# Chapter VIII

# *Ligandless copper catalysed rapid and selective C-$NH_2$ arylation of 4-quinolone at ambient condition*

## VIII.A. Introduction

The development of aromatic C–N bond is one of the most important breakthrough in organic synthesis due to the pervasiveness of N-arylamine derivatives in various molecules of biological importance.[1]Particularly, the formation of N-aryl bond formation can actually determine the biological activity of the molecules during structure–activity relationship (SAR) studies.[2]Now a days, significant development has been done on the transition-metal-catalyzed C(aryl)–N bond formations.[3]Generally, these studies have primarily based on the Ullmann (Cu –mediated)[4]or Buchwald–Hartwig cross-coupling reactions (Pd-promoted).[5]In recent years, Cham-Lam coupling through Cu-mediated N-,O- and S-arylation with aryl or aliphatic boronic acids is paid main attention for C-heteroatom bond synthesis.[6,7]Main highlight of this coupling reaction is the mild reaction conditions such as weak base, room temperature and an ambient condition. Several researchers have engrossed their thinking's to find the various aspects of this coupling method.[8]

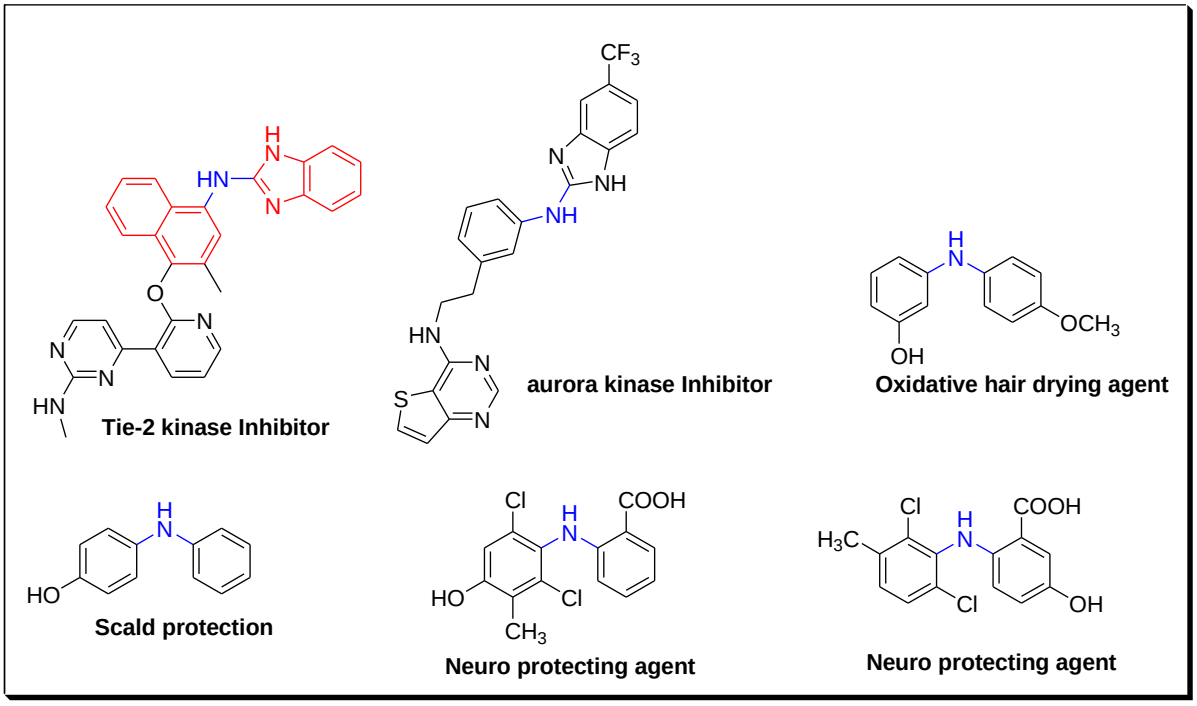
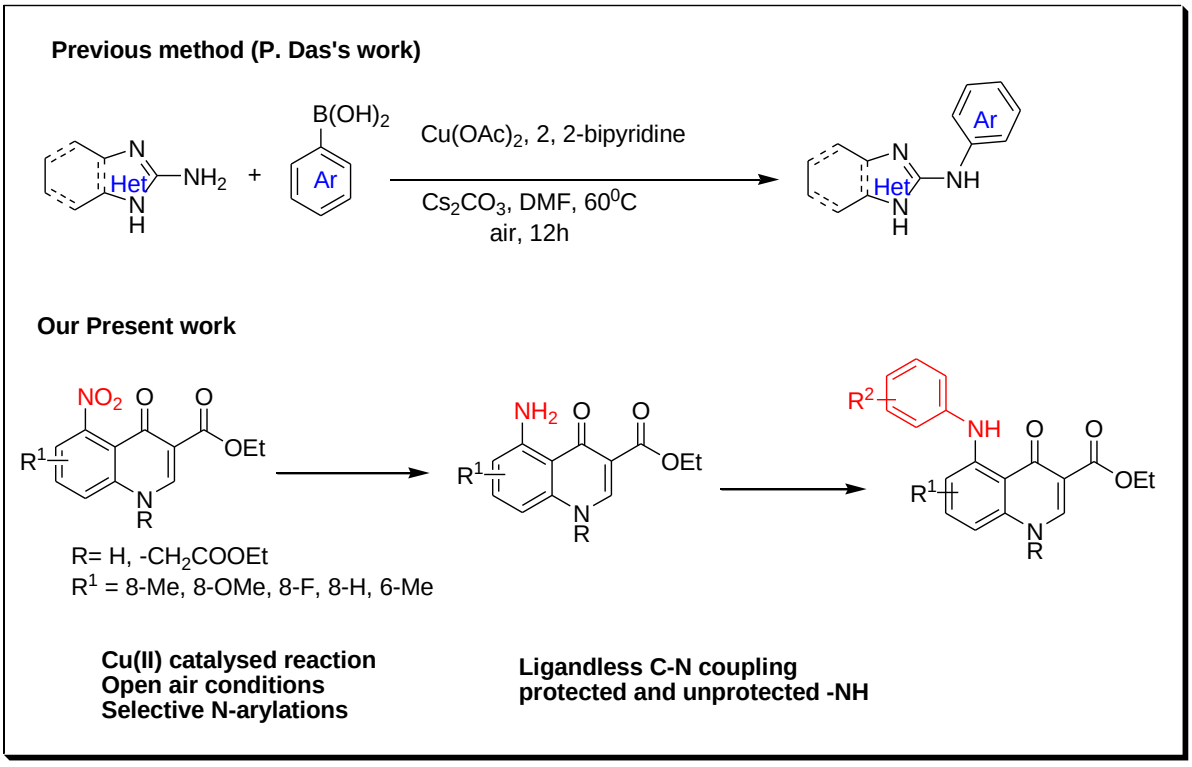


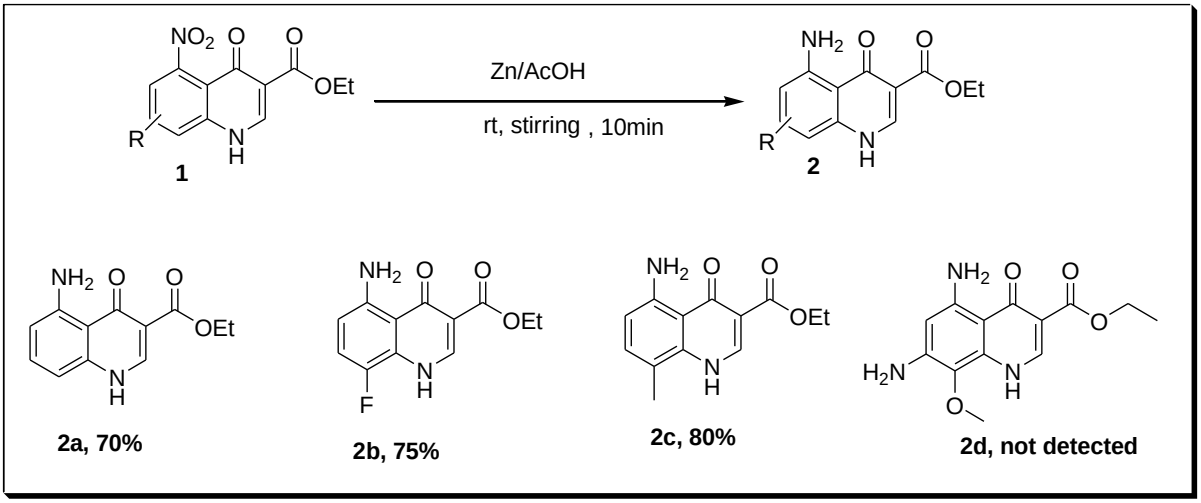

**Fig-VIII.1.** Biologically important N-arylated 2-aminobenzimidazole and N-arylated amino phenols

## VIII.B. Present work: Background and objective

Derivatives of 4-quinolones are widely accepted owing to its impressive antibiotic activity. Now a day's tremendous investigations are continued on this due to its prolific activity as an anticancer, anti-HIV, anti malarial, anti diabetic agent etc. Most of the biologically active potent quinolones enriched with amino, nitro group or any other alkylating group at C-5, C-6 and N-1 position. In our previous papers, we mainly accomplished to synthesize the highly functionalized 6-arylsubstituted-4-quinolones via regioselective bromination[9] and regiocontrolled nitration under ambient condition.[10] Afterwards, it has opened an avenue for the quest of newly better functionalized quinolone moieties. In recent times, our laboratory has also been focused on the development of N-arylated derivatives of 4-quinolones via the Chan–Lam type cross-coupling reactions because various N-arylated heterocyclic motifs such as 2-amino benzimidazole[11] N-arylated amino phenols [12] are found in numerous medicinally important compounds. In this context, we have unfolded a copper (II) catalysed rapid selective C-$NH_2$ arylation of both unprotected and protected 4-quinolone derivatives under ambient condition.



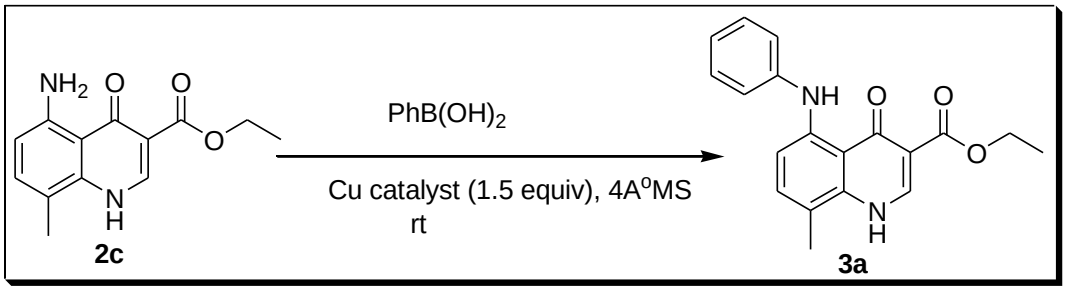
**VIII.B.1. Present work: Result and Discussion**




**Scheme-VIII.1** reduction of nitro derivatives of 4-quinolones at ambient condition.

To accomplish our pathway, we reduced the nitro group to amine (2) in presence of zinc and acetic acid because most of the biologically active quinolone scaffolds contained the amine group, cyclic amine, or heterocyclic amine moiety etc. Most promising finding of this reaction was to complete the reduction fully in just 10 minutes. Both electron rich (-Me) and electron deficient (-H, -F) substituted nitro derivatives easily reduced and the corresponding amine derivatives were formed in good yields (Scheme-VIII.1; entry **2a-2c**). Unfortunately, no desired product was detected in case of 8-methoxy-5-nitro 4-quinolone derivative (Scheme-VIII.1; entry **2d**).

**Table-VIII.1. Optimization of the reaction condition**

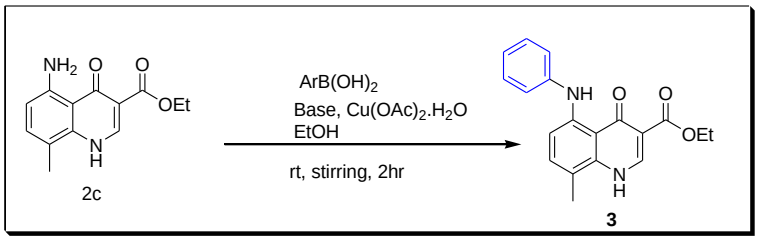


| entry | catalyst (equiv) | base (equiv) | solvent (ml) | time (h) | yield (%) |
|---|---|---|---|---|---|
| 1 | $Cu(OAc)_2.H_2O$ | $K_2CO_3$ | EtOH | 12 | 80 |
| 2 | $Cu(OAc)_2.H_2O$ | $Cs_2CO_3$ | EtOH | 12 | 25 |
| 3 | $Cu(OAc)_2.H_2O$ | $K_3PO_4$ | EtOH | 12 | 15 |
| 4 | $Cu(OAc)_2.H_2O$ | $Et_3N$ | EtOH | 12 | 56 |
| 5 | $Cu(OAc)_2.H_2O$ | $Na_2CO_3$ | EtOH | 12 | 42 |
| 6 | $Cu(OAc)_2.H_2O$ | $K_2CO_3$ | DCM | 24 | - |
| 7 | $Cu(OAc)_2.H_2O$ | $K_2CO_3$ | 1,4-dioxane | 24 | - |
| 8 | $Cu(OAc)_2.H_2O$ | $K_2CO_3$ | toluene | 24 | trace |
| 9 | $Cu(OAc)_2.H_2O$ | $K_2CO_3$ | THF | 24 | NR |
| 10 | $Cu(OAc)_2.H_2O$ | $K_2CO_3$ | DMF | 12 | 60 |
| 11 | $Cu(OTf)_2$ | $K_2CO_3$ | EtOH | 12 | 66 |
| 12 | $Cu(OAc)_2.H_2O$ | $K_2CO_3$ | EtOH | 9 | 79 |
| 13 | $Cu(OAc)_2.H_2O$ | $K_2CO_3$ | EtOH | 6 | 72 |
| **14** | **$Cu(OAc)_2.H_2O$** | **$K_2CO_3$** | **EtOH** | **2** | **81%** |
| 15 | CuI | $K_2CO_3$ | EtOH | 24 | - |
| 16 | CuBr | $K_2CO_3$ | EtOH | 24 | - |
| 17 | $CuSO_4.5H_20$ | $K_2CO_3$ | EtOH | 24 | - |

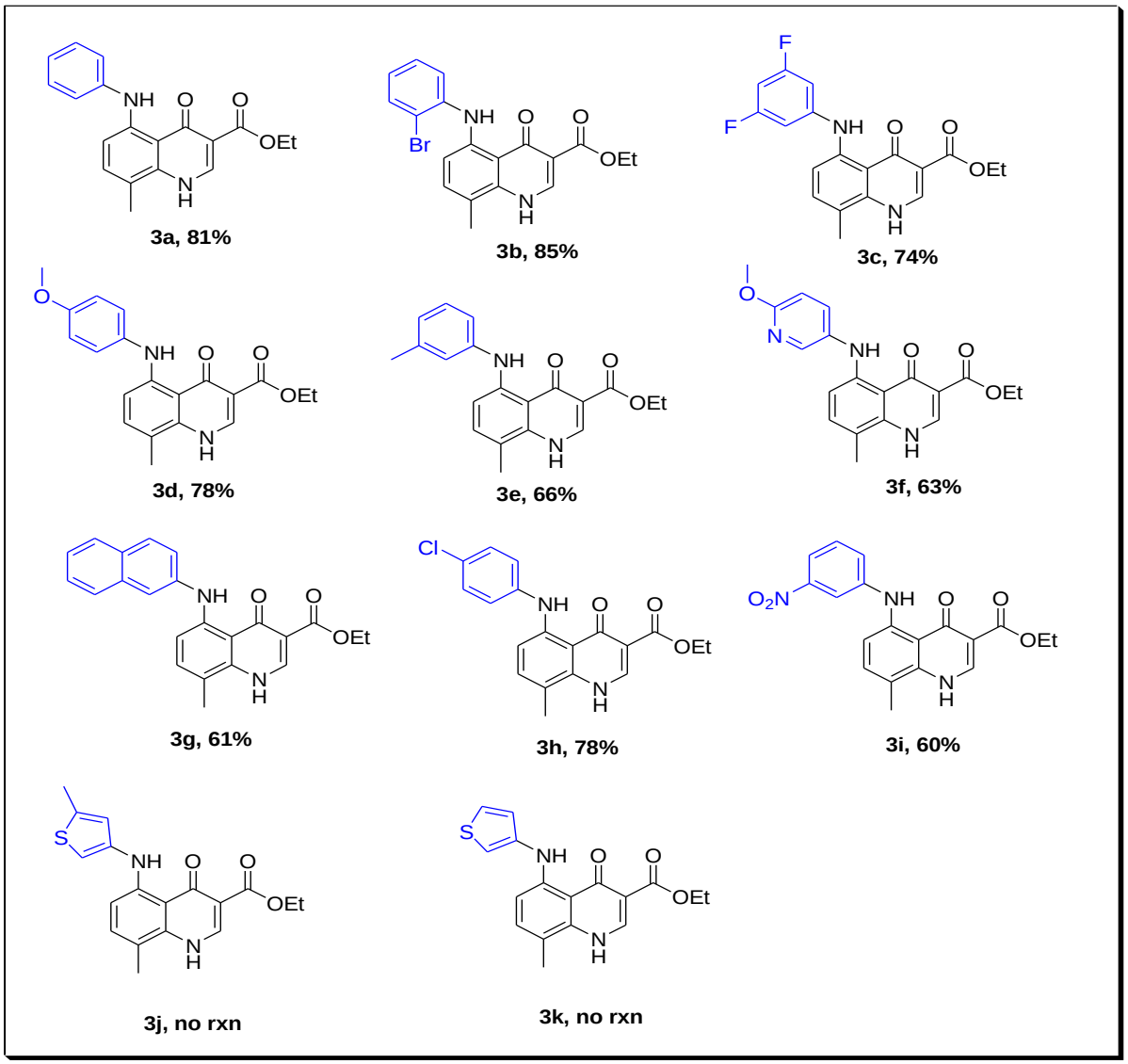
**Reaction condition:** 0.25 mmol (62 mg) of **2c**, $ArB(OH)_2$ (0.375 mmol, 46mg), Base (2 equiv), Cu catalyst (1.5 equiv), 4A°MS (100 mg) in 2ml solvent at rt stirring in air . Yield = Isolated yield after column chromatography.

To accomplish our journey, we initially screened the reaction conditions with **2c** and phenylboronic acid as coupling partners by using $Cu(OAc)_2.H_2O/K_2CO_3$ combination in EtOH at room temperature and we isolated the major N-5 arylated product (**3a**) in 80% yield after 12h (Table-VIII.1; entry-1). Next, we change the bases ($Cs_2CO_3$, $K_3PO_4$ and $Et_3N$) for the improvement of the result but the product yield was not quite promising (Table-VIII.1; entries 2, 3 and 4). $Na_2CO_3$ was remained inferior to the combination of $Cu(OAc)_2.H_2O/K_2CO_3$ in EtOH at room temperature (Table-VIII.1; entry-5). We also tried our reaction in various solvents (DCM, THF, 1,4-dioxane and DMF) but all gave trace to moderate yield of the corresponding product(Table-VIII.1; entry 6-10). Different Cu sources were employed to furnish better yield of the product, only $Cu(OAc)_2.H_2O$ served the best result (Table-VIII.1; entries-11, 14-17). Furthermore by varying the time it was observed that

only 2h was required for this smooth coupling (Table-VIII.1; entry-14). Eventually, it was evident that the combination of $Cu(OAc)_2.H_2O/K_2CO_3$ in EtOH at room temperature for 2h afforded the highest yield of the desired N-arylated product (Table-VIII.1; entry-14).

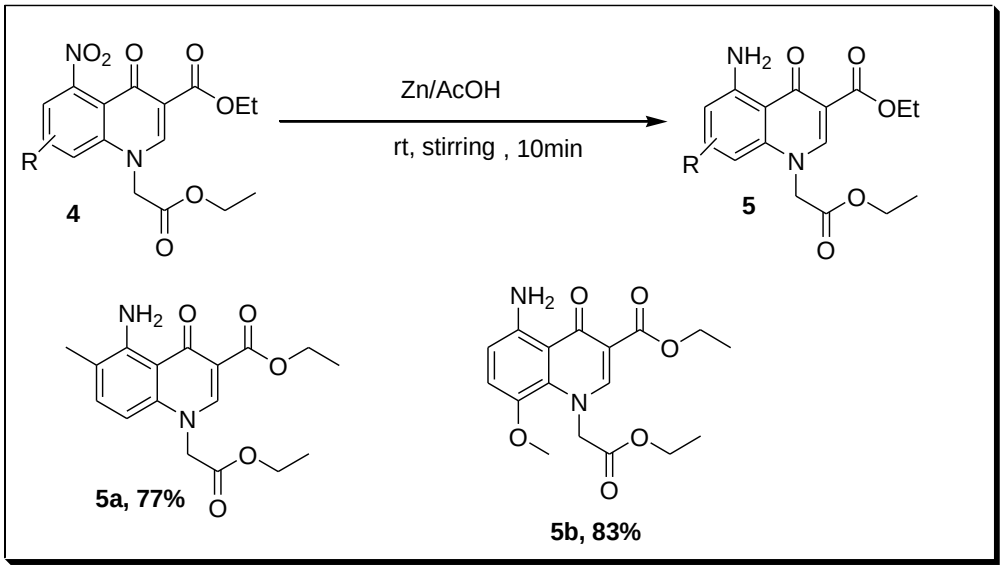



**Scheme-VIII.2** Scope of Cu catalysed C-5 $NH_2$ arylation of 4-quinolone derivative




**Reaction condition:** 0.25 mmol (62 mg) of **2c** , $ArB(OH)_2$ (0.375 mmol, 46mg), $K_2CO_3$ (0.5 mmol, 69 mg), Cu $(OAc)_2.H_2O$ (0.375 mmol, 75mg), 4A°MS (100 mg) in 2ml EtOH at rt stirring for 2h . Yield = Isolated yield.

With the optimized condition in our hand, we examined the scope of various arylboronic acids with 5-amino derivatives of 8-methyl substituted 4-quinolone. The reaction proceeded smoothly with different arylboronic acid and afforded the N-arylated quinolones (**3a**-**3i**) in excellent yields (60-81%). Electronic factors of arylboronic acid did not influence so much towards the product yield. Rather both electron donating (4-OMe, 3-Me) groups and electron withdrawing group (4-Cl) substituted arylboronic acids proved to be a good coupling partners for this coupling (scheme-VIII.2.; entry-**3d, 3e** and **3h**). ortho bromo substituted phenylboronic acid afforded the desired N-arylated derivative in excellent yield (**3b**). 5-methyl-2-thienyl and 2-thienyl boronic acid did not produce any result due to the formation of complex in between 4-quinolone derivatives and Cu(II) species.

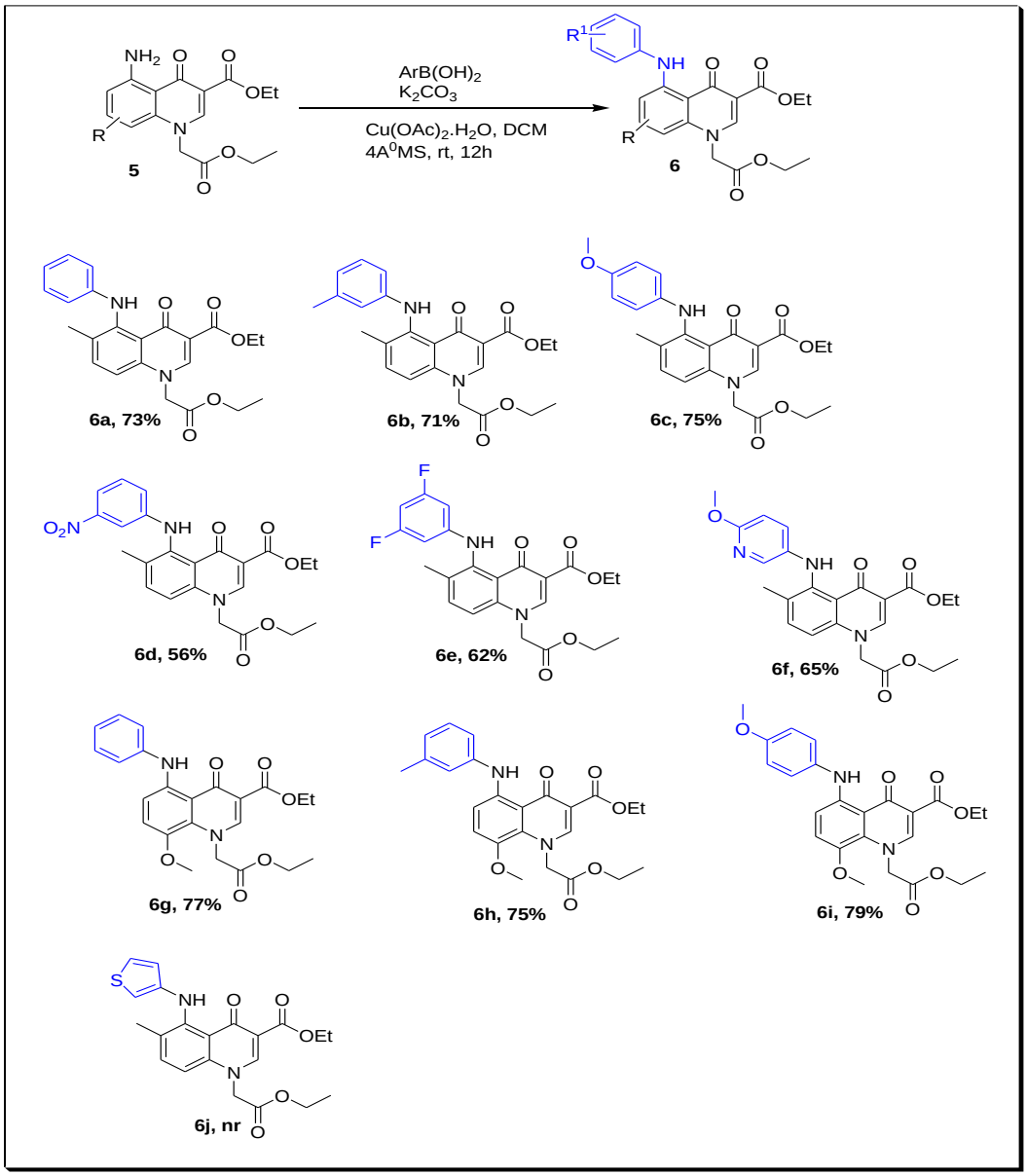



**Scheme-VIII.3.** reduction of N-protected nitro derivatives of 4-quinolones at ambient condition

To establish our proof of concept for N-arylation at 5-$NH_2$ instead of N-H, we proceeded our journey with N-protected nitro derivative (4). Primarily, we reduced the nitro derivative to amine *via* employing similar technique as stated earlier.6-methyl and 8-methoxy substituted 4-quinolone derivatives afforded the corresponding amine product with excellent yields in a very short span.

Next, we further investigated scope of the Cu catalysed N-arylation of 5-$NH_2$ with protected 4-quinolone and substituted arylboronic acid. Our catalytic system performed very well with both electron releasing and electron deficient arylboronic acid. *m*-tolylboronic acid and 4-methoxyboronic acid coupled with (Scheme-VIII.3.entry-**5a)** in a very facile manner and

produced the desired products with good yields (Scheme-VIII.4, entry **6b** and **6c**). Electron-withdrawing group such as –F, -$NO_2$ have an effect to reduce the yield of the N-arylated product (Scheme-VIII.4, entry **6d-6e**) on the cross-coupling reaction than compared to electron-donating group.2-methoxy-pyridin-5-boronic acid participated in cross-coupling reaction with **5a** and afforded 65% yield of the product (Scheme-VIII.4, entry **6f**). The optimized condition also employed with **5b** and it furnished the corresponding N-arylated derivatives in 75-79% yield respectively. Surprisingly, 2-thienylboronic acid could not afford any product due to the formation of complex.




**Scheme-VIII.4.** Scope of Cu catalysed C-5 $NH_2$ arylation of -NH protected 4-quinolone derivative

## VIII.C. Conclusion:

In conclusion, we have developed the copper catalysed selective C-$NH_2$ arylation of 4-quinolones under ambient condition. This method offers several advantages such as room temperature, short reaction and ligand free condition. Various functional groups (-Br, -Cl,-$NO_2$) are well tolerable in this present protocol. Moreover, we have synthesized a broad array of functionally diverse 4-quinolone derivatives which may possess some biological activity and it will be reported in due course.

## VIII.D. Experimental section:

### VIII.D.1. General Information

Unless stated otherwise, all reagents such as Copper acetate, boronic acids and solvents were used as received from commercial suppliers. NMR spectra were recorded on 300 MHz spectrometer at 298 K with calibration done on the basis of solvent residual peak. Mass spectra were performed using ion trap mode. Products were purified using column chromatography on silica gel (60-120 mesh). Ethyl acetate and petroleum ether (60-80$^oC$) were used as eluents. Progress of reaction was monitored using silica gel TLC

### VIII.D.2. Preparation of Amine derivatives of 4-quinolones (2a-2d, 5a-5b):

At first, various 5-nitro derivatives (1, 4) of 4-quinolone (0.5 mmol), Zn (0.75 mmol, 47.5mg) and AcOH (2ml) were taken in 5ml methanol in a 25 ml round bottomed flask. Then it was stirring at room temp for 10 minutes. The reaction became exothermic. After completion of the reaction, it was cooled and diluted with water. The excess acetic acid was neutralized by $NaHCO_3$ solution. Then, it was extracted with 30 ml ethyl acetate and dried over $Na_2SO_4$. The crude product was then purified using column chromatography.

### VIII.D.3 Preparation of N-arylated derivatives of 4-quinolones (3a-3i):

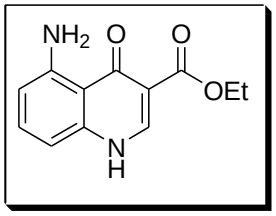
0.25 mmol (62 mg) of 2c, $ArB(OH)_2$ (0.375 mmol, 1.5 equiv), $K_2CO_3$ (0.5 mmol, 69 mg), Cu $(OAc)_2.H_2O$ (0.375 mmol, 75mg), 4A°MS (100 mg) were dissolved in 5ml ethanol. Then, the reaction mixture was stirred for 2h under ambient condition for the completion of reaction. Afterwards, it was evaporated to dryness under reduced pressure. Then, it was diluted with water and extracted via 30ml ethyl acetate. The crude reaction mixture was dried over $Na_2SO_4$. The crude product was then purified using column chromatography.

**VIII.D.4. Preparation of N-arylated derivatives of 4-quinolones (6a-6i):**

0.25 mmol) of 5, $ArB(OH)_2$ (0.375 mmol, 1.5 equiv), $K_2CO_3$ (0.5 mmol, 69 mg), Cu $(OAc)_2.H_2O$ (0.375 mmol, 75mg), 4A°MS (100 mg) were dissolved in 5ml DCM . Then, the reaction mixture was stirred for 12h under ambient condition for the completion of reaction. Then, it was diluted with water and extracted via 30ml ethyl acetate. The crude reaction mixture was dried over $Na_2SO_4$ and evaporated to dryness under reduced pressure. The crude product was then purified using column chromatography.

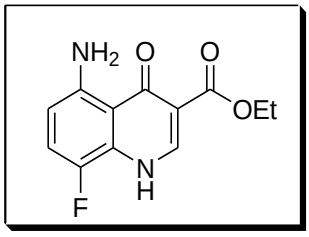
**VIII.D.5. Physical characteristics and spectral data of compounds**

1. **Ethyl-5-amino-1,4-dihydro-4-oxoquinoline-3-carboxylate (2a)**



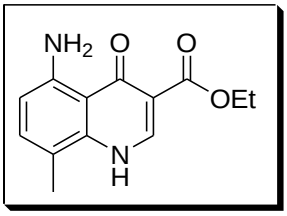

Brown solid, melting point:225-227°C, $^1$H NMR (300 MHz, DMSO-$d_6$) δ 1.29 (t, *J* = 7.2 Hz, 3H), 4.24 (q, *J* = 7.2Hz, 2H), 7.59 (t, *J* = 8.1Hz, 1H), 8.56-8.66 (m, 3H), 12.20 (s, 1H), $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 14.7, 60.5, 111.9, 124.2, 124.6, 130.7, 133.6, 134,3, 137.2, 146.7, 164.3, 172.5.

2. **Ethyl-5-amino-1,4-dihydro-8-fluoro-4-oxoquinoline-3-carboxylate (2b)**



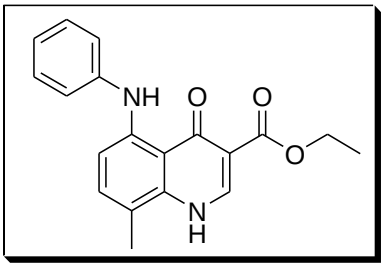

Black solid, melting point: 212-215°C; $^1$H NMR (300 MHz, DMSO-$d_6$) δ 1.16 (t, *J* = 7.2 Hz, 3H), 4.08 (q, *J* = 7.2Hz, 2H), 6.25 (dd, *J* = 9.0Hz, 4.2Hz, 1H), 8.09 (s, 1H),7.14-7.20 (m, 1H), 7.28 (s, 2H), 11.80 (s, 1H), $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 14.8, 60.1, 107.2, 107.3, 110.6, 112.2, 116.1, 119.2, 119.4, 129.1, 140.0, 143.1, 144.4, 148.3, 164.7, 177.8 HRMS ($ESI^+$): $[M+H]^+$, found 251.0739. $C_{12}H_{12}FN_2O_3$ requires 251.0753.

**3. Ethyl-5-amino-1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylate (2c)**



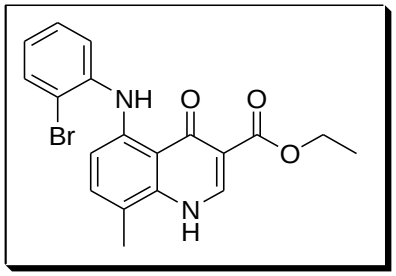

Yellow solid, melting point: 236-238°C; $^{1}$H NMR (300 MHz, DMSO-$d_6$) δ 1.24 (t, *J* = 7.2 Hz, 3H), 2.20 (s, 3H), 4.16 (q, *J* = 7.2Hz, 2H), 6.34 (d, *J* = 8.1Hz, 1H), 7.09 (d, *J* = 8.4Hz, 1H), 7.40 (s, 2H), 8.18 (d, *J* = 5.1Hz, 1H), 11.00 (s, 1H), $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 14.8, 16.7, 59.9, 108.9, 109.9, 110.0, 112.7, 134.8, 139.1, 144.2, 150.3, 165.0, 178.7.

**4. Ethyl-1,4-dihydro-8-methyl-4-oxo-5-(phenylamino)quinolone-3-carboxylate (3a)**




Light Yellow solid, Melting point: 262-264°C; $^{1}$H NMR (300 MHz, DMSO-$d_6$) δ 1.27 (t, *J* = 7.2 Hz, 3H), 2.31 (s, 3H), 4.20 (q, *J* = 7.2Hz, 2H), 6.96-6.98 (m, 2H), 7.25-7.34 (m, 5H), 8.30 (s, 1H), 11.45 (s, 1H), 11. 80 (s, 1H) , $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 14.8, 17.0, 60.2, 106.2, 110.5, 113.6, 113.6, 121.2, 123.0, 129.9, 134.9, 139.6, 141.3, 144.4, 145.7, 164.8, 179.0. HRMS (ESI$^{+}$): $[M+H]^{+}$, found 323.1388. $C_{19}H_{18}N_2O_3$ requires 322.3578.

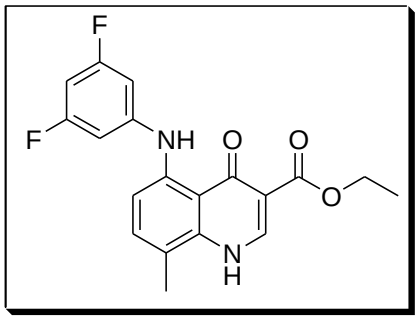
**5. Ethyl-5-(2-bromophenylamino)1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylate (3b)**




Light Yellow solid, melting point:235-237°C, $^{1}$H NMR (300 MHz, DMSO-$d_6$) δ 1.28 (t, *J* = 7.2Hz, 3H), 2.34 (s, 3H), 4.22 (q, *J* = 7.2Hz, 2H), 6.87 (d, *J* = 8.4Hz, 1H), 7.00 ( t, *J* = 6.1 Hz, 1H), 7.29-7.34 (m, 2H), 7.57-7.60 (m, 1H), 7.69 (dd, *J* = 7.8Hz, 1.2Hz, 1H), 8.32 (s, 1H), 11.50 (s, 1H), 11.90 (s, 1H), $^{13}$C NMR (75

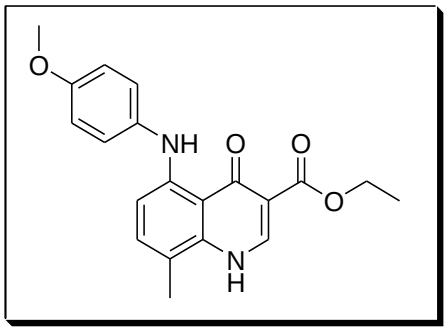
MHz, DMSO-$d_6$) δ 14.8, 17.0, 60.2, 107.0, 110.6, 114.1, 114.9, 116.7, 121.9, 124.6 , 128.8, 133.8, 134.7, 139.6, 139.8, 144.4, 144.7.

**6. Ethyl-5-(3,5-difluorophenylamino)1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylate (3c)**



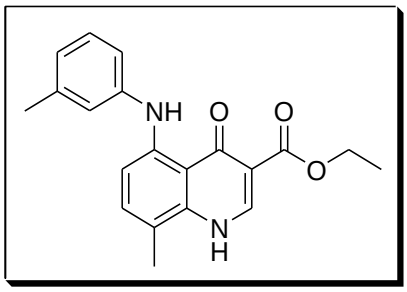

Light Yellow solid, melting point:240-242°C, $^1$H NMR (300 MHz, DMSO-$d_6$) δ 1.28 (t, *J* = 7.2Hz, 3H), 2.36 (s, 3H), 4.21 (q, *J* =7.2Hz, 2H), 6.75 (s, 1H), 6.96 (d, *J* = 7.8Hz, 2H), 7.15 (d, *J* = 8.4 Hz, 1H), 7.39 (d, *J* = 8.4 Hz, 1H), 8.33 (s, 1H), 11.50 (s, 1H), 12.10 (s, 1H), $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 11.3, 13.6, 56.8, 93.5, 98.5, 98.9, 105.1, 107.4, 111.0, 112.8, 131.4, 136.1, 140.0, 141.0, 141.3, 158.5, 158.7, 161.3, 162.0, 175.4. HRMS (ESI$^+$): $[M+H]^+$, found 359.1206. $C_{19}H_{17}F_2N_2O_3$ requires 359.1202.

**7. Ethyl-5-(4-methoxyphenylamino)1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylate (3d)**



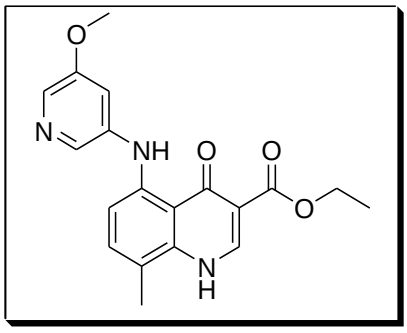

Yellow solid, melting point:260-262°C,$^1$H NMR (300 MHz, DMSO-$d_6$) δ 1.28 (t, *J* = 7.2 Hz, 3H), 2.29 (s, 3H), 3.40 (s, 3H), 4.21 (q, *J* = 7.2Hz, 2H), 6.68 (d, *J* = 7.8Hz, 1H), 6.95 (d, *J* = 8.8Hz, 2H), 7.21 (t, *J* = 9.0Hz, 3H), 8.28 (s, 1H), 11.37 (s, 1H), 11.58 (s, 1H) , $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 14.8, 16.9, 55.7, 60.1, 105.1, 110.4, 112.2, 113.0, 115.2, 124.7, 133.9, 135.0, 139.5, 144.3, 147.54, 156.1, 164.8, 179.0.

**8. Ethyl-5-(m- tolylphenylamino)1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylate (3e)**



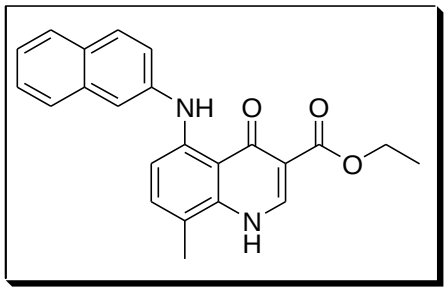

Yellow solid, melting point: 252-254°C, $^{1}$H NMR (300 MHz, DMSO-$d_6$) δ 1.28 (t, *J* = 7.2Hz, 3H), 2.30 (s, 3H), 2.33 (s, 3H), 4.22 (q, *J* = 7.2Hz, 2H), 6.85 ( d, *J* = 7.2Hz, 1H), 6.98 (d, *J* = 8.3Hz, 1H), 7.08 (s, 2H), 7.20-7.23 (m, 1H), 7.30 (d, *J* = 8.5Hz, 1H), 8.31 (s, 1H), 11.45 (s, 1H), 11.85 (s, 1H), $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ11.3, 13.5, 18.0, 56.7, 102.9, 107.2, 110.1, 110.2, 114.8, 118.4, 120.4, 126.2, 131.4, 135.8, 136.3, 137.9, 140.9, 142.5, 161.4, 175.5.

**9. Ethyl-5-(5-methoxypyridin-3-ylamino)1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylate (3f)**



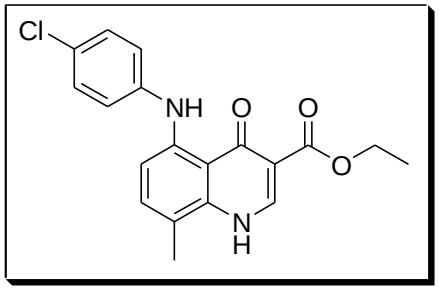

Yellow solid, melting point:235-237°C, $^{1}$H NMR (300 MHz, DMSO-$d_6$) δ 1.27 (t, *J* = 7.2Hz, 3H), 2.30 (s, 3H), 3.85 (s, 3H), 4.21 (q, *J* = 7.2Hz, 2H), 6.58 ( d, J = 8.4 Hz, 1H), 6.85 (d, *J* = 8.7Hz, 1H), 7.23 (d, *J* = 8.4Hz, 1H), 7.66 (dd, *J* = 8.7Hz, 2.7Hz, 1H), 8.08 (d, *J* = 2.6Hz, 1H), 8.30 (s, 1H), 11.45 (s, 1H), 11.55 (s, 1H), $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 11.3, 13.4, 50.2, 56.7, 101.7, 107.0, 107.9, 109.6, 109.8, 128.3, 131.6, 132.3, 136.1, 138.5, 141.0, 143.9, 157.2, 161.4, 175.5.

**10. Ethyl-1,4-dihydro-8-methyl-5-(naphthalene-3-ylamino) 4-oxo-quinolone-3-carboxylate (3g)**



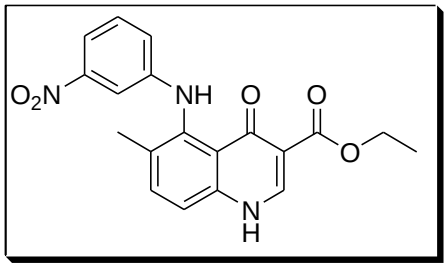

Yellow solid, melting point:>260°C, $^{1}$H NMR (300 MHz, DMSO-$d_6$) δ 1.28 (t, *J* = 7.2Hz, 3H), 2.33 (s, 3H), 4.22 (q, *J* = 7.2Hz, 2H), 7.16 (d, *J* = 8.4Hz, 1H), 7.33-7.45 (m, 4H), 7.75-7.89 (m, 4H), 8.33 (s, 1H), 11.50 (s, 1H), 12.13 (s, 1H), $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 14.7, 17.0, 60.2, 106.8, 110.6, 113.8, 114.2, 115.2, 122.4, 124.6, 126.9, 127.2, 127.9, 129.5, 129.9, 134.5, 135.0, 139.1, 139.6, 144.4, 145.3, 164.8, 179.0.

**11. Ethyl-5-(4-chlorophenylamino)1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylate (3h)**




Yellow solid, melting point: 246-248°C, $^{1}$H NMR (300 MHz, DMSO-$d_6$) δ 1.27 (t, *J* = 7.2Hz, 3H), 2.33 (s, 3H), 4.20 (q, *J* = 7.2Hz, 2H), 6.98 (d, *J* = 8.4Hz, 1H), 7.27-7.38 (m, 5H), 8.31 (s, 1H), 11.50 (s, 1H), 11.94 (s, 1H), $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 14.7, 17.0, 60.2, 106.6, 110.6, 113.8, 114.4, 122.4, 126.1, 129.7, 134.9, 139.7, 140.5, 144.5, 145.1, 164.8, 178.9.

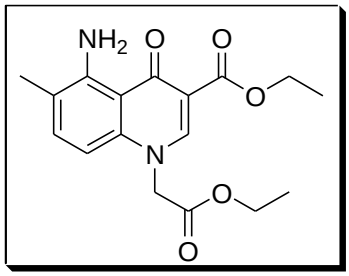
**12. Ethyl-5-(3-nitrophenylamino)1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylate (3h)**




Yellow solid, melting point:238-240°C; $^{1}$H NMR (300 MHz, DMSO-$d_6$) δ 1.28 (t, *J* = 7.2Hz, 3H), 2.36 (s, 3H), 4.32 (q, *J* = 7.2Hz, 2H), 7.13 (d, *J* = 8.4Hz, 1H), 7.38 (d, *J* = 8.1Hz, 1H), 7.58 (d, *J* = 8.1Hz, 1H), 7.67 (d, *J* =

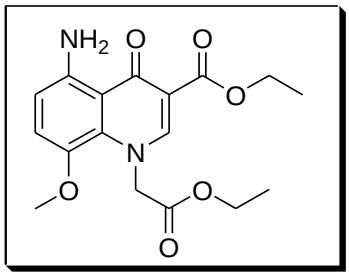
7.8Hz, 1H), 7.78 (d, *J* = 7.8Hz, 1H), 8.04 (s, 1H), 8.33 (s, 1H), 12.20 (s, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 14.7, 17.1, 60.2, 107.7, 110.7, 113.1, 114.4, 116.1, 116.5, 126.2, 131.2, 134.7, 139.7, 143.2, 143.8, 144.5, 149.1, 164.7, 178.8. HRMS (ESI$^+$): $[M+H]^+$ , found 368.1243. $C_{19}H_{18}N_3O_5$ requires 368.1241.

**13. Ethyl-1-((ethoxycarbonyl)methyl-5-amino-1,4-dihydro-6-methyl-4-oxo-quinoline-3-carboxylate (5a)**



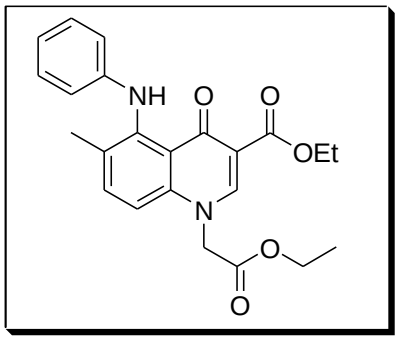

Brownish white, melting point:200-202°C; $^1$H NMR (300 MHz, $CDCl_3$) δ 1.20 (t, *J* = 7.2Hz, 2H), 2.08 (s, 3H), 4.16 (q, *J* = 7.2Hz, 2H), 4.21 (q, *J* = 7.2Hz, 2H), 6.30 (d, *J* = 8.4Hz, 1H), 7.24 (d, *J* = 8.4Hz, 1H), 8.50 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 14.5, 14.8, 17.4, 100.4, 110.4, 111.8, 117.0, 134.7, 140.2, 149.5, 150.3, 164.8, 168.4, 168.5, 178.4.

**14. Ethyl-1-((ethoxycarbonyl)methyl-5-amino-1,4-dihydro-8-methoxy-4-oxo-quinoline-3-carboxylate (5b)**



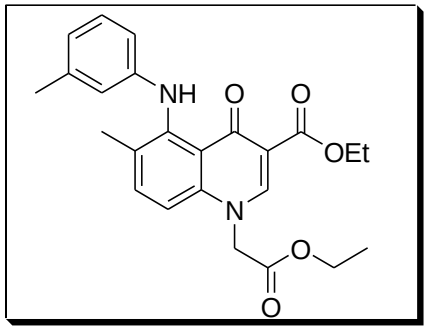

Yellow solid, melting point:182-184°C, $^1$H NMR (300 MHz, $CDCl_3$) δ 1.30 (t, J = 7.2Hz, 3H), 1.40 (t, *J* = 7.2Hz, 3H), 3.78 (s, 3H), 4.29 (q, *J* = 7.2Hz, 2H), 4.39 (q, *J* = 7.2Hz, 2H), 4.99 (s, 2H), 6.85 (d, *J* = 8.7Hz, 1H), 7.10 (d, *J* = 9.0Hz, 1H), 8.20 (s,1H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 14.3, 56.6, 60.2, 61.1, 61.9, 112.0, 112. 6, 120.3, 130.5, 143.1, 152.0, 152.3, 164.2, 167.2, 170.5.

**15. Ethyl-1-((ethoxycarbonyl)methyl)-1,4-dihydro-6-methyl-4-oxo-5-(phenylamino)-quinoline-3-carboxylate (6a)**



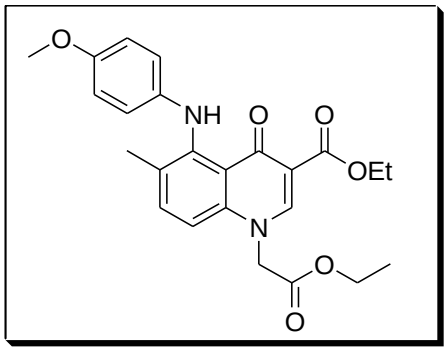

Yellow solid, melting point: 172-174°C, $^{1}$H NMR (300 MHz, $CDCl_3$) δ 1.28(t, *J* = 7.2 Hz, 3H), 1.36 (t, *J* = 7.2 Hz, 3H), 1.98 (s, 3H), 4.27 (q, *J* = 7.2 Hz, 2H), 4.34 (q, *J* = 7.2 Hz, 2H), 4.80 (s, 2H), 6.63 (d, *J* = 8.7 Hz, 1H), 6.82 (d, *J* = 8.4 Hz, 2H), 6.90-6.94 (m , 1H), 7.19 (t, *J* = 7.8 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 1H), 8.31 (s, 1H), $^{13}$C NMR (75 MHz, $CDCl_3$) δ 14.1, 14.5, 20.2, 55.2, 60.8, 62.6, 106.2, 111.3, 119.8, 121.7, 128.6, 136.5, 139.4, 143.6, 146.6, 148.6, 166.80, 178.7

**16. Ethyl-1-((ethoxycarbonyl)methyl)-5-(*m*-tolylamino)-1,4-dihydro-6-methyl-4-oxoquinoline-3-carboxylate (6b)**



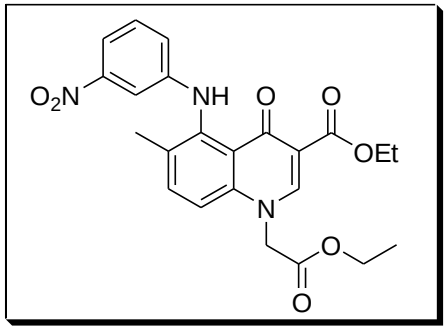

Light Yellow solid, melting point: 158-160°C; $^{1}$H NMR (300 MHz, $CDCl_3$) δ 1.25(t, *J* = 7.2 Hz, 3H), 1.36 (t, *J* = 7.2 Hz, 3H), 2.04 (s, 3H), 2.26 (s, 3H), 4.26 (q, *J* = 7.2 Hz, 2H), 4.34 (q, *J* = 7.2 Hz, 2H), 4.78 (s, 2H), 6.58-6.65 (m, 3H), 6.73 (d, *J* = 7.5 Hz, 1H), 7.07 (t, *J* = 7.8 Hz, 1H), 7.33 (d, *J* = 8.4 Hz, 1H), 8.28 (s, 1H), $^{13}$C NMR (75 MHz, $CDCl_3$) δ 14.1, 14.5, 20.2, 21.4, 55.2, 60.8, 62.5, 106.0, 111.30, 116.7, 120.5, 122.4, 125.7, 128.3, 136.4, 138.3, 139.4, 143.5, 146.5, 148.7, 166.80.

**17. Ethyl-1-((ethoxycarbonyl)methyl)-5-(4-methoxyphenylamino)-1,4-dihydro-6-methyl-4-oxoquinoline-3-carboxylate (6c)**



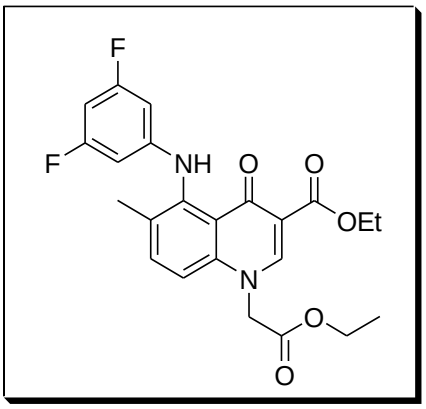

Yellow solid, melting point:184-186°C; $^{1}$H NMR (300 MHz, $CDCl_3$) δ 1.24 (t, *J* = 7.2 Hz, 3H), 1.33(t, *J* = 7.2 Hz, 3H), 1.91 (s, 3H), 3.72 (s, 3H), 4.23 (q, *J* = 7.2 Hz, 2H), 4.29 (q, *J* = 7.2 Hz, 2H), 4.78 (s, 2H), 6.55 (d, J = 8.4 Hz, 1H), 6.70-6.83 (m, 4H), 7.21 (s, 1H), 7.27 (d, *J* = 8.7 Hz, 1H), 8.32 (s, 1H), $^{13}$C NMR (75 MHz, $CDCl_3$) δ 14.5, 14.7, 54.4, 55.6, 60.4, 62.0,107.7, 111.1, 114.6, 117.7, 121.3, 124.2, 136.9, 137.4, 140.0, 146.5, 149.6, 154.8, 164.7, 168.4, 178.3.

**18. Ethyl-1-((ethoxycarbonyl)methyl)-5-(3-nitrophenylamino)-1,4-dihydro-6-methyl-4-oxoquinoline-3-carboxylate (6d)**



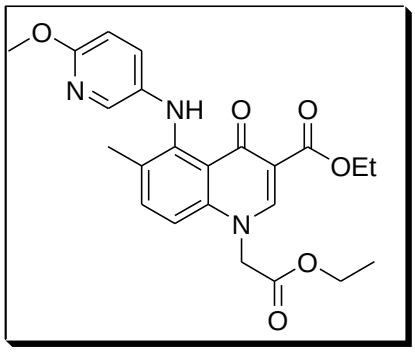

Yellow solid, melting point: 138-140°C, $^{1}$H NMR (300 MHz, $CDCl_3$) δ 1.30 (t, *J* = 7.2 Hz, 3H), 1.38 (t, *J* = 7.2 Hz, 3H), 2.04 (s, 3H), 4.30 (q, *J* = 7.2 Hz, 2H), 4.37 (q, *J* = 7.2 Hz, 2H), 4.85 (s, 2H), 6.81 (d, *J* = 8.7 Hz, 1H), 7.17 (d, J = 8.1 Hz, 1H), 7.35 (d, *J* = 8.1 Hz, 1H), 7.43-7.49 (m, 2H), 7.73 ( dd, *J* = 8.1Hz, 1.2 Hz, 1H), 8.38 (s, 1H), $^{13}$C NMR (75 MHz, $CDCl_3$) δ 14.1, 14.5, 29.7, 55.3, 61.0, 62.8, 108.0, 111.8, 112.3, 115.7,116.1,125.1, 126.3, 129.3, 136.7, 139.5, 144.6, 145.0, 148.8, 148.9, 166.5,168.7, 178.5.

**19. Ethyl-1-((ethoxycarbonyl)methyl)-5-(3,5-difluorophenylamino)-1,4-dihydro-6-methyl-4-oxoquinoline-3-carboxylate (6e)**



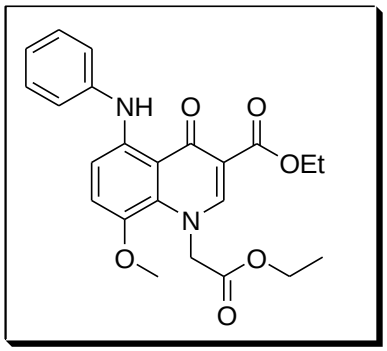

Yellow solid, melting point:162-164°C, $^{1}$H NMR (300 MHz, $CDCl_3$) δ 1.29(t, *J* = 7.2 Hz, 3H), 1.38 (t, *J* = 7.2 Hz, 3H), 2.08 (s, 3H), 4.31 (q, *J* = 7.2 Hz, 2H), 4.37 (q, *J* = 7.2 Hz, 2H), 4.82 (s, 2H), 6..25-6.28 (m, 3H), 6.79 (s, 1H), 7.43 (d, J = 8.4 Hz, 1H), 8.35 (s, 1H), 11.50 (s, 1H), $^{13}$C NMR (75 MHz, $CDCl_3$) δ 14.1, 14.4, 29.7, 55.3, 61.0, 62.7, 95.9, 96.2, 96.6, 101.5, 101.7, 101.8, 107.9, 111.7, 126.8, 136.5, 139.4, 144.8, 146.4, 148.8, 161.8, 162.0, 165.0, 165.2, 166.5,178.5.

**20. Ethyl-1-((ethoxycarbonyl)methyl)-5-(6-pyridin-3-ylamino)-1,4-dihydro-6-methyl-4-oxoquinoline-3-carboxylate (6f)**



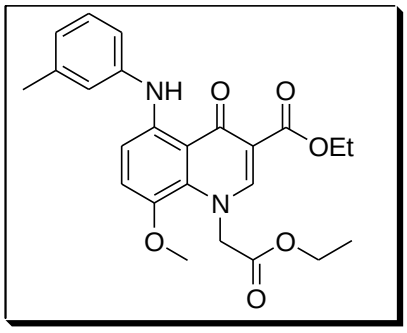

Greenish yellow solid, melting point:175-177°C, $^{1}$H NMR (300 MHz, $CDCl_3$) δ 1.21-1.30 (m, 6H), 1.88 (s, 3H), 3.80 (s, 3H), 4.17-4.25 (m, 4H), 5.32 (s, 2H), 6.73 (d, *J* = 8.7Hz, 1H), 6.96 (s, 1H), 7.18 (dd, *J* = 9.0Hz, 2.7Hz, 1H), 7.49 (d, J = 8.7Hz, 1H), 7.72 (d, *J* = 8.7Hz, 1H), 8.68 (s, 1H), 11.46 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 14.5, 14.8, 17.6, 20.0, 53.5, 60.4, 62.0, 86.2, 110.7, 111.1, 123.9, 131.9, 135.0, 137.1, 138.2, 140.1, 145.9,149.8, 159.4, 164.6, 168.3, 178.3.

**21. Ethyl-1-((ethoxycarbonyl)methyl)-1,4-dihydro-8-methoxy-4-oxo-5-(phenylamino)- quinoline-3-carboxylate (6g)**



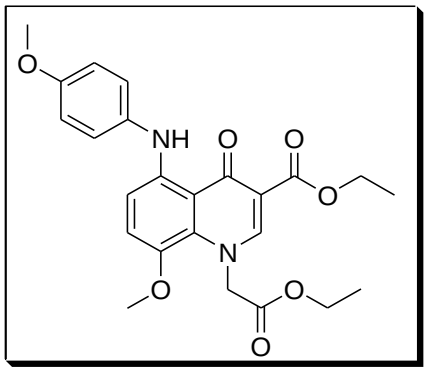

Yellow solid, melting point:162-164°C; $^{1}$H NMR (300 MHz, $CDCl_3$) δ 1.29 (t, *J* = 7.2 Hz, 3H), 1.38 (t, *J* = 7.2 Hz, 3H), 3.72 (s, 3H), 4.27 (q, *J* = 7.2 Hz, 2H), 4.37 (q, *J* = 7.2 Hz, 2H), 4.95 (s, 2H), 6.98-7.11 (m, 3H), 7.23-7.32 (m, 4H), 8.14 (s, 1H), $^{13}$C NMR (75 MHz, $CDCl_3$) δ 14.2, 14.5, 57.3, 60.3, 60.8, 61.7, 108.5, 111.9, 115.6, 118.7, 122.0, 123.0, 129.2, 131.9, 139.5, 141.5, 151.6, 164.7, 167.5, 178.7.

**22. Ethyl-1-((ethoxycarbonyl)methyl)-5-(*m*-tolylamino)-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylate (6h)**



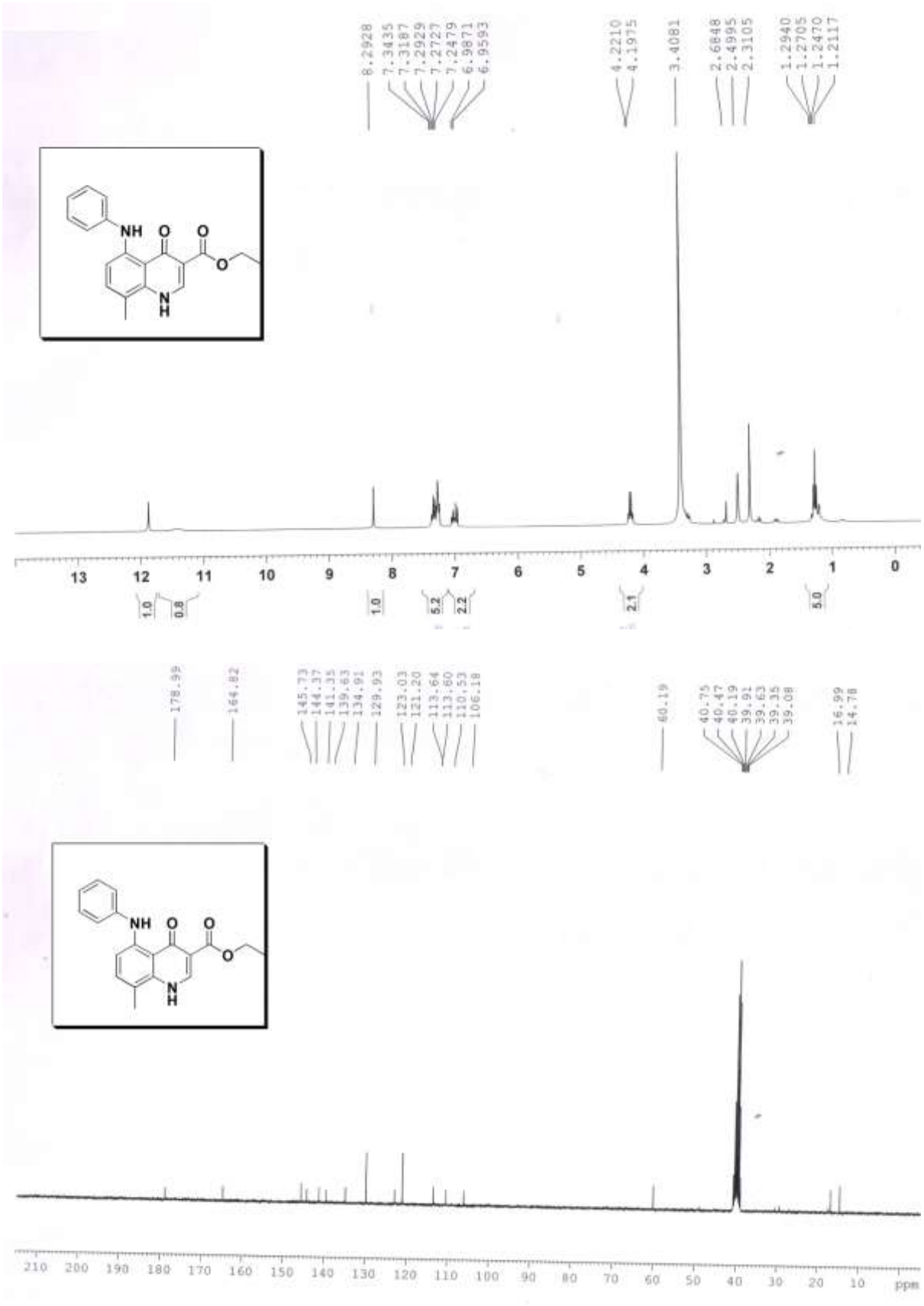

Yellow solid, melting point: 155-157°C; $^{1}$H NMR ($CDCl_3$, 300 MHz,) δ 1.30 (t, *J* = 7.2 Hz, 3H), 1.39 (t, *J* = 7.2 Hz, 3H), 2.32 (s, 3H), 3.74 (s, 3H), 4.28 (q, *J* = 7.2 Hz, 2H), 4.38 (q, *J* = 7.2 Hz, 2H), 4.96 (s, 2H), 6.86 (d, *J* = 7.2 Hz, 1H), 7.00-7.18 (m, 5H), 8.15 (s, 1H), $^{13}$C NMR (75 MHz, $CDCl_3$) δ 14.2, 14.5, 21.4, 57.4, 60.2, 60.8, 60.9, 61.7, 108.9, 111.0, 115.7, 118.8, 118.8, 119.2, 123.0, 124.0, 129.0, 132.0, 139.1, 139.5, 141.3, 143.3, 143.4, 151.6, 167.4, 178.6.

**23. Ethyl-1-((ethoxycarbonyl)methyl-5-(4-methoxyphenylamino)-)-1,4-dihydro-8-methoxy-4-oxo-quinoline-3-carboxylate (6i)**

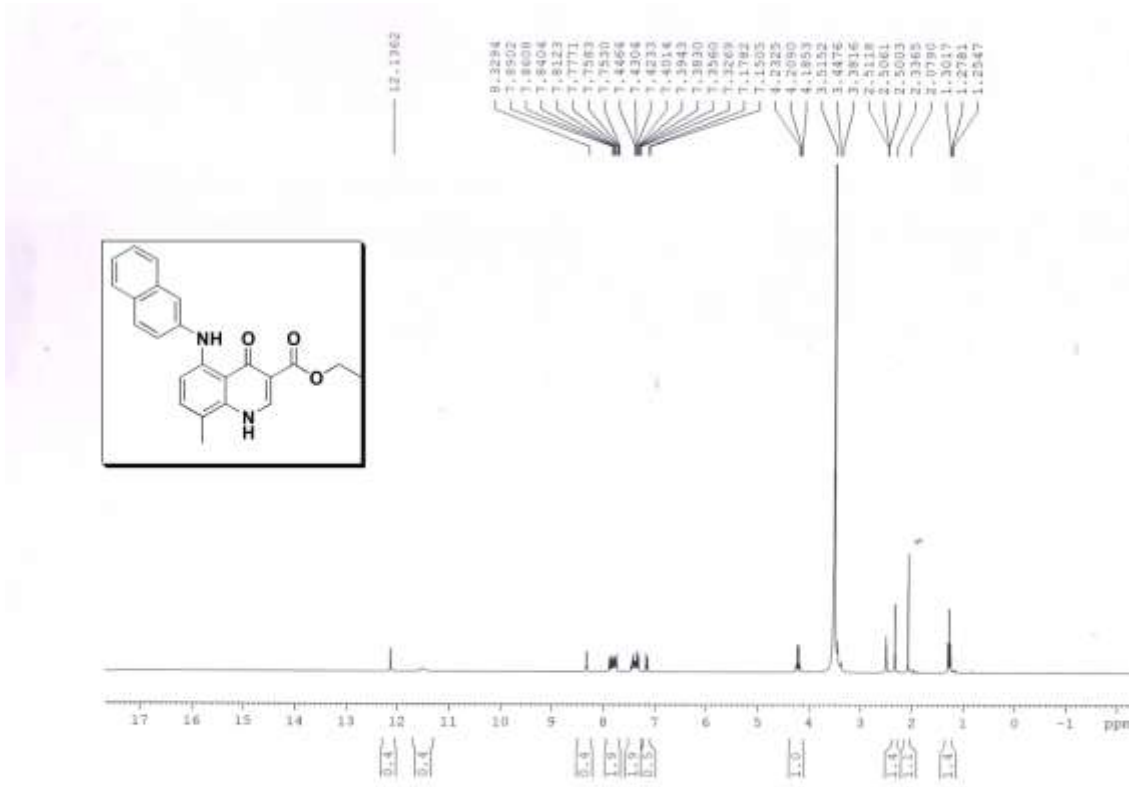


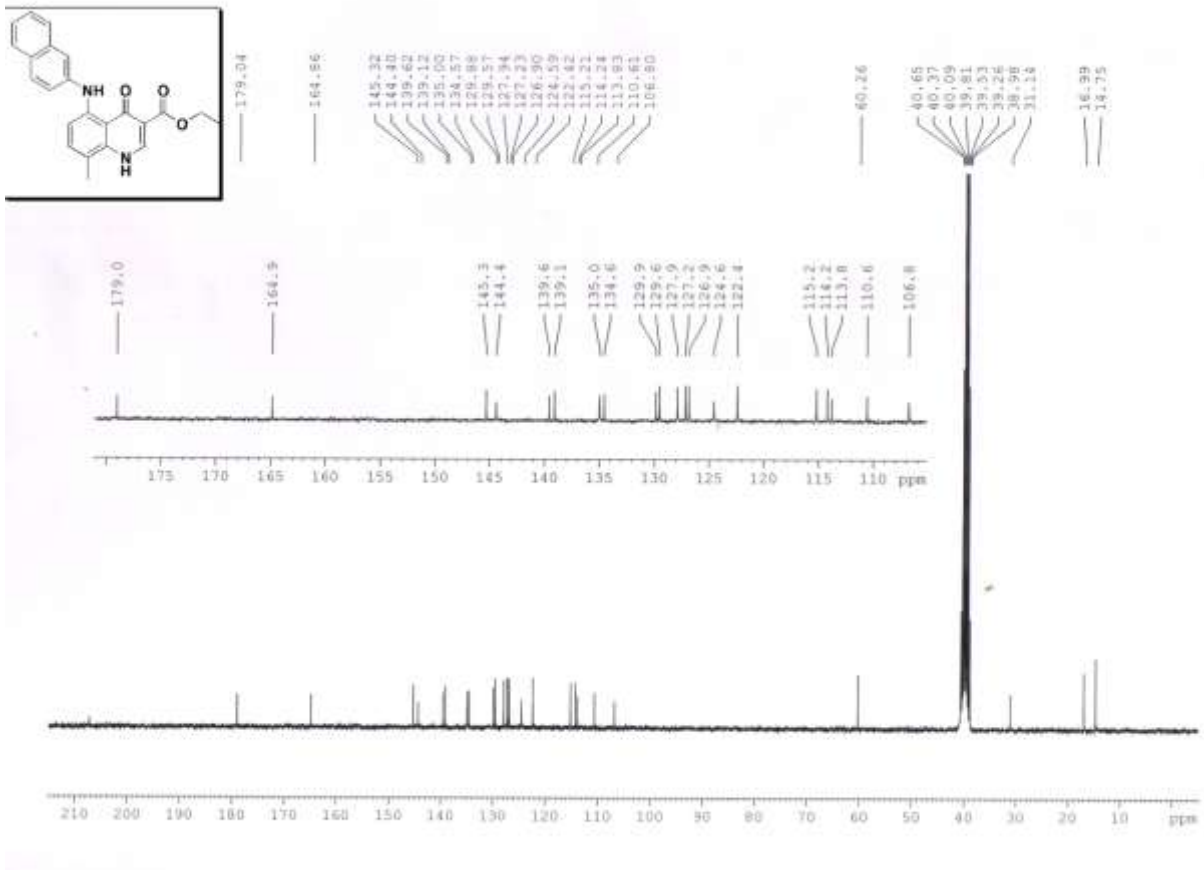

Yellow solid, melting point:170-172°C,$^{1}$H NMR ($CDCl_3$,300 MHz) δ 1.25 (t, *J* = 7.2Hz, 3H), 1.36 (t, *J* = 7.2Hz, 3H), 3.70 (s, 3H), 3.80 (s, 3H), 4.28 (q, *J* = 7.2Hz, 2H), 4.37 (q, *J* = 7.2Hz, 2H), 4.94 (s, 2H), 6.82-6.88 (m, 3H), 6.97 (d, *J* = 9.3Hz, 1H), 7.16 (d, *J* = 8.7Hz, 2H), 8.12 (s, 1H), 11.50 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 14.2, 14.5, 55.5, 57.5, 60.2, 60.8, 61.7, 107.3, 110.8, 114.6, 114.8, 119.4, 125.4, 131.9, 134.2, 138.5, 145.4, 151.6, 156.3, 164.9, 167.5, 178.8.

**$^{1}$H and $^{13}$C NMR spectra of entry 3a (Scheme-VIII.2.) in DMSO-$d_6$**

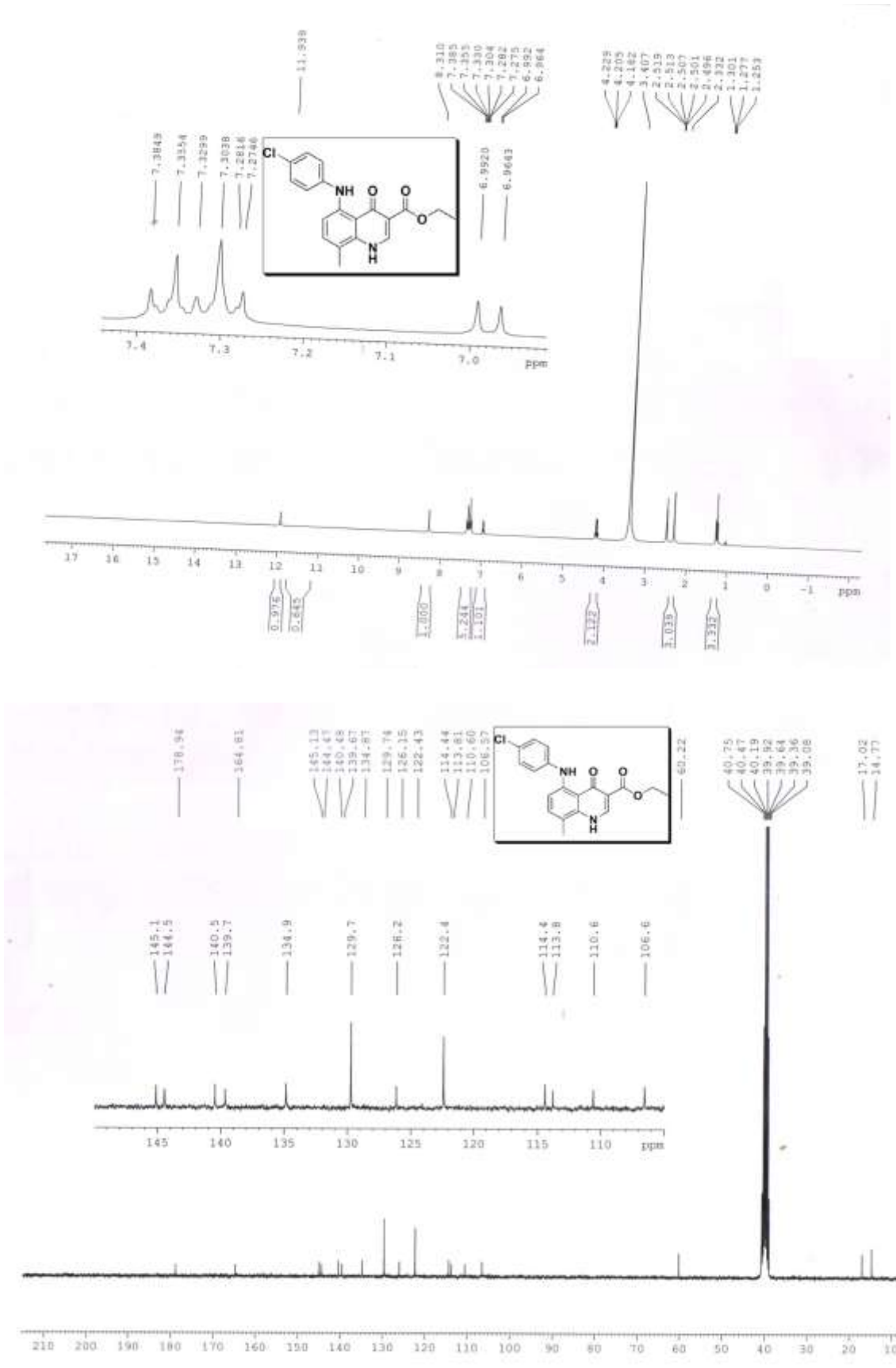


**$^{1}$H and $^{13}$C NMR spectra of entry 3g (Scheme-VIII.2.) in DMSO-$d_6$**

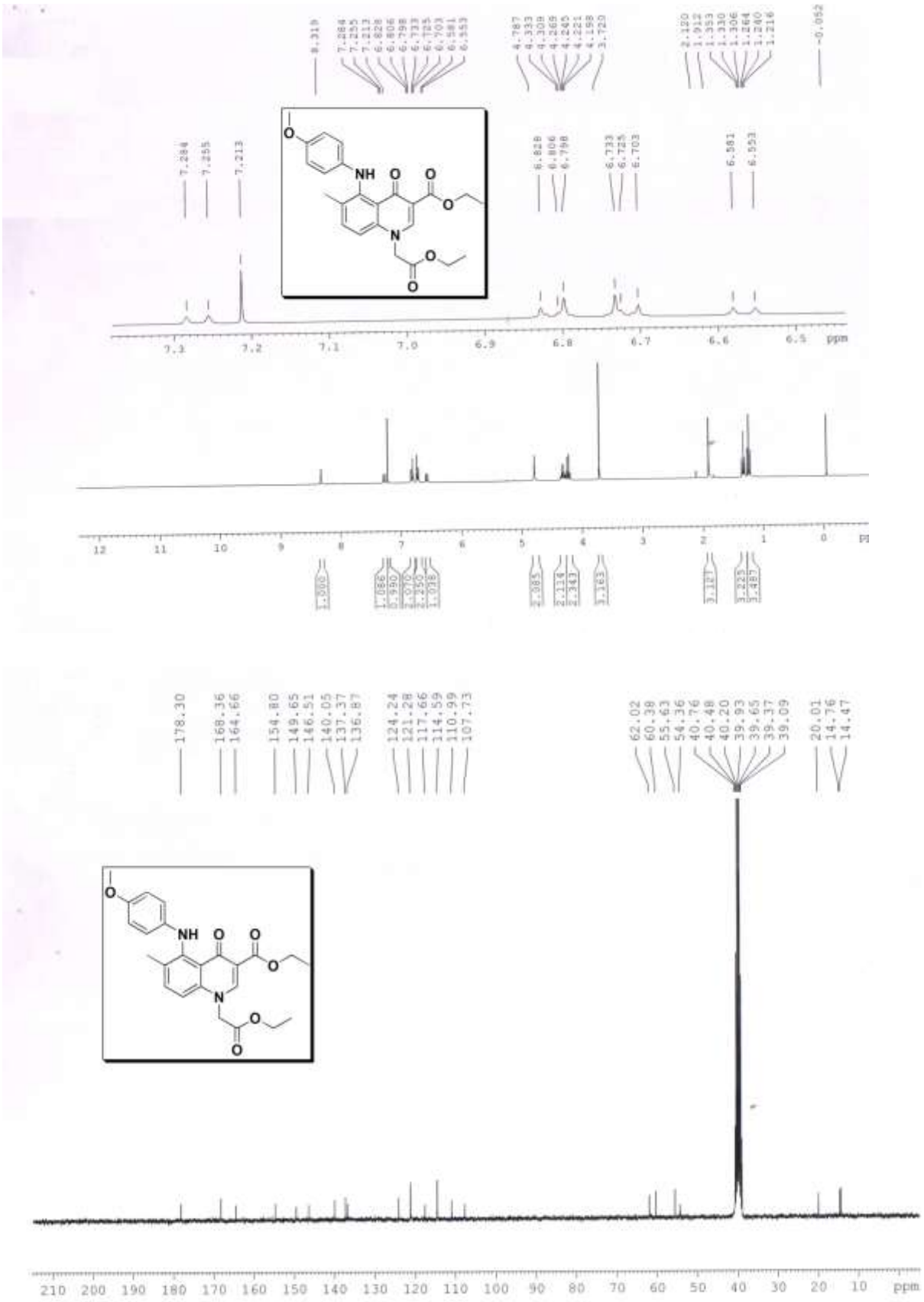




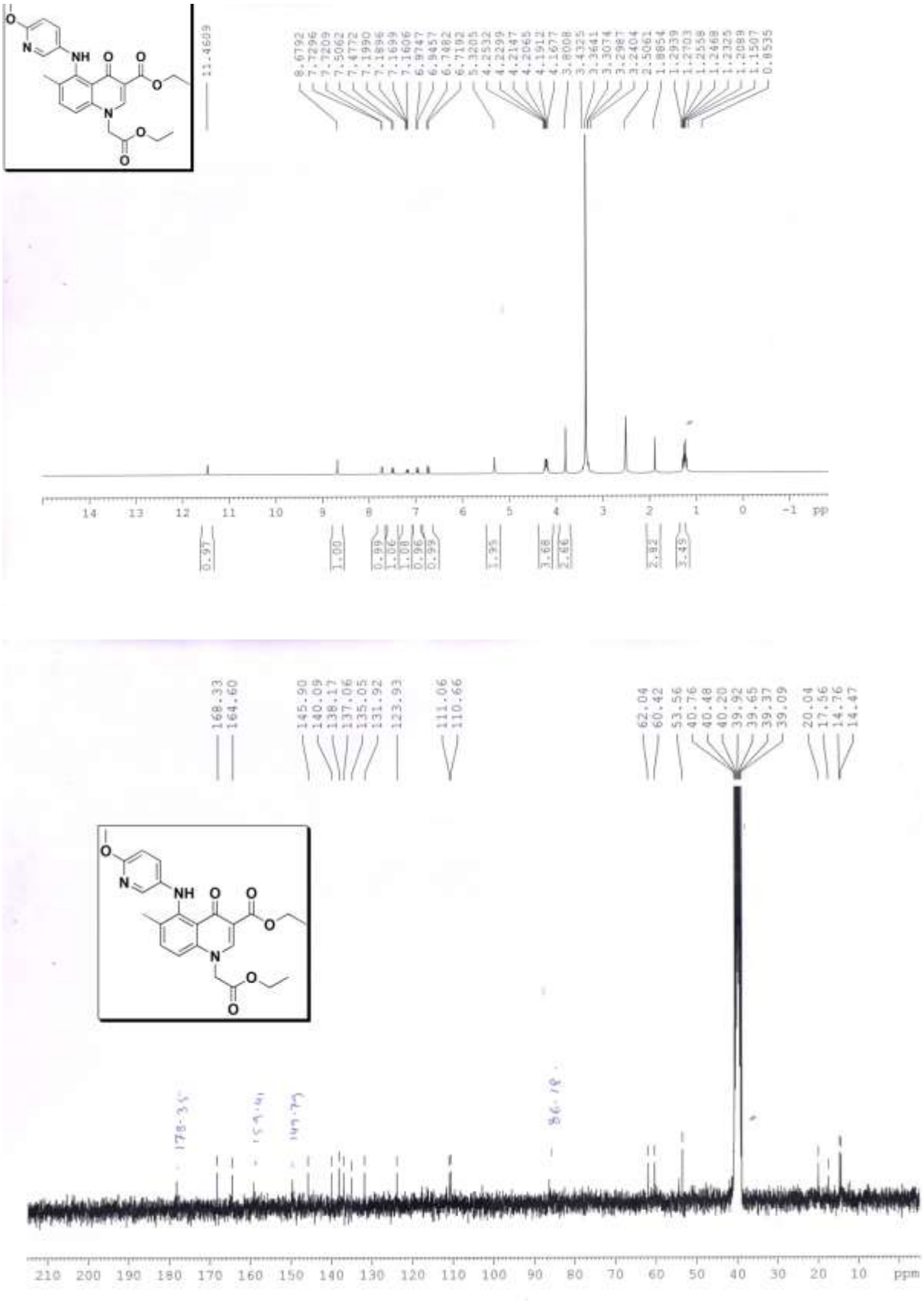
**$^{1}$H and $^{13}$C NMR spectra of entry 3h (Scheme-VIII.2.) in DMSO-$d_6$**



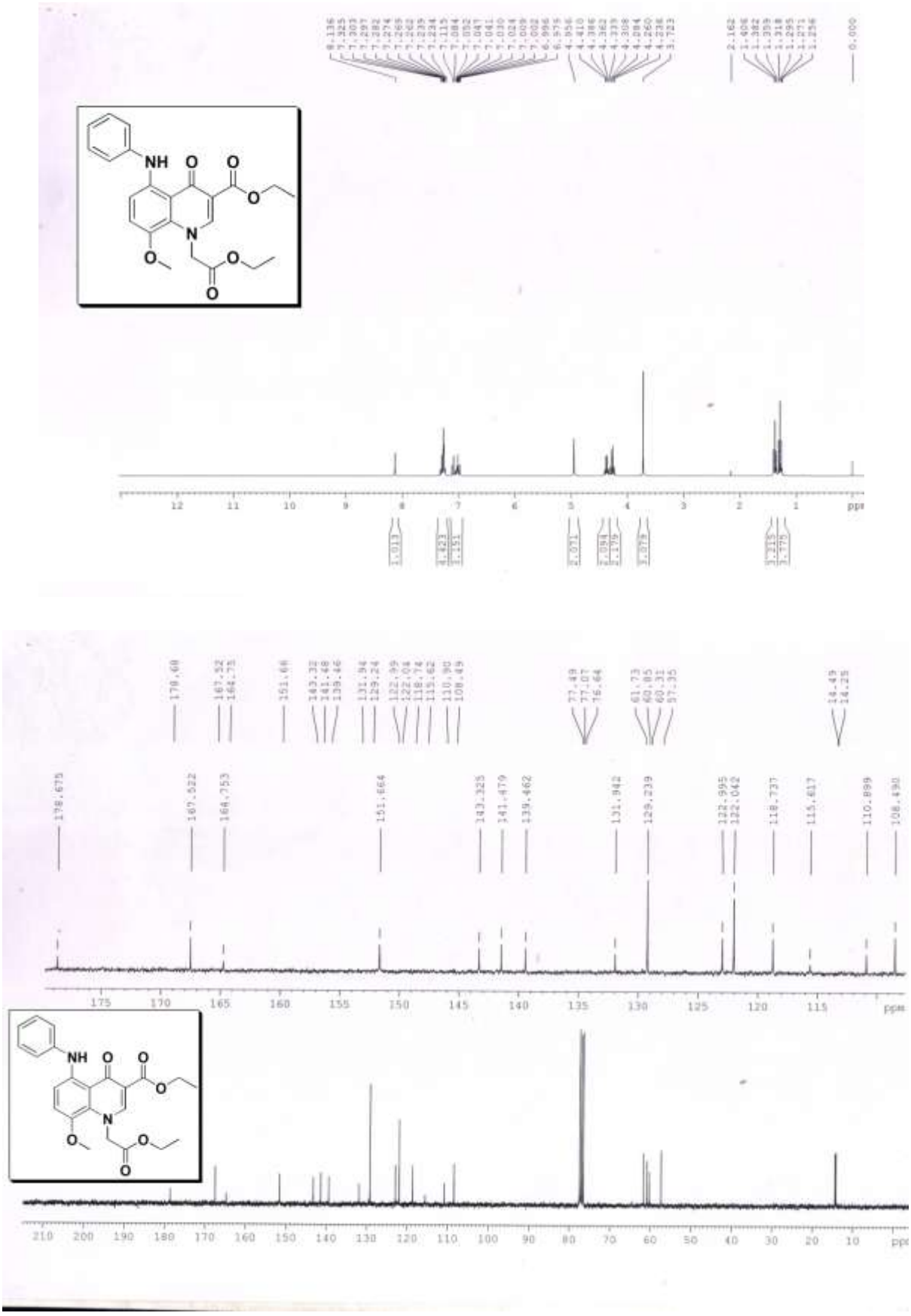
**$^{1}$H and $^{13}$C NMR spectra of entry 6c (Scheme-VIII.4.) in DMSO-$d_6$**



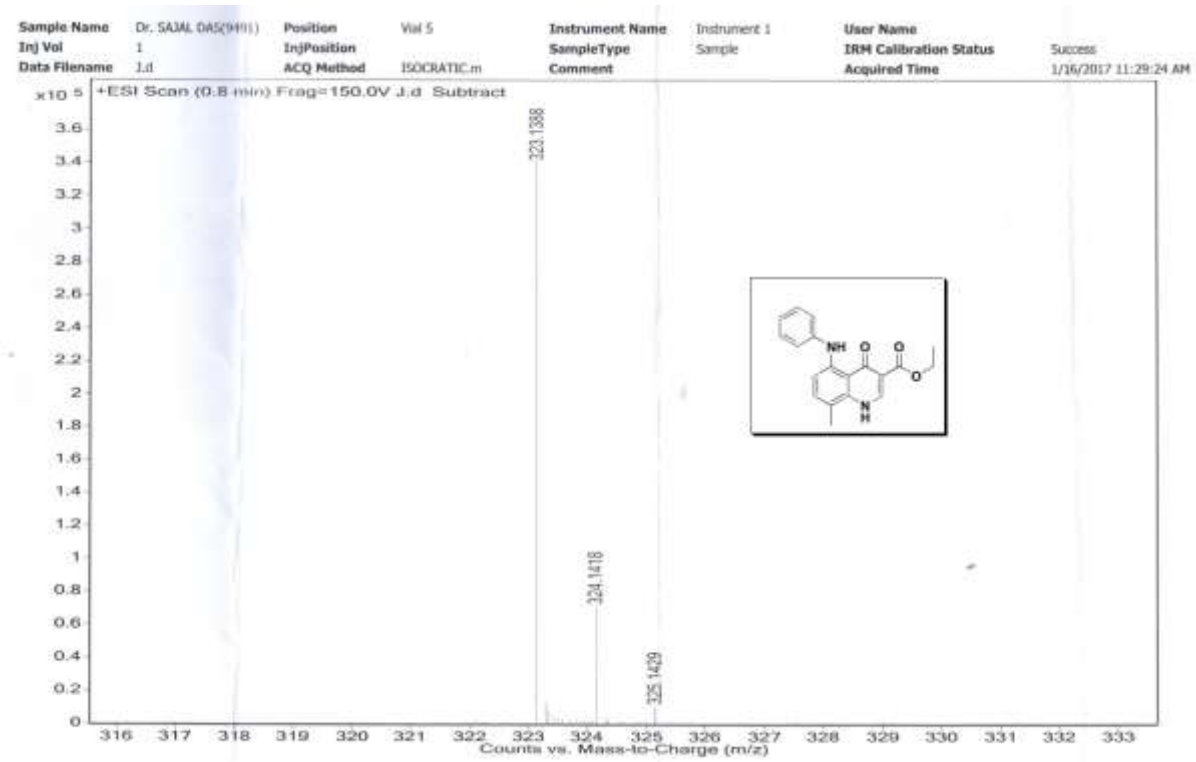
**$^{1}$H and $^{13}$C NMR spectra of entry 6f (Scheme-VIII.4.) in DMSO-$d_6$**



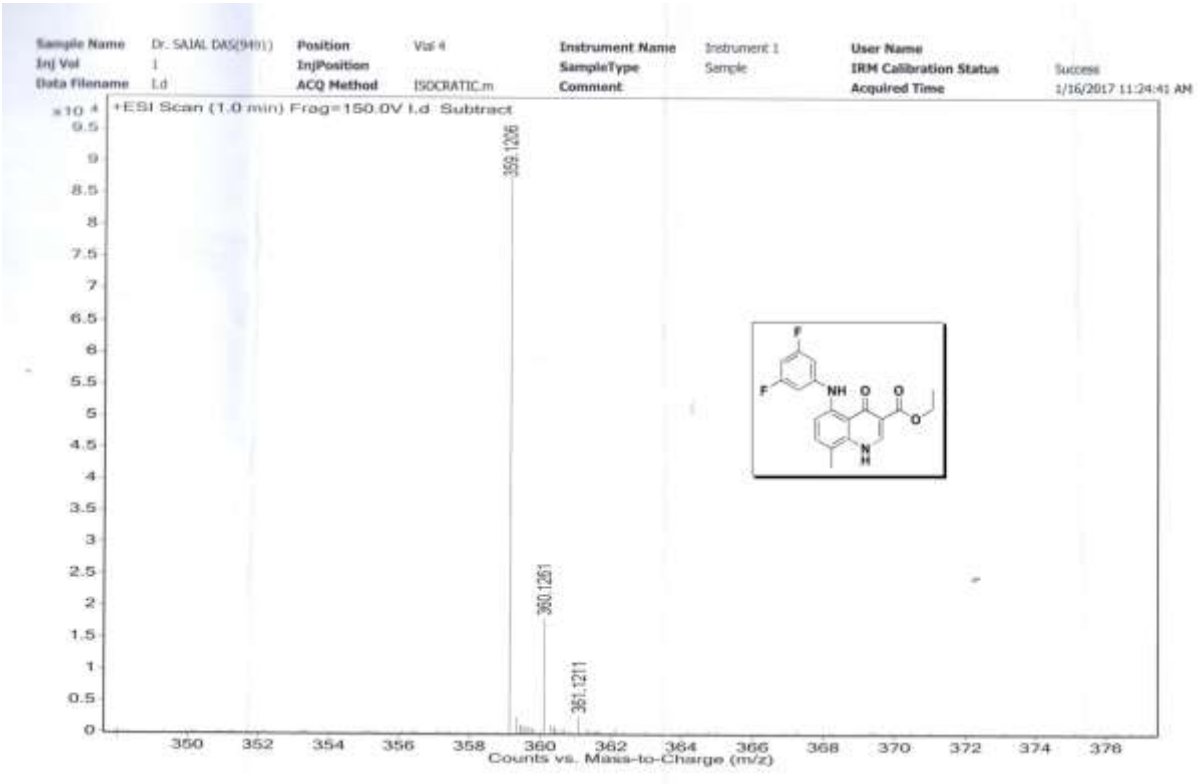
**$^{1}$H and $^{13}$C NMR spectra of entry 6g (Scheme-VIII.4.) in DMSO-$d_6$**



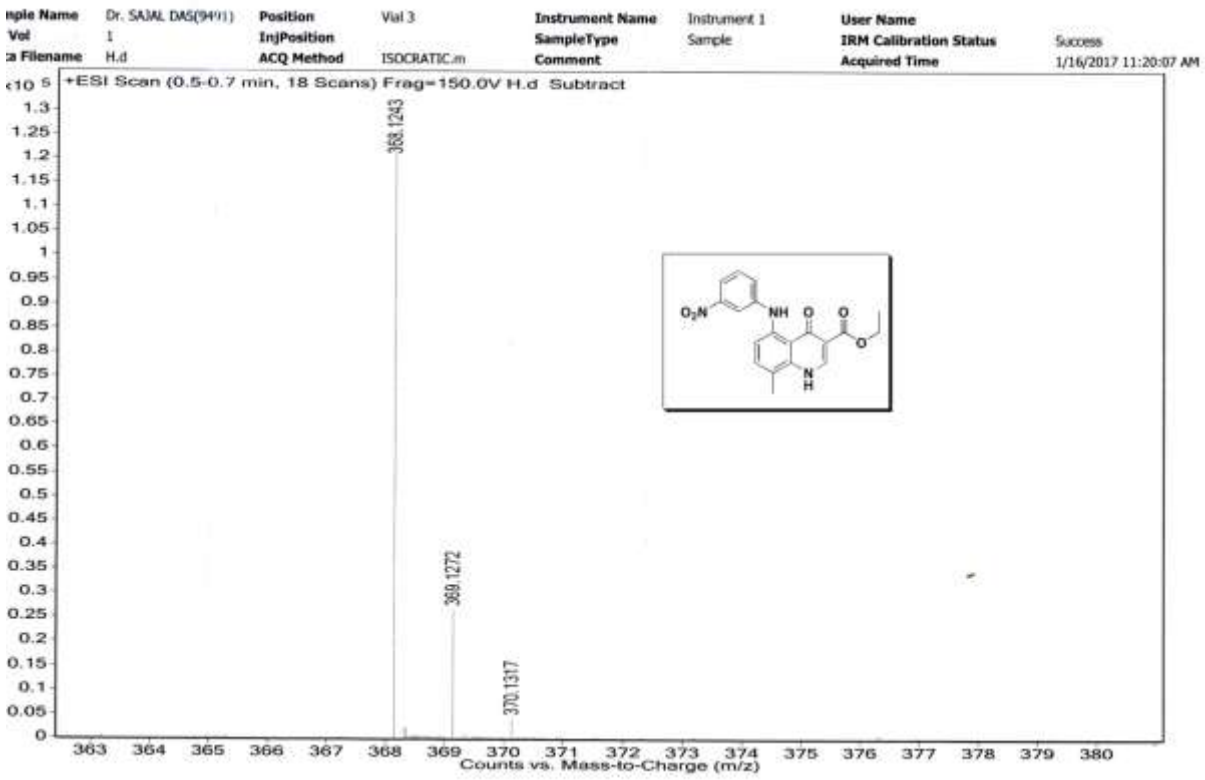
**Scan copy of HRMS of entry-3a (Scheme-VIII.2.)**




**Scan copy of HRMS of entry-3c (Scheme-VIII.2.)**



**Scan copy of HRMS of entry-3i (Scheme-VIII.2.)**




## VIII.E. References

References of chapter VIII are given in the Bibliography (pp-237-239)