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A $POCl_3$-mediated synthesis of substituted fused azoacridones derivatives

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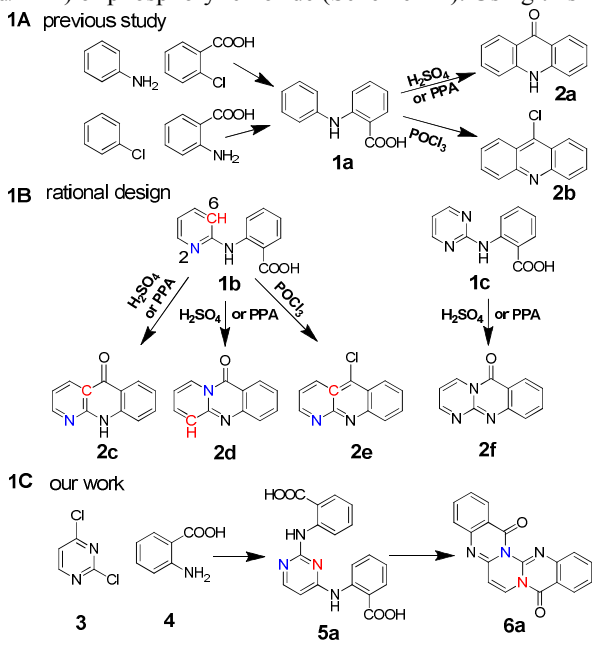
A highly facile and efficient approach to synthesize fused azoacridone derivatives containing various functional groups has been developed. This reaction starts with a substitution reaction between the corresponding benzoic acids andpyrimidines, followed by $POCl_3$-mediated cyclization reaction. The desired pure fused azoacridones were afforded in high yields.

Introduction

Acridone and acridine derivatives are naturally occurring compounds, which have л-conjugated planar structure and exhibit a wide range of physical, physicochemical, biological and pharmacological activities.[1] A large number of acridones and acridines, as well as their synthetic methods have been developed due to their diverse properties.[2] Usually, the Ullman-Jourdan reaction occurs to form diphenylamine-2-carboxylic acids,[3] which are then cyclized to the corresponding acridones or acridines under strong acids (such as H_2SO_4, polyphosphoric acid/PPA) or phosphoryl chloride (Scheme 1A). Using this method we have synthesized a series of acridine derivatives with antitumor activity.[1j,4] Comparison to a huge amount of acridone and acridine derivatives, their azo-derivatives are little reported because of their limited synthetic methods.[5] As replacement of just one carbon atom of carbocylic ring with a heteroatom could lead to great changes in physical as well as chemical properties, such as anthracene and acridine, development of azoacridones, azoacridines and their synthetic methods to broaden the application of acridine derivatives are very important.[1j] Herein, we report a simple efficient route for the synthesis of fused azoacridone derivatives.

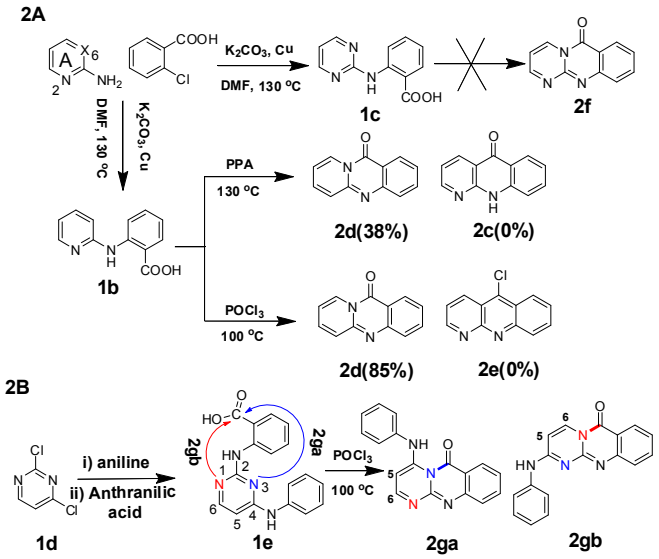


Scheme 1 1A) Traditional synthesis methods for acridine derivatives; 1B) Rational construction of fused azoacridones; 1C) Our synthesis methods for fused azoacridones.

Our work was inspired by the traditional synthetic routes for the preparation of the acridine and acridone derivatives. As shown in Scheme 1A, acridone **2a** and acridine **2b** were obtained by the cyclization reaction between the carboxyl group and C2-positin of the benzene ring. According to the traditional methods, we speculated that the replacement of carbon to nitrogen in the C2-positin could lead to three cyclization products, **2c**, **2d** and **2e**. As nitrogen has higher electron density than carbon, **2d** may be the main product,[6] as seen in Scheme 1B. If both C2 and C6 positions were replaced by nitrogens, one product (**2f**) will be obtained with lower yields or stronger reaction conditions needed because of the reduced electron density of the nitrogen. Furthermore, if 2,2'-(2,4-pyrimidinediyldiimino)-bisbenzoic acid (**5a**) was synthesized,[7] two cyclodehydration reactions would be occurred, and the novel fused azoacridone derivatives **6a** might be yielded.

Results and discussion

Our study began with an examination of the importance of electron density in A ring on the cycloclization reaction. As shown in Scheme 2, compound **1b** with one nitrogen at 2



Scheme 2 Preliminary study of synthesizing azoacridones

position and **1c** with two nitrogens at 2 and 6 positions were firstly obtained,[8] which were then reacted in PPA or $POCl_3$ to try to get the cyclization products. In accordance with our analysis, compound **1b** reacted smoothly in PPA, and the primary product was **2d** in 38% isolated yield, with no **2c** detected. Under the same reaction conditions, compound **1c** showed much lower reactivity and no azoacridone **2f** was detected, which indicated that the electron density in the A ring played an important role in the reaction. When compound **1b** was treated in $POCl_3$,[9] to our surprise, no **2e** or other 9-chloroacridine derivatives were detected, but we were delighted to find that azoacridone compound **2d** was obtained in 85% yield, which inspired us to synthesize azoacridones using $POCl_3$. We then tried to use the reaction conditions to get compound **2f**. Unfortunately, compound **1c** did not react, and no compound **2f** was detected, which might be due to the low electro-density in the pyrimidine ring. If electron-donating groups were introduced to the pyrimidine, the scaffold of compound **2f** may be obtained. The intermediate **1e** with aniline group at 4-position was synthesized from the commercial material 2,4-dichloropyrimidine, which was then cyclized in $POCl_3$. The cyclization reaction occurred and compounds **2ga** and **2gb** might be existed simultaneously (Scheme 2B). Interestingly, we only obtained one product in 93% yield, and the structure of which was characterized by ^{1}H NMR (Figure 1), The signals of hydrogens of C5 and C6 positions of compound

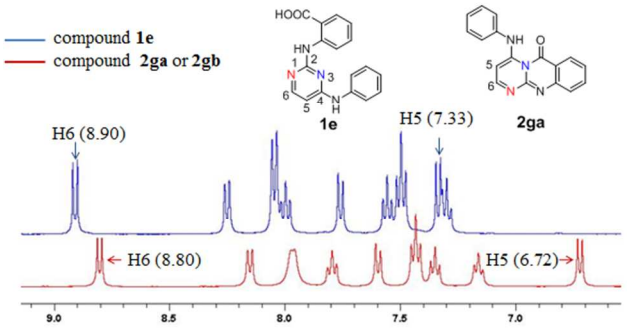


Figure 1 ^{1}H NMR of compounds **1e** and its cyclization product

1e (Scheme 1B) are 7.33 ppm and 8.90 ppm, respectively. If the cyclization occurred between N1 and the carboxy group, the δ value of hydrogen of C6 would have a big change. Compared with ^{1}H NMR spectra of **1e** and its cyclization product, the chemical shift of hydrogen of C5 position reduced greatly from 7.33 ppm to 6.72 ppm, while only small change was seen for δ value of hydrogen of C6 (from 8.90 ppm to 8.80 ppm), which suggested that **2ga** was the only product.

The similar results were also observed when 2-aminobenzoic acid was introduced to the C4-position of pyrimidine (**1f-1j**,

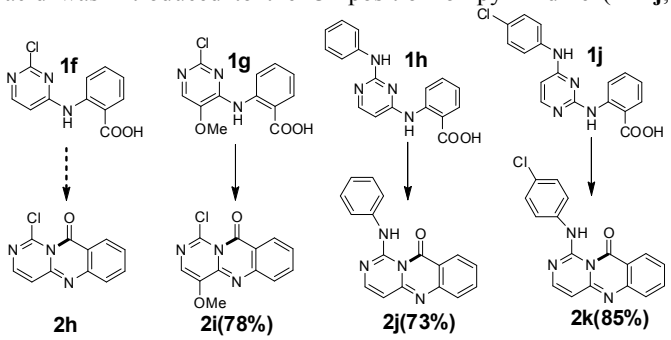


Figure 2 Electronic effects on cyclization reaction

Figure 2). For compound **1f**, no cyclization product **2h** was obtained due to the electro-withdrawing chloro group. However, when electro-donating groups were introduced to the pyrimidine ring, such as **1g** with methoxyl group and **1h-1j** with anilino group, the cyclization reaction occurred and compound **2i-2k** were obtained in good yields. The results indicated that the cyclization reaction was obviously dependent on the substitution pattern of the pyrimidine part.

The above results suggested that whenever 2-aminobenzoic acid was introduced to the C2-position or C4-position of pyrimidine ring, the cyclization reaction selectively occurred at N3-position. If both hydrogens of C2 and C4 positions of pyrimidine were substituted by 2-aminobenzoic acid (**5a**), four cyclization products (Figure 3) might be formed. Under the

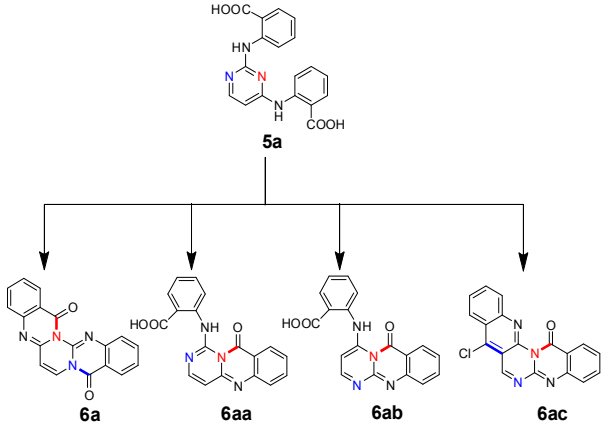
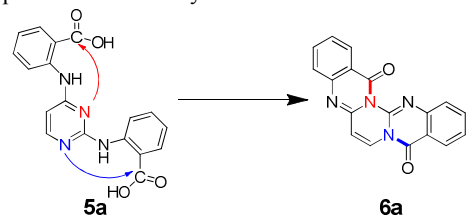


Figure 3 Predicted products from the reaction of **5a**

similar reaction conditions (**5a** in $POCl_3$ was stirred overnight at 100 °C), only one product **6a** was obtained in high yield (85%). To optimize the reaction conditions, the temperature, time, molar ratio between **5a** and $POCl_3$, and solvents were screened. Under these reaction conditions, no compounds **6aa-6ac** were detected. As shown in Table 1, the yield of **6a** decreased with temperature decreased and 100 °C was found to be suitable (Table 1, entries 1-4). We next evaluated the reaction time (Table 1, entries 5-8), and found that 3 h is enough for this

reaction. As $POCl_3$ is corrosive and extremely toxic, the reaction was further carried out in various solvents containing equivalent amount of $POCl_3$, anddioxane was found to be the best choice (Table 1, entries 9-14). However, the yield (64%) in dioxane is needed to be further improved. Therefore, the molar ratio between **3a** and $POCl_3$ was investigated (Table 1, entries 15-19), and 1: 13.2 was found to be suitable for this reaction.
With the optimal reaction conditions (Table 1, entry 17), the substrate scope for the cyclization reaction was investigated. As shown in Table 2, most of the substrates examined provided moderate to good yields. For pyrimidine group, the substrates containing methy group at C5 (**5b**) or C6 (**5c**) position showed reduced reactivity (Table 2, entries 1-3). As **5b** produced higher yield (70%) than **5c** (58%), the reactivity of compounds **5d-5h** with different electron properties at C5 position was conducted (Table 2, entries 4-7). For the substituted 5-halo-pyrimidine derivatives, their relative reactivity was in the order of aryl fluorides (**5d**, 81%) > aryl chlorides (**5e**, 74%) > aryl bromides (**5f**, 62%).

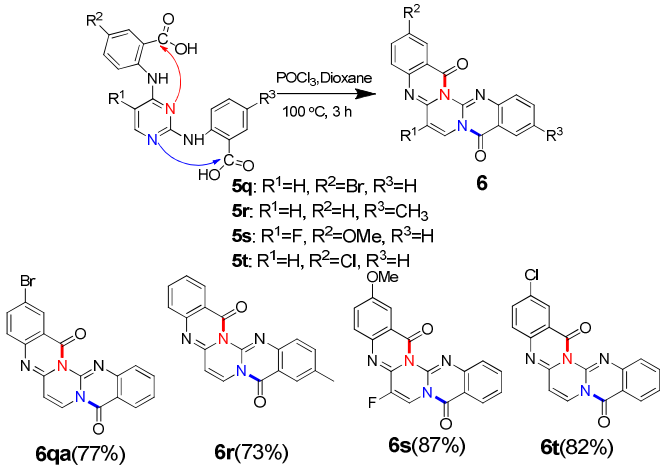
Table 1 Optimization of the cyclization reaction conditions[a]



entry	temp (°C)	time (h)	solvent	ratio (**5a**:$POCl_3$)	yield[b] (%)
1	100	6	$POCl_3$	/	91
2	80	6	$POCl_3$	/	43
3	60	6	$POCl_3$	/	26
4	40	6	$POCl_3$	/	0
5	100	1	$POCl_3$	/	51
6	100	2	$POCl_3$	/	76
7	100	3	$POCl_3$	/	90
8	100	12	$POCl_3$	/	85
9	100	3	dioxane	1: 8.8	64
10	100	3	$ClCH_2CH_2Cl$	1: 8.8	11
11	100	3	toluene	1: 8.8	31
12	100	3	cyclohexane	1: 8.8	0
13	100	3	acetonitrile	1: 8.8	0
14	100	3	benzene	1: 8.8	0
15	100	3	dioxane	1: 2.2	33
16	100	3	dioxane	1: 4.4	43
17	100	3	dioxane	1: 13.2	81
18	100	3	dioxane	1: 17.6	81
19	100	3	dioxane	1: 26.4	85

[a]All reactions were started with compound **5a** (175 mg, 0.5 mmol) which was dissolved in 5 mL solvent. The pure product 6a was obtained after filtration without further purification, as the starting material **5a** is easy to dissolve in alkaline aqueous solutionand no byproducts were detected. [b]Isolated yield.

However, compound **5g** with nitro group did not afford the corresponding cyclization product. The results suggested that the electron-negativity and steric hindrance in the pirimidine ring might play an important role in the cyclization reaction activity. For substituted *o*-aminobenzoic acid group, the beneficial substituted position was firstly investigated (Table 2, entries 8-10), among which compound **5j** with methyl group at C6 position displayed the highest reactivity. Although **5i** displayed a lower yield (54%) than **5j** (62%), we can obtain a series of 5-substituted-2-aminobenzoic acid commercially (Table 2, entries 11-16). Therefore, the electronic properties at C5 position in the benzene ring were examined in reactivity. High yields were observed for methoxyl and fluoryl substituted azoacridone derivatives (**6k** and **6l**). Interestingly, when the reaction time was prolonged to 12 h, the corresponding cyclization products (**6c**, **6f**, **6h-6j**, **6m-6o**) were also obtained in higher yields (Table 2, entries3, 6, 8-10, 13-15). The results indicated that the reactions showed broad substrate scope and good tolerance of functional groups.
In addition, the cyclization of compound **5q-5t** with different substituted anthranilic acid was investigated (Scheme 3). As 5-



Scheme 3 Cyclization reaction of compound **5q-5t** with asymmetrically substituted anthranilicacids[a]
[a]Reaction conditions: **5** (0.5 mmol), $POCl_3$ (0.6 mL) in dioxane (5 mL) at 100 °C.

bromo-anthranilic acidis was less active than anthranilic acid (Table 2, entry 14 and entry 1), two cyclization products may be formed, and **6qb** may be the main product (Figure 4). However, the result

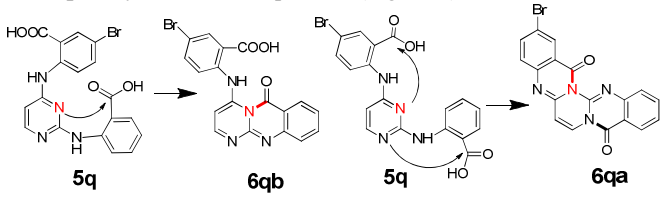
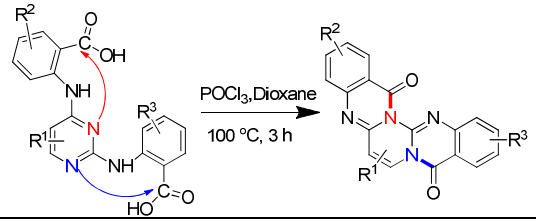
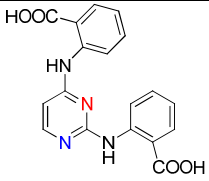
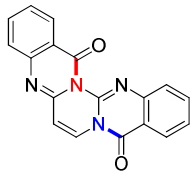
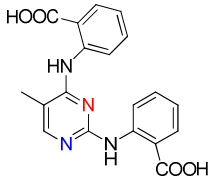
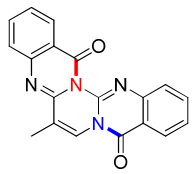
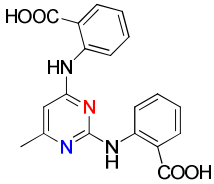
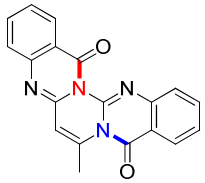
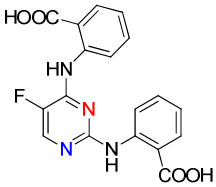
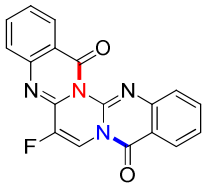
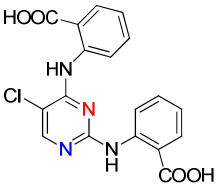
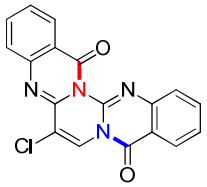
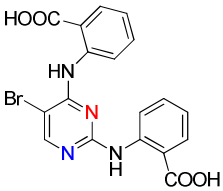
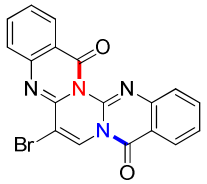
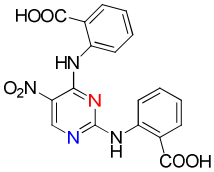


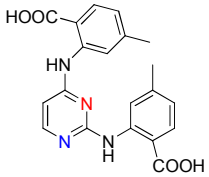
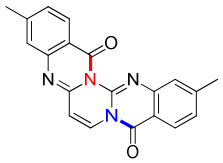
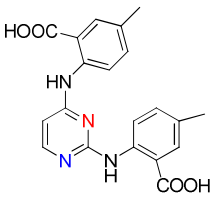
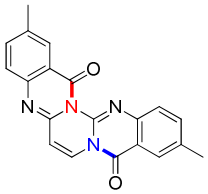
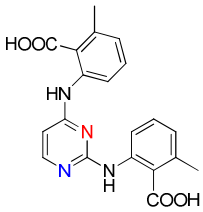
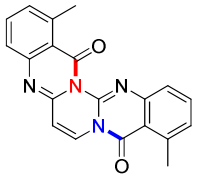
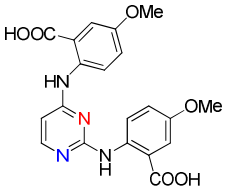
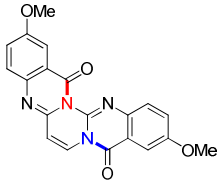
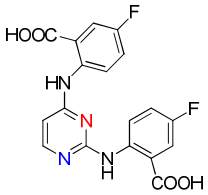
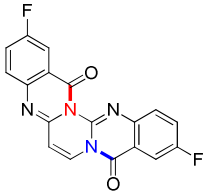
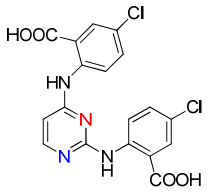
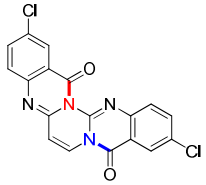
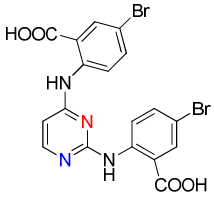
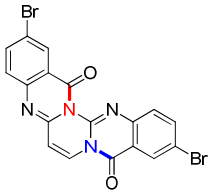
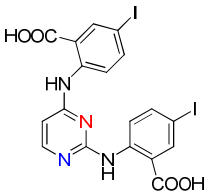
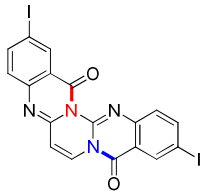
Figure 4 Possible cyclization reactions of **5q**

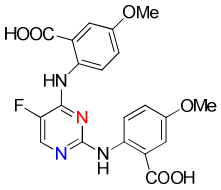
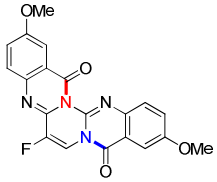
indicated that no **6qb** was detected even if the reaction conversion was less than 10%, and compound **6qa** was the only product. The similar products **6r-6t** were obtained from the cyclization reaction of **5r-5t**.

Table 2 The scope of $POCl_3$ – mediated cyclization reaction[a]



entry	compound **5**		compound **6**		yield[b](%)
	label	structure	label	structure	
1	**5a**		**6a**		81
2	**5b**		**6b**		70
3	**5c**		**6c**		58 (82[c])
4	**5d**		**6d**		81
5	**5e**		**6e**		74
6	**5f**		**6f**		62 (88[c])
7	**5g**			/	0

8	**5h**		**6h**		36 (77[c])
9	**5i**		**6i**		54 (91[c])
10	**5j**		**6j**		62 (85[c])
11	**5k**		**6k**		88
12	**5l**		**6l**		82
13	**5m**		**6m**		7 (84[c])
14	**5n**		**6n**		9 (87[c])
15	**5o**		**6o**		9 (67[c])

16	**5p**		**6p**		85

[a]Reaction conditions: **5** (0.5 mmol), $POCl_3$ (0.6 mL) in dioxane (5 mL) at 100 °C for 3 h. [b]Isolated yield. [c]The yields were meassured after the reactions were prolonged to 12 h.

Conclusions

To summarize, we have developed a simple and efficient method for the synthesis of fused azoacridone derivatives. This protocol uses readily available inexpensive substituted 2,4-dichloropyrimidine and anthranilic acid as the starting materials, and the corresponding fused azoacridone derivatives were prepared in good yields. Investigations on further application of this reaction are in progress.

Experimental Section

See supporting information for synthetic methods of compounds **1b, 1e-1i, 5a-5t.**

The general experimental procedure for the synthesis of compounds 2d, 2ga-2k
Compound **1** (**1b, 1e, 1g, 1h**) (0.5 mmol) was dissolved in $POCl_3$ (5.0 mL), and the solution was refluxed for 6 h, which was then pooled into ice water. 20% sodium hydroxide solution was used to adjust the pH to 7-8. After stirring for 0.5 h, the precipitate was filtered, and washed with EtOH and dried to give the pure products **2d, 2ga-2k**.

11H-pyrido[2,1-b]quinazolin-11-one (2d). White powder. Yield: 84mg, 85%. m.p. 214-215 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.82 (d, 1H, J = 6.8 Hz), 8.32 (d, 1H, J = 7.6 Hz), 7.92 (dd, 1H, J = 6.4 Hz), 7.81 (d, 1H, 8.0 Hz), 7.76 (dd, 1H, J = 6.8 Hz), 7.60 (d, 1H, J = 9.2 Hz), 8.32 (dd, 1H, J = 6.8 Hz), 7.09 (s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 158.7, 148.6, 148.0, 135.9, 135.5, 127.2, 127.1, 127.0, 126.2, 125.5, 116.2, 113.8. ESI-MS $[M + H]^+$: 197.0715, found: 197.0717.

4-(phenylamino)-6H-pyrimido[2,1-b]quinazolin-6-one (2ga). White powder. Yield: 134 mg, 93%. m.p. over 300 °C. ^{1}H NMR (DMSO-d_6, 400 MHz)δ 10.38 (s, 1H), 8.80 (d, 1H, J = 7.6Hz), 8.15 (d, 1H, J = 7.6 Hz), 7.96 (d, 1H, J = 6.4Hz), 7.79 (dd, 1H, J = 7.4 Hz), 7.59 (d, 1H, J = 8.4 Hz), 7.43 (dd, 2H, J = 7.8Hz), 7.35 (dd, 1H, J = 7.4 Hz), 7.16 (dd, 1H, J = 7.2Hz), 6.72 (d, 1H, J = 7.6Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 159.5, 158.0, 150.8, 148.5, 139.2, 135.6, 134.5, 129.3, 127.2, 126.7, 124.4, 123.9, 121.0, 115.8, 105.0. ESI-MS $[M + H]^+$: 289.1089, found: 289.1089.

1-chloro-4-methoxy-10H-pyrimido[6,1-b]quinazolin-10-one (2i). White powder. Yield: 100 mg, 78%. m.p. 218-220 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.80 (dd, 1H, J = 8.0Hz), 7.93 (dd, 1H, J = 8.4 Hz), 7.76 (d, 1H, J = 8.0Hz), 7.59 (d, 1H, J = 8.0 Hz), 7.52 (s, 1H), 3.94 (s, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 170.2, 158.9, 147.1, 146.2, 143.6, 136.2, 131.7, 127.4, 127.2, 121.7, 120.1, 57.4. ESI-MS $[M + H]^+$: 262.0383, found: 262.0379.

1-(phenylamino)-10H-pyrimido[6,1-b]quinazolin-10-one (2j). White powder. Yield: 105 mg, 73%. m.p. 183-184 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.49 (s, 1H), 8.23 (d, 1H, J = 8.0Hz), 8.15 (ddd, 1H, J = 8.0 Hz), 7.73 (d, 1H, J = 8.0Hz), 7.67 (d, 1H, J = 6.4 Hz), 7.60 (d, 1H, J = 8.0 Hz), 7.48 (dd, 1H, J = 7.6Hz), 7.41 (dd, 2H, J = 8.0 Hz), 7.17 (d, 1H, J = 7.6Hz), 6.58 (d, 1H, J = 6.4Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 164.7, 148.9, 147.9, 147.2, 138.1, 139.7, 129.3, 129.0, 125.9, 124.9, 122.3, 119.0, 109.1. ESI-MS $[M + H]^+$: 289.1089, found: 289.1085.

1-((4-chlorophenyl)amino)-10H-pyrimido[6,1-b]quinazolin-10-one (2k). Light green powder.Yield: 137 mg, 85%. m.p. over 300°C. ^{1}H NMR (DMSO-d_6, 400 MHz)δ 12.54 (s, 1H), 8.22 (d, 1H, J = 8.0Hz), 7.88 (dd, 1H, J = 7.6 Hz), 7.77 (d, 2H, J = 8.4Hz), 7.66 (d, 1H, J = 6.4 Hz), 7.60 (d, 1H, J = 8.4 Hz), 7.48 (dd, 1H, J = 7.6Hz), 7.45 (d, 2H, J = 8.4 Hz), 6.60 (d, 1H, J = 6.4Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 164.60, 148.77, 148.68, 147.89, 146.91, 137.05, 136.74, 129.21, 128.44, 127.66, 126.52, 125.97, 123.79, 118.95, 109.56. ESI-MS $[M + H]^+$: 323.0700, found: 323.0706.

General procedure for the synthesis of 6a-6f, 6h-6t.
Compound **5** (0.5 mmol) was dissolved in dioxane (5.0 mL), then $POCl_3$ (0.6 mL) was added. After stirring for 3 h at 100 °C, the solvent was removed under reduce pressure. Water was added to the residue, and 20% sodium hydroxide solution was used to adjust the pH to 7-8. After stirring for 0.5 h, the precipitate was filtered, and washed with EtOH and dried to give the pure products **6a-6f, 6h-6t.**

Pyrimido[2,1-b:4,3-b']diquinazoline-9,16-dione (6a). White powder.Yield: 126 mg, 81%. m.p. 269-271 °C. ^{1}H NMR (DMSO-d_6, 400 MHz)δ 8.40 (d, 1H, J = 8.0Hz), 8.23 (dd, 2H, J = 7.5 Hz), 7.95-7.87 (m, 2H), 7.69 (d, 2H, J = 7.6 Hz), 7.68 (d, 1H, J = 8.0 Hz), 7.62–7.57 (m, 2H), 6.67 (d, 1H, J = 8.0 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 159.2, 158.2, 146.4, 145.9, 145.7, 139.7, 136.4, 135.8, 128.9, 127.8, 127.7, 127.6, 127.5, 127.1, 121.6, 118.7, 110.4. ESI-MS $[M + H]^+$: 315.0882, found: 315.0896

6-methylpyrimido[2,1-b:4,3-b']diquinazoline-9,16-dione (6b). White powder. Yield: 115 mg, 70%. m.p. 258-260 °C. ^{1}H NMR (DMSO-d_6, 400 MHz)δ 8.34 (s, 1H), 8.20 (dd, 2H, J = 7.6 Hz), 7.91-7.86 (m, 2H), 7.69 (d, 1H, J = 8.0 Hz), 7.64 (d, 1H, J = 8.0 Hz), 7.59–7.54 (m, 2H), 6.67 (d, 1H, J = 8.0 Hz), 2.25 (s, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 159.5, 158.0, 146.5, 145.8, 145.6, 139.9, 136.2, 135.8, 127.8, 127.6, 127.5, 127.4, 127.3, 125.4, 121.6, 118.7, 117.5. ESI-MS $[M + H]^+$: 329.1039, found: 329.1044

7-methylpyrimido[2,1-b:4,3-b']diquinazoline-9,16-dione (6c). White powder.Yield: 95 mg, 58%. m.p. 253-255 °C. ^{1}H NMR (DMSO-d_6, 400 MHz)δ 8.17-8.14 (m, 2H), 7.91-7.83 (m, 2H), 7.64-7.61 (m, 2H), 7.58-7.51 (m, 2H), 6.42 (s, 1H), 2.67 (s, 3H).^{13}C NMR (DMSO-d_6, 100 MHz) δ 160.8, 158.9, 146.6, 146.0, 144.6, 144.5,

139.6, 136.1, 135.8, 127.6, 127.4, 127.2, 127.0, 121.3, 120.9, 110.2. ESI-MS $[M + H]^+$: 329.1039, found: 329.1047

6-fluoropyrimido[2,1-*b*:4,3-*b*']diquinazoline-9,16-dione (6d). Light brown powder. Yield: 134 mg, 81%. m.p. 252-254 °C. ^{1}H NMR (DMSO-d_6, 400 MHz)δ 8.67 (d, 1H, J = 6.4 Hz), 8.24 (dd, 2H, J = 7.4 Hz), 7.94 (dd, 2H, J = 7.6 Hz), 7.78 (d, 1H, J = 8.0 Hz), 7.70 (d, 1H, J = 8.0 Hz), 7.67-7.62 (m, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 158.6, 15739, 145.5, 145.2, 142.8, 141.1, 140.8, 138.6, 136.5, 136.1, 128.7, 127.8(4), 127.7(9), 127.6(9), 127.6(7), 127.4, 121.9, 118.2, 114.4, 114.0. ESI-MS $[M + H]^+$: 333.0788, found: 333.0782.

6-chloropyrimido[2,1-*b*:4,3-*b*']diquinazoline-9,16-dione (6e). Light brown powder. Yield: 129 mg, 74%. m.p. 282-285 °C. ^{1}H NMR (DMSO-d_6, 400 MHz)δ 8.67 (d, 1H, J = 6.4 Hz), 8.24 (dd, 2H, J = 7.4 Hz), 7.94 (dd, 2H, J = 7.6 Hz), 7.78 (d, 1H, J = 8.0 Hz), 7.70 (d, 1H, J = 8.0 Hz), 7.67-7.62 (m, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 158.6, 15739, 145.5, 145.2, 142.8, 141.1, 140.8, 138.6, 136.5, 136.1, 128.7, 127.8(4), 127.7(9), 127.6(9), 127.6(7), 127.4, 121.9, 118.2, 114.4, 114.0. ESI-MS $[M + H]^+$: 349.0492, found: 349.0499.

6-bromopyrimido[2,1-*b*:4,3-*b*']diquinazoline-9,16-dione (6f). Light brown powder. Yield: 122 mg, 62%. m.p. 298-300 °C. ^{1}H NMR (DMSO-d_6, 400 MHz)δ 8.69 (s, 1H), 8.25-8.22 (m, 2H), 7.94-7.92 (m, 2H), 7.68 (d, 1H, J = 8.0 Hz), 7.66-7.59 (m, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 159.1, 157.4, 145.6, 145.2, 143.4, 139.2, 136.7, 136.1, 129.2, 128.6, 127.7, 127.6, 121.4, 118.5, 105.2. ESI-MS $[M + H]^+$: 392.9987, found: 392.9979.

3,12-dimethylpyrimido[2,1-*b*:4,3-*b*']diquinazoline-9,16-dione (6h). Light brown powder. Yield :62 mg, 36%. m.p. 254-256 °C. ^{1}H NMR (DMSO-d_6, 400 MHz)δ 8.34 (s, 1H), 8.08 (s, 2H), 7.46 (s, 2H), 7.39 (s, 2H), 6.62 (s, 1H).^{13}C NMR (DMSO-d_6, 100 MHz) δ 159.0, 158.0, 147.4, 146.6, 146.5, 146.0, 145.8, 139.7, 129.1, 129.0, 128.8, 127.5, 127.4, 127.3, 126.8, 119.2, 116.2, 110.2, 21.9, 21.8. ESI-MS $[M + H]^+$: 343.1195, found: 343.1190.

2,11-dimethylpyrimido[2,1-*b*:4,3-*b*']diquinazoline-9,16-dione (6i). Light brown powder. Yield: 93 mg, 54%. m.p. 291-293 °C. ^{1}H NMR (DMSO-d_6, 400 MHz)δ 8.34 (d, 2H, J = 8.4 Hz), 7.99 (d, 2H, J = 10.0 Hz), 7.73 (d, 1H, J = 8.0 Hz), 7.69 (d, 1H, J = 8.0 Hz), 7.56 (d, 2H, J = 8.4 Hz), 6.61 (d, 1H, J = 8.4 Hz), 2.47 (s, 6H). ESI-MS $[M + H]^+$: 343.1195, found: 343.1188.

1,10-dimethylpyrimido[2,1-*b*:4,3-*b*']diquinazoline-9,16-dione (6j). Light brown powder. Yield: 106 mg, 62%. m.p. 291-293 °C. ^{1}H NMR (DMSO-d_6, 400 MHz)δ 8.33 (d, 1H, J = 7.6 Hz), 7.70 (d, 2H, J = 8.4 Hz), 7.46 (d, 2H, J = 6.4 Hz), 7.34 (s, 2H), 7.58 (d, 1H, J = 8.0 Hz), 2.80 (s, 3H), 2.77 (s, 3H). ESI-MS $[M + H]^+$: 343.1195, found: 343.1194.

2,11-dimethoxypyrimido[2,1-*b*:4,3-*b*']diquinazoline-9,16-dione (6k). Light brown powder. Yield: 165 mg, 88%. m.p. over 300 °C. ^{1}H NMR (DMSO-d_6, 400 MHz)δ 8.34 (d, 1H, J = 7.6 Hz), 7.62 (s, 4H), 7.53-7.47 (m, 2H), 6.63 (d, 1H, J = 8.0 Hz), 3.92 (s, 6H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 163.5, 163.2, 155.0, 150.5, 135.3, 124.2, 117.5, 115.2, 108.5, 56.0.ESI-MS $[M + H]^+$: 375.1093, found: 345.1094

2,11-difluoropyrimido[2,1-*b*:4,3-*b*']diquinazoline-9,16-dione (6l). Light brown powder. Yield: 145 mg, 82%. m.p. 299-300 °C. ^{1}H NMR (DMSO-d_6, 400 MHz)δ 8.37 (d, 1H, J = 8.0 Hz), 7.91 (s, 2H), 7.81-7.75 (m, 4H), 6.68 (d, 1H, J = 8.0 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 163.7, 162.7, 160.5, 158.9, 156.6, 150.5, 137.7, 134.9, 125.2, 125.0, 123.6, 123.4, 122.5, 121.2, 118.2, 118.1.115.6, 115.5, 112.7, 112.5, 112.3, 112.1.ESI-MS $[M + H]^+$: 351.0694, found: 351.0689.

2,11-dichloropyrimido[2,1-*b*:4,3-*b*']diquinazoline-9,16-dione (6m). Light brown powder. Yield: 160 mg, 84%. m.p. over 300 °C. ^{1}H NMR (DMSO-d_6, 400 MHz)δ 8.41 (d, 1H, J = 8.4 Hz), 8.18 (dd, 2H, J = 6.0 Hz), 7.97-7.92 (m, 2H), 7.71 (dd, 2H, J = 8.6 Hz), 6.71 (d, 1H, J = 8.4 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 163.6, 162.4, 161.3, 158.8, 150.5, 140.0, 137.1, 136.7, 135.3, 133.5, 127.0, 126.2, 121.8, 121.0, 118.1, 116.0.ESI-MS $[M + H]^+$: 383.0102, found: 383.0087.

2,11-dibromopyrimido[2,1-*b*:4,3-*b*']diquinazoline-9,16-dione (6n). Light brown powder. Yield: 205 mg, 87%. m.p. over 300 °C. ^{1}H NMR (DMSO-d_6, 400 MHz)δ 8.39 (d, 1H, J = 8.0 Hz), 8.27 (dd, 2H, J = 8.0 Hz), 8.06-8.01 (m, 2H), 7.60 (dd, 2H, J = 8.4 Hz), 6.68 (d, 1H, J = 8.0 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 163.5, 162.2, 150.4, 140.5, 138.0, 129.7, 129.3, 118.3, 116.6, 114.4.ESI-MS $[M + H]^+$: 470.9092, found: 470.9100.

2,11-diiodopyrimido[2,1-*b*:4,3-*b*']diquinazoline-9,16-dione (6o). Light brown powder.Yield :192 mg, 67%. m.p. over 300 °C. ^{1}H NMR (DMSO-d_6, 400 MHz)δ 8.45 (d, 2H, J = 7.6 Hz), 8.38 (d, 1H, J = 8.0 Hz), 8.18 (dd, 2H, J = 9.4 Hz), 7.44 (dd, 2H, J = 8.4 Hz), 6.67 (d, 1H, J = 8.0 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 163.6, 162.2, 161.4, 150.5, 145.0, 143.5, 140.7, 135.2, 118.3, 116.7.ESI-MS $[M + H]^+$: 566.8815, found: 566.8815.

6-fluoro-2,11-dimethoxypyrimido[2,1-*b*:4,3-*b*']diquinazoline-9,16-dione (6p). Light brown powder. Yield: 170 mg, 87%. m.p. 285-287 °C. ^{1}H NMR (DMSO-d_6, 400 MHz)δ 8.61 (d, 1H, J = 6.4 Hz), 7.40 (d, 1H, J = 8.8 Hz), 7.66-7.62 (m, 2H), 7.59 (d, 1H, J = 2.8 Hz), 7.56-7.51 (m, 2H), 3.94 (s, 3H), 3.92 (s, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 159.4, 158.6, 158.5, 157.7, 143.0, 139.8, 139.1, 136.8, 129.5, 129.4, 126.0, 125.0, 122.9, 119.0, 113.6, 113.2, 108.5, 107.3, 56.37, 56.33.ESI-MS $[M + H]^+$: 393.0999, found: 393.0992.

2-bromopyrimido[2,1-*b*:4,3-*b*']diquinazoline-9,16-dione (6qa). Light brown powder. Yield: 151 mg, 77%. m.p. over 300 °C. ^{1}H NMR (DMSO-d_6, 400 MHz)δ 8.41 (d, 1H, J = 8.0 Hz), 8.30 (s, 1H), 8.23 (d, 1H, J = 7.6 Hz), 8.03 (d, 1H, J = 8.4 Hz), 7.93 (dd, 1H, J = 8.0 Hz), 7.68 (d, 1H, J = 8.4 Hz), 7.63-7.61 (m, 2H), 6.67 (d, 1H, J = 8.0 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 158.2, 146.9, 145.6, 145.0, 139.5, 138.6, 136.5, 129.7, 129.5, 129.4, 127.7, 127.5, 123.1, 120.0, 118.8, 110.3.ESI-MS $[M + H]^+$: 392.9987, found: 392.9991.

11-methylpyrimido[2,1-*b*:4,3-*b*']diquinazoline-9,16-dione (6r). Light brown powder. Yield: 120 mg, 73%. m.p. 266-268 °C. ^{1}H NMR (DMSO-d_6, 400 MHz)δ 8.37 (d, 1H, J = 8.4 Hz), 8.19 (d, 1H, J = 7.6 Hz), 8.00 (s, 1H), 7.87 (dd, 1H, J = 7.6 Hz), 7.2 (dd, 1H, J = 8.0 Hz), 7.66 (d, 1H, J = 8.0 Hz), 7.59-7.56 (m, 2H), 6.63 (d, 1H, J = 8.0 Hz), 2.47 (s, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 158.1, 146.4, 146.0, 143.7, 137.8, 137.5, 135.8, 129.0, 127.7, 127.6, 127.5, 127.1, 126.8, 121.6, 118.5, 110.3, 21.2.ESI-MS $[M + H]^+$:329.0978, found: 329.0974.

6-fluoro-2-methoxypyrimido[2,1-*b*:4,3-*b*']diquinazoline-9,16-dione (6s). Light brown powder. Yield: 153 mg, 85%. m.p. 281-283 °C. ^{1}H NMR (DMSO-d_6, 400 MHz)δ 8.61 (d, 1H, J = 6.0 Hz), 8.23 (d, 1H, J = 7.6 Hz), 7.94 (dd, 2H), 7.74 (d, 1H, J = 8.8 Hz), 7.68-

7.60 (m, 3H), 7.20 (dd, 1H, J = 8.4 Hz), 3.94 (s, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 159.4, 158.5, 158.0, 145.5, 139.1, 138.7, 136.5, 129.5, 127.8, 127.6, 127.4, 125.1, 122.9, 118.2, 113.5, 113.1, 108.5, 56.39.ESI-MS $[M + H]^+$: 363.0893, found: 363.0885.

2-chloropyrimido[2,1-b:4,3-b']diquinazoline-9,16-dione (6t). Light brown powder. Yield: 142 mg, 82%. m.p. over 300°C. ^{1}H NMR (DMSO-d_6, 400 MHz)δ 8.37 (d, 1H, J = 8.0 Hz), 8.20 (d, 1H, J = 8.0 Hz), 8.16 (s, 1H), 7.95-7.89 (m, 2H), 7.70 (dd, 1H, J = 8.0 Hz), 7.59 (dd, 1H, J = 8.0 Hz), 6.70 (d, 1H, J = 8.4 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 146.19, 145.87, 144.53, 136.45, 135.95, 131.71, 129.84, 128.83, 127.90, 127.70, 127.22, 126.35, 121.58, 120.05, 110.94. ESI-MS $[M + H]^+$: 349.0492, found: 349.0506.

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