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DMAP-Catalyzed One-Pot Synthesis of Quinazoline-2,4-diones from 2-Aminobenzamides and Di-*tert*-butyl Dicarbonate

Hui Chen, Peng Li, Rongfei Qin, Hong Yan, Gang Li,* and Haihong Huang*

Cite This: *ACS Omega* 2020, 5, 9614−9623

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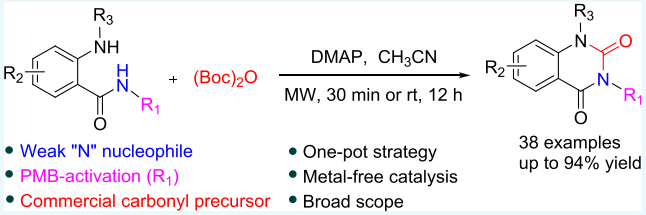
ABSTRACT: The one-pot synthesis of quinazoline-2,4-diones was developed in the presence of 4-dimethylaminopyridine (DMAP) by metal-free catalysis. The commercially available $(Boc)_2O$ acted as a key precursor in the construction of the 2-position carbonyl of quinazolinediones. The *p*-methoxybenzyl (PMB)-activated heterocyclization could smoothly proceed at room temperature instead of the microwave condition. This strategy is compatible with a variety of substrates with different functional groups. Furthermore, this protocol was utilized to smoothly prepare Zenarestat with a total yield of 70%.



INTRODUCTION

Quinazolinediones are an important class of nitrogen-containing heterocycles in medicinal chemistry with a broad range of bioactivities, such as antihypertensive,[1,2] antidiabetic,[3] antimicrobial,[4,5] antimalarial,[6,7] and anticancer activities.[8−10] Structures shown in Figure 1 are representative examples of commercial drugs or biologically active compounds and natural products containing the quinazoline-2,4-dione core.[11−15] Among them, Zenarestat is a therapeutic agent against diabetic neuropathy. Due to the importance of quinazoline-2,4-diones in medicinal chemistry, various synthetic methods have been reported to construct this core.[16−31] The representative strategies for the construction of quinazoline-2,4-diones have been summarized in the introduction part of our previous article.[32] The key precursor reagents such as urea, triphosgene, CO, CO_2, dimethylformamide (DMF), 1,1′-carbonyldiimidazole (CDI), and KOCN are crucial to the introduction of the 2-position carbonyl group. However, there are limited methods available to construct quinazoline-2,4-diones with electron-withdrawing groups from 2-aminobenzamides.

Di-*tert*-butyl dicarbonate $[(Boc)_2O]$ is widely used in organic synthesis to introduce the *tert*-butoxycarbonyl (Boc) protecting group into amines. In some cases, $(Boc)_2O$ is also used to form ureas in the presence of 4-dimethylaminopyridine (DMAP).[33] DMAP, as a well-known superacylation catalyst, is used to address difficult acylations.[34] The combined use of $(Boc)_2O$ and DMAP may be a good option to embed the carbonyl group in the quinazolinediones.

Recently, our group developed a *p*-toluenesulfonic acid (PTSA)-catalyzed hydrogenation condensation strategy to synthesize various quinazoline-2,4(1*H*,3*H*)-diones using oxalyl chloride as the key precursor reagent (Scheme 1). This two-step approach has several advantages, such as no further purification, mild reaction conditions, high yields, and low-toxicity reagents, but limited in substrate applicability.[32] To further simplify the procedure and extend the substrate scope, we focus on the exploration of an appropriate 2-position carbonyl precursor to construct quinazoline-2,4-dione. Herein, we report on the development of the one-pot synthesis of quinazoline-2,4-diones from 2-aminobenzamides using $(Boc)_2O$ as the key precursor in the presence of DMAP (Scheme 1).

RESULTS AND DISCUSSION

Initially, 2-aminobenzamide (**1a**) and 2-amino-*N*-methylbenzamide (**2a**) were chosen as the model substrates to explore the possible formation of quinazoline-2,4-diones using $(Boc)_2O$ as the carbonyl donor. The results are summarized in Table 1. The first reaction from substrate **1a** was attempted at room temperature under the Boc protecting condition in the solvent of CH_2Cl_2, with Et_3N as the base and DMAP as the catalyst.

Inspiringly, the desired product **5a** was obtained in 33% yield, although the side product **3a** was obtained in 9% yield (Table 1, entry 1). The result indicated that it is feasible to construct the quinazoline-2,4-dione scaffold using $(Boc)_2O$ from **1a**. It was found that the reaction yield decreased without the catalyst of DMAP (Table 1, entry 2), while it showed significant improvement without the additional base Et_3N with a yield of 79% (Table 1, entry 3). The heterocyclization could not proceed completely in the absence of DMAP after 12 h (Table 1, entry 4). The replacement of DMAP with 1,5,7-

Received: March 12, 2020
Accepted: April 9, 2020
Published: April 16, 2020

https://dx.doi.org/10.1021/acsomega.0c01104
ACS Omega 2020, 5, 9614−9623

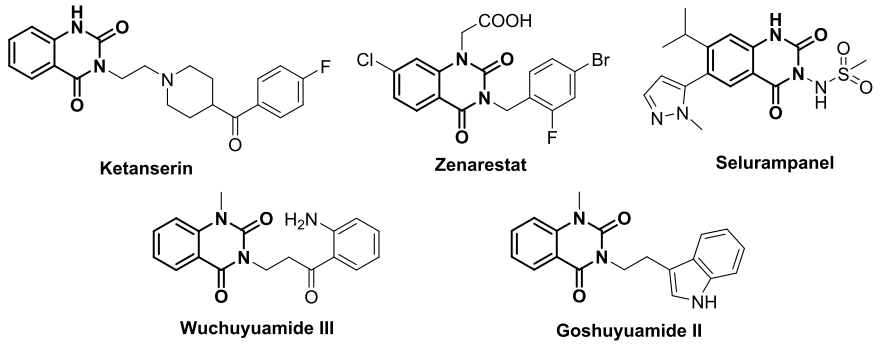


Figure 1. Representative examples of quinazoline-2,4-diones.

Scheme 1. Strategies for the Construction of Substituted Quinazoline-2,4-diones

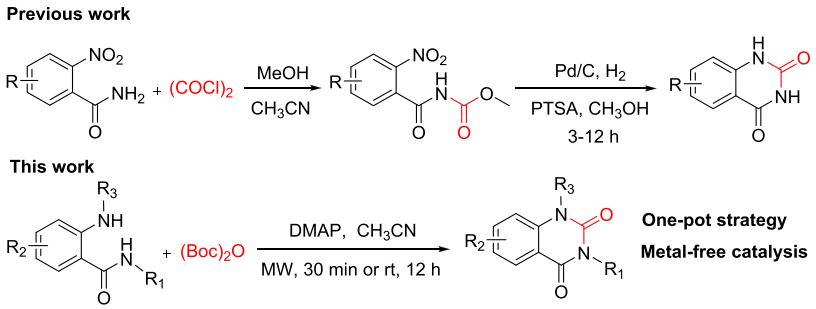
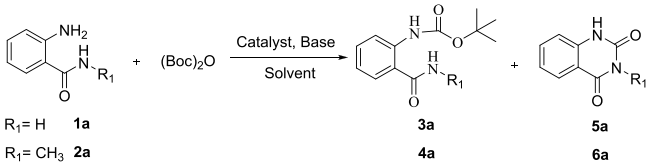


Table 1. Optimization of Reaction Conditions[a]



					yield (%)	
entry	R_1	catalyst	base	solvent	3a/4a	5a/6a
1[b]	H	DMAP	Et_3N	CH_2Cl_2	9	33
2[b]	H		Et_3N	CH_2Cl_2	9	13
3[b]	H	DMAP		CH_2Cl_2		79
4[b]	H			CH_2Cl_2	10	47
5[b]	H	TBD		CH_2Cl_2		NR[e]
6[b]	H	DBU		CH_2Cl_2		NR[e]
7[b]	H	DABCO		CH_2Cl_2		36
8[b]	H	DMAP		THF		58
9[b]	H	DMAP		DMF		61
10[b]	H	DMAP		CH_3CN		94
11[b]	CH_3	DMAP		CH_3CN	46	46
12[c]	CH_3	DMAP		CH_3CN	21	59
13[d]	CH_3	DMAP		CH_3CN		92

[a]All reactions were conducted using **1a**/**2a** (1 mmol, 1.0 equiv), $(Boc)_2O$ (1.5 mmol, 1.5 equiv), catalyst (0.1 mmol, 0.1 equiv), solvent (3 mL), isolated yield. [b]The reaction was run at room temperature for 12 h. [c]The reaction was run at reflux for 12 h. [d]The reaction was run under the microwave (MW) condition for 30 min. [e]No reaction.

triazabicyclo(4.4.0)dec-5-ene (TBD), 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU), and 1,4-diazabicyclo[2.2.2]octane (DABCO) failed to obtain any improvement (Table 1, entries 5−7). Prompted by this result, optimal solvents were examined to afford more satisfactory results. Changing CH_2Cl_2 to other organic solvents such as tetrahydrofuran (THF) and DMF led to lower yields in the range 58−61% (Table 1, entries 8, 9 vs entry 3). To our delight, the result showed that CH_3CN was the optimal solvent toward the formation of **5a** in 94% yield (Table 1, entry 10).

However, when we used the protocol of entry 10 to treat substrate **2a**, the heterocyclization could not transform completely to **6a** even under the reflux condition for 12 h (Table 1, entries 11 and 12). Fortunately, the yield of **6a** increased to 92% under the microwave (MW) condition, and the reaction time for complete conversion was shortened to 30 min (Table 1, entry 13). Consequently, we decided to use entries 13 and 10 as the optimal condition to investigate the scope and application of the reaction separately.

With the optimal conditions in hand, we then attempted to apply them to synthesize a series of 3-substituted quinazoline-2,4-diones. As shown in Table 2, the 2-amino-*N*-substituted benzamide substrates **2a**−**p** smoothly underwent heterocyclization to afford 3-substituted quinazoline-2,4-diones **6a**−**p** in good to excellent yields. We were pleased to find that the reaction was tolerant to alkyl groups (**6a**−**c**, **6k**), benzyl groups (**6d**−**j**), and aryl groups (**6l**−**p**) at the 3-position of quinazoline-2,4-dione. When the R_1 were electron-donating groups such as alkyl and benzyl, the target products were obtained in excellent yield up to 90%, especially for **6a**, **6f**, **6g**, **6j**, and **6k**. It is noticed that substrates with aryl substituents gave moderate to good yields ranging from 57 to 82% under MW conditions (**6l**−**p**). Among them, the *p*-methoxyphenyl group had a strong positive effect on this transformation in 82% yield (**6n**). Based on the capability of the benzyl group to facilitate heterocyclization under MW conditions, we further investigated the outcome when the reaction was run at room temperature. We were pleased to see that the target *N*-benzyl substituted quinazolinediones were obtained in moderate to good yields ranging from 53 to 82% at room temperature (**6d**−**j**).

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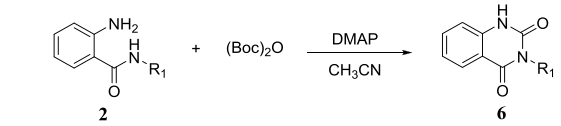
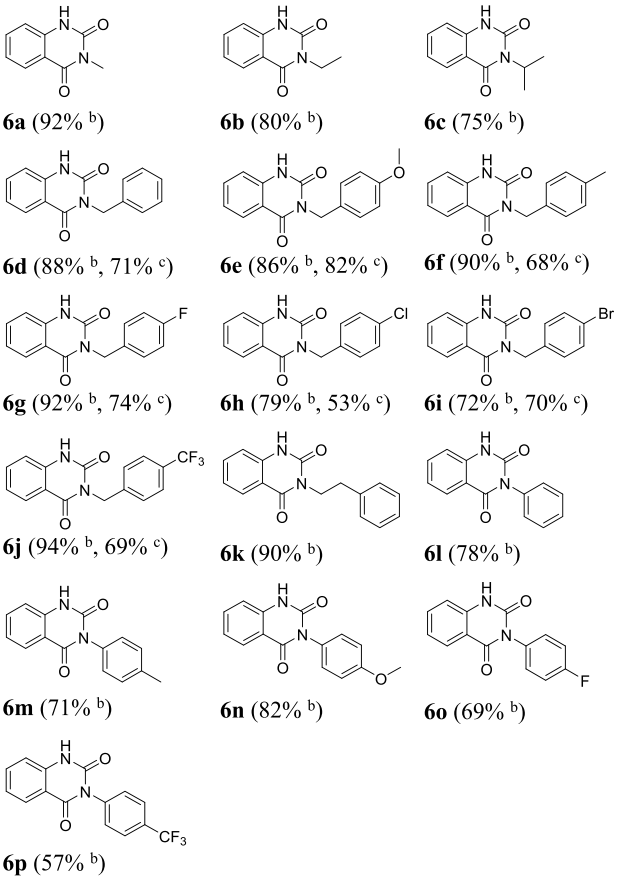
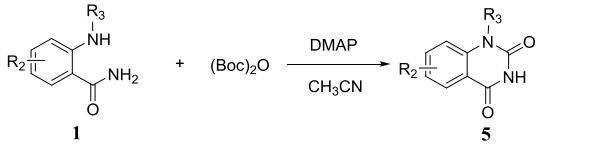
Table 2. Synthesis of 3-Substituted Quinazoline-2,4-diones 6a−p[a]

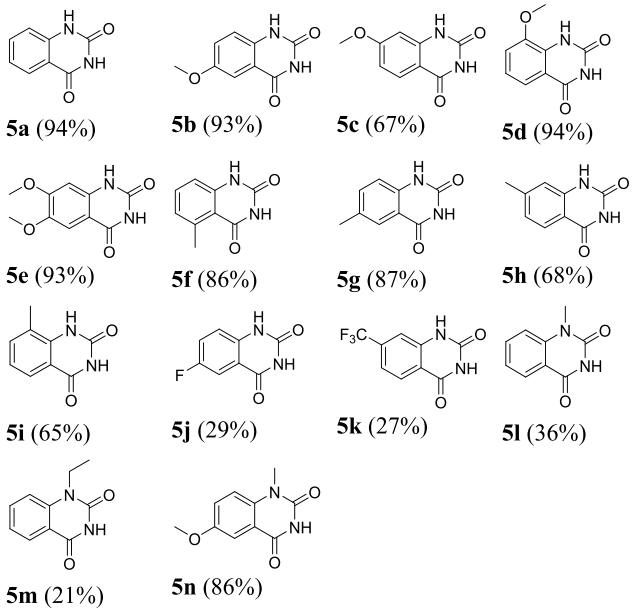




[a]All reactions were conducted using **2a−p** (1 mmol, 1.0 equiv), $(Boc)_2O$ (1.5 mmol, 1.5 equiv), DMAP (0.1 mmol, 0.1 equiv), isolated yield. [b]The reaction was run in 3 mL of CH_3CN under the MW condition for 30 min. [c]The reaction was run in 10 mL of CH_3CN at room temperature for 12 h.

Table 3. Synthesis of Quinazolin-2,4-diones Derivative 5a−n[a]





[a]All reactions were conducted using **1a−n** (1 mmol, 1.0 equiv), $(Boc)_2O$ (1.5 mmol, 1.5 equiv), DMAP (0.1 mmol, 0.1 equiv), CH_3CN (3.0 mL), under the MW condition for 30 min, isolated yield.

To investigate the substrate profile of this reaction, various substituted 2-aminobenzamide substrates with electron-donating and electron-withdrawing substituents on the phenyl ring were employed to react with $(Boc)_2O$ under the optimized conditions. It was indicated that the substrates containing electron-donating groups such as methoxyl and methyl generally gave higher yields (**5b−i** in Table 3), while the substrates containing an electron-deficient group like fluorine and trifluoromethyl substituents gave very low yields (**5j**, **5k** in Table 3). Moreover, the para-substituted amino group with methoxyl or methyl, which improves the nucleophilicity of the amino group, gave higher yields (**5b**, **5e**, **5g** in Table 3). Additionally, the 1-substituted quinazoline-2,4-diones could also be constructed in the current reaction system but in very low yields (**5l**, **5m** in Table 3). The possible reason may be the steric hindrance effect, as the compound **5m** with the ethyl group gave a lower yield compared to **5l** with the methyl group. It demonstrated that the electron-donating group on the phenyl ring was a crucial factor to facilitate the heterocyclization exemplified by **5n** vs **5l** with the yields of 86% and 36%, respectively.

Subsequently, we focused on addressing how to improve the yield of substrates with various electron-deficient groups. Inspired by the benzyl group to activate the reaction based on the results in Table 2, a series of substrates containing the *N*-*p*-methoxybenzyl (PMB) (*N*-PMB) group with various electron-deficient substitutes at different positions were investigated. We were pleased to find that PMB-activated products **8** were obtained with obviously improved yields even at room temperature compared to the corresponding nonactivated substrates under MW conditions (**8a**/**8b** in Scheme 2 vs yields for **5m**/**5j** in Table 3). Furthermore, the PMB-activated heterocyclization could smoothly occur at room temperature in moderate to good yields (**8a−h** in Scheme 2). The quinazoline-2,4-diones (**5m**, **5j**, and **5o−t**) were afforded through the *N*-PMB deprotection of **8** in the presence of ceric ammonium nitrate (CAN) in good to excellent yields. The results proved that this method is noteworthy for its utility in preparing quinazoline-2,4-diones with various functional groups at different positions in high efficiency.

Zenarestat (Figure 1), an aldose reductase inhibitor, attracted our attention due to its particular structure containing the *N*-substituted benzyl group. To validate the methodology, we synthesized the Zenarestat by the optimized reaction condition. A convenient synthetic route is shown in Scheme 3. First, the substituted 2-aminobenzamide **11** was obtained from commercially available starting materials **9** and

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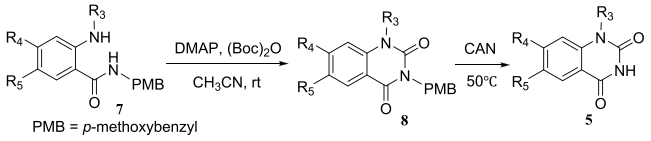
Scheme 2. PMB-Activated Substituted Quinazoline-2,4-dione Formation



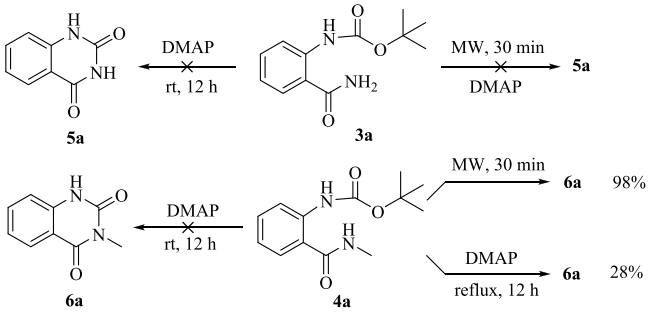
7a: R_3 = CH_2CH_3, R_4 = H, R_5 = H	**8a**: 82%	**5m**: 96%
7b: R_3 = H, R_4 = H, R_5 = F	**8b**: 53%	**5j**: 74%
7c: R_3 = H, R_4 = F, R_5 = H	**8c**: 52%	**5o**: 79%
7d: R_3 = H, R_4 = H, R_5 = Cl	**8d**: 80%	**5p**: 93%
7e: R_3 = H, R_4 = Cl, R_5 = H	**8e**: 66%	**5q**: 85%
7f: R_3 = H, R_4 = H, R_5 = Br	**8f**: 64%	**5r**: 97%
7g: R_3 = H, R_4 = Br, R_5 = H	**8g**: 51%	**5s**: 93%
7h: R_3 = H, R_4 = H, R_5 = CF_3	**8h**: 40%	**5t**: 71%

10 in 98% yield. Then, the heterocyclization could transform from **11** to **12** at room temperature for 12 h in 78% yield without column chromatographical purification. Zenarestat was afforded from the key intermediate **12** through substitution and hydrolysis in good yield. Notably, this novel method not only displayed high efficiency with total yield of 70% but also avoided regioselective alkylation of quinazolinedione disclosed in the literature.[35]

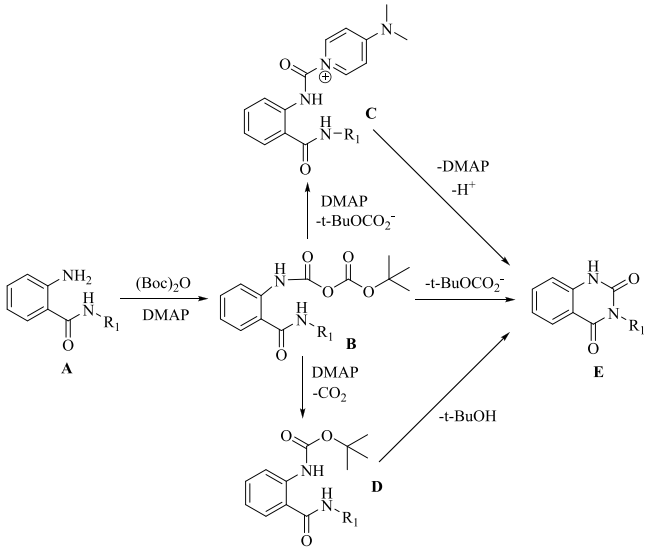
To elucidate the possible pathway of this heterocyclization, we first investigated the transformation of compounds **3a** and **4a**. However, compound **3a** did not undergo cyclization to form **5a** at room temperature or MW conditions in the presence of DMAP as speculated (Scheme 4). Meanwhile, compound **4a** could smoothly convert to the corresponding quinazolinedione **6a** in the absence of DMAP under the microwave condition for 30 min. It indicated that the alkyl-substituted amido group contributed to the cyclization.

For the formation of the target product quinazoline-2,4-diones **E**, two reaction pathways are proposed according to the reactions of amines with $(Boc)_2O$−DMAP via the unstable carbamic−carbonic anhydride intermediate **B**[34] (Scheme 5). One way is the intramolecular ammonolysis from **B** to **E**. The other way is the formation of the active intermediate **C** catalyzed by DMAP, followed by the intramolecular attack to afford **E**. Based on the above result in Scheme 4, the third pathway from **D** to **E** was suggested. Although the reaction could not occur from **D** to **E** at room temperature due to the weak nucleophilicity of benzamide and poor reactivity of bulky ester, it took place smoothly under the MW condition (R_1 = CH_3) to form **E** (Scheme 4). This could be the possible reason

Scheme 4. Exploration of the Possible Pathway



Scheme 5. Proposed Pathway for the Synthesis of Quinazolinediones with $(Boc)_2O$−DMAP

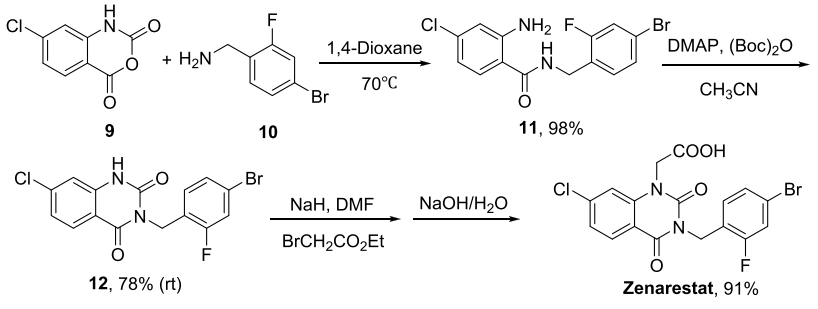


why substrates under the MW condition generally gave higher yields.

CONCLUSIONS

In summary, we have developed a novel metal-free catalysis approach to construct substituted quinazoline-2,4-diones, starting from 2-aminobenzamides and $(Boc)_2O$, based on DMAP-catalyzed heterocyclization in good to excellent yields. In particular, the PMB-activated strategy could broaden the reaction scope and offer an additional route to the formation of quinazolinediones under mild conditions. The reaction is applicable to a wide range of substrates with various functional groups at different positions, and most desired products can be obtained without requiring column chromatographical purifi-

Scheme 3. Synthetic Strategy of Zenarestat by the Optimized Reaction Condition



https://dx.doi.org/10.1021/acsomega.0c01104
ACS Omega 2020, 5, 9614−9623

cation. The high efficiency and simple manipulation render this one-pot reaction an attractive method for the synthesis of quinazolinediones.

EXPERIMENTAL SECTION

General. The reagents and solvents were obtained from commercial suppliers and used without further purification. ^{1}H and ^{13}C NMR spectra were recorded on a Varian 400 or 500 MHz NMR spectrometer with dimethyl sulfoxide (DMSO)-d_6 as a solvent. Chemical shifts are referenced to the residual solvent peak and reported in parts per million (ppm) (δ scale), and all coupling constant (J) values are given in hertz. Electrospray ionization-high-resolution mass spectrometry (ESI-HRMS) data were measured on a Thermo Exactive Orbitrap plus spectrometer. Melting points were determined on a Yanaco MP-J3 microscope melting point apparatus. All microwave reactions were carried out in single-mode CEM Explorer SP 48. Substrates **1**, **2**, and **11** were prepared according to the reported procedures.[36−40]

General Procedure for the Formation of 2-Aminobenzamides 7a−h. To a stirred suspension of isatoic anhydride (1.0 equiv) in dioxane was added 4-methoxybenzylamine (1.5 equiv) at room temperature. The mixture was then warmed up to 100 °C and stirred for 2 h. The reaction mixture was evaporated in vacuo and then purified by column chromatography (petroleum ether (PE)/ethyl acetate (EA) = 100:80) to give the desired product.

General Procedure A for the Formation of Quinazoline-2,4-diones (5a−n, 6a−p). A 10 mL sealed tube was charged with 2-aminobenzamide (1.0 mmol), $(Boc)_2O$ (1.5 mmol), and DMAP (0.1 mmol) in CH_3CN (3 mL). The reaction mixture was heated at 150 °C in MW at 150 W, 10 psi for 30 min. After cooling to room temperature, the mixture was filtrated. The obtained solid was washed with 3 mL of CH_3CN and dried to give the desired product.

General Procedure B for the Formation of Quinazoline-2,4-diones (6d−j, 8a−h, 12). To a solution of 2-aminobenzamide (1.0 mmol) in CH_3CN (10 mL) were added $(Boc)_2O$ (1.5 mmol) and DMAP (0.1 mmol). The reaction mixture was stirred at room temperature for 12 h and then filtrated. The obtained solid was washed with 3 mL of CH_3CN and dried to give the desired product.

General Procedure C for Deprotection of PMB (5m, 5j, 5o−t). To a solution of obtained **8** (1.0 equiv) in CH_3CN was added ceric ammonium nitrate (CAN) (4.0 equiv). The reaction mixture was heated at 50 °C for 2−3 h. After cooling to room temperature, the mixture was filtrated. The obtained solid was washed with 3 mL of CH_3CN and dried to give the desired product.

*Quinazoline-2,4(1H,3H)-dione (**5a**).* A white solid (152 mg, 94% yield, general procedure A), mp > 250 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.24 (brs, 2H), 7.92 (d, J = 8.0 Hz, 1H), 7.66 (t, J = 8.0 Hz, 1H), 7.22−7.19 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.0, 150.4, 141.0, 135.0, 127.1, 122.4, 115.4, 114.5; ESI-HRMS m/z calcd for $C_8H_7N_2O_2$ $[M + H]^+$ 163.0502, found: 163.0499.

*6-Methoxyquinazoline-2,4(1H,3H)-dione (**5b**).* A white solid (178 mg, 93% yield, general procedure A), mp > 250 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.25 (brs, 1H), 11.00 (brs, 1H), 7.33 (s, 1H), 7.28 (dd, J = 9.0, 2.5 Hz, 1H), 7.12 (d, J = 9.0 Hz, 1H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.8, 154.7, 150.1, 135.1, 123.9, 117.0, 114.9, 108.1, 55.6; ESI-HRMS m/z calcd for $C_9H_9N_2O_3$ $[M + H]^+$ 193.0608, found: 193.0615.

*7-Methoxyquinazoline-2,4(1H,3H)-dione (**5c**).* A white solid (129 mg, 67% yield, general procedure A), mp > 250 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.10 (brs, 1H), 11.02 (brs, 1H), 7.80 (d, J = 8.8 Hz, 1H), 6.76 (dd, J = 8.8, 2.4 Hz, 1H), 6.62 (d, J = 2.4 Hz, 1H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.4, 162.4, 150.6, 142.9, 128.9, 110.6, 107.8, 98.4, 55.7; ESI-HRMS m/z calcd for $C_9H_9N_2O_3$ $[M + H]^+$ 193.0608, found: 193.0613.

*8-Methoxyquinazoline-2,4(1H,3H)-dione (**5d**).* A white solid (180 mg, 94% yield, general procedure A), mp > 250 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.28 (brs, 1H), 10.49 (brs, 1H), 7.47 (d, J = 8.0 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 7.13 (t, J = 8.0 Hz, 1H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.8, 150.1, 146.3, 131.1, 122.3, 118.0, 115.5, 115.1, 56.3; ESI-HRMS m/z calcd for $C_9H_9N_2O_3$ $[M + H]^+$ 193.0608, found: 193.0615.

*6,7-Dimethoxyquinazoline-2,4(1H,3H)-dione (**5e**).* A white solid (207 mg, 93% yield, general procedure A), mp > 250 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.10 (brs, 1H), 10.92 (brs, 1H), 7.26 (s, 1H), 6.68 (s, 1H), 3.83 (s, 3H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.5, 155.0, 150.5, 145.1, 136.6, 107.2, 106.3, 97.8, 55.9, 55.8; ESI-HRMS m/z calcd for $C_{10}H_{11}N_2O_4$ $[M + H]^+$ 223.0713, found: 223.0708.

*5-Methylquinazoline-2,4(1H,3H)-dione (**5f**).* A white solid (151 mg, 86% yield, general procedure A), mp > 250 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.06 (brs, 1H), 11.01 (brs, 1H), 7.45 (t, J = 8.0 Hz, 1H), 7.02 (d, J = 8.0 Hz, 1H), 6.94 (d, J = 7.2 Hz, 1H), 2.65 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.7, 150.1, 142.2, 141.0, 133.8, 125.2, 113.5, 112.6, 22.2; ESI-HRMS m/z calcd for $C_9H_9N_2O_2$ $[M + H]^+$ 177.0659, found: 177.0662.

*6-Methylquinazoline-2,4(1H,3H)-dione (**5g**).* A white solid (153 mg, 87% yield, general procedure A), mp > 250 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.20 (brs, 1H), 11.05 (brs, 1H), 7.69 (dd, J = 1.6, 0.8 Hz, 1H), 7.47−7.45 (m, 1H), 7.08 (d, J = 8.4 Hz, 1H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.9, 150.4, 138.8, 136.0, 131.6, 126.5, 115.3, 114.2, 20.3; ESI-HRMS m/z calcd for $C_9H_9N_2O_2$ $[M + H]^+$ 177.0659, found: 177.0664.

*7-Methylquinazoline-2,4(1H,3H)-dione (**5h**).* A white solid (120 mg, 68% yield, general procedure A), mp > 250 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.12 (brs, 2H), 7.77 (s, 1H), 7.00−6.95 (m, 2H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.8, 150.5, 145.6, 141.0, 127.0, 123.7, 115.1, 112.1, 21.5; ESI-HRMS m/z calcd for $C_9H_9N_2O_2$ $[M + H]^+$ 177.0659, found: 177.0659.

*8-Methylquinazoline-2,4(1H,3H)-dione (**5i**).* A white solid (114 mg, 65% yield, general procedure A), mp > 250 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.33 (brs, 1H), 10.39 (brs, 1H), 7.78−7.76 (m, 1H), 7.49−7.47 (m, 1H), 7.09 (t, J = 7.6 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.0, 150.6, 139.3, 136.1, 124.8, 124.2, 122.1, 114.6, 17.3; ESI-HRMS m/z calcd for $C_9H_9N_2O_2$ $[M + H]^+$ 177.0659, found: 177.0663.

*6-Fluoroquinazoline-2,4(1H,3H)-dione (**5j**).* A white solid (52 mg, 29% yield, general procedure A; 71 mg, 74% yield, general procedure C), mp > 250 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.40 (brs, 1H), 11.19 (brs, 1H), 7.60−7.55 (m, 1H), 7.55−7.51 (m, 1H), 7.22−7.17 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.1, 157.3 (d, $J_{F,C}$ = 238 Hz), 150.0, 137.5, 122.9 (d, $J_{F,C}$ = 25 Hz), 117.6, 115.4, 112.0 (d, $J_{F,C}$ = 24

https://dx.doi.org/10.1021/acsomega.0c01104
ACS Omega 2020, 5, 9614−9623

Hz); ESI-HRMS m/z calcd for $C_8H_6FN_2O_2$ $[M + H]^+$ 181.0408, found: 181.0404.

*7-(Trifluoromethyl)quinazoline-2,4(1H,3H)-dione (**5k**).* A white solid (63 mg, 27% yield, general procedure A), mp > 250 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.54 (brs, 1H), 11.40 (brs, 1H), 8.09 (d, J = 8.4 Hz, 1H), 7.49 (dd, J = 8.4, 1.6 Hz, 1H), 7.46 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.1, 150.2, 141.3, 134.2 (q, $J_{F,C}$ = 32 Hz), 128.8, 123.4 (q, $J_{F,C}$ = 271 Hz), 118.4, 117.5, 112.3; ESI-HRMS m/z calcd for $C_9H_6F_3N_2O_2$ $[M + H]^+$ 231.0371, found: 231.0376.

*1-Methylquinazoline-2,4(1H,3H)-dione (**5l**).* A white solid (64 mg, 36% yield, general procedure A), mp > 250 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.54 (brs, 1H), 8.0 (dd, J = 8.0, 1.6 Hz, 1H), 7.79−7.74 (m, 1H), 7.42 (d, J = 8.4 Hz, 1H), 7.30−7.26 (m, 1H), 3.45 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.9, 150.3, 141.7, 135.3, 127.4, 122.5, 115.6, 114.7, 29.5; ESI-HRMS m/z calcd for $C_9H_9N_2O_2$ $[M + H]^+$ 177.0659, found: 177.0659.

*1-Ethylquinazoline-2,4(1H,3H)-dione (**5m**).* A white solid (39 mg, 21% yield, general procedure A; 149 mg, 96% yield, general procedure C), mp 219−221 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.53 (brs, 1H), 8.02 (d, J = 6.5 Hz, 1H), 7.75 (d, J = 7.0 Hz, 1H), 7.48 (d, J = 8.0 Hz, 1H), 7.27 (t, J = 7.0 Hz, 1H), 4.08 (d, J = 6.5 Hz, 2H), 1.18 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.8, 149.8, 140.6, 135.4, 127.7, 122.4, 115.8, 114.5, 37.0, 12.4; ESI-HRMS m/z calcd for $C_{10}H_{11}N_2O_2$ $[M + H]^+$ 191.0815, found: 191.0812.

*6-Methoxy-1-methylquinazoline-2,4(1H,3H)-dione (**5n**).* A white solid (178 mg, 86% yield, general procedure A), mp > 250 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.51 (brs, 1H), 7.45 (s, 1H), 7.38 (s, 2H), 3.82 (s, 3H), 3.43 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.7, 154.7, 150.1, 135.9, 123.3, 116.5, 116.4, 109.1, 55.7, 29.6; ESI-HRMS m/z calcd for $C_{10}H_{11}N_2O_3$ $[M + H]^+$ 207.0764, found: 207.0761.

*7-Fluoroquinazoline-2,4(1H,3H)-dione (**5o**).* A white solid (75 mg, 79% yield, general procedure C), mp > 250 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.34 (brs, 1H), 11.24 (brs, 1H), 7.97−7.89 (m, 1H), 7.04−6.96 (m, 1H), 6.91−6.83 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.8 (d, $J_{F,C}$ = 249 Hz), 162.0, 150.3, 142.9 (d, $J_{F,C}$ = 13 Hz), 130.2 (d, $J_{F,C}$ = 11 Hz), 111.3, 110.3 (d, $J_{F,C}$ = 23 Hz), 101.5 (d, $J_{F,C}$ = 26 Hz); ESI-HRMS m/z calcd for $C_8H_6FN_2O_2$ $[M + H]^+$ 181.0408, found: 181.0406.

*6-Chloroquinazoline-2,4(1H,3H)-dione (**5p**).* A white solid (145 mg, 93% yield, general procedure C), mp > 250 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.43 (brs, 1H), 11.27 (brs, 1H), 7.81 (t, J = 2.2 Hz, 1H), 7.70−7.64 (m, 1H), 7.18 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.8, 150.0, 139.7, 134.8, 126.3, 125.9, 117.5, 115.8; ESI-HRMS m/z calcd for $C_8H_6ClN_2O_2$ $[M + H]^+$ 197.0112, found: 197.0109.

*7-Chloroquinazoline-2,4(1H,3H)-dione (**5q**).* A white solid (110 mg, 85% yield, general procedure C), mp > 250 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.39 (brs, 1H), 11.23 (brs, 1H), 7.88 (d, J = 8.4 Hz, 1H), 7.21 (d, J = 8.4 Hz, 1H), 7.17 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.1, 150.2, 141.9, 139.3, 129.0, 122.5, 114.7, 113.3; ESI-HRMS m/z calcd for $C_8H_6ClN_2O_2$ $[M + H]^+$ 197.0112, found: 197.0113.

*6-Bromoquinazoline-2,4(1H,3H)-dione (**5r**).* A white solid (149 mg, 97% yield, general procedure C), mp > 250 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.43 (brs, 1H), 11.26 (brs, 1H), 7.93 (s, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.11 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.7, 150.0, 140.1, 137.5, 128.9, 117.8, 116.2, 113.8; ESI-HRMS m/z calcd for $C_8H_6BrN_2O_2$ $[M + H]^+$ 240.9607, found: 240.9602.

*7-Bromoquinazoline-2,4(1H,3H)-dione (**5s**).* A white solid (114 mg, 93% yield, general procedure C), mp > 250 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.39 (brs, 1H), 11.22 (brs, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.36−7.33 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.2, 150.1, 142.0, 129.0, 128.2, 125.3, 117.6, 113.6; ESI-HRMS m/z calcd for $C_8H_6BrN_2O_2$ $[M + H]^+$ 240.9607, found: 240.9602.

*6-(Trifluoromethyl)quinazoline-2,4(1H,3H)-dione (**5t**).* Following general procedure C, **5t** was purified by column chromatography (CH_2Cl_2/CH_3OH = 100:1) to afford a white solid (65 mg, 71% yield), mp > 250 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.55 (brs, 1H), 11.37 (brs, 1H), 8.07 (d, J = 8.0 Hz, 1H), 7.47 (d, J = 8.0 Hz, 1H), 7.44 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.0, 150.1, 141.2, 134.2 (q, $J_{F,C}$ = 32 Hz), 128.7, 123.4 (q, $J_{F,C}$ = 272 Hz), 118.3, 117.4, 112.2; ESI-HRMS m/z calcd for $C_9H_6F_3N_2O_2$ $[M + H]^+$ 231.0376, found: 231.0376.

*3-Methylquinazoline-2,4(1H,3H)-dione (**6a**).* A white solid (162 mg, 92% yield, general procedure A), mp > 250 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.43 (brs, 1H), 7.93 (d, J = 7.0 Hz, 1H), 7.64 (d, J = 7.0 Hz, 1H), 7.19 (dd, J = 13.5, 7.5 Hz, 2H), 3.26 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.2, 150.4, 139.4, 134.9, 127.3, 122.5, 115.1, 113.8, 27.1; ESI-HRMS m/z calcd for $C_9H_9N_2O_2$ $[M + H]^+$ 177.0659, found: 177.0659.

*3-Ethylquinazoline-2,4(1H,3H)-dione (**6b**).* A white solid (153 mg, 80% yield, general procedure A), mp 202−204 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.40 (brs, 1H), 7.93 (d, J = 6.5 Hz, 1H), 7.65 (s, 1H), 7.20−7.17 (m, 2H), 3.90−3.95 (m, 2H), 1.15 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.7, 150. 0, 139.4, 134.9, 127.4, 122.5, 115.1, 113.9, 35.1, 13.0; ESI-HRMS m/z calcd for $C_{10}H_{11}N_2O_2$ $[M + H]^+$ 191.0815, found: 191.0813.

*3-Isopropylquinazoline-2,4(1H,3H)-dione (**6c**).* A white solid (153 mg, 75% yield, general procedure A), mp 97−98 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.27 (brs, 1H), 7.92 (d, J = 8.0 Hz, 1H), 7.63 (t, J = 7.5 Hz, 1H), 7.20−7.14 (m, 2H), 5.17−5.12 (m, 1H), 1.44 (s, 3H), 1.43 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.3, 150.2, 139.5, 134.9, 127.5, 122.4, 114.9, 114.3, 44.4, 19.3; ESI-HRMS m/z calcd for $C_{11}H_{13}N_2O_2$ $[M + H]^+$ 205.0972, found: 205.0970.

*3-Benzylquinazoline-2,4(1H,3H)-dione (**6d**).* A white solid (223 mg, 88% yield, general procedure A; 179 mg, 71% yield, general procedure B), mp 230−231 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.53 (brs, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.70−7.65 (m, 1H), 7.32−7.30 (m, 4H), 7.25−7.19 (m, 3H), 5.09 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.1, 150.3, 139.5, 137.5, 135.3, 128.4, 127.6, 127.2, 122.7, 115.3, 113.8, 43.2; ESI-HRMS m/z calcd for $C_{15}H_{13}N_2O_2$ $[M + H]^+$ 253.0972, found: 253.0978.

*3-(4-Methoxybenzyl)quinazoline-2,4(1H,3H)-dione (**6e**).* A white solid (243 mg, 86% yield, general procedure A; 232 mg, 82% yield, general procedure B), mp 224−225 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.49 (brs, 1H), 7.94 (d, J = 7.5 Hz, 1H), 7.66 (t, J = 7.5 Hz, 1H), 7.28 (d, J = 8.5 Hz, 2H), 7.21 (dd, J = 12.5, 8.0 Hz, 2H), 6.86 (d, J = 8.5 Hz, 2H), 5.02 (s, 2H), 3.71 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.0, 158.5, 150.3, 139.5, 135.2, 129.5, 129.4, 127.5, 122.7, 115.3, 113.8, 55.1, 42.6; ESI-HRMS m/z calcd for $C_{16}H_{15}N_2O_3$ $[M + H]^+$ 283.1077, found: 283.1086.

https://dx.doi.org/10.1021/acsomega.0c01104
ACS Omega 2020, 5, 9614−9623

3-(4-Methylbenzyl)quinazoline-2,4(1H,3H)-dione (**6f**). A white solid (240 mg, 90% yield, general procedure A; 182 mg, 68% yield, general procedure B), mp 240−242 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.51 (brs, 1H), 7.94 (dd, J = 8.8, 1.6 Hz, 1H), 7.69−7.65 (m, 1H), 7.23−7.19 (m, 4H), 7.11 (d, J = 8.0 Hz, 2H), 5.05 (s, 2H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.0, 150.3, 139.5, 136.3, 135.2, 134.5, 130.8, 128.9, 127.7, 127.5, 115.3, 113.8, 43.0, 20.7; ESI-HRMS m/z calcd for $C_{16}H_{15}N_2O_2$ $[M + H]^+$ 267.1128, found: 267.1134.

3-(4-Fluorobenzyl)quinazoline-2,4(1H,3H)-dione (**6g**). A white solid (248 mg, 92% yield, general procedure A; 200 mg, 74% yield, general procedure B), mp > 250 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.54 (brs, 1H), 7.95 (d, J = 7.5 Hz, 1H), 7.66 (t, J = 7.5 Hz, 1H), 7.40 (dd, J = 8.0, 6.0 Hz, 2H), 7.20 (t, J = 7.5 Hz, 2H), 7.14 (t, J = 9.0 Hz, 2H), 5.08 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.0, 161.4 (d, $J_{F,C}$ = 242 Hz), 150.3, 139.5, 135.3, 133.7, 129.9, 127.5, 122.7, 115.3, 115.2 (d, $J_{F,C}$ = 26 Hz), 113.8, 42.6; ESI-HRMS m/z calcd for $C_{15}H_{12}FN_2O_2$ $[M + H]^+$ 271.0877, found: 271.0883.

3-(4-Chlorobenzyl)quinazoline-2,4(1H,3H)-dione (**6h**). A white solid (226 mg, 79% yield, general procedure A; 151 mg, 53% yield, general procedure B), mp 245−247 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.55 (brs, 1H), 7.95 (dd, J = 8.0, 1.6 Hz, 1H), 7.70−7.66 (m, 1H), 7.39−7.33 (m, 4H), 7.28−7.15 (m, 2H), 5.07 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.0, 150.2, 139.5, 136.5, 135.3, 131.8, 129.6, 128.4, 127.5, 122.7, 115.3, 113.7, 42.7; ESI-HRMS m/z calcd for $C_{15}H_{12}ClN_2O_2$ $[M + H]^+$ 287.0582, found: 287.0570.

3-(4-Bromobenzyl)quinazoline-2,4(1H,3H)-dione (**6i**). A white solid (239 mg, 72% yield, general procedure A; 232 mg, 70% yield, general procedure B), mp > 250 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.56 (brs, 1H), 7.95 (dd, J = 8.8, 1.2 Hz, 1H), 7.70−7.66 (m, 1H), 7.52−7.49 (m, 2H), 7.31−7.27 (m, 2H), 7.22 (t, J = 8.0 Hz, 2H), 5.06 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.0, 150.2, 139.5, 136.9, 135.3, 131.3, 129.9, 127.5, 122.7, 120.3, 115.3, 113.7, 42.7; ESI-HRMS m/z calcd for $C_{15}H_{12}BrN_2O_2$ $[M + H]^+$ 331.0077, found: 331.0071.

3-(4-(Trifluoromethyl)benzyl)quinazoline-2,4(1H,3H)-dione (**6j**). A white solid (300 mg, 94% yield, general procedure A; 221 mg, 69% yield, general procedure B), mp > 250 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.60 (brs, 1H), 7.96 (d, J = 8.0 Hz, 1H), 7.71−7.66 (m, 3H), 7.54 (d, J = 8.0 Hz, 2H), 7.25−7.23 (m, 2H), 5.19 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.1, 150.3, 142.2, 139.6, 135.3, 128.2, 127.8 (q, $J_{F,C}$ = 32 Hz), 127.5, 125.3, 124.3 (q, $J_{F,C}$ = 270 Hz), 122.8, 115.4, 113.7, 43.0; ESI-HRMS m/z calcd for $C_{16}H_{12}F_3N_2O_2$ $[M + H]^+$ 321.0845, found: 321.0852.

3-Phenethylquinazoline-2,4(1H,3H)-dione (**6k**). A white solid (239 mg, 90% yield, general procedure A), mp 219−221 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.44 (brs, 1H), 7.94 (dd, J = 8.0, 1.6 Hz, 1H), 7.68−7.64 (m, 1H), 7.32−7.29 (m, 2H), 7.25−7.19 (m, 5H), 4.13−4.09 (m, 2H), 2.90−2.86 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.8, 150.1, 139.5, 138.7, 135.0, 128.7, 128.5, 127.4, 126.4, 122.5, 115.2, 113.8, 41.3, 33.4; ESI-HRMS m/z calcd for $C_{16}H_{15}N_2O_2$ $[M + H]^+$ 267.1128, found: 267.1121.

3-Phenylquinazoline-2,4(1H,3H)-dione (**6l**). A white solid (185 mg, 78% yield, general procedure A), mp > 250 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.54 (brs, 1H), 7.94 (d, J = 7.5 Hz, 1H), 7.70 (t, J = 7.5 Hz, 1H), 7.48 (t, J = 7.5 Hz, 2H), 7.42 (t, J = 7.5 Hz, 1H), 7.32 (d, J = 7.0 Hz, 2H), 7.23 (t, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.3, 150.3, 139.9, 135.8, 135.3, 129.2, 128.9, 128.2, 127.7, 122.6, 115.3, 114.4; ESI-HRMS m/z calcd for $C_{14}H_{11}N_2O_2$ $[M + H]^+$ 239.0815, found: 239.0821.

3-(4-Methylphenyl)quinazoline-2,4(1H,3H)-dione (**6m**). A white solid (178 mg, 71% yield, general procedure A), mp > 250 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.51 (brs, 1H), 7.93 (dd, J = 8.4, 1.6 Hz, 1H), 7.71−7.67 (m, 1H), 7.29−7.26 (m, 2H), 7.24−7.21 (m, 2H), 7.20−7.16 (m, 2H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.3, 150.3, 139.9, 137.5, 135.2, 133.2, 129.4, 128.9, 127.7, 122.6, 115.3, 114.4, 20.8; ESI-HRMS m/z calcd for $C_{15}H_{13}N_2O_2$ $[M + H]^+$ 253.0972, found: 253.0968.

3-(4-Methoxyphenyl)quinazoline-2,4(1H,3H)-dione (**6n**). A white solid (219 mg, 82% yield, general procedure A), mp > 250 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.50 (brs, 1H), 7.93 (dd, J = 8.4, 1.6 Hz, 1H), 7.71−7.67 (m, 1H), 7.24−7.20 (m, 4H), 7.03−6.99 (m, 2H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.5, 158.9, 150.5, 139.9, 135.2, 130.1, 128.3, 127.7, 122.5, 115.2, 114.4, 114.1, 55.4; ESI-HRMS m/z calcd for $C_{15}H_{13}N_2O_3$ $[M + H]^+$ 269.0921, found: 269.0919.

3-(4-Fluorophenyl)quinazoline-2,4(1H,3H)-dione (**6o**). A white solid (177 mg, 69% yield, general procedure A), mp > 250 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.55 (brs, 1H), 7.94 (d, J = 8.0 Hz, 1H), 7.70 (t, J = 8.0 Hz, 1H), 7.40−7.37 (m, 2H), 7.31 (t, J = 9.0 Hz, 2H), 7.24−7.22 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.3, 161.6 (d, $J_{F,C}$ = 243 Hz), 150.3, 139.9, 135.3, 132.0, 131.3, 127.7, 122.6, 115.7 (d, $J_{F,C}$ = 22 Hz), 115.3, 114.4; ESI-HRMS m/z calcd for $C_{14}H_{10}FN_2O_2$ $[M + H]^+$ 257.0721, found: 257.0715.

3-(4-(Trifluoromethyl)phenyl)quinazoline-2,4(1H,3H)-dione (**6p**). A white solid (175 mg, 57% yield, general procedure A), mp > 250 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.64 (brs, 1H), 7.95 (d, J = 7.5 Hz, 1H), 7.88 (d, J = 8.0 Hz, 2H), 7.72 (t, J = 7.5 Hz, 1H), 7.62 (d, J = 8.0 Hz, 2H), 7.25 (d, J = 7.0 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.2, 150.0, 140.0, 139.7, 135.4, 130.4, 128.8 (d, $J_{F,C}$ = 32 Hz), 127.7, 126.0, 124.6 (d, J = 271 Hz), 122.7, 115.4, 114.4; ESI-HRMS m/z calcd for $C_{15}H_{10}F_3N_2O_2$ $[M + H]^+$ 307.0689, found: 307.0682.

2-(Ethylamino)-N-(4-methoxybenzyl)benzamide (**7a**). A white solid (1.00 g, 84% yield), mp 90−92 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.79 (brs, 1H), 7.74 (brs, 1H), 7.59 (d, J = 7.5 Hz, 1H), 7.27 (d, J = 7.5 Hz, 1H), 7.23 (d, J = 8.5 Hz, 2H), 6.88 (d, J = 8.0 Hz, 2H), 6.65 (d, J = 8.5 Hz, 1H), 6.54 (t, J = 7.5 Hz, 1H), 4.35 (d, J = 5.5 Hz, 2H), 3.72 (s, 3H), 3.13−3.08 (m, 2H), 1.18 (t, J = 7.0 Hz, 3H); ESI-HRMS m/z calcd for $C_{17}H_{21}N_2O_2$ $[M + H]^+$ 285.1598, found: 285.1590.

2-Amino-5-fluoro-N-(4-methoxybenzyl)benzamide (**7b**). A white solid (1.20 g, 88% yield), mp 114−116 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.77 (t, J = 8.0 Hz, 1H), 7.38 (dd, J = 10.4, 3.2 Hz, 1H), 7.23 (d, J = 8.8 Hz, 2H), 7.07−7.02 (m, 1H), 6.88 (d, J = 8.8 Hz, 2H), 6.70 (dd, J = 9.2, 5.2 Hz, 1H), 6.32 (brs, 2H), 4.34 (d, J = 6.0 Hz, 2H), 3.72 (s, 3H); ESI-HRMS m/z calcd for $C_{15}H_{16}FN_2O_2$ $[M + H]^+$ 275.1190, found: 275.1185.

2-Amino-4-fluoro-N-(4-methoxybenzyl)benzamide (**7c**). A white solid (1.13 g, 82% yield), mp 110−112 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.71 (t, J = 6.0 Hz, 1H), 7.59 (dd, J = 8.8, 6.8 Hz, 1H), 7.23 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 6.76 (brs, 2H), 6.47 (dd, J = 12.0, 2.8 Hz, 1H), 6.33−6.29 (m, 1H), 4.34 (d, J = 6.0 Hz, 2H), 3.72 (s, 3H); ESI-

https://dx.doi.org/10.1021/acsomega.0c01104
ACS Omega 2020, 5, 9614−9623

HRMS m/z calcd for $C_{15}H_{16}FN_2O_2$ $[M + H]^+$ 275.1190, found: 275.1186.

*2-Amino-5-chloro-N-(4-methoxybenzyl)benzamide (**7d**).* A white solid (1.23 g, 85% yield), mp 142−144 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.83 (t, J = 6.0 Hz, 1H), 7.58 (d, J = 2.4 Hz, 1H), 7.23 (d, J = 8.8 Hz, 2H), 7.16 (dd, J = 8.8, 2.4 Hz, 1H), 6.90−6.87 (m, 2H), 6.72 (d, J = 8.8 Hz, 1H), 6.57 (brs, 2H), 4.33 (d, J = 5.6 Hz, 2H), 3.72 (s, 3H); ESI-HRMS m/z calcd for $C_{15}H_{16}ClN_2O_2$ $[M + H]^+$ 291.0895, found: 291.0890.

*2-Amino-4-chloro-N-(4-methoxybenzyl)benzamide (**7e**).* A white solid (0.95 g, 82% yield), mp 122−124 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, J = 7.5 Hz, 2H), 7.21 (d, J = 8.0 Hz, 1H), 6.89 (d, J = 8.5 Hz, 2H), 6.68 (s, 1H), 6.57 (d, J = 7.5 Hz, 1H), 6.19 (brs, 1H), 5.73 (brs, 2H), 4.51 (d, J = 5.0 Hz, 2H), 3.80 (s, 3H); ESI-HRMS m/z calcd for $C_{15}H_{16}ClN_2O_2$ $[M + H]^+$ 291.0895, found: 291.0891.

*2-Amino-5-bromo-N-(4-methoxybenzyl)benzamide (**7f**).* A white solid (1.48 g, 88% yield), mp 153−155 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.84 (t, J = 6.0 Hz, 1H), 7.69 (d, J = 2.4 Hz, 1H), 7.26 (dd, J = 9.2, 2.8 Hz, 1H), 7.23 (d, J = 8.4 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 6.67 (d, J = 8.8 Hz, 1H), 6.59 (brs, 2H), 4.33 (d, J = 5.6 Hz, 2H), 3.72 (s, 3H); ESI-HRMS m/z calcd for $C_{15}H_{16}BrN_2O_2$ $[M + H]^+$ 335.0390, found: 335.0381.

*2-Amino-4-bromo-N-(4-methoxybenzyl)benzamide (**7g**).* A white solid (1.16 g, 87% yield), mp 141−143 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.78 (t, J = 6.0 Hz, 1H), 7.46 (d, J = 8.4 Hz, 1H), 7.23 (d, J = 8.8 Hz, 2H), 6.92 (d, J = 2.0 Hz, 1H), 6.88 (d, J = 8.4 Hz, 2H), 6.75−6.54 (m, 3H), 4.33 (d, J = 5.6 Hz, 2H), 3.72 (s, 3H); ESI-HRMS m/z calcd for $C_{15}H_{16}BrN_2O_2$ $[M + H]^+$ 335.0390, found: 335.0382.

*2-Amino-N-(4-methoxybenzyl)-5-(trifluoromethyl)-benzamide (**7h**).* A white solid (370 mg, 85% yield), mp 175−177 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.93 (t, J = 6.0 Hz, 1H), 7.69 (d, J = 8.4 Hz, 1H), 7.24 (d, J = 8.8 Hz, 2H), 7.05 (d, J = 1.6 Hz, 1H), 6.89 (d, J = 8.4 Hz, 2H), 6.79 (dd, J = 8.4, 2.0 Hz, 1H), 6.74 (brs, 2H), 4.37 (d, J = 5.6 Hz, 2H), 3.73 (s, 3H); ESI-HRMS m/z calcd for $C_{16}H_{16}F_3N_2O_2$ $[M + H]^+$ 325.1158, found: 325.1157.

*1-Ethyl-3-(4-methoxybenzyl)quinazoline-2,4(1H,3H)-dione (**8a**).* Following general procedure B, **8a** was purified by column chromatography (CH_2Cl_2/CH_3OH = 100:1) to afford a white solid (253 mg, 82% yield), mp 120−121 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.08 (dd, J = 8.0, 1.6 Hz, 1H), 7.80−7.76 (m, 1H), 7.51 (d, J = 8.4 Hz, 1H), 7.32−7.28 (m, 3H), 6.89−6.85 (m, 2H), 5.07 (s, 2H), 4.15 (q, J = 7.2 Hz, 2H), 3.71 (s, 3H), 1.21 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.1, 158.5, 150.0, 139.4, 135.6, 129.4, 129.3, 128.2, 122.8, 115.0, 114.5, 113.8, 55.1, 43.7, 38.4, 12.5; ESI-HRMS m/z calcd for $C_{18}H_{19}N_2O_3$ $[M + H]^+$ 311.1390, found: 311.1382.

*6-Fluoro-3-(4-methoxybenzyl)quinazoline-2,4(1H,3H)-dione (**8b**).* A white solid (160 mg, 53% yield, general procedure B), mp > 250 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.56 (brs, 1H), 7.64 (dd, J = 8.6, 3.0 Hz, 1H), 7.57 (td, J = 8.7, 3.0 Hz, 1H), 7.28 (d, J = 8.4 Hz, 2H), 7.23 (dd, J = 8.8, 4.2 Hz, 1H), 6.86 (d, J = 8.4 Hz, 2H), 5.00 (s, 2H), 3.71 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.2, 158.5, 157.4 (d, $J_{F,C}$ = 239 Hz), 149.9, 136.1, 129.3, 129.2, 123.1 (d, $J_{F,C}$ = 24 Hz), 117.5, 114.7, 113.7, 112.3 (d, $J_{F,C}$ = 23 Hz), 55.0, 42.7; ESI-HRMS m/z calcd for $C_{16}H_{14}FN_2O_3$ $[M + H]^+$ 301.0983, found: 301.0979.

*7-Fluoro-3-(4-methoxybenzyl)quinazoline-2,4(1H,3H)-dione (**8c**).* A white solid (157 mg, 52% yield, general procedure B), mp > 250 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.61 (brs, 1H), 7.99 (dd, J = 8.8, 6.2 Hz, 1H), 7.28 (d, J = 8.7 Hz, 2H), 7.05 (td, J = 8.7, 2.5 Hz, 1H), 6.91 (dd, J = 9.8, 2.5 Hz, 1H), 6.85 (d, J = 8.7 Hz, 2H), 4.99 (s, 2H), 3.70 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.8 (d, $J_{F,C}$ = 250 Hz), 161.1, 158.4, 150.1, 141.4, 130.8, 129.3, 129.2, 113.7, 110.8, 110.7 (d, $J_{F,C}$ = 23 Hz), 101.3 (d, $J_{F,C}$ = 23 Hz), 55.0, 42.6; ESI-HRMS m/z calcd for $C_{16}H_{14}FN_2O_3$ $[M + H]^+$ 301.0983, found: 301.0978.

*6-Chloro-3-(4-methoxybenzyl)quinazoline-2,4(1H,3H)-dione (**8d**).* A white solid (252 mg, 80% yield, general procedure B), mp > 250 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.63 (brs, 1H), 7.86 (d, J = 2.5 Hz, 1H), 7.69 (dd, J = 8.7, 2.5 Hz, 1H), 7.28 (d, J = 8.8 Hz, 2H), 7.20 (d, J = 8.7 Hz, 1H), 6.85 (d, J = 8.7 Hz, 2H), 4.99 (s, 2H), 3.70 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.9, 158.5, 149.9, 138.3, 134.9, 129.3, 129.1, 126.5, 126.3, 117.4, 115.1, 113.7, 55.0, 42.8; ESI-HRMS m/z calcd for $C_{16}H_{14}ClN_2O_3$ $[M + H]^+$ 317.0687, found: 317.0682.

*7-Chloro-3-(4-methoxybenzyl)quinazoline-2,4(1H,3H)-dione (**8e**).* A white solid (210 mg, 66% yield, general procedure B), mp > 250 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.61 (brs, 1H), 7.93 (d, J = 8.5 Hz, 1H), 7.33−7.22 (m, 3H), 7.20 (s, 1H), 6.86 (d, J = 8.1 Hz, 2H), 4.99 (s, 2H), 3.71 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.2, 158.5, 150.0, 140.4, 139.4, 129.5, 129.3, 129.1, 122.8, 114.5, 113.7, 112.7, 55.0, 42.7; ESI-HRMS m/z calcd for $C_{16}H_{14}ClN_2O_3$ $[M + H]^+$ 317.0687, found: 317.0686.

*6-Bromo-3-(4-methoxybenzyl)quinazoline-2,4(1H,3H)-dione (**8f**).* A white solid (230 mg, 64% yield, general procedure B), mp > 250 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.63 (brs, 1H), 8.00 (d, J = 2.4 Hz, 1H), 7.82 (dd, J = 8.7, 2.4 Hz, 1H), 7.28 (d, J = 8.2 Hz, 2H), 7.14 (d, J = 8.7 Hz, 1H), 6.85 (d, J = 8.2 Hz, 2H), 5.00 (s, 2H), 3.71 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.8, 158.5, 149.9, 138.6, 137.6, 129.3, 129.1, 117.7, 115.5, 114.0, 113.7, 55.0, 42.8; ESI-HRMS m/z calcd for $C_{16}H_{14}BrN_2O_3$ $[M + H]^+$ 361.0182, found: 361.0189.

*7-Bromo-3-(4-methoxybenzyl)quinazoline-2,4(1H,3H)-dione (**8g**).* A white solid (185 mg, 51% yield, general procedure B), mp > 250 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.58 (brs, 1H), 7.85 (d, J = 8.4 Hz, 1H), 7.37 (d, J = 8.4 Hz, 1H), 7.35 (d, J = 1.7 Hz, 1H), 7.27 (d, J = 8.7 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H), 4.99 (s, 2H), 3.70 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.3, 158.4, 150.0, 140.5, 129.5, 129.3, 129.1, 128.4, 125.6, 117.5, 113.7, 113.0, 55.0, 42.7; ESI-HRMS m/z calcd for $C_{16}H_{14}BrN_2O_3$ $[M + H]^+$ 361.0182, found: 361.0180.

*6-(Trifluoromethyl)-3-(4-methoxybenzyl)quinazoline-2,4-(1H,3H)-dione (**8h**).* Following general procedure B, **8h** was purified by column chromatography (CH_2Cl_2/CH_3OH = 100:1) to afford a white solid (140 mg, 40% yield), mp > 250 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.76 (brs, 1H), 8.14 (d, J = 8.2 Hz, 1H), 7.52 (d, J = 8.2 Hz, 1H), 7.48 (s, 1H), 7.29 (d, J = 8.2 Hz, 2H), 6.86 (d, J = 8.5 Hz, 2H), 5.02 (s, 2H), 3.71 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.1, 158.5, 150.0, 139.7, 134.2 (q, $J_{F,C}$ = 32 Hz), 129.3, 129.2, 129.0, 123.3 (q, $J_{F,C}$ = 272 Hz), 118.5, 116.7, 113.7, 112.1, 55.0, 42.8; ESI-HRMS m/z calcd for $C_{17}H_{14}F_3N_2O_3$ $[M + H]^+$ 351.0951, found: 351.0949.

https://dx.doi.org/10.1021/acsomega.0c01104
ACS Omega 2020, 5, 9614−9623

*3-(4-Bromo-2-fluorobenzyl)-7-chloroquinazoline-2,4-(1H,3H)-dione (**12**).* A white solid (300 mg, 78% yield, general procedure B), mp > 250 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.70 (brs, 1H), 7.93 (d, J = 8.4 Hz, 1H), 7.53 (dd, J = 10.0, 2.0 Hz, 1H), 7.33 (dd, J = 8.0, 1.6 Hz, 1H), 7.26 (dd, J = 8.4, 1.6 Hz, 1H), 7.22−7.21 (m, 1H), 7.18 (d, J = 8.0 Hz, 1H), 5.07 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.3, 159.9 (q, $J_{F,C}$ = 249 Hz), 150.0, 140.7, 139.6, 130.4, 129.6, 127.6, 123.7, 122.9, 120.3, 118.6, 114.7, 112.7, 37.2; ESI-HRMS m/z calcd for $C_{15}H_{10}BrClFN_2O_2$ $[M + H]^+$ 382.9593, found: 382.9578.

General Procedures for the Preparation of Zenarestat. To a suspension of **12** (0.30 g, 0.78 mmol) in dry DMF (4 mL) was added NaH (0.031 g, 60% dispersion in mineral oil, 0.78 mmol) in batches cooled with an ice bath. The reaction mixture was stirred at 0 °C for 4 h, followed by the addition of a solution of ethyl bromoacetate (0.19 g, 1.17 mmol) in dry DMF (4.0 mL) dropwise. The reaction mixture was stirred at room temperature for an additional 6 h. The solvent was removed under reduced pressure, and to the residue was added aqueous sodium hydroxide solution (0.049 g in 12 mL of H_2O). The reaction mixture was heated to reflux and stirred for 1 h until the completion of the reaction. The hot solution was filtered to remove insoluble particulate. After cooling to room temperature, the filtrate was acidified with 1 N HCl to pH 3−4. The suspension was cooled with an ice bath for 1 h and then filtrated. The obtained solid was washed with 5 mL of aqueous methanol (1:1) and dried to afford the Zenarestat (313 mg, 91%, two-step) as a white solid. mp 225−226 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.33 (brs, 1H), 8.08 (d, J = 8.0 Hz, 1H), 7.65 (s, 1H), 7.54 (d, J = 9.5 Hz, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.34 (d, J = 8.0 Hz, 1H), 7.15 (t, J = 8.0 Hz, 1H), 5.14 (s, 2H), 4.90 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.4, 160.4, 159.9 (d, $J_{F,C}$ = 249 Hz), 150.4, 141.2, 140.6, 130.4, 130.1, 127.7, 123.6, 123.4, 120.6, 118.8 (d, $J_{F,C}$ = 25 Hz), 114.8, 113.5, 45.3, 38.2; ESI-HRMS m/z calcd for $C_{17}H_{12}BrClFN_2O_4$ $[M + H]^+$ 440.9648, found: 440.9666.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.0c01104.

Copies of ^{1}H NMR and ^{13}C NMR spectra for quinazoline-2,4-diones (**5**, **6**, **8**, and **12**), 2-aminobenzamide (**7**), and Zenarestat (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Gang Li − *Beijing Key Laboratory of Active Substance Discovery and Druggability Evaluation & Chinese Academy of Medical Sciences Key Laboratory of Anti-DR TB Innovative Drug Research, Institute of Materia Medica, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing 100050, P. R. China*; Email: ligang@imm.ac.cn

Haihong Huang − *Beijing Key Laboratory of Active Substance Discovery and Druggability Evaluation & Chinese Academy of Medical Sciences Key Laboratory of Anti-DR TB Innovative Drug Research, Institute of Materia Medica, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing 100050, P. R. China*; Email: joyce@imm.ac.cn

Authors

Hui Chen − *Beijing Key Laboratory of Environmental and Viral Oncology, College of Life Science and Bio-engineering, Beijing University of Technology, Beijing 100124, P. R. China*

Peng Li − *Beijing Key Laboratory of Active Substance Discovery and Druggability Evaluation & Chinese Academy of Medical Sciences Key Laboratory of Anti-DR TB Innovative Drug Research, Institute of Materia Medica, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing 100050, P. R. China*

Rongfei Qin − *Beijing Key Laboratory of Active Substance Discovery and Druggability Evaluation & Chinese Academy of Medical Sciences Key Laboratory of Anti-DR TB Innovative Drug Research, Institute of Materia Medica, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing 100050, P. R. China*

Hong Yan − *Beijing Key Laboratory of Environmental and Viral Oncology, College of Life Science and Bio-engineering, Beijing University of Technology, Beijing 100124, P. R. China*; orcid.org/0000-0002-3832-9261

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.0c01104

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the National Natural Science Foundation of China under Grant no. 81703362 and the CAMS Innovation Fund for Medical Sciences under Grant CAMS-2016-I2M-1-010.

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https://dx.doi.org/10.1021/acsomega.0c01104
ACS Omega 2020, 5, 9614−9623