Synthesis of 2-Amino 3-Substituted Quinazolin-4(3H)-one Derivatives *via* Iodine-Mediated Guanidinylation of Pbf-Activated Thiourea

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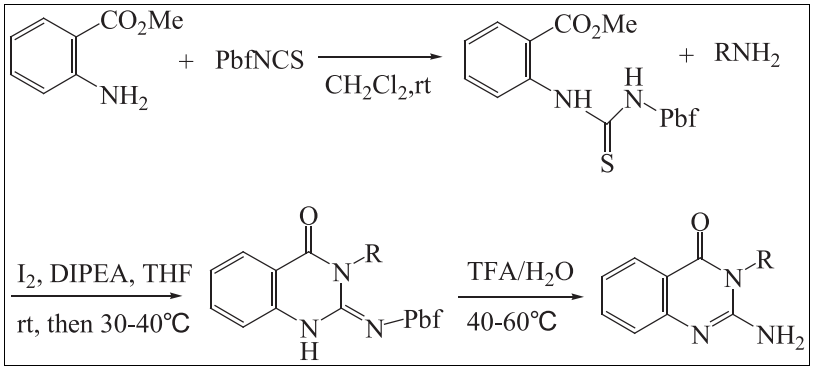

2-Amino 3-substituted-quinazolin-4(3H)-one derivatives were synthesized from Pbf-isothiocyanate and methyl anthranilate. The construction of the guanidine-containing quinazolinone heterocyclic skeleton was achieved using Pbf-activated thiourea treated with primary amines *via* iodine-mediated guanidinylation. The desired compounds were obtained after Pbf cleavage by trifluoroacetic acid.

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INTRODUCTION

4(3H)-Quinazolinone derivatives exhibit a range of biological properties such as anti-inflammatory and antihypertensive activities [1,2]. As a result, there are a number of synthetic methods reported for this class of compounds, especially concerning 2-amino derivatives. The majority of these methods generally fall into the category of either utilizing guanidine transformation of S-methylthiourea with isatoic anhydride [3], or utilizing aza-wittig-mediated annulation reaction from *o*-azido benzoic acid or iminophosphoranes [4]. Furthermore, novel synthesis method involving Friedel-Craft's type substitution from aniline was reported recently [5]. However, despite the simple skeleton of 2-amino 3-substituted-quinazolin-4(3H)-ones with a free amino group at position 2, to date, only a limited number of synthesis strategies have been disclosed [6a,6b,7,8]. Among them, the representative pathways involved one-carbon compounds as synthetic intermediate [7] and the guanidine conversion of S-methyl isothiourea, respectively [8]. The major limitations of the methods mentioned above to 2-amino 3-substituted-quinazolin-4 (3H)-ones are the harsh reaction conditions and the difficulties in introducing substitutions at the 3-position. Therefore, novel synthesis method to the title compounds is still desirable.

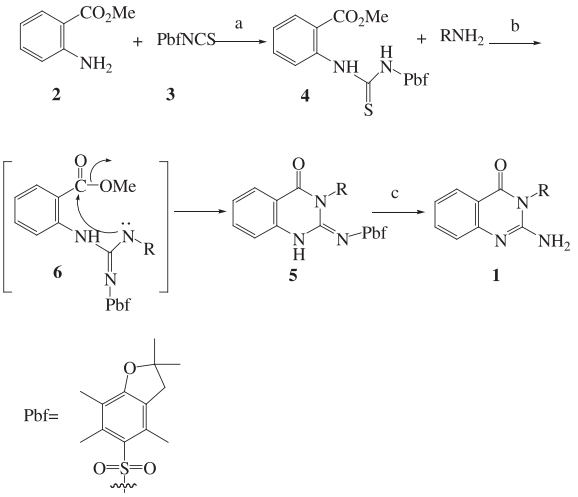
The reaction of thioureas with amines in the presence of a desulfurization reagent is one common method in the construction of guanidine functionality [9]. We have developed thiourea guanylating reagents *N*-(Ar or alkyl) substituted-*N*′-Pbf thiourea (Pbf: 2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl) [10], and provided efficient access to guanidine-containing heterocycles of five-membered [11] and six-membered rings from α or β-amino acids, respectively [12]. Moreover, due to the strong electron-withdrawing ability of the Pbf group, we also found in our previous work that iodine is a good desulfurization reagent promoting guanidine formation through a carbodiimide intermediate [13].

In our efforts directed toward developing new methodology for the synthesis of guanidine-containing heterocycles, we report herein a direct synthetic route to 2-amino 3-substituted-quinazolin-4(3H)-one derivatives **1** *via* iodine-mediated guanidine transformation of Pbf-activated thiourea **4** with primary amines, shown in Scheme 1.

RESULTS AND DISCUSSION

As illustrated in Scheme 1, our synthesis journey commenced from Pbf-isothiocyanate **3** and methyl anthranilate **2** to afford Pbf-activated thiourea **4**. The reaction of PbfNCS with 1 equiv methyl anthranilate in dichloromethane at room temperature produced Pbf-activated thiourea **4** in 90% yield, which can be easily purified through recrystallization in petroleum ether. Highly reactive Pbf-isothiocyanate may be obtained from Pbf-Cl

Scheme 1. Synthesis of 2-amino 3-substituted-quinazolin-4(3H)-one derivatives *via* Pbf-activated thiourea. Reagents and conditions: (a) CH_2Cl_2, 4 h, rt; (b) I_2, DIPEA, THF, 20 min, rt, then 30–40 h, 30–40°C; (c) TFA/H_2O = 95:5, 12 h, 40–60°C.



and Bu_4NNCS directly [14], or by treatment of Pbf-NH_2 with KOH and CS_2 followed by triphosgene in toluene, similar to the preparation of Pmc-isothiocyanate (Pmc: 2,2,5,7,8-pentamethyl chroman-6-sulfonyl) reported by Madalengoitia and Flemer [15].

Subsequently, at room temperature, 1 equiv iodine was added slowly to the solution of thiourea **4** and DIPEA (*N*, *N*′-diisopropylethylamine) in THF. About 20 min later, when thiourea was completely consumed in the reaction, primary amine was added to allow the guanidine formation. After removing solvent, the corresponding Pbf-protected heterocycle **5** was purified by column chromatography using ethyl acetate and petroleum ether as eluent. Finally, deprotection was accomplished by treatment with trifluoroacetic acid (TFA) and water (95:5) at 40–60°C for about 12 h to afford the desired product **1**. Final purification was performed by washing the residue with petroleum ether, neutralization with triethyl amine, and recrystallization from toluene. Thus, the synthesis route provided 2-amino 3-substituted-quinazolin-4(3H)-ones **1** in three short steps from starting materials methyl anthranilate and Pbf-isothiocyanate.

During the reaction process, the heterocyclic framework was constructed *via* the guanidine intermediate **6**, which smoothly underwent intramolecular cyclization reaction. According to this mechanism, from thiourea **4** to heterocycles **5**, prolonged reaction time and elevated reaction temperature helped product formation in high yield. Additionally, using 1 equiv iodine was critical to the reaction, because excess of iodine decreased the product yield. It is also noteworthy that the cyclization procedures are different between the guanidine heterocyclic skeletons of **1** and six-membered 2-(*N*-alkylamino)-pyrimidin-4-one derivatives [12]. In the latter case, the guanidine heterocycle was constructed after Pbf cleavage.

With the reaction conditions described above, we screened a range of different primary amines to explore the scope and limitations of the synthetic methodology. The result was shown in Table 1. To our delight, unhindered aliphatic amines and aromatic amine afforded the desired Pbf-protected guanidine heterocycles **5** (entries 1–4, 6, and 7) in moderate to good isolated yields, showing that the guanidine transformation procedure can easily tolerate a range of substituted functional groups such as hydroxy or ester groups on the amines (entries 3 and 4). But Pbf cleavage of compound **5d** with ester group cannot afford the isolated product **1d** due to the formation of multicomponent mixtures. Unexpectedly, severely hindered amines such as *t*-butylamine under these reaction conditions or even upon heating at reflux for 2 days, did not produce detectable amount of cyclized compound **5e**, indicating that steric bulk in the primary amines used is of consequence to the reaction outcome. We then investigated the effect of substituents on the phenyl ring of the amines on the reactivity of the reaction. Aromatic amines with electron-donating substituents promote the guanidinylation reaction (entries 8–11), at the same time electron-withdrawing substituents such as a nitro or a chloro group failed to afford compounds **5l** and **5m** (entries 12 and 13). This result was consistent with our previous reported study on iodine-mediated guanidinylation reaction with benzosulfonyl-activated thiourea [13]. All the desired compounds except **1d** were obtained in high isolated yield after the Pbf cleavage by TFA and identified by standard spectroscopic techniques. The spectral data of compounds **1a** and **1g** is identical to that reported earlier [7,8].

Compared to the literature reports [6a,6b,7,8], the substituted groups were readily introduced from available diverse primary amines in our synthetic protocol. Moreover, all the reaction procedures were carried out under

Table 1

Conversion of Pbf-thiourea to 2-amino 3-substituted-4(3H)-one derivatives.

Entries	R	Product	Yield (%)	Product	Yield (%)
1	*n*-C_4H_9	**5a**	61	**1a**	85
2	*n*-C_3H_7	**5b**	75	**1b**	84
3	$HOCH_2CH_2$	**5c**	57	**1c**	83
4	$EtO_2CCH_2CH_2$	**5d**	42	**1d**	/
5	*t*-C_4H_9	**5e**	0	**1e**	/
6	$C_6H_5CH_2$	**5f**	72	**1f**	88
7	C_6H_5	**5g**	64	**1g**	86
8	*p*-CH_3O-C_6H_4	**5h**	73	**1h**	87
9	*p*-C_2H_5O-C_6H_4	**5i**	74	**1i**	75
10	*o*-CH_3O-C_6H_4	**5j**	69	**1j**	80
11	*o*-CH_3-C_6H_4	**5k**	66	**1k**	83
12	*p*-NO_2-C_6H_4	**5l**	0	**1l**	/
13	*m*-Cl-C_6H_4	**5m**	0	**1m**	/

mild reaction conditions, and the chemical reagents such as methyl anthranilate and iodine were inexpensive and easy to handle.

In summary, we have developed a simple method for the synthesis of 2-amino 3-substituted-quinazolin-4(3H)-ones derivatives that introduced substitutions at the 3-position from commonly available primary amines at the step of guanidine formation. Our research result reaffirms the advantage of Pbf-activated thiourea as guanidinylating reagent in the synthesis of diverse guanidine-containing heterocycles.

EXPERIMENTAL

All reagents were purchased from commercial sources and used without treatment, unless otherwise indicated. Melting points were determined on a X-5 melting point apparatus and are uncorrected. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Varian mercury 300 and 75 MHz FT-NMR spectrometer, chemical shifts (δ) were given with $(CH_3)_4Si$ as an internal reference (δ = 0). Element analyses were taken on a perkin-Elmer CHN2400 elemental analysis instrument. Mass spectra (MS) data were obtained on a Bruker HCT system. PbfNCS **3** was synthesized according to refs. 14 and 15.

***N*-(2′-Methyl benzoate)-*N*′-(2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-sulfonyl)-thiourea (4).** At room temperature, Pbf-isothiocyanate (1.51 g, 0.01 moL) in dichloromethane (2 mL) was added dropwise to the stirring solution of methyl anthranilate (3.11 g, 0.01 moL) in 20 mL of anhydrous dichloromethane, the reaction mixture was kept for 4 h. Solvent was removed under reduced pressure and recrystallization from petroleum ether, produced compound **4** 4.15 g, yield 90%.

White solid, mp 115–117°C. ^{1}H-NMR (300 MHz, $CDCl_3$), δ: 1.45 (s, 6H), 2.12 (s, 3H), 2.50 (s, 3H), 2.65 (s, 3H), 2.92 (s, 2H), 3.96 (s, 3H), 7.19–7.24 (m, 1H), 7.43–7.48 (m, 1H), 7.97–8.05 (m, 2H), 8.18 (s, 1H), 11.39 (s, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$), δ: 12.5, 17.6, 19.2, 28.4, 42.8, 52.7, 87.3, 116.7, 118.6, 125.0, 125.2, 125.6, 130.7, 132.5, 134.0, 134.8, 139.3, 140.2, 160.8, 166.9, 177.8. MS: 463.0 $(M+H)^+$, 484.8 $(M+Na)^+$. Anal. Calcd. for $C_{22}H_{26}N_2O_5S_2$: C, 57.12; H, 5.67; N, 6.06. Found: C, 57.19; H, 5.63; N, 6.09.

General synthesis procedure of Pbf protective guanidine heterocycles 5a–5m. At room temperature, thiourea **4** (0.33 mmoL) and DIPEA (0.97 mmoL) were dissolved in anhydrous THF 5 mL, then iodine (0.33 mmoL) was added slowly to the stirring mixture. After 20 min, RNH_2 (0.33 mmoL) was added to the solution, and the reaction was kept for about 30–40 h at 30–40°C. The solvent was evaporated under vacuum and the residue was purified on silica gel chromatography (eluent: EtOAc/petroleum ether = 1:5) to give compounds **5a**–**5d** and **5f**–**5k**.

3-Butyl-2-[(2′,2′,4′,6′,7′-pentamethyl-2′,3′-dihydrobenzofuran-5′-sulfonyl)imino]-4-oxo-1,2,3,4-tetrahydroquinazoline (5a). White solid, mp 155–157°C. ^{1}H-NMR (300 MHz, $CDCl_3$), δ: 0.85–0.90 (t, *J* = 7.2Hz, 3H), 1.26–1.39 (m, 2H), 1.47 (s, 6H), 1.55–1.64 (m, 2H), 2.12 (s, 3H), 2.57 (s, 3H), 2.67 (s, 3H), 2.97 (s, 2H), 4.04–4.09 (t, *J* = 7.2 Hz, 2H), 7.13–7.15 (d, *J* = 7.5 Hz, 1H), 7.26–7.32 (m, 1H), 7.62–7.68 (m, 1H), 8.13–8.15 (d, *J* = 7.5 Hz, 1H), 11.00 (s, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$), δ: 11.2, 12.4, 13.6, 19.2, 20.1, 20.6, 28.5, 42.2, 43.1, 86.7, 115.1, 115.6, 117.8, 124.47, 124.9, 128.2, 131.4, 132.6, 135.3, 136.9, 138.9, 147.7, 159.3, 160.5. MS: 470.0 $(M+H)^+$, 491.8 $(M+Na)^+$. Anal. Calcd. for $C_{25}H_{31}N_3O_4S$: C, 63.94; H, 6.65; N, 8.95. Found: C, 63.89; H, 6.62; N, 9.01.

3-Propyl-2-[(2′,2′,4′,6′,7′-pentamethyl-2′,3′-dihydrobenzofuran-5′-sulfonyl)imino]-4-oxo-1,2,3,4-tetrahydroquinazoline (5b). White solid, mp 172–174°C. ^{1}H-NMR (300 MHz, $CDCl_3$), δ: 0.89–0.94 (t, *J* = 7.5 Hz, 3H), 1.47 (s, 6H), 1.59–1.69 (m, 2H), 2.12 (s, 3H), 2.57 (s, 3H), 2.64 (s, 3H), 2.98 (s, 2H), 4.01–4.06 (t, *J* = 7.5 Hz, 2H), 7.13–7.15 (d, *J* = 7.5 Hz, 1H), 7.29–7.32 (m, 1H), 7.62–7.68 (m, 1H), 8.13–8.16 (d, *J* = 7.5 Hz, 1H), 11.00 (s, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$), δ: 11.2, 12.4, 17.3, 18.6, 20.6, 28.5, 43.0, 43.8, 86.7, 115.1, 115.6, 117.8, 124.5, 124.6, 126.2, 131.4, 132.5, 136.3, 136.9, 138.8, 147.7, 159.3, 160.5. MS: 456.7 $(M+H)^+$, 478.0 $(M+Na)^+$. Anal. Calcd. for $C_{24}H_{29}N_3O_4S$: C, 63.27; H, 6.42; N, 9.22. Found: C, 63.31; H, 6.49; N, 9.27.

3-(2′-Hydroxyethyl)-2-[(2′,2′,4′,6′,7′-pentamethyl-2′,3′-dihydrobenzofuran-5′-sulfonyl)imino]-4-oxo-1,2,3,4-tetrahydroquinazoline (5c). White solid, mp 168–170°C. ^{1}H-NMR (300 MHz, $CDCl_3$), δ: 1.47 (s, 6H), 2.11 (s, 3H),2.17 (s, 1H), 2.55 (s, 3H), 2.61 (s, 3H), 2.98 (s, 2H), 3.85–3.86 (t, *J* = 4.8 Hz, 2H), 4.35–4.38 (t, *J* = 4.8 Hz, 2H), 7.16–7.19 (d, *J* = 8.1 Hz, 1H), 7.30–7.35 (m, 1H), 7.66–7.71 (m, 1H), 8.14–8.17 (d, *J* = 8.1 Hz,

1H), 11.03 (s, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$), δ: 12.4, 17.9, 19.2, 28.5, 43.0, 44.5, 61.0, 86.8, 114.9, 115.8, 117.9, 124.8, 126.0, 128.3, 130.9, 132.8, 135.7, 137.0, 138.9, 148.3, 158.6, 161.4. MS: 457.9 $(M+H)^+$, 479.7 $(M+Na)^+$. Anal. Calcd. for $C_{23}H_{27}N_3O_5S$: C, 60.38; H, 5.95; N, 9.18. Found: C, 60.43; H, 5.92; N, 9.22.

3-[3′-(Carbonyl ethyl ester)-propyl]-2-[(2′,2′,4′,6′,7′-pentamethyl-2′,3′-dihydrobenzofuran-5′-sulfonyl)imino]-4-oxo-1,2,3,4-tetrahydroquinazoline (5d). White solid, mp 125–128°C. ^{1}H-NMR (300 MHz, $CDCl_3$), δ: 1.20–1.27 (t, *J* = 7.2 Hz, 3H), 1.49 (s, 6H), 2.13 (s, 3H), 2.57 (s, 3H), 2.63 (s, 3H), 2.63–2.69 (t, *J* = 7.8 Hz, 2H), 2.99 (s, 2H), 4.07–4.14 (q, *J* = 7.2 Hz, 2H), 4.36–4.41 (t, *J* = 7.8 Hz, 2H), 7.15–7.18 (d, *J* = 7.5 Hz, 1H), 7.29–7.34 (m, 1H), 7.65–7.71 (m, 1H), 8.14–8.17 (d, *J* = 7.5 Hz, 1H), 11.02 (s, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$), δ: 12.3, 14.0, 17.8, 19.1, 28.5, 31.3, 31.9, 43.1, 61.3, 86.7, 115.0, 115.7, 117.9, 122.4, 124.6, 128.3, 130.2, 133.9, 135.5, 137.0, 138.9, 147.5, 159.5, 160.3, 171.1. MS: 513.9 $(M+H)^+$, 535.8 $(M+Na)^+$. *Anal.* Calcd. for $C_{26}H_{31}N_3O_6S$: C, 60.80; H, 6.08; N, 8.18. Found: C, 60.84; H, 6.06; N, 8.93.

3-Benzyl-2-[(2′,2′,4′,6′,7′-pentamethyl-2′,3′-dihydrobenzofuran-5′-sulfonyl)imino]-4-oxo-1,2,3,4-tetrahydroquinazoline (5f). White solid, mp 201–203°C.^{1}H-NMR (300 MHz, $CDCl_3$), δ: 1.50 (s, 6H), 2.07 (s, 3H), 2.41 (s, 3H), 2.46 (s, 3H), 2.96 (s, 2H), 5.26 (s, 2H), 7.05–7.17 (m, 3H), 7.28–7.33 (m, 4H), 7.63–7.69 (m, 1H), 8.15–8.18 (m, 1H), 10.93 (s, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$), δ: 12.4, 17.7, 19.1, 38.5, 43.1, 45.0, 86.7, 115.1, 115.7, 117.7, 124.6, 124.8, 127.5, 128.1, 128.5, 129.9, 131.1, 132.8, 135.5, 136.1, 137.0, 139.0, 147.7, 159.4, 160.6. MS: 504.9 $(M+H)^+$, 526.0 $(M+Na)^+$. Anal. Calcd. for $C_{28}H_{29}N_3O_4S$: C, 66.78; H, 5.80; N, 8.34. Found: C, 66.81; H, 5.78; N, 8.36.

3-Phenyl-2-[(2′,2′,4′,6′,7′-pentamethyl-2′,3′-dihydrobenzofuran-5′-sulfonyl)imino]-4-oxo-1,2,3,4-tetrahydroquinazoline (5g). White solid, mp 120–122°C.^{1}H-NMR (300 MHz, $CDCl_3$), δ: 1.45 (s, 6H), 2.02 (s, 3H), 2.10 (s, 3H), 2.33 (s, 3H), 2.91 (s, 2H), 7.15–7.18 (m, 2H), 7.20–7.23 (d, *J* = 8.1 Hz, 1H), 7.30–7.35 (m, 1H), 7.42–7.48 (m, 3H), 7.68–7.74 (m, 1H), 8.15–8.18 (m, 1H), 11.06 (s,1H). ^{13}C-NMR (75 MHz, $CDCl_3$), δ: 12.3, 17.4, 18.9, 28.5, 43.0, 86.5, 115.5, 115.8, 117.5, 124.1, 124.5, 124.6, 126.2, 128.5, 128.7, 129.2, 132.4, 135.1, 135.7, 137.3, 139.1, 148.2, 159.2, 160.8. MS: 490.0 $(M+H)^+$, 511.8 $(M+Na)^+$. Anal. Calcd. for $C_{27}H_{27}N_3O_4S$: C, 66.24; H, 5.56; N, 8.58. Found: C, 66.27; H, 5.52; N, 8.63.

3-(4′-Methoxy-phenyl)-2-[(2′,2′,4′,6′,7′-pentamethyl-2′,3′-dihydrobenzofuran-5′-sulfonyl)imino]-4-oxo-1,2,3,4-tetrahydroquinazoline (5h). White solid, mp 228–230°C. ^{1}H-NMR (300 MHz, $CDCl_3$), δ: 1.45 (s, 6H), 2.03 (s, 3H), 2.27 (s, 3H), 2.36 (s, 3H), 2.91 (s, 2H), 3.85 (s, 3H), 6.94–6.97 (d, *J* = 9.0 Hz, 2H), 7.05–7.08 (d, *J* = 9.0 Hz, 2H), 7.18–7.20 (d, *J* = 8.1 Hz, 1H), 7.28–7.34 (t, *J* = 7.5 Hz, 1H), 7.67–7.72 (t, *J* = 7.5 Hz, 1H), 8.14–8.17 (d, *J* = 8.1 Hz, 1H), 11.03 (s, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$), δ: 12.3, 17.6, 19.0, 28.6, 43.1, 55.5, 87.0, 114.5, 115.0, 115.8, 117.1, 124.6, 126.7, 127.7, 128.7, 129.4, 130.5, 132.5, 133.5, 135.6, 137.3, 139.1, 148.5, 155.5, 159.6. MS: 519.9 $(M+H)^+$, 541.8 $(M+Na)^+$. Anal. Calcd. for $C_{28}H_{29}N_3O_5S$: C, 64.72; H, 5.63; N, 8.09. Found: C, 64.73; H, 5.60; N, 8.11.

x3-(4′-Ethoxy-phenyl)-2-[(2′,2′,4′,6′,7′-pentamethyl-2′,3′-dihydrobenzofuran-5′-sulfonyl)imino]-4-oxo-1,2,3,4-tetrahydroquinazoline (5i). White solid, mp 180–182°C. ^{1}H-NMR (300 MHz, $CDCl_3$), δ: 1.42–1.47 (m, 9H), 2.04 (s, 3H), 2.27 (s, 3H), 2.37 (s, 3H), 2.92 (s, 2H), 4.04–4.12 (q, *J* = 7.2 Hz, 2H), 6.93–6.95 (d, *J* = 8.7 Hz, 2H), 7.04–7.06 (d, *J* = 8.7 Hz, 2H), 7.19–7.21 (d, *J* = 8.1 Hz, 1H), 7.29–7.34 (t, *J* = 8.1 Hz, 1H), 7.67–7.72 (t, *J* = 8.1 Hz, 1H), 8.15–8.17 (d, *J* = 8.1 Hz, 1H), 11.02 (s, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$), δ: 12.3, 14.8, 17.6, 18.9, 28.5, 43.2, 63.8, 86.6, 115.2, 115.6, 115.8, 117.6, 124.6, 127.6, 128.7, 129.5, 131.4, 132.6, 135.6, 135.7, 137.4, 139.2, 148.6, 159.1, 159.3, 161.0. MS: 534.0 $(M+H)^+$, 555.8 $(M+Na)^+$. Anal. Calcd. for $C_{29}H_{31}N_3O_5S$: C, 65.27; H, 5.86; N, 7.87. Found: C, 65.28; H, 5.90; N, 7.82.

3-(2′-Methoxy-phenyl)-2-[(2′,2′,4′,6′,7′-pentamethyl-2′,3′-dihydrobenzofuran-5′-sulfonyl)imino]-4-oxo-1,2,3,4-tetrahydroquinazoline (5j). White solid, mp 210–213°C. ^{1}H-NMR (300 MHz, $CDCl_3$), δ: 1.45 (s, 3H), 1.46 (s, 3H), 2.04 (s, 3H), 2.23 (s, 3H), 2.36 (s, 3H), 2.92 (s, 2H), 3.52 (s, 3H), 6.91–6.94 (d, *J* = 8.1 Hz, 1H), 7.00–7.05 (m, 1H), 7.12–7.15 (m, 1H), 7.19–7.22 d, *J* = 8.1 Hz, 1H), 7.29–7.34 (m, 1H), 7.37–7.43 (m, 1H), 7.68–7.73 (m, 1H), 8.16–8.18 (m, 1H), 11.01 (s, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$), δ: 12.4, 17.3, 18.9, 28.4, 43.0, 55.2, 86.5, 111.6, 115.8, 117.4, 120.7, 122.2, 124.0, 126.6, 129.0, 129.6, 130.2, 130.5, 131.6, 132.4, 135.5, 137.4, 139.0, 148.0, 154.4, 159.0, 160.4. MS: 520.2 $(M+H)^+$, 541.9 $(M+Na)^+$. Anal. Calcd. for $C_{28}H_{29}N_3O_5S$: C, 64.72; H, 5.63; N, 8.09. Found: C, 64.71; H, 5.66; N, 8.05.

3-(2′-Methyl-phenyl)-2-[(2′,2′,4′,6′,7′-pentamethyl-2′,3′-dihydrobenzofuran-5′-sulfonyl)imino]-4-oxo-1,2,3,4-tetrahydroquinazoline (5k). White solid, mp 203–205°C.^{1}H-NMR (300 MHz, $CDCl_3$), δ: 1.45 (s, 6H), 1.99 (s, 3H), 2.02 (s, 3H), 2.19 (s, 3H), 2.31 (s, 3H), 2.90 (s, 2H), 7.02–7.05 (d, *J* = 8.1 Hz, 1H), 7.20–7.23 (d, *J* = 8.1 Hz, 1H), 7.29–7.35 (m, 4H), 7.68–7.74 (m, 1H), 8.15–8.18 (m, 1H), 11.06 (s, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$), δ: 12.3, 17.2, 17.3, 18.8, 28.4, 43.0, 85.5, 115.4, 115.8, 117.5, 124.6, 126.9, 128.3, 129.0, 129.0, 130.8, 131.0, 132.4, 134.4, 135.6, 135.7, 137.4, 139.1, 147.8, 152.0, 159.1, 160.3. MS: 504.0 $(M+H)^+$, 525.9 $(M+Na)^+$. Anal. Calcd. for $C_{28}H_{29}N_3O_4S$: C, 66.78; H, 5.80; N, 8.34. Found: C, 66.74; H, 5.86; N, 8.39.

General synthesis procedure of target compound 1. Compound **5** (0.06 mmoL) was dissolved in solution of TFA/H_2O (95:5) (3 mL), stirred for about 12 h at 40–60°C, the reaction was monitored by TLC until starting material **5** disappeared completely. The solvent was evaporated under reduced pressure, then washed the residue with petroleum ether and neutralized with the solution of Et_3N in water separately. The precipitate was collected by filtration and air-dried. The desired compounds **1a–1c** and **1f–1k** were obtained after recrystallization from toluene.

2-Amino-3-butyl-4-oxo-3,4-dihydro-quinazoline (1a). White solid, mp 185–187°C. ^{1}H-NMR (300 MHz, DMSO), δ: 0.89–0.94 (t, *J* = 7.2 Hz, 3H), 1.28–1.40 (m, 2H), 1.52–1.62 (m, 2H), 3.97–4.01 (t, *J* = 7.2 Hz, 2H), 7.01 (s, 2H), 7.06–7.11 (d, *J* = 7.5 Hz, 1H), 7.16–7.19 (t, *J* = 8.4 Hz, 1H), 7.53–7.58 (d, *J* = 7.2 Hz, 1H), 7.88–7.91 (t, *J* = 7.5 Hz, 1H). ^{13}C-NMR (75 MHz, DMSO), δ: 18.7, 24.4, 34.3, 45.8, 121.1, 126.3, 128.6, 131.5, 139.0, 154.6, 156.9, 166.7. MS: 218.0 $(M+H)^+$, 239.9 $(M+Na)^+$. Anal. Calcd. for $C_{12}H_{15}N_3O$: C, 66.34; H, 6.96; N, 19.34. Found: C, 66.37; H, 7.02; N, 19.36.

2-Amino-3-propyl-4-oxo-3,4-dihydro-quinazoline (1b). White solid, mp 215–218°C. ^{1}H-NMR (300 MHz, DMSO), δ: 0.89–0.94 (t, *J* = 7.5 Hz, 3H), 1.56–1.67 (m, 2H), 3.92–3.97 (t, *J* = 7.5 Hz, 2H), 7.03–7.12 (m, 3H), 7.16–7.19 (m, 1H), 7.54–7.59 (m, 1H), 7.88–7.91 (m, 1H). ^{13}C-NMR (75 MHz, DMSO), δ: 10.8, 19.8, 43.3, 114.5, 116.8, 125.0, 127.4, 136.0, 137.9, 151.0, 159.3. MS: 203.8 $(M+H)^+$, 225.7 $(M+Na)^+$. Anal. Calcd. for $C_{11}H_{13}N_3O$: C, 65.01; H, 6.45; N, 20.68. Found: C, 65.03; H, 6.43; N, 20.65.

2-Amino-3-(2′-hydroxyethyl)-4-oxo-3,4-dihydro-quinazoline (1c). White solid, mp 190–192°C. ^{1}H-NMR (300 MHz, DMSO), δ: 3.65–3.69 (t, *J* = 5.7 Hz, 2H), 4.10–4.14 (t, *J* = 5.7 Hz, 2H), 5.13 (s, 1H), 7.18–7.29 (m, 2H), 7.48 (s, 2H), 7.62–7.68 (m, 1H), 7.93–7.96 (m, 1H). ^{13}C-NMR (75 MHz, DMSO), δ: 44.2, 58.4, 115.9, 121.8, 122.4, 126.7, 134.6, 152.4, 161.3. MS: 205.9 $(M+H)^+$, 227.8 $(M+Na)^+$. Anal. Calcd. for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.40; N, 20.48. Found: C, 58.45; H, 5.42; N, 20.52.

2-Amino-3-benzyl-4-oxo-3,4-dihydro-quinazoline (1f). White solid, mp 197–199°C. ^{1}H-NMR (300 MHz, DMSO), δ: 5.30 (s, 2H), 7.09–7.17 (m, 3H), 7.24–7.36 (m, 6H), 7.59–7.64 (t, *J* = 7.5 Hz, 1H), 7.93–7.96 (d, *J* = 7.5 Hz, 1H). ^{13}C-NMR (75 MHz, DMSO), δ: 48.9, 121.0, 126.7, 128.6, 131.7, 131.7, 132.2, 133.4, 139.4, 141.2, 154.3, 156.9, 166.6. MS: 251.7 $(M+H)^+$, 273.7 $(M+Na)^+$. Anal. Calcd. for $C_{15}H_{13}N_3O$: C, 71.70; H, 5.21; N, 16.72. Found: C, 71.75; H, 5.23; N, 16.75.

2-Amino-3-phenyl-4-oxo-3,4-dihydro-quinazoline (1g). White solid, mp 220–222°C. ^{1}H-NMR (300 MHz, DMSO), δ: 6.25 (s, 2H), 7.11–7.15 (t, *J* = 7.2 Hz, 1H), 7.24–7.27 (d, *J* = 7.8 Hz, 1H), 7.36–7.38 (d, *J* = 7.2 Hz, 2H), 7.53–7.65 (m, 4H), 7.89–7.91 (d, *J* = 7.8 Hz, 1H). ^{13}C-NMR (75 MHz, DMSO), δ: 121.8, 126.5, 128.9, 131.5, 133.8, 134.2, 135.0, 139.4, 140.5, 155.1, 156.6, 166.8. MS: 237.9 $(M+H)^+$, 259.7 $(M+Na)^+$. Anal. Calcd. for $C_{14}H_{11}N_3O$: C, 70.87; H, 4.67; N, 17.71. Found: C, 70.95; H, 4.69; N, 17.73.

2-Amino-3-(4′-methoxy-phenyl)-4-oxo-3,4-dihydro-quinazoline (1h). White solid, mp 233–235°C. ^{1}H-NMR (300 MHz, DMSO), δ: 3.83 (s, 3H), 6.29 (s, 2H), 7.08–7.13 (m, 3H), 7.22–7.28 (m, 3H), 7.57–7.63 (m, 1H), 7.87–7.90 (m, 1H). ^{13}C-NMR (75 MHz, DMSO), δ: 60.4, 120.2, 121.8, 126.4, 128.9, 131.5, 132.9, 134.9, 139.3, 155.1, 157.1, 164.5, 167.0. MS: 267.7 $(M+H)^+$, 289.7 $(M+Na)^+$. Anal. Calcd. for $C_{15}H_{13}N_3O_2$: C, 67.40; H, 4.90; N, 15.72. Found: C, 67.48; H, 4.94; N, 15.67.

2-Amino-3-(4′-ethoxy-phenyl)-4-oxo-3,4-dihydro-quinazoline (1i). White solid, mp 243–245°C. ^{1}H-NMR (300 MHz, DMSO), δ: 1.35–1.39 (t, *J* = 6.9 Hz, 3H), 4.06–4.13 (q, *J* = 6.9 Hz, 2H), 6.26 (s, 2H), 7.06–7.13 (m, 3H), 7.21–7.25 (m, 3H), 7.57–7.62 (t, *J* = 8.7 Hz, 1H), 7.86–7.90 (d, *J* = 8.1 Hz, 1H). ^{13}C-NMR (75 MHz, DMSO), δ: 14.7, 63.3, 115.5, 116.8, 121.4, 123.9, 126.5, 127.7, 129.9, 134.3, 150.1, 152.1, 158.8, 162.0. MS: 281.8 $(M+H)^+$. Anal. Calcd. for $C_{16}H_{15}N_3O_2$: C, 68.31; H, 5.37; N, 14.94. Found: C, 68.38; H, 5.45; N, 14.96.

2-Amino-3-(2′-methoxy-phenyl)-4-oxo-3,4-dihydro-quinazoline (1j). White solid, mp 228–230°C. ^{1}H-NMR (300 MHz, DMSO), δ: 3.74 (s, 3H), 6.29 (s, 2H), 7.08–7.13 (t, *J* = 7.5Hz, 2H), 7.22–7.25 (d, *J* = 7.5 Hz, 2H), 7.29–7.30 (m, 1H), 7.47–7.53 (m, 1H), 7.58–7.63 (m, 1H), 7.85–7.88 (m, 1H). ^{13}C-NMR (75 MHz, DMSO), δ: 55.7, 112.9, 116.6, 121.3, 121.4, 123.5, 123.8, 126.5, 130.1, 130.9, 134.4, 150.2, 151.8, 154.9, 161.4. MS: 267.9 $(M+H)^+$, 298.0 $(M+Na)^+$. Anal. Calcd. for $C_{15}H_{13}N_3O_2$: C, 67.40; H, 4.90; N, 15.72. Found: C, 67.37; H, 4.98; N, 15.68.

2-Amino-3-(2′-methyl-phenyl)-4-oxo-3,4-dihydro-quinazoline (1k). White solid, mp 169–172°C. ^{1}H-NMR (300 MHz, DMSO), δ: 2.11 (s, 3H), 734–7.39 (t, *J* = 7.8 Hz, 1H), 7.39–7.43 (m, 6H), 7.79–7.85 (m, 2H), 7.99–7.02 (m, 1H). ^{13}C-NMR (75 MHz, DMSO), δ: 16.7, 115.4, 119.0, 124.1, 127.3, 127.9, 128.9, 130.3, 131.6, 132.3, 135.8, 136.2, 141.8, 151.3, 159.6. MS: 251.7 $(M+H)^+$, 273.7 $(M+Na)^+$. Anal. Calcd. for $C_{15}H_{13}N_3O$: C, 71.70; H, 5.21; N, 16.72. Found: C, 71.73; H, 5.18; N, 16.65.

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