Parallel Solution Phase Synthesis of 3,6,7−4(3*H*)-Quinazolinones and Evaluation of Their Antitumor Activities against Human Cancer

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Three diversity points of 4(3*H*)-quinazolinone are introduced at the 3-, 6-, and 7-positions with an efficient parallel solution-phase synthetic method. A one-pot synthesis was developed that gave the key intermediate in high yield. Five hit compounds exhibit preferable activities against a panel of human tumor cell lines, which pointed out preliminary structure−activity relationships.

Introduction

The 4(3*H*)-quinazolinone core is well-known as a "privileged structure"[1] for drug design, which is defined as a class of molecules that are capable of binding to multiple receptors with high affinity.[2] The potential therapeutic applications of 4(3*H*)-quinazolinones include antiviral,[3] antihypertensive,[4] cardiotonic,[5] antiulcerative,[6] anticoccidia,[7] antineoplastic,[8] 5-HT_3 antagonist,[9]and antiemetic[10]activities. Two of its derivatives have been clinically used as a muscle relaxant (afloqualone **I**[11]) or as an antifolate (raltiterxed **II**[12]) for the first-line palliative treatment of advanced colorectal cancer. Some others, exhibiting activities of calcium channel antagonist **III**,[13] 5-hydroxytryptamine release inhibitor **IV**,[14] antiulcer **V**,[15] and antifungal activity **VI**,[16] have been studied in preclinic or clinical trials (Figure 1).

A standard procedure in literature for synthesis of 4(3*H*)-quinazolinones is the condensation of a C1-source with 2-aminobenzonitrile,[17] 2-aminobenzoic acid,[18] or 2-aminobenzamide[19] (Scheme 1). The relevant methods are well documented in a recent review.[20] In this article, we report a one-pot synthetic route to synthesize 4(3*H*)-quinazolinones to further extend our "scaffold-directed" strategy by using a raw material of 5-chloro-2,4-dinitrobenzoic acid (CDBC, **1**)[19,21] instead of 1,5-difluoro-2,4-dinitrobenzene (DFDNB).[22] This method not only afforded 4(3*H*)-quinazolinones skeleton from *o*-nitrobenzamides in one-pot but also introduced three diversity points at 3-, 6-, 7-positions.

Results and Discussion

The new synthetic route for the synthesis of 3,6,7-trisubstituted 4(3*H*)-quinazolinones (**12**, **14**, and **15**) is depicted in Scheme 2. Starting from **1**, three types of nucleophilic reagents (secondary amines, phenols, and alcohols) were used for the introduction of the first diversity element at 6-position of 4(3*H*)-quinazolinone (R^1H, Figure 2). Nucleophilic substitutions of chlorine atom with phenols in the presence of $NaHCO_3$ were achieved in both high yield and purity by reflux in water. The chlorine atom was also quantitatively replaced by secondary amines catalyzed by organic base, such as diisopropylethylamine (DIPEA), triethylamine (TEA) or N-methylmorpholine (NMM). However, substitutions of chlorine atom with alcohols [**2**{*6*} and **2**{*7*}, Figure 2] were difficult that required the assistant of quaternary ammonium salt as phase-transfer catalyst and KOH as base.

Benzamide **6**, as a key intermediate, was readily gained by amidation of compound **4** with primary amines **5** (R^2NH_2, Figure 3). Noticeably, the phenoxyl moieties (R^1) were able to be replaced by excess primary amines **5** (R^2NH_2) under amidation condition so that equal molar primary amine should be added. In fact, it was unnecessary to further purify the crude product (**6**) for the next step synthesis as a result of high yield.

A one-pot synthetic procedure is anticipated to prepare **9** from **6** directly because the intermidiate **7** is unstable when it is exposed to the air. Many methods are well documented for quantitative reduction of the aromatic nitro group into aniline under an acid condition,[23a–d] a neutral condition,[23e,f] or a basic condition.[23g] HCO_2H as an acid resource was selected in this paper to provide a carbon atom to simultaneously construct quinazolinone **9** through intermolecular cyclization of **7** in one pot. After several explorations of correspounding synthetic methods, Fe/HCO_2H reductant gave the satisfied results although it provided 7-formylated byproduct **8** in high yield. Indeed, the formyl group of **8** is easily removed by using concentrated HCl in ethyl alcohol. Thus, this method is fairly beneficial to construct the quinazolinone ring in one-pot avoiding the oxidation of **7** exposured into air. To modify the 7-aromatic amino group of **9**, chloroacetylation (**10**) and chloroformylation (**13**) were carried out that subsequently gave **12** and **14** (Table 1) through the nucleophilic substitutions. These reactions resulted in a urea functional group for **14** and an amide compound **12** at 7-position by secondary amines [**11**{*1*−*10*}, Figure 4], respectively. In addition, a direct acylation by acyl

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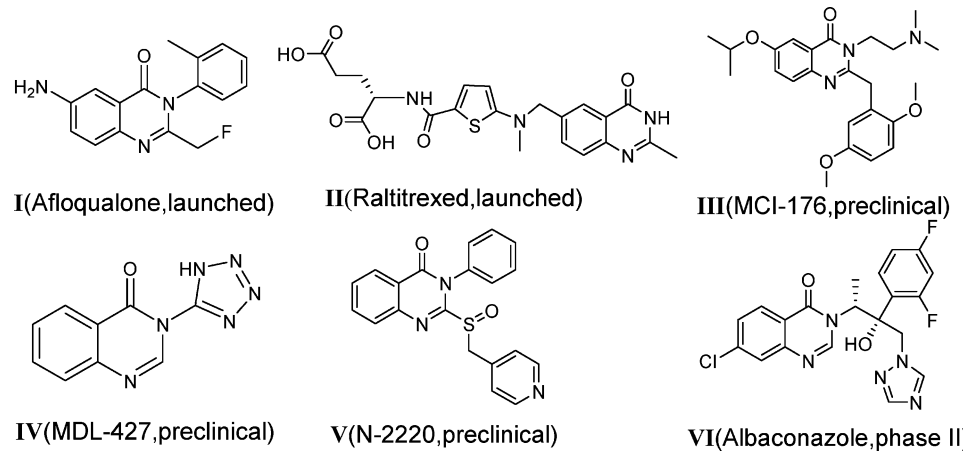
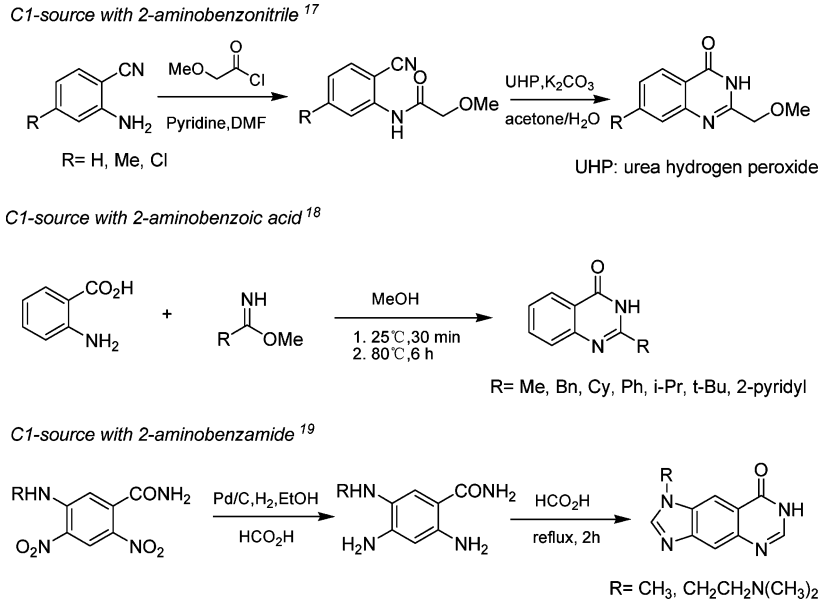


Figure 1. 4(3*H*)-Quinazolinones entered into preclinical or clinical trials.

Scheme 1. Literature Methods for Synthesis of 4(3*H*)-Quinazolinones

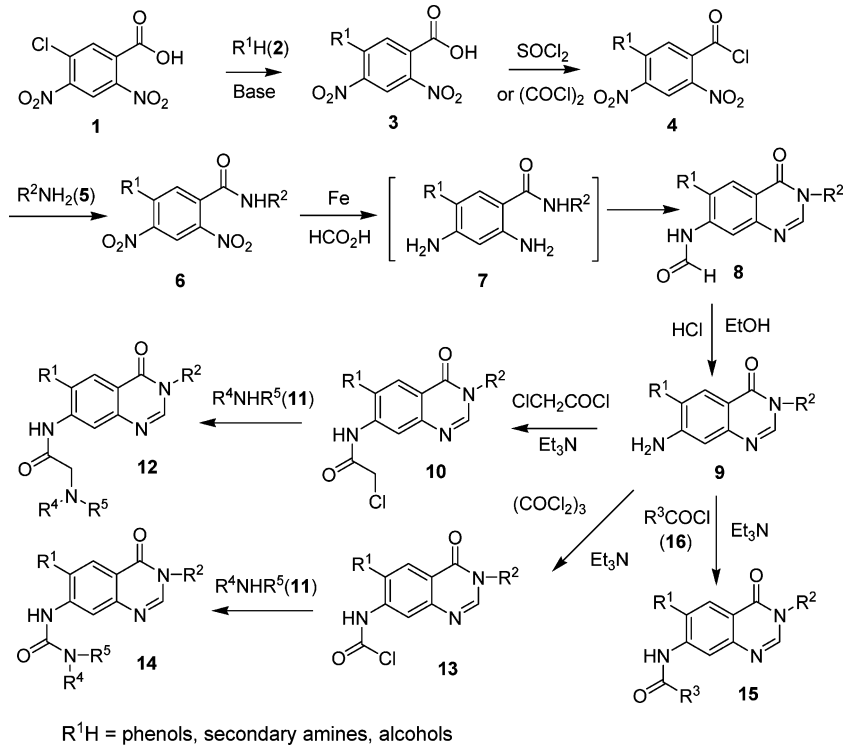


chlorides [**16**(1−6), Figure 4] was also performed to yield **15** without an additional N-atom introduction at 7-position (Table 1).

To overcome the difficulty of direct introduction of more alcohols at 6-position, an alternative synthetic route of 4(3*H*)-quinazolinone was developed (Scheme 3). The 6-position was first protected through benzoxylation (**3**, R^1 = BnO, Scheme 2), which smoothly generated **8** as above-described method (Scheme 2). Attempt to convert **6** (R^1 = BnO) into **17** in one pot (debenzylation and ring closure steps) by using Pd/C+HCO_2H was unsuccessful because of the fairly low yield of intermidiate **17** under this condation. Considering that acylations occur at the last reaction step to vary the diversities at 6- and 7-positions, respectively, in a parallel manner, the benzyl protected group of 6-position was then removed from **8** (R^1 = BnO) by hydrogenation or transfer hydrogenation method that offered the **17** in good yield (Scheme 3). Intermediate **17** was efficiently diversified on its free phenol group of 6-position to obtain **18** through a Mitsunobu reaction from various commercially available alcohols. Quantitative removal of the formyl group of **18** was performed at the last reaction step to obtain **19** that was completely acylated to gain the aimed compound **20** (Table 2).

The synthesized compounds were partially tested after diversity selection by the developmental therapeutics program (DTP) of drug discovery at the National Cancer Institute (NCI) for antitumor activity evaluation. Five compounds are giving the 50% growth inhibitory activities (GI_{50}) at 0.11 μM−3.38 μM of level range to the specific tumor cell lines (Table 3). The most potent compound is **12**{*6*,*3*,*5*} that is particularly active to a non-small tumor cell line (HOP-92) of lung cancer at 0.11 μM of GI_{50} value. After comparison of **15**{*4*,*3*,*4*} and **12**{*6*,*3*,*5*} that share the same 1-phenylethanamine at 3-position, the modification at 6- and 7-positions is concluded for significantly improving the antitumor activity. Further consideration of the similarity of **12**{*6*,*3*,*5*} and **15**{*4*,*3*,*4*}, **15**{*4*,*3*,*4*}, and **15**{*1*,*5*,*4*} in structure, 7-position replacement by [2-(4-methylpiperiazin-1-yl)acetamide] is the key feature for the activity improvement. In addition, introducing α,β-unsaturated moiety at 7-position (**15**{*1*,*5*,*4*}

Scheme 2. Synthetic Route to 3,6,7-Trisubstituted 4(3*H*)-Quinazolinones (**12**, **14**, **15**)



and **15**{*4*,*3*,*4*}) did not further increase the potency indicating that Michael acceptor fragment could not contribute its antitumor activity significantly.

4(3*H*)-Quinazolinones exhibit multiple inhibitory mechanisms against tumors, such as inhibition of KSP (kinesin spindle protein),[24] poly(ADP-ribose)polymerase[25] (ADP, adenosine diphosphate), and targeting the Hedgehog pathway, [26] etc. It is not clear yet for our compounds to target a certain tumor cell growth life cycle. The continuous outline of structure−activity relationships (SARs) through the

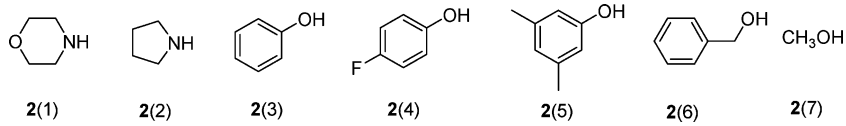


Figure 2. Reagents for the introduction of the first diversity element at 6-position of 4(3*H*)-quinazolinone (**2**, R^1H).

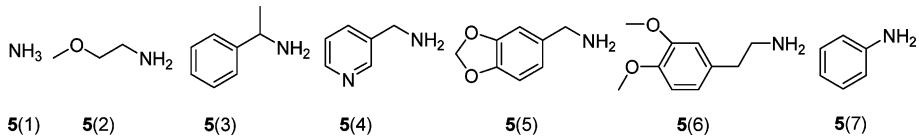


Figure 3. Primary amines for the introduction of the second diversity element at 3-position of 4(3*H*)-quinazolinone (**5**, R_2NH_2).

Table 1. Characterization of the Representative Substituted 4(3*H*)-Quinazolinones **12**{R^1,R^2,R^4NR^5}, **14**{R^1,R^2,R^4NR^5}, and **15**{R^1,R^2,R^3}

entry	compound	purity[a] (%)	yield[b](%)	entry	compound	purity[a] (%)	yield[b](%)
1	**12**{*3*,*1*,*2*}	100.0	52.0	16	**14**{*4*,*3*,*5*}	100.0	45.6
2	**12**{*3*,*1*,*3*}	100.0	50.5	17	**15**{*3*,*6*,*3*}	100.0	61.9
3	**12**{*3*,*1*,*7*}	97.6	54.0	18	**15**{*3*,*6*,*1*}	98.0	54.1
4	**12**{*3*,*1*,*1*}	100.0	51.2	19	**15**{*7*,*4*,*3*}	100.0	50.5
5	**12**{*3*,*1*,*8*}	97.1	51.5	20	**15**{*5*,*6*,*5*}	95.6	54.4
6	**12**{*5*,*6*,*4*}	96.2	52.1	21	**15**{*1*,*5*,*5*}	99.5	55.9
7	**12**{*5*,*6*,*10*}	95.2	51.5	22	**15**{*1*,*5*,*3*}	94.4	40.5
8	**12**{*5*,*6*,*6*}	99.4	58.1	23	**15**{*7*,*4*,*6*}	100.0	44.0
9	**12**{*7*,*6*,*5*}	95.3	60.9	24	**15**{*6*,*4*,*4*}	96.7	50.3
10	**12**{*7*,*4*,*9*}	100.0	59.0	25	**15**{*4*,*3*,*2*}	99.7	59.9
11	**12**{*6*,*3*,*5*}	99.6	69.3	26	**15**{*2*,*2*,*4*}	99.6	56.9
12	**12**{*5*,*6*,*5*}	96.4	51.0	27	**15**{*1*,*5*,*4*}	94.9	40.1
13	**12**{*3*,*7*,*10*}	100.0	54.6	28	**15**{*4*,*3*,*4*}	98.2	30.8
14	**14**{*7*,*4*,*8*}	99.3	46.8	29	**15**{*3*,*7*,*3*}	99.4	64.2
15	**14**{*7*,*4*,*9*}	95.4	54.4				

[a] Purity based on the integration area of the HPLC peaks (the detection wavelength was 254 nm). [b] Isolated yield.

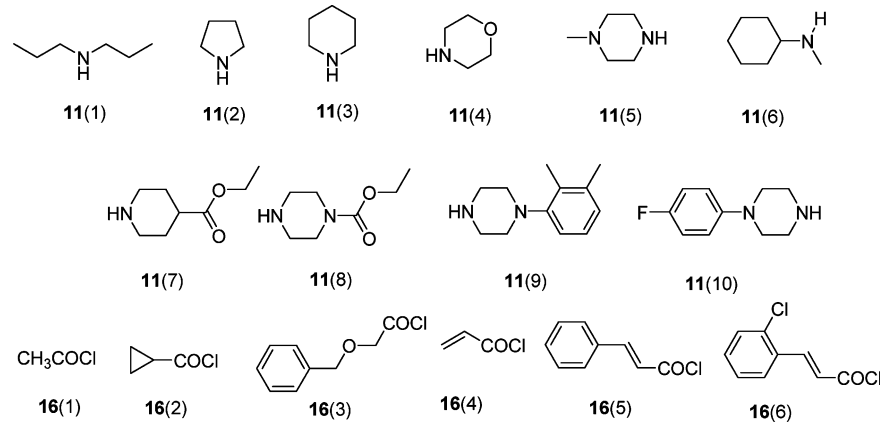


Figure 4. Secondary amines (**11**) and acyl chlorides (**16**) as building blocks at 7-position of 4(3*H*)-quinazolinones.

Scheme 3. Alternative Synthetic Route of 3,6-Disubstituted-4(3*H*)-Quinazolinones

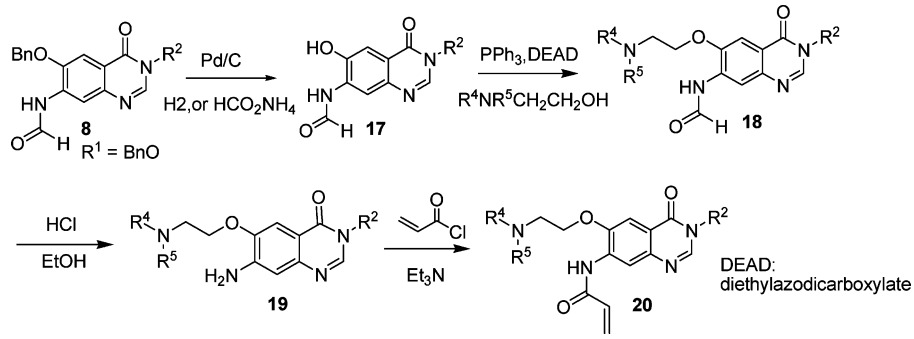


Table 2. Characterization of the Representative Substituted 4(3*H*)-Quinazolinones **20**{R^4NR^5,R^2}

entry	compound	purity[a] (%)	yield[b](%)
1	**20**{*4,3*}	96.1	51.3
2	**20**{*2,3*}	98.9	62.6
3	**20**{*3,3*}	99.3	65.4
4	**20**{*4,4*}	99.1	50.9

[a] Purity based on the integration area of the HPLC peaks (the detection wavelength was 254 nm). [b] Isolated yield.

construction of sublibrary is underway based on these preliminary observations.

Conclusion

An efficient solution-phase method was described in this paper for the synthesis of 3,6,7-position diverse 4(3*H*)-quinazolinones. A one-pot synthesis was developed that gave the key intermediate **9** in high yield and good purity. A library of 4(3*H*)-quinazolinone was synthesized and evaluated for their anti tumor activity. Five hit compounds exhibit good activities against a panel of human tumor cell lines, which pointed out preliminary structure−activity relationships.

Experimental Section

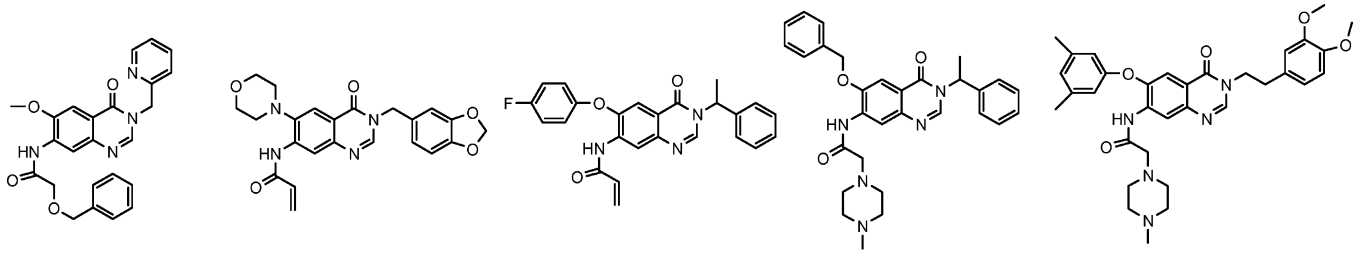
All chemical reagents were purchased from Acros Organics (Geel, Belgium) and were used without further purification. Tetrahydrofuran (THF) was dried over molecular sieves and redistilled from sodium before usage. Acetone was treated with anhydrous K_2CO_3. *N*,*N*-dimethylformamide (DMF) was treated with anhydrous $MgSO_4$. All NMR experiments were carried out on a Varian Mercury 300 MHz NMR spectrometer using DMSO-d_6 or $CDCl_3$ as the solvent. Parallel synthesis was carried out on an H + P Labortechnik parallel synthesizer. The detailed HPLC equipment and procedures are available in the Supporting Information.

Preparation of 1 (5-Chloro-2,4-dintrobenzoic Acid). 3-Chlorobenzoic acid (10 g, 63.8 mmol) was dissolved in 120 mL of concentrated sulfuric acid with stirring at room temperature. Potassium nitrate (16.5 g, 163.2 mmol) was added in portions over 15 min. The reaction mixture was then warmed to 80 °C and held at this temperature for 30 min. After it was warmed to 110 °C, the reaction was allowed to continue for an additional 2 h at 110 °C and at 120 °C for 2 more hours. The reaction mixture was continuously cooled down to the room temperature and poured into 660 g of ice to precipitate an off-white solid. This solid was collected by filtration and washed with water. The resultant crude product was purified by recrystallization from the mixed solvent of 40 mL of ethanol/200 mL of H_2O to afford 6.74 g of a faintly yellow solid in 42.7% yield. ESI-MS *m*/*z*: 245 $(M - H)^-$.^{1}H NMR (300 MHz, DMSO-d_6): δ 8.29 (s, 1H), 8.85 (s, 1H).

General Procedure for the Synthesis of 3. Method 1. A mixture of **1** (3 g, 12 mmol), $NaHCO_3$ (2.16 g, 25.68 mmol), and phenol (**2**(3), 12.78 mmol) in water (18 mL) was heated under reflux for 2 h. The reaction mixture was cooled to room temperature; 30 mL of methylene chloride and 30 mL of water were added. After separation of the organic layer, the aqueous layer was acidified with concentrated HCl and extracted with methylene chloride (2 × 50 mL). The organic extract was washed with water and dried over anhydrous Na_2SO_4, then concentrated under reduced pressure to give the desired **3**. For 2,4-dinitro-5-phenoxybenzoic acid, as an example compound, 3.2 g of yellow solid was obtained in 86.5% yield with an HPLC purity >98% that was directly

Table 3. Activity of 4(3*H*)-Quinazolinones against Human Cancer Cell Lines[a]

	GI_{50} values (μM) in cell lines[b]				
panel/cell line	**15**{*7,4,3*}	**15**{*1,5,4*}	**15**{*4,3,4*}	**12**{*6,3,5*}	**12**{*5,6,5*}
CCRF-CEM	3.18	0.17	1.97	2.87	2.01
SR	2.26	1.53	1.50	0.86	1.97
HOP-92	1.87	2.63	1.92	0.11	1.70
COLO 205	1.58	2.77	1.65	0.88	1.90
HT 29	1.98	3.38	1.79	0.79	1.98
SK-MEL-28	1.82	2.07	1.85	0.93	1.83



15 {7,4,3} **15** {1,5,4} **15** {4,3,4} **12** {6,3,5} **12** {5,6,5}

[a] Determined by MTT assay. [b] Cancer cell line origin: CCRF-CEM (leukemia), SR (leukemia), HOP-92 (nonsmall cell lung), COLO 205 (colon), HT 29 (colon), and SK-MEL-28 (melanoma).

used for the next reaction without further purification. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.20 (s, 1H), 7.28 (d, 1H, J = 7.8 Hz), 7.36 (t, 2H, J = 7.8 Hz), 7.53 (t, 2H, J = 7.8 Hz), 8.82 (s, 1H).

5-(4-Fluorophenoxy)-2,4-dinitrobenzoic Acid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.21 (d, 1H, J = 1.0 Hz), 7.36 (brs, 2H), 7.38 (brs, 2H), 8.82 (d, 1H, J = 1.0 Hz).

5-(3,5-Dimethylphenoxy)-2,4-dinitrobenzoic Acid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.29 (s, 6H), 6.89 (s, 2H), 6.98 (s, 1H), 7.15 (s, 1H), 8.77 (s, 1H).

Method 2. A mixture of **1** (1 g, 4 mmol) and triethyl amine (1.224 mL, 8.8 mmol) in THF (6 mL) was stirred at room temperature. Secondary amine (**2**(1), 6 mmol) was added dropwise. The reaction was monitored by LC-MS analysis. After 12 h, the reaction mixture was acidified with concentrated HCl. The resulting precipitate was collected by filtration and washed with water, then dried in vacuo to gain the desired **3**. For 5-morpholino-2,4-dinitrobenzoic acid, as an example compound, 0.97 g of yellow solid was obtained in 80.3% yield with an HPLC purity >98% that was directly used for the next reaction without further purification. ESI-MS m/z: 296 $(M - H)^-$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.29 (m, 4H), 3.69 (m, 4H), 7.48 (s, 1H), 8.56 (s, 1H).

2,4-Dinitro-5-(pyrrolidin-1-yl)benzoic Acid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.93 (m, 4H), 3.28 (m, 4H), 7.14 (s, 1H), 8.54 (s, 1H).

Method 3. A mixture of **1** (3 g, 12.2 mmol) and KOH (1.62 g, 28.9 mmol) in alcohol (**2**(6), 40 mL) was stirred at room temperature. (n-Bu)$_4$NBr (100 mg) was added. Stirring was continued for 12 h. Methylene chloride (150 mL) was added. The resulting precipitate was collected by filtration and washed with methylene chloride and then dissolved in 200 mL water. The mixture was acidified with concentrated HCl, and the desired **3** was obtained by filtration and dried. For 5-(benzyloxy)-2,4-dinitrobenzoic acid, as an example compound, 2.8 g of white solid was obtained in 72.2% yield, with an HPLC purity >98%. ESI-MS m/z: 317 $(M - H)^-$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 5.50 (s, 2H), 7.42 (m, 5H), 7.81 (s, 1H), 8.72 (s, 1H).

5-(Methoxy)-2,4-dinitrobenzoic Acid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.09 (s, 3H),7.69 (s, 1H), 8.70 (s, 1H). ESI-MS m/z: 241 $(M - H)^-$.

General Procedure for the Synthesis of 6. Method 1. Compound **3** (1.84 mmol) was suspended or dissolved in 5 mL of thionyl chloride containing 2 drops of DMF under stirring. The suspension or solution was heated to reflux for 2 h. Thionyl chloride was evaporated under reduced pressure. After the mixture was cooled to room temperature, 5 mL of toluene was added, and the solution was evaporated under reduced pressure. The solid or liquid **4** was dissolved in 3 mL of methylene chloride (or acetone) and added dropwise to a cooled solution (0 °C) of 2 equiv of primary amine **5** (or 1 equiv of primary amine **5** and 1 equiv of Et_3N) in 5 mL of methylene chloride over 5 min. Stirring was continued for 1 h. The reaction mixture was diluted with 50 mL of methylene chloride and washed subsequently with 2% aqueous HCl, water, saturated $NaHCO_3$, and water. The organic phase was dried and concentrated to yield **6**.

Method 2. Compound **3** (6.28 mmol) was dissolved in 40 mL of methylene chloride containing 4 drops of DMF under stirring. Oxalyl chloride (1.9 mL) was added dropwise. The reaction mixture was heated to reflux for 2 h. The reaction mixture was evaporated to dryness under reduced pressure to give the compound **4**. Forty milliliters of methylene chloride was added, and resultant solution was added dropwise to a cooled solution (0 °C) of 1 equiv of primary amine **5** and 1 equiv of triethyl amine in 40 mL of methylene chloride over 5 min. Stirring was continued for an additional hour. The reaction mixture was diluted with 50 mL of methylene chloride and washed successively with 2% aqueous HCl, water, saturated $NaHCO_3$, and water. The organic phase was dried and concentrated to yield **6**.

For *N*-(3,4-dimethoxyphenethyl)-5-(3,5-dimethylphenoxy)-2,4-dinitrobenz amide, as an example compound, a brown solid was obtained in 96.6% yield, with an HPLC purity >98%. ESI-MS m/z: 496 $(M + H)^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.30 (s, 6H), 2.68 (t, 2H, J = 7.2 Hz), 3.37 (m, 2H), 3.67 (s, 3H), 3.69 (s, 3H), 6.21−6.71 (m, 2H), 6.80

(brs, 1H), 6.87 (brs, 2H), 6.96 (s, 1H), 7.00 (brs, 1H), 8.77 (t, 1H, J = 5.4 Hz), 8.81 (s, 1H).

5-(Benzyloxy)-2,4-dinitro-*N*-(pyridin-2-ylmethyl)benzamide. ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.57 (d, 2H, J = 6.0 Hz), 5.50 (s, 2H), 7.29−7.48 (m, 7H), 7.72 (s, 1H), 7.83 (t, 1H, J = 8.1 Hz), 8.53 (d, 1H, J = 4.2 Hz), 8.74 (s, 1H), 9.30 (t, 1H, J = 6.0 Hz). ESI-MS (m/z): 409 $[M + H]^+$.

2,4-Dinitro-5-phenoxybenzamide. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.01 (s, 1H), 7.26 (d, 2H, J = 7.8 Hz), 7.36 (t, 1H, J = 7.8 Hz), 7.53 (t, 2H, J = 7.8 Hz), 7.85 (s, 1H), 8.18 (s, 1H), 8.81 (s, 1H).

General Procedure for the Synthesis of 8. Compound **6** (2.94 mmol) was dissolved in 40 mL of HCOOH (98%) under stirring at room temperature. Five grams of Fe powder was added. The reaction mixture was heated to reflux for 8 h; 100 mL of ethyl acetate was added. The solid was removed by filtration. The filtrate was evaporated to dryness. The residue was treated with 50 mL methylene chloride and 50 mL of water. The organic phase was washed with water and then evaporated under reduced pressure to give crude **8**. If necessary, simple column chromatography or recrystallization was used to further purify the crude **8**. For *N*-(6-(4-fluorophenoxy)-4-oxo-3-(1-phenylethyl)-3,4-dihydroquinazolin-7-yl)formamide, as an example compound, 0.61 g of white solid was obtained in 51.5% yield after column chromatography eluting with ethyl acetate/petroleum (1:1.5) and an HPLC purity >98%. ESI-MS m/z: 404 $(M + H)^+$.^{1}H NMR (300 MHz, DMSO-d_6): δ 1.80 (d, 3H, J = 7.2 Hz), 6.00 (q, 1H, J = 7.2 Hz), 7.27−7.36 (m, 10H), 8.36 (s, 1H), 8.46 (s, 1H), 8.65 (s, 1H), 10.50 (s, 1H).

***N*-(3-(3,4-Dimethoxyphenethyl)-6-methoxy-4-oxo-3,4-dihydroquinazolin-7-yl)formamide.** ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.92 (t, 2H, J = 6.9 Hz), 3.65 (s, 3H), 3.69 (s, 3H), 3.98 (s, 3H), 4.17 (t, 2H, J = 6.9 Hz), 6.64 (d, 1H, J = 8.1 Hz), 6.78−6.83 (m, 3H), 7.57 (s, 1H), 7.97 (s, 1H), 8.42 (s, 1H), 8.50 (s, 1H), 10.13 (s, 1H). ESI-MS m/z: 384 $(M + H)^+$. Eluting agent: petroleum/ethyl acetate (5: 1).

***N*-(3-(2-Methoxyethyl)-4-oxo-6-(pyrrolidin-1-yl)-3,4-dihydroquinazolin-7-yl)formamide.** ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.92 (brs, 4H), 3.12 (brs, 4H), 3.23 (s, 3H), 3.58 (t, 2H, J = 5.1 Hz), 4.11 (t, 2H, J = 5.1 Hz), 7.63 (s, 1H), 8.12 (s, 1H), 8.29 (s, 1H), 8.45 (s, 1H), 9.75 (s, 1H). ESI-MS m/z: 317 $(M + H)^+$. Eluting agent: ethyl acetate.

General Procedure for the Synthesis of 9. Compound **8** (4.69 mmol) was suspended into 20 mL of anhydrous ethanol under stirring at room temperature. Two milliliters of concentrated hydrochloric acid (36%) was added. Stirring was continued for 12 h. Fifty milliliters of anhydrous diethyl ether was added. The resulted solid was collected by filtration and washed with 20 mL of anhydrous diethyl ether and then dried to afford **9** as hydrochloride salt. For 3-(3,4-dimethoxyphenethyl)-7-amino-6-methoxyquinazolin-4(3*H*)-one hydrochloride, as an example compound, 1.5 g of yellow solid was obtained in 81.5% yield with an HPLC purity >95%. ESI-MS m/z: 356 $(M + H)^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.89 (t, 2H, J = 7.2 Hz), 3.64 (s, 3H), 3.69 (s, 3H), 3.87 (s, 3H), 4.10 (t, 2H, J = 7.2 Hz), 5.82 (brs, 2H, N−H), 6.63−6.68 (m, 2H), 6.74 (brs, 1H), 6.81 (d, 1H, J = 8.1 Hz), 7.32 (s, 1H), 7.79 (s, 1H).

7-Amino-6-(4-fluorophenoxy)-3-(1-phenylethyl)quinazolin-4(3*H*)-one. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.75 (d, 3H, J = 7.2 Hz), 5.99 (q, 1H, J = 7.2 Hz), 6.14 (brs, 2H, N−H), 6.85 (s, 1H), 7.08−7.34 (m, 10H), 8.16 (s, 1H). ESI-MS m/z: 376 $(M + H)^+$.

3-(3,4-Dimethoxyphenethyl)-7-amino-6-(3,5-dimethylphenoxy)quinazolin-4(3*H*)-one. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.29 (s, 6H), 2.85 (t, 2H, J = 6.9 Hz), 3.64 (s, 3H), 3.69 (s, 3H), 4.05 (t, 2H, J = 6.9 Hz), 6.03 (brs, 2H, N−H), 6.65 (m, 3H), 6.74 (brs, 1H), 6.82 (m, 3H), 7.20(s, 1H), 7.85 (s, 1H). ESI-MS m/z: 446 $(M + H)^+$.

Derivatization of 9 on 7-Aromatic Amino Group. Method 1 (Compound 12). To an ice-cooled and stirred suspension of **9** hydrochloride (1.2 mmol) in 20 mL of anhydrous methylene chloride, 0.7 mL of triethyl amine (5.04 mmol) was added. After 5 min, 0.42 mL of chloroacetic chloride (4.88 mmol) was subsequently added dropwise. Stirring was continued for an additional hour. Fifty milliliters of methylene chloride was added. The organic layer was washed with saturated $NaHCO_3$ and further washed with water (2 × 50 mL), dried, and concentrated to yield **10** which was directly used without further purification for the next reaction. For *N*-(3-(benzo[*d*][1,3]dioxol-5-ylmethyl)-6-morpholino-4-oxo-3,4-dihydroquinazolin-7-yl)-2-chloroacetamide, as an example compound, 0.49 g of brown solid was obtained in 89.42% yield with an HPLC purity >95%. ESI-MS m/z: 457 $(M + H)^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.89 (brs, 4H), 3.81 (brs, 4H), 4.52 (s, 2H), 5.06 (s, 2H), 5.97 (s, 2H), 6.85 (brs, 2H), 7.00 (s, 1H), 7.84 (s, 1H), 8.39 (s, 1H), 8.50 (s, 1H), 9.73 (s, 1H). To a mixture of **10** (50 mg) and KI (10−20 mg) in 2 mL of anhydrous ethanol and 1.5 mL of anhydrous methylene chloride, 5 equiv of secondary amine **11** was added. The reaction mixture was stirred mechanically on an H + P Labortechnik parallel synthesizer at 40 °C until completion of the reaction. The solvent was evaporated in vacuo to obtain the crude product **12**. The final products were characterized after chromatographic purification on silica gel. The yields ranged from 50%−65%, a major loss of yields was due to column chromatography because of adsorption or solubility. For *N*-(3-(3,4-dimethoxyphenethyl)-6-methoxy-4-oxo-3,4-dihydroquinazolin-7-yl)-2-(4-methylpi-perazin-1-yl)acet amide, as an example compound, 35 mg of brown solid was obtained in 60.9% yield with an HPLC purity >95%.

***N*-(4-Oxo-6-phenoxy-3,4-dihydroquinazolin-7-yl)-2-(pyrrolidin-1-yl)acetamide 12{*3,1,2*}.** ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.59 (m, 4H), 2.51 (m, 4H), 3.31 (s, 2H), 7.12 (m, 2H), 7.24 (m, 1H), 7.43−7.49 (m, 3H), 8.04 (s, 1H), 8.64 (s, 1H), 10.08 (s, 1H), 12.20 (brs, 1H). HRESIMS obsd m/z 365.1601, calcd for 365.1608.

***N*-(4-Oxo-6-phenoxy-3,4-dihydroquinazolin-7-yl)-2-(piperidin-1-yl)acetamide 12{*3,1,3*}.** ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.40 (brs, 6H), 2.44 (brs, 4H), 3.13 (s, 2H), 7.17 (d, 2H, J = 7.8 Hz), 7.27 (t, 1H, J = 7.8 Hz), 7.38 (s, 1H), 7.48 (t, 2H, J = 7.8 Hz), 8.04 (s, 1H), 8.66 (s, 1H), 10.32 (s, 1H), 12.19 (brs, 1H). HRESIMS obsd m/z 379.1770, calcd for 379.1764.

Ethyl 1-(2-Oxo-2-(4-oxo-6-phenoxy-3,4-dihydroquinazolin-7-ylamino)ethyl)piperidine-4-carboxylate 12{*3,1,7*}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.12 (t, 3H, J = 6.9 Hz), 1.38 (m, 2H), 1.70 (m, 2H), 2.23 (m, 3H), 2.36 (m, 2H), 3.17 (s, 2H), 4.01 (q, 2H, J = 6.9 Hz), 7.13 (d, 2H, J = 7.5 Hz), 7.23 (t, 1H, J = 7.5 Hz), 7.41 (s, 1H), 7.45 (t, 2H, J = 7.5 Hz), 8.04 (s, 1H), 8.65 (s, 1H), 10.25 (s, 1H), 12.20 (brs, 1H). HRESIMS obsd *m*/*z* 451.1969, calcd for 451.1981.

2-(Dipropylamino)-*N*-(4-oxo-6-phenoxy-3,4-dihydroquinazolin-7-yl)acetamide 12{*3,1,1*}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.77 (t, 6H, J = 6.9 Hz), 1.33 (sex, 4H, J = 7.2 Hz), 2.40 (t, 4H, J = 6.9 Hz), 3.21 (s, 2H), 7.12 (d, 2H, J = 7.5 Hz), 7.24 (t, 1H, J = 7.5 Hz), 7.32 (s, 1H), 7.49 (t, 2H, J = 7.5 Hz), 8.02 (d, 1H, J = 3.3 Hz), 8.70 (s, 1H), 10.32 (s, 1H), 12.18 (s, 1H). HRESIMS obsd *m*/*z* 395.2087, calcd for 395.2077.

2-(Methyl(2-(pyridin-2-yl)ethyl)amino)-*N*-(4-oxo-6-phenoxy-3,4-dihydroquinazolin-7-yl) acetamide 12{*3,1,8*}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.21 (s, 3H), 2.83 (brs, 4H), 3.25 (s, 2H), 7.08−7.26 (m, 5H), 7.36 (s, 1H), 7.45 (t, 2H, J = 7.8 Hz), 7.57 (t, 1 H, J = 7.8 Hz), 8.03 (s, 1H), 8.39 (d, 1H, J = 4.2 Hz), 8.64 (s, 1H), 9.95 (s, 1H), 12.19 (s, 1H). HRESIMS obsd *m*/*z* 452.1927, calcd for 452.1934.

2-(Dipropylamino)-*N*-(4-oxo-6-phenoxy-3,4-dihydroquinazolin-7-yl)acetamide 12{*5,6,4*}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.77 (t, 6H, J = 6.9 Hz), 1.33 (m, 4H), 2.40 (t, 4H, J = 6.9 Hz), 3.21 (s, 2H), 7.12 (d, 2H, J = 7.5 Hz), 7.24 (t, 1H, J = 7.5 Hz), 7.32 (s, 1H), 7.49 (t, 2H, J = 7.5 Hz), 8.02 (d, 1H, J = 3.3 Hz), 8.70 (s, 1H), 10.32 (s, 1H), 12.18 (s, 1H). HRESIMS obsd *m*/*z* 573.2706, calcd for 573.2713.

Ethyl 4-(2-Oxo-2-(4-oxo-6-phenoxy-3,4-dihydroquinazolin-7-ylamino)ethyl)piperazine-1-carboxylate 12{*5,6,10*}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.16 (t, 3H, J = 6.9 Hz), 2.45 (brs, 4H), 3.18 (brs, 4H), 3.24 (s, 2H), 4.01 (q, 2H, J = 6.9 Hz), 7.18 (d, 2H, J = 7.8 Hz), 7.26 (t, 1H, J = 7.8 Hz), 7.38 (s, 1H), 7.47 (t, 2H, J = 7.8 Hz), 8.04 (d, 1H, J = 3.9 Hz, 8.61 (s, 1H), 10.15 (s, 1H), 12.20 (s, 1H). HRESIMS obsd *m*/*z* 666.3100, calcd for 666.3092.

***N*-(3-(3,4-Dimethoxyphenethyl)-6-(3,5-dimethylphenoxy)-4-oxo-3,4-dihydroquinazolin-7-yl)-2-(cyclohexyl(methyl)amino)acetamide 12{*5,6,6*}.** ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.20 (m, 6H), 1.62 (m, 4H), 2.16 (s, 3H), 2.26 (s, 6H), 2.45 (m, 1H), 2.90 (t, 2H, J = 7.2 Hz), 3.18 (s, 2H), 3.65 (s, 3H), 3.69 (s, 3H), 4.13 (t, 2H, J = 7.2 Hz), 6.64−6.88 (m, 6H), 7.48 (s, 1H), 8.06 (s, 1H), 8.63 (s, 1H), 10.29 (s, 1H). HRESIMS obsd *m*/*z* 599.3239, calcd for 599.3233.

***N*-(3-(3,4-Dimethoxyphenethyl)-6-(3,5-dimethylphenoxy)-4-oxo-3,4-dihydroquinazolin-7-yl)-2-(4-(4-fluorophenyl)piperazin-1-yl)acetamide 12{*7,6,5*}.** ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.19 (s, 6H), 2.63 (brs, 4H), 2.89 (m, 6H), 3.26 (s, 2 H), 3.65 (s, 3H), 3.69 (s, 3H), 4.13 (t, 2H, J = 6.9 Hz), 6.65 (m, 3H), 6.77−6.86 (m, 5H), 7.03 (t, 2H, J = 7.8 Hz), 7.54 (s, 1H), 8.09 (s, 1H), 8.64 (s, 1H), 10.24 (s, 1H). HRESIMS obsd *m*/*z* 496.2536, calcd for 496.2560.

2-(4-(2,3-Dimethylphenyl)piperazin-1-yl)-*N*-(6-methoxy-4-oxo-3-(pyridin-2-ylmethyl)-3,4-dihydroquinazolin-7-yl)acetamide 12{*7,4,9*}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.16 (s, 3H), 2.20 (s, 3H), 2.75 (brs, 4H), 2.89 (brs, 4H), 3.31 (s, 2H), 4.00(s, 3H), 5.28 (s, 2H), 6.88 (d, 1H, J = 7.2 Hz), 6.94 (d, 1H, J = 8.1 Hz), 7.07 (t, 1H, J = 8.1 Hz), 7.26 (t, 1H, J = 7.2 Hz), 7.38 (d, 1H, J = 7.8 Hz), 7.54 (s, 1H), 7.78 (t, 1H, J = 7.8 Hz), 8.40 (s, 1H), 8.45 (d, 1H, J = 4.2 Hz), 8.58 (s, 1H), 10.22 (s, 1H). HRESIMS obsd *m*/*z* 513.2610, calcd for 513.2608.

***N*-(6-(Benzyloxy)-4-oxo-3-(1-phenylethyl)-3,4-dihydroquinazolin-7-yl)-2-(4-methylpiperazin-1-yl)acetamide 12{*6,3,5*}.** ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.83 (d, 3H, J = 6.9 Hz), 2.49 (brs, 4H), 2.59 (s, 3H), 2.95 (brs, 4H), 3.31 (s, 2H), 5.35 (s, 2H), 6.09 (q, 1H, J = 6.9 Hz), 7.29−7.58 (m, 10H), 7.72 (s, 1H), 8.34 (s, 1H), 8.55 (s, 1H), 9.82 (s, 1H). HRESIMS obsd *m*/*z* 512.2645, calcd for 512.2656.

***N*-(3-(3,4-Dimethoxyphenethyl)-6-(3,5-dimethylphenoxy)-4-oxo-3,4-dihydroquinazolin-7-yl)-2-(4-methylpiperazin-1-yl)acetamide 12{*5,6,5*}.** ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.28 (s, 9H), 2.71 (s, 8H), 2.89 (t, 2H, J = 6.9 Hz), 3.24 (s, 2H), 3.65 (s, 3H), 3.69 (s, 3H), 4.11 (t, 2H, J = 6.9 Hz), 6.65 (d, 1H, J = 7.8 Hz), 6.76 (m, 3H), 6.82 (d, 1H, J = 7.8 Hz), 6.89 (s, 1H), 7.48 (s, 1H), 8.07 (s, 1H), 8.59 (s, 1H), 10.10 (brs, 1H). HRESIMS obsd *m*/*z* 586.3024, calcd for 586.3029.

2-(4-(4-Fluorophenyl)piperazin-1-yl)-*N*-(4-oxo-6-phenoxy-3-phenyl-3,4-dihydroquinazolin-7-yl) acetamide 12{*3,7,10*}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.66 (brs, 4H), 2.89 (brs, 4H), 3.30 (s, 2H), 6.83 (m, 2H), 7.02 (t, 2H, J = 9 Hz), 7.12−7.22 (m, 3H), 7.40 (t, 2H, J = 7.5 Hz), 7.50−7.57 (m, 6H), 8.31 (s, 1H), 8.74 (s, 1H), 10.32 (s, 1H). HRESIMS obsd *m*/*z* 550.2252, calcd for 550.2254.

Method 2 (compound 14). To an ice-cooled and stirred suspension of **9** hydrochloride (50 mg) in 5 mL of anhydrous methylene chloride, 5 equiv of triethylamine was added, followed by addition of 10 equiv of triphosgene. Stirring was continued for 1 h. The solvent was evaporated in vacuo to dryness. The residue **13** was dissolved in 2 mL of anhydrous methylene chloride and added to a solution of 3 equiv of secondary amine **11** in 3 mL of anhydrous methylene chloride. After 1 h, the solvent was evaporated under the reduced pressure to yield the crude compound **14.** The crude compound **14** was purified on silica gel and characterized by ^{1}H NMR.

Ethyl 4-((6-Methoxy-4-oxo-3-(pyridin-2-ylmethyl)-3,4-dihydroquinazolin-7-yl)carbamoyl) piperazine-1-carboxylate 14{*7,4,8*}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.19 (t, 3H, J = 6.9 Hz), 3.44 (brs, 4H), 3.46 (brs, 4H), 3.94 (s, 3H), 4.05 (q, 2H, J = 6.9 Hz), 5.27 (s, 2H), 7.28 (t, 1H, J = 6.3 Hz), 7.36 (d, 1H, J = 7.8 Hz), 7.47 (s, 1H), 7.78 (t, 1H, J = 7.5 Hz), 8.08 (s, 1H), 8.21 (s, 1H), 8.36 (s, 1H), 8.45 (d, 1H, J = 4.2 Hz). HRESIMS obsd *m*/*z* 467.2045, calcd for 467.2037.

4-(2,3-Dimethylphenyl)-*N*-(6-methoxy-4-oxo-3-(pyridin-2-ylmethyl)-3,4-dihydroquinazolin-7-yl) piperazine-1-carboxamide 14{*7,4,9*}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.19 (s, 3H), 2.21 (s, 3H), 2.83 (brs, 4H), 3.62 (brs, 4H), 3.95 (s, 3H), 5.27 (s, 2H), 6.89 (d, 2H, J = 7.5 Hz), 7.05 (t, 1H, J = 7.5 Hz), 7.28 (t, 1H, J = 6.9 Hz), 7.36 (d, 1H, J = 7.5 Hz), 7.48 (s, 1H), 7.77 (t, 1H, J = 7.8 Hz), 8.08 (s, 1H), 8.27 (s, 1H), 8.37 (s, 1H), 8.45 (d, 1H, J = 4.2 Hz). HRESIMS obsd *m*/*z* 499.2451, calcd for 499.2452.

***N*-(6-(4-Fluorophenoxy)-4-oxo-3-(1-phenylethyl)-3,4-dihydroquinazolin-7-yl)-4-methylpiperazine-1-carboxamide 14{*4*,*3*,*5*}.** ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.81 (d, 3H, J = 6.9 Hz), 2.33 (s, 3H), 2.46 (brs, 4H), 3.55 (brs, 4H), 6.24 (q, 1H, J = 6.9 Hz), 7.05 (m, 4H), 7.27−7.48 (m, 6H), 7.52 (s, 1H), 7.88 (s, 1H), 8.59 (s, 1H). HRESIMS obsd *m*/*z* 502.2261, calcd for 502.2249.

Method 3 (Compound 15). To an ice-cooled and stirred suspension of **9** hydrochloride (50 mg) in 5 mL of anhydrous methylene chloride, 3.5 equiv of triethyl amine was added. After 5 min, 2−4 equiv of acyl chloride **16** was added dropwise. Stirring was continued for 1 h. 50 mL of methylene chloride was added. The organic layer was washed with saturated $NaHCO_3$ and then washed with water (2 × 50 mL), and concentrated to yield crude compound **15.** Crude compound **15** was purified on silica gel with the ethyl acetate/petroleum ether system as an eluent.

***N*-(3-(3,4-Dimethoxyphenethyl)-4-oxo-6-phenoxy-3,4-dihydroquinazolin-7-yl)-2-(benzyloxy) acetamide 15{*3*,*6*,*3*}.** ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.87 (t, 2H, J = 6.9 Hz), 3.65 (s, 3H), 3.68 (s, 3H), 4.12 (t, 2H, J = 6.9 Hz), 4.25 (s, 2H), 4.62 (s, 2H), 6.63 (dd, 1H, J = 1.8 Hz, 7.8 Hz), 6.76 (d, 1H, J = 1.8 Hz), 6.81 (d, 1H, J = 7.8 Hz), 7.18−7.35 (m, 8H), 7.36 (s, 1H), 7.51 (t, 2H, J = 7.8 Hz), 8.04 (s, 1H), 8.59 (s, 1H), 9.60 (s, 1H). HRESIMS obsd *m*/*z* 566.2286, calcd for 566.2291.

***N*-(3-(3,4-Dimethoxyphenethyl)-4-oxo-6-phenoxy-3,4-dihydroquinazolin-7-yl)acetamide 15{*3*,*6*,*1*}.** ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.18 (s, 3H), 2.87 (t, 2H, J = 6.9 Hz), 3.64 (s, 3H), 3.68 (s, 3H), 4.10 (t, 2H, J = 6.9 Hz), 6.62 (dd, 1H, J = 2.1 Hz, 8.1 Hz), 6.75 (d, 1H, J = 1.8 Hz), 6.81 (d, 1H, J = 8.1 Hz), 7.18 (d, 2H, J = 7.5 Hz), 7.28 (t, 2H, J = 7.5 Hz), 7.50 (t, 2H, J = 7.5 Hz), 8.01 (s, 1H), 8.51 (s, 1H), 9.89 (s, 1H). HRESIMS obsd *m*/*z* 460.1870, calcd for 460.1872.

2-(Benzyloxy)-*N*-(6-methoxy-4-oxo-3-(pyridin-2-ylmethyl)-3,4-dihydroquinazolin-7-yl)acetamide 15{*7*,*4*,*3*}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.94 (s, 3H), 4.24 (s, 2H), 4.67 (s, 2H), 5.28 (s, 2H), 7.26−7.43 (m, 7H), 7.54 (s, 1H), 7.78 (m, 1H), 8.40 (s, 1H), 8.45 (m, 1H), 8.57 (s, 1H), 9.38 (s, 1H). HRESIMS obsd *m*/*z* 431.1716, calcd for 431.1719.

***N*-(3-(3,4-Dimethoxyphenethyl)-6-(3,5-dimethylphenoxy)-4-oxo-3,4-dihydroquinazolin-7-yl)cinnamamide 15{*5*,*6*,*5*}.** ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.36 (s, 6H), 2.88 (t, 2H, J = 6.9 Hz), 3.65 (s, 3H), 3.69 (s, 3H), 4.12 (t, 2H, J = 6.9 Hz), 6.64 (d, 1H, J = 8.1 Hz), 6.80 (m, 4H), 6.94 (s, 1H), 7.30−7.44 (m, 5H), 7.66 (m, 3H), 8.03 (s, 1H), 8.72 (s, 1H), 10.03 (s, 1H). HRESIMS obsd *m*/*z* 576.2485, calcd for 576.2498.

***N*-(3-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-6-morpholino-4-oxo-3,4-dihydroquinazolin-7-yl)cinnamamide 15{*1*,*5*,*5*}.** ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.90 (brs, 4H), 3.89 (brs, 4H), 5.06 (s, 2H), 5.98 (s, 2H), 6.85 (m, 2H), 7.00 (s, 1H), 7.25 (d, 1H, J = 15.6 Hz), 7.46 (m, 3H), 7.64 (d, 1H, J = 15.9 Hz), 7.71−7.73 (m, 2H), 7.81 (s, 1H), 8.49 (s, 1H), 8.56 (s, 1H), 9.37 (s, 1H). HRESIMS obsd *m*/*z* 511.1983, calcd for 511.1981.

***N*-(3-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-6-morpholino-4-oxo-3,4-dihydroquinazolin-7-yl)-2-(benzyloxy)acetamide 15{*1*,*5*,*3*}.** ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.79 (brs, 4H), 3.48 (brs, 4H), 4.24 (s, 2H), 4.68 (s, 2H), 5.05 (s, 2H), 5.97 (s, 2H), 6.86 (m, 2H), 6.99 (s, 1H), 7.35−7.46 (m, 5H), 7.82 (s, 1H), 8.49 (s, 1H), 8.56 (s, 1H), 9.70 (s, 1H). HRESIMS obsd *m*/*z* 529.2096, calcd for 529.2088.

(*E*)-3-(2-Chlorophenyl)-*N*-(6-methoxy-4-oxo-3-(pyridin-2-ylmethyl)-3,4-dihydroquinazolin-7-yl) acrylamide 15{*7*,*4*,*6*}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.00 (s, 3H), 5.32 (s, 2H), 7.33−7.58 (m, 6H), 7.80−7.95 (m, 3H), 8.45 (s, 1H), 8.50 (d, 1H, J = 4.2 Hz), 8.71 (s, 1H), 8.84 (s, 1H), 9.84 (s, 1H). HRESIMS obsd *m*/*z* 447.1226, calcd for 447.1218.

***N*-(6-(Benzyloxy)-4-oxo-3-(pyridin-2-ylmethyl)-3,4-dihydroquinazolin-7-yl)acrylamide 15{*6*,*4*,*4*}.** ^{1}H NMR (300 MHz, DMSO-d_6): δ 5.25 (s, 2H), 5.39 (s, 2H), 5.82 (dd, 1H, J = 2.1 Hz, 9.9 Hz), 6.32 (dd, 1H, J = 2.1 Hz, 16.8 Hz), 6.81 (dd, 1H, J = 9.9 Hz, 16.8 Hz), 7.25−7.40 (m, 5H), 7.51 (d, 2H, J = 7.5 Hz), 7.55 (s, 1H), 7.79 (m, 1H), 8.38(s, 1H), 8.44 (m, 1H), 8.54 (s, 1H), 9.73 (s, 1H). HRESIMS obsd *m*/*z* 413.1610, calcd for 413.1608.

***N*-(6-(4-Fluorophenoxy)-4-oxo-3-(1-phenylethyl)-3,4-dihydroquinazolin-7-yl)cyclopropane carboxamide 15{*4*,*3*,*2*}.** ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.84 (m, 4H), 1.78 (d, 3H, J = 6.9 Hz), 2.24 (m, 1H), 6.00 (q, 1H, J = 6.9 Hz), 7.25−7.35(m, 10H), 8.33 (s, 1H), 8.54 (s, 1H), 10.15 (s, 1H). HRESIMS obsd *m*/*z* 444.1716, calcd for 444.1715.

***N*-(3-(2-Methoxyethyl)-4-oxo-6-(pyrrolidin-1-yl)-3,4-dihydroquinazolin-7-yl)acrylamide 15{*2*,*2*,*4*}.** ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.91 (brs, 4H), 3.19 (brs, 4H), 3.23 (s, 3H), 3.59 (t, 2H, J = 5.1 Hz), 4.12(t, 2H, J = 5.1 Hz), 5.78 (dd, 1H, J = 1.8 Hz, J = 9.9 Hz), 6.29 (dd, 1H, J = 1.8 Hz, J = 16.8 Hz), 6.63 (dd, 1H, J = 9.9 Hz, 16.8 Hz), 7.49 (s, 1H), 7.91 (s, 1H), 8.09 (s, 1H), 9.69 (s, 1H). HRESIMS obsd *m*/*z* 343.1766, calcd for 343.1765.

***N*-(3-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-6-morpholino-4-oxo-3,4-dihydroquinazolin-7-yl)acrylamide 15{*1*,*5*,*4*}.** ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.65 (brs, 4H), 3.83 (brs, 4H), 5.06 (s, 2H), 5.83 (d, 1H, J = 9.9 Hz), 5.97 (s, 2H), 6.32 (d, 1H, J = 16.8 Hz), 6.75 (dd, 1H, J = 9.9 Hz, J = 16.8 Hz),6.87 (s, 2H), 6.99 (s, 1H), 7.78 (s, 1H), 8.42 (s, 1H), 8.48 (s, 1H), 9.40 (s, 1H). HRESIMS obsd *m*/*z* 435.1670, calcd for 435.1663.

***N*-(6-(4-Fluorophenoxy)-4-oxo-3-(1-phenylethyl)-3,4-dihydroquinazolin-7-yl)acrylamide 15{*4*,*3*,*4*}.** ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 1.79 (d, 3H, J = 7.2 Hz), 5.80 (dd, 1H, J = 2.1 Hz, 9.9 Hz), 6.01 (q, 1H, J = 7.5 Hz), 6.36 (dd, 1H, J = 2.1 Hz, 16.8 Hz), 6.86 (dd, 1H, J = 9.9 Hz, 16.8 Hz), 7.23−7.35 (m,10H), 8.35 (s, 1H), 8.66 (s, 1H), 10.10 (s, 1H). HRESIMS obsd *m*/*z* 430.1567, calcd for 430.1567.

2-(Benzyloxy)-*N*-(4-oxo-6-phenoxy-3-phenyl-3,4-dihydroquinazolin-7-yl)acetamide 15{*3*,*7*,*3*}. ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 4.27 (s, 2H), 4.63 (s, 2H), 7.18−7.36 (m, 8H), 7.41 (s, 1H), 7.46−7.56 (m, 7H), 8.29 (s, 1H), 8.71 (s, 1H), 9.65 (s, 1H). HRESIMS obsd *m*/*z* 478.1769, calcd for 478.1767.

General Procedure for the Synthesis of 17. Method 1. Compound **8** (R^1 = BnO) (0.7 g) was dissolved in 4.2 mL

of anhydrous THF (or DMF) under stirring at room temperature; 0.3−0.7 g of Pd/C (10%) was added, and the mixture was hydrogenated under the atmospheric pressure for 3 h. Fifty milliliters of anhydrous THF (or DMF) was added. Pd/C was removed by filtration. The filtrate was evaporated to give **17**. For *N*-(6-hydroxy-4-oxo-3-(pyridin-2-ylmethyl)-3,4-dihydroquinazolin-7-yl)formamide, as an example compound, 0.46 g of white solid was obtained in 85.8% yield with an HPLC purity >95%. ESI-MS (*m*/*z*): 297 $[M + H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 5.24 (s, 2H), 7.27 (m, 1H), 7.34 (d, 1H, J = 7.8 Hz), 7.47 (s, 1H), 7.77 (m, 1H), 8.31 (s, 1H), 8.45 (m, 2H), 8.52 (s, 1H), 10.00 (s, 1H), 10.88 (brs, 1H).

Method 2. Compound **8** (R^1 = BnO, 0.5 g) was dissolved in 5 mL of anhydrous THF (or DMF), and 5 mL of anhydrous ethanol under stirring at room temperature; 0.25−0.5 g of Pd/C (10%) and 2 g of ammonium formate were added. Stirring was continued for 3 h. Twenty milliliters of THF (or DMF) was added. Pd/C was removed by filtration. The filtrate was concentrated to yield crude **17**. Crude **17** was purified on silica gel with the ethyl acetate/petroleum ether (or methylene chloride/methanol) system as an eluent. For N-(6-hydroxy- 4-oxo-3-(1-phenylethyl)-3,4-dihydroqui nazolin-7-yl)formamide, as an example compound, 0.34 g of white solid, was obtained in 88% yield with an HPLC purity >95%. ESI-MS (*m*/*z*): 310 $[M + H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.80 (d, 3H, J = 7.2 Hz), 6.06 (q, 1H, J = 7.2 Hz), 7.25−7.39 (m, 5H), 7.51 (s, 1H), 8.23 (s, 1H), 8.41 (d, 1H, J = 1.5 Hz), 8.49 (s, 1H), 10.00 (s, 1H), 10.91 (s, 1H).

General Procedure for the Synthesis of 18. A solution of **17** (0.113 mmol) in 0.4 mL of anhydrous THF (or DMF) was stirred at 0 °C. After addition of triphenylphosphine (0.168 mmol) and alcohol (0.128 mmol), diethylazodicarboxylate (DEAD, 0.168 mmol) was added dropwise. Stirring was continued for 2 h. An additional aliquot of triphenylphosphine (0.168 mmol) and diethylazodicarboxylate (DEAD, 0.168 mmol) was added. Stirring was continued for 2 h. The solvent was evaporated in vacuo to give crude **18**. The crude **18** was purified on silica gel with the ethyl acetate/petroleum ether (or methylene chloride/ methanol) system as an eluent. For *N*-(4-oxo-3-(1-phenylethyl)-6-(2-(piperidin-1-yl)ethoxy)-3,4-dihydroquinazolin-7-yl)formamide, as an example compound, 21 mg of white solid was obtained in 44.2% yield with an HPLC purity >95%. ESI-MS (*m*/*z*): 421 $[M + H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.39−1.62 (m, 6H), 1.82 (d, 3H, J = 7.2 Hz), 2.49 (brs, 4H), 2.81 (brs, 2H), 4.27(brs, 2H), 6.09 (q, 1H, J = 7.2 Hz), 7.31 (m, 5H), 7.61 (s, 1H), 8.31 (s, 1H), 8.47 (s, 1H), 8.54 (s, 1H), 10.03 (s, 1H).

Compound 20. Compound **20** was prepared with same method as compound **15**.

***N*-(6-(2-Morpholinoethoxy)-4-oxo-3-(1-phenylethyl)-3,4-dihydroquinazolin-7-yl)acrylamide 20{*4*,*3*}.** ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.83 (d, 3H, J = 7.2 Hz), 2.64 (brs, 4H), 2.92 (t, 2H, J = 5.4 Hz), 3.79 (brs, 4H), 4.34 (t, 2H, J = 5.4 Hz), 5.82 (m, 1H), 6.32 (q, 1H, J = 7.2 Hz), 6.46 (brs, 2H), 7.29−7.38 (m, 5H), 7.74 (s, 1H), 7.90 (s, 1H), 8.75 (brs, 1 H), 8.83 (s, 1H). HRESIMS obsd *m*/*z* 449.2183, calcd for 449.2183.

***N*-(4-Oxo-3-(1-phenylethyl)-6-(2-(piperidin-1-yl)ethoxy)-3,4-dihydroquinazolin-7-yl)acrylamide 20{*3*,*3*}.** ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.61 (brs, 2H), 1.83 (d, 3H, J = 6.9 Hz), 1.89 (brs, 4H), 2.91 (brs, 4H), 3.22 (brs, 2H), 4.38 (t, 2H, J = 5.4 Hz), 5.78 (d, 1H, J = 9.9 Hz), 6.32 (q, 1H, J = 6.9 Hz), 6.48 (d, 1H, J = 16.8 Hz), 6.93 (m, 1H), 7.37 (m, 5H), 7.67 (s, 1H), 7.90 (s, 1H), 8.87 (s, 1H), 9.49 (brs, 1H). HRESIMS obsd *m*/*z* 447.2391, calcd for 447.2391.

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Supporting Information Available. Full NCI GI_{50} values for compounds **15**{*7*,*4*,*3*}, **15**{*1*,*5*,*4*}, **15**{*4*,*3*,*4*}, **12**{*6*,*3*,*5*}, and **12**{*5*,*6*,*5*} and additional experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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