IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

PFIZER INC., PF PRISM C.V., C.P. PHARMACEUTICALS INTERNATIONAL C.V., PFIZER PHARMACEUTICALS LLC and PFIZER PFE IRELAND PHARMACEUTICALS HOLDING 1 B.V.,	)	
Plaintiffs,	)	C.A. No. _____
v.	)	
AJANTA PHARMA LTD. and AJANTA PHARMA USA INC.,	)	
Defendants.	)	

COMPLAINT

Pfizer Inc., PF PRISM C.V., C.P. Pharmaceuticals International C.V., Pfizer Pharmaceuticals LLC, and Pfizer PFE Ireland Pharmaceuticals Holding 1 B.V. (collectively "Plaintiffs" or "Pfizer"), for their Complaint against Ajanta Pharma Ltd. and Ajanta Pharma USA Inc. (collectively "Ajanta"), allege as follows:

NATURE OF THE ACTION

1. This is an action by Pfizer against Ajanta for infringement of United States Patent No. 6,965,027 (the "'027 patent") and United States Reissue Patent No. RE41,783 (the "RE'783 patent").

2. This action arises out of Ajanta's submission of Abbreviated New Drug Application ("ANDA") No. 212943 seeking approval by the United States Food and Drug Administration ("FDA") to sell generic copies of Pfizer's 5 mg Xeljanz® (tofacitinib) tablets ("Xeljanz 5 mg Tablets") prior to the expiration of the '027 and RE'783 patents. The proposed Ajanta ANDA product is referred to hereinafter as "Ajanta Generic Tablets."

THE PARTIES

3. Plaintiff Pfizer Inc. is a corporation organized and existing under the laws of Delaware and having a place of business at 235 East 42nd Street, New York, New York 10017.

4. Plaintiff PF PRISM C.V. is a limited partnership (*commanditaire vennootschap*) organized under the laws of the Netherlands, having its registered seat in Rotterdam, the Netherlands, and registered at the Trade Register held by the Chamber of Commerce in Rotterdam, the Netherlands, under number 51840456. Pfizer Inc. is the ultimate parent company of PF PRISM C.V.

5. Plaintiff C.P. Pharmaceuticals International C.V. is a limited partnership (*commanditaire vennootschap*) organized under the laws of the Netherlands, having a place of business at 235 East 42nd Street, New York, New York 10017. Pfizer Inc. is the ultimate parent company of C.P. Pharmaceuticals International C.V.

6. Plaintiff Pfizer Pharmaceuticals LLC is a limited liability company organized and existing under the laws of Delaware and having its principal place of business at Bo. Carmelitas, Road 689, Km. 1.9, Vega Baja, Puerto Rico. Pfizer Inc. is the ultimate parent company of Pfizer Pharmaceuticals LLC.

7. Plaintiff Pfizer PFE Ireland Pharmaceuticals Holding 1 B.V. is a private company with limited liability (*besloten vennootschap met beperkte aansprakelijkheid*) under Dutch law, having its registered seat in Rotterdam, the Netherlands, having its business address at Rivium Westlaan 142, 2909 LD, Capelle aan den IJssel, the Netherlands, and registered with the Dutch Trade Register under number 60558814. Pfizer Inc. is the ultimate parent company of Pfizer PFE Ireland Pharmaceuticals Holding 1 B.V.

8. On information and belief, Defendant Ajanta Pharma Ltd. is a corporation organized and existing under the laws of India, having its principal place of business at No. 98,

Ajanta House, Government Industrial Area, Charkop, Kandivali (West) Mumbai, Maharashtra 400067 India.

9. On information and belief, Defendant Ajanta Pharma USA Inc. is a corporation organized and existing under the laws of New Jersey, having its principal place of business at One Grande Commons, 440 U.S. Highway 22 East, Suite 150, Bridgewater, NJ 08807. On information and belief, Ajanta Pharma USA Inc. is a wholly-owned subsidiary of Ajanta Pharma Ltd. On information and belief, Ajanta Pharma USA Inc. is the U.S. agent for Ajanta Pharma Ltd.

JURISDICTION AND VENUE

10. This action arises under the patent laws of the United States, Title 35, United States Code. The Court has subject matter jurisdiction over this action pursuant to the provisions of 28 U.S.C. §§ 1331, 1338(a), 2201, and 2202.

11. Defendants have consented to this Court's jurisdiction for the purposes of Plaintiffs' claims against Defendants in this case.

12. Defendants have consented to venue in this district.

BACKGROUND

Pfizer's Xeljanz 5 mg Tablets

13. Pfizer's Xeljanz 5 mg Tablets are indicated for: the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate; the treatment of adult patients with active psoriatic arthritis who have had an inadequate response or intolerance to methotrexate or other disease-modifying antirheumatic drugs; or the treatment of adult patients with moderately to severely active ulcerative colitis.

14. Xeljanz 5 mg Tablets contain tofacitinib citrate in an amount equivalent to 5 mg of tofacitinib base in a tablet formulated for twice-daily administration. The active ingredient in Xeljanz 5 mg Tablets, tofacitinib, is a Janus kinase (JAK) inhibitor.

15. The FDA-approved Prescribing Information for Xeljanz 5 mg Tablets states that tofacitinib citrate has the following chemical name: (3R,4R)-4-methyl-3-(methyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)-ß-oxo-1-piperidinepropanenitrile,2-hydroxy-1,2,3-propanetricarboxylate (1:1).

Orange Book Listing for Xeljanz 5 mg Tablets

16. PF PRISM C.V. holds approved New Drug Application ("NDA") No. 203214 for Xeljanz 5 mg Tablets.

17. Pursuant to 21 U.S.C. § 355(b)(1) and the regulations the FDA has promulgated pursuant thereto, the '027 and RE'783 patents are listed in the FDA publication titled "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book") for the NDA No. 203214.

18. The Orange Book lists the expiration dates for the '027 patent as March 25, 2023, and the RE'783 patent as December 8, 2025.

19. The Orange Book also lists five additional patents for Xeljanz 5 mg Tablets that are not at issue: U.S. Patent Nos. 6,956,041 (expiring December 8, 2020); 7,091,208 (expiring December 8, 2020); 7,265,221 (expiring December 8, 2020); 7,301,023 (expiring May 23, 2022), and 7,842,699 (expiring December 8, 2020).

The '027 Patent

20. On November 15, 2005, the USPTO issued the '027 patent, titled "Crystalline 3-{4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-3-oxo-

propionitrile citrate." The '027 patent is duly and legally assigned to Pfizer Inc. A copy of the '027 patent is attached hereto as Exhibit A.

21. C.P. Pharmaceuticals International C.V. is the exclusive licensee of the '027 patent.

22. C.P. Pharmaceuticals International C.V. conveyed rights under the '027 patent to Pfizer Pharmaceuticals LLC, PF PRISM C.V., and Pfizer PFE Ireland Pharmaceuticals Holding 1 Coöperatief U.A.

23. Pursuant to a Deed of Conversion and Amendment to Articles of Association dated December 30, 2017, Pfizer PFE Ireland Pharmaceuticals Holding 1 Coöperatief U.A. changed its name to Pfizer PFE Ireland Pharmaceuticals Holding 1 B.V.

The RE'783 Patent

24. On September 28, 2010, the USPTO issued the RE'783 patent, titled "Pyrrolo[2,3-D]pyrimidine Compounds." The RE'783 patent is a reissue of U.S. Patent No. 6,627,754, which issued on September 30, 2003. The RE'783 patent is duly and legally assigned to Pfizer Inc. A copy of the RE'783 patent is attached hereto as Exhibit B.

25. On December 14, 2016, the USPTO issued a Notice of Final Determination extending the expiration date of the RE'783 patent to December 8, 2025.

26. C.P. Pharmaceuticals International C.V. is the exclusive licensee of the RE'783 patent.

27. C.P. Pharmaceuticals International C.V. conveyed rights under the RE'783 patent to Pfizer Pharmaceuticals LLC, PF PRISM C.V., and Pfizer PFE Ireland Pharmaceuticals Holding 1 Coöperatief U.A.

28. Pursuant to a Deed of Conversion and Amendment to Articles of Association dated December 30, 2017, Pfizer PFE Ireland Pharmaceuticals Holding 1 Coöperatief U.A. changed its name to Pfizer PFE Ireland Pharmaceuticals Holding 1 B.V.

Ajanta's ANDA

29. By letter dated February 4, 2019 (the "Ajanta Notice Letter") and received by Pfizer on February 5, 2019, Ajanta notified Pfizer that it had submitted ANDA No. 212943 to the FDA, seeking approval under the Federal Food, Drug and Cosmetic Act ("FDCA") to market and sell Ajanta Generic Tablets prior to the expiration of the '027 and RE'783 patents.

30. The Ajanta Notice Letter asserts that ANDA No. 212943 contains a "Paragraph IV" certification under 21 U.S.C. §§ 355(j)(1) and (j)(2)(A) alleging that each of the '027 and RE'783 patents "are invalid, unenforceable and/or will not be infringed by" Ajanta Generic Tablets.

31. The Ajanta Notice Letter indicates that Ajanta Generic Tablets will contain tofacitinib citrate as the active ingredient.

32. The Ajanta Notice Letter states that ANDA No. 212943 requests "approval to engage in the commercial manufacture, use or sale of" Ajanta Generic Tablets prior to the expiration of the '027 and RE'783 patents.

33. Attached to the Ajanta Notice Letter was Ajanta's Detailed Statement ("Ajanta's Detailed Statement") asserting the purported factual and legal bases for Ajanta's contention that the '027 and RE'783 patents are invalid, unenforceable, and/or will not be infringed by the manufacture, use, offer for sale, and/or sale of Ajanta Generic Tablets.

34. Ajanta's Detailed Statement alleges that all claims of the '027 and RE'783 patents are invalid. Ajanta's Detailed Statement does not contain a noninfringement argument with respect to the '027 and RE'783 patents, other than that all claims are invalid.

35. On information and belief, Ajanta Pharma Ltd. and Ajanta Pharma USA Inc. collaborated and acted in concert in the decision to prepare and submit and in the preparation and submission of ANDA No. 212943.

36. On information and belief, upon approval of ANDA No. 212943, Ajanta will distribute Ajanta Generic Tablets throughout the United States.

COUNT I
(Infringement of the '027 Patent)

37. The allegations of paragraphs 1-36 above are repeated and re-alleged as if set forth fully herein.

38. Pursuant to 35 U.S.C. § 271(e)(2)(A), Ajanta's submission of ANDA No. 212943 seeking approval to market Ajanta Generic Tablets was an act of infringement of one or more claims of the '027 patent entitling Pfizer to the relief provided by 35 U.S.C. § 271(e)(4), including, *inter alia*, an order of this Court that the effective date of approval for ANDA No. 212943 be a date which is not earlier than the expiration date of the '027 patent.

39. Ajanta had knowledge of the '027 patent when it submitted ANDA No. 212943 to the FDA.

40. On information and belief, upon FDA approval, Ajanta intends to engage in the manufacture, use, offer for sale, sale, and/or importation of Ajanta Generic Tablets and will thereby infringe at least claim 1 of the '027 patent.

41. The foregoing actions by Ajanta constitute and/or would constitute infringement of at least claim 1 of the '027 patent.

42. Pfizer will be substantially and irreparably harmed if Ajanta is not enjoined from infringing the '027 patent. Pfizer has no adequate remedy at law.

COUNT II
(Infringement of the RE'783 Patent)

43. The allegations of paragraphs 1-42 above are repeated and re-alleged as if set forth fully herein.

44. Pursuant to 35 U.S.C. § 271(e)(2)(A), Ajanta's submission of ANDA No. 212943 seeking approval to market Ajanta Generic Tablets was an act of infringement of one or more claims of the RE'783 patent entitling Pfizer to the relief provided by 35 U.S.C. § 271(e)(4), including, *inter alia*, an order of this Court that the effective date of approval for ANDA No. 212943 be a date which is not earlier than the expiration date of the RE'783 patent.

45. Ajanta had knowledge of the RE'783 patent when it submitted ANDA No. 212943 to the FDA.

46. On information and belief, upon FDA approval, Ajanta intends to engage in the manufacture, use, offer for sale, sale, and/or importation of Ajanta Generic Tablets and will thereby infringe at least claim 1 of the RE'783 patent.

47. The foregoing actions by Ajanta constitute and/or would constitute infringement of at least claim 1 of the RE'783 patent.

48. Pfizer will be substantially and irreparably harmed if Ajanta is not enjoined from infringing the RE'783 patent. Pfizer has no adequate remedy at law.

PRAYER FOR RELIEF

WHEREFORE, Pfizer requests the following relief:

A. A judgment that Ajanta's submission of ANDA No. 212943 was an act of infringement and that Ajanta's making, using, offering to sell, selling or importing Ajanta Generic Tablets prior to the expiration of the '027 and RE'783 patents will infringe each of those patents;

B. A judgment that the effective date of any FDA approval for Ajanta to make, use offer for sale, sell, market, distribute, or import the Ajanta Generic Tablets be no earlier than the dates on which the '027 and RE'783 patents expire, or any later expiration of exclusivity to which Pfizer is or becomes entitled;

C. A permanent injunction enjoining Ajanta, its officers, agents, servants, and employees, and those persons in active concert or participation with any of them, from making, using, selling, offering for sale, marketing, distributing, or importing Ajanta Generic Tablets, and from inducing or contributing to any of the foregoing, prior to the expiration of the '027 and RE'783 patents, or any later expiration of exclusivity to which Pfizer is or becomes entitled;

D. A judgment that this case is an exceptional case under 35 U.S.C. § 285, entitling Pfizer to an award of its reasonable attorneys' fees for bringing and prosecuting this action;

E. An award of Pfizer's costs and expenses in this action; and

Such further and additional relief as this Court deems just and proper.

MORRIS, NICHOLS, ARSHT & TUNNELL LLP

/s/ Jack B. Blumenfeld

Jack B. Blumenfeld (#1014)
Megan E. Dellinger (#5739)
1201 North Market Street
P.O. Box 1347
Wilmington, DE 19899
(302) 658-9200
jblumenfeld@mnat.com
mdellinger@mnat.com

Attorneys for Plaintiffs

OF COUNSEL:

Aaron Stiefel
Daniel P. DiNapoli
Jeffrey Martin
Philip Smithback
Stephanie Piper
ARNOLD & PORTER KAYE SCHOLER LLP
250 West 55th Street
New York, NY 10019-9710
(212) 836-8000

Soumitra Deka
ARNOLD & PORTER KAYE SCHOLER LLP
Three Embarcadero Center
San Francisco, CA 94111-4024
(415) 471-3100

March 15, 2019

EXHIBIT A

US006965027B2

(12) **United States Patent**
Flanagan et al.

(10) **Patent No.: US 6,965,027 B2**
(45) **Date of Patent: Nov. 15, 2005**

(54) **CRYSTALLINE 3-{4-METHYL-3-[METHYL-(7H-PYRROLO[2,3-D]PYRIMIDIN-4-YL)-AMINO]-PIPERIDIN-1-YL}-3-OXO-PROPIONITRILE CITRATE**

(75) Inventors: **Mark E. Flanagan**, Gales Ferry, CT (US); **Zheng J. Li**, Quaker Hill, CT (US)

(73) Assignee: **Pfizer Inc.**, New York, NY (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 7 days.

(21) Appl. No.: **10/310,078**

(22) Filed: **Dec. 4, 2002**

(65) **Prior Publication Data**

US 2003/0130292 A1 Jul. 10, 2003

Related U.S. Application Data

(60) Provisional application No. 60/338,984, filed on Dec. 6, 2001.

(51) **Int. Cl.**[7] **C07D 401/12**
(52) **U.S. Cl.** **544/280**
(58) **Field of Search** 514/265.1; 544/280

(56) **References Cited**

FOREIGN PATENT DOCUMENTS

WO	WO 9965908	12/1999
WO	WO 99 65909	12/1999
WO	WO 0142246	6/2001
WO	WO 02/96909	12/2002

OTHER PUBLICATIONS

Groom, Colin R. et al, Drug Discovery Today, vol. 7, No. 15, 2002, pp. 801–802.*

Hong, J.C. et al, Semin. Nephrol., vol. 20, No. 2, 2000, pp. 1080125.*

Malaviya, R. et al. Pharm. Exper. Therap., vol. 295, No. 3, 2000, pp. 912–926.*

Aringer, M. et al, Life Sci., vol. 64, No. 24, 1999, pp. 2173–2186.*

Wilcox, et al., U.S. Appl. No US 2003/0073719, Published Apr. 17, 2003.

Blumenkopl, et al., U.S. Pat. Appl. No. US 2001/0053782, Published Dec. 20, 2001.

Blumenkopl, et al., U.S. Appl. No. US 2004/0053947, Published Mar 18, 2004.

Wilcox, et al., U.S. Pat,. Appl. No. 10/869,101, filed Jun. 15, 2004 (continuation of U.S. Pat. Appl. No. US 2003/0073719, published Apr. 17, 2003).

* cited by examiner

Primary Examiner—Munkund J. Shah
Assistant Examiner—Thomas McKenzie
(74) *Attorney, Agent, or Firm*—Peter C Richardson; Gregg C. Benson; Lance Y. Liu

(57) **ABSTRACT**

This invention relates to novel amorphous and crystallline forms of 3-{(3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-3-oxo-propionitrile mono citrate salt, useful as inhibitors of protein kinases, and to their methods of preparation.

6 Claims, 1 Drawing Sheet

FIG. 1

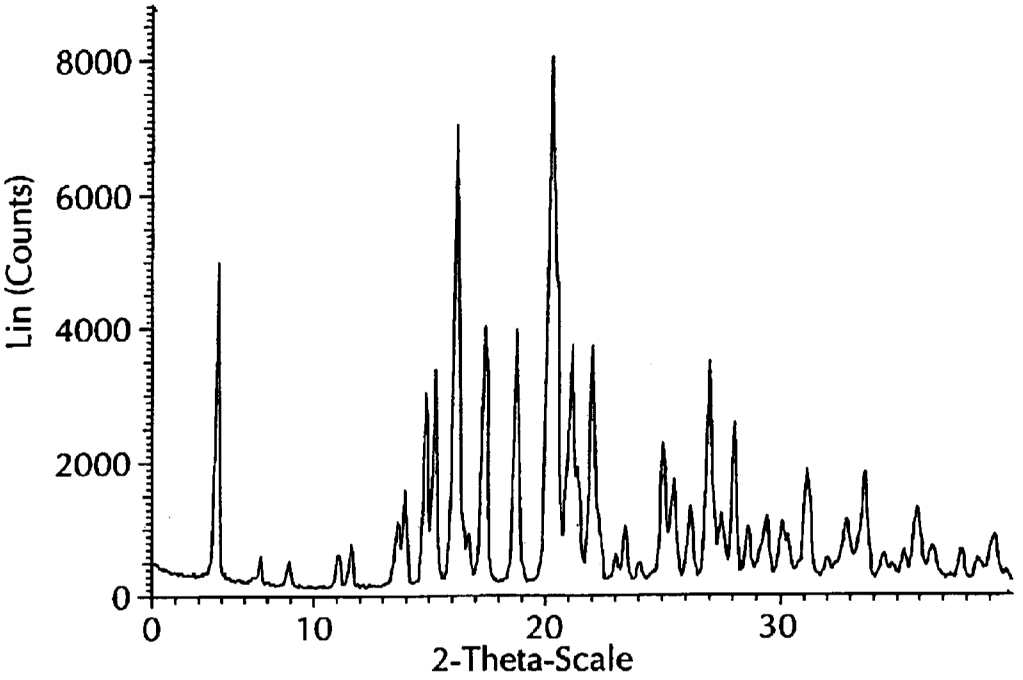
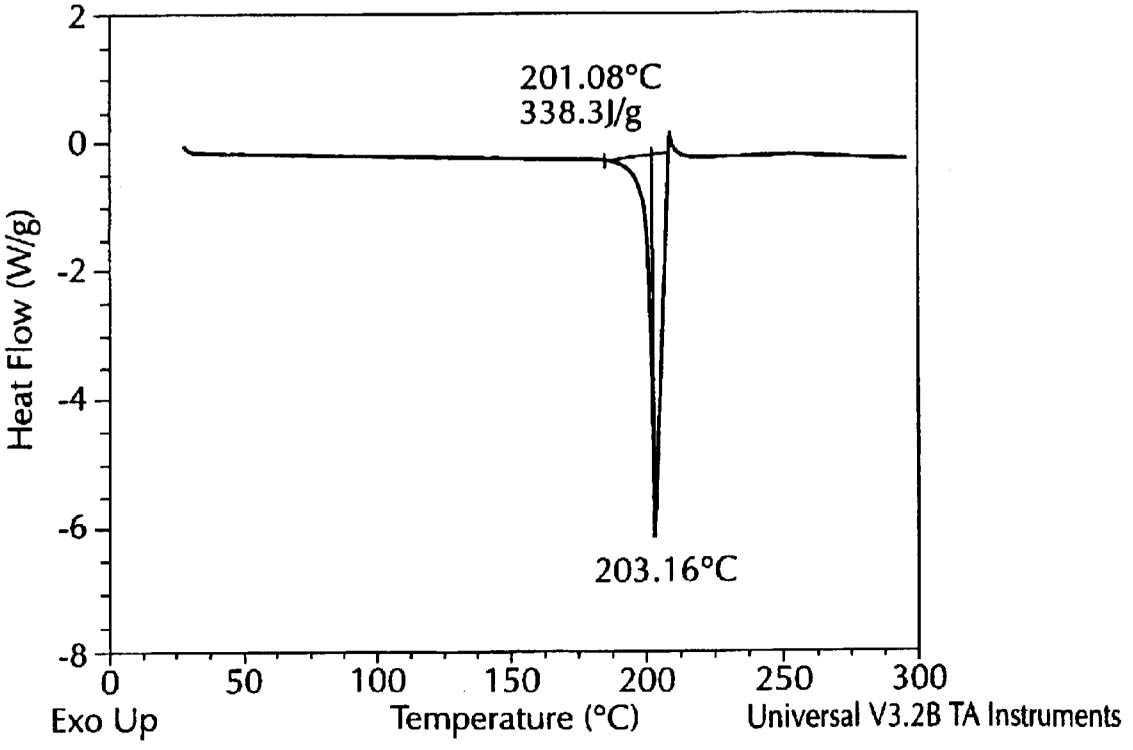

8000
6000
4000
2000
0
Lin (Counts)
0
10
20
30
2-Theta-Scale

FIG. 2


2
0
-2
-4
-6
-8
Heat Flow (W/g)
201.08°C
338.3J/g
203.16°C
0
50
100
150
200
250
300
Exo Up
Temperature (°C)
Universal V3.2B TA Instruments

CRYSTALLINE 3-{4-METHYL-3-[METHYL-(7H-PYRROLO[2,3-D]PYRIMIDIN-4-YL)-AMINO]-PIPERIDIN-1-YL}-3-OXO-PROPIONITRILE CITRATE

CROSS-REFERENCE TO RELATED APPLICATIONS

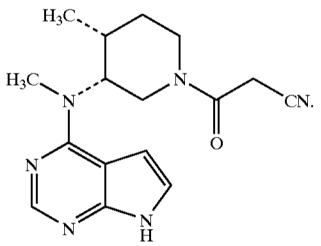
This application claims benefit of priority under 35 U.S.C. §119 (e) to U.S. Provisional Application No. 60/338,984, filed on Dec. 6, 2001 which is herein incorporated by reference in its entirety.

BACKGROUND OF THE INVENTION

This invention relates to a novel crystalline form of 3-{(3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-3-oxo-propionitrile mono citrate salt and to its method of preparation.

3-{(3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-3-oxo-propionitrile has the chemical formula $C_{16}H_{20}N_6O$ and the following structural formula

II



Its synthesis is described in co-pending U.S. patent application Ser. No. 09/732,669, filed Dec. 8, 2000 and U.S. provisional patent application serial No. 60/294,775, filed May 31, 2001, commonly assigned to the assignee of the present invention and which are incorporated herein by reference in their entirety. 3-{(3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-3-oxo-propionitrile, and its corresponding citrate salt, are useful as inhibitors of protein kinases, such as the enzyme Janus Kinase 3 (hereinafter also referred to as JAK3) and as such are useful therapy as immunosuppressive agents for organ transplants, xeno transplation, lupus, multiple sclerosis, rheumatoid arthritis, psoriasis, Type I diabetes and complications from diabetes, cancer, asthma, atopic dermatitis, autoimmune thyroid disorders, ulcerative colitis, Crohn's disease, Alzheimer's disease, Leukemia and other indications where immunosuppression would be desirable.

The crystalline form of 3-{(3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-3-oxo-propionitrile mono citrate salt was determined to have solid state properties which are acceptable to support tablet development.

The present invention is also directed to processes for preparing crystalline 3-{(3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-3-oxo-propionitrile mono citrate salt.

SUMMARY OF THE INVENTION

This invention relates to a novel crystalline form of 3-{(3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-3-oxo-propionitrile mono citrate salt which is useful in (a) treating or preventing

a disorder or condition selected from organ transplant rejection, xeno transplation, lupus, multiple sclerosis, rheumatoid arthritis, psoriasis, Type I diabetes and complications from diabetes, cancer, asthma, atopic dermatitis, autoimmune thyroid disorders, ulcerative colitis, Crohn's disease, Alzheimer's disease, leukemia and other autoimmune diseases or (b) the inhibition of protein kinases or Janus Kinase 3 (JAK3) in a mammal, including a human. The novel crystalline form melts at a temperature of about 203° C. to about 210° C., and exhibits an X-ray diffraction pattern with characteristic peaks expressed in degrees 2-theta (2θ) at 5.7, 16.1, 20.2 and 20.5, as depicted in FIG. **1**. A discussion of the theory of X-ray powder diffraction patterns can be found in Stout & Jensen, *X-Ray Structure Determination; A Practical Guide*, MacMillan Co., New York, N.Y. (1968), which is incorporated by reference in its entirety.

This invention also relates to the crystalline form of 3-{(3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-3-oxo-propionitrile mono citrate salt with a differential scanning calorimetry thermogram, as depicted in FIG. **2**, having a characteristic peak at a temperature between about 203° C. to about 210° C., having an onset at a temperature between about 199° C. to about 206° C. at a scan rate of 5° C. per minute.

The invention also relates to an amorphous form of 3-{(3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-3-oxo-propionitrile mono citrate salt.

The present invention also relates to a pharmaceutical composition for (a) treating or preventing a disorder or condition selected from organ transplant rejection, xeno transplation, lupus, multiple sclerosis, rheumatoid arthritis, psoriasis, Type I diabetes and complications from diabetes, cancer, asthma, atopic dermatitis, autoimmune thyroid disorders, ulcerative colitis, Crohn's disease, Alzheimer's disease, Leukemia, and other autoimmune diseases or (b) the inhibition of protein kinases or Janus Kinase 3 (JAK3) in a mammal, including a human, comprising an amount of a compound of formula I, effective in such disorders or conditions and a pharmaceutically acceptable carrier.

The present invention also relates to a method for the inhibition of protein typrosine kinases or Janus Kinase 3 (JAK3) in a mammal, including a human, comprising administering to said mammal an effective amount of a compound of formula I.

The present invention also relates to a method for treating or preventing a disorder or condition selected from organ transplant rejection, xeno transplation, lupus, multiple sclerosis, rheumatoid arthritis, psoriasis, Type I diabetes and complications from diabetes, cancer, asthma, atopic dermatitis, autoimmune thyroid disorders, ulcerative colitis, Crohn's disease, Alzheimer's disease, Leukemia, and other autoimmune diseases in a mammal, including a human, comprising administering to said mammal an amount of a compound of formula I, effective in treating such a condition.

The present invention also relates to a process for for preparing 3-{(3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-3-oxo-propionitrile mono citrate salt comprising reacting 3-{(3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-3-oxo-propionitrile with citric acid.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a characteristic X-ray powder diffraction pattern for 3-{(3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]

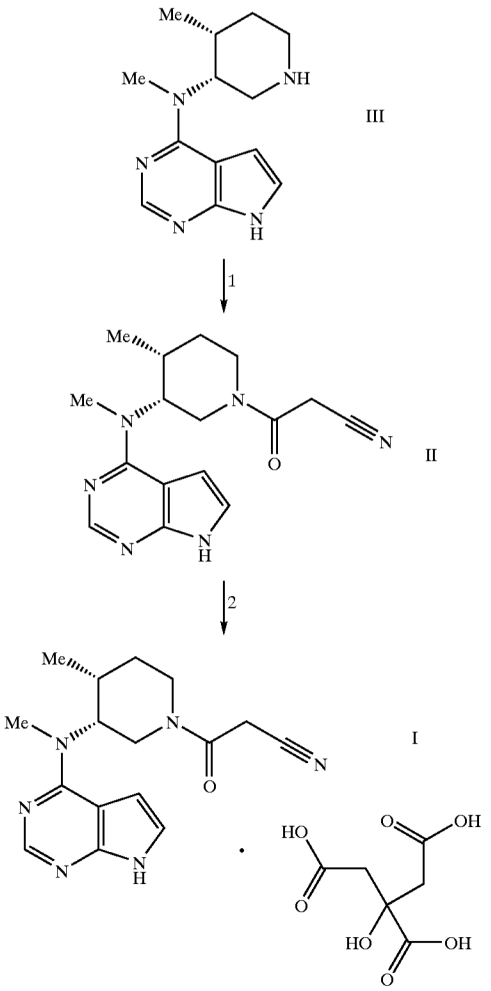
pyrimidin-4-yl)-amino]-piperidin-1-yl}-3-oxo-propionitrile mono citrate salt. (Vertical Axis: Intensity (counts); Horizontal Axis: Two Theta (Degrees)).

FIG. **2** is a characteristic differential scanning calorimetry thermogram of 3-{(3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-y)-amino]-piperidin-1-yl}-3-oxo-propionitrile mono citrate salt. (Scan Rate: 5° C. per minute; Vertical Axis: Heat Flow (w/g); Horizontal Axis: Temperature (° C.)).

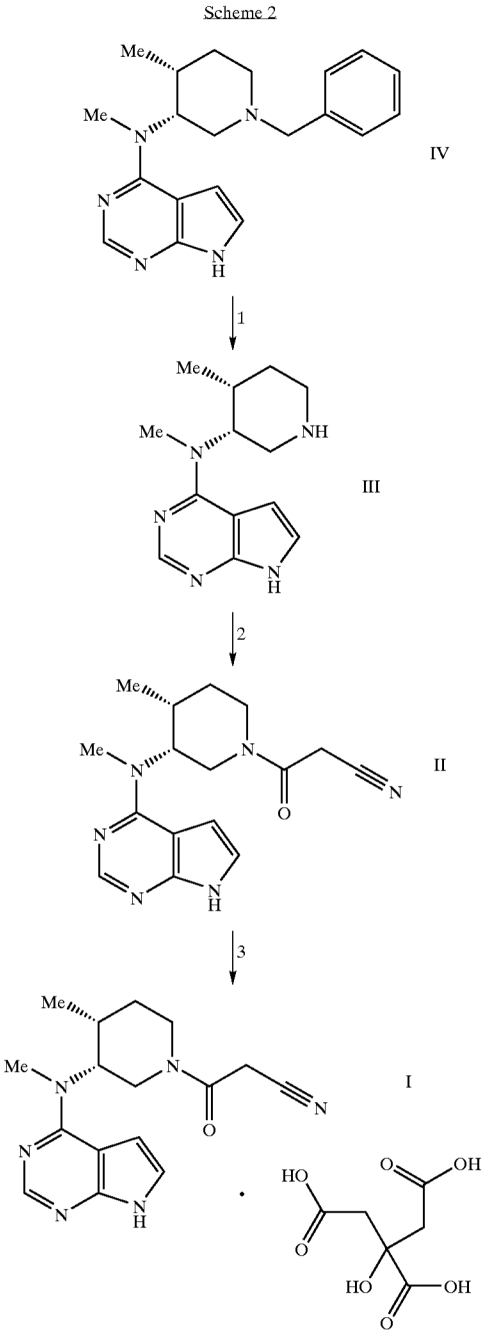
DETAILED DESCRIPTION OF THE INVENTION

The crystalline form of the compound of this invention 3-{4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-3-oxo-propionitrile mono citrate salt is prepared as described below.

Scheme 1



Scheme 2



In reaction 1 of Scheme 1, the (3R,4R)-methyl-(4-methyl-piperidin-3-yl)-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amine compound of formula III is converted to the corresponding 3-{(3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-3-oxo-propionitrile compound of formula II by reacting III with cyano-acetic acid 2,5-dioxo-pyrrolidin-1-yl ester in the presence of a base, such as triethylamine. The reaction mixture is stirred, at room temperature, for a time period between about 15 minutes to about 2 hours, preferably about 30 minutes.

In reaction 2 of Scheme I, the 3-{(3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-3-oxo-propionitrile compound of formula II is converted to the corresponding 3-{(3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-

piperidin-1-yl}-3-oxo-propionitrile mono citrate salt compound of formula I by reacting II with aqueous citric acid.

In reaction 1 of Scheme 2, the ((3R,4R)-1-benzyl-4-methyl-piperidin-3-yl)-methyl-(7H-pyrrolo[2,3-d] pyrimidin-4-yl)-amine compound of formula IV is converted tot the corresponding the (3R,4R)-methyl-(4-methyl-piperidin-3-yl)-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amine compound of formula III by treating IV with hydrogen in the presence of 20% palladium hydroxide on carbon (50% water by weight) and a polar protic solvent, such as ethanol. The reaction mixture is stirred at a temperature between about 45° C. to about 75° C., preferably about 60° C., under a pressure of about 60 psi, preferably about 50 psi, for a time period between about two days to about four days, preferably about three days.

In reaction 2 of Scheme 2, the (3R,4R)-methyl-(4-methyl-piperidin-3-yl)-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amine compound of formula III is converted to the corresponding 3-{(3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d] pyrimidin-4-yl)-amino]-piperidin-1-yl}-3-oxo-propionitrile compound of formula II by reaction III with cyano-acetic acid 2,5-dioxo-pyrrolidin-1-yl ester in the presence of a polar protic solvent, such as ethanol. The reaction mixture is stirred, at room temperature, for a time period between about 30 minutes to about 3 hours, preferably about 1 hour.

In reaction 3 of Scheme 2, the 3-{(3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-3-oxo-propionitrile compound of formula II is converted to the corresponding 3-{(3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-3-oxo-propionitrile mono citrate salt compound of formula I by reacting II with citric acid in the presence of a polar solvent, such as acetone. The reaction mixture is stirred at a, temperature between about 30° C. to about 50° C., preferably about 40° C., for a time period between about 1 hour to about 3 hours, preferably about 2 hours. The resulting reaction mixture may optionally be further stirred at a temperature between about 20° C. to about 40° C., preferably about 30° C., for a time period between about 3 hours to about 5 hours, preferably about 4 hours, followed by additional stirring, at room temperature, for a time period between about 16 hours to about 20 hours, preferably about 18 hours.

The compositions of the present invention may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers.

For oral administration, the pharmaceutical compositions may take the form of tablets 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.

A proposed dose of the active compounds of the invention for oral, parenteral or buccal administration to the average adult human for the treatment of the conditions referred to above (e.g., rheumatoid arthritis) is 0.1 to 1000 mg of the active ingredient per unit dose which could be administered, for example, 1 to 4 times per day.

A compound of formula I administered in a pharmaceutically acceptable form either alone or in combination with one or more additional agents which modulate a mammlian immune system or with antiinflammatory agents, agents which may include but are not limited to cyclosporin A (e.g. Sandimmune® or Neoral®, rapamycin, FK-506 (tacrolimus), leflunomide, deoxyspergualin, mycophenolate (e.g. Cellcept®, azathioprine (e.g. Imuran®), daclizumab (e.g. Zenapax®), OKT3 (e.g. Orthocolone®), AtGam, aspirin, acctaminophen, ibuprofen, naproxen, piroxicam, and antiinflmmatory steroids (e.g. prednisolone or dexamethasone); and such agents may be administered as part of the same or separate dosage forms, via the same or different routes of administration, and on the same or different administration schedules according to standard pharmaceutical practice.

FK506 (Tacrolimus) is given orally at 0.10–0.15 mg/kg body weight, every 12 hours, within first 48 hours postoperative. Dose is monitored by serum Tacrolimus trough levels.

Cyclosporin A (Sandimmune oral or intravenous formulation, or Neoral®, oral solution or capsules) is given orally at 5 mg/kg body weight, every 12 hours within 48 hours postoperative. Dose is monitored by blood Cyclosporin A trough levels.

The active agents can 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 U.S. Pat. Nos. 3,538,214, 4,060,598, 4,173,626, 3,119,742, and 3,492,397.

The ability of the compound of formula I; to inhibit Janus Kinase 3 and, consequently, demonstrate its 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-Sepaharose. 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 1–2×10^6/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 10 ug/ml PHA (Murex Diagnostics, Cat #

HA 16). After 3 days at 37° C. in 5% CO_2, cells are washed 3 times in Media, resuspended to a density of 1–2×10^6 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/0.1 ml) 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 uM. After one hour, 10 Units/ml of IL-2 is added to each test well. Plates are then incubated at 37° C., 5% CO_2 for 72 hours. Plates are then pulsed with ^{3}H-thymidine (0.5 uCi/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 ^{3}H-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 IC_{50} value (uM) is determined from this plot.

The following Examples illustrate the preparation of the compounds of the present invention 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).

EXAMPLE 1

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

Ethanol (13 liters), (3R, 4R)-methyl-(4-methyl-piperidin-3-yl)-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine (1.3 kg), cyano-acetic acid 2,5-dioxo-pyrrolidin-1-yl ester (1.5 kg), and triethylamine (1.5 liters) were combined and stirred at ambient temperature. Upon reaction completion (determined by High Pressure Liquid Chromotography (HPLC) analysis, approximately 30 minutes), the solution was filtered, concentrated and azeotroped with 15 liters of methylene chloride. The reaction mixture was washed sequentially with 12 liters of 0.5 N sodium hydroxide solution, 12 liters of brine and 12 liters of water. The organic layer was concentrated and azeotroped with 3 liters of acetone (final pot temperature was 42° C.). The resulting solution was cooled to 20° C. to 25° C. followed by addition of 10 liters of acetone. This solution was filtered and then aqueous citric acid (0.8 kg in 4 liters of water) added via in-line filter. The reaction mixture was allowed to granulate. The slurry was cooled before collecting the solids by filtration. The solids were dried to yield 1.9 kg (71%) (3R, 4R)-3-{4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-3-oxo-propionitrile mono citrate. This material was then combined with 15 liters of a 1:1 ratio of ethanol/water and the slurry was agitated overnight. The solids were filtered and dried to afford 1.7 kg (63% from (3R, 4R)-methyl-(4-methyl-piperidin-3-yl)-(7H-pyrrolo[2, 3-d]pyrimidin-4-yl)-amine) of the title compound as a white crystalline solid.

^{1}H NMR (400 MHZ)(D_2O) δ HOD: 0.92 (2H, d, J=7.2 Hz), 0.96 (1H, d, J=7.6 Hz), 1.66 (1H, m), 1.80 (1H, m), 2.37 (1H, m), 2.58 (2H, ½ ABq, J=15.4 Hz), 2.70 (2H, ½ ABq, J=154 Hz), 3.23 (2H, s), 3.25 (1H, s), 3.33 (1H, m), 3.46 (1H, m), 3.81 (4H, m), 4.55 (1H, m), 6.65 (1H, d, J=3.2 Hz), 7.20 (1H, t, J=3.2 Hz), 8.09 (1H, m).

EXAMPLE 2

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

To a solution of 79 grams of ((3R, 4R)-1-Benzyl-4-methyl-piperidin-3-yl)-methyl-(7H-pyrrolo[2,3-d] pyrimidin-4-yl)-amine dissolved in 2 liters of ethanol was added 79 grams of 20% palladium hydroxide on carbon (50% water by weight) and the mixture agitated under an atmospheric pressure of 50 psi hydrogen for three days (conducting the hydrogenolysis at elevated temperature [50° C. to 70° C.] significantly decreases reaction times). After the catalyst was removed by filtration through Celite®, 51 grams of cyano-acetic acid 2,5-dioxo-pyrrolidin-1-yl ester was added to the ethanolic solution and the resulting mixture stirred at room temperature for 1 hour, at which time the ethanol was removed under reduced pressure. The residue was redissolved in 1.0 liters of dichloromethane and the solution sequentially washed with 0.6 liters of saturated aqueous sodium bicarbonate and 0.4 liters saturated sodium bicarbonate. The combined aqueous layers were back-washed with 0.4 liters of dichloromethane, the dichloromethane layers combined, dried over magnesium sulfate, filtered and concentrated in vacuo affording 61 grams of amber oil. This material was then redissolved in 2.1 liters of acetone and the solution heated to 40° C. Finely ground citric acid (37 grams) was added slowly (as a solid) to the solution. The mixture continued stirring at 40° C. for two hours (granulation was complete). After cooling to room temperature, the solids were collected by filtration, washed with acetone and dried in vacuo affording 78.5 grams (66% from ((3R, 4R)-1-Benzyl-4-methyl-piperidin-3-yl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine) of the title compound as a slightly off-white crystalline solid.

EXAMPLE 3

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

A stirred solution of (3R,4R)-3-{4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-3-oxo-propionitrile (230 mg/0.74 mmol) dissolved in 23 mL of acetone was heated to 40° C. To this solution was added 155 mg (0.81 mmol) of finely ground citric acid. The resulting mixture stirred at 40° C. for 2 hours, then at 30° C. for 4 hours followed by stirring at room temperature for an additional 18 hours. At this point, the solids were collected by filtration, washed with acetone and dried in vacuo affording 280 mg (75%) of the title compound as a white crystalline solid.

EXAMPLE 4

Method for Collecting Powder X-Ray Diffraction for 3-{(3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2, 3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-3-oxo-propionitrile Mono Citrate Salt

Powder x-ray diffraction patterns for 3-{(3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-3-oxo-propionitrile mono citrate salt

were collected using a Bruker D5000 diffractometer (Madison, Wis.) equipped with copper radiation, fixed slits (1.0, 1.0, 0.6 mm) and a Kevex solid state detector. Data was collected as follows: Cu anode; wavelength 1: 1.54056; wavelength 2: 1.54439 (rel. intensity: 0.500); from 3.0 to 40.0 degrees in 2 theta using a step size of 0.04 degrees and a step time of 1.0 seconds. The results are summarized in Table 1.

TABLE 1

List of Powder X-ray Diffraction Peaks (±0.2 degrees)

Angle 2-theta	d-value angstrom	Intensity* (rel.) %	Angle 2-theta	d-value angstrom	Intensity* (rel.) %
5.7	**15.4**	**62.4**	25.5	3.5	21.5
7.7	11.5	7.5	26.2	3.4	16.7
8.9	9.9	6.8	27.0	3.3	43.6
11.0	8.0	7.7	27.5	3.2	15.1
11.5	7.7	9.7	28.1	3.2	32.1
13.6	6.5	13.7	28.7	3.1	12.6
13.9	6.4	19.6	29.4	3.0	14.8
14.8	6.0	38	30.1	3.0	13.8
15.2	5.8	42.4	30.3	2.9	11
16.1	**5.5**	**87.8**	31.1	2.9	23.4
16.6	5.3	11.4	32.0	2.8	6.8
17.3	5.1	50.8	32.8	2.7	14.1
18.7	4.7	49.7	33.6	2.7	22.9
20.2	**4.4**	**100**	34.4	2.6	7.7
20.5	**4.3**	**59.4**	34.8	2.6	5.7
21.1	4.2	46.7	35.3	2.5	8.5
21.4	4.1	24	35.9	2.5	16.3
22.0	4.0	46.5	36.5	2.5	9.2
23.0	3.9	7.5	37.8	2.4	8.5
23.4	3.8	12.8	38.5	2.3	6.8
24.0	3.7	6	39.2	2.3	11.1
25.0	3.6	28.3			

*The peak intensities may change depending on the crystal size and habit.

What is claimed is:

1. A crystalline form of 3-{(3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-3-oxo-propionitrile mono citrate salt.

2. A crystalline form of 3-{(3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-3-oxo-propionitrile mono citrate salt according to claim **1**, comprising an x-ray powder diffraction pattern having characteristic peaks expressed in degrees two-theta at approximately 5.7, 16.1, 20.2 and 20.5.

3. A crystalline form according to claim **2**, comprising a powder diffraction pattern having characteristic peaks expressed in degree of 2-theta at approximately:

Angle 2-theta	Angle 2-theta	Angle 2-theta	Angle 2-theta
5.7	17.3	25.5	32.8
7.7	18.7	26.2	33.6
8.9	20.2	27.0	34.4
11.0	20.5	27.5	34.8
11.5	21.1	28.1	35.3
13.6	21.4	28.7	35.9
13.9	22.0	29.4	36.5
14.8	23.0	30.1	37.8
15.2	23.4	30.3	38.5
16.1	24.0	31.1	39.2
16.6	25.0	32.0.	

4. A crystalline form of 3-{(3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-3-oxo-propionitrile mono citrate salt according to claim **1**, having an onset melting temperature of between about 199° C. to about 206° C.

5. An amorphous form of 3-{(3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-3-oxo-propionitrile mono citrate salt.

6. A process for preparing 3-{(3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-3-oxo-propionitrile mono citrate salt comprising reacting 3-{(3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-3-oxo-propionitrile with citric acid.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,965,027 B2
APPLICATION NO. : 10/310078
DATED : November 15, 2005
INVENTOR(S) : Mark E. Flanagan et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title Page

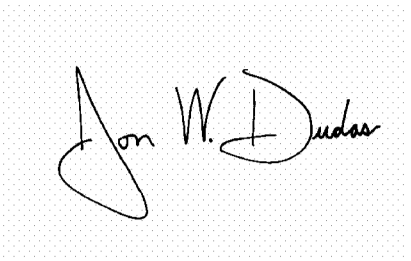
(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 7 days.

should read

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 111 days.

Signed and Sealed this

Thirtieth Day of January, 2007



JON W. DUDAS
Director of the United States Patent and Trademark Office

EXHIBIT B

US00RE41783E

(19) **United States**

(12) **Reissued Patent**

Blumenkopf et al.

(10) **Patent Number: US RE41,783 E**

(45) **Date of Reissued Patent: Sep. 28, 2010**

(54) **PYRROLO[2,3-D]PYRIMIDINE COMPOUNDS**

(75) Inventors: **Todd A. Blumenkopf**, Old Lyme, CT (US); **Mark E. Flanagan**, Gales Ferry, CT (US); **Michael J. Munchhof**, Salem, CT (US)

(73) Assignee: **Pfizer Inc.**, Madison, NJ (US)

(21) Appl. No.: **12/577,790**

(22) Filed: **Oct. 13, 2009**

Related U.S. Patent Documents

Reissue of:

(64) Patent No.: **6,627,754**
Issued: **Sep. 30, 2003**
Appl. No.: **09/732,669**
Filed: **Dec. 8, 2000**

U.S. Applications:

(60) Provisional application No. 60/170,179, filed on Dec. 10, 1999.

(51) **Int. Cl.**
C07D 487/04 (2006.01)
A61K 31/519 (2006.01)
A61P 11/06; A61P 17/06; A61P 19/02; A61P 37/06

(52) **U.S. Cl.** **514/265.1**; 544/280

(58) **Field of Classification Search** 544/280; 514/265.1

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,037,980	A	6/1962	Hitchings et al.	260/256.4
3,119,742	A	1/1964	Heimlich et al.	167/82
3,492,397	A	1/1970	Peters et al.	424/20
3,538,214	A	11/1970	Polli et al.	424/19
4,060,598	A	11/1977	Groppenbacher et al.	424/33
4,173,626	A	11/1979	Dempski et al.	424/19
4,725,599	A	2/1988	Glazer et al.	514/258
4,814,477	A	3/1989	Wijnberg et al.	658/86
4,977,159	A	12/1990	Sevrin et al.	514/292
5,389,509	A	2/1995	Maskasky	430/567
5,496,946	A	3/1996	Akimoto et al.	544/321
5,559,128	A	9/1996	Chakravarty et al.	514/323
5,686,457	A	11/1997	Traxler et al.	514/258
6,080,747	A	6/2000	Uckun et al.	514/259
6,136,595	A	10/2000	Ihle et al.	435/320.1
6,180,636	B1	1/2001	Traxler et al.	514/258
6,187,552	B1	2/2001	Roberds et al.	435/7.93
6,310,063	B1	10/2001	Ge et al.	514/234.5
6,610,847	B2	8/2003	Blumenkopf et al.	544/280
6,627,754	B2	9/2003	Blumenkopf et al.	544/280
6,635,762	B1	10/2003	Blumenkopf et al.	544/280
6,696,567	B2	2/2004	Blumenkopf et al.	544/280
6,890,929	B2	5/2005	Blumenkopf et al.	514/258
6,956,041	B2	10/2005	Blumenkopf et al.	514/258.1
6,962,993	B2	11/2005	Blumenkopf et al.	544/280
6,965,027	B2	11/2005	Flanagan et al.	544/280
7,079,208	B2	7/2006	Kim et al.	349/119
7,192,963	B2	3/2007	Blumenkopf et al.	514/265.1
7,250,420	B2	7/2007	Changelian	514/265.1
7,301,023	B2	11/2007	Flanagan et al.	544/280
7,432,370	B2	10/2008	Wilcox et al.	540/280
7,569,569	B2	8/2009	Blumenkopf et al.	514/258.1
2002/0019526	A1	2/2002	Blumenkopf et al.	544/280
2002/0068746	A1	6/2002	Blumenkopf et al.	514/265.1
2004/0053947	A1	3/2004	Blumenkopf et al.	514/265.1
2004/0102627	A1	5/2004	Ripin	544/60
2005/0159433	A1	7/2005	Changelian	514/265.1
2005/0159434	A1	7/2005	Flanagan et al.	514/265.1
2005/0171128	A1	8/2005	Blumenkopf et al.	514/265.1
2006/0040965	A1	2/2006	Farthing et al.	514/265.1
2007/0292430	A1	12/2007	Blumenkopf et al.	424/141.1

FOREIGN PATENT DOCUMENTS

EP	111864	6/1984
EP	302788	2/1989
EP	0334636	9/1989
EP	478363	4/1992
EP	618196	10/1994
EP	0795556	9/1997
EP	0682027	10/1997
GB	0915303	1/2003
JP	0710877	1/1995
JP	7330732	12/1995

(Continued)

OTHER PUBLICATIONS

U.S. Appl. No. 09/335,121, filed Jun. 17, 1999, Blumenkopf.

Baird, A.M., et al., *J. Leukocyte Biology*. "T Cell Development and Activation in JAK–3–Deficient Mice", vol. 63, pp. 669–672 (1998).

Candotti, F., et al. *Springer Semin. Immunopathology*, "Severe Combined Immune Deficiencies due to Defects in the Common y Chain–JAK3 Signaling Pathway", vol. 19, pp. 401–415 (1998).

(Continued)

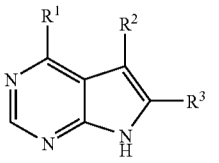
Primary Examiner—Venkataraman Balasubramanian

(74) *Attorney, Agent, or Firm*—Ram W. Sabnis

(57) **ABSTRACT**

A compound of the formula

I



wherein R^1, R^2 and R^3 are as defined above, which are inhibitors of the enzyme protein kinases such as Janus Kinase 3 and as such are useful therapy as immunosuppressive agents for organ transplants, xeno transplation, lupus, multiple sclerosis, rheumatoid arthritis, psoriasis, Type I diabetes and complications from diabetes, cancer, asthma, atopic dermatitis, autoimmune thyroid disorders, ulcerative colitis, Crohn's disease, Alzheimer's disease, Leukemia and other autoimmune diseases.

4 Claims, No Drawings

FOREIGN PATENT DOCUMENTS

WO	WO 9519774	7/1995
WO	9802438	7/1996
WO	WO 9640142	12/1996
WO	9702262	1/1997
WO	9702266	1/1997
WO	WO 9713771	4/1997
WO	WO 9718212	5/1997
WO	9727199	7/1997
WO	9728161	8/1997
WO	9732879	9/1997
WO	9749706	12/1997
WO	9802437	1/1998
WO	9807726	2/1998
WO	9823613	6/1998
WO	WO9824446	6/1998
WO	9833798	8/1998
WO	WO9900368	1/1999
WO	WO 9951599	10/1999
WO	WO 9961428	12/1999
WO	WO 9965908	12/1999
WO	WO 9965909	12/1999
WO	WO 0000202	1/2000
WO	WO 0010981	3/2000
WO	WO 0017203	3/2000
WO	WO 0142246	6/2001
WO	WO0170673	9/2001
WO	WO0181347	11/2001
WO	WO 0200661	1/2002
WO	WO02057244	7/2002
WO	WO0296909	12/2002
WO	WO03048162	6/2003
WO	WO04021979	3/2004

OTHER PUBLICATIONS

Chen, E., et al., *Transplantation Proceedings*, Advances in Cytokine Signaling: The Role of Jaks and STATs, vol. 31, pp. 1482–1487 (1999).

Eynon, E.E., et al., *Journal of Interferon and Cytokine Research*, "Disruption of Cytokine Signaling in Lymphoid Development: Unique Contributions of the Common Cytokine Gamma Chaine and the Jak3 Kinase", vol. 16, pp. 677–684 (1996).

Ghosh, S., et al., *Acta Crystallographica Section C, Crystal Struction Communications,* "4–[(3–Bromo–4–hydroxyphenyl)amino]–6,7–dimethoxyquinazolin–1–ium chloride methanol solvate and 4–[(3–hydroxyphenyl)amino]–6,7–di–methoxy–1–quinazolinium chloride", vol. C57, pp. 76–78 (2001).

Hanke, J., et al., *Inflammation Research*, "Role of Tyrosine Kinases in Lymphocyte Activation: Targets for drug Intervention", vol. 44, pp. 357–371 (1995).

Ihle, J., *Advances in Immunology*, "The Janus Protein Tyrosine Kinase Family and Its Role in Cytokine Signaling", vol. 60, pp. 1–35 (1995).

Ihle, J., *Semin. Immunology*, "The Janus Protein Tyrosine Kinases in hematopoietic Cytokine Signaling", vol. 7, pp. 247–254 (1995).

Kirken, R.A., et al., *Cytokine*, "Activation of JAK3, but Not JAK1, is Critical for IL–2–Induced Proliferation and Stats 5 Recruitment by a Cooh–Terminal Region of the IL–2 Receptor β–Chain", vol. 7, pp. 689–700 (1995).

Liu, K., et al., Current Opinion of Immunology, "JAK/STAT Signaling by Cytokine Receptors", vol. 10, pp. 271–278 (1998).

Li, X.C., et al. *Journal of Immunology*, "Blocking the Commonγ–Chain of Cytokine Receptors Induces T Cell Apoptosis and Long–ter Islet Allograft Survival", vol. 164, pp. 1193–1199 (2000).

Leonard, W., et al., *Annual Review of Immunology*, "JAKS and STATS: Biological Implications", vol. 16, pp. 293–322 (1998).

Malaviya, R., et al., *Journal of Pharmacology and Experimental Therapeutics*, "Treatment of Allergic Asthma by Targeting Janus Kinase 3–Dependent Leukotrene Synthesis in Mast Cells with 4–(3–hydroxyphenyl)amino–6,7–demethoxyquinazoline (WHI–P97)", vol. 295, No. 3, pp. 912–926 (2000).

Malaviya, R., et al. *Biochemical and Biophysical Research Communications*, "Genetic and Biochemical Evidence for a Critical Role of Janus Kinase (JAK)–3 in Mast Cell Mediated Type I Hypersensitivity Reactions", vol. 257, pp. 807–813 (1999).

Malaviya, R., et al., *Journal of Biological Chemistry*, "Targeting Janus Kinase 3 in Mast Cells Prevents Immediate Hypersensitivity Reactions and Anaphylaxis", vol. 274(38), pp. 27028–27038 (1999).

Malabarba, M.G., et al., *Journal of Biological Chemistry*, "Activation of JAK3, but not JAK1, Is Critical to Interleukin–4 (IL4) Stimulated Proliferation and Requires a Membrane–proximal Region of IL4 Receptor *" vol. 270(16), pp. 9630–9637 (1995).

Moriggi, R., et al., *Immunity*, "Stat5 Activation is Uniquely Associated with Cytokine Signaling in Peripheral T Cells", vol. 11, pp. 225–230 (1999).

Musso, T., et al., *Journal of Experimental Medicine*, "Regulation of JAK3 Expression in Human Monocytes: Phosphorylation in Response to Interleukins 2, 4, and 7", vol. 181, pp. 1425–1431 (1995).

Nelson B., et al., *Proceedings of National Academy of Science USA*, "Requirement for an initial signal from the membrane–proximal Region of the Interleukin 2 Receptor γ_c Chain for Janus Kinase Activation Leading to T Cell Proliferation", vol. 94, pp. 1878–1883 (1997).

Notarangelo, L.D., et al., *Progressive in Immunodeficiency*, "Severe Combined Immune Deficiency Due to Defects of the JAK3 Tyrosine Kinase", vol. 6, pp. 61–68 (1996).

Oakes, S.A., et al., *Immunity*, "Signaling via IL–2 and IL–4 in JAK3–Deficient Severe Combined Immunodeficiency Lymphocytes: JAK3–Dependent and Independent Pathways", vol. 5, pp. 605–615 (1996).

O'Shea, J.J., et al., *Nature*, "Phosphorylation and Activation of the Jak–3 Janus Kinase in Response to Interleukin–2", vol. 370(14), pp. 151–153 (1994).

Russell, S.M., et al., Science, "Interaction of IL–2Rβ and γ^c Chains with Jak1 and Jak3: Implications for XSCID and XCID" vol. 266, pp. 1042–1045 (1994).

Sudebeck, E. A., et al., *Clinical Cancer Research*, "Struture–based Design of Specific Inhibitors of Janus Kinase 3 as Apoptosis–Inducing Antileukemic Agents" vol. 5 pp. 1569–1582 (1999).

Sudebeck, E.A. et al., *IDRUGS*, "Recent Advances in JAK3 Kinase Inhibitors", vol. 2(10), pp. 1026–1030 (1999).

Sudebeck, E.A. et al., *Acta Crystallogr..Section C :Structure Communications*, "An Inhibitor of Janus Kinase 3:4–4(4–hydroyphenynlamino)–6–7–dimethoxyquinazolin–1–ium chloride methanol solvate" vol. C56, pp. 1282–1283 (2000).

Thomis, D.C., et al., *The Journal of Immunology*, "The JAK Family Tyrosine Kinase JAK3 is Required for IL–2 Synthesis by Naïve/Resting CD4 T Cells", vol. 163 pp. 5411–5417 (1999).

Thomis, D.C. et al., *Journal of Experimental Medicine*, "Peripheral Expression of JAK3 is Required to Maintain T Lymphocyte Function", vol. 185(2) pp. 197–206 (1997).

Traxler, et al., *Expert Opinion on Therapeutic Patents*, "Protein Tyrosine Kinase Inhibitors in Cancer Treatment", vol. 7, pp. 571–588 (1997).

Traxler, et al. *J.Med. Chem.*, "4–(Phenylamino)pyrrolopyrimidines: Potent and Selective, ATP Site Directed Inhibitors of the EGF–Receptor Protein Tyrosine Kinase", vol. 39, pp. 2285–2292 (1996).

Trieu, V.N. et al., *Biochemical and Biophysical Research Communications*, "A Specific Inhibitor of Janus Kinase–3 Increases Survival In a Transgenic Mouse Model of Amyotrophic Lateral Sclerosis", vol. 267, pp. 22–25 (2000).

Uckun, F.M., et al., *Clinical Cancer Research*, "In Vivo Toxicity and Pharmacokinetic Features of the Janus Kinase 3 Inhibitor WHI–P131[4–(4^1–Hydroxphenyl)–Amino–6, 7–Dimethoxyquinazoline]", vol. 5, pp. 2954–2962 (1999).

Wang, L.H., et al., *Journal of Immunology*, "JAK3, STAT, and MAPK Signaling Pathways as Novel Molecular Targets for the Tyrphostin AG–490 regulation of IL–2–Mediated T Cell Response" vol. 162, pp. 3897–3904 (1999).

Shouda et al., *Journal of Clinical Invest.*, "Induction of the cytokine signal regulator SOCS3/CIS3 as a therapeutic strategy for treating inflammatory arthritis" 108(2):1781–1788 (1988).

Aringer et al., *Life Sciences*, "Janus Kinases and Their Role in Growth and Disease" vol. 64(24):2173–2186 (1999).

Bayley, C.R., et al. Chirality in Industry: the commercial manufacture and application of optically active compounds, J. Riley & Sons, Inc. XP002208814, pp. 69–77 (1992).

Jacques, Jean, Enantiomers, Racemates, and Resolutions, J. Riley & Sons, Inc. XP002208813, pp. 251–273; 252;259–260 (1981).

March, Jerry, Advanced Organic Chemistry: Reactions, Mechanisms and Structure, 4th ed., Wiley & Sons, pp. 641–644 (1992).

Groom, Colin R. et al., "Protein kinase drugs– optimism doesn't wait on facts, " *Drug Discovery Today*, vol. 7, No. 15, pp. 801–802 (2002).

Hong, J.C. et al, "Immunosuppressive Agents in Organ Transplantation: Past, Present, and Future," *Semin. Nephrol.*, vol. 20, No. 2, pp. 108–125 (2000).

Baldwin et al., "Anti–thymocyte globulin treatment is addocaited with complement deposition in early cardiac transplant biopsies," *J. of Heart and Lung Transplantation*, vol. 20(2), pp. 155–156 (2001).

Berge et al., "Pharmaceutical Salts," *Journal of Pharmaceutical Sciences*, vol. 66(1), pp. 1–19 (1977).

Hartinick et al, "Reversible sensorineural hearing loss following administration of muronab–CD3 (OKT3) for cardiac renal transplant immunosuppression," *Ann Otol. Rhinol. Laryngol.*, vol. 109(1), pp. 45–47 (2000).

Palmer, A.M., "Pharmacotherapy for Alzheimer's disease: progress and prospects," *Trends in Pharmacological Sciences*, vol. 23(9), pp. 426–433 (2002).

Armour, D.R., et al., "Tetrazole NKI Receptor Antagonists: The Identification of an Exceptionally Potent Orally Active Antiemetic Compound" *Bioorg. Med. Chem. Lett.*, vol. 6, No. 9, pp. 1015–1020 (1996).

Biel, J.H., et al., "Aminolysis and Hydrazinolysis Products of N–Methyl–3–chloropiperidine. Non–mercurial Diuretic Agents," *J. Am. Chem. Soc.* vol. 81, pp. 2527–2532 (1959).

Cooper, G.H., et al., "Synthesis of 5–Acetamido–2–acetylpiperidine," *J. Chem. Soc.* (*C*), pp. 772–777 (1971).

Crider, A.M., et al., "Synthesis of Nitrosourea Derivatives of Pyridine and Piperidine as Potential Anticancer Agents," *J. Med. Chem.*, vol. 23, pp. 848–851 (1980).

Duhamel, et al., "Synthesis of Bicyclic Aza–enones via Lewis Acid Catalysed Michael–type Addition with Silyl Enol Ethers bearing a Nitrogen Atom." *Tetrahedron Letters*, vol. 34, No. 24, pp. 3863–3866 (1993).

Ebnoether, A., et al., "Uber Azetidin–2,4–dione (Malonimide)," *Helv. Chim. Acta*, vol. 42, pp. 918–955 (1959).

Fukuyama, T., et al., "2– and 4–Nitrobenzenesulfonamides: Exceptionally Versatile Means for Preparation of Secondary Amines and Protection of Amines," *Tetrahedron Lett.* vol. 36, pp. 6373–6374 (1995).

Glennon, R.A., et al., "2,3–Dihydro and Carbocyclic Analogues of Tryptamines: Interaction with Serotonin Receptors," *J. Med. Chem.*, vol. 25, pp. 68–70 (1982).

Iorio, M.A., et al., "Synthesis and Conformational Study of Diastereoisomeric 4–Methyl–3–Phenyl–3–Piperidinols and Related Esters," *Tetrahedron*, vol. 26, pp. 5519–5527 (1970).

Knight, D. W., et al., "β–Hydroxypiperidinecarboxylates: additions to the chiral pool from bakers' yeast reductions of β–ketopiperidinecarboxylates," *J. Chem. Soc. Perkin Trans. 1*, vol. 22, pp. 3673–3684 (1998).

Matsumura, Y., et al., "A Convenient Method for Introducing Oxo Group into the β–Position of Cyclic Amines and Its Application to Synthesis of δ–Aminolevulinic Acid," *Bull. Chem. Soc. Jpn.*, vol. 67, pp. 304–306 (1994).

Moon, M.W., et al, "Dopaminergic and Serotonergic Activities of Imidazoquinolinones and Related Compounds," *J. Med. Chem.*, vol. 35, pp. 1076–1092 (1992).

Nienburg, H., "3–amino–piperidin," *Chem. Ber.*, vol. 70, pp. 635–638 (1937).

Quick, J., et al., "A Convenient Synthesis of Pelletierine (2–Piperidylpropanone)," *Synthesis*, pp. 745–746 (1976).

Reitsema, R.H., et al., "Syntheses of 3–Aminopiperidines," *J. Am. Chem. Soc.*, vol. 71, pp. 1680–1682 (1949).

Ripin, David. H.B., et al., "Development of a scaleable route for the production of cis–N–benzyl–3–methylamino–4–methylpiperidine", *Org. Proc. Res. Dev.*, vol. 7 (1), pp. 115–120 (2003).

Scully Jr., F.E., "Regioselective 2–Alkylation and 2–Arylation of Piperidine and Pyrrolidine via Organolithiation of Cyclic Amines," *J. Org. Chem. Soc.*, vol. 45, pp. 1515–1517 (1980).

Scully Jr., F.E., et al., "Superoxide in Organic Synthesis: A New Mild Method for the Oxidation of Amines to Carbonyls via N–Chloramines," *J. Org. Chem. Soc.*, vol. 43, pp. 1467–1468 (1978).

Shono, T., et al., "Acetoxylation of Piperidine Derivatives at the 3–Position. Stereoselective Synthesis of Pseudoconhydrine and N–Methylpseudoconhydrine," *Chem. Lett.*, pp. 1101–1104 (1984).

Shono, T., et al., "Electroorganic Chemistry. 99. β–acetoxylation and β–Halogenation of N–Methoxycarbonyl Cyclic Amines," *J. Org. Chem.*, vol. 52, pp. 536–541 (1987).

Shono, T., et al., Electroorganic Chemistry. 60. "Electroorganic Synthesis of Enamides and Enecarbamates and Their Utilization in Organic Synthesis," *J. Am. Chem. Soc.*, vol. 104, pp. 6697–6703 (1982).

Shono, T., et al., "Anodic Oxidation of N–carbomethoxypyrrolidine: 2–Methoxy–N–Carbomethoxypyrrolidine," *Org. Synth.*, vol. 63, pp. 206–213 (1985).

Patent Abstracts of Japan, Publication No. 11158147, Published Jun. 15, 1999.

Patent Abstracts of Japan, Publication No. 2002201192, published Jul. 16, 2002.

Barlocco et al., "Analogues of 3,8–diazabicyclo[3.2.1]octanes," *Tetrahedron*, vol. 51, No. 42, pp. 11549–11556 (1995).

Cai et al., "Investigation of Practical Routes for the Kilogram–Scale Production of cis–3–Methylamino–4–methylpiperidines," *Org. Proc. Research and Dev.*, vol. 9, No. 1, pp. 51–56 (2005).

Glorius et al., "Efficient Asymmetric Hydrogenation of Pyridines," *Agnes. Chem. Int. Ed.*, vol. 43, p. 2859 (2004).

Kazimierczuk et al., "Synthesis of 2"–Deoxytubercidin, 2"–Deoxyadenosine, and Related 2"–Deoxynucleosides via a Novel Direct Stereospecific Sodium Salt Glycosylation Procedure," *J. Am. Chem. Soc.*, vol. 106, pp. 6379–6382 (1984).

Saxena et al., "Synthesis and Intiviral Activity of Certain 4–Substituted and 2,4–Disubstituted 7–[(2–Hydroxyethoxy)methyl)pyrrolo[2,3–d]pyrimidines,"*J. Med. Chem.*, vol. 31, pp. 1501–1506 (1998).

Legault et al, "Catalytic Asymmetric Hydrogenation of N–Iminopyridinium Ylides: Expedient Approach to Enantioenriched Substituted Piperidine Derivatives," *J. Am. Chem. Soc.*, vol. 127, p. 8966 (2005).

K. D. Liu, et al., *JAK/STAT signaling by cytokine receptors, Curr. Opin. Immunol.**

R. Moriggi, et al., *Stat5 Activation is Uniquely Associated with Cytokine Signaling in Peripheral T Cells, Immunity*, 11, 222 (1995).*

* cited by examiner

PYRROLO[2,3-D]PYRIMIDINE COMPOUNDS

Matter enclosed in heavy brackets [ ] appears in the original patent but forms no part of this reissue specification; matter printed in italics indicates the additions made by reissue.

This application *is a reissue of application Ser. No. 09/732,669, filed Dec. 8, 2000, now U.S. Pat. No. 6,956,041, which* claims benefit of U.S. [Divisional] *Provisional* Application No. 60/170,179, filed on Dec. 10, 1999.

BACKGROUND OF THE INVENTION

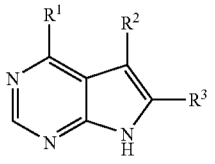
The present invention relates to pyrrolo[2,3-d]pyrimidine compounds which are inhibitors of protein kinases, such as the enzyme Janus Kinase 3 (hereinafter also referred to as JAK3) and as such are useful therapy as immunosuppressive agents for organ transplants, xeno transplation, lupus, multiple sclerosis, rheumatoid arthritis, psoriasis, Type I diabetes and complications from diabetes, cancer, asthma, atopic dermatitis, autoimmune thyroid disorders, ulcerative colitis, Crohn's disease, Alzheimer's disease, Leukemia and other indications where immunosuppression would be desirable.

This invention also relates to a method of using such compounds in the treatment of the above indications in mammals, especially humans, and the phamaceutical compositions useful therefor. 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 hematopoetic cells. This is consistent with its essential role in signaling through the receptors for IL-2, IL-4, IL-7, IL-9 and IL-15 by non-covalent association of JAK3 with the gamma chain common to these multichain receptors. XSCID 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.

SUMMARY OF THE INVENTION

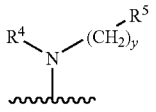
The present invention relates to a compound of the formula

I



or the pharmaceutically acceptable salt thereof; wherein

R^1 is a group of the formula

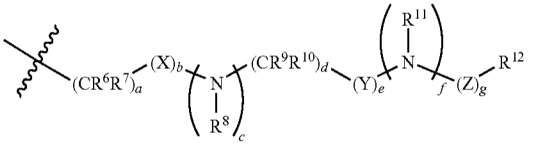


wherein y is 0, 1 or 2;

R^4 is selected from the group consisting of hydrogen, $(C_1–C_6)$alkyl, $(C_1–C_6)$alkylsulfonyl, $(C_2–C_6)$alkenyl, and $(C_2–C_6)$alkynyl wherein the alkyl, alkenyl and alkynyl groups are optionally substituted by deuterium, hydroxy, amino, trifluoromethyl, $(C_1–C_4)$alkoxy, $(C_1–C_6)$acyloxy, $(C_1–C_6)$alkylamino, $((C_1–C_6\text{alkyl})_2$ amino, cyano, nitro, $(C_2–C_6)$alkenyl, $(C_2–C_6)$alkynyl or $(C_1–C_6)$acylamino or R^4 is $(C_3–C_{10})$cycloalkyl wherein the cycloalkyl group is optionally substituted by deuterium, hydroxy, amino, trifluoromethyl, $(C_1–C_6)$acyloxy, $(C_1–C_6)$acylamino, (C_1C_6) alkylamino, $((C_1–C_6)$alkylamino, cyano, cyano$(C_1–C_6)$ alkyl, trifluoromethyl$(C_1–C_6)$alkyl, nitro, nitro$(C_1–C_6)$ alkyl or $(C_1–C_6)$alkylamino;

R^5 is $(C_2–C_9)$heterocycloalkyl wherein the heterocycloalkyl groups must be 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_1C_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, trilluoromethyl$((C_1–C_6)$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$(O)_m$, $R^5R^{16}NS(O)_m$, $R^{15}R^{16}NS(O)_m$ $(C_1–C_6)$ alkyl, $R^{15}S(O)_m$ $R^{16}N$, $R^{15}S(O)_mR^{16}N(C_1–C_6)$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

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—, 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 and $(C_1–C_6)$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, hydoxy, nitro, carboxy, $(C_2–C_6)$alkenyl, $(C_2–C_6)$alkynyl, trifluoromethyl, trifluoromethoxy, $(C_1–C_6)$alkyl, $(C_1–C_6)$alkoxy, and $(C_3–C_{10})$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—, $(C_1–C_6)$alkyamino-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, $(C_1–C_6)$aIkylsulfonylamino, $(C_1–C_6)$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.

The present invention also relates to the pharmaceutically acceptable acid addition salts of compounds of the formula I.

The acids which are used to prepare the pharmaceutically acceptable acid addition salts of the aforementioned base compounds of this invention 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 invention also relates to base addition salts of formula I. 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.

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 compounds of this invention may contain double bonds. When such bonds are present, the compounds of the invention exist as cis and trans configurations and as mixtures thereof.

Unless otherwise indicated, the alkyl and alkenyl groups referred to herein, as well as the alkyl moieties of other groups referred to herein (e.g., alkoxy), may be linear or branched, and they may also be cyclic (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl) or be linear or branched and contain cyclic moieties. Unless otherwise indicated, halogen includes fluorine, chlorine, bromine, and iodine.

$(C_2–C_9)$ Heterocycloalkyl when used herein refers to pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydropyranyl, pyranyl, thiopyranyl, aziridinyl, oxiranyl, methylenedioxyl, 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 $(C_2–C_9)$ heterocycloalkyl rings is through a carbon or a sp^3 hybridized nitrogen heteroatom.

$(C_2–C_9)$ Heteroaryl when 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, cinnolinyl, pteridinyl, purinyl, 6,7-dihydro-5H-[1]pyrindinyl, benzo[b]thiophenyl, 5,6,7,8-tetrahydroquinolin-3-yl, benzoxazolyl, benzothiazolyl, benzisothiazolyl,

benzisoxazolyl, benzimidazolyl, thianaphthenyl, isothianaphthenyl, benzofuranyl, isobenzofuranyl, isoindolyl, indolyl, indolizinyl, indazolyl, isoquinolyl, quinolyl, phthalazinyl, quinoxalinyl, quinazolinyl, benzoxazinyl, etc. One of ordinary skill in the art will understand that the connection of said (C_2–C_9) heteroaryl rings is through a carbon atom or a sp^3 hybridized nitrogen heteroatom.

(C_6–C_{10})aryl when used herein refers to phenyl or naphthyl.

Compounds of formula (I) may be administered in a pharmaceutically acceptable form either alone or in combination with one or more additional agents which modulate a mammalian immune system or with antiinflammatory agents. These agents may include but are not limited to cyclosporin A (e.g. Sandimmune® or Neoral®, rapamycin, FK-506 (tacrolimus), leflunomide, deoxyspergualin, mycophenolate (e.g. Cellcept®), azathioprine (e.g. Imuran®), daclizumab (e.g. Zenapax®. OKT3 (e.g. Orthoclone®), AtGam, aspirin, acetaminophen, ibuprofen, naproxen, piroxicam, and antiinflammatory steroids (e.g. prednisolone or dexamethasone). These agents may be administered as part of the same or separate dosage forms, via the same or different routes of administration, and on the same or different administration schedules according to standard pharmaceutical practice.

The compounds of this invention include all conformational isomers (e.g., cis and trans isomers. The compounds of the present invention have asymmetric centers and therefore exist in different enantiomeric and diastereomeric forms. This invention relates to the use of all optical isomers and stereoisomers of the compounds of the present invention, and mixtures thereof, and to all pharmaceutical compositions and methods of treatment that may employ or contain them. In this regard, the invention includes both the E and Z configurations. The compounds of formula I may also exist as tautomers. This invention relates to the use of all such tautomers and mixtures thereof.

This invention also encompasses pharmaceutical compositions containing prodrugs of compounds of the formula I. This invention also encompasses methods of treating or preventing disorders that can be treated or prevented by the inhibition of protein kinases, such as the enzyme Janus Kinase 3 comprising administering prodrugs of compounds of the formula I. 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 methioine 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.

Preferred compounds of formula I include those 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.

Other preferred compounds of formula I include those 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.

Other preferred compounds of formula I include those 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.

Other preferred compounds of formula I include those 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.

Other preferred compounds of formula I include those 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—.

Other preferred compounds of formula I include those 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.

Other preferred compounds of formula I include those 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.

Other preferred compounds of formula I include those 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.

Other preferred compounds of formula I include those 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.

Other preferred compounds of formula I include those 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.

Other preferred compounds of formula I include those wherein a is 1; b is 1; X is carbonyl; c is 1; d is 0; e is 0; f is 0; and g is 0.

Other preferred compounds of formula I include those wherein a is 0; b is 1; X is $S(O)_n$; c is 0; d is 1; e is 1; Y is $S(O)_n$; n is 2; f is 0; and g is 0.

Other preferred compounds of formula I include those wherein a is 0; b is 1; X is $S(O)_n$; c is 0; d is 1; e is 1; Y is $S(O)_n$; n is 2; f is 1; and g is 0.

Other preferred compounds of formula I include those wherein a is 0; b is 1; X is oxygen; c is 0; d is 1; e is 1; Y is $S(O)_n$; n is 2; f is 1; and g is 0.

Other preferred compounds of formula I include those wherein a is 0; b is 1; X is oxygen; c is 0; d is 1; e is 1; Y is $S(O)_n$; n is 2; f is 0; and g is 0.

Other preferred compounds of formula I include those wherein a is 0; b is 1; X is carbonyl; c is 1; d is 1; e is 1; Y is $S(O)_n$; f is 0; and g is 0.

Other preferred compounds of formula I include those wherein a is 0; b is 1; X is carbonyl; c is 1; d is 1; e is 1; Y is $S(O)_n$; n is 2; f is 1; and g is 0.

Other preferred compounds of formula I include those 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_1–C_6)alkynyl, cyano(C_1–C_6)alkyl, (C_1–C_6)alkyl-$S(O)_m$ wherein m is 0, 1 or 2.

Specific preferred compounds of formula I include those wherein said compound 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)-methylamino]-4-methylpiperidin-1-yl}-propan-1-one;

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

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

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

The present invention also relates to a pharmaceutical composition for (a) treating or preventing a disorder or condition selected from organ transplant rejection, xeno transplation, lupus, multiple sclerosis, rheumatoid arthritis, psoriasis, Type I diabetes and complications from diabetes, cancer, asthma, atopic dermatitis, autoimmune thyroid disorders, ulcerative colitis, Crohn's disease, Alzheimer's disease, Leukemia, and other autoimmune diseases or (b) the inhibition of protein kinases or Janus Kinase 3 (JAK3) in a mammal, including a human, comprising an amount of a compound of formula I or a pharmaceutically acceptable salt thereof, effective in such disorders or conditions and a pharmaceutically acceptable carrier.

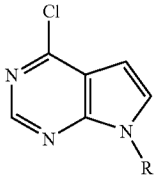
The present invention also relates to a method for the inhibition of protein typrosine kinases or Janus Kinase 3 (JAK3) in a mammal, including a human, comprising administering to said mammal an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof.

The present invention also relates to a method for treating or preventing a disorder or condition selected from organ transplant rejection, xeno transplation, lupus, multiple sclerosis, rheumatoid arthritis, psoriasis, Type I diabetes and complications from diabetes, cancer, asthma, atopic dermatitis, autoimmune thyroid disorders, ulcerative colitis, Crohn's disease, Alzheimer's disease, Leukemia, and other autoimmune diseases in a mammal, including a human, comprising administering to said mammal an amount of a compound of formula I or a pharmaceutically acceptable salt thereof, effective in treating such a condition.

DETAILED DESCRIPTION OF THE INVENTION

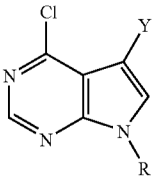
The following reaction Schemes illustrate the preparation of the compounds of the present invention. Unless otherwise indicated R^2, R^3, R^4 and R^5 in the reaction Schemes and the discussion that follow are defined as above.

PREPARATION A

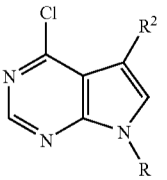


XXI

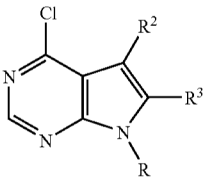
-continued



XX

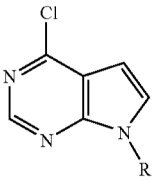


XIX

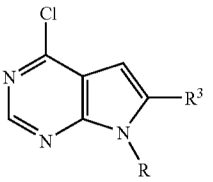


XVI

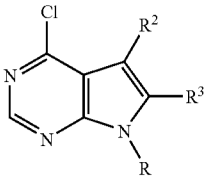
PREPARATION B



XXI

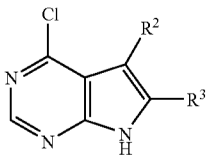


XXII



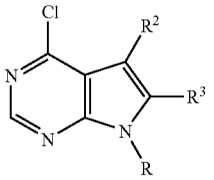
XVI

SCHEME 1



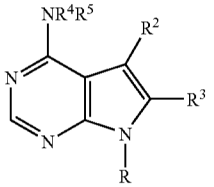
XVII

1



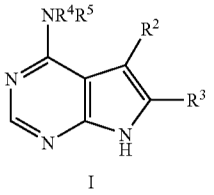
XVI

2



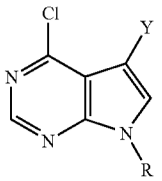
XV

3



I

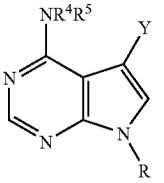
SCHEME 2



XX

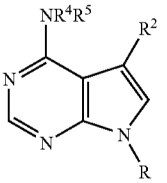
1

-continued



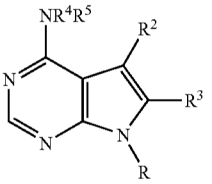
XXIV

2



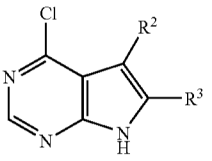
XXII

3



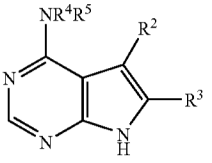
XV

SCHEME 3



XVII

1



I

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 R^2 is (C_1–C_6)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-hydroxypyrrolo[2,3-d]pyrimidine compound of formula XIX, wherein R^2 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 R^2 is (C_6–C_{12})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 aryliodide 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 R^3 is alkyl or benzyl; (b) an aldehyde or ketone, at a temperature between about −78° C. to room temperature, preferably −78° C., when R^3 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 aryliodide 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-hydroxypyrrolo[2,3-d] pyrimidine compound of formula XVI, wherein R^3 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. 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 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 present of hydrogen and a catalyst, such as palladium hydroxide on carbon. The R^5 nitrogen containing hetrocycloalkyl 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 R^5 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 R^2 is aryl, in an aprotic solvent, such 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 R^2 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 R^2 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 1, according to the procedure described above in reaction 2 of Scheme 1.

The compounds of the present invention that 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 invention 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 invention 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.

Those compounds of the present invention that are acidic in nature, 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 invention are those which form non-toxic base salts with the acidic compounds of the present invention. 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.

The compositions of the present invention may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers. Thus, the active compounds of the invention may be formulated for oral, buccal, intranasal, parenteral (e.g, intravenous, intramuscular or subcutaneous) or rectal administration or in a form suitable for administration by inhalation or insufflation. The active compounds of the invention may also be formulated for sustained delivery.

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.

The active compounds of the invention 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 invention 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 intranasal administration or administration by inhalation, the active compounds of the invention 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 invention and a suitable powder base such as lactose or starch.

A proposed dose of the active compounds of the invention for oral, parenteral or buccal administration to the average adult human for the treatment of the conditions referred to above (e.g., rheumatoid arthritis) is 0.1 to 1000 mg of the active ingredient per unit dose which could be administered, for example, 1 to 4 times per day.

Aerosol formulations for treatment of the conditions referred to above (e.g., asthma) 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 invention. 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.

A compound of formula (I) administered in a pharmaceutically acceptable form either alone or in combination with one or more additional agents which modulate a mammlian immune system or with antiinflammatory agents, agents which may include but are not limited to cyclosporin A (e.g. Sandimmune® or Neoral®, rapamycin, FK-506 (tacrolimus), leffunomide, deoxyspergualin, mycophenolate (e.g. Cellcept®, azathioprine (e.g. Imuran®), daclizumab (e.g. Zenapax®), OKT3 (e.g. Orthocolone®), AtGam, aspirin, acetaminophen, ibuprofen, naproxen, piroxicam, and antiinflmmatory steroids (e.g. prednisolone or dexamethasone); and such agents may be administered as part of the same or separate dosage forms, via the same or different routes of administration, and on the same or different administration schedules according to standard pharmaceutical practice.

FK506 (Tacrolimus) is given orally at 0.10–0.15 mg/kg body weight, every 12 hours, within first 48 hours postoperative. Does is monitored by serum Tacrolimus trough levels.

Cyclosporin A (Sandimmune oral or intravenous formulation, or Neoral®, oral solution or capsules) is given orally at 5 mg/kg body weight, every 12 hours within 48 hours postoperative. Dose is monitored by blood Cyclosporin A trough levels.

The active agents can 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 U.S. Pat. Nos. 3,538,214, 4,060,598, 4,173,626, 3,119,742, and 3,492,397.

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-Sepaharose. 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 antiphospholyrosine 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 $1–2\times10^{9}$/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 10 ug/ml PHA(Murex Diagnostics, Cat # HA 16). After 3 days at 37° C. in 5% CO_2, cells are washed 3 times in Media, resuspended to a density of $1–2\times10^{6}$ 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/0.1 ml) in a Flat-bottom 96-well microliter 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 uM. After one hour, 10 Units/ml of IL-2 is added to each test well. Plates are then incubated at 37° C., 5% CO_2 for 72 hours. Plates are then pulsed with ^{3}H-thymidine (0.5 uCi/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 ^{3}H-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 IC_{50} value (uM) is determined from this plot.

The following Examples illustrate the preparation of the compounds of the present invention 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 59890®, 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.

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 3×80 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 dichoromethane) 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).

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.

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.

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.

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.

EXAMPLE 6

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

N-[2-(4-Methyl-3-methylamino-piperidine-1-sulfonyl)-ethyl]-propionamide. LRMS: 409.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

EXAMPLE 26

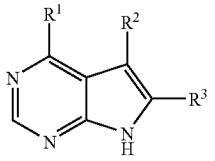
Methyl-[4-methyl-1-(2-methylamino-ethanesulfonyl)-piperidin-3-yl]-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Methyl-[4-methyl-1-(2-methylamino-ethanesulfonyl)-piperidin-3-yl]-amine. LRMS: 367.

What is claimed is:

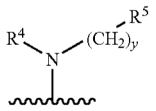
1. A compound of the formula

I



or a pharmaceutically acceptable salt thereof; wherein

R^1 is a group of the formula

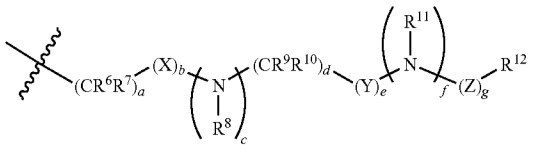


wherein y is 0, 1 or 2;

R^4 is selected from the group consisting of hydrogen, $(C_1–C_6)$alkyl, $(C_1–C_6)$alkylsulfonyl, $(C_2–C_6)$alkenyl, $(C_2–C_6)$alkynyl wherein the alkyl, alkenyl and alkynyl groups are optionally substituted by deuterium, hydroxy, amino, trifluoromethyl, $(C_1–C_4)$alkoxy, $(C_1–C_6)$acyloxy, $(C_1–C_6)$alkylamino, $((C_1–C_6)alkyl)_2$ amino, cyano, nitro, $(C_2–C_6)$alkenyl, $(C_2–C_6)$alkynyl or $(C_1–C_6)$acylamino; or R^4 is $(C_3–C_{10})$cycloalkyl wherein the cycloalkyl group is 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^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, $((C_1–C_6)alkyl)_2$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 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

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;

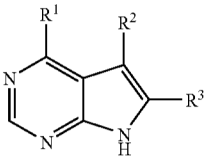
R^6, R^7, R^8, R^9, R^{10} and R^{11} are each independently selected from the group consisting of hydrogen or $(C_1–C_6)$alkyl optionally substituted by deuterium, hydroxy, amino, trifluoromethyl, $(C_1–C_6)$acyloxy, $(C_1–C_6)$acylamino, $(C_1–C_6)$alkylamino, $((C_1–C_6)$ alkyl$)_2$amino, cyano, cyano$(C_1–C_6)$alkyl,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

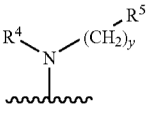
2. A compound of the formula

I



or a pharmaceutically acceptable salt thereof wherein

R^1 is a group of the formula

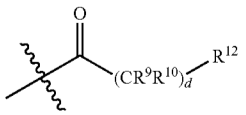


wherein y is 0;

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)$_2$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 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; and

R^2 and R^3 are each H.

3. A compound 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;

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; and

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

4. [A compound of claim **3**, wherein said compound 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.

* * * * *

CIVIL COVER SHEET

The JS 44 civil cover sheet and the information contained herein neither replace nor supplement the filing and service of pleadings or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. *(SEE INSTRUCTIONS ON NEXT PAGE OF THIS FORM.)*

I. (a) PLAINTIFFS

PFIZER INC., et al.

(b) County of Residence of First Listed Plaintiff _____
(EXCEPT IN U.S. PLAINTIFF CASES)

(c) Attorneys *(Firm Name, Address, and Telephone Number)*
Jack B. Blumenfeld 302-658-9200
Morris, Nichols, Arsht & Tunnell LLP
1201 North Market Street; P.O. Box 1347; Wilmington, DE 19899

DEFENDANTS

AJANTA PHARMA LTD. and
AJANTA PHARMA USA INC.

County of Residence of First Listed Defendant _____
(IN U.S. PLAINTIFF CASES ONLY)

NOTE: IN LAND CONDEMNATION CASES, USE THE LOCATION OF THE TRACT OF LAND INVOLVED.

Attorneys *(If Known)*

II. BASIS OF JURISDICTION *(Place an "X" in One Box Only)*

- ❒ 1 U.S. Government Plaintiff
- ☒ 3 Federal Question *(U.S. Government Not a Party)*
- ❒ 2 U.S. Government Defendant
- ❒ 4 Diversity *(Indicate Citizenship of Parties in Item III)*

III. CITIZENSHIP OF PRINCIPAL PARTIES *(Place an "X" in One Box for Plaintiff and One Box for Defendant)*

(For Diversity Cases Only)

	PTF	DEF		PTF	DEF
Citizen of This State	❒ 1	❒ 1	Incorporated *or* Principal Place of Business In This State	❒ 4	❒ 4
Citizen of Another State	❒ 2	❒ 2	Incorporated *and* Principal Place of Business In Another State	❒ 5	❒ 5
Citizen or Subject of a Foreign Country	❒ 3	❒ 3	Foreign Nation	❒ 6	❒ 6

IV. NATURE OF SUIT *(Place an "X" in One Box Only)*

Click here for: Nature of Suit Code Descriptions.

CONTRACT
- ❒ 110 Insurance
- ❒ 120 Marine
- ❒ 130 Miller Act
- ❒ 140 Negotiable Instrument
- ❒ 150 Recovery of Overpayment & Enforcement of Judgment
- ❒ 151 Medicare Act
- ❒ 152 Recovery of Defaulted Student Loans (Excludes Veterans)
- ❒ 153 Recovery of Overpayment of Veteran's Benefits
- ❒ 160 Stockholders' Suits
- ❒ 190 Other Contract
- ❒ 195 Contract Product Liability
- ❒ 196 Franchise

REAL PROPERTY
- ❒ 210 Land Condemnation
- ❒ 220 Foreclosure
- ❒ 230 Rent Lease & Ejectment
- ❒ 240 Torts to Land
- ❒ 245 Tort Product Liability
- ❒ 290 All Other Real Property

TORTS

PERSONAL INJURY
- ❒ 310 Airplane
- ❒ 315 Airplane Product Liability
- ❒ 320 Assault, Libel & Slander
- ❒ 330 Federal Employers' Liability
- ❒ 340 Marine
- ❒ 345 Marine Product Liability
- ❒ 350 Motor Vehicle
- ❒ 355 Motor Vehicle Product Liability
- ❒ 360 Other Personal Injury
- ❒ 362 Personal Injury - Medical Malpractice

PERSONAL INJURY
- ❒ 365 Personal Injury - Product Liability
- ❒ 367 Health Care/ Pharmaceutical Personal Injury Product Liability
- ❒ 368 Asbestos Personal Injury Product Liability

PERSONAL PROPERTY
- ❒ 370 Other Fraud
- ❒ 371 Truth in Lending
- ❒ 380 Other Personal Property Damage
- ❒ 385 Property Damage Product Liability

CIVIL RIGHTS
- ❒ 440 Other Civil Rights
- ❒ 441 Voting
- ❒ 442 Employment
- ❒ 443 Housing/ Accommodations
- ❒ 445 Amer. w/Disabilities - Employment
- ❒ 446 Amer. w/Disabilities - Other
- ❒ 448 Education

PRISONER PETITIONS

Habeas Corpus:
- ❒ 463 Alien Detainee
- ❒ 510 Motions to Vacate Sentence
- ❒ 530 General
- ❒ 535 Death Penalty

Other:
- ❒ 540 Mandamus & Other
- ❒ 550 Civil Rights
- ❒ 555 Prison Condition
- ❒ 560 Civil Detainee - Conditions of Confinement

FORFEITURE/PENALTY
- ❒ 625 Drug Related Seizure of Property 21 USC 881
- ❒ 690 Other

LABOR
- ❒ 710 Fair Labor Standards Act
- ❒ 720 Labor/Management Relations
- ❒ 740 Railway Labor Act
- ❒ 751 Family and Medical Leave Act
- ❒ 790 Other Labor Litigation
- ❒ 791 Employee Retirement Income Security Act

IMMIGRATION
- ❒ 462 Naturalization Application
- ❒ 465 Other Immigration Actions

BANKRUPTCY
- ❒ 422 Appeal 28 USC 158
- ❒ 423 Withdrawal 28 USC 157

PROPERTY RIGHTS
- ❒ 820 Copyrights
- ❒ 830 Patent
- ☒ 835 Patent - Abbreviated New Drug Application
- ❒ 840 Trademark

SOCIAL SECURITY
- ❒ 861 HIA (1395ff)
- ❒ 862 Black Lung (923)
- ❒ 863 DIWC/DIWW (405(g))
- ❒ 864 SSID Title XVI
- ❒ 865 RSI (405(g))

FEDERAL TAX SUITS
- ❒ 870 Taxes (U.S. Plaintiff or Defendant)
- ❒ 871 IRS—Third Party 26 USC 7609

OTHER STATUTES
- ❒ 375 False Claims Act
- ❒ 376 Qui Tam (31 USC 3729(a))
- ❒ 400 State Reapportionment
- ❒ 410 Antitrust
- ❒ 430 Banks and Banking
- ❒ 450 Commerce
- ❒ 460 Deportation
- ❒ 470 Racketeer Influenced and Corrupt Organizations
- ❒ 480 Consumer Credit
- ❒ 490 Cable/Sat TV
- ❒ 850 Securities/Commodities/ Exchange
- ❒ 890 Other Statutory Actions
- ❒ 891 Agricultural Acts
- ❒ 893 Environmental Matters
- ❒ 895 Freedom of Information Act
- ❒ 896 Arbitration
- ❒ 899 Administrative Procedure Act/Review or Appeal of Agency Decision
- ❒ 950 Constitutionality of State Statutes

V. ORIGIN *(Place an "X" in One Box Only)*

☒ 1 Original Proceeding ❒ 2 Removed from State Court ❒ 3 Remanded from Appellate Court ❒ 4 Reinstated or Reopened ❒ 5 Transferred from Another District *(specify)* ❒ 6 Multidistrict Litigation - Transfer ❒ 8 Multidistrict Litigation - Direct File

VI. CAUSE OF ACTION

Cite the U.S. Civil Statute under which you are filing ***(Do not cite jurisdictional statutes unless diversity)***:
35 U.S.C. § 271

Brief description of cause:
Patent Infringement

VII. REQUESTED IN COMPLAINT:

❒ CHECK IF THIS IS A **CLASS ACTION** UNDER RULE 23, F.R.Cv.P.

DEMAND $

CHECK YES only if demanded in complaint:
JURY DEMAND: ❒ Yes ☒ No

VIII. RELATED CASE(S) IF ANY

(See instructions):

JUDGE Stark DOCKET NUMBER 17-158 Consolidated

DATE 03/15/2019

SIGNATURE OF ATTORNEY OF RECORD /s/ Jack B. Blumenfeld

FOR OFFICE USE ONLY

RECEIPT # _____ AMOUNT _____ APPLYING IFP _____ JUDGE _____ MAG. JUDGE _____