# An Efficient Method to Prepare 4-Aminoquinazolines: Potential Application to Conformation-Restricted Bleomycin Analogs



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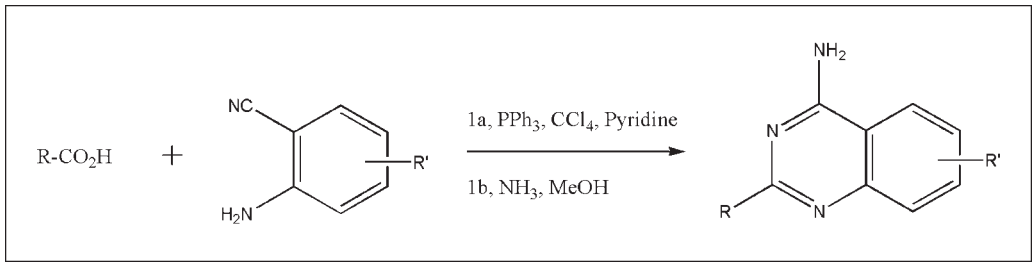


To enhance the iron-chelating ability of P-3A, 4-aminoquinazolines were designed as conformation-restricted bleomycin analogs. An efficient method was developed to prepare the 4-aminoquinazoline heterocyclic nucleus, which entails a two-step one-pot procedure leading to 4-aminoquinazolines in good yields. The application of this method to synthesis 4-aminoquinazoline bleomycin analogs is envisioned.

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## INTRODUCTION

Bleomycins are a family of glycopeptide natural products and have been used clinically to treat various cancers for decades. However, dose-dependent undesired side effects, such as pulmonary toxicity are limiting the therapeutic efficacy of bleomycins. Thus, it has been suggested that improved bleomycin analogs may have enhanced therapeutic index between anticancer activity and undesired toxicity [1]. The seminal studies by Hecht [2–4], and Boger [5] groups not only established synthetic methodologies to access bleomycin analogs but also contributed to the understanding of mechanism of action for this important class of compounds.

Bleomycins exert their antitumor activities through sequence-specific cleavages of DNA, which requires the activation of oxygen *via* the formation of a complex consisting of the metal-binding domain of bleomycins, a transition metal such as Fe(II) or Cu(I) and molecular oxygen [6]. In medicinal chemistry, conformational restriction is commonly used to improve potency [7]. We envision that the application of such a strategy to the metal-binding domain of bleomycin could lead to analogs that promote more efficient formation of the oxygen-Fe(II)-bleomycin complex. To test this concept, P-3A, the smallest member of the bleomycin family but still retaining DNA cleavage properties was selected (Figure 1). The four atoms of **P-3A** responsible for metal-coordination are highlighted in bold (Figure 1), and it is evident that the —NH— of the amide group participates in the metal binding, but the carbonyl group does not. Therefore, the cyclization of the carbonyl group onto the 6-position of the pyrimidine nucleus *via* a benzene ring, leading to compounds **1**. The quinazoline ring system in compounds **1** should fix the —NH— group in a position that has higher propensity for metal binding compared with the relatively flexible amide group in **P-3A** and other bleomycins.

Syntheses of quinazolines are widely reported as a result of efforts towards natural product total synthesis and medicinal chemistry programs [8]. For example, the quinazoline scaffold is common to numerous kinase inhibitors including Iressa [9]. 4-Aminoquinazolines were prepared from 2-aminobenzonitrile with either a nitrile [10] or an orthoester [11] under microwave conditions. Recently, 2-aminonitrile was cyclized with formic acid at the elevated temperature of 200°C leading to 5,6-dihydro-quinazolines [12]; 2-aminobenzamide was cyclized with anilines and orthoesters to give 4-arylaminoquinazolines [13]. We envisioned that 2-aminobenzonitrile (**2**) also could react with a carboxylic acid in an one-pot two-step procedure to produce the key intermediate (**4**) required for our conformation-restricted P-3A analogs (Scheme 1).

## RESULTS AND DISCUSSION

Imidoyl chlorides were readily prepared from carboxylic acids and amines under the mild conditions of $PPh_3$-$CCl_4$ [14], and this method has been applied to the synthesis of various heterocycles [15]. Our strategy is to generate the imidoyl chloride **3** *in situ* and then

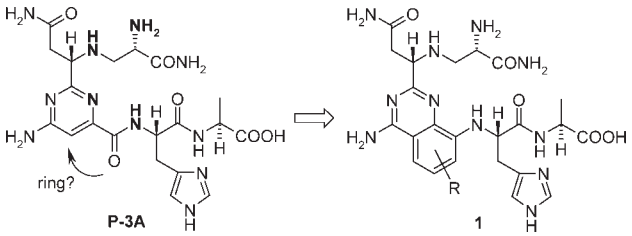



**Figure 1.** Design of conformationally restricted P-3A analogs.

substitute it with ammonia; the resulting amidine should readily be cyclized onto the neighboring nitrile group leading to the desired 4-aminoquinazolines (**4**). To test this one-pot procedure, 2-aminobenzonitrile **2a** was reacted with various aromatic carboxylic acids, and the results are summarized in Table 1.

Most benzoic acid studies gave the desired quinazolines in good-to-high yields (entries 1–5, Table 1). However, para-methoxybenzoic gave lower yield compared to other benzoic acids (entry 6, Table 1), and it is possible that the strong electron-donating property of the MeO group reduces the reactivity of the benzoic acid. Heterocyclic aromatic acids were also suitable substrates for this reaction leading to desired quinazolines in moderate yields (entries 7–9). Encouraged by the success with aromatic acids, aliphatic acids including *N*-Cbz-L-asparagine (*N*-Cbz-Asn) required for the synthesis of bleomycin analogs were studied and the results are summarized in Table 2.

As evident from Table 2, aliphatic carboxylic acids are also suitable for this one-pot two-step reaction leading to 4-aminoquinazolines in good yields (entries 1–4, Table 2). To compare this new one-pot procedure against the conventional stepwise approach, phenylacetic acid was coupled with 2-aminobenzonitrile *via* its acyl chloride to give 2-*N*-(phenylacetyl) aminobenzonitrile in 72% yield; the resulting amide was subjected to the new one-pot two-step procedure and give compound **6d** in 54% yield (entry 5, Table 2). This indicates that preformation of the amide bond did not lead to higher yield of the desired 4-aminoquinazoline. More importantly, *N*-Cbz-Asn reacted with 2-aminobenzonitrile to give 4-aminoquinazoline **6f** in good yield (entry 7, Table 2),

**Scheme 1.** Synthesis of 4-aminoquinazolines (**4**) from carboxylic acids.

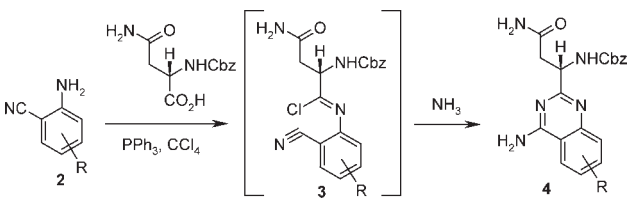
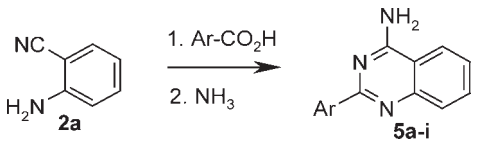



**Table 1**

Cyclization of 2-aminobenzonitrile and Ar-$CO_2H$.[a]



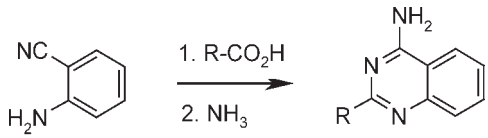

| Entry | Ar | $T_1/T_2$[b] | Pdt | Yield (%) |
|---|---|---|---|---|
| 1 | Ph- | 8h/6h | **5a** | 75 |
| 2 | 4-Me-Ph- | 8h/6h | **5b** | 74 |
| 3 | 4-F-Ph- | 8h/6h | **5c** | 81 |
| 4 | 4-$NO_2$-Ph- | 8h/6h | **5d** | 60 |
| 5 | 4-Br-Ph- | 8h/6h | **5e** | 72 |
| 6 | 4-MeO-Ph- | 48h/6h | **5f** | 30 |
| 7 | 3-pyridyl | 12h/6h | **5g** | 58 |
| 8 | Quinoline-2-yl | 12h/6h | **5h** | 40 |
| 9 | Furan-2-yl | 8h/6h | **5i** | 46 |

[a] Reaction conditions: 3.3 equiv $Ph_3P$, 3.3 equiv pyridine, 24 equiv $CCl_4/CH_3CN$, reflux, then $NH_3$-MeOH, 100°C.
[b] $T_1$ and $T_2$, reaction times for step 1 and 2, respectively.

suggesting that our planned syntheses of conformation-restricted bleomycin analogs **1** are likely feasible. To gain confidence of our planned synthesis of bleomycin analog **1**, substituted 2-aminobenzonitriles were studied to expand the scope of this new one-pot procedure (Table 3).

2-Aminobenzonitriles with halo groups reacted with either *N*-Cbz-L-asparagine or phenylacetic acid to give the desired products **7a–d** in moderate yields (entries 1–

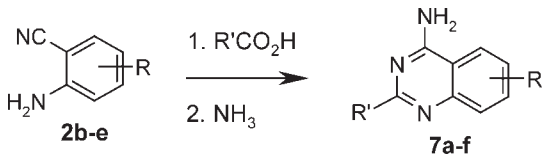
**Table 2**
Cyclization of 2-aminobenzonitrile and R-$CO_2H$.[a]




| Entry | R | $T_1/T_2$[b] | Pdt | Yield (%) |
|---|---|---|---|---|
| 1 | Me- | 12 h/6 h | **6a** | 73 |
| 2 | *i*-Pr | 12 h/6 h | **6b** | 58 |
| 3 | Cyclohexyl | 12 h/6 h | **6c** | 81 |
| 4 | Ph-$CH_2$- | 12 h/6 h | **6d** | 62 |
| 5 | Ph-$CH_2$- | 12 h/6 h | **6d** | 54[c] |
| 6 | Ph-CH(OH)- | 14 h/6 h | **6e** | 54 |
| 7 | Asn[d] | 16 h/6 h[e] | **6f** | 69 |
| 8 | Gly[f] | 14 h/6 h[e] | **6g** | 40 |

[a] Reaction conditions: 3.3 equiv $Ph_3P$, 3.3 equiv pyridine, 24 equiv $CCl_4/CH_3CN$, reflux, then $NH_3$-MeOH, 100°C.
[b] $T_1$ and $T_2$, reaction times for step 1 and step 2, respectively.
[c] A stepwise procedure was used (see text).
[d] Asn, *N*-Cbz-L-asparagine.
[e] Reaction temperature 50°C.
[f] Gly, *N*-Cbz-glycine.

**Table 3**
Cyclization of substituted 2-aminobenzonitriles.[a]




| Entry | R | R′ | $T_1/T_2$[b] | Pdt | Yield (%) |
|---|---|---|---|---|---|
| 1 | 5-Cl (**2b**) | Asn[c] | 16 h/6 h[d] | **7a** | 32 |
| 2 | 5-Cl (**2b**) | Bn | 12 h/6 h | **7b** | 35 |
| 3 | 4-Cl (**2c**) | Asn[c] | 16 h/6 h[d] | **7c** | 29 |
| 4 | 4-Cl (**2c**) | Bn | 12 h/6 h | **7d** | 32 |

[a] Reaction conditions: 3.3 equiv $Ph_3P$, 3.3 equiv pyridine, 24 equiv $CCl_4/CH_3CN$, reflux, then $NH_3$-MeOH, 100°C.
[b] $T_1$ and $T_2$, reaction times for step 1 and step 2, respectively.
[c] Asn, *N*-Cbz-L-asparagine.
[d] Reaction temperature 50°C.

4, Table 3). The electron-withdrawing effects of the halo groups likely decreased the nucleophilicity of the aniline group, which may account for the observed lower yields compared to reactions with compound **2a**.

In summary, a series of 4-aminoquinazolines were designed as conformationally restricted bleomycin analogs, which may have improved metal-binding efficiency. A new one-pot two-step procedure was developed to prepare 4-aminoquinazolines from carboxylic acids and 2-aminobenzonitriles. Various carboxylic acids, including aromatic, aliphatic, and amino acids, are suitable substrates for this new method. Given there are numerous carboxylic acids available, this method should complement existing methods to access broad range of quinazolines. The application of this new method to 4-aminoquinazoline bleomycin analogs are in progress and will be reported in due course.

## EXPERIMENTAL

Melting points are uncorrected. Mass spectra and HPLC (ELSD) data were recorded on an 1100 LC/MS system (Agilent Technology) with Alltech ELSD 2000, using a 4.6 × 50 mm Column (CenturySIL C-18 $AQ^+$, 5 μm) with a linear gradient 30–90% (v/v) acetonitrile–water with 0.035% trifluoroacetic acid over 5 min with a flow rate of 3.5 mL/min. Analytical TLC was performed using 2 × 5 cm plates coated with a 0.25-mm thickness of silica gel 60 $F_{254}$. Column chromatography was performed using silica gel G (200–300 mesh). All $^1H$ NMR spectra (300 MHz) and $^{13}C$ NMR spectra (75 MHz) were measured on a Varian 300 MHz spectrometer using TMS as an internal standard and $CDCl_3$ or DMSO-$d_6$ as solvent. The ammonia methanol solution was prepared by the saturation of anhydrous methanol with ammonia gas at 0°C.

**General procedure for the one-pot two-step synthesis of compounds 5a.** A solution of benzoic acid (1.0 mmol, 122 mg), 2-aminobenzonitrile **2a** (1.1 mmol, 130 mg), and pyridine (3.3 mmol, 260 mg, and 0.26 mL) in 4 mL $CCl_4$ and 6 mL acetonitrile was stirred at room temperature for 10 min, and triphenylphosphine (3.3 mmol, 866 mg) was added. The mixture was refluxed at 80°C for 8 h and then the mixture and a 10 mL ammonia methanol solution (2 *M*) were added into a sealed steel reactor. The reactor was heated at 100°C for 6 h and then concentrated. The residue was purified by column chromatography (hexanes/EtOAc, 6/1) affording 2-phenyl-4-aminoquinazoline **5a** (166 mg, 75%) as a white solid. white solid, mp 144–145°C; 1H NMR (300 MHz, DMSO-d6) δ = 8.48–8.44 (m, 2H), 8.25 (d, J = 7.8 Hz, 1H), 7.84 (br., 2H), 7.81–7.76 (m, 2H), 7.51–7.44 (m, 4H). 13C NMR (75 MHz, DMSO-$d_6$): δ = 161.7, 159.3, 149.9, 138.1, 132.5, 129.4, 127.7, 127.4, 127.2, 124.6, 123.1, and 112.8. ES-MS: *m/z* 222 [M+$H^+$].

**4-Amino-2-phenylquinazoline (5a).** White solid, mp 144–145°C; $^1H$ NMR (300 MHz, DMSO-$d_6$): δ = 8.48–8.44 (m, 2H), 8.25 (d, *J* = 7.8 Hz, 1H), 7.84 (br., 2H), 7.81–7.76 (m, 2H), 7.51–7.44 (m, 4H). $^{13}C$ NMR (75 MHz, DMSO-$d_6$): δ = 161.7, 159.3, 149.9, 138.1, 132.5, 129.4, 127.7, 127.4, 127.2, 124.6, 123.1, and 112.8. ES-MS: *m/z* 222 [M + $H^+$].

**4-Amino-2-(*p*-tolyl)quinazoline (5b).** White solid, mp 139–140°C; $^1H$ NMR (300 MHz, DMSO-$d_6$): δ = 8.36 (d, *J* = 6.6 Hz, 2H), 8.23 (d, *J* = 8.1 Hz, 1H), 7.79–7.74 (m, 4H), 7.47–7.43 (m, 1H), 7.29 (d, *J* = 7.2 Hz, 2H), 2.38 (s, 3H). $^{13}C$ NMR (75 MHz, DMSO-$d_6$): δ = 161.6, 159.3, 150.0, 139.0, 135.4, 132.4, 128.3, 127.4, 127.1, 124.4, 123.1, 112.8, and 20.5. ES-MS: *m/z* 236 [M + $H^+$].

**4-Amino-2-(4-fluorophenyl)quinazoline (5c).** White solid, mp 156–158°C; $^1H$ NMR (300 MHz, DMSO-$d_6$): δ = 8.52–8.47 (m, 2H), 8.24 (d, *J* = 8.1 Hz, 1H), 7.86 (br., 2H), 7.81–7.73 (m, 2H), 7.47 (t, *J* = 6.9 Hz, 1H), 7.31 (t, *J* = 8.7 Hz, 2H). $^{13}C$ NMR (75 MHz, DMSO-$d_6$): δ = 163.5 (d, *J* = 245.2 Hz), 162.2, 158.9, 150.3, 135.1, 133.0, and 130.1 (d, *J* = 8.6 Hz), 127.6, 125.1, 123.6, and 115.0 (d, *J* = 21.1 Hz), 113.2. ES-MS: *m/z* 240 [M + $H^+$].

**4-Amino-2-(4-nitrophenyl)quinazoline (5d).** Yellow solid, mp 218–220°C; $^1H$ NMR (300 MHz, DMSO-$d_6$): δ = 8.68 (d, *J* = 9.3 Hz, 2H), 8.38 (d, *J* = 8.7 Hz, 2H), 8.29 (d, *J* = 7.8 Hz, 1H), 8.03 (br, 2H), 7.83–7.82 (m, 2H), 7.57–7.52 (m, 1H). $^{13}C$ NMR (75 MHz, DMSO-$d_6$): δ = 162.3, 157.8, 150.1, 148.3, 144.7, 133.3, 128.8, 127.9, 126.1, 123.7, 123.5, and 113.4. ES-MS: *m/z* 267 [M + $H^+$].

**4-Amino-2-(4-bromophenyl)quinazoline (5e).** White solid, mp 167–168°C; $^1H$ NMR (300 MHz, DMSO-$d_6$): δ = 8.38 (d, *J* = 7.5 Hz, 2H), 8.24 (d, *J*=8.1 Hz, 1H), 7.89 (br., 2H), 7.81–7.68 (m, 4H), 7.51–7.46 (m, 1H). $^{13}C$ NMR (75 MHz, DMSO-$d_6$): δ = 162.2, 158.8, 150.3, 137.8, 133.0, 131.2, 129.8, 127.7, 125.3, 123.7, 123.6, and 113.3. ES-MS: *m/z* 300, 302 [M + $H^+$].

**4-Amino-2-(4-methoxyphenyl)quinazoline (5f).** White solid, mp 177–179°C; $^1H$ NMR (300 MHz, DMSO-$d_6$): δ = 8.41 (d, *J* = 8.7 Hz, 2H), 8.21 (d, *J* = 8.1 Hz, 1H), 7.77–7.70 (m, 4H), 7.45–7.40 (m, 1H), 7.04 (d, *J* = 9.0 Hz, 2H), 3.84 (s, 3H). $^{13}C$ NMR (75 MHz, DMSO-$d_6$): δ = 162.0, 161.0, 159.7, 150.6, 132.9, 131.2, 129.5, 127.5, 124.7, 123.6, 113.5, 113.1, and 55.2. ES-MS: *m/z* 252 [M + $H^+$].

**4-Amino-2-(pyridin-3-yl)quinazoline (5g).** White solid, mp 226–227°C; $^1H$ NMR (300 MHz, DMSO-$d_6$): δ = 9.56 (s, 1H), 8.71–8.66 (m, 2H), 8.27 (d, *J* = 8.1 Hz, 1H), 7.96 (br.,

2H), 7.84–7.77 (m, 2H), 7.55–7.48 (m, 2H). $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ = 162.2, 158.2, 150.6, 150.2, 149.2, 135.0, 133.8, 133.1, 127.7, 125.6, 123.7, 123.4, and 113.4. ES-MS: *m*/*z* 223 [M + H$^+$].

**4-Amino-2-(quinolin-2-yl)quinazoline (5h).** White solid, mp 261–262°C; $^1$H NMR (300 MHz, DMSO-$d_6$): δ = 8.59 (d, *J* = 9.0 Hz, 1H), 8.49 (d, *J* = 8.1 Hz, 1H), 8.31 (d, *J* = 8.1 Hz, 1H), 8.16 (d, *J* = 9.0 Hz, 1H), 8.07 (br. 2H), 8.04 (s, 1H), 7.90–7.80 (m, 3H), 7.66 (t, *J* = 7.5 Hz, 1H), 7.56 (t, *J* = 7.2 Hz, 1H). $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ = 162.6, 160.0, 156.2, 150.2, 147.4, 136.3, 133.1, 129.7, 129.5, 128.0, 127.9, 127.8, 127.1, 126.0, 123.6, 121.1, and 113.6. ES-MS: *m*/*z* 273 [M + H$^+$].

**4-Amino-2-(furan-2-yl)quinazoline (5i).** White solid, mp 221°C (decomp.); $^1$H NMR (300 MHz, DMSO-$d_6$): δ = 8.21 (d, *J* = 8.1 Hz, 1H), 7.86–7.68 (m, 5H), 7.47–7.42 (m, 1H), 7.18 (d, *J* = 2.7 Hz, 1H), 6.65 (t, *J* = 1.5 Hz, 1H). $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ= 162.1, 153.7, 153.1, 150.2, 144.7, 133.2, 127.4, 125.1, 123.7, 113.4, 112.2, and 112.1. ES-MS: *m*/*z* 212 [M + H$^+$].

**4-Amino-2-methylquinazoline (6a).** White solid, mp 226°C (decomp.); $^1$H NMR (300 MHz, DMSO-$d_6$): δ = 8.47 (br., 2H), 8.27 (d, *J* = 8.7 Hz, 1H), 7.83 (t, *J* = 7.5 Hz, 1H), 7.67 (d, *J* = 8.1 Hz, 1H), 7.53 (t, *J* = 7.5 Hz, 1H), 1.76 (s, 3H). $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ = 171.7, 162.8, 162.4, 134.1, 125.8, 124.2, 123.4, 111.9, and 24.2. ES-MS: *m*/*z* 160 [M + H$^+$].

**4-Amino-2-isopropylquinazoline (6b).** White solid, mp 117–119°C; $^1$H NMR (300 MHz, DMSO-$d_6$): δ = 8.17 (d, *J* = 8.1 Hz, 1H), 7.74–7.68 (m, 3H), 7.61 (d, *J* = 8.1 Hz, 1H), 7.43–7.38 (m ,1H), 2.95–2.90 (m, 1H), 1.26 (d, *J* = 8.7 Hz, 6H). $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ = 170.8, 162.0, 150.1, 132.6, 127.0, 124.5, 123.4, 113.0, 37.1, and 21.7. ES-MS: *m*/*z* 188 [M + H$^+$].

**4-Amino-2-cyclohexylquinazoline (6c).** White solid, mp 210–213°C; $^1$H NMR (300 MHz, DMSO-$d_6$): δ = 8.16 (d, *J* = 8.7 Hz, 1H), 7.72–7.55 (m, 4H), 3.39 (t, *J* = 7.8 Hz, 1H), 2.64–2.56 (m, 1H), 1.92–1.55 (m, 7H), 1.41–1.21 (m, 3H). $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ = 170.0, 162.0, 150.3, 132.4, 127.1, 124.4, 123.4, 113.0, 47.1, 31.4, and 25.9. ES-MS: *m*/*z* 228 [M + H$^+$].

**4-Amino-2-benzylquinazoline (6d).** White solid, mp 240–242°C; $^1$H NMR (300 MHz, DMSO-$d_6$): δ = 8.16 (d, *J* = 8.7 Hz, 1H), 7.75–7.69 (m, 3H), 7.65–7.62 (m, 1H), 7.44–7.39 (m, 1H), 7.34–7.24 (m, 4H), 7.20–7.15 (m, 1H), 3.99 (s, 2H). $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ = 165.4, 162.1, 150.1, 139.3, 132.7, 128.9, 128.1, 127.0, 125.9, 124.7, 123.4, 112.7, and 45.6. ES-MS: *m*/*z* 236 [M + H$^+$].

**4-Amino-2-(hydroxy(phenyl)methyl)quinazoline (6e).** Yellow oil; $^1$H NMR (300 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 8.1 Hz, 1H), 7.79 (td, *J* = 1.5, 6.6 Hz, 1H), 7.66 (d, *J* = 8.1 Hz, 1H), 7.54–7.44 (m, 4H), 7.36–7.28 (m, 2H), 5.68 (br., 2H), 5.42 (br., 1H). $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 165.3, 161.8, 148.9, 142.7, 133.4, 128.4, 127.9, 127.8, 127.7, 126.0, 121.8, 113.3, and 75.1. ES-MS: *m*/*z* 252 [M + H$^+$].

**Benzyl 3-amino-1-(4-aminoquinazolin-2-yl)-3-oxopropylcarbamate (6f).** White solid, mp 244–246°C; $[\alpha]_D^{15}$= −77.2 (*c* = 1, MeOH:TFA = 10:1); $^1$H NMR (300 MHz, DMSO-$d_6$): δ = 8.18 (d, *J* = 8.1 Hz, 1H), 7.73 (t, *J* = 6.9 Hz, 3H), 7.59 (d, *J* = 8.1 Hz, 1H), 7.45–7.43 (m, 2H), 7.26 (s, 5H), 7.05 (s, 1H), 5.04–4.93 (m, 2H), 4.63–4.62 (m, 1H), 3.16–3.09 (m, 1H), 2.98–2.90 (m, 1H). $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ = 170.0, 161.9, 150.2, 132.4, 131.5, 128.8, 128.6, 127.1, 124.3, 123.4, 113.0, 47.0, 31.4, and 25.9. ES-MS: *m*/*z* 366 [M + H$^+$].

**Benzyl (4-aminoquinazolin-2-yl)methylcarbamate (6g).** White solid, mp 209°C (decomp.); $^1$H NMR (300 MHz, DMSO-$d_6$): δ = 8.19 (d, *J* = 8.4 Hz, 1H), 7.77–7.72 (m, 3H), 7.63 (d, *J* = 8.1 Hz, 1H), 7.50–7.35 (m, 6H), 5.07 (s, 2H), 4.22 (d, *J* = 6.0 Hz, 2H). $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ = 163.1, 162.0, 156.3, 149.8, 137.3, 132.8, 128.3, 127.7, 127.6, 127.0, 124.9, 123.6, 113.3, 65.2, and 46.5. ES-MS: *m*/*z* 309 [M + H$^+$].

**Benzyl 3-amino-1-(4-amino-6-chloroquinazolin-2-yl)-3-oxopropylcarbamate (7a).** Yellow solid, mp 252–254°C; $[\alpha]_D^{15}$= −92.2 (*c* = 1, MeOH:TFA = 10:1); $^1$H NMR (300 MHz, DMSO-$d_6$): δ = 8.34 (d, *J* = 2.4 Hz, 1H), 7.82 (br., 2H), 7.74 (dd, *J* = 2.1 Hz, 8.7 Hz, 1H), 7.60 (d, *J* = 9.0 Hz, 1H), 7.40 (d, *J* = 8.4 Hz, 1H), 7.27 (s, 5H), 7.24 (s, 1H), 7.03 (br, 1H), 5.03–4.96 (t, 2H), 4.62–4.60 (t, 1H), 3.32–3.09 (t, 1H), 3.97–3.92 (t, 1H). $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ = 173.4, 164.2, 161.0, 155.7, 148.6, 137.0, 133.0, 129.2, 128.7, 128.2, 127.6, 127.4, 122.7, 113.7, 65.2, 53.4, and 40.9; ES-MS: *m*/*z* 400 [M + H$^+$].

**4-amino-6-chloro-2-benzylquinazoline (7b).** White solid, mp 239–242°C; $^1$H NMR (300 MHz, DMSO-$d_6$): δ = 8.36 (d, *J* = 2.1 Hz, 1H), 8.19 (d, *J* = 2.4 Hz, 1H), 8.03 (br., 2H), 7.35–7.25 (m, 5H), 7.21–7.18 (m, 1H), 4.02 (s, 2H). $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ = 166.9, 161.7, 146.6, 138.7, 135.7, 128.9, 128.6, 128.2, 126.1, 123.6, 122.6, 114.2, and 45.6. ES-MS: *m*/*z* 270 [M + H$^+$].

**Benzyl 3-amino-1-(4-amino-7-chloroquinazolin-2-yl)-3-oxopropylcarbamate (7c).** Yellow solid, mp 259–261°C; $[\alpha]_D^{15}$= −57.6 (*c* = 1, MeOH:TFA = 10:1); $^1$H NMR (300 MHz, DMSO-$d_6$): δ = 8.22 (d, *J* = 8.7 Hz, 1H), 7.88 (br., 2H), 7.62 (d, *J* = 1.8 Hz, 1H), 7.48 (dd, *J* = 1.8 Hz, 8.7 Hz, 1H), 7.41 (d, *J* = 8.4 Hz, 1H), 7.27 (s, 6H), 7.05 (s, 1H), 5.05–4.93 (m, 2H), 4.65–4.60 (m, 1H), 3.16–3.09 (m, 1H), 2.97–2.90 (m, 1H). $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ = 173.5, 165.7, 165.0, 161.6, 155.7, 150.9, 137.3, 128.2, 127.6, 127.4, 125.7, 125.1, 111.5, 65.2, 53.6, and 40.9.; ES-MS: *m*/*z* 400 [M + H$^+$].

**4-Amino-7-chloro-2-benzylquinazoline (7d).** White solid, mp 210–212°C; $^1$H NMR (300 MHz, DMSO-$d_6$): δ = 8.20 (d, *J* = 8.7 Hz, 1H), 7.90 (br., 2H), 7.68 (d, *J* = 2.1 Hz, 1H), 7.49–7.46 (m, 1H), 7.36–7.16 (m, 5H), 3.98 (s, 2H). $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ = 166.9, 162.0, 151.3, 139.0, 137.4, 128.9, 128.2, 127.7, 126.1, 125.7, 125.2, 111.4, and 45.5. ES-MS: *m*/*z* 270 [M + H$^+$].

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