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

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3-Amino-*N*-methylfuro[3,2-*b*]pyridine-2-carboxamides
[6-Chloro-5-(2-ethoxy-2-oxoethoxy) pyridin-3-yl]benzoic acid
Heteroannulation

ABSTRACT

The synthesis of novel functionalized 3-amino-*N*-methylfuro[3,2-*b*]pyridine-2-carboxamides is described from cyanopyridine intermediates. Based on the difference in halogen reactivity, ethyl [(5-bromo-2-chloropyridin-3-yl)oxy]acetate was functionalized by a palladium-catalyzed reaction, before the cyclization to the desired furo[3,2-*b*]pyridines.

1. Introduction

As part of our continuing interest in aminofuro[3,2-*b*]pyridine carboxamides as potent kinase inhibitors, we investigated the synthesis of new functionalized 3-aminofuro[3,2-*b*]pyridine-2-carboxamides of general structure **I** (Fig. 1). The fused aromatic heterocycles like furopyridines seem to have especially attracted much attention as pharmacophore units in medicinal chemistry,[1] due to their isosterism with benzofurans, indoles or azaindoles,[2] which are important moieties in many biological activities. Various synthetic methodologies are described to obtain unsubstituted[3] or substituted[4] furo[3,2-*b*]pyridines and biological activity of this heterocycle depends on the type and the position of the substituents in the skeleton.[2,5]

In previous works, we have developed an efficient access of 3-amino-6-bromofuro[3,2-*b*]pyridine-2-carboxamide derivatives via a heteroannulation of 5-bromo-3-(cyanomethoxy)pyridine-2-carbonitrile.[6] In order to prepare the target 6-functionalized 3-amino-*N*-methylfuro[3,2-*b*]pyridine-2-carboxamides **I**, we decided to apply the same strategy via the cyclization of an ethyl [(2-cyanopyridin-3-yl)oxy]acetate with appropriate substituents (route A in Fig. 1). To obtain the *N*-methylcarboxamide function, the cyclization of a 2-[(2-cyanopyridin-3-yl)oxy]-*N*-methylacetamide could be envisaged, but this synthesis required the use of a toxic reagent (2-bromo-*N*-methylacetamide)[7] to prepare the *N*-methyl [(5-bromo-2-chloropyridin-3-yl)oxy] acetamide intermediate (route B in Fig. 1). Then, we envisioned to synthesize the ethyl 3-aminofuro [3,2-*b*]pyridine-2-carboxylates giving direct access to the corresponding *N*-methylcarboxamide by aminolysis of the ester function. Herein, we report our procedure for the access of 6-substituted 3-amino-*N*-methylfuro[3,2-*b*]pyridine-2-carboxamide (route A in Fig. 1).

2. Results and discussion

The synthetic route for the preparation of the key functionalized pyridines **9** and **10** is outlined in Scheme 1. Heating at 180 °C 3,5-dibromopyridine with benzyl alcohol in the presence of NaH in DMF led to 3-benzyloxy-5-bromopyridine **2** in 63% yield, by nucleophilic substitution of only one bromine.[8]

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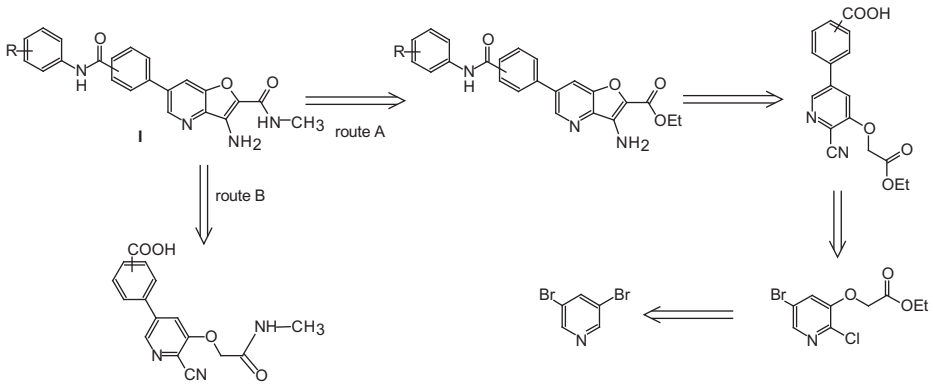
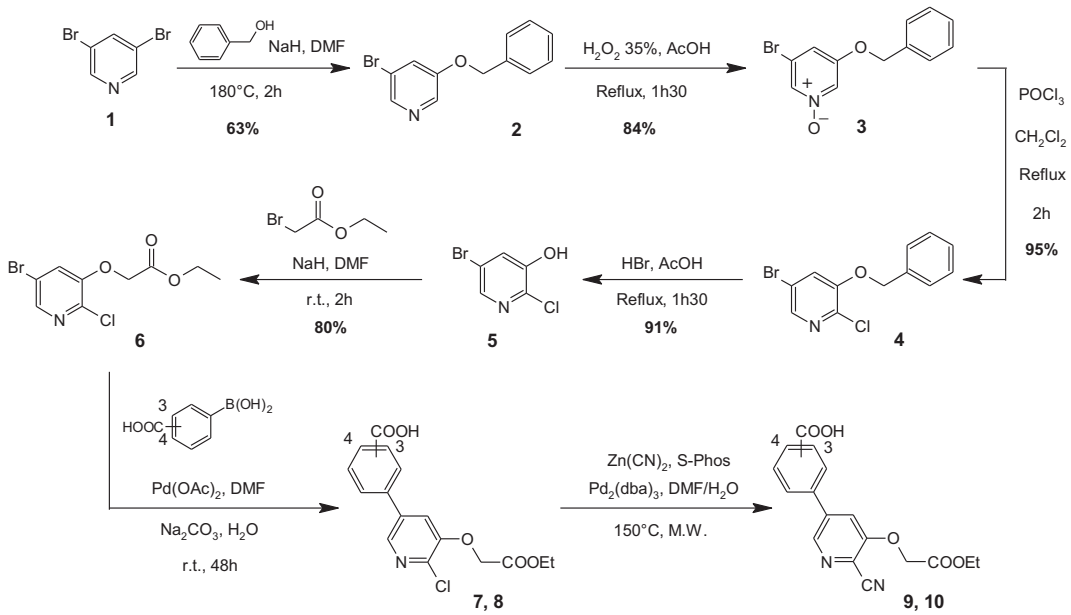


Fig. 1. Retro-synthetic plan of compounds **I**.



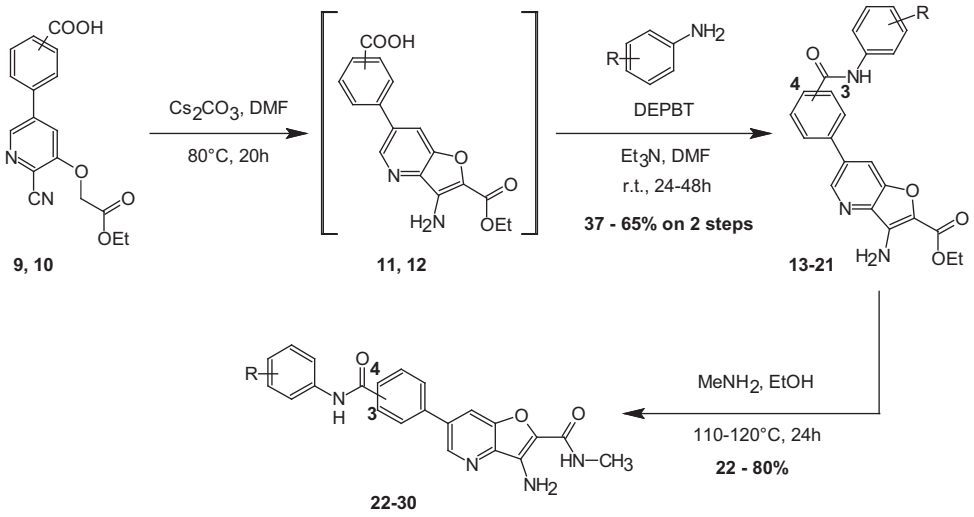
	Position	Yield (%)
7	3	**77**
8	4	**58**

	Position	Reaction time	Yield (%)
9	3	18 mn	**71**
10	4	5 mn	**71**

Scheme 1. Synthesis of functionalized pyridines **9** and **10**.

Selective chlorination with $POCl_3$ at position 2 of the pyridine ring was performed on the *N*-oxide **3**, prepared by oxidation of **2** with hydrogen peroxide in acetic acid at reflux.[9] It can be noticed that direct chlorination of 5-bromopyridin-3-ol provided a mixture of 5-bromo-2-chloropyridin-3-ol with the C-6-chloro isomer and the C-2,6-dichloro derivative.[10] Then, the synthesis via the *O*-protected *N*-oxide **3** was more efficient.[8] Benzyl group cleavage was carried out using a mixture of bromhydric and acetic acids at reflux for 1.5 h to afford **5** in good yield.[8] For this last step, 2,5-dibromopyridin-3-ol could be obtained in mixture with **5** when a longer reaction time was used. After formation of the sodium salt of the hydroxypyridine **5** using NaH in DMF, reaction with ethyl bromoacetate provided ethyl [(5-bromo-2-chloropyridin-3-yl)oxy] acetate **6** in 80% yield. Then, our strategy consisted in the introduction of phenyl groups at C-5 position of the pyridine ring before the cyanation, considering that the reaction of compound **6** with a cyanide source would give the brome displacement. Therefore, based on this difference in halogen reactivity, incorporation of a phenyl moiety was realized via a selective Suzuki cross-coupling reaction of 3- or 4-phenylboronic acids with **6**, using palladium acetate as catalyst and sodium carbonate as base in DMF at room temperature. Attempts to cyanate compounds **7** and **8** by the Rosenmund–von Braun reaction were unsuccessful. Ultimately, this conversion was carried out by a palladium-catalyzed cyanation as reported for aryl or heteroaryl chlorides.[11] Using $Pd_2(dba)_3$, ddpf as ligand, $Zn(CN)_2$ as the cyanide source, and addition of a catalytic amount of Zn dust in DMF, the desired pyridine carbonitriles **9** and **10** were prepared but in low yields. Under microwave activation, yields improved slightly. Finally, when the dppf ligand was replaced with the *S*-Phos ligand, cyanation of **7** and **8** with $Zn(CN)_2$, in the presence of 4 mol % $Pd_2(dba)_3$, 10 mol % *S*-Phos in wet DMF led to 71% yield of **9** and **10** under microwave-assisted conditions.[12]

As depicted in Scheme 2, heteroannulation of nitriles **9** and **10** proceeded efficiently under basic conditions. The use of Cs_2CO_3 in DMF for 20 h at 80 °C was required to have a complete conversion and to produce 3-[3-amino-2-(ethoxycarbonyl)furo[3,2-*b*]pyridin-



Scheme 2. Synthesis of functionalized 3-amino-*N*-methylfuro[3,2-*b*]pyridine-2-carboxamides **22**–**30**.

6-yl]benzoic acid **11** and 4-[3-amino-2-(ethoxycarbonyl)furo[3,2-*b*]pyridin-6-yl]benzoic acid **12**. These acids were used in the next step without further purification. Amidation with several anilines was then performed. Use of triethylamine or *N*-methylmorpholine in combination with EDCI/HOBt, CMPI or DCP gave only low yields. The amides **13**–**18** for the position 3 and **19**–**21** for the position 4 were obtained in 37–65% overall yield starting from **9** or **10** when coupling was mediated by 1.2 equiv of recrystallized DEPBT[13] in the presence of triethylamine in DMF at room temperature (entries 1–9 in Table 1). The ethyl pyridine carboxylates **13**–**21** were finally converted to the desired carboxamides **22**–**30** by aminolysis under pressure with a solution of methylamine in ethanol (entries 10–18 in Table 1).

Table 1
Synthesis of ethyl 3-aminofuro[3,2-*b*]pyridine-2-carboxylates **13**–**21** and 3-amino-*N*-methylfuro[3,2-*b*]pyridine-2-carboxamides **22**–**30**

Entry	Compd	Position	R	Yield[a] (%)
1	**13**	3	3-Cl	50[b]
2	**14**	3	3-F	43[b]
3	**15**	3	3-Ph	65[b]
4	**16**	3	4-Cl	52[b]
5	**17**	3	4-F	47[b]
6	**18**	3	4-Ph	63[b]
7	**19**	4	3-Cl	37[b]
8	**20**	4	3-Ph	43[b]
9	**21**	4	4-Ph	48[b]
10	**22**	3	3-Cl	71
11	**23**	3	3-F	54
12	**24**	3	3-Ph	77
13	**25**	3	4-Cl	30
14	**26**	3	4-F	22
15	**27**	3	4-Ph	52
16	**28**	4	3-Cl	80
17	**29**	4	3-Ph	65
18	**30**	4	4-Ph	73

[a] Isolated yield.
[b] Isolated yield in two steps.

3. Conclusion

In this work, we have described the access of new 6-functionalized 3-amino-*N*-methylfuro[3,2-*b*]pyridine-2-carboxamides, based on selective functionalizations of a dihalogenopyridine ring via palladium cross-coupling reactions (Suzuki and cyanation).

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 an 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), br (broad). Mass spectra were recorded on Waters ZQ 2000 spectrometer. Elemental analyses were found within ±0.4% of the theoretical values. Microwave experiments were carried out under pressure (0–20 bar, tubes of 10 mL sealed with a septum), using a focused microwave reaction (CEM Discover™). Reactions were performed in a glass vessel. The target temperature was reached with a ramp of 1 min (for compound **10**) or 2 min (for compound **9**) and the chosen microwave power stayed constant to hold the mixture at this temperature. The reaction time does not include the ramp period.

*4.1.1. 3-Benzyloxy-5-bromopyridine (**2**).* Benzylalcohol (10 mL, 96 mmol) was dissolved in dry DMF (30 mL) and sodium hydride (60% suspension in mineral oil) (2.5 g, 62.50 mmol) was slowly added. When no more gas evolved, 3,5-dibromopyridine (10 g, 42.21 mmol) was added and the reaction mixture was stirred at 180 °C for 2 h. After addition of water, the aqueous phase was extracted with ethyl acetate. The organic layers were dried over sodium sulfate, filtered, and evaporated to dryness. The resulting oil was purified by column chromatography eluting with an 8/2 mixture of petroleum ether and diethyl ether and then a second column chromatography eluting with a 9/1 mixture of CH_2Cl_2 and ethyl acetate to afford **2** (7.02 g, 63%) as a beige needle. Mp 67–68 °C (lit.:[14] 64–65 °C); IR (KBr): 1553, 1425, 1259, 990 cm^{-1}; ^{1}H NMR (400 MHz): 5.25 (s, 2H, –OCH_2Ph), 7.37–7.51 (m, 5H, Ph–*H*), 7.84 (dd, J=J'=2.0 Hz, 1H, pyridine–*H*), 8.33 (d, J=2.0 Hz, 1H, pyridine–*H*), 8.40 (d, J=2.0 Hz, 1H, pyridine–*H*); ^{13}C NMR (100 MHz): 70.2, 120.2, 124.3, 128.2, 128.4, 128.7, 136.2, 137.4, 142.5, 155.3; the data are in

conformity with the literature.[14] MS (ESI) *m*/*z* (%): 265.9 [(M+H)$^+$, 100], 267.9 [(M+H)+2, 100]. Anal. Calcd for $C_{12}H_{10}BrNO$: C, 54.57; H, 3.82; N, 5.30. Found: C, 54.63; H, 3.83; N, 5.31.

*4.1.2. 3-Benzyloxy-5-bromopyridine N-oxide (**3**).* To a solution of 3-(benzyloxy)-5-bromopyridine **2** (11 g, 41.65 mmol) in acetic acid (124 mL) was added a 35% aqueous solution of hydrogen peroxide (38 mL) and the reaction mixture was refluxed for 1 h 30 min. The solution was cooled to room temperature and was slowly poured into saturated aqueous solution of sodium carbonate (548 mL). The solid was filtered off, washed with cold water, and dried to yield **3** (9.80 g, 84%) as a beige solid. Mp 117–118 °C; IR (KBr): 1591, 1552, 1445, 1184, 991 cm^{-1}; ^{1}H NMR (400 MHz): 5.24 (s, 2H, –OC*H*$_2$Ph), 7.40–7.51 (m, 6H, Ph–*H* and pyridine–*H*), 8.21 (dd, *J*=1.6, 2.0 Hz, 1H, pyridine–*H*), 8.25 (dd, *J*=1.6, 2.0 Hz, 1H, pyridine–*H*); ^{13}C NMR (100 MHz): 70.9, 116.3, 119.8, 127.7, 128.3, 128.6, 128.7, 133.5, 135.6, 156.9; MS (ESI) *m*/*z* (%): 281.9 [(M+H)$^+$, 100], 283.9 [(M+H)+2, 100]. Anal. Calcd for $C_{12}H_{10}BrNO_2$: C, 51.45; H, 3.60; N, 5.0. Found: C, 51.53; H, 3.61; N, 5.01.

*4.1.3. 3-Benzyloxy-5-bromo-2-chloropyridine (**4**).* To a solution of 3-benzyloxy-5-bromopyridine *N*-oxide **3** (9 g, 32.13 mmol) in dry CH_2Cl_2 wad added dropwise $POCl_3$ (30 mL, 327.72 mmol) and the reaction mixture was refluxed for 2 h. The solvent was evaporated under vacuum and the residue was slowly poured into saturated aqueous solution of sodium carbonate. The solid was filtered off, washed with cold water, and dried to yield **4** (9.10 g, 95%) as a beige solid. Mp 76–77 °C; IR (KBr): 1547, 1415, 1266, 1071 cm^{-1}; ^{1}H NMR (400 MHz): 5.34 (s, 2H, –OC*H*$_2$Ph), 7.41–7.52 (m, 5H, Ph–*H*), 8.03 (d, *J*=2.0 Hz, 1H, pyridine–*H*), 8.19 (d, *J*=2.0 Hz, 1H, pyridine–*H*); ^{13}C NMR (100 MHz): 70.8, 119.2, 124.6, 127.7, 128.3, 128.6, 135.5, 138.4, 140.8, 150.7; MS (ESI) *m*/*z* (%): 297.8 [(M+H)$^+$, 72], 299.8 [(M+H)+2, 100], 301.8 [(M+H)+4, 27]. Anal. Calcd for $C_{12}H_9BrClNO$: C, 48.27; H, 3.04; N, 4.69. Found: C, 48.37; H, 3.05; N, 4.71.

*4.1.4. 5-Bromo-2-chloropyridin-3-ol (**5**).* A solution of 3-(benzyloxy)-5-bromo-2-chloropyridine **4** (4.8 g, 16.08 mmol) in a mixture of AcOH (55 mL) and 40% HBr (14 mL) was refluxed for 1 h 30 min. The reaction mixture was cooled to room temperature and was slowly poured into saturated aqueous solution of sodium carbonate. The resulting precipitate was collected by filtration and washed with cold water. The solid was dissolved in ethyl acetate, dried over sodium sulfate, and concentrated to dryness. The resulting oil was purified by column chromatography eluting with an 8/2 mixture of petroleum ether and diethyl ether to afford **5** (3.05 g, 91%) as a white solid. Mp 182–183 °C; IR (KBr): 3448, 1558, 1411, 1173 cm^{-1}; ^{1}H NMR (400 MHz): 7.53 (d, *J*=2.1 Hz, 1H, pyridine–*H*), 8.04 (d, *J*=2.0 Hz, 1H, pyridine–*H*), 11.35 (s, 1H, –O*H*); ^{13}C NMR (100 MHz): 118.8, 126.2, 137.5, 139.8, 150.7; the data are in conformity with the literature.[10,15] MS (ESI) *m*/*z* (%): 207.8 [(M+H)$^+$, 71], 209.8 [(M+H)+2, 100], 211.8 [(M+H)+4, 28]. Anal. Calcd for $C_5H_3BrClNO$: C, 28.81; H, 1.445; N, 6.72. Found: C, 28.75; H, 1.44; N, 6.71.

*4.1.5. Ethyl [(5-bromo-2-chloropyridin-3-yl)oxy]acetate (**6**).* Sodium hydride (60% suspension in mineral oil) (0.95 g, 23.75 mmol) was slowly added to a solution of 5-bromo-2-chloropyridin-3-ol **5** (3.3 g, 15.83 mmol) in dry DMF (36 mL). When no more gas evolved, ethyl bromoacetate (2.1 mL, 18.94 mmol) was added dropwise and the reaction mixture was stirred at room temperature for 2 h. After addition of water, the aqueous phase was extracted with CH_2Cl_2. The organic layers were washed with brine, dried over sodium sulfate, filtered, and evaporated to dryness. The resulting oil was purified by column chromatography eluting with CH_2Cl_2 to afford **6** (3.70 g, 80%) as a beige solid. Mp 53–54 °C; IR (KBr): 1754, 1563, 1423, 1201, 1083 cm^{-1}; ^{1}H NMR (250 MHz): 1.25 (t, *J*=7.3 Hz, 3H, –COOCH$_2$C*H*$_3$), 4.21 (q, *J*=7.3 Hz, 2H, –COOC*H*$_2$CH$_3$), 5.10 (s, 2H, –OC*H*$_2$COOCH$_2$CH$_3$), 7.96 (d, *J*=2.1 Hz, 1H, pyridine–*H*), 8.21 (d, *J*=2.1 Hz, 1H, pyridine–*H*); ^{13}C NMR (100 MHz): 14.1, 61.1, 65.7, 119.2, 124.7, 138.4, 141.6, 150.4, 167.8; MS (ESI) *m*/*z* (%): 293.8 [(M+H)$^+$, 75], 295.8 [(M+H)+2, 100], 297.8 [(M+H)+4, 25]. Anal. Calcd for $C_9H_9BrClNO_3$: C, 36.70; H, 3.08; N, 4.76. Found: C, 36.82; H, 3.09; N, 4.77.

*4.1.6. 3-[6-Chloro-5-(2-ethoxy-2-oxoethoxy)pyridin-3-yl]benzoic acid (**7**).* Ethyl [(5-bromo-2-chloropyridin-3-yl)oxy]acetate **6** (4.69 g, 15.94 mmol) was dissolved in dry DMF (47 mL). The solution was degassed during 30 min and $Pd(OAc)_2$ (107.26 mg, 0.48 mmol) was added. The reaction mixture was degassed during 15 min and a solution of Na_2CO_3 2 M (24.2 mL, 48.4 mmol) was added dropwise under vigorous stirring followed by 3-phenyl boronic acid (2.64 g, 15.94 mmol). The mixture was stirred at room temperature for 48 h. After acidification with HCl 1 M, the solution was extracted by ethyl acetate. The organic layers were washed with brine, dried over sodium sulfate, filtered, and evaporated to dryness. The resulting solid was purified by column chromatography eluting with a 9/1 mixture of CH_2Cl_2 and ethanol to afford **7** (4.12 g, 77%) as a white solid. Mp 207–208 °C; IR (KBr): 3442, 1747, 1692, 1586, 1397, 1216, 1105, 1064 cm^{-1}; ^{1}H NMR (400 MHz): 1.25 (t, *J*=7.3 Hz, 3H, –COOCH$_2$C*H*$_3$), 4.23 (q, *J*=7.3 Hz, 2H, –COOC*H*$_2$CH$_3$), 5.21 (s, 2H, –OC*H*$_2$COOCH$_2$CH$_3$), 7.69 (dd, *J*=7.6, 8.0 Hz, 1H, Ph–*H*), 7.91 (d, *J*=2.0 Hz, 1H, pyridine–*H*), 8.03–8.06 (m, 2H, Ph–*H*), 8.29 (br s, 1H, Ph–*H*), 8.40 (d, *J*=2.0 Hz, 1H, pyridine–*H*), 13.25 (s, 1H, –COO*H*); ^{13}C NMR (100 MHz): 14.2, 61.1, 65.5, 120.2, 128.1, 129.5, 129.6, 131.8, 131.9, 135.8, 136.4, 138.8, 139.2, 149.9, 167.2, 168.2; MS (ESI) *m*/*z* (%): 335.9 [(M+H)$^+$, 100], 337.9 [(M+H)+2, 33]. Anal. Calcd for $C_{16}H_{14}ClNO_5$: C, 57.24; H, 4.20; N, 4.17. Found: C, 57.32; H, 4.21; N, 4.18.

*4.1.7. 4-[6-Chloro-5-(2-ethoxy-2-oxoethoxy)pyridin-3-yl]benzoic acid (**8**).* The title compound was prepared in 58% yield as a pale yellow solid from **6** by a similar method to that described for **7** using 4-phenylboronic acid. Mp 230–231 °C; IR (KBr): 3452, 1757, 1681, 1609, 1578, 1393, 1301, 1214, 1104, 1057 cm^{-1}; ^{1}H NMR (400 MHz): 1.25 (t, *J*=7.3 Hz, 3H, –COOCH$_2$C*H*$_3$), 4.22 (q, *J*=7.3 Hz, 2H, –COOC*H*$_2$CH$_3$), 5.19 (s, 2H, –OC*H*$_2$COOCH$_2$CH$_3$), 7.93 (d, *J*=1.2 Hz, 1H, pyridine–*H*), 7.94 (d, *J*=8.2 Hz, 2H, Ph–*H*), 8.09 (d, *J*=8.2 Hz, 2H, Ph–*H*), 8.44 (d, *J*=1.2 Hz, 1H, pyridine–*H*), 13.16 (s, 1H, –COO*H*); ^{13}C NMR (100 MHz): 14.2, 61.1, 65.5, 120.1, 127.6, 130.1, 130.9, 135.4, 139.1, 139.3, 140.0, 150.0, 167.1, 168.1; MS (ESI) *m*/*z* (%): 335.9 [(M+H)$^+$, 100], 337.9 [(M+H)+2, 33]. Anal. Calcd for $C_{16}H_{14}ClNO_5$: C, 57.24; H, 4.20; N, 4.17. Found: C, 57.34; H, 4.21; N, 4.19.

*4.1.8. 3-[6-Cyano-5-(2-ethoxy-2-oxoethoxy)pyridin-3-yl]benzoic acid (**9**).* To a mixture of 3-[6-chloro-5-(2-ethoxy-2-oxoethoxy) pyridin-3-yl]benzoic acid **7** (0.5 g, 1.49 mmol), $Pd_2(dba)_3$ (54 mg, 0.06 mmol), *S*-Phos (10%) (61 mg, 0.15 mmol), and $Zn(CN)_2$ (199 mg, 1.69 mmol) in a sealed tube was added DMF/H_2O 1% (6 mL). The reaction mixture was degassed during 15 min and then stirred at 150 °C under microwave irradiation (150 W) for 18 min. After cooling at room temperature, the mixture was filtered over Celite and solids were washed with acetone. The filtrate was evaporated to dryness. The resulting oil was purified by column chromatography eluting with CH_2Cl_2 and then 9/1 mixture of CH_2Cl_2 and ethanol to afford **9** (345 mg, 71%) as a white solid. Mp 229–230 °C; IR (KBr): 3448, 2232, 1743, 1697, 1585, 1453, 1397, 1219, 1163 cm^{-1}; ^{1}H NMR (400 MHz): 1.26 (t, *J*=7.1 Hz, 3H, –COOCH$_2$C*H*$_3$), 4.23 (q, *J*=7.1 Hz, 2H, –COOC*H*$_2$CH$_3$), 5.31 (s, 2H, –OC*H*$_2$COOCH$_2$CH$_3$), 7.73 (dd, *J*=*J*′=7.6 Hz, 1H, Ph–*H*), 8.10 (d, *J*=7.6 Hz, 1H, Ph–*H*), 8.12 (d, *J*=7.6 Hz, 1H, Ph–*H*), 8.15 (d, *J*=1.6 Hz, 1H, pyridine–*H*), 8.36 (br, 1H, Ph–*H*), 8.75 (d, *J*=1.6 Hz, 1H, pyridine–*H*); ^{13}C NMR (100 MHz): 14.2, 61.2, 65.6, 115.6, 120.1, 121.1, 128.6, 129.7, 130.4, 132.1, 135.8, 140.1, 142.2, 157.6, 167.2, 168.0, 197.8; MS (ESI) *m*/*z* (%): 327.0

[(M+H)$^+$, 100]. Anal. Calcd for $C_{17}H_{14}N_2O_5$: C, 62.57; H, 4.32; N, 8.59. Found: C, 62.69; H, 4.33; N, 8.61.

*4.1.9. 4-[6-Cyano-5-(2-ethoxy-2-oxoethoxy)pyridin-3-yl]benzoic acid (**10**).* The title compound was prepared in 71% yield as a white solid from **8** by a similar method to that described for **9**. Mp 246–247 °C; IR (KBr): 3445, 2232, 1751, 1691, 1610, 1584, 1428, 1394, 1299, 1214, 1160 cm^{-1}; ^{1}H NMR (400 MHz): 1.26 (t, *J*=7.0 Hz, 3H, −COOCH$_2$C*H*$_3$), 4.23 (q, *J*=7.0 Hz, 2H, −COOC*H*$_2$CH$_3$), 5.29 (s, 2H, −OC*H*$_2$COOCH$_2$CH$_3$), 8.02 (d, *J*=7.8 Hz, 2H, Ph−*H*), 8.12 (d, *J*=7.8 Hz, 2H, Ph−*H*), 8.17 (s, 1H, pyridine−*H*), 8.79 (s, 1H, pyridine−*H*), 13.26 (s, 1H, −COO*H*); ^{13}C NMR (100 MHz): 14.2, 61.2, 65.6, 115.6, 120.2, 121.4, 128.1, 130.1, 131.7, 139.4, 139.6, 142.2, 157.5, 167.0, 168.0; MS (ESI) *m*/*z* (%): 327.0 [(M+H)$^+$, 100]. Anal. Calcd for $C_{17}H_{14}N_2O_5$: C, 62.57; H, 4.32; N, 8.59. Found: C, 62.69; H, 4.34; N, 8.61.

*4.1.10. Ethyl 3-amino-6-(3-{[(3-chlorophenyl)amino]carbonyl}phenyl)furo[3,2-b]pyridine-2-carboxylate (**13**).* To a solution of 3-[6-cyano-5-(2-ethoxy-2-oxoethoxy)pyridin-3-yl]benzoic acid **9** (0.6 g, 1.84 mmol) in dry DMF (4 mL) was added Cs_2CO_3 (0.6 g, 1.84 mmol). The reaction mixture was stirred at 80 °C for 20 h. After cooling at room temperature, ethyl acetate was added. The solid was filtered off, washed with HCl 1 M and dried to yield 3-[3-amino-2-(ethoxycarbonyl)furo[3,2-*b*]pyridin-6-yl]benzoic acid **11** as a light brown solid. To a solution of this crude solid in dry DMF (24 mL) was added DEPBT (0.66 g, 2.21 mmol). The reaction mixture was stirred at room temperature for 45 min and Et_3N (0.51 mL, 3.67 mmol) followed by 3-chloroaniline (0.24 mL, 2.27 mmol) were added. The mixture was stirred at room temperature for 48 h and then diluted with ethyl acetate. The organic layer was washed with NaOH 1 M, HCl 1 M, brine, dried over sodium sulfate, filtered, and evaporated to dryness. The resulting solid was washed with ethyl acetate and dried to afford **13** (402 mg, 50%) as a beige solid. Mp 144–145 °C; IR (KBr): 3401, 3287, 1682, 1649, 1615, 1593, 1531, 1321, 1240, 1092 cm^{-1}; ^{1}H NMR (400 MHz): 1.38 (t, *J*=7.1 Hz, 3H, −COOCH$_2$C*H*$_3$), 4.38 (q, *J*=7.1 Hz, 2H, −COOC*H*$_2$CH$_3$), 6.35 (s, 2H, −N*H*$_2$), 7.23 (dd, *J*=1.8, 8.0 Hz, 1H, PhCl−*H*), 7.45 (dd, *J*=*J*′=8.0 Hz, 1H, PhCl−*H*), 7.75 (dd, *J*=*J*′=8.0 Hz, 1H, Ph−*H*), 7.78 (dd, *J*=1.8, 8.0 Hz, 1H, PhCl−*H*), 8.03 (dd, *J*=*J*′=1.8 Hz, 1H, PhCl−*H*), 8.05 (d, *J*=8.0 Hz, 1H, Ph−*H*), 8.10 (d, *J*=8.0 Hz, 1H, Ph−*H*), 8.40 (br, 1H, Ph−*H*), 8.45 (d, *J*=1.7 Hz, 1H, furo[3,2-*b*]pyridine−*H*), 9.05 (d, *J*=1.7 Hz, 1H, furo[3,2-*b*]pyridine−*H*), 10.56 (s, 1H, −N*H*); ^{13}C NMR (100 MHz): 14.6, 60.1, 118.0, 118.9, 120.0, 123.7, 126.5, 126.8, 128.0, 129.7, 130.6, 131.0, 133.2, 135.4, 135.7, 137.3, 138.5, 139.5, 140.7, 144.7, 147.8, 160.6, 165.7; MS (ESI) *m*/*z* (%): 436.07 [(M+H)$^+$, 100], 438.07 [(M+H)+2, 35]. Anal. Calcd for $C_{23}H_{18}ClN_3O_4$: C, 63.38; H, 4.16; N, 9.64. Found: C, 63.28; H, 4.14; N, 9.62.

*4.1.11. Ethyl 3-amino-6-(3-{[(3-fluorophenyl)amino]carbonyl}phenyl)furo[3,2-b]pyridine-2-carboxylate (**14**).* The title compound was prepared in 43% yield as a beige solid from **9** by a similar method to that described for **13** using 3-fluoroaniline. Mp 218–219 °C; IR (KBr): 3404, 3290, 1700, 1677, 1655, 1614, 1542, 1440, 1238, 1144 cm^{-1}; ^{1}H NMR (400 MHz): 1.38 (t, *J*=7.1 Hz, 3H, −COOCH$_2$C*H*$_3$), 4.38 (q, *J*=7.1 Hz, 2H, −COOC*H*$_2$CH$_3$), 6.36 (s, 2H, −N*H*$_2$), 7.00 (ddd, *J*=*J*′=8.2 Hz, *J*=2.0 Hz, 1H, PhF−*H*), 7.46 (ddd, *J*=*J*′=*J*″=8.2 Hz, 1H, PhF−*H*), 7.62 (d, *J*=8.2 Hz, 1H, PhF−*H*), 7.75 (dd, *J*=*J*′=7.6 Hz, 1H, Ph−*H*), 7.82 (ddd, *J*=11.6 Hz, *J*=*J*′=2.0 Hz, 1H, PhF−*H*), 8.05 (d, *J*=7.6 Hz, 1H, Ph−*H*), 8.10 (d, *J*=7.6 Hz, 1H, Ph−*H*), 8.39 (br s, 1H, Ph−*H*), 8.45 (d, *J*=1.8 Hz, 1H, furo[3,2-*b*]pyridine−*H*), 9.05 (d, *J*=1.8 Hz, 1H, furo[3,2-*b*]pyridine−*H*), 10.59 (s, 1H, NH); ^{13}C NMR (100 MHz): 14.6, 60.1, 107.2 (d, J_{C-F}=26 Hz), 110.5 (d, J_{C-F}=21 Hz), 116.2 (d, J_{C-F}=2 Hz), 118.0, 126.5, 126.8, 128.0, 129.7, 130.5 (d, J_{C-F}=9 Hz), 130.9, 135.4, 135.8, 137.3, 138.5, 139.5, 141.0(d, J_{C-F}=11 Hz), 144.7, 147.8, 160.6, 162.3 (d, J_{C-F}=240.0 Hz), 165.7; MS (ESI) *m*/*z* (%): 420.0 [(M+H)$^+$, 100]. Anal. Calcd for $C_{23}H_{18}FN_3O_4$: C, 65.87; H, 4.33; N, 10.02. Found: C, 65.95; H, 4.34; N, 10.05.

*4.1.12. Ethyl 3-amino-6-(3-{[(3-biphenyl)amino]carbonyl}phenyl)furo[3,2-b]pyridine-2-carboxylate (**15**).* The title compound was prepared in 65% yield as a brown solid from **9** by a similar method to that described for **13** using 3-phenylaniline. Mp 187–188 °C; IR (KBr): 3398, 3282, 1705, 1675, 1645, 1621, 1577, 1544, 1420, 1321, 1244, 1139 cm^{-1}; ^{1}H NMR (400 MHz): 1.38 (t, *J*=7.0 Hz, 3H, −COOCH$_2$C*H*$_3$), 4.38 (q, *J*=7.0 Hz, 2H, −COOC*H*$_2$CH$_3$), 6.35 (s, 2H, −N*H*$_2$), 7.43–7.55 (m, 5H, 3Ph−Ph−*H* and 2Ph−*H*−Ph), 7.71 (d, *J*=6.8 Hz, 2H, Ph−Ph−*H*), 7.76 (dd, *J*=8.0, 7.6 Hz, 1H, Ph−*H*), 7.89 (d, *J*=7.6 Hz, 1H, Ph−*H*−Ph), 8.08–8.10 (m, 2H, Ph−*H*), 8.16 (s, 1H, Ph−*H*−Ph), 8.44 (s, 1H, Ph−*H*), 8.47 (s, 1H, furo[3,2-*b*]pyridine−*H*), 9.07 (s, 1H, furo[3,2-*b*]pyridine−*H*), 10.50 (s, 1H, −NH); ^{13}C NMR (100 MHz): 14.6, 60.1, 118.0, 118.9, 119.5, 122.3, 126.5, 126.7, 126.8, 127.8, 127.9, 129.2, 129.5, 129.6, 130.8, 135.4, 136.0, 137.2, 138.5, 139.5, 139.8, 140.3, 140.8, 144.7, 147.8, 160.6, 165.4; MS (ESI) *m*/*z* (%): 478.0 [(M+H)$^+$, 100]. Anal. Calcd for $C_{29}H_{23}N_3O_4$: C, 72.94; H, 4.85; N, 8.80. Found: C, 73.13; H, 4.86; N, 8.82.

*4.1.13. Ethyl 3-amino-6-(3-{[(4-chlorophenyl)amino]carbonyl}phenyl)furo[3,2-b]pyridine-2-carboxylate (**16**).* The title compound was prepared in 52% yield as a beige solid from **9** by a similar method to that described for **13** using 4-chloroaniline. Mp 272–273 °C; IR (KBr): 3390, 1699, 1661, 1625, 1527, 1139 cm^{-1}; ^{1}H NMR (400 MHz): 1.38 (t, *J*=7.0 Hz, 3H, −COOCH$_2$C*H*$_3$), 4.38 (q, *J*=7.0 Hz, 2H, −COOC*H*$_2$CH$_3$), 6.36 (s, 2H, −N*H*$_2$), 7.47 (d, *J*=8.8 Hz, 2H, PhCl−*H*), 7.74 (dd, *J*=*J*′=7.8 Hz, 1H, Ph−*H*), 7.91 (d, *J*=8.8 Hz, 2H, PhCl−*H*), 8.06 (d, *J*=7.8 Hz, 1H, Ph−*H*), 8.09 (d, *J*=7.8 Hz, 1H, Ph−*H*), 8.42 (br s, 1H, Ph−*H*), 8.48 (d, *J*=1.8 Hz, 1H, furo[3,2-*b*]pyridine−*H*), 9.06 (d, *J*=1.8 Hz, 1H, furo[3,2-*b*]pyridine−*H*), 10.63 (s, 1H, −NH); ^{13}C NMR (100 MHz): 14.6, 60.1, 118.0, 112.2, 126.5, 126.9, 127.5, 128.1, 128.6, 128.7, 129.6, 130.8, 135.4, 135.7, 137.2, 138.5, 139.5, 144.8, 147.8, 160.6, 165.5; MS (ESI) *m*/*z* (%): 436.2 [(M+H)$^+$, 100], 438.2 [(M+H)+2, 36]. Anal. Calcd for $C_{23}H_{18}ClN_3O_4$: C, 63.38; H, 4.16; N, 9.64. Found: C, 63.28; H, 4.15; N, 9.63.

*4.1.14. Ethyl 3-amino-6-(3-{[(4-fluorophenyl)amino]carbonyl}phenyl)furo[3,2-b]pyridine-2-carboxylate (**17**).* The title compound was prepared in 47% yield as a beige solid from **9** by a similar method to that described for **13** using 4-fluoroaniline. Mp 281–282 °C; IR (KBr): 3388, 1696, 1662, 1623, 1580, 1538, 1509, 1324, 1262, 1227, 1138 cm^{-1}; ^{1}H NMR (400 MHz): 1.38 (t, *J*=7.0 Hz, 3H, −COOCH$_2$C*H*$_3$), 4.38 (q, *J*=7.0 Hz, 2H, −COOC*H*$_2$CH$_3$), 6.34 (s, 2H, −N*H*$_2$), 7.25 (dd, *J*=*J*′=9.0 Hz, 2H, PhF−*H*), 7.73 (dd, *J*=7.6, 8.0 Hz, 1H, Ph−*H*), 7.85 (dd, *J*=9.0, 5.1 Hz, 2H, PhF−*H*), 8.04 (dd, *J*=8.0, 1.6 Hz, 1H, Ph−*H*), 8.08 (dd, *J*=7.6, 1.6 Hz, 1H, Ph−*H*), 8.39 (dd, *J*=*J*′=1.6 Hz, 1H, Ph−*H*), 8.44 (d, *J*=2.0 Hz, 1H, furo[3,2-*b*]pyridine−*H*), 9.05 (d, *J*=2.0 Hz, 1H, furo[3,2-*b*]pyridine−*H*), 10.46 (s, 1H, −NH); ^{13}C NMR (100 MHz): 14.2, 59.6, 115.0 (d, J_{C-F}=22 Hz), 117.5, 122.0 (d, J_{C-F}=8 Hz), 126.1, 126.2, 127.5, 129.2, 130.3, 135.0, 135.1 (d, J_{C-F}=3 Hz), 135.5, 136.8, 138.1, 139.1, 144.3, 147.4, 159.0 (d, J_{C-F}=220.0 Hz),160.2, 164.9; MS (ESI) *m*/*z* (%): 420.1 [(M+H)$^+$, 100]. Anal. Calcd for $C_{23}H_{18}FN_3O_4$: C, 65.87; H, 4.33; N, 10.02. Found: C, 66.07; H, 4.35; N, 10.05.

*4.1.15. Ethyl 3-amino-6-(3-{[(4-biphenyl)amino]carbonyl}phenyl)furo[3,2-b]pyridine-2-carboxylate (**18**).* The title compound was prepared in 63% yield as an yellow-brown solid from **9** by a similar method to that described for **13** using 4-phenylaniline. Mp 270–271 °C; IR (KBr): 3400, 3286, 1677, 1644, 1616, 1529, 1484, 1374, 1320, 1239, 1139 cm^{-1}; ^{1}H NMR (400 MHz): 1.39 (t, *J*=7.1 Hz, 3H, −COOCH$_2$C*H*$_3$), 4.38 (q, *J*=7.1 Hz, 2H, −COOC*H*$_2$CH$_3$), 6.36 (s, 2H, −N*H*$_2$), 7.39 (dd, *J*=*J*′=7.2 Hz, 1H, Ph−Ph−*H*), 7.50 (dd, *J*=*J*′=7.6 Hz, 2H, Ph−Ph−*H*), 7.73–7.78 (m, 5H, 2Ph−Ph−*H*, 2Ph−*H*−Ph, Ph−*H*),

7.95 (d, *J*=8.8 Hz, 2H, Ph–*H*–Ph), 8.07 (d, *J*=8.4 Hz, 1H, Ph–*H*), 8.09 (d, *J*=8.4 Hz, 1H, Ph–*H*), 8.42 (br s, 1H, Ph–*H*), 8.47 (d, *J*=1.9 Hz, 1H, furo[3,2-*b*]pyridine–*H*), 9.07 (d, *J*=1.9 Hz, 1H, furo[3,2-*b*]pyridine–*H*), 10.51 (s, 1H, –NH); ^{13}C NMR (100 MHz): 14.6, 60.1, 118.0, 120.9, 126.5, 126.8, 127.0, 127.3, 128.0, 129.1, 129.6, 130.8, 135.5, 135.6, 136.0, 136.3, 137.2, 138.6, 138.8, 139.5, 139.8, 144.8, 147.8, 160.6, 165.4; MS (ESI) *m*/*z* (%): 478.1 [(M+H)$^+$, 100]. Anal. Calcd for $C_{29}H_{23}N_3O_4$: C, 72.94; H, 4.85; N, 8.80. Found: C, 73.13; H, 4.86; N, 8.83.

*4.1.16. Ethyl 3-amino-6-(4-{[(3-chlorophenyl)amino]carbonyl}phenyl)furo[3,2-b]pyridine-2-carboxylate (**19**).* The title compound was prepared in 37% yield as a beige solid from **10** by a similar method to that described for **13** using 3-chloroaniline. Mp 246–247 °C; IR (KBr): 3499, 3394, 1690, 1624, 1594, 1535, 1484, 1378, 1310, 1261, 1140 cm^{-1}; ^{1}H NMR (400 MHz): 1.38 (t, *J*=7.1 Hz, 3H, –COOCH$_2$C*H*$_3$), 4.38 (q, *J*=7.1 Hz, 2H, –COOC*H*$_2$CH$_3$), 6.35 (s, 2H, –N*H*$_2$), 7.22 (ddd, *J*=8.0, 2.0, 0.8 Hz, 1H, PhCl–*H*), 7.45 (dd, *J*=8.4, 8.0 Hz, 1H, PhCl–*H*), 7.79 (ddd, *J*=8.4, 2.0, 0.8 Hz, 1H, PhCl–*H*), 8.04–8.05 (m, 1H, PhCl–*H*), 8.06 (d, *J*=8.4 Hz, 2H, Ph–*H*), 8.16 (d, *J*=8.4 Hz, 2H, Ph–*H*), 8.46 (d, *J*=2.0 Hz, 1H, furo[3,2-*b*]pyridine–*H*), 9.04 (d, *J*=2.0 Hz, 1H, furo[3,2-*b*]pyridine–*H*), 10.54 (s, 1H, –NH); ^{13}C NMR (100 MHz): 14.6, 60.1, 118.0, 118.8, 119.9, 123.6, 126.2, 127.6, 128.7, 130.5, 132.4, 133.1, 134.3, 134.9, 139.7, 140.3, 140.8, 144.7, 147.8, 160.6, 165.4; MS (ESI) *m*/*z* (%): 435.9 [(M+H)$^+$, 100], 437.9 [(M+H)+2, 33]. Anal. Calcd for $C_{23}H_{18}ClN_3O_4$: C, 63.38; H, 4.16; N, 9.64. Found: C, 63.53; H, 4.17; N, 9.67.

*4.1.17. Ethyl 3-amino-6-(4-{[(3-biphenyl)amino]carbonyl}phenyl) furo[3,2-b]pyridine-2-carboxylate (**20**).* The title compound was prepared in 43% yield as a beige solid from **10** by a similar method to that described for **13** using 3-phenylaniline. Mp 213–214 °C; IR (KBr): 3493, 3396, 1673, 1623, 1542, 1479, 1374, 1314, 1256, 1137 cm^{-1}; ^{1}H NMR (400 MHz): 1.39 (t, *J*=7.1 Hz, 3H, –COOCH$_2$C*H*$_3$), 4.38 (q, *J*=7.1 Hz, 2H, –COOC*H*$_2$CH$_3$), 6.36 (s, 2H, –N*H*$_2$), 7.47–7.56 (m, 5H, 3Ph–Ph–*H*, 2Ph–*H*–Ph), 7.71 (dd, *J*=8.4, 1.0 Hz, 2H, Ph–Ph–*H*), 7.89 (dt, *J*=8.0, 1.0 Hz, 1H, Ph–*H*–Ph), 8.07 (d, *J*=8.4 Hz, 2H, Ph–*H*), 8.20 (d, *J*=8.4 Hz, 2H, Ph–*H*), 8.19–8.20 (m, 1H, Ph–*H*–Ph), 8.47 (d, *J*=2.0 Hz, 1H, furo[3,2-*b*]pyridine–*H*), 9.05 (d, *J*=2.0 Hz, 1H, furo[3,2-*b*]pyridine–*H*), 10.48 (s, 1H, –NH); ^{13}C NMR (100 MHz): 14.6, 60.1, 117.9, 118.8, 119.5, 122.2, 126.5, 126.8, 127.5, 127.7, 128.7, 129.1, 129.4, 134.6, 134.8, 134.9, 139.7, 139.8, 140.0, 140.3, 140.8, 144.6, 147.8, 160.6, 165.2; MS (ESI) *m*/*z* (%): 478.0 [(M+H)$^+$, 100]. Anal. Calcd for $C_{29}H_{23}N_3O_4$: C, 72.94; H, 4.85; N, 8.80. Found: C, 73.13; H, 4.87; N, 8.81.

*4.1.18. Ethyl 3-amino-6-(4-{[(4-biphenyl)amino]carbonyl}phenyl) furo[3,2-b]pyridine-2-carboxylate (**21**).* The title compound was prepared in 48% yield as a yellow-brown solid from **10** by a similar method to that described for **13** using 4-phenylaniline. Mp 311–312 °C; IR (KBr): 3402, 3270, 1679, 1644, 1619, 1566, 1532, 1488, 1375, 1312, 1258, 1167 cm^{-1}; ^{1}H NMR (400 MHz): 1.39 (t, *J*=7.1 Hz, 3H, –COOCH$_2$C*H*$_3$), 4.38 (q, *J*=7.1 Hz, 2H, –COOC*H*$_2$CH$_3$), 6.35 (s, 2H, –N*H*$_2$), 7.38 (dd, *J*=*J*′=7.2 Hz, 1H, Ph–Ph–*H*), 7.50 (dd, *J*=8.2, 7.2 Hz, 2H, Ph–Ph–*H*), 7.72–7.75 (m, 2H, Ph–Ph–*H*), 7.74 (d, *J*=8.8 Hz, 2H, Ph–*H*–Ph), 7.97 (d, *J*=8.8 Hz, 2H, Ph–*H*–Ph), 8.07 (d, *J*=8.4 Hz, 2H, Ph–*H*), 8.19 (d, *J*=8.4 Hz, 2H, Ph–*H*), 8.46 (d, *J*=1.8 Hz, 1H, furo[3,2-*b*]pyridine–*H*), 9.05 (d, *J*=1.8 Hz, 1H, furo[3,2-*b*]pyridine–*H*), 10.50 (s, 1H, –NH); ^{13}C NMR (100 MHz): 14.6, 60.1, 118.0, 120.9, 126.5, 126.6, 127.0, 127.6, 128.7, 129.1, 131.5, 134.6, 134.9, 135.5, 138.8, 139.7, 139.9, 140.0, 144.6, 147.8, 160.6, 165.1; MS (ESI) *m*/*z* (%): 478.1 [(M+H)$^+$, 100]. Anal. Calcd for $C_{29}H_{23}N_3O_4$: C, 72.94; H, 4.85; N, 8.80. Found: C, 72.85; H, 4.84; N, 8.78.

*4.1.19. 3-Amino-6-(3-{[(3-chlorophenyl)amino]carbonyl}phenyl)-N-methylfuro[3,2-b]pyridine-2-carboxamide (**22**).* A solution of MeNH$_2$ in ethanol (8 M) (21.8 mL, 174.40 mmol) was added to the ester **13** (378 mg, 0.86 mmol) in an Schlenk apparatus. The reaction mixture was stirred at 110 °C for 24 h. After cooling at room temperature, the solution was evaporated. The resulting solid was washed with CH_2Cl_2 and dried to afford **22** (260 mg, 71%) as a beige solid. Mp 201–202 °C; IR (KBr): 3620, 3290, 1656, 1594, 1534, 1481, 1371, 1326, 1255, 1161 cm^{-1}; ^{1}H NMR (400 MHz): 2.83 (d, *J*=4.5 Hz, 3H, –NHC*H*$_3$), 5.95 (s, 2H, –N*H*$_2$), 7.23 (dd, *J*=8.0, 1.2 Hz, 1H, PhCl–*H*), 7.45 (dd, *J*=8.0, 8.4 Hz, 1H, PhCl–*H*), 7.74 (dd, *J*=8.0, 8.4 Hz, 1H, Ph–*H*), 7.78 (dd, *J*=8.0, 1.2 Hz, 1H, PhCl–*H*), 8.03 (br s, 1H, PhCl–*H*), 8.04 (d, *J*=8.4 Hz, 1H, Ph–*H*), 8.10 (d, *J*=8.0 Hz, 1H, Ph–*H*), 8.17 (q, *J*=4.5 Hz, 1H, –N*H*CH$_3$), 8.29 (d, *J*=1.6 Hz, 1H, furo[3,2-*b*]pyridine–*H*), 8.39 (br s, 1H, Ph–*H*), 9.01 (d, *J*=1.6 Hz, 1H, furo[3,2-*b*]pyridine–*H*), 10.57 (s, 1H, –N*H*); ^{13}C NMR (100 MHz): 25.5, 117.3, 118.9, 119.9, 123.7, 126.8, 127.8, 129.6, 130.4, 130.6, 131.0, 133.2, 134.3, 134.7, 135.6, 137.5, 140.6, 140.8, 144.5, 146.4, 161.5, 165.7; MS (ESI) *m*/*z* (%): 421.1 [(M+H)$^+$, 100], 423.1 (M+H)+2, 33]. Anal. Calcd for $C_{22}H_{17}ClN_4O_3$: C, 62.79; H, 4.07; N, 13.31. Found: C, 62.88; H, 4.09; N, 13.35.

*4.1.20. 3-Amino-6-(3-{[(3-fluorophenyl)amino]carbonyl}phenyl)-N-methylfuro[3,2-b]pyridine-2-carboxamide (**23**).* The title compound was prepared in 54% yield as a beige solid from **14** by a similar method to that described for **22**. Mp 218–219 °C; IR (KBr): 3359, 3303, 1656, 1610, 1540, 1490, 1370, 1328, 1254, 1146 cm^{-1}; ^{1}H NMR (400 MHz): 2.83 (d, *J*=4.6 Hz, 3H, –NHC*H*$_3$), 5.95 (s, 2H, –NH$_2$), 7.00 (ddd, *J*=*J*′=8.2, 2.0 Hz, 1H, PhF–*H*), 7.46 (ddd, *J*=*J*′=*J*″=8.2 Hz, 1H, PhF–*H*), 7.62 (dd, *J*=8.2, 1.2 Hz, 1H, PhF–*H*), 7.74 (dd, *J*=*J*′=8.0 Hz, 1H, Ph–*H*), 7.82 (dt, *J*=11.6, 2.0 Hz, 1H, PhF–*H*), 8.04 (d, *J*=8.0 Hz, 1H, Ph–*H*), 8.10 (d, *J*=8.0 Hz, 1H, Ph–*H*), 8.18 (q, *J*=4.6 Hz, 1H, –N*H*CH$_3$), 8.29 (d, *J*=1.8 Hz, 1H, furo[3,2-*b*]pyridine–*H*), 8.38 (br s, 1H, Ph–*H*), 9.01 (d, *J*=1.8 Hz, 1H, furo[3,2-*b*]pyridine–*H*), 10.59 (s, 1H, –NH); ^{13}C NMR (100 MHz): 25.5, 107.1 (d, J_{C-F}=26 Hz), 110.4 (d, J_{C-F}=21 Hz), 116.2 (d, J_{C-F}=2 Hz), 117.3, 126.8, 127.8, 129.6, 130.3, 130.5 (d, J_{C-F}=9 Hz), 131.0, 134.3, 134.6, 135.7, 137.4, 140.6, 141.0 (d, J_{C-F}=11 Hz), 144.5, 146.3, 161.5, 162.3 (d, J_{C-F}=240 Hz), 165.7; MS (ESI) *m*/*z* (%): 405.1 [(M+H)$^+$, 100]. Anal. Calcd for $C_{22}H_{17}FN_4O_3$: C, 65.34; H, 4.24; N, 13.85. Found: C, 65.50; H, 4.26; N, 13.88.

*4.1.21. 3-Amino-6-(3-{[(3-biphenyl)amino]carbonyl}phenyl)-N-methylfuro[3,2-b]pyridine-2-carboxamide (**24**).* The title compound was prepared in 77% yield as a beige solid from **15** by a similar method to that described for **22**. Mp 247–248 °C; IR (KBr): 3357, 3308, 1648, 1615, 1544, 1500, 1479, 1420, 1370, 1327, 1255, 1160 cm^{-1}; ^{1}H NMR (400 MHz): 2.83 (d, *J*=4.5 Hz, 3H, –NHC*H*$_3$), 5.96 (s, 2H, –N*H*$_2$), 7.41–7.56 (m, 5H, 3Ph–Ph–*H* and 2Ph–*H*–Ph), 7.71 (d, *J*=7.2 Hz, 2H, Ph–Ph–*H*), 7.75 (dd, *J*=*J*′=8.0 Hz, 1H, Ph–*H*), 7.89 (d, *J*=8.0 Hz, 1H, Ph–*H*–Ph), 8.08 (d, *J*=8.0 Hz, 1H, Ph–*H*), 8.10 (d, *J*=8.0 Hz, 1H, Ph–*H*), 8.16 (br s, 1H, Ph–*H*–Ph), 8.17 (q, *J*=4.5 Hz, 1H, –N*H*CH$_3$), 8.31 (d, *J*=1.6 Hz, 1H, furo[3,2-*b*]pyridine–*H*), 8.43 (br s, 1H, Ph–*H*), 9.03 (d, *J*=1.6 Hz, 1H, furo[3,2-*b*]pyridine–*H*), 10.51 (s, 1H, –NH); ^{13}C NMR (100 MHz): 25.4, 117.3, 118.9, 119.5, 122.3, 126.7, 126.8, 127.8, 129.2, 129.5, 129.6, 130.3, 130.8, 134.4, 134.6, 135.9, 137.4, 139.8, 140.3, 140.6, 140.9, 145.0, 146.4, 161.5, 165.5; MS (ESI) *m*/*z* (%): 463.2 [(M+H)$^+$, 100]. Anal. Calcd for $C_{28}H_{22}N_4O_3$: C, 72.71; H, 4.79; N, 12.11. Found: C, 72.93; H, 4.80; N, 12.14.

*4.1.22. 3-Amino-6-(3-{[(4-chlorophenyl)amino]carbonyl}phenyl)-N-methylfuro[3,2-b]pyridine-2-carboxamide (**25**).* The title compound was prepared in 30% yield as a beige solid from **16** by a similar method to that described for **22**. Mp 274–275 °C; IR (KBr): 3276, 1647, 1529, 1325, 1252, 1163, 1093 cm^{-1}; ^{1}H NMR (400 MHz): 2.83 (d, *J*=4.6 Hz, 3H, –NHC*H*$_3$), 5.94 (s, 2H, –N*H*$_2$), 7.48 (d, *J*=8.8 Hz, 2H, PhCl–*H*), 7.74 (dd, *J*=7.6, 8.0 Hz, 1H, Ph–*H*), 7.88 (d, *J*=8.8 Hz, 2H, PhCl–*H*), 8.03 (dt, *J*=8.0, 1.2 Hz, 1H, Ph–*H*), 8.09 (dt, *J*=7.6, 1.2 Hz, 1H, Ph–*H*), 8.16 (q, *J*=4.6 Hz, 1H, –N*H*CH$_3$), 8.28 (d, *J*=1.7 Hz, 1H,

furo[3,2-*b*]pyridine–*H*), 8.38 (dd, *J*=*J*′=1.2 Hz, 1H, Ph–*H*), 9.01 (d, *J*=1.7 Hz, 1H, furo[3,2-*b*]pyridine–*H*), 10.53 (s, 1H, –NH); ^{13}C NMR (100 MHz): 25.4, 117.3, 122.1, 126.7, 127.6, 127.8, 128.8, 129.6, 130.3, 130.8, 134.3, 134.6, 135.8, 137.4, 138.2, 140.6, 144.5, 146.3, 161.5, 165.5; MS (ESI) *m*/*z* (%): 421.2 [(M+H)$^+$, 100], 423.2 (M+H)+2, 35]. Anal. Calcd for $C_{22}H_{17}ClN_4O_3$: C, 62.79; H, 4.07; N, 13.31. Found: C, 62.90; H, 4.09; N, 13.33.

*4.1.23. 3-Amino-6-(3-{[(4-fluorophenyl)amino]carbonyl}phenyl)-N-methylfuro[3,2-b]pyridine-2-carboxamide (**26**).* The title compound was prepared in 22% yield as a beige solid from **17** by a similar method to that described for **22**. Mp 269–270 °C; IR (KBr): 3263, 1644, 1567, 1514, 1408, 1325, 1237, 1162 cm^{-1}; ^{1}H NMR (400 MHz): 2.83 (d, *J*=4.6 Hz, 3H, –NHC*H*$_3$), 5.94 (s, 2H, –N*H*$_2$), 7.26 (dd, *J*=*J*′=9.0 Hz, 2H, PhF–*H*), 7.73 (dd, *J*=7.6, 8.0 Hz, 1H, Ph–*H*), 7.85 (dd, *J*=9.0, 5.1 Hz, 2H, PhF–*H*), 8.04 (d, *J*=7.6 Hz, 1H, Ph–*H*), 8.08 (d, *J*=8.0 Hz, 1H, Ph–*H*), 8.15 (q, *J*=4.6 Hz, 1H, –N*H*CH$_3$), 8.28 (d, *J*=1.8 Hz, 1H, furo[3,2-*b*]pyridine–*H*), 8.38 (s, 1H, Ph–*H*), 9.01 (d, *J*=1.8 Hz, 1H, furo[3,2-*b*]pyridine–*H*), 10.46 (s, 1H, –NH); ^{13}C NMR (100 MHz): 26.4, 116.4 (*J*$_{C-F}$=22 Hz), 118.3, 123.5 (*J*$_{C-F}$=8 Hz), 127.7, 128. 8, 130.6, 131.4, 131.8, 135.4, 135.6, 136.6 (*J*$_{C-F}$=2 Hz), 136.9, 138.4, 141.6, 145.5, 147.4, 159.6 (*J*$_{C-F}$=239 Hz), 162.5, 166.3; MS (ESI) *m*/*z* (%): 405.6[(M+H)$^+$, 100]. Anal. Calcd for $C_{22}H_{17}FN_4O_3$: C, 65.34; H, 4.24; N, 13.85. Found: C, 65.48; H, 4.26; N, 13.89.

*4.1.24. 3-Amino-6-(3-{[(4-biphenyl)amino]carbonyl}phenyl)-N-methylfuro[3,2-b]pyridine-2-carboxamide (**27**).* The title compound was prepared in 52% yield as a beige solid from **18** by a similar method to that described for **22**. Mp 300–301 °C; IR (KBr): 3359, 3271, 1640, 1570, 1524, 1446, 1372, 1323, 1286, 1239, 1163 cm^{-1}; ^{1}H NMR (400 MHz): 2.84 (d, *J*=4.5 Hz, 3H, –NHC*H*$_3$), 5.95 (s, 2H, –N*H*$_2$), 7.38 (dd, *J*=7.2, 7.6 Hz, 1H, Ph–Ph–*H*), 7.50 (dd, *J*=7.6, 8.0 Hz, 2H, Ph–Ph–*H*), 7.72–7.78 (m, 5H, 2Ph–Ph–*H*, 2Ph–*H*–Ph, Ph–*H*), 7.96 (d, *J*=8.8 Hz, 2H, Ph–*H*–Ph), 8.07 (d, *J*=8.0 Hz, 1H, Ph–*H*), 8.10 (d, *J*=8.0 Hz, 1H, Ph–*H*), 8.18 (q, *J*=4.5 Hz, 1H, –N*H*CH$_3$), 8.30 (d, *J*=1.6 Hz, 1H, furo[3,2-*b*]pyridine–*H*), 8.41 (br s, 1H, Ph–*H*), 9.03 (d, *J*=1.6 Hz, 1H, furo[3,2-*b*]pyridine–*H*), 10.52 (s, 1H, –NH); ^{13}C NMR (100 MHz): 25.4, 117.3, 120.9, 126.5, 126.8, 127.0, 127.3, 127.8, 129.1, 129.6, 130.3, 130.8, 134.4, 134.6, 135.6, 136.0, 137.4, 138.8, 139.8, 140.6, 144.5, 146.4, 161.5, 165.4; MS (ESI) *m*/*z* (%): 463.2 [(M+H)$^+$, 100]. Anal. Calcd for $C_{28}H_{22}N_4O_3$: C, 72.71; H, 4.79; N, 12.11. Found: C, 72.86; H, 4.81; N, 12.14.

*4.1.25. 3-Amino-6-(4-{[(3-chlorophenyl)amino]carbonyl}phenyl)-N-methylfuro[3,2-b]pyridine-2-carboxamide (**28**).* The title compound was prepared in 80% yield as a light yellow solid from **19** by a similar method to that described for **22**. Mp 258–259 °C; IR (KBr): 3452, 3363, 1666, 1641, 1594, 1527, 1481, 1418, 1292, 1256, 1160 cm^{-1}; ^{1}H NMR (400 MHz): 2.83 (d, *J*=4.7 Hz, 3H, –NHC*H*$_3$), 5.95 (s, 2H, –N*H*$_2$), 7.22 (ddd, *J*=8.0, 2.0, 0.8 Hz, 1H, PhCl–*H*), 7.44 (dd, *J*=*J*′=8.0 Hz, 1H, PhCl–*H*), 7.79 (ddd, *J*=8.0, 2.0, 0.8 Hz, 1H, PhCl–*H*), 8.05–8.06 (m, 1H, PhCl–*H*), 8.06 (d, *J*=8.4 Hz, 2H, Ph–*H*), 8.15 (d, *J*=8.4 Hz, 2H, Ph–*H*), 8.18 (q, *J*=4.7 Hz, 1H, –N*H*CH$_3$), 8.26 (d, *J*=1.9 Hz, 1H, furo[3,2-*b*]pyridine–*H*), 8.99 (d, *J*=1.9 Hz, 1H, furo[3,2-*b*]pyridine–*H*), 10.54 (s, 1H, –NH); ^{13}C NMR (100 MHz): 25.4, 117.3, 118.8, 119.9, 123.6, 127.6, 128.7, 130.4, 130.5, 133.1, 133.8, 134.1, 134.6, 140.5, 140.8, 144.4, 146.3, 161.5, 165.4; MS (ESI) *m*/*z* (%): 421.1 [(M+H)$^+$, 100], 123.1 (M+H)+2, 33]. Anal. Calcd for $C_{22}H_{17}ClN_4O_3$: C, 62.79; H, 4.07; N, 13.31. Found: C, 62.63; H, 4.05; N, 13.28.

*4.1.26. 3-Amino-6-(4-{[(3-biphenyl)amino]carbonyl}phenyl)-N-methylfuro[3,2-b]pyridine-2-carboxamide (**29**).* The title compound was prepared in 65% yield as a beige solid from **20** by a similar method to that described for **22**. Mp 249–250 °C; IR (KBr): 3383, 3296, 1671, 1639, 1610, 1547, 1478, 1375, 1314, 1259, 1160 cm^{-1}; ^{1}H NMR (400 MHz): 2.84 (d, *J*=4.6 Hz, 3H, –NHC*H*$_3$), 5.95 (s, 2H, –N*H*$_2$), 7.42–7.56 (m, 5H, 3Ph–Ph–*H*, 2Ph–*H*–Ph), 7.71 (dd, *J*=8.8, 1.6 Hz, 2H, Ph–Ph–*H*), 7.89 (d, *J*=8.0 Hz, 1H, Ph–*H*–Ph), 8.07 (d, *J*=8.6 Hz, 2H, Ph–*H*), 8.19 (d, *J*=8.6 Hz, 2H, Ph–*H*), 8.18–8.20 (m, 2H, Ph–*H*–Ph, –N*H*CH$_3$), 8.28 (d, *J*=1.9 Hz, 1H, furo[3,2-*b*]pyridine–*H*), 9.01 (d, *J*=1.9 Hz, 1H, furo[3,2-*b*]pyridine–*H*), 10.48 (s, 1H, –NH); ^{13}C NMR (100 MHz): 25.4, 117.3, 118.9, 119.5, 122.3, 126.8, 127.6, 127.8, 128.7, 129.2, 129.4, 130.4, 133.9, 134.4, 134.6, 139.9, 140.3, 140.8, 144.4, 146.3, 161.5, 165.2; MS (ESI) *m*/*z* (%): 463.2 [(M+H)$^+$, 100]. Anal. Calcd for $C_{28}H_{22}N_4O_3$: C, 72.71; H, 4.79; N, 12.11. Found: C, 72.86; H, 4.80; N, 12.15.

*4.1.27. 3-Amino-6-(4-{[(4-biphenyl)amino]carbonyl}phenyl)-N-methylfuro[3,2-b]pyridine-2-carboxamide (**30**).* The title compound was prepared in 73% yield as a yellow solid from **21** by a similar method to that described for **22**. Mp 324–325 °C; IR (KBr): 3390, 3274, 1642, 1568, 1533, 1482, 1401, 1371, 1318, 1257, 1162 cm^{-1}; ^{1}H NMR (400 MHz): 2.84 (d, *J*=4.8 Hz, 3H, –NHC*H*$_3$), 5.95 (s, 2H, –N*H*$_2$), 7.38 (dd, *J*=*J*′=7.3 Hz, 1H, Ph–Ph–*H*), 7.50 (dd, *J*=7.3, 7.0 Hz, 2H, Ph–Ph–*H*), 7.73 (d, *J*=7.0 Hz, 2H, Ph–Ph–*H*), 7.74 (d, *J*=8.8 Hz, 2H, Ph–*H*–Ph), 7.97 (d, *J*=8.8 Hz, 2H, Ph–*H*–Ph), 8.06 (d, *J*=8.2 Hz, 2H, Ph–*H*), 8.18 (d, *J*=8.2 Hz, 2H, Ph–*H*), 8.17 (br, 1H, –N*H*CH$_3$), 8.27 (d, *J*=1.6 Hz, 1H, furo[3,2-*b*]pyridine–*H*), 9.01 (d, *J*=1.6 Hz, 1H, furo [3,2-*b*]pyridine–*H*), 10.49 (s, 1H, –NH); ^{13}C NMR (100 MHz): 25.5, 117.3, 120.9, 126.5, 127.0, 127.3, 127.6, 128.7, 129.1, 130.4, 133.9, 134.5, 134.6, 135.5, 138.8, 139.9, 140.3, 140.8, 144.4, 146.3, 161.5, 165.2; MS (ESI) *m*/*z* (%): 463.2 [(M+H)$^+$, 100]. Anal. Calcd for $C_{28}H_{22}N_4O_3$: C, 72.71; H, 4.79; N, 12.11. Found: C, 72.91; H, 4.81; N, 12.15.

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