Chapter VI

Microwave assisted synthesis of 6-aryl substituted 4-quinolones via regioselective bromination at C-6 position-"precursor of bioactive molecules"

VI.A. Introduction

4-quinolones scaffold has been widely occurred in both biologically active molecules and natural products. After the isolation of first quinolone antibiotic i.e.; nalidixic acid, it attracted a lot of attention in the medicinal chemistry.[1] Later, QSAR (quantitative structure activity relationship) studies have made a pitch for the development of quinolones with enhanced pharmacokinetic and pharmacodynamic properties.[2] Nowadays, these potent scaffolds are mainly serving as active components in various drugs such as antiviral,[3] antimalarial,[4] antibacterial,[5] antitumor[6],anticancer,[7]and anti-HIV[4a,8] agents. Some quinolone based drug molecules are shown below (figure 1). These potent quinolone based drugs also have some limitations such as oral side effects and poor adsorption etc.[9] Therefore; efforts are still going on to synthesize the efficient drug molecule with good oral absorption, minimal secondary effects and selective binding ability.

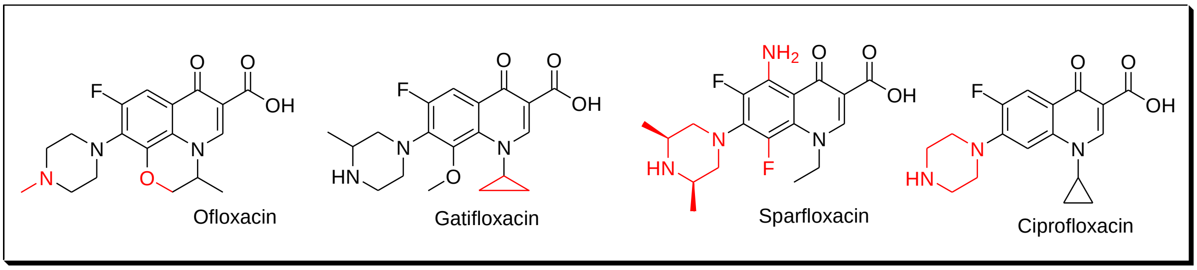
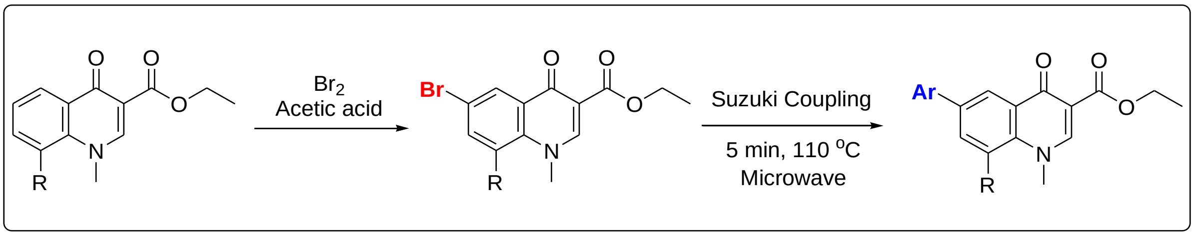


Fig –VI.1. Various quinolone base effective drug molecules

VI.B. Present work: Background & objectives

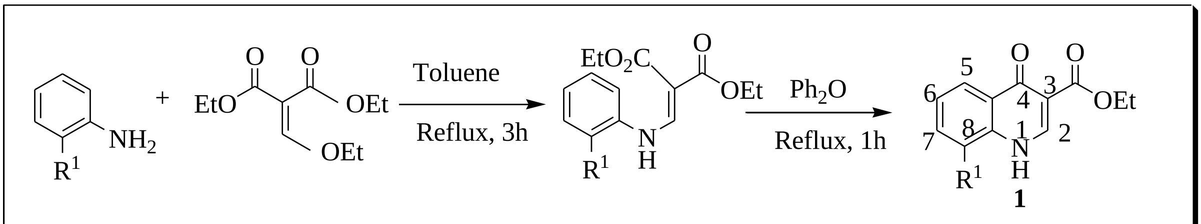
Many facile and well developed methods are easily available in the literature for the synthesis of 4-quinolones.Unfortunately, these methods allied with some drawback that the substituents needed on the quinolone scaffold could only be incorporated/launched during the formation of the main skeleton.[10] So, it is desirable to design the new strategies for introducing the substituents on the quinolone moiety as per our requirement. In recent years, researchers have been synthesized many quinolone derivatives bearing diverse C-6 substituents with high active therapeutic capabilities.[10f,11,12] Previous studies were mainly the introduction of aryl group at 1 and 2-postion of quinolone moiety. C-6 aryl substituted 4-quinolone derivatives acts as an inhibitors of hepatitis C virus (HCV), reported by Chen and his co-workers.[11b] It was reported that 6-substituted 4-quinolone-3-carboxamides showed high selective affinity for the human CB2 (cannabinoid-2) receptor over CB1.[11c] such reports inspired us to design a library of newly 6-aryl substituted 4-quinolone scaffolds. We execute selective functionalization at C-6 atom of quinolone skeleton *via* regioselective bromination at C-6 position and followed by Suzuki miyaura cross coupling reaction. (Scheme-VI.1).



Scheme-VI.1

VI.B. Present work: Result and discussion

Preliminary, we started our journey with the synthesis of starting material [ethyl-4-quinolone-3-carboxylate] compound **1** *via* the classic Gould-Jacobs method[10a] (Scheme-VI.2). It is found that the C-8 substituents of 4-quinolone increases the antibacterial activity.[9b] Again, fluoro group at C-8 position gave better oral absorption of the drug molecules.[13] In this regard, we took various substituents at C-8 position that could be isosteres and synthesized the compounds (**1a-1c**) as the starting materials of our present work (Scheme-VI.2).



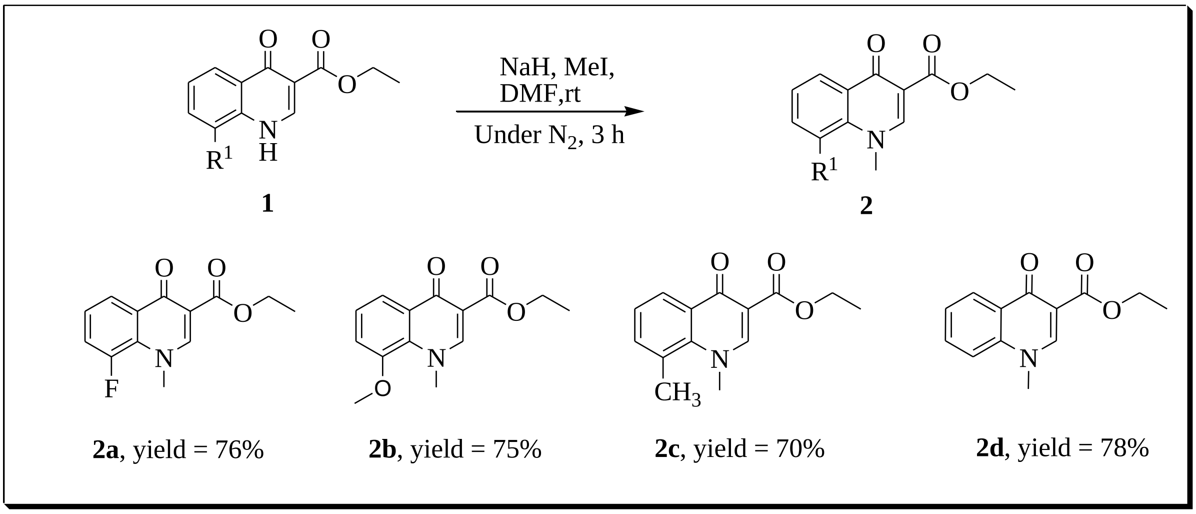
1a (R^1=F)= 52%, **1b**(R^1=OMe)= 55%,
1c (R^1=Me)= 70%, **1d**(R^1=H)= 50%

[All the entries were performed by the presenting author P. Ghosh]

Scheme-VI.2. General method for the synthesis of 4-quinolones **1.**

Most of the potent and effective quinolone drug molecules possessed with pre-functionalised –NH with smaller alkyl groups like ethyl, methyl and cyclopropyl groups. [14] Therefore before going for further functionalization of **1,** we replaced the -NH of compound with a methyl substituent. Several synthetic procedures for N-alkylation are well known in literature. [15]

After optimizing the reaction condition, NaH (sodium hydride) as a base and DMF as a solvent were found to be suitable in our system. Thus, to proceed the N-methylation, compound **1** was dissolved in DMF (*N,N*-dimethyl formamide) followed by gradual addition of MeI (methyl iodide) under inert atmosphere at 60ºC. No side product (O-methylated) was obtained. Electron donating or withdrawing group at C-8 position showed no significant change in the yield of N-methylated product.



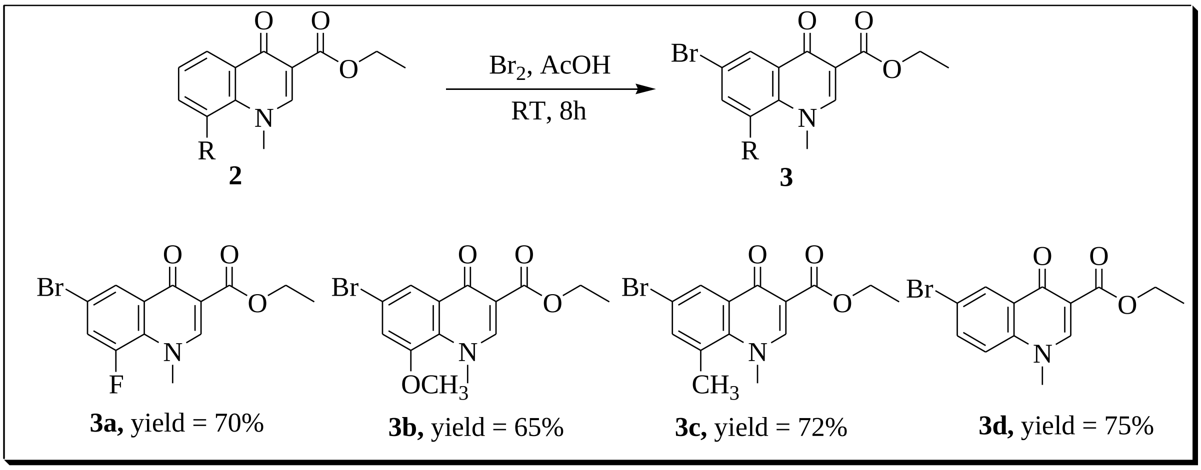
2a, yield = 76% **2b**, yield = 75% **2c**, yield = 70% **2d**, yield = 78%

[Entries 2a-2b were performed by the co–author S. Gupta and rest of the entries were performed by the presenting author P. Ghosh]

Scheme-VI.3. Synthesis of *N*-methylated derivatives **2** from compound **1**

VI.C. Regioselective bromination at C-6 position

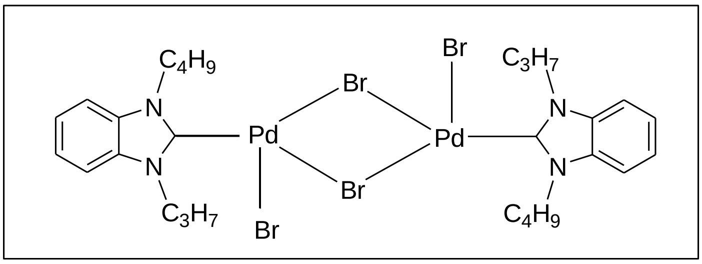
Bromination is one of the most imperative transformations in organic synthesis and can be carried out using bromine and many other brominating agents. Initially, we tried the bromination of compound **2** with NBS (*N*-Bromosuccinimide) in $CHCl_3$ (chloform) at ambient condition but yield of the desired product was not up to the benchmark. Then, performing the same reaction at higher temperature (50ºC) afforded only poor yield (yield<50%) of desired product even after 24 hours. Finally, Bromine in acetic acid medium at room temperature resulted regioselectively C-6 bromo derivatives with moderate yields (65-75%) (Scheme-VI.4)



3a, yield = 70% **3b,** yield = 65% **3c,** yield = 72% **3d,** yield = 75%

[Entries 3a-3b were performed by the co–author S. Gupta and rest of the entries were performed by the presenting author P. Ghosh]

Scheme-VI.4. Regioselective synthesis of C-6 substituted bromo derivatives **3**



After successful bromination of 4-quinolone at C-6 position, we attempted the functionalisation of **3** *via* transitional metal catalysed Suzuki Miyuara cross coupling reaction. In quest of appropriate conditions for the Suzuki coupling reaction we initiated the coupling of phenyl boronic acid with **3d** using various solvents and catalysts (common palladium salts) in the presence of K_2CO_3 (potassium carbonate). The results are shown below (Table-VI.1). Preferably, the combination of DMF as solvent and K_2CO_3 (potassium carbonate) as base was optimum for this cross-coupling reaction in presence of our pre-developed Pd-NHC catalyst (catalyst-A).

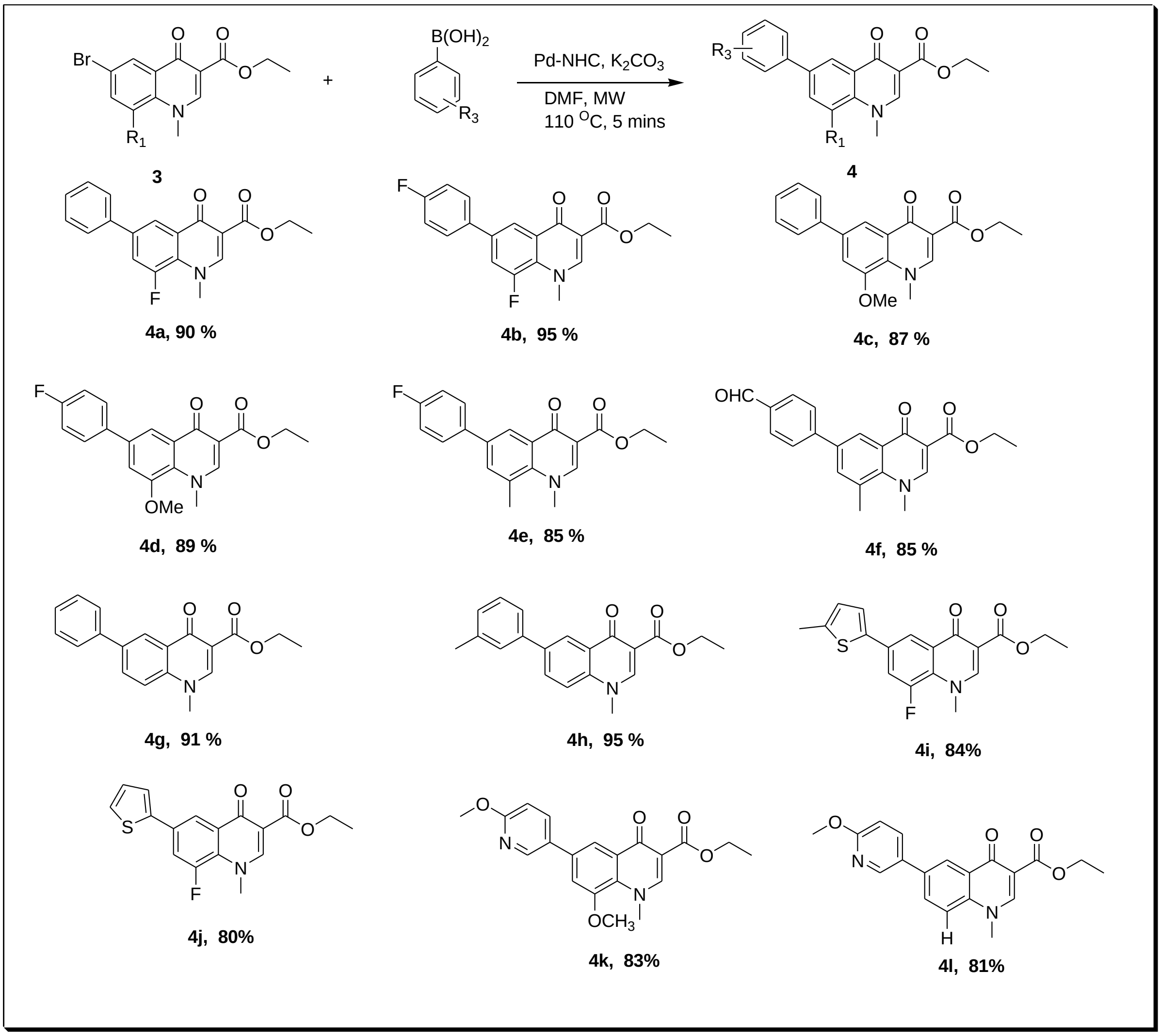
Table-VI.1. Screening of Suzuki coupling

entry	Pd-Catalyst	solvent	yield (%)
1	$Pd(OAc)_2$	DMF	73
2	$PdCl_2$	DMF	NR
3	$Pd(OAc)_2$	Toluene	63
4	$Pd_2(dba)_3$	DMF	64
5	Pd-NHC	DMF	91
6	Pd-NHC	DMF+H_2O (1:1)	55

Reaction conditions: compound **3d** (310 mg, 1 mmol), Phenylboronic acid (146 mg, 1.2 mmol), K_2CO_3 (276mg, 2 mmol), Pd-catalyst (19.2 mg, 2 mol%), 110ºC (microwave). Yield = Isolated yield after purification.

The desired cross-coupled product **4g** was rapidly formed within 5 minutes under microwave irradiation at 110ºC. Under our optimized condition, the compound **3** participated in Suzuki cross-coupling reaction with different arylboronic acids in a very facile manner to provide corresponding products in excellent yields (Scheme-VI.5). Compounds **3a** and **3b** furnished **4a** and **4c** in 90% and 87% yield. 4-fluorophenyl boronic acid effectively coupled with **3b, 3c** and **3d** to afford the **4d, 4e** and **4d** in 95%, 85% and 89% yields respectively.Sensitive functional group bearing phenyl boronic acid such as 4-formyl phenylboronic acid easily coupled with **3c** to give the cross-coupling product **4f** in excellent yield (85%). Substrates containing both electron-donating and withdrawing groups underwent smooth coupling to furnish the desired products within a short span of time (5 minutes).

In the literature, it was found that the heterocyclic ring substituent in quinolone ring showed profound anti-bacterial activity,[13] xanthine oxidase inhibition.[14] tubulin based assays,[15] and increased activity in-vitro cytotoxicity. Therefore, we explored our approach towards the cross-coupling reaction with heteroarylboronic and achieved prominent yields of corresponding coupled products (Scheme-VI.5). Compound **3a** suitably coupled with 5-methyl-2-thienylboronic acid and 2-thienylboronic acid and resulted the desired compounds **4i** and **4j** in 84% and 80% yields respectively. 6-methoxy-3-pyridinylboronicacid also effectively coupled with **3b** and **3a** to afford **4k** and **4l** in 83% and 81% yields respectively. A library of 6-aryl and heteroaryl substituted quinolones have been easily synthesized utilizing the regioselective bromination approach.



Reaction conditions: compound **3** (1 mmol), aryl(Het)boronic acid (1.2 mmol), K_2CO_3 (2 mmol), Pd-NHC (0.0192g, 2 mol%), DMF (3 mL), Microwave, 110ºC, 5 min. Yield = Isolated yields after column chromatography purification. [Entries 4a–4e were performed by the co–author S. Gupta and rest of the entries were performed by the presenting author P. Ghosh]

Scheme-VI.5. Suzuki cross coupling with heteroarylboronic acids forming products **4**

VI.D. Conclusion

We have unfolded a suitable synthetic way to provide 6-aryl substituted 4-quinolones. Our approach has some distinct advantages of easily forming substrates, regioselective bromination at C-6 position and corresponding arylation via Suzuki coupling reaction. The 6- bromo and 6- arylated entities isolated (**3→4**) are all newly synthesized compounds which are anticipated to be important components in drug designing. Various biological activities of these compounds are still going on in our laboratory.

VI.E. Experimental

VI.E.1. General Consideration

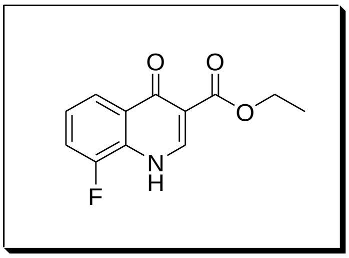
Unless stated otherwise, all reagents such as aromatic anilines, EMME, Palladium acetate, boronic acids and solvents were used as received from commercial suppliers. NMR spectra were recorded on 300 MHz spectrometer at 298 K with calibration done on the basis of solvent residual peak. Mass spectra were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

VI.E.2. Preparation of Compound 1

A reaction mixture of aniline (10 mmol), EMME (11 mmol) and toluene (30 mL) was refluxed in a 250 ml round bottom flask for 5 hours. It was then cooled and washed with 3(N) 100 mL H_2SO_4. Toluene was distilled out afterwards. The mixture was scratched vigorously to get solid anil product. This product (**5g**) was refluxed with biphenyloxide (50 mL) for 2 hours at 280 ºC. It was then cooled and stirred for an hour after addition of small amount (100 mL) of petroleumether. Crude compound **1** was obtained by filtration on Buchner funnel.

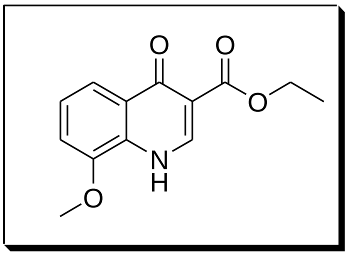
VI.E.3. Physical characteristics and spectral data of compounds

1. **Ethyl 8-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (1a)**



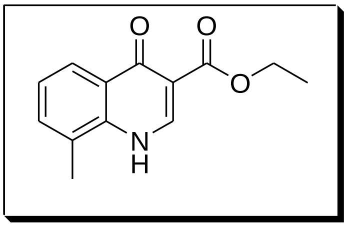
White solid; m.p. 217ºC-219ºC; ^{1}H NMR (300MHz, DMSO-d_6,25ºC, TMS):δ=1.28 (t, *J*=6.9 Hz, 3H), 4.22(q, *J*=6.9 Hz, 2H), 7.40 (m, 1H), 7.65 (t, *J*=9 Hz, 1H), 7.96 (d, *J*=7.8 Hz, 1H), 8.39 (s, 1H), 12.5 (bs, 1H);^{13}C NMR (75MHz,DMSO-d_6, 25ºC, TMS,): δ 14.23, 59.78, 110.47, 117.17, 117.40, 121.28, 121.33, 124.48, 124.57, 128.08, 128.26, 129.09, 144.67, 150.12, 153.41, 164.38, 172.53; HRMS (EI$^+$): [M]$^+$, found 235.0634. $C_{12}H_{10}FNO_3$ requires 234.0645.

2. Ethyl 1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylate (1b)



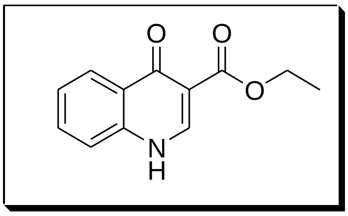
Greyish white; m.p. 243ºC-245ºC; ^{1}HNMR (300MHz, DMSO-d_6,25ºC, TMS): δ=1.26 (t, *J*=7.2Hz, 3H), 3.99 (s, 3H), 4.20 (q, *J*=7.2Hz, 2H), 7.29-7.37 (m, 2H), 7.70 (dd, *J*=7.2Hz, 1.2 Hz, 1H), 8.34 (s, 1H), 11.9 (s, 1H); ^{13}C NMR (75MHz, DMSO-d_6, 25ºC, TMS):δ=14.81, 56.81, 60.09, 110.44, 117.26, 125.06, 128.61, 129.79, 144.34, 144.66, 149.17, 165.12, 173.68; MS(ESI$^+$) m/z 270.31[M+Na]$^+$, elemental analysis calcd (%) for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.67. found C, 63.11; H, 5.34; N, 5.64.

3. Ethyl 1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylate (1c)



White solid; m.p. 249ºC-251ºC; ^{1}H NMR (300 MHz, DMSO-d_6,25ºC, TMS):δ=1.28 (t, *J*=7.2 Hz, 3H), 4.22 (q, *J*=7.2 Hz, 2H), 7.31 (t, *J*=7.8 Hz, 1H), 7.55 (d, *J*=6.9 Hz, 1H), 8.03 (d, *J*=7.8 Hz, 1H), 8.39 (s, 1H), 11.63 (s, 1H); ^{13}C NMR (75MHz, DMSO-d_6,25ºC, TMS):δ=14.77, 17.43, 60.11, 110.12, 124.02, 124.83, 127.45, 127.90, 133.71, 137.94, 145.01, 165.23, 174.11; HRMS (EI$^+$): [M]$^+$, found 231.0891. $C_{13}H_{13}NO_3$ requires 231.0895.

4. Ethyl 1,4-dihydro-4-oxoquinoline-3-carboxylate (1d)

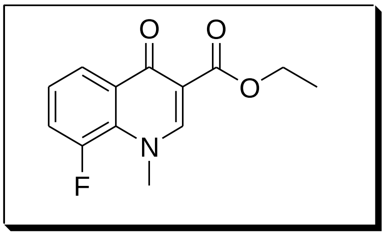


White solid; m.p. 251ºC-253ºC; ^{1}H NMR (300 MHz, DMSO-d_6,25ºC, TMS): δ=1.27 (t, *J*=7.2 Hz, 3H),4.21 (q, *J*=7.2Hz, 2H), 7.41 (t, *J*=6.9 Hz, 1H), 7.68 (m, 2H), 8.16 (dd, *J*=6.9 Hz, 0.9 Hz, 1H), 8.55(s,1H), 12.3 (s, 1H); ^{13}C NMR (75MHz, DMSO-d_6,25ºC, TMS):δ=14.80, 60.04, 110.22, 119.25, 125.17, 126.09, 127.72, 132.38, 139.42, 145.38, 165.28, 173.92.

VI.E.4. Preparation of N-methylated derivatives (2)

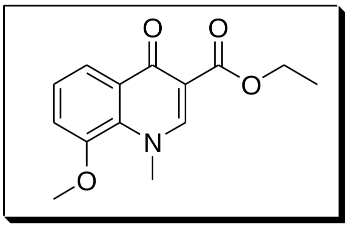
Compound **1** (1 mmol) and DMF (5 ml) were taken in a round bottom flask fitted with guard tube. NaH (36 mg, 1.5 mmol) was added and the reaction mixture was stirred at room temperature until H_2 gas ceased to evolve. Methyl iodide (284 mg, 2mmol) was then introduced drop-wise into the reaction mixture and it was further stirred at 60°C for 4 hours. The mixture was diluted with water and the product was extracted with DCM (3 x 20 mL). Organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was then purified using column chromatography.

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



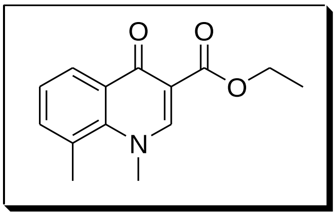
White solid; m.p. 121ºC-124ºC; ^{1}H NMR (300MHz,$CDCl_3$, 25ºC, TMS):δ=1.40 (t, *J*=7.2Hz, 3H), 4.10(d, *J*=8.1Hz, 3H), 4.38 (q, *J*=7.2Hz, 2H), 7.37 (m, 2H), 8.31 (m, 1H), 8.36 (s, 1H); ^{13}C NMR (75MHz,$CDCl_3$, 25ºC, TMS):δ=14.33, 46.06, 46.27, 61.06, 109.48, 120.34, 120.63, 122.47, 122.51, 126.30, 126.41, 129.22, 129.31, 130.44, 150.83, 152.51, 154.16, 165.10, 173.26; MS(ESI$^+$) m/z 271.95 [M+Na]$^+$, elemental analysis calcd (%) for $C_{13}H_{12}FNO_3$: C, 62.65; H, 4.85; N, 5.62. found C, 62.51; H, 4.88; N, 5.64.

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



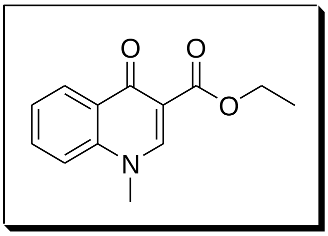
Light brown solid; m.p. 113ºC-116ºC;^{1}H NMR(300MHz,$CDCl_3$,25ºC, TMS):δ=1.23 (t, *J*=7.2Hz, 3H), 3.75 (s, 3H), 3.98 (s, 3H), 4.20 (q, *J*=7.2Hz, 2H), 6.96 (d, *J*=7.8Hz, 1H), 7.14 (m, 1H), 7.96 (d, *J*=8.1Hz, 1H), 8.16(s, 1H); ^{13}C NMR (75MHz,$CDCl_3$,25ºC, TMS):δ=14.78, 47.60, 57.24, 60.11, 109.64, 115.90, 118.57, 125.92, 130.98, 131.15, 151.12, 152.37, 164.98, 172.55; MS(ESI$^+$) m/z 284.31 [M+Na]$^+$, elemental analysis calcd (%) for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36. found C, 64.40; H, 5.75; N, 5.39.

7. Ethyl 1,4-dihydro-1,8-dimethyl-4-oxoquinoline-3-carboxylate (2c)



White solid; m.p. 91ºC-93ºC;^{1}H NMR (300MHz,$CDCl_3$,25ºC, TMS):δ=1.41(t, *J*=7.2Hz, 3H), 2.80(s, 3H), 4.11(s, 3H), 4.38(q, *J*=7.2Hz, 2H), 7.29 (m, 1H), 7.43 (m, 1H), 8.37(s, 1H), 8.42(d, *J*=8.1Hz, 1H);^{13}CNMR (75MHz,$CDCl_3$,25ºC, TMS): δ=14.45, 24.20, 46.99, 60.93, 110.23, 125.31, 126.38, 126.43, 130.66, 137.45, 140.36, 152.48, 165.83, 174.23; MS(ESI$^+$) m/z 268.32 $[M+Na]^+$, elemental analysis calcd (%) for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. found C, 68.40; H, 6.05; N, 5.74.

8. Ethyl 1,4-dihydro-1-methyl-4-oxoquinoline-3-carboxylate (2d)

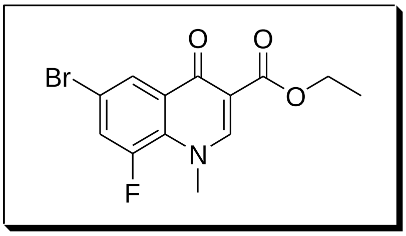


Brown solid; m.p.102ºC-105ºC; ^{1}H NMR (300MHz, $CDCl_3$, 25ºC, TMS): δ=1.44 (t, *J*=7.2Hz, 3H), 4.00 (s, 3H), 4.43 (q, *J*=7.2Hz, 2H), 7.53 (m, 2H), 7.78 (m, 1H), 8.55 (m, 1H), 8.80 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25ºC, TMS): δ=14.44, 41.40, 60.81, 110.66, 115.72, 125.23, 127.66, 128.78, 132.66, 139.66, 149.70, 165.63, 174.44.

VI.E.5 Preparation of bromo derivatives (3)

N-methylated product (compound **2**) was dissolved in minimum amount of acetic acid and equivalent quantity of bromine was added drop wise. The resulting mixture was stirred at room temperature for 8 hours. Then it was poured into water and the organic layer was extracted with DCM and concentrated under reduced pressure. The crude material was further purified using column chromatography.

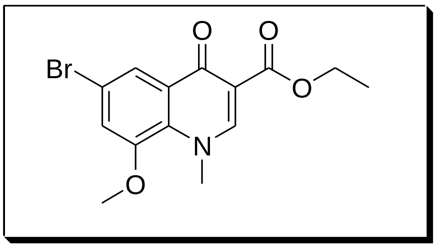
9. Ethyl 6-bromo-8-fluoro-1,4-dihydro-1-methyl-4-oxoquinoline-3-carboxylate (3a)



White solid; m.p. 150^{o}C-153^{o}C; ^{1}H NMR (300MHz $CDCl_3$,25ºC, TMS):δ=1.27 (t, *J*=7.2 Hz, 3H), 4.02 (d, *J*=8.7 Hz, 3H), 4.20 (q, *J*=7.2 Hz, 2H), 7.91 (dd, *J*=13.5Hz, 2.4 Hz, 1H), 8.03 (d, *J*=1.2 Hz, 1H), 8.52(s, 1H);^{13}C NMR (75

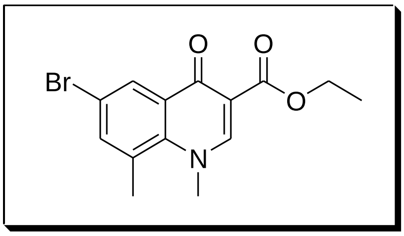
MHz,CDCl$_3$,25ºC, TMS):δ=14.75, 45.56, 60.43, 110.44, 117.23, 117.36, 122.74, 123.17, 124.90, 125.09, 129.08, 129.18, 131.93, 151.07, 152.35, 152.65, 154.46, 164.41, 170.48; HRMS (ESI+): $[M+1]^+$, found 327.9902. $C_{13}H_{11}BrFNO_3$ requires 327.9906.

10. Ethyl 6-bromo-1,4-dihydro-8-methoxy-1-methyl-4-oxoquinoline-3-carboxylate (3b)



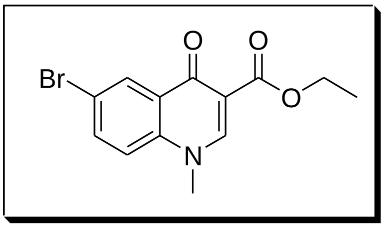
Yellowish white solid; m.p. 155ºC-157ºC; ^{1}H NMR (300MHz, CDCl$_3$, 25ºC, TMS):δ=1.40 (t, *J*=7.2Hz, 3H), 3.93 (s, 3H), 4.17 (s, 3H), 4.38 (q, *J*=7.2Hz, 2H), 7.18(d, *J*=2.1Hz, 1H), 8.20 (d, *J*=2.1Hz, 1H), 8.43 (s, 1H); ^{13}C NMR (75MHz, CDCl$_3$, 25ºC, TMS):δ=14.46, 48.32, 56.80, 61.30, 110.12, 117.75, 119.56, 121.96, 130.02, 131.71, 151.20, 152.12, 165.62, 172.09; HRMS (ESI$^+$): $[M+1]^+$, found 340.0119. $C_{14}H_{14}BrNO_4$ requires 340.0106.

11. Ethyl 6-bromo-1,4-dihydro-1,8-dimethyl-4-oxoquinoline-3-carboxylate (3c)



Yellowish white solid, m.p. 205ºC-208ºC; ^{1}H NMR (300MHz,CDCl$_3$,25ºC, TMS):δ=1.40 (t, *J*=7.2 Hz, 3H), 2.76 (s, 3H), 4.09 (s, 3H), 4.37 (q, *J*=7.2 Hz, 2H), 7.49 (d, *J*=2.4 Hz, 1H), 8.30 (s, 1H), 8.43 (d, *J*=2.4 Hz, 1H); ^{13}C NMR (75MHz,CDCl$_3$,25ºC, TMS): δ=14.43, 23.94, 47.08, 60.96, 110.36, 119.01, 128.52, 129.06, 131.69, 139.18, 139.65, 152.40, 165.09, 172.74; HRMS (ESI$^+$): $[M+1]^+$, found 324.0129. $C_{14}H_{14}BrNO_3$ requires 324.0157.

12. Ethyl 6-bromo-1,4-dihydro-4-oxoquinoline-3-carboxylate (3d)



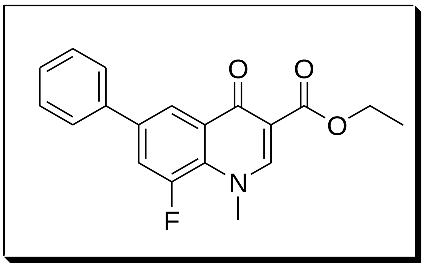
White solid, m.p. 108ºC-111ºC; ^{1}H NMR (300MHz,CDCl$_3$,25ºC, TMS):δ=1.39 (t, *J*=7.2 Hz, 3H), 3.85 (s, 3H), 4.36 (q, *J*=7.2 Hz, 2H), 7.28 (d, *J*=2.1 Hz, 1H), 7.70 (dd, *J*=9.0 Hz , 2.4 Hz, 1H), 8.36 (s, 1H), 8.49 (d, *J*=2.4 Hz, 1H); ^{13}C NMR (75 MHz,$CDCl_3$,25°C, TMS):δ=14.43, 41.52, 60.91, 111.04, 117.74, 119.27, 129.89, 130.06, 135.56, 138.44, 149.69, 165.02, 172.94; MS(ESI$^+$) m/z 332.05([M+Na]$^+$, ^{79}Br), 334.04 ([M+Na]$^+$, ^{81}Br), elemental analysis calcd (%) for $C_{14}H_{14}BrNO_3$: C, 50.34; H, 3.90; N, 4.52. found C, 50.31; H, 3.94; N, 4.48.

VI.E.6. Preparation of 6-arylated derivatives (4)

Compound **3** (1 mmol), aryl boronic acid (1.2 mmol), K_2CO_3 (276 mg, 2 mmol), Pd-NHC (0.0096 g, 1 mol %) and DMF (2 mL) were taken in a microwave reaction vessel. The mixture was placed in the focused microwave reactor and heated at 110℃ for 5 minutes. Then the solution was diluted with water and extracted with DCM (3 x 10 ml). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography.

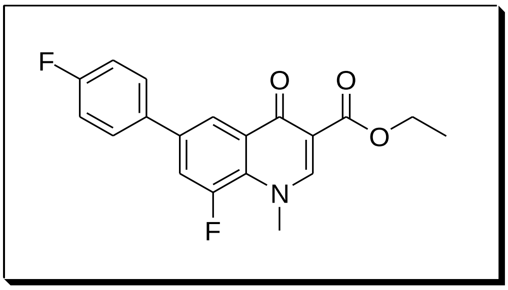
Spectral Analysis of 6-aryl substituted 4-quinolones

13. Ethyl 8-fluoro-1,4-dihydro-1-methyl-4-oxo-6-phenylquinoline-3-carboxylate (4a)



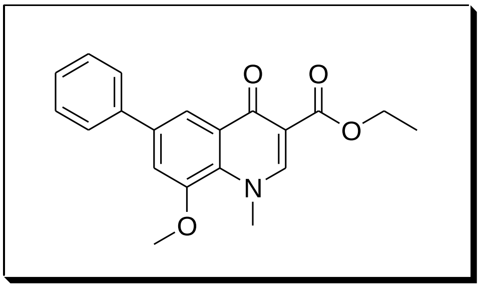
Light brown solid; m.p. 168°C-170°C; ^{1}H NMR (300MHz, $CDCl_3$, 25°C, TMS): δ=1.43 (t, *J*=7.2 Hz, 3H), 4.14 (d, *J*=8.1Hz, 3H), 4.41 (q, *J*=7.2Hz, 2H), 7.47 (m, 3H), 7.67 (m, 3H), 8.40 (s, 1H), 8.59 (d, *J*=2.4 Hz, 1H); ^{13}C NMR (75MHz, $CDCl_3$, 25°C, TMS): δ=14.43, 45.94, 46.15, 61.19, 110.85, 117.98, 118.29, 121.18, 127.03, 128.47, 129.16, 129.32, 131.68, 138.04, 138.72, 138.82, 151.01, 151.47, 165.62, 166.50, 173.00; MS(ESI$^+$) m/z 347.91 [M+Na]$^+$, $C_{19}H_{16}FNO_3$, elemental analysis calcd (%) for $C_{19}H_{16}FNO_3$: C, 70.14; H, 4.96; N, 4.31. found C, 70.07; H, 5.01; N, 4.33.

14. Ethyl8-fluoro-6-(4-fluorophenyl)-1,4-dihydro-1-methyl-4-oxoquinoline-3-carboxylate (4b)



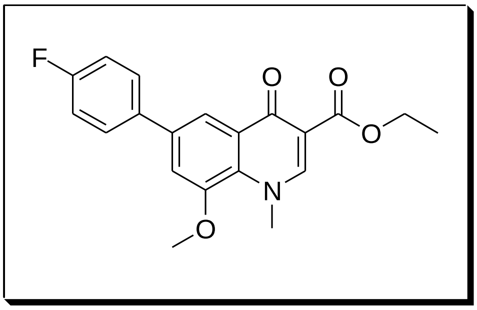
White solid; m.p. 184°C-187°C; ^{1}H NMR (300MHz, $CDCl_3$,25°C, TMS):δ=1.41(t, *J*=7.2Hz, 3H), 4.10 (d, *J*=8.1Hz, 3H), 4.39 (q, *J*=7.2 Hz, 2H), 7.15 (m, 2H), 7.58 (m, 3H), 8.33 (s, 1H), 8.48 (d, *J*=1.5Hz 1H); ^{13}C NMR (75MHz, CDCl$_3$, 25ºC, TMS):δ=14.47, 46.05, 46.24, 61.20, 110.96, 115.99, 116.28, 116.51, 117.80, 118.11, 121.01, 128.12, 128.21, 128.69, 128.80, 128.96, 131.76, 134.21, 137.66, 137.76, 151.01, 151.57, 154.32, 161.46, 164.76, 165.48, 166.39, 172.91; HRMS(ESI$^+$): [M+Na]$^+$, found 366.0868. $C_{19}H_{15}F_2NO_3Na$ requires 366.0918.

15. Ethyl 1,4-dihydro-8-methoxy-1-methyl-4-oxo-6-phenylquinoline-3-carboxylate (4c)



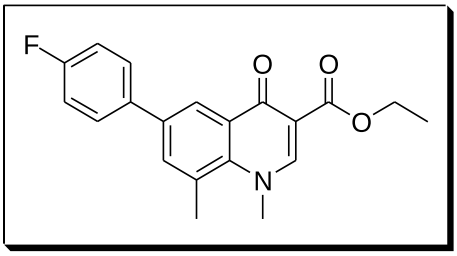
White solid; m.p. 182ºC-185ºC; ^{1}H NMR (300MHz, CDCl$_3$, 25ºC, TMS): δ=1.38 (t, *J*=7.2 Hz, 3H), 3.78 (s, 3H), 4.05 (s, 3H), 4.35 (q, *J*=7.2Hz, 2H), 7.21 (d, *J*=1.8Hz, 1H), 7.39 (m, 3H), 7.62 (d, *J*=7.2 Hz, 2H), 8.17 (s, 1H) 8.31(d, *J*= 1.8 Hz, 1H); ^{13}C NMR (CDCl$_3$,75MHz) δ 14.44, 47.82, 56.37, 60.68, 109.88, 112.91, 116.94, 126.87, 127.92, 128.91, 129.87, 131.35, 137.89, 139.19, 150.76, 151.48, 165.55, 173.55 ; MS(ESI+): m/z 337.95 [M]$^+$, elemental analysis calcd (%) for $C_{20}H_{19}NO_4$: C, 71.20; H, 5.68; N, 4.15. found C, 71.13; H, 5.60; N, 4.16.

16. Ethyl-6-(4-fluorophenyl)-1,4-dihydro-8-methoxy-1-methyl-4-oxoquinoline-3-carboxylate (4d)



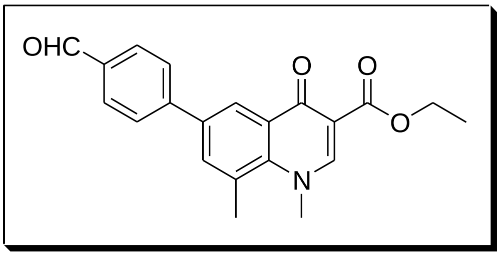
White solid; m.p. 178ºC-180ºC; ^{1}H NMR (300 MHz, CDCl$_3$, 25ºC, TMS): δ=1.44 (t, *J*=7.2 Hz, 3H), 4.03 (s, 3H), 4.22 (s, 3H), 4.42 (q, *J*=7.2 Hz, 2H), 7.17 (m, 2H), 7.32 (d, *J*=2.1 Hz, 1H), 7.65 (m, 2H), 8.35 (d, *J*=2.1Hz, 1H), 8.40 (s, 1H); ^{13}C NMR (75 MHz,CDCl$_3$,25ºC, TMS): δ=14.44, 47.87, 56.51, 60.93, 110.18, 113.07, 115.73, 116.02, 117.34, 128.66, 128.77, 130.04, 131.56, 135.56, 135.60, 137.40, 150.90, 151.71, 161.16, 164.44, 165.85, 173.60; MS(ESI$^+$): m/z 355.89 [M]$^+$, elemental analysis calcd (%) for $C_{20}H_{18}FNO_4$: C, 67.60; H, 5.11; N, 3.94. found C, 67.49; H, 5.01; N, 3.98.

17. Ethyl-6-(4-fluorophenyl)-1,4-dihydro-1,8-dimethyl-4-oxoquinoline-3-carboxylate (4e)



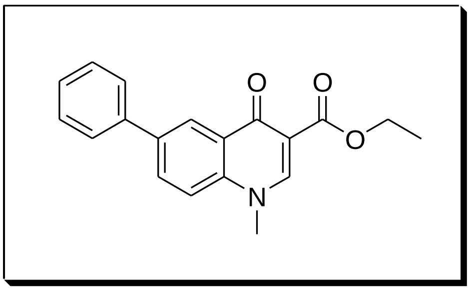
Light yellow solid; m.p. 217°C-220°C; ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ=1.41 (t, *J*=7.2Hz, 3H), 2.83 (s, 3H), 4.11 (s, 3H), 4.38 (q, *J*=7.2 Hz, 2H), 7.13 (t, *J*=8.7 Hz, 2H), 7.60 (m, 3H), 8.34 (s, 1H), 8.56 (d, *J*= 2.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C, TMS):δ=14.43, 24.34, 47.03, 60.86, 110.14, 115.71, 115.99, 123.61, 127.26, 128.51, 128.62, 130.89, 135.00, 135.77, 136.52, 139.38, 152.18, 161.09, 164.37, 165.46, 174.21; MS(ESI^{+}): m/z 361.92 [M+Na]$^{+}$, elemental analysis calcd (%) for $C_{20}H_{18}FNO_3$: C, 70.78; H, 5.35; N, 4.13. found C, 70.75; H, 5.08; N, 4.11.

18. Ethyl 6-(4-formylphenyl)-1,4-dihydro-1,8-dimethyl-4-oxoquinoline-3-carboxylate (4f)



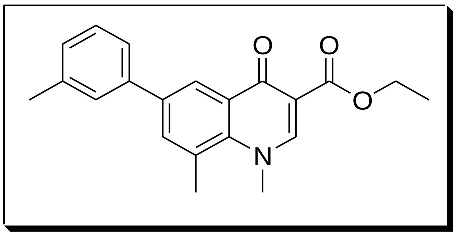
White solid; m.p. 230°C-233°C;^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ=1.39 (t, *J*=7.2 Hz, 3H), 2.87 (s, 3H), 4.14 (s, 3H),4.38 (q, *J*=7.2 Hz, 2H), 7.70 (s, 1H), 7.80 (d, *J*=8.1Hz, 2H), 7.95 (d, *J*=8.1Hz, 2H), 8.38 (s, 1H), 8.68 (s, 1H), 10.04 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C, TMS): δ=14.43, 24.38, 47.04, 61.02,110.62, 124.66, 127.53, 130.39, 131.00 ,135.50, 135.94, 136.01, 140.31, 144.84, 152.48, 165.49, 174.13, 191.85; MS(ESI^{+}) m/z 372.23 [M+Na]$^{+}$, elemental analysis calcd (%) for $C_{21}H_{19}NO_4$: C, 72.19; H, 5.48; N, 4.01. found C, 72.11; H, 5.40; N, 3.98.

19. Ethyl 1,4-dihydro-1-methyl-4-oxo-6-phenylquinoline-3-carboxylate (4g)



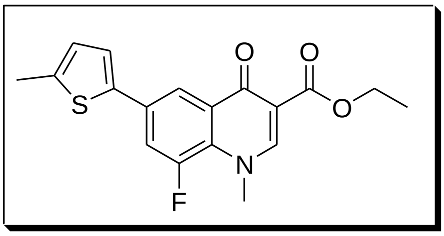
White solid, m.p. 137ºC-140ºC; ^{1}H NMR (300 MHz, CDCl$_3$, 25ºC, TMS): δ=1.31 (t, *J*=7.2Hz, 3H), 3.77 (s, 3H), 4.27 (q, *J*=7.2Hz, 2H), 7.35 (m, 4H), 7.55 (m, 2H), 7.76 (dd, *J*=8.7Hz, 2.1Hz, 1H), 8.29 (s, 1H), 8.58 (d, *J*=2.1 Hz, 1H); ^{13}C NMR (75 MHz, CDCl$_3$, 25ºC, TMS): δ=13.34, 40.42, 59.76, 109.40, 115.44, 123.97, 125.95, 126.84, 127.64, 127.93, 130.28, 136.80, 137.69, 137.89, 148.35, 164.38, 173.34; MS(ESI+): m/z 329.94 [M+Na]$^+$, elemental analysis calcd (%) for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56. found C, 74.21; H, 5.62; N, 4.60.

20. Ethyl 1, 4-dihydro-1-methyl-4-oxo-6-m-tolylquinoline-3-carboxylate (4h)



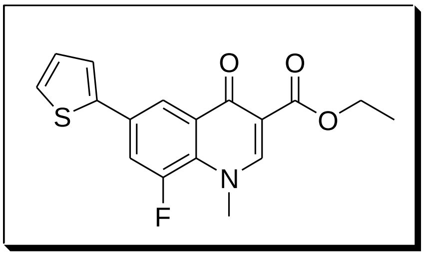
Light yellow solid; m.p. 98ºC-101ºC; ^{1}H NMR (300MHz, CDCl$_3$, 25ºC, TMS):δ=1.41(t, *J*=7.2 Hz, 3H), 2.44 (s, 3H), 3.97 (s, 3H), 4.42 (q, *J*=7.2 Hz, 2H), 7.21 (d, *J*=7.5 Hz, 1H), 7.36 (t, *J*=7.8 Hz, 1H), 7.51 (m, 3H), 7.97 (dd, *J*=8.7 Hz, 2.1 Hz, 1H), 8.61 (s, 1H), 8.75 (d, *J*=2.4 Hz, 1H); ^{13}CNMR (75MHz, CDCl$_3$, 25ºC, TMS):δ=14.43, 21.56, 41.64, 61.00, 110.54, 116.53, 125.12, 125.37, 127.81, 128.03, 128.69, 138.27, 138.71, 138.84, 139.00,149.37, 149.68, 165.79, 174.34; HRMS (EI$^+$): [M]$^+$, found 321.1366. $C_{20}H_{19}NO_3$ requires 321.1365.

21. Ethyl 8-fluoro-1, 4-dihydro-1-methyl-6-(5-methylthiophen-2-yl)-4-oxoquinolone-3-carboxylate (4i)



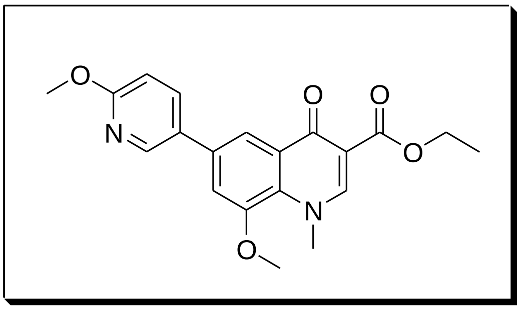
Light yellow solid; m.p. 158ºC-161ºC; ^{1}H NMR (300MHz, CDCl$_3$, 25ºC, TMS): δ=1.37 (t, *J*=6.9 Hz, 3H), 2.49 (s, 3H), 4.03 (m, 3H), 4.36 (q, *J*=6.9 Hz, 2H), 6.72 (m , 1H), 7.16 (d, *J*=3.6 Hz, 1H), 7.44 (dd, *J*=15Hz, 2.4 Hz, 1H), 8.23 (s, 1H), 8.36 (m, 1H); ^{13}C NMR (75MHz, $CDCl_3$, 25ºC, TMS): δ=14.42, 15.54, 45.91, 46.12, 61.15, 110.62, 116.25,116.57, 119.00, , 124.70, 126.72,127.54, 127.64, 131.65, 132.61,132.73, 138.87, 141.56, 150.87, 151.21, 154.18, 165.60, 172.70; HRMS (EI$^+$): $[M]^+$, found 345.0832. $C_{18}H_{16}FNO_3S$ requires 345.0835.

22. Ethyl 8-fluoro-1,4-dihydro-1-methyl-4-oxo-6-(thiophen-2-yl) quinolone-3-carboxylate (4j)



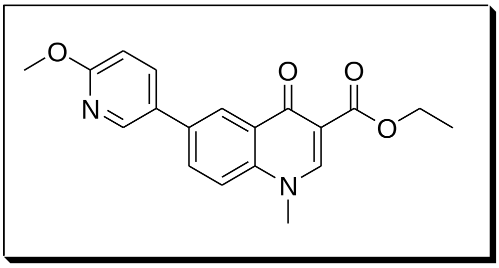
Light yellow solid; m.p. 185^{o}C-188^{o}C; ^{1}H NMR (300MHz, $CDCl_3$, 25ºC, TMS): δ=1.42 (t, *J*=7.2 Hz, 3H), 4.10 (d, *J*=8.1 Hz, 3H), 4.40 (q, *J*=7.20 Hz, 2H), 7.10-7.13 (m, 1H), 7.36 (dd, *J*=5.1Hz, 0.9 Hz, 1H), 7.44 (dd, *J*=3.6Hz, 1.2 Hz, 1H), 7.61 (dd, *J*=15Hz, 2.1 Hz, 1H), 8.34 (s, 1H), 8.54 (m, 1H); ^{13}C NMR(75 MHz, $CDCl_3$,25ºC, TMS):δ=14.43, 45.91, 46.12, 61.14, 110.78, 116.62, 116.94, 119.63, 119.67, 124.70, 126.46, 127.97, 128.47, 131.80, 132.16, 132.27, 141.37, 150.87, 151.31, 154.17, 165.51, 172.75; HRMS (EI$^+$): $[M]^+$, found 331.0676. $C_{17}H_{14}FNO_3S$ requires 331.0678.

23. Ethyl 1,4-dihydro-8-methoxy-6-(6-methoxypyridin-3-yl)-1-methyl-4-oxoquinoline-3-carboxylate (4k)



White solid; m.p. 181^{o}C-184^{o}C;^{1}H NMR (300MHz, $CDCl_3$, 25ºC, TMS): δ=1.42 (t, *J*=7.2 Hz, 3H), 4.00 (s, 6H), 4.18 (s, 3H), 4.40 (q, *J*=7.2 Hz, 2H), 6.85 (d, *J*=8.4 Hz, 1H), 7.27 (s, 1H), 7.90 (dd, *J*=5.4, 2.1 Hz, 1H), 8.31 (m, 2H), 8.46 (s, 1H); ^{13}C NMR (75MHz,$CDCl_3$,25ºC, TMS):δ=14.45, 47.87, 53.77, 56.52, 60.92, 110.28, 111.12, 112.55, 117.03, 128.55, 130.08, 131.76, 135.12, 137.54, 144.89, 151.04, 151.74, 163.91, 165.81, 173.57; MS(ESI+): m/z 391.20 $[M+Na]^+$, elemental analysis calcd (%) for $C_{20}H_{20}N_2O_5$: C, 65.21; H, 5.47; N, 7.60. found C, 65.23; H, 5.45; N, 7.62.

24. Ethyl 1,4-dihydro-6-(6-methoxypyridin-3-yl)-1-methyl-4-oxoquinoline-3-carboxylate (4l)



White solid; m.p. 169^{o}C-171^{o}C; ^{1}H NMR (300MHz, CDCl$_3$,25ºC, TMS):δ 1.40 (t, *J* = 7.2 Hz, 3H), 3.88 (s, 3H), 3.99 (s,3H), 4.37(q, *J*=7.2Hz, 2H), 6.82 (d, *J*=8.7Hz, 1H), 7.46 (d, *J*=8.7Hz, 1H), 7.82(m, 2H), 8.39 (d, *J*=10.8Hz, 2H), 8.56 (d, *J*=1.5Hz, 1H); ^{13}C NMR (CDCl$_3$, 75MHz) δ : 14.42, 41.45, 53.66, 60.79, 110.71, 116.69, 124.56, 128.08, 128.97, 130.62, 134.64, 138.74, 144.98, 149.91, 163.88, 165.39, 174.18; MS(ESI^{+}): m/z 361.24 [M+Na]$^{+}$, elemental analysis calcd (%) for $C_{19}H_{18}N_2O_4$: C, 67.44; H, 5.79; N, 5.36. found C, 67.41; H, 5.82; N, 5.39.

VI.F. References

References are given in BIBLIOGRAPHY under Chapter VI (pp-234-236)