2,6-DIAMINO-PYRIMIDIN-5-YL-CARBOXAMIDES AS ~~INHIBITORS OF~~ SYK OR JAK ~~PROTEIN~~ KINASES INHIBITORS

CROSS REFERENCES TO RELATED APPLICATIONS

[0001] This application is claims the benefit of U.S. Provisional Patent Application No. 61/120,348, filed December 5, 2008; U.S. Provisional Patent Application No. 61/120,346, filed December 5, 2008; U.S. Provisional Patent Application No. 61/045,406, filed April 16, 2008; and U.S. Provisional Patent Application No. 61/045,499, filed April 16, 2008; the entire disclosures of which are incorporated herein by reference.

BACKGROUND OF THE INVENTION

[0002] This invention is directed to pyrimidine-5-carboxamide compounds which act as inhibitors of Spleen tyrosine kinase (syk) and/or `JAK kinases. This invention is also directed to pharmaceutical compositions containing the pyrimidine-5-carboxamide compounds and methods of using the compounds or compositions to treat a condition characterized by other indications. The invention is also directed to methods of making the compounds described herein.

State of the Art

[0003] Protein kinases constitute a large family of structurally related enzymes that are responsible for the control of a variety of signal transduction processes within cells (see, e.g., Hardie and Hanks, The Protein Kinase Facts Book, I and II, Academic Press, San Diego, Calif., 1995). Protein kinases are thought to have evolved from a common ancestral gene due to the conservation of their structure and catalytic function. Almost all kinases contain a similar 250-300 amino acid catalytic domain. The kinases can be categorized into families by the substrates they phosphorylate (e.g., protein-tyrosine, protein-serine/threonine, lipids, etc.). Sequence motifs have been identified that generally correspond to each of these families (see, e.g., Hanks & Hunter, (1995), FASEB J. 9:576-596; Knighton et al., (1991), Science 253:407-414; Hiles et al., (1992), Cell 70:419-429; Kunz et al., (1993), Cell 73:585-596; Garcia-Bustos et al., (1994), EMBO J. 13:2352-2361).

[0004] Many diseases are associated with abnormal cellular responses triggered by protein kinase-mediated events. These diseases include autoimmune diseases, inflammatory diseases, bone diseases, metabolic diseases, neurological and neurodegenerative diseases, cancer, cardiovascular diseases, allergies, asthma, alzheimer's disease and hormone-related diseases.

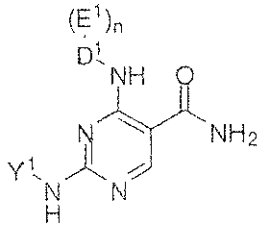
As a consequence, there has been substantial efforts in medicinal chemistry to find inhibitors of protein kinases for use as therapeutic agents.

(WO 05/016893), the disclosures of which are incorporated herein by reference. Substituted pyrimidinediamine compounds are also described in international patent application publication numbers: WO 02/059110, WO 03/074515, WO 03/106416, WO 03/066601, WO 03/063794, WO 04/046118, WO 05/016894, WO 05/122294, WO 05/066156, WO 03/002542, WO 03/030909, WO 00/39101, WO 05/037800 and U.S. Pat. Pub. No. 2003/0149064.

[0028] While progress has been made in this field, there remains a need in the art for compounds that inhibit syk kinase, as well as for methods for treating conditions in a patient, such as restenosis, thrombosis, and/or inflammation that can benefit from such inhibition. Moreover, the availability of compounds that selectively inhibit one of these kinases as compared to other kinases would also be desirable. The present invention satisfies this and other needs.

~~BRIEF~~ SUMMARY ~~OF THE INVENTION~~

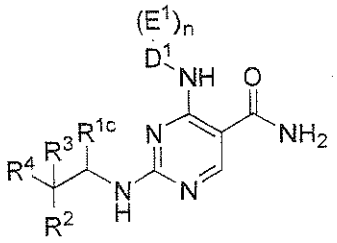
[0029] The present ~~invention~~disclosure provides novel compounds having activity inhibitors of syk activity (also referred to herein as "syk inhibitors") kinase activity (also referred to herein as "JAK inhibitors"), as well as to methods for their preparation and use, and to pharmaceutical compositions containing the same. Such compounds have the following structure (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein D^1, E^1 and Y^1 are as defined below.

[0029a] In one aspect, there is provided a compound having formula (I):



(I)

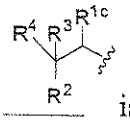
or a tautomer thereof or a pharmaceutically acceptable salt thereof,

wherein:

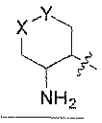
D^1 is phenyl substituted with heteroaryl;

each E^1 is independently selected from the group consisting of C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8}alkynyl, C_{1-8}alkoxy, C_{1-8}alkylthio, aminocarbonyl, C_{1-8}alkoxycarbonylC_{1-8}alkylene, C_{1-8}alkoxycarbonyl$C_{1-8}C_{1-8}$alkoxy, C_{1-8}alkoxycarbonylamino, oxo, halo, cyano, haloC_{1-8}alkyl, haloC_{1-8}alkoxy, aminosulfonyl, heteroarylsulfinyl; amino, hydroxyl, C_{1-8}arylalkylene, phenyl, aminoC_{1-8}alkyl, aminoC_{3-8}cycloalkyl, heterocyclyl, heteroaryl, C_{1-8}acyl, C_{1-8}alkylsulfonyl, acylamino and heterocyclylC_{1-8}alkylene;

the subscript n is 0, 1, 2, 3 or 4; the moiety:

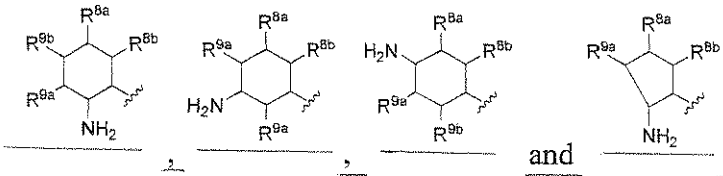
 is either:

(a)

 ; and

wherein X and Y is each independently selected from the group consisting of: CH_2, NH, $NCOCH_3$ and S;

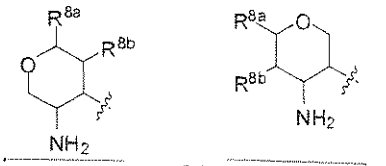
(b) selected from the group consisting of:

 and ; and

wherein each R^{8a} and R^{8b} is independently H, hydroxyl, halo or if on adjacent carbon atoms, may be combined with the atoms to which they are attached to form a fused benzene ring; and

each R^{9a} and R^{9b} is independently H, hydroxyl, halo or, if on adjacent carbon atoms, may be combined with the atoms to which they are attached to form a fused benzene ring; and the wavy line indicates the point of attachment to the rest of the molecule; or

(c)

 or ;

wherein each R^{8a} and R^{8b} is independently H or may be combined with the atoms to which they are attached to form a fused benzene ring; and the wavy line indicates the point of attachment to the rest of the molecule; and "cycloalkyl" refers to a mono- or polycyclic aliphatic hydrocarbon group, which may form a bridged ring or a spiro ring, and which may have one or more double or triple bond(s).

[0030] The present ~~invention~~disclosure also provides a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula I, or a pharmaceutical acceptable salt thereof, and a pharmaceutically acceptable carrier and/or diluent.

[0030a] In another aspect, there is provided a composition comprising a compound as defined herein in combination with a pharmaceutically acceptable carrier or diluent.

[0031] The compounds of the present ~~invention~~disclosure have utility over a wide range of therapeutic applications, and may be used to treat a variety of conditions, mediated at least in

part by syk activity, in both men and women, as well as a mammal in general (also referred to herein as a "subject"). For example, such conditions include, but are not limited to, those associated with cardiovascular disease, inflammatory disease or autoimmune disease. More specifically, the compounds of the present ~~invention~~disclosure have utility for treating conditions or disorders including, but not limited to: restenosis, thrombosis, inflammation, heparin induced thrombocytopenia, dilated cardiomyopathy, sickle cell disease, atherosclerosis, myocardial infarction, vascular inflammation, unstable angina, acute coronary syndromes, allergy, asthma, rheumatoid arthritis, B-cell mediated diseases such as Non Hodgkin's lymphoma, anti-phospholipid syndrome, lupus, psoriasis, multiple sclerosis, end stage renal disease, hemolytic anemia, immune thrombocytopenic purpura, and chronic lymphocytic leukemia. Thus, in one embodiment, methods are disclosed which include the administration of an effective amount of a compound of formula (I), typically in the form of a pharmaceutical composition, to a subject in need thereof.

[0031a] In another aspect, there is provided a compound or a composition as defined herein for use in a method for treating a condition or disorder mediated at least in part by syk kinase activity in a subject.

[0032] The conditions associated with cardiovascular disease is selected from the group consisting of acute coronary syndrome, myocardial infarction, unstable angina, refractory angina, occlusive coronary thrombosis occurring post-thrombolytic therapy or post-coronary angioplasty, a thrombotically mediated cerebrovascular syndrome, embolic stroke, thrombotic stroke, transient ischemic attacks, venous thrombosis, deep venous thrombosis, pulmonary embolism, coagulopathy, disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, thromboangiitis obliterans, thrombotic disease associated with heparin-induced thrombocytopenia, thrombotic complications associated with extracorporeal circulation, thrombotic complications associated with instrumentation such as cardiac or other intravascular catheterization, intra-aortic balloon pump, coronary stent or cardiac valve, and conditions requiring the fitting of prosthetic devices.

[0033] The present ~~invention~~disclosure also provides a method for inhibiting the syk kinase activity of a blood sample comprising contacting said sample with a compound of the present ~~invention~~disclosure.

[0033a] In another aspect, there is provided a compound or a composition as defined herein for use in a method for inhibiting syk or JAK kinase or a signal transduction pathway mediated at least in part by syk kinase activity.

In another aspect, there is provided a kit comprising a composition as defined herein for use in a method for inhibiting syk or JAK kinase or a signal transduction pathway mediated at least in part by syk kinase activity, packaging and instructions for use.

[0034] The present ~~invention~~disclosure further provides compounds in purified forms, as well as chemical intermediates.

[0035] These and other aspects, objects, features and advantages of the ~~invention~~disclosure will be apparent upon reference to the following detailed description and figures. To this end, various references are set forth herein which describe in more detail certain background