

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
6 January 2011 (06.01.2011)

(10) International Publication Number
WO 2011/002772 A1

PCT

(51) International Patent Classification:
A61K 31/535 (2006.01)

MURA, Yusuke [JP/JP]; 3-1, Hongo 7-chome, Bunkyo-ku, Tokyo 1138654 (JP).

(21) International Application Number:
PCT/US2010/040394

(74) Agents: **BASTIAN, Kevin, L.** et al.; Townsend and Townsend and Crew LLP, Two Embarcadero Center, 8th Floor, San Francisco, CA 94111-3834 (US).

(22) International Filing Date:
29 June 2010 (29.06.2010)

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/221,437 29 June 2009 (29.06.2009) US

(71) Applicant (for all designated States except US): **ONCOTHERAPY SCIENCE, INC.** [JP/JP]; 2-1, Sakado 3-chome, Takatsu-ku, Kawasaki-shi, Kanagawa 2130012 (JP).

(72) Inventors; and

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(75) Inventors/Applicants (for US only): **MATSUO, Yo** [JP/JP]; 2-1, Sakado 3-chome, Takatsu-ku, Kawasaki-shi, Kanagawa 2130012 (JP). **HISADA, Shoji** [JP/JP]; 2-1, Sakado 3-chome, Takatsu-ku, Kawasaki-shi, Kanagawa 2130012 (JP). **OHSAWA, Ryuji** [JP/JP]; 2-1, Sakado 3-chome, Takatsu-ku, Kawasaki-shi, Kanagawa 2130012 (JP). **WALKER, Joel, R.** [US/US]; 38 Terry Avenue, Schenectady, NY 12303 (US). **LI, Yingfu** [CN/CN]; 1 Dong 39 Hao, Zhixin Lidu Garden C, 6 Lidu Road, Chengdu, Sichuan 610041 (CN). **AHMED, Feryan** [PK/US]; 23 Belle Avenue, Latham, NY 12110 (US). **NAKA-**

Published:

— with international search report (Art. 21(3))

(54) Title: IMIDAZOPYRIDINE DERIVATIVES AND PBK INHIBITORS CONTAINING THE SAME

(57) Abstract: Imidazopyridine Derivatives, which are useful for PBK inhibitors, are provided. For example, the present invention provides compounds having following general formula described herein.



WO 2011/002772 A1

IMIDAZOPYRIDINE DERIVATIVES AND PBK INHIBITORS CONTAINING THE SAME

CROSS-REFERENCES TO RELATED APPLICATIONS

5

[0001] This application claims the benefit of U.S. Provisional Application Serial No.61/221,437 filed June 29, 2009, the contents of which are hereby incorporated by reference in its entirety.

10

STATEMENT AS TO RIGHTS TO INVENTIONS MADE UNDER FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

[0002] NOT APPLICABLE

15

REFERENCE TO A "SEQUENCE LISTING," A TABLE, OR A COMPUTER PROGRAM LISTING APPENDIX SUBMITTED ON A COMPACT DISK

[0003] NOT APPLICABLE

20

FIELD OF THE INVENTION

[0004] The present invention relates to a compound for inhibiting PBK activity, a method for the preparation thereof, and a pharmaceutical composition containing the compound as an active ingredient.

25

BACKGROUND OF THE INVENTION

[0005] Previous studies revealed that PDZ binding kinase (PBK) is a serine/threonine kinase related to the dual specific mitogen-activated protein kinase kinase (MAPKK) family (NPL 1, NPL 2 and NPL 3). PBK was also indicated to be involved in mitosis as shown by its significant role in highly proliferating spermatocytes (NPL 4 and NPL 5). In fact, abundant expression of

PBK was observed in testis, while almost no PBK expression was detected in other normal organs (NPL 6). PBK regulates cell cycle progression. In accordance with this, its significant overexpression was detected in clinical breast cancer samples (NPL 6), Burkitt's lymphoma (NPL 7) and a variety of hematologic malignancies (NPL 8).

- 5 [0006] Immunohistochemical analysis of testis revealed the expression of PBK protein around the outer region of seminiferous tubules where repeated mitosis of sperm germ cells followed by meiosis occurs (NPL 5). Especially, at prophase and metaphase, the subcellular localization of PBK was detected around the condensed chromosome in breast cancer cells (NPL 6). Moreover the knockdown of PBK expression with gene specific siRNAs caused dysfunction of cytokinesis
10 and subsequently led to apoptosis of the cancer cells (NPL 6). These indicated the critical function of PBK at mitosis, in testicular and cancer cells.

- [0007] Taken together, PBK-specific inhibitors can be used as a drug applicable for a broad spectrum of cancers. PBK is an excellent target for cancer therapy for the following reasons: i) almost no expression in normal organs (except for testis); ii) frequent overexpression in clinical
15 cancer samples; iii) a serine/threonine kinase related to the essential function for cell mitosis.

[0008] The present inventors have endeavored to develop an effective inhibitor of PBK and have found that an imidazopyridine derivative can selectively inhibit the activity of PBK.

Citation List

[0009] Non Patent Literature

- 20 NPL 1: Abe Y, et al, J Biol Chem. 275: 21525–21531, 2000
NPL 2: Gaudet S, et al, Proc Natl Acad Sci. 97: 5167–5172, 2000
NPL 3: Matsumoto S, et al, Biochem Biophys Res Commun. 325: 997–1004, 2004
NPL 4: Gaudet S, et al, Proc Natl Acad Sci. 97: 5167–5172, 2000
NPL 5: Fujibuchi T, et al, Dev Growth Differ. 47:637–44, 2005
25 NPL 6: Park JH, et al, Cancer Res. 66: 9186-95, 2006
NPL 7: Simons-Evelyn M, et al, Blood Cells Mol Dis. 27: 825– 829, 2001
NPL 8: Nandi A, et al, Blood Cells Mol Dis. 32: 240-5, 2004

BRIEF SUMMARY OF THE INVENTION

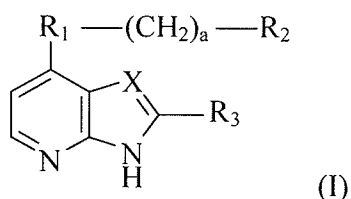
[0010] Accordingly, it is an object of the present invention to provide a PBK inhibitor having high inhibitory activity against PBK.

[0011] It is another object of the present invention to provide a method for preparing such inhibitor.

[0012] It is a further object of the present invention to provide a pharmaceutical composition comprising said compound, a pharmaceutically acceptable salt, hydrate, solvate, or isomer thereof.

[0013] In accordance with one aspect of the present invention, there is provided a compound of formula (I), and a pharmaceutically acceptable salt, hydrate, solvate, or isomer thereof as follow:

(.1) A compound represented by formula (I), or a salt, hydrate, solvate, or isomer thereof:



wherein

X is C or N;

R₁ is -CH₂NH-, -CONH-, -CON(CH₃)-, -NHCO-, or single bond;

R₂ is 3-10 membered heterocyclic group, 5-10 membered heteroaryl, C₃-C₁₀ cycloalkyl or C₅-C₁₀ aryl, each optionally substituted by one or more substituents each independently selected from the group consisting of hydroxy, oxo, nitro, cyano, amino, amide, halogen, sulfamoyl, phosphoryl, phosphate group, carbonyl, acyl, carboxyl, C₁-C₆ alkyl, C₁-C₆ alkenyl, C₁-C₆ alkynyl, C₁-C₆ alkoxy, C₁-C₆ alkylamino, aminoC₁-C₆ alkyl, C₁-C₆ alkylcarbonylamino, C₁-C₆ alkylaminocarbonyl, aminocarbonylC₁-C₆ alkyl, C₁-C₆ alkylsulfonyl, C₁-C₆ alkylsulfonylamino, aminosulfonylC₁-C₆ alkyl, aminoC₁-C₆ alkylsulfonyl, tert-butoxycarbonyl, tert-butoxycarbonyl-aminomethyl, 3-10 membered heterocyclic group, 5-10 membered heteroaryl, C₃-C₁₀ cycloalkyl and C₅-C₁₀aryl;

R₃ is hydrogen, bicyclo[2.2.1]heptan-2-yl, C₁-C₆ alkyl, phenyl, thiophen-2-yl, furan-2-yl, cyclopropyl, or cyclopentyl, each optionally substituted by one or more substituents each independently selected from the group consisting of hydroxy, oxo, nitro, cyano, amino, amide, halogen, sulfamoyl, phosphoryl, phosphate group, carbonyl, acyl, carboxyl, C₁-C₆

alkyl, C₃-C₁₀ cycloalkyl, -NR'R'', 3-10 membered heterocyclic group, and 5-10 membered heteroaryl, each optionally substituted by halogen, amino or hydroxy, wherein R' or R'' is each independently selected from the group consisting of hydrogen, C₁-C₆ alkyl and hydroxyC₁-C₆alkyl; and

5 a is 0-5 integer.

(2) The compound of (1), wherein R₂ is 3-10 membered heterocyclic group which is bound to pyridine ring on its hetero atom when R₁ is single bond and a is 0.

(3) The compound of (1), wherein R₃ is hydrogen, bicyclo[2.2.1]heptan-2-yl, C₁-C₆ alkyl, cyclopropyl, furan-2-yl, phenyl, or thiophen-2-yl, wherein the C₁-C₆ alkyl is optionally substituted by 1 or 2 substituents each independently selected from the group consisting of hydroxy, oxo, cyclopropyl, and thiophen-2-yl, wherein the furan-2-yl is optionally substituted by 1 or 2 substituents each independently selected from the group consisting of halogen and piperazine-1-yl, wherein the phenyl is optionally substituted by 1 or 2 halogen, or wherein the thiophen-2-yl is optionally substituted by 1 or 2 substituents each independently selected from the group consisting of halogen, morpholine-4-yl, di(hydroxyethyl)amino, (hydroxyethyl)(methyl)amino, piperazine-1-yl which is optionally substituted by 1 or 2 hydroxy, piperidine-1-yl which is optionally substituted by 1 or 2 hydroxy, and pyrrolidine-1-yl which is optionally substituted by 1 or 2 substituents each independently selected from the group consisting of hydroxy and amino.

(4) The compound of (1) or (2), wherein R₂ is adamantyl, azetidine-3-yl, cyclohexyl, imidazole-2-yl, imidazole-4-yl, phenyl, piperidine-1-yl, piperidine-2-yl, piperidine-3-yl, pyrrolidine-3-yl, or quinuclidin-3-yl, which are optionally substituted by 1 to 4 substituents each independently selected from hydroxy, aminomethyl, methyl, aminocarboonyl(amide), amino, tert-butoxycarbonyl and tert-butoxycarbonyl-aminomethyl.

(5) The compound of (2) or (3), wherein the C₁-C₆ alkyl substituted by 1 or 2 substituents is cyclopropylmethyl, thiophen-2-ylmethyl, hydroxyl(thiophen-2-yl)methyl or thiophene-2-ylcarbonyl.

(6) The compound of (3) or (4), wherein the furan-2-yl substituted by 1 or 2 substituents is 5-bromofuran-2-yl or 5-(piperazin-1-yl)furan-2-yl.

(7) The compound of (3) or (4), the phenyl substituted by 1 or 2 halogen is 4-chlorophenyl.

(8) The compound of (3) or (4), the thiophen-2-yl substituted by 1 or 2 substituents is 4-bromothiophen-2-yl, 5-morpholinothiophen-2-yl, {4-[Bis(2-hydroxyethyl)amino]thiophen-2-

yl, 5-[(2-Hydroxyethyl)(methyl)amino]thiophen-2-yl, 5-(Piperazin-1-yl)thiophen-2-yl, 5-(piperidin-1-yl)thiophen-2-yl, 5-(3-hydroxypiperidin-1-yl)thiophen-2-yl, 5-(3-Aminopyrrolidin-1-yl)thiophen-2-yl, 5-(3-hydroxypiperidin-1-yl)thiophen-2-yl, 5-(3-hydroxypyrrolidin-1-yl)thiophen-2-yl, 5-(3-hydroxypyrrolidin-1-yl)thiophen-2-yl, 4-morpholinothiophen-2-yl, 4-(3-hydroxypyrrolidin-1-yl)thiophen-2-yl, or 4-(piperazin-1-yl)thiophen-2-yl.

(9) The compound of (1), which is selected from the group consisting of:

N-[2-(1H-imidazol-4-yl)ethyl]-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide (Example No. 12),

N-[2-(1H-Imidazol-4-yl)ethyl]-2-(4-chlorophenyl)-3H-imidazo[4,5-b]pyridine-7-carboxamide (Example No. 13),

2-(4-Chlorophenyl)-N-(piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide (Example No. 14),

N-(Piperidin-3-yl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide (Example No. 15),

N-(Piperidin-3-ylmethyl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide (Example No. 16),

N-[3-(1H-Imidazol-2-yl)propyl]-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide (Example No. 17),

(R)-N-(Piperidin-3-yl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide (Example No. 18),

(S)-N-(Piperidin-3-yl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide (Example No. 19),

N-(4-Aminocyclohexyl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide (Example No. 20),

(R)-N-(Piperidin-3-ylmethyl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide (Example No. 21),

(S)-N-(Piperidin-3-ylmethyl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide (Example No. 22),

(R)-N-[2-(Piperidin-3-yl)ethyl]-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide (Example No. 23),

(S)-N-[2-(Piperidin-3-yl)ethyl]-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide (Example No. 24),

N-(Pyrrolidin-3-yl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide (Example No. 25),

5 N-(Piperidin-2-ylmethyl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide (Example No. 26),

N-(Azetidin-3-ylmethyl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide (Example No. 27),

10 N-(3-Aminocyclohexyl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide (Example No. 28),

N-(3-Aminoadamantyl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide (Example No. 29),

N-{[(1S,4S)-4-Aminocyclohexyl]methyl}-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide (Example No. 30),

15 trans-N-[4-(Aminomethyl)cyclohexyl]-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide (Example No. 31),

trans-N-{[4-(Aminomethyl)cyclohexyl]methyl}-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide (Example No. 32),

20 N-(1-Methylpiperidin-3-yl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide (Example No. 33),

N-{[3-(Aminomethyl)cyclohexyl]methyl}-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide (Example No. 34),

N-[3-(Aminomethyl)-3,5,5-trimethylcyclohexyl]-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide (Example No. 35),

25 N-Methyl-N-(piperidin-3-yl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide (Example No. 36),

N-(3-Aminophenyl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide (Example No. 37),

N-(Piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide (Example No. 38),

30 N-(Aminoadamant-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide (Example No. 39),

N-(Piperidin-3-ylmethyl)-3H-imidazo[4,5-b]pyridine-7-carboxamide (Example No. 40),

N-(3-Aminocyclohexyl)-3H-imidazo[4,5-b]pyridine-7-carboxamide (Example No. 41),

(S)-2-(5-Bromothiophen-2-yl)-N-(piperidin-3-ylmethyl)-3H-imidazo[4,5-b]pyridine-7-carboxamide (Example No. 42),

(R)-2-(5-Bromothiophen-2-yl)-N-(piperidin-3-ylmethyl)-3H-imidazo[4,5-b]pyridine-7-carboxamide (Example No. 43),

5 2-(5-Bromothiophen-2-yl)-N-(piperidin-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-7-carboxamide (Example No. 44),

(S)-2-(5-Bromothiophen-2-yl)-N-(piperidin-3-yl)-1H-imidazo[4,5-b]pyridine-7-carboxamide (Example No. 45),

10 (S)-2-(4-Bromothiophen-2-yl)-N-(piperidin-3-yl)-1H-imidazo[4,5-b]pyridine-7-carboxamide (Example No. 49),

(S)-2-(4-bromothiophen-2-yl)-N-(piperidin-3-ylmethyl)-3H-imidazo[4,5-b]pyridine-7-carboxamide (Example No. 50),

(S)-tert-Butyl 3-[2-(5-bromofuran-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamido]piperidine-1-carboxylate (Example No. 51),

15 (S)-2-(5-bromofuran-2-yl)-N-(piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide (Example No. 52),

(S)-tert-Butyl 3-{{2-(5-bromofuran-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamido}methyl}piperidine-1-carboxylate (Example No. 53),

20 (R)-2-(5-Bromofuran-2-yl)-N-(piperidin-3-ylmethyl)-3H-imidazo[4,5-b]pyridine-7-carboxamide (Example No. 54),

(S)-2-Cyclopropyl-N-(piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide (Example No. 55),

(S)-2-Cyclopropyl-N-(piperidin-3-ylmethyl)-3H-imidazo[4,5-b]pyridine-7-carboxamide (Example No. 56),

25 tert-Butyl [(1R,4R)-4-(2-cyclopropyl-3H-imidazo[4,5-b]pyridine-7-carboxamido)cyclohexyl]methylcarbamate (Example No. 57),

N-[(1R,4R)-4-(Aminomethyl)cyclohexyl]-2-cyclopropyl-3H-imidazo[4,5-b]pyridine-7-carboxamide (Example No. 58),

30 N-[(1R,4R)-4-Aminocyclohexyl]-2-cyclopropyl-3H-imidazo[4,5-b]pyridine-7-carboxamide (Example No. 59),

N-(4-Aminocadamantyl)-2-cyclopropyl-3H-imidazo[4,5-b]pyridine-7-carboxamide (Example No. 60),

(S)-2-(Cyclopropylmethyl)-N-(piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide
(Example No. 62),

2-(Bicyclo[2.2.1]heptan-2-yl)-N-[(S)-piperidin-3-yl]-3H-imidazo[4,5-b]pyridine-7-
carboxamide (Example No. 63a),

5 2-(Bicyclo[2.2.1]heptan-2-yl)-N-[(S)-piperidin-3-yl]-3H-imidazo[4,5-b]pyridine-7-
carboxamide (Example No. 63b),

N-{[(1R,4R)-4-(aminomethyl)cyclohexyl]methyl}-2-(bicyclo[2.2.1]heptan-2-yl)-3H-
imidazo[4,5-b]pyridine-7-carboxamide (Example No. 64),

10 N-(piperidin-2-ylmethyl)-2-(thiophene-2-carbonyl)-3H-imidazo[4,5-b]pyridine-7-
carboxamide (Example No. 66),

(S)-N-(Piperidin-3-yl)-2-(thiophene-2-carbonyl)-3H-imidazo[4,5-b]pyridine-7-carboxamide
(Example No. 67),

(R)-tert-Butyl 3-[(2-(thiophene-2-carbonyl)-3H-imidazo[4,5-b]pyridine-7-
carboxamido)methyl]piperidine-1-carboxylate (Example No. 68),

15 (S)-tert-Butyl 3-[(2-(thiophene-2-carbonyl)-3H-imidazo[4,5-b]pyridine-7-
carboxamido)methyl]piperidine-1-carboxylate (Example No. 69),

(S)-N-(Piperidin-3-ylmethyl)-2-(thiophene-2-carbonyl)-3H-imidazo[4,5-b]pyridine-7-
carboxamide (Example No. 70),

20 (R)-N-(piperidin-3-ylmethyl)-2-(thiophene-2-carbonyl)-3H-imidazo[4,5-b]pyridine-7-
carboxamide (Example No. 71),

(S)-2-[Hydroxy(thiophen-2-yl)methyl]-N-(piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-
carboxamide (Example No. 72),

2-[Hydroxy(thiophen-2-yl)methyl]-N-[(S)-piperidin-3-ylmethyl]-3H-imidazo[4,5-
b]pyridine-7-carboxamide (Example No. 73),

25 2-[Hydroxy(thiophen-2-yl)methyl]-N-[(R)-piperidin-3-ylmethyl]-3H-imidazo[4,5-
b]pyridine-7-carboxamide (Example No. 74),

(S)-N-(Piperidin-3-yl)-2-(thiophen-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-7-carboxamide
(Example No. 75),

30 (S)-N-(Piperidin-3-ylmethyl)-2-(thiophen-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-7-
carboxamide (Example No. 76),

(R)-N-(piperidin-3-ylmethyl)-2-(thiophen-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-7-
carboxamide (Example No. 77),

- (S)-2-[5-(Piperazin-1-yl)thiophen-2-yl]-N-(piperidin-3-yl)-1H-imidazo[4,5-b]pyridine-7-carboxamide (Example No. 78),
- (S)-2-(5-morpholinothiophen-2-yl)-N-(piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide (Example No. 79),
- 5 (S)-2-[5-(piperidin-1-yl)thiophen-2-yl]-N-(piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide (Example No. 80),
- 2-[5-(3-hydroxypyrrolidin-1-yl)thiophen-2-yl]-N-[(S)-piperidin-3-yl]-3H-imidazo[4,5-b]pyridine-7-carboxamide (Example No. 81),
- 2-[5-(3-hydroxypiperidin-1-yl)thiophen-2-yl]-N-((S)-piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide (Example No. 82),
- 10 (S)-2-{5-[(2-Hydroxyethyl)(methyl)amino]thiophen-2-yl}-N-(piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide (Example No. 83),
- 2-{5-[(R)-3-Aminopyrrolidin-1-yl]thiophen-2-yl}-N-[(S)-piperidin-3-yl]-3H-imidazo[4,5-b]pyridine-7-carboxamide (Example No. 84),
- 15 (S)-2-(4-Morpholinothiophen-2-yl)-N-(piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide (Example No. 88),
- 2-[4-(3-Hydroxypyrrolidin-1-yl)thiophen-2-yl]-N-[(S)-piperidin-3-yl]-3H-imidazo[4,5-b]pyridine-7-carboxamide (Example No. 89),
- (S)-2-{4-[Bis(2-hydroxyethyl)amino]thiophen-2-yl}-N-(piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamid (Example No. 90),
- 20 (S)-2-[4-(Piperazin-1-yl)thiophen-2-yl]-N-(piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide (Example No. 91),
- (R)-2-[5-(Piperazin-1-yl)furan-2-yl]-N-(piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide (Example No. 92),
- 25 N-[2-(Thiophen-2-yl)-3H-imidazo[4,5-b]pyridin-7-yl]methyl)piperidin-3-amine (Example No. 94),
- 1-(Piperidin-3-yl)-N-{[2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridin-7-yl]methyl}methanamine (Example No. 95),
- 1-[2-(Thiophen-2-yl)-3H-imidazo[4,5-b]pyridin-7-yl]piperidin-3-amine (Example No. 101),
- 30 1-[2-(Thiophen-2-yl)-3H-imidazo[4,5-b]pyridin-7-yl]piperidin-3-yl)methanamine (Example No. 102),

N-[2-(Thiophen-2-yl)-3H-imidazo[4,5-b]pyridin-7-yl]piperidine-3-carboxamide (Example No. 106),

1-(1H-Pyrrolo[2,3-b]pyridin-4-yl)piperidin-3-amine (Example No. 108),

1-(1H-Pyrrolo[2,3-b]pyridin-4-yl)piperidine-3-carboxamide (Example No. 109),

5 N-[2-(1H-Imidazol-4-yl)ethyl]-1H-pyrrolo[2,3-b]pyridine-4-carboxamide (Example No. 112),

1-[-(Thiophen-2-yl)-1H-pyrrolo[2,3-b]pyridin-4-yl]piperidin-3-amine (Example No. 115),

N-(Piperidin-3-yl)-2-(thiophen-2-yl)-1H-pyrrolo[2,3-b]pyridine-4-carboxamide (Example No. 118), and

10 N-(Piperidin-3-ylmethyl)-2-(thiophen-2-yl)-1H-pyrrolo[2,3-b]pyridine-4-carboxamide (Example No. 119).

(10) A pharmaceutical composition comprising at least one compound of any one of (1) to (9) and pharmaceutically acceptable carrier.

15 (11) A pharmaceutical composition for preventing or treating PBK dependent diseases comprising at least one compound of any one of (1) to (9) and pharmaceutically acceptable carrier.

(12) The pharmaceutical composition of (11), wherein PBK dependent disease is cancer.

(13) A PBK inhibitor comprising at least one compound of any one of (1) to (9).

20 (14) A method for treating or preventing PBK dependent diseases in a subject, comprising administering to said subject an effective amount of the compound of any one of (1) to (9).

(15) Use of the compound of any one of (1) to (9) in manufacturing a pharmaceutical composition for treating or preventing PBK dependent diseases.

(16) A compound or a pharmaceutically acceptable salt thereof of at least one compound of any one of (1) to (9) for use in a treatment or prevention of PKB dependent diseases.

25 **[0014]** It must be noted that as used in the specification and in the appended claims, the singular forms “a”, “an”, and “the” include plural reference unless the context clearly dictates otherwise. Thus, for example, reference to “a group” is a reference to one or more groups.

BRIEF DESCRIPTION OF THE DRAWINGS

30 **[0015]** In the present invention, “a heterocyclic group” refers to a non-aromatic heterocyclic group having one or more than one hetero atom in the ring system which is saturated or

unsaturated. "3-10 membered heterocyclic group" refers to a heterocyclic group whose ring consists of 3-10 atoms.

[0016] Examples of "3-10 membered heterocyclic group" include, but are not limited to, aziridinyl, azetidiny, pyrrolidinyl, imidazolidinyl, piperazinyl, piperidinyl, azepanyl, and morpholinyl.

[0017] In the present invention, "heteroaryl" refers to an aryl having one or more than one hetero atom in the ring system. "5-10 membered heteroaryl" refers to a heteroaryl whose ring consists of 5-10 atoms. "5-10 membered aromatic heterocyclic group" refers to an aromatic heterocyclic group whose ring consists of 5-10 atoms.

[0018] Examples of "5-10 membered heteroaryl" include, but are not limited to, imidazolyl, pyrrolyl, pyridyl, thienyl, furyl, thiazolyl, pyrazolyl, pyrazolinyl, oxazolyl, isoxazolyl, and indolyl.

[0019] In the present invention, "cycloalkyl" refers to a saturated carbohydrate ring system. "C₃-C₁₀ cycloalkyl" refers to 3-10 membered cycloalkyl.

[0020] Examples of "C₃-C₁₀ cycloalkyl" include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptanyl, cyclooctanyl, bicyclo[2.2.1]heptan-2-yl, adamantane-1-yl, and adamantane-2-yl.

DETAILED DESCRIPTION OF THE INVENTION

[0021] In the present invention, "aryl" refers to an aromatic carbohydrate ring system. "C₅-C₁₀ aryl" refers to 5-10 membered aryl.

[0022] Examples of "C₅-C₁₀ aryl" include, but are not limited to, phenyl, and naphthyl.

[0023] In this invention, "alkyl" refers to a straight chain or a branched chain hydrocarbon group which does not contain any hetero atoms or unsaturated carbon-carbon bonds. "C₁-C₆ alkyl" refers to an alkyl group which has 1-6 carbon atoms. "C₁-C₄ alkyl" refers to an alkyl group which has 1-4 carbon atoms.

[0024] Examples of "C₁-C₆ alkyl" include, but are not limited to, following groups: methyl, ethyl, 1-propyl, 2-propyl, 2-methyl-1-propyl, 2-methyl-2-propyl (tert-butyl(1,1-dimethyl-ethyl), 1-butyl, 2-butyl, 1-pentyl, 2-pentyl, 3-pentyl, 2-methyl-1-butyl, 3-methyl-1-butyl, 2-methyl-2-

butyl, 3-methyl-2-butyl, 2,2-dimethyl-1-propyl, 1-hexyl, 2-hexyl, 3-hexyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2-methyl-3-pentyl, 3-methyl-3-pentyl, 2,3-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2,2-dimethyl-1-butyl, 2-ethyl-1-butyl, 3,3-dimethyl-2-butyl, and 2,3-dimethyl-2-butyl.

- 5 **[0025]** In this invention, “alkenyl” refers to a straight chain or a branched chain hydrocarbon group which contains one or more than one unsaturated carbon-carbon bonds and does not contain any hetero atoms. “C₁-C₆ alkenyl” refers to an alkenyl group which has 1-6 carbon atoms.

[0026] Examples of “C₁-C₆ alkenyl” include, but are not limited to, following groups:

- 10 vinyl(ethenyl), 1-propenyl, 2-propenyl, 3-propenyl, 2-methyl-prop-1-en-1-yl (2-methyl-1-propenyl), 2-methyl-prop-1-en-3-yl (2-methyl-2-propenyl), but-1-en-1-yl (1-butenyl), but-1-en-2-yl (1-ethyl-ethenyl), but-1-en-3-yl (1-methyl-2-propenyl), but-2-en-1-yl (2-butenyl), but-2-en-2-yl (1-methyl-1-propenyl), pent-1-en-1-yl (1-pentenyl), pent-1-en-2-yl (1-propyl-ethenyl), pent-1-en-3-yl (1-ethyl-2-propenyl), pent-1-en-4-yl (1-methyl-3-butenyl), pent-1-en-5-yl (4-pentenyl),
 15 pent-2-en-1-yl (2-pentenyl), pent-2-en-2-yl (1-methyl-1-butenyl), pent-2-en-3-yl (1-ethyl-1-propenyl), pent-2-en-4-yl (1-methyl-2-butenyl), pent-2-en-5-yl (3-pentenyl), 2-methyl-but-1-en-1-yl (2-methyl-1-butenyl), 2-methyl-but-1-en-2-yl, 2-methyl-but-1-en-3-yl (1-methyl-2-methyl-2-propenyl), 2-methyl-but-1-en-4-yl (3-methyl-3-butenyl), 2-methyl-but-2-en-1-yl (2-methyl-2-butenyl), 2-methyl-but-2-en-3-yl (1,2-dimethyl-1-propenyl), 2-methyl-but-2-en-4-yl (3-methyl-2-butenyl), 3-methyl-but-1-en-1-yl (3-methyl-1-butenyl), 3-methyl-but-1-en-2-yl (1-isobutyl-ethenyl), 3-methyl-but-1-en-3-yl (1,1-dimethyl-2-propenyl), 3-methyl-but-1-en-4-yl (2-methyl-3-butenyl), 2,2-dimethyl-prop-1-en-1-yl, 2,2-dimethyl-prop-1-en-2-yl, hex-1-en-1-yl (1-hexenyl), hex-1-en-2-yl (1-butyl-ethenyl), hex-1-en-3-yl (1-propyl-2-propenyl), hex-1-en-4-yl (1-ethyl-3-butenyl), hex-1-en-5-yl (1-methyl-4-pentenyl), hex-1-en-6-yl (5-hexenyl), hex-2-en-1-yl (2-hexenyl), hex-2-en-2-yl (1-methyl-1-pentenyl), hex-2-en-3-yl (1-propyl-1-propenyl), hex-2-en-4-yl (1-ethyl-2-butenyl), hex-2-en-5-yl (1-methyl-3-pentenyl), hex-2-en-6-yl (4-hexenyl), hex-3-en-1-yl (3-hexenyl), hex-3-en-2-yl (1-methyl-2-pentenyl), hex-3-en-3-yl (1-ethyl-1-butenyl), 2-methyl-pent-1-en-1-yl (2-methyl-1-pentenyl), 2-methyl-pent-1-en-3-yl (1-ethyl-2-methyl-2-propenyl), 2-methyl-pent-1-en-4-yl (1,3-dimethyl-3-butenyl), 2-methyl-pent-1-en-5-yl (4-methyl-4-pentenyl), 2-methyl-pent-2-en-1-yl (2-methyl-2-pentenyl), 2-methyl-pent-2-en-3-yl (1-ethyl-2-methyl-1-propenyl), 2-methyl-pent-2-en-4-yl (1,3-dimethyl-2-butenyl), 2-methyl-pent-2-
- 20
25
30

en-5-yl (4-methyl-3-pentenyl), 3-methyl-pent-1-en-1-yl (3-methyl-1-pentenyl), 3-methyl-pent-1-en-2-yl (1-sec-butyl-ethenyl), 3-methyl-pent-1-en-3-yl (1-methyl-1-ethyl-2-propenyl), 3-methyl-pent-1-en-4-yl (1,2-dimethyl-3-butenyl), 3-methyl-pent-1-en-5-yl (3-methyl-4-pentenyl), 3-methyl-pent-2-en-1-yl (3-methyl-2-pentenyl), 3-methyl-pent-2-en-2-yl (1,2-dimethyl-1-butenyl),
 5 3-methyl-pent-2-en-4-yl (1,2-dimethyl-2-butenyl), 3-methyl-pent-2-en-5-yl (3-methyl-3-pentenyl), 4-methyl-pent-1-en-1-yl (4-methyl-1-pentenyl), 4-methyl-pent-1-en-2-yl (1-isobutyl-ethenyl), 4-methyl-pent-1-en-3-yl (1-isopropyl-2-propenyl), 4-methyl-pent-1-en-4-yl (1,1-dimethyl-3-butenyl), 4-methyl-pent-1-en-5-yl (2-methyl-4-pentenyl), 4-methyl-pent-2-en-1-yl (4-methyl-2-pentenyl), 4-methyl-pent-2-en-2-yl (1,3-dimethyl-1-butenyl), 4-methyl-pent-2-en-3-yl (1-isopropyl-1-propenyl), 4-methyl-pent-2-en-4-yl (1,1-dimethyl-2-butenyl), 4-methyl-pent-2-en-5-yl (2-methyl-3-pentenyl), 2,3-dimethyl-but-1-en-1-yl (2,3-dimethyl-1-butenyl), 2,3-dimethyl-but-1-en-3-yl (1,1,2-trimethyl-2-propenyl), 2,3-dimethyl-but-1-en-4-yl (2,3-dimethyl-3-butenyl), 2,3-dimethyl-but-2-en-1-yl (2,3-dimethyl-2-butenyl), 3,3-dimethyl-but-1-en-1-yl (3,3-dimethyl-1-butenyl), 3,3-dimethyl-but-1-en-2-yl (1-(1,1-dimethyl-ethyl)-ethenyl), 3,3-dimethyl-but-1-en-4-yl (2,2-dimethyl-3-butenyl), 2-ethyl-but-1-en-1-yl (2-ethyl-1-butenyl), 2-ethyl-but-1-en-3-yl (1-methyl-2-ethyl-2-propenyl), 2-ethyl-but-1-en-4-yl (3-ethyl-3-butenyl), 3-ethyl-but-1-en-1-yl (3-methyl-1-pentenyl), 3-ethyl-but-1-en-2-yl (1-(1-methyl-propyl)-ethenyl), 3-ethyl-but-1-en-3-yl (1-methyl-1-ethyl-2-propenyl), 3-ethyl-but-1-en-4-yl (2-ethyl-3-butenyl), 2-ethyl-but-2-en-1-yl (2-ethyl-2-butenyl), 2-ethyl-but-2-en-3-yl (1-methyl-2-ethyl-1-propenyl)
 10 and 2-ethyl-but-2-en-4-yl (3-ethyl-2-butenyl).

[0027] In this invention, “alkynyl” refers to a straight chain or a branched chain hydrocarbon group which contains at least one triple carbon-carbon bonds and does not contain any hetero atoms. “C₁-C₆ alkynyl” refers to an alkynyl group which has 1-6 carbon atoms.

[0028] Examples of “C₁-C₆ alkynyl” include, but are not limited to, following groups:
 25 ethinyl, 1-propinyl, 2-propinyl, 3-propinyl, 2-methyl-prop-1-in-1-yl, 2-methyl-prop-1-in-3-yl, but-1-in-1-yl (1-butyne), but-1-in-2-yl, but-1-in-3-yl (1-methyl-2-propynyl), but-2-in-1-yl (2-butyne), but-2-in-2-yl, pent-1-in-1-yl (1-pentyne), pent-1-in-2-yl, pent-1-in-3-yl (1-ethyl-2-propynyl), pent-1-in-4-yl (1-methyl-3-butyne), pent-1-in-5-yl (4-pentyne), pent-2-in-1-yl (2-pentyne), pent-2-in-2-yl, pent-2-in-3-yl, pent-2-in-4-yl (1-methyl-2-butyne), pent-2-in-5-yl (3-pentyne),
 30 2-methyl-but-1-in-1-yl, 2-methyl-but-1-in-2-yl, 2-methyl-but-1-in-3-yl, 2-methyl-but-1-in-4-yl, 2-methyl-but-2-in-1-yl, 2-methyl-but-2-in-3-yl, 2-methyl-but-2-in-4-yl, 3-methyl-but-1-in-1-yl (3-methyl-1-butyne), 3-methyl-but-1-in-2-yl, 3-methyl-but-1-in-3-yl (1,1-dimethyl-2-

propynyl), 3-methyl-but-1-in-4-yl (2-methyl-3-butynyl), 2,2-dimethyl-prop-1-in-1-yl, 2,2-dimethyl-prop-1-in-2-yl, hex-1-in-1-yl (1-hexynyl), hex-1-in-2-yl, hex-1-in-3-yl (1-propyl-2-propynyl), hex-1-in-4-yl (1-ethyl-3-butynyl), hex-1-in-5-yl (1-methyl-4-pentynyl), hex-1-in-6-yl (5-hexynyl), hex-2-in-1-yl (2-hexynyl), hex-2-in-2-yl, hex-2-in-3-yl, hex-2-in-4-yl (1-ethyl-2-butynyl), hex-2-in-5-yl (1-methyl-3-pentynyl), hex-2-in-6-yl (4-hexynyl), hex-3-in-1-yl (3-hexynyl), hex-3-in-2-yl (1-methyl-2-pentynyl), hex-3-in-3-yl, 2-methyl-pent-1-in-1-yl, 2-methyl-pent-1-in-3-yl, 2-methyl-pent-1-in-4-yl, 2-methyl-pent-1-in-5-yl, 2-methyl-pent-2-in-1-yl, 2-methyl-pent-2-in-3-yl, 2-methyl-pent-2-in-4-yl, 2-methyl-pent-2-in-5-yl, 3-methyl-pent-1-in-1-yl (3-methyl-1-pentynyl), 3-methyl-pent-1-in-2-yl, 3-methyl-pent-1-in-3-yl (1-methyl-1-ethyl-2-propynyl), 3-methyl-pent-1-in-4-yl (1,2-dimethyl-3-butynyl), 3-methyl-pent-1-in-5-yl (3-methyl-4-pentynyl), 3-methyl-pent-2-in-1-yl, 3-methyl-pent-2-in-2-yl, 3-methyl-pent-2-in-4-yl, 3-methyl-pent-2-in-5-yl, 4-methyl-pent-1-in-1-yl (4-methyl-1-pentynyl), 4-methyl-pent-1-in-2-yl, 4-methyl-pent-1-in-3-yl (1-isopropyl-2-propynyl), 4-methyl-pent-1-in-4-yl (1,1-dimethyl-3-butynyl), 4-methyl-pent-1-in-5-yl (2-methyl-4-pentynyl), 4-methyl-pent-2-in-1-yl (4-methyl-2-pentynyl), 4-methyl-pent-2-in-2-yl, 4-methyl-pent-2-in-3-yl, 4-methyl-pent-2-in-4-yl (1,1-dimethyl-2-butynyl), 4-methyl-pent-2-in-5-yl (2-methyl-3-pentynyl), 2,3-dimethyl-but-1-in-1-yl, 2,3-dimethyl-but-1-in-3-yl, 2,3-dimethyl-but-1-in-4-yl, 2,3-dimethyl-but-2-in-1-yl, 3,3-dimethyl-but-1-in-1-yl (3,3-dimethyl-1-butynyl), 3,3-dimethyl-but-1-in-2-yl, 3,3-dimethyl-but-1-in-4-yl (2,2-dimethyl-3-butynyl), 2-ethyl-but-1-in-1-yl, 2-ethyl-but-1-in-3-yl, 2-ethyl-but-1-in-4-yl, 3-ethyl-but-1-in-1-yl (3-methyl-1-pentynyl), 3-ethyl-but-1-in-2-yl, 3-ethyl-but-1-in-3-yl (1-methyl-1-ethyl-2-propynyl), 3-ethyl-but-1-in-4-yl (2-ethyl-3-butynyl), 2-ethyl-but-2-in-1-yl, 2-ethyl-but-2-in-3-yl and 2-ethyl-but-2-in-4-yl.

[0029] In the present invention, “alkoxy” refers to a group represented by -OR, wherein R is alkyl.

[0030] “C1-C6 alkoxy” refers to an alkoxy group which has 1-6 carbon atoms. “C1-C4 alkoxy” refers to an alkoxy group which has 1-4 carbon atoms.

[0031] Examples of “C1-C6 alkoxy” include, but are not limited to, following groups: methoxy, ethoxy, 1-propyloxy, 2-propyloxy, 2-methyl-1-propyloxy, 2-methyl-2-propyloxy, 1-butyloxy, and 2-butyloxy.

[0032] In this invention, “C₁-C₆ alkylcarbonyl” refers to R-C=O- wherein R is C₁-C₆alkyl “C₁-C₄ alkylcarbonyl” refers to R-C=O- wherein R is C₁-C₄alkyl.

[0033] Examples of “C₁-C₆ alkylcarbonyl” include, but are not limited to, methylcarbonyl(acetyl), ethylcarbonyl, propylcarbonyl, isopropylcarbonyl, n-butylcarbonyl, s-butylcarbonyl, t-butylcarbonyl, and 2-ethylbutylcarbonyl.

[0034] In this invention, “amino” refers to a group represented by -NH₂ whose hydrogens may each be optionally substituted by a substituent.

[0035] In the present invention, “C₁-C₆ alkylamino” refers to an amino group bound to the said C₁-C₆ alkyl.

[0036] Examples of “C₁-C₆ alkylamino” include, but are not limited to, methylamino, ethylamino, propylamino, isopropylamino, n-butylamino, s-butylamino, t-butylamino, and 2-ethylbutylamino.

[0037] In the present invention, “C₁-C₆ alkylcarbonylamino” refers to R-C=O-NH- wherein R is C₁-C₆ alkyl. “C₁-C₄ alkylcarbonylamino” refers to R-C=O-NH- wherein R is C₁-C₄ alkyl. an amino group bound to the said C₁-C₄ alkylcarbonyl.

[0038] Examples of “C₁-C₆ alkylcarbonylamino” include, but are not limited to, methylcarbonylamino(acetyl amino), ethylcarbonylamino, 1-propylcarbonylamino, 2-propylcarbonylamino, n-butylcarbonylamino, s-butylcarbonylamino, t-butylcarbonylamino, and 2-ethylbutylcarbonylamino.

[0039] In the present invention, “C₃-C₈ cycloalkylamino” refers to R-NH- wherein R is C₃-C₈cycloalkyl.

[0040] Examples of “C₃-C₈ cycloalkyl amino” include, but are not limited to, cyclopropylamino, cyclobutylamino, cyclopentylamino, cyclohexylamino, cycloheptylamino, and cyclooctanyl amino.

[0041] In this invention, “sulfonyl” is a group represented by -SO₂-.

[0042] In this invention, “C₁-C₆ alkylsulfonyl” refers to R-SO₂- wherein R is C₁-C₆ alkyl. “C₁-C₄ alkylsulfonyl” refers to R-SO₂- wherein R is C₁-C₄ alkyl.

[0043] Examples of “C₁-C₆ alkylsulfonyl” include, but are not limited to, methylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, n-butylsulfonyl, s-butylsulfonyl, t-butylsulfonyl, and 2-ethylbutylsulfonyl.

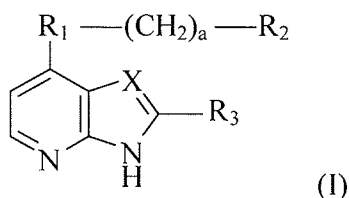
[0044] In the present invention, “C₁-C₆ alkylsulfonylamino” refers to R-SO₂-NH- wherein R is “C₁-C₆ alkyl”. “C₁-C₄ alkylsulfonylamino” refers to R-SO₂-NH- wherein R is “C₁-C₄ alkyl”.

[0045] Examples of “C₁-C₆ alkylsulfonylamino” include, but are not limited to, methylsulfonylamino, ethylsulfonylamino, propylsulfonylamino, isopropylsulfonylamino, n-butylsulfonylamino, s-butylsulfonylamino, t-butylsulfonylamino, and 2-ethylbutylsulfonylamino.

[0046] A salt is defined as the product formed from the neutralisation reaction of acids and bases. Salts are ionic compounds composed of cations (positively charged ions) and anions (negative ions) so that the product is electrically neutral. These component ions can be inorganic as well as organic.

[0047] Hydrate is a term used in inorganic chemistry and organic chemistry to indicate that a substance contains water. Solvate refers to a molecule in a solution complexed by solvent molecules. Isomers are compounds with the same molecular formula but different structural formulae. More specifically, isomer includes geometric isomer, optical isomer, stereoisomer, tautomer of the compound, and mixtures thereof.

[0048] The present invention provides a compound represented by formula (I):



wherein

X is C or N;

R₁ is -CH₂NH-, -CONH-, -CONH-, -CON(CH₃)-, -NHCO-, or single bond;

R₂ is 3-10 membered heterocyclic group, 5-10 membered heteroaryl, C₃-C₁₀ cycloalkyl or C₅-C₁₀ aryl, each optionally substituted by one or more substituents each independently selected from the group consisting of hydroxy, oxo, nitro, cyano, amino, amide, halogen, sulfamoyl, phosphoryl, phosphate group, carbonyl, acyl, carboxyl, C₁-C₆ alkyl, C₁-C₆ alkenyl, C₁-C₆ alkynyl, C₁-C₆ alkoxy, C₁-C₆ alkylamino, aminoC₁-C₆ alkyl, C₁-C₆ alkylcarbonylamino, C₁-C₆ alkylaminocarbonyl, aminocarbonylC₁-C₆ alkyl, C₁-C₆ alkylsulfonyl, C₁-C₆ alkylsulfonylamino, aminosulfonylC₁-C₆ alkyl, aminoC₁-C₆ alkylsulfonyl, tert-butoxycarbonyl, tert-butoxycarbonyl-

aminomethyl, 3-10 membered heterocyclic group, 5-10 membered heteroaryl, C₃-C₁₀ cycloalkyl and C₅-C₁₀ aryl;

R₃ is hydrogen, bicyclo[2.2.1]heptan-2-yl, C₁-C₆ alkyl, phenyl, thiophen-2-yl, furan-2-yl, cyclopropyl, or cyclopentyl, each optionally substituted by one or more substituents each
5 independently selected from the group consisting of hydroxy, oxo, nitro, cyano, amino, amide, halogen, sulfamoyl, phosphoryl, phosphate group, carbonyl, acyl, carboxyl, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, -NR'R'', 3-10 membered heterocyclic group, and 5-10 membered heteroaryl, each optionally substituted by halogen, amino or hydroxyl, wherein R' or R'' is each independently selected from the group consisting of hydrogen, C₁-C₆ alkyl and hydroxyc₁-C₆ alkyl; and
10 a is 0-5 integer.

[0049] Preferably, R₂ is adamantantyl, azetidine-3-yl, cyclohexyl, imidazole-2-yl, imidazole-4-yl, phenyl, piperidine-1-yl, piperidine-2-yl piperidine-3-yl, pyrrolidine-3-yl, or quinuclidin-3-yl which are optionally substituted by 1 to 4 substituents each independently selected from the group consisting of hydroxy, aminomethyl, methyl, aminocarbonyl(amide), amino, tert-
15 butoxycarbonyl and tert-butoxycarbonyl-aminomethyl. When R₁ is single bond and a is 0, R₂ is preferably C₃-C₁₀ heterocyclic group, more preferably piperidine (piperidine-1-yl), which is bound to pyridine ring on its hetero atom.

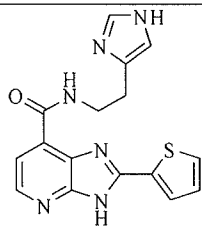
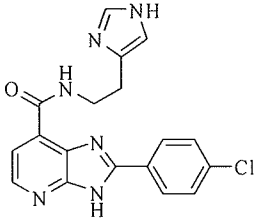
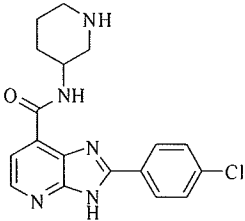
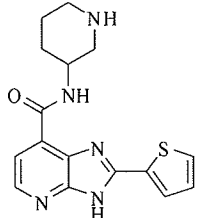
[0050] Preferably, R₃ is hydrogen, bicyclo[2.2.1]heptan-2-yl, C₁-C₆ alkyl, cyclopropyl, furan-2-yl, phenyl, or thiophen-2-yl, wherein the C₁-C₆ alkyl is optionally substituted by 1 or 2
20 substituents each independently selected from the group consisting of hydroxy, oxo, cyclopropyl, and thiophen-2-yl, wherein the furan-2-yl is optionally substituted by 1 or 2 substituents each independently selected from the group consisting of halogen and piperazine-1-yl, wherein the phenyl is optionally substituted by 1 or 2 halogen, or wherein the thiophen-2-yl is optionally substituted by 1 or 2 substituents each independently selected from the group consisting of
25 halogen, morpholine-4-yl, di(hydroxyethyl)amino, (hydroxyethyl)(methyl)amino, piperazine-1-yl which is optionally substituted by 1 or 2 hydroxyl, piperidine-1-yl which is optionally substituted by 1 or 2 hydroxy, and pyrrolidin-1-yl which is optionally substituted by 1 or 2 substituents each independently selected from the group consisting of hydroxyl and amino.

[0051] More preferably, R₃ is cyclopropylmethyl, thiophen-2-ylmethyl, hydroxyl(thiophen-2-yl)methyl, thiophene-2-ylcarbonyl, 5-bromofuran-2-yl, 5-(piperazin-1-yl)furan-2-yl, 4-chlorophenyl, 4-bromothiophen-2-yl, 5-morpholinothiophen-2-yl, {4-[Bis(2-

hydroxyethyl)amino]thiophen-2-yl, 5-[(2-Hydroxyethyl)(methyl)amino]thiophen-2-yl, 5-(Piperazin-1-yl)thiophen-2-yl, 5-(piperidin-1-yl)thiophen-2-yl, 5-(3-hydroxypiperidin-1-yl)thiophen-2-yl, 5-(3-Aminopyrrolidin-1-yl)thiophen-2-yl, 5-(3-hydroxypiperidin-1-yl)thiophen-2-yl, 5-(3-hydroxypyrrolidin-1-yl)thiophen-2-yl, 5-(3-hydroxypyrrolidin-1-yl)thiophen-2-yl, 4-morpholinothiophen-2-yl, 4-(3-hydroxypyrrolidin-1-yl)thiophen-2-yl, or 4-(piperazin-1-yl)thiophen-2-yl.

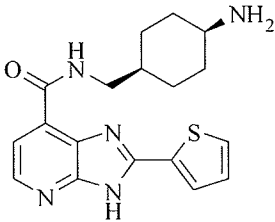
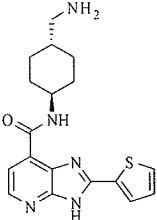
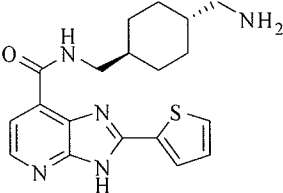
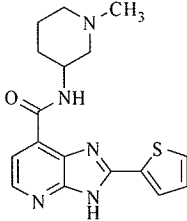
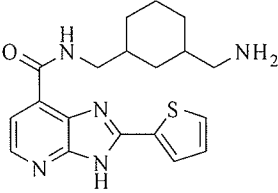
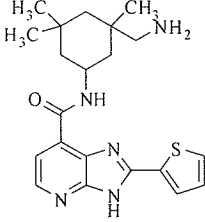
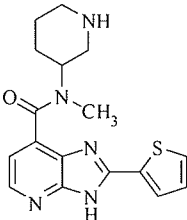
[0052] Preferred compounds include those selected from the group consisting of: Example No. 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59a, 59b, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 93, 94, 98, 100, 104, 107, 110, and 111 listed in Table 1 below; and the pharmaceutically acceptable salts, prodrugs, hydrates and solvates of the foregoing compounds.

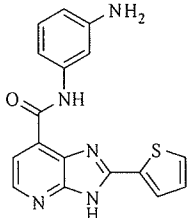
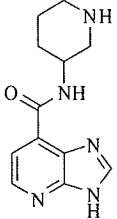
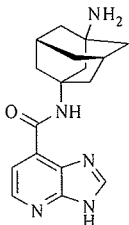
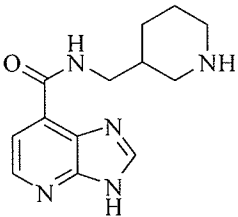
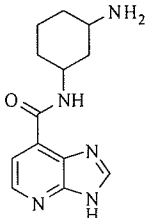
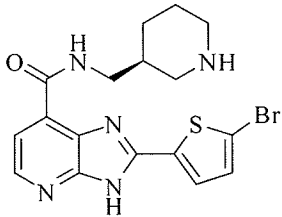
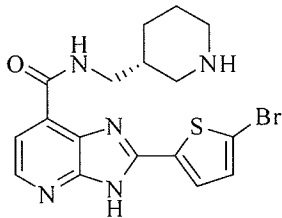
Table 1

Example No.	Structure	compound
12		N-[2-(1H-imidazol-4-yl)ethyl]-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide
13		N-[2-(1H-imidazol-4-yl)ethyl]-2-(4-chlorophenyl)-3H-imidazo[4,5-b]pyridine-7-carboxamide
14		2-(4-Chlorophenyl)-N-(piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide
15		N-(Piperidin-3-yl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide

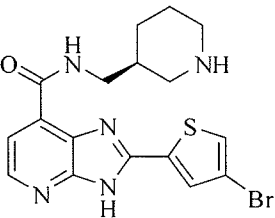
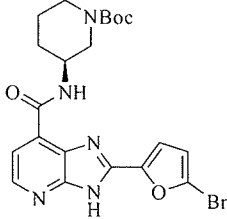
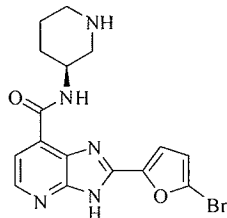
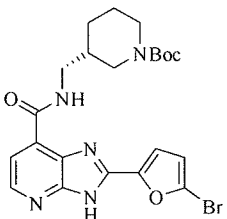
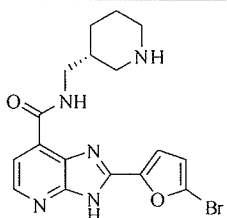
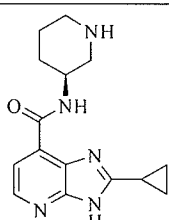
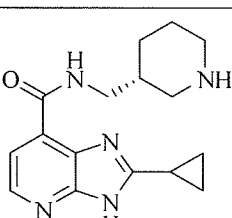
Example No.	Structure	compound
16		N-(Piperidin-3-ylmethyl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide
17		N-[3-(1H-imidazol-2-yl)propyl]-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide
18		(R)-N-(Piperidin-3-yl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide
19		(S)-N-(Piperidin-3-yl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide
20		N-(4-Aminocyclohexyl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide
21		(R)-N-(Piperidin-3-ylmethyl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide
22		(S)-N-(Piperidin-3-ylmethyl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide

Example No.	Structure	compound
23		(R)-N-[2-(Piperidin-3-yl)ethyl]-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide
24		(S)-N-[2-(Piperidin-3-yl)ethyl]-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide
25		N-(Pyrrolidin-3-yl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide
26		N-(Piperidin-2-ylmethyl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide
27		N-(Azetidin-3-ylmethyl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide
28		N-(3-Aminocyclohexyl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide
29		N-(3-Aminoadamantyl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide

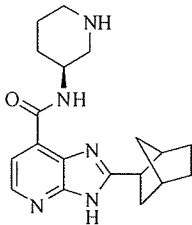
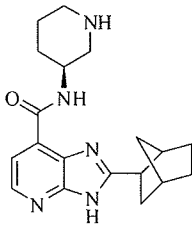
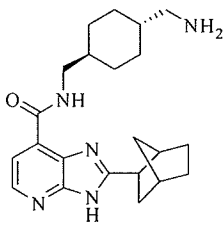
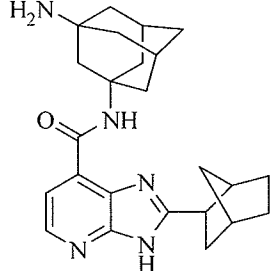
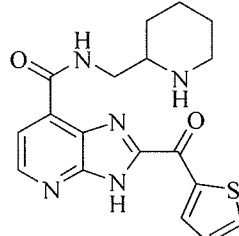
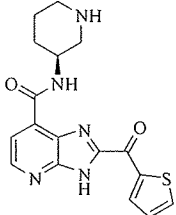
Example No.	Structure	compound
30		N-[(1S,4S)-4-Aminocyclohexyl]methyl-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide
31		trans-N-[4-(Aminomethyl)cyclohexyl]-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide
32		trans-N-{[4-(Aminomethyl)cyclohexyl]methyl}-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide
33		N-(1-Methylpiperidin-3-yl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide
34		N-{[3-(Aminomethyl)cyclohexyl]methyl}-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide
35		N-[3-(Aminomethyl)-3,5,5-trimethylcyclohexyl]-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide
36		N-Methyl-N-(piperidin-3-yl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide

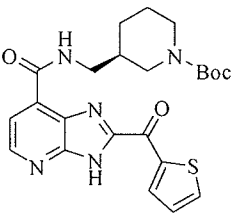
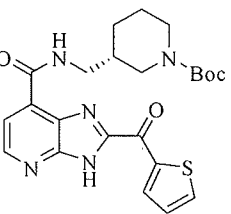
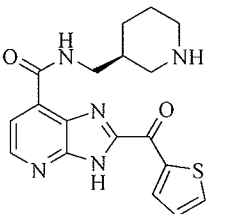
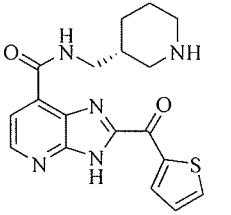
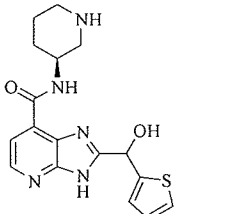
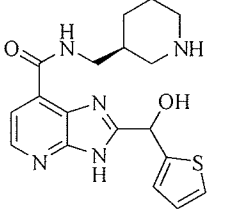
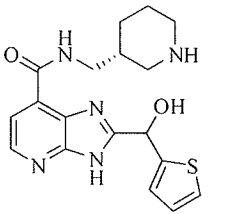
Example No.	Structure	compound
37		N-(3-Aminophenyl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide
38		N-(Piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide
39		N-(Aminoadamant-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide
40		N-(Piperidin-3-ylmethyl)-3H-imidazo[4,5-b]pyridine-7-carboxamide
41		N-(3-Aminocyclohexyl)-3H-imidazo[4,5-b]pyridine-7-carboxamide
42		(S)-2-(5-Bromothiophen-2-yl)-N-(piperidin-3-ylmethyl)-3H-imidazo[4,5-b]pyridine-7-carboxamide
43		(R)-2-(5-Bromothiophen-2-yl)-N-(piperidin-3-ylmethyl)-3H-imidazo[4,5-b]pyridine-7-carboxamide

Example No.	Structure	compound
44		2-(5-Bromothiophen-2-yl)-N-(piperidin-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-7-carboxamide
45		(S)-2-(5-Bromothiophen-2-yl)-N-(piperidin-3-yl)-1H-imidazo[4,5-b]pyridine-7-carboxamide
46		2-(5-bromothiophen-2-yl)-N-3-(aminoadamane-1-ol)-3-yl)-1H-imidazo[4,5-b]pyridine-7-carboxamide
47		2-(5-bromothiophen-2-yl)-N-(quinuclidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide
48		2-(5-bromothiophen-2-yl)-N-(1,3-diaminoadamane-3-yl)-1H-imidazo[4,5-b]pyridine-7-carboxamide
49		(S)-2-(4-Bromothiophen-2-yl)-N-(piperidin-3-yl)-1H-imidazo[4,5-b]pyridine-7-carboxamide

Example No.	Structure	compound
50		(S)-2-(4-bromothiophen-2-yl)-N-(piperidin-3-ylmethyl)-3H-imidazo[4,5-b]pyridine-7-carboxamide
51		(S)-tert-Butyl-3-[2-(5-bromofuran-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamido]piperidine-1-carboxylate
52		(S)-2-(5-bromofuran-2-yl)-N-(piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide
53		(S)-tert-Butyl-3-{[2-(5-bromofuran-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamido]methyl}piperidine-1-carboxylate
54		(R)-2-(5-Bromofuran-2-yl)-N-(piperidin-3-ylmethyl)-3H-imidazo[4,5-b]pyridine-7-carboxamide
55		(S)-2-Cyclopropyl-N-(piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide
56		(S)-2-Cyclopropyl-N-(piperidin-3-ylmethyl)-3H-imidazo[4,5-b]pyridine-7-carboxamide

Example No.	Structure	compound
57		tert-Butyl [(1R,4R)-4-(2-cyclopropyl-3H-imidazo[4,5-b]pyridine-7-carboxamido)cyclohexyl]methylcarbamate
58		N-[(1R,4R)-4-(Aminomethyl)cyclohexyl]-2-cyclopropyl-3H-imidazo[4,5-b]pyridine-7-carboxamide
59		N-[(1R,4R)-4-Aminocyclohexyl]-2-cyclopropyl-3H-imidazo[4,5-b]pyridine-7-carboxamide
60		N-(4-Aminocadamantyl)-2-cyclopropyl-3H-imidazo[4,5-b]pyridine-7-carboxamide
61		N-(4-Hydroxyadamantyl)-2-cyclopropyl-3H-imidazo[4,5-b]pyridine-7-carboxamide
62		(S)-2-(Cyclopropylmethyl)-N-(piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide

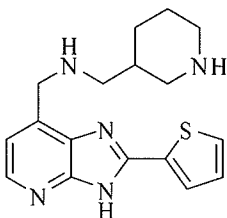
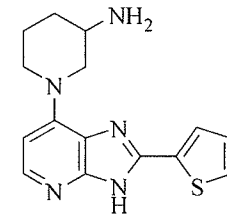
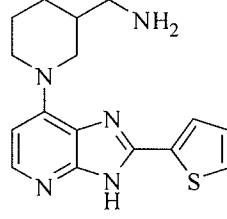
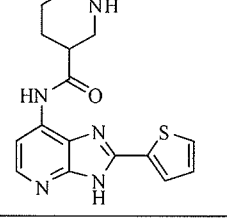
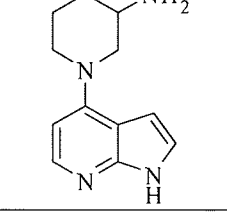
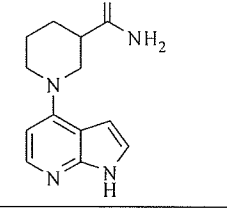
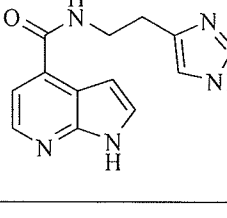
Example No.	Structure	compound
63a		2-(Bicyclo[2.2.1]heptan-2-yl)-N-[(S)-piperidin-3-yl]-3H-imidazo[4,5-b]pyridine-7-carboxamide
63b		2-(Bicyclo[2.2.1]heptan-2-yl)-N-[(S)-piperidin-3-yl]-3H-imidazo[4,5-b]pyridine-7-carboxamide
64		N-([(1R,4R)-4-(aminomethyl)cyclohexyl]methyl)-2-(bicyclo[2.2.1]heptan-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide
65		N-(3-aminoadamantyl)-2-(bicyclo[2.2.1]heptan-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide
66		N-(piperidin-2-ylmethyl)-2-(thiophene-2-carbonyl)-3H-imidazo[4,5-b]pyridine-7-carboxamide
67		(S)-N-(Piperidin-3-yl)-2-(thiophene-2-carbonyl)-3H-imidazo[4,5-b]pyridine-7-carboxamide

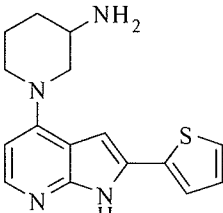
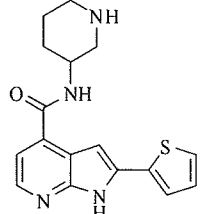
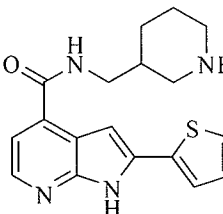
Example No.	Structure	compound
68		(R)-tert-Butyl 3-[(2-(thiophene-2-carbonyl)-3H-imidazo[4,5-b]pyridine-7-carboxamido)methyl]piperidine-1-carboxylate
69		(S)-tert-Butyl 3-[(2-(thiophene-2-carbonyl)-3H-imidazo[4,5-b]pyridine-7-carboxamido)methyl]piperidine-1-carboxylate
70		(S)-N-(Piperidin-3-ylmethyl)-2-(thiophene-2-carbonyl)-3H-imidazo[4,5-b]pyridine-7-carboxamide
71		(R)-N-(piperidin-3-ylmethyl)-2-(thiophene-2-carbonyl)-3H-imidazo[4,5-b]pyridine-7-carboxamide
72		(S)-2-[Hydroxy(thiophen-2-yl)methyl]-N-(piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide
73		2-[Hydroxy(thiophen-2-yl)methyl]-N-[(S)-piperidin-3-ylmethyl]-3H-imidazo[4,5-b]pyridine-7-carboxamide
74		2-[Hydroxy(thiophen-2-yl)methyl]-N-[(R)-piperidin-3-ylmethyl]-3H-imidazo[4,5-b]pyridine-7-carboxamide

Example No.	Structure	compound
75		(S)-N-(Piperidin-3-yl)-2-(thiophen-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-7-carboxamide
76		(S)-N-(Piperidin-3-ylmethyl)-2-(thiophen-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-7-carboxamide
77		(R)-N-(piperidin-3-ylmethyl)-2-(thiophen-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-7-carboxamide
78		(S)-2-[5-(Piperazin-1-yl)thiophen-2-yl]-N-(piperidin-3-yl)-1H-imidazo[4,5-b]pyridine-7-carboxamide
79		(S)-2-(5-morpholinothiophen-2-yl)-N-(piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide
80		(S)-2-[5-(piperidin-1-yl)thiophen-2-yl]-N-(piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide
81		2-[5-(3-hydroxypyrrolidin-1-yl)thiophen-2-yl]-N-[(S)-piperidin-3-yl]-3H-imidazo[4,5-b]pyridine-7-carboxamide

Example No.	Structure	compound
82		2-[5-(3-hydroxypiperidin-1-yl)thiophen-2-yl]-N-((S)-piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide
83		(S)-2-{5-[(2-Hydroxyethyl)(methyl)amino]thiophen-2-yl}-N-(piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide
84		2-{5-[(R)-3-Aminopyrrolidin-1-yl]thiophen-2-yl}-N-[(S)-piperidin-3-yl]-3H-imidazo[4,5-b]pyridine-7-carboxamide
85		2-{5-[(R)-3-hydroxypyrrolidin-1-yl]thiophen-2-yl}-N-((S)-piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide
86		2-{5-[(S)-3-hydroxypyrrolidin-1-yl]thiophen-2-yl}-N-((S)-piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide
87		2-[5-(3-hydroxypyrrolidin-1-yl)thiophen-2-yl]-N-(1,3-diaminoadamane-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide

Example No.	Structure	compound
88		(S)-2-(4-Morpholinothiophen-2-yl)-N-(piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide
89		2-[4-(3-Hydroxypyrrolidin-1-yl)thiophen-2-yl]-N-[(S)-piperidin-3-yl]-3H-imidazo[4,5-b]pyridine-7-carboxamide
90		(S)-2-{4-[Bis(2-hydroxyethyl)amino]thiophen-2-yl}-N-(piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamid
91		(S)-2-[4-(Piperazin-1-yl)thiophen-2-yl]-N-(piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide
92		(R)-2-[5-(Piperazin-1-yl)furan-2-yl]-N-(piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide
94		N-[2-(Thiophen-2-yl)-3H-imidazo[4,5-b]pyridin-7-ylmethyl]piperidin-3-amine

Example No.	Structure	compound
95		1-(Piperidin-3-yl)-N-{[2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridin-7-yl]methyl}methanamine
101		1-[2-(Thiophen-2-yl)-3H-imidazo[4,5-b]pyridin-7-yl]piperidin-3-amine
102		1-[2-(Thiophen-2-yl)-3H-imidazo[4,5-b]pyridin-7-yl]piperidin-3-ylmethanamine
106		N-[2-(Thiophen-2-yl)-3H-imidazo[4,5-b]pyridin-7-yl]piperidine-3-carboxamide
108		1-(1H-Pyrrolo[2,3-b]pyridin-4-yl)piperidin-3-amine
109		1-(1H-Pyrrolo[2,3-b]pyridin-4-yl)piperidine-3-carboxamide
112		N-[2-(1H-Imidazol-4-yl)ethyl]-1H-pyrrolo[2,3-b]pyridine-4-carboxamide

Example No.	Structure	compound
115		1-[-(Thiophen-2-yl)-1H-pyrrolo[2,3-b]pyridin-4-yl]piperidin-3-amine
118		N-(Piperidin-3-yl)-2-(thiophen-2-yl)-1H-pyrrolo[2,3-b]pyridine-4-carboxamide
119		N-(Piperidin-3-ylmethyl)-2-(thiophen-2-yl)-1H-pyrrolo[2,3-b]pyridine-4-carboxamide

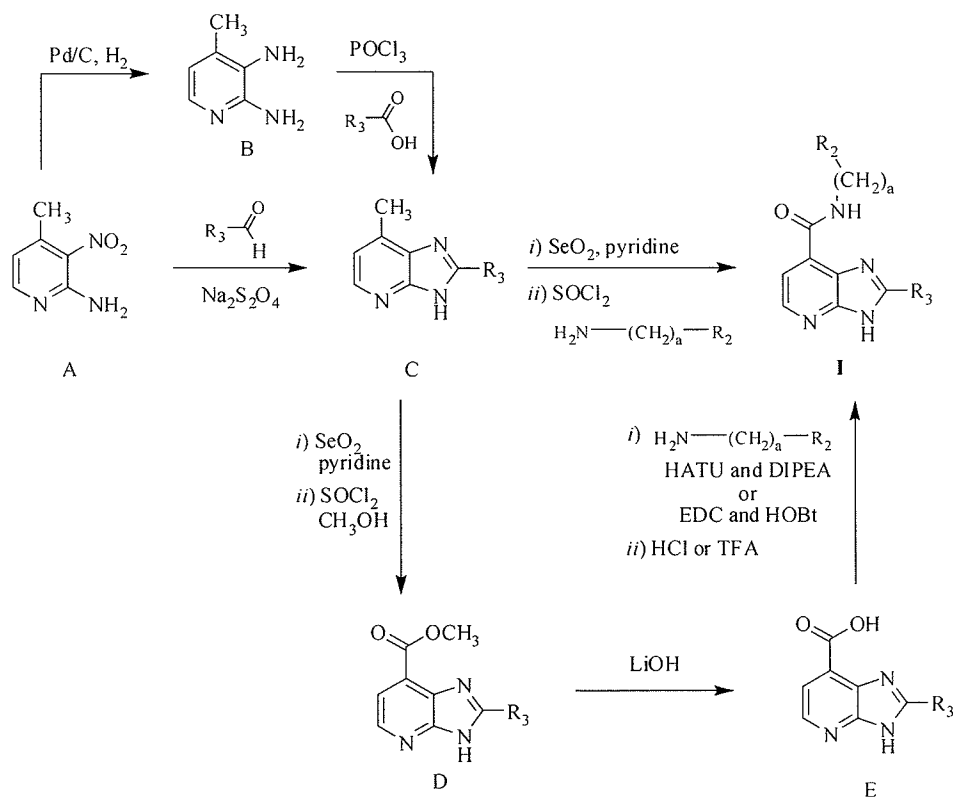
[0053] The compound of formula (I) of the present invention may be in the form of a pharmaceutically acceptable salt derived from an inorganic or organic acid, and representative examples of the pharmaceutically acceptable salt derived from an inorganic or organic acid include salts obtained by adding an inorganic acid such as hydrochloric acid, hydrobromic acid, phosphoric acid or sulfonic acid, or organic carboxylic acids such as acetic acid, trifluoroacetic acid, citric acid, formic acid, maleic acid, oxalic acid, succinic acid, benzoic acid, tartaric acid, fumaric acid, mandelic acid, ascorbic acid or malic acid, methanesulfonic acid, or para toluenesulfonic acid, which do not limit its scope, to the compound of formula (I). Such acids may be prepared by the conventional processes, and other acids, which themselves are not pharmaceutically acceptable, including oxalic acid may be employed in the preparation of the salts.

[0054] Alternatively, the compound of formula (I) of the present invention may also be in the form of a pharmaceutically acceptable salt derived from an inorganic or organic base include salts obtained by adding an inorganic or organic base. For example, alkalis including sodium hydroxide or potassium hydroxide, or alkaline earth metal hydroxides including calcium hydroxide, magnesium hydroxide, aluminum hydroxide or ammonium hydroxide may be used for the preparation of inorganic salt of the compound. Further, organic bases including

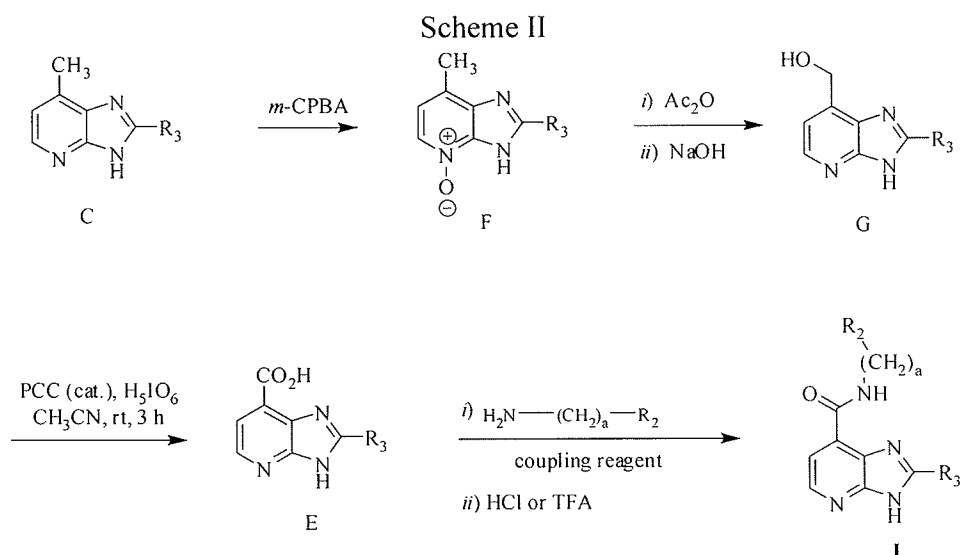
triethylamine or diisopropylethylamine may also be used for the preparation of organic salt of the compound.

[0055] The preferred inventive compound of formula (I) may be prepared as in Scheme I to IX.

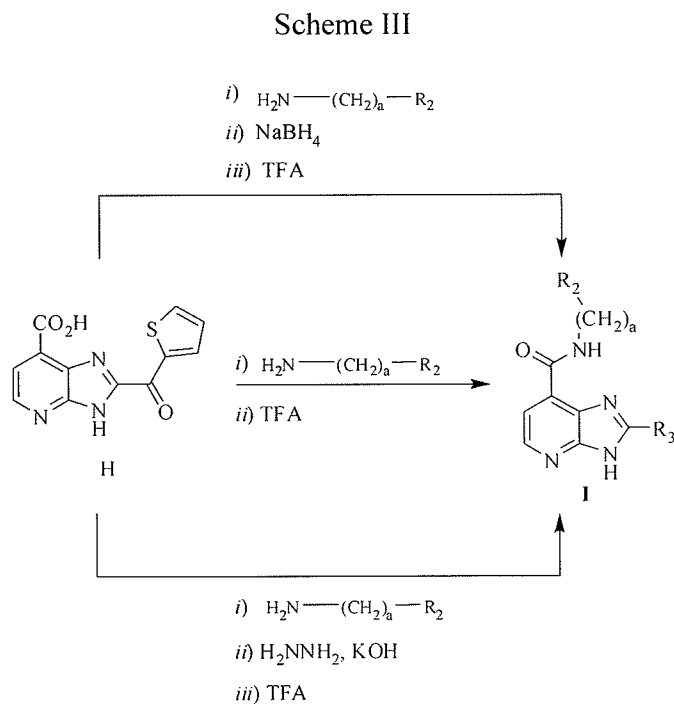
Scheme I



[0056] Nitroaniline A was reduced under hydrogenation conditions to afford di-amine B which was treated with a variety of acids in the presence of phosphorous oxychloride to afford intermediate imidazopyridines C (Scheme I). In some instances nitroaniline A was reacted with a variety of aldehydes in the presence of various aldehydes to afford compounds C. Compounds C were oxidized to the corresponding acid using selenium dioxide and in some cases the intermediate acid was converted to the acid chloride and coupled with the requisite amines, followed by a deprotection to afford compounds of formula I. In other cases the intermediate acids and converted to the esters D. The esters D were hydrolyzed to give acids E which were reacted with a variety of amines with the appropriate coupling reagent and after a final deprotection afforded compounds of formula I.



[0057] Compounds C was treated with *m*-CPBA to afford the *N*-oxide intermediate F which was reacted with acetic anhydride followed by sodium hydroxide to afford alcohol G (Scheme II). Primary alcohol G was oxidized to the corresponding acid E using PCC in the presence of periodic acid. The acid was reacted with the requisite amine followed by deprotection to afford compounds of formula I.

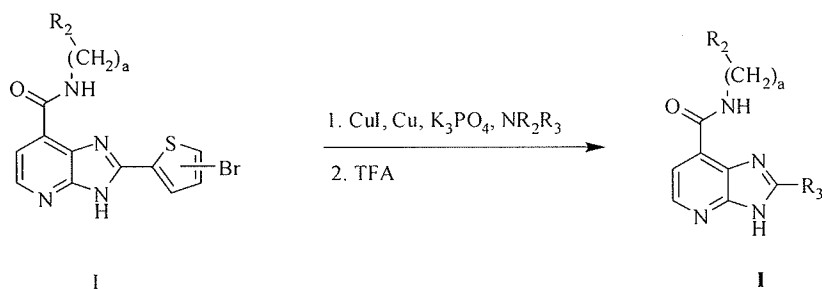


[0058] Acids H were converted to the requisite amides followed by sodium borohydride reduction of the ketone and deprotection to afford compounds of formula I (Scheme III). In

some cases, acids H were converted to the requisite amide followed by deprotection to afford compounds of formula I. Finally, in some instances, acids H were converted to the requisite amide followed by reduction of the ketone using hydrazine and potassium hydroxide followed by deprotection to afford compounds of formula I (Scheme III).

5

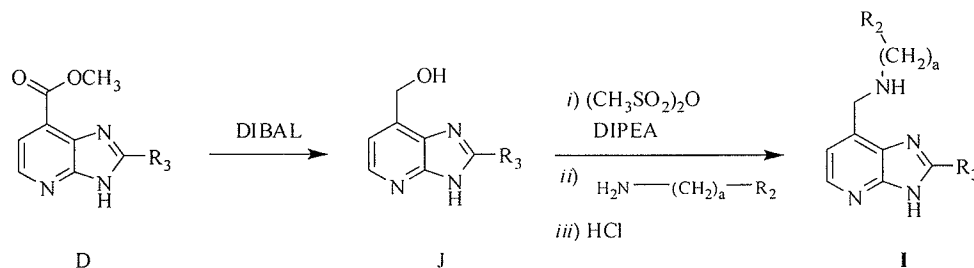
Scheme IV



[0059] In some instances, compounds I were reacted with various amines in the presence of copper and copper (I) iodide followed by deprotection to afford compounds of formula I (Scheme IV).

10

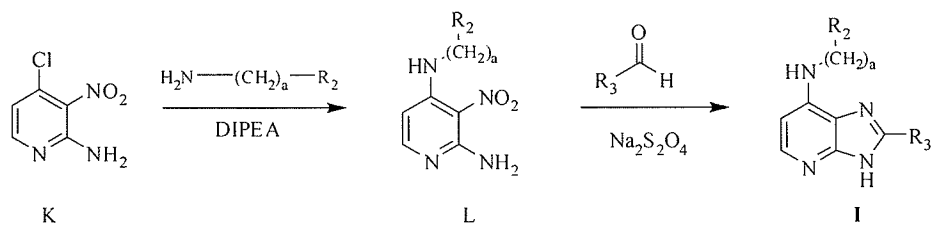
Scheme V



[0060] Compounds D were treated with DIBAL to afford the corresponding alcohols J. The primary alcohols were reacted with triflic anhydride in the presence of diisopropylethyl amine followed by the addition of the requisite amine and deprotection to afford compounds of formula I (Scheme V).

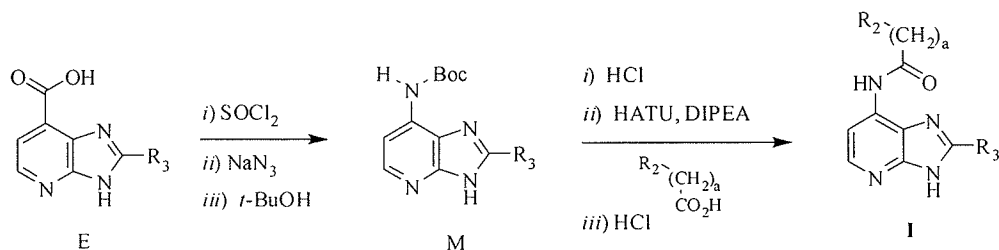
15

Scheme VI



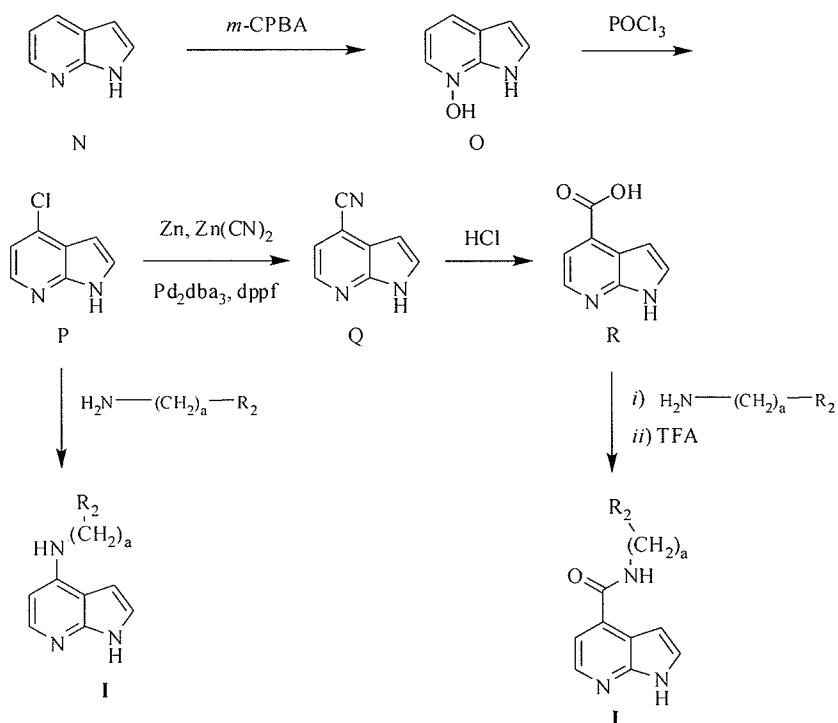
[0061] Intermediate K was reacted with the requisite amine in the presence of diisopropylethyl
amine to afford compounds L. Intermediates L were reacted with the requisite aldehyde to
5 afford compounds of formula I (Scheme VI).

Scheme VII



[0062] Acids E were converted to the corresponding acyl azides which were heated in *tert*-butanol to afford the protected anilines M. Removal of the Boc-protecting group followed by coupling with the requisite acid and a final deprotection afforded compounds of formula I (Scheme VII).

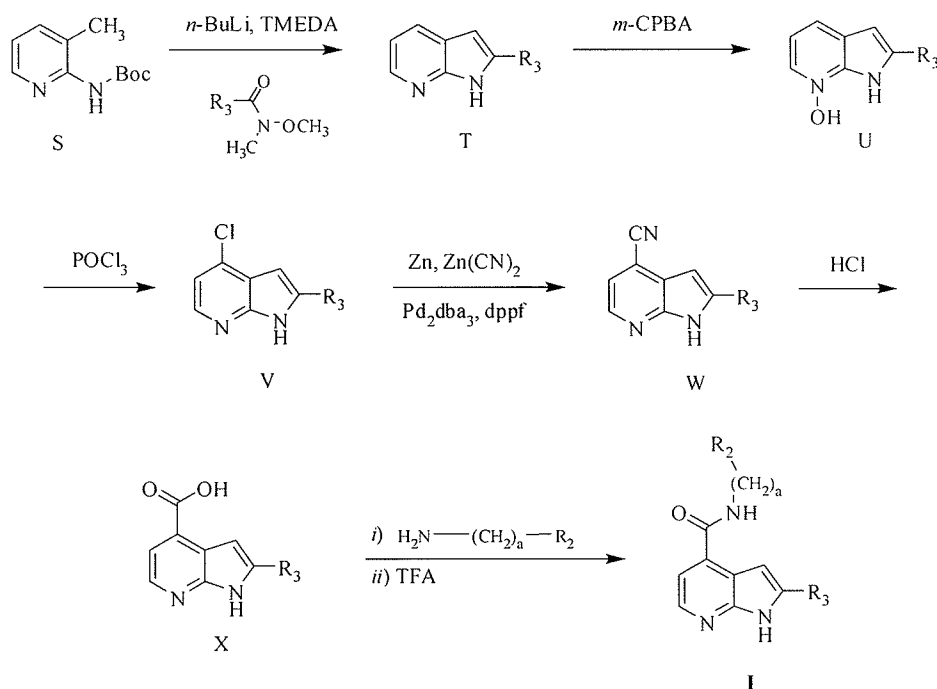
Scheme VIII



[0063] Pyridindole N was converted to the *N*-oxide O followed by treatment with phosphorous oxychloride to afford intermediate P. The chloride P was displaced with requisite amines to afford compounds of formula I (Scheme VIII). Chloride P were also converted to the nitrile Q using the palladium catalyzed cross-coupling conditions followed by hydrolysis of the

nitrile to afford acid R. Acid R was coupled with the requisite amine followed by deprotection to afford compounds of formula I (Scheme VIII).

Scheme IX



- 5 [0064] Compound S can be reacted with the requisite Weinreb amide to afford pyridoindoles T. Intermediates T can be converted to the *N*-oxide followed by treatment with phosphorous oxychloride to afford chlorides V. The chlorides can be converted to the corresponding nitriles W followed by hydrolysis of the nitrile to afford acids X. The acids can be coupled to the requisite amines followed by deprotection to afford compounds of formula I (Scheme IX).
- 10 [0065] Accordingly, the present invention includes a pharmaceutical composition which comprises a therapeutically effective amount of the compound of formula (I), a salt, hydrate, solvate or isomer thereof as an active ingredient and a pharmaceutically acceptable carrier; therefore, the pharmaceutical composition of the present invention exerts superior preventive and treating effects on PBK dependent diseases.
- 15 [0066] A pharmaceutical formulation may be prepared in accordance with any of the conventional procedures. In preparing the formulation, the active ingredient is preferably admixed or diluted with a carrier, or enclosed within a carrier, sachet or other container. When the carrier serves as a diluent, it may be a solid, semi-solid or liquid material acting as a vehicle,

excipient or medium for the active ingredient. Thus, the formulations may be in the form of a tablet, pill, powder, sachet, elixir, suspension, emulsion, solution, syrup, aerosol, soft and hard gelatin capsule, sterile injectable solution, sterile packaged powder and the like.

[0067] Examples of suitable carriers, excipients, and diluents are lactose, dextrose, sucrose, sorbitol, mannitol, calcium silicate, cellulose, methyl cellulose, microcrystalline cellulose, polyvinylpyrrolidone, water, and mineral oil. The formulations may additionally include fillers, antiemulsifiers, preservatives and the like. The compositions of the invention may be formulated so as to provide quick, sustained or delayed release of the active ingredient after their administration to a mammal by employing any of the procedures well known in the art.

[0068] The pharmaceutical composition of the present invention can be administered via various routes including oral, transdermal, subcutaneous, intravenous and intramuscular introduction.

[0069] In addition to the above, the present composition may contain other pharmaceutical active ingredients so long as they do not inhibit the in vivo function of the compound of the present invention. For example, the composition may further contain chemotherapeutic agents conventionally used for treating cancers.

[0070] The compounds disclosed here can be used to treat or prevent PBK dependent diseases including cancer. For example, the present invention provides methods for treating or preventing PBK dependent diseases including cancer in a subject by administering to said subject the compounds disclosed here. In a preferred embodiment, such compound can be administered to the subject in the form of pharmaceutical composition comprising the compound of the present invention and pharmaceutically or physiologically acceptable carrier. The pharmaceutical composition of the present invention can be administered via various routes including oral, transdermal, subcutaneous, intravenous and intramuscular introduction for treating a PBK dependent diseases including cancer in a subject.

[0071] In another embodiment, the present invention also provides the use of the compound of the present invention in manufacturing a pharmaceutical composition for treating or preventing a PBK dependent diseases including cancer. For example, the present invention relates to a use of the compound of the present invention for manufacturing a pharmaceutical composition for treating or preventing a PBK dependent diseases including cancer. In addition, the present

invention further provides the compound of the present invention for use in treating or preventing a PBK dependent diseases including cancer.

[0072] Alternatively, the present invention further provides a method or process for manufacturing a pharmaceutical composition for treating or preventing PBK dependent diseases including cancer, wherein the method or process comprises step for formulating a pharmaceutically or physiologically acceptable carrier with the compound of the present invention as active ingredients.

[0073] In another embodiment, the present invention also provides a method or process for manufacturing a pharmaceutical composition for treating or preventing a PBK dependent diseases including cancer, wherein the method or process comprises step for admixing an active ingredient with a pharmaceutically or physiologically acceptable carrier, wherein the active ingredient is the compound of the present invention.

[0074] The dosage and method of administration vary according to the body-weight, age, and symptoms of the patient; however, one skilled in the art can suitably select them.

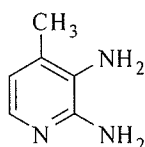
[0075] For example, although the dose of a compound of the present invention that regulates its activity depends on the symptoms, the dose is generally about 0.1 mg to about 100 mg per day, preferably about 1.0 mg to about 50 mg per day and more preferably about 1.0 mg to about 20 mg per day, when administered orally to a normal adult human (weight 60 kg).

[0076] When administering the compound parenterally, in the form of an injection to a normal adult human (weight 60 kg), although there are some differences according to the patient, target organ, symptoms and method of administration, it is convenient to intravenously inject a dose of about 0.01 mg to about 30 mg per day, preferably about 0.1 to about 20 mg per day and more preferably about 0.1 to about 10 mg per day. In the case of other animals, the appropriate dosage amount may be routinely calculated by converting to 60 kg of body-weight.

Examples:

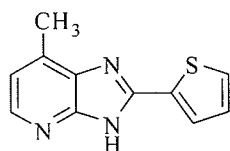
[0077] The following examples are intended to further illustrate the present invention without limiting its scope.

Example 1
4-Methylpyridine-2,3-diamine



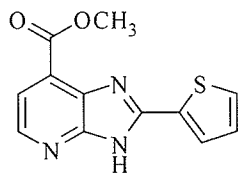
[0078] A mixture of 4-Methyl-3-nitropyridin-2-amine (5.6 g, 37 mmol) and 10 wt % palladium on carbon (800 mg) was suspended in MeOH (200 mL) at room temperature and the reaction mixture was stirred under an atmosphere of hydrogen for 2 d. The reaction was filtered through diatomaceous earth and the filtrate was concentrated to afford the product (4.39 g, 97% yield) as a brown solid: ESI MS m/z 124 [$C_6H_9N_3 + H$]⁺.

Example 2
7-Methyl-2-(thiophen-2-yl)-3*H*-imidazo[4,5-*b*]pyridine



[0079] Step 1: A mixture of 4-methylpyridine-2,3-diamine (1.1 g, 8.9 mmol) and 2-thiophene carboxylic acid (1.16 g, 8.93 mmol) was suspended in phosphorous oxychloride (5 mL) and the reaction mixture was heated at 150 °C for 6 h. The reaction mixture was cooled, poured onto ice and the pH was adjusted to 12 using 6 M NaOH. The resulting solid was filtered and washed with water to afford the product (1.9 g, 95% yield) as a brown solid: ¹H NMR (300 MHz, DMSO-*d*₆) δ 13.38–13.20 (m, 1H), 8.17 (d, *J* = 5.0 Hz, 1H), 7.96–7.95 (m, 1H), 7.78 (dd, *J* = 1.2, 5.0 Hz, 1H), 7.25 (dd, *J* = 3.6, 5.0 Hz, 1H), 7.05 (d, *J* = 5.0 Hz, 1H), 2.51 (s, 3H); ESI MS m/z 216 [$C_{11}H_9N_3S + H$]⁺.

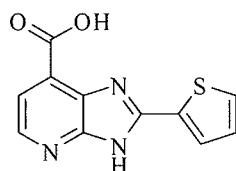
Methyl 2-(thiophen-2-yl)-3*H*-imidazo[4,5-*b*]pyridine-7-carboxylate



[0080] Step 2: A mixture of 7-methyl-2-(thiophen-2-yl)-3*H*-imidazo[4,5-*b*]pyridine (4.5 g, 21 mmol) and selenium dioxide (9.3 g, 84 mmol) was suspended in pyridine (120 mL) and the reaction mixture was heated at 120 °C for 18 h. The reaction mixture was cooled, filtered

through diatomaceous earth, the filter cake was washed with hot water and the filtrate was concentrated. To the crude carboxylic acid in MeOH (200 mL) at 0 °C was added thionyl chloride (15 mL, 0.21 mol) dropwise and the reaction mixture was heated at 75 °C for 3 h. The reaction mixture was cooled, concentrated and the pH of the residue was adjusted to 12 using 3 M NaOH. The desired product was extracted with 3:1 CHCl₃/*i*-PrOH (3 × 30 mL), the combined organic layers were concentrated and purified by chromatography (silica gel, CH₂Cl₂/MeOH gradient) to afford the product (4.2 g, 78% yield) as a orange-brown solid: ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.99 (s, 1H), 8.53–8.52 (m, 1H), 8.37–8.36 (m, 1H), 7.88 (d, *J* = 4.5 Hz, 1H), 7.64 (d, *J* = 4.5 Hz, 1H), 7.30 (dd, *J* = 4.5, 3.6 Hz, 1H), 4.02 (s, 3H); ESI MS *m/z* 260 [C₁₂H₉N₃O₂S + H]⁺.

2-(Thiophen-2-yl)-3*H*-imidazo[4,5-*b*]pyridine-7-carboxylic Acid

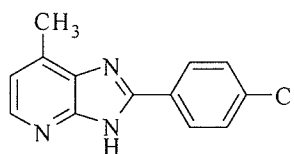


[0081] Step 3: A mixture of methyl 2-(thiophen-2-yl)-3*H*-imidazo[4,5-*b*]pyridine-7-carboxylate (1.2 g, 4.6 mmol) and lithium hydroxide (4.6 mL, 2 M, 9.2 mmol) was suspended in THF (40 mL) and the reaction mixture was heated at 60 °C for 18 h. The reaction mixture was cooled, diluted with water (10 mL) and the pH was adjusted to 2 using 1 M HCl. The mixture was concentrated to afford the crude product (1.5 g) as a bright yellow solid: ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.48 (d, *J* = 5.1 Hz, 1H), 8.41 (d, *J* = 3.6 Hz, 1H), 7.87 (dd, *J* = 5.1, 0.9 Hz, 1H), 7.62 (d, *J* = 5.1 Hz, 1H), 7.28 (dd, *J* = 5.1, 3.6 Hz, 1H); ESI MS *m/z* 246 [C₁₁H₇N₃O₂S + H]⁺.

[0049]

Example 3

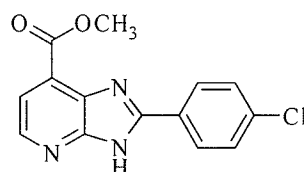
2-(4-Chlorophenyl)-7-methyl-3*H*-imidazo[4,5-*b*]pyridine



[0082] Step 1: A mixture of 4-methylpyridine-2,3-diamine (0.75 g, 6.1 mmol) and 4-chlorobenzoic acid (1.1 g, 7.3 mmol) were suspended in polyphosphoric acid (5 mL) and the mixture was heated at 160 °C for 18 h. The mixture was cooled, diluted with water and the pH

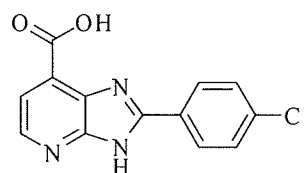
was adjusted to 12 using 6 M NaOH. The resultant solid was filtered and washed with water to afford the product (1.3 g, 87% yield) as a brown solid: ^1H NMR (300 MHz, DMSO- d_6) δ 13.36–13.34 (m, 1H), 8.26 (d, J = 8.4 Hz, 2H), 8.21 (d, J = 4.8 Hz, 1H), 7.65 (d, J = 8.4 Hz, 2H), 7.08 (d, J = 4.8 Hz, 1H), 2.60 (s, 3H); ESI MS m/z 244 [$\text{C}_{13}\text{H}_{10}\text{ClN}_3 + \text{H}$] $^+$.

5 Methyl 2-(4-chlorophenyl)-3*H*-imidazo[4,5-*b*]pyridine-7-carboxylate



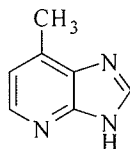
[0083] Step 2: To a mixture of 2-(4-chlorophenyl)-7-methyl-3*H*-imidazo[4,5-*b*]pyridine (250 mg, 1.0 mmol) in *t*-BuOH was added potassium permanganate (1.6 g, 10.2 mmol) in water (10 mL) and the reaction mixture was heated at 70 °C for 18 h. The reaction was filtered through diatomaceous earth, the filter cake was washed with hot water and the filtrate was concentrated. To the crude carboxylic acid in MeOH (20 mL) at 0 °C was added thionyl chloride (0.75 mL, 10 mmol) dropwise and the reaction mixture was heated at 75 °C for 18 h. The reaction was cooled, concentrated and the pH of the residue was adjusted to 12 using 3 M NaOH. The basic aqueous solution was extracted with ethyl acetate (3 $\times$ 30 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated to afford the product (200 mg, 67% yield) as a yellow solid: ^1H NMR (300 MHz, CDCl_3) δ 8.68 (d, J = 5.0 Hz, 1H), 8.13 (d, J = 8.5 Hz, 2H), 7.69 (d, J = 5.0 Hz, 1H), 7.55 (d, J = 8.4 Hz, 2H), 4.02 (s, 3H); ESI MS m/z 288 [$\text{C}_{14}\text{H}_{10}\text{ClN}_3\text{O}_2 + \text{H}$] $^+$.

2-(4-Chlorophenyl)-3*H*-imidazo[4,5-*b*]pyridine-7-carboxylic Acid

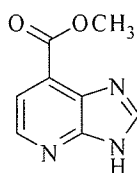


[0084] Step 3: A mixture of methyl 2-(4-chlorophenyl)-3*H*-imidazo[4,5-*b*]pyridine-7-carboxylate (190 mg, 0.66 mmol) and lithium hydroxide (1.6 mL, 2 M, 3.3 mmol) in THF (5 mL) was stirred at rt for 18 h. The mixture was diluted with water (10 mL) and the pH was adjusted to 2 using 1 N HCl. The mixture was concentrated under vacuum to afford the crude product as a dark brown solid: ESI MS m/z 274 [$\text{C}_{13}\text{H}_8\text{ClN}_3\text{O}_2 + \text{H}$] $^+$.

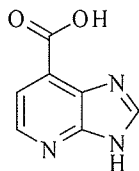
Example 4

7-Methyl-3*H*-imidazo[4,5-*b*]pyridine

[0085] Step 1: A mixture of 4-methylpyridine-2,3-diamine (2.4 g, 19 mmol) was dissolved in formic acid (50 mL) and the reaction mixture was heated at 100 °C for 18 h. The mixture was cooled, diluted with water and the pH was adjusted to 12 using conc. NH₄OH. The mixture was extracted with 3:1 CHCl₃/*i*-PrOH (3 × 30 ml), the combined organic layers were concentrated and the residue was purified by chromatography (silica gel, CH₂Cl₂/MeOH gradient) to afford the product (0.75 g, 30% yield) as a brown solid: ¹H NMR (300 MHz, CD₃OD) δ 8.35 (s, 1H), 8.24 (d, *J* = 4.8 Hz, 1H), 7.15 (dd, *J* = 4.8, 0.9 Hz, 1H), 2.64 (s, 3H); ESI MS *m/z* 134 [C₇H₇N₃ + H]⁺.

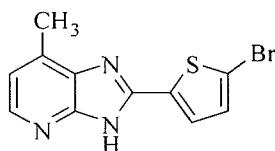
Methyl 3*H*-imidazo[4,5-*b*]pyridine-7-carboxylate

[0086] Step 2: A mixture of 7-methyl-3*H*-imidazo[4,5-*b*]pyridine (0.75 g, 5.6 mmol) and selenium dioxide (3.1 g, 28 mmol) in pyridine (50 mL) was heated at 120 °C for 18 h. Upon cooling the reaction was filtered through diatomaceous earth, washed with hot water and concentrated. The crude carboxylic acid was dissolved in MeOH (20 mL) and thionyl chloride (0.4 mL, 0.28 mol) was added dropwise at 0 °C. The reaction mixture was heated at 50 °C for 18 h, concentrated, cooled to 0 °C, and the pH was adjusted to 12 using 1 N NaOH. The mixture was extracted with 3:1 CHCl₃/*i*-PrOH (3 × 30 ml), the combined organic layers were concentrated and the residue was purified by chromatography (silica gel, CH₂Cl₂/MeOH gradient) to afford the product (340 mg, 34% yield) as a white solid: ¹H NMR (300 MHz, CD₃OD) δ 8.59 (d, *J* = 5.1 Hz, 1H), 8.54 (s, 1H), 7.84 (d, *J* = 5.1 Hz, 1H), 4.06 (s, 3H); ESI MS *m/z* 178 [C₈H₇N₃O₂ + H]⁺.

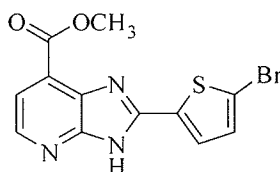
3*H*-Imidazo[4,5-*b*]pyridine-7-carboxylic Acid

[0087] Step 3: A suspension of methyl 3*H*-imidazo[4,5-*b*]pyridine-7-carboxylate (330 mg, 1.9 mmol) and lithium hydroxide (1.9 mL, 2 M, 3.7 mmol) in THF (20 mL) was heated at 60 °C for 18 h. The reaction mixture was cooled, diluted with water (10 mL), the pH was adjusted to 2 using 1 N HCl and the mixture was concentrated to afford the crude product as a white solid: ESI MS *m/z* 164 [C₇H₅N₃O₂ + H]⁺.

Example 5
2-(5-Bromothiophen-2-yl)-7-methyl-1*H*-imidazo[4,5-*b*]pyridine



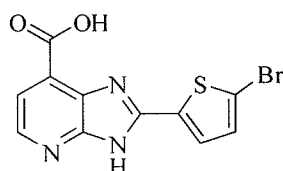
[0088] Step 1: To a mixture of 4-methyl-3-nitropyridin-2-amine (1.5 g, 10 mmol), and 5-bromothiophene-2-carbaldehyde (1.9 g, 10 mmol) in ethanol (35 mL) was added a solution of Na₂S₂O₄ (5.2 g, 30 mmol) in water (25 mL) and the resulting mixture was stirred at 80 °C for 4 d. The reaction mixture was cooled, concentrated and the residue was diluted with water (50 mL) and the pH of the mixture was adjusted to 7 using conc. NH₄OH. The mixture was extracted with EtOAc (3 × 60 mL) and the combined organic layers were washed with brine (50 mL), dried over Na₂SO₄, and concentrated to provide the product as yellow solid (2.0 g, 68% yield): ESI MS *m/z* 294 [C₁₁H₈BrN₃S + H]⁺.

Methyl 2-(5-bromothiophen-2-yl)-1*H*-imidazo[4,5-*b*]pyridine-7-carboxylate

[0089] Step 2: A mixture of 2-(5-bromothiophen-2-yl)-7-methyl-1*H*-imidazo[4,5-*b*]pyridine (1.9 g, 6.5 mmol) and selenium dioxide (2.9 g, 26 mmol) in pyridine (23 mL) was heated at 110

°C for 3 h. The hot reaction mixture was filtered through diatomaceous earth, the filter cake was washed with hot pyridine (10 mL) and CH₃OH (20 mL), and the filtrate was concentrated and dried. The crude residue was dissolved in CH₃OH (50 mL) followed by the dropwise addition of SOCl₂ (0.48 mL, 6.5 mmol) at room temperature. The reaction mixture was stirred at reflux for 5 h, cooled, concentrated, suspended in ice-water (25 mL) and filtered. The pH of the filtrate was adjusted to 7 using conc. NH₄OH followed by extraction with EtOAc (3 × 50 mL). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated to provide the desired product as brown-yellow solid (1.5g, 68% yield): ESI MS m/z 338 [C₁₂H₈BrN₃O₂S + H]⁺.

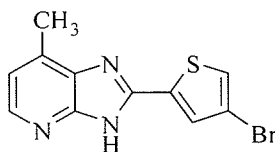
2-(5-Bromothiophen-2-yl)-1H-imidazo[4,5-b]pyridine-7-carboxylic Acid



[0090] Step 3: To a solution of methyl 2-(5-bromothiophen-2-yl)-1H-imidazo[4,5-b]pyridine-7-carboxylate (1.3 g, 3.9 mmol) in THF (20 mL) was added a solution of LiOH (0.65 g, 15 mmol) in water (10 mL) and the resulting mixture was stirred at reflux for 4 h. The reaction mixture was cooled, concentrated, diluted with ice-water (15 mL) and the pH was adjusted to 4 using glacial acetic acid. The resulting brown precipitate was filtered, washed with water (20 mL) and dried to provide the desired product (0.89 g, 71% yield): ESI MS m/z 324 [C₁₁H₆BrN₃O₂S + H]⁺.

Example 6

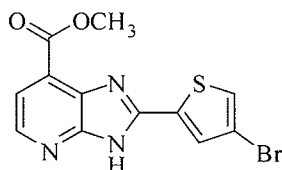
2-(4-Bromothiophen-2-yl)-7-methyl-1H-imidazo[4,5-b]pyridine



[0091] Step 1: To a mixture of 4-methyl-3-nitropyridin-2-amine (1.5 g, 10 mmol), and 4-bromothiophene-2-carbaldehyde (1.9 g, 10 mmol) in ethanol (35 mL) was added a solution of Na₂S₂O₄ (5.2 g, 30 mmol) in water (25 mL) and the resulting mixture was stirred at 80 °C for 3 d. The reaction mixture was cooled, concentrated, diluted with water (50 mL) and the pH of the mixture was adjusted to 7 using conc. NH₄OH. The mixture was extracted with EtOAc (3 × 60

mL) and the combined organic layers were washed with brine (50 mL), dried over Na₂SO₄, and concentrated to provide the product as yellow solid (1.7 g, 58% yield): ESI MS m/z 294 [C₁₁H₈BrN₃S + H]⁺.

Methyl 2-(4-bromothiophen-2-yl)-1H-imidazo[4,5-b]pyridine-7-carboxylate

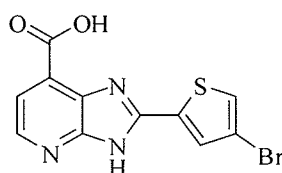


5

[0092] Step 2: A mixture of 2-(4-bromothiophen-2-yl)-7-methyl-1H-imidazo[4,5-b]pyridine (1.7 g, 5.4 mmol) and selenium dioxide (2.4 g, 21 mmol) in pyridine (15 mL) was heated at 110 °C for 3 h. The hot reaction mixture was filtered through diatomaceous earth, washed with hot pyridine (10 mL) and CH₃OH (20 mL), and the filtrate was concentrated and dried. The crude residue was dissolved in CH₃OH (50 mL) followed by the dropwise addition of SOCl₂ (0.40 mL, 6.5 mmol) at room temperature. The reaction mixture was stirred at reflux for 5 h, cooled, concentrated, suspended in ice-water (25 mL) and filtered. The pH of the filtrate was adjusted to 7 using conc. NH₄OH followed by extraction with EtOAc (3 × 50 mL). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated to provide the desired product as brown-yellow solid (1.5 g, 68% yield): ESI MS m/z 338 [C₁₂H₈BrN₃O₂S + H]⁺.

15

2-(4-Bromothiophen-2-yl)-1H-imidazo[4,5-b]pyridine-7-carboxylic Acid

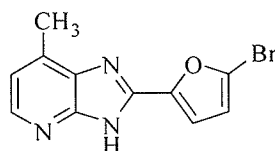


[0093] Step 3: To a solution of methyl 2-(4-bromothiophen-2-yl)-1H-imidazo[4,5-b]pyridine-7-carboxylate (0.60 g, 1.8 mmol) in THF (10 mL) was added a solution of LiOH (0.45 g, 11 mmol) in water (5 mL) and the resulting mixture was stirred at rt for 4 h. The reaction mixture was concentrated, diluted with ice-water (15 mL) and the pH was adjusted to 5 using glacial acetic acid. The resulting brown precipitate was filtered, washed with water (20 mL) and dried to provide the desired product (0.52 g, 91% yield): ESI MS m/z 324 [C₁₁H₆BrN₃O₂S + H]⁺.

20

Example 7

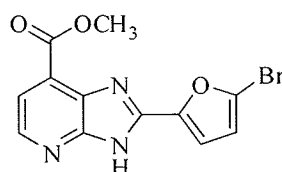
2-(5-Bromofuran-2-yl)-7-methyl-3H-imidazo[4,5-b]pyridine



[0094] Step 1: Following the procedure outlined for step 1 in Example 6, 4-methyl-3-

5 nitropyridin-2-amine (3.0 g, 20 mmol) was reacted with 5-bromofuran-2-carbaldehyde (3.42 g, 20 mmol) to obtain the product (1.3 g, 27% yield) as yellow solid: ESI MS m/z 278 $[C_{11}H_8BrN_3O + H]^+$.

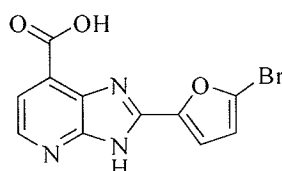
Methyl 2-(5-bromofuran-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxylate



10 [0095] Step 2: Following the procedure outlined for step 2 in Example 6, 2-(5-Bromofuran-2-yl)-7-methyl-3H-imidazo[4,5-b]pyridine (1.3 g, 4.7 mmol) was reacted with selenium dioxide (2.1 g, 19 mmol) and $SOCl_2$ (0.35 mL, 4.7 mmol) to provide the desired product (0.95 g, 63% yield) as brown-yellow solid: ESI MS m/z 322 $[C_{12}H_8BrN_3O_3 + H]^+$.

2-(5-Bromofuran-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxylic Acid

15

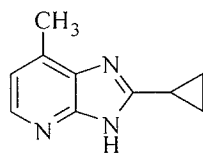


[0096] Step 3: Following the procedure outlined for step 3 in Example 6, methyl 2-(5-

bromofuran-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxylate (0.95 g, 2.9 mmol) was reacted with LiOH (0.52 g, 12 mmol) to provide the desired product (0.95, 63% yield) as a brown solid: ESI

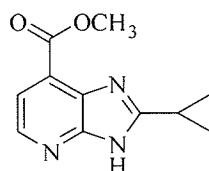
20 MS m/z 308 $[C_{11}H_6BrN_3O_3 + H]^+$.

Example 8
2-Cyclopropyl-7-methyl-1H-imidazo[4,5-b]pyridine



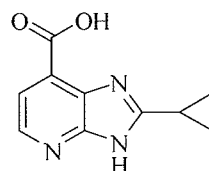
5 [0097] Step 1: Following the procedure outlined for step 1 in Example 6, 1, 4-methyl-3-nitropyridin-2-amine (1.5 g, 10 mmol) was reacted with cyclopropanecarbaldehyde (0.70 g, 10 mmol) to afford the product as brown solid (1.1 g, 64% yield). ESI MS m/z 174 [C₁₀H₁₁N₃ + H]⁺.

Methyl 2-cyclopropyl-1H-imidazo[4,5-b]pyridine-7-carboxylate



10 [0098] Step 2: Following the procedure outlined for step 2 in Example 6, 2-cyclopropyl-7-methyl-1H-imidazo[4,5-b]pyridine (0.98 g, 5.6 mmol) was reacted with SeO₂ (1.4 g, 13 mmol) and then SOCl₂ (0.42 mL, 5.6 mmol) to afford the product as brown solid (0.89 g, 73% yield): ESI MS m/z 218 [C₁₁H₁₁N₃O₂ + H]⁺.

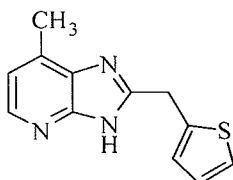
2-Cyclopropyl-1H-imidazo[4,5-b]pyridine-7-carboxylic Acid



15

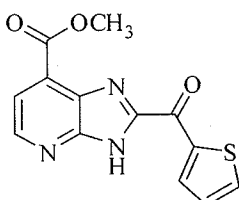
[0099] Step 3: Following the procedure outlined for step 3 in Example 6, methyl 2-cyclopropyl-1H-imidazo[4,5-b]pyridine-7-carboxylate (0.8 g, 3.7 mmol) was reacted with LiOH (0.93 g, 22 mmol) to afford the product as brown-yellow solid (0.72 g, 96% yield): ESI MS m/z 204 [C₁₀H₉N₃O₂ + H]⁺.

Example 9
7-Methyl-2-(thiophen-2-ylmethyl)-3H-imidazo[4,5-b]pyridine



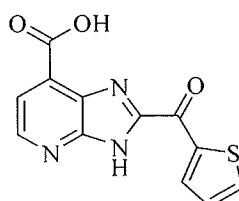
[0100] Step 1: Following the procedure outlined for step 1 in Example 6, 4-methylpyridine-
5 2,3-diamine (0.99 g, 8.0 mmol) was reacted with 2-(thiophen-2-yl)acetic acid (1.1 g, 8.0 mmol)
to provide the desired product (1.6 g, 88% yield): ESI MS m/z 230 [C₁₂H₁₁N₃S + H]⁺.

Methyl 2-(thiophene-2-carbonyl)-3H-imidazo[4,5-b]pyridine-7-carboxylate



[0101] Step 2: Following the procedure outlined for step 2 in Example 6, 7-methyl-2-
10 (thiophen-2-ylmethyl)-3H-imidazo[4,5-b]pyridine (1.1 g, 4.8 mmol) was reacted with SeO₂ (2.1
g, 19 mmol) and then SOCl₂ (0.36 mL, 4.8 mmol) to afford the product as brown solid (0.68 g,
49% yield): ESI MS m/z 274 [C₁₃H₁₁N₃O₂S + H]⁺.

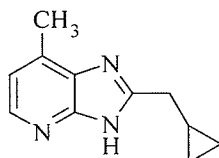
2-(Thiophene-2-carbonyl)-3H-imidazo[4,5-b]pyridine-7-carboxylic Acid



15

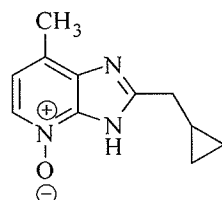
[0102] Step 3: Following the procedure outlined for step 3 in Example 6, methyl 2-(thiophene-
2-carbonyl)-3H-imidazo[4,5-b]pyridine-7-carboxylate (0.6 g, 4.8 mmol) was reacted with LiOH
(0.35 g, 8.4 mmol) to afford the product as a brown-yellow solid (0.53 g, 93% yield): ESI MS
m/z 260 [C₁₂H₉N₃O₂S + H]⁺.

Example 10
2-(Cyclopropylmethyl)-7-methyl-3H-imidazo[4,5-b]pyridine



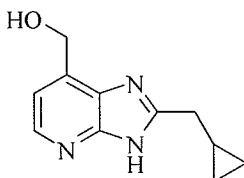
[0103] Step 1: A mixture of 4-methylpyridine-2,3-diamine (1.1 g, 8.9 mmol), 2-cyclopropylacetic acid (0.89 g, 8.9 mmol) in phosphorous oxychloride (10 mL) was heated at reflux for 3 h. The reaction mixture was cooled, concentrated, diluted in cold water (50 ml) and the pH was adjusted to 8 using 2 N NaOH and satd. aq. NaHCO₃. The resulting basic mixture was extracted with methylene chloride (3 × 50 mL) and the combined organic layers were dried over sodium sulfate, filtered, concentrated and the residue was purified by column chromatography (silica gel, 5% methanol/methylene chloride) to afford the product (1.3 g, 81% yield) as a yellow solid: ¹H NMR (CDCl₃, 500 MHz) δ 8.16 (d, *J* = 5.0 Hz, 1H), 7.03 (d, *J* = 5.0 Hz, 1H), 2.96 (d, *J* = 7.0 Hz, 2H), 2.69 (s, 3H), 1.30–1.26 (m, 1H), 0.69–0.65 (m, 2H), 0.41–0.38 (m, 2H); ESI MS *m/z* 188 [M + H]⁺.

2-(Cyclopropylmethyl)-7-methyl-3H-imidazo[4,5-b]pyridine 4-oxide



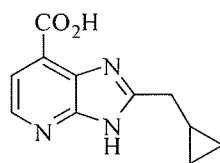
[0104] Step 2: To a solution of 2-(cyclopropylmethyl)-7-methyl-3H-imidazo[4,5-b]pyridine (0.42 g, 2.3 mmol) in methylene chloride (13 mL) at 0 °C was added *m*-chloroperoxybenzoic acid (0.78 g, 3.5 mmol) and the mixture was stirred at rt for 18 h. The reaction mixture was concentrated and the residue was used in the next step without further purification or characterization.

[2-(cyclopropylmethyl)-3H-imidazo[4,5-b]pyridin-7-yl]methanol



[0105] Step 3: The crude 2-(cyclopropylmethyl)-7-methyl-3H-imidazo[4,5-b]pyridine 4-oxide (2.3 mmol) was diluted in acetic anhydride (5 mL) and the reaction mixture was heated at 70 °C for 1 h. The reaction mixture was cooled using an ice-water bath and neutralized to pH 7 using 1 N NaOH. The mixture was extracted with methylene chloride (3 × 50 mL) and the combined organic layers were concentrated. The residue was dissolved in methanol (20 mL) and 1 N NaOH (20 mL) and stirred at rt for 30 min. The reaction mixture was extracted with methylene chloride (3 × 50 mL) and the combined organic layers were dried over sodium sulfate, filtered, concentrated and the residue was purified by column chromatography (silica gel, 5% methanol/methylene chloride) to provide the desired product (0.18 g, 39% yield) as a yellow solid: ¹H NMR (CD₃OD, 500 MHz) δ 8.28 (d, *J* = 5.0 Hz, 1H), 7.33 (d, *J* = 5.0 Hz, 1H), 5.03 (s, 2H), 2.85 (d, *J* = 7.5 Hz, 2H), 1.27–1.23 (m, 1H), 0.62–0.58 (m, 2H), 0.37–0.35 (m, 2H); ESI MS *m/z* 204 [M + H]⁺.

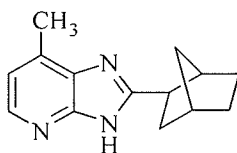
2-(Cyclopropylmethyl)-3H-imidazo[4,5-b]pyridine-7-carboxylic acid



[0106] Step 4: A suspension of H₅IO₆ (221 mg, 0.97 mmol) in CH₃CN was stirred at rt for 15 min followed by the addition of (2-(cyclopropylmethyl)-3H-imidazo[4,5-b]pyridin-7-yl)methanol (89 mg, 0.44 mmol) and pyridinium chlorochromate (9 mg, 0.044 mmol). The reaction mixture was stirred at rt for 3 h and the precipitate was filtered. The filtrate was concentrated and purified by preparative HPLC (C18 silica, 10–90% acetonitrile/water with 0.05% TFA) to afford the product (62 mg, 65% yield) as a yellow solid: ¹H NMR (CD₃OD, 500 MHz) δ 8.76 (d, *J* = 5.0 Hz, 1H), 8.05 (d, *J* = 5.0 Hz, 1H), 3.14 (d, *J* = 7.0 Hz, 2H), 1.33–1.30 (m, 1H), 0.74–0.70 (m, 2H), 0.47–0.44 (m, 2H); ESI MS *m/z* 218 [M + H]⁺.

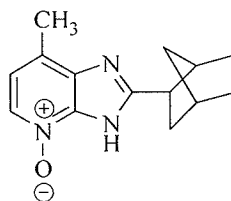
Example 11

2-(Bicyclo[2.2.1]heptan-2-yl)-7-methyl-3H-imidazo[4,5-b]pyridine



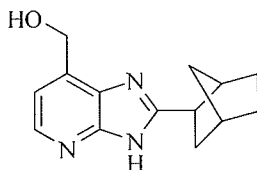
[0107] Step 1: A mixture of 4-methylpyridine-2,3-diamine (1.52 g, 12.4 mmol), bicyclo[2.2.1]heptane-2-carboxylic acid (1.73 g, 12.4 mmol) in phosphorous oxychloride (15 mL) was refluxed for 3 h. The reaction mixture was cooled, concentrated, diluted in cold water (50 ml) and the pH was adjusted to 8 using 2 N NaOH and satd. aq. NaHCO₃. The resulting basic mixture was extracted with methylene chloride (3 × 50 mL) and the combined organic layers were dried over sodium sulfate, filtered, concentrated and the residue was purified by column chromatography (silica gel, 5% methanol/methylene chloride) to afford the product (1.88 g, 67% yield) as a yellow solid (mixture of diastereomers): ¹H NMR (CDCl₃, 500 MHz) δ 8.17 (d, *J* = 5.0 Hz, 1H), 7.02 (d, *J* = 5.0 Hz, 1H), 3.56–3.49 (m, 1H, minor), 3.15–3.12 (m, 1H, major), 2.83 (s, 1H, minor), 2.74 (s, 1H, major), 2.71 (s, 3H), 2.50 (s, 1H, major), 2.46 (s, 1H, minor), 2.34–1.23 (m, 8H); ESI MS *m/z* 228 [M + H]⁺.

2-(Bicyclo[2.2.1]heptan-2-yl)-7-methyl-3H-imidazo[4,5-b]pyridine 4-oxide



[0108] Step 2: To a solution of 2-(bicyclo[2.2.1]heptan-2-yl)-7-methyl-3H-imidazo[4,5-b]pyridine 1.65 g, 7.3 mmol) in methylene chloride (30 mL) at 0 °C was added *m*-chloroperoxybenzoic acid (2.50 g, 11.2 mmol) and the reaction mixture was stirred at rt for 3 h. The reaction was quenched by the addition of satd. aq. NaHCO₃ (20 mL) and the layers were separated. The organic phase was dried over sodium sulfate, filtered, concentrated and the residue was used in the next step without further purification or characterization.

[-(Bicyclo[2.2.1]heptan-2-yl)-3H-imidazo[4,5-b]pyridin-7-yl]methanol

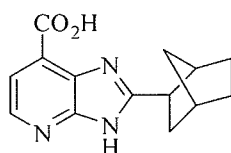


[0109] Step 3: A solution of 2-(bicyclo[2.2.1]heptan-2-yl)-7-methyl-3H-imidazo[4,5-b]pyridine 4-oxide (7.3 mmol) in acetic anhydride (40 mL) was heated at 70 °C for 1 h. The reaction mixture was cooled using an ice-water bath and the pH was adjusted to 7 using 1 N NaOH. The mixture was extracted with methylene chloride (3 × 50 mL) and the combined

organic layers were concentrated. The residue was dissolved in methanol (20 mL) and 1 N NaOH (20 mL) and stirred at rt for 30 min. The reaction mixture was extracted with methylene chloride (3 × 50 mL) and the combined organic layers were dried over sodium sulfate, filtered, concentrated and the residue was purified by column chromatography (silica gel, 5%

5 methanol/methylene chloride) to provide the desired product (0.52 g, 27% yield) as an off-white solid (mixture of diastereomers): ¹H NMR (CDCl₃, 500 MHz) ¹H NMR (CDCl₃, 500 MHz) δ 8.26 (s, 1H), 7.09 (s, 1H), 5.16 (s, 2H), 3.46 (br, 1H, minor), 3.04 (br, 1H, major), 2.76 (s, 1H, minor), 2.71 (s, 1H, major), 2.48 (s, 1H, major), 2.46 (s, 1H, minor), 2.29–1.23 (m, 8H); ESI MS *m/z* 244 [M + H]⁺.

10 2-(Bicyclo[2.2.1]heptan-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxylic acid



[0110] Step 4: A suspension of H₅IO₆ (412 mg, 1.8 mmol) in CH₃CN was stirred at rt for 15 min followed by the addition of (2-(bicyclo[2.2.1]heptan-2-yl)-3H-imidazo[4,5-b]pyridin-7-yl)methanol (200 mg, 0.82 mmol) and pyridinium chlorochromate (18 mg, 0.082 mmol). The
15 reaction mixture was stirred at rt for 3 h and the precipitate was filtered. The filtrate was concentrated and the residue was used in the next step without further purification or characterization.

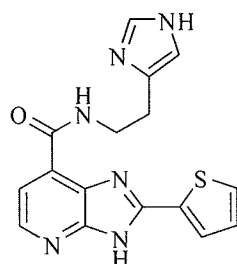
General Procedure A – synthesis of compounds of formula I as described in Scheme (1):

[0111] The crude carboxylic acids E (0.22 – 0.94 mmol) were dissolved in mixture of
20 THF/DMF (2:1) followed by the addition of HATU (1.5 equiv), diisopropylethyl amine (3 equiv) and the requisite amine (2 equiv) and the reaction mixture was stirred at rt for 5 – 18 h. The reaction mixture was diluted with water, the pH was adjusted to 12, and the mixture was extracted with ethyl acetate. The combined organic layers were concentrated and purified by preparative HPLC (C18 silica, 10–90% acetonitrile/water with 0.05% TFA). The desired
25 fractions were combined, concentrated and eluted through an ion-exchange column (using methanol and 7 N methanol in ammonia) to obtain the desired products. In some instances, the combined organic layers were dissolved in THF, followed by the addition of 6 M HCl (5 equiv) and the reaction mixture was heated at 60 °C for 1 h. The reaction mixture was cooled,

concentrated and purified by preparative HPLC (C18 silica, 10–90% acetonitrile/water with 0.05% TFA). The desired fractions were combined, concentrated and eluted through an ion-exchange column (using methanol and 7 N methanol in ammonia) to obtain the desired products.

Example 12

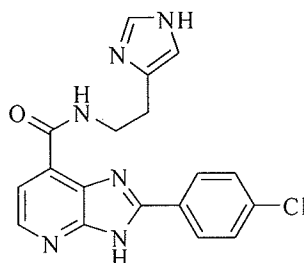
5 *N*-[2-(1*H*-imidazol-4-yl)ethyl]-2-(thiophen-2-yl)-3*H*-imidazo[4,5-*b*]pyridine-7-carboxamide



[0112] Following General Procedure A, 2-(thiophene-2-yl)-3*H*-imidazo[4,5-*b*]pyridine-7-carboxylic acid (139 mg, 0.56 mmol) was reacted with histamine hydrochloride (205 mg, 1.1 mmol) to afford the desired product (37 mg, 19% yield) as a light yellow solid: ¹H NMR (300 MHz, CD₃OD) δ8.42 (d, *J* = 5.1 Hz, 1H), 7.94–7.91 (m, 2H), 7.77 (d, *J* = 5.1 Hz, 2H), 7.29–7.26 (m, 1H), 7.12 (s, 1H), 3.89 (t, *J* = 6.8 Hz, 2H), 3.08 (t, *J* = 6.8 Hz, 2H); ESI MS *m/z* 339 [C₁₆H₁₄N₆OS + H]⁺; HPLC 95.7% (AUC), *t_R* = 9.36 min.

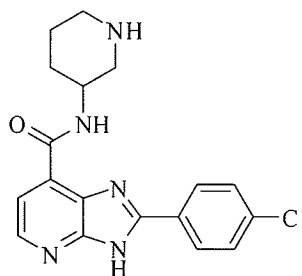
Example 13

15 *N*-[2-(1*H*-Imidazol-4-yl)ethyl]-2-(4-chlorophenyl)-3*H*-imidazo[4,5-*b*]pyridine-7-carboxamide



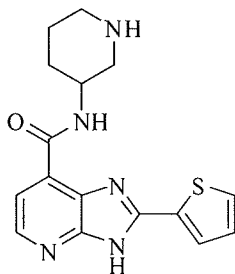
[0113] Following General Procedure A, 2-(4-chlorophenyl)-3*H*-imidazo[4,5-*b*]pyridine-7-carboxylic acid (140 mg, 0.51 mmol) was reacted with histamine hydrochloride (185 mg, 1.0 mmol) to afford the desired product (9 mg, 5% yield) as a light yellow solid: ¹H NMR (500 MHz, CD₃OD) δ8.44 (d, *J* = 5.0 Hz, 1H), 8.10 (d, *J* = 8.5 Hz, 2H), 7.79 (d, *J* = 5.0 Hz, 1H), 7.75 (s, 1H), 7.61 (d, *J* = 8.5 Hz, 2H), 7.01 (s, 1H), 3.90 (t, *J* = 6.5 Hz, 2H), 3.02 (t, *J* = 6.5 Hz, 2H); ESI MS *m/z* 367 [C₁₈H₁₅ClN₆O + H]⁺; HPLC 95.7% (AUC), *t_R* = 10.53 min.

Example 14

2-(4-Chlorophenyl)-*N*-(piperidin-3-yl)-3*H*-imidazo[4,5-*b*]pyridine-7-carboxamide

[0114] Following General Procedure A, 2-(4-chlorophenyl)-3*H*-imidazo[4,5-*b*]pyridine-7-carboxylic acid (130 mg, 0.47 mmol) was reacted with *tert*-butyl 3-aminopiperidine-1-carboxylate (190 mg, 0.94 mmol) to afford the desired product (8 mg, 3% yield) as a light yellow solid: ¹H NMR (300 MHz, CD₃OD) δ 8.45 (d, *J* = 5.1 Hz, 1H), 8.25–8.22 (m, 2H), 7.78 (d, *J* = 5.1 Hz, 1H), 7.62–7.59 (m, 2H), 4.21–4.18 (m, 1H), 3.08–3.04 (m, 1H), 2.90–2.83 (m, 2H), 2.24–2.15 (m, 1H), 2.01–1.92 (m, 1H), 1.83–1.77 (m, 2H); ESI MS *m/z* 356 [C₁₈H₁₈ClN₅O + H]⁺; HPLC 98.4% (AUC), *t*_R = 10.55 min.

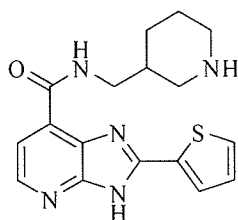
Example 15

N-(Piperidin-3-yl)-2-(thiophen-2-yl)-3*H*-imidazo[4,5-*b*]pyridine-7-carboxamide

[0115] Following General Procedure A, 2-(thiophen-2-yl)-3*H*-imidazo[4,5-*b*]pyridine-7-carboxylic acid (200 mg, 0.63 mmol) was reacted with *tert*-butyl 3-aminopiperidine-1-carboxylate (250 mg, 1.3 mmol) to afford the desired product (67 mg, 32% yield) as a yellow solid: ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.87 (d, *J* = 7.5 Hz, 1H), 8.36 (d, *J* = 5.1 Hz, 1H), 7.99–7.98 (m, 1H), 7.82–7.80 (m, 1H), 7.60 (d, *J* = 5.1 Hz, 1H), 7.27 (dd, *J* = 3.6, 5.1 Hz, 1H), 4.07–4.04 (m, 1H), 3.14–3.09 (m, 1H), 2.86–2.68 (m, 3H), 2.02–1.79 (m, 2H), 1.69–1.53 (m, 2H); ESI MS *m/z* 328 [C₁₆H₁₇N₅OS + H]⁺; HPLC 98.5% (AUC), *t*_R = 10.19 min.

Example 16

N-(Piperidin-3-ylmethyl)-2-(thiophen-2-yl)-3*H*-imidazo[4,5-*b*]pyridine-7-carboxamide

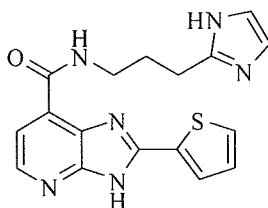


[0116] Following General Procedure A, 2-(thiophen-2-yl)-3*H*-imidazo[4,5-*b*]pyridine-7-carboxylic acid (170 mg, 0.53 mmol) was reacted with *tert*-butyl 3-(aminomethyl)piperidine-1-carboxylate (230 mg, 1.1 mmol) to afford the desired product (28 mg, 16% yield) as a yellow-brown solid: ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.05–9.98 (m, 1H), 8.24 (d, *J* = 7.5 Hz, 1H), 7.88 (d, *J* = 3.3 Hz, 1H), 7.68 (d, *J* = 5.1 Hz, 1H), 7.45 (d, *J* = 4.8 Hz, 1H), 7.23–7.20 (m, 1H), 3.42–3.38 (m, 2H), 3.28–3.24 (m, 1H), 3.12–3.08 (m, 1H), 2.71–2.57 (m, 2H), 1.99–1.85 (m, 2H), 1.81–1.70 (m, 1H), 1.63–1.46 (m, 1H), 1.41–1.29 (m, 1H); ESI MS *m/z* 342 [C₁₇H₁₉N₅OS + H]⁺; HPLC 97.6% (AUC), *t*_R = 8.87 min.

10

Example 17

N-[3-(1*H*-Imidazol-2-yl)propyl]-2-(thiophen-2-yl)-3*H*-imidazo[4,5-*b*]pyridine-7-carboxamide

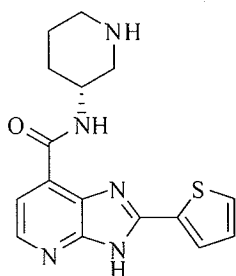


[0117] Following General Procedure A, 2-(thiophen-2-yl)-3*H*-imidazo[4,5-*b*]pyridine-7-carboxylic acid (150 mg, 0.47 mmol) was reacted with 3-(1*H*-imidazol-2-yl)propan-1-amine (120 mg, 0.94 mmol) to afford the desired product (33 mg, 20% yield) as a light yellow solid: ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.46–9.39 (m, 1H), 8.44 (d, *J* = 4.8 Hz, 1H), 8.11–8.07 (m, 1H), 7.87 (d, *J* = 5.1 Hz, 1H), 7.67 (d, *J* = 5.1 Hz, 1H), 7.31–7.28 (m, 1H), 6.89 (s, 2H), 3.54–3.47 (m, 2H), 2.80 (t, *J* = 7.5 Hz, 2H), 2.00 (t, *J* = 7.5 Hz, 2H); ESI MS *m/z* 353 [C₁₇H₁₆N₆OS + H]⁺; HPLC 98.8% (AUC), *t*_R = 8.78 min.

20

Example 18

(R)-N-(Piperidin-3-yl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide

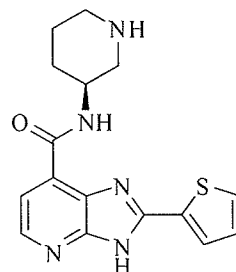


[0118] Following General Procedure A, 2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-

carboxylic acid (140 mg, 0.44 mmol) was reacted with (R)-tert-butyl 3-aminopiperidine-1-
 5 carboxylate (180 mg, 0.88 mmol) to afford the desired product (30 mg, 21% yield) as a light
 yellow solid: ^1H NMR (300 MHz, DMSO- d_6) δ 9.84 (d, $J = 7.2$ Hz, 1H), 8.38 (d, $J = 5.0$ Hz,
 1H), 8.00 (dd, $J = 1.2, 3.8$ Hz, 1H), 7.82 (dd, $J = 1.2, 5.0$ Hz, 1H), 7.61 (d, $J = 5.0$ Hz, 1H), 7.28
 (dd, $J = 3.8, 5.0$ Hz, 1H), 4.07–4.05 (m, 1H), 3.17–3.10 (m, 1H), 2.87–2.69 (m, 3H), 2.02–1.80
 10 (m, 2H), 1.66–1.60 (m, 2H); ESI MS m/z 328 [$\text{C}_{16}\text{H}_{17}\text{N}_5\text{OS} + \text{H}$] $^+$; HPLC >99% (AUC), $t_R =$
 8.68 min.

Example 19

(S)-N-(Piperidin-3-yl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide

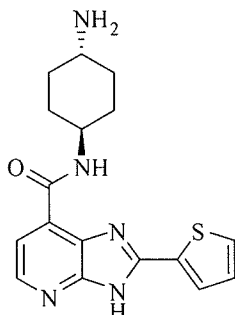


[0119] Following General Procedure A, 2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-

carboxylic acid (210 mg, 0.66 mmol) was reacted with (S)-tert-butyl 3-aminopiperidine-1-
 15 carboxylate (260 mg, 1.3 mmol) to afford the desired product (40 mg, 19% yield) as a light
 yellow solid: ^1H NMR (300 MHz, DMSO- d_6) δ 9.87 (d, $J = 7.5$ Hz, 1H), 8.37 (d, $J = 5.1$ Hz,
 1H), 7.99 (d, $J = 2.7$ Hz, 1H), 7.81 (d, $J = 4.2$ Hz, 1H), 7.60 (d, $J = 5.1$ Hz, 1H), 7.29–7.26 (m,
 20 1H), 4.07–4.05 (m, 1H), 3.13–3.09 (m, 1H), 2.89–2.68 (m, 3H), 2.02–1.79 (m, 2H), 1.69–1.53
 (m, 2H); ESI MS m/z 328 [$\text{C}_{16}\text{H}_{17}\text{N}_5\text{OS} + \text{H}$] $^+$; HPLC >99% (AUC), $t_R = 10.40$ min.

Example 20

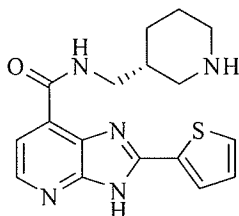
N-(4-Aminocyclohexyl)-2-(thiophen-2-yl)-3*H*-imidazo[4,5-*b*]pyridine-7-carboxamide



[0120] Following General Procedure A, 2-(thiophen-2-yl)-3*H*-imidazo[4,5-*b*]pyridine-7-carboxylic acid (100 mg, 0.33 mmol) was reacted with *trans-tert*-butyl 4-aminocyclohexylcarbamate (140 mg, 0.66 mmol) to afford the desired product (44 mg, 39% yield) as a light yellow solid: ¹H NMR (300 MHz, CD₃OD) δ 8.34 (d, *J* = 5.1 Hz, 1H), 7.92 (dd, *J* = 1.2, 3.6 Hz, 1H), 7.69 (d, *J* = 5.1 Hz, 1H), 7.67 (dd, *J* = 1.2, 5.1 Hz, 1H), 7.23 (dd, *J* = 3.6, 5.1 Hz, 1H), 4.01–3.91 (m, 1H), 3.08–2.96 (m, 1H), 2.28–2.45 (m, 2H), 2.12–2.08 (m, 2H), 1.61–1.47 (m, 4H); ESI MS *m/z* 342 [C₁₇H₁₉N₅OS + H]⁺; HPLC 97.2% (AUC), *t*_R = 8.60 min.

Example 21

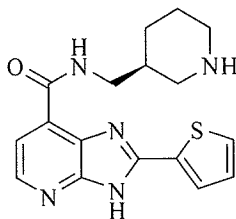
(*R*)-*N*-(Piperidin-3-ylmethyl)-2-(thiophen-2-yl)-3*H*-imidazo[4,5-*b*]pyridine-7-carboxamide



[0121] Following General Procedure A, 2-(thiophen-2-yl)-3*H*-imidazo[4,5-*b*]pyridine-7-carboxylic acid (160 mg, 0.51 mmol) was reacted with (*S*)-*tert*-butyl 3-(aminomethyl)piperidine-1-carboxylate (220 mg, 1.0 mmol) to afford the desired product (54 mg, 31% yield) as a light yellow solid: ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.07–10.05 (m, 1H), 8.23 (d, *J* = 5.1 Hz, 1H), 7.86 (dd, *J* = 1.2, 3.6 Hz, 1H), 7.67–7.65 (m, 1H), 7.43 (d, *J* = 5.1 Hz, 1H), 7.20 (dd, *J* = 3.6, 4.0 Hz, 1H), 3.41–3.37 (m, 2H), 3.27–3.23 (m, 1H), 3.10–3.06 (m, 1H), 2.70–2.55 (m, 2H), 1.98–1.83 (m, 2H), 1.80–1.71 (m, 1H), 1.62–1.45 (m, 1H), 1.40–1.29 (m, 1H); ESI MS *m/z* 342 [C₁₇H₁₉N₅OS + H]⁺; HPLC >99% (AUC), *t*_R = 8.69 min.

Example 22

(S)-N-(Piperidin-3-ylmethyl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide

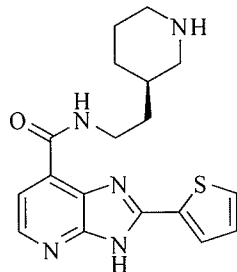


[0122] Following General Procedure A, 2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-

- 5 carboxylic acid (160 mg, 0.51 mmol) was reacted with (R)-tert-butyl 3-(aminomethyl)piperidine-1-carboxylate (220 mg, 1.0 mmol) to afford the desired product (62 mg, 35% yield) as a light yellow solid: ^1H NMR (300 MHz, DMSO- d_6) δ 10.07–10.05 (m, 1H), 8.23 (d, J = 5.1 Hz, 1H), 7.86 (dd, J = 1.2, 3.6 Hz, 1H), 7.67–7.65 (m, 1H), 7.43 (d, J = 5.1 Hz, 1H), 7.20 (dd, J = 3.6, 4.2 Hz, 1H), 3.41–3.37 (m, 2H), 3.27–3.23 (m, 1H), 3.10–3.06 (m, 1H), 2.70–2.55 (m, 2H), 1.99–
- 10 1.83 (m, 2H), 1.80–1.70 (m, 1H), 1.61–1.46 (m, 1H), 1.40–1.25 (m, 1H); ESI MS m/z 342 [$\text{C}_{17}\text{H}_{19}\text{N}_5\text{OS} + \text{H}$] $^+$; HPLC >99% (AUC), t_R = 8.40 min.

Example 23

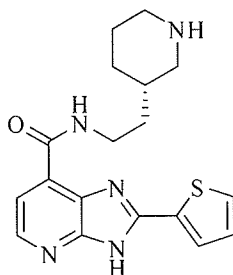
(R)-N-[2-(Piperidin-3-yl)ethyl]-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide



- 15 [0123] Following General Procedure A, 2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxylic acid (130 mg, 0.39 mmol) was reacted with (R)-tert-butyl 3-(2-aminoethyl)piperidine-1-carboxylate (180 mg, 0.78 mmol) to afford the desired product (30 mg, 21% yield) as a light yellow solid: ^1H NMR (300 MHz, DMSO- d_6) δ 10.03–10.00 (m, 1H), 8.21 (d, J = 5.1 Hz, 1H), 7.86 (dd, J = 0.9, 3.6 Hz, 1H), 7.65 (dd, J = 0.9, 5.1 Hz, 1H), 7.42 (d, J = 5.1 Hz, 1H), 7.20 (dd, J
- 20 = 3.6, 5.1 Hz, 1H), 3.57–3.42 (m, 2H), 3.22–3.01 (m, 2H), 2.69–2.58 (m, 1H), 1.99–1.89 (m, 1H), 1.80–1.67 (m, 2H), 1.67–1.46 (m, 3H), 1.25–1.14 (m, 1H); ESI MS m/z 356 [$\text{C}_{18}\text{H}_{21}\text{N}_5\text{OS} + \text{H}$] $^+$; HPLC >99% (AUC), t_R = 8.78 min.

Example 24

(*S*)-*N*-[2-(Piperidin-3-yl)ethyl]-2-(thiophen-2-yl)-3*H*-imidazo[4,5-*b*]pyridine-7-carboxamide

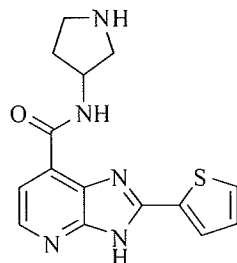


[0124] Following General Procedure A, 2-(thiophen-2-yl)-3*H*-imidazo[4,5-*b*]pyridine-7-

carboxylic acid (140 mg, 0.42 mmol) was reacted with (*S*)-*tert*-butyl 3-(2-aminoethyl)piperidine-1-carboxylate (190 mg, 0.84 mmol) to afford the desired product (23 mg, 15% yield) as a light yellow solid: ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.00–9.98 (m, 1H), 8.21 (d, *J* = 5.1 Hz, 1H), 7.87 (dd, *J* = 0.9, 3.6 Hz, 1H), 7.65 (dd, *J* = 0.9, 5.1 Hz, 1H), 7.43 (d, *J* = 5.1 Hz, 1H), 7.20 (dd, *J* = 3.6, 5.1 Hz, 1H), 3.58–3.42 (m, 2H), 3.22–3.02 (m, 2H), 2.70–2.59 (m, 1H), 1.99–1.89 (m, 1H), 1.82–1.67 (m, 2H), 1.67–1.47 (m, 3H), 1.28–1.13 (m, 1H); ESI MS *m/z* 356 [C₁₈H₂₁N₅OS + H]⁺; HPLC >99% (AUC), *t*_R = 8.77 min.

Example 25

N-(Pyrrolidin-3-yl)-2-(thiophen-2-yl)-3*H*-imidazo[4,5-*b*]pyridine-7-carboxamide

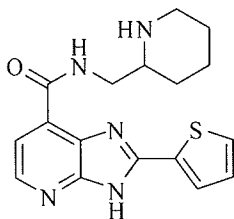


[0125] Following General Procedure A, 2-(thiophen-2-yl)-3*H*-imidazo[4,5-*b*]pyridine-7-

carboxylic acid (150 mg, 0.46 mmol) was reacted with *tert*-butyl 3-aminopyrrolidine-1-carboxylate (170 mg, 0.92 mmol) to afford the desired product (49 mg, 34% yield) as a light yellow solid: ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.95 (d, *J* = 6.6 Hz, 1H), 8.32 (d, *J* = 5.1 Hz, 1H), 7.95 (dd, *J* = 0.9, 3.6 Hz, 1H), 7.76 (dd, *J* = 0.9, 5.1 Hz, 1H), 7.52 (d, *J* = 5.1 Hz, 1H), 7.24 (dd, *J* = 3.6, 3.8 Hz, 1H), 4.54–4.45 (m, 1H), 3.35–3.28 (m, 1H), 3.23–3.05 (m, 2H), 3.00–2.93 (m, 1H), 2.28–2.19 (m, 1H), 1.93–1.82 (m, 1H); ESI MS *m/z* 314 [C₁₅H₁₅N₅OS + H]⁺; HPLC 98.5% (AUC), *t*_R = 7.77 min.

Example 26

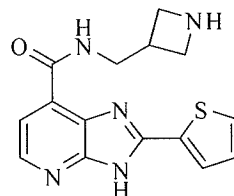
N-(Piperidin-2-ylmethyl)-2-(thiophen-2-yl)-3*H*-imidazo[4,5-*b*]pyridine-7-carboxamide



- [0126] Following General Procedure A, 2-(thiophen-2-yl)-3*H*-imidazo[4,5-*b*]pyridine-7-carboxylic acid (150 mg, 0.47 mmol) was reacted *tert*-butyl 2-(aminomethyl)piperidine-1-carboxylate (200 mg, 0.94 mmol) to afford the desired product (42 mg, 26% yield) as a yellow solid: ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.81–9.78 (m, 1H), 8.34 (d, *J* = 5.1 Hz, 1H), 7.98 (dd, *J* = 0.9, 3.8 Hz, 1H), 7.80 (dd, *J* = 0.9, 5.1 Hz, 1H), 7.57 (d, *J* = 5.1 Hz, 1H), 7.26 (dd, *J* = 3.8, 5.1 Hz, 1H), 3.52–3.44 (m, 2H), 3.13–3.04 (m, 1H), 2.94–2.84 (m, 1H), 2.74–2.61 (m, 1H), 1.86–1.77 (m, 2H), 1.62–1.55 (m, 1H), 1.47–1.29 (m, 2H); ESI MS *m/z* 342 [C₁₇H₁₉N₅OS + H]⁺; HPLC 98.9% (AUC), *t*_R = 8.36 min.

Example 27

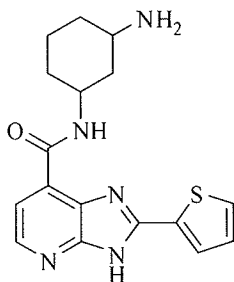
N-(Azetidin-3-ylmethyl)-2-(thiophen-2-yl)-3*H*-imidazo[4,5-*b*]pyridine-7-carboxamide



- [0127] Following General Procedure A, 2-(thiophen-2-yl)-3*H*-imidazo[4,5-*b*]pyridine-7-carboxylic acid (140 mg, 0.43 mmol) was reacted *tert*-butyl 3-(aminomethyl)azetidine-1-carboxylate (160 mg, 0.86 mmol) to afford the desired product (26 mg, 19% yield) as a light yellow solid: ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.06–9.97 (m, 1H), 8.23 (d, *J* = 4.5 Hz, 1H), 7.85 (s, 1H), 7.66 (d, *J* = 4.5 Hz, 1H), 7.42 (d, *J* = 4.5 Hz, 1H), 7.22–7.19 (m, 1H), 3.97 (t, *J* = 9.0 Hz, 2H), 3.80–3.74 (m, 1H), 3.68 (t, *J* = 6.0 Hz, 4H); ESI MS *m/z* 314 [C₁₅H₁₅N₅OS + H]⁺.

Example 28

N-(3-Aminocyclohexyl)-2-(thiophen-2-yl)-3*H*-imidazo[4,5-*b*]pyridine-7-carboxamide

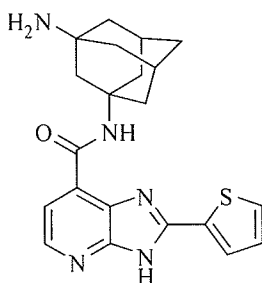


[0128] Following General Procedure A, 2-(thiophen-2-yl)-3*H*-imidazo[4,5-*b*]pyridine-7-

carboxylic acid (300 mg, 0.94 mmol) was reacted *tert*-butyl 3-aminocyclohexylcarbamate (400 mg, 1.9 mmol) to afford the desired product (77 mg, 24% yield) as a light yellow solid: ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.35 (s, 1H, minor diastereomer), 9.88 (s, 1H, major diastereomer), 8.29–8.25 (m, 1H), 7.91–7.87 (m, 1H), 7.74–7.69 (m, 1H), 7.50–7.46 (m, 1H), 7.25–7.22 (m, 1H), 4.48–4.42 (m, 1H, minor diastereomer), 4.01–3.88 (m, 1H, major diastereomer), 3.21–3.11 (m, 1H), 2.42–2.32 (m, 1H), 2.09–2.00 (m, 1H), 1.98–1.80 (m, 2H), 1.51–1.20 (m, 4H); ESI MS *m/z* 342 [C₁₇H₁₉N₅OS + H]⁺; HPLC >99% (AUC), *t*_R = 9.06 min (major diastereomer), 9.33 min (minor diastereomer).

Example 29

N-(3-Aminoadamantyl)-2-(thiophen-2-yl)-3*H*-imidazo[4,5-*b*]pyridine-7-carboxamide

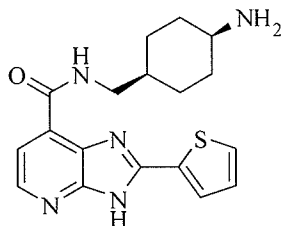


[0129] Following General Procedure A, 2-(thiophen-2-yl)-3*H*-imidazo[4,5-*b*]pyridine-7-

carboxylic acid (110 mg, 0.34 mmol) was reacted *tert*-butyl 3-aminoadamantylcarbamate (180 mg, 0.68 mmol) to afford the desired product (51 mg, 38% yield over two steps) as a white solid: ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.80 (s, 1H), 8.35 (d, *J* = 5.1 Hz, 1H), 7.95 (d, *J* = 3.6 Hz, 1H), 7.80 (d, *J* = 5.1 Hz, 1H), 7.56 (d, *J* = 5.1 Hz, 1H), 7.27 (dd, *J* = 5.1, 3.6 Hz, 1H), 2.32 (s, 4H), 2.23–2.19 (m, 2H), 2.01–1.97 (m, 2H), 1.85–1.56 (m, 6H); ESI MS *m/z* 394 [C₂₁H₂₃N₅OS + H]⁺; HPLC 96.2% (AUC), *t*_R = 10.22 min.

Example 30

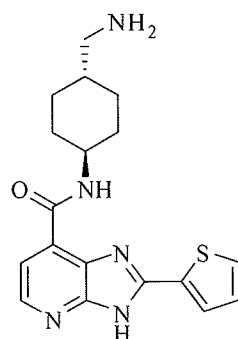
N-{[(1S,4S)-4-Aminocyclohexyl]methyl}-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide



- 5 **[0130]** Following General Procedure A, 2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxylic acid (110 mg, 0.33 mmol) was reacted *cis-tert*-butyl 4-(aminomethyl)cyclohexylcarbamate (150 mg, 0.66 mmol) to afford the desired product (79 mg, 67% yield) as a light yellow solid: ^1H NMR (300 MHz, DMSO- d_6) δ 9.68–9.60 (m, 1H), 8.37 (d, J = 5.1 Hz, 1H), 8.00 (d, J = 4.5 Hz, 1H), 7.82 (d, J = 4.5 Hz, 1H), 7.60 (d, J = 4.5 Hz, 1H), 7.28 (dd, J = 5.1, 3.6 Hz, 1H), 3.45–3.42 (m, 2H), 3.26–3.18 (m, 2H), 1.88–1.59 (m, 8H); ESI MS m/z 356 [$\text{C}_{18}\text{H}_{21}\text{N}_5\text{OS} + \text{H}$] $^+$; HPLC >99% (AUC), t_R = 8.96 min.

Example 31

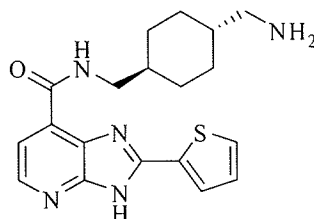
trans-N-[4-(Aminomethyl)cyclohexyl]-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide



- 15 **[0131]** Following General Procedure A, 2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxylic acid (110 mg, 0.33 mmol) was reacted *trans-tert*-butyl (4-aminocyclohexyl)methylcarbamate (150 mg, 0.66 mmol) to afford the desired product (70 mg, 60% yield) as a light yellow solid: ^1H NMR (300 MHz, DMSO- d_6) δ 9.96 (d, J = 7.5 Hz, 1H), 8.24 (d, J = 5.1 Hz, 1H), 7.86 (dd, J = 3.6, 1.2 Hz, 1H), 7.68 (dd, J = 5.1, 1.2 Hz, 1H), 7.45 (d, J = 5.1 Hz, 1H), 7.21 (dd, J = 5.1, 3.6 Hz, 1H), 3.85–3.80 (m, 1H), 2.70 (d, J = 6.6 Hz, 2H), 2.17–2.07 (m, 2H), 1.93–1.82 (m, 2H), 1.66–1.52 (m, 1H), 1.44–1.27 (m, 2H), 1.24–1.07 (m, 2H); ESI MS m/z 356 [$\text{C}_{18}\text{H}_{21}\text{N}_5\text{OS} + \text{H}$] $^+$; HPLC >99% (AUC), t_R = 9.02 min.

Example 32

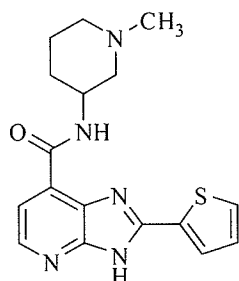
trans-*N*-{[4-(Aminomethyl)cyclohexyl]methyl}-2-(thiophen-2-yl)-3*H*-imidazo[4,5-*b*]pyridine-7-carboxamide



- 5 [0132] Following General Procedure A, 2-(thiophen-2-yl)-3*H*-imidazo[4,5-*b*]pyridine-7-carboxylic acid (70 mg, 0.22 mmol) was reacted *trans*-*tert*-butyl [4-(aminomethyl)cyclohexyl]methylcarbamate (110 mg, 0.44 mmol) to afford the desired product (60 mg, 74% yield) as a light yellow solid: ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.03–10.01 (m, 1H), 8.24 (d, *J* = 4.8 Hz, 1H), 7.87 (dd, *J* = 3.6, 0.9 Hz, 1H), 7.68 (dd, *J* = 4.8, 0.9 Hz, 1H), 7.46 (d, *J* = 4.8 Hz, 1H), 7.22 (dd, *J* = 4.8, 3.6 Hz, 1H), 3.35 (t, *J* = 6.0 Hz, 2H), 2.69–2.65 (m, 2H), 2.02–1.93 (m, 2H), 1.90–1.80 (m, 2H), 1.61–1.44 (m, 2H), 1.23–0.92 (m, 4H); ESI MS *m/z* 370 [C₁₉H₂₃N₅OS + H]⁺; HPLC >99% (AUC), *t*_R = 9.55 min.

Example 33

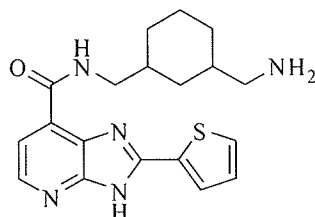
N-(1-Methylpiperidin-3-yl)-2-(thiophen-2-yl)-3*H*-imidazo[4,5-*b*]pyridine-7-carboxamide



- 15 [0133] Following General Procedure A, 2-(thiophen-2-yl)-3*H*-imidazo[4,5-*b*]pyridine-7-carboxylic acid (62 mg, 0.19 mmol) was reacted 1-methylpiperidin-3-amine (45 mg, 0.38 mmol) to afford the desired product (24 mg, 36% yield) as a light yellow semi-solid: ¹H NMR (300 MHz, CD₃OD) δ 8.42 (d, *J* = 5.1 Hz, 1H), 7.94 (dd, *J* = 3.6, 0.9 Hz, 1H), 7.77–7.75 (m, 2H), 7.27 (dd, *J* = 5.1, 0.9 Hz, 1H), 4.45–4.34 (m, 1H), 3.66–3.52 (m, 1H), 3.24–3.12 (m, 1H), 2.88 (s, 3H), 2.33–2.15 (m, 2H), 2.11–1.86 (m, 2H); ESI MS *m/z* 342 [C₁₇H₁₉N₅OS + H]⁺; HPLC >99% (AUC), *t*_R = 9.94 min.

Example 34

N-{[3-(Aminomethyl)cyclohexyl]methyl}-2-(thiophen-2-yl)-3*H*-imidazo[4,5-*b*]pyridine-7-carboxamide

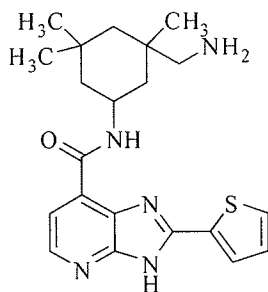


- 5 **[0134]** Following General Procedure A, 2-(thiophen-2-yl)-3*H*-imidazo[4,5-*b*]pyridine-7-carboxylic acid (80 mg, 0.25 mmol) was reacted *tert*-butyl [3-(aminomethyl)cyclohexyl]methylcarbamate (120 mg, 0.50 mmol) to afford the desired product (48 mg, 52% yield) as an off-white solid: ¹H NMR (300 MHz, DMSO-*d*₆) δ9.87–9.83 (m, 1H), 8.36 (d, *J* = 5.1 Hz, 1H, minor diastereomer), 8.31 (d, *J* = 5.1 Hz, 1H, major diastereomer), 7.93 (d, *J* = 3.6 Hz, 1H), 7.75 (d, *J* = 5.1 Hz, 1H), 7.59 (d, *J* = 5.1 Hz, 1H, minor diastereomer), 7.53 (d, *J* = 5.1 Hz, 1H, major diastereomer), 7.26–7.24 (m, 1H), 3.52–3.26 (m, 2H), 2.82–2.77 (m, 2H, minor diastereomer), 2.71–2.64 (m, 2H, major diastereomer), 2.01–1.75 (m, 4H), 1.69–1.51 (m, 2H), 1.35–1.03 (m, 2H), 0.97–0.75 (m, 2H); ESI MS *m/z* 370 [C₁₉H₂₃N₅OS + H]⁺; HPLC >99% (AUC), *t*_R = 10.88 min.

15

Example 35

N-[3-(Aminomethyl)-3,5,5-trimethylcyclohexyl]-2-(thiophen-2-yl)-3*H*-imidazo[4,5-*b*]pyridine-7-carboxamide

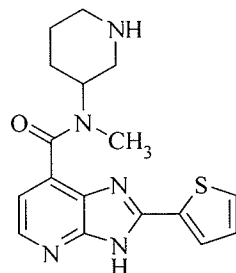


- 20 **[0135]** Following General Procedure A, 2-(thiophen-2-yl)-3*H*-imidazo[4,5-*b*]pyridine-7-carboxylic acid (80 mg, 0.25 mmol) was reacted *tert*-butyl (5-amino-1,3,3-trimethylcyclohexyl)methylcarbamate (140 mg, 0.50 mmol) to afford the desired product (15 mg, 15% yield) as a light yellow semi-solid: ¹H NMR (300 MHz, CD₃OD) δ9.75–9.70 (m, 1H), 8.44 (d, *J* = 5.1 Hz, 1H), 7.97–7.95 (m, 1H), 7.81–7.76 (m, 2H), 7.30–7.27 (m, 1H), 4.55–4.42

(m, 1H), 2.81 (s, 2H), 2.05–1.95 (m, 2H), 1.52–1.11 (m, 13H); ESI MS m/z 398 [$C_{21}H_{27}N_5OS + H$] $^+$; HPLC >99% (AUC), t_R = 12.24 min.

Example 36

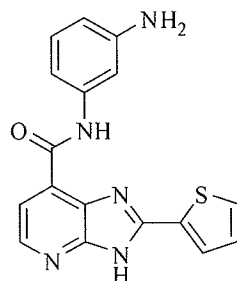
N-Methyl-*N*-(piperidin-3-yl)-2-(thiophen-2-yl)-3*H*-imidazo[4,5-*b*]pyridine-7-carboxamide



[0136] Following General Procedure A, 2-(thiophen-2-yl)-3*H*-imidazo[4,5-*b*]pyridine-7-carboxylic acid (84 mg, 0.26 mmol) was reacted *tert*-butyl 3-(methylamino)piperidine-1-carboxylate (111 mg, 0.52 mmol) to afford the desired product (55 mg, 62% yield) as a white solid: 1H NMR (300 MHz, CD_3OD) δ 8.42 (d, J = 5.1 Hz, 1H), 7.96–7.32 (m, 1H), 7.77–7.75 (m, 1H), 7.32–7.27 (m, 2H), 3.90–3.80 (m, 1H, tautomer), 3.68–3.58 (m, 1H, tautomer), 3.48–3.39 (m, 1H, tautomer), 3.17–2.80 (m, 5H), 2.20–1.93 (m, 3H), 1.48–1.31 (m, 1H, tautomer); ESI MS m/z 342 [$C_{17}H_{19}N_5OS + H$] $^+$; HPLC >99% (AUC), t_R = 9.14 min.

Example 37

N-(3-Aminophenyl)-2-(thiophen-2-yl)-3*H*-imidazo[4,5-*b*]pyridine-7-carboxamide

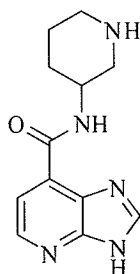


[0137] A solution of *N*-(3-nitrophenyl)-2-(thiophen-2-yl)-3*H*-imidazo[4,5-*b*]pyridine-7-carboxamide (42 mg, 0.12 mmol) and tin (II) chloride (109 mg, 0.58 mmol) in EtOH (5 mL) was heated at 75 °C for 18 h. The reaction mixture was diluted with water (20 mL), the pH was adjusted to 12 using NaOH (1 M) and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were dried, concentrated and purified using preparative HPLC (C18 silica, 10–90% acetonitrile/water with 0.05% TFA). The desired fractions were combined, concentrated and eluted through an ion-exchange column (using methanol and 7 N methanol in ammonia) to

obtain the desired product (5 mg, 13% yield) as a light yellow-brown solid: ^1H NMR (500 MHz, DMSO- d_6) δ 14.27 (s, 1H), 11.49 (s, 1H), 8.51 (d, J = 5.0 Hz, 1H), 8.11 (s, 1H), 7.94 (d, J = 5.0 Hz, 1H), 7.78 (d, J = 5.0 Hz, 1H), 7.48 (s, 1H), 7.35 (t, J = 5.0 Hz, 1H), 7.22 (t, J = 8.0 Hz, 1H), 7.09–7.07 (m, 1H), 6.61–6.60 (m, 1H); ESI MS m/z 336 [$\text{C}_{17}\text{H}_{13}\text{N}_5\text{OS} + \text{H}$] $^+$; HPLC 98.8% (AUC), t_R = 11.56 min.

Example 38

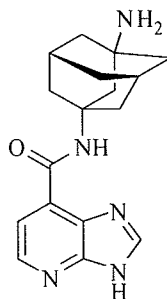
N-(Piperidin-3-yl)-3*H*-imidazo[4,5-*b*]pyridine-7-carboxamide



[0138] Following General Procedure A, 3*H*-imidazo[4,5-*b*]pyridine-7-carboxylic acid (84 mg, 0.52 mmol) was reacted *tert*-butyl 3-aminopiperidine-1-carboxylate (154 mg, 1.0 mmol) to afford the desired product (37 mg, 29% yield) as a light yellow solid: ^1H NMR (300 MHz, CD_3OD) δ 8.55–8.53 (m, 2H), 7.81 (d, J = 4.8 Hz, 1H), 4.38–4.35 (m, 1H), 3.62–3.56 (m, 1H), 3.18–3.07 (m, 2H), 2.21–2.12 (m, 2H), 1.93–1.85 (m, 2H); ESI MS m/z 246 [$\text{C}_{12}\text{H}_{15}\text{N}_5\text{O} + \text{H}$] $^+$; HPLC 99.0% (AUC), t_R = 7.98 min.

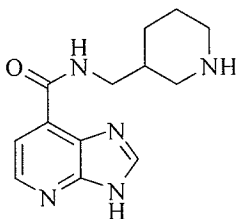
Example 39

N-(Aminoadamant-3-yl)-3*H*-imidazo[4,5-*b*]pyridine-7-carboxamide



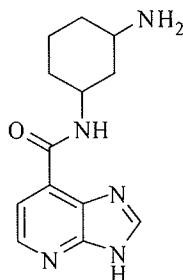
[0139] Following General Procedure A, 3*H*-imidazo[4,5-*b*]pyridine-7-carboxylic acid (80 mg, 0.49 mmol) was reacted *tert*-butyl 3-aminoadamantylcarbamate (260 mg, 1.0 mmol) to afford the desired product (52 mg, 34% yield) as a light yellow solid: ^1H NMR (300 MHz, CD_3OD) δ 8.47 (d, J = 5.1 Hz, 1H), 8.44 (s, 1H), 7.75 (d, J = 5.1 Hz, 1H), 2.34–2.03 (m, 8H), 1.84–1.66 (m, 6H); ESI MS m/z 312 [$\text{C}_{17}\text{H}_{21}\text{N}_5\text{O} + \text{H}$] $^+$; HPLC >99% (AUC), t_R = 9.28 min.

Example 40
N-(Piperidin-3-ylmethyl)-3*H*-imidazo[4,5-*b*]pyridine-7-carboxamide



[0140] Following General Procedure A, 3*H*-imidazo[4,5-*b*]pyridine-7-carboxylic acid (65 mg, 0.39 mmol) was reacted *tert*-butyl 3-(aminomethyl)piperidine-1-carboxylate (130 mg, 0.78 mmol) to afford the desired product (10 mg, 10% yield) as a clear glass: ¹H NMR (500 MHz, CD₃OD) δ8.53–8.49 (m, 2H), 7.79 (d, *J* = 5.0 Hz, 1H), 3.54–3.52 (m, 2H), 3.46–3.44 (m, 1H), 2.97–2.90 (m, 1H), 2.86–2.79 (m, 1H), 2.23–2.14 (m, 1H), 2.04–1.95 (m, 2H), 1.81–1.71 (m, 1H), 1.48–1.25 (m, 2H); ESI MS *m/z* 260 [C₁₃H₁₇N₅O + H]⁺; HPLC 96.4% (AUC), *t_R* = 8.05 min.

Example 41
N-(3-Aminocyclohexyl)-3*H*-imidazo[4,5-*b*]pyridine-7-carboxamide



[0141] Following General Procedure A, 3*H*-imidazo[4,5-*b*]pyridine-7-carboxylic acid (60 mg, 0.37 mmol) was reacted *tert*-butyl 3-aminocyclohexylcarbamate (118 mg, 0.74 mmol) to afford the desired product (30 mg, 31% yield over two steps) as a white solid: ¹H NMR (300 MHz, CD₃OD) δ8.52–8.47 (m, 2H), 7.83–7.78 (m, 1H), 4.54–4.48 (m, 1H, minor diastereomer), 4.13–4.01 (m, 1H, major diastereomer), 3.23–3.11 (m, 1H), 2.46–2.38 (m, 1H, major diastereomer), 2.20–2.27 (m, 1H, minor diastereomer), 2.15–1.71 (m, 4H), 1.63–1.25 (m, 3H); ESI MS *m/z* 260 [C₁₃H₁₇N₅O + H]⁺; HPLC >99% (AUC), *t_R* = 8.36 min (major diastereomer), 8.58 (minor diastereomer).

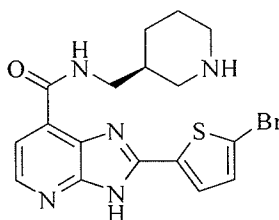
[0142] General Procedure B – synthesis of compounds of formula I as described in Scheme (I): A suspension of crude carboxylic acid E (1.0 equiv) HOBt (1.1 equiv) and EDCI (1.3 equiv) in

THF were stirred at rt for 20 min followed by the addition of the requisite amine (1.2 equiv). The mixture was stirred at rt for 18 h, diluted with EtOAc and washed with water, 5% NaHCO₃ and brine. The combined organic layers were dried and concentrated and purified by preparative HPLC (C18 silica, 10–90% acetonitrile/water with 0.05% TFA). The desired fractions were combined, concentrated and eluted through an ion-exchange column (using methanol and 7 N methanol in ammonia) to obtain the desired products. In some instances, the combined organic layers were dissolved in TFA and stirred at rt for 1 h. The reaction mixture was concentrated and purified by preparative HPLC (C18 silica, 10–90% acetonitrile/water with 0.05% TFA). The desired fractions were combined, concentrated and eluted through an ion-exchange column (using methanol and 7 N methanol in ammonia) to obtain the desired products.

[0143] General Procedure C – synthesis of compounds of formula I as described in Scheme (II): A mixture of intermediate C (1.0 equiv) and selenium dioxide (5.0 equiv) in pyridine were heated at 110 °C for 18 h. The hot reaction mixture was filtered through diatomaceous earth, washed with hot pyridine and CH₃OH and the filtrate was concentrated and dried. The residue was heated with SOCl₂ (10 equiv) at 80 °C for 2 h and the reaction mixture was cooled and concentrated. The residue was dissolved in THF followed by the addition of the requisite amine (1.2 equiv) and triethylamine (2.5 equiv) and the reaction mixture was stirred at rt for 18 h. The reaction was concentrated and purified by preparative HPLC (C18 silica, 10–90% acetonitrile/water with 0.05% TFA). The desired fractions were combined, concentrated and eluted through an ion-exchange column (using methanol and 7 N methanol in ammonia) to obtain the desired products. In some instances, the combined organic layers were dissolved in TFA and stirred at rt for 1 h. The reaction mixture was concentrated and purified by preparative HPLC (C18 silica, 10–90% acetonitrile/water with 0.05% TFA). The desired fractions were combined, concentrated and eluted through an ion-exchange column (using methanol and 7 N methanol in ammonia) to obtain the desired products.

Example 42

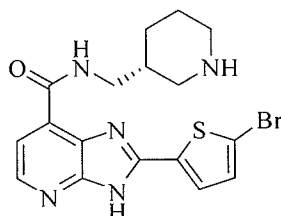
(S)-2-(5-Bromothiophen-2-yl)-N-(piperidin-3-ylmethyl)-3H-imidazo[4,5-b]pyridine-7-carboxamide



[0144] Following General Procedure B, (R)-tert-butyl 3-{[2-(5-bromothiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamido]methyl}piperidine-1-carboxylate (crude) was reacted with TFA to afford the desired product (25 mg, 20% yield) as yellow solid: ^1H NMR (300 MHz, CD_3OD) δ 8.32 (d, $J = 5.1$ Hz, 1H), 8.09 (d, $J = 4.5$ Hz, 1H), 7.68 (d, $J = 3.9$ Hz, 1H), 7.65 (d, $J = 5.4$ Hz, 1H), 7.22 (d, $J = 3.9$ Hz, 1H), 3.54 (d, $J = 6.0$ Hz, 1H), 2.88–2.70 (m, 2H), 2.11–2.08 (m, 2H), 1.98–1.88 (m, 1H), 1.79–1.70 (m, 1H), 1.53–1.45 (m, 1H), 1.30 (d, $J = 7.5$ Hz, 1H); ESI MS m/z 419 $[\text{C}_{17}\text{H}_{17}\text{N}_5\text{O}_2\text{S}]^+$; HPLC 98.4% (AUC), $t_R = 9.70$ min.

Example 43

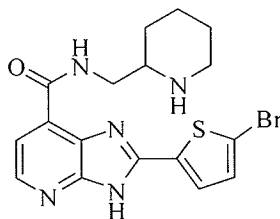
(R)-2-(5-Bromothiophen-2-yl)-N-(piperidin-3-ylmethyl)-3H-imidazo[4,5-b]pyridine-7-carboxamide



[0145] Following General Procedure B, (R)-tert-butyl 3-[(2-(5-bromothiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamido)methyl]piperidine-1-carboxylate (crude) was reacted with TFA to afford the desired product (16 mg, 13% yield) as yellow solid: ^1H NMR (300 MHz, CD_3OD) δ 8.31 (d, $J = 5.4$ Hz, 1H), 7.69 (d, $J = 6.3$ Hz, 1H), 7.64 (d, $J = 5.1$ Hz, 1H), 7.22 (d, $J = 3.9$ Hz, 1H), 3.54 (d, $J = 6.0$ Hz, 1H), 2.87–2.65 (m, 3H), 2.11–2.07 (m, 2H), 1.96–1.91 (m, 2H), 1.78–1.69 (m, 1H), 1.52–1.43 (m, 1H), 1.30 (d, $J = 7.5$ Hz, 1H); ESI MS m/z 419 $[\text{C}_{17}\text{H}_{17}\text{N}_5\text{O}_2\text{S}]^+$; HPLC >99% (AUC), $t_R = 10.41$ min.

Example 44

2-(5-Bromothiophen-2-yl)-N-(piperidin-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-7-carboxamide

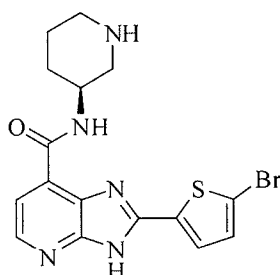


[0146] Following General Procedure B, tert-butyl 3-{[2-(5-bromothiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamido]methyl}piperidine-1-carboxylate (crude) was reacted with TFA to afford the desired product (27 mg, 36% yield) as a yellow solid: ^1H NMR (500 MHz, CD_3OD) δ 8.32 (d, $J = 5.5$ Hz, 1H), 7.68 (d, $J = 4.0$ Hz, 1H), 7.64 (d, $J = 5.5$ Hz, 1H),

7.22 (d, $J = 4.0$ Hz, 1H), 3.68–3.61 (m, 2H), 3.35–3.33 (m, 1H), 3.26–3.14 (m, 2H), 2.86–2.81 (m, 1H), 2.02 (d, $J = 14.5$ Hz, 1H), 1.94 (d, $J = 6.0$ Hz, 1H), 1.61–1.48 (m, 2H), 1.30 (s, 1H); ESI MS m/z 420 $[C_{17}H_{17}N_5O_2S]^+$; HPLC >99% (AUC), $t_R = 11.85$ min.

Example 45

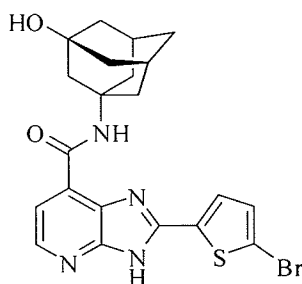
5 (S)-2-(5-Bromothiophen-2-yl)-N-(piperidin-3-yl)-1H-imidazo[4,5-b]pyridine-7-carboxamide



[0147] Following General Procedure B, 2-(5-Bromothiophen-2-yl)-7-methyl-1H-imidazo[4,5-b]pyridine (0.16 g, 0.59 mmol) was reacted (S)-tert-butyl 3-aminopiperidine-1-carboxylate (0.15 g, 0.77 mmol) to afford the desired product (31 mg, 13% yield) as yellow solid: 1H NMR (300 MHz, DMSO- d_6) δ 9.86 (d, $J = 8.5$ Hz, 1H), 8.33 (d, $J = 5.1$ Hz, 1H), 7.73 (d, $J = 3.9$ Hz, 1H), 7.54 (d, $J = 5.1$ Hz, 1H), 7.37 (d, $J = 3.9$ Hz, 1H), 4.11 (bs, 1H), 2.88–2.85 (m, 1H), 2.84–2.81 (m, 2H), 2.01 (bs, 2H), 1.75–1.68 (m, 2H); ESI MS m/z 406 $[C_{16}H_{16}BrN_5OS + H]^+$.

Example 46

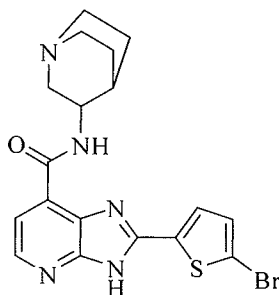
15 2-(5-bromothiophen-2-yl)-N-3-(aminoadamane-1-ol)-3-yl)-1H-imidazo[4,5-b]pyridine-7-carboxamide



[0148] Following General Procedure B, 2-(5-bromothiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxylic acid (300 mg, 0.92 mmol) was reacted with 3-aminoadamantan-1-ol (310 mg, 1.8 mmol) to afford the desired product (170 mg, 40% yield) as a light yellow solid: 1H NMR (500 MHz, DMSO) δ 14.18 (s, 1H), 9.34 (s, 1H), 8.45 (d, $J = 5.0$ Hz, 1H), 7.83 (d, $J = 4.0$ Hz, 1H), 7.68 (d, $J = 5.0$ Hz, 1H), 7.46 (d, $J = 4.0$ Hz, 1H), 4.62 (s, 1H), 4.02 (s, 1H), 3.16 (s, 1H), 2.24 (bs, 2H), 1.91 (s, 1H), 2.08–1.99 (m, 6H), 1.66–1.58 (m, 5H), 1.52 (d, $J = 12.5$ Hz, 1H); APCI MS m/z , 474 $[(C_{21}H_{21}BrN_4O_2S + 2) H]^+]^+$; HPLC >99% (AUC), $t_R = 13.73$ min.

Example 47

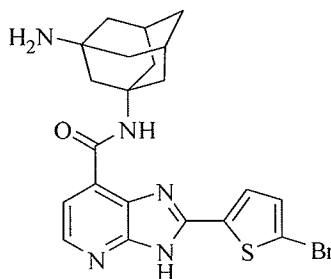
2-(5-bromothiophen-2-yl)-N-(quinuclidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide



[0149] Following General Procedure B, 2-(5-bromothiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxylic acid (300 mg, 0.92 mmol) was reacted with quinuclidin-3-amine (370 mg, 1.8 mmol) to afford the desired product (64 mg, 20% yield) as a yellow solid: ^1H NMR (500 MHz, CD_3OD) δ 8.38 (d, $J = 5.0$ Hz, 1H), 7.70 (d, $J = 5.0$ Hz, 1H), 7.62 (d, $J = 4.0$ Hz, 1H), 7.22 (d, $J = 4.0$ Hz, 1H), 4.50–4.47 (m, 1H), 3.85–3.80 (m, 1H), 3.45 (t, $J = 8.0$ Hz, 2H), 3.35–3.26 (m, 3H), 1.91 (s, 1H), 2.44–2.39 (m, 2H), 2.13–2.04 (m, 2H), 2.00 (d, $J = 8.0$ Hz, 1H), 1.13–1.01 (m, 2H); ESI MS m/z , 433 $[\text{C}_{18}\text{H}_{18}\text{BrN}_5\text{OS} + \text{H}]^+$; HPLC 94.5% (AUC), $t_R = 9.14$ min.

Example 48

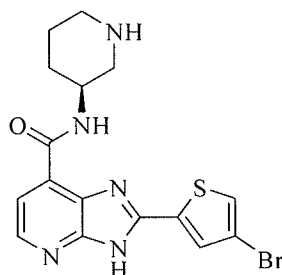
2-(5-bromothiophen-2-yl)-N-(1,3-diaminoadamane-3-yl)-1H-imidazo[4,5-b]pyridine-7-carboxamide



[0150] Following General Procedure #, (S)-tert-butyl 3-(2-(5-bromothiophen-2-yl)-1H-imidazo[4,5-b]pyridine-7-carboxamido)1,3-diaminoadamantane-1-carboxylate (60 mg, 0.105 mmol) was reacted with TFA:DCM (50:50) to afford the desired product (32 mg, 66% yield) as a white solid: ^1H NMR (500 MHz, DMSO) δ 10.07 (s, 1H), 8.21 (d, $J = 5.0$ Hz, 1H), 7.59 (d, $J = 4.0$ Hz, 1H), 7.53 (bs, 1H), 7.39 (d, $J = 5.0$ Hz, 1H), 7.30 (d, $J = 4.0$ Hz, 1H), 2.32 (bs, 4H), 2.18 (d, $J = 11.0$ Hz, 2H), 2.06 (t, $J = 12$ Hz, 2H), 1.90–1.68 (m, 7H), 1.58 (d, $J = 12.5$ Hz, 1H); ESI MS m/z 473 $[\text{C}_{21}\text{H}_{22}\text{BrN}_5\text{OS}]^+$; HPLC 95.12% (AUC), $t_R = 11.79$ min.

Example 49

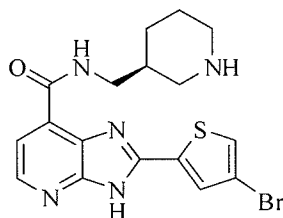
(S)-2-(4-Bromothiophen-2-yl)-N-(piperidin-3-yl)-1H-imidazo[4,5-b]pyridine-7-carboxamide



[0151] Following General Procedure B, 2-(4-bromothiophen-2-yl)-1H-imidazo[4,5-b]pyridine-7-carboxylic acid (0.032 g, 0.10 mmol) was reacted (S)-tert-butyl 3-aminopiperidine-1-carboxylate (0.024 g, 1.2 mmol) to afford the desired product (25 mg, 61% yield) as yellow solid: ^1H NMR (500 MHz, CD_3OD) δ 8.37 (d, $J = 5.0$ Hz, 1H), 7.82 (d, $J = 1.0$ Hz, 1H), 7.70 (d, $J = 5.0$ Hz, 1H), 7.64 (d, $J = 1.0$ Hz, 1H), 4.20–4.17 (m, 1H), 3.32 (s, 1H), 3.07–3.04 (m, 1H), 2.94–2.89 (m, 2H), 2.17–2.16 (m, 1H), 2.04–2.02 (m, 1H), 1.93 (s, 1H), 1.85–1.77 (m, 2H), 1.30 (d, $J = 11.5$ Hz, 2H); ESI MS m/z 407 $[\text{C}_{16}\text{H}_{16}\text{BrN}_5\text{OS} + \text{H}]^+$ HPLC 98.8% (AUC), $t_R = 10.21$ min.

Example 50

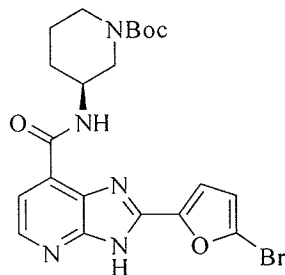
(S)-2-(4-bromothiophen-2-yl)-N-(piperidin-3-ylmethyl)-3H-imidazo[4,5-b]pyridine-7-carboxamide



[0152] Following General Procedure B, 2-(4-bromothiophen-2-yl)-1H-imidazo[4,5-b]pyridine-7-carboxylic acid (0.064 g, 0.20 mmol) was reacted (R)-tert-butyl 3-(aminomethyl)piperidine-1-carboxylate (0.051 g, 0.24 mmol) to afford the desired product (25 mg, 30% yield) as brown solid: ^1H NMR (500 MHz, CD_3OD) δ 8.30 (d, $J = 5.5$ Hz, 1H), 7.81 (d, $J = 1.5$ Hz, 1H), 7.63 (d, $J = 5.0$ Hz, 1H), 7.55 (d, $J = 1.0$ Hz, 1H), 3.44–3.43 (m, 2H), 3.41–3.34 (m, 2H), 3.27–3.16 (m, 1H), 2.84–2.78 (m, 1H), 2.79 (t, $J = 11.5$ Hz, 1H), 2.09–2.07 (m, 2H), 1.95–1.91 (m, 1H), 1.73–1.69 (m, 1H), 1.51–1.45 (m, 2H), 1.30 (d, $J = 12.0$ Hz, 1H); ESI MS m/z 421 $[\text{C}_{17}\text{H}_{18}\text{BrN}_5\text{OS} + \text{H}]^+$; HPLC 97.9% (AUC), $t_R = 10.25$ min.

Example 51

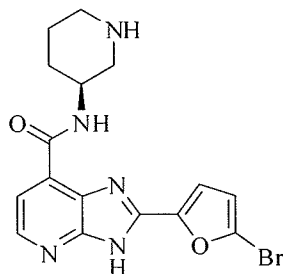
(S)-tert-Butyl 3-[2-(5-bromofuran-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamido]piperidine-1-carboxylate



- 5 [0153] Following General Procedure B, 2-(5-bromofuran-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxylic acid (150 mg, 0.49 mmol) was reacted with (S)-tert-butyl 3-aminopiperidine-1-carboxylate (195 mg, 0.97 mmol) to afford the desired product (110 mg, 47% yield) as a yellow solid: ^1H NMR (500 MHz, CD_3OD) δ 10.12 (bs, 1H), 8.46 (d, $J = 5.0$ Hz, 1H), 7.82 (d, $J = 5.0$ Hz, 1H), 7.40 (d, $J = 3.5$ Hz, 1H), 6.76 (d, $J = 3.5$ Hz, 1H), 4.25–4.24 (m, 1H), 3.93 (bs, 3H),
 10 3.16 (s, 1H), 2.05–2.02 (m, 2H), 1.91 (s, 1H), 1.72 (s, 1H), 1.48–1.45 (m, 2H), 1.35–1.03 (m, 10H); ESI MS m/z , 490 [$\text{C}_{21}\text{H}_{24}\text{BrN}_5\text{O}_4 + \text{H}$] $^+$; HPLC >99% (AUC), $t_R = 14.41$ min.

Example 52

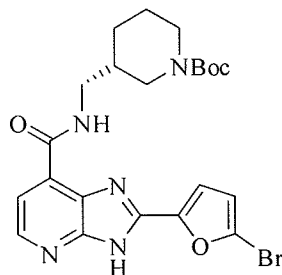
(S)-2-(5-bromofuran-2-yl)-N-(piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide



- 15 [0154] Following General Procedure B, (S)-tert-butyl 3-(2-(5-bromofuran-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamido)piperidine-1-carboxylate (100 mg, 0.20 mmol) to afford the desired product (47 mg, 58% yield) as a yellow solid: ^1H NMR (500 MHz, DMSO) δ 8.49 (d, $J = 5.0$ Hz, 1H), 7.17 (bs, 2H), 6.97 (s, 1H), 4.28–4.23 (m, 1H), 3.46 (d, $J = 9.5$ Hz, 1H), 3.24 (d, $J = 12.5$ Hz, 1H), 3.10–2.98 (m, 2H), 2.09 (bs, 1H), 1.98 (bs, 1H), 1.79–1.75 (m, 2H), 1.27–
 20 1.23 (m, 1H); ESI MS m/z 390 [$\text{C}_{16}\text{H}_{16}\text{BrN}_5\text{O}_2$] $^+$; HPLC 97.0% (AUC), $t_R = 8.12$ min.

Example 53

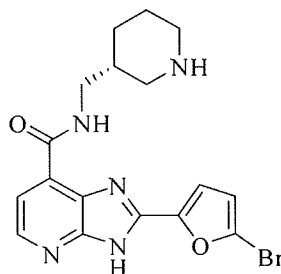
(S)-*tert*-Butyl 3-{{[2-(5-bromofuran-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamido]methyl}piperidine-1-carboxylate



- 5 [0155] Following General Procedure B, (2-(5-bromofuran-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxylic acid (150 mg, 0.49 mmol) was reacted with (S)-*tert*-butyl 3-(aminomethyl)piperidine-1-carboxylate (210 mg, 0.97 mmol) to afford the desired product (70 mg, 28% yield) as a yellow solid: ^1H NMR (500 MHz, CD_3OD) δ 8.36 (d, J = 5.0 Hz, 1H), 7.69 (d, J = 5.0 Hz, 1H), 7.35 (bs, 1H), 6.65 (d, J = 3.0 Hz, 1H), 3.99 (d, J = 11.0 Hz, 1H), 3.79 (d, J = 13.0 Hz, 1H), 3.43–3.34 (m, 2H), 2.79 (d, J = 5.0 Hz, 2H), 1.89–1.76 (m, 2H), 1.6–1.64 (m, 1H), 1.44–1.22 (m, 12H); ESI MS m/z 505 [$\text{C}_{22}\text{H}_{26}\text{BrN}_5\text{O}_4 + \text{H}$] $^+$; HPLC >99% (AUC), t_R = 14.90 min.

Example 54

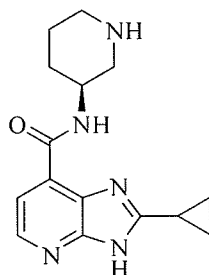
(R)-2-(5-Bromofuran-2-yl)-N-(piperidin-3-ylmethyl)-3H-imidazo[4,5-b]pyridine-7-carboxamide



- 15 [0156] Following General Procedure B, (S)-*tert*-butyl 3-((2-(5-bromofuran-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamido)methyl)piperidine-1-carboxylate (50 mg, 0.10 mmol) was reacted with TFA to afford the desired product (11 mg, 30% yield) as a yellow glass: ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 9.66 (s, 1H), 8.36 (d, J = 5.0 Hz, 1H), 7.57 (d, J = 4.5 Hz, 1H), 7.37 (d, J = 3.0 Hz, 1H), 6.87 (d, J = 3.5 Hz, 1H), 3.47–3.38 (m, 2H), 3.33 (d, J = 10.5 Hz, 1H), 3.24 (d, J = 11.0 Hz, 1H), 2.80 (t, J = 11.6 Hz, 1H), 2.71 (t, J = 11.9 Hz, 1H), 2.07 (s, 1H), 1.84–1.65 (m, 2H), 1.68–1.60 (m, 2H), 1.38–1.31 (m, 1H), 0.65 (bs, 1H); ESI MS m/z 405 [$\text{C}_{17}\text{H}_{18}\text{BrN}_5\text{O}_2 + \text{H}$] $^+$; HPLC 98.3% (AUC), t_R = 8.22 min.

Example 55

(S)-2-Cyclopropyl-N-(piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide

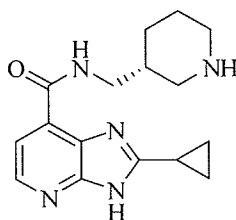


[0157] Following General Procedure B, 2-cyclopropyl-3H-imidazo[4,5-b]pyridine-7-carboxylic acid (0.081 g, 0.40 mmol) was reacted (S)-tert-butyl 3-aminopiperidine-1-carboxylate (0.096 g, 0.48 mmol) to afford the desired product (69 mg, 60% yield) as yellow solid: ¹H NMR (300 MHz, CD₃OD) δ 8.32 (d, *J* = 5.1 Hz, 1H), 7.67 (d, *J* = 5.1 Hz, 1H), 4.14–4.11 (m, 1H), 3.04–3.00 (m, 1H), 2.80–2.72 (m, 2H), 2.23–2.22 (m, 1H), 2.14–2.11 (m, 1H), 1.91–1.86 (m, 1H), 1.74–1.68 (m, 2H), 1.31–1.24 (m, 5H); ESI MS *m/z* 286 [C₁₅H₁₉N₅O + H]⁺.

10

Example 56

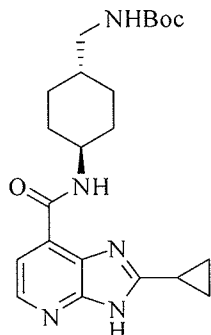
(S)-2-Cyclopropyl-N-(piperidin-3-ylmethyl)-3H-imidazo[4,5-b]pyridine-7-carboxamide



[0158] Following General Procedure B, 2-cyclopropyl-3H-imidazo[4,5-b]pyridine-7-carboxylic acid (0.081 g, 0.40 mmol) was reacted (R)-tert-butyl 3-(aminomethyl)piperidine-1-carboxylate (0.10 g, 0.48 mmol) to afford the desired product (78 mg, 65% yield) as brown solid: ¹H NMR (300 MHz, CD₃OD) δ 8.32 (d, *J* = 5.1 Hz, 1H), 7.67 (d, *J* = 5.1 Hz, 1H), 3.42 (d, *J* = 6.3 Hz, 2H), 3.18 (d, *J* = 12.3 Hz, 1H), 3.07–3.01 (m, 1H), 2.64–2.55 (m, 1H), 2.50 (t, *J* = 10.8 Hz, 1H), 2.28–2.20 (m, 1H), 1.98–1.74 (m, 3H), 1.63–1.50 (m, 1H), 1.36–1.22 (m, 5H); ESI MS *m/z* 300 [C₁₆H₂₁N₅O + H]⁺; HPLC >99% (AUC), *t_R* = 6.58 min.

Example 57

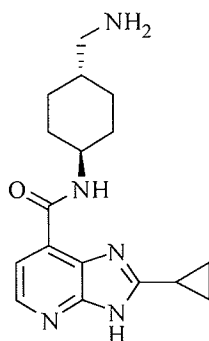
tert-Butyl [(1R,4R)-4-(2-cyclopropyl-3H-imidazo[4,5-b]pyridine-7-carboxamido)cyclohexyl]methylcarbamate



- 5 **[0159]** Following General Procedure B, 2-cyclopropyl-3H-imidazo[4,5-b]pyridine-7-carboxylic acid (80 mg, 0.39 mmol) was reacted with tert-butyl ((1r,4r)-4-aminocyclohexyl) methylcarbamate (110 mg, 0.48 mmol) to afford the desired product (45 mg, 30% yield) as a white solid: ¹H NMR (500 MHz, CD₃OD) δ 8.33 (d, *J* = 5.2 Hz, 1H), 7.68 (d, *J* = 5.5 Hz, 1H), 3.91–3.87 (m, 1H), 2.95 (d, *J* = 6.5 Hz, 2H), 2.27–2.24 (m, 1H), 2.15 (d, *J* = 10.5 Hz, 2H), 1.88
10 (d, *J* = 11.5 Hz, 2H), 1.44 (s, 9H), 1.40–1.35 (m, 2H), 1.26–1.24 (m, 4H), 1.18–1.15 (m, 2H); ESI MS *m/z* 414 [C₂₂H₃₁N₅O₃ + H]⁺; HPLC >99% (AUC), *t_R* = 10.41 min.

Example 58

N-[(1R,4R)-4-(Aminomethyl)cyclohexyl]-2-cyclopropyl-3H-imidazo[4,5-b]pyridine-7-carboxamide



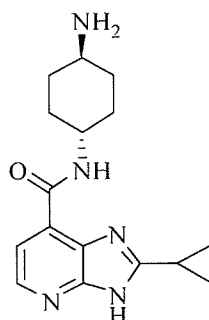
15

- [0160]** Following General Procedure B, tert-butyl ((1r,4r)-4-(2-cyclopropyl-3H-imidazo[4,5-b]pyridine-7-carboxamido)cyclohexyl)methylcarbamate (50 mg, 0.12 mmol) was reacted with TFA to afford the desired product (17 mg, 46% yield) as a white solid: ¹H NMR (500 MHz, DMSO) δ 9.36 (s, 1H), 8.31 (d, *J* = 5.0 Hz, 1H), 7.58 (d, *J* = 5.5 Hz, 1H), 3.81–3.75 (m, 1H),
20 2.56 (d, *J* = 6.5 Hz, 2H), 2.24–2.21 (m, 1H), 2.05 (d, *J* = 12.0 Hz, 2H), 1.85 (d, *J* = 12.5 Hz, 2H),

1.43 (bs, 1H), 1.30–1.25 (m, 2H), 1.20–1.17 (m, 6H); ESI MS m/z 314 [$C_{17}H_{23}N_5O + H$] $^+$; HPLC 97.7% (AUC), $t_R = 12.97$ min.

Example 59

N-[(1R,4R)-4-Aminocyclohexyl]-2-cyclopropyl-3H-imidazo[4,5-b]pyridine-7-carboxamide



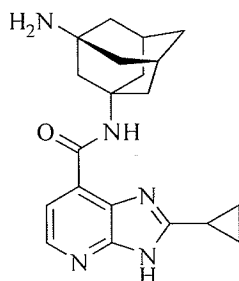
5

[0161] Following General Procedure B, 2-cyclopropyl-3H-imidazo[4,5-b]pyridine-7-carboxylic acid (100 mg, 0.49 mmol) was reacted with (1R,4R)-cyclohexane-1,4-diamine (210 mg, 0.98 mmol) to afford the desired product (31 mg, 27% yield) as a yellow solid: 1H NMR (500 MHz, CD_3OD) 8.45 (dd, $J = 5.0, 1.0$ Hz, 1H), 7.76 (d, $J = 5.5$ Hz, 1H), 3.96–3.93 (m, 1H), 3.31–3.30 (m, 1H), 3.24–3.20 (m, 1H), 2.25–2.15 (m, 5H), 1.64–1.54 (m, 4H), 1.25–1.22 (m, 4H); ESI MS m/z 300 [$C_{16}H_{21}N_5O + H$] $^+$; HPLC >99% (AUC), $t_R = 11.65$ min.

10

Example 60

N-(4-Aminocadamantyl)-2-cyclopropyl-3H-imidazo[4,5-b]pyridine-7-carboxamide



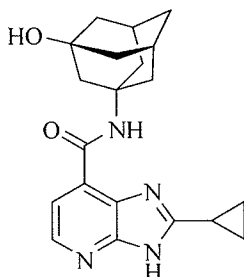
15

[0162] Following General Procedure B, 2-cyclopropyl-3H-imidazo[4,5-b]pyridine-7-carboxylic acid (100 mg, 0.49 mmol) was reacted with 1,3-diamineadamantane hydrochloride (334 mg, 0.98 mmol) to afford the desired product (7 mg, 22% yield) as a yellow solid: 1H NMR (500 MHz, DMSO) δ 9.27 (bs, 1H), 8.42 (bs, 1H), 8.25 (s, 3H), 7.72–7.61 (m, 1H), 2.69 (s, 1H), 2.36 (bs, 3H), 2.30 (s, 2H), 2.12 (d, $J = 11.5$ Hz, 2H), 2.00 (d, $J = 11.5$ Hz, 2H), 1.82 (q, $J = 11.5$ Hz, 4H), 1.66 (d, $J = 12.0$ Hz, 1H), 1.56 (d, $J = 12.0$ Hz, 1H), 1.26 (d, $J = 22.0$ Hz, 4H); ESI MS m/z 352 [$C_{20}H_{25}N_5O + H$] $^+$; HPLC 96.2% (AUC), $t_R = 7.42$ min.

20

Example 61

N-(4-Hydroxyadamantyl)-2-cyclopropyl-3H-imidazo[4,5-b]pyridine-7-carboxamide

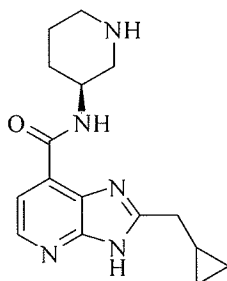


[0163] Following General Procedure B, 2-cyclopropyl-3H-imidazo[4,5-b]pyridine-7-

- 5 carboxylic acid (150 mg, 0.73 mmol) was reacted with 3-aminoadamantan-1-ol (247 mg, 1.48 mmol) to afford the desired product (130 mg, 50% yield) as a white solid: ^1H NMR (500 MHz, DMSO) δ 13.33 (s, 1H), 9.49 (s, 1H), 8.31 (d, $J = 5.0$ Hz, 1H), 7.58 (d, $J = 5.0$ Hz, 1H), 5.75 (bs, 1H), 2.20 (s, 3H), 3.16 (s, 1H), 2.03–1.93 (m, 5H), 1.78–1.73 (m, 1H), 1.63–1.54 (m, 5H), 1.50–1.47 (m, 1H), 1.20–1.14 (m, 3H); APCI MS m/z , 353 $[(\text{C}_{20}\text{H}_{24}\text{N}_4\text{O}_2 + \text{H})^+]$; HPLC >96.05%
 10 (AUC), $t_R = 10.82$ min.

Example 62

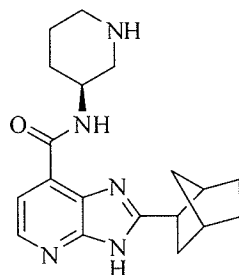
(S)-2-(Cyclopropylmethyl)-N-(piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide



- [0164] Following General Procedure B, 2-(cyclopropylmethyl)-3H-imidazo[4,5-b]pyridine-7-
 15 carboxylic acid (61 mg, 0.28 mmol) was reacted with (S)-1-Boc-3-aminopiperidine (58 mg, 0.29 mmol) to afford the desired product (42 mg, 50% yield) as an off-white solid: ^1H NMR (CD_3OD , 500 MHz) δ 8.39 (d, $J = 5.0$ Hz, 1H), 7.71 (d, $J = 5.0$ Hz, 1H), 4.12 (br, 1H), 3.30–3.35 (m, 1H), 3.16 (br, 1H), 2.89 (d, $J = 7.0$ Hz, 2H), 2.70–2.66 (m, 2H), 2.14 (br, 1H), 1.87 (br, 1H), 1.67 (br, 2H), 1.27–1.23 (m, 1H), 0.62–0.62 (m, 2H), 0.39–0.36 (m, 2H); ESI MS m/z 300 $[\text{C}_{16}\text{H}_{21}\text{N}_5\text{O} + \text{H}]^+$.
 20

Example 63a and 63b

2-(Bicyclo[2.2.1]heptan-2-yl)-N-[(S)-piperidin-3-yl]-3H-imidazo[4,5-b]pyridine-7-carboxamide



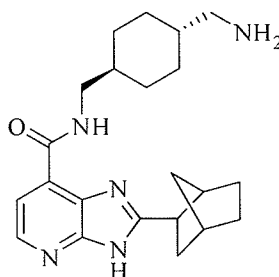
[0165] Following General Procedure B, 2-(bicyclo[2.2.1]heptan-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxylic acid (110 mg, 0.29 mmol) was reacted with (S)-1-Boc-3-aminopiperidine (104 mg, 0.52 mmol) to afford the desired product as two pairs of diastereomers:

[0166] Example 63a – Diastereomers A and B (8 mg, 12% yield) obtained as a white solid: ^1H NMR (CD_3OD , 500 MHz) δ 8.37 (d, $J = 5.0$ Hz, 1H), 7.73 (d, $J = 5.0$ Hz, 1H), 4.15 (br, 1H), 3.49–3.47 (m, 1H), 3.05–3.02 (m, 1H), 2.80–2.77 (m, 3H), 2.41 (s, 1H), 2.19–1.20 (m, 13H); ESI MS m/z 340 [$\text{C}_{19}\text{H}_{25}\text{N}_5\text{O} + \text{H}$] $^+$.

[0167] Example 63b – Diastereomers C and D (36 mg, 53% yield) obtained as a white solid: ^1H NMR (CD_3OD , 500 MHz) δ 8.36 (d, $J = 5.0$ Hz, 1H), 7.71 (d, $J = 5.0$ Hz, 1H), 4.10 (br, 1H), 3.24 (d, $J = 7.5$ Hz, 1H), 3.06–3.03 (m, 1H), 2.96–2.93 (m, 1H), 2.75–2.70 (m, 2H), 2.72 (br, 1H), 2.45 (s, 1H), 2.26 (br, 1H), 2.16 (br, 1H), 1.91–1.28 (m, 10H); ESI MS m/z 340 [$\text{C}_{19}\text{H}_{25}\text{N}_5\text{O} + \text{H}$] $^+$.

Example 64

N-[(1R,4R)-4-(aminomethyl)cyclohexyl]methyl}-2-(bicyclo[2.2.1]heptan-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide

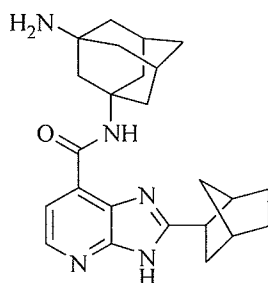


[0168] Following General Procedure B, 2-(bicyclo[2.2.1]heptan-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxylic acid (110 mg, 0.29 mmol) was reacted with tert-butyl [(1R,4R)-4-

(aminomethyl)cyclohexyl)methylcarbamate (120 mg, 0.52 mmol) to afford the desired product (28 mg, 25% yield) as a white solid: ^1H NMR (CD_3OD , 500 MHz) δ 8.36 (d, $J = 5.0$ Hz, 1H), 7.71 (d, $J = 5.0$ Hz, 1H), 3.35 (t, $J = 6.0$ Hz, 2H), 2.69–2.65 (m, 2H), 2.02–1.93 (m, 2H), 1.90–1.80 (m, 2H), 1.61–1.44 (m, 2H), 1.23–0.92 (m, 4H), 2.16 (br, 1H), 1.91–1.28 (m, 10H); ESI MS m/z 382 [$\text{C}_{22}\text{H}_{31}\text{N}_5\text{O} + \text{H}$] $^+$; HPLC >99% (AUC), $t_R = 9.17$ min.

Example 65

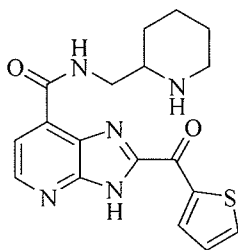
N-(3-aminoadamantyl)-2-(bicyclo[2.2.1]heptan-2-yl)-3H-imidazo[4,5-*b*]pyridine-7-carboxamide



[0169] Following General Procedure B, 2-(bicyclo[2.2.1]heptan-2-yl)-3H-imidazo[4,5-*b*]pyridine-7-carboxylic acid (110 mg, 0.29 mmol) was reacted with *N*-(3-aminoadamantyl)-2-(bicyclo[2.2.1]heptan-2-yl)-3H-imidazo[4,5-*b*]pyridine-7-carboxamide (mixtures of diastereomers: 10 mg, 9%) as a white solid: ^1H NMR (CD_3OD , 500 MHz) δ 8.36 (m, 1H), 7.71 (m, 1H), 2.61–1.28 (m, 25H); ESI MS m/z 406 [$\text{M} + \text{H}$] $^+$; HPLC 97.3% (AUC), $t_R = 9.42$ min.

Example 66

N-(piperidin-2-ylmethyl)-2-(thiophene-2-carbonyl)-3H-imidazo[4,5-*b*]pyridine-7-carboxamide

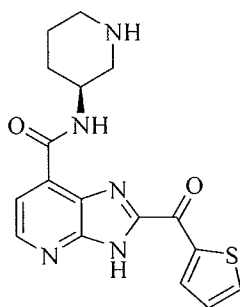


[0170] Following General Procedure C, 7-methyl-2-(thiophen-2-ylmethyl)-3H-imidazo[4,5-*b*]pyridine (0.16 g, 0.50 mmol) was reacted SeO_2 (2.9 g, 6.7 mmol) and SOCl_2 (10 mL) to afford 0.96 g of the intermediate acid chloride. An aliquot of the crude acid chloride (0.16 g) was reacted with piperidin-3-ylmethanamine (0.13 g, 0.60 mmol) to afford the product as brown-yellow solid (0.011 g, 6% yield): ^1H NMR (500 MHz, CD_3OD) δ 8.21 (d, $J = 3.5$ Hz, 1H), 8.09 (d, $J = 4.5$ Hz, 1H), 7.85 (d, $J = 3.5$ Hz, 1H), 7.38 (d, $J = 4.5$ Hz, 1H), 7.16 (t, $J = 4.0$ Hz, 1H),

3.87 (d, $J = 11.5$ Hz, 1H), 3.78–3.68 (m, 2H), 3.48–3.44 (m, 1H), 3.17–3.12 (m, 2H), 2.15 (d, $J = 14.0$ Hz, 1H), 2.03 (d, $J = 10.0$ Hz, 1H), 1.93 (d, $J = 8.0$ Hz, 1H), 1.78–1.72 (m, 1H), 1.65–1.60 (m, 1H); ESI MS m/z 370 [$C_{17}H_{17}N_5O_2S + H$] $^+$; HPLC >99% (AUC), $t_R = 9.41$ min.

Example 67

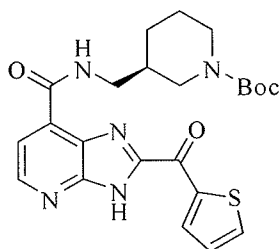
5 (S)-N-(Piperidin-3-yl)-2-(thiophene-2-carbonyl)-3H-imidazo[4,5-b]pyridine-7-carboxamide



[0171] Following General Procedure C, 7-methyl-2-(thiophen-2-ylmethyl)-3H-imidazo[4,5-b]pyridine (0.16 g, 0.50 mmol) was reacted with SeO_2 (2.9 g, 6.7 mmol) and $SOCl_2$ (10 mL) to afford 0.96 g of the intermediate acid chloride. An aliquot of the crude acid chloride (0.16 g) was
 10 reacted with (S)-tert-butyl 3-aminopiperidine-1-carboxylate (0.096 g, 0.48 mmol) to afford the desired product (9 mg, 5% yield) as yellow solid: 1H NMR (500 MHz, $DMSO-d_6$) δ 9.77 (bs, 1H), 8.52 (bs, 1H), 8.40 (bs, 1H), 8.1 (bs, 1H), 7.56 (bs, 1H), 7.30 (bs, 1H), 3.07 (bs, 2H), 2.09–2.55 (m, 2H), 1.80–1.74 (m, 3H); ESI MS m/z 356 [$C_{17}H_{17}N_5O_2S + H$] $^+$.

Example 68

15 (R)-tert-Butyl 3-([2-(thiophene-2-carbonyl)-3H-imidazo[4,5-b]pyridine-7-carboxamido]methyl)piperidine-1-carboxylate

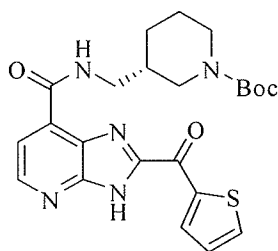


[0172] Following General Procedure B, 2-(thiophene-2-carbonyl)-3H-imidazo[4,5-b]pyridine-7-carboxylic acid (0.18 g, 0.68 mmol) was reacted with (R)-piperidin-3-ylmethanamine (0.17 g, 0.78 mmol) to afford the desired product (0.20 g, 67% yield) as a brown-yellow solid: 1H NMR (500 MHz, $DMSO-d_6$) δ 9.23 (s, 1H), 8.73 (d, $J = 5.0$ Hz, 1H), 8.63 (s, 1H), 8.26 (d, $J = 4.5$ Hz, 1H), 7.85 (d, $J = 4.5$ Hz, 1H), 7.37 (d, $J = 8.5$ Hz, 1H), 3.98 (bs, 1H), 3.77 (d, $J = 11.5$ Hz, 1H),
 20

3.44 (m, 2H), 2.83–2.79 (m, 2H), 1.90–1.65 (m, 3H), 1.34 (m, 11H); ESI MS m/z 470 $[C_{17}H_{17}N_5O_2S + H]^+$; HPLC 98.1% (AUC), $t_R = 16.73$ min.

Example 69

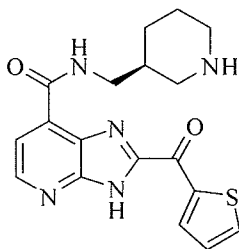
(S)-tert-Butyl 3-{[(2-(thiophene-2-carbonyl)-3H-imidazo[4,5-b]pyridine-7-carboxamido)methyl]piperidine-1-carboxylate



[0173] Following General Procedure B, 2-(thiophene-2-carbonyl)-3H-imidazo[4,5-b]pyridine-7-carboxylic acid (0.18 g, 0.68 mmol) was reacted with (S)-piperidin-3-ylmethanamine (0.17 g, 0.78 mmol) to afford the desired product (0.21 g, 69% yield) as a brown-yellow solid: 1H NMR (500 MHz, $DMSO-d_6$) δ 9.23 (s, 1H), 8.73 (d, $J = 5.0$ Hz, 1H), 8.63 (s, 1H), 8.26 (d, $J = 4.5$ Hz, 1H), 7.85 (d, $J = 4.0$ Hz, 1H), 7.37 (d, $J = 8.0$ Hz, 1H), 3.98 (bs, 1H), 3.77 (d, $J = 14.0$ Hz, 1H), 3.45 (m, 2H), 2.83–2.79 (m, 1H), 1.90–1.76 (m, 2H), 1.66 (d, $J = 9.0$ Hz, 1H), 1.34 (m, 11H); ESI MS m/z 470 $[C_{17}H_{17}N_5O_2S + H]^+$ HPLC >99% (AUC), $t_R = 18.91$ min.

Example 70

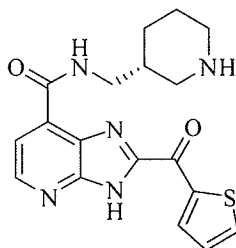
(S)-N-(Piperidin-3-ylmethyl)-2-(thiophene-2-carbonyl)-3H-imidazo[4,5-b]pyridine-7-carboxamide



[0174] Following General Procedure B, (R)-tert-butyl 3-{[2-(thiophene-2-carbonyl)-3H-imidazo[4,5-b]pyridine-7-carboxamido)methyl]piperidine-1-carboxylate (0.025 g, 0.053 mmol) was treated with TFA to afford the desired product (0.019 g, 97% yield) as a brown-yellow solid: 1H NMR (500 MHz, $DMSO-d_6$) δ 10.13 (bs, 1H), 8.51 (d, $J = 3.0$ Hz, 1H), 8.46 ($J = 4.5$ Hz, 1H), 8.07 (d, $J = 4.5$ Hz, 1H), 7.56 (d, $J = 4.0$ Hz, 1H), 7.15 (t, $J = 4.0$ Hz, 1H), 3.51–3.42 (m, 4H), 3.16 (s, 2H), 2.82–2.71 (m, 2H), 2.08 (bs, 1H), 1.92 (d, $J = 11.5$ Hz, 1H), 1.82 (d, $J = 14.0$ Hz, 1H), 1.62–1.60 (m, 1H), 1.39–1.34 (m, 1H); ESI MS m/z 370 $[C_{17}H_{17}N_5O_2S + H]^+$.

Example 71

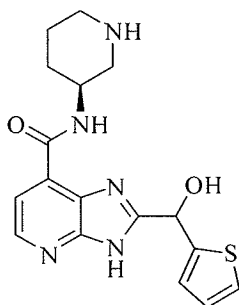
(R)-N-(piperidin-3-ylmethyl)-2-(thiophene-2-carbonyl)-3H-imidazo[4,5-b]pyridine-7-carboxamide



- 5 **[0175]** Following General Procedure B, (S)-tert-butyl 3-{[2-(thiophene-2-carbonyl)-3H-imidazo[4,5-b]pyridine-7-carboxamido]methyl}piperidine-1-carboxylate (0.025 g, 0.053 mmol) was treated with TFA to afford the desired product (0.018 g, 92% yield) as a brown-yellow solid: ¹H NMR (500 MHz, DMSO-*d*₆) δ 10.13 (bs, 1H), 8.50 (d, *J* = 4.0 Hz, 1H), 8.45 (d, *J* = 4.0 Hz, 1H), 8.06 (d, *J* = 5.0 Hz, 1H), 7.55 (d, *J* = 4.5 Hz, 1H), 7.31 (t, *J* = 4.0 Hz, 1H), 3.49–3.44 (m, 4H), 2.82–2.71 (m, 2H), 2.08 (bs, 1H), 1.91 (d, *J* = 12.0 Hz, 1H), 1.82 (d, *J* = 15.0 Hz, 1H), 1.62–1.59 (m, 1H), 1.38–1.34 (m, 1H); ESI MS 370 m/z [C₁₈H₁₉N₅O₂S + H]⁺; HPLC 98.1% (AUC), *t*_R = 10.84 min.
- 10

Example 72

(S) 2-[Hydroxy(thiophen-2-yl)methyl]-N-(piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide

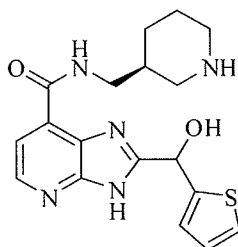


- 15 **[0176]** To a solution of tert-butyl 3-[2-(thiophene-2-carbonyl)-3H-imidazo[4,5-b]pyridine-7-carboxamido]piperidine-1-carboxylate (30 mg, 0.066 mmol) in THF (5 mL) was added NaBH₄ (9.5 mg, 0.25 mmol) and AcOH (2 drops) and the reaction mixture was stirred at rt for 1 h. The reaction mixture was concentrated, diluted in ice-water (5 mL) and the pH was adjusted to 7 using glacial AcOH. The reaction mixture was extracted with EtOAc (3 × 15 mL) and the combined extracts were washed with brine, dried over Na₂SO₄ and concentrated. The crude product was purified by preparative HPLC (C18 silica, 10–90% acetonitrile/water with 0.05%
- 20

TFA). The desired fractions were combined and concentrated and the residue was dissolved in CH_2Cl_2 (2 mL) and TFA (1 mL) and the mixture was stirred at rt for 30 min. The reaction mixture was concentrated and the residue was eluted through an ion-exchange column (SCX-2) (using methanol and 7 N methanol in ammonia) to obtain the product (8.0 mg, 34%) as yellow solid: ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 9.51 (bs, 1H), 8.45–8.44 (m, 1H), 7.68 (d, $J = 5.0$ Hz, 1H), 7.52–7.50 (m, 1H), 7.17–7.15 (m, 1H), 7.02–7.00 (m, 2H), 6.27 (bs, 1H), 4.03 (bs, 1H), 3.15–3.13 (m, 2H), 2.88 (bs, 1H), 2.66–2.64 (m, 2H), 1.94 (bs, 1H), 1.75 (bs, 1H), 1.56–1.54 (m, 2H); ESI MS m/z 358 [$\text{C}_{17}\text{H}_{19}\text{N}_5\text{O}_2\text{S} + \text{H}$] $^+$.

Example 73

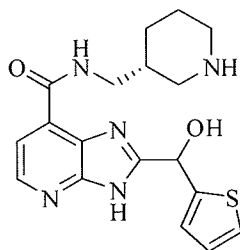
2-[Hydroxy(thiophen-2-yl)methyl]-N-[(S)-piperidin-3-ylmethyl]-3H-imidazo[4,5-b]pyridine-7-carboxamide



[0177] Following the procedure outlined for Example 72, (R)-tert-butyl 3-{[2-(thiophene-2-carbonyl)-3H-imidazo[4,5-b]pyridine-7-carboxamido]methyl}piperidine-1-carboxylate (0.030 g, 0.064 mmol) was treated with NaBH_4 (9.5 mg, 2.5 mmol) to afford the desired product (0.015 g, 63% yield) as a brown-yellow solid: ^1H NMR (500 MHz, CD_3OD) δ 8.43 (d, $J = 5.0$ Hz, 1H), 7.75 (d, $J = 5.5$ Hz, 1H), 7.47 (s, 1H), 7.15 (d, $J = 2.5$ Hz, 1H), 7.02 (m, 1H), 6.33 (s, 1H), 4.57 (s, 1H), 3.50–3.42 (m, 3H), 3.18 (m, 1H), 2.85 (bs, 1H), 2.76–2.72 (m, 1H), 2.64–2.58 (m, 1H), 2.02–1.84 (m, 6H), 1.68–1.60 (m, 2H), 0.89–0.78 (bs, 1H); ESI MS m/z 372 [$\text{C}_{17}\text{H}_{17}\text{N}_5\text{O}_2\text{S} + \text{H}$] $^+$; HPLC 96.5% (AUC), $t_R = 8.17$ min.

Example 74

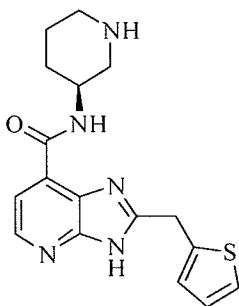
2-[Hydroxy(thiophen-2-yl)methyl]-N-[(R)-piperidin-3-ylmethyl]-3H-imidazo[4,5-b]pyridine-7-carboxamide



[0178] Following the procedure outlined for Example 72, (S)-tert-butyl 3-{[2-(thiophene-2-carbonyl)-3H-imidazo[4,5-b]pyridine-7-carboxamido]methyl}piperidine-1-carboxylate (0.030 g, 0.064 mmol) was treated with NaBH₄ (9.5 mg, 2.5 mmol) to afford the desired product (0.006 g, 25%) as a brown-yellow solid: ¹H NMR (500 MHz, CD₃OD) δ 8.42 (d, *J* = 5.0 Hz, 1H), 7.75 (d, *J* = 5.0 Hz, 1H), 7.40 (dd, *J* = 5.0, 0.5 Hz, 1H), 7.15 (d, *J* = 3.0 Hz, 1H), 7.00 (dd, *J* = 5, 3.5 Hz, 1H), 3.49 (m, 3H), 3.21–3.16 (m, 2H), 3.09 (d, *J* = 12.0 Hz, 1H), 2.68 (m, 1H), 2.54 (m, 1H), 1.95 (bs, 3H), 1.81–1.78 (m, 1H), 1.62–1.57 (m, 1H), 1.34–1.28 (m, 1H); ESI MS *m/z* 372 [C₁₇H₁₇N₅O₂S + H]⁺; HPLC 98.4% (AUC), *t_R* = 14.33 min.

Example 75

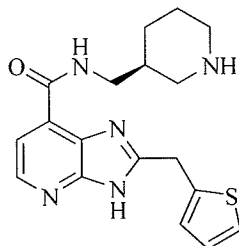
(S)-N-(Piperidin-3-yl)-2-(thiophen-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-7-carboxamide



[0179] To the suspension of (S)-tert-butyl 3-[2-(thiophene-2-carbonyl)-3H-imidazo[4,5-b]pyridine-7-carboxamido]piperidine-1-carboxylate (55 mg, 0.12 mmol) in ethylene glycol (2 mL) was added NH₂NH₂•H₂O (90 mg, 1.8 mmol) and the mixture was heated at 80 °C for 1 h and 150 °C for 5 h. The reaction mixture was cooled to rt and a solution of KOH (34 mg, 0.6 mmol) in water (0.5 mL) was added and the reaction mixture was stirred at 100 °C for 1 h. The reaction was cooled, concentrated and the residue was diluted in CH₃OH (3 mL) and filtered. The filtrate was concentrated and purified by preparative HPLC (C18 silica, 10–90% acetonitrile/water with 0.05% TFA). The desired fractions were combined, concentrated and the residue was dissolved in CH₂Cl₂ (2 mL) and TFA (1 mL) and the mixture was stirred at rt for 30 min. The reaction was concentrated and the residue was eluted through an ion-exchange column (using 7 N methanol in ammonia) to obtain the product (16 mg, 39% yield) as yellow solid: ¹H NMR (500 MHz, CD₃OD) δ 8.41–8.40 (m, 1H), 7.72–7.73 (m, 1H), 7.33–7.32 (m, 1H), 7.06–7.05 (m, 1H), 7.00–6.98 (m, 1H), 4.55 (s, 2H), 4.15–4.12 (m, 1H), 3.04–3.02 (m, 1H), 2.79–2.74 (m, 1H), 2.13–2.11 (m, 1H), 1.89 (bs, 1H), 1.71–1.66 (m, 2H; ESI MS *m/z* 342 [C₁₇H₁₉N₅OS + H]⁺.

Example 76

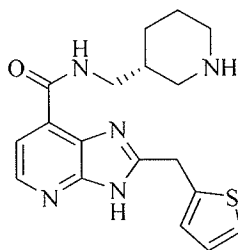
(S)-N-(Piperidin-3-ylmethyl)-2-(thiophen-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-7-carboxamide



- 5 **[0180]** Following the procedure outlined for Example 75, (R)-tert-butyl 3-{{2-(thiophene-2-carbonyl)-3H-imidazo[4,5-b]pyridine-7-carboxamido}methyl}piperidine-1-carboxylate (56 mg, 0.12 mmol) was treated with $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$ (31 mg, 0.60 mmol) and KOH (34 mg, 0.60 mmol). The intermediate (R)-tert-butyl 3-((2-(thiophen-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-7-carboxamido)methyl)piperidine-1-carboxylate was treated with TFA (1 mL) to afford the desired
- 10 product (8 mg, 19% yield) as a brown-yellow solid: ^1H NMR (500 MHz, CD_3OD) δ 8.40 (d, $J = 5.5$ Hz, 1H), 7.72 (d, $J = 5.0$ Hz, 1H), 7.31 (dd, $J = 5.0$ Hz, 1.0 Hz, 1H), 7.03 (m, 1H), 6.98 (dd, $J = 5.5, 3.5$ Hz, 1H), 4.53 (s, 2H), 3.44 (d, $J = 6.0$ Hz, 2H), 3.27 (d, $J = 15.5$ Hz, 1H), 3.13 (d, $J = 11.5$ Hz, 1H), 2.70 (t, $J = 11.0$ Hz, 1H), 2.57 (t, $J = 11.5$ Hz, 1H), 1.96–1.93 (m, 3H), 1.83–1.80 (m, 1H), 1.65–1.60 (m, 1H), 1.34–1.27 (m, 2H), 0.77 (bs, 1H); ESI MS m/z 356
- 15 $[\text{C}_{18}\text{H}_{21}\text{N}_5\text{OS} + \text{H}]^+$; HPLC >99% (AUC), $t_R = 8.71$ min.

Example 77

(R)-N-(piperidin-3-ylmethyl)-2-(thiophen-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-7-carboxamide

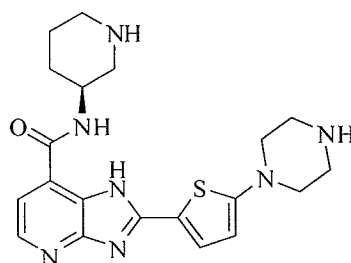


- 20 **[0181]** Following the procedure outlined for Example 75, (S)-tert-butyl 3-{{2-(thiophene-2-carbonyl)-3H-imidazo[4,5-b]pyridine-7-carboxamido}methyl}piperidine-1-carboxylate (47 mg, 0.12 mmol) was treated with $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$ (25 mg, 0.50 mmol) and KOH (20 mg, 0.50 mmol). The intermediate (S)-tert-butyl 3-((2-(thiophen-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-7-carboxamido)methyl)piperidine-1-carboxylate was treated with TFA (1 mL) to afford the desired

product (11 mg, 26% yield) as a brown-yellow solid: ^1H NMR (500 MHz, CD_3OD) δ 8.40 (d, J = 5.5 Hz, 1H), 7.72 (d, J = 4.0 Hz, 1H), 7.31 (dd, J = 5.0, 1.0 Hz, 1H), 7.03 (d, J = 3.5 Hz, 1H), 6.98 (dd, J = 5.5, 3.5 Hz, 1H), 4.53 (s, 2H), 3.44 (d, J = 6.0 Hz, 2H), 3.25 (d, J = 13.0 Hz, 1H), 3.12 (d, J = 12.5 Hz, 1H), 2.70–2.64 (m, 1H), 2.56 (t, J = 11.0 Hz, 1H), 1.98–1.93 (m, 3H), 1.83–1.80 (m, 1H), 1.62–1.59 (m, 1H), 1.32–1.29 (m, 2H), 0.80 (bs, 1H); ESI MS m/z 356 $[\text{C}_{18}\text{H}_{21}\text{N}_5\text{OS} + \text{H}]^+$; HPLC 96.3% (AUC), t_R = 8.75 min.

Example 78

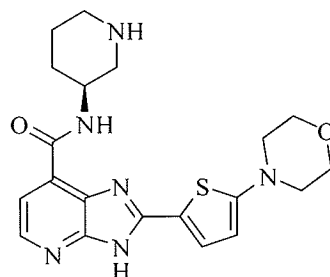
(S)-2-[5-(Piperazin-1-yl)thiophen-2-yl]-N-(piperidin-3-yl)-1H-imidazo[4,5-b]pyridine-7-carboxamide



[0182] A mixture of (S)-tert-butyl 3-[2-(5-bromothiophen-2-yl)-1H-imidazo[4,5-b]pyridine-7-carboxamido]piperidine-1-carboxylate (61 mg, 0.12 mmol), tert-butyl piperazine-1-carboxylate (224 mg, 1.2 mmol), CuI (5.0 mg, 0.02 mmol), Cu (1.5 mg, 0.02 mmol), $\text{K}_3\text{PO}_4 \cdot \text{H}_2\text{O}$ (83 mg, 0.36 mmol) in 2-(dimethylamino)ethanol (2 mL) was stirred at 75 °C for 18 h. The reaction mixture was cooled, concentrated, dissolved in CH_3OH (3 mL) and filtered. The filtrate was purified by preparative HPLC (C18 silica, 10–90% acetonitrile/water with 0.05% TFA). The desired fractions were combined, concentrated and the residue was dissolved in CH_2Cl_2 (2 mL) and TFA (1 mL) and stirred at rt for 30 min. The reaction mixture was concentrated and the residue was eluted through an ion-exchange column (using 7 N methanol in ammonia) to obtain the desired product (10 mg, 20% yield) as a yellow solid: ^1H NMR (500 MHz, CD_3OD) δ 8.28 (d, J = 5.5 Hz, 1H), 7.68–7.67 (m, 1H), 6.29 (d, J = 4.0 Hz, 1H), 4.17–4.16 (m, 1H), 3.03–2.99 (m, 5H), 2.88–2.84 (m, 2H), 2.46 (bs, 1H), 2.18 (bs, 1H), 2.01 (bs, 1H), 1.80–1.76 (m, 2H); ESI MS m/z 412 $[\text{C}_{20}\text{H}_{25}\text{N}_7\text{OS} + \text{H}]^+$.

Example 79

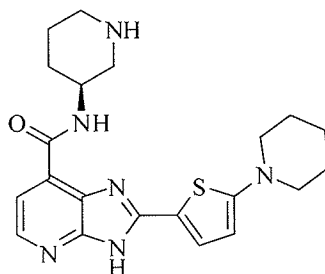
(S)-2-(5-morpholinothiophen-2-yl)-N-(piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide



- 5 **[0183]** Following the procedure outlined for example 78, (S)-tert-butyl 3-[2-(5-bromothiophen-2-yl)-1H-imidazo[4,5-b]pyridine-7-carboxamido]piperidine-1-carboxylate (51 mg, 0.10 mmol) was reacted with morpholine (44 mg, 5.0 mmol) to afford the product (18 mg, 86% yield) as yellow solid: ^1H NMR (500 MHz, DMSO- d_6) δ 9.60 (s, 1H), 8.30 (d, J = 5.0 Hz, 1H), 7.80 (d, J = 4.5 Hz, 1H), 7.59 (d, J = 5.5 Hz, 1H), 6.36 (d, J = 4.0 Hz, 1H), 4.11 (m, 1H), 3.78 (t, J = 4.5 Hz, 1H), 3.32 (bs, 9H), 2.96 (bs, 2H), 2.87-2.79 (m, 2H), 1.99 (bs, 1H), 1.90 (bs, 1H), 1.67-1.64 (m, 2H); ESI MS m/z 413 [$\text{C}_{17}\text{H}_{17}\text{N}_5\text{O}_2\text{S} + \text{H}$] $^+$; HPLC 96.2% (AUC), t_R = 8.99 min.

Example 80

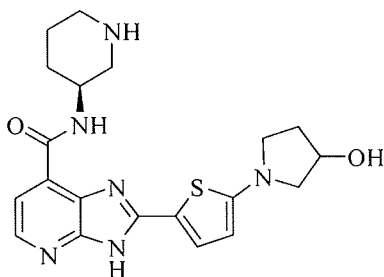
15 (S)-2-[5-(piperidin-1-yl)thiophen-2-yl]-N-(piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide



- 20 **[0184]** Following the procedure outlined for example 78, (S)-tert-butyl 3-[2-(5-bromothiophen-2-yl)-1H-imidazo[4,5-b]pyridine-7-carboxamido]piperidine-1-carboxylate (51 mg, 0.10 mmol) was reacted with piperidine (43 mg, 5.0 mmol) to afford the product (8 mg, 8% yield) as red-orange solid: ^1H NMR (300 MHz, CD $_3$ OD) δ 8.25 (dd, J = 5.1, 2.4 Hz, 1H), 7.81 (t, J = 2.4 Hz, 2H), 3.14-3.10 (m, 1H), 3.01-2.97 (m, 1H), 2.83-2.76 (m, 2H), 2.20-2.14 (m, 1H), 2.01-1.92 (m, 2H), 1.75-1.65 (m, 9H); ESI MS m/z 411 [$\text{C}_{21}\text{H}_{26}\text{N}_6\text{OS} + \text{H}$] $^+$; HPLC 96.2% (AUC), t_R = 10.63 min.

Example 81

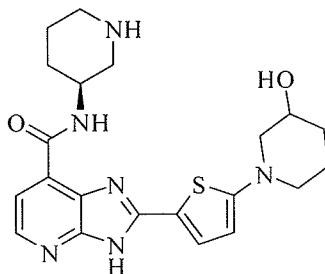
2-[5-(3-hydroxypyrrolidin-1-yl)thiophen-2-yl]-N-[(S)-piperidin-3-yl]-3H-imidazo[4,5-b]pyridine-7-carboxamide



- 5 **[0185]** Following the same procedure as described for example 78, (S)-tert-butyl 3-[2-(5-bromothiophen-2-yl)-1H-imidazo[4,5-b]pyridine-7-carboxamido]piperidine-1-carboxylate (112 mg, 0.20 mmol) was reacted with pyrrolidin-3-ol (87 mg, 1.0 mmol) to afford the desired product (9.0 mg, 9% yield) as an orange-red solid: ^1H NMR (500 MHz, DMSO- d_6) δ 8.21 (d, J = 5.0 Hz, 1H), 7.67–7.63 (m, 2H), 5.93 (d, J = 4.0 Hz, 1H), 4.58–4.57 (m, 1H), 4.14–4.13 (m, 1H), 3.61–3.57 (m, 2H), 3.47–3.44 (m, 1H), 2.99 (bs, 1H), 2.84–2.80 (m, 2H), 2.39–2.10 (m, 3H), 1.99–1.93 (m, 1H), 1.75–1.73 (m, 2H); ESI MS m/z 413 [$\text{C}_{20}\text{H}_{24}\text{N}_6\text{O}_2\text{S} + \text{H}$] $^+$.
- 10

Example 82

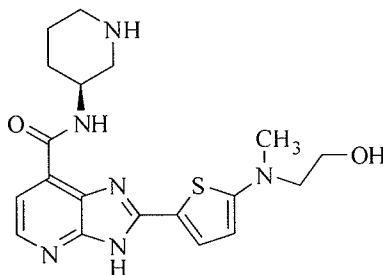
2-[5-(3-hydroxypiperidin-1-yl)thiophen-2-yl]-N-[(S)-piperidin-3-yl]-3H-imidazo[4,5-b]pyridine-7-carboxamide



- 15 **[0186]** Following the procedure outlined for example 78, (S)-tert-butyl 3-[2-(5-bromothiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamido]piperidine-1-carboxylate (76 mg, 0.15 mmol) was reacted with piperidin-3-ol (76 mg, 0.75 mmol) to afford the desired product as red-brown solid (4.7 mg, 7% yield): ^1H NMR (300 MHz, CD_3OD) δ 8.26 (d, J = 5.4 Hz, 1H), 7.66 (dd, J = 5.1, 3.0 Hz, 1H), 6.24 (d, J = 4.5 Hz, 1H), 4.17–4.15 (m, 1H), 3.85–3.80 (m, 1H), 3.65–3.60 (m, 2H), 3.10–3.04 (m, 3H), 2.98–2.83 (m, 4H), 2.45 (s, 1H), 2.18 (bs, 1H), 2.01–1.93 (m, 4H), 1.80–1.71 (m, 4H), 1.58–1.47 (m, 1H), 1.30 (m, 1H); ESI MS m/z 427 [$\text{C}_{21}\text{H}_{26}\text{N}_6\text{O}_2\text{S} + \text{H}$] $^+$; HPLC 98.8% (AUC), t_R = 8.75 min.
- 20

Example 83

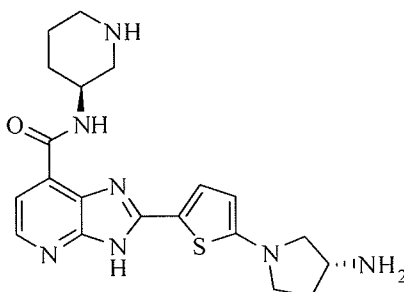
(S)-2-{5-[(2-Hydroxyethyl)(methyl)amino]thiophen-2-yl}-N-(piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide



- 5 [0187] Following the procedure outlined for example 78, (S)-tert-butyl 3-[2-(5-bromothiophen-2-yl)-1H-imidazo[4,5-b]pyridine-7-carboxamido]piperidine-1-carboxylate (76 mg, 0.15 mmol) was reacted with 2-(methylamino)ethanol (76 mg, 0.75 mmol) to afford the desired product (11 mg, 76% yield) as a red-brown solid: ^1H NMR (500 MHz, CD_3OD) δ 8.22 (d, $J = 5.5$ Hz, 1H), 7.66 (dd, $J = 8.5, 4.5$ Hz, 1H), 6.05 (d, $J = 4.5$ Hz, 1H), 4.61–4.59 (m, 3H), 4.15–4.07 (m, 1H), 3.82 (t, $J = 5.5$ Hz, 2H), 3.70–3.65 (m, 1H), 3.54 (t, $J = 5.5$ Hz, 2H), 3.26–3.24 (m, 1H), 2.97–2.94 (m, 1H), 2.85–2.76 (m, 3H), 2.52 (s, 1H), 2.15 (s, 1H), 1.97–1.93 (m, 2H), 1.74–1.69 (m, 2H); ESI MS m/z 401 [$\text{C}_{19}\text{H}_{24}\text{N}_6\text{O}_2\text{S} + \text{H}$] $^+$; HPLC 97.7% (AUC), $t_R = 9.63$ min.

Example 84

- 15 2-{5-[(R)-3-Aminopyrrolidin-1-yl]thiophen-2-yl}-N-[(S)-piperidin-3-yl]-3H-imidazo[4,5-b]pyridine-7-carboxamide

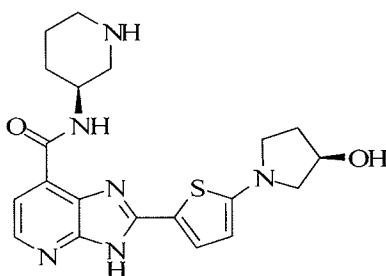


- [0188] Following the procedure outlined for example 78, (S)-tert-butyl 3-[2-(5-bromothiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamido]piperidine-1-carboxylate (150 mg, 0.29 mmol) was reacted with (R)-pyrrolidin-3-amine (110 mg, 0.59 mmol) to afford the desired product (27mg, 30% yield) as a red-brown solid: ^1H NMR (500 MHz, CD_3OD) δ 8.45 (d, $J = 5.0$ Hz, 1H), 7.78 (d, $J = 5.5$ Hz, 1H), 7.72 (d, $J = 4.0$ Hz, 1H), 7.30 (d, $J = 4.0$ Hz, 1H), 4.37–4.34 (m, 1H), 3.61 (dd, $J = 12.5, 3.5$ Hz, 1H), 3.26–3.15 (m, 2H), 2.65 (s, 2H), 2.27–2.20

(m, 3H), 2.02–1.94 (m, 3H); ESI MS m/z 412 $[C_{20}H_{25}N_7OS + H]^+$; HPLC 94.0% (AUC), t_R = 9.58 min.

Example 85

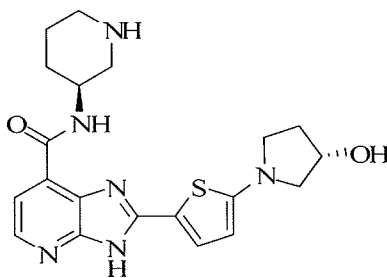
2-{5-[(R)-3-hydroxypyrrolidin-1-yl]thiophen-2-yl}-N-((S)-piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide



[0189] Following the procedure outlined for example 78, (S)-tert-butyl 3-[2-(5-bromothiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamido]piperidine-1-carboxylate (200 mg, 0.39 mmol) was reacted with (R)-pyrrolidin-3-ol (255 mg, 1.97 mmol) to afford the desired product (34 mg, 34% yield) as red-brown solid: 1H NMR (500 MHz, CD_3OD) δ 8.19 (d, J = 5.5 Hz, 1H), 7.64 (d, J = 4.0 Hz, 1H), 7.60 (d, J = 5.0 Hz, 1H), 5.90 (d, J = 4.0 Hz, 1H), 4.59–4.57 (m, 1H), 4.27–4.20 (m, 1H), 3.80 (t, J = 5.5 Hz, 3H), 3.78–3.68 (m, 3H), 3.59–3.55 (m, 2H), 3.30–3.22 (m, 4H), 3.05 (t, J = 5.5 Hz, 3H), 3.26–3.23 (m, 2H), 1.13–1.28 (m, 1H); ESI MS m/z , 413 $[C_{20}H_{24}N_6O_2S + H]^+$; HPLC 98.08% (AUC), t_R = 7.04 min.

Example 86

2-{5-[(S)-3-hydroxypyrrolidin-1-yl]thiophen-2-yl}-N-((S)-piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide

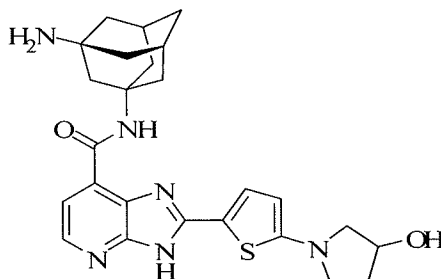


[0190] Following the procedure outlined for example 78, (S)-tert-butyl 3-[2-(5-bromothiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamido]piperidine-1-carboxylate (200 mg, 0.39 mmol) was reacted with (S)-pyrrolidin-3-ol (255 mg, 1.97 mmol) to afford the desired product (37 mg, 35% yield) as red-brown solid: 1H NMR (500 MHz, CD_3OD) δ 8.22 (d, J = 5.0 Hz, 1H), 7.70 (t, J = 2.5 Hz, 1H), 7.63 (d, J = 5.5 Hz, 1H), 5.95 (d, J = 4.0 Hz, 1H), 4.59–4.58

(m, 1H), 4.36-3.34 (m, 1H), 3.85-3.83 (m, 1H), 3.59-3.55 (m, 3H), 3.27-3.23 (m, 4H), 2.91 (d, J = 6.5 Hz, 6H), 2.26-2.22 (m, 3H), 3.26-3.23 (m, 4H), 1.13-1.28 (m, 1H); ESI MS m/z , 413 $[C_{20}H_{24}N_6O_2S + H]^+$; HPLC 98.6% (AUC), t_R = 7.03 min.

Example 87

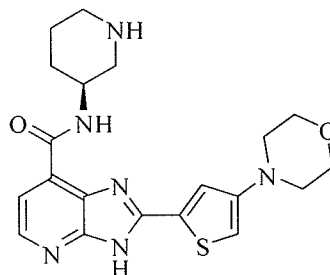
- 5 2-[5-(3-hydroxypyrrolidin-1-yl)thiophen-2-yl]-N-(1,3-diaminoadamane-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide



- [0191] Following the procedure outlined for example 78, (S)-tert-butyl 3-[2-(5-bromothiophen-2-yl)-1H-imidazo[4,5-b]pyridine-7-carboxamido]1,3-diaminoadamantane 1-carboxylate (100 mg, 0.17 mmol) was reacted with pyrrolidin-3-ol (110 mg, 0.85 mmol) to afford the desired product (68 mg, 82% yield) as a red-brown solid. 1H NMR (500 MHz, CD_3OD) δ 9.87 (s, 1H), 8.19 (d, J = 5.5 Hz, 1H), 7.65 (d, J = 2.5 Hz, 1H), 7.60 (d, J = 5.5 Hz, 1H), 5.92 (d, J = 4.5 Hz, 1H), 4.59-4.57 (m, 1H), 3.60-3.56 (m, 2H), 3.44-3.43 (m, 1H), 2.45 (bs, 3H), 2.38 (d, J = 9.0 Hz, 2H), 2.30 (bs, 1H), 2.25 (s, 2H), 2.13 (t, J = 12.5 Hz, 4H), 1.98-1.83 (m, 11H), 1.75-1.65 (m, 2H); ESI MS m/z 479 $[C_{25}H_{30}N_6O_2S]^+$; HPLC >99% (AUC), t_R = 8.10 min.

Example 88

- (S)-2-(4-Morpholinothiophen-2-yl)-N-(piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide

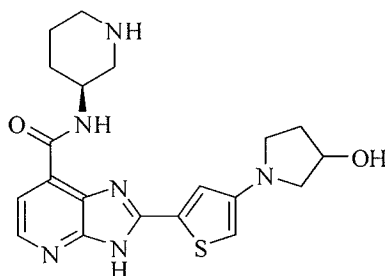


- [0192] Following the procedure outlined for example 78, (S)-tert-butyl 3-[2-(4-bromothiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamido]piperidine-1-carboxylate (61 mg, 0.12 mmol) was reacted with morpholine (100 mg, 1.2 mmol) to afford the product (12 mg,

24% yield) as a yellow-brown solid: ^1H NMR (500 MHz, CD_3OD) δ 8.39 (t, $J = 5.5$ Hz, 1H), 7.73 (t, $J = 1.5$ Hz, 2H), 6.66 (d, $J = 1.5$ Hz, 1H), 4.18–4.16 (m, 1H), 3.86 (t, $J = 4.5$ Hz, 4H), 3.16 (t, $J = 4.5$ Hz, 5H), 3.05–3.02 (m, 1H), 2.91 (t, $J = 12.0$ Hz, 1H), 2.17 (bs, 1H), 2.02 (bs, 1H), 1.79 (t, $J = 3.5$ Hz, 2H); ESI MS m/z 413 [$\text{C}_{20}\text{H}_{24}\text{N}_6\text{O}_2\text{S} + \text{H}$] $^+$; HPLC >99% (AUC), $t_R =$
 5 10.64 min.

Example 89

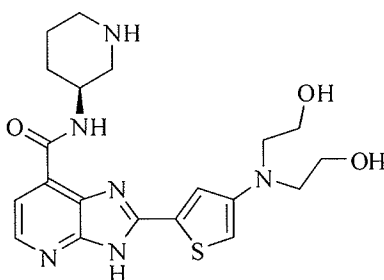
2-[4-(3-Hydroxypyrrolidin-1-yl)thiophen-2-yl]-N-[(S)-piperidin-3-yl]-3H-imidazo[4,5-b]pyridine-7-carboxamide



10 [0193] Following the procedure outlined for example 78, (S)-tert-butyl 3-[2-(4-bromothiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamido]piperidine-1-carboxylate (61 mg, 0.12 mmol) was reacted with 3-hydroxy pyrrolidine (105 mg, 1.2 mmol) to afford the product (6 mg, 12% yield) as a brown solid: ^1H NMR (500 MHz, CD_3OD) δ 8.39 (d, $J = 5.0$ Hz, 1H), 7.74 (d, $J = 5.0$ Hz, 1H), 7.54 (d, $J = 1.0$ Hz, 1H), 6.22 (d, $J = 1.5$ Hz, 1H), 4.55–4.53 (m, 2H), 4.22–4.17 (m, 1H), 3.76 (t, $J = 6.0$ Hz, 1H), 3.55–3.48 (m, 2H), 3.44–3.43 (m, 1H), 3.17–
 15 3.15 (m, 1H), 3.10–3.05 (m, 1H), 2.96–2.89 (m, 2H), 2.81–2.75 (m, 1H), 2.52 (s, 2H), 2.23–2.19 (m, 2H), 2.07–1.99 (m, 2H), 1.93 (s, 1H), 1.85–1.80 (m, 2H); ESI MS m/z 413 [$\text{C}_{20}\text{H}_{24}\text{N}_6\text{O}_2\text{S} + \text{H}$] $^+$; HPLC 97.4% (AUC), $t_R = 10.31$ min.

Example 90

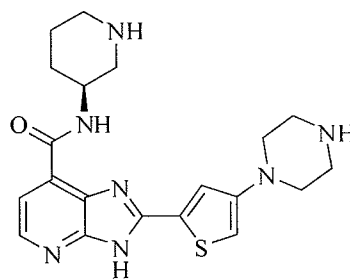
20 (S)-2-{4-[Bis(2-hydroxyethyl)amino]thiophen-2-yl}-N-(piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamid



[0194] Following the procedure outlined for example 78, (S)-tert-butyl 3-[2-(4-bromothiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamido]piperidine-1-carboxylate (61 mg, 0.12 mmol) was reacted with 2,2'-azanediyldiethanol (126 mg, 1.2 mmol) to afford the product (5.6 mg, 11% yield) as a brown solid: ^1H NMR (500 MHz, CD_3OD) δ 8.39–8.37 (m, 1H), 7.73–7.72 (m, 1H), 7.65 (t, $J = 1.0$ Hz, 1H), 6.32 (t, $J = 1.0$ Hz, 1H), 4.22–4.15 (m, 1H), 3.79–3.77 (m, 4H), 3.73–3.68 (m, 1H), 3.53–3.51 (m, 4H), 3.05–2.99 (m, 2H), 2.95–2.88 (m, 2H), 2.71–2.68 (m, 1H), 2.45 (s, 3H), 2.17 (bs, 1H), 2.05–2.01 (m, 1H), 1.93–1.92 (m, 3H), 1.79 (bs, 1H); ESI MS m/z 431 [$\text{C}_{20}\text{H}_{26}\text{N}_6\text{O}_3\text{S} + \text{H}$] $^+$; HPLC 96.0% (AUC), $t_R = 9.88$ min.

Example 91

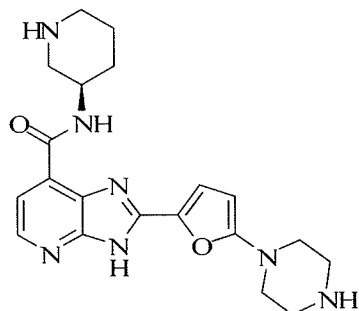
(S)-2-[4-(Piperazin-1-yl)thiophen-2-yl]-N-(piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide



[0195] Following the procedure outlined for example 78, (S)-tert-butyl 3-[2-(4-bromothiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamido]piperidine-1-carboxylate (61 mg, 0.12 mmol) was reacted with piperazine (224 mg, 1.2 mmol) to afford the product (6 mg, 12% yield) as a brown solid: ^1H NMR (500 MHz, CD_3OD) δ 8.38 dd, $J = 5.0, 1.0$ Hz, 1H), 7.73–7.71 (m, 2H), 6.66 (d, $J = 1.5$ Hz, 1H), 4.19–4.15 (m, 1H), 3.18 (t, $J = 4.5$ Hz, 4H), 3.04 (t, $J = 5.5$ Hz, 5H), 2.90 (q, 2H), 2.19–2.16 (m, 1H), 2.04–2.00 (m, 1H), 1.93 (s, 2H), 1.86–1.75 (m, 2H), 1.32–1.28 (m, 2H); ESI MS m/z 412 [$\text{C}_{20}\text{H}_{25}\text{N}_7\text{OS} + \text{H}$] $^+$; HPLC 97.6% (AUC), $t_R = 8.98$ min.

Example 92

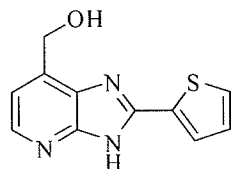
(R)-2-[5-(Piperazin-1-yl)furan-2-yl]-N-(piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide



- 5 [0196] Following the procedure outlined for example 78, (S)-*tert*-butyl 3-{[2-(5-bromofuran-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamido]methyl}piperidine-1-carboxylate (100 mg, 0.20 mmol) was reacted with piperazine (190 mg, 1.00 mmol) to afford the desired product (12 mg, 14 % yield) as a yellow solid: ^1H NMR (500 MHz, CD_3OD) δ 8.28 (d, $J = 5.0$ Hz, 1H), 7.62 (d, $J = 5.0$ Hz, 1H), 7.34 (d, $J = 4.0$ Hz, 1H), 5.62 (d, $J = 3.5$ Hz, 1H), 4.29–4.24 (m, 1H), 3.58–3.56 (m, 4H), 3.51–3.48 (m, 2H), 3.34–3.29 (m, 5H), 3.12–3.02 (m, 3H), 2.14–2.05 (m, 3H), 1.87–1.83 (m, 3H); ESI MS m/z 396 [$\text{C}_{20}\text{H}_{25}\text{N}_7\text{O}_2\text{S} + \text{H}$] $^+$.
- 10

Example 93

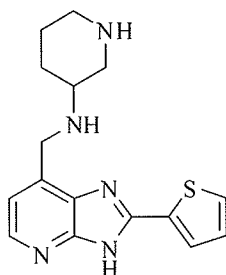
[2-(Thiophen-2-yl)-3H-imidazo[4,5-b]pyridin-7-yl]methanol



- 15 [0197] To a solution of methyl 2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxylate (750 mg, 2.90 mmol) in THF (30 mL) at 0 °C was added Diisobutylaluminium hydride (11.5 mL, 1.0 M, 11.6 mmol) and the reaction mixture was stirred at rt for 1 h. The reaction was diluted with water (100 mL) and extracted with 3:1 $\text{CHCl}_3/i\text{-PrOH}$ (3×30 mL). The combined organic layers were dried, concentrated and the crude product was stirred with AcOH (1 mL) for
- 20 30 min, concentrated and purified by flash chromatography (silica, methanol/methylene chloride gradient) to provide the product (377 mg, 56% yield) as a tan solid: ESI MS m/z 232 [$\text{C}_{11}\text{H}_9\text{N}_3\text{OS} + \text{H}$] $^+$.

Example 94

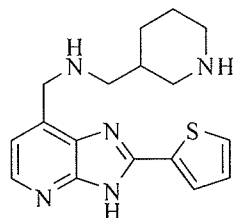
N-[2-(Thiophen-2-yl)-3*H*-imidazo[4,5-*b*]pyridin-7-yl]methyl]piperidin-3-amine



[0198] A suspension of [2-(thiophen-2-yl)-3*H*-imidazo[4,5-*b*]pyridin-7-yl]methanol (75 mg, 0.32 mmol), diisopropylethylamine (0.17 mL, 0.97 mmol) and methanesulfonic acid anhydride (120 mg, 0.71 mmol) in THF (10 mL) was stirred at 0 °C for 2 h and at rt for 30 min. The reaction mixture was concentrated and the residue was dissolved in DMF (5 mL) followed by the addition of *tert*-Butyl 3-aminopiperidine-1-carboxylate (130 mg, 0.65 mmol) in DMF (1 mL). The reaction mixture was heated at 75 °C for 4 h, cooled, diluted with water (10 mL) and extracted with ethyl acetate (3 × 30 ml). The combined organic layers were dried, concentrated and the crude product was purified by flash chromatography (silica gel, methanol/methylene chloride gradient) to provide the crude product (36 mg) as a light yellow solid. The crude intermediate was dissolved in THF (5 mL) followed by the addition of 6 M HCl (2 mL). The reaction mixture was heated at 60 °C for 1 h, cooled, concentrated and the residue was purified by preparative HPLC (C18 silica, 10–90% acetonitrile/water with 0.05% TFA) to afford the desired product (15 mg, 15% yield) as a light yellow semi-solid: ¹H NMR (300 MHz, CD₃OD) δ 8.39 (d, *J* = 5.1 Hz, 1H), 7.97 (dd, *J* = 1.2, 3.8 Hz, 1H), 7.78 (dd, *J* = 1.2, 5.1 Hz, 1H), 7.42 (d, *J* = 5.1 Hz, 1H), 7.29 (dd, *J* = 3.6, 5.1 Hz, 1H), 4.69 (s, 2H), 3.85–3.78 (m, 1H), 3.59–3.48 (m, 1H), 3.24–3.14 (m, 1H), 3.12–3.00 (m, 1H), 2.49–2.39 (m, 1H), 2.22–2.11 (m, 1H), 1.86–1.76 (m, 2H); ESI MS *m/z* 314 [C₁₆H₁₉N₅S + H]⁺; HPLC 98.7% (AUC), *t_R* = 6.38 min.

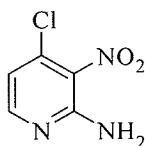
Example 95

1-(Piperidin-3-yl)-*N*-{[2-(thiophen-2-yl)-3*H*-imidazo[4,5-*b*]pyridin-7-yl]methyl}methanamine



[0199] A suspension of [2-(thiophen-2-yl)-3*H*-imidazo[4,5-*b*]pyridin-7-yl]methanol (75 mg, 0.32 mmol), diisopropylethylamine (0.17 mL, 0.97 mmol) and methanesulfonic acid anhydride (120 mg, 0.71 mmol) in THF (10 mL) was stirred at 0 °C for 2 h and at rt for 18 h. The reaction mixture was concentrated and the residue was dissolved in DMF (5 mL) followed by the addition of *tert*-butyl 3-(aminomethyl)piperidine-1-carboxylate (140 mg, 0.65 mmol) in DMF (2 mL). The reaction mixture was stirred at rt for 18 h, diluted with water (50 mL), extracted with ethyl acetate (3 × 30 mL). The combined organic layers were dried, concentrated and the crude product was purified by flash chromatography (silica gel, methanol/methylene chloride, gradient) to provide the crude product (77 mg) as a light yellow solid. The crude intermediate was dissolved in THF (5 mL) followed by the addition of 6 M HCl (2 mL). The reaction mixture was stirred at rt for 18 h, concentrated and the residue was purified by preparative HPLC (C18 silica, 10–90% acetonitrile/water with 0.05% TFA) to afford the desired product (20 mg, 19% yield) as a light yellow-orange semi-solid: ¹H NMR (300 MHz, CD₃OD) δ 8.29 (d, *J* = 5.1 Hz, 1H), 7.93 (dd, *J* = 1.2, 3.6 Hz, 1H), 7.72 (dd, *J* = 1.2, 5.1 Hz, 1H), 7.30–7.25 (m, 2H), 4.21 (s, 2H), 3.50–3.41 (m, 1H), 3.30–3.26 (m, 1H), 2.91–2.80 (m, 1H), 2.71–2.55 (m, 3H), 2.03–1.88 (m, 3H), 1.80–1.63 (m, 1H), 1.36–1.19 (m, 1H); ESI MS *m/z* 328 [C₁₇H₂₁N₅S + H]⁺; HPLC 99.0% (AUC), *t_R* = 8.54 min.

Example 96
4-Chloro-3-nitropyridin-2-amine

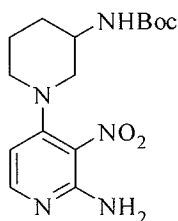


20

[0200] To a solution of 4-chloro-2-aminopyridine (2.5 g, 19.4 mmol) in conc. H₂SO₄ (10 mL) at 0 °C was added a solution of HNO₃ (70%, 1.23 mL, 19.4 mmol) in conc. H₂SO₄ (5 mL) dropwise. Upon complete addition the ice-bath was removed and the mixture was stirred at rt for 2 h. The reaction mixture was poured onto (ice-water) and the pH was adjusted to 6 using 6 N NaOH. The resulting precipitate was collected by filtration, washed with water and dried to obtain the desired product (1.1 g, 34% yield) as a yellow solid: ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.12 (d, *J* = 9.0 Hz, 1H), 7.24 (s, 2H), 6.87 (d, *J* = 8.5 Hz, 1H); ESI MS *m/z* 174 [C₅H₄ClN₃O₂ + H]⁺.

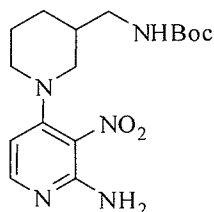
25

Example 97

tert-Butyl 1-(2-amino-3-nitropyridin-4-yl)piperidin-3-ylcarbamate

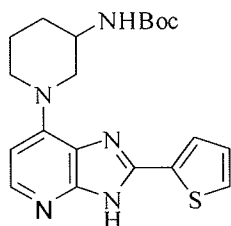
[0201] A mixture of 4-chloro-3-nitropyridin-2-amine (170 mg, 1.0 mmol), *tert*-butyl piperidin-3-ylcarbamate (200 mg, 1 mmol) and diisopropylethyl amine (200 mg, 2.0 mmol) in isopropanol (20 mL) was heated in a sealed tube at 90 °C for 3 h. The reaction mixture was cooled, concentrated and the residue was purified by column chromatography (silica, 0-10% methanol/methylene chloride) to afford the desired product (190 mg, 57% yield) as a yellow solid: ESI MS *m/z* 338 [C₁₅H₂₃N₅O₄ + H]⁺.

Example 98

tert-Butyl [1-(2-amino-3-nitropyridin-4-yl)piperidin-3-yl]methylcarbamate

[0202] Following the procedure outlined for Example 97, 4-chloro-3-nitropyridin-2-amine (173 mg, 1 mmol) was reacted with *tert*-butyl piperidin-3-ylmethylcarbamate (214 mg, 1 mmol) to afford the desired product (223 mg, 64% yield) as a yellow solid: ESI MS *m/z* 352 [C₁₆H₂₅N₅O₄ + H]⁺.

Example 99

tert-Butyl 1-[2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridin-7-yl]piperidin-3-ylcarbamate

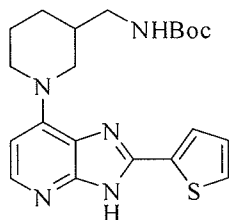
[0203] To a solution of *tert*-butyl 1-(2-amino-3-nitropyridin-4-yl)piperidin-3-ylcarbamate (100 mg, 0.30 mmol) and thiophene-2-carbaldehyde (51 mg, 1.5 mmol) in ethanol (9 mL) and DMSO

(5 mL) was added a freshly prepared solution of $\text{Na}_2\text{S}_2\text{O}_4$ (1 M, 1.3 mL, 1.3 mmol) and the reaction mixture was heated at 70 °C for 16 h and 90 °C for 8 h. The reaction mixture was cooled, concentrated and purified by column chromatography to give the desired product (17 mg, 14% yield) as an off-white solid: ESI MS m/z 400 [$\text{C}_{20}\text{H}_{25}\text{N}_5\text{O}_2\text{S} + \text{H}$] $^+$.

5

Example 100

tert-Butyl {1-[2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridin-7-yl]piperidin-3-yl}methylcarbamate

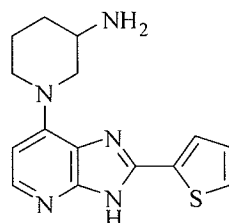


10

[0204] Following the procedure outlined in Example 99, *tert*-butyl [1-(2-amino-3-nitropyridin-4-yl)piperidin-3-yl]methylcarbamate (220 g, 0.63 mmol) is reacted with thiophene-2-carbaldehyde (110 mg, 0.95 mmol) to afford the desired product (34 mg, 13% yield) as an off-white solid: ESI MS m/z 414 [$\text{C}_{21}\text{H}_{27}\text{N}_5\text{O}_2\text{S} + \text{H}$] $^+$.

Example 101

1-[2-(Thiophen-2-yl)-3H-imidazo[4,5-b]pyridin-7-yl]piperidin-3-amine



15

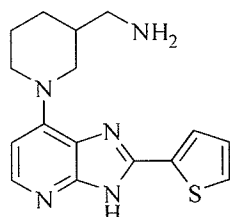
[0205] To a solution of *tert*-butyl 1-[2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridin-7-yl]piperidin-3-ylcarbamate (17 mg, 0.043 mmol) in CH_2Cl_2 (2 mL) was added TFA (2 mL) and the reaction mixture was stirred at room temperature for 16 h. The mixture was concentrated and purified by preparative HPLC (C18 silica, 10–90% acetonitrile/water with 0.05% TFA). The desired product was eluted through an ion-exchange column (using methanol and 7 N methanol in ammonia) to afford the desired product (12 mg, 94% yield) as a white solid: ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 7.92 (d, $J = 5.5$ Hz, 1H), 7.82 (d, $J = 3.0$ Hz, 1H), 7.68 (d, $J = 5.0$ Hz, 1H), 7.21–7.19 (m, 1H), 6.52 (d, $J = 5.5$ Hz, 1H), 4.71 (d, $J = 13.0$ Hz, 1H), 4.47 (d, $J = 9.0$ Hz, 1H), 3.26–3.09 (m, 2H), 3.10–3.05 (m, 3H), 1.98 (d, $J = 12.0$ Hz, 1H); 1.82–1.79 (m, 1H), 1.62–1.58

20

(m, 1H), 1.60–1.46 (m, 1H); ESI MS m/z 300 [$C_{15}H_{17}N_5S + H$] $^+$; HPLC >99% (AUC), t_R = 12.36 min.

Example 102

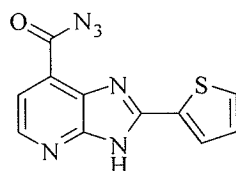
1-[2-(Thiophen-2-yl)-3H-imidazo[4,5-b]pyridin-7-yl]piperidin-3-ylmethanamine



[0206] Following the procedure outlined for Example 101, *tert*-butyl {1-[2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridin-7-yl]piperidin-3-yl} methylcarbamate (34 g, 0.082 mmol) was treated with TFA to afford the desired product (24 mg, 93% yield) as a white solid: 1H NMR (500 MHz, DMSO- d_6) δ 7.89 (d, J = 6.0 Hz, 1H), 7.77 (d, J = 3.5 Hz, 1H), 7.66 (d, J = 5.0 Hz, 1H), 7.20 – 7.18 (m, 1H), 6.50 (d, J = 6.0 Hz, 1H), 4.44 (d, J = 11.5 Hz, 1H), 4.33 (d, J = 12.5 Hz, 1H), 3.39 – 3.17 (m, 4H), 2.71 – 2.67 (m, 1H), 2.60 – 2.57 (m, 1H), 1.84 – 1.81 (m, 1H), 1.76 – 1.73 (m, 2H), 1.58 – 1.37 (m, 1H), 1.36 – 1.33 (m, 1H); ESI MS m/z 314 [$C_{16}H_{19}N_5S + H$] $^+$; HPLC >99% (AUC), t_R = 13.23 min.

Example 103

2-(Thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carbonyl Azide

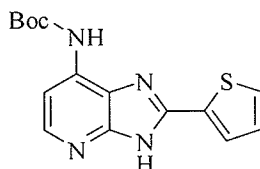


[0207] To a suspension of 2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxylic acid (0.31 g, 1.3 mmol) in toluene (10 mL) was added thionyl chloride (0.74 mL, 5.0 mmol). The reaction mixture was heated at 70 °C for 21 h, cooled to room temperature and concentrated.

The residue was dissolved in acetone (7 mL) followed by dropwise addition of sodium azide (0.25 g, 3.8 mmol) in water (3.8 mL) at 0 °C. The mixture was stirred at 0 °C for 3 h and filtered to afford the desired product (220 mg, crude) as an off-white solid. ESI MS m/z 271 [$C_{11}H_6N_6OS + H$] $^+$.

Example 104

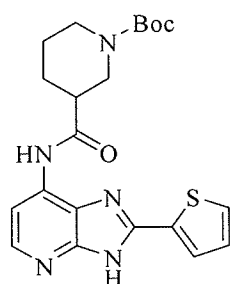
tert-Butyl 2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridin-7-ylcarbamate



[0208] A suspension of crude 2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carbonyl azide (220 mg) in toluene (10 mL) and *tert*-butanol (10 mL) was heated at reflux for 3.5 h. The reaction mixture was cooled, concentrated, and the residue was purified by flash chromatography (silica gel, ethyl acetate/dichloromethane/methanol gradient) to provide the desired product (44 mg, 11% yield over three steps): ESI MS m/z 317 [$C_{16}H_{15}N_4O_2S + H$]⁺.

Example 105

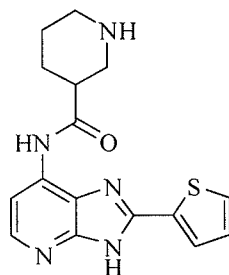
tert-Butyl 3-[2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridin-7-ylcarbamoyl]piperidine-1-carboxylate



[0209] To a solution of *tert*-butyl 2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridin-7-ylcarbamate (44 mg, 0.14 mmol) in THF (5 mL) was added HCl (6.0 M, 2.0 mL, 12 mmol) and the reaction mixture was stirred at room temperature for 16 h, heated at 60 °C for 4 h, cooled, and concentrated. The residue was suspended in a mixture of THF (3 mL) and DMF (1.5 mL) followed by the addition of 1-(*tert*-butoxycarbonyl)piperidine-3-carboxylic acid (64 mg, 0.28 mmol), diisopropylethylamine (74 micro L, 0.417 mmol) and HATU (106 mg, 0.28 mmol). The reaction mixture was stirred at room temperature for 3 d, diluted with H₂O (15 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with satd. aq. NaHCO₃ (20 mL), dried over Na₂SO₄ and concentrated. The residue was purified by flash chromatography (silica gel, ethyl acetate/dichloromethane gradient) to give the desired product (41 mg, 79% yield) as a colorless oil: ESI MS m/z 428 [$C_{21}H_{25}N_5O_3S + H$]⁺.

Example 106

N-[2-(Thiophen-2-yl)-3H-imidazo[4,5-b]pyridin-7-yl]piperidine-3-carboxamide



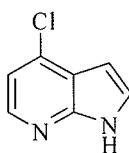
[0210] To a solution of *tert*-butyl 3-[2-(thiophen-2-yl)-3*H*-imidazo[4,5-*b*]pyridin-7-

ylcarbamoyl]piperidine-1-carboxylate (41 mg, 0.10 mmol) in THF (3 mL) was added HCl (6.0 M in H₂O, 1.5 mL, 9.0 mmol) and the reaction mixture was heated at 50 °C for 3.5 h, cooled and concentrated. The residue was purified by preparative HPLC (C18 silica, 10–90%

acetonitrile/water with 0.05% TFA). The desired fractions were combined, concentrated and eluted through an ion-exchange column (using methanol and 7 N methanol in ammonia) to

provide the desired product (6.2 mg, 19% yield) as a white semisolid: ¹H NMR (300 MHz, CD₃OD) δ 8.18 (d, *J* = 5.7 Hz, 1H), 8.06 (d, *J* = 5.7 Hz, 1H), 7.87 (dd, *J* = 3.7, 1.1 Hz, 1H), 7.70 (dd, *J* = 5.0, 1.1 Hz, 1H), 7.25 (dd, *J* = 5.0, 3.8 Hz, 1H), 3.30–3.23 (m, 1H), 3.14–2.96 (m, 2H), 2.89–2.73 (m, 2H), 2.24–2.12 (m, 1H), 1.95–1.78 (m, 2H) 1.77–1.62 (m, 1H); ESI MS *m/z* 328 [C₁₆H₁₇N₅OS + H]⁺; HPLC >99% (AUC), *t_R* = 13.80 min.

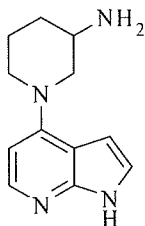
Example 107

4-Chloro-1*H*-pyrrolo[2,3-*b*]pyridine

[0211] To a solution of 7-Azaindole (3.6 g, 30 mmol) in a mixture of dimethoxyethane/heptane (50 mL, 1:2) was added *m*-CPBA (8.1 g, 77%, 36 mmol) portionwise at rt and the reaction mixture was stirred for 2 h. The solids were filtered and washed with dimethoxyethane/heptane (1:2) to afford the intermediate *N*-oxide which was suspended in phosphorus oxychloride (22 mL, 0.24 mol) and heated at 85 °C for 18 h. The reaction was cooled, diluted with water (150 mL) and the pH was adjusted to 10 using 6 N NaOH. The resulting precipitate was filtered and washed with water to afford the product (4.1 g, 90% yield) as a brown solid: ¹H NMR (300

MHz, DMSO- d_6) δ 12.05 (s, 1H), 8.18–8.16 (m, 1H), 7.61–7.57 (m, 1H), 7.20–7.19 (m, 1H), 6.51–6.50 (m, 1H); ESI MS m/z 153 [$C_7H_5ClN_2 + H$] $^+$.

Example 108

1-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yl)piperidin-3-amine

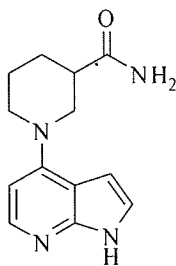
5

[0212] To a solution of 4-chloro-1*H*-pyrrolo[2,3-*b*]pyridine (50 mg, 0.33 mmol) in *N*-methylpyrrolidone was added *tert*-butyl 3-aminopiperidine-1-carboxylate (130 mg, 0.66 mmol) and the reaction was heated to 160 °C for 2 h in a microwave. The reaction mixture was cooled and eluted through an ion-exchange column (using methanol and 7 N methanol in ammonia).

10 The residue was purified by preparative HPLC (C18 silica, 10–90% acetonitrile/water with 0.05% TFA). The desired fractions were combined, concentrated and eluted through an ion-exchange column (using methanol and 7 N methanol in ammonia) to provide the desired product (23 mg, 32% yield) as a light orange semi-solid: 1H NMR (300 MHz, CD_3OD) δ 7.93 (d, $J = 5.7$ Hz, 1H), 7.19 (d, $J = 3.6$ Hz, 1H), 6.57 (d, $J = 3.6$ Hz, 1H), 6.50 (d, $J = 5.7$ Hz, 1H), 3.99–3.94 (m, 1H), 3.84–3.80 (m, 1H), 3.10–2.98 (m, 2H), 2.91–2.84 (m, 1H), 2.08–2.03 (m, 1H), 1.94–1.72 (m, 2H), 1.49–1.38 (m, 1H); ESI MS m/z 217 [$C_{12}H_{16}N_4 + H$] $^+$.

15

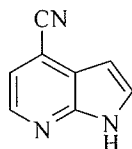
Example 109

1-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yl)piperidine-3-carboxamide

20 **[0213]** Following the procedure outlined in Example 108, 4-chloro-1*H*-pyrrolo[2,3-*b*]pyridine (75 mg, 0.49 mmol) was reacted with piperidine-3-carboxamide (130 mg, 1.0 mmol) to afford the desired product (10 mg, 8% yield) as a light yellow solid: 1H NMR (300 MHz, CD_3OD) δ 7.94 (d, $J = 5.7$ Hz, 1H), 7.20 (d, $J = 3.6$ Hz, 1H), 6.55–6.52 (m, 2H), 4.14–4.01 (m, 2H), 3.21–

3.09 (m, 1H), 3.08–2.97 (m, 1H), 2.75–2.63 (m, 1H), 2.13–2.02 (m, 1H), 1.95–1.74 (m, 3H); ESI MS m/z 217 [$C_{12}H_{16}N_4 + H$] $^+$.

Example 110
1*H*-Pyrrolo[2,3-*b*]pyridine-4-carbonitrile



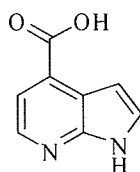
5

[0214] A suspension of 4-chloro-1*H*-pyrrolo[2,3-*b*]pyridine (200 mg, 1.31 mmol), zinc dust (17 mg, 0.26 mmol), zinc cyanide (150 mg, 1.31 mmol), tris(dibenzylideneacetone)dipalladium (120 mg, 0.13 mmol) and 1,1'-bis(diphenylphosphino)ferrocene (73 mg, 0.13 mmol) in *N,N*-dimethylacetamide (3 mL) was degassed with N_2 and heated in a microwave at 120 °C for 3 h.

10 The mixture was cooled, diluted with water (10 mL) and filtered. The pH of the filtrate was adjusted to 12 using 6 M NaOH and the basic aqueous solution was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were dried and concentrated to provide the product (100 mg, 53% yield) as a yellow solid: 1H NMR (300 MHz, $DMSO-d_6$) δ 12.39 (s, 1H), 8.41–8.40 (m, 1H), 7.84–7.83 (m, 1H), 7.57–7.55 (m, 1H), 6.65–6.64 (m, 1H); ESI MS m/z 144

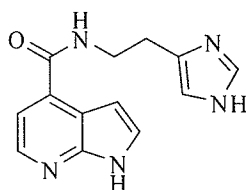
15 [$C_8H_5N_3 + H$] $^+$.

Example 111
1*H*-Pyrrolo[2,3-*b*]pyridine-4-carboxylic acid



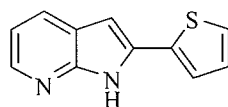
20 [0215] A solution of 1*H*-pyrrolo[2,3-*b*]pyridine-4-carbonitrile (90 mg, 0.63 mol) in HCl (10 mL, 6 M) was heated at 100 °C for 2 d. The reaction mixture was cooled and concentrated to afford the crude product as yellow solid: ESI MS m/z 163 [$C_8H_6N_2O_2 + H$] $^+$.

Example 112

N-[2-(1*H*-Imidazol-4-yl)ethyl]-1*H*-pyrrolo[2,3-*b*]pyridine-4-carboxamide

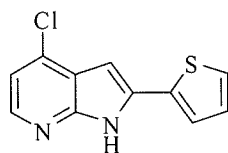
[0216] Following General Procedure A, crude 1*H*-pyrrolo[2,3-*b*]pyridine-4-carboxylic acid (0.63 mmol) was reacted with histamine hydrochloride (230 mg, 1.3 mmol) to afford the desired product (41 mg, 25% yield) as an orange-brown solid: ¹H NMR (500 MHz, DMSO-*d*₆) δ 11.95 (s, 1H), 11.82 (s, 1H), 8.57 (t, *J* = 5.5 Hz, 1H), 8.29 (d, *J* = 4.5 Hz, 1H), 7.57–7.56 (m, 2H), 7.33 (d, *J* = 5.0 Hz, 1H), 6.86 (s, 1H), 6.76–6.75 (m, 1H), 3.54 (q, *J* = 7.5 Hz, 2H), 2.80 (t, *J* = 7.5 Hz, 2H); ESI MS *m/z* 256 [C₁₃H₁₃N₅O + H]⁺.

Example 113

2-(Thiophen-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridine

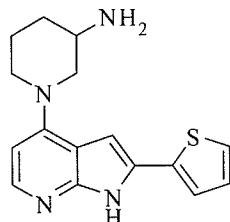
[0217] To a solution of *tert*-butyl 3-methylpyridin-2-ylcarbamate (2.0 g, 9.6 mmol) in THF (100 mL) at –30 °C was added butyl lithium (12 mL, 2.5 M, 29 mmol) and the reaction mixture was warmed to 0 °C and stirred for 1.5 h. A solution of *N*-methoxy-*N*-methylthiophene-2-carboxamide (1.6 g, 9.6 mmol) in THF (10 mL) was slowly added and the reaction was stirred at 0 °C for 1 h. The reaction mixture was slowly treated with HCl (20 mL, 6 M) followed by heating at 60 °C for 18 h. The reaction mixture was cooled, the layers were separated and the aqueous layer was made basic with NaOH (6 M) and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were dried, concentrated and the residue was purified by flash chromatography (silica gel, methanol/methylene chloride gradient) to afford the product (1.2 g, 64% yield) as a yellow solid: ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.36–7.34 (m, 1H), 7.14–7.11 (m, 1H), 6.73–6.72 (m, 1H), 6.64–6.63 (m, 1H), 6.34–6.36 (m, 1H); ESI MS *m/z* 201 [C₁₁H₈N₂S + H]⁺.

Example 114
4-Chloro-2-(thiophen-2-yl)-1H-pyrrolo[2,3-b]pyridine



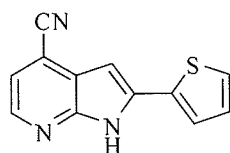
[0218] Following the procedure outlined in Example 107, 2-(thiophen-2-yl)-1H-pyrrolo[2,3-
5 b]pyridine (1.3 g, 6.2 mmol) was reacted with *m*-CPBA (1.9 g, 77%, 7.5 mmol) followed by phosphorus oxychloride (6.0 mL, 65 mmol) to afford the product (0.80 g, 55% yield) as a brown solid: ESI MS m/z 235 [$C_{11}H_7ClN_2S + H$] $^+$.

Example 115
1-[(Thiophen-2-yl)-1H-pyrrolo[2,3-b]pyridin-4-yl]piperidin-3-amine



[0219] Following the procedure outlined in Example 108, 4-chloro-2-(thiophen-2-yl)-1H-
pyrrolo[2,3-b]pyridine (75 mg, 0.32 mmol) was reacted with *tert*-Butyl 3-aminopiperidine-1-
carboxylate (130 mg, 0.64 mmol) to afford the desired product (43 mg, 45% yield) as a light
yellow solid: 1H NMR (300 MHz, DMSO- d_6) δ 7.92 (d, $J = 5.7$ Hz, 1H), 7.58–7.57 (m, 1H),
15 7.52–7.50 (m, 1H), 7.14–7.11 (m, 2H), 6.67 (s, 1H), 6.40 (d, $J = 5.7$ Hz, 1H), 3.88–3.67 (m, 2H),
2.95–2.79 (m, 2H), 2.71–2.61 (m, 1H), 1.95–1.73 (m, 2H), 1.69–1.54 (m, 1H), 1.31–1.16 (m,
1H); ESI MS m/z 299 [$C_{16}H_{18}N_4S + H$] $^+$; HPLC 98.1% (AUC), $t_R = 7.43$ min.

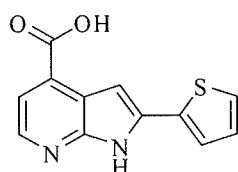
Example 116
2-(Thiophen-2-yl)-1H-pyrrolo[2,3-b]pyridine-4-carbonitrile



[0220] A suspension of 4-chloro-2-(thiophen-2-yl)-1H-pyrrolo[2,3-b]pyridine (200 mg, 0.85
mmol), zinc dust (11 mg, 0.17 mmol), zinc cyanide (100 mg, 0.85 mmol),
tris(dibenzylideneacetone)dipalladium (78 mg, 0.090 mmol) and 1,1'-

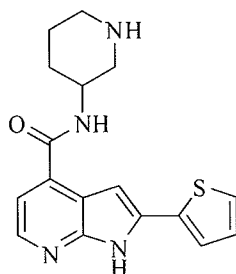
bis(diphenylphosphino)ferrocene (47 mg, 0.090 mmol) in N,N-dimethylacetamide (3 mL) was flushed with N₂ and heated in a microwave at 120 °C for 3 h. The mixture was cooled, diluted with ethyl acetate (20 mL) and filtered. The filtrate was washed with a 5% aq. LiCl, dried, concentrated and the residue was purified by flash chromatography (silica gel, methanol/methylene chloride gradient) to afford crude product (170 mg) as a gummy solid: ¹H NMR (300 MHz, CD₃OD) δ 8.30 (d, *J* = 5.1 Hz, 1H), 7.66–7.64 (m, 1H), 7.57–7.55 (m, 1H), 7.39 (d, *J* = 5.1 Hz, 1H), 7.19–7.16 (m, 1H), 6.82 (s, 1H); ESI MS *m/z* 226 [C₁₂H₇N₃S+ H]⁺.

Example 117

2-(Thiophen-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridine-4-carboxylic Acid

[0221] A solution of 2-(thiophen-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridine-4-carbonitrile (170 mg, 0.76 mmol) in HCl (10 mL, 6 M) was refluxed for 2 d. The reaction mixture was cooled and concentrated to afford the crude product (280 mg) as a brown solid: ESI MS *m/z* 245 [C₁₂H₈N₂O₂S+ H]⁺.

Example 118

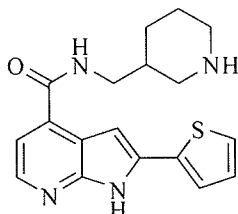
N-(Piperidin-3-yl)-2-(thiophen-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridine-4-carboxamide

[0222] Following General Procedure A, 2-(thiophen-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridine-4-carboxylic acid (0.38 mmol) was reacted *tert*-butyl 3-aminopiperidine-1-carboxylate (200 mg, 1.0 mmol) to afford the desired product (17 mg, 14% yield) as a yellow solid: ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.44 (s, 1H), 8.34 (d, *J* = 7.8 Hz, 1H), 8.28 (d, *J* = 5.1 Hz, 1H), 7.71–7.70 (m, 1H), 7.63 (dd, *J* = 0.9, 5.1 Hz, 1H), 7.38 (d, *J* = 5.1 Hz, 1H), 7.18 (dd, *J* = 3.6, 5.1 Hz, 1H), 6.96 (s, 1H), 3.40–3.86 (m, 2H), 3.09–3.01 (m, 1H), 2.90–2.80 (m, 1H), 1.95–1.85 (m, 1H),

1.73–1.63 (m, 1H), 1.61–1.41 (m, 2H); ESI MS m/z 327 [$C_{17}H_{18}N_4OS + H$] $^+$; HPLC >99% (AUC), t_R = 8.36 min.

Example 119

N-(Piperidin-3-ylmethyl)-2-(thiophen-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridine-4-carboxamide



5

[0223] Following General Procedure A, 2-(thiophen-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridine-4-carboxylic acid (130 mg, 0.41 mmol) was reacted *tert*-butyl 3-(aminomethyl)piperidine-1-carboxylate (180 mg, 0.82 mmol) to afford the desired product (37 mg, 28% yield) as a yellow solid: 1H NMR (500 MHz, DMSO- d_6) δ 8.57–8.55 (m, 1H), 8.28 (d, J = 5.0 Hz, 1H), 7.70 (d, J = 3.5 Hz, 1H), 7.63 (d, J = 5.0 Hz, 1H), 7.37 (d, J = 5.0 Hz, 1H), 7.18–7.17 (m, 1H), 6.98 (s, 1H), 3.20–3.15 (m, 2H), 2.98–2.94 (m, 1H), 2.85–2.81 (m, 1H), 2.47–2.41 (m, 1H), 2.27–2.21 (m, 1H), 1.81–1.67 (m, 2H), 1.62–1.55 (m, 1H), 1.39–1.29 (m, 1H), 1.15–1.06 (m, 1H); ESI MS m/z 341 [$C_{18}H_{20}N_4OS + H$] $^+$; HPLC >99% (AUC), t_R = 8.51 min.

10

Kinase assay

[0224] PBK activity was determined in the presence or absence of compounds using fluorescein isothiocyanate-labeled (FITC-labeled) histone H3 peptide as a substrate. The extent of FITC-labeled histone H3 peptide phosphorylation was measured by immobilized metal ion affinity-based fluorescence polarization (IMAP) technology (Sportsman JR, et al, Assay Drug Dev. Technol. 2: 205-14, 2004) using IMAP FP Progressive Binding System (Molecular Devices Corporation). Test compounds were dissolved in DMSO at 12.5 mM and then serially diluted as the DMSO concentration in the assays to be 1%. The serially diluted compounds, 0.8 ng/micro-L PBK (Carna Biosciences) and 100 nM FITC-labeled histone H3 peptide were reacted in a reaction buffer (20 mM HEPES, 0.01% Tween-20, 0.3 mM $MgCl_2$, 2 mM dithiothreitol, 50micro-M ATP, pH 7.4) at room temperature for 1 hour. The reaction was stopped by the addition of three fold assay volume of progressive binding solution. Following 0.5 hour incubation at room temperature, fluorescence polarization was measured by Wallac EnVision 2103 multilabel reader (PerkinElmer). IC_{50} values were calculated by nonlinear four parameter fit using SigmaPlot, version 10.0 (Systat Software, Inc.).

20

25

[0225] IC₅₀ values of the typical compounds of the present invention are shown in following table 2:

Table 2

Example No.	compound	(micro M) TOPK
78	(S)-2-[5-(Piperazin-1-yl)thiophen-2-yl]-N-(piperidin-3-yl)-1H-imidazo[4,5-b]pyridine-7-carboxamide	0.0052
60	N-(4-Aminocadamantyl)-2-cyclopropyl-3H-imidazo[4,5-b]pyridine-7-carboxamide	0.0053
29	N-(3-Aminoadamantyl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	0.024
59	N-[(1R,4R)-4-Aminocyclohexyl]-2-cyclopropyl-3H-imidazo[4,5-b]pyridine-7-carboxamide	0.033
55	(S)-2-Cyclopropyl-N-(piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	0.034
56	(S)-2-Cyclopropyl-N-(piperidin-3-ylmethyl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	0.034
28	N-(3-Aminocyclohexyl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	0.035
62	(S)-2-(Cyclopropylmethyl)-N-(piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	0.036
21	(R)-N-(Piperidin-3-ylmethyl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	0.039
58	N-[(1R,4R)-4-(Aminomethyl)cyclohexyl]-2-cyclopropyl-3H-imidazo[4,5-b]pyridine-7-carboxamide	0.055
75	(S)-N-(Piperidin-3-yl)-2-(thiophen-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	0.059
34	N-{[3-(Aminomethyl)cyclohexyl]methyl}-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	0.063
84	2-{5-[(R)-3-Aminopyrrolidin-1-yl]thiophen-2-yl}-N-[(S)-piperidin-3-yl]-3H-imidazo[4,5-b]pyridine-7-carboxamide	0.063
30	N-{[(1S,4S)-4-Aminocyclohexyl]methyl}-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	0.072
16	N-(Piperidin-3-ylmethyl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	0.074
19	(S)-N-(Piperidin-3-yl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	0.078
76	(S)-N-(Piperidin-3-ylmethyl)-2-(thiophen-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	0.098
22	(S)-N-(Piperidin-3-ylmethyl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	0.099
81	2-[5-(3-hydroxypyrrolidin-1-yl)thiophen-2-yl]-N-[(S)-piperidin-3-yl]-3H-imidazo[4,5-b]pyridine-7-carboxamide	0.11
31	trans-N-[4-(Aminomethyl)cyclohexyl]-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	0.14

Example No.	compound	(micro M) TOPK
83	(S)-2-{5-[(2-Hydroxyethyl)(methyl)amino]thiophen-2-yl}-N-(piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	0.15
15	N-(Piperidin-3-yl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	0.16
63b	2-(Bicyclo[2.2.1]heptan-2-yl)-N-[(S)-piperidin-3-yl]-3H-imidazo[4,5-b]pyridine-7-carboxamide	0.18
91	(S)-2-[4-(Piperazin-1-yl)thiophen-2-yl]-N-(piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	0.22
54	(R)-2-(5-Bromofuran-2-yl)-N-(piperidin-3-ylmethyl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	0.29
20	N-(4-Aminocyclohexyl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	0.3
32	trans-N-{[4-(Aminomethyl)cyclohexyl]methyl}-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	0.33
35	N-[3-(Aminomethyl)-3,5,5-trimethylcyclohexyl]-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	0.34
79	(S)-2-(5-morpholinothiophen-2-yl)-N-(piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	0.34
27	N-(Azetidin-3-ylmethyl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	0.41
77	(R)-N-(piperidin-3-ylmethyl)-2-(thiophen-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	0.43
25	N-(Pyrrolidin-3-yl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	0.45
57	tert-Butyl [(1R,4R)-4-(2-cyclopropyl-3H-imidazo[4,5-b]pyridine-7-carboxamido)cyclohexyl]methylcarbamate	0.46
80	(S)-2-[5-(piperidin-1-yl)thiophen-2-yl]-N-(piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	0.46
64	N-{[(1R,4R)-4-(aminomethyl)cyclohexyl]methyl}-2-(bicyclo[2.2.1]heptan-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	0.49
24	(S)-N-[2-(Piperidin-3-yl)ethyl]-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	0.59
82	2-[5-(3-hydroxypiperidin-1-yl)thiophen-2-yl]-N-((S)-piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	0.63
67	(S)-N-(Piperidin-3-yl)-2-(thiophene-2-carbonyl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	0.7
26	N-(Piperidin-2-ylmethyl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	0.74
63a	2-(Bicyclo[2.2.1]heptan-2-yl)-N-[(S)-piperidin-3-yl]-3H-imidazo[4,5-b]pyridine-7-carboxamide	0.88
23	(R)-N-[2-(Piperidin-3-yl)ethyl]-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	1.0

Example No.	compound	(micro M) TOPK
45	(S)-2-(5-Bromothiophen-2-yl)-N-(piperidin-3-yl)-1H-imidazo[4,5-b]pyridine-7-carboxamide	1.0
12	N-[2-(1H-imidazol-4-yl)ethyl]-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	1.2
42	(S)-2-(5-Bromothiophen-2-yl)-N-(piperidin-3-ylmethyl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	1.2
72	(S)-2-[Hydroxy(thiophen-2-yl)methyl]-N-(piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	1.5
39	N-(Aminoadamant-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	1.8
73	2-[Hydroxy(thiophen-2-yl)methyl]-N-[(S)-piperidin-3-ylmethyl]-3H-imidazo[4,5-b]pyridine-7-carboxamide	1.9
43	(R)-2-(5-Bromothiophen-2-yl)-N-(piperidin-3-ylmethyl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	2.2
70	(S)-N-(Piperidin-3-ylmethyl)-2-(thiophene-2-carbonyl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	2.3
92	(R)-2-[5-(Piperazin-1-yl)furan-2-yl]-N-(piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	2.5
108	1-(1H-Pyrrolo[2,3-b]pyridin-4-yl)piperidin-3-amine	3.3
14	2-(4-Chlorophenyl)-N-(piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	3.6
41	N-(3-Aminocyclohexyl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	4
17	N-[3-(1H-Imidazol-2-yl)propyl]-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	4.1
89	2-[4-(3-Hydroxypyrrolidin-1-yl)thiophen-2-yl]-N-[(S)-piperidin-3-yl]-3H-imidazo[4,5-b]pyridine-7-carboxamide	4.2
33	N-(1-Methylpiperidin-3-yl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	4.8
52	(S)-2-(5-bromofuran-2-yl)-N-(piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	4.9
18	(R)-N-(Piperidin-3-yl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	5.9
118	N-(Piperidin-3-yl)-2-(thiophen-2-yl)-1H-pyrrolo[2,3-b]pyridine-4-carboxamide	7.1
90	(S)-2-{4-[Bis(2-hydroxyethyl)amino]thiophen-2-yl}-N-(piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamid	7.4
38	N-(Piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	8.3
49	(S)-2-(4-Bromothiophen-2-yl)-N-(piperidin-3-yl)-1H-imidazo[4,5-b]pyridine-7-carboxamide	8.8
74	2-[Hydroxy(thiophen-2-yl)methyl]-N-[(R)-piperidin-3-ylmethyl]-3H-imidazo[4,5-b]pyridine-7-carboxamide	8.8
71	(R)-N-(piperidin-3-ylmethyl)-2-(thiophene-2-carbonyl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	9.9

Example No.	compound	(micro M) TOPK
50	(S)-2-(4-bromothiophen-2-yl)-N-(piperidin-3-ylmethyl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	11
44	2-(5-Bromothiophen-2-yl)-N-(piperidin-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	12
115	1-[-(Thiophen-2-yl)-1H-pyrrolo[2,3-b]pyridin-4-yl]piperidin-3-amine	16
119	N-(Piperidin-3-ylmethyl)-2-(thiophen-2-yl)-1H-pyrrolo[2,3-b]pyridine-4-carboxamide	16
106	N-[2-(Thiophen-2-yl)-3H-imidazo[4,5-b]pyridin-7-yl]piperidine-3-carboxamide	20
109	1-(1H-Pyrrolo[2,3-b]pyridin-4-yl)piperidine-3-carboxamide	20
88	(S)-2-(4-Morpholinothiophen-2-yl)-N-(piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	22
13	N-[2-(1H-Imidazol-4-yl)ethyl]-2-(4-chlorophenyl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	23
40	N-(Piperidin-3-ylmethyl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	37
102	1-[2-(Thiophen-2-yl)-3H-imidazo[4,5-b]pyridin-7-yl]piperidin-3-ylmethanamine	77
37	N-(3-Aminophenyl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	96

Examples 49 Western blot analysis

- 5 [0226] To evaluate the expression status of PBK in several cell lines, western blot analysis was performed using crude cell lysate collected from those cells. Anti-PBK antibody (clone 31, BD Biosciences) was used to visualize the expression. Breast cancer lines, T47D and BT-549 expressed PBK significantly although Bladder cancer line and HT-1197 showed no expression of PBK.

10 Examples 50 Cell-based assay

- [0227] Active candidate inhibitors against PBK were evaluated for their target-specific cytotoxicity using T47D, BT-549, and HT-1197 cells was used for negative control. 100 micro-L of cell suspension was seeded onto 96-well microtiter plate (ViewPlate-96FTC, PerkinElmer).
- 15 The initial cell concentration of T47D, BT-549 and HT-1197 were 3,000cells/well, 2,000cells/well and 2,500cells/well respectively. Cellular growth was determined using Cell Counting Kit-8 (DOJINDO) at 72 hours after the exposure of the candidate inhibitors. IC₅₀ was

used as an indicator of the anti-proliferative activity of the inhibitors, and calculated by serial dilution method (0, 1.5625, 3.125, 6.25, 12.5, 25, 50, 100 micro-M). Accurate IC₅₀ values were calculated as described previously.

[0228] IC₅₀ values of the typical compounds of the present invention are shown in following table 3:

Table 3;

Example No.	Compound	IC ₅₀ (microM) (BT549)	IC ₅₀ (microM) (T47D)	IC ₅₀ (microM) (HT1197)
19	(S)-N-(Piperidin-3-yl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	0.14	0.19	0.41
15	N-(Piperidin-3-yl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	0.22	0.45	0.89
45	(S)-2-(5-Bromothiophen-2-yl)-N-(piperidin-3-yl)-1H-imidazo[4,5-b]pyridine-7-carboxamide	0.35	0.42	1.8
31	trans-N-[4-(Aminomethyl)cyclohexyl]-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	0.46	0.32	3.4
29	N-(3-Aminoadamantyl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	0.49	0.32	1.2
14	2-(4-Chlorophenyl)-N-(piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	0.52	0.42	1.7
60	N-(4-Aminocadamantyl)-2-cyclopropyl-3H-imidazo[4,5-b]pyridine-7-carboxamide	0.55	0.87	0.78
59	N-[(1R,4R)-4-Aminocyclohexyl]-2-cyclopropyl-3H-imidazo[4,5-b]pyridine-7-carboxamide	0.71	0.72	2.6
79	(S)-2-(5-morpholinothiophen-2-yl)-N-(piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	0.72	0.12	10
49	(S)-2-(4-Bromothiophen-2-yl)-N-(piperidin-3-yl)-1H-imidazo[4,5-b]pyridine-7-carboxamide	0.73	0.72	7.6
20	N-(4-Aminocyclohexyl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	0.75	0.42	3.2
34	N-{[3-(Aminomethyl)cyclohexyl]methyl}-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	0.76	0.76	2.3
81	2-[5-(3-hydroxypyrrolidin-1-yl)thiophen-2-yl]-N-[(S)-piperidin-3-yl]-3H-imidazo[4,5-b]pyridine-7-carboxamide	0.76	0.79	57
28	N-(3-Aminocyclohexyl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	0.78	0.61	1.8

Example No.	Compound	IC ₅₀ (microM) (BT549)	IC ₅₀ (microM) (T47D)	IC ₅₀ (microM) (HT1197)
21	(R)-N-(Piperidin-3-ylmethyl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	1.3	0.95	2.6
22	(S)-N-(Piperidin-3-ylmethyl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	1.3	0.94	2.9
16	N-(Piperidin-3-ylmethyl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	1.5	1.0	3.1
32	trans-N-{[4-(Aminomethyl)cyclohexyl]methyl}-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	1.5	2.4	1.8
63b	2-(Bicyclo[2.2.1]heptan-2-yl)-N-[(S)-piperidin-3-yl]-3H-imidazo[4,5-b]pyridine-7-carboxamide	1.7	2.1	1.5
80	(S)-2-[5-(piperidin-1-yl)thiophen-2-yl]-N-(piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	1.8	0.94	1.4
42	(S)-2-(5-Bromothiophen-2-yl)-N-(piperidin-3-ylmethyl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	1.8	2.6	11
55	(S)-2-Cyclopropyl-N-(piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	2.1	2.1	2.9
63a	2-(Bicyclo[2.2.1]heptan-2-yl)-N-[(S)-piperidin-3-yl]-3H-imidazo[4,5-b]pyridine-7-carboxamide	2.2	2.9	2.3
50	(S)-2-(4-bromothiophen-2-yl)-N-(piperidin-3-ylmethyl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	2.3	2.4	13
25	N-(Pyrrolidin-3-yl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	2.4	3.2	11
35	N-[3-(Aminomethyl)-3,5,5-trimethylcyclohexyl]-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	2.7	2.6	6.1
18	(R)-N-(Piperidin-3-yl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	2.7	6.6	10
30	N-[(1S,4S)-4-Aminocyclohexyl]methyl}-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	2.8	1.6	12
58	N-[(1R,4R)-4-(Aminomethyl)cyclohexyl]-2-cyclopropyl-3H-imidazo[4,5-b]pyridine-7-carboxamide	2.9	2.7	6.2

Example No.	Compound	IC ₅₀ (microM) (BT549)	IC ₅₀ (microM) (T47D)	IC ₅₀ (microM) (HT1197)
83	(S)-2-{5-[(2-Hydroxyethyl)(methyl)amino]thiophen-2-yl}-N-(piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	2.9	0.83	39
78	(S)-2-[5-(Piperazin-1-yl)thiophen-2-yl]-N-(piperidin-3-yl)-1H-imidazo[4,5-b]pyridine-7-carboxamide	3.0	1.5	7.9
43	(R)-2-(5-Bromothiophen-2-yl)-N-(piperidin-3-ylmethyl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	3.0	2.5	19
84	2-{5-[(R)-3-Aminopyrrolidin-1-yl]thiophen-2-yl}-N-[(S)-piperidin-3-yl]-3H-imidazo[4,5-b]pyridine-7-carboxamide	3.3	2.5	23
82	2-[5-(3-hydroxypiperidin-1-yl)thiophen-2-yl]-N-((S)-piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	3.6	1.1	53
26	N-(Piperidin-2-ylmethyl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	3.9	6.2	15
13	N-[2-(1H-Imidazol-4-yl)ethyl]-2-(4-chlorophenyl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	4.0	3.6	40
39	N-(Aminoadamant-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	4.1	21	75
33	N-(1-Methylpiperidin-3-yl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	4.4	5.5	5.4
67	(S)-N-(Piperidin-3-yl)-2-(thiophene-2-carbonyl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	5.4	6.6	22
23	(R)-N-[2-(Piperidin-3-yl)ethyl]-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	5.7	5.2	8.1
52	(S)-2-(5-bromofuran-2-yl)-N-(piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	5.7	4.7	12
88	(S)-2-(4-Morpholinothiophen-2-yl)-N-(piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	5.8	4.3	>100
24	(S)-N-[2-(Piperidin-3-yl)ethyl]-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	6.3	4.4	7.3
54	(R)-2-(5-Bromofuran-2-yl)-N-(piperidin-3-ylmethyl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	6.9	7.5	10

Example No.	Compound	IC ₅₀ (microM) (BT549)	IC ₅₀ (microM) (T47D)	IC ₅₀ (microM) (HT1197)
118	N-(Piperidin-3-yl)-2-(thiophen-2-yl)-1H-pyrrolo[2,3-b]pyridine-4-carboxamide	6.9	12	9.5
27	N-(Azetidin-3-ylmethyl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	7.1	4.3	45
12	N-[2-(1H-imidazol-4-yl)ethyl]-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	8.0	3.0	62
62	(S)-2-(Cyclopropylmethyl)-N-(piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	8.1	9	8.5
17	N-[3-(1H-Imidazol-2-yl)propyl]-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	8.6	7.4	32
56	(S)-2-Cyclopropyl-N-(piperidin-3-ylmethyl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	12	13	17
64	N-[(1R,4R)-4-(aminomethyl)cyclohexyl]methyl}-2-(bicyclo[2.2.1]heptan-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	13	16	8.1
57	tert-Butyl [(1R,4R)-4-(2-cyclopropyl-3H-imidazo[4,5-b]pyridine-7-carboxamido)cyclohexyl]methylcarbamate	14	14	13
70	(S)-N-(Piperidin-3-ylmethyl)-2-(thiophene-2-carbonyl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	16	39	50
71	(R)-N-(piperidin-3-ylmethyl)-2-(thiophene-2-carbonyl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	16	20	60
75	(S)-N-(Piperidin-3-yl)-2-(thiophen-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	22	23	39
91	(S)-2-[4-(Piperazin-1-yl)thiophen-2-yl]-N-(piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	23	20	87
89	2-[4-(3-Hydroxypyrrolidin-1-yl)thiophen-2-yl]-N-[(S)-piperidin-3-yl]-3H-imidazo[4,5-b]pyridine-7-carboxamide	29	15	>100
72	(S)-2-[Hydroxy(thiophen-2-yl)methyl]-N-(piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	35	29	79
108	1-(1H-Pyrrolo[2,3-b]pyridin-4-yl)piperidin-3-amine	47	>100	>100
106	N-[2-(Thiophen-2-yl)-3H-imidazo[4,5-b]pyridin-7-yl]piperidine-3-carboxamide	47	60	>100

Example No.	Compound	IC ₅₀ (microM) (BT549)	IC ₅₀ (microM) (T47D)	IC ₅₀ (microM) (HT1197)
76	(S)-N-(Piperidin-3-ylmethyl)-2-(thiophen-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-7-carboxamide	75	>100	64
73	2-[Hydroxy(thiophen-2-yl)methyl]-N-[(S)-piperidin-3-ylmethyl]-3H-imidazo[4,5-b]pyridine-7-carboxamide	83	>100	>100
90	(S)-2-{4-[Bis(2-hydroxyethyl)amino]thiophen-2-yl}-N-(piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamid	91	42	>100

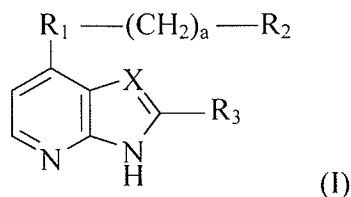
“>100” in the table means over 100 microM.

Industrial Applicability

[0229] The present invention provides a novel imidazopyridine derivative compound having PBK inhibitory effect. The compounds of the present invention may be used for pharmaceutical composition for inhibiting PBK. Such pharmaceutical compositions are suitable for treating or preventing cancer.

WHAT IS CLAIMED IS:

1. A compound represented by formula (I), or a salt, hydrate, solvate, or isomer thereof:



wherein

X is C or N;

R₁ is -CH₂NH-, -CONH-, -CON(CH₃)-, -NHCO-, or single bond;

R₂ is 3-10 membered heterocyclic group, 5-10 membered heteroaryl, C₃-C₁₀ cycloalkyl or C₅-C₁₀ aryl, each optionally substituted by one or more substituents each independently selected from the group consisting of hydroxy, oxo, nitro, cyano, amino, amide, halogen, sulfamoyl, phosphoryl, phosphate group, carbonyl, acyl, carboxyl, C₁-C₆ alkyl, C₁-C₆ alkenyl, C₁-C₆ alkynyl, C₁-C₆ alkoxy, C₁-C₆ alkylamino, aminoC₁-C₆ alkyl, C₁-C₆ alkylcarbonylamino, C₁-C₆ alkylaminocarbonyl, aminocarbonylC₁-C₆ alkyl, C₁-C₆ alkylsulfonyl, C₁-C₆ alkylsulfonylamino, aminosulfonylC₁-C₆ alkyl, aminoC₁-C₆ alkylsulfonyl, tert-butoxycarbonyl, tert-butoxycarbonyl-aminomethyl, 3-10 membered heterocyclic group, 5-10 membered heteroaryl, C₃-C₁₀ cycloalkyl and C₅-C₁₀ aryl;

R₃ is hydrogen, bicyclo[2.2.1]heptan-2-yl, C₁-C₆ alkyl, phenyl, thiophen-2-yl, furan-2-yl, cyclopropyl, or cyclopentyl, each optionally substituted by one or more substituents each independently selected from the group consisting of hydroxy, oxo, nitro, cyano, amino, amide, halogen, sulfamoyl, phosphoryl, phosphate group, carbonyl, acyl, carboxyl, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, -NR'R'', 3-10 membered heterocyclic group, and 5-10 membered heteroaryl, each optionally substituted by halogen, amino or hydroxy, wherein R' or R'' is each independently selected from the group consisting of hydrogen, C₁-C₆ alkyl and hydroxyC₁-C₆alkyl; and

a is 0-5 integer.

2. The compound of claim 1, wherein R₂ is 3-10 membered heterocyclic group which is bound to pyridine ring on its hetero atom when R₁ is single bond and a is 0.

3. The compound of claim 1, wherein R₃ is hydrogen, bicyclo[2.2.1]heptan-2-yl, C₁-C₆ alkyl, cyclopropyl, furan-2-yl, phenyl, or thiophen-2-yl, wherein the C₁-C₆ alkyl is optionally substituted by 1 or 2 substituents each independently selected from the group consisting of hydroxy, oxo, cyclopropyl, and thiophen-2-yl, wherein the furan-2-yl is optionally substituted by 1 or 2 substituents each independently selected from the group consisting of halogen and piperazine-1-yl, wherein the phenyl is optionally substituted by 1 or 2 halogen, or wherein the thiophen-2-yl is optionally substituted by 1 or 2 substituents each independently selected from the group consisting of halogen, morpholine-4-yl, di(hydroxyethyl)amino, (hydroxyethyl)(methyl)amino, piperazine-1-yl which is optionally substituted by 1 or 2 hydroxy, piperidine-1-yl which is optionally substituted by 1 or 2 hydroxy, and pyrrolidine-1-yl which is optionally substituted by 1 or 2 substituents each independently selected from the group consisting of hydroxy and amino.

4. The compound of Claim 1 or 2, wherein R₂ is adamantyl, azetidine-3-yl, cyclohexyl, imidazole-2-yl, imidazole-4-yl, phenyl, piperidine-1-yl, piperidine-2-yl, piperidine-3-yl, pyrrolidine-3-yl, or quinuclidin-3-yl, which are optionally substituted by 1 to 4 substituents each independently selected from hydroxy, aminomethyl, methyl, aminocarbonyl(amide), amino, tert-butoxycarbonyl and tert-butoxycarbonyl-aminomethyl.

5. The compound of any one of claim 2 or 3, wherein the C₁-C₆ alkyl substituted by 1 or 2 substituents is cyclopropylmethyl, thiophen-2-ylmethyl, hydroxyl(thiophen-2-yl)methyl or thiophene-2-ylcarbonyl.

6. The compound of any one of claim 3 or 4, wherein the furan-2-yl substituted by 1 or 2 substituents is 5-bromofuran-2-yl or 5-(piperazin-1-yl)furan-2-yl.

7. The compound of any one of claim 3 or 4, the phenyl substituted by 1 or 2 halogen is 4-chlorophenyl.

8. The compound of any one of claim 3 or 4, the thiophen-2-yl substituted by 1 or 2 substituents is 4-bromothiophen-2-yl, 5-morpholinothiophen-2-yl, {4-[Bis(2-

hydroxyethyl)amino]thiophen-2-yl, 5-[(2-Hydroxyethyl)(methyl)amino]thiophen-2-yl, 5-(Piperazin-1-yl)thiophen-2-yl, 5-(piperidin-1-yl)thiophen-2-yl, 5-(3-hydroxypiperidin-1-yl)thiophen-2-yl, 5-(3-Aminopyrrolidin-1-yl)thiophen-2-yl, 5-(3-hydroxypiperidin-1-yl)thiophen-2-yl, 5-(3-hydroxypyrrolidin-1-yl)thiophen-2-yl, 5-(3-hydroxypyrrolidin-1-yl)thiophen-2-yl, 4-morpholinothiophen-2-yl, 4-(3-hydroxypyrrolidin-1-yl)thiophen-2-yl, or 4-(pyperazin-1-yl)thiophen-2-yl.

9. The compound of claim 1, which is selected from the group consisting of:

N-[2-(1H-imidazol-4-yl)ethyl]-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide (Example No. 12),

N-[2-(1H-Imidazol-4-yl)ethyl]-2-(4-chlorophenyl)-3H-imidazo[4,5-b]pyridine-7-carboxamide (Example No. 13),

2-(4-Chlorophenyl)-N-(piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide (Example No. 14),

N-(Piperidin-3-yl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide (Example No. 15),

N-(Piperidin-3-ylmethyl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide (Example No. 16),

N-[3-(1H-Imidazol-2-yl)propyl]-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide (Example No. 17),

(R)-N-(Piperidin-3-yl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide (Example No. 18),

(S)-N-(Piperidin-3-yl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide (Example No. 19),

N-(4-Aminocyclohexyl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide (Example No. 20),

(R)-N-(Piperidin-3-ylmethyl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide (Example No. 21),

(S)-N-(Piperidin-3-ylmethyl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide (Example No. 22),

(R)-N-[2-(Piperidin-3-yl)ethyl]-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide (Example No. 23),

26 (S)-N-[2-(Piperidin-3-yl)ethyl]-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-
27 carboxamide (Example No. 24),
28 N-(Pyrrolidin-3-yl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide
29 (Example No. 25),
30 N-(Piperidin-2-ylmethyl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-
31 carboxamide (Example No. 26),
32 N-(Azetidin-3-ylmethyl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-
33 carboxamide (Example No. 27),
34 N-(3-Aminocyclohexyl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-
35 carboxamide (Example No. 28),
36 N-(3-Aminoadamantyl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-
37 carboxamide (Example No. 29),
38 N-{[(1S,4S)-4-Aminocyclohexyl]methyl}-2-(thiophen-2-yl)-3H-imidazo[4,5-
39 b]pyridine-7-carboxamide (Example No. 30),
40 trans-N-[4-(Aminomethyl)cyclohexyl]-2-(thiophen-2-yl)-3H-imidazo[4,5-
41 b]pyridine-7-carboxamide (Example No. 31),
42 trans-N-{[4-(Aminomethyl)cyclohexyl]methyl}-2-(thiophen-2-yl)-3H-
43 imidazo[4,5-b]pyridine-7-carboxamide (Example No. 32),
44 N-(1-Methylpiperidin-3-yl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-
45 carboxamide (Example No. 33),
46 N-{[3-(Aminomethyl)cyclohexyl]methyl}-2-(thiophen-2-yl)-3H-imidazo[4,5-
47 b]pyridine-7-carboxamide (Example No. 34),
48 N-[3-(Aminomethyl)-3,5,5-trimethylcyclohexyl]-2-(thiophen-2-yl)-3H-
49 imidazo[4,5-b]pyridine-7-carboxamide (Example No. 35),
50 N-Methyl-N-(piperidin-3-yl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-
51 carboxamide (Example No. 36),
52 N-(3-Aminophenyl)-2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide
53 (Example No. 37),
54 N-(Piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide (Example No. 38),
55 N-(Aminoadamant-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide (Example
56 No. 39),

57 N-(Piperidin-3-ylmethyl)-3H-imidazo[4,5-b]pyridine-7-carboxamide (Example
58 No. 40),
59 N-(3-Aminocyclohexyl)-3H-imidazo[4,5-b]pyridine-7-carboxamide (Example
60 No. 41),
61 (S)-2-(5-Bromothiophen-2-yl)-N-(piperidin-3-ylmethyl)-3H-imidazo[4,5-
62 b]pyridine-7-carboxamide (Example No. 42),
63 (R)-2-(5-Bromothiophen-2-yl)-N-(piperidin-3-ylmethyl)-3H-imidazo[4,5-
64 b]pyridine-7-carboxamide (Example No. 43),
65 2-(5-Bromothiophen-2-yl)-N-(piperidin-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-
66 7-carboxamide (Example No. 44),
67 (S)-2-(5-Bromothiophen-2-yl)-N-(piperidin-3-yl)-1H-imidazo[4,5-b]pyridine-7-
68 carboxamide (Example No. 45),
69 (S)-2-(4-Bromothiophen-2-yl)-N-(piperidin-3-yl)-1H-imidazo[4,5-b]pyridine-7-
70 carboxamide (Example No. 49),
71 (S)-2-(4-bromothiophen-2-yl)-N-(piperidin-3-ylmethyl)-3H-imidazo[4,5-
72 b]pyridine-7-carboxamide (Example No. 50),
73 (S)-tert-Butyl 3-[2-(5-bromofuran-2-yl)-3H-imidazo[4,5-b]pyridine-7-
74 carboxamido]piperidine-1-carboxylate (Example No. 51),
75 (S)-2-(5-bromofuran-2-yl)-N-(piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-
76 carboxamide (Example No. 52),
77 (S)-tert-Butyl 3-{[2-(5-bromofuran-2-yl)-3H-imidazo[4,5-b]pyridine-7-
78 carboxamido]methyl}piperidine-1-carboxylate (Example No. 53),
79 (R)-2-(5-Bromofuran-2-yl)-N-(piperidin-3-ylmethyl)-3H-imidazo[4,5-b]pyridine-
80 7-carboxamide (Example No. 54),
81 (S)-2-Cyclopropyl-N-(piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-carboxamide
82 (Example No. 55),
83 (S)-2-Cyclopropyl-N-(piperidin-3-ylmethyl)-3H-imidazo[4,5-b]pyridine-7-
84 carboxamide (Example No. 56),
85 tert-Butyl [(1R,4R)-4-(2-cyclopropyl-3H-imidazo[4,5-b]pyridine-7-
86 carboxamido)cyclohexyl]methylcarbamate (Example No. 57),
87 N-[(1R,4R)-4-(Aminomethyl)cyclohexyl]-2-cyclopropyl-3H-imidazo[4,5-
88 b]pyridine-7-carboxamide (Example No. 58),

- 89 N-[(1R,4R)-4-Aminocyclohexyl]-2-cyclopropyl-3H-imidazo[4,5-b]pyridine-7-
90 carboxamide (Example No. 59),
91 N-(4-Aminocadamantyl)-2-cyclopropyl-3H-imidazo[4,5-b]pyridine-7-
92 carboxamide (Example No. 60),
93 (S)-2-(Cyclopropylmethyl)-N-(piperidin-3-yl)-3H-imidazo[4,5-b]pyridine-7-
94 carboxamide (Example No. 62),
95 2-(Bicyclo[2.2.1]heptan-2-yl)-N-[(S)-piperidin-3-yl]-3H-imidazo[4,5-b]pyridine-
96 7-carboxamide (Example No. 63a),
97 2-(Bicyclo[2.2.1]heptan-2-yl)-N-[(S)-piperidin-3-yl]-3H-imidazo[4,5-b]pyridine-
98 7-carboxamide (Example No. 63b),
99 N-{[(1R,4R)-4-(aminomethyl)cyclohexyl]methyl}-2-(bicyclo[2.2.1]heptan-2-yl)-
100 3H-imidazo[4,5-b]pyridine-7-carboxamide (Example No. 64),
101 N-(piperidin-2-ylmethyl)-2-(thiophene-2-carbonyl)-3H-imidazo[4,5-b]pyridine-7-
102 carboxamide (Example No. 66),
103 (S)-N-(Piperidin-3-yl)-2-(thiophene-2-carbonyl)-3H-imidazo[4,5-b]pyridine-7-
104 carboxamide (Example No. 67),
105 (R)-tert-Butyl 3-[(2-(thiophene-2-carbonyl)-3H-imidazo[4,5-b]pyridine-7-
106 carboxamido)methyl]piperidine-1-carboxylate (Example No. 68),
107 (S)-tert-Butyl 3-[(2-(thiophene-2-carbonyl)-3H-imidazo[4,5-b]pyridine-7-
108 carboxamido)methyl]piperidine-1-carboxylate (Example No. 69),
109 (S)-N-(Piperidin-3-ylmethyl)-2-(thiophene-2-carbonyl)-3H-imidazo[4,5-
110 b]pyridine-7-carboxamide (Example No. 70),
111 (R)-N-(piperidin-3-ylmethyl)-2-(thiophene-2-carbonyl)-3H-imidazo[4,5-
112 b]pyridine-7-carboxamide (Example No. 71),
113 (S)-2-[Hydroxy(thiophen-2-yl)methyl]-N-(piperidin-3-yl)-3H-imidazo[4,5-
114 b]pyridine-7-carboxamide (Example No. 72),
115 2-[Hydroxy(thiophen-2-yl)methyl]-N-[(S)-piperidin-3-ylmethyl]-3H-imidazo[4,5-
116 b]pyridine-7-carboxamide (Example No. 73),
117 2-[Hydroxy(thiophen-2-yl)methyl]-N-[(R)-piperidin-3-ylmethyl]-3H-
118 imidazo[4,5-b]pyridine-7-carboxamide (Example No. 74),
119 (S)-N-(Piperidin-3-yl)-2-(thiophen-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-7-
120 carboxamide (Example No. 75),

121 (S)-N-(Piperidin-3-ylmethyl)-2-(thiophen-2-ylmethyl)-3H-imidazo[4,5-
122 b]pyridine-7-carboxamide (Example No. 76),
123 (R)-N-(piperidin-3-ylmethyl)-2-(thiophen-2-ylmethyl)-3H-imidazo[4,5-
124 b]pyridine-7-carboxamide (Example No. 77),
125 (S)-2-[5-(Piperazin-1-yl)thiophen-2-yl]-N-(piperidin-3-yl)-1H-imidazo[4,5-
126 b]pyridine-7-carboxamide (Example No. 78),
127 (S)-2-(5-morpholinothiophen-2-yl)-N-(piperidin-3-yl)-3H-imidazo[4,5-
128 b]pyridine-7-carboxamide (Example No. 79),
129 (S)-2-[5-(piperidin-1-yl)thiophen-2-yl]-N-(piperidin-3-yl)-3H-imidazo[4,5-
130 b]pyridine-7-carboxamide (Example No. 80),
131 2-[5-(3-hydroxypyrrolidin-1-yl)thiophen-2-yl]-N-[(S)-piperidin-3-yl]-3H-
132 imidazo[4,5-b]pyridine-7-carboxamide (Example No. 81),
133 2-[5-(3-hydroxypiperidin-1-yl)thiophen-2-yl]-N-((S)-piperidin-3-yl)-3H-
134 imidazo[4,5-b]pyridine-7-carboxamide (Example No. 82),
135 (S)-2-{5-[(2-Hydroxyethyl)(methyl)amino]thiophen-2-yl}-N-(piperidin-3-yl)-3H-
136 imidazo[4,5-b]pyridine-7-carboxamide (Example No. 83),
137 2-{5-[(R)-3-Aminopyrrolidin-1-yl]thiophen-2-yl}-N-[(S)-piperidin-3-yl]-3H-
138 imidazo[4,5-b]pyridine-7-carboxamide (Example No. 84),
139 (S)-2-(4-Morpholinothiophen-2-yl)-N-(piperidin-3-yl)-3H-imidazo[4,5-
140 b]pyridine-7-carboxamide (Example No. 88),
141 2-[4-(3-Hydroxypyrrolidin-1-yl)thiophen-2-yl]-N-[(S)-piperidin-3-yl]-3H-
142 imidazo[4,5-b]pyridine-7-carboxamide (Example No. 89),
143 (S)-2-{4-[Bis(2-hydroxyethyl)amino]thiophen-2-yl}-N-(piperidin-3-yl)-3H-
144 imidazo[4,5-b]pyridine-7-carboxamid (Example No. 90),
145 (S)-2-[4-(Piperazin-1-yl)thiophen-2-yl]-N-(piperidin-3-yl)-3H-imidazo[4,5-
146 b]pyridine-7-carboxamide (Example No. 91),
147 (R)-2-[5-(Piperazin-1-yl)furan-2-yl]-N-(piperidin-3-yl)-3H-imidazo[4,5-
148 b]pyridine-7-carboxamide (Example No. 92),
149 N-[2-(Thiophen-2-yl)-3H-imidazo[4,5-b]pyridin-7-yl]methyl)piperidin-3-amine
150 (Example No. 94),
151 1-(Piperidin-3-yl)-N-{[2-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridin-7-
152 yl]methyl}methanamine (Example No. 95),

153 1-[2-(Thiophen-2-yl)-3H-imidazo[4,5-b]pyridin-7-yl]piperidin-3-amine (Example
154 No. 101),
155 1-[2-(Thiophen-2-yl)-3H-imidazo[4,5-b]pyridin-7-yl]piperidin-3-yl)methanamine
156 (Example No. 102),
157 N-[2-(Thiophen-2-yl)-3H-imidazo[4,5-b]pyridin-7-yl]piperidine-3-carboxamide
158 (Example No. 106),
159 1-(1H-Pyrrolo[2,3-b]pyridin-4-yl)piperidin-3-amine (Example No. 108),
160 1-(1H-Pyrrolo[2,3-b]pyridin-4-yl)piperidine-3-carboxamide (Example No. 109),
161 N-[2-(1H-Imidazol-4-yl)ethyl]-1H-pyrrolo[2,3-b]pyridine-4-carboxamide
162 (Example No. 112),
163 1-[-(Thiophen-2-yl)-1H-pyrrolo[2,3-b]pyridin-4-yl]piperidin-3-amine (Example
164 No. 115),
165 N-(Piperidin-3-yl)-2-(thiophen-2-yl)-1H-pyrrolo[2,3-b]pyridine-4-carboxamide
166 (Example No. 118), and
167 N-(Piperidin-3-ylmethyl)-2-(thiophen-2-yl)-1H-pyrrolo[2,3-b]pyridine-4-
168 carboxamide (Example No. 119).

1 10. A pharmaceutical composition comprising at least one compound of any
2 one of claims 1 to 9 and pharmaceutically acceptable carrier.

1 11. A pharmaceutical composition for preventing or treating PBK dependent
2 diseases comprising at least one compound of any one of claims 1 to 9 and pharmaceutically
3 acceptable carrier.

1 12. The pharmaceutical composition of claim 11, wherein PBK dependent
2 disease is cancer.

1 13. A PBK inhibitor comprising at least one compound of any one of claims 1
2 to 9.

1 14. A method for treating or preventing PBK dependent diseases in a subject,
2 comprising administering to said subject an effective amount of the compound of any one of
3 claims 1 to 9.

1 15. Use of the compound of any one of claims 1 to 9 in manufacturing a
2 pharmaceutical composition for treating or preventing PBK dependent diseases.

1 16. A compound or a pharmaceutically acceptable salt thereof of at least one
2 compound of any one of claims 1 to 9 for use in a treatment or prevention of PKB dependent
3 diseases.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 10/40394

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/535 (2010.01)

USPC - 514/234.2

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)

USPC: 514/234.2

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/258.1; 514/233.8; 514/233.5; 514/186; 544/236; 546/119; 546/120 (see search terms below)

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

WEST: DB=PGPB,USPT,USOC,EPAB,JPAB

Google: Scholar/patents: pkb kinase inhibitors imidazopyridine benzoimidazoles serine threonine akt cancer crystal structure

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ----- Y	US 2009/0163524 A1 (JOHNSON et al) 25 June 2009 (25.06.2009) para [0009]-[0010], [0161], [0169]-[0170])	1-4 ----- 5, 9
Y	YANG et al. Crystal Structure of an Activated Akt/Protein Kinase B Ternary Complex with GSK3-peptide and AMP-PNP, Nature Structural Biology, 2002, Vol 9, pp 941-944; pg 941, fig 1, entire page	5, 9

☐ Further documents are listed in the continuation of Box C.

* 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

13 August 2010 (13.08.2010)

Date of mailing of the international search report

30 AUG 2010

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-3201

Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300

PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 10/40394

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.: 6-8 and 10-16
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:

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.:

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.