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Graphical Abstract

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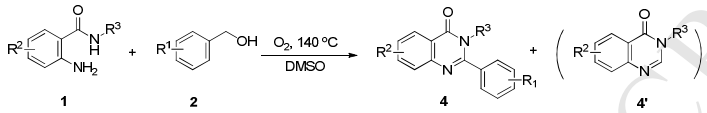

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Mechanistic insights into a catalyst-free method to construct quinazolinones through multiple oxidative cyclization

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ABSTRACT

A novel one-pot benign oxidative cyclization of alcohols with 2-aminobenzamides was successfully developed without catalyst to afford the quinazolinones under O_2. This one-pot protocol involved oxidations and cyclizations to construct the skeleton of quinazolinones through possibly three kinds of distinct reaction mechanisms.

1. Introduction

Quinazolinone and its derivatives widely exist in plants, animals and microorganisms, showing diverse range of biological and pharmacological properties. For example, they exhibit anticancer, anti-inflammatory, anticonvulsant, antimalarial, antihypertensive, antituberculous and diuretic activities.[1] Futhermore, numerous clinical drugs consist of the quinazolinone core (Fig. 1), including Mecloqualone[2] which was famous for its useful insomnia resistant effect, Nolatrexed[3] as a thymidylate synthase inhibitor for the treatment of cancer and Cloroqualone[4] which was used for cancer as well.

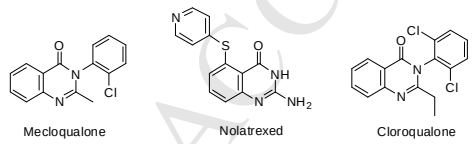

Figure 1. Representative quinazolinones in clinical drugs.

In view of the significant potential application, there have been various methods to build the quinazolinone skeleton via oxidation in the past few years (Fig. 2).[5] However, the one-pot and environment-friendly synthesis of quinazolinone continues to be one of the major challenges in synthetic organic chemistry. In previous work, the 4(3*H*)–quinazolinone could be prepared through one pot reaction from 2-aminobenzamide and benzaldehyde under the effect of MnO_2,[6] I_2,[7] DDQ,[8] PIDA,[9] $KMnO_4$,[10] Cu(II),[11] $FeCl_3$,[12] DMSO[13] or using 2-aminobenzamide with benzyl alcohol under the influence of metal catalyst including zinc,[14] iridium,[15] ruthenium,[16] platnium,[17] or palladium.[18]

Herein, developing green oxidative methods have drawn extensive and enduring attention in the last few decades. There are already some reports using O_2 for the synthesis of quinazolinones without catalysts under mild conditions.[19] Here we developed a four-step oxidative cyclization using O_2 without any other additives to generate a series of quinazolinone compounds from 2-aminobenzamide with benzyl alcohol. Furthermore, it is amazing for us to find three kinds of possibly distinct reaction mechanisms from the same substrate.

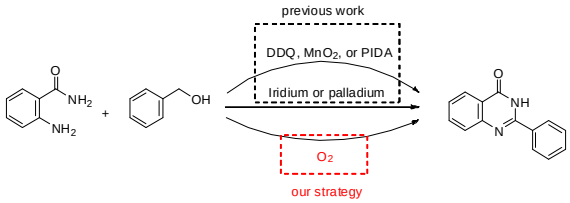

Figure 2. Methods for the synthesis of Quinazolinones

2. Results and discussion

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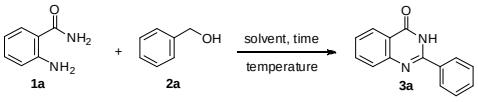
In the beginning, 2-aminobenzamide and benzyl alcohol were used as the model reaction to test the possibility of four-step oxidative cyclization under O_2 in DMSO. Not surprisingly, **3a** was detected as the main product after the reaction was complete.

Table 1. Optimization of reaction conditions[a]

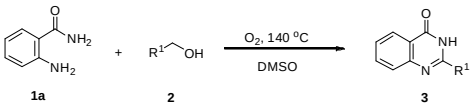


Entry	Solvent	Temperature (^{o}C)	Ambient	Time (h)	Yield[b] (%)
1	DMF	140	O_2	8	10
2	NMP	140	O_2	8	77
3	H_2O	Refluxing	O_2	8	Trace
4	DMSO	140	O_2	4	82
5	DMSO	140	Air	4	72
6	DMSO	140	N_2	4	Trace
7	DMSO	120	O_2	4	25
8	DMSO	160	Air	4	62
9	DMSO	160	O_2	4	80

[a]Reaction condition: 2-aminobenzamide (**1a**) (0.5mmol), benzyl alcohol (**2a**) (2mmol), solvent (1ml);

[b]Yield of isolated product;

Table 2. Substrate scope for 2-substituted quinazolinones **3**[a]



Entry	R^1	Time (h)	Yield (%)[c]
1	Ph (**a**)	4	82
2	2-Me-C_6H_4 (**b**)	8	68
3	4-Me-C_6H_4 (**c**)	8	83
4	4-MeO-C_6H_4 (**d**)	8	65
5	2-OH-C_6H_4 (**e**)	8	50
6[b]	2-Cl-C_6H_4 (**f**)	4	59
7[b]	4-Cl-C_6H_4 (**g**)	6	79
8[b]	4-NO_2-C_6H_4 (**h**)	7	14
9[b]	2-Br-C_6H_4 (**i**)	5	27 (8%)[d]
10	4-Br-C_6H_4 (**j**)	8	67
11[b]	2-Pyridyl (**k**)	6	51
12[e]	2-Furyl (**l**)	20	Nd[e]

[a]Reaction condition: 2-aminobenzamide (**1a**) (0.5mmol), alcohol (**2**) (2mmol), DMSO (1mL);

[b]The reaction temperature was 160 ^{o}C;

[c]Isolated yield of product **3**;

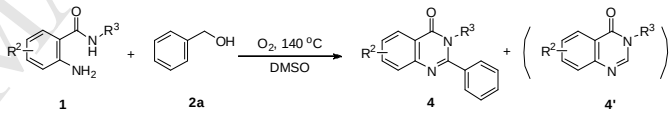
[d]Isolated yield of debrominated product **3a**;

[e] Temperature was attempted from 100 ^{o}C to 160 ^{o}C.

Our initial work focused on optimizing the reaction conditions. As shown in Table 1, 2-aminobenzamide and benzyl alcohol was smoothly converted into 2-phenyl-4(*3H*)-quinazolinone in 82% yield under O_2 in DMSO at 140 ^{o}C after 4 h (Table 1, entry 4). A lower yield was obtained when the solvent was NMP (Table 1, entry 2). However, when DMF was used as the solvent, the yield was only 10 %. (Table 1, entry 1) and trace product was obtained in water. It also gave dissatisfactory results when we used the air balloon instead of oxygen balloon. No desired product was detected when the reaction was carried out under N_2, which also demonstrated the importance of O_2 in this protocol. Besides, the attempt to optimize the reaction was unsuccessful by increasing or decreasing the temperature. Judging by the yield of the desired product, the entry 4 in table 1 was concluded as the best condition.

With an optimized procedure in hand, we next investigated the reactions with various primary alcohols in the presence of O_2. The variation of alcohol derivatives did not affect the efficiency of this protocol, and the corresponding results were summarized in Table 2. By treating 2-aminobenzamide **1a** with substituted benzyl alcohol (**2a**-**2k**), bearing electron-donating groups, the desired products **3a**-**3j** were conveniently obtained in moderate to good yields (entries 2-5). The reactions with substrates of electron-poor groups were carried out at a much higher temperature 160 ^{o}C, but the yield was relatively low (entry 8). The halogen substituents such as chloro and bromo groups afforded the corresponding products in acceptable to good yields (entries 6, 7and 10). The debrominated product was obtained when the reaction was run at high temperature (entry 9). This phenomenon was also observed with the 2-(hydroxymethyl)-pyridine in 51% yield (entry 11). However, furyl alcohol was not applicable to this condition with a wide range of temperature from 100 to 160 ^{o}C (entry 12).

Table 3. Synthesis of 2,4-disubstituted quinazolinones **4**[a]



Entry	R^2	R^3	Time (h)	Yield (%) [c]
1	H	CH_3 (**b**)	8	67
2	H	CH_2CH_3(**c**)	6	68
3[b]	H	CH_2Ph (**d**)	9	13 (37%)[d]
4	H	Ph (**e**)	6	75
5	4-NO_2	H (**f**)	4	29
6	4-F	H (**g**)	10	80
7	4-F	CH_3(**h**)	10	73 (6%)[d]
8[b]	4-F	CH_2CH_3(**i**)	9	40 (18%)[d]
9	5-CH_3	H (**j**)	6	76
10	5-CH_3	CH_3 (**k**)	7	58
11[b]	5-CH_3	Ph (**l**)	4	15 (39%)[d]
12	6-Cl	H (**m**)	4	70

[a]Reaction condition: 2-aminobenzamide (**1a**) (0.5mmol), alcohol (**2**) (2mmol), DMSO (1mL);

[b]The reaction temperature was 160 ^{o}C;

[c]Isolated yield of product **4**;

[d]Isolated yield of product **4'**;

To further investigate the substrate scope, a series of 2-aminobenzamide substrates were used in the reaction (Table 3), including electron-rich (Table 3, entries 1, 2, 7, 8 and 10) and electron-deficient ones (Table 3, entry 5). They were useful substrates for this reaction and gave the corresponding products in low to good yield. However, the

substrates with a bulky group such as ethyl, phenyl and benzyl were more likely to form the byproducts **4'** (Table 3, entries 3, 8, 11) than the ones with a small group such as methyl (Table 3, entry 7). Notably, DMSO was an efficient carbon source, which had been reported by Zhao[20]. Based on these related research, we hypothesized that nucleophilic attack and a sequential C–S bond cleavage were involved. Then the following redox process occurred similarly to those in Figure 4. The fluorine and chlorine substituted substrates were also applied to the synthesis of quinazolinones with good yields (Table 3, entries 6, 12). Moreover, the condition was tolerated the dual substitution in phenyl group and nitrogen atom (Table 3, entries 7, 8, 10 and 11).

The intermediate 2-(benzylamino)benzamide **5a** (9%) and the desired product 2-phenyl-4(3*H*)-quinazolinone **3a** (63%) were obtained at 160 °C under the air after 2 h (Fig. 3, a). Moreover, **5a** could be transformed into the final product **3a** if the reaction time was prolonged or the reaction was run under the optimized condition. Since we knew that the benzyl alcohol could be easily converted to benzaldehyde, it's confuseing to find the generation of **5a** in the reaction. These experimental results prompted us to further explore the mechanism.

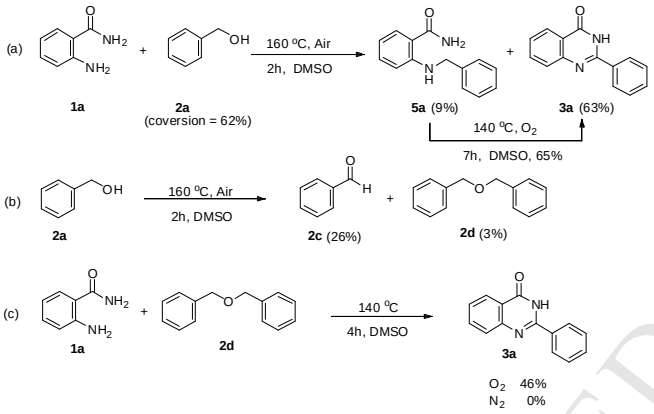


Figure 3. The blank and control experiments for the mechanism.

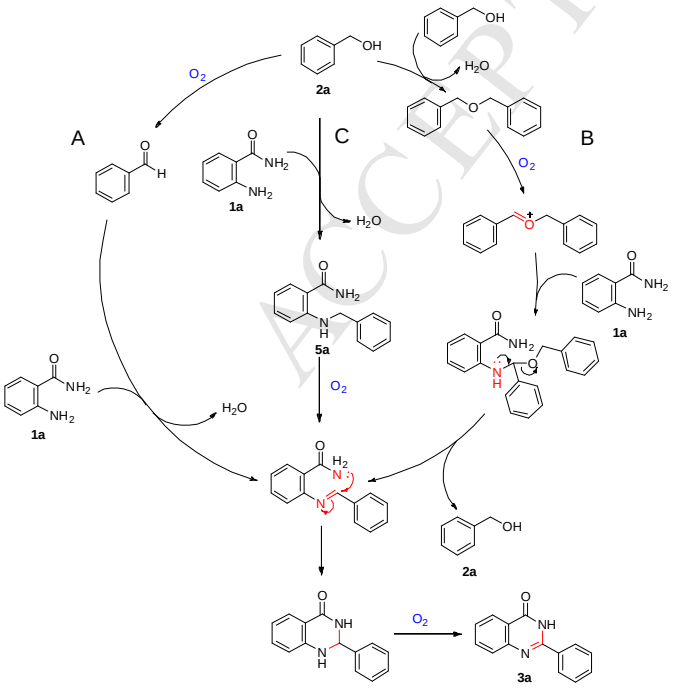


Figure 4. The plausible mechanisms.

To elucidate the proposed mechanism, a series of background experiments were firstly performed. By treating benzyl alcohol **2a** under the established conditions (160 °C, air, DMSO) without the addition of 2-aminobenzamide, 26% of benzaldehyde **2c** and 3% of benzyl ether **2d** were formed (Fig. 3, b). Therefore we speculated that intermediate **5a** was probably obtained from reaction of **1a** with benzyl alcohol **2a** or benzyl ether **2d**. However, **5a** was not detected either under the O_2 or under air conditions when **1a** reacted with **2d**, which proved that intermediate **5a** was not constructed from benzyl ether **2d**. Delightfully, 46% of **3a** was generated when **1a** reacted with **2d** under the optimized conditions (Fig. 3, c). Besides, the substrate was stable when the reaction was carried out under the protection of nitrogen. Based on the above results, it was concluded that 2-(benzylamino)benzamide **5a** was generated from reaction of 2-aminobenzamide **1a** and benzyl alcohol **2a** through nucleophilic substitution.

Based on the above results, we proposed three kinds of possibly mechanisms in the reaction (Fig. 4, A, B and C). In the pathway A, the alcohol was first oxidized under O_2 to form the corresponding aldehyde which reacted with 2-aminobenzamide to generate the imine. Then the nitrogen atom of the amine attacked the imine to construct the dihydrogenated quinazolinone, which was oxidized once again to build the quinazolinone under the effect of O_2 (Fig. 4, A). At the same time, a slight amount of dibenzyl ether was also obtained and transformed to the imine by treatment with 2-aminobenzamide (Fig. 4, B). Specifically, the benzyl ether cation was generated under the effect of O_2, which could be attacked by the amine to form the intermediate. Elimination of the intermediate gave the imine, which was converted to the final product on the same theory. We also detected the intermediate **5a** formed through nucleophilic substitution when the reaction was carried out in the air (Fig. 4, C). Then the **5a** was oxidized to construct the imine and the imine was transformed to the desired product through two steps. The reason why we could not find the intermediate **5a** in the O_2 was that **5a** might easily be converted to the desired product **3a** once it was generated.

3. Conclusion

In summary, we have developed a tandem sequence oxidation and cyclization to construct quinazolinones skeleton using green oxidant O_2 without any other additives. The method has proved to apply to a broad scope of substrates and to afford the final 4(*3H*)-quinazolinones via a novel one-pot, catalyst-free and environment-friendly transformation from 2-aminobenzamide and primary alcohol in satisfactory to good yields.

4. Experimental section

4.1. General information

All reactions were performed under oxygen atmosphere and stirred magnetically in standard glassware heated at 70 °C for 3h before use. Reagents and solvents were purchased as reagent grade and without further purification. ^{1}H and ^{13}C NMR spectra were recorded on a 600 or 400 MHz BRUKER AVANCE spectrometer at 25 °C. Chemical shifts values are given in ppm with TMS as the internal standard. The peak patterns are defined as follows: s, singlet; d, doublet; t, triplet; q, quartet; qui, quintet; m, multiplet; dd, doublet of doublets; td, triplet of doublets and brs, broad singlet. The coupling constants J, are reported in Hertz

(Hz). Flash column chromatography was performed over silica gel (200–300 mesh) using a mixture of petroleum ether (PE) and ethyl acetate (EtOAc) or a mixture of petroleum ether and tetrahydrofuran (THF) as the eluent. TLC plates (Silica gel GF254) were visualized by exposure to ultraviolet light. Mass spectrum was obtained on Agilent 6310 Ion Trap and HP5989A mass spectrometer. High resolution mass spectrometry (HRMS) was obtained on a Q-TOF micro (BRUKER) spectrometer. Melting points were determined with a national Micro Melting point apparatus without corrections. Organic solutions were concentrated by rotary evaporation below 40 °C in vacuum.

4.2. Synthesis of the N-substituted 2-aminobenzamide 1b-m

To a solution of 2-amino-5-methylbenzamide (1.5 g, 10mmol) in THF (20 mL) was added triphosgene (0.99g , 3.3mmol) portionwise about 20 min. The mixture was cooled to r.t. when the reaction was completed. Through filtration, the crude isatoic anhydride was got. A stirred solution of isatoic anhydride was suspending in THF which was heated to 60°C, then the solution of amine was added dropwise. Progress of the reaction was monitored using TLC. After completion of the reaction, the resulting solution was cooled to room temperature and the solvent was removed under high vacuum to give the crude product. Then recrystallization from Et_2O afforded the pure product.

4.2.1 2-amino-N-methylbenzamide ***(1b)***: Orange solid; mp: 79-80 °C; R_f = 0.22 (40% ethyl acetate in petroleum ether); ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 2.96 (d, 3H, *J* = 4.8 Hz), 5.50 (brs, 2H), 6.10 (brs, 1H), 6.63 (t, 1H, *J* = 7.5 Hz), 6.67 (d, 1H, *J* = 8.2 Hz), 7.19 (t, 1H, *J* = 7.7 Hz), 7.29 (d, 1H, *J* = 7.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 26.5, 116.3, 116.6, 117.2, 127.3, 132.1, 148.5, 170.1; mass spectrum(ESI): *m/e* (% relative intensity) 173.4 (100) $(M+Na)^+$.

4.2.2 2-amino-N-ethylbenzamide ***(1c)***: White solid; mp: 97-100 oC; Rf = 0.52 (40% ethyl acetate in petroleum ether); 1H NMR (600 MHz, CDCl3) δ (ppm): 1.19 (t, 3H, J = 7.3 Hz), 3.35-3.43 (m, 2H), 5.36 (brs, 2H), 6.45 (brs, 1H), 6.60 (t, 1H, J = 7.5 Hz), 6.65 (d, 1H, J = 8.1 Hz), 7.10-7.22 (m, 1H), 7.31 (d, 1H, J = 7.8 Hz); 13C NMR (150 MHz, CDCl3) δ (ppm): 14.8, 34.5, 116.5, 117.2, 127.3, 132.0, 148.5, 169.4; mass spectrum (ESI): m/e (% relative intensity) 187.7 (100) (M+Na)+.

4.2.3 2-amino-N-benzylbenzamide ***(1d)***: Pale yellow solid; mp: 123-125 °C; R_f = 0.65 (40% ethyl acetate in petroleum ether); ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 4.60 (d, *J* = 5.6 Hz, 2H), 5.59 (brs, 2H), 6.34 (brs, 1H), 6.62 (t, 1H, *J* = 7.5 Hz), 6.69 (d, 1H, *J* = 8.2 Hz), 7.20 (t, 1H, J = 7.5 Hz), 7.27-7.38 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 43.7, 115.9, 116.6, 117.3, 127.3, 127.5, 127.8, 128.8, 132.4, 138.4, 148.9, 169.3; mass spectrum (ESI): *m/e* (% relative intensity) 249.8 (100) $(M+Na)^+$.

4.2.4 2-amino-N-phenylbenzamide ***(1e)***: White solid; mp: 130-131 °C; R_f = 0.56 (20% ethyl acetate in petroleum ether); ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 5.51 (brs, 2H), 6.69-6.72 (m, 2H), 7.14 (t, 1H, *J* = 7.4 Hz), 7.25(t, 1 H, *J* = 8.0 Hz), 7.36 (t, 2H, *J* = 7.9 Hz), 7.46 (d, 1H, *J* = 7.2 Hz), 7.56 (d, 2H, *J* = 7.8 Hz), 7.76 (brs, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 116.4, 116.9, 117.6, 120.7, 124.5, 127.3, 129.0, 132.7, 137.9, 148.9, 167.6; mass spectrum (ESI): *m/e* (% relative intensity) 235.7 (100) $(M+Na)^+$.

4.2.5 2-amino-4-nitrobenzamide ***(1f)***: Yellow solid; mp: 218-220 °C; R_f = 0.31 (40% ethyl acetate in petroleum ether); ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 7.02 (s, 2H), 7.25 (dd, 1H, *J* = 2.2, 8.6 Hz), 7.47 (brs, 1H), 7.57 (d, 1H, *J* = 2.2 Hz) , 7.73 (d, 1H, *J* = 8.6 Hz), 8.04 (brs, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 107.9, 110.1, 118.7, 130.2, 149.5, 150.6, 169.6; mass spectrum (ESI): *m/e* (% relative intensity) 179.8 (100) $(M-H)^-$.

4.2.6 2-amino-4-fluorobenzamide ***(1g)***: White solid; mp: 130-133 °C; R_f = 0.38 (40% ethyl acetate in petroleum ether); ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 6.28 (td, 1H, *J* = 2.6, 8.6 Hz), 6.44 (dd, 1H, *J* =2.6, 11.9 Hz), 6.90 (s, 2H), 7.08 (brs, 1H), 7.60 (dd, 1H, *J* = 6.7, 8.8 Hz), 7.73 (brs, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 101.3 (dd, *J* = 5.8, 20.8 Hz), 101.4 (dd, *J* = 3.3, 19.1 Hz), 110.3, 131.3 (dd, *J* = 3.2, 11.4 Hz), 152.6 (d, *J* = 12.6 Hz), 164.46 (d, *J* = 245.1 Hz), 170.4; ^{19}F NMR (376 MHz, CDCl3) δ (ppm): -106.9 – -107.0 (m, 1F); mass spectrum (ESI): m/e (% relative intensity) 177.4 (100) $(M+Na)^+$.

4.2.7 2-amino-4-fluoro-N-methylbenzamide ***(1h)***: White solid; mp: 72-74 °C; R_f = 0.46 (40% ethyl acetate in petroleum ether); ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 2.72 (d, 3H, *J* = 4.5 Hz), 6.31 (td, 1H, *J* = 2.7, 8.6 Hz), 6.46 (dd, 1H, *J* = 2.6, 11.9 Hz), 6.75 (brs, 2H), 7.51 (dd, 1H, *J* = 6.8, 8.6 Hz), 8.17 (d, 1H, *J* = 3.5 Hz); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 25.9 (d, *J* = 7.5 Hz), 101.3 (dd, *J* = 6.2, 22.4 Hz), 101.5 (dd, *J* = 5.0, 22.6 Hz), 111.4, 130.4(dd, *J* = 3.0, 11.3 Hz), 152.0 (d, *J* = 12.6 Hz), 164.3 (d, *J* = 244.9 Hz), 168.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): -108.3 – -108.4 (m, 1F); mass spectrum (ESI): *m/e* (% relative intensity) 191.4 (100) $(M+Na)^+$.

4.2.8 2-amino-4-fluoro-N-ethylbenzamide ***(1i)***: White solid; mp: 78-82 °C; R_f = 0.49 (40% ethyl acetate in petroleum ether); ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 1.11 (t, 3H, *J* = 7.2 Hz), 3.18-3.30 (m, 2H), 6.31 (td, 1H, *J* = 2.7, 8.6 Hz), 6.46 (dd, 1H, *J* = 2.6, 11.9 Hz), 6.75 (brs, 2H), 7.52-7.56 (m, 1H), 8.20 (brs, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 14.7 (d, *J* = 2.9 Hz), 33.6, 101.3 (dd, *J* = 6.4, 20.9 Hz), 101.5 (dd, *J* = 5.0, 19.2 Hz), 111.6, 130.5 (dd, *J* = 3.2, 11.1 Hz), 152.0 (d, *J* = 12.4 Hz), 164.3 (d, *J* = 245.0 Hz), 167.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): -108.3 – -108.5 (m, 1F); mass spectrum (ESI): *m/e* (% relative intensity) 205.6 (100) $(M+Na)^+$.

4.2.9 2-amino-5-methylbenzamide ***(1j)***: White solid; mp: 173-175 °C; R_f = 0.29 (40% ethyl acetate in petroleum ether); ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 2.15 (s, 3H), 6.33 (brs, 2H), 6.60 (d, 1H, *J* = 8.3 Hz), 6.96 (d, 1H, *J* = 8.1 Hz), 7.02 (brs, 1H), 7.36 (s, 1H), 7.68 (brs, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 20.0, 113.7, 116.5, 122.7, 128.6, 132.7, 147.8, 171.3; mass spectrum (ESI): *m/e* (% relative intensity) 173.4 (100) $(M+Na)^+$.

4.2.10 2-amino-N, 5-dimethylbenzamide ***(1k)***: White solid; mp: 122-124 °C; R_f = 0.34 (40% ethyl acetate in petroleum ether); ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 2.15 (s, 3H), 2.71 (d, 3H, *J* = 3.8 Hz), 6.17 (brs, 2H), 6.60 (d, 1H, *J* = 8.1 Hz), 6.95 (d, 1H, *J* = 7.8 Hz), 7.27 (s, 1H), 8.12 (brs, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 20.0, 25.9, 114.8, 116.4, 122.9, 127.9, 132.3, 147.1, 169.3. mass spectrum (ESI): *m/e* (% relative intensity) 187.4 (100) $(M+Na)^+$.

4.2.11 2-amino-5-methyl-N-phenylbenzamide ***(1l)***: White solid; mp: 160-162 °C; R_f = 0.74 (20% ethyl acetate in petroleum ether); ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 2.22 (s, 3H), 6.11 (brs, 2H), 6.69 (d, 1H, *J* = 8.2 Hz), 7.03 (d, 1H, *J* = 8.1 Hz), 7.07 (t, 1H, *J* = 7.2 Hz) , 7.33 (t, 2H, *J* = 7.6 Hz), 7.45 (s, 1H), 7.73 (d, 2H, *J* = 7.9 Hz), 10.0 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 20.0, 115.4, 116.5, 120.4, 123.1, 123.3, 128.4, 128.5, 132.9, 139.3, 147.4, 167.9. mass spectrum (ESI): *m/e* (% relative intensity) 249.8 (100) $(M+Na)^+$.

4.2.12 2-amino-6-chlorobenzamide ***(1m)***: White solid; mp: 132-134 °C; R_f = 0.28 (40% ethyl acetate in petroleum ether); ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 5.22 (brs, 2H), 6.57 (d, 1H, *J* = 7.8 Hz), 6.63 (d, 1H, *J* = 8.2 Hz), 7.01 (t, 1H, *J* = 8.0

Hz), 7.60 (brs, 1H), 7.82 (brs, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 113.6, 116.1, 121.6, 129.8, 130.0, 147.0, 167.6; mass spectrum (ESI): *m/e* (% relative intensity) 193.6 (100) $(M+Na)^+$.

4.3. Synthesis of 2-substituted-4(*3H*)-quinazolinones: 3a–k

2-aminobenzamide (1a) (0.5 mmol) and alcohol (2) (2 mmol) were added to an oven-dried glassware with DMSO (1 mL). Then the system was degassed and filled with oxygen. The reaction mixture was stirred and heated to 140 oC. Progress of the reaction was monitored by TLC. After completion of the reaction, the resulting solution was cooled to room temperature, and diluted with dichloromethane, washed with water and brine, dried over anhydrous Na2SO4 and concentrated with the aid of a rotary evaporator. The residue was purified by column chromatography on silica gel using petroleum ether/tetrahydrofuran (5:1 to 2:1) as eluent to provide the desired product.

4.3.1 2-phenyl-4(3H)-quinazolinone ***(3a)***: White solid; mp: 239-241^{o}C; R_f = 0.52 (40% ethyl acetate in petroleum ether); ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.52 (dt, 1H, *J* = 1.2 Hz, 7.8 Hz), 7.57-7.63 (m, 3H), 7.82 (dt, 1H, *J* = 1.2 Hz, 7.2 Hz), 7.87 (d, 1H, *J* = 8.1 Hz), 8.25 (dd, 2H, *J* = 2.9, 6.7 Hz), 8.33 (dd, 1H, *J* = 1.2, 7.8 Hz), 11.46 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 120.8, 126.4, 126.8, 127.5, 128.0, 129.1, 131.7, 132.7, 134.9, 149.4, 151.8, 163.8; mass spectrum (ESI): *m/e* (% relative intensity) 223.4 (100) $(M+H)^+$.

4.3.2 2-(2-methylphenyl)-4(3H)-quinazolinone ***(3b)***: White solid; mp: 215-217 ^{o}C; R_f = 0.56 (40% ethyl acetate in petroleum ether); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.40 (s, 3H), 7.30-7.34 (m, 2H), 7.43 (t, 1H, *J* = 6.8 Hz), 7.49-7.59 (m, 2H), 7.70 (d, 1H, *J* = 8.0 Hz), 7.85 (t, 1H, *J* = 7.6 Hz), 8.19 (d, 1H, *J* = 7.1 Hz), 12.47 (brs, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 19.6, 121.0, 125.7, 125.8, 126.6, 127.4, 129.1, 129.9, 130.5, 134.2, 134.5, 136.1, 148.7, 154.4, 161.8; mass spectrum (ESI): *m/e* (% relative intensity) 258.8 (100) $(M+Na)^+$.

4.3.3 2-(4-methylphenyl)-4(3H)-quinazolinone ***(3c)***: White solid; mp: 236-239 ^{o}C; R_f = 0.71 (40% ethyl acetate in petroleum ether); ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 2.46 (s, 3H), 7.38 (d, 2H, *J* = 7.9 Hz), 7.50 (t, 1H, *J* = 7.4 Hz), 7.80 (t, 1H, *J* = 7.5 Hz), 7.84 (d, 1H, *J* = 7.9 Hz), 8.16 (d, 2H, *J* = 8.0 Hz), 8.32 (d, 1H, *J* = 7.8 Hz), 11.71 (brs, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 21.6, 120.7, 126.4, 126.6, 127.4, 127.8, 129.8, 134.9, 142.3, 149.5, 151.9, 163.9; mass spectrum (ESI): *m/e* (% relative intensity) 236.6 (100) $(M+H)^+$.

4.3.4 2-(4-methoxyphenyl)-4(3H)-quinazolinone ***(3d)***: Pale-yellow solid; mp: 245-248 ^{o}C; R_f = 0.36 (40% ethyl acetate in petroleum ether); ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 3.86 (s, 3H), 7.09 (d, 2H, *J* = 8.9 Hz), 7.49 (t, 1H, *J* = 8.0 Hz), 7.71 (d, 1H, *J* = 8.0 Hz), 7.82 (t, 1H, *J* = 7.6 Hz), 8.14 (d, 1H, *J* = 8.9 Hz), 8.20 (d, 2H, *J* = 8.9 Hz), 12.39 (s, 1H); mass spectrum (ESI): *m/e* (% relative intensity) 274.5 (100) $(M+Na)^+$.

4.3.5 2-(2-hydroxyphenyl)-4(3H)-quinazolinone ***(3e)***: White solid; mp > 300^{o}C; R_f = 0.56 (40% ethyl acetate in petroleum ether); ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 6.97 (t, 1H, *J* = 7.5 Hz), 7.02 (d, 1H, *J* = 8.2 Hz), 7.46 (t, 1H, *J* = 7.6 Hz), 7.56 (t, 1H, *J* = 7.4 Hz,), 7.78 (d, 1H, *J* = 8.1 Hz), 7.87 (t, 1H, *J* = 7.6 Hz), 8.17 (d, 1H, *J* = 7.8 Hz), 8.24 (d, 1H, *J* = 8.0 Hz), 12.50 (s, 1H), 13.81 (s, 1H); mass spectrum (ESI): *m/e* (% relative intensity) 261.7 (100) $(M+Na)^+$.

4.3.6 2-(2-chlorolphenyl)-4(3H)-quinazolinone ***(3f)***: White solid; mp: 160-165 ^{o}C; R_f = 0.38 (40% ethyl acetate in petroleum ether); ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 7.52 (t, 1H, *J* = 7.5 Hz), 7.55-7.60 (m, 2H), 7.63 (d, 1H, *J* = 8.0 Hz) , 7.69 (dd, 1H, *J* = 1.4, 7.5 Hz), 7.73 (d, 1H, *J* = 8.1 Hz), 7.87 (td, 1H, *J* = 1.6, 7.5 Hz), 8.20 (d, 1H, *J* = 7.9 Hz), 12.64 (s, 1H); mass spectrum (ESI): *m/e* (% relative intensity) 278.8 (100) $(M+Na)^+$.

4.3.7 2-(4-chlorolphenyl)-4(3H)-quinazolinone ***(3g)***: Pale-yellow solid; mp: 295-297 ^{o}C; R_f = 0.23 (40% ethyl acetate in petroleum ether); ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 7.54 (t, 1H, *J* = 7.5 Hz), 7.63 (d, 2H, *J* = 8.5 Hz), 7.75 (d, 1H, *J* = 8.0 Hz), 7.85 (t, 1H, *J* = 8.2 Hz), 8.16 (d, 1H, *J* = 7.8 Hz), 8.21 (d, 2H, *J* = 8.6 Hz), 12.59 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 121.5, 126.3, 127.2, 128.0, 129.1, 130.1, 132.0, 135.1, 136.8, 149.1, 151.8, 162.6; mass spectrum (ESI): *m/e* (% relative intensity) 278.8 (100) $(M+Na)^+$.

4.3.8 2-(4-nitrophenyl)-4(3H)-quinazolinone ***(3h)***: Pale-yellow solid; mp >300 ^{o}C; R_f = 0.43 (40% ethyl acetate in petroleum ether); ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 7.59 (t, 1H, *J* = 7.9 Hz), 7.81 (d, 1H, *J* = 7.9 Hz), 7.89 (t, 1H, *J* = 7.6 Hz), 8.19 (d, 1H, *J* = 8.8 Hz), 8.41 (q, 4H, *J* = 9.0 Hz), 12.86 (s, 1H); mass spectrum (ESI): *m/e* (% relative intensity) 265.7 (100) $(M-H)^-$.

4.3.9 2-(2-bromophenyl)-4(3H)-quinazolinone ***(3i)***: White solid; mp: 148-152 ^{o}C; R_f = 0.52 (40% ethyl acetate in petroleum ether); ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.41 (t, 1H, *J* = 7.4 Hz), 7.49 (t, 1H, *J* = 7.5 Hz), 7.54 (t, 1H, *J* = 7.8 Hz), 7.68-7.76 (m, 2H), 7.80-7.88 (m, 2H), 8.27 (d, 1H, *J* = 8.0 Hz), 10.54 (brs, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 121.0, 121.1, 126.5, 127.4, 127.9, 128.0, 131.3, 132.0, 133.8, 134.9, 135.0, 148.9, 152.1, 162.4; mass spectrum (ESI): *m/e* (% relative intensity) 322.7 (100) [M (^{79}Br) + Na]$^+$, 324.7 (100) [M (^{81}Br) + Na]$^+$.

4.3.10 2-(4-bromophenyl)-4(3H)-quinazolinone ***(3j)***: Pale-Yellow solid; mp >300 ^{o}C; R_f = 0.23 (20% ethyl acetate in petroleum ether); ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 7.54 (t, 1H, *J* = 7.5 Hz), 7.74-7.77 (m, 3H), 7.85 (dt, 1H, *J* = 1.3, 7.9 Hz), 8.13 (d, 2H, *J* = 8.6 Hz), 8.16 (dd, 1H, *J* = 1.2, 7.9 Hz), 12.60 (s, 1H); mass spectrum (ESI): *m/e* (% relative intensity) 322.7 (100) [M (^{79}Br) + Na]$^+$, 324.7 (100) [M (^{81}Br) + Na]$^+$.

4.3.11 2-(2-pyridylphenyl)-4(3H)-quinazolinone ***(3k)***: White solid; mp: 168-165 ^{o}C; R_f = 0.37 (40% ethyl acetate in petroleum ether); ^{1}H NMR (600 MHz, $CDCl_3$), 7.44-7.48 (m, 1H), 7.51 (t, 1H, *J* = 7.4 Hz), 7.75-7.84 (m, 2H), 7.90 (t, 1H, *J* = 7.7 H), 8.35 (d, 1H, *J* = 7.9 Hz), 8.56 (d, 1H, *J* = 7.9 Hz), 8.65 (d, 1H, *J* = 4.3 Hz), 10.95 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 122.1, 122.6, 126.3, 126.9, 127.4, 128.1, 134.6, 137.6, 148.6, 148.8, 149.1, 149.2, 161.5; mass spectrum (ESI): *m/e* (% relative intensity) 224.4 (100) $(M+H)^+$.

4.4. Synthesis of 2,3-disubstituted-4(*3H*)-quinazolinones: 4b–m

4.4.1 3-methyl-2-phenyl-4(3H)-quinazolinone ***(4b)***: White solid; mp: 135-139 ^{o}C; R_f = 0.27 (20% ethyl acetate in petroleum ether); ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 3.37 (s, 3H), 7.53-5.58 (m, 4H), 7.65-7.71 (m, 3H), 7.84 (t, 1H, *J* = 7.6 Hz), 8.19 (d, 1H, *J* = 7.9 Hz); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 33.8, 120.1, 126.1, 126.8, 127.1, 128.2, 128.4, 129.7, 134.3, 135.4, 147.0, 156.1, 161.6; mass spectrum (ESI): *m/e* (% relative intensity) 237.3 (100) $(M+H)^+$.

4.4.2 3-ethyl-2-phenyl-4(3H)-quinazolinone ***(4c)***: White solid; mp: 124-127 ^{o}C; R_f = 0.74 (40% ethyl acetate in petroleum ether); ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 1.22 (t, 3H, *J* = 7.0 Hz), 4.05 (q, 2H, *J* = 7.0 Hz), 7.45-7.60 (m, 6H), 7.70-7.82 (m, 2H), 8.34 (d, 1H, *J* = 8.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 14.1, 41.2, 120.9, 126.7, 127.0, 127.4, 127.7, 128.8, 129.8, 134.3, 135.5, 147.1, 156.2, 162.0; mass spectrum (ESI): *m/e* (% relative intensity) 273.8 (100) $(M+Na)^+$.

4.4.3 3-benzyl-2-phenyl-4(3H)-quinazolinone ***(4d)***: White solid; mp: 135-139 °C; R_f = 0.38 (20% ethyl acetate in petroleum ether); ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 5.28 (s, 2H), 6.86-6.99(m, 2H), 7.16-7.23 (m, 3H), 7.35 (d, 2H, *J* = 7.4 Hz), 7.41 (t, 2H, *J* = 7.5 Hz), 7.48 (t, 1H, *J* = 7.4 Hz), 7.54 (t, 1H, *J* = 7.9 Hz), 7.75-7.85 (m, 2H), 8.38 (d, 1H, *J* = 7.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 48.8, 120.8, 127.0 , 127.1 , 127.2, 127.4, 127.5, 128.0, 128.5, 128.6, 129.9, 134.6, 135.1, 136.5, 147.1, 156.4, 162.4; mass spectrum (ESI): *m/e* (% relative intensity) 334.9 (100) $(M+Na)^+$.

4.4.4 3-benzyl-4(3H)-quinazolinone ***(4'd)***: White solid; mp: 118-120 °C; R_f = 0.18 (40% ethyl acetate in petroleum ether); ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 5.21 (s, 2H), 7.28-7.40 (m, 5H), 7.51 (t, 1H, *J* = 7.3 Hz), 7.71 (d, 1H, *J* = 8.0 Hz), 7.79-7.73 (t, 1H, *J* = 7.8 Hz), 8.12 (s, 1H), 8.33 (d, 1H, *J* = 7.9 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 49.6, 122.2, 126.9, 127.4, 127.5, 128.0, 128.3, 129.1, 134.4, 135.7, 146.4, 148.0, 161.1; mass spectrum (ESI): *m/e* (% relative intensity) 259.7 (100) $(M+Na)^+$.

4.4.5 2,3-diphenyl-4(3H)-quinazolinone ***(4e)***: White solid; mp: 150-152 °C; R_f = 0.43 (40% ethyl acetate in petroleum ether); ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 7.19-7.28 (m, 4H), 7.28-7.34 (m, 4H), 7.38 (d, 2H, *J* = 7.2 Hz), 7.61 (t, 1H, *J* = 7.2 Hz) 7.78 (d, 1H, *J* = 8.1 Hz), 7.91 (t, 1H, *J* = 7.6 Hz), 8.21 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 120.7, 126.4, 127.2, 127.4, 127.5, 128.1, 128.5, 128.8, 128.9, 129.4, 134.8, 135.5, 137.7, 147.2, 155.1, 161.4; mass spectrum (ESI): *m/e* (% relative intensity) 299.4 (100) $(M+H)^+$.

4.4.6 7-nitro-2-phenyl-4(3H)-quinazolinone ***(4f)***: Yellow solid; mp >300 °C; R_f = 0.62 (40% ethyl acetate in petroleum ether); ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 7.59 (t, 2H, *J* = 7.2 Hz), 7.61-7.67 (m, 1H), 8.18-8.27 (m, 3H), 8.37 (d, 1H, *J* = 8.6 Hz), 8.44 (s, 1H), 12.93 (brs, 1H); mass spectrum (ESI): *m/e* (% relative intensity) 265.7 (100) $(M-H)^-$.

4.4.7 7-fluror-2-phenyl-4(3H)-quinazolinone ***(4g)***: White solid; mp: 120-126 °C; R_f = 0.56 (40% ethyl acetate in petroleum ether); ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 7.39 (t, 1H, *J* = 8.6 Hz), 7.52 (d, 1H, *J* = 8.6 Hz), 7.57 (t, 2H, *J* = 7.4 Hz), 7.59-7.64 (m, 1H), 8.14-8.26 (m, 3H), 12.64 (brs, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 112.4 (d, *J* = 22.9 Hz), 115.1 (d, *J* = 23.3 Hz), 118.0, 127.9, 128.6, 128.9 (d, *J* = 11.2 Hz), 131.6, 132.4, 150.9 (d, *J* = 13.5 Hz), 153.7, 161.5, 165.8 (d, *J* = 246.5Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ(ppm): -102.0 (s, 1F); mass spectrum (ESI): *m/e* (% relative intensity) 239.0 (100) $(M-H)^-$.

4.4.8 7-fluoro-3-methyl-2-phenyl-4(3H)-quinazolinone ***(4h)***: White solid; mp: 151-154 °C; R_f = 0.65 (40% ethyl acetate in petroleum ether); ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 3.51 (s, 3H), 7.24 (td, 1H, *J* = 2.5, 8.7 Hz), 7.46 (d, 1H, *J* = 8.0 Hz), 7.52-7.62 (m, 5H), 8.35 (dd, 1H, *J* = 6.1, 8.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm):34.3, 112.7 (d, *J* = 21.9 Hz), 115.9 (d, *J* = 23.6 Hz), 117.3, 127.9, 128.9, 129.5 (d, *J* = 10.6 Hz), 130.3, 135.1, 149.5, 157.4, 162.0, 166.5 (d, *J* = 254.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): -103.3 (q, 1F, *J* = 8.6 Hz); mass spectrum (ESI): *m/e* (% relative intensity) 277.9 (100) $(M+Na)^+$; HRMS (ESI) *m/z* calcd for $C_{15}H_{11}FN_2ONa^+$ 277.0748, found 277.0735.

4.4.9 7-fluoro-3-methyl-4(3H)-quinazolinone ***(4'h)***: White solid; mp: 127-130 °C; R_f = 0.23 (40% ethyl acetate in petroleum ether); ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 3.60 (s, 3H), 7.22 (t, 1H, *J* = 8.1 Hz), 7.34 (d, 1H, *J* = 9.3 Hz), 8.07 (s, 1H), 8.31 (t, 1H, *J* = 6.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 34.1, 112.8 (d, *J* = 21.8 Hz), 116.1 (d, *J* = 23.5 Hz), 118.7, 129.2 (d, *J* = 10.5 Hz), 148.0, 150.4 (d, *J* = 12.9 Hz), 160.8, 166.2 (d, *J* = 254.3 Hz); ^{19}F NMR (564 MHz, $CDCl_3$) δ (ppm): -103.5 (q, 1F, *J* = 8.0 Hz); mass spectrum (ESI): *m/e* (% relative intensity) 179.4 (100) $(M+H)^+$.

4.4.10 7-fluoro-3-ethyl-2-phenyl-4(3H)-quinazolinone ***(4i)***: White solid; mp: 120-124 °C; R_f = 0.64 (20% ethyl acetate in petroleum ether); ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 1.22 (t, 3H, *J* = 7.1 Hz), 4.03 (q, 2H, *J* = 7.0 Hz), 7.22 (td, 1H, *J* = 2.5, 8.6 Hz), 7.38 (dd, 1H, *J* = 2.5, 9.6 Hz), 7.49-7.57 (m, 5H), 8.35 (dd, 1H, *J* = 6.1, 8.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 14.1, 41.3, 112.6 (d, *J* = 21.8 Hz), 115.9 (d, *J* = 23.6 Hz), 117.7, 127.5, 128.9, 129.5 (d, *J* = 10.6 Hz), 130.0, 135.2, 149.2 (d, *J* = 12.9 Hz), 157.5, 161.3, 166.5 (d, *J* = 254.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): -102.9 (s, 1F); mass spectrum (ESI): *m/e* (% relative intensity) 291.3 (100) $(M+Na)^+$; HRMS (ESI) *m/z* calcd for $C_{16}H_{13}FN_2ONa^+$ 291.0904, found 291.0885.

4.4.11 7-fluoro-3-ethyl-4(3H)-quinazolinone ***(4'i)***: Pale-yellow solid; mp: 90-93 °C; R_f = 0.14 (20% ethyl acetate in petroleum ether); ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 1.43 (t, 3H, *J* = 7.2 Hz), 4.07 (q, 2H, *J* = 7.2 Hz), 7.22 (td, 1H, *J* = 2.5, 8.5 Hz), 7.35 (dd, 1H, *J* = 2.5, 9.5 Hz), 8.06 (s, 1H), 8.33 (dd, 1H, *J* = 6.1, 8.9 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 14.9, 42.2, 112.7 (d, *J* = 21.9 Hz), 116.0 (d, *J* = 23.5 Hz), 118.9 (d, *J* = 1.9 Hz), 129.4 (d, *J* = 10.5 Hz), 147.5, 150.3 (d, *J* = 13.0 Hz), 160.2, 166.3 (d, *J* = 254.4 Hz) ; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): -102.5 (s, 1F); mass spectrum (ESI): *m/e* (% relative intensity) 193.6 (100) $(M+H)^+$; HRMS (ESI) *m/z* calcd for $C_{10}H_9FN_2OH^+$ 193.0772, found 193.0757.

4.4.12 6-methy-2-phenyl-4(3H)-quinazolinone ***(4j)***: White solid; mp: 259-262 °C; R_f = 0.74 (40% ethyl acetate in petroleum ether); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.47 (s, 3H), 7.50-7.60 (m, 3H), 7.73-7.70 (m, 2H), 7.96 (s, 1H), 8.18 (d, 2H, *J* = 7.1 Hz), 12.47 (brs, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 20.8, 120.6, 125.1, 127.3, 127.5, 128.5, 131.1, 132.7, 135.8, 136.2, 146.6, 151.3, 162.0; mass spectrum (ESI): *m/e* (% relative intensity) 258.9 (100) $(M+Na)^+$.

4.4.13 3,6-dimethyl-2-phenyl-4(3H)-quinazolinone ***(4k)***: White solid; mp: 135-139 °C; R_f = 0.77 (40% ethyl acetate in petroleum ether); ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 2.51 (s, 3H) , 3.49 (s, 3H), 7.50-7.54 (m, 3H), 7.55-7.59 (m, 3H), 7.65 (d, 1H, *J* = 8.3 Hz), 8.12 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 21.4, 34.3, 120.2, 126.0, 127.3, 128.0, 128.9, 130.0, 135.4, 135.8, 137.2, 145.3, 155.3, 162.7; mass spectrum (ESI): *m/e* (% relative intensity) 273.9 (100) $(M+Na)^+$; HRMS (ESI) *m/z* calcd for $C_{17}H_{15}NONa^+$ 273.0998, found 273.0995.

4.4.14 6-methyl-2,3-diphenyl-4(3H)-quinazolinone ***(4l)***: White solid; mp: 175-179 °C; R_f = 0.54 (20% ethyl acetate in petroleum ether); ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 2.54 (s, 3H), 7.15 (d, 2H, *J* = 7.1 Hz), 7.22 (t, 2H, *J* = 7.3 Hz), 7.23-7.36 (m, 6H), 7.65 (d, 1H, *J* = 9.6 Hz), 7.83 (d, 1H, *J* = 5.4 Hz), 8.15 (s, 1H); mass spectrum (ESI): *m/e* (% relative intensity) 334.8 (100) $(M+Na)^+$.

4.4.15 6-methyl-3-phenyl-4(3H)-quinazolinone ***(4'l)***: White solid; mp: 105-109 °C; R_f = 0.23 (20% ethyl acetate in petroleum ether); ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 2.51 (s, 3H), 7.42 (d, 2H, *J* = 7.6 Hz), 7.49 (t, 1H, *J* = 7.3 Hz), 7.55 (t, 2H, *J* = 7.5 Hz), 7.61 (d, 1H, *J* = 8.2 Hz), 7.67 (d, 1H, *J* = 8.3 Hz), 8.08 (s, 1H), 8.15 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 21.4, 122.1, 126.6, 127.0, 127.4, 129.1, 129.6, 136.0, 137.6, 138.0, 145.4, 145.8, 160.8; mass spectrum (ESI): *m/e* (% relative intensity) 237.9 (100) $(M+H)^+$.

*4.4.16 5-chloro-2-phenyl-4(3H)-quinazolinone (**4m**)*: White solid; mp: 280-282 °C; R_f = 0.71 (40% ethyl acetate in petroleum ether); ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 7.52 (d, 1H, *J* = 7.4 Hz), 7.56 (t, 2H, *J* = 7.5 Hz) ,7.61 (t, 1H, *J* = 7.2 Hz), 7.68 (d, 1H, *J* = 7.8 Hz), 7.75 (t, 1H, *J* = 7.9 Hz), 8.18 (d, 2H, *J* = 7.4 Hz), 12.57 (brs, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 117.9, 127.0, 127.8, 128.6, 128.9, 131.7, 132.1, 132.5, 134.3, 151.2, 153.0, 160.4; mass spectrum (ESI): *m/e* (% relative intensity) 257.5 (100) $(M+H)^+$; HRMS (ESI) *m/z* calcd for $C_{15}H_{10}ClNOH^+$ 257.0476, found 257.0463.

*4.4.17 benzyl ether (**2b**)*: R_f = 0.50 (5% ethyl acetate in petroleum ether); ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 4.56 (s, 4H), 7.26-7.31 (m, 2H), 7.32-7.38 (m, 8H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 72.3, 127.8, 127.9, 128.5, 138.5; mass spectrum (ESI): *m/e* (% relative intensity) 220.9 (100) $(M+Na)^+$.

*4.4.18 benzylaldehyde (**2c**)*: R_f = 0.50 (5% ethyl acetate in petroleum ether); ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.46 (t, 2H, *J* = 7.8 Hz), 7.53-7.59 (m, 1H), 7.83 (d, 2H, *J* = 9.0 Hz), 9.97 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 128.7, 129.4, 134.1, 136.1, 192.1; mass spectrum (ESI): *m/e* (% relative intensity) 128.9 (100) $(M+Na)^+$.

*4.4.19 2-(benzylamino)benzamide (**5a**)*: White solid; mp: 165-167 °C; R_f = 0.33 (40% EtOAc in PE); ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 4.43 (s, 2H), 5.72 (brs, 2H), 6.60 (t, 1H, *J* = 7.5 Hz), 6.65 (d, 1H, *J* = 8.4 Hz), 7.23-7.28 (m, 2H), 7.32 (t, 2H, *J* = 7.6 Hz), 7.36 (d, 2H, *J* = 7.3 Hz), 7.40 (dd, 1H, *J* = 1.3, 7.9 Hz), 8.40 (brs, 1H); mass spectrum(ESI): *m/e* (% relative intensity) 248.9 (100) $(M+Na)^+$.

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6. References and notes

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