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Synthesis of 6-aryl-5*H*-quinazolino[4,3-*b*]quinazolin-8(6*H*)-one derivatives in ionic liquids catalyzed by iodine

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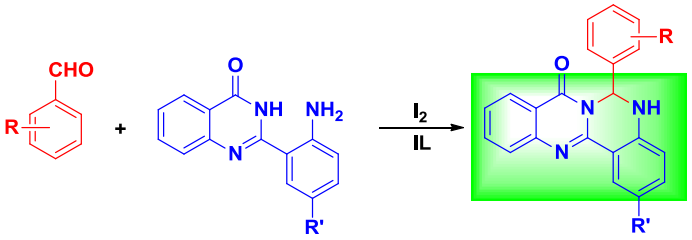
Abstract The iodine-catalyzed reaction of 2-(2-aminophenyl)quinazolin-4(3*H*)-ones and benzaldehydes was treated in ionic liquids, giving a series of 6-aryl-5*H*-quinazolino[4,3-*b*]quinazolin-8(6*H*)-one derivatives in high yields. This novel procedure has the advantages of high yields, being metal-free and having a mild reaction condition.

Graphical Abstract



Keywords Quinazolinoquinazoline · Ionic liquids · Iodine · Synthesis

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Introduction

It is well known that quinazoline derivatives always indicate good anti-tumor activities [1–4]. A noteworthy compound is *lapatinib* (Fig. 1), which is an orally active drug mainly used for the treatment of breast cancer [5]. In addition, it is reported that quinazoline derivatives have other remarkable pharmacological and biological activities, such as anti-inflammatory [6], anti-microbial [7], anti-tobacco mosaic virus (TMV) [8], and anti-tubercular activities [9]. Quinazolinoquinazoline is a tetracyclic heterocycle containing two quinazoline analogs, and its derivatives have significant hypnotic activity [10] and are also used as anti-inflammatory agents [11]. They are likely to indicate particular bio-activities, especially for anti-tumor activity for biological activity screening.

Therefore, many procedures involving synthesis of quinazolinoquinazolines have been reported in recent years [12–18]. In addition, to obtain these potentially bio-active quinazolino[4,3-*b*]quinazoline derivatives, 2-(2-aminophenyl)quinazolin-4(3*H*)-one is usually used as a catalyst to react with another reagent, such as Schiff bases [19], ortho esters [20], and anhydrides [21]. Although theses useful synthetic procedures have been developed, several limitations still remain, for example, low yields or flammable organic solvents. Thus, a simple, efficient, and "green" method for synthesis of quinazolinoquinazolines is attractive.

In our recent study, it was surprising to find that quinazolino[4,3-*b*]quinazoline derivatives were very easy to obtain in high yields via simple condensation of 2-(2-aminophenyl)quinazolin-4(3*H*)-ones and aldehydes. As a continuation of synthesising polycyclic heterocycles catalyzed by iodine [22–25], herein, we report on the synthesis of 6-aryl-5*H*-quinazolino[4,3-*b*]quinazolin-8(6*H*)-one derivatives in ionic liquids catalyzed by iodine.

Results and discussion

Treatment of benzaldehyde (**1a**) and 2-(2-aminophenyl)quinazolin-4(3*H*)-one (**2a**) in an ionic liquid of [BMIm]Br in the presence of 5 mol% iodine at 80 °C resulted in the corresponding 6-phenyl-5*H*-quinazolino[4,3-*b*]quinazolin-8(6*H*)-one (**3a**) at a 96 % yield (Eq. 1).

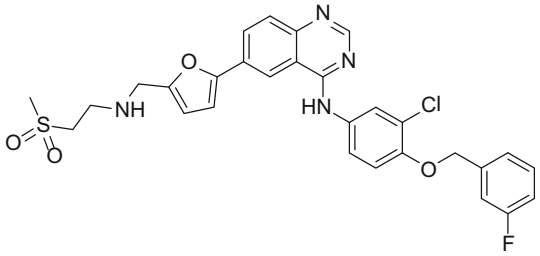
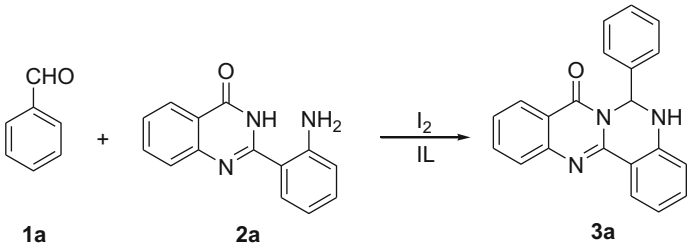


Fig. 1 The structure of *lapatinib*



Equation 1. The model reaction

In our initial study, using the reaction of benzaldehyde (**1a**) and **2a** as a model, several parameters, including reaction temperature, catalysts and the type of ionic liquids, were explored, as shown in Table 1. **3a** was not detected by thin layer chromatography (TLC) in the absence of iodine at 80 °C (Table 1, entry 1), and was successfully obtainable in the presence of various quantities of the catalyst. In the presence of 5 mol% iodine, only trace amounts of **3a** were monitored by TLC at room temperature (Table 1, entry 2). With increased temperature, it gave a maximum yield of 96 % at 80 °C (Table 1, entries 3–5). At the same temperature, increasing the amount of catalyst did not improve the yield of **3a** to a great extent (Table 1, entries 4, 6 and 7). Different imidazolium-based ionic liquids were also tested, such as [EMIm]Br, [PMIm]Br, [EMIm][BF_4], [PMIm][BF_4] and

Table 1 Synthetic results of **3a** under different reaction conditions

Entry	Temp. (°C)	Ionic liquid[a]	Time (h)	I_2 (mol%)	Yields (**3a**, %)[b]
1	80	[BMIm]Br	24	0	0
2	r.t.	[BMIm]Br	24	5	Trace
3	50	[BMIm]Br	12	5	82
4	80	[BMIm]Br	8	5	96
5	100	[BMIm]Br	8	5	96
6	80	[BMIm]Br	8	10	92
7	80	[BMIm]Br	8	20	89
8	80	[EMIm]Br	9	5	89
9	80	[PMIm]Br	10	5	90
10	80	[EMIm][BF_4]	8	5	87
11	80	[PMIm][BF_4]	10	5	85
12	80	[BMIm][BF_4]	10	5	86

Reaction condition: 2 mL solvent, **2a** (0.237 g, 1.0 mmol), and benzaldehyde (0.106 g, 1.0 mmol)

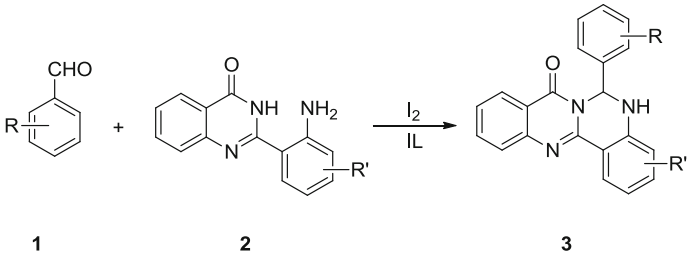
[a] *BMIm* 1-butyl-3-methylimidazolium, *EMIm* 1-ethyl-3-methylimidazolium, *PMIm* 1-methyl-3-propylimidazolium

[b] Isolated yields

[BMIm][BF_4], and [BMIm]Br appeared to be the best medium for this transformation (entry 4 vs. 8–12).

After the completion of reaction monitored by TLC, products were isolated by simple filtration after adding a small amount of water to the cooled reaction mixture. Water in the filtrate was removed by distillation under reduced pressure, and the [BMIm]Br in the residue was reused after being evaporated at 80 °C for 4 h in a *vacuum*. Successive reuse of the recycled ionic liquid of [BMIm]Br in the model reaction gave high yields of **3a** (92 %) even after the fourth cycle (Table 2).

The generality of this transformation was examined under the above optimized reaction conditions, and the results are summarized in Table 3. A broad range of benzaldehydes (Eq. 2) reacted with 2-(2-aminophenyl)quinazolin-4(3*H*)-one (**2a**) successfully. Benzaldehydes **1** bearing both electron-donating (such as alkyl and alkoxy groups) and electron-withdrawing substituents (such as halogens) on the benzene ring can be used in the direct reaction to synthesize the desired 6-aryl-5*H*-quinazolino[4,3-*b*]quinazolin-8(6*H*)-one derivatives (Table 3, entries 1–11) in high yields (86–96 %). In addition, other 2-(2-aminophenyl)quinazolin-4(3*H*)-ones (**2b**–**2d**) were prepared according to the corresponding nitro compounds via a reduction reaction by 50 % hydrazine hydrate [26]. And they were then submitted to react with **1** under the same reaction condition. To our delight, they were all carried out smoothly to afford **3l**–**3p** in 86–94 % yields (Table 3, entries 12–16).



Equation 2. The reaction of **1** and **2**

According to the structure of the **3** products, we suggest that iodine catalyzes the reaction as a mild Lewis acid. A Schiff base may be formed first in the presence of iodine, and then intra-molecular cyclization takes place to give the final **3** products. The possible reaction mechanism is shown as follows (Scheme 1),

Table 2 Yields of **3a** in the reuse of recycled ionic liquid

Cycle	1	2	3	4
Yields (**3a** %)	92	90	90	92

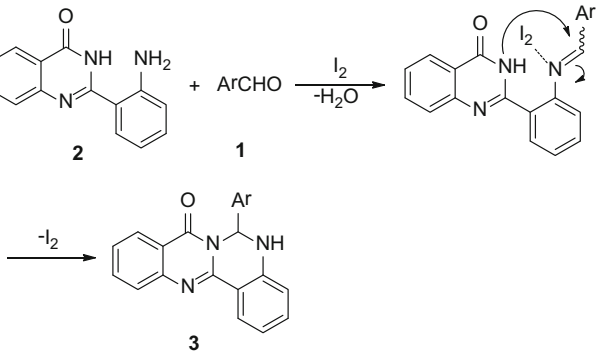
Reaction condition: 2 mL [BMIm]Br, **2a** (0.237 g, 1.0 mmol), and **1a** (0.106 g, 1.0 mmol), 80 °C

Table 3 Synthetic results for the **3** products

Entry	R	R′	Products	Time (h)	Yields[a] (%)
1	H	H	**3a**	8	96
2	4-Br	H	**3b**	8	92
3	2,4-Cl_2	H	**3c**	6	90
4	2,3-$(MeO)_2$	H	**3d**	10	90
5	4-F	H	**3e**	10	87
6	4-Cl	H	**3f**	10	94
7	3,4-$(MeO)_2$	H	**3g**	12	92
8	2-F	H	**3h**	8	89
9	3-OH	H	**3i**	9	92
10	3,4-Cl_2	H	**3j**	10	86
11	4-Me	H	**3k**	10	84
12	4-Cl	2-Cl	**3l**	8	94
13	4-Me	2-Cl	**3m**	10	86
14	4-Br	2-Cl	**3n**	8	91
15	4-Br	3-Cl	**3o**	8	90
16	4-Me	2-Br	**3p**	9	92

Reagents and conditions: **1** (1.0 mmol), **2** (1.0 mmol), iodine (0.05 mmol), and [BMIm]Br (2 mL)

[a] Isolated yields



Scheme 1 The possible reaction mechanism

Conclusion

In conclusion, we have developed a novel procedure leading to 6-aryl-5*H*-quinazolino[4,3-*b*]quinazolin-8(6*H*)-one derivatives catalyzed by iodine in ionic liquids. The procedure includes a simple reaction of 2-(2-aminophenyl)quinazolin-4(3*H*)-one and benzaldehyde, and has the advantages of high yields (86–96 %), being metal-free and mild reaction conditions.

Experimental

Melting points were determined in open capillaries and were uncorrected. Infrared (IR) spectra were recorded on a Tensor 27 spectrometer using a KBr pellet. Proton nuclear magnetic resonance (^{1}H NMR) spectra were obtained from a solution in deuterated dimethyl sulfoxide (DMSO-d_6) or deuterated chloroform ($CDCl_3$ with tetramethylsilane (Me_4Si) as the internal standard using a Bruker-400 spectrometer. High-resolution mass spectrometry (HRMS) analyses were carried out using a Bruker-micro-TOF-Q-MS analyzer.

General procedure for the syntheses of 3

A 25-mL flask was charged with benzaldehyde (1.0 mmol), 2-(2-aminophenyl)quinazolin-4(3*H*)-one (1.0 mmol), I_2 (0.05 mmol), and [BMIm]Br (2 mL). The mixture was stirred at 80 °C before reaching completion, which was monitored by TLC. When it was cooled down to room temperature, water (5 mL) was added to the mixture. The solid was filtered off and purified by recrystallization from 95 % EtOH to give pure **3**.

6-Phenyl-5H-quinazolino[4,3-b]quinazolin-8(6H)-one (**3a**) Pale yellow powder, m.p. 228–229 °C (Lit [19]. 226–227 °C); ^{1}H NMR (DMSO-d_6, 400 MHz): δ_H 6.80–6.85 (m, 1H, ArH), 6.93 (d, J = 8.0 Hz, 1H, ArH), 7.17–7.19 (m, 2H, ArH), 7.23–27 (m, 4H, ArH), 7.32–7.36 (m, 1H, ArH), 7.51–7.54 (m, 1H, ArH), 7.75 (d, J = 8.4 Hz, 1H, ArH), 7.85–7.90 (m, 1H, ArH), 8.01 (d, J = 3.6 Hz, 1H, NH), 8.11–8.14 (m, 1H, ArH), 8.20 (dd, J = 8.0 Hz, J' = 1.2 Hz, 1H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 63.7, 116.3, 120.7, 126.0, 126.2, 127.1, 127.2, 127.3, 127.5, 127.7, 128.6, 128.7, 133.5, 134.6, 139.2, 143.6, 147.1, 148.2, 160.7. IR (KBr): v 3356, 3062, 3029, 2968, 1665, 1594, 1556, 1498, 1468, 1382, 1317, 1255, 1173, 1076, 768, 750, 700 cm^{-1}. HRMS (ESI, *m/z*): Calcd. for $C_{21}H_{16}N_3O$ $[M + H]^+$ 326.1293, found 326.1275.

6-(4-Bromophenyl)-5H-quinazolino[4,3-b]quinazolin-8(6H)-one (**3b**) Pale yellow powder, m.p. 267–269 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ_H 6.82–6.86 (m, 1H, ArH), 6.93 (d, J = 8.0 Hz, 1H, ArH), 7.19 (d, J = 8.4 Hz, 2H, ArH), 7.25 (d, J = 3.6 Hz, 1H, CH), 7.33–7.37 (m, 3H, ArH), 7.50–7.54 (m, 1H, ArH), 7.75 (d, J = 8.4 Hz, 1H, ArH), 7.85–7.89 (m, 1H, ArH), 7.99 (d, J = 3.6 Hz, 1H, NH), 8.12 (d, J = 7.2 Hz, 1H, ArH), 8.19 (dd, J = 8.0 Hz, J' = 0.8 Hz, 1H, ArH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ_C 62.5, 116.1, 116.5, 119.5, 120.3, 122.0, 126.8, 127.2, 127.4, 127.8, 128.5, 132.0, 134.3, 135.6, 139.4, 145.3, 147.5, 148.2, 160.1. IR (KBr): v 3340, 3062, 2927, 1682, 1595, 1556, 1485, 1385, 1324, 1274, 1154, 1066, 1006, 895, 822, 766, 700 cm^{-1}. HRMS (ESI, *m/z*): Calcd. for $C_{21}H_{15}BrN_3O$ $[M + H]^+$ 404.0398, found 404.0392.

6-(2,4-Dichlorophenyl)-5H-quinazolino[4,3-b]quinazolin-8(6H)-one (**3c**) Pale yellow powder, m.p. 249–250 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ_H 6.84–6.90 (m, 3H, ArH), 7.20 (dd, J = 8.4 Hz, J' = 2.0 Hz, 1H, ArH), 7.30–7.34 (m, 1H, ArH), 7.37 (d, J = 3.6 Hz, 1H, CH), 7.47–7.51 (m, 1H, ArH), 7.70–7.72 (m, 2H, NH + ArH),

7.78 (d, $J = 7.6$ Hz, 1H, ArH), 7.85–7.89 (m, 1H, ArH), 8.08 (dd, $J = 8.0$ Hz, $J' = 1.2$ Hz, 1H, ArH), 8.24 (dd, $J = 8.0$ Hz, $J' = 1.2$ Hz, 1H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 61.6, 115.8, 116.8, 120.3, 120.7, 126.6, 127.15, 127.23, 127.4, 127.6, 127.7, 130.3, 132.7, 133.7, 134.4, 134.9, 135.2, 142.8, 147.5, 148.1, 160.0.IR (KBr): *v* 3421, 3065, 2965, 1626, 1484, 1415, 1346, 1305, 1154, 1045, 864, 749, 700, 666 cm^{-1}. HRMS (ESI, *m/z*): Calcd. for $C_{21}H_{12}Cl_2N_3O$ $[M–H]^-$ 392.0358, found 392.0353.

6-(2,3-Dimethoxyphenyl)-5H-quinazolino[4,3-b]quinazolin-8(6H)-one (**3d**) Pale yellow powder, m.p. 238–240 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ_H 3.78 (s, 3H, CH_3O), 3.93 (s, 3H, CH_3O), 6.30 (d, $J = 7.6$ Hz, 1H, ArH), 6.80–6.83 (m, 3H, ArH), 6.96 (d, $J = 8.4$ Hz, 1H, CH), 7.25–7.29 (m, 1H, ArH), 7.36 (s, 1H, ArH), 7.41 (s, 1H, ArH), 7.46–7.49 (m, 1H, ArH), 7.76 (d, $J = 8.4$ Hz, 1H, NH), 7.83–7.87 (m, 1H, ArH), 8.08 (d, $J = 8.0$ Hz, 1H, ArH), 8.21 (d, $J = 8.0$ Hz, 1H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 55.8, 60.8, 61.0, 112.9, 115.6, 116.5, 117.5, 120.0, 120.5, 124.0, 126.2, 127.0, 127.4 127.6, 132.4, 133.4, 134.7, 144.2, 145.9, 148.1, 148.3, 152.7, 160.4. IR (KBr): *v* 3333, 3006, 2932, 2832, 1667, 1596, 1558, 1482, 1385, 1321, 1271, 1225, 1155, 1067, 1005, 926, 864, 745, 700, 637 cm^{-1}. HRMS (ESI, *m/z*): Calcd. for $C_{23}H_{20}N_3O_3$ $[M + H]^+$ 386.1505, found 386.1512.

6-(4-Fluorophenyl)-5H-quinazolino[4,3-b]quinazolin-8(6H)-one (**3e**) Pale yellow powder, m.p. 234–235 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 5.00 (d, $J = 3.2$ Hz, 1H, NH), 6.82 (d, $J = 8.0$ Hz, 1H, ArH), 6.86–6.91 (m, 2H, ArH), 6.98–7.02 (m, 1H, ArH), 7.28–7.30 (m, 2H, ArH), 7.34–7.39 (m, 2H, ArH), 7.43–7.47 (m, 1H, ArH), 7.75–7.77 (m, 2H, ArH), 8.31 (d, $J = 8.0$ Hz, 1H, ArH), 8.34 (d, $J = 8.0$ Hz, 1H, ArH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ_C 62.5, 115.9 (d, $J_{F–C} = 21.5$ Hz), 116.0, 116.4, 119.4, 120.4, 126.8, 127.1, 127.4, 127.7, 128.4 (d, $J_{F–C} = 8.4$ Hz), 134.3, 135.5, 136.2 (d, $J_{F–C} = 3.0$ Hz), 145.4, 147.6, 148.2, 160.1, 162.2 (d, $J_{F–C} = 243.1$ Hz). IR (KBr): *v* 3357, 3064, 2961, 2871, 1685, 1604, 1555, 1503, 1469, 1386, 1328, 1236, 1154, 1103, 1021, 991, 894, 846, 767, 697, 616 cm^{-1}. HRMS (ESI, *m/z*): Calcd. for $C_{21}H_{13}FN_3O$ $[M–H]^-$ 342.1043, found 342.1048.

6-(4-Chlorophenyl)-5H-quinazolino[4,3-b]quinazolin-8(6H)-one (**3f**) Pale yellow powder, m.p. 259–260 °C (Lit [19]. 251 °C); ^{1}H NMR (DMSO-d_6, 400 MHz): δ_H 6.82–6.86 (m, 1H, ArH), 6.93 (d, $J = 8.0$ Hz, 1H, ArH), 7.19 (d, $J = 8.4$ Hz, 2H, ArH), 7.25 (d, $J = 3.6$ Hz, 1H, CH), 7.33–7.37 (m, 3H, ArH), 7.50–7.54 (m, 1H, ArH), 7.75 (d, $J = 8.4$ Hz, 1H, ArH), 7.85–7.89 (m, 1H, ArH), 7.99 (d, $J = 3.6$ Hz, 1H, NH), 8.12 (d, $J = 7.2$ Hz, 1H, ArH), 8.19 (dd, $J = 8.0$ Hz, $J' = 0.8$ Hz, 1H, ArH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ_C 62.5, 116.1, 116.5, 119.5, 120.3, 126.8, 127.2, 127.4, 127.8, 128.1, 129.1, 133.4, 134.3, 135.6, 138.9, 145.3, 147.5, 148.2, 160.1. IR (KBr): *v* 3344, 3063, 1682, 1595, 1556, 1487, 1469, 1385, 1325, 1274, 1258, 1154, 1084, 1010, 895, 824, 766, 704, 611 cm^{-1}. HRMS (ESI, *m/z*): Calcd. for $C_{21}H_{15}ClN_3O$ $[M + H]^+$ 360.0904, found 360.0887.

6-(3,4-Dimethoxyphenyl)-5H-quinazolino[4,3-b]quinazolin-8(6H)-one (**3g**) Pale yellow powder, m.p. 176–177 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ_H 3.62 (s, 3H,

CH_3O), 3.64 (s, 3H, CH_3O), 6.39 (dd, $J = 8.4$ Hz, $J' = 2.4$ Hz, 1H, ArH), 6.74 (d, $J = 8.4$ Hz 1H, ArH), 6.81–6.85 (m, 1H, ArH), 6.92 (d, $J = 8.0$ Hz, 1H, ArH), 7.04 (d, $J = 2.0$ Hz, 1H, ArH), 7.18 (d, $J = 3.6$ Hz, 1H, CH), 7.32–7.36 (m, 1H, ArH), 7.50–7.54 (m, 1H, ArH), 7.75 (d, $J = 8.0$ Hz, 1H, ArH), 7.85–7.89 (m, 1H, ArH), 7.94 (d, $J = 3.6$ Hz, 1H, NH), 8.13 (d, $J = 8.0$ Hz, 1H, ArH), 8.20 (dd, $J = 8.0$ Hz, $J' = 1.2$ Hz, 1H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 55.7, 55.8, 63.6, 109.3, 110.9, 116.2, 117.7, 118.6, 120.6, 120.7, 126.2, 127.1, 127.5, 127.7, 132.1, 133.5, 134.6, 143.8, 147.1, 148.1, 148.9, 149.2, 160.7. IR (KBr): *v* 3390, 3061, 2996, 2936, 2837, 1668, 1596, 1557, 1514, 1467, 1386, 1321, 1258, 1137, 1018, 859, 743, 699, 639 cm^{-1}. HRMS (ESI, *m/z*): Calcd. for $C_{23}H_{20}N_3O_3$ $[M + H]^+$ 386.1505, found 386.1508.

6-(2-Fluorophenyl)-5H-quinazolino[4,3-b]quinazolin-8(6H)-one (**3h**) Pale yellow powder, m.p. 202–204 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 5.13 (s, 1H, NH), 6.65–6.72 (m, 2H, ArH), 6.86–6.93 (m, 1H, ArH), 6.92–6.95 (m, 1H, ArH), 7.06–7.11 (m, 1H, ArH), 7.19–7.22 (m, 1H, ArH), 7.25–7.29 (m, 1H, ArH), 7.44–7.47 (m, 1H, ArH), 7.58 (s, 1H, CH), 7.78–7.83 (m, 2H, ArH), 8.28 (d, $J = 8.0$ Hz, 1H, ArH), 8.35 (d, $J = 8.0$ Hz, 1H, ArH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ_C 59.8 (d, $J_{F–C} = 3.7$ Hz), 115.7, 116.0 (d, $J_{F–C} = 21.0$ Hz), 116.9, 120.4, 120.5, 124.2 (d, $J_{F–C} = 3.5$ Hz), 126.0 (d, $J_{F–C} = 12.1$ Hz), 126.4, 126.7 (d, $J_{F–C} = 3.1$ Hz), 127.2, 127.5, 127.6, 130.4 (d, $J_{F–C} = 8.3$ Hz), 133.5, 134.8, 143.5, 147.6, 148.2, 160.1, 160.3 (d, $J_{F–C} = 244.0$ Hz). IR (KBr): *v* 3402, 3067, 3029, 1669, 1555, 1484, 1388, 1321, 1259, 1221, 1160, 1000, 1035, 887, 828, 758, 702, 632 cm^{-1}. HRMS (ESI, *m/z*): Calcd. for $C_{21}H_{15}FN_3O$ $[M + H]^+$ 344.1199, found 344.1204.

6-(3-Hydroxyphenyl)-5H-quinazolino[4,3-b]quinazolin-8(6H)-one (**3i**) Pale yellow powder, m.p. 276–278 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ_H 6.52 (s, 1H, ArH), 6.59–6.64 (m, 2H, ArH), 6.80–6.84 (m, 1H, ArH), 6.91 (d, $J = 8.0$ Hz, 1H, ArH), 7.03–7.07 (m, 1H, ArH), 7.15 (d, $J = 3.6$ Hz, 1H, CH), 7.31–7.36 (m, 1H, ArH), 7.50–7.54 (m, 1H, ArH), 7.75 (d, $J = 8.0$ Hz, 1H, ArH), 7.85–7.89 (m, 1H, ArH), 7.94 (d, $J = 3.6$ Hz, 1H, NH), 8.12 (d, $J = 8.0$ Hz, 1H, ArH), 8.20 (d, $J = 8.0$ Hz, 1H, ArH), 9.46 (s, 1H, OH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ_C 62.8, 113.2, 115.5, 116.0, 116.3, 116.9, 119.2, 120.4, 126.7, 127.2, 127.4, 127.7, 130.1, 134.2, 135.5, 141.4, 145.7, 147.8, 148.2, 157.9, 160.1. IR (KBr): *v* 3461, 3401, 3075, 2991, 1653, 1589, 1556, 1489, 1392, 1318, 1279, 1153, 998, 878, 761, 703, 664 cm^{-1}. HRMS (ESI, *m/z*): Calcd. for $C_{21}H_{14}N_3O_2$ $[M–H]^-$ 340.1086, found 340.1085.

6-(3,4-Dichlorophenyl)-5H-quinazolino[4,3-b]quinazolin-8(6H)-one (**3j**) Pale yellow powder, m.p. 218–220 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ_H 6.85–6.89 (m, 1H, ArH), 6.97 (d, $J = 8.0$ Hz, 1H, ArH), 7.02 (dd, $J = 8.4$ Hz, $J' = 1.6$ Hz, 1H, ArH), 7.28 (d, $J = 3.6$ Hz, 1H, CH), 7.35–7.39 (m, 1H, ArH), 7.50–7.55 (m, 3H, ArH), 7.76 (d, $J = 8.0$ Hz, 1H, ArH), 7.86–7.90 (m, 1H, ArH), 8.01 (d, $J = 3.6$ Hz, 1H, NH), 8.12–8.14 (m, 1H, ArH), 8.21 (dd, $J = 8.0$ Hz, $J' = 0.8$ Hz, 1H, ArH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ_C 62.1, 116.0, 116.5, 119.7, 120.3, 126.4, 126.9, 127.2, 127.4, 127.8, 128.6, 131.2, 131.5, 131.9, 134.4, 135.6, 141.1, 145.1, 147.3, 148.1, 160.1. IR (KBr): *v* 3309, 3026, 2956, 1682, 1613, 1554, 1469, 1376, 1323,

1244, 1150, 1027, 905, 763, 744, 709, 621 cm^{-1}. HRMS (ESI, *m*/*z*): Calcd. for $C_{21}H_{12}Cl_2N_3O$ $[M–H]^-$ 392.0358, found 392.0353.

6-(p-Tolyl)-5H-quinazolino[4,3-b]quinazolin-8(6H)-one (**3k**) Pale yellow powder, m.p. 197–198 °C (Lit [19]. 202–203 °C); ^{1}H NMR (DMSO-d_6, 400 MHz): δ_H 2.17 (s, 3H, CH_3), 6.79–6.83 (m, 1H, ArH), 6.91 (d, J = 8.0 Hz, 1H, ArH), 7.05 (s, 4H, ArH), 7.21 (d, J = 4.0 Hz, 1H, CH), 7.30–7.35 (m, 1H, ArH), 7.49–7.53 (m, 1H, ArH), 7.74 (d, J = 8.0 Hz, 1H, ArH), 7.84–7.88 (m, 1H, ArH), 7.96 (d, J = 4.0 Hz, 1H, NH), 8.11 (dd, J = 8.0 Hz, J' = 1.2 Hz, 1H, ArH), 8.19 (dd, J = 8.0 Hz, J' = 1.2 Hz, 1H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 21.0, 63.6, 116.3, 117.7, 120.6, 120.7, 125.9, 126.1, 127.1, 127.5, 127.7, 129.4, 133.5, 134.6, 136.4, 138.4, 143.7, 147.2, 148.2, 160.7. IR (KBr): *v* 3324, 3031, 2954, 1658, 1614, 1555, 1469, 1382, 1329, 1260, 1154, 1113, 1025, 897, 757, 696, 617 cm^{-1}. HRMS (ESI, *m*/*z*): Calcd. for $C_{22}H_{17}N_3ONa$ $[M + Na]^+$ 362.1269, found 362.1267.

2-Chloro-6-(4-chlorophenyl)-5H-quinazolino[4,3-b]quinazolin-8(6H)-one (**3l**) Pale yellow powder, m.p. 246–248 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ_H 6.97 (d, J = 8.8 Hz, 1H, ArH), 7.18 (d, J = 8.4 Hz, 2H, ArH), 7.27 (d, J = 2.8 Hz, 1H, CH), 7.34–7.39 (m, 3H, ArH), 7.52–7.56 (m, 1H, ArH), 7.78 (d, J = 8.0 Hz, 1H, ArH), 7.87–7.90 (m, 1H, ArH), 8.05 (d, J = 2.0 Hz, 1H, ArH), 8.19–8.20 (m, 2H, ArH + NH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ_C 62.6, 117.1, 118.4, 120.5, 123.1, 126.2, 127.17, 127.19, 127.9, 128.1, 129.2, 133.5, 133.9, 135.7, 138.7, 144.2, 146.3, 147.9, 160.0. IR (KBr): *v* 3344, 3063, 1682, 1595, 1556, 1487, 1469, 1385, 1325, 1274, 1258, 1154, 1084, 1010, 895, 824, 766, 704, 611 cm^{-1}. HRMS (ESI, *m*/*z*): Calcd. for $C_{21}H_{14}Cl_2N_3O$ $[M + H]^+$ 394.0514, found 394.0516.

2-Chloro-6-(p-tolyl)-5H-quinazolino[4,3-b]quinazolin-8(6H)-one (**3m**) Pale yellow powder, m.p. 255–256 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ_H 2.17 (s, 3H, CH_3), 6.96 (d, J = 8.8 Hz, 1H, ArH), 7.03 (d, J = 8.4 Hz, 2H, ArH), 7.07 (d, J = 8.4 Hz, 2H, ArH), 7.23 (d, J = 3.2 Hz, 1H, CH), 7.35 (d, J = 8.4 Hz, J' = 2.4 Hz, 1H, ArH), 7.51–7.55 (m, 1H, ArH), 7.77 (d, J = 8.0 Hz, 1H, ArH), 7.85–7.89 (m, 1H, ArH), 8.05 (d, J = 2.4 Hz, 1H, ArH), 8.18–8.20 (m, 2H, ArH + NH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ_C 21.0, 62.9, 117.2, 118.3, 120.5, 122.8, 126.0, 126.1, 127.1, 127.2, 127.9, 129.6, 133.8, 135.6, 136.7, 138.2, 144.5, 146.6, 147.9, 160.0. IR (KBr): *v* 3324, 3080, 3024, 2920, 1655, 1559, 1468, 1424, 1317, 1232, 1171, 1143, 1018, 902, 818, 775, 706, 620 cm^{-1}. HRMS (ESI, *m*/*z*): Calcd. for $C_{22}H_{15}ClN_3O$ $[M–H]^-$ 372.0904, found 372.0910.

6-(4-Bromophenyl)-2-chloro-5H-quinazolino[4,3-b]quinazolin-8(6H)-one (**3n**) Pale yellow powder, m.p. 262–264 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ_H 6.97 (d, J = 8.8 Hz, 1H, ArH), 7.12 (d, J = 8.4 Hz, 2H, ArH), 7.25 (d, J = 3.6 Hz, 1H, CH), 7.38 (d, J = 8.4 Hz, J' = 2.4 Hz, 1H, ArH), 7.48 (d, J = 8.4 Hz, 2H, ArH), 7.53–7.56 (m, 1H, ArH), 7.78 (d, J = 8.0 Hz, 1H, ArH), 7.87–7.91 (m, 1H, ArH), 8.05 (d, J = 2.4 Hz, 1H, ArH), 8.18–8.20 (m, 2H, ArH + NH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ_C 62.6, 117.1, 118.5, 120.5, 122.1, 123.1, 126.2, 127.18, 127.21, 127.9, 128.4, 132.1, 133.9, 135.7, 139.1, 144.2, 146.3, 147.9, 160.0. IR (KBr): *v* 3314, 3079, 2965, 1657, 1558, 1469, 1424, 1371, 1339, 1311, 1246, 1172, 1143,

1071, 1009, 902, 818, 776, 695 614 cm^{-1}. HRMS (ESI, *m/z*): Calcd. for $C_{21}H_{14}BrClN_3O$ $[M + H]^+$ 438.0009, found 438.0012.

6-(4-Bromophenyl)-3-chloro-5H-quinazolino[4,3-b]quinazolin-8(6H)-one (**3o**) Pale yellow powder, m.p. 219–220 °C; ^1H NMR (DMSO-d_6, 400 MHz): δ_H 6.86 (dd, $J = 8.4$ Hz, $J' = 2.0$ Hz, 1H, ArH), 6.99 (d, $J = 2.0$ Hz, 1H, CH), 7.12 (d, $J = 8.4$ Hz, 2H, ArH), 7.26 (d, $J = 3.6$ Hz, 1H, ArH), 7.48–7.55 (m, 3H, ArH), 7.74 (d, $J = 8.0$ Hz, 1H, ArH), 7.85–7.89 (m, 1H, ArH), 8.10 (d, $J = 8.4$ Hz, 1H, ArH), 8.17–8.24 (m, 2H, ArH + NH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ_C 62.6, 114.8, 115.5, 119.6, 120.3, 122.2, 127.1, 127.2, 127.8, 128.4, 129.3, 132.1, 135.7, 138.8, 139.1, 146.4, 146.8, 147.9, 160.0. IR (KBr): *v* 3298, 3060, 1657, 1592, 1559, 1470, 1370, 1346, 1320, 1260, 1159, 1089, 1009, 903, 833, 763, 697 cm^{-1}. HRMS (ESI, *m/z*): Calcd. for $C_{21}H_{14}BrClN_3O$ $[M + H]^+$ 438.0009, found 438.0005.

2-Bromo-6-(p-tolyl)-5H-quinazolino[4,3-b]quinazolin-8(6H)-one (**3p**) Pale yellow powder, m.p. 230–231 °C; ^1H NMR (DMSO-d_6, 400 MHz): δ_H 2.17 (s, 3H, CH_3), 6.89 (d, $J = 8.4$ Hz, 1H, ArH), 7.01–7.07 (m, 4H, ArH), 7.22 (d, $J = 3.6$ Hz, 1H, CH), 7.46 (dd, $J = 8.8$ Hz, $J' = 2.4$ Hz, 1H, ArH), 7.51–7.55 (m, 1H, ArH), 7.77 (d, $J = 8.0$ Hz, 1H, ArH), 7.84–7.89 (m, 1H, ArH), 8.17–8.20 (m, 3H, ArH + NH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ_C 21.0, 62.8, 110.2, 117.7, 118.7, 120.5, 126.0, 127.1, 127.9, 129.1, 129.7, 135.6, 136.5, 136.6, 138.2, 144.8, 146.5, 147.9, 160.0. IR (KBr): *v* 3375, 3062, 2920, 2832, 1672, 1592, 1560, 1495, 1469, 1421, 1370, 1323, 1167, 1143, 1092, 1024, 898, 817, 766, 696 cm^{-1}. HRMS (ESI, *m/z*): Calcd. for $C_{22}H_{17}BrN_3O$ $[M + H]^+$ 418.0555, found 418.0528.

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