-16-carbonitrile	CAS 1434-54-4	<chem>CC(=O)[C@H]1[C@H]2[C@@H]3[C@H]([C@@H]2[C@@]1(C)[C@H]3C[C@H]4[C@@H]([C@@H](C4)O)C)C#N</chem>	pregnenolone-16alpha-carbonitrile		Discovery agent
1-(5-chloropyridin-2-yl)-3-[2-(3-cyano-2,6-difluorophenyl)ethyl]thiourea	CAS 181305-20-4	<chem>C1=CC(=NC=C1C1)NC(=S)NCCC2=C(C=CC(=C2F)C#N)F</chem>	PT-110		Discovery agent
pyrrolidine-1-carbonitrile	CAS 1530-88-7	<chem>C1CCN(C1)C#N</chem>	Pyrrolidine-1-carbonitrile		Discovery agent
4-[(5R)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridin-5-yl]benzonitrile		<chem>C1C[C@H]([N2C=NC=C2C1)C3=CC=C(C=C3)C#N</chem>	R-fadrozole		Discovery agent
2-[(3,4-dihydroxyphenyl)methylidene]propanedinitrile	CAS 118409-57-7	<chem>C1=CC(=C(C=C1C=C(C#N)C#N)O)O</chem>	RG-50810		Discovery agent
2-(trifluoromethyl)-4-(3,4,4-trimethyl-5-oxo-2-sulfanylideneimidazolidin-1-yl)benzonitrile	CAS 143782-25-6	<chem>CC1(C(=O)N(C(=S)N1C)C2=CC(=C(C=C2)C#N)C(F)F)C</chem>	RU-56187		Discovery agent
4-[3-(4-hydroxybutyl)-4,4-dimethyl-5-oxo-2-sulfanylideneimidazolidin-1-yl]-2-(trifluoromethyl)benzonitrile	CAS 155180-53-3	<chem>CC1(C(=O)N(C(=S)N1CCCCO)C2=CC(=C(C=C2)C#N)C(F)F)C</chem>	RU-59063		Discovery agent
(2-cyanoquinolin-8-yl) dihydrogen phosphate		<chem>C1=CC2=C(C(=C1)OP(=O)(O)O)N=C(C=C2)C#N</chem>	RU79072		Discovery agent
(4-cyanophenyl)methyl carbamimidothioate;hydrobromide		<chem>C1=CC(=CC=C1CSC(=N)N)C#N.Br</chem>	S-(4-Cyanobenzyl)isothioure a hydrobromide		Discovery agent
N-[[[(1R,2S,10R,12R,13S)-12-cyano-7,18-dimethoxy-6,17,21-trimethyl-5,8,16,19-tetraoxo-11,21-diazapentacyclo[11.7.1.02,11.04,9.015,20]henico sa-4(9),6,15(20),17-tetraen-10-yl]methyl]-2-oxopropanamide	CAS 66082-27-7	<chem>CC1=C(C(=O)C2=C(C1=O)C[C@H]3[C@H]4C5=C(C[C@H]([N4C])C[C@H]([N3][C@H]2CNC(=O)C(=O)C)C#N)C(=O)C(=C(C5=O)OC)C)OC</chem>	Saframycin A		Discovery agent

IUPAC Name	CAS #	SMILES Notation	USAN Name / Trade Name	Representative Tx Class	Representative Disease
N-[4-[2-(7-cyano-3,4-dihydro-1H-isoquinolin-2-yl)ethyl]cyclohexyl]-1H-indole-2-carboxamide		<chem>C1CC(CCC1CCN2CCC3=C(C2)C=C(C=C3)C#N)NC(=O)C4=CC5=CC=CC=C5N4</chem>	SB269652		Discovery agent
2-fluoro-5-[[5-(3-morpholin-4-ylphenoxy)pyrimidin-2-yl]amino]benzonitrile		<chem>C1COC(CN1C2=CC(=CC=C2)OC3=CN=C(N=C3)NC4=CC(=C(C=C4)F)C#N</chem>	SEN-1500		Alzheimer disease
4-[2,4-dichloro-5-methoxyanilino]-6-methoxy-7-[4-(4-methylpiperazin-1-yl)but-1-ynyl]quinoline-3-carbonitrile		<chem>CN1CCN(CC1)CCC#CC2=CC3=NC=C(C(C=C3C=C2OC)NC4=CC(=C(C=C4)C)OC)C#N</chem>	SKS-927		Discovery agent
(Z)-3-amino-3-(4-aminophenyl)sulfanyl-2-[2-(trifluoromethyl)phenyl]prop-2-enenitrile	CAS 305350-87-2	<chem>C1=CC=C(C(=C1)C(=C(C\N)/SC2=CC=C(C=C2)N)/C#N)C(F)F</chem>	SL-327		Discovery agent
3-fluoro-5-[2-[2-(fluoromethyl)-1,3-thiazol-4-yl]ethynyl]benzonitrile	CAS 945933-41-5	<chem>C1=C(C(C=C(C1C#N)F)C#CC2=CSC(=N2)CF</chem>	SP203		Discovery agent
3-amino-6,6-dimethyl-2-phenyl-8H-pyrano[3,4-c]pyridazine-4-carbonitrile		<chem>CC1(C=C2C(=NN(C(=C2C#N)N)C3=CC=CC=C3)CO1)C</chem>	ST074946		Discovery agent
3-fluoro-4-[4-methoxy-3-[[[(2S,3S)-2-phenylpiperidin-3-yl]amino]methyl]phenyl]benzonitrile		<chem>COC1=C(C(C=C1)C2=C(C=C(C(=C2)C#N)F)CN[C@H]3CCCN[C@H]3C4=CC=CC=C4</chem>	T2328		Discovery agent
5-(4,4-dimethyl-2-sulfanylidene-1H-3,1-benzoxazin-6-yl)-1-methylpyrrole-2-carbonitrile	CAS 304853-42-7	<chem>CC1(C2=C(C(=CC(=C2)C3=CC=C(C(=N3)C#N)NC(=S)O1)C</chem>	Tanaproget		Estrogen deficiency
tert-butyl 1-cyanopyrrolidine-2-carboxylate		<chem>CC(C)(C)OC(=O)C1CCCN1C#N</chem>	Tert-butyl (2S)-1-cyanopyrrolidine-2-carboxylate		Discovery agent
tert-butyl N-[cyano(methyl)amino]carbamate		<chem>CC(C)(C)OC(=O)NN(C)C#N</chem>	TERT-BUTYL 2-CYANO-2-METHYLHYDRAZINECARBOXYLATE		Discovery agent
3-(3-chloro-4-fluorophenyl)-1-(7-cyano-1,2,3,4-tetrahydronaphthalen-2-yl)-1-[3-(4-methylpiperazin-1-yl)propyl]urea		<chem>CN1CCN(CC1)CCCN(C2CCCC3=C(C2)C=C(C(=C3)C#N)C(=O)NC4=CC(=C(C=C4)F)Cl</chem>	tetralin_urea analogue (7o)		Discovery agent
1-cyano-3-[2-[[2-(diaminomethylideneamino)-1,3-thiazol-4-yl]methylsulfanyl]ethyl]-2-methylguanidine	CAS 69014-14-8	<chem>CN=C(NCCSCC1=CSC(=N1)N=C(N)N)NC#N</chem>	tiotidine		Discovery agent

IUPAC Name	CAS #	SMILES Notation	USAN Name / Trade Name	Representative Tx Class	Representative Disease
5-fluoro-2-[2-fluoro-5-[8-fluoro-7-(2-hydroxypropan-2-yl)imidazo[1,2-a]pyridin-3-yl]phenyl]benzonitrile	CAS 628690-75-5	<chem>CC(C)(C1=C(C2=NC=C(N2C=C1)C3=CC(=C(C=C3)F)C4=C(C=C(C4)F)C#N)F)O</chem>	TP003		Discovery agent
4-(3-chloro-4-fluoroanilino)-6-(pyridin-3-ylmethylamino)-1,7-naphthyridine-3-carbonitrile	CAS 871307-18-5	<chem>C1=CC(=CN=C1)CNC2=NC=C3C(=C2)C(=C(C=N3)C#N)NC4=CC(=C(C=C4)F)Cl</chem>	Tpi2 kinase inhibitor		Discovery agent
3-[4-[2-[2-(cyanomethyl)phenyl]ethynyl]-2-fluorophenyl]propanoic acid	CAS 1402601-82-4	<chem>C1=CC=C(C(=C1)CC#N)C#CC2=C(C=C(C=C2)CCC(=O)O)F</chem>	TUG-770		Discovery agent
(2Z,3Z)-2,3-bis[amino-(2-aminophenyl)sulfanylmethylidene]butanedinitrile	CAS 218601-62-8	<chem>C1=CC=C(C(=C1)N)S/C(=C/C(=C(C(=C(C#N)N)C#N)N)C#N)N</chem>	U0126		Discovery agent
(8R)-8-(dipropylamino)-6,7,8,9-tetrahydro-3H-benzof[e]indole-2-carbonitrile	CAS 149654-41-1	<chem>CCCN(CCC)[C@@H]1CCCC2=C(C1)C3=C(C=C2)NC(=C3)C#N</chem>	U92016A		Discovery agent
4-(3-piperidin-1-ylpropoxy)benzonitrile	CAS 146440-20-2	<chem>C1CCN(CC1)CCCCO2=CC=C(C=C2)C#N</chem>	UCL-2138		Discovery agent
2-amino-4-(4-methoxyphenyl)-7-naphthalen-1-yl-5-oxo-4,6,7,8-tetrahydrochromene-3-carbonitrile	CAS 1118460-77-7	<chem>COC1=CC=C(C(=C1)C2C(=C(OC3=C2C(=O)CC(C3)C4=CC=CC5=CC=CC=C54)N)C#N)C#N</chem>	UCPH-101		Discovery agent
methyl N-[3-[4-[cyano-(2-methylpyridin-3-yl)methyl]piperazin-1-yl]-3-oxo-1-phenylpropyl]carbamate	CAS 149692-09-1	<chem>CC1=C(C=C(C=C1)C(C#N)N2CCN(CC2)C(=O)CC(C3=CC=CC=C3)N(C(=O)OC</chem>	UR-12519		Discovery agent
3-fluoro-5-(3-pyridin-2-yl)-1,2,4-oxadiazol-5-yl]benzonitrile		<chem>C1=CC=NC(=C1)C2=NOC(=N2)C3=CC(=CC(=C3)C#N)F</chem>	VU0285683		Discovery agent
2-[4-(2-phenylmethoxyacetyl)piperazin-1-yl]benzonitrile		<chem>C1CN(CCN1C2=CC=CC=C2C#N)C(=O)COC3=CC=CC=C3</chem>	VU0364289		Discovery agent
2-(1,3-benzoxazol-2-ylamino)-4-(4-fluorophenyl)pyrimidine-5-carbonitrile		<chem>C1=CC=C2C(=C1)N=C(O2)NC3=NC=C(C(=N3)C4=CC=C(C(=C4)F)C#N</chem>	VU0366058		Discovery agent
1-(5-chloropropylidene-2-yl)-3-(3-cyano-5-fluorophenyl)urea		<chem>C1=CC(=NC=C1Cl)NC(=O)NC2=CC(=CC(=C2)C#N)F</chem>	VU0463841		Discovery agent
3-[(3R)-3-methyl-4-(4-methyladamantane-1-carbonyl)piperazin-1-yl]pyridine-2-carbonitrile		<chem>C[C@H]1CN(CCN1C(=O)C23C4CC(C2)C(C(4)C3)C)C5=C(N=CC=C5)C#N</chem>	VU0469650		Discovery agent
5-(7-fluoro-3,3-dimethyl-2-oxo-1H-indol-5-yl)-1-methylpyrrole-2-carbonitrile		<chem>CC1(C2=C(C(=CC(=C2)C3=CC=C(C(N3C)C#N)F)NC1=O)C</chem>	WAY-255348		Solid tumour/cancer

IUPAC Name	CAS #	SMILES Notation	USAN Name / Trade Name	Representative Tx Class	Representative Disease
(E)-3-[4-[[2,4-bis(trifluoromethyl)phenyl]methoxy]-3-methoxyphenyl]-2-cyano-N-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]prop-2-enamide	CAS 725247-18-7	<chem>COC1=C(C=CC(=C1)/C=C(\C#N)/C(=O)NC2=NN=C(S2)C(F)(F)F)OCC3=C(C=C(C=C3)C(F)(F)F)C(F)(F)F</chem>	XCT790		Discovery agent
N-[(3S,4R)-6-cyano-3-hydroxy-2,2-dimethyl-3,4-dihydrochromen-4-yl]-N-hydroxyacetamide	CAS 127408-31-5	<chem>CC(=O)N([C@H]1[C@@H]([C@@H]([C@O]C2=C1C=C(C=C2)C#N)(C)C)O)O</chem>	Y-26763		Discovery agent
(2R,5S)-4-[4-cyano-3-(trifluoromethyl)phenyl]-N-(2,4-difluorophenyl)-2,5-dimethylpiperazine-1-carboxamide		<chem>C[C@@H]1CN([C@H]([C@H]([CN1C(=O)NC2=C(C=C(C=C2)F)C)C3=CC(=C(C=C3)C#N)C(F)(F)F</chem>	YM-175735		Discovery agent
3-cyano-N-[(2S)-2-(3,4-dichlorophenyl)-4-[4-[2-[(S)-methylsulfinyl]phenyl]piperidin-1-yl]butyl]-N-methylnaphthalene-1-carboxamide		<chem>CN[C[C@@H]([CCN1CCCC(C1)C2=CC=CC=C2S@](=O)C)C3=C(C=C(C=C3)C)C(=O)C4=CC(=CC5=CC=CC=C5)C#N</chem>	ZD-6021		Discovery agent
4-[(1S,9S,11S,12R,15S,16R,24R)-12-hydroxy-12-[(E)-3-hydroxyprop-1-enyl]-11-methyl-21-oxo-5-hexacyclo[14.7.1.01,19.03,8.09,24.011,15]tetraosa-3(8),4,6,19-tetraenyl]benzonitrile		<chem>C[C@@]12C[C@H]3[C@H]4[C@@H]([C@@H]1CC[C@]2(/C=C/CO)O)CCC5=CC(=O)CC[C@]45C6=C3C=CC(=C6)C7=CC=C(C=C7)C#N</chem>	ZK-136798		Discovery agent

Table 6. Cyano-containing small molecule drugs that have been discontinued during the pre-registration or clinical trial stage.

IUPAC Name	CAS #	SMILES Notation	USAN Name / Trade Name	Representative Tx Class	Representative Disease
(6-benzoyloxy-3-cyanopyridin-2-yl) 3-[3-(ethoxymethyl)-5-fluoro-2,6-dioxypyrimidine-1-carbonyl]benzoate	CAS 110690-43-2	<chem>CCOCN1C=C(C(=O)N(C1=O)C(=O)C2=CC(=CC=C2)C(=O)OC3=C(C=CC(=N3)OC(=O)C4=CC=CC=C4)C#N)F</chem>	EMITEFUR		Solid tumour/cancer
N-[2-[[3-(2-cyanophenoxy)-2-hydroxypropyl]amino]ethyl]-2-(4-hydroxyphenyl)acetamide	CAS 86880-51-5	<chem>C1=CC=C(C(=C1)C#N)OCC(CNCCNC(=O)CC2=CC=C(C=C2)O)O</chem>	Epanolol		Angina pectoris
(3S,4R)-3-hydroxy-2,2-dimethyl-4-(2-oxopyrrolidin-1-yl)-3,4-dihydrochromene-6-carbonitrile	CAS 94535-50-9	<chem>CC1([C@H]([C@@H]([C2=C(O1)C=CC(=C2)C#N)N3CCCC3=O)O)C</chem>	Levcromakalim		Chronic obstructive pulmonary disease
4-cyano-5,5-bis(4-methoxyphenyl)pent-4-enoic acid	CAS 111753-73-2	<chem>COC1=CC=C(C=C1)C(=C(CCC(=O)O)C#N)C2=CC=C(C=C2)OC</chem>	Satigrel		Thrombosis

IUPAC Name	CAS #	SMILES Notation	USAN Name / Trade Name	Representative Tx Class	Representative Disease
4-[3-[ethyl(3-propylsulfinylpropyl)amino]-2-hydroxypropoxy]benzonitrile	CAS 123955-10-2	<chem>CCCS(=O)CCCN(CC)CC(COC1=CC=C(C=C1)C#N)O</chem>	Almokalant		Cardiac arrhythmias
2-[3-methoxyphenyl]-2-[3-[2-(3-methoxyphenyl)ethyl-methylamino]propyl]tetradecanenitrile	CAS 83200-10-6	<chem>CCCCCCCCCCCC(CCCN(C)CCCC1=CC(=CC=C1)OC)(C#N)C2=CC(=CC=C2)O</chem>	Anipamil		Hypertension
4-cyano-4-(3-cyclopentyl-4-methoxyphenyl)cyclohexane-1-carboxylic acid	CAS 153259-65-5	<chem>COC1=C(C=C(C=C1)C2(CCC(CCC2)C(=O)O)C#N)OC3CCCC3</chem>	Cilomilast		Chronic obstructive pulmonary disease; Bronchitis; Emphysema
2-amino-2-(hydroxymethyl)propane-1,3-diol; 2-cyano-3-(1-methylpyrrol-2-yl)-3-oxo-N-phenylpropanamide	CAS 109636-76-2	<chem>CN1C=CC=C1C(=O)C(C#N)C(=O)NC2=CC=CC=C2.C(C(CO)(CO)N)O</chem>	PRINOMIDE TROMETHAMINE		Inflammation
N-[(2S,3S)-4-(4-chlorophenyl)-3-(3-cyanophenyl)butan-2-yl]-2-methyl-2-[5-(trifluoromethyl)pyridin-2-yl]oxypropanamide	CAS 701977-09-5	<chem>C[C@@H]([C@H]([C@H](CC1=CC=C(C=C1)C1)C2=CC=CC(=C2)C#N)NC(=O)C(C)(C)OC3=NC=C(C(C=C3)C(F)F)</chem>	Taranabant		Obesity
N-[1-(cyanomethylcarbamoyle)cyclohexyl]-4-(4-propylpiperazin-1-yl)benzamide	CAS 354813-19-7	<chem>CCCN1CCN(CC1)C2=CC=C(C=C2)C(=O)NCC3(CCCCC3)C(=O)NCC#N</chem>	Ballicatib		Osteoporosis
1-(4-chlorophenyl)-3-cyano-2-[(3S,4R)-6-cyano-3-hydroxy-2,2-dimethyl-3,4-dihydrochromen-4-yl]guanidine	CAS 144301-94-0	<chem>CC1([C@H]([C@H]([C@H](C2=C(C(O1)C=CC(=C2)C#N)N=C(NC#N)NC3=CC=C(C(=C3)C)O)C</chem>	BMS-180448		Angina pectoris
5-[[[(5S,9R)-9-(4-cyanophenyl)-3-(3,5-dichlorophenyl)-1-methyl-2,4-dioxo-1,3,7-triazaspiro[4.4]nonan-7-yl]methyl]thiophene-3-carboxylic acid	CAS 509083-77-6	<chem>CN1C(=O)N(C(=O)C[C@]12CN(C[C@H]2C3=CC=C(C(=C3)C#N)CC4=CC(=CC(=C4)C(=O)O)C5=CC(=CC(=C5)C)C)C</chem>	BMS-587101		Psoriasis vulgaris
3-[(1S,5R)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octan-3-yl]-2,2-diphenylpropanenitrile	CAS 850689-51-9	<chem>C[N+](1([C@H]2CC[C@H]1CC(C2)C(C#N)(C3=CC=CC=C3)C4=CC=CC=C4)C</chem>	Darotropium		Chronic obstructive pulmonary disease
4-[(1R,2S)-3-(4-fluorophenyl)-2-hydroxy-1-(1,2,4-triazol-1-yl)propyl]benzonitrile	CAS 160146-17-8	<chem>C1=CC(=CC=C1C[C@H]([C@@H]([C@H](C2=CC=C(C(=C2)C#N)N3C=NC=N3)O)F</chem>	FINROZOLE		Prostate disease
(Z)-2,5-dicyano-3-hydroxy-N-[4-(trifluoromethyl)phenyl]pent-2-enamide		<chem>C1=CC(=CC=C1C(F)F)NC(=O)C(=O)C(=O)C(=O)C(=O)C#N</chem>	FK778		Kidney/heart transplant rejection

IUPAC Name	CAS #	SMILES Notation	USAN Name / Trade Name	Representative Tx Class	Representative Disease
2-cyano-3-cyclopropyl-3-hydroxy-N-[3-methyl-4-(trifluoromethyl)phenyl]prop-2-enamide	CAS 134431-49-5	<chem>CC1=C(C=CC(=C1)NC(=O)C(=C(C2CC2)O)C#N)C(F)(F)F</chem>	HR325		Rheumatoid arthritis
2-[[[(cyanoamino)-pyridin-3-ylmethylidene]amino]ethyl nitrate;methanesulfonic acid		<chem>CS(=O)(=O)O.C1=CC(=CN=C1)C(=NC)CO[N+](=O)[O-]NC#N</chem>	KRN-2391		Angina pectoris
4-cyano-4-[5-methoxy-2,3-dihydro-1,4-benzodioxin-8-yl]cyclohexane-1-carboxylic acid	CAS 150481-98-4	<chem>COC1=C2C(=C(C=C1)C3(CCC(C3)C(=O)O)C#N)OCCO2</chem>	KW-4490		Asthma
N-[(4R)-1'-[(2R)-6-cyano-1,2,3,4-tetrahydronaphthalen-2-yl]-4-hydroxyspiro[3,4-dihydrochromene-2,4'-piperidine]-6-yl]methanesulfonamide		<chem>CS(=O)(=O)NC1=CC2=C(C=C1)OC3(CCN(C3)[C@H]4CCCC5=C(C4)C=CC(=C5)C#N)C[C@H]2O</chem>	MK-499		Cardiac arrhythmias
2-chloro-6-[(2R)-2-hydroxy-3-[(2-methyl-1-naphthalen-2-yl)propan-2-yl]amino]propoxy]benzonitrile	CAS 284035-33-2	<chem>CC(C)(CC1=CC2=CC=CC=C2C=C1)NC[C@H]([COC3=C(C(=CC=C3)C)C#N)O</chem>	NPS-2143		Osteoporosis
6-[2-[[2-[(2S)-2-cyanopyrrolidin-1-yl]-2-oxoethyl]amino]ethylamino]pyridine-3-carbonitrile	CAS 247016-69-9	<chem>C1C[C@H]([N(C1)C(=O)CNCNC2=N C=C(C=C2)C#N)C#N</chem>	NVP-DPP728		Type-2 diabetes
4-chloro-2-[2-hydroxy-3-[[[2-methyl-1-[4-(4-methyl-6-oxo-4,5-dihydro-1H-pyridazin-3-yl)anilino]propan-2-yl]amino]propoxy]benzonitrile	CAS 114856-44-9	<chem>CC1CC(=O)NN=C1C2=CC=C(C=C2)NCC(C)(C)NCCC(COC3=C(C=CC(=C3)C)C#N)O</chem>	OBERADILOL MONOETHYL MALEATE		Hypertension
1-cyano-2-(2-methylbutan-2-yl)-3-pyridin-3-ylguanidine	CAS 60559-98-0	<chem>CCC(C)(C)N=C(NC#N)NC1=CN=CC=C1</chem>	P-1075		Hypertension
4-[[7-hydroxy-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl]amino]benzonitrile	CAS 105365-76-2	<chem>C1CC2=C(C1O)N=CN=C2NC3=CC=C(C=C3)C#N</chem>	RS-8359		Major depressive disorder
18-(cyclopentylmethyl)-8-oxa-18-azatetracyclo[13.5.0.0.2,7.0.9,14]icosa-1(15),2(7),3,5,9,11,13-heptaene-4-carbonitrile;methanesulfonic acid	CAS 79262-47-8	<chem>CS(=O)(=O)O.C1CCCC(C1)CN2CCCC3=C(C2)C4=C(C=CC(=C4)C#N)OC5=CC=CC=C35</chem>	SAVOXEPIN MESYLATE		Psychotic disorder
N-[(3S,4R)-6-cyano-3-hydroxy-2,2-dimethyl-3,4-dihydrochromen-4-yl]-N-phenylmethoxyacetamide	CAS 127408-30-4	<chem>CC(=O)N([C@H]1[C@@H]([C@@H]([C@H]1C(OC2=C1C=C(C(=C2)C#N)(C)C)O)OCC3=CC=C3C=C3</chem>	Y-27152		Angina pectoris

IUPAC Name	CAS #	SMILES Notation	USAN Name / Trade Name	Representative Tx Class	Representative Disease
1-[3-cyano-4-(2,2-dimethylpropoxy)phenyl]pyrazole-4-carboxylic acid	CAS 206884-98-2	CC(C)(C)COC1=C(C=C(C1)N2C=C(C=N2)C(=O)O)C#N	Y-700		Gout
4-[(4-bromophenyl)methyl-(1,2,4-triazol-4-yl)amino]benzonitrile	CAS 148869-05-0	C1=CC(=CC=C1CN(C2=CC=C(C=C2)C#N)N3C=NN=C3)Br	YM-511		Breast cancer
3-[(4S)-5-oxo-2-(trifluoromethyl)-4,6,7,8-tetrahydro-1H-quinolin-4-yl]benzonitrile	CAS 172649-40-0	C1CC2=C([C@@H]([C=C(C(N2)C(F)(F)F)C3=CC=CC(=C3)C#N)C(=O)C1	ZD-0947		Overactive bladder
2-[4-[(2S,5R)-2-cyano-5-ethynylpyrrolidin-1-yl]-2-oxoethyl]amino]-4-methylpiperidin-1-yl]pyridine-4-carboxylic acid	CAS 676559-83-4	CC1(CCN(CCC1)C2=NC=CC(=C2)C(=O)O)NCC(=O)N3[C@H]([CC([C@H]3C#N)C#C	ABT-279		Type-2 diabetes
2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-1H-indole-5-carbonitrile	CAS 612487-72-6	C1COCCN1CC2=CN=C(C(C=C2)C3=C(NC4=C3C=C(C=C4)C#N)O	AZD-1080		Alzheimer disease
3-fluoro-5-[3-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-5-yl]benzonitrile	CAS 327056-26-8	C1=CC(=NC=C1F)C2=NOC(=N2)C3=C(C=C(C=C3)C#N)F	AZD-9272	Analgesics	Neuropathic pain
(3R,4S)-4-[4-chloro-N-(1H-imidazol-2-ylmethyl)anilino]-3-hydroxy-2,2-dimethyl-3,4-dihydrochromene-6-carbonitrile		CC1([C@@H]([C@H]([C2=C(C(O1)C=CC(=C2)C#N)N(CCC3=NC=CN3)C4=CC=C(C=C4)C)O)C	BMS-191095		Angina pectoris
calcium;(2S)-3-[[3-[(2S)-4-(4-chloro-2-cyanophenoxy)-2-fluoropropoxy]phenyl]-2-propan-2-yloxypropanoate	CAS 913722-93-7	CC(C)O[C@@@H]([C@H]([CC1=CC(=CC=C1)O)C[C@@H]([COC2=C(C=C(C=C2)Cl)C#N]F)(=O)O-].[Ca+2]	E-3030		Hyperlipidaemia
(3S,4R)-3-hydroxy-2,2-dimethyl-4-(2-oxopyridin-1-yl)-3,4-dihydrochromene-6-carbonitrile	CAS 129729-66-4	CC1([C@H]([C@@H]([C2=C(C(O1)C=CC(=C2)C#N)N3C=CC=CC3=O)O)C	Emakalim		Angina pectoris
3-(3-fluoro-4-hydroxyphenyl)-7-hydroxynaphthalene-1-carbonitrile	CAS 550997-55-2	C1=CC(=CC2=C(C=C(C(C=C21)C3=CC(=C(C=C3)O)F)C#N)O	ERB-196		Inflammatory bowel disease
6-[(4R)-4-methyl-1,1-dioxo-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile	CAS 1612755-71-1	C[C@@H]1CN(S(=O)(=O)N(C1)C2=CC3=C(C=C2)C(=NC=C3)C#N	PF-06260414		Cachexia; Pain
N-(6-aminopyridin-2-yl)-4-(4-cyanophenyl)benzenesulfonamide	CAS 857290-04-1	C1=CC(=NC(=C1)NS(=O)(=O)C2=CC=C(C=C2)C3=CC=C(C=C3)C#N)N	PF-915275		Non-insulin dependent diabetes

IUPAC Name	CAS #	SMILES Notation	USAN Name / Trade Name	Representative Tx Class	Representative Disease
2,2-dimethyl-4-(1-oxidopyridin-1-ium-2-yl)chromene-6-carbonitrile	CAS 120280-37-7	<chem>CC1(C=C(C2=C(O1)C=CC(=C2)C#N)C3=CC=CC=[N+][3O-])C</chem>	Ro-31-6930		Hypertension
4-[3-(4-hydroxybutyl)-4,4-dimethyl-2,5-dioximidazolidin-1-yl]-2-(trifluoromethyl)benzonitrile	CAS 154992-24-2	<chem>CC1(C(=O)N(C(=O)N1CCCCO)C2=CC(=C(C=C2)C#N)C(F)F)C</chem>	RU-58841		Acne vulgaris
N-[4-[2-[(3aS,9bR)-8-cyano-3,3a,4,9b-tetrahydro-1H-chromeno[3,4-c]pyrrol-2-yl]ethyl]phenyl]acetamide		<chem>CC(=O)NC1=CC=C(C=C1)CCN2C[C@H]3COC4=C([C@@H]3C2)C=C(C=C4)C#N</chem>	S-33138		Psychotic disorder
(3Z,3R)-N-methoxy-1-azabicyclo[2.2.2]octane-3-carboximidoyl cyanide	CAS 159912-53-5	<chem>CO/N=C(\C#N)/[C@H]1CN2CCC1C2</chem>	Sabcomeline		
(3S,4R)-3-hydroxy-2,2-dimethyl-4-(3-oxocyclopenten-1-yl)oxy-3,4-dihydrochromene-6-carbonitrile	CAS 121055-10-5	<chem>CC1([C@H]([C@H]([C@H]1C2=C(O1)C=CC(=C2)C#N)OC3=CC(=O)CC3)O)C</chem>	SDZ-PCO-400		Asthma
[1-(2,2-dimethyl-6-nitrochromen-4-yl)pyridin-2-ylidene]cyanamide	CAS 135809-60-8	<chem>CC1(C=C(C2=C(O1)C=CC(=C2)C#N)O)[O-]N3C=CC=CC3=NC#N)C</chem>	SR-47063		Cardiac arrhythmias
3-hydroxy-2,2-dimethyl-4-(1-methyl-6-oxopyridazin-3-yl)oxy-3,4-dihydrochromene-6-carbonitrile		<chem>CC1(C(C(C2=C(O1)C=CC(=C2)C#N)OC3=NN(C(O)C=C3)C)O)C</chem>	Symkalim		Hypertension
4-cyano-N-[3-(cyclopropyl-(4-hydroxy-2-oxo-5,6,7,8,9,10-hexahydrocycloocta[b]pyran-3-yl)methyl]phenyl]benzenesulfonamide	CAS 166335-18-8	<chem>C1CCCC2=C(CC1)C(=C(C(=O)O2)C(C3CC3)C4=CC(=CC=C4)NS(=O)(=O)C5=CC=C(C=C5)C#N)O</chem>	U-103017		Human immunodeficiency virus infection

Table 7. Cyano-containing small molecule drugs that have been terminated.

IUPAC Name	CAS #	SMILES Notation	USAN Name / Trade Name	Representative Tx Class	Representative Disease
4-[(2S)-2-(4-cyanophenyl)-2-hydroxy-2-(3-methylimidazol-4-yl)ethoxy]-3-[4-(trifluoromethoxy)phenyl]benzonitrile	CAS 450839-40-4	<chem>CN1C=NC=C1[C@](COC2=C(C=C(C=C2)C#N)C3=CC=C(C=C3)OC(F)F)(C4=CC=C(C=C4)C#N)O</chem>	ABT-100		Solid tumour/cancer
(E)-N-benzyl-2-cyano-3-(3,4-dihydroxyphenyl)prop-2-enamide	CAS 133550-30-8	<chem>C1=CC=C(C=C1)CNC(=O)/C(=C/C2=CC(=C(C=C2)O)O)/C#N</chem>	AG490		Multiple myeloma; Renal transplantation
1-(6-aminopyridin-3-yl)-2-[(1S,2R,4R)-2-bicyclo[2.2.1]heptan-1-yl]-3-cyanoguanidine;hydrochloride		<chem>C1C[C@H]2C[C@H]1C[C@H]2N=C(NC#N)NC3=CN=C(C=C3)N.Cl</chem>	AL-0671		Arteriosclerosis

IUPAC Name	CAS #	SMILES Notation	USAN Name / Trade Name	Representative Tx Class	Representative Disease
1,3,4-thiadiazol-2-ylcyanamide	CAS 111393-84-1	<chem>C1=NN=C(S1)NC#N</chem>	Amitivir		Virus infection
4-[3-(1-benzhydrylazetidino-3-yl)oxy-2-hydroxypropoxy]-1H-indole-2-carbonitrile	CAS 120838-62-2	<chem>C1C(CN1C(C2=CC=CC=C2)C3=CC=CC=C3)OCC(COC4=CC=CC5=C4C=C(N5)C#N)O</chem>	BDF-9148		Cardiac failure
4-chloro-5-cyano-N-[2-(diethylamino)ethyl]-2-methoxybenzamide;hydrochloride		<chem>CCN(CC)CCNC(=O)C1=C(C=C(C(=C1)C#N)C)OC.Cl</chem>	CGP-25454A		Major depressive disorder
4-[3-(4-benzhydrylpiperazin-1-yl)-2-hydroxypropoxy]-1H-indole-2-carbonitrile	CAS 97730-95-5	<chem>C1CN(CCN1CC(COC2=CC=CC3=C2C=C(C(N3)C#N)O)C(C4=CC=CC=C4)C5=CC=CC=C5</chem>	DPI-201-106		Cardiovascular disease
5-[methyl(2-phenylethyl)amino]-2-phenyl-2-propan-2-ylpentanenitrile	CAS 78370-13-5	<chem>CC(C)C(CCN(C)C)CCC1=CC=CC=C1)(C#N)C2=CC=CC=C2</chem>	Emopamil		Cerebrovascular ischaemia
1-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)pyrazole-3-carbonitrile		<chem>C5(=O)C(=O)C1=CC=C(C(=C1)C2=CC(=NN)C2C3=CC(C(=C3)F)C#N</chem>	FR-123826		Rheumatoid arthritis
N-(2-cyanoethyl)-2,2-bis(fluoromethyl)-6-nitrochromene-4-carbothioamide		<chem>C1=CC2=C(C(=C1[N+](=O)[O-])C(=CC(O2)(CF)CF)C(=S)NCCC#N</chem>	KC-399		Alopecia
N-cyano-N'-(2-phenylethyl)pyridine-3-carboximidamide	CAS 133300-00-2	<chem>C1=CC=C(C(=C1)CCN=C(C2=CN=CC=C2)NC#N</chem>	Ki-1769		Hypertension
N-[1'-[(2R)-6-cyano-1,2,3,4-tetrahydronaphthalen-2-yl]-4-oxospiro[3H-chromene-2,4'-piperidine]-6-yl]methanesulfonamide;hydrochloride	CAS 136078-58-5	<chem>CS(=O)C(=O)NC1=CC2=C(C(=C1)OC3(CCN(C(C3)[C@@H]4CCCC5=C(C4)C=CC(=C5)C#N)CC2=O.Cl</chem>	L-702958		Cardiac arrhythmias
(3S,3aR)-2-(3-chloro-4-cyanophenyl)-3-cyclopentyl-3,3a,4,5-tetrahydrobenzo[g]indazole-7-carboxylic acid	CAS 1023650-66-9	<chem>C1CCC(C1)[C@H]2[C@H]3CCCC4=C(C3=NN2C5=CC(=C(C(=C5)C#N)C)C=CC(=C4)C(=O)O</chem>	PF-03882845		Diabetic nephropathy
(Z)-3-(3,4-dimethoxyphenyl)-2-pyridin-3-ylprop-2-enenitrile	CAS 136831-48-6	<chem>COC1=C(C(=C(C(=C1)/C=C(C(=C(N)C2=CC=CC2)OC</chem>	RG-13022		
(2S,3S,5R)-3-[(E)-2-cyanoethenyl]-3-methyl-4,4,7-trioxo-4lambda6-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid	CAS 768335-49-5	<chem>C[C@@]1([C@@H](N2[C@H]3[C@H]([S1](=O)=O)CC2=O)C(=O)O)/C=C/C#N</chem>	Ro-48-1220		Bacterial infection
N-[4-[2-(6-cyano-3,4-dihydro-1H-isoquinolin-2-yl)ethyl]cyclohexyl]quinoline-4-carboxamide	CAS 215803-78-4	<chem>C1CC(CCC1CCN2CCC3=C(C2)C=CC(=C3)C#N)NC(=O)C4=CC=CC5=CC=CC=C45</chem>	SB-277011		Schizophrenia
2-(4-cyclohexylpiperazin-1-yl)-2-[4-(4-methoxyphenyl)sulfinylphenyl]acetoneitrile		<chem>COC1=CC=C(C(=C1)S(=O)C2=CC=C(C(=C2)C(C#N)N3CCN(CC3)C4CCCCC4</chem>	Sch-57790		Alzheimer disease
1-cyano-2-methyl-3-[4-(4-methyl-6-oxo-4,5-dihydro-1H-pyridazin-3-yl)phenyl]guanidine	CAS 115344-47-3	<chem>CC1CC(=O)NN=C1C2=CC=C(C(=C2)NC(=NC)NC#N</chem>	Signazodan		Allergy

IUPAC Name	CAS #	SMILES Notation	USAN Name / Trade Name	Representative Tx Class	Representative Disease
sodium;(4-chlorophenyl)sulfonyl-[(4-cyano-5-methyl-2-phenylpyrazol-3-yl)carbamoyl]azanide		<chem>CC1=NN(C(=C1C#N)NC(=O)[N-]S(=O)(=O)C2=CC=C(C(=C2)Cl)C3=CC=CC=C3.[Na+]</chem>	SM-19712		Hypertension
4-[3-(1H-imidazol-5-yl)propoxy]benzonitrile		<chem>C1=CC(=CC=C1C#N)OCCCC2=CN=CN2</chem>	UCL-1390	Analgesics	Pain; Epilepsy; Eating disorder
2-[4-[2-(benzhydrylamino)acetyl]piperazin-1-yl]-2-[2-(2-methylpyridin-3-yl)acetonitrile		<chem>CC1=C(C(=CC=N1)C(C#N)N2CCN(CC2)C(=O)CNC(C3=CC=CC=C3)C4=CC=CC=C4</chem>	UR-12460		Thrombosis
6,6-dimethyl-5-oxo-8-(2-oxopyridin-1-yl)naphthalene-2-carbonitrile	CAS 149455-36-7	<chem>CC1(C=C(C2=C(C(=O)C=C(C(=C2)C#N)N3C=CC=CC3=O)C</chem>	UR-8225		Asthma
4-[2-(7-chloro-2-phenylpyrazolo[4,3-c]quinolin-4-yl)ethylamino]benzonitrile	CAS 136917-40-3	<chem>C1=CC=C(C(=C1)N2C=C3C(=NC4=C(C3=N2)C=CC(=C4)Cl)CCNC5=CC=C(C(=C5)C#N</chem>	WY-48989		Rheumatoid arthritis

Administration Routes

[00130] The compound, i.e., a therapeutic agent of the invention which is a nitrile-containing JAK inhibitors as described herein which are either (i) nitrile group reversibly conjugated to a thiol group of a thiolated hydrogel, such as hyaluronic acid, to form a thioimide adduct or (ii) in the absence of a hydrogel, and a pharmaceutical composition comprising the same can be administered to a subject by any method known to a person skilled in the art. These methods include, but are not limited to, transdermally, intradermally, subcutaneously, intraarticularly, intramuscularly, orally, parenterally, intravascularly, paracancerally, transmucosally, intranasally, intravenously, sublingually, intraperitoneally, intraventricularly, intracranially, intravaginally, by inhalation, rectally, or intratumorally. These methods include any means in which the compound or the pharmaceutical composition comprising the same can be delivered to tissue (e.g., needle or catheter). Alternatively, a topical administration may be desired for application to dermal, ocular, or mucosal surfaces. Another method of administration is via aspiration or aerosol formulation.

[00131] It is also contemplated that local administration, such as by subcutaneous injection or intramuscular injection, of the hydrogels and compositions provided herein may be used for systemic delivery of the active agent contained in those hydrogels and compositions.

[00132] The compound or the pharmaceutical composition may be administered topically to body surfaces and are thus formulated in a form suitable for topical administration. Suitable topical formulations include gels, ointments, creams, lotions, drops and the like. For topical administrations, the compositions are prepared and applied as solutions, suspensions, or emulsions in a physiologically acceptable diluent with or without a pharmaceutical carrier.

[00133] Transdermal formulations may be prepared by incorporating the active agent in a thixotropic or gelatinous carrier such as a cellulosic medium, e.g., methyl cellulose or hydroxyethyl cellulose, with the resulting formulation then being packed in a transdermal device adapted to be secured in dermal contact with the skin of a wearer.

[00134] Transdermal administration may comprise application to the area to be treated, e.g., the skin affected by one of the disorders described herein, by transdermal injection or a transdermal delivery system comprising a microneedle coated with the therapeutic agent (i.e., the JAK inhibitor), a solid polymer matrix having the therapeutic agent (the JAK inhibitor) incorporated therein, dissolving polymer microneedles that dissolve after insertion into the skin and release the therapeutic agent; a transdermal patch comprising a reservoir storing the agent and a semi-

permeable membrane, a transdermal gel comprising the agent dissolved therein, a transdermal spray comprising the agent dissolved therein, or a metered dose transdermal spray comprising the agent dissolved therein.

[00135] In certain embodiments, the microneedles for transdermal delivery of a JAK inhibitor are hydrogel-forming microneedles, as described by Turner, J.G, et al., *Macromol. Biosci.* 2021, 21, 2000307. Such hydrogel-forming microneedles are made of a swellable polymer such as a cross-linked hydrogel, which swells upon water uptake when inserted into the skin and comprise the JAK inhibitor in the hydrogel. In another embodiment, the hydrogel-forming microneedles comprise a therapeutic-agent-loaded (i.e., JAK inhibitor loaded) reservoir attached to the tops of the microneedles. Such hydrogel-forming microneedles are minimally invasive, have a higher drug loading capacity and a tunable therapeutic-agent release rate, and are biocompatible.

[00136] In an embodiment, administration is effected by intradermal (into the dermis) or subcutaneous injection of a nitrile-containing JAK inhibitor in the absence of a thiolated polymer, i.e., without formation of a hydrogel, wherein the JAK inhibitor crystallizes or precipitates out of the injected composition and sustains its own release in the dermis. In some embodiment, administration is effected by transdermal injection.

[00137] In preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed. Thus, for liquid oral preparations, such as, suspensions, elixirs, and solutions, suitable carriers and additives include water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents, and the like. For solid oral preparations such as, powders, capsules, and tablets, suitable carriers and additives include starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like. For parenteral formulations, the carrier will usually comprise sterile water, though other ingredients may be included, such as ingredients that aid solubility or for preservation. Injectable solutions may also be prepared in which case appropriate stabilizing agents may be employed. In some applications, it may be advantageous to utilize the active agent in a “vectorized” form, such as by encapsulation of the active agent in a liposome or other encapsulant medium, or by fixation of the active agent, e.g., by covalent bonding, chelation, or associative coordination, on a suitable biomolecule, such as those selected from proteins, lipoproteins, glycoproteins, and polysaccharides.

[00138] Methods of treatment using formulations suitable for oral administration may be presented as discrete units such as capsules, cachets, tablets, or lozenges, each containing a

predetermined amount of the active ingredient. Optionally, a suspension in an aqueous liquor or a non-aqueous liquid may be employed, such as a syrup, an elixir, an emulsion, or a draught.

[00139] A tablet may be made by compression or molding, or wet granulation, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine, with the active compound being in a free-flowing form such as a powder or granules which optionally is mixed with, for example, a binder, disintegrant, lubricant, inert diluent, surface active agent, or discharging agent. Molded tablets comprised of a mixture of the powdered active compound with a suitable carrier may be made by molding in a suitable machine.

[00140] A syrup may be made by adding the active compound to a concentrated aqueous solution of a sugar, for example sucrose, to which may also be added any accessory ingredient(s). Such accessory ingredient(s) may include flavorings, suitable preservative, agents to retard crystallization of the sugar, and agents to increase the solubility of any other ingredient, such as a polyhydroxy alcohol, for example glycerol or sorbitol.

[00141] Formulations suitable for parenteral administration may comprise a sterile aqueous preparation of the active compound, which, in some embodiments, is isotonic with the blood of the recipient (e.g., physiological saline solution). Such formulations may include suspending agents and thickening agents and liposomes or other microparticulate systems which are designed to target the compound to blood components or one or more organs. The formulations may be presented in unit-dose or multi-dose form.

[00142] Parenteral administration may comprise any suitable form of systemic delivery. Administration may for example be intravenous, intra-arterial, intrathecal, intramuscular, subcutaneous, intramuscular, intra-abdominal (e.g., intraperitoneal), etc., and may be carried out by infusion pumps (external or implantable) or any other suitable means appropriate to the desired administration modality.

[00143] For administration to mammals, and particularly humans, it is expected that the physician will determine the actual dosage and duration of treatment, which will be most suitable for an individual and can vary with the age, weight, genetics and/or response of the particular individual. In some embodiments, the subject is a mammal (e.g., a human or non-human mammal). In some embodiments, the subject is a human.

[00144] The methods of the invention comprise administration of a compound of the invention, or a pharmaceutically acceptable salt thereof, at a therapeutically effective amount. The therapeutically effective amount may include various dosages.

[00145] A dosage unit of the compounds used in the present invention may comprise a single compound or mixtures thereof with additional therapeutic agents. A “dose” or “dosage unit” or “unit dosage” of a compound of the invention as measured in milligrams refers to the milligrams of the compound of the invention present in a composition, regardless of the form of the composition.

[00146] In some embodiments, a dosage unit can be prepared for oral dosage forms, such as tablets, capsules, pills, powders, liquid suspensions, and granules.

[00147] In some embodiments, a compound of the invention is administered at a dosage of 1-3000 mg per day. In some embodiments, a compound of the invention as described herein is administered at a dosage of 1-1000 mg per day. In some embodiments, a compound of the invention as described herein is administered at a dosage of 1-500 mg per day. In some embodiments, a compound of the invention as described herein is administered at a dosage of 10-500 mg per day. In some embodiments, a compound of the invention as described herein is administered at a dosage of 25-500 mg per day. In some embodiments, a compound of the invention as described herein is administered at a dosage of 50-500 mg per day. In some embodiments, a compound of the invention as described herein is administered at a dosage of 5-250 mg per day. In some embodiments, a compound of the invention as described herein is administered at a dosage of 10-250 mg per day. In some embodiments, a compound of the invention as described herein is administered at a dosage of 20-250 mg per day. In some embodiments, a compound of the invention as described herein is administered at a dosage of 25-250 mg per day. In some embodiments, a compound of the invention as described herein is administered at a dosage of 25-200 mg per day. In some embodiments, a compound of the invention as described herein is administered at a dosage of 25-150 mg per day. In some embodiments, a compound of the invention as described herein is administered at a dosage of 25-125 mg per day. In some embodiments, a compound of the invention as described herein is administered at a dosage of 25-100 mg per day.

[00148] In other embodiments, a compound of the invention is administered at a dose of 1-10 mg per day, 3-26 mg per day, 3-60 mg per day, 3-16 mg per day, 3-30 mg per day, 10-26 mg per

day, 10-100 mg per day, 15-60 mg per day, 15-100 mg per day, 25-100 mg per day, 50-100 mg per day, 50-200 mg per day, 100-200 mg per day, 100-250 mg per day, 125-300 mg per day, 20-50 mg per day, 5-50 mg per day, 200-500 mg per day, 125-500 mg per day, 500-1000 mg per day, 200-1000 mg per day, 1000-2000 mg per day, 1000-3000 mg per day, 125-3000 mg per day, 2000-3000 mg per day, 300-1500 mg per day or 100-1000 mg per day.

[00149] The methods may comprise administering a compound at various dosages. For example, the compound may be administered per day at a dosage of 3 mg, 10 mg, 30 mg, 40 mg, 50 mg, 80 mg, 100 mg, 120 mg, 125 mg, 200 mg, 250 mg, 300 mg, 450 mg, 500 mg, 600 mg, 900 mg, 1000 mg, 1500 mg, 2000 mg, 2500 mg or 3000 mg.

[00150] Alternatively, the compound may be administered at a dosage of 0.1 mg/kg/day. The compound may be administered at a dosage between 0.2 to 30 mg/kg/day, or 0.2 mg/kg/day, 0.3 mg/kg/day, 1 mg/kg/day, 3 mg/kg/day, 5 mg/kg/day, 10 mg/kg/day, 20 mg/kg/day, 30 mg/kg/day, 50 mg/kg/day or 100 mg/kg/day.

[00151] In some embodiments, the compound of the invention is prepared for once daily administration. In another embodiment, the compound of the invention is prepared for more than once daily administration, for example, twice daily, three times daily, four times daily, etc. In some embodiments, the compound or the pharmaceutical composition of the invention is administered in the form of a capsule, a tablet, or a liquid suspension. In other embodiments, the compound or the pharmaceutical composition of the invention is administered in an oral dosage unit form.

[00152] The methods of treatment of the present invention can additionally include administering to the subject one or more additional therapeutic agents for a combination therapy. Such additional therapeutic agents may be administered, by a route and in an amount commonly used therefore, simultaneously or sequentially with a compound or composition of the present invention.

[00153] The term “combination therapy” means the administration of two or more therapeutic agents to treat a cancer described in the present invention. Such administration encompasses co-administration of these therapeutic agents in a substantially simultaneous manner, such as in a single capsule having a fixed ratio of active ingredients or in multiple, separate capsules for each active ingredient. In addition, such administration also encompasses use of each type of therapeutic agent in a sequential manner. In either case, the treatment regimen will provide beneficial effects of the drug combination in treating the disorders described herein.

[00154] The following examples are presented in order to more fully illustrate particular embodiments of the invention. They should in no way be construed, however, as limiting the broad scope of the invention.

EXAMPLES

Example 1

Thioimide Bond Formation and Hydrogel Formation and Baricitinib Release

Methods

[00155] *Materials:* Thiolated hyaluronic acid was purchased from a supplier (HAWorks LLC, Bedminster, NJ), synthesized as previously described through an amidation reaction at the carboxyl of hyaluronic acid with 30% or 50% degree of modification of disaccharides. Polymers were stored under vacuum in a desiccator at room temperature. All other chemical reagents were purchased from Sigma-Aldrich (St. Louis, MO) and stored according to manufacturer's instructions unless otherwise indicated. All experiments were performed in triplicate unless otherwise indicated.

[00156] *Liquid chromatography-mass spectrometry (LCMS):* Samples were prepared by mixing 500 μ M of baricitinib with cysteamine, L-cysteine, or levamisole in distilled water. Samples were filtered through a 0.2 μ m syringe filter before use. Nominal mass accuracy LCMS data were obtained using a Waters Acquity ultra-performance liquid chromatography (UPLC) system equipped with a Waters TUV detector (254 nm) and a Waters SQD single quadrupole mass analyzer with electrospray ionization. LC gradient 500 μ L/min: 30 seconds hold 95:5 (water:acetonitrile 0.1% v/v formic acid), 2 minute gradient to 5:95, and 30 seconds hold using the Acquity UPLC high strength silica C18, 1.7 μ m, 2.1 $\times$ 50 mm column.

[00157] *Nuclear magnetic resonance (NMR):* Samples were prepared by mixing 1 mg of baricitinib or thiolated hyaluronic acid in 400 μ L D₂O. Samples were centrifuged to remove insoluble fractions prior to use. ¹H and ¹³C spectra were recorded at 500.20 MHz and 125.78 MHz on a Bruker AVIII 500 MHz NMR spectrometer equipped with a Bruker 5mm DCH Helium Cryoprobe. ¹H spectra of hyaluronic acid and baricitinib-hyaluronic acid were obtained in 32 K data points over 8 kHz spectral width using the water suppression pulse program, noesygppr1d, to suppress the water peak. ¹H spectrum of baricitinib was obtained in 64K data points over 10 kHz spectral width using a 30° flip-angle pulse. ¹³C spectra were obtained in 64K data points over 29.761 kHz spectral width using the pulse program, zgpgsezr, a z-restored spin-echo ¹³C pulse

sequence with power-gated ^1H decoupling. A 2s relaxation delay was used between acquisitions. The free induction decays were processed using exponential window function (line-broadening 0.3 Hz for ^1H and 1 Hz for ^{13}C) before Fourier transformation.

[00158] *Thiol quantification assays:* The Free Thiol Assay Kit (ab112158, Abcam, Waltham, MA) was used for all thiol quantification measurements. Solutions of thiolated hyaluronic acid in distilled water were mixed with a solution of baricitinib in 1:1 dimethyl sulfoxide (DMSO) to distilled water to the indicated final concentrations in 100 μL total volume including 50 μL of assay reaction mixture. Solutions prior to addition of reaction mixture were gently vortexed and products were allowed to form for 20 minutes. After mixing, 50 μL of product was transferred to a black walled 96-well plate and products were incubated with 50 μL of the assay reaction mixture according to manufacturer's protocols. Analyses were performed using the Biotek Synergy H1 microplate reader (ex/em: 490/520 nm).

[00159] *Hydrogel formation and in vitro release:* Hydrogels were formed by evenly mixing stock solutions of thiolated hyaluronic acid in phosphate-buffered saline (PBS) with stock solutions of baricitinib in DMSO to the final desired weight percent concentration (w/v) and allowed to mix and crosslink for 24 hours. After 24 hours, hydrogels were briefly centrifuged and DMSO was removed by briefly washing hydrogels in PBS (3 x 5 minutes). For release studies, 100 μL of hydrogel was incubated in 200 μL of PBS at room temperature and releasates were collected and replaced with fresh PBS at days 2, 4, 8, 12, 16, 20, 28, and 42. At the final timepoint, hydrogels were manually disrupted. Absorbances were measured at 300 nm the Biotek Synergy H1 microplate reader and baricitinib concentrations were determined from a standard curve and summed to obtain cumulative release. For *in vivo* studies, hydrogels were transferred to a 27G x $\frac{1}{2}$ " insulin syringe and subsequently sterilized under ultraviolet irradiation.

[00160] *Shear oscillatory rheometry:* Hydrogels were formed as described and deposited on the bottom plate of an HR 20 (TA Instruments, New Castle, DE) rheometer immediately after mixing or after 24 hours of gelation. The rheometer was fitted with a 20 mm diameter stainless steel parallel plate geometry and placed at a 350 μm gap. Oscillatory rheological time sweeps (1% strain, 10 Hz) were performed to obtain the average storage (G') and loss (G'') moduli, and oscillatory frequency sweeps (1% strain, 0.1 Hz to 100 Hz) were obtained to characterize dynamic viscoelastic properties.

RESULTS AND DISCUSSION

Thioimide Bond Formation

[00161] Previous studies suggest that the nitrile on baricitinib is reactive to thiols and able to form reversible thioimides through a Pinner-like mechanism (**Figure 1A**). To confirm that baricitinib has a reactive nitrile, cysteamine was mixed with baricitinib for one hour, in concordance of previous reports that the thioimide forms efficiently at physiologic pH within this time. Using LC-MS, resolution of baricitinib (373 Da), cysteamine (77 Da), and the thioimide adduct of cysteamine and baricitinib (449 Da) eluting with retention times of 0.3, 1.5 and 1.4 seconds, respectively at equimolar concentrations (**Figure 1B**) was demonstrated. A product form with baricitinib and L-cysteine (122 Da), yielding an adduct (494 Da) was similarly observed. (**Figure 9**). It also was shown that levamisole (205 Da), a thiazole, does not react with baricitinib to form a product, suggesting that the reactivity with baricitinib is specific to thiol-containing molecules. In the presence of primary amines such as in cysteamine or cysteine, the thioimide may further be stabilized to form a thiazoline ring; however, the difference in molecular weight is too small between the products to differentiate thioimide from thiazoline. Importantly, a tetrahedral bisadduct that was previously reported to occur with low frequency was not observed; this would appear as a product with molecular weight that combines two cysteamines or cysteines and one baricitinib.

[00162] Having shown the specificity of baricitinib with thiols, a hydrogel was designed from thiolated hyaluronic acid that directly binds to baricitinib, which also forms disulfide bonds with itself for gel formation. Specifically, thiolated hyaluronic acid formed from the amidation reaction between the carboxyl of hyaluronic acid to cysteamine with a degree of thiol modification of either 30% or 50%, and a molecular weight of approximately 100 kDa was used (**Figure 2A**). The thiols function to form thioimides with baricitinib as well as disulfide crosslinks between polymer chains to form hydrogels (**Figure 2B**).

[00163] To test that thiolated hyaluronic acid reacts with baricitinib, a commercially available and sensitive fluorogenic substrate which creates a fluorescent product to detect thiols in solution was used. This reagent was validated against a standard dose of glutathione (GSH), while also confirming that a 10 μ M concentration of GSH exhibits an equivalent signal to 10 μ M concentration of thiolated hyaluronic acid with 30% modification, consistent with approximately 1 thiol per 3.33 disaccharide repeats (**Figure 3A**). Next, baricitinib was titrated into a solution of

25 μ M thiolated hyaluronic acid. Increasing concentrations of baricitinib consumed thiols and decreased detection; at equimolar baricitinib nitrile to thiol concentrations, only ~27% of thiols were consumed on hyaluronic acid (**Figure 3B**). However, increasing concentrations of baricitinib yielded near complete consumption (~90%) of free thiols at a molar excess of nitrile of 16 to 1.

[00164] By assuming equilibrium after one hour, K_{eq} was calculated. In keeping with the dynamic nature of the thioimide bond, the K_{eq} was highest at a nitrile to thiol ratio of 4 to 1 (**Figure 3C**). These values likely overestimate thiol consumption by baricitinib given their ability to also form disulfides. Importantly, consuming thiols on hyaluronic acid suggest that thioimides are formed. Another reactive moiety on hyaluronic acid is the primary alcohol, which may also form imides with baricitinib, although this reaction is typically base-catalyzed.

[00165] ^{13}C NMR was used to confirm that the formed products between baricitinib and thiolated hyaluronic acid were thioimides. ^{13}C NMR revealed distinct peaks for both baricitinib and thiolated hyaluronic acid that are consistent with predicted and expected spectra. The ^{13}C NMR spectra of the combined product demonstrated a distinct peak at 170 ppm that was not present in the spectra of the reactants (**Figure 4A**). This is consistent with prior reports for thioimide carbons as well as the predicted peak from the NMR predict tool at nmrd.org (Universidad del Valle). Thioimide product formation using ^1H NMR. Using ^1H NMR was further characterized, and it was shown that baricitinib has five distinct aromatic protons with peaks between 7-9 ppm. When baricitinib was combined with thiolated hyaluronic acid, the product spectra had a new set of distinct aromatic protons with downfield shifts compared to baricitinib alone, suggesting a second modified baricitinib species was present (**Figure 4B**). The downfield shift most likely represents a deshielding effect from conjugation of the hyaluronic acid polymer to baricitinib through the thioimide. In support of this, four of the five aromatic protons of baricitinib were shifted; the peak at ~7.7 ppm corresponding to the hydrogen furthest from the thioimide was not affected, which suggests that the deshielding effect may be related to atomic proximity. Aromatic protons corresponding to the ^1H NMR signals are highlighted (**Figure 10**).

Hydrogel Formation and Baricitinib Release

[00166] Hydrogels were assembled by mixing baricitinib in solution with thiolated hyaluronic acid (**Figure 5A**). At 2 wt%, shear oscillatory rheometry was used to confirm formation of a viscoelastic hydrogel where the storage modulus (G') was higher than the loss modulus (G'') (**Figure 5B**). Disulfide crosslinks formed over at least 24 hours, reaching a final G' of ~100 Pa

and G'' of ~10 Pa at this timepoint. Moduli were frequency dependent, indicating the dynamic and viscoelastic nature of the material (**Figure 11**). No significant differences in moduli were observed between hydrogels without and with baricitinib (**Figure 5C**).

[00167] To measure baricitinib release, its absorption properties were determined in the ultraviolet (UV) range, where baricitinib absorbs due to its aromatic ring. It was determined that baricitinib absorbs most in the ultraviolet B range (280-320 nm), with absorbances increasing linearly with concentration (**Figure 6A**), consistent with prior methods for measuring baricitinib in solution. Next, baricitinib hydrogels were assembled with varying baricitinib loading (0.2 mg/mL, 2 mg/mL, corresponding to 40-fold or 4-fold thiol excess), hydrogel concentration (%w/v), and thiol modification (30% or 50%). Baricitinib hydrogels were incubated in PBS at room temperature with releasates collected and replaced regularly over six weeks. At six weeks, hydrogels had nearly fully eroded and were manually disrupted in PBS. Baricitinib in releasates was measured by absorbance at 300 nm on a standard curve. Cumulative release demonstrates similar release profiles with 0.2 mg/mL of baricitinib included (**Figure 6B**). In these formulations, approximately 40% was released by one week, 50% by two weeks, and 60% by three weeks. By four weeks, differences in release were observed; 90% of baricitinib was released in 2 wt% 30% mod hydrogels, while ~70% was released in 5 wt% 50% mod hydrogels. In this instance, the latter formulation has four-times the concentration of thiols in solution. This sustains baricitinib release through thioimide formation and by increasing disulfide crosslinking, thereby decreasing network mesh size. At 2 mg/mL baricitinib, there is a larger concentration gradient due to the higher amount of baricitinib loaded. Consistent with this, release was much faster with up to ~70% released by one week, 80% by two weeks, and 90% by four weeks. Significant differences in release were observed before two weeks, where there was faster release observed in formulations assembled at 2 wt% compared to formulations assembled at 5 wt%, consistent with the role of thiols in forming thioimides and disulfides to slow release. At 2 mg/mL, baricitinib also began to precipitate over time within the hydrogel, which may also partially contribute to its sustained release. Using the data above, formulations of baricitinib were selected at 2 wt% and 30% thiol modification for biologic activity – release profiles of relevant formulations are plotted (**Figure 6C**). Higher concentrations of hydrogel could not be injected through a 27G syringe while higher thiol modifications did not change release profiles.

Example 2

In Vitro Activity on JAK-STAT Signaling

MATERIALS

[00168] *HEK 293 culture*: Cells (BPS Bioscience, San Diego, CA) were thawed in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% fetal bovine serum (FBS) and 1% penicillin/streptomycin. In subsequent studies, media was supplemented with 400 µg/ml of geneticin. Prior to use, cells were split into 96 well black-walled, clear bottom plates (30,0000/well) in media without geneticin 24 hours prior.

[00169] *Luciferase Assays*: For the interferon (IFNα) titration, varying concentrations from 10⁻¹ to 10⁴ U/mL of IFNα at 100 µL total volume were incubated for 6 hours. For the baricitinib condition, concentrations of 10⁻³ to 10³ µg/mL baricitinib were added to wells and incubated for 1 hour. IFNα was added to each well at a final concentration of 100 U/mL at 100 µL total per well and incubated for 6 hours. For the releasate assay, releasate volumes of 5 µL or 20 µL were added to cells in triplicate from each timepoint and incubated for 1 hour. IFNα volume was added to a total of 100 µL and 100 U/mL and then incubated for 6 hours. After the 6-hour incubation of IFNα, luciferase activity was quantified for each of the three tests using the ONE-Step™ Luciferase Assay System (BPS Bioscience, San Diego, CA) with 100 µL master mix was added for a total volume of 200 µL. The 96 well plate was placed on an orbital shaker for 15 minutes covered from light before taking fluorescence measurements using the Biotek Synergy H1 microplate reader.

[00170] *HaCAT culture and proliferation assay*: HaCaT cells were cultured in calcium-free DMEM with 10% FBS, and 1% penicillin/streptomycin as previously described. Cells were split into 24-well plates 24 hours at 100,000/well. After 24 hours, hydrogels were formed and 50 µL was transferred to a polycarbonate membrane transwell insert with 6.5 mm diameter, 0.1 µm pore size (Corning, Corning, NY) and coincubated with cells for the indicated times. The CellTiter 96® AQueous One Solution Cell Proliferation MTS Assay (Promega, Madison, WI) was utilized according to manufacturer's protocols after incubation with one hour. Absorbance was measured at 490 nm using the Biotek Synergy H1 microplate reader.

RESULTS AND DISCUSSION

In vitro activity on JAK-STAT signaling

[00171] To test the effect of released baricitinib *in vitro*, a recombinant HEK293 cell line which contains the firefly luciferase gene stable integrated and under the control of interferon-stimulated

response element was used. In this line, interferon- α (IFN α) binding and activation of JAK1 leads to luciferase expression, enabling rapid and high-through testing of baricitinib release from hydrogels. This approach was validated by measuring luminescence in response to IFN α stimulation, showing a dose-dependent increase and EC⁵⁰ of 10.4 U/mL (**Figure 7A**). After stimulating cells with 100 U/mL IFN α , it was shown that baricitinib decreased luminescence signal with maximal inhibition occurring at 20 μ g/mL (**Figure 7B**). For *in vitro* measurements, hydrogels were assembled at 0.2 or 2 mg/mL baricitinib at 2 wt% and 30% thiol modification (also referred to herein as “mod”). Releasates were collected at indicated timepoints and added to HEK293 culture followed by IFN α stimulation. To validate differences between baricitinib loading, 5 μ L or 20 μ L of releasate was added to culture from either 0.2 mg/mL or 2 mg/mL baricitinib hydrogels at 2 wt% or 30% mod (**Figure 7D**). With 5 μ L releasate added from the 0.2 mg/mL formulations, inhibition from releasates occurred early, and activity was diminished after three weeks. In contrast, 5 μ L of releasates from the 2 mg/mL formulation demonstrated sustained inhibition at all timepoints. At 20 μ L of releasate added from either formulation, near complete inhibition was attained at every timepoint tested, which could overcome the difference in baricitinib loading. Together, the data suggested that 0.2 mg/mL baricitinib was sufficient in achieving sustained release and activity in inhibiting JAK-STAT signaling in response to IFN α *in vitro*.

Example 3

In Vivo Mouse Model of Psoriasis

METHODS

[00172] *In vivo studies and tissue processing:* C57BL/6 female mice were used for imiquimod assays. After chemical epilation, hydrogels were injected into four sites intradermally into dorsal mouse skin. Imiquimod 5% cream was subsequently applied daily for five days before sacrifice at seven days. Standard histologic protocols using 4% paraformaldehyde and paraffin-embedding were utilized. Investigators were blinded through the histology process and imaging process. Images were analyzed using a Leica Microsystems DM6 B microscope equipped with a DFC9000 Camera or Keyence imaging system. At least two injection sites and four sections were stained with hematoxylin and eosin per mouse. Quantification of epidermal thickness was performed on stitched 10x slides of 6-10 mm skin sections by selecting the entire region-of-interest (ROI) of the epidermis using the Wand Tool on FIJI on Legacy Mode. The smooth feature was utilized to ensure the ROI appropriate captured the entire region between the granular layer and basal layer. The ROI

area was measured and subsequently divided by the length of epidermis. Average epidermal thickness was obtained for two sections per mouse.

RESULTS AND DISCUSSION

Hydrogel injections *in vivo* in a mouse model of psoriasis

[00173] To test the baricitinib hydrogel prepared as described above, for activity *in vivo*, a mouse model was utilized in which imiquimod, a ligand for Toll-like receptors 7 and 8, is applied daily to dorsal mouse skin to induce a psoriasis-like dermatitis characterized by erythema, scaling, and thickening of the epidermis from JAK-STAT signaling. Baricitinib has previously been shown to be effective in this mouse model of psoriasis as well as in human psoriasis. In this model, baricitinib hydrogel or PBS, hydrogel, and baricitinib alone controls were injected (4 x 25 μ L) intradermally into dorsal mouse skin followed by application of 5% imiquimod cream daily for five days (**Figure 8A**). Dorsal skin with erythema and scale was present by five days with improvement in the baricitinib hydrogel treatment groups (**Figure 8B**). Scaling was not observed in any of the baricitinib hydrogel groups. At seven days, mice were sacrificed, and tissue was examined through hematoxylin and eosin (H&E) staining (**Figure 8C**). In keeping with the psoriasis phenotype, imiquimod treated groups exhibited thickened, acanthotic epidermis with parakeratosis, retention of nuclei in the stratum corneum. Epidermal thickness from the granular to basal layer was measured in ImageJ by dividing the entire epidermal area by the length (**Figure 12**) In response to imiquimod treatment, epidermal thickness increased nearly five-fold (**Figure 8D**). Thickness was significantly higher in PBS, hydrogel, and baricitinib treated groups but was not statistically different from the baricitinib hydrogel, suggesting a treatment effect from baricitinib hydrogel. Representative H&E of skin demonstrates consistency in these trends across the entire epidermis (**Figure 13**). Weight loss of up to 15% was observed in all imiquimod groups; baricitinib hydrogel-treated mice exhibited the least weight loss but this effect was not significant (**Figures 14A-14B**). The data indicate that the hydrogel improves baricitinib activity likely through an effect on retention and ameliorates the epidermal thickening seen in psoriasis; of note, baricitinib alone injected had no effect which indicate that systemic absorption is not a mechanism for therapeutic response. The hydrogel was not observed in the dermis in H&E sections, consistent with prior reports that soft, hyaluronic acid-based hydrogels are lost during the processing steps. However, few sections demonstrate hydrogel in the subcutaneous space which may indicate migration over time or inadvertent injection (**Figure 15**).

Conclusion

[00174] An injectable hydrogel that sustains the release of baricitinib through reversible thioimide chemistry was engineered. It was shown that thioimides form between baricitinib and thiolated hyaluronic acid. In hydrogels, release of baricitinib was sustained from a hydrogel over six weeks that was subsequently active in inhibiting JAK-STAT signaling *in vitro* and *in vivo* in a mouse model of psoriasis. These data support the use of hydrogels for delivery of small molecules in the skin and this platform can be further explored with other JAK inhibitors containing nitrile groups in other inflammatory skin disorders. Further studies are needed to understand the pharmacokinetics of the hydrogel and duration of efficacy *in vivo* before pursuit of safety and efficacy in large animal models.

[00175] *Statistics:* All data in **Examples 1 to 3** were reported as mean $\pm$ standard deviation. Comparisons were performed between groups using Student's t-test or one-way ANOVA with post hoc testing. Bonferroni correction was used to account for multiple comparisons with $\alpha=0.05$. All statistical analyses were performed in Graphpad Prism 9.

Example 4

In Vivo Mouse Model of Alopecia Areata

[00176] Baricitinib hydrogels prepared as described above were tested *in vivo*, using a mouse model for alopecia areata, as described in McElwee *et al.* (1998) *J Invest Dermatol* **111**:797-803. Briefly, in this model, alopecia develops in ~10-20% of aging mice after six months which are subsequently be transferred to younger C3H/HeJ mice through skin grafts, reliably producing alopecia areata in up to 95-100% of mice six to ten weeks after grafting. Baricitinib (Jabbari *et al.* (2015) *EBioMedicine* **2**:351-355) and other JAK inhibitors (Xing *et al.* (2014) *Nat Med* **20**:1043-49) have been validated in these models, where they are highly effective in preventing and treating alopecia arcata. Following grafting, baricitinib hydrogels or controls were injected intradermally ($3 \times 200 \mu\text{L}$) and ventral hair loss was followed through serial images over time. Hair loss index was quantified based on ventral surface area. Animals treated with controls proceeded to lose nearly all their ventral hair, while animals treated with baricitinib hydrogels retained significantly more hair. Differences in hair loss index between baricitinib hydrogels and controls were observed in hair loss as early as 7 days and were significant as far as 93 days.

Example 5

Thioimide Bond Formation Between Thiolated Hyaluronic Acid and the aromatic nitrile of CHIR 99021

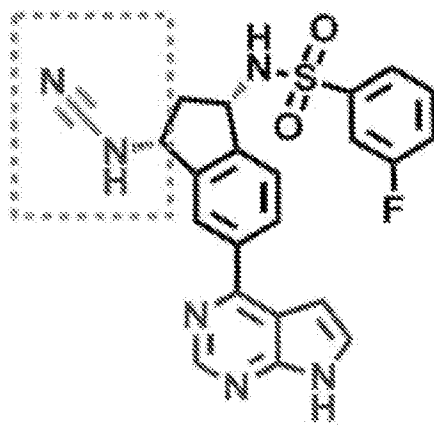
[00177] In this Example, ^1H NMR is used to show the reaction between an aromatic nitrile containing molecule, CHIR 99021 (a Wnt signaling pathway agonist), and thiolated hyaluronic acid. The nitrile group is expected to react with the thiol group in a reversible manner to form a thioimide. A 20 mM solution of CHIR 99021 dissolved in ethanol was combined with thiolated hyaluronic acid in D_2O . The solution was left to sit overnight and filtered for ^1H NMR analysis. As shown in **Figure 16**, the aromatic nitrile in CHIR 99021 reacts in a reversible manner with the thiolated hyaluronic acid to form a thioimide. In particular, the ^1H NMR data shows the formation of a new set of peaks in the aromatic region downfield from those in CHIR99021 alone. Thiolated hyaluronic acid alone shows no peaks in this region.

[00178] All references, including publications, patent applications, and patents, cited herein are hereby incorporated by reference in their entirety herein.

[00179] While certain features of the invention have been illustrated and described herein with some degree of particularity, it is understood that this description has been given only by way of example and that numerous changes in the details of construction, fabrication, and use, including the combination and arrangement of parts may be made without departing from the spirit and scope of the invention, and that many modifications, substitutions, changes, and equivalents will now occur to those of ordinary skill in the art. It is, therefore, to be understood that the appended claims are intended to cover all such modifications and changes as fall within the true spirit of the invention.

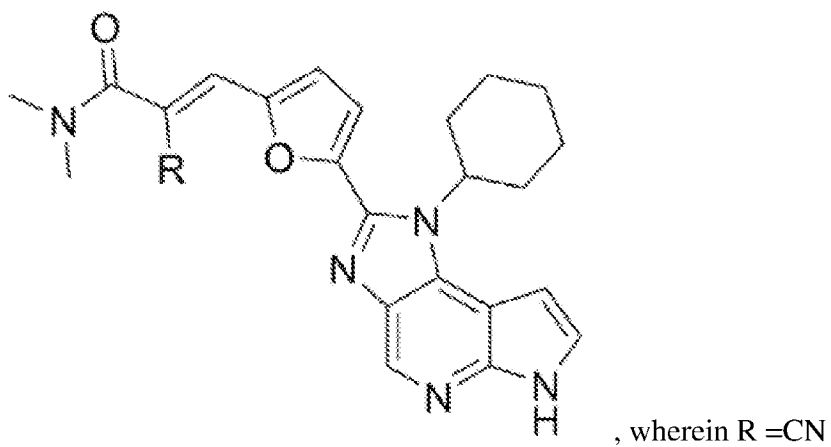
WHAT IS CLAIMED IS:

1. A sustained delivery JAK inhibitor hydrogel for treatment of an inflammatory disorder, an autoimmune disease, an autoimmune and inflammatory hair loss, and/or a non-inflammatory disorder hair loss, the sustained delivery JAK inhibitor hydrogel comprising a JAK inhibitor having a nitrile group reversibly conjugated to a thiol group of a thiolated polymer to form a thioimide adduct.
2. The sustained delivery JAK inhibitor hydrogel of claim 1, wherein the thiolated polymer is a thiolated hyaluronic acid, a thiolated chitosan, a thiolated cyclodextrin, a thiolated poly(ethylene glycol), a thiolated polyvinyl alcohol, a thiolated polyacrylamide, a thiolated polyethylene oxide, a thiolated polymethacrylate, a thiolated dextran, a thiolated alginate, a thiolated cellulose, a thiolated gelatin, a thiolated collagen, a thiolated silk, a thiolated keratin or a thiolated elastin.
3. The sustained delivery JAK inhibitor hydrogel of claim 1, wherein the thiolated polymer is a thiolated hyaluronic acid.
4. The sustained delivery JAK inhibitor hydrogel of claim 3, wherein the thiolated hyaluronic acid has an average molecular weight of from 1 KD to 1,000,000 KD when the hyaluronic acid is polydispersed in solution.
5. The sustained delivery JAK inhibitor hydrogel of claim 4, wherein the thiolated hyaluronic acid has an average molecular weight of from 10,000 KD to 1,000,000 KD when the hyaluronic acid is polydispersed in solution.
6. The sustained delivery JAK inhibitor hydrogel of claim 5, wherein the thiolated hyaluronic acid has an average molecular weight of 100,000 KD when the hyaluronic acid is polydispersed in solution.
7. The sustained delivery JAK inhibitor hydrogel of claim 1, wherein the nitrile-containing JAK inhibitor is baricitinib, delgocitinib, ruxolitinib, deuruxolitinib, tofacitinib, momelotinib, gusacitinib, itacitinib, izencitinib, lorpucitinib, povorcitinib or a nitrile-containing metabolite thereof.
8. The sustained delivery JAK inhibitor hydrogel of claim 1, wherein the nitrile-containing JAK inhibitor is a compound having chemical structure (A):

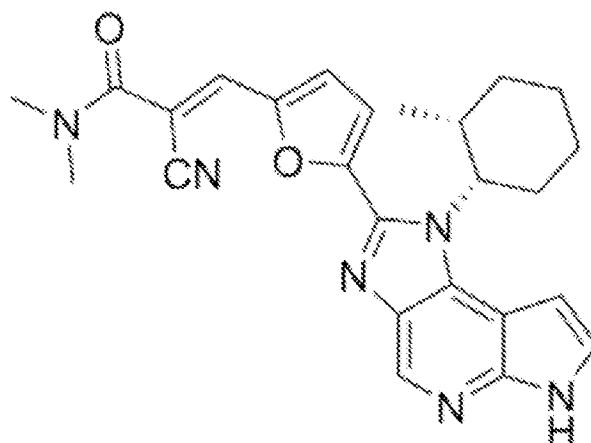


(A)

9. The sustained delivery JAK inhibitor hydrogel of claim 1, wherein the nitrile-containing JAK inhibitor is a compound having structure (I) or (II):



(I)



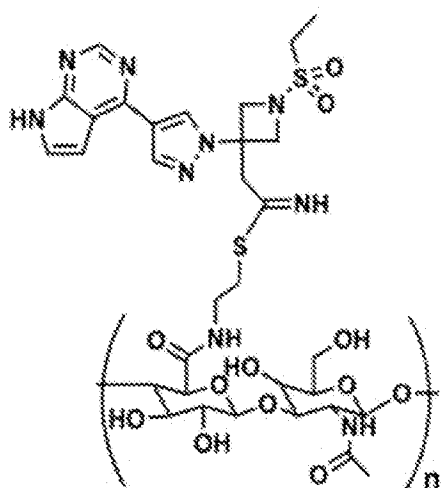
(II)

10. The sustained delivery JAK inhibitor hydrogel of claim 1 formulated for local administration.
11. The sustained delivery JAK inhibitor hydrogel of claim 10, wherein the local administration comprises intradermal injection, intramuscular injection, subcutaneous injection or intra-articular injection.
12. The sustained delivery JAK inhibitor hydrogel of claim 10, wherein the local administration comprises transdermal administration.
13. The sustained delivery JAK inhibitor hydrogel of claim 12, wherein the transdermal administration comprises transdermal delivery via microneedles coated with the JAK inhibitor, a solid polymer matrix having the JAK inhibitor incorporated therein, dissolving polymer microneedles having the JAK inhibitor incorporated therein, hydrogel-forming microneedles comprising the JAK inhibitor in the hydrogel, or a transdermal patch.
14. The sustained delivery JAK inhibitor hydrogel of claim 1, wherein the inflammatory disorder is an inflammatory skin disorder.
15. The sustained delivery JAK inhibitor hydrogel of claim 14, wherein the inflammatory skin disorder is atopic dermatitis, cicatricial alopecia, central centrifugal cicatricial alopecia, hidradenitis suppurativa, lichen planopilaris, frontal fibrosing alopecia, alopecia areata, lichen planus, mucosal lichen planus, psoriasis, pemphigus or vitiligo.

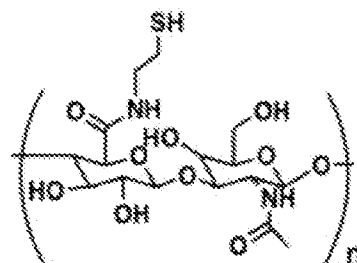
16. The sustained delivery JAK inhibitor hydrogel of claim 1, wherein the autoimmune disease is alopecia arcata, persistent patchy alopecia arcata, alopecia totalis, alopecia universalis, ophiasis alopecia, alopecia barbae, rheumatoid arthritis, psoriatic arthritis or reactive arthritis.
17. The sustained delivery JAK inhibitor hydrogel of claim 1, wherein the autoimmune and inflammatory hair loss is alopecia areata and the non-inflammatory disorder hair loss is male or female androgenetic alopecia or telogen effluvium.
18. A sustained delivery baricitinib hydrogel comprising baricitinib having a nitrile group reversibly conjugated to a thiol group of a thiolated polymer to form a thioimide adduct for treatment of an inflammatory disorder, an autoimmune disease, an autoimmune and inflammatory hair loss, and/or a non-inflammatory disorder hair loss.
19. The sustained delivery baricitinib hydrogel of claim 18, wherein the thiolated polymer is a thiolated hyaluronic acid, a thiolated chitosan, a thiolated cyclodextrin, a thiolated poly(ethylene glycol), a thiolated polyvinyl alcohol, a thiolated polyacrylamide, a thiolated polyethylene oxide, a thiolated polymethacrylate, a thiolated dextran, a thiolated alginate, a thiolated cellulose, a thiolated gelatin, a thiolated collagen, a thiolated silk, a thiolated keratin or a thiolated elastin.
20. The sustained delivery baricitinib hydrogel of claim 18, wherein the thiolated polymer is a thiolated hyaluronic acid.
21. The sustained delivery baricitinib hydrogel of claim 20, wherein the thiolated hyaluronic acid has an average molecular weight of from 1 KD to 1,000,000 KD when the hyaluronic acid is polydispersed in solution.
22. The sustained delivery baricitinib hydrogel of claim 19, wherein the thiolated hyaluronic acid has an average molecular weight of from 10,000 KD to 1,000,000 KD when the hyaluronic acid is polydispersed in solution.
23. The sustained delivery baricitinib hydrogel of claim 22, wherein the thiolated hyaluronic acid has an average molecular weight of 100,000 KD when the hyaluronic acid is polydispersed in solution.
24. The sustained delivery baricitinib hydrogel of claim 18 formulated for local administration, wherein the local administration comprises intradermal injection, intramuscular injection, subcutaneous injection or intra-articular injection.

- 25.** The sustained delivery baricitinib hydrogel of claim 18 formulated for local administration, wherein the local administration comprises transdermal injection.
- 26.** The sustained delivery baricitinib hydrogel of claim 18, wherein the inflammatory disorder is an inflammatory skin disorder.
- 27.** The sustained delivery baricitinib hydrogel of claim 26, wherein the inflammatory skin disorder is atopic dermatitis, cicatricial alopecia, central centrifugal cicatricial alopecia, hidradenitis suppurativa, lichen planopilaris, frontal fibrosing alopecia, alopecia areata, lichen planus, mucosal lichen planus, psoriasis, pemphigus or vitiligo.
- 28.** The sustained delivery baricitinib hydrogel of claim 18, wherein the autoimmune disease is alopecia areata, persistent patchy alopecia areata, alopecia totalis, alopecia universalis, ophiasis alopecia, alopecia barbae, rheumatoid arthritis, psoriatic arthritis or reactive arthritis.
- 29.** The sustained delivery baricitinib hydrogel of claim 18, wherein the autoimmune and inflammatory hair loss is alopecia areata and the non-inflammatory disorder hair loss is male or female androgenetic alopecia or telogen effluvium.

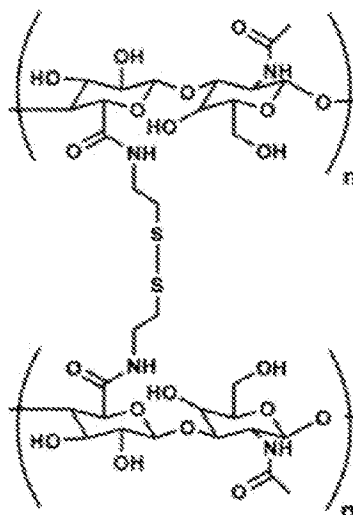
30. The sustained delivery baricitinib hydrogel of claim 18 comprising chemical substructures (a), (b) and (c):



(a)



(b)

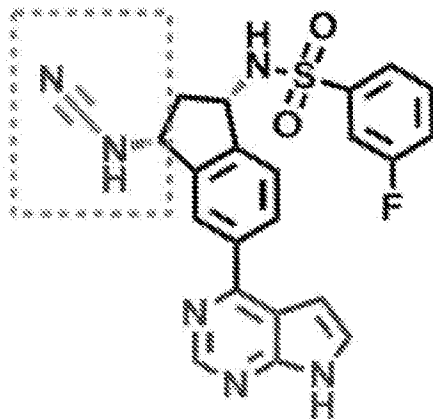


(c).

31. An injectable pharmaceutical composition for treatment of an inflammatory disorder, an autoimmune disease, an autoimmune and inflammatory hair loss, and/or a non-inflammatory disorder hair loss, the pharmaceutical composition comprising a nitrile-containing JAK inhibitor and a pharmaceutically acceptable carrier.

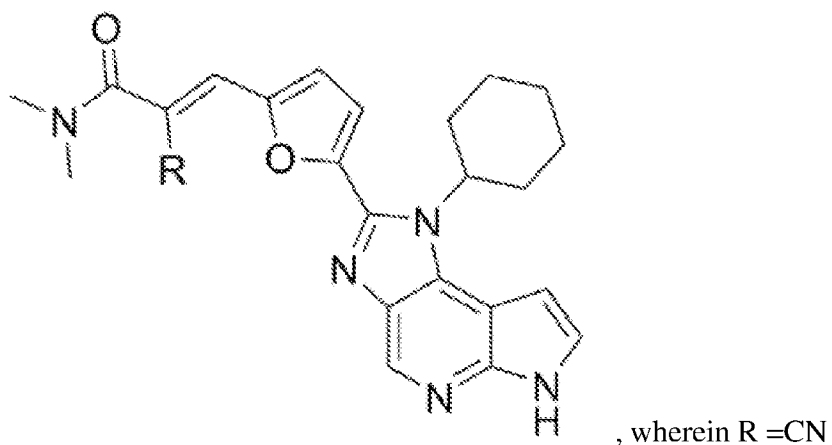
32. The injectable pharmaceutical composition of claim 31, wherein the nitrile-containing JAK inhibitor is baricitinib, delgocitinib, ruxolitinib, deuruxolitinib, tofacitinib, momelotinib, gusacitinib, itacitinib, izencitinib, lorpucitinib, povorcitinib or a nitrile-containing metabolite thereof.

33. The injectable pharmaceutical composition of claim 31, wherein the nitrile-containing JAK inhibitor is a compound having chemical structure (A):

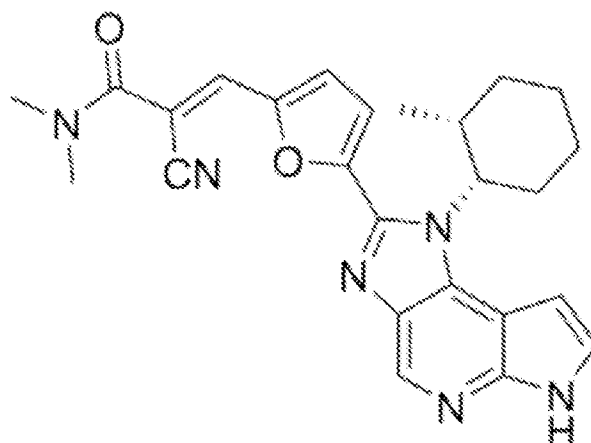


(A)

34. The injectable pharmaceutical composition of claim 31, wherein the nitrile-containing JAK inhibitor is a compound having structure (I) or (II):



(I)



(II).

35. The injectable pharmaceutical composition of claim 31 formulated for local administration.
36. The injectable pharmaceutical composition of claim 35, wherein the local administration comprises intradermal injection, intramuscular injection, subcutaneous injection or intra-articular injection.
37. The injectable pharmaceutical composition of claim 35, wherein the local administration comprises transdermal administration.
38. The injectable pharmaceutical composition of claim 37, wherein the transdermal administration comprises transdermal delivery via microneedles coated with the JAK inhibitor, a solid polymer matrix having the JAK inhibitor incorporated therein, dissolving polymer microneedles having the JAK inhibitor incorporated therein, hydrogel-forming microneedles comprising the JAK inhibitor in the hydrogel, or a transdermal patch.
39. The injectable pharmaceutical composition of claim 35, wherein the local administration comprises administration with hollow microneedles that allow delivery of the composition a the injectable pharmaceutical composition upon application of pressure.
40. The injectable pharmaceutical composition of claim 31, wherein the inflammatory disorder is an inflammatory skin disorder.
41. The injectable pharmaceutical composition of claim 40, wherein the inflammatory skin disorder is atopic dermatitis, cicatricial alopecia, central centrifugal cicatricial alopecia,

hidradenitis suppurativa, lichen planopilaris, frontal fibrosing alopecia, alopecia areata, lichen planus, mucosal lichen planus, psoriasis, pemphigus or vitiligo.

42. The injectable pharmaceutical composition of claim 31, wherein the autoimmune disease is alopecia areata, persistent patchy alopecia areata, alopecia totalis, alopecia universalis, ophiasis alopecia, alopecia barbae, rheumatoid arthritis, psoriatic arthritis or reactive arthritis.

43. The injectable pharmaceutical composition of claim 31, wherein the autoimmune and inflammatory hair loss is alopecia areata and the non-inflammatory disorder hair loss is male or female androgenetic alopecia or telogen effluvium.

44. A method for treating an inflammatory disorder, an autoimmune disease, an autoimmune and inflammatory hair loss, and/or a non-inflammatory disorder hair loss in a subject in need thereof, the method comprising administering the sustained delivery nitrile-containing JAK inhibitor hydrogel according to any one of claims 1 to 9 to a body part of the subject affected by the inflammatory disorder, the autoimmune disease, the autoimmune and inflammatory hair loss, and/or the non-inflammatory disorder hair loss.

45. The method of claim 44, wherein the nitrile-containing JAK inhibitor hydrogel is formulated for local administration.

46. The method of claim 45, wherein the local administration comprises intradermal injection, intramuscular injection, subcutaneous injection or intra-articular injection.

47. The method of claim 45, wherein the local administration comprises transdermal administration,

48. The method of claim 47, wherein the transdermal administration comprises transdermal delivery via microneedles coated with the JAK inhibitor, a solid polymer matrix having the JAK inhibitor incorporated therein, dissolving polymer microneedles having the JAK inhibitor incorporated therein, hydrogel-forming microneedles comprising the JAK inhibitor in the hydrogel, or a transdermal patch.

49. The method of claim 44, wherein the inflammatory disorder is an inflammatory skin disorder.

50. The method of claim 49, wherein the inflammatory skin disorder is atopic dermatitis, cicatricial alopecia, central centrifugal cicatricial alopecia, hidradenitis suppurativa, lichen

planopilaris, frontal fibrosing alopecia, alopecia areata, lichen planus, mucosal lichen planus, psoriasis, pemphigus or vitiligo.

51. The method of claim 44, wherein the autoimmune disease is alopecia areata, persistent patchy alopecia areata, alopecia totalis, alopecia universalis, ophiasis alopecia, alopecia barbae, rheumatoid arthritis, psoriatic arthritis or reactive arthritis.

52. The method of claim 44, wherein the autoimmune and inflammatory hair loss is alopecia areata and the non-inflammatory disorder hair loss is male or female androgenetic alopecia or telogen effluvium.

53. A method for treating an inflammatory disorder, an autoimmune disease, an autoimmune and inflammatory hair loss, and/or a non-inflammatory disorder hair loss in a subject in need thereof, the method comprising administering the sustained delivery baricitinib hydrogel according to any one of claims 18 to 23 to a body part of the subject affected by the inflammatory disorder, the autoimmune disease, the autoimmune and inflammatory hair loss, and/or the non-inflammatory disorder hair loss.

54. The method of claim 53, wherein the sustained delivery baricitinib hydrogel is formulated for local administration, wherein the local administration comprises intradermal injection, intramuscular injection, subcutaneous injection or intra-articular injection.

55. The method of claim 53, wherein the sustained delivery baricitinib hydrogel is formulated for local administration, wherein the local administration comprises transdermal injection

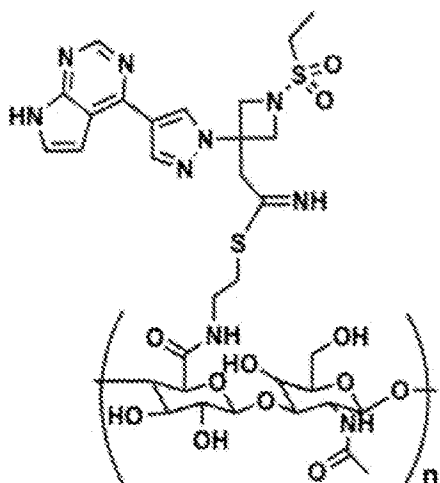
56. The method of claim 53, wherein the inflammatory disorder is an inflammatory skin disorder.

57. The method of claim 56, wherein the inflammatory skin disorder is atopic dermatitis, cicatricial alopecia, central centrifugal cicatricial alopecia, hidradenitis suppurativa, lichen planopilaris, frontal fibrosing alopecia, alopecia areata, lichen planus, mucosal lichen planus, psoriasis, pemphigus or vitiligo.

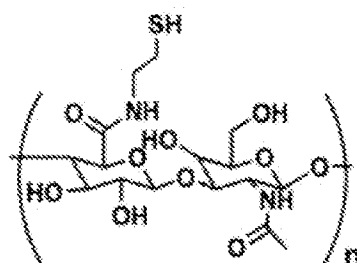
58. The method of claim 53, wherein the autoimmune disease is alopecia areata, persistent patchy alopecia areata, alopecia totalis, alopecia universalis, ophiasis alopecia, alopecia barbae, rheumatoid arthritis, psoriatic arthritis or reactive arthritis.

59. The method of claim 53, wherein the autoimmune and inflammatory hair loss is alopecia areata and the non-inflammatory disorder hair loss is male or female androgenetic alopecia or telogen effluvium.

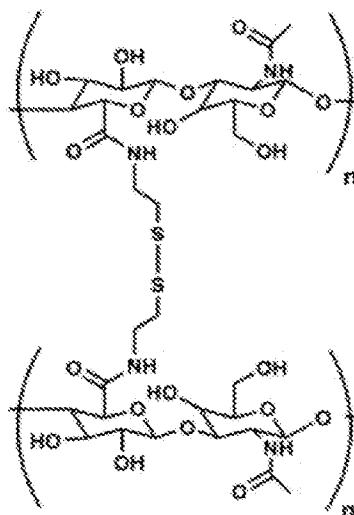
60. The method of claim 53, wherein the sustained delivery baricitinib hydrogel comprises chemical substructures (a), (b) and (c):



(a)



(b)



(c).

- 61.** A method for treating an inflammatory disorder, an autoimmune disease, an autoimmune and inflammatory hair loss, and/or a non-inflammatory disorder hair loss in a subject in need thereof, the method comprising administering the injectable pharmaceutical composition according to any one of claims 31 to 34 to a body part of the subject affected by the inflammatory disorder, the autoimmune disease, the autoimmune and inflammatory hair loss, and/or the non-inflammatory disorder hair loss.
- 62.** The method of claim 61, wherein the injectable pharmaceutical composition is formulated for local administration.
- 63.** The method of claim 62, wherein the local administration comprises intradermal injection, intramuscular injection, subcutaneous injection or intra-articular injection.
- 64.** The method of claim 62, wherein the local administration comprises transdermal administration.
- 65.** The method of claim 64, wherein the transdermal administration comprises transdermal delivery via microneedles coated with the JAK inhibitor, a solid polymer matrix having the JAK inhibitor incorporated therein, dissolving polymer microneedles having the JAK inhibitor

incorporated therein, hydrogel-forming microneedles comprising the JAK inhibitor in the hydrogel, or a transdermal patch.

66. The method of claim 62, wherein the local administration comprises administration with hollow microneedles that allow delivery of the injectable pharmaceutical composition upon application of pressure.

67. The method of claim 61, wherein the inflammatory disorder is an inflammatory skin disorder.

68. The method of claim 67, wherein the inflammatory skin disorder is atopic dermatitis, cicatricial alopecia, central centrifugal cicatricial alopecia, hidradenitis suppurativa, lichen planopilaris, frontal fibrosing alopecia, alopecia areata, lichen planus, mucosal lichen planus, psoriasis, pemphigus or vitiligo.

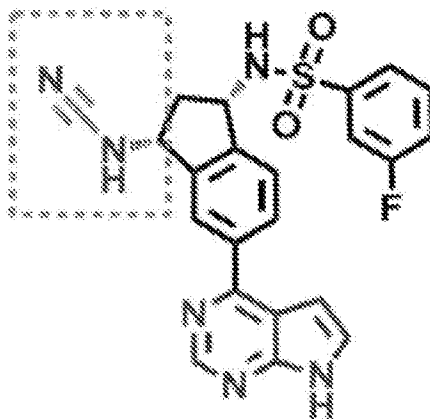
69. The method of claim 61, wherein the autoimmune disease is alopecia areata, persistent patchy alopecia areata, alopecia totalis, alopecia universalis, ophiasis alopecia, alopecia barbae, rheumatoid arthritis, psoriatic arthritis or reactive arthritis.

70. The method of claim 61, wherein the autoimmune and inflammatory hair loss is alopecia areata and the non-inflammatory disorder hair loss is male or female androgenetic alopecia or telogen effluvium.

71. A method for producing a sustained delivery JAK inhibitor hydrogel for treatment of an inflammatory disorder, an autoimmune disease, an autoimmune and inflammatory hair loss, and/or a non-inflammatory disorder hair loss in a subject in need thereof, wherein the JAK inhibitor hydrogel comprises a nitrile-containing JAK inhibitor and the nitrile group is reversibly conjugated to a thiol group of a thiolated polymer to form a thioimide adduct, the method comprising:

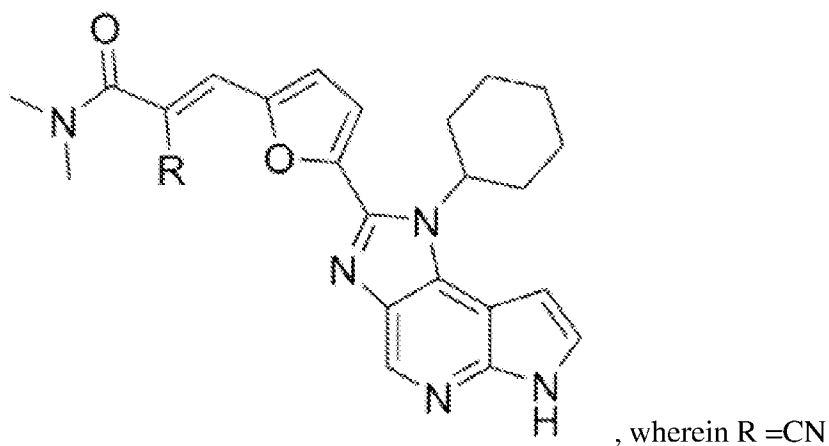
- (a) mixing a thiolated polymer with the nitrile-containing JAK inhibitor having a nitrile group to a desired weight percent concentration (w/v) of from 0.5 to 10 wt.% for 24 hours to form a crosslinked JAK inhibitor hydrogel, wherein the thiolated polymer and the JAK inhibitor are each dissolved in a respective solvent;
- (b) centrifuging the crosslinked JAK inhibitor hydrogel; and
- (c) washing the centrifuged crosslinked JAK inhibitor hydrogel to remove the solvent.

72. The method of claim 71, wherein the thiolated polymer is a thiolated hyaluronic acid, a thiolated chitosan, a thiolated cyclodextrin, a thiolated poly(ethylene glycol), a thiolated polyvinyl alcohol, a thiolated polyacrylamide, a thiolated polyethylene oxide, a thiolated polymethacrylate, a thiolated dextran, a thiolated alginate, a thiolated cellulose, a thiolated gelatin, a thiolated collagen, a thiolated silk, a thiolated keratin or a thiolated elastin.
73. The method of claim 72, wherein the thiolated polymer is a thiolated hyaluronic acid.
74. The method of claim 73, wherein the thiolated hyaluronic acid has an average molecular weight of from 1 KD to 1,000,000 KD when polydispersed in solution.
75. The method of claim 74, wherein the thiolated hyaluronic acid has an average molecular weight of from 10,000 KD to 1,000,000 KD when polydispersed in solution.
76. The method of claim 75, wherein the thiolated hyaluronic acid has an average molecular weight of 100,000 KD when polydispersed in solution.
77. The method of claim 71, wherein the nitrile-containing JAK inhibitor is baricitinib, delgocitinib, ruxolitinib, deuruxolitinib, tofacitinib, momelotinib, gusacitinib, itacitinib, izencitinib, lorpucitinib, povorcitinib or a nitrile-containing metabolite thereof.
78. The method of claim 71, wherein the nitrile-containing JAK inhibitor is a compound having chemical structure (A):

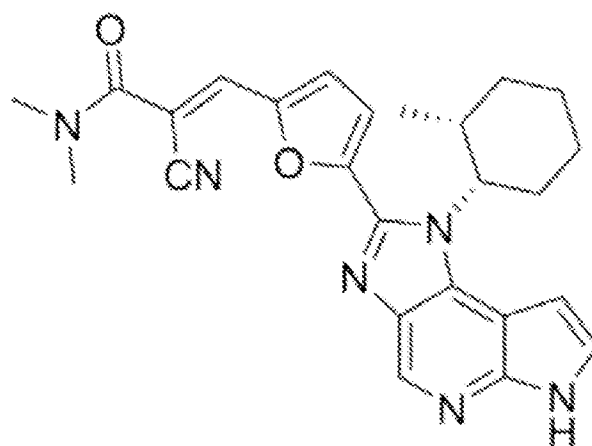


(A)

79. The method of claim 71, wherein the nitrile-containing JAK inhibitor is a compound having structure (I) or (II):



(I)



(II).

80. The method of claim 71, further comprising formulating the sustained delivery JAK inhibitor hydrogel for local administration.

81. The method of claim 80, wherein the local administration comprises intradermal injection, intramuscular injection, subcutaneous injection or intra-articular injection.

82. The method of claim 80, wherein the local administration comprises transdermal administration.

- 83.** The method of claim 82, wherein the transdermal administration comprises transdermal delivery via microneedles coated with the JAK inhibitor, a solid polymer matrix having the JAK inhibitor incorporated therein, dissolving polymer microneedles having the JAK inhibitor incorporated therein, hydrogel-forming microneedles comprising the JAK inhibitor in the hydrogel, or a transdermal patch.
- 84.** The method of claim 71, wherein the inflammatory disorder is an inflammatory skin disorder.
- 85.** The method of claim 84, wherein the inflammatory skin disorder is atopic dermatitis, cicatricial alopecia, central centrifugal cicatricial alopecia, hidradenitis suppurativa, lichen planopilaris, frontal fibrosing alopecia, alopecia areata, lichen planus, mucosal lichen planus, psoriasis, pemphigus or vitiligo.
- 86.** The method of claim 71, wherein the autoimmune disease is alopecia areata, persistent patchy alopecia areata, alopecia totalis, alopecia universalis, ophiasis alopecia, alopecia barbae, rheumatoid arthritis, psoriatic arthritis or reactive arthritis.
- 87.** The method of claim 71, wherein the autoimmune and inflammatory hair loss is alopecia areata and the non-inflammatory disorder hair loss is male or female androgenetic alopecia or telogen effluvium.

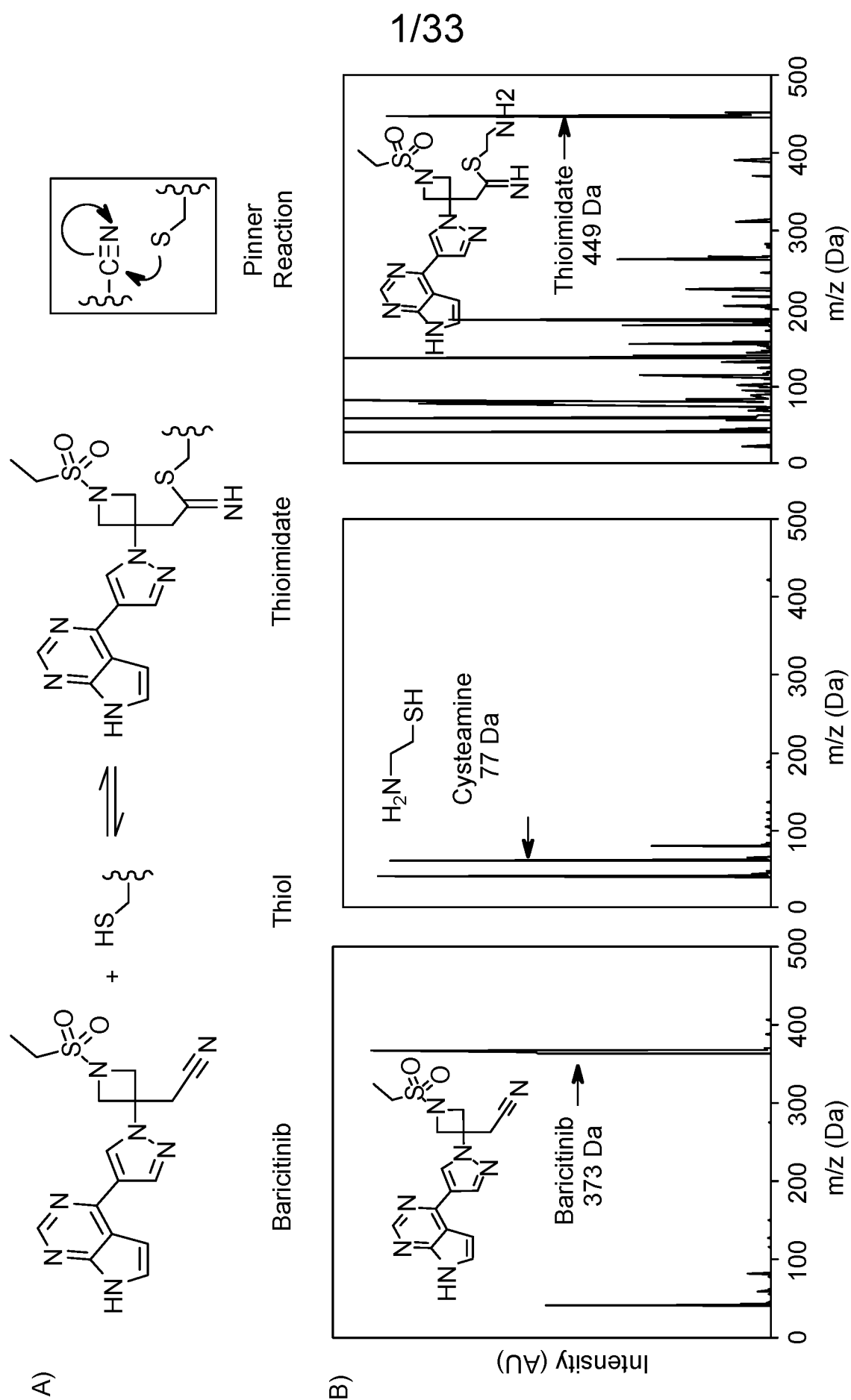


FIG. 1

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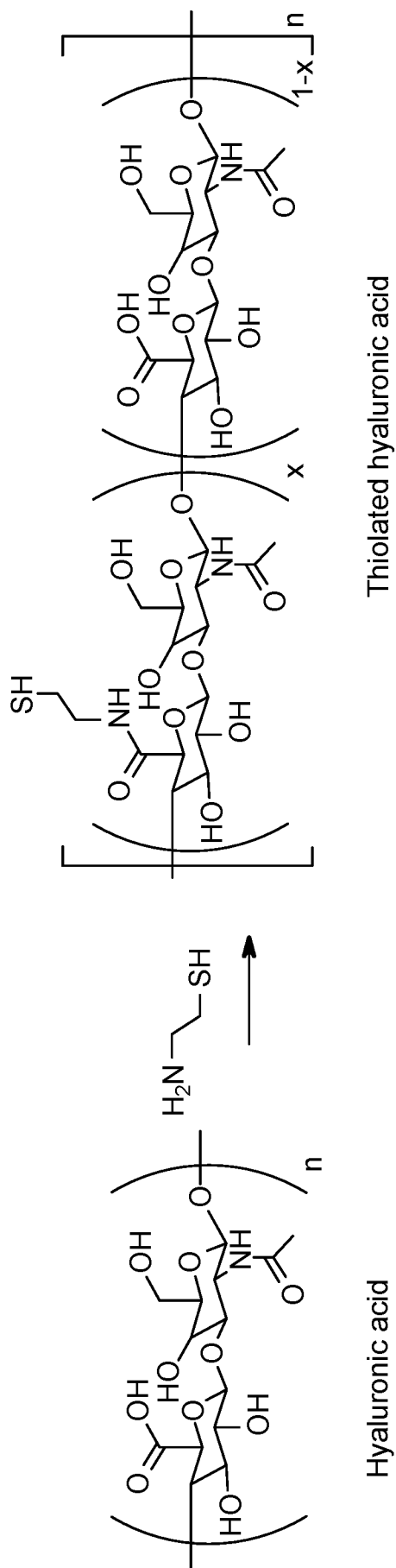


FIG. 2A

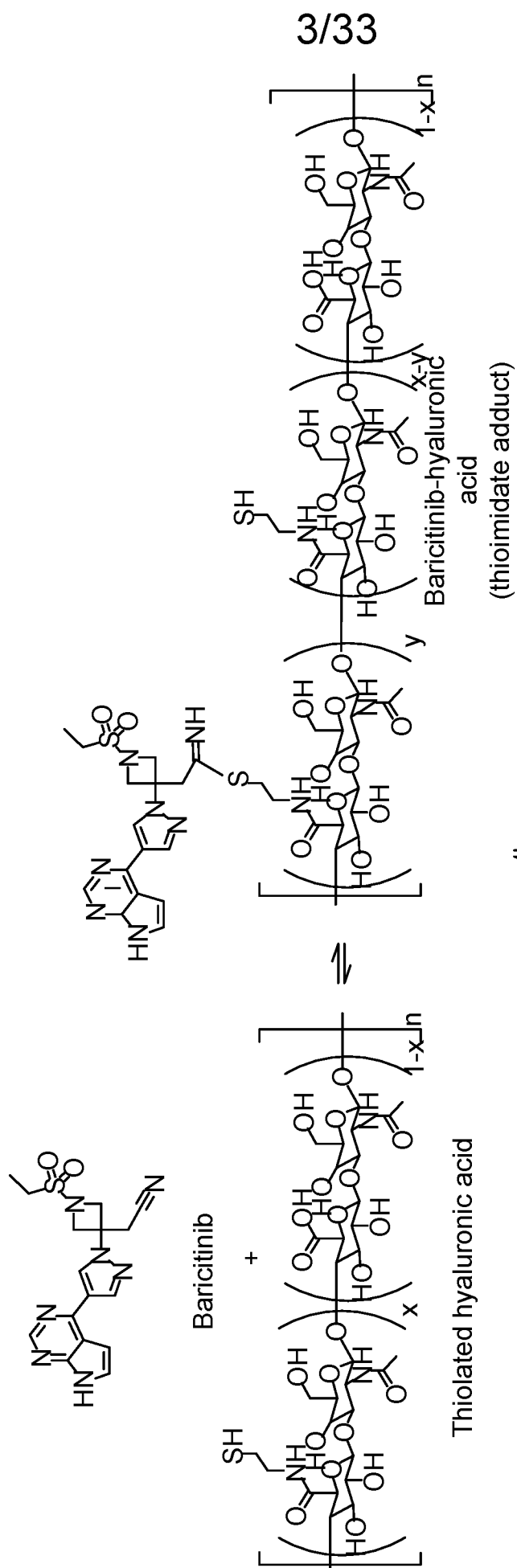


FIG. 2B

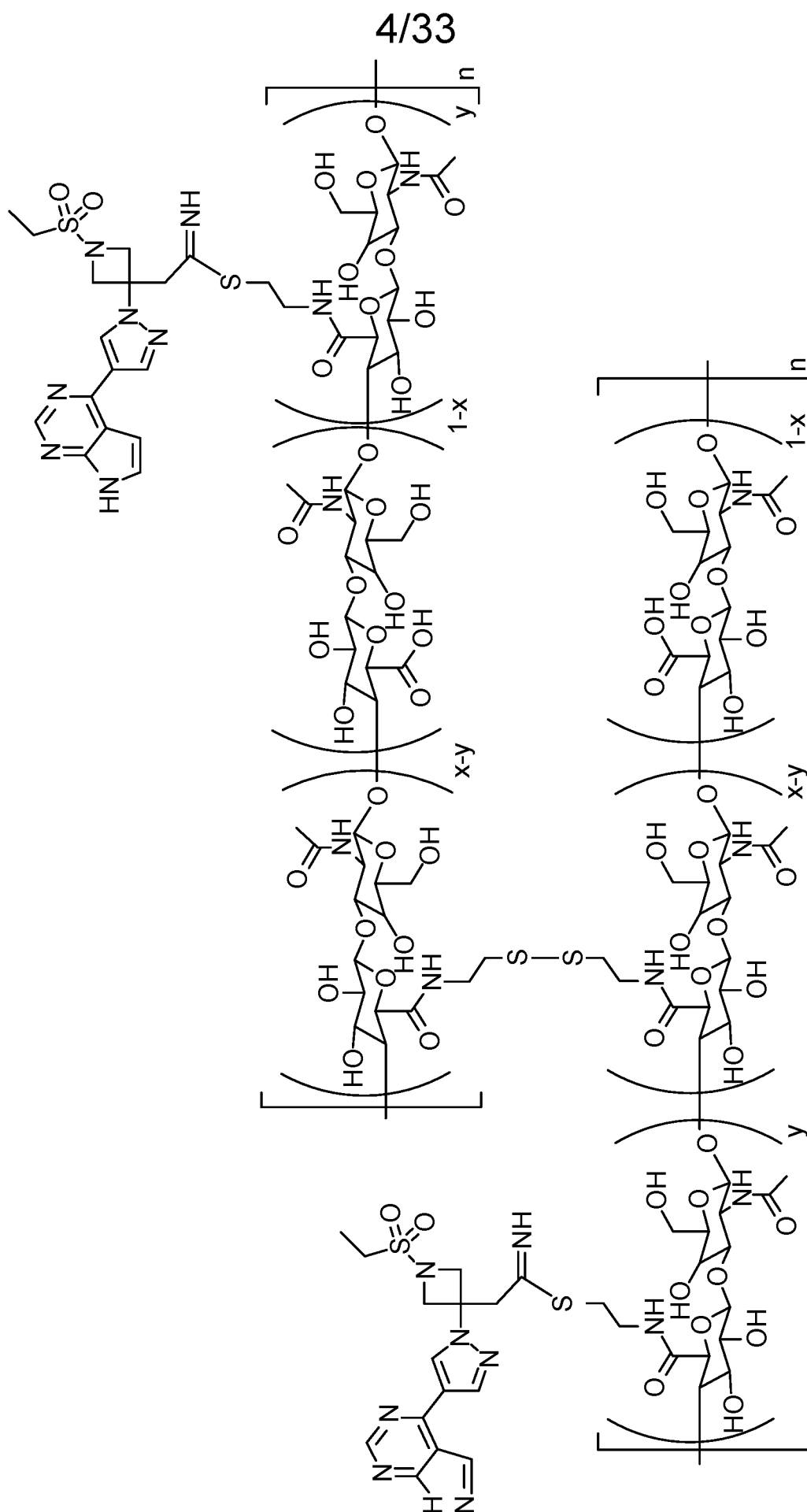


FIG. 2B(Cont.)

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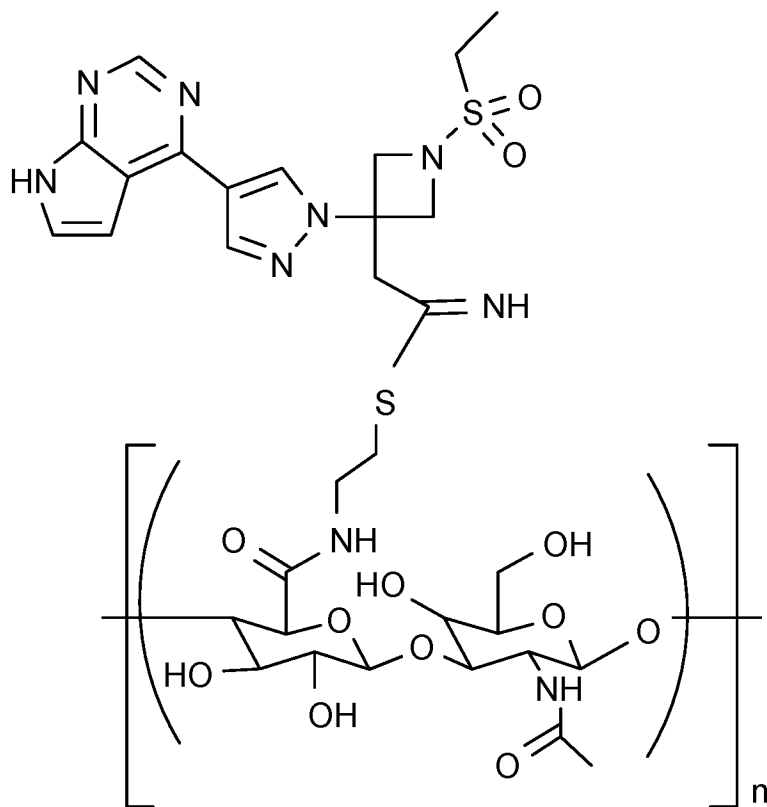


FIG. 2C

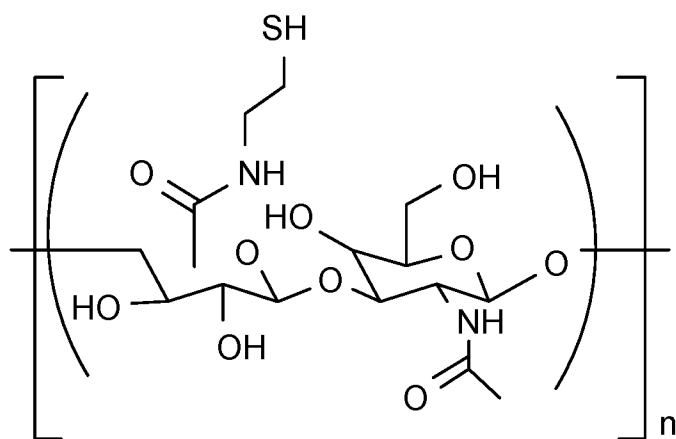


FIG. 2D

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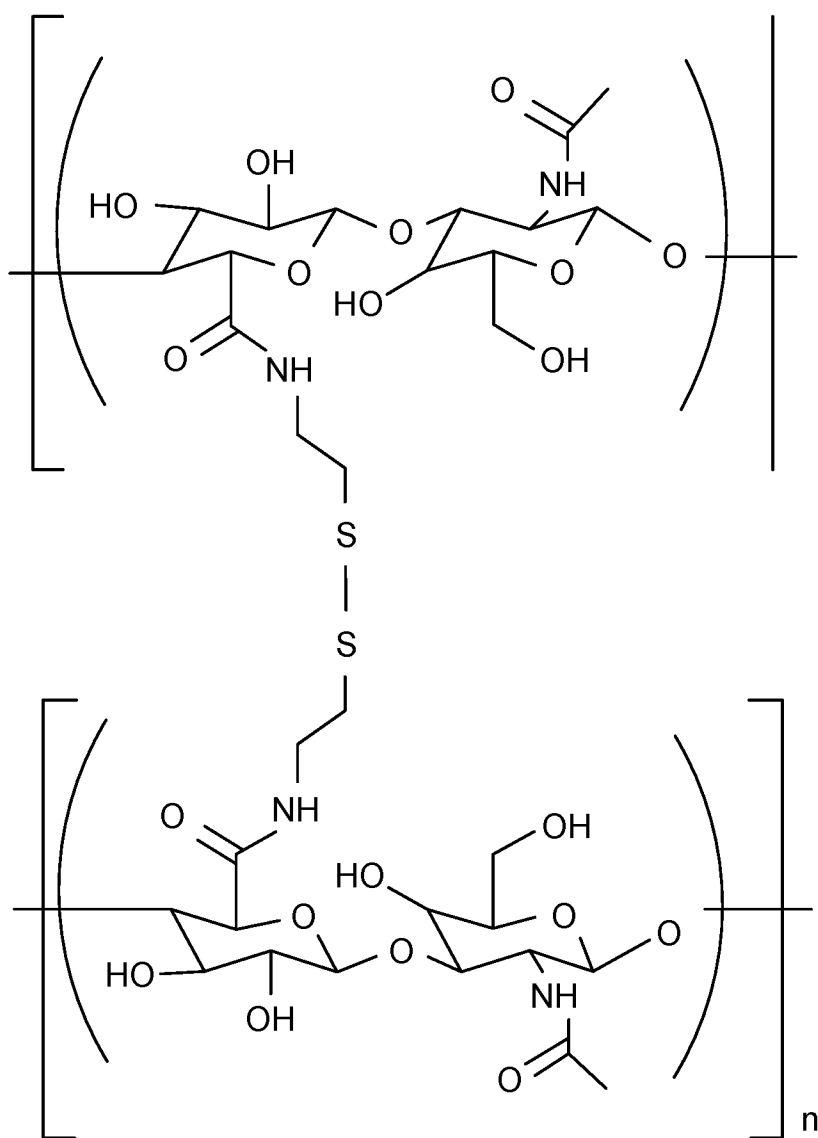


FIG. 2E

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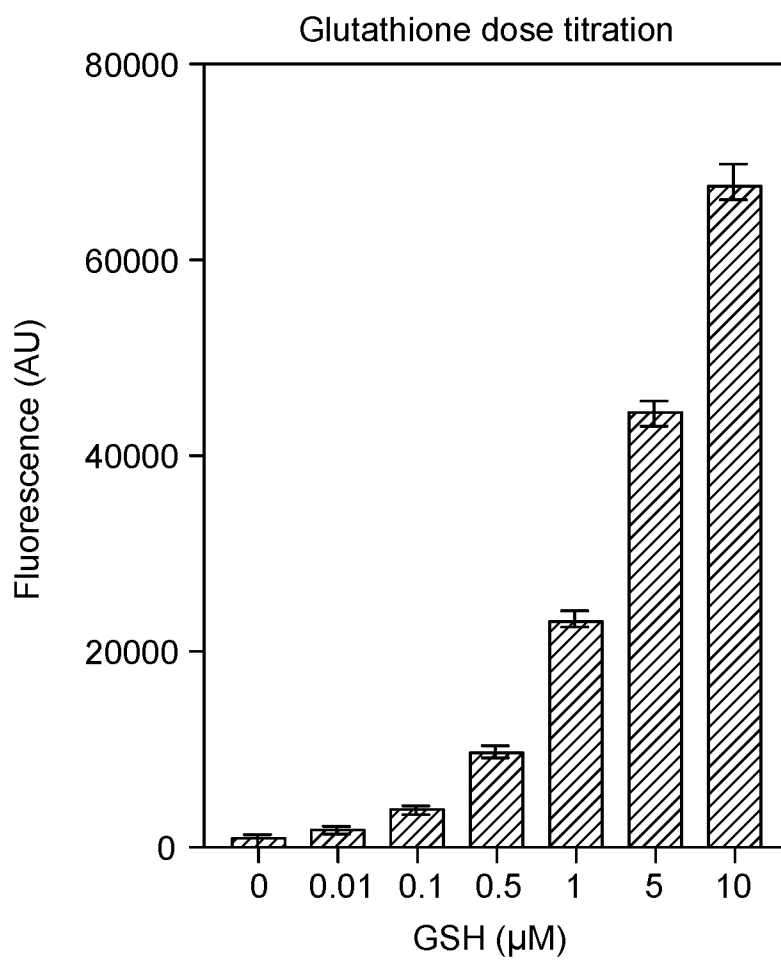
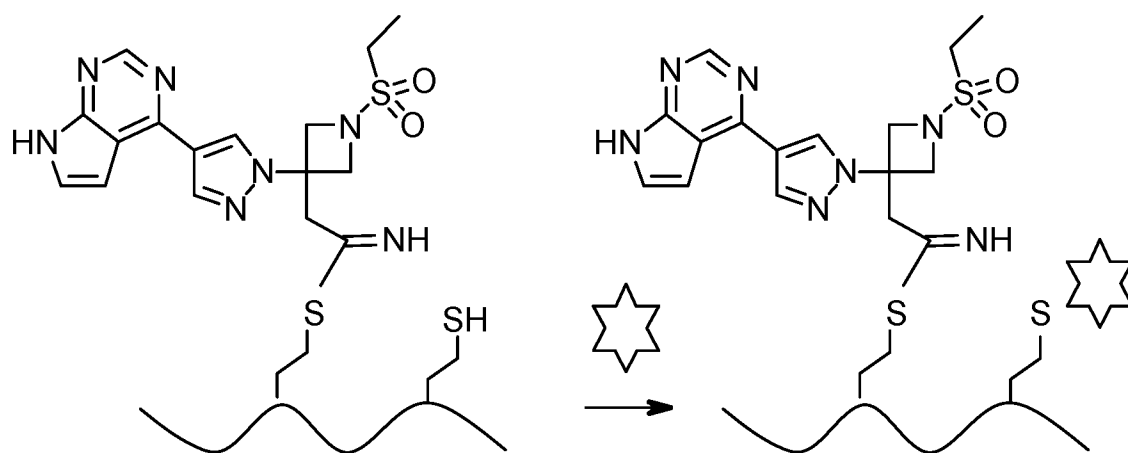


FIG. 3A

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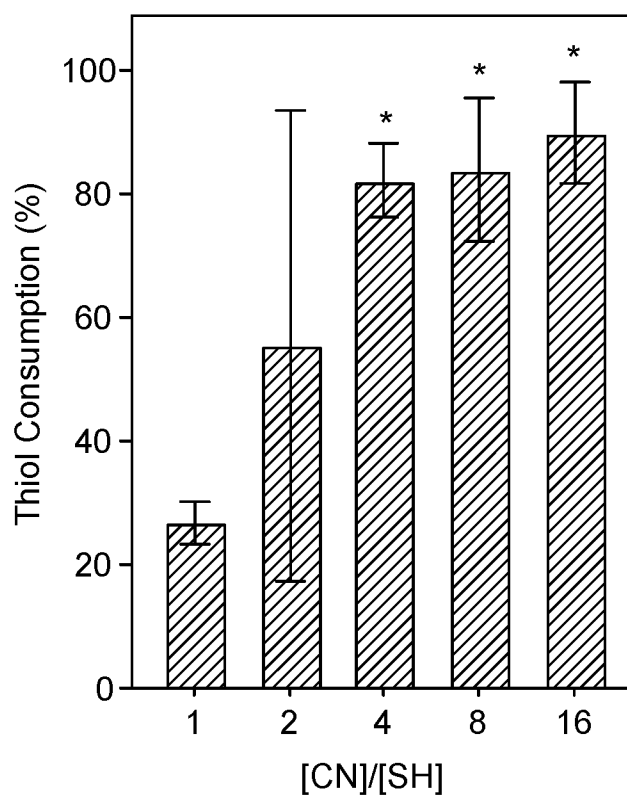
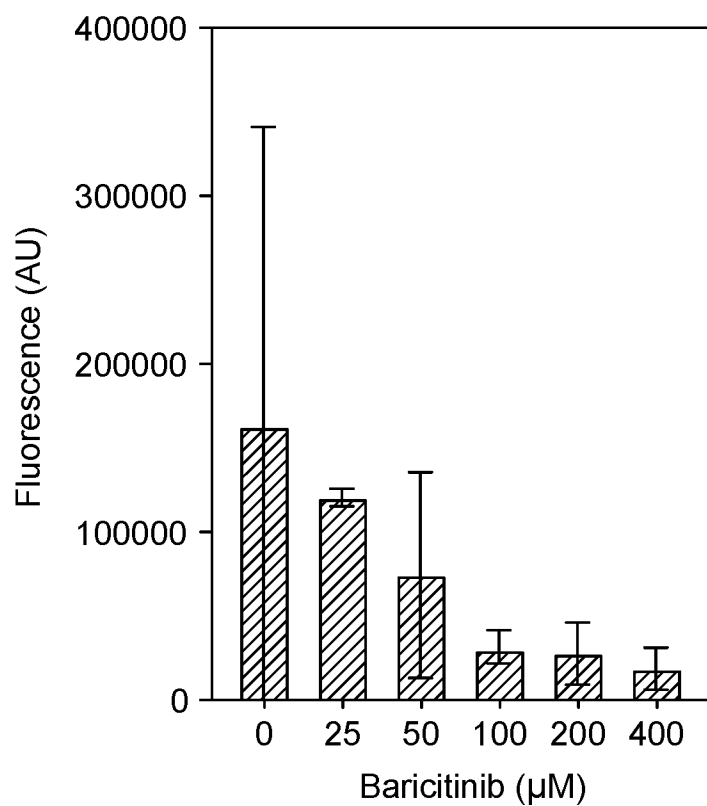


FIG. 3B

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[Thiolated hyaluronic acid] ₀	[Baricitinib] ₀	[Thiolated hyaluronic acid] _{eq}	[Baricitinib] _{eq}	[Baricitinib- hyaluronic acid] _{eq}	K _{eq} (10 ⁴ M ⁻¹)
25	25	18.3	18.3	6.7	2.00
25	50	11.1	36.1	13.9	3.46
25	100	4.4	79.4	20.6	5.88
25	200	4.0	179.0	21.0	2.94
25	400	2.5	377.5	22.5	2.40

FIG. 3C

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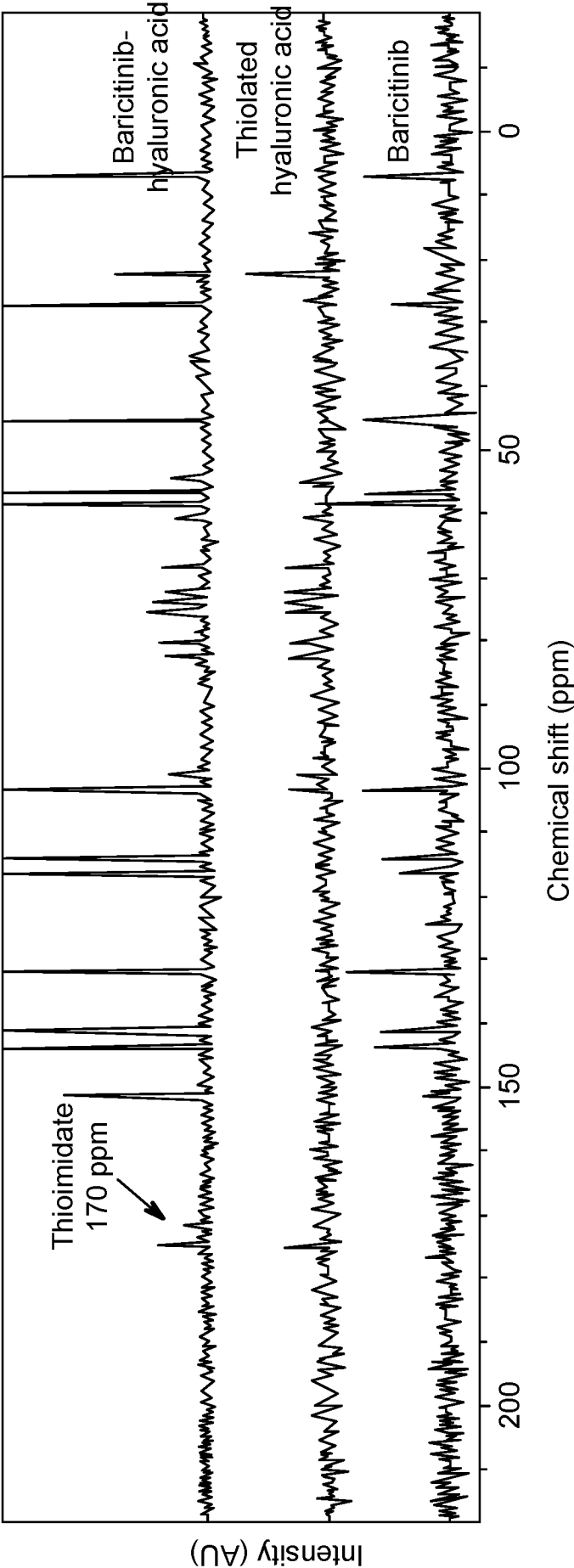


FIG. 4A

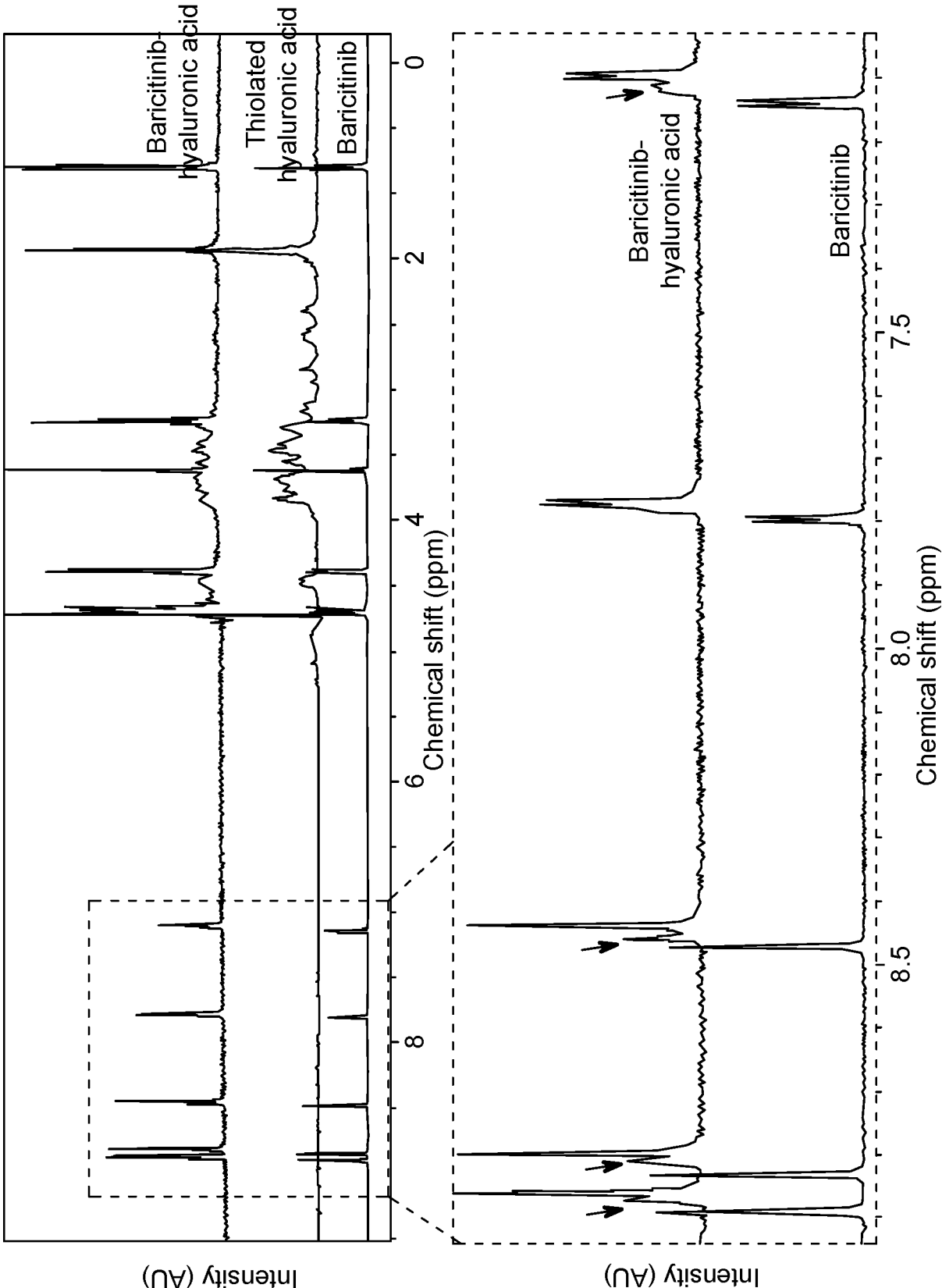


FIG. 4B

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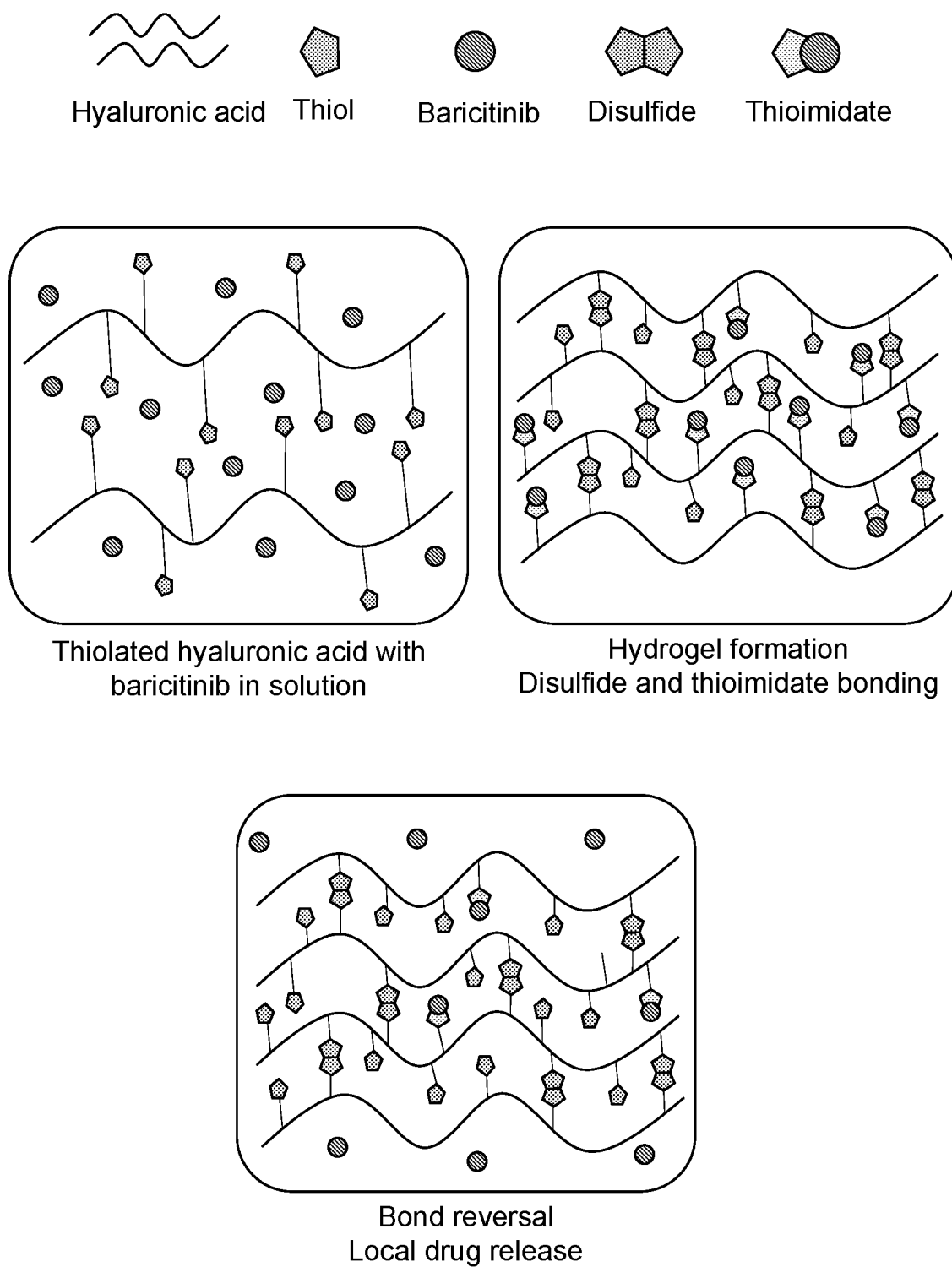


FIG. 5A

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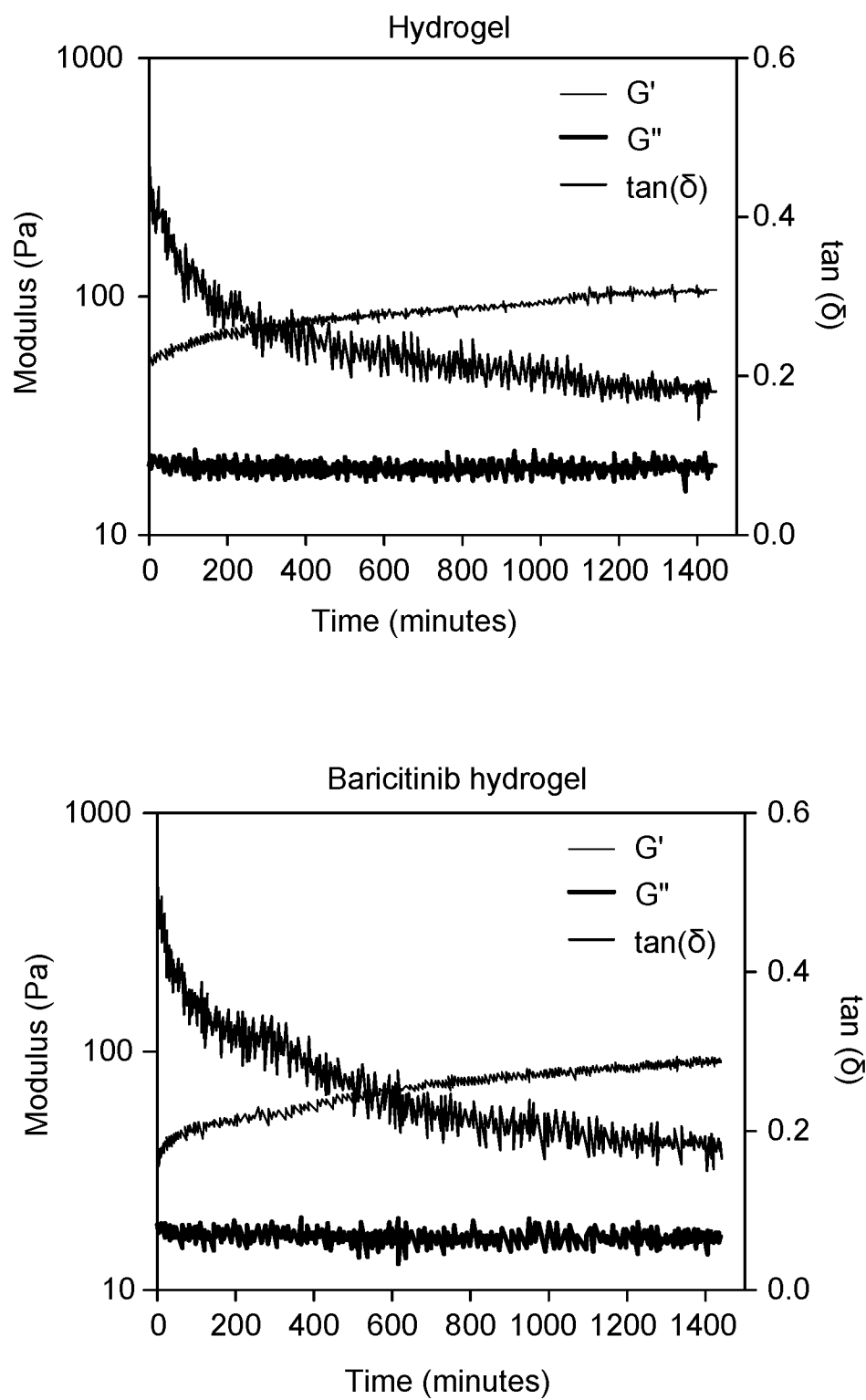


FIG. 5B

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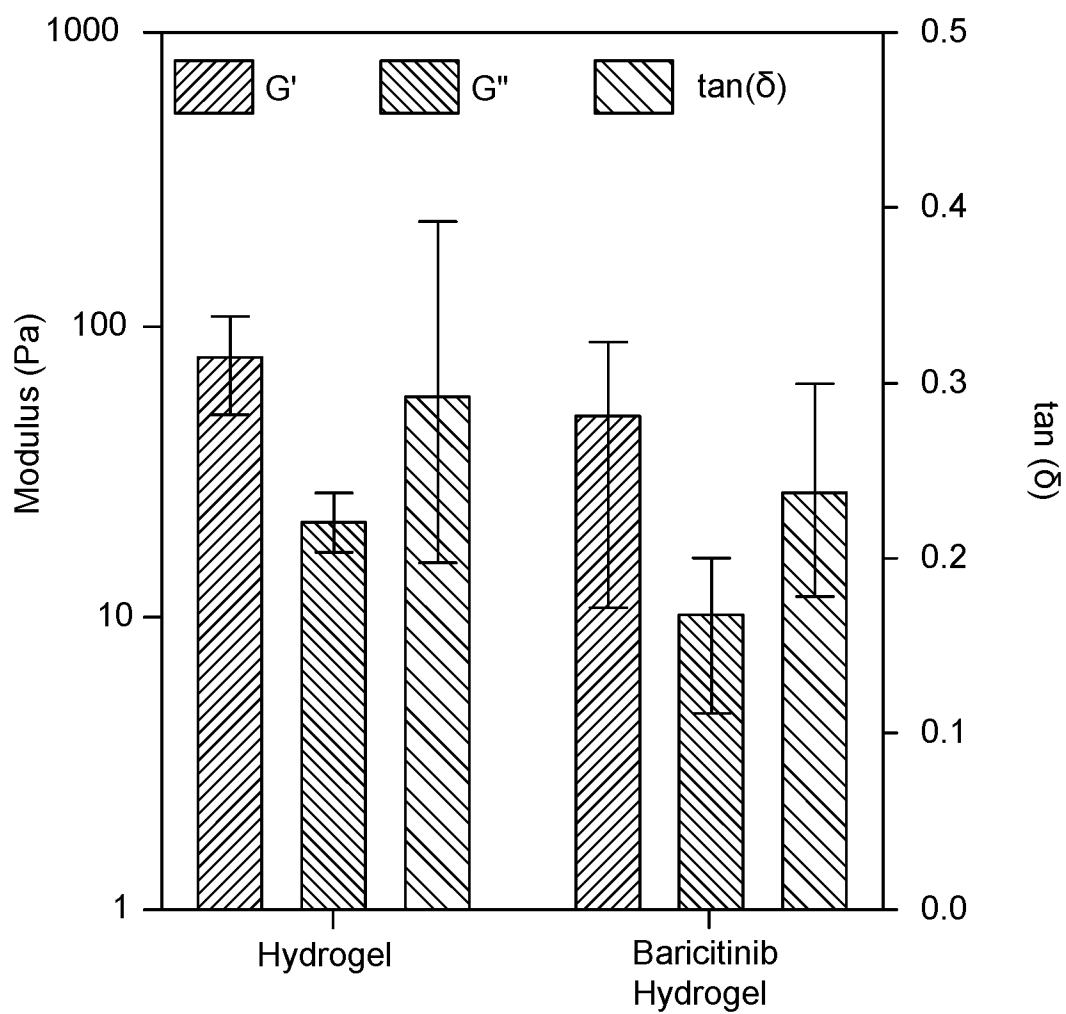


FIG. 5C

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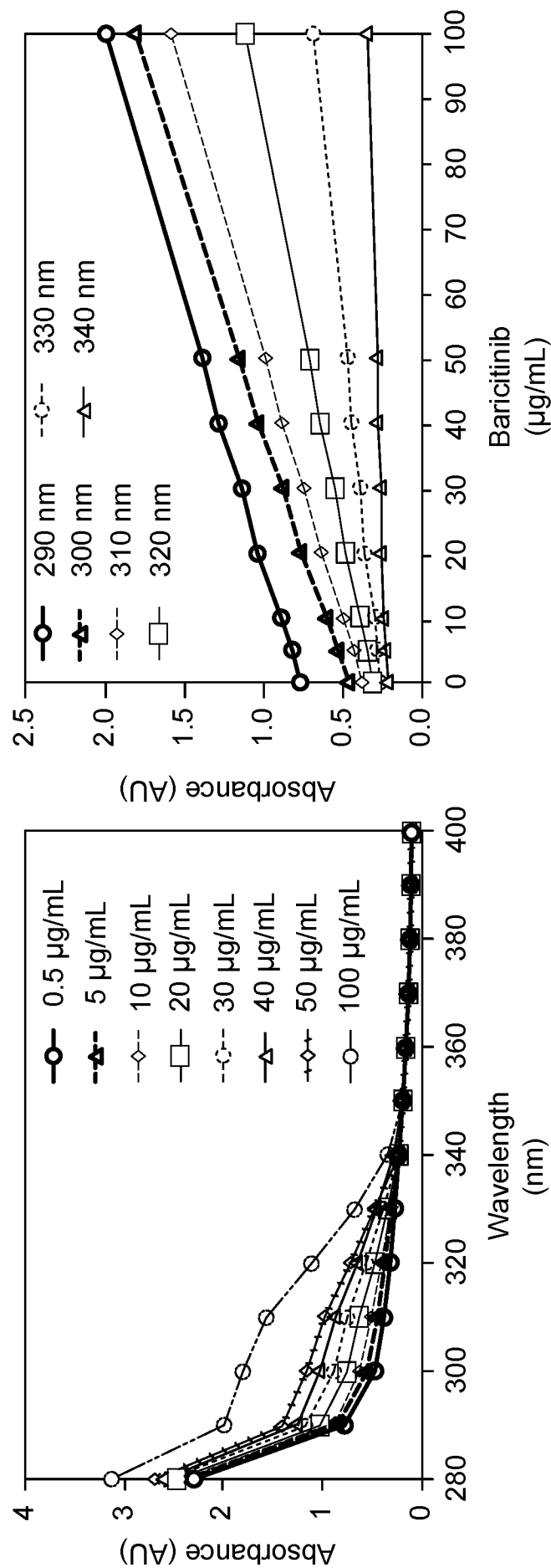


FIG. 6A

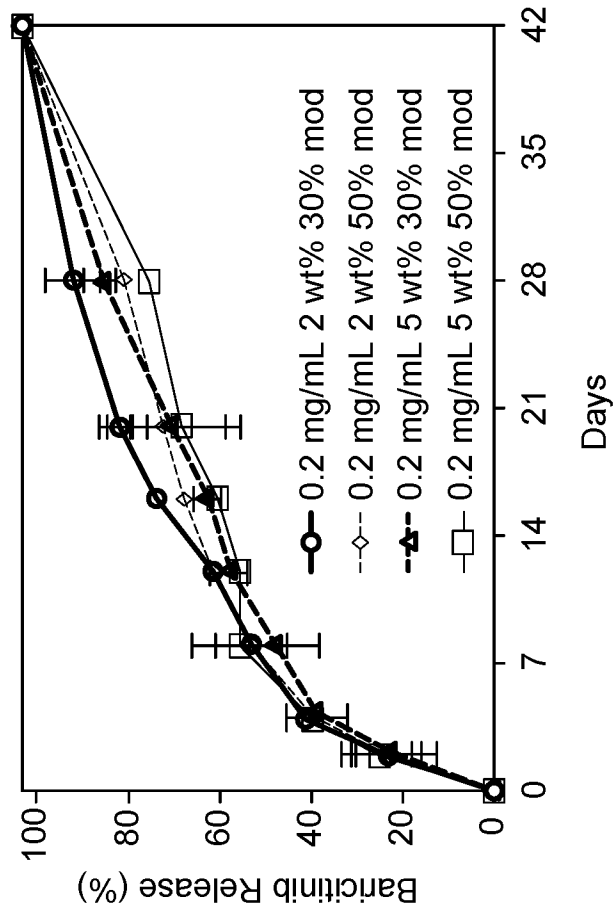
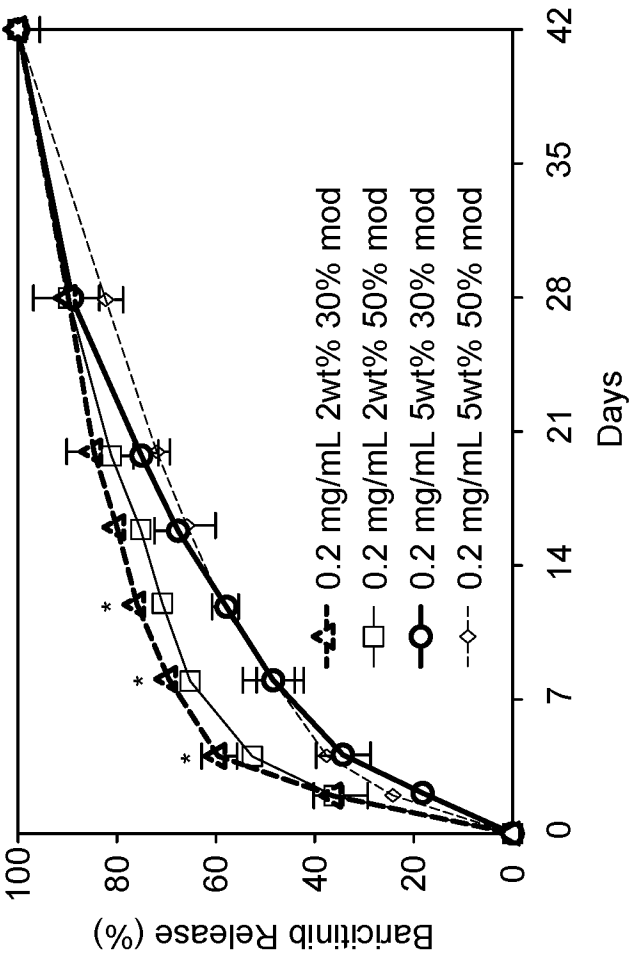


FIG. 6B

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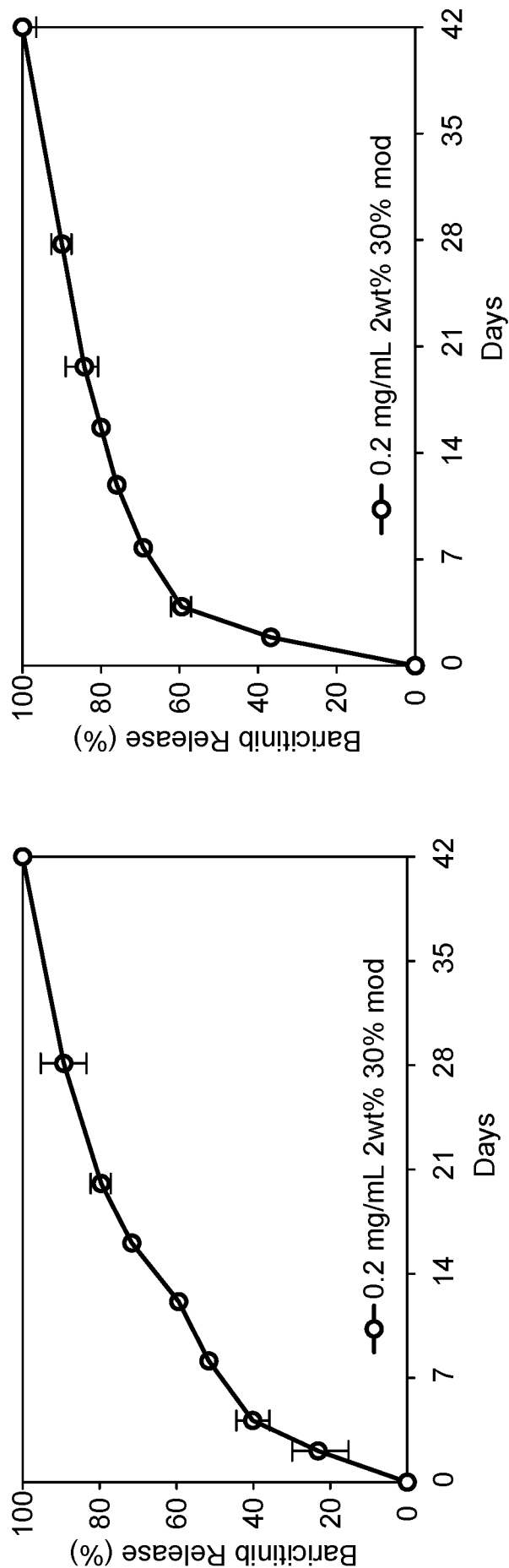


FIG. 6C

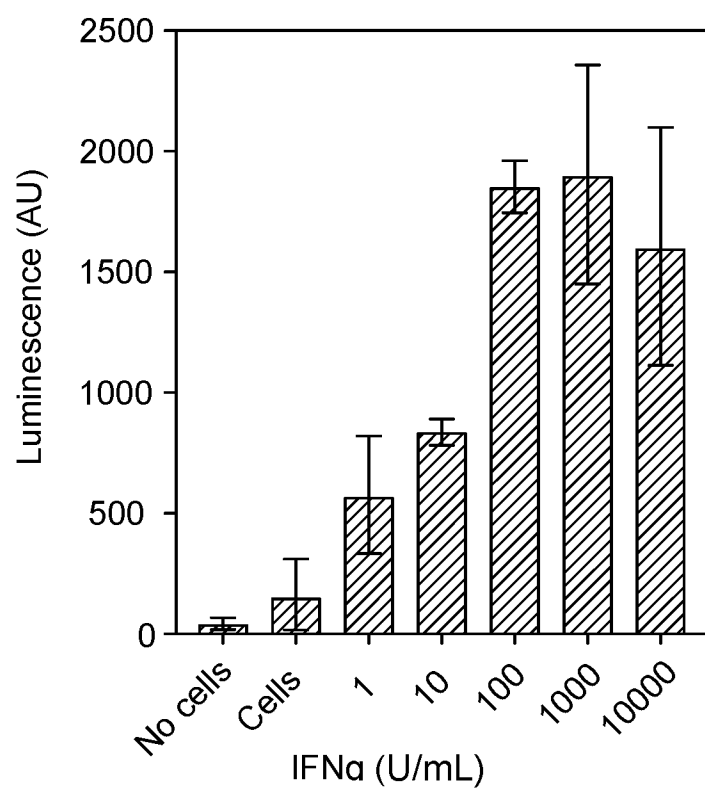
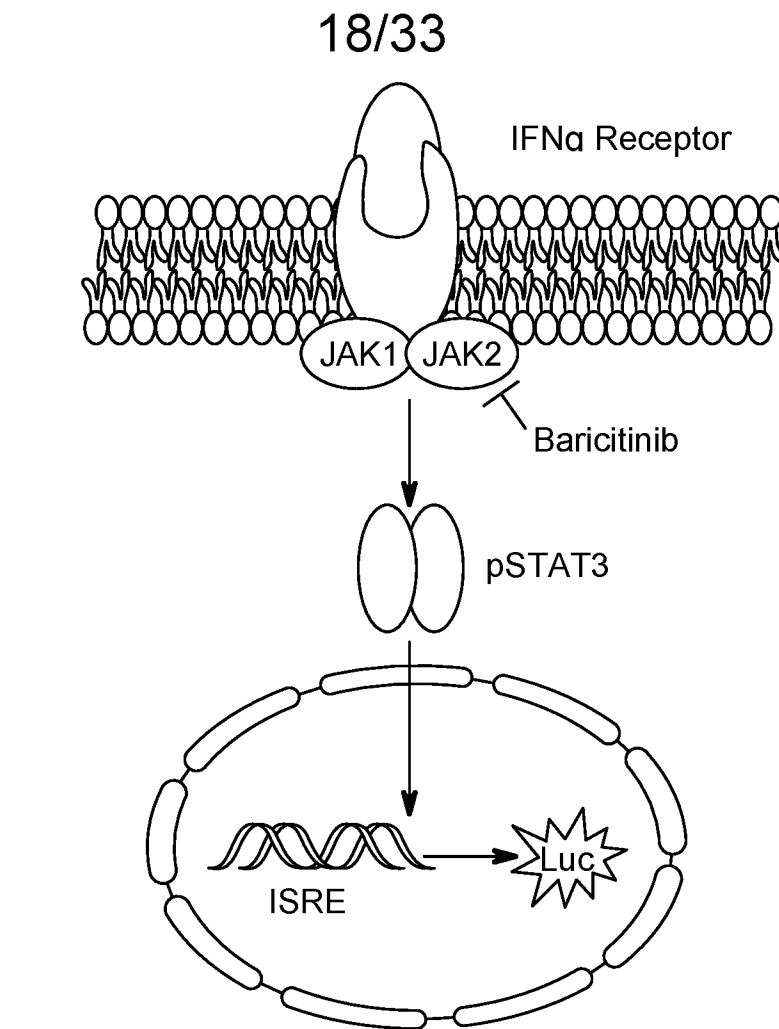


FIG. 7A

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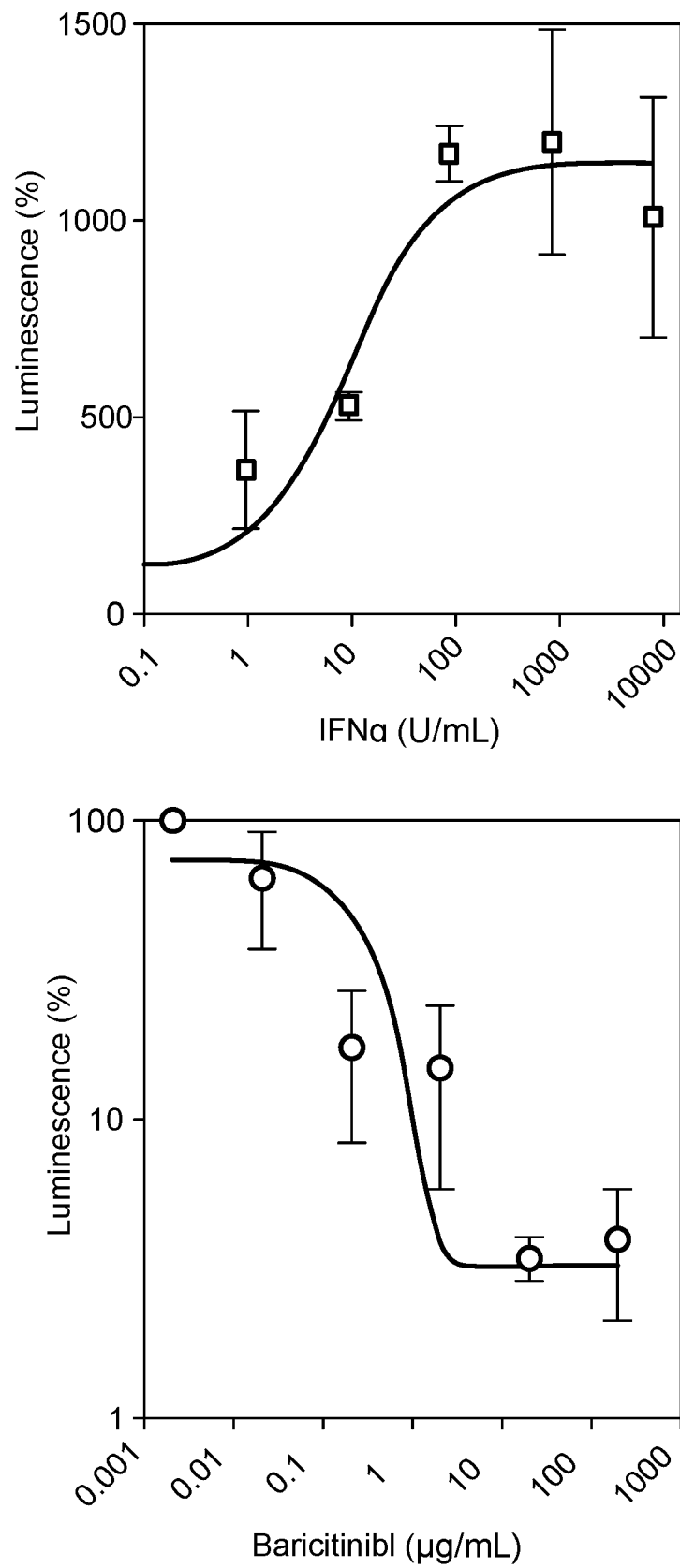


FIG. 7B

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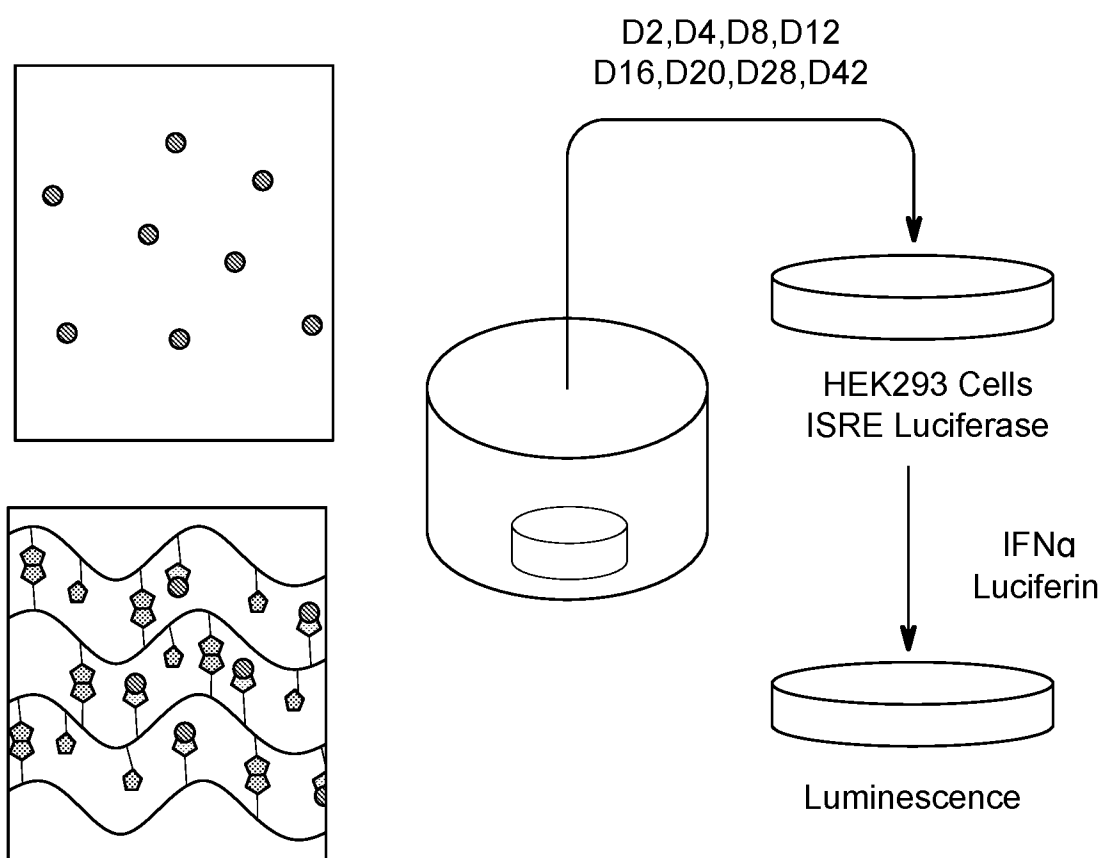


FIG. 7C

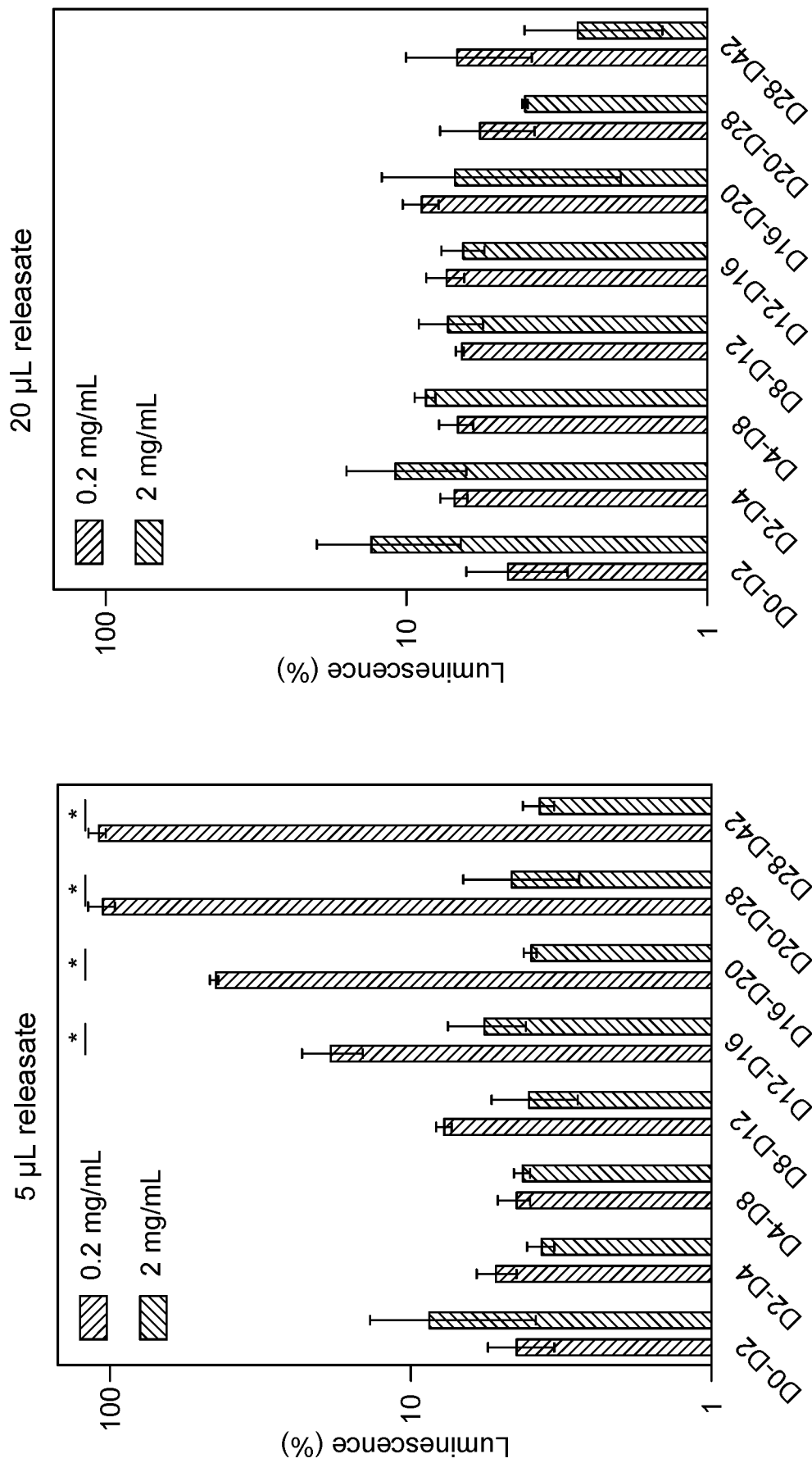
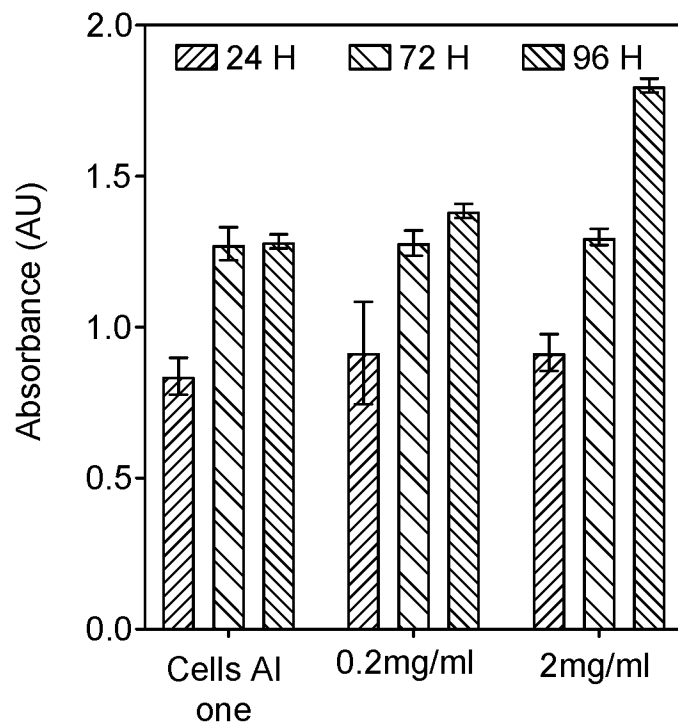


FIG. 7D

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Cells Alone

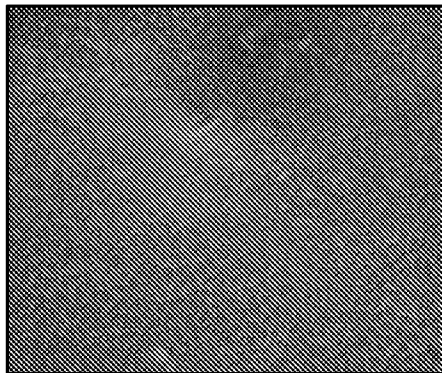
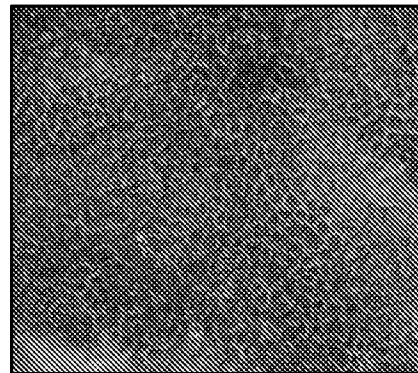
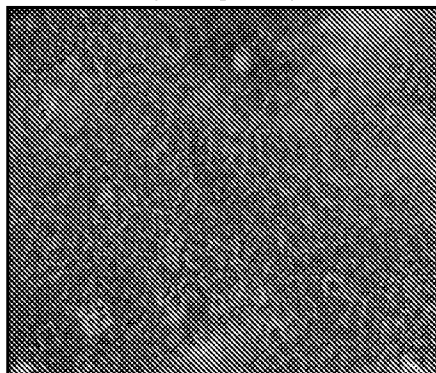
Baricitinib hydrogel
(0.2 mg/mL)Baricitinib hydrogel
(2 mg/mL)

FIG. 7E

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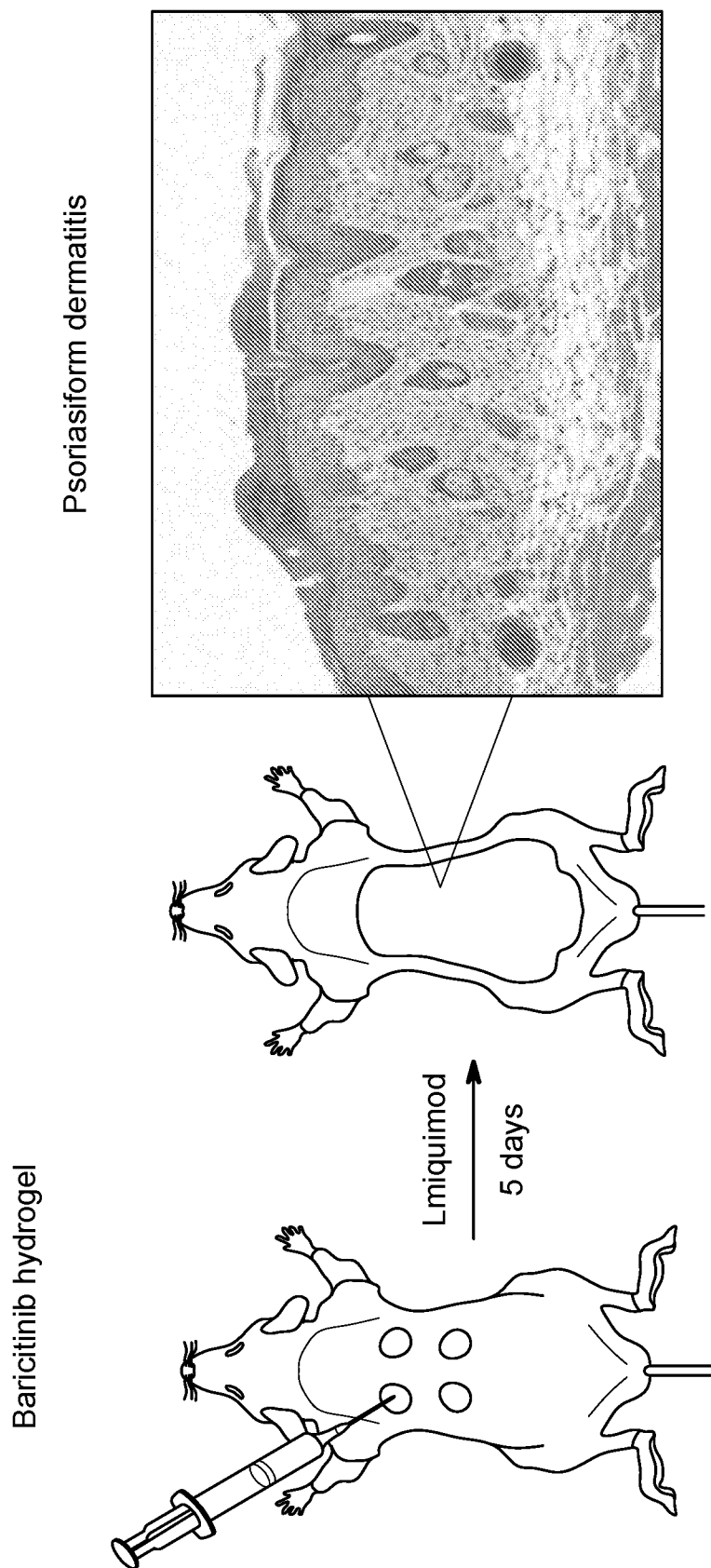


FIG. 8A

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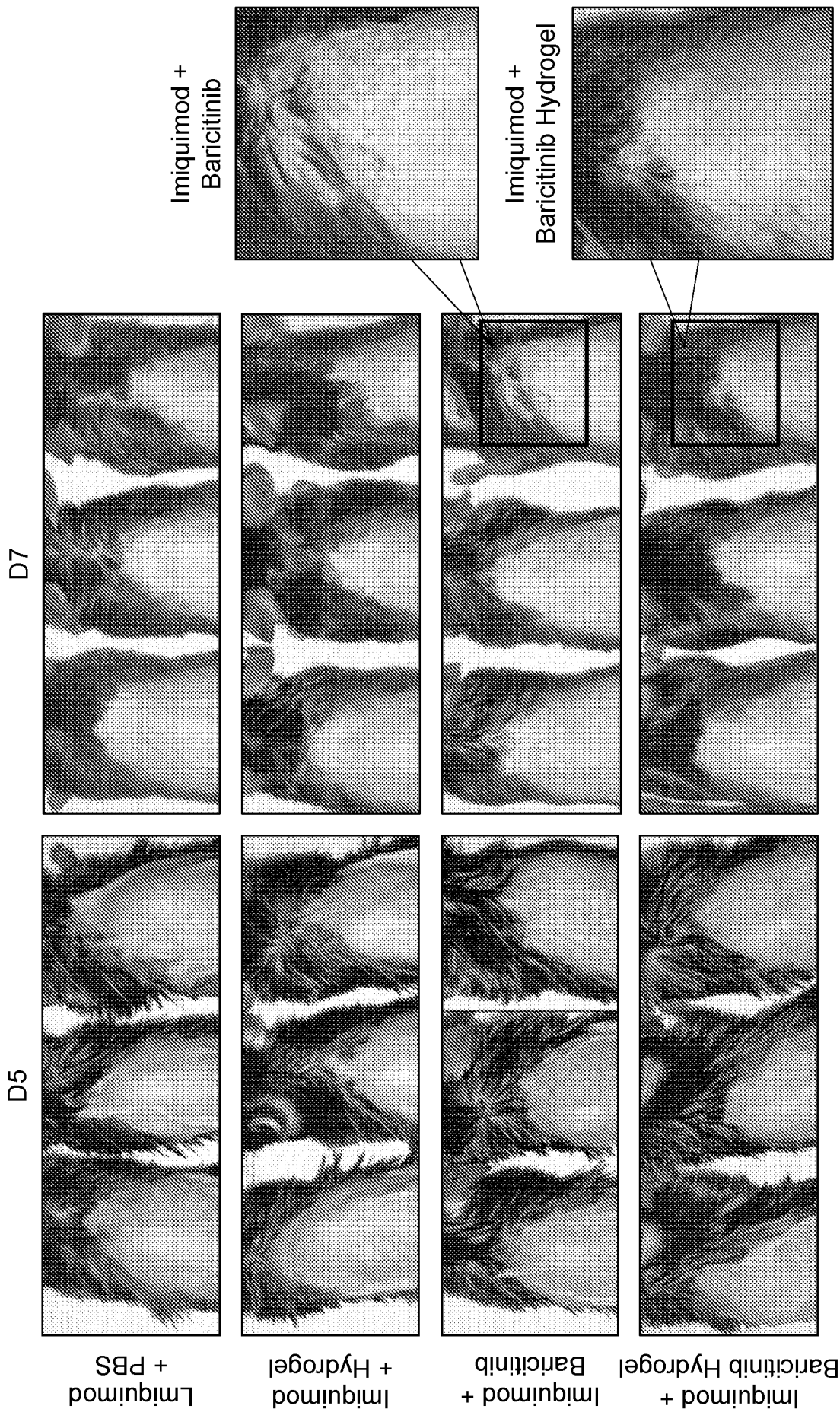
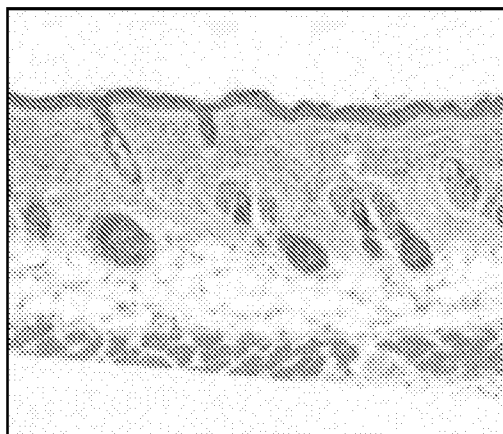


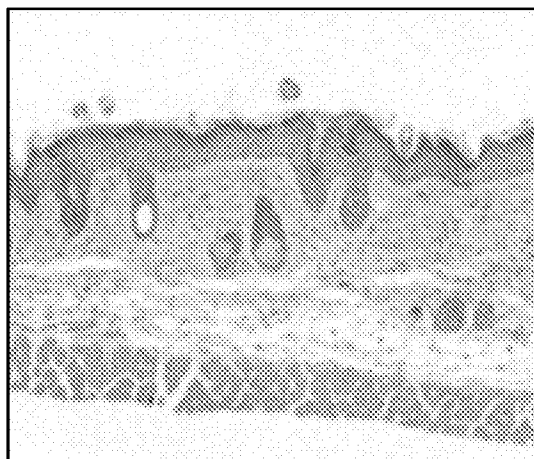
FIG. 8B

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Control



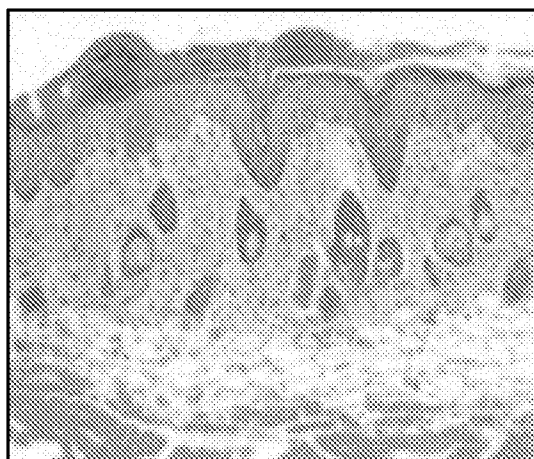
Imiquimod + PBS



Imiquimod + Hydrogel



Imiquimod + Baricitinib Hydrogel



Imiquimod + Baricitinib

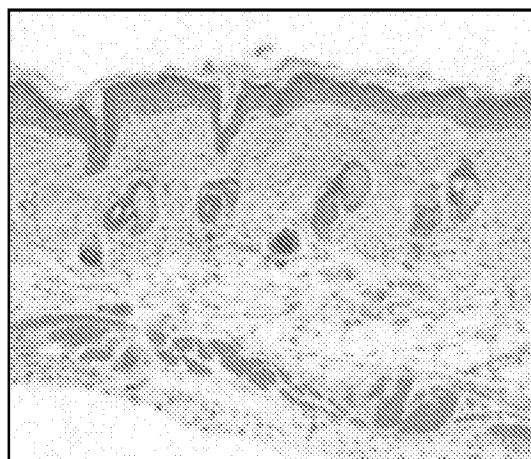


FIG. 8C

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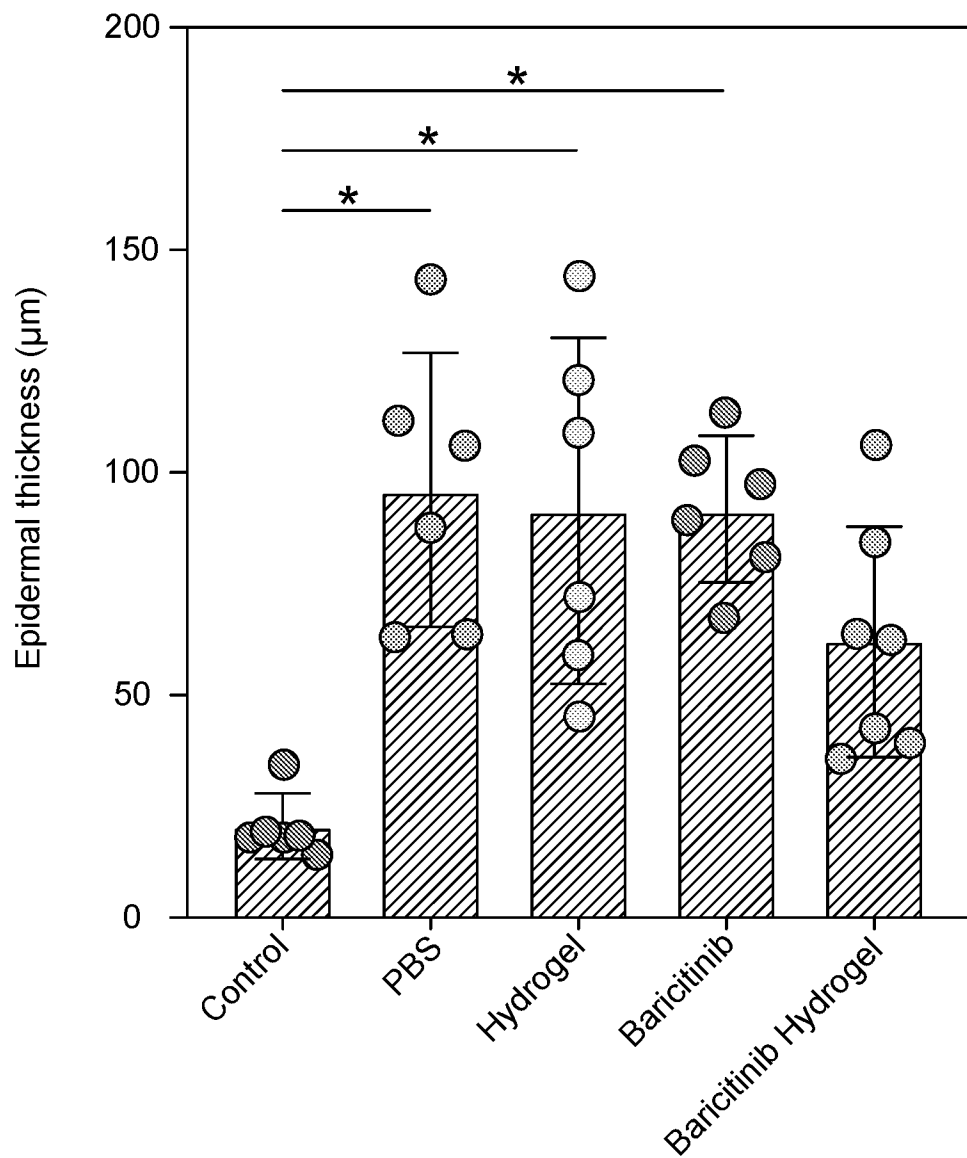


FIG. 8D

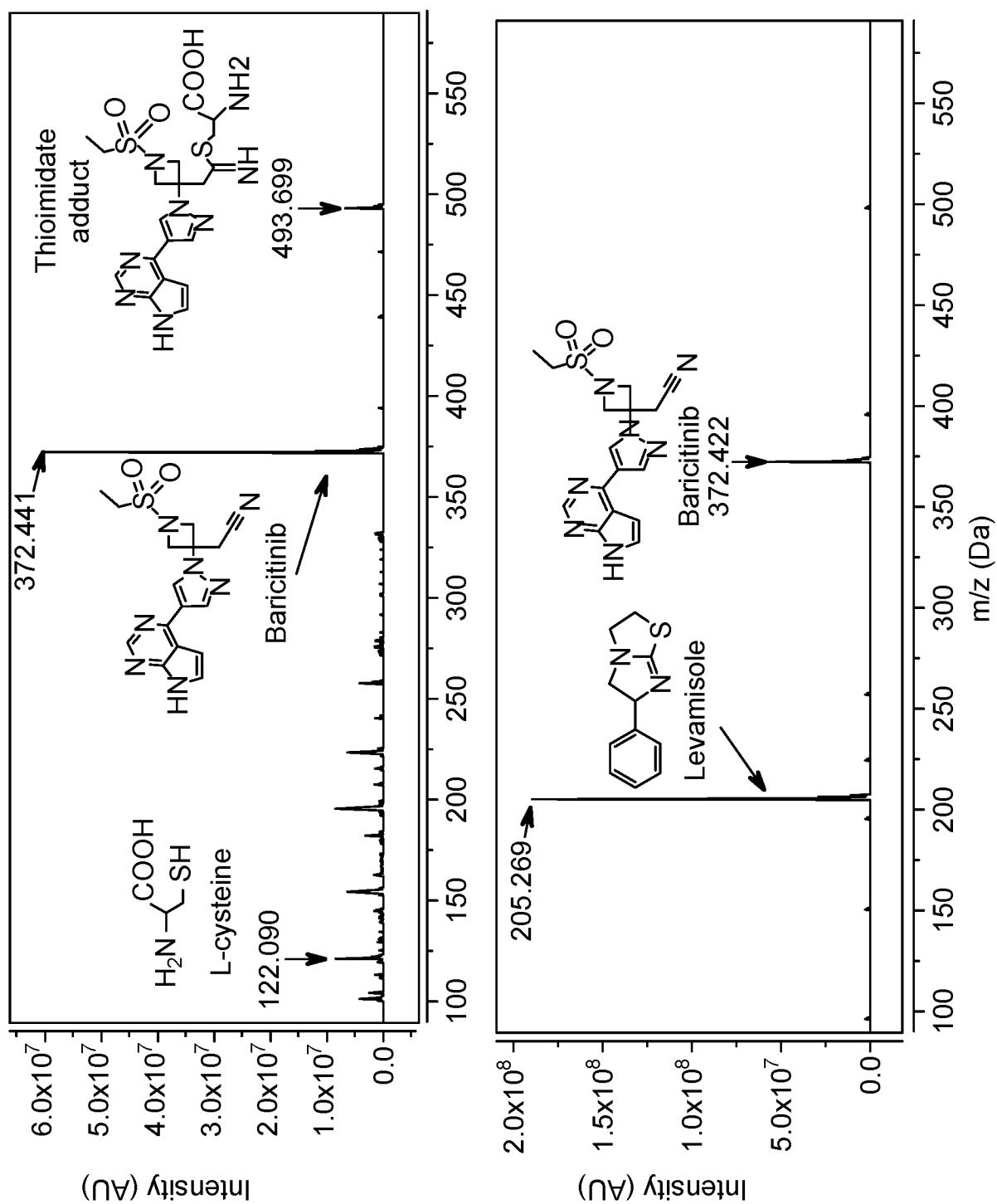


FIG. 9

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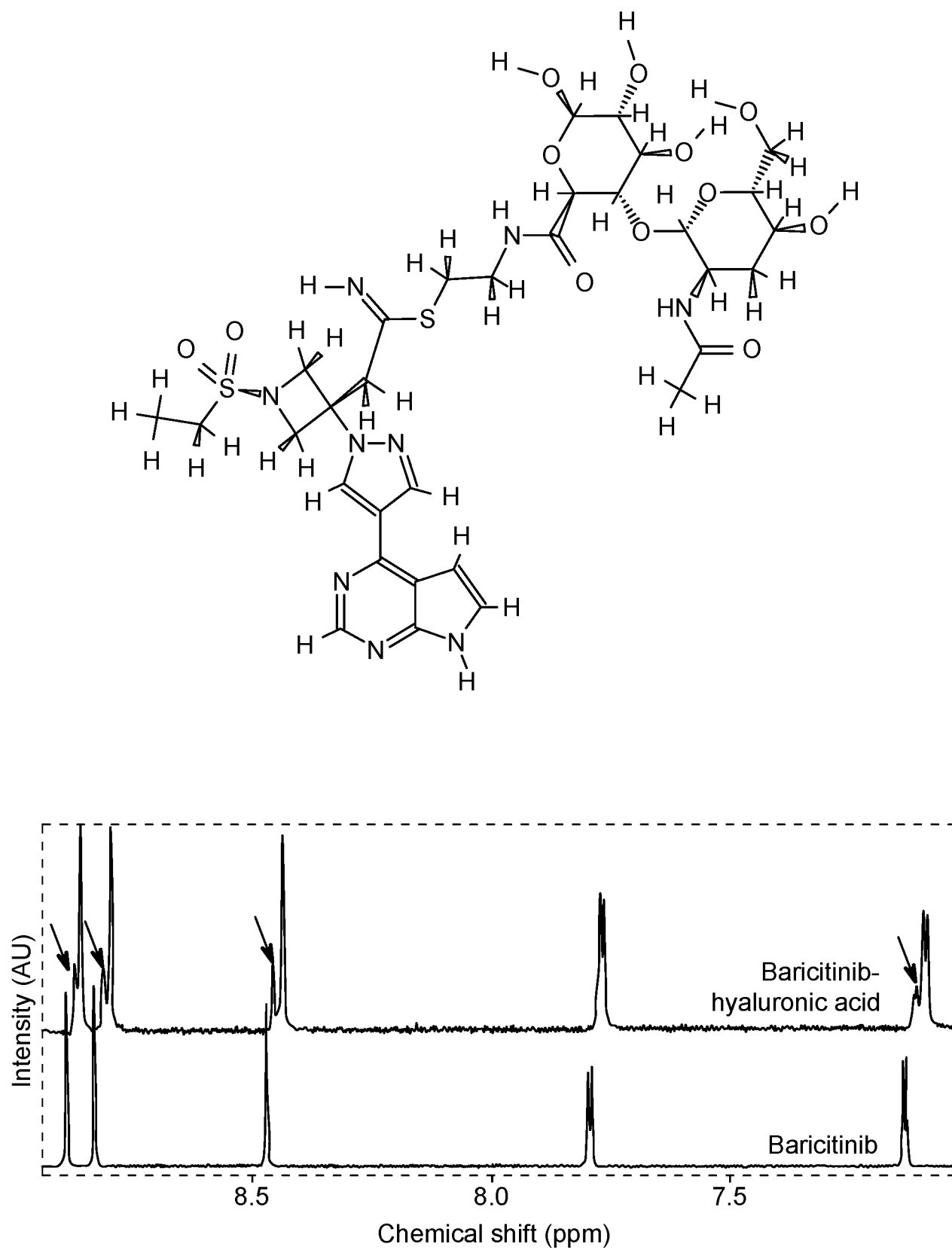


FIG. 10

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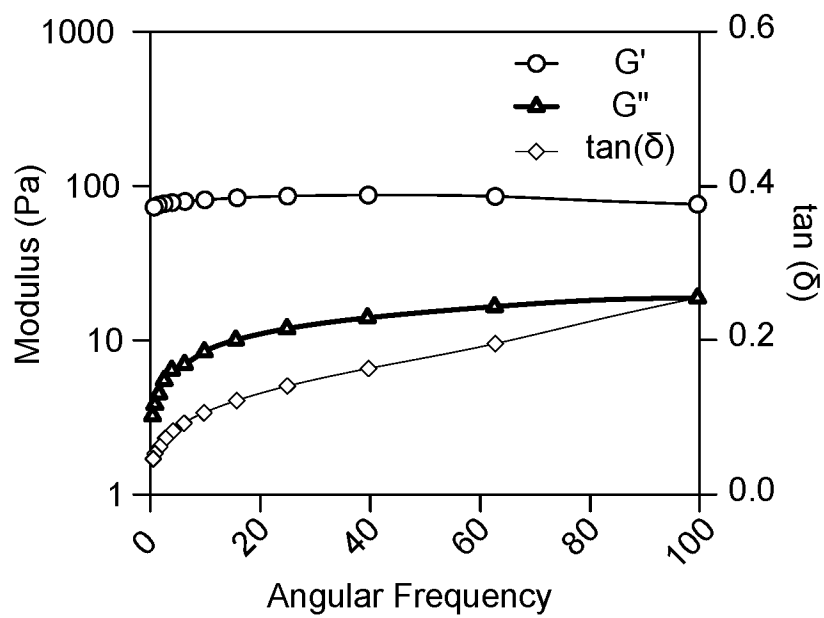
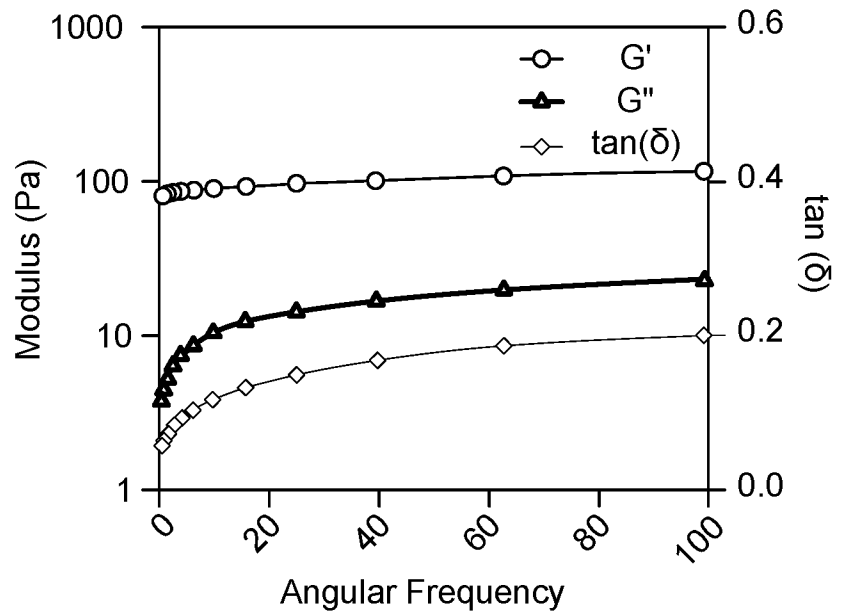


FIG. 11

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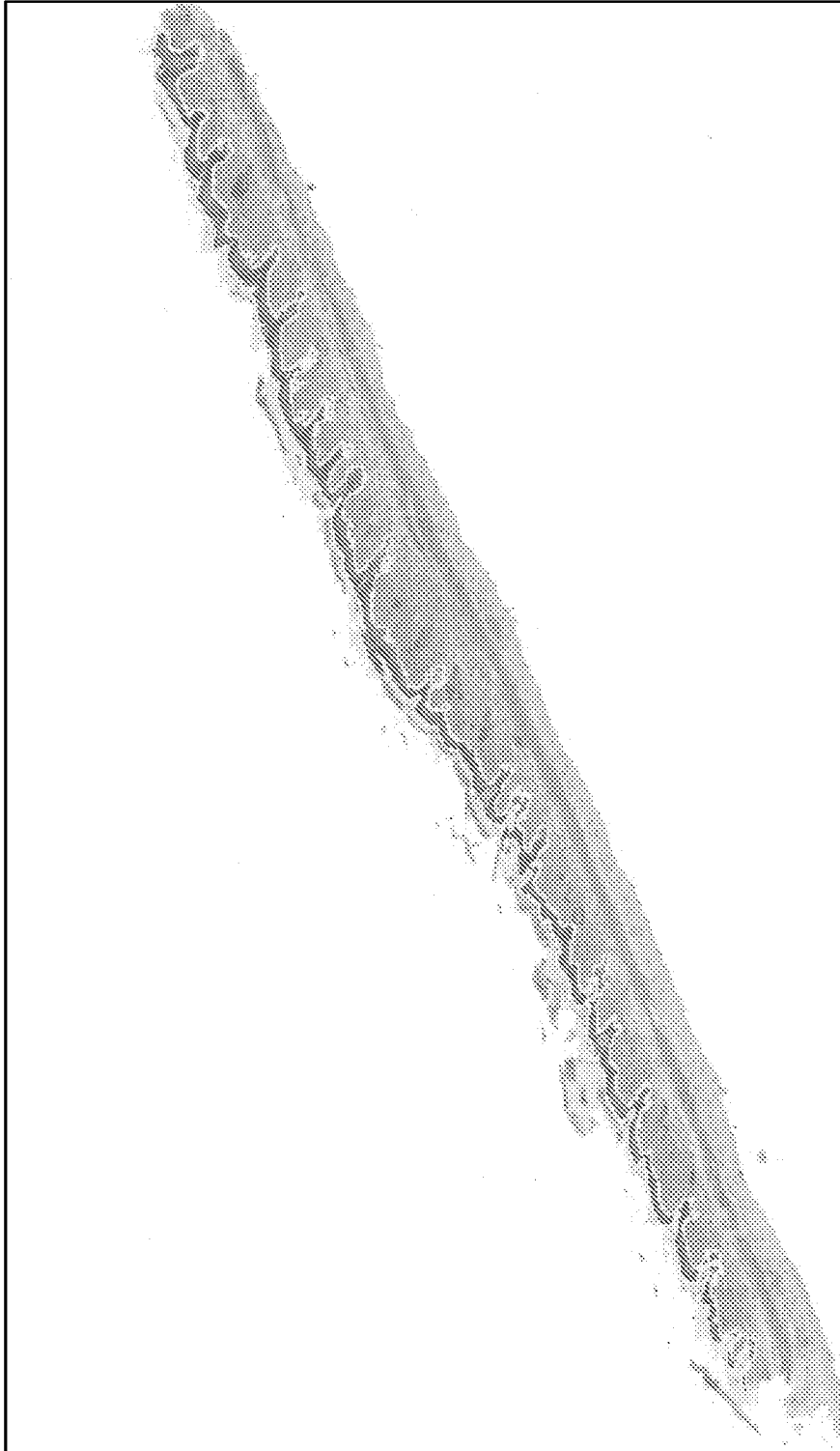


FIG. 12

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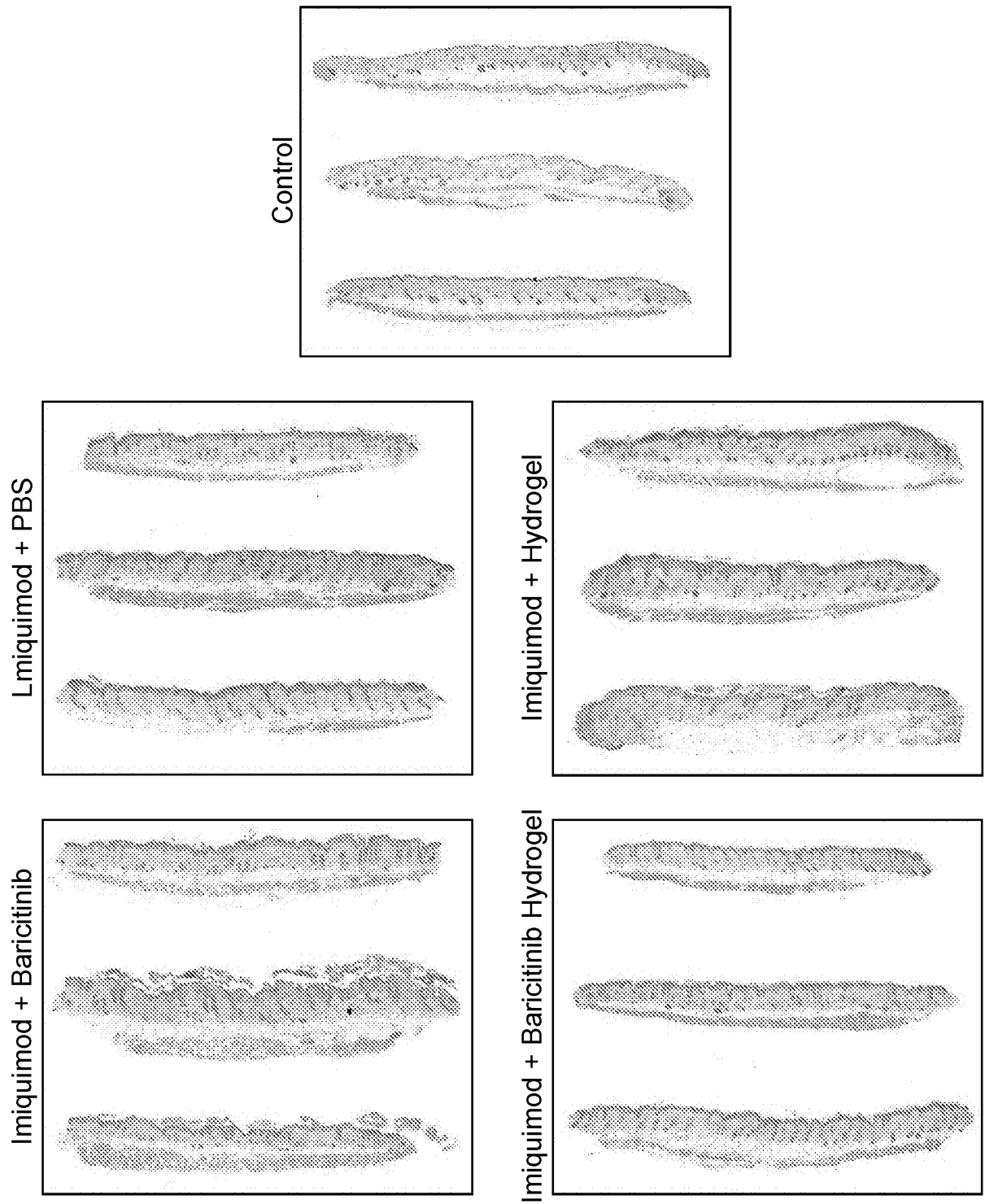


FIG. 13

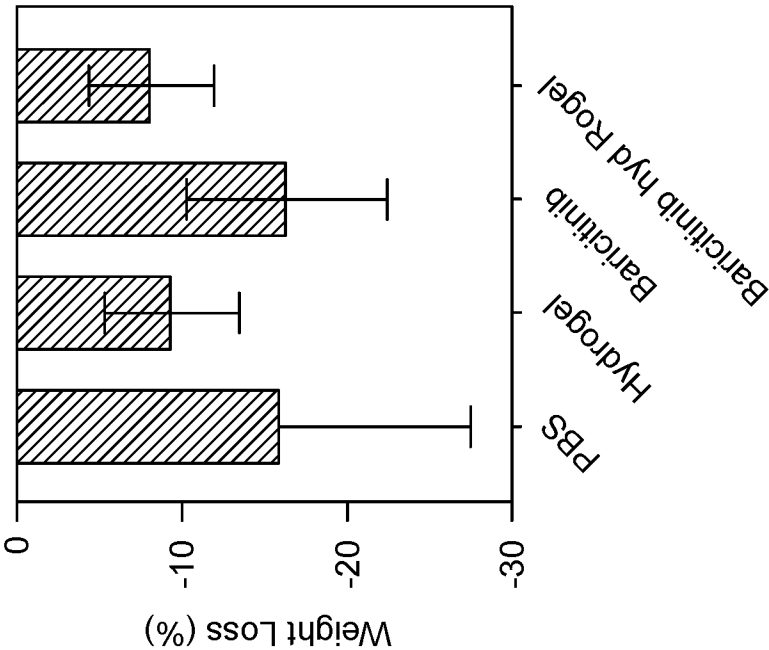


FIG. 14B

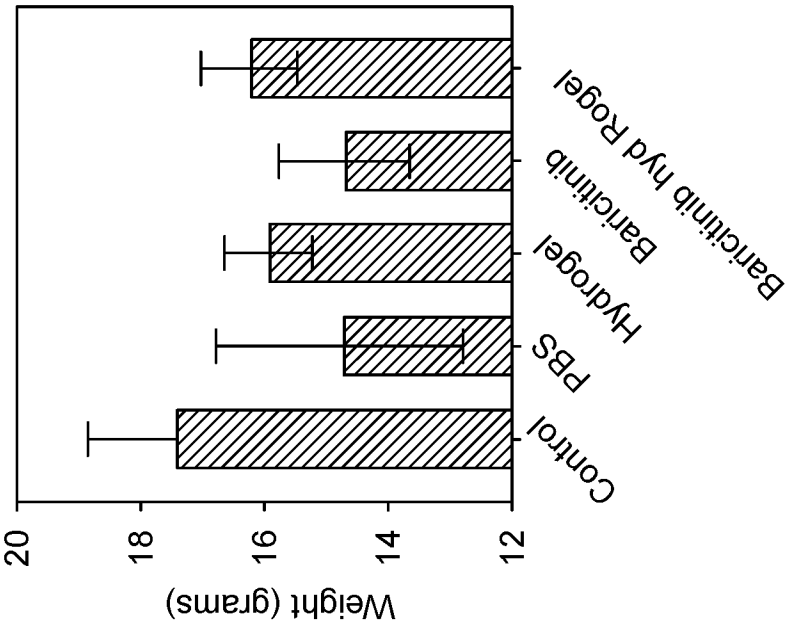
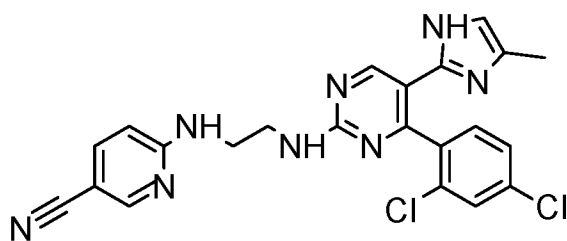


FIG. 14A

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FIG. 16



CHIR99021

Thiolated HA



CHIR99021



Thioimide complex

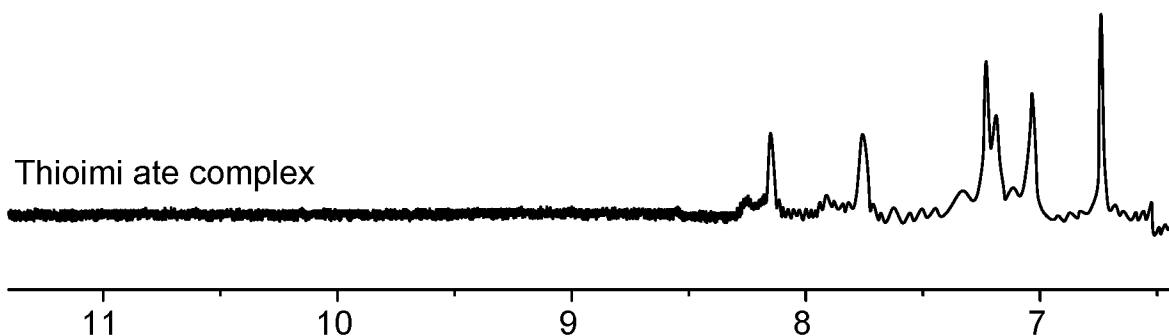


FIG. 16

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2024/056342

A. CLASSIFICATION OF SUBJECT MATTERIPC: **A61K 31/395** (2025.01); **A61K 31/18** (2025.01); **A61K 31/505** (2025.01); **A61K 31/33** (2025.01)CPC: **A61K 31/395**; **A61K 31/18**; **A61K 31/505**; **A61K 31/33**

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History Document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

See Search History Document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2018/0243481 A1 (The Johns Hopkins University) 20 August 2018 (20.08.2018) para [0118], [0263], [0300]	1-7, 10-11, 14-15, 18-24, 26-27, 30
A	US 2022/0257600 A1 (Progenity, Inc) 18 August 2022 (18.08.2022) entire document	1-7, 10-11, 14-15, 18-24, 26-27, 30- 32, 35-36, 39-41
A	US 2021/0338834 A1 (Ascendis Pharma) 04 November 2021 (04.11.2021) entire document	1-7, 10-11, 14-15, 18-24, 26-27, 30- 32, 35-36, 39-41

☒ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

“A” document defining the general state of the art which is not considered to be of particular relevance

“D” document cited by the applicant in the international application

“E” earlier application or patent but published on or after the international filing date

“L” document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

“O” document referring to an oral disclosure, use, exhibition or other means

“P” document published prior to the international filing date but later than the priority date claimed

“T” later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

“X” document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

“Y” document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

“&” document member of the same patent family

Date of the actual completion of the international search

13 January 2025 (13.01.2025)

Date of mailing of the international search report

19 March 2025 (19.03.2025)

Name and mailing address of the ISA/US

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KARI RODRIQUEZ

Facsimile No. 571-273-8300

Telephone No. PCT Help Desk: 571-272-4300

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

Group I+: Claims 1-43 are directed to a sustained delivery JAK inhibitor hydrogel for treatment of an inflammatory disorder, an autoimmune disease, an autoimmune and inflammatory hair loss, and/or a non-inflammatory disorder hair loss, the sustained delivery JAK inhibitor hydrogel comprising a JAK inhibitor having a nitrile group reversibly conjugated to a thiol group of a thiolated polymer to form a thioimide adduct. Claim 1 will be searched to the extent that it encompasses the first species of sustained delivery JAK inhibitor hydrogel of claim 1, wherein the treatment is inflammatory disorder, the sustained delivery JAK inhibitor hydrogel comprising a JAK inhibitor having a nitrile group selected from the first choice of instant claim 7, i.e., baricitinib reversibly conjugated to a thiol group of a thiolated polymer of first choice of instant claim 2, i.e., thiolated hyaluronic acid to form a thioimide adduct and the formation is formulated to first choice of instant claim 11, i.e., local administration comprises intradermal injection. It is believed that claims 1-7, 10-11, 14-15, 18-24, 26-27, 30-32, 35-36, and 39-41 read on this first named invention, and thus these claims will be searched without fee.

Group II: claims 44-87 are directed towards a method for treating an inflammatory disorder, an autoimmune disease, an autoimmune and inflammatory hair loss, and/or a non-inflammatory disorder hair loss in a subject in need thereof, the method comprising administering the sustained delivery nitrile-containing JAK inhibitor hydrogel according to any one of claims 1 to 9 to a body part of the subject affected by the inflammatory disorder, the autoimmune disease, the autoimmune and inflammatory hair loss, and/or the non-inflammatory disorder hair loss.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: **1-7, 10-11, 14-15, 18-24, 26-27, 30-32, 35-36, 39-41**

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Zheng et al, "Controlled release of baricitinib from a thermos-responsive hydrogel system inhibits inflammation by suppressing JAK2/STAT3 pathway in acute spinal cord injury" 29 December 2020 abstract	31-32, 35-36, 39
Y	entire document	1-7, 10-11, 14-15, 18-24, 26-27, 30, 40-41
Y	Noddeland et al, "Design and characterization of matrix metalloproteinase-responsive hydrogels for the treatment of inflammatory skin diseases" 13 December 2022 page 150, col 2, paragraph 2, page 160, col 1, paragraph 1	14-15, 26-27, 40-41