AO 120 (Rev. 08/10)

TO: **Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450**	**REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK**

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court for the District of Delaware on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	2/4/2022	for the District of Delaware

PLAINTIFF	DEFENDANT
ACERTA PHARMA B.V., ASTRAZENECA UK LIMITED, ASTRAZENECA PHARMACEUTICALS LP, ASTRAZENECA AB, and MERCK SHARP & DOHME B.V.	CIPLA LIMITED and CIPLA USA, INC.

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1 9,758,524	9/12/2017	Merck Sharp & Dohme B.V. & AstraZeneca UK Limited
2 10,239,883	3/26/2019	Merck Sharp & Dohme B.V. & AstraZeneca UK Limited
3 9,796,721	10/24/2017	Acerta Pharma B.V. & AstraZeneca UK Limited
4 10,167,291	1/1/2019	Acerta Pharma B.V. & AstraZeneca UK Limited
5 10,272,083	4/30/2019	Acerta Pharma B.V. & AstraZeneca UK Limited

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	**DATE OF PATENT OR TRADEMARK**	**HOLDER OF PATENT OR TRADEMARK**
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

Copy 1—Upon initiation of action, mail this copy to Director Copy 3—Upon termination of action, mail this copy to Director
Copy 2—Upon filing document adding patent(s), mail this copy to Director Copy 4—Case file copy

AO 120 (Rev. 08/10)

TO: **Mail Stop 8** **Director of the U.S. Patent and Trademark Office** **P.O. Box 1450** **Alexandria, VA 22313-1450**	**REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK**

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☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED 2/4/2022	U.S. DISTRICT COURT for the District of Delaware
PLAINTIFF ACERTA PHARMA B.V., ASTRAZENECA UK LIMITED, ASTRAZENECA PHARMACEUTICALS LP, ASTRAZENECA AB, and MERCK SHARP & DOHME B.V.		DEFENDANT MSN PHARMACEUTICALS INC.

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1 9,290,504	3/22/2016	Merck Sharp & Dohme B.V. & AstraZeneca UK Limited
2 9,758,524	9/12/2017	Merck Sharp & Dohme B.V. & AstraZeneca UK Limited
3 10,239,883	3/26/2019	Merck Sharp & Dohme B.V. & AstraZeneca UK Limited
4 9,796,721	10/24/2017	Acerta Pharma B.V. & AstraZeneca UK Limited
5 10,167,291	1/1/2019	Acerta Pharma B.V. & AstraZeneca UK Limited

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In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court for the District of Delaware on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED 2/2/2022	U.S. DISTRICT COURT for the District of Delaware
PLAINTIFF ACERTA PHARMA B.V., ASTRAZENECA UK LIMITED, ASTRAZENECA PHARMACEUTICALS LP, ASTRAZENECA AB, and MERCK SHARP & DOHME B.V.		DEFENDANT NATCO PHARMA LIMITED and NATCO PHARMA, INC.

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1 9,290,504	3/22/2016	Merck Sharp & Dohme B.V. & AstraZeneca UK Limited
2 9,758,524	9/12/2017	Merck Sharp & Dohme B.V. & AstraZeneca UK Limited
3 10,239,883	3/26/2019	Merck Sharp & Dohme B.V. & AstraZeneca UK Limited
4 9,796,721	10/24/2017	Acerta Pharma B.V. & AstraZeneca UK Limited
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☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED 2/2/2022	U.S. DISTRICT COURT for the District of Delaware
PLAINTIFF ACERTA PHARMA B.V., ASTRAZENECA UK LIMITED, ASTRAZENECA PHARMACEUTICALS LP, ASTRAZENECA AB, and MERCK SHARP & DOHME B.V.		DEFENDANT ALEMBIC PHARMACEUTICALS LIMITED and ALEMBIC PHARMACEUTICALS, INC.

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1 9,758,524	9/12/2017	Merck Sharp & Dohme B.V. & AstraZeneca UK Limited
2 10,239,883	3/26/2019	Merck Sharp & Dohme B.V. & AstraZeneca UK Limited
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☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED 2/4/2022	U.S. DISTRICT COURT for the District of Delaware
PLAINTIFF ACERTA PHARMA B.V., ASTRAZENECA UK LIMITED, ASTRAZENECA PHARMACEUTICALS LP, ASTRAZENECA AB, and MERCK SHARP & DOHME B.V.		DEFENDANT SANDOZ INC.

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1 9,290,504	3/22/2016	Merck Sharp & Dohme B.V. & AstraZeneca UK Limited
2 9,758,524	9/12/2017	Merck Sharp & Dohme B.V. & AstraZeneca UK Limited
3 10,239,883	3/26/2019	Merck Sharp & Dohme B.V. & AstraZeneca UK Limited
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UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/019,543	09/12/2017	9758524	015332.1182-US02	1984

26853 7590 08/23/2017

COVINGTON & BURLING, LLP
Attn: Patent Docketing
One CityCenter
850 Tenth Street, NW
Washington, DC 20001-4956

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

Tjeerd A. Barf, Ravenstein, NETHERLANDS;
Merck Sharp & Dohme B.V., Haarlem, NETHERLANDS;
Christiaan Gerardus Johannes Maria Jans, Cuijk, NETHERLANDS;
Adrianus Petrus Antonius de Man, Hurwenen, NETHERLANDS;
Arthur A. Oubrie, Wijchen, NETHERLANDS;
Hans C. A. Raaijmakers, Eindhoven, NETHERLANDS;
Johannes Bernardus Maria Rewinkel, Berghem, NETHERLANDS;
Jan Gerard Sterrenburg, Renkum, NETHERLANDS;
Jacobus C. H. M. Wijkmans, Oss, NETHERLANDS;

IR103 (Rev. 10/09)

PART B–FEE(S) TRANSMITTAL

Complete and send this form, together with the applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22314-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note Use Block 1 for any change of address)

COVINGTON & BURLING LLP
Attn: Patent Docketing
One CityCenter
850 Tenth Street, NW
Washington, DC 20001-4956

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, EFS-Web transmitted, or facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's Name)
(S-signature)
(Date)

APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
15/019,543	02/09/2016	Tjeerd A. Barf	015332.1182-US02	1984

TITLE OF INVENTION: 4-IMIDAZOPYRIDAZIN-1-YL-BENZAMIDES AS BTK INHIBITORS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960.00			$960.00	08/04/2017

EXAMINER	ART UNIT	CLASS-SUBCLASS
Golam M. Shameem	1626	

1. Change of correspondence address or indication of "Fee Address" (37CFR 1.363).
   - [ ] Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
   - [ ] "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
   (1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
   (2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered attorney or agent. If no name is listed, no name will be printed

   1. Covington & Burling LLP
   2. Einar Stole
   3. Melody Wu

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

1a. NAME OF ASSIGNEE: Merck Sharp & Dohme B.V.

(B) RESIDENCE: (CITY and STATE OR COUNTRY): Haarlem, Netherlands

Please check the appropriate assignee categories (will not be printed on the patent): [ ] Individual [x] Corporation or other private group entity [ ] Government

4a. The following fee(s) are submitted:
- [x] Issue Fee
- [ ] Publication Fee (No small entity discount permitted)
- [ ] Advance Order - # of Copies

4b. Payment of Fees(s): **(Please first reapply and previously paid fee shown above)**
- [ ] A check is enclosed
- [ ] Payment be credit card. Form PTO-2038 is attached
- [x] The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number 50-0740 (enclose an extra copy of this form)

5. Change of Entity Status (from status indicated above)
- [ ] Applicant certifying micro entity status. See 37 CFR 1.29 — NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
- [ ] Applicant asserting small entity status. See 37 CFR 1.27 — NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
- [ ] Applicant changing to regular undiscounted fee status. — NOTE: Checking this box will be taken to be notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature [signature] Date August 3, 2017

Typed or printed name Melody H. Wu Registration No. 52,376

Electronic Patent Application Fee Transmittal

Application Number:	15019543
Filing Date:	09-Feb-2016
Title of Invention:	4-IMIDAZOPYRIDAZIN-1-YL-BENZAMIDES AS BTK INHIBITORS
First Named Inventor/Applicant Name:	Tjeerd A. Barf
Filer:	Andrea Reister/Jenn Augsburger
Attorney Docket Number:	015332.1182-US02

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
UTILITY APPL ISSUE FEE	1501	1	960	960

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**960**

Electronic Acknowledgement Receipt

EFS ID:	29979320
Application Number:	15019543
International Application Number:	
Confirmation Number:	1984
Title of Invention:	4-IMIDAZOPYRIDAZIN-1-YL-BENZAMIDES AS BTK INHIBITORS
First Named Inventor/Applicant Name:	Tjeerd A. Barf
Customer Number:	26853
Filer:	Andrea Reister/Jenn Augsburger
Filer Authorized By:	Andrea Reister
Attorney Docket Number:	015332.1182-US02
Receipt Date:	03-AUG-2017
Filing Date:	09-FEB-2016
Time Stamp:	17:03:50
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$960
RAM confirmation Number	080417INTEFSW00003971500740
Deposit Account	
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		15019543-IF.pdf	84093 9babb4764fc0dce563d3fb0209a31c943705f6a9	yes	3

Multipart Description/PDF files in .zip description

Document Description	Start	End
Transmittal Letter	1	2
Issue Fee Payment (PTO-85B)	3	3

Warnings:

Information:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
2	Fee Worksheet (SB06)	fee-info.pdf	30528 09ddbf106cdd23b847e3143f6544d9b1fbb03366	no	2

Warnings:

Information:

Total Files Size (in bytes):	114621

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.
National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.
New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Docket No.: 015332.1182-US02
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Tjeerd A. Barf et al.	Allowed: May 4, 2017
Application No.: 15/019,543	Confirmation No.: 1984
Filed: February 9, 2016	Art Unit: 1626
For: 4-IMIDAZOPYRIDAZIN-1-YL-BENZAMIDES AS BTK INHIBITORS	Examiner: Golam M. Shameem

TRANSMITTAL LETTER

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Enclosed are the following items for filing in connection with the above-referenced Patent Application:

1. Fee(s) Transmittal.

Please charge our Deposit Account No. 50-0740 in the amount of $960.00 in payment of the required fee. The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed, or that should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 50-0740, under Docket No. 015332.1182-US02.

It is not believed that extensions of time or fees for net addition of claims are required beyond those that may otherwise be provided for in documents accompanying this paper. However, if additional extensions of time are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned under 37 C.F.R. § 1.136(a), and any fees required therefor

DC: 6485703-1

(including fees for net addition of claims) are hereby authorized to be charged to our Deposit Account No. 50-0740.

Dated: August 3, 2017

Respectfully submitted,

By

Einar Stole
Registration No.: 47,272
Melody H. Wu
Registration No.: 52,376
COVINGTON & BURLING LLP
One CityCenter
850 Tenth Street, NW
Washington, DC 20001-4956
(202) 662-6000
Attorneys for Applicant

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
15/019,543	02/09/2016	1626	1740	015332.1182-US02	19	2

CONFIRMATION NO. 1984

CORRECTED FILING RECEIPT

OC000000091870569

26853
COVINGTON & BURLING, LLP
Attn: Patent Docketing
One CityCenter
850 Tenth Street, NW
Washington, DC 20001-4956

Date Mailed: 06/06/2017

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Tjeerd A. Barf, Ravenstein, NETHERLANDS;
Christiaan Gerardus Johannes Maria Jans, Cuijk, NETHERLANDS;
Adrianus Petrus Antonius de Man, Hurwenen, NETHERLANDS;
Arthur A. Oubrie, Wijchen, NETHERLANDS;
Hans C. A. Raaijmakers, Eindhoven, NETHERLANDS;
Johannes Bernardus Maria Rewinkel, Berghem, NETHERLANDS;
Jan Gerard Sterrenburg, Renkum, NETHERLANDS;
Jacobus C. H. M. Wijkmans, Oss, NETHERLANDS;

Applicant(s)

Merck Sharp & Dohme B.V., Haarlem, NETHERLANDS;

Power of Attorney: None

Domestic Priority data as claimed by applicant

This application is a DIV of 14/233,418 01/17/2014 PAT 9290504
which is a 371 of PCT/EP2012/063552 07/11/2012
which claims benefit of 61/509,397 07/19/2011

Foreign Applications (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.)
EUROPEAN PATENT OFFICE (EPO) 11174578.2 07/19/2011

Permission to Access Application via Priority Document Exchange: No

Permission to Access Search Results: No

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

Request to Retrieve - This application either claims priority to one or more applications filed in an intellectual property Office that participates in the Priority Document Exchange (PDX) program or contains a proper **Request to Retrieve Electronic Priority Application(s)** (PTO/SB/38 or its equivalent). Consequently, the USPTO will attempt to electronically retrieve these priority documents.

If Required, Foreign Filing License Granted: 06/05/2017

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 15/019,543**

Projected Publication Date: Not Applicable

Non-Publication Request: No

Early Publication Request: No

Title

4-IMIDAZOPYRIDAZIN-1-YL-BENZAMIDES AS BTK INHIBITORS

Preliminary Class

544

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

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The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The U.S. offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to promote and facilitate business investment. SelectUSA provides information assistance to the international investor community; serves as an ombudsman for existing and potential investors; advocates on behalf of U.S. cities, states, and regions competing for global investment; and counsels U.S. economic development organizations on investment attraction best practices. To learn more about why the United States is the best country in the world to develop technology, manufacture products, deliver services, and grow your business, visit http://www.SelectUSA.gov or call +1-202-482-6800.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

26853 7590 05/04/2017

COVINGTON & BURLING, LLP
Attn: Patent Docketing
One CityCenter
850 Tenth Street, NW
Washington, DC 20001-4956

EXAMINER	
SHAMEEM, GOLAM M	
ART UNIT	**PAPER NUMBER**
1626	

DATE MAILED: 05/04/2017

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/019,543	02/09/2016	Tjeerd A. Barf	015332.1182-US02	1984

TITLE OF INVENTION: 4-IMIDAZOPYRIDAZIN-1-YL-BENZAMIDES AND 4-IMIDAZOTRIAZIN-1-YL-BENZAMIDES AS BTK INHIBITORS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	08/04/2017

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

26853 7590 05/04/2017

COVINGTON & BURLING, LLP
Attn: Patent Docketing
One CityCenter
850 Tenth Street, NW
Washington, DC 20001-4956

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)

(Signature)

(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/019,543	02/09/2016	Tjeerd A. Barf	015332.1182-US02	1984

TITLE OF INVENTION: 4-IMIDAZOPYRIDAZIN-1-YL-BENZAMIDES AND 4-IMIDAZOTRIAZIN-1-YL-BENZAMIDES AS BTK INHIBITORS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	08/04/2017

EXAMINER	ART UNIT	CLASS-SUBCLASS
SHAMEEM, GOLAM M	1626	544-350000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
   - ❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
   - ❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

   (1) The names of up to 3 registered patent attorneys or agents OR, alternatively,

   (2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

   1 ______________________
   2 ______________________
   3 ______________________

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

   PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

   (A) NAME OF ASSIGNEE

   (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:
- ❑ Issue Fee
- ❑ Publication Fee (No small entity discount permitted)
- ❑ Advance Order - # of Copies ______________

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
- ❑ A check is enclosed.
- ❑ Payment by credit card. Form PTO-2038 is attached.
- ❑ The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number ____________ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
   - ❑ Applicant certifying micro entity status. See 37 CFR 1.29
   - ❑ Applicant asserting small entity status. See 37 CFR 1.27
   - ❑ Applicant changing to regular undiscounted fee status.

<u>NOTE:</u> Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

<u>NOTE:</u> If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

<u>NOTE:</u> Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature ______________________ Date ______________________

Typed or printed name ______________________ Registration No. ______________________

PTOL-85 Part B (10-13) Approved for use through 10/31/2013. OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/019,543	02/09/2016	Tjeerd A. Barf	015332.1182-US02	1984

26853 7590 05/04/2017

COVINGTON & BURLING, LLP
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One CityCenter
850 Tenth Street, NW
Washington, DC 20001-4956

EXAMINER	
SHAMEEM, GOLAM M	
ART UNIT	PAPER NUMBER
1626	

DATE MAILED: 05/04/2017

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	**Application No.** 15/019,543	**Applicant(s)** BARF ET AL.	
	Examiner GOLAM M M SHAMEEM	**Art Unit** 1626	**AIA (First Inventor to File) Status** No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *04/10/2017*.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on______.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are *19-32*. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.
4. ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☒ All b) ☐ Some *c) ☐ None of the:
   1. ☒ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
5. ☒ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

DETAILED ACTION

Status of Claims

Claims 19-32 are currently pending in the application. Claims 1-18 have been cancelled.

Receipt is acknowledged of Applicant's response / amendment filed on April 10, 2017 and that has been entered.

Applicant's response, amendments and arguments have been fully considered and found persuasive with respect to the rejection of claims 1-11 (cancelled) under 35 U.S.C. §112 first paragraph, and the rejection is hereby withdrawn and hence, all currently pending claims 19-32 have been examined and found allowable over the prior art of record.

Telephone Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Golam Shameem, Ph.D., whose telephone number is (571) 272-0706. The examiner can normally be reached on Monday-Thursday from 7:30 AM - 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph. McKane, can be reached at (571) 272-0699. The Unofficial fax phone number for this Group is (703) 308-7922. The Official fax phone numbers for this Group are (571) 273-8300. When filing a FAX in Technology Center 1600, please indicate in the Header (upper right) "Official" for papers that are to be entered into the file, and "Unofficial" for draft documents and other communications with the PTO that are not for entry into the file of the application. This will expedite processing of your papers.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [joseph.mckane@uspto.gov]. All Internet e-mail communications will be made of record in the application file. PTO employees will not communicate with applicant via Internet e-mail where sensitive data will be exchanged or where there exists a possibility that sensitive data could be identified unless there is of record an express waiver of the confidentiality requirements under 35 U.S.C. 122 by the applicant. See the Interim Internet Usage Policy published by the Patent and Trademark Office Official Gazette on February 25, 1997 at 1195 OG 89.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or public PAIR only. For more information about the pair system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866) 217-9197.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (571) 272-1600.

/Golam M. M. Shameem/
Primary Examiner
Art Unit 1626
Technology Center 1600

Search Notes	Application/Control No. 15019543	Applicant(s)/Patent Under Reexamination BARF ET AL.
	Examiner GOLAM M SHAMEEM	Art Unit 1626

CPC- SEARCHED

Symbol	Date	Examiner
A61K 31/4985	12/01/16	GS
C07D 487/04	12/01/16	GS

CPC COMBINATION SETS - SEARCHED

Symbol	Date	Examiner

US CLASSIFICATION SEARCHED

Class	Subclass	Date	Examiner

SEARCH NOTES

Search Notes	Date	Examiner
EAST, STN, INVENTOR SEARCH	12/01/16	GS
UPDATED	04/17/17	GS

INTERFERENCE SEARCH

US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
A61K	31/4985	04/17/17	GS
C07D	487/04	04/17/17	GS

Issue Classification	Application/Control No. 15019543	Applicant(s)/Patent Under Reexamination BARF ET AL.
	Examiner GOLAM M SHAMEEM	Art Unit 1626

CPC					
Symbol				Type	Version
C07D	487	/	04	F	2013-01-01
C07D	519	/	00	I	2013-01-01
A61K	31	/	4985	I	2013-01-01
A61K	31	/	501	I	2013-01-01
A61K	31	/	506	I	2013-01-01
A61K	31	/	55	I	2013-01-01
A61K	31	/	5377	I	2013-01-01
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CPC Combination Sets							
Symbol				Type	Set	Ranking	Version
		/					
		/					

NONE (Assistant Examiner) (Date)	Total Claims Allowed: 14	
/GOLAM M M SHAMEEM/ Primary Examiner.Art Unit 1626 04/28/17 (Primary Examiner) (Date)	O.G. Print Claim(s) 1	O.G. Print Figure NONE

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15019543	BARF ET AL.
	Examiner	**Art Unit**
	GOLAM M SHAMEEM	1626

US ORIGINAL CLASSIFICATION	
CLASS	SUBCLASS

CROSS REFERENCE(S)

CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)				

INTERNATIONAL CLASSIFICATION

CLAIMED					NON-CLAIMED
A	6	1	K	31 / 4985 (2006.0)	
C	0	7	D	487 / 04	

NONE (Assistant Examiner)	(Date)	Total Claims Allowed: 14	
/GOLAM M M SHAMEEM/ Primary Examiner.Art Unit 1626 (Primary Examiner)	04/28/17 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure NONE

U.S. Patent and Trademark Office

Part of Paper No. 20170417-2371

Issue Classification	**Application/Control No.**	**Applicant(s)/Patent Under Reexamination**
	15019543	BARF ET AL.
	Examiner	**Art Unit**
	GOLAM M SHAMEEM	1626

☒ **Claims renumbered in the same order as presented by applicant** ☐ **CPA** ☐ **T.D.** ☐ **R.1.47**

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 14	
/GOLAM M M SHAMEEM/ Primary Examiner.Art Unit 1626 (Primary Examiner)	04/28/17 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure NONE

U.S. Patent and Trademark Office

Part of Paper No. 20170417-2371

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	15/019,543-Conf. #1984
Filing Date	February 9, 2016
First Named Inventor	Tjeerd A. Barf
Art Unit	1626
Examiner Name	Golam M. Shameem
Attorney Docket Number	015332.1182-US02

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] Number[4] Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	BA	WO-2000017203-A1	03-30-2000	BASF AG		
	BB	WO-2005014599-A1	02-17-2005	Cellular Genomics, Inc.		

Examiner Signature	/GOLAM M SHAMEEM/	Date Considered	04/17/2017

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

DC: 6383483-1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /G.M.S/

Index of Claims	Application/Control No. 15019543	Applicant(s)/Patent Under Reexamination BARF ET AL.
	Examiner GOLAM M SHAMEEM	Art Unit 1626

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE									
Final	Original	12/01/2016	04/17/2017								
	1	✓	-								
	2	✓	-								
	3	✓	-								
	4	✓	-								
	5	✓	-								
	6	✓	-								
	7	✓	-								
	8	✓	-								
	9	✓	-								
	10	✓	-								
	11	✓	-								
	12	N	-								
	13	N	-								
	14	N	-								
	15	N	-								
	16	N	-								
	17	N	-								
	18	N	-								
1	19		=								
2	20		=								
3	21		=								
4	22		=								
5	23		=								
6	24		=								
7	25		=								
8	26		=								
9	27		=								
10	28		=								
11	29		=								
12	30		=								
13	31		=								
14	32		=								

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UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
15/019,543	02/09/2016	1626	1740	015332.1182-US02	19	2

CONFIRMATION NO. 1984
UPDATED FILING RECEIPT

26853
COVINGTON & BURLING, LLP
Attn: Patent Docketing
One CityCenter
850 Tenth Street, NW
Washington, DC 20001-4956

Date Mailed: 04/18/2017

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Tjeerd A. Barf, Ravenstein, NETHERLANDS;
Christiaan Gerardus Johannes Maria Jans, Cuijk, NETHERLANDS;
Adrianus Petrus Antonius de Man, Hurwenen, NETHERLANDS;
Arthur A. Oubrie, Wijchen, NETHERLANDS;
Hans C. A. Raaijmakers, Eindhoven, NETHERLANDS;
Johannes Bernardus Maria Rewinkel, Berghem, NETHERLANDS;
Jan Gerard Sterrenburg, Renkum, NETHERLANDS;
Jacobus C. H. M. Wijkmans, Oss, NETHERLANDS;

Applicant(s)

Merck Sharp & Dohme B.V., Haarlem, NETHERLANDS;

Power of Attorney: None

Domestic Priority data as claimed by applicant

This application is a DIV of 14/233,418 01/17/2014 PAT 9290504
which is a 371 of PCT/EP2012/063552 07/11/2012
which claims benefit of 61/509,397 07/19/2011

Foreign Applications (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.)
EUROPEAN PATENT OFFICE (EPO) 11174578.2 07/19/2011

Permission to Access Application via Priority Document Exchange: No

Permission to Access Search Results: No

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

Request to Retrieve - This application either claims priority to one or more applications filed in an intellectual property Office that participates in the Priority Document Exchange (PDX) program or contains a proper **Request to Retrieve Electronic Priority Application(s)** (PTO/SB/38 or its equivalent). Consequently, the USPTO will attempt to electronically retrieve these priority documents.

If Required, Foreign Filing License Granted:

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 15/019,543**

Projected Publication Date: Not Applicable

Non-Publication Request: No

Early Publication Request: No
Title

4-IMIDAZOPYRIDAZIN-1-YL-BENZAMIDES AND 4-IMIDAZOTRIAZIN-1-YL-BENZAMIDES AS BTK INHIBITORS

Preliminary Class

544

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

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Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

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No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
15/019,543	02/09/2016	Tjeerd A. Barf	015332.1182-US02

CONFIRMATION NO. 1984

26853
COVINGTON & BURLING, LLP
Attn: Patent Docketing
One CityCenter
850 Tenth Street, NW
Washington, DC 20001-4956

37 CFR 1.48(f)
ACKNOWLEDGEMENT LETTER

OC000000090557988

Date Mailed: 04/18/2017

NOTICE OF ACCEPTANCE OF REQUEST UNDER 37 CFR 1.48(f)

This is in response to the applicant's request under 37 CFR 1.48(f) submitted on 04/10/2017.

The request under 37 CFR 1.48(f) to correct the inventorship, to correct or update the name of an inventor, or to correct the order of names of joint inventors is accepted.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/mmasfaw/

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 15/019,543	Filing Date 02/09/2016	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	NUMBER FILED (Column 1)	NUMBER EXTRA (Column 2)	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter “0” in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT

04/10/2017	CLAIMS REMAINING AFTER AMENDMENT (Column 1)		HIGHEST NUMBER PREVIOUSLY PAID FOR (Column 2)	PRESENT EXTRA (Column 3)	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 14	Minus	** 20	= 0	x $80 =	0
Independent (37 CFR 1.16(h))	* 1	Minus	***3	= 0	x $420 =	0
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	**0**

AMENDMENT

	CLAIMS REMAINING AFTER AMENDMENT (Column 1)		HIGHEST NUMBER PREVIOUSLY PAID FOR (Column 2)	PRESENT EXTRA (Column 3)	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write “0” in column 3.
** If the “Highest Number Previously Paid For” IN THIS SPACE is less than 20, enter “20”.
*** If the “Highest Number Previously Paid For” IN THIS SPACE is less than 3, enter “3”.
The “Highest Number Previously Paid For” (Total or Independent) is the highest number found in the appropriate box in column 1.

LIE
VERONICA DAY EVERETT

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Docket No.: 015332.1182-US02
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Tjeerd A. Barf et al.

Application No.: 15/019,543

Confirmation No.: 1984

Filed: February 9, 2016

Art Unit: 1626

For: 4-IMIDAZOPYRIDAZIN-1-YL-BENZAMIDES AND 4-IMIDAZOTRIAZIN-1-YL-BENZAMIDES AS BTK INHIBITORS

Examiner: Golam M. Shameem

AMENDMENT IN RESPONSE TO NON-FINAL OFFICE ACTION UNDER 37 C.F.R. § 1.111

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

INTRODUCTORY COMMENTS

In response to the Office Action dated January 10, 2017 (Paper No. 20161201-2371), Applicant submits the following comments regarding the above-identified U.S. patent application.

Amendments to the Specification begin on page 3 of this paper.

Amendments to the Claims begin on page 4 of this paper.

Remarks begin on page 7 of this paper.

It is not believed that extensions of time or fees for net addition of claims are required beyond those that may otherwise be provided for in documents accompanying this paper. However, if additional extensions of time are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned under 37 C.F.R. § 1.136(a), and any fees required therefor (including fees for net addition of claims) are hereby authorized to be charged to our Deposit Account No. 50-0740.

AMENDMENTS TO THE SPECIFICATION

Please amend the title as follows:

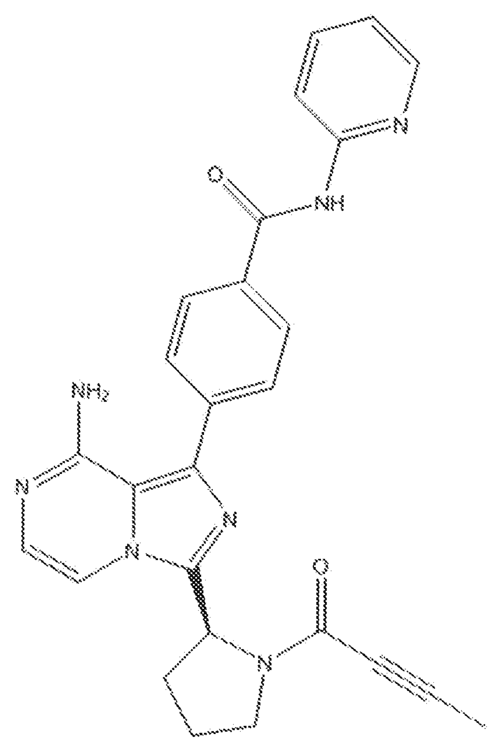
4-Imidazopyridazin-1-yl-benzamides ~~and 4-Imidazotriazin-1-yl-benzamides~~ as BTK Inhibitors

AMENDMENTS TO THE CLAIMS

Please cancel claims 1-18 including both instances of claim 4 without prejudice to or disclaimer of the subject matter recited therein; and please add new claims 19-32 as follows.

1-18. (Cancelled)

19. (New) A method of treating Mantle Cell Lymphoma (MCL) in a human subject, the method comprising administering to the human subject a compound which is (*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide, having the structure:



or a pharmaceutically acceptable salt thereof, in an amount effective to treat the MCL in the human subject.

20. (New) The method of claim 19, wherein the compound is present in a pharmaceutical composition.

21. (New) The method of claim 20, wherein the pharmaceutical composition comprises one or more pharmaceutically acceptable auxiliaries.

22. (New) The method of claim 20, wherein the pharmaceutical composition is administered to the human subject by oral administration.

23. (New) The method of claim 21, wherein the pharmaceutical composition is administered to the human subject by oral administration.

24. (New) The method of claim 22, wherein the pharmaceutical composition is a tablet.

25. (New) The method of claim 23, wherein the pharmaceutical composition is a tablet.

26. (New) The method of claim 22, wherein the pharmaceutical composition is a capsule.

27. (New) The method of claim 23, wherein the pharmaceutical composition is a capsule.

28. (New) The method of claim 22, wherein the pharmaceutical composition is a suspension.

29. (New) The method of claim 23, wherein the pharmaceutical composition is a suspension.

30. (New) The method of claim 19, wherein the amount administered to the human subject is 0.0001-25 mg per kg body weight.

31. (New) The method of claim 19, wherein the compound (*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide is administered to the human subject.

32. (New) The method of claim 19, wherein a pharmaceutically acceptable salt of the compound (*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide is administered to the human subject.

REMARKS

Applicant requests reconsideration and allowance of the subject application in view of the foregoing amendments and the following remarks.

Claim status

Claims 19-32 are pending in this application, with claim 19 being an independent claim. Claims 1-18 have been cancelled without prejudice to or disclaimer of the subject matter recited therein. Claims 19-32 are newly presented herein, based on support in the specification and claims as originally filed, such as in the paragraph beginning at page 19, line 30; the paragraph beginning at page 20, line 1; the paragraph beginning at page 20, line 29; the paragraph beginning at page 22, line 21; and original claims 1, 2, and 8. No new matter has been added.

Claims 19-32 are readable on the elected invention of Group I and on the elected species, consistent with the Response to Restriction Requirement filed in this application on November 30, 2016.

Rejection under 35 U.S.C. 112

Claims 1-11 have been rejected under 35 U.S.C. § 112, first paragraph, as not complying with the written description requirement. This rejection is respectfully traversed. Without conceding that the rejection is proper, Applicant has herein cancelled claims 1-11 without prejudice or disclaimer, and the rejection has been made moot.

Applicant notes that new independent claim 19 and its dependent claims are directed to a method of treating mantle cell lymphoma, which is in line with the Examiner's guidance on pages 4-5 of the Office Action to recite "specific diseases." New claims 19-32 claims are submitted to meet the written description requirement of § 112, first paragraph.

Objection to the claims

The claims have been objected to as containing two claims each numbered as claim 4. Applicant has herein cancelled claims 1-18 including both instances of claim 4. Because the last claim in the original claim set was numbered as claim 18, and all of the original claims have been cancelled herein, Applicant has numbered the newly presented claims beginning with 19.

Conclusion

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue.

Dated: April 10, 2017

Respectfully submitted,

By [signature]
Einar Stole
Registration No.: 47,272
Melody H. Wu
Registration No.: 52,376
COVINGTON & BURLING LLP
One CityCenter
850 Tenth Street, NW
Washington, DC 20001-4956
(202) 662-6000
Attorneys for Applicant

Docket No.: 015332.1182-US02
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Tjeerd A. Barf et al.

Application No.: 15/019,543 — Confirmation No.: 1984

Filed: February 9, 2016 — Art Unit: 1626

For: 4-IMIDAZOPYRIDAZIN-1-YL-BENZAMIDES AND 4-IMIDAZOTRIAZIN-1-YL-BENZAMIDES AS BTK INHIBITORS — Examiner: Golam M. Shameem

REQUEST TO CORRECT INVENTORSHIP UNDER 37 C.F.R. § 1.48

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Pursuant to 37 C.F.R. § 1.48, Applicant respectfully requests that the names of two of the eight inventors of the above-referenced Patent Application be corrected as follows:

Petrus Antonius de Adrianu Man should be **Adrianus Petrus Antonius de Man**; and

Jan-Gerard Sterrenburg should be **Jan Gerard Sterrenburg**.

As required by 37 C.F.R. § 1.48(a)(1), a Corrected Application Data Sheet that identifies each inventor by his or her legal name is being filed concurrently herewith.

Please charge Deposit Account No. 50-0740 in the amount of $740 in payment of the fees set forth in 37 C.F.R. §§ 1.17(d) and 1.17(i), as required by 37 C.F.R. §§ 1.48(a)(2) and 1.48(c). The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed, or that should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 50-0740, under Docket No. 015532.1182-US02.

DC: 6383541-1

Dated: April 10, 2017

Respectfully submitted,

By ____________________

Einar Stole
Registration No.: 47,272
Melody H. Wu
Registration No.: 52,376
COVINGTON & BURLING LLP
One CityCenter
850 Tenth Street, NW
Washington, DC 20001-4956
(202) 662-6000
Attorneys for Applicant

<u>Corrected Application Data Sheet</u>

Inventor Information

Inventor Number::	1
Given Name::	Tjeerd
Middle Name::	A.
Family Name::	Barf
City of Residence::	Ravenstein
Country of Residence::	Netherlands
Street of mailing address::	St. Luciastraat 7
City of mailing address::	Ravenstein
Country of mailing address::	Netherlands
Postal or Zip Code of mailing address::	~~5371AS~~ <u>5371 AS</u>

Inventor Number::	2
Given Name::	Christiaan
Middle Name::	Gerardus Johannes Maria
Family Name::	Jans
City of Residence::	Cuijk
Country of Residence::	Netherlands
Street of mailing address::	Heggerank 134
City of mailing address::	Cuijk
Country of mailing address::	Netherlands
Postal or Zip Code of mailing address::	5432 CC

Inventor Number::	3

Given Name::	~~Petrus~~ Adrianus
Middle Name::	~~Antonius de Adrianus~~ Petrus Antonius
Family Name::	de Man
City of Residence::	Hurwenen
Country of Residence::	Netherlands
Street of mailing address::	H.W. Van Heelstraat 4
City of mailing address::	Hurwenen
Country of mailing address::	Netherlands
Postal or Zip Code of mailing address::	5327 AH

Inventor Number::	4
Given Name::	Arthur
Middle Name::	A.
Family Name::	Oubrie
City of Residence::	~~Wychen~~ Wijchen
Country of Residence::	Netherlands
Street of mailing address::	1106 Saltshof 1106
City of mailing address::	~~Wychen~~ Wijchen
Country of mailing address::	Netherlands
Postal or Zip Code of mailing address::	6604 EB

Inventor Number::	5
Given Name::	Hans

Middle Name::	C.A.
Family Name::	Raaijmakers
City of Residence::	Eindhoven
Country of Residence::	Netherlands
Street of mailing address::	Eikakkerhoven 26
City of mailing address::	Eindhoven
Country of mailing address::	Netherlands
Postal or Zip Code of mailing address::	5242 KK

Inventor Number::	6
Given Name::	Johannes
Middle Name::	Bernardus Maria
Family Name::	Rewinkel
City of Residence::	Berghem
Country of Residence::	Netherlands
Street of mailing address::	Molenweg 16
City of mailing address::	Berghem
Country of mailing address::	Netherlands
Postal or Zip Code of mailing address::	5351 EV

Inventor Number::	7
Given Name::	~~Jan-Gerard~~ Jan
Middle Name::	Gerard
Family Name::	Sterrenburg

City of Residence::	Renkum
Country of Residence::	Netherlands
Street of mailing address::	Grote Omloop 18
City of mailing address::	Renkum
Country of mailing address::	Netherlands
Postal or Zip Code of mailing address::	6871 TE

Inventor Number::	8
Given Name::	Jacobus
Middle Name::	C. H. M.
Family Name::	Wijkmans
City of Residence::	Oss
Country of Residence::	Netherlands
Street of mailing address::	Jupiterweg 17
City of mailing address::	Oss
Country of mailing address::	Netherlands
Postal or Zip Code of mailing address::	5345 LR

Signature:

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). **However, if this Application Data Sheet is submitted with the INITIAL filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).**

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	[signature]	Date (YYYY-MM-DD)	2017-04-10
Name	Melody H. Wu	Registration Number	52,376

PTO/AIA/01 (06-12)
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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	4-IMIDAZOPYRIDAZIN-1-YL-BENZAMIDES AND 4-IMIDAZOTRIAZIN-1-YL-BENZAMIDES AS BTK INHIBITORS

As the below named inventor, I hereby declare that:

This declaration is directed to:

[ ] The attached application, or

[X] United States application or PCT international application number 15/019,543 filed on 02/09/2016.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

WARNING:

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LEGAL NAME OF INVENTOR

Inventor: Tjeerd A. Barf Date (Optional): 18-Nov-2016

Signature: [signature]

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

DC: 6003642-1

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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	4-IMIDAZOPYRIDAZIN-1-YL-BENZAMIDES AND 4-IMIDAZOTRIAZIN-1-YL-BENZAMIDES AS BTK INHIBITORS

As the below named inventor, I hereby declare that:

This declaration is directed to:
- [ ] The attached application, or
- [x] United States application or PCT international application number 15/019,643 filed on 02/09/2016.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

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LEGAL NAME OF INVENTOR

Inventor: Christiaan Gerardus Johannes Maria Jans   Date (Optional): 23-11-2016

Signature: [signature]

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	4-IMIDAZOPYRIDAZIN-1-YL-BENZAMIDES AND 4-IMIDAZOTRIAZIN-1-YL-BENZAMIDES AS BTK INHIBITORS

As the below named inventor, I hereby declare that:

This declaration is directed to:

- [ ] The attached application, or
- [x] United States application or PCT international application number 15/019,643 filed on 02/09/2016.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

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LEGAL NAME OF INVENTOR

Inventor: ADRIANUS PETRUS ANTONIUS DE MAN Date (Optional): 01-11-2016

Signature: [signature]

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

PTO/AIA/01 (06-12)
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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	4-IMIDAZOPYRIDAZIN-1-YL-BENZAMIDES AND 4-IMIDAZOTRIAZIN-1-YL-BENZAMIDES AS BTK INHIBITORS

As the below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application, or

☒ United States application or PCT international application number 15/019,543 filed on 02/09/2016

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

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LEGAL NAME OF INVENTOR

Inventor: A Arthur A. Oubrie Date (Optional): 7th DEC-2016

Signature: [signature]

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

PTO/AIA/01 (06-12)
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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	4-IMIDAZOPYRIDAZIN-1-YL-BENZAMIDES AND 4-IMIDAZOTRIAZIN-1-YL-BENZAMIDES AS BTK INHIBITORS

As the below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application, or

☒ United States application or PCT international application number 15/019,843 filed on 02/09/2016.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

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LEGAL NAME OF INVENTOR

Inventor: Hans C. A. Raaijmakers   Date (Optional): 22/11/2016

Signature: [signature]

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

PTO/AIA/01 (06-12)
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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	4-IMIDAZOPYRIDAZIN-1-YL-BENZAMIDES AND 4-IMIDAZOTRIAZIN-1-YL-BENZAMIDES AS BTK INHIBITORS

As the below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application, or

☒ United States application or PCT international application number 15/018,543 filed on 02/09/2016.

The above-identified application was made or authorized to be made by me.

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LEGAL NAME OF INVENTOR

Inventor: Johannes Bernardus Maria Rewinkel   Date (Optional): 21 Nov 2016

Signature: [signature]

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	4-IMIDAZOPYRIDAZIN-1-YL-BENZAMIDES AND 4-IMIDAZOTRIAZIN-1-YL-BENZAMIDES AS BTK INHIBITORS

As the below named inventor, I hereby declare that:

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☐ The attached application, or

☒ United States application or PCT international application number 15/019,543 filed on 02/09/2016.

The above-identified application was made or authorized to be made by me.

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LEGAL NAME OF INVENTOR

Inventor: JAN GERARD STERRENBURG Date (Optional): 22/11/2016

Signature: [signature]

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

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Title of Invention	4-IMIDAZOPYRIDAZIN-1-YL-BENZAMIDES AND 4-IMIDAZOTRIAZIN-1-YL-BENZAMIDES AS BTK INHIBITORS

As the below named inventor, I hereby declare that:

This declaration is directed to:

- [ ] The attached application, or
- [x] United States application or PCT international application number 15/019,543 filed on 02/09/2016 .

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

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WARNING:

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LEGAL NAME OF INVENTOR

Inventor: Jacobus C H.M. Wijkmans Date (Optional) : 07/12/16

Signature: [signature]

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

Docket No.: 015332.1182-US02
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Tjeerd A. Barf et al.

Application No.: 15/019,543

Confirmation No.: 1984

Filed: February 9, 2016

Art Unit: 1626

For: 4-IMIDAZOPYRIDAZIN-1-YL-BENZAMIDES AND 4-IMIDAZOTRIAZIN-1-YL-BENZAMIDES AS BTK INHIBITORS

Examiner: Golam M. Shameem

INFORMATION DISCLOSURE STATEMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Listed on the accompanying Form PTO/SB/08, in compliance with the duty of disclosure requirements of 37 C.F.R. §§ 1.56, 1.97, and 1.98, are documents that may be considered material to the examination of this application.

Where the publication date of a listed document does not provide a month of publication, the year of publication of the listed document is sufficiently earlier than the effective U.S. filing date and any foreign priority date that the month of publication is not at issue. Applicant has listed publication dates on the attached Form PTO/SB/08 based on information presently available to the undersigned. However, the listed publication dates should not be construed as an admission that the information was actually published on the date indicated.

Applicant reserves the right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered.

This statement should not be construed as a representation that a search has been made, or that information more material to the examination of the present patent application does not exist. The Examiner is specifically requested not to rely solely on the material submitted herewith. It is further understood that the Examiner will consider information that had been cited by or submitted to the U.S. Patent and Trademark Office in a prior application relied on under 35 U.S.C. § 120. 1138 OG 37, 38 (May 19, 1992).

Applicant has checked the appropriate boxes below.

☐ 1. This Information Disclosure Statement is being filed within three months of the U.S. filing date OR before the mailing date of a first Office Action on the merits. No statement under 37 C.F.R. § 1.97(e) or fee is required.

☒ 2. This Information Disclosure Statement is being filed more than three months after the U.S. filing date AND after the mailing date of the first Office Action on the merits, but before the mailing date of a Final Rejection or Notice of Allowance. Please charge our Deposit Account No. 50-0740 in the amount of $180.00 in payment of the fee under 37 C.F.R. § 1.17(p).

- ☐ a. I hereby state that each item of information contained in this Information Disclosure Statement was cited in a communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this Information Disclosure Statement. 37 C.F.R. § 1.97(e)(1).
- ☐ b. I hereby state that no item of information in this Information Disclosure Statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to my knowledge after making reasonable inquiry, no item of

information contained in this Information Disclosure Statement was known to any individual designated in 37 C.F.R. § 1.56(c) more than three months prior to the filing of this Information Disclosure Statement. 37 C.F.R. § 1.97(e)(2).

☐ 3. This Information Disclosure Statement is being filed more than three months after the U.S. filing date and after the mailing date of a Final Rejection or Notice of Allowance, but before payment of the Issue Fee. It is hereby requested that the Information Disclosure Statement be considered. Attached is our Check No. _________ in the amount of $ ______ in payment of the fee under 37 C.F.R. § 1.17(i).

☐ a. I hereby state that each item of information contained in this Information Disclosure Statement was cited in a communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this Information Disclosure Statement. 37 C.F.R. § 1.97(e)(1).

☐ b. I hereby state that no item of information in this Information Disclosure Statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to my knowledge after making reasonable inquiry, no item of information contained in this Information Disclosure Statement was known to any individual designated in 37 C.F.R. § 1.56(c) more than three months prior to the filing of this Information Disclosure Statement. 37 C.F.R. § 1.97(e)(2).

☐ 4. This Information Disclosure Statement is being filed more than three months after the U.S. filing date, but before the mailing of a first Office Action on the merits AFTER the filing of a Request for Continued Examination under 37 C.F.R. § 1.97(b)(4). It is hereby requested that the Information Disclosure Statement be considered. Attached is our Check No. _________ in the amount of $ ______ in payment of the fee under 37 C.F.R. § 1.17(i).

☐ a. I hereby state that each item of information contained in this Information Disclosure Statement was cited in a communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this Information Disclosure Statement. 37 C.F.R. § 1.97(e)(1).

☐ b. I hereby state that no item of information in this Information Disclosure Statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to my knowledge after making reasonable inquiry, no item of information contained in this Information Disclosure Statement was known to any individual designated in 37 C.F.R. § 1.56(c) more than three months prior to the filing of this Information Disclosure Statement. 37 C.F.R. § 1.97(e)(2).

☐ 5. Relevance of the non-English language document(s) is discussed in the present specification.

☐ 6. The document(s) was/were cited in a corresponding foreign application. An English language version of the foreign search report is attached for the Examiner's information.

☐ 7. A concise explanation of the relevance of the non-English language document(s) appears below:

☐ 8. The Examiner's attention is directed to co-pending U.S. Patent Application No. __________, filed ____________, which is directed to related technical subject matter. The identification of this U.S. Patent Application is not to be construed as a waiver of secrecy as to that application now or upon issuance of the present application as a patent. The Examiner is respectfully requested to consider the cited application, the rejection(s) made therein, and the art cited therein during examination.

☒ 9. In accordance with 37 CFR 1.98(a)(2)(ii), Applicant has not submitted copies of U.S. Patents and U.S. patent applications. Applicant submits herewith copies of foreign patents and non-patent literature in accordance with 37 CFR 1.98(a)(2).

☐ 10. Copies of the documents were cited by or submitted to the Office in Application No. ___________, filed __________, which is relied upon for an earlier filing date under 35 U.S.C. § 120. Thus, copies of these documents are not attached. 37 C.F.R. § 1.98(d).

It is respectfully requested that the Examiner initial and return a copy of the enclosed Form PTO/SB/08, and indicate in the official file wrapper of this patent application that the documents have been considered.

The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 50-0740 referencing Docket No. 015332.1182-US02.

Dated: April 10, 2017

Respectfully submitted,

By ______________________

Einar Stole
Registration No.: 47,272
Melody H. Wu
Registration No.: 52,376
COVINGTON & BURLING LLP
One CityCenter
850 Tenth Street, NW
Washington, DC 20001-4956
(202) 662-6000
Attorneys for Applicant

Substitute for form 1449/PTO				*Complete if Known*	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	15/019,543-Conf. #1984
				Filing Date	February 9, 2016
				First Named Inventor	Tjeerd A. Barf
				Art Unit	1626
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(71) Applicant (*for all designated States except US*): BASF AKTIENGESELLSCHAFT [DE/DE]; D-67056 Ludwigshafen (DE).

(72) Inventors; and
(75) Inventors/Applicants (*for US only*): HIRST, Gavin, C. [GB/US]; 112 Robert Road, Marlborough, MA 01752 (US). CALDERWOOD, David [GB/US]; 4 McCarthy Circle, Framingham, MA 01702 (US). WISHART, Neil [GB/US]; 406 Sterling Road, Holden, MA 01520 (US). RITTER, Kurt [DE/US]; 30 Ashmont Avenue, Newton, MA 02160 (US). ARNOLD, Lee, D. [CA/US]; 216 Ruggles Street, Westboro, MA 01581 (US).

(74) Agents: WAGNER, Richard, W. et al.; Hamilton, Brook, Smith & Reynolds, P.C., Two Militia Drive, Lexington, MA 02421 (US).

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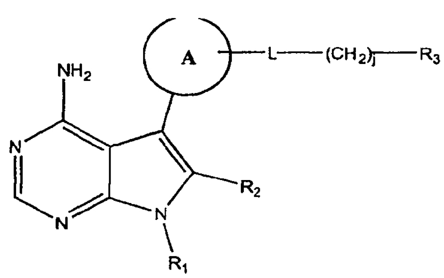

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(57) Abstract

Chemical compounds having structural formula (I) and physiologically acceptable salts and metabolites thereof, are inhibitors of serine/threonine and tyrosine kinase activity. Several of the kinases, whose activity is inhibited by these chemical compounds, are involved in immunologic, hyperproliferative, or angiogenic processes. Thus, these chemical compounds can ameliorate disease states where angiogenesis or endothelial cell hyperproliferation is a factor. These compounds can be used to treat cancer and hyper proliferative disorders, rheumatoid arthritis, disorders of the immune system, transplant rejections and imflammatory disorders.

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PYRROLOPYRIMIDINES AS PROTEIN KINASE INHIBITORS

RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application Numbers 60/100,832, filed September 18, 1998; 60/100,833, filed September 18, 1998; 60/100,834, filed September 18, 1998, and 60/100,946, filed September 18, 1998. The teachings of each of these referenced applications are expressly incorporated herein by reference in their entirety.

BACKGROUND OF THE INVENTION

There are at least 400 enzymes identified as protein kinases. These enzymes catalyze the phosphorylation of target protein substrates. The phosphorylation is usually a transfer reaction of a phosphate group from ATP to the protein substrate. The specific structure in the target substrate to which the phosphate is transferred is a tyrosine, serine or threonine residue. Since these amino acid residues are the target structures for the phosphoryl transfer, these protein kinase enzymes are commonly referred to as tyrosine kinases or serine/threonine kinases.

The phosphorylation reactions, and counteracting phosphatase reactions, at the tyrosine, serine and threonine residues are involved in countless cellular processes that underlie responses to diverse intracellular signals (typically mediated through cellular receptors), regulation of cellular functions, and activation or deactivation of cellular processes. A cascade of protein kinases often participate in intracellular signal transduction and are necessary for the realization of these cellular processes. Because of their ubiquity in these processes, the protein kinases can be found as an integral part of the plasma membrane or as cytoplasmic enzymes or localized in the nucleus, often as components of enzyme complexes. In many instances, these protein kinases are an essential element of enzyme and structural protein complexes that determine where and when a cellular process occurs within a cell.

Protein Tyrosine Kinases. Protein tyrosine kinases (PTKs) are enzymes which catalyse the phosphorylation of specific tyrosine residues in cellular proteins. This post-translational modification of these substrate proteins, often enzymes themselves, acts as a molecular switch regulating cell proliferation, activation or differentiation (for review, see Schlessinger and Ulrich, 1992, *Neuron* 9:383-391). Aberrant or excessive PTK activity has been observed in many disease states including benign and malignant proliferative disorders as well as diseases resulting from inappropriate activation of the immune system (e.g., autoimmune disorders), allograft rejection, and graft vs. host disease. In addition, endothelial-cell specific receptor PTKs such as KDR and Tie-2 mediate the angiogenic process, and are thus involved in supporting the progression of cancers and other diseases involving inappropriate vascularization (e.g., diabetic retinopathy, choroidal neovascularization due to age-related macular degeneration, psoriasis, arthritis, retinopathy of prematurity, infantile hemangiomas).

Tyrosine kinases can be of the receptor-type (having extracellular, transmembrane and intracellular domains) or the non-receptor type (being wholly intracellular).

Receptor Tyrosine Kinases (RTKs). The RTKs comprise a large family of transmembrane receptors with diverse biological activities. At present, at least nineteen (19) distinct RTK subfamilies have been identified. The receptor tyrosine kinase (RTK) family includes receptors that are crucial for the growth and differentiation of a variety of cell types (Yarden and Ullrich, *Ann. Rev. Biochem.* 57:433-478, 1988; Ullrich and Schlessinger, *Cell* 61:243-254, 1990). The intrinsic function of RTKs is activated upon ligand binding, which results in phosphorylation of the receptor and multiple cellular substrates, and subsequently in a variety of cellular responses (Ullrich & Schlessinger, 1990, *Cell* 61:203-212). Thus, receptor tyrosine kinase mediated signal transduction is initiated by extracellular interaction with a specific growth factor (ligand), typically followed by receptor dimerization, stimulation of the intrinsic protein tyrosine kinase activity and receptor trans-phosphorylation. Binding sites are thereby created for intracellular signal transduction molecules and lead to the formation of complexes with a spectrum of cytoplasmic signaling molecules that facilitate the appropriate cellular response.

(e.g., cell division, differentiation, metabolic effects, changes in the extracellular microenvironment) see Schlessinger and Ullrich, 1992, *Neuron* 9:1-20.

Proteins with SH2 (src homology -2) or phosphotyrosine binding (PTB) domains bind activated tyrosine kinase receptors and their substrates with high affinity to propagate signals into cell. Both of the domains recognize phosphotyrosine. (Fantl *et al.*, 1992, *Cell* 69:413-423; Songyang *et al.*, 1994, *Mol. Cell. Biol.* 14:2777-2785; Songyang *et al.*, 1993, *Cell* 72:767-778; and Koch *et al.*, 1991, *Science* 252:668-678; Shoelson, *Curr. Opin. Chem. Biol.* (1997), 1(2), 227-234; Cowburn, *Curr. Opin. Struct. Biol.* (1997), 7(6), 835-838). Several intracellular substrate proteins that associate with receptor tyrosine kinases (RTKs) have been identified. They may be divided into two principal groups: (1) substrates which have a catalytic domain; and (2) substrates which lack such a domain but serve as adapters and associate with catalytically active molecules (Songyang *et al.*, 1993, *Cell* 72:767-778). The specificity of the interactions between receptors or proteins and SH2 or PTB domains of their substrates is determined by the amino acid residues immediately surrounding the phosphorylated tyrosine residue. For example, differences in the binding affinities between SH2 domains and the amino acid sequences surrounding the phosphotyrosine residues on particular receptors correlate with the observed differences in their substrate phosphorylation profiles (Songyang *et al.*, 1993, *Cell* 72:767-778). Observations suggest that the function of each receptor tyrosine kinase is determined not only by its pattern of expression and ligand availability but also by the array of downstream signal transduction pathways that are activated by a particular receptor as well as the timing and duration of those stimuli. Thus, phosphorylation provides an important regulatory step which determines the selectivity of signaling pathways recruited by specific growth factor receptors, as well as differentiation factor receptors.

Several receptor tyrosine kinases such as FGFR-1, PDGFR, TIE-2 and c-Met, and growth factors that bind thereto, have been suggested to play a role in angiogenesis, although some may promote angiogenesis indirectly (Mustonen and Alitalo, *J. Cell Biol.* 129:895-898, 1995). One such receptor tyrosine kinase, known as "fetal liver kinase 1" (FLK-1), is a member of the type III subclass of RTKs. An alternative designation for human FLK-1 is "kinase insert domain-containing receptor" (KDR) (Terman *et al.*, *Oncogene* 6:1677-83, 1991). Another alternative designation for FLK-1/KDR is "vascular endothelial cell growth factor receptor 2" (VEGFR-2) since it binds VEGF with high affinity. The murine version of FLK-1/VEGFR-2 has also been called NYK (Oelrichs *et al*, *Oncogene* 8(1):11-15, 1993). DNAs encoding mouse, rat and human FLK-1 have been isolated, and the nucleotide and encoded amino acid sequences reported (Matthews *et al.*, *Proc. Natl. Acad. Sci.* USA, 88:9026-30, 1991; Terman *et al.*, 1991, *supra*; Terman *et al.*, *Biochem. Biophys. Res. Comm.* 187:1579-86, 1992; Sarzani *et al.*, *supra*; and Millauer *et al.*, *Cell* 72:835-846, 1993). Numerous studies such as those reported in Millauer *et al.*, *supra*, suggest that VEGF and FLK-1/KDR/VEGFR-2 are a ligand-receptor pair that play an important role in the proliferation of vascular endothelial cells, and formation and sprouting of blood vessels, termed vasculogenesis and angiogenesis, respectively.

Another type III subclass RTK designated "fms-like tyrosine kinase-1" (Flt-1) is related to FLK-1/KDR (DeVries et al. *Science* 255;989-991, 1992; Shibuya et al., *Oncogene* 5:519-524, 1990). An alternative designation for Flt-1 is "vascular endothelial cell growth factor receptor 1" (VEGFR-1). To date, members of the FLK-1/ KDR/VEGFR-2 and Flt-1/ VEGFR-1 subfamilies have been found expressed primarily on endothelial cells. These subclass members are specifically stimulated by members of the vascular endothelial cell growth factor (VEGF) family of ligands (Klagsburn and D'Amore, *Cytokine & Growth Factor Reviews* 7: 259-270, 1996). Vascular endothelial cell growth factor (VEGF) binds to Flt-1 with higher affinity than to FLK-1/KDR and is mitogenic toward vascular endothelial cells (Terman et al., 1992, *supra*; Mustonen et al. *supra*; DeVries et al., *supra*). Flt-1 is believed to be essential for endothelial organization during vascular development. Flt-1 expression is associated with early vascular development in mouse embryos, and with neovascularization during wound healing (Mustonen and Alitalo, *supra*). Expression of Flt-1 in monocytes, osteoclasts, and osteoblasts, as well as in adult tissues such as kidney glomeruli suggests an additional function for this receptor that is not related to cell growth (Mustonen and Alitalo, *supra*).

As previously stated, recent evidence suggests that VEGF plays a role in the stimulation of both normal and pathological angiogenesis (Jakeman *et al.*, *Endocrinology* 133: 848-859, 1993; Kolch *et al.*, *Breast Cancer Research and Treatment* 36: 139-155, 1995; Ferrara *et al.*, *Endocrine Reviews* 18(1); 4-25, 1997; Ferrara et al., Regulation of Angiogenesis (ed. L. D. Goldberg and E.M. Rosen), 209-232, 1997). In addition, VEGF has been implicated in the control and enhancement of vascular permeability (Connolly, *et al.*, *J. Biol. Chem.* 264: 20017-20024, 1989; Brown *et al.*, *Regulation of Angiogenesis* (ed. L.D. Goldberg and E.M. Rosen), 233-269, 1997). Different forms of VEGF arising from alternative splicing of mRNA have been reported, including the four species described by Ferrara *et al.* (*J. Cell. Biochem.* 47:211-218, 1991). Both secreted and predominantly cell-associated species of VEGF have been identified by Ferrara *et al. supra*, and the protein is known to exist in the form of disulfide linked dimers.

Several related homologs of VEGF have recently been identified. However, their roles in normal physiological and disease processes have not yet been elucidated. In addition, the members of the VEGF family are often coexpressed with VEGF in a number of tissues and are, in general, capable of forming heterodimers with VEGF. This property likely alters the receptor specificity and biological effects of the heterodimers and further complicates the elucidation of their specific functions as illustrated below (Korpelainen and Alitalo, *Curr. Opin. Cell Biol.*, 159-164, 1998 and references cited therein).

Placenta growth factor (PlGF) has an amino acid sequence that exhibits significant homology to the VEGF sequence (Park *et al.*, *J. Biol. Chem.* 269:25646-54, 1994; Maglione *et al. Oncogene* 8:925-31, 1993). As with VEGF, different species of PlGF arise from alternative splicing of mRNA, and the protein exists in dimeric form (Park *et al.*, *supra*). PlGF-1 and PlGF-2 bind to Flt-1 with high affinity, and PlGF-2 also avidly binds to neuropilin-1 (Migdal *et al*, *J. Biol. Chem.* 273 (35): 22272-22278), but neither binds to FLK-1/KDR (Park *et al.*, *supra*). PlGF has been reported to potentiate both the vascular permeability and mitogenic effect of VEGF on endothelial cells when VEGF is present at low concentrations (purportedly due to heterodimer formation) (Park *et al.*, *supra*).

VEGF-B is produced as two isoforms (167 and 185 residues) that also appear to bind Flt-1/VEGFR-1. It may play a role in the regulation of extracellular matrix degradation, cell adhesion, and migration through modulation of the expression and activity of urokinase type plasminogen activator and plasminogen activator inhibitor 1 (Pepper *et al*, *Proc. Natl. Acad. Sci. U. S. A.* (1998), 95(20): 11709-11714).

VEGF-C was originally cloned as a ligand for VEGFR-3/Flt-4 which is primarily expressed by lymphatic endothelial cells. In its fully processed form, VEGF-C can also bind KDR/VEGFR-2 and stimulate proliferation and migration of endothelial cells *in vitro* and angiogenesis in *in vivo* models (Lymboussaki *et al*, *Am. J. Pathol.* (1998), 153(2): 395-403; Witzenbichler *et al*, *Am. J. Pathol.* (1998), 153(2), 381-394). The transgenic overexpression of VEGF-C causes proliferation and enlargement of only lymphatic vessels, while blood vessels are unaffected. Unlike VEGF, the expression of VEGF-C is not induced by hypoxia (Ristimaki *et al*, *J. Biol. Chem.* (1998), 273(14),8413-8418).

The most recently discovered VEGF-D is structurally very similar to VEGF-C. VEGF-D is reported to bind and activate at least two VEGFRs, VEGFR-3/Flt-4 and KDR/VEGFR-2. It was originally cloned as a c-fos inducible mitogen for fibroblasts and is most prominently expressed in the mesenchymal cells of the lung and skin (Achen *et al*, *Proc. Natl. Acad. Sci. U. S. A.* (1998), 95(2), 548-553 and references therein).

As for VEGF, VEGF-C and VEGF-D have been claimed to induce increases in vascular permeability *in vivo* in a Miles assay when injected into cutaneous tissue (PCT/US97/14696; WO98/07832, Witzenbichler *et al*., *supra*). The physiological role and significance of these ligands in modulating vascular hyperpermeability and endothelial responses in tissues where they are expressed remains uncertain.

There has been recently reported a virally encoded, novel type of vascular endothelial growth factor, VEGF-E (NZ-7 VEGF), which preferentially utilizes KDR/Flk-1 receptor and carries a potent mitotic activity without heparin-binding domain (Meyer *et al*, *EMBO J.* (1999), 18(2), 363-374; Ogawa *et al*, *J. Biol. Chem.* (1998), 273(47), 31273-31282.). VEGF-E sequences possess 25% homology to mammalian VEGF and are encoded by the parapoxvirus Orf virus (OV). This parapoxvirus that affects sheep and goats and occasionally, humans, to generate lesions with angiogenesis. VEGF-E is a dimer of about 20 kDa with no basic domain nor affinity for heparin, but has the characteristic cysteine knot motif present in all mammalian VEGFs, and was surprisingly found to possess potency and bioactivities similar to the heparin-binding VEGF165 isoform of VEGF-A, i.e. both factors stimulate the release of tissue factor (TF), the proliferation, chemotaxis and sprouting of cultured vascular endothelial cells in vitro and angiogenesis in vivo. Like VEGF165, VEGF-E was found to bind with high affinity to VEGF receptor-2 (KDR) resulting in receptor autophosphorylation and a biphasic rise in free intracellular Ca^{2+} concentrations, while in contrast to VEGF165, VEGF-E did not bind to VEGF receptor-1 (Flt-1).

Based upon emerging discoveries of other homologs of VEGF and VEGFRs and the precedents for ligand and receptor heterodimerization, the actions of such VEGF homologs may involve formation of VEGF ligand heterodimers, and/or heterodimerization of receptors, or binding to a yet undiscovered VEGFR (Witzenbichler *et al., supra*). Also, recent reports suggest neuropilin-1 (Migdal *et al, supra*) or VEGFR-3/Flt-4 (Witzenbichler *et al., supra*), or receptors other than KDR/VEGFR-2 may be involved in the induction of vascular permeability (Stacker, S.A., Vitali, A., Domagala, T., Nice, E., and Wilks, A.F., "Angiogenesis and Cancer" Conference, Amer. Assoc. Cancer Res., Jan. 1998, Orlando, FL; Williams, *Diabetelogia* 40: S118-120 (1997)).

Tie-2 (TEK) is a member of a recently discovered family of endothelial cell specific receptor tyrosine kinases which is involved in critical angiogenic processes, such as vessel branching, sprouting, remodeling, maturation and stability. Tie-2 is the first mammalian receptor tyrosine kinase for which both agonist ligand(s) (e.g., Angiopoietin1 ("Ang1"), which stimulates receptor autophosphorylation and signal transduction), and antagonist ligand(s) (e.g., Angiopoietin2 ("Ang2")), have been identified. Knock-out and transgenic manipulation of the expression of Tie-2 and its ligands indicates tight spatial and temporal control of Tie-2 signaling is essential for the proper development of new vasculature. The current model suggests that stimulation of Tie-2 kinase by the Ang1 ligand is directly involved in the branching, sprouting and outgrowth of new vessels, and recruitment and interaction of periendothelial support cells important in maintaining vessel integrity and inducing quiescence. The absence of Ang1 stimulation of Tie-2 or the inhibition of Tie-2 autophosphorylation by Ang2, which is produced at high levels at sites of vascular regression, may cause a loss in vascular structure and matrix contacts resulting in endothelial cell death, especially in the absence of growth/survival stimuli. The situation is however more complex, since at least two additional Tie-2 ligands (Ang3 and Ang4) have recently been reported, and the capacity for heterooligomerization of the various agonistic and antagonistic angiopoietins, thereby modifying their activity, has been demonstrated. Targeting Tie-2 ligand-receptor interactions as an antiangiogenic therapeutic approach is thus less favored and a kinase inhibitory strategy preferred.

The soluble extracellular domain of Tie-2 ("ExTek") can act to disrupt the establishment of tumor vasculature in a breast tumor xenograft and lung metastasis models and in tumor-cell mediated ocular neovasculatization. By adenoviral infection, the *in vivo* production of mg/ml levels ExTek in rodents may be achieved for 7-10 days with no adverse side effects. These results suggest that disruption of Tie-2 signaling pathways in normal healthy animals may be well tolerated. These Tie-2 inhibitory responses to ExTek may be a consequence sequestration of ligand(s) and/or generation of a nonproductive heterodimer with full-length Tie-2.

Recently, significant upregulation of Tie-2 expression has been found within the vascular synovial pannus of arthritic joints of humans, consistent with a role in the inappropriate neovascularization. This finding suggests that Tie-2 plays a role in the progression of rheumatoid arthritis. Point mutations producing constitutively activated forms of Tie-2 have been identified in association with human venous malformation disorders. Tie-2 inhibitors are, thereful, useful in treating such disorders, and in other situations of inappropriate neovascularization.

The Non-Receptor Tyrosine Kinases. The non-receptor tyrosine kinases represent a collection of cellular enzymes which lack extracellular and transmembrane sequences. At present, over twenty-four individual non-receptor tyrosine kinases, comprising eleven (11) subfamilies (Src, Frk, Btk, Csk, Abl, Zap70, Fes/Fps, Fak, Jak, Ack and LIMK) have been identified. At present, the Src subfamily of non-receptor tyrosine kinases is comprised of the largest number of PTKs and include Src, Yes, Fyn, Lyn, Lck, Blk, Hck, Fgr and Yrk. The Src subfamily of enzymes has been linked to oncogenesis and immune responses. A more detailed discussion of non-receptor tyrosine kinases is provided in Bohlen, 1993, *Oncogene* 8:2025-2031, which is incorporated herein by reference.

Many of the tyrosine kinases, whether an RTK or non-receptor tyrosine kinase, have been found to be involved in cellular signaling pathways involved in numerous pathogenic conditions, including cancer, psoriasis, and other hyperproliferative disorders or hyper-immune responses.

Development of Compounds to Modulate the PTKs. In view of the surmised importance of PTKs to the control, regulation, and modulation of cell proliferation, the diseases and disorders associated with abnormal cell proliferation, many attempts have been made to identify receptor and non-receptor tyrosine kinase "inhibitors" using a variety of approaches, including the use of mutant ligands (U.S. Application No. 4,966,849), soluble receptors and antibodies (Application No. WO 94/10202; Kendall & Thomas, 1994, *Proc. Natl. Acad. Sci* 90:10705-09; Kim *et al.*, 1993, *Nature* 362:841-844), RNA ligands (Jellinek, *et al.*, *Biochemistry* 33:10450-56; Takano, *et al.*, 1993, *Mol. Bio. Cell* 4:358A; Kinsella, *et al.* 1992, *Exp. Cell Res.* 199:56-62; Wright, *et al.*, 1992, *J. Cellular Phys.* 152:448-57) and tyrosine kinase inhibitors (WO 94/03427; WO 92/21660; WO 91/15495; WO 94/14808; U.S. Patent No. 5,330,992; Mariani, *et al.*, 1994, *Proc. Am. Assoc. Cancer Res.* 35:2268).

More recently, attempts have been made to identify small molecules which act as tyrosine kinase inhibitors. For example, bis monocyclic, bicyclic or heterocyclic aryl compounds (PCT WO 92/20642) and vinylene-azaindole derivatives (PCT WO 94/14808) have been described generally as tyrosine kinase inhibitors. Styryl compounds (U.S. Patent No. 5,217,999), styryl-substituted pyridyl compounds (U.S. Patent No. 5,302,606), certain quinazoline derivatives (EP Application No. 0 566 266 A1; *Expert Opin. Ther. Pat.* (1998), 8(4): 475-478), selenoindoles and selenides (PCT WO 94/03427), tricyclic polyhydroxylic compounds (PCT WO 92/21660) and benzylphosphonic acid compounds (PCT WO

91/15495) have been described as compounds for use as tyrosine kinase inhibitors for use in the treatment of cancer. Anilinocinnolines (PCT WO97/34876) and quinazoline derivative compounds (PCT WO97/22596; PCT WO97/42187) have been described as inhibitors of angiogenesis and vascular permeability.

In addition, attempts have been made to identify small molecules which act as serine/threonine kinase inhibitors. For example, bis(indolylmaleimide) compounds have been described as inhibiting particular PKC serine/threonine kinase isoforms whose signal transducing function is associated with altered vascular permeability in VEGF-related diseases (PCT WO97/40830; PCT WO97/40831).

Plk-1 Kinase Inhibitors

Plk-1 is a serine/threonine kinase which is an important regulator of cell cycle progression. It plays critical roles in the assembly and the dynamic function of the mitotic spindle apparatus. Plk-1 and related kinases have also been shown to be closely involved in the activation and inactivation of other cell cycle regulators, such as cyclin-dependent kinases. High levels of Plk-1 expression are associated with cell proliferation activities. It is often found in malignant tumors of various origins. Inhibitors of Plk-1 are expected to block cancer cell proliferation by disrupting processes involving mitotic spindles and inappropriately activated cyclin-dependent kinases.

Cdc2/Cyclin B Kinase Inhibitors (Cdc2 is also known as cdk1)

Cdc2/cyclin B is another serine/threonine kinase enzyme which belongs to the cyclin-dependent kinase (cdks) family. These enzymes are involved in the critical transition between various phases of cell cycle progression. It is believed that uncontrolled cell proliferation, which is the hallmark of cancer is dependent upon elevated cdk activities in these cells. The inhibition of elevated cdk activities in cancer cells by cdc2/cyclin B kinase inhibitors could suppress proliferation and may restore the normal control of cell cycle progression.

The regulation of CDK activation is complex, but requires the association of the CDK with a member of the cyclin family of regulatory subunits (Draetta, *Trends* *in Cell Biology*, **3**:287-289 (1993)); Murray and Kirschner, *Nature*, **339**:275-280 (1989); Solomon *et al.*, *Molecular Biology of the Cell*, **3**:13-27 (1992)). A further level of regulation occurs through both activating and inactivating phosphorylations of the CDK subunit (Draetta, *Trends in Cell Biology*, **3**:287-289 (1993)); Murray and Kirschner, *Nature*, **339**:275-280 (1989); Solomon *et al.*, *Molecular Biology of the Cell*, **3**:13-27 (1992); Ducommun *et al., EMBO Journal*, **10**:3311-3319 (1991); Gautier *et al.*, *Nature* **339**:626-629 (1989); Gould and Nurse, *Nature*, **342**:39-45 (1989); Krek and Nigg, *EMBO Journal,* **10**:3331-3341 (1991); Solomon *et al.*, *Cell*, **63**:1013-1024 (1990)). The coordinate activation and inactivation of different cyclin/CDK complexes is necessary for normal progression through the cell cycle (Pines, *Trends in Biochemical Sciences*, **18**:195-197 (1993); Sherr, *Cell*, **73**:1059-1065 (1993)). Both the critical G1-S and G 2-M transitions are controlled by the activation of different cyclin/CDK activities. In G1, both cyclin D/CDK4 and cyclin E/CDK2 are thought to mediate the onset of S-phase (Matsushima *et al.*, *Molecular & Cellular Biology*, **14**:2066-2076 (1994); Ohtsubo and Roberts, *Science*, **259**:1908-1912 (1993); Quelle *et al.*, *Genes & Development*, **7**:1559-1571 (1993); Resnitzky *et al.*, *Molecular & Cellular Biology*, **14**:1669-1679 (1994)). Progression through S-phase requires the activity of cyclin A/CDK2 (Girard *et al.*, *Cell*, **67**:1169-1179 (1991); Pagano *et al.*, *EMBO Journal*, **11**:961-971 (1992); Rosenblatt *et al.*, *Proceedings of the National Academy of Science USA*, **89**:2824-2828 (1992); Walker and Maller, *Nature*, **354**:314-317 (1991); Zindy *et al.*, *Biochemical & Biophysical Research Communications*, **182**:1144-1154 (1992)) whereas the activation of cyclin A/cdc2 (CDK1) and cyclin B/cdc2 are required for the onset of metaphase (Draetta, *Trends in Cell Biology*, **3**:287-289 (1993)); Murray and Kirschner, *Nature*, **339**:275-280 (1989); Solomon *et al.*, *Molecular Biology of the Cell*, **3**:13-27 (1992); Girard *et al.*, *Cell*, **67**:1169-1179 (1991); Pagano *et al.*, *EMBO Journal*, **11**:961-971 (1992); Rosenblatt *et al.*, *Proceedings of the National Academy of Science USA*, **89**:2824-2828 (1992); Walker and Maller, *Nature*, **354**:314-317 (1991); Zindy *et al.*, *Biochemical & Biophysical Research Communications*, **182**:1144-1154 (1992)). It is not surprising, therefore, that the loss of control of CDK regulation is a frequent event in hyperproliferative diseases and cancer.

(Pines, *Current Opinion in Cell Biology*, **4**:144-148 (1992); Lees, *Current Opinion in Cell Biology*, **7**:773-780 (1995); Hunter and Pines, *Cell*, **79**:573-582 (1994)).

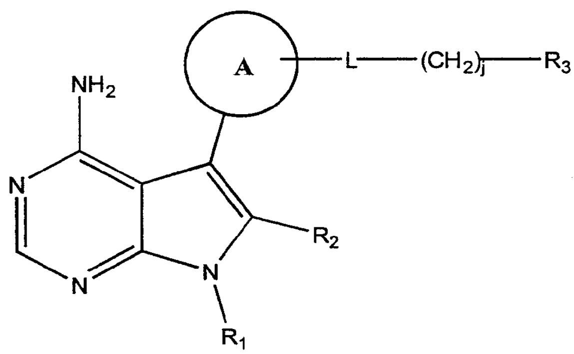
Inhibitors of kinases involved in mediating or maintaining disease states represent novel therapies for these disorders. Examples of such kinases include, but are not limited to: (1) inhibition of c-Src (Brickell, *Critical Reviews in Oncogenesis*, **3**:401-406 (1992); Courtneidge, *Seminars in Cancer Biology*, **5**:236-246 (1994), raf (Powis, *Pharmacology & Therapeutics*, **62**:57-95 (1994)) and the cyclin-dependent kinases (CDKs) 1, 2 and 4 in cancer (Pines, *Current Opinion in Cell Biology*, 4:144-148 (1992); Lees, *Current Opinion in Cell Biology*, 7:773-780 (1995); Hunter and Pines, *Cell*, **79**:573-582 (1994)), (2) inhibition of CDK2 or PDGF-R kinase in restenosis (Buchdunger *et al.*, *Proceedings of the National Academy of Science USA*, **92**:2258-2262 (1995)), (3) inhibition of CDK5 and GSK3 kinases in Alzheimers (Hosoi *et al.*, *Journal of Biochemistry (Tokyo)*, **117**:741-749 (1995); Aplin *et al.*, *Journal of Neurochemistry*, **67**:699-707 (1996), (4) inhibition of c-Src kinase in osteoporosis (Tanaka *et al.*, *Nature*, **383**:528-531 (1996), (5) inhibition of GSK-3 kinase in type-2 diabetes (Borthwick *et al.*, *Biochemical & Biophysical Research Communications*, **210**:738-745 (1995), (6) inhibition of the p38 kinase in inflammation (Badger *et al.*, *The Journal of Pharmacology and Experimental Therapeutics*, **279**:1453-1461 (1996)), (7) inhibition of VEGF-R 1-3 and TIE-1 and -2 kinases in diseases which involve angiogenesis (Shawver *et al.*, *Drug Discovery Today*, **2**:50-63 (1997)), (8) inhibition of UL97 kinase in viral infections (He *et al.*, *Journal of Virology*, **71**:405-411 (1997)), (9) inhibition of CSF-1R kinase in bone and hematopoetic diseases (Myers *et al.*, *Bioorganic & Medicinal Chemistry Letters*, **7**:421-424 (1997), and (10) inhibition of Lck kinase in autoimmune diseases and transplant rejection (Myers *et al.*, *Bioorganic & Medicinal Chemistry Letters*, **7**:417-420 (1997)).

It is additionally possible that inhibitors of certain kinases may have utility in the treatment of diseases when the kinase is not misregulated, but it nonetheless essential for maintenance of the disease state. In this case, inhibition of the kinase activity would act either as a cure or palliative for these diseases. For example, many viruses, such as human papilloma virus, disrupt the cell cycle and drive cells into the S-phase of the cell cycle (Vousden, *FASEB Journal*, **7**:8720879 (1993)). Preventing cells from entering DNA synthesis after viral infection by inhibition of essential S-phase initiating activities such as CDK2, may disrupt the virus life cycle by preventing virus replication. This same principle may be used to protect normal cells of the body from toxicity of cycle-specific chemotherapeutic agents (Stone *et al.*, *Cancer Research*, **56**:3199-3202 (1996); Kohn *et al.*, *Journal of Cellular Biochemistry*, **54**:44-452 (1994)). Inhibition of CDKs 2 or 4 will prevent progression into the cycle in normal cells and limit the toxicity of cytotoxics which act in S-phase, G2 or mitosis. Furthermore, CDK2/cyclin E activity has also been shown to regulate NF-kB. Inhibition of CDK2 activity stimulates NF-kB-dependent gene expression, an event mediated through interactions with the p300 coactivator (Perkins *et al.*, *Science*, **275**:523-527 (1997)). NF-kB regulates genes involved in inflammatory responses (such as hematopoetic growth factors, chemokines and leukocyte adhesion molecules) (Baeuerle and Henkel, *Annual Review of Immunology*, **12**:141-179 (1994)) and may be involved in the suppression of apoptotic signals within the cell (Beg and Baltimore, *Science*, **274**:782-784 (1996); Wang *et al.*, *Science*, **274**:784-787 (1996); Van Antwerp *et al.*, *Science*, **274**:787-789 (1996)). Thus, inhibition of CDK2 may suppress apoptosis induced by cytotoxic drugs via a mechanism which involves NF-kB. This therefore suggests that inhibition of CDK2 activity may also have utility in other cases where regulation of NF-kB plays a role in etiology of disease. A further example may be take from fungal infections: Aspergillosis is a common infection in immune-compromised patients (Armstrong, *Clinical Infectious Diseases*, **16**:1-7 (1993)). Inhibition of the Aspergillus kinases Cdc2/CDC28 or Nim A (Osmani *et al.*, *EMBO Journal*, **10**:2669-2679 (1991); Osmani *et al.*, *Cell*, **67**:283-291 (1991)) may cause arrest or death in the fungi, improving the therapeutic outcome for patients with these infections.

The identification of effective small compounds which specifically inhibit signal transduction and cellular proliferation by modulating the activity of receptor and non-receptor tyrosine and serine/threonine kinases to regulate and modulate abnormal or inappropriate cell proliferation, differentiation, or metabolism is therefore desirable. In particular, the identification of methods and compounds that specifically inhibit the function of a tyrosine kinase which is essential for antiogenic processes or the formation of vascular hyperpermeability leading to edema, ascites, effusions, exudates, and macromolecular extravasation and matrix deposition as well as associated disorders would be beneficial.

SUMMARY OF THE INVENTION

The present invention provides compounds of Formula I,



(I)

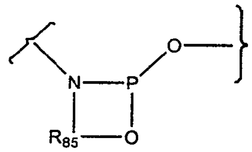
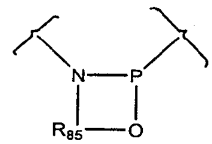
and pharmaceutically acceptable salts thereof.

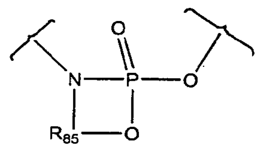
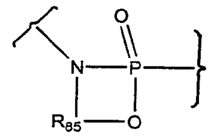
In Formula I, Ring A is a six membered aromatic ring or a five or six membered heteroaromatic ring. Ring A is optionally substituted with one or more of the following substituents: a substituted or unsubstituted aliphatic group, a halogen, a substituted or unsubstituted aromatic group, substituted or unsubstituted heteroaromatic group, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, cyano, nitro, $-NR_4R_5$, $-C(O)_2H$, -OH, a substituted or unsubstituted alkoxycarbonyl, $-C(O)_2$-haloalkyl, a substituted or unsubstituted alkylthio ether, a substituted or unsubstituted alkylsulfoxide, a substituted or unsubstituted alkylsulfone, a substituted or unsubstituted arylthio ether, a substituted or unsubstituted arylsulfoxide, a substituted or unsubstituted arylsulfone, a substituted or unsubstituted alkyl carbonyl, -C(O)-haloalkyl, a substituted or unsubstituted aliphatic ether, a substituted or unsubstituted aromatic ether, carboxamido, tetrazolyl, trifluoromethylsulphonamido, trifluoromethylcarbonylamino, a substituted or unsubstituted alkynyl, a substituted or unsubstituted alkyl amido, a substituted or unsubstituted aryl amido, a substituted or unsubstituted styryl and a substituted or unsubstituted aralkyl amido.

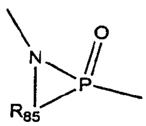
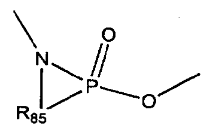
L is one of the following linkers: -O-; -S-; -S(O)-; -$S(O)_2$-; -N(R)-; -N(C(O)OR)-; -N(C(O)R)-; -N(SO_2R)-; -CH_2O-; -CH_2S-; -CH_2N(R)-; -CH(NR)-;-CH_2N(C(O)R))-; -CH_2N(C(O)OR)-;-CH_2N(SO_2R)-; -CH(NHR)-; -CH(NHC(O)R)-; -CH(NHSO_2R)-; -CH(NHC(O)OR)-;-CH(OC(O)R)-;-CH(OC(O)NHR)-; -CH=CH-; -C(=NOR)-; -C(O)-; -CH(OR)-;-C(O)N(R)-; -N(R)C(O)-; -N(R)S(O)-;-N(R)$S(O)_2$-;-OC(O)N(R)-;-N(R)C(O)N(R)-; -NRC(O)O-;-S(O)N(R)-;-$S(O)_2$N(R)-; N(C(O)R)S(O)-; N(C(O)R)$S(O)_2$-; -N(R)S(O)N(R)-; -N(R)$S(O)_2$N(R)-; -C(O)N(R)C(O)-; -S(O)N(R)C(O)-; -$S(O)_2$N(R)C(O)-; -OS(O)N(R)-; -O$S(O)_2$N(R)-; -N(R)S(O)O-; -N(R)$S(O)_2$O-; -N(R)S(O)C(O)-; -N(R)$S(O)_2$C(O)-; -SON(C(O)R)-; -SO_2N(C(O)R)-; -N(R)SON(R)-; -N(R)SO_2N(R)-; -C(O)O-; -N(R)P(OR')O-; -N(R)P(OR')-; -N(R)P(O)(OR')O-; -N(R)P(O)(OR')-; -N(C(O)R)P(OR')O-; -N(C(O)R)P(OR')-; -N(C(O)R)P(O)(OR')O- or -N(C(O)R)P(OR')-. R and R' are each, independently, -H, an acyl group, a substituted or unsubstituted aliphatic group, a substituted or unsubstituted aromatic group, a substituted or unsubstituted heteroaromatic group, or a substituted or unsubstituted cycloalkyl group.

Alternatively, L is –R_bN(R)$S(O)_2$-, -R_bN(R)P(O)-, or -R_bN(R)P(O)O-. R_b is an alkylene group which when taken together with the sulphonamide, phosphinamide, or phosphonamide group to which it is bound forms a five or six membered ring fused to ring A.

Alternatively, L is represented by one of the following structural formulas:

,
,

,
,

 or 

R_{85} taken together with the phosphinamide, or phophonamide is a 5-, 6-, or 7-membered, aromatic, heteroaromatic or heterocycloalkyl ring system.

In Formula I, R_1 is a substituted aliphatic group, a substituted cycloalkyl, a substituted bicycloalkyl, a substituted cycloalkenyl, an optionally substituted aromatic group, an optionally substituted heteroaromatic group, an optionally substituted heteroaralkyl, an optionally substituted heterocycloalkyl, an optionally substituted heterobicycloalkyl, an optionally substituted alkylamindo, and optionally substituted arylamido, an optionally substituted -S(O)$_2$-alkyl or optionally substituted -S(O)$_2$-cycloalkyl, a -C(O)-alkyl or an optionally substituted –C(O)-alkyl.

R_1 can be substituted with one or more substituents. Preferably, R_1 is substituted with a substituted or unsubstituted aliphatic group, a substituted or unsubstituted aromatic group, a substituted or unsubstituted heteroaromatic, a substituted or unsubstituted aralkyl, a substituted or unsubstituted heteroaralkyl, a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted aromatic ether, a substituted or unsubstituted aliphatic ether, a substituted or unsubstituted alkoxycarbonyl, a substituted or unsubstituted alkylcarbonyl, a substituted or unsubstituted arylcarbonyl, a substituted or unsubstituted heteroarylcarbonyl, substituted or unsubstituted aryloxycarbonyl, -OH, a substituted or unsubstituted aminocarbonyl, an oxime, a substituted or unsubstituted azabicycloalkyl, heterocycloalkyl, oxo, aldehyde, a substituted or unsubstituted alkyl sulfonamido group, a substituted or unsubstituted aryl sulfonamido group, a substituted or unsubstituted bicycloalkyl, a substituted or unsubstituted heterobicycloalkyl, cyano, $-NH_2$, an alkylamino, ureido, thioureido and –B-E.

B is a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted aromatic, a substituted or unsubstituted heteroaromatic, an alkylene, an aminoalkyl, an alkylenecarbnonyl, or an aminoalkylcarbonyl.

E is a substituted or unsubstituted azacycloalkyl, a substituted or unsubstituted azacycloalkylcarbonyl, a substituted or unsubstituted azacycloalkylsulfonyl, a substituted or unsubstituted azacycloalkylalkyl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted heteroarylcarbonyl, a substituted or unsubstituted heteroarylsulfonyl, a substituted or unsubstituted heteroaralkyl, a substituted or unsubstituted alkyl sulfonamido, a substituted or unsubstituted aryl sulfonamido, a substituted or unsubstituted bicycloalkyl, a substituted or unsubstituted ureido, a substituted or unsubstituted thioureido or a substituted or unsubstituted aryl.

However, when R_1 is an aliphatic group or cycloalkyl group, R_1 is not exclusively substituted with one or more substitutent selected from the group consisting of hydroxyl and lower alkyl ethers. In addition, a heterocycloalkyl is not 2-phenyl-1,3-dioxan-5-yl, and an aliphatic group is not substituted exclusively with one or more aliphatic groups.

In Formula I, R_2 is –H, a substituted or unsubstituted aliphatic group, a substituted or unsubstituted cycloalkyl, a halogen, -OH, cyano, a substituted or unsubstituted aromatic group, a substituted or unsubstituted heteroaromatic group, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted aralkyl, a substituted or unsubstituted heteroaralkyl, $-NR_4R_5$, or $-C(O)NR_4R_5$.

In Formula I, R_3 is a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted aromatic group, a substituted or unsubstituted heteroaromatic group, or a substituted or unsubstituted heterocycloalkyl.

In Formula I, R_4, R_5 and the nitrogen atom together form a 3, 4, 5, 6 or 7-membered, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heterobicycloalkyl or a substituted or unsubstituted heteroaromatic.

Alternatively, R_4 and R_5 are each, independently, -H, azabicycloalkyl, heterocycloalkyl, a substituted or unsubstituted alkyl group or Y-Z.

Y is selected from the group consisting of -C(O)-, $-(CH_2)_p-$,$-S(O)_2-$, -C(O)O-, $-SO_2NH-$, -CONH-, $(CH_2)_pO-$, $-(CH_2)_pNH-$, $-(CH_2)_pS-$, $-(CH_2)_pS(O)-$, and -$(CH_2)_pS(O)_2-$.

p is an integer from 0 to to about 6.

Z is a substituted or unsubstituted alkyl, substituted or unsubstituted amino, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl or substituted or unsubstituted heterocycloalkyl group.

j an integer from 0 to 6.

However, when L is $-CH_2NR-$, -C(O)NR- or –NRC(O)- and R_3 is azacycloalkyl or azaheteroaryl, j is 0. In addition, when L is –O- and R_3 is phenyl, j is 0.

The compounds of this invention are useful as inhibitors of serine/threonine and tyrosine kinases. In particular, compounds of this invention are useful as inhibitors of tyrosine kinases that are important in hyperproliferative diseases, especially in cancer and in the process of angiogenesis. For example, certain of these compounds are inhibitors of such receptor kinases as KDR, Flt-1, FGFR, PDGFR, c-Met, TIE-2 or IGF-1-R. Since certain of these compounds are anti-angiogenic, they are important substances for inhibiting the progression of disease states where angiogenesis is an important component. Certain compounds of the invention are effective as inhbitors of such serine/threonine kinases as PKCs, erk, MAP kinases, MAP kinase kinases, MAP kinase kinase kinases, cdks, Plk-1 or Raf-1. These compounds are useful in the treatment of cancer, and hyperproliferative disorders. In addition, certain compounds are effective inhibitors of non-receptor kinases such as those of the Src (for example, lck, blk and lyn), Tec, Csk, Jak, Map, Nik and Syk families. These compunds are useful in the treatment of cancer, hyperproliferative disorders and immunologic diseases.

Certain compounds of this invention are selective TIE-2 kinase inhibitors which may be anti-angiogenic (especially in combination with one or more VEGFR inhibitors), or pro-angiogenic, when employed in the presence of, or in conjunction with, a VEGF-related stimulus. In this manner such inhibitors can be used in the promotion of therapeutic angiogenesis to treat, for example, ischemia, infarct or occlusion, or to promote wound healing.

The present invention provides a method of inhibiting the kinase activity of tyrosine kinases and serine/threonine kinases comprising the administration of a compound represented by formula I to said kinase in sufficient concentration to inhibit the enzyme activity of said kinase.

The present invention further includes the use of these compounds in pharmaceutical compositions with a pharmaceutically effective amount of the above-described compounds and a pharmaceutically acceptable carrier or excipient. These pharmaceutical compositions can be administered to individuals to slow or halt the process of angiogenesis in angiogenesis-aided diseases, or to treat edema, effusions, exudates or ascites and other conditions associated with vascular hyperpermeability. Certain pharmaceutical compositions can be administered to individuals to treat cancer and hyperproliferative disorders by inhibiting serine/threonine kinases such as cdk, Plk-1, erk, etc.

DETAILED DESCRIPTION OF THE INVENTION

The values of substituents in a first preferred group of compounds of formula I are given below.

Preferably, L is $-N(R)S(O)_2-$, $-S(O)_2N(R)-$, $-N(R)C(O)-$, $-C(O)N(R)-$, or $–O-$.

Preferably, R_3 is a substituted or unsubstituted phenyl, a substituted or unsubstituted naphthyl, a substituted or unsubstituted pyridyl, a substituted or unsubstituted thienyl, a substituted or unsubstituted benzotriazole, a substituted or unsubstituted tetrahydropyranyl, a substituted or unsubstituted tetrahydrofuranyl, a substituted or unsubstituted dioxane, a substituted or unsubstituted dioxolane, a substituted or unsubstituted quinoline, a substituted or unsubstituted thiazole, substituted or unsubstituted isoxazole, substituted or unsubstituted cyclopentanyl, a substituted or unsubstituted bezofuran, substituted or unsubstituted benzothiophene, substituted or unsubstituted benzisoxazole, substituted or unsubstituted benzisothiazole, substituted or unsubstituted benzothiazole, substituted or unsubstituted bezoxazole, substituted or unsubstituted benzoxazole, substituted or unsubstituted bezimidazole, substituted or unsubstituted benzoxadiazole, substituted or unsubstituted benzothiadiazole, substituted or unsubstituted isoquinoline, substituted or unsubstituted quinoxaline, substituted or unsubstituted indole or substituted or unsubstituted pyrazole. Alternatively, R_3 can be a substituted or unsubstituted aliphatic group or a substituted or unsubstituted alkenyl, provided that L is -SN(R)-, -S(O)N(R)-, $-S(O)_2N(R)-$, -N(R)S-, -N(R)S(O)-, $-N(R)S(O)_2-$, -N(R)SN(R')-, -N(R)S(O)N(R')-, or $-N(R)S(O)_2N(R')-$;

In one embodiment, R_3 is a substituted or unsubstituted phenyl.

R_3 can be substituted by one or more substituents. Preferable substituents for R_3 are F, Cl, Br, I, CH_3, NO_2, OCF_3, OCH_3, CN, CO_2CH_3, CF_3, t-butyl, pyridyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted benzyl, substituted or unsubstituted benzenesulfonyl, substituted or unsubstituted phenoxy, substituted or unsubstituted phenyl, substituted or unsubstituted amino, carboxyl, substituted or unsubstituted tetrazolyl, styryl, -S-(substituted or unsubstituted aryl), -S-(substituted or unsubstituted heteroaryl), substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, alkynyl, $-C(O)NR_fR_g$, R_c , CH_2OR_c.

R_f, R_g and the nitrogen atom together form a 3-, 4-, 5-, 6- or 7-membered, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heterobicycloalkyl or a substituted or unsubstituted heteroaromatic.

Alternatively, R_f and R_g are each, independently, a substituted or unsubstituted aliphatic group or a substituted or unsubstuituted aromatic group.

R_c is hydrogen, or substituted or unsubstituted alkyl or substituted or unsubstituted aryl; -W-$(CH_2)_t$-NR_dR_e, -W-$(CH_2)_t$-O-alkyl, , -W-$(CH_2)_t$-S-alkyl, or -W-$(CH_2)_t$-OH.

t is an integer from 0 to about 6.

W is a bond or –O-, -S-, -S(O)-, -$S(O)_2$-, or –NR_k-.

R_k is -H or alkyl.

R_d, R_e and the nitrogen atom to which they are attached together form a 3, 4, 5, 6 or 7-membered substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heterobicyclic group.

Alternatively, R_d and R_e are each, independently, -H, alkyl, alkanoyl or –K-D.

K is -$S(O)_2$-, -C(O)-, -C(O)NH-, -$C(O)_2$-, or a direct bond.

D is a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted aralkyl, a substituted or unsubstituted heteroaromatic group, a substituted or unsubstituted heteroaralkyl, a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted amino, a substituted or unsubstituted aminoalkyl, a substituted or unsubstituted aminocycloalkyl, $COOR_i$, or substituted or unsubstituted alkyl.

R_i is a substituted or unsubstituted aliphatic group or a substituted or unsubstituted aromatic group.

More preferred substituents for R_3 are F, Cl, Br, I, cyano, nitro, OCF_3, CH_3, and CF_3.

Preferably, ring A is a substituted or unsubstituted phenyl, a substituted or unsubstituted naphthyl, a substituted or unsubstituted pyridyl, or a substituted or unsubstituted indole. In one embodiment, ring A is a substituted or unsubstituted phenyl.

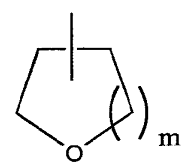
Ring A can be substituted by one or more substituents. Preferable substituents for ring A are F, Cl, Br, I, CH_3, NO_2, OCF_3, OCH_3, CN, CO_2CH_3, CF_3, t-butyl, pyridyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted benzyl, substituted or unsubstituted benzenesulfonyl, substituted or unsubstituted phenoxy, substituted or unsubstituted phenyl, substituted or unsubstituted amino, carboxyl, substituted or unsubstituted tetrazolyl, styryl, -S-(substituted or unsubstituted aryl), -S-(substituted or unsubstituted heteroaryl), substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, alkynyl, -C(O)NR$_f$R$_g$, R$_c$ and CH$_2$OR$_c$. R$_f$, R$_g$ and R$_c$ are defined as above.

Ring A is more preferably substituted with F, Cl, and nitro.

R_2 is preferably hydrogen.

In one embodiment, R_1 is of the formula

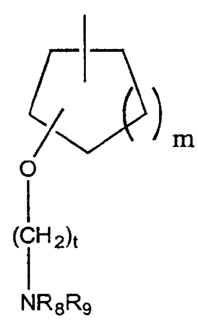
I(a)



m is an integer from 0 to about 3.

In another embodiment, R_1 is of the formula

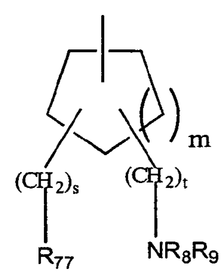
I(b)



m, t are defined as above. R_8, R_9 and the nitrogen atom together form a 3-, 4-, 5-, 6- or 7-membered, substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted heteroaromatic or substituted or unsubstituted heterobicyclicalkyl group. Alternatively, R_8 and R_9 are each, independently, -H, azabicycloalkyl, heterocycloalkyl or Y_2-Z_2. Y_2 is -C(O)-, -$(CH_2)_q$-,-$S(O)_2$-, -C(O)O-, -SO_2NH-, -CONH-, $(CH_2)_q$O-, -$(CH_2)_q$NH-, -$(CH_2)_q$S-, -$(CH_2)_q$S(O)-, or -$(CH_2)_q S(O)_2$-. q is an integer from 0 to 6. Z_2 is a substituted or unsubstituted alkyl, a substituted or unsubstituted amino, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl or a substituted or unsubstituted heterocycloalkyl group.

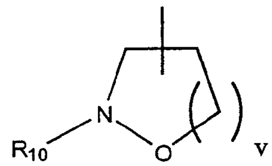
In another embodiment, R_1 is of the formula

I(c)



m, t , R_8, and R_9 are defined as above. s is an integer from 0 to 6. q is an integer from 0 to about 6. R_{77} is –OR_{78}, or –$NR_{79}R_{80}$. R_{78} is –H or a substituted or unsubstituted aliphatic group. R_{79}, R_{80} and the nitrogen atom together form a 3, 4, 5, 6 or 7-membered, substituted or unsubstituted heterocycloalkyl group, substituted or unsubstituted heteroaryl group, or a substituted heterobicyclicalkyl group. R_{79} and R_{80} are each, independently, -H, azabicycloalkyl, heterocycloalkyl or –Y_3-Z_3. Y_3 is selected from the group consisting of -C(O)-, -$(CH_2)_q$-,-$S(O)_2$-, -C(O)O-, -SO_2NH-, -CONH-, $(CH_2)_q$O-, -$(CH_2)_q$NH-, -$(CH_2)_q$S-, -$(CH_2)_q$S(O)- and-$(CH_2)_q S(O)_2$-. Z_3 is –H, a substituted or unsubstituted alkyl, a substituted or unsubstituted amino, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl or a substituted or unsubstituted heterocycloalkyl.

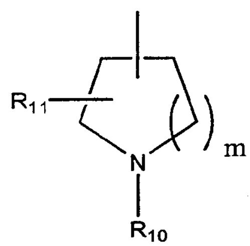
In another embodiment, R_1 is of the formula



I(d)

v is an integer from 1 to about 3. R_{10} is -H, azabicycloalkyl, heterocycloalkyl or Y_2-Z_2. Y_2 and Z_2 are as defined previously.

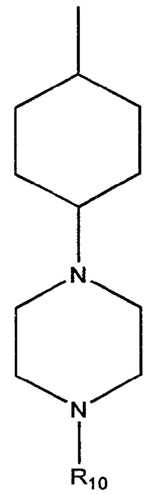
In another embodiment, R_1 is of the formula



I(e)

m and R_{10} are as previously defined. R_{11} represents one or more substituents independently selected from the group consisting of hydrogen, hydroxy, oxo, a substituted or unsubstituted aliphatic group, a substituted or unsubstituted aromatic group, a substituted or unsubstituted heteroaromatic group, a substituted or unsubstituted alkoxycarbonyl, a substituted or unsubstituted alkoxyalkyl, a substituted or unsubstituted aminocarbonyl, a substituted or unsubstituted alkylcarbonyl, a substituted or unsubstituted arylcarbonyl, a substituted or unsubstituted heteroarylcarbonyl, a substituted or unsubstituted aminoalkyl and a substituted or unsubstituted aralkyl groups, provided that the carbon atoms adjacent to the nitrogen atom are not substituted by a hydroxy group.

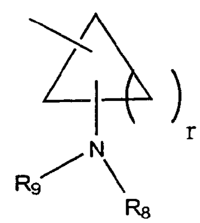
In another embodiment, R_1 is of the formula



I(f)

R_{10} is as previously defined.

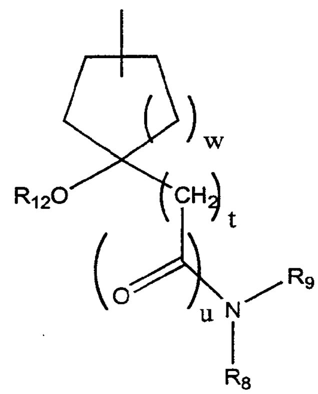
In another embodiment, R_1 is of the formula



I(g)

r is an integer from 1 to about 6. R_8 and R_9 are as previously defined.

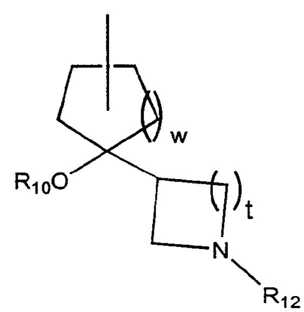
In another embodiment, R_1 is of the formula



I(h)

R_8, R_9 and t are as previously defined. w is an integer from 0 to about 4. u is 0 or 1. R_{12} is hydrogen or a substituted or unsubstituted alkyl group.

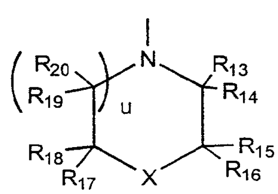
In another embodiment, R_1 is of the formula



I(i)

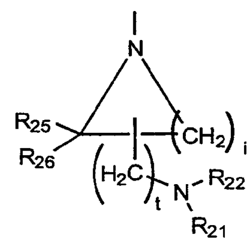
w, t, R_{10}, R_{12} are as previously defined.

In another embodiment, when R_1 is I(g) or I(H), R_8, R_9 and the nitrogen atom together form a heterocycloalkyl group of the formula



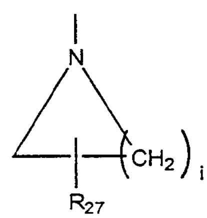
u is as previously defined. R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, R_{18}, R_{19} and R_{20} are each, independently, lower alkyl or hydrogen. Alternatively, at least one pair of substituents R_{13} and R_{14}; R_{15} and R_{16}; R_{17} and R_{18}; or R_{19} and R_{20} together are an oxygen atom. Alternatively, at least one of R_{13} and R_{15} is cyano, $CONHR_{21}$, $COOR_{21}$, CH_2OR_{21} or $CH_2NR_{21}(R_{22})$. R_{21}, R_{22} and the nitrogen atom together form a 3-, 4-, 5-, 6- or 7-membered, substituted or unsubstituted heterocycloalkyl group, substituted or unsubstituted heteroaryl group, or a substituted heterobicyclicalkyl group. Alternatively, R_{21} and R_{22} are each, independently, -H, azabicycloalkyl, heterocycloalkyl or Y_3-Z_3; Y_3 and Z_3 are as previously defined. X is –O-, -S-, -SO-, $-SO_2-$, $-CH_2-$, $-CH(OR_{23})-$ or NR_{23}. R_{23} is -H, substituted or unsubstituted alkyl, a substituted or unsubstituted aryl, a substituted or unsubstituted aralkyl, $-C(NH)NH_2$, $-C(O)R_{24}$, or $-C(O)OR_{24}$. R_{24} is hydrogen, substituted or unsubstituted alkyl, a substituted or unsubstituted aryl or a substituted or unsubstituted aralkyl.

In another embodiment, R_8, R_9 and the nitrogen atom together form a heterocycloalkyl of the formula



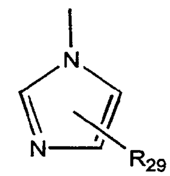
t, R_{21} and R_{22} are as previously defined. R_{25} and R_{26} are each, independently, hydrogen or lower alkyl. Alternatively, R_{25} and R_{26} together are an oxygen atom. i is an integer from 1 to about 6.

In another embodiment, R_8, R_9 and the nitrogen atom together form a heterocycloalkyl group; of the formula



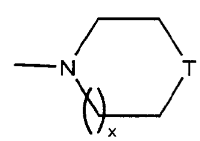
i is as previously defined. R_{27} is CH_2OH, $C(O)NR_{24}R_{28}$ or $COOR_{24}$. R_{24} and R_{28} are as previously defined.

In another embodiment, R_8, R_9 and the nitrogen atom together form a heteroaromatic group of the formula



R_{29} is a substituted or unsubstituted alkyl, a substituted or unsubstituted aryl or a substituted or unsubstituted aralkyl group, carboxylic acid, cyano, $C(O)OR_{30}$, CH_2OR_{30}, $CH_2NR_{21}R_{22}$ or $C(O)NR_{21}R_{22}$. R_{30} is a substituted or unsubstituted alkyl, a substituted or unsubstituted aryl, a substituted or unsubstituted aralkyl, a substituted or unsubstituted heterocycloalkyl or heterocycloaryl group. R_{21} and R_{22} are as previously defined.

In another embodiment, at least one of R_8 and R_9 is of the formula Y_3-D, wherein D is of the formula



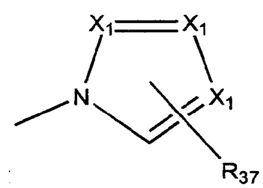
Y_3 is as previously defined. x is 0, 1 or 2. T is –O-, -C(O)-, -S-, -SO-, $-SO_2-$, $-CH_2-$, $-CH(OR_{24})-$ or $-N(R_{24})-$. R_{24} is as previously defined.

In another embodiment, at least one of R_8 and R_9 is of the formula Y_3-$N(R_{31})R_{32}$, Y_3 is as previously defined. R_{31} and R_{32} are each, independently, substituted or unsubstituted carboxyalkyl, a substituted or unsubstituted alkoxycarbonylalkyl, a substituted or unsubstituted hydroxyalkyl, a substituted or unsubstituted alkylsulfonyl, a substituted or unsubstituted alkylcarbonyl or a substituted or unsubstituted cyanoalkyl. Alternatively, R_{31} and R_{32}, together with the nitrogen atom, form a five- or six-membered heterocycloalkyl group, a substituted or unsubstituted heteroaromatic or a substitutituted or unsubstituted heterobicycloalkyl.

In another embodiment, when R_1 is I(e), Z_2 is of the formula $N(R_{35})R_{36}$. R_{35}

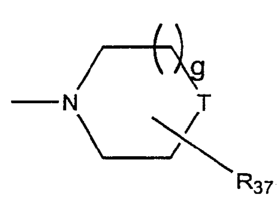
and R_{36} are each, independently, hydrogen, alkyl, alkoxycarbonyl, alkoxyalkyl, hydroxyalkyl, aminocarbonyl, cyano, alkylcarbonyl or aralkyl.

In another embodiment, when R_1 is I(e), Z_2 is of the formula



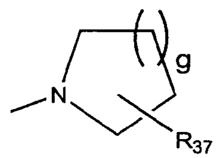
Each X_1 is, independently, CH or N. R_{37} is hydrogen, cyano or a substituted or unsubstituted alkyl, a substituted or unsubstituted alkoxycarbonyl, a substituted or unsubstituted alkoxyalkyl, a substituted or unsubstituted hydroxyalkyl, a substituted or unsubstituted aminocarbonyl, a substituted or unsubstituted alkylcarbonyl or a substituted or unsubstituted aralkyl group.

In another embodiment, when R_1 is I(e), Z_2 is of the formula



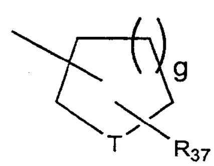
g is an integer from 0 to about 3. T is as previously defined. R_{37} is hydrogen, cyano or a substituted or unsubstituted alkyl, a substituted or unsubstituted alkoxycarbonyl, a substituted or unsubstituted alkoxyalkyl, a substituted or unsubstituted hydroxyalkyl, a substituted or unsubstituted aminocarbonyl, a substituted or unsubstituted alkylcarbonyl or a substituted or unsubstituted aralkyl group.

In another embodiment, when R_1 is I(e), Z_2 is of the formula



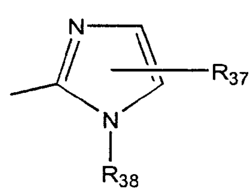
g and R_{37} are as previously defined unsubstituted aralkyl group.

In another embodiment, when R_1 is I(e), Z_2 is of the formula



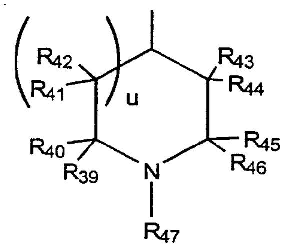
T, g and R_{37} are as previously defined.

In another embodiment, when R_1 is I(e), Z_2 is of the formula

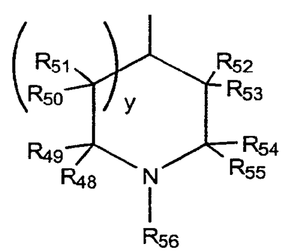


R_{37} is as previously defined. R_{38} is hydrogen, substituted or unsubstituted alkyl, a substituted or unsubstituted alkoxycarbonyl, a substituted or unsubstituted alkoxyalkyl, a substituted or unsubstituted aminocarbonyl, perhaloalkyl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkylcarbonyl or a substituted or unsubstituted aralkyl.

In another embodiment, R_1 is of the formula

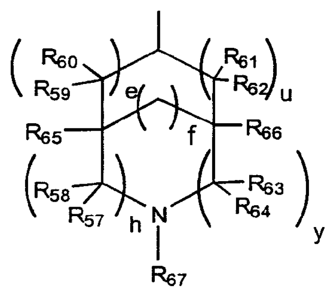


u is as previously defined. R_{39}, R_{40}, R_{41}, R_{42}, R_{43}, R_{44}, R_{45} and R_{46} are each, independently,methyl or hydrogen. Alternatively, at least one pair of substituents R_{39} and R_{40}; R_{36} and R_{37}; R_{38} and R_{39}. Alternatively, R_{40} and R_{41} together are an oxygen atom. R_{47} is H, azabicycloalkyl, heterocycloalkyl or Y_2-Z_2. Y_2 and Z_2 are as previously defined. Alternatively, R_{47} is of the formula

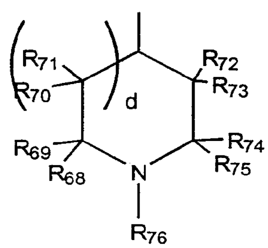


y is 0 or 1. R_{48}, R_{49}, R_{50}, R_{51}, R_{52}, R_{53}, R_{54} and R_{55} are each, independently, methyl or hydrogen. Alternatively, at least one pair of substituents R_{48} and R_{49}; R_{50} and R_{51}; R_{52} and R_{53}; or R_{54} and R_{55} together are an oxygen atom. R_{56} is -H, azabicycloalkyl, heterocycloalkyl or Y_3-Z_3. Y_3 and Z_3 are defined as above.

In another embodiment, R_1 is of the formula



e, f, h, u and y are independently 0 or 1. R_{57}, R_{58}, R_{59}, R_{60}, R_{61}, R_{62}, R_{63}, R_{64}, R_{65} and R_{66} are each, independently, methyl or hydrogen. Alternatively, at least one pair of substituents R_{57} and R_{58}; R_{59} and R_{60}; R_{61} and R_{62}; or R_{63} and R_{64} together are an oxygen atom. R_{67} is H, azabicycloalkyl, heterocycloalkyl or Y_2-Z_2. Y_2 and Z_2 are defined as above. Alternatively, R_{67} is of the formula



d is 0 or 1. R_{68}, R_{69}, R_{70}, R_{71}, R_{72}, R_{73}, R_{74} and R_{75} are each, independently, lower alkyl or hydrogen. Alternatively, at least one pair of substituents R_{68} and R_{69}; R_{70} and R_{71}; R_{72} and R_{73}. R_{74} and R_{75} together are an oxygen atom. R_{76} is -H, azabicycloalkyl, heterocycloalkyl or Y_3-Z_3. Y_3 and Z_3 are defined as above.

As used herein, aromatic groups include carbocyclic ring systems (e.g. benzyl and cinnamyl) and fused polycyclic aromatic ring systems (e.g. naphthyl and 1,2,3,4-tetrahydronaphthyl). Arromatic groups are also referred to as aryl groups herein.

Heteroaromatic groups, as used herein, include heteroaryl ring systems (e.g., thienyl, pyridyl, pyrazole, isoxazolyl, thiadiazolyl, oxadiazolyl, indazolyl, furans, pyrroles, imidazoles, pyrazoles, triazoles, pyrimidines, pyrazines, thiazoles, isoxazoles, isothiazoles, tetrazoles, or oxadiazoles) and heteroaryl ring systems in which a carbocyclic aromatic ring, carbocyclic non-aromatic ring or heteroaryl ring is fused to one or more other heteroaryl rings (e.g., benzo(b)thienyl, benzimidazole, indole, tetrahydroindole, azaindole, indazole, quinoline, imidazopyridine, purine, pyrrolo[2,3-d]pyrimidine, pyrazolo[3,4-d]pyrimidine) and their N-oxides.

An aralkyl group, as used herein, is an aromatic substituent that is linked to a compound by an aliphatic group having from one to about six carbon atoms.

An heteroaralkyl group, as used herein, is a heteroaromatic substituent that is linked to a compound by an aliphatic group having from one to about six carbon atoms.

A heterocycloalkyl group, as used herein, is a non-aromatic ring system that has 3 to 8 atoms and includes at least one heteroatom, such as nitrogen, oxygen, or sulfur.

An acyl group, as used herein, is an $-C(O)NR_xRz$, $-C(O)OR_x$, $-C(O)R_x$, in which R_x and R_z are each, independently, -H, a substituted or unsubstituted aliphatic group or a substituted or unsubstituted aromatic group.

As used herein, aliphatic groups include straight chained, branched or cyclic C_1-C_8 hydrocarbons which are completely saturated or which contain one or more units of unsaturation. A "lower alkyl group" is a saturated aliphatic group having form 1-6 carbon atoms.

Compounds of formula I may exist as salts with pharmaceutically acceptable acids. The present invention includes such salts. Examples of such salts include hydrochlorides, hydrobromides, sulfates, methanesulfonates, nitrates, maleates, acetates, citrates, fumarates, tartrates [eg (+)-tartrates, (-)-tartrates or mixtures thereof including racemic mixtures], succinates, benzoates and salts with amino acids such as glutamic acid. These salts may be prepared by methods known to those skilled in the art.

Certain compounds of formula I which have acidic substituents may exist as salts with pharmaceutically acceptable bases. The present invention includes such salts. Example of such salts include sodium salts, potassium salts, lysine salts and arginine salts. These salts may be prepared by methods known to those skilled in the art.

Certain compounds of formula I and their salts may exist in more than one crystal form and the present invention includes each crystal form and mixtures thereof.

Certain compounds of formula I and their salts may also exist in the form of solvates, for example hydrates, and the present invention includes each solvate and mixtures thereof.

Certain compounds of formula I may contain one or more chiral centres, and exist in different optically active forms. When compounds of formula I contain one chiral centre, the compounds exist in two enantiomeric forms and the present invention includes both enantiomers and mixtures of enantiomers, such as racemic mixtures. The enantiomers may be resolved by methods known to those skilled in the art, for example by formation of diastereoisomeric salts which may be separated, for example, by crystallization; formation of diastereoisomeric derivatives or complexes which may be separated, for example, by crystallization, gas-liquid or liquid chromatography; selective reaction of one enantiomer with an enantiomer-specific reagent, for example enzymatic esterification; or gas-liquid or liquid chromatography in a chiral environment, for example on a chiral support for example silica with a bound chiral ligand or in the presence of a chiral solvent. It will be appreciated that where the desired enantiomer is converted into another chemical entity by one of the separation procedures described above, a further step is required to liberate the desired enantiomeric form. Alternatively, specific enantiomers may be synthesized by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting one enantiomer into the other by asymmetric transformation.

When a compound of formula I contains more than one chiral centre it may exist in diastereoisomeric forms. The diastereoisomeric pairs may be separated by methods known to those skilled in the art, for example chromatography or crystallization and the individual enantiomers within each pair may be separated as described above. The present invention includes each diastereoisomer of compounds of formula I and mixtures thereof.

Certain compounds of formula I may exist in different tautomeric forms or as different geometric isomers, and the present invention includes each tautomer and/or geometric isomer of compounds of formula I and mixtures thereof.

Certain compounds of formula I may exist in different stable conformational forms which may be separable. Torsional asymmetry due to restricted rotation about an asymmetric single bond, for example because of steric hindrance or ring strain, may permit separation of different conformers. The present invention includes each conformational isomer of compounds of formula I and mixtures thereof.

Certain compounds of formula I may exist in zwitterionic form and the present invention includes each zwitterionic form of compounds of formula I and mixtures thereof.

A preferred group of compounds of the present invention are:

Cis-5-(4-phenoxyphenyl)-7-(4-pyrrolidinocyclohex-1-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine

Trans-5-(4-phenoxyphenyl)-7-(4-pyrrolidinocyclohex-1-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine

Cis-5-(4-phenoxyphenyl)-7-(4-piperidinocyclohex-1-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine hydrochloride

Trans-5-(4-phenoxyphenyl)-7-(4-piperidinocyclohex-1-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine

Trans-7-(4-dimethylaminocyclohexyl)-5-(4-phenoxyphenyl)-7H-pyrrolo [2,3-d]pyrimidin-4-ylamine

Cis-7-(4-dimethylaminocyclohexyl)-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine

5-(4-phenoxyphenyl)-7-(4-piperidyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-ylamine dihydrochloride

5-(4-phenoxyphenyl)-7-(3-pyrrolidinyl) -7*H*-pyrrolo[2,3-*d*]pyrimidin-4-ylamine dihydrochloride

Cis-7-[4-(4-isopropylpiperazino)cyclohexyl]-5-(4-phenoxyphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine

Trans-7-[4-(4-isopropylpiperazino)cyclohexyl]-5-(4-phenoxyphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine

Cis-7-{4-[4-(2-methoxyethyl)piperazino]cyclohexyl}-5-(4-phenoxyphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine

Trans-7-{4-[4-(2-methoxyethyl)piperazino]cyclohexyl}-5-(4-phenoxyphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine

Cis-7-[-4-(4-ethylpiperazino)cyclohexyl]-5-(4-phenoxyphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine

trans-7-[4-(4-ethylpiperazino)cyclohexyl]-5-(4-phenoxyphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine

Cis-7-[4-(4-isopropylpiperazino)cyclohexyl]-5-(4-phenoxyphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine tris maleate

Trans-7-[4-(4-isopropylpiperazino)cyclohexyl]-5-(4-phenoxyphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine tris maleate

Cis-7-{4-[4-(2-methoxyethyl)piperazino]cyclohexyl}-5-(4-phenoxyphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine tris maleate

Trans-7-{4-[4-(2-methoxyethyl)piperazino]cyclohexyl}-5-(4-phenoxyphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine tris maleate

Cis-7-(4-{[3-(1*H*-1-imidazolyl)propyl]amino}cyclohexyl)-5-(4-phenoxyphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine trimaleate salt

Trans-7-(4-{[3-(1*H*-1-imidazolyl)propyl]amino}cyclohexyl)-5-(4-phenoxyphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine dimaleate salt

Cis-7-[4-(dimethylamino)cyclohexyl]-5-(4-phenoxyphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine dimaleate salt

Trans-5-(4-phenoxyphenyl)-7-(4-piperidinocyclohexyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine dimaleate salt

Trans-5-(4-phenoxyphenyl)-7-(4-tetrahydro-1*H*-1-pyrrolylcyclohexyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine dimaleate salt

Cis-5-(4-phenoxyphenyl)-7-(4-piperazinocyclohexyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine trimaleate salt

Trans-5-(4-phenoxyphenyl)-7-(4-piperazinocyclohexyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine trimaleate salt

7-[3-(4-methylpiperazino)cyclopentyl]-5-(4-phenoxyphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine tri-maleate

Trans-7-[3-(4-methylpiperazino)cyclohexyl]-5-(4-phenoxyphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine

Trans-7-[3-(4-methylpiperazino)cyclohexyl]-5-(4-phenoxyphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine tri-maleate

trans-7-[3-(4-methylpiperazino)cyclohexyl]-5-(4-phenoxyphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine tri-hydrochloride

cis-7 -[3-(4-methylpiperazino)cyclohexyl]-5-(4-phenoxyphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine tri-maleate salt

cis-7 -[3-(4-methylpiperazino)cyclohexyl]-5-(4-phenoxyphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine tri-hydrochloride

Trans-5-(2-methyl-4-phenoxyphenyl)-7-[4-(4-methylpiperazino)cyclohexyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine trimaleate

Cis- benzyl N-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}2-methoxyphenyl)carbamate tri-maleate

Trans- benzyl N-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-methoxyphenyl)carbamate tri-maleate

Trans-N1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-methoxyphenyl)benzamide

Trans-N1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-methoxyphenyl)benzamide tri-maleate

Cis-N1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-

d]pyrimidin-5-yl}-2-methoxyphenyl)-3-phenylpropanamide

Trans- N1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-methoxyphenyl)-3-phenylpropanamide

cis- *N*1-(4-4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl-2-methoxyphenyl)-3-phenylpropanamide trimaleate salt

trans-*N*1-(4-4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl-2-methoxyphenyl)-3-phenylpropanamide tri-maleate

cis-2-(4-4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-ylphenoxy)-6-[(3-methoxypropyl)amino]benzonitrile tri-maleate

trans-2-(4-4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-ylphenoxy)-6-[(3-methoxypropyl)amino]benzonitrile tri-maleate

cis-2-amino-6-(4-4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-ylphenoxy)benzonitrile tri-maleate

trans-2-amino-6-(4-4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-ylphenoxy)benzonitrile tri-maleate

cis-2-(4-4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-ylphenoxy)-6-[(4-methylphenyl)sulfanyl]benzonitrile tri-maleate

trans-2-(4-4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-ylphenoxy)-6-[(4-methylphenyl)sulfanyl]benzonitrile tri-maleate

cis-2-(4-4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-ylphenoxy)-6-(2-pyridylsulfanyl)benzonitrile tri-maleate *trans*-2-(4-4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-ylphenoxy)-6-(2-pyridylsulfanyl)benzonitrile tri-maleate

cis-5-(2-methyl-4-phenoxyphenyl)-7-[4-(4-methylpiperazino)cyclohexyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine tri-maleate

trans-5-(2-methyl-4-phenoxyphenyl)-7-[4-(4-methylpiperazino)cyclohexyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine tri-maleate

cis-N1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-4-fluoro-1-benzenesulfonamide tri-maleate

trans-N1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-4-fluoro-1-benzenesulfonamide tri-maleate

N1-4-[4-amino-7-(1-benzyl-4-piperidyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-2-fluorophenyl-4-fluoro-1-benzenesulfonamide

N1-4-[4-amino-7-(1-benzyl-4-piperidyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-2-fluorophenyl-2,3-dichloro-1-benzenesulfonamide

N1-4-[4-amino-7-(4-piperidyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-2-fluorophenyl-4-fluoro-1-benzenesulfonamide

N1-4-[4-amino-7-(1-formyl-4-piperidyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-2-fluorophenyl-4-fluoro-1-benzenesulfonamide

N1-[4-(4-amino-7-1-[(1-methyl-1H-4-imidazolyl)sulfonyl]-4-piperidyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl]-4-fluoro-1-benzenesulfonamide dimaleate

N1-[4-(4-amino-7-1-[(1,2-dimethyl-1H-4-imidazolyl)sulfonyl]-4-piperidyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl]-4-fluoro-1-benzenesulfonamide

N1-[4-(4-amino-7-1-[(1,3-dimethyl-1H-5-pyrazolyl)carbonyl]-4-piperidyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl]-4-fluoro-1-benzenesulfonamide

N1-(4-{4-amino-7-[1-(2-pyridylcarbonyl)-4-piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-4-fluoro-1-benzenesulfonamide

N1-4-(4-amino-7-{4-[1-(1-methylpiperid-4-yl)piperidyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl})-2-fluorophenyl-4-fluoro-1-benzenesulfonamide tri-maleate

trans-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2-(trifluoromethoxy)-1-benzenesulfonamide trimaleate

trans-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-5-chloro-2-thiophenesulfonamide benzenesulfonamide trimaleate

trans-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2-chloro-4-fluoro-1-benzenesulfonamide benzenesulfonamide trimaleate

trans-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2,3-dichloro-1-benzenesulfonamide trimaleate cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2-chloro-4-fluoro-1-benzenesulfonamide trimaleate

cis-N-1-(4-4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl-2-fluorophenyl)-2,5-difluoro-1-benzenesulfonamide trimaleate

trans-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2,6-difluoro-1-benzenesulfonamide trimaleate

trans- N-4-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2,1,3-benzothiadiazole-4-sulfonamide trimaleate

trans-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2,3,4-trifluoro-1-benzenesulfonamide trimaleate

cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2-nitro-1-benzenesulfonamide trimaleate

cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2-fluoro-1-benzenesulfonamide trimaleate

cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2,4,6-trichloro-1-benzenesulfonamide trimaleate

cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2,6-dichloro-1-benzenesulfonamide trimaleate

cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2-chloro-1-benzenesulfonamide trimaleate cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)- 3-fluoro-1-benzenesulfonamide dimaleate

cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-5-chloro-2-thiophenesulfonamide dimaleate

cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-4-bromo-2,6-difluoro-1-benzenesulfonamide trimaleate

cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-3-chloro-4-fluoro-1-benzenesulfonamide trimaleate

cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl-2-iodo-1-benzenesulfonamide trimaleate

cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2-(trifluoromethoxy)-1-benzenesulfonamide trimaleate

cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2,3-dichloro-1-benzenesulfonamide trimaleate

cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2-chloro-6-methyl-1-benzenesulfonamide trimaleate

cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2-chloro-4-cyano-1-benzenesulfonamide trimaleate

cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-

5-yl}-2-fluorophenyl)-2,3,4-trifluoro-1-benzenesulfonamide trimaleate

cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-3,4-difluoro-1-benzenesulfonamide trimaleate

cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-4-bromo-2-fluoro-1-benzenesulfonamide trimaleate

cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-5-bromo-2-thiophenesulfonamide trimaleate

cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2,4-dichloro-1-benzenesulfonamide trimaleate

cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2,3,4-trichloro-1-benzenesulfonamide trimaleate

cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-3-bromo-5-chloro-2-thiophenesulfonamide trimaleate

cis- N-4-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2,1,3-benzothiadiazole-4-sulfonamide trimaleate

cis- N-4-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2,1,3-benzoxadiazole-4-sulfonamide trimaleate

cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2,5-dichloro-1-thiophenesulfonamide trimaleate

cis- N-4-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-(7-chloro-2,1,3-benzoxadiazole)-4-sulfonamide trimaleate

cis- N-4-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-(7-methyl-2,1,3-benzothiadiazole)-4-sulfonamide trimaleate

cis- N-4-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-(5-methyl-2,1,3-benzothiadiazole)-4-sulfonamide trimaleate

cis- N-4-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-(5-chloro-2,1,3-benzothiadiazole)-4-sulfonamide trimaleate

cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-3-chloro-2-methyl-1-benzenesulfonamide trimaleate

cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2-bromo-1-benzenesulfonamide trimaleate

cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2,5-dibromo-3,6-difluoro-1-benzenesulfonamide trimaleate

cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2,3-dichloro-1-benzenesulfonamide trimaleate

cis-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)- (2-nitrophenyl)methanesulfonamide trimaleate

trans-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2-nitro-1-benzenesulfonamide trimaleate trans-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2-fluoro-1-benzenesulfonamide trimaleate

trans-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2,4,6-trichloro-1-benzenesulfonamide trimaleate

trans-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2,6-dichloro-1-benzenesulfonamide trimaleate

trans-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2-chloro-1-benzenesulfonamide trimaleate

trans-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)- 3-fluoro-1-benzenesulfonamide dimaleate

trans-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-4-bromo-2,5-difluoro-1-benzenesulfonamide trimaleate

trans-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-3-chloro-4-fluoro-1-benzenesulfonamide trimaleate
trans-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl-2-iodo-1-benzenesulfonamide trimaleate

trans-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2,3-dichloro-1-benzenesulfonamide trimaleate

trans-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2-chloro-6-methyl-1-benzenesulfonamide trimaleate

trans-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-

d]pyrimidin-5-yl}-2-fluorophenyl)-2-chloro-4-cyano-1-benzenesulfonamide trimaleate

trans-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-3,4-difluoro-1-benzenesulfonamide trimaleate

trans-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-4-bromo-2-fluoro-1-benzenesulfonamide trimaleate

trans-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-5-bromo-2-thiophenesulfonamide trimaleate

trans-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2,4-dichloro-1-benzenesulfonamide trimaleate

trans-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2,3,4-trichloro-1-benzenesulfonamide trimaleate

trans-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-3-bromo-5-chloro-2-thiophenesulfonamide trimaleate

trans- N-4-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2,1,3-benzoxadiazole-4-sulfonamide trimaleate

trans-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2,5-dichloro-1-thiophenesulfonamide trimaleate

trans- N-4-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-(7-chloro-2,1,3-benzoxadiazole)-4-sulfonamide trimaleate

trans- N-4-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-

d]pyrimidin-5-yl}-2-fluorophenyl)-(7-methyl-2,1,3-benzothiadiazole)-4-sulfonamide trimaleate

trans- N-4-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-(5-methyl-2,1,3-benzothiadiazole)-4-sulfonamide trimaleate

trans- N-4-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-(5-chloro-2,1,3-benzothiadiazole)-4-sulfonamide trimaleate

trans-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-3-chloro-2-methyl-1-benzenesulfonamide trimaleate

trans-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2-bromo-1-benzenesulfonamide trimaleate

trans-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)-2,5-dibromo-3,6-difluoro-1-benzenesulfonamide trimaleate

trans-N-1-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-fluorophenyl)- (2-nitrophenyl)methanesulfonamide trimaleate

The compounds of this invention have antiangiogenic properties. These antiangiogenic properties are due at least in part to the inhibition of protein tyrosine kinases essential for angiogenic processes. For this reason, these compounds can be used as active agents against such disease states as arthritis, atherosclerosis, restenosis, psoriasis, hemangiomas, myocardial angiogenesis, coronary and cerebral collaterals, ischemic limb angiogenesis, ischemia/reperfusion injury, wound healing, peptic ulcer Helicobacter related diseases, virally-induced angiogenic disorders, fractures, Crow-Fukase syndrome (POEMS), preeclampsia, menometrorrhagia, cat scratch fever, rubeosis, neovascular glaucoma and retinopathies such as those associated with diabetic retinopathy, retinopathy of prematurity, or age-related macular degeneration. In addition, some of these compounds can be used as active agents against solid tumors, malignant ascites, von Hippel Lindau disease, hematopoietic cancers and hyperproliferative disorders such as thyroid hyperplasia (especially Grave's disease), and cysts (such as hypervascularity of ovarian stroma characteristic of polycystic ovarian syndrome (Stein-Leventhal syndrome) and polycystic kidney disease since such diseases require a proliferation of blood vessel cells for growth and/or metastasis.

Further, some of these compounds can be used as active agents against burns, chronic lung disease, stroke, polyps, anaphylaxis, chronic and allergic inflammation, delayed-type hypersensitivity, ovarian hyperstimulation syndrome, brain tumor-associated cerebral edema, high-altitude, trauma or hypoxia induced cerebral or pulmonary edema, ocular and macular edema, ascites, glomerulonephritis and other diseases where vascular hyperpermeability, effusions, exudates, protein extravasation, or edema is a manifestation of the disease. The compounds will also be useful in treating disorders in which protein extravasation leads to the deposition of fibrin and extracellular matrix, promoting stromal proliferation (e.g. keloid, fibrosis, cirrhosis and carpal tunnel syndrome). Increased VEGF production potentiates inflammatory processes such as monocyte recruitment and activation. The compounds of this invention will also be useful in treating inflammatory disorders such as inflammatory bowel disease (IBD) and Crohn's disease.

VEGF's are unique in that they are the only angiogenic growth factors known to contribute to vascular hyperpermeability and the formation of edema. Indeed, vascular hyperpermeability and edema that is associated with the expression or administration of many other growth factors appears to be mediated via VEGF production. Inflammatory cytokines stimulate VEGF production. Hypoxia results in a marked upregulation of VEGF in numerous tissues, hence situations involving infarct, occlusion, ischemia, anemia, or circulatory impairment typically invoke VEGF/VPF mediated responses. Vascular hyperpermeability, associated edema, altered transendothelial exchange and macromolecular extravasation, which is often accompanied by diapedesis, can result in excessive matrix deposition, aberrant stromal proliferation, fibrosis, etc. Hence, VEGF-mediated hyperpermeability can significantly contribute to disorders with these etiologic features.

Because blastocyst implantation, placental development and embryogenesis are angiogenesis dependent, certain compounds of the invention areuseful as contraceptive agents and antifertility agents.

It is envisaged that the disorders listed above are mediated to a significant extent by protein tyrosine kinase activity involving the KDR/VEGFR-2 and/or the Flt-1/VEGFR-1 and/or TIE-2 tyrosine kinases. By inhibiting the activity of these tyrosine kinases, the progression of the listed disorders is inhibited because the angiogenic or vascular hyperpermeability component of the disease state is severely curtailed. The action of certain compounds of this invention, by their selectivity for specific tyrosine kinases, result in a minimization of side effects that would occur if less selective tyrosine kinase inhibitors were used. Certain compounds of the invention are also effective inhibitors of FGFR, PDGFR, c-Met and IGF-1-R. These receptor kinases can directly or indirectly potentiate angiogenic and hyperproliferative responses in various disorders, hence their inhibition can impede disease progression.

The compounds of this invention have inhibitory activity against protein kinases. That is, these compounds modulate signal transduction by protein kinases. Compounds of this invention inhibit protein kinases from serine/threonine and tyrosine kinase classes. In particular, these compounds selectively inhibit the activity of the KDR/FLK-1/VEGFR-2 tyrosine kinases. Certain compounds of this invention also inhibit the activity of additional tyrosine kinases such as Flt-1/VEGFR-1, Tie-2, FGFR, PDGFR, IGF-1R, c-Met, Src-subfamily kinases such as Lck, Src, fyn, yes, etc. Additionally, some compounds of this invention significantly inhibit serine/threonine kinases such as PKC, MAP kinases, erk, CDKs, Plk-1, or Raf-1 which play an essential role in cell proliferation and cell-cycle progression. The potency and specificity of the generic compounds of this invention towards a particular protein kinase can often be altered and optimized by variations in the nature, number and arrangement of the substituents (i.e., R_1, R_2, R_3, A and ring

1) and conformational restrictions. In addition the metabolites of certain compounds may also possess significant protein kinase inhibitory activity.

The compounds of this invention, when administered to individuals in need of such compounds, inhibit vascular hyperpermeability and the formation of edema in these individuals. These compounds act, it is believed, by inhibiting the activity of KDR tyrosine kinase which is involved in the process of vascular hyperpermeability and edema formation. The KDR tyrosine kinase may also be referred to as FLK-1 tyrosine kinase, NYK tyrosine kinase or VEGFR-2 tyrosine kinase. KDR tyrosine kinase is activated when vascular endothelial cell growth factor (VEGF) or another activating ligand (such as VEGF-C, VEGF-D, VEGF-E or HIV Tat protein) binds to a KDR tyrosine kinase receptor which lies on the surface of vascular endothelial cells. Following such KDR tyrosine kinase activation, hyperpermeability of the blood vessels occurs and fluid moves from the blood stream past the blood vessel walls into the interstitial spaces, thereby forming an area of edema. Diapedesis also often accompanies this response. Similarly, excessive vascular hyperpermeability can disrupt normal molecular exchange across the endothelium in critical tissues and organs (e.g., lung and kidney), thereby causing macromolecular extravasation and deposition. Following this acute response to KDR stimulation which is believed to facilitate the subsequent angiogenic process, prolonged KDR tyrosine kinase stimulation results in the proliferation and chemotaxis of vascular endothelial cells and formation of new vessels. By inhibiting KDR tyrosine kinase activity, either by blocking the production of the activating ligand, by blocking the activating ligand binding to the KDR tyrosine kinase receptor, by preventing receptor dimerization and transphosphorylation, by inhibiting the enzyme activity of the KDR tyrosine kinase (inhibiting the phosphorylation function of the enzyme) or by some other mechanism that interrupts its downstream signaling (D. Mukhopedhyay *et al., Cancer Res. 58:*1278-1284 (1998) and references therein), hyperpermeability, as well as associated extravasation, subsequent edema formation and matrix deposition, and angiogenic responses, may be inhibited and minimized.

One group of preferred compounds of this invention have the property of inhibiting KDR tyrosine kinase activity without significantly inhibiting Flt-1 tyrosine kinase activity (Flt-1 tyrosine kinase is also referred to as VEGFR-1 tyrosine kinase). Both KDR tyrosine kinase and Flt-1 tyrosine kinase are activated by VEGF binding to KDR tyrosine kinase receptors and to Flt-1 tyrosine kinase receptors, respectively. Certain preferred compounds of this invention are unique because they inhibit the activity of one VEGF-receptor tyrosine kinase (KDR) that is activated by activating ligands but do not inhibit other receptor tyrosine kinases, such as Flt-1, that are also activated by certain activating ligands. In this manner, certain preferred compounds of this invention are, therefore, selective in their tyrosine kinase inhibitory activity.

In one embodiment, the present invention provides a method of treating a protein kinase-mediated condition in a patient, comprising adiminstering to the patient a therapeutically or prophylactically effective amount of one or more compounds of Formula I.

A "protein kinase-mediated condition" is a medical condition, such as a disease or other undesirable physical condition, the genesis or progression of which depends, at least in part, on the activity of at least one protein kinase. The protein kinase can be, for example, a protein tyrosine kinase or a protein serine/threonine kinase.

The patient to be treated can be any animal, and is preferably a mammal, such as a domesticated animal or a livestock animal. More preferably, the patient is a human.

A therapeutically effective amount" is an amount of a compound of Formula I or a combination of two or more such compounds, which inhibits, totally or partially, the progression of the condition or alleviates, at least partially, one or more symptoms of the condition. A therapeutically effective amount can also be an amount which is prophylactically effective. The amount which is therapeutically effective will depend upon the patient's size and gender, the condition to be treated, the severity of the condition and the result sought. For a given patient, a therapeutically effective amount can be determined by methods known to those of skill in the art.

The method of the present invention is useful in the treatment of protein kinase-mediated conditions, such as any of the conditions described above. In one embodiment, the protein kinase-mediated condition is characterized by undesired angiogenesis, edema, or stromal deposition. For example, the condition can be one or more more ulcers, such as ulcers caused by bacterial or fungal infections, Mooren ulcers and ulcerative colitis. The condition can also be due to a microbial infection, such as Lyme disease, sepsis, septic shock or infections by Herpes simplex, Herpes Zoster, human immunodeficincy virus, protozoa, toxoplasmosis or parapoxvirus; an angiogenic disorders, such as von Hippel Lindau disease, polycystic kidney disease, pemphigoid, Paget's disease and psoriasis; a reproductive condition, such as endometriosis, ovarian hyperstimulation syndrome, preeclampsia or menometrorrhagia; a fibrotic and edemic condition, such as sarcoidosis, fibrosis, cirrhosis, thyroiditis, hyperviscosity syndrome systemic, Osler-Weber-Rendu disease, chronic occlusive pulmonary disease, asthma, and edema following burns, trauma, radiation, stroke, hypoxia or ischemia; or an inflammatory/immunologic condition, such as systemic lupus, chronic inflammation, glomerulonephritis, synovitis, inflammatory bowel disease, Crohn's disease, rheumatoid arthritis, osteoarthritis, multiple sclerosis and graft rejection. Suitable protein kinase-mediated conditions also include sickle cell anaemia, osteoporosis, osteopetrosis, tumor-induced hypercalcemia and bone metastases. Additional protein kinase-mediated conditions which can be treated by the method of the present invention include ocular conditions such as ocular and macular edema, ocular neovascular disease, scleritis, radial keratotomy, uveitis, vitritis, myopia, optic pits, chronic retinal detachment, post-laser complications, conjunctivitis, Stargardt's disease and Eales disease, in addition to retinopathy and macular degeneration.

The compounds of the present invention are also useful in the treatment of cardiovascular conditions such as atherosclerosis, restenosis, vascular occlusion and carotid obstructive disease.

The compounds of the present invention are also useful in the treatment of cancer related indications such as solid tumors, sarcomas (especially Ewing's sarcoma and osteosarcoma), retinoblastoma, rhabdomyosarcomas, neuroblastoma, hematopoietic malignancies, including leukaemia and lymphoma, tumor-induced pleural or pericardial effusions, and malignant ascites.

The compounds of the present invention are also useful in the treatment of Crow-Fukase (POEMS) syndrome and diabetic conditions such as glaucoma, diabetic retinopathy and microangiopathy.

The Src, Tec, Jak, Map, Csk, NFκB and Syk families of kinases play pivotal roles in the regulation of immune function. The Src family currently includes Fyn, Lck, Fgr, Fes, Lyn, Src, Yrk, Fyk, Yes, Hck, and Blk. The Syk family is currently understood to include only Zap and Syk. The TEC family includes Tec, Btk, Rlk and Itk. The Janus family of kinases is involved in the transduction of growth factor and proinflammatory cytokine signals through a number of receptors. Although BTK and ITK, members of the Tec family of kinases, play a less well understood role in immunobiology, their modulation by an inhibitor may prove therapeutically beneficial. The Csk family is currently understood to include Csk and Chk. The kinases RIP, IRAK-1, IRAK-2, NIK, p38 MAP kinases, Jnk, IKK-1 and IKK-2 are involved in the signal transduction pathways for key pro-inflammatory cytokines, such as TNF and IL-1. By virtue of their ability to inhibit one or more of these kinases, compounds of formula I may function as immunomodulatory agents useful for the maintenance of allografts, the treatment of autoimmune disorders and treatment of sepsis and septic shock. Through their ability to regulate the migration or activation of T cells, B-cells, mast cells, monocytes and neutrophils, these compounds could be used to treat such autoimmune diseases and sepsis. Prevention of transplant rejection, either host versus graft for solid organs or graft versus host for bone marrow, are limited by the toxicity of currently available immunosuppressive agents and would benefit from an efficacious drug with improved therapeutic index. Gene targeting experiments have demonstrated the essential role of Src in the biology of osteoclasts, the cells responsible for bone resorption. Compounds of formula I, through their ability to regulate Src, may also be useful in the treatment of osteoporosis, osteopetrosis, Paget's disease, tumor-induced hypercalcemia and in the treatment of bone metastases.

A number of protein kinases have been demonstrated to be protooncogenes.

Chromosome breakage (at the ltk kinase break point on chromosome 5), translocation as in the case of the Abl gene with BCR (Philadelphia chromosome), truncation in instances such as c-Kit or EGFR, or mutation (e.g., Met) result in the creation of dysregulated proteins converting them from protooncogene to oncogene products. In other tumors, oncogenesis is driven by an autocrine or paracrine ligand/growth factor receptor interactions. Members of the src-family kinases are typically involved in downstream signal transduction thereby potentiating the oncogenesis and themselves may become oncogenic by over-expression or mutation. By inhibiting the protein kinase activity of these proteins the disease process may be disrupted. Vascular restenosis may involve FGF and/or PDGF - promoted smooth muscle and endothelial cell proliferation. The ligand stimulation of FGFR, PDGFR, IGF1-R and c-Met *in vivo* is proangiogenic, and potentiates angiogenesis dependent disorders. Inhibition of FGFr, PDGFr , c-Met, or IGF1-R kinase activities individually or in combination may be an efficacious strategy for inhibiting these phenomena. Thus compounds of formula I which inhibit the kinase activity of normal or aberrant c-kit, c-met, c-fms, src-family members, EGFr, erbB2, erbB4, BCR-Abl, PDGFr, FGFr, IGF1-R and other receptor or cytosolic tyrosine kinases may be of value in the treatment of benign and neoplastic proliferative diseases.

In many pathological conditions (for example, solid primary tumors and metastases, Kaposi's sarcoma, rheumatoid arthritis, blindness due to inappropriate ocular neovascularization, psoriasis and atherosclerosis) disease progression is contingent upon persistent angiogenesis. Polypeptide growth factors often produced by the disease tissue or associated inflammatory cells, and their corresponding endothelial cell specific receptor tyrosine kinases (e.g., KDR/VEGFR-2, Flt-1/VEGFR-1, Tie-2/Tek and Tie) are essential for the stimulation of endothelial cell growth, migration, organization, differentiation and the establishment of the requisite new functional vasculature. As a result of the vascular permeability factor activity of VEGF in mediating vascular hyperpermeability, VEGF-stimulation of a VEGFR kinase is also believed to play an important role in the formation of tumor ascites, cerebral and pulmonary edema, pleural and pericardial effusions, delayed-type hypersensitivity reactions, tissue edema and organ dysfunction following trauma, burns, ischemia, diabetic complications, endometriosis, adult respiratory distress syndrome (ARDS), post-cardiopulmonary bypass-related hypotension and hyperpermeability, and ocular edema leading to glaucoma or blindness due to inappropriate neovascularization. In addition to VEGF, recently identified VEGF-C and VEGF-D, and virally-encoded VEGF-E or HIV-Tat protein can also cause a vascular hyperpermeability response through the stimulation of a VEGFR kinase. KDR/VEGFR-2 and/or Tie-2 are expressed also in a select population of hematopoietic stem cells. Certain members of this population are pluripotent in nature and can be stimulated with growth factors to differentiate into endothelial cells and participate in vasculogenetic angiogenic processes. For this reason these have been called Endothelial Progenitor Cells (EPCs) (*J. Clin. Investig.* **103** : 1231-1236 (1999)). In some progenitors, Tie-2 may play a role in their recruitment, adhesion, regulation and differentiation (*Blood* , 4317-4326 (1997)). Certain agents according to formula I capable of blocking the kinase activity of endothelial cell specific kinases could therefore inhibit disease progression involving these situations.

Vascular destabilization of the antagonist ligand of Tie-2 (Ang2) is believed to induce an unstable "plastic" state in the endothelium. In the presence of high VEGF levels a robust angiogenic response may result; however, in the absence of VEGF or a VEGF-related stimulus, frank vessel regression and endothelial apoptosis can occur (Genes and Devel. 13: 1055-1066 (1999)). In an analogous manner a Tie-2 kinase inhibitor can be proangiogenic or antiangiogenic in the presence or absence of a VEGF-related stimulus, respectively. Hence, Tie-2 inhibitors can be employed with appropriate proangiogenic stimuli, such as VEGF, to promote therapeutic angiogenesis in situations such as wound healing, infarct and ischemia.

The compounds of formula I or a salt thereof or pharmaceutical compositions containing a therapeutically effective amount thereof may be used in the treatment of protein kinase-mediated conditions, such as benign and neoplastic proliferative diseases and disorders of the immune system, as described above. For example, such diseases include autoimmune diseases, such as rheumatoid arthritis, thyroiditis, type 1 diabetes, multiple sclerosis, sarcoidosis, inflammatory bowel disease, Crohn's disease, myasthenia gravis and systemic lupus erythematosus; psoriasis, organ transplant rejection (eg. kidney rejection, graft versus host disease), benign and neoplastic proliferative diseases, human cancers such as lung, breast, stomach, bladder, colon, pancreas, ovarian, prostate and rectal cancer and hematopoietic malignancies (leukemia and lymphoma), and diseases involving inappropriate vascularization for example diabetic retinopathy, retinopathy of prematurity, choroidal neovascularization due to age-related macular degeneration, and infantile hemangiomas in human beings. In addition, such inhibitors may be useful in the treatment of disorders involving VEGF mediated edema, ascites, effusions, and exudates, including for example macular edema, cerebral edema, acute lung injury and adult respiratory distress syndrome (ARDS).

The compounds of the present invention may also be useful in the prophylaxis of the above diseases.

It is envisaged that the disorders listed above are mediated to a significant extent by protein tyrosine kinase activity involving the VEGF receptors (e.g. KDR, Flt-1 and/or Tie-2). By inhibiting the activity of these receptor tyrosine kinases, the progression of the listed disorders is inhibited because the angiogenic component of the disease state is severely curtailed. The action of the compounds of this invention, by their selectivity for specific tyrosine kinases, result in a minimization of side effects that would occur if less selective tyrosine kinase inhibitors were used.

In another aspect the present invention provides compounds of formula I as defined initially above for use as medicaments, particularly as inhibitors of protein kinase activity for example tyrosine kinase activity, serine kinase activity and threonine kinase activity. In yet another aspect the present invention provides the use of compounds of formula I as defined initially above in the manufacture of a medicament for use in the inhibition of protein kinase activity.

In this invention, the following definitions are applicable:

"Physiologically acceptable salts" refers to those salts which retain the biological effectiveness and properties of the free bases and which are obtained by reaction with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid or organic acids such as sulfonic acid, carboxylic acid, organic phosphoric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, lactic acid, tartaric acid and the like.

"Alkyl" refers to a saturated aliphatic hydrocarbon, including straight-chain and branched-chain groups having 1 to 6 carbons or cyclic hydrocarbons having 3 to 6 carbons.

"Alkoxy" refers to an "O-alkyl" group, where "alkyl" is defined as described above.

Phamaceutical Formulations

The compounds of this invention can be administered to a human patient by themselves or in pharmaceutical compositions where they are mixed with suitable carriers or excipient(s) at doses to treat or ameliorate vascular hyperpermeability, edema and associated disorders. Mixtures of these compounds can also be administered to the patient as a simple mixture or in suitable formulated pharmaceutical compositions. A therapeutically effective dose further refers to that amount of the compound or compounds sufficient to result in the prevention or attenuation of inappropriate neovascularization, progression of hyperproliferative disorders, edema, VEGF-associated hyperpermeability and/or VEGF-related hypotension. Techniques for formulation and administration of the compounds of the instant application may be found in "Remington's Pharmaceutical Sciences," Mack Publishing Co., Easton, PA, latest edition.

Routes of Administration

Suitable routes of administration may, for example, include oral, eyedrop, rectal, transmucosal, topical, or intestinal administration; parenteral delivery, including intramuscular, subcutaneous, intramedullary injections, as well as intrathecal, direct intraventricular, intravenous, intraperitoneal, intranasal, or intraocular injections.

Alternatively, one may administer the compound in a local rather than a systemic manner, for example, via injection of the compound directly into an edematous site, often in a depot or sustained release formulation.

Furthermore, one may administer the drug in a targeted drug delivery system, for example, in a liposome coated with endothelial cell-specific antibody.

Composition/Formulation

The pharmaceutical compositions of the present invention may be manufactured in a manner that is itself known, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes.

Pharmaceutical compositions for use in accordance with the present invention thus may be formulated in conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen.

For injection, the agents of the invention may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks's solution, Ringer's solution, or physiological saline buffer. For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

For oral administration, the compounds can be formulated readily by combining the active compounds with pharmaceutically acceptable carriers well known in the art. Such carriers enable the compounds of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained by combining the active compound with a solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). If desired, disintegrating agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. All formulations for oral administration should be in dosages suitable for such administration.

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

For administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebuliser, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of e.g. gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

The compounds can be formulated for parenteral administration by injection, e.g. bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g.in ampoules 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 formulatory agents such as suspending, stabilizing and/or dispersing agents.

Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

The compounds 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.

In addition to the formulations described previously, the compounds may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly or by intramuscular injection). Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

An example of a pharmaceutical carrier for the hydrophobic compounds of the invention is a cosolvent system comprising benzyl alcohol, a nonpolar surfactant, a water-miscible organic polymer, and an aqueous phase. The cosolvent system may be the VPD co-solvent system. VPD is a solution of 3% w/v benzyl alcohol, 8% w/v of the nonpolar surfactant polysorbate 80, and 65% w/v polyethylene glycol

300, made up to volume in absolute ethanol. The VPD co-solvent system (VPD:5W) consists of VPD diluted 1:1 with a 5% dextrose in water solution. This co-solvent system dissolves hydrophobic compounds well, and itself produces low toxicity upon systemic administration. Naturally, the proportions of a co-solvent system may be varied considerably without destroying its solubility and toxicity characteristics. Furthermore, the identity of the co-solvent components may be varied: for example, other low-toxicity nonpolar surfactants may be used instead of polysorbate 80; the fraction size of polyethylene glycol may be varied; other biocompatible polymers may replace polyethylene glycol, e.g. polyvinyl pyrrolidone; and other sugars or polysaccharides may substitute for dextrose.

Alternatively, other delivery systems for hydrophobic pharmaceutical compounds may be employed. Liposomes and emulsions are well known examples of delivery vehicles or carriers for hydrophobic drugs. Certain organic solvents such as dimethysulfoxide also may be employed, although usually at the cost of greater toxicity. Additionally, the compounds may be delivered using a sustained-release system, such as semipermeable matrices of solid hydrophobic polymers containing the therapeutic agent. Various sustained-release materials have been established and are well known by those skilled in the art. Sustained-release capsules may, depending on their chemical nature, release the compounds for a few weeks up to over 100 days. Depending on the chemical nature and the biological stability of the therapeutic reagent, additional strategies for protein stabilization may be employed.

The pharmaceutical compositions also may comprise suitable solid or gel phase carriers or excipients. Examples of such carriers or excipients include but are not limited to calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols.

Many of the compounds of the invention may be provided as salts with pharmaceutically compatible counterions. Pharmaceutically compatible salts may be formed with many acids, including but not limited to hydrochloric, sulfuric, acetic, lactic, tartaric, malic, succinic, etc. Salts tend to be more soluble in aqueous or other protonic solvents than are the corresponding free base forms.

Effective Dosage

Pharmaceutical compositions suitable for use in the present invention include compositions wherein the active ingredients are contained in an effective amount to achieve its intended purpose. More specifically, a therapeutically effective amount means an amount effective to prevent development of or to alleviate the existing symptoms of the subject being treated. Determination of the effective amounts is well within the capability of those skilled in the art.

For any compound used in the method of the invention, the therapeutically effective dose can be estimated initially from cellular assays. For example, a dose can be formulated in cellular and animal models to achieve a circulating concentration range that includes the IC_{50} as determined in cellular assays (i.e., the concentration of the test compound which achieves a half-maximal inhibition of a given protein kinase activity). In some cases it is appropriate to determine the IC_{50} in the presence of 3 to 5% serum albumin since such a determination approximates the binding effects of plasma protein on the compound. Such information can be used to more accurately determine useful doses in humans. Further, the most preferred compounds for systemic administration effectively inhibit protein kinase signaling in intact cells at levels that are safely achievable in plasma.

A therapeutically effective dose refers to that amount of the compound that results in amelioration of symptoms in a patient. Toxicity and therapeutic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the maximum tolerated dose (MTD) and the ED_{50} (effective dose for 50% maximal response). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio between MTD and ED_{50}. Compounds which exhibit high therapeutic indices are preferred. The data obtained from these cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED_{50} with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. The exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient's condition. (See e.g. Fingl *et al.*, 1975, in "The Pharmacological Basis of Therapeutics", Ch. 1 p1). In the treatment of crises, the administration of an acute bolus or an infusion approaching the MTD may be required to obtain a rapid response.

Dosage amount and interval may be adjusted individually to provide plasma levels of the active moiety which are sufficient to maintain the kinase modulating effects, or minimal effective concentration (MEC). The MEC will vary for each compound but can be estimated from *in vitro* data; e.g. the concentration necessary to achieve 50-90% inhibition of protein kinase using the assays described herein. Dosages necessary to achieve the MEC will depend on individual characteristics and route of administration. However, HPLC assays or bioassays can be used to determine plasma concentrations.

Dosage intervals can also be determined using the MEC value. Compounds should be administered using a regimen which maintains plasma levels above the MEC for 10-90% of the time, preferably between 30-90% and most preferably between 50-90% until the desired amelioration of symptoms is achieved. In cases of local administration or selective uptake, the effective local concentration of the drugmay not be related to plasma concentration.

The amount of composition administered will, of course, be dependent on the subject being treated, on the subject's weight, the severity of the affliction, the manner of administration and the judgment of the prescribing physician.

Packaging

The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack may for example comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration. Compositions comprising a compound of the invention formulated in a compatible pharmaceutical carrier may also be prepared, placed in an appropriate container, and labeled for treatment of an indicated condition.

In some formulations it may be beneficial to use the compounds of the present invention in the form of particles of very small size, for example as obtained by fluid energy milling.

The use of compounds of the present invention in the manufacture of pharmaceutical compositions is illustrated by the following description. In this description the term "active compound" denotes any compound of the invention but particularly any compound which is the final product of one of the preceding Examples.

a) Capsules

In the preparation of capsules, 10 parts by weight of active compound and 240 parts by weight of lactose can be de-aggregated and blended. The mixture can be filled into hard gelatin capsules, each capsule containing a unit dose or part of a unit dose of active compound.

b) Tablets

Tablets can be prepared from the following ingredients.

Parts by weight	
Active compound	10
Lactose	190
Maize starch	22
Polyvinylpyrrolidone	10
Magnesium stearate	3

The active compound, the lactose and some of the starch can be de-aggregated, blended and the resulting mixture can be granulated with a solution of the polyvinyl- pyrrolidone in ethanol. The dry granulate can be blended with the magnesium stearate and the rest of the starch. The mixture is then compressed in a tabletting machine to give tablets each containing a unit dose or a part of a unit dose of active compound.

c) Enteric coated tablets

Tablets can be prepared by the method described in (b) above. The tablets can be enteric coated in a conventional manner using a solution of 20% cellulose acetate phthalate and 3% diethyl phthalate in ethanol:dichloromethane (1:1).

d) Suppositories

In the preparation of suppositories, 100 parts by weight of active compound can be incorporated in 1300 parts by weight of triglyceride suppository base and the mixture formed into suppositories each containing a therapeutically effective amount of active ingredient.

In the compositions of the present invention the active compound may, if desired, be associated with other compatible pharmacologically active ingredients. For example, the compounds of this invention can be administered in combination with one or more additional pharmaceutical agents that inhibit or prevent the production of VEGF or angiopoietins, attenuate intracellular responses to VEGF or angiopoietins, block intracellular signal transduction, inhibit vascular hyperpermeability, reduce inflammation, or inhibit or prevent the formation of edema or neovascularization. The compounds of the invention can be administered prior to, subsequent to or simultaneously with the additional pharmaceutical agent, whichever course of administration is appropriate. The additional pharmaceutical agents include but are not limited to anti-edemic steroids, NSAIDS, ras inhibitors, anti-TNF agents, anti-IL1 agents, antihistamines, PAF-antagonists, COX-1 inhibitors, COX-2 inhibitors, NO synthase inhibitors, Akt/PTB inhibitors, IGF-1R inhibitors, PKC inhibitors and PI3 kinase inhibitors. The compounds of the invention and the additional pharmaceutical agents act either additively or synergistically. Thus, the administration of such a combination of substances that inhibit angiogenesis, vascular hyperpermeability and/or inhibit the formation of edema can provide greater relief from the deletrious effects of a hyperproliferative disorder, angiogenesis, vascular hyperpermeability or edema than the administration of either substance alone. In the treatment of malignant disorders combinations with antiproliferative or cytotoxic chemotherapies or radiation are anticipated.

The present invention also comprises the use of a compound of formula I as a medicament.

A further aspect of the present invention provides the use of a compound of formula I or a salt thereof in the manufacture of a medicament for treating vascular hyperpermeability, angiogenesis-dependent disorders, proliferative diseases and/or disorders of the immune system in mammals, particularly human beings.

The present invention also provides a method of treating vascular hyperpermeability, inappropriate neovascularization, proliferative diseases and/or disorders of the immune system which comprises the administration of a therapeutically effective amount of a compound of formula I to a mammal, particularly a human being, in need thereof.

The *in vitro* potency of compounds in inhibiting these protein kinases may be determined by the procedures detailed below.

The potency of compounds can be determined by the amount of inhibition of the phosphorylation of an exogenous substrate (e.g., synthetic peptide (Z. Songyang *et al., Nature*. 373:536-539) by a test compound relative to control.

KDR Tyrosine Kinase Production Using Baculovirus System:

The coding sequence for the human KDR intra-cellular domain (aa789-1354) was generated through PCR using cDNAs isolated from HUVEC cells. A poly-His6 sequence was introduced at the N-terminus of this protein as well. This fragment was cloned into transfection vector pVL1393 at the Xba 1 and Not 1 site. Recombinant baculovirus (BV) was generated through co-transfection using the BaculoGold Transfection reagent (PharMingen). Recombinant BV was plaque purified and verified through Western analysis. For protein production, SF-9 cells were grown in SF-900-II medium at 2 x 106/ml, and were infected at 0.5 plaque forming units per cell (MOI). Cells were harvested at 48 hours post infection.

Purification of KDR

SF-9 cells expressing $(His)_6$KDR(aa789-1354) were lysed by adding 50 ml of Triton X-100 lysis buffer (20 mM Tris, pH 8.0, 137 mM NaCl, 10% glycerol, 1% Triton X-100, 1mM PMSF, 10μg/ml aprotinin, 1 μg/ml leupeptin) to the cell pellet from 1L of cell culture. The lysate was centrifuged at 19,000 rpm in a Sorval SS-34 rotor for 30 min at 4°C. The cell lysate was applied to a 5 ml $NiCl_2$ chelating sepharose column, equilibrated with 50 mM HEPES, pH7.5, 0.3 M NaCl. KDR was eluted using the same buffer containing 0.25 M imidazole. Column fractions were analyzed using SDS-PAGE and an ELISA assay (below) which measures kinase activity. The purified KDR was exchanged into 25mM HEPES, pH7.5, 25mM NaCl, 5 mM DTT buffer and stored at -80°C.

Human Tie-2 Kinase Production and Purification

The coding sequence for the human Tie-2 intra-cellular domain (aa775-1124) was generated through PCR using cDNAs isolated from human placenta as a template. A poly-His_6 sequence was introduced at the N-terminus and this construct was cloned into transfection vector pVL 1939 at the Xba 1 and Not 1 site. Recombinant BV was generated through co-transfection using the BaculoGold Transfection reagent (PharMingen). Recombinant BV was plaque purified and verified through Western analysis. For protein production, SF-9 insect cells were grown in SF-900-II medium at 2 x 106/ml, and were infected at MOI of 0.5. Purification of the His-tagged kinase used in screening was analogous to that described for KDR.

Human Flt-1 Tyrosine Kinase Production and Purification

The baculoviral expression vector pVL1393 (Phar Mingen, Los Angeles, CA) was used. A nucleotide sequence encoding poly-His6 was placed 5' to the nucleotide region encoding the entire intracellular kinase domain of human Flt-1 (amino acids 786-1338). The nucleotide sequence encoding the kinase domain was generated through PCR using cDNA libraries isolated from HUVEC cells. The histidine residues enabled affinity purification of the protein as a manner analogous to that for KDR and ZAP70. SF-9 insect cells were infected at a 0.5 multiplicity and harvested 48 hours post infection.

EGFR Tyrosine Kinase Source

EGFR was purchased from Sigma (Cat # E-3641; 500 units/50 μl) and the EGF ligand was acquired from Oncogene Research Products/Calbiochem (Cat # PF011-100).

Expression of ZAP70

The baculoviral expression vector used was pVL1393. (Pharmingen, Los Angeles, Ca.) The nucleotide sequence encoding amino acids M(H)6 LVPR$_9$S was placed 5' to the region encoding the entirety of ZAP70 (amino acids 1-619). The nucleotide sequence encoding the ZAP70 coding region was generated through PCR using cDNA libraries isolated from Jurkat immortalized T-cells. The histidine residues enabled affinity purification of the protein (vide infra). The LVPR$_9$S bridge constitutes a recognition sequence for proteolytic cleavage by thrombin, enabling removal of the affinity tag from the enzyme. SF-9 insect cells were infected at a multiplicity of infection of 0.5 and harvested 48 hours post infection.

Extraction and purification of ZAP70

SF-9 cells were lysed in a buffer consisting of 20 mM Tris, pH 8.0, 137 mM NaCl, 10% glycerol, 1% Triton X-100, 1 mM PMSF, 1 μg/ml leupeptin, 10 μg/ml aprotinin and 1 mM sodium orthovanadate. The soluble lysate was applied to a chelating sepharose HiTrap column (Pharmacia) equilibrated in 50 mM HEPES, pH 7.5, 0.3 M NaCl. Fusion protein was eluted with 250 mM imidazole. The enzyme was stored in buffer containing 50 mM HEPES, pH 7.5, 50 mM NaCl and 5 mM DTT.

Protein kinase source

Lck, Fyn, Src, Blk, Csk, and Lyn, and truncated forms thereof may be commercially obtained (e.g. from Upstate Biotechnology Inc. (Saranac Lake, N.Y) and Santa Cruz Biotechnology Inc. (Santa Cruz, Ca.)) or purified from known natural or recombinant sources using conventional methods.

Enzyme Linked Immunosorbent Assay (ELISA) For PTKs

Enzyme linked immunosorbent assays (ELISA) were used to detect and measure the presence of tyrosine kinase activity. The ELISA were conducted according to known protocols which are described in, for example, Voller, *et al.*, 1980, "Enzyme-Linked Immunosorbent Assay," In: *Manual of Clinical Immunology, 2d ed.*, edited by Rose and Friedman, pp 359-371 Am. Soc. of Microbiology, Washington, D.C.

The disclosed protocol was adapted for determining activity with respect to a specific PTK. For example, preferred protocols for conducting the ELISA experiments is provided below. Adaptation of these protocols for determining a compound's activity for other members of the receptor PTK family, as well as non-receptor tyrosine kinases, are well within the abilities of those in the art. For purposes of determining inhibitor selectivity, a universal PTK substrate (e.g., random copolymer of poly(Glu_4 Tyr), 20,000-50,000 MW) was employed together with ATP (typically 5 μM) at concentrations approximately twice the apparent Km in the assay.

The following procedure was used to assay the inhibitory effect of compounds of this invention on KDR, Flt-1, Tie-2, EGFR, FGFR, PDGFR, IGF-1-R, c-Met, Lck, Blk, Csk, Src, Lyn, Fyn and ZAP70 tyrosine kinase activity:

Buffers and Solutions:

PGTPoly (Glu,Tyr) 4:1

Store powder at -20°C. Dissolve powder in phosphate buffered saline (PBS) for 50mg/ml solution. Store 1ml aliquots at -20°C. When making plates dilute to 250μg/ml in Gibco PBS.

Reaction Buffer: 100mM Hepes, 20mM $MgCl_2$, 4mM $MnCl_2$, 5mM DTT, 0.02%BSA, 200μM $NaVO_4$, pH 7.10

ATP: Store aliquots of 100mM at -20°C. Dilute to 20μM in water

Washing Buffer: PBS with 0.1% Tween 20

Antibody Diluting Buffer: 0.1% bovine serum albumin (BSA) in PBS

TMB Substrate: mix TMB substrate and Peroxide solutions 9:1 just before use or use K-Blue Substrate from Neogen

Stop Solution: 1M Phosphoric Acid

Procedure

1. Plate Preparation:

Dilute PGT stock (50mg/ml, frozen) in PBS to a 250μg/ml. Add 125μl per well of Corning modified flat bottom high affinity ELISA plates (Corning #25805-96). Add 125μl PBS to blank wells. Cover with sealing tape and incubate overnight 37°C. Wash 1x with 250μl washing buffer and dry for about 2hrs in 37°C dry incubator. Store coated plates in sealed bag at 4°C until used.

2. Tyrosine Kinase Reaction:

-Prepare inhibitor solutions at a 4x concentration in 20% DMSO in water.

-Prepare reaction buffer

-Prepare enzyme solution so that desired units are in 50μl, e.g. for KDR make to 1 ng/μl for a total of 50ng per well in the reactions. Store on ice.

-Make 4x ATP solution to 20μM from 100mM stock in water. Store on ice

-Add 50μl of the enzyme solution per well (typically 5-50 ng enzyme/well depending on the specific activity of the kinase)

-Add 25μl 4x inhibitor

-Add 25μl 4x ATP for inhibitor assay

-Incubate for 10 minutes at room temperature

-Stop reaction by adding 50μl 0.05N HCl per well

-Wash plate

**Final Concentrations for Reaction: 5μM ATP, 5% DMSO

3. Antibody Binding

-Dilute 1mg/ml aliquot of PY20-HRP (Pierce) antibody(a phosphotyrosine

antibody)to 50ng/ml in 0.1% BSA in PBS by a 2 step dilution (100x, then 200x)
-Add 100μl Ab per well. Incubate 1 hr at room temp. Incubate 1hr at 4C.
-Wash 4x plate
4. Color reaction
-Prepare TMB substrate and add 100μl per well
-Monitor OD at 650nm until 0.6 is reached
-Stop with 1M Phosphoric acid. Shake on plate reader.
-Read OD immediately at 450nm

Optimal incubation times and enzyme reaction conditions vary slightly with enzyme preparations and are determined empirically for each lot.

For Lck, the Reaction Buffer utilized was 100 mM MOPSO, pH 6.5, 4 mM $MnCl_2$, 20 mM $MgCl_2$, 5 mM DTT, 0.2% BSA, 200 mM $NaVO_4$ under the analogous assay conditions.

Compounds of formula I may have therapeutic utility in the treatment of diseases involving both identified, including those not mentioned herein, and as yet unidentified protein tyrosine kinases which are inhibited by compounds of formula I. All compounds exemplified herein significantly inhibit either FGFR, PDGFR, KDR, Tie-2, Lck, Fyn, Blk, Lyn or Src at concentrations of 50 micromolar or below. Some compounds of this invention also significantly inhibit other tyrosine or serine/threonine kinases such as cdc2 (cdk1) at concentrations of 50 micromolar or below.

Cdc2 source

The human recombinant enzyme and assay buffer may be obtained commercially (New England Biolabs, Beverly, MA. USA) or purified from known natural or recombinant sources using conventional methods.

Cdc2 Assay

The protocol used was that provided with the purchased reagents with minor modifications. In brief, the reaction was carried out in a buffer consisting of 50mM

Tris pH 7.5, 100mM NaCl, 1mM EGTA, 2mM DTT, 0.01% Brij, 5% DMSO and 10mM $MgCl_2$ (commercial buffer) supplemented with fresh 300 μM ATP (31 μCi/ml) and 30 μg/ml histone type IIIss final concentrations. A reaction volume of 80μL, containing units of enzyme, was run for 20 minutes at 25 degrees C in the presence or absence of inhibitor. The reaction was terminated by the addition of 120μL of 10% acetic acid. The substrate was separated from unincorporated label by spotting the mixture on phosphocellulose paper, followed by 3 washes of 5 minutes each with 75mM phosphoric acid. Counts were measured by a betacounter in the presence of liquid scintillant.

Certain compounds of this invention significantly inhibit cdc2 at concentrations below 50 uM.

PKC kinase source

The catalytic subunit of PKC may be obtained commercially (Calbiochem).

PKC kinase assay

A radioactive kinase assay was employed following a published procedure (Yasuda, I., Kirshimoto, A., Tanaka, S., Tominaga, M., Sakurai, A., Nishizuka, Y. *Biochemical and Biophysical Research Communication 3*:166, 1220-1227 (1990)). Briefly, all reactions were performed in a kinase buffer consisting of 50 mM Tris-HCl pH7.5, 10mM $MgCl_2$, 2mM DTT, 1mM EGTA, 100 μM ATP, 8 μM peptide, 5% DMSO and ^{33}P ATP (8Ci/mM). Compound and enzyme were mixed in the reaction vessel and the reaction initiated by addition of the ATP and substrate mixture. Following termination of the reaction by the addition of 10 μL stop buffer (5 mM ATP in 75mM phosphoric acid), a portion of the mixture was spotted on phosphocellulose filters. The spotted samples were washed 3 times in 75 mM phosphoric acid at room temperature for 5 to 15 minutes. Incorporation of radiolabel was quantified by liquid scintillation counting.

Erk2 enzyme source

The recombinant murine enzyme and assay buffer may be obtained commercially (New England Biolabs, Beverly MA. USA) or purified from known natural or recombinant sources using conventional methods.

Erk2 enzyme assay

In brief, the reaction was carried out in a buffer consisting of 50 mM Tris pH 7.5, 1mM EGTA, 2mM DTT, 0.01% Brij, 5% DMSO and 10 mM $MgCl_2$ (commercial buffer) supplemented with fresh 100 μM ATP (31 μCi/ml) and 30μM myelin basic protein under conditions recommended by the supplier. Reaction volumes and method of assaying incorporated radioactivity were as described for the PKC assay (vide *supra*).

In Vitro Models for T-cell Activation

Upon activation by mitogen or antigen, T-cells are induced to secrete IL-2, a growth factor that supports their subsequent proliferative phase. Therefore, one may measure either production of IL-2 from or cell proliferation of, primary T-cells or appropriate T-cell lines as a surrogate for T-cell activation. Both of these assays are well described in the literature and their parameters well documented (in Current Protocols in Immunology, Vol 2, 7.10.1-7.11.2).

In brief, T-cells may be activated by co-culture with allogenic stimulator cells, a process termed the one-way mixed lymphophocyte reaction. Responder and stimulator peripheral blood mononuclear cells are purified by Ficoll-Hypaque gradient (Pharmacia) per directions of the manufacturer. Stimulator cells are mitotically inactivated by treatment with mitomycin C (Sigma) or gamma irradiation. Responder and stimulator cells are co-cultured at a ratio of two to one in the presence or absence of the test compound. Typically 10^5 responders are mixed with 5×10^4 stimulators and plated (200 μl volume) in a U bottom microtiter plate (Costar Scientific). The cells are cultured in RPMI 1640 supplemented with either heat inactivated fetal bovine serum (Hyclone Laboratories) or pooled human AB serum from male donors, 5×10^{-5} M 2mercaptoethanol and 0.5% DMSO, The cultures are pulsed with 0.5 μCi of ^{3}H thymidine (Amersham) one day prior to harvest (typically day three). The cultures are harvested (Betaplate harvester, Wallac) and isotope uptake assessed by liquid scintillation (Betaplate, Wallac).

The same culture system may be used for assessing T-cell activation by measurement of IL-2 production. Eighteen to twenty-four hours after culture initiation, the supernatants are removed and the IL-2 concentration is measured by ELISA (R and D Systems) following the directions of the manufacturer.

In-vivo Models of T-Cell Activation

The *in vivo* efficacy of compounds can be tested in animal models known to directly measure T-cell activation or for which T-cells have been proven the effectors. T-cells can be activated *in vivo* by ligation of the constant portion of the T-cell receptor with a monoclonal anti-CD3 antibody (Ab). In this model, BALB/c mice are given 10μg of anti-CD3 Ab intraperitoneally two hours prior to exsanguination. Animals to receive a test drug are pre-treated with a single dose of the compound one hour prior to anti-CD3 Ab administration. Serum levels of the proinflammatory cytokines interferon-γ (IFN-γ) and tumor necrosis factor-α(TNF-α), indicators of T-cell activation, are measured by ELISA. A similar model employs *in vivo* T-cell priming with a specific antigen such as keyhole limpet hemocyanin (KLH) followed by a secondary *in vitro* challenge of draining lymph node cells with the same antigen. As previously, measurement of cytokine production is used to assess the activation state of the cultured cells. Briefly, C57BL/6 mice are immunized subcutaneously with 100 μg KLH emulsified in complete Freund's adjuvant (CFA) on day zero. Animals are pre-treated with the compound one day prior to immunization and subsequently on days one, two and three post immunization. Draining lymph nodes are harvested on day 4 and their cells cultured at 6 x 10^6 per ml in tissue culture medium (RPMI 1640 supplemented with heat inactivated fetal bovine serum (Hyclone Laboratories) 5 x 10^{-5} M 2-mercaptoethanol and 0.5% DMSO) for both twenty-four and forty-eight hours. Culture supernatants are then assessed for the autocrine T-cell growth factor Interleukin-2 (IL-2) and/or IFN-γ levels by ELISA.

Lead compounds can also be tested in animal models of human disease. These are exemplified by experimental auto-immune encephalomyelitis (EAE) and collagen-induced arthritis (CIA). EAE models which mimic aspects of human multiple sclerosis have been described in both rats and mice (reviewed FASEB J. 5:2560-2566, 1991; murine model: Lab. Invest. 4(3):278, 1981; rodent model:J. Immunol 146(4):1163-8, 1991). Briefly, mice or rats are immunized with an emulsion of myelin basic protein (MBP), or neurogenic peptide derivatives thereof, and CFA. Acute disease can be induced with the addition of bacterial toxins such as *bordetella pertussis*. Relapsing/remitting disease is induced by adoptive transfer of T-cells from MBP/ peptide immunized animals.

CIA may be induced in DBA/1 mice by immunization with type II collagen (J. Immunol:142(7):2237-2243). Mice will develop signs of arthritis as early as ten days following antigen challenge and may be scored for as long as ninety days after immunization. In both the EAE and CIA models, a compound may be administered either prophylactically or at the time of disease onset. Efficacious drugs should reduce severity and/or incidence.

Certain compounds of this invention which inhibit one or more angiogenic receptor PTK, and/or a protein kinase such as lck involved in mediating inflammatory responses can reduce the severity and incidence of arthritis in these models.

Compounds can also be tested in mouse allograft models, either skin (reviewed in Ann. Rev. Immunol., 10:333-58, 1992; Transplantation: 57(12): 1701-17D6, 1994) or heart (Am.J.Anat.:113:273, 1963). Briefly, full thickness skin grafts are transplanted from C57BL/6 mice to BALB/c mice. The grafts can be examined daily, beginning at day six, for evidence of rejection. In the mouse neonatal heart transplant model, neonatal hearts are ectopically transplanted from C57BL/6 mice into the ear pinnae of adult CBA/J mice. Hearts start to beat four to seven days post transplantation and rejection may be assessed visually using a dissecting microscope to look for cessation of beating.

Cellular Receptor PTK Assays

The following cellular assay was used to determine the level of activity and effect of the different compounds of the present invention on KDR/VEGFR2. Similar receptor PTK assays employing a specific ligand stimulus can be designed along the same lines for other tyrosine kinases using techniques well known in the art.

VEGF-Induced KDR Phosphorylation in Human Umbilical Vein Endothelial Cells (HUVEC) as Measured by Western Blots:

1. HUVEC cells (from pooled donors) were purchased from Clonetics (San Diego, CA) and cultured according to the manufacturer directions. Only early passages (3-8) were used for this assay. Cells were cultured in 100 mm dishes (Falcon for tissue culture; Becton Dickinson; Plymouth, England) using complete EBM media (Clonetics).

2. For evaluating a compound's inhibitory activity, cells were trypsinized and seeded at 0.5-1.0 x 10^5 cells/well in each well of 6-well cluster plates (Costar; Cambridge, MA).

3. 3-4 days after seeding, plates were 90-100% confluent. Medium was removed from all the wells, cells were rinsed with 5-10ml of PBS and incubated 18-24h with 5ml of EBM base media with no supplements added (i.e., serum starvation).

4. Serial dilutions of inhibitors were added in 1ml of EBM media (25μM, 5μM, or 1μM final concentration to cells and incubated for one hour at 37 C. Human recombinant $VEGF_{165}$ (R & D Systems) was then added to all the wells in 2 ml of EBM medium at a final concentration of 50ng/ml and incubated at 37 C for 10 minutes. Control cells untreated or treated with VEGF only were used to assess background phosphorylation and phosphorylation induction by VEGF.

All wells were then rinsed with 5-10ml of cold PBS containing 1mM Sodium Orthovanadate (Sigma) and cells were lysed and scraped in 200μl of RIPA buffer (50mM Tris-HC1) pH7, 150mM NaCl, 1% NP-40, 0.25% sodium deoxycholate, 1mM EDTA) containing protease inhibitors (PMSF 1mM, aprotinin 1μg/ml, pepstatin 1μg/ml, leupeptin 1μg/ml, Na vanadate 1mM, Na fluoride 1mM) and

1μg/ml of Dnase (all chemicals from Sigma Chemical Company, St Louis, MO). The lysate was spun at 14,000 rpm for 30min, to eliminate nuclei.

Equal amounts of proteins were then precipitated by addition of cold (-20 C) Ethanol (2 volumes) for a minimum of 1 hour or a maximum of overnight. Pellets were reconstituted in Laemli sample buffer containing 5% -mercaptoethanol (BioRad; Hercules, CA) and boiled for 5min. The proteins were resolved by polyacrylamide gel electrophoresis (6%, 1.5mm Novex, San Deigo, CA) and transferred onto a nitrocellulose membrane using the Novex system. After blocking with bovine serum albumin (3%), the proteins were probed overnight with anti-KDR polyclonal antibody (C20, Santa Cruz Biotechnology; Santa Cruz, CA) or with anti-phosphotyrosine monoclonal antibody (4G10, Upstate Biotechnology, Lake Placid, NY) at 4 C. After washing and incubating for 1 hour with HRP-conjugated $F(ab)_2$ of goat anti-rabbit or goat-anti-mouse IgG the bands were visualized using the emission chemiluminescience (ECL) system (Amersham Life Sciences, Arlington Height, IL). Certain examples of the present invention significantly inhibit cellular VEGF-induced KDR tyrosine kinase phosphorylation at concentrations of less than 50 μM.

In vivo Uterine Edema Model

This assay measures the capacity of compounds to inhibit the acute increase in uterine weight in mice which occurs in the first few hours following estrogen stimulation. This early onset of uterine weight increase is known to be due to edema caused by increased permeability of uterine vasculature. Cullinan-Bove and Koss (*Endocrinology* (1993), *133*:829-837) demonstrated a close temporal relationship of estrogen-stimulated uterine edema with increased expression of VEGF mRNA in the uterus. These results have been confirmed by the use of neutralizing monoclonal antibody to VEGF which significantly reduced the acute increase in uterine weight following estrogen stimulation (WO 97/42187). Hence, this system can serve as a model for *in vivo* inhibition of VEGF signalling and the associated hyperpermeability and edema.

Materials: All hormones were purchased from Sigma (St. Louis, MO) or Cal Biochem (La Jolla, CA) as lyophilized powders and prepared according to supplier instructions.

Vehicle components (DMSO, Cremaphor EL) were purchased from Sigma (St. Louis, MO).

Mice (Balb/c, 8-12 weeks old) were purchased from Taconic (Germantown, NY) and housed in a pathogen-free animal facility in accordance with institutional Animal Care and Use Committee Guidelines.

Method:

Day 1: Balb/c mice were given an intraperitoneal (i.p.) injection of 12.5 units of pregnant mare's serum gonadotropin (PMSG).

Day 3: Mice received 15 units of human chorionic gonadotropin (hCG) i.p.

Day 4: Mice were randomized and divided into groups of 5-10. Test compounds were administered by i.p., i.v. or p.o. routes depending on solubility and vehicle at doses ranging from 1-100 mg/kg. Vehicle control group received vehicle only and two groups were left untreated.

Thirty minutes later, experimental, vehicle and 1 of the untreated groups were given an i.p. injection of 17 -estradiol (500 μg/kg). After 2-3 hours, the animals were sacrificed by CO_2 inhalation. Following a midline incision, each uterus was isolated and removed by cutting just below the cervix and at the junctions of the uterus and oviducts. Fat and connective tissue were removed with care not to disturb the integrity of the uterus prior to weighing (wet weight). Uteri were blotted to remove fluid by pressing between two sheets of filter paper with a one liter glass bottle filled with water. Uteri were weighed following blotting (blotted weight). The difference between wet and blotted weights was taken as the fluid content of the uterus. Mean fluid content of treated groups was compared to untreated or vehicle treated groups. Significance was determined by Student's test. Non-stimulated control group was used to monitor estradiol response.

Results demonstrate that certain compounds of the present invention inhibit the formation of edema when administered systemically by various routes.

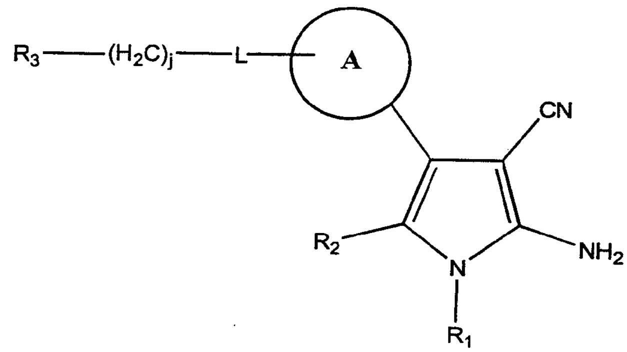
Certain compounds of this invention which are inhibitors of angiogenic receptor tyrosine kinases can also be shown active in a Matrigel implant model of neovascularization. The Matrigel neovascularization model involves the formation of new blood vessels within a clear "marble" of extracellular matrix implanted subcutaneously which is induced by the presence of proangiogenic factor producing tumor cells (for examples see: Passaniti, A., *et al*, Lab. Investig. (1992), 67(4), 519-528; Anat. Rec. (1997), 249(1), 63-73; Int. J. Cancer (1995), 63(5), 694-701; Vasc. Biol. (1995), 15(11), 1857-6). The model preferably runs over 3-4days and endpoints include macroscopic visual/image scoring of neovascularization, microscopic microvessel density determinations, and hemoglobin quantitation (Drabkin method) following removal of the implant versus controls from animals untreated with inhibitors. The model may alternatively employ bFGF or HGF as the stimulus.

Certain compounds of this invention which inhibit one or more oncogenic, protooncogenic, or proliferation-dependent protein kinases, or angiogenic receptor PTK also inhibit the growth of primary murine, rat or human xenograft tumors in mice, or inhibit metastasis in murine models.

EXAMPLES

Processes for the preparation of compounds of formula I will now be described. These processes form a further aspect of the present invention. The processes are preferably carried out at atmospheric pressure.

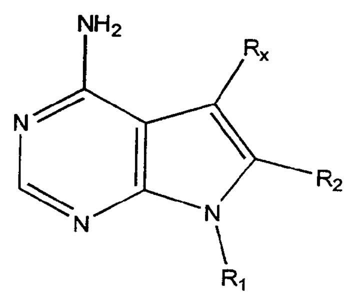
Compounds of formula I may be prepared by condensing a compound of formula



(II)

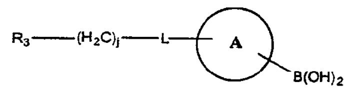
in which R_1, R_2, R_3, L and ring A are as previously defined with formamide at a temperature in the range of 50 to 250°C optionally in the presence of a catalyst for example 4-dimethylaminopyridine.

Compounds of formula I may be prepared by reacting a compound of formula (III)



(III)

wherein R_x is bromo or iodo bromo or iodo with one of the following compounds: $R_3B(OH)_2$, $R_3Sn(CH_3)_3$ or a compound represented by formula IV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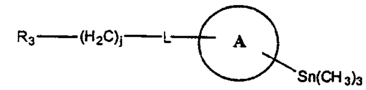

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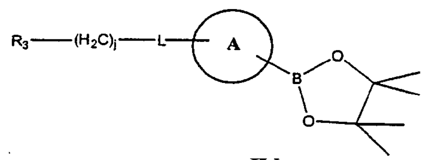
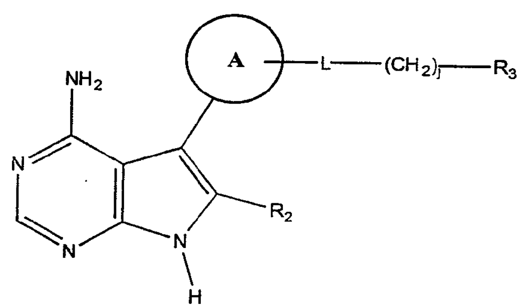


IV

in which R_3 is as defined above, in the presence of a catalyst for example palladium (0) compounds eg. $Pd(PPh_3)_4$.

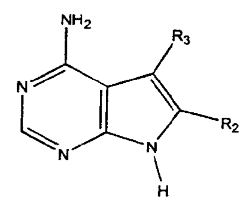
Compounds of formula I in which R_1 represents an alkyl group or an aralkyl group may be prepared by alkylating a compound of formula (V)



(V)

in which R_2 and R_3 are as previously defined with a compound of formula R_1X' in which R_1 represents an alkyl group or an aralkyl group and X' represents a leaving group, for example halo, mesyloxy or tosyloxy.

Compounds of formula I in which R_1 represents an optionally substituted cyclic ether, such as tetrahydrofuryl or tetrahydropyranyl, may be prepared by alkylating a compound of formula VI



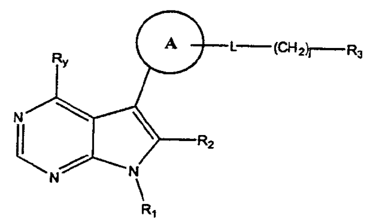
(VI)

in which R_2 and R_3 are as previously defined with a compound of formula R_1X' in which X' is as previously defined and R_1 is an optionally substituted cyclic ether.

Compounds of formula I in which R_1 represents cyclic ether, such as tetrahydrofuryl or tetrahydropyranyl, optionally substituted by formyl may be prepared by alkylating a compound of formula VI with a compound R_1X in which R_1 represents a cyclic ether substituted by a formyl group which has been protected, by a method known to those skilled in the art, for example by means of an acetal, (See for example *Tet. Letts. 30*(46):6259-6262 (1989)) followed by deprotection. Compounds in which R_1 represents a cyclic ether, such as tetrahydrofuryl or tetrahydropyranyl, substituted by an (optionally substituted amino)methyl group may be prepared by reductive amination of a compound in which R_1 represents a cyclic ether substituted by formyl.

Compounds of formula I in which R_1 represents optionally substituted furyl, thienyl or pyrrolyl may be prepared by reacting 4-chloro-5-iodo-7*H*-pyrrolo[2,3-d]pyrimidine with the appropriate heteroarylboronic acid in the presence of a copper salt catalyst, for example copper (II) acetate in the presence of a solvent for the reactants, e.g. a halogenated solvent for example, dichloromethane, in the presence of a drying agent, for example 4Å molecular sieves, in the presence of an organic base, e.g. triethylamine or pyridine, at a temperature in the range of 0-50°C, preferably at ambient temperature. (For conditions see *Tet. Letts.* (1998), *39*:2942-2944 and references cited therein. This paper is incorporated herein by reference.) These compounds may be formulated by methods known to those skilled in the art to give compounds in which R_1 represents furyl, thienyl or pyrrolyl substituted by formyl. The formyl group in these compounds may be productively aminated by methods known to those skilled in the art to give compounds in which R_1 represents furyl, thienyl or pyrrolyl substituted by aminomethyl groups. Alternatively intermediates in which R_1 represents furyl, thienyl or pyrrolyl may be subjected to a Mannich reaction to give intermediates in which R_1 represents furyl, thienyl or pyrrolyl substituted by an aminomethyl group.

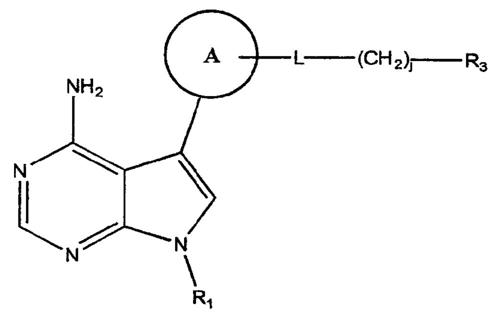
Compounds of formula I may be prepared by reacting a compound of formula VII



VII

in which R_1, R_2, R_3, L and ring A are as previously defined and R_y represents a leaving group, for example halo or phenoxy, with ammonia or an ammonium salt, for example ammonium acetate, at a temperature in the range of 15-250°C, preferably in a pressure vessel.

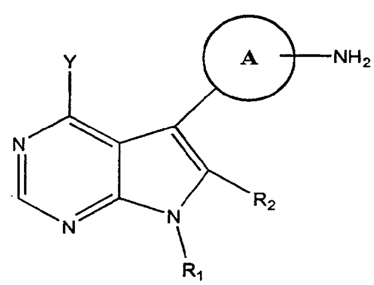
Compounds of formula I in which R_2 represents chloro, bromo or iodo may be prepared by reacting a compound of formula VIII



(VIII)

in which R_1, R_3, L and ring A are as previously defined with a halogenating agent for example an iodinating agent, e.g. N-iodosuccinimide, or a brominating agent, e.g. N-bromosuccinimide, or a chlorinating agent, e.g. N-chlorosuccinimide.

Compounds of formula I in which $-L-R_3$ represents $-NHC(O)R_3$ may be prepared by reacting a compound of formula IX

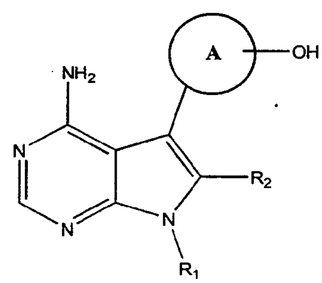


IX

in which R_1, R_2 and ring A are as previously defined and Y represents a protected amine, with a compound of formula R_3COR_x in which R_x represents a leaving group, for example chloro. Alternatively compounds of formula IX in which Y represents halo, for example chloro, may be reacted with a compound of formula R_3COR_x and the product reacted with ammonia to give a compound of formula I. Analogous methods may be used to prepare compounds of formula I in which $-L-R_3$ is -

$NRSO_2R_3$. Analogous methods may be used to prepare compound of formula I in which $-L-R_3$ is $-NRCO_2-R_3$ or $-NRCONR'$. R and R' are as previously defined.

Compounds of formula I in which $-L-R_3$ is $-OSO_2-$ may be prepared by reacting a compound of formula X

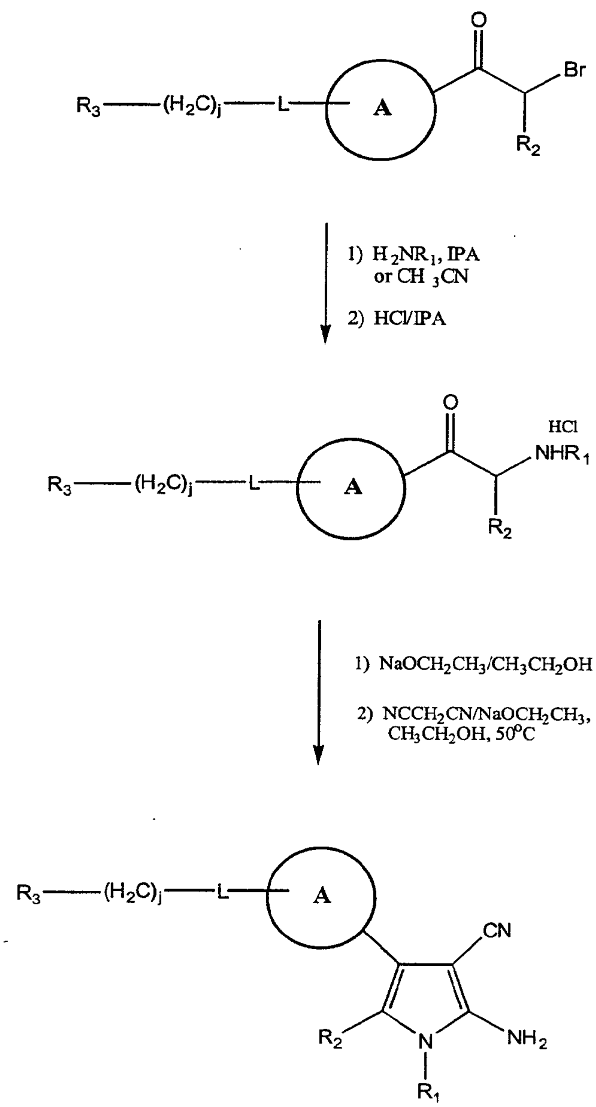


X

in which R_1, R_2 and ring A are as previously defined with a compound of formula $R_4SO_2R_x$.

Compounds of formula I may then be prepared from such intermediates following Scheme 2 or the alternative for Scheme 2, which is described later.

Compounds of formula II may be prepared as shown in Scheme 1 in which IPA represents propan-2-ol, Scheme I

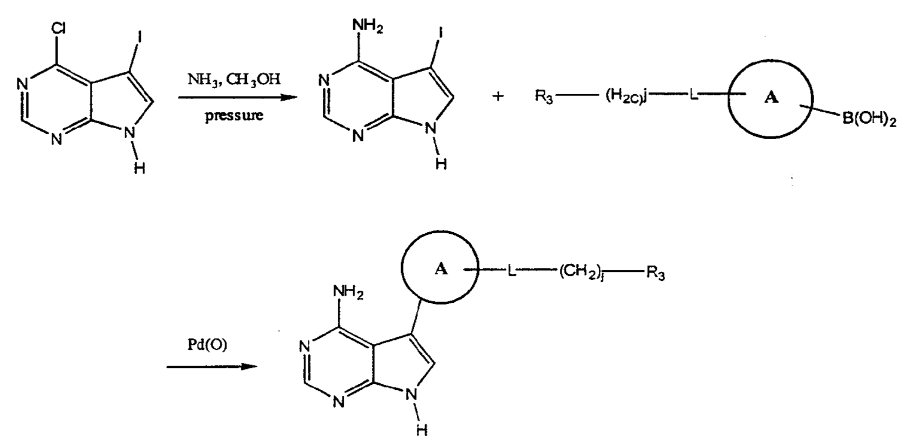


It will be appreciated by those skilled in the art that compounds of formula I may be converted into other compounds of formula I by known chemical reactions. For example, an alkoxy group may be cleaved to give hydroxy, nitro groups may be reduced to amines, amines may be acylated or sulfonylated and N-acyl compounds may be hydrolyzed to amines. Compounds of formula I in which –L- is S may be oxidized to give compounds of formula I in which –L- represents SO and SO_2, respectively, by methods known to those skilled in the art.

Compounds of formula III are commercially available or may be prepared by methods known to those skilled in the art.

Compounds of formula V in which R_2 represents hydrogen may be prepared as shown in Scheme 2. The amino group may be protected prior to the final step and then deprotected after the final step of scheme 2 by methods known to those skilled in the art. Compounds of formula V in which R_2 is other than hydrogen may be prepared by analogous methods. (see *J. Med. Chem.* (1990), *33*, 1984.)

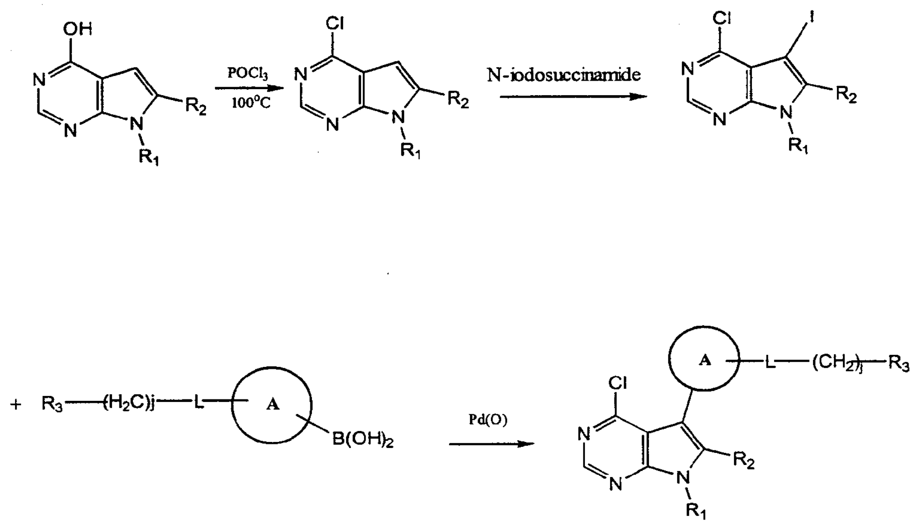
Scheme 2



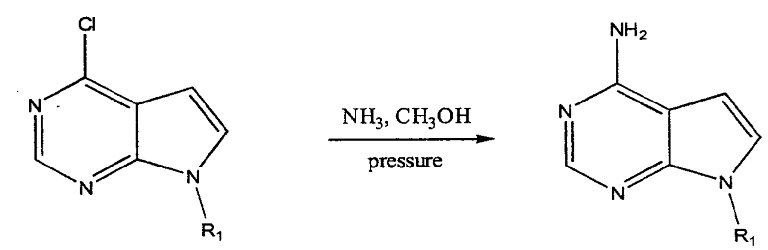
Alternatively in Scheme 2, (ring A)-L-R_3 may be coupled first, prior to amination. Alternatively a substituent R_1 as defined previously may be present prior to carrying out either process.

Compounds of formula VII, in which R_y is a –Cl, may be prepared as shown in Scheme 3.

Scheme 3



Compounds in which (ring A)-L-R_3 is absent may be prepared as in Scheme 4 and as described in *J.Med. Chem.*, (1988), *31*:390 and references cited therein. Compounds in which (ring A)-L-R_3 is other than hydrogen may be prepared by analogous methods.

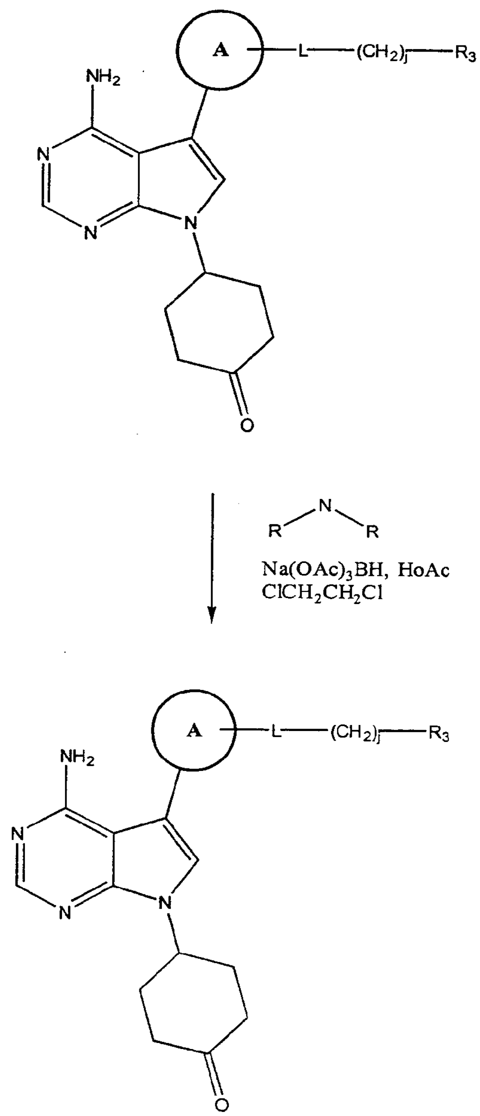


Scheme 4

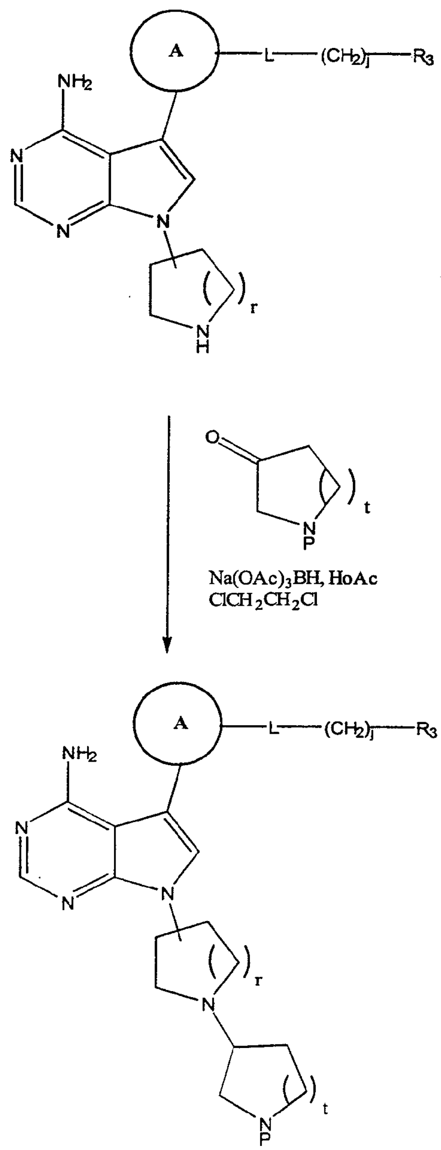
Compounds of formula VII may be prepared by coupling a 5-iodo compound in an analogous manner to that described for the preparation of compounds of formula V.

R_1 may be modified by the method depicted in Schemes 5 and 6. In Schemes 5 and 6 P represents a protecting group.

Scheme 5



Scheme 6



It will be appreciated by those skilled in the art that in cases where a substituent is identical with, or similar to, a functional group which has been modified in one of the above processes that these substituents will require protection before the process is undertaken, followed by deprotection after the process.

Otherwise competing sidereactions will occur. Alternatively, another of the processes described above, in which the substituent does not interfere, may be used. Examples of suitable protecting groups and methods for their addition and removal may be found in the textbook "Protective Groups in Organic Synthesis" by T.W. Green, John Wiley and Sons, 1981. For example suitable protecting groups for amines are formyl or acetyl.

The following synthetic examples were prepared using the general preparative procedures described above:

Example 1: Benzyl N-(4-(4-amino-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-methoxyphenyl)carbamate

a) Tetrahydro-2H-4-pyranyl trifluoromethanesulfonate. Pyridine (1.7 ml, 20.97 mmol) was added to a solution of tetrahydro-2H-4-pyranol (2 ml, 20.97 mmol) in dichloromethane (16 ml). The flask was immersed in an ice water bath and trifluoromethanesulfonic anhydride (3.6 ml, 20.97 mmol) in dichloromethane (7 ml) was added dropwise over 10 minutes. After 20 minutes, the reaction mixture was filtered and the solid was washed with minimum amount of dichloromethane. The combined filtrate was washed with water, 1.0 N HCl, water and brine. The organic layer was dried ($MgSO_4$) and filtered. The solvent was evaporated to give tetrahydro-2H-4-pyranyl trifluoromethanesulfonate. ^1H NMR ($CDCl_3$) δ 1.99 (m, 2H), 2.11 (m, 2H), 3.58 (m, 2H), 3.96 (m, 2H), 5.17 (m, 1H).

b) 4-chloro-5-iodo-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidine. 4-Chloro-5-iodo-7H-pyrrolo[2,3-d]pyrimidine (3.0 g, 10.73 mmol) was added in small portions to a solution of sodium hydride (0.891g 22.2 mmol) in N,N-dimethylformamide (40 ml) at 0°C. After completed the addition the ice water bath was removed and the resulting mixture was stirred for 30 minutes. Tetrahydro-2H-4-pyranyl trifluoromethanesulfonate was added dropwise and the reaction mixture was stirred at ambient temperature for 24 hours. The mixture was poured to ice water (100ml) and the solid was collected by filtration and purified by re-crystallization to give 4-chloro-5-iodo-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidine. [1]H NMR ($CDCl_3$) δ 2.06 (m, 2H), 3.63 (m, 2H), 4.16 (m, 2H), 5.00 (m, 1H), 7.45 (s, 1H), 8.61 (s, 1H). LC/MS (MH^+=364)

c) tert-Butyl N-(4-(4-chloro-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-methoxyphenyl)carbamate. tert-Butyl N-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]carbamate (1.66g, 4.75 mmol) in water was degassed by sonication under vacuum for 1 minute. 4-Chloro-5-iodo-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidine (1.1g, 3.17 mmol), tetrakis(triphenylphosphine) palladium(0) (0.22g, 0.19 mmol), Sodium carbonate (0.8g, 7.60 mmol) and 1,2-dimethoxyethane (30 ml) was added to the aqueous mixture. The resulting suspension was degassed again for 2 minutes and then headed to 85°C for 24 hours. The reaction mixture was cooled to ambient temperature and solvent was evaporated. The residue was dissolved in ethyl acetate. The organic layer washed and dried ($MgSO_4$). The solid was purified by flash column chromatography on silica using heptane/ethyl acetate (7:3) as the mobile phase to give tert-butyl N-(4-(4-chloro-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-methoxyphenyl) carbamate. [1]H NMR ($CDCl_3$) δ 1.55 (s, 9H), 2.10 (m, 4H), 3.66 (m, 2H), 3.92 (s, 3H), 4.16 (m, 2H), 5.05 (m, 1H), 7.06 (m, 2H), 7.14 (s, 1H), 7.32 (s, 1H), 8.13 (br.d, J=8 Hz, 1H), 8.64(s, 1H). LC/MS (MH^+=459)

d) 4-(4-chloro-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-methoxyaniline. A solution of ten percent trifluoroacetic acid in dichloromethane (50 ml) was added to tert-butyl N-(4-(4-chloro-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-methoxyphenyl)carbamate at 0°C. After 20 minutes, the ice water bath was removed and the resulting solution was stirred at ambient temperature for 4 hours. The solvent was removed and the residue taken into dichloromethane. Saturated sodium bicarbonate was added and the layers separated. The aqueous layer was extracted with dichloromethane. The combined organic layer was washed with brine, dried (MgSO4), filtered and concentrated. The solid was purified by passing though a pat of silica gel using heptane/ethyl acetate (3:2) as the mobile phase to give 4-(4-chloro-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-methoxyaniline. ^{1}H NMR ($CDCl_3$) δ 2.09 (m, 4H), 2.51 (br. s, NH_2), 3.66 (m, 2H), 3.91 (s, 3H), 4.16 (m, 2H), 5.05 (m, 1H), 6.79 (d, J=8 Hz, 2H), 6.93 (d, J=8 Hz, 1H), 6.98 (s, 1H), 7.28 (s, 1H), 8.63 (s, 1H). LC/MS (MH^+=359)

e) 5-(4-Amino-3-methoxyphenyl)-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine. Ammonium hydroxide (25 ml) was added to a solution of 4-(4-chloro-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-methoxyaniline (0.73g, 2.03 mmol) in dioxane (25 ml) in a pressure tube. The pressure tube was sealed and heated to 122°C for 2 days. The tube was cooled to ambient temperature and the solvent was evaporated. Ethyl acetate was added and the organic layer was washed, dried ($MgSO_4$), filtered and concentrated to give 5-(4-amino-3-methoxyphenyl)-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine. ^{1}H NMR (DMSO-d_6) δ 1.87 (m, 2H), 2.11 (m, 2H), 3.52 (m, 2H), 3.79 (s, 3H), 3.99 (m, 2H), 4.87 (m, 3H), 6.02 (br. s, NH_2), 6.73 (d, J=8 Hz, 2H), 6.77 (d, J=8 Hz, 1H), 6.88 (s, 1H), 7.33 (s, 1H), 8.10 (s, 1H). LC/MS (MH^+=340)

f) Benzyl N-(4-(4-amino-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-methoxyphenyl)carbamate. Benzylchloroformate(16 uL, 0.110 mmol) was added dropwise to a stirring solution of 5-(4-amino-3-methoxyphenyl)-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine (25 mg, 0.074 mmol) in pyridine (0.7 ml) and dichloromethane (0.7 ml) under nitrogen at 0°C. After 10 minutes, the ice water bath was removed and the resulting mixture was stirred for 4 hours. The solvent was evaporated and the residue was purified by preparative TLC using dichloromethane/methanol (95:5) as the mobile phase to give benzyl N-(4-(4-amino-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-methoxyphenyl) carbamate. ^{1}H NMR ($CDCl_3$) δ 2.07 (m, 4H), 3.65 (m, 2H), 3.9 (s, 3H), 4.13 (m, 2H), 4.97 (m, 1H), 5.23 (s, 2H), 6.96 (s, 1H), 7.03 (s, 1H), 7.08 (d, J=8 Hz, 1H), 7.42 (m, 6H), 8.20 (br. s, J=8 Hz, 1H). 8.32 (s, 1H). LC/MS (MH^+=474).

Example 2: Neopentyl N-(4-(4-amino-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-methoxyphenyl)carbamate.

Neopentylchloroformate(13 uL, 0.110 mmol) was added dropwise to a stirring solution of 5-(4-amino-3-methoxyphenyl)-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine (25 mg, 0.074 mmol) in pyridine (0.7 ml) and dichloromethane (0.7 ml) under nitrogen at 0°C. After 10 minutes, the ice water bath was removed and the resulting mixture was stirred for 4 hours. The solvent was evaporated and the residue was purified by preparative TLC using dichloromethane/methanol (95:5) as the mobile phase to give neopentyl N-(4-(4-amino-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-methoxyphenyl)carbamate. ^{1}H NMR ($CDCl_3$) δ 1.00 (s, 3H), 2.07 (m, 4H), 3.65 (m, 2H), 3.91 (s, 2H), 3.94 (s, 3H), 4.13 (m, 2H), 4.97 (m, 1H), 5.18 (s, 2H), 6.97 (s, 1H), 7.03 (s, 1H), 7.07 (d, J=8 Hz, 1H), 7.25 (s, 1H), 8.19 (br. s, J=8 Hz, 1H). 8.33 (s, 1H). LC/MS (MH^+=454).

Example 3: Phenyl N-[4-(4-amino-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-methoxyphenyl]carbamate

5-(4-Amino-3-methoxyphenyl)-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine (100 mg, 0.294 mmol) was dissolved in dichloromethane (2 mL). Pyridine (2mL) was added followed by phenylchloroformate (44 uL, 0.353 mmol). After stirring for 3 hours, another 44 uL of phenylmethanesulfonyl chloride was added and the reaction mixture was stirred overnight. The solvent was removed and the residue was purified by preparative LC/MS to give phenyl N-[4-(4-amino-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-methoxyphenyl] carbamate (52 mg, 0.113 mmol). 1H NMR ($CDCl_3$-d) δ 2.09 (m, 4H), 3.66 (m, 2H), 3.98 (s, 3H), 4.16 (m, 2H), 4.98 (m, 1H), 5.24 (s, 2H), 7.09 (m ,3H), 7.23 (m, 4H), 7.41 (m, 2H), 7.62 (s, 1H), 8.20(bd, J=7.80 Hz, 1H), 8.33 (s, 1H). LC/MS MH^+=460.

Example 4: Tetrahydro-2H-4-pyranyl N-[4-(4-amino-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-methoxyphenyl]carbamate 4-nitrophenyl tetrahydro-2H-4-pyranyl carbonate

Tetrahydro-2H-4-pyranol (1.0 ml, 10.5 mmol) was mixed with 4-methylmorpholine (2.0 ml) in dichloromethane (20 mL). 4- Nitrochloroformate (1.98 g, 9.82 mmol) was added slowly to the reaction mixture. After stirring for 5 hours, the reaction mixture was diluted with dichloromethane. The organic layer was washed with water, 1.0 N HCl, saturated sodium bicarbonate, brine, dried over $MgSO_4$, filtered and evaporated. The crude product was purified by flash column chromatography chromatography using ethyl acetate/heptane (4:1) as the mobile phase to give 4-nitrophenyl tetrahydro-2H-4-pyranyl carbonate (1.5 g, 5.62 mmol). 1H NMR ($CDCl_3$-d) δ 1.87 (m, 2H), 2.06 (m, 2H), 3.58 (m, 2H), 3.98 (m, 2H), 4.97 (m,1H), 7.40(d, J=9.0Hz, 2H), 8.30 (d, J=9.0Hz, 2H).

a) Tetrahydro-2H-4-pyranyl N-[4-(4-amino-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-methoxyphenyl]carbamate. 5-(4-Amino-3-methoxyphenyl)-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine (57 mg, 0.168 mmol) and 4-nitrophenyl tetrahydro-2H-4-pyranyl carbonate (90 mg, 0.336 mmol) was mixed in pyridine (1 mL). After stirring for 5 hours, another 90 mg of 4-nitrophenyl tetrahydro-2H-4-pyranyl carbonate was added and the reaction mixture was stirred for 2 days. The reaction mixture was heated at 70°C for 2 hours. The solvent was removed and the residue was purified by preparative thin layer chromatography to give tetrahydro-2H-4-pyranyl N-[4-(4-amino-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-methoxyphenyl]carbamate (30 mg, 0.064 mmol). 1H NMR ($CDCl_3$-d) δ 1.78 (m, 4H), 2.08 (m, 4H), 3.60 (m, 4H), 3.94 (s, 3H), 3.97 (m, 2H), 4.15 (m, 2H), 4.98 (m, 2H), 5.23 (s, 2H), 6.78 (s ,1H), 7.04 (s, 1H), 7.07 (d, J=8.3 Hz, 1H), 8.16(bd, J=7.90 Hz, 1H), 8.33 (s, 1H). LC/MS MH^+=468.

Example 5: 3-Pyridylmethyl N-[4-(4-amino-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-methoxyphenyl]carbamate hydrochloride

a) 4-Nitrophenyl (3-pyridylmethyl) carbonate. 4- Nitrochloroformate (2.49 g, 12.3 mmol) in dichloromethane (20 mL) was cooled on an ice-water bath. 3-pyridylmethanol (1.0 mL, 10.3 mmol) and 4-methylmorpholine (2.0 mL, 18.5 mmol) was added slowly. After 20 minutes, the ice-water bath was removed and the reaction mixture was allowed to warm up to room temperature. 30 minues later, ethyl acetate was added and the reaction mixture was filtered. The filtrate was washed with water, saturated sodium bicarbonate, brine, dried over MgSO4, filtered and evaporated to give a dark brown solid which was re-crystallized with ethyl acetate/heptane to give 4-nitrophenyl (3-pyridylmethyl) carbonate (1.52 g, 5.54 mmol).1H NMR (CDCl-d) δ 7.38 (m, 3H), 7.79 (m, 1H), 8.28 (d, J=9.09Hz, 2H), 8.65 (m, 1H), 8.72 (s,1H).

b) 3-Pyridylmethyl N-[4-(4-amino-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-methoxyphenyl]carbamate. 5-(4-Amino-3-methoxyphenyl)-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine (25 mg, 0.074 mmol) was dissolved in dichloromethane (0.7 mL). Pyridine (0.7 mL) was added followed by 4-nitrophenyl (3-pyridylmethyl) carbonate (30 mg, 0.110 mmol). After heating at 100°C overnight, the solvent was removed and the residue was purified by preparative LC/MS to give 3-pyridylmethyl N-[4-(4-amino-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-methoxyphenyl]carbamate (12 mg, 0.025 mmol). 1H NMR ($CDCl_3$-d) δ 2.08 (m, 4H), 3.65 (m, 2H), 3.92 (s, 3H), 4.15 (m, 2H), 4.96 (m, 1H), 5.26 (s, 2H), 5.54 (bs, 2H), 6.97 (s, 1H), 7.04(s, 1H), 7.08 (d, J=8.2Hz, 1H), 7.35 (m, 2H), 7.79 (d, J=7.8Hz, 1H), 8.15 (m, 1H), 8.29 (s, 1H), 8.61 (s, 1H), 8.71 (s, 1H). LC/MS MH^+=475

c) 3-Pyridylmethyl N-[4-(4-amino-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-methoxyphenyl]carbamate hydrochloride. 3-Pyridylmethyl N-[4-(4-amino-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-methoxyphenyl]carbamate (12 mg, 0.025 mmol) was dissolved in ethyl acetate (2.0mL). 1.0N HCl in ether (1 mL) was added slowly. The precipatate was collected through filtration under nitrogen to give 3-pyridylmethyl N-[4-(4-amino-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-methoxyphenyl]carbamate hydrochloride(13 mg, 0.25 mmol). 1H NMR (DMSO-d_6) δ 1.91 (m, 2H), 2.17(m, 2H), 3.54 (m, 2H), 3.87 (s, 3H), 4.03 (m, 2H), 4.97(m, 1H), 5.23 (s, 2H), 7.05 (d, J=8.2Hz, 1H), 7.13 (s, 1H), 7.51 (m, 1H), 7.81 (d, J=8.2Hz, 1H), 7.84 (s, 1H), 7.95 (m, 1H), 8.42 (s, 1H), 8.60(s, 1H), 8.71 (s, 1H), 8.82 (s, 1H). LC/MS MH^+=475.

Example 6: 2-Morpholinoethyl N-[4-(4-amino-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-methoxyphenyl]carbamate hydrochloride

Phenyl N-[4-(4-amino-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-methoxyphenyl]carbamate (25 mg, 0.054 mmol) was mixed with 2-morpholino-1-ethanol (0.1 mL) in pyridine (0.7 mL). The reaction mixture was heated at 100°C overnight. The solvent was removed and the residue was purified by preparative reverse phase HPLC to give 2-morpholinoethyl N-[4-(4-amino-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-methoxyphenyl] carbamate (24 mg, 0.048mmol). The solid was dissolved in ethyl acetate (2 mL) and 1.0N HCl in ether (0.2 mL) was added slowly. The precipitate was collected through filtration under nitrogen to give 2-morpholinoethyl N-[4-(4-amino-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-methoxyphenyl] carbamate hydrochloride (24 mg, 0.045 mmol). 1H NMR (DMSO-d_6) δ 1.88(m, 2H), 2.16(m, 2H), 3.55 (m, 8H), 3.90 (s, 3H), 4.03 (m, 4H), 4.49(m, 2H), 4.92 (m, 1H), 7.07 (m, 1H), 7.15 (s, 1H), 7.65 (bs, 2H), 7. 84 (s, 1H), 8.45 (s, 1H), 8.75(s, 1H) 10.95 (bs, 1H). LC/MS MH^+=497.

Example 7 (4-Bromo-1,3-thiazol-5-yl)methyl N-[4-(4-amino-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-methoxyphenyl]carbamate.

a) 2,4-Dibromo-1,3-thiazole-5-carbaldehyde. 1,3-Thiazolane-2,4-dione (3.52 g, 30 mmol) and phosphorus oxybromide (43 g, 150 mmol) were mixed with dimethyl formamide (2.56 mL, 34 mmol). The mixture was then heated at 75°C for 1 hours and at 100oC for 5 hours. After cooled to room temperature, the mixture was added to ice-water (500ml) and the aqueous layer was extracted with dichloromethane. The combined organic layer was washed with saturated sodium bicarbonate, dried over MgSO4, filtered and evaporated to give a brown solid which was washed with petroleum ether. Evaporation of solvent gave 2,4-dibromo-1,3-thiazole-5-carbaldehyde (1.74 g, 6.42 mmol). 1H NMR ($CDCl_3$-d) δ 9.90 (S, 1H).

b) (2,4-Dibromo-1,3-thiazol-5-yl)methanol. 2,4-Dibromo-1,3-thiazole-5-carbaldehyde (1.74 g, 6.42 mmol) was dissolved in methanol (70 ml) at 0°C. Sodium borohydride (0.244 g, 6.42 mmol) was added in small portions. The ice-water bath was removed 10 minutes later and the reaction mixture was stirred at room temperature overnight. Solvent was removed and saturated ammonium chloride was added. 1.0N NaOH was added to adjust the pH to 10. The aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over MgSO4, filtered and evaporated. The residue was purified by flash column chromatogrphy to give (2,4-dibromo-1,3-thiazol-5-yl)methanol (0.946 g, 3.47 mmol). 1H NMR ($CDCl_3$-d) δ 2.11 (bs, 1H) δ 4.79 (S, 2H).

c) (4-Bromo-1,3-thiazol-5-yl)methanol. (2,4-Dibromo-1,3-thiazol-5-yl)methanol (0.94 g, 3.44 mmol), sodium carbonate tri-hydrade (1.34 g) and palladium on carbon (10%, 0.07g) were mixed in methanol (33 mL). The resulting mixture was hydrogenated at 60 psi for 2 days. The solid was filtered off through a pat of celite. The solvent was evaporated and the residue was purified by frash column chromatography to give (4-bromo-1,3-thiazol-5-yl)methanol (0.32 g, 2.78 mmol). 1H NMR ($CDCl_3$-d) δ 2.29 (bs, 1H) δ 4.86 (s, 2H), 8.72 (s, 1H).

d) (4-Bromo-1,3-thiazol-5-yl)methyl N-[4-(4-amino-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-methoxyphenyl]carbamate. Phenyl N-[4-(4-amino-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-methoxyphenyl]carbamate (28 mg, 0.061 mmol) was mixed with (4-bromo-1,3-thiazol-5-yl)methanol (50 mg, 0.434 mmol) in pyridine (0.5 mL). The reaction mixture was heated at 100°C overnight. The solvent was removed and the residue was purified by preparative reverse phase LC/MS to give (4-bromo-1,3-thiazol-5-yl)methyl N-[4-(4-amino-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-methoxyphenyl]carbamate. 1H NMR (CDCl-d) δ 2.07(m, 4H), 3.65 (m, 2H), 3.92 (s, 3H), 4.13 (m, 2H), 4.98 (m, 1H), 5.35 (s, 1H), 5.40(s, 2H), 6.97 (s, 1H), 7.04 (s, 1H), 7.09 (m, 1H), 7.35 (s, 1H), 8.17 (s, 1H), 8.32 (s, 1H), 8.78(s, 1H). LC/MS MH^+=481.

Example 8: Tetrahydro-3-furanyl N-[4-(4-amino-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-methoxyphenyl]carbamate

Phenyl N-[4-(4-amino-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-methoxyphenyl]carbamate (30 mg, 0.065 mmol) was mixed with tetrahydro-3-furanol (0.05 mL) in pyridine (0.5 mL). The reaction mixture was heated at 100°C overnight. The solvent was removed and the residue was purified by preparative reverse phase PHLC to give tetrahydro-3-furanyl N-[4-(4-amino-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-methoxyphenyl] carbamate (14 mg, 0.031mmol). 1H NMR (CDCl-d) δ 2.07(m, 6H), 3.66 (m, 2H), 3.96 (m, 7H), 4.13 (m, 2H), 4.98 (m, 1H), 5.26 (s, 2H), 5.40(m, 1H), 6.97 (s, 1H), 7.04 (s, 1H), 7.08 (d, J=8.2Hz, 1H), 7.26 (s, 1H), 8.30 (s, 1H), 8.32 (s, 1H). LC/MS MH^+=455.

Examples 9 and 10: 1,3-Dioxan-5-yl N-[4-(4-amino-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-methoxyphenyl]carbamate

1,3-Dioxolan-4-ylmethyl N-(4-(4-amino-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-methoxyphenyl)carbamate

Phenyl N-[4-(4-amino-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-methoxyphenyl]carbamate (30 mg, 0.065 mmol) was mixed glycerol formal (0.05 mL) in pyridine (0.5 mL). The reaction mixture was heated at 100°C overnight. The solvent was removed and the residue was purified by preparative reverse phase PHLC to give tetrahydro-3-furanyl N-[4-(4-amino-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-methoxyphenyl] carbamate (2 mg, 0.004mmol). 1H NMR (CDCl-d) δ 2.06(m, 4H), 3.66 (m, 2H), 3.92 (m, 3H), 4.07 (m, 6H), 4.79 (m, 1H), 4.83 (d, J=6.3Hz, 1H), 4.96 (m, 1H), 5.04(d, J=6.3Hz, 1H), 6.15 (vbs, 2H), 6.96 (s, 1H), 7.05 (m, 2H), 7.53 (s, 1H), 8.15 (d, J=8.2Hz, 1H), 8.22 (s, 1H). LC/MS MH^+=471 and 1,3-dioxolan-4-ylmethyl N-(4-(4-amino-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-methoxyphenyl) carbamate(6.0mg, 0.013 mmol). 1H NMR (CDCl-d) δ 2.06(m, 4H), 3.66 (m, 2H), 3.75 (m, 1H), 3.92 (m, 3H), 4.03 (m, 1H), 4.13 (m, 1H), 4.34 (m, 2H), 4.94 (s, 1H), 4.97 (m, 1H), 5.10(s, 1H), 5.32 (bs, 2H), 6.97 (s, 1H), 7.03 (m, 2H), 7.06 (d, J=8.2Hz, 1H), 7.38(s, 1H), 8.15 (d, J=7.9Hz, 1H), 8.31 (s, 1H). LC/MS MH^+=471.

Example 11: 2-Pyridylmethyl N-[4-(4-amino-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-methoxyphenyl]carbamate hydrochloride

Phenyl N-[4-(4-amino-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-methoxyphenyl]carbamate (30 mg, 0.065 mmol) was mixed 2-pyridylmethanol (0.05 mL) in pyridine (0.5 mL). The reaction mixture was heated at 100°C overnight. The solvent was removed and the residue was purified by preparative reverse phase LC/MS to give 2-pyridylmethyl N-[4-(4-amino-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-methoxyphenyl] carbamate (11 mg, 0.023 mmol). The solid was dissolved in ethyl acetate (2 mL) and 1.0N HCl in ether (0.1 mL) was added slowly. The precipitate was collected through filtration under nitrogen to give 2-pyridylmethyl N-[4-(4-amino-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-methoxyphenyl] carbamate hydrochloride (12 mg, 0.023 mmol). 1H NMR (DMSO-d_6) δ 1.92(m, 2H), 2.16(m, 2H), 3.55 (m, 2H), 3.89 (s, 3H), 4.02 (m, 2H), 4.91 (m, 1H), 5.23 (s, 2H), 7.05 (d, J=8.2Hz, 1H), 7.14 (s, 1H), 7.37 (m, 1H), 7. 53 (d, J=7.8Hz, 1H), 7.87 (m, 3H), 8.42(s, 1H), 8.57 (d, J=4.2Hz, 1H), 8.85 (s, 1H). LC/MS MH^+=475.

Example 12: 4-Pyridylmethyl N-[4-(4-amino-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-methoxyphenyl]carbamate Hydrochloride

Phenyl N-[4-(4-amino-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-methoxyphenyl]carbamate (30 mg, 0.065 mmol) was mixed 4-pyridylmethanol (0.05 mL) in pyridine (0.5 mL). The reaction mixture was heated at 100°C overnight. The solvent was removed and the residue was purified by preparative reverse phase LC/MS to give 2-pyridylmethyl N-[4-(4-amino-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-methoxyphenyl] carbamate (11 mg, 0.023 mmol). The solid was dissolved in ethyl acetate (2 mL) and 1.0N HCl in ether (0.1 mL) was added slowly. The precipatate was collected through filtration under nitrogen to give 4-pyridylmethyl N-[4-(4-amino-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-methoxyphenyl] carbamate hydrochloride (12 mg, 0.023 mmol). 1H NMR (DMSO-d_6) δ 1.91(m, 2H), 2.16(m, 2H), 3.55 (m, 2H), 3.90 (s, 3H), 4.03 (m, 2H), 4.92 (m, 1H), 5.34 (s, 2H), 7.06 (d, J=8.2Hz, 1H), 7.16 (s, 1H), 7.73 (m, 1H), 7. 81 (m, 1H), 7.87 (s, 1H), 8.46(s, 1H), 8.76 (d, J=5.6Hz, 1H), 9.05 (s, 1H). LC/MS: MH^+=475.

Example 13: (5-Methyl-3-isoxazolyl)methyl N-[4-(4-amino-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-methoxyphenyl]carbamate

Phenyl N-[4-(4-amino-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-methoxyphenyl]carbamate (30 mg, 0.065 mmol) was mixed with (5-methyl-3-isoxazolyl)methanol (0.05 mL) in pyridine (0.5 mL). The reaction mixture was heated at 100°C overnight. The solvent was removed and the residue was purified by preparative reverse phase LC/MS to give (5-methyl-3-

isoxazolyl)methyl N-[4-(4-amino-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-methoxyphenyl]carbamate (18 mg, 0.038mmol). 1H NMR (CDCl-d) δ 2.06(m, 4H), 2.44 (s, 3H), 3.64 (m, 2H), 3.91 (s, 3H), 4.13 (m, 2H), 4.96 (m, 1H), 5.26 (s, 2H), 6.12(s, 1H), 6.95 (s, 1H), 7.06 (m, 2H), 7.39 (s, 1H), 8.17 (bs, 1H), 8.21(s, 1H). LC/MS: MH^+ 479.

Example 14: [(2S)-5-Oxotetrahydro-1H-2-pyrrolyl]methyl N-[4-(4-amino-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-methoxyphenyl]carbamate

Phenyl N-[4-(4-amino-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-methoxyphenyl]carbamate (30 mg, 0.065 mmol) was mixed with (5S)-5-(hydroxymethyl)tetrahydro-1H-2-pyrrolone (0.05 mL) in pyridine (0.5 mL). The reaction mixture was heated at 100°C overnight. The solvent was removed and the residue was purified by preparative reverse phase LC/MS to give [(2S)-5-oxotetrahydro-1H-2-pyrrolyl]methyl N-[4-(4-amino-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-methoxyphenyl]carbamate (10 mg, 0.021mmol). 1H NMR (CDCl-d) δ 1.90 (m, 1H), 2.06(m, 4H), 2.34 (m, 1H), 2.41 (m, 2H), 3.64 (m, 2H), 3.94 (s, 3H), 4.04(m, 2H), 4.14 (m, 2H), 4.98 (m, 1H), 5.33 (m, 3H), 6.10(s, 1H), 6.98 (s, 1H), 7.04 (s, 1H), 7.09 (m, 1H), 7.31(s, 1H), 8.11 (bs, 1H), 8.32 (s, 1H). LC/MS: MH^+ 481.

Example 15: 4-Aminobenzyl N-(4-(4-amino-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-methoxyphenyl)carbamate

a) tert-Butyl N-(4-(hydroxymethyl)phenyl)carbamate. (4-Aminophenyl)methanol (1.23 g, 10 mmol) and diisopropylethylamine (2.6 mL, 15 mmol) was mixed with di-tert-butyl dicarbonate (2.62 g, 12 mmol) in dichloromethane (50 mL). The mixture was stirred at room temperature overnight. Ethyl acetate was added and the organic layer was washed with water, 1.0N HCl, saturated sodium carbonate, water, brine, dried over MgSO4, filtered and evaporated. The crude product was purified by flash column chromatography with Ethyl acetate/

heptane (2:3) to give tert-butyl N-(4-(hydroxymethyl)phenyl) carbamate (2.16g, 9.67 mmol). 1H NMR (CDCl-d) δ 1.52 (s, 9H), 4.63 (s, 2H), 6.47 (bs, 1H), 7.30 (d, 8.5Hz, 2H), 7.36 (d, 8.5Hz,2H).

b) 4-Aminobenzyl N-(4-(4-amino-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-methoxyphenyl)carbamate. Phenyl N-[4-(4-amino-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-methoxyphenyl]carbamate (51mg, 0.111 mmol) was mixed with tert-butyl N-(4-(hydroxymethyl)phenyl)carbamate (119 mg, 0.533) in pyridine (0.8 mL). The reaction mixture was heated at 100°C overnight. The solvent was removed and the residue was purified by preparative reverse phase LC/MS to give 4-aminobenzyl N-(4-(4-amino-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-methoxyphenyl)carbamate (9 mg, 0.015mmol). 1H NMR (CDCl-d) δ 1.52(s, 1H), 2.08(m, 4H), 3.65 (m, 2H), 3.90 (s, 3H), 4.14(m, 2H), 4.97 (m, 1H), 5.17 (s, 2H), 5.37(bs, 1H), 6.55 (s, 1H), 6.95 (s, 1H), 7.03 (s, 1H), 7.06 (m, 1H), 7.31(s, 1H), 7.38 (m, 3H), 8.16 (bs, 1H), 8.30 (s, 1H). LC/MS: MH^+ 589.

Example 16: N1-[4-(4-Amino-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-methoxyphenyl]benzamide

5-(4-Amino-3-methoxyphenyl)-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine (80mg, 0.236 mmol) was dissolved in dichloromethane (2.0 mL). Pyridine (2.0 mL) was added followed by benzoyl chloride (41 uL, 0.353 mmol). After stirring at room temperature for 2 hours, the solvent was removed and the residue was dissolved in 1 ml DMSO, methanol (1 mL) was added and precipitate was formed. The solid was collected by filtration to give N1-[4-(4-amino-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-methoxyphenyl]benzamide (64 mg, 0.144 mmol). 1H NMR ($CDCl_3$-d) δ 2.12 (m, 4H), 3.67 (m, 2H), 3.99 (s, 3H), 4.17(m, 2H), 4.99 (m, 1H), 7.03(s, 1H), 7.04 (s, 1H), 7.14 (d, J=8.2Hz, 1H), 7.53 (m, 3H), 7.94(d, J=7.8Hz, 1H), 8.33 (s, 1H), 8.58 (s, 1H), 8.63 (d, J=8.2Hz, 1H). LC/MS: MH^+=444

Example 17: N2-[4-(4-Amino-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-methoxyphenyl]-2-pyridinecarboxamide

5-(4-Amino-3-methoxyphenyl)-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine (80mg, 0.236 mmol) was dissolved in dichloromethane (2.0 mL). Pyridine (2.0 mL) was added followed by 2-pyridinecarbonyl chloride hydrochloride (63 mg, 0.353 mmol). After stirring at room temperature for 2 hours, the solvent was removed and the residue was dissolved in 1 ml DMSO, methanol (1 mL) was added and precipitate was formed. The solid was collected by filtration to give N1-[4-(4-amino-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-methoxyphenyl]benzamide (84 mg, 0.189 mmol). 1H NMR ($CDCl_3$-d) δ 2.12 (m, 4H), 3.67 (m, 2H), 4.03 (s, 3H), 4.14(m, 2H), 5.00 (m, 1H), 5.37 (s, 1H), 7.04(s, 1H), 7.09 (s, 1H), 7.14 (d, J=8.2Hz, 1H), 7.50 (m, 1H), 7.92 (m, 1H), 8.33 (s, 1H), 8.70(d, J=8.2Hz, 1H), 10.62 (s, 1H). LC/MS: MH^+=445.

Example 18: N5-[4-(4-Amino-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-methoxyphenyl]-1,3-dimethyl-1H-5-pyrazolecarboxamide

5-(4-Amino-3-methoxyphenyl)-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine (80mg, 0.236 mmol) was dissolved in dichloromethane (2.0 mL). Pyridine (2.0 mL) was added followed by 2-pyridinecarbonyl chloride hydrochloride (63 mg, 0.353 mmol). After stirring at room temperature for 2 hours, the solvent was removed and the residue was dissolved in 1 ml DMSO, methanol (1 mL) was added and precipitate was formed. The solid was collected by filtration to give N5-[4-(4-amino-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-methoxyphenyl]-1,3-dimethyl-1H-5-pyrazolecarboxamide (30 mg, 0.065 mmol). 1H NMR ($CDCl_3$-d) δ 2.11 (m, 4H), 2.32 (s, 3H), 3.66 (m, 2H), 3.99 (s, 3H), 4.13(m, 2H), 4.17 (s, 3H), 4.99 (m, 1H), 5.22 (bs, 2H), 6.46 (s, 1H), 7.03 (s, 1H), 7.07 (s, 1H), 7.12 (d, J=8.2Hz, 1H), 8.33 (2, 2H), 8.49(d, J=8.2Hz, 1H). LC/MS: MH^+=462.

Example 19: N1-[4-(4-Amino-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-methoxyphenyl]-2,2-dimethylpropanamide

5-(4-Amino-3-methoxyphenyl)-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine (50mg, 0.147 mmol) was dissolved in dichloromethane (1.5 mL). Pyridine (1.5 mL) was added followed by 2,2-dimethylpropanoyl chloride (31 mg, 0.221 mmol). After stirring at room temperature for 2 hours, the solvent was removed and the residue was dissolved in 1 ml DMSO, methanol (1 mL) was added and precipitate was formed. The solid was collected by filtration to give N1-[4-(4-amino-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-methoxyphenyl]-2,2-dimethylpropanamide (27 mg, 0.064 mmol). 1H NMR ($CDCl_3$-d) δ 1.35 (s, 9H), 2.09 (m, 4H), 3.66 (m, 2H), 3.96 (s, 3H), 4.13(m, 2H), 4.97 (m, 1H), 5.46(bs, 2H), 6.98 (s, 1H), 7.04 (s, 1H), 7.07 (d, J=8.2Hz, 1H), 8.15 (s, 1H), 8.29 (s, 1H), 8.49(d, J=8.2Hz, 1H). LC/MS: MH^+=424.

Example 20: N1-[4-(4-Amino-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-methoxyphenyl]-1-cyclopentanecarboxamide

5-(4-Amino-3-methoxyphenyl)-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine (50mg, 0.147 mmol) was dissolved in dichloromethane (1.5 mL). Pyridine (1.5 mL) was added followed by 1-cyclopentanecarbonyl chloride (31 mg, 0.221 mmol). After stirring at room temperature for 2 hours, the solvent was removed and the residue was dissolved in 1 ml DMSO, methanol (1 mL) was added and precipitate was formed. The solid was collected by filtration to give N1-[4-(4-amino-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-methoxyphenyl]-2,2-dimethylpropanamide (33 mg, 0.076mmol). 1H NMR ($CDCl_3$-d) δ 1.66 (m, 2H), 1.81 (m, 2H), 1.95 (m, 4H), 2.06 (m, 4H), 2.77 (m, 1H), 3.65 (m, 2H), 3.94 (s, 3H), 4.15(m, 2H), 4.96 (m, 1H), 5.37(bs, 2H), 6.98 (s, 1H), 7.03 (s, 1H), 7.07 (d, J=8.2Hz, 1H), 7.84 (s, 1H), 8.30 (s, 1H), 8.49(d, J=8.2Hz, 1H). LC/MS: MH^+=437.

Example 21: N1-[4-(4-Amino-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-methoxyphenyl]-3-phenylpropanamide

5-(4-Amino-3-methoxyphenyl)-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine (50mg, 0.147 mmol) was dissolved in dichloromethane (1.5 mL). Pyridine (1.5 mL) was added followed by 3-phenylpropanoyl chloride (37 mg, 0.221 mmol). After stirring at room temperature for 2 hours, the solvent was removed and the residue was dissolved in 1 ml DMSO, methanol (1 mL) was added and precipitate was formed. The solid was collected by filtration to give N1-[4-(4-amino-7-tetrahydro-2H-4-pyranyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-methoxyphenyl]-2,2-dimethylpropanamide (7 mg, 0.015mmol). 1H NMR ($CDCl_3$-d) δ 2.07 (m, 4H), 2.75 (m, 2H), 3.09 (m,2H), 3.65 (m, 2H), 3.88 (s, 3H), 4.13(m, 2H), 4.96 (m, 1H), 5.97(bs, 2H), 6.93 (s, 1H), 7.05 (m, 2H), 7.26 (m, 5H), 7.70 (s, 1H), 8.24 (s, 1H), 8.46(d, J=8.2Hz, 1H). LC/MS: MH^+=472.

Example 22: 5-(4-phenoxyphenyl)-7-(3-tetrahydrofuryl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine.

a) Tosyl chloride (12.0 g) was added in portions to a mixture of 3-hydroxytetrahydofuran (5.0 g) in pyridine (100 ml) at 0 C under nitrogen with stirring. The mixture was stirred at 0°C for 2 hours and then warmed to ambient temperature. The mixture was stirred at ambient temperature for 72 hours. The mixture was cooled to 0°C and 5M hydrochloric acid (200 ml) was added. The mixture was extracted with ethyl acetate and the combined ethyl acetate extracts were washed with 2M hydrochloric acid and then with brine, then dried, filtered and evaporated to give 3-tosyloxytetrahydrofuran as an oil.

b) Sodium hydride (120 mg, of a 60% dispersion in mineral oil) was added to a solution of 4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidine (906 mg) and dimethylformamide (30 ml) with stirring under nitrogen. The mixture was stirred for 30 minutes and then a solution of 3-(tosyloxy) tetrahydrofuran (750 mg) in dimethyl formamide (10 ml) was added with stirring. The mixture was stirred and heated at 95°C for 18 hours and then evaporated under vacuum. The residue was partitioned between ethyl acetate and water. The ethyl acetate layer was separated, dried and evaporated to give a residual gummy solid which was triturated with ether and filtered to give 5-(4-phenoxyphenyl)-7-(3-tetrahydrofuryl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine m.p. 196-196.5°C.

Example 23: 5-(4-phenoxyphenyl)-7-(4-tetrahydropyranyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine.

In a similar manner to Example 1, 4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidine was reacted with 4-tosyloxytetrahydropyran to give after flash column chromatography 5-(4-phenoxyphenyl)-7-(4-tetrahydropyranyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine, m.p. 193-193.5°C.

Example 24: 4-amino-5-(4-phenoxyphenyl)-7-[4-(N-tert-butoxycarbonyl) tetrahydroisoxazolyl]-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine.

a) Di-tert-butyl dicarbonate (4.56 g) was added to a solution of 4-hydroxytetrahydroisoxazole (2.4 g) and triethylamine (4.2 g) in tetrahydrofuran (100 ml) with stirring at 0°C under nitrogen. The mixture was stirred at ambient temperature for 72 hours and then filtered. The filtrate was evaporated under reduced pressure to give N-(tert-butoxycarbonyl)-4-hydroxytetrahydroisoxazole as an oil which was used directly in the next part of this example.

b) The product from a) above (3.6 g) was stirred in pyridine (50 ml) at 0°C under nitrogen and then tosyl chloride (3.62 g) was added in portions at 0°C with stirring. The mixture was stirred at 0°C for 1 hour and then allowed to warm to ambient temperature over 18 hours. The pyridine was removed under reduced pressure and ethyl acetate (50 ml) and citric acid (50 ml of a 1M solution in water) were added. The organic layer was separated and washed with 1M citric acid solution and then brine, then dried, filtered and evaporated to give an oil which was purified by flash column chromatography using petroleum ether, b.p 40-60°C containing 20-30% of ethyl acetate as the mobile phase. Appropriate fractions were collected and combined to give N-(tert-butoxycarbonyl)-4-tosyloxy tetrahydroisoxazole, m.p. 63-65°C.

c) A solution of 4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidine (1.0 g) in dimethylformamide (40 ml) was added dropwise with stirring to a suspension of sodium hydride (0.145 g, of a 60% dispersion in mineral oil) in dimethylformamide (60 ml) with stirring under nitrogen at 0°C. The mixture was stirred at 0°C for 1 hour and then the product from b) (1.25 g) was added. The mixture was heated at 100°C for 3 hours and then cooled to ambient temperature, quenched with water and extracted with ethyl acetate to give an oil. The oil was triturated with ethyl acetate and the solid obtained was collected by filtration to give 4-amino-5-(4-phenoxyphenyl)-7-[4-(N-tert-butoxycarbonyl)tetrahydroisoxazolyl]-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine, m.p. 162-163°C.

Example 25: 5-(4-phenoxyphenyl)-7-(4-tetrahydroisoxazolyl)-7H-pyrrolo[2,3-d]-pyrimidin-4-ylamine dihydrochloride.

The product from Example 3 (0.29 g) was dissolved in dichloromethane (8 ml) and then stirred at 0°C whilst trifluoroacetic acid (2.0 ml) was added. The mixture was allowed to warm to ambient temperature and stirred at ambient temperature for 2 hours. The mixture was basified with sodium bicarbonate solution and extracted with dichloromethane to give an oil which was purified by flash column chromatography using ethyl acetate and then ethyl acetate/methanol (9:1) as the mobile phase. The appropriate fractions were collected and combined, then evaporated to give a solid which was dissolved in ethyl acetate and then treated with ethereal hydrogen chloride (3.0 ml, of a 1M solution). The solid obtained was collected by filtration, washed with ether and dried under vacuum at 45°C for 2 hours to give 5-(4-phenoxyphenyl)-7-(4-tetrahydroisoxazolyl)-7H-pyrrolo[2,3-d]-pyrimidin-4-ylamine dihydrochloride, m.p. 208°C (with decomposition).

Example 26: 4-chloro-5-iodo-7-(3-tetrahydrofuryl)-7H-pyrrolo[2,3-d]pyrimidine

a) 4-Chloro-5-iodo-7H-pyrrolo[2,3-d]pyrimidine (5.0 g) was added to a mixture of sodium hydride (0.79 g of a 60% dispersion in mineral oil) in dimethylformamide (100 ml) with stirring under nitrogen at 0°C. The mixture was stirred until hydrogen evolution ceased. 3-Tosyloxytetrahydrofuran (4.65 g) was added at 0°C and then the mixture was warmed to 90°C. The mixture was stirred at this temperature for 2 hours and then overnight at ambient temperature. Water (100 ml) was added cautiously and the mixture was extracted with ethyl acetate to give 4-chloro-5-iodo-7-(3-tetrahydrofuryl)-7H-pyrrolo[2,3-d]pyrimidine, m.p. 184-186°C.

b) A mixture of 4-iodophenol (25.0 g), 2-fluorobenzaldehyde (14.14 g), potassium carbonate (31.5 g) and dimethylformamide (500 ml) was heated at 120°C under nitrogen with stirring for 15 hours. The mixture was cooled to ambient temperature and filtered. Water (500 ml) was added to the filtrate and the mixture was extracted with ethyl acetate to give a solid which was triturated with hot hexane (500 ml). The supernatant liquid was decanted from a residual gum and cooled. The solid which precipitated was collected by filtration to give 2-(4-iodophenoxy) benzaldehyde, m.p. 84.5-86°C.

c) Toluene (250 ml) was deoxygenated and then nitrogenated for 30 minutes. 2-(4-Iodophenoxy)benzaldehyde (6.46 g), hexamethylditin (10.0 g) and tetrakis (triphenylphosphine) palladium (0) (1.4 g) were added to the toluene. The mixture was boiled under reflux under nitrogen with stirring for 7 hours. The mixture was cooled to ambient temperature then filtered. The filtrate was evaporated and the residue was purified by flash column chromatography on silica using 3% ethyl acetate in petroleum ether, b.p. 40-60°C as the mobile phase to give 2-(4-trimethylstannylphenoxy)benzaldehyde as an oil.

d) A mixture of the product from c) (1.80 g), the product from b) (1.76 g), tris(dibenzylideneacetone)dipalladium (228 mg), triphenylarsine (383 mg) and dimethylformamide (75 ml) was heated at 65°C under nitrogen with stirring for 70 hours. The mixture was cooled to ambient temperature and quenched with water. The mixture was extracted with ethyl acetate to give a residue which was purified by flash column chromatography on silica using increasing amounts of ethyl acetate from 30-50% in petroleum ether, b.p. 40-60°C as the mobile phase to give a solid which was triturated with diethyl ether and filtered to give 2-[(4-(4-chloro-7-(3-tetrahydrofuryl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)phenoxy]benzaldehyde as a solid.

e) The product from d) (360 mg) was dissolved in methanol (5 ml) and sodium borohydride (65 mg) was added at 0°C with stirring. The mixture was warmed to ambient temperature and stirred at this temperature for 1 hour. The mixture was quenched with dilute sodium hydroxide solution and then evaporated under reduced pressure to give a residue which was extracted with ethyl acetate to give 2-[(4-(4-chloro-7-(3-tetrahydrofuryl)-7H-pyrrolo[2,3-d]pyrimidin-5-ylphenoxy]benzyl alcohol.

f) A mixture of the product from e) (280 mg), 1,4-dioxane (15 ml) and concentrated aqueous ammonia solution (15 ml, S.G. 0.88) was heated at 120°C in a pressure vessel for 20 hours. The mixture was cooled to ambient temperature and the solvent removed under reduced pressure. The residue was taken up in ethyl acetate, washed with water, then dried, filtered and evaporated to give an oil which was purified by flash column chromatography on silica using ethyl acetate/methanol (9:1) as the mobile phase to give 2-[(4-(4-amino-7-(3-tetrahydrofuryl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)phenoxy]benzyl alcohol as a glassy solid, m.p. 92-96°C.

Example 27: 2-[4-(4-amino-7-(3-tetrahydrofuryl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)phenoxy]-N,N-diethylbenzylamine

a) Sodium triacetoxyborohydride (264 mg) was added to a mixture of 2-[(4-(4-chloro-7-(3-tetrahydrofuryl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)phenoxy]benzaldehyde (330 mg) and diethylamine (121 mg) in 1,2-dichloroethane in a vial (5 ml) and the vial septum sealed. The mixture was stirred at ambient temperature for 20 hours then quenched with saturated aqueous sodium bicarbonate solution (5 ml). The mixture was extracted with ethyl acetate to give 2-[4-(4-chloro-7-(3-tetrahydrofuryl)-7H-pyrrolo[2,3-d)pyrimidin-5-yl)phenoxy]-N,N-diethylbenzylamine.

b) A mixture of the product from a) (280 mg), concentrated aqueous ammonia solution (10 ml, S.G. 0.88) and 1,4-dioxane (10 ml) was heated in a pressure vessel for 16 hours at 120°C. The mixture was cooled and the solvent removed under reduced pressure. The residue was taken up in ethyl acetate, washed with water, then dried, filtered and evaporated to give an oil which was purified by flash column chromatography using ethyl acetate/methanol as a mobile phase to give 2-[4-(4-amino-7-(3-tetrahydrofuryl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)phenoxy]-N,N-diethylbenzylamine, m.p. 107-110°C.

Example 28: 2-[4-(4-amino-7-(3-tetrahydrofuryl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)phenoxy]-benzonitrile

a) A mixture of 2-fluorobenzonitrile (28.8 g), 4-bromophenol (36.9 g), potassium carbonate (58.9 g) and dimethylformamide (30 ml) was heated with stirring under nitrogen at 120°C for 5 hours. The mixture was allowed to stand overnight at ambient temperature and then partitioned between ethyl acetate and water. The organic layer was separated, washed, dried and evaporated to give an oil which solidified on standing. The solid was triturated with petroleum ether b.p. 40-60°C and filtered to give 2-(4-bromophenoxy)benzonitrile.

b) A mixture from the product of part a) (5.57 g), hexamethylditin (10.0 g), tetrakis (triphenylphosphine) palladium (0) (1.4 g) and degassed toluene (250 ml) was heated at 110°C with stirring under nitrogen for 4.5 hours. The mixture was allowed to stand for 18 hours at ambient temperature and then filtered through a silica pad. The pad was washed with ethyl acetate and the combined filtrate and washes evaporated to dryness. The residue was purified by flash column chromatography on silica using petroleum ether b.p. 40-60°C and diethyl ether (2%) increasing to 5% as the mobile phase. Appropriate fractions were collected combined and evaporated to give 2-(4-trimethylstannylphenoxy)benzonitrile.

c) A mixture 4-chloro-5-iodo-7-(3-tetrahydrofuryl)pyrrolo[2,3-d]pyrimidine (1.8 g, prepared as described in Example 5) and the product from part b) (1.23 g) were reacted and then worked up in a similar manner to Example 5d) to give 2-[4-(4-chloro-7-(3-tetrahydrofuryl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)phenoxy]benzonitrile.

d) A mixture of the product from c) (470 mg), concentrated aqueous ammonia (33 ml, SG 0.880) and 1,4-dioxane (33 ml) were heated together in a pressure vessel at 120°C for 18 hours and then worked up on a similar manner to Example 5 to give 2-[4-(4-amino-7-(3-tetrahydrofuryl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)phenoxy]-benzonitrile, m.p. 201-203°C.

Example 29: 2-[4-(4-amino-7-(3-tetrahydrofuryl)-7H-pyrrolo[2,3-d)pyrimidin-5-yl)phenoxy]benzaldehyde

a) In a similar manner to Example 2, 3-tosyloxytetrahydrofuran (1.84 g) was reacted with 5-(4-benzyloxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine (2.9 g) using sodium hydride (0.30 g, of a 60% dispersion in mineral oil) and dimethylformamide (40 ml) except that the mixture was heated for 4.5 hours at

90°C to give 5-(4-benzyloxyphenyl)-7-(3-tetrahydrofuryl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine as a solid.

b) A mixture of the product from part a) (6.0 g), 10% palladium on charcoal (3.0 g), ammonium formate (4.9 g) and ethanol (500 ml) was heated on a steam bath with stirring under nitrogen for 2 hours. The mixture was cooled and filtered and the solvent evaporated. The filtrate was concentrated to half volume and filtered to give a solid which was identified as 4-[4-amino-7-(3-tetrahydrofuryl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]phenol m.p. 257-259°C.

c) A mixture of 4-[4-amino-7-(3-tetrahydrofuryl-7H-pyrrolo[2,3-d]pyrimidin-5-yl]phenol (2.55 g), 2-fluorobenzaldehyde (1.07 g), potassium carbonate (2.13 g) and dimethylformamide (80 ml) was heated at 120°C with stirring under nitrogen for 5 hours. The mixture was cooled to ambient temperature quenched with water and extracted with ethyl acetate to give 2-[4-(4-amino-7-(3-tetrahydrofuryl)-7H-pyrrolo[2,3-d)pyrimidin-5-yl)phenoxy]benzaldehyde, m.p. 185-187°C.

Example 30: 4-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo-[2,3-d]pyrimidin-7-yl]tetrahydrofuran-3-ol

Sodium hydride (120 mg of a 60% dispersion in mineral oil) was added to a solution of 4-amino-5-(4-phenoxyphenyl-7H-pyrrolo[2,3-d]pyrimidine (902 mg) and dimethylformamide (30 ml) with stirring under nitrogen. The mixture was stirred for 30 minutes and then 3,6-dioxabicyclo[3.1.0]hexane (300 mg) was added and the mixture was warmed to 80°C. The mixture was left for 64 hours and then evaporated under reduced pressure. The residue was triturated with water which left an oily gum. Ether was added and the mixture was stirred rapidly for 30 minutes which gave a solid which was collected by filtration and washed with methanol. The solid was discarded. The filtrate produced a second crop of solid which was recrystallised from ethanol to give 4-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo-

[2,3-d]pyrimidin-7-yl]tetrahydrofuran-3-ol, m.p. 234.5-235.5°C.

Example 31: 5-[4-(2-morpholinomethylphenoxy)phenyl]-7-(3-tetrahydrofuryl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine

A mixture of 2-[4-(4-amino-7-(3-tetrahydrofuryl)-7H-pyrrolo[2,3-d)pyrimidin-5-yl)phenoxy]benzaldehyde (0.15 g), morpholine (64 mg), sodium triacetoxyborohydride (117 mg) and 1,2 dichloroethane (5 ml) was stirred at ambient temperature for 18 hours. Saturated aqueous sodium bicarbonate solution was added and the mixture was filtered through an EMPORE® cartridge. The filtrate was evaporated and the residue was dissolved in dichloromethane (5 ml) and then tris(2-aminoethyl)amine-polymer bound (0.3 g) and 2 drops of glacial acetic acid were added and the mixture was stirred at ambient temperature overnight. The polymer was removed by filtration and washed with dichloromethane and then with methanol. The combined organic filtrate and washings were evaporated under reduced pressure to give an oil which was triturated with diethyl ether/ethyl acetate with warming to dissolve the solid and then the solution was cooled in ice and filtered to give 5-[4-(2-morpholinomethylphenoxy)phenyl]-7-(3-tetrahydrofuryl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine, m.p. 169-171°C.

Example 32: 5-[4-(2-piperidinomethylphenoxy)phenyl]-7-(3-tetrahydrofuryl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine

In a similar manner to Example 10, 2-[4-(4-amino-7-(3-tetrahydrofuryl)-7H-pyrrolo[2,3-d)pyrimidin-5-yl)phenoxy]benzaldehyde (0.15 g) was reacted with piperidine (63 mg) to give 5-[4-(2-piperidinomethylphenoxy)phenyl]-7-(3-tetrahydrofuryl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine m.p. 76-78°C (glassy foam).

Example 33: 5-{4-[2-(2-methoxyethyl)aminomethylphenoxy]phenyl}-7-(3-tetrahydrofuryl)-7H-pyrrolo[2,3-d]-pyrimidin-4-ylamine

In a similar manner to Example 10, 2-[4-(4-amino-7-(3-tetrahydrofuryl)-7H-pyrrolo[2,3-d)pyrimidin-5-yl)phenoxy]benzaldehyde (0.15 g) and 2-methoxyethylamine (56 mg) were reacted together to give 5-{4-[2-(2-methoxyethyl)aminomethylphenoxy]phenyl}-7-(3-tetrahydrofuryl)-7H-pyrrolo[2,3-d]-pyrimidin-4-ylamine m.p. 66-68°C (glassy foam).

Example 34: 4-[(4-(4-amino-7-(3-tetrahydrofuryl)-7H-pyrrolo[2,3-d]-pyrimidin-5-yl)phenoxy]benzyl alcohol

a) In a similar manner to Example 9, 4-[4-amino-7-(3-tetrahydrofuryl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]phenol was reacted with 4-fluorobenzaldehyde to give 4-[4-(4-amino-7-(3-tetrahydrofuryl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)phenoxy] benzaldehyde.

b) The product from a) (0.35 g) was dissolved in methanol (10 ml) and to this solution was added sodium borohydride (32 mg) at 0°C. The mixture was warmed at ambient temperature and stirred at this temperature for 10 minutes. 1,2-Dichloroethane (4 ml) was added to aid solubility. The mixture was stirred to ambient temperature for 18 hours and then glacial acetic acid (1 ml) was added and the mixture evaporated under reduced pressure. The residue was partitioned between ethyl acetate and saturated aqueous sodium carbonate solution. The ethyl acetate was separated, dried, filtered and evaporated to give 4-[(4-(4-amino-7-(3-tetrahydrofuryl)-7H-pyrrolo[2,3-d]-pyrimidin-5-yl)phenoxy]benzyl alcohol, m.p. 92-95°C.

Example 35: 5-[4-(4-fluorophenoxy)phenyl]-7-(3-tetrahydrofuryl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine

A mixture of 4-[4-amino-7-(3-tetrahydrofuryl-7H-pyrrolo[2,3-d]pyrimidin-5-yl]phenol (0.59 g), 4-fluorophenylboronic acid (0.56 g), copper (II) acetate (0.36 g), triethylamine (1.01 g), dichloromethane (20 ml) and activated ground 4 molecular sieves (0.5 g) was stirred under nitrogen in a dry atmosphere for 64 hours. The reaction mixture was filtered through a small pre-flushed silica pad and eluted with dichloromethane (200 ml) then ethyl acetate (250 ml) and finally ethyl acetate/methanol 9:1 (250 ml). The dichlormethane and ethyl acetate fractions were combined and purified by flash column chromatography on silica using ethyl acetate/methanol as the mobile phase to give 5-[4-(4-fluorophenoxy)phenyl]-7-(3-tetrahydrofuryl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine, m.p. 198-199°C.

Example 36: 5-[4-(4-morpholinomethylphenoxy)-phenyl]-7-(3-tetrahydrofuryl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine

In a similar manner to Example 10 a mixture of 4-[4-(4-amino-7-(3-tetrahydrofuryl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)phenoxy]benzaldehyde (336 mg), and morpholine (146 mg) were reacted to give 5-[4-(4-morpholinomethylphenoxy)-phenyl]-7-(3-tetrahydrofuryl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine, m.p 142-144°C.

Example 37: 5-[4-(3-morpholinomethylphenoxy)phenyl]-7-(3-tetrahydrofuryl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine

a) A mixture of 4-[4-amino-7-(3-tetrahydrofuryl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)phenol (0.297 g), was reacted with 3-formylphenylboronic acid in a similar manner to Example 14 to give 3-[4-(4-amino-7-(3-tetrahydrofuryl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)phenoxy]benzaldehyde.

b) The product from part a) (100 mg) and morpholine (44 mg) were reacted together using similar reagents and conditions as described in Example 10 to give 5-[4-(3-morpholinomethylphenoxy)phenyl]-7-(3-tetrahydrofuryl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine, m.p. 83-85°C.

Example 38: 2-[4-(4-amino-7-(3-tetrahydrofuryl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)phenoxy]-6-(2-(4-pyridyl)ethylamino)-benzonitrile

A mixture of 4-[4-amino-7-(3-tetrahydrofuryl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-phenol (0.517 g), 2-fluoro-6-(2-(4-pyridinyl)ethylamino)benzonitrile (0.42 g), potassium carbonate (0.48 g) and dimethylformamide (20 ml) were heated at 120°C under nitrogen for 8 hours. The mixture was allowed to cool, diluted with water then extracted with ethyl acetate to give a solid which was recrystallised from ethyl acetate to give solid which was purified by flash column chromatography on silica using ethyl acetate and then ethyl acetate/methanol (9:1, 8:1, 4:1) to give 2-[4-(4-amino-7-(3-tetrahydrofuryl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)phenoxy]-6-(2-(4-pyridyl) ethylamino)-benzonitrile, m.p 212-213°C.

Example 39: 2-[4-(4-amino-7-(3-tetrahydrofuryl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)phenoxy]-6-(3-imidazol-1-yl)propylaminobenzonitrile

4-[4-Amino-7-(3-tetrahydrofuryl)-7H-pyrrolo[2,3-d]pyrimidin-5-ylphenol (0.49 g), 2-fluoro-6-(3-imidazol-1-yl)propylamino benzonitrile, potassium carbonate (0.45 g) and dimethylformamide were reacted in a similar manner to Example 17 to give 2-[4-(4-amino-7-(3-tetrahydrofuryl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)phenoxy]-6-(3-imidazol-1-yl)propylaminobenzonitrile, m.p.110°C (glassy foam).

Example 40: 4-amino-6-bromo-5-(4-phenoxyphenyl)-7-(3-tetrahydrofuryl)-7H-pyrrolo[2,3-d]pyrimidine

a) A mixture of 4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidine (302 mg) was dissolved in dimethylacetamide (10 ml) and dichloromethane (50 ml) and then treated with N-bromosuccinimide (178 mg) in dichloromethane (10 ml). The mixture was left stirring ambient temperature for 16 hours. The mixture was evaporated under reduced pressure and the residue was triturated with water to give a solid which was collected by filtration and dried to give 4-amino-6-bromo-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidine, m.p. 282-283°C.

b) A mixture of the product from a) (1.14 g) in dry dimethylformamide (30 ml) was stirred under nitrogen whilst sodium hydride (120 mg of a 60% dispersion in mineral oil) was added. This was followed by 3-tosyloxytetrahydrofuran (0.8 g) in dimethylformamide (10 ml). The mixture was heated at 90°C overnight. The mixture was evaporated under reduced pressure and the residue was triturated with water to give a solid which was collected by filtration and dried to give a solid which was purified by dissolving in ethanol, adding water to cloud point and filtering. The filtrate was evaporated under reduced pressure to give a residue which was purified by flash column chromatography on silica to give 4-amino-6-bromo-5-(4-phenoxyphenyl)-7-(3-tetrahydrofuryl)-7H-pyrrolo[2,3-d]pyrimidine, m.p. 205-206°C.

Example 41: 2-[4-(4-amino-7-(3-tetrahydrofuryl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)phenoxy]-6-(3-methoxypropylamino) benzonitrile

In a similar manner to Example 17, 4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidine (0.65 g), 2-fluoro-6-(3-methoxypropylamino)benzonitrile (0.46 g), potassium carbonate (0.61 g) and dimethylformamide (40 ml) was heated under nitrogen at 120°C for 8 hours to give, after workup, 2-[4-(4-amino-7-(3-tetrahydrofuryl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)phenoxy]-6-(3-methoxypropylamino) benzonitrile, m.p.183-184°C.

Example 42: 2-[4-(4-amino-7-(4-tetrahydropyranyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)phenoxy]benzonitrile

a) A mixture of 5-(4-benzyloxyphenyl)-7-(tetrahydropyran-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine (2.83 g), 10% palladium on carbon (1.41 g), ammonium formate (2.31 g) and ethanol (250 ml) was boiled under reflux under nitrogen with stirring for 1.5 hours. The mixture was cooled to ambient temperature, filtered, then the filtrate cooled and filtered. The filtrate was evaporated to give a solid 4-[4-amino-7-(4-tetrahydropyranyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]phenol.

b) A warm solution of 4-[4-amino-7-(4-tetrahydropyranyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]phenol (0.082 g) in dimethylformamide (3.4 ml) was added to a mixture of 2-fluorobenzonitrile (80 mg) and potassium carbonate (76 mg) in a vial. The vial was flushed with nitrogen then sealed. The mixture was shaken at 120°C for 6 hours and then left to cool to ambient temperature over 16 hours. The mixture was diluted with water (11 ml) and then extracted with ethyl acetate to give 2-[4-(4-amino-7-(4-tetrahydropyranyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)phenoxy]benzonitrile, m.p. 125°C (softens).

Examples 43-48 were prepared in a similar manner to the previous example by reacting 4-[4-amino-7-(4-tetrahydropyranyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]phenol with the appropriate nitrile except that the mixtures were shaken together for periods up to 48 hours. The reactions were monitored for the disappearance of starting material and heated for the appropriate time.

Example 49: 2-[4-(4-Amino-7-(4-tetrahydropyranyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)phenoxy]-6-(3-imidazol-1-yl)propylaminobenzonitrile from 2-fluoro-6-(3-(imidazol-1-yl)propylamino)-benzonitrile.

Example 50: 2-(4-(4-Amino-7-(4-tetrahydropyranyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)phenoxy]- 6-(2-morpholinoethoxy)benzonitrile, m.p. 110°C (glass), from 2-fluorobenzonitrile.

Example 51: 2-[4-(4-Amino-7-(4-tetrahydropyranyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)phenoxy]-6-(2-(4-pyridyl)ethylamino)benzonitrile, m.p. 120-123°C (glass), from 2-fluoro-6-(2-(4-pyridyl)ethylamino)benzonitrile.

Example 52: 2-[4-(4-Amino-7-(4-tetrahydropyranyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)phenoxy)-6-(3-methoxypropylamino)benzonitrile, m.p. 205-207°C, from 2-fluoro-6-(3-methoxy-propylamino)benzonitrile.

Example 53: 2-[4-(4-Amino-7-(4-tetrahydropyranyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)phenoxy]-5-fluorobenzonitrile, m.p. 216-217°C, from 2,5-difluorobenzonitrile.

Examples 54-101

General Method

Portions of the amines listed in Table 1 (9 molar equivalents with respect to the ester employed, weights ranging from 47.5 mg to 184.5 mg) were weighed into separate vials and methanol (1 ml) was added to each vial. A solution of ethyl 2-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl acetate (1 molar equivalent) in a mixture of methanol and triethylamine (4 ml, ratio of methanol to triethylamine is 23.2:1 v/v. The reaction mixtures were shaken at 60-65° C for 36 hours. The methanol and triethylamine were removed under reduced pressure at 50°C for 3 hours and to each vial was added water (3 ml) followed by dichloromethane (3 ml). The vials were agitated for 15 seconds and then allowed to stand for 18 hours. The mixtures were poured into EMPORE®(10 mm/6 ml) extraction disk cartridges and the dichloromethane phases were collected and evaporated at 50°C for 3 hours. During work-up it was observed that solid had separated out in the vials on standing for 18 hours. Consequently the aqueous layer in each cartridge was forced through with compressed air. Dichloromethane (4 ml) was added to each extraction cartridge. Each filtrate was evaporated under reduced pressure at 50°C for 3 hours. The desired products were either found in the original dichloromethane extract, in which case they are indicated as being present in the liquid, or were found in the insoluble solid on reworking and are referred to as being found in the solid. Certain products were found in both phases. These phases are indicated in Table 1.

Each sample was analysed by LCMS and in each case the target ion was found. The retention time for each product is given in Table 1. The conditions used are given below.

Column:	5 µm hypersil BDS c18 (100 x 2.1 mm).
Mobile Phase:	0.1M NH40Ac [pH 4.55] : MeCN (gradient - see below).
Conditions:	10-100% MeCN in 8 minutes.
(Gradient)	100% MeCN for 1 minute.
	100-10% MeCN in 2 minutes.
	(Total analysis run time 11 minutes.
Flow Rate:	1 ml/minute (no split in MS).
Wavelength Range:	250-320 nm
Injection Volume:	20 µl.
MS	
Method:	APCI11H.
Ionisation	APcI +ve/-ve.
Mass Range:	100-700 m/z.
Cone voltage:	20.

In a similar manner to Examples 54-101, the amines listed in Table 2 were reacted, respectively, with ethyl 2-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]-pyrimidin-7-yl]propionate to give the products listed in Examples 102-146 respectively. The work-up and the analysis conditions were identical to those used for Examples 54-101. In each case the target ion was found by LCMS.

TABLE 1

Amine Number	Name	Phase	RT / min Product
54	Ethanolamine	Solid	3.44
55	dl-2-Amino-1-propanol	Solid	3.58
56	1-Amino-2-propanol	Solid	3.56
57	2-Methoxyethylamine	Liquid	3.78
58	3-Amino-1-propanol	Both	3.50
59	(S)-(+)-2-Amino-1-propanol	Both	3.58
60	(R)-(-)-1-Amino-2-propanol	Both	3.56
61	N,N-Dimethylethylenediamine	Both	3.31
62	(+/-)-2-Amino-1-butanol	Solid	3.77
63	1-Amino-2-butanol	Both	3.77
64	3-Amino-1,2-propanediol	Solid	3.32
65	(S)-3-Amino-1,2-propanediol	Solid	3.32
66	(R)-3-Amino-1,2-propanediol	Solid	3.32
67	1-Methylpiperazine	Both	3.28
68	N,N-Dimethyl-1,3-propanediamine	Liquid	3.29
69	N2,N2-Dimethyl-1,2-propanediamine	Both	3.37
70	1-Dimethylamino-2-propylamine	Liquid	3.44
71	dl-2-Amino-3-methyl-1-butanol	Solid	3.98
72	N-{2-[1-(N-Morpholine)-1-oxo]ethyl}piperazine	Liquid	3.56
73	2-Amino-2-methyl-1-propanol	Both	3.86
74	2-Amino-2-methyl-1,3-propanediol	Both	3.49
45	2-(2-Aminoethoxy)ethanol	Both	3.47
76	1-(2-Aminoethyl)pyrrolidine	Liquid	3.40
77	N-Methylhomopiperazine	Liquid	3.32

Amine Number	Name	Phase	RT / min Product
78	1-Amino-1-cyclopentane methanol	Both	4.16
79	2-Aminocyclohexanol	Solid	3.98
80	N,N-Diethylethylenediamine	Liquid	3.44
81	N-(3-Hydroxypropyl)ethylenediamine	Both	3.24
82	2-((2-Aminoethyl)thio)ethanol	Both	3.69
83	2-(2-Aminoethyl)pyridine	Liquid	3.89
84	3-(2-Aminoethyl)pyridine	Liquid	3.79
85	N-(3-Aminopropyl)imidazole	Liquid	3.37
86	1-[2-(N-Morpholine)ethyl]piperazine	Liquid	3.39
87	2-(Aminomethyl)-1-ethylpyrrolidine	Both	3.48
88	1-(2-Aminoethyl)piperidine	Both	3.49
89	1-Pyrrolidinepropanamine	Liquid	3.37
90	(R)-(+)-2-Aminomethyl-1-ethylpyrrolidine	Both	3.48
91	4-(2-Aminoethyl)morpholine	Both	3.39
92	3-Diethylaminopropylamine	Both	3.43
93	N,N-Dimethylneopentanediamine	Both	3.47
94	Ethyl 1-piperazinecarboxylate	Liquid	4.34
95	2-(Aminomethyl)-2-ethyl-1,3-propanediol	Both	3.69
96	1-(3-Aminopropyl)-2-pyrrolidinone	Both	3.68
97	1-Piperidinepropylamine	Liquid	3.46
98	4-(3-Aminopropyl)morpholine	Liquid	3.33
99	N,N-Diisopropylethylenediamine	Liquid	3.59
100	N,N-Bis(3-aminopropyl)methylamine	Liquid	3.03
101	Tris(2-aminoethyl)amine	Liquid	3.01

The compounds prepared are given below.

Example 54: 4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl-N-(2-hydroxyethyl)acetamide

Example 55: 4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl-N-(1-hydroxyprop-2-yl)acetamide

Example 56: 4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl-N-(2-hydroxypropyl)acetamide

Example 57: 4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl-N-(2-methoxyethyl)acetamide

Example 58: 4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl-N-(3-hydroxypropyl)acetamide

Example 59: (S)-4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl-N-(1-hydroxyprop-2-yl)acetamide

Example 60: (R)-4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl-N-(2-hydroxypropyl)acetamide

Example 61: 4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl-N-[2-(N,N-dimethylamino)ethyl]acetamide

Example 62: 4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl-N-(1-hydroxybut-2-yl)acetamide

Example 63: 4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl-N-(2-hydroxybutyl)acetamide

Example 64: 4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl-N-(2,3-dihydroxypropyl)acetamide

Example 65: (S)-4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl-N-(2,3-dihydroxypropyl)acetamide

Example 66: (R)-4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl-N-(2,3-dihydroxypropyl)acetamide

Example 67: 4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl-N,N-(3-azapentamethylene)acetamide

Example 68: 4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl-N-[3-(N,N-dimethylamino)propyl]acetamide

Example 69: 4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl-N-[1-(N,N-dimethylamino)prop-2-yl]acetamide

Example 70: 4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl-N-[2-(N,N-dimethylamino)propyl]acetamide

Example 71: 4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl-N-(1-hydroxy-3-methylbut-2-yl)acetamide

Example 72: 7-{2-[4-(2-Morpholino-2-oxoethyl)piperazin-1-yl]-2-oxo-ethyl}-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine

Example 73: 4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl-N-(1-hydroxy-3-methylprop-2-yl)acetamide

Example 74: 4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl-N-(1,3-dihydroxy-2-methylprop-2-yl)acetamide

Example 75: 4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl-N-[2-(2-hydroxyethoxy)ethyl]acetamide

Example 76: 4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl-N-[2-(pyrrolidin-1-yl)ethyl]acetamide

Example 77: 4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl-N,N-(3-azahexamethylene)acetamide

Example 78: 4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl-N-[1-(hydroxymethyl)cyclopentyl]acetamide

Example 79: 4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl-N-(2-hydroxycyclohexyl)acetamide

Example 80: 4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl-N-[2-(N,N-diethylamino)ethyl]acetamide

Example 81: 4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl-N-[2-(3-hydroxypropylamino)ethyl]acetamide

Example 82: 4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl-N-[2-(2-hydroxyethylthio)ethyl]acetamide

Example 83: 4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl-N-[2-(pyrid-2-yl)ethyl]acetamide

Example 84: 4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl-N-[2-(pyrid-3-yl)ethyl]acetamide

Example 85: 4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl-N-[3-(imidazol-1-yl)propyl]acetamide

Example 86: 7-{2-[4-(2-Morpholinoethyl)piperazin-1-yl]-2-oxo-ethyl}-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine

Example 87: 4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl-N-(N-ethylpyrrolidin-2-yl)methylacetamide

Example 88: 4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl-N-(2-piperidinoethyl)acetamide

Example 89: 4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl-N-[3-(pyrrolidin-1-yl)propyl]acetamide

Example 90: (R)-4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl-N-(N-ethylpyrrolidin-2-yl)methylacetamide

Example 91: 4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl-N-(2-morpholinoethyl)acetamide

Example 92: 4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl-N-[3-(N,N-diethylamino)propyl]acetamide

Example 93: 4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl-N-[3-(N,N-dimethylamino)-2,2-dimethylpropyl]acetamide

Example 94: 7-[2-(4-Ethoxycarbonylpiperazin-1-yl)-2-oxoethyl]-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine

Example 95: 4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl-N-[2,2-bis(hydroxymethyl)butyl]acetamide

Example 96: 4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl-N-[3-(2-pyrrolidinon-1-yl)propyl]acetamide

Example 97: 4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl-N-(3-piperidinopropyl)acetamide

Example 98: 4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl-N-(3-morpholinopropyl)acetamide

Example 99: 4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl-N-(3-hydroxy-1-methylprop-2-yl)acetamide

Example 100: 4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl-N-[3-(N-3-aminopropyl,N-methyl)aminopropyl]acetamide

Example 101: 4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl-N-[N-bis(2-aminoethyl)aminoethyl]acetamide

TABLE 2

Amine Number	Name	Phase	RT / min Product
102	Ethanolamine	Both	3.68
103	dl-2-Amino-1-propanol	Both	3.78
104	1-Amino-2-propanol	Both	3.81
105	2-Methoxyethylamine	Both	4.08
106	3-Amino-1-propanol	Both	3.73
107	(S)-(+)-2-Amino-1-propanol	Both	3.78
108	(R)-(-)-1-Amino-2-propanol	Liquid	3.81
109	N,N-Dimethylethylenediamine	Liquid	3.50
110	(+/-)-2-Amino-1-butanol	Both	3.96
111	1-Amino-2-butanol	Both	4.06
112	3-Amino-1,2-propanediol	Both	3.52
113	(S)-3-Amino-1,2-propanediol	Both	3.53
114	(R)-3-Amino-1,2-propanediol	Both	3.53
115	N,N-Dimethyl-1,3-propanediamine	Liquid	3.47
116	N2,N2-Dimethyl-1,2-propanediamine	Liquid	3.57
117	1-Dimethylamino-2-propylamine	Liquid	3.67
118	Dl-2-Amino-3-methyl-1-butanol	Both	4.15
119	2-(2-Aminoethylamino)ethanol	Liquid	3.40
120	2-Amino-2-methyl-1-propanol	Both	4.17
121	2-Amino-2-methyl-1,3-propanediol	Both	3.76
122	2-(2-Aminoethoxy)ethanol	Liquid	3.71
123	1-(2-Aminoethyl)pyrrolidine	Both	3.61
124	1-Amino-1-cyclopentane methanol	Both	4.48
125	2-Aminocyclohexanol	Both	4.19
126	N,N-Diethylethylenediamine	Both	3.68
127	N-(3-Hydroxypropyl)ethylenediamine	Both	3.42

Amine Number	Name	Phase	RT / min Product
128	2-((2-Aminoethyl)thio)ethanol	Liquid	3.94
129	2-(2-Aminoethyl)pyridine	Liquid	4.13
130	3-(2-Aminoethyl)pyridine	Both	4.05
131	N-(3-Aminopropyl)imidazole	Liquid	3.58
132	2-(2-Aminoethylamino)-1-methylpyrrolidine	Both	3.56
133	2-(Aminomethyl)-1-ethylpyrrolidine	Both	3.70
134	1-(2-Aminoethyl)piperidine	Both	3.70
135	1-Pyrrolidinepropanamine	Both	3.60
136	(R)-(+)-2-Aminomethyl-1-ethylpyrrolidine	Both	3.70
137	4-(2-Aminoethyl)morpholine	Both	3.63
138	3-Diethylaminopropylamine	Both	3.64
139	N,N-Dimethylneopentanediamine	Both	3.68
140	2-(Aminomethyl)-2-ethyl-1,3-propanediol	Both	3.94
141	1-(3-Aminopropyl)-2-pyrrolidinone	Liquid	3.91
142	1-Piperidinepropylamine	Both	3.70
143	4-(3-Aminopropyl)morpholine	Liquid	3.53
144	N,N-Diisopropylethylenediamine	Liquid	3.86
145	N,N-Bis(3-aminopropyl)methylamine	Solid	3.21
146	Tris(2-aminoethyl)amine	Both	3.17

Example 102: 1-[4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]-N-(2-hydroxyethyl)propanamide

Example 103: 1-[4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]-N-(1-hydroxyprop-2-yl)propanamide

Example 104: 1-[4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]-N-(2-hydroxypropyl)propanamide

Example 105: 1-[4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]-N-(2-methoxyethyl)propanamide

Example 106: 1-[4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]-N-(3-hydroxypropyl)propanamide

Example 107: (S)-1-[4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]-N-(1-hydroxyprop-2-yl)propanamide

Example 108: (R)-1-[4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]-N-(2-hydroxypropyl)propanamide

Example 109: 1-[4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]-N-[2-(N,N-dimethylamino)ethyl]propanamide

Example 110: 1-[4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]-N-(1-hydroxybut-2-yl)propanamide

Example 111: 1-[4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]-N-(2-hydroxybutyl)propanamide

Example 112: 1-[4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]-N-(2,3-dihydroxypropyl)propanamide

Example 113: (S)-1-[4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]-N-(2,3-dihydroxypropyl)propanamide

Example 114: (R)-1-[4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]-N-(2,3-dihydroxypropyl)propanamide

Example 115: 1-[4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]-N-[3-(N,N-dimethylamino)propyl]propanamide

Example 116: 1-[4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]-N-[2-(N,N-dimethylamino)propyl]propanamide

Example 117: 1-[4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]-N-[1-(N,N-dimethylamino)prop-2-yl]propanamide

Example 118: 1-[4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]-N-(1-hydroxy-3-methylbut-2-yl)propanamide

Example 119: 1-[4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]-N-[2-(2-hydroxyethylamino)ethyl]propanamide

Example 120: 1-[4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]-N-(1-hydroxy-2-methylprop-2-yl)propanamide

Example 121: 1-[4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]-N-(1,3-dihydroxy-2-methylprop-2-yl)propanamide

Example 122: 1-[4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]-N-[2-(2-hydroxyethoxy)ethyl]propanamide

Example 123: 1-[4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]-N-[2-(pyrrolidin-1-yl)ethyl]propanamide

Example 124: 1-[4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]-N-[1-(hydroxymethyl)cyclopentyl]propanamide

Example 125: 1-[4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]-N-(2-hydroxycyclohexyl)propanamide

Example 126: 1-[4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]-N-[2-(N,N-diethylamino)ethyl]propanamide

Example 127: 1-[4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]-N-[2-(3-hydroxypropylamino)ethyl]propanamide

Example 128: 1-[4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]-N-[2-(2-hydroxyethylthio)ethyl]propanamide

Example 129: 1-[4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]-N-[2-(pyrid-2-yl)ethyl]propanamide

Example 130: 1-[4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]-N-[2-(pyrid-3-yl)ethyl]propanamide

Example 131: 1-[4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]-N-[3-(imidazol-1-yl)propyl]propanamide

Example 132: 1-[4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]-N-[2-(N-methylpyrrolidin-2-yl)ethyl]propanamide

Example 133: 1-[4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]-N-[(N-ethylpyrrolidin-2-yl)methyl]propanamide

Example 134: 1-[4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]-N-(2-piperidinoethyl)propanamide

Example 135: 1-[4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]-N-[3-(pyrrolidin-1-yl)propyl]propanamide

Example 136: (R)-1-[4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]-N-[(N-ethylpyrrolidin-2-yl)methyl]propanamide

Example 137: 1-[4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]-N-(2-morpholinoethyl)propanamide

Example 138: 1-[4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]-N-[3-(N,N-diethylamino)propyl]propanamide

Example 139: 1-[4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]-N-[3-(N,N-dimethylamino)-2,2-dimethylpropyl]propanamide

Example 140: 1-[4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]-N-[2,2-bis(hydroxymethyl)butyl]propanamide

Example 141: 1-[4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]-N-[3-(2-pyrrolidinon-1-yl)propyl]propanamide

Example 142: 1-[4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]-N-(3-piperidinopropyl)propanamide

Example 143: 1-[4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]-N-(3-morpholinopropyl)propanamide

Example 144: 1-[4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]-N-[2-(N,N-di-isopropylamino)ethyl]propanamide

Example 145: 1-[Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]-N-[3-(N-3-aminopropyl,N-methyl)aminopropyl]propanamide

Example 146: 1-[4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]-N-[N-bis(2-aminoethyl)aminoethyl]propanamide

Example 147: 2-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]--butyrolactone

a) 4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidine (1.0 g) was added to a mixture of sodium hydride (0.158 g of a 60% dispersion in mineral oil) in dimethyl formamide (70 ml) with stirring under nitrogen at 0°C. The mixture was stirred at 0°C for 1 hour and then α-bromo-γ-butyrolactone (0.60 g) in dimethylformamide (6 ml) was added dropwise with stirring at 0°C. The mixture was stirred at ambient temperature for 18 hours and then quenched with water (100 ml). The mixture was extracted with ethyl acetate. The combined extracts were dried and evaporated to give 2-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]--butyrolactone as an oil which was used directly in b).

b) N,N-Dimethylethylenediamine (5.0 ml) was added to a mixture of the product from a) (1.2 g) and pyridin-2-one (50 mg) in toluene (100 ml). The mixture was heated to 100°C for 2 hours and then evaporated to dryness under reduced pressure. The residue was suspended in ethyl acetate and washed with water. The organic extracts were then extracted with 5M hydrochloric acid (3 x 50 ml) and the acidic extracts were washed with ethyl acetate then basified with 6M sodium hydroxide solution at 0°C and then back extracted with ethyl acetate and then dichloromethane. The combined organic extracts were dried, filtered and evaporated to give an oil which was crystallised from ethyl acetate/ether to give 2-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]-4-hydroxy-N-[2-dimethylamino)ethyl]utyramide, m.p. 178-179°C.

Example 148: Ethyl 2-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]propionate

Sodium hydride (120 mg, of a 60% dispersion in mineral oil) was added to a mixture of 4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidine (906 mg) in dry dimethyformamide (30 ml) and the mixture was stirred under nitrogen for 30 minutes at ambient temperature. A solution of ethyl 2-bromopropionate (543 mg) in dry DMF (10 ml) was added dropwise via a syringe over 10 minutes. The mixture was stirred at ambient temperature for 2 hours and then left for 18 hours. The mixture was evaporated under vacuum and the residue was washed with water to give a solid which was triturated with ether and filtered to give ethyl 2-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]propionate, m.p. 139-140°C.

Example 149: N-(2-dimethylaminoethyl)-2-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)propionamide

A mixture of ethyl 2-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]propionate (425 mg), N,N-dimethylethylenediamine (2 ml) and methanol (20 ml) was boiled under reflux for 18 hours with the exclusion of carbon dioxide. The mixture was cooled and filtered, the filtrate was diluted with water (50 ml) and stirred with ether. The mixture was left standing for 18 hours and the solid which precipitated was collected by filtration, washed with water and then ether and dried to give N-(2-dimethylaminoethyl)-2-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)propionamide, m.p. 163-164°C.

Example 150: Ethyl 2-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetate

A mixture of 4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidine (906 mg), sodium hydride (120 mg, of a 60% dispersion in mineral oil) and dry dimethylformamide (30 ml) was stirred at ambient temperature under nitrogen for 30 minutes. Ethyl bromoacetate (0.5 g) in dimethylformamide (10 ml) was added over 5 minutes at 0-5°C with stirring. The mixture was stirred for 30 minutes at ambient temperature and then allowed to stand for 18 hours. The mixture was evaporated under vacuum and the residue was triturated with water and ether. The solid obtained was collected by filtration, washed with water and then with ether to give ethyl 2-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetate, m.p. 161-161.3°C.

Examples 151-156

General Method

Ethyl 2-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetate (194 mg) was heated at 62°C and stirred with 10 molar equivalents of the appropriate amine as listed below in methanol (12 ml) for 18 hours to give after work up the following compounds:

Example 151

N-[2-hydroxyethyl-1,1-di(hydroxymethyl)]-2-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetamide, m.p. 222-223°C with decomposition, from 2-hydroxyethyl-1,1-di(hydroxymethyl)ethylamine.

Example 152

N-[2-(piperazin-1-yl)ethyl]-2-[4-amino-5-[4-phenoxyphenyl)-7H-pyrrolo[2,3-d]-pyrimidin-7-yl]acetamide, m.p.138-140°C, from 2-(piperazin-1-yl)ethylamine.

Example 153

N-(2-morpholinoethyl)-2-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetamide, m.p. 164-165°C, from 2-morpholinoethylamine.

Example 154

N-[3-(1-imidazol)propyl]-2-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]acetamide, m.p. 170-171°C, from 3-(1-imidazolyl)propylamine.

Example 155

N-(N-ethylpyrrolidin-2-ylmethyl)-2-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]-pyrimidin-7-yl]acetamide, m.p. 122-122.5°C, from 1-(N-ethylpyrrolodin-2-yl)methyl-amine.

Example 156

N-[-2(2-hydroxyethoxy)ethyl]-2-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]-pyrimidin-7-yl]acetamide, m.p. 145-147°C, from 2-(2-hydroxyethoxy)ethylamine.

Example 157: 2-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]propionic acid

A mixture of ethyl 2-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]propionate (201 mg), aqueous potassium hydroxide solution (4 ml of 2M solution) and methanol (20 ml) was boiled under reflux for 1 hour. The mixture was concentrated under reduced pressure to around 5 ml and then diluted with water (30 ml). The mixture was hot filtered and filtrate was cooled and then acidified with dilute acetic acid until no further precipitation occurred. The mixture was heated on a hot plate until the gel which had been obtained became a finely divided solid. The solid was collected by filtration to give 2-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]propionic acid, m.p. 239.5-241°C.

Example 158: Ethyl 4-[4-amido-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]butyrate

A mixture of 5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine (1.5 g) was dissolved in DMF (30 ml) and treated with sodium hydride (0.22 g of a

60% dispersion in mineral oil) and then with ethyl 4-bromobutyrate (1.08 g) in DMF (15 ml) in a similar manner to Example 95 to give ethyl 4-[4-amido-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]butyrate, m.p. 104-104.5°C.

Example 159: ethyl 2-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]carbox-amide

In a similar manner to Example 97, 5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]-pyrimidin-4-yl amine (1.0 g), sodium hydride (1.032 g of a 60% dispersion in mineral oil), 2-bromoacetamide (0.55 g) and dimethylformamide (50 ml) were reacted together to give after work-up a solid which was recrystallised from isopropanol to give ethyl 2-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]carbox-amide, m.p. 232-233°C.

Example 160: 2-[4-amino-5-(4-phenoxyphenyl)pyrrolo[2,3-d]pyrimidin-7-yl]-2-methylpropionamide

4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidine (200 mg) was dissolved in 1,3-dimethyl-3,4,5,6-tetrahydro-2-(1H)-pyrimidinone (1.5 ml) with stirring and sodium hydroxide (0.158 g) was added at ambient temperature and the mixture stirred for 15 minutes. 2-Bromo-2-methylpropanamide (0.5 g) was added and the mixture was stirred vigorously for 18 hours at ambient temperature under a water-free atmosphere, then further 2-bromo-2-methylpropanamide (0.15 g) was added and stirred for a further 24 hours. Water (3 ml) was added to the reaction mixture together with dilute hydrochloric acid (5M) to adjust the pH to 0. The suspension was added to water (60 ml) and the mixture left to stand for 18 hours at ambient temperature. The solid was collected by filtration, washed well with water and dried under high vacuum at 50°C. The solid was purified by preparative HPLC (reverse phase). Appropriate fractions were collected and combined and extracted with dichloromethane. Evaporation of the dichloromethane gave 2-[4-amino-5-(4-phenoxyphenyl)pyrrolo[2,3-d]pyrimidin-7-yl]-2-methylpropionamide, m.p. 227-228°C.

Example 161: 4-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimin-7-yl] N-(2-dimethylaminoethyl)butyramide

A mixture of ethyl 4-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimin-7-yl]butyrate (100 mg) in 30 ml methanol was heated under reflux with 0.6 ml 2-dimethylaminoethylamine for 18 hours. The mixture was evaporated under reduced pressure and the residue was heated with 2-dimethylaminoethylamine (10 ml) on a steam bath for 18 hours. Excess amine was removed under reduced pressure. Water was added to the residue and the mixture filtered to give 4-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimin-7-yl] N-(2-dimethylaminoethyl)butyramide.

Examples 162, 163 and 164 were prepared in a similar manner to Example 108 by reacting the same ester with the appropriate amine listed.

Example 165

4-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimin-7-yl]-N-[3-(1-imidazolyl)propyl]butyramide from 3-(1-imidazolyl)propylamine.

Example 166

4-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimin-7-yl]-N-(2-morpholinoethyl)butyramide from 2-morpholinoethylamine.

Example 167

4-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimin-7-yl]-N-(3-morpholinopropyl)butyramide from 3-morpholinopropylamine.

Preparation of Starting Materials

a) Tert-butylamine (15 ml) was added with stirring to a solution of 2-bromo-4′-phenoxyacetophenone (12.7 g, prepared by bromination of 4′-phenoxyacetophenone according to Tetrahedron Letters, 1993, 34, 3177) in propan-2-ol and the mixture heated at 80°C for 3 hours. The mixture was cooled to 0°C and concentrated hydrochloric acid (10 ml) added. The suspension was stirred at ambient temperature for 18 hours and the solid collected by filtration to give 4′-phenoxy-2-(tert-butylamino)acetophenone hydrochloride (3.75 g), m.p. 210-212°C.

1) 4′-Phenoxy-2-(tert-butylamino)acetophenone hydrochloride (3.75 g) was added in one portion to sodium ethoxide (prepared by dissolving sodium (93 mg) in ethanol (50 ml)) and the mixture was stirred at 40°C for 30 minutes under nitrogen.

2) In a separate flask sodium (331 mg) was dissolved in ethanol (50 ml) and malononitrile (858 mg) was added. The solution was stirred at ambient temperature for 5 minutes and then to this solution was added the solution of 4′-phenoxy-2-(tert-butylamino)acetophenone obtained in part (1) in one portion excluding the precipitated sodium chloride. The resultant mixture was heated at 50°C for 3 hours and then at 80°C for 2 hours. The solvent was removed under reduced pressure and the resultant oil was partitioned between water and ethyl acetate. The organic phase was separated, dried and evaporated to give a black solid. This solid was dissolved in hot ethanol and triturated with water, filtered and dried to give 2-amino-3-cyano-4-(4-phenoxyphenyl)-1-(tert-butyl)pyrrole.

b) A mixture of 2-amino-3-cyano-4-(4-phenoxyphenyl)-1-(tert-butyl)pyrrole (1.9 g), formamide (30 ml) and 4-dimethylaminopyridine (10 mg) was heated at 180°C for 6 hours. The mixture was cooled to ambient temperature and water was added to precipitate a dark solid. The solid was collected by filtration, washed with water, then boiled up in ethanol and the insoluble material collected by hot filtration and dried. The solid was purified by preparative HPLC on a silica column using dichloromethane/propan-2-ol/ethanol, 98:1:1 as the mobile phase to give 7-tert-butyl-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine (4-amino-5-(4-phenoxyphenyl)-7-(tert-butyl)pyrrolo[2,3-d]pyrimidine), m.p. 157-158°C. 1H NMR (d6 DMSO) δ 8.15 (1H,s), 7.50-7.35 (4H,m), 7.30 (1H,s), 7.15 (1H,t), 7.10 (4H,m), 6.05 (2H,brs), 1.75 (9H,s).

c) A mixture of 4-amino-5-(4-phenoxyphenyl)-7-(tert-butyl)pyrrolo[2,3-d]-pyrimidine (5.8 g), glacial acetic acid (55 ml) and hydrobromic acid (55 ml of a 48% solution) was boiled under reflux for 18 hours under nitrogen. The mixture was allowed to cool and a solid was collected by filtration. This solid was washed with methanol and then with ether to give 4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]-pyrimidine hydrobromide, m.p. 288-292°C. The hydrobromide salt was converted into the free base by warming with dilute sodium hydroxide solution (100 ml of 5% w/v solution) and ethanol (60 ml) with stirring and removing the ethanol by distillation. The mixture was cooled and the solid was collected by filtration and washed well with water to give 5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine, m.p. 272°C.

Example 168: 7-cyclopentanesulphonyl-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine

Sodium hydride (0.132 g of a 60% dispersion in mineral oil) was added to a solution of 5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine (1.0 g) in dry dimethylformamide (30 ml) with stirring under nitrogen. The mixture was stirred for 30 minutes and then cyclopentanesulphonyl chloride (0.558 g, prepared as described in J.O.C.1952, 17, 1529-1533) in dry dimethylformamide (5 ml) was added dropwise. The mixture was allowed to stand for 72 hours and then evaporated under vacuum. The residue was triturated with water and filtered to give a solid which was washed well with water, then stirred with ethyl acetate then filtered. The filtrate was purified by flash column chromatography on silica using ethyl acetate as the mobile phase. Appropriate fractions were collected and evaporated to give 7-cyclopentanesulphonyl-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine, m.p. 188-188.5°C.

Example 169: 5-(4-phenoxyphenyl)-7-(8-phthalimidooctyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine

Sodium hydride (120 mg of a 60% dispersion in mineral oil) was added to a solution of 5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine (906 mg) in dry dimethylformamide (30 ml) with stirring under nitrogen. The mixture was stirred for 30 minutes under nitrogen and then N-(8-bromooctyl)phthalimide (1.4 g) in dimethyl-formamide (5 ml) was added. The mixture was stirred at ambient temperature for 18 hours under nitrogen and then partitioned between water and ethyl acetate. The ethyl acetate layer was separated and purified by flash column chromatography using ethyl acetate as the mobile phase to give 5-(4-phenoxyphenyl)-7-(8-phthalimidooctyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine, m.p. 85-86°C.

Example 170: 7-(8-aminooctyl)-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine dihydrochloride dihydrate

A mixture of 5-(4-phenoxyphenyl)-7-(8-phthalimidooctyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine (1.0 g), hydrazine hydrate (1.0 ml) and ethanol (40 ml) was boiled under reflux for 2 hours with the exclusion of carbon dioxide. The mixture was cooled for 18 hours and a solid which precipitated was collected by filtration and discarded. The filtrate was evaporated under reduced pressure and the residue was dissolved in ethyl acetate, dried and then treated with a solution of concentrated hydrochloric acid in isopropanol dropwise until no further precipitation occurred. The mixture was left to stand overnight, then supernatent liquid was decanted off and the semi-solid residue was triturated with ethyl acetate to give 7-(8-aminooctyl)-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine dihydrochloride dihydrate, m.p 120°C.

Example 171: N-{2-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]ethyl}phthalimide

In a similar manner to Example 468, but with additional heating at 90°C for 3 hours, 5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine was reacted with 2-bromoethylphthalimide to give N-{2-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]ethyl}phthalimide, m.p. 111-112°C.

Example 172: 7-(2-aminoethyl)-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine hydrochloride

In a similar manner to Example 469, the product from the previous example was treated with hydrazine hydrate to give 7-(2-aminoethyl)-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine hydrochloride, m.p. 284-285°C.

Example 173: 7-isobutyryl-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine

Isobutyryl chloride (1.8 g) was added dropwise to a mixture of 5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine (4.32 g), dry dimethylformamide (200 ml) and dry pyridine (2 ml) with stirring under nitrogen at 20°C. The mixture was stirred at ambient temperature for 1 hour and evaporated under vacuum. The residue was partitioned between water and ethyl acetate. The ethyl acetate was separated, dried and evaporated and the residue obtained was recrystallised from toluene to give 7-isobutyryl-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine, m.p. 160.5-161°C.

Example 174: 5-(4-phenoxyphenyl)-7-(1,4-dioxaspiro[4,5]decan-8-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine

Sodium hydride (0.26 g of a 60% dispersion in mineral oil) was added to a mixture of 5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine (1.94 g) in dimethylformamide (50 ml) at ambient temperature with stirring. The mixture was stirred until the evolution of hydrogen ceased and then 8-tosyloxy-1,4-dioxaspiro[4,5] decane (2.0 g, prepared as described in US 4,360,531 from 1,4-dioxaspiro[4,5]decan-8-one, (which was prepared according to J. Med. Chem. 1992, 2246)) was added. The mixture was heated at 120°C for 5 hours under nitrogen, cooled to ambient temperature, quenched with water and extracted with ethyl acetate to give a residue which was purified by flash column chromatography on silica using ethyl acetate followed by ethyl acetate containing increasing amounts of methanol up to 6% to give 5-(4-phenoxyphenyl)-7-(1,4-dioxaspiro[4,5]decan-8-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine, m.p. 193-194°C..

Example 175: 4-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]cyclohexanone

The product from the previous example (500 mg), acetone (20 ml) and 3M hydrochloric acid (10 ml) was stirred under nitrogen at ambient temperature for 20 minutes. The mixture was then heated at 60°C for 1 hour and then the acetone was removed under reduced pressure. The residue was basified with aqueous 5M sodium hydroxide solution and then extracted with ethyl acetate to give a solid which was triturated with diethyl ether and filtered to give 4-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]cyclohexanone, m.p. 252-254°C.

Example 176 and 177: cis-5-(4-phenoxyphenyl)-7-(4-morpholinocyclohex-1-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine, and trans-5-(4-phenoxyphenyl)-7-(4-morpholinocyclohex-1-yl)-7H-pyrrolo[2,3-d] pyrimidin-4-ylamine

Sodium triacetoxyborohydride (42 mg) and glacial acetic acid (18 mg) were added to the product from the previous example (120 mg) and morpholine (31 mg) in 1,2-dichloroethane. The mixture was stirred at 40°C for 2 hours and then a further portion of morpholine (0.15 g) and sodium triacetoxyborohydride (0.21 g) were added. The mixture was stirred at ambient temperature for 20 hours then quenched with saturated aqueous bicarbonate solution. The mixture was filtered through an EMPORE® cartridge and the filtrate was extracted with 3M hydrochloric acid. The acidic extracts were basified with 5M sodium hydroxide solution and extracted with dichloromethane to give a residue which was purified by chromatography on silica to give cis-5-(4-phenoxyphenyl)-7-(4-morpholinocyclohex-1-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine, and trans-5-(4-phenoxyphenyl)-7-(4-morpholinocyclohex-1-yl)-7H-pyrrolo[2,3-d] pyrimidin-4-ylamine.

Examples 178 and 179: cis-7-(4-N-ethoxycarbonyl)piperazin-1-ylcyclohexyl)-5-(4-phenoxy-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine and trans-7-(4-N-ethoxycarbonyl)-piperazin-1-ylcyclohexyl)-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine

In a similar manner to the previous Example, 4-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]cyclohexanone (0.4 g from 1.0 g of 40% pure material) and 1-ethoxycarbonyl-piperidine (158 mg) were reacted together in the presence of sodium triacetoxyborohydride (296 mg) in dichloromethane (15 ml) containing glacial acetic acid (60 mg) to give after workup and chromatography cis-7-(4-N-ethoxycarbonyl)piperazin-1-ylcyclohexyl)-5-(4-phenoxy-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine and trans-7-(4-N-ethoxycarbonyl)-piperazin-1-ylcyclohexyl)-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine.

Example 180: 2-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]pyridine-3-carbonitrile

5-(4-Phenoxyphenyl)-7H-pyrrolo[2,3-d]-pyrimidin-4-ylamine (906 mg) was reacted with 2-chloronicotinonitrile (510 mg) in the presence of sodium hydride (150 mg) in dimethylformamide (30 ml) at 100°C for 5 hours to give 2-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]pyridine-3-carbonitrile, m.p. 242-242.5°C, after workup.

Example 181: 7-[3-(aminomethyl)pyrid-2-yl]-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]-pyrimidin-4-ylamine dimaleate

The product from the previous example (468 mg), ethanol saturated with ammonia (200 ml) and Raney® nickel (2 ml) was shaken under hydrogen at a pressure of 26 bar at 80°C for 6 hours and then left standing at ambient temperature for 68 hours. The mixture was filtered and the residue was washed well with ethanol. The filtrate was evaporated under reduced pressure and the residue was taken up in ethyl acetate and filtered. Maleic acid (135 mg) dissolved in ethyl acetate (20 ml) was added in portions to the filtrate until no further precipitation occurred. The mixture was warmed and decanted from a small residual amount of gum. The gum was further heated with ethyl acetate and decanted. The combined ethyl acetate extracts were cooled and the solid which precipitated was collected by filtration to give 7-[3-(aminomethyl)pyrid-2-yl]-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]-pyrimidin-4-ylamine dimaleate, m.p. 131-134°C.

Example 182: 3-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]-8-methyl-8-azabicyclo[3.2.1]octane

Sodium hydride (168 mg, of a 60% dispersion in mineral oil) was added to a mixture of 5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine (770 mg, in dimethylformamide (30 ml). 3-Mesyloxy-8-methyl-8-azabicyclo[3.2.1]octane (900 mg, prepared as described in J.A.C.S. 1958, 80, 4679) in dimethylformamide (10 ml) was added under nitrogen with stirring. The mixture was warmed at 75°C for 5 hours (and left standing at ambient temperature for 7 days). The solvent was removed under reduced pressure. Water was added to the residue and the mixture was extracted with ethyl acetate to give a residue which was purified by flash column chromatography on silica using ethyl acetate/methanol (50:50) as the mobile phase to remove starting material and then a mixture of ethyl acetate/methanol/triethylamine (5:5:1) as the mobile phase to elute the product. Appropriate fractions were combined and evaporated to give a solid which was triturated with ether and filtered to give 3-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]-8-methyl-8-azabicyclo[3.2.1]octane, m.p. 238-250°C.

Examples 183 and 184: cis-7-(N-methylhomopiperazin-1-ylcyclohexyl)-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]prymidin-4-ylamine and trans 7-(N-methylhomo-piperazin-1-ylcyclohexyl)-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]prymidin-4-

ylamine

In a similar manner to Examples 176 and 177, 4-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]cyclohexanone (0.4 g from 1.0 g of a 40% pure material), N-methylhomopiperazine (114 mg), sodium triacetoxyborohydride (296 mg), glacial acetic acid (60 mg) and 1,2-dichloroethane (15 ml) were reacted together. After filtration, the filtrate was evaporated and the residue was purified by chromatography on silica to give cis-7-(N-methylhomopiperazin-1-ylcyclohexyl)-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]prymidin-4-ylamine and trans 7-(N-methylhomo-piperazin-1-ylcyclohexyl)-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]prymidin-4-ylamine.

Examples 185 and 186: cis 7-(N-methylpiperazin-1-ylcyclohexyl)-5-(4-phenoxyphenyl)-7-pyrrolo[2,3-d]prymidin-4-ylamine and trans 7-(N-methylpiperazin-1-ylcyclohexyl)-5-(4-phenoxy-phenyl)-7-pyrrolo[2,3-d]prymidin-4-ylamine

In a similar manner to the previous Example, N-methylpiperazine (100 mg) was reacted with the same amounts of cyclohexanone derivative and other reagents to give cis 7-(N-methylpiperazin-1-ylcyclohexyl)-5-(4-phenoxyphenyl)-7-pyrrolo[2,3-d]prymidin-4-ylamine and trans 7-(N-methylpiperazin-1-ylcyclohexyl)-5-(4-phenoxy-phenyl)-7-pyrrolo[2,3-d]prymidin-4-ylamine.

Example 187: 3-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]-cyclopentan-1-one

A mixture of 3-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]-cyclopentan-1-ol (100 mg), activated manganese dioxide (500 mg) and dichloromethane (100 ml) was stirred at ambient temperature for 18 hours to give, after filtration, a solution of 3-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]-cyclopentan-1-one in dichloromethane which was used in the next Example.

Example 188: cis-7-(3-morpholinocyclopent-1-yl)-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine and trans-7-(3-morpholinocyclopent-1-yl)-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]-pyrimidin-4-ylamine

Morpholine (45 mg) was added to the solution obtained in the previous Example followed by sodium triacetoxyborohydride (151 mg) and glacial acetic acid (47 mg). The mixture was stirred at ambient temperature under nitrogen for 18 hours during which time the dichloromethane evaporated. Tetrahydrofuran (100 ml) was added and the mixture was stirred for a further 8 hours. The mixture was worked up to give cis-7-(3-morpholinocyclopent-1-yl)-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine and trans-7-(3-morpholinocyclopent-1-yl)-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]-pyrimidin-4-ylamine.

Example 189: 3-(4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)cyclopentyl N-(2-morpholinoethyl)-carbamate hydrochloride

a) To a solution of 3-(4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)cyclopentanol (20 mg) in dichloromethane (1 ml) at 0°C was added N-methylmorpholine (7 ml) and the mixture stirred for 20 minutes. The cooling bath was removed and 4-nitrophenylchloroformate (12.5 mg) was added and the resulting mixture stirred overnight at ambient temperature. The mixture was diluted with dichloromethane, washed with water, saturated aqueous sodium bicarbonate solution and brine. The organic solution was dried over magnesium sulphate and evaporated to give crude product.

b) The crude product from a) in dichloromethane (2 ml) was added to 2-morpholinoethylamine (0.2 ml) and the mixture stirred overnight at ambient temperature. The mixture was diluted with ethyl acetate and washed with water and brine. The organics were dried, filtered and evaporated to give a crude product which was purified by preparative HPLC to give 3-(4-amino-5-(4-phenoxyphenyl)-7H- pyrrolo[2,3-d]pyrimidin-7-yl)cyclopentyl N-(2-morpholinoethyl)carbamate.

c) The product from b) was dissolved in ethyl acetate (2 ml) and hydrogen chloride gas was bubbled through the solution for 2 minutes. A precipitate formed and stirring was continued for a further 10 minutes. The solvent was evaporated and water added to dissolve the solid. Lyophilisation gave 3-(4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)cyclopentyl N-(2-morpholinoethyl)-carbamate hydrochloride as a solid.

Example 190: 3-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]cyclopentyl 2-aminoacetate hydrochloride

a) 3-[4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]cyclopentanol (50 mg, 0.129 mmol) and N-tert-butoxycarbonyl glycine (34 mg, 0.194 mmol) was mixed in N,N-dimethylformamide (1 ml). 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (31 mg, 0.155 mmol) and 4-dimethylamino pyridine (16 mg, 0.129 mmol) was added. The resulting mixture was stirred under nitrogen at ambient temperature for 24 hours. The reaction mixture was poured into ice water and extracted with ethyl acetate. The organic extracts were washed with brine, dried (MgSO4), filtered and evaporated. The solid was purified by flash column chromatography on silica using ethyl acetate as the mobile phase to give 3-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]cyclopentyl 2-[(tert-butoxycarbonyl)amino]acetate. The structure was confirmed by ^{1}H NMR.

b) 3-[4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]cyclopentyl 2-[(tert-butoxycarbonyl)amino]acetate (39 mg, 0.072 mmol) was disolved in ethyl ecetate (2.5 ml). Hydrogen chloride gas was passed through for 1 minute. The flask was capped and the solution stirred for additional 30 minutes. Diethyl ether was added and precipitate formed. The solid was collected by filtration to give 3-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]cyclopentyl 2-aminoacetate hydrochloride. The structure was confirmed by ^{1}H

NMR and LC/MS (MH^+ = 444).

Example 191: 3-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]cyclopentyl (2S)-2-amino-3-methylbutanoate hydrochloride

a) (2S)-1-[(tert-Butoxycarbonyl)amino]-2-methylbutanoic 2,5-dioxo-2,5-dihydro-1H-1-pyrrolecarboxylic anhydride (114 mg, 0.362 mmol) was added to a solution of 3-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]cyclopentanol (66 mg, 0.171 mmol) in dichloromethane (1 ml). The resulting mixture was stirred under nitrogen at ambient temperature for 24 hours. The reaction mixture was diluted with ethyl acetate and washed, dried ($MgSO_4$), filtered and evaporated. The solid was purified by flash column chromatography on silica using ethyl acetate as the mobile phase to give 3-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]cyclopentyl (2S)-2-[(tert-butoxycarbonyl)amino]-3-methylbutanoate. The structure was confirmed by ^1H NMR and LC/MS (MH^+ = 586).

b) 3-[4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]cyclopentyl (2S)-2-[(tert-butoxycarbonyl)amino]-3-methylbutanoate (35 mg, 0.060 mmol) was dissolved in ethyl acetate (2.5 ml). Hydrogen chloride gas was passed through for 5 minutes. The flask was capped and the solution stirred for additional 30 minutes. Diethyl ether was added and precipitate formed. The solid was collected by filtration to give 3-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]cyclopentyl (2S)-2-amino-3-methylbutanoate hydrochloride. The structure was confirmed by ^1H NMR and LC/MS (MH^+ = 486).

Example 192: 3-(4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)cyclopentyl N-(2-morpholinoethyl)carbamate hydrochloride

a) N-Methylmorpholine (0.007 ml, 0.062 mmol) was added dropwise to solution of 4-nitrophenyl chloroformate (12.5 mg, 0.062 mmol) in dichloromethane (1 ml) with stirring under nitrogen at 0°C. After 20 minutes, the ice-water bath was removed and the mixture was allowed to warm up to ambient temperature. 3-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]cyclopentanol (20 mg, 0.052 mmol) was added to the mixture and the resulting solution was stirred for 24 hours. The reaction mixture was diluted with dichloromethane and washed with water, saturated sodium bicarbonate, and brine. The organic layer was dried ($MgSO_4$), filtered and evaporated to give 3-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]cyclopentyl (4-nitrophenyl) carbonate. The structure was confirmed by ^1H NMR.

b) 3-[4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]cyclopentyl (4-nitrophenyl) carbonate (0.052 mmol) in dichloromethane (1 ml) was added to 2-morpholinoethylamine (0.2 ml). The resulting mixture was stirred under nitrogen at ambient temperature for 24 hours. The reaction mixture was diluted with ethyl acetate and washed, dried ($MgSO_4$), filtered and evaporated. The solid was purified by preparative HPLC to give 3-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]cyclopentyl N-(2-morpholinoethyl)carbamate. The structure was confirmed by ^1H NMR and LC/MS ($MH^+ = 543$).

c) 3-[4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]cyclopentyl N-(2-morpholinoethyl)carbamate (10 mg, 0.018 mmol) was dissolved in ethyl acetate (2.5 ml). Hydrogen chloride gas was passed through for 2 minutes, and a precipitate formed. The flask was capped and the solution stirred for additional 10 minutes. The solid was collected by filtration to give 3-(4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)cyclopentyl N-(2-

morpholinoethyl)carbamate hydrochloride. The structure was confirmed by ^1H NMR and LC/MS (MH^+ = 543).

Preparation of Starting Materials

a) Tert-butylamine (15 ml) was added with stirring to a solution of 2-bromo-4′-phenoxyacetophenone (12.7 g, prepared by bromination of 4′-phenoxyacetophenone according to Tetrahedron Letters, 1993, 34, 3177) in propan-2-ol and the mixture heated at 80°C for 3 hours. The mixture was cooled to 0°C and concentrated hydrochloric acid (10 ml) added. The suspension was stirred at ambient temperature for 18 hours and the solid collected by filtration to give 4′-phenoxy-2-(tert-butylamino)acetophenone hydrochloride (3.75 g), m.p. 210-212°C.

b) (1) 4′-Phenoxy-2-(tert-butylamino)acetophenone hydrochloride (3.75 g) was added in one portion to sodium ethoxide (prepared by dissolving sodium (93 mg) in ethanol (50 ml)) and the mixture was stirred at 40°C for 30 minutes under nitrogen.

(2) In a separate flask sodium (331 mg) was dissolved in ethanol (50 ml) and malononitrile (858 mg) was added. The solution was stirred at ambient temperature for 5 minutes and then to this solution was added the solution of 4′-phenoxy-2-(tert-butylamino)acetophenone obtained in part (1) in one portion excluding the precipitated sodium chloride. The resultant mixture was heated at 50°C for 3 hours and then at 80°C for 2 hours. The solvent was removed under reduced pressure and the resultant oil was partitioned between water and ethyl acetate. The organic phase was separated, dried and evaporated to give a black solid. This solid was dissolved in hot ethanol and triturated with water, filtered and dried to give 2-amino-3-cyano-4-(4-phenoxyphenyl)-1-(tert-butyl)pyrrole.

c) A mixture of 2-amino-3-cyano-4-(4-phenoxyphenyl)-1-(tert-butyl)pyrrole (1.9 g), formamide (30 ml) and 4-dimethylaminopyridine (10 mg) was heated at 180°C for 6 hours. The mixture was cooled to ambient temperature and water was added to precipitate a dark solid. The solid was collected by filtration, washed with water, then boiled up in ethanol and the insoluble material collected by hot filtration and dried. The solid was purified by preparative HPLC on a silica column using dichloromethane/propan-2-ol/ ethanol, 98:1:1 as the mobile phase to give 7-tert-butyl-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine (4-amino-5-(4-phenoxyphenyl)-7-(tert-butyl)pyrrolo[2,3-d]pyrimidine), m.p. 157-158°C. 1H NMR (d6 DMSO) δ 8.15 (1H,s), 7.50-7.35 (4H,m), 7.30 (1H,s), 7.15 (1H,t), 7.10 (4H,m), 6.05 (2H,brs), 1.75 (9H,s).

d) A mixture of 4-amino-5-(4-phenoxyphenyl)-7-(tert-butyl)pyrrolo[2,3-d]-pyrimidine (5.8 g), glacial acetic acid (55 ml) and hydrobromic acid (55 ml of a 48% solution) was boiled under reflux for 18 hours under nitrogen. The mixture was allowed to cool and a solid was collected by filtration. This solid was washed with methanol and then with ether to give 4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]-pyrimidine hydrobromide, m.p. 288-292°C. The hydrobromide salt was converted into the free base by warming with dilute sodium hydroxide solution (100 ml of 5% w/v solution) and ethanol (60 ml) with stirring and removing the ethanol by distillation. The mixture was cooled and the solid was collected by filtration and washed well with water to give 5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine.

e) A mixture of 5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine (600 mg) and tetrakis(triphenylphosphine) palladium (40 ml) and dry dimethyl sulphoxide (30 ml) was stirred under nitrogen in an ice/water bath and then a solution of cyclopentadiene monoepoxide (200 mg) in tetrahydrofuran (10 ml) was added via syringe under nitrogen at 0°C. The mixture was stirred at ambient temperature (with exclusion of light) for 66 hours and then the tetrahydrofuran was removed under reduced pressure and water was added to the residue. The mixture was allowed to stand for 18 hours and then extracted with ethyl acetate to give a residue which was purified by flash column chromatography on silica using ethyl acetate/industrial methylated spirit (9:1) as the mobile phase to give 4-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]-cyclopent-2-enol, as an oil. The structure was confirmed by ^{1}Hnmr and mass spectra.

f) 4-[4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]cyclopent-2-enol (110 mg) was hydrogenated in ethanol (20 ml) with gaseous hydrogen at atmospheric pressure using 10% palladium on charcoal (50 mg) as the catalyst. The catalyst was removed by filtration and the filtrate was evaporated to give 3-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]cyclopentanol, as an oil. The structure was confirmed by 1H nmr and mass spectra.

Example 193: Cis-5-(4-phenoxyphenyl)-7-(4-pyrrolidinocyclohex-1-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine
Trans-5-(4-phenoxyphenyl)-7-(4-pyrrolidinocyclohex-1-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine

To a stirred suspension of 4-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidinyl-7-yl]cyclohexanone (2.34 g, 5.9 mmol) in 1,2 dichloroethane (250 mL) was added, under an atmosphere of nitrogen, pyrrolidine (1.25 g, 17.6 mmol) and glacial acetic acid (1.00 mL, 17.6 mmol), and the resultant mixture stirred at room temperature for 30 minutes. Sodium triacetoxyborohydride (1.87 g, 8.8 mmol) was added in one portion, and the resultant mixture stirred for 70 hours. The mixture was extracted with 2M aqueous hydrochloric acid (2 x 200 mL). The combined extracts were washed with dichloromethane (300 mL), made basic with 12.5M aqueous sodium hydroxide solution, and extracted with dichloromethane (3 x 200 mL). The combined extracts were dried over sodium sulphate, and purified by chromatography with a Biotage 40S column using ethyl acetate / triethylamine (95:5) and ethyl acetate / triethylamine / methanol (85:10:5) as a mobile phase to yield Cis-5-(4-phenoxyphenyl)-7-(4-pyrrolidinocyclohex-1-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine as an off-white solid (0.65 g, 1.4 mmol), melting point 101 –

104 deg.C., LC/MS Hypersil BDS c18 (100 x 2.1 mm) 0.1M ammoniumacetate/acetonitrile, 10-100% acetonitrile in 8 min.): MH^+ 454 t_r= 3.56 minutes and Trans-5-(4-phenoxyphenyl)-7-(4-pyrrolidinocyclohex-1-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine as an off-white solid (0.93 g, 2.1 mmol), melting point 183 – 185 deg.C, LC/MS (Hypersil BDS c18 (100 x 2.1 mm) 0.1M ammoniumacetate/acetonitrile, 10-100% acetonitrile in 8 min.): MH^+ 454 , t_r = 3.68 minutes

Example 194: Cis-5-(4-phenoxyphenyl)-7-(4-piperidinocyclohex-1-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine hydrochloride
Trans-5-(4-phenoxyphenyl)-7-(4-piperidinocyclohex-1-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine

To a stirred suspension of 4-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimin-7-yl]cyclohexanone (2.34 g, 5.9 mmol) in 1,2 dichloroethane (250 mL) was added, under an atmosphere of nitrogen, piperidine (1.50 g, 17.6 mmol) and glacial acetic acid (1.00 mL, 17.6 mmol), and the resultant mixture stirred at room temperature for 30 minutes. Sodium triacetoxyborohydride (1.87 g, 8.8 mmol) was added in one portion, and the resultant mixture stirred for 70 hours. The mixture was extracted with 2M aqueous hydrochloric acid (2 x 200 mL). The combined extracts were washed with dichloromethane (300 mL), made basic with 12.5M aqueous sodium hydroxide solution, and extracted with dichloromethane (3 x 200 mL). The combined extracts were dried over sodium sulphate, and purified by chromatography with a Biotage 40S column using ethyl acetate / triethylamine (95:5) as a mobile phase to yield Cis-5-(4-phenoxyphenyl)-7-(4-piperidinocyclohex-1-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine (0.23 g) as a clear oil., LC/MS :ypersil BDS c18 (100 x 2.1 mm) 0.1M ammoniumacetate/acetonitrile, 10-100% acetonitrile in 8 min.) MH^+ 468 t_r = 3.67 minutes and Trans-5-(4-phenoxyphenyl)-7-(4-piperidinocyclohex-1-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine as an off-white solid (193 mg, 0.4 mmol), melting point 192 - 195 deg.C, LC/MS: Hypersil BDS c18 (100 x 2.1 mm) 0.1M ammoniumacetate/acetonitrile, 10-100% acetonitrile in 8 min.)MH^+ 468 t_r= 3.71 minutes

Example 195: Cis-5-(4-phenoxyphenyl)-7-(4-piperidinocyclohex-1-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine was dissolved in ethyl acetate (50 mL), diluted with diethyl ether (50 mL) and treated with a 1M solution of hydrogen chloride in diethyl ether until no further precipitation occurred. The resultant solid was collected and re-crystallised from absolute ethanol to give Cis-5-(4-phenoxyphenyl)-7-(4-piperidinocyclohex-1-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine hydrochloride as a colourless solid (75 mg, 0.2 mmol) melting point 185 – 189 deg.C.

Example 196: Trans-7-(4-dimethylaminocyclohexyl)-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine

Cis-7-(4-dimethylaminocyclohexyl)-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine

To a stirred solution of 4-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimin-7-yl]cyclohexanone (3.24 g, 8.1 mmol) in dichloromethane (1000 mL) was added, under an atmosphere of nitrogen, N-methylpiperazine (1.20 g, 12.0 mmol) and glacial acetic acid (0.69 mL, 12.0 mmol), and the resultant solution stirred at room temperature for 10 minutes. Sodium triacetoxyborohydride (1.70 g, 8.0 mmol) was added in one portion, and the resultant solution stirred for 6 hours. The additions were repeated on the same scale and the resultant solution stirred for 70 hours. The solution was extracted with 2M aqueous hydrochloric acid (2 x 300 mL). The combined extracts were washed with dichloromethane (300 mL), made basic with .880 aqueous ammonia solution, and extracted with ethyl acetate (3 x 250 mL). The combined extracts were washed with saturated aqueous sodium chloride solution, dried over sodium sulphate, and purified by chromatography with a Biotage 40M column using ethyl acetate / methanol / triethylamine (8:1:1) as a mobile phase to yield Cis-7-(4-dimethylaminocyclohexyl)-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine as an off-white solid (220 mg, 0.5 mmol.) melting point 180 – 182 deg.C, LC/MS: Hypersil BDS c18 (100 x 2.1 mm) 0.1M ammoniumacetate/acetonitrile, 10-100% acetonitrile in 8 min.)MH^+ 428 t_r = 3.43 minutes

The column was flushed with ethyl acetate / methanol / triethylamine (4:1:1, 500 mL), and the solvent removed under reduced pressure. The residue was dissolved in dichloromethane (200 mL)and purified by chromatography with a Biotage 40M column using dichloromethane/methanol (9:1 to 7:3) to yield Trans-7-(4-dimethylamino-cyclohexyl)-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine as an off-white solid (320 mg, 0.75 mmol) melting point 207.5 – 210 deg. C, LC/MS: Hypersil BDS c18 (100 x 2.1 mm) 0.1M ammoniumacetate/acetonitrile, 10-100% acetonitrile in 8 min.)MH^+ 428 t_r = 3.48 minutes

R - (+) - 4 -[4-amino-5-(4-phenoxyphenyl)-7- (3-tetrahydrofuryl)-7H-pyrrolo[2,3-d]pyrimidine.

Example 197: 4 -{(S) - tetrahydrofuran-3-yl}toluenesulphonate

To a solution of (S)-3-hydroxytetrahydrofuran (2.0 g, 23 mmol) in pyridine (40 ml) at 0°C was added tosylchloride portionwise (4.8 g, 25 mmol). The solution was stirred at 0°C for 1 hr and then at room temperature overnight. The pyridine was evaporated in vacuo and the residue was partioned between EtOAc and saturated aquoeus citric acid (200 ml each). The aqueous layer was extracted with EtOAc (2 x 200 ml) and the combined organics were dried (sodium sulphate), filtered and evaporated to leave an oil (4.5 g, 85%). ^1H NMR ($CDCl_3$, 250 MHz): 7.78 (2H, d), 7.35 (2H, d), 5.12 (1H, m), 3.76-3.93 (4H, m), 2.45 (3H, s), 2.01-2.20 (2H, m).

To a stirred suspension of 4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidine (4.83 g, 16 mmol) in N,N-dimethylformamide (80 mL), under an atmosphere of nitrogen, was added 60% sodium hydride in mineral oil (0.75 g, 19 mmol), and the mixture stirred at room temperature for 30 minutes. The resultant dark solution was treated with a solution of 4 -{(S) - tetrahydrofuran-3-yl}toluenesulphonate (4.20 g, 18 mmol) in N,N-dimethylformamide (20 mL) in 2 mL aliquots. The resultant solution was stirred at room temperature for 30 minutes, then at 95 deg.C. for 18 hours. The solution was allowed to cool to ambient temperature, then poured onto ice/water (200 mL). The aqueous was extracted with ethyl acetate (3 x 200 mL). The combined organic extracts were washed with water (4 x 150 mL), dried over sodium sulphate, and the solvent was removed under reduced pressure. The residue was warmed with dichloromethane (1000 mL) until a solution was obtained, cooled to ambient temperature, and purified by chromatography with a Biotage 40M column using ethyl acetate/ triethylamine (95:5), then ethyl acetate / triethylamine / methanol (90:5:5) as a mobile phase, to yield R - (+) - 4 -[4-amino-5-(4-phenoxyphenyl)-7- (3-tetrahydrofuryl)-7H-pyrrolo[2,3-d]pyrimidine as an off-white solid (4.35 g, 12 mmol) melting point 165-166 deg. C, LC/MS : Hypersil BDS c18 (100 x 2.1 mm) 0.1M ammoniumacetate/acetonitrile, 10-100% acetonitrile in 8 min.) MH^+ 373 t_r = 4.44 minutes. $[]_D$ + 20.5 ± 0.6 (dichloromethane, 22.6 deg.C.)

Example 198: 5-(4-phenoxyphenyl)-7-(4-piperidyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine

N-tert-butoxycarbonylpiperidinol

To a solution of N-tert-butoxycarbonylpiperidone (10.0 g, 50 mmol) in MeOH (100 ml) at 0°C was added sodium borohydride (1.9 g, 50 mmol) portionwise. Stir at 0°C for 1 hr and then at room temperature for 20 hr. Quench with 2N NaOH (20 ml), evaporate solvent and partition residue between ethylacetate and water (100 ml each). Extract the aqueous layer with ethylacetate (3 x 100ml) and wash the combined organic layers with brine and water (1 x 100 ml each). Dry (Na_2SO_4), filter and concentrate to leave N-tert-butoxycarbonylpiperidinol as a colourless oil (10.5 g, 100%). R_f in 20% EtOAc / hexane = 0.05 ($KMnO_4$ dip). IR (thin film) : 3428, 2939, 1693 cm^{-1}

Example 199: tert-butyl 4-[(4-methylphenyl)sulfonyl]oxy-1-piperidinecarboxylate

To a solution of N-tert-butoxycarbonylpiperidinol (10.5 g, 0.052 mol) in pyridine (150 ml) at 0°C under nitrogen was added tosylchloride (9.94 g, 0.052 mol) portionwise. Stir at 0°C for 2 hr. Warm to room temperature and stir at room temperature overnight. Evaporate the solvent and partition between citric acid solution (1M, 100 ml) and ethylacetate (200 ml). Extract acidic layer with ethylacetate (1 x 100 ml) and wash combined organics with citric acid solution (1M, 2 x 100 ml), brine (100 ml) and water (100 ml). Dry (Na_2SO_4) , filter and evaporate to leave an oil which was purifed by flash column chromatography using 10%

EtOAc / cyclohexane then 15% EtOAc / cyclohexane to give in F 30-68 tert-butyl 4-[(4-methylphenyl)sulfonyl]oxy-1-piperidinecarboxylate as a white solid (11.0 g, 60%) Rf in 20% EtOAc / cyclohexane = 0.17 ^{1}H NMR ($CDCl_3$, 250 MHz) : δ 7.79 (2H, d), 7.34 (2H, d), 4.67 (1H, m), 3.58 (2H, m), 3.27 (2H, m), 2.45 (3H, s), 1.59 – 1.83 (4H, m), 1.43 (9H, s)

Example 200: tert-butyl 4-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]-1-piperidinecarboxylate

To a solution of 4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidine (2.0 g, 6.6 mmol) in dry DMF (100 ml) under nitrogen at 0oC was added NaH (0.264 g, 60% dispersion, 6.6 mmol) and the reaction mixture warmed to room temperature and stirred for 1hr. Tert-butyl 4-[(4-methylphenyl)sulfonyl]oxy-1-piperidinecarboxylate (2.34 g, 6.6 mmol) was added and the resulting solution heated at 95°C for 72 hr. The reaction was quenched by careful addition of water (150 ml). Extract with EtOAc (3 x 100 ml) and wash with water (4 x 100 ml) and brine (2 x 100 ml). The organic solution was dried (Na_2SO_4), filtered and evaporated to leave a solid which was adsorbed onto silica and purified by flash silica gel column chromatography using EtOAc then 5% MeOH/EtOAc as eluent to give in F 13-22 tert-butyl4-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]-1-piperidinecarboxylate (1.0 g, 31%) as a white solid, m.pt. 168.5-169.5oC. R_f in 10% EtOAc/MeOH = 0.4 . ^{1}H NMR (d_6 DMSO, 250 MHz) : δ 8.14 (1H, s), 7.38-7.49 (5H, m), 7.07-7.23 (5H, m), 6.14 (2H, bs), 4.76 (1H, m), 4.11 (2H, m), 2.93 (2H, m), 1.92-2.02 (4H, m), 1.43 (9H, s). Mass spec. $C_{28}H_{31}O_3N_5$ (485.2430).IR (KBr disc) : 3059, 1695, 1588, 1235 cm^{-1}

Example 201: 5-(4-phenoxyphenyl)-7-(4-piperidyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine

To a solution of tert-butyl 4-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]-1-piperidinecarboxylate (0.69 g, 1.4 mmol) in dry CH_2Cl_2 (25 ml) at 0°C was added TFA (5 ml). The solution was stirred at room temperature for 20 hr and the solvent evaporated. NaOH solution (5N, 10 ml) was added and the resulting slurry was extracted with EtOAc (3 x 50 ml). Wash with brine (1 x 50 ml). Dry, filter and concentrate to leave a solid which was triturated with diethylether and filtered to leave 5-(4-phenoxyphenyl)-7-(4-piperidyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine (433258) as a white solid (500 mg, 91%). M.pt 209-211°C. R_f in 1:1 EtOAc : MeOH = 0.1. . ^{1}H NMR (d_6 DMSO, 250 MHz) 8.13 (1H, s), 7.36-7.48 (4H, m), 7.29 (1H, s), 7.04-7.16 (5H, m), 5.80 (2H, bs), 4.64 (1H, m), 3.10 (2H, m), 2.80 (1H, bs), 2.67 (2H, m), 1.94 (4H, m). Mass spec. $C_{23}H_{23}ON_5$ (385.1902). IR (KBr disc) : 3278, 1620, 1585, 1490, 1245 cm^{-1}

Example 202: 5-(4-phenoxyphenyl)-7-(4-piperidyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine dihydrochloride

To 5-(4-phenoxyphenyl)-7-(4-piperidyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine (433258) (200 mg) in EtOAc/MeOH (15 ml, 1:1) was added ether.HCl solution (1.0 M, 3 ml). The resulting white precipitate was filtered under a stream of nitrogen and dried in vacuo for 6 hr to leave 5-(4-phenoxyphenyl)-7-(4-piperidyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine dihydrochloride (1.4 hydrate) as a white solid (120 mg), m.pt. 304°C (dec.). ^{1}H NMR (D_2O, 250 MHz) 8.48(1H, s), 7.69 (1H, s), 7.50-7.58 (4H, m), 7.18-7.34 (5H, m), 5.16 (1H, m), 3.81 (2H, d), 3.46 (2H, m), 2.49 (4H, m).). IR (KBr disc) : 3937, 1657. 1231 cm^{-1}

Example 203: tert-butyl 3-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]-1-pyrrolidinecarboxylate
N-tert-butoxycarbonylpyrrolidin-3-ol

To a solution of pyrrolidin-3-ol (10.0 g, 0.11 mol) in dichloromethane (200 mL) was added triethylamine (22.2 g, 30.5 ml, 0.22 mol) followed by di-tert-butyldicarbonate (28.8 g, 0.13 mol) at 0°C. Warm to room temperature and stir at room temperature overnight. Quench with saturated aqueous citric acid (150 ml) amd wash the organic layer with water, brine and water again (1 x 100 ml each). The organic layer was dried (sodium sulphate), filtered and evaporated to leave N-tert-butoxycarbonylpyrrolidin-3-ol (20.0g, 93% crude) as a golden oil.

Example 204: tert-butyl 3-[(4-methylphenyl)sulfonyl]oxy-1-pyrrolidinecarboxylate

To a solution of N-tert-butoxycarbonylpyrrolidin-3-ol (19.8 g, 0.106 mol) in pyridine (200 ml) at 0°C under nitrogen was added tosyl chloride (22.3 g, 0.117 mol) portionwise. Stir at 0°C for 2 hr, warm to room temperature and stir at room temperature overnight. The pyridine was evaporated in vacuo and the residue was partioned between EtOAc and saturated aquoeus citric acid (200 ml each). The aqueous layer was extracted with EtOAc (2 x 200 ml) and the combined organics were dried (sodium sulphate), filtered and evaporated to leave an oil which was purified by flash silica gel column chromatography using 10% EtOAc/cyclohexane as eluent to give in F40-85 an oil. The oil was dissolved in a small volume of cyclohexane/ diethylether (5:1, 50 ml), cooled and scratched with a spatula to induce crystallisation. The resulting solid was filtered to give tert-butyl 3-[(4-methylphenyl)sulfonyl]oxy-1-pyrrolidinecarboxylate (10.5 g, 29%) as a white solid. R_f in EtOAc/cyclohexane = 0.13. ^{1}H NMR ($CDCl_3$, 250 MHz): 7.79 (2H, d), 7.35 (2H, d), 5.04 (1H, m), 3.43 (4H, m), 2.46 (3H, s), 2.03-2.20 (2H, bm), 1.43 (9H, s)

To a solution of 4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidine (2.0 g, 6.6 mmol) in dry DMF (120 ml) under nitrogen at 0°C was added NaH (0.264 g, 60% dispeersion, 6.6 mmol) and then reaction mixture warmed to room temperature and stirred for 1hr. tert-butyl 3-[(4-methylphenyl)sulfonyl]oxy-1-pyrrolidinecarboxylate (2.25 g, 6.6 mmol) was added portionwise and the mixture heated at 95°C for 72 hr. Quench with water and extract with EtOAc (4 x 100 ml). Wash the combined organic solutions with water (4 x 100 ml) and brine (2 x 100 ml). The organics were dried (sodium sulphate), filtered and evaporated to leave a solid which was dissolved in EtOAc/MeOH and adsorbed onto silica. Purification using flash silica gel column chromatography with 5% MeOH/ EtOAc as eluent gave in F17-25 tert-butyl 3-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]-1-pyrrolidinecarboxylate (1.0 g, 32%) as a white solid m.pt. 168-170°C. R_f in 9:1 EtOAc: MeOH = 0.46. ^{1}H NMR (d_6 DMSO, 250 MHz): 8.17 (1H, s), 7.38 –7.50 (5H, m), 6.19 (2H, bs), 5.31 (1H, m), 3.77 (1H, m), 3.42-3.60 (3H, m), 2.38 (2H, m), 1.40 (9H, s). Mass spec. 471.2250 ($C_{27}H_{29}O_3N_5$) IR (KBr disc): 3130, 1683, 1585, 1404, 1245 cm^{-1}

Example 205: 5-(4-phenoxyphenyl)-7-(3-pyrrolidinyl) -7H-pyrrolo[2,3-d]pyrimidin-4-ylamine

To a solution of tert-butyl 3-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]-1-pyrrolidinecarboxylate (0.8 g, 1.7 mmol) in dichloromethane (25 ml) at 0°C was added trifluoroacetic acid (5 ml). The reaction mixture was warmed to room temperature and stirred at room temperature for 20 hr. The solvent was evaporated and dilute NaOH added (5N, 10 ml). The resulting residue solution was extracted with EtOAc (3 x 50 ml) and the combined organics were washed with brine (1 x 75 ml). The organic solution was dried (sodium sulphate), filtered and evaporated in vacuo to leave 5-(4-phenoxyphenyl)-7-(3-pyrrolidinyl) -7H-pyrrolo[2,3-d]pyrimidin-4-ylamine as a white solid (0.5 g, 79%) m.pt. 182-184°C. R_f in 1:1 EtOAc : MeOH = 0.15. ^{1}H NMR (d_6 DMSO, 250 MHz): 8.14 (1H, s), 7.37-7.50 (5H, m), 7.05 – 7.18 (5H, m), 6.14 (2H, bs), 5.23 (1H, m), 3.09 –3.27 (2H, m), 2.83-2.98 (2H, m), 2.19-2.33 (1H, m), 1.88-2.01 (1H, m). Mass spec. 371.1758 ($C_{22}H_{21}ON_5$). IR (KBr disc): 3106, 1585, 1489, 1232 cm^{-1}

Example 206: 5-(4-phenoxyphenyl)-7-(3-pyrrolidinyl) -7H-pyrrolo[2,3-d]pyrimidin-4-ylamine dihydrochloride

To a solution of 5-(4-phenoxyphenyl)-7-(3-pyrrolidinyl) -7H-pyrrolo[2,3-d]pyrimidin-4-ylamine (200 mg) in EtOAc/MeOH (2:1, 20 ml) was added ether.HCl (1.0 M, 3 ml) and the resulting precipitate was filtered under nitrogen to give 5-(4-phenoxyphenyl)-7-(3-pyrrolidinyl) -7H-pyrrolo[2,3-d]pyrimidin-4-ylamine dihydrochloride (0.4 hydrate) as a white solid (190 mg) m.pt. 298°C (dec.). IR (KBr disc): 2909, 1658, 1249 cm^{-1}

Example 207: 7-perhydro-1-pyrrolizinyl-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3,d] pyrimidin-4-amine dihydrochloride salt

a) perhydro-1-pyrrolizinol

Prepared as described by Schnekenburger J, Briet E, Arch. Pharm. (Wienheim) 310, 152-160 (1977).

b) perhydro-1-pyrrolizinyl methanesulfonate

A mixture of perhydro-1-pyrrolizinol (0.5 g, 3.94 mmol) and triethylamine (0.60 g, 5.91 mmol) in dichloromethane (10 ml) was stirred at 0°C under an atmosphere of nitrogen. Methanesulfonyl chloride (0.68 g, 5.91 mmol) was added, then the mixture was allowed to warm to ambient temperature and stirred for 8 hours. Saturated aqueous ammonium chloride (10 ml), dichloromethane (25 ml) and saturated aqueous sodium bicarboante (10 ml) were added. The organic layer was dried over magnesium sulfate filtered and the filtrate evaporated under reduced pressure to give a residue. Purification of the material by flash chromatography on silica gel using heptane/ethyl acetate (1:3) as an eluent yielded perhydro-1-pyrrolizinyl methanesulfonate (0.54 g): ^{1}H NMR (DMSO-d_6, 400MHz) δ 4.96 (m, 1H), 3.61 (m, 1H), 2.9-3.3 (m, 6H), 2.35 (m, 1H), 1.55-2.25 (m, 6H).

c) 7-perhydro-1-pyrrolizinyl-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3,d]pyrimidin-4-amine dihydrochloride salt

A mixture of 5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (0.49g, 1.62 mmol) and 60% sodium hydride in oil (100 mg, 2.43 mmol) in DMF was stirred at ambient temperature for 15 minutes under an atmosphere of nitrogen . The mixture was heated at 100°C for 18 hours then cooled to ambient temperature. Additional 60% sodium hydride in oil (100 mg, 2.43 mmol) was added and heating continued for another 2 hours. The mixture was cooled to ambient temperature and the solvents removed under reduced pressure. The residue was partitioned between water (10 ml) and dichloromethane (30 ml). The organic layer was dried over magnesium sulfate, filtered and the solvent was removed from the filtrate under reduced pressure. The resulting residue was purified by preparative C-18 RP HPLC to give 150 mg of white solid which was dissolved in ethyl acetate (10 ml) and treated with 1 N hydrogen chloride in diethyl ether to give 7-perhydro-1-pyrrolizinyl-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3,d] pyrimidin-4-amine dihydrochloride salt as a white solid: ^{1}H NMR (DMSO-d_6, 400MHz) δ 8.52 (s, 1H), 7.95 (s, 1H), 7.02-7.58 (m, 1H), 5.38 (m, 1H0, 4.40 (m, 1H), 1.9-3.9 (m, 10H); (Hypersil HS C18, 5 μm, 100A, 250 x 4.6 mm; 25-100% acetonitrile-0.1 M ammonium acetate over 10min, 1ml/min) t_r=7.62 min; MS: MH^+ 412.

Example 208: 7-(2-methylperhydrocyclopenta[c]pyrrol-5-yl)-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine dihydrochloride salt

a) 2-methylperhydrocyclopenta[c]pyrrol-5-ol

Prepared as described by Bohme H, Setiz G, Arch. Pharm. (Wienheim) 301, 341 (1968).

b) 4-chloro-5-iodo-7-(2-methylperhydrocyclopenta[c]pyrrol-5-yl)-7H-pyrrolo[2,3-d]pyrimidine

A mixture of 4-chloro-5-iodo-7H-pyrrolo[2,3-d]pyrimidine (0.38 g, 1.36 mmol), 2-methylperhydrocyclopenta[c]pyrrol-5-ol (0.23 g, 1.63 mmol) and triphenylphosphine (0.71 g, 2.72 mmol) in tetrahydrofuran (20 mL) was treated with diethylazodicarboxylate (0.474 g, 2.72 mmol) and stirred for 2 hours at ambient temperature. The solvent was removed under reduced pressure and the residue was partitioned between dichloromethane (30 ml) and water (10 ml). The organic layer was washed with saturated aqueous sodium chloride (10 ml) then dried over magnesium sulfate then filtered and the filtrate evaporated under reduced pressure to give a residue. The residue was purified by flash chromatography on silica using dichloromethane/ methanol (8:2) as mobile phase to yield 4-chloro-5-iodo-7-(2-methylperhydrocyclopenta[c]pyrrol-5-yl)-7H-pyrrolo[2,3-d]pyrimidine (0.25 g): ^{1}H NMR (DMSO-d_6, 400MHz) δ 8.62 (s, 1H), 7.44 (s, 1H), 7.26 (s, 2H), 5.36 (m, 1H), 2.88 (m, 2H), 2.68 (m, 2H), 2.43 (m, 2H), 2.36 (s, 3H), 2.06-2.02 (m, 4H); TLC (dichloromethane/methanol 8:2) R_f = 0.29; RP-HPLC (Hypersil HS C18, 5 µm, 100A, 250 x 4.6 mm; 25-100% acetonitrile-0.1 M ammonium acetate over 10min, 1ml/min) t_r=6.50 min; MS: MH^+ 403.

c) 7-(2-methylperhydrocyclopenta[c]pyrrol-5-yl)-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine dihydrochloride salt

A mixture of 4-chloro-5-iodo-7-(2-methylperhydrocyclopenta[c]pyrrol-5-yl)-7H-pyrrolo[2,3-d]pyrimidine (0.25 g, 0.622 mmol), 4-phenoxyphenyl boronic acid (0.16 g, 0.746 mmol), tetrakis(triphenylphosphine)palladium (0.043 g, 0.037 mmol) and sodium carbonate (0.172 g, 1.62 mmol) was heated in a mixture of ethylene glycol dimethyl ether (8 mL) and water (4 mL) at 90° C for 18 hours under an atmosphere of nitrogen. The mixture was allowed to cool to ambient temperature and solvents were removed under reduced pressure. The residue was partitioned between water (10 mL) and dichloromethane (30 ml) The layers were separated and the organic solution was dried over magnesium sulfate, filtered and the filtrate concentrated to a residue under reduced pressure (0.354 g). The material was dissolved in 1,4-dioxane (10 ml) and concentrated (28%) ammonium hydroxide (10 ml). The mixture was heated in a sealed tube at 120°C for 20 hours then cooled to ambient temperature. The solvents were evaporated under reduced pressure then purified by flash column chromatography on silica using dichloromethane/methanol 7:3) as an eluent to give 7-(2-methylperhydrocyclopenta [c]pyrrol-5-yl)-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (0.05 g): ^{1}H NMR (DMSO-d_6, 400MHz) shows two sets of peaks due to the cis and trans isomers of the desired compound δ 10.6-10.8 (bs, 1H), 8.49 (s, 1H), 6.99-7.98 (m, 11H), 5.39 and 5.48 (m, 1H), 2-3.8 (m, 10H); PH 454098: RP-HPLC (Hypersil HS C18, 5 µm, 100A, 250 x 4.6 mm; 25-100% acetonitrile-0.1 M ammonium acetate over 10min, 1ml/min) t_r=7.53 min; MS: MH^+ 426. The dihydrochloride salt of 7-(2-methylperhydrocyclopenta[c]pyrrol-5-

yl)-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine was prepared by dissolving the free base in 10 ml 1 N hydrochloric acid and lyophilizing.

Example 209: Cis and trans-7-[4-(N-tert-butoxycarbonyl-1S, 4S-2,5-diaza[2.2.1] heptanyl)cyclohexyl]-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine

A suspension of 4-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]-1-cyclohexanone (0.67 g, 1.68 mmol) in dichloroethane (40 ml) was treated with tert-Butyl (1S, 4S)-(-) 2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (1.0 g, 5.04 mmol) and glacial acetic acid (0.30 g, 5.04 mmol) at room temperature for 1 h. Subsequently, $Na(OAc)_3BH$ (0.46 g, 2.17 mmol) was added and stirred for 8 days at 80°C. To the cooled reaction solution, a solution of $NaHCO_3$ (0.377 g, 10.08 mmol) in water (15 ml) was added and stirred for 15 min. The layers were separated and the organic layer was washed with water and brine (3 x 100 ml each). The aqueous layer was extracted with CH_2Cl_2, the organic layers combined , dried ($MgSO_4$), filtered and concentrated. The solid was purified by flash silica gel column chromatography , (2 L, 6% MeOH in CH_2Cl_2, then 2 L 10% MeOH / 5% NH_4OH in CH_2Cl_2) to give :

Example 210: Cis-7-[4-(N-tert-butoxycarbonyl-1S, 4S-2,5-diaza[2.2.1]heptanyl) cyclohexyl]-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (605 mg, 64%)

^{1}H NMR (d_6 DMSO, 400 MHz) : δ 8.13 (1H, s), 7.39-7.49 (4H, m), 7.32 (1H, m), 7.07-7.17 (5H,m), 6.09 (2H, bs), 4.63 (1H, m), 4.15 (1H, m), 3.30-3.70 (2H, m), 3.03-3.08 (2H, m), 2.80-2.90 (1H, m), 2.70-2.75 (1H, m), 2.29-2.35, (1H, m), 2.09-2.21 (1H, m), 1.81-1.93 (4H, m), 1.60-1.80 (4H, m), 1.39 (9H, m). HPLC/MS: Perkin Elmer Pecosphere C18, 3μM, 33 x 4.6, 3.5 ml/min 100 – 100% 50 mM ammonium acetate to acetonitrile in 4.5 minutes, $C_{36}H_{44}N_6O_3$ (581.2), 95%.

Example 211: Trans-7-[4-(N-tert-butoxycarbonyl-1S, 4S-2,5-diaza[2.2.1]heptanyl) cyclohexyl]-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (183 mg, 20%)

^{1}H NMR (d_6 DMSO, 400 MHz) : δ 8.13 (1H, s), 7.39-7.47 (5H, m), 7.15-7.17 (1H, m), 7.07-7.11 (4H,m), 6.10 (2H, bs), 4.62 (1H, m), 4.1-4.2 (1H, m), 3.71 (1H, bs), 3.03 (2H, m), 2.35 (2H, m), 1.93-2.01 (6H, m), 1.60-1.68 (2H, m), 1.40 (9H, s). HPLC/MS Perkin Elmer Pecosphere C18, 3μM, 33 x 4.6, 3.5 ml/min 100 – 100% 50 mM ammonium acetate to acetonitrile in 4.5 minutes, $C_{30}H_{36}N_6O$ (581.2), 99%.

Example 212: Cis-N1-{4-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl] cyclohexyl}-N1,N2,N2-trimethyl-1,2-ethanaediamine trimaleate salt

Trans-N1-{4-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]cyclohexyl}-N1,N2,N2-trimethyl-1,2-ethanaediamine trimaleate salt

A mixture of 4-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidine-7-yl]-1-cyclohexanone (1.0 g, 2.51 mmol), N,N,N'-trimethylethylenediamine (0.77 g, 7.54 mmol) and acetic acid (0.45 g, 7.54 mmol) in 1,2-dichloroethane (50 ml) was stirred at ambient temperature under an atmosphere of nitrogen for 30 minutes. Sodium triacetoxyborohydride (0.69 g, 3.26 mmol) was added and the mixture stirred at ambient temperature for 18 hours. Water (20 ml) and sodium bicarbonate (1.26 g, 15.1 mmol) were added, the mixture was stirred for one hour, filtered through a pad of celite and the pad was washed with dichloromethane (75 ml). The filtrate was transferred to a separatory funnel and the layers were separated. The organic layer was dried over magnesium sulfate, filtered and the filtrate evaporated under reduced pressure. The cis and trans isomers were purified by flash chromatography on silica gel using dichloromethane/methanol (7:3) as an eluent to give cis-N1-{4-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]cyclohexyl}-N1,N2,N2-trimethyl-1,2-ethanaediamine (0.442 g) and trans-N1-{4-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]cyclohexyl}-N1,N2,N2-trimethyl-1,2-ethanaediamine (0.336 g). The cis-N1-{4-[4-amino-5-(4-

phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]cyclohexyl}-N1,N2,N2-trimethyl-1,2-ethanaediamine (0.44 g, 0.909 mmol) was dissolved in warm ethyl acetate (100 ml) then maleic acid (0.32 g, 2.73 mmol) in ethyl acetate (30 ml) was added. The resulting salt formed an oily residue on the bottom and sides of the flask. The supernatant was poured off and the residue was dissolved in water and lyophilized to give cis-N1-{4-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]cyclohexyl}-N1,N2,N2-trimethyl-1,2-ethanaediamine trimaleate salt (0.55 g): ^{1}H NMR (DMSO-d_6, 400MHz) δ 8.22 (s, 1H), 7.41-7.50 (m, 5H), 7.08-7.19 (m, 5H), 6.5 (bs, 2H), 6.15 (s, 6H), 4.78 (m, 1H), 3.28 (m, 2H), 3.00 (m, 2H), 2.80 (m, 1H), 2.79 (s, 6H), 2.50 (s, 3H), 2.19 (m, 2H), 1.99 (m, 2H), 1.78 (m, 4H); RP-HPLC (Hypersil CPS, 5 μm, 100A, 250 x 4.6 mm; 25-100% acetonitrile-0.1 M ammonium acetate over 10min, 1ml/min) t_r=9.27 min; MS: MH^+ 485.

trans-N1-{4-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]cyclohexyl}-N1,N2,N2-trimethyl-1,2-ethanaediamine trimaleate salt was prepared from the free base in the same manner: ^{1}H NMR (DMSO-d_6, 400MHz) δ 8.20 (s, 1H), 7.41-7.48 (m, 5H), 7.08-7.19 (m, 5H), 6.45 (bs, 2H), 6.15 (s, 6H), 4.62 (m, 1H), 2.9-3.3 (m, 5H), 2.74 (s, 6H), 2.56 (s, 3H), 1.9-2.2 (m, 6H), 1.73 (m, 2H); RP-HPLC (Hypersil CPS, 5 μm, 100A, 250 x 4.6 mm; 25-100% acetonitrile-0.1 M ammonium acetate over 10min, 1ml/min) t_r=8.17 min; MS: MH^+ 485.

The following compounds were made in a similar manner to cis-N1-{4-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]cyclohexyl}-N1,N2,N2-trimethyl-1,2-ethanaediamine

Example 214: Cis-7-[4-(4-isopropylpiperazino)cyclohexyl]-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine: ^{1}H NMR (d_6 DMSO, 400 MHz): δ 8.13 (1H, s), 7.39-7.50 (4H, m), 7.28 (1H, s), 7.07-7.16 (5H, m), 6.08 (2H, bs), 4.67 (1H, m), 2.49-2.67 (9H, m), 2.06-2.16 (5H, m), 1.70-1.72 (2H, m), 1.53-1.59 (2H, m), 0.97 (d, J = 6.5 Hz, 6H). Mass spec. $C_{31}H_{38}N_6O$ (511.2). HPLC: (Hypersil HS C18, 5μm, 254 nm, 250 x 4.6 mm; 25-100% acetonitrile-0.1N ammonium acetate over 10 min, 1 ml/min) t_r=7.817 min., 99% TLC: R_f in 90% CH_2Cl_2/MeOH = 0.30 (UV visible).

Example 215: Trans-7-[4-(4-isopropylpiperazino)cyclohexyl]-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine: ^{1}H NMR (d_6 DMSO, 400 MHz): δ 8.13 (1H, s), 7.40-7.47 (5H, m), 7.08-7.18 (5H, m), 6.08 (2H, bs), 4.53 (1H, m), 2.45-2.55 (9H, m), 2.17-2.20 (1H, m), 1.86-1.96 (6H, m), 1.44-1.49 (2H, m), 0.97 (d, J = 5.5 Hz, 6H). Mass spec. $C_{31}H_{38}N_6O$ (511.2). HPLC: (Hypersil HS C18, 5μm, 254 nm, 250 x 4.6 mm; 25-100% acetonitrile-0.1N ammonium acetate over 10 min, 1 ml/min) t_r=7.367 min., 91% TLC: R_f in 90% CH_2Cl_2/MeOH = 0.21 (UV visible).

Example 216: Cis-7-{4-[4-(2-methoxyethyl)piperazino]cyclohexyl}-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine: ^{1}H NMR (d_6 DMSO, 400 MHz): δ 8.13 (1H, s), 7.39-7.50 (4H, m), 7.27 (1H, s), 7.07-7.11 (5H, m), 6.09 (2H, bs), 4.68 (1H, m), 3.42 (2H, t, J = 5.9 Hz), 3.22 (3H, s), 2.43-2.55 (9H, m), 2.03-2.16 (6H, m), 1.60-1.71 (2H, m), 1.52-1.59 (2H, m). Mass spec. $C_{31}H_{38}N_6O_2$ (527.2). HPLC: (Hypersil HS C18, 5μm, 254 nm, 250 x 4.6 mm; 25-100% acetonitrile-0.1N ammonium acetate over 10 min, 1 ml/min) t_r=7.317 min, 95% TLC: R_f in 90% CH_2Cl_2/MeOH = 0.22 (UV visible).

Example 217: Trans-7-{4-[4-(2-methoxyethyl)piperazino]cyclohexyl}-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine: ^{1}H NMR (d_6 DMSO, 400 MHz): δ 8.13 (1H, s), 7.39-7.47 (5H, m), 7.07-7.16 (5H, m), 6.09 (2H, bs), 4.55 (1H, m), 3.36-3.42 (2H, m), 3.23 (3H, s), 2.33-2.55 (11H, m), 1.90-1.96 (6H, m), 1.44-1.47 (2H, m). Mass spec. $C_{31}H_{38}N_6O_2$ (527.2). HPLC: (Hypersil HS C18, 5μm, 254 nm, 250 x 4.6 mm; 25-100% acetonitrile-0.1N ammonium acetate over 10 min, 1 ml/min) t_r=7.200 min, 99% TLC: R_f in 90% CH_2Cl_2/MeOH = 0.31 (UV visible).

Example 218: Cis-7-[-4-(4-ethylpiperazino)cyclohexyl]-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine

^{1}H NMR (d_6 DMSO, 400 MHz) : δ 8.23 (1H, s), 7.41-7.49 (4H, m), 7.07-7.17 (6H,m), 6.57 (2H, bs), 6.20 (5H, s), 4.77 (1H, m), 2.04-2.13 (8H, m), 1.62-1.77 (5H, m), 1.21 (3H, t). HPLC (Waters delta pack C18, 150 x 3.9 mm; 5 - 95% acetonitrile-0.1 M ammonium acetate over 30min, 1ml/min) t_r=13.851, 100%.

trans-7-[4-(4-ethylpiperazino)cyclohexyl]-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine

^{1}H NMR (d_6 DMSO, 400 MHz) : δ 8.19 (1H,s), 7.40-7.47 (4H, m), 7.19 (1H, m), 7.08-7.19 (5H,m), 6.40 (2H, bs), 6.18 (6H, s), 4.95 (1H, m), 3.17 (2H, bs), 2.98 (2H, bs), 2.69 (2H, bs), 1.94-2.01 (8H, m), 1.54-1.57 (2H, d, J =7.5 Hz), 1.17 (3H, t). HPLC (Waters delta pack C18, 150 x 3.9 mm; 5 - 95% acetonitrile-0.1 M ammonium acetate over 30min, 1ml/min) t_r=13.701, 96%.

The following compounds were prepared as salts in a similar manner to that of trans-N1-{4-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]cyclohexyl}-N1,N2,N2-trimethyl-1,2-ethanaediamine trimaleate salt:

Example 219: Cis-7-[4-(4-isopropylpiperazino)cyclohexyl]-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine tris maleate: ^{1}H NMR (d_6 DMSO, 400 MHz): δ 8.23 (1H, s), 7.40-7.49 (5H, m), 7.07-7.19 (5H, m), 6.55 (2H, bs), 6.16 (6H, s), 4.74 (1H, m), 3.26 (6H, bs), 2.04-2.49 (13H, m), 1.63-1.75 (5H, m), 1.25 (d, J = 6.6 Hz, 6H). Mass spec. $C_{31}H_{38}N_6O$ (511.1). HPLC: (Hypersil HS C18, 5µm, 254 nm, 250 x 4.6 mm; 25-100% acetonitrile-0.1N ammonium acetate over 10 min, 1 ml/min) t_r=7.967 min, 99%

Example 220: Trans-7-[4-(4-isopropylpiperazino)cyclohexyl]-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine tris maleate: [1]H NMR (d_6 DMSO, 400 MHz): δ 8.20 (1H, s), 7.40-7.65 (5H, m), 7.08-7.19 (5H, m), 6.46 (2H, bs), 6.14 (6H, s), 4.60 (1H, m), 2.50-3.45 (17H, m), 1.95-2.02 (5H, m), 1.56-1.59 (2H, m), 1.20 (d, J = 6.5 Hz, 6H). Mass spec. $C_{31}H_{38}N_6O$ (511.2). HPLC: (Hypersil HS C18, 5μm, 254 nm, 250 x 4.6 mm; 25-100% acetonitrile-0.1N ammonium acetate over 10 min, 1 ml/min) t_r=7.733 min, 90%

Example 221: Cis-7-{4-[4-(2-methoxyethyl)piperazino]cyclohexyl}-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine tris maleate: [1]H NMR (d_6 DMSO, 400 MHz): δ 8.23 (1H, s), 7.41-7.49 (5H, m), 7.07-7.19 (5H, m), 6.55 (2H, bs), 6.16 (6H, s), 4.75 (1H, m), 3.62 (2H, m), 3.30 (3H, s), 3.17 (6H, bs), 2.50 (9H, m), 2.02-2.16 (5H, m), 1.74 (5H, m). Mass spec. $C_{31}H_{38}N_6O_2$ (527.2). HPLC: (Hypersil HS C18, 5μm, 254 nm, 250 x 4.6 mm; 25-100% acetonitrile-0.1N ammonium acetate over 10 min, 1 ml/min) t_r=7.750 min, 99%

Example 222: Trans-7-{4-[4-(2-methoxyethyl)piperazino]cyclohexyl}-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine tris maleate: [1]H NMR (d_6 DMSO, 400 MHz): δ 8.21 (1H, s), 7.41-7.48 (5H, m), 7.08-7.17 (5H, m), 6.53 (2H, bs), 6.17 (6H, s), 4.61 (1H, m), 3.45 (3H, s), 2.50-3.56 (19H, m), 1.99-2.08 (6H, m), 1.64 (2H, m). Mass spec. $C_{31}H_{38}N_6O_2$ (527.2). HPLC: (Hypersil HS C18, 5μm, 254 nm, 250 x 4.6 mm; 25-100% acetonitrile-0.1N ammonium acetate over 10 min, 1 ml/min) t_r=7.383 min, 99%

Example 223: Cis-N1-{4-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]cyclohexyl}-N2,N2-dimethyl-1,2-ethanaediamine trimaleate salt Trans-N1-{4-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]cyclohexyl}-N2,N2-dimethyl-1,2-ethanaediamine monomaleate salt

cis-N1-{4-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]cyclohexyl}-N2,N2-dimethyl-1,2-ethanaediamine trimaleate salt: [1]H NMR

(DMSO-d_6, 400MHz) δ 8.19 (s, 1H), 7.40-7.49 (m, 5H), 7.08-7.19 (m, 5H), 6.35 (bs, 2H), 6.13 (s, 6H), 4.78 (m, 1H), 3.15-3.45 (m, 5H), 2.74 (s, 6H), 1.8-2.25 (m, 8H); RP-HPLC (Hypersil CPS, 5 μm, 100A, 250 x 4.6 mm; 25-100% acetonitrile-0.1 M ammonium acetate over 10min, 1ml/min) t_r=8.90 min; MS: MH^+ 471.

Example 224: trans-N1-{4-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]cyclohexyl}-N2,N2-dimethyl-1,2-ethanaediamine monomaleate salt: ^1H NMR (DMSO-d_6, 400MHz) δ 9.5 (bs, 1H), 8.26 (s, 1H), 7.41-7.55 (m, 5H), 7.08-7.19 (m, 5H), 6.7 (bs, 2H), 6.16 (s, 2H), 4.63 (m, 1H), 3.12-3.55 (m, 5H), 2.85 (s, 3H), 2.27 (m, 2H), 1.99-2.05 (m, 4H), 1.67-1.75 (m, 2H); RP-HPLC (Hypersil CPS, 5 μm, 100A, 250 x 4.6 mm; 25-100% acetonitrile-0.1 M ammonium acetate over 10min, 1ml/min) t_r=8.6 min; MS: MH^+ 471.

Example 225: Cis-7-(4-{[3-(1H-1-imidazolyl)propyl]amino}cyclohexyl)-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine trimaleate salt

Trans-7-(4-{[3-(1H-1-imidazolyl)propyl]amino}cyclohexyl)-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine dimaleate salt

Example 227: cis-7-(4-{[3-(1H-1-imidazolyl)propyl]amino}cyclohexyl)-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine trimaleate salt: ^1H NMR (DMSO-d_6, 400MHz) δ 8.78 (bs, 1H), 8.48 (bs, 2H), 8.18 (s, 1H), 7.66 (s, 1H), 7.55 (s, 1H), 7.41-7.49 (m, 5H), 7.08-7.19 (m, 5H), 6.33 (bs, 2H), 6.12 (s, 6H), 4.78 (m, 1H), 4.27 (t, 2H), 2.99 (m, 3H), 1.8-2.25 (m, 10 H); RP-HPLC (Hypersil CPS, 5 μm, 100A, 250 x 4.6 mm; 25-100% acetonitrile-0.1 M ammonium acetate over 10min, 1ml/min) t_r=9.07 min; MS: MH^+ 508.

Example 228: trans-7-(4-{[3-(1H-1-imidazolyl)propyl]amino}cyclohexyl)-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine dimaleate salt: ^1H NMR (DMSO-d_6, 400MHz) δ 8.76 (bs, 1H), 8.51 (bs, 2H), 8.18 (s, 1H), 7.66 (s, 1H), 7.55 (s, 1H), 7.40-7.47 (m, 5H), 7.08-7.21 (m, 5H), 6.3 (bs, 2H), 6.11 (s, 4H), 4.60 (m, 1H), 4.26 (t, 2H), 3.14 (m, 1H), 2.97 (m, 2H), 1.9-2.25 (m, 8H), 1.53-1.61 (m, 2H);

RP-HPLC (Hypersil CPS, 5 µm, 100A, 250 x 4.6 mm; 25-100% acetonitrile-0.1 M ammonium acetate over 10min, 1ml/min) t_r=8.72 min; MS: MH^+ 508.

Example 229: Cis-7-[4-(dimethylamino)cyclohexyl]-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine dimaleate salt

^1H NMR (DMSO-d_6, 400MHz) δ 9.06 (bs, 1H), 8.2 (s, 1H), 7.41-7.50 (m, 5H), 7.08-7.19 (m, 5H), 6.4 (bs, 2H), 6.13 (s, 4H), 4.83 (m, 1H), 3.34 (m, 1H), 2.88 (s, 6H), 2.10-2.17 (m, 4H), 1.88-1.99 (m, 4H); RP-HPLC (Hypersil HS C-18, 5 µm, 100A, 250 x 4.6 mm; 25-100% acetonitrile-0.1 M ammonium acetate over 10min, 1ml/min) t_r=7.38 min; MS: MH^+ 428.

Example 230: Trans-5-(4-phenoxyphenyl)-7-(4-piperidinocyclohexyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine dimaleate salt

^1H NMR (DMSO-d_6, 400MHz) δ 8.92 (bs, 1H), 8.18 (s, 1H), 7.4-7.5 (m, 5H), 7.08-7.19 (m, 5H), 6.3 (bs, 2H), 6.13 (s, 4H), 4.63 (m, 1H), 3.15-3.5 (m, 3H), 2.9-3.1 (m, 2H), 1.16-2.18 (m, 14H); RP-HPLC (Hypersil HS C-18, 5 µm, 100A, 250 x 4.6 mm; 25-100% acetonitrile-0.1 M ammonium acetate over 10min, 1ml/min) t_r=7.98 min; MS: MH^+ 468. Trans-5-(4-phenoxyphenyl)-7-(4-tetrahydro-1H-1-pyrrolylcyclohexyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine dimaleate salt

^1H NMR (DMSO-d_6, 400MHz) δ 9.54 (bs, 1H), 8.18 (s, 1H), 7.40-7.47 (m, 5H), 7.08-7.18 (m, 5H), 6.3 (bs, 1H), 6.12 (s, 4H), 4.63 (m, 1H), 3.1-3.55 (m, 5H), 2.24 (m, 2H), 2.00 (m, 6H), 1.86 (m, 2H), 1.67 (m, 2H); RP-HPLC (Hypersil HS C-18, 5 µm, 100A, 250 x 4.6 mm; 25-100% acetonitrile-0.1 M ammonium acetate over 10min, 1ml/min) t_r=7.82 min; MS: MH^+ 454.

Example 231: Cis-7-[4-(4-methyl-1,4-diazepan-1-yl)cyclohexyl]-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine dihydrochloride salt
Trans-7-[4-(4-methyl-1,4-diazepan-1-yl)cyclohexyl]-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine dihydrochloride salt

cis-7-[4-(4-methyl-1,4-diazepan-1-yl)cyclohexyl]-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine dihydrochloride salt: ^1H NMR (DMSO-d_6, 400MHz) δ 11.7 (d, 1H), 11.38 (d, 1H), 8.57 (s, 1H), 8.34 (d, 1H), 7.42-7.51 (m, 4H), 7.03-7.20 (m, 5H), 4.93 (m, 1H), 4.7 (bs, 2H), 3.4-3.99 (m, 9H), 2.8 (s, 3H), 1.86-2.57 (10 H); RP-HPLC (Hypersil HS C-18, 5 μm, 100A, 250 x 4.6 mm; 25-100% acetonitrile-0.1 M ammonium acetate over 10min, 1ml/min) t_r=7.67 min; MS: MH^+ 497.

trans-7-[4-(4-methyl-1,4-diazepan-1-yl)cyclohexyl]-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine dihydrochloride salt: ^1H NMR (DMSO-d_6, 400MHz) δ 11.94 (d, 1H), 11.52 (d, 1H), 8.56 (s, 1H), 7.8 (s, 1H), 7.42-7.51 (m, 4H), 7.10-7.20 (m, 5H), 4.76 (1H, m)< 3.2-4.0 (m, 9H), 2.80 (s, 3H), 1.78-2.4 (m, 10H); RP-HPLC (Hypersil HS C-18, 5 μm, 100A, 250 x 4.6 mm; 25-100% acetonitrile-0.1 M ammonium acetate over 10min, 1ml/min) t_r=7.42 min; MS: MH^+ 497.

Example 232: Cis-5-(4-phenoxyphenyl)-7-(4-piperazinocyclohexyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine trimaleate salt

Trans-5-(4-phenoxyphenyl)-7-(4-piperazinocyclohexyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine trimaleate salt

a) cis and trans-tert-butyl 4-{4-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]cyclohexyl}-1-piperazinecarboxylate

Example 233: cis-tert-butyl 4-{4-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]cyclohexyl}-1-piperazinecarboxylate: ^1H NMR (DMSO-d_6, 400MHz) δ 8.14 (s, 1H), 7.3-7.5 (m, 6H), 7.07-7.16 (m, 5H), 6.1 (bs, 2H), 4.69 (m, 1H), 3.2-3.4 (4H, m), 2.38 (m, 4H), 2.0-2.25 (m, 5H), 1.5-1.8 (m, 4H), 1.41 (s, 9H); RP-HPLC (Hypersil HS C-18, 5 μm, 100A, 250 x 4.6 mm; 25-100% acetonitrile-0.1 M ammonium acetate over 10min, 1ml/min) t_r=13.60 min.

trans-tert-butyl 4-{4-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]cyclohexyl}-1-piperazinecarboxylate: ^{1}H NMR (DMSO-d_6, 400MHz) δ 8.13 (s, 1H), 7.40-7.47 (m, 6H), 7.08-7.16 (m, 5H), 6.1 (bs, 2H), 4.55 (m, 1H), 3.34 (m, 4H), 2.35-2.51 (m, 3H), 1.89-1.99 (m, 6H), 1.38-1.49 (m, 4H), 1.39 (s, 9H); RP-HPLC (Hypersil HS C-18, 5 µm, 100A, 250 x 4.6 mm; 25-100% acetonitrile-0.1 M ammonium acetate over 10min, 1ml/min) t_r=10.40 min.

b) Cis-5-(4-phenoxyphenyl)-7-(4-piperazinocyclohexyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine trimaleate salt

The cis-tert-butyl 4-{4-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]cyclohexyl}-1-piperazinecarboxylate (1.85 g, 3.27 mmol) was treated with a 20% trifluoroacetic acid/dichloromethane solution (60 ml) and stirred for 30 minutes at ambient temperature. The solvents were removed under reduced pressure then the residue was partitioned between dichloromethane (200 ml) and aqueous saturated sodium bicarbonate solution (30 ml). The organic solution was dried over magnesium sulfate, filtered and the filtrate evaporated to a residue (1.55 g). A portion of this material (1.0 g, 2.15 mmol) was dissolved in warm ethyl acetate (220 ml) then treated with maleic acid (0.75 g, 0.44 mmol) in warm ethyl acetate (75 ml). The mixture was cooled to ambient temperature then the solid was collected by filtration and dried to give Cis-5-(4-phenoxyphenyl)-7-(4-piperazinocyclohexyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine trimaleate salt (1.15 g) as a white solid: ^{1}H NMR (DMSO-d_6, 400MHz) δ 8.5 (bs, 1H), 8.23 (s, 1H), 7.41-7.51 (m, 5H), 7.08-7.19 (m, 5H), 6.65 (bs, 2H), 6.16 (s, 6H), 4.74 (m, 1H), 1.16-3.2 (m, 17H); RP-HPLC (Hypersil CPS, 5 µm, 100A, 250 x 4.6 mm; 25-100% acetonitrile-0.1 M ammonium acetate over 10min, 1ml/min) t_r=8.63 min; MS: MH^+ 469.

c) trans-5-(4-phenoxyphenyl)-7-(4-piperazinocyclohexyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine trimaleate salt

^{1}H NMR (DMSO-d_6, 400MHz) δ 8.22 (s, 1H), 7.41-7.51 (m, 5H), 7.08-7.19 (m, 5H), 6.6 (bs, 2H), 6.16 (s, 6H), 4.58 (m, 1H), 1.4-3.2 (m, 17 H); RP-HPLC

(Hypersil HS C-18, 5 µm, 100A, 250 x 4.6 mm; 25-100% acetonitrile-0.1 M ammonium acetate over 10min, 1ml/min) t_r=8.08 min; MS: MH^+ 469.

Example 234: 7-[3-(4-methylpiperazino)cyclopentyl]-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine tri-maleate

3-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]cyclopentan-1-ol (2.14 g, 0.0055 mol) in 1 l dichloromethane was stirred with 12 g active manganese dioxide for 5 hours, filtered and fresh manganese dioxide (8 g) added to the filtrate. After stirring for a further 17 hours, the mixture was filtered and used directly. HPLC/MS showed starting material and 3-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]-1-cyclopentanone 62.7% t_r 4.38 minutes. The dichloromethane solution was stirred with 1.0 g N-methylpiperazine (0.01 mol) and acetic acid (0.6 g, 0.01 mol) for 15 minutes then sodium triacetoxyborohydride (0.89 g, 0.0042 mol) was added. After 2 hours 1.0 g N-methylpiperazine, 0.6 g acetic acid and 0.89 g sodium triacetoxyborohydride was added and the mixture stirred for 17 hours. Further addition of 2.0 g N-methylpiperazine, 1.2 g acetic acid and 1.2 g sodium triacetoxyborohydride and stirring for 3 days gave a mixture which was evaporated under reduced pressure. The residue was treated with water (200 ml) and 6M – hydrochloric acid (50 ml) then washed with ethyl acetate (discarded) and basified with excess aqueous ammonia. The mixture was extracted with ethyl acetate and the extract dried (sodium sulphate) then purified by flash chromatography in 9:1 ethyl acetate : ethanol to remove impurities followed by 8:1:1 ethyl acetate : ethanol : triethylamine to elute the product. Solvent was removed under reduced pressure, the residue dissolved in ethyl acetate and treated with a solution of maleic acid in ethyl acetate giving 7-[3-(4-methylpiperazino) cyclopentyl]-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine tri-maleate (444395) as a 1.4 solvate with ethyl acetate after drying at 80° C under reduced pressure (0.95 g, 0.001 mol) m.pt. 168-170° C (decomposes).

Example 235: [4-(4-amino-7-cyclopentyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)phenyl](phenyl)-methanol, Sodium borohydride (0.052 g, 0.0013 mol) was added to a solution of [4-(4-amino-7-cyclopentyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)phenyl](phenyl)methanone (0.1 g, 0.00026 mol) in tetrahydrofuran (4 mL) followed by the addition of Amberlyst-15 H^+. The mixture was stirred at ambient temperature under an atmosphere of nitrogen for 15 min, filtered through a celite pad and the solvent removed under reduced pressure. The residue was purified by preparative RP-HPLC (Rainin, Hypersil C18, 8 μm, 100A, 25 cm; 5%-85% acetonitrile – 0.1% ammonium acetate over 20 min, 21 mL/min) to yield [4-(4-amino-7-cyclopentyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)phenyl](phenyl)methanol (0.005 g, 0.000013 mol):

^{1}H NMR (DMSO-d_6, 400MHz) δ 8.12 (s, 1H), 7.31 (m, 10H), 6.01 (br, 2H), 5.91 (d, 1H), 5.75 (d, 1H), 5.06 (m, 1H), 2.10(br, 2H), 1.88 (br, 4 H), 1.67 (br, 2H) RP-HPLC(Delta Pak C18, 5μm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL / min) R_t 16.74 min. MH^+ 385

Example 236: Trans-7-[3-(4-methylpiperazino)cyclohexyl]-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine tri-maleate

trans-7-[3-(4-methylpiperazino)cyclohexyl]-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (1.30 g, 0.0027 mol) in 300 ml warm ethyl acetate was treated with a solution of maleic acid (0.94 g, 0.0081 mol) in 100 ml ethyl acetate and allowed to cool. The colourless solid was collected, washed with ethyl acetate and dried to constant weight at 90° C / 3 mbar giving 1.85 g (0.0022 mol) of trans-7-[3-(4-methylpiperazino)cyclohexyl]-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine tri-maleate solvated with 0.18 mol ethyl acetate m.p. 189° C (decomposes).

Example 237: trans-7-[3-(4-methylpiperazino)cyclohexyl]-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine tri-hydrochloride

trans-7-[3-(4-methylpiperazino)cyclohexyl]-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (0.36 g, 0.00075 mol) in 25 ml warm isopropanol was treated with a solution of 0.225 ml 12M hydrochloric acid (0.0027 mol) in 2 ml isopropanol and the suspension heated briefly to boiling then volatile material was removed under reduced pressure. The resulting colourless solid was dried to constant weight at 84° C / 5 mbar giving the trans-7-[3-(4-methylpiperazino)cyclohexyl]-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine tri-hydrochloride (444626) solvated with 1 mol water and 0.25 mol isopropanol (0.25 g, 0.0004 mol) m.p. 304-306° C(dec).

Example 238: cis-7 -[3-(4-methylpiperazino)cyclohexyl]-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine tri-maleate salt

cis-7 -[3-(4-methylpiperazino)cyclohexyl]-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (1.45 g, 0.0030 mol) in ethyl acetate with 1.05 g (0.0091 mol) maleic acid giving colourless solid after drying to constant weight at 90° C / 3 mbar. 2.15 g cis-7 -[3-(4-methylpiperazino)cyclohexyl]-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine tri-maleate salt solvated with 0.14 mol ethyl acetate and 0.5 mol water (0.0025 mol) obtained m.p. 186 (dec).

Example 239: cis-7 -[3-(4-methylpiperazino)cyclohexyl]-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine tri-hydrochloride

cis-7 -[3-(4-methylpiperazino)cyclohexyl]-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine 0.80 g (0.0017 mol) in isopropanol was treated with 0.5 ml 12M hydrochloric acid (0.006 mol). The resulting solid was filtered to give cis-7 -[3-(4-methylpiperazino)cyclohexyl]-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine tri-hydrochloride as a hygroscopic solid until dried at 80° C / 3 mbar to constant weight. (0.75 g, 0.0011 mol) m.p. 224.5-226.5 (dec).

Example 240: Trans-5-(2-methyl-4-phenoxyphenyl)-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-4-amine trimaleate

A mixture of 3-phenoxytoluene (2.5 g, 0.0136 mol) and N-bromosuccinimide (2.54 g, 0.0142 mol) was stirred in acetonitrile (20 mL) for 2.5 hours under an atmosphere of nitrogen. The solvent was removed under reduced pressure. Carbon tetrachloride was added to the residue and the resulting solid was removed by filtration. The filtrate was concentrated to yield 4-bromo-3-methylphenyl phenyl ether as yellow oil (3.5 g, 0.0133 mol):

^{1}H NMR (Chloroform-d, 400 MHz) δ 7.45 (d, 1H), 7.33 (m, 2H), 7.12 (t, 1H), 7.00 (d, 2H), 6.89 (s, 1H), 6.71 (d, 1H), 2.34 (s, 3H) RP-HPLC (Hypersil C18, 5μm, 250 x 4.6 mm; 25% - 100% over 23 min with 0.1 M ammonium acetate, 1mL/min) R_t 14.72 min.

A mixture of 4-bromo-3-methylphenyl phenyl ether (1.7 g, 0.00646 mol), diboron pinacol ester (2.0 g, 0.00775 mol), [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II) complex with dichloromethane (1:1) (0.16 g, 0.00019 mol) and potassium acetate (1.9 g, 0.01938 mol) in N,N-dimethylformamide (65 mL) was heated at 80 °C under an atmosphere of nitrogen for 22 hours. The mixture was allowed to cool to ambient temperature and the solvent was removed under reduced pressure. Dichloromethane was added to the residue and the resulting solid was removed by filtration through a pad of celite. The filtrate was concentrated into black mixture, which was purified by flash chromatography on silica using ethyl acetate/n-heptane (3:97) as mobile phase to yield 3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl phenyl ether (1.05 g, 0.00338 mol):

^{1}H NMR (Chloroform-d, 400 MHz) δ 7.73 (d, 1H), 7.33(m, 2H), 7.08 (t, 1H), 7.01 (d, 2H), 6.79 (d, 2H), 2.51 (s, 3H), 1.34 (s, 12H) TLC (ethyl acetate / n-heptane = 3 : 97) R_f 0.28

A mixture of 4-chloro-7-(1,4-dioxaspiro[4.5]dec-8-yl)-5-iodo-7H-pyrrolo[2,3-d]pyrimidine (20 g, 47.7 mmol) and 6 N HCl(aq) (60 mL, 360 mmol) in tetrahydrofuran (120 mL) and acetone (600 mL) was stirred at ambient temperature under an atmosphere of nitrogen for 17 hours. The solvent was removed under reduced pressure and 6NHCl(aq) (20 mL), tetrahydrofuran (60 mL), and acetone (300 mL) were added to the mixture. The mixture was stirred at ambient temperature under an atmosphere of nitrogen for 4.5 hour. The solvent was removed under reduced pressure and the yellow colored residue was washed with water to yield 4-(4-chloro-5-iodo-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-1-cyclohexanone (12.3 g, 32.7 mmol). RP-HPLC (Hypersil C18, 5μm, 250 x 4.6 mm; 25% - 100% over 15 min with 0.05 M ammonium acetate, 1mL/min) R_t 10.20 min.

A mixture of 4-(4-chloro-5-iodo-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-1-cyclohexanone (5.6 g, 14.9 mmol), N-methylpiperazine (3.3 mL, 29.8 mmol), acetic acid (2.6 mL, 44.7 mmol), and trimethylorthoformate (9.9 mL, 89.4 mmol) in dichloroethane (100 mL) was stirred at ambient temperature under an atmosphere of nitrogen for 1 hr. Sodium triacetoxyborohydride (14.2 g, 67.05 mmol) was added into the mixture and stirred at ambient temperature under an atmosphere of nitrogen for 18 hours. The solvent was removed under reduced pressure. The residue was partitioned between saturated aqueous sodium bicarbonate solution and ethyl acetate. The water phase was further extracted with ethyl acetate and the combined organic extracts were dried over sodium sulfate. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel using triethylamine/ dichloromethane (2:98) followed by methanol/triethylamine/dichloromethane (2:3:95) as mobile phase to yield trans-4-chloro-5-iodo-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidine (1.7 g, 3.7 mmol). ^{1}H NMR (DMSO-d_6, 400 MHz) 8.63(s, 1H), 8.12 (s, 1H), 4.63 (br, 1H), 2.15 (s, 3H), 1.94 (br, 6H), 1.45 (br, 2H) RP-HPLC (Hypersil C18, 5μm, 250 x 4.6 mm; 25% - 100% over 15 min with 0.05 M ammonium acetate, 1mL/min) R_t 6.17 min.

Trans-4-chloro-5-iodo-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidine (0.89 g, 1.9 mmol) in concentrated ammonium hydroxide (40 mL) and dioxane (40 mL) was heated at 120 °C in a pressure vessel for 18 hours. The mixture was allowed to cool to ambient temperature and the solvent was removed under reduced pressure. The residue was partitioned between saturated aqueous sodium bicarbonate solution and ethyl acetate. The water phase was further extracted with ethyl acetate and the combined organic extracts were washed with brine and dried over sodium sulfate. The solvent was removed under reduced pressure to yield trans-5-iodo-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-

d]pyrimidin-4-amine (0.35 g, 0.8 mmol). RP-HPLC (Hypersil C18, 5μm, 250 x 4.6 mm; 25% - 100% over 15 min with 0.1 M ammonium acetate, 1mL/min) R_t 4.01 min. MS: MH^+ 441

A mixture of trans-5-iodo-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-4-amine (0.347 g, 0.000788 mol), 3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl phenyl ether (0.27 g, 0.000867 mol), tetrakis(triphenyl-phosphine)palladium(0) (0.054 g, 0.000047 mmol), and sodium carbonate (0.209 g, 0.00197 mol) in N,N-dimethylformamide (15 mL) and water (10 mL) was heated at 80 °C under an atmosphere of nitrogen for 16 hours. The mixture was allowed to cool to ambient temperature and the solvent removed under reduced pressure. The residue was partitioned between saturated aqueous sodium bicarbonate solution and ethyl acetate. The water phase was further extracted with ethyl acetate and the combined organic extracts were dried over sodium sulfate. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel using triethylamine/dichloromethane (5:95) followed by methanol/ triethylamine/ dichloromethane (3:5:92) as mobile phase to yield trans-5-(2-methyl-4-phenoxyphenyl)-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-4-amine (0.376 g, 0.000757 mol). Trans-5-(2-methyl-4-phenoxyphenyl)-7-[4-(4-methylpiperazino)-cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-4-amine (0.376 g, 0.000757 mol) was dissolved in refluxing ethanol (10 mL) and a preheated solution of maleic acid (0.264 g, 0.00227 mol) in ethanol (5 mL) was added. The mixture was refluxed for 15 minutes, cooled to ambient temperature and the precipitate collected by filtration, washed with cool ethanol and dried to give trans-5-(2-methyl-4-phenoxyphenyl)-7-[4-(4-methylpiperazino)-cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-4-amine trimaleate (0.153 g, 0.000181 mol): ^1H NMR (DMSO-d_6, 400 MHz) 8.22 (s, 1H), 7.42 (m, 3H), 7.25 (d, 1H), 7.17 (t, 1H), 7.09 (d, 2H), 7.02 (s, 1H), 6.89 (d, 1H), 6.16 (s, 6H), 4.58 (m, 1H), 3.3 (br, 9H), 2.68 (s, 3H), 2.22 (s, 3H), 2.01 (br, 6H), 1.57 (br, 2H) RP-HPLC (Hypersil C18, 5μm, 250 x 4.6 mm; 25% - 100% over 23 min with 0.1 M ammonium acetate, 1mL/min) R_t 7.30 min. MS: MH^+ 497

Example 241: 3-[4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]cyclopentyl 2-aminoacetate hydrochloride

A mixture of 3-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]-1-cyclopentanol (50 mg, 0.129 mmol), 2-[(tert-butoxycarbonyl)amino]acetic acid (34 mg, 0.194 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (31 mg, 0.155 mmol) and 4-(dimethylamino)pyridine (16 mg, 0.129 mmol) in DMF (1 mL) was stirred under nitrogen for 24 hours. The mixture was pour onto ice-water. The aqueous layer was extracted with ethyl acetate three times. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated. The residue was purified by flash column chromatography using ethyl acetate as mobile phase to give 3-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]cyclopentyl 2-[(tert-butoxycarbonyl)amino]acetate (39 mg, 0.072 mmol). HPLC: t_r=19.22 min. (Delta-Pack, C-18, 5um, 300A, 3.9x150 mm; 5-85% acetonitrile-0.1 M ammonium acetate over 20 min, 1ml/min)

3-[4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]cyclopentyl 2-[(tert-butoxycarbonyl)amino]acetate (39 mg, 0.072 mmol) was dissolved in ethyl acetate (2.5 mL). Hydrochloride gas was bubbled through the solution for 3 minutes. The reaction mixture was stirred for additional 30 minutes. Ether was added and the precipatate was collected through filtration under nitrogen to give 3-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]cyclopentyl 2-aminoacetate hydrochloride (39 mg) as white solid. 1H NMR ($DMSO-d_6$) δ 2.20 (m, 5H), 2.67 (m, 1H), 3.83 (s, 2H), 5.25 (m, 1H), 5.31 (m, 1H), 7.14 (m, 2H), 7.43, (m, 1H), 7.50 (m, 1H), 7.68 (m, 1H), 8.26 (bs, 2H), 8.40 (s, 1H). LC/MS: MH^+=444, t_r=2.25 min. (Pecospher, 3C-18, 3um, 4.6x33 mm; 0-100% acetonitrile-0.1 M ammonium acetate over 5 min, 3.5 ml/min)

Example 242: 3-[4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]cyclopentyl N-(2-morpholinoethyl)carbamate hydrochloride

4- Nitrochloroformate (12.5 mg, 0.062 mmol) in dichloromethane (1 mL) was cooled on an ice-water bath. 4-Methylmorpholine (7 uL, 0.062 mmol) was added slowly. After 20 minutes, the ice-water bath was removed and the reaction mixture was allowed to warm up to room temperature. 3-(4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-1-cyclopentanol (20 mg, 0.052 mmol) was added and the reaction mixture was stirred for 4days. The reaction mixture was diluted with dichloromethane. The organic layer was washed with water, saturated sodium bicarbonate, brine, dried over MgSO4, filtered and evaporated to give a yellow solid. A solution of the yellow solid in dichloromethane (1 mL) was added to 2-morpholino-1-ethanamine (0.2 mL). After stirring at room temperature overnight, the reaction mixture was diluted with ethyl acetate. The organic layer was washed with water (3 times), brine, dried over MgSO4, filtered and evaporated. The crude product was purified by HPLC to give 3-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]cyclopentyl N-(2-morpholinoethyl)carbamate (17 mg, 0.031 mmol). 1H NMR ($CDCl_3$-d) δ 2.08 (m, 4H), 2.43 (m, 7H), 2.73 (m, 1H), 3.29 (m, 2H), 3.67, (m, 4H), 5.28 (m, 5H), 7.09 (m, 6H), 7.40 (m, 4H), 8.30 (s, 1H). LC/MS: MH^+=543, t_r=2.13 min. (Pecospher, 3C-18, 3um, 4.6x33 mm; 0-100% acetonitrile-0.1 M ammonium acetate over 5 min, 3.5 ml/min).

3-[4-Amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]cyclopentyl N-(2-morpholinoethyl)carbamate (10 mg, 0.0184 mmol) was dissolved in ethyl acetate (2.5 mL). Hydrochloride gas was bubbled through the solution for 3 minutes. The reaction mixture was stirred for additional 10 minutes. The precipitate was collected through filtration under nitrogen to give 3-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]cyclopentyl N-(2-morpholinoethyl)carbamate hydrochloride as white solid. 1H NMR (DMSO-d_6) δ 1.99 (m, 4H), 2.55(m, 2H), 3.32 (m, 12H), 5.08(m, 1/2H), 5.19 (m, 1/2H), 7.16 (m, 5H), 7.45, (m, 5H), 8.26 (s, 1H). LC/MS: MH^+=543, t_r=2.16 min. (Pecospher, 3C-18, 3um, 4.6x33 mm; 0-100% acetonitrile-0.1 M ammonium acetate over 5 min, 3.5 ml/min).

Example 243: 4-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]cyclohexanol

Sodium borohydride (500mg, 13 mmol) was added in one portion to a stirred solution of 4-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimin-7-yl]cyclohexan-1-one (780mg, 2.0 mmol) in methanol (500 mL), and the mixture stirred under an atmosphere of nitrogen for 1 hour, then left to stand overnight. The solvent was removed under reduced pressure, and the residue partitioned between 2M aqueous sodium hydroxide solution (100 mL) and dichloromethane (100 mL). The organic layer was separated and the aqueous layer further extracted with dichloromethane (2 x 100 mL). The combined organic extracts were washed with water (150 mL), dried over potassium carbonate, and purified by chromatography with a Biotage 40S column using ethyl acetate / triethylamine (98:2 to 95:5) and ethyl acetate / ethanol (95:5) as a mobile phase to yield 4-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]cyclohexanol as a white solid (750mg, 1.9 mmol), melting point: 199-200 deg. C.LC/MS: Hypersil BDS c18 (100 x 2.1 mm) 0.1M ammoniumacetate/acetonitrile, 10-100% acetonitrile in 8 min.)MH^+ 401 , t_r = 4.12 minutes.

Example 244

Phenyl *N*-[4-(4-amino-7-tetrahydro-2*H*-4-pyranyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-methoxyphenyl]carbamate

-(4-Amino-3-methoxyphenyl)-7-tetrahydro-2*H*-4-pyranyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (100 mg, 0.294 mmol) was dissolved in dichloromethane (2 mL). Pyridine (2mL) was added followed by phenylchloroformate (44 uL, 0.353 mmol). After stirring for 3 hours, another 44 uL of phenylmethanesulfonyl chloride was added and the reaction mixture was stirred overnight. The solvent was removed and the residue was purified by preparative LC/MS to give phenyl *N*-[4-(4-amino-7-tetrahydro-2*H*-4-pyranyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-methoxyphenyl]carbamate (52 mg, 0.113 mmol). 1H NMR ($CDCl_3$-*d*) δ 2.09 (m, 4H), 3.66 (m, 2H), 3.98 (s, 3H), 4.16 (m, 2H), 4.98 (m, 1H), 5.24 (s, 2H), 7.09 (m ,3H), 7.23 (m, 4H), 7.41 (m, 2H), 7.62 (s, 1H), 8.20(bd, J=7.80 Hz, 1H), 8.33 (s, 1H). LC/MS MH^+=460.

Example 245

Tetrahydro-2*H*-4-pyranyl *N*-[4-(4-amino-7-tetrahydro-2*H*-4-pyranyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-methoxyphenyl]carbamate 4-nitrophenyl tetrahydro-2*H*-4-pyranyl carbonate

Tetrahydro-2*H*-4-pyranol (1.0 ml, 10.5 mmol) was mixed with 4-methylmorpholine (2.0 ml) in dichloromethane (20 mL). 4- Nitrochloroformate (1.98 g, 9.82 mmol) was added slowly to the reaction mixture. After stirring for 5 hours, the reaction mixture was diluted with dichloromethane. The organic layer was washed with water, 1.0 N HCl, saturated sodium bicarbonate, brine, dried over MgSO4, filtered and evaporated. The crude product was purified by flash column chromatography chromatography using ethyl acetate/heptane (4:1) as the mobile phase to give 4-nitrophenyl tetrahydro-2*H*-4-pyranyl carbonate (1.5 g, 5.62 mmol). 1H NMR ($CDCl_3$-*d*) δ 1.87 (m, 2H), 2.06 (m, 2H), 3.58 (m, 2H), 3.98 (m, 2H), 4.97 (m,1H), 7.40(d, J=9.0Hz, 2H), 8.30 (d, J=9.0Hz, 2H).

a) Tetrahydro-2*H*-4-pyranyl *N*-[4-(4-amino-7-tetrahydro-2*H*-4-pyranyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-methoxyphenyl]carbamate

5-(4-Amino-3-methoxyphenyl)-7-tetrahydro-2*H*-4-pyranyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (57 mg, 0.168 mmol) and 4-nitrophenyl tetrahydro-2*H*-4-pyranyl carbonate (90 mg, 0.336 mmol) was mixed in pyridine (1 mL). After stirring for 5 hours, another 90 mg of 4-nitrophenyl tetrahydro-2*H*-4-pyranyl carbonate was added and the reaction mixture was stirred for 2 days. The reaction mixture was heated at 70°C for 2 hours. The solvent was removed and the residue was purified by preparative thin layer chromatography to give tetrahydro-2*H*-4-pyranyl *N*-[4-(4-amino-7-tetrahydro-2*H*-4-pyranyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-methoxyphenyl]carbamate (30 mg, 0.064 mmol). 1H NMR ($CDCl_3$-*d*) δ 1.78 (m, 4H), 2.08 (m, 4H), 3.60 (m, 4H), 3.94 (s, 3H), 3.97 (m, 2H), 4.15 (m, 2H), 4.98 (m, 2H), 5.23 (s, 2H), 6.78 (s ,1H), 7.04 (s, 1H), 7.07 (d, J=8.3 Hz, 1H), 8.16(bd, J=7.90 Hz, 1H), 8.33 (s, 1H). LC/MS MH^+=468.

Example 246

3-Pyridylmethyl *N*-[4-(4-amino-7-tetrahydro-2*H*-4-pyranyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-methoxyphenyl]carbamate hydrochloride

a) 4-Nitrophenyl (3-pyridylmethyl) carbonate

4- Nitrochloroformate (2.49 g, 12.3 mmol) in dichloromethane (20 mL) was cooled on an ice-water bath. 3-pyridylmethanol (1.0 mL, 10.3 mmol) and 4-methylmorpholine (2.0 mL, 18.5 mmol) was added slowly. After 20 minutes, the ice-water bath was removed and the reaction mixture was allowed to warm up to room temperature. 30 minues later, ethyl acetate was added and the reaction mixture was filtered. The filtrate was washed with water, saturated sodium bicarbonate, brine, dried over MgSO4, filtered and evaporated to give a dark brown solid which was re-crystallized with ethyl acetate/heptane to give 4-nitrophenyl (3-pyridylmethyl) carbonate (1.52 g, 5.54 mmol).1H NMR (CDCl-*d*) δ 7.38 (m, 3H), 7.79 (m, 1H), 8.28 (d, J=9.09Hz, 2H), 8.65 (m, 1H), 8.72 (s,1H).

b) 3-Pyridylmethyl *N*-[4-(4-amino-7-tetrahydro-2*H*-4-pyranyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-methoxyphenyl]carbamate

5-(4-Amino-3-methoxyphenyl)-7-tetrahydro-2*H*-4-pyranyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (25 mg, 0.074 mmol) was dissolved in dichloromethane (0.7 mL). Pyridine (0.7 mL) was added followed by 4-nitrophenyl (3-pyridylmethyl) carbonate (30 mg, 0.110 mmol). After heating at 100°C overnight, the solvent was removed and the residue was purified by preparative LC/MS to give 3-pyridylmethyl *N*-[4-(4-amino-7-tetrahydro-2*H*-4-pyranyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-methoxyphenyl]carbamate (12 mg, 0.025 mmol). 1H NMR ($CDCl_3$-*d*) δ 2.08 (m, 4H), 3.65 (m, 2H), 3.92 (s, 3H), 4.15 (m, 2H), 4.96 (m, 1H), 5.26 (s, 2H), 5.54 (bs, 2H), 6.97 (s, 1H), 7.04(s, 1H), 7.08 (d, J=8.2Hz, 1H), 7.35 (m, 2H), 7.79 (d, J=7.8Hz, 1H), 8.15 (m, 1H), 8.29 (s, 1H), 8.61 (s, 1H), 8.71 (s, 1H). LC/MS MH^+=475

b) 3-Pyridylmethyl *N*-[4-(4-amino-7-tetrahydro-2*H*-4-pyranyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-methoxyphenyl]carbamate hydrochloride

3-Pyridylmethyl *N*-[4-(4-amino-7-tetrahydro-2*H*-4-pyranyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-methoxyphenyl]carbamate (12 mg, 0.025 mmol) was dissolved in ethyl acetate (2.0mL). 1.0N HCl in ether (1 mL) was added slowly. The precipatate was collected through filtration under nitrogen to give 3-pyridylmethyl *N*-[4-(4-amino-7-tetrahydro-2*H*-4-pyranyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-methoxyphenyl]carbamate hydrochloride(13 mg, 0.25 mmol). 1H NMR (DMSO-d_6) δ 1.91 (m, 2H), 2.17(m, 2H), 3.54 (m, 2H), 3.87 (s, 3H), 4.03 (m, 2H), 4.97(m, 1H), 5.23 (s, 2H), 7.05 (d, J=8.2Hz, 1H), 7.13 (s, 1H), 7.51 (m, 1H), 7.81 (d, J=8.2Hz, 1H), 7.84 (s, 1H), 7.95 (m, 1H), 8.42 (s, 1H), 8.60(s, 1H), 8.71 (s, 1H), 8.82 (s, 1H). LC/MS MH^+=475.

Example 247

2-Morpholinoethyl *N*-[4-(4-amino-7-tetrahydro-2*H*-4-pyranyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-methoxyphenyl]carbamate hydrochloride

Phenyl *N*-[4-(4-amino-7-tetrahydro-2*H*-4-pyranyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-methoxyphenyl]carbamate (25 mg, 0.054 mmol) was mixed with 2-morpholino-1-ethanol (0.1 mL) in pyridine (0.7 mL). The reaction mixture was heated at 100°C overnight. The solvent was removed and the residue was purified by preparative reverse phase HPLC to give 2-morpholinoethyl *N*-[4-(4-amino-7-tetrahydro-2*H*-4-pyranyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-methoxyphenyl]carbamate (24 mg, 0.048mmol). The solid was dissolved in ethyl acetate (2 mL) and 1.0N HCl in ether (0.2 mL) was added slowly. The precipitate was collected through filtration under nitrogen to give 2-morpholinoethyl *N*-[4-(4-amino-7-tetrahydro-2*H*-4-pyranyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-methoxyphenyl]carbamate hydrochloride (24 mg, 0.045 mmol). 1H NMR (DMSO-d_6) δ 1.88(m, 2H), 2.16(m, 2H), 3.55 (m, 8H), 3.90 (s, 3H), 4.03 (m, 4H), 4.49(m, 2H), 4.92 (m, 1H), 7.07 (m, 1H), 7.15 (s, 1H), 7.65 (bs, 2H), 7. 84 (s, 1H), 8.45 (s, 1H), 8.75(s, 1H) 10.95 (bs, 1H). LC/MS MH^+=497.

Example 248

(4-Bromo-1,3-thiazol-5-yl)methyl *N*-[4-(4-amino-7-tetrahydro-2*H*-4-pyranyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-methoxyphenyl]carbamate

a)2,4-Dibromo-1,3-thiazole-5-carbaldehyde

1,3-Thiazolane-2,4-dione (3.52 g, 30 mmol) and phosphorus oxybromide (43 g, 150 mmol) were mixed with dimethyl formamide (2.56 mL, 34 mmol). The mixture was then heated at 75°C for 1 hours and at 100oC for 5 hours. After cooled to room temperature, the mixture was added to ice-water (500ml) and the aqueous layer was extracted with dichloromethane. The combined organic layer was washed with saturated sodium bicarbonate, dried over MgSO4, filtered and evaporated to give a brown solid which was washed with petroleum ether. Evaporation of solvent gave 2,4-dibromo-1,3-thiazole-5-carbaldehyde (1.74 g, 6.42 mmol). 1H NMR ($CDCl_3$-*d*) δ 9.90 (S, 1H).

b) (2,4-Dibromo-1,3-thiazol-5-yl)methanol

2,4-Dibromo-1,3-thiazole-5-carbaldehyde (1.74 g, 6.42 mmol) was dissolved in methanol (70 ml) at 0°C. Sodium borohydride (0.244 g, 6.42 mmol) was added in small portions. The ice-water bath was removed 10 minutes later and the reaction mixture was stirred at room temperature overnight. Solvent was removed and saturated ammonium chloride was added. 1.0N NaOH was added to adjust the pH to 10. The aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over MgSO4, filtered and evaporated. The residue was purified by flash column chromatogrphy to give (2,4-dibromo-1,3-thiazol-5-yl)methanol (0.946 g, 3.47 mmol). 1H NMR ($CDCl_3$-*d*) δ 2.11 (bs, 1H), 4.79 (S, 2H).

c) (4-Bromo-1,3-thiazol-5-yl)methanol

(2,4-Dibromo-1,3-thiazol-5-yl)methanol (0.94 g, 3.44 mmol), sodium carbonate tri-hydrade (1.34 g) and palladium on carbon (10%, 0.07g) were mixed in methanol (33 mL). The resulting mixture was hydrogenated at 60 psi for 2 days. The solid was filtered off through a pat of celite. The solvent was evaporated and the residue was purified by frash column chromatography to give (4-bromo-1,3-thiazol-5-yl)methanol (0.32 g, 2.78 mmol). 1H NMR ($CDCl_3$-*d*) δ 2.29 (bs, 1H), 4.86 (s, 2H), 8.72 (s, 1H).

d) (4-Bromo-1,3-thiazol-5-yl)methyl *N*-[4-(4-amino-7-tetrahydro-2*H*-4-pyranyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-methoxyphenyl]carbamate

Phenyl *N*-[4-(4-amino-7-tetrahydro-2*H*-4-pyranyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-methoxyphenyl]carbamate (28 mg, 0.061 mmol) was mixed with (4-bromo-1,3-thiazol-5-yl)methanol (50 mg, 0.434 mmol) in pyridine (0.5 mL). The reaction mixture was heated at 100°C overnight. The solvent was removed and the residue was purified by preparative reverse phase LC/MS to give (4-bromo-1,3-thiazol-5-yl)methyl *N*-[4-(4-amino-7-tetrahydro-2*H*-4-pyranyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-methoxyphenyl]carbamate. 1H NMR (CDCl-*d*) δ 2.07(m, 4H), 3.65 (m, 2H), 3.92 (s, 3H), 4.13 (m, 2H), 4.98 (m, 1H), 5.35 (s, 1H), 5.40(s, 2H), 6.97 (s, 1H), 7.04 (s, 1H), 7.09 (m, 1H), 7.35 (s, 1H), 8.17 (s, 1H), 8.32 (s, 1H), 8.78(s, 1H). LC/MS MH^+=481.

Example 249

Tetrahydro-3-furanyl *N*-[4-(4-amino-7-tetrahydro-2*H*-4-pyranyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-methoxyphenyl]carbamate

Phenyl *N*-[4-(4-amino-7-tetrahydro-2*H*-4-pyranyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-methoxyphenyl]carbamate (30 mg, 0.065 mmol) was mixed with tetrahydro-3-furanol (0.05 mL) in pyridine (0.5 mL). The reaction mixture was heated at 100°C overnight. The solvent was removed and the residue was purified by preparative reverse phase PHLC to give tetrahydro-3-furanyl *N*-[4-(4-amino-7-tetrahydro-2*H*-4-pyranyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-methoxyphenyl]carbamate (14 mg, 0.031mmol). 1H NMR (CDCl-*d*) δ 2.07(m, 6H), 3.66 (m, 2H), 3.96 (m, 7H), 4.13 (m, 2H), 4.98 (m, 1H), 5.26 (s, 2H), 5.40(m, 1H), 6.97 (s, 1H), 7.04 (s, 1H), 7.08 (d, J=8.2Hz, 1H), 7.26 (s, 1H), 8.30 (s, 1H), 8.32 (s, 1H). LC/MS MH^+=455.

Examples 250

1,3-Dioxan-5-yl *N*-[4-(4-amino-7-tetrahydro-2*H*-4-pyranyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-methoxyphenyl]carbamate

1,3-Dioxolan-4-ylmethyl *N*-(4-(4-amino-7-tetrahydro-2*H*-4-pyranyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-methoxyphenyl)carbamate

Phenyl *N*-[4-(4-amino-7-tetrahydro-2*H*-4-pyranyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-methoxyphenyl]carbamate (30 mg, 0.065 mmol) was mixed glycerol formal (0.05 mL) in pyridine (0.5 mL). The reaction mixture was heated at 100°C overnight. The solvent was removed and the residue was purified by preparative reverse phase PHLC to give tetrahydro-3-furanyl *N*-[4-(4-amino-7-tetrahydro-2*H*-4-pyranyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-methoxyphenyl]carbamate (2 mg, 0.004mmol). 1H NMR (CDCl-*d*) δ 2.06(m, 4H), 3.66 (m, 2H), 3.92 (m, 3H), 4.07 (m, 6H), 4.79 (m, 1H), 4.83 (d, J=6.3Hz, 1H), 4.96 (m, 1H), 5.04(d, J=6.3Hz, 1H), 6.15 (vbs, 2H), 6.96 (s, 1H), 7.05 (m, 2H), 7.53 (s, 1H), 8.15 (d, J=8.2Hz, 1H), 8.22 (s, 1H). LC/MS MH^+=471 and 1,3-dioxolan-4-ylmethyl *N*-(4-(4-amino-7-tetrahydro-2*H*-4-pyranyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-methoxyphenyl)carbamate(6.0mg, 0.013 mmol). 1H NMR (CDCl-*d*) δ 2.06(m, 4H), 3.66 (m, 2H), 3.75 (m, 1H), 3.92 (m, 3H), 4.03 (m, 1H), 4.13 (m, 1H), 4.34 (m, 2H), 4.94 (s, 1H), 4.97 (m, 1H), 5.10(s, 1H), 5.32 (bs, 2H), 6.97 (s, 1H), 7.03 (m, 2H), 7.06 (d, J=8.2Hz, 1H), 7.38(s, 1H), 8.15 (d, J=7.9Hz, 1H), 8.31 (s, 1H). LC/MS MH^+=471.

Example 251

2-Pyridylmethyl *N*-[4-(4-amino-7-tetrahydro-2*H*-4-pyranyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-methoxyphenyl]carbamate hydrochloride

Phenyl *N*-[4-(4-amino-7-tetrahydro-2*H*-4-pyranyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-methoxyphenyl]carbamate (30 mg, 0.065 mmol) was mixed 2-pyridylmethanol (0.05 mL) in pyridine (0.5 mL). The reaction mixture was heated at 100°C overnight. The solvent was removed and the residue was purified by preparative reverse phase LC/MS to give 2-pyridylmethyl *N*-[4-(4-amino-7-tetrahydro-2*H*-4-pyranyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-methoxyphenyl]carbamate (11 mg, 0.023 mmol). The solid was dissolved in ethyl acetate (2 mL) and 1.0N HCl in ether (0.1 mL) was added slowly. The precipitate was collected through filtration under nitrogen to give 2-pyridylmethyl *N*-[4-(4-amino-7-tetrahydro-2*H*-4-pyranyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-methoxyphenyl]carbamate hydrochloride (12 mg, 0.023 mmol). 1H NMR (DMSO-d_6) δ 1.92(m, 2H), 2.16(m, 2H), 3.55 (m, 2H), 3.89 (s, 3H), 4.02 (m, 2H), 4.91 (m, 1H), 5.23 (s, 2H), 7.05 (d, J=8.2Hz, 1H), 7.14 (s, 1H), 7.37 (m, 1H), 7. 53 (d, J=7.8Hz, 1H), 7.87 (m, 3H), 8.42(s, 1H), 8.57 (d, J=4.2Hz, 1H), 8.85 (s, 1H). LC/MS MH^+=475.

Example 252

4-Pyridylmethyl *N*-[4-(4-amino-7-tetrahydro-2*H*-4-pyranyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-methoxyphenyl]carbamate Hydrochloride

Phenyl *N*-[4-(4-amino-7-tetrahydro-2*H*-4-pyranyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-methoxyphenyl]carbamate (30 mg, 0.065 mmol) was mixed 4-pyridylmethanol (0.05 mL) in pyridine (0.5 mL). The reaction mixture was heated at 100°C overnight. The solvent was removed and the residue was purified by preparative reverse phase LC/MS to give 2-pyridylmethyl *N*-[4-(4-amino-7-tetrahydro-2*H*-4-pyranyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-methoxyphenyl]carbamate (11 mg, 0.023 mmol). The solid was dissolved in ethyl acetate (2 mL) and 1.0N HCl in ether (0.1 mL) was added slowly. The precipatate was collected through filtration under nitrogen to give 4-pyridylmethyl *N*-[4-(4-amino-7-tetrahydro-2*H*-4-pyranyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-methoxyphenyl]carbamate hydrochloride (12 mg, 0.023 mmol). 1H NMR (DMSO-d_6) δ 1.91(m, 2H), 2.16(m, 2H), 3.55 (m, 2H), 3.90 (s, 3H), 4.03 (m, 2H), 4.92 (m, 1H), 5.34 (s, 2H), 7.06 (d, J=8.2Hz, 1H), 7.16 (s, 1H), 7.73 (m, 1H), 7. 81 (m, 1H), 7.87 (s, 1H), 8.46(s, 1H), 8.76 (d, J=5.6Hz, 1H), 9.05 (s, 1H). LC/MS: MH^+=475.

Example 253

(5-Methyl-3-isoxazolyl)methyl *N*-[4-(4-amino-7-tetrahydro-2*H*-4-pyranyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-methoxyphenyl]carbamate

Phenyl *N*-[4-(4-amino-7-tetrahydro-2*H*-4-pyranyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-methoxyphenyl]carbamate (30 mg, 0.065 mmol) was mixed with (5-methyl-3-isoxazolyl)methanol (0.05 mL) in pyridine (0.5 mL). The reaction mixture was heated at 100°C overnight. The solvent was removed and the residue was purified by preparative reverse phase LC/MS to give (5-methyl-3-isoxazolyl)methyl *N*-[4-(4-amino-7-tetrahydro-2*H*-4-pyranyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-methoxyphenyl]carbamate (18 mg, 0.038mmol). 1H NMR (CDCl-*d*) δ 2.06(m, 4H), 2.44 (s, 3H), 3.64 (m, 2H), 3.91 (s, 3H), 4.13 (m, 2H), 4.96 (m, 1H), 5.26 (s, 2H), 6.12(s, 1H), 6.95 (s, 1H), 7.06 (m, 2H), 7.39 (s, 1H), 8.17 (bs, 1H), 8.21(s, 1H). LC/MS: MH^+ 479.

Example 254

[(2*S*)-5-Oxotetrahydro-1*H*-2-pyrrolyl]methyl *N*-[4-(4-amino-7-tetrahydro-2*H*-4-pyranyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-methoxyphenyl]carbamate

Phenyl *N*-[4-(4-amino-7-tetrahydro-2*H*-4-pyranyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-methoxyphenyl]carbamate (30 mg, 0.065 mmol) was mixed with (5*S*)-5-(hydroxymethyl)tetrahydro-1*H*-2-pyrrolone (0.05 mL) in pyridine (0.5 mL). The reaction mixture was heated at 100°C overnight. The solvent was removed and the residue was purified by preparative reverse phase LC/MS to give [(2*S*)-5-oxotetrahydro-1*H*-2-pyrrolyl]methyl *N*-[4-(4-amino-7-tetrahydro-2*H*-4-pyranyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-methoxyphenyl]carbamate (10 mg, 0.021mmol). 1H NMR (CDCl-*d*) δ 1.90 (m, 1H), 2.06(m, 4H), 2.34 (m, 1H), 2.41 (m, 2H), 3.64 (m, 2H), 3.94 (s, 3H), 4.04(m, 2H), 4.14 (m, 2H), 4.98 (m, 1H), 5.33 (m, 3H), 6.10(s, 1H), 6.98 (s, 1H), 7.04 (s, 1H), 7.09 (m, 1H), 7.31(s, 1H), 8.11 (bs, 1H), 8.32 (s, 1H). LC/MS: MH^+ 481.

Example 255

4-Aminobenzyl *N*-(4-(4-amino-7-tetrahydro-2*H*-4-pyranyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-methoxyphenyl)carbamate

a) *tert*-Butyl *N*-(4-(hydroxymethyl)phenyl)carbamate

(4-Aminophenyl)methanol (1.23 g, 10 mmol) and diisopropylethylamine (2.6 mL, 15 mmol) was mixed with di-*tert*-butyl dicarbonate (2.62 g, 12 mmol) in dichloromethane (50 mL). The mixture was stirred at room temperature overnight. Ethyl acetate was added and the organic layer was washed with water, 1.0N HCl, saturated sodium carbonate, water, brine, dried over MgSO4, filtered and evaporated. The crude product was purified by flash column chromatography with Ethyl acetate/heptane (2:3) to give *tert*-butyl *N*-(4-(hydroxymethyl)phenyl)carbamate (2.16g, 9.67 mmol). 1H NMR (CDCl-*d*) δ 1.52 (s, 9H), 4.63 (s, 2H), 6.47 (bs, 1H), 7.30 (d, 8.5Hz, 2H), 7.36 (d, 8.5Hz,2H).

b) 4-Aminobenzyl *N*-(4-(4-amino-7-tetrahydro-2*H*-4-pyranyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-methoxyphenyl)carbamate

Phenyl *N*-[4-(4-amino-7-tetrahydro-2*H*-4-pyranyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-methoxyphenyl]carbamate (51mg, 0.111 mmol) was mixed with *tert*-butyl *N*-(4-(hydroxymethyl)phenyl)carbamate (119 mg, 0.533) in pyridine (0.8 mL). The reaction mixture was heated at 100°C overnight. The solvent was removed and the residue was purified by preparative reverse phase LC/MS to give 4-aminobenzyl *N*-(4-(4-amino-7-tetrahydro-2*H*-4-pyranyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-methoxyphenyl)carbamate

(9 mg, 0.015mmol). 1H NMR (CDCl-*d*) δ 1.52(s, 1H), 2.08(m, 4H), 3.65 (m, 2H), 3.90 (s, 3H), 4.14(m, 2H), 4.97 (m, 1H), 5.17 (s, 2H), 5.37(bs, 1H), 6.55 (s, 1H), 6.95 (s, 1H), 7.03 (s, 1H), 7.06 (m, 1H), 7.31(s, 1H), 7.38 (m, 3H), 8.16 (bs, 1H), 8.30 (s, 1H). LC/MS: MH^+ 589.

Example 256

*N*1-[4-(4-Amino-7-tetrahydro-2*H*-4-pyranyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-methoxyphenyl]benzamide

5-(4-Amino-3-methoxyphenyl)-7-tetrahydro-2*H*-4-pyranyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (80mg, 0.236 mmol) was dissolved in dichloromethane (2.0 mL). Pyridine (2.0 mL) was added followed by benzoyl chloride (41 uL, 0.353 mmol). After stirring at room temperature for 2 hours, the solvent was removed and the residue was dissolved in 1 ml DMSO, methanol (1 mL) was added and precipitate was formed. The solid was collected by filtration to give *N*1-[4-(4-amino-7-tetrahydro-2*H*-4-pyranyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-methoxyphenyl]benzamide (64 mg, 0.144 mmol). 1H NMR ($CDCl_3$-*d*) δ 2.12 (m, 4H), 3.67 (m, 2H), 3.99 (s, 3H), 4.17(m, 2H), 4.99 (m, 1H), 7.03(s, 1H), 7.04 (s, 1H), 7.14 (d, J=8.2Hz, 1H), 7.53 (m, 3H), 7.94(d, J=7.8Hz, 1H), 8.33 (s, 1H), 8.58 (s, 1H), 8.63 (d, J=8.2Hz, 1H). LC/MS: MH^+=444

Example 257

*N*2-[4-(4-Amino-7-tetrahydro-2*H*-4-pyranyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-methoxyphenyl]-2-pyridinecarboxamide

5-(4-Amino-3-methoxyphenyl)-7-tetrahydro-2*H*-4-pyranyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (80mg, 0.236 mmol) was dissolved in dichloromethane (2.0 mL). Pyridine (2.0 mL) was added followed by 2-pyridinecarbonyl chloride hydrochloride (63 mg, 0.353 mmol). After stirring at room temperature for 2 hours, the solvent was removed and the residue was dissolved in 1 ml DMSO, methanol (1 mL) was added and precipitate was formed. The solid was collected by filtration to give *N*1-[4-(4-amino-7-tetrahydro-2*H*-4-pyranyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-methoxyphenyl]benzamide (84 mg, 0.189 mmol). 1H NMR ($CDCl_3$-*d*) δ 2.12 (m, 4H), 3.67 (m, 2H), 4.03 (s, 3H), 4.14(m, 2H), 5.00 (m, 1H), 5.37 (s, 1H), 7.04(s, 1H), 7.09 (s, 1H), 7.14 (d, J=8.2Hz, 1H), 7.50 (m, 1H), 7.92 (m, 1H), 8.33 (s, 1H), 8.70(d, J=8.2Hz, 1H), 10.62 (s, 1H). LC/MS: MH^+=445.

Example 258

*N*5-[4-(4-Amino-7-tetrahydro-2*H*-4-pyranyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-methoxyphenyl]-1,3-dimethyl-1*H*-5-pyrazolecarboxamide

5-(4-Amino-3-methoxyphenyl)-7-tetrahydro-2*H*-4-pyranyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (80mg, 0.236 mmol) was dissolved in dichloromethane (2.0 mL). Pyridine (2.0 mL) was added followed by 2-pyridinecarbonyl chloride hydrochloride (63 mg, 0.353 mmol). After stirring at room temperature for 2 hours, the solvent was removed and the residue was dissolved in 1 ml DMSO, methanol (1 mL) was added and precipitate was formed. The solid was collected by filtration to give *N*5-[4-(4-amino-7-tetrahydro-2*H*-4-pyranyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-methoxyphenyl]-1,3-dimethyl-1*H*-5-pyrazolecarboxamide (30 mg, 0.065 mmol). 1H NMR ($CDCl_3$-*d*) δ 2.11 (m, 4H), 2.32 (s, 3H), 3.66 (m, 2H), 3.99 (s, 3H), 4.13(m, 2H), 4.17 (s, 3H), 4.99 (m, 1H), 5.22 (bs, 2H), 6.46 (s, 1H), 7.03 (s, 1H), 7.07 (s, 1H), 7.12 (d, J=8.2Hz, 1H), 8.33 (2, 2H), 8.49(d, J=8.2Hz, 1H). LC/MS: MH^+=462.

Example 259

*N*1-[4-(4-Amino-7-tetrahydro-2*H*-4-pyranyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-methoxyphenyl]-2,2-dimethylpropanamide

5-(4-Amino-3-methoxyphenyl)-7-tetrahydro-2*H*-4-pyranyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (50mg, 0.147 mmol) was dissolved in dichloromethane (1.5 mL). Pyridine (1.5 mL) was added followed by 2,2-dimethylpropanoyl chloride (31 mg, 0.221 mmol). After stirring at room temperature for 2 hours, the solvent was removed and the residue was dissolved in 1 ml DMSO, methanol (1 mL) was added and precipitate was formed. The solid was collected by filtration to give *N*1-[4-(4-amino-7-tetrahydro-2*H*-4-pyranyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-methoxyphenyl]-2,2-dimethylpropanamide (27 mg, 0.064 mmol). 1H NMR ($CDCl_3$-*d*) δ 1.35 (s, 9H), 2.09 (m, 4H), 3.66 (m, 2H), 3.96 (s, 3H), 4.13(m, 2H), 4.97 (m, 1H), 5.46(bs, 2H), 6.98 (s, 1H), 7.04 (s, 1H), 7.07 (d, J=8.2Hz, 1H), 8.15 (s, 1H), 8.29 (s, 1H), 8.49(d, J=8.2Hz, 1H). LC/MS: MH^+=424.

Example 260

*N*1-[4-(4-Amino-7-tetrahydro-2*H*-4-pyranyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-methoxyphenyl]-1-cyclopentanecarboxamide

5-(4-Amino-3-methoxyphenyl)-7-tetrahydro-2*H*-4-pyranyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (50mg, 0.147 mmol) was dissolved in dichloromethane (1.5 mL). Pyridine (1.5 mL) was added followed by 1-cyclopentanecarbonyl chloride (31 mg, 0.221 mmol). After stirring at room temperature for 2 hours, the solvent was removed and the residue was dissolved in 1 ml DMSO, methanol (1 mL) was added and precipitate was formed. The solid was collected by filtration to give *N*1-[4-(4-amino-7-tetrahydro-2*H*-4-pyranyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-methoxyphenyl]-2,2-dimethylpropanamide (33 mg, 0.076mmol). 1H NMR ($CDCl_3$-*d*) δ 1.66 (m, 2H), 1.81 (m, 2H), 1.95 (m, 4H), 2.06 (m, 4H), 2.77 (m, 1H), 3.65 (m, 2H), 3.94 (s, 3H), 4.15(m, 2H), 4.96 (m, 1H), 5.37(bs, 2H), 6.98 (s, 1H), 7.03 (s, 1H), 7.07 (d, J=8.2Hz, 1H), 7.84 (s, 1H), 8.30 (s, 1H), 8.49(d, J=8.2Hz, 1H). LC/MS: MH^+=437.

Example 261

*N*1-[4-(4-Amino-7-tetrahydro-2*H*-4-pyranyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-methoxyphenyl]-3-phenylpropanamide

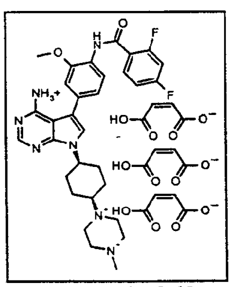
5-(4-Amino-3-methoxyphenyl)-7-tetrahydro-2*H*-4-pyranyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (50mg, 0.147 mmol) was dissolved in dichloromethane (1.5 mL). Pyridine (1.5 mL) was added followed by 3-phenylpropanoyl chloride (37 mg, 0.221 mmol). After stirring at room temperature for 2 hours, the solvent was removed and the residue was dissolved in 1 ml DMSO, methanol (1 mL) was added and precipitate was formed. The solid was collected by filtration to give *N*1-[4-(4-amino-7-tetrahydro-2*H*-4-pyranyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-methoxyphenyl]-2,2-dimethylpropanamide (7 mg, 0.015mmol). 1H NMR ($CDCl_3$-*d*) δ 2.07 (m, 4H), 2.75 (m, 2H), 3.09 (m,2H), 3.65 (m, 2H), 3.88 (s, 3H), 4.13(m, 2H), 4.96 (m, 1H), 5.97(bs, 2H), 6.93 (s, 1H), 7.05 (m, 2H), 7.26 (m, 5H), 7.70 (s, 1H), 8.24 (s, 1H), 8.46(d, J=8.2Hz, 1H). LC/MS: MH^{+}=472.

Examples 262-267 were synthesized using the following procedure:

a)

A mixture of cis-5-(4-amino-3-methoxyphenyl0-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-4-amine (0.25 g, 0.575 mmol), pyridine (2.5 ml) and dichloromethane (2.5 ml) was treated with the appropriate acid chloride (0.862 mmol) and then stirred at ambient temperature under an atmosphere of nitrogen for 1 hour. The solvents were removed under reduced pressure and the residue was purified by preparative reverse phase chromatography. The compound (280 mg, 0.460 mmol) was dissolved in hot ethyl acetate (25 ml) then treated with maleic acid (160 mg, 1.38 mmol) dissolved in ethyl acetate (10 ml) the mixture was allowed to cool to ambient temperature then stirred for 1 hour. The solid was collected by filtration and dried to give the compound as the trimaleate salt. (370 mg).

Analytical RP-HPLC RT listed in the table were obtained on a Hypersil HS C18 column ((5 um, 100A) 250 x 4.6 mm) using a linear gradient of 25-100% acetonitrile/0.1 M ammonium acetate over 10 min at 1ml/min. Retention time is indicated by "RT" Mass spectrum molecular weights are indicated by "MH+".

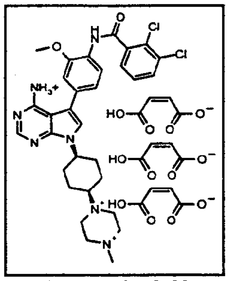


Example 262

RT 6.62

MH+ 576.3

Gradient a

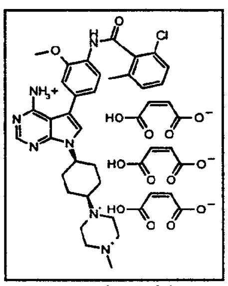


Example 263

RT 7.7

MH+ 608.2

Gradient a

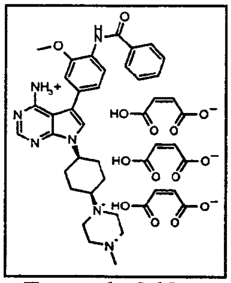


Example 264

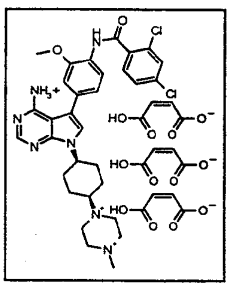
RT 14.23

MH+ 588.3

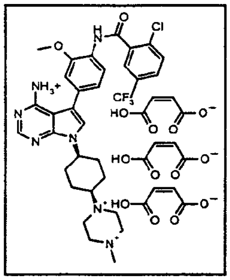
Gradient b



Example 265
RT 6.85
MH+540.2
Gradient a



Example 266
RT 8.15
MH+ 608.2
Gradient a



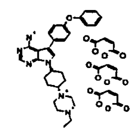
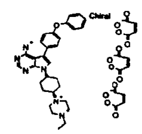
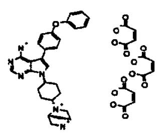
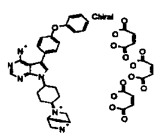
Example 267
RT 8.15
MH+ 642.3

General salt formation procedure:

Trans- benzyl *N*-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-2-methoxyphenyl)carbamate was dissolved in ethylacetate and treated with maleic acid (280 mg) in ethylacetate. The resulting solid was filtered under a stream of nitrogen and dried *in vacuo* for 4 hr to give *Cis*-benzyl *N*-(4-{4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-2-methoxyphenyl)carbamate tri-maleate salt (580 mg) as a cream solid. M.pt. 158°C (dec.) ^{1}H NMR (d_6 DMSO, 400 MHz):8.74 (1H, s), 8.27 (1H, s), 7.78 (1H, d), 7.35-7.77 (5H, m), 7.10 (1H, s), 7.04 (1H, s), 6.16 (6H, s), 5.17 (2H, s), 4.74 (1H, m), 3.82 (3H, s), 3.23 (5H, m), 2.78 (3H, s), 2.51 (3H, m), 2.41 (1H, s), 2.09 (4H, m), 1.70 (4H, m). HPLC: (5 to 95% CH_3CN in 0.1 N aqueous ammonium acetate over 20 min.) t_r = 13.30 min , 94%.

In a similar manner were prepared the following salts. The LCMS conditions are described below.

LSMS data: Perkin Elmer Pecosphere C18, 3mM, 33 x 4.6, 3.5 ml/min 100 – 100% 50 mM ammonium acetate to acetonitrile in 4.5 minutes

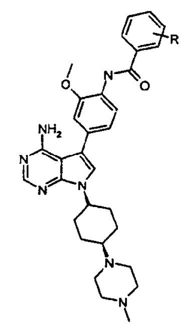
Structure	Ret. Time	MH+
	2.92	497.1
	3.02	497.2
	2.64	481.2
	2.7	481.2

Example 268: *Cis* and *trans*-*N*1-(4-4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl-2-methoxyphenyl)-3-phenylpropanamide

To 4-[4-amino-5-(4-amino-3-methoxyphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl]-1-cyclohexanone (0.8 g, 2.3 mmol) in pyridine/dichloromethane (1:2.5, 45 ml) was added hydrocinnamylchloride (0.57 g, 3.4 mmol) in dichloromethane (2 ml) at 0°C under a flow of nitrogen. The solution was stirred at 0°C for 2 hr. The solution was quenched with saturated aquoeus citric acid solution (50 ml) and the organic layer was washed with saturated aquoeus citric acid solution (2 x 50 ml). Dry, filter and concentrate to leave a brown foam (1.0 g). This was dissolved in dichloroethane (100 ml) and N-methylpiperazine (0.63 g, 6.3 mmol) and acetic acid (0.38 g, 6.3

mmol) was added. Sodium triacetoxyborohydride (0.67 g, 3.15 mmol) was added portionwise under nitrogen and the mixture stirred overnight at room temperature. Quench with saturated aq. NaHCO3 solution (50 ml) and extract with dichloromethane (3 x 100 ml). The combined organics were dried (sodium sulphate), filtered and evaporated to leave a sludge which was purified by flash silica gel column chromatography using dichloromethane / methanol (100/0 to 50/50 in 5%increments). The fractions corresponding to the faster running material were combined to give *cis*- *N*1-(4-4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl-2-methoxyphenyl)-3-phenylpropanamide (0.26 g) as a glass. This was dissolved in ethylacetate (5 ml) and maleic acid (160 mg) in ethylacetate (2 ml) added. The resulting solid was filtered to give cis- *N*1-(4-4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl-2-methoxyphenyl)-3-phenylpropanamide trimaleate salt (260 mg) as a white solid. Analytical LC/MS conditions: Column: Pecosphere, C18, 3 um, 33x4.6 mm. Eluent: 0% B/A to 100% B/A in 4.5 min.(B: acetonitrile, A: 50 mM ammonia acetate buffer, PH 4.5) , 3.5 mL/min. (r_t = 2.86 mins, 568.4).

The fractions corresponding to the slower running material were combined to give trans-*N*1-(4-4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl-2-methoxyphenyl)-3-phenylpropanamide (0.11 g) as a glass. This was dissolved in ethylacetate (5 ml) and treated with a solution of maleic acid (68 mg) in ethylacetate (2 ml). The resulting solid was filtered to give trans-*N*1-(4-4-amino-7-[4-(4-methylpiperazino)cyclohexyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl-2-methoxyphenyl)-3-phenylpropanamide tri-maleate (94 mg) as a white solid. Analytical LC/MS conditions: Column: Pecosphere, C18, 3 um, 33x4.6 mm. Eluent: 0% B/A to 100% B/A in 4.5 min.(B: acetonitrile, A: 50 mM ammonia acetate buffer, PH 4.5) , 3.5 mL/min. (r_t = 2.68mins, 568.2).



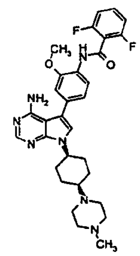
4-[4-amino-5-(4-amino-3-methoxyphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl]-1-cyclohexanone (2.25 g, 6.5 mmol), acetic acid (1.17 g, 19.5 mmol) and N-methylpiperazine (1.95 g, 19.5 mmol) were dissolved in dichloroethane (200 ml). Sodium triacetoxyborohydride (2.07 g, 9.75 mmol) was added portionwise and the mixture stirred at room temperature overnight. Saturated sodium bicarbonate solution (150 ml) was added and the aqueous layer extracted with dichloromethane (3 x 100 ml). The combined organics were washed with water, dried (sodium sulphate), filtered and evaporated to leave a semi-solid whaich was purified by flash silica gel column chromatography using CH_2Cl_2 / methanol (0% MeOH to 50% MeOH in 5% increments). The fractions corresponding to the faster running material were combined and evaporated to give *cis*- 5-(4-amino-3-methoxyphenyl)-7-[4-(4-methylpiperazino)cyclohexyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (1.2 g, 43%) as a cream solid. ^{1}H NMR (d_6-DMSO): δ 8.1 (1H, s), 7.11 (1H, s), 6.87 (1H, s), 6.79 (1H, d), 6.05 (2H, bs), 4.80 (2H, bs), 4.64 (1H, m), 4.08 (1H, m), 3.82 (3H, s), 3.17 (2H, m), 2.37 (6H, m), 2.21 (3H, s), 2.08 (4H, m), 1.70 (2H, m), 1.53 (2H, m). HPLC (r_t = 11.24 min, 97.6%).

The fractions corresponding to the slower running material were combined and evaporated to give *trans*- 5-(4-amino-3-methoxyphenyl)-7-[4-(4-methylpiperazino)cyclohexyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (0.4 g, 14%) as a white solid. ^{1}H NMR (d_6-DMSO): δ 8.10 (1H, s), 7.26 (1H, s), 6.87 (1H, s), 6.77 (1H, d), 6.71 (1H, d), 6.05 (2H, bs), 4.79 (2H, s), 4.52 (1H, m), 3.81 (3H, s), 3.35

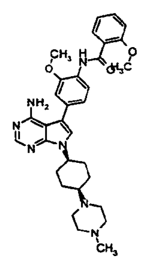
(1H, m), 2.50 (5H, m), 2.31 (5H, m), 2.14 (1H, m), 1.97 (6H, m), 1.45 (2H, m). HPLC (r_t= 10.13 min, 97.9%).

To a solution of *cis*- 5-(4-amino-3-methoxyphenyl)-7-[4-(4-methylpiperazino)cyclohexyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (30 mg, 0.069 mmol) in pyridine (0.5 ml) was added the appropriate acid chloride (2 eq., 0.138 mmol).. The vials were capped and shaken overnight on an orbital shaker. Another two equivalent of acid chlorides (0.138 mmol) was added in two portions (1 equivalent each) and the resulting mixtures were shaken overnight again. LCMS (Micromass- Column: Pecosphere, C18, 3 um, 33x4.6 mm. Eluents: 0% B/A to 100% B/A in 4.5 min.(B: acetonitrile, A: 50 mM ammonia acetate buffer, PH 4.5) , 3.5 mL/min.) of the resulting mixtures showed presence of product in all cases. The solutions were evaporated to dryness and the resulting residues were re- dissolved in a small volume of DMF and purified by reverse phase prep. HPLC. The structures are detailed below alongwith the appropriate LCMS data.

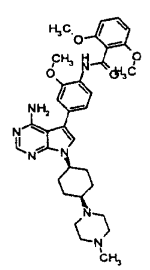
Examples 269 to 293 were made by methods analogous to Example 268.



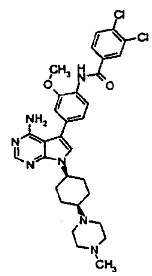
Example 269
RT 2.61
MH+ 576.3



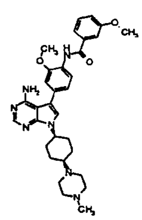
Example 270
RT 3.02
MH+ 570.3



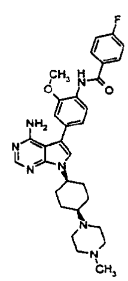
Example 271
RT 2.61
MH+ 600.3



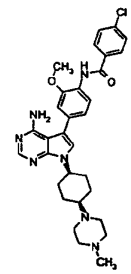
Example 272
RT 3.26
MH+ 608.3



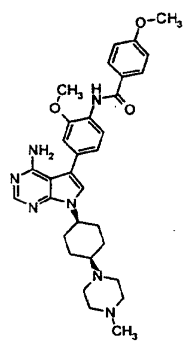
Example 273
RT 2.74
MH+ 570.3



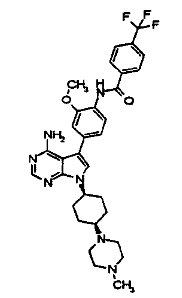
Example 274
RT 2.78
MH+ 558.4



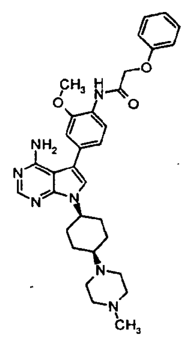
Example 275
RT 3.00
MH+ 574.3



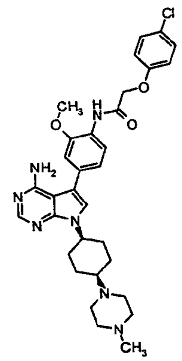
Example 276
RT 2.76
570.3



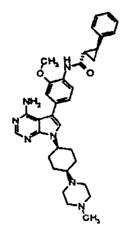
Example 277
RT 3.26
MH+ 608.3



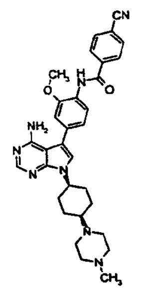
Example 278
RT 2.94
MH+ 570.3



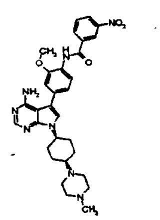
Example 279
RT 3.13
MH+ 604.3



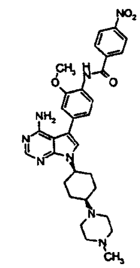
Example 280
RT 3.16
580.3



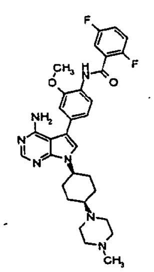
Example 281
RT 2.68
MH+ 565.3



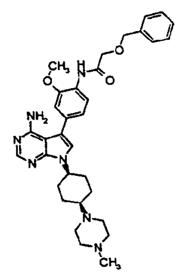
Example 282
RT 2.90
MH+ 585.3



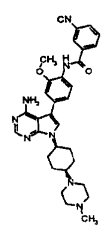
Example 283
RT 2.84
MH+ 585.3



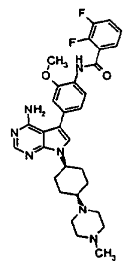
Example 284
RT 2.90
MH+ 576.3



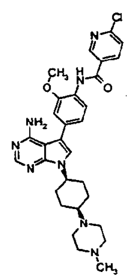
Example 285
RT 2.90
MH+ 584.4



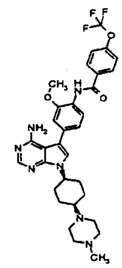
Example 286
RT 2.74
MH+ 565.6



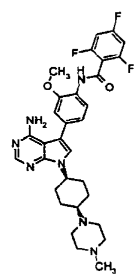
Example 287
RT 3.06
MH+ 576.3



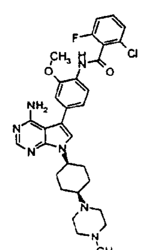
Example 288
RT 2.53
MH+ 575.3



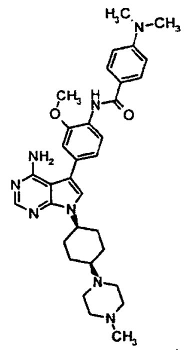
Example 289
RT 3.32
MH+ 624.3



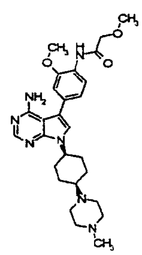
Example 290
RT 2.85
MH+ 594.4



Example 291
RT 2.76
MH+ 592.3



Example 292
RT 2.86
MH+ 583.3



Example 293
RT 2.29
MH+ 508.3

General Synthesis for examples 294-301:

Method A

A mixture of the appropriate piperazine (7.60 mmol), 4-[4-amino-5-(4-phenoxyphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl]-1-cyclohexanone (2.53 mmol), and glacial acetic acid (7.60 mmol) in 50 mL of dichloroethane was stirred at room temperature for 1.5 hours. Sodium triacetoxyborohydride (3.28 mmol) was added and the mixture was stirred at room temperature for 16 hours. A solution of 1.35 g of sodium bicarbonate in 50 mL of water was added and the reaction mixture was stirred for 1 hour. The organic portion was separated, dried over magnesium sulfate, filtered, and the filtrate concentrated to afford a brown oil. Purification by flash chromatography on silica gel afforded the *cis*- and *trans*-7-[(4-piperazino)cyclohexyl]-5-(4-phenoxyphenyl)-7*H*-pyrrolo[2,3-d]pyrimidin-4-amines.

Method B

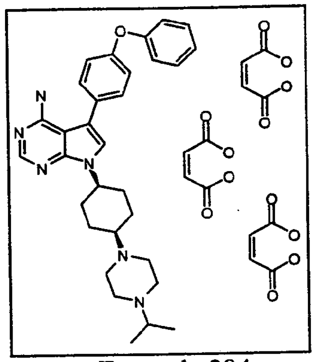
A mixture of the appropriate pyrrolidine (7.53 mmol), 4-[4-amino-5-(4-phenoxyphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl]-1-cyclohexanone (2.51 mmol), and glacial acetic acid (7.35 mmol) in 45 mL of dichloroethane was stirred at room temperature for 30 minutes. Sodium triacetoxyborohydride (3.26 mmol) was added and the mixture was stirred at room temperature for 22 hours. A solution of 1.35 g of sodium bicarbonate in 50 mL of water was added and the reaction mixture was stirred for 1 hour. The organic portion was separated, dried over magnesium sulfate, filtered, and the filtrate concentrated to afford a brown oil. Purification by flash chromatography on silica gel afforded the *cis*- and *trans*-7-(4-pyrrolidino)cyclohexyl]-5-(4-phenoxyphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amines.

Salt Formation

To a warm solution of pyrrolopyrimidine (2.48 mmol; from methods A or B, above) in ethanol was added a solution of maleic acid (7.28 mmol) in ethanol. A white precipitate formed as the solution was cooled to ambient temperature. The resulting solid was isolated by filtration and dried under vacuum to yield the desired tris maleate salt.

Analytical RP-HPLC RT listed in the table were obtained on a Hypersil HyPurity Elite

C18 column ((5uM, 200 A) 250 x 4.6 mm) using a linear gradient of 25-100% acetonitrile/0.1 M ammonium acetate over 10 min. (gradient a) or 25 min. (gradient b) at 1 mL/min.

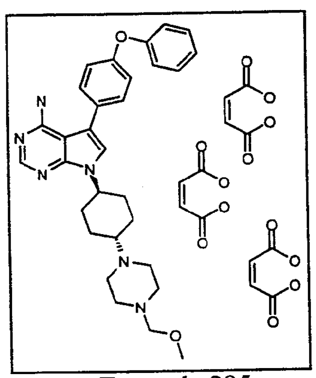


Example 294

RT 7.967

MH+ 511.1

Gradient a

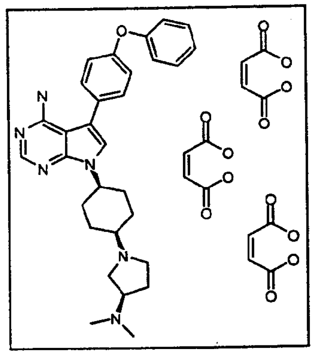


Example 295

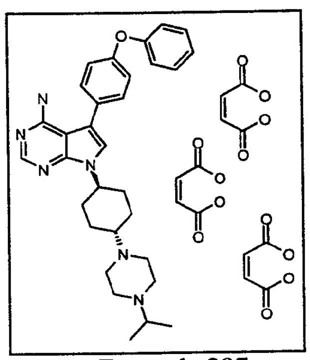
RT 7.383

MH+ 527.2

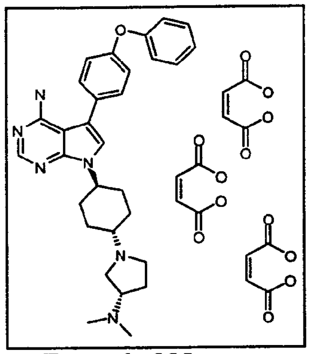
Gradient a



Example 296
RT 13.941
MH+ 497.1
Gradient b



Example 297
RT 7.733
MH+ 511.2
Gradient a

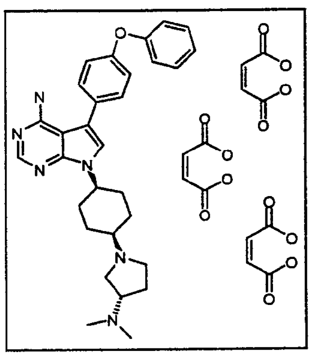


Example 298

RT 14.067

MH+ 497.1

Gradient b

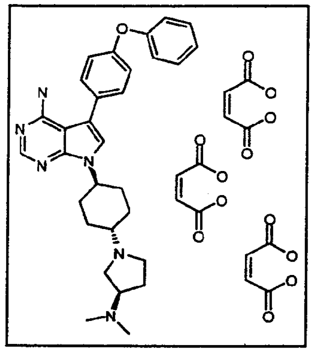


Example 299

RT 13.891

MH+ 497.1

Gradient b

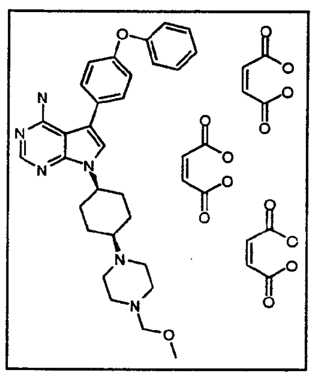


Example 300

RT 14.076

MH+ 497.1

Gradient b



Example 301

RT 7.750

MH+ 527.2

Gradient a

Example 302: Cis and trans 4-[4-amino-5-(4-phenoxyphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl]-1-hydroxycyclohexylmethyl cyanide

A solution of diisopropylamine (0.649 g, 0.0050 mol) in tetrahydrofuran (10 mL) was cooled to 0° C. A solution of 1.6 M n-butyl lithium (3.14 mL, 0.0050 mol) in hexanes was added dropwise, keeping the temperature less than 5° C. After the addition was complete, the mixture was stirred for 20 minutes at 0° C. The mixture was cooled to –78° C, and dry acetonitrile (0.175 g, 0.0043 mol) was added, keeping the temperature less than –70° C. After the addition was complete, the mixture was stirred for 20 minutes at
-78° C, and a mixture of 4-[4-amino-5-(4-phenoxyphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl]-1-cyclohexanone (1.000 g, 0.0025 mmol) in tetrahydrofuran (10 mL) and hexamethylphosphoramide (10 mL) was added, keeping the temperature less than –70° C. After the addition was complete, the mixture was stirred for 30 minutes at -78° C, then stirred at ambient temperature for 18 hours. The mixture was partitioned between dichloromethane and saturated ammonium chloride (aq). The organic phase was washed with water and saturated sodium bicarbonate (aq), and dried over magnesium sulfate. The solvent was removed *in vacuo* and the cis and trans isomers were separated by flash column chromatography on silica using dichloromethane/methanol (95:5) as an eluent to give less polar 4-[4-amino-5-(4-phenoxyphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl]-1-hydroxycyclohexylmethyl cyanide (0.120g, 0.00027 mol) and more polar 4-[4-amino-5-(4-phenoxyphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl]-1-hydroxycyclohexylmethyl cyanide (0.170g, 0.00038 mol):

Less polar:

^{1}H NMR (DMSO-d_6, 400MHz) δ 8.13 (s, 1H), 7.48 (d, 2H), 7.41 (t, 2H), 7.37 (s, 1H), 7.15 (t, 1H), 7.093 (d, 2H), 7.088 (d, 2H), 6.11 (b, 2H) 5.05 (s, 1H), 4.53-4.61 (m, 1H), 2.66 (s, 2H), 2.18 (q, 2H), 1.80 (t, 4H) 1.66 (t, 2H); RP-HPLC (Delta Pak C18, 5μm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 15.90. MH^+ 440.

More polar: (Probably trans, aryl-axial, OH-axial)

^{1}H NMR (DMSO-d_6, 400MHz) δ 8.13 (s, 1H), 7.63 (s, 1H), 7.48 (d, 2H), 7.41 (t, 2H), 7.15 (t, 1H), 7.11 (d, 2H), 7.08 (d, 2H), 6.11 (b, 2H) 5.22 (s, 1H), 4.62-4.67 (m, 1H), 2.98 (s, 2H), 1.82-1.99 (m, 6H), 1.65-1.73 (m, 2H); RP-HPLC (Delta Pak C18, 5μm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 15.88. MH$^+$ 440.

Example 303: *cis- and trans- 5-(4-amino-3-fluorophenyl)-7-[4-(4-methylpiperazino)cyclohexyl]-7H-pyrrolo[2,3-d]pyrimidin-4-amine*

a) tert-Butyl N-(4-bromo-2-fluorophenyl)carbamate

Sodium bis(trimethylsilyl)amide solution (1.0*M* soln. in THF, 2.05 equiv., 270 mL, 270 mmol) was added dropwise to a solution of 4-bromo-2-fluoroaniline (24.78 g, 130.4 mmol) in THF (250 mL) over 15 min. under nitrogen. After a further 15 min., di-*tert*-butyl dicarbonate (1.2 equiv., 34.12 g, 156.3 mmol) was added portionwise (note: a slight exotherm was observed). The reaction became very viscous and after 4 h. reached completion (t.l.c. analysis using 1:9 EtOAc:heptane as the eluent). The reaction was concentrated *in vacuo* and the residue was partitioned between EtOAc (300 mL) and saturated aq. $NaHCO_3$ (150 mL). The aqueous layer was further extracted EtOAc (2 x 200 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. Purification by column chromatography using a 10% to 15% EtOAc : heptane gradient afforded *tert-butyl N-(4-bromo-2-fluorophenyl)carbamate* a light yellow waxy solid (30.0 g, 79%), ^{1}H NMR (400 MHz, $CDCl_3$) 1.51 (9H, *s*), 7.22 (1H, *m*), and 7.24 (2H, *m*).

b) tert-Butyl N-[2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]carbamate

A solution of the tert-butyl N-(4-bromo-2-fluorophenyl)carbamate (54.0 g, 0.186 mmol), *bis*-pinacolatodiborane (1.2 equiv, 56.8 g, 223.3 mmol), potassium