Tandem Synthesis of 2,3-Dihydroquinazolin-4(1*H*)-ones on Grinding under Solvent-Free Conditions

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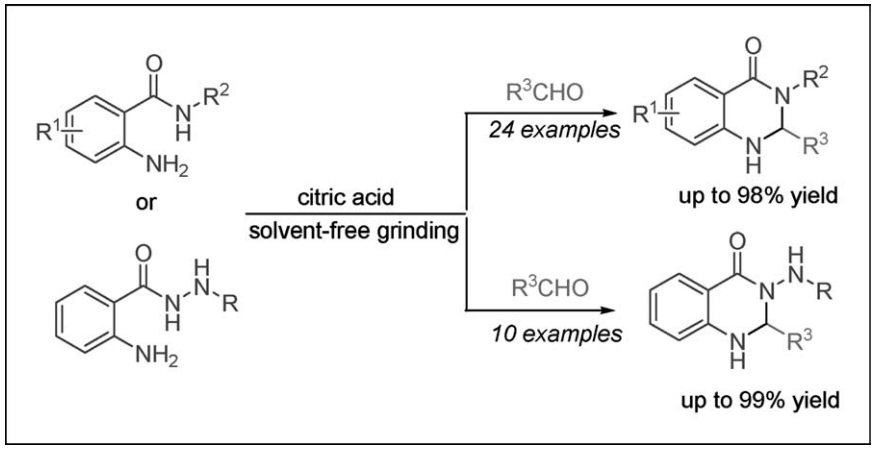

Citric acid promoted synthesis of a mini-library 2,3-dihydroquinazolin-4(1*H*)-ones with good to excellent yields is achieved by tandem reaction of anthranilamides (or anthranilhydrazides) with aldehydes on grinding at room temperature under solvent-free conditions. This method has notable advantages in terms of simple workup, short reaction time, cost-effective, and environmentally benign.

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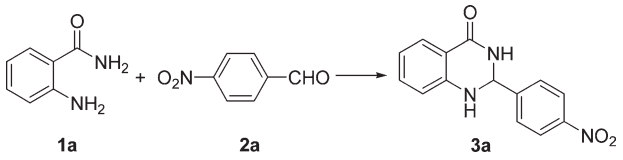
INTRODUCTION

2,3-Dihydroquinazolin-4(1*H*)-ones are an important class of fused heterocyclic compounds that have drawn much attention because of their potential biological and pharmaceutical activities [1]. On the other hand, 2,3-dihydroquinazolin-4(1*H*)-ones could be easily oxidized to quinazolin-4(3*H*)-ones, which are important building blocks in the synthesis of natural and pharmacological compounds, by $NaHSO_3$ [2] or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone [3]. The typical procedure for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones involves the condensation reaction of anthranilamide with aldehyde using *p*-TSA as catalyst under vigorous conditions [4]. However, it is worth pointing out that the intermediate 1,2-dihydro derivatives could not be isolated because of a spontaneous oxidation to quinazolin-4(3*H*)-ones [4(b)]. In 2002, Su et al. [5] and Lu and coworkers [6] independently reported the preparation of 2,3-dihydroquinazolin-4(1*H*)-ones by reductive cyclization of *o*-nitrobenzamide or *o*-azido-benzamide with aldehyde and ketone using metallic samarium in the presence of iodine or SmI_2. In addition, using 2-nitrobenzamide and aldehyde or ketone as reactants with the aid of a low-valent titanium reagent was also reported as a facile process to synthesize 2,3-dihydroquinazolin-4(1*H*)-ones in the literature [7]. Later, some improved methods have been reported for the synthesis of these compounds by one-pot condensation of isatoic anhydride, amine with aldehyde [8]. Recently, List and coworkers [9] and Rueping et al. [10] independently reported enantioselective synthesis of these compounds using chiral phosphoric acid as catalyst. In our previous work, we reported improved procedures for the preparation of 2,3-dihydroquinazolin-4(1*H*)-ones in ionic liquids without additional catalyst [11] and gallium triflate-catalyzed one-pot selective synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones and quinazolin-4(3*H*)-ones [12].

To the best of our knowledge, most of aforementioned studies on the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones are focused on 2-monosubstituted ones using anthranilamide as reactant in organic solvent or metal-catalyzed [4–12]. Few examples has been given to obtain 2,3-disubstituted substituents 2,3-dihydroquinazolin-4(1*H*)-ones from *N*-substituted o-aminobenzamide.

Scheme 1



Although an alternative new methodology has also been employed in ionic liquid, for example, a recent report about synthesis of 2,2-disubstituted quinazolin-4(1*H*)-ones catalyzed by iodine in ionic liquids [13]. However, ionic liquids, especially imidazolium-based systems containing BF_4 or PF_6 anions, are toxic in nature because they liberate hazardous HF, and their high cost and disposability make their utility limited [14]. Therefore, development of a facile and green method to synthesize 2,3-dihydroquinazolin-4(1*H*)-ones appeared to be of great importance.

In the past few years, significant articles have appeared reporting solid-state reactions by grinding [15]. Most of these reactions are carried out at room temperature in absolutely solvent-free environment using only a mortar and pestle, and therefore the common merit of these processes is that they are efficient, economical, and environmentally friendly.

Citric acid, as a very inexpensive, commercially available and the relatively nontoxic, water-solubility organoacid has been widely used in organic reactions [16], but it has been unexplored as a catalyst in the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones until now.

As a continuing interest in developing novel synthetic routes for the formations of quinazolin-4(1*H*)-one derivatives [11], we herein reported a metal-free, cost-effective, and environmentally benign approach for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-one derivatives on grinding at room temperature under solvent-free conditions.

RESULTS AND DISCUSSION

A model condensation reaction between anthranilamide (**1a**) and *p*-nitrobenzaldehyde (**2a**) was initially conducted to screen the optimal reaction conditions (Scheme 1).

As shown in Table 1, entries 1–5 show blank reactions without addition of any catalyst, only trace product was reached for even longer time. However, we were delighted to find that the yield could be improved to 86%, when citric acid was employed with silica gel as grinding medium at room temperature (Table 1, entry 6). Encouraged by these promising results, different reaction media (neutral Al_2O_3, basic Al_2O_3, acidic Al_2O_3, silica gel, and celatom) were tested to find more optimal reaction conditions (Table 1, entries 7–10). The results showed that the combination of acidic Al_2O_3 and citric acid was found to be the couple of choice, which afforded the desired product of 2-(4-nitrophenyl)-2,3-dihydroquinazolin-4(1*H*)-one (3a) with excellent yield (Table 1, entry 10). Furthermore, the present route to 3a was successfully applied to a large-scale reaction (Table 1, entry 11).

With the optimized conditions in hand, the reactions of different anthranilamides with various aldehydes were examined to explore the scope and generality of this present protocol for the synthesis of various 2,3-dihydroquinazolin-4(1*H*)-ones and the results were listed in Table 2. First, we examined the steric effect in our system. A monosubstitution group such as nitro on the *ortho*-, *meta*- or *para*-position for the aromatic aldehydes had little effect on the yields in the reaction (Table 2, entries 1–3). Next, a series of aromatic aldehydes with either electron-donating or electron-withdrawing groups attaching to aromatic ring were investigated. In our system, the substitution groups on the phenyl ring make a bit of difference on the yields. For instance, anthranilamide reacted with aromatic aldehydes **2a**, **2d**, and **2f–2j** efficiently and afforded the corresponding products in 95%, 85%, 86%, 85%, 88%, 87%, and 86% yields, respectively (Table 2, entries 1, 4, 6–10). Moreover, we also examined reaction of aromatic heterocyclic aldehydes such as thiophene-2-carbaldehyde (**2l**) and picolinaldehyde (**2m**) with anthranilamide, and the desired products of **3l** and **3m** were obtained in high yields (Table 2, entries 12–13). When aliphatic aldehyde, such as butanal (**2n**) was used as substrate, the desired product of **3n** was obtained with excellent yield (Table 2, entry 14). However, attempt to the reaction of a long chain aliphatic aldehyde such as decanal (**2o**) with anthranilamide, the corresponding product of **3o** was obtained with moderate yield (Table 2, entry 15; Scheme 2).

Table 1

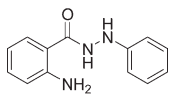
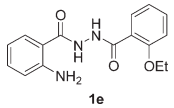
Effect of reaction conditions.[a]

Entry	Media	Organoacid	Yield (%)[b]
1	silica gel	none	trace
2	celatom	none	trace
3	neutral Al_2O_3	none	trace
4	basic Al_2O_3	none	trace
5	acidic Al_2O_3	none	trace
6	silica gel	citric acid	86
7	celatom	citric acid	90
8	neutral Al_2O_3	citric acid	45
9	basic Al_2O_3	citric acid	trace
10	acidic Al_2O_3	citric acid	95
11	acidic Al_2O_3	citric acid	94[c]

[a] Reaction conditions: anthranilamide **1a** (0.4 mmol), *p*-nitrobenzaldehyde **2a** (0.48 mmol), organoacid (0.4 mmol), and media (500 mg), room temperature, 10 min.
[b] Isolated yields.
[c] **1a** (0.68 g, 5 mmol), **2a** (0.83 g, 5.5 mmol), citric acid (5 mmol), and acidic Al_2O_3 (5 g).

Table 2

Tandem synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones on grinding under solvent-free conditions.[a]

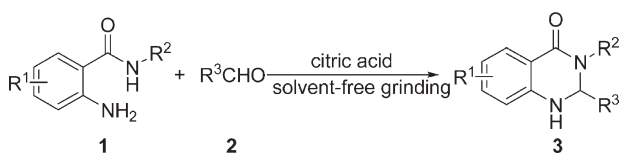
	1							
Entry	R^1	R^2	R^3 (**2**)	Time (min)	Product	Yield (%)[b]	Mp (°C)	Mp (°C) [Lit.]
1	H	H	*p*-$(NO_2)C_6H_4$ **2a**	10	**3a**	95	204–206	213–214 [12]
2	H	H	*o*-$(NO_2)C_6H_4$ **2b**	10	**3b**	98	191–192	193–194 [12]
3	H	H	*m*-$(NO_2)C_6H_4$ **2c**	10	**3c**	94	210–212	216–217 [12]
4	H	H	*p*-$(Br)C_6H_4$ **2d**	10	**3d**	85	200–202	205–206 [11]
5	H	H	*o*-$(Br)C_6H_4$ **2e**	10	**3e**	87	173–175	–
6	H	H	*p*-$(F)C_6H_4$ **2f**	10	**3f**	86	203–204	199–200 [12]
7	H	H	*p*-$(Cl)C_6H_4$ **2g**	15	**3g**	85	205–206	205–206 [12]
8	H	H	*p*-$(CH_3)C_6H_4$ **2h**	10	**3h**	88	230–232	233–234 [12]
9	H	H	*p*-$(CH_3CH_2)C_6H_4$ **2i**	15	**3i**	87	191–193	–
10	H	H	*p*-$(OCH_3)C_6H_4$ **2j**	10	**3j**	86	191–192	192–193 [12]
11	H	H	C_6H_5 **2k**	10	**3k**	83	220–222	218–219 [12]
12	H	H	2-thienyl **2l**	10	**3l**	83	211–213	213–215 [17a]
13	H	H	2-pyridyl **2m**	10	**3m**	86	184–185	187–188 [12]
14	H	H	*n*-Bu **2n**	10	**3n**	88	160–162	162–164 [17(b)]
15	H	H	*n*-C_9H_{19} **2o**	20	**3o**	65	145–147	–
16	5-Cl	H	*o*-$(NO_2)C_6H_4$ **2b**	10	**3p**	83	200–202	–
17	5-Cl	H	*p*-$(Br)C_6H_4$ **2d**	10	**3q**	80	204–206	–
18	5-Cl	H	*o*-$(Br)C_6H_4$ **2e**	10	**3r**	86	187–189	–
19	5-Cl	H	*p*-$(Cl)C_6H_4$ **2g**	10	**3s**	83	203–205	–
20	5-Cl	H	*p*-$(CH_3)C_6H_4$ **2h**	10	**3t**	82	248–250	250–251 [12]
21	H	*n*-Bu	*p*-$(NO_2)C_6H_4$ **2a**	10	**3u**	95	141–143	–
22	H	*n*-Bu	*p*-$(Cl)C_6H_4$ **2g**	10	**3v**	94	127–129	Not reported [17c]
23	H	*n*-Bu	*p*-$(CH_3)C_6H_4$ **2h**	10	**3w**	94	148–149	–
24	H	*n*-Bu	C_6H_5 **2k**	10	**3x**	96	131–132	120–122 [17d]
25	 **1d**		*p*-$(NO_2)C_6H_4$ **2a**	10	**4a**	96	212–214	–
26			*o*-$(Br)C_6H_4$ **2e**	10	**4b**	99	182–184	–
27			*p*-$(CH_3)C_6H_4$ **2h**	10	**4c**	92	198–201	–
28			C_6H_5 **2k**	10	**4d**	99	203–205	–
29	 **1e**		2,6-$(Cl)_2C_6H_3$ **2p**	10	**4e**	86	203–205	–
30			*p*-$(NO_2)C_6H_4$ **2a**	20	**4f**	95	209–211	–
31			*o*-$(Br)C_6H_4$ **2e**	10	**4g**	91	195–197	–
32			*p*-$(CH_3)C_6H_4$ **2h**	10	**4h**	98	209–211	–
33			C_6H_5 **2k**	10	**4i**	96	192–194	–
34			2,6-$(Cl)_2C_6H_3$ **2p**	10	**4j**	85	223–225	–

[a] All reactions were run with anthranilamides or anthranilhydrazides **1** (0.4 mmol), aldehydes **2** (0.48 mmol), citric acid (0.4 mmol), and acidic Al_2O_3 (500 mg) on grinding at room temperature under solvent-free conditions.
[b] Isolated yields.

On the other hand, we investigated the influence of electronic factors of anthranilamides on the results. The desired product of **3p–3t** in good yields were obtained from the reaction of 5-chloroanthranilamide (**1b**) with aldehydes bearing either electron-donating or electron-withdrawing groups on the benzene ring (Table 2, entries 16–20). As expected, *N*-alkyl substitution anthranilamide such as 2-amino-*N*-butylbenzamide (**1c**) was still good partner for the condensation reaction, and the corresponding products of **3u–3x** were isolated in excellent yields (Table 2, entries 21–24).

Next, we investigated synthesis of several new 2,3-dihydroquinazolin-4(1*H*)-one derivatives from tandem reaction of anthranilhydrazides such as 2-amino-*N*'-phenylbenzohydrazide (**1d**) and 2-amino-*N*'-(2-ethoxybenzoyl)benzohydrazide (**1e**) with aldehydes. In all cases, citric acid-promoted tandem reactions proceeded smoothly and gave the corresponding products in good to excellent yield (Table 2, entries 25–34). Using the present protocol, the sterically hindered amines such as 2,6-dichlorobenzaldehyde (**2p**), smoothly reacted with **1d** and **1e**, the desired

Scheme 2



1 **2** **3**

products of **4e** and **4j** were afforded in 86% and 85%, respectively (Table 2, entries 29 and 34).

In summary, we have demonstrated a mild and efficient eco-friendly tandem synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones under solvent-free conditions, using citric acid as a novel organoacid green promoter, which uses neither harsh conditions nor the use of hazardous or toxicant catalysts and reagents. When compared with previous reported methodologies, notable advantages of our protocol include simple operations, short reaction time, metal-free, the relatively nontoxic, inexpensive, water-solubility organoacid, broad substrates scope, and high yields.

EXPERIMENTAL

Chemicals and solvents were either purchased or purified by standard techniques. The melting points were uncorrected and were recorded on Digital Melting Point Apparatus WRS-1B. IR spectra were recorded on an AVATAR 370 FI-Infrared Spectrophotometer. NMR spectroscopy was performed on a Bruker-300 spectrometer or Bruker-500 spectrometer using DMSO-d_6 or $CDCl_3$ as the solvent with tetramethylsilane as an internal standard at room temperature. The mass spectrometric identification of the products was performed on Thermo Finnigan LCQ-Advantage or SHIMADZU GCMS-QP2010 system. Elemental analysis was determined on a Carlo-Erba 1108 instrument.

General procedure for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-one derivatives (3). An anthranilamide or anthranilhydrazide **1** (0.4 mmol), aldehyde **2** (0.48 mmol), and citric acid (0.4 mmol) were dissolved in 5 mL of ethanol in a round-bottomed flask, then acidic Al_2O_3 (200–300 mesh, 500 mg) was added. After 5 min stirring, the solvent was removed to obtain the mixture of reactants adsorbed on the acidic Al_2O_3 surface (note: the recovered solvent could be reused in the next batch). The dry mixture was transferred into a glass mortar. Then the mixture was ground at room temperature with a glass pestle for the appropriate time in the glass mortar. A mixture example was taken out and dissolved in ethyl acetate to monitor the progress of the reaction using TLC. After completion of the reaction, the mixture was washed with ethyl acetate. The Al_2O_3 was collected by filtration, which precipitated from the organic phase and the product was left in the organic phase. The recovered Al_2O_3 could be reused in the next batch after it was dried in oven. The pure products of **3** and **4** were obtained by silica gel column chromatography. Here, the full spectral characterization is given for only the previously unknown products.

2-(2-Bromophenyl)-2,3-dihydroquinazolin-4(1H)-one (3e). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.24 (s, 1H), 7.69–7.65 (m, 3H), 7.47–7.24 (m, 3H), 7.01 (s, 1H), 6.79–6.70 (m, 2H), 6.10 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 163.6, 147.7, 139.1, 133.4, 132.8, 130.7, 129.1, 128.0, 127.4, 122.2, 117.5, 114.7, 114.6, 66.4. IR (KBr): 3361 (NH), 1645 (C=O) cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 304 ([M+2]$^+$, 5), 302 (M$^+$, 6), 147 (100), 120 (30), 92 (21). Anal. Calcd for $C_{14}H_{11}BrN_2O$: C, 55.47; H, 3.66; Found: C 55.64; H 3.72 (Table 2, entry 5).

2-(4-Ethylphenyl)-2,3-dihydroquinazolin-4(1H)-one (3i). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.24 (s, 1H), 7.62–7.60 (m, 1H), 7.41–7.21 (m, 5H), 7.06 (s, 1H), 6.74–6.64 (m, 2H), 5.71 (s, 1H), 2.59 (q, *J* = 7.6, 2H), 1.16 (t, *J* = 7.6, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 163.6, 147.9, 144.1, 138.8, 133.2, 127.7, 127.3, 126.9, 117.0, 114.9, 114.3, 66.4, 27.9, 15.7. IR (KBr): 3299 (NH), 1652 (C=O) cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 252 (M$^+$, 11), 207 (23), 147 (70), 119 (100). Anal. Calcd for $C_{16}H_{11}N_2O$: C, 76.16; H, 6.39; Found: C 76.23; H 6.33 (Table 2, entry 9).

2-Nonyl-2,3-dihydroquinazolin-4(1H)-one (3o). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.89 (s, 1H), 7.58–7.55 (m, 1H), 7.24–7.19 (m, 1H), 6.73–6.62 (m, 2H), 6.56 (s, 1H), 4.67 (s, 1H), 1.62–1.60 (m, 2H), 1.25–1.19 (m, 14H), 0.85–0.83 (m, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 163.9, 148.5, 133.0, 127.3, 116.8, 115.0, 114.3, 64.4, 34.9, 31.3, 29.0, 28.9, 28.7, 23.2, 22.1, 14.0. IR (KBr): 3324 (NH), 1640 (C=O) cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 272 (M$^+$, 5), 160 (100), 173 (32), 120 (10). Anal. Calcd for $C_{17}H_{26}N_2O$: C, 74.41; H, 9.55; Found: C 74.34; H 9.73 (Table 2, entry 15).

6-Chloro-2-(2-nitrophenyl)-2,3-dihydroquinazolin-4(1H)-one (3p). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.41 (s, 1H), 8.09–8.06 (m, 1H), 7.82–7.62 (m, 3H), 7.58 (s, 1H), 7.31–7.29 (m, 1H), 7.24 (m, 1H), 6.82–6.79 (m, 1H), 6.36 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 162.1, 147.5, 145.8, 135.5, 134.0, 133.3, 130.0, 138.9 126.3, 124.8, 121.2, 116.9, 115.5, 62.1. IR (KBr): 3406 (NH), 1677 (C=O) cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 305 ([M+2]$^+$, 5), 303 (M$^+$, 16), 268 (67), 181 (99), 153 (100). Anal. Calcd for $C_{14}H_{10}ClN_3O_3$: C, 55.37; H, 3.32; Found: C 55.43; H 3.39 (Table 2, entry 16).

2-(4-Bromophenyl)-6-choloro-2,3-dihydroquinazolin-4(1H)-one (3q). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.53 (s, 1H), 7.62–7.53 (m, 3H), 7.44–7.41 (m, 2H), 7.38 (s, 1H), 7.31–7.27 (m, 2H), 6.79–6.76 (m, 1H), 5.79 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 162.3, 146.3, 140.7, 133.2, 131.3, 129.0, 126.4, 121.7, 120.9, 116.5, 116.0, 65.6. IR (KBr): 3325(NH), 1655 (C=O) cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 338 ([M+2]$^+$, 4), 336 (M$^+$, 15), 207 (100), 153 (59). Anal. Calcd for $C_{14}H_{10}BrClN_2O$: C, 49.81; H, 2.99; Found: C 49.88; H 3.04 (Table 2, entry 17).

2-(2-Bromophenyl)-6-choloro-2,3-dihydroquinazolin-4(1H)-one (3r). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.40 (s, 1H), 7.68–7.65 (m, 2H), 7.59 (s, 1H), 7.49–7.29 (m, 3H), 7.24 (s, 1H), 6.81–6.78 (m, 1H), 6.12 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 162.4, 146.4, 138.8, 133.2, 132.8, 130.8, 129.1, 128. 1, 126.4, 122.1, 121.1, 116. 6, 115.7, 66.3. IR (KBr): 3328 (NH), 1643 (C=O) cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 340 ([M+4]$^+$, 3), 338 ([M+2]$^+$, 10), 336 (M$^+$, 9), 181 (100), 183 (30), 154 (28). Anal. Calcd for $C_{14}H_{10}BrClN_2O$: C, 49.81; H, 2.99; Found: C 49.89; H 3.04 (Table 2, entry 18).

6-Choloro-2-(4-chlorophenyl)-2,3-dihydroquinazolin-4(1H)-one (3s). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.53 (s, 1H), 7.53–7.45 (m, 5H), 7.37 (s, 1H), 7.30–7.27 (m, 1H), 6.79–6.76 (m, 1H), 5.81 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 162.3, 146.4, 140.2, 133.1, 133.1, 128.7, 128.4, 126.4, 120.9, 116.5, 116.0, 65.6. IR (KBr): 3311 (NH), 1655 (C=O) cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 296 ([M+4]$^+$, 2), 294 ([M+2]$^+$, 17), 292 (M$^+$, 30), 181 (100), 154 (62), 126 (33). Anal. Calcd for $C_{14}H_{10}Cl_2N_2O$: C, 57.36; H, 3.44; Found: C 57.44; H 3.51 (Table 2, entry 19).

3-Butyl-2-(4-nitrophenyl)-2,3-dihydroquinazolin-4(1H)-one (3u). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.21–8.19 (m, 2H), 7.67–7.52 (m, 4H), 7.21–7.18 (m, 1H), 6.68–6.64 (m, 2H), 6.02 (s, 1H), 4.00–3.94 (m, 1H), 2.81–2.77 (m, 1H), 1.58–1.46

(m, 2H), 1.30–1.26 (m, 2H), 0.85 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 162.0, 148.6, 147.4, 145.6, 133.3, 127.5, 127.3, 123.7, 117.5, 115.1, 114.4, 69.0, 44.4, 29.6, 19.5, 13.6. IR (KBr): 3286 (NH), 1628 (C=O) cm^{-1}. MS (EI, 70 eV): m/z (%) = 325 (M^+, 11), 203 (100), 147 (72), 119 (20). Anal. Calcd for $C_{18}H_{19}N_3O_3$: C, 66.45; H, 5.89; Found: C 66.50; H 5.83 (Table 2, entry 21).

3-Butyl-2-p-tolyl-2,3-dihydroquinazolin-4(1H)-one (3w). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.65–7.63 (m, 1H), 7.26–7.13 (m, 6H), 6.65–6.61 (m, 2H), 5.78 (s, 1H), 3.89–3.86 (m, 1H), 2.73–2.71 (m, 1H), 2.25 (s, 3H), 1.53–1.43 (m, 2H), 1.28–1.24 (m, 2H), 0.85 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 162.2, 146.2, 138.2, 137.6, 133.0, 129.0, 127.3, 126.1, 117.0, 115.1, 114.2, 69.9, 44.0, 29.5, 20.6, 19.5, 13.6. IR (KBr): 3299 (NH), 1625 (C=O) cm^{-1}. MS (EI, 70 eV): m/z (%) = 294 (M^+, 13), 203 (100), 147 (60), 119 (12). Anal. Calcd for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53; Found: C 77.59; H 7.60 (Table 2, entry 23).

2-(4-Nitrophenyl)-3-(phenylamino)-2,3-dihydroquinazolin-4(1H)-one (4a). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.52 (s, 1H), 8.24–8.21 (m, 2H), 7.78 (s, 1H), 7.72–7.63 (m, 3H), 7.33–7.16 (m, 3H), 6.86–6.71 (m, 5H), 6.10 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 162.3, 148.0, 147.6, 147.4, 146.4, 134.0, 128.9, 127.8, 127.6, 123.5, 119.4, 117.8, 114.7, 114.1, 112.4, 72.7. IR (KBr): 3266 (NH), 1612 (C=O) cm^{-1}. MS (EI, 70 eV): m/z (%) = 360 (M^+, 51), 253 (100), 207 (37), 120 (17). Anal. Calcd for $C_{20}H_{16}N_4O_3$: C, 66.66; H, 4.48; Found: C 66.71; H 4.55 (Table 2, entry 25).

2-(2-Bromophenyl)-3-(phenylamino)-2,3-dihydroquinazol-in-4(1H)-one (4b). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.27 (s, 1H), 7.70–7.64 (m, 2H), 7.48–7.29 (m, 5H), 7.19–7.14 (m, 2H), 6.82–6.72 (m, 5H), 6.22 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 162.7, 147.5, 146.0, 138.7, 134.0, 133.1, 130.6, 128.9, 128.1, 127.5, 127.4, 122.2, 119.3, 117.7, 114.9, 113.7, 112.2, 73.3. IR (KBr): 3236 (NH), 1651 (C=O) cm^{-1}. MS (EI, 70 eV): m/z (%) = 393 (M^+, 53), 395 ([M+2]$^+$, 51), 286 (100), 288 (99). Anal. Calcd for $C_{20}H_{16}BrN_3O$: C, 60.93; H, 4.09; Found: C 60.89; H 4.16 (Table 2, entry 26).

3-(Phenylamino)-2-p-tolyl-2,3-dihydroquinazolin-4(1H)-one (4c). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.36 (s, 1H), 7.64–7.58 (m, 2H), 7.32–7.13 (m, 7H), 6.86–6.69 (m, 5H), 5.85 (s, 1H), 2.26 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 162.6, 147.9, 146.9, 137.8, 137.6, 133.7, 128.9, 128.8, 127.5, 126.3, 119.1, 117.3, 114.6, 114.3, 112.3, 73.4, 20.6. IR (KBr): 3266 (NH), 1609 (C=O) cm^{-1}. MS (EI, 70 eV): m/z (%) = 329 (M^+, 54), 330 (M+1, 13), 222 (100), 130 (15). Anal. Calcd for $C_{21}H_{19}N_3O$: C, 76.57; H, 5.81; Found: C 76.62; H 5.89 (Table 2, entry 27).

3-(Phenylamino)-2-phenyl-2,3-dihydroquinazolin-4(1H)-one (4d). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.35 (s, 1H), 7.66–7.61 (m, 2H), 7.45–7.15 (m, 8H), 6.87–6.68 (m, 5H), 5.90 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 162.6, 147.8, 146.8, 140.7, 133.7, 128.9, 128.3, 127.5, 126.4, 119.2, 117.4, 114.6, 114.3, 112.4, 73.6. IR (KBr): 3311(NH), 1640(C=O) cm^{-1}. MS (EI, 70 eV): m/z (%) = 315 (M^+, 56), 208 (100), 152 (20), 77 (25). Anal. Calcd for $C_{20}H_{17}N_3O$: C, 76.17; H, 5.43; Found: C 76.22; H 5.51 (Table 2, entry 28).

2-(2,6-Dichlorophenyl)-3-(phenylamino)-2,3-dihydroquinazolin-4(1H)-one (4e). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.97 (s, 1H), 7.61–7.59 (m, 1H), 7.48–7.46 (m, 2H), 7.42 (s, 1H), 7.38–7.35 (m, 1H), 7.27–7.24 (m, 1H), 7.16 (s, 1H), 7.11–7.09 (m, 2H), 6.75–6.68 (m, 3H), 6.64–6.60 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 161.8, 147.6, 146.7, 135.4, 134.0, 133.8, 130.6, 129.7, 128.7, 127.2, 119.0, 116.1, 113.0, 112.3, 111.6, 71.2. IR (KBr): 3247 (NH), 1652 (C=O) cm^{-1}. MS (EI, 70 eV): m/z (%) = 387 ([M+4]$^+$, 6), 385 ([M+2]$^+$, 33), 383 (M^+, 51), 276 (100), 278 (72). Anal. Calcd for $C_{20}H_{15}Cl_2N_3O$: C, 76.17; H, 5.43; Found: C 76.24; H 5.51 (Table 2, entry 29).

2-Ethoxy-N-(2-(nitrophenyl)-4-oxo-1,2-dihydroquinazolin-3(4H)-yl)benzamide (4f). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.91 (s, 1H), 8.29–8.26 (m, 2H), 7.83–7.72 (m, 3H), 7.58–7.34 (m, 4H), 7.06–6.97 (m, 2H), 6.83–6.78 (m, 2H), 6.33 (s, 1H), 3.99 (q, J = 7.0 Hz, 2H), 1.10 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 164.8, 162.4, 156.2, 148.0, 147.1, 145.8, 134.3, 132.9, 130.4, 129.3, 128.1, 123.5, 121.5, 120.5, 118.2, 114.6, 113.4, 113.1, 73.5, 64.2, 14.1. IR (KBr): 3274 (NH), 1677, 1651 (C=O) cm^{-1}. MS (ESI): m/z (%) = 432 (M^+, 100). Anal. Calcd for $C_{23}H_{20}N_4O_5$: C, 63.88; H, 4.66; Found: C 63.95; H 4.60 (Table 2, entry 30).

N-(2-(2-bromophenyl)-4-oxo-1,2-dihydroquinazolin-3(4H)-yl)-2-ethoxybenzamide (4g). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.76 (s, 1H), 7.75–7.63 (m, 4H), 7.48–7.31 (m, 5H), 7.08–6.99 (m, 2H), 6.80–6.77 (m, 2H), 6.62 (s, 1H), 4.00 (q, J = 6.9 Hz, 2H), 1.10 (t, J = 6.9 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 164.3, 162.6, 156.4, 147.0, 137.4, 134.2, 133.1, 132.9, 131.0, 130.7, 129.7, 128.2, 128.0, 123.0, 120.9, 120.6, 117.8, 114.5, 113.2, 113.0, 73.5, 64.4, 14.2. IR (KBr): 3290 (NH), 1675, 1651 (C=O) cm^{-1}. MS (ESI): m/z (%) = 467 (M^+, 100), 385 ([M+2]$^+$, 94). Anal. Calcd for $C_{23}H_{20}BrN_3O_3$: C, 59.24; H, 4.32; Found: C 59.29; H 4.40 (Table 2, entry 31).

2-Ethoxy-N-(4-oxo-2-p-tolyl-1,2-dihydroquinazolin-3(4H)-yl)benzamide (4h). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.73 (s, 1H), 7.72–7.60 (m, 2H), 7.46–7.31 (m, 5H), 7.21–7.19 (m, 2H), 7.08–6.99 (m, 2H), 6.80–6.75 (m, 2H), 6.14 (s, 1H), 4.01 (q, J = 7.0 Hz, 2H), 2.29 (s, 3H), 1.14 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 164.2, 162.7, 156.3, 147.6, 138.5, 135.7, 134.0, 132.9, 130.5, 128.9, 127.9, 127.5, 121.2, 120.5, 117.6, 114.5, 113.4, 113.2, 74.1, 64.4, 20.7, 14.1. IR (KBr): 3290 (NH), 1682, 1645 (C=O) cm^{-1}. MS (ESI,): m/z (%) = 401 (M^+, 100). Anal. Calcd for $C_{24}H_{23}N_3O_3$: C, 71.80; H, 5.77; Found: C 71.73; H 5.83 (Table 2, entry 32).

2-Ethoxy-N-(4-oxo-2-phenyl-1,2-dihydroquinazolin-3(4H)-yl)benzamide (4i). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.77 (s, 1H), 7.74–7.73 (m, 1H), 7.60–7.33 (m, 9H), 7.08–6.99 (m, 2H), 6.82–6.77 (m, 2H), 6.19 (s, 1H), 4.01 (q, J = 7.0 Hz, 2H), 1.15 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 164.2, 162.7, 156.3, 147.5, 138.6, 134.0, 132.9, 130.5, 129.1, 128.4, 128.0, 127.6, 121.2, 120.5, 117.6, 114.5, 113.4, 113.2, 74.3, 64.3, 14.2. IR (KBr): 3307 (NH), 1709, 1680 (C=O) cm^{-1}. MS (ESI): m/z (%) = 387 (M^+, 100). Anal. Calcd for $C_{23}H_{21}N_3O_3$: C, 71.30; H, 5.46; Found: C 71.24; H 5.54 (Table 2, entry 33).

N-(2-(2,6-dichlorophenyl)-4-oxo-1,2-dihydroquinazolin-3(4H)-yl)-2-ethoxybenzamide (4j). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.68 (s, 1H), 7.71–7.68 (m, 2H), 7.52–7.42 (m, 5H), 7.33–7.30 (m, 1H), 7.22 (s, 1H), 7.08–7.01 (m, 2H), 6.73–6.67 (m, 2H), 4.02 (q, J = 6.5 Hz, 2H), 1.15 (t, J = 6.5 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 164.9, 161.7, 156.5, 147.3, 135.8, 134.1, 133.3, 132.0, 131.2, 130.8, 127.8, 120.6, 120.4, 116.9, 113.7, 113.2, 111.8, 71.0, 64.4, 14.1. IR (KBr): 3319 (NH), 1645, 1615 (C=O) cm^{-1}. MS (ESI): m/z (%) = 459

([M+4]$^+$, 11), 457 ([M+2]$^+$, 63), 455 (M^+, 100). Anal. Calcd for $C_{23}H_{19}Cl_2N_3O_3$: C, 60.54; H, 4.20; Found: C 60.59; H 4.27 (Table 2, entry 34).

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