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Synthesis of Pyrimidine Fused Quinolines by Ligand-Free Copper-Catalyzed Domino Reactions

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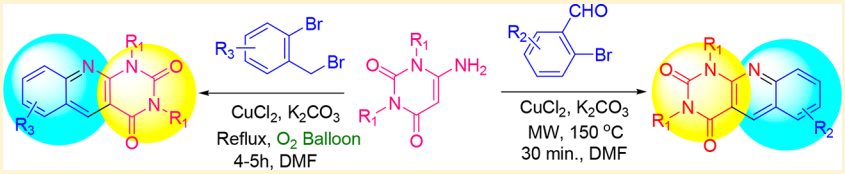
Supporting Information



ABSTRACT: Herein, we report two novel methods for the synthesis of pyrimidine fused quinolines using a one-pot C−C and C−N bond forming strategy from the reaction of 6-aminouracils with 2-bromobenzaldehydes or 2-bromobenzyl bromide derivatives in the presence of 10 mol % $CuCl_2$ without using any ligand. The reaction of 2-bromobenzaldehyde or its derivatives with 6-aminouracils in the presence of K_2CO_3 as base and a catalytic amount of $CuCl_2$ in DMF medium under microwave heating conditions provides corresponding pyrimidine fused quinoline derivatives in good yields within 30 min. Alternatively, pyrimidine fused quinoline derivatives have been synthesized from the reaction of 2-bromobenzyl bromides with 6-aminouracil derivatives in the presence of molecular oxygen, $CuCl_2$ (10 mol %), and K_2CO_3 as base in DMF under reflux conditions. Structures of all the products were unambiguously confirmed by spectroscopic techniques and by recording single crystal XRD of **3a**.

INTRODUCTION

Synthesis of fused heterocycles has remained a promising area in organic synthesis due to their abundance in natural as well as synthetic molecules with diverse applications in pharmaceuticals, chemosensors, polymers and as ligands.[1] Specially fused N-heterocycles, having privileged motifs like pyrimidine and quinolines, are found in many drugs and bioactive natural products.[2]

Hybrid molecules having a pyrimidine ring fused with quinoline as shown in Figure 1 are also known as deazaflavins or 5-deazaisoalloxazines. The N-5 analogues of these molecules are known as flavins and available in biomolecules riboflavin and flavin adenine dinucleotide (FAD). Considering their structural resemblance with flavins, they are very useful molecules in medicinal chemistry. A wide range of medicinal properties such as antibacterial,[3] antifungal,[3] anticancer,[4] analgesic,[5] antimalarial,[6] antitumor,[7] anti-inflammatory,[5] antiviral,[8] and antioxidant[5] are known for pyrimidine fused quinoline derivatives. Apart from their biological activities, Reetz et al. have explored deazaflavins as mediators in cytochrome P450-BM3 catalyzed light driven C-H activating hydroxylation.[9]

Considering their wide applications, design and development of novel and efficient routes for the synthesis of pyrimidine fused quinoline derivatives has remained an important topic. Langer et al. reported a three step synthesis of 5-polyfluoroalkyl pyrimidine fused quinolines starting from 6-chloro-1,3-dimethyluracil.[10] Although a plethora of methods are known for the construction of a quinoline moiety by either classical[11] or modern methods,[12] still very limited one-pot single step methods are available in the literature for the synthesis of pyrimidine fused quinolines. Most of the known methods employ either multistep reaction, harsh reaction conditions or expensive catalyst, long reaction time, limited substrate scope, or poor yields, etc. Considering the limitations of the existing methods, as well as the wide applications of pyrimidine fused quinolines, and in continuation of our work on the synthesis of pyrimidine fused heterocycles,[13] we shifted our attention to develop an efficient and cost-effective one-pot domino method for the synthesis of a series of novel pyrimidine fused quinolines from the readily available substrates and catalyst.

Copper catalysis is a very popular, cost-effective, and efficient strategy for the synthesis of diverse heterocycles.[14] Very recently, Xie and Su et al. have reported a copper(II) catalyzed synthesis of chromene fused quinolines using DMF as a one-carbon source.[15] Guo and Fossey et al. have demonstrated a $Cu(OTf)_2$ catalyzed synthesis of purin fused polycycles.[16] Considering the virtue of copper catalysis, recently copper-catalyzed cross-coupling reactions have been explored for the construction of diverse fused N-heterocycles including quinoline derivatives.[17] However, to the best of our knowledge, copper-catalyzed pyrimidine fused quinolines have not yet been reported. 2-Halobenzaldehydes or their derivatives are very popular starting materials for the synthesis of diverse fused *N*-heterocycles by copper-catalyzed cross-coupling reactions.

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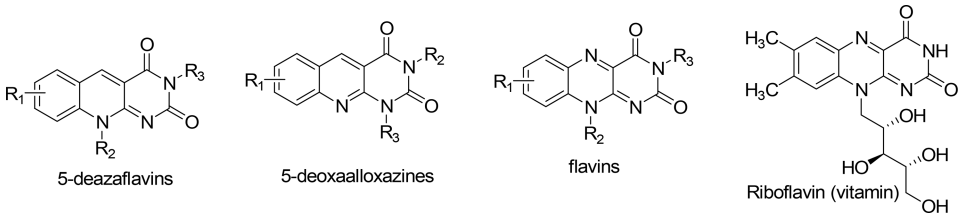
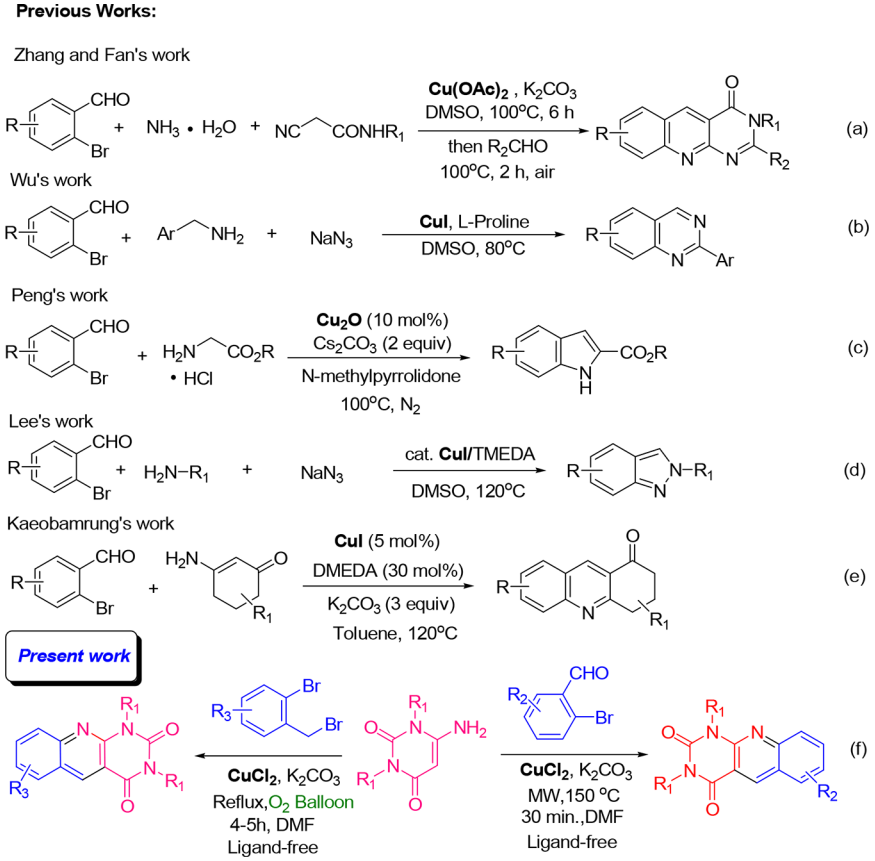


Figure 1. Structures and names of representative fused pyrimidines and their naturally available analogues.

Scheme 1. Comparison of Present Method with Other Known Methods for the Synthesis of Fused N-Heterocycles via Copper-Catalyzed Coupling Reactions of 2-Bromobenzaldehydes



Zhang et al. reported a $Cu(OAc)_2$ catalyzed and K_2CO_3 promoted one-pot multicomponent reactions of 2-bromobenzaldehydes with cyanoacetamides and aqueous ammonia, followed by addition of aldehydes for the synthesis of 2-aminoquinoline-3-carboamides and pyrimido[4,5-*b*]quinolin-4-ones (Scheme 1a).[18] Wu and co-workers have developed a copper(I) iodide catalyzed three-component domino reaction of 2-bromoarylaldehyde, benzylamines, and sodium azide for the synthesis of quinazoline derivatives in the presence of proline as ligand (Scheme 1b).[19] Peng's group reported a copper(I) oxide catalyzed one-pot synthesis of indole-2-carboxylic esters in the presence of cesium carbonate as base and *N*-methylpyrolidone as solvent (Scheme 1c).[20] Lee et al. reported copper(I) iodide catalyzed, one-pot, three-component reactions of 2-bromobenzaldehydes, primary amines, and sodium azide in the presence of TMEDA as ligand and DMSO as solvent for the synthesis of 2*H*-indazoles (Scheme 1d).[21] Very recently, Kaeobamrung et al. have reported copper(I) iodide catalyzed domino reactions of enaminones and 2-bromo- or 2-iodobenzaldehydes for the synthesis of fused quinoline derivatives in the presence of DMEDA as ligand and toluene as solvent (Scheme 1e).[22] In this paper, we are reporting two novel methods for the synthesis of pyrimidine fused quinolines from the reaction of 6-aminouracils with 2-bromobenzaldehydes or 2-bromobenzyl bromide derivatives using copper(II) catalyzed Ullman type domino reactions generating two new bonds in one pot without using any ligand as shown in Scheme 1f.

RESULTS AND DISCUSSION

Recently, we have explored 6-aminouracil derivatives for the one-pot synthesis of diverse pyrimidine fused heterocycles.[13] In continuation of our works on development of one-pot, time and cost-effective methodologies for the synthesis of fused heterocycles, initially we started our investigation for the synthesis of pyrimidine fused quinolines from the reaction of 2-bromobenzaldehyde (**1a**) with 6-amino-1,3-dimethyluracil (**2a**) as model reaction. When a 1:1 mixture of these starting materials was refluxed in the presence of K_2CO_3 (2 equiv) in DMF as solvent for 12 h, only a trace amount of fused

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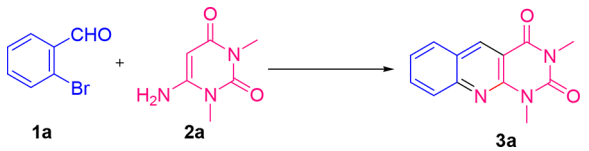
pyrimidines **3a** was observed (Table 1, entry 1). Next, the same combination was tried under microwave heating at 150 °C in the presence of K_2CO_3. In this case, also only 5% of the desired product **3a** was observed (Table 1, entry 2). Interestingly, when this model reaction was tried in the presence of 10 mol % of CuI as catalyst along with 2 equiv of K_2CO_3 as base in DMF medium under microwave heating at 150 °C under sealed conditions for 30 min, the corresponding fused quinoline **3a** was obtained in 55% yield (Table 1, entry 3). The product was fully characterized by IR, ^{1}H, and ^{13}C NMR as well as by HRMS. After having this encouraging result, next we wanted to optimize the yield by screening various copper catalysts such as CuBr, $CuBr_2$, CuCl, $CuCl_2$, CuO, Cu_2O, $CuSO_4.5H_2O$, $Cu(OTf)_2$, and $Cu(OAc)_2$, keeping base and solvent constants under similar microwave conditions, and the results are summarized in Table 1 (entries 4–12). Among all the screened catalysts, $CuCl_2$ was found as the best catalyst in terms of yield obtained (81%) of the product (Table 1, entry 7). To screen the effect of solvent, the model reaction was performed in various solvents like CH_3CN, DMSO, and H_2O (Table 1, entries 13–15); however, in all of these screened solvents, yields obtained were found lower as compared to DMF. We also tried to find the best base for this transformation and various bases like Cs_2CO_3, NaOH, $KHCO_3$, $NaHCO_3$, Et_3N, and Na_2CO_3 were screened in the presence of $CuCl_2$ as catalyst (Table 1, entries 16–21), and the observed results were not encouraging. Interestingly, reaction without using any base in the presence of $CuCl_2$ provided only 10% yield of the product **3a** (Table 1, entry 22). We also performed the model reaction in the presence of 20 mol % PPh_3 as well as in the presence of 1,10-phenanthroline as ligands and did not observe any advantage of using ligands (Table 1, entries 23 and 24). After having the best result using microwave heating under sealed conditions at 150 °C (74–75 W), for 30 min in the presence of $CuCl_2$ (10 mol %) and 2 equiv of K_2CO_3 in DMF as solvent (Table 1, entry 7), we also wanted to check if the same reaction can be performed using a sealed tube and conventional heating. Therefore, next we tried the model reaction in a sealed tube keeping the temperature at 120 °C for 15 h without changing any other parameters, and the corresponding fused quinoline **3a** was obtained in 63%. Interestingly, when the same reaction was performed at 150 °C in a sealed tube, within 12 h a better yield (75%) was obtained (Table 1, entry 26). From these observations, it is evident that pyrimidine fused quinolines can be synthesized by either conventional or microwave heating under sealed conditions. However, the best yield in this reaction was obtained in microwave heating. Thus, the reaction in the presence of 10 mol % $CuCl_2$ along with 2 equiv of K_2CO_3 in DMF under sealed and microwave heating at 150 °C (74–75 W) for 30 min was considered as the optimum reaction conditions.

Table 1. Screening of the Reaction Conditions[a]



entry	catalyst	base	solvent	yield (%)[b]
1.		K_2CO_3	DMF	trace[c]
2		K_2CO_3	DMF	5
3	CuI	K_2CO_3	DMF	55
4	CuBr	K_2CO_3	DMF	43
5	$CuBr_2$	K_2CO_3	DMF	58
6	CuCl	K_2CO_3	DMF	48
7	**$CuCl_2$**	**K_2CO_3**	**DMF**	**81**
8	CuO	K_2CO_3	DMF	34
9	Cu_2O	K_2CO_3	DMF	64
10	$CuSO_4{\cdot}5H_2O$	K_2CO_3	DMF	59
11	$Cu(OTf)_2$	K_2CO_3	DMF	45
12	$Cu(OAc)_2$	K_2CO_3	DMF	61
13	$CuCl_2$	K_2CO_3	CH_3CN	50
14	$CuCl_2$	K_2CO_3	DMSO	48
15	$CuCl_2$	K_2CO_3	H_2O	30
16	$CuCl_2$	Cs_2CO_3	DMF	64
17	$CuCl_2$	NaOH	DMF	63
18	$CuCl_2$	$NaHCO_3$	DMF	18
19	$CuCl_2$	$KHCO_3$	DMF	20
20	$CuCl_2$	Et_3N	DMF	12
21	$CuCl_2$	Na_2CO_3	DMF	67
22	$CuCl_2$		DMF	10
23	$CuCl_2$ + PPh_3 (20 mol %)	K_2CO_3	DMF	76
24	$CuCl_2$ + 1,10-phenanthroline (20 mol %)	K_2CO_3	DMF	77
25	$CuCl_2$	K_2CO_3	DMF	63[d]
26	$CuCl_2$	K_2CO_3	DMF	75[e]

[a]Reaction conditions: 2-Bromobenzaldehyde (0.5 mmol), 6-amino-1,3-dimethyluracil (0.5 mmol), K_2CO_3 (2.0 equiv), catalyst (10 mol %). [b]Isolated yield. [c]Refluxed for 12 h. Except entries 1, 25, and 26, all reactions were performed under microwave (74–75 W, monitored by IR temperature sensor) heating for 30 min. [d]Heating was performed using silicon oil bath for 15 h in sealed tube at 120 °C. [e]Heating was performed using silicon oil bath for 12 h in sealed tube at 150 °C.

After having the optimized reaction conditions in hand, then we explored the scope and generality of this method by varying 2-bromobenzaldehydes and 6-aminouracils. The results are summarized in Table 2. A wide variety of 2-bromobenzaldehyde derivatives having both electron donating and withdrawing substituents at different positions of the aryl ring such as $-CH_3$, $-OCH_3$, $-CN$, $-NO_2$, $-F$, $-Br$, $-CF_3$ were tested with 6-amino-1,3-dimethyluracil, and the corresponding pyrimidine fused quinoline derivatives were obtained in moderate to good yields (Table 2, **3a–3o**). It was observed that 2-bromobenzaldehydes having electron donating substituents provided better yields than that of having electron withdrawing substituents. Heterocyclic aldehyde such as 2-bromo-3-pyridinecarboxaldehyde was also found suitable for this strategy, and the corresponding product **3p** was obtained in 62% yield.

Similar to 6-amino-1,3-dimethyluracil, 6-amino-1,3-dipropyluracil was also found suitable for this one-pot C–C and C–N bond forming reactions under the similar reaction conditions, and the corresponding fused molecules **3q–3t** were found in good yields. It is noteworthy to mention that, in these reactions, solvent plays a very important role. A majority of copper-catalyzed C–N coupling reactions are reported in the presence of ligands. However, in this method, we have not used any additive or ligand. We have observed that, when the reaction is carried out in DMF as solvent even without adding any additive or ligand, Cu(II) catalysts give good results. This may be due to the good coordinating as well as reducing property of DMF.

After having these encouraging results for the synthesis of pyrimidie fused quinolines using 2-bromobenzaldehydes, next

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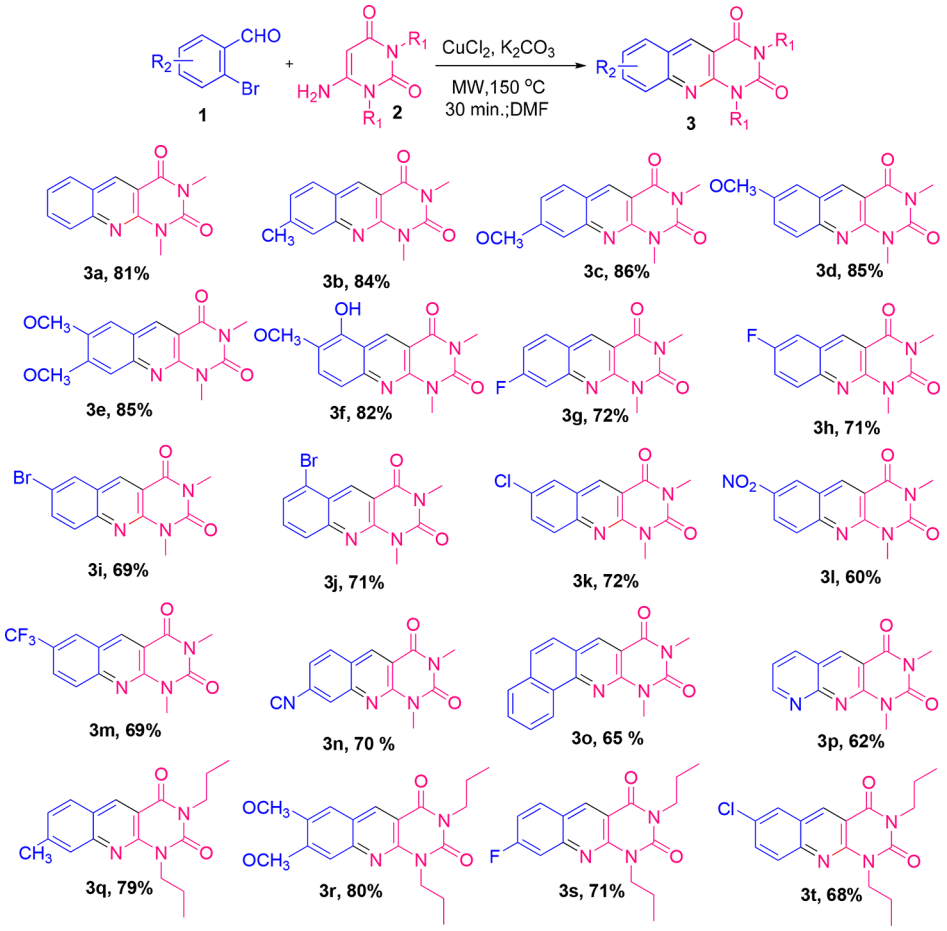
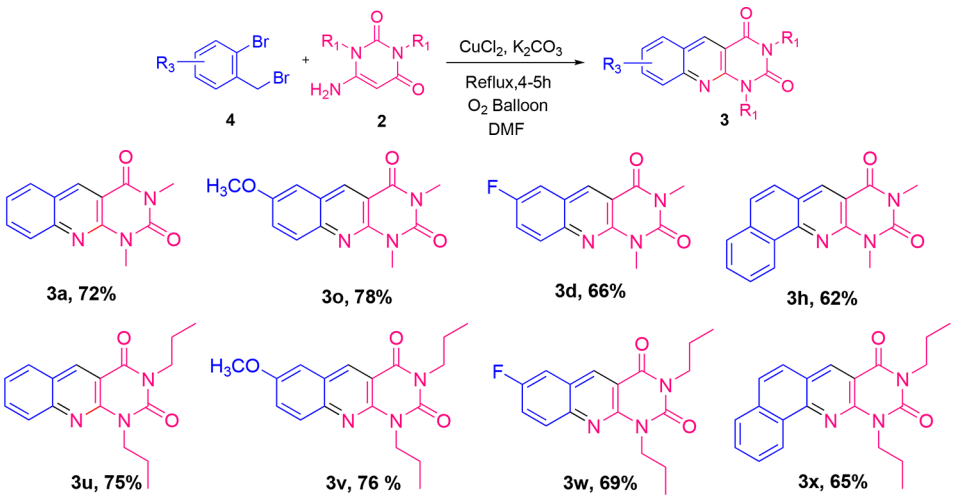
Table 2. Substrate Scope for the Synthesis of Pyrimidine Fused Quinolines[a,b,c]



[a]Conditions: **1** (0.5 mmol), **2** (0.5 mmol), K_2CO_3 (1.0 mmol), and $CuCl_2$ (10-mol %) in DMF (2.0 mL). [b]Isolated yield. [c]Microwave heating was performed at (74−75 W), 150 °C, for 30 min.

Table 3. Copper-Catalyzed Synthesis of Pyrimidine Fused Quinolines from the Reaction of 2-Bromobenzyl Bromides and 6-Aminouracils[a]



[a]Conditions: **1** (1.0 mmol), **2** (1.0 mmol), K_2CO_3 (2.0 mmol), and $CuCl_2$ (10-mol %) in DMF (5.0 mL) under O_2 balloon at reflux (150 °C) for 4−5 h. [b]Isolated yield.

we wanted to develop an alternative method where we can access the same products using 2-bromobenzyl bromides as the starting materials. When we tried to do the reaction of 2-bromobenzyl bromide with 6-amino-1,3-dimethyluracil using the similar procedure used in Table 2, we obtained only 30% yield of corresponding tricyclic product **3a**. Then we tried to optimize the reaction conditions for this method by changing reaction conditions from microwave heating to reflux

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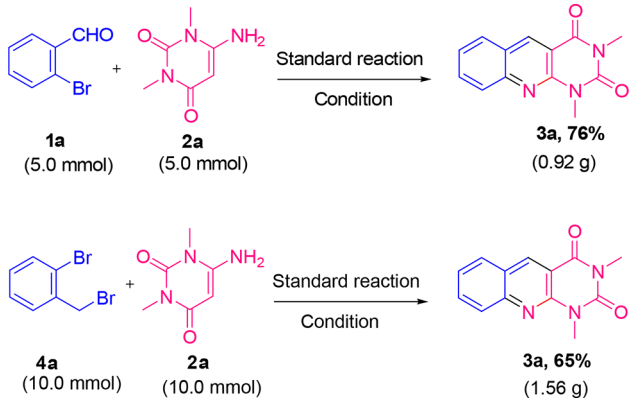
conditions. When the reaction was performed in the presence of 10 mol % $CuCl_2$ and 2 equiv of K_2CO_3 in DMF (5.0 mL) under reflux conditions, within 5 h the corresponding desired product **3a** was obtained in 62% yield. Interestingly, when we performed the reaction in the presence of an oxygen balloon, within 4 h considerably good yield (72%) of the corresponding product was observed. By increasing the reaction time, we did not observe any significant change in yield obtained. Thus, the reaction of benzyl bromides with aminouracil derivatives in the presence of $CuCl_2$ (10 mol %) and K_2CO_3 (2 equiv) and an oxygen balloon in DMF under reflux conditions was considered as optimum reaction conditions. Next, using these optimized reaction conditions and by varying benzyl bromide derivatives, we have prepared some pyrimidine fused quinolines (**3o**, **3d**, and **3h**), and the results are summarized in Table 3. Likewise, 6-amino-1,3-dipropyluracils were reacted with different 2-bromobenzyl bromide derivatives, and the corresponding fused quinolines (Table 3, **3u**−**3x**) were obtained in satisfactory to good yields.

To demonstrate the synthetic utility of this developed protocol, next we tried to scale up the synthesis of pyridine fused quinoline (**3a**) by performing the reaction of 2-bromobenzaldehyde **1a** (5.0 mmol) and 1,3-dimethyl-6-amino-uracil **2a** (5.0 mmol) under the standard reaction conditions in 10.0 mL of DMF in a 25 mL microwave vial (Scheme 2). This

Scheme 2. Gram Scale Synthesis of Pyrimidine Fused Quinolines by Both the Methods



transformation proceeded smoothly to afford 0.92 g (76%) yield of the desired product **3a**. Similarly, using conventional heating, the reaction of 2-bromobenzyl bromide **4a** (10.0 mmol) with 1,3-dimethyl-6-aminouracil **2a** (10.0 mmol) provided 1.56 g (65%) of product **3a**.

All the products were fully characterized by IR, ^1H and ^{13}C NMR as well as by HRMS. The structure of the products have also been confirmed by X-ray crystallographic analysis of compound **3a** (see the Supporting Information). Next, to understand the mechanism, we wanted to know the initial step for this domino reaction, from the reaction of 2-bromobenzaldehyde and 6-amino-1,3-dimethyluracil. For this study, we did the control reaction between **1a** and **2a** in the presence of K_2CO_3 (2.0 equiv) and DMF medium without adding any copper catalyst, and the mixture was heated under microwave for 15 min. The reaction can follow either path I (Scheme 3a) to give intermediate $\mathbf{A_1}$ or path II to provide intermediate $\mathbf{B_1}$. After characterization of the product obtained from this control experiment, we found that the obtained product is $\mathbf{B_1}$. Again, when $\mathbf{B_1}$ was subjected to microwave heating in DMF in the presence of 2.0 equiv of K_2CO_3, and 10 mol % $CuCl_2$, within 20 min the corresponding cyclic product **3a** was obtained in 80% yield. We also tried to isolate intermediate $\mathbf{A_1}$ by performing reaction of **1a** and **2a** in DMF in the presence of $CuCl_2$ (10 mol %), K_2CO_3 (2.0 equiv) under the MW heating and stopping the reaction after 5 min. However, in this case, also we could not isolate our expected intermediate $\mathbf{A_1}$. Interestingly, the mass analysis of crude reaction mixture, we found a very low abundant peak corresponding to $\mathbf{A_1}$. Thus, we believe that both the paths are feasible for the formation of **3a**.

Similarly, to know the intermediate involved from the reaction of **4a** and **2a**, we did a control experiment between these two substrates in the presence of K_2CO_3 (2.0 equiv) in DMF without adding any copper catalyst, and the mixture was refluxed at 150 °C for 2 h (Scheme 3b). From this control experiment, the obtained product was found to be $\mathbf{C_1}$ as characterized by NMR and HRMS. Next, $\mathbf{C_1}$ was again refluxed in DMF in the presence of $CuCl_2$ and K_2CO_3 (2.0 equiv) and an oxygen balloon for 3 h, and the desired product **3a** was obtained in 66%. From this study, we believe the reaction follows path I (Scheme 3b) for the formation of **3a** from **4a** and **2a** using our methodology.

CONCLUSION

In conclusion, we have developed two efficient methodologies for the synthesis of pyrimidine fused quinoline derivatives by Cu-catalyzed coupling reaction of 2-bromobenzaldehyde/2-bromobenzyl bromide and 6-aminouracils. The present methods are efficient and versatile methods for the synthesis of diverse pyrimidine fused quinolines. Considering the presence of bioactive quinoline and pyrimidine moiety in all the products, it is expected that these molecules will find applications in organic and medicinal chemistry.

EXPERIMENTAL SECTION

General Information. All reagents and solvents were purchased from commercial suppliers and were used without further purification. Microwave irradiation was carried out with Initiator 2.5 Microwave Synthesizers from Biotage, Uppsala, Sweden. All reactions were monitored by TLC, followed by exposure of the mixtures to UV light and/or an iodine chamber to visualize the reaction spots. Column chromatography was performed using silica gel [ethyl acetate/hexane (in different ratios) solvent system]. FTIR spectra were recorded by ATR mode with the absorption in cm^{-1}. NMR spectra were recorded on a Bruker 400 MHz machine. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in $CDCl_3$ or DMSO-d_6 solvent at 25 °C. Chemical shifts (in ppm) were reported using tetramethylsilane ($\delta = 0$) as an internal standard in $CDCl_3$ ($\delta = 7.26$) or DMSO-d_6 ($\delta = 2.50$) solvent. The following abbreviations were used to define the multiplicities: s = singlet; d = doublet; t = triplet; m = multiplet; dd (doublet of doublets); td (triplet of doublets); brs (broad singlet), coupling constants (J, in Hz). ^{13}C NMR data were recorded in terms of the chemical shift (ppm, scale), using the central peak of $CDCl_3$ (77.0 ppm) or DMSO-d_6 (δ = 39.5 ppm) as the internal standard. HRMS analysis was carried out using a BRUKER Impact HD mass spectrometer (Impact HD UHR-TOF, ESI with positive mode) and Agilent 6520 Q-TOF mass spectrometer. Melting points were recorded using a SRS EZ-Melt automated melting point apparatus by capillary methods without correction.

Experimental Procedures. *Typical Experimental Procedure for the Synthesis of **3a** Using Microwave Heating.* A mixture of 6-amino-1,3-dimethyluracil (0.5 mmol), 2-bromobenzaldehyde (0.5 mmol), and K_2CO_3 (1.0 mmol) in DMF (2.0 mL) was stirred at room temperature for 5−10 min. To this mixture, 10 mol % of $CuCl_2$ catalyst was added. Then the reaction mixture was kept under

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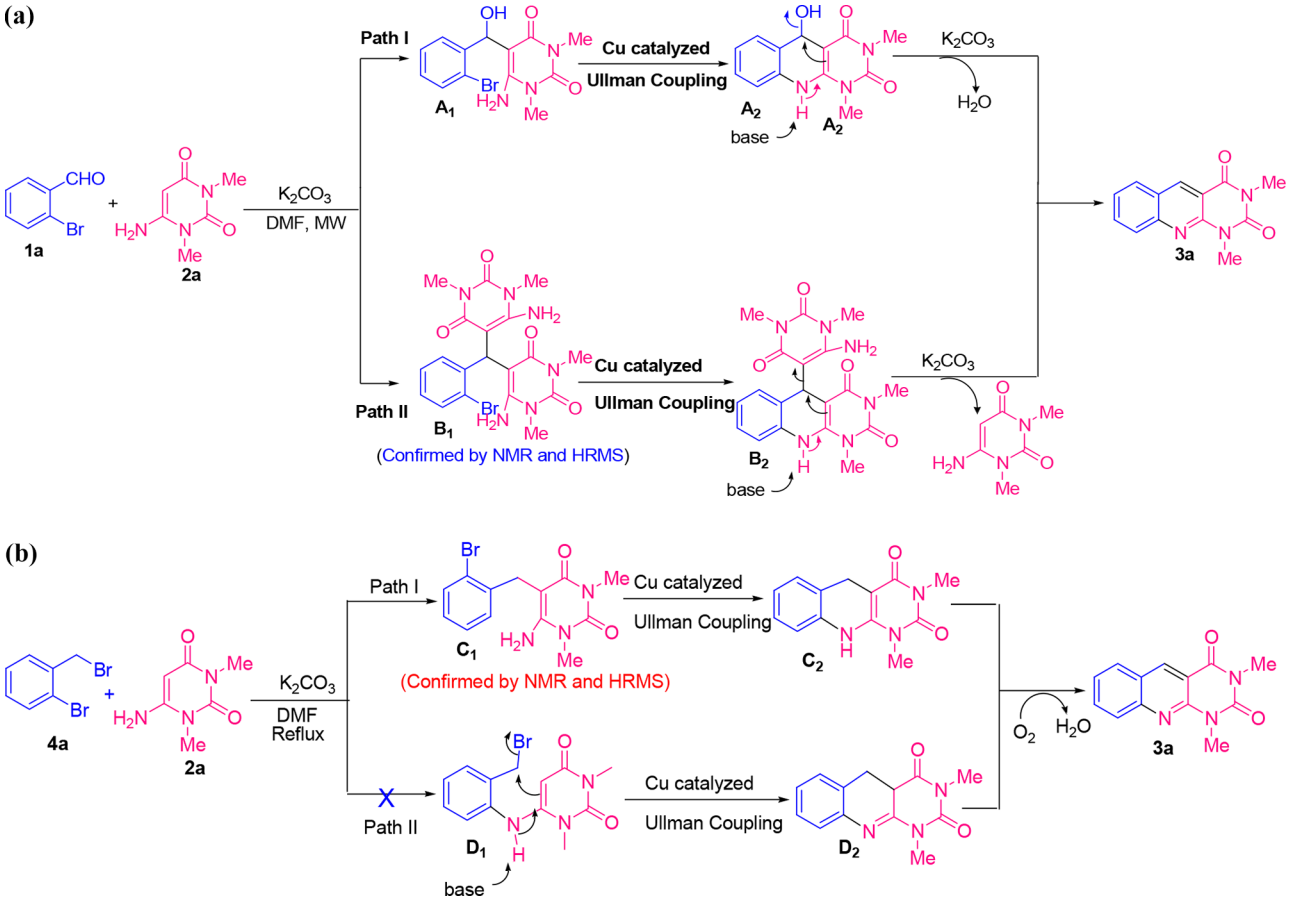
Scheme 3. (a) Proposed Mechanism for the Formation of 3a from 1a and 2a under MW Heating. (b) Proposed Mechanism for the Formation of 3a from 4a and 2a under Reflux Conditions



microwave heating (74−75 W, monitored by IR temperature sensor) under sealed and stirring conditions for 30 min, keeping the temperature at 150 °C. After completion of the reaction, the reaction mixture was cooled to room temperature and poured in ice. Solid product was separated by just filtration and washed with cold water twice. Finally, the pure product was obtained by recrystallization from methanol. Using a similar procedure, all other products were prepared. In some cases, compounds were purified by column chromatography using silica gel and ethyl acetate mixture.

*Typical Experimental Procedure for the Synthesis of **3a** from 2-Bromobenzyl Bromide and 6-Amino-1,3-dimethyluracil Using Conventional Reflux Conditions.* A mixture of 2-bromobenzyl bromide (1.0 mmol), K_2CO_3 (2.0 mmol), 5.0 mL of DMF, and 6-amino 1,3-dimethyluracil (1.0 mmol) was stirred at room temperature for 10 min in a 25 mL round-bottom flask. Then 10 mol % of $CuCl_2$ was added to the above mixture and stirred under reflux conditions for 4−5 h at 150 °C in the presence of an O_2 balloon. After completion of the reaction (monitored by TLC), the mixture was poured in ice. Solid product was separated by just filtration and washed with cold water twice. Finally, the pure product was obtained by recrystallization from methanol or by column chromatography. Using a similar procedure, all other products were prepared in Table 3.

*1,3-Dimethylpyrimido[4,5-b]quinoline-2,4(1H,3H)-dione (**3a**).*[23] Purified by recrystallization from MeOH. Yield 98 mg (81%); white solid; mp 210−211 °C. IR (ATR) 1708, 1654 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 9.01 (s, 1H), 8.00 (d, J = 8.0 Hz, 1H), 7.94 (d, J = 8.0 Hz, 1H), 7.82 (t, J = 8.0 Hz, 1H), 7.52 (t, J = 8.0 Hz, 1H), 3.83 (s, 3H), 3.53 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.6, 151.8, 150.1, 148.6, 140.2, 133.3, 129.4, 128.3, 125.9, 124.9, 111.1, 29.8, 28.7 ppm. HRMS (ESI-TOF): m/z $[M + H]^+$ calcd for $C_{13}H_{12}N_3O_2$ 242.0924; found 242.0923.

*1,3,8-Trimethylpyrimido[4,5-b]quinoline-2,4(1H,3H)-dione (**3b**).* Eluent: hexane/ethyl acetate (4:1). Yield 108 mg (84%); white solid; mp 224−225 °C. IR (ATR) 1701, 1659 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.93 (s, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.77 (s, 1H), 7.34 (d, J = 8.0 Hz, 1H), 3.80 (s, 3H), 3.51 (s, 3H), 2.58 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.7, 151.8, 150.3, 148.7, 144.5, 139.7, 129.0, 128.3, 127.3, 122.9, 110.2, 29.7, 28.6, 22.4 ppm. HRMS (ESI-TOF): m/z $[M + H]^+$ calcd for $C_{14}H_{14}N_3O_2$ 256.1081; found 256.1104.

*8-Methoxy-1,3-dimethylpyrimido[4,5-b]quinoline-2,4(1H,3H)-dione (**3c**).* Eluent: hexane/ethyl acetate (4:1). Yield 117 mg (86%); white solid; mp 258−259 °C. IR (ATR) 1702, 1660 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.87 (s, 1H), 7.80 (d, J = 8.0 Hz, 1H), 7.28 (s, 1H), 7.15 (d, J = 12.0 Hz, 1H), 4.00 (s, 3H), 3.81 (s, 3H), 3.52 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 161.7, 152.4, 151.9, 149.2, 139.4, 130.5, 120.1, 119.5, 108.7, 106.4, 55.9, 29.7, 28.6 ppm. HRMS (ESI-TOF): m/z $[M + H]^+$ calcd for $C_{14}H_{14}N_3O_3$ 272.1030; found 272.1057.

*7-Methoxy-1,3-dimethylpyrimido[4,5-b]quinoline-2,4(1H,3H)-dione (**3d**).* Eluent: hexane/ethyl acetate (5:1). Yield 116 mg (85%); white solid; mp 260−261 °C. IR (ATR) 1701, 1653 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.91 (s, 1H), 7.91 (d, J = 8.0 Hz, 1H), 7.49 (dd, J = 8.0 Hz & 4.0 Hz, 1H), 7.19 (d, J = 8.0 Hz, 1H), 3.95 (s, 3H), 3.82 (s, 3H), 3.53 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.7, 157.3, 151.8, 147.1, 146.2, 138.4, 129.6, 126.6, 125.7, 111.1, 106.0, 55.8, 29.7, 28.7 ppm. HRMS (ESI-TOF): m/z $[M + H]^+$ calcd for $C_{14}H_{14}N_3O_3$ 272.1030; found 272.1054.

*7,8-Dimethoxy-1,3-dimethylpyrimido[4,5-b]quinoline-2,4-(1H,3H)-dione (**3e**).*[23] Purified by recrystallization from MeOH. Yield 128 mg (85%); white solid; mp 280−281 °C. IR (ATR) 1702, 1652 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.77 (s, 1H), 7.29 (s, 1H), 7.11 (s, 1H), 4.08 (s, 3H), 4.02 (s, 3H), 3.79 (s, 3H), 3.50 (s, 3H) ppm.

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^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 154.8, 150.8, 148.5, 146.9, 146.7, 136.3, 119.3, 107.8, 105.8, 105.0, 55.5, 55.3, 28.6, 27.5 ppm. HRMS (ESI-TOF): m/z $[M + H]^+$ calcd for $C_{15}H_{16}N_3O_4$ 302.1135; found 302.1132.

*6-Hydroxy-7-methoxy-1,3-dimethylpyrimido[4,5-b]quinoline-2,4-(1H,3H)-dione (**3f**).* Eluent: hexane/ethyl acetate (4:1). Yield 118 mg (82%); white solid; mp 271−272 °C. IR (ATR) 3061, 1710, 1667 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.27 (s, 1H), 7.67 (d, J = 8.0 Hz, 1H), 7.02 (d, J = 8.0 Hz, 1H), 4.06 (s, 3H), 3.86 (s, 3H), 3.53 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1, 154.4, 151.6, 148.3, 142.5, 140.1, 129.2, 125.1, 113.3, 111.9, 111.8, 56.6, 30.0, 28.8 ppm. HRMS (ESI-TOF): m/z $[M + H]^+$ calcd for $C_{14}H_{14}N_3O_4$ 288.0979; found 288.0955.

*8-Fluoro-1,3-dimethylpyrimido[4,5-b]quinoline-2,4(1H,3H)-dione (**3g**).* Purified by recrystallization from MeOH. Yield 94 mg (72%); white solid; mp 215−216 °C. IR (ATR) 1707, 1660 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (s, 1H), 7.96−7.92 (m, 1H), 7.62 (d, J = 8.0, 1H), 7.33−7.29 (m, 1H), 3.81 (s, 3H), 3.52 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0 and 164.5 (d, $J_{(C\text{-}F)}$ = 254 Hz), 161.4, 151.7, 151.6, and 151.5 (d, $J_{(C\text{-}F)}$ = 13.9 Hz), 149.5, 140.0, 131.8, and 131.7 (d, $J_{(C\text{-}F)}$ = 10.7 Hz), 121.9,116.9 and 116.6 (d, $J_{(C\text{-}F)}$ = 25.6 Hz), 112.4 and 112.2 (d, $J_{(C\text{-}F)}$ = 20.9 Hz), 110.5, 29.8, 28.7 ppm. HRMS (ESI-TOF): m/z $[M + H]^+$ calcd for $C_{13}H_{11}FN_3O_2$ 260.0830; found 260.0828.

*7-Fluoro-1,3-dimethylpyrimido[4,5-b]quinoline-2,4(1H,3H)-dione (**3h**).* Purified by recrystallization from MeOH. Yield 92 mg (71%); white solid; mp 232−233 °C. IR (ATR) 1716, 1657 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.96 (s, 1H), 8.02−7.99 (m, 1H), 7.63−7.55 (m, 2H), 3.82 (s, 3H), 3.53 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 161.1, and 158.6 (d, $J_{(C\text{-}F)}$= 247 Hz), 151.7, 148.2, 147.1, 139.5, and 139.4 (d, $J_{(C\text{-}F)}$= 5.6 Hz), 130.7 and 130.6 (d, $J_{(C\text{-}F)}$= 8.8 Hz), 125.2 and 125.1 (d, $J_{(C\text{-}F)}$= 10 Hz), 123.7 and 123.5 (d, $J_{(C\text{-}F)}$= 25 Hz), 112.2 and 112.0 (d, $J_{(C\text{-}F)}$= 21.8 Hz), 111.7, 29.8, 28.7 ppm. HRMS (ESI-TOF): m/z $[M + H]^+$ calcd for $C_{13}H_{11}FN_3O_2$ 260.0830; found 260.0827.

*7-Bromo-1,3-dimethylpyrimido[4,5-b]quinoline-2,4(1H,3H)-dione (**3i**).* Eluent: hexane/ethyl acetate (3:1). Yield 110 mg (69%); white solid; mp 232−233 °C. IR (ATR) 1712, 1656 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.00 (s, 1H), 8.50 (s, 1H), 8.20 (d, J = 8.0 Hz, 1H), 7.99 (d, J = 8.0 Hz, 1H), 3.65 (s, 3H), 3.36 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.6, 147.5, 138.8, 138.4, 136.5, 135.9, 131.4, 129.7, 129.5, 125.6, 117.9, 29.8, 28.7 ppm. HRMS (ESI-TOF): m/z $[M + H]^+$ calcd for $C_{13}H_{11}BrN_3O_2$ 320.0029; found 320.0027.

*6-Bromo-1,3-dimethylpyrimido[4,5-b]quinoline-2,4(1H,3H)-dione (**3j**).* Eluent: hexane/ethyl acetate (2:1). Yield 114 mg (71%); white solid; mp 240−241 °C. IR (ATR) 1710, 1657 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.00 (s, 1H), 7.97−7.92 (m, 2H), 7.80 (t, J = 8.0 Hz, 1H), 3.66 (s, 3H), 3.30 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.9, 151.5, 150.1, 149.7, 138.1, 134.2, 129.9, 128.1, 123.8, 122.8, 112.8, 29.9, 28.7 ppm. HRMS (ESI-TOF): m/z $[M + H]^+$ calcd for $C_{13}H_{11}BrN_3O_2$ 320.0029; found 320.0027.

*7-Chloro-1,3-dimethylpyrimido[4,5-b]quinoline-2,4(1H,3H)-dione (**3k**).* Eluent: hexane/ethyl acetate (5:1). Yield 99 mg (72%); white solid; mp 271−272 °C. IR (ATR) 1716, 1657 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (s, 1H), 7.96−7.91 (m, 2H), 7.75 (dd, J = 8.0 Hz & 4.0 Hz, 1H), 3.82 (s, 3H), 3.53 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 151.6, 148.8, 148.5, 139.2, 134.1, 131.6, 129.9, 127.7, 125.4, 111.8, 29.8, 28.7 ppm. HRMS (ESI-TOF): m/z $[M + H]^+$ calcd for $C_{13}H_{11}ClN_3O_2$ 276.0534; found 276.0533.

*1,3-Dimethyl-7-nitropyrimido[4,5-b]quinoline-2,4(1H,3H)-dione (**3l**).* Eluent: hexane/ethyl acetate (3:1). Yield 86 mg (60%); white solid; mp 300−301 °C. IR (ATR) 1716, 1666, 1577, 1347 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (s, 1H), 8.50 (s, 1H), 8.41 (s, 1H), 7.89 (s, 1H), 3.95 (s, 3H), 3.62 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.9, 150.6, 147.4, 139.1, 132.2, 130.8, 126.0, 125.5, 117.5, 114.7, 113.0, 28.8, 27.6 ppm. HRMS (ESI-TOF): m/z $[M + H]^+$ calcd for $C_{13}H_{11}N_4O_4$ 287.0775; found 287.0796.

*1,3-Dimethyl-7-(trifluoromethyl)pyrimido[4,5-b]quinoline-2,4-(1H,3H)-dione (**3m**).* Eluent: hexane/ethyl acetate (5:1). Yield 107 mg (69%); white solid; mp 228−229 °C. IR (ATR) 1716, 1682 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.11 (s, 1H), 8.26 (s, 1H), 8.11 (d, J = 8.0 Hz, 1H), 7.98 (d, J = 8.0 Hz, 1H), 3.85 (s, 3H), 3.55 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 158.8, 153.8, 151.5, 151.0, 150.1, 141.0, 129.4, 128.7 (q, $J_{(C\text{-}F)}$ = 3.0 Hz), 127.23 (q, $J_{(C\text{-}F)}$ = 4.0 Hz), 123.8 (q, $J_{(C\text{-}F)}$ = 271.0 Hz), 112.1, 29.9, 28.8 ppm. HRMS (ESI-TOF): m/z $[M + H]^+$ calcd for $C_{14}H_{11}F_3N_3O_2$ 310.0798; found 310.0796.

*1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimido[4,5-b]-quinoline-8-carbonitrile (**3n**).* Eluent: hexane/ethyl acetate (3:1). Yield 93 mg (70%); white solid; mp 258−259 °C. IR (ATR) 2230, 1716, 1680 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.26 (s, 1H), 8.51 (s, 1H), 8.43 (d, J = 8.0 Hz, 1H), 7.91 (s, 1H), 3.90 (s, 3H), 3.66 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.8, 150.6, 149.4, 147.3, 139.1, 132.2, 130.8, 126.0, 125.5, 117.5, 114.7, 113.0, 28.8, 27.6 ppm. HRMS (ESI-TOF): m/z $[M + H]^+$ calcd for $C_{14}H_{11}N_4O_2$ 267.0877; found 267.0876.

*9,11-Dimethylbenzo[h]pyrimido[4,5-b]quinoline-8,10(9H,11H)-dione (**3o**).* Eluent: hexane/ethyl acetate (4:1). Yield 95 mg (65%); white solid; mp 295−296 °C. IR (ATR) 1701, 1653 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.15 (d, J = 8.0 Hz, 1H), 8.91(s, 1H), 7.90 (d, J = 8.0 Hz, 1H), 7.77−7.69 (m, 4H), 3.92 (s, 3H), 3.54 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.6, 151.8, 149.3, 148.4, 138.7, 135.3, 130.4, 130.0, 128.2, 127.3, 127.1, 125.6, 125.4, 122.7, 110.4, 29.8, 28.7 ppm. HRMS (ESI-TOF): m/z $[M + H]^+$ calcd for $C_{17}H_{14}N_3O_2$ 292.1081; found 292.1078.

*1,3-Dimethylpyrimido[4,5-b][1,8]naphthyridine-2,4(1H,3H)-dione (**3p**).*[23] Eluent: hexane/ethyl acetate (3:1). Yield 75 mg (62%); white solid; mp 265−266 °C. IR (ATR) 1715, 1670 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.18 (s, 1H), 9.06 (s, 1H), 8.33 (d, J = 8.0, 1H), 7.52−7.49 (m, 1H), 3.89 (s, 3H), 3.54 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 157.3, 157.1, 151.5, 151.4, 141.7, 138.6, 121.8, 119.4, 112.2, 30.3, 28.8 ppm. HRMS (ESI-TOF): m/z $[M + H]^+$ calcd for $C_{12}H_{11}N_4O_2$ 243.0877; found 243.0876.

*8-Methyl-1,3-dipropylpyrimido[4,5-b]quinoline-2,4(1H,3H)-dione (**3q**).* Eluent: hexane/ethyl acetate (6:1). Yield 123 mg (79%); white solid; mp 125−126 °C. IR (ATR) 1707, 1652 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.95 (s, 1H), 7.83−7.78 (m, 2H), 7.34 (d, J = 8.0 Hz, 1H), 4.43 (t, J = 8.0 Hz, 2H), 4.08 (t, J = 8.0 Hz, 2H), 2.58 (s, 3H), 1.86−1.82 (m, 2H), 1.78−1.72 (m, 2H), 1.05−0.98 (m, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5, 151.3, 150.3, 148.4, 144.2, 139.7, 128.9, 128.1, 127.4, 122.9, 110.4, 44.2, 43.5, 22.4, 21.4, 21.2, 11.5, 11.4 ppm. HRMS (ESI-TOF): m/z $[M + H]^+$ calcd for $C_{18}H_{22}N_3O_2$ 312.1707; found 312.1733.

*7,8-Dimethoxy-1,3-dipropylpyrimido[4,5-b]quinoline-2,4(1H,3H)-dione (**3r**).* Eluent: hexane/ethyl acetate (6:1). Yield 143 mg (80%); white solid; mp 180−181 °C. IR (ATR) 1696, 1649 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (s, 1H), 7.42 (s, 1H), 7.39 (s, 1H), 4.54 (t, J = 8.0 Hz, 2H), 4.22 (s, 3H), 4.20 (t, J = 8.0 Hz, 2H), 4.16 (s, 3H), 1.99−1.94 (m, 2H), 1.90−1.85 (m, 2H), 1.17 (t, J = 8.0 Hz, 3H), 1.12 (t, J = 8.0 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.7, 155.7, 151.3, 149.5, 148.0, 147.5, 137.3, 120.4, 109.1, 107.0, 106.0, 56.5, 56.3, 44.1, 43.5, 21.4, 21.3, 11.5 ppm. HRMS (ESI-TOF): m/z $[M + H]^+$ calcd for $C_{19}H_{24}N_3O_4$ 358.1761; found 358.1758.

*8-Fluoro-1,3-dipropylpyrimido[4,5-b]quinoline-2,4(1H,3H)-dione (**3s**).* Eluent: hexane/ethyl acetate (5:1). Yield 112 mg (71%); white solid; mp 140−141 °C. IR (ATR) 1704, 1655 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (s, 1H), 7.93 (t, J = 8.0 Hz, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 4.41 (t, J = 8.0 Hz, 2H), 4.07 (t, J = 8.0 Hz, 2H), 1.83−1.73 (m, 4H, CH_2), 1.05−0.97 (m, 6H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9 and 164.4 (d, $J_{(C\text{-}F)}$ = 253.0 Hz), 161.3, 151.64, and 151.50 (d, $J_{(C\text{-}F)}$ = 14.0 Hz), 151.2, 149.2, 140.0, 131.69, and 131.58 (d, $J_{(C\text{-}F)}$ = 11.0 Hz), 121.9, 116.74, and 116.48 (d, $J_{(C\text{-}F)}$ = 26.0 Hz), 112.39 and 112.18 (d, $J_{(C\text{-}F)}$ = 21.0 Hz), 110.66 and 110.64 (d, $J_{(C\text{-}F)}$ = 20.0 Hz), 44.3, 43.6, 21.4, 21.2, 11.49, 11.47 ppm. HRMS (ESI-TOF): m/z $[M + H]^+$ calcd for $C_{17}H_{19}FN_3O_2$ 316.1456; found 316.1455.

*7-Chloro-1,3-dipropylpyrimido[4,5-b]quinoline-2,4(1H,3H)-dione (**3t**).* Eluent: hexane/ethyl acetate (5:1). Yield 113 mg (68%); white solid; mp 186−187 °C. IR (ATR) 1702, 1655 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (s, 1H), 7.94−7.91 (m, 2H), 7.73 (d, J = 8.0 Hz,

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1H), 4.41 (t, J = 8.0 Hz, 2H), 4.07 (t, J = 8.0 Hz, 2H), 1.85−1.80 (m, 2H), 1.77−1.72 (m, 2H), 1.05−0.98 (m, 6H) ppm. ^{13}CNMR (100 MHz, $CDCl_3$) δ 161.1, 151.1, 148.5, 148.4, 139.2, 133.8, 131.4, 129.9, 127.6, 125.3, 111.9, 44.3, 43.7, 21.3, 21.2, 11.5, 11.4 ppm. HRMS (ESI-TOF): m/z $[M + H]^+$ calcd for $C_{17}H_{19}ClN_3O_2$ 332.1160; found 332.1191.

*1,3-Dipropylpyrimido[4,5-b]quinoline-2,4(1H,3H)-dione (**3u**).* Eluent: hexane/ethyl acetate (6:1). Yield 224 mg (75%); white solid; mp 148−149 °C. IR (ATR) 1704, 1655 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99 (s, 1H), 7.97 (d, J = 8.0 Hz, 1H), 7.92 (d, J = 8.0 Hz, 1H), 7.80 (t, J = 8.0 Hz, 1H), 7.50 (t, J = 8.0 Hz, 1H), 4.43 (t, J = 8.0 Hz, 2H), 4.08 (t, J = 8.0 Hz, 2H), 1.87−1.81 (m, 2H), 1.78−1.72 (m, 2H), 1.05−0.98 (m, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4, 151.3, 150.1, 148.3, 140.1, 133.0, 129.3, 128.4, 125.8, 124.8, 111.2, 44.2, 43.6, 21.4, 21.2, 11.5 ppm. HRMS (ESI-TOF): m/z $[M + H]^+$ calcd for $C_{17}H_{20}N_3O_2$ 298.1550; found 298.1547.

*7-Methoxy-1,3-dipropylpyrimido[4,5-b]quinoline-2,4(1H,3H)-dione (**3v**).* Eluent: hexane/ethyl acetate (4:1). Yield 249 mg (76%); white solid; mp 114−115 °C. IR (ATR) 1696, 1652 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (s, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.48−7.45 (m, 1H), 7.16 (s, 1H), 4.41 (t, J = 8.0 Hz, 2H), 4.07 (t, J = 8.0 Hz, 2H), 3.94 (s, 3H), 1.86−1.72 (m, 4H), 1.05−0.98 (m, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4, 157.1, 151.1, 146.7, 146.2, 138.2, 129.6, 126.2, 125.5, 111.1, 105.8, 55.7, 44.0, 43.4, 21.3, 21.1, 11.38, 11.36 ppm. HRMS (ESI-TOF): m/z $[M + H]^+$ calcd for $C_{18}H_{22}N_3O_3$ 328.1656; found 328.1688.

*7-Fluoro-1,3-dipropylpyrimido[4,5-b]quinoline-2,4(1H,3H)-dione (**3w**).* Eluent: hexane/ethyl acetate (6:1). Yield 218 mg (69%); white solid; mp 179−180 °C. IR (ATR) 1702, 1657 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.95 (s, 1H), 7.99 (q, J = 4.0 Hz, 1H), 7.60−7.53 (m, 2H), 4.41 (t, J = 8.0 Hz, 2H), 4.08 (t, J = 8.0 Hz, 2H), 1.88−1.80 (m, 2H), 1.78−1.70 (m, 2H), 1.05−0.98 (m, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2, 161.0, and 158.6 (d, $J_{(C-F)}$= 247 Hz), 151.1, 147.96, and 147.94 (d, $J_{(C-F)}$= 2.0 Hz), 147.2, 139.44, and 139.39 (d, $J_{(C-F)}$= 5.6 Hz), 130.80 and 130.71 (d, $J_{(C-F)}$= 9.0 Hz), 125.19 and 125.09 (d, $J_{(C-F)}$= 10 Hz), 123.53 and 123.27 (d, $J_{(C-F)}$= 26.0 Hz), 112.08 and 111.86 (d, $J_{(C-F)}$= 22.0 Hz), 111.9, 44.3, 43.7, 21.4, 21.2, 11.49, 11.47 ppm. HRMS (ESI-TOF): m/z $[M + H]^+$ calcd for $C_{17}H_{19}FN_3O_2$ 316.1456; found 316.1454.

*9,11-Dipropylbenzo[h]pyrimido[4,5-b]quinoline-8,10(9H,11H)-dione (**3x**).* Eluent: hexane/ethyl acetate (6:1). Yield 226 mg (65%); white solid; mp 183−184 °C. IR (ATR) 1704, 1657 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.12 (d, J = 8.0 Hz, 1H), 8.91 (s, 1H), 7.91−7.89 (m, 1H), 7.77−7.70 (m, 4H), 4.55 (t, J = 8.0 Hz, 2H), 4.10 (t, J = 8.0 Hz, 2H), 1.99−1.90 (m, 2H), 1.83−1.73 (m, 2H), 1.11 (t, J = 8.0 Hz, 3H), 1.02 (t, J = 8.0 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4, 151.3, 149.3, 148.1, 138.7, 135.3, 130.5, 129.9, 128.2, 127.3, 127.0, 125.5, 125.4, 122.7, 110.6, 44.6, 43.6, 21.4, 21.3, 11.7, 11.5 ppm. HRMS (ESI-TOF): m/z $[M + H]^+$ calcd for $C_{21}H_{22}N_3O_2$ 348.1707; found 348.1737.

*General Procedure for the Preparation of **B$_1$**.* A mixture of 2-bromobenzaldehyde (1.0 mmol) and 6-amino-1,3-dimethyluracil (1.0 mmol) in 4.0 mL of DMF in the presence of K_2CO_3 (2.0 mmol) was heated under microwave conditions at 150 °C for 15 min. After completion of the reaction, the mixture was poured to ice water (20.0 mL) and the crude product was separated by just filtration. Finally, compound **B$_1$** was purified by recrystallization from hot methanol.

*5,5′-((2-Bromophenyl)methylene)bis(6-amino-1,3-dimethylpyrimidine-2,4(1H,3H)-dione) (**B$_1$**).* Purified by recrystallization from MeOH. Yield 429 mg (90%); white solid; mp 223−224 °C. IR (ATR) 3374, 1668, 1594 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.47−7.40 (m, 3H), 7.31 (d, J = 8.0 Hz, 1H), 7.19 (t, J = 7.2 Hz, 1H), 7.01 (t, J = 8.0 Hz, 1H), 6.90 (br s, 2H), 5.66 (s, 1H), 3.35 (s, 6H), 3.19 (s, 3H), 3.04 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ 163.0, 162.0, 154.1, 154.0, 150.5, 139.9, 132.8, 129.1, 127.2, 126.7, 122.9, 86.7, 85.5, 36.8, 29.9, 28.2, 27.7 ppm. HRMS (ESI-TOF): m/z $[M + H]^+$ calcd for $C_{19}H_{22}BrN_6O_4$ 477.0880; found 477.0886.

*General Procedure for the Preparation of **C$_1$**.* A mixture of 2-bromobenzyl bromide (1.0 mmol) and 6-amino-1,3-dimethyluracil (1.0 mmol) in 4 mL of DMF in the presence of K_2CO_3 (2.0 mmol) was stirred under reflux conditions for 2 h. After completion of the reaction, the mixture was poured to ice water and the crude product was separated by just filtration. Finally, compound **C$_1$** was purified by column chromatography.

*6-Amino-5-(2-bromobenzyl)-1,3-dimethylpyrimidine-2,4(1H,3H)-dione (**C$_1$**).* Eluent: hexane/ethyl acetate (2:1). Yield 294 mg (85%); white solid; mp 255−256 °C. IR (ATR) 3341, 1635, 1574 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6) δ 7.47 (d, J = 8.0 Hz, 1H), 7.14 (t, J = 8.0 Hz, 1H), 7.02−6.95 (m, 2H), 6.21 (s, 2H), 3.66 (s, 2H), 3.36 (s, 3H), 3.17 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ 161.9, 152.4, 151.0, 138.7, 131.8, 128.0, 127.2, 127.1, 124.5, 82.8, 29.8, 29.6, 27.5 ppm. HRMS (ESI-TOF): m/z $[M + H]^+$ calcd for $C_{13}H_{14}BrN_3O_2Na$ $[M + Na]^+$ 346.0162; found 346.0159.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b03272.

NMR spectra (PDF)

Crystallographic data for **3a** (CIF)

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Notes

The authors declare no competing financial interest.

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