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(54) Title: HETEROCYCLIC INHIBITORS OF PTPN11

(57) Abstract: The present invention relates to compounds which may be useful as inhibitors of PTPN11 for the treatment or prevention of cancer and other PTP-mediated diseases. The compounds are based on various substituted ring-fused pyrimidin-4-ones.

HETEROCYCLIC INHIBITORS OF PTPN11

[001] This application claims the benefit of priority of United States provisional Application No 62/307,103, filed March 11, 2016, the disclosure of which is hereby incorporated by reference as if written herein in its entirety.

[002] Disclosed herein are new compounds and compounds based on ring-fused pyrimidin-4-ones and their application as pharmaceuticals for the treatment of disease. Methods of inhibition of PTPN11 (SHP2) activity in a human or animal subject are also provided for the treatment diseases such as cancer, including leukemia and melanoma, and cancers of the breast, lung, and colon.

[003] Tyrosyl phosphorylation regulates human cellular processes from cell differentiation to growth and apoptosis, and others. Tyrosyl phosphorylation is regulated by protein-tyrosine kinases (PTK) and protein-tyrosine phosphatases (PTP). The breakdown of regulation governed by PTK and PTP activity is thought to lead to cancer. PTK inhibitors have been developed as potential cancer therapeutic agents. Recent studies disclose a possible role for PTPs in cellular regulation as well. (AJ Barr et al. Cell 2009, 136, 352-363. JN Andersen et al Mol. Cell. Biol. 2001, 21, 7117-7136).

[004] Protein-tyrosine phosphatase non-receptor type 11 (PTPN11, also known as Src Homology-2 phosphatase (SHP2)) is a non-receptor protein tyrosine phosphatase encoded by the PTPN11 gene. This PTP contains two tandem Src homology-2 (SH2) domains, which function as phospho-tyrosine binding domains, a catalytic domain, and a C-terminal tail. In the basal state the protein typically exists in an inactive, self-inhibited conformation with the N-terminal SH2 domain blocking the active site. When stimulated by signal transduction mediated by cytokines and growth factor binding of phosphorylated proteins to the SH2 domains the auto-inhibition is relieved, this makes the active site available for dephosphorylation of PTPN11 substrates (MG Mohl, BG Neel, Curr. Opin. Genetics Dev. 2007, 17, 23–30. KS Grossmann, Adv. Cancer Res. 2010, 106, 53-89. W.Q. Huang et. al. Curr. Cancer Drug Targets 2014, 14, 567-588. C. Gordon et. al. Cancer Metastasis Rev. 2008, 27, 179-192.).

[005] Germ-line and somatic mutations in PTPN11 have been reported in several human disease resulting in gain-of-function in the catalytic activity, including Noonan Syndrome and Leopard Syndrome; as well as multiple cancers such as juvenile myelomonocytic leukemia, neuroblastoma, myelodysplastic syndrome, B cell acute lymphoblastic leukemia/lymphoma, melanoma, acute myeloid leukemia and cancers of the breast, lung and colon (MG Mohl, BG

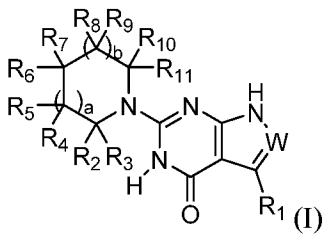
Neel, Curr. Opin. Genetics Dev. 2007, 17, 23–30). Recent studies have demonstrated that single PTPN11 mutations are able to induce Noonan syndrome, JMML-like myeloproliferative disease and acute leukemia in mice. These mutations disrupt the auto-inhibition between the N-SH2 domains and the catalytic site allowing constitutive access of substrates to the catalytic site of the enzyme (E. Darian et al, Proteins, 2011, 79, 1573-1588. Z-H Yu et al, JBC, 2013, 288, 10472, W Qiu et al BMC Struct. Biol. 2014, 14, 10).

[006] PTPN11 is widely expressed in most tissues and plays a regulatory role in various cell signaling events that are important for a diversity of cell functions that includes proliferation, differentiation, cell cycle maintenance, EMT transition, mitogenic activation, metabolic control, transcription regulation, and cell migration, through multiple signaling pathways including the Ras-MAPK, the JAK-STAT or the PI3K-AKT pathways (Tajan, M. et. al. Eur. J. Medical Genetics, 2015, 58, 509-525. Prahallad, A. et. al. Cell Reports, 2015, 12, 1978-1985).

[007] Additionally there is growing evidence that PTPN11/SHP2 may be implicated in immune evasion during tumoregenesis, and hence a SHP2 inhibitor could stimulate the immune response in cancer patients (Cancer Res. 2015 Feb 1;75(3):508-18. T Yokosuka T, J Exp Med. 2012, 209(6), 1201. S Amarnath Sci Transl Med. 2011, 3, 111ra120. T Okazaki, PNAS 2001, 98:24, 13866-71).

[008] Novel compounds and pharmaceutical compositions, certain of which have been found to inhibit PTPN11 (SHP2) have been discovered, together with methods of synthesizing and using the compounds including methods for the treatment of PTP-mediated diseases in a patient by administering the compounds.

[009] In certain embodiments of the present invention, compounds have structural Formula I:



(I)

or a salt, ester, or prodrug thereof, wherein:

a is selected from 0 and 1;

b is selected from 0 and 1;

W is selected from CR_{14} and N;

R_1 is selected from halo, C_{6-10}aryl, C_{3-8}cycloalkyl, C_{3-8}cycloalkenyl, and a 5-9 membered heteroaryl group containing 1 to 4 heteroatoms or groups independently selected from N, C(O), O, and S;

said aryl or heteroaryl of R_1 is optionally substituted with 1 to 5 R_{12} groups independently selected from halo, hydroxy, amino, dimethylamino, CN, C_{1-4} alkyl, C_{1-4}hydroxyalkyl, C_{1-4}haloalkyl, C_{1-4}aminoalkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkenyl, $NR_{15a}C(O)R_{13}$, $NR_{15a}C(O)OR_{13}$, $NR_{13}C(O)N(R_{15a})(R_{15b})$, $NR_{15a}S(O)R_{13}$, $NR_{15a}S(O)_2R_{13}$, $C(O)N(R_{15a})(R_{15b})$, $S(O)N(R_{15a})(R_{15b})$, $S(O)_2N(R_{15a})(R_{15b})$, $C(O)R_{13}$, $C(O)OR_{13}$, SR_{13}, $S(O)R_{13}$, and $S(O)_2R_{13}$;

R_2, R_3, R_{10}, and R_{11} are independently selected from hydrogen, C_{1-4}alkyl, ,and C_{3-8}cycloalkyl;

R_4, R_5, R_8, and R_9 are independently selected from hydrogen, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, amino, hydroxy, C_{3-8}cycloalkyl, halo, and C_{1-4} alkylamino;

R_6 is selected from amino, C_{1-4}aminoalkyl, and methylamino;

R_7 is selected from hydrogen, halo, and hydroxy, or is selected from C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{3-6}cycloalkyl, phenyl, and 5- or 6- membered heteroaryl, any of which may be optionally substituted with one or more substituents chosen from amino, halo, hydroxy, cyano, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, and C_{1-4}alkoxy;

or R_6 and R_7 together with the carbon atom to which they are both attached can form a 3- to 7- membered ring that can optionally contain 1 to 3 heteroatoms or groups independently selected from N, C(O), O, and $S(O)_m$, and said ring formed by R_6 and R_7 can be unsubstituted or substituted with 1 to 3 groups independently selected from halo, hydroxy, methoxy, amino, methylamino, C_1-C_4alkylaminoalkyl, and C_1-C_4 alkyl;

m is selected from 0,1, and 2;

said saturated ring formed by R_6 and R_7 can be unsubstituted or substituted with 1 to 3 groups independently selected from amino, hydroxy, methoxy, halo, methyl, methylamino, C_1-C_4 alkyl, C_1-C_4aminoalkyl and isobutyroxy;

any two groups selected from R_2, R_3, R_4, R_5, R_7, R_8, R_9, R_{10} and R_{11} can form a 5- to 6- membered ring, optionally containing a N, O or S heteroatom;

R_2, R_4, R_6, R_8 and R_{10} can form a direct bond, or a 1 or 2 atom carbon bridge;

R_{14} is selected from hydrogen and C_{1-4}alkyl; and

R_{13}, R_{15}, and R_{16} are independently selected from hydrogen, C_{1-4}alkyl, and C_{3-8}cycloakyl, wherein said alkyl or cycloalkyl is optionally substituted by one or more substituents chosen from hydroxyl, cyano and halo.

[010] Certain compounds disclosed herein may possess useful PTPN11 inhibiting activity, and may be used in the treatment or prophylaxis of a disease or condition in which PTPN11 plays an active role. Thus, in broad aspect, certain embodiments also provide pharmaceutical compositions comprising one or more compounds disclosed herein together with a pharmaceutically acceptable carrier, as well as methods of making and using the compounds and compositions. Certain embodiments provide methods for inhibiting PTPN11. Other embodiments provide methods for treating a PTPN11-mediated disorder in a patient in need of such treatment, comprising administering to said patient a therapeutically effective amount of a compound or composition according to the present invention. Also provided is the use of certain compounds disclosed herein for use in the manufacture of a medicament for the treatment of a disease or condition ameliorated by the inhibition of PTPN11.

[011] In certain embodiments,

R_1 is selected from C_{6-10}aryl, and a 5- to 9- membered heteroaryl group containing 1 to 4 heteroatoms or groups independently selected from N, C(O), O, and S;

said aryl or heteroaryl of R_1 is optionally substituted with 1 to 5 R_{12} groups independently selected from halo, hydroxy, amino, dimethylamino, cyano, C_{1-4} alkyl, C_{1-4}hydroxyalkyl, C_{1-4}haloalkyl, C_{1-4}aminoalkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkenyl, $NR_{15a}C(O)R_{13}$, $NR_{15a}C(O)OR_{13}$, $NR_{13}C(O)N(R_{15a})(R_{15b})$, $NR_{15a}S(O)R_{13}$, $NR_{15a}S(O)_2R_{13}$, $C(O)N(R_{15a})(R_{15b})$, $S(O)N(R_{15a})(R_{15b})$, $S(O)_2N(R_{15a})(R_{15b})$, $C(O)R_{13}$, $C(O)OR_{13}$, SR_{13}, $S(O)R_{13}$, and $S(O)_2R_{13}$; and

R_{13}, R_{15}, and R_{16} are independently selected from hydrogen, C_{1-4}alkyl, and C_{3-8}cycloakyl, wherein said alkyl or cycloalkyl is optionally substituted by one or more substituents chosen from hydroxyl, cyano and halo.

[012] In certain embodiments,

R_1 is selected from C_{6-10}aryl, and a 5- to 9- membered heteroaryl group containing 1 to 4 heteroatoms or groups independently selected from N, C(O), O, and S;

said aryl or heteroaryl of R_1 is optionally substituted with 1 to 5 R_{12} groups independently selected from hydroxy, amino, C_{1-4}alkyl, C_{1-4}haloalkyl, and C_{1-4}aminoalkyl;

when R_6 and R_7 together with the carbon atom to which they are both attached form a 3- to 7- membered ring that can optionally contain 1 to 3 heteroatoms or groups independently selected from N, C(O), O, and $S(O)_m$; wherein m is selected from 0,1, and 2;

then said ring formed by R_6 and R_7 can be unsubstituted or substituted with 1 to 3 groups independently selected from halo, hydroxy, methoxy, amino, methylamino, C_1-C_4alkylaminoalkyl, and C_1-C_4 alkyl.

[013] In certain embodiments,

R_1 is selected from halo, C_{6-10}aryl, and a 5- to 9- membered heteroaryl group containing 1 to 4 heteroatoms or groups independently selected from N, C(O), O, and S;

said aryl or heteroaryl of R_1 is optionally substituted with 1 to 5 R_{12} groups independently selected from hydroxy, amino, C_{1-4}alkyl, C_{1-4}haloalkyl, and C_{1-4}aminoalkyl;

R_6 is selected from amino, C_{1-4}aminoalkyl, and methylamino; and

R_7 is selected from hydrogen, halo, and hydroxy, or is selected from C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{3-6}cycloalkyl, phenyl, and 5- or 6- membered heteroaryl, any of which may be optionally substituted with one or more substituents chosen from amino, halo, hydroxy, cyano, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, and C_{1-4}alkoxy.

[014] In certain embodiments,

W is N;

R_1 is selected from C_{6-10}aryl, and a 5- to 9- membered heteroaryl group containing 1 to 4 heteroatoms or groups independently selected from N, C(O), O, and S;

said aryl or heteroaryl of R_1 is optionally substituted with 1 to 5 R_{12} groups independently selected from hydroxy, amino, C_{1-4}alkyl, C_{1-4}haloalkyl, and C_{1-4}aminoalkyl; and

R_4, R_5, R_8, and R_9 are independently selected from hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy, amino, hydroxy, C_{3-8}cycloalkyl, and C_{1-4} alkylamino.

[015] In certain embodiments, R_2, R_3, R_4, R_5, R_8, R_9, R_{10} and R_{11} are hydrogen.

[016] In certain embodiments,

R_6 and R_7 together with the carbon atom to which they are both attached form a 3- to 7- membered saturated or partially unsaturated ring; and

said saturated ring formed by R_6 and R_7 can be unsubstituted or substituted with 1 to 3 groups independently selected from amino, hydroxy, methoxy, methylamino, and C_1-C_4 alkyl.

[017] Also provided are embodiments wherein any embodiment above may be combined with any one or more of these embodiments, provided the combination is not mutually exclusive.

[018] As used herein, two embodiments are "mutually exclusive" when one is defined to be something which is different than the other. For example, an embodiment wherein two groups combine to form a cycloalkyl is mutually exclusive with an embodiment in which one group is ethyl the other group is hydrogen. Similarly, an embodiment wherein one group is CH_2 is mutually exclusive with an embodiment wherein the same group is NH.

[019] Also provided is a compound chosen from the Examples disclosed herein.

[020] The present invention also relates to a method of inhibiting at least one PTPN11 function comprising the step of contacting PTPN11 with a compound as described herein. The cell phenotype, cell proliferation, activity of PTPN11, change in biochemical output produced by active PTPN11, expression of PTPN11, or binding of PTPN11 with a natural binding partner may be monitored. Such methods may be modes of treatment of disease, biological assays, cellular assays, biochemical assays, or the like.

[021] Also provided herein is a method of treatment of a PTPN11-mediated disease comprising the administration of a therapeutically effective amount of a compound as disclosed herein, or a salt thereof, to a patient in need thereof.

[022] In certain embodiments, the disease is chosen from Noonan Syndrome and Leopard Syndrome.

[023] In certain embodiments, the disease is cancer.

[024] In certain embodiments, the cancer is chosen from breast cancer, colon cancer, leukemia, or melanoma.

[025] Also provided herein is a method of treatment of a PTP-mediated disease comprising the administration of a therapeutically effective amount of a compound as disclosed herein, or a salt thereof, to a patient in need thereof.

[026] In certain embodiments, the disease is chosen from Noonan Syndrome and Leopard Syndrome.

[027] In certain embodiments, the disease is cancer.

[028] In certain embodiments, the cancer is chosen from breast cancer, colon cancer, leukemia, or melanoma.

[029] Also provided herein is a compound as disclosed herein for use as a medicament.

[030] Also provided herein is a compound as disclosed herein for use as a medicament for the treatment of a PTPN11-mediated disease.

[031] Also provided herein is a compound as disclosed herein for use as a medicament for the treatment of a PTP-mediated disease.

[032] Also provided is the use of a compound as disclosed herein as a medicament.

[033] Also provided is the use of a compound as disclosed herein as a medicament for the treatment of a PTPN11-mediated disease.

[034] Also provided is a compound as disclosed herein for use in the manufacture of a medicament for the treatment of a PTPN11-mediated disease.

[035] Also provided is the use of a compound as disclosed herein for the treatment of a PTPN11-mediated disease.

[036] Also provided is the use of a compound as disclosed herein for the treatment of a PTP-mediated disease.

[037] Also provided herein is a method of inhibition of PTPN11 comprising contacting PTPN11 with a compound as disclosed herein, or a salt thereof.

[038] Also provided herein is a method of inhibition of PTP comprising contacting PTP with a compound as disclosed herein, or a salt thereof.

[039] Also provided herein is a method for achieving an effect in a patient comprising the administration of a therapeutically effective amount of a compound as disclosed herein, or a salt thereof, to a patient, wherein the effect is chosen from cognition enhancement.

[040] In certain embodiments, the PTPN11-mediated disease is chosen from Noonan Syndrome and Leopard Syndrome.

[041] In certain embodiments, the PTPN11-mediated disease is cancer.

[042] In certain embodiments, the PTPN11-mediated disease is chosen from breast cancer, colon cancer, leukemia, or melanoma.

[043] Also provided is a method of modulation of a PTPN11-mediated function in a subject comprising the administration of a therapeutically effective amount of a compound as disclosed herein.

[044] Also provided is a pharmaceutical composition comprising a compound as disclosed herein, together with a pharmaceutically acceptable carrier.

[045] In certain embodiments, the pharmaceutical composition is formulated for oral administration.

[046] In certain embodiments, the pharmaceutical composition is formulated for parenteral administration.

[047] In certain embodiments, the pharmaceutical composition is formulated for intravenous administration.

[048] In certain embodiments, the pharmaceutical composition is formulated for subcutaneous administration.

[049] In certain embodiments, the oral pharmaceutical composition is chosen from a tablet and a capsule.

[050] As used herein, the terms below have the meanings indicated.

[051] When ranges of values are disclosed, and the notation "from n_1 … to n_2" or "between n_1 … and n_2" is used, where n_1 and n_2 are the numbers, then unless otherwise specified, this notation is intended to include the numbers themselves and the range between them. This range may be integral or continuous between and including the end values. By way of example, the range "from 2 to 6 carbons" is intended to include two, three, four, five, and six carbons, since carbons come in integer units. Compare, by way of example, the range "from 1 to 3 μM (micromolar)," which is intended to include 1 μM, 3 μM, and everything in between to any number of significant figures (e.g., 1.255 μM, 2.1 μM, 2.9999 μM, etc.).

[052] The term "about," as used herein, is intended to qualify the numerical values which it modifies, denoting such a value as variable within a margin of error. When no particular margin of error, such as a standard deviation to a mean value given in a chart or table of data, is recited, the term "about" should be understood to mean that range which would encompass the recited value and the range which would be included by rounding up or down to that figure as well, taking into account significant figures.

[053] The term "acyl," as used herein, alone or in combination, refers to a carbonyl attached to an alkenyl, alkyl, aryl, cycloalkyl, heteroaryl, heterocycle, or any other moiety were the atom attached to the carbonyl is carbon. An "acetyl" group refers to a $-C(O)CH_3$ group. An "alkylcarbonyl" or "alkanoyl" group refers to an alkyl group attached to the parent molecular moiety through a carbonyl group. Examples of such groups include methylcarbonyl and ethylcarbonyl. Examples of acyl groups include formyl, alkanoyl and aroyl.

[054] The term "alkenyl," as used herein, alone or in combination, refers to a straight-chain or branched-chain hydrocarbon radical having one or more double bonds and containing from 2 to 20 carbon atoms. In certain embodiments, said alkenyl will comprise from 2 to 6 carbon atoms. The term "alkenylene" refers to a carbon-carbon double bond system attached at two or more positions such as ethenylene [(-CH=CH-),(-C::C-)]. Examples of suitable alkenyl radicals include ethenyl, propenyl, 2-methylpropenyl, 1,4-butadienyl and the like. Unless otherwise specified, the term "alkenyl" may include "alkenylene" groups.

[055] The term "alkoxy," as used herein, alone or in combination, refers to an alkyl ether radical, wherein the term alkyl is as defined below. Examples of suitable alkyl ether radicals include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy, and the like.

[056] The term "alkyl," as used herein, alone or in combination, refers to a straight-chain or branched-chain alkyl radical containing from 1 to 20 carbon atoms. In certain

embodiments, said alkyl will comprise from 1 to 10 carbon atoms. In further embodiments, said alkyl will comprise from 1 to 8 carbon atoms. Alkyl groups may be optionally substituted as defined herein. Examples of alkyl radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl, octyl, noyl and the like. The term "alkylene," as used herein, alone or in combination, refers to a saturated aliphatic group derived from a straight or branched chain saturated hydrocarbon attached at two or more positions, such as methylene
(-CH_2-). Unless otherwise specified, the term "alkyl" may include "alkylene" groups.

[057] The term "alkylamino," as used herein, alone or in combination, refers to an alkyl group attached to the parent molecular moiety through an amino group. Suitable alkylamino groups may be mono- or dialkylated, forming groups such as, for example, N-methylamino, N-ethylamino, N,N-dimethylamino, N,N-ethylmethylamino and the like.

[058] The term "alkylthio," as used herein, alone or in combination, refers to an alkyl thioether (R–S–) radical wherein the term alkyl is as defined above and wherein the sulfur may be singly or doubly oxidized. Examples of suitable alkyl thioether radicals include methylthio, ethylthio, n-propylthio, isopropylthio, n-butylthio, iso-butylthio, sec-butylthio, tert-butylthio, methanesulfonyl, ethanesulfinyl, and the like.

[059] The terms "amido" and "carbamoyl,"as used herein, alone or in combination, refer to an amino group as described below attached to the parent molecular moiety through a carbonyl group, or vice versa. The term "C-amido" as used herein, alone or in combination, refers to a -C(O)N(RR') group with R and R' as defined herein or as defined by the specifically enumerated "R" groups designated. The term "N-amido" as used herein, alone or in combination, refers to a RC(O)N(R')- group, with R and R' as defined herein or as defined by the specifically enumerated "R" groups designated. The term "acylamino" as used herein, alone or in combination, embraces an acyl group attached to the parent moiety through an amino group. An example of an "acylamino" group is acetylamino ($CH_3C(O)NH$-).

[060] The term "amino," as used herein, alone or in combination, refers to -NRR', wherein R and R' are independently chosen from hydrogen, alkyl, acyl, heteroalkyl, aryl, cycloalkyl, heteroaryl, and heterocycloalkyl, any of which may themselves be optionally substituted. Additionally, R and R' may combine to form heterocycloalkyl, either of which may be optionally substituted.

[061] The term "aryl," as used herein, alone or in combination, means a carbocyclic aromatic system containing one, two or three rings wherein such polycyclic ring systems are

fused together. The term "aryl" embraces aromatic groups such as phenyl, naphthyl, anthracenyl, and phenanthryl.

[062] The term “arylalkenyl” or “aralkenyl,” as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an alkenyl group.

[063] The term “arylalkoxy” or “aralkoxy,” as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an alkoxy group.

[064] The term “arylalkyl” or “aralkyl,” as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an alkyl group.

[065] The term aryloxy as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an oxy.

[066] The term “carbamate,” as used herein, alone or in combination, refers to an ester of carbamic acid (-NHCOO-) which may be attached to the parent molecular moiety from either the nitrogen or acid end, and which may be optionally substituted as defined herein.

[067] The term “O-carbamyl” as used herein, alone or in combination, refers to a -OC(O)NRR’, group-with R and R’ as defined herein.

[068] The term “N-carbamyl” as used herein, alone or in combination, refers to a ROC(O)NR’- group, with R and R’ as defined herein.

[069] The term “carbonyl,” as used herein, when alone includes formyl [-C(O)H] and in combination is a -C(O)- group.

[070] The term “carboxyl” or “carboxy,” as used herein, refers to -C(O)OH or the corresponding “carboxylate” anion, such as is in a carboxylic acid salt. An “O-carboxy” group refers to a RC(O)O- group, where R is as defined herein. A “C-carboxy” group refers to a -C(O)OR groups where R is as defined herein.

[071] The term “cyano,” as used herein, alone or in combination, refers to -CN.

[072] The term “cycloalkyl,” or, alternatively, “carbocycle,” as used herein, alone or in combination, refers to a saturated or partially saturated monocyclic, bicyclic or tricyclic alkyl group wherein each cyclic moiety contains from 3 to 12 carbon atom ring members and which may optionally be a benzo fused ring system which is optionally substituted as defined herein. In certain embodiments, said cycloalkyl will comprise from 5 to 7 carbon atoms. Examples of such cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, tetrahydronapthyl, indanyl, octahydronaphthyl, 2,3-dihydro-1H-indenyl, adamantyl and the like. “Bicyclic” and “tricyclic” as used herein are intended to include both fused ring systems, such as decahydronaphthalene, octahydronaphthalene as well as the multicyclic (multicentered) saturated or partially unsaturated type. The latter type

of isomer is exemplified in general by, bicyclo[1,1,1]pentane, camphor, adamantane, and bicyclo[3,2,1]octane.

[073] The term "ester," as used herein, alone or in combination, refers to a carboxy group bridging two moieties linked at carbon atoms.

[074] The term "ether," as used herein, alone or in combination, refers to an oxy group bridging two moieties linked at carbon atoms.

[075] The term "halo," or "halogen," as used herein, alone or in combination, refers to fluorine, chlorine, bromine, or iodine.

[076] The term "haloalkoxy," as used herein, alone or in combination, refers to a haloalkyl group attached to the parent molecular moiety through an oxygen atom.

[077] The term "haloalkyl," as used herein, alone or in combination, refers to an alkyl radical having the meaning as defined above wherein one or more hydrogens are replaced with a halogen. Specifically embraced are monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have an iodo, bromo, chloro or fluoro atom within the radical. Dihalo and polyhaloalkyl radicals may have two or more of the same halo atoms or a combination of different halo radicals. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl. "Haloalkylene" refers to a haloalkyl group attached at two or more positions. Examples include fluoromethylene
(-CFH-), difluoromethylene (-CF_2 -), chloromethylene (-CHCl-) and the like.

[078] The term "heteroalkyl," as used herein, alone or in combination, refers to a stable straight or branched chain, or combinations thereof, fully saturated or containing from 1 to 3 degrees of unsaturation, consisting of the stated number of carbon atoms and from one to three heteroatoms chosen from N, O, and S, and wherein the N and S atoms may optionally be oxidized and the N heteroatom may optionally be quaternized. The heteroatom(s) may be placed at any interior position of the heteroalkyl group. Up to two heteroatoms may be consecutive, such as, for example, -CH_2-NH-OCH_3.

[079] The term "heteroaryl," as used herein, alone or in combination, refers to a 3 to 15 membered unsaturated heteromonocyclic ring, or a fused monocyclic, bicyclic, or tricyclic ring system in which at least one of the fused rings is aromatic, which contains at least one atom chosen from N, O, and S. In certain embodiments, said heteroaryl will comprise from 1 to 4 heteroatoms as ring members. In further embodiments, said heteroaryl will comprise

from 1 to 2 heteroatoms as ring members. In certain embodiments, said heteroaryl will comprise from 5 to 7 atoms. The term also embraces fused polycyclic groups wherein heterocyclic rings are fused with aryl rings, wherein heteroaryl rings are fused with other heteroaryl rings, wherein heteroaryl rings are fused with heterocycloalkyl rings, or wherein heteroaryl rings are fused with cycloalkyl rings. Examples of heteroaryl groups include pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazolyl, pyranyl, furyl, thienyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, thiadiazolyl, isothiazolyl, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, quinoxalinyl, quinazolinyl, indazolyl, benzotriazolyl, benzodioxolyl, benzopyranyl, benzoxazolyl, benzoxadiazolyl, benzothiazolyl, benzothiadiazolyl, benzofuryl, benzothienyl, chromonyl, coumarinyl, benzopyranyl, tetrahydroquinolinyl, tetrazolopyridazinyl, tetrahydroisoquinolinyl, thienopyridinyl, furopyridinyl, pyrrolopyridinyl and the like. Exemplary tricyclic heterocyclic groups include carbazolyl, benzidolyl, phenanthrolinyl, dibenzofuranyl, acridinyl, phenanthridinyl, xanthenyl and the like.

[080] The terms “heterocycloalkyl” and, interchangeably, “heterocycle,” as used herein, alone or in combination, each refer to a saturated, partially unsaturated, or fully unsaturated (but nonaromatic) monocyclic, bicyclic, or tricyclic heterocyclic group containing at least one heteroatom as a ring member, wherein each said heteroatom may be independently chosen from nitrogen, oxygen, and sulfur. In certain embodiments, said hetercycloalkyl will comprise from 1 to 4 heteroatoms as ring members. In further embodiments, said hetercycloalkyl will comprise from 1 to 2 heteroatoms as ring members. In certain embodiments, said hetercycloalkyl will comprise from 3 to 8 ring members in each ring. In further embodiments, said hetercycloalkyl will comprise from 3 to 7 ring members in each ring. In yet further embodiments, said hetercycloalkyl will comprise from 5 to 6 ring members in each ring. “Heterocycloalkyl” and “heterocycle” are intended to include sulfones, sulfoxides, N-oxides of tertiary nitrogen ring members, and carbocyclic fused and benzo fused ring systems; additionally, both terms also include systems where a heterocycle ring is fused to an aryl group, as defined herein, or an additional heterocycle group. Examples of heterocycle groups include aziridinyl, azetidinyl, 1,3-benzodioxolyl, dihydroisoindolyl, dihydroisoquinolinyl, dihydrocinnolinyl, dihydrobenzodioxinyl, dihydro[1,3]oxazolo[4,5-b]pyridinyl, benzothiazolyl, dihydroindolyl, dihy-dropyridinyl, 1,3-dioxanyl, 1,4-dioxanyl, 1,3-dioxolanyl, isoindolinyl, morpholinyl, piperazinyl, pyrrolidinyl, tetrahydropyridinyl, piperidinyl, thiomorpholinyl, and the like. The heterocycle groups may be optionally substituted unless specifically prohibited.

[081] The term "hydrazinyl" as used herein, alone or in combination, refers to two amino groups joined by a single bond, i.e., -N-N-.

[082] The term "hydroxy," as used herein, alone or in combination, refers to -OH.

[083] The term "hydroxyalkyl," as used herein, alone or in combination, refers to a hydroxy group attached to the parent molecular moiety through an alkyl group.

[084] The term "iminohydroxy," as used herein, alone or in combination, refers to =N(OH) and =N-O-.

[085] The term "lower amino," as used herein, alone or in combination, refers to -NRR', wherein R and R' are independently chosen from hydrogen and lower alkyl, either of which may be optionally substituted.

[086] The term "mercaptyl" as used herein, alone or in combination, refers to an RS- group, where R is as defined herein.

[087] The term "nitro," as used herein, alone or in combination, refers to $-NO_2$.

[088] The terms "oxy" or "oxa," as used herein, alone or in combination, refer to –O–.

[089] The term "oxo," as used herein, alone or in combination, refers to =O.

[090] The term "perhaloalkoxy" refers to an alkoxy group where all of the hydrogen atoms are replaced by halogen atoms.

[091] The term "perhaloalkyl" as used herein, alone or in combination, refers to an alkyl group where all of the hydrogen atoms are replaced by halogen atoms.

[092] The terms "sulfonate," "sulfonic acid," and "sulfonic," as used herein, alone or in combination, refer the $-SO_3H$ group and its anion as the sulfonic acid is used in salt formation.

[093] The term "sulfanyl," as used herein, alone or in combination, refers to –S–.

[094] The term "sulfinyl," as used herein, alone or in combination, refers to –S(O)–.

[095] The term "sulfonyl," as used herein, alone or in combination, refers to $-S(O)_2-$.

[096] The term "N-sulfonamido" refers to a $RS(=O)_2NR'$- group with R and R' as defined herein.

[097] The term "S-sulfonamido" refers to a $-S(=O)_2NRR'$, group, with R and R' as defined herein.

[098] The terms "thia" and "thio," as used herein, alone or in combination, refer to a –S– group or an ether wherein the oxygen is replaced with sulfur. The oxidized derivatives of the thio group, namely sulfinyl and sulfonyl, are included in the definition of thia and thio.

[099] The term "thiol," as used herein, alone or in combination, refers to an –SH group.

[0100] The term "thiocarbonyl," as used herein, when alone includes thioformyl –C(S)H and in combination is a –C(S)– group.

[0101] The term "N-thiocarbamyl" refers to an ROC(S)NR'– group, with R and R'as defined herein.

[0102] The term "O-thiocarbamyl" refers to a –OC(S)NRR', group with R and R'as defined herein.

[0103] The term "thiocyanato" refers to a –CNS group.

[0104] Any definition herein may be used in combination with any other definition to describe a composite structural group. By convention, the trailing element of any such definition is that which attaches to the parent moiety. For example, the composite group alkylamido would represent an alkyl group attached to the parent molecule through an amido group, and the term alkoxyalkyl would represent an alkoxy group attached to the parent molecule through an alkyl group.

[0105] When a group is defined to be "null," what is meant is that said group is absent.

[0106] The term "optionally substituted" means the anteceding group may be substituted or unsubstituted. When substituted, the substituents of an "optionally substituted" group may include, without limitation, one or more substituents independently selected from the following groups or a particular designated set of groups, alone or in combination: lower alkyl, lower alkenyl, lower alkynyl, lower alkanoyl, lower heteroalkyl, lower haloalkyl, lower haloalkenyl, lower haloalkynyl, lower perhaloalkyl, lower perhaloalkoxy, phenyl, aryl, aryloxy, lower alkoxy, lower haloalkoxy, oxo, lower acyloxy, carbonyl, carboxyl, lower alkylcarbonyl, lower carboxyester, lower carboxamido, cyano, hydrogen, halogen, hydroxy, amino, lower alkylamino, arylamino, amido, nitro, thiol, lower alkylthio, lower haloalkylthio, lower perhaloalkylthio, arylthio, sulfonate, sulfonic acid, trisubstituted silyl, N_3, SH, SCH_3, $C(O)CH_3$, CO_2CH_3, CO_2H, pyridinyl, thiophene, furanyl, lower carbamate, and lower urea. Where structurally feasible, two substituents may be joined together to form a fused five-, six-, or seven-membered carbocyclic or heterocyclic ring consisting of zero to three heteroatoms, for example forming methylenedioxy or ethylenedioxy. An optionally substituted group may be unsubstituted (e.g., $-CH_2CH_3$), fully substituted (e.g., $-CF_2CF_3$), monosubstituted (e.g., $-CH_2CH_2F$) or substituted at a level anywhere in-between fully substituted and monosubstituted (e.g., $-CH_2CF_3$). Where substituents are recited without qualification as to substitution, both substituted and unsubstituted forms are encompassed. Where a substituent is qualified as "substituted," the substituted form is specifically intended. Additionally, different sets of optional substituents to a particular moiety may be defined as

needed; in these cases, the optional substitution will be as defined, often immediately following the phrase, "optionally substituted with."

[0107] The term R or the term R', appearing by itself and without a number designation, unless otherwise defined, refers to a moiety chosen from hydrogen, alkyl, cycloalkyl, heteroalkyl, aryl, heteroaryl and heterocycloalkyl, any of which may be optionally substituted. Such R and R' groups should be understood to be optionally substituted as defined herein. Whether an R group has a number designation or not, every R group, including R, R' and R^n where n=(1, 2, 3, ...n), every substituent, and every term should be understood to be independent of every other in terms of selection from a group. Should any variable, substituent, or term (e.g. aryl, heterocycle, R, etc.) occur more than one time in a formula or generic structure, its definition at each occurrence is independent of the definition at every other occurrence. Those of skill in the art will further recognize that certain groups may be attached to a parent molecule or may occupy a position in a chain of elements from either end as written. For example, an unsymmetrical group such as -C(O)N(R)- may be attached to the parent moiety at either the carbon or the nitrogen.

[0108] Asymmetric centers exist in the compounds disclosed herein. These centers are designated by the symbols "R" or "S," depending on the configuration of substituents around the chiral carbon atom. It should be understood that the invention encompasses all stereochemical isomeric forms, including diastereomeric, enantiomeric, and epimeric forms,as well as d-isomers and 1-isomers, and mixtures thereof. Individual stereoisomers of compounds can be prepared synthetically from commercially available starting materials which contain chiral centers or by preparation of mixtures of enantiomeric products followed by separation such as conversion to a mixture of diastereomers followed by separation or recrystallization, chromatographic techniques, direct separation of enantiomers on chiral chromatographic columns, or any other appropriate method known in the art. Starting compounds of particular stereochemistry are either commercially available or can be made and resolved by techniques known in the art. Additionally, the compounds disclosed herein may exist as geometric isomers. The present invention includes all cis, trans, syn, anti, entgegen (E), and zusammen (Z) isomers as well as the appropriate mixtures thereof. Additionally, compounds may exist as tautomers; all tautomeric isomers are provided by this invention. Additionally, the compounds disclosed herein can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. In general, the solvated forms are considered equivalent to the unsolvated forms.

[0109] The term “bond” refers to a covalent linkage between two atoms, or two moieties when the atoms joined by the bond are considered to be part of larger substructure. A bond may be single, double, or triple unless otherwise specified. A dashed line between two atoms in a drawing of a molecule indicates that an additional bond may be present or absent at that position.

[0110] The term “disease” as used herein is intended to be generally synonymous, and is used interchangeably with, the terms “disorder,” “syndrome,” and “condition” (as in medical condition), in that all reflect an abnormal condition of the human or animal body or of one of its parts that impairs normal functioning, is typically manifested by distinguishing signs and symptoms, and causes the human or animal to have a reduced duration or quality of life.

[0111] The term "combination therapy" means the administration of two or more therapeutic agents to treat a therapeutic condition or disorder described in the present disclosure. Such administration encompasses co-administration of these therapeutic agents in a substantially simultaneous manner, such as in a single capsule having a fixed ratio of active ingredients or in multiple, separate capsules for each active ingredient. In addition, such administration also encompasses use of each type of therapeutic agent in a sequential manner. In either case, the treatment regimen will provide beneficial effects of the drug combination in treating the conditions or disorders described herein.

[0112] “PTPN11 inhibitor" is used herein to refer to a compound that exhibits an $IC_{50}$with respect to PTPN11 activity of no more than about 100 μM and more typically not more than about 50 μM, as measured in the PTPN11 assay described generally herein. "IC_{50}" is that concentration of inhibitor which reduces the activity of an enzyme (e.g., PTPN11) to half-maximal level. Certain compounds disclosed herein have been discovered to exhibit inhibition against PTPN11. In certain embodiments, compounds will exhibit an IC_{50} with respect to PTPN11 of no more than about 50 μM; in further embodiments, compounds will exhibit an IC_{50} with respect to PTPN11 of no more than about 10 μM; in yet further embodiments, compounds will exhibit an IC_{50} with respect to PTPN11 of not more than about 1 μM; in yet further embodiments, compounds will exhibit an IC_{50} with respect to PTPN11 of not more than about 200 nM, as measured in the PTPN11 assay described herein.

[0113] The phrase "therapeutically effective" is intended to qualify the amount of active ingredients used in the treatment of a disease or disorder or on the effecting of a clinical endpoint.

[0114] The term “therapeutically acceptable” refers to those compounds (or salts, prodrugs, tautomers, zwitterionic forms, etc.) which are suitable for use in contact with the

tissues of patients without undue toxicity, irritation, and allergic response, are commensurate with a reasonable benefit/risk ratio, and are effective for their intended use.

[0115] As used herein, reference to "treatment" of a patient is intended to include prophylaxis. Treatment may also be preemptive in nature, i.e., it may include prevention of disease. Prevention of a disease may involve complete protection from disease, for example as in the case of prevention of infection with a pathogen, or may involve prevention of disease progression. For example, prevention of a disease may not mean complete foreclosure of any effect related to the diseases at any level, but instead may mean prevention of the symptoms of a disease to a clinically significant or detectable level. Prevention of diseases may also mean prevention of progression of a disease to a later stage of the disease.

[0116] The term “patient” is generally synonymous with the term “subject” and includes all mammals including humans. Examples of patients include humans, livestock such as cows, goats, sheep, pigs, and rabbits, and companion animals such as dogs, cats, rabbits, and horses. Preferably, the patient is a human.

[0117] The term "prodrug" refers to a compound that is made more active in vivo. Certain compounds disclosed herein may also exist as prodrugs. Prodrugs of the compounds described herein are structurally modified forms of the compound that readily undergo chemical changes under physiological conditions to provide the compound. Additionally, prodrugs can be converted to the compound by chemical or biochemical methods in an ex vivo environment. For example, prodrugs can be slowly converted to a compound when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent. Prodrugs are often useful because, in some situations, they may be easier to administer than the compound, or parent drug. They may, for instance, be bioavailable by oral administration whereas the parent drug is not. The prodrug may also have improved solubility in pharmaceutical compositions over the parent drug. A wide variety of prodrug derivatives are known in the art, such as those that rely on hydrolytic cleavage or oxidative activation of the prodrug. An example, without limitation, of a prodrug would be a compound which is administered as an ester (the "prodrug"), but then is metabolically hydrolyzed to the carboxylic acid, the active entity. Additional examples include peptidyl derivatives of a compound.

[0118] The compounds disclosed herein can exist as therapeutically acceptable salts. The present invention includes compounds listed above in the form of salts, including acid addition salts. Suitable salts include those formed with both organic and inorganic acids.

Such acid addition salts will normally be pharmaceutically acceptable. However, salts of non-pharmaceutically acceptable salts may be of utility in the preparation and purification of the compound in question. Basic addition salts may also be formed and be pharmaceutically acceptable..

[0119] The term "therapeutically acceptable salt," as used herein, represents salts or zwitterionic forms of the compounds disclosed herein which are water or oil-soluble or dispersible and therapeutically acceptable as defined herein. The salts can be prepared during the final isolation and purification of the compounds or separately by reacting the appropriate compound in the form of the free base with a suitable acid. Representative acid addition salts include acetate, adipate, alginate, L-ascorbate, aspartate, benzoate, benzenesulfonate (besylate), bisulfate, butyrate, camphorate, camphorsulfonate, citrate, digluconate, formate, fumarate, gentisate, glutarate, glycerophosphate, glycolate, hemisulfate, heptanoate, hexanoate, hippurate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethansulfonate (isethionate), lactate, maleate, malonate, DL-mandelate, mesitylenesulfonate, methanesulfonate, naphthylenesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylproprionate, phosphonate, picrate, pivalate, propionate, pyroglutamate, succinate, sulfonate, tartrate, L-tartrate, trichloroacetate, trifluoroacetate, phosphate, glutamate, bicarbonate, para-toluenesulfonate (p-tosylate), and undecanoate. Also, basic groups in the compounds disclosed herein can be quaternized with methyl, ethyl, propyl, and butyl chlorides, bromides, and iodides; dimethyl, diethyl, dibutyl, and diamyl sulfates; decyl, lauryl, myristyl, and steryl chlorides, bromides, and iodides; and benzyl and phenethyl bromides. Examples of acids which can be employed to form therapeutically acceptable addition salts include inorganic acids such as hydrochloric, hydrobromic, sulfuric, and phosphoric, and organic acids such as oxalic, maleic, succinic, and citric. Salts can also be formed by coordination of the compounds with an alkali metal or alkaline earth ion. Hence, the present invention contemplates sodium, potassium, magnesium, and calcium salts of the compounds disclosed herein, and the like.

[0120] Basic addition salts can be prepared during the final isolation and purification of the compounds by reacting a carboxy group with a suitable base such as the hydroxide, carbonate, or bicarbonate of a metal cation or with ammonia or an organic primary, secondary, or tertiary amine. The cations of therapeutically acceptable salts include lithium, sodium, potassium, calcium, magnesium, and aluminum, as well as nontoxic quaternary amine cations such as ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, diethylamine, ethylamine,

tributylamine, pyridine, *N,N*-dimethylaniline, *N*-methylpiperidine, *N*-methylmorpholine, dicyclohexylamine, procaine, dibenzylamine, *N,N*-dibenzylphenethylamine, 1-ephenamine, and *N,N'*-dibenzylethylenediamine. Other representative organic amines useful for the formation of base addition salts include ethylenediamine, ethanolamine, diethanolamine, piperidine, and piperazine.

[0121] A salt of a compound can be made by reacting the appropriate compound in the form of the free base with the appropriate acid.

[0122] While it may be possible for the compounds of the subject invention to be administered as the raw chemical, it is also possible to present them as a pharmaceutical formulation. Accordingly, provided herein are pharmaceutical formulations which comprise one or more of certain compounds disclosed herein, or one or more pharmaceutically acceptable salts, esters, prodrugs, amides, or solvates thereof, together with one or more pharmaceutically acceptable carriers thereof and optionally one or more other therapeutic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. Proper formulation is dependent upon the route of administration chosen. Any of the well-known techniques, carriers, and excipients may be used as suitable and as understood in the art. The pharmaceutical compositions disclosed herein may be manufactured in any manner known in the art, *e.g.*, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or compression processes.

[0123] The formulations include those suitable for oral, parenteral (including subcutaneous, intradermal, intramuscular, intravenous, intraarticular, and intramedullary), intraperitoneal, transmucosal, transdermal, rectal and topical (including dermal, buccal, sublingual and intraocular) administration although the most suitable route may depend upon for example the condition and disorder of the recipient. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Typically, these methods include the step of bringing into association a compound of the subject invention or a pharmaceutically acceptable salt, ester, amide, prodrug or solvate thereof ("active ingredient") with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

[0124] Formulations of the compounds disclosed herein suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a

predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

[0125] Pharmaceutical preparations which can be used orally include tablets, push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. Tablets may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with binders, inert diluents, or lubricating, surface active or dispersing agents. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein. All formulations for oral administration should be in dosages suitable for such administration. 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. 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.

[0126] The compounds may be formulated for parenteral administration by injection, *e.g.*, by 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. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in powder form or in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example, saline or sterile pyrogen-free water, immediately prior to use. Extemporaneous

injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

[0127] Formulations for parenteral administration include aqueous and non-aqueous (oily) sterile injection solutions of the active compounds which may contain antioxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. 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.

[0128] 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.

[0129] For buccal or sublingual administration, the compositions may take the form of tablets, lozenges, pastilles, or gels formulated in conventional manner. Such compositions may comprise the active ingredient in a flavored basis such as sucrose and acacia or tragacanth.

[0130] 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, polyethylene glycol, or other glycerides.

[0131] Certain compounds disclosed herein may be administered topically, that is by non-systemic administration. This includes the application of a compound disclosed herein externally to the epidermis or the buccal cavity and the instillation of such a compound into the ear, eye and nose, such that the compound does not significantly enter the blood stream. In contrast, systemic administration refers to oral, intravenous, intraperitoneal and intramuscular administration.

[0132] Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin to the site of inflammation such as gels, liniments, lotions, creams, ointments or pastes, and drops suitable for administration to the

eye, ear or nose. The active ingredient for topical administration may comprise, for example, from 0.001% to 10% w/w (by weight) of the formulation. In certain embodiments, the active ingredient may comprise as much as 10% w/w. In other embodiments, it may comprise less than 5% w/w. In certain embodiments, the active ingredient may comprise from 2% w/w to 5% w/w. In other embodiments, it may comprise from 0.1% to 1% w/w of the formulation.

[0133] For administration by inhalation, compounds may be conveniently delivered from an insufflator, nebulizer pressurized packs or other convenient means of delivering an aerosol spray. Pressurized packs may comprise a suitable propellant such as dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. Alternatively, for administration by inhalation or insufflation, the compounds according to the invention may take the form of a dry powder composition, for example a powder mix of the compound and a suitable powder base such as lactose or starch. The powder composition may be presented in unit dosage form, in for example, capsules, cartridges, gelatin or blister packs from which the powder may be administered with the aid of an inhalator or insufflator.

[0134] Preferred unit dosage formulations are those containing an effective dose, as herein below recited, or an appropriate fraction thereof, of the active ingredient.

[0135] It should be understood that in addition to the ingredients particularly mentioned above, the formulations described above may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

[0136] Compounds may be administered orally or via injection at a dose of from 0.1 to 500 mg/kg per day. The dose range for adult humans is generally from 5 mg to 2 g/day. Tablets or other forms of presentation provided in discrete units may conveniently contain an amount of one or more compounds which is effective at such dosage or as a multiple of the same, for instance, units containing 5 mg to 500 mg, usually around 10 mg to 200 mg.

[0137] The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

[0138] The compounds can be administered in various modes, e.g. orally, topically, or by injection. The precise amount of compound administered to a patient will be the responsibility of the attendant physician. The specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound

employed, the age, body weight, general health, sex, diets, time of administration, route of administration, rate of excretion, drug combination, the precise disorder being treated, and the severity of the indication or condition being treated. Also, the route of administration may vary depending on the condition and its severity.

[0139] In certain instances, it may be appropriate to administer at least one of the compounds described herein (or a pharmaceutically acceptable salt, ester, or prodrug thereof) in combination with another therapeutic agent. By way of example only, if one of the side effects experienced by a patient upon receiving one of the compounds herein is hypertension, then it may be appropriate to administer an anti-hypertensive agent in combination with the initial therapeutic agent. Or, by way of example only, the therapeutic effectiveness of one of the compounds described herein may be enhanced by administration of an adjuvant (i.e., by itself the adjuvant may only have minimal therapeutic benefit, but in combination with another therapeutic agent, the overall therapeutic benefit to the patient is enhanced). Or, by way of example only, the benefit of experienced by a patient may be increased by administering one of the compounds described herein with another therapeutic agent (which also includes a therapeutic regimen) that also has therapeutic benefit. By way of example only, in a treatment for diabetes involving administration of one of the compounds described herein, increased therapeutic benefit may result by also providing the patient with another therapeutic agent for diabetes. In any case, regardless of the disease, disorder or condition being treated, the overall benefit experienced by the patient may simply be additive of the two therapeutic agents or the patient may experience a synergistic benefit.

[0140] Specific, non-limiting examples of possible combination therapies include use of certain compounds of the invention with anti-cancer (chemotherapeutic) drugs. Classes of anti-cancer drugs include, but are not limited to: alkylating agents, anti-metabolites, antimitotics, checkpoint inhibitors, plant alkaloids and terpenoids, topoisomerase inhibitors, cytotoxic antibiotics, aromatase inhibitors, angiogenesis inhibitors, anti-steroids and anti-androgens, mTOR inhibitors, tyrosine kinase inhibitors, and others.

[0141] For use in cancer and neoplastic diseases a PTPN11 (SHP2) inhibitor may be optimally used together with one or more of the following non-limiting examples of anti-cancer agents:

(1) alkylating agents, including but not limited to carmustine, chlorambucil (LEUKERAN), cisplatin (PLATIN), carboplatin (PARAPLATIN), oxaliplatin (ELOXATIN), streptozocin (ZANOSAR), busulfan (MYLERAN), dacarbazine, ifosfamide, lomustine (CCNU), melphalan (ALKERAN), procarbazine

(MATULAN), temozolomide(TEMODAR), thiotepa, and cyclophosphamide (ENDOXAN);

(2) anti-metabolites, including but not limited to cladribine (LEUSTATIN), mercaptopurine (PURINETHOL), thioguanine, pentostatin (NIPENT), cytosine arabinoside (cytarabine, ARA-C), gemcitabine (GEMZAR), fluorouracil (5-FU, CARAC), capecitabine (XELODA), leucovorin (FUSILEV), methotrexate (RHEUMATREX), raltitrexed;

(3) antimitotics, which are often plant alkaloids and terpenoids, or derivateves thereof, including but not limited to taxanes such as docetaxel (TAXITERE) and paclitaxel (ABRAXANE, TAXOL); vinca alkaloids such as vincristine (ONCOVIN), vinblastine, vindesine, and vinorelbine (NAVELBINE);

(4) checkpoint inhibitors, such as anti- PD-1 or PD-L1 antibodies pembrolizumab (KEYTRUDA), nivolumab (OPDIVO), MEDI4736, and MPDL3280A; anti-CTLA-4 antibody ipilimumab (YERVOY); and those that target LAG3 (lymphocyte activation gene 3 protein), KIR (killer cell immunoglobulin-like receptor), 4-1BB (tumour necrosis factor receptor superfamily member 9), TIM3 (T-cell immunoglobulin and mucin-domain containing-3) and OX40 (tumour necrosis factor receptor superfamily member 4);

(5) topoisomerase inhibitors, including but not limited to camptothecin (CTP), irinotecan (CAMPTOSAR), topotecan (HYCAMTIN), teniposide (VUMON), and etoposide (EPOSIN);

(6) cytotoxic antibiotics, including but not limited to actinomycin D (dactinomycin, COSMEGEN), bleomycin (BLENOXANE) doxorubicin (ADRIAMYCIN), daunorubicin (CERUBIDINE), epirubicin (ELLENCE), fludarabine (FLUDARA), idarubicin, mitomycin (MITOSOL), mitoxantrone (NOVANTRONE), plicamycin;

(7) aromatase inhibitors, including but not limited to aminoglutethimide, anastrozole (ARIMIDEX), letrozole (FEMARA), vorozole (RIVIZOR), exemestane (AROMASIN);

(8) angiogenesis inhibitors, including but not limited to genistein, sunitinib (SUTENT) and bevacizumab (AVASTIN);

(9) anti-steroids and anti-androgens such as aminoglutethimide (CYTADREN), bicalutamide (CASODEX), cyproterone, flutamide (EULEXIN), nilutamide(NILANDRON);

(10) tyrosine kinase inhibitors, including but not limited to imatinib (GLEEVEC), erlotinib (TARCEVA), lapatininb (TYKERB), sorafenib (NEXAVAR), and axitinib (INLYTA);

(11) mTOR inhibitors such as everolimus, temsirolimus (TORISEL), and sirolimus;

(12) monoclonal antibodies such as trastuzumab (HERCEPTIN) and rituximab (RITUXAN);

(13) other agents, such as amsacrine; Bacillus Calmette–Guérin (B-C-G) vaccine; buserelin (ETILAMIDE); chloroquine (ARALEN); clodronate, pamidronate, and other bisphosphonates; colchicine; demethoxyviridin; dichloroacetate; estramustine; filgrastim (NEUPOGEN); fludrocortisone (FLORINEF); goserelin (ZOLADEX); interferon; leucovorin; leuprolide (LUPRON); levamisole; lonidamine; mesna; metformin; mitotane (o,p'-DDD, LYSODREN); nocodazole; octreotide (SANDOSTATIN); perifosine; porfimer (particularly in combination with photo- and radiotherapy); suramin; tamoxifen; titanocene dichloride; tretinoin; anabolic steroids such as fluoxymesterone(HALOTESTIN); estrogens such as estradiol, diethylstilbestrol (DES), and dienestrol; progestins such as medroxyprogesterone acetate (MPA) and megestrol; and testosterone.

[0142] In any case, the multiple therapeutic agents (at least one of which is a compound disclosed herein) may be administered in any order or even simultaneously. If simultaneously, the multiple therapeutic agents may be provided in a single, unified form, or in multiple forms (by way of example only, either as a single pill or as two separate pills). One of the therapeutic agents may be given in multiple doses, or both may be given as multiple doses. If not simultaneous, the timing between the multiple doses may be any duration of time ranging from a few minutes to four weeks.

[0143] Thus, in another aspect, certain embodiments provide methods for treating PTPN11-mediated disorders in a human or animal subject in need of such treatment comprising administering to said subject an amount of a compound disclosed herein effective to reduce or prevent said disorder in the subject, in combination with at least one additional agent for the treatment of said disorder that is known in the art. In a related aspect, certain embodiments provide therapeutic compositions comprising at least one compound disclosed herein in combination with one or more additional agents for the treatment of PTPN11-mediated disorders.

[0144] In some embodiments, methods described herein are used to treat a disease condition comprising administering to a subject in need thereof a therapeutically effective amount of a compound of Formula I or pharmaceutically acceptable salt thereof, wherein the condition is cancer which has developed resistance to chemotherapeutic drugs and/or ionizing radiation.

[0145] In some embodiments, methods described herein are used to treat a disease condition comprising administering to a subject in need thereof a therapeutically effective amount of a compound of Formula I or pharmaceutically acceptable salt thereof, wherein the condition is cancer which has developed resistance to chemotherapeutic drugs and/or ionizing radiation.

[0146] The compounds, compositions, and methods disclosed herein are useful for the treatment of disease. In certain embodiments, the disease is one of dysregulated cellular proliferation, including cancer. The cancer may be hormone-dependent or hormone-resistant, such as in the case of breast cancers. In certain embodiments, the cancer is a solid tumor. In other embodiments, the cancer is a lymphoma or leukemia. In certain embodiments, the cancer is and a drug resistant phenotype of a cancer disclosed herein or known in the art. Tumor invasion, tumor growth, tumor metastasis, and angiogenesis may also be treated using the compositions and methods disclosed herein. Precancerous neoplasias are also treated using the compositions and methods disclosed herein.

[0147] Cancers to be treated by the methods disclosed herein include colon cancer, breast cancer, ovarian cancer, lung cancer and prostrate cancer; cancers of the oral cavity and pharynx (lip, tongue, mouth, larynx, pharynx), esophagus, stomach, small intestine, large intestine, colon, rectum, liver and biliary passages; pancreas, bone, connective tissue, skin, cervix, uterus, corpus endometrium, testis, bladder, kidney and other urinary tissues, including renal cell carcinoma (RCC); cancers of the eye, brain, spinal cord, and other components of the central and peripheral nervous systems, as well as associated structures such as the meninges; and thyroid and other endocrine glands. The term “cancer” also encompasses cancers that do not necessarily form solid tumors, including Hodgkin’s disease, non-Hodgkin’s lymphomas, multiple myeloma and hematopoietic malignancies including leukemias (Chronic Lymphocytic Leukemia (CLL), Acute Lymphocytic Leukemia (ALL), Chronic Myelogenous Leukemia (CML), Acute Myelogenous Leukemia (AML),) and lymphomas including lymphocytic, granulocytic and monocytic. Additional types of cancers which may be treated using the compounds and methods of the invention include, but are not limited to, adrenocarcinoma, angiosarcoma, astrocytoma, acoustic neuroma, anaplastic

astrocytoma, basal cell carcinoma, blastoglioma, chondrosarcoma, choriocarcinoma, chordoma, craniopharyngioma, cutaneous melanoma, cystadenocarcinoma, endotheliosarcoma, embryonal carcinoma, ependymoma, Ewing's tumor, epithelial carcinoma, fibrosarcoma, gastric cancer, genitourinary tract cancers, glioblastoma multiforme, head and neck cancer, hemangioblastoma, hepatocellular carcinoma, hepatoma, Kaposi's sarcoma, large cell carcinoma, leiomyosarcoma, leukemias, liposarcoma, lymphatic system cancer, lymphomas, lymphangiosarcoma, lymphangioendotheliosarcoma, medullary thyroid carcinoma, medulloblastoma, meningioma mesothelioma, myelomas, myxosarcoma neuroblastoma, neurofibrosarcoma, oligodendroglioma, osteogenic sarcoma, epithelial ovarian cancer, papillary carcinoma, papillary adenocarcinomas, paraganglioma, parathyroid tumours, pheochromocytoma, pinealoma, plasmacytomas, retinoblastoma, rhabdomyosarcoma, sebaceous gland carcinoma, seminoma, skin cancers, melanoma, small cell lung carcinoma, non-small cell lung carcinoma, squamous cell carcinoma, sweat gland carcinoma, synovioma, thyroid cancer, uveal melanoma, and Wilm's tumor.

[0148] In certain embodiments, the compositions and methods disclosed herein are useful for preventing or reducing tumor invasion and tumor metastasis.

[0149] Besides being useful for human treatment, certain compounds and formulations disclosed herein may also be useful for veterinary treatment of companion animals, exotic animals and farm animals, including mammals, rodents, and the like. More preferred animals include horses, dogs, and cats.

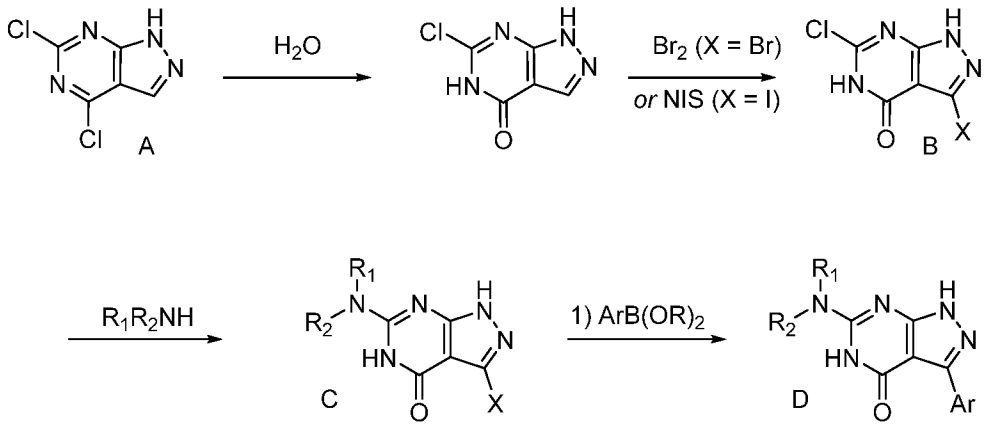
List of Abbreviations:

[0150] NaOH = sodium hydroxide; M = molar; mL = milliliter; h = hour; min. = minute; HCl = hydrogen chloride; H_2O = water; MS = mass spectrometry; ES+ = electrospray positive ionization; ^{1}H-NMR = proton nuclear magnetic resonance; MHz = megahertz; DMSO-d_6 = dimethyl sulfoxide deuterated-6; H = hydrogen; rt = room temperature; °C = Celsius; Br_2 = bromine; $NaHSO_3$ = sodium bisulfite; , NMP = N-Methyl-2-pyrrolidone; MW = microwave; KF = potassium fluoride; Pd(dppf)Cl_2 = [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride; PE = petroleum ether; EA = ethyl acetate; $CDCl_3$ = deuterated chloroform;, MeOH = methanol; D_2O = deuterated water; HPLC = high pressure liquid chromatography; DMSO = dimethyl sulfoxide; MeCN = acetonitrile; NIS = N-iodosuccinimide; DMF = dimethylformamide; K_3PO_4 = potassium phosphate, tribasic; N_2 = nitrogen; TFA = trifluoroacetic acid; DCM = dichloromethane; K_2CO_3 = potassium carbonate; ul = microliter.

General Synthetic Methods for Preparing Compounds

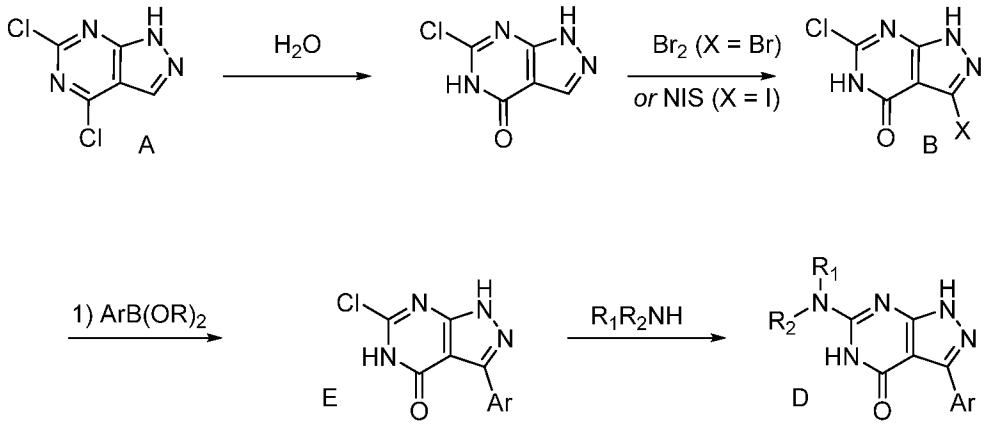
[0151] The following schemes can be used to practice the present invention.

Scheme I



[0152] Examples disclosed herein can be synthesized using the general synthetic procedure set forth in Scheme I. Regioselective hydrolysis of commercially available dichloride A is followed by regioselective oxidative halogenation at C3 to give B. Reaction with a selected amine displaces the activated chlorine to give C. Coupling of the aryl halide with a selected aryl boronate under Suzuki conditions gives the target compound. Deprotection steps can be incorporated either before or after the Suzuki reaction as appropriate for the scheme.

Scheme II



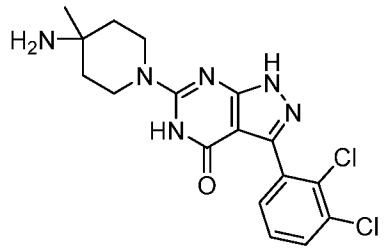
[0153] Alternatively, examples disclosed herein can be synthesized using an alternate synthetic procedure set forth in Scheme II, with the order of steps altered. Regioselective hydrolysis of commercially available dichloride A is followed by regioselective oxidative halogenation at C3 to give B. Coupling of the aryl halide B with a selected aryl boronate under Suzuki conditions gives compound E. Reaction with a selected amine displaces the

activated chlorine to give D. Deprotection steps can be incorporated either before or after the amine displacement reaction as appropriate for the scheme.

[0154] The invention is further illustrated by the following examples which employ Scheme I for synthesis.

EXAMPLE 1

6-(4-Amino-4-methylpiperidin-1-yl)-3-(2,3-dichlorophenyl)-1H-pyrazolo[3,4-d]-pyrimidin-4(5H)-one TFA salt



[0155] **6-Chloro-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one** A solution of 4,6-dichloro-1H-pyrazolo[3,4-d]pyrimidine (1g, 5.3 mmol) in NaOH (2M, aq, 5 mL) and dioxane (0.5 mL) was stirred at 100 °C for 1.5h. The mixture was acidified with HCl (6M, aq) to pH 6.5 at 0 °C and stirred for 30 min. The reaction mixture was filtered, and the filter cake was washed with cold H_2O (10 mL) and dried to obtain the product as a white solid (500 mg, 55%).

[0156] MS (ES+) $C_5H_3ClN_4O$ requires: 170, found: 171 $[M+H]^+$.

[0157] ^1H NMR (500 MHz, DMSO-d_6) δ 13.92 (s, 1H), 12.89 (s, 1H), 8.68 (s, 1H).

[0158] **3-Bromo-6-chloro-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one** To a mixture of 6-chloro-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one (1.35 g, 6.4 mmol) in H_2O (50 mL) was added Br_2 (2 mL, 41 mmol) and the reaction mixture was stirred at rt for 1h, then refluxed for 1h. The reaction mixture was allowed to cool to rt and $NaHSO_3$ (20 mL, 2M) was added. The mixture was stirred at 0 °C for 20 min, filtered, and the filter cake was dried to obtain the product as a light yellow solid (1.5 g, 76%).

[0159] MS (ES+) $C_5H_2BrClN_4O$ requires: 250, found: 251 $[M+H]^+$.

[0160] ^1H NMR (500 MHz, DMSO-d_6) δ 13.92 (s, 1H), 8.5 (s, 1H).

[0161] ***tert*-Butyl 1-(3-bromo-4-oxo-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl)-4-methylpiperidin-4-ylcarbamate** A mixure of 3-bromo-6-chloro-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one (500 mg, 1.2 mmol) and *tert*-butyl 4-methylpiperidin-4-ylcarbamate (582 mg, 1.8 mmol) in NMP (5 mL) was stirred at 75 °C for 1h. H_2O was added

(50 mL), the mixture was stirred at 0 °C for 30 min, filtered and the filter cake was dried to obtain the product as a gray solid (700 mg, 82%).

[0162] MS (ES+) $C_{16}H_{23}BrN_6O_3$ requires: 426, found: 427 $[M+H]^+$.

[0163] ^1H NMR (500 MHz, DMSO-d_6) δ 13.11 (s, 1H), 10.88 (s, 1H), 6.62 (d, J = 2.2 Hz, 1H), 3.88 (m, 2H), 3.32 (m, 4H), 2.06 (m, 2H), 1.47 (s, 9H), 1.36 (s, 3H).

[0164] ***tert*-Butyl 1-(3-(2,3-dichlorophenyl)-4-oxo-4,5-dihydro-1H-pyrazolo[3,4-d]-pyrimidin-6-yl)-4-methylpiperidin-4-ylcarbamate** A MW vial was charged with 2,3-dichlorophenylboronic acid (267 mg, 1.4 mmol), *tert*-butyl (1-(3-bromo-4-oxo-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl)-4-methylpiperidin-4-yl)carbamate, (300 mg, 0.70 mmol), KF (122 mg, 2.1 mmol), $Pd(dppf)Cl_2$ (51 mg, 0.069 mmol), 1,4-dioxane (5 mL) and H_2O (0.5 mL). The reaction mixture was heated to 140 °C for 2h and was purified by flash column chromatography (PE:EA=1:1 to 0:1) to obtain the product as a beige solid (100 mg crude, 29%).

[0165] MS (ES+) $C_{22}H_{26}Cl_2N_6O_3$ requires: 492, found: 493 $[M+H]^+$.

[0166] ^1H NMR (500 MHz, $CDCl_3$) δ 11.29 (s, 1H), 10.95 (s, 1H), 7.56 (dt, J = 11.3, 5.7 Hz, 1H), 7.45 (dd, J = 7.6, 1.4 Hz, 1H), 7.31 (t, J = 7.8 Hz, 1H), 4.44 (s, 1H), 3.91 (d, J = 13.4 Hz, 2H), 3.39 (t, J = 11.0 Hz, 2H), 1.93 (d, J = 11.5 Hz, 2H), 1.74 – 1.50 (m, 2H), 1.48 (d, J = 16.7 Hz, 9H), 1.35 (s, 3H).

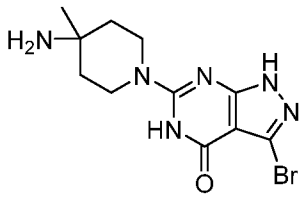
[0167] **6-(4-Amino-4-methylpiperidin-1-yl)-3-(2,3-dichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one TFA salt** A mixture of *tert*-butyl (1-(3-(2,3-dichlorophenyl)-4-oxo-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl)-4-methylpiperidin-4-yl)carbamate (100 mg; crude) in HCl/MeOH (3M, 3 mL) was stirred at rt for 16h. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in DMSO (2 mL) and purified by prep-HPLC (Mobile phase: A = 6.7 mM TFA/H_2O, B = acetonitrile; Gradient: B = 5% - 95 % in 18 min; Column: SunFire C18, 5um, 30 mm × 150 mm) to obtain the product as a white solid (50 mg, 63%).

[0168] MS (ES+) $C_{17}H_{18}Cl_2N_6O$ requires: 392, found: 393$[M+H]^+$.

[0169] ^1H NMR (500 MHz, D_2O) δ 7.57 (m, J = 1H), 7.32 (m, 2H), 2.95 (d, J = 13.9 Hz, 2H), 3.27 (m, 2H), 1.77 (m, 4H), 1.35 (s, 3H).

EXAMPLE 2

6-(4-Amino-4-methylpiperidin-1-yl)-3-bromo-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one HCl salt



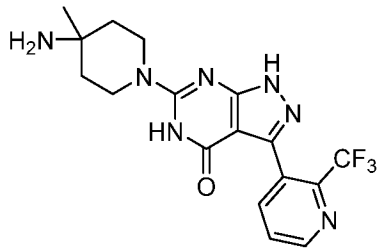
[0170] **6-(4-Amino-4-methylpiperidin-1-yl)-3-bromo-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one HCl salt** A mixture of *tert*-butyl (1-(3-bromo-4-oxo-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl)-4-methylpiperidin-4-yl)carbamate (150 mg, 0.25 mmol) (Example 1) in HCl/MeOH (3M, 3 mL) was stirred at rt 16h. The reaction mixture was concentrated, MeCN (5 mL) was added, the mixture was stirred for 10 min. and filtered to obtain the product as a white solid (65 mg, 56%).

[0171] MS (ES+) $C_{11}H_{15}BrN_6O$ requires: 326, found: 327$[M+H]^+$.

[0172] ^{1}H NMR (400 MHz, D_2O) δ 3.93 (m, 2H), 3.32 (m, 2H), 1.78 (m, 4H), 1.37 (s, 3H).

EXAMPLE 3

6-(4-Amino-4-methylpiperidin-1-yl)-3-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one TFA salt



[0173] **6-Chloro-3-iodo-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one** A solution of 6-chloro-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one (2.3 g, 13 mmol) and NIS (4.5 g, 22 mmol) in DMF (25 mL) was stirred at 80 °C for 16h. $NaHSO_3$ (2M, 100 mL) was added and reaction mixture was stirred at 0 °C for 1h. The reaction mixture was filtered, and the filter cake was dried to obtain the product as a white solid (3 g, 90%).

[0174] MS (ES+) $C_5H_2ClIN_4O$ MS: 296.45 found: 297 $[M+H]^+$.

[0175] ^{1}H-NMR (DMSO-d_6, 500M), δ14.169(s, 1H), δ13.161 (s, 1H).

[0176] ***tert*-Butyl (1-(3-iodo-4-oxo-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl)-4-methylpiperidin-4-yl)carbamate** A solution of 6-chloro-3-iodo-1,5-dihydro-4H-pyrazolo-[3,4-d]pyrimidin-4-one (300 mg, 1.0 mmol) and tert-butyl (4-methylpiperidin-4-yl)carbamate (325 mg, 1.5 mmol) in NMP (3 mL) was stirred at 75 °C for 1h. H_2O (10 mL) was added and

the mixture was stirred at 0 °C for 30 min, filtered and the filter cake was dried to obtain the product as a white solid (500 mg, crude).

[0177] MS (ES+) $C_{16}H_{23}IN_6O_3$ requires: 474.30, found 475 $[M+H]^+$.

[0178] ***tert*-Butyl (4-methyl-1-(4-oxo-3-(2-(trifluoromethyl)pyridin-3-yl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl)piperidin-4-yl)carbamate** A solution of *tert*-butyl (1-(3-iodo-4-oxo-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl)-4-methylpiperidin-4-yl)carbamate (300mg, 0.63 mmol), 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan -2-yl)-2-(trifluoromethyl)pyridine (518 mg, 1.9 mmol), $Pd(dppf)Cl_2$ (46 mg, 0.063 mmol), K_3PO_4 (534 mg, 2.52 mmol) in dioxane (5 mL) and H_2O (2 mL) was flushed with N_2 and stirred at 100 °C in the MW for 3 h. The mixture was concentrated, and the residue was purified by silica gel column chromatography (PE:EA=1:1 to 0:1) to obtain the product as a brown solid (48 mg, crude).

[0179] MS (ES+) $C_{22}H_{26}F_3N_7O_3$ requires: 493.49, found 494 $[M+H]^+$.

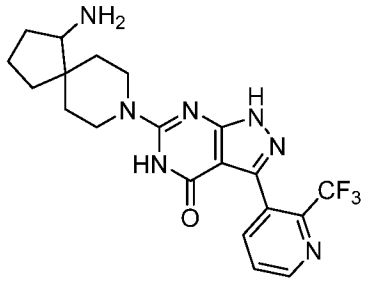
[0180] **6-(4-Amino-4-methylpiperidin-1-yl)-3-(2-(trifluoromethyl)pyridin-3-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one TFA salt** A solution of *tert*-butyl (4-methyl-1-(4-oxo-3-(2-(trifluoromethyl)pyridin-3-yl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl)piperidin-4-yl)carbamate (48 mg, crude) in TFA (2 mL) was stirred for 30 min. The mixture was concentrated and purified by Prep-HPLC (Mobile phase: A = 6.7 mM TFA/H_2O, B = acetonitrile; Gradient: B = 5% - 95 % in 18 min; Column: SunFire C18, 5um, 30 mm × 150 mm) to obtain the product as a white solid (15 mg, 30 %).

[0181] MS (ES+) $C_{17}H_{18}F_3N_7O$ requires: 393.37, found 394 $[M+H]^+$.

[0182] ^1H NMR (500 MHz, DMSO) δ 13.29 (s, 1H), 11.02 (s, 1H), 8.81 (d, J = 4.3 Hz, 1H), 8.07-7.95 (m, 1H), 7.81 (dd, J = 7.8, 4.7 Hz, 1H), 4.03 (m, 2H), 3.39 (m, 2H), 5.5-4.0 (bz, 2H), 1.98-1.61 (m, 4H), 1.36 (s, 3H).

EXAMPLE 4

6-(1-Amino-8-azaspiro[4.5]decan-8-yl)-3-(2-(trifluoromethyl)pyridin-3-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one TFA salt



[0183] **3-Iodo-6-(1-((4-methoxybenzyl)amino)-8-azaspiro[4.5]decan-8-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one** A solution of 6-chloro-3-iodo-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one (100 mg, 0.34 mmol), K_2CO_3 (93 mg, 0.67 mmol), N-(4-methoxybenzyl)-8-azaspiro[4.5]decan-1-amine hydrochloride (110 mg, 0.50 mmol) in NMP (2 mL) was stirred at 100 °C for 2h. H_2O was added (10 mL), the mixture was filtered and the filter cake was dried to obtain the product as a white solid (120 mg, crude).

[0184] MS (ES+) $C_{22}H_{27}IN_6O_2$, requires: 534.40, found 535$[M+H]^+$.

[0185] **6-(1-((4-Methoxybenzyl)amino)-8-azaspiro[4.5]decan-8-yl)-3-(2-(trifluoromethyl)pyridin-3-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one** A solution of 3-iodo-6-(1-((4-methoxybenzyl)amino)-8-azaspiro[4.5]decan-8-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one (120 mg, 0.225 mmol), 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan -2-yl)-2-(trifluoromethyl)pyridine (184 mg, 0.67 mmol), $Pd(dppf)Cl_2$ (17 mg, 0.023 mmol), and K_3PO_4 (143 mg, 0.67 mmol) in dioxane (5 mL) and H_2O (2 mL) was flushed with N_2 and stirred at 100 °C in the MW for 3 hours. The mixture was concentrated and purified by reverse phase silica gel column chromatography to obtain the product as a brown solid (40 mg, crude).

[0186] MS (ES+) $C_{28}H_{30}F_3N_7O_2$ requires: 553.59, found 554 $[M+H]^+$.

[0187] **6-(1-Amino-8-azaspiro[4.5]decan-8-yl)-3-(2-(trifluoromethyl)pyridin-3-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one TFA salt** A solution of 6-(1-((4-methoxybenzyl)amino)-8-azaspiro[4.5]decan-8-yl)-3-(2-(trifluoromethyl)pyridin-3-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one (40 mg, crude) in TFA (0.5 mL) was heated to 160 °C in the MW for 30 min. The reaction mixture was concentrated and purified by Prep-HPLC Prep-HPLC (Mobile phase: A = 6.7 mM TFA/H_2O, B = acetonitrile; Gradient: B = 5% - 95 % in 18 min; Column: SunFire C18, 5um, 30 mm × 150 mm) to obtain the product as a white solid (2.2 mg, 5 %).

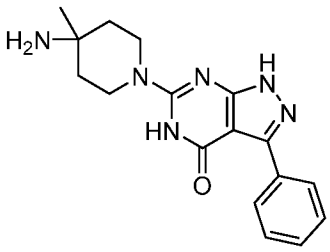
[0188] MS (ES+) $C_{20}H_{22}F_3N_7O$ requires: 433.4, found 434 $[M+H]^+$.

[0189] ^1H NMR (500 MHz, DMSO) δ 13.22 (s, 1H), 10.93 (s, 1H), 8.80 (d, J = 4.2 Hz, 1H), 8.09 (d, J = 7.8 Hz, 1H), 7.81 (m, 1H), 4.32-4.11 (m, 2H), 3.25-3.02 (m, 3H), 2.13-1.98 (m, 1H), 1.82-1.32 (m, 9H).

[0190] The following compounds were made employing Scheme I for synthesis.

EXAMPLE 5

6-(4-Amino-4-methylpiperidin-1-yl)-3-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one TFA salt

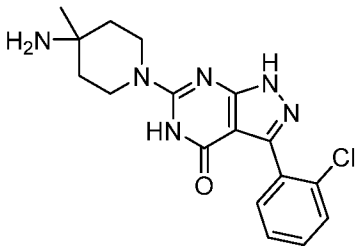


[0191] The title compound was prepared as described for Example 1.MS (ES+) $C_{17}H_{20}N_6O$ requires: 324, found: 325$[M+H]^+$.

[0192] ^1H NMR (500 MHz, DMSO-d_6) δ 13.10 (s, 1H), 11.00 (s, 1H), 8.34 (d, J = 7.6 Hz, 2H), 7.43 (m, 3H), 4.04 (d, J = 14.4 Hz, 2H), 3.75-3.5 (bs, 2H), 3.38 – 3.33 (m, 2H), 1.82 – 1.66 (m, 4H), 1.37 (s, 3H).

EXAMPLE 6

6-(4-Amino-4-methylpiperidin-1-yl)-3-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one TFA salt



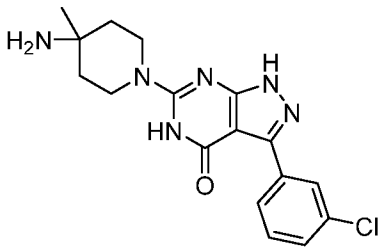
[0193] The title compound was prepared as described for Example 1.

[0194] MS (ES+) $C_{17}H_{19}ClN_6O$ requires: 358, found: 359$[M+H]^+$.

[0195] ^1H NMR (500 MHz, DMSO-d_6) δ 13.14 (s, 1H), 10.93 (s, 1H), 7.52 (dd, J = 22.7, 6.8 Hz, 2H), 7.47 – 7.34 (m, 2H), 4.03 (d, J = 14.1 Hz, 2H), 3.5-3.3 (bs, 2H), 3.36 – 3.33 (m, 2H), 1.81 – 1.63 (m, 4H), 1.36 (s, 3H).

EXAMPLE 7

6-(4-Amino-4-methylpiperidin-1-yl)-3-(3-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one TFA salt



[0196] The title compound was prepared as described for Example 1.

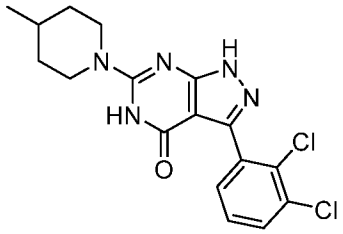
[0197] MS (ES+) $C_{17}H_{19}ClN_6O$ requires: 358, found: 359$[M+H]^+$.

[0198] ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.25 (s, 1H), 11.08 (s, 1H), 8.50 (s, 1H), 8.33 (d, J = 7.6 Hz, 1H), 7.47 (t, J = 7.8 Hz, 1H), 7.42 (d, J = 8.0 Hz, 1H), 4.2-3.3 (bs, 2H), 4.08 – 4.00 (m, 2H), 3.40 – 3.34 (m, 2H), 1.78 – 1.67 (m, 4H), 1.37 (s, 3H).

[0199] The invention is further illustrated by the following examples which employ Scheme II for synthesis.

EXAMPLE 8

3-(2,3-Dichlorophenyl)-6-(4-methylpiperidin-1-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one TFA salt



[0200] **6-Chloro-3-(2,3-dichlorophenyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one** A solution of 6-chloro-3-iodo-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one (1 g, 3.4 mmol), (2,3-dichlorophenyl)boronic acid (1.29 g, 6.7 mmol), Pd(dppf)Cl_2 (248 mg, 0.34 mmol), and KF (588 mg, 10.1 mmol) in dioxane (25 mL) and H_2O (5 mL) was flushed with N_2 and stirred at 100 °C for 48 h. The mixture was concentrated, DCM (50 mL) and H_2O (50 mL) was added and the mixture was stirred rapidly for 10 min. The reaction mixture was filtered and dried to obtain the product (1 g, crude).

[0201] MS (ES+) $C_{11}H_5Cl_3N_4O$ requires: 315.54, found: 316 $[M+H]^+$.

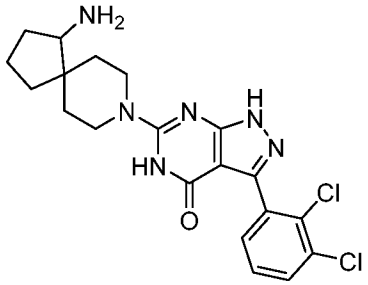
[0202] **3-(2,3-Dichlorophenyl)-6-(4-methylpiperidin-1-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one TFA salt** A solution of 6-chloro-3-(2,3-dichlorophenyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one (50 mg, 0.16 mmol) and 4-methylpiperidine (80 mg, 0.8 mmol) in NMP (1 mL) was stirred at 75 °C for 1 hour. The mixture was purified by Prep-HPLC Prep-HPLC (Mobile phase: A = 6.7 mM TFA/H_2O, B = acetonitrile; Gradient: B = 5% - 95 % in 18 min; Column: SunFire C18, 5um, 30 mm × 150 mm) to obtain the product as a white solid (3.6 mg, 5%).

[0203] MS (ES+) $C_{17}H_{17}Cl_2N_5O$ requires: 378.26, found: 379 $[M+H]^+$.

[0204] ^{1}H-NMR (DMSO-d_6, 500M), δ 13.10 (s, 1H), 10.78 (s, 1H), 7.711 (m, 1H), 7.46 (m, 2H), 4.32 (m, 2H), 2.90 (m, 2H), 1.63 (m, 3H), 1.14 (m, 2H), 0.91 (d, *J*=5.5, 3H).

EXAMPLE 9

6-(1-amino-8-azaspiro[4.5]decan-8-yl)-3-(2,3-dichlorophenyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one TFA salt



[0205] **3-(2,3-Dichlorophenyl)-6-(1-((4-methoxybenzyl)amino)-8-azaspiro[4.5]decan-8-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one** A solution of 6-chloro-3-(2,3-dichlorophenyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one (90 mg, crude, about 0.28 mmol), K_2CO_3 (98.6 mg, 0.72 mmol), and N-(4-methoxybenzyl)-8-azaspiro[4.5]decan-1-amine hydrochloride (174 mg, 0.56 mmol) in NMP (2 mL) was stirred at 100 °C 16h. H_2O was added (10 mL) and the reaction mixture was filtered to obtain the product as a white solid (50 mg, crude).

[0206] MS (ES+) $C_{28}H_{30}Cl_2N_6O_2$, required: 553.49, found 554$[M+H]^+$.

[0207] **6-(1-Amino-8-azaspiro[4.5]decan-8-yl)-3-(2,3-dichlorophenyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one TFA salt** A mixture of 3-(2,3-dichlorophenyl)-6-(1-((4-methoxybenzyl)amino)-8-azaspiro[4.5]decan-8-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one (50 mg, crude) in TFA (0.5 mL) was heated in the MW at 160 °C for 35 min. The mixture was purified by Prep-HPLC (Mobile phase: A = 6.7 mM TFA/H_2O, B = acetonitrile; Gradient: B = 5% - 95 % in 18 min; Column: SunFire C18, 5um, 30 mm × 150 mm) to obtain the product as a white solid (9.3 mg, 20%).

[0208] MS (ES+) $C_{20}H_{22}Cl_2N_6O$ requires: 433.34, found 434 $[M+H]^+$.

[0209] ^1H NMR (500 MHz, DMSO-d_6) δ 13.14 (s, 1H), 10.86 (s, 1H), 7.72 (m, 1H), 7.52-7.37 (m, 2H), 4.25 (m, 2H), 4.2-3.2 (bs, 2H), 3.17-3.09 (m, 3H), 2.08 (m, 1H), 2.04 (m, 1H), 1.83-1.34 (m, 8H).

Separation of enantiomers:

The enantiomers of the racemic mixture were separated by the conditions as follows: Column : OJ-H (250*4.6mm 5um); Mobile Phase n-Hexane (0.1% Et_2NH) : EtOH (0.1% Et_2NH) = 70:30; Temperature: 40 °C; Flow:1.0 mL/min; Wavelength: 214 nm & 254 nm; Instrument: SHIMADZU; Inject Volume: 12 ul.

[0210] Retention times: P1(9a, 15.203 min), P2 (9b, 25.039 min).

Biological Activity Assay

[0211] The activity of the compounds in the Examples disclosed herein as PTPN11 inhibitors is illustrated in the following assays. Other compounds listed herein, which have not yet been made and/or tested, are predicted to have activity in these assays as well.

PTPN11 enzymatic assay

[0212] Recombinant full-length wild-type and E76K mutant human PTPN11 proteins were cloned, expressed (E. coli system), and isolated via a two-step purification of Ni affinity followed by S75 size exclusion chromatography.

[0213] Phosphatase activity of full length wild-type PTPN11(PTPN11-WT) or PTPN11-E76K mutant enzyme was measured using the fluorogenic 6,8-difluoro-4-methylumbelliferyl phosphate (DiFMUP; Molecular Probes) as the substrate. Enzyme (250 pM) was incubated with or without increasing concentrations of compounds in assay buffer (62.5 mM HEPES, 125 mM NaCl, 1 mM EDTA, 1.25 mM TECP, 0.1% BSA) for 30 min at room temperature. Reaction was initiated by addition of DiFMUP (50 μM) at room temperature in 384-well black plate with a final reaction volume of 20 uL in assay buffer. After 1 hour, DiFMUP fluorescence signal was measured (Ex:340/Em:460) using Envision plate reader. Dose-response curves were analyzed using IC_{50} regression curve fitting (GeneData Screener). Curves were normalized to a high controls without inhibitor, and low controls without substrate. Results are given below in Table 1.

Table 1. Biological Activity for inhibition of PTPN11-E76K mutant enzyme

Example #	IC_{50}, μM
1	0.038
2	14
3	3.6
4	2.1
5	0.13
6	0.078
7	0.100
8	17
9(a)	0.0019
9(b)	0.047

ERK phosphorylation (phospho-ERK) target engagement assay

[0214] KYSE-520 cells (10k cells/well) are plated onto 384-well plate in 20 uL of medium (RPMI-1640, without phenol red, containing 10% FBS) and incubated at 37°C, 5% CO_2 16h. DMSO (control) or increasing concentrations of compounds are diluted in medium, added to the 384-well plate (10 uL/well, final DMSO concentration of 1%), and cells are then incubated with compounds for 2 hr. Phospho-ERK levels are measured using a TR-FRET based phospho-ERK1/2 HTRF kit (CisBio, 64ERKPEH) following manufacturer's recommendations, and fluoresence signal was measured at 665 nm and 620 nm using Synergy Neo plate reader. Dose-response curves were analyzed using IC_{50} regression curve fitting (GeneData Screener). Curves were normalized to a high controls without inhibitor, and low controls with 1μM of selumetinib. Some compounds of this invention showed IC_{50}<1μM.

Colony formation assay

[0215] KYSE-520 cells (2000 cells/well) are plated in 6-well plate containing 2 mL of medium (RPMI-1640, containing 10% FBS), in presence of DMSO (control; 1% final concentration) or increasing compound concentration. After 14 days of culture at 37°C in a humidified 5% CO_2 incubator, colonies are fixed and stained with 0.1% crystal violet and 15% ethanol solution. Plates are imaged and colony area quantified and normalized to DMSO with ImageJ, Colony Area plugin. (Guzmán, Camilo, PloS one 2014). Some compounds of this invention displayed IC_{50}<1μM).

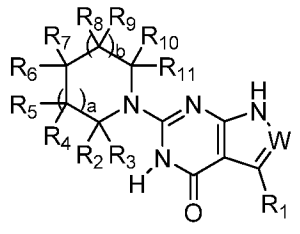
[0216] All references, patents or applications, U.S. or foreign, cited in the application are hereby incorporated by reference as if written herein in their entireties. Where any inconsistencies arise, material literally disclosed herein controls.

[0217] From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

CLAIMS

What is claimed is:

1. A compound of structural Formula I



(I)

or a salt, ester, or prodrug thereof, wherein:

a is selected from 0 and 1;

b is selected from 0 and 1;

W is selected from CR_{14} and N;

R_1 is selected from halo, C_{6-10}aryl, C_{3-8}cycloalkyl, C_{3-8}cycloalkenyl, and a 5-9 membered heteroaryl group containing 1 to 4 heteroatoms or groups independently selected from N, C(O), O, and S;

said aryl or heteroaryl of R_1 is optionally substituted with 1 to 5 R_{12} groups independently selected from halo, hydroxy, amino, dimethylamino, CN, C_{1-4} alkyl, C_{1-4}hydroxyalkyl, C_{1-4}haloalkyl, C_{1-4}aminoalkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkenyl, $NR_{15a}C(O)R_{13}$, $NR_{15a}C(O)OR_{13}$, $NR_{13}C(O)N(R_{15a})(R_{15b})$, $NR_{15a}S(O)R_{13}$, $NR_{15a}S(O)_2R_{13}$, $C(O)N(R_{15a})(R_{15b})$, $S(O)N(R_{15a})(R_{15b})$, $S(O)_2N(R_{15a})(R_{15b})$, $C(O)R_{13}$, $C(O)OR_{13}$, SR_{13}, $S(O)R_{13}$, and $S(O)_2R_{13}$;

R_2, R_3, R_{10}, and R_{11} are independently selected from hydrogen, C_{1-4}alkyl, ,and C_{3-8}cycloalkyl;

R_4, R_5, R_8, and R_9 are independently selected from hydrogen, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, amino, hydroxy, C_{3-8}cycloalkyl, halo, and C_{1-4} alkylamino;

R_6 is selected from amino, C_{1-4}aminoalkyl, and methylamino;

R_7 is selected from hydrogen, halo, and hydroxy, or is selected from C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{3-6}cycloalkyl, phenyl, and 5- or 6- membered heteroaryl, any of which may be optionally substituted with one or more substituents chosen from amino, halo, hydroxy, cyano, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, and C_{1-4}alkoxy;

or R_6 and R_7 together with the carbon atom to which they are both attached can form a 3- to 7- membered ring that can optionally contain 1 to 3 heteroatoms or groups independently selected from N, C(O), O, and $S(O)_m$, and said ring formed by R_6 and R_7

can be unsubstituted or substituted with 1 to 3 groups independently selected from halo, hydroxy, methoxy, amino, methylamino, C_1-C_4alkylaminoalkyl, and C_1-C_4 alkyl;

m is selected from 0,1, and 2;

said saturated ring formed by R_6 and R_7 can be unsubstituted or substituted with 1 to 3 groups independently selected from amino, hydroxy, methoxy, halo, methyl, methylamino, C_1-C_4 alkyl, C_1-C_4aminoalkyl and isobutyroxy;

any two groups selected from R_2, R_3, R_4, R_5, R_7, R_8, R_9, R_{10} and R_{11} can form a 5- to 6- membered ring, optionally containing a N, O or S heteroatom;

R_2, R_4, R_6, R_8 and R_{10} can form a direct bond, or a 1 or 2 atom carbon bridge;

R_{14} is selected from hydrogen and C_{1-4}alkyl; and

R_{13}, R_{15}, and R_{16} are independently selected from hydrogen, C_{1-4}alkyl, and C_{3-8}cycloakyl, wherein said alkyl or cycloalkyl is optionally substituted by one or more substituents chosen from hydroxyl, cyano and halo.

2. The compound as recited in Claim 1 wherein:

R_1 is selected from C_{6-10}aryl, and a 5- to 9- membered heteroaryl group containing 1 to 4 heteroatoms or groups independently selected from N, C(O), O, and S;

said aryl or heteroaryl of R_1 is optionally substituted with 1 to 5 R_{12} groups independently selected from halo, hydroxy, amino, dimethylamino, cyano, C_{1-4} alkyl, C_{1-4}hydroxyalkyl, C_{1-4}haloalkyl, C_{1-4}aminoalkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkenyl, $NR_{15a}C(O)R_{13}$, $NR_{15a}C(O)OR_{13}$, $NR_{13}C(O)N(R_{15a})(R_{15b})$, $NR_{15a}S(O)R_{13}$, $NR_{15a}S(O)_2R_{13}$, $C(O)N(R_{15a})(R_{15b})$, $S(O)N(R_{15a})(R_{15b})$, $S(O)_2N(R_{15a})(R_{15b})$, $C(O)R_{13}$, $C(O)OR_{13}$, SR_{13}, $S(O)R_{13}$, and $S(O)_2R_{13}$; and

R_{13}, R_{15}, and R_{16} are independently selected from hydrogen, C_{1-4}alkyl, and C_{3-8}cycloakyl, wherein said alkyl or cycloalkyl is optionally substituted by one or more substituents chosen from hydroxyl, cyano and halo.

3. The compound as recited in Claim 2 wherein:

R_1 is selected from C_{6-10}aryl, and a 5- to 9- membered heteroaryl group containing 1 to 4 heteroatoms or groups independently selected from N, C(O), O, and S;

said aryl or heteroaryl of R_1 is optionally substituted with 1 to 5 R_{12} groups independently selected from hydroxy, amino, C_{1-4}alkyl, C_{1-4}haloalkyl, and C_{1-4}aminoalkyl;

when R_6 and R_7 together with the carbon atom to which they are both attached form a 3- to 7- membered ring that can optionally contain 1 to 3 heteroatoms or groups

independently selected from N, C(O), O, and $S(O)_m$; wherein m is selected from 0,1, and 2;

then said ring formed by R_6 and R_7 can be unsubstituted or substituted with 1 to 3 groups independently selected from halo, hydroxy, methoxy, amino, methylamino, C_1-C_4alkylaminoalkyl, and C_1-C_4 alkyl.

4. The compound as recited in Claim 2 wherein:

R_1 is selected from halo, C_{6-10}aryl, and a 5- to 9- membered heteroaryl group containing 1 to 4 heteroatoms or groups independently selected from N, C(O), O, and S;

said aryl or heteroaryl of R_1 is optionally substituted with 1 to 5 R_{12} groups independently selected from hydroxy, amino, C_{1-4}alkyl, C_{1-4}haloalkyl, and C_{1-4}aminoalkyl;

R_6 is selected from amino, C_{1-4}aminoalkyl, and methylamino; and

R_7 is selected from hydrogen, halo, and hydroxy, or is selected from C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{3-6}cycloalkyl, phenyl, and 5- or 6- membered heteroaryl, any of which may be optionally substituted with one or more substituents chosen from amino, halo, hydroxy, cyano, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, and C_{1-4}alkoxy.

5. The compound as recited in Claim 1 wherein:

W is N;

R_1 is selected from C_{6-10}aryl, and a 5- to 9- membered heteroaryl group containing 1 to 4 heteroatoms or groups independently selected from N, C(O), O, and S;

said aryl or heteroaryl of R_1 is optionally substituted with 1 to 5 R_{12} groups independently selected from hydroxy, amino, C_{1-4}alkyl, C_{1-4}haloalkyl, and C_{1-4}aminoalkyl; and

R_4, R_5, R_8, and R_9 are independently selected from hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy, amino, hydroxy, C_{3-8}cycloalkyl, and C_{1-4} alkylamino.

6. The compound as recited in Claim 5 wherein R_2, R_3, R_4, R_5, R_8, R_9, R_{10} and R_{11} are hydrogen.

7. The compound as recited in Claim 6 wherein

R_6 and R_7 together with the carbon atom to which they are both attached form a 3- to 7- membered saturated or partially unsaturated ring; and

said saturated ring formed by R_6 and R_7 can be unsubstituted or substituted with 1 to 3 groups independently selected from amino, hydroxy, methoxy, methylamino, and C_1-C_4 alkyl.

8. The compound as recited in Claim 7 wherein:

R_1 is selected from halo, C_{6-10}aryl, and a 5- to 9- membered heteroaryl group containing 1 to 4 heteroatoms or groups independently selected from N, C(O), O, and S;

said aryl or heteroaryl of R_1 is optionally substituted with 1 to 5 R_{12} groups independently selected from hydroxy, amino, C_{1-4}alkyl, C_{1-4}haloalkyl, and C_{1-4}aminoalkyl;

when R_6 and R_7 together with the carbon atom to which they are both attached form a 3- to 7- membered ring that can optionally contain 1 to 3 heteroatoms or groups independently selected from N, C(O), O, and $S(O)_m$; wherein m is selected from 0,1, and 2;

then said ring formed by R_6 and R_7 can be unsubstituted or substituted with 1 to 3 groups independently selected from halo, hydroxy, methoxy, amino, methylamino, C_1-C_4alkylaminoalkyl, and C_1-C_4 alkyl.

9. The compound as recited in Claim 7 wherein:

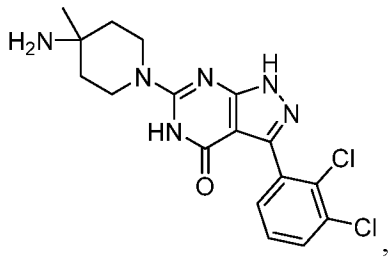
R_1 is selected from halo, C_{6-10}aryl, and a 5- to 9- membered heteroaryl group containing 1 to 4 heteroatoms or groups independently selected from N, C(O), O, and S;

said aryl or heteroaryl of R_1 is optionally substituted with 1 to 5 R_{12} groups independently selected from hydroxy, amino, C_{1-4}alkyl, C_{1-4}haloalkyl, and C_{1-4}aminoalkyl;

R_6 is selected from amino, C_{1-4}aminoalkyl, and methylamino; and

R_7 is selected from hydrogen, halo, and hydroxy, or is selected from C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{3-6}cycloalkyl, phenyl, and 5- or 6- membered heteroaryl, any of which may be optionally substituted with one or more substituents chosen from amino, halo, hydroxy, cyano, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, and C_{1-4}alkoxy.

10. The compound as recited in Claim 1 wherein the structure is chosen from:



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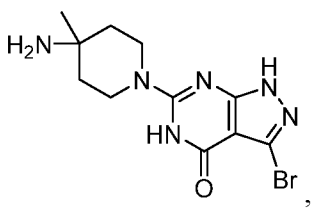

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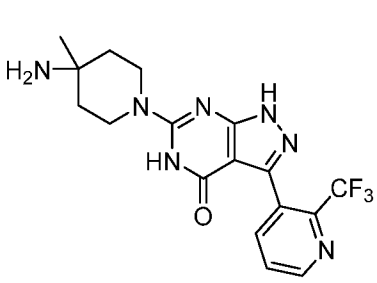
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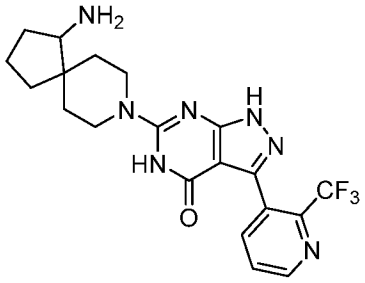
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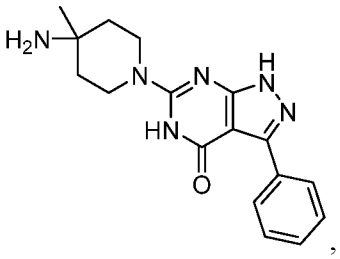
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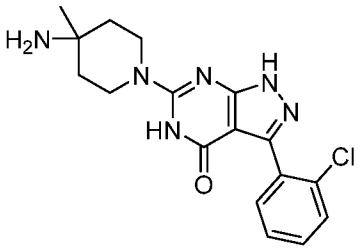
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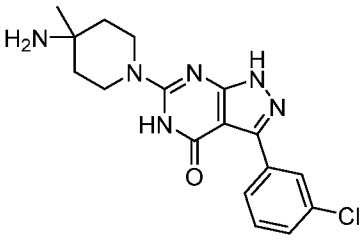
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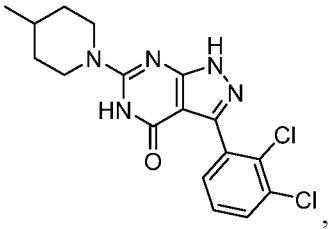
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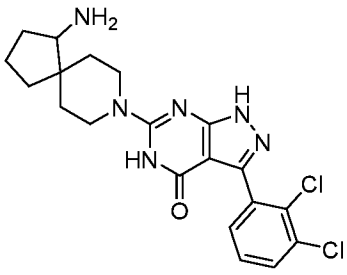
, or a salt, ester, or prodrug thereof.

11. A compound as recited in Claim 1 for use as a medicament.
12. A compound as recited in Claim 1 for use in the treatment of a disease driven by PTPN11 mutations.
13. The compound as recited in Claim 11, wherein the disease is chosen from Noonan Syndrome or LEOPARD Syndrome.
14. A compound as recited in Claim 1 for use in the treatment of cancer.
15. The compound as recited in Claim 14, wherein the cancer is chosen from leukemia, melanoma, breast cancer, and colon cancer.
16. A compound as recited in Claim 1 for use in the manufacture of a medicament for the prevention or treatment of a disease or condition ameliorated by the inhibition of PTPN11.
17. A pharmaceutical composition comprising a compound as recited in Claim 1 together with a pharmaceutically acceptable carrier.
18. A method of inhibition of PTPN11 comprising contacting PTPN11 with a compound as recited in Claim 1.

19. A method of treatment of a PTPN11-mediated disease comprising the administration of a therapeutically effective amount of a compound as recited in Claim 1 to a patient in need thereof.
20. The method as recited in Claim 19 wherein said disease is cancer.
21. The method as recited in Claim 20 wherein said cancer is chosen from breast cancer, colon cancer, leukemia, and melanoma.
22. A method of treatment of a PTPN11-mediated disease comprising the administration of:
    a. a therapeutically effective amount of a compound as recited in Claim 1; and
    b. another therapeutic agent.
23. The method as recited in Claim 22 wherein said disease is cancer.
24. The method as recited in Claim 23 wherein said cancer is chosen from breast cancer, colon cancer, leukemia, and melanoma.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 17/21784

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/495, A61K 31/506 (2017.01)
CPC - A61K 9/0053, A61K 31/519, A61K 45/06, A61K 31/5377

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History Document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History Document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 7,897,607 B2 (Gyorkos et al.) 01 March 2011 (01.03.2011); col 116, ln 55-65	1, 4,11-17
A	US 2011/152242 A1 (Bayliss et al.) 23 June 2011 (23.06.2011); para [0130]	1, 4,11-17
A	"Pubchem CID 57384833" Create Date: 23 July 2012 (23.07.2012) Date Accessed: 19 June 2017 (19.06.2017); pg. 3	1, 4,11-17
P, X	WO 2016/203404 A1 (NOVARTIS AG) 22 December 2016 (22.12.2016); entire document	1, 4,11-17

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 June 2017	07 JUL 2017

Name and mailing address of the ISA/US	Authorized officer:
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 17/21784

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
(see supplemental page)

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1, 4 and 11-17

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

--continued from Box No. III--

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

Group I+: Claims 1-17, directed to compounds having the general formula of claim 1, formula I. The compound of claim 1 will be searched to the extent that it encompasses the first species of claim 1, represented by the first formula of claim 1, wherein a is 0; b is 0; W is CR14; R1 is halo; R2, R3, R10, and R11 are hydrogen; R6 is amino; R7 is hydrogen; R14 is hydrogen. It is believed that claims 1, 4 and 11-17 read on this first named invention, and thus these claims will be searched without fee to the extent that they encompass the first species of claim 1. Applicant is invited to elect additional compounds of claim 1, wherein each additional compound elected will require one additional invention fee. Applicants must specify the claims that encompass any additionally elected compound. Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the '+' group(s) will result in only the first claimed invention to be searched. Additionally, an exemplary election wherein different actual variables are selected is suggested. An exemplary election would be a compound of claim 1, a is 0; b is 0; W is CR14; R1 is C6 aryl; R2, R3, R10, and R11 are hydrogen; R6 is amino; R7 is hydrogen; R14 is hydrogen (i.e., claims 1-2, 4 and 11-17).

Group II: Claims 18-24, directed to methods of inhibition of PTPN11 comprising contacting PTPN11 with a compound as recited in Claim 1/treatment of a PTPN11-mediated disease comprising the administration of a therapeutically effective amount of a compound as recited in Claim 1 to a patient in need thereof.

The group of inventions listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Special Technical Features:

Group I+ includes the technical feature of a unique compound of claim 1, which is not required by any other invention of Group I+ or II.

Group II includes the technical feature of methods of inhibition of PTPN11/treatment of a PTPN11-mediated disease, which is not required by any other invention of Group I+.

Common technical features:

The inventions of Group I+ and II share the technical feature of a compound having the formula of claim 1, formula I.

These shared technical features, however, do not provide a contribution over the prior art, as being obvious over US 7,897,607 B2 to Gyorkos et al. (hereinafter Gyorkos). Gyorkos discloses a compound similar to the compound of claim 1, wherein a is 1; b is 1; W is CR14; R1 is a C6 aryl; said aryl substituted with 3 R12 groups selected from C1 alkyl; R2, R3, R10 and R11 are hydrogen; R4, R5, R10, and R11 are hydrogen; R7 is hydrogen; and R14 is hydrogen (col 116, ln 55-65), but does not disclose wherein R6 is amino or where the nitrogens of the bicyclic core structure are substituted with hydrogen. However, Gyorkos further discloses wherein optional substituents of the piperidine ring include optionally substituted amino groups (col 12, ln 46-55: Examples of the substituent for 5- or 6-membered ring' an optionally substituted amino). It would have been obvious to one with skill in the art to prepare all reasonable derivatives of the compound disclosed by Gyorkos, including an amino substituent of the piperidine ring and an unmethylated pyrazolo[3,4-d]pyrimidinone; in order to optimize the pharmacological properties of said compound.

As said compound and compositions were known in the art at the time of the invention, these cannot be considered special technical features that would otherwise unify the inventions of Groups I+ or II.

The inventions of Group I+ and II thus lack unity under PCT Rule 13.