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Synthesis of 6-aryl substituted 4-quinolones *via* Suzuki cross coupling†

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A convenient way to introduce aryl functionalization in the 6-position of 4-quinolones is developed *via* selective bromination and subsequent arylation by Suzuki cross-coupling. Ethyl 4-quinolone 3-carboxylates were subjected to selective bromination at C-6 followed by arylation under microwave irradiation that yielded the desired cross-coupling products within 5 minutes. This approach can expediently be used for library synthesis of the aryl functionalized 4-quinolone derivative, an important class of biologically active compounds.

Introduction

4-Quinolones are the most privileged scaffolds found in both natural products and biologically active molecules. They have experienced 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 now serve 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 the quinolone scaffold are shown in Fig. 1. In spite of the wide applicability of quinolone based drugs, they are often associated with limitations like poor absorption, side effects *etc.*[9] Hence, efforts are still required to synthesize highly efficient drugs with good oral absorption, selective binding ability and minimal secondary effects.

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 can only be introduced during the synthesis of the main skeleton.[10] This confines the scope of fine tuning of the structure activity relationships. As substituents play a crucial role in deciding drug efficacy, for an effective library synthesis of 4-quinolones, it is desirable to develop new strategies that permit the introduction of substituents at later stage or as per the requirements. So, we endeavored to create a way to undertake sequential functionalization of quinolones. Many research works in the recent past have reported quinolone derivatives bearing diverse C-6 substituents that exhibit highly active therapeutic capabilities.[10f,11,12] This fostered our interest to execute selective functionalization at the C-6 atom of the quinolone skeleton. In this context, herein, we disclose a simple and convenient route for the selective bromination of compound **2** which effectively yields 6-bromo-4-quinolones. These bromoquinolones can then participate in various kinds of organic transformations, and the access of structurally diverse 6-substituted quinolones is prevailed. Here we have studied only the Suzuki coupling reactions for the synthesis of 6-aryl substituted 4-quinolones.

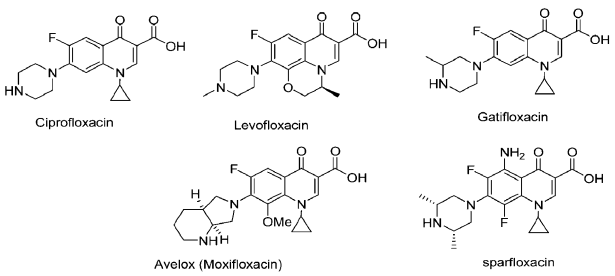
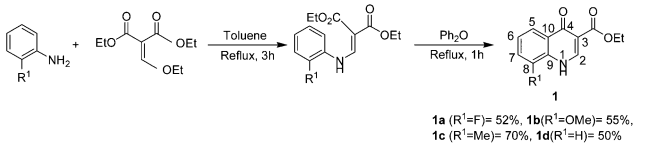


Fig. 1 Structures of several biologically active quinolones.

Results and discussion

We began by synthesising the starting scaffolds [ethyl-4-quinolone-3-carboxylate] compound **1** *via* the classic Gould–Jacobs approach[10a] (Scheme 1). It is reported that the presence of the substituent at the C-8 position of 4-quinolone enhances the



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

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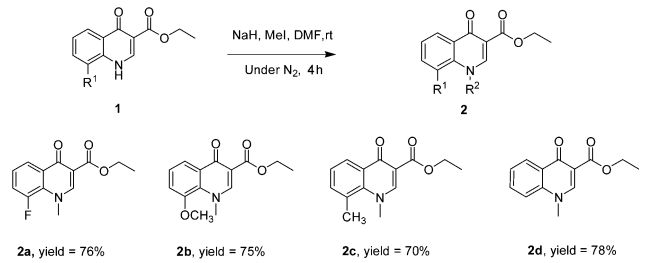
† Electronic supplementary information (ESI) available: Copies of ^{1}H and ^{13}C NMR of all compounds. See DOI: 10.1039/c3ra45056b

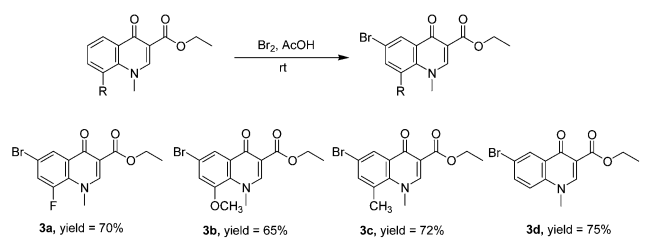


Scheme 2 Synthesis of *N*-methylated derivatives **2** from compound **1**. *Reaction conditions*: compound **1** (1 mmol), NaH (0.036 mg, 1.5 mmol), MeI (0.284 g, 2 mmol) in DMF at 60 °C. Stirring under N_2 atmosphere, 4 h. Isolated yields after column chromatography.

antibacterial activity.[9b] Again, the fluoro group at C-8 owes better oral absorption of the drug.[13] So, we considered different substituents at the C-8 position that can be isosteres or analogues and accordingly synthesized compounds (**1a–1c**) as the starting materials (8-substituted-4-quinolones) for this present work.

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.[14] Therefore we have replaced the N–H of compound **1** with a methyl substituent. Synthetic procedures of *N*-alkylation are well documented in literature.[15] 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 60 °C. The desired *N*-methylated product **2** was obtained in good yields (Scheme 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.

Initially, we attempted the bromination of compound **2** with NBS (*N*-bromosuccinimide) in chloroform at room temperature. Here the rate of the reaction as well as the yield of desired product was not satisfactory. Conducting the reaction at higher temperature (50 °C) which also resulted poor yield (yield < 50%) of the 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 resulted in the corresponding 6-bromo derivatives selectively in satisfactory yields (65–75%, Scheme 3).

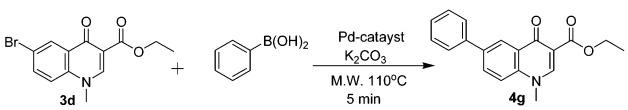


Scheme 3 Synthesis of 6-bromo-4-quinolone derivatives. *Reaction conditions*: **2** (1 mmol), bromine (1.2 equiv., 0.1 mL), AcOH (4 mL), stir rt (8 h). Isolated yields after column chromatography.

Aryl substituted 4-quinolones are known to be effective drugs as *Plasmodium falciparum* Type II NADH,[16] M1 positive allosteric modulators with reduced plasma protein binding,[17] selective agonists of somatostatin receptor subtype 2,[12a] antimitotic and antitumor agents.[7b] Earlier studies include aryl substitution mostly at the 1 and 2 positions of the quinolone moiety. Scientists are now investigating the influence of 6-aryl substitution on the therapeutic applications of quinolones which are yet to be well explored. Recent work by Chen and co-workers reported C-6 aryl substituted 4-quinolone derivatives as inhibitors of the hepatitis C virus (HCV).[12b] 6-Substituted 4-quinolone-3-carboxamides having high selective affinity for the human CB2 (cannabinoid-2) receptor over CB1 are also reported.[12c] Such promising perspectives of 6-arylated-4-quinolones inspired us to synthesize such entities *via* Suzuki cross coupling of compounds **3**. This method offered the opportunity to enrich the library of 6-aryl substituted quinolone scaffolds.

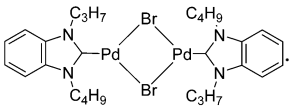
In the search for suitable conditions for the Suzuki coupling reaction, we first examined the coupling of phenylboronic acid with **3d** using different solvents and catalysts (common palladium salts) in the presence of potassium carbonate. The results are shown in Table 1. Notably, the combination of DMF as solvent and K_2CO_3 (potassium carbonate) as base was best suited for this coupling reaction in presence of our newly developed Pd-NHC catalyst.[18] The desired coupled product **4g** was formed within 5 minutes under microwave irradiation at 110 °C. Suzuki cross-coupling reaction of compound **3** with different aryl boronic acids under this optimized condition furnished the corresponding cross-coupled products in excellent yields (Scheme 4). Compounds **3a** and **3b** were successfully coupled with phenylboronic acid and correspondingly produced **4a** and **4c** in 90% and 87% yield. With 4-fluorophenylboronic acid they provided coupled products **4b** and **4d**

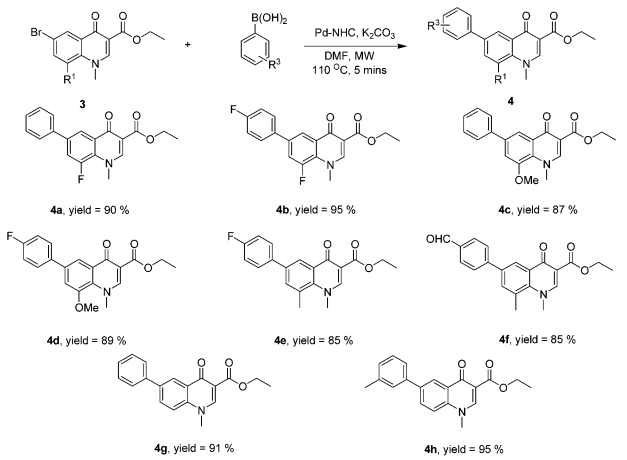
Table 1 Standardization of Suzuki coupling[a]



Entry	Pd-catalyst	Solvent	Yield[b] (%)
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[c]	DMF	91
6	Pd-NHC[c]	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 (276 mg, 2 mmol), Pd-catalyst (19.2 mg, 2 mol%), 110 °C (microwave). [b] Isolated yield after purification.

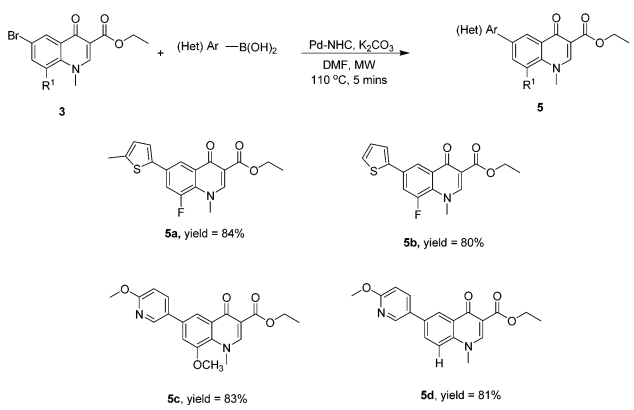
[c] Structure of Pd-NHC =  .



Scheme 4 Synthesis of 6-aryl-4-quinolones. *Reaction conditions*: compound **3** (1 mmol), aryl boronic acid (1.2 mmol), K_2CO_3 (2 mmol), Pd-NHC (0.0192 g, 2 mol%), dry DMF (3 mL), Microwave, 110 °C, 5 min. Isolated yields after column chromatography purification.

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 optimized conditions. Substrates having both electron-donating and withdrawing groups easily participated in the reaction to afford the desired couple products within a short time (5 minutes).

It is reported that the presence of heterocyclic ring substituents in many quinolone derivatives attribute enhanced antibacterial activity,[13] increased activity in *in vitro* cytotoxicity and tubulin based assays,[19] and xanthine oxidase inhibition.[20] Therefore, we further explored the influence of heteroarylboronic acids on the reaction performance and employed similar reaction conditions to couple thienyl and pyridinyl boronic acid derivatives with 6-bromoquinolones **3**. The corresponding coupling products with the general structure **5** were achieved in high yields. 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 heteroarylboronic acids. A family of 6-aryl and heteroaryl substituted quinolones have successfully been synthesized utilizing the 6-bromoquinolones **3** (Scheme 5).



Scheme 5 Suzuki cross coupling with heteroarylboronic acids forming products **5**. *Reaction conditions*: compound **3** (1 mmol), heteroarylboronic acid (1.2 mmol), K_2CO_3 (2 mmol), Pd-NHC (0.0192 g, 2 mol%), DMF (3 mL), microwave, 110 °C, 5 min. Isolated yields after column chromatography purification.

Conclusions

In summary, 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) were 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 for drug design. Exploring antimicrobial activities of these compounds in future may also add to the current knowledge about their structural activity relationships.

Experimental

General methods

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 a 300 MHz spectrometer at 298 K with calibration on the basis of the solvent residual peak. Mass spectra were performed using an ion trap mode. Products were purified using column chromatography on silica gel (60–120 mesh). Ethyl acetate and petroleum ether (60–80 °C) were used as eluents. Progress of the reaction was monitored using silica gel TLC.

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 aniline product. This product (**5g**) was refluxed with biphenyloxide (50 mL) for 2 hours at 280 °C. It was then cooled and stirred for an hour after the addition of a small

amount (100 mL) of petroleum ether. Crude compound **1** was obtained by filtration on a Buchner funnel.

Preparation of *N*-methylated derivatives (2)

Compound **1** (1 mmol) and DMF (5 mL) were placed in a round bottom flask fitted with a 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. Methyliodide (284 mg, 2 mmol) 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 × 20 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was then purified using column chromatography.

Preparation of bromo derivatives (3)

The *N*-Methylated product (compound **2**) was dissolved in a minimum amount of acetic acid and an 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.

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 p[laced in a microwave reaction vessel. The mixture was placed in the focused microwave reactor and heated at 110 °C for 5 minutes. Then the solution was diluted with water and extracted with DCM (3 × 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

Ethyl 8-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (1a). White solid, yield 52% (1.220 g); m.p. 217–219 °C; ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C, TMS): $\delta = 1.28$ (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 (75 MHz, DMSO-d_6, 25 °C, TMS): δ = 14.2, 59.8, 110.5, 117.17, 117.4, 121.3, 121.3, 124.5, 124.6, 128.1, 128.3, 129.1, 144.7, 150.1, 153.4, 164.4, 172.5; HRMS (EI$^+$): $[M]^+$, found 235.0634. $C_{12}H_{10}FNO_3$ requires 235.0645.

Ethyl 1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylate (1b). Greyish white, yield 55% (1.358 g); m.p. 243–245 °C; ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C, TMS): $\delta = 1.26$ (t, $J = 7.2$ Hz, 3H), 3.99 (s, 3H), 4.20 (q, $J = 7.2$ Hz, 2H), 7.29–7.37 (m, 2H), 7.70 (dd, $J = 7.2$ Hz, 1.2 Hz, 1H), 8.34 (s, 1H), 11.9 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6, 25 °C, TMS): δ = 14.8, 56.8, 60.1, 110.4, 117.3, 125.1, 128.6, 129.8, 144.3, 144.7, 149.2, 165.1, 173.7; 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, yield 70% (1.617 g); m.p. 249–251 °C; ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C, TMS): $\delta = 1.28$ (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 (75 MHz, DMSO-d_6, 25 °C, TMS): $\delta = 14.8, 17.4, 60.1, 110.1, 124.0, 124.8, 127.4, 127.9, 133.7, 137.9, 145.0, 165.2, 174.1$; HRMS (EI$^+$): $[M]^+$, found 231.0891. $C_{13}H_{13}NO_3$ requires 231.0895.

Ethyl 1,4-dihydro-4-oxoquinoline-3-carboxylate (1d).[21] White solid, yield 50% (1.085 g); m.p. 251–253 °C; ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C, TMS): δ = 1.27 (t, J = 7.2 Hz, 3H), 4.21 (q, J = 7.2 Hz, 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 (75 MHz, DMSO-d_6, 25 °C, TMS): δ = 14.8, 60.0, 110.2, 119.2, 125.2, 126.1, 127.7, 132.4, 139.4, 145.4, 165.3, 173.9.

Ethyl 8-fluoro 1,4-dihydro-1-methyl-4-oxoquinoline-3-carboxylate (2a). White solid, yield 76% (0.189 g); m.p. 121–124 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 1.40$ (t, $J = 7.2$ Hz, 3H), 4.10 (d, $J = 8.1$ Hz, 3H), 4.38 (q, $J = 7.2$ Hz, 2H), 7.37 (m, 2H), 8.31 (m, 1H), 8.36 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 14.33, 46.1, 46.3, 61.1, 109.5, 120.3, 120.6, 122.47, 122.51, 126.3, 126.4, 129.2, 129.3, 130.4, 150.8, 152.5, 154.2, 165.1, 173.3; 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, yield 75% (0.196 g); m.p. 113–116 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 1.23$ (t, $J = 7.2$ Hz, 3H), 3.75 (s, 3H), 3.98 (s, 3H), 4.20 (q, $J = 7.2$ Hz, 2H), 6.96 (d, J = 7.8 Hz, 1H), 7.14 (m, 1H), 7.96 (d, J = 8.1 Hz, 1H), 8.16 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 14.8, 47.6, 57.2, 60.1, 109.6, 115.9, 118.6, 125.9, 131.0, 131.1, 151.1, 152.4, 165.0, 172.5; 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, yield 70% (0.171 g); m.p. 91–93 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 1.41$ (t, $J = 7.2$ Hz, 3H), 2.80 (s, 3H), 4.11 (s, 3H), 4.38 (q, $J = 7.2$ Hz, 2H), 7.29 (m, 1H), 7.43 (m, 1H), 8.37 (s, 1H), 8.42 (d, $J = 8.1$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 14.4, 24.2, 47.0, 60.9, 110.2, 125.3, 126.38, 126.43, 130.7, 137.4, 140.4, 152.5, 165.8, 174.2; 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).[21] Brown solid, yield 78% (0.180 g); m.p.102–105 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 1.44$ (t, $J = 7.2$ Hz, 3H), 4.00 (s, 3H), 4.43 (q, $J = 7.2$ Hz, 2H), 7.53 (m, 2H), 7.78 (m, 1H), 8.55 (m, 1H), 8.80 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 14.4, 41.4, 60.8, 110.7, 115.7, 125.2, 127.7, 128.8, 132.7, 139.7, 149.7, 165.6, 174.4.

Ethyl 6-bromo-8-fluoro-1,4-dihydro-1-methyl-4-oxoquinoline-3-carboxylate (3a). White solid, yield 70% (0.229 g); m.p. 150–153 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 1.27$ (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, $J = 13.5$ Hz, 2.4 Hz, 1H), 8.03 (d, $J = 1.2$ Hz, 1H), 8.52 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 14.7$, 45.6, 60.4, 110.4, 117.2, 117.4, 122.7, 123.2, 124.9, 125.1, 129.1, 129.2, 131.9, 151.1, 152.3, 152.6, 154.5, 164.4, 170.5; HRMS (ESI-TOF) m/z: $[M + H]^+$, found 327.9902. $C_{13}H_{12}BrFNO_3$ requires 327.9985.

Ethyl 6-bromo-1,4-dihydro-8-methoxy-1-methyl-4-oxoquinoline-3-carboxylate (3b). Yellowish white solid, yield 65% (0.221 g); m.p. 155–157 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta =$ 1.40 (t, $J = 7.2$ Hz, 3H), 3.93 (s, 3H), 4.17 (s, 3H), 4.38 (q, $J = 7.2$ Hz, 2H), 7.18 (d, $J = 2.1$ Hz, 1H), 8.20 (d, $J = 2.1$ Hz, 1H), 8.43 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 14.5$, 48.3, 56.8, 61.3, 110.1, 117.7, 119.6, 122.0, 130.0, 131.7, 151.2, 152.1, 165.6, 172.1; HRMS (ESI-TOF) m/z: $[M + H]^+$, found 340.0119. $C_{14}H_{15}BrNO_4$ requires 340.0184.

Ethyl 6-bromo-1,4-dihydro-1,8-dimethyl-4-oxoquinoline-3-carboxylate (3c). Yellowish white solid, yield 72% (0.232 g); m.p. 205–208 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 1.40$ (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 (75 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 14.4$, 23.9, 47.1, 61.0, 110.4, 119.0, 128.5, 129.1, 131.7, 139.2, 139.6, 152.4, 165.1, 172.7; HRMS (ESI-TOF) m/z: $[M + H]^+$, found 324.0129. $C_{14}H_{15}BrNO_3$ requires 324.0235.

Ethyl 6-bromo-1,4-dihydro-1-methyl-4-oxoquinoline-3-carboxylate (3d). White solid, yield 75% (0.232 g); m.p. 108–111 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 1.39$ (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): $\delta = 14.4$, 41.5, 60.9, 111.0, 117.7, 119.2, 129.9, 130.1, 135.6, 138.4, 149.7, 165.0, 172.9; MS (ESI$^+$) m/z 332.05 ($[M + Na]^+$, ^{79}Br), 334.04 ($[M + Na]^+$, ^{81}Br), elemental analysis calcd (%) for $C_{13}H_{12}BrNO_3$: C, 50.34; H, 3.90; N, 4.52, found C, 50.31; H, 3.94; N, 4.48.

Ethyl 8-fluoro-1,4-dihydro-1-methyl-4-oxo-6-phenylquinoline-3-carboxylate (4a). Light brown solid, yield 90% (0.292 g); m.p. 168–170 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta =$ 1.43 (t, $J = 7.2$ Hz, 3H), 4.14 (d, $J = 8.1$ Hz, 3H), 4.41 (q, $J = 7.2$ Hz, 2H), 7.47 (m, 3H), 7.67 (m, 3H), 8.40 (s, 1H), 8.59 (d, $J = 2.4$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 14.4$, 45.9, 46.1, 61.2, 110.8, 118.0, 118.3, 121.2, 127.0, 128.5, 129.2, 129.3, 131.7, 138.0, 138.7, 138.8, 151.0, 151.5, 165.6, 166.5, 173.0; 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.

Ethyl 8-fluoro-6-(4-fluorophenyl)-1,4-dihydro-1-methyl-4-oxoquinoline-3-carboxylate (4b). White solid, yield 95% (0.326 g); m.p. 184–187 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 1.41$ (t, $J = 7.2$ Hz, 3H), 4.10 (d, $J = 8.1$ Hz, 3H), 4.39 (q, $J =$ 7.2 Hz, 2H), 7.15 (m, 2H), 7.58 (m, 3H), 8.33 (s, 1H), 8.48 (d, $J =$ 1.5 Hz 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 14.5$, 46.0, 46.2, 61.2, 111.0, 116.0, 116.3, 116.5, 117.8, 118.1, 121.0, 128.1, 128.2, 128.7, 128.8, 129.0, 131.8, 134.2, 137.7, 137.8, 151.0, 151.6, 154.3, 161.5, 164.8, 165.5, 166.4, 172.9; 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, yield 87% (0.293 g); m.p. 182–185 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 1.38$ (t, $J = 7.2$ Hz, 3H), 3.78 (s, 3H), 4.05 (s, 3H), 4.35 (q, $J = 7.2$ Hz, 2H), 7.21 (d, $J = 1.8$ Hz, 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 ($CDCl_3$, 75 MHz) δ 14.4, 47.8, 56.4, 60.7, 109.9, 112.9, 116.9, 126.9, 127.9, 128.9, 129.9, 131.3, 137.9, 139.2, 150.8, 151.5, 165.5, 173.5; 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, yield 89% (0.316 g); m.p. 178–180 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta =$ 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, $J = 2.1$ Hz, 1H), 8.40 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 14.4$, 47.9, 56.5, 60.9, 110.2, 113.1, 115.7, 116.0, 117.3, 128.7, 128.8, 130.0, 131.6, 135.56, 135.60, 137.4, 150.9, 151.7, 161.2, 164.4, 165.8, 173.6; 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.

Ethyl-6-(4-fluorophenyl)-1,4-dihydro-1,8-dimethyl-4-oxoquinoline-3-carboxylate (4e). Light yellow solid, yield 85% (0.288 g); m.p. 217–220 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta =$ 1.41 (t, $J = 7.2$ Hz, 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): $\delta =$ 14.4, 24.3, 47.0, 60.9, 110.1, 115.7, 116.0, 123.6, 127.3, 128.5, 128.6, 130.9, 135.0, 135.8, 136.5, 139.4, 152.2, 161.1, 164.4, 165.5, 174.2; 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, yield 85% (0.296 g); m.p. 230–233 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 1.39$ (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, $J = 8.1$ Hz, 2H), 7.95 (d, $J = 8.1$ Hz, 2H), 8.38 (s, 1H), 8.68 (s, 1H), 10.04 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 14.4$, 24.4, 47.0, 61.0, 110.6, 124.7, 127.5, 130.4, 131.0, 135.5, 135.9, 136.0, 140.3, 144.8, 152.5, 165.5, 174.1, 191.8; 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, yield 91% (0.279 g); m.p. 137–140 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 1.31$ (t, $J = 7.2$ Hz, 3H), 3.77 (s, 3H), 4.27 (q, $J = 7.2$ Hz, 2H), 7.35 (m, 4H), 7.55 (m, 2H), 7.76 (dd, $J = 8.7$ Hz, 2.1 Hz, 1H), 8.29 (s, 1H), 8.58 (d, $J = 2.1$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 13.3$, 40.4, 59.8, 109.4, 115.4, 124.0, 125.9, 126.8, 127.6, 127.9, 130.4, 136.8, 137.7, 137.9, 148.3, 164.4, 173.3; 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, yield 95% (0.305 g); m.p. 98–101 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 1.41$ (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}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 14.4$, 21.6, 41.6, 61.0, 110.5, 116.5, 125.1, 125.4, 127.8, 128.0, 128.7, 138.3, 138.7, 138.8, 139.0, 149.4, 149.7, 165.8, 174.3; 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, yield 84% (0.290 g); m.p. 158–161 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 1.37$ (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, $J = 15$ Hz, 2.4 Hz, 1H), 8.23 (s, 1H), 8.36 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 14.4$, 15.5, 45.9, 46.1, 61.1, 110.6, 116.2, 116.6, 119.0, 124.7, 126.7, 127.54, 127.6, 131.6, 132.6, 132.7, 138.9, 141.6, 150.9, 151.2, 154.2, 165.6, 172.7; 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, yield 80% (0.265 g); m.p. 185–188 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 1.42$ (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, $J = 5.1$ Hz, 0.9 Hz, 1H), 7.44 (dd, $J = 3.6$ Hz, 1.2 Hz, 1H), 7.61 (dd, $J = 15$ Hz, 2.1 Hz, 1H), 8.34 (s, 1H), 8.54 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 14.4$, 45.9, 46.1, 61.1, 110.8, 116.6, 116.9, 119.6, 119.7, 124.7, 126.5, 128.0, 128.5, 131.8, 132.2, 132.3, 141.4, 150.9, 151.3, 154.2, 165.5, 172.7; 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, yield 83% (0.305 g); m.p. 181–184 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 1.42$ (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 (75 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 14.4$, 47.9, 53.8, 56.5, 60.9, 110.3, 111.1, 112.5, 117.0, 128.5, 130.1, 131.8, 135.1, 137.5, 144.9, 151.0, 151.7, 163.9, 165.8, 173.6; 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-oxo-quinoline-3-carboxylate (5d). White solid, yield 81% (0.274 g); m.p. 169–171 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 1.40$ (t, $J = 7.2$ Hz, 3H), 3.88 (s, 3H), 3.99 (s, 3H), 4.37 (q, $J = 7.2$ Hz, 2H), 6.82 (d, $J = 8.7$ Hz, 1H), 7.46 (d, $J = 8.7$ Hz, 1H), 7.82 (m, 2H), 8.39 (d, $J = 10.8$ Hz, 2H), 8.56 (d, $J = 1.5$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 14.4, 41.4, 53.7, 60.8, 110.7, 116.7, 124.6, 128.1, 129.0, 130.6, 134.6, 138.7, 145.0, 149.9, 163.9, 165.4, 174.2; MS (ESI^+): m/z 361.24 $[M + Na]^+$, elemental analysis calcd (%) for $C_{19}H_{18}N_2O_4$: C, 67.44; H, 5.36; N, 8.28, found C, 67.48; H, 5.32; N, 8.22.

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