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A facile one-pot synthesis of 2-substituted-3-aminoquinolines: preparation of benzo[*b*]naphthyridine-3-carbonitriles

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Abstract—A facile one-pot synthesis of 3-aminoquinolines from *ortho*-aminobenzaldehydes was developed. Ethyl 6,7-dimethoxy-3-aminoquinoline-2-carboxylate, a key intermediate for the preparation of a 4-anilino-benzo[*b*][1,5]-naphthyridine-3-carbonitrile, was efficiently prepared by this method. Synthetic routes to 4-anilino-benzo[*b*][1,5]-naphthyridine-3-carbonitrile and 4-anilino-benzo[*b*][1,8]-naphthyridine-3-carbonitrile are described
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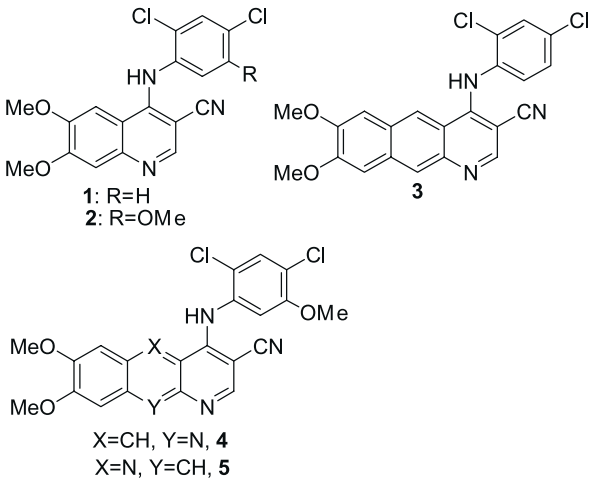
1. Introduction

Protein tyrosine kinases (PTKS), including Src,[1] are key elements in signal transduction pathways regulating a number of cellular functions such as cell growth and differentiation. The activation and over-expression of Src has been implicated in a number of diseases, including cancer.[2] Small molecule inhibitors of Src activity could be beneficial for the treatment of various diseases. Several classes of Src kinase inhibitors have been reported in the literature.[3]

We previously reported that 4-anilino-3-quinolinecarbonitriles,[4,5] **1** and **2**, were potent inhibitors of Src kinase activity. It was subsequently shown that 4-anilino-benzo[*g*]-quinoline-3-carbonitrile **3**,[6] which has a phenyl ring fused to the 3-quinolinecarbonitrile, also inhibited Src kinase activity. Aza analogs of 3-quinolinecarbonitriles (**1** and **2**), which have [1,7], [1,5] or [1,8]-naphthyridine bicyclic cores, were also reported to be inhibitors of PTKs.[7] Compounds **4** and **5**, which have a 5-aza/10-aza tricyclic scaffold, were therefore designed as potential Src inhibitors.

2. Results and discussion

Treatment of 6-nitroveratraldehyde with methyl cyanoacetate followed by reduction provided 2-aminoquinoline **8** (Scheme 1). Reaction of **8** with *N*,*N*-dimethylformamide dimethyl acetal (DMF-DMA) followed by addition of the anion of acetonitrile gave **10**. Subsequent chlorination of **10** and coupling reaction of **11** with 2,4-dichloro-5-methoxy-aniline gave the final product **4**.



To synthesize 4-anilino-benzo[*b*][1,5]-naphthyridine-3-carbonitrile **5** using an analogous approach to the one described above, the major challenge would be the preparation of 3-amino-2-quinolinecarboxylate **C** (Scheme 2). At the inception of our work, there was only one report of the synthesis of a 3-amino-2-quinoline-carboxylate in the literature.

Westphal et al. disclosed[8] that the condensation of *ortho*-aminobenzaldehyde with 1-(2-ethoxycarbonyl-2-oxoethyl)-pyridinium bromide **D**, prepared from pyridine and ethyl 2-bromopyruvate, gave 3-pyridino-quinoline **E** (Scheme 3). Upon treatment with pyrrolidine, **E** was converted to 3-aminoquinoline **F**. A major drawback of this approach

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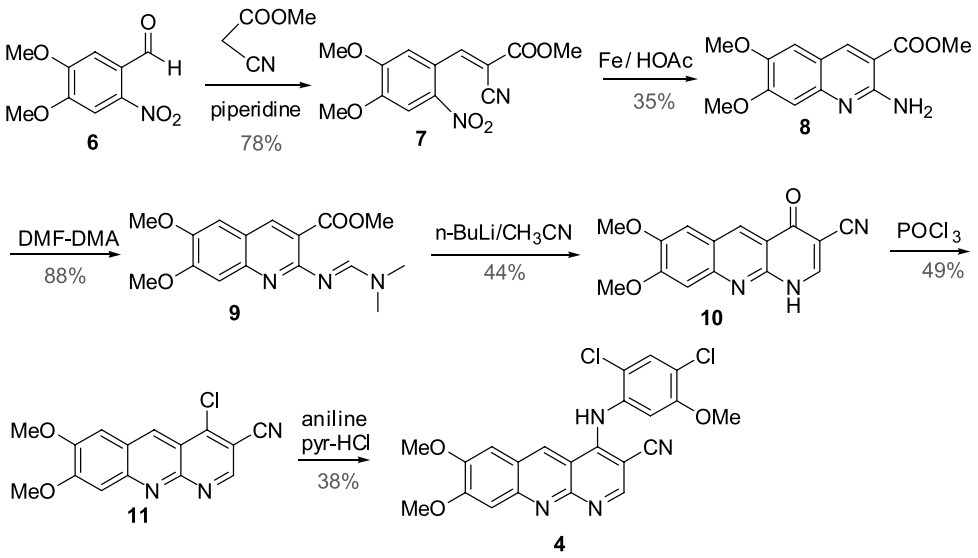
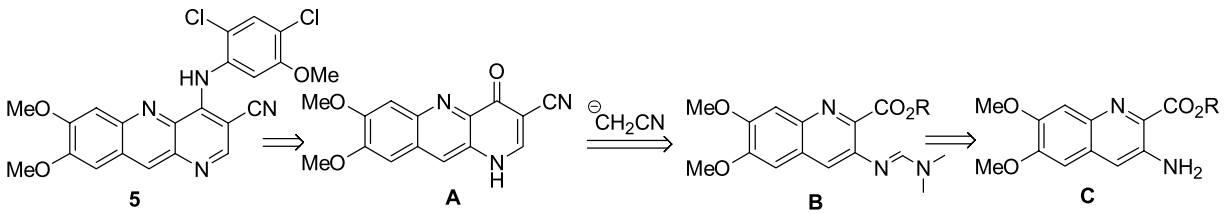
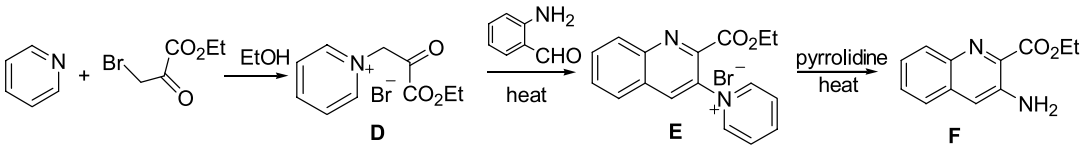


Scheme 1.



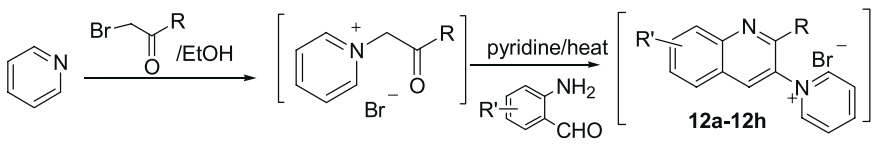
Scheme 2.



Scheme 3.

was that the coupling reaction of **D** with *ortho*-aminobenzaldehyde gave a poor yield (~30%) of **E**. It did, however, offer an efficient and concise approach to functionalized 3-aminoquinolines from readily accessible starting materials.

This prompted us to investigate possible modifications to improve the existing procedure. We found that the poor reproducibility in pyridinium formation and the low yield in its subsequent condensation with *ortho*-aminobenzaldehydes were mainly due to the hydroscopicity and instability of compounds **D** and **E** when exposed to the atmosphere. A one-pot procedure, that did not require separation and purification of intermediates **D** and **E**, was therefore

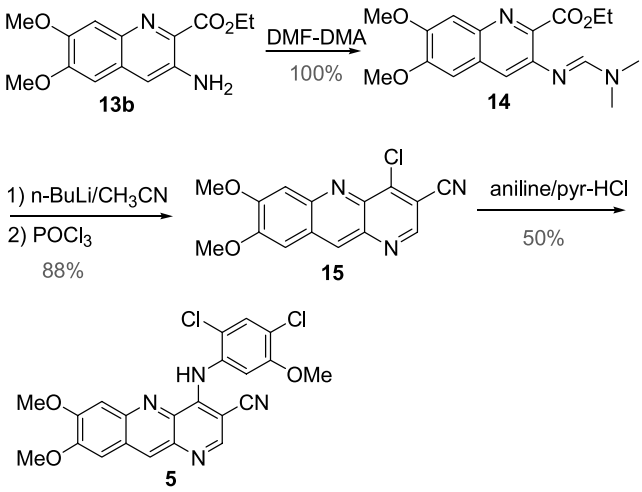


13a R=CO_2Et, R'=H, 90%
13b R=CO_2Et, R'=6,7-dimethoxy, 79%
13c R=CO_2Et, R'=6-Cl, 48%
13d R=CO_2Et, R'=7-Cl, 71%
13e R=CO_2Et, R'=6,8-dibromo, 39%
13f R=phenyl, R'=H, 65%
13g R=phenyl, R'=6,7-dimethoxy, 75%
13h R=methyl, R'=H, 52%

Scheme 4.

developed. In order to improve the overall yield of this one-pot approach, we also optimized the reaction conditions, including temperature, time and the ratio of reagents and substrates. Under the optimal reaction conditions, **13a** (Scheme 4) was obtained in 90% overall yield from *ortho*-aminobenzaldehyde. This method also provided satisfactory yields for the condensations of various substituted *ortho*-aminobenzaldehydes (**13b**-**13e** and **13g**, Scheme 4). By preparing other 2-substituted-3-aminoquinolines (**13f**-**13h**, Scheme 4), the versatility of this methodology was demonstrated. It is worthwhile to note that the coupling reactions of the pyridinium salt with *ortho*-aminobenzaldehydes, when the R group is Me or Ph, were somewhat sluggish. We found that the addition of a catalytic amount of a relatively strong base such as 4-(dimethylamino)pyridine facilitated the reaction.

With ethyl 3-aminoquinoline-2-carboxylate **13b** in hand, we embarked on converting it to the target 4-anilino-benzo-[*b*][1,5]-naphthyridine-3-carbonitrile **5** (Scheme 5). Treatment of **13b** with DMF-DMA gave amidine **14**. Reaction of **14** with the anion of acetonitrile followed by chlorination with phosphorus oxychloride provided **15**. Coupling of **15** with 2,4-dichloro-5-methoxyaniline gave target compound **5**.



Scheme 5.

In summary, we present here an efficient one-pot synthesis of 2-substituted-3-aminoquinolines from *ortho*-amino-benzaldehydes. We demonstrated that this method can potentially be utilized for the preparation of other 3-aminoquinolines with different functional groups at C-2. In addition, first synthetic routes to a benzo[*b*][1,5]-naphthyridine-3-carbonitrile and a benzo[*b*][1,8]-naphthyridine-3-carbonitrile were described. The activities of target molecules **4** and **5** will be disclosed elsewhere.

3. Experimental

3.1. General

Melting points were determined in open capillary tubes on a Meltemp melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a NT-300 WB spectrometer. Electrospray (ES) mass spectra were recorded on a Microma Platform mass spectrometer. Flash chromatography was performed with Baker 40 μM silica gel. Reactions were generally carried out under an inert atmosphere of nitrogen.

3.2. Compounds 7-11 and 4

3.2.1. Methyl (*E*)-2-cyano-3-(4,5-dimethoxy-2-nitrophenyl)-2-propenoate (7). To a mixture of 6-nitroveratraldehyde (80%) (7.00 g, 33.2 mmol) and methyl cyanoacetate (3.4 mL, 38.4 mmol) in methanol (170 mL) was added piperidine (0.70 mL). The reaction mixture was stirred at room temperature for 1 h. The resultant solid was collected by filtration washing with methanol and diethyl ether to provide **7** (7.57 g, 78%) as a pale yellow solid; mp 162–164 °C; ^{1}H NMR (δ, ppm, DMSO-d_6): 3.90 (s, 3H), 3.94 (s, 3H), 3.96 (s, 3H), 7.56 (s, 1H), 7.83 (s, 1H), 8.77 (s, 1H); *m*/*z* (ES) $(MH)^-$=292.1. Anal. Calcd for $C_{13}H_{12}N_2O_6$: C, 53.43; H, 4.14; N, 9.59. Found: C, 53.03; H, 4.02; N, 9.59.

3.2.2. Methyl 2-amino-6,7-dimethoxy-3-quinolinecarboxylate (8). A mixture of **7** (7.00 g, 24.0 mmol) and iron (5.00 g, 89.6 mmol) in acetic acid (100 mL) was heated at reflux for 10 min. The reaction mixture was cooled slightly and the solids were removed by filtration, washing with ethyl acetate. The filtrate was concentrated in vacuo and the residue was partitioned between ethyl acetate and aqueous sodium bicarbonate. The organic layer was dried over magnesium sulfate, filtered and concentrated in vacuo. Trituration of the residue with diethyl ether provided **8** (652 mg, 10%) as a pale yellow solid. Acidification of the aqueous layer with concentrated hydrochloric acid caused additional product to precipitate out. This material was collected by filtration, washed with water and ethyl acetate to provide an additional amount of **8** (1.57 g, 25%); mp 227–229 °C; ^{1}H NMR (δ, ppm, DMSO-d_6): 3.81 (s, 3H), 3.87 (s, 3H), 3.88 (s, 3H), 6.89 (s, 1H), 6.95 (br s, 2H), 7.27 (s, 1H), 8.59 (s, 1H); *m*/*z* (ES) $(MH)^+$=263.1. Anal. Calcd for $C_{13}H_{14}N_2O_4$: C, 59.54; H, 5.38; N, 10.68. Found: C, 59.56; H, 5.46; N, 10.55.

3.2.3. Methyl 2-{[(*E*)-(dimethylamino)methylidene]-amino}-6,7-dimethoxy-3-quinoline-carboxylate (9). A mixture of **8** (3.6 g, 13.0 mmol), *N*,*N*-dimethylformamide dimethyl acetal (4.1 mL, 31.0 mmol) and *p*-toluenesulfonic acid (40 mg) in toluene (60 mL) was heated at reflux for 2 h. The reaction mixture was cooled to room temperature and the solid was collected by filtration to provide **9** (737 mg, 18%) as an off-white solid. Concentration of the filtrate provided an additional 2.86 g (70%) of **9**; mp 166–168 °C; ^{1}H NMR (δ, ppm, DMSO-d_6): 3.00 (s, 3H), 3.12 (s, 3H), 3.81 (s, 3H), 3.85 (s, 3H), 3.90 (s, 3H), 7.14 (s, 1H), 7.29 (s, 1H), 8.20 (s, 1H), 8.50 (s, 1H); *m*/*z* (ES) $(MH)^+$=318.1. Anal. Calcd for $C_{16}H_{19}N_3O_4$: C, 60.56; H, 6.03; N, 13.24. Found: C, 60.63; H, 6.08; N, 13.32.

3.2.4. 4-Hydroxy-7,8-dimethoxybenzo[*b*][1,8]-naphthyridine-3-carbonitrile (10). To a −78 °C solution of *n*-butyl lithium (9.0 mL of a 2.5 M solution, 22.5 mmol) in tetrahydrofuran (40 mL) was added acetonitrile (1.3 mL,

24.9 mmol). After stirring for 15 min, a solution of **9** (2.86 g, 9.0 mmol) in tetrahydrofuran (100 mL) was added dropwise over 30 min. The mixture was stirred at −78 °C for 30 min then allowed to come to room temperature. The reaction mixture was cooled to −78 °C and acetic acid (3 mL) was added. The reaction mixture was allowed to warm to room temperature. The solids were collected by filtration washing with water, methanol, and ethyl acetate to provide **10** (1.11 g, 44%) as a light yellow solid; mp >300 °C; ^{1}H NMR (δ, ppm, DMSO-d_6): 3.93 (s, 3H), 4.00 (s, 3H), 7.29 (s, 1H), 7.60 (s, 1H), 8.68 (s, 1H), 8.97 (s, 1H); *m/z* (ES) $(MH)^+$=281.9. Anal. Calcd for $C_{15}H_{11}N_3O_3$ −0.65 H_2O: C, 61.49; H, 4.23; N, 14.34. Found: C, 61.40; H, 4.40; N, 14.70.

3.2.5. 4-Chloro-7,8-dimethoxybenzo[*b*][1,8]-naphthyridine-3-carbonitrile (11). A mixture of **10** (500 mg, 1.8 mmol) and phosphorous oxychloride (5 mL) was heated at reflux for 1 h. The reaction mixture was cooled to room temperature and hexane was added. The resultant solid was collected by filtration washing with hexane, water, methanol and ethyl acetate to provide **11** (258 mg, 49%) as a brown solid; mp >300 °C; ^{1}H NMR (δ, ppm, DMSO-d_6): 4.01 (s, 3H), 4.07 (s, 3H), 7.58 (s, 1H), 7.77 (s, 1H), 9.27 (s, 1H), 9.34 (s, 1H); *m/z* (ES) $(MH)^+$=299.9. Anal. Calcd for $C_{15}H_{10}ClN_3O_2$ −0.40 H_2O: C, 58.70; H, 3.55; N, 13.69. Found: C, 58.85; H, 3.33; N, 13.97.

3.2.6. 4-(2,4-Dichloro-5-methoxyanilino)-7,8-dimethoxybenzo[*b*][1,8]naphthyridine-3-carbonitrile (4). A mixture of **11** (150 mg, 0.50 mmol), 2,4-dichloro-5-methoxyaniline (160 mg, 0.83 mmol) and pyridine hydrochloride (70 mg, 0.60 mmol) in 2-ethoxyethanol (15 mL) was heated at reflux for 25 min. The resultant black solution was cooled to room temperature and partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The organic layer was dried over magnesium sulfate, filtered and concentrated in vacuo to provide 143 mg of a 10:1 mixture of **4** and **10**. This material was dissolved in ethyl acetate and washed with a solution of saturated aqueous sodium bicarbonate and sodium hydroxide (pH 11) to remove **10**. The organic layer was dried over magnesium sulfate, filtered and reduced in vacuo to about 10 mL. The solids were collected by filtration washing with diethyl ether to provide **4** (86 mg, 38%) as a bright orange solid; mp >290 °C; ^{1}H NMR (δ, ppm, DMSO-d_6): 3.82 (s, 3H), 3.92 (s, 3H), 4.00 (s, 3H), 6.78 (s, 1H), 7.28 (s, 1H), 7.47 (s, 1H), 7.62 (s, 1H), 8.28 (s, 1H), 9.19 (s, 1H); *m/z* (ES) $(MH)^+$=455.0. Anal. Calcd for $C_{22}H_{16}Cl_2N_4O_3$: C, 58.04; H, 3.54; N, 12.31. Found: C, 57.86; H, 3.48; N, 12.30.

3.3. Compounds 13a-13h

3.3.1. Ethyl 3-amino-2-quinolinecarboxylate (13a). To a mixture of pyridine (342 mg, 4.34 mol) and ethanol (12 mL) was added ethyl 2-bromopyruvate (846 mg, 4.34 mmol) in ethanol (8 mL) dropwise over 20 min. The resulting mixture was heated at 60–70 °C for one hour and cooled to room temperature. *ortho*-Aminobenzaldehyde (500 mg, 4.13 mmol) and pyridine (0.80 mL) were added. After heating at reflux for 5 h, pyrrolidine (698 mg, 9.83 mmol) was added. The resulting mixture was heated for an additional 2 h and concentrated. The residue was chromatographed (ethyl acetate/hexanes 1:3) to give **13a** as a yellow solid (762 mg, 90%); mp 148–150 °C; ^{1}H NMR (δ, ppm, DMSO-d_6): 1.38 (t, *J*=5 Hz, 3H), 4.40 (q, *J*=5 Hz, 2H), 6.42 (s, 2H), 7.41 (dt, *J*=5, 1 Hz, 1H), 7.47 (dt, *J*=5, 1 Hz, 1H), 7.51 (s, 1H), 7.67 (d, *J*=5 Hz, 1H), 7.86 (d, *J*=5 Hz, 1H); *m/z* (ES) $(MH)^+$=217.1. Anal. Calcd for $C_{12}H_{12}N_2O_2$ −0.10H_2O: C, 66.10; H, 5.62; N, 12.85. Found: C, 65.82; H, 5.50; N, 12.74.

3.3.2. Ethyl 3-amino-6,7-dimethoxy-2-quinolinecarboxylate (13b). Following the route used to prepare **13a**, **13b** was obtained from 2-amino-4,5-dimethoxybenzaldehyde (1.0 g, 4.74 mmol) as a yellow solid (1.04 g, 79%); mp 168–170 °C; ^{1}H NMR (δ, ppm, DMSO-d_6): 1.35 (t, *J*=5 Hz, 3H), 3.32 (s, 6H), 4.35 (q, *J*=5 Hz, 2H), 6.31 (s, br, 2H), 7.00 (s, 1H), 7.16 (s, 1H), 7.40 (s, 1H); *m/z* (ES) $(MH)^+$=277.2. Anal. Calcd for $C_{14}H_{16}N_2O_4$ −0.10 H_2O: C, 60.46; H, 5.85; N, 10.08. Found: C, 60.20; H, 6.00; N, 9.91.

2-Amino-4,5-dimethoxybenzaldehyde was prepared as follows: A mixture of 3,4-dimethoxy-6-nitrobenzaldehyde (2.0 g, 9,47 mmol) and 10% Pd–C (200 mg) in ethanol (50 mL) was hydrogenated at 40 psi for 2 h. The resulting suspension was filtered and washed with ethanol. The filtrate was used directly in the next step.

3.3.3. Ethyl 3-amino-6-chloro-2-quinolinecarboxylate (13c). Following the route used to prepare **13a**, **13c** was obtained from 2-amino-5-chlorobenzaldehyde (500 mg, 3.21 mmol) as a yellow solid (385 mg, 48%): mp 151–153 °C; ^{1}H NMR (δ, ppm, DMSO-d_6): 1.37 (t, *J*=5 Hz, 3H), 4.41 (q, *J*=5 Hz, 2H), 6.58 (s, 2H), 7.36 (dt, *J*=7, 2 Hz, 1H), 7.46 (s, 1H), 7.82 (d, *J*=2 Hz, 1H), 7.85 (d, *J*=7 Hz, 1H); *m/z* (ES) $(MH)^+$=251.1. Anal. Calcd for $C_{12}H_{11}ClN_2O_2$ −0.1 $C_4H_8O_2$: C, 57.39; H, 4.57; N, 10.80. Found: C, 57.35; H, 4.33; N, 10.53.

3.3.4. Ethyl 3-amino-7-chloro-2-quinolinecarboxylate (13d). Following the route used to prepare **13a**, **13d** was obtained from 2-amino-4-chlorobenzaldehyde[9] (500 mg, 3.21 mmol) as a yellow solid (71%); mp 128–130 °C; ^{1}H NMR (δ, ppm, DMSO-d_6): 1.37 (t, *J*=5 Hz, 3H), 4.40 (q, *J*=5 Hz, 2H), 6.51 (s, 2H), 7.48 (dt, *J*=7, 2 Hz, 1H), 7.55 (s, 1H), 7.74 (d, *J*=7 Hz, 1H), 7.90 (d, *J*=2 Hz, 1H); *m/z* (ES) $(MH)^+$=251.0. Anal. Calcd for $C_{12}H_{11}ClN_2O_2$: C, 57.50; H, 4.42; N, 11.17. Found: C, 57.38; H, 4.22; N, 11.05.

3.3.5. Ethyl 3-amino-6,8-dibromo-2-quinolinecarboxylate (13e). Following the route used to prepare **13a**, **13e** was obtained from 2-amino-3,5-dibromobenzaldehyde (896 mg, 3.21 mmol) as a yellow solid (470 mg, 39%); mp 143–145 °C; ^{1}H NMR (δ, ppm, DMSO-d_6): 1.36 (t, *J*=5 Hz, 3H); 4.41 (q, *J*=5 Hz, 2H), 6.71 (s, br, 2H), 7.48 (s, 1H), 7.88 (d, *J*=2 Hz, 1H), 8.03 (d, *J*=2 Hz, 1H); (*m/z* (ES) $(MH)^+$=374.9. Anal. Calcd for $C_{12}H_{10}Br_2N_2O_2$: C, 38.53; H, 2.53; N, 7.49. Found: C, 38.22; H, 2.53; N, 7.30.

3.3.6. 2-Phenyl-quinoline-3-ylamine (13f). A mixture of 1-phenacylpyridinium bromide (1.20 g, 4.34 mmol), *ortho*-aminobenzaldehyde (0.5 g, 4.13 mmol), pyridine (0.2 mL)

and DMAP (catalytic amount) in ethanol was heated at reflux for 48 h. The reaction mixture was cooled to room temperature and pyrrolidine (0.82 mL, 9.83 mmol) was added. After heating at reflux overnight, the resulting mixture was concentrated. The residue was partitioned between saturated aqueous sodium bicarbonate and methylene chloride. The combined organics were dried over sodium sulfate, concentrated and chromatographed (ethyl acetate/hexanes 1:3) to give **13f** (588 mg, 65%) as a yellow solid; mp 100–101 °C; ^{1}H NMR (δ, ppm, DMSO-d_6): 5.25 (s, br, 2H), 7.36–7.40 (m, 3H), 7.47–7.55 (m, 3H), 7.64 (d, J=6 Hz, 1H), 7.73 (dd, J=1, 6 Hz, 2H), 7.79 (d, J=5 Hz, 1H); m/z (ES) $(MH)^+$=221.1. Anal. Calcd for $C_{15}H_{12}N_2$ −0.05 H_2O C, 81.45; H, 5.50; N, 12.67. Found: C, 81.29; H, 5.35; N, 12.69.

3.3.7. 6,7-Dimethoxy-2-phenyl-quinoline-3-ylamine (13g). Following the route used to prepare **13f**, **13g** was obtained from 2-amino-4,5-dimethoxybenzaldehyde (1.0 g, 4.75 mmol) as a yellow solid (996 mg, 75%); mp 148–149 °C; ^{1}H NMR (δ, ppm, DMSO-d_6): 3.84 (s, 3H), 3.87 (s, 3H), 4.98 (s, br, 2H), 7.03 (s, 1H), 7.19 (s, 1H), 7.32 (s, 1H), 7.41–7.52 (m, 3H), 7.72–7.74 (m, 2H); m/z (ES) $(MH)^+$=281.1. Anal. Calcd for $C_{17}H_{16}N_2O_2$ C, 72.84; H, 5.75; N, 9.99. Found: C, 72.44; H, 5.56; N, 9.66.

3.3.8. 2-Methyl-quinoline-3-ylamine (13h). Following the route used to prepare **13f**, **13h** was obtained from *ortho*-aminobenzaldehyde (388 mg, 3.21 mmol) and N-acetonyl-pyridinium bromide (762 mg, 3.53 mmol) as a off-white solid (262 mg, 52%): mp 142–143 °C; ^{1}H NMR (δ, ppm, DMSO-d_6): 2.48 (s, 3H), 5.39 (s, br, 2H), 7.16 (s, 1H), 7.27–7.34 (m, 2H), 7.57 (dd, J=6, 3 Hz, 1H), 7.70 (dd, J=6, 3 Hz, 1H); m/z (ES) $(MH)^+$=159.0. Anal. Calcd for $C_{10}H_{10}N_2$ −0.1 CH_2Cl_2 C, 71.31; H, 6.06; N, 16.39. Found: C, 71.33; H, 5.67; N, 16.28.

3.4. Compounds 13-15 and 5

3.4.1. Ethyl 3-{([(*E*)-(dimethylamino)methylidene]-amino}-6,7-dimethoxy-2-quinoline-carboxylate (14). A mixture of **13b** (1.0 g, 3.61 mmol) and *N*,*N*-dimethylformamide dimethyl acetal (1.34 g, 9.04 mmol) in toluene (30 mL) was heated at 80 °C for 5 h and concentrated. The solid residue was slurried in hexanes, filtered and washed with hexanes to give **14** (1.22 g, 100%) as an off-white solid; mp 135–140 °C; ^{1}H NMR (δ, ppm, DMSO-d_6): 1.31 (t, J=5 Hz, 3H), 2.93 (s, 3H), 3.05 (s, 3H), 4.31 (q, J=5 Hz, 2H), 3.89 (s, 6H), 7.16 (s, 1H), 7.29 (s, 1H), 7.69 (s, 1H), 7.89 (s, 1H); m/z (ES) $(MH)^+$=332.2. Anal. Calcd for $C_{17}H_{21}N_3O_4$ C, 61.62; H, 6.39; N, 12.68. Found: C, 61.78; H, 6.37; N, 12.65.

3.4.2. 4-Chloro-7,8-dimethoxy-benzo[*b*][1,5]naphthyridine-3-carbonitrile (15). To an oven-dried three-necked flask was charged tetrahydrofuran (10 mL) and n-butyl lithium (2.5 M in hexanes, 2.8 mL, 6.93 mmol). The mixture was cooled to −78 °C and acetonitrile (284 mg, 6.93 mmol) was added dropwise over 20 min. The resulting mixture was stirred for 30 min and **14** (1.12 g, 3.30 mmol) in tetrahydrofuran (20 mL) was added dropwise via syringe over 30 min. The reaction was allowed to stir at −78 °C for 3 h and quenched with acetic acid (590 mg, 9.90 mmol). The resulting mixture was stirred at room temperature overnight and concentrated. The residue was dissolved in tetrahydrofuran (50 mL) and a few drops of conc. hydrochloric acid were added. The reaction mixture was heated to 70 °C, stirred for 2 h and concentrated. The solid residue was slurried in water (30 mL), filtered and washed with water and ether to provide 7,8-dimethoxy-4-hydroxy-benzo[*b*][1,5]naphthyridine-3-carbonitrile (525 mg, 58%) as an off-white solid that was used as it is in next step;

A mixture of 7,8-dimethoxy-4-hydroxy-benzo[*b*][1,5]-naphthyridine-3-carbonitrile (428 mg, 1.52 mmol) and phosphorous oxychloride (4.94 g, 32.2 mmol) was heated at reflux for 1 h and concentrated. The residue was carefully neutralized with saturated sodium bicarbonate with cooling on an ice-bath, filtered and washed thoroughly with water to give **15** (454 mg, 88%) as a light brown solid; mp >340 °C; ^{1}H NMR (δ, ppm, DMSO-d_6): 4.02 (s, 3H), 4.07 (s, 3H), 7.56 (s, 1H), 7.57 (s, 1H), 9.04 (s, 1H), 9.18 (s, 1H); m/z (ES) $(MH)^+$=300.1. Anal. Calcd for $C_{15}H_{10}ClN_3O_2$ −2.0 HCl 48.34; H, 3.24; N, 11.08. Found: C, 48.57; H, 3.42; N, 10.75.

3.4.3. 4-(2,4-Dichloro-5-methoxyanilino)-7,8-dimethoxy-benzo[*b*][1,5]naphthyridine-3-carbonitrile (5). A mixture of **15** (100 mg, 0.334 mmol), 2,4-dichloro-5-methoxy-aniline (67 mg, 0.351 mmol) and pyridine-HCl (43 mg, 0.368 mmol) in 2-ethoxyethanol (2.2 mL) was heated at 100 °C for 5 h. The resultant reaction mixture was diluted with saturated sodium bicarbonate and was allowed to stir one hour at room temperature. The suspension was filtered and washed thoroughly with water, followed by a minimum amount of methanol and hexanes to give **5** (75 mg, 50%) as a light yellow solid; mp >360 °C; ^{1}H NMR (δ, ppm, DMSO-d_6): 3.76 (s, 3H), 3.89 (s, 3H), 3.95 (s, 3H), 6.69 (s, 1H), 7.14 (s, 1H), 7.32 (s, 2H), 7.98 (s, 1H), 8.20 (s, 1H); m/z (ES) $(MH)^+$=455.1. Anal. Calcd for $C_{22}H_{16}Cl_2N_4O_3$ −0.5 H_2O C, 56.91; H, 3.67; N, 12.07. Found: C, 56.74; H, 3.70; N, 11.77.

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