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An alternative synthesis of pyrimido[4,5-*b*]quinoline-4-ones via metal-free amination in water and Vilsmeier–Haack cyclization

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ABSTRACT

Two-step synthesis of pyrimido[4,5-*b*]quinoline-4-ones is described from 2-chloroquinoline-3-carbonitries via amination and cyclization reactions, respectively. The amination reactions proceeded much faster in water via simple S_NAr displacement reactions of chlorine. The cyclization reactions using Vilsmeier reagent at 60 °C gave the best yield of the products. The isolation of starting compound from the reaction of cyclized product with I_2/K_2CO_3 provided further chemical proof of the structure of the cyclized product. Plausible mechanism for cyclization is proposed.

1. Introduction

Vilsmeier–Haack reagent is an economical and mild reagent and has been used extensively for different course of reactions namely formylation,[1] cyclization[2] and ring annulations.[3] 2-Chloroquinoline-3-carboxaldehydes[4] an example of annulations reactions, are conveniently prepared in one-pot from acetanilides using Vilsmeier–Haack reagent and widely used for nitrogen, oxygen and sulfur hetero-annulation reactions.[5] Many of them are the constituents of natural products, agrochemicals and pharmaceuticals.[6] In contrast, 3-cyano analogues, prepared from 2-chloroquinoline-3-carboxaldehydes with aqueous ammonia and iodine,[7a] are not much explored as precursors in annulations reactions.[7b,c]

The amination of aryl and heteroaryl halides is an important reaction for the synthesis of organic compounds containing the *N*-aryl moiety. Transition metal-catalyzed,[8] microwave-assisted[9] and metal-free[10] procedures are generally used for carbon–nitrogen bond forming processes. The amination of quinoline derivatives are generally reported with 2- and 4-chloroquinoline either with bases,[11] metal catalysts[12] or under solvent free conditions.[13] All these reactions required harsh conditions such as high temperature and longer reaction periods. The reactions in aqueous media are of great interest for both economic and safety reasons and have been successfully adopted in copper-catalyzed N-arylation reactions.[14] Recently, Jiao J. et al. have reported organic solvent and ligand-free Cu powder catalyzed Ullmann arylation with aqueous methyl amine.[12f] Although, Sreedhar et al. have reported base and catalyst free synthesis of biaryl sulphides in aqueous medium from the reaction of heteroaryl halides with thiols via S_NAr pathway.[15] However, the amination of haloquinolines was not reported in water. Thus, this has prompted us to study the amination reaction of 2-chloroquinoline-3-carbonitriles with or without metal catalysts in water.

Pyrimido annulated quinolines are of particular importance because of the biological properties exhibited by this class of compounds such as antimalarial,[16] antiallergic,[17] antimicrobial,[18] anti-inflammatory[19] and anticancer[20] activities, which mainly depend on nature and position of the substituent. The traditional preparations of pyrimido[4,5-*b*]quinoline derivatives involve the cyclization reactions of 2-aminoquinoline-3-carbonitriles with formamide, formic acid, urea, thiourea, carbon disulfide or isothiocyanate.[21] 2-Aminoquinoline-3-carbonitrile framework was generally prepared from the multi component reactions involving cyclohexanone or cyclohexandione, α,β-unsaturated malanonitrile and amines.[22] Similarly, pyrimidine nucleus in analogues furo-, thieno- and benzo-fused pyrimidine derivatives are reported from 2-amino-3-cyano derivatives in two steps by conventional or microwave irradiation methods, respectively.[23] All these methods however suffer from some drawbacks such as high temperature, longer reaction period and anhydrous reaction conditions. Zhang R. et al. have recently used Vilsmeier reagent for the synthesis of pyrimidin-4(3*H*)-ones.[24]

Recently, we reported the synthesis of 2-amino-3*H*-pyrimidio [4,5-*b*]quinoline-4-ones from the base-catalyzed reaction of 2-

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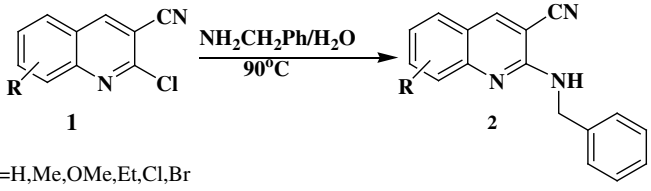
chloroquinoline-3-carbonitriles with guanidine hydrochloride in high yields.[25] As a part of our current interest in developing of new methodology for annulated quinolines, we envisioned that pyrimido[4,5-*b*]quinoline framework could be synthesized from 2-chloroquinoline-3-carbonitriles by an alternative route such as amination followed by cyclization reactions. Thus, we describe herein two-step synthesis of pyrimido[4,5-*b*]quinoline-4-ones from 2-chloroquinoline-3-carbonitriles involving the metal-free amination reaction with aliphatic amines in water and subsequent cyclization reaction with Vilsmeier–Haack reagent.

2. Results and discussion

In our initial study, reaction between 2-chloroquinoline-3-carbonitrile **1a** and benzyl amine was selected for optimizing the reaction conditions. The reaction was carried out using 3 equiv of benzyl amine in various organic solvents at 90 °C in 3 h. The reaction proceeded smoothly via S_NAr displacement of the chlorine atom and gave the desired product **2a** in moderate to good yields, Scheme 1. Among the various solvents such as EtOH, MeOH, CH_3CN and DMF screened, ethanol was found to be the best solvent (Table 1, entries 1–4). Surprisingly, reaction with aqueous methyl amine in ethanol at 90 °C proceeded much faster and completed in 10 min with 95% yield (entry 5). Encouraged by this finding, the reaction of benzyl amine with **1a** was reinvestigated in water, reaction completed in 55 min with 82% yield (entry 6). Using 2 equiv of benzyl amine did not reach full conversion even after 24 h (entry 7). Noteworthy, without solvent the amination reaction resulted in incomplete conversion even at higher temperature (130 °C) on prolonged heating (entry 8).



Scheme 1. Synthesis of 2-aminosubstituted quinoline-3-carbonitriles (**2**) from 2-choloroquinoline-3-carbonitriles (**1**).

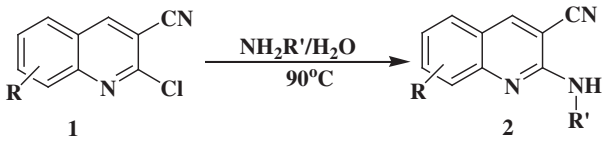
Table 1
Optimization of amination reaction conditions on 2-choloroquinoline-3-carbonitrile (**1a**) with benzyl amine[a]

Entry	Solvent	Time (h)	Yield of **2a**[b] (%)
1.	EtOH	3.0	92
2.	MeOH	3.5	62
3.	CH_3CN	5.0	78
4.	DMF	3.5	50
5.[c]	H_2O	10 (min)	95
6.	*H2O*	*55 (min)*	*82*
7.[d]	H_2O	24	30
8.	—	49	40

[a] 2-Choloroquinoline-3-carbonitrile (1 mmol), benzyl amine (3.0 mmol), solvent(1 ml/mmol), 90 °C.
[b] Isolated yields.
[c] 2-Choloroquinoline-3-carbonitrile (1 mmol), methyl amine (3.0 mmol), water(1 ml/mmol), 90 °C.
[d] Using 2 equiv of benzyl amine.

Next, we examined the generality of amination with other amines under similar reaction conditions in water. The reactions proceeded smoothly with primary and secondary amines. The results are summarized in Table 2 (entries 1–9). Lengthening of the alkyl chain does not show significant variation in the yields (entries 2–4). However, branching of the alkyl chain enhances the yield of the products under similar reaction conditions. This variation of yields could be attributed to inductive effect of alkyl groups (entries 5 and 6). In contrast to secondary aliphatic amine (entry 7), cyclic secondary amines enhance the yields significantly (entries 8 and 9). It is noteworthy that aromatic amine failed to react even at higher temperature (entry 10).

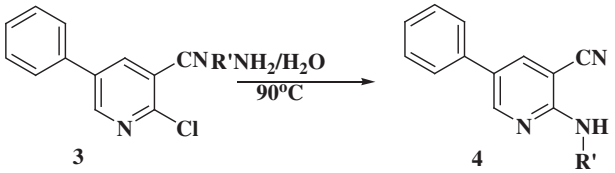
Table 2
Amination of 2-choloroquinoline/pyridine-3-carbonitriles with different amines in aqueous medium



Entry	R	R'	Product	Time (min)	Yield (%)
1.	H	Benzyl	**2a**	55	82
2.	H	Methyl	**2ab**	10	85
3.	H	Ethyl	**2ac**	25	82
4.	H	*n*-Butyl	**2ad**	80	80
5.	H	Cyclohexyl	**2ae**	30	87
6.	H	Isopropyl	**2af**	35	90
7.	H	*N*,*N*-Dimethyl	**2ag**	20	80
8.	H	Piperidine	**2ah**	25	92
9.	H	Morpholine	**2ai**	25	90
10.	H	Aniline	SM	30h	00
11.	6-Me	Benzyl	**2b**	55	82
12.	6-OMe	Benzyl	**2c**	60	85
13.	7-Me	Benzyl	**2d**	55	80
14.	7-OMe	Benzyl	**2e**	60	82
15.	8-Me	Benzyl	**2f**	55	86
16.	8-Et	Benzyl	**2g**	55	90
17.	6-Br	Benzyl	**2h**	45	80
18.	7-Cl	Benzyl	**2i**	45	78
19.	3	Benzyl	**4a**	65	80
20.	3	Methyl	**4b**	15	82
21.	3	*n*-Butyl	**4c**	90	82
22.	3	*N*,*N*-Dimethyl	**4d**	35	78
23.	3	Morpholine	**4e**	30	82

We further examined the general scope of amination reactions with other 2-chloroquinoline-3-carbonitrile derivatives (**1b**–**i**) and benzyl amine. Results are summarized in Table 2 (entries 11–18). The electron withdrawing groups at benzene ring increase the rate of the reaction while electron donating groups decrease the rate of the reaction with little enhancement in the yields.

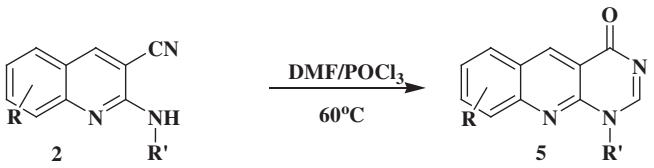
Next, we examined the pyridine derivative with various aliphatic amines under optimized conditions with a view to further generalize the scope of reactions and effect of fused-benzene ring in quinoline moiety **1** on the rates and yields (Scheme 2). Thus, the reaction of 2-chloro-5-phenylpyridin-3-carbonitrile (**3**) with various amines afforded amino pyridines **4a**–**e** in good yields. The results are summarized in Table 2 (entries 19–23). The longer reaction times show that fused-benzene ring in quinolines accelerate the reaction rates.



Scheme 2. Synthesis of 2-aminosubstituted pyridine-3-carbonitrile (**4a**) from 2-choloropyridine-3-carbonitrile (**3**).

We next focused our attention to develop the optimal reaction conditions for cyclization of 2-aminoquinoline-3-carbonitriles **2**

with Vilsmeier reagent to afford pyrimidoquinoline moiety. Thus, 2-benzylaminoquinoline-3-carbonirtile **2a** was chosen as the model system for cyclization reaction with Vilsmeier reagent (Scheme 3). Initially, our previous cyclization reaction conditions for the quinoline synthesis via Vilsmeier reagent using 1:3 molar ratios of DMF and $POCl_3$ at 90 °C were attempted with **2a**. The reaction completed in 20 min affording the cyclized product **5a** in 78% yield (Table 3, entry 1), which was characterized as 1-benzyl-1*H*-pyrimido[4,5-*b*]quinolin-4-one from the spectral and analytical data. On lowering reaction temperature the yield of cyclized product was enhanced (entries 2 and 3) and the best yield up to 98% was obtained at 60 °C in 45 min. On increasing the reaction temperature to 100 °C provided lower yield of the product (entry 4).



R= H,Me,Et,OMe,Cl,Br
R'=Bz,Me,Et,n-Butyl,cyclohexyl

Scheme 3. Synthesis of 1-benzyl-1*H*-pyrimido[4,5-*b*]quinolin-4-ones, **5** from 2-aminosubstituted quinoline-3-carbonitriles, **2**.

Table 3
Optimization of Vilsmeier–Haack reaction condition

Entry	DMF	$POCl_3$	Temp (°C)	Time (min)	Yield (%)
1.	1	3	90	20	78
2.	1	3	70	30	82
3.	*1*	*3*	*60*	*45*	*98*
4.	1	3	100	10	68
5.	1	2	60	60	70
6.	1	1	60	24 (h)	SM

Changing the molar ratio to 1:2 of DMF and $POCl_3$ in Vilsmeier reagent reduced both the reaction rate and yield of the product (entry 5). Notably, no product was obtained using 1:1 molar ratio even after prolonged reaction time could be presumed to non existence of Vilsmeier reagent (entry 6). Thus, Vilsmeier reaction with 1:3 molar ratios of DMF and $POCl_3$ at 60 °C was found the best optimal reaction conditions for cyclization to afford excellent yield of the product (98%). The generality of the cyclization reaction was further screened with various 2-alkylaminosubstituted quinoline-3-carbonitriles **2ab**–**ae** (Table 4, entries 2–5). Lengthening and branching of alkyl chain of amines decrease both reaction rates and yields of the products significantly.

To examine the scope of Vilsmeier reagent for the cyclization, other 2-benzylaminoquinoline-3-carbonitriles **2b**–**i** were screened. The reaction proceeded smoothly as indicated from TLC and afforded the desired cyclized products **5b**–**i** in excellent yields. The results are summarized in Table 4 (entries 6–13). The electron donating substituents at position-7 afforded better yields of the products than the substituents at position-6 (entries 6–9). Notably, ethyl group afforded the better yield of the product than the methyl group at position-8 (entries 10 and 11). However, the electron withdrawing substituent at position-6/7 gave the better yield of the product (entries 12 and 13). Noteworthy, the faster reaction rates with methoxy group could be attributed to the resonance effect of the group.

To further generalize the scope of reactions, pyridine derivative was screened with Vilsmeier reagent. Thus, compound **4a** was allowed to react with Vilsmeier reagent under optimized reaction conditions and found that the reaction proceeded smoothly affording the cyclized product **6** in good yield (entry 14), which was

Table 4
Synthesis of pyrimido[4,5-*b*]quinolin-4-ones

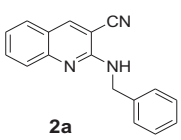
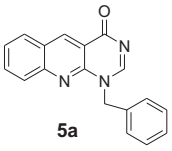
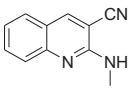
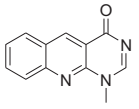
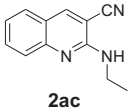
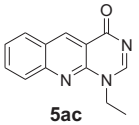
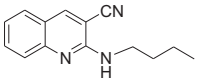
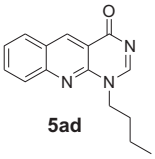
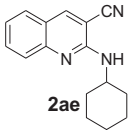
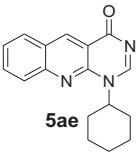
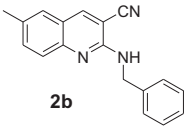
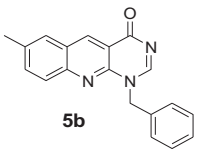
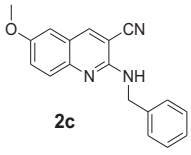
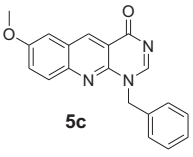
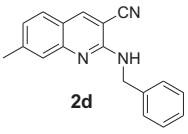
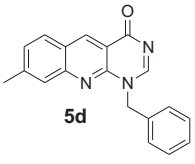
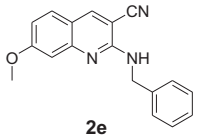
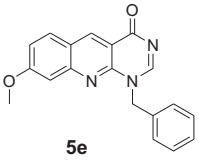
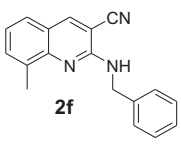
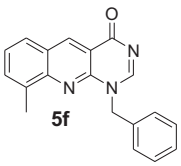
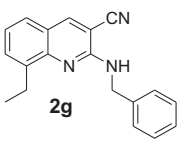
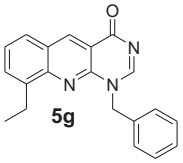
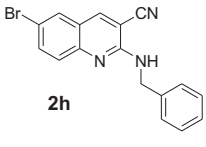
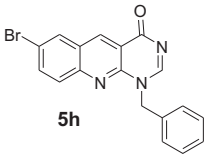
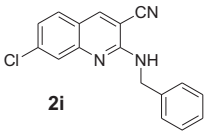
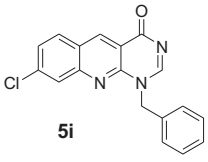
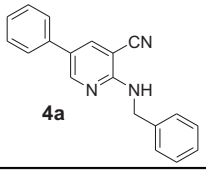
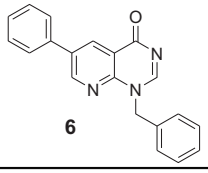
Entry	Substrate	Product	Time (min)	Yield[a] (%)
1.	 **2a**	 **5a**	45	98
2.	 **2ab**	 **5ab**	120	89
3.	 **2ac**	 **5ac**	150	87
4.	 **2ad**	 **5ad**	270	90
5.	 **2ae**	 **5ae**	150	86
6.	 **2b**	 **5b**	35	82
7.	 **2c**	 **5c**	15	85
8.	 **2d**	 **5d**	42	90
9.	 **2e**	 **5e**	20	92
10.	 **2f**	 **5f**	40	86

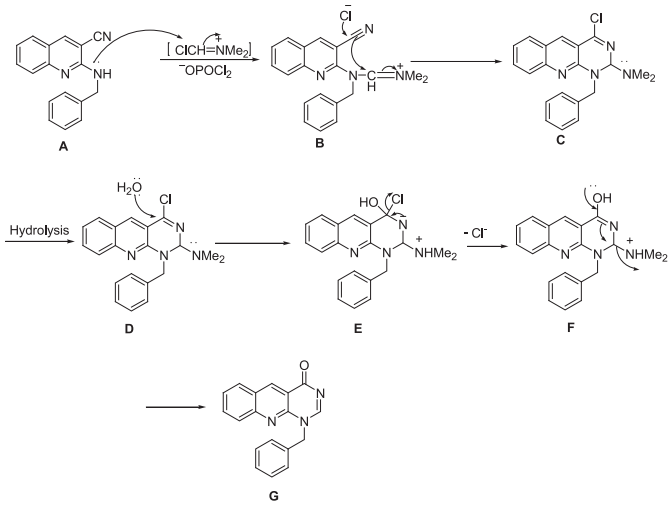
Table 4 (*continued*)

Entry	Substrate	Product	Time (min)	Yield[a] (%)
11.	 **2g**	 **5g**	45	95
12.	 **2h**	 **5h**	45	90
13.	 **2i**	 **5i**	40	85
14.	 **4a**	 **6**	40	82

[a] Isolated yields.

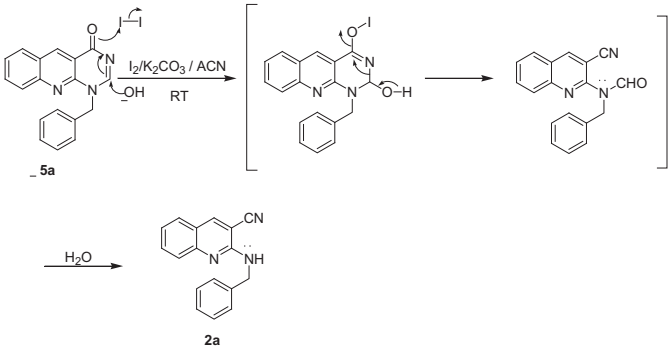
characterized as 1-benzyl-6-phenyl-1*H*-pyrido[2,3-*d*]pyrimidin-4-one from spectral and analytical data. The result illustrated that fused-benzene ring in quinoline framework enhances the yield.

A Plausible mechanism using Vilsmeier–Haack reaction for cyclization is illustrated in Scheme 4.



Scheme 4. Plausible mechanism.

The amidines type skeleton present in pyrimidine nucleus in product **5** could be readily hydrolyzed by acids and alkalis, in turn, open the pyrimidine ring to afford quinoline derivatives. Thus, the reaction of product **5a** with I_2/K_2CO_3 in acetonitrile at room temperature for 1.5 h afforded compound **2a** identified from TLC, spectral and elemental data, supporting chemically the cyclic structure of **5a**. The reaction transformations are shown in Scheme 5.



Scheme 5.

Although, spectral data and chemical evidence were sufficient to establish the structure of cyclized products **5**, single crystal X-ray crystallographic analysis[26] of **5g** was performed to establish the structure of the cyclized products **5**. An ORTEP representation of the molecule **5g** is given in Fig. 1.

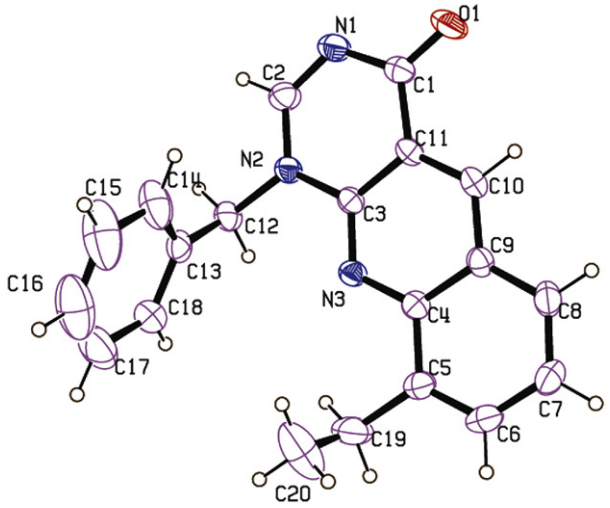


Fig. 1. ORTEP drawing of the X-ray structure of **5g**.

3. Conclusions

In conclusion, we have developed conditions for amination of 2-chloroquinoline-3-carbonitriles in water with good yields. The reaction in water proceeded with faster rates via simple S_NAr displacement. We have also developed new methodology to the synthesis of pyrimido[4,5-*b*]quinolin-4-ones from the reaction of 2-benzylaminoquinoline-3-carbonitriles with Vilsmeier reagent at lower temperature in good to excellent yields.

4. Experimental section

4.1. General

Melting points are measured using Buchi Melting-point apparatus in an open capillary tube and are uncorrected. IR spectra were recorded on VARIAN 3300 FTIR spectrophotometers. ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on JEOL AL 300 MHz spectrometer. The chemical shifts (δ ppm) and

coupling constants (Hz) are reported in the standard fashion with reference to either internal tetramethylsilane (for ^{1}H) or the central line (77.0 ppm) of $CDCl_3$ (for ^{13}C). Elemental analyses were performed on Exter Analytical Inc. 'Model CE-400 CHN Analyzer' from Department of Chemistry, BHU, Varanasi and Mass spectral analyses were performed on Thermo LCQ Advantage Max (ESI and APCI) Ion Trap (LC–MS/MS) from SAIF CDRI, Lucknow. Thin-layer chromatographies (TLC) were performed on glass plates (7.5×2.5 and 7.5×5.0 cm) coated with Loba Chemie's silica gel GF_{254} and various combinations of ethyl acetate and hexane were used as eluent. Visualization of spots was accomplished by exposure to UV light. Qualigen's silica gel (60–120 mesh) was used for column chromatography (approximately 15–20 g per 1 g of the crude product).

4.2. General procedure for synthesis of 2-aminoquinoline-3-carbonitriles (2)

A mixture of 2-chloroquinoline-3-carbonitrile **1** (1.0 equiv) and amine (3.0 equiv) in 3 ml water was stirred at 90 °C. After completion of the reaction, the reaction mixture was poured into ice-cold water, solid product was filtered and washed with water (3–5 mL) and dried. The crude product was characterized and was pure enough for further use.

*4.2.1. 2-Benzylaminoquinoline-3-carbonitrile (**2a**).* Light green solid; yield: 82%; mp 118 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=4.83 (d, J=5.1 Hz, 2H), 5.54 (s, 1H, D_2O exchangeable), 7.33–7.44 (m, 3H), 7.59–7.73 (m, 6H), 8.23 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=45.4, 95.7, 116.3, 121.3, 123.4, 126.9, 127.5, 128.0, 128.1, 128.7, 132.8, 138.4, 143.8, 149.3, 153.6; IR (KBr, cm^{-1}): 2216 (CN), 3380 (NH). Anal. Calcd for $C_{17}H_{13}N_3$: C, 78.74; H, 5.05; N, 16.20%. Found: C, 78.64; H, 5.01; N, 16.18%.

*4.2.2. 2-Methylaminoquinoline-3-carbonitrile (**2ab**).* Light green solid; yield: 85%; mp 120 °C (d); ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.17 (d, J=4.5 Hz, 3H), 5.83 (s, 1H, D_2O exchangeable), 7.58–7.74 (m, 4H), 8.20 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=48.3, 95.7, 116.5, 121.0, 123.2, 126.8, 128.1, 132.8, 143.6, 149.4, 154.4; IR (KBr, cm^{-1}): 2223 (CN), 3386 (NH). Anal. Calcd for $C_{11}H_9N_3$ C, 72.11; H, 4.95; N, 22.94%. Found: C, 72.09; H, 4.94; N, 21.31%.

*4.2.3. 2-Ethylaminoquinoline-3-carbonitrile (**2ac**).* Light green solid; yield: 82%; mp 60–63 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.33 (t, J=7.2 Hz, 3H), 3.65 (q, J=7.2 Hz, 2H), 5.18 (br s, 1H, D_2O exchangeable), 7.57–7.68 (m, 4H), 8.19 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.6, 36.3, 95.7, 116.5, 121.0, 123.2, 126.8, 128.0, 132.8, 143.7, 149.5, 153.8; IR (KBr, cm^{-1}): 2220 (CN), 3398 (NH). Anal. Calcd for $C_{12}H_{11}N_3$ C, 73.06; H, 5.62; N, 21.31%. Found: C, 73.03; H, 5.60; N, 21.31%.

*4.2.4. 2-n-Butylaminoquinoline-3-carbonitrile (**2ad**).* Light green solid; yield: 80%; mp: 190 °C (decomp.); ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.99 (t, J=7.2 Hz, 3H), 1.43–1.54 (m, 1H), 1.64–1.73 (m, 2H), 3.62 (m, 2H); 5.20 (br s, 1H, D_2O exchangeable), 7.56–7.70 (m, 4H), 8.19 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.8, 20.1, 31.4, 41.1, 95.6, 116.5, 121.0, 123.1, 126.8, 128.0, 132.7, 143.6, 149.4, 153.9; IR (KBr): 2216 (CN), 3367 (NH). Anal. Calcd for $C_{14}H_{15}N_3$ C, 74.64; H, 6.71; N, 18.65%. Found: C, 74.63; H, 5.60; N, 18.60%.

*4.2.5. 2-Cyclohexylaminoquinoline-3-carbonitrile (**2ae**).* Yellow solid; yield: 87%; mp: 132 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.25–1.30 (m, 4H), 1.66–1.83 (m, 4H), 2.11–2.15 (m, 2H), 4.13–4.23 (m, 1H), 5.09 (br s, 1H, D_2O exchangeable), 7.55–7.68 (m, 4H), 8.18 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=13.8, 20.1, 31.3, 41.1, 95.6, 116.4, 120.9, 123.0, 126.7, 128.0, 132.7, 143.6, 149.4, 153.8; IR (KBr): 2218 (CN), 3400 (NH). Anal. Calcd for $C_{16}H_{17}N_3$ C, 74.92; H, 6.37; N, 17.71%. Found: C, 74.90; H, 6.36; N, 17.70%.

*4.2.6. 2-Isopropylaminoquinoline-3-carbonitrile (**2af**).* Yellow solid; yield: 90%; mp: 110–112 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.32 (d, J=6.3 Hz, 6H), 4.44–4.55 (m, 1H), 5.01 (s, 1H, D_2O exchangeable), 7.55–7.72 (m, 3H); 7.92 (t, J=7.8 Hz, 1H), 8.18 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=22.6, 42.8, 95.7, 116.5, 120.9, 123.1, 126.8, 128.6, 132.7, 143.7, 149.5, 153.1; IR (KBr, cm^{-1}): 2228 (CN), 3447 (NH). Anal. Calcd for $C_{13}H_{13}N_3$ C, 73.91; H, 6.20; N, 19.89%. Found: C, 73.89; H, 6.19; N, 19.88%.

*4.2.7. 2-Dimethylaminoquinoline-3-carbonitrile (**2ag**).* Light green solid; yield: 80%; mp 192 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.33 (s, 6H), 7.60–7.71 (m, 4H), 8.32 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=40.6, 96.2, 118.5, 121.3, 123.6, 126.9, 127.6, 132.8, 146.8, 148.7, 156.6; IR (KBr, cm^{-1}): 2221 (CN), 3382 (NH). Anal. Calcd for $C_{12}H_{11}N_3$ C, 73.07; H, 5.62; N, 21.30%. Found: C, 72.03; H, 5.60; N, 21.29%.

*4.2.8. 2-Piperidine-1-yl-quinoline-3-carbonitrile (**2ah**).* Yellow solid; yield: 92%; mp 170 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.69–1.78 (m, 6H), 3.66 (t, J=4.8 Hz, 4H), 7.34 (t, J=7.4 Hz, 1H); 7.63–7.76 (m, 3H), 8.33 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.5, 25.7, 50.1, 99.3, 117.8, 122.0, 124.3, 127.3, 127.6, 132.6, 146.0, 148.5, 158.2; IR (KBr): 2231 (CN), 3421 (NH). Anal. Calcd for $C_{15}H_{15}N_3$: C, 75.92; H, 6.37; N, 17.71%. Found: C, 74.90; H, 6.36; N, 17.70%.

*4.2.9. 2-Morpholine-4-yl-quinoline-3-carbonitrile (**2ai**).* Light Green solid; yield: 90%; mp 80 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.70 (t, J=4.5 Hz, 4H), 3.91 (t, J=4.8 Hz, 4H), 7.40 (t, J=6.9 Hz, 1H), 7.67–7.81 (m, 3H), 8.38 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=49.2, 66.7, 99.0, 117.5, 122.4, 125.1, 127.6, 127.7, 132.9, 146.2, 148.3, 157.6; IR (KBr, cm^{-1}): 2216 (CN). Anal. Calcd for $C_{14}H_{13}N_3O$: C, 70.28; H, 5.48; N, 17.56%. Found: C, 70.20; H, 5.45; N, 17.57%.

*4.2.10. 2-Benzylamino-6-methyl-quinoline-3-carbonitrile (**2b**).* Light green solid; yield: 82%; mp 135 °C (decomp.); ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.45 (s, 3H), 4.81 (d, J=5.7 Hz, 2H), 5.46 (s, 1H, D_2O exchangeable), 7.26–7.44 (m, 5H), 7.50 (d, J=9.3 Hz, 1H), 7.62–7.65 (m, 2H), 8.15 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=21.0, 45.4, 95.4, 116.5, 121.2, 126.6, 126.9, 127.4, 127.9, 128.6, 133.1, 135.0, 138.5, 143.2, 147.6, 153.2; IR (KBr, cm^{-1}): 2214 (CN), 3337 (NH). Anal. Calcd for $C_{18}H_{15}N_3$: C, 79.10; H, 5.53; N, 15.37%. Found: C, 78.92; H, 5.41; N, 15.18%.

*4.2.11. 2-Benzylamino-6-methoxy-quinoline-3-carbonitrile (**2c**).* Light green solid; yield: 85%; mp 122 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.87 (s, 3H), 4.79 (d, J=5.4 Hz, 2H), 5.39 (s, 1H, D_2O exchangeable), 6.90 (s, 1H), 7.25–7.43 (m, 6H), 7.64 (d, J=9.3 Hz, 1H), 8.14 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=45.5, 55.5, 95.6, 105.9, 116.6, 121.7, 125.1, 127.4, 128.0, 128.4, 128.6, 138.7, 142.4, 145.2, 152.8, 155.6; IR (KBr, cm^{-1}): 2221 (CN), 3379 (NH). Anal. Calcd for $C_{18}H_{15}N_3O$: C, 74.72; H, 5.23; N, 14.52%. Found: C, 74.69; H, 5.04; N, 14.48%.

*4.2.12. 2-Benzylamino-7-methyl-quinoline-3-carbonitrile (**2d**).* Light green solid; yield: 80%; mp 122–125 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.49 (s, 3H), 4.81 (d, J=5.4 Hz, 2H), 5.49 (br s, 1H, D_2O exchangeable), 7.11 (d, J=7.5 Hz, 1H), 7.29–7.52 (m, 7H), 8.18 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=22.1, 45.2, 94.5, 116.6, 120.3, 125.6, 126.2, 127.4, 127.7, 127.8, 128.6, 138.4, 143.4, 143.8, 149.4, 153.7; IR (KBr, cm^{-1}): 2214 (CN), 3429 (NH). Anal. Calcd for $C_{18}H_{15}N_3$: C, 79.10; H, 5.53; N, 15.37%. Found: C, 79.04; H, 5.47; N, 15.35%.

*4.2.13. 2-Benzylamino-7-methoxy-quinoline-3-carbonitrile (**2e**).* Light green solid; yield: 82%; mp 125 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.96 (s, 3H), 4.79 (d, J=5.4 Hz, 2H), 5.38 (br s, 1H, D_2O

exchangeable), 6.91 (s, 1H), 7.11 (s, 1H), 7.25–7.41 (m, 2H), 7.51–7.54 (m, 1H), 7.65 (d, *J*=9.3 Hz, IH), 7.96 (d, *J*=9.3 Hz, 1H), 8.14 (s, 1H), 8.43 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=42.7, 55.5, 97.6, 105.7, 112.0, 116.5, 117.6, 123.6, 126.7, 127.2, 128.0, 128.6, 138.6, 143.1, 148.5, 152.4; IR (KBr, cm^{-1}): 2214 (CN), 3390 (NH). Anal. Calcd for $C_{18}H_{15}N_3$: C, 74.72; H, 5.23; N, 14.52%. Found: C, 74.70; H, 5.19; N, 14.42%.

*4.2.14. 2-Benzylamino-8-methyl-quinoline-3-carbonitrile (**2f**).* Light green solid; yield: 86%; mp 121 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.60 (s, 3H), 4.83 (d, *J*=5.7 Hz, 2H), 5.62 (br s, 1H, D_2O exchangeable), 7.17 (t, *J*=7.5 Hz, 1H), 7.25–7.37 (m, 2H), 7.43–7.52 (m, 5H), 8.20 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=17.7, 45.4, 95.0, 116.6, 121.0, 123.0, 125.8, 127.3, 127.9, 128.5, 132.9134.9, 138.8, 144.0, 148.0, 152.7; IR (KBr, cm^{-1}): 2222 (CN), 3450 (NH). Anal. Calcd for $C_{18}H_{15}N_3$: C, 79.10; H, 5.53; N, 15.37%. Found: C, 78.99; H, 5.46; N, 15.19%.

*4.2.15. 2-Benzylamino-8-ethyl-quinoline-3-carbonitrile (**2g**).* Light green solid; yield: 90%; mp 119–121 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.26 (t, *J*=7.5 Hz, 3H), 3.06 (q, *J*=7.5 Hz, 2H), 4.83 (d, *J*=5.4 Hz, 1H), 5.62 (s, 1H, D_2O exchangeable), 7.18–7.37 (m, 3H), 7.42–7.52 (m, 5H), 8.22 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.5, 24.5, 45.5, 95.0, 116.6, 121.2, 123.3, 125.8, 127.3, 127.8, 128.6, 131.4, 138.9, 140.7, 144.1, 147.4, 152.7; IR (KBr, cm^{-1}): 2226 (CN), 3446 (NH). Anal. Calcd for $C_{19}H_{17}N_3$: C, 79.41; H, 5.96; N, 14.62%. Found: C, 79.37; H, 5.58; N, 14.60%.

*4.2.16. 2-Benzylamino-6-bromoquinoline-3-carbonitrile (**2h**).* Light green solid; yield: 80%; mp: 160 °C (decomp.); ^{1}H NMR (300 MHz, $CDCl_3$): δ=4.83 (d, *J*=5.4 Hz, 2H), 5.54 (br s, 1H, D_2O exchangeable), 7.33–7.44 (m, 3H), 7.59–7.73 (m, 5H), 8.23 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=45.4, 95.8, 116.0, 119.7, 124.4, 127.6, 128.0, 128.4, 128.5, 128.6131.5, 138.2, 143.4, 149.8, 154.1; IR (KBr): 2216 (CN), 3371 (NH). Anal. Calcd for $C_{17}H_{12}BrN_3$: C, 60.37; H, 3.58; N, 12.43%. Found: C, 60.30; H, 3.57; N, 12.42%.

*4.2.17. 2-Benzylamino-7-chloroquinoline-3-carbonitrile (**2i**).* Light green solid; yield: 78%; mp: 142 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=4.82 (d, *J*=5.4 Hz, 2H), 5.53 (br s, 1H, D_2O exchangeable), 7.25–7.44 (m, 4H), 7.59–7.73 (m, 4H), 8.23 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=43.9, 94.0, 116.5, 119.3, 125.6, 126.2, 127.5, 128.6, 138.5, 143.2, 143.8, 149.4, 153.7; IR (KBr, cm^{-1}): 2212 (CN), 3390 (NH). Anal. Calcd for $C_{17}H_{12}ClN_3$: C, 69.51; H, 4.12; N, 14.30%. Found: C, 69.50; H, 4.10; N, 14.24%.

*4.2.18. 2-Benzylamino-5-phenyl-pyridine-3-carbonitrile (**4a**).* White solid; yield: 80%; mp: 132 °C (decomp.); ^{1}H NMR (300 MHz, $CDCl_3$): δ=4.76 (d, *J*=5.4 Hz, 2H), 5.50 (br s, 1H, D_2O exchangeable), 7.37–7.38 (m, 4H), 7.44–7.46 (m, 4H), 7.89 (s, 1H), 8.55 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=40.3, 45.4, 91.6, 116.6, 126.1, 127.6, 128.7, 129.1, 136.9, 138.2, 139.4, 142.3, 150.2, 151.2, 157.2; IR (KBr, cm^{-1}): 2215 (CN), 3362 (NH). Anal. Calcd for $C_{19}H_{15}N_3$: C, 79.98; H, 5.30; N, 14.73%. Found: C, 79.92; H, 5.28; N, 14.70%.

*4.2.19. 2-Methylamino-5-phenyl-pyridine-3-carbonitrile (**4b**).* Light green solid; yield: 82%; mp: 118 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.11 (d, *J*=4.8 Hz, 3H), 5.23 (br s, 1H, D_2O exchangeable), 7.44–7.46 (m, 5H), 7.86 (s, 1H), 8.55 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=41.5, 91.5, 116.6, 125.7, 125.8, 126.3, 127.2, 129.1, 136.1, 139.4, 151.8, 157.6; IR (KBr, cm^{-1}): 2216 (CN), 3360 (NH). Anal. Calcd for $C_{13}H_{11}N_3$: C, 74.62; H, 5.30; N, 20.08%. Found: C, 74.60; H, 5.19; N, 19.92%.

*4.2.20. 2-Butylamino-5-phenyl-pyridine-3-carbonitrile (**4c**).* Green solid; yield: 82%; mp: 82 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.98–1.00 (m, 3H), 1.41–1.48 (m, 2H), 1.63–1.68 (m, 2H), 3.51–3.58 (m, 2H), 5.18 (br s, 1H, D_2O exchangeable), 7.34–7.45 (m, 5H), 7.84 (s, 1H), 8.52 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=13.8, 20.0, 31.5, 41.4, 91.2, 116.8, 125.2, 126.1, 127.4, 129.0, 136.5, 139.3, 151.1, 157.5; IR (KBr, cm^{-1}): 2216 (CN), 3360 (NH). Anal. Calcd for $C_{16}H_{17}N_3$: C, 76.46; H, 6.82; N, 16.72%. Found: C, 76.40; H, 6.79; N, 16.58%.

*4.2.21. 2-Dimethylamino-5-phenyl-pyridine-3-carbonitrile (**4d**).* Light green solid; yield: 78%; mp: 121 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.34 (s, 6H), 7.34–7.49 (m, 5H), 7.93 (s, 1H), 8.53 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=40.3, 90.8, 119.2, 125.3, 126.0, 127.5, 129.1, 136.2, 142.3, 150.2, 158.4; IR (KBr, cm^{-1}): 2215 (CN), 3362 (NH). Anal. Calcd for $C_{14}H_{13}N_3$: C, 75.31; H, 5.87; N, 18.82%. Found: C, 75.10; H, 5.80; N, 18.78%.

*4.2.22. 2-Morpholin-4-yl-5-phenyl-pyridine-3-carbonitrile (**4e**).* Light brown solid; yield: 82%; mp: 108 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.76 (d, *J*=4.5 Hz, 4H), 3.85 (d, *J*=4.8 Hz, 4H), 7.40–7.48 (m, 5H), 7.98 (s, 1H), 8.58 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=48.4, 66.7, 94.8, 117.9, 126.2, 127.8, 127.9, 129.2, 135.8, 141.9, 150.1, 159.5; IR (KBr, cm^{-1}): 2221 (CN), 3362 (NH). Anal. Calcd for $C_{16}H_{15}N_3O$: C, 72.43; H, 5.70; N, 15.84%. Found: C, 72.30; H, 5.68; N, 15.78%.

4.3. General synthetic method for synthesis of *N*-benzyl-1*H*-pyrimido[4,5-*b*]quinoline-4-ones (5)

To a solution of 2-alkylaminoquinoline-3-carbonitrile **2** (1.0 equiv) in DMF (1.0 equiv) was dropwise added $POCl_3$ (3.0 equiv), the reaction mixture was stirred at 60 °C. After completion of the reaction (as monitored by TLC), the reaction mixture was poured into ice-cold water, solid product was filtered and washed with water (3×5 mL) and dried. The crude product was purified by column chromatography using EtOAc/hexane as eluent in 4:6 ratio to yield pure product **5**.

*4.3.1. 1-Benzyl-1H-pyrimido[4,5-b]quinolin-4-one (**5a**).* Yellow solid; yield: 98%; mp 129–131 °C; R_f (40% EtOAc/hexane) 0.30; ^{1}H NMR (300 MHz, $CDCl_3$): δ=5.64 (s, 2H, NCH_2), 7.33–7.45 (m, 5H, phenyl), 7.60 (t, *J*=7.5 Hz, 1H, H-8), 7.88 (t, *J*=7.8 Hz, 1H, H-7), 8.03 (d, *J*=8.4 Hz, 1H, H-9), 8.08 (d, *J*=8.7 Hz, 1H, H-6), 8.58 (s, 1H, H-5), 9.21 (s, 1H, H-2); ^{13}C NMR (75 MHz, $CDCl_3$): δ=50.8, 115.1, 126.5, 127.1, 128.1, 128.3, 128.4, 128.9, 129.4, 133.1, 135.3, 140.4, 147.8, 149.3, 155.4, 170.3; IR (KBr, cm^{-1}): 1659 (CO). MS: *m*/*z* 288 $(M+H)^+$. Anal. Calcd for $C_{18}H_{13}N_3O$: C, 75.25; H, 4.56; N, 14.63%. Found: C, 75.18; H, 4.52; N, 14.60%.

*4.3.2. 1-Methyl-1H-pyrimido[4,5-b]quinolin-4-one (**5ab**).* Yellow solid; yield: 89%; mp 133 °C; R_f (40% EtOAc/hexane) 0.28; ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.97 (s, 3H, NCH_3), 7.32 (t, *J*=7.5 Hz, 1H, H-8), 7.44 (d, *J*=8.4 Hz, 1H, H-9), 7.60 (t, *J*=7.5 Hz, 1H, H-7), 8.05 (d, *J*=8.7 Hz, 1H, H-6), 8.50 (s, 1H, H-5), 9.22 (s, 1H, H-2); ^{13}C NMR (75 MHz, $CDCl_3$): δ=35.7, 126.6, 128.1, 128.3, 129.5, 129.7, 133.2, 133.6, 140.2, 140.3, 155.7, 170.4; IR (KBr, cm^{-1}): 1655 (CO). Anal. Calcd for $C_{12}H_9N_3O$: C, 68.24; H, 4.29; N, 19.89%. Found: C, 68.20; H, 4.25; N, 19.80%.

*4.3.3. 1-Ethyl-1H-pyrimido[4,5-b]quinolin-4-one (**5ac**).* Yellow solid; yield: 87%; mp 146 °C; R_f (40% EtOAc/hexane) 0.26; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.33 (t, *J*=7.2 Hz, 3H, CH_3), 4.46 (q, *J*=7.2 Hz, 2H, NCH_2), 7.60 (t, *J*=7.5 Hz, 1H, H-8), 7.82 (t, *J*=7.5 Hz, 1H, H-7), 8.05 (d, *J*=8.4 Hz, 1H, H-9), 8.08 (d, *J*=8.7 Hz, 1H, H-6), 8.48 (s, 1H, H-5), 9.20 (s, 1H, H-2); ^{13}C NMR (75 MHz, $CDCl_3$): δ=32.7, 48.8, 114.8, 126.2, 127.6, 128.5, 129.6, 133.4, 140.4, 144.1, 149.3, 155.3, 170.4; IR (KBr, cm^{-1}): 1654 (CO). Anal. Calcd for $C_{13}H_{11}N_3O$: C, 69.32; H, 4.92; N, 18.66%. Found: C, 69.27; H, 4.85; N, 18.60%.

*4.3.4. 1-Butyl-1H-pyrimido[4,5-b]quinolin-4-one (**5ad**).* Yellow solid; yield: 90%; mp 170 °C (decomp.); R_f (40% EtOAc/hexane) 0.23; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.01 (t, *J*=7.2 Hz, 3H, CH_3), 1.43–1.55

(m, 2H, CH_2), 1.89–1.99 (m, 2H, CH_2), 4.43 (t, J=7.5 Hz, 2H, NCH_2), 7.60 (t, J=8.1 Hz, 1H, H-8), 7.88 (t, J=8.4 Hz, 1H, H-7), 8.03 (d, J=8.4 Hz, 1H, H-9), 8.05 (d, J=8.7 Hz, 1H, H-6), 8.44 (s, 1H, H-5), 9.21 (s, 1H, H-2); ^{13}C NMR (75 MHz, $CDCl_3$): δ=13.6, 19.8, 31.4, 48.3, 115.2, 126.4, 127.1, 128.2128.4, 129.4, 133.0, 140.2, 149.4, 155.5, 170.5; IR (KBr, cm^{-1}): 1652 (CO). Anal. Calcd for $C_{15}H_{15}N_3O$: C, 71.13; H, 5.97; N, 16.59. Found: C, 71.12; H, 5.95; N, 16.55.

*4.3.5. 1-Cyclohexyl-1H-pyrimido[4,5-b]quinolin-4-one (**5ae**).* Yellow solid; yield: 86%; mp 112 °C; R_f (40% EtOAc/hexane) 0.27; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.25–1.40 (m, 2H, CH_2), 1.56–1.80 (m, 4H, CH_2CH_2), 1.85–1.90 (m, 2H, CH_2), 2.01–2.15 (m, 2H, CH_2), 5.43–5.51 (m, 1H, NCH), 7.60 (t, J=7.5 Hz, 1H, H-8), 7.88 (t, J=7.2 Hz, 1H, H-7), 8.02 (d, J=8.4 Hz, 1H, H-9), 8.04 (d, J=8.7 Hz, 1H, H-6), 8.56 (s, 1H, H-5), 9.23 (s, 1H, H-2); ^{13}C NMR (75 MHz, $CDCl_3$): δ=25.3, 25.9, 32.7, 54.9, 115.2, 126.4, 126.9, 128.4, 129.4, 133.0, 140.3, 147.6, 149.2, 153.2, 170.2; IR (KBr, cm^{-1}): 1671 (CO). Anal. Calcd for $C_{17}H_{17}N_3O$: C, 73.10; H, 6.13; N, 15.04. Found: C, 73.08; H, 6.11; N, 15.01.

*4.3.6. 1-Benzyl-7-methyl-1H-pyrimido[4,5-b]quinolin-4-one (**5b**).* Yellow solid; yield: 82%; mp 152 °C (decomp.); R_f (40% EtOAc/hexane) 0.42; ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.57 (s, 3H, CH_3), 5.63 (s, 2H, NCH_2), 7.33–7.45 (m, 5H, phenyl), 7.72 (d, J=8.1 Hz, 1H, H-8), 7.78 (s, 1H, H-6), 7.99 (d, J=8.7 Hz, 1H, H-9), 8.54 (s, 1H, H-5), 9.12 (s, 1H, H-2); ^{13}C NMR (75 MHz, $CDCl_3$): δ=21.5, 50.8, 115.1, 127.3, 127.9, 128.0, 128.1, 128.5, 129.0, 135.3, 135.8, 136.8, 139.3, 147.2, 148.0, 155.2, 170.2; IR (KBr, cm^{-1}): 1584 (CO). Anal. Calcd for $C_{19}H_{15}N_3O$: C, 75.73; H, 5.02; N, 13.94%. Found: C, 75.70; H, 5.01; N, 13.94%.

*4.3.7. 1-Benzyl-7-methoxy-1H-pyrimido[4,5-b]quinolin-4-one (**5c**).* Yellow solid; yield: 85%; mp 135 °C; R_f (40% EtOAc/hexane) 0.26; ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.96 (s, 3H, OCH_3), 5.62 (s, 2H, NCH_2), 7.11–7.44 (m, 5H, phenyl), 7.54 (d, J=9.3 Hz, 1H, H-8), 7.97 (d, J=9.3 Hz, 1H, H-9), 8.43 (s, 1H, H-6), 8.53 (s, 1H, H-5), 9.07 (s, 1H, H-2); ^{13}C NMR (75 MHz, $CDCl_3$): δ=50.7, 55.8, 105.1, 107.9, 115.2, 126.6, 127.0, 128.0, 128.2, 129.6, 130.1, 135.3, 143.1, 154.8, 157.7, 159.1, 170.4; IR (KBr, cm^{-1}): 1660 (CO). MS: m/z 318 $(M+H)^+$. Anal. Calcd for $C_{19}H_{15}N_3O_2$: C, 71.91; H, 4.76; N, 13.24%. Found: C, 71.80; H, 4.68; N, 13.20%.

*4.3.8. 1-Benzyl-8-methyl-1H-pyrimido[4,5-b]quinolin-4-one (**5d**).* Yellow solid; yield: 90%; mp 139 °C; R_f (40% EtOAc/hexane) 0.38; ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.61 (s, 3H, CH_3), 5.62 (s, 2H, NCH_2), 7.33–7.42 (m, 5H, phenyl), 7.45 (d, J=8.4 Hz, H-6), 7.86 (s, 1H, H-9), 7.93 (d, J=8.4 Hz, 1H, H-7), 8.54 (s, 1H, H-5), 9.15 (s, 1H, H-2); ^{13}C NMR (75 MHz, $CDCl_3$): δ=22.3, 50.7, 114.1, 125.4, 127.2, 128.0, 128.4, 129.0, 129.1, 135.4, 139.8, 144.4, 147.9, 149.6, 155.2, 159.5, 170.4; IR (KBr, cm^{-1}): 1654 (CO). Anal. Calcd for $C_{19}H_{15}N_3O$: C, 75.73; H, 5.02; N, 13.94%. Found: C, 75.72; H, 5.00; N, 13.90%.

*4.3.9. 1-Benzyl-8-methoxy-1H-pyrimido[4,5-b]quinolin-4-one (**5e**).* Yellow solid; yield: 92%; mp 169 °C (decomp.); R_f (40% EtOAc/hexane) 0.24; ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.98 (s, 3H, OCH_3), 5.63 (s, 2H, NCH_2), 7.31–7.36 (m, 5H, phenyl), 7.74 (d, J=9.0 Hz, 1H, H-7), 7.98 (s, 1H, H-9), 8.02 (d, J=9.0 Hz, 1H, H-6), 8.42 (s, 1H, H-5), 9.08 (s, 1H, H-2); ^{13}C NMR (75 MHz, $CDCl_3$): δ=50.6, 55.9, 104.9, 105.8, 107.1, 115.4, 120.4, 120.7, 121.9, 127.9, 128.4, 129.0, 129.1, 130.6, 143.7, 150.6, 164.2; IR (KBr, cm^{-1}): 1659 (CO). Anal. Calcd for $C_{19}H_{15}N_3O_2$: C, 71.91; H, 4.76; N, 13.24%. Found: C, 71.89; H, 4.73; N, 13.22%.

*4.3.10. 1-Benzyl-9-methyl-1H-pyrimido[4,5-b]quinolin-4-one (**5f**).* Yellow solid; yield: 86%; mp 135 °C; R_f (40% EtOAc/hexane) 0.45; ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.77 (s, 3H, CH_3), 5.64 (s, 2H, NCH_2), 7.34–7.51 (m, 5H, Ph), 7.51 (t, J=7.5 Hz, 1H, H-7), 7.72 (d, J=8.1 Hz, 1H, H-8), 7.88 (d, J=8.1 Hz, 1H, H-6), 8.65 (s, 1H, H-5), 9.18 (s, 1H, H-2); ^{13}C NMR (75 MHz, $CDCl_3$): δ=20.1, 51.7, 114.8, 126.2, 126.4, 127.2, 128.9, 133.0, 135.4, 136.3, 139.7, 146.4, 146.7, 148.4, 148.5, 155.4, 163.1, 170.4; IR (KBr, cm^{-1}): 1654 (CO). Anal. Calcd for $C_{19}H_{15}N_3O$: C, 75.73; H, 5.02; N, 13.94%. Found: C, 75.70; H, 5.01; N, 13.93%.

*4.3.11. 1-Benzyl-9-ethyl-1H-pyrimido[4,5-b]quinolin-4-one (**5g**).* Yellow solid; yield: 95%; mp 129–132 °C; R_f (40% EtOAc/hexane) 0.44; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.30 (t, J=7.5 Hz, 3H, CH_3), 3.23 (q, J=7.5 Hz, 2H, CH_2), 5.62 (s, 2H, NCH_2), 7.30–7.42 (m, 5H, phenyl), 7.51 (t, J=7.1 Hz, 1H, H-7), 7.71 (d, J=6.6 Hz, 1H, H-8), 7.87 (d, J=8.1 Hz, 1H, H-6), 8.59 (s, 1H, H-5), 9.18 (s, 1H, H-2); ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.6, 24.6, 51.2, 114.7, 125.9, 126.5, 127.2, 127.5, 128.9, 131.5, 135.4, 140.3, 141.9, 146.6, 147.7, 155.5, 163.1, 170.4; IR (KBr, cm^{-1}): 1652 (CO). Anal. Calcd for $C_{20}H_{17}N_3O$: C, 76.17; H, 5.43; N, 13.32%. Found: C, 76.15; H, 5.40; N, 13.27%.

*4.3.12. 1-Benzyl-7-bromo-1H-pyrimido[4,5-b]quinolin-4-one (**5h**).* Yellow solid; Yield: 90%; mp145 °C; R_f (40% EtOAc/hexane) 0.38; ^{1}H NMR (300 MHz, $CDCl_3$): δ=5.64 (s, 2H, NCH_2), 7.33–7.46 (m, 4H, phenyl and H-6), 7.45 (t, J=8.1 Hz, 1H, phenyl), 7.60 (t, J=8.1 Hz, 1H, phenyl), 7.85–8.09 (m, 2H, H-6 and H-8), 8.56 (s, 1H, H-5), 9.21 (s, 1H, H-2); ^{13}C NMR (75 MHz, $CDCl_3$): δ=50.8, 115.1, 126.5, 127.1, 128.1, 128.3, 128.4, 128.9, 129.4, 133.1, 135.3, 140.2, 147.7, 149.2, 155.4, 170.3; IR (KBr, cm^{-1}): 1654 (CO). Anal. Calcd for $C_{18}H_{12}N_3OBr$: C, 59.03; H, 3.30; N, 11.47%. Found: C, 59.00; H, 3.20; N, 11.45%.

*4.3.13. 1-Benzyl-8-chloro-1H-pyrimido[4,5-b]quinolin-4-one (**5i**).* Yellow solid; yield: 85%; mp 165 °C; R_f (40% EtOAc/hexane) 0.25; ^{1}H NMR (300 MHz, $CDCl_3$): δ=5.64 (s, 2H, NCH_2), 7.33–7.45 (m, 4H, H-9 and phenyl), 7.60 (t, J=7.2 Hz, 1H, phenyl), 7.88 (t, J=7.2 Hz, 1H, phenyl), 8.02–8.09 (m, 2H, H-6 and H-7), 8.56 (s, 1H, H-5), 9.21 (s, 1H, H-2); ^{13}C NMR (75 MHz, $CDCl_3$): δ=50.8, 115.2, 126.5, 127.2, 128.1, 128.3, 128.5, 129.0, 129.4, 133.1, 135.3, 140.3, 147.8, 149.3, 155.4, 170.3; IR (KBr, cm^{-1}): 1656 (CO). Anal. Calcd for $C_{18}H_{12}N_3OCl$: C, 67.19; H, 3.76; N, 13.06%. Found: C, 67.15; H, 3.70; N, 13.00%.

*4.3.14. 1-Benzyl-6-phenyl-1H-pyrido[2,3-d]pyrimidin-4-one (**6**).* White solid; yield: 82%; mp 148 °C; R_f (40% EtOAc/hexane) 0.42; ^{1}H NMR (300 MHz, $CDCl_3$): δ=5.67 (s, 2H, NCH_2), 7.36–7.38 (m, 2H, phenyl), 7.42 (s, 2H, phenyl), 7.50–7.52 (m, 3H, phenyl), 7.64–7.67 (m, 3H, phenyl), 8.83 (s, 1H, H-6), 8.97 (s, 1H, H-5), 9.07 (s, 1H, H-2); ^{13}C NMR (75 MHz, $CDCl_3$): δ=51.3, 116.0, 127.0, 128.0, 128.6, 128.8, 129.0, 129.3, 134.8, 135.2, 135.7, 136.3, 148.5, 152.4, 154.0, 168.4; IR (KBr, cm^{-1}): 1599 (CO). Anal. Calcd for $C_{20}H_{15}N_3O$: C, 76.66; H, 4.82; N, 13.41%. Found: C, 76.64; H, 4.80; N, 13.40%.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2012.10.004.

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26. Crystal data for **5g**: Empirical formula, $C_{20}H_{17}N_3O$; formula weight, 315.36; crystal colour, habit: colourless, block; crystal system, monoclinic; lattice parameters, a=12.1269(13), b=8.3449(6), c=16.871(3) Å; V=1657.0(4) Å^3; space group $P21/n$; Z=4; D_{calcd}=1.264 g/cm^3; F_{000}=664.00; residuals: R=0.0594; Rw=0.1657. Crystallographic data (excluding structure factors) for the structures in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 902280. Copies of the data can be obtained free of charge on an application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223336033 or e-mail: deposit@ccdc.cam.ac.uk].