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Viewpoint

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JAK Kinase Inhibitors as Possible Treatment for Myeloproliferative Disorders and Cancer

Patent Highlight

Ahmed F. Abdel-Magid*

Therachem Research Medilab (India) Pvt. Ltd., Jaipur, India

Title:	2-(Imidazolylamino)pyridine Derivatives and Their Use as JAK kinase Inhibitors		
Patent/Patent Application Number:	WO 2010/020810A1	**Publication Date:**	February 25, 2010
Priority Application:	61/090,122	**Priority Date:**	August 19, 2008, US
Inventors:	Almeida, Lynsie; Chuaqui, Claudio E.; Ioannidis, Stephanos; Lamb, Michelle; Peng, Bo; Su, Qibin		
Assignee Company:	AstraZeneca UK Limited		
Disease Area:	Myeloproliferative Disorders and Cancer	**Biological Target:**	JAK kinase

Summary:

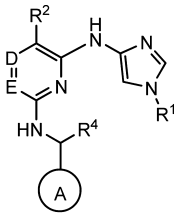
The compounds of **Formula (I)** are believed to possess JAK kinase inhibitory activity and may provide a treatment for myeloproliferative disorder and cancer (myeloproliferative disorders are the name for a group of conditions that cause blood cells, platelets, white blood cells, and red blood cells to grow abnormally in the bone marrow).

JAK (Janus-associated kinase)/STAT (signal transducers and activators of transcription) pathway transmits information from chemical signals outside the cell, through the cell membrane, and into gene promoters on the DNA in the cell nucleus, which causes DNA transcription and activity in the cell. It is involved in a variety of hyperproliferative and cancer-related processes.

The patent application states that the compounds of formula (**1**) "*are expected to be of value in the treatment or prophylaxis of myeloproliferative disorders.*" Examples of such disorders are "*chronic myeloid leukemia, polycythemia vera, essential thrombocythemia, myeloid metaplasia with myelofibrosis, idiopathic myelofibrosis, chronic myelomonocytic leukemia and hypereosinophilic syndrome, myelodysplasticsyndromes and cancers selected from oesophageal cancer, myeloma, hepatocellular, pancreatic, cervical, cancer, Ewings sarcoma, neuroblastoma, Kaposi's sarcoma, ovarian cancer, breast cancer, colorectal cancer, prostate cancer, bladder cancer, melanoma, lung cancer – non small cell lung cancer (NSCLC), and small cell cancer (SCLC), gastric cancer, head and nick cancer, mesothelioma, renal cancer, lymphoma and leukemia; particularly myeloma, leukemia, ovarian cancer, breast cancer and prostate cancer.*"

Important Compound Classes:

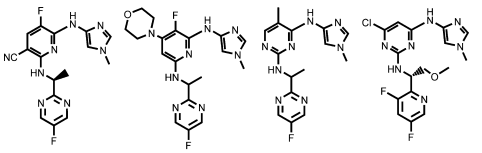
The structures claimed in the application are represented generally by formula (I):



Formula (I)

Key Structures:

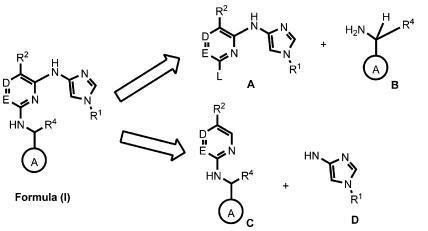
The patent application describes the synthesis of 27 examples of the compounds of formula (I) in the racemic and the enantomeric forms; the following four structures are representative of these examples:



Example 3(a) Example 11 Example 13 Example 23

Synthesis:

The compounds of **Formula (1)** were prepared by either reacting A with B or reacting C with D as illustrated below:



Formula (I) A B C D

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Claims:	Claims 1−8: composition of matter; variations of formula (I)
	Claim 9: 67 compounds are claimed specifically by name
	Claims 10−14: a pharmaceutical composition and method for treating cancer
	Claim 15: a process for preparation of compounds of formula (I)
Recent Review Articles:	Seavey, M. M.; Dobrzanski, P. The many faces of Janus kinase. *Biochem. Pharmacol.* **2012**, *83* (9), 1136−1145.
	Mair, M.; Blaas, L.; Osterreicher, C. H.; Casanova, E.; Eferl, R. JAK-STAT signaling in hepatic fibrosis. *Front. Biosci., Landmark Ed.* **2011**, *16* (7), 2794−2811.
	Quintaas-Cardama, A.; Verstovsek, S. New JAK2 inhibitors for myeloproliferative neoplasms. *Expert Opin. Invest. Drugs* **2011**, *20* (7), 961−972.
	Alicea-Velazquez, N. L.; Boggon, T. J. The use of structural biology in Janus kinase targeted drug discovery. *Curr. Drug Targets* **2011**, *12* (4), 546−555.

AUTHOR INFORMATION

Corresponding author

*Address: 1383 Jasper Drive, Ambler, Pennsylvania, 19002, United States. Tel: 215-913-7202. E-mail: afmagid@comcast.net.

Notes

The authors declare no competing financial interest.