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ARTICLE

Copper-Catalyzed Synthesis of Quinoline Derivatives via Tandem Knoevenagel Condensation, Amination and Cyclization[§]

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A novel regioselective synthesis of 2-aminoquinolines and 2-arylquinoline-3-carbonitriles is described via copper-mediated tandem reaction. Formation of substituted quinolines involves Knoevenagel condensation of ortho-bromobenzaldehyde with active methylene nitriles followed by copper-catalyzed reductive amination and intramolecular cyclization.

Introduction

Quinoline skeleton is one of the most prevalent motifs found in many drugs, natural products and pharmacologically active substances.[1] Compounds with this motif have been found to possess a broad range of biological activities such as anticancer,[2] antifungal,[3] antimalarial,[4] antituberculosis,[5] antiprotozoal,[6] antiinflammatory,[7] and antineoplastic,[8] inhibition of epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor-2 (HER-2) kinases.[9] Functionalized quinolines are also used as dyestuff,[10] asymmetric catalysts,[11] ligands for transition metal complexes and for the preparation of nano- and mesostructures with improved electronic and photonic properties.[12] Some promising compounds with quinoline motif are shown in Figure 1.

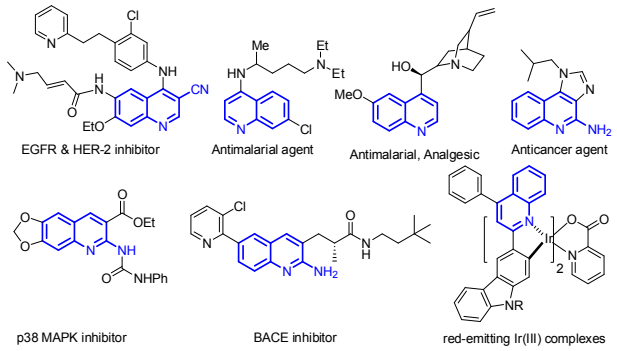

Figure 1: Some promising quinoline derivatives

Generally, quinoline and its derivatives are prepared by conventional methods including Friedländer, Pfitzinger, Doebner–von Miller, Skraup, Combes and Conrad–Limpach reactions.[13] In past, these reactions have been successfully employed for quinoline synthesis but they require stoichiometric amounts of acidic reagents and are often performed under harsh conditions. Moreover, use of harsh reaction conditions and highly reactive acid catalysts restrict involvement of functionally substituted substrates for synthesis of corresponding quinolines. In recent years, several approaches based on tandem reactions, transition metal catalysts and alternative starting materials have been developed for mild and efficient syntheses of quinolines.[14] For example, Li *et. al* have developed a copper-catalyzed synthesis of quinolines from *ortho*-acylanilines and alkenyl iodides.[15] Yu and co-workers developed synthesis of quinolines from 2-aminobenzylamine and ketones *via* copper-catalyzed C–N bond cleavage.[16] Consisting CuI and a secondary amine, Patil group developed a co-operative catalytic system for the synthesis of 2-substituted quinolines by utilizing 2-aminobenzaldehydes and terminal alkynes.[17] In particular, 2-aminoquinolines are important target molecules because of their sub-nanomolar potency for BACE inhibition[18] and selective neuronal nitric oxide synthase (nNOS) inhibition activities.[19] Only a handful reports are available for synthesis of 2-aminoquinoline derivatives.[20] Tomioka *et. al* have reported one-pot synthesis of 2-aminoquinolines from 2-nitrobenzaldehydes and acetonitrile *via* stereoselective olefination followed by reductive cyclization.[20a] Jiang group have synthesized 2-aminoquinolines by Pd-catalyzed reactions of *gem*-dibromovinylanilines and *tert*-butyl isocyanide.[20b, 20c] Liu *et. al* have utilized 4-halo-2-aminoquinolines in a Pd-catalyzed intermolecular aerobic oxidative cyclization of 2-ethynylanilines with isocyanide to prepare 2-aminoquinolines.[20d] Owing to potential applications in various fields, quinolines continue to attract the attention of scientists from different areas, and the development of new synthetic methods for quinolines are still of great interest.

Furthermore, the direct amination of aryl halides using NaN_3 or $TMSN_3$ as the amino source in the presence of copper or copper salt has been reported.[21] Trapping of the intermediate azide or amine of this copper catalyzed reductive amination have resulted in the synthesis of bioactive heterocycles such as quinolones, 3-aminoquinolines, 3-aminocoumarines, tetracyclic indoloindol-3-ones, *pseudo*-indoxyl derivatives, indazole and 2-aroylindoles.[22] As a

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Electronic Supplementary Information (ESI) available: [Copies of ^{1}H NMR, ^{13}C NMR spectra for all the synthesized compounds and tables for single X-ray data of **10**]. See DOI: 10.1039/x0xx00000x

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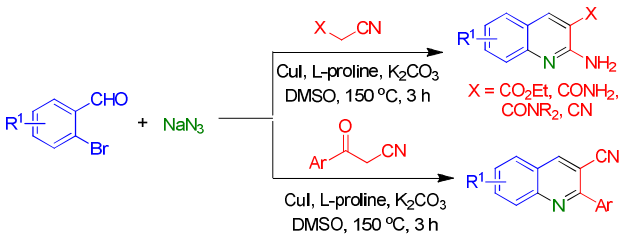
part of our continuous efforts in the development of new synthetic methods for heterocyclic compounds by employing C–C /C–N coupling reactions,[23] herein we report our results on one-pot copper-catalyzed regioselective synthesis of 2-aminoquinolines and 2-arylquinoline-3-carbonitriles *via* tandem reactions involving 2-bromobenzaldehydes, active methylene nitriles and sodium azide (Scheme 1).



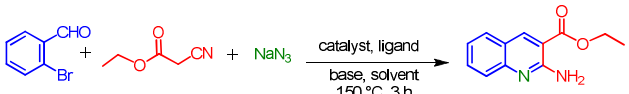
Scheme 1: Synthesis of 2-aminoquinolines and 2-arylquinoline-3-carbonitriles

Results and discussion

Our initial study began with the reaction of 2-bromobenzaldehyde (**1a**) with ethyl cyanoacetate (**2a**) and sodium azide (**3**) in the presence of CuI (10 mol %), L-proline (20 mol %), K_2CO_3 (2.5 equiv) in *N,N'*-dimethylformamide (DMF) at 150 °C under air atmosphere for 3 h. Gratifyingly, ethyl 2-aminoquinoline-3-carboxylate (**4aa**) was isolated in 35% yield (entry 1). The structure of **4aa** was characterized by various spectroscopic techniques such as IR, NMR and mass spectrometry. In IR spectrum of **4aa,** strong peaks at 3410 and 1697 cm^{-1} are indicative of -NH_2 and -C=O functionalities, respectively. In ^{1}H NMR spectrum, characteristic singlets at δ 8.77 and δ 7.26 (broad) for C_4–H and NH_2 protons were observed. The carbonyl carbon of CO_2Et appeared at δ 166.5 along with all other expected peaks in ^{13}C NMR spectrum of **4aa**. Further, the structure was ascertained by HRMS analysis of **4aa** which showed a molecular ion $C_{12}H_{13}N_2O_2^+$ $[M+H]^+$ peak at *m/z* 217.0976 in agreement with the calculated mass 217.0972.

To further improve the yield of tandem product **4aa**, various experimental conditions were screened by varying copper catalysts, ligands, bases and solvents (Table 1). Firstly, screening of various copper salts such as CuI, $CuCl_2.H_2O$, CuBr, $Cu(OAc)_2.H_2O$, CuOTf and $CuSO_4$ revealed that CuI was the best catalyst for this transformation giving highest yield of **4aa** (Table 1, entries 1–6). Further investigations on the effect of catalyst loading suggested that 20 mol % CuI afforded **4aa** in highest yield (55%) (Table 1, entries 1, 7- 8). Among various bases (K_2CO_3, K_3PO_4, tBuOK, Cs_2CO_3, Na_2CO_3, NaOMe, Et_3N and DBU) examined (Table 1, entries 7, 9–16), K_2CO_3 was found to be the most suitable base. In case of triethylamine, the reaction exclusively led to Knoevenagel adduct (Table 1, entry 14). Reactions in different solvents namely DMSO, *N,N*-dimethylacetamide (DMA), toluene, *N*-methyl-2-pyrrolidone (NMP), 1,4–dioxane and PEG-400 (Table 1, entries 16–21) revealed DMSO as a the solvent of choice for this reaction. When the reaction was performed in toluene at 120 °C only Knoevenagel adduct was obtained in 45% yield (Table 1, entry 20). Finally, by screening of different ligands (Table 1, entries 16, 21–25), L-proline was found to be the most effective ligand. The reaction was stopped at the Knoevenagel adduct in the absence of catalyst (Table 1, entry 26) and yield of desired product **4aa** was diminished in the absence of L-proline (Table 1, entry 27).

Table 1: Optimization of reaction conditions.[a]



1a **2a** **3** **4aa**

Entry	Catalyst (mol %)	Ligand (mol %)	Base (2.5 equiv)	Solvent	Yield (%)[b]
1	CuI (10)	L-proline (20)	K_2CO_3	DMF	35
2	$CuCl_2$ (10)	L-proline (20)	K_2CO_3	DMF	9
3	CuBr (10)	L-proline (20)	K_2CO_3	DMF	20
4	$Cu(OAc)_2$ (10)	L-proline (20)	K_2CO_3	DMF	13
5	CuOTf (10)	L-proline (20)	K_2CO_3	DMF	31
6	$CuSO_4$ (10)	L-proline (20)	K_2CO_3	DMF	26
7	CuI (20)	L-proline (40)	K_2CO_3	DMF	55
8	CuI (30)	L-proline (60)	K_2CO_3	DMF	50
9	CuI (20)	L-proline (40)	K_3PO_4	DMF	38
10	CuI (20)	L-proline (40)	^{t}BuOK	DMF	30
11	CuI (20)	L-proline (40)	$CsCO_3$	DMF	10
12	CuI (20)	L-proline (40)	Na_2CO_3	DMF	8
13	CuI (20)	L-proline (40)	NaOMe	DMF	11
14	CuI (20)	L-proline (40)	Et_3N	DMF	-[c]
15	CuI (20)	L-proline (40)	DBU	DMF	6
16	CuI (20)	L-proline (40)	K_2CO_3	DMSO	62
17	CuI (20)	L-proline (40)	K_2CO_3	NMP	28
18	CuI (20)	L-proline (40)	K_2CO_3	DMA	37
19	CuI (20)	L-proline (40)	K_2CO_3	Dioxane	10[d]
20	CuI (20)	L-proline (40)	K_2CO_3	Toluene	-[c]
21	CuI (20)	L-proline (40)	K_2CO_3	PEG-400	-
22	CuI (20)	Glycine (40)	K_2CO_3	DMSO	38
23	CuI (20)	DMEDA (40)	K_2CO_3	DMSO	42
24	CuI (20)	1,10-Phen[e] (40)	K_2CO_3	DMSO	12
25	CuI (20)	8-HQ[f] (40)	K_2CO_3	DMSO	9
26	-	L-proline (40)	K_2CO_3	DMSO	-
27	CuI (20)	-	K_2CO_3	DMSO	20

[a]Reaction conditions: **1a** (0.54 mmol), **2a** (0.65 mmol) NaN_3 (**3**) (0.81 mmol), catalyst, ligand, base (2.5 equiv.), 150 °C, air atmosphere, 3 h. [b]Isolated yields. [c]Reaction time 12h, only Knoevenagel adduct **6**. [d]Knoevenagel adduct **6** (120 °C, 45%). [e]1,10-Phen = 1,10-Phenanthroline. [f]8-HQ = 8-Hydroxyquinoline.

With the optimized reaction condition in hand (Table 1, entry 16), we explored the substrate generality for this tandem reaction by employing the substituted 2-bromobenzaldehydes and active methylene nitriles (Table 2). Reactions of substituted 2-bromobenzaldehydes **1a-c** with different active methylene nitriles **2a-e** gave corresponding 2-aminoquinolines in moderate to good yields (**4aa–ae**). The method tolerated different functional groups such as cyano, methoxy, ester, and amide. Structures of all the

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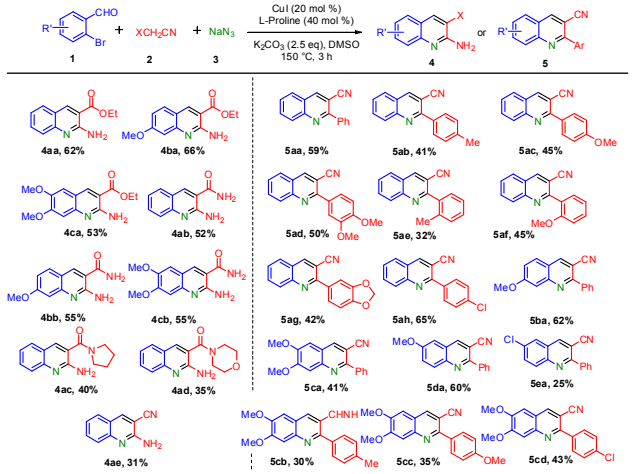
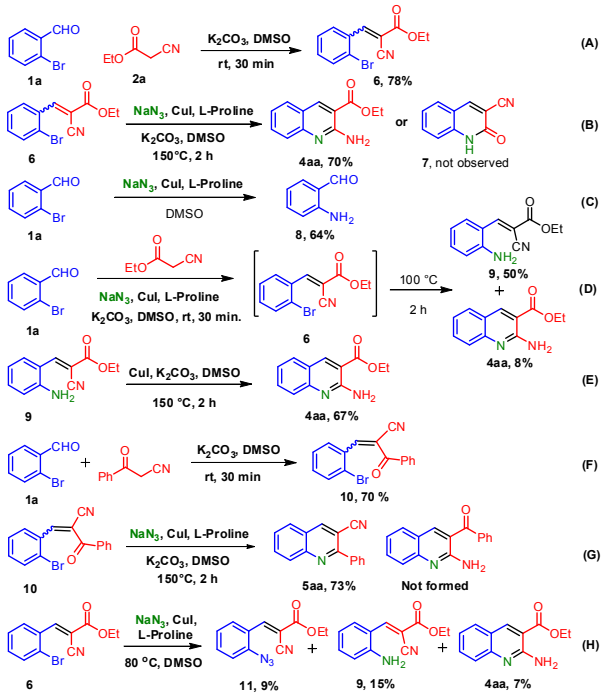
compounds were confirmed by IR, NMR (^{1}H & ^{13}C) and HRMS data (Supporting Information).

Notably, when benzoylacetonitrile (X = ArCO**, 2**) was used as an active methylene nitrile, instead of expected 2-aminoquinoline, 2-phenylquinoline-3-carbonitrile (**5aa**) was obtained in 62% yield. Formation of **5aa** prompted us to evaluate the regioselectivity of this reaction for benzoylacetonitriles. As can be seen from Table 2, benzoylacetonitriles containing methyl, methoxy, dioxole and chloro substituent reacted efficiently with 2-bromobenzaldehydes to give corresponding quinoline-3-carbonitriles (**5aa-ah**) in moderate to good yields. Similarly, 2-bromobenzaldehydes bearing methoxy and chloro groups were treated with different substituted benzoylacetonitriles to give corresponding 2-arylquinoline-3-carbonitriles in moderate to good yields (**5ca–cd**).

Table 2 Synthesis of 2-aminoquinolines.[a,b]



Control experiments were performed to evaluate the possible reaction pathway for the tandem sequences to produce **4aa** and **5aa** (Scheme 2). Initially, 2-bromobenzaldehyde (**1a)** was reacted with ethyl cyanoacetate using K_2CO_3 in DMSO at room temperature for 30 min, only Knoevenagel adduct **6** was obtained in 78% yield (Scheme 2A). When adduct **6**, NaN_3, CuI, L-proline and K_2CO_3were heated at 150 °C for 2 h, only the desired product **4aa** was isolated in 70% yield (Scheme 2B). Exclusive formation of **4aa** can be due to the relative reactivity of cyano group over ester in **6**. Reaction of **1a** with NaN_3, CuI, L-proline and K_2CO_3 at 120 °C gave 2-aminobenzaldehyde (**8**) in 64% yield (Scheme 2C). However, treatment of **1a** with ethyl cyanoacetate in the presence of NaN_3, CuI, L-proline and K_2CO_3 at room temperature exclusively resulted in adduct **6**. When the same reaction mixture was heated at 100 °C, ethyl 3-(2-aminophenyl)-2-cyanoacrylate (**9)** was obtained in 50% yield along with the desired product **4aa** in 8% yield (Scheme 2D). Further, when **9** was heated at 150 °C in the presence of K_2CO_3 in DMSO, **4aa** was obtained in 33% yield after 5 h, and **9** was recovered in 46% yield (Scheme 2E)**.** From these control experiments, we concluded that ethyl 3-(2-bromophenyl)-2-cyanoacrylate (**6)** and ethyl 3-(2-aminophenyl)-2-cyanoacrylate (**9**) are key intermediates for the formation of 2-aminoquinoline. Similarly, reaction of **1a** with **4** in absence of copper catalyst gave 2-benzoyl-3-(2-bromophenyl)acrylonitrile (**10**) which on reaction with NaN_3, CuI, L-proline and K_2CO_3 at 150 °C after 2 h resulted in exclusive formation of **5aa** (Scheme 2G and 2H). This may be attributed to the relative electrophilicity of carbonyl group over nitrile group. Structure of **10** was confirmed NMR, mass and single X-ray analysis (CCDC 1433055, Figure 2).



Scheme 2: Control experiments.

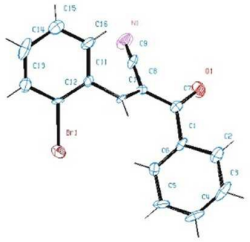


Figure 2: ORTEP diagram (with 35% ellipsoid probability) for **10** (CCDC 1433055).

On the basis of control experiments and literature reports,[22a, 24] a possible mechanism for the copper-catalyzed tandem reaction has been described (Scheme 3). Initially, the reaction of 2-brombenzaldehye and ethyl cyanoacetate generated Knoevenagel adduct **6**. Reductive amination of **6** using sodium azide in the presence of copper catalyst produced 2-(2-aminobenzylidene)malononitrile (**9**). This is in accordance with earlier reports wherein sodium azide has been used as ammonia surrogate to prepare primary amines and nitrogen containing heterocycles in a copper catalyzed reductive amination of aryl halides.[14f, 22c, 22d] Subsequently, intramolecular cyclization of **9** led to the formation of ethyl 2-aminoquinoline-3-carboxylate (**4**) *via* nucleophilic attack of amine onto nitrile followed by tautomerization. In case of benzoylacetonitrile, intermediate **10**

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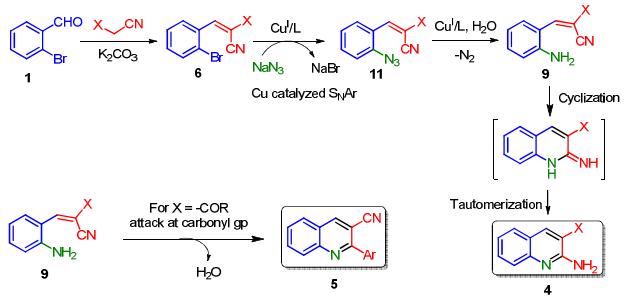
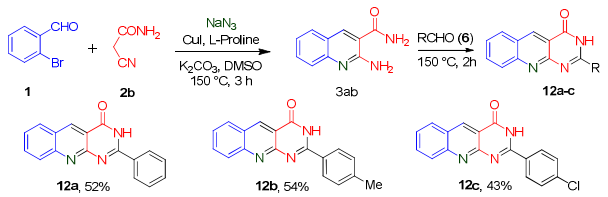
formed after Knoevenagel condensation underwent reductive amination followed by intramolecular condensation to afford 2-arylquinoline-3-carbonitrile (**5**).



Scheme 3: A plausible mechanism for the synthesis of **4** and **5**.

Next, the synthetic worth of the developed methodology was demonstrated by one-pot synthesis of pyrimido[4,5-*b*]quinolin-4(3H)-one derivatives (**12a-c**). In all the cases, reactions underwent smooth conversion to afford the corresponding pyrimido[4,5-*b*]quinolin-4(3H)-ones **12a-c** in moderate to good (52-43%) yields (Scheme 4).



Scheme 4: Synthesis of pyrimido[4,5-b]quinolin-4(3H)-one.

Conclusions

In conclusion, we have successfully developed an efficient and straightforward copper-catalyzed regioselective synthesis of 2-aminoquinolines and 2-arylquinoline-3-carbonitriles from readily available 2-bromobenzaldehydes, active methylene nitriles and sodium azide. The developed three-component, one-pot tandem protocol displays broad substrate scope, good functional group tolerance and gives quinolines in moderate to good yields. The developed methodology can further be utilized for one-pot synthesis of pyrimido[4,5-*b*]quinolin-4(3H)-ones.

Experimental Section

Melting points were determined in open capillary tubes on an automated melting point apparatus and are uncorrected. Reactions were monitored by using thin layer chromatography (TLC) on 0.2 mm silica gel F_{254} plates. The chemical structures of final products were determined by their NMR spectra (^{1}H and ^{13}C NMR). Chemical shifts are reported in parts per million (ppm) using deuterated solvent peak or tetramethylsilane as an internal standard. The HRMS data were recorded on a mass spectrometer with electrospray ionization and TOF mass analyzer. Some of benzoyl acetonitriles and 2-cyano acetamides were synthesized according to published procedure.[25] All other chemicals were obtained from the commercial suppliers and used without further purification.

Representative procedure for synthesis of 2–aminoquinolines (4): A mixture of 2-bromobenzaldehyde (100 mg, 0.54 mmol), ethyl cyanoacetate (73 mg. 0.65 mmol), sodium azide (52 mg, 0.81 mmol), CuI (20 mol %), L-proline (40 mol %) and K_2CO_3 (186 mg, 2.5 equiv.) in DMSO (2 mL) was mixed under air atmosphere at room temperature and then heated to 150 °C for 3 h. After cooling to ambient temperature, the reaction mass was quenched with ice-cold aqueous solution of NH_4Cl (30 mL), filtered through a bed of celite and the plug washed with ethyl acetate (20 mL). The resulting filtrate was extracted with ethyl acetate (2 × 20 mL) and the combined organic layers dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Desired product **4aa** (72 mg, 62%) was isolated by column chromatography on silica gel (100-200 mesh) using ethyl acetate/ hexane (30%, *v/v*) as eluant.

Ethyl 2-aminoquinoline-3-carboxylate (4aa): Yellow solid; 72 mg (62%); mp 134 – 136 °C; ^{1}H NMR (400 MHz, DMSO–d_6) δ 8.77 (s, 1H), 7.86 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.63 (ddd, *J* = 8.4, 6.8, 1.5 Hz, 1H), 7.49 (d, *J* = 8.2 Hz, 1H), 7.26 (bs, 2H), 7.25 – 7.21 (m, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 1.37 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, DMSO–d_6) δ 166.5, 156.7, 150.0, 142.8, 133.0, 129.9, 125.1, 122.7, 122.0, 110.5, 61.6, 14.6; IR (KBr): 3418, 1697, 1628, 1288, 1080 cm^{-1}; HRMS for $C_{12}H_{13}N_2O_2$ [M+H$^+$] calcd 217.0972, found 217.0976.

Ethyl 2-amino-7-methoxyquinoline-3-carboxylate (4ba): Yellow solid; 87 mg (66%); mp 138 – 140 °C; ^{1}H NMR (400 MHz, DMSO–d_6) δ 8.65 (s, 1H), 7.74 (d, *J* = 9.5 Hz, 1H), 7.23 (bs, 2H), 6.86 (d, *J* = 6.2 Hz, 2H), 4.33 (q, *J* = 7.0 Hz, 2H), 3.86 (s, 3H), 1.35 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, DMSO–d_6) δ 166.8, 163.5, 157.4, 152.5, 142.1, 131.2, 117.1, 115.1, 107.1, 104.5, 61.3, 55.8, 14.6; IR (KBr): 3433, 1697, 1620, 1257, 1080 cm^{-1}; HRMS for $C_{13}H_{15}N_2O_3$ [M+H$^+$] calcd 247.1077, found 247.1087.

Ethyl 2-amino-6,7-dimethoxyquinoline-3-carboxylate (4ca): Brown solid; 79 mg (53%); mp 190 – 193 °C; ^{1}H NMR (400 MHz, DMSO–d_6) δ 8.60 (s, 1H), 7.28 (s, 1H), 6.99 (bs, 2H), 6.89 (s, 1H), 4.33 (q, *J* = 7.1 Hz, 2H), 3.88 (s, 3H), 3.82 (s, 3H), 1.35 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, DMSO–d_6) δ 166.9, 156.3, 155.3, 148.0, 146.9, 140.4, 116.7, 107.8, 106.8, 105.0, 61.2, 56.1, 56.0, 14.6; IR (KBr): 3410, 1697, 1628, 1227, 1080 cm^{-1}; HRMS for $C_{14}H_{17}N_2O_4$ [M+H$^+$] calcd 277.1183, found 277.1189.

2-Aminoquinoline-3-carboxamide (4ab): Light orange solid; 53 mg (52%); mp 195 – 196 °C; ^{1}H NMR (400 MHz, DMSO–d_6) δ 8.48 (s, 1H), 8.24 (bs, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.61 (bs, 1H), 7.57 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H), 7.47 (d, *J* = 8.4 Hz, 1H), 7.29 – 7.17 (m, 3H); ^{13}C NMR (100 MHz, DMSO–d_6) δ 170.4, 157.1, 149.2, 138.6, 131.6, 129.1, 125.3, 122.3, 122.2, 114.6; IR (KBr): 3410, 3194, 1636, 1389, 1227 cm^{-1}; HRMS for $C_{10}H_{10}N_3O$ [M+H$^+$] calcd 188.0818, found 188.0824.

2-Amino-7-methoxyquinoline-3-carboxamide (4bb): Orange solid; 64 mg (55%); mp 221 – 224 °C; ^{1}H NMR (400 MHz, DMSO–d_6) δ 8.42 (s, 1H), 8.14 (bs, 1H), 7.56 (d, *J* = 8.6 Hz, 1H), 7.50 (bs, 1H), 7.27 (bs, 2H), 6.91 – 6.81 (m, 2H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, DMSO–d_6) δ 170.2, 162.4, 157.6, 151.3, 138.3, 130.3, 117.0, 114.4, 111.6, 104.7, 55.7; IR (KBr): 3378, 3209, 1620, 1381, 1227 cm^{-1}; HRMS for $C_{11}H_{12}N_3O_2$ [M+H$^+$] calcd 218.0924, found 218.0930.

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2-Amino-6,7-dimethoxyquinoline-3-carboxamide (4cb): Yellow solid; 73 mg (55%); mp 232 – 234 °C; ^{1}H NMR (400 MHz, DMSO–d_6) δ 8.33 (s, 1H), 8.07 (bs, 1H), 7.43 (bs, 1H), 7.02 (s, 1H), 6.98 (bs, 2H), 6.89 (s, 1H), 3.87 (s, 3H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, DMSO–d_6) δ 170.4, 156.3, 154.1, 146.6, 146.3, 137.0, 116.4, 111.5, 107.2, 105.3, 56.0; IR (KBr): 3380, 3210, 1623, 1381, 1225 cm^{-1}; HRMS for $C_{12}H_{14}N_3O_3$ [M+H$^+$] calcd 248.1030, found 248.1037.

(2-Aminoquinolin-3-yl)(pyrrolidin-1-yl)methanone (4ac): Brown oil; 52 mg (40%); ^{1}H NMR (400 MHz, DMSO–d_6) δ 8.07 (s, 1H), 7.71 (d, *J* = 7.7 Hz, 1H), 7.57 – 7.46 (m, 2H), 7.20 (t, *J* = 7.2 Hz, 1H), 6.49 (s, 2H), 3.52 (t, *J* = 6.7 Hz, 2H), 3.38 (t, *J* = 6.3 Hz, 2H), 1.92 – 1.80 (m, 4H); ^{13}C NMR (100 MHz, DMSO–d_6) δ 166.6, 155.1, 148.1, 136.2, 130.7, 128.6, 125.4, 122.3, 120.1, 48.7, 46.2, 26.2, 24.4; IR (KBr): 3410, 1651, 1457, 1380 cm^{-1}; HRMS for $C_{14}H_{16}N_3O$ [M+H$^+$] calcd 242.1288, found 242.1292.

(2-Aminoquinolin-3-yl)(morpholino)methanone (4ad): Yellow semisolid; 49 mg (35%); ^{1}H NMR (400 MHz, DMSO– d_6) δ 7.94 (s, 1H), 7.72 (d, *J* = 7.4 Hz, 1H), 7.57 – 7.49 (m, 2H), 7.22 (t, *J* = 7.9 Hz, 1H), 6.38 (bs, 2H), 3.62 (bs, 2H), 3.26 (bs, 2H), 1.60 (bs, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 155.0, 147.6, 136.0, 130.9, 127.9, 125.8, 123.2, 122.6, 118.0, 65.9, 24.5; IR (KBr): 3410, 1653, 1458, 1381 cm^{-1}; HRMS for $C_{10}H_8N_3$ [M+H$^+$] calcd 258.1237, found 258.1243.

2-Aminoquinoline-3-carbonitrile (4ae): Yellow semisolid; 28 mg (31%); ^{1}H NMR (400 MHz, DMSO–d_6) δ 8.69 (s, 1H), 7.75 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.66 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H), 7.51 (d, *J* = 8.6 Hz, 1H), 7.28 (ddd, *J* = 8.0, 6.9, 1.1 Hz, 1H), 6.98 (bs, 2H); ^{13}C NMR (100 MHz, DMSO–d_6) δ 156.2, 149.6, 145.8, 133.3, 129.0, 125.9, 123.2, 121.4, 117.0, 95.0; IR (KBr): 3444, 2253, 1659, 1480, 1373 cm^{-1}; HRMS for $C_{10}H_8N_3$ [M+H$^+$] calcd 170.0713, found 170.0719.

Representative procedure for synthesis of 2-arylquinoline-3-carbonitriles (5): A mixture of 2-bromobenzaldehyde (100 mg, 0.54 mmol), benzoylacetonitriles (94 mg, 0.65 mmol), sodium azide (52 mg, 0.81 mmol), CuI (20 mol %), L-proline (40 mol %) and K_2CO_3 (186 mg, 2.5 equiv.) in DMSO (2 mL) was mixed under air atmosphere at room temperature and then heated to 150 °C for 3 h. After cooling to ambient temperature, the reaction mass was quenched with ice-cold aqueous solution of NH_4Cl (30 mL), filtered through a bed of celite and the plug washed with ethyl acetate (20 mL). The resulting filtrate was extracted with ethyl acetate (2 × 20 mL) and the combined organic layers dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Desired product **5aa** (73 mg, 59%) was isolated by column chromatography on silica gel (100-200 mesh) using ethyl acetate/ hexane (10%, *v/v*) as eluant.

2-Phenylquinoline-3-carbonitrile (5aa): Off white solid; 73 mg (59%); m.p 193 – 195 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (s, 1H), 8.23 (d, *J* = 8.4 Hz, 1H), 8.02 (dd, *J* = 7.8, 1.7 Hz, 2H), 7.97 – 7.89 (m, 2H), 7.75 – 7.66 (m, 1H), 7.64 – 7.52 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 148.7, 144.3, 137.7, 133.1, 130.1, 129.9, 129.2, 128.8, 128.1, 127.8, 125.0, 117.9, 105.5; IR (KBr): 3055, 2222, 1620, 1450, 1373 cm^{-1}; HRMS for $C_{16}H_{11}N_2$ [M+H$^+$] calcd 231.0917, found 231.0920.

2-p-Tolylquinoline-3-carbonitrile (5ab): Pale yellow solid; 54 mg (41%); mp 174 – 177 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.21 (d, *J* = 9.1 Hz, 1H), 8.01 – 7.84 (m, 4H), 7.67 (td, *J* = 7.4, 1.0 Hz, 1H), 7.40 (d, *J* = 7.9 Hz, 2H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 148.7, 144.2, 140.6, 134.9, 132.9, 129.9, 129.5, 129.1, 127.9, 127.7, 124.9, 118.1, 105.5, 21.4; IR (KBr): 2916, 2222, 1612, 1481, 1188 cm^{-1}; HRMS for $C_{17}H_{13}N_2$ [M+H$^+$] calcd 245.1073, found 245.1070.

2-(4-Methoxyphenyl)quinoline-3-carbonitrile (5ac): Off white solid; 63 mg (45%); mp 174 – 177 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.19 (d, *J* = 9.0 Hz, 1H), 8.07 – 7.99 (m, 2H), 7.95 – 7.87 (m, 2H), 7.69 – 7.61 (m, 1H), 7.14 – 7.06 (m, 2H), 3.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5, 157.5, 148.7, 144.3, 132.9, 130.7, 130.2, 129.8, 127.8, 127.7, 124.8, 118.3, 114.2, 105.3, 55.5; IR (KBr): 2914, 2221, 1612, 1481, 1173 cm^{-1}; HRMS for $C_{17}H_{13}N_2O$ [M+H$^+$] calcd 261.1022, found 261.1028.

2-(3,4-Dimethoxyphenyl)quinoline-3-carbonitrile (5ad): Off white solid; 78 mg (50%); mp 174 – 177 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.21 (d, *J* = 9.0 Hz, 1H), 7.92 (s, 1H), 7.89 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.67 (ddd, *J* = 9.2, 8.2, 1.6 Hz, 2H), 7.62 (d, *J* = 2.1 Hz, 1H), 7.07 (d, *J* = 8.4 Hz, 1H), 4.04 (s, 3H), 4.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4, 150.8, 149.1, 148.7, 144.4, 133.0, 130.2, 129.8, 127.8, 127.7, 124.8, 122.4, 118.3, 112.1, 111.0, 105.3, 56.1, 56.0; IR (KBr): 2916, 2222, 1615, 1483, 1180 cm^{-1}; HRMS for $C_{18}H_{15}N_2O_2$ [M+H$^+$] calcd 291.1128, found 291.1124.

2-*o*-Tolylquinoline-3-carbonitrile (5ae): Yellow solid; 42 mg (32%); mp 163 – 164 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H), 8.11 (d, *J* = 8.5 Hz, 1H), 7.84 (d, *J* = 7.5 Hz, 1H), 7.82 – 7.78 (m, 1H), 7.60 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 1H), 7.33 (ddd, *J* = 9.6, 6.4, 2.7 Hz, 2H), 7.27 (d, *J* = 7.0 Hz, 2H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 148.3, 142.5, 137.6, 136.1, 132.9, 130.8, 129.8, 129.6, 129.2, 128.2, 127.9, 126.0, 125.1, 117.1, 107.5, 19.7; IR (KBr): 3015, 2222, 1616, 1473, 1170 cm^{-1}; HRMS for $C_{17}H_{13}N_2$ [M+H$^+$] calcd 245.1073, found 245.1076.

2-(2-Methoxyphenyl)quinoline-3-carbonitrile (5af): Pale yellow solid; 63 mg (45%); mp 150 – 153 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (s, 1H), 8.23 (d, *J* = 9.3 Hz, 1H), 7.93 (d, *J* = 8.1 Hz, 1H), 7.89 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H), 7.69 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 1H), 7.59 – 7.49 (m, 2H), 7.17 (td, *J* = 7.5, 0.9 Hz, 1H), 7.09 (d, *J* = 8.3 Hz, 1H), 3.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.3, 157.0, 148.7, 142.3, 132.5, 131.5, 131.0, 130.0, 128.0, 127.3, 125.1, 121.2, 117.7, 111.3, 108.8, 55.4; IR (KBr): 3015, 2222, 1616, 1473, 1170 cm^{-1}; HRMS for $C_{17}H_{13}N_2O$ [M+H$^+$] calcd 261.1022, found 261.1032.

2-(Benzo[*d*][1,3]dioxol-5-yl)quinoline-3-carbonitrile (5ag): Light brown solid; 62 mg (42%); mp 187 – 189°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (s, 1H), 8.16 (d, *J* = 8.9 Hz, 1H), 7.88 (t, *J* = 7.4 Hz, 2H), 7.64 (t, *J* = 7.2 Hz, 1H), 7.55 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.50 (d, *J* = 1.6 Hz, 1H), 6.99 (d, *J* = 8.1 Hz, 1H), 6.07 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.3, 149.4, 148.6, 148.2, 144.4, 133.0, 131.7, 129.8, 127.9, 127.7, 124.9, 123.9, 118.1, 109.5, 108.5, 105.3, 101.6; IR (KBr): 3015, 2222, 1616, 1473, 1170 cm^{-1}; HRMS for $C_{17}H_{11}N_2O_2$ [M+H$^+$] calcd 275.0815, found 275.0820.

2-(4-Chlorophenyl)quinoline-3-carbonitrile (5ah): White solid; 93 mg (65%); mp 188 – 190 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.21 (d, *J* = 8.8 Hz, 1H), 7.99 (d, *J* = 8.5 Hz, 2H), 7.93 (t, *J* = 7.1 Hz, 2H), 7.70 (t, *J* = 7.5 Hz, 1H), 7.56 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7, 148.6, 144.3, 136.5, 136.1, 133.2, 130.5, 129.9, 129.0, 128.3, 127.8, 125.1, 117.8, 105.3; IR (KBr): 2914, 2221, 1612,

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1481, 1173 cm^{-1}; HRMS for $C_{16}H_{10}ClN_2$ $[M+H^+]$ calcd 265.0527, found 265.0524.

7-Methoxy-2-phenylquinoline-3-carbonitrile (5ba): Off white solid; 87 mg (62%); mp 164 – 166 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H), 7.99 (d, *J* = 6.2 Hz, 2H), 7.80 (d, *J* = 9.0 Hz, 1H), 7.60 – 7.51 (m, *J* = 5.8 Hz, 3H), 7.52 (d, *J* = 1.9 Hz, 1H), 7.31 (dd, *J* = 9.0, 2.3 Hz, 1H), 4.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6, 158.8, 150.9, 143.3, 137.9, 130.0, 129.1, 128.9, 128.7, 121.7, 120.4, 118.4, 107.7, 102.9, 55.9; IR (KBr): 3015, 2214, 1620, 1443, 1142 cm^{-1}; HRMS for $C_{17}H_{13}N_2O$ $[M+H^+]$ calcd 261.1022, found 261.1028.

6,7-Dimethoxy-2-phenylquinoline-3-carbonitrile (5ca): Pale yellow solid; 64 mg (41%); mp 196 – 199 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.97 (dd, *J* = 8.0, 1.4 Hz, 2H), 7.59 – 7.52 (m, 3H), 7.51 (s, 1H), 7.10 (s, 1H), 4.08 (s, 3H), 4.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 155.3, 151.0, 146.5, 141.2, 138.0, 129.7, 129.0, 128.7, 121.0, 118.6, 108.3, 104.6, 103.2, 56.5, 56.3; IR (KBr): 2924, 2222, 1620, 1504, 1185 cm^{-1}; HRMS for $C_{18}H_{15}N_2O_2$ $[M+H^+]$ calcd 291.1128, found 291.1125.

6-Methoxy-2-phenylquinoline-3-carbonitrile (5da): Yellow solid; 84 mg (60%); mp 167 – 168 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 1H), 8.11 (d, *J* = 9.2 Hz, 1H), 8.00 (dd, *J* = 8.0, 1.5 Hz, 2H), 7.63 – 7.50 (m, 4H), 7.13 (d, *J* = 2.7 Hz, 1H), 3.99 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.9, 155.7, 145.0, 142.5, 137.8, 131.3, 129.8, 129.0, 128.7, 126.2, 126.1, 118.2, 105.7, 104.6, 55.8; IR (KBr): 2945, 2222, 1620, 1489, 1034 cm^{-1}; HRMS for $C_{17}H_{13}N_2O$ $[M+H^+]$ calcd 261.1022, found 261.1025.

6-Chloro-2-phenylquinoline-3-carbonitrile (5ea): Pale yellow solid; 36 mg (25%); mp 190 – 193 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.61 (s, 1H), 8.17 (d, *J* = 9.0 Hz, 1H), 8.04 – 8.00 (m, 2H), 7.92 (d, *J* = 2.3 Hz, 1H), 7.85 (dd, *J* = 9.0, 2.3 Hz, 1H), 7.62 – 7.57 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.2, 147.1, 143.2, 137.3, 134.1, 133.9, 131.5, 130.4, 129.1, 128.8, 126.3, 125.6, 117.6, 106.6; IR (KBr): 3053, 2222, 1597, 1489, 1026, 764 cm^{-1}; HRMS for $C_{16}H_{10}ClN_2$ $[M+H^+]$ calcd 265.0527, found 265.0524.

6,7-Dimethoxy-2-*p*-tolylquinoline-3-carbonitrile (5cb): Pale yellow solid; 49 mg (30%); mp 198 – 200 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.44 (s, 1H), 7.88 (d, *J* = 8.2 Hz, 2H), 7.51 (s, 1H), 7.37 (d, *J* = 7.9 Hz, 2H), 7.09 (s, 1H), 4.08 (s, 3H), 4.06 (s, 3H), 2.46 (s, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.6, 155.3, 150.9, 146.5, 141.3, 139.9, 135.1, 129.4, 128.9, 120.9, 118.7, 108.27, 104.6, 103.1, 56.5, 56.3, 21.4; IR (KBr): 2924, 2214, 1690, 1504, 1211 cm^{-1}; HRMS for $C_{19}H_{17}N_2O_2$ $[M+H^+]$ calcd 305.1285, found 305.1291.

6,7-Dimethoxy-2-(4-methoxyphenyl)quinoline-3-carbonitrile (5cc): Pale yellow solid; 60 mg (35%); mp 178 – 180 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1H), 7.96 (d, *J* = 8.8 Hz, 2H), 7.48 (s, 1H), 7.08 (d, *J* = 5.0 Hz, 2H), 7.06 (s, 1H), 4.07 (s, 3H), 4.05 (s, 3H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 156.1, 155.2, 150.8, 146.5, 141.3, 130.5, 130.4, 120.7, 118.83, 114.1, 108.2, 104.5, 102.9, 56.5, 56.3, 55.4; IR (KBr): 2925, 2213, 1612, 1494, 1173 cm^{-1}; HRMS for $C_{19}H_{17}N_2O_3$ $[M+H^+]$ calcd 321.1234, found 321.1238.

2-(4-Chlorophenyl)-6,7-dimethoxyquinoline-3-carbonitrile (5cd): White solid; 75 mg (43%); mp 234 – 235 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.98 – 7.90 (m, 2H), 7.57 – 7.51 (m, 2H), 7.49 (s, 1H), 7.11 (s, 1H), 4.09 (s, 3H), 4.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5, 155.2, 151.2, 146.5, 141.3, 136.4, 136.1, 130.3, 128.9, 121.2, 118.4, 108.2, 104.5, 102.9, 56.54, 56.3; IR (KBr): 2947, 2222, 1697, 1504, 1165 cm^{-1}; HRMS for $C_{18}H_{14}ClN_2O_2$ $[M+H^+]$ calcd 325.0738, found 325.0734.

Ethyl 3-(2-bromophenyl)-2-cyanoacrylate (6): Colorless oil, 78%; ^1H NMR (400 MHz, $CDCl_3$) δ 8.63 (s, 1H), 8.17 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.71 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.46 (td, *J* = 7.4, 0.8 Hz, 1H), 7.38 (td, *J* = 7.7, 1.7 Hz, 1H), 4.41 (q, *J* = 7.1 Hz, 1H), 1.41 (t, *J* = 7.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8, 153.9, 133.7, 133.6, 131.7, 130.1, 128.1, 126.6, 114.7, 106.4, 63.0, 14.2; HRMS for $C_{12}H_{11}BrNO_2$ $[M+H^+]$ calcd 279.9968, found 279.9973 and 281.9954 $[M+2+H^+]$.

2-Aminobenzaldehyde (8): Pale yellow liquid; 42 mg (64%); ^1H NMR (400 MHz, DMSO–d_6) δ 9.81 (d, *J* = 0.4 Hz, 1H), 7.53 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.30 (ddd, *J* = 8.5, 7.0, 1.7 Hz, 1H), 7.12 (bs, 2H), 6.76 (d, *J* = 8.4 Hz, 1H), 6.64 (ddd, *J* = 7.9, 7.0, 1.0 Hz, 1H).; ^{13}C NMR (100 MHz, DMSO–d_6) δ 194.5, 151.2, 136.0, 135.5, 118.2, 116.3, 115.4; HRMS for C_7H_8NO $[M+H^+]$ calcd 122.0600, found 121.0581.

Ethyl 3-(2-aminophenyl)-2-cyanoacrylate (9): Brown solid; 58 mg (50%); mp 123-125 °C; ^1H NMR (400 MHz, DMSO–d_6) δ 8.55 (s, 1H), 8.32 (d, *J* = 8.6 Hz, 1H), 8.09 (d, *J* = 7.9 Hz, 1H), 7.84 (d, *J* = 8.2 Hz, 3H), 7.47 (t, *J* = 7.4 Hz, 1H), 4.42 (q, *J* = 7.1 Hz, 2H), 1.40 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, DMSO–d_6) δ 165.50, 147.65, 141.08, 133.74, 130.93, 130.68, 125.00, 120.86, 117.26, 110.72, 62.23, 14.54; ^1H NMR (400 MHz, DMSO–d_6, D_2O exchange) δ 8.58 (s, 1H), 8.26 (d, *J* = 8.5 Hz, 1H), 8.04 (d, *J* = 7.7 Hz, 1H), 7.85 (t, *J* = 7.6 Hz, 1H), 7.47 (t, *J* = 7.3 Hz, 1H), 4.39 (q, *J* = 6.9 Hz, 2H), 1.37 (t, *J* = 7.0 Hz, 3H); HRMS for $C_{12}H_{13}N_2O_2$ $[M+H^+]$ calcd 217.0972, found 217.0975.

2-Benzoyl-3-(2-bromophenyl)acrylonitrile (10): Crystalline off white solid; 234 mg (70%); mp 126 — 128 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1H), 8.25 (d, *J* = 7.1 Hz, 1H), 7.94 (d, *J* = 7.3 Hz, 2H), 7.73 (d, *J* = 7.8 Hz, 1H), 7.68 (t, *J* = 7.4 Hz, 1H), 7.57 (t, *J* = 7.6 Hz, 2H), 7.51 (t, *J* = 7.6 Hz, 1H), 7.42 (t, *J* = 7.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.8, 154.1, 135.3, 133.8, 133.7, 133.6, 132.1, 130.10, 129.6, 128.8, 128.2, 126.5, 115.7, 113.6; HRMS for $C_{16}H_{11}BrNO$ $[M+H^+]$ calcd 312.0019, found 312.0015.

Ethyl 3-(2-azidophenyl)-2-cyanoacrylate (**11**): ^1H NMR (400 MHz, $CDCl_3$) δ 8.79 (s, 1H), 8.78 (d, *J* = 9.0 Hz, 1H), 8.14 (dd, *J* = 8.1, 1.1 Hz, 1H), 8.04 (td, *J* = 8.4, 7.9, 1.3 Hz, 1H), 7.85 – 7.80 (m, 1H), 4.64 (q, *J* = 7.1 Hz, 2H), 1.55 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6, 145.7, 138.1, 133.6, 132.0, 130.5, 128.6, 122.7, 117.2, 117.1, 62.7, 14.4. MS (ESI) *m/z* cacld for $C_{12}H_{11}N_4O_2$ $[M+H^+]$ 243.09, found 243.15.

Representative procedure for synthesis of pyrimido[4,5-*b*]quinolin-4(3H)-ones (12): A mixture of 2-bromobenzaldehyde (100 mg, 0.54 mmol), 2-cyanoacetamide (54 mg, 0.65 mmol), sodium azide (52 mg, 0.81 mmol), CuI (20 mol %), L-proline (40 mol %) and K_2CO_3 (186 mg, 2.5 equiv.) in DMSO (2 mL) was mixed under air atmosphere at room temperature and then heated to 150 °C for 3 h. After cooling to ambient temperature, benzaldehyde (69 mg, 0.65 mmol) was added and reaction mixture was then again heated to 150 °C for 2 h. After cooling to ambient temperature, the reaction mass was quenched with ice-cold aqueous solution of NH_4Cl (30 mL), filtered through a bed of celite and the plug washed with ethyl acetate (20 mL). The resulting filtrate was extracted with

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ethyl acetate (2 × 20 mL) and the combined organic layers dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Desired product **12a** (77 mg, 52%) was isolated by column chromatography on silica gel (100-200 mesh) using ethyl acetate/ hexane (30%, *v/v*) as eluent.

2-Phenylpyrimido[4,5-*b*]quinolin-4(3H)-one (12a): Yellow solid; 77 mg (52%); mp 356-357 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.71 (s, 1H), 9.32 (s, 1H), 8.30 – 8.27 (m, 3H), 8.10 (d, *J* = 8.6 Hz, 1H), 7.96 (t, *J* = 7.6 Hz, 1H), 7.72 – 7.57 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.7, 156.8, 156.3, 151.6, 138.6, 133.3, 133.1, 132.6, 130.0, 129.2, 128.9, 128.6, 126.9, 126.7, 116.1; HRMS for $C_{17}H_{12}N_3O$ [M + H]$^+$ calcd 274.0975, found 274.0978.

2-(*p*-Tolyl)pyrimido[4,5-*b*]quinolin-4(3H)-one (12b): Orange solid; 84 mg (54%); mp 304-306 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.62 (s, 1H), 9.29 (s, 1H), 8.26 (d, *J* = 8.1 Hz, 1H), 8.20 (d, *J* = 8.0 Hz, 2H), 8.08 (d, *J* = 8.6 Hz, 1H), 7.94 (t, *J* = 8.5 Hz, 1H), 7.66 (t, *J* = 7.3 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 2H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.7, 156.9, 156.1, 151.6, 142.8, 138.6, 133.3, 130.2, 130.0, 129.8, 128.9, 128.6, 126.8, 126.6, 116.0, 21.5; HRMS for $C_{18}H_{14}N_3O$ [M + H]$^+$ calcd 288.1131, found 288.1127.

2-(4-Chlorophenyl)pyrimido[4,5-*b*]quinolin-4(3H)-one (12c): Yellow solid; 72 mg (43%); mp 376-378 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.80 (s, 1H), 9.32 (s, 1H), 8.32 – 8.28 (m, 3H), 8.10 (d, *J* = 8.6 Hz, 1H), 7.96 (t, *J* = 7.4 Hz, 1H), 7.70 – 7.67 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.6, 151.5, 138.7, 137.5, 133.4, 132.0, 130.5, 130.1, 130.0, 129.3, 129.0, 128.9, 127.0, 126.7, 116.1; HRMS for $C_{17}H_{11}ClN_3O$ [M + H]$^+$ calcd 308.0585, found 308.0582.

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