CHAPTER III

Synthesis of 6-Aryl Substituted 4-quinolones *via* Pd-NHC Complex Catalyzed Suzuki Cross-Coupling

III.A. Introduction

4-Quinolones are the most privileged scaffolds found in both natural products and biologically active molecules. It has experienced a prolific development after the accidental discovery of the first synthetic antibiotic i.e.; nalidixic acid in 1962.[1] Further, SAR (structure activity relationship) studies have facilitated the development of quinolones with better pharmacokinetic properties and good tolerability.[2] These potent quinolone derivatives are now serving as active components in diverse families of drugs such as antibacterial,[3] antiviral,[4] antimalarial,[5] anticancer,[6] antitumor[7] and anti-HIV[4a,8] agents. A few important biologically active moieties based on quinolone scaffold are shown in figure-III.1. In spite of wide applicability of quinolone based drugs, these are often associated with limitations like poor absorption, side effects etc.[9] Hence, efforts are still inevitable in synthesizing highly efficient drugs with good oral absorption, selective binding ability and minimal secondary effects.

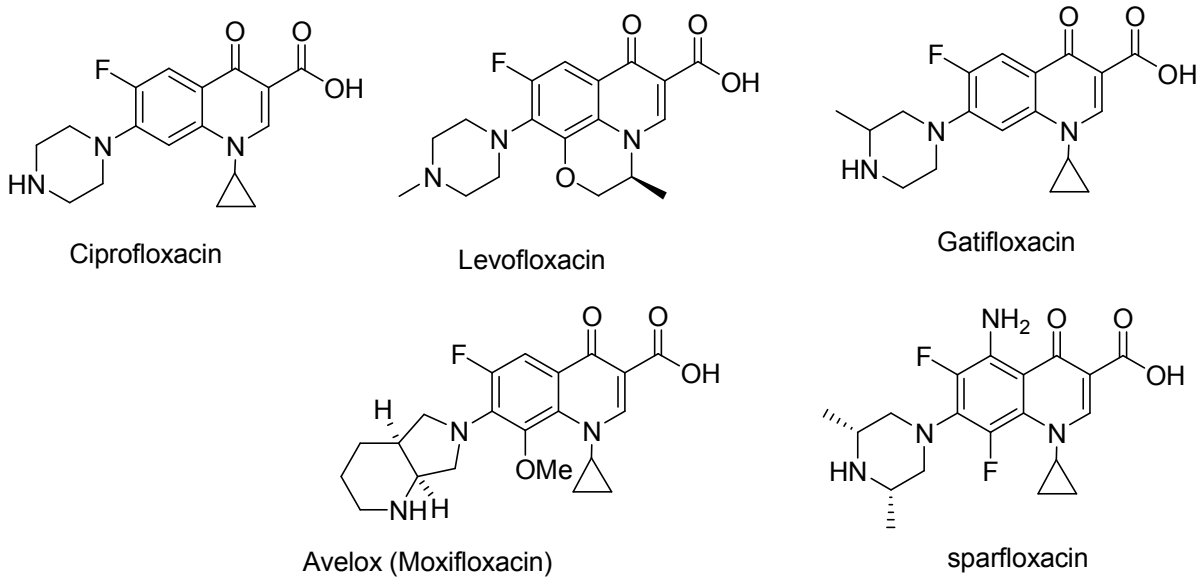


Figure-III.1: Structures of several biologically active quinolones.

Many reliable and well established methods are available for the library synthesis of 4-quinolones, but majority of them are allied with the drawback that the substituents required on the quinolone moiety could only be introduced during the synthesis of the main skeleton.[10] This confines the scope of fine tuning of structure activity relationships. As substituents play

crucial role in deciding the drug efficacy, for the effective library synthesis of 4-quinolones, it is desirable to develop new strategies permitting introduction of substituents at later stage or as per requirement.

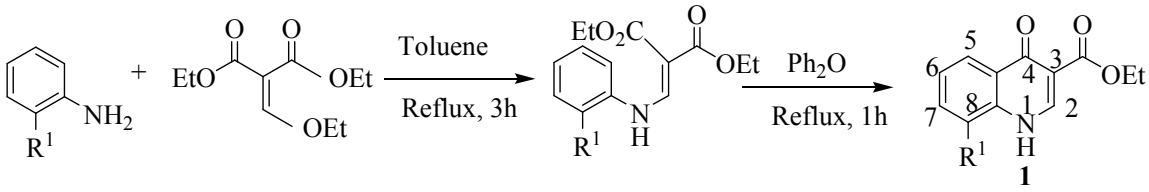
III.B. Present work: Background, objective and strategy

Aryl substituted 4-quinolones are known to be effective drugs as Plasmodium falciparum Type II NADH: Quinone Oxidoreductase (PfNDH2) inhibitors,[11] M1 positive allosteric modulators with reduced plasma protein binding,[12]selective agonists of somatostatin receptor subtype 2,[13a] inhibitors of tubulin polymerization and binding of radiolabeled colchicines to tubuline.[7b] Earlier studies include aryl substitution mostly at 1 and 2 positions of the quinolone moiety. Scientists are now investigating the influence of 6- aryl substitution on therapeutic applications of quinolones which are yet to be explored well. Recent work by Chen and co-workers reported C-6 aryl substituted 4-quinolone derivatives as inhibitors of hepatitis C virus (HCV).[13b] 6-substituted 4-quinolone-3-carboxamides having high selective affinity for the human CB2 (cannabinoid-2) receptor over CB1 are also reported.[13c] Such promising perspectives of 6-arylated-4-quinolones inspired us to synthesize such entities via Suzuki cross coupling of compounds **3**. This method offered opportunity to enrich the library of 6-aryl substituted quinolone scaffolds.

we endeavored to create the way for sequential functionalization of quinolones. Many research works in recent past have reported quinolone derivatives bearing diverse C-6 substituents exhibiting highly active therapeutic capabilities.[10f,13,14] This indulged our interest to execute selective functionalization at C-6 atom of quinolone skeleton. In this context, herein we disclose a simple and convenient route for the selective bromination of 4-quinolone motifs which effectively results 6-bromo-4-quinolones. These bromoquinolones then can be participated various kind of organic transformations prevailing the access of structurally diverse 6-substituted quinolones. Here we have only studied the Pd-NHC catalyzed Suzuki coupling reactions for the synthesis of 6-aryl substituted 4-quinolones.

III.C. Present work: Result and discussion

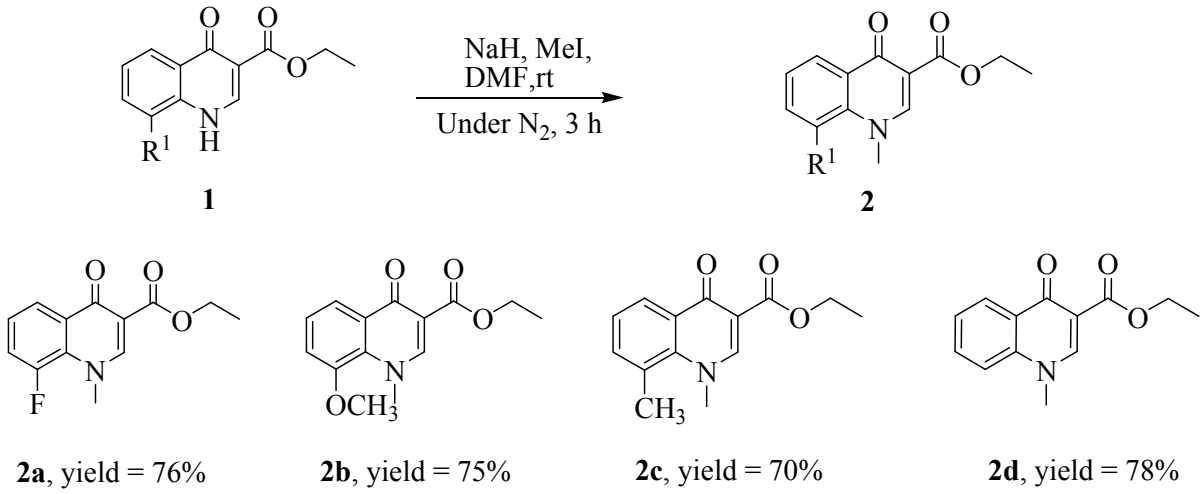
We began our journey with the synthesis of starting scaffolds [ethyl-4-quinolone-3-carboxylate] compound **1** *via* the classic Gould-Jacobs approach[10a] (scheme-III.1). It is reported that the presence of substituent at C-8 position of 4-quinolone enhances the antibacterial activity.[9b] Again, fluoro group at C-8 owes better oral absorption of the drug.[15] So, we considered different substituents at C-8 position that could be isosteres or analogs and accordingly synthesized compounds (**1a-1c**) as the starting materials of the present work, 8-substituted-4-quinolones (scheme-III.1).



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

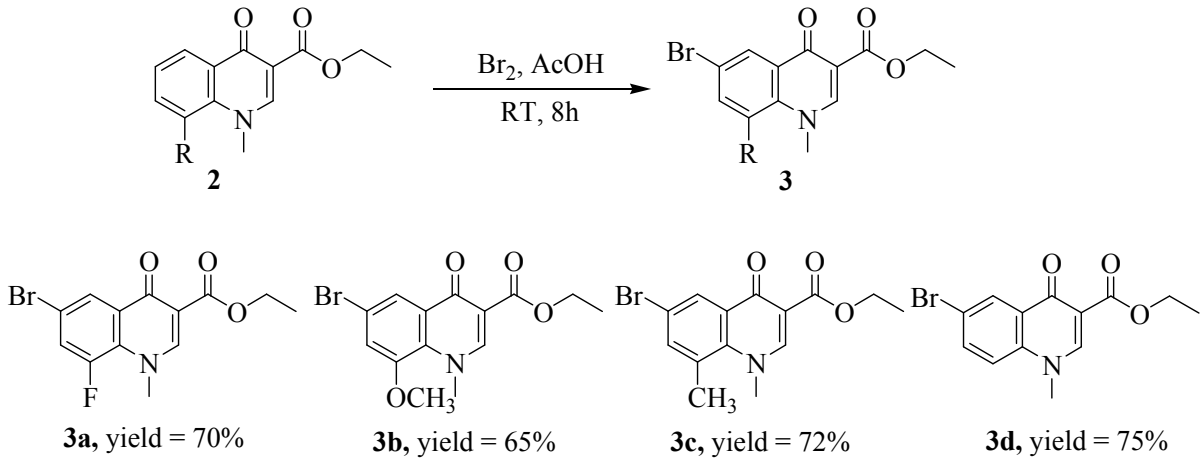
Scheme-III.1: General synthesis of 4-quinolones **1.**

It is known that the protection of the N-H of compound **1** with alkyl group (preferable smaller alkyl groups like methyl, ethyl and cyclopropyl) is essential to enhance drug potency and efficiency.[16] Therefore we have replaced the N-H of compound **1** with a methyl substituent. Synthetic procedures of N-alkylation are well documented in literature.[17]After screening of standard techniques, use of NaH (sodium hydride) as base was found to be best suited in our system. Hence, to carry out N-methylation, compound **1** was treated with NaH in dry DMF (*N,N*-dimethyl formamide) followed by the addition of methyliodide under inert atmosphere at 60ºC. The desired N-methylated product **2** was obtained in good yields (scheme-III.2) without formation of the possible side product (O-methylated). Presence of electron donating or withdrawing group at C-8 position literally has no significant role in this reaction. Selective bromination followed by the Suzuki coupling was studied next to access the structurally diverse 4-quinolones.



Scheme-III.2: Synthesis of *N*-methylated derivatives **2** from compound **1**

Initially, we attempted the bromination of compound **2** with NBS (*N*-Bromosuccinimide) in chloroform at room temperature but the rate of the reaction as well as the yield of desired product was not satisfactory. Conducting the reaction at higher temperature (50ºC) which also resulted poor yield (yield<50%) of desired compound even after continuing the reaction up to 24 hours. Finally, the treatment of compound **2** with bromine in acetic acid medium at room temperature resulting the corresponding 6-bromo derivatives selectively in satisfactory yields (65-75 %). (Scheme-III.3)



Scheme-III.3: Synthesis of 6-bromo-4-quinolone derivatives **3**

In search of suitable conditions for the Suzuki coupling reaction we first examined the coupling of phenyl boronic acid with **3d** using different solvents and catalysts (common palladium salts) in the presence of potassium carbonate. The results are shown in table-III.1. Notably, the combination of DMF as solvent and K_2CO_3 (potassium carbonate) as base was best suited for this coupling reaction in presence of our developed Pd-NHC catalyst (catalyst-A).

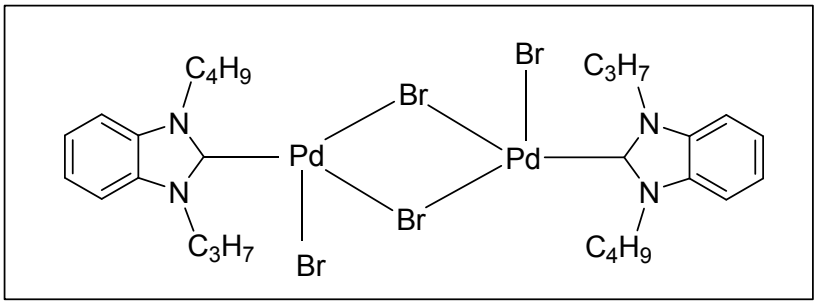


Figure-III.2: Benzimidazole base Pd-NHC complex (catalyst-A)

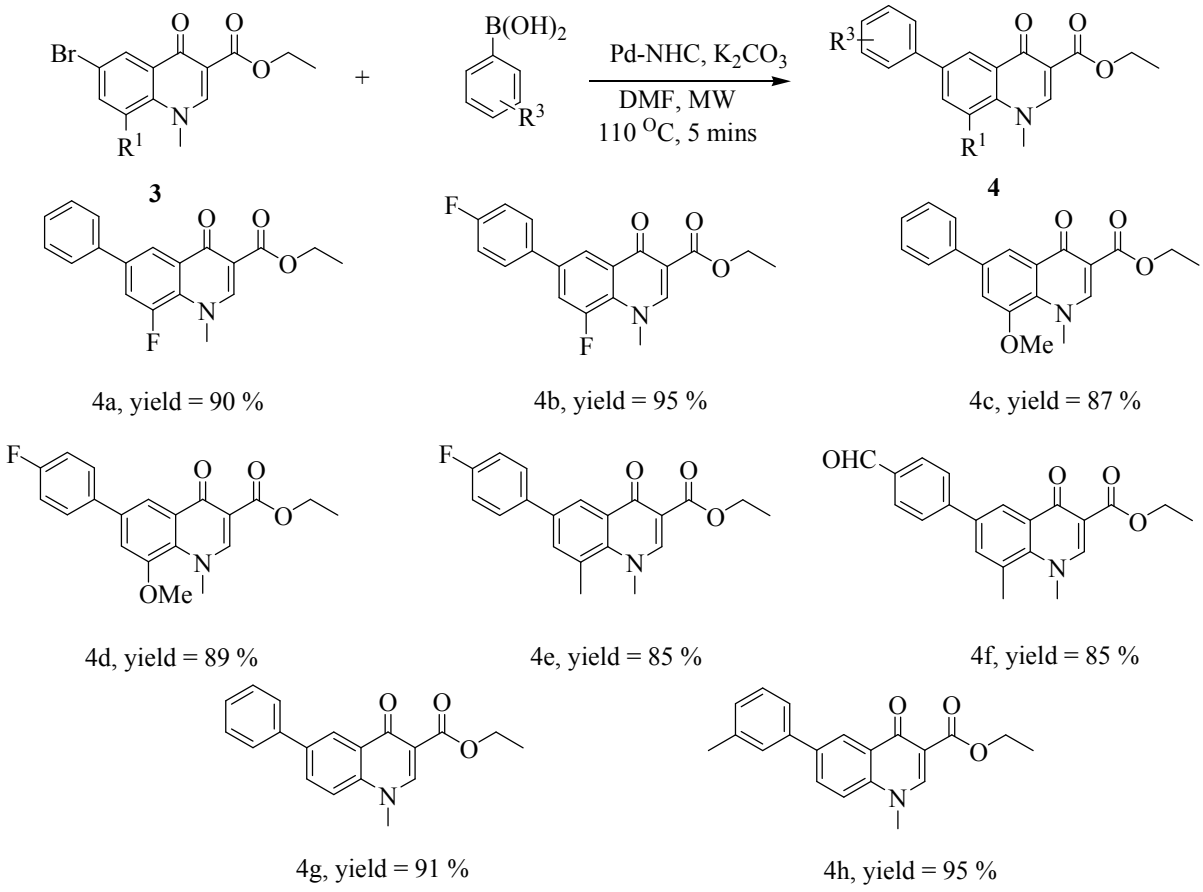
Table-III.1: Standardization of Suzuki coupling[a]

Entry	Pd-Catalyst	Solvent	Yield (%)[b]
1	$Pd(OAc)_2$	DMF	73
2	$PdCl_2$	DMF	NR
3[c]	$Pd(OAc)_2$	Toluene	63
4	$Pd_2(dba)_3$	DMF	64
5	Pd-NHC	DMF	91
6	Pd-NHC	DMF+H_2O (1:1)	55

[a]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). [b]Isolated yield after purification.

The desired coupled product **4g** was formed within 5 minutes under microwave irradiation at 110ºC. Suzuki cross-coupling reaction of compound **3** with different arylboronic acids under this optimized condition furnished the corresponding cross-coupled products in excellent yields (scheme-III.4). Compounds **3a** and **3b** were successfully coupled with phenylboronic acid and correspondingly produced **4a** and **4c**

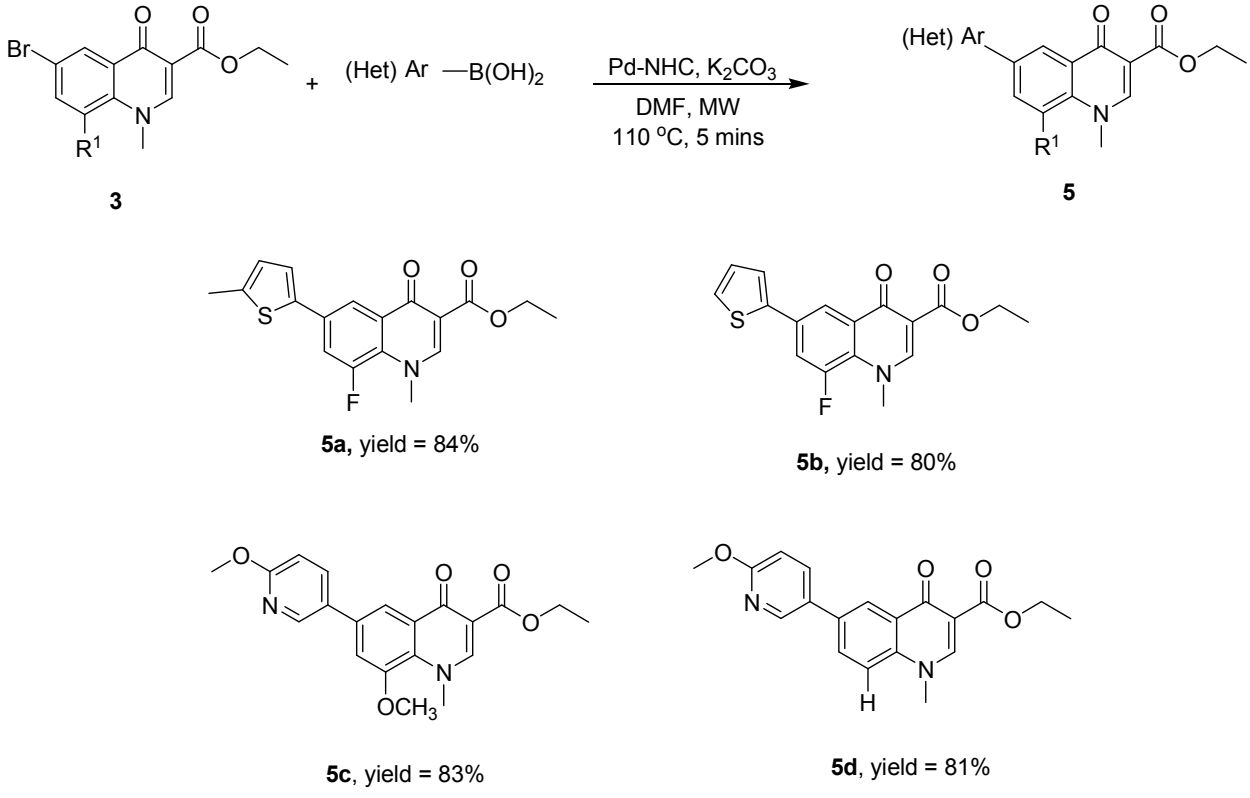
in 90% and 87% yield. With 4-fluorophenyl boronic acid they provided coupled products **4b** and **4d** in 95% and 89% yields respectively. The compound **3c** coupled with 4-fluoroboronic acid to afford **4e** in 85% yield. The compound **3d** underwent smooth coupling with phenylboronic acid and 3-methyl phenylboronic acid to yield the desired cross-couple products in 91% and 95% respectively. Highly active, 4-formyl phenylboronic acid was also successfully coupled with **3c** to furnish the cross-coupling product **4f** in high yield (85%). Hence our potential catalytic system allowed the smooth coupling of compound **3** with different aryl boronic acids under the optimized condition. Substrates having both electron-donating and withdrawing groups are easily participated in the reaction to afford the desired couple products within a short time (5 minutes).



Reaction conditions: compound **3** (1 mmol), aryl boronicacid (1.2 mmol) , K_2CO_3 (2 mmol), Pd-NHC (0.0192g, 2 mol%), Dry DMF (3mL), Microwave, 110ºC, 5 min. Isolated yields after column chromatography purification

Scheme-III.4: Synthesis of 6-aryl-4-quinolones

It is reported that the presence of heterocyclic ring substituents in many quinolone derivatives attribute enhanced anti-bacterial activity,[15] increased activity in in-vitro cytotoxicity and tubulin based assays,[18] and xanthine oxidase inhibition.[19] Therefore, we further explored the influence of heteroarylboronic acids on reaction performance and employed similar reaction condition to couple thienyl and pyridinyl boronicacid derivatives with 6-bromoquinolones **3** and achieved high yields of corresponding coupling products with general structure **5** (scheme-III.5). Compound **3a** coupled with 5-methyl thienylboronic acid and thienylboronic acid and furnished compounds **5a** and **5b** in 84% and 80% yields respectively. 6-methoxy-3-pyridinylboronicacid also coupled to provide **5c** and **5d** in 83% and 81% yields respectively. Hence, our reaction system was found compatible with variety of substituted aryl and heteroarylbronic acids. A family of 6-aryl and heteroaryl substituted quinolones have successfully been synthesized utilizing the 6-bromoquinolones **3**.



Reaction conditions: compound **3** (1 mmol), heteroaryl boronic acid (1.2 mmol), K_2CO_3 (2 mmol), Pd-NHC (0.0192g, 2 mol%), DMF (3 mL), Microwave, 110ºC, 5 min. Isolated yields after column chromatography purification.

Scheme-III.5: Suzuki cross coupling with heteroarylboronic acids forming products **5**

III.D. Conclusion

We have demonstrated a suitable synthetic approach to obtain bromo and aryl substitution at 6-position of 4-quinolones. The bromo group may easily be substituted by different functional groups using various common synthetic reactions, thus opening opportunity to access variety of substituted quinolones. For instance we employed these bromoquinolones to Suzuki cross coupling reaction and produced a set of arylated quinolones. Both electron donating and withdrawing groups are well tolerated to provide excellent yields. Heterocyclic groups (thiophene and pyridine derivatives) are also successfully coupled in high yields. The 6- bromo and 6- arylated entities synthesized (**3→5**) are all new compounds which are anticipated to be valuable components in drug designing. Exploring antimicrobial activities of these compounds in future may also add upon the current knowledge about the structural activity relationships.

III.E. Experimental

III.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.

III.E.2. Preparation of Compound 1

A 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.

III.E.3. Spectral Analysis of 1a, 1b, 1c and 1d

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.

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.

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.

Ethyl 1,4-dihydro-4-oxoquinoline-3-carboxylate (1d)[20]

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.

III.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.

III.E.5. Spectral analysis of N-methylated derivatives (2) of 4-quinolones (1)

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.

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.

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.

Ethyl 1,4-dihydro-1-methyl-4-oxoquinoline-3-carboxylate (2d)[20]

Brown solid; m.p.102ºC-105ºC; ^{1}HNMR (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.

III.E.6. 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.

III.E.7. Spectral analysis of 6-bromo 4-quinolone derivatives (3)

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

White solid; m.p. 150ºC-153ºC; ^{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.

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.

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.

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,$CDCl_3$,25ºC, 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.

III.E.8. Preparation of 6-arylated derivatives (4 and 5)

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.

III.E.9. Spectral Analysis of 6-aryl substituted 4-quinolones

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

Light brown solid; m.p. 168ºC-170ºC; ^{1}H NMR (300MHz, $CDCl_3$, 25ºC, 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, $CDCl_3$, 25ºC, 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.

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

White solid; m.p. 184ºC-187ºC; ^{1}H NMR (300MHz, $CDCl_3$,25ºC, 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.

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.

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.

E**thyl-6-(4-fluorophenyl)-1,4-dihydro-1,8-dimethyl-4-oxoquinoline-3-carboxylate (4e)**

Light yellow solid; m.p. 217^{o}C-220^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$, 25ºC, 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, $CDCl_3$, 25ºC, 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.

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

White solid; m.p. 230ºC-233ºC;^{1}H NMR (300 MHz, $CDCl_3$, 25ºC, 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, $CDCl_3$, 25ºC, 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.

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.

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.

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

Light yellow solid; m.p. 158^{o}C-161^{o}C; ^{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.

Ethyl 8-fluoro-1,4-dihydro-1-methyl-4-oxo-6-(thiophen-2-yl) quinolone-3-carboxylate (5b)

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.

Ethyl 1,4-dihydro-8-methoxy-6-(6-methoxypyridin-3-yl)-1-methyl-4-oxoquinoline-3-carboxylate (5c)

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.

Ethyl 1,4-dihydro-6-(6-methoxypyridin-3-yl)-1-methyl-4-oxoquinoline-3-carboxylate (5d)

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.

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