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A convenient route to functionalized 3-amino-6-bromofuro[3,2-*b*]-pyridine-2-carboxamides

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ABSTRACT

An efficient synthesis of 3-amino-6-bromofuro[3,2-*b*]pyridine-2-carboxamides is described via the formation of 3-amino-6-bromofuro[3,2-*b*]pyridine-2-carbonitrile. Functionalization of the amino group at position 3 of the heterocycle will be discussed.

1. Introduction

We recently started a research program aimed at the synthesis of a new class of 3-amino-6-bromofuro[3,2-*b*]pyridine-2-carboxamide derivatives as potent kinase inhibitors. Furopyridines are important scaffolds in medicinal chemistry. Unsubstituted pyridine containing furo[3,2-*b*], [3,2-*c*], [2,3-*c*], [2,3-*b*]pyridine-2-carboxamides were described as FXa inhibitors,[1] for treatment of adenosine A2A receptor-related diseases[2] or as inhibitors of leukotriene biosynthesis.[3] Furopyridines have also been used as bioisosteres of the indole core.[4]

The preparation of furo[3,2-*b*]pyridines was recently described using a one-pot Sonogashira coupling-heteroannulation sequence followed by a regioselective functional approach at position 2.[5] 2-Substituted furo[3,2-*b*]pyridines were previously obtained through a coupling-cyclisation process starting from 2-ethynyl-3-pyridinols.[6] In 2007, the access to ethyl 3-aminofuropyridine-2-carboxylates from 1-chloro-2-cyano or 1-hydroxy-2-cyano-substituted pyridines was developed in a one-pot procedure.[7]

In order to synthesize the key intermediate 3-amino-6-bromofuro[3,2-*b*]pyridine-2-carboxamide, we decided to apply such a strategy via the cyclisation of the 5-(bromo-3-cyanomethoxy)pyridine-2-carbonitrile. Instead of preparing carboxylic ester or acid precursors, we envisioned to obtain the corresponding furo[3,2-*b*]pyridine-2-carbonitrile, still not reported in the literature, and giving direct access to the target report an efficient amide by hydration of the nitrile function. Herein, we report the procedure for the synthesis of 3-(benzylamino)-6-bromofuro[3,2-*b*]pyridine-2-carboxamides.

2. Results and discussion

The synthetic route used for the preparation of the 6-bromofuro[3,2-*b*]pyridine-2-carbonitrile is outlined in Scheme 1. 3,5-Dibromopyridine **1** reacted with sodium methoxide in DMF at 65 °C to give 3-bromo-5-methoxypyridine **2** in good yield by nucleophilic substitution of one bromine atom only.[8] Methoxy group cleavage was performed using boron tribromide in CH_2Cl_2 at 0 °C to afford 3-pyridinol **3** in 72% yield. Selective iodination at position 2 of the pyridine ring was carried out by action of iodine in the presence of Na_2CO_3 in H_2O at room temperature.[9] Subsequent alkylation of the hydroxypyridine **4** was obtained by formation of the potassium salt using potassium carbonate followed by its reaction with bromoacetonitrile at room temperature as described for phenol analogs.[10] The corresponding nitrile **6** was synthesized by heating the iodo derivative **5** at 100 °C with CuCN in pyridine via a Rosenmund–von Braun reaction.[11] Finally, heteroannulation of **6** under basic conditions produced 3-amino-6-bromofuro[3,2-*b*]pyridine-2-carbonitrile **7** in good yield and its hydrolysis using concentrated H_2SO_4 led to the corresponding primary amide **8**.

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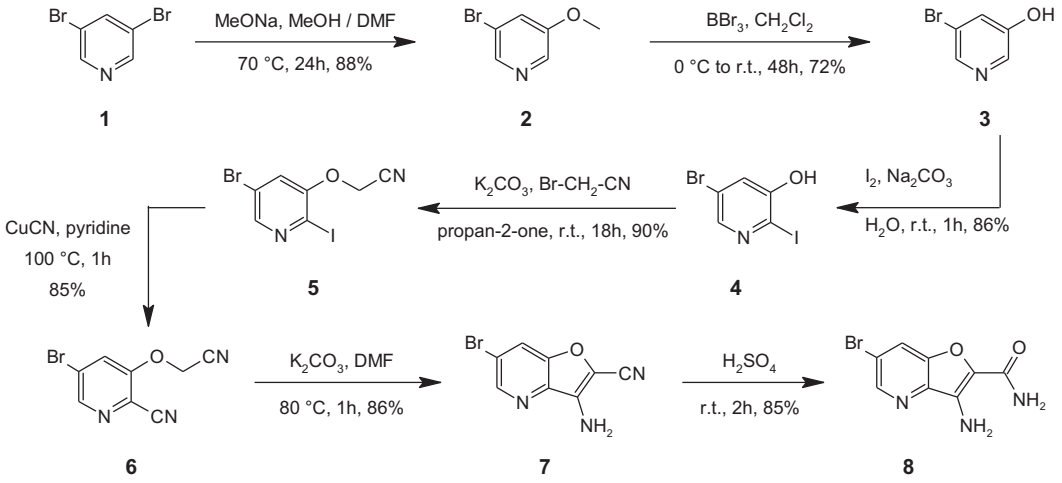


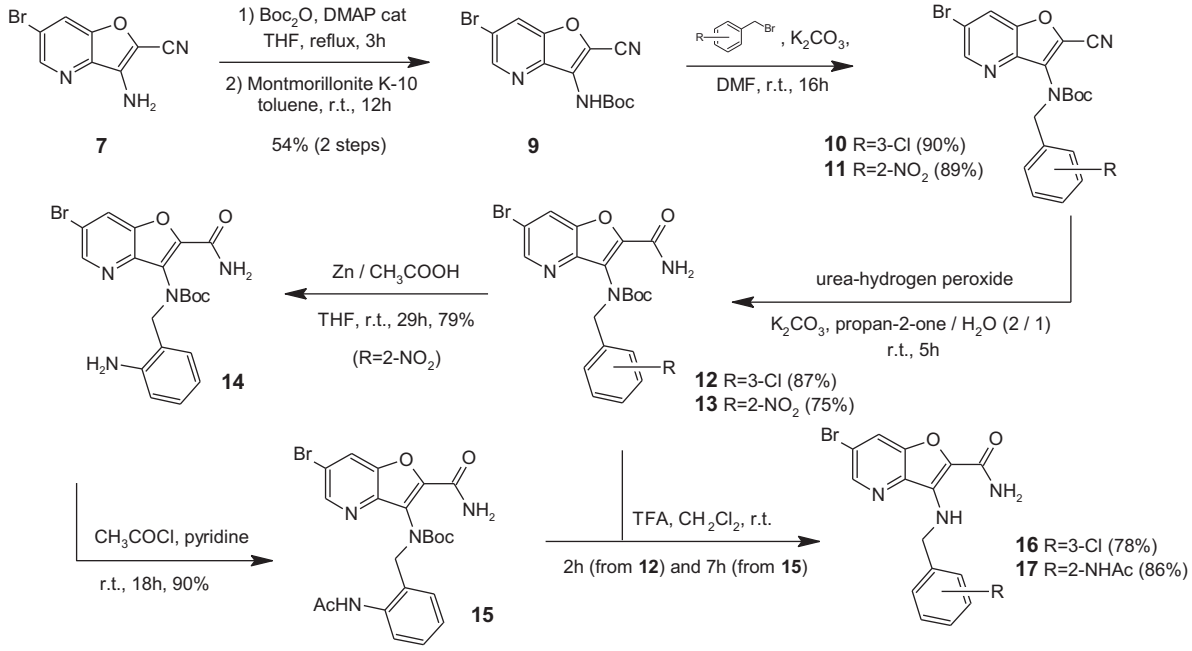
Scheme 1. Synthesis of 3-amino-6-bromofuro[3,2-*b*]pyridine-2-carboxamide **8**.

We then tried to introduce a benzyl moiety on the amino group at position 3 of the furo[3,2-*b*]pyridine-2-carboxamide scaffold. Heterocyclic amine **8** was reacted with 3-chlorobenzaldehyde in the presence of $NaBH_3CN$ in methanolic acid acetic solution (2% v/v) at room temperature and then at reflux. However, only starting material was recovered using reductive amination conditions. From the nitrile containing precursor **7**, the same reaction conditions did not provide the requested benzylamino derivative but 3-amino-6-bromofuro[3,2-*b*]pyridine-2-carbonitrile **7** remained unchanged. We planed to carry out the reaction in two steps by synthesizing the Schiff base before subjecting it to reduction. According to the methods previously described,[12] (PTSA, toluene, reflux; piperidine, EtOH, reflux or mixture of EtOH/toluene (5/1), catalytic amount of glacial acetic acid, reflux), the condensation between the arylamine **7** and 3-chlorobenzaldehyde was unsuccessful.

Benzylation reaction can be performed by nucleophilic substitution in the presence of a base and a benzyl halide. From the primary amine, in order to avoid the formation of the dibenzylated byproduct and to facilitate deprotonation, an electron-withdrawing group was introduced on the primary amine in a first step.[13] *N-tert*-Butoxycarbonylation was achieved by treating heterocyclic amine **7** with di-*tert*-butyl dicarbonate (Boc_2O) in the presence of DMAP in THF at reflux (Scheme 2). Excess of Boc_2O (6 equiv) was employed to obtain exclusively the *N*,*N*-di-Boc derivative instead of a mixture of monoprotected and diprotected analogs.[14]

Subsequent removal of one of the Boc groups, involving a mild procedure[15] using montmorillonite K-10 in toluene at room temperature, gave access to *tert*-butyl 6-bromo-2-cyanofuro[3,2-*b*]pyridin-3-ylcarbamate **9** with 54% yield for two steps. Benzylation of the carbamate intermediate **9** with 3-chloro or 2-nitrobenzyl bromide, in the presence of K_2CO_3 as base in DMF at room temperature, furnished compounds **10** and **11** in good yields (90% and 89%, respectively).

Carbonitrile derivative **7** was converted above to the corresponding carboxamide **8** with 85% yield under usual harsh conditions, using strong mineral acid (H_2SO_4). We decided to check the possibility to perform this reaction under milder conditions using the urea–hydrogen peroxide complex[16], as previously described. Carboxamides **12** and **13** were obtained in good yields, without observing any deprotection of the primary amino group, by treating



Scheme 2. Functionalization of 3-amino-6-bromofuro[3,2-*b*]pyridine-2-carbonitrile **7**.

the corresponding carbonitrile precursors **10** and **11** with urea–hydrogen peroxide (UHP) and K_2CO_3 in a mixture of propan-2-one/water (2/1) at room temperature. Reduction of the nitro group of compound **13**, by action of zinc/acetic acid in THF afforded the corresponding amino derivative **14**, followed by its acetylation with acetyl chloride in pyridine at room temperature. Finally, Boc cleavage with trifluoroacetic acid provided target carboxamides **16** and **17** from **12** and **15**, respectively.

3. Conclusion

In conclusion, we have developed a method for synthesizing 3-(benzylamino)-6-bromofuro[3,2-*b*]pyridine-2-carboxamide derivatives via a ring closure reaction of 5-bromo-3-(cyanomethoxy) pyridine-2-carbonitrile. We have obtained a promising scaffold (compounds **7**) for medicinal chemistry allowing the possibility of a broad pharmacomodulation at the positions 2, 3 or 6 of the furo [3,2-b]pyridine. Functionalization at the level of the bromine atom, involving metal-catalyzed procedure, will be discussed in future publications. Moreover, by functionalization of the amino group at position 3 to give amides and ureas, we are currently looking forward to obtaining new biological activities for these compounds.

4. Experimental section

4.1. General

All reactions were carried out under argon. All reactions were monitored by TLC analysis using Merck silica gel 60F-254 thin-layer plates. Column chromatography was carried out on silica gel Merck 60 (70–230 mesh ASTM). Melting points were determined on a Electrothermal IA 9000 melting point apparatus and are uncorrected. Infrared spectra (IR) were recorded on a Paragon 1000 PC Perkin–Elmer spectrometer. ^{1}H and ^{13}C NMR spectra were performed in DMSO-d_6 using a Bruker AC 250 MHz or an AVANCE 400 MHz spectrometer. Chemical shifts are reported as δ values relative to tetramethylsilane as internal standard and coupling constants (*J*) are given in hertz (Hz). The following abbreviations are used to describe peak patterns when appropriate: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Mass spectra were recorded on Waters ZQ 2000 spectrometer. Elemental analyses were found within ±0.4% of the theoretical values.

*4.1.1. 3-Bromo-5-methoxypyridine (**2**).* A solution of 3,5-dibromopyridine (15.00 g, 63.31 mmol) in dry DMF (60 mL) and sodium methoxide (30% in MeOH) (20.50 mL) was stirred at 63–68 °C for 4 h. Additional sodium methoxide (30% in MeOH) (10 mL) was then added and the reaction mixture was allowed to stir at 63–68 °C for 23 h. After cooling at room temperature, H_2O (80 mL) was added and the mixture was extracted with Et_2O. The organic layers were washed with brine, dried over Na_2SO_4, filtered, and evaporated to dryness. The resulting oil was purified by column chromatography eluting with a 8/2 mixture of petroleum ether and ethyl acetate to afford **2** (10.48 g, 88%) as a light yellow solid. Mp 35–36 °C (lit.[8]: 37–39 °C); IR (KBr): 2954, 1632, 1610, 1032 cm^{-1}; ^{1}H NMR (250 MHz): 3.88 (s, 3H, –OC*H*$_3$), 7.76 (d, *J*=2.4 Hz, 1H, pyridine–*H*), 8.33 (m, 2H, pyridine–*H*); ^{13}C NMR (100 MHz): 58.0, 120.3, 124.6, 135.8, 143.8, 155.9; The data are in conformity with the literature.[8] MS (ESI) *m*/*z* (%): 188.0 [(M+H)$^+$, 100], 190.0 [(M+H)+2, 100]. Anal. Calcd for C_6H_6BrNO: C, 38.33; H, 3.22; N, 7.45. Found: C, 38.39; H, 3.28; N, 7.48.

*4.1.2. 3-Bromo-5-hydroxypyridine (**3**).* Boron tribromide (sol 1 M in CH_2Cl_2) (96 mL, 96.00 mmol) was added dropwise to a cold (0 °C) solution of **2** (6.00 g, 31.91 mmol) in dry CH_2Cl_2. The mixture was stirred at room temperature for 42.5 h, then MeOH (44 mL) was added dropwise and the solvent was evaporated. MeOH (63 mL) was added and the mixture was refluxed for 2 h. After cooling at room temperature and evaporation to dryness, water was added and pH was adjusted to 7–8 with solid Na_2CO_3 before extracting with ethyl acetate. The organic layers were dried over Na_2SO_4, filtered, and evaporated to dryness. The resulting oil was purified by column chromatography eluting with a 7/3 mixture of petroleum ether and ethyl acetate to yield **3** (4.00 g, 72%) as a white solid. Mp 165–166 °C (lit.[8]: 162–164 °C); IR (KBr): 2413, 1650, 1608, 1044 cm^{-1}; ^{1}H NMR (250 MHz): 7.43 (m, 1H, pyridine–*H*), 8.16 (m, 2H, pyridine–*H*), 10.48 (s, 1H, -O*H*); ^{13}C NMR (100 MHz): 117.5, 126.6, 137.3, 147.8, 155.9. The data are in conformity with the literature.[8] MS (ESI) *m*/*z* (%): 174.1 [(M+H)$^+$, 100], 176.1 [(M+H)+2, 100]. Anal. Calcd for C_5H_4BrNO: C, 34.51; H, 2.32; N, 8.05. Found: C, 34.47; H, 2.40; N, 8.09.

*4.1.3. 5-Bromo-2-iodo-3-hydroxypyridine (**4**).* To a solution of **3** (1.00 g, 5.75 mmol) and Na_2CO_3 (1.28 g, 12.08 mmol) in H_2O (100 mL), iodine (1.46 g, 5.75 mmol) was added and the mixture was stirred at 20 °C for 2 h. Then HCl 1 M was added carefully until approximate pH 4. The solid was filtered off, washed with cold H_2O and dried to yield **4** (1.48 g, 86%) as a beige solid. Mp 202–203 °C; IR (KBr): 3447, 1546, 1407, 1334, 1181, 1044 cm^{-1}; ^{1}H NMR (400 MHz): 7.32 (d, *J*=2.1 Hz, 1H, pyridine–*H*), 8.04 (d, *J*=2.1 Hz, 1H, pyridine–*H*), 11.44 (s, 1H, -O*H*); ^{13}C NMR (100 MHz): 109.4, 119.8, 123.3, 141.9, 155.0; MS (ESI) *m*/*z* (%): 299.8 [(M+H)$^+$, 100], 301.8 [(M+H)+2, 100]. Anal. Calcd for C_5H_3BrINO: C, 20.03; H, 1.01; N, 4.67. Found: C, 20.09; H, 1.07; N, 4.70.

*4.1.4. [(5-Bromo-2-iodopyridin-3-yl)oxy]acetonitrile (**5**).* A solution of **4** (0.86 g, 2.87 mmol) in acetone (29 mL) was treated with K_2CO_3 (405 mg, 2.93 mmol), followed by bromoacetonitrile (0.21 mL, 3.01 mmol) and stirred at room temperature overnight. The mixture was filtered and evaporated to dryness. The residue was purified by column chromatography eluting with a 8/2 mixture of petroleum ether and diethyl ether to afford **5** (0.87 g, 90%) as a beige solid. Mp 112–113 °C; IR (KBr): 3050, 2956, 2362, 1549, 1393, 1270, 1186, 1046 cm^{-1}; ^{1}H NMR (250 MHz): 5.40 (s, 2H, –OC*H*$_2$CN), 7.89 (d, *J*=1.9 Hz, 1H, pyridine–*H*), 8.31 (d, *J*=1.9 Hz, 1H, pyridine–*H*); ^{13}C NMR (100 MHz): 55.1, 110.5, 115.9, 120.1, 122.9, 145.1, 153.3; MS (ESI) *m*/*z* (%): 338.7 [(M+H)$^+$, 100], 340.7 [(M+H)+2, 100]. Anal. Calcd for C_5H_3BrINO: C, 24.81; H, 1.19; N, 8.27. Found: C, 24.88; H, 1.24; N, 8.24.

*4.1.5. 5-Bromo-3-(cyanomethoxy)pyridine-2-carbonitrile (**6**).* A solution of **5** (0.25 g, 0.74 mmol), CuCN (86 mg, 0.96 mmol) and dry pyridine (2 mL) was refluxed for 1 h at 100 °C with magnetic stirring under argon. The solution was cooled to room temperature and was poured into 56 g/L aqueous potassium cyanide solution (5.3 mL). The solution was extracted with CH_2Cl_2. The organic layers were washed with brine, dried over Na_2SO_4, filtered, and evaporated to dryness. The crude product was purified by column chromatography eluting with a 7/3 mixture of petroleum ether and ethyl acetate to give **6** (149 mg, 85%) as a beige solid. Mp 142–143 °C; IR (KBr): 2927, 2360, 2216, 1560, 1406, 1236, 1155, 1015 cm^{-1}; ^{1}H NMR (250 MHz): 5.49 (s, 2H, –OC*H*$_2$CN), 8.39 (s, 1H, pyridine–*H*), 8.65 (s, 1H, pyridine–*H*); ^{13}C NMR (100 MHz): 55.3, 114.7, 115.6, 121.2, 125.4, 124.6, 145.7, 156.0; MS (ESI) *m*/*z* (%): 238.0 [(M+H)$^+$, 100], 240.0 [(M+H)+2, 100]. Anal. Calcd for $C_8H_4BrN_3O$: C, 40.37; H, 1.69; N, 17.65. Found: C, 40.31; H, 1.64; N, 17.59.

*4.1.6. 3-Amino-6-bromofuro[3,2-b]pyridine-2-carbonitrile (**7**).* A solution of **6** (0.28 g, 1.18 mmol) in dry *N*,*N*-dimethylformamide (3.7 mL) was treated with K_2CO_3 (0.15 g, 1.08 mmol) and the mixture was stirred at 80 °C for 1 h. After cooling at room temperature, cold water was added and the resulting precipitate was collected by

filtration and dried to yield **7** (241 mg, 86%) as a yellow-brown solid. Mp 236–237 °C; IR (KBr): 3424, 2367, 1647, 1458, 1382, 1244 cm^{-1}; ^1H NMR (250 MHz): 6.85 (s, 2H, $-NH_2$), 8.46 (s, 1H, furo[3,2-*b*]pyridine–*H*), 8.75 (s, 1H, furo[3,2-*b*]pyridine–*H*); ^{13}C NMR (100 MHz): 117.0, 119.9, 121.9, 132.7, 135.1, 140.9, 144.3, 151.1; MS (ESI) *m*/*z* (%): 237.9 [$(M+H)^+$, 100], 239.9 [(M+H)+2, 100]. Anal. Calcd for $C_8H_4BrN_3O$: C, 40.37; H, 1.69; N, 17.65. Found: C, 40.30; H, 1.63; N, 17.60.

*4.1.7. 3-Amino-6-bromofuro[3,2-b]pyridine-2-carboxamide (**8**).* A mixture of **7** (0.36 g, 1.51 mmol) in concentrated H_2SO_4 (3.1 mL) was stirred at room temperature for 2 h. The mixture was poured into ice-water and the solution was basified with aqueous NaOH. The solid was filtered off, washed with cold water and dried to give **8** (271 mg, 70%) as a yellow solid. Mp 240–241 °C; IR (KBr): 3404, 3297, 3140, 1663, 1564, 1440, 1383, 1147 cm^{-1}; ^1H NMR (400 MHz): 5.95 (s, 2H, $-NH_2$), 7.53 (m, 2H, $-CONH_2$), 8.31 (d, *J*=1.7 Hz, 1H, furo[3,2-*b*]pyridine–*H*), 8.69 (d, *J*=1.7 Hz, 1H, furo[3,2-*b*]pyridine–*H*); ^{13}C NMR (100 MHz): 118.0, 122.3, 130.1, 135.0, 134.0, 146.0, 146.1, 162.8; MS (ESI) *m*/*z* (%): 255.9 [$(M+H)^+$, 100], 257.9 [(M+H)+2, 100]. Anal. Calcd for $C_8H_6BrN_3O_2$: C, 37.53; H, 2.36; N, 16.41. Found: C, 37.61; H, 2.39; N, 16.46.

*4.1.8. tert-Butyl 6-bromo-2-cyanofuro[3,2-b]pyridin-3-ylcarbamate (**9**).* Compound **7** (2.30 g, 9.66 mmol) was dissolved in dry THF (92 mL), Boc_2O (12.66 g, 58.01 mmol) and a catalytic amount of DMAP was added. The solution was heated at reflux for 3 h. After cooling and evaporated to dryness, the crude product was purified by column chromatography eluting with a 9/1 mixture of petroleum ether and ethyl acetate to yield di-*tert*-butyl(6-bromo-2-cyanofuro[3,2-*b*]pyridin-3-yl) imidodicarbonate. Commercially available montmorillonite K-10 (4.60 g) was added to a stirred solution of this intermediate (4.20 g, 9.58 mmol) in dry toluene (42 mL). The mixture was stirred at room temperature for 12 h. The reaction mixture was filtered, and the solid was washed with ethyl acetate. The solution was concentrated and a column chromatography purification eluting with a 9/1 then 8/2 mixture of petroleum ether and ethyl acetate yielded **9** (1.76 g, 54%) as a beige solid. Mp 156–157 °C; IR (KBr): 3316, 3075, 2972, 2229, 1712, 1564, 1523, 1455, 1372, 1253, 1152 cm^{-1}; ^1H NMR (250 MHz): 1.53 (s, 9H, Boc), 8.66 (d, *J*=1.8 Hz, 1H, furo[3,2-*b*]pyridine–*H*), 8.87 (d, *J*=1.8 Hz, 1H, furo[3,2-*b*]pyridine–*H*), 10.48 (s, 1H, –N*H*Boc); ^{13}C NMR (100 MHz): 27.9, 81.4, 112.0, 119.8, 120.0, 123.2, 129.7, 138.1, 147.5, 148.6, 152.4; MS (ESI) *m*/*z* (%): 281.9 [$(M+H)^+$, 100], 283.8 [(M+H)+2, 100]. Anal. Calcd for $C_{13}H_{12}BrN_3O_3$: C, 46.17; H, 3.58; N, 12.43. Found: C, 46.24; H, 3.63; N, 12.47.

*4.1.9. tert-Butyl 6-bromo-2-cyanofuro[3,2-b]pyridin-3-yl(3-chlorobenzyl)carbamate (**10**).* K_2CO_3 (368 mg, 2.66 mmol) followed by 3-chlorobenzyl bromide (0.39 mL, 2.96 mmol) were added to a solution of **9** (0.90 g, 2.66 mmol) in dry DMF (27 mL). The reaction mixture was stirred at room temperature for 16 h. H_2O was added and the solution was extracted with diethyl ether. The organic layers were washed with a saturated $NaHCO_3$ solution, brine, dried over Na_2SO_4, filtered, and evaporated to dryness. The crude product was purified by column chromatography eluting with a 95/5 then 9/1 mixture of petroleum ether and ethyl acetate to afford **10** (1.11 g, 90%) as a white solid. Mp 80–81 °C; IR (KBr): 3080, 2983, 2230, 1720, 1598, 1413, 1369, 1322, 1251, 1149 cm^{-1}; ^1H NMR (250 MHz): 1.45 (s, 9H, Boc), 5.18 (s, 2H, $-CH_2$PhCl), 7.25 (m, 1H, PhCl–*H*), 7.39 (m, 3H, PhCl–*H*), 8.77 (m, 1H, furo[3,2-*b*]pyridine–*H*), 8.95 (m, 1H, furo[3,2-*b*]pyridine–*H*); ^{13}C NMR (100 MHz): 27.8, 48.0, 80.9, 115.1, 116.0, 117.4, 120.1, 122.9, 125.0, 128.4, 129.6, 142.2, 145.3, 146.7, 148.0, 153.8, 159.1; MS (ESI) *m*/*z* (%): 462.0 [$(M+H)^+$, 78], 464.0 [(M+H)+2, 100], 466.0 [(M+H)+4, 27]. Anal. Calcd for $C_{20}H_{17}BrClN_3O_3$: C, 51.91; H, 3.70; N, 9.08. Found: C, 51.86; H, 3.64; N, 9.04.

*4.1.10. tert-Butyl 6-bromo-2-cyanofuro[3,2-b]pyridin-3-yl(2-nitrobenzyl)carbamate (**11**).* The title compound was prepared in 89% yield as a yellow solid from **9** by a similar method to that described for **10** using 2-nitrobenzyl bromide. Mp 90–91 °C; IR (KBr): 3062, 2945, 2241, 1712, 1542, 1420, 1346, 1244, 1132 cm^{-1}; ^1H NMR (250 MHz): δ 1.41 (s, 9H, Boc), 5.59 (s, 2H, $-CH_2PhNO_2$), 7.59 (dd, *J*=7.1, 8.0 Hz, 1H, $PhNO_2$–*H*), 7.63 (d, *J*=8.0 Hz, 1H, $PhNO_2$-*H*), 7.79 (dd, *J*=7.1, 8.0 Hz, 1H, $PhNO_2$-*H*), 8.06 (d, *J*=8.0 Hz, 1H, $PhNO_2$–*H*), 8.76 (d, *J*=1.8 Hz, 1H, furo[3,2-*b*]pyridine–*H*), 8.92 (d, *J*=1.8 Hz, 1H, furo[3,2-*b*]pyridine–*H*). ^{13}C NMR (100 MHz): 27.8, 49.6, 81.6, 117.3, 119.9, 122.6, 123.3, 128.0, 129.8, 129.9, 131.4, 134.3, 140.6, 147.2, 148.0, 148.9, 152.9, 159.8; MS (ESI) *m*/*z* (%): 473.0 [$(M+H)^+$, 100], 475.0 [(M+H)+2, 100]. Anal. Calcd for $C_{20}H_{17}BrN_4O_5$: C, 50.76; H, 3.62; N, 11.84. Found: C, 50.86; H, 3.66; N, 11.80.

*4.1.11. tert-Butyl 2-(aminocarbonyl)-6-bromofuro[3,2-b]pyridin-3-yl (3-chlorobenzyl)carbamate (**12**).* A solution of **10** (0.50 g, 1.08 mmol), urea–hydrogen peroxide (1.03 g, 10.94 mmol), and K_2CO_3 (15 mg, 0.11 mmol) in acetone–water (v/v, 2/1, 16.5 mL) was stirred at room temperature for 5 h. It was then diluted with ethyl acetate and washed with saturated aqueous NH_4Cl solution and brine. The organic layer was concentrated, and the residue was purified by column chromatography eluting with a 99/1 then 98/2 mixture of CH_2Cl_2 and EtOH to afford **12** (452 mg, 87%) as a white solid. Mp 159–160 °C; IR (KBr): 3409, 3245, 3181, 3071, 2976, 1678, 1603, 1433, 1368, 1303, 1164 cm^{-1}; ^1H NMR (400 MHz): 1.34 (s, 9H, Boc), 5.18 (s, 2H, $-CH_2$PhCl), 7.25 (m, 2H, PhCl–*H*), 7.33 (m, 1H, PhCl–*H*), 7.55 (s, 1H, PhCl–*H*), 8.02 (s, 1H, $-CONH_2$), 8.22 (s, 1H, $-CONH_2$), 8.48 (s, 1H, furo[3,2-*b*]pyridine–*H*), 8.82 (s, 1H, furo[3,2-*b*]pyridine–*H*); ^{13}C NMR (100 MHz): 27.9, 51.0, 80.9, 117.7, 123.1, 126.1, 127.1, 127.4, 130.1, 133.2, 140.2, 142.2, 144.7, 145.5, 148.2, 153.7, 159.3, 159.5; MS (ESI) *m*/*z* (%): 479.9 [$(M+H)^+$, 73], 481.9 [(M+H)+2, 100], 483.9 [(M+H)+4, 29]. Anal. Calcd for $C_{20}H_{19}BrClN_3O_4$: C, 49.97; H, 3.98; N, 8.74. Found: C, 49.89; H, 3.94; N, 8.70.

*4.1.12. tert-Butyl 2-(aminocarbonyl)-6-bromofuro[3,2-b]pyridin-3-yl (2-nitrobenzyl)carbamate (**13**).* The title compound was prepared in 75% yield as a yellow solid from **11** by a similar method to that described for **12**. Mp 164–165 °C; IR (KBr): 3412, 3232, 3165, 3057, 2967, 1663, 1613, 1423, 1354, 1313, 1132 cm^{-1}; ^1H NMR (250 MHz): 1.33 (s, 9H, Boc), 5.29 (s, 2H, $-CH_2PhNO_2$), 7.49 (m, 1H, $PhNO_2$–*H*), 7.69 (m, 1H, $PhNO_2$–*H*), 7.97 (s, 1H, $-CONH_2$), 8.00 (s, 1H, $-CONH_2$), 8.22 (m, 1H, $PhNO_2$–*H*), 8.27 (m, 1H, $PhNO_2$–*H*), 8.50 (s, 1H, furo[3,2-*b*]pyridine–*H*), 8.83 (s, 1H, furo[3,2-*b*]pyridine–*H*); ^{13}C NMR (100 MHz): 28.0, 52.2, 82.0, 119.5, 124.3, 127.6, 128.4, 129.6, 132.6, 135.7, 142.5, 143.2, 145.5, 147.3, 149.8, 154.9, 159.4, 160.8; MS (ESI) *m*/*z* (%): 491.1 [$(M+H)^+$, 100], 493.1 [(M+H)+2, 100]. Anal. Calcd for $C_{20}H_{19}BrN_4O_6$: C, 48.89; H, 3.90; N, 11.40. Found: C, 48.96; H, 3.93; N, 11.43.

*4.1.13. tert-Butyl 2-aminobenzyl[2-(aminocarbonyl)-6-bromofuro[3,2-b]-pyridin-3-yl]carbamate (**14**).* Acetic acid (0.69 mL, 12.04 mmol) followed by zinc (1.60 g, 24.48 mmol) were added to a solution of **13** (0.30 g, 0.61 mmol) in dry THF (30 mL). The reaction mixture was stirred at room temperature for 29 h. Ethyl acetate was added and the mixture was filtered. The filtrate was washed with a saturated aqueous $NaHCO_3$ solution, dried over Na_2SO_4, filtered, and evaporated to dryness. The residue was purified by column chromatography eluting with a 99/1 then 98/2 mixture of CH_2Cl_2 and EtOH to yield **14** (223 mg, 79%) as a beige solid. Mp 105–106 °C; IR (KBr): 3362, 3253, 3190, 2977, 1689, 1606, 1432, 1371, 1312, 1159 cm^{-1}; ^1H NMR (400 MHz): 1.34 (s, 9H, Boc), 5.01 (s, 2H, $-CH_2PhNH_2$), 5.06 (s, 2H, $-NH_2$), 6.31 (dd, *J*=7.2, 6.8 Hz, 1H, $PhNH_2$–*H*), 6.58 (d, *J*=7.2 Hz,

1H, $PhNH_2$–*H*), 6.87 (m, 2H, $PhNH_2$–*H*), 7.99 (s, 1H, –CON*H*$_2$), 8.05 (s, 1H, –CON*H*$_2$), 8.47 (d, *J*=1.6 Hz, 1H, furo[3,2-*b*]pyridine–*H*), 8.78 (d, *J*=1.6 Hz, 1H, furo[3,2-*b*]pyridine–*H*); ^{13}C NMR (100 MHz): 27.8, 47.9, 80.9, 115.1, 116.1, 117.4, 120.1, 121.7, 122.9, 125.0, 128.4, 129.6, 133.5, 135.6, 145.3, 148.0, 159.1, 163.1; MS (ESI) *m*/*z* (%): 460.9 [(M+H)$^+$, 100], 462.9 [(M+H)+2, 100]. Anal. Calcd for $C_{20}H_{21}BrN_4O_4$: C, 52.07; H, 4.59; N, 12.15. Found: C, 52.18; H, 4.63; N, 12.19.

*4.1.14. tert-Butyl 2-(acetylamino)benzyl[2-(aminocarbonyl)-6-bromofuro[3,2-b]pyridin-3-yl]carbamate (**15**).* Acetyl chloride (0.025 mL, 0.35 mmol) was added dropwise to a cold solution of **14** (161 mg, 0.35 mmol) in pyridine (1.6 mL). The reaction mixture was stirred at room temperature for 18 h. Ethyl acetate was added. The organic layers were washed with HCl 1 M, dried over Na_2SO_4, filtered, and evaporated to dryness afforded **15** (158 mg, 90%) as a beige solid. Mp 186–187 °C; IR (KBr): 3324, 3234, 3151, 2978, 1674, 1612, 1543, 1434, 1369, 1301, 1160 cm^{-1}; ^{1}H NMR (400 MHz): 1.35 (s, 9H, Boc), 2.05 (s, 3H, –NHCOC*H*$_3$), 5.10 (s, 2H, –C*H*$_2$PhNHAc), 6.97 (m, 1H, PhNHAc–*H*), 7.15 (dd, *J*=7.2, 7.6 Hz, 1H, PhNHAc–*H*), 7.31 (d, *J*=6.8 Hz, 1H, PhNHAc–*H*), 7.39 (d, *J*=7.6 Hz, 1H, PhNHAc–*H*), 8.02 (s, 1H, –CON*H*$_2$), 8.18 (s, 1H, –CON*H*$_2$), 8.46 (d, *J*=1.8 Hz, 1H, furo [3,2-*b*]pyridine–*H*), 8.82 (d, *J*=1.8 Hz, 1H, furo[3,2-*b*]pyridine–*H*), 9.41 (s, 1H, –N*H*COCH$_3$); ^{13}C NMR (100 MHz): 23.4, 27.8, 47.7, 81.0, 117.6, 121.0, 119.7, 123.0, 125.0, 125.2, 127.8, 129.3, 130.5, 136.5, 138.8, 145.3, 148.1, 159.3, 160.1, 168.3; MS (ESI) *m*/*z* (%): 502.9 [(M+H)$^+$, 100], 505.0 [(M+H)+2, 100]. Anal. Calcd for $C_{22}H_{23}BrN_4O_5$: C, 52.50; H, 4.61; N, 11.13. Found: C, 52.38; H, 4.57; N, 11.09.

*4.1.15. 6-Bromo-3-[(3-chlorobenzyl)amino]furo[3,2-b]pyridine-2-carboxamide (**16**).* Trifluoroacetic acid (1.23 mL, 16.57 mmol) was added dropwise to a cold solution of **12** (0.40 g, 0.83 mmol) in CH_2Cl_2 (1.3 mL). The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was evaporated to dryness. The resulting solid was recrystallized in Et_2O to give **16** (247 mg, 78%) as a beige solid. Mp 183–184 °C; IR (KBr): 3451, 3341, 3133, 1666, 1602, 1452, 1372 cm^{-1}; ^{1}H NMR (400 MHz): 5.09 (d, *J*=7.2 Hz, 2H, –C*H*$_2$PhCl), 6.96 (dd, *J*=*J*′=7.2 Hz, 1H, PhCl–*H*), 7.31 (m, 3H, PhCl–*H*), 7.41 (d, *J*=7.2 Hz, 1H, –N*H*), 7.70 (s, 1H, –CON*H*$_2$), 7.54 (s, 1H, –CON*H*$_2$), 8.32 (d, *J*=1.8 Hz, 1H, furo[3,2-*b*]pyridine–*H*), 8.68 (d, *J*=1.8 Hz, 1H, furo [3,2-*b*]pyridine–*H*); ^{13}C NMR (100 MHz): 46.3, 113.7, 115.0, 116.3, 118.1, 126.0, 127.2, 130.5, 130.7, 133.8, 133.0, 135.4, 144.4, 146.4, 163.0; MS (ESI) *m*/*z* (%): 380.1 [(M+H)$^+$, 76], 382.1 [(M+H)+2, 100], 484.1 [(M+H)+4, 29]. Anal. Calcd for $C_{15}H_{11}BrClN_3O_2$: C, 47.33; H, 2.91; N, 11.04. Found: C, 47.45; H, 2.93; N, 11.07.

*4.1.16. 3-{[2-(Acetylamino)benzyl]amino}-6-bromofuro[3,2-b]pyridine-2-carboxamide (**17**).* The title compound was prepared in 86% yield as a beige solid from **15** by a similar method to that described for **16**. Mp 191–192 °C; IR (KBr): 3452, 3373, 3273, 1654, 1602, 1530, 1452, 1375, 1180, 1153 cm^{-1}; ^{1}H NMR (400 MHz): 2.07 (s, 3H, –NHCOC*H*$_3$), 5.06 (s, 2H, –C*H*$_2$PhNHAc), 6.83 (s, 1H, –N*H*), 7.10 (dd, *J*=7.8, 6.6 Hz, 1H, PhNHAc–*H*), 7.22 (dd, *J*=7.8, 6.6 Hz, 1H, PhNHAc–*H*), 7.36 (d, *J*=7.8 Hz, 1H, PhNHAc–*H*), 7.41 (d, *J*=7.8 Hz, 1H, PhNHAc–*H*), 7.50 (s, 1H, –CON*H*$_2$), 7.66 (s, 1H, –CON*H*$_2$), 8.32 (d, *J*=2.0 Hz, 1H, furo[3,2-*b*]pyridine–*H*), 8.68 (d, *J*=2.0 Hz, 1H, furo[3,2-*b*]pyridine–*H*), 9.55 (s, 1H, –N*H*COCH$_3$); ^{13}C NMR (100 MHz): 23.5, 43.6, 117.9, 119.5, 122.6, 125.5, 127.2, 128.3, 130.6, 134.5, 135.7, 135.9, 140.0, 146.1, 146.3, 162.9, 168.6; MS (ESI) *m*/*z* (%): 402.9 [(M+H)$^+$, 100], 404.9 [(M+H)+2, 100]. Anal. Calcd for $C_{17}H_{15}BrN_4O_3$: C, 50.64; H, 3.75; N, 13.89. Found: C, 50.70; H, 3.78; N, 13.83.

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