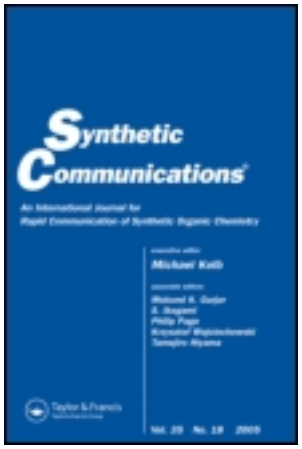

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Yao Wang [a], Mei Zhang [a], Shengli Cao [a b], Huihui Lin [a], Man Gao [a] & Zhongfeng Li [a]

[a] Department of Chemistry, Capital Normal University, Beijing, China
[b] State Key Laboratory of Natural and Biomimetic Drugs, Peking University, Beijing, China

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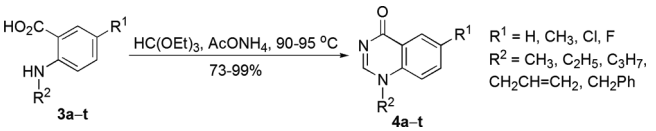
SYNTHESIS OF 1-SUBSTITUTED 4(1*H*)-QUINAZOLINONES UNDER SOLVENT-FREE CONDITIONS

Yao Wang,[1] Mei Zhang,[1] Shengli Cao,[1,2] Huihui Lin,[1] Man Gao,[1] and Zhongfeng Li[1]

[1]*Department of Chemistry, Capital Normal University, Beijing, China*
[2]*State Key Laboratory of Natural and Biomimetic Drugs, Peking University, Beijing, China*

GRAPHICAL ABSTRACT



Abstract *Heating a mixture of 2-(*N*-alkylamino)benzoic acids, triethyl orthoformate, and ammonium acetate under solvent-free conditions generated 1-substituted 4(1*H*)-quinazolinones in 73–99% yields. Moreover, a possible reaction pathway was proposed.*

Keywords Cyclization; 4(1*H*)-quinazolinone; solvent-free; triethyl orthoformate

INTRODUCTION

4-Quinazolinone and its derivatives, such as 2-substituted, 3-substituted, and 2,3-disubstituted 4-quinazolinones, exhibit a wide variety of biological activities, the synthetic methodologies of which have attracted intense attention.[1–3] In fact, many naturally occurring or synthetic 1-substituted 4(1*H*)-quinazolinones also present attractive biological activities. For example, 1-methyl-4(1*H*)-quinazolinone, commonly named glycorine, isolated from *Glycosmis arborea*, is an alkaloid with anti-inflammatory activity,[4,5] some 1-alkenyl-4(1*H*)-quinazolinones have analgesic effects equal to or better than that of codeine, and 1-allyl-4(1*H*)-quinazolinone was selected for clinical trials.[6] However, few methods for the synthesis of 1-substituted 4(1*H*)-quinazolinones have been reported until now.[6–9]

The Niementowski ring closure was shown to be applicable to the formation of 1-substituted 4(1*H*)-quinazolinones. For instance, *N*-aryl-substituted anthranilic acids and excess formamide reacted in a sealed tube at 150–160 °C or under atmospheric pressure at 170–180 °C to give 1-substituted 4(1*H*)-quinazolinones in 20–40%

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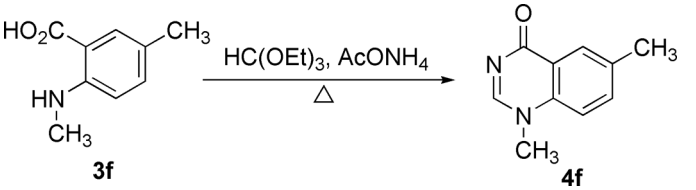
Address correspondence to Shengli Cao, Department of Chemistry, Capital Normal University, Beijing 100048, China. E-mail: sl_cao@sohu.com

yields.[7] However, only the *N*-methylanthranilic acid salt of 1-methyl-4(1-*H*)-quinazolinone was isolated in very poor low yield as *N*-methylanthranilic acid was heated with formamide.[8] For the synthesis of 1-alkenyl-4(1*H*)-quinazolinones, Vincent and coworkers prepared 2-(*N*-alkenylamino)benzamides either through the reaction of 2-aminobenzamides with alkenyl bromide or through the ammonolysis of the *N*-alkenyl isatoic anhydrides, which were heated in boiling triethyl orthoformate for 35 h while distilling off the ethanol formed, and then the reactions were continued at room temperature for another 15 h.[6] However, no yield was stated by the authors. Kametani et al. described another method in which *N*-methylsulphinamide anhydride, prepared from the reaction of *N*-methylanthranilic acid with thionyl chloride, was treated with formamide to form 1-methyl-4(1*H*)-quinazolinone hydrochloride in 47% yield.[9] The aforementioned methods for the synthesis of 1-substituted 4(1*H*)-quinazolinones have some drawbacks such as unsatisfactory yields, long reaction times, and complicated procedures. Herein, we report one-step method to synthesize 1-substituted 4(1*H*)-quinazolinones under solvent-free conditions in good to excellent yields.

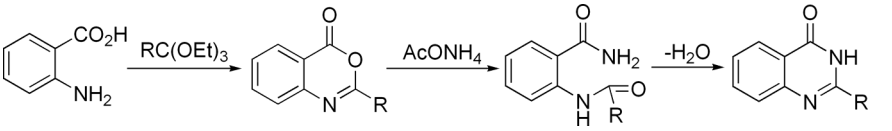
RESULTS AND DISCUSSION

In an attempt to prepare 1-substituted 4(1*H*)-quinazolinones as intermediates for the synthesis of new anticancer agents, we heated 5-methyl-2-(*N*-methylamino)-benzoic acid (**3f**) in excess formamide according to the Niementowski reaction, but the cyclized product desired was hardly obtained because it was difficult to be separated from formamide. Inspired by the reaction of anthranilic acids with orthoesters and ammonium acetate under microwave irradiation to afford 2-substituted-4(3-*H*)-quinazolinones,[10] we heated 5-methyl-2-(*N*-methylamino)benzoic acid (**3f**), triethyl orthoformate and ammonium acetate under solvent-free condition, generating 1,6-dimethyl-4(1*H*)-quinazolinone (**4f**) as expected (Scheme 1). As presumed by Rad-Moghadam et al.,[10] the reaction of anthranilic acid with orthoesters first generated 4*H*-benzo[*d*][1,3]oxazin-4-ones, which then interacted with ammonium acetate and were converted into 2-(*N*-acylamino)benzamides, followed by cyclization through the elimination of a molecule of H_2O to give 4(3*H*)-quinazolinones (Scheme 2).

As for the reaction of **3f** with triethyl orthoformate, it was impossible to form an intermediate like 4*H*-benzo[*d*][1,3]oxazin-4-one as supposed by Rad-Moghadam et al. because of the substituent linked at the nitrogen atom of **3f**. Therefore, we reckoned that **3f** was alkylated first by triethyl orthoformate to form the *N*-alkylated



Scheme 1. Reaction of **3f** with triethyl orthoformate and ammonium acetate.

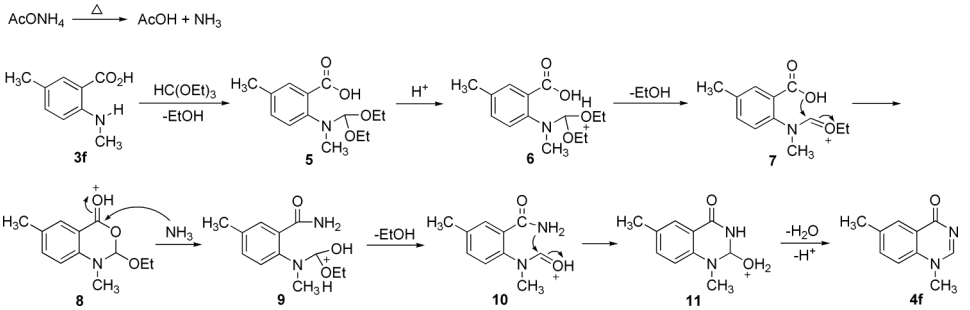


Scheme 2. Synthesis of 2-substituted 4(3*H*)-quinazolinone by Rad-Moghadam et al.[10]

product **5**, as shown in Scheme 3. One of ethoxy groups in **5** was protonated, and then the formed intermediate **6** underwent elimination to lose a molecule of EtOH. Subsequently, the hydroxyl added to the double bond of the formed intermediate **7** generated **8**. The polarized carbonyl in **8** was nucleophilly attacked by ammonia released from heated ammonium acetate to generate **9**, followed by the elimination of EtOH to form the protonated *N*-formyl intermediate **10**. The intramolecular addition of amino onto the protonated formyl group formed the cyclized product **11**, which lost a molecule of H_2O and a proton to give the final product **4f** (Scheme 3).

To search for the optimal reaction conditions from **3f** to **4f**, the effects of temperature, solvent, and the relative molar ratio of **3f** to triethyl orthoformate and ammonium acetate on the yield were investigated, and the results are listed in Table 1. The mixture of **3f**, $HC(OEt)_3$, and $AcONH_4$ in a molar ratio of 1:5:3 was refluxed in ethanol within 3h, giving **4f** in only 46% yield. Replacing ethanol by *N,N*-dimethylformamide (DMF) and increasing the temperature to 90–95 °C obviously enhanced the yield to 83%. However, the yield decreased drastically when the reaction temperature was further increased to 120–130 °C. Interestingly, the reaction was carried out in the absence of solvent at 80–85 °C, affording the product in 82% yield, and the yield was even enhanced to 97% if the temperature was raised to 90–95 °C. However, the decreasing molar ratio of **3f**, $HC(OEt)_3$, and $AcONH_4$ to 1:3:2 would lower the yield to 88% (entry 6). Thus, it could be concluded that the treatment of **3f**, $HC(OEt)_3$, and $AcONH_4$ in the molar ratio of 1:5:3 at 90–95 °C under solvent-free conditions is the most suitable choice to obtain **4f**.

To further investigate the application scope of this method, 2-(*N*-substituted amino)benzoic acids (**3a**–**e**) were prepared starting from isatin (**1a**) (Scheme 4). As far as we know, the substituents at the C6 position of quinazolinones are of importance for their biological activities, and moreover, 6-methyl-quinazolinones are the



Scheme 3. Possible reaction pathway of **3f** to **4f**.

Table 1. Yields of **4f** in the reaction of **3f** with $HC(OEt)_3$ and $AcONH_4$ under various conditions

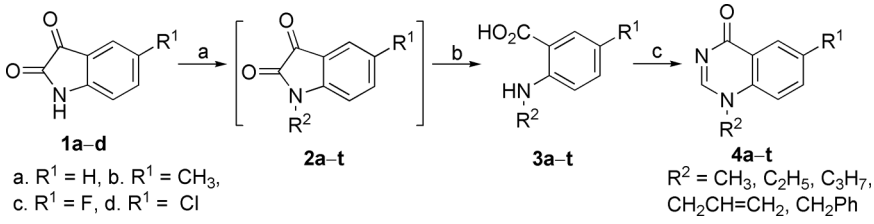
Entry	Temperature (°C)	Solvent	Molar ratio [**3f**/$HC(OEt)_3$/$AcONH_4$]	Yield (%)[a,b]
1	75–80	EtOH	1:5:3	46
2	90–95	DMF	1:5:3	83
3	120–130	DMF	1:5:3	45
4	80–85	Solvent-free	1:5:3	82
5	90–95	Solvent-free	1:5:3	97
6	90–95	Solvent-free	1:3:2	88

[a]Yields of pure isolated products.
[b]Reaction time: 3 h.

key intermediates in the synthesis of the folate analogs as anticancer agents.[11–13] Therefore, 2-(*N*-substituted amino)benzoic acids (**3f–t**) bearing CH_3, F or Cl at the C5 position were also chosen and prepared in this research. Thus, *N*-alkylation of isatins **1a–d** was undertaken first to generate the alkylated products **2a–t** accordingly, which were subjected to the cycle-opening reaction to furnish **3a–t** in satisfactory yields. Furthermore, 20 2-(*N*-alkyl, alkenyl, or benzylamino)benzoic acids (**3a–t**) were treated with triethyl orthoformate and ammonium acetate under optimized conditions, generating the corresponding 1-substituted 4(1*H*)-quinazolinones (**4a–t**) (Scheme 4). The reaction proceedings were monitored by thin-layer chromatography (TLC) to determine their reaction times, and the results are summarized in Table 2.

As shown in Table 2, the reactions were completed within 3–4h in moderate to excellent yields, when R^1 is a hydrogen or methyl group. Nevertheless, it could be seen that the yields decreased as the R^2 groups became bulky, which could be ascribed to the steric hindrance effect on the cyclization. In the cases when R^1 are electronegative atoms, namely fluorine or chlorine atoms, the yields were still as good as when R^1 are hydrogen or methyl groups, although longer reaction times were required.

It is worth mentioning that Süsse and Johne synthesized quinazolin-4-on-1-ylacetic acid esters in a similar way, using 3,1-benzoxaine-2,4-diones as starting materials treated with ammonia to give the intermediates 2-aminobenzamides, which is different from the present procedure. Subsequent cyclization of 2-aminobenzamides with triethyl orthoformate gave 4-quinazolion-1-yl-acetic acid esters in 60–78% yields.[14] Recently, Nikpour and Paibast reported that the treatment of 2-(methylamino)benzoic acid with urea in *N,N*-dimethylacetamide or H_2O under microwave



Scheme 4. Reagents and conditions: (a) R^2X, K_2CO_3, DMF, rt, 2.5–6.5 h or 50–100 °C, 1–6 h; (b) (i) H_2O_2/NaOH, (ii) AcOH; and (c) $HC(OEt)_3$, $AcONH_4$, 90–95 °C.

Table 2. Synthesis of 1-substituted 4(1*H*)-quinazolinones **4a**–**t**

Entry	Compound	R^1	R^2	Time (h)	Mp (°C)	Yield (%)[a]
1	**4a**	H	CH_3	3	133–135 (lit.[8] 136–137)	99
2	**4b**	H	CH_2CH_3	3	128–129	94
3	**4c**	H	$CH_2CH_2CH_3$	3	148–149	88
4	**4d**	H	$CH_2CH{=}CH_2$	3	134–136 (lit.[6] 136–137)	81
5	**4e**	H	CH_2Ph	3	206–207	84
6	**4f**	CH_3	CH_3	3	192–193	97
7	**4g**	CH_3	CH_2CH_3	3	188–189	92
8	**4h**	CH_3	$CH_2CH_2CH_3$	3	143–144	85
9	**4i**	CH_3	$CH_2CH{=}CH_2$	4	133–135 (lit.[6] 135–137)	82
10	**4j**	CH_3	CH_2Ph	4	166–167	73
11	**4k**	Cl	CH_3	10	225–226	92
12	**4l**	Cl	CH_2CH_3	10	190–191	91
13	**4m**	Cl	$CH_2CH_2CH_3$	10	138–140	87
14	**4n**	Cl	$CH_2CH{=}CH_2$	10	127–129 (lit.[6] 126–128)	89
15	**4o**	Cl	CH_2Ph	14	144–145	85
16	**4p**	F	CH_3	7	201–202	99
17	**4q**	F	CH_2CH_3	7	175–176	88
18	**4r**	F	$CH_2CH_2CH_3$	7	129–131	85
19	**4s**	F	$CH_2CH{=}CH_2$	7	102–103 (lit.[6] 104–105)	83
20	**4t**	F	CH_2Ph	7	166–167	88

[a]Yields of pure isolated products.

irradiation gave 1-methyl-2,4(1*H*,3*H*)-quinazolinedione in good yield.[15] However, their product has a different structure from 1-substituted 4(1*H*)-quinazolinones.

In summary, we have developed a convenient and efficient method for the synthesis of 1-substituted 4(1*H*)-quinazolinones from isatins via three steps. The new method possesses the advantages of readily available starting materials, mild reaction conditions, simple workup procedure, and good yield. It will be useful for the synthesis of 4(1*H*)-quinazolinone derivatives as either synthetic intermediates or biologically active compounds.

EXPERIMENTAL

Melting points were determined on an X-6 or XT5B microscopic melting-point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AC-200P spectrometer at 200 MHz or a Varian VNMRS-600 spectrometer at 600 MHz using tetramethylsilane (TMS) as internal standard. ^{13}C NMR spectra were recorded on a Varian VNMRS-600 spectrometer at 150 MHz using tetramethylsilane (TMS) as internal standard. Electron impact (EI) mass spectrum was recorded on a Shimadzu GCMS-QP2010 Plus mass spectrometer. Low-resolution electrospray ionization (ESI) mass spectra were recorded on a Bruker Daltonics Esquire-LC 00136 mass spectrometer, and high-resolution electrospray ionization (HR-ESI) mass spectra were recorded on an Agilent LC/SMD TOF mass spectrometer. Elemental analyses were performed by the Institute of Chemistry, Chinese Academy of Science, on a Flash EA 1112 elemental analyzer. Column chromatography was carried out on silica gel (200–300 mesh). 2-Amino-5-methylbenzoic acid

was prepared according to the reported method.[16] Triethyl orthoformate was distilled before use, and other commercially available reagents were used without further purification.

2-(*N*-Substituted Amino)Benzoic Acids 3a–t

General procedure. Finely powered potassium carbonate (1 g, 7.2 mmol) and alkyl halide (30 mmol) were added to a solution of isatin (**1**) (10 mmol) in DMF (10 mL). After reacting at room temperature for 2.5–6.5 h or heating at 50–100 °C for 1–6 h (monitored by TLC), the mixture was poured into ice water. The precipitate was filtered and dried to give compounds **2a**–**t**, which were directly used in the next step.

A solution of sodium hydroxide (0.84 g, 21 mmol) in water (10 mL) was cooled in an ice-water bath. After the temperature was below 30 °C, compound **2** (7.0 mmol) was added and dissolved with stirring. The temperature of the reaction mixture was kept below 15 °C, while a 30% aqueous solution of hydrogen peroxide (1.8 g, 52.8 mmol) was added dropwise. Stirring was continued at 15–20 °C for 0.5–2 h (monitored by TLC). The mixture was cooled in an ice bath and adjusted to pH 5–6 with glacial acetic acid. After several hours in a refrigerator, the precipitate was collected by filtration, washed with ice water three times, and dried in air to give the pure products **3a, 3f, 3g, 3i, 3j, 3k, and 3m**–**t**. Otherwise, purification by recrystallization from methanol/H_2O (3:1) afforded compounds **3b–e, 3h**, and **3l**.

2-(Methylamino)benzoic acid (3a). Yield (two steps, hereinafter the same): 64%; yellowish solid; mp 150–152 °C (lit.[17] mp 159–171 °C).^{1}H NMR (600 MHz, $CDCl_3$): δ 2.94 (s, 3 H, CH_3), 6.62 (t, $J = 7.8$ Hz, 1 H, Ph-H), 6.69 (d, $J = 7.8$ Hz, 1 H, Ph-H), 7.43 (t, $J = 7.8$ Hz, 1 H, Ph-H), 7.97 (d, $J = 7.8$ Hz, 1 H, Ph-H), 11.50 (br s, 1 H, COOH). MS (EI): m/z 151 [M^+].

2-(Ethylamino)benzoic acid (3b). Yield: 34%; yellowish solid; mp 141–143 °C (lit.[18] mp 152.0–155.0 °C). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.33 (t, $J = 7.2$ Hz, 3 H, CH_2CH_3), 3.26 (q, $J = 7.2$ Hz, 2 H, CH_2CH_3), 6.60 (t, $J = 7.8$ Hz, 1 H, Ph-H), 6.69 (d, $J = 7.8$ Hz, 1 H, Ph-H), 7.39 (t, $J = 7.8$ Hz, 1 H, Ph-H), 7.98 (d, $J = 7.8$ Hz, 1 H, Ph-H), 12.0 (br s, 1 H, COOH). MS (EI): m/z 165 [M^+].

2-(Propylamino)benzoic acid (3c). Yield: 52%; yellowish solid; mp 114–115 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.04 (t, $J = 7.2$ Hz, 3 H, CH_2CH_3), 1.72 (m, 2 H, CH_2CH_3), 3.18 (t, $J = 7.2$ Hz, 2 H, CH_2CH_2), 6.59 (t, $J = 7.8$ Hz, 1 H, Ph-H), 6.69 (d, $J = 7.8$ Hz, 1 H, Ph-H), 7.38 (t, $J = 7.8$ Hz, 1 H, Ph-H), 7.98 (d, $J = 7.8$ Hz, 1 H, Ph-H), 12.10 (br s, 1 H, COOH). MS (EI): m/z 179 [M^+]. HRMS-ESI: m/z [M +H]$^+$ calcd. for $C_{10}H_{14}NO_2$: 180.1025; found: 180.1018.

2-(Allylamino)benzoic acid (3d). Yield: 39%; yellowish solid; mp 115–117 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.91 (d, 2 H, $J = 4.2$ Hz, NCH_2) 5.20 (d, $J = 10.2$ Hz, 1 H, =C*H*H), 5.30 (d, $J = 16.8$ Hz, 1 H, =CH*H*), 5.96 (m, 1 H, CH=), 6.63 (t, $J = 7.8$ Hz, 1 H, Ph-H), 6.68 (d, $J = 7.8$ Hz, 1 H, Ph-H), 7.39 (t, $J = 7.8$ Hz, 1 H, Ph-H), 7.78 (br s, 1 H, NH), 7.99 (d, $J = 7.8$ Hz, 1 H, Ph-H), 11.80 (br s, 1 H, COOH). MS (EI): m/z 177 [M^+]. HRMS-ESI: m/z [M +H]$^+$ calcd. for $C_{10}H_{12}NO_2$: 178.0868; found: 178.0860.

2-(Benzylamino)benzoic acid (3e). Yield: 73%; yellowish solid; mp 170–171 °C; (lit.[18] mp 170.0–173.0 °C). ^{1}H NMR (600 MHz, $CDCl_3$): δ 4.49 (s, 2 H, NCH_2), 6.62 (t, $J = 7.8$ Hz, 1 H, Ph-H), 6.64 (d, $J = 7.8$ Hz, 1 H, Ph-H), 7.27–7.36 (m, 6 H, Ph-H and Bz-H), 7.99 (d, $J = 7.8$ Hz, 1 H, Ph-H), 8.09 (br s, 1 H, NH), 11.20 (br s, 1 H, COOH). MS (EI): m/z 227 [M^+]. HRMS-ESI: m/z [M +H]$^+$ calcd. for $C_{14}H_{14}NO_2$: 228.1025; found: 228.1024.

5-Methyl-2-(methylamino)benzoic acid (3f). Yield: 62%; yellowish solid; mp 148–149 °C (lit.[18] mp 146.0–148.5 °C). ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.26 (s, 3 H, CH_3), 2.92 (s, 3 H, NCH_3), 6.63 (d, $J = 8.6$ Hz, 1 H, Ph-H), 7.27 (dd, $J = 8.6$, 2.0 Hz, 1 H, Ph-H), 7.79 (d, $J = 2.0$ Hz, 1 H, Ph-H), 9.50 (br s, 1 H, NH). MS (ESI): m/z 166 [M +H]$^+$.

2-(Ethylamino)-5-methylbenzoic acid (3g). Yield: 60%; yellowish solid; mp 158–159 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.31 (t, $J = 7.2$ Hz, 3 H, CH_2CH_3), 2.24 (s, 3 H, CH_3), 3.24 (q, $J = 7.2$ Hz, 2 H, CH_2CH_3), 6.63 (d, $J = 8.6$ Hz, 1 H, Ph-H), 7.23 (d, $J = 8.6$ Hz, 1 H, Ph-H), 7.78 (s, 1H, Ph-H). MS (ESI): m/z 180 [M +H]$^+$. HRMS-ESI: m/z [M +H]$^+$ calcd. for $C_{10}H_{14}NO_2$: 180.1025; found: 180.1012.

5-Methyl-2-(propylamino)benzoic acid (3h). Yield: 76%; yellowish solid; mp 108–109 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.03 (t, $J = 7.2$ Hz, 3 H, CH_2CH_3), 1.71 (m, 2 H, CH_2CH_3), 2.24 (s, 3 H, CH_3), 3.17 (t, $J = 7.2$ Hz, 2 H, NCH_2), 6.63 (d, $J = 8.6$ Hz, 1 H, Ph-H), 7.23 (d, $J = 8.6$ Hz, 1 H, Ph-H), 7.78 (s, 1 H, Ph-H). MS (ESI): m/z 194 [M +H]$^+$. HRMS-ESI: m/z [M +H]$^+$ calcd. for $C_{11}H_{16}NO_2$: 194.1181; found: 194.1173.

2-(Allylamino)-5-methylbenzoic acid (3i). Yield: 51%; yellowish solid; mp 117–118 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.24 (s, 3 H, CH_3), 3.88 (d, $J = 4.8$ Hz, Hz, 2 H, NCH_2), 5.18 (d, $J = 10.2$ Hz, 1 H, =C*H*H), 5.29 (d, $J = 16.8$ Hz, 1 H, =CH*H*), 5.95 (m, 1 H, CH =), 6.61 (d, $J = 8.4$ Hz, 1 H, Ph-H), 7.21 (d, $J = 8.4$ Hz, 1 H, Ph-H), 7.79 (s, 1 H, Ph-H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 20.1, 45.3, 108.6, 111.9, 116.0, 123.9, 132.2, 134.7, 136.7, 149.7, 173.9. MS (ESI): m/z 192 [M +H]$^+$. HRMS-ESI: m/z [M +H]$^+$ calcd. for $C_{11}H_{14}NO_2$: 192.1025; found: 192.1015.

2-(Benzylamino)-5-methylbenzoic acid (3j). Yield: 81%; yellowish solid; mp 152–153 °C. ^{1}H NMR (200 MHz, DMSO-d_6): δ 2.15 (s, 3 H, CH_3), 4.43 (s, 2 H, NCH_2), 6.59 (d, $J = 8.6$ Hz, 1 H, Ph-H), 7.13 (d, $J = 8.6$ Hz, 1 H, Ph-H), 7.32 (m, 5 H, Bz-H), 7.61 (s, 1 H, Ph-H). MS (ESI): m/z 242 [M +H]$^+$. HRMS-ESI: m/z [M +H]$^+$ calcd. for $C_{15}H_{16}NO_2$: 242.1181; found: 242.1172.

5-Chloro-2-(methylamino)benzoic acid (3k). Yield: 45%; yellowish solid; mp 174–176 °C (lit.[18] mp 178.0–181.0 °C). ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.91 (s, 3 H, CH_3), 6.62 (d, $J = 9.0$ Hz, 1 H, Ph-H), 7.35 (dd, $J = 9.0$, 2.4 Hz, 1 H, Ph-H), 7.91 (d, $J = 2.4$ Hz, 1 H, Ph-H). MS (EI): m/z 185, 187 [M^+]. HRMS-ESI: m/z [M +H]$^+$ calcd. for $C_8H_9ClNO_2$: 186.0322; found: 186.0312.

5-Chloro-2-(ethylamino)benzoic acid (3l). Yield: 69%; yellowish solid; mp 102–103 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.32 (t, $J = 7.2$ Hz, 3 H, CH_2CH_3), 3.24 (q, $J = 7.2$ Hz, 2 H, CH_2CH_3), 6.63 (d, $J = 9.0$ Hz, 1 H, Ph-H), 7.32 (dd, $J = 9.0$,

2.4 Hz, 1 H, Ph-H), 7.93 (d, $J = 2.4$ Hz, 1 H, Ph-H). MS (EI): m/z 199, 201 [M^+]. HRMS-ESI: m/z [M +H]$^+$ calcd. for $C_9H_{11}ClNO_2$: 200.0478; found: 200.0473.

5-Chloro-2-(propylamino)benzoic acid (3m). Yield: 72%; yellowish solid; mp 154–156 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.03 (t, $J = 7.2$ Hz, 3 H, CH_2CH_3), 1.71 (m, 2 H, $CH_2CH_2CH_3$), 3.16 (t, $J = 7.2$ Hz, 2 H, NCH_2CH_2), 6.64 (d, $J = 9.0$ Hz, 1 H, Ph-H), 7.31 (dd, $J = 9.0$, 2.4 Hz, 1 H, Ph-H), 7.92 (d, $J = 2.4$ Hz, 1 H, Ph-H). MS (EI): m/z 213, 215 [M^+]. HRMS-ESI: m/z [M +H]$^+$ calcd. for $C_{10}H_{13}ClNO_2$: 214.0635; found: 214.0631.

2-(Allylamino)-5-chlorobenzoic acid (3n). Yield: 37%; yellowish solid; mp 102–104 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.89 (d, $J = 4.8$ Hz, 2 H, NCH_2CH), 5.22 (dd, $J = 10.2$, 1.2 Hz, 1 H, $=CHH$), 5.28 (dd, $J = 17.4$, 1.2 Hz, 1 H, $=CHH$), 5.93 (m, 1 H, CH =), 6.62 (d, $J = 9.0$ Hz, 1 H, Ph-H), 7.31 (dd, $J = 9.0$, 2.4 Hz, 1 H, Ph-H), 7.74 (br s, 1 H, NH), 7.94 (d, $J = 2.4$ Hz, 1 H, Ph-H), 11.92 (br s, 1 H, COOH). ^{13}C NMR (150 MHz, $CDCl_3$): δ 45.3, 109.5, 113.3, 116.5, 119.5, 131.6, 133.9, 135.5, 150.2, 173.0. MS (EI): m/z 211, 213 [M^+]. HRMS-ESI: m/z [M +H]$^+$ calcd. for $C_{10}H_{11}ClNO_2$: 212.0478, 214.0449; found: 212.0478, 214.0446.

2-(Benzylamino)-5-chlorobenzoic acid (3o). Yield: 79%; yellowish solid; mp 154–155 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 4.47 (s, 2 H, NCH_2), 6.58 (d, $J = 9.0$ Hz, 1 H, Ph-H), 7.27 (m, 2 H, Ph-H), 7.34 (m, 4 H, Ph-H), 7.94 (d, $J = 2.4$ Hz, Hz, 1 H, Ph-H), 8.10 (br s, 1 H, NH). MS (EI): m/z 261, 263 [M^+]. HRMS-ESI: m/z [M +H]$^+$ calcd. for $C_{14}H_{13}ClNO_2$: 262.0635; found: 262.0632.

5-Fluoro-2-(methylamino)benzoic acid (3p). Yield: 49%; yellowish solid; mp 139–142 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ 2.83 (s, 3 H, NCH_3), 6.69 (dd, $J = 9.6$, 4.2 Hz, 1 H, Ph-H), 7.29 (td, $J = 9.6$, 3.0 Hz, 1 H, Ph-H), 7.49 (dd, $J = 9.6$, 3.0 Hz, 1 H, Ph-H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 30.0, 110.3 (d, $J = 6.2$ Hz), 112.6 (d, $J = 7.2$ Hz), 116.8 (d, $J = 22.8$ Hz), 122.4 (d, $J = 22.8$ Hz), 149.2, 152.4 (d, $J = 229.2$ Hz), 169.4. MS (EI): m/z 169 [M^+]. HRMS-ESI: m/z [M +H]$^+$ calcd. for $C_8H_9FNO_2$: 170.0617; found: 170.0613.

2-(Ethylamino)-5-fluorobenzoic acid (3q). Yield: 73%; yellowish solid; mp 90–93 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.32 (t, $J = 7.2$ Hz, 3 H, CH_2CH_3), 3.24 (q, $J = 7.2$ Hz, 2 H, CH_2CH_3), 6.64 (dd, $J = 9.0$, 4.2 Hz, 1 H, Ph-H), 7.16 (m, 1 H, Ph-H), 7.65 (dd, $J = 9.6$, 3.0 Hz, 1 H, Ph-H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.5, 37.8, 108.1, 112.6 (d, $J = 6.8$ Hz), 117.4 (d, $J = 22.8$ Hz), 123.6 (d, $J = 23.0$ Hz), 148.7, 152.3 (d, $J = 213.9$ Hz), 172.89. MS (EI): m/z 183 [M^+]. Anal. calcd. for $C_9H_{10}FNO_2$: C, 59.01; H, 5.50; N, 7.65. Found: C, 59.25; H, 5.68; N, 7.70.

5-Fluoro-2-(propylamino)benzoic acid (3r). Yield: 74%; yellowish solid; mp 98–100 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.03 (t, $J = 7.2$ Hz, 3 H, CH_2CH_3), 1.71 (m, 2 H, $CH_2CH_2CH_3$), 3.16 (t, $J = 7.2$ Hz, 2 H, NCH_2CH_2), 6.63 (dd, $J = 9.0$, 4.2 Hz, 1 H, Ph-H), 7.15 (m, 1 H, Ph-H), 7.65 (dd, $J = 9.6$, 3.0 Hz, 1 H, Ph-H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 11.7, 22.4, 45.1, 108.1, 112.6 (d, $J = 6.8$ Hz),), 117.4 (d, $J = 22.8$ Hz), 123.6 (d, $J = 23.0$ Hz), 148.9, 152.8 (d, $J = 232.1$ Hz), 173.2. MS (EI): m/z 197 [M^+]. HRMS-ESI: m/z [M +H]$^+$ calcd. for $C_{10}H_{13}FNO_2$: 198.0930; found: 198.0923.

2-(Allylamino)-5-fluorobenzoic acid (3s). Yield: 49%; yellowish solid; mp 107–109 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.89 (d, $J = 4.8$ Hz, 2 H, NCH_2CH), 5.21 (dd, $J = 10.2$, 1.2 Hz, 1 H, $=CHH$), 5.29 (dd, $J = 17.4$, 1.2 Hz, 1 H, $=CHH$), 5.94 (m, 1 H, CH =), 6.62 (dd, $J = 9.0$, 1.2 Hz, 1 H, Ph-H), 7.15 (m, 1 H, Ph-H), 7.66 (dd, $J = 9.6$, 3.0 Hz, 1 H, Ph-H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 45.5, 108.5 (d, $J = 6.6$ Hz), 113.0 (d, $J = 6.8$ Hz), 116.3, 117.4 (d, $J = 23.4$ Hz), 123.5 (d, $J = 22.8$ Hz),134.3, 148.5, 153.0 (d, $J = 232.5$ Hz), 173.1. MS (EI): m/z 195 [M^+]. HRMS-ESI: m/z [M +H]$^+$ calcd. for $C_{10}H_{11}FNO_2$: 196.0774; found: 196.0773.

2-(Benzylamino)-5-fluorobenzoic acid (3t). Yield: 79%; yellowish solid; mp 97–99 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 4.44 (s, 2 H, NCH_2), 6.56 (dd, $J = 9.0$, 4.2 Hz, 1 H, Ph-H), 7.06 (m, 1 H, Ph-H), 7.27 (m, 1 H, Ph-H), 7.32 (m, 4 H, Ph-H), 7.66 (dd, $J = 9.0$, 3.0 Hz, 1 H, Ph-H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 29.7, 47.2, 113.2 (d, $J = 6.8$ Hz), 117.5 (d, $J = 23.4$ Hz), 123.4 (d, $J = 25.7$ Hz), 126.9, 127.3, 128.8, 138.5, 148.4, 153.2 (d, $J = 233.1$ Hz), 172.8. MS (EI): m/z 245 [M^+]. HRMS-ESI: m/z [M +H]$^+$ calcd. for $C_{14}H_{13}FNO_2$: 246.0830; found: 246.0930.

1-Substituted 4(1*H*)-Quinazolinone 4a–t

General procedure. A mixture of 2-(*N*-substituted amino)benzoic acid **3** (3 mmol), ammonium acetate (9 mmol) and triethyl orthoformate (15 mmol) was stirred at 90–95 °C for 3–14 h (monitored by TLC). Most of excess triethyl orthoformate was removed by rotary evaporation, and the residue was applied to a silica-gel column and eluted with dichloromethane/methanol (95:5) to give compounds **4a**–**t**.

1-Methylquinazolin-4(1*H*)-one (4a). ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.78 (s, 3 H, CH_3), 7.35 (d, $J = 8.4$ Hz, 1 H, 8-H), 7.51 (t, $J = 7.8$ Hz, 1 H, 6-H), 7.77 (t, $J = 8.4$ Hz, 1 H, 7-H), 8.22 (s, 1 H, 2-H), 8.35 (d, $J = 7.8$ Hz, 1 H, 5-H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 37.4, 114.6, 120.5, 126.7, 128.9, 134.0, 139.9, 153.3, 169.2. MS (EI): m/z 160 [M^+]. HRMS-ESI: m/z [M +H]$^+$ calcd. for $C_9H_9N_2O$: 161.0715; found: 161.0704.

1-Ethylquinazolin-4(1*H*)-one (4b). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.54 (t, $J = 7.2$ Hz, 3 H, CH_2CH_3), 4.20 (q, $J = 7.2$ Hz, 2 H, CH_2CH_3), 7.38 (d, $J = 8.4$ Hz, 1 H, 8-H), 7.50 (t, $J = 7.8$ Hz, 1 H, 6-H), 7.76 (t, $J = 8.4$ Hz, 1 H, 7-H), 8.27 (s, 1 H, 2-H), 8.38 (d, $J = 7.8$ Hz, 1 H, 5-H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.6, 45.3, 114.5, 120.8, 126.4, 129.2, 133.8, 138.8, 152.7, 169.1. MS (EI): m/z 174 [M^+]. HRMS-ESI: m/z [M +H]$^+$ calcd. for $C_{10}H_{11}N_2O$: 175.0871; found: 175.0864.

1-Propylquinazolin-4(1*H*)-one (4c). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.04 (t, $J = 7.2$ Hz, 3 H, CH_2CH_3), 1.92 (m, 2H, $CH_2CH_2CH_3$), 4.09 (t, $J = 7.2$ Hz, 2 H, CH_2CH_2), 7.36 (d, $J = 8.4$ Hz, 1 H, 8-H), 7.49 (t, $J = 7.8$ Hz, 1 H, 6-H), 7.75 (t, $J = 8.4$ Hz, 1 H, 7-H), 8.23 (s, 1 H, 2-H), 8.38 (d, $J = 7.8$ Hz, 1 H, 5-H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 11.0, 22.0, 52.0, 114.7, 120.8, 126.4, 129.1, 133.8, 139.0, 153.1, 169.4. MS (EI): m/z 188 [M^+]. HRMS-ESI: m/z [M +H]$^+$ calcd. for $C_{11}H_{13}N_2O$: 189.1028; found: 189.1023.

1-Allylquinazolin-4(1*H*)-one (4d). ^{1}H NMR (600 MHz, $CDCl_3$): δ 4.75 (m, 2 H, NCH_2), 5.24 (d, $J = 17.4$ Hz, 1 H, =C*H*H), 5.38 (d, $J = 10.8$ Hz, 1 H, =CH*H*), 6.01 (m, 1 H, CH =), 7.33 (d, $J = 8.4$ Hz, 1 H, 8-H), 7.48 (t, $J = 7.8$ Hz, 1 H, 6-H), 7.72 (t, $J = 8.4$ Hz, 1 H, 7-H), 8.24 (s, 1 H, 2-H), 8.36 (d, $J = 7.8$ Hz, 1 H, 5-H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 52.2, 115.2, 119.6, 120.7, 126.5, 129.1, 130.5, 133.8, 139.2, 153.1, 169.3. MS (EI): m/z 186 [M^+]. HRMS-ESI: m/z [M +H]$^+$ calcd. for $C_{11}H_{11}N_2O$: 187.0871; found: 187.0868.

1-Benzylquinazolin-4(1*H*)-one (4e). ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.31 (s, 2 H, NCH_2), 7.22 (m, 3 H, Ar-H), 7.37 (m, 3 H, Ar-H), 7.46 (t, $J = 7.8$ Hz, 1 H, 6-H), 7.61 (t, $J = 7.8$ Hz, 1 H, 7-H), 8.37 (s, 1 H, 2-H), 8.39 (d, $J = 7.8$ Hz, 1 H, 5-H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 53.9, 115.5, 120.8, 126.2, 126.6, 128.8, 129.1, 129.5, 133.8, 133.9, 139.3, 153.5, 169.3. MS (ESI): m/z 237 [M +H]$^+$. HRMS-ESI: m/z [M +H]$^+$ calcd. for $C_{15}H_{13}N_2O$: 237.1028; found: 237.1022.

1,6-Dimethylquinazolin-4(1*H*)-one (4f). ^{1}H NMR (600 MHz, DMSO-d_6): δ 2.43 (s, 3 H, CH_3), 3.74 (s, 3H, CH_3), 7.52 (d, $J = 8.4$ Hz, 1 H, 8-H), 7.67 (d, $J = 8.4$ Hz, 1 H, 7-H), 7.88 (s, 1 H, 5-H), 8.43 (s, 1 H, 2-H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 23.7, 40.0, 119.1, 122.8, 129.8, 137.9, 138.8, 141.2, 156.9, 171.6. MS (ESI): m/z 175 [M +H]$^+$. Anal. calcd. for $C_{10}H_{10}N_2O \cdot 0.1H_2O$: C, 68.24; H, 5.84; N, 15.92. Found: C, 68.06; H, 5.83; N, 15.88.

1-Ethyl-6-methylquinazolin-4(1*H*)-one (4g). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.52 (t, $J = 7.2$ Hz, 3 H, CH_2CH_3), 2.46 (s, 3 H, CH_3), 4.19 (q, $J = 7.2$ Hz, 2 H, CH_2CH_3), 7.29 (d, $J = 8.6$ Hz, 1 H, 8-H), 7.56 (d, $J = 8.6$ Hz, 1 H, 7-H), 8.16 (s, 1 H, 5-H), 8.23 (s, 1 H, 2-H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.7, 21.0, 45.4, 114.5, 120.7, 128.6, 135.0, 136.6, 136.7, 152.2, 169.6. MS (EI): m/z 188 [M^+]. Anal. calcd. for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 69.93; H, 6.44; N, 14.87.

6-Methyl-1-propylquinazolin-4(1*H*)-one (4h). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.03 (t, $J = 7.2$ Hz, 3 H, CH_2CH_3), 1.90 (m, 2 H, $CH_2CH_2CH_3$), 2.47 (s, 3 H, CH_3), 4.06 (t, $J = 7.2$ Hz, 2 H, NCH_2CH_2), 7.26 (d, $J = 8.4$ Hz, 1 H, 8-H), 7.55 (d, $J = 8.6$ Hz, 1 H, 7-H), 8.18 (s, 2 H, 5-H and 2-H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 11.0, 21.0, 22.0, 51.9, 114.6, 120.6, 128.6, 134.9, 136.5, 136.9, 152.5, 169.5. MS (ESI): m/z 203 [M +H]$^+$. Anal. calcd. for $C_{12}H_{14}N_2O \cdot H_2O$: C, 65.43; H, 7.32; N, 12.72. Found: C, 65.60; H, 7.23; N, 12.50.

1-Allyl-6-methylquinazolin-4(1*H*)-one (4i). ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.46 (s, 3 H, CH_3), 4.71 (d, $J = 4.8$ Hz, 2 H, NCH_2CH), 5.22 (d, $J = 16.8$ Hz, 1 H, =C*H*H), 5.37 (d, $J = 10.8$ Hz, 1 H, =CH*H*), 5.99 (m, 1 H, CH =), 7.22 (d, $J = 8.4$ Hz, Hz, 1 H, 8-H), 7.53 (d, $J = 8.4$ Hz, 1 H, 7-H), 8.17 (s, 1 H, 5-H), 8.20 (s, 1 H, 2-H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 21.0, 52.2, 115.1, 119.4, 120.4, 128.4, 130.6, 135.0, 136.8, 137.1, 152.6, 169.5. MS (ESI): m/z 201 [M +H]$^+$. HRMS-ESI: m/z [M +H]$^+$ calcd. for $C_{12}H_{13}N_2O$: 201.1028; found: 201.1013.

1-Benzyl-6-methylquinazolin-4(1*H*)-one (4j). ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.42 (s, 3 H, CH_3), 5.30 (s, 2 H, NCH_2), 7.10-7.43 (m, 7 H, Ar-H), 8.17 (s, 1 H, 5-H), 8.36 (s, 1 H, 2-H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 21.0, 53.9, 115.5, 120.6, 126.2, 128.4, 128.6, 129.4, 134.1, 135.0, 136.8, 137.2, 153.0, 169.5. MS (ESI): m/z

251 $[M+H]^+$. Anal. calcd. for $C_{16}H_{14}N_2O \cdot 0.5H_2O$: C, 74.11; H, 5.83; N, 10.80. Found: C, 73.83; H, 5.93; N, 10.61.

6-Chloro-1-methylquinazolin-4(1*H*)-one (4k). ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.77 (s, 3 H, CH_3), 7.30 (d, $J = 9.0$ Hz, 1H, 8-H), 7.71 (dd, $J = 9.0$, 2.4 Hz, 1H, 7-H), 8.19 (s, 1 H, 2-H), 8.32 (d, $J = 2.4$ Hz, 1 H, 5-H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 37.5, 116.3, 121.5, 128.5, 132.6, 134.2, 138.4, 153.2, 168.2. MS (EI): m/z 194, 196 $[M^+]$. Anal. calcd. for $C_9H_7ClN_2O \cdot 0.4H_2O$: C, 53.56; H, 3.90; N, 13.88. Found: C, 53.95; H, 3.89; N, 13.52.

6-Chloro-1-ethylquinazolin-4(1*H*)-one (4l). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.53 (t, $J = 7.8$ Hz, 3 H, CH_2CH_3), 4.19 (q, $J = 7.8$ Hz, 2 H, CH_2CH_3), 7.33 (d, $J = 9.0$ Hz, 1H, 8-H), 7.71 (dd, $J = 9.0$, 2.4 Hz, 1 H, 7-H), 8.23 (s, 1 H, 2-H), 8.34 (d, $J = 2.4$ Hz, 1 H, 5-H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.6, 45.5, 116.3, 121.9, 128.7, 132.3, 134.2, 137.3, 152.7, 168.2. MS (EI): m/z 208, 210 $[M^+]$. Anal. calcd. for $C_{10}H_9ClN_2O$: C, 57.57; H, 4.35; N, 13.43. Found: C, 57.61; H, 4.43; N, 13.03.

6-Chloro-1-propylquinazolin-4(1*H*)-one (4m). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.05 (t, $J = 7.2$ Hz, 3 H, CH_2CH_3), 1.91 (m, 2 H, CH_2CH_3), 4.10 (t, $J = 7.2$ Hz, 2 H, CH_2CH_2), 7.32 (d, $J = 9.0$ Hz, 1 H, 8-H), 7.70 (dd, $J = 9.0$, 2.4 Hz, 1 H, 7-H), 8.32 (s, 1 H, 2-H), 8.36 (d, $J = 2.4$ Hz, 1 H, 5-H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 11.0, 22.0, 52.1, 116.5, 121.8, 128.6, 132.3, 134.1, 137.5, 153.1, 168.3. MS (EI): m/z 222, 224 $[M^+]$. Anal. calcd. for $C_{11}H_{11}ClN_2O$: C, 59.33; H, 4.98; N, 12.58. Found: C, 59.29; H, 5.00; N, 12.36.

1-Allyl-6-chloroquinazolin-4(1*H*)-one (4n). ^{1}H NMR (600 MHz, $CDCl_3$): δ 4.77 (d, $J = 4.8$ Hz, 2 H, NCH_2CH), 5.24 (d, $J = 17.4$ Hz, 1 H, $=CHH$), 5.40 (d, $J = 10.2$ Hz, 1 H, $=CHH$), 6.00 (m, 1 H, $CH=$), 7.31 (d, $J = 9.0$ Hz, 1 H, 8-H), 7.65 (dd, $J = 9.0$, 1.8 Hz, 1 H, 7-H), 8.24 (d, $J = 1.8$ Hz, 1 H, 5-H), 8.26 (s, 1 H, 2-H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 52.4, 117.3, 119.8, 121.5, 128.2, 130.2, 132.4, 134.1, 137.6, 153.3, 168.2. MS (EI): m/z 220, 222 $[M^+]$. HRMS-ESI: m/z $[M+H]^+$ calcd. for $C_{11}H_{10}ClN_2O$: 221.0482; found: 221.0470.

1-Benzyl-6-chloroquinazolin-4(1*H*)-one (4o). ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.32 (s, 2 H, CH_2Ph), 7.19 (m, 3 H, Ar-H), 7.38 (m, 3 H, Ar-H), 7.55 (dd, $J = 9.0$, 2.4 Hz, 1 H, 7-H), 8.35 (d, $J = 2.4$ Hz, 1 H, 5-H), 8.45 (s, 1 H, 2-H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 54.1, 117.4, 121.8, 126.2, 128.4, 128.9, 129.5, 132.5, 133.5, 134.2, 137.7, 153.6, 168.1. MS (EI): m/z 270, 272 $[M^+]$. Anal. calcd. for $C_{15}H_{11}ClN_2O \cdot 0.2H_2O$: C, 65.68; H, 4.19; N, 10.21. Found: C, 65.81; H, 4.12; N, 9.96.

6-Fluoro-1-methylquinazolin-4(1*H*)-one (4p). ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.78 (s, 3 H, CH_3), 7.36 (dd, $J = 9.0$, 3.6 Hz, 1 H, 8-H), 7.51 (m, 1 H, 7-H), 8.02 (dd, $J = 8.4$, 3.0 Hz, 1 H, 5-H), 8.19 (s, 1 H, 2-H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 37.6, 114.4 (d, $J = 23.0$ Hz), 117.0 (d, $J = 7.8$ Hz), 122.1 (d, $J = 6.6$ Hz), 122.3 (d, $J = 24.6$ Hz), 136.4, 153.0, 160.6 (d, $J = 247.5$ Hz), 168.7. MS (EI): m/z 178 $[M^+]$. Anal. calcd. for $C_9H_7FN_2O \cdot 0.6H_2O$: C, 57.20; H, 4.37; N, 14.82. Found: C, 57.09; H, 4.39; N, 14.78.

1-Ethyl-6-fluoroquinazolin-4(1*H*)-one (4q). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.54 (t, $J = 7.2$ Hz, 3 H, CH_2CH_3), 4.21 (q, $J = 7.2$ Hz, 2 H, CH_2CH_3), 7.40 (dd, $J = 9.0$, 4.2 Hz, 1 H, 8-H), 7.49 (m, 1 H, 7-H), 8.04 (dd, $J = 7.8$, 3.0 Hz, 1 H, 5-H), 8.29 (s, 1 H, 2-H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.6, 45.6, 114.4 (d, $J = 23.0$ Hz), 116.9 (d, $J = 7.8$ Hz), 122.2 (d, $J = 24.6$ Hz), 122.6 (d, $J = 7.4$ Hz), 152.4, 135.3, 160.4 (d, $J = 245.9$ Hz), 168.7. MS (EI): m/z 192 [M^+]. Anal. calcd. for $C_{10}H_9FN_2O$: C, 62.49; H, 4.72; N, 14.58. Found: C, 62.67; H, 4.80; N, 14.57.

6-Fluoro-1-propylquinazolin-4(1*H*)-one (4r). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.05 (t, $J = 7.2$ Hz, 3 H, CH_2CH_3), 1.91 (m, 2 H, $CH_2CH_2CH_3$), 4.10 (t, $J = 7.2$ Hz, 2 H, CH_2CH_2), 7.38 (dd, $J = 9.6$, 4.2 Hz, 1 H, 8-H), 7.48 (m, 1 H, 7-H), 8.02 (dd, $J = 7.8$, 3.0 Hz, 1 H, 5-H), 8.22 (s, 1 H, 2-H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 11.0, 22.1, 52.2, 114.2 (d, $J = 23.0$ Hz), 117.1 (d, $J = 7.8$ Hz), 122.2 (d, $J = 24.6$ Hz), 122.5 (d, $J = 6.6$ Hz), 135.5, 152.8, 160.4 (d, $J = 247.5$ Hz), 168.7. MS (EI): m/z 206 [M^+]. Anal. calcd. for $C_{11}H_{11}FN_2O$: C, 64.07; H, 5.38; N, 13.58. Found: C, 64.16; H, 5.32; N, 13.55.

1-Allyl-6-fluoroquinazolin-4(1*H*)-one (4s). ^{1}H NMR (600 MHz, $CDCl_3$): δ 4.74 (d, $J = 4.8$ Hz, 2 H, NCH_2CH), 5.25 (d, $J = 17.4$ Hz, 1 H, =C*H*H), 5.41 (d, $J = 10.2$ Hz, 1 H, =CH*H*), 6.00 (m, 1 H, CH=), 7.35 (dd, $J = 9.6$, 4.2 Hz, 1 H, 8-H), 7.45 (m, 1 H, 7-H), 8.03 (dd, $J = 7.8$, 3.0 Hz, 1 H, 5-H), 8.26 (s, 1 H, 2-H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 52.5, 114.1 (d, $J = 22.8$ Hz), 117.7 (d, $J = 7.8$ Hz), 119.8, 122.1 (d, $J = 24.6$ Hz), 122.3, 130.3, 135.7, 152.9, 160.4 (d, $J = 248.3$ Hz), 168.7. MS (EI): m/z 204 [M^+]. HRMS-ESI: m/z [M +H]$^+$ calcd. for $C_{11}H_{10}FN_2O$: 205.0777; found: 205.0763.

1-Benzyl-6-fluoroquinazolin-4(1*H*)-one (4t). ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.35 (s, 2 H, NCH_2), 7.20 (d, $J = 7.2$ Hz, 2 H, Ar-H), 7.25 (dd, $J = 9.6$, 4.2 Hz, 1 H, 8-H), 7.31–7.40 (m, 4 H, Ar-H), 7.96 (dd, $J = 7.8$, 3.0 Hz, 1 H, 5-H), 8.37 (s, 1 H, 2-H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 54.2, 114.0 (d, $J = 22.8$ Hz), 118.1 (d, $J = 7.4$ Hz), 122.2 (d, $J = 24.6$ Hz), 122.4 (d, $J = 7.2$ Hz), 126.2, 128.9, 129.5, 133.6, 135.7, 153.3, 160.4 (d, $J = 248.3$ Hz), 168.7. MS (EI): m/z 254 [M^+]. Anal. calcd. for $C_{15}H_{11}FN_2O \cdot 0.5H_2O$: C, 68.43; H, 4.59; N, 10.64. Found: C, 68.52; H, 4.57; N, 10.35.

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