Oxidative Synthesis of Quinazolinones under Metal-free Conditions

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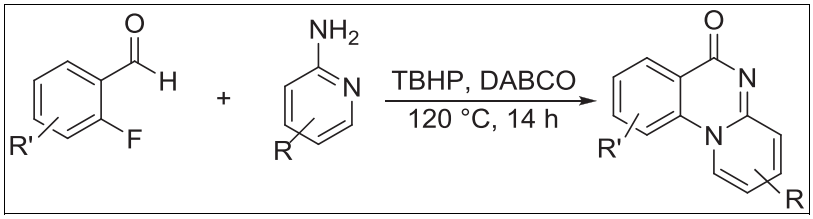

A metal-free procedure for the synthesis of quinazolinones under oxidative conditions has been developed. In the presence of DABCO and TBHP, the desired products can be obtained in moderate yields with 2-fluorobenzaldehydes and 2-aminopyridines as the substrates.

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INTRODUCTION

As the development of our society, the concept of "Sustainable Development" has been accepted and raises the demand of "Green Chemistry" [1]. Under this background, the establishment of metal-free synthetic procedures will be under current interests.

On the other hand, the syntheses of *N*-heterocyclic compounds have attracted general attention for their wide and distinct pharmaceutical activities [2]. Among the known *N*-heterocycles, quinazolinones is a class of representative example, which is reported with various activities including anticancer [3], anti-inflammation [4], antibacterial [5], and anti-diabetes [6]. Regarding the importance of quinazolinones, numerous elegant methods have been developed for their preparation [7]. In the transition metal-catalyzed methodologies, good to excellent yields of the desired products can be obtained with Pd, Ru, Ir, Cu, and Fe as the catalysts. However, besides the high costs of these catalytic systems, the heterocyclic products are usually contaminated by the metals. Furthermore, in the known oxidative procedures, oxidants like $KMnO_4$, N,N′-dicyclohexylcarbodiimide, and TBHP together with catalyst are usually required. In our group, we were succeeded in developing several new procedures for the synthesis of quinazolinones as well, such as palladium-catalyzed carbonylation of aryl bromides with 2-aminobenzamides [8] and metal-free procedures with aldehydes and 2-aminobenzamides and analogs as the substrates [9]. As our continuing interests on this topic, we wish to report our new results on the metal-free synthesis of quinazolinones from 2-fluorobenzaldehydes and 2-aminopyridines here.

EXPERIMENTAL

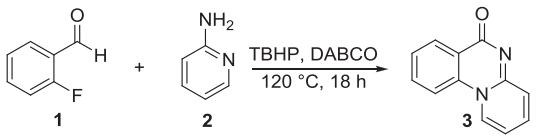
In a 25-mL pressure tube equipped with a stirring bar, 2-fluorobenzaldehyde (1 mmol), 2-aminopyridine (1.5 mmol), and DABCO (2 equiv.) were added in DMF (2 mL); then, TBHP (70 wt % in H_2O; 2 equiv.) was injected by syringe. After that, the tube was closed and heated up to 120 °C for 14 h. When the reaction is completed, cool the reaction mixture to room temperature. The reaction was quenched with distilled water, and the solution was extracted with ethyl acetate. The combined organic phases were washed with saturated NaCl solution and dried over Na_2SO_4. The crude product was purified by column chromatography (ethyl acetate/pentane = 1:4).

RESULTS AND DISCUSSION

The first set of reactions was performed with solvents testing (Table 1, entries 1–4). We using 2-fluorobenzaldehyde and 2-aminopyridine as the model substrates; in the presence of TBHP and DABCO, different solvents were tested. Gratingly, 28% of the desired product was produced in DMF, while only low yield of the product was formed in the other tested solvents. To our surprise, the yield dropped dramatically when TBHP in decane was applied as the oxidant (Table 1, entry 5). In the other tested oxidants, cumene hydroperoxide gave similar yield of the desired product (Table 1, entry 6). Notably, full conversion of 2-fluorobenzaldehyde was detected in all the cases. 2-Fluorobenzoic acid, 2-Fluorobenzamide, and non-characterizable compounds are the by-products in general. Then the effects of bases were checked. Among all the tested

Table 1

Metal-free quinazolinones synthesis: optimization.[a]



Entry	Oxidant	Base	Solvent	Yield (%)[b]
1	TBHP	DABCO	DMF	28 (26)[c]
2	TBHP	DABCO	DMSO	6
3	TBHP	DABCO	DMAc	7
4	TBHP	DABCO	1,4-Dioxane	9
5	TBHP	DABCO	DMF	3[d]
6	CHP	DABCO	DMF	26
7	DTBP	DABCO	DMF	Trace
8	BPO	DABCO	DMF	Trace
9	H_2O_2	DABCO	DMF	5
10	TBHP	DABCO	DMF	23[e]
11	TBHP	DABCO	DMF	83 (81)[c,f]
12	TBHP	DABCO	DMF	21[g]

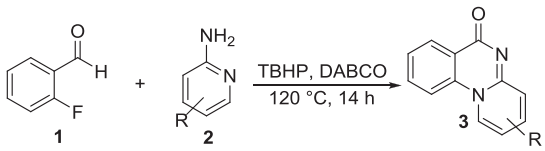
[a]Reaction conditions: 2-fluorobenzaldehyde (**1**, 1 mmol), 2-aminopyridine (**2**, 1.5 mmol), TBHP (70 wt % in H_2O; 2 equiv.), DABCO (3 equiv.), solvent (2 mL), 18 h.
[b]GC yield, using hexadecane as the internal standard.
[c]Isolated yield.
[d]5.5 M TBHP in decane.
[e]DABCO (2 equiv.), 10 h.
[f]DABCO (2 equiv.), 14 h.
[g]DABCO (2 equiv.), 24 h.

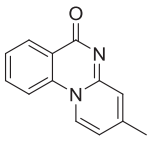
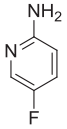
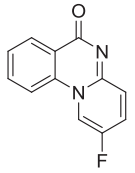
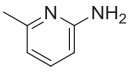
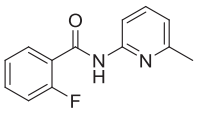
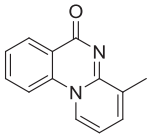
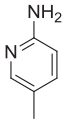
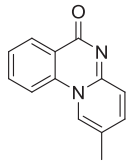
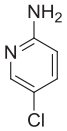
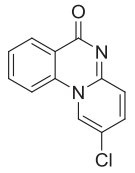
bases [K_2CO_3, K_3PO_4, KO^{t}Bu, DBU, 1,5-diazabicyclo[4.3.0] non-5-ene, and N,N-diisopropylethylamine (DIPEA)], DABCO was still proven to be the best base. Interestingly, the reaction time was found to be important for the outcome of this transformation. Shortened reaction time gave non-complete conversion, while the decomposition of the product was observed in the reaction with prolonged reaction time (Table 1, entries 10–12). Reaction temperatures were tested as well, but no better results can be obtained. At this stage, 81% of the product can be isolated in DMF, at 120 °C with DABCO (2 equiv.) as the base and TBHP (2 equiv.) as the oxidant (Table 1, entry 11).

With the best reaction conditions in hand, we started the scope and limitation testing subsequently (Tables 2 and 3). Various functional group substituted 2-aminopyridines were tested at the beginning. Moderate yields of quinazolinones can be isolated from the corresponding 2-aminopyridines. Methyl, chloro, and fluoro are tolerable under this reaction conditions. However, 2-aminopyridine with functional groups like bromo, cyano and nitro can only give traces of the corresponding product under standard conditions. This phenomenon might be due to the reduced electron density on NH–Ar anion and subsequently decreased the ability of nucleophilic substitution with 2-F–Ar. This situation cannot be improved by varying the reaction temperature and time. On the other hand, steric effect acts as another important role for this transformation. Only the non-cyclized amide was isolated when 6-methylpyridin-2-amine was applied as the reaction

Table 2

Metal-free quinazolinones synthesis: 2-aminopyridines testing.[a]

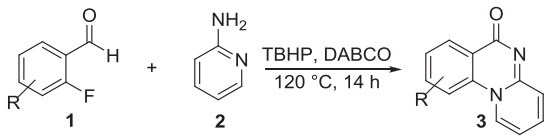


Entry	**2**	**3**	Yield[b]
1			48
2			52
3			48
4			52
5			38
6			30

[a]Reaction conditions: 2-fluorobenzaldehyde (**1**, 1 mmol), 2-aminopyridine (**2**, 1.5 mmol), TBHP (2 equiv.), DABCO (2 equiv.), DMF (2 mL), 14 h, 120 °C.
[b]Isolated yield.

Table 3

Metal-free quinazolinones synthesis: 2-fluorobenzaldehydes testing.[a]



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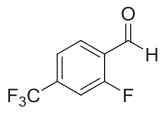
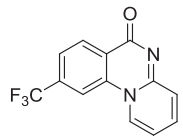
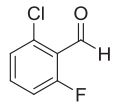
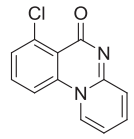
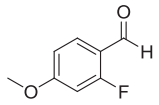
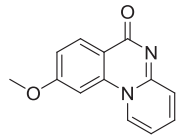
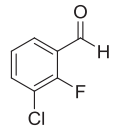
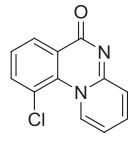
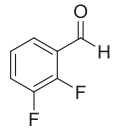
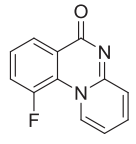
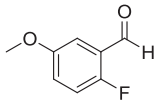
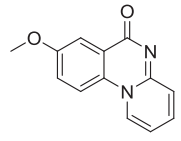
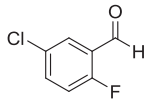
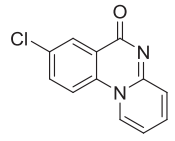
1			8
2			22
3			46
4			11
5			33
6			16
7			15

[a]Reaction conditions: 2-fluorobenzaldehyde (**1**, 1 mmol), 2-aminopyridine (**2**, 1.5 mmol), TBHP (2 equiv.), DABCO (2 equiv.), DMF (2 mL), 14 h.
[b]Isolated yield.

partner (Table 2, entry 3). Quinolin-2-amine was tested with 2-fluorobenzaldehyde as well, but only trace of the desired product was detected, which may due to the steric issue.

Then, different 2-fluorobenzaldehydes were reacted with 2-aminopyridine. As shown in Table 3, low to moderate of the corresponding quinazolinones were isolated. Compared with 2-fluorobenzaldehyde, the substituted substrates resulted decreased yields that can be explained as follows: (1) nucleophilic substitution can be favored by electron-withdrawing substituents, while this can lead the aldehyde to be activated and the trend to be oxidized to the acid; (2) electron-donating substituted aldehydes are more stable in oxidative conditions, but this can increase the difficulty in nucleophilic substitution.

Additionally, 2-bromobenzaldehyde and 2-nitrobenzaldehyde were tested as substrates with 2-aminopyridine under the same reaction conditions; 36% and 10% yields of the quinazolinone were produced (Scheme 1). Remarkably, no reaction occurred when 2-fluorobenzoic acid was applied as the starting material. By using 2-aminophenol as the reaction partner, good yield of the desired dibenzo[*b*,*f*][1,4]oxazepin-11(10*H*)-one can be achieved (Scheme 2). Based on these experiments, a possible reaction pathway has been proposed. As shown in Scheme 3, the reaction starts with amide formation via oxidative amidation. Then the rearrangement of the C=N occurred and followed by nucleophilic substitution to give the final product.

CONCLUSIONS

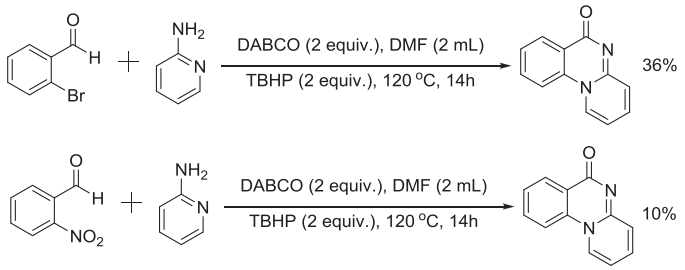
In summary, we have explored the possibility of using 2-aminopyridines and 2-fluorobenzaldehydes as starting materials for quinazolinone synthesis. In the neutral substrate, excellent yield can be achieved, while this transformation is very sensitive to the electron properties and steric character of the substrates.

EXPERIMENTAL

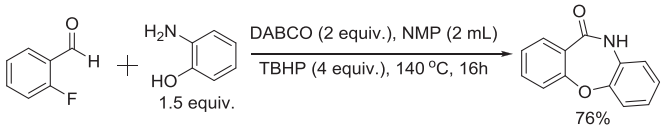
General comments. All reactions were carried out under air. Reactions were monitored by TLC analysis (precoated silica gel plates with fluorescent indicator UV254, 0.2 mm) and visualized with 254 nm ultraviolet light. Chemicals were purchased from Aldrich, Alfa-Aesar (Ward Hill, MA, USA) and, unless otherwise noted, were used without further purification. All compounds were characterized by ^{1}H NMR and ^{13}C NMR spectroscopy and recorded on Bruker AV 300 and AV 400 spectrometers. GC was performed on Agilent 6890 chromatograph with a 30-m HP5 column.

General procedure for the synthesis of quinazolinone. In a 25-mL pressure tube equipped with a stirring bar, 2-fluorobenzaldehyde (1 mmol), 2-aminopyridine (1.5 mmol), and DABCO (2 equiv.) were added in DMF (2 mL), then TBHP (70 wt % in H_2O; 2 equiv.) was injected by syringe.

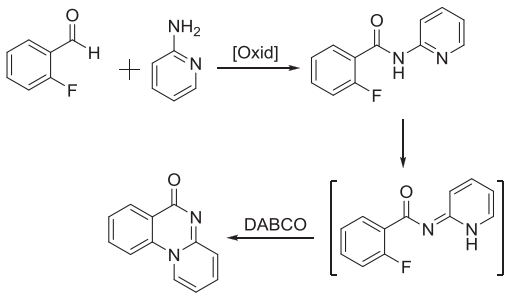
Scheme 1. Metal-free quinazolinones synthesis from 2-bromobenzaldehyde and 2-nitrobenzaldehyde.



Scheme 2. Oxidative synthesis of dibenzo[*b*,*f*][1,4]oxazepin-11(10*H*)-one.



Scheme 3. Proposed reaction mechanism.



After that, the tube was closed and heated up to 120 °C for 14 h. When the reaction was completed, cool the reaction mixture to room temperature. The reaction was quenched with distilled water, and the solution was extracted with ethyl acetate. The combined organic phases were washed with saturated NaCl solution and dried over Na_2SO_4. The crude product was purified by column chromatography (ethyl acetate/pentane = 1:4).

6H-Pyrido[1–9]quinazolin-6-one [8b]. **^{1}H NMR (300 MHz, DMSO-*d*^{6})** δ 8.80 (ddd, *J* = 7.3, 1.5, 0.9 Hz, 1H), 8.31 (ddd, *J* = 8.1, 1.6, 0.6 Hz, 1H), 7.91 (ddd, *J* = 8.5, 6.9, 1.6 Hz, 1H), 7.82–7.62 (m, 2H), 7.59–7.43 (m, 2H), 7.07 (ddd, *J* = 7.6, 6.4, 1.4 Hz, 1H). **^{13}C NMR (75 MHz, DMSO-*d*^{6})** δ 158.25, 148.18, 147.35, 135.16, 135.00, 126.69, 126.42, 125.78, 124.94, 115.68, 113.19.

2-Fluoro-6H-pyrido[1,2-a]quinazolin-6-one [8b]. **^{1}H NMR (300 MHz, DMSO-*d*^{6})** δ 8.74 (ddd, *J* = 5.3, 2.8, 0.7 Hz, 1H), 8.29 (ddd, *J* = 8.2, 1.7, 0.6 Hz, 1H), 7.99–7.79 (m, 2H), 7.76 (ddd, *J* = 8.5, 1.2, 0.6 Hz, 1H), 7.68–7.43 (m, 2H). **^{13}C NMR (101 MHz, DMSO-*d*^{6})** δ 157.84 (d, *J* = 2.1 Hz), 153.40, 151.02, 147.74, 145.62, 134.98, 128.81–128.01 (m), 126.82, 126.48, 125.57, 115.06, 112.05, 111.63.

3-Methyl-6H-pyrido[1,2-a]quinazolin-6-one [7a]. **^{1}H NMR (300 MHz, DMSO-*d*^{6})** δ 8.69 (dd, *J* = 7.4, 0.7 Hz, 1H), 8.26 (ddd, *J* = 8.2, 1.6, 0.6 Hz, 1H), 7.87 (ddd, *J* = 8.5, 6.9, 1.6 Hz, 1H), 7.68 (ddd, *J* = 8.4, 1.2, 0.6 Hz, 1H), 7.46 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 7.29 (dt, *J* = 2.0, 1.1 Hz, 1H), 6.91 (dd, *J* = 7.5, 1.8 Hz, 1H), 2.38 (d, *J* = 1.2 Hz, 3H). **^{13}C NMR (101 MHz, DMSO-*d*^{6})** δ 158.19, 148.55, 147.35, 146.36, 134.89, 126.65, 126.52, 125.68, 127.47–126.16 (m), 124.45, 123.05, 115.95, 115.38, 20.78.

2-Fluoro-N-(6-methylpyridin-2-yl)benzamide [8b]. **^{1}H NMR (300 MHz, DMSO-*d*^{6})** δ 10.69 (s, 1H), 8.00 (d, *J* = 8.2 Hz, 1H), 7.81–7.63 (m, 2H), 7.57 (dddd, *J* = 8.6, 7.2, 5.3, 1.8 Hz, 1H), 7.39–7.22 (m, 2H), 7.03 (dd, *J* = 7.5, 1.0 Hz, 1H), 2.42 (s, 3H). **^{13}C NMR (101 MHz, DMSO-*d*^{6})** δ 163.18, 160.38, 157.90, 156.66, 150.96, 138.54, 130.11 (d, *J* = 2.7 Hz), 126.68–121.90 (m), 119.22, 116.03 (d, *J* = 22.2 Hz), 110.99, 23.57.

4-Methyl-6H-pyrido[1,2-a]quinazolin-6-one [8b]. **^{1}H NMR (300 MHz, DMSO-*d*^{6})** δ 8.98 (ddd, *J* = 7.5, 1.4, 0.7 Hz, 1H), 8.47 (dd, *J* = 8.6, 0.9 Hz, 1H), 8.26 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.92 (ddd, *J* = 8.8, 7.2, 1.7 Hz, 1H), 7.82–7.58 (m, 2H), 6.97 (t, *J* = 7.0 Hz, 1H), 2.40–2.30 (m, 3H). **^{13}C NMR (101 MHz, DMSO-*d*^{6})** δ 165.11, 151.55, 137.54, 136.01, 133.32, 132.15, 128.31, 127.86, 127.67, 121.02, 116.29, 112.37, 18.46.

2-Chloro-6H-pyrido[1,2-a]quinazolin-6-one [8b]. **^{1}H NMR (300 MHz, DMSO-*d*^{6})** δ 8.78 (dd, *J* = 2.4, 0.7 Hz, 1H), 8.30 (ddd, *J* = 8.1, 1.7, 0.6 Hz, 1H), 7.93 (ddd, *J* = 8.5, 7.0, 1.6 Hz, 1H), 7.82–7.69 (m, 2H), 7.62–7.48 (m, 2H). **^{13}C NMR (75 MHz, DMSO-*d*^{6})** δ 157.45, 147.78, 145.75, 135.73, 135.22, 127.59, 126.89, 126.74, 125.66, 123.88, 120.18, 115.72.

9-(Trifluoromethyl)-6H-pyrido[1,2-a]quinazolin-6-one [7a]. **^{1}H NMR (300 MHz, DMSO-d^6)** δ 8.83 (ddd, *J* = 7.3, 1.5, 0.9 Hz, 1H), 8.48 (dt, *J* = 8.4, 0.8 Hz, 1H), 8.04 (dt, *J* = 1.7, 0.8 Hz, 1H), 7.90–7.66 (m, 2H), 7.58 (ddd, *J* = 9.2, 1.4, 0.8 Hz, 1H), 7.15 (ddd, *J* = 7.3, 6.5, 1.4 Hz, 1H). **^{13}C NMR (75 MHz, DMSO-d^6)** δ 157.92, 148.45, 147.95, 136.34, 134.33 (d, *J* = 32.1 Hz), 128.76, 126.71, 125.80, 123.92 (d, *J* = 4.4 Hz), 119.83 (d, *J* = 3.6 Hz), 118.05, 113.99.

7-Chloro-6H-pyrido[1,2-a]quinazolin-6-one [7a]. **^{1}H NMR (300 MHz, DMSO-d^6)** δ 8.78 (ddd, *J* = 7.4, 1.6, 0.9 Hz, 1H), 7.85–7.71 (m, 2H), 7.65 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.56–7.43 (m, 2H), 7.09 (ddd, *J* = 7.4, 6.5, 1.4 Hz, 1H). **^{13}C NMR (101 MHz, DMSO-d^6)** δ 156.18, 150.54, 147.87, 136.14, 134.40, 132.76, 126.93, 126.55, 126.24, 125.51, 113.50, 112.68.

9-Methoxy-6H-pyrido[1,2-a]quinazolin-6-one [7a]. **^{1}H NMR (300 MHz, DMSO-d^6)** δ 8.78 (ddd, *J* = 7.3, 1.6, 0.8 Hz, 1H), 8.20 (dd, *J* = 8.8, 0.5 Hz, 1H), 7.72 (ddd, *J* = 9.2, 6.5, 1.6 Hz, 1H), 7.46 (dt, *J* = 9.2, 1.1 Hz, 1H), 7.22–6.92 (m, 3H), 3.93 (s, 3H). **^{13}C NMR (75 MHz, DMSO-d^6)** δ 164.62, 157.48, 150.62, 147.89, 135.45, 128.39, 126.52, 125.40, 116.20, 112.93, 109.45, 106.26, 55.74.

10-Chloro-6H-pyrido[1,2-a]quinazolin-6-one [7a]. **^{1}H NMR (300 MHz, DMSO-d^6)** δ 8.80 (ddd, *J* = 7.3, 1.6, 0.9 Hz, 1H), 8.25 (dd, *J* = 8.1, 1.5 Hz, 1H), 8.05 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.79 (ddd, *J* = 9.2, 6.5, 1.6 Hz, 1H), 7.60 (ddd, *J* = 9.2, 1.4, 0.8 Hz, 1H), 7.45 (dd, *J* = 8.1, 7.6 Hz, 1H), 7.13 (ddd, *J* = 7.3, 6.5, 1.4 Hz, 1H). **^{13}C NMR (75 MHz, DMSO-d^6)** δ 158.03, 147.76, 144.55, 136.15, 134.77, 129.90, 126.67, 126.06, 125.96, 124.69, 117.20, 113.90.

10-Fluoro-6H-pyrido[1,2-a]quinazolin-6-one [8b]. **^{1}H NMR (300 MHz, DMSO-d^6)** δ 8.82 (ddd, *J* = 7.3, 1.6, 0.9 Hz, 1H), 8.12 (dt, *J* = 8.2, 1.1 Hz, 1H), 7.87–7.71 (m, 2H), 7.65–7.58 (m, 1H), 7.48 (td, *J* = 8.0, 4.8 Hz, 1H), 7.13 (ddd, *J* = 7.6, 6.5, 1.4 Hz, 1H). **^{13}C NMR (75 MHz, DMSO-d^6)** δ 158.44–157.42 (m), 154.33, 147.73, 138.13 (d, *J* = 12.8 Hz), 135.88, 126.61, 126.02, 124.47 (d, *J* = 7.6 Hz), 122.47 (d, *J* = 4.8 Hz), 119.54, 119.30, 117.63 (d, *J* = 2.6 Hz), 113.77.

8-Methoxy-6H-pyrido[1,2-a]quinazolin-6-one [7a]. **^{1}H NMR (300 MHz, DMSO-d^6)** δ 8.78 (ddd, *J* = 7.4, 1.5, 0.9 Hz, 1H), 7.73 (dd, *J* = 9.0, 0.5 Hz, 1H), 7.68–7.60 (m, 2H), 7.56 (dd, *J* = 9.0, 3.0 Hz, 1H), 7.50 (ddd, *J* = 9.2, 1.4, 0.9 Hz, 1H), 7.04 (ddd, *J* = 7.4, 6.4, 1.4 Hz, 1H), 3.91 (s, 3H). **^{13}C NMR (101 MHz, DMSO-d^6)** δ 157.81, 156.60, 145.67, 143.21, 133.85, 128.61, 126.16, 126.07, 125.84, 116.24, 113.24, 104.97, 55.63.

8-Chloro-6H-pyrido[1,2-a]quinazolin-6-one [7a]. **^{1}H NMR (300 MHz, DMSO-d^6)** δ 8.79 (ddd, *J* = 7.3, 1.6, 0.9 Hz, 1H), 8.23 (dd, *J* = 2.6, 0.5 Hz, 1H), 7.91 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.84–7.68 (m, 2H), 7.54 (ddd, *J* = 9.2, 1.4, 0.9 Hz, 1H), 7.11 (ddd, *J* = 7.3, 6.4, 1.4 Hz, 1H). **^{13}C NMR (101 MHz, DMSO-d^6)** δ 157.47, 147.63, 146.89, 135.66, 135.13, 129.03, 128.82, 126.53, 125.83, 125.30, 116.62, 113.73.

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