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[Continued on next page]

(54) Title: PHARMACEUTICAL COMBINATIONS USEFUL FOR TREATING RHEUMATOID ARTHRITIS

Mean Plasma Concentrations of Prednisone After Oral Administration Without (Day 1) and With (Day 7) Compound 1, Linear Scale (PK Set)

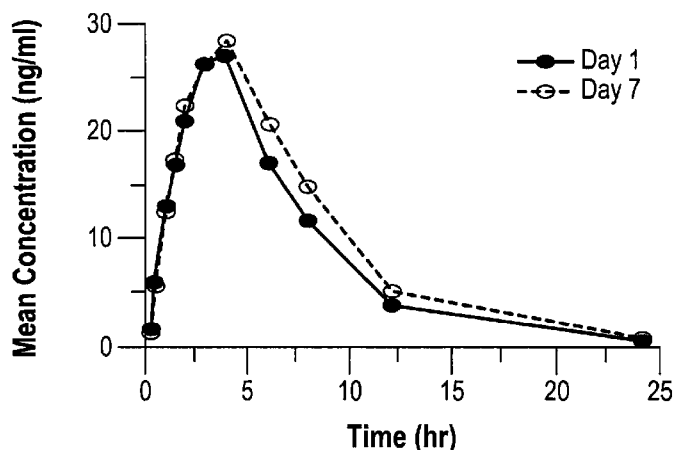


FIG. 1

(57) Abstract: The present invention provides a method of treating or lessening the severity of a disease or disorder mediated by an abnormal immune response (e.g., rheumatoid arthritis) comprising the administration of a compound of Formula I and a corticosteroid.



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**PHARMACEUTICAL COMBINATIONS USEFUL FOR TREATING RHEUMATOID
ARTHRITIS**

CROSS REFERENCE TO RELATED APPLICATION

[0001] The present PCT Application claims the benefit of U.S. Application Serial No. 61/835,095, filed on June 14, 2013. This application is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

[0002] The present invention relates to pharmaceutical combinations and methods for treating or lessening the severity of rheumatoid arthritis with a compound of Formula I and a second API.

BACKGROUND

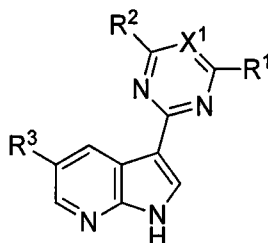
[0003] The Janus kinases (JAK) are a family of tyrosine kinases consisting of JAK1, JAK2, JAK3, and TYK2. The JAKs play a critical role in cytokine signaling. The down-stream substrates of the JAK family of kinases include the signal transducer and activator of transcription (STAT) proteins. JAK/STAT signaling has been implicated in the mediation of many abnormal immune responses such as SLE, rheumatoid arthritis (RA), and spondyloarthropathies including peripheral spondyloarthropathy, axial spondyloarthropathy, UC, Crohn's disease, ankylosing spondylitis, reactive arthritis, Reiter's syndrome, and psoriatic arthritis. Moreover, JAK kinases represent an established therapeutic target for these diseases. For example, JAK kinases are an established therapeutic target for treating SLE, RA, spondyloarthropathies including peripheral spondyloarthropathy, axial spondyloarthropathy, UC, Crohn's disease, ankylosing spondylitis, reactive arthritis, Reiter's syndrome, and psoriatic arthritis. Stump K. L., et al., *Arthritis Res. Ther.* (2011) 13:R68; Fridman J.S., et al., *J. Immunol.* (2010) 184:5298-5307; West K., *Curr. Op. Investig. Drugs* (2009) 10:491-504; Kremer J. M. et al., *Arthritis Rheumatism* (2009) 60(7):1895-1905; Xiong, W. et al., *Ther Adv Musculoskelet Dis.* (2011) 3(5): 255–266; Panes, J. et al. 19th Ann. Eur. Gastroenterology Week (Oct 22-26, 2011) Stockholm, SE, P1456; and *Drugs in R & D “Tofacitinib”* (2010) 10(4):271-84.

[0004] Compounds described as kinase inhibitors, particularly the JAK family kinases, are disclosed in WO 2005/095400 and WO 2007/084557. Also disclosed in these publications are processes and intermediates for preparing these compounds. There remains, however, a need for alternative pharmaceutical therapies for patients suffering from abnormal immune response mediated diseases that include co-therapies and methods of administering the same.

SUMMARY OF THE INVENTION

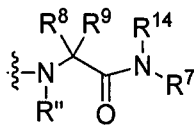
[0005] In general, the invention relates to pharmaceutical compositions and methods for treating or lessening the severity of rheumatoid arthritis with a compound of Formula I or a combination of a compound of Formula I and a co-therapy.

[0006] In one aspect, the present invention provides a method for treating or lessening the severity of rheumatoid arthritis or other disease mediated by an abnormal immune response comprising administering to a patient in need thereof a corticosteroid and a compound of Formula I



I

or a pharmaceutically acceptable salt thereof, wherein X¹ is N or CR⁴; R² is H or halo; R³ is



H or halo; R⁴ is H or halo; R¹ is ; R'' is H or an unsubstituted C₁₋₂ aliphatic; R⁸ is an unsubstituted C₁₋₄ aliphatic; R⁹ is an unsubstituted C₁₋₄ aliphatic; R⁷ is a C₁₋₃ aliphatic optionally substituted with up to 3 occurrences of F; and R¹⁴ is H or unsubstituted C₁₋₂ alkyl.

[0007] In some embodiments, R² is H or F.

[0008] In some embodiments, R³ is H or Cl.

[0009] In some embodiments, each of R⁸ and R⁹ is independently selected from methyl, ethyl, propyl, iso-propyl, butyl, or tert-butyl. For example, each of R⁸ and R⁹ is independently selected from methyl or ethyl.

[0010] In some embodiments, R¹⁴ is H or methyl.

[0011] In some embodiments, R⁷ is an unsubstituted C₁₋₃ aliphatic.

[0012] In some embodiments, R⁷ is a C₁₋₃ aliphatic substituted with 1-3 occurrences of F. For instance, R⁷ is a group selected from -CH₂CH₃, -CH₂CF₃, -CH₂CH₂CH₃, or -CHCH₃CH₃.

[0013] In some embodiments, the compound of Formula I is selected from Table 1.

[0014] In some embodiments, the compound of Formula I is administered at least once per day.

[0015] In some embodiments, the compound of Formula I is administered from 1 to 4 times per day.

[0016] In some embodiments, the compound of Formula I is orally administered to the patient in need thereof.

[0017] In some embodiments, at least about 20 mg of the compound of Formula I is administered to the patient at least once per day.

[0018] In some embodiments, at least about 100 mg of the compound of Formula I is administered to the patient once per day.

[0019] In some embodiments, at least about 150 mg of the compound of Formula I is administered to the patient once per day.

[0020] In some embodiments, at least about 200 mg of the compound of Formula I is administered to the patient once per day.

[0021] In some embodiments, at least about 20 mg of the compound of Formula I is administered to the patient twice per day.

[0022] In some embodiments, at least about 50 mg of the compound of Formula I is administered to the patient twice per day.

[0023] In some embodiments, at least about 100 mg of the compound of Formula I is administered to the patient twice per day.

[0024] In some embodiments, at least about 150 mg of the compound of Formula I is administered to the patient twice per day.

[0025] In some embodiments, the corticosteroid is hydrocortisone, hydrocortisone acetate, cortisone acetate, tixocortol pivalate, prednisone, prednisolone, methylprednisone, methylprednisolone, or any combination thereof.

[0026] In some embodiments, the corticosteroid is prednisone.

[0027] In some embodiments, the corticosteroid is methylprednisone.

[0028] In some embodiments, the corticosteroid is orally administered to the patient in need thereof.

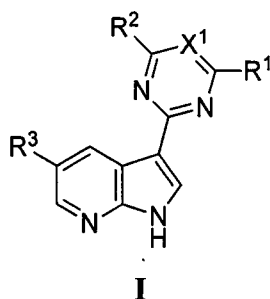
[0029] In some embodiments, at least about 5 mg of corticosteroid is administered at least once per week.

[0030] In some embodiments, at least about 8 mg of corticosteroid is administered at least once per week.

[0031] In some embodiments, at least about 8 mg of corticosteroid is administered at least twice per week.

[0032] In some embodiments, the corticosteroid is prednisone or methylprednisone.

[0033] Another aspect of the present invention provides a method for treating or lessening the severity of rheumatoid arthritis comprising administering to a patient in need thereof a corticosteroid and a pharmaceutical composition comprising a compound of Formula I



or a pharmaceutically acceptable salt thereof, wherein X^1 is N or CR^4 ; R^2 is H or halo; R^3 is

H or halo; R^4 is H or halo; R^1 is ; R'' is H or an unsubstituted C_{1-2} aliphatic; R^8 is an unsubstituted C_{1-4} aliphatic; R^9 is an unsubstituted C_{1-4} aliphatic; R^7 is a C_{1-3} aliphatic optionally substituted with up to 3 occurrences of F; and R^{14} is H or unsubstituted C_{1-2} alkyl.

[0034] In some embodiments, R^2 is H or F.

[0035] In some embodiments, R^3 is H or Cl.

[0036] In some embodiments, each of R^8 and R^9 is independently selected from methyl, ethyl, propyl, iso-propyl, butyl, or tert-butyl. For example, each of R^8 and R^9 is independently selected from methyl or ethyl.

[0037] In some embodiments, R^{14} is H or methyl.

[0038] In some embodiments, R^7 is an unsubstituted C_{1-3} aliphatic.

[0039] In some embodiments, R^7 is a C_{1-3} aliphatic substituted with 1-3 occurrences of F.

[0040] In some embodiments, R^7 is a group selected from $-CH_2CH_3$, $-CH_2CF_3$, $-CH_2CH_2CH_3$, or $-CHCH_3CH_3$.

[0041] In some embodiments, the compound of Formula I is selected from Table 1.

[0042] In some embodiments, the pharmaceutical composition further comprises a tablet.

[0043] In some embodiments, the tablet further comprises a diluent, a binder, a glidant, a disintegrant, a surfactant, a lubricant, or any combination thereof.

[0044] In some embodiments, the tablet comprises at least about 10 mg of the compound of Formula I.

[0045] In some embodiments, the tablet comprises from about 15 mg to about 100 mg of the compound of Formula I.

[0046] In some embodiments, the tablet is administered at least once per day.

[0047] Some embodiments further comprise administering once per day at least one tablet comprising the pharmaceutical composition.

[0048] Some embodiments further comprise administering twice per day at least one tablet comprising the pharmaceutical composition.

[0049] In some embodiments, each tablet further comprises from about 20 mg to about 100 mg of the compound of Formula I.

[0050] In some embodiments, the corticosteroid is hydrocortisone, hydrocortisone acetate, cortisone acetate, tixocortol pivalate, prednisone, prednisolone, methylprednisone, methylprednisolone, or any combination thereof.

[0051] In some embodiments, the corticosteroid is prednisone.

[0052] In some embodiments, the corticosteroid is methylprednisone.

[0053] In some embodiments, the corticosteroid is orally administered to the patient in need thereof.

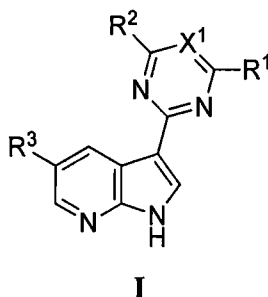
[0054] In some embodiments, at least about 5 mg of corticosteroid is administered at least once per week.

[0055] In some embodiments, at least about 8 mg of corticosteroid is administered at least once per week.

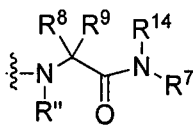
[0056] In some embodiments, at least about 8 mg of corticosteroid is administered at least twice per week.

[0057] In some embodiments, the corticosteroid is prednisone or methylprednisone.

[0058] Another aspect of the present invention provides a method for treating or lessening the severity of rheumatoid arthritis comprising administering to a patient in need thereof a corticosteroid and compound of Formula I



or a pharmaceutically acceptable salt thereof, wherein X^1 is N or CR^4 ; R^2 is H or halo; R^3 is

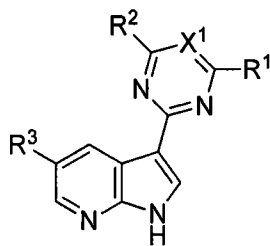


H or halo; R^4 is H or halo; R^1 is H or halo; R'' is H or an unsubstituted C_{1-2} aliphatic; R^8 is an unsubstituted C_{1-4} aliphatic; R^9 is an unsubstituted C_{1-4} aliphatic; R^7 is a C_{1-3} aliphatic optionally substituted with up to 3 occurrences of F; and R^{14} is H or unsubstituted C_{1-2} alkyl, or a pharmaceutically acceptable salt thereof wherein at least about 25 mg of the compound of Formula I is administered to the patient at least once per day.

[0059] In some embodiments, from about 25 mg to about 250 mg of the compound of formula I is administered to the patient once per day or twice per day.

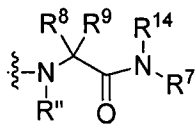
- [0060] In some embodiments, from about 100 mg to about 200 mg of the compound of formula I is administered to the patient once per day or twice per day.
- [0061] In some embodiments, the corticosteroid is hydrocortisone, hydrocortisone acetate, cortisone acetate, tixocortol pivalate, prednisone, prednisolone, methylprednisone, methylprednisolone, or any combination thereof.
- [0062] In some embodiments, the corticosteroid is prednisone.
- [0063] In some embodiments, the corticosteroid is methylprednisone.
- [0064] In some embodiments, the corticosteroid is orally administered to the patient in need thereof.
- [0065] In some embodiments, at least about 5 mg of corticosteroid is administered at least once per week.
- [0066] In some embodiments, at least about 8 mg of corticosteroid is administered at least once per week.
- [0067] In some embodiments, at least about 8 mg of corticosteroid is administered at least twice per week.
- [0068] In some embodiments, the corticosteroid is prednisone or methylprednisone.
- [0069] In some embodiments, R^2 is H or F.
- [0070] In some embodiments, R^3 is H or Cl.
- [0071] In some embodiments, each of R^8 and R^9 is independently selected from methyl, ethyl, propyl, iso-propyl, butyl, or tert-butyl.
- [0072] In some embodiments, each of R^8 and R^9 is independently selected from methyl or ethyl.
- [0073] In some embodiments, R^{14} is H or methyl.
- [0074] In some embodiments, R^7 is an unsubstituted C_{1-3} aliphatic.
- [0075] In some embodiments, R^7 is a C_{1-3} aliphatic substituted with 1-3 occurrences of F.
- [0076] In some embodiments, R^7 is a group selected from $-CH_2CH_3$, $-CH_2CF_3$, $-CH_2CH_2CH_3$, or $-CHCH_3CH_3$.
- [0077] In some embodiments, the compound of Formula I is selected from Table 1.

[0078] Another aspect of the present invention provides a pharmaceutical composition comprising a corticosteroid and a compound of Formula I



I

or a pharmaceutically acceptable salt thereof, wherein X¹ is N or CR⁴; R² is H or halo; R³ is



H or halo; R⁴ is H or halo; R¹ is ; R^{''} is H or an unsubstituted C₁₋₂ aliphatic; R⁸ is an unsubstituted C₁₋₄ aliphatic; R⁹ is an unsubstituted C₁₋₄ aliphatic; R⁷ is a C₁₋₃ aliphatic optionally substituted with up to 3 occurrences of F; and R¹⁴ is H or unsubstituted C₁₋₂ alkyl.

[0079] In some embodiments, R² is H or F.

[0080] In some embodiments, R³ is H or Cl.

[0081] In some embodiments, each of R⁸ and R⁹ is independently selected from methyl, ethyl, propyl, iso-propyl, butyl, or tert-butyl. For example, each of R⁸ and R⁹ is independently selected from methyl or ethyl.

[0082] In some embodiments, R¹⁴ is H or methyl.

[0083] In some embodiments, R⁷ is an unsubstituted C₁₋₃ aliphatic.

[0084] In some embodiments, R⁷ is a C₁₋₃ aliphatic substituted with 1-3 occurrences of F.

[0085] In some embodiments, R⁷ is a group selected from -CH₂CH₃, -CH₂CF₃, -CH₂CH₂CH₃, or -CHCH₃CH₃.

[0086] In some embodiments, the compound of Formula I is selected from Table 1, below.

[0087] And, in some embodiments, the corticosteroid is hydrocortisone, hydrocortisone acetate, cortisone acetate, tixocortol pivalate, prednisone, prednisolone, methylprednisone, methylprednisolone, or any combination thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

[0088] FIG. 1 is a plot of mean plasma concentration as a function of time generated from the study the effect of Compound 1 on PK of prednisone described in Example 18.

[0089] FIG. 2 is a plot of mean plasma concentration as a function of time generated from the study the effect of Compound 1 on PK of prednisolone described in Example 18.

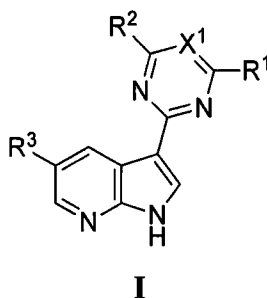
[0090] FIG. 3 is a plot of mean plasma concentration as a function of time generated from the study the effect of Compound 1 on PK of methylprednisone described in Example 18.

DETAILED DESCRIPTION

[0091] The present invention provides methods of treating or lessening the severity of rheumatoid arthritis comprising the administration of a compound of Formula I and a corticosteroid, and pharmaceutical compositions thereof.

[0092] I. DEFINITIONS

[0093] As used herein, the term "active pharmaceutical ingredient" or "API" refers to a biologically active compound. One exemplary API is a corticosteroid (e.g., prednisone, prednisolone, methylprednisone, or methylprednisolone). Another exemplary API includes a protein kinase inhibitor (e.g., a JAK inhibitor) such as a compound of Formula I:



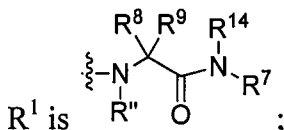
or a pharmaceutically acceptable salt thereof, wherein:

X^1 is N or CR^4 ;

R^2 is H or halo;

R^3 is H or halo;

R^4 is H or halo;



R'' is H or an unsubstituted C_{1-2} aliphatic;

R^8 is an unsubstituted C_{1-4} aliphatic;

R^9 is an unsubstituted C_{1-4} aliphatic;

R^7 is a C_{1-3} aliphatic optionally substituted with up to 3 occurrences of F; and

R^{14} is H or unsubstituted C_{1-2} alkyl.

[0094] As used herein, a "protein kinase inhibitor" refers to a compound that exhibits biological activity characterized by blocking the action of one or more protein kinases.

[0095] As used herein, an "excipient" is an inactive ingredient in a pharmaceutical composition. Examples of excipients include fillers or diluents, wetting agents (e.g., surfactants), binders, glidants, lubricants, disintegrants, or the like.

[0096] As used herein, a "disintegrant" is an excipient that hydrates a pharmaceutical composition and aids in tablet dispersion. Examples of disintegrants include sodium croscarmellose and/or sodium starch glycolate.

[0097] As used herein, a "diluent" or "filler" is an excipient that adds bulkiness to a pharmaceutical composition. Examples of fillers include lactose, sorbitol, celluloses, calcium phosphates, starches, sugars (e.g., mannitol, sucrose, or the like) or any combination thereof.

[0098] As used herein, a "wetting agent" or a "surfactant" is an excipient that imparts pharmaceutical compositions with enhanced solubility and/or wettability. Examples of wetting agents include sodium lauryl sulfate (SLS), sodium stearyl fumarate (SSF), polyoxyethylene 20 sorbitan mono-oleate (e.g., Tween™), or any combination thereof.

[0099] As used herein, a "binder" is an excipient that imparts a pharmaceutical composition with enhanced cohesion or tensile strength (e.g., hardness). Examples of binders include dibasic calcium phosphate, sucrose, corn (maize) starch, microcrystalline cellulose, and modified cellulose (e.g., hydroxymethyl cellulose).

[0100] As used herein, a "glidant" is an excipient that imparts a pharmaceutical compositions with enhanced flow properties. Examples of glidants include colloidal silica and/or talc.

[0101] As used herein, a "colorant" is an excipient that imparts a pharmaceutical composition with a desired color. Examples of colorants include commercially available pigments such as FD&C Blue # 1 Aluminum Lake, FD&C Blue #2, other FD&C Blue colors, titanium dioxide, iron oxide, and/or combinations thereof.

[0102] As used herein, a "lubricant" is an excipient that is added to pharmaceutical compositions that are pressed into tablets. The lubricant aids in compaction of granules into tablets and ejection of a tablet of a pharmaceutical composition from a die press. Examples of lubricants include magnesium stearate, stearic acid (stearin), hydrogenated oil, sodium stearyl fumarate, or any combination thereof.

[0103] As used herein, "friability" refers to the property of a tablet to remain intact and withhold its form despite an external force of pressure. Friability can be quantified using the mathematical expression presented in equation 1:

$$\% \text{ friability} = 100 \times \frac{(W_0 - W_f)}{W_0} \quad (1)$$

wherein W_0 is the original weight of the tablet and W_f is the final weight of the tablet after it is put through the friabilator.

[0104] Friability is measured using a standard USP testing apparatus that tumbles experimental tablets for 100 revolutions. Some tablets of the present invention have a

friability of less than about 1% (e.g., less than about 0.75%, less than about 0.50%, or less than about 0.30%).

[0105] For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed. Additionally, general principles of organic chemistry are described in "Organic Chemistry", Thomas Sorrell, University Science Books, Sausalito: 1999, and "March's Advanced Organic Chemistry", 5th Ed., Ed.: Smith, M.B. and March, J., John Wiley & Sons, New York: 2001, the entire contents of which are hereby incorporated by reference.

[0106] As described herein, compounds of the invention may optionally be substituted with one or more substituents, such as are illustrated generally above, or as exemplified by particular classes, subclasses, and species of the invention.

[0107] As used herein the term "aliphatic" encompasses the terms alkyl, alkenyl, alkynyl, each of which being optionally substituted as set forth below.

[0108] As used herein, an "alkyl" group refers to a saturated aliphatic hydrocarbon group containing 1-12 (e.g., 1-3, 1-8, 1-6, or 1-4) carbon atoms. An alkyl group can be straight or branched. Examples of alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, n-heptyl, or 2-ethylhexyl. An alkyl group can be substituted (i.e., optionally substituted) with one or more substituents such as halo, phospho, cycloaliphatic [e.g., cycloalkyl or cycloalkenyl], heterocycloaliphatic [e.g., heterocycloalkyl or heterocycloalkenyl], aryl, heteroaryl, alkoxy, aroyl, heteroaroyl, acyl [e.g., (aliphatic)carbonyl, (cycloaliphatic)carbonyl, or (heterocycloaliphatic)carbonyl], nitro, cyano, amido [e.g., (cycloalkylalkyl)carbonylamino, arylcarbonylamino, aralkylcarbonylamino, (heterocycloalkyl)carbonylamino, (heterocycloalkylalkyl)carbonylamino, heteroarylcarbonylamino, heteroaralkylcarbonylamino alkylaminocarbonyl, cycloalkylaminocarbonyl, heterocycloalkylaminocarbonyl, arylaminocarbonyl, or heteroarylaminocarbonyl], amino [e.g., aliphaticamino, cycloaliphaticamino, or heterocycloaliphaticamino], sulfonyl [e.g., aliphatic-SO₂-], sulfinyl, sulfanyl, sulfoxy, urea, thiourea, sulfamoyl, sulfamide, oxo, carboxy, carbamoyl, cycloaliphaticoxy, heterocycloaliphaticoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroarylalkoxy, alkoxycarbonyl, alkylcarbonyloxy, or hydroxy. Without limitation, some examples of substituted alkyls include carboxyalkyl (such as HOOC-alkyl, alkoxycarbonylalkyl, and alkylcarbonyloxyalkyl), cyanoalkyl, hydroxyalkyl, alkoxyalkyl, acylalkyl, aralkyl, (alkoxyaryl)alkyl, (sulfonylamino)alkyl (such as (alkyl-SO₂-amino)alkyl), aminoalkyl, amidoalkyl, (cycloaliphatic)alkyl, or haloalkyl.

[0109] As used herein, an "alkenyl" group refers to an aliphatic carbon group that contains 2-8 (e.g., 2-12, 2-6, or 2-4) carbon atoms and at least one double bond. Like an alkyl group, an alkenyl group can be straight or branched. Examples of an alkenyl group include, but are not limited to allyl, isoprenyl, 2-butenyl, and 2-hexenyl. An alkenyl group can be optionally substituted with one or more substituents such as halo, phospho, cycloaliphatic [e.g., cycloalkyl or cycloalkenyl], heterocycloaliphatic [e.g., heterocycloalkyl or heterocycloalkenyl], aryl, heteroaryl, alkoxy, aroyl, heteroaroyl, acyl [e.g., (aliphatic)carbonyl, (cycloaliphatic)carbonyl, or (heterocycloaliphatic)carbonyl], nitro, cyano, amido [e.g., (cycloalkylalkyl)carbonylamino, arylcarbonylamino, aralkylcarbonylamino, (heterocycloalkyl)carbonylamino, (heterocycloalkylalkyl)carbonylamino, heteroarylcarbonylamino, heteroaralkylcarbonylamino alkylaminocarbonyl, cycloalkylaminocarbonyl, heterocycloalkylaminocarbonyl, arylaminocarbonyl, or heteroarylaminocarbonyl], amino [e.g., aliphaticamino, cycloaliphaticamino, heterocycloaliphaticamino, or aliphatic-sulfonylamino], sulfonyl [e.g., alkyl-SO₂-, cycloaliphatic-SO₂-, or aryl-SO₂-], sulfinyl, sulfanyl, sulfoxy, urea, thiourea, sulfamoyl, sulfamide, oxo, carboxy, carbamoyl, cycloaliphaticoxy, heterocycloaliphaticoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkoxy, alkoxycarbonyl, alkylcarbonyloxy, or hydroxy. Without limitation, some examples of substituted alkenyls include cyanoalkenyl, alkoxyalkenyl, acylalkenyl, hydroxyalkenyl, aralkenyl, (alkoxyaryl)alkenyl, (sulfonylamino)alkenyl (such as (alkyl-SO₂-amino)alkenyl), aminoalkenyl, amidoalkenyl, (cycloaliphatic)alkenyl, or haloalkenyl.

[0110] As used herein, an "alkynyl" group refers to an aliphatic carbon group that contains 2-8 (e.g., 2-12, 2-6, or 2-4) carbon atoms and has at least one triple bond. An alkynyl group can be straight or branched. Examples of an alkynyl group include, but are not limited to, propargyl and butynyl. An alkynyl group can be optionally substituted with one or more substituents such as aroyl, heteroaroyl, alkoxy, cycloalkyloxy, heterocycloalkyloxy, aryloxy, heteroaryloxy, aralkyloxy, nitro, carboxy, cyano, halo, hydroxy, sulfo, mercapto, sulfanyl [e.g., aliphatic-sulfanyl or cycloaliphatic-sulfanyl], sulfinyl [e.g., aliphatic-sulfinyl or cycloaliphatic-sulfinyl], sulfonyl [e.g., aliphatic-SO₂-, aliphaticamino-SO₂-, or cycloaliphatic-SO₂-], amido [e.g., aminocarbonyl, alkylaminocarbonyl, alkylcarbonylamino, cycloalkylaminocarbonyl, heterocycloalkylaminocarbonyl, cycloalkylcarbonylamino, arylaminocarbonyl, arylcarbonylamino, aralkylcarbonylamino, (heterocycloalkyl)carbonylamino, (cycloalkylalkyl)carbonylamino, heteroaralkylcarbonylamino, heteroarylcarbonylamino or heteroarylaminocarbonyl], urea, thiourea, sulfamoyl, sulfamide, alkoxycarbonyl, alkylcarbonyloxy, cycloaliphatic,

heterocycloaliphatic, aryl, heteroaryl, acyl [e.g., (cycloaliphatic)carbonyl or (heterocycloaliphatic)carbonyl], amino [e.g., aliphaticamino], sulfoxy, oxo, carboxy, carbamoyl, (cycloaliphatic)oxy, (heterocycloaliphatic)oxy, or (heteroaryl)alkoxy.

[0111] As used herein, an "amido" encompasses both "aminocarbonyl" and "carbonylamino". These terms when used alone or in connection with another group refer to an amido group such as $-N(R^X)-C(O)-R^Y$ or $-C(O)-N(R^X)_2$, when used terminally, and $-C(O)-N(R^X)-$ or $-N(R^X)-C(O)-$ when used internally, wherein R^X and R^Y can be aliphatic, cycloaliphatic, aryl, araliphatic, heterocycloaliphatic, heteroaryl or heteroaraliphatic. Examples of amido groups include alkylamido (such as alkylcarbonylamino or alkylaminocarbonyl), (heterocycloaliphatic)amido, (heteroaralkyl)amido, (heteroaryl)amido, (heterocycloalkyl)alkylamido, arylamido, aralkylamido, (cycloalkyl)alkylamido, or cycloalkylamido.

[0112] As used herein, an "amino" group refers to $-NR^X R^Y$ wherein each of R^X and R^Y is independently hydrogen, aliphatic, cycloaliphatic, (cycloaliphatic)aliphatic, aryl, araliphatic, heterocycloaliphatic, (heterocycloaliphatic)aliphatic, heteroaryl, carboxy, sulfanyl, sulfinyl, sulfonyl, (aliphatic)carbonyl, (cycloaliphatic)carbonyl, ((cycloaliphatic)aliphatic)carbonyl, arylcarbonyl, (araliphatic)carbonyl, (heterocycloaliphatic)carbonyl, ((heterocycloaliphatic)aliphatic)carbonyl, (heteroaryl)carbonyl, or (heteroaraliphatic)carbonyl, each of which being defined herein and being optionally substituted. Examples of amino groups include alkylamino, dialkylamino, or arylamino. When the term "amino" is not the terminal group (e.g., alkylcarbonylamino), it is represented by $-NR^X-$. R^X has the same meaning as defined above.

[0113] As used herein, an "aryl" group used alone or as part of a larger moiety as in "aralkyl", "aralkoxy", or "aryloxyalkyl" refers to monocyclic (e.g., phenyl); bicyclic (e.g., indenyl, naphthalenyl, tetrahydronaphthyl, tetrahydroindenyl); and tricyclic (e.g., fluorenyl, tetrahydrofluorenyl, or tetrahydroanthracenyl, anthracenyl) ring systems in which the monocyclic ring system is aromatic or at least one of the rings in a bicyclic or tricyclic ring system is aromatic. The bicyclic and tricyclic groups include benzo fused 2-3 membered carbocyclic rings. For example, a benzofused group includes phenyl fused with two or more C_{4-8} carbocyclic moieties. An aryl is optionally substituted with one or more substituents including aliphatic [e.g., alkyl, alkenyl, or alkynyl]; cycloaliphatic; (cycloaliphatic)aliphatic; heterocycloaliphatic; (heterocycloaliphatic)aliphatic; aryl; heteroaryl; alkoxy; (cycloaliphatic)oxy; (heterocycloaliphatic)oxy; aryloxy; heteroaryloxy; (araliphatic)oxy; (heteroaraliphatic)oxy; aroyl; heteroaroyl; amino; oxo (on a non-aromatic carbocyclic ring of a benzofused bicyclic or tricyclic aryl); nitro; carboxy; amido; acyl [e.g., (aliphatic)carbonyl];

(cycloaliphatic)carbonyl; ((cycloaliphatic)aliphatic)carbonyl; (araliphatic)carbonyl; (heterocycloaliphatic)carbonyl; ((heterocycloaliphatic)aliphatic)carbonyl; or (heteroaraliphatic)carbonyl]; sulfonyl [e.g., aliphatic-SO₂- or amino-SO₂-]; sulfinyl [e.g., aliphatic-S(O)- or cycloaliphatic-S(O)-]; sulfanyl [e.g., aliphatic-S-]; cyano; halo; hydroxy; mercapto; sulfoxy; urea; thiourea; sulfamoyl; sulfamide; or carbamoyl. Alternatively, an aryl can be unsubstituted.

[0114] Non-limiting examples of substituted aryls include haloaryl [e.g., mono-, di (such as *p,m*-dihaloaryl), and (trihalo)aryl]; (carboxy)aryl [e.g., (alkoxycarbonyl)aryl, ((aralkyl)carbonyloxy)aryl, and (alkoxycarbonyl)aryl]; (amido)aryl [e.g., (aminocarbonyl)aryl, (((alkylamino)alkyl)aminocarbonyl)aryl, (alkylcarbonyl)aminoaryl, (arylaminocarbonyl)aryl, and (((heteroaryl)amino)carbonyl)aryl]; aminoaryl [e.g., ((alkylsulfonyl)amino)aryl or ((dialkyl)amino)aryl]; (cyanoalkyl)aryl; (alkoxy)aryl; (sulfamoyl)aryl [e.g., (aminosulfonyl)aryl]; (alkylsulfonyl)aryl; (cyano)aryl; (hydroxyalkyl)aryl; ((alkoxy)alkyl)aryl; (hydroxy)aryl, ((carboxy)alkyl)aryl; (((dialkyl)amino)alkyl)aryl; (nitroalkyl)aryl; (((alkylsulfonyl)amino)alkyl)aryl; ((heterocycloaliphatic)carbonyl)aryl; ((alkylsulfonyl)alkyl)aryl; (cyanoalkyl)aryl; (hydroxyalkyl)aryl; (alkylcarbonyl)aryl; alkylaryl; (trihaloalkyl)aryl; *p*-amino-*m*-alkoxycarbonylaryl; *p*-amino-*m*-cyanoaryl; *p*-halo-*m*-aminoaryl; or (*m*-(heterocycloaliphatic)-*o*-(alkyl))aryl.

[0115] As used herein, an "araliphatic" such as an "aralkyl" group refers to an aliphatic group (e.g., a C₁₋₄ alkyl group) that is substituted with an aryl group. "Aliphatic," "alkyl," and "aryl" are defined herein. An example of an araliphatic such as an aralkyl group is benzyl.

[0116] As used herein, an "aralkyl" group refers to an alkyl group (e.g., a C₁₋₄ alkyl group) that is substituted with an aryl group. Both "alkyl" and "aryl" have been defined above. An example of an aralkyl group is benzyl. An aralkyl is optionally substituted with one or more substituents such as aliphatic [e.g., alkyl, alkenyl, or alkynyl, including carboxyalkyl, hydroxyalkyl, or haloalkyl such as trifluoromethyl], cycloaliphatic [e.g., cycloalkyl or cycloalkenyl], (cycloalkyl)alkyl, heterocycloalkyl, (heterocycloalkyl)alkyl, aryl, heteroaryl, alkoxy, cycloalkyloxy, heterocycloalkyloxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, aroyl, heteroaroyl, nitro, carboxy, alkoxycarbonyl, alkylcarbonyloxy, amido [e.g., aminocarbonyl, alkylcarbonylamino, cycloalkylcarbonylamino, (cycloalkylalkyl)carbonylamino, arylcarbonylamino, aralkylcarbonylamino, (heterocycloalkyl)carbonylamino, (heterocycloalkylalkyl)carbonylamino, heteroarylcarbonylamino, or heteroaralkylcarbonylamino], cyano, halo, hydroxy, acyl,

mercapto, alkylsulfanyl, sulfoxy, urea, thiourea, sulfamoyl, sulfamide, oxo, or carbamoyl.

[0117] As used herein, a "bicyclic ring system" includes 8-12 (e.g., 9, 10, or 11) membered structures that form two rings, wherein the two rings have at least one atom in common (e.g., 2 atoms in common). Bicyclic ring systems include bicycloaliphatics (e.g., bicycloalkyl or bicycloalkenyl), bicycloheteroaliphatics, bicyclic aryls, and bicyclic heteroaryls.

[0118] As used herein, a "cycloaliphatic" group encompasses a "cycloalkyl" group and a "cycloalkenyl" group, each of which being optionally substituted as set forth below.

[0119] As used herein, a "cycloalkyl" group refers to a saturated carbocyclic mono- or bicyclic (fused or bridged) ring of 3-10 (e.g., 5-10) carbon atoms. Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl, norbornyl, cubyl, octahydro-indenyl, decahydro-naphthyl, bicyclo[3.2.1]octyl, bicyclo[2.2.2]octyl, bicyclo[3.3.1]nonyl, bicyclo[3.3.2]decyl, bicyclo[2.2.2]octyl, adamantyl, or ((aminocarbonyl)cycloalkyl)cycloalkyl.

[0120] A "cycloalkenyl" group, as used herein, refers to a non-aromatic carbocyclic ring of 3-10 (e.g., 4-8) carbon atoms having one or more double bonds. Examples of cycloalkenyl groups include cyclopentenyl, 1,4-cyclohexa-di-enyl, cycloheptenyl, cyclooctenyl, hexahydro-indenyl, octahydro-naphthyl, cyclohexenyl, cyclopentenyl, bicyclo[2.2.2]octenyl, or bicyclo[3.3.1]nonenyl.

[0121] A cycloalkyl or cycloalkenyl group can be optionally substituted with one or more substituents such as phosphor, aliphatic [e.g., alkyl, alkenyl, or alkynyl], cycloaliphatic, (cycloaliphatic) aliphatic, heterocycloaliphatic, (heterocycloaliphatic) aliphatic, aryl, heteroaryl, alkoxy, (cycloaliphatic)oxy, (heterocycloaliphatic)oxy, aryloxy, heteroaryloxy, (araliphatic)oxy, (heteroaraliphatic)oxy, aroyl, heteroaroyl, amino, amido [e.g., (aliphatic)carbonylamino, (cycloaliphatic)carbonylamino, ((cycloaliphatic)aliphatic)carbonylamino, (aryl)carbonylamino, (araliphatic)carbonylamino, (heterocycloaliphatic)carbonylamino, ((heterocycloaliphatic)aliphatic)carbonylamino, (heteroaryl)carbonylamino, or (heteroaraliphatic)carbonylamino], nitro, carboxy [e.g., HOOC-, alkoxycarbonyl, or alkylcarbonyloxy], acyl [e.g., (cycloaliphatic)carbonyl, ((cycloaliphatic) aliphatic)carbonyl, (araliphatic)carbonyl, (heterocycloaliphatic)carbonyl, ((heterocycloaliphatic)aliphatic)carbonyl, or (heteroaraliphatic)carbonyl], cyano, halo, hydroxy, mercapto, sulfonyl [e.g., alkyl-SO₂- and aryl-SO₂-], sulfinyl [e.g., alkyl-S(O)-], sulfanyl [e.g., alkyl-S-], sulfoxy, urea, thiourea, sulfamoyl, sulfamide, oxo, or carbamoyl.

[0122] As used herein, the term "heterocycloaliphatic" encompasses a heterocycloalkyl group and a heterocycloalkenyl group, each of which being optionally substituted as set forth below.

[0123] As used herein, a "heterocycloalkyl" group refers to a 3-10 membered mono- or bicyclic (fused or bridged) (e.g., 5- to 10-membered mono- or bicyclic) saturated ring structure, in which one or more of the ring atoms is a heteroatom (e.g., N, O, S, or combinations thereof). Examples of a heterocycloalkyl group include piperidyl, piperazyl, tetrahydropyranyl, tetrahydrofuryl, 1,4-dioxolanyl, 1,4-dithianyl, 1,3-dioxolanyl, oxazolidyl, isoxazolidyl, morpholinyl, thiomorpholyl, octahydrobenzofuryl, octahydrochromenyl, octahydrothiochromenyl, octahydroindolyl, octahydropyrindinyl, decahydroquinolinyl, octahydrobenzo[*b*]thiophenyl, 2-oxa-bicyclo[2.2.2]octyl, 1-aza-bicyclo[2.2.2]octyl, 3-aza-bicyclo[3.2.1]octyl, and 2,6-dioxa-tricyclo[3.3.1.0^{3,7}]nonyl. A monocyclic heterocycloalkyl group can be fused with a phenyl moiety to form structures, such as tetrahydroisoquinoline, which would be categorized as heteroaryls.

[0124] A "heterocycloalkenyl" group, as used herein, refers to a mono- or bicyclic (e.g., 5- to 10-membered mono- or bicyclic) non-aromatic ring structure having one or more double bonds, and wherein one or more of the ring atoms is a heteroatom (e.g., N, O, or S). Monocyclic and bicyclic heterocycloaliphatics are numbered according to standard chemical nomenclature.

[0125] A heterocycloalkyl or heterocycloalkenyl group can be optionally substituted with one or more substituents such as phosphor, aliphatic [e.g., alkyl, alkenyl, or alkynyl], cycloaliphatic, (cycloaliphatic)aliphatic, heterocycloaliphatic, (heterocycloaliphatic)aliphatic, aryl, heteroaryl, alkoxy, (cycloaliphatic)oxy, (heterocycloaliphatic)oxy, aryloxy, heteroaryloxy, (araliphatic)oxy, (heteroaraliphatic)oxy, aroyl, heteroaroyl, amino, amido [e.g., (aliphatic)carbonylamino, (cycloaliphatic)carbonylamino, ((cycloaliphatic)aliphatic)carbonylamino, (aryl)carbonylamino, (araliphatic)carbonylamino, (heterocycloaliphatic)carbonylamino, ((heterocycloaliphatic)aliphatic)carbonylamino, (heteroaryl)carbonylamino, or (heteroaraliphatic)carbonylamino], nitro, carboxy [e.g., HOOC-, alkoxy carbonyl, or alkyl carbonyloxy], acyl [e.g., (cycloaliphatic)carbonyl, ((cycloaliphatic)aliphatic)carbonyl, (araliphatic)carbonyl, (heterocycloaliphatic)carbonyl, ((heterocycloaliphatic)aliphatic)carbonyl, or (heteroaraliphatic)carbonyl], nitro, cyano, halo, hydroxy, mercapto, sulfonyl [e.g., alkylsulfonyl or arylsulfonyl], sulfinyl [e.g., alkylsulfinyl], sulfanyl [e.g., alkylsulfanyl], sulfoxy, urea, thiourea, sulfamoyl, sulfamide, oxo, or carbamoyl.

[0126] A "heteroaryl" group, as used herein, refers to a monocyclic, bicyclic, or tricyclic ring system having 4 to 15 ring atoms wherein one or more of the ring atoms is a heteroatom (e.g., N, O, S, or combinations thereof) and in which the monocyclic ring system is aromatic or at least one of the rings in the bicyclic or tricyclic ring systems is aromatic. A heteroaryl

group includes a benzofused ring system having 2 to 3 rings. For example, a benzofused group includes benzo fused with one or two 4 to 8 membered heterocycloaliphatic moieties (e.g., indolizyl, indolyl, isoindolyl, 3H-indolyl, indolinyl, benzo[*b*]furyl, benzo[*b*]thiophenyl, quinolinyl, or isoquinolinyl). Some examples of heteroaryl are pyridyl, 1H-indazolyl, furyl, pyrrolyl, thienyl, thiazolyl, oxazolyl, imidazolyl, tetrazolyl, benzofuryl, isoquinolinyl, benzthiazolyl, xanthene, thioxanthene, phenothiazine, dihydroindole, benzo[1,3]dioxole, benzo[*b*]furyl, benzo[*b*]thiophenyl, indazolyl, benzimidazolyl, benzthiazolyl, puryl, cinnolyl, quinolyl, quinazolyl, cinnolyl, phthalazyl, quinazolyl, quinoxalyl, isoquinolyl, 4H-quinolizyl, benzo-1,2,5-thiadiazolyl, or 1,8-naphthyridyl.

[0127] Without limitation, monocyclic heteroaryls include furyl, thiophenyl, 2H-pyrrolyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, 1,3,4-thiadiazolyl, 2H-pyranyl, 4-H-pranyl, pyridyl, pyridazyl, pyrimidyl, pyrazolyl, pyrazyl, or 1,3,5-triazyl. Monocyclic heteroaryls are numbered according to standard chemical nomenclature.

[0128] Without limitation, bicyclic heteroaryls include indolizyl, indolyl, isoindolyl, 3H-indolyl, indolinyl, benzo[*b*]furyl, benzo[*b*]thiophenyl, quinolinyl, isoquinolinyl, indolizyl, isoindolyl, indolyl, benzo[*b*]furyl, benzo[*b*]thiophenyl, indazolyl, benzimidazolyl, benzthiazolyl, purinyl, 4H-quinolizyl, quinolyl, isoquinolyl, cinnolyl, phthalazyl, quinazolyl, quinoxalyl, 1,8-naphthyridyl, or pteridyl. Bicyclic heteroaryls are numbered according to standard chemical nomenclature.

[0129] A heteroaryl is optionally substituted with one or more substituents such as aliphatic [e.g., alkyl, alkenyl, or alkynyl]; cycloaliphatic; (cycloaliphatic)aliphatic; heterocycloaliphatic; (heterocycloaliphatic)aliphatic; aryl; heteroaryl; alkoxy; (cycloaliphatic)oxy; (heterocycloaliphatic)oxy; aryloxy; heteroaryloxy; (araliphatic)oxy; (heteroaraliphatic)oxy; aroyl; heteroaroyl; amino; oxo (on a non-aromatic carbocyclic or heterocyclic ring of a bicyclic or tricyclic heteroaryl); carboxy; amido; acyl [e.g., aliphaticcarbonyl; (cycloaliphatic)carbonyl; ((cycloaliphatic)aliphatic)carbonyl; (araliphatic)carbonyl; (heterocycloaliphatic)carbonyl; ((heterocycloaliphatic)aliphatic)carbonyl; or (heteroaraliphatic)carbonyl]; sulfonyl [e.g., aliphaticsulfonyl or aminosulfonyl]; sulfinyl [e.g., aliphaticsulfinyl]; sulfanyl [e.g., aliphatic sulfanyl]; nitro; cyano; halo; hydroxy; mercapto; sulfoxy; urea; thiourea; sulfamoyl; sulfamide; or carbamoyl. Alternatively, a heteroaryl can be unsubstituted.

[0130] Non-limiting examples of substituted heteroaryls include (halo)heteroaryl [e.g., mono- and di-(halo)heteroaryl]; (carboxy)heteroaryl [e.g., (alkoxycarbonyl)heteroaryl]; cyanoheteroaryl; aminoheteroaryl [e.g., ((alkylsulfonyl)amino)heteroaryl and

((dialkyl)amino)heteroaryl]; (amido)heteroaryl [e.g., aminocarbonyl]heteroaryl, ((alkylcarbonyl)amino)heteroaryl, (((alkyl)amino)alkyl)aminocarbonyl]heteroaryl, (((heteroaryl)amino)carbonyl)heteroaryl, ((heterocycloaliphatic)carbonyl)heteroaryl, and ((alkylcarbonyl)amino)heteroaryl]; (cyanoalkyl)heteroaryl; (alkoxy)heteroaryl; (sulfamoyl)heteroaryl [e.g., (aminosulfonyl)heteroaryl]; (sulfonyl)heteroaryl [e.g., (alkylsulfonyl)heteroaryl]; (hydroxyalkyl)heteroaryl; (alkoxyalkyl)heteroaryl; (hydroxy)heteroaryl; ((carboxy)alkyl)heteroaryl; (((dialkyl)amino)alkyl)]heteroaryl; (heterocycloaliphatic)heteroaryl; (cycloaliphatic)heteroaryl; (nitroalkyl)heteroaryl; (((alkylsulfonyl)amino)alkyl)heteroaryl; ((alkylsulfonyl)alkyl)heteroaryl; (cyanoalkyl)heteroaryl; (acyl)heteroaryl [e.g., (alkylcarbonyl)heteroaryl]; (alkyl)heteroaryl, and (haloalkyl)heteroaryl [e.g., trihaloalkyl]heteroaryl].

[0131] A "heteroaraliphatic" (such as a heteroaralkyl group) as used herein, refers to an aliphatic group (e.g., a C₁₋₄ alkyl group) that is substituted with a heteroaryl group.

"Aliphatic," "alkyl," and "heteroaryl" have been defined above.

[0132] A "heteroaralkyl" group, as used herein, refers to an alkyl group (e.g., a C₁₋₄ alkyl group) that is substituted with a heteroaryl group. Both "alkyl" and "heteroaryl" have been defined above. A heteroaralkyl is optionally substituted with one or more substituents such as alkyl (including carboxyalkyl, hydroxyalkyl, and haloalkyl such as trifluoromethyl), alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, heterocycloalkyl, (heterocycloalkyl)alkyl, aryl, heteroaryl, alkoxy, cycloalkyloxy, heterocycloalkyloxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, aroyl, heteroaroyl, nitro, carboxy, alkoxycarbonyl, alkylcarbonyloxy, aminocarbonyl, alkylcarbonylamino, cycloalkylcarbonylamino, (cycloalkylalkyl)carbonylamino, arylcarbonylamino, aralkylcarbonylamino, (heterocycloalkyl)carbonylamino, (heterocycloalkylalkyl)carbonylamino, heteroarylcarbonylamino, heteroaralkylcarbonylamino, cyano, halo, hydroxy, acyl, mercapto, alkylsulfanyl, sulfoxy, urea, thiourea, sulfamoyl, sulfamide, oxo, or carbamoyl.

[0133] As used herein, "cyclic moiety" and "cyclic group" refer to mono-, bi-, and tri-cyclic ring systems including cycloaliphatic, heterocycloaliphatic, aryl, or heteroaryl, each of which has been previously defined.

[0134] As used herein, a "bridged bicyclic ring system" refers to a bicyclic heterocycloaliphatic ring system or bicyclic cycloaliphatic ring system in which the rings are bridged. Examples of bridged bicyclic ring systems include, but are not limited to, adamantanyl, norbornanyl, bicyclo[3.2.1]octyl, bicyclo[2.2.2]octyl, bicyclo[3.3.1]nonyl, bicyclo[3.3.2]decyl, 2-oxabicyclo[2.2.2]octyl, 1-azabicyclo[2.2.2]octyl, 3-azabicyclo[3.2.1]octyl, and 2,6-dioxa-tricyclo[3.3.1.0^{3,7}]nonyl. A bridged bicyclic ring

system can be optionally substituted with one or more substituents such as alkyl (including carboxyalkyl, hydroxyalkyl, and haloalkyl such as trifluoromethyl), alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, heterocycloalkyl, (heterocycloalkyl)alkyl, aryl, heteroaryl, alkoxy, cycloalkyloxy, heterocycloalkyloxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, aroyl, heteroaroyl, nitro, carboxy, alkoxycarbonyl, alkylcarbonyloxy, aminocarbonyl, alkylcarbonylamino, cycloalkylcarbonylamino, (cycloalkylalkyl)carbonylamino, arylcarbonylamino, aralkylcarbonylamino, (heterocycloalkyl)carbonylamino, (heterocycloalkylalkyl)carbonylamino, heteroarylcarbonylamino, heteroaralkylcarbonylamino, cyano, halo, hydroxy, acyl, mercapto, alkylsulfanyl, sulfoxy, urea, thiourea, sulfamoyl, sulfamide, oxo, or carbamoyl.

[0135] As used herein, an "acyl" group refers to a formyl group or $R^X-C(O)-$ (such as alkyl- $C(O)-$), also referred to as "alkylcarbonyl") where R^X and "alkyl" have been defined previously. Acetyl and pivaloyl are examples of acyl groups.

[0136] As used herein, an "aroyl" or "heteroaroyl" refers to an aryl- $C(O)-$ or a heteroaryl- $C(O)-$, respectively. The aryl and heteroaryl portion of the aroyl or heteroaroyl is optionally substituted as previously defined.

[0137] As used herein, an "alkoxy" group refers to an alkyl-O- group where "alkyl" has been defined previously.

[0138] As used herein, a "carbamoyl" group refers to a group having the structure $-O-CO-NR^X R^Y$ or $-NR^X-CO-O-R^Z$, wherein R^X and R^Y have been defined above and R^Z can be aliphatic, aryl, araliphatic, heterocycloaliphatic, heteroaryl, or heteroaraliphatic.

[0139] As used herein, a "carboxy" group refers to $-COOH$, $-COOR^X$, $-OC(O)H$, $-OC(O)R^X$, when used as a terminal group; or $-OC(O)-$ or $-C(O)O-$ when used as an internal group.

[0140] As used herein, a "haloaliphatic" group refers to an aliphatic group substituted with 1-3 halogen. For instance, the term haloalkyl includes the group $-CF_3$.

[0141] As used herein, a "mercapto" group refers to $-SH$.

[0142] As used herein, a "sulfo" group refers to $-SO_3H$ or $-SO_3R^X$ when used terminally or $-S(O)_3-$ when used internally.

[0143] As used herein, a "sulfamide" group refers to the structure $-NR^X-S(O)_2-NR^Y R^Z$ when used terminally and $-NR^X-S(O)_2-NR^Y-$ when used internally, wherein R^X , R^Y , and R^Z have been defined above.

[0144] As used herein, a "sulfamoyl" group refers to the structure $-O-S(O)_2-NR^Y R^Z$ wherein R^Y and R^Z have been defined above.

[0145] As used herein, a "sulfonamide" group refers to the structure $-S(O)_2-NR^X R^Y$ or $-NR^X-S(O)_2-R^Z$ when used terminally; or $-S(O)_2-NR^X-$ or $-NR^X-S(O)_2-$ when used internally, wherein R^X , R^Y , and R^Z are defined above.

[0146] As used herein a "sulfanyl" group refers to $-S-R^X$ when used terminally and $-S-$ when used internally, wherein R^X has been defined above. Examples of sulfanyls include aliphatic-S-, cycloaliphatic-S-, aryl-S-, or the like.

[0147] As used herein a "sulfinyl" group refers to $-S(O)-R^X$ when used terminally and $-S(O)-$ when used internally, wherein R^X has been defined above. Exemplary sulfinyl groups include aliphatic-S(O)-, aryl-S(O)-, (cycloaliphatic(aliphatic))-S(O)-, cycloalkyl-S(O)-, heterocycloaliphatic-S(O)-, heteroaryl-S(O)-, or the like.

[0148] As used herein, a "sulfonyl" group refers to $-S(O)_2-R^X$ when used terminally and $-S(O)_2-$ when used internally, wherein R^X has been defined above. Exemplary sulfonyl groups include aliphatic-S(O)₂-, aryl-S(O)₂-, (cycloaliphatic(aliphatic))-S(O)₂-, cycloaliphatic-S(O)₂-, heterocycloaliphatic-S(O)₂-, heteroaryl-S(O)₂-, (cycloaliphatic(amido(aliphatic)))-S(O)₂- or the like.

[0149] As used herein, a "sulfoxy" group refers to $-O-SO-R^X$ or $-SO-O-R^X$, when used terminally and $-O-S(O)-$ or $-S(O)-O-$ when used internally, where R^X has been defined above.

[0150] As used herein, a "halogen" or "halo" group refers to fluorine, chlorine, bromine or iodine.

[0151] As used herein, an "alkoxycarbonyl," which is encompassed by the term carboxy, used alone or in connection with another group refers to a group such as alkyl-O-C(O)-.

[0152] As used herein, an "alkoxyalkyl" refers to an alkyl group such as alkyl-O-alkyl-, wherein alkyl has been defined above.

[0153] As used herein, a "carbonyl" refer to $-C(O)-$.

[0154] As used herein, an "oxo" refers to $=O$.

[0155] As used herein, the term "phospho" refers to phosphinates and phosphonates. Examples of phosphinates and phosphonates include $-P(O)(R^P)_2$, wherein R^P is aliphatic, alkoxy, aryloxy, heteroaryloxy, (cycloaliphatic)oxy, (heterocycloaliphatic)oxy aryl, heteroaryl, cycloaliphatic or amino.

[0156] As used herein, an "aminoalkyl" refers to the structure $(R^X)_2N$ -alkyl-.

[0157] As used herein, a "cyanoalkyl" refers to the structure (NC) -alkyl-.

[0158] As used herein, a "urea" group refers to the structure $-NR^X-CO-NR^Y R^Z$ and a "thiourea" group refers to the structure $-NR^X-CS-NR^Y R^Z$ when used terminally and $-NR^X-CO-NR^Y-$ or $-NR^X-CS-NR^Y-$ when used internally, wherein R^X , R^Y , and R^Z have been defined above.

[0159] As used herein, a "guanidine" group refers to the structure $-N=C(N(R^X R^Y))N(R^X R^Y)$ or $-NR^X-C(=NR^X)NR^X R^Y$ wherein R^X and R^Y have been defined above.

[0160] As used herein, the term "amidino" group refers to the structure $-C(=NR^X)N(R^X R^Y)$ wherein R^X and R^Y have been defined above.

[0161] In general, the term "vicinal" refers to the placement of substituents on a group that includes two or more carbon atoms, wherein the substituents are attached to adjacent carbon atoms.

[0162] In general, the term "geminal" refers to the placement of substituents on a group that includes two or more carbon atoms, wherein the substituents are attached to the same carbon atom.

[0163] The terms "terminally" and "internally" refer to the location of a group within a substituent. A group is terminal when the group is present at the end of the substituent not further bonded to the rest of the chemical structure. Carboxyalkyl, i.e., $R^X O(O)C$ -alkyl is an example of a carboxy group used terminally. A group is internal when the group is present in the middle of a substituent of the chemical structure. Alkylcarboxy (e.g., alkyl- $C(O)O$ - or alkyl- $OC(O)$ -) and alkylcarboxyaryl (e.g., alkyl- $C(O)O$ -aryl- or alkyl- $O(CO)$ -aryl-) are examples of carboxy groups used internally.

[0164] As used herein, an "aliphatic chain" refers to a branched or straight aliphatic group (e.g., alkyl groups, alkenyl groups, or alkynyl groups). A straight aliphatic chain has the structure $-[CH_2]_v-$, where v is 1-12. A branched aliphatic chain is a straight aliphatic chain that is substituted $-[CQQ]_v-$ where Q is independently a hydrogen or an aliphatic group; however, Q shall be an aliphatic group in at least one instance. The term aliphatic chain includes alkyl chains, alkenyl chains, and alkynyl chains, where alkyl, alkenyl, and alkynyl are defined above.

[0165] The phrase "optionally substituted" is used interchangeably with the phrase "substituted or unsubstituted." As described herein, compounds of the invention can optionally be substituted with one or more substituents, such as are illustrated generally above, or as exemplified by particular classes, subclasses, and species of the invention. As described herein, the variables R^1 , R^2 , R^3 , R^4 , R^5 , R' , and other variables contained in Formula I, described herein, encompass specific groups, such as alkyl and aryl. Unless otherwise noted, each of the specific groups for the variables R^1 , R^2 , R^3 , R^4 , R^5 , R' , and other variables contained therein can be optionally substituted with one or more substituents described herein. Each substituent of a specific group is further optionally substituted with one to three of halo, cyano, oxo, alkoxy, hydroxy, amino, nitro, aryl, cycloaliphatic, heterocycloaliphatic, heteroaryl, haloalkyl, and alkyl. For instance, an alkyl group can be

substituted with alkylsulfanyl and the alkylsulfanyl can be optionally substituted with one to three of halo, cyano, oxo, alkoxy, hydroxy, amino, nitro, aryl, haloalkyl, and alkyl. As an additional example, the cycloalkyl portion of a (cycloalkyl)carbonylamino can be optionally substituted with one to three of halo, cyano, alkoxy, hydroxy, nitro, haloalkyl, and alkyl. When two alkoxy groups are bound to the same atom or adjacent atoms, the two alkoxy groups can form a ring together with the atom(s) to which they are bound.

[0166] In general, the term "substituted," whether preceded by the term "optionally" or not, refers to the replacement of hydrogen radicals in a given structure with the radical of a specified substituent. Specific substituents are described above in the definitions and below in the description of compounds and examples thereof. Unless otherwise indicated, an optionally substituted group can have a substituent at each substitutable position of the group, and when more than one position in any given structure can be substituted with more than one substituent selected from a specified group, the substituent can be either the same or different at every position. A ring substituent, such as a heterocycloalkyl, can be bound to another ring, such as a cycloalkyl, to form a spiro-bicyclic ring system, e.g., both rings share one common atom. As one of ordinary skill in the art will recognize, combinations of substituents envisioned by this invention are those combinations that result in the formation of stable or chemically feasible compounds.

[0167] The phrase "stable or chemically feasible," as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and preferably their recovery, purification, and use for one or more of the purposes disclosed herein. In some embodiments, a stable compound or chemically feasible compound is one that is not substantially altered when kept at a temperature of 40 °C or less, in the absence of moisture or other chemically reactive conditions, for at least a week.

[0168] As used herein, an "effective amount" is defined as the amount required to confer a therapeutic effect on the treated patient, and is typically determined based on age, surface area, weight, and condition of the patient. The interrelationship of dosages for animals and humans (based on milligrams per meter squared of body surface) is described by Freireich et al., *Cancer Chemother. Rep.*, 50: 219 (1966). Body surface area may be approximately determined from height and weight of the patient. See, e.g., *Scientific Tables*, Geigy Pharmaceuticals, Ardsley, New York, 537 (1970). As used herein, "patient" refers to a mammal, including a human.

[0169] Unless otherwise stated, structures depicted herein are also meant to include all isomeric (e.g., enantiomeric, diastereomeric, and geometric (or conformational)) forms of the structure; for example, the R and S configurations for each asymmetric center, (Z) and (E)

double bond isomers, and (Z) and (E) conformational isomers. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures of the present compounds are within the scope of the invention. Unless otherwise stated, all tautomeric forms of the compounds of the invention are within the scope of the invention. Additionally, unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ^{13}C - or ^{14}C - enriched carbon are within the scope of this invention. Such compounds are useful, for example, as analytical tools or probes in biological assays, or as therapeutic agents.

[0170] As used herein, an "excipient" is an inactive ingredient in a pharmaceutical composition. Examples of excipients include.

[0171] As used herein, a "disintegrant" is an excipient that hydrates a pharmaceutical composition and aids in tablet dispersion. Examples of disintegrants include sodium croscarmellose and/or sodium starch glycolate.

[0172] As used herein, a "diluent" or "filler" is an excipient that adds bulkiness to a pharmaceutical composition. Examples of fillers include lactose, sorbitol, celluloses, calcium phosphates, starches, sugars (e.g., mannitol, sucrose, or the like) or any combination thereof.

[0173] As used herein, a "wetting agent" or a "surfactant" is an excipient that imparts pharmaceutical compositions with enhanced solubility and/or wettability. Examples of wetting agents include sodium lauryl sulfate (SLS), sodium stearyl fumarate (SSF), polyoxyethylene 20 sorbitan mono-oleate (e.g., TweenTM), or any combination thereof.

[0174] As used herein, a "binder" is an excipient that imparts a pharmaceutical composition with enhanced cohesion or tensile strength (e.g., hardness). Examples of binders include dibasic calcium phosphate, sucrose, corn (maize) starch, microcrystalline cellulose, and modified cellulose (e.g., hydroxymethyl cellulose).

[0175] As used herein, a "glidant" is an excipient that imparts a pharmaceutical compositions with enhanced flow properties. Examples of glidants include colloidal silica and/or talc.

[0176] As used herein, a "colorant" is an excipient that imparts a pharmaceutical composition with a desired color. Examples of colorants include commercially available pigments such as FD&C Blue # 1 Aluminum Lake, FD&C Blue #2, other FD&C Blue colors, titanium dioxide, iron oxide, and/or combinations thereof. Other colorants include commercially available pigments such as FD&C Green #3.

[0177] As used herein, a "lubricant" is an excipient that is added to pharmaceutical compositions that are pressed into tablets. The lubricant aids in compaction of granules into tablets and ejection of a tablet of a pharmaceutical composition from a die press. Examples of lubricants include magnesium stearate, stearic acid (stearin), hydrogenated oil, sodium stearyl fumarate, or any combination thereof.

[0178] As used herein, "friability" refers to the property of a tablet to remain intact and withhold its form despite an external force of pressure. Friability can be quantified using the mathematical expression presented in equation 1:

$$\% \text{friability} = 100 \times \frac{(W_0 - W_f)}{W_0} \quad (1)$$

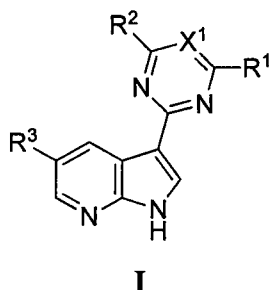
wherein W_0 is the original weight of the tablet and W_f is the final weight of the tablet after it is put through the friabilator.

[0179] Friability is measured using a standard USP testing apparatus that tumbles experimental tablets for 100 revolutions. Some tablets of the present invention have a friability of less than about 1% (e.g., less than about 0.75%, less than about 0.50%, or less than about 0.30%).

[0180] As used herein, "DMARD" refers to a disease-modifying antirheumatoid drug. Examples of DMARDs include adalimumab, leflunomide, sulfasalazine, infliximab, minocycline, rituximab, golimumab, or any combination thereof.

[0181] II. METHODS OF TREATMENT

[0182] One aspect of the present invention provides a method for treating or lessening the severity of rheumatoid arthritis (e.g., active rheumatoid arthritis) comprising administering to a patient in need thereof a corticosteroid and compound of Formula I



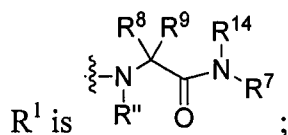
or a pharmaceutically acceptable salt thereof, wherein:

X^1 is N or CR^4 ;

R^2 is H or halo;

R^3 is H or halo;

R^4 is H or halo;



R" is H or an unsubstituted C₁₋₂ aliphatic;

R⁸ is an unsubstituted C₁₋₄ aliphatic;

R⁹ is an unsubstituted C₁₋₄ aliphatic;

R⁷ is a C₁₋₃ aliphatic optionally substituted with up to 3 occurrences of F; and

R¹⁴ is H or unsubstituted C₁₋₂ alkyl.

[0183] In some embodiments, R² is H or F.

[0184] In some embodiments, R³ is H or Cl.

[0185] In some embodiments, each of R⁸ and R⁹ is independently selected from methyl, ethyl, propyl, iso-propyl, butyl, or tert-butyl. For instance, each of R⁸ and R⁹ is independently selected from methyl or ethyl.

[0186] In some embodiments, R¹⁴ is H or methyl.

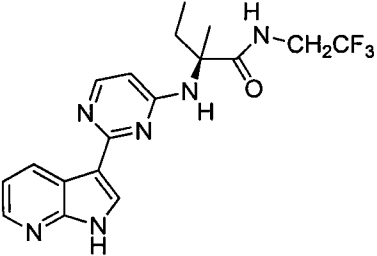
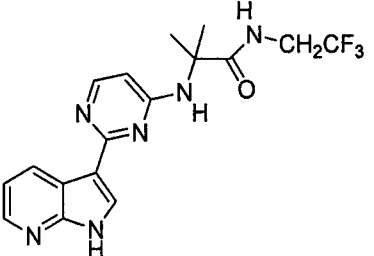
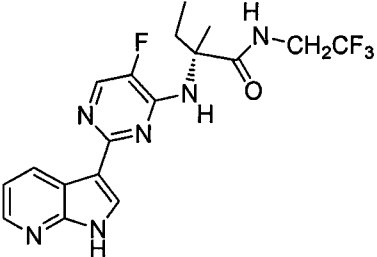
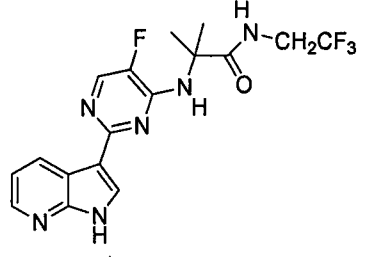
[0187] In some embodiments, R⁷ is an unsubstituted C₁₋₃ aliphatic.

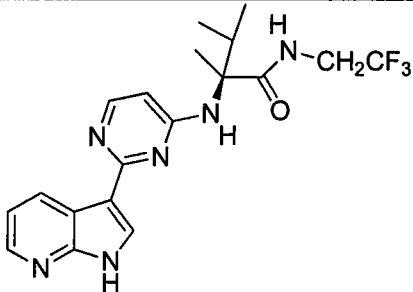
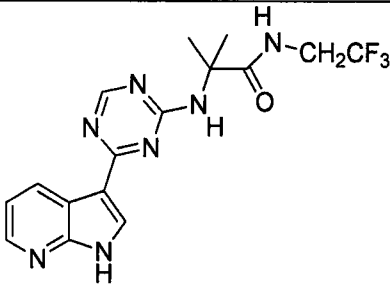
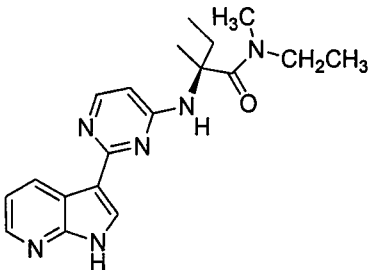
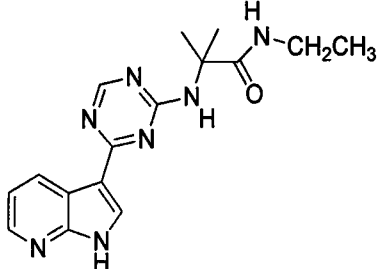
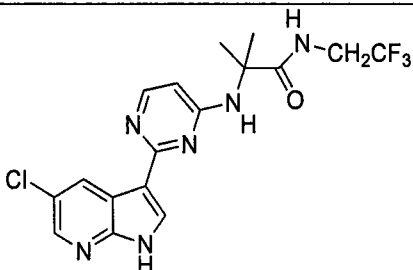
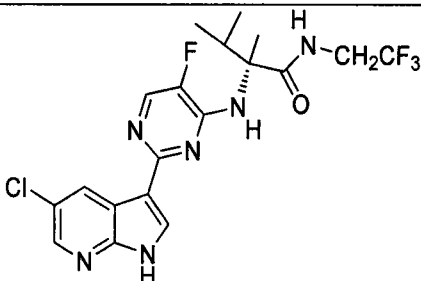
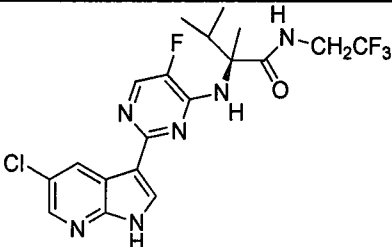
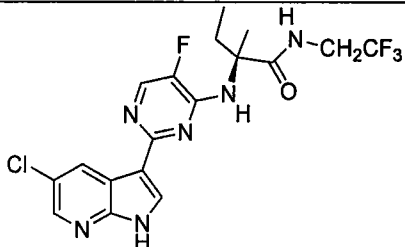
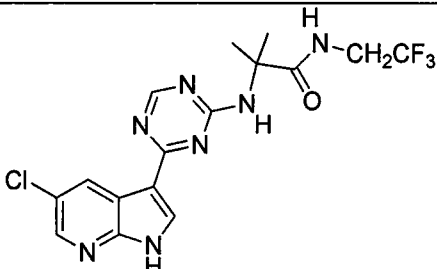
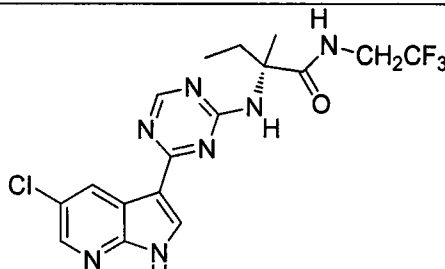
[0188] In some embodiments, R⁷ is a C₁₋₃ aliphatic substituted with 1-3 occurrences of F.

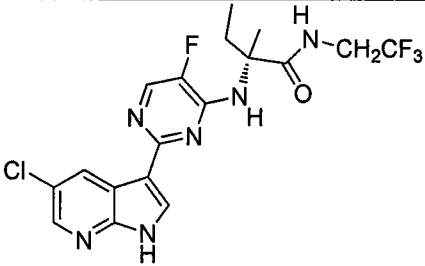
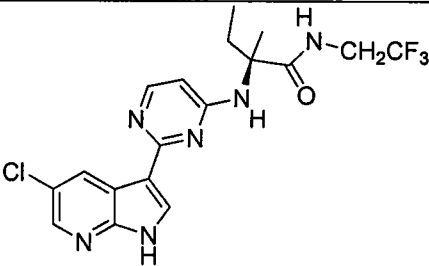
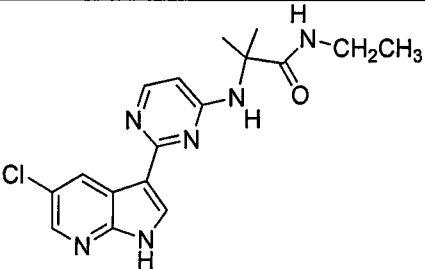
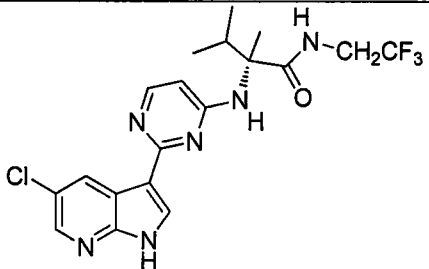
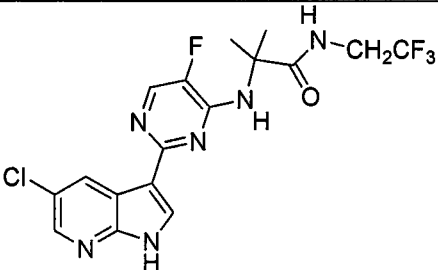
[0189] In some embodiments, R⁷ is a group selected from -CH₂CH₃, -CH₂CF₃, -CH₂CH₂CH₃, or -CHCH₃CH₃.

[0190] In some embodiments, the compound of Formula I is selected from Table 1:

Table 1:

1	2
	
3	4
	

5	6
	
7	8
	
9	10
	
11	12
	
13	14
	

15	16
	
17	18
	
19	
	

[0191] In some embodiments, the compound of Formula I is administered at least once per day (e.g., q.d. or b.i.d. administration). In other embodiments, the compound of Formula I is administered at least twice per day (e.g., b.i.d. administration).

[0192] In some embodiments, the compound of Formula I is orally administered to the patient.

[0193] In some embodiments, at least about 20 mg (e.g., at least about 25 mg, at least about 50 mg, at least about 75 mg, at least about 100 mg, at least about 150 mg, at least about 200 mg, or at least about 250 mg) of the compound of Formula I is administered to the patient once per day. For example, at least about 100 mg of the compound of Formula I is administered to the patient once per day. In other examples, at least about 200 mg of the compound of Formula I is administered to the patient once per day.

[0194] In other embodiments, at least about 20 mg (e.g., at least about 25 mg, at least about 50 mg, at least about 75 mg, at least about 100 mg, at least about 150 mg, at least about

200 mg, or at least about 250 mg) of the compound of Formula I is administered to the patient twice per day.

[0195] In some embodiments, the corticosteroid is hydrocortisone, hydrocortisone acetate, cortisone acetate, tixocortol pivalate, prednisone, prednisolone, methylprednisone, methylprednisolone, or any combination thereof.

[0196] In some embodiments, the corticosteroid is prednisone, prednisolone, methylprednisone, or methylprednisolone.

[0197] In some embodiments, the corticosteroid is methylprednisone or methylprednisolone.

[0198] In some embodiments, the corticosteroid is orally administered to the patient in need thereof.

[0199] In some embodiments, at least about 5 mg of corticosteroid is administered at least once per week. For example, at least about 5 mg of prednisone, prednisolone, methylprednisone, or methylprednisolone is administered at least once per week. In some instances, from about 8 mg to about 15 mg of prednisone or prednisolone is orally administered at least once per week. In other instances, from about 6 mg to about 12 mg of methylprednisone or methylprednisolone is orally administered at least once per week.

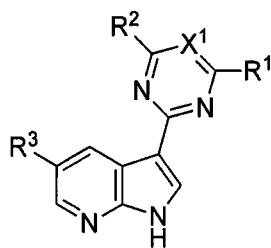
[0200] In some embodiments, at least about 8 mg of corticosteroid is administered at least once per week.

[0201] In some embodiments, at least about 5 mg of corticosteroid (e.g., prednisone, prednisolone, methylprednisone, or methylprednisolone) is administered at least twice per week. In some instances, from about 8 mg to about 15 mg of prednisone or prednisolone is orally administered at least twice per week. In other instances from about 6 mg to about 12 mg of methylprednisone or methylprednisolone is orally administered at least twice per week.

[0202] In some embodiments, the corticosteroid is prednisone or methylprednisone.

[0203] In some embodiments, the corticosteroid is administered concurrently with the compound of Formula I. In other embodiments, the corticosteroid is administered prior to or subsequent to the administration of the compound of Formula I.

[0204] Another aspect of the present invention provides a method for treating or lessening the severity of rheumatoid arthritis comprising administering to a patient in need thereof a corticosteroid and a pharmaceutical composition comprising a compound of Formula I



I

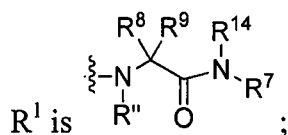
or a pharmaceutically acceptable salt thereof, wherein:

X^1 is N or CR^4 ;

R^2 is H or halo;

R^3 is H or halo;

R^4 is H or halo;



R'' is H or an unsubstituted C_{1-2} aliphatic;

R^8 is an unsubstituted C_{1-4} aliphatic;

R^9 is an unsubstituted C_{1-4} aliphatic;

R^7 is a C_{1-3} aliphatic optionally substituted with up to 3 occurrences of F; and

R^{14} is H or unsubstituted C_{1-2} alkyl.

[0205] In some embodiments, R^2 is H or F.

[0206] In some embodiments, R^3 is H or Cl.

[0207] In some embodiments, each of R^8 and R^9 is independently selected from methyl, ethyl, propyl, iso-propyl, butyl, or tert-butyl. For example, each of R^8 and R^9 is independently selected from methyl or ethyl.

[0208] In some embodiments, R^{14} is H or methyl.

[0209] In some embodiments, R^7 is an unsubstituted C_{1-3} aliphatic.

[0210] In some embodiments, R^7 is a C_{1-3} aliphatic substituted with 1-3 occurrences of F.

[0211] In some embodiments, R^7 is a group selected from $-CH_2CH_3$, $-CH_2CF_3$, $-CH_2CH_2CH_3$, or $-CHCH_3CH_3$.

[0212] In some embodiments, the compound of Formula I is a compound selected from Table 1.

[0213] In some embodiments, the pharmaceutical composition further comprises an oral formulation (e.g., tablet).

[0214] In some embodiments, the pharmaceutical composition further comprises a tablet. And, in some of these embodiments, the tablet further comprises a diluent, a binder, a glidant, a disintegrant, a surfactant, a lubricant, or any combination thereof.

[0215] In some embodiments, the tablet is administered at least once per day (e.g., q.d. or b.i.d. administration).

[0216] In some embodiments, the tablet comprises at least about 10 mg (e.g., at least about 15 mg, at least about 20 mg, at least about 25mg, at least about 50 mg, at least about 75 mg, at least about 100 mg, at least about 150 mg, at least about 175 mg, at least about 200 mg, at least about 250 mg,) of the compound of Formula I.

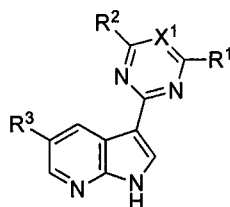
[0217] In some embodiments, the tablet comprises from about 5 mg to about 150 mg (e.g., from about 10 mg to about 100 mg, 20 mg to about 75 mg, or from about 25 mg to about 50 mg) of the compound of Formula I.

[0218] Some embodiments further comprise administering once per day at least one tablet (e.g., 1-6 tablets) comprising the pharmaceutical composition. For example, some embodiments further comprise administering once per day at least one table comprising from about 5 mg to about 150 mg (e.g., from about 10 mg to about 100 mg, 20 mg to about 75 mg, or from about 25 mg to about 50 mg) of the compound of Formula I.

[0219] Some embodiments further comprise administering twice per day at least one tablet comprising the pharmaceutical composition. For example, some embodiments further comprise administering twice per day at least one table comprising from about 5 mg to about 150 mg (e.g., from about 10 mg to about 100 mg, 20 mg to about 75 mg, or from about 25 mg to about 50 mg) of the compound of Formula I.

[0220] In several embodiments, the pharmaceutical composition comprises:

- a. a compound of Formula I



I

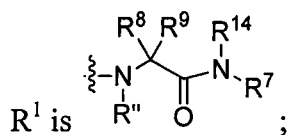
or a pharmaceutically acceptable salt thereof, wherein:

X¹ is N or CR⁴;

R² is H or halo;

R³ is H or halo;

R⁴ is H or halo;



R'' is H or an unsubstituted C_{1-2} aliphatic;

R^8 is an unsubstituted C_{1-4} aliphatic;

R^9 is an unsubstituted C_{1-4} aliphatic

R^7 is a C_{1-3} aliphatic optionally substituted with up to 3 occurrences of F; and

R^{14} is H or unsubstituted C_{1-2} alkyl;

- b. a diluent;
- c. a disintegrant;
- d. a wetting agent;
- e. a binder;
- f. a glidant; and
- g. a lubricant.

[0221] In some embodiments, X^1 is N, CH, or CF.

[0222] In some embodiments, R'' is H or methyl.

[0223] In some embodiments, R^2 is H or F.

[0224] In some embodiments, R^8 is an unsubstituted C_{1-4} aliphatic, for example a straight or branched unsubstituted C_{1-4} aliphatic.

[0225] In some embodiments, R^9 is an unsubstituted C_{1-4} aliphatic, for example a straight or branched unsubstituted C_{1-4} aliphatic.

[0226] In some embodiments, each of R^8 and R^9 is independently selected from methyl, ethyl, propyl, iso-propyl, butyl, or tert-butyl, each of which is unsubstituted. For example, each of R^8 and R^9 is independently selected from methyl or ethyl.

[0227] In some embodiments, R^{14} is H or methyl.

[0228] In some embodiments, R^7 is an unsubstituted C_{1-3} aliphatic. For example, R^7 is a straight or branched unsubstituted C_{1-3} aliphatic.

[0229] In some embodiments, R^7 is a C_{1-3} aliphatic substituted with 1-3 occurrences of F.

[0230] In some embodiments, R^7 is a group selected from $-\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CF}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_3$, or $-\text{CHCH}_3\text{CH}_3$.

[0231] In some embodiments, the pharmaceutical composition comprises from about 20 mg to about 250 mg (e.g., from about 25 mg to about 200 mg, from about 50 mg to about 175 mg, or from about 75 mg to about 150 mg) of a compound of Formula I.

[0232] In some embodiments, the pharmaceutical composition comprises about 25 mg of a compound of Formula I.

[0233] In some embodiments, the pharmaceutical composition comprises about 50 mg of a compound of Formula I.

[0234] In some embodiments, the pharmaceutical composition comprises about 75 mg of a compound of Formula I.

[0235] In some embodiments, the pharmaceutical composition comprises about 100 mg of a compound of Formula I.

[0236] In some embodiments, the pharmaceutical composition comprises about 150 mg of a compound of Formula I.

[0237] In some embodiments, the pharmaceutical composition comprises about 200 mg of a compound of Formula I.

[0238] In some embodiments, the pharmaceutical composition comprises from about 20 mg to about 200 mg (e.g., from about 25 mg to about 100 mg) of a compound selected from Table 1.

[0239] In some embodiments, the pharmaceutical composition comprises about 25 mg of a compound selected from Table 1.

[0240] In some embodiments, the pharmaceutical composition comprises about 50 mg of a compound selected from Table 1.

[0241] In some embodiments, the pharmaceutical composition comprises about 75 mg of a compound selected from Table 1.

[0242] In some embodiments, the pharmaceutical composition comprises about 100 mg of a compound selected from Table 1.

[0243] In some embodiments, the pharmaceutical composition comprises about 150 mg of a compound selected from Table 1.

[0244] Some embodiments further comprise the administration of one or more additional therapies to the patient.

[0245] In some embodiments, the corticosteroid is hydrocortisone, hydrocortisone acetate, cortisone acetate, tixocortol pivalate, prednisone, prednisolone, methylprednisone, methylprednisolone, or any combination thereof.

[0246] In some embodiments, the corticosteroid is prednisone, prednisolone, methylprednisone, or methylprednisolone.

[0247] In some embodiments, the corticosteroid is methylprednisone or methylprednisolone.

[0248] In some embodiments, the corticosteroid is orally administered to the patient in need thereof.

[0249] In some embodiments, at least about 5 mg of corticosteroid is administered at least once per week. For example, at least about 5 mg of prednisone, prednisolone, methylprednisone, or methylprednisolone is administered at least once per week. In some instances, from about 8 mg to about 15 mg of prednisone or prednisolone is orally administered at least once per week. In other instances, from about 6 mg to about 12 mg of methylprednisone or methylprednisolone is orally administered at least once per week.

[0250] In some embodiments, at least about 8 mg of corticosteroid is administered at least once per week.

[0251] In some embodiments, at least about 5 mg of corticosteroid (e.g., prednisone, prednisolone, methylprednisone, or methylprednisolone) is administered at least twice per week. In some instances, from about 8 mg to about 15 mg of prednisone or prednisolone is orally administered at least twice per week. In other instances from about 6 mg to about 12 mg of methylprednisone or methylprednisolone is orally administered at least twice per week.

[0252] In some embodiments, the corticosteroid is prednisone or methylprednisone.

[0253] In some embodiments, the corticosteroid is administered concurrently with the compound of Formula I. In other embodiments, the corticosteroid is administered prior to or subsequent to the administration of the compound of Formula I.

[0254] Another aspect of the present invention provides a method of treating or reducing the severity of rheumatoid arthritis comprising administering to a patient once daily or twice daily a pharmaceutical composition comprising a compound of Formula I, wherein the pharmaceutical composition is as described herein, and a corticosteroid (e.g., prednisone or methylprednisone).

[0255] Some embodiments further comprise the administration of one or more additional therapies to the patient.

[0256] In some embodiments, the pharmaceutical composition comprising a JAK inhibitor API (e.g., a compound of Formula I) and optionally other excipients (e.g., a diluent, a disintegrant, a wetting agent, a binder, a glidant, a colorant, a lubricant, or any combination thereof).

[0257] In some embodiments, the pharmaceutical composition comprises:

- a. a compound of Formula I, as described above;
- b. a diluent;
- c. a disintegrant;
- d. a surfactant;
- e. a binder;

- f. a glidant; and
- g. a lubricant.

[0258] In other embodiments, the pharmaceutical composition comprises about 25 mg of a compound of Formula I, a diluent, a disintegrant, a surfactant, a binder, a glidant, and a lubricant.

[0259] In other embodiments, the pharmaceutical composition comprises about 50 mg of a compound of Formula I, a diluent, a disintegrant, a surfactant, a binder, a glidant, and a lubricant.

[0260] In some embodiments, the corticosteroid is prednisone or methylprednisone.

[0261] In some embodiments, the pharmaceutical composition comprises about 20 mg or less of the corticosteroid.

[0262] In other embodiments, the pharmaceutical compositions of the present invention also comprise one or more excipients such as diluents, disintegrants, surfactants, binders, glidants, lubricants, colorants, or fragrances, such as any of those described below.

[0263] In some embodiments, the pharmaceutical composition can comprise tablets and the tablets can be coated with a colorant and optionally labeled with a logo, other image and/or text using a suitable ink. In still other embodiments, the pharmaceutical composition can be made into tablets and the tablets can be coated with a colorant, waxed, and optionally labeled with a logo, other image and/or text using a suitable ink. Suitable colorants and inks are compatible with the ingredients of the pharmaceutical composition, i.e., they do not substantially reduce the solubility, the chemical stability, the physical stability, the hardness, or the biological activity of the pharmaceutical composition. The suitable colorants and inks can be any color and are water based or solvent based. In some embodiments, tablets made from the pharmaceutical composition are coated with a colorant and then labeled with a logo, other image, and/or text using a suitable ink. For example, tablets comprising a pharmaceutical composition as described herein can be coated with about 3 wt% (e.g., less than about 6 wt% or less than about 4 wt%) of film coating comprising a colorant. The colored tablets can be labeled with a logo and text indicating the strength of the active ingredient in the tablet using a suitable ink. The colored tablets can be labeled with a logo and text indicating the strength and/or mass of the active ingredient in the tablet using a black ink (e.g., Opacode® WB, commercially available from Colorcon, Inc. of West Point, PA.). In another embodiment, tablets made from the pharmaceutical composition are coated with a colorant, waxed, and then labeled with a logo, other image, and/or text using a suitable ink. The colored tablets can be waxed with Carnauba wax powder weighed out in the amount of

about 0.01 % w/w of the starting tablet core weight. The waxed tablets can be labeled with a logo and text indicating the strength of the active ingredient in the tablet using a suitable ink.

[0264] In some embodiments, the pharmaceutical composition comprises from about 5 wt% to about 50 wt% of a compound of Formula I; by weight of the composition; from about 25 wt% to about 50 wt% of a diluent; from about 1 wt% to about 10 wt% of a disintegrant; from about 2 wt% to about 0.3 wt% of a wetting agent (e.g., surfactant); from about 5 wt% to about 50 wt% of a binder; from about 2 wt% to about 0.05 wt% of a glidant; and from about 2 wt% to about 0.1 wt% of a lubricant. Or, the pharmaceutical composition comprises from about 35 wt% to about 50 wt% of a compound of Formula I; from about 25 wt% to about 50 wt% of a diluent; from about 1 wt% to about 10 wt% of a disintegrant; from about 2 wt% to about 0.3 wt% of a wetting agent (e.g., surfactant); from about 5 wt% to about 50 wt% of a binder; from about 2 wt% to about 0.05 wt% of a glidant; and from about 2 wt% to about 0.1 wt% of a lubricant.

[0265] In some embodiments, the pharmaceutical composition comprises from about 30 wt% to about 50 wt% of a compound of Formula I; from about 35 wt% to about 55 wt% of microcrystalline cellulose by weight of the composition; from about 35 wt% to about 55 wt% of lactose by weight of the composition; from about 1 wt% to about 5 wt% of sodium croscarmellose by weight of the composition; from about 0.5 wt% to about 1.5 wt% of SLS by weight of the composition; from about 0.5 wt% to about 1.5 wt% of colloidal silicon dioxide by weight of the composition; and from about 0.5 wt% to about 1.0 wt% of magnesium stearate by weight of the composition.

[0266] Or, the pharmaceutical composition of the present invention comprises about 20 wt% of a compound of Formula I, about 37 wt% of microcrystalline cellulose by weight of the composition, about 37 wt% of lactose by weight of the composition, about 3 wt% of sodium croscarmellose by weight of the composition, about 1 wt% of SLS by weight of the composition, about 1 wt% of colloidal silicon dioxide by weight of the composition, and about 0.75 wt% of magnesium stearate by weight of the composition.

[0267] In some embodiments, the pharmaceutical composition of the present invention comprises about 10 wt% of a compound of Formula I; about 42 wt% of microcrystalline cellulose by weight of the composition; about 42 wt% of lactose by weight of the composition; about 3 wt% of sodium croscarmellose by weight of the composition; about 1 wt% of SLS by weight of the composition; about 1 wt% of colloidal silicon dioxide by weight of the composition; and about 0.75 wt% of magnesium stearate by weight of the composition.

[0268] In some embodiments, the pharmaceutical composition consists of a tablet that comprises a protein kinase inhibitor API (e.g., a compound of Formula I) and other excipients (e.g., a filler, a disintegrant, a surfactant, a binder, a glidant, a colorant, a lubricant, or any combination thereof), each of which is described above and in the Examples below, wherein the tablet has a hardness of about 5 Kp or greater. In one example, the pharmaceutical composition consists of a tablet that comprises a JAK inhibitor API (e.g., a compound of Formula I) and other excipients (e.g., a filler, a disintegrant, a surfactant, a binder, a glidant, a colorant, a lubricant, or any combination thereof), each of which is described above and in the Examples below, wherein the tablet has a hardness of about 5 Kp or greater (e.g., about 5.5 Kp or greater, about 6 Kp or greater, or about 7 Kp or greater).

[0269] In some embodiments, the pharmaceutical composition comprises a compound of Formula I; a diluent; a disintegrant; a wetting agent; a binder; a glidant; and a lubricant.

[0270] In some embodiments, the diluent is lactose, sorbitol, cellulose, calcium phosphate, starch, sugar, or any combination thereof.

[0271] In some embodiments, the diluent is lactose and has a concentration of about 10 wt% or greater by weight of the composition.

[0272] In some embodiments, the disintegrant is sodium croscarmellose, sodium starch glycolate, or a combination thereof. For example the disintegrant is sodium croscarmellose and has a concentration of about 10 wt% or less by weight of the composition.

[0273] In some embodiments, the wetting agent is sodium lauryl sulfate, sodium stearyl fumarate, polyoxyethylene 20 sorbitan mono-oleate, or any combination thereof. For example, the wetting agent is sodium lauryl sulfate and has a concentration of about 10 wt% or less by weight of the composition.

[0274] In some embodiments, the binder is microcrystalline cellulose, dibasic calcium phosphate, sucrose, corn starch, modified cellulose, or any combination thereof. For example, the binder is microcrystalline cellulose and has a concentration of about 1 wt% or greater by weight of the composition.

[0275] In some embodiments, the glidant is colloidal silicon dioxide, talc, or a combination thereof. For example, the glidant is colloidal silicon dioxide and has a concentration of 2 wt% or less by weight of the composition.

[0276] In some embodiments, the lubricant is magnesium stearate, stearic acid, hydrogenated oil, sodium stearyl fumarate, or any combination thereof. For example, the lubricant is magnesium stearate and has a concentration of less than about 2 wt% by weight of the composition.

[0277] In some embodiments, the pharmaceutical composition further comprises a colorant.

[0278] In some embodiments, the pharmaceutical composition comprises a tablet having a hardness of about 5 Kp or greater (e.g., about 5.5 Kp or greater, about 6 Kp or greater, or about 7 Kp or greater).

[0279] In some embodiments, the tablet has a dissolution of about 50% or greater in about 30 minutes. For example, the pharmaceutical composition consists of a tablet that comprises a compound of Formula I, a diluent, a disintegrant, a surfactant, a binder, a glidant, and a lubricant, wherein the tablet has a dissolution of about 50% or greater in about 30 minutes.

[0280] Note that dissolution can be measured with a standard USP Type II apparatus that employs a dissolution media of 0.6% sodium lauryl sulfate dissolved in 900 mL of DI water, stirring at about 50-75 rpm at a temperature of about 37 °C. A single experimental tablet is tested in each test vessel of the apparatus. Dissolution can also be measured with a standard USP Type II apparatus that employs a dissolution media of 0.7% sodium lauryl sulfate dissolved in 900 mL of 50 mM sodium phosphate buffer (pH 6.8), stirring at about 65 rpm at a temperature of about 37 °C. A single experimental tablet is tested in each test vessel of the apparatus. Dissolution can also be measured with a standard USP Type II apparatus that employs a dissolution media of 0.5% sodium lauryl sulfate dissolved in 900 mL of 50 mM sodium phosphate buffer (pH 6.8), stirring at about 65 rpm at a temperature of about 37 °C, wherein a single experimental tablet is tested in each test vessel of the apparatus.

[0281] In some embodiments, the pharmaceutical composition comprises a compound of Formula I, a binder, a glidant, a surfactant, a lubricant, a disintegrant, and a filler, wherein each of these ingredients comprises a powder (e.g., provided as particles having a mean diameter, measured by light scattering, of about 250 µm or less (e.g., about 150 µm or less, about 100 µm or less, about 50 µm or less, about 45 µm or less, about 40 µm or less, or about 35 µm or less)). For instance, the pharmaceutical composition comprises a compound of Formula I, wherein the compound of Formula I comprises a powder having a mean diameter of about 250 µm or less (e.g., about 150 µm or less, about 100 µm or less, about 50 µm or less, about 45 µm or less, about 40 µm or less, or about 35 µm or less). In other instances, the pharmaceutical composition comprises one or more excipients selected from a binder, a glidant, a surfactant, a lubricant, a disintegrant, and a filler, wherein the excipient comprises a powder having a mean particle diameter of about 250 µm or less (e.g., about 150 µm or less, about 100 µm or less, about 50 µm or less, about 45 µm or less, about 40 µm or less, or about 35 µm or less)).

[0282] In some embodiments, the pharmaceutical composition comprises a tablet, a capsule, or a suspension.

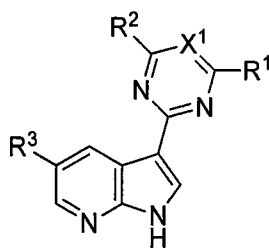
[0283] In some embodiments, the pharmaceutical composition comprises:

- a. about 20 wt% of a compound of Formula I by weight of the composition;
- b. about 37 wt% of microcrystalline cellulose by weight of the composition;
- c. about 37 wt% of lactose by weight of the composition;
- d. about 3 wt% of sodium croscarmellose by weight of the composition;
- e. about 1 wt% of SLS by weight of the composition;
- f. about 1 wt% of colloidal silicon dioxide by weight of the composition;
- and
- g. about 0.75 wt% of magnesium stearate by weight of the composition.

[0284] In some embodiments, the pharmaceutical composition comprises:

- a. about 10 wt% of a compound of Formula I by weight of the composition;
- b. about 47 wt% of microcrystalline cellulose by weight of the composition;
- c. about 47 wt% of lactose by weight of the composition;
- d. about 3 wt% of sodium croscarmellose by weight of the composition;
- e. about 1 wt% of SLS by weight of the composition;
- f. about 1 wt% of colloidal silicon dioxide by weight of the composition;
- and
- g. about 0.75 wt% of magnesium stearate by weight of the composition.

[0285] Another aspect of the present invention provides a method for treating or lessening the severity of rheumatoid arthritis comprising administering to a patient in need thereof a corticosteroid and a compound of Formula I



I

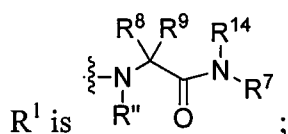
or a pharmaceutically acceptable salt thereof, wherein:

X¹ is N or CR⁴;

R² is H or halo;

R³ is H or halo;

R⁴ is H or halo;



R'' is H or an unsubstituted C₁₋₂ aliphatic;

R⁸ is an unsubstituted C₁₋₄ aliphatic;

R⁹ is an unsubstituted C₁₋₄ aliphatic

R⁷ is a C₁₋₃ aliphatic optionally substituted with up to 3 occurrences of F; and

R¹⁴ is H or unsubstituted C₁₋₂ alkyl,

wherein at least about 25 mg of the compound of Formula I is administered to the patient at least once per day.

[0286] Some embodiments further comprise administering the compound of Formula I from 1 to 4 times per day.

[0287] In some embodiments, from about 20 mg to about 250 mg (e.g., from about 25 mg to about 200 mg, from about 50 mg to about 175 mg, or from about 75 mg to about 150 mg) of the compound of formula I is administered to the patient at least once per day (e.g., from 1 to 4 times per day).

[0288] In some embodiments, about 25 mg of the compound of formula I is administered to the patient once per day.

[0289] In some embodiments, about 50 mg of the compound of formula I is administered to the patient once per day.

[0290] In some embodiments, about 75 mg of the compound of formula I is administered to the patient once per day.

[0291] In some embodiments, about 100 mg of the compound of formula I is administered to the patient once per day.

[0292] In other embodiments, about 150 mg of the compound of formula I is administered to the patient once per day.

[0293] In other embodiments, about 200 mg of the compound of formula I is administered to the patient once per day.

[0294] In other embodiments, about 250 mg of the compound of formula I is administered to the patient once per day.

[0295] And, in some embodiments, from about 20 mg to about 250 mg (e.g., from about 25 mg to about 200 mg, from about 50 mg to about 175 mg, or from about 75 mg to about 150 mg) of the compound of formula I is administered to the patient twice per day.

[0296] In some embodiments, the corticosteroid is hydrocortisone, hydrocortisone acetate, cortisone acetate, tixocortol pivalate, prednisone, prednisolone, methylprednisone, methylprednisolone, or any combination thereof.

[0297] In some embodiments, the corticosteroid is prednisone, prednisolone, methylprednisone, or methylprednisolone.

[0298] In some embodiments, the corticosteroid is methylprednisone or methylprednisolone.

[0299] In some embodiments, the corticosteroid is orally administered to the patient in need thereof.

[0300] In some embodiments, at least about 5 mg of corticosteroid is administered at least once per week. For example, at least about 5 mg of prednisone, prednisolone, methylprednisone, or methylprednisolone is administered at least once per week. In some instances, from about 8 mg to about 15 mg of prednisone or prednisolone is orally administered at least once per week. In other instances, from about 6 mg to about 12 mg of methylprednisone or methylprednisolone is orally administered at least once per week.

[0301] In some embodiments, at least about 8 mg of corticosteroid is administered at least once per week.

[0302] In some embodiments, at least about 5 mg of corticosteroid (e.g., prednisone, prednisolone, methylprednisone, or methylprednisolone) is administered at least twice per week. In some instances, from about 8 mg to about 15 mg of prednisone or prednisolone is orally administered at least twice per week. In other instances from about 6 mg to about 12 mg of methylprednisone or methylprednisolone is orally administered at least twice per week.

[0303] In some embodiments, the corticosteroid is prednisone or methylprednisone.

[0304] In some embodiments, the corticosteroid is administered concurrently with the compound of Formula I. In other embodiments, the corticosteroid is administered prior to or subsequent to the administration of the compound of Formula I.

[0305] In some embodiments, R^2 is H or F.

[0306] In some embodiments, each of R^8 and R^9 is independently selected from methyl, ethyl, propyl, iso-propyl, butyl, or tert-butyl. For example, each of R^8 and R^9 is independently selected from methyl or ethyl.

[0307] In some embodiments, R^{14} is H or methyl.

[0308] In some embodiments, R^7 is an unsubstituted C_{1-3} aliphatic.

[0309] In some embodiments, R^7 is a C_{1-3} aliphatic substituted with 1-3 occurrences of F.

[0310] In some embodiments, R^7 is a group selected from $-CH_2CH_3$, $-CH_2CF_3$, $-CH_2CH_2CH_3$, or $-CHCH_3CH_3$.

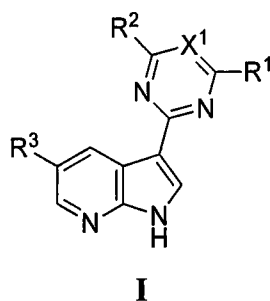
[0311] In some embodiments, the compound of Formula I is a compound selected from Table 1.

[0312] In some embodiments, the compound of Formula I is administered to the patient in the form of an oral tablet. In some examples, the tablet comprises 50 mg of the compound of

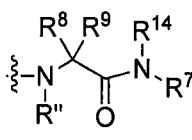
Formula I (e.g., Tablet 1, described below). In some embodiments, 100 mg of the compound of Formula I is administered, either once per day (q.d.) or twice per day (b.i.d.), and the administration may further include the oral administration of two 50 mg tablets (e.g., $2 \times$ Tablet 1) once per day or twice per day depending on the dosage regime. In some embodiments, 150 mg of the compound of Formula I is administered, either once per day (q.d.) or twice per day (b.i.d.), and the administration may further include the oral administration of three of the 50 mg tablets (e.g., $3 \times$ Tablet 1) once per day or twice per day depending on the dosage regime. And, in some embodiments, 200 mg of the compound of Formula I is administered, either once per day (q.d.) or twice per day (b.i.d.), the administration may further include the oral administration of four 50 mg tablets (e.g., $4 \times$ Tablet 1) once per day or twice per day depending on the dosage regime.

[0313] III. PHARMACEUTICAL COMPOSITIONS

[0314] Another aspect of the present invention provides a pharmaceutical composition comprising a corticosteroid and a compound of Formula I



or a pharmaceutically acceptable salt thereof, wherein X^1 is N or CR^4 ; R^2 is H or halo; R^3 is



H or halo; R^4 is H or halo; R^1 is H or halo; R'' is H or an unsubstituted C_{1-2} aliphatic; R^8 is an unsubstituted C_{1-4} aliphatic; R^9 is an unsubstituted C_{1-4} aliphatic; R^7 is a C_{1-3} aliphatic optionally substituted with up to 3 occurrences of F; and R^{14} is H or unsubstituted C_{1-2} alkyl.

[0315] In some embodiments, R^2 is H or F.

[0316] In some embodiments, R^3 is H or Cl.

[0317] In some embodiments, each of R^8 and R^9 is independently selected from methyl, ethyl, propyl, iso-propyl, butyl, or tert-butyl. For example, each of R^8 and R^9 is independently selected from methyl or ethyl.

[0318] In some embodiments, R^{14} is H or methyl.

[0319] In some embodiments, R^7 is an unsubstituted C_{1-3} aliphatic.

[0320] In some embodiments, R^7 is a C_{1-3} aliphatic substituted with 1-3 occurrences of F.

[0321] In some embodiments, R^7 is a group selected from $-\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CF}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_3$, or $-\text{CHCH}_3\text{CH}_3$.

[0322] In some embodiments, the compound of Formula I is selected from Table 1, above.

[0323] And, in some embodiments, the corticosteroid is hydrocortisone, hydrocortisone acetate, cortisone acetate, tixocortol pivalate, prednisone, prednisolone, methylprednisone, methylprednisolone, or any combination thereof.

[0324] In some embodiments, the pharmaceutical composition comprises a tablet.

[0325] In some embodiments, the tablet comprises from about 20 mg to about 250 mg (e.g., from about 25 mg to about 200 mg, from about 50 mg to about 175 mg, or from about 75 mg to about 150 mg) of the compound of formula I.

[0326] In other embodiments, the tablet comprises from about 1 mg to about 25 mg (e.g., from about 2.5 mg to about 8 mg) of the corticosteroid.

[0327] And, in other embodiments, the tablet comprises from about 20 mg to about 250 mg (e.g., from about 25 mg to about 200 mg, from about 50 mg to about 175 mg, or from about 75 mg to about 150 mg) of the compound of formula I and from about 1 mg to about 25 mg (e.g., from about 2.5 mg to about 8 mg) of the corticosteroid.

[0328] Tablets and other pharmaceutical compositions of the present invention may optionally comprise one or more excipients selected from fillers or diluents, wetting agents (e.g., surfactants), binders, glidants, lubricants, disintegrants, or any combination thereof. Examples of suitable excipients are provided in PCT publication no. WO 2013/070606, which is incorporated herein by reference in its entirety.

[0329] For instance, the pharmaceutical composition of the present invention comprises one or more excipients selected from diluents, disintegrants, surfactants, binders, glidants, lubricants, colorants, fragrances, or any combination thereof.

[0330] Diluents suitable for the present invention are compatible with the ingredients of the pharmaceutical composition, i.e., they do not substantially reduce the solubility, the hardness, the chemical stability, the physical stability, or the biological activity of the pharmaceutical composition. Exemplary diluents include lactose, sorbitol, celluloses, calcium phosphates, starches, sugars (e.g., mannitol, sucrose, or the like), or any combination thereof. In one embodiment, the pharmaceutical composition comprises at least one diluent in an amount of about 10 wt% or greater (e.g., about 20 wt% or greater, about 25 wt% or greater, or about 35 wt% or greater) by weight of the composition. For example, the pharmaceutical composition comprises from about 30 wt% to about 50 wt% (e.g., from about 35 wt% to about 45 wt%), by weight of the composition, of at least one diluent. In another example, the pharmaceutical composition comprises from about 40 wt% to about 60 wt% (e.g., from about

45 wt% to about 55 wt%), by weight of the composition, of at least one diluent. In another example, the pharmaceutical composition comprises about 20 wt% or greater (e.g., about 25 wt% or greater, or about 30 wt% or greater) of lactose, by weight of the composition. In yet another example, the pharmaceutical composition comprises from about 20 wt% to about 60 wt% (e.g., from about 25 wt% to about 55 wt% or from about 27 wt% to about 45 wt%) of lactose, by weight of the composition.

[0331] Disintegrants suitable for the present invention enhance the dispersal of the pharmaceutical composition and are compatible with the ingredients of the pharmaceutical composition, i.e., they do not substantially reduce the chemical stability, the physical stability, the hardness, or the biological activity of the pharmaceutical composition. Exemplary disintegrants include sodium croscarmellose, sodium starch glycolate, or a combination thereof. In one embodiment, the pharmaceutical composition comprises disintegrant in an amount of about 10 wt% or less (e.g., about 9 wt% or less, about 8.5 wt% or less, about 8 wt% or less, or about 7.5 wt% or less) by weight of the composition. For example, the pharmaceutical composition comprises from about 1 wt% to about 10 wt% (e.g., from about 1 wt% to about 9 wt% or from about 2 wt% to about 8 wt%) of disintegrant, by weight of the composition. In another example, the pharmaceutical composition comprises about 10 wt% or less (e.g., about 9 wt% or less, about 8 wt% or less, or about 7.5 wt% or less) of sodium croscarmellose, by weight of the composition. In some examples, the pharmaceutical composition comprises from about 0.1% to about 10 wt% (e.g., from about 0.5 wt% to about 7.5 wt% or from about 1.5 wt% to about 6 wt%) of disintegrant, by weight of the composition. In still other examples, the pharmaceutical composition comprises from about 0.5% to about 10 wt% (e.g., from about 1.5 wt% to about 7.5 wt% or from about 2.5 wt% to about 6 wt%) of disintegrant, by weight of the composition.

[0332] Wetting agents (e.g., surfactants) suitable for the present invention enhance the solubility of the pharmaceutical composition and are compatible with the ingredients of the pharmaceutical composition, i.e., they do not substantially reduce the chemical stability, the physical stability, the hardness, or the biological activity of the pharmaceutical composition. Exemplary surfactants include sodium lauryl sulfate (SLS), sodium stearyl fumarate (SSF), polyoxyethylene 20 sorbitan mono-oleate (e.g., TweenTM), any combination thereof, or the like. In one embodiment, the pharmaceutical composition comprises a surfactant in an amount of about 10 wt% or less (e.g., about 5 wt% or less, about 2 wt% or less, or about 1.5 wt% or less) by weight of the composition. For example, the pharmaceutical composition includes from about 10 wt% to about 0.1 wt% (e.g., from about 5 wt% to about 0.2 wt% or from about 2 wt% to about 0.3 wt%) of surfactant, by weight of the composition. In another

example, the pharmaceutical composition comprises 10 wt% or less (e.g., about 5 wt% or less, about 2 wt% or less, about 1 wt% or less, about 0.8 wt% or less, or about 0.6 wt% or less) of sodium lauryl sulfate, by weight of the composition. In yet another example, the pharmaceutical composition comprises from about 10 wt% to about 0.1 wt% (e.g., from about 5 wt% to about 0.2 wt% or from about 2 wt% to about 0.3 wt%) of sodium lauryl sulfate, by weight of the composition.

[0333] Binders suitable for the present invention enhance the tablet strength of the pharmaceutical composition and are compatible with the ingredients of the pharmaceutical composition, i.e., they do not substantially reduce the chemical stability, the physical stability, or the biological activity of the pharmaceutical composition. Exemplary binders include microcrystalline cellulose, dibasic calcium phosphate, sucrose, corn (maize) starch, modified cellulose (e.g., hydroxymethyl cellulose), or any combination thereof. In one embodiment, the pharmaceutical composition comprises a binder in an amount of about 1 wt% or greater (e.g., about 10 wt% or greater, about 15 wt% or greater, about 20 wt% or greater, or about 25 wt% or greater) by weight of the composition. For example, the pharmaceutical composition comprises from about 5 wt% to about 50 wt% (e.g., from about 10 wt% to about 45 wt% or from about 20 wt% to about 45 wt%) of binder, by weight of the composition. In another example, the pharmaceutical composition comprises about 1 wt% or greater (e.g., about 10 wt% or greater, about 15 wt% or greater, about 20 wt% or greater, or about 22 wt% or greater) of microcrystalline cellulose, by weight of the composition. In yet another example, the pharmaceutical composition comprises from about 5 wt% to about 50 wt% (e.g., from about 10 wt% to about 45 wt% or from about 20 wt% to about 45 wt%) of microcrystalline cellulose, by weight of the composition.

[0334] Glidants suitable for the present invention enhance the flow properties of the pharmaceutical composition and are compatible with the ingredients of the pharmaceutical composition, i.e., they do not substantially reduce the solubility, the hardness, the chemical stability, the physical stability, or the biological activity of the pharmaceutical composition. Exemplary glidants include colloidal silicon dioxide, talc, or a combination thereof. In one embodiment, the pharmaceutical composition comprises a glidant in an amount of about 2 wt% or less (e.g., about 1.75 wt% or less, about 1.25 wt% or less, or about 1.00 wt% or less) by weight of the composition. For example, the pharmaceutical composition comprises from about 2 wt% to about 0.05 wt% (e.g., from about 1.5 wt% to about 0.07 wt% or from about 1.0 wt% to about 0.09 wt%) of glidant, by weight of the composition. In another example, the pharmaceutical composition comprises about 2 wt% or less (e.g., about 1.75 wt% or less, about 1.25 wt% or less, or about 1.00 wt% or less) of colloidal silicon

dioxide, by weight of the composition. In yet another example, the pharmaceutical composition comprises from about 2 wt% to about 0.05 wt% (e.g., from about 1.5 wt% to about 0.07 wt% or from about 1.0 wt% to about 0.09 wt%) of colloidal silicon dioxide, by weight of the composition.

[0335] Lubricants suitable for the present invention improve the compression and ejection of compressed pharmaceutical compositions from a die press and are compatible with the ingredients of the pharmaceutical composition, i.e., they do not substantially reduce the solubility, the hardness, or the biological activity of the pharmaceutical composition. Exemplary lubricants include magnesium stearate, stearic acid (stearin), hydrogenated oil, sodium stearyl fumarate, or any combination thereof. In one embodiment, the pharmaceutical composition comprises a lubricant in an amount of about 2 wt% or less (e.g., about 1.75 wt% or less, about 1.25 wt% or less, or about 1.00 wt% or less) by weight of the composition. For example, the pharmaceutical composition comprises from about 2 wt% to about 0.10 wt% (e.g., from about 1.5 wt% to about 0.15 wt% or from about 1.3 wt% to about 0.30 wt%) of lubricant, by weight of the composition. In another example, the pharmaceutical composition comprises about 2 wt% or less (e.g., about 1.75 wt% or less, about 1.25 wt% or less, or about 1.00 wt% or less) of magnesium stearate, by weight of the composition. In yet another example, the pharmaceutical composition comprises from about 2 wt% to about 0.10 wt% (e.g., from about 1.5 wt% to about 0.15 wt% or from about 1.3 wt% to about 0.30 wt%) of magnesium stearate, by weight of the composition.

[0336] In some embodiments, the pharmaceutical composition can optionally comprise one or more colorants, flavors, and/or fragrances to enhance the visual appeal, taste, and/or scent of the composition. Suitable colorants, flavors, or fragrances are compatible with the ingredients of the pharmaceutical composition, i.e., they do not substantially reduce the solubility, the chemical stability, the physical stability, the hardness, or the biological activity of the pharmaceutical composition. In some embodiments, the pharmaceutical composition comprises a colorant, a flavor, and/or a fragrance. For example, the pharmaceutical composition comprises less than about 1 wt% (e.g., less than about 0.75 wt% or less than about 0.5 wt%) of each optionally ingredient, i.e., colorant, flavor and/or fragrance, by weight of the composition. In another example, the pharmaceutical composition comprises less than about 1 wt% (e.g., less than about 0.75 wt% or less than about 0.5 wt%) of a colorant.

[0337] In some embodiments, the pharmaceutical composition can comprise tablets and the tablets can be coated with a colorant and optionally labeled with a logo, other image and/or text using a suitable ink. In still other embodiments, the pharmaceutical composition can be made into tablets and the tablets can be coated with a colorant, waxed, and optionally labeled

with a logo, other image and/or text using a suitable ink. Suitable colorants and inks are compatible with the ingredients of the pharmaceutical composition, i.e., they do not substantially reduce the solubility, the chemical stability, the physical stability, the hardness, or the biological activity of the pharmaceutical composition. The suitable colorants and inks can be any color and are water based or solvent based. In some embodiments, tablets made from the pharmaceutical composition are coated with a colorant and then labeled with a logo, other image, and/or text using a suitable ink. For example, tablets comprising a pharmaceutical composition as described herein can be coated with about 3 wt% (e.g., less than about 6 wt% or less than about 4 wt%) of film coating comprising a colorant. The colored tablets can be labeled with a logo and text indicating the strength of the active ingredient in the tablet using a suitable ink. The colored tablets can be labeled with a logo and text indicating the strength and/or mass of the active ingredient in the tablet using a black ink (e.g., Opacode® WB, commercially available from Colorcon, Inc. of West Point, PA.). In another embodiment, tablets made from the pharmaceutical composition are coated with a colorant, waxed, and then labeled with a logo, other image, and/or text using a suitable ink. The colored tablets can be waxed with Carnauba wax powder weighed out in the amount of about 0.01 % w/w of the starting tablet core weight. The waxed tablets can be labeled with a logo and text indicating the strength of the active ingredient in the tablet using a suitable ink.

[0338] IV. ADMINISTRATIONS

[0339] In another aspect, the invention also provides a method of treating or lessening the severity of rheumatoid arthritis comprising administering to said patient one of the compositions as defined herein and a corticosteroid.

[0340] In some embodiments, the corticosteroid is hydrocortisone, hydrocortisone acetate, cortisone acetate, tixocortol pivalate, prednisone, prednisolone, methylprednisone, methylprednisolone, or any combination thereof.

[0341] In some embodiments, the corticosteroid is prednisone, prednisolone, methylprednisone, or methylprednisolone.

[0342] In some embodiments, the corticosteroid is methylprednisone or methylprednisolone.

[0343] In some embodiments, the corticosteroid is orally administered to the patient in need thereof.

[0344] In some embodiments, at least about 5 mg of corticosteroid is administered at least once per week. For example, at least about 5 mg of prednisone, prednisolone, methylprednisone, or methylprednisolone is administered at least once per week. In some instances, from about 8 mg to about 15 mg of prednisone or prednisolone is orally

administered at least once per week. In other instances, from about 6 mg to about 12 mg of methylprednisone or methylprednisolone is orally administered at least once per week.

[0345] In some embodiments, at least about 8 mg of corticosteroid is administered at least once per week.

[0346] In some embodiments, at least about 5 mg of corticosteroid (e.g., prednisone, prednisolone, methylprednisone, or methylprednisolone) is administered at least twice per week. In some instances, from about 8 mg to about 15 mg of prednisone or prednisolone is orally administered at least twice per week. In other instances from about 6 mg to about 12 mg of methylprednisone or methylprednisolone is orally administered at least twice per week.

[0347] In some embodiments, the corticosteroid is prednisone or methylprednisone.

[0348] In some embodiments, the corticosteroid is administered concurrently with the compound of Formula I. In other embodiments, the corticosteroid is administered prior to or subsequent to the administration of the compound of Formula I.

[0349] Another aspect of the present invention provides a method of administering a pharmaceutical composition by orally administering to a patient a pharmaceutical composition comprising about 20 mg or greater (e.g., about 25 mg) of a compound of Formula I at least once per day and orally administering to the patient at least about 5 mg of a corticosteroid at least once per week.

[0350] Another aspect of the present invention provides a method of administering a pharmaceutical composition by orally administering to a patient a pharmaceutical composition comprising about 45 mg or greater (e.g., about 50 mg) of a compound of Formula I at least once per day and orally administering to the patient at least about 5 mg of a corticosteroid at least once per week.

[0351] Another aspect of the present invention provides a method of administering a pharmaceutical composition by orally administering to a patient a pharmaceutical composition comprising about 150 mg or greater (e.g., about 200 mg) of a compound of Formula I at least once per day and orally administering to the patient at least about 5 mg of a corticosteroid at least once per week.

[0352] Another aspect of the present invention provides a method of administering a corticosteroid and a pharmaceutical composition comprising orally administering to a patient at least once per day at least one tablet comprising a pharmaceutical composition comprising:

- a. a compound of Formula I;
- b. a diluent;
- c. a binder;

- d. a glidant;
- e. a disintegrant;
- f. a surfactant; and
- g. a lubricant.

[0353] In several embodiments, the tablet comprising the pharmaceutical composition comprising a compound of Formula I, the diluent, the binder, the glidant, the disintegrant, the surfactant, and the lubricant is orally administered to the patient once per day or twice per day (e.g., about every 12 hours). In other embodiments, the tablet comprising the pharmaceutical composition comprising a compound of Formula I, the diluent, the binder, the glidant, the disintegrant, the surfactant, and the lubricant is orally administered to the patient twice per day.

[0354] In some embodiments, the tablet comprises about 25 mg or greater of a compound of Formula I.

[0355] In some instances, the tablet comprises about 25 mg of a compound of Formula I. In other instances, the tablet comprises about 50 mg of a compound of Formula I.

[0356] Another aspect of the present invention provides a method of administering a pharmaceutical composition by orally administering to a patient at least once per day the composition comprising about 20 mg or greater of a compound of Formula I.

[0357] Another aspect of the present invention provides a method of administering a pharmaceutical composition by orally administering to a patient at least once per day the composition comprising about 25 mg of a compound of Formula I.

[0358] Another aspect of the present invention provides a method of administering a pharmaceutical composition by orally administering to a patient at least once per day the composition comprising about 50 mg of a compound of Formula I.

[0359] Another aspect of the present invention provides a method of administering a pharmaceutical composition by orally administering to a patient twice per day the composition comprising a compound of Formula I.

[0360] Another aspect of the present invention provides a method of administering a pharmaceutical composition by orally administering to a patient twice per day the composition comprising about 25 mg of a compound of Formula I.

[0361] Another aspect of the present invention provides a method of administering a pharmaceutical composition by orally administering to a patient twice per day the composition comprising about 50 mg of a compound of Formula I.

[0362] Another aspect of the present invention provides a method of administering a pharmaceutical composition by orally administering to a patient twice per day the composition comprising about 100 mg of a compound of Formula I.

[0363] Another aspect of the present invention provides a method of administering a pharmaceutical composition by orally administering to a patient twice per day the composition comprising about 150 mg of a compound of Formula I.

[0364] Another aspect of the present invention provides a method of administering a pharmaceutical composition by orally administering to a patient a pharmaceutical composition once every 12 hours. The composition comprises about 25 mg or greater of a compound of Formula I.

[0365] Another aspect of the present invention provides a method of administering a pharmaceutical composition by orally administering to a patient once every 12 hours, about 50 mg or greater of a compound of Formula I.

[0366] Another aspect of the present invention provides a method of administering a pharmaceutical composition by orally administering to a patient once every 12 hours, about 100 mg or greater of a compound of Formula I.

[0367] Another aspect of the present invention provides a method of administering a pharmaceutical composition by orally administering to a patient once every 12 hours, about 150 mg or greater of a compound of Formula I.

[0368] In still other aspects of the present invention, a pharmaceutical composition as described herein is orally administered to a patient once every 24 hours.

[0369] Another aspect of the present invention provides a method of administering a pharmaceutical composition comprising orally administering to a patient at least once per day at least one tablet comprising a pharmaceutical composition comprising a compound of Formula I, a diluent, a binder, a glidant, a disintegrant, a surfactant, and a lubricant, each of which is described above and in the Examples below, wherein the composition comprises about 25 mg or greater (e.g., at least 35 mg, at least 40 mg, or at least 45 mg) of a compound of Formula I.

[0370] In some embodiments, the present invention provides a method of administering a pharmaceutical composition comprising orally administering to a patient at least one tablet comprising:

- a. about 25 mg of a compound of Formula I;
- b. a diluent;
- c. a disintegrant;
- d. a wetting agent;

- e. a binder;
- f. a glidant; and
- g. a lubricant.

[0371] In some embodiments, the present invention provides a method of administering a pharmaceutical composition comprising orally administering to a patient at least one tablet comprising:

- a. about 50 mg of a compound of Formula I;
- b. a diluent;
- c. a disintegrant;
- d. a surfactant;
- e. a binder;
- f. a glidant; and
- g. a lubricant.

[0372] In some embodiments, the present invention provides for a method of orally administering the pharmaceutical composition described herein once a day. In other embodiments, the present invention provides for a method of orally administering the pharmaceutical composition described herein twice a day.

[0373] Another aspect of the present invention provides a method of administering a pharmaceutical composition by orally administering to a patient at least once per day at least one tablet comprising about 25 mg or greater of a compound of Formula I, a diluent, a binder, a glidant, a disintegrant, a surfactant, and a lubricant. In some embodiments, the tablet is orally administered to the patient once per day. In other embodiments, the administration comprises orally administering to a patient twice per day at least one tablet comprising about 25 mg or greater of a compound of Formula I, a diluent, a binder, a glidant, a disintegrant, a surfactant, and a lubricant. Some tablets useful in this method comprise about 50 mg of a compound of Formula I. In another method, the administration includes orally administering to a patient twice per day at least one tablet comprising about 50 mg or greater of a compound of Formula I, a diluent, a binder, a glidant, a disintegrant, a surfactant, and a lubricant.

[0374] In one embodiment, the method of administering a pharmaceutical composition includes orally administering to a patient at least once per day at least one tablet comprising a pharmaceutical composition containing from about 20 mg to about 55 mg of a compound of Formula I; and a diluent, a binder, a glidant, a disintegrant, a surfactant, and a lubricant.

[0375] In another embodiment, the method of administering a pharmaceutical composition includes orally administering to a patient once per day at least one tablet comprising a

pharmaceutical composition containing a compound of Formula I, a filler, a binder, a glidant, a disintegrant, a surfactant, and a lubricant, each of which is described above and in the Examples below, wherein the compound of Formula I is present in an amount of about 25 mg or greater (e.g., about 35 mg or greater, about 40 mg or greater, about 45 mg or greater, about 75 mg or greater, about 100 mg or greater, about 150 mg or greater, or about 250 mg or greater). In another example, the method of administering a pharmaceutical composition includes orally administering to a patient once per day a plurality of tablets (e.g., two tablets, three tablets, four or five tablets), wherein each tablet comprises a pharmaceutical composition comprising a compound of Formula I, a filler, a binder, a glidant, a disintegrant, a surfactant, and a lubricant, wherein the compound of Formula I is present in an amount of about 25 mg or greater (e.g., about 35 mg or greater, about 40 mg or greater, about 45 mg or greater, about 75 mg or greater, about 150 mg or greater, or about 250 mg or greater).

[0376] In another embodiment, the method of administering a pharmaceutical composition includes orally administering to a patient twice per day at least one tablet comprising a pharmaceutical composition containing a compound of Formula I, a filler, a binder, a glidant, a disintegrant, a surfactant, and a lubricant, each of which is described above and in the Examples below, wherein the compound of Formula I is present in an amount of about 25 mg or greater (e.g., about 35 mg or greater, about 40 mg or greater, about 45 mg or greater, about 50 mg or greater, about 75 mg or greater, about 150 mg or greater, or about 250 mg or greater). In another example, the method of administering a pharmaceutical composition includes orally administering to a patient twice per day a plurality of tablets (e.g., two tablets, three tablets, four tablets or five tablets), wherein each tablet comprises a pharmaceutical composition comprising a compound of Formula I, a filler, a binder, a glidant, a disintegrant, a surfactant, and a lubricant, wherein the compound of Formula I is present in an amount of about 20 mg or greater (e.g., about 25 mg or greater, about 30 mg or greater, about 35 mg or greater, about 45 mg or greater, about 75 mg or greater, about 150 mg or greater, or about 250 mg or greater) per tablet. In embodiments wherein a plurality of tablets are administered, each of the tablets may comprise about the same amount of a compound of Formula I or at least two of the tablets may comprise different amounts of the compound of Formula I.

[0377] It will also be appreciated that the compound and pharmaceutically acceptable compositions of the present invention can be employed in combination therapies, that is, the compound and pharmaceutically acceptable compositions can be administered concurrently with, prior to, or subsequent to, one or more other desired therapeutics or medical procedures. The particular combination of therapies (therapeutics or procedures) to employ in a combination regimen will take into account compatibility of the desired therapeutics and/or

procedures and the desired therapeutic effect to be achieved. It will also be appreciated that the therapies employed may achieve a desired effect for the same disorder (for example, an inventive compound may be administered concurrently with another agent used to treat the same disorder), or they may achieve different effects (e.g., control of any adverse effects). As used herein, additional therapeutic agents that are normally administered to treat or prevent a particular disease, or condition, are known as "appropriate for the disease, or condition, being treated".

[0378] In another embodiment, the additional agent is a nutritional agent. Exemplary agents include vitamin a, vitamin b, vitamin c, vitamin e, pancrelipase (pancreatic enzyme replacement), including Pancrease®, Pancreacarb®, Ultrase®, or Creon®, Liprotomase® (formerly Trizyte®), Aquadeks®, or glutathione inhalation. In one embodiment, the additional nutritional agent is pancrelipase.

[0379] IV. EXAMPLES

[0380] In order that the invention described herein may be more fully understood, the following examples are set forth. It should be understood that these examples are for illustrative purposes only and are not to be construed as limiting this invention in any manner.

[0381] Compounds of Formula I can be synthesized according to methods described in PCT publication nos. WO 2013006634, WO 2007084557, and WO 2005095400, each of which is incorporated herein by reference.

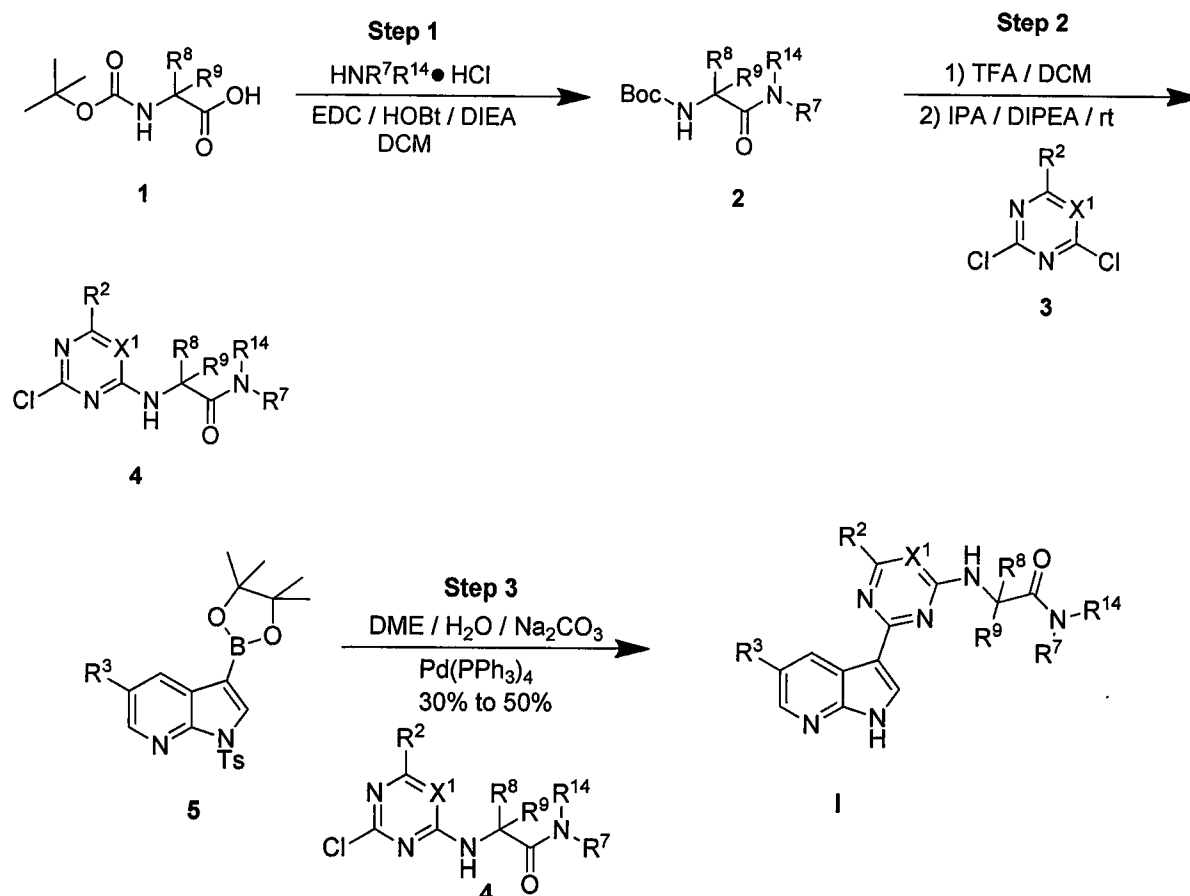
[0382] Example 1: Analytical Methods Used

[0383] (A) HPLC on C18 column. Mobile phase was acetonitrile/water/TFA (60:40:0.1). Flow rate was 1.0 mL/min. Detection at wavelength of 230 nm. Run time was 25-26 minutes.

[0384] (B) HPLC on C18 column. Mobile phase was acetonitrile/water/TFA (90:10:0.1). Flow rate was 1.0 mL/min. Detection at wavelength of 230 nm.

[0385] (C) HPLC on a Waters XBridge Phenyl column, 4.6 x 150 mm, 3.5 µm. Mobile phase A was water/1M ammonium formate, pH 4.0 (99:1). Mobile phase B was acetonitrile/water/ 1M ammonium formate, pH 4.0 (90:9:1). Gradient 5 % to 90 % B in 15 minutes. Total run time 22 minutes. Flow rate 1.5 mL/min. Detection at UV, 245 nm. T = 25 °C.

[0386] (D) HPLC on a Waters XBridge Phenyl column, 4.6 x 150 mm, 3.5 µm. Mobile phase A was water/1M ammonium formate, pH 4.0 (99:1). Mobile phase B was acetonitrile/water/ 1M ammonium formate, pH 4.0 (90:9:1). Gradient 15% to 90 % B in 15 minutes. Total run time 22 minutes. Flow rate 1.5 mL/min. Detection at UV, 220 nm. T = 35 °C.

[0387] Example 2: Preparation of Compounds of Formula I*a. General Synthetic Scheme*

[0388] The Boc-protected amino acid starting material (1) undergoes amidation in the presence of an activating agent, a coupling reagent, and the acid salt of the amine $\text{HNR}^7\text{R}^{17}$ to generate the Boc-protected amide intermediate (2). The amide intermediate (2) is deprotected under acidic conditions and reacted with the halogenated heteroaryl (3) to generate the aminoheteroaryl intermediate (4). Boronated azaindole (5) is coupled with the aminoheteroaryl intermediate (4) under cross-coupling condition to generate the compound of Formula I.

[0389] Example 3: Synthesis of 2-(2-(1H-pyrrolo[2,3-b]pyridin-3-yl)pyrimidin-4-ylamino)-2-methyl-N-(2,2,2-trifluoroethyl)butanamide

[0390] 3-bromo-1H-pyrrolo[2,3-b]pyridine:

[0391] Commercially available 7-Azaindole (6.9 kg, 58.4 moles) was added to a 200 L glass-lined reactor containing 52.6 kg DMF. A solution of Br_2 in DMF (9.7 kg Br_2 in 14.7 kg DMF) was added drop wise to maintain the mixture temperature of about 0-10 °C. After the addition was complete, the temperature was maintained at about 0-10 °C. The completeness of the reaction was measured by HPLC (method A) with sample aliquots after 30 minutes. The reaction was considered complete when the 7-azaindole was less than 3% (after about 2

hours and 40 minutes). Typical retention time for 3-bromo-1H-pyrrolo[2,3-b]pyridine was 3.228 minutes.

[0392] The reaction was quenched with 10% aqueous solution of NaHSO₃ (17.5 kg) while maintaining the temperature below 15 °C. A saturated aqueous solution of NaHCO₃ (61.6 kg) below 25 °C was added to adjust the pH to about 7 to 8. After neutralization, the mixture was transferred into a 50 L vacuum filter and filtered. The resultant cake was washed with water (18 kg) and then petroleum ether (12 kg). The cake was dried in a tray dryer at about 50-60 °C until the water content detected by KF (Karl Fisher reaction) was less than 0.8%. A yellow solid resulted (10.3 kg, 99.1% purity as measured by HPLC (method A), 89.6% yield of 3-bromo-1H-pyrrolo[2,3-b]pyridine).

[0393] *3-bromo-1-tosyl-1H-pyrrolo[2,3-b]pyridine*:

[0394] 3-bromo-1H-pyrrolo[2,3-b]pyridine (10.7 kg, 54.3 moles) was added to 94.3 kg of THF in a 200 L glass-lined reactor. The solid was dissolved completely by stirring. After the mixture was cooled to about 10-15 °C, NaH (3.4 kg, 85 moles) was added in portions (about 200-250 g each portion) every 3 to 5 minutes while venting any H₂ gas released by the reaction. After the addition of NaH, the mixture was stirred for one hour while maintaining the temperature of about 10-20 °C. 4-methylbenzenesulfonylchloride (12.4 kg, 65.0 moles) was added at a rate of 0.5 kg/10 minutes at about 10-20 °C. After the addition was complete, the temperature was maintained at about 10-20 °C. The completeness of the reaction was measured by HPLC (method A) with sample aliquots after 30 minutes. The reaction was considered complete when the peak area of 3-bromo-1H-pyrrolo[2,3-b]pyridine was less than 1% (after about 1.5 hours). Typical retention time for 3-bromo-1-tosyl-1H-pyrrolo[2,3-b]pyridine was 20.2 minutes.

[0395] The reaction was quenched with water (10.7 kg) while maintaining the temperature below 20 °C. Dichloromethane (41.3 kg) was added to the mixture. Then 3% HCl acid (42.8 kg) was added into the mixture while maintaining the temperature below 25 °C. After the addition, the phases were allowed to separate for 0.5 hour. The aqueous phase was extracted twice with dichloromethane. During each extraction, the mixture was stirred for 15 minutes and then held for 15 minutes. All the organic phases were combined. The combined organic phases were washed with 3% HCl acid (33.4 kg) and water (40 kg). During each wash, the mixture was stirred for 15 minutes and then held for 30 minutes.

[0396] The mixture was transferred into a 50 L vacuum filter and filtered through silica gel (3 kg). The cake was washed with dichloromethane (35 kg) twice. The filtrate and washings were combined. The organic phase was concentrated below 40 °C under vacuum of a pressure less than -0.085 MPa until 10 L mixture remained. Petroleum ether (9 kg) was

added into the residue. The mixture was stirred until it was homogeneous. The slurry was transferred into a 50 L vacuum filter and filtered. The cake was washed with petroleum ether (9 kg). A light brown solid resulted (17 kg, 99.7% purity as measured by HPLC analysis (method A), 94% yield of 3-bromo-1-tosyl-1H-pyrrolo[2,3-b]pyridine).

[0397] *1-tosyl-1H-pyrrolo[2,3-b]pyridin-3-ylboronic acid*:

[0398] THF (28.5 kg) and 3-bromo-1-tosyl-1H-pyrrolo[2,3-b]pyridine (4 kg) were added to a 72L flask. The mixture was stirred until the solid dissolved completely. Triisopropyl borate (3.2 kg) was added and the mixture was cooled to below -80 °C. n-BuLi (4.65 kg) was added drop wise at a rate of about 0.6-0.9 kg/hour maintaining the temperature of about -80 to -90 °C. After the addition, the temperature was maintained at about -80 to -90 °C. The completeness of the reaction was measured by HPLC (method A) with sample aliquots after 30 minutes. The reaction was considered complete when the peak area of 3-bromo-1-tosyl-1H-pyrrolo[2,3-b]pyridine was less than 4%. Typical retention time for 1-tosyl-1H-pyrrolo[2,3-b]pyridin-3-ylboronic acid was 4.6 minutes. Extra triisopropyl borate and n-BuLi was added to lower the peak area of 3-bromo-1-tosyl-1H-pyrrolo[2,3-b]pyridine.

[0399] Water (2 kg) was slowly added to the mixture to quench the reaction. The mixture temperature returned to about 15-25 °C. The mixture was transferred to a 50 L reactor to be concentrated below 40 °C under vacuum of a pressure less than -0.08 MPa until no THF distilled out. The residue was dissolved into water (25 kg) and 10% aqueous NaOH solution (26 kg). The mixture was stirred until the solid dissolved completely. The mixture was transferred into a vacuum filter and filtered. The filtrate was extracted twice with MTBE (21 kg each) at about 20-30 °C. During each extraction, the mixture was stirred 15 minutes and held 15 minutes. HCl acid (28L) was added into the aqueous phase to adjust the pH to between 3 and 4 while maintaining the temperature of about 10-20 °C. The mixture was stirred at about 10-15 °C for 1 hour. The mixture was transferred into a centrifuge and filtered. The resultant cake after filtering was washed with water (5 kg) and petroleum ether (5 kg). The cake was dried at 35-45 °C until the LOD (loss on drying) was less than 3%. An off-white solid resulted (2.5 kg and 98.8% purity as measured by HPLC analysis (method A), 69.4% yield of 1-tosyl-1H-pyrrolo[2,3-b]pyridin-3-ylboronic acid).

[0400] *3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-tosyl-1H-pyrrolo[2,3-b]pyridine*:

[0401] Dichloromethane (165.6 kg) and pinacolate alcohol (3.54 kg) was added to a 200 L glass-lined reactor. The mixture was stirred until the solid dissolved completely. Then, 1-tosyl-1H-pyrrolo[2,3-b]pyridin-3-ylboronic acid (8.65 kg) was added in portions (2 kg every 5 minutes) while maintaining the temperature of about 20-30 °C. After the addition, the temperature was maintained at about 20-30 °C while stirring. The completeness of the

reaction was measured by HPLC (method B) with sample aliquots every 60 minutes. The reaction was considered complete when the peak area of 31-tosyl-1H-pyrrolo[2,3-b]pyridin-3-ylboronic acid was less than 1%. Typical retention time for 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-tosyl-1H-pyrrolo[2,3-b]pyridine) was 6.4 minutes.

[0402] The mixture was filtered through silica gel (3 kg). The cake was rinsed twice with dichloromethane (15 kg each rinse). The filtrate was combined with the washing liquids, and then concentrated below 30 °C under vacuum at a pressure less than -0.08 MPa until no fraction distilled out. Solvent was continued to be removed by vacuum for 2 hours.

Isopropanol (17.2 kg) was added to the residue. The mixture was heated to reflux at about 80-85 °C. The mixture refluxed for 30 minutes until the solid dissolved completely. The mixture was cooled below 35 °C, and then to about 0-10 °C. The mixture crystallized at 0-10 °C for 2 hours and then filtered. After filtration, the resultant cake was dried at about 35-45 °C until the water content detected by KF (Karl Fisher reaction) was less than 0.5% and the LOD (loss on drying) was less than 0.5%. An off-white solid resulted (8.8 kg and 99.7% purity as measured by HPLC analysis (method B), 81.5% yield of 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-tosyl-1H-pyrrolo[2,3-b]pyridine).

[0403] *(R)-2-methyl-2-(2-(1-tosyl-1H-pyrrolo[2,3-b]pyridin-3-yl)pyrimidin-4-ylamino)butanoic acid:*

[0404] Tripotassium phosphate (K_3PO_4) (7.20 kg, 3 equiv.) was mixed with three volumes of water (9.0 kg). The mixture was agitated for at least 20 minutes, cooled to a temperature of ≤ 30 °C and added to acetonitrile (16.8 g, 7 volumes) into a 120 L reactor. The resultant mixture was agitated. 3.0 kg (11.3 moles, 1.0 equiv.) of (R)-2-(2-chloropyrimidin-4-ylamino)-2-methylbutanoic acid hydrochloride were added to the reaction mixture in the reactor while maintaining a temperature ≤ 30 °C. The mixture was agitated for at least 20 minutes. 5.16 kg (13.0 moles, 1.15 equiv.) of 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-tosyl-1H-pyrrolo[2,3-b]pyridine were then added to the reactor. The reaction mixture was agitated and de-gassed with N_2 sparging for at least 30 minutes. The mixture was heated to 65 ± 5 °C.

[0405] In a separate vessel, 0.075 kg (0.03 equiv.) of palladium(II) acetate was mixed with 4.80 kg (2 volumes) of de-gassed acetonitrile (CH_3CN). This mixture was agitated until homogenous. 0.267 kg (1.02 moles, 0.09 equiv.) of triphenylphosphine (PPh_3) was added and the resultant mixture was agitated for at least 30 minutes at 20 ± 5 °C. The palladium(II) acetate/ PPh_3 / CH_3CN mixture was then added to the reactor above while maintaining the nitrogen purge. The reactor contents were heated to 75 ± 5 °C for at least 17 hours under nitrogen purge. After 5 hours the conversion was shown to be about 86% complete as

measured by HPLC analysis (method C) of a 1.0 mL aliquot. Typical retention times are 6.2 minutes for (R)-2-(2-chloropyrimidin-4-ylamino)-2-methylbutanoic acid hydrochloride and 10.6 minutes for (R)-2-methyl-2-(2-(1-tosyl-1H-pyrrolo[2,3-b]pyridin-3-yl)pyrimidin-4-ylamino)butanoic acid. Additional catalyst and 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-tosyl-1H-pyrrolo[2,3-b]pyridine (900 g, 2.26 moles, 0.2 equiv.) were then added to the reaction mixture and the mixture was stirred. After an additional 12 hours, the reaction was shown to be 99.7% complete as measured by HPLC analysis (method C) of a 1.0 mL aliquot. The additional catalyst added above was prepared by dissolving 37.5 g Palladium(II) acetate in 1 volume of acetonitrile (which was de-gassed for 20 minutes), and then adding 133.5 g of triphenylphosphine.

[0406] *(R)-2-(2-(1H-pyrrolo[2,3-b]pyridin-3-yl)pyrimidin-4-ylamino)-2-methylbutanoic acid:*

[0407] A solution of 4N aqueous KOH, which was previously prepared with 6.0 kg of KOH in 27.0 kg of water at a rate to control the temperature rise, was added to the reactor above and the reaction was heated to 75 ± 5 °C for at least 5 hours while agitating the mixture. An aliquot of about 1.0 mL was removed from the reaction mixture and analyzed by HPLC (method C) to show 98.6% (R)-2-(2-(1H-pyrrolo[2,3-b]pyridin-3-yl)pyrimidin-4-ylamino)-2-methylbutanoic acid and 1.4% (R)-2-methyl-2-(2-(1-tosyl-1H-pyrrolo[2,3-b]pyridin-3-yl)pyrimidin-4-ylamino)butanoic acid. Typical retention times are 10.6 minutes for (R)-2-methyl-2-(2-(1-tosyl-1H-pyrrolo[2,3-b]pyridin-3-yl)pyrimidin-4-ylamino)butanoic acid and 5.5 minutes for (R)-2-(2-(1H-pyrrolo[2,3-b]pyridin-3-yl)pyrimidin-4-ylamino)-2-methylbutanoic acid.

[0408] 15.0 kg (5 volumes) of water was added to the reactor. The reaction mixture was cooled to 35 ± 5 °C. Isopropyl acetate (7.8 g, 3 volumes) was added, and the reaction mixture was agitated for at least 5 minutes. The reaction mixture was filtered through a 4-cm pad of celite in an 18-inch Nutsche filter. The reactor was rinsed with 9.0 kg of water and the water was then used to rinse the celite pad. The aqueous and organic phases were separated. 0.9 kg of Darco G-60 activated carbon (30% w/w) was added to the aqueous phase in a 120-liter reactor. The pH of the mixture was adjusted to less than 1.0 with concentrated HCl solution at 25 ± 10 °C and held for at least 4 hours. If necessary, the pH was readjusted with 6N NaOH. The mixture was then filtered through a Nutsche filter, which was equipped with a filter cloth, and the solids were rinsed with 6.0 kg (2 volumes) of 1N HCl. The filter cake was maintained under positive pressure of nitrogen for at least 30 minutes. The HCl filtrate was agitated and heated to 25 ± 5 °C. 0.9 kg of Darco G-60 activated carbon was added to the HCl filtrate and the mixture was stirred for at least 4 hours. The mixture was then filtered

through a Nutshce filter, which was equipped with a filter cloth, and the solids were washed with 6.0 kg (2 volumes) of 1N HCl. The second filter cake was maintained under positive pressure of nitrogen for at least 30 minutes. The HCl filtrate was again agitated and heated, charcoal was added and filtering step was repeated with a Nutshce filter, which was equipped with a 0.45 um in-line filter between the Nutsche filter and the receiver flask, to yield a third filter cake and a final filtrate. The solids were washed with 6.0 kg of 1N HCl. The third filter cake was maintained under positive pressure of nitrogen for at least 30 minutes.

[0409] The pH of the final filtrate was adjusted to between 4.5 and 5.0 using 6N NaOH while the temperature was maintained between 25 ± 5 °C. If necessary, the pH was readjusted using 1N HCl. The final filtrate was then cooled to 5 ± 5 °C and agitated for at least 2 hours. The mixture was filtered with a Nutshce filter, which was equipped with a filter cloth. The solids were rinsed with 6.0 kg (2 volumes) of water. The final filter cake was maintained under positive pressure of nitrogen for at least 30 minutes.

[0410] The wet solids (i.e., filter cakes) were dried in a drying oven at ≤ 60 °C under vacuum, with a nitrogen purge, over 5 days to yield 3.561 kg of (R)-2-(2-(1H-pyrrolo[2,3-b]pyridin-3-yl)pyrimidin-4-ylamino)-2-methylbutanoic acid (yield of 102%).

[0411] *2-(2-(1H-pyrrolo[2,3-b]pyridin-3-yl)pyrimidin-4-ylamino)-2-methyl-N-(2,2,2-trifluoroethyl)butanamide:*

[0412] Diisopropylethylamine (DIEA) (3.61 kg, 28.1 moles, 2.5 equiv.) was added to (R)-2-(2-(1H-pyrrolo[2,3-b]pyridin-3-yl)pyrimidin-4-ylamino)-2-methylbutanoic acid (3.5 kg, 11.24 moles, 1.0 equiv.) in 7 volumes (32.6 kg) of dichloromethane (CH_2Cl_2 or DCM) while keeping the temperature at ≤ 30 °C. Water (0.103 kg) was added to make $5.5 \pm 0.5\%$ total water content for the reaction system, and the mixture was stirred at ≤ 30 °C for at least 30 minutes. The reaction mixture was cooled to 0 ± 5 °C. Propylphosphonic anhydride solution (17.9 kg, 28.1 moles, 2.5 equiv.) was added to the mixture while maintaining the temperature below 20 °C. The mixture was agitated for at least an hour keeping the temperature at 20 ± 5 °C, then 2,2,2-trifluoroethylamine (1.68 kg, 16.86 moles, 1.5 equiv.) was added while maintaining the temperature below 20 °C. The reaction mixture was warmed to 25 ± 5 °C and agitated for 5 hours while holding the temperature. A 1.0 mL aliquot was removed and the reaction was determined to be 100% complete. Water (17.5 kg, 5 volumes) was added to the reaction mixture, and the resultant mixture was agitated for at least 30 minutes while maintaining the temperature below 30 °C.

[0413] The mixture was concentrated under vacuum with a rotary evaporator at a temperature ≤ 45 °C. Isopropylacetate (1.55 kg, 0.5 volumes) was added to the concentrated aqueous solution, and the pH of the solution was adjusted to 7.5-8.0 using 6N NaOH solution

at ≤ 35 °C. The mixture was cooled to 10 ± 5 °C and stirred at for at least one hour. If necessary, 6N HCl was added to readjust the pH of mixture to 7.5-8.0. The resultant slurry was filtered and washed with water (10.5 kg, 3 volumes). The filter cake was maintained under positive pressure of nitrogen for at least 30 minutes. The wet cake was dissolved in methanol (44.7 kg, 12 volumes) by agitation, and the solution was treated with PL-BnSH MP- Resin (BNSHMP) polymer resin (0.235 kg of 5 % wt of resin) at 25 ± 5 °C. After agitating at 25 ± 5 °C for at least 12 hours, the mixture was filtered. The solids were washed with methanol (2.77 kg, 1 volume). The filtrate was concentrated under vacuum in a rotary evaporator at a temperature ≤ 50 °C. The filtrate was not concentrated to dryness. The concentrated filtrate was allowed to sit at room temperature for about 2.5 days. The mixture was then stirred until homogeneous and heated to 40 °C, followed by slow addition of pre-heated water (56.1 kg at 45 °C) while maintaining a temperature of 45 ± 5 °C. After the mixture was spun for 1 hour, the remaining methanol was concentrated further, but not concentrated to dryness. The resultant mixture was cooled down to at least 5 ± 5 °C and agitated for at least 2 hours. The product was filtered, and the solids were washed with water (10.5 kg, 3 volumes). The filter cake was maintained under positive pressure of nitrogen for at least 30 minutes. The isolated product was dried to a constant weight under vacuum in a drying oven at a temperature of ≤ 70 °C with a nitrogen purge to yield 2-(2-(1H-pyrrolo[2,3-b]pyridin-3-yl)pyrimidin-4-ylamino)-2-methyl-N-(2,2,2-trifluoroethyl)butanamide (4.182 kg, white powder, 0.18% water content, 98.6% AUC using HPLC (method D)). Typical retention times are 4.4 minutes for (R)-2-(2-(1H-pyrrolo[2,3-b]pyridin-3-yl)pyrimidin-4-ylamino)-2-methylbutanoic acid and 6.2 minutes for 2-(2-(1H-pyrrolo[2,3-b]pyridin-3-yl)pyrimidin-4-ylamino)-2-methyl-N-(2,2,2-trifluoroethyl)butanamide.

[0414] Then general scheme, provided in Example 2 and the experimental description provided in Example 3 were used to generate the compounds in Table 1.

[0415] **Example 4: Synthesis of (R)-2-(2-(1H-pyrrolo[2,3-b]pyridin-3-yl)pyrimidin-4-ylamino)-2-methylbutanoic acid**

[0416] *Example 4a: 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-tosyl-1H-pyrrolo[2,3-b]pyridine*

[0417] *3-bromo-1H-pyrrolo[2,3-b]pyridine*

[0418] 7-azaindole (6.9 kg, 58.4 moles) was added to a 200 L glass-lined reactor containing 52.6 kg DMF. A solution of Br₂ in DMF (9.7 kg Br₂ in 14.7 kg DMF) was added drop wise to maintain the mixture temperature of about 0-10 °C. After the addition was complete, the temperature was maintained at about 0-10 °C. The completeness of the reaction was measured by HPLC (method A) with sample aliquots after 30 minutes. The reaction was

considered complete when the 7-azaindole was less than 3% (after about 2 hours and 40 minutes).

[0419] The reaction was quenched with 10% aqueous solution of NaHSO_3 (17.5 kg) while maintaining the temperature below 15 °C. A saturated aqueous solution of NaHCO_3 (61.6 kg) below 25 °C was added to adjust the pH to about 7 to 8. After neutralization, the mixture was transferred into a 50 L vacuum filter and filtered. The resultant cake was washed with water (18 kg) and then petroleum ether (12 kg). The cake was dried in a tray dryer at about 50-60 °C until the water content detected by KF (Karl Fisher reaction) was less than 0.8%. A yellow solid resulted (10.3 kg, 99.1% purity as measured by HPLC (method A), 89.6% yield of 3-bromo-1H-pyrrolo[2,3-b]pyridine).

[0420] *3-bromo-1-tosyl-1H-pyrrolo[2,3-b]pyridine*

[0421] 3-bromo-1H-pyrrolo[2,3-b]pyridine (10.7 kg, 54.3 moles) was added to 94.3 kg of THF in a 200 L glass-lined reactor. The solid was dissolved completely by stirring. After the mixture was cooled to about 10-15 °C, NaH (3.4 kg, 85 moles) was added in portions (about 200-250 g each portion) every 3 to 5 minutes while venting any H_2 gas released by the reaction. After the addition of NaH, the mixture was stirred for one hour while maintaining the temperature of about 10-20 °C. 4-methylbenzenesulfonylchloride (12.4 kg, 65.0 moles) was added at a rate of 0.5 kg/10 minutes at about 10-20 °C. After the addition was complete, the temperature was maintained at about 10-20 °C. The completeness of the reaction was measured by HPLC (method A) with sample aliquots after 30 minutes. The reaction was considered complete when the peak area of 3-bromo-1H-pyrrolo[2,3-b]pyridine was less than 1% (after about 1.5 hours).

[0422] The reaction was quenched with water (10.7 kg) while maintaining the temperature below 20 °C. Dichloromethane (41.3 kg) was added to the mixture. Then 3% HCl (42.8 kg) was added into the mixture while maintaining the temperature below 25 °C. After the addition, the phases were allowed to separate for 0.5 hour. The aqueous phase was extracted twice with dichloromethane. During each extraction, the mixture was stirred for 15 minutes and then held for 15 minutes. All the organic phases were combined. The combined organic phases were washed with 3% HCl (33.4 kg) and water (40 kg). During each wash, the mixture was stirred for 15 minutes and then held for 30 minutes.

[0423] The mixture was transferred into a 50 L vacuum filter and filtered through silica gel (3 kg). The cake was washed with dichloromethane (35 kg) twice. The filtrate and washings were combined. The organic phase was concentrated below 40 °C under vacuum of a pressure less than -0.085 MPa until 10 L mixture remained. Petroleum ether (9 kg) was added into the residue. The mixture was stirred until it was homogeneous. The slurry was

transferred into a 50 L vacuum filter and filtered. The cake was washed with petroleum ether (9 kg). A light brown solid resulted (17 kg, 99.7% purity as measured by HPLC analysis (method A), 94% yield of 3-bromo-1-tosyl-1H-pyrrolo[2,3-b]pyridine).

[0424] *1-tosyl-1H-pyrrolo[2,3-b]pyridin-3-ylboronic acid*

[0425] THF (28.5 kg) and 3-bromo-1-tosyl-1H-pyrrolo[2,3-b]pyridine (4 kg) were added to a 72 L flask. The mixture was stirred until the solid dissolved completely. Triisopropyl borate (3.2 kg) was added and the mixture was cooled to below -80 °C. n-BuLi (4.65 kg) was added drop wise at a rate of about 0.6-0.9 kg/hour maintaining the temperature of about -80 to -90 °C. After the addition, the temperature was maintained at -80 to -90 °C. The completeness of the reaction was measured by HPLC (method A) with sample aliquots after 30 minutes. The reaction was considered complete when the peak area of 3-bromo-1-tosyl-1H-pyrrolo[2,3-b]pyridine was less than 4%.

[0426] Water (2 kg) was slowly added to the mixture to quench the reaction. The mixture temperature returned to about 15-25 °C. The mixture was transferred to a 50 L reactor to be concentrated below 40 °C under vacuum of a pressure less than -0.08 MPa until no THF distilled out. The residue was dissolved into water (25 kg) and 10% aqueous NaOH solution (26 kg). The mixture was stirred until the solid dissolved completely. The mixture was transferred into a vacuum filter and filtered. The filtrate was extracted twice with MTBE (21 kg each) at about 20-30 °C. During each extraction, the mixture was stirred 15 minutes and held 15 minutes. HCl (28L) was added into the aqueous phase to adjust the pH to between 3 and 4 while maintaining the temperature of about 10-20 °C. The mixture was stirred at about 10-15 °C for 1 hour. The mixture was transferred into a centrifuge and filtered. The resultant cake after filtering was washed with water (5 kg) and petroleum ether (5 kg). The cake was dried at 35-45 °C until the LOD (loss on drying) was less than 3%. An off-white solid resulted (2.5 kg and 98.8% purity as measured by HPLC analysis (method A), 69.4% yield of 1-tosyl-1H-pyrrolo[2,3-b]pyridin-3-ylboronic acid).

[0427] *3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-tosyl-1H-pyrrolo[2,3-b]pyridine*

[0428] Dichloromethane (165.6 kg) and pinacolate alcohol (3.54 kg) were added to a 200 L glass-lined reactor. The mixture was stirred until the solid dissolved completely. Then, 1-tosyl-1H-pyrrolo[2,3-b]pyridin-3-ylboronic acid (8.65 kg) was added in portions (2 kg every 5 minutes) while maintaining the temperature of about 20-30 °C. After the addition, the temperature was maintained at about 20-30 °C while stirring. The completeness of the reaction was measured by HPLC (method B) with sample aliquots every 60 minutes. The reaction was considered complete when the peak area of 1-tosyl-1H-pyrrolo[2,3-b]pyridin-3-ylboronic acid as less than 1%.

[0429] The mixture was filtered through silica gel (3 kg). The cake was rinsed twice with dichloromethane (15 kg each rinse). The filtrate was combined with the washing liquids, and then concentrated below 30 °C under vacuum at a pressure less than -0.08 MPa until no fraction distilled out. Solvent was continued to be removed by vacuum for 2 hours. Isopropanol (17.2 kg) was added to the residue. The mixture was heated to reflux at about 80-85 °C. The mixture refluxed for 30 minutes until the solid dissolved completely. The mixture was cooled below 35 °C, and then to about 0-10 °C. The mixture crystallized at 0-10 °C for 2 hours and was then filtered. After filtration, the resultant cake was dried at about 35-45 °C until the water content detected by KF (Karl Fisher reaction) was less than 0.5% and the LOD (loss on drying) was less than 0.5%. An off-white solid resulted (8.8 kg and 99.7% purity as measured by HPLC analysis (method B) of 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-tosyl-1H-pyrrolo[2,3-b]pyridine).

[0430] *Example 4b: (R)-2-methyl-2-(2-(1-tosyl-1H-pyrrolo[2,3-b]pyridin-3-yl)pyrimidin-4-ylamino)butanoic acid*

[0431] Tripotassium phosphate (K_3PO_4) (7.20 kg, 3 equiv.) was mixed with three volumes of water (9.0 kg). The mixture was agitated for at least 20 minutes, cooled to a temperature of ≤ 30 °C and added to acetonitrile (16.8 g, 7 volumes) into a 120 L reactor. The resultant mixture was agitated. 3.0 kg (11.3 moles, 1.0 equiv.) of (R)-2-(2-chloropyrimidin-4-ylamino)-2-methylbutanoic acid hydrochloride were added to the reaction mixture in the reactor while maintaining a temperature ≤ 30 °C. The mixture was agitated for at least 20 minutes. 5.16 kg (13.0 moles, 1.15 equiv.) of 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-tosyl-1H-pyrrolo[2,3-b]pyridine were then added to the reactor. The reaction mixture was agitated and de-gassed with N_2 sparging for at least 30 minutes. The mixture was heated to 65 ± 5 °C.

[0432] In a separate vessel, 0.075 kg (0.03 equiv.) of palladium(II) acetate was mixed with 4.80 kg (2 volumes) of de-gassed acetonitrile (CH_3CN). This mixture was agitated until homogenous. 0.267 kg (1.02 moles, 0.09 equiv.) of triphenylphosphine (PPh_3) was added and the resultant mixture was agitated for at least 30 minutes at 20 ± 5 °C. The palladium(II) acetate/ PPh_3 / CH_3CN mixture was then added to the reactor above while maintaining the nitrogen purge. The reactor contents were heated to 75 ± 5 °C for at least 17 hours under nitrogen purge. After 5 hours the conversion was shown to be about 86% complete as measured by HPLC analysis (method C) of a 1.0 mL aliquot. Additional catalyst and 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-tosyl-1H-pyrrolo[2,3-b]pyridine (900 g, 2.26 moles, 0.2 equiv.) were then added to the reaction mixture and the mixture was stirred. After an additional 12 hours, the reaction was shown to be 99.7% complete as measured by

HPLC analysis (method C) of a 1.0 mL aliquot. The additional catalyst added above was prepared by dissolving 37.5 g palladium(II) acetate in 1 volume of acetonitrile (which was de-gassed for 20 minutes), and then adding 133.5 g of triphenylphosphine.

[0433] *Example 4c: (R)-2-methyl-2-((1-tosyl-1H-pyrrolo[2,3-b]pyridin-3-yl)pyrimidin-4-ylamino)butanoic acid*

[0434] To (R)-2-(2-chloropyrimidin-4-ylamino)-2-methylbutanoic acid hydrochloride (limiting reagent) and 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-tosyl-1H-pyrrolo[2,3-b]pyridine (1.15 eq) add 2-propanol (0.6 vol) and begin degassing with nitrogen. Add 6N aqueous NaOH (3.2 eq.) and continue degassing. Charge PdCl₂(Amphos)₂ (0.0014 eq) as a slurry in 2-propanol (0.06 vol). Continue the degassing for at least 30 minutes then warm the mixture to a temperature of between 70-75 °C to generate (R)-2-methyl-2-((2-(1-tosyl-1H-pyrrolo[2,3-b]pyridin-3-yl)pyrimidin-4-yl)amino)butanoic acid. The reaction is deemed complete when HPLC analysis shows <1.0% of (R)-2-(2-chloropyrimidin-4-ylamino)-2-methylbutanoic acid hydrochloride remaining.

[0435] *Example 4d: (R)-2-((2-(1H-pyrrolo[2,3-b]pyridin-3-yl)pyrimidin-4-ylamino)-2-methylbutanoic acid*

[0436] A solution of 4N aqueous KOH, which was previously prepared with 6.0 kg of KOH in 27.0 kg of water at a rate to control the temperature rise, was added to the reactor above and the reaction was heated to 75 ± 5 °C for at least 5 hours while agitating the mixture. An aliquot of about 1.0 mL was removed from the reaction mixture and analyzed by HPLC (method C) to show 98.6% (R)-2-((2-(1H-pyrrolo[2,3-b]pyridin-3-yl)pyrimidin-4-yl)amino)-2-methylbutanoic acid and 1.4% (R)-2-methyl-2-((2-(1-tosyl-1H-pyrrolo[2,3-b]pyridin-3-yl)pyrimidin-4-yl)amino)butanoic acid.

[0437] 15.0 kg (5 volumes) of water was added to the reactor. The reaction mixture was cooled to 35 ± 5 °C. Isopropyl acetate (7.8 g, 3 volumes) was added, and the reaction mixture was agitated for at least 5 minutes. The reaction mixture was filtered through a 4-cm pad of celite in an 18-inch Nutsche filter. The reactor was rinsed with 9.0 kg of water and the water was then used to rinse the celite pad. The aqueous and organic phases were separated. 0.9 kg of Darco G-60 activated carbon (30% w/w) was added to the aqueous phase in a 120-liter reactor. The pH of the mixture was adjusted to less than 1.0 with concentrated HCl solution at 25 ± 10 °C and held for at least 4 hours. If necessary, the pH was readjusted with 6N NaOH. The mixture was then filtered through a Nutsche filter, which was equipped with a filter cloth, and the solids were rinsed with 6.0 kg (2 volumes) of 1N HCl. The filter cake was maintained under positive pressure of nitrogen for at least 30 minutes. The HCl filtrate was agitated and heated to 25 ± 5 °C. 0.9 kg of Darco G-60 activated carbon was added to

the HCl filtrate and the mixture was stirred for at least 4 hours. The mixture was then filtered through a Nutsch filter, which was equipped with a filter cloth, and the solids were washed with 6.0 kg (2 volumes) of 1N HCl. The second filter cake was maintained under positive pressure of nitrogen for at least 30 minutes.

[0438] The HCl filtrate was again agitated and heated, charcoal was added and filtering step was repeated with a Nutsch filter, which was equipped with a 0.45 μm in-line filter between the Nutsche filter and the receiver flask, to yield a third filter cake and a final filtrate. The solids were washed with 6.0 kg of 1N HCl. The third filter cake was maintained under positive pressure of nitrogen for at least 30 minutes.

[0439] The pH of the final filtrate was adjusted to between 4.5 and 5.0 using 6N NaOH while the temperature was maintained between 25 ± 5 °C. If necessary, the pH was readjusted using 1N HCl. The final filtrate was then cooled to 5 ± 5 °C and agitated for at least 2 hours. The mixture was filtered with a Nutsch filter, which was equipped with a filter cloth. The solids were rinsed with 6.0 kg (2 volumes) of water. The final filter cake was maintained under positive pressure of nitrogen for at least 30 minutes.

[0440] The wet solids (i.e., filter cakes) were dried in a drying oven at ≤ 60 °C under vacuum, with a nitrogen purge, over 5 days to yield 3.561 kg of (R)-2-(2-(1H-pyrrolo[2,3-b]pyridin-3-yl)pyrimidin-4-ylamino)-2-methylbutanoic acid.

[0441] *Example 4e: (R)-2-(2-(1H-pyrrolo[2,3-b]pyridin-3-yl)pyrimidin-4-ylamino)-2-methylbutanoic acid*

[0442] To the reaction mixture in Example 4b, charge a solution of KOH (8.8 eq) in water (7.3 vol) and agitate the batch at a temperature of from 70-75 °C until HPLC analysis shows conversion from the intermediate to (R)-2-(2-(1H-pyrrolo[2,3-b]pyridin-3-yl)pyrimidin-4-ylamino)-2-methylbutanoic acid reaches > 99%. Cool the batch to 20-25 °C then charge Darco G-60 activated carbon (30wt% based on (R)-2-((2-chloropyrimidin-4-yl)amino)-2-methylbutanoic acid) and agitate the batch for 12-24 hrs at 20-25 °C. Filter the slurry, rinsing the solids with water (2×1 vol). Cool the batch to 15-20 °C then adjust the pH of the batch to < 5 with conc. HCl while maintaining a batch temperature no more than 20-25 °C. Perform fine adjustment of pH back to 5.5 – 6 (target pH 6) via 6M NaOH. Adjust the batch temperature to 20-25 °C then seed with (R)-2-((2-chloropyrimidin-4-yl)amino)-2-methylbutanoic acid (0.4wt% dry seed). Stir the slurry for no less than 2 hrs. Charge water (12 vol) over 8 hrs then stir the slurry for no less than 4 hrs. Filter the batch and rinse the cake with water (2×2 vol) then n-heptane (2 vol). Dry the solids at 80 °C to give (R)-2-(2-(1H-pyrrolo[2,3-b]pyridin-3-yl)pyrimidin-4-ylamino)-2-methylbutanoic acid.

[0443] Example 4f: (R)-2-(2-(1H-pyrrolo[2,3-b]pyridin-3-yl)pyrimidin-4-ylamino)-2-methylbutanoic acid

[0444] To the reaction mixture in Example 4b, charge a solution of KOH (8.8 eq) in water (7.3 vol) and agitate the batch at a temperature of from 70-75 °C until HPLC analysis shows conversion from the intermediate to (R)-2-(2-(1H-pyrrolo[2,3-b]pyridin-3-yl)pyrimidin-4-ylamino)-2-methylbutanoic acid reaches > 99%. Cool the batch to 15-25 °C and adjust the pH to < 5 with conc. HCl. Perform a fine adjustment of the pH to 5.5 – 6 using 6M NaOH. Adjust the batch temperature to 20-25 °C, and seed the seed with (R)-2-((2-chloropyrimidin-4-yl)amino)-2-methylbutanoic acid (0.4wt% dry seed). Stir the slurry for not less than 2 hrs. Charge water (12 vol) over 8 hrs then stir the slurry for not less than 4 hrs. Filter the batch and rinse the cake with water (2 × 2 vol) then n-heptane (2 vol). Dry the solids at 80 °C to give (R)-2-(2-(1H-pyrrolo[2,3-b]pyridin-3-yl)pyrimidin-4-ylamino)-2-methylbutanoic acid.

[0445] Example 4g: Preparation of (R)-2-(2-(1H-pyrrolo[2,3-b]pyridin-3-yl)pyrimidin-4-ylamino)-2-methyl-N-(2,2,2-trifluoroethyl)butanamide

[0446] Diisopropylethylamine (DIEA) (3.61 kg, 28.1 moles, 2.5 equiv.) was added to (R)-2-(2-(1H-pyrrolo[2,3-b]pyridin-3-yl)pyrimidin-4-ylamino)-2-methylbutanoic acid (3.5 kg, 11.24 moles, 1.0 equiv.) in 7 volumes (32.6 kg) of dichloromethane (CH₂Cl₂ or DCM) while keeping the temperature at ≤ 30 °C. Water (0.103 kg) was added to make 5.5 ± 0.5% total water content for the reaction system, and the mixture was stirred at ≤ 30 °C for at least 30 minutes. The reaction mixture was cooled to 0 ± 5 °C. Propylphosphonic anhydride solution (17.9 kg, 28.1 moles, 2.5 equiv.) was added to the mixture while maintaining the temperature below 20 °C. The mixture was agitated for at least an hour keeping the temperature at 20 ± 5 °C, then 2,2,2-trifluoroethylamine (1.68 kg, 16.86 moles, 1.5 equiv.) was added while maintaining the temperature below 20 °C. The reaction mixture was warmed to 25 ± 5 °C and agitated for 5 hours while holding the temperature. A 1.0 mL aliquot was removed and the reaction was determined to be 100% complete. Water (17.5 kg, 5 volumes) was added to the reaction mixture, and the resultant mixture was agitated for at least 30 minutes while maintaining the temperature below 30 °C.

[0447] The mixture was concentrated under vacuum with a rotary evaporator at a temperature ≤ 45 °C. Isopropylacetate (1.55 kg, 0.5 volumes) was added to the concentrated aqueous solution, and the pH of the solution was adjusted to 7.5-8.0 using 6N NaOH solution at ≤ 35 °C. The mixture was cooled to 10 ± 5 °C and stirred for at least one hour. If necessary, 6N HCl was added to readjust the pH of mixture to 7.5-8.0. The resultant slurry was filtered and washed with water (10.5 kg, 3 volumes). The filter cake was maintained under positive pressure of nitrogen for at least 30 minutes. The wet cake was dissolved in

methanol (44.7 kg, 12 volumes) by agitation, and the solution was treated with PL-BnSH MP- Resin (BNSHMP) polymer resin (0.235 kg of 5% wt of resin) at 25 ± 5 °C. After agitating at 25 ± 5 °C for at least 12 hours, the mixture was filtered. The solids were washed with methanol (2.77 kg, 1 volume). The filtrate was concentrated under vacuum in a rotary evaporator at a temperature ≤ 50 °C. The filtrate was not concentrated to dryness. The concentrated filtrate was allowed to sit at room temperature for about 2.5 days. The mixture was then stirred until homogeneous and heated to 40 °C, followed by slow addition of pre-heated water (56.1 kg at 45 °C) while maintaining a temperature of 45 ± 5 °C. After the mixture was spun for 1 hour, the remaining methanol was concentrated further, but not concentrated to dryness. The resultant mixture was cooled down to at least 5 ± 5 °C and agitated for at least 2 hours. The product was filtered, and the solids were washed with water (10.5 kg, 3 volumes). The filter cake was maintained under positive pressure of nitrogen for at least 30 minutes. The isolated product was dried to a constant weight under vacuum in a drying oven at a temperature of ≤ 70 °C with a nitrogen purge to yield (R)-2-(2-(1H-pyrrolo[2,3-b]pyridin-3-yl)pyrimidin-4-ylamino)-2-methyl-N-(2,2,2-trifluoroethyl)butanamide (4.182 kg, white powder, 0.18% water content, 98.6% AUC using HPLC (method D)).

[0448] Example 4h: Preparation of (R)-2-(2-(1H-pyrrolo[2,3-b]pyridin-3-yl)pyrimidin-4-ylamino)-2-methyl-N-(2,2,2-trifluoroethyl)butanamide

[0449] To (R)-2-(2-(1H-pyrrolo[2,3-b]pyridin-3-yl)pyrimidin-4-ylamino)-2-methylbutanoic acid (limiting reagent) charge 2-methylTHF (7.5 vol), then charge $T_3P^{\circledR}$ (2.0 eq, 50% w/w in 2-MeTHF). Heat the mixture to 60-65 °C and maintain this temperature for no less than 3 hrs and the solids are completely dissolved. Cool to 20-25 °C then charge 2,2,2-trifluoroethylamine (2.0 eq). Continue agitation for no less than 6 hrs at 20-25 °C and until HPLC analysis showed $< 1.0\%$ of (R)-2-(2-(1H-pyrrolo[2,3-b]pyridin-3-yl)pyrimidin-4-ylamino)-2-methylbutanoic acid. Slowly charge a Na_2CO_3 solution (15 vol, 1.165M) while maintaining a batch temperature < 30 °C. Stir the mixture for 30 min then separate the phases. Wash the organic phase with water (4 vol). Emulsions have been observed at this point and can be addressed through addition of NaCl solution. Charge methanol (7 vol) then distill to 4 vol. Repeat 3 times. Prior to crystallization, adjust the total volume to approximately 11 vol. Heat the mixture to 50-55 °C then add water (2.45vol, final solvent composition 22% water in methanol) over 30 min. Seed the batch with (R)-2-(2-(1H-pyrrolo[2,3-b]pyridin-3-yl)pyrimidin-4-ylamino)-2-methyl-N-(2,2,2-trifluoroethyl)butanamide (1wt% seed based on (R)-2-((2-(1H-pyrrolo[2,3-b]pyridin-3-yl)pyrimidin-4-yl)amino)-2-methylbutanoic acid). Stir for 4 hrs at 50-55 °C then add water

over 24 h until the mixture is approximately 58wt% water in methanol. Cool to 20-25 °C, stir 1 h, then filter. Wash the cake with water (2 vol). Dry the solids at 60-65 °C to give (R)-2-(2-(1H-pyrrolo[2,3-b]pyridin-3-yl)pyrimidin-4-ylamino)-2-methyl-N-(2,2,2-trifluoroethyl)butanamide.

[0450] Example 4i: Preparation of (R)-2-(2-chloropyrimidin-4-ylamino)-2-methylbutanoic acid hydrochloride

[0451] To a solution of K₂CO₃ (2 eq.) in water (3 vol) was added D-isovaline•HCl (1.0 eq.). The resulting solution was stirred for 20 min. then 2,4-dichloropyrimidine (1.1 eq.) and IPA (7 vol) were added to the reaction mixture consecutively. The resulting mixture was heated to reflux (~82 °C). After checking completion of the reaction by HPLC analysis (NMT 3.0% (AUC) of 2,4-dichloropyrimidine, ca. 5-6 h), the solution was concentrated to 4 vol. Water (4 vol) and IPAC (4 vol) were added and the mixture was stirred and acidified to pH = 1.2 - 1.4 using 6N HCl aqueous solution. After stirring no less than 20 min, the layers were separated. IPAC (6 vol) was added to the aqueous layer and the pH of the mixture was adjusted to 3.0 - 3.5 with 50% aqueous NaOH. After stirring no less than 20 min., the layers were separated. The aqueous layer was extracted with IPAC (3 vol). The combined IPAC layers were dried (Na₂SO₄) and filtered. IPA (1 vol) was added to the filtrate. 5-6N HCl / IPA (0.85 eq.) was added dropwise. The mixture was seeded with (R)-2-(2-chloropyrimidin-4-ylamino)-2-methylbutanoic acid hydrochloride (0.01 wt. eq.) to crystallize the product with vigorous stirring. After stirring no less than 4 h, the product was collected by filtration, washed (4:1 IPAC/IPA, 2 × 1.2 vol), and dried in a vacuum oven at 50 °C with a N₂ bleed to constant weight to afford (R)-2-(2-chloropyrimidin-4-ylamino)-2-methylbutanoic acid hydrochloride as an off-white solid.

[0452] Example 4j: Preparation of (R)-2-(2-(1H-pyrrolo[2,3-b]pyridin-3-yl)pyrimidin-4-ylamino)-2-methylbutanoic acid

[0453] (R)-2-(2-chloropyrimidin-4-ylamino)-2-methylbutanoic acid (10.00g, 37.58 mmol) and 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-tosyl-1H-pyrrolo[2,3-b]pyridine (17.21g, 43.22 mmol) were charged into a 250 mL reactor and purged with nitrogen gas. Under nitrogen gas degassing and stirring, 52.00 mL of IPA was charged into the reactor followed by 6M NaOH (20.05 mL). After degassing the stirring mixture for 15 min, 4-ditert-butylphosphanyl-N,N-dimethyl-aniline palladium(II)dichloride (37.25 mg, 0.05261 mmol) was charged into the reactor as a slurry with 2.00 mL of IPA. The resulting mixture was further degassed for another 20 min. Under positive nitrogen pressure, the reaction mixture was heated to 74 °C until the HPLC samples confirmed that the reaction was complete. Once the reaction was complete, 6M NaOH (6.263 mL) was charged into the

reactor as a solution in water (74.00 mL) and the reaction was maintained at 74 °C until HPLC showed complete de-tosylation of the product.

[0454] The reaction mixture was cooled to 25 °C and adjusted to have a pH of 0.4-0.6 using 11M HCl (3.146 mL). Activated charcoal (0.3 g, 30 wt%) was charged into the reactor, and the resulting mixture was stirred for > 12 Hr. The reaction mixture was filtered to remove the charcoal, and water (50 mL) was added to the filtrate after returning it to the cleaned reactor. The pH of the reaction mixture was adjusted to 5.5-6.0 using 6M NaOH (6.263 mL). The reaction mixture was heated to 64 °C under stirring. The reaction mixture was maintained under stirring at 64 °C for a period of 60 min. after the formation of a solution. The reactor was cooled at a rate of 20 °C/hr until reaching a temperature of 25 °C. The reaction mixture was continuously stirred at 25 °C for at least 4 hr. The batch was then filtered and washed with water (10 mL) followed by heptane (20 mL). The solids were collected and dried under vacuum at 60 °C.

[0455] Example 5: JAK3 Inhibition Assay

[0456] Compounds were screened for their ability to inhibit JAK3 using the assay shown below. Reactions were carried out in a kinase buffer containing 100 mM HEPES (pH 7.4), 1 mM DTT, 10 mM MgCl₂, 25 mM NaCl, and 0.01% BSA. Substrate concentrations in the assay were 5 µM ATP (200 uCi/µmole ATP) and 1 µM poly(Glu)₄Tyr. Reactions were carried out at 25°C and 1 nM JAK3.

[0457] To each well of a 96 well polycarbonate plate was added 1.5 µl of a compound of Formula I along with 50 µl of kinase buffer containing 2 µM poly(Glu)₄Tyr and 10 µM ATP. This was then mixed and 50 µl of kinase buffer containing 2 nM JAK3 enzyme was added to start the reaction. After 15 minutes at room temperature (25°C), the reaction was stopped with 50 µl of 20% trichloroacetic acid (TCA) that also contained 0.4 mM ATP. The entire contents of each well were then transferred to a 96 well glass fiber filter plate using a TomTek Cell Harvester. After washing, 60 µl of scintillation fluid was added and ³³P incorporation detected on a Perkin Elmer TopCount.

[0458] Example 6: JAK2 Inhibition Assay

[0459] The assays were as described above in Example 4 except that JAK-2 enzyme, at a concentration of 5 nM, was used, the final poly(Glu)₄Tyr concentration was 15 µM, and final ATP concentration was 12 µM.

[0460] The data generated from these assays is provided in Table 2, below:

Table 2: Inhibition data for selected compounds of Formula I.

Compound No.	JAK2 (μ M)	JAK3 (μ M)
1	0.015	0.003
2	0.028	0.0032
3	0.028	0.0042
4	0.091	0.0056
5	0.0042	0.0024
6	0.046	0.0045
7	0.056	0.018
8	0.083	0.019
9	0.001	0.001
10	0.001	0.002
11	0.055	0.006
12	0.037	0.006
13	0.003	0.001
14	0.002	0.003
15	0.001	0.002
16	0.01	0.002
17	0.003	0.001
18	0.0007	0.001
19	0.001	0.004

[0461] Example 7: JAK3 Cellular Inhibition Assay

[0462] HT-2 clone A5E cells (ATCC Cat. # CRL-1841) were grown and maintained at 37 °C in a humidified incubator in cell culture medium (RPMI 1640 supplemented with 2 mM L-glutamine adjusted to contain 1.5 g/L sodium bicarbonate, 4.5 g/L glucose, 10 mM HEPES, 1.0 mM sodium pyruvate, 0.05 mM 2-mercaptoethanol, 10% fetal bovine serum, and 10% by volume rat T-STIM factor [Fisher Scientific Cat # CB40115] with Con A). On the day of the experiment, HT-2 cells were washed, resuspended at a density of 5×10^6 cells per ml in fresh cell culture medium without T-STIM and incubated for 4 hours without T-STIM. After four hours, 50 μ l (0.25×10^6 cells) of the resuspended cells were added to each well of a 96 well plate. Serial dilutions of compounds were made in DMSO and then added to RPMI. 100 μ l of the diluted compounds were added to each well and the plates were

incubated for 1 hour at 37 °C. 50 µl of recombinant murine interleukin-2 (rmIL-2) at 40 ng/ml (R & D systems Inc. Cat # 402-ML) was added and the plates were incubated for 15 minutes at 37 °C.

[0463] The plates were then centrifuged for 5 minutes at 1000 rpm, the supernatant was aspirated and 50 µl of 3.7% formaldehyde in phosphate buffered saline (PBS) was added per well. The plates were incubated for 5 minutes at room temperature on a plate shaker. The plates were again centrifuged at 1000 rpm for 5 minutes. The supernatant was aspirated, 50 µl of 90% methanol was added to each well, and the plate was incubated on ice for 30 minutes. The supernatant was aspirated and the plate washed with PBS. 25 µl per well of 1:10 diluted Phospho STAT-5 (Y694) PE conjugated antibody (PS-5 PE antibody; Becton-Dickinson Cat. # 61256) was added to the plates and the plates were incubated for 45 minutes at room temperature on a plate shaker. 100 µl PBS was added and the plates were centrifuged. The supernatant was aspirated and the cells resuspended in 100 µl PBS. The plate was then read on a 96 well FACS reader (Guava PCA-96).

[0464] Compounds of the invention were found to inhibit JAK3 in this cellular assay.

[0465] Example 8: JAK2 Cellular Inhibition Assay

[0466] TF-1 cells (ATCC Cat. # CRL-2003) were grown and maintained at 37 °C in a humidified incubator in cell culture medium (RPMI 1640 supplemented with 2 mM L-glutamine adjusted to contain 1.5 g/L sodium bicarbonate, 4.5 g/L glucose, 10 mM HEPES, 1.0 mM sodium pyruvate, 10% fetal bovine serum and recombinant human granulocyte-macrophage colony stimulating factor [rhGMCSF, R&D Systems Inc. Cat. # 215-GM]). On the day of the experiment, TF-1 cells were washed, resuspended at a density of 5×10^6 cells per ml in fresh cell culture medium without rhGMCSF and incubated for 4 hours without rhGMCSF. After four hours, 50 µl (0.25×10^6 cells) of the resuspended cells were added to each well of a 96 well plate. Serial dilutions of compounds were made in DMSO and then added to RPMI. 100 µl of the diluted compounds were added to each well and the plates were incubated for 1 hour at 37 °C. 50 µl of rhGMCSF at 10 ng/ml was added and the plates were incubated for 15 minutes at 37 °C. The plates were then processed for FACS analysis as detailed above in Example 6.

[0467] Compounds of the invention were found to inhibit JAK2 in this cellular assay.

[0468] Example 9: Manufacture of Tablets

[0469] A formulation is provided in Table 3 for Exemplary Tablet 1 comprising 50 mg of API, i.e., a compound of Formula I.

Table 3: Exemplary Tablet 1

Ingredient	Amt. Per Tablet (mg)	wt%
Compound of Formula I	50.00	20
Binder (Avicel PH 102)	92.8125	37.125
Diluent (Lactose Monohydrate, NF (Fast-Flo 316))	92.8125	37.125
Disintegrant (AcDiSol)	7.5	3
Glidant (CaBoSil)	2.5	1
Wetting Agent (Sodium Lauryl Sulfate, NF)	2.5	1
Lubricant (Magnesium Stearate)	1.875	0.75
Total	250	100

[0470] A formulation is provided in Table 4 for Exemplary Tablet 2 comprising 25 mg of API, i.e., a compound of Formula I.

Table 4: Exemplary Tablet 2.

Ingredient	Amt. Per Tablet (mg)	wt %
Compound of Formula I	25.00	10
Binder (Avicel PH 102)	105.31	42.125
Diluent (Lactose Monohydrate, NF (Fast-Flo 316))	105.31	42.125
Disintegrant (AcDiSol)	7.5	3
Glidant (CaBoSil)	2.5	1
Wetting Agent (Sodium Lauryl Sulfate, NF)	2.5	1
Lubricant (Magnesium Stearate)	1.875	0.75
Total	250	100

[0471] Example 10: Exemplary Tablet 1 (Formulated to have 50 mg of a Compound of Formula I)

[0472] A batch of 250 mg total weight tablets can be formulated to have approximately 50 mg of compound of Formula I per tablet using the amounts of ingredients recited in Table 3, above.

[0473] Sieve the compound of Formula I, microcrystalline cellulose (FMC MCC Avicel® PH102, commercially available from FMC BioPolymer Corporation of Philadelphia, PA), lactose (Foremost FastFlo® Lactose #316 commercially available from Foremost Farms USA of Baraboo, WI), sodium croscarmellose (FMC Ac-Di-Sol®, commercially available from FMC BioPolymer Corporation of Philadelphia, PA), sodium lauryl sulfate (commercially available from Stepan Company of Northfield, IL), and colloidal silicon dioxide (Cabot Cab-O-Sil® M-5P Fumed Silicon Dioxide, commercially available from Cabot Corporation of Alpharetta, GA) through a 20 mesh screen to remove lumps.

[0474] Add these sieved ingredients to a 16 quart V-blender and blend for about 20 minutes in a V-blender at 10-12 rpm.

[0475] Sieve magnesium stearate (commercially available from Mallinckrodt, Inc.) through a 20 mesh screen to remove lumps, and add to the blended mixture. Blend the second mixture containing the newly added magnesium stearate for another 4 minutes at a speed of about 10 to 24 rpm.

[0476] Once the final blend has been completed, transfer the mixture to a tablet press (e.g., a Piccola B-Tooling, 10 Station rotary tablet press (half tooled)) for compression into 250 mg tablets having approximately 50 mg of a compound of Formula I.

[0477] Example 11: Exemplary Tablet 2 (Formulated to have 25 mg of a Compound of Formula I)

[0478] A batch of 250 mg total weight tablets can be formulated to have approximately 25 mg of a compound of Formula I per tablet using the amounts of ingredients recited in Table B, above.

[0479] Sieve the compound of Formula I, microcrystalline cellulose (FMC MCC Avicel® PH102, commercially available from FMC BioPolymer Corporation of Philadelphia, PA), lactose (Foremost FastFlo® Lactose #316 commercially available from Foremost Farms USA of Baraboo, WI), sodium croscarmellose (FMC Ac-Di-Sol®, commercially available from FMC BioPolymer Corporation of Philadelphia, PA), sodium lauryl sulfate (commercially available from Stepan Company of Northfield, IL.), and colloidal silicon dioxide (Cabot Cab-O-Sil® M-5P Fumed Silicon Dioxide, commercially available from Cabot Corporation of Alpharetta, GA) through a 20 mesh screen to remove lumps.

[0480] Add these sieved ingredients to a 16 quart V-blender and blend for about 20 minutes in a V-blender at 10-12 rpm.

[0481] Sieve magnesium stearate (commercially available from Mallinckrodt, Inc.) through a 20 mesh screen to remove lumps, and add to the blended mixture. Blend the second mixture containing the newly added magnesium stearate for another 4 minutes at a speed of about 10 to 24 rpm.

[0482] Once the final blend has been completed, transfer the mixture to a tablet press (e.g., a Piccola B-Tooling, 10 Station rotary tablet press (half tooled)) for compression into 250 mg tablets having approximately 25 mg of the compound of Formula I.

[0483] Example 12: Exemplary Capsule (Formulated to have 25 mg of the compound of Formula I)

[0484] Add 25 mg of a compound of Formula I to one half of a 2-piece gelatin capsule, and cap the filled half of the gelatin capsule with the second half of the 2-piece capsule.

[0485] Example 13: Exemplary Capsule (Formulated to have 50 mg of a Compound of Formula I)

[0486] Add 50 mg of a compound of Formula I to one half of a 2-piece gelatin capsule, and cap the filled half of the gelatin capsule with the second half of the 2 piece capsule.

[0487] Example 14: Exemplary Capsule (Formulated to have 75 mg of a compound of Formula I)

[0488] Add 75 mg of the compound of Formula I to one half of a 2-piece gelatin capsule, and cap the filled half of the gelatin capsule with the second half of the 2 piece capsule.

[0489] Example 15: Administration of Pharmaceutical Formulations

[0490] *Example 15A: Exemplary Administration A*

[0491] Human patients are orally administered a pharmaceutical formulation comprising a compound of Formula I according to Table 5:

Table 5: Exemplary administration of pharmaceutical formulations of the present invention.

Frequency of dosing	Dosage of API
q.d.	25 mg (e.g., Tablet 2)
q.d.	50 mg (e.g., Tablet 1 or 2 × Tablet 2)
q.d.	100 mg (e.g., 2 × Tablet 1 or 4 × Tablet 2)
q.d.	150 mg (e.g., 3 × Tablet 1 or 6 × Tablet 2)
q.d.	200 mg (e.g., 4 × Tablet 1 or 8 × Tablet 2)
q.d.	250 mg (e.g., 5 × Tablet 1)
q.d.	300 mg (e.g., 6 × Tablet 1)

[0492] The pharmaceutical formulations may be administered to subjects anytime during the day, and in some administrations, the pharmaceutical formulation is given at approximately the same time (within a 1-hour window) on each dosing occasion.

[0493] Furthermore, the tablets (e.g., Tablet 1 and/or Tablet 2) may be administered with or without a fluid (e.g., water or other beverage). Also, human patients being administered the tablet(s) may fast for a period of time prior to or after the administration.

[0494] In several instances, the administration of the tablet(s) may last for a period of about 12 weeks.

[0495] *Example 15B: Exemplary Administration B*

[0496] Human patients are orally administered a pharmaceutical formulation comprising a compound of Formula I according to Table 6:

Table 6: Exemplary administration of pharmaceutical formulations of the present invention.

Frequency of dosing	Dosage of Compound of Formula I
12 hr. intervals	25 mg (e.g., Tablet 2)
12 hr. intervals	50 mg (e.g., Tablet 1 or 2 × Tablet 2)
12 hr. intervals	100 mg (e.g., 2 × Tablet 1 or 4 × Tablet 2)
12 hr. intervals	150 mg (e.g., 3 × Tablet 1 or 6 × Tablet 2)

[0497] The pharmaceutical formulations may be administered to subjects in the morning, e.g., between 5:00 AM and 12:00 PM, and evening, e.g., between 5:00 PM and 12:00 AM, and in some administrations, the pharmaceutical formulation is given at approximately the same time (within a 1-hour window) on each dosing occasion.

[0498] Furthermore, the tablet(s) (e.g., Tablet 1 and/or Tablet 2) may be administered with or without a fluid (e.g., water or other beverage). Also, human patients being administered the tablet may fast for a period of time prior to or after the administration.

[0499] In several instances, the administration of the tablet(s) lasts for a period of about 12 weeks.

[0500] *Example 15C: Exemplary Administration C*

[0501] Human patients are orally administered a pharmaceutical formulation comprising a compound of Formula I and an oral formulation of a corticosteroid according to Table 7:

Table 7: Exemplary administration of pharmaceutical formulations of the present invention.

Dosing	Therapy
Day 1 Qd	10 mg prednisone or 8 mg methylprednisone
Days 2-7 qd	200 mg of compound of Formula I (e.g., 4 × Tablet 1 or 8 × Tablet 2)
Day 7 qd	10 mg prednisone or 8 mg methylprednisone

[0502] The pharmaceutical formulations may be administered to subjects in the morning, e.g., between 5:00 AM and 12:00 PM, and evening, e.g., between 5:00 PM and 12:00 AM, and in some administrations, the pharmaceutical formulation is given at approximately the same time (within a 1-hour window) on each dosing occasion.

[0503] Furthermore, the tablet(s) (e.g., Tablet 1 and/or Tablet 2) may be administered with or without a fluid (e.g., water or other beverage). Also, human patients being administered the tablet may fast for a period of time prior to or after the administration.

[0504] In several instances, the administration of the tablet(s) lasts for a period of about 12 weeks.

[0505] Example 16: Administration of Pharmaceutical Formulations

[0506] Example 16A: Exemplary Administration A

[0507] Human patients are orally administered a pharmaceutical formulation comprising a compound of Formula I according to Table 8:

Table 8: Exemplary administration of pharmaceutical formulations of the present invention.

Frequency of dosing (per day)	Dosage of API
b.i.d.	25 mg (e.g., Tablet 2)
q.d.	50 mg (e.g., Tablet 1 or 2 × Tablet 2)
q.d.	100 mg (e.g., 2 × Tablet 1 or 4 × Tablet 2)
q.d.	150 mg (e.g., 3 × Tablet 1 or 6 × Tablet 2)
q.d.	200 mg (e.g., 4 × Tablet 1 or 8 × Tablet 2)

[0508] When frequency of dosing is twice a day, the pharmaceutical formulations may be administered to subjects in the morning, e.g., between 6:00 AM and 12:00 PM, and evening, e.g., between 5:00 PM and 11:00 PM, and in some administrations, the pharmaceutical formulation is given at approximately the same time (within a 1-hour window) on each dosing occasion. In instances where the frequency dosing is once per day, the pharmaceutical formulation may be given anytime during the day, and in some administrations, the pharmaceutical formulation is given at approximately the same time (within a 1-hour window) on each dosing occasion.

[0509] Furthermore, the tablets (e.g., Tablet 1 and/or Tablet 2) may be administered with or without a fluid (e.g., water or other beverage). Also, human patients being administered the tablet(s) may fast for a period of time prior to or after the administration.

[0510] In several instances, the administration of the tablet(s) may last for a period of about 12 weeks.

[0511] Example 16B: Exemplary Administration B

[0512] Human patients are orally administered a pharmaceutical formulation comprising a compound of Formula I according to Table 9:

Table 9: Exemplary administration of pharmaceutical formulations of the present invention.

Frequency of dosing	Dosage of API
24 hr. intervals	Tablet 2
24 hr. intervals	Tablet 1 or 2 × Tablet 2
24 hr. intervals	2 × Tablet 1 or 4 × Tablet 2
24 hr. intervals	3 × Tablet 1 or 6 × Tablet 2
24 hr. intervals	4 × Tablet 1

[0513] The pharmaceutical formulations may be administered to subjects anytime during the 24 hr. interval, and in some administrations, the pharmaceutical formulation is given at approximately the same time (within a 1-hour window) on each dosing occasion.

[0514] Furthermore, the tablet(s) (e.g., Tablet 1 and/or Tablet 2) may be administered with or without a fluid (e.g., water or other beverage). Also, human patients being administered the tablet may fast for a period of time prior to or after the administration.

[0515] In several instances, the administration of the tablet(s) lasts for a period of about 12 weeks.

[0516] Example 17: Administration of Pharmaceutical Formulations

[0517] Example 17A: Exemplary Administration A

[0518] Human patients are orally administered a pharmaceutical formulation comprising a compound of Formula I according to Table 10:

Table 10: Exemplary administration of pharmaceutical formulations of the present invention.

Frequency of dosing (per day)	Dosage
q.d.	50 mg of API (e.g., Tablet 1)
q.d.	100 mg of API (e.g., 2 × Tablet 1)
q.d.	150 mg of API (e.g., 3 × Tablet 1)
q.d.	200 mg of API (e.g., 4 × Tablet 1)
b.i.d.	25 mg of API (e.g., Tablet 2)
b.i.d.	50 mg of API (e.g., Tablet 1)
b.i.d.	75 mg of API (e.g., Tablet 1 + Tablet 2)
b.i.d.	100 mg of API (e.g., 2 × Tablet 1)
b.i.d.	150 mg of API (e.g., 3 × Tablet 1)

[0519] The pharmaceutical formulations may be administered to subjects in the morning, e.g., between 6:00 AM and 12:00 PM, and evening, e.g., between 5:00 PM and 11:00 PM, and in some administrations, the pharmaceutical formulation is given at approximately the same time (within a 1-hour window) on each dosing occasion.

[0520] Furthermore, the tablets (e.g., Tablet 1) may be administered with or without a fluid (e.g., water or other beverage). Also, human patients being administered the tablet(s) may fast for a period of time prior to or after the administration.

[0521] In several instances, the administration of the tablet(s) may last for a period of about 12 weeks.

[0522] Some embodiments further comprise administering to the patient a co-therapy. Co-therapies that are useful in the methods of the present invention may be administered concurrently with the compound of Formula I or sequentially.

[0523] Some embodiments further comprise administering to the patient an additional agent selected from a corticosteroid, cyclosporine, methotrexate, an oral retinoid, mycophenolate mofetil, thioguanine, hydroxyurea, sirolimus, azathioprine, or any combination thereof.

[0524] Some embodiments further comprise administering a chemotherapy agent to the patient. And, in some instances, the chemotherapy agent comprises methotrexate, azathioprine (e.g., Imuran), cyclophosphamide (e.g., Cytosan), cyclosporine, 6-mercaptopurine, or any combination thereof.

[0525] In some embodiments, the chemotherapy agent comprises an injectable formulation or an oral formulation. And, in some instances, the patient is administered from about 5 mg to about 100 mg of the chemotherapy agent per month.

[0526] Example 18: Clinical Study

[0527] A drug-drug interaction study in healthy male subjects was conducted. The study was designed to evaluate the effect of Compound 1 200 mg daily (qd) on the PK of a single dose of a corticosteroid (prednisone or methylprednisolone) and the effect of a single dose of a corticosteroid (prednisone or methylprednisolone) and the effect of a single dose of a corticosteroid on the PK of Compound 1.

[0528] There were 2 cohorts. There were 28 subjects and 14 subjects were enrolled in each cohort. Healthy male subjects between the ages of 18 and 55 years, inclusive, with a total body weight over 50 kg and a body mass index of 18.0 to 31.0 kg/m², inclusive.

[0529] On Day 1, subjects in Cohort 1 received a single oral dose of 10 mg prednisone (one 10-mg tablet), and subjects in Cohort 2 received a single oral dose of 8 mg methylprednisolone (one 8-mg tablet). On Days 2 through 7, all subjects received oral doses of 200 mg Compound 1 (four 50-mg tablets) qd. On Day 7, subjects in Cohort 1 received a single oral dose of 10 mg prednisone, and subjects in Cohort 2 received a single oral dose of 8 mg methylprednisolone. The dosing schedule is shown in Table 11.

[0530] Table 11: Dosing schedule for Compound 1.

Study Drug	Cohort 1: Compound 1 and Prednisone Cohort 2: Compound 2 and Methylprednisolone		
	Day 1	Days 2 through 6	Day 7
Prednisone 10 mg (Cohort 1) or methylprednisolone 8 mg (Cohort 2)	X		X
Compound 1 200 mg qd		X	X

All study drugs were administered orally to subjects in the fasting state.

[0531] Blood samples for prednisone and prednisolone PK analysis (in Cohort 1) or methylprednisolone PK analysis (in Cohort 2) were collected over Days 1 and 2 and over Days 7 and 8 at 0 (predose) and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours after the steroid dose.

[0532] Blood samples for Compound 1 PK analysis were collected on Day 2 at 0 (predose) and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours postdose; on Days 3 through 6 at predose only; and over Days 7 through 10 at 0 (predose) and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, and 72 hours postdose.

[0533] *Pharmacokinetic Summary Results: Effect of Compound 1 on PK of Prednisone.*

[0534] Referring to FIG. 1, the mean PK profile of prednisone on Day 7 (with Compound 1 at steady state) was similar to that on Day 1 (without Compound 1). Prednisone C_{max} was not significantly changed in the presence of Compound 1.

[0535] *Pharmacokinetic Summary Results: Effect of Compound 1 on PK of Prednisolone.*

[0536] Referring to FIG. 2, the mean PK profile of prednisolone on Day 7 (with Compound 1 at steady state) was similar to that on Day 1 (without Compound 1). Prednisolone C_{max} was not significantly changed in the presence of Compound 1.

[0537] *Pharmacokinetic Summary Results: Effect of Compound 1 on PK of Methylprednisolone*

[0538] Referring to FIG. 3, concentrations of methylprednisolone were higher on Day 7 (with Compound 1 at steady state) than on Day 1 (without Compound 1).

Methylprednisolone GLSM C_{max} increased approximately 1.7-fold in the presence of Compound 1 (90% CI: 1.54, 1.95) and GLSM $AUC_{0-\infty}$ increased approximately 4.3-fold (90% CI: 3.98, 4.72) in the presence of Compound 1.

[0539] *Safety results: Drug exposure levels*

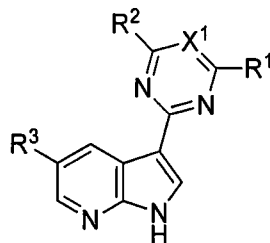
[0540] Safety evaluations included adverse events, clinical laboratory assessments, clinical evaluation of vital signs and physical examinations, and 12-lead electrocardiograms (ECGs). Compound 1 was safe and well tolerated when co-administered with prednisone and methylprednisolone in healthy male subjects. There were no death or other serious adverse events and no adverse events leading to discontinuation of study drug.

OTHER EMBODIMENTS

[0541] All publications and patents referred to in this disclosure are incorporated herein by reference to the same extent as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference. Should the meaning of the terms in any of the patents or publications incorporated by reference conflict with the meaning of the terms used in this disclosure, the meaning of the terms in this disclosure are intended to be controlling. Furthermore, the foregoing discussion discloses and describes merely exemplary embodiments of the present invention. One skilled in the art will readily recognize from such discussion and from the accompanying drawings and claims, that various changes, modifications and variations can be made therein without departing from the spirit and scope of the invention as defined in the following claims.

WHAT IS CLAIMED IS:

1. A method for treating or lessening the severity of rheumatoid arthritis comprising administering to a patient in need thereof a corticosteroid and a compound of Formula I

**I**

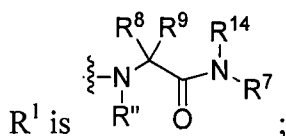
or a pharmaceutically acceptable salt thereof, wherein:

X^1 is N or CR^4 ;

R^2 is H or halo;

R^3 is H or halo;

R^4 is H or halo;



R'' is H or an unsubstituted C_{1-2} aliphatic;

R^8 is an unsubstituted C_{1-4} aliphatic;

R^9 is an unsubstituted C_{1-4} aliphatic;

R^7 is a C_{1-3} aliphatic optionally substituted with up to 3 occurrences of F; and

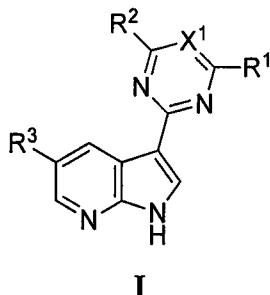
R^{14} is H or unsubstituted C_{1-2} alkyl.

2. The method of claim 1, wherein R^2 is H or F.
3. The method of either of claims 1 or 2, wherein R^3 is H or Cl.
4. The method of any one of claims 1-3, wherein each of R^8 and R^9 is independently selected from methyl, ethyl, propyl, iso-propyl, butyl, or tert-butyl.
5. The method of claim 4, wherein each of R^8 and R^9 is independently selected from methyl or ethyl.
6. The method of any one of claims 1-5, wherein R^{14} is H or methyl.

7. The method of any one of claims 1-6, wherein R^7 is an unsubstituted C_{1-3} aliphatic.
8. The method of any one of claims 1-6, wherein R^7 is a C_{1-3} aliphatic substituted with 1-3 occurrences of F.
9. The method of any one of claims 1-6, wherein R^7 is a group selected from $-CH_2CH_3$, $-CH_2CF_3$, $-CH_2CH_2CH_3$, or $-CHCH_3CH_3$.
10. The method of claim 1, wherein the compound of Formula I is selected from Table 1.
11. The method of any one of claims 1-10, wherein the compound of Formula I is administered at least once per day.
12. The method of any one of claims 1-11, wherein the compound of Formula I is administered from 1 to 4 times per day.
13. The method of any one of claims 1-12, wherein the compound of Formula I is orally administered to the patient in need thereof.
14. The method of any one of claims 1-13, wherein at least about 20 mg of the compound of Formula I is administered to the patient at least once per day.
15. The method of any one of claims 1-14, wherein at least about 100 mg of the compound of Formula I is administered to the patient once per day.
16. The method of any one of claims 1-15, wherein at least about 150 mg of the compound of Formula I is administered to the patient once per day.
17. The method of any one of claims 1-16, wherein at least about 200 mg of the compound of Formula I is administered to the patient once per day.
18. The method of any one of claims 1-13, wherein at least about 20 mg of the compound of Formula I is administered to the patient twice per day.

19. The method of any one of claims 1-13 or 18, wherein at least about 50 mg of the compound of Formula I is administered to the patient twice per day.
20. The method of any one of claims 1-13, 18, or 19, wherein at least about 100 mg of the compound of Formula I is administered to the patient twice per day.
21. The method of any one of claims 1-13 or 18-20, wherein at least about 150 mg of the compound of Formula I is administered to the patient twice per day.
22. The method of any one of claims 1-21, wherein the corticosteroid is hydrocortisone, hydrocortisone acetate, cortisone acetate, tixocortol pivalate, prednisone, prednisolone, methylprednisone, methylprednisolone, or any combination thereof.
23. The method of any one of claims 1-22, wherein the corticosteroid is prednisone.
24. The method of any one of claims 1-23, wherein the corticosteroid is methylprednisone.
25. The method of any one of claims 1-24, wherein the corticosteroid is orally administered to the patient in need thereof.
26. The method of any one of claims 1-25, wherein at least about 5 mg of corticosteroid is administered at least once per week.
27. The method of any one of claims 1-25, wherein at least about 8 mg of corticosteroid is administered at least once per week.
28. The method of claim 27, wherein at least about 8 mg of corticosteroid is administered at least twice per week.
29. The method of any one claims 25-28, wherein the corticosteroid is prednisone or methylprednisone.

30. A method for treating or lessening the severity of rheumatoid arthritis comprising administering to a patient in need thereof a corticosteroid and a pharmaceutical composition comprising a compound of Formula I



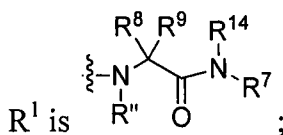
or a pharmaceutically acceptable salt thereof, wherein:

X¹ is N or CR⁴;

R² is H or halo;

R³ is H or halo;

R⁴ is H or halo;



R'' is H or an unsubstituted C₁₋₂ aliphatic;

R⁸ is an unsubstituted C₁₋₄ aliphatic;

R⁹ is an unsubstituted C₁₋₄ aliphatic;

R⁷ is a C₁₋₃ aliphatic optionally substituted with up to 3 occurrences of F; and

R¹⁴ is H or unsubstituted C₁₋₂ alkyl.

31. The method of claim 30, wherein R² is H or F.

32. The method of either of claims 30 or 31, wherein R³ is H or Cl.

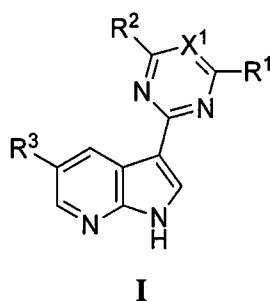
33. The method of any one of claims 30-32, wherein each of R⁸ and R⁹ is independently selected from methyl, ethyl, propyl, iso-propyl, butyl, or tert-butyl.

34. The method of claims 33, wherein each of R⁸ and R⁹ is independently selected from methyl or ethyl.

35. The method of any one of claims 30-34, wherein R¹⁴ is H or methyl.

36. The method of any one of claims 30-35, wherein R^7 is an unsubstituted C_{1-3} aliphatic.
37. The method of any one of claims 30-36, wherein R^7 is a C_{1-3} aliphatic substituted with 1-3 occurrences of F.
38. The method of any one of claims 30-37, wherein R^7 is a group selected from $-CH_2CH_3$, $-CH_2CF_3$, $-CH_2CH_2CH_3$, or $-CHCH_3CH_3$.
39. The method of any one of claims 30-38, wherein the compound of Formula I is selected from Table 1.
40. The method of any one of claims 30-39, wherein the pharmaceutical composition further comprises a tablet.
41. The method of claim 40, wherein the tablet further comprises a diluent, a binder, a glidant, a disintegrant, a surfactant, a lubricant, or any combination thereof.
42. The method of claim 41, wherein the tablet comprises at least about 10 mg of the compound of Formula I.
43. The method of claim 42, wherein the tablet comprises from about 15 mg to about 100 mg of the compound of Formula I.
44. The method of either of claims 40-43, wherein the tablet is administered at least once per day.
45. The method of either of claims 43 or 44, further comprising administering once per day at least one tablet comprising the pharmaceutical composition.
46. The method of either of claims 44 or 45, further comprising administering twice per day at least one tablet comprising the pharmaceutical composition.
47. The method of either of claims 45 or 46, wherein each tablet further comprises from about 20 mg to about 100 mg of the compound of Formula I.

48. The method of any one of claims 30-47, wherein the corticosteroid is hydrocortisone, hydrocortisone acetate, cortisone acetate, tixocortol pivalate, prednisone, prednisolone, methylprednisone, methylprednisolone, or any combination thereof.
49. The method of any one of claims 1-48, wherein the corticosteroid is prednisone.
50. The method of any one of claims 1-48, wherein the corticosteroid is methylprednisone.
51. The method of any one of claims 1-50, wherein the corticosteroid is orally administered to the patient in need thereof.
52. The method of any one of claims 1-51, wherein at least about 5 mg of corticosteroid is administered at least once per week.
53. The method of any one of claims 1-52, wherein at least about 8 mg of corticosteroid is administered at least once per week.
54. The method of claim 53, wherein at least about 8 mg of corticosteroid is administered at least twice per week.
55. The method of any one claims 25-28, wherein the corticosteroid is prednisone or methylprednisone.
56. A pharmaceutical composition comprising a corticosteroid and a compound of Formula I



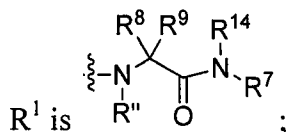
or a pharmaceutically acceptable salt thereof, wherein:

X^1 is N or CR^4 ;

R^2 is H or halo;

R^3 is H or halo;

R⁴ is H or halo;



R'' is H or an unsubstituted C₁₋₂ aliphatic;

R⁸ is an unsubstituted C₁₋₄ aliphatic;

R⁹ is an unsubstituted C₁₋₄ aliphatic;

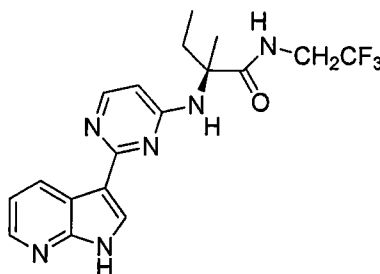
R⁷ is a C₁₋₃ aliphatic optionally substituted with up to 3 occurrences of F; and

R¹⁴ is H or unsubstituted C₁₋₂ alkyl.

57. The pharmaceutical composition of claim 56, wherein R² is H or F.
58. The pharmaceutical composition of either of claims 56 or 57, wherein R³ is H or Cl.
59. The pharmaceutical composition of any one of claims 56-58, wherein each of R⁸ and R⁹ is independently selected from methyl, ethyl, propyl, iso-propyl, butyl, or tert-butyl.
60. The pharmaceutical composition of claim 59, wherein each of R⁸ and R⁹ is independently selected from methyl or ethyl.
61. The pharmaceutical composition of any one of claims 56-60, wherein R¹⁴ is H or methyl.
62. The pharmaceutical composition of any one of claims 56-62, wherein R⁷ is an unsubstituted C₁₋₃ aliphatic.
63. The pharmaceutical composition of any one of claims 56-62, wherein R⁷ is a C₁₋₃ aliphatic substituted with 1-3 occurrences of F.
64. The pharmaceutical composition of any one of claims 1-6, wherein R⁷ is a group selected from -CH₂CH₃, -CH₂CF₃, -CH₂CH₂CH₃, or -CHCH₃CH₃.
65. The pharmaceutical composition of claim 56, wherein the compound of Formula I is selected from Table 1.

66. The pharmaceutical composition of any one of claims 56-65, wherein the corticosteroid is hydrocortisone, hydrocortisone acetate, cortisone acetate, tixocortol pivalate, prednisone, prednisolone, methylprednisone, methylprednisolone, or any combination thereof.

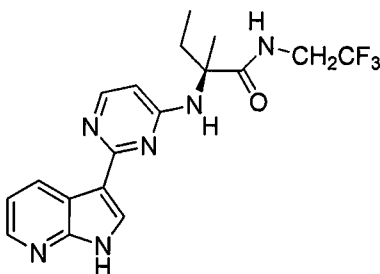
67. A pharmaceutical composition comprising a corticosteroid and a compound having the formula



or a pharmaceutically acceptable salt thereof.

68. The pharmaceutical composition of claim 67, wherein the corticosteroid is selected from prednisone, prednisolone, methylprednisone, methylprednisolone, or any combination thereof.

69. A pharmaceutical composition comprising prednisone and a compound having the formula



or a pharmaceutically acceptable salt thereof.

Mean Plasma Concentrations of Prednisone After Oral Administration Without (Day 1) and With (Day 7) Compound 1, Linear Scale (PK Set)

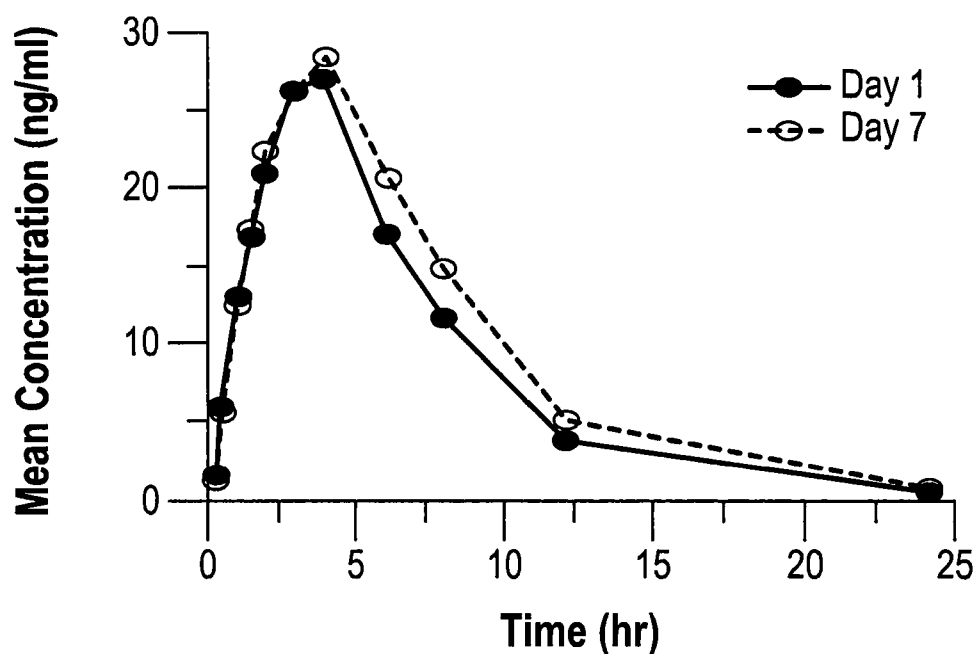


FIG. 1

Mean Plasma Concentrations of Prednisone After Oral Administration Without (Day 1) and With (Day 7) Compound 1, Linear Scale (PK Set)

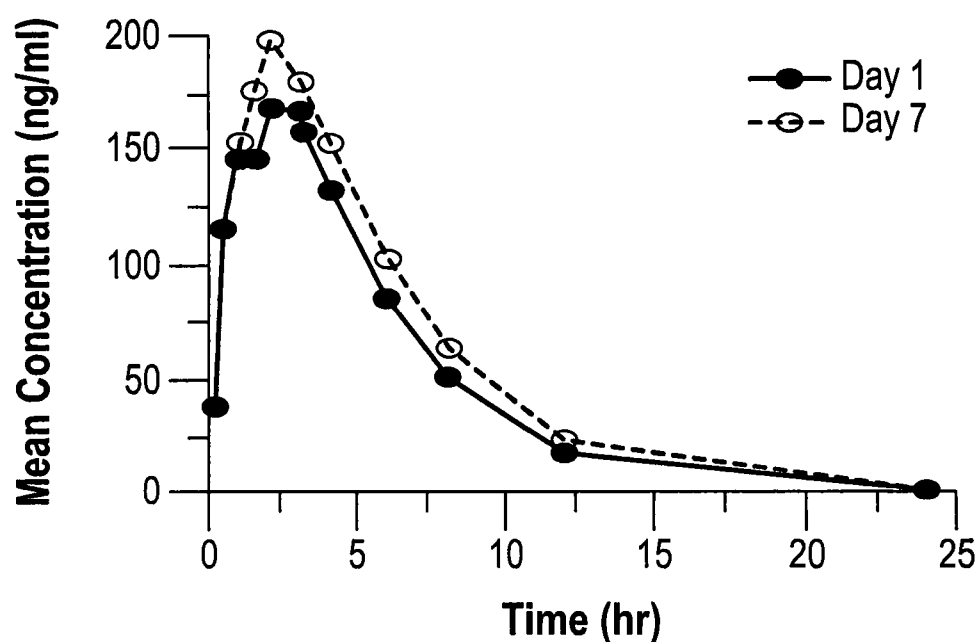


FIG. 2

Mean Plasma Concentrations of Methylprednisolone After Oral
Administration Without (Day 1) and With (Day 7)
Compound 1, Linear Scale (PK Set)

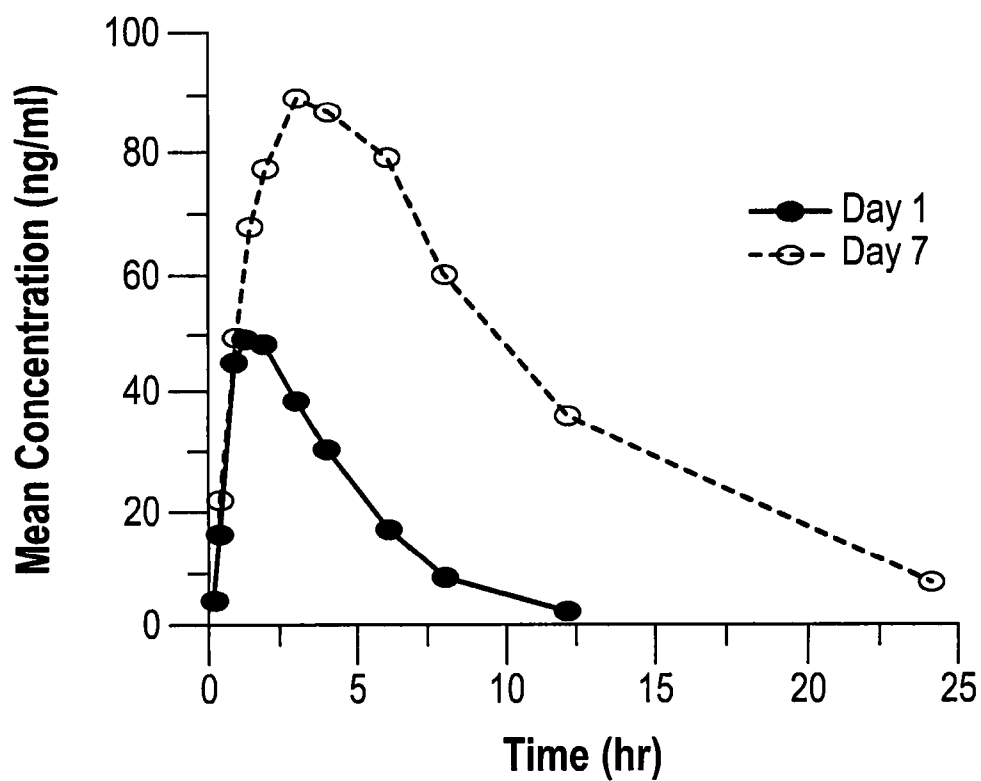


FIG. 3

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2014/042275

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/506 A61K31/573 A61K45/06 A61P19/02
ADD.

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)

A61K

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

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

EPO-Internal, CHEM ABS Data, WPI Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2007/203142 A1 (FARMER LUC [US] ET AL) 30 August 2007 (2007-08-30) page 61; table 6; compound 346 claims 40, 50 -----	1-69
Y	WO 2013/070606 A1 (VERTEX PHARMA [US]) 16 May 2013 (2013-05-16) cited in the application claims 67-81 -----	1-69
Y	WO 00/54780 A2 (ARAKIS LTD [GB]; BARDSLEY HAZEL JUDITH [GB]) 21 September 2000 (2000-09-21) claims 6, 8, 13 -----	1-69



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

"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

5 August 2014

Date of mailing of the international search report

12/08/2014

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
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Authorized officer

Terenzi, Carla

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2014/042275

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