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Base-catalyzed cyclization reaction of 2-chloroquinoline-3-carbonitriles and guanidine hydrochloride: a rapid synthesis of 2-amino-3*H*-pyrimido[4,5-*b*] quinolin-4-ones

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ABSTRACT

t-BuOK-catalyzed cyclization of 2-chloroquinoline-3-carbonitriles with guanidine hydrochloride provided simple and rapid synthesis of 2-amino-3*H*-pyrimido[4,5-*b*]quinolin-4-ones in very short reaction time with good yield. Other 1,3-binucleophiles are found to react at the same rate. This methodology could be extended with their 3-formyl and 3-ester derivatives for the synthesis of pyrimido annulated quinolines.

1. Introduction

Quinoline derivatives are the core structure in the many alkaloid family[1] and well recognised by both synthetic and medicinal chemists because of their wide ranging applications as pharmaceuticals, agrochemicals, dyestuffs[2] and synthetic building blocks.[3] Pyrimidoquinoline derivatives are of particular interest because biological properties displayed by this class of compounds mainly depend on nature and position of substituents and possess antimalerial,[4] antiallergic,[5] antimicrobial,[6] anti-inflammatory[7] and anticancer[8] activities.

Because of their importance as drug molecules, interest has stimulated for the development of new methodology providing an efficient synthesis of pyrimido[4,5-*b*]quinoline framework. The classical synthesis reported to pyrimido[4,5-*b*]quinoline framework involves either formation of the quinoline ring by cyclization of suitable substituent of a pyrimidine or formation of the pyrimidine ring from the reaction of 2-aminoquinolines with 1,3-binucleophioles and isothiocyanate, respectively.[9] Similarly, in pyrimido[4,5-*b*]pyridine derivative, formation of the pyrimidine ring is reported from 2-chloropyridine-3-carbonitrile with guanidine in anhydrous DMSO.[10] All these methods, however, suffer from some drawbacks, such as high temperature, longer reaction time, anhydrous conditions and poor yield of the products.

We have been engaged in exploring the reactivity and synthetic applications of 2-chloroquinoline-3-carboxaldehyde derivatives.[11] The easy accessibility of these precursors from the anilides via Vilsmeier approach and their formyl group interconversion into cyano and ester groups makes them attractive intermediates for their further synthetic applications. We have recently demonstrated that fused nitrogen and oxygen heterocycles with diverse structural features and functionalities are accessible from 2-chloroquinoline-3-carboxaldehyde by choice of suitable reagents, catalyst and other reactive partners.[12] However, their 3-carbonitrile analogues for the synthesis of fused heterocycles are less explored.[13] In continuation of these studies, we now report the base-catalyzed cyclization reaction of 2-chloroquinoline-3-carbonitriles and guanidine hydrochlorides providing an efficient route to the synthesis of 2-amino-3*H*-pyrimido[4,5-*b*]quinolin-2-ones.

2. Results and discussion

The required 2-chloroquinoline-3-carbonitriles (**1**) were easily prepared from their corresponding aldehydes using iodine in aqueous ammonia.[11b] To study the construction of pyrimidine ring in pyrimidine-fused quinolines, we first examined the reaction of 2-chloroquinoline-3-carbonitrile (**1a**) and guanidine hydrochloride using several bases and solvents to optimize the reaction conditions and found that it proceeds readily and completed in very shorter time when 1 mmol of **1a** and 1 mmol of **2a** in 3 mL ethanol on heating with 0.5 equiv of *t*-BuOK[14] at 90 °C afforded the cyclized

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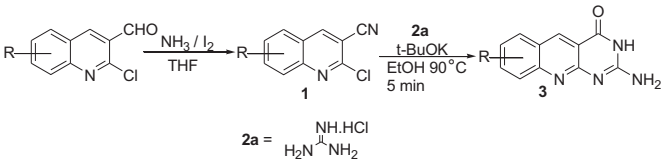
product **3a**[9m] in 80% yield, which was characterized as 2-amino-3*H*-pyrimido[4,5-*b*]quinolin-4-one from their spectral and analytical data (Scheme 1, Table 1, entry 1). Increasing the amount of base to 1 equiv did not improve the yield (entry 2). Further, increasing or



Scheme 1. Synthesis of pyrimido[4,5-*b*]quinoline.

Table 1
Optimization of reaction in different solvents and bases

Entry	Base (equivalent)	Solvent	Time (min)	Yield (%)
1	*t*-BuOK (0.5)	EtOH	5	80
2	*t*-BuOK (1.0)	EtOH	5	80
3	*t*-BuOK (1.5)	EtOH	5	70
4	*t*-BuOK (0.2)	EtOH	90	73
5	KOH (0.5)	EtOH	5	72
6	K_3PO_4 (0.5)	EtOH	5	70
7	K_2CO_3 (0.5)	EtOH	510	72
8	Na_2CO_3 (0.5)	EtOH	450	70
9	Et_3N (0.5)	EtOH	—	—
10	*t*-BuOK (0.5)	*t*-BuOH	5	80
11	*t*-BuOK (0.5)	DMF	5	79
12	*t*-BuOK (0.5)	CH_3CN	180	70
13	*t*-BuOK (0.5)	THF	360	60
14	*t*-BuOK (0.5)	Benzene	15	50
15	*t*-BuOK (0.5)	Water	Overnight	Sm

decreasing the base lowered the yield (entries 3 and 4). The use of KOH and K_3PO_4 bases did not improve the yield under similar reaction conditions (entries 5 and 6). K_2CO_3 and Na_2CO_3 required longer reaction time for completion (entries 7 and 8). No reaction occurred when triethylamine was used (entry 9). Among the various solvents screened for reaction media (entries 1 and 10–14), ethanol, *t*-BuOH and DMF were found equally effective with 80%, 80% and 79% yields, respectively (entries 1, 10 and 11). Further, no cyclization reaction occurred in water (entry 15).

After optimizing cyclization reaction conditions with **1a**, various 2-chloroquinoline-3-carbonitriles (**1b**–**i**) with guanidine hydrochloride were screened under similar reaction conditions and found to proceed smoothly providing the desired cyclized products **3b**–**i** in excellent yields. The results are summarized in Table 2 (entries 1–9). The electron donating and electron withdrawing substituent at benzene ring of quinoline moiety have slightly better yields of the cyclized products. To generalize the scope of the reaction, 5-phenyl-2-chloropyridine-3-carbonitrile (**1j**) was then tested with guanidine hydrochloride under optimized reaction conditions and found that the reaction proceeds at the same time with better yield (entry 10).

After optimizing cyclization reaction conditions with guanidine hydrochloride, the scope of other 1,3-binucleophiles such as urea, thiourea, *S*-benzylisothiourea chloride and cyano-guanidine with **1a** was examined under similar reaction conditions and found that the reactions completed at the same rate. The results are summarized in Table 2 (entries 11–18, Scheme 2).

The cyclized products with urea were characterized as pyrimido[4,5-*b*]quinoline-2,4-diones **4a** and **4b**, respectively, from spectral and analytical data (entries 11 and 12) presuming that products with guanidine hydrochloride and urea proceed via similar tautomeric structures. However, the cyclized products with thiourea and other binucleophiles were characterized as 2-substituted-4-amino-1*H*-pyrimido[4,5-*b*]quinoline derivatives indicating the absence of such tautomeric structure (entries 14–18, Scheme 3). The substrate bearing electron donating substituent gave better yield of the cyclized products (entries 12 and 15). The cyclization reactions with substrate bearing electron withdrawing substituent proceeded at the same rate, providing unidentified products. It is noteworthy, no cyclization reactions were found without base assuming anions of binucleophiles were involved in the cyclization reactions.

Table 2
Synthesis of pyrimido[4,5-*b*]quinolines

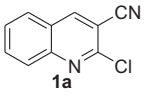
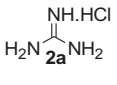
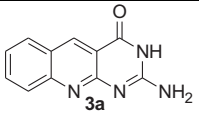
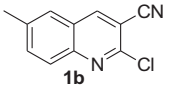
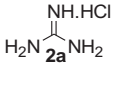
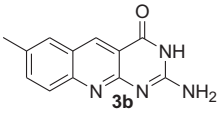
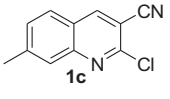
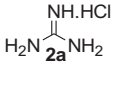
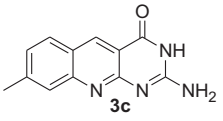
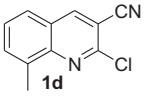
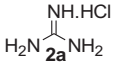
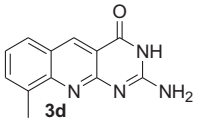
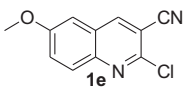
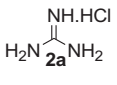
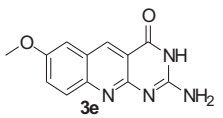
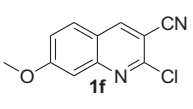
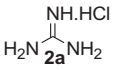
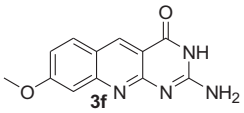
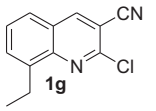
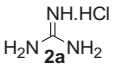
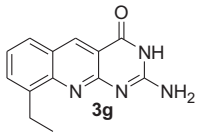
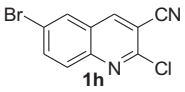
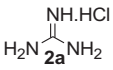
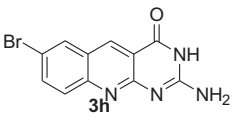
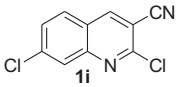
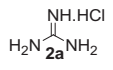
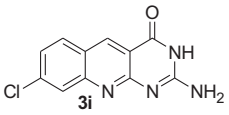
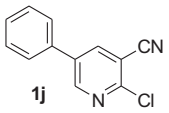
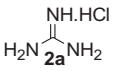
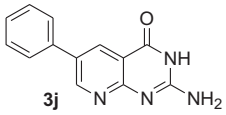
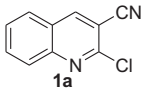
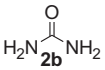
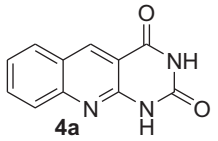
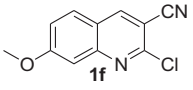
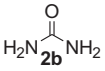
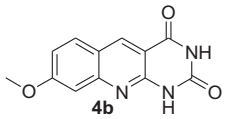
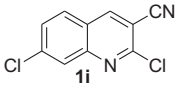
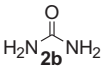
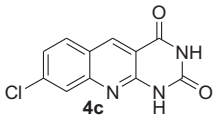
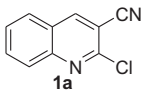
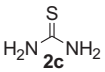
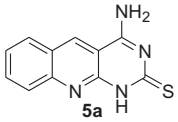
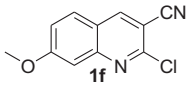
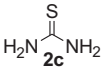
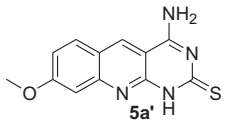
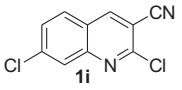
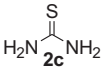
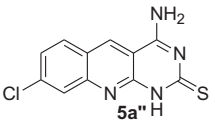
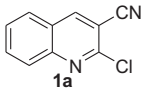
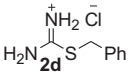
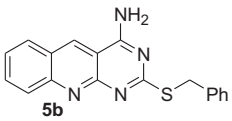
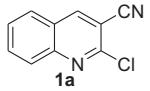
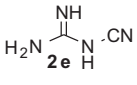
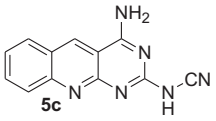
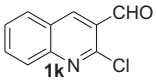
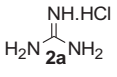
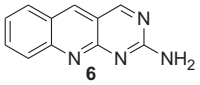
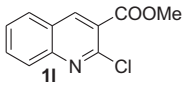
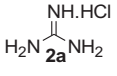
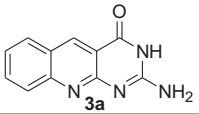
Entry	Substrate	Binucleophile	Product	Time (min)	Yield (%)
1				5	80
2				5	89
3				10	85
4				10	89
5				5	85

Table 2 (*continued*)

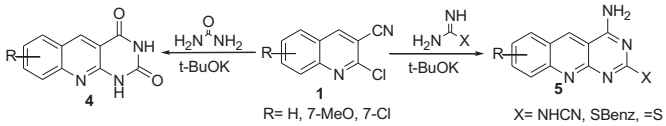
Entry	Substrate	Binucleophile	Product	Time (min)	Yield (%)
6	 **1f**	 **2a**	 **3f**	5	90
7	 **1g**	 **2a**	 **3g**	20	85
8	 **1h**	 **2a**	 **3h**	10	88
9	 **1i**	 **2a**	 **3i**	10	90
10	 **1j**	 **2a**	 **3j**	5	90
11	 **1a**	 **2b**	 **4a**	5	79
12	 **1f**	 **2b**	 **4b**	5	82
13	 **1i**	 **2b**	 **4c**	Overnight	0[a]
14	 **1a**	 **2c**	 **5a**	5	62
15	 **1f**	 **2c**	 **5a'**	5	72
16	 **1i**	 **2c**	 **5a''**	Overnight	0[a]
17	 **1a**	 **2d**	 **5b**	5	79

(*continued on next page*)

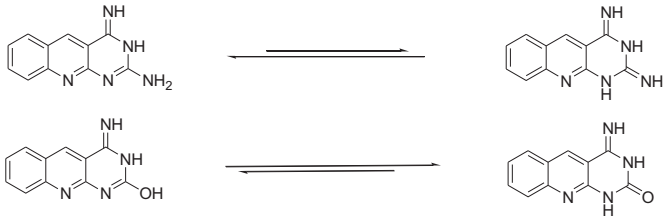
Table 2 (*continued*)

Entry	Substrate	Binucleophile	Product	Time (min)	Yield (%)
18	 **1a**	 **2e**	 **5c**	5	70
19	 **1k**	 **2a**	 **6**	10	79
20	 **1l**	 **2a**	 **3a**	5	80

[a] Unidentified products.

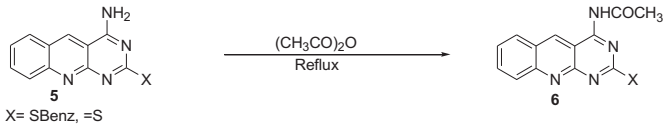


Scheme 2. Reaction of 2-chloroquinoline-3-carbonitrile with different binucleophile.



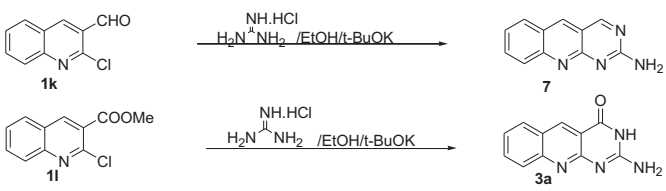
Scheme 3. Tautomeric structures.

The presence of amino group at 4-position in cyclized compounds **5a**–**c** derived from the reaction of **1a** with 1,3-binucleophiles **2c**–**e** was further confirmed by their acetylations with acetic anhydride providing 4-acetylamino-2-substituted-pyrimido[4,5-*b*]quinoline derivatives (**6**) (Scheme 4).



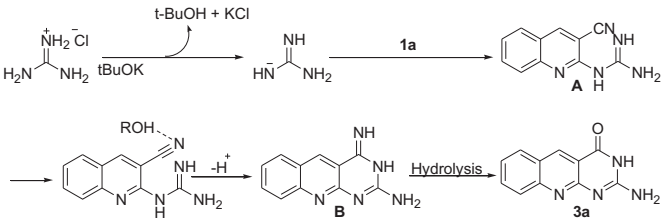
Scheme 4. Acetylation of functionalized pyrimidoquinolines.

Encouraged by facile cyclization reaction of 2-chloroquinoline-3-carbonitriles with guanidine hydrochloride, we extended the same strategy to their 3-formyl and 3-carbomethoxy derivatives **1k** and **1l**. Thus, the treatment of **1k** and **1l** with guanidine hydrochloride under optimized reaction condition provided the desired pyrimido [4,5-*b*]quinoline derivatives **7** and **3a** in short of time with 79% and 80% yields, respectively (Scheme 5, Table 2, entries 19 and 20).



Scheme 5. Reaction of guanidine with different functionalized chloroquinolines.

A plausible mechanism for one-pot cyclization is presented in Scheme 6. First step involves the release of free guanidine from the reaction of its hydrochloride with *t*-BuOK. The second step is nucleophilic aromatic substitution at 2-chloro carbon of 2-chloroquinoline-3-carbonitrile **1a** to generate **A** in situ, which on subsequent intramolecular cyclization might provide 4-iminopyrimido-fused quinoline **B**. Imine **B** on work up provides the desired 2-amino-3*H*-pyrimido[4,5-*b*]quinolin-4-one (**3a**).



Scheme 6. Plausible mechanism.

3. Conclusions

In summary, we have developed a simple and rapid synthesis of 2-amino-3*H*-pyrimido[4,5-*b*]quinolin-4-ones from *t*-BuOK-catalyzed cyclization of 2-chloroquinoline-3-carbonitriles with guanidine hydrochlorides in very short reaction time in good yields. This cyclization reaction is equally facile with other 1,3-binucleophiles and with formyl and carbomethoxy derivatives of quinoline.

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. ^{1}H (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. 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 the synthesis of 2-amino-3*H*-pyrimido[4,5-*b*]quinolin-4-one (3)

To a mixture of **1** (1 mmol) and binucleophile **2** (1 mmol) in 2–3 mL of EtOH was added *t*-BuOK (0.5 mmol), reaction mixture was stirred at 90 °C. After completion of the reaction, mixture poured into ice-cold water, solid product filtered and washed with water (3×5 mL) and further purified by column chromatography on silica gel (60–120 mesh) using EtOAc/hexane as eluent in 4:6 ratio to yielded pure product **3**.

*4.2.1. 2-Amino-3H-pyrimido[4,5-b]quinolin-4-one (**3a**).* Yellow solid; yield: 80%; mp 296–298 °C; R_f (40% EtOAc/hexane) 0.13; ^{1}H NMR (300 MHz, DMSO-d_6): δ=6.54 (br s, 2H, D_2O exchangeable), 7.35 (t, J=7.8 Hz, 1H), 7.69–7.82 (m, 4H, 1H, D_2O exchangeable), 9.03 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=113.2, 122.3, 126.3, 126.9, 127.8, 128.2, 128.4, 131.8, 137.4, 153.6, 170.1; IR (KBr, cm^{-1}): 1654, 3402. Anal. Calcd for $C_{11}H_8N_4O$: C, 62.26; H, 3.80; N, 26.40. Found: C, 61.98; H, 3.74; N, 26.51.

*4.2.2. 2-Amino-7-methyl-3H-pyrimido[4,5-b]quinolin-4-one (**3b**).* Yellow solid; yield: 89%; mp 305–307 °C; R_f (40% EtOAc/hexane) 0.50; ^{1}H NMR (300 MHz, DMSO-d_6): δ=2.50 (s, 3H), 6.54 (br s, 2H, D_2O exchangeable), 7.21 (d, J=7.8 Hz, 1H), 7.54 (s, 1H), 7.72–7.73 (m, 2H, 1H, D_2O exchangeable), 8.99 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=21.5, 127.3, 127.9, 128.0, 128.1, 128.5, 129.0, 135.3, 136.8, 148.0, 155.2, 170.3; IR (KBr, cm^{-1}) 1651, 3447. Anal. Calcd for $C_{12}H_{10}N_4O$: C, 63.71; H, 4.46; N, 24.76. Found: C, 63.87; H, 4.40; N, 24.67.

*4.2.3. 2-Amino-8-methyl-3H-pyrimido[4,5-b]quinolin-4-one (**3c**).* Yellow solid; yield: 85%; mp 307 °C; R_f (40% EtOAc/hexane) 0.40; ^{1}H NMR (300 MHz, DMSO-d_6): δ=2.45 (s, 3H), 6.54 (br s, 2H, D_2O exchangeable), 7.21 (d, J=7.81 Hz, 1H), 7.54 (s, 1H), 7.71–7.73 (m, 2H, 1H, D_2O exchangeable), 8.99 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=22.3, 127.2, 128.0, 128.4, 129.0, 129.2, 135.4, 139.8, 147.9, 149.6, 155.2, 170.4; IR (KBr, cm^{-1}): 1654, 3447. Anal. Calcd for $C_{12}H_{10}N_4O$: C, 63.71; H, 4.46; N, 24.76. Found: C, 63.91; H, 4.37; N, 24.65.

*4.2.4. 2-Amino-9-methyl-3H-pyrimido[4,5-b]quinolin-4-one (**3d**).* Yellow solid; yield: 89%; mp 380 °C (d); R_f (40% EtOAc/hexane) 0.16; ^{1}H NMR (300 MHz, DMSO-d_6): δ=2.61 (s, 3H), 6.57 (br s, 2H, D_2O exchangeable), 6.90 (s, 1H, D_2O exchangeable), 7.26 (t, J=8.8 Hz, 1H), 7.57(d, J=6.6 Hz, 1H), 7.66(d, J=8.1 Hz, 1H), 9.02 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz,): δ=18.1, 126.2, 126.4, 127.2, 127.9, 128.4, 133.0, 135.4, 136.3, 140.4, 155.4, 170.4; IR (KBr, cm^{-1}): 1654, 3401. Anal. Calcd for $C_{12}H_{10}N_4O$: C, 63.71; H, 4.46; N, 24.76. Found: C, 63.78; H, 4.50; N, 24.69.

*4.2.5. 2-Amino-7-methoxy-3H-pyrimido[4,5-b]quinolin-4-one (**3e**).* Yellow solid; yield: 85%; mp 298–301 °C; R_f (40% EtOAc/hexane) 0.29; ^{1}H NMR (300 MHz, DMSO-d_6): δ=3.90 (s, 3H), 6.52 (br s, 2H, D_2O exchangeable), 6.95–7.08 (m, 3H, 1H, D_2O exchangeable), 7.70 (t, J=8.4 Hz, 1H), 8.92 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz,): δ=55.8, 126.6, 127.0, 128.0, 128.2, 129.6, 130.1, 135.3, 143.1, 154.8, 157.7, 170.4; IR (KBr, cm^{-1}): 1656, 3404. Anal. Calcd for $C_{12}H_{10}N_4O_2$: C, 59.50; H, 4.16; N, 23.13. Found: C, 59.70; H, 4.09; N, 23.11.

*4.2.6. 2-Amino-8-methoxy-3H-pyrimido[4,5-b]quinolin-4-one (**3f**).* Yellow solid; yield: 90%; mp 300–303 °C; R_f (40% EtOAc/hexane) 0.20; ^{1}H NMR (300 MHz, DMSO-d_6): δ=3.92 (s, 3H), 6.74 (br s, 2H, D_2O exchangeable), 6.99–7.10 (m, 3H, 1H, D_2O exchangeable), 7.72 (t, J=9.0 Hz, 1H), 8.97 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=55.8, 115.3, 126.4, 127.0, 128.3, 129.0, 130.2, 135.4, 144.4, 154.8, 157.7, 170.4; IR (KBr, cm^{-1}): 1654, 3444. Anal. Calcd for $C_{12}H_{10}N_4O_2$: C, 59.50; H, 4.16; N, 23.13. Found: C, 59.62; H, 4.12; N, 23.15.

*4.2.7. 2-Amino-9-ethyl-3H-pyrimido[4,5-b]quinolin-4-one (**3g**).* Yellow solid; yield: 85%; mp 242 °C; R_f (40% EtOAc/hexane) 0.31; ^{1}H NMR (300 MHz, DMSO-d_6): δ=1.27 (t, J=6.9 Hz, 3H), 3.12 (q, J=7.2 Hz, 2H), 6.50 (br s, 2H, D_2O exchangeable), 7.27 (t, J=7.5 Hz, 1H), 7.53–7.66 (m, 3H, 1H, D_2O exchangeable), 9.01 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=21.5, 50.8, 127.3, 127.9, 128.0, 128.1, 128.5, 129.0, 135.7, 139.3, 148.0, 155.2, 170.5; IR (KBr, cm^{-1}): 1654, 3447. Anal. Calcd for $C_{13}H_{12}N_4O$: C, 64.99; H, 5.03; N, 23.32. Found: C, 65.12; H, 5.01; N, 23.28.

*4.2.8. 2-Amino-7-bromo-3H-pyrimido[4,5-b]quinolin-4-one (**3h**).* Yellow solid; yield: 88%; mp 321 °C; R_f (40% EtOAc/hexane) 0.10; ^{1}H NMR (300 MHz, DMSO-d_6): δ=6.55 (br s, 2H, D_2O exchangeable), 7.36 (t, J=7.5 Hz, 1H), 7.67–7.84 (m, 3H, 1H, D_2O exchangeable), 9.05 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz,): δ=115.1, 126.6, 128.3, 128.4, 128.5, 133.2, 135.3, 140.3, 149.3, 155.4, 170.3; IR (KBr, cm^{-1}): 1655, 3404. Anal. Calcd for $C_{11}H_7N_4OBr$: C, 45.39; H, 2.42; N, 19.25. Found: C, 45.53; H, 2.47; N, 19.21.

*4.2.9. 2-Amino-8-chloro-3H-pyrimido[4,5-b]quinolin-4-one (**3i**).* Yellow solid; yield: 90%; mp 370 °C (d); R_f (40% EtOAc/hexane) 0.30; ^{1}H NMR (300 MHz, DMSO-d_6): δ=6.53 (br s, 2H, D_2O exchangeable), 7.36 (t, J=8.8 Hz, 1H), 7.67–7.84 (m, 3H, 1H, D_2O exchangeable), 9.05 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz,): δ=115.9, 127.0, 127.8, 128.6, 129.0, 134.9, 135.3, 148.6, 152.3, 153.9, 169.1; IR (KBr, cm^{-1}): 1655, 3404. Anal. Calcd for $C_{11}H_7N_4OCl$: C, 53.56; H, 2.86; N, 22.71. Found: C, 53.47; H, 2.91; N, 22.58.

*4.2.10. 2-Amino-6-phenyl-3H-pyrido[2,3-d]pyrimidin-4-one (**3j**).* Yellow solid; yield: 89%; mp 235 °C; R_f (40% EtOAc/hexane) 0.15; ^{1}H NMR (300 MHz, DMSO-d_6): δ=6.42 (br s, 2H, D_2O exchangeable), 7.41–7.46 (m, 3H, 1H, D_2O exchangeable), 7.68 (d, J=7.2 Hz, 1H), 7.76 (d, J=7.2 Hz, 1H), 8.29 (s, 1H), 8.71 (d, J=5.4 Hz, 1H), 8.99 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=127.0, 128.0, 128.6, 128.8, 129.0, 129.3, 134.8, 135.2, 135.7, 136.3, 168.4; IR (KBr, cm^{-1}): 1654, 3401. Anal. Calcd for $C_{13}H_{10}N_4O$: C, 65.54; H, 4.23; N, 23.52. Found: C, 65.71; H, 4.19; N, 23.45.

*4.2.11. 1H-Pyrimido[4,5-b]quinoline-2,4-dione (**4a**).* Green solid; yield: 79%; mp 225 °C; R_f (10% EtOAc/hexane) 0.40; ^{1}H NMR (300 MHz, DMSO-d_6): δ=7.32–7.44 (m, 2H), 7.72–7.85 (m, 3H, 1H, D_2O exchangeable), 8.83 (s, 1H), 12.52 (s, 1H, D_2O exchangeable); ^{13}C NMR (DMSO-d_6, 75 MHz,): δ=95.4, 122.0, 122.7, 124.5, 126.4, 134.5, 142.7, 143.6, 157.6, 170.4, 179.4; IR (KBr, cm^{-1}): 1656, 3321. Anal. Calcd for $C_{11}H_7N_3O_2$: C, 61.97; H, 3.31; N, 19.71. Found: C, 62.15; H, 3.28; N, 19.63.

*4.2.12. 8-Methoxy-1H-pyrimido[4,5-b]quinoline-2,4-dione (**4b**).* Yellow solid; yield: 82%; mp 278–280 °C; R_f (70% EtOAc/hexane) 0.12; ^{1}H NMR (300 MHz, DMSO-d_6): δ=3.78 (s, 3H), 6.80–6.91 (m, 3H, 1H, D_2O exchangeable), 7.68 (s, 1H), 8.63 (s, 1H), 12.29 (s, 1H, D_2O exchangeable); ^{13}C NMR (DMSO-d_6, 75 MHz,): δ=55.7, 97.9, 101.9, 112.2, 112.6, 131.1, 137.4, 142.4, 149.0, 159.1, 163.8, 184.3; IR (KBr, cm^{-1}): 1651. Anal. Calcd for $C_{12}H_9N_3O_3$: C, 59.26; H, 3.73; N, 17.28. Found: C, 59.31; H, 3.78; N, 17.22.

*4.2.13. 4-Amino-1H-pyrimido[4,5-b]quinoline-2-thione (**5a**).* Yellow solid; yield: 62%; mp 220 °C; R_f (4% MeOH/Chloroform) 0.23; ^{1}H NMR (300 MHz, DMSO-d_6): δ=7.12 (m, 1H), 7.86–7.96 (m, 3H), 8.70

(s, 2H, D_2O exchangeable), 9.17 (s, 1H), 12.56 (s, 1H, D_2O exchangeable); ^{13}C NMR (75 MHz, $CDCl_3$): δ=126.6, 127.2, 128.1, 128.3, 128.5, 129.0, 129.5, 135.3, 140.3, 149.3, 155.4; IR (KBr, cm^{-1}): 1614, 3386. Anal. Calcd for $C_{11}H_8N_4S$: C, 57.88; H, 3.53; N, 24.54. Found: C, 57.65; H, 3.56; N, 24.71.

*4.2.14. 4-Amino-8-methoxy-1H-pyrimido[4,5-b]quinoline-2-thione (**5a′**).* Yellow solid; yield: 72%; mp 240 °C; R_f (4% MeOH/Chloroform) 0.21; ^1H NMR (300 MHz, DMSO-d_6): δ=3.94 (s, 3H), 7.15–7.19 (m, 2H), 7.80 (d, J=9.0 Hz, 1H), 8.58 (br s, 2H, D_2O exchangeable), 9.03 (s, 1H), 12.48 (br s, 1H, D_2O exchangeable); ^{13}C NMR (75 MHz, $CDCl_3$): δ=55.8, 103.8, 105.2, 118.9, 120.2, 130.7, 135.0, 149.6, 151.9, 159.1, 163.5, 183.9; IR (KBr, cm^{-1}): 1615. Anal. Calcd for $C_{12}H_{10}N_4OS$: C, 55.80; H, 3.90; N, 21.69. Found: C, 55.68; H, 3.98; N, 21.75.

*4.2.15. 2-Benzylsulfanyl-pyrimido[4,5-b]quinolin-4-ylamine (**5b**).* Yellow solid; yield: 79%; mp 278 °C; R_f (40% EtOAc/hexane) 0.30; ^1H NMR (300 MHz, DMSO-d_6): δ=4.65 (s, 2H), 7.24–7.34 (m, 5H, 2H D_2O exchangeable), 7.52–7.54 (m, 2H), 7.65 (t, J=7.5 Hz, 1H), 7.91–8.05 (m, 3H), 8.97 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ=43.8, 113.9, 113.9, 114.0, 121.3, 122.0, 125.2, 126.7, 127.4, 128.3, 128.6, 131.4, 138.0, 139.8, 148.4, 154.7; IR (KBr, cm^{-1}): 1644, 3448. Anal. Calcd for $C_{18}H_{14}N_4S$: C, 67.90; H, 4.43; N, 17.60. Found: C, 67.72; H, 4.49; N, 17.73.

*4.2.16. 4-Amino-pyrimido[4,5-b]quinolin-2-yl-cyanamide (**5c**).* Green solid; yield: 70%; mp 232 °C; R_f (10% EtOAc/hexane) 0.40; ^1H NMR (300 MHz, DMSO-d_6): δ=6.90 (br s, 3H, D_2O exchangeable), 7.22 (t, J=7.2 Hz, 1H), 7.54–7.61 (m, 2H), 7.77 (d, J=7.8 Hz, 1H) 8.14 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=95.4, 116.5, 121.3, 126.7, 126.9, 127.4, 128.0, 128.6, 135.0, 138.6, 143.2, 153.3; IR (KBr, cm^{-1}): 3423, 2233. Anal. Calcd for $C_{12}H_8N_6$: C, 61.01; H, 3.41; N, 35.57. Found: C, 61.17; H, 3.48; N, 35.43.

*4.2.17. Pyrimido[4,5-b]quinolin-2-ylamine (**5f**).* Yellow solid; yield: 80%; mp 298 °C; R_f (40% EtOAc/hexane) 0.60; ^1H NMR (300 MHz, DMSO-d_6): δ=6.57 (br s, 2H, D_2O exchangeable), 7.36 (t, J=7.2 Hz, 1H), 7.70–7.83 (m, 3H), 9.05 (s, 1H,); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=126.6, 128.1, 128.3, 128.5, 129.0, 129.5, 133.2, 135.3, 140.3, 149.3, 155.4; IR (KBr, cm^{-1}): 1639, 3447. Anal. Calcd for $C_{11}H_8N_4$: C, 67.34; H, 4.11; N, 28.55. Found: C, 67.42; H, 4.08; N, 28.64.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2011.09.032.

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