

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
13 March 2008 (13.03.2008)

PCT

(10) International Publication Number
WO 2008/029237 A2

(51) International Patent Classification:
A61K 45/06 (2006.01) *A61P 29/00* (2006.01)

(21) International Application Number:
PCT/IB2007/002468

(22) International Filing Date: 24 August 2007 (24.08.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/842,704 5 September 2006 (05.09.2006) US

(71) Applicant (for all designated States except US): **PFIZER PRODUCTS INC.** [US/US]; Eastern Point Road, Groton, CT 06340 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **CHANGELIAN, Paul, Steven** [US/US]; Pfizer Global Research & Development, 2800 Plymouth Road, Ann Arbor, MI 48105 (US). **ZWILLICH, Samuel, Hyman** [US/US]; Pfizer Global Research and Development, 50 Pequot Avenue MS6025-B3139, New London, CT 06320 (US).

(74) Agents: **FULLER, Grover, F., Jr.** et al.; c/o Lawrence, Jackie, Pfizer Inc. MS8260-1615, Eastern Point Road, Groton, CT 06340 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— without international search report and to be republished upon receipt of that report

(54) Title: COMBINATION THERAPIES FOR RHEUMATOID ARTHRITIS

(57) Abstract: This disclosure relates to pharmaceutical combination therapies for the treatment or prevention of arthritis, such as rheumatoid arthritis, in a human comprising a Janus Kinase inhibitor or a pharmaceutically acceptable salt thereof and at least one anti-arthritis agent or a pharmaceutically acceptable salt thereof. This disclosure also relates to certain methods for treating or preventing arthritis, such as rheumatoid arthritis, in a human comprising co-administering to a human a Janus Kinase inhibitor or a pharmaceutically acceptable salt thereof and at least one anti-arthritis agent or a pharmaceutically acceptable salt thereof.



WO 2008/029237 A2

COMBINATION THERAPIES FOR RHEUMATOID ARTHRITIS

This disclosure relates to pharmaceutical combination therapies for the treatment or prevention of arthritic disorders or conditions in a human, such as rheumatoid arthritis, comprising a Janus Kinase inhibitor such as the presently disclosed pyrrolo[2,3-d]pyrimidine compounds or a pharmaceutically acceptable salt thereof, which are inhibitors of protein kinases, such as the enzyme Janus Kinase 3 (sometimes referred to herein as JAK3) and at least one anti-arthritic agent or a pharmaceutically acceptable salt thereof. This disclosure also relates to methods for the treatment or prevention of such arthritic disorders or conditions and uses of such pharmaceutical combination therapies, and pharmaceutical compositions thereof.

BACKGROUND

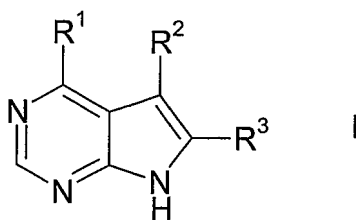
JAK3 is a member of the Janus family of protein kinases. Although the other members of this family are expressed by essentially all tissues, JAK3 expression is limited to hematopoietic cells. This is consistent with its essential role in signaling through the receptors for IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21 by non-covalent association of JAK3 with the gamma chain common to these multichain receptors. SCID patient populations have been identified with severely reduced levels of JAK3 protein or with genetic defects to the common gamma chain, suggesting that immunosuppression should result from blocking signaling through the JAK3 pathway. Animal studies have suggested that JAK3 not only plays a critical role in B and T lymphocyte maturation, but that JAK3 is constitutively required to maintain T cell function. Modulation of immune activity through this novel mechanism can prove useful in the treatment of T cell proliferative disorders such as transplant rejection and autoimmune diseases, such as rheumatoid arthritis.

Previous methods of treating or preventing rheumatoid arthritis with pyrrolo[2,3-d]pyrimidine compounds are mentioned in U.S. Patent No. 7,091,208, the contents of which are hereby incorporated herein by reference for all purposes. Certain pyrrolo[2,3-d]pyrimidine compounds discussed herein are also discussed in U.S. Patent No. 6,627,754 and U.S. Publication No. 2003/0073719, the contents of both are hereby incorporated herein by reference for all purposes. It has now been found that certain pharmaceutical combination therapies comprising certain Janus kinase inhibitors such as the presently disclosed pyrrolo[2,3-d]pyrimidine compounds are effective for treating or preventing arthritic disorders or conditions in a human, such as arthritis including rheumatoid arthritis.

SUMMARY

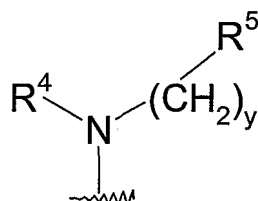
In one aspect, this disclosure relates to a pharmaceutical combination therapy for the treatment or prevention of rheumatoid arthritis in a human comprising a Janus Kinase inhibitor or a pharmaceutically acceptable salt thereof and at least one anti-arthritic agent or a pharmaceutically acceptable salt thereof.

In certain embodiments, the Janus Kinase inhibitor is a compound of the formula



or a pharmaceutically acceptable salt thereof; wherein

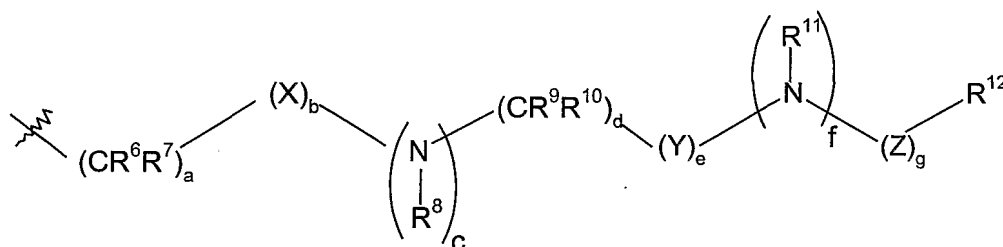
R¹ is a group of the formula



wherein y is 0, 1 or 2;

R⁴ is selected from the group consisting of hydrogen, (C₁-C₆)alkyl, (C₁-C₆)alkylsulfonyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl wherein the alkyl, alkenyl and alkynyl groups are optionally substituted by deuterium, hydroxy, amino, trifluoromethyl, (C₁-C₄)alkoxy, (C₁-C₆)acyloxy, (C₁-C₆)alkylamino, ((C₁-C₆)alkyl)₂amino, cyano, nitro, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl or (C₁-C₆)acylamino; or R⁴ is (C₃-C₁₀)cycloalkyl wherein the cycloalkyl group is optionally substituted by deuterium, hydroxy, amino, trifluoromethyl, (C₁-C₆)acyloxy, (C₁-C₆)acylamino, (C₁-C₆)alkylamino, ((C₁-C₆)alkyl)₂amino, cyano, cyano(C₁-C₆)alkyl, trifluoromethyl(C₁-C₆)alkyl, nitro, nitro(C₁-C₆)alkyl or (C₁-C₆)acylamino;

R⁵ is (C₂-C₉)heterocycloalkyl wherein the heterocycloalkyl groups must be substituted by one to five carboxy, cyano, amino, deuterium, hydroxy, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, halo, (C₁-C₆)acyl, (C₁-C₆)alkylamino, amino(C₁-C₆)alkyl, (C₁-C₆)alkoxy-CO-NH, (C₁-C₆)alkylamino-CO-, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₁-C₆)alkylamino, amino(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, (C₁-C₆)alkoxy(C₁-C₆)alkyl, (C₁-C₆)acyloxy(C₁-C₆)alkyl, nitro, cyano(C₁-C₆)alkyl, halo(C₁-C₆)alkyl, nitro(C₁-C₆)alkyl, trifluoromethyl, trifluoromethyl(C₁-C₆)alkyl, (C₁-C₆)acylamino, (C₁-C₆)acylamino(C₁-C₆)alkyl, (C₁-C₆)alkoxy(C₁-C₆)acylamino, amino(C₁-C₆)acyl, amino(C₁-C₆)acyl(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)acyl, ((C₁-C₆)alkyl)₂amino(C₁-C₆)acyl, R¹⁵R¹⁶N-CO-O-, R¹⁵R¹⁶N-CO-(C₁-C₆)alkyl, (C₁-C₆)alkyl-S(O)ₘ, R¹⁵R¹⁶NS(O)ₘ, R¹⁵R¹⁶NS(O)ₘ(C₁-C₆)alkyl, R¹⁵S(O)ₘR¹⁶N, R¹⁵S(O)ₘR¹⁶N(C₁-C₆)alkyl wherein m is 0, 1 or 2 and R¹⁵ and R¹⁶ are each independently selected from hydrogen or (C₁-C₆)alkyl; or a group of the formula



II

wherein a is 0, 1, 2, 3 or 4;

b, c, e, f and g are each independently 0 or 1;

d is 0, 1, 2, or 3;

X is $S(O)_n$ wherein n is 0, 1 or 2; oxygen, carbonyl or $-C(=N\text{-cyano})-$;

Y is $S(O)_n$ wherein n is 0, 1 or 2; or carbonyl; and

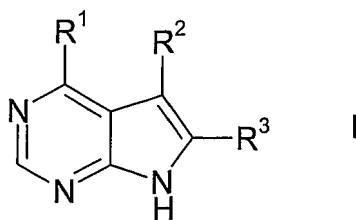
Z is carbonyl, $C(O)O-$, $C(O)NR-$ or $S(O)_n$ wherein n is 0, 1 or 2;

R^6 , R^7 , R^8 , R^9 , R^{10} and R^{11} are each independently selected from the group consisting of hydrogen or (C_1-C_6) alkyl optionally substituted by deuterium, hydroxy, amino, trifluoromethyl, (C_1-C_6) acyloxy, (C_1-C_6) acylamino, (C_1-C_6) alkylamino, $((C_1-C_6)alkyl)_2$ amino, cyano, cyano $(C_1-C_6)alkyl$, trifluoromethyl $(C_1-C_6)alkyl$, nitro, nitro $(C_1-C_6)alkyl$ or (C_1-C_6) acylamino;

R^{12} is carboxy, cyano, amino, oxo, deuterium, hydroxy, trifluoromethyl, $(C_1-C_6)alkyl$, trifluoromethyl $(C_1-C_6)alkyl$, $(C_1-C_6)alkoxy$, halo, $(C_1-C_6)acyl$, $(C_1-C_6)alkylamino$, $((C_1-C_6)alkyl)_2$ amino, amino $(C_1-C_6)alkyl$, $(C_1-C_6)alkoxy-CO-NH$, $(C_1-C_6)alkylamino-CO-$, $(C_2-C_6)alkenyl$, $(C_2-C_6)alkynyl$, $(C_1-C_6)alkylamino$, hydroxy $(C_1-C_6)alkyl$, $(C_1-C_6)alkoxy(C_1-C_6)alkyl$, $(C_1-C_6)acyloxy(C_1-C_6)alkyl$, nitro, cyano $(C_1-C_6)alkyl$, halo $(C_1-C_6)alkyl$, nitro $(C_1-C_6)alkyl$, trifluoromethyl, trifluoromethyl $(C_1-C_6)alkyl$, $(C_1-C_6)acylamino$, $(C_1-C_6)acylamino(C_1-C_6)alkyl$, $(C_1-C_6)alkoxy(C_1-C_6)acylamino$, amino $(C_1-C_6)acyl$, amino $(C_1-C_6)acyl(C_1-C_6)alkyl$, $(C_1-C_6)alkylamino(C_1-C_6)acyl$, $((C_1-C_6)alkyl)_2$ amino $(C_1-C_6)acyl$, $R^{15}R^{16}N-CO-O-$, $R^{15}R^{16}N-CO-(C_1-C_6)alkyl$, $R^{15}C(O)NH$, $R^{15}OC(O)NH$, $R^{15}NHC(O)NH$, $(C_1-C_6)alkyl-S(O)_m$, $(C_1-C_6)alkyl-S(O)_m-(C_1-C_6)alkyl$, $R^{15}R^{16}NS(O)_m$, $R^{15}R^{16}NS(O)_m(C_1-C_6)alkyl$, $R^{15}S(O)_mR^{16}N$, $R^{15}S(O)_mR^{16}N(C_1-C_6)alkyl$ wherein m is 0, 1 or 2 and R^{15} and R^{16} are each independently selected from hydrogen or $(C_1-C_6)alkyl$;

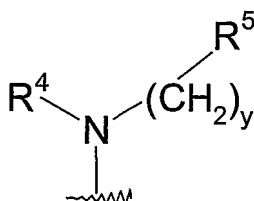
R^2 and R^3 are each independently selected from the group consisting of hydrogen, deuterium, amino, halo, hydroxy, nitro, carboxy, $(C_2-C_6)alkenyl$, $(C_2-C_6)alkynyl$, trifluoromethyl, trifluoromethoxy, $(C_1-C_6)alkyl$, $(C_1-C_6)alkoxy$, $(C_3-C_{10})cycloalkyl$ wherein the alkyl, alkoxy or cycloalkyl groups are optionally substituted by one to three groups selected from halo, hydroxy, carboxy, amino $(C_1-C_6)alkylthio$, $(C_1-C_6)alkylamino$, $((C_1-C_6)alkyl)_2$ amino, $(C_5-C_9)heteroaryl$, $(C_2-C_9)heterocycloalkyl$, $(C_3-C_9)cycloalkyl$ or $(C_6-C_{10})aryl$; or R^2 and R^3 are each independently $(C_3-C_{10})cycloalkyl$, $(C_3-C_{10})cycloalkoxy$, $(C_1-C_6)alkylamino$, $((C_1-C_6)alkyl)_2$ amino, $(C_6-C_{10})arylamino$, $(C_1-C_6)alkylthio$, $(C_6-C_{10})arylthio$, $(C_1-C_6)alkylsulfinyl$, $(C_6-C_{10})arylsulfinyl$, $(C_1-C_6)alkylsulfonyl$, $(C_6-C_{10})arylsulfonyl$, $(C_1-C_6)acyl$, $(C_1-C_6)alkoxy-CO-NH-$, $(C_1-C_6)alkylamino-CO-$, $(C_5-C_9)heteroaryl$, $(C_2-C_9)heterocycloalkyl$ or $(C_6-C_{10})aryl$ wherein the heteroaryl, heterocycloalkyl and aryl groups are optionally substituted by one to three halo, $(C_1-C_6)alkyl$, $(C_1-C_6)alkyl-CO-NH-$, $(C_1-C_6)alkoxy-CO-NH-$, $(C_1-C_6)alkyl-CO-NH-(C_1-C_6)alkyl$, $(C_1-C_6)alkoxy-CO-NH-(C_1-C_6)alkyl$, $(C_1-C_6)alkoxy-CO-NH-(C_1-C_6)alkoxy$, carboxy, carboxy $(C_1-C_6)alkyl$, carboxy $(C_1-C_6)alkoxy$, benzyloxycarbonyl $(C_1-C_6)alkoxy$, $(C_1-C_6)alkoxycarbonyl(C_1-C_6)alkoxy$, $(C_6-C_{10})aryl$, amino, amino $(C_1-C_6)alkyl$, $(C_1-C_6)alkoxycarbonylamino$, $(C_6-C_{10})aryl(C_1-C_6)alkoxycarbonylamino$, $(C_1-C_6)alkylamino$, $((C_1-C_6)alkyl)_2$ amino, $(C_1-C_6)alkylamino(C_1-C_6)alkyl$, $((C_1-C_6)alkyl)_2$ amino $(C_1-C_6)alkyl$, hydroxy, $(C_1-C_6)alkoxy$, carboxy, carboxy $(C_1-C_6)alkyl$, $(C_1-C_6)alkoxycarbonyl$, $(C_1-C_6)alkoxycarbonyl(C_1-C_6)alkyl$, $(C_1-C_6)alkoxy-CO-NH-$, $(C_1-C_6)alkyl-CO-NH-$, cyano, $(C_5-C_9)heterocycloalkyl$, amino $-CO-NH-$, $(C_1-C_6)alkylamino-CO-NH-$, $((C_1-C_6)alkyl)_2$ amino $-CO-NH-$, $(C_6-C_{10})arylamino-CO-NH-$, $(C_5-C_9)heteroarylamino-CO-NH-$, $(C_1-C_6)alkylamino-CO-NH-(C_1-C_6)alkyl$, $((C_1-C_6)alkyl)_2$ amino $-CO-NH-(C_1-C_6)alkyl$, $(C_6-C_{10})arylamino-CO-NH-(C_1-C_6)alkyl$, $(C_5-C_9)heteroarylamino-CO-NH-(C_1-C_6)alkyl$, $(C_1-C_6)alkylsulfonyl$, $(C_1-C_6)alkylsulfonylamino$, $(C_1-C_6)alkylsulfonylamino(C_1-C_6)alkyl$, $(C_6-C_{10})arylsulfonyl$, $(C_6-C_{10})arylsulfonylamino$, $(C_6-C_{10})arylsulfonylamino(C_1-C_6)alkyl$, $(C_1-C_6)alkylsulfonylamino$, $(C_1-C_6)alkylsulfonylamino(C_1-C_6)alkyl$, $(C_5-C_9)heteroaryl$ or $(C_2-C_9)heterocycloalkyl$.

In certain embodiments, the Janus Kinase inhibitor is a compound of the Formula I;



or a pharmaceutically acceptable salt thereof; wherein

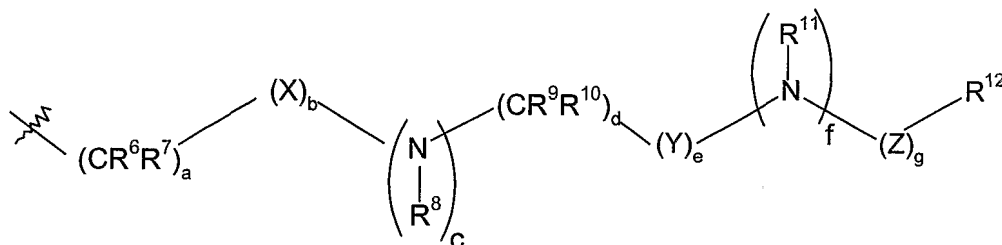
R^1 is a group of the formula



wherein y is 0, 1 or 2:

R⁴ is selected from the group consisting of hydrogen, (C₁-C₆)alkyl, (C₁-C₆)alkylsulfonyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl wherein the alkyl, alkenyl and alkynyl groups are optionally substituted by deuterium, hydroxy, amino, trifluoromethyl, (C₁-C₄)alkoxy, (C₁-C₆)acyloxy, (C₁-C₆)alkylamino, ((C₁-C₆)alkyl)₂amino, cyano, nitro, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl or (C₁-C₆)acylamino; or R⁴ is (C₃-C₁₀)cycloalkyl wherein the cycloalkyl group is optionally substituted by deuterium, hydroxy, amino, trifluoromethyl, (C₁-C₆)acyloxy, (C₁-C₆)acylamino, (C₁-C₆)alkylamino, ((C₁-C₆)alkyl)₂amino, cyano, cyano(C₁-C₆)alkyl trifluoromethyl(C₁-C₆)alkyl, nitro, nitro(C₁-C₆)alkyl or (C₁-C₆)acylamino;

R^5 is a piperidinyl substituted by one to five carboxy, cyano, amino, deuterium, hydroxy, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, halo, (C_1-C_6) acyl, (C_1-C_6) alkylamino, amino (C_1-C_6) alkyl, (C_1-C_6) alkoxy-CO-NH, (C_1-C_6) alkylamino-CO-, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, (C_1-C_6) alkylamino, amino (C_1-C_6) alkyl, hydroxy (C_1-C_6) alkyl, (C_1-C_6) alkoxy (C_1-C_6) alkyl, (C_1-C_6) acyloxy (C_1-C_6) alkyl, nitro, cyano (C_1-C_6) alkyl, halo (C_1-C_6) alkyl, nitro (C_1-C_6) alkyl, trifluoromethyl, trifluoromethyl (C_1-C_6) alkyl, (C_1-C_6) acylamino, (C_1-C_6) acylamino (C_1-C_6) alkyl, (C_1-C_6) alkoxy (C_1-C_6) acylamino, amino (C_1-C_6) acyl, amino (C_1-C_6) acyl (C_1-C_6) alkyl, (C_1-C_6) alkylamino (C_1-C_6) acyl, $((C_1-C_6)alkyl)_2amino(C_1-C_6)acyl$, $R^{15}R^{16}N-CO-O-$, $R^{15}R^{16}N-CO-(C_1-C_6)alkyl$, $(C_1-C_6)alkyl-S(O)_m$, $R^{15}R^{16}NS(O)_m$, $R^{15}R^{16}NS(O)_m(C_1-C_6)alkyl$, $R^{15}S(O)_mR^{16}N$, $R^{15}S(O)_mR^{16}N(C_1-C_6)alkyl$ wherein m is 0, 1 or 2 and R^{15} and R^{16} are each independently selected from hydrogen or $(C_1-C_6)alkyl$; or a group of the formula



11

wherein a is 0, 1, 2, 3 or 4;

b, c, e, f and g are each independently 0 or 1:

d is 0, 1, 2, or 3;

X is $S(O)_n$ wherein n is 0, 1 or 2; oxygen, carbonyl or $-C(=N\text{-cyano})-$;

Y is $S(O)_n$ wherein n is 0, 1 or 2; or carbonyl; and

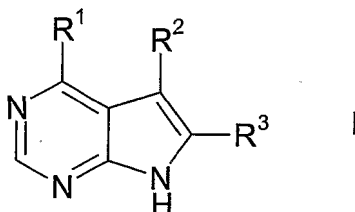
Z is carbonyl, $C(O)O-$, $C(O)NR-$ or $S(O)_n$ wherein n is 0, 1 or 2;

R^6 , R^7 , R^8 , R^9 , R^{10} and R^{11} are each independently selected from the group consisting of hydrogen or (C_1-C_6) alkyl optionally substituted by deuterium, hydroxy, amino, trifluoromethyl, (C_1-C_6) acyloxy, (C_1-C_6) acylamino, (C_1-C_6) alkylamino, $((C_1-C_6)alkyl)_2$ amino, cyano, cyano $(C_1-C_6)alkyl$, trifluoromethyl $(C_1-C_6)alkyl$, nitro, nitro $(C_1-C_6)alkyl$ or (C_1-C_6) acylamino;

R^{12} is carboxy, cyano, amino, oxo, deuterium, hydroxy, trifluoromethyl, $(C_1-C_6)alkyl$, trifluoromethyl $(C_1-C_6)alkyl$, $(C_1-C_6)alkoxy$, halo, $(C_1-C_6)acyl$, $(C_1-C_6)alkylamino$, $((C_1-C_6)alkyl)_2$ amino, amino $(C_1-C_6)alkyl$, $(C_1-C_6)alkoxy-CO-NH$, $(C_1-C_6)alkylamino-CO-$, $(C_2-C_6)alkenyl$, (C_2-C_6) alkynyl, $(C_1-C_6)alkylamino$, hydroxy $(C_1-C_6)alkyl$, $(C_1-C_6)alkoxy(C_1-C_6)alkyl$, $(C_1-C_6)acyloxy(C_1-C_6)alkyl$, nitro, cyano $(C_1-C_6)alkyl$, halo $(C_1-C_6)alkyl$, nitro $(C_1-C_6)alkyl$, trifluoromethyl, trifluoromethyl $(C_1-C_6)alkyl$, $(C_1-C_6)acylamino$, $(C_1-C_6)acylamino(C_1-C_6)alkyl$, $(C_1-C_6)alkoxy(C_1-C_6)acylamino$, amino $(C_1-C_6)acyl$, amino $(C_1-C_6)acyl(C_1-C_6)alkyl$, $(C_1-C_6)alkylamino(C_1-C_6)acyl$, $((C_1-C_6)alkyl)_2$ amino $(C_1-C_6)acyl$, $R^{15}R^{16}N-CO-O-$, $R^{15}R^{16}N-CO-(C_1-C_6)alkyl$, $R^{15}C(O)NH$, $R^{15}OC(O)NH$, $R^{15}NHC(O)NH$, $(C_1-C_6)alkyl-S(O)_m$, $(C_1-C_6)alkyl-S(O)_m-(C_1-C_6)alkyl$, $R^{15}R^{16}NS(O)_m$, $R^{15}R^{16}NS(O)_m(C_1-C_6)alkyl$, $R^{15}S(O)_mR^{16}N$, $R^{15}S(O)_mR^{16}N(C_1-C_6)alkyl$ wherein m is 0, 1 or 2 and R^{15} and R^{16} are each independently selected from hydrogen or $(C_1-C_6)alkyl$;

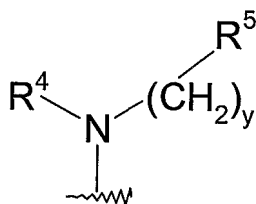
R^2 and R^3 are each hydrogen.

In certain embodiments, the Janus Kinase inhibitor is a compound of the Formula I;



or a pharmaceutically acceptable salt thereof; wherein

R^1 is a group of the formula

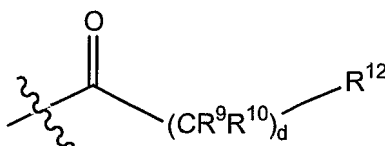


wherein y is 0;

R^4 is $(C_1-C_6)alkyl$;

R^5 is piperidinyl substituted by one to five carboxy, cyano, amino, deuterium, hydroxy, $(C_1-C_6)alkyl$, $(C_1-C_6)alkoxy$, halo, $(C_1-C_6)acyl$, $(C_1-C_6)alkylamino$, amino $(C_1-C_6)alkyl$, $(C_1-C_6)alkoxy-CO-NH$, $(C_1-C_6)alkylamino-CO-$, $(C_2-C_6)alkenyl$, (C_2-C_6) alkynyl, $(C_1-C_6)alkylamino$, amino $(C_1-C_6)alkyl$, hydroxy $(C_1-C_6)alkyl$, $(C_1-C_6)alkoxy(C_1-C_6)alkyl$, $(C_1-C_6)acyloxy(C_1-C_6)alkyl$, nitro, cyano $(C_1-C_6)alkyl$, halo $(C_1-C_6)alkyl$, nitro $(C_1-C_6)alkyl$, trifluoromethyl, trifluoromethyl $(C_1-C_6)alkyl$, $(C_1-C_6)acylamino$, $(C_1-C_6)acylamino(C_1-C_6)alkyl$, $(C_1-C_6)alkoxy(C_1-C_6)acylamino$, amino $(C_1-C_6)acyl$, amino $(C_1-C_6)acyl(C_1-C_6)alkyl$, $(C_1-C_6)alkylamino(C_1-C_6)acyl$, $((C_1-C_6)alkyl)_2$ amino $(C_1-C_6)acyl$, $R^{15}R^{16}N-CO-O-$, $R^{15}R^{16}N-CO-(C_1-C_6)alkyl$, $(C_1-$

C_6 alkyl-S(O)_m, $R_{15}R_{16}NS(O)_m$, $R_{15}R_{16}NS(O)_m(C_1-C_6)alkyl$, $R_{15}S(O)_mR_{16}N$, $R_{15}S(O)_mR_{16}N(C_1-C_6)alkyl$, or a group of the formula



wherein:

m is 0, 1 or 2;

R_{15} and R_{16} are each independently selected from hydrogen or $(C_1-C_6)alkyl$;

d is 1;

R^9 and R^{10} are each independently selected from the group consisting of hydrogen or $(C_1-C_6)alkyl$ optionally substituted by deuterium, hydroxy, amino, trifluoromethyl, $(C_1-C_6)acyloxy$, $(C_1-C_6)acylamino$, $(C_1-C_6)alkylamino$, $((C_1-C_6)alkyl)_2amino$, cyano, cyano $(C_1-C_6)alkyl$, trifluoromethyl $(C_1-C_6)alkyl$, nitro, nitro $(C_1-C_6)alkyl$ or $(C_1-C_6)acylamino$;

R^{12} is cyano, trifluoromethyl, $(C_1-C_6)alkyl$, trifluoromethyl $(C_1-C_6)alkyl$, $(C_1-C_6)alkylamino$, $((C_1-C_6)alkyl)_2amino$, $(C_2-C_6)alkynyl$, cyano $(C_1-C_6)alkyl$, $(C_1-C_6)alkyl-S(O)_m$ wherein m is 0, 1 or 2; and

R^2 and R^3 are each H.

In certain embodiments in the compound of formula I, a is 0; b is 1; X is carbonyl; c is 0; d is 0; e is 0; f is 0; and g is 0.

In certain embodiments in the compound of formula I, a is 0; b is 1; X is carbonyl; c is 0; d is 1; e is 0; f is 0, and g is 0.

In certain embodiments in the compound of formula I, a is 0; b is 1; X is carbonyl; c is 1; d is 0; e is 0; f is 0; and g is 0.

In certain embodiments in the compound of formula I, a is 0; b is 1; X is $-C(=N=cyano)-$; c is 1; d is 0; e is 0; f is 0; and g is 0.

In certain embodiments in the compound of formula I, a is 0; b is 0; c is 0; d is 0; e is 0; f is 0; g is 1; and Z is $-C(O)-O-$.

In certain embodiments in the compound of formula I, a is 0; b is 1; X is $S(O)_n$; n is 2; c is 0; d is 0; e is 0; f is 0; and g is 0.

In certain embodiments in the compound of formula I, a is 0; b is 1; X is $S(O)_n$; n is 2; c is 0; d is 2; e is 0; f is 1; g is 1; and Z is carbonyl.

In certain embodiments in the compound of formula I, a is 0; b is 1; X is $S(O)_n$; n is 2; c is 0; d is 2; e is 0; f is 1; and g is 0.

In certain embodiments in the compound of formula I, a is 0; b is 1; X is carbonyl; c is 1; d is 0; e is 1; Y is $S(O)_n$; n is 2; f is 0; and g is 0.

In certain embodiments in the compound of formula I, a is 0; b is 1; X is $S(O)_n$; n is 2; c is 1; d is 0; e is 0; f is 0; and g is 0.

In certain embodiments in the compound of formula I, R^{12} is cyano, trifluoromethyl, $(C_1-C_6)alkyl$, trifluoromethyl $(C_1-C_6)alkyl$, $(C_1-C_6)alkylamino$, $((C_1-C_6)alkyl)_2amino$, $(C_2-C_6)alkynyl$, cyano $(C_1-C_6)alkyl$, $(C_1-C_6)alkyl-S(O)_m$ wherein m is 0, 1 or 2.

In certain embodiments in the compound of formula I, the Janus Kinase inhibitor is selected from the group consisting of:

- Methyl-[4-methyl-1-(propane-1-sulfonyl)-piperidin-3-yl]-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine;
- 4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-carboxylic acid methyl ester;
- 3,3,3-Trifluoro-1-{4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-propan-1-one;
- 4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-carboxylic acid dimethylamide;
- {(4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-carbonyl)-amino}-acetic acid ethyl ester;
- 3-{4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-3-oxo-propionitrile;
- 3,3,3-Trifluoro-1-{4-methyl-3-[methyl-(5-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-propan-1-one;
- 1-{4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-but-3-yn-1-one;
- 1-{3-[(5-Chloro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-methyl-amino]-4-methyl-piperidin-1-yl}-propan-1-one;
- 1-{3-[(5-Fluoro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-methyl-amino]-4-methyl-piperidin-1-yl}-propan-1-one;
- N-cyano-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-N'-propyl-piperidine-1-carboxamide;
- N-cyano-4,N',N'-Trimethyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-carboxamide;
- Methyl-[(3R,4R)-4-methyl-1-(propane-1-sulfonyl)-piperidin-3-yl]-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine;
- (3R,4R)-4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-carboxylic acid methyl ester;
- 3,3,3-Trifluoro-1-[(3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl]-propan-1-one;
- (3R,4R)-4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-carboxylic acid dimethylamide;
- {(3R,4R)-4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-carbonyl)-amino}-acetic acid ethyl ester;
- 3-[(3R,4R)-4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl]-3-oxo-propionitrile;
- 3,3,3-Trifluoro-1-[(3R,4R)-4-methyl-3-[methyl-(5-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl]-propan-1-one;
- 1-[(3R,4R)-4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl]-but-3-yn-1-one;
- 1-[(3R,4R)-3-[(5-Chloro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-methyl-amino]-4-methyl-piperidin-1-yl]-propan-1-one;

1-((3R,4R)-3-[(5-Fluoro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-methyl-amino]-4-methyl-piperidin-1-yl)-propan-1-one;

(3R,4R)-N-cyano-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-N'-propyl-piperidine-1-carboxamide; and

(3R,4R)-N-cyano-4,N',N'-Trimethyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-carboxamide,
or a pharmaceutically acceptable salt thereof.

In certain embodiments in the compound of formula I, the Janus Kinase inhibitor is selected from the group consisting of:

Methyl-[4-methyl-1-(propane-1-sulfonyl)-piperidin-3-yl]-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine;
4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-carboxylic acid methyl ester;

3,3,3-Trifluoro-1-{4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-propan-1-one;

4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-carboxylic acid dimethylamide;

((4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-carbonyl)-amino)-acetic acid ethyl ester;

3-{4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-3-oxo-propionitrile;

3,3,3-Trifluoro-1-{4-methyl-3-[methyl-(5-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-propan-1-one;

1-{4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-but-3-yn-1-one;

1-{3-[(5-Chloro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-methyl-amino]-4-methyl-piperidin-1-yl}-propan-1-one;

1-{3-[(5-Fluoro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-methyl-amino]-4-methyl-piperidin-1-yl}-propan-1-one;

N-cyano-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-N'-propyl-piperidine-1-carboxamide; and

N-cyano-4,N',N'-Trimethyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-carboxamide,

or a pharmaceutically acceptable salt thereof.

In certain embodiments in the compound of formula I, the Janus Kinase inhibitor is selected from the group consisting of:

Methyl-[(3R,4R)-4-methyl-1-(propane-1-sulfonyl)-piperidin-3-yl]-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine;

(3R,4R)-4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-carboxylic acid methyl ester;

3,3,3-Trifluoro-1-[(3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl]-propan-1-one;

(3R,4R)-4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-carboxylic acid dimethylamide;

{{(3R,4R)-4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-carbonyl}-amino)-acetic acid ethyl ester;

3-{{(3R,4R)-4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-3-oxo-propionitrile;

3,3,3-Trifluoro-1-{{(3R,4R)-4-methyl-3-[methyl-(5-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-propan-1-one;

1-{{(3R,4R)-4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-but-3-yn-1-one;

1-{{(3R,4R)-3-[(5-Chloro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-methyl-amino]-4-methyl-piperidin-1-yl}-propan-1-one;

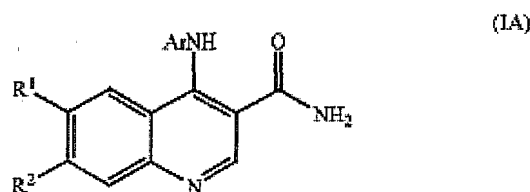
1-{{(3R,4R)-3-[(5-Fluoro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-methyl-amino]-4-methyl-piperidin-1-yl}-propan-1-one;

(3R,4R)-N-cyano-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-N'-propyl-piperidine-1-carboxamide; and

(3R,4R)-N-cyano-4,N',N'-Trimethyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-carboxamide,

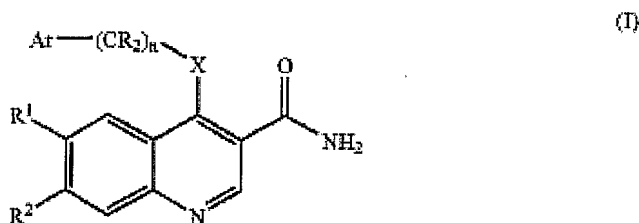
or a pharmaceutically acceptable salt thereof.

In certain embodiments, the Janus Kinase inhibitor is a compound of the formula IA:



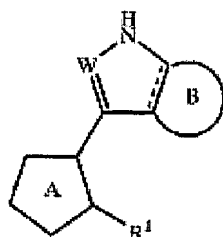
wherein Ar, R¹, and R² are as defined by claim 1 of U.S. 7,037,925, the contents of which are generally and specifically hereby incorporated here by reference for all purposes. The Janus Kinase inhibitor can also be any other compound specifically described in U.S. 7,037,925.

In certain embodiments, the Janus Kinase inhibitor is a compound of the formula I:



wherein Ar, R, X, R¹, R², and a are as defined by claim 1 of U.S. Publication No. 2006/0173034, the contents of which are generally and specifically hereby incorporated here by reference for all purposes. The Janus Kinase inhibitor can also be any other compound specifically described in U.S. Publication No. 2006/0173034.

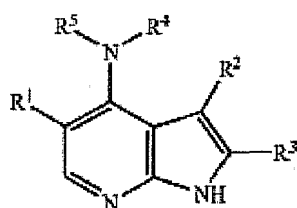
In certain embodiments, the Janus Kinase inhibitor is a compound of the formula



wherein R^1 , A, B, and W are as defined by claim 1 of U.S. Publication No. 2005/0137201, the contents of which are generally and specifically hereby incorporated here by reference for all purposes. The Janus Kinase inhibitor can also be any other compound specifically described in U.S. Publication No. 2005/0137201, particularly those which are mentioned as being JAK3 inhibitors at Example 173.

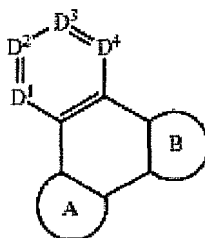
In certain embodiments, the Janus Kinase inhibitor is a compound of any one of the formula 500-511 that is substituted with one or more groups A^0 as defined by U.S. Publication No. 2005/0261253, the contents of which are generally and specifically hereby incorporated here by reference for all purposes. The Janus Kinase inhibitor can also be any other compound specifically described in U.S. Publication No. 2005/0261253.

In certain embodiments, the Janus Kinase inhibitor is a compound of the formula I:



wherein R^1 , R^2 , R^3 , R^4 , and R^5 are as defined by claim 1 of U.S. Publication No. 2006/0183906, the contents of which are generally and specifically hereby incorporated here by reference for all purposes. The Janus Kinase inhibitor can also be any other compound specifically described in U.S. Publication No. 2006/0183906.

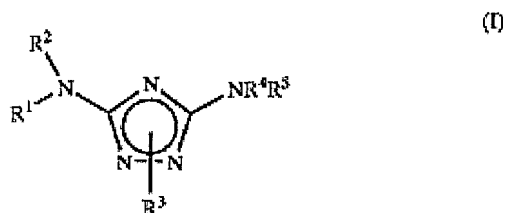
In certain embodiments, the Janus Kinase inhibitor is a compound of the formula I:



wherein D^1 , D^2 , D^3 , D^4 , A, and B are as defined by claim 1 of U.S. Publication No. 2006/0106020, the contents of which are generally and specifically hereby incorporated here by reference for all purposes. The Janus Kinase inhibitor can also be any other compound specifically described in U.S. Publication No. 2006/0106020.

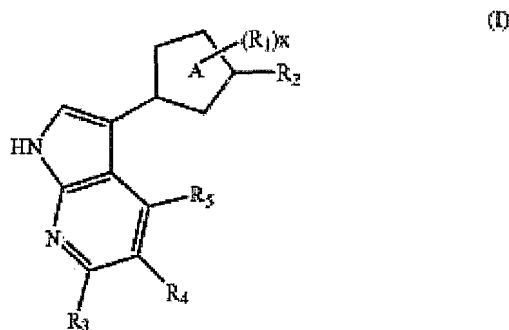
In certain embodiments, the Janus Kinase inhibitor is a compound mentioned as being a JAK3 kinase inhibitor in WO 2005/105146, particularly at pages 12-17, the contents of which are generally and specifically hereby incorporated here by reference for all purposes.

In certain embodiments, the Janus Kinase inhibitor is a compound of the formula I:



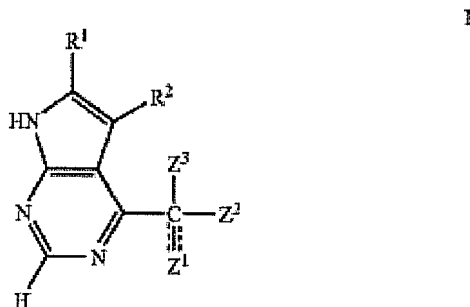
wherein R^1 , R^2 , R^3 , R^4 , and R^5 are as defined by claim 1 of U.S. Publication No. 2004/0214817, the contents of which are generally and specifically hereby incorporated here by reference for all purposes. The Janus Kinase inhibitor can also be any other compound specifically described in U.S. Publication No. 2004/0214817, particularly those which are mentioned as being JAK3 inhibitors at Example 9.

In certain embodiments, the Janus Kinase inhibitor is a compound of the formula I:



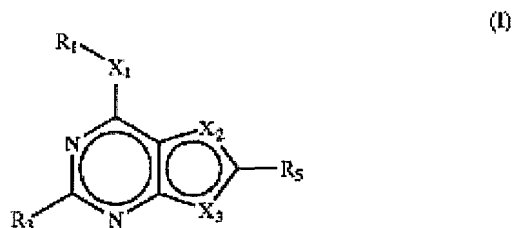
wherein R^1 , R^2 , R^3 , R^4 , R^5 , A and x are as defined by claim 1 of U.S. Publication No. 2006/0122213, the contents of which are generally and specifically hereby incorporated here by reference for all purposes. The Janus Kinase inhibitor can also be any other compound specifically described in U.S. Publication No. 2006/0122213, particularly those shown at Tables I and II.

In certain embodiments, the Janus Kinase inhibitor is a compound of the formula I:



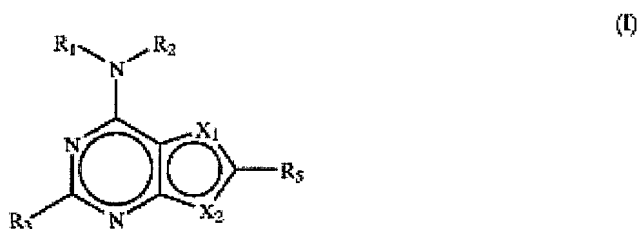
wherein R^1 , R^2 , Z^1 , Z^2 , and Z^3 are as defined by claim 1 of U.S. Publication No. 2006/0183761, the contents of which are generally and specifically hereby incorporated here by reference for all purposes. The Janus Kinase inhibitor can also be any other compound specifically described in U.S. Publication No. 2006/0183761, particularly those shown at Tables I and II.

In certain embodiments, the Janus Kinase inhibitor is a compound of the formula I:



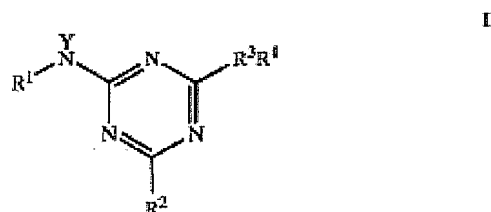
wherein R^1 , R^3 , R^5 , X^1 , X^2 and X^3 are as defined by claim 1 of U.S. Publication No. 2005/0165029, the contents of which are generally and specifically hereby incorporated here by reference for all purposes. The Janus Kinase inhibitor can also be any other compound specifically described in U.S. Publication No. 2005/0165029.

In certain embodiments, the Janus Kinase inhibitor is a compound of the formula I:



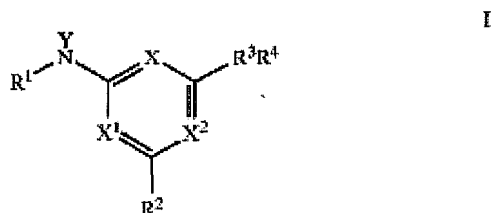
wherein R^1 , R^2 , R^3 , R^5 , X^1 , and X^2 are as defined by claim 1 of U.S. Publication No. 2005/0187389, the contents of which are generally and specifically hereby incorporated here by reference for all purposes. The Janus Kinase inhibitor can also be any other compound specifically described in U.S. Publication No. 2005/0187389.

In certain embodiments, the Janus Kinase inhibitor is a compound of the formula I:



wherein R^1 , R^2 , R^3 , R^4 , and Y are as defined by claim 1 of U.S. 6,943,161, the contents of which are generally and specifically hereby incorporated here by reference for all purposes. The Janus Kinase inhibitor can also be any other compound specifically described in U.S. 6,943,161, particularly those shown at Table I.

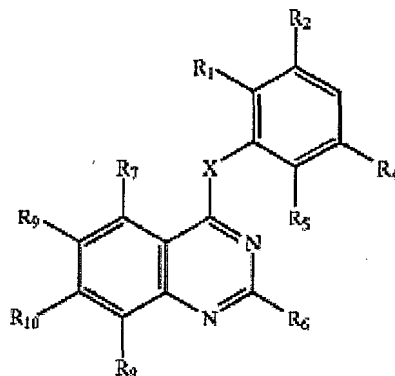
In certain embodiments, the Janus Kinase inhibitor is a compound of the formula I:



wherein R^1 , R^2 , R^3 , R^4 , X , X^1 , X^2 , and Y are as defined by claim 1 of U.S. Publication No. 2005/0277642, the contents of which are generally and specifically hereby incorporated here by reference for all

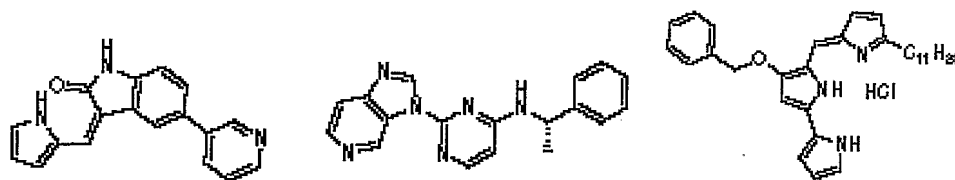
purposes. The Janus Kinase inhibitor can also be any other compound specifically described in U.S. Publication No. 2005/0277642, particularly those shown at Table I.

In certain embodiments, the Janus Kinase inhibitor is a compound of the formula I:



wherein R^1 , R^2 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , and X are as defined by U.S. Nos. 6,452,005 and related U.S. Nos. 6,313,129; 6,313,130; 6,177,433; 6,080,747; 6,326,373; 6,080,748 and U.S. Publication Nos. 2004/0192711 and 2005/0187233, the contents all of which are generally and specifically hereby incorporated here by reference for all purposes. The Janus Kinase inhibitor can also be any other compound specifically described in U.S. Nos. 6,452,005 and related U.S. Nos. 6,313,129; 6,313,130; 6,177,433; 6,080,747; 6,326,373; 6,080,748 and U.S. Publication Nos. 2004/0192711 and 2005/0187233.

In certain embodiments, the Janus Kinase inhibitor is any one of the JAK3 inhibitors shown in Figure 1 of Jack J. Chen, *et al.*, Development of Pyrimidine-Based Inhibitors of Janus Tyrosine Kinase 3, *Bioorganic & Medicinal Chemistry Letters* (2006), doi.1016/j.bmcl.2006.08.0822.



which is hereby incorporated herein by reference for all purposes. The Janus Kinase inhibitor can also be any other compound specifically described therein, particularly in Tables I and II.

In certain embodiments, the anti-arthritic agent is an NSAID (Non-Steroidal Anti-Inflammatory Drug) or a COX-2 (Cyclo-oxygenase 2) inhibitor selected from the group consisting of acetylsalicylic acid and other salicylates such as choline magnesium trisalicylate, azapropazone, carprofen, celecoxib, diclofenac potassium, diclofenac sodium, diflunisal, etodolac, fenbufen, fenoprofen, flufenamic acid, flurbiprofen, ibuprofen, indomethacin, ketoprofen, mefenamic acid, meloxicam, nabumetone, naproxen, naproxen sodium, oxaprozin, pirofen, suprofen, salsalate, sulindac, tenoxicam, tiaprofenic acid, and tolmetin. Other suitable NSAIDs and/or COX-2 inhibitors will be readily apparent to those of skill in the art given the benefit of the present disclosure.

In certain embodiments, the anti-arthritic agent is a glucocorticoid (oral, parenteral and/or intra-articular) selected from the group consisting of hydrocortisone acetate, hydrocortisone *tert* butyl acetate, dexamethasone acetate, dexamethasone *tert* butyl acetate, prednisolone, prednisolone acetate, prednisolone *tert* butyl acetate, prednisone, methylprednisolone methylprednisolone acetate, triamcinolone acetonide, triamcinolone diacetate, and triamcinolone hexacetate. Other suitable

glucocorticoids will be readily apparent to those of skill in the art given the benefit of the present disclosure.

In certain embodiments, the anti-arthritis agent is a SCE (Small Chemical Entity) DMARD (Disease Modifying Anti-Rheumatic Drug) selected from the group consisting of hydroxychloroquine, chloroquine, dapsone, sulfasalazine, methotrexate, leflunomide, azathioprine, d-penicillamine, cyclosporine A, and gold compounds such as gold sodium thiomalate, aurothioglucose, and auranofin.

In certain embodiments, the anti-arthritis agent is a biologic DMARD selected from the group consisting of etanercept, infliximab, adalimumab, anakinra, abatacept, rituximab, tocilizumab, and certolizumab pegol. Other suitable DMARDs (SCE or biologic) will be readily apparent to those of skill in the art given the benefit of the present disclosure.

In certain embodiments, the anti-arthritis agent is an analgesic such as acetaminophen. Other suitable analgesics will be readily apparent to those of skill in the art given the benefit of the present disclosure.

In certain embodiments, the anti-arthritis agent is an opioid optionally in combination with acetaminophen selected from the group consisting of morphine, codeine, propoxyphene, hydrocodone, methadone, hydromorphone, oxycodone, fentanyl, buprenorphine, and butorphanol. Other suitable opioids will be readily apparent to those of skill in the art given the benefit of the present disclosure.

In another aspect, this disclosure relates to a method for treating or preventing rheumatoid arthritis in a human comprising co-administering to human a therapeutically effective amount of both a Janus Kinase inhibitor or a pharmaceutically acceptable salt thereof and at least one anti-arthritis agent or a pharmaceutically acceptable salt thereof, wherein the Janus Kinase inhibitor and the anti-arthritis agents are defined as described herein.

In another aspect, this disclosure relates to a pharmaceutical combination therapy for the treatment or prevention of psoriatic arthritis comprising a Janus Kinase inhibitor or a pharmaceutically acceptable salt thereof and at least one anti-arthritis agent or a pharmaceutically acceptable salt thereof, wherein the Janus Kinase inhibitor and the anti-arthritis agents are defined as described herein.

In another aspect, this disclosure relates to a method for treating or preventing psoriatic arthritis in a human comprising co-administering to human a therapeutically effective amount of both a Janus Kinase inhibitor or a pharmaceutically acceptable salt thereof and at least one anti-arthritis agent or a pharmaceutically acceptable salt thereof, wherein the Janus Kinase inhibitor and the anti-arthritis agents are defined as described herein.

In another aspect, this disclosure relates to a pharmaceutical combination therapy for the treatment or prevention of ankylosing spondylitis comprising a Janus Kinase inhibitor or a pharmaceutically acceptable salt thereof and at least one anti-arthritis agent or a pharmaceutically acceptable salt thereof, wherein the Janus Kinase inhibitor and the anti-arthritis agents are defined as described herein.

In another aspect, this disclosure relates to a method for treating or preventing ankylosing spondylitis in a human comprising co-administering to human a therapeutically effective amount of both a Janus Kinase inhibitor or a pharmaceutically acceptable salt thereof and at least one anti-arthritis agent or a pharmaceutically acceptable salt thereof, wherein the Janus Kinase inhibitor and the anti-arthritis agents are defined as described herein.

Additional features and advantages of the pharmaceutical combinations and methods thereof disclosed herein will be apparent from the following detailed description of certain embodiments.

DETAILED DESCRIPTION

Although specific embodiments of the present disclosure will now be described with reference to certain preferred embodiments described in the preparations and schemes, it should be understood that such embodiments are by way of example only and merely illustrative of but a small number of the many possible specific embodiments which can represent applications of the principles of the present disclosure. Various changes and modifications will be obvious to those of skill in the art given the benefit of the present disclosure and are deemed to be within the spirit and scope of the present disclosure as further defined in the appended claims.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one having ordinary skill in the art to which this disclosure belongs.

Definitions

The term "alkyl", as used herein, unless otherwise indicated, includes saturated monovalent hydrocarbon radicals having straight or branched moieties or combinations thereof.

The term "alkoxy", as used herein, includes O-alkyl groups wherein "alkyl" is defined above.

The term "halo", as used herein, unless otherwise indicated, includes fluoro, chloro, bromo or iodo.

The term "(C₂-C₉)heterocycloalkyl", as used herein, refers to pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydropyranyl, pyranal, thiopyranal, aziridinyl, oxiranyl, methylenedioxy, chromenyl, isoxazolidinyl, 1,3-oxazolidin-3-yl, isothiazolidinyl, 1,3-thiazolidin-3-yl, 1,2-pyrazolidin-2-yl, 1,3-pyrazolidin-1-yl, piperidinyl, thiomorpholinyl, 1,2-tetrahydrothiazin-2-yl, 1,3-tetrahydrothiazin-3-yl, tetrahydrothiadiazinyl, morpholinyl, 1,2-tetrahydrodiazin-2-yl, 1,3-tetrahydrodiazin-1-yl, tetrahydroazepinyl, piperazinyl, chromanyl, etc. One of ordinary skill in the art will understand that the connection of said (C₂-C₉)heterocycloalkyl rings is through a carbon or a sp³ hybridized nitrogen heteroatom.

The term "(C₂-C₉)heteroaryl", as used herein, refers to furyl, thienyl, thiazolyl, pyrazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyrrolyl, triazolyl, tetrazolyl, imidazolyl, 1,3,5-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,3-oxadiazolyl, 1,3,5-thiadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, 1,3,5-triazinyl, pyrazolo[3,4-b]pyridinyl, cinnolyl, pteridinyl, purinyl, 6,7-dihydro-5H-[1]pyrindinyl, benzo[b]thiophenyl, 5, 6, 7, 8-tetrahydro-quinolin-3-yl, benzoxazolyl, benzothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, thianaphthenyl, isothianaphthenyl, benzofuranyl, isobenzofuranyl, isoindolyl, indolyl, indoliziny, indazolyl, isoquinolyl, quinolyl, phthalazinyl, quinoxalyl, quinazolinyl, benzoxazinyl; etc. One of ordinary skill in the art will understand that the connection of said (C₂-C₉)heterocycloalkyl rings is through a carbon atom or a sp³ hybridized nitrogen heteroatom.

(C₆-C₁₀)aryl when used herein refers to phenyl or naphthyl.

The term "pharmaceutical combination therapy" or just "combination therapy" as used herein generally refers to the administration of a Janus Kinase inhibitor in combination with one or more anti-arthritis agents disclosed herein. In other words, the term "pharmaceutical combination therapy" means the

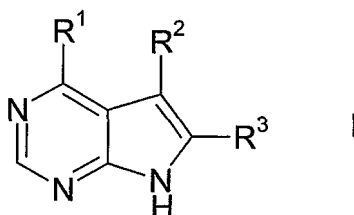
Janus Kinase inhibitor, such as a compound of formula (I), may be administered concomitantly in a pharmaceutically acceptable form with one or more of the anti-arthritic agents disclosed herein: (i) in the same dosage form, e.g., the same tablet or pharmaceutical composition meaning a pharmaceutical composition comprising a Janus Kinase inhibitor, such as a compound of formula (I), one or more anti-arthritic agents disclosed herein, and a pharmaceutically acceptable carrier; (ii) in a separate dosage form having the same mode of administration, e.g., a kit comprising a first pharmaceutical composition suitable for oral administration comprising a Janus Kinase inhibitor, such as a compound of formula (I) and a pharmaceutically acceptable carrier, and a second pharmaceutical composition suitable for oral administration comprising one or more anti-arthritic agents disclosed herein and a pharmaceutically acceptable carrier; and (iii) in a separate dosage form having different modes of administration, e.g., a kit comprising a first pharmaceutical composition suitable for oral administration comprising a Janus Kinase inhibitor, such as a compound of formula (I) and a pharmaceutically acceptable carrier, and a second pharmaceutical composition suitable for parenteral administration comprising one or more anti-arthritic agents disclosed herein and a pharmaceutically acceptable carrier. Further, those of skill in the art given the benefit of the present disclosure will appreciate that when more than one anti-arthritic agent disclosed herein is being administered, the agents need not share the same mode of administration, e.g., a kit comprising a first pharmaceutical composition suitable for oral administration comprising a Janus Kinase inhibitor, such as a compound of formula (I) and a pharmaceutically acceptable carrier, a second pharmaceutical composition suitable for oral administration comprising a first anti-arthritic agent disclosed herein and a pharmaceutically acceptable carrier, and a third pharmaceutical composition suitable for parenteral administration comprising a second anti-arthritic agent disclosed herein and a pharmaceutically acceptable carrier. Those of skill in the art will appreciate that the concomitant administration referred to above in the context of a "pharmaceutical combination therapy" means that the pharmaceutical composition comprising a Janus Kinase inhibitor and a pharmaceutical composition(s) comprising the anti-arthritic agent can be administered on the same schedule, i.e., at the same time and day, or on a different schedule, i.e., on different, although not necessarily distinct, schedules. In that regard, when the pharmaceutical composition comprising a Janus Kinase inhibitor and a pharmaceutical composition(s) comprising the anti-arthritic agent is administered on a different schedule, such a different schedule may also be referred to herein as "background" or "background administration." For example, the pharmaceutical composition comprising a Janus Kinase inhibitor may be administered in a certain dosage form twice a day, and the pharmaceutical composition(s) comprising the anti-arthritic agent may be administered once a day, such that the pharmaceutical composition comprising the Janus Kinase inhibitor may but not necessarily be administered at the same time as the pharmaceutical composition(s) comprising the anti-arthritic agent during one of the daily administrations. Of course, other suitable variations to "pharmaceutical combination therapy" will be readily apparent to those of skill in the art given the benefit of the present disclosure and are part of the meaning of this term.

The term "Janus Kinase inhibitor" as used herein means a compound(s) that demonstrates an inhibitory effect against one or more Janus Kinases, i.e., one of JAK1, JAK2, and JAK3, as measured by the Biological Assays disclosed herein. Exemplary Janus Kinase inhibitors include those of Formula I disclosed here. A preferable Janus Kinase inhibitor is 3-((3R,4R)-4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxo-propionitrile or a pharmaceutically acceptable salt thereof.

The term "co-administering" means the "concomitant" administering of a Janus Kinase inhibitor and one or more anti-arthritis agents, as the term "concomitant" is used in the definition of "pharmaceutical combination therapy".

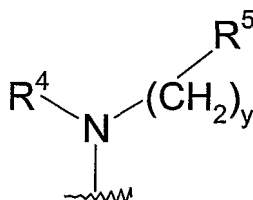
In one aspect, this disclosure relates to a pharmaceutical combination therapy for the treatment or prevention of rheumatoid arthritis in a human comprising a Janus Kinase inhibitor or a pharmaceutically acceptable salt thereof and at least one anti-arthritis agent or a pharmaceutically acceptable salt thereof.

In certain embodiments, the Janus Kinase inhibitor is a compound of the formula



or a pharmaceutically acceptable salt thereof; wherein

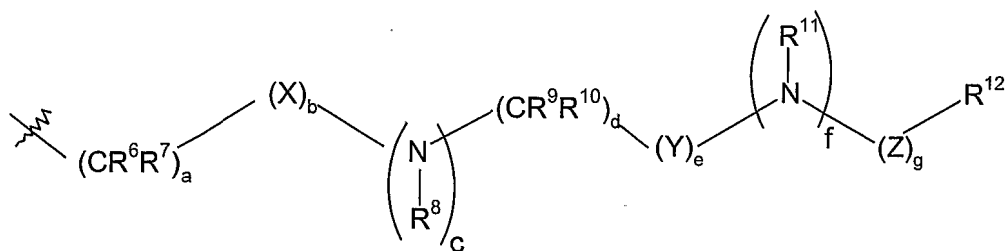
R¹ is a group of the formula



wherein y is 0, 1 or 2;

R⁴ is selected from the group consisting of hydrogen, (C₁-C₆)alkyl, (C₁-C₆)alkylsulfonyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl wherein the alkyl, alkenyl and alkynyl groups are optionally substituted by deuterium, hydroxy, amino, trifluoromethyl, (C₁-C₄)alkoxy, (C₁-C₆)acyloxy, (C₁-C₆)alkylamino, ((C₁-C₆)alkyl)₂amino, cyano, nitro, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl or (C₁-C₆)acylamino; or R⁴ is (C₃-C₁₀)cycloalkyl wherein the cycloalkyl group is optionally substituted by deuterium, hydroxy, amino, trifluoromethyl, (C₁-C₆)acyloxy, (C₁-C₆)acylamino, (C₁-C₆)alkylamino, ((C₁-C₆)alkyl)₂amino, cyano, cyano(C₁-C₆)alkyl, trifluoromethyl(C₁-C₆)alkyl, nitro, nitro(C₁-C₆)alkyl or (C₁-C₆)acylamino;

R⁵ is (C₂-C₉)heterocycloalkyl wherein the heterocycloalkyl groups must be substituted by one to five carboxy, cyano, amino, deuterium, hydroxy, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, halo, (C₁-C₆)acyl, (C₁-C₆)alkylamino, amino(C₁-C₆)alkyl, (C₁-C₆)alkoxy-CO-NH, (C₁-C₆)alkylamino-CO-, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₁-C₆)alkylamino, amino(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, (C₁-C₆)alkoxy(C₁-C₆)alkyl, (C₁-C₆)acyloxy(C₁-C₆)alkyl, nitro, cyano(C₁-C₆)alkyl, halo(C₁-C₆)alkyl, nitro(C₁-C₆)alkyl, trifluoromethyl, trifluoromethyl(C₁-C₆)alkyl, (C₁-C₆)acylamino, (C₁-C₆)acylamino(C₁-C₆)alkyl, (C₁-C₆)alkoxy(C₁-C₆)acylamino, amino(C₁-C₆)acyl, amino(C₁-C₆)acyl(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)acyl, ((C₁-C₆)alkyl)₂amino(C₁-C₆)acyl, R¹⁵R¹⁶N-CO-O-, R¹⁵R¹⁶N-CO-(C₁-C₆)alkyl, (C₁-C₆)alkyl-S(O)_m, R¹⁵R¹⁶NS(O)_m, R¹⁵R¹⁶NS(O)_m (C₁-C₆)alkyl, R¹⁵S(O)_mR¹⁶N, R¹⁵S(O)_mR¹⁶N(C₁-C₆)alkyl wherein m is 0, 1 or 2 and R¹⁵ and R¹⁶ are each independently selected from hydrogen or (C₁-C₆)alkyl; or a group of the formula



II

wherein a is 0, 1, 2, 3 or 4;

b, c, e, f and g are each independently 0 or 1;

d is 0, 1, 2, or 3;

X is $S(O)_n$ wherein n is 0, 1 or 2; oxygen, carbonyl or $-C(=N\text{-cyano})-$;

Y is $S(O)_n$ wherein n is 0, 1 or 2; or carbonyl; and

Z is carbonyl, $C(O)O-$, $C(O)NR-$ or $S(O)_n$ wherein n is 0, 1 or 2;

R^6 , R^7 , R^8 , R^9 , R^{10} and R^{11} are each independently selected from the group consisting of hydrogen or (C_1-C_6) alkyl optionally substituted by deuterium, hydroxy, amino, trifluoromethyl, (C_1-C_6) acyloxy, (C_1-C_6) acylamino, (C_1-C_6) alkylamino, $((C_1-C_6)\text{alkyl})_2$ amino, cyano, cyano (C_1-C_6) alkyl, trifluoromethyl (C_1-C_6) alkyl, nitro, nitro (C_1-C_6) alkyl or (C_1-C_6) acylamino;

R^{12} is carboxy, cyano, amino, oxo, deuterium, hydroxy, trifluoromethyl, (C_1-C_6) alkyl, trifluoromethyl (C_1-C_6) alkyl, (C_1-C_6) alkoxy, halo, (C_1-C_6) acyl, (C_1-C_6) alkylamino, $((C_1-C_6)\text{alkyl})_2$ amino, amino (C_1-C_6) alkyl, (C_1-C_6) alkoxy-CO-NH, (C_1-C_6) alkylamino-CO-, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, (C_1-C_6) alkylamino, hydroxy (C_1-C_6) alkyl, (C_1-C_6) alkoxy (C_1-C_6) alkyl, (C_1-C_6) acyloxy (C_1-C_6) alkyl, nitro, cyano (C_1-C_6) alkyl, halo (C_1-C_6) alkyl, nitro (C_1-C_6) alkyl, trifluoromethyl, trifluoromethyl (C_1-C_6) alkyl, (C_1-C_6) acylamino, (C_1-C_6) acylamino (C_1-C_6) alkyl, (C_1-C_6) alkoxy (C_1-C_6) acylamino, amino (C_1-C_6) acyl, amino (C_1-C_6) acyl (C_1-C_6) alkyl, (C_1-C_6) alkylamino (C_1-C_6) acyl, $((C_1-C_6)\text{alkyl})_2$ amino (C_1-C_6) acyl, $R^{15}R^{16}N\text{-CO-O-}$, $R^{15}R^{16}N\text{-CO-}(C_1-C_6)$ alkyl, $R^{15}C(O)NH$, $R^{15}OC(O)NH$, $R^{15}NHC(O)NH$, (C_1-C_6) alkyl- $S(O)_m$, (C_1-C_6) alkyl- $S(O)_m$ - (C_1-C_6) alkyl, $R^{15}R^{16}NS(O)_m$, $R^{15}R^{16}NS(O)_m$ (C_1-C_6) alkyl, $R^{15}S(O)_m$ $R^{16}N$, $R^{15}S(O)_m$ $R^{16}N$ (C_1-C_6) alkyl wherein m is 0, 1 or 2 and R^{15} and R^{16} are each independently selected from hydrogen or (C_1-C_6) alkyl;

R^2 and R^3 are each independently selected from the group consisting of hydrogen, deuterium, amino, halo, hydroxy, nitro, carboxy, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, trifluoromethyl, trifluoromethoxy, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, (C_3-C_{10}) cycloalkyl wherein the alkyl, alkoxy or cycloalkyl groups are optionally substituted by one to three groups selected from halo, hydroxy, carboxy, amino (C_1-C_6) alkylthio, (C_1-C_6) alkylamino, $((C_1-C_6)\text{alkyl})_2$ amino, (C_5-C_9) heteroaryl, (C_2-C_9) heterocycloalkyl, (C_3-C_9) cycloalkyl or (C_6-C_{10}) aryl; or R^2 and R^3 are each independently (C_3-C_{10}) cycloalkyl, (C_3-C_{10}) cycloalkoxy, (C_1-C_6) alkylamino, $((C_1-C_6)\text{alkyl})_2$ amino, (C_6-C_{10}) arylamino, (C_1-C_6) alkylthio, (C_6-C_{10}) arylthio, (C_1-C_6) alkylsulfinyl, (C_6-C_{10}) arylsulfinyl, (C_1-C_6) alkylsulfonyl, (C_6-C_{10}) arylsulfonyl, (C_1-C_6) acyl, (C_1-C_6) alkoxy-CO-NH-, (C_1-C_6) alkylamino-CO-, (C_5-C_9) heteroaryl, (C_2-C_9) heterocycloalkyl or (C_6-C_{10}) aryl wherein the heteroaryl, heterocycloalkyl and aryl groups are optionally substituted by one to three halo, (C_1-C_6) alkyl, (C_1-C_6) alkyl-CO-NH-, (C_1-C_6) alkoxy-CO-NH-, (C_1-C_6) alkyl-CO-NH- (C_1-C_6) alkyl, (C_1-C_6) alkoxy-CO-NH- (C_1-C_6) alkyl, (C_1-C_6) alkoxy-CO-NH- (C_1-C_6) alkoxy, carboxy, carboxy (C_1-C_6) alkyl, carboxy (C_1-C_6) alkoxy, benzyloxycarbonyl (C_1-C_6) alkoxy, (C_1-C_6) alkoxycarbonyl (C_1-C_6) alkoxy, (C_6-C_{10}) aryl, amino, amino $(C_1-$

C₆)alkyl, (C₁-C₆)alkoxycarbonylamino, (C₆-C₁₀)aryl(C₁-C₆)alkoxycarbonylamino, (C₁-C₆)alkylamino, ((C₁-C₆)alkyl)₂amino, (C₁-C₆)alkylamino(C₁-C₆)alkyl, ((C₁-C₆)alkyl)₂amino(C₁-C₆)alkyl, hydroxy, (C₁-C₆)alkoxy, carboxy, carboxy(C₁-C₆)alkyl, (C₁-C₆)alkoxycarbonyl, (C₁-C₆)alkoxycarbonyl(C₁-C₆)alkyl, (C₁-C₆)alkoxy-CO-NH-, (C₁-C₆)alkyl-CO-NH-, cyano, (C₅-C₉)heterocycloalkyl, amino-CO-NH-, (C₁-C₆)alkylamino-CO-NH-, ((C₁-C₆)alkyl)₂amino-CO-NH-, (C₆-C₁₀)arylamino-CO-NH-, (C₅-C₉)heteroarylamino-CO-NH-, (C₁-C₆)alkylamino-CO-NH-(C₁-C₆)alkyl, ((C₁-C₆)alkyl)₂amino-CO-NH-(C₁-C₆)alkyl, (C₆-C₁₀)arylamino-CO-NH-(C₁-C₆)alkyl, (C₅-C₉)heteroarylamino-CO-NH-(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonyl, (C₁-C₆)alkylsulfonylamino, (C₁-C₆)alkylsulfonylamino(C₁-C₆)alkyl, (C₆-C₁₀)arylsulfonyl, (C₆-C₁₀)arylsulfonylamino, (C₆-C₁₀)arylsulfonylamino(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonylamino, (C₁-C₆)alkylsulfonylamino(C₁-C₆)alkyl, (C₅-C₉)heteroaryl or (C₂-C₉)heterocycloalkyl.

In certain embodiments in the compound of formula I, the Janus Kinase inhibitor is selected from the group consisting of:

- Methyl-[4-methyl-1-(propane-1-sulfonyl)-piperidin-3-yl]-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine;
- 4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-carboxylic acid methyl ester;
- 3,3,3-Trifluoro-1-{4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-propan-1-one;
- 4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-carboxylic acid dimethylamide;
- {[4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-carbonyl]-amino}-acetic acid ethyl ester;
- 3-{4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-3-oxo-propionitrile;
- 3,3,3-Trifluoro-1-{4-methyl-3-[methyl-(5-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-propan-1-one;
- 1-{4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-but-3-yn-1-one;
- 1-{3-[(5-Chloro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-methyl-amino]-4-methyl-piperidin-1-yl}-propan-1-one;
- 1-{3-[(5-Fluoro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-methyl-amino]-4-methyl-piperidin-1-yl}-propan-1-one;
- N-cyano-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-N'-propyl-piperidine-1-carboxamide;
- N-cyano-4,N',N'-Trimethyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-carboxamide;
- Methyl-[(3R,4R)-4-methyl-1-(propane-1-sulfonyl)-piperidin-3-yl]-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine;
- (3R,4R)-4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-carboxylic acid methyl ester;
- 3,3,3-Trifluoro-1-[(3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl]-propan-1-one;
- (3R,4R)-4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-carboxylic acid dimethylamide;

{(3R,4R)-4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-carbonyl}-amino)-acetic acid ethyl ester;

3-{(3R,4R)-4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-3-oxo-propionitrile;

3,3,3-Trifluoro-1-{(3R,4R)-4-methyl-3-[methyl-(5-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-propan-1-one;

1-{(3R,4R)-4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-but-3-yn-1-one;

1-{(3R,4R)-3-[(5-Chloro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-methyl-amino]-4-methyl-piperidin-1-yl}-propan-1-one;

1-{(3R,4R)-3-[(5-Fluoro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-methyl-amino]-4-methyl-piperidin-1-yl}-propan-1-one;

(3R,4R)-N-cyano-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-N'-propyl-piperidine-1-carboxamidine; and

(3R,4R)-N-cyano-4,N',N'-Trimethyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-carboxamidine,

or a pharmaceutically acceptable salt thereof.

In certain embodiments, the Janus Kinase inhibitor is 3-{4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-3-oxo-propionitrile or a pharmaceutically acceptable salt thereof.

In certain embodiments, the Janus Kinase inhibitor is 3-{(3R,4R)-4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-3-oxo-propionitrile or a pharmaceutically acceptable salt thereof.

In certain embodiments the pharmaceutically acceptable salt of 3-{4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-3-oxo-propionitrile and/or 3-{(3R,4R)-4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-3-oxo-propionitrile is a citrate salt, such as a mono citrate salt. In certain embodiments, such compounds are crystalline, as discussed in U.S. Patent No. 6,965,027, the contents of which are hereby incorporated here by reference.

The Janus Kinase inhibitors of the present disclosure can be in the form of a pharmaceutically acceptable acid addition salt. The acids which are used to prepare the pharmaceutically acceptable acid addition salts of the aforementioned base compounds of this disclosure are those which form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, acetate, lactate, citrate, acid citrate, tartrate, bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)]salts.

The Janus Kinase inhibitors of the present disclosure can be in the form of a pharmaceutically acceptable base addition salt. The chemical bases that may be used as reagents to prepare pharmaceutically acceptable base salts of those compounds of formula I that are acidic in nature are those that form non-toxic base salts with such compounds. Such non-toxic base salts include, but are not limited to those derived from such pharmacologically acceptable cations such as alkali metal cations (e.g., potassium and sodium) and alkaline earth metal cations (e.g., calcium and magnesium), ammonium or

water-soluble amine addition salts such as N-methylglucamine-(meglumine), and the lower alkanolammonium and other base salts of pharmaceutically acceptable organic amines.

Certain of the Janus Kinase inhibitors mentioned here are basic in nature are capable of forming a wide variety of different salts with various inorganic and organic acids. Although such salts must be pharmaceutically acceptable for administration to animals, it is often desirable in practice to initially isolate the compound of the present disclosure from the reaction mixture as a pharmaceutically unacceptable salt and then simply convert the latter back to the free base compound by treatment with an alkaline reagent and subsequently convert the latter free base to a pharmaceutically acceptable acid addition salt. The acid addition salts of the base compounds of this disclosure are readily prepared by treating the base compound with a substantially equivalent amount of the chosen mineral or organic acid in an aqueous solvent medium or in a suitable organic solvent, such as methanol or ethanol. Upon careful evaporation of the solvent, the desired solid salt is readily obtained. The desired acid salt can also be precipitated from a solution of the free base in an organic solvent by adding to the solution an appropriate mineral or organic acid.

Certain of the Janus Kinase inhibitors mentioned here are acidic in nature, and are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include the alkali metal or alkaline-earth metal salts and particularly, the sodium and potassium salts. These salts are all prepared by conventional techniques. The chemical bases which are used as reagents to prepare the pharmaceutically acceptable base salts of this disclosure are those which form non-toxic base salts with the acidic compounds of the present disclosure. Such non-toxic base salts include those derived from such pharmacologically acceptable cations as sodium, potassium calcium and magnesium, etc. These salts can easily be prepared by treating the corresponding acidic compounds with an aqueous solution containing the desired pharmacologically acceptable cations, and then evaporating the resulting solution to dryness, preferably under reduced pressure. Alternatively, they may also be prepared by mixing lower alkanolic solutions of the acidic compounds and the desired alkali metal alkoxide together, and then evaporating the resulting solution to dryness in the same manner as before. In either case, stoichiometric quantities of reagents are preferably employed in order to ensure completeness of reaction and maximum yields of the desired final product.

In certain embodiments, the Janus Kinase inhibitor is a compound specified and/or exemplified in:

USN 09/335030, which issued as U.S. Patent No. 6,635,762;

USN 10/640079, which published as U.S. Publication No. 2004-0058922A1;

USN 09/335121;

USN 09/956645, which issued as U.S. Patent No. 6,610,847;

USN 10/442807, which issued as U.S. Patent No. 6,890,929;

USN 11/064,873, which published as U.S. Publication No. 2005-0171128;

USN 09/732669, which issued as U.S. Patent No. 6,627,754;

USN 10/640227, which issued as U.S. Patent No. 6,956,041;

USN 11/211,217, which issued as U.S. Patent No. 7,091,208;

USN 11/474,233;

USN 09/891028, which issued as U.S. Patent No. 6,696,567;

USN 10/463724, which issued as U.S. Patent No. 6,962,993;

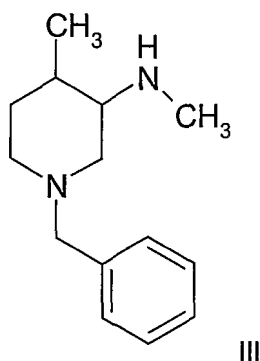
USSN 11/112307, which published as U.S. Publication No. 2005-0197349;
USSN 10/154699, which published as U.S. Publication No. 2003-0073719A1;
USSN 10/869101, which published as U.S. Publication No. 2004-0229923 A1;
USSN 10/310078, which issued as U.S. Patent No. 6,965,027;
USSN 11/032990, which published as U.S. Publication No. 2005-0159434A1,
the contents of all of which are hereby incorporated here by reference for all purposes.

The Janus Kinase inhibitors of the present disclosure include all conformational isomers (e.g., cis and trans isomers) and mixtures thereof. Such compounds have asymmetric centers readily apparent to those of skill in the art and therefore exist in different enantiomeric and diastereomeric forms. This disclosure relates to the use of all optical isomers and stereoisomers of such compounds used in the present disclosure, and mixtures thereof, and to all pharmaceutical compositions and methods of treatment that may employ or contain them. In this regard, this disclosure includes both the E and Z configurations. In particular, resolution of racemic mixtures of enantiomers of compounds, used in providing the R¹ substituent of formula I, is effected by treating the racemic mixture of the compound of formula HNR⁴R⁵, e.g., a compound of formula III below, with a specific optical isomer of a disubstituted tartaric acid or tartrate in an appropriate solvent such as ethanol with or without water as a co-solvent. The desired enantiomer can be obtained in excess of 90% using such methods disclosed in U.S. Serial No. 10/154,699, the contents of which are hereby incorporated herein by reference for all purposes. Specific resolving agents useful in said resolution include optical isomers of tartaric acid and tartaric acid derivatives such as di-p-toluoyl-L-tartaric acid and (S)-(+)-Andeno acid (pencyphos, (S)-(+)-2-hydroxy-5,5-dimethyl-4-phenyl-1,3,2-dioxaphosphorinane-2-oxide) salt. Of course, those of skill in the art given the benefit of the present disclosure will appreciate other suitable resolving agents potentially useful for resolving such compounds of formula HNR⁴R⁵.

The Janus Kinase inhibitors of the present disclosure may also exist as tautomers. This disclosure relates to the use of all such tautomers and mixtures thereof.

Interaction between antipodes of the resolving material and specific enantiomer provides a resolution of the racemic mixture whereby a precipitate of the resolving material and enantiomer provides one of the desired stereospecific materials and wherein the remaining enantiomer in solution can be separately isolated thereby. Thus, depending on the specific enantiomer desired and the separation method to be used (i.e., from precipitate or solution), the stereospecific nature of the resolving nature can be concomitantly selected; e.g. an "L" form of the resolving agent such as a tartrate derivative provides a precipitate of an "R" form of the R¹ substituent and a solution containing the "L" form and vice versa.

The aforementioned resolving agents are effective in providing a 3R,4R enantiomer of the compound of the formula III (either in precipitate or solution, as described):



In certain embodiments, resolution of the compound of formula III is effected by the steps of:

- a) mixing a racemic mixture of the compound of formula III in an appropriate solution with a resolving compound, having a defined stereospecificity, for a time sufficient to allow substantial precipitation of a stereospecific isomer of the racemic mixture from the solution;
- b) depending on the stereospecific form of the compound which is desired, collecting either the precipitate and purifying it or collecting the mother liquor and recrystallizing the enantiomer contained therein.

With some materials a slurry rather than a solution is formed with the resolution of the present disclosure involving a slurry to slurry conversion. The term "solution" encompasses both a solution and a slurry.

The temperature at which the resolution and precipitation is effected is preferably ambient temperature and while precipitation time is not restricted for efficiency the time is preferably no more than about four hours. In order to facilitate the resolution it is desirable to use enantiomers in the racemic mixture which are in a stable form and the compound of formula II is most stable in acid addition salt form such as a hydrochloride salt, rather than a free base form and it is preferred that the racemic compound mixture be accordingly converted prior to resolution. Thus, for example, formation of the hydrochloride salt of the compound of formula II is effected preferably in ethanol with a small amount of toluene as cosolvent. Alternatively, methanol, isopropanol, acetonitrile, or tetrahydrofuran (or mixtures thereof with or without water as a cosolvent) with cosolvents of toluene, ethylacetate, dichloromethane, dichloroethane, or tetrahydrofuran may be used in the salt formation. The HCl salt is particularly preferred since this form provides a superior purification and enriched of other stereoisomers from the prior step.

A preferred displacement solvent used in the resolution is ethyl acetate. Toluene, acetonitrile, or heptanes are also useful as solvents.

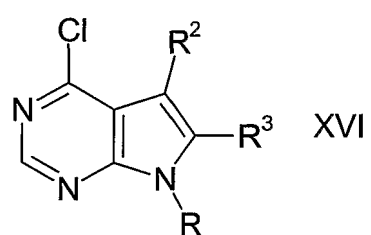
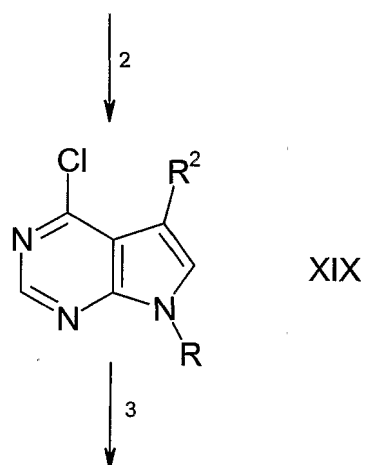
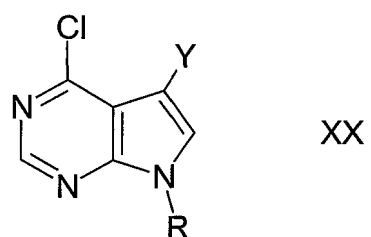
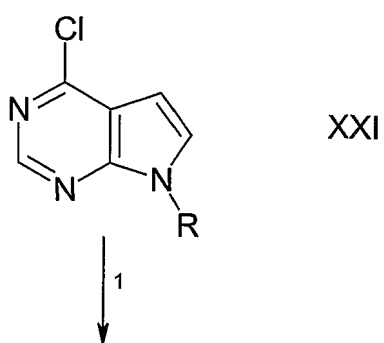
A preferred isolation solvent is acetone. Other solvents useful in this regard include isopropanol, ethanol, methyl ethyl ketone, methyl isopropyl ketone, acetonitrile, and tetrahydrofuran. The solvents may also be used as co-solvents with each other or with water.

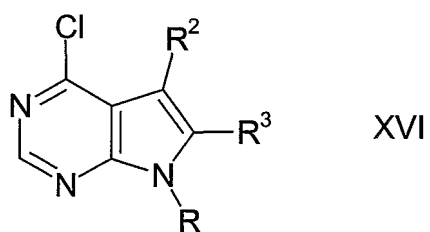
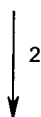
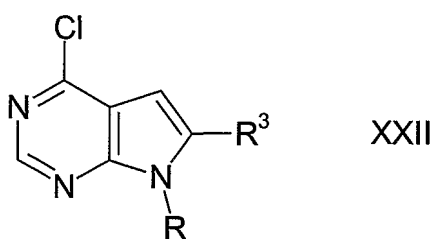
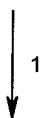
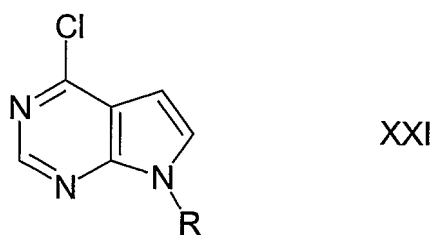
Preferred resolution compounds include tartaric acid and its derivatives such as toluoyl and benzoyl tartaric acids in stereospecific conformation, as described. Other resolution compounds include stereospecific adeno acid and derivatives thereof.

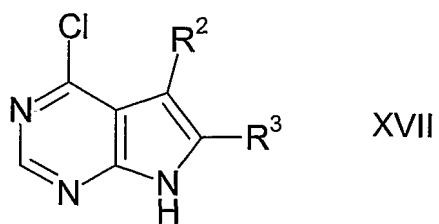
To facilitate precipitation and recrystallization addition of seeds is optional, but preferred in order to obtain higher ee material with fewer recrystallizations.

This disclosure also encompasses pharmaceutical compositions containing prodrugs of the Janus Kinase inhibitors of the present disclosure such as the compounds of the formula I and the use of such

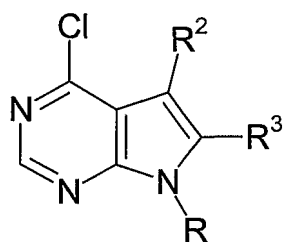
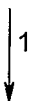
prodrugs in the presently disclosed pharmaceutical combination therapies. Compounds of formula I having free amino, amido, hydroxy or carboxylic groups can be converted into prodrugs. Prodrugs include compounds wherein an amino acid residue, or a polypeptide chain of two or more (e.g., two, three or four) amino acid residues which are covalently joined through peptide bonds to free amino, hydroxy or carboxylic acid groups of compounds of formula I. The amino acid residues include the 20 naturally occurring amino acids commonly designated by three letter symbols and also include, 4-hydroxyproline, hydroxylysine, demosine, isodemosine, 3-methylhistidine, norvlin, beta-alanine, gamma-aminobutyric acid, citrulline, homocysteine, homoserine, ornithine and methionine sulfone. Prodrugs also include compounds wherein carbonates, carbamates, amides and alkyl esters which are covalently bonded to the above substituents of formula I through the carbonyl carbon prodrug sidechain.

PREPARATION A

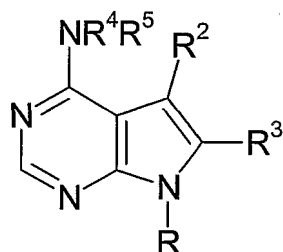
PREPARATION B

SCHEME 1

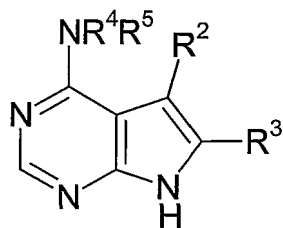
XVII



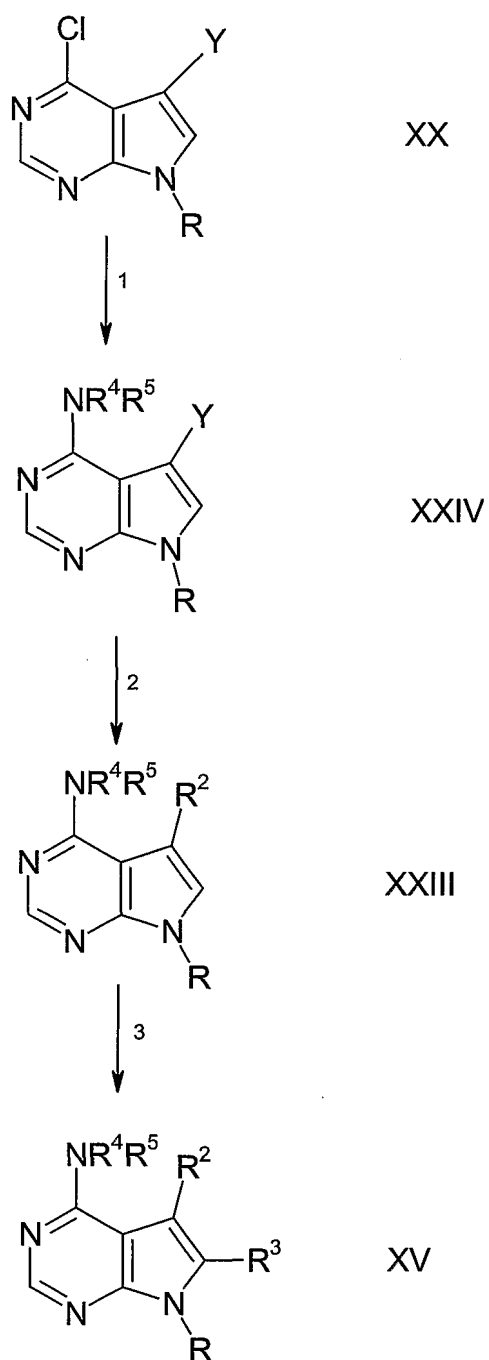
XVI

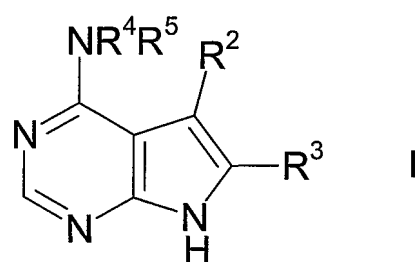
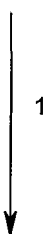
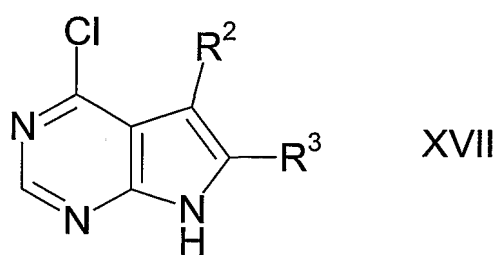


XV



I

SCHEME 2

SCHEME 3

In reaction 1 of Preparation A, the 4-chloropyrrolo[2,3-d]pyrimidine compound of formula **XXI**, wherein R is hydrogen or a protecting group such as benzenesulfonyl or benzyl, is converted to the 4-chloro-5-halopyrrolo[2,3-d]pyrimidine compound of formula **XX**, wherein Y is chloro, bromo or iodo, by reacting **XXI** with N-chlorosuccinimide, N-bromosuccinimide or N-iodosuccinimide. The reaction mixture is heated to reflux, in chloroform, for a time period between about 1 hour to about 3 hours, preferably about 1 hour. Alternatively, in reaction 1 of Preparation A, the 4-chloropyrrolo[2,3-d]pyrimidine of formula **XXI**, wherein R is hydrogen, is converted to the corresponding 4-chloro-5-nitropyrrolo[2,3-d]pyrimidine of formula **XX**, wherein Y is nitro, by reacting **XXI** with nitric acid in sulfuric acid at a temperature between about -10°C to about 10°C, preferably about 0°C, for a time period between about 5 minutes to about 15 minutes, preferably about 10 minutes. The compound of formula **XXI**, wherein Y is nitro, is converted to the corresponding 4-chloro-5-aminopyrrolo[2,3-d]pyrimidine of the formula **XX**, wherein Y is amino, by reacting **XXI** under a variety of conditions known to one skilled in the art such as palladium hydrogenolysis or tin(IV)chloride and hydrochloric acid.

In reaction 2 of Preparation A, the 4-chloro-5-halopyrrolo[2,3-d]pyrimidine compound of formula **XX**, wherein R is hydrogen, is converted to the corresponding compound of formula **XIX**, wherein R² is (C₁-C₆)alkyl or benzyl, by treating **XX** with N-butyllithium, at a temperature of about -78°C, and reacting the dianion intermediate so formed with an alkylhalide or benzylhalide at a temperature between about -78°C to room temperature, preferably room temperature. Alternatively, the dianion so formed is reacted with molecular oxygen to form the corresponding 4-chloro-5-hydroxypyrrrolo[2,3-d]pyrimidine compound of formula **XIX**, wherein R² is hydroxy. The compound of formula **XX**, wherein Y is bromine or iodine and R is benzenesulfonate, is converted to the compound of formula **XIX**, wherein R² is (C₆-C₁₂)aryl or vinyl, by treating **XX** with N-butyllithium, at a temperature of about -78°C, followed by the addition of zinc chloride, at a temperature of about -78°C. The corresponding organo zinc intermediate so formed is then reacted with aryl iodide or vinyl iodide in the presence of a catalytic quantity of palladium. The reaction mixture is stirred at a temperature between about 50°C to about 80°C, preferably about 70°C, for a time period between about 1 hour to about 3 hours, preferably about 1 hour.

In reaction 3 of Preparation A, the compound of formula **XIX** is converted to the corresponding compound of formula **XVI** by treating **XIX** with N-butyllithium, lithium diisopropylamine or sodium hydride, at a temperature of about -78°C, in the presence of a polar aprotic solvent, such as tetrahydrofuran. The anionic intermediate so formed is further reacted with (a) alkylhalide or benzylhalide, at a temperature between about -78°C to room temperature, preferably -78 °C, when R³ is alkyl or benzyl; (b) an aldehyde or ketone, at a temperature between about -78°C to room temperature, preferably -78°C, when R³ is alkoxy; and (c) zinc chloride, at a temperature between about -78°C to room temperature, preferably -78°C, and the corresponding organozinc intermediate so formed is then reacted with aryl iodide or vinyl iodide in the presence of a catalytic quantity of palladium. The resulting reaction mixture is stirred at a temperature between about 50°C to about 80°C, preferably about 70°C, for a time period between about 1 hour to about 3 hours, preferably about 1 hour. Alternatively, the anion so formed is reacted with molecular oxygen to form the corresponding 4-chloro-6-hydroxypyrrrolo[2,3-d]pyrimidine compound of formula **XVI**, wherein R³ is hydroxy.

In reaction 1 of Preparation B, the 4-chloropyrrolo[2,3-d]pyrimidine compound of formula **XXI** is converted to the corresponding compound of formula **XXII**, according to the procedure described above in reaction 3 of Preparation A.

In reaction 2 of Preparation B, the compound of formula **XXII** is converted to the corresponding compound of formula **XVI**, according to the procedures described above in reactions 1 and 2 of Preparation A.

In reaction 1 of Scheme 1, the 4-chloropyrrolo[2,3-d]pyrimidine compound of formula **XVII** is converted to the corresponding compound of formula **XVI**, wherein R is benzenesulfonyl or benzyl, by treating **XVII** with benzenesulfonyl chloride, benzylchloride or benzylbromide in the presence of a base, such as sodium hydride or potassium carbonate, and a polar aprotic solvent, such as dimethylformamide or tetrahydrofuran. The reaction mixture is stirred at a temperature between about 0°C to about 70°C, preferably about 30°C, for a time period between about 1 hour to about 3 hours, preferably about 2 hours.

In reaction 2 of Scheme 1, the 4-chloropyrrolo[2,3-d]pyrimidine compound of formula **XVI** is converted to the corresponding 4-aminopyrrolo[2,3-d]pyrimidine compound of formula **XV** by coupling **XVI** with an amine of the formula HNR^4R^5 . In certain embodiments, the 4-chloropyrrolo[2,3-d]pyrimidine compound of formula **XVI** is coupled with the enantiomer obtained with the resolution of NHR^4R^5 , i.e. a single stereoisomer of formula **III**, to arrive at the corresponding 4-aminopyrrolo[2,3-d]pyrimidine compound of formula **XV**, which has the same stereochemistry as the resolved reactant of formula NHR^4R^5 . That is, the coupling reaction 2 in such embodiments proceeds without inversion or loss of stereochemistry and instead proceeds with retention of stereochemistry. Such lack of inversion or loss of stereochemistry and retention of stereochemistry continues for the remainder of the synthesis described below to arrive at the compounds of formula **I**. The reaction is carried out in an alcohol solvent, such as tert-butanol, methanol or ethanol, or other high boiling organic solvents, such as dimethylformamide, triethylamine, 1,4-dioxane or 1,2-dichloroethane, at a temperature between about 60°C to about 120°C, preferably about 80°C. Typical reaction times are between about 2 hours to about 48 hours, preferably about 16 hours. When R^5 is a nitrogen containing heterocycloalkyl group, each nitrogen must be protected by a protecting group, such as a benzyl. Removal of the R^5 protecting group is carried out under conditions appropriate for that particular protecting group in use which will not affect the R protecting group on the pyrrolo[2,3-d]pyrimidine ring. Removal of the R^5 protecting group, when benzyl, is carried out in an alcohol solvent, such as ethanol, in the presence of hydrogen and a catalyst, such as palladium hydroxide on carbon. The R^5 nitrogen containing heterocycloalkyl group so formed may be further reacted with a variety of different electrophiles of formula **II**. For urea formation, electrophiles of formula **II** such as isocyanates, carbamates and carbamoyl chlorides are reacted with the R^5 nitrogen of the heteroalkyl group in a solvent, such as acetonitrile or dimethylformamide, in the presence of a base, such as sodium or potassium carbonate, at a temperature between about 20°C to about 100 °C for a time period between about 24 hours to about 72 hours. For amide and sulfonamide formation, electrophiles of formula **II**, such as acylchlorides and sulfonyl chlorides, are reacted with the R^5 nitrogen of the heteroalkyl group in a solvent such as methylene chloride in the presence of a base such as pyridine at ambient temperatures for a time period between about 12 hours to about 24 hours. Amide formation may also be carried out by reacting a carboxylic acid with the heteroalkyl group in the presence of a carbodiimide such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide in a solvent such as methylene

chloride at ambient temperatures for 12-24 hours. For alkyl formation, electrophiles of formula **II**, such as α,β -unsaturated amides, acids, nitriles, esters, and α -halo amides, are reacted with the R⁵ nitrogen of the heteroalkyl group in a solvent such as methanol at ambient temperatures for a time period between about 12 hours to about 18 hours. Alkyl formation may also be carried out by reacting aldehydes with the heteroalkyl group in the presence of a reducing agent, such as sodium cyanoborohydride, in a solvent, such as methanol, at ambient temperature for a time period between about 12 hours to about 18 hours.

In reaction 3 of Scheme 1, removal of the protecting group from the compound of formula **XV**, wherein R is benzenesulfonyl, to give the corresponding compound of formula **I**, is carried out by treating **XV** with an alkali base, such as sodium hydroxide or potassium hydroxide, in an alcohol solvent, such as methanol or ethanol, or mixed solvents, such as alcohol/tetrahydrofuran or alcohol/water. The reaction is carried out at room temperature for a time period between about 15 minutes to about 1 hour, preferably 30 minutes. Removal of the protecting group from the compound of formula **XV**, wherein R is benzyl, is conducted by treating **XV** with sodium in ammonia at a temperature of about -78°C for a time period between about 15 minutes to about 1 hour.

In reaction 1 of Scheme 2, the 4-chloropyrrolo[2,3-d]pyrimidine compound of formula **XX** is converted to the corresponding 4-aminopyrrolo[2,3-d]pyrimidine compound of formula **XXIV**, according to the procedure described above in reaction 2 of Scheme 1.

In reaction 2 of Scheme 2, the 4-amino-5-halopyrrolo[2,3-d]pyrimidine compound of formula **XXIV**, wherein R is benzenesulfonate and Z is bromine or iodine, is converted to the corresponding compound of formula **XXIII** by reacting **XXIV** with (a) arylboronic acid, when R² is aryl, in an aprotic solvent, such as tetrahydrofuran or dioxane, in the presence of a catalytic quantity of palladium (0) at a temperature between about 50°C to about 100°C, preferably about 70°C, for a time period between about 2 hours to about 48 hours, preferably about 12 hours; (b) alkynes, when R² is alkynyl, in the presence of a catalytic quantity of copper (I) iodide and palladium (0), and a polar solvent, such as dimethylformamide, at room temperature, for a time period between about 1 hour to about 5 hours, preferably about 3 hours; and (c) alkenes or styrenes, when R² is vinyl or styrenyl, in the presence of a catalytic quantity of palladium in dimethylformamide, dioxane or tetrahydrofuran, at a temperature between about 80°C to about 100°C, preferably about 100°C, for a time period between about 2 hours to about 48 hours, preferably about 48 hours.

In reaction 3 of Scheme 2, the compound of formula **XXIII** is converted to the corresponding compound of formula **XV**, according to the procedure described above in reaction 3 of Preparation A.

In reaction 1 of Scheme 3, the compound of formula **XVII** is converted to the corresponding compound of formula **I**, according to the procedure described above in reaction 2 of Scheme 1.

In certain embodiments, the anti-arthritis agent is an NSAID (Non-Steroidal Anti-Inflammatory Drug) or COX-2 (Cyclo-Oxygenase 2) inhibitor selected from the group consisting of acetylsalicylic acid (e.g., Aspirin®) and other salicylates such as choline magnesium trisalicylate (e.g., Trilisate®), azapropazone, carprofen, celecoxib (e.g., Celebrex®, as described in U.S. Patent Nos. 5,466,823; 5,563,165; 5,760,068; 5,972,986); valdecoxib (e.g., Bextra®, as described in U.S. Patent Nos. 5,633,272; 6,441,014); rofecoxib (e.g., Vioxx®, as described in U.S. Patent Nos. 5,474,995; 5,691,374; 6,063,811; 6,239,173), diclofenac potassium, diclofenac sodium (e.g., Voltaren®, Cataflam®, as described in U.S. Patent Nos. 5,601,843; 5,698,225), diflunisal (e.g., Dolobid®), etodolac (e.g., Lodine®), fenbufen,

fenoprofen (e.g., Nalfon®), flufenamic acid, flurbiprofen (e.g., Ansaid®), ibuprofen (e.g., Advil®), indomethacin (e.g., Indocin®), ketoprofen (e.g., Orudis®), meclofenamate (e.g., Meclomen®), mefenamic acid (e.g., Ponstel®), meloxicam (e.g., Mobic®, as described in U.S. Patent No. 6,184,220), nabumetone (e.g., Relafen®), naproxen (e.g., Aleve®), naproxen sodium, oxaprozin (e.g., Daypro®), pirofen, suprofen, salsalate (e.g., Disalcid®, Salflex®), sulindac (e.g., Clinoril®), tenoxicam, tiaprofenic acid, and tolmetin (e.g., Tolectin®). Other suitable NSAIDs will be readily apparent to those of skill in the art given the benefit of the present disclosure.

In certain embodiments, the anti-arthritis agent is a glucocorticoid (oral, parenteral and/or intra-articular) selected from the group consisting of hydrocortisone acetate, hydrocortisone *tert* butyl acetate, dexamethasone acetate, dexamethasone *tert* butyl acetate, prednisolone, prednisolone acetate, prednisolone *tert* butyl acetate, prednisone, methylprednisolone methylprednisolone acetate, triamcinolone acetonide, triamcinolone diacetate, and triamcinolone hexacetate. Other suitable glucocorticoids will be readily apparent to those of skill in the art given the benefit of the present disclosure.

In certain embodiments, the anti-arthritis agent is a SCE DMARD (Disease Modifying Anti-Rheumatic Drug) selected from the group consisting of hydroxychloroquine (e.g., Plaquenil®), chloroquine, dapsone, sulfasalazine (e.g., Azulfidine®), methotrexate (e.g., Trexall®, Methotrex®), leflunomide (e.g., Arava®), azathioprine (e.g., Imuran®), D-penicillamine (e.g., Cuprimine®), cyclosporine A (e.g., Sandimmune®) and gold compounds including gold sodium thiomalate (e.g., Aurolate), aurothioglucose (e.g., Solganal), and auranofin (e.g., Ridauro®).

In certain embodiments, the anti-arthritis agent is a biologic DMARD selected from the group consisting of etanercept (e.g., Enbrel®), infliximab (e.g., Remicade®), adalimumab (e.g., Humira®), anakinra (e.g., Kineret®), abatacept (e.g., Orencia®), rituximab (e.g., Rituxan®), tocilizumab (e.g., Actemra®), and certolizumab pegol. Other suitable DMARDs (SCE or biologic) will be readily apparent to those of skill in the art given the benefit of the present disclosure.

In certain embodiments when the anti-arthritis agent is a DMARD, the anti-arthritis agent preferably is methotrexate (sometimes referred to herein as "MTX").

In certain embodiments, the anti-arthritis agent is an analgesic, such as acetaminophen (e.g., Tylenol®). Other suitable analgesics will be readily apparent to those of skill in the art given the benefit of the present disclosure.

In certain embodiments, the anti-arthritis agent is an opioid optionally in combination with acetaminophen selected from the group consisting of morphine, codeine, propoxyphene (e.g., Darvocet®), hydrocodone (e.g., Vicodin®), methadone (e.g., Dolophine®), hydromorphone (e.g., Dilaudid®), oxycodone (e.g., Percocet®), fentanyl, buprenorphine (e.g., Subutex®), and butorphanol (e.g., Stadol®). Other suitable opioids will be readily apparent to those of skill in the art given the benefit of the present disclosure.

In certain embodiments when the anti-arthritis agent administered in the pharmaceutical combination therapies or methods disclosed here is not a DMARD, such administration generally may be referred to by those of skill in the art as a monotherapy even though more than one pharmaceutical composition is being administered since the pharmaceutical compositions disclosed here comprising a

Janus Kinase inhibitors are considered a DMARD. Nevertheless, the term "pharmaceutical combination therapy" as used herein also includes such "monotherapies".

The compositions of the present disclosure may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers. The pharmaceutically acceptable carrier can be any such carrier known in the art including those described in, for example, Remington's Pharmaceutical Sciences, Mack Publishing Co., (A. R. Gennaro edit. 1985). Pharmaceutical compositions of the compounds presently disclosed may be prepared by conventional means known in the art including, for example, mixing at least one presently disclosed compound with a pharmaceutically acceptable carrier.

The compounds presently disclosed may also be formulated for sustained delivery according to methods well known to those of ordinary skill in the art. Examples of such formulations can be found in United States Patent Nos. 3,119,742, 3,492,397, 3,538,214, 4,060,598, and 4,173,626.

Thus, the active compounds of the disclosure may be formulated for oral, buccal, intranasal, parenteral (e.g., intravenous, intramuscular or subcutaneous), rectal administration, in a form suitable for administration by inhalation or insufflation, or the active compounds may be formulated for topical administration.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g., pregelatinized maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g., lactose, microcrystalline cellulose or calcium phosphate); lubricants (e.g., magnesium stearate, talc or silica); disintegrants (e.g., potato starch or sodium starch glycolate); or wetting agents (e.g., sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g., sorbitol syrup, methyl cellulose or hydrogenated edible fats); emulsifying agents (e.g., lecithin or acacia); non-aqueous vehicles (e.g., almond oil, oily esters or ethyl alcohol); and preservatives (e.g., methyl or propyl p-hydroxybenzoates or sorbic acid).

For buccal administration, the composition may take the form of tablets or lozenges formulated in conventional manner.

For intranasal administration or administration by inhalation, the active compounds of the disclosure are conveniently delivered in the form of a solution or suspension from a pump spray container that is squeezed or pumped by the patient or as an aerosol spray presentation from a pressurized container or a nebulizer, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurized container or nebulizer may contain a solution or suspension of the active compound. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the disclosure and a suitable powder base such as lactose or starch.

The active compounds of the disclosure may be formulated for parenteral administration by injection, including using conventional catheterization techniques or infusion. Formulations for injection

may be presented in unit dosage form, e.g., in ampules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulating agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form for reconstitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

The active compounds of the disclosure may also be formulated in rectal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

For topical administration, a presently disclosed compound may be formulated as an ointment or cream.

Typically, the Janus Kinase inhibitors and the anti-arthritis agents are administered in a therapeutically effective amount in the pharmaceutical combination therapies and associated methods disclosed herein, the amount of which is readily apparent to those of skill in the art to achieve the desired pharmacological and/or physiological effect. In certain embodiments, the Janus Kinase inhibitor or a pharmaceutically acceptable salt thereof (sometimes referred to herein as "the active compounds") is administered in a dose of 0.1 to 1000 mg of the active ingredient per unit dose which could be administered, for example, 1 to 4 times per day. The dosage level can vary either between one or more dosing regimens or within the same dosing regimen. In certain embodiments where the Janus Kinase inhibitor or a pharmaceutically acceptable salt thereof is administered orally, the dose for the active compounds can be in a range from 1 to 50 mg BID (i.e., twice a day) or from 5 to 20 mg QD (i.e., daily), and preferably 1 mg BID, 2 mg BID, 3 mg BID, 4 mg BID, 5 mg BID, 6 mg BID, 7 mg BID, 8 mg BID, 9 mg BID, 10 mg BID, 11 mg BID, 12 mg BID, 13 mg BID, 14 mg BID, 15 mg BID, 20 mg BID, 25 mg BID, or 30 mg BID, and preferably 0.25 mg BID, 0.5 mg BID, 1 mg BID, 5 mg BID, 10 mg BID, 20 mg BID, and more preferably 1 mg BID, 3 mg BID, 5 mg BID, 15 mg BID, 20 mg QD.

In certain embodiments, the anti-arthritis agent (sometimes referred to herein as just "agent") is administered in a dose of 1 mg to 5 g (i.e., 5000 mg), e.g., 5 mg, 10 mg, 25 mg, 50 mg, 100 mg, 250 mg, 500 mg, 750 mg, 1000 mg, 1250 mg, 1500 mg, 1750 mg, 2000 mg, or combinations thereof. For each of the dosage amounts provided for the anti-arthritis agents, the agent can be dosed twice a day, daily, weekly, etc. as would be apparent to those of skill in the art, e.g., a prescribed amount. Methotrexate ("MTX") typically is dosed in a weekly amount of 5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg, 17.5 mg, 20 mg, 22.5 mg, and 25 mg. In certain embodiments, the dose of MTX is increased (i.e., titrated up), typically in 2.5 mg increments over time, e.g., from week to week, month to month, etc. depending, of course, on toxicity or lack of tolerability. In certain embodiments, the dose of MTX is decreased (i.e., titrated down) if the patient has excellent response or if dosed with another agent, such as a biological agent. In other embodiments, the dose of MTX is administered in a divided dose, such as 5 mg Q 12 hours x 3 doses on a weekly basis. Of course, other suitable dosage levels for the compounds of the disclosure and the anti-arthritis agents administered in a combination therapy will be readily apparent to those of skill in the art given the benefit of the present disclosure.

In certain embodiments in the pharmaceutical combination therapies disclosed herein, the active compounds are administered in a dose of 0.25 mg BID, and methotrexate is administered in a dose of 5 mg once weekly.

In certain embodiments in the pharmaceutical combination therapies disclosed herein, the active compounds are administered in a dose of 0.25 mg BID, and methotrexate is administered in a dose of 7.5 mg once weekly.

In certain embodiments in the pharmaceutical combination therapies disclosed herein, the active compounds are administered in a dose of 0.25 mg BID, and methotrexate is administered in a dose of 15 mg once weekly.

In certain embodiments in the pharmaceutical combination therapies disclosed herein, the active compounds are administered in a dose of 0.5 mg BID, and methotrexate is administered in a dose of 5 mg once weekly.

In certain embodiments in the pharmaceutical combination therapies disclosed herein, the active compounds are administered in a dose of 0.5 mg BID, and methotrexate is administered in a dose of 7.5 mg once weekly.

In certain embodiments in the pharmaceutical combination therapies disclosed herein, the active compounds are administered in a dose of 0.5 mg BID, and methotrexate is administered in a dose of 15 mg once weekly.

In certain embodiments in the pharmaceutical combination therapies disclosed herein, the active compounds are administered in a dose of 1 mg BID, and methotrexate is administered in a dose of 5 mg once weekly.

In certain embodiments in the pharmaceutical combination therapies disclosed herein, the active compounds are administered in a dose of 1 mg BID, and methotrexate is administered in a dose of 7.5 mg once weekly.

In certain embodiments in the pharmaceutical combination therapies disclosed herein, the active compounds are administered in a dose of 1 mg BID, and methotrexate is administered in a dose of 15 mg once weekly.

In certain embodiments in the pharmaceutical combination therapies disclosed herein, the active compounds are administered in a dose of 3 mg BID, and methotrexate is administered in a dose of 5 mg once weekly.

In certain embodiments in the pharmaceutical combination therapies disclosed herein, the active compounds are administered in a dose of 3 mg BID, and methotrexate is administered in a dose of 7.5 mg once weekly.

In certain embodiments in the pharmaceutical combination therapies disclosed herein, the active compounds are administered in a dose of 3 mg BID, and methotrexate is administered in a dose of 15 mg once weekly.

In certain embodiments in the pharmaceutical combination therapies disclosed herein, the active compounds are administered in a dose of 5 mg BID, and methotrexate is administered in a dose of 5 mg once weekly.

In certain embodiments in the pharmaceutical combination therapies disclosed herein, the active compounds are administered in a dose of 5 mg BID, and methotrexate is administered in a dose of 7.5 mg once weekly.

In certain embodiments in the pharmaceutical combination therapies disclosed herein, the active compounds are administered in a dose of 5 mg BID, and methotrexate is administered in a dose of 15 mg once weekly.

In certain embodiments in the pharmaceutical combination therapies disclosed herein, the active compounds are administered in a dose of 10 mg BID, and methotrexate is administered in a dose of 5 mg once weekly.

In certain embodiments in the pharmaceutical combination therapies disclosed herein, the active compounds are administered in a dose of 10 mg BID, and methotrexate is administered in a dose of 7.5 mg once weekly.

In certain embodiments in the pharmaceutical combination therapies disclosed herein, the active compounds are administered in a dose of 10 mg BID, and methotrexate is administered in a dose of 15 mg once weekly.

In certain embodiments in the pharmaceutical combination therapies disclosed herein, the active compounds are administered in a dose of 15 mg BID, and methotrexate is administered in a dose of 5 mg once weekly.

In certain embodiments in the pharmaceutical combination therapies disclosed herein, the active compounds are administered in a dose of 15 mg BID, and methotrexate is administered in a dose of 7.5 mg once weekly.

In certain embodiments in the pharmaceutical combination therapies disclosed herein, the active compounds are administered in a dose of 15 mg BID, and methotrexate is administered in a dose of 15 mg once weekly.

In certain embodiments in the pharmaceutical combination therapies disclosed herein, the active compounds are administered in a dose of 5 mg QD, and methotrexate is administered in a dose of 5 mg once weekly.

In certain embodiments in the pharmaceutical combination therapies disclosed herein, the active compounds are administered in a dose of 5 mg QD, and methotrexate is administered in a dose of 7.5 mg once weekly.

In certain embodiments in the pharmaceutical combination therapies disclosed herein, the active compounds are administered in a dose of 5 mg QD, and methotrexate is administered in a dose of 15 mg once weekly.

In certain embodiments in the pharmaceutical combination therapies disclosed herein, the active compounds are administered in a dose of 10 mg QD, and methotrexate is administered in a dose of 5 mg once weekly.

In certain embodiments in the pharmaceutical combination therapies disclosed herein, the active compounds are administered in a dose of 10 mg QD, and methotrexate is administered in a dose of 7.5 mg once weekly.

In certain embodiments in the pharmaceutical combination therapies disclosed herein, the active compounds are administered in a dose of 10 mg QD, and methotrexate is administered in a dose of 15 mg once weekly.

In certain embodiments in the pharmaceutical combination therapies disclosed herein, the active compounds are administered in a dose of 20 mg QD, and methotrexate is administered in a dose of 5 mg once weekly.

In certain embodiments in the pharmaceutical combination therapies disclosed herein, the active compounds are administered in a dose of 20 mg QD, and methotrexate is administered in a dose of 7.5 mg once weekly.

In certain embodiments in the pharmaceutical combination therapies disclosed herein, the active compounds are administered in a dose of 20 mg QD, and methotrexate is administered in a dose of 15 mg once weekly.

Aerosol formulations in the average adult human are preferably arranged so that each metered dose or "puff" of aerosol contains 20 µg to 1000 µg of the compound of the disclosure. The overall daily dose with an aerosol will be within the range 0.1 mg to 1000 mg. Administration may be several times daily, for example 2, 3, 4 or 8 times, giving for example, 1, 2 or 3 doses each time.

The ability of the compounds of formula I or their pharmaceutically acceptable salts to inhibit Janus Kinase 3 and, consequently, demonstrate their effectiveness for treating disorders or conditions characterized by Janus Kinase 3 is shown by the following in vitro assay tests.

Biological Assay

JAK3 (JH1:GST) Enzymatic Assay

The JAK3 kinase assay utilizes a protein expressed in baculovirus-infected SF9 cells (a fusion protein of GST and the catalytic domain of human JAK3) purified by affinity chromatography on glutathione-Sepharose. The substrate for the reaction is poly-Glutamic acid-Tyrosine (PGT (4:1), Sigma catalog # P0275), coated onto Nunc Maxi Sorp plates at 100 µg/ml overnight at 37°C. The morning after coating, the plates are washed three times and JAK3 is added to the wells containing 100 µl of kinase buffer (50 mM HEPES, pH 7.3, 125 mM NaCl, 24 mM MgCl₂) + 0.2 uM ATP + 1 mM Na orthovanadate.) The reaction proceeds for 30 minutes at room temperature and the plates is washed three more times. The level of phosphorylated tyrosine in a given well is quantitated by standard ELISA assay utilizing an anti-phosphotyrosine antibody (ICN PY20, cat. #69-151-1).

Inhibition of Human IL-2 Dependent T-Cell Blast Proliferation

This screen measures the inhibitory effect of compounds on IL-2 dependent T-Cell blast proliferation *in vitro*. Since signaling through the IL-2 receptor requires JAK-3, cell active inhibitors of JAK-3 should inhibit IL-2 dependent T-Cell blast proliferation.

The cells for this assay are isolated from fresh human blood. After separation of the mononuclear cells using Accuspin System-Histopaque-1077 (Sigma # A7054), primary human T-Cells are isolated by negative selection using Lympho-Kwik T (One Lambda, Inc., Cat # LK-50T). T-Cells are cultured at 1-2 x 10⁶/ml in Media (RPMI + 10% heat-inactivated fetal calf serum (Hyclone Cat # A-1111-L) + 1% Penicillin/Streptomycin (Gibco)) and induce to proliferate by the addition of 10ug/ml PHA (Murex Diagnostics, Cat # HA 16). After 3 days at 37°C in 5% CO₂, cells are washed 3 times in Media, resuspended to a density of 1-2 x 10⁶ cells/ml in Media plus 100 Units/ml of human recombinant IL-2 (R&D Systems, Cat # 202-IL). After 1 week the cells are IL-2 dependent and can be maintained for up to 3 weeks by feeding twice weekly with equal volumes of Media + 100 Units/ml of IL-2.

To assay for a test compounds ability to inhibit IL-2 dependent T-Cell proliferation, IL-2 dependent cells are washed 3 times, resuspended in media and then plated (50,000 cells/well/0.1ml) in a Flat-bottom 96-well microtiter plate (Falcon # 353075). From a 10 mM stock of test compound in DMSO, serial 2-fold dilutions of compound are added in triplicate wells starting at 10 μ M. After one hour, 10 Units/ml of IL-2 is added to each test well. Plates are then incubated at 37°C, 5% CO₂ for 72 hours. Plates are then pulsed with ³H-thymidine (0.5 μ Ci/well) (NEN Cat # NET-027A), and incubated an additional 18 hours. Culture plates are then harvested with a 96-well plate harvester and the amount of ³H-thymidine incorporated into proliferating cells is determined by counting on a Packard Top Count scintillation counter. Data is analyzed by plotting the % inhibition of proliferation verses the concentration of test compound. An IC₅₀ value (μ M) is determined from this plot.

EXAMPLES

A Randomized, Double-Blind, Placebo-Controlled Trial of 3 Dose Levels of 3-[(3R,4R)-4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl]-3-oxo-propionitrile Versus Placebo in the Treatment of Active Rheumatoid Arthritis

3-[(3R,4R)-4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl]-3-oxo-propionitrile ("the Test Compound") is an orally active, moderately selective inhibitor of JAK3 which has demonstrated efficacy in rodent models of inflammatory arthritis and subjects with psoriasis. This study was designed to compare the efficacy, safety, tolerability and effects on health and functional status of 3 dose levels of the Test Compound versus placebo, administered for 6 weeks, with 6 weeks post-dosing follow-up, to subjects with moderate to severe active rheumatoid arthritis ("RA").

Subjects were enrolled if they had had an inadequate response to, or had discontinued for unacceptable toxicity, methotrexate or a TNF inhibitor, had discontinued all DMARD or biologic anti-rheumatic therapies and presented with at least 9 painful / tender joints, 6 swollen joints and evidence of systemic inflammation. They were randomized 1:1:1:1 to placebo, the Test Compound 5 mg BID, 15 mg BID or 30 mg BID. Background NSAIDs, coxibs, low-dose glucocorticoids and analgesics were allowed.

RESULTS

Two hundred sixty four subjects were randomized, and all received at least one dose of the Test Compound.

Test Compound Treatment (BID)	(Randomized)	Week 6 Percent Responders				Number Withdrawn		
		ACR 20	ACR 50	ACR 70	Improved HAQ-DI	Due to LOE	Due to AE	Any
Placebo	(N=65)	29%	6%	3%	31%	12%	2%	26%
5 mg	(N=61)	70%	33%	13%	57%	2%	2%	5%
15 mg	(N=69)	81%	54%	22%	71%	1%	4%	13%
30 mg	(N=69)	77%	51%	28%	70%	1%	7%	25%

ACR 20 at Week 6 is the primary analysis. Improvement in the HAQ-DI is defined as at least 0.3 units. Missing data were replaced with the last observation carried forward. All p values < 0.05 comparing Test Compound groups to placebo. LOE = "Lack of Efficacy" AE = adverse event related to study drug (Withdrawals were not compared statistically.)

Adverse events increased dose-dependently and the most commonly reported were headache and nausea. Neutrophil counts decreased dose dependently, with counts $\leq 1000 / \text{mm}^3$

observed in 1 subject in the 5 mg BID and 2 subjects in the 30 mg BID dose groups. Infection rates appeared increased in the 15 and 30 mg BID (30.4% each) compared to placebo dose group (26.2% of subjects), but no opportunistic infections occurred. Dose dependent increases in both LDL and HDL cholesterol, without changes in the LDL / HDL ratio, and reversible increases in mean serum creatinine, of 0.04 - 0.06 mg/dL, were also observed.

CONCLUSIONS

All 3 dose levels of the Test Compound were highly efficacious, compared to placebo, in the treatment of signs and symptoms of RA, beginning at week 1 and sustained greater than or equal to 6 weeks. Dose levels of 15 mg BID and below also appeared safe and generally well tolerated.

A Phase 1, Open Label Study Of The Pharmacokinetics Of Multiple Doses Of Oral 3-((3R,4R)-4-Methyl-3-[Methyl-(7H-Pyrrolo[2,3-D]Pyrimidin-4-Yl)-Amino]-Piperidin-1-Yl)-3-Oxo-Propionitrile And Single Doses Of Oral Methotrexate In Rheumatoid Arthritis Subjects

STUDY OBJECTIVES

- To estimate the effects of MTX on the pharmacokinetics of 3-((3R,4R)-4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxo-propionitrile, the Test Compound, when administered to subjects with RA;
- To estimate the effects of multiple doses of the Test Compound (30 mg Q 12 h) on the pharmacokinetics of MTX;
- To evaluate the short-term safety and tolerability of co-administration of the Test Compound (30 mg Q 12 h) and MTX.

Twelve subjects (eight female/four male) between 18 and 65 years of age, inclusive, with a diagnosis of rheumatoid arthritis and satisfying all entry criteria, entered into the study.

This was an open-label, non-randomized, fixed sequence, drug-drug interaction study. Subjects were admitted on Day 0. On the morning of Day 1, subjects received their weekly-individualized MTX dose after an overnight fast and 2 hours before the first meal; MTX blood PK samples were collected for 48 hours through Day 3. On Day 3, after the last MTX blood PK sample was collected, through Day 6, subjects received 30 mg of the Test Compound Q 12 h. On Day 6, full 12-hour Test Compound blood PK samples were collected. On Day 7, subjects received their weekly-individualized MTX dose co-administered with a 30-mg dose of the Test Compound, followed by collection of complete 48-hour Test Compound and MTX blood PK samples. Each subject participated for a total of approximately 14 days; and remained under supervision from Day 0 until discharge on Day 9. Subjects were discharged after the last pharmacokinetic blood sample was obtained on Day 9, but were required to return for a follow-up visit which was scheduled before the subject's next weekly MTX dose (approximately Days 11-13).

Subjects were assigned to the following treatments as indicated below:

Day 1	Day 2	Days 3-6	Day 7	Days 8 & 9
MTX individual treatment	No Treatment	Test Compound 30 mg Q 12 h	Test Compound 30 mg (morning dose only) PLUS	No treatment

single dose		MTX individual single dose	
-------------	--	----------------------------	--

Multiple dose pharmacokinetic parameters were calculated where possible for plasma concentrations of oral dose Test Compound following Study Days 6 & 7. Single dose pharmacokinetic parameters were calculated where possible for plasma concentrations of oral dose MTX following Study Days 1 & 7. The pharmacokinetic parameters were defined as the following: area under the plasma concentration time-curve from time 0 to the last observed time point (last) after dosing [AUC_{last}], area under the plasma concentration time-curve from time 0 to 12 hours postdose (AUC_{12}); the maximum observed concentration at steady state (C_{max}); the time to maximum observed concentration at steady state (T_{max}). Point and interval estimates of the pharmacokinetic parameters [AUC and C_{max}] were made. For interval estimates, the 90% confidence intervals (CI) were constructed. The data are presented in graphical and/or tabular form and summarized descriptively.

Matrix	PK Parameter	Analysis Scale	Test Compound	MTX
Plasma	AUC_{12}	ln	A, D	-
	AUC_{last}	ln	-	A, D
	C_{max}	ln	A, D	A, D
	T_{max}	R	A, D	A, D
	$t_{1/2}$	R	A, D	A, D
	CL/F	ln	A, D	A, D
Urine	Ae_{0-24}	ln	A, D	A, D
	CL_R	ln	A, D	A, D

Key; A=analyzed using statistical model D=displayed with descriptive statistics ln=natural-log transformed
R=raw (untransformed) *=if data permits

Whole blood samples (5 mL each, sufficient to provide a minimum of 2.0 mL plasma) were collected into appropriately labeled tubes containing sodium heparin at the following times:

PK Sampling Scheme

Study Day	MTX	Test Compound
1	0 (predose) and 30 minutes and at 1, 1.5, 2, 2.5, 3, 4, 6, 8 and 12 hours postdose	0 (predose)
2	24 hours post Day 1 dosing	
3	48 hours post Day 1 dosing (predose Test Compound)	
6		0 (predose), 15 and 30 minutes and at 1, 2, 3, 4, 8 and 12 hours postdose (the 12-hour sample must be taken prior to the evening dose)
7	0 (predose) and 30 minutes and at 1, 1.5, 2, 2.5, 3, 4, 6, 8 and 12 hours postdose	0 (predose), 15 and 30 minutes and at 1, 2, 3, 4, 8 and 12 hours postdose
8	24 hours post Day 7 dosing	24 hours post Day 7 dosing
9	48 hours post Day 7 dosing	48 hours post Day 7 dosing

All efforts were made to obtain the pharmacokinetic samples at the exact nominal time relative to dosing. However, samples obtained within 10% of the nominal time (e.g., within 3 minutes of a 30-minute sample) from dosing were not captured as a protocol deviation, as long as the exact time of the sample collection was noted on the source document and data collection tool (e.g., CRF).

Pharmacokinetic (PK)

Subjects included in the statistical analysis of pharmacokinetic parameters had at least one pharmacokinetic parameter of interest. Analysis sets might contain different numbers of subjects for different pharmacokinetic parameters based on the availability of data.

For the parameters AUC_{12} , AUC_{last} , C_{max} , CL/F , CL_{renal} and Ae_{24} a statistical analyses was performed to estimate the ratio (Test/Reference) of adjusted geometric means and the associated 90% confidence interval will be presented. Likewise, for the parameters T_{max} and $t_{1/2}$ statistical analyses to estimate the difference (Test-Reference) of medians or adjusted means respectively and the associated 90% confidence interval were presented. For each analyte, natural-log transformed parameters (AUC_{12} , AUC_{last} , C_{max} , CL/F , CL_{renal} and Ae_{24}) and untransformed parameters ($t_{1/2}$) were analyzed with a mixed effects model with treatment considered a fixed effect and subject considered a random effect. Estimates of adjusted mean differences (Test-Reference) and corresponding 90% confidence intervals were estimated from this model. For AUC_{12} , AUC_{last} , C_{max} , CL/F , CL_{renal} and Ae_{24} , the adjusted mean difference and 90% confidence limits for the difference were exponentiated to derive estimates of the ratio of adjusted geometric means (Test/Reference) and the 90% confidence interval for this ratio. Each analyte in co-administration with the other compound was the Test Compound and each analyte administered alone was the Reference.

The mixed effects model was implemented using SAS Proc Mixed, with REML estimation method, variance-covariance structure of compound symmetry and Satterthwaite degrees of freedom algorithm.

Nonparametric analyses were performed on untransformed (raw) PK parameter T_{max} within each analyte. SAS[®]/Proc-StatXact 5[®] procedure Paired was used for these analyses. Point estimates of the median differences between treatments (Hodges-Lehmann), and exact 90% CI around the differences (Lehmann) were constructed.

For the parameters AUC_{12} , AUC_{last} , C_{max} , T_{max} , $t_{1/2}$, oral clearance CL/F , amount excreted in urine (Ae_{24}) and renal clearance (CL_{renal}), descriptive statistics (N, mean, median, CV%, standard deviation, minimum and maximum) summarizing data by analyte, were provided in the study report. In addition to the above descriptive statistics, the geometric means were provided for AUC_{12} , AUC_{last} , C_{max} , CL/F , CL_{renal} and Ae_{24} . Graphical presentation of concentration by time was provided for each analyte.

RESULTS

Data Sets Analyzed (Subject Inclusions/Exclusions):

All 12 subjects who received study medication were included in the pharmacokinetic, adverse event and laboratory analyses.

Statistical and Analytical Issues:

The SAS software program Version 8.2 was used to perform the data summarization and statistical analyses.

Summary of Statistical Findings PK Parameters:

Test Compound:

A summary of the results from the statistical analyses of the pharmacokinetic parameters of the Test Compound are provided in the following table.

Parameters	Test (T)	Reference (R)	Adjusted Geometric Means		Ratio (%) T/R	90% Confidence Interval (%)	
			Test	Reference		Lower	Upper
AUC ₁₂ (ng·h/mL)	C	B	1344.12	1304.20	103.06	99.00	107.29
C _{max} (ng/mL)	C	B	374.26	364.39	102.71	93.79	112.47
CL/F (L/hr)	C	B	19673.5	21989.1	89.47	82.92	96.53
Ae ₁₂ (mg)	C	B	6.25	6.32	98.86	87.90	111.19
CL _{renal} (L/hr)	C	B	4647.20	4844.60	95.93	86.07	106.91
			Adjusted Means		Difference T-R		
t _{1/2} (hr)	C	B	2.70	2.57		-0.02	0.28
			Medians				
T _{max} (hr)	C	B	1.00	1.00		-0.25	0.25

Treatment labels: B = Test Compound 30 mg; C = Test Compound 30 mg + MTX individualized dosing.

Steady-state Test Compound 30 mg mean exposure following co-administration with single dose MTX (individualized dosing) was unaffected, compared to that with steady-state Test Compound 30 mg administered alone. All 90% confidence intervals for log-transformed data were wholly within the 80-125% no effect limit. Similarly, all 90% confidence intervals for both time parameters contained zero.

Methotrexate (MTX):

A summary of the results from the statistical analyses of the pharmacokinetic parameters of MTX are provided in the following table.

Parameters	Test (T)	Reference (R)	Adjusted Geometric Means		Ratio (%) T/R	90% Confidence Interval (%)	
			Test	Reference		Lower	Upper
AUC ₂₄ (ng·h/mL)	C	A	1489.14	1661.30	89.64	76.92	104.46
C _{max} (ng/mL)	C	A	408.36	468.06	87.25	76.03	100.12
CL/F (L/hr)	C	A	10067.0	9217.12	109.22	93.35	127.79
Ae ₂₄ (mg)	C	A	7.32	9.24	79.18	56.13	111.69
CL _{renal} (L/hr)	C	A	4813.95	5271.06	91.33	69.49	120.03
			Adjusted Means		Difference T-R		
t _{1/2} (hr)	C	A	3.00	2.64		0.24	0.50
			Medians				
T _{max} (hr)	C	A	1.25	1.00		0.00	0.25

Treatment labels: A = MTX individualized dosing; C = Test Compound 30 mg + MTX individualized dosing.

Single dose MTX mean exposure following co-administration with steady state Test Compound 30 mg was decreased by ~10% for AUC₂₄ and ~13% for C_{max} compared to that with single dose MTX administered alone. Similarly, AE₂₄ and CL_{renal} were decreased by ~21% and ~9% respectively, while CL/F increased by ~9% and t_{1/2} was delayed by 0.37 hours. T_{max} appeared to be unaffected. All 90% confidence intervals of the log-transformed PK parameters were not entirely contained within the 80-125% no effect limit and the 90% confidence interval did not contain zero.

There were no deaths or serious adverse events reported from this study. No subjects discontinued prematurely from the study due to adverse events. Two (2) subjects had study drug temporarily discontinued due to non-treatment related adverse events.

All treatment-emergent related adverse events were considered to be mild in severity with the exception of two moderate episodes in one subject (tension headache and migraine headache).

All observed or volunteered adverse events occurring during treatment or within the lag time [(infinite) days] after the last day of treatment were tabulated using the MedDRA dictionary according to treatment-emergence, body system, preferred term, and investigator assessment of severity (mild, moderate, or severe) and causality. Treatment-emergent events were defined as 1) those events that were not present at baseline or during the baseline period and which occurred after treatment with study drug began and 2) events that were present at baseline but increased in severity after treatment with study drug began. If more than one severity was given for any one adverse event for an individual subject, the greatest severity was used in summary tables; missing severities were classified as severe.

Clinical Laboratory Tests:

Laboratory test results collected during treatment or within the lag time [(infinite) days] after the last day of treatment were assessed for abnormalities that were potentially clinically significant. A laboratory test that resulted in discontinuation from treatment or a change in study drug was recorded as an adverse event, at which time then the relationship to treatment was assessed by the investigator. Laboratory abnormalities were notable only for one subject with an increase in ALT on Day 1 (MTX alone) which was sustained through study but resolved back to normal range during follow-up.

Vital Signs:

The majority of incidences on the categorical summary table of vital signs data of potential clinical concern occurred during the combination therapy [Test Compound (30 mg Q 12h) + MTX SD] as presented below.

Parameter	Criteria	Subject (Study Day)	Treatment
Supine Systolic Blood Pressure	≥ 30 mm Hg decrease from baseline	XXXXXXX4 (1)	MTX SD
Supine Systolic Blood Pressure	≥ 30 mm Hg decrease from baseline	XXXXXXX4 (7, 8, 9 & 11)	Combo
Supine Diastolic Blood Pressure	< 50 mm Hg	XXXXXXX5 (5 & 6)	CP alone BID
Supine Diastolic Blood Pressure	< 50 mm Hg	XXXXXXX5 (7)	Combo
Supine Diastolic Blood Pressure	≥ 20 mm Hg decrease from baseline	XXXXXXX4 (11)	Combo
Supine Diastolic Blood Pressure	≥ 20 mm Hg decrease from baseline	XXXXXXX6 (7)	Combo
Supine Diastolic Blood Pressure	≥ 20 mm Hg increase from baseline	XXXXXXX8 (11)	Combo

Electrocardiograms:

There were no notable findings in ECG reports. There were moderate decreases in both systolic and diastolic blood pressure for 3 subjects during treatment with MTX and Test Compound in the combination therapy. Of these subjects, one subject also experienced a slight decrease in systolic (MTX alone) or diastolic (Test Compound alone). There was one subject with a slight increase in supine diastolic blood pressure during treatment with MTX and Test Compound in the combination therapy. Specifically, there were no subjects that exhibited a QT or QTcF greater than 500 msec, or a change from baseline of QTcB or QTcF greater than 60 msec in any of the treatment regimens. One Subject [Test Compound (30 mg Q12h) + MTX SD] experienced a QTcB of greater than 500 msec [~ 500 msec (Day

7)]. The same Subject experienced a greater than 30 msec increase from baseline in both QTcB and QTcF (~46 & ~33 msec respectively) while receiving MTX SD on Day 1. The same Subject also experienced a greater than 30 msec increase from baseline in both QTcB (~37 msec) while receiving Test Compound (30 mg q12h) on Day 3.

CONCLUSIONS

Review of PK data on the 12 subjects showed that there was no effect of MTX co-administration on the AUC(0-12) or C_{max} of the Test Compound. However, Test Compound co-administration reduces MTX AUC₂₄ by ~ 10% and C_{max} ~13% compared to that with single dose MTX administered alone. Steady state exposure of Test Compound (30 mg) in a pharmaceutical combination therapy with single dose MTX was unaffected, compared to steady state Test Compound (30 mg) administered alone. Single dose exposure of MTX in a pharmaceutical combination therapy with steady state Test Compound (30 mg) was decreased by ~10% for AUC₂₄ and ~13% for C_{max}, compared to MTX administered alone. Treatments of steady state Test Compound (30 mg) and single dose MTX administered alone as well as administered in a pharmaceutical combination therapy were generally very well tolerated.

The following Examples illustrate the preparation of the compounds of the present disclosure but it is not limited to the details thereof. Melting points are uncorrected. NMR data are reported in parts per million (δ) and are referenced to the deuterium lock signal from the sample solvent (deuteriochloroform unless otherwise specified). Commercial reagents were utilized without further purification. THF refers to tetrahydrofuran. DMF refers to N,N-dimethylformamide. Low Resolution Mass Spectra (LRMS) were recorded on either a Hewlett Packard 5989®, utilizing chemical ionization (ammonium), or a Fisons (or Micro Mass) Atmospheric Pressure Chemical Ionization (APCI) platform which uses a 50/50 mixture of acetonitrile/water with 0.1% formic acid as the ionizing agent. Room or ambient temperature refers to 20-25°C. The IC₅₀ values reported below were obtained from the JAK3 (JH1:GST) Enzymatic Assay described above (with the exception of Example 33) and are the result of multiple experiments (n=4 to 6, wherein n=1 represents a triplicate of runs).

Example 1

1-{4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-ethanone

Method A

(1-Benzyl-4-methyl-piperidin-3-yl)-methyl-amine

To a stirred solution of 1-benzyl-4-methyl-piperidin-3-one (2.3 grams, 11.5 mmol), prepared by the methods of Iorio, M.A. and Damia, G., Tetrahedron, **26**, 5519 (1970) and Grieco *et al.*, Journal of the American Chemical Society, **107**, 1768 (1985), (modified using 5% methanol as a co-solvent), both references are incorporated by reference in their entirety, dissolved in 23 mL of 2 M methylamine in tetrahydrofuran was added 1.4 mL (23 mmol) of acetic acid and the resulting mixture stirred in a sealed tube for 16 hours at room temperature. Triacetoxy sodium borohydride (4.9 grams, 23 mmol) was added and the new mixture stirred at room temperature in a sealed tube for 24 h, at which time, the reaction was quenched upon addition of 1 N sodium hydroxide (50 mL). The reaction mixture was then extracted 3 x

80 mL with ether, the combined ether layers dried over sodium sulfate (Na_2SO_4) and concentrated to dryness in vacuo affording 1.7 grams (69%) of the title compound as a white solid. LRMS: 219.1 (M+1).

Method B

(1-Benzyl-4-methyl-piperidin-3-yl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

A solution of 4-chloropyrrolo[2,3-d]pyrimidine (2.4 grams, 15.9 mmol), prepared by the method of Davoll, J. Am. Chem. Soc., **82**, 131 (1960), which is incorporated by reference in its entirety, and the product from Method A (1.7 grams, 7.95 mmol) dissolved in 2 equivalents of triethylamine was heated in a sealed tube at 100 °C for 3 days. Following cooling to room temperature and concentration under reduced pressure, the residue was purified by flash chromatography (silica; 3% methanol in dichloromethane) affording 1.3 grams (50%) of the title compound as a colorless oil. LRMS: 336.1 (M+1).

Method C

Methyl-(4-methyl-piperidin-3-yl)-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

To the product from Method B (0.7 grams, 2.19 mmol) dissolved in 15 mL of ethanol was added 1.5 mL of 2 N hydrochloric acid and the reaction mixture degassed by nitrogen purge. To the reaction mixture was then added 0.5 grams of 20% palladium hydroxide on carbon (50% water) (Aldrich) and the resulting mixture shaken (Parr-Shaker) under a 50 psi atmosphere of hydrogen at room temperature for 2 days. The Celite filtered reaction mixture was concentrated to dryness in vacuo and the residue purified by flash chromatography (silica; 5% methanol in dichloromethane) affording 0.48 grams (90%) of the title compound. LRMS: 246.1 (M+1).

Method D

1-(4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-ethanone

To a stirred solution of the product from Method C (0.03 grams, 0.114 mmol) dissolved in 5 mL of 10:1 dichloromethane/pyridine was added (0.018 grams, 0.228 mmol) of acetylchloride and the resulting mixture stirred at room temperature for 18 hours. The reaction mixture was then partitioned between dichloromethane and saturated sodium bicarbonate (NaHCO_3). The organic layer was washed again with saturated NaHCO_3 , dried over sodium sulfate and concentrated to dryness in vacuo. The residue was purified by preparative thin layer chromatography (PTLC) (silica; 4% methanol in dichloromethane) affording 0.005 mg (15%) of the title compound as a colorless oil. LRMS: 288.1 (M+1). $\text{IC}_{50} = 0.1475 \mu\text{M}$.

The title compounds for examples 2-26 were prepared by a method analogous to that described in Example 1.

Example 2

[1-(2-Amino-ethanesulfonyl)-4-methyl-piperidin-3-yl]-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

[1-(2-Amino-ethanesulfonyl)-4-methyl-piperidin-3-yl]-methyl-amine. LRMS: 353. $\text{IC}_{50} = 0.103 \mu\text{M}$.

Example 3

(1-Ethanesulfonyl-4-methyl-piperidin-3-yl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

(1-Ethanesulfonyl-4-methyl-piperidin-3-yl)-methyl-amine. LRMS: 338. $\text{IC}_{50} = 0.1365 \mu\text{M}$.

Example 4**[1-(Butane-1-sulfonyl)-4-methyl-piperidin-3-yl]-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine**

[1-(Butane-1-sulfonyl)-4-methyl-piperidin-3-yl]-methyl-amine. LRMS: 366. $IC_{50} = 0.3725 \mu M$.

Example 5**4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-carboxylic acid isobutyl ester**

4-Methyl-3-methylamino-piperidine-1-carboxylic acid isobutyl ester. LRMS: 346. $IC_{50} = 0.5595 \mu M$.

Example 6**N-(2-{4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-sulfonyl}-ethyl)-propionamide**

N-[2-(4-Methyl-3-methylamino-piperidine-1-sulfonyl)-ethyl]-propionamide. LRMS: 409. $IC_{50} = 0.1915 \mu M$.

Example 7**(2-{4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-sulfonyl}-ethyl)-carbamic acid methyl ester**

[2-(4-Methyl-3-methylamino-piperidine-1-sulfonyl)-ethyl]-carbamic acid methyl ester. LRMS: 411. $IC_{50} = 0.0415 \mu M$.

Example 8**N-(2-{4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-sulfonyl}-ethyl)-isobutyramide**

N-[2-(4-Methyl-3-methylamino-piperidine-1-sulfonyl)-ethyl]-isobutyramide. LRMS: 423. $IC_{50} = 0.0485 \mu M$.

Example 9**(1-Methanesulfonyl-piperidin-3-yl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine**

(1-Methanesulfonyl-piperidin-3-yl)-methyl-amine. LRMS: 310. $IC_{50} = 0.346333333 \mu M$.

Example 10**(1-Ethanesulfonyl-piperidin-3-yl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine**

(1-Ethanesulfonyl-piperidin-3-yl)-methyl-amine. LRMS: 324. $IC_{50} = 0.6255 \mu M$.

Example 11**Methyl-[1-(propane-1-sulfonyl)-piperidin-3-yl]-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine**

(1-Propylsulfonyl-piperidin-3-yl)-methyl-amine. LRMS: 338. $IC_{50} = 0.4585 \mu M$.

Example 12**[1-(Butane-1-sulfonyl)-piperidin-3-yl]-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine**

(1-Butylsulfonyl-piperidin-3-yl)-methyl-amine. LRMS: 352. $IC_{50} = 0.4125 \mu M$.

Example 13**2,2-Dimethyl-N-(2-{4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-sulfonyl}-ethyl)-propionamide**

2,2-Dimethyl-N-[2-(4-methyl-3-methylamino-piperidine-1-sulfonyl)-ethyl]-propionamide. LRMS: 437. IC₅₀ = 0.788 µM.

Example 14**3-{4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-piperidin-1-yl}-3-oxo-propionitrile**

3-(4-Methyl-3-methylamino-piperidin-1-yl)-3-oxo-propionitrile. LRMS: 313. IC₅₀ = 0.0034 µM.

Example 15**(3-{4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-3-oxo-propyl)-carbamic acid tert-butyl ester**

[3-(4-Methyl-3-methylamino-piperidin-1-yl)-3-oxo-propyl]-carbamic acid tert-butyl ester. LRMS: 417. IC₅₀ = 0.5479 µM.

Example 16**Methyl-[4-methyl-1-(propane-1-sulfonyl)-piperidin-3-yl]-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine**

Methyl-[4-methyl-1-(propane-1-sulfonyl)-piperidin-3-yl]-amine. LRMS: 352. IC₅₀ = 0.0595 µM.

Example 17**3-Amino-1-{4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-propan-1-one**

3-Amino-1-(4-methyl-3-methylamino-piperidin-1-yl)-propan-1-one. LRMS: 317. IC₅₀ = 1.588 µM.

Example 18**2-Methoxy-1-{4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-ethanone**

2-Methoxy-1-(4-methyl-3-methylamino-piperidin-1-yl)-ethanone. LRMS: 318. IC₅₀ = 0.44333333 µM.

Example 19**2-Dimethylamino-1-{4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-ethanone**

2-Dimethylamino-1-(4-methyl-3-methylamino-piperidin-1-yl)-ethanone. LRMS: 331. IC₅₀ = 2.5465 µM.

Example 20**(3-{4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-3-oxo-propyl)-carbamic acid tert-butyl ester**

[3-(4-Methyl-3-methylamino-piperidin-1-yl)-3-oxo-propyl]-carbamic acid tert-butyl ester. LRMS: 417. IC₅₀ = 5.479 µM.

Example 21**3,3,3-Trifluoro-1-(4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-propan-1-one**

3,3,3-Trifluoro-1-(4-methyl-3-methylamino-piperidin-1-yl)-propan-1-one. LRMS: 356.3. IC_{50} = 0.019333333 μ M.

Example 22**N-(2-(4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-2-oxo-ethyl)-acetamide**

N-[2-(4-Methyl-3-methylamino-piperidin-1-yl)-2-oxo-ethyl]-acetamide. LRMS: 345. IC_{50} = 7.13033333 μ M.

Example 23**3-Ethoxy-1-(4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-propan-1-one**

3-Ethoxy-1-(4-methyl-3-methylamino-piperidin-1-yl)-propan-1-one. LRMS: 346. IC_{50} = 0.7686 μ M.

Example 24**4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-carboxylic acid methylamide**

4-Methyl-3-methylamino-piperidine-1-carboxylic acid methylamide. LRMS: 303. IC_{50} = 0.2355 μ M.

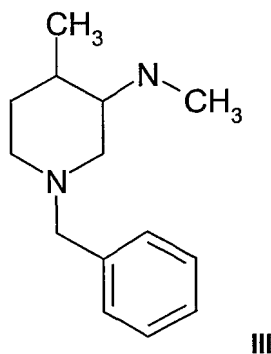
Example 25**4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-carboxylic acid diethylamide**

4-Methyl-3-methylamino-piperidine-1-carboxylic acid diethylamide. LRMS: 345. IC_{50} = 0.205 μ M.

Example 26**Methyl-[4-methyl-1-(2-methylamino-ethanesulfonyl)-piperidin-3-yl]-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine**

Methyl-[4-methyl-1-(2-methylamino-ethanesulfonyl)-piperidin-3-yl]-amine. LRMS: 367. IC_{50} = 1.124 μ M.

Examples 27-31 demonstrate resolution of the compound of formula III:



III

Example 27 (stable salt formation)**(1-benzyl-4-methylpiperidin-3-yl)-methylamine bishydrochloride**

To a solution of 23.4kg of (1-benzyl-4-methylpiperidin-3-yl)-methylamine in 10 liters of toluene and 120 liters of ethanol at 3°C was added 25 liters of 32% HCl in water, keeping the reaction temperature below 10°C. 100 liters of solvent was distilled off under partial vacuum, and 215 liters of ethyl acetate was added at 30°C. 210 liters of solvent was distilled off under partial vacuum, and a second 215 liters of ethyl acetate was added and another 210 liters of solvent was distilled off under partial vacuum. 111 liters of acetone was added at 35°C, the suspension was cooled to 0°C, and then the product, (1-benzyl-4-methylpiperidin-3-yl)-methylamine bishydrochloride, was filtered off and washed with 55 liters of acetone. The wet-cake was reslurried 3 times in ethanol (10 volume equivalents at reflux) to upgrade the diastomeric ratio of cis:trans from 91:9 to greater than 97:3. Total recovery was 19.4kg, 62% yield. ¹H NMR (CD₃OD, 400 MHz): δ 7.55 (m, 5H), 4.88 (s, 3H), 4.52 (d, J = 12.8 Hz, 1H), 4.45 (d, J = 12.8 Hz, 1H), 3.76 (m, 1H), 3.67 (m, 1H), 3.40-3.00 (m, 3H), 2.78 (s, 3H), 2.55 (m, 1H), 2.14 (m, 1H), 1.90 (m, 1H), 1.16 (d, J = 7.2 Hz, 3H)

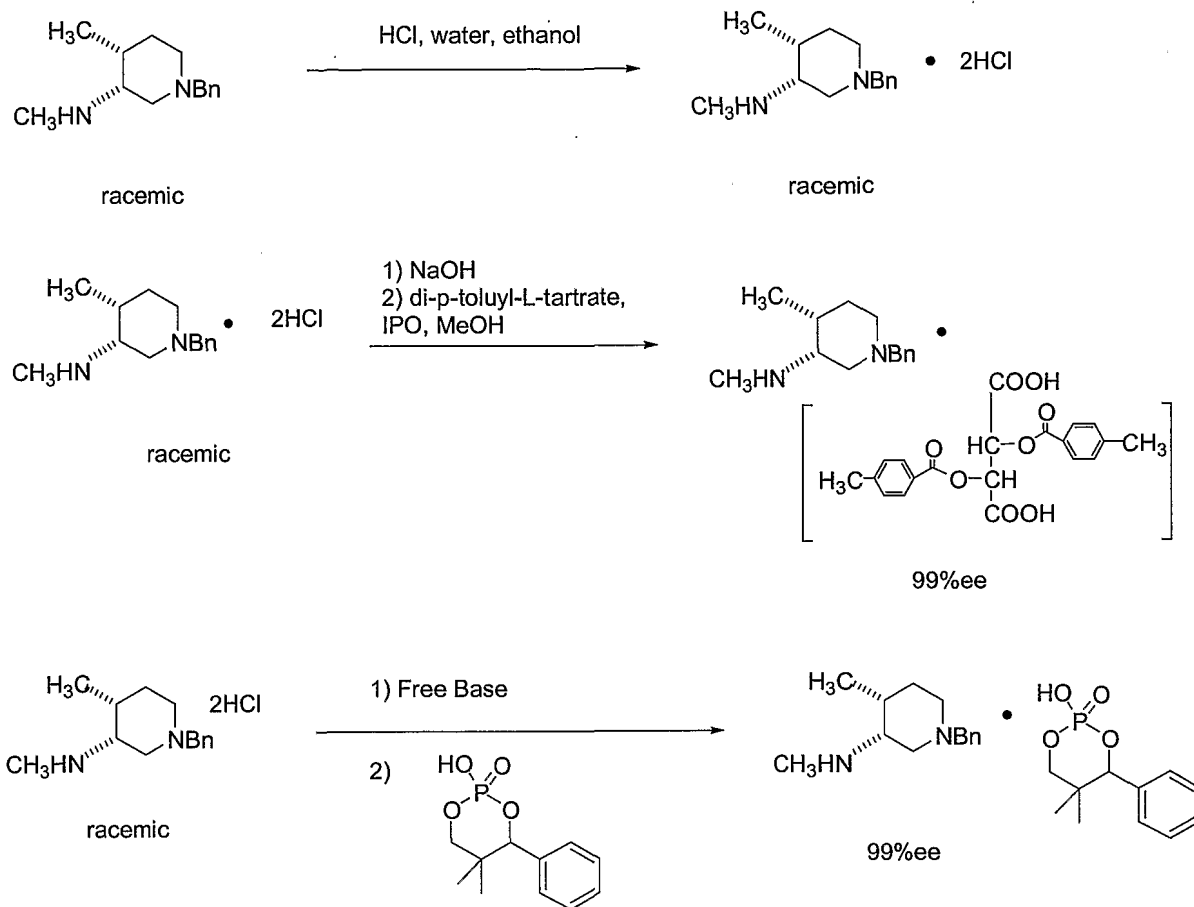
Example 28 (resolution)**bis[(1-benzyl-4-methylpiperidin-3-yl)-methylamine] di-p-toluyyl-L-tartrate**

To a solution of 9.5kg of (1-benzyl-4-methylpiperidin-3-yl)-methylamine bishydrochloride in 16 liters of water was added 33 liters of 2N sodium hydroxide. Solids precipitated from the mixture. The slurry was diluted with 43 liters of isopropanol and 11 liters of methanol to redissolve the solids. Di-p-toluyyl-L-tartaric acid (6.3kg) was added, with precipitation of solids. The slurry was heated to reflux to redissolve the solids, then slowly cooled to 72°C. Seeds of bis[(1-benzyl-4-methylpiperidin-3-yl)-methylamine] di-p-toluyyl-L-tartrate were added (180grams), and the hazy solution was slowly cooled to 15°C. The solids were filtered and washed with isopropanol to yield 5.9kg of bis[(1-benzyl-4-methylpiperidin-3-yl)-methylamine] di-p-toluyyl-L-tartrate in 44% yield. ¹H NMR (CD₃OD, 400 MHz): δ 8.04 (d, J = 8.4 Hz, 2H), 7.30 (m, 7H), 5.86 (s, 1H), 4.91 (s, 3H), 3.64 (d, J = 12.8 Hz, 1H), 3.41 (d, J = 12.8 Hz, 1H), 3.09 (s, 1H), 2.90 (m, 2H), 2.40 (s, 3H), 2.22 (m, 2H), 1.92 (m, 1H), 1.57 (m, 2H), 1.03 (d, J = 7.2 Hz, 3H)

Example 29 (phencyphos resolution)

To a solution of 6.83 grams (31.3 mmol) in 250 ml IPA and 10 ml water was added 7.57 g (+) phencyphos (31.3 mmol), and the mixture was heated to reflux in order to obtain a clear solution. At a temperature of approximately 65° C seeding crystals with an ee of 90% were added. Crystallization started within one hour and the mixture was allowed to reach room temperature overnight. Isolation afforded 6.85 g (47%) with an ee of 99%. The filtrate was concentrated, TBME, water and K₂CO₃ were added, and the layers separated. The organic layer was dried (Na₂SO₄) and the solvent evaporated. The resulting oil (3.99 grams) was dissolved in 200 ml IPA and 10 ml water and 4.4 grams (-) phencyphos was added. The mixture was heated to reflux and allowed to cool to room temperature overnight. This afforded 6 grams (41%) salt with an ee of 99.9+%. Analyses were performed on the free amine. The free amine was obtained by treatment of the salt with TBME, water and K₂CO₃.

The following schematically illustrate the methods of Examples 27 to 29 (wherein Bn is defined as benzyl (-CH₂-C₆H₅)):



Example 30

Sample processing:

A compound of formula III was filtered through a 0.2 um nylon 66 filter disc.

Procedure: (96% ethanol 4% water as solvent)

0.8711 grams of the compound of formula III, of the filtrate, was dissolved in 5.0 ml of a 96:4 ratio of ethanol/water. 1.544 grams of di-p-toluoyl-L-tartaric acid was added and the mixture was stirred to obtain a clear solution. The solution was allowed to stand at room temperature for approximately 4 hours. The resulting slurry was filtered onto Whatman #2 filter paper and washed with 4.0 ml of a 96:4 ratio of ethanol/water. The solids were air dried to give 0.488 grams of the diastereomer salt.

0.488 grams of the diastereomer salt was suspended in 50 ml of water then 50 ml of methylene chloride was added. The pH of the mixture was adjusted to approximately 9 using saturated sodium bicarbonate followed by 1.0N sodium hydroxide. Upon completion of the pH adjustment, the layers were separated and the methylene chloride layer was filtered through Whatman #2 filter paper. Solvents were then removed by reduced pressure evaporation to give a light orange colored oil. Weight not determined. This oil was evaluated by gas chromatography.

Analytical assay: 97.3% desired enantiomer by normalized area percent.

Example 31

Procedure: (100% ethanol as solvent)

0.8714 grams of (1-benzyl-4-methyl-piperidin-3-yl)-methyl-amine was dissolved in 5.0 ml of 200 proof ethanol. 1.544 grams of di-p-toluoyl-L-tartaric acid was added and the mixture was stirred to obtain a clear solution. The solution was allowed to stand at room temperature for approximately 4 hours. The resulting slurry was filtered onto Whatman #2 filter paper and washed with 4.0 ml of a 96:4 ratio of ethanol/water. The solids were air dried to give 0.628 grams of the diastereomer salt.

0.628 grams of the diastereomer salt was suspended in 50 ml of water then 50 ml of methylene chloride was added. The pH of the mixture was adjusted to approximately 9 using saturated sodium bicarbonate followed by 0.1N sodium hydroxide. Upon completion of the pH adjustment, the layers were separated and the methylene chloride layer was filtered through Whatman #2 filter paper. Solvents were then removed by reduced pressure evaporation to give a light yellow colored oil. Weight not determined. Evaluation of the oil provided the analytical assay: 90.5% desired enantiomer by normalized area percent.

Example 32

3-((3R, 4R)-4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxo-propionitrile

Method A

(3R, 4R)-(1-Benzyl-4-methyl-piperidin-3-yl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

4-Chloropyrrolo[2,3-d]pyrimidine (5.37 grams, 34.9 mmol), prepared by the method of Davoll, J. Am. Chem. Soc., 82, 131 (1960), which is incorporated by reference in its entirety, the product from Example 28 (6 grams, 27.5 mmol) and potassium carbonate (11.4 grams, 82.5 mmol) were combined in water (60 ml). The slurry was heated at reflux for 90 hrs. The mixture was cooled to 90°C and toluene (60 ml) was added. The biphasic mixture was filtered through filter aid and the layers were separated. The aqueous layer was extracted with toluene. The combined toluene layers were washed with 1N NaOH, treated with activated charcoal, and filtered through filter aid. The toluene was evaporated in vacuo and the residue crystallized from a 1:1 mixture of isopropyl acetate and hexanes to afford 5 grams of an off-white solid; 54% yield. LRMS: 336.1 (M+1).

Method B

Methyl-((3R, 4R)-4-methyl-piperidin-3-yl)-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

To the product from Method A (0.7 grams, 2.19 mmol) dissolved in 15 mL of ethanol was added 1.5 mL of 2 N hydrochloric acid and the reaction mixture degassed by nitrogen purge. To the reaction mixture was then added 0.5 grams of 20% palladium hydroxide on carbon (50% water) (Aldrich) and the resulting mixture shaken (Parr-Shaker) under a 50 psi atmosphere of hydrogen at room temperature for 2 days. The Celite filtered reaction mixture was concentrated to dryness in vacuo and the residue purified by flash chromatography (silica; 5% methanol in dichloromethane) affording 0.48 grams (90%) of the title compound. LRMS: 246.1 (M+1).

Method C

3-((3R, 4R)-4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxo-propionitrile

To a stirred solution of the product from Method B (1.0 g) dissolved in 30 mL of ethanol was added 0.82 g of cyano-acetic acid 2,5-dioxo-pyrrolidin-1-yl ester and the resulting mixture stirred at room temperature for 2 h. The reaction mixture was filtered through Celite® and concentrated in vacuo. The residue was redissolved in dichloromethane, washed with saturated, aqueous sodium bicarbonate, dried over sodium sulfate, filtered and concentrated to dryness in vacuo affording 1.1 g (86%) of the title compound as a yellow foam. LRMS: 313 (M + 1). IC₅₀ = 0.0024 µM.

Example 33

1-((3R, 4R)-4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-ethanone

To a stirred solution of the product from Method B (0.03 grams, 0.114 mmol) dissolved in 5 mL of 10:1 dichloromethane/pyridine was added (0.018 grams, 0.228 mmol) of acetylchloride and the resulting mixture stirred at room temperature for 18 hours. The reaction mixture was then partitioned between dichloromethane and saturated sodium bicarbonate (NaHCO₃). The organic layer was washed again with saturated NaHCO₃, dried over sodium sulfate and concentrated to dryness in vacuo. The residue was purified by preparative thin layer chromatography (PTLC) (silica; 4% methanol in dichloromethane) affording 0.005 g (15%) of the title compound as a colorless oil. LRMS (M+1): 288.2. IC₅₀ = 0.523 µM.

The title compounds for Examples 34-35 and 47 were prepared by a method analogous to that described in Example 33. The title compounds for Examples 36-46 and 48-57 are prepared by a method analogous to that described in Example 33.

Example 34

(3R,4R)-[1-(2-Amino-ethanesulfonyl)-4-methyl-piperidin-3-yl]-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

LRMS (M+1): 353.4. IC₅₀ = 0.0435 µM.

Example 35

(3R,4R)-[1-Ethanesulfonyl-4-methyl-piperidin-3-yl]-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

LRMS (M+1): 338.3. IC₅₀ = 0.0143 µM.

Example 36

(3R,4R)-[1-(Butane-1-sulfonyl)-4-methyl-piperidin-3-yl]-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Example 37

(3R,4R)-4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-carboxylic acid isobutyl ester

Example 38

N-(2-((3R,4R)-4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-sulfonyl)-ethyl)-propionamide

Example 39

(2-((3R,4R)-4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-sulfonyl)-ethyl)-carbamic acid methyl ester

Example 40

N-(2-((3R,4R)-4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-sulfonyl)-ethyl)-isobutyramide

Example 41

(3R,4R)-(1-Methanesulfonyl-piperidin-3-yl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Example 42

((3R,4R)-1-Ethanesulfonyl-piperidin-3-yl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Example 43

(3R,4R)-Methyl-[1-(propane-1-sulfonyl)-piperidin-3-yl]-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Example 44

(3R,4R)-[1-(Butane-1-sulfonyl)-piperidin-3-yl]-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Example 45

2,2-Dimethyl-N-((3R,4R)-2-{4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-sulfonyl}-ethyl)-propionamide

Example 46

(3-((3R,4R)-4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxo-propyl)-carbamic acid tert-butyl ester

Example 47

Methyl-[(3R,4R)-4-methyl-1-(propane-1-sulfonyl)-piperidin-3-yl]-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

LRMS (M+1): 352.3. IC₅₀ = 0.0173 μM.

Example 48

3-Amino-1-((3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-propan-1-one

Example 49

2-Methoxy-1-((3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-ethanone

Example 50

2-Dimethylamino-1-((3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-ethanone

Example 51

(3-((3R,4R)-4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxo-propyl)-carbamic acid tert-butyl ester

Example 52

3,3,3-Trifluoro-1-((3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-propan-1-one

Example 53

N-(2-((3R,4R)-4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-2-oxo-ethyl)-acetamide

Example 54

3-Ethoxy-1-((3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-propan-1-one

Example 55

(3R,4R)-4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-carboxylic acid methylamide

Example 56

(3R,4R)-4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-carboxylic acid diethylamide

Example 57

(3R,4R)-Methyl-[4-methyl-1-(2-methylamino-ethanesulfonyl)-piperidin-3-yl]-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

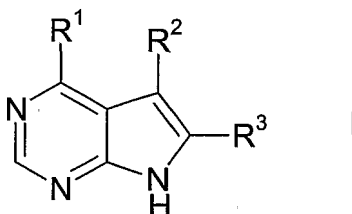
References to other documents, such as patents, patent applications, journals, books, etc., have been made throughout this disclosure. All such documents are hereby incorporated herein by reference in their entirety for all purposes.

It is to be understood that the foregoing description is exemplary and explanatory in nature, and is intended to illustrate the presently disclosed general inventive concept and its preferred embodiments. Through routine experimentation, those of skill in the art given the benefit of the present disclosure may recognize apparent modifications and variations without departing from the spirit and scope of the present disclosure. Thus, the present disclosure is not limited by the above description, but rather by the following claims and their equivalents.

CLAIMS

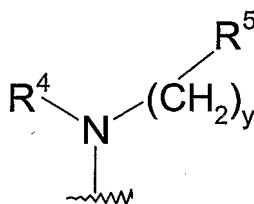
What is claimed is:

1. A pharmaceutical combination therapy for the treatment or prevention of rheumatoid arthritis in a human comprising:
 - a Janus Kinase inhibitor or a pharmaceutically acceptable salt thereof; and
 - at least one anti-arthritic agent or a pharmaceutically acceptable salt thereof.
2. The pharmaceutical combination therapy of claim 1, wherein the Janus Kinase inhibitor is a compound of the formula



or a pharmaceutically acceptable salt thereof; wherein

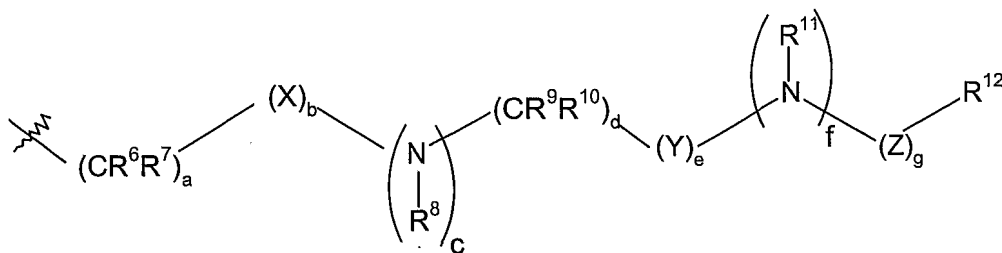
R¹ is a group of the formula



wherein y is 0, 1 or 2;

R⁴ is selected from the group consisting of hydrogen, (C₁-C₆)alkyl, (C₁-C₆)alkylsulfonyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl wherein the alkyl, alkenyl and alkynyl groups are optionally substituted by deuterium, hydroxy, amino, trifluoromethyl, (C₁-C₄)alkoxy, (C₁-C₆)acyloxy, (C₁-C₆)alkylamino, ((C₁-C₆)alkyl)₂amino, cyano, nitro, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl or (C₁-C₆)acylamino; or R⁴ is (C₃-C₁₀)cycloalkyl wherein the cycloalkyl group is optionally substituted by deuterium, hydroxy, amino, trifluoromethyl, (C₁-C₆)acyloxy, (C₁-C₆)acylamino, (C₁-C₆)alkylamino, ((C₁-C₆)alkyl)₂amino, cyano, cyano(C₁-C₆)alkyl, trifluoromethyl(C₁-C₆)alkyl, nitro, nitro(C₁-C₆)alkyl or (C₁-C₆)acylamino;

R⁵ is (C₂-C₉)heterocycloalkyl wherein the heterocycloalkyl groups must be substituted by one to five carboxy, cyano, amino, deuterium, hydroxy, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, halo, (C₁-C₆)acyl, (C₁-C₆)alkylamino, amino(C₁-C₆)alkyl, (C₁-C₆)alkoxy-CO-NH, (C₁-C₆)alkylamino-CO-, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₁-C₆)alkylamino, amino(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, (C₁-C₆)alkoxy(C₁-C₆)alkyl, (C₁-C₆)acyloxy(C₁-C₆)alkyl, nitro, cyano(C₁-C₆)alkyl, halo(C₁-C₆)alkyl, nitro(C₁-C₆)alkyl, trifluoromethyl, trifluoromethyl(C₁-C₆)alkyl, (C₁-C₆)acylamino, (C₁-C₆)acylamino(C₁-C₆)alkyl, (C₁-C₆)alkoxy(C₁-C₆)acylamino, amino(C₁-C₆)acyl, amino(C₁-C₆)acyl(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)acyl, ((C₁-C₆)alkyl)₂amino(C₁-C₆)acyl, R¹⁵R¹⁶N-CO-O-, R¹⁵R¹⁶N-CO-(C₁-C₆)alkyl, (C₁-C₆)alkyl-S(O)ₘ, R¹⁵R¹⁶NS(O)ₘ, R¹⁵R¹⁶NS(O)ₘ(C₁-C₆)alkyl, R¹⁵S(O)ₘR¹⁶N, R¹⁵S(O)ₘR¹⁶N(C₁-C₆)alkyl wherein m is 0, 1 or 2 and R¹⁵ and R¹⁶ are each independently selected from hydrogen or (C₁-C₆)alkyl; or a group of the formula



II

wherein a is 0, 1, 2, 3 or 4;

b, c, e, f and g are each independently 0 or 1;

d is 0, 1, 2, or 3;

X is $S(O)_n$ wherein n is 0, 1 or 2; oxygen, carbonyl or $-C(=N\text{-cyano})-$;

Y is $S(O)_n$ wherein n is 0, 1 or 2; or carbonyl; and

Z is carbonyl, $C(O)O-$, $C(O)NR-$ or $S(O)_n$ wherein n is 0, 1 or 2;

R^6 , R^7 , R^8 , R^9 , R^{10} and R^{11} are each independently selected from the group consisting of hydrogen or (C_1-C_6) alkyl optionally substituted by deuterium, hydroxy, amino, trifluoromethyl, (C_1-C_6) acyloxy, (C_1-C_6) acylamino, (C_1-C_6) alkylamino, $((C_1-C_6)alkyl)_2$ amino, cyano, cyano $(C_1-C_6)alkyl$, trifluoromethyl $(C_1-C_6)alkyl$, nitro, nitro $(C_1-C_6)alkyl$ or (C_1-C_6) acylamino;

R^{12} is carboxy, cyano, amino, oxo, deuterium, hydroxy, trifluoromethyl, $(C_1-C_6)alkyl$, trifluoromethyl $(C_1-C_6)alkyl$, $(C_1-C_6)alkoxy$, halo, $(C_1-C_6)acyl$, $(C_1-C_6)alkylamino$, $((C_1-C_6)alkyl)_2$ amino, amino $(C_1-C_6)alkyl$, $(C_1-C_6)alkoxy-CO-NH$, $(C_1-C_6)alkylamino-CO-$, $(C_2-C_6)alkenyl$, $(C_2-C_6)alkynyl$, $(C_1-C_6)alkylamino$, hydroxy $(C_1-C_6)alkyl$, $(C_1-C_6)alkoxy(C_1-C_6)alkyl$, $(C_1-C_6)acyloxy(C_1-C_6)alkyl$, nitro, cyano $(C_1-C_6)alkyl$, halo $(C_1-C_6)alkyl$, nitro $(C_1-C_6)alkyl$, trifluoromethyl, trifluoromethyl $(C_1-C_6)alkyl$, $(C_1-C_6)acylamino$, $(C_1-C_6)acylamino(C_1-C_6)alkyl$, $(C_1-C_6)alkoxy(C_1-C_6)acylamino$, amino $(C_1-C_6)acyl$, amino $(C_1-C_6)acyl(C_1-C_6)alkyl$, $(C_1-C_6)alkylamino(C_1-C_6)acyl$, $((C_1-C_6)alkyl)_2$ amino $(C_1-C_6)acyl$, $R^{15}R^{16}N-CO-O-$, $R^{15}R^{16}N-CO-(C_1-C_6)alkyl$, $R^{15}C(O)NH$, $R^{15}OC(O)NH$, $R^{15}NHC(O)NH$, $(C_1-C_6)alkyl-S(O)_m$, $(C_1-C_6)alkyl-S(O)_m-(C_1-C_6)alkyl$, $R^{15}R^{16}NS(O)_m$, $R^{15}R^{16}NS(O)_m(C_1-C_6)alkyl$, $R^{15}S(O)_mR^{16}N$, $R^{15}S(O)_mR^{16}N(C_1-C_6)alkyl$ wherein m is 0, 1 or 2 and R^{15} and R^{16} are each independently selected from hydrogen or $(C_1-C_6)alkyl$;

R^2 and R^3 are each independently selected from the group consisting of hydrogen, deuterium, amino, halo, hydroxy, nitro, carboxy, $(C_2-C_6)alkenyl$, $(C_2-C_6)alkynyl$, trifluoromethyl, trifluoromethoxy, $(C_1-C_6)alkyl$, $(C_1-C_6)alkoxy$, $(C_3-C_{10})cycloalkyl$ wherein the alkyl, alkoxy or cycloalkyl groups are optionally substituted by one to three groups selected from halo, hydroxy, carboxy, amino $(C_1-C_6)alkylthio$, $(C_1-C_6)alkylamino$, $((C_1-C_6)alkyl)_2$ amino, $(C_5-C_9)heteroaryl$, $(C_2-C_9)heterocycloalkyl$, $(C_3-C_9)cycloalkyl$ or $(C_6-C_{10})aryl$; or R^2 and R^3 are each independently $(C_3-C_{10})cycloalkyl$, $(C_3-C_{10})cycloalkoxy$, $(C_1-C_6)alkylamino$, $((C_1-C_6)alkyl)_2$ amino, $(C_6-C_{10})arylamino$, $(C_1-C_6)alkylthio$, $(C_6-C_{10})arylthio$, $(C_1-C_6)alkylsulfinyl$, $(C_6-C_{10})arylsulfinyl$, $(C_1-C_6)alkylsulfonyl$, $(C_6-C_{10})arylsulfonyl$, $(C_1-C_6)acyl$, $(C_1-C_6)alkoxy-CO-NH-$, $(C_1-C_6)alkylamino-CO-$, $(C_5-C_9)heteroaryl$, $(C_2-C_9)heterocycloalkyl$ or $(C_6-C_{10})aryl$ wherein the heteroaryl, heterocycloalkyl and aryl groups are optionally substituted by one to three halo, $(C_1-C_6)alkyl$, $(C_1-C_6)alkyl-CO-NH-$, $(C_1-C_6)alkoxy-CO-NH-$, $(C_1-C_6)alkyl-CO-NH-(C_1-C_6)alkyl$, $(C_1-C_6)alkoxy-CO-NH-(C_1-C_6)alkyl$, $(C_1-C_6)alkoxy-CO-NH-(C_1-C_6)alkoxy$, carboxy, carboxy $(C_1-C_6)alkyl$, carboxy $(C_1-C_6)alkoxy$, benzyloxycarbonyl $(C_1-C_6)alkoxy$, $(C_1-C_6)alkoxycarbonyl(C_1-C_6)alkoxy$, $(C_6-C_{10})aryl$, amino, amino $(C_1-$

C₆)alkyl, (C₁-C₆)alkoxycarbonylamino, (C₆-C₁₀)aryl(C₁-C₆)alkoxycarbonylamino, (C₁-C₆)alkylamino, ((C₁-C₆)alkyl)₂amino, (C₁-C₆)alkylamino(C₁-C₆)alkyl, ((C₁-C₆)alkyl)₂amino(C₁-C₆)alkyl, hydroxy, (C₁-C₆)alkoxy, carboxy, carboxy(C₁-C₆)alkyl, (C₁-C₆)alkoxycarbonyl, (C₁-C₆)alkoxycarbonyl(C₁-C₆)alkyl, (C₁-C₆)alkoxy-CO-NH-, (C₁-C₆)alkyl-CO-NH-, cyano, (C₅-C₉)heterocycloalkyl, amino-CO-NH-, (C₁-C₆)alkylamino-CO-NH-, ((C₁-C₆)alkyl)₂amino-CO-NH-, (C₆-C₁₀)arylamino-CO-NH-, (C₅-C₉)heteroarylamino-CO-NH-, (C₁-C₆)alkylamino-CO-NH-(C₁-C₆)alkyl, ((C₁-C₆)alkyl)₂amino-CO-NH-(C₁-C₆)alkyl, (C₆-C₁₀)arylamino-CO-NH-(C₁-C₆)alkyl, (C₅-C₉)heteroarylamino-CO-NH-(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonyl, (C₁-C₆)alkylsulfonylamino, (C₁-C₆)alkylsulfonylamino(C₁-C₆)alkyl, (C₆-C₁₀)arylsulfonyl, (C₆-C₁₀)arylsulfonylamino, (C₆-C₁₀)arylsulfonylamino(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonylamino, (C₁-C₆)alkylsulfonylamino(C₁-C₆)alkyl, (C₅-C₉)heteroaryl or (C₂-C₉)heterocycloalkyl.

3. The pharmaceutical combination therapy of claim 2, wherein a is 0; b is 1; X is carbonyl; c is 0; d is 0; e is 0; f is 0; and g is 0.

4. The pharmaceutical combination therapy of claim 2, wherein a is 0; b is 1; X is carbonyl; c is 0; d is 1; e is 0; f is 0, and g is 0.

5. The pharmaceutical combination therapy of claim 2, wherein a is 0; b is 1; X is carbonyl; c is 1; d is 0; e is 0; f is 0; and g is 0.

6. The pharmaceutical combination therapy of claim 2, wherein a is 0; b is 1; X is -C(=N=cyano)-; c is 1; d is 0; e is 0; f is 0; and g is 0.

7. The pharmaceutical combination therapy of claim 2, wherein a is 0; b is 0; c is 0; d is 0; e is 0; f is 0; g is 1; and Z is -C(O)-O-.

8. The pharmaceutical combination therapy of claim 2, wherein a is 0; b is 1; X is S(O)_n; n is 2; c is 0; d is 0; e is 0; f is 0; and g is 0.

9. The pharmaceutical combination therapy of claim 2, wherein a is 0; b is 1; X is S(O)_n; n is 2; c is 0; d is 2; e is 0; f is 1; g is 1; and Z is carbonyl.

10. The pharmaceutical combination therapy of claim 2, wherein a is 0; b is 1; X is S(O)_n; n is 2; c is 0; d is 2; e is 0; f is 1; and g is 0.

11. The pharmaceutical combination therapy of claim 2, wherein a is 0; b is 1; X is carbonyl; c is 1; d is 0; e is 1; Y is S(O)_n; n is 2; f is 0; and g is 0.

12. The pharmaceutical combination therapy of claim 2, wherein a is 0; b is 1; X is S(O)_n; n is 2; c is 1; d is 0; e is 0; f is 0; and g is 0.

13. The pharmaceutical combination therapy of claim 2, wherein R¹² is cyano, trifluoromethyl, (C₁-C₆)alkyl, trifluoromethyl(C₁-C₆)alkyl, (C₁-C₆)alkylamino, ((C₁-C₆)alkyl)₂amino, (C₂-C₆)alkynyl, cyano(C₁-C₆)alkyl, (C₁-C₆)alkyl-S(O)_m wherein m is 0, 1 or 2.

14. The pharmaceutical combination therapy of claim 2, wherein the Janus Kinase inhibitor is selected from the group consisting of:

- Methyl-[4-methyl-1-(propane-1-sulfonyl)-piperidin-3-yl]-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine;
 4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-carboxylic acid methyl ester;
 3,3,3-Trifluoro-1-{4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-propan-1-one;
 4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-carboxylic acid dimethylamide;
 ({4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-carbonyl}-amino)-acetic acid ethyl ester;
 3-{4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-3-oxo-propionitrile;
 3,3,3-Trifluoro-1-{4-methyl-3-[methyl-(5-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-propan-1-one;
 1-{4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-but-3-yn-1-one;
 1-{3-[(5-Chloro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-methyl-amino]-4-methyl-piperidin-1-yl}-propan-1-one;
 1-{3-[(5-Fluoro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-methyl-amino]-4-methyl-piperidin-1-yl}-propan-1-one;
 N-cyano-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-N'-propyl-piperidine-1-carboxamide;
 N-cyano-4,N',N'-Trimethyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-carboxamide;
 Methyl-[(3R,4R)-4-methyl-1-(propane-1-sulfonyl)-piperidin-3-yl]-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine;
 (3R,4R)-4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-carboxylic acid methyl ester;
 3,3,3-Trifluoro-1-[(3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl]-propan-1-one;
 (3R,4R)-4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-carboxylic acid dimethylamide;
 [(3R,4R)-4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-carbonyl]-amino)-acetic acid ethyl ester;
 3-[(3R,4R)-4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl]-3-oxo-propionitrile;
 3,3,3-Trifluoro-1-[(3R,4R)-4-methyl-3-[methyl-(5-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl]-propan-1-one;
 1-[(3R,4R)-4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl]-but-3-yn-1-one;
 1-[(3R,4R)-3-[(5-Chloro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-methyl-amino]-4-methyl-piperidin-1-yl]-propan-1-one;

1-((3R,4R)-3-[(5-Fluoro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-methyl-amino]-4-methyl-piperidin-1-yl)-propan-1-one;

(3R,4R)-N-cyano-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-N'-propyl-piperidine-1-carboxamide; and

(3R,4R)-N-cyano-4,N',N'-Trimethyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-carboxamide,
or a pharmaceutically acceptable salt thereof.

15. The pharmaceutical combination therapy of claim 1, wherein the Janus Kinase inhibitor is 3-((3R,4R)-4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxo-propionitrile or a pharmaceutically acceptable salt thereof.

16. The pharmaceutical combination therapy of claim 1, wherein the anti-arthritis agent is a DMARD.

17. The pharmaceutical combination therapy of claim 16, wherein the DMARD is selected from the group consisting of: etanercept, infliximab, adalimumab, anakinra, abatacept, rituximab, tocilizumab, certolizumab pegol, hydroxychloroquine, chloroquine, dapsone, sulfasalazine, gold sodium thiomalate, aurothioglucose, auranofin, methotrexate, leflunomide, azathioprine, d-penicillamine, abatacept and cyclosporine A.

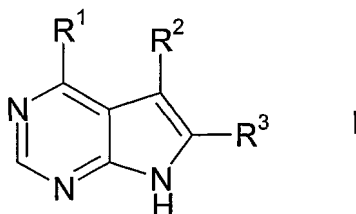
18. The pharmaceutical combination therapy of claim 17, wherein the DMARD is methotrexate.

19. The pharmaceutical combination therapy of claim 1, wherein the Janus Kinase inhibitor is 3-((3R,4R)-4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxo-propionitrile or a pharmaceutically acceptable salt thereof and the anti-arthritis agent is methotrexate or a pharmaceutically acceptable salt thereof.

20. The pharmaceutical combination therapy of claim 19, wherein 3-((3R,4R)-4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxo-propionitrile or a pharmaceutically acceptable salt thereof is dosed in an amount of about 1 mg BID, 5 mg BID, 10 mg BID, 15 mg BID, 20 mg BID, 25 mg BID, or 30 mg BID, and methotrexate is dosed weekly in an amount of 5 mg, 7.5 mg, or 15 mg.

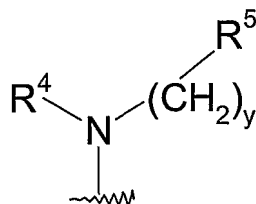
21. Use of a Janus Kinase inhibitor or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating or preventing rheumatoid arthritis in a human for co-administration with at least one anti-arthritis agent or a pharmaceutically acceptable salt thereof.

22. The use of claim 21, wherein the Janus Kinase inhibitor is a compound of the formula



or a pharmaceutically acceptable salt thereof; wherein

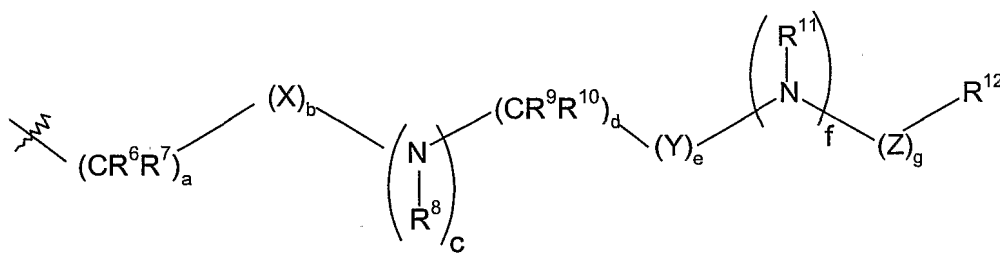
R¹ is a group of the formula



wherein y is 0, 1 or 2;

R⁴ is selected from the group consisting of hydrogen, (C₁-C₆)alkyl, (C₁-C₆)alkylsulfonyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl wherein the alkyl, alkenyl and alkynyl groups are optionally substituted by deuterium, hydroxy, amino, trifluoromethyl, (C₁-C₄)alkoxy, (C₁-C₆)acyloxy, (C₁-C₆)alkylamino, ((C₁-C₆)alkyl)₂amino, cyano, nitro, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl or (C₁-C₆)acylamino; or R⁴ is (C₃-C₁₀)cycloalkyl wherein the cycloalkyl group is optionally substituted by deuterium, hydroxy, amino, trifluoromethyl, (C₁-C₆)acyloxy, (C₁-C₆)acylamino, (C₁-C₆)alkylamino, ((C₁-C₆)alkyl)₂amino, cyano, cyano(C₁-C₆)alkyl, trifluoromethyl(C₁-C₆)alkyl, nitro, nitro(C₁-C₆)alkyl or (C₁-C₆)acylamino;

R⁵ is (C₂-C₉)heterocycloalkyl wherein the heterocycloalkyl groups must be substituted by one to five carboxy, cyano, amino, deuterium, hydroxy, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, halo, (C₁-C₆)acyl, (C₁-C₆)alkylamino, amino(C₁-C₆)alkyl, (C₁-C₆)alkoxy-CO-NH, (C₁-C₆)alkylamino-CO-, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₁-C₆)alkylamino, amino(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, (C₁-C₆)alkoxy(C₁-C₆)alkyl, (C₁-C₆)acyloxy(C₁-C₆)alkyl, nitro, cyano(C₁-C₆)alkyl, halo(C₁-C₆)alkyl, nitro(C₁-C₆)alkyl, trifluoromethyl, trifluoromethyl(C₁-C₆)alkyl, (C₁-C₆)acylamino, (C₁-C₆)acylamino(C₁-C₆)alkyl, (C₁-C₆)alkoxy(C₁-C₆)acylamino, amino(C₁-C₆)acyl, amino(C₁-C₆)acyl(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)acyl, ((C₁-C₆)alkyl)₂amino(C₁-C₆)acyl, R¹⁵R¹⁶N-CO-O-, R¹⁵R¹⁶N-CO-(C₁-C₆)alkyl, (C₁-C₆)alkyl-S(O)_m, R¹⁵R¹⁶NS(O)_m, R¹⁵R¹⁶NS(O)_m(C₁-C₆)alkyl, R¹⁵S(O)_mR¹⁶N, R¹⁵S(O)_mR¹⁶N(C₁-C₆)alkyl wherein m is 0, 1 or 2 and R¹⁵ and R¹⁶ are each independently selected from hydrogen or (C₁-C₆)alkyl; or a group of the formula



II

wherein a is 0, 1, 2, 3 or 4;

b, c, e, f and g are each independently 0 or 1;

d is 0, 1, 2, or 3;

X is S(O)_n wherein n is 0, 1 or 2; oxygen, carbonyl or -C(=N-cyano)-;

Y is S(O)_n wherein n is 0, 1 or 2; or carbonyl; and

Z is carbonyl, C(O)O-, C(O)NR- or S(O)_n wherein n is 0, 1 or 2;

R⁶, R⁷, R⁸, R⁹, R¹⁰ and R¹¹ are each independently selected from the group consisting of hydrogen or (C₁-C₆)alkyl optionally substituted by deuterium, hydroxy, amino, trifluoromethyl, (C₁-

C₆)acyloxy, (C₁-C₆)acylamino, (C₁-C₆)alkylamino, ((C₁-C₆)alkyl)₂amino, cyano, cyano(C₁-C₆)alkyl, trifluoromethyl(C₁-C₆)alkyl, nitro, nitro(C₁-C₆)alkyl or (C₁-C₆)acylamino;

R¹² is carboxy, cyano, amino, oxo, deuterium, hydroxy, trifluoromethyl, (C₁-C₆)alkyl, trifluoromethyl(C₁-C₆)alkyl, (C₁-C₆)alkoxy, halo, (C₁-C₆)acyl, (C₁-C₆)alkylamino, ((C₁-C₆)alkyl)₂ amino, amino(C₁-C₆)alkyl, (C₁-C₆)alkoxy-CO-NH, (C₁-C₆)alkylamino-CO-, (C₂-C₆)alkenyl, (C₂-C₆) alkynyl, (C₁-C₆)alkylamino, hydroxy(C₁-C₆)alkyl, (C₁-C₆)alkoxy(C₁-C₆)alkyl, (C₁-C₆)acyloxy(C₁-C₆)alkyl, nitro, cyano(C₁-C₆)alkyl, halo(C₁-C₆)alkyl, nitro(C₁-C₆)alkyl, trifluoromethyl, trifluoromethyl(C₁-C₆)alkyl, (C₁-C₆)acylamino, (C₁-C₆)acylamino(C₁-C₆)alkyl, (C₁-C₆)alkoxy(C₁-C₆)acylamino, amino(C₁-C₆)acyl, amino(C₁-C₆)acyl(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)acyl, ((C₁-C₆)alkyl)₂amino(C₁-C₆)acyl, R¹⁵R¹⁶N-CO-O-, R¹⁵R¹⁶N-CO-(C₁-C₆)alkyl, R¹⁵C(O)NH, R¹⁵OC(O)NH, R¹⁵NHC(O)NH, (C₁-C₆)alkyl-S(O)_m, (C₁-C₆)alkyl-S(O)_m-(C₁-C₆)alkyl, R¹⁵R¹⁶NS(O)_m, R¹⁵R¹⁶NS(O)_m (C₁-C₆)alkyl, R¹⁵S(O)_m R¹⁶N, R¹⁵S(O)_mR¹⁶N(C₁-C₆)alkyl wherein m is 0, 1 or 2 and R¹⁵ and R¹⁶ are each independently selected from hydrogen or (C₁-C₆)alkyl;

R² and R³ are each independently selected from the group consisting of hydrogen, deuterium, amino, halo, hydroxy, nitro, carboxy, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, trifluoromethyl, trifluoromethoxy, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₃-C₁₀)cycloalkyl wherein the alkyl, alkoxy or cycloalkyl groups are optionally substituted by one to three groups selected from halo, hydroxy, carboxy, amino (C₁-C₆)alkylthio, (C₁-C₆)alkylamino, ((C₁-C₆)alkyl)₂amino, (C₅-C₉)heteroaryl, (C₂-C₉)heterocycloalkyl, (C₃-C₉)cycloalkyl or (C₆-C₁₀)aryl; or R² and R³ are each independently (C₃-C₁₀)cycloalkyl, (C₃-C₁₀)cycloalkoxy, (C₁-C₆)alkylamino, ((C₁-C₆)alkyl)₂amino, (C₆-C₁₀)arylamino, (C₁-C₆)alkylthio, (C₆-C₁₀)arylthio, (C₁-C₆)alkylsulfinyl, (C₆-C₁₀)arylsulfinyl, (C₁-C₆)alkylsulfonyl, (C₆-C₁₀)arylsulfonyl, (C₁-C₆)acyl, (C₁-C₆)alkoxy-CO-NH-, (C₁-C₆)alkylamino-CO-, (C₅-C₉)heteroaryl, (C₂-C₉)heterocycloalkyl or (C₆-C₁₀)aryl wherein the heteroaryl, heterocycloalkyl and aryl groups are optionally substituted by one to three halo, (C₁-C₆)alkyl, (C₁-C₆)alkyl-CO-NH-, (C₁-C₆)alkoxy-CO-NH-, (C₁-C₆)alkyl-CO-NH-(C₁-C₆)alkyl, (C₁-C₆)alkoxy-CO-NH-(C₁-C₆)alkyl, (C₁-C₆)alkoxy-CO-NH-(C₁-C₆)alkoxy, carboxy, carboxy(C₁-C₆)alkyl, carboxy(C₁-C₆)alkoxy, benzyloxycarbonyl(C₁-C₆)alkoxy, (C₁-C₆)alkoxycarbonyl(C₁-C₆)alkoxy, (C₆-C₁₀)aryl, amino, amino(C₁-C₆)alkyl, (C₁-C₆)alkoxycarbonylamino, (C₆-C₁₀)aryl(C₁-C₆)alkoxycarbonylamino, (C₁-C₆)alkylamino, ((C₁-C₆)alkyl)₂amino, (C₁-C₆)alkylamino(C₁-C₆)alkyl, ((C₁-C₆)alkyl)₂amino(C₁-C₆)alkyl, hydroxy, (C₁-C₆)alkoxy, carboxy, carboxy(C₁-C₆)alkyl, (C₁-C₆)alkoxycarbonyl, (C₁-C₆)alkoxycarbonyl(C₁-C₆)alkyl, (C₁-C₆)alkoxy-CO-NH-, (C₁-C₆)alkyl-CO-NH-, cyano, (C₅-C₉)heterocycloalkyl, amino-CO-NH-, (C₁-C₆)alkylamino-CO-NH-, ((C₁-C₆)alkyl)₂amino-CO-NH-, (C₆-C₁₀)arylamino-CO-NH-, (C₅-C₉)heteroarylamino-CO-NH-, (C₁-C₆)alkylamino-CO-NH-(C₁-C₆)alkyl, ((C₁-C₆)alkyl)₂amino-CO-NH-(C₁-C₆)alkyl, (C₆-C₁₀)arylamino-CO-NH-(C₁-C₆)alkyl, (C₅-C₉)heteroarylamino-CO-NH-(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonyl, (C₁-C₆)alkylsulfonylamino, (C₁-C₆)alkylsulfonylamino(C₁-C₆)alkyl, (C₆-C₁₀)arylsulfonyl, (C₆-C₁₀)arylsulfonylamino, (C₆-C₁₀)arylsulfonylamino(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonylamino, (C₁-C₆)alkylsulfonylamino(C₁-C₆)alkyl, (C₅-C₉)heteroaryl or (C₂-C₉)heterocycloalkyl.

23. The use of claim 22, wherein a is 0; b is 1; X is carbonyl; c is 0; d is 0; e is 0; f is 0; and g is 0.
24. The use of claim 22, wherein a is 0; b is 1; X is carbonyl; c is 0; d is 1; e is 0; f is 0, and g is 0.
25. The use of claim 22, wherein a is 0; b is 1; X is carbonyl; c is 1; d is 0; e is 0; f is 0; and g is 0.

26. The use of claim 22, wherein a is 0; b is 1; X is $-C(=N=\text{cyano})-$; c is 1; d is 0; e is 0; f is 0; and g is 0.
27. The use of claim 22, wherein a is 0; b is 0; c is 0; d is 0; e is 0; f is 0; g is 1; and Z is $-C(O)-O-$.
28. The use of claim 22, wherein a is 0; b is 1; X is $S(O)_n$; n is 2; c is 0; d is 0; e is 0; f is 0; and g is 0.
29. The use of claim 22, wherein a is 0; b is 1; X is $S(O)_n$; n is 2; c is 0; d is 2; e is 0; f is 1; g is 1; and Z is carbonyl.
30. The use of claim 22, wherein a is 0; b is 1; X is $S(O)_n$; n is 2; c is 0; d is 2; e is 0; f is 1; and g is 0.
31. The use of claim 22, wherein a is 0; b is 1; X is carbonyl; c is 1; d is 0; e is 1; Y is $S(O)_n$; n is 2; f is 0; and g is 0.
32. The use of claim 22, wherein a is 0; b is 1; X is $S(O)_n$; n is 2; c is 1; d is 0; e is 0; f is 0; and g is 0.
33. The use of claim 22, wherein R^{12} is cyano, trifluoromethyl, (C_1-C_6) alkyl, trifluoromethyl (C_1-C_6) alkyl, (C_1-C_6) alkylamino, $((C_1-C_6)alkyl)_2$ amino, (C_2-C_6) alkynyl, cyano (C_1-C_6) alkyl, $(C_1-C_6)alkyl-S(O)_m$ wherein m is 0, 1 or 2.
34. The use of claim 22, wherein the Janus Kinase inhibitor is selected from the group consisting of:
 Methyl-[4-methyl-1-(propane-1-sulfonyl)-piperidin-3-yl]-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine;
 4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-carboxylic acid methyl ester;
 3,3,3-Trifluoro-1-{4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-propan-1-one;
 4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-carboxylic acid dimethylamide;
 ({4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-carbonyl}-amino)-acetic acid ethyl ester;
 3-{4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-3-oxo-propionitrile;
 3,3,3-Trifluoro-1-{4-methyl-3-[methyl-(5-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-propan-1-one;
 1-{4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-but-3-yn-1-one;
 1-{3-[(5-Chloro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-methyl-amino]-4-methyl-piperidin-1-yl}-propan-1-one;
 1-{3-[(5-Fluoro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-methyl-amino]-4-methyl-piperidin-1-yl}-propan-1-one;
 N-cyano-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-N'-propyl-piperidine-1-carboxamide;
 N-cyano-4,N',N'-Trimethyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-carboxamide;

Methyl-[(3R,4R)-4-methyl-1-(propane-1-sulfonyl)-piperidin-3-yl]-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine;

(3R,4R)-4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-carboxylic acid methyl ester;

3,3,3-Trifluoro-1-[(3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl]-propan-1-one;

(3R,4R)-4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-carboxylic acid dimethylamide;

{[(3R,4R)-4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-carbonyl]-amino}-acetic acid ethyl ester;

3-{[(3R,4R)-4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl]-3-oxo-propionitrile};

3,3,3-Trifluoro-1-[(3R,4R)-4-methyl-3-[methyl-(5-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl]-propan-1-one;

1-[(3R,4R)-4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl]-but-3-yn-1-one;

1-[(3R,4R)-3-[(5-Chloro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-methyl-amino]-4-methyl-piperidin-1-yl]-propan-1-one;

1-[(3R,4R)-3-[(5-Fluoro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-methyl-amino]-4-methyl-piperidin-1-yl]-propan-1-one;

(3R,4R)-N-cyano-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-N'-propyl-piperidine-1-carboxamide; and

(3R,4R)-N-cyano-4,N',N'-Trimethyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidine-1-carboxamide,

or a pharmaceutically acceptable salt thereof.

35. The method of claim 22, wherein the Janus Kinase inhibitor is 3-{[(3R,4R)-4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl]-3-oxo-propionitrile} or a pharmaceutically acceptable salt thereof.

36. The use of claim 21, wherein the anti-arthritis agent is a DMARD.

37. The use of claim 36, wherein the DMARD is selected from the group consisting of: etanercept, infliximab, adalimumab, anakinra, abatacept, rituximab, tocilizumab, certolizumab pegol, hydroxychloroquine, chloroquine, dapsone, sulfasalazine, gold sodium thiomalate, aurothioglucose, auranofin, methotrexate, leflunomide, azathioprine, d-penicillamine, abatacept and cyclosporine A.

38. The use of claim 37, wherein the DMARD is methotrexate.

39. The use of claim 21, wherein the Janus Kinase inhibitor is 3-{[(3R,4R)-4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl]-3-oxo-propionitrile} or a pharmaceutically acceptable salt thereof and the anti-arthritis agent is methotrexate or a pharmaceutically acceptable salt thereof.

40. The use of claim 39, wherein 3-((3R,4R)-4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)-3-oxo-propionitrile or a pharmaceutically acceptable salt thereof is dosed in an amount of about 1 mg BID, 5 mg BID, 10 mg BID, 15 mg BID, 20 mg BID, 25 mg BID, or 30 mg BID, and methotrexate is dosed weekly in an amount of 5 mg, 7.5 mg, or 15 mg.