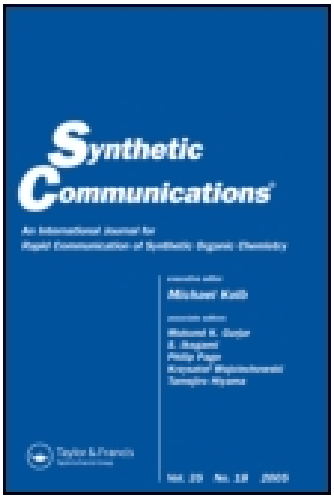

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A Regioselective S_NAr Reaction of Poly-halo-quinoline-3-carboxylates with Phenol, Thiophenol, or N-Methylaniline

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A REGIOSELECTIVE S_NAr REACTION OF POLY-HALO-QUINOLINE-3-CARBOXYLATES WITH PHENOL, THIOPHENOL, OR *N*-METHYLANILINE

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By S_NAr reaction, poly-halo-quinoline-3-carboxylates such as ethyl 4-chloro-2-cyclopropyl-6, 7-difluoro-quinoline-3-carboxylate and ethyl 4-chloro-2-cyclopropyl-5,6-difluoro-quinoline-3-carboxylate were transformed into the 4-phenoxy or 4-phenylthio or 4-(N-methyl) phenylamino-6,7 (or 5,6)-difluoro-quinoline-3-carboxylates or the 4,7-disubstituted, 4,5-disubstituted, 4,6,7-trisubstituted and 4,5,6-trisubstituted products under mild conditions in moderate to excellent yields. Highly regioselective mono- or multi-substitution was observed.

Keywords: N-Methylaniline; phenol; poly-halo-quinoline-3-carboxylates; S_NAr reaction; synthesis; thiophenol

INTRODUCTION

The structural modifications on the quinoline scaffold may result in a variety of compounds possessing antimalarial, antibacterial, antihypertensitive or antihyperlipidemic activities.[1,2] The fluoroquinolones have become the mainstay of totally synthesized antibacterials in the infectious treatment, and the antihyperlipidemic Pitavastatin, a quinoline compound is a new kind of hydroxymethylglutaryl-coenzyme A (HMG CoA) inhibitors. As part of our investigations on quinoline derivatives with pharmacological interests, we required a series of quinoline-3-carboxylates substituted with phenylthio, phenoxy or *N*-methylphenylamino groups at position 4, 5, 6, or 7 which would expedite the discovery of new potential HMG CoA inhibitors. A very straight forward method for this synthesis could be the direct nucleophilic substitution of halogen in the poly-halo-quinoline-3-carboxylates by phenol, thiophenol or *N*-methylaniline. It is well known that the S_NAr of 1-alkyl-6-fluoro-7-chloro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid with some secondary amines such as piperazine afforded the fluoroquinolone antibacterials, e.g., Ciprofloxacin and Norfloxacin.[3] The 4-substitued-aminoquinoline-3-carboxylates might be synthesized from 4-chloroquinoline-3-carboxylates[4] In continuation of our interest in the structural modifications on the quinoline scaffold,[5] we report

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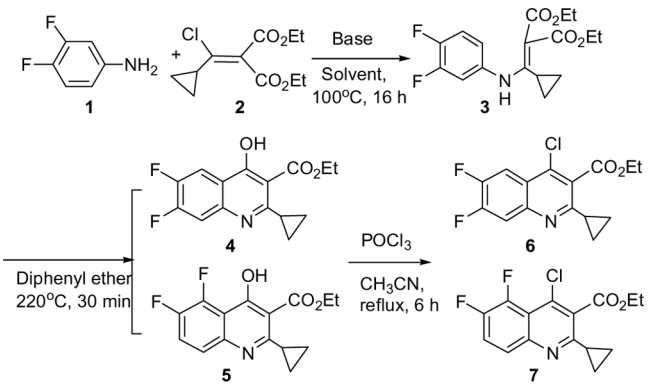
here a regioselective S_NAr reaction of 4-chloro-6,7-difluoro-quinoline-3-carboxylates or 4-chloro-5,6-difluoro-quinoline-3-carboxylates with thiophenol, phenol or *N*-methylaniline to give a series of novel quinoline-3-carboxylates substituted with phenylthio, phenoxy or *N*-methylphenylamino groups at position 4, 5, 6, or 7.

RESULTS AND DISCUSSION

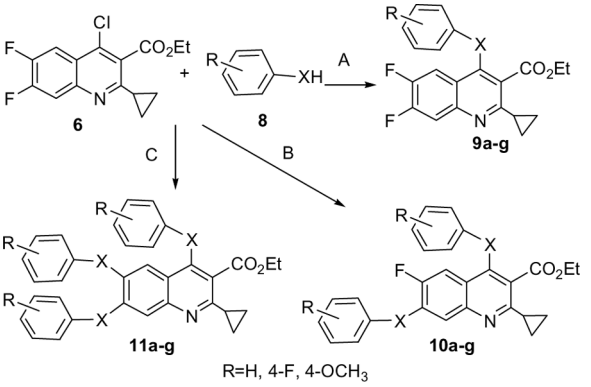
3,4-Difluoroaniline (**1**) was reacted with diethyl [chloro(cyclopropyl)methylene] malonate (**2**, prepared from diethyl malonate and cyclopanecarboxylic acid chloride)[6] to form diethyl [cyclopropyl(3,4-difluorophenylamino)methylene] malonate (**3**) in high yield (Scheme 1), which underwent by thermal cyclization to give **4**, mixed with a trace of isomer **5**. The mixture of **4** and **5** was refluxed in acetonitrile with phosphous oxychloride to give **6** and **7**, which were separated by flash chromatography.

The monosubstitution of **6** with phenol was investigated at first, and the reaction was contaminated with 4-monosubstituted and 4,7-disubstituted products when it was carried out in DMF with K_2CO_3 as base. Fortunately, it worked well with 1.1 equiv of the nucleophile mixed with NaH (60%, 1.1 equiv) in THF at reflux to give 4-monsubstitution **9a** in 91% yield (Scheme 2, entry 1 in Table 1). The similar reactions with 4-fluorophenol and 4-methoxylphenol gave the satisfactory results (Table 1, entries 2 and 3). When 4-fluorothiophenol or 4-methoxythiophenol was served as the nucleophile, the reaction condition was a bit milder than the phenol case (entries 4 and 5). However, the reaction was harsher for the *N*-methylanilines case. The reaction of **6** with *N*-methyl-4-fluoroaniline or *N*-methyl-4-methoxyaniline was failed in NaH/THF and finally it worked well when BuLi was employed in the THF at ice bath (Table 1, entries 6 and 7).

The investigation on 4,7-disubstitution of substrate **6** were easier than the 4-monosubstitution. For phenols and thiophenols, the amounts of nucleophile were increased to 2.1 equivalents and the reaction functioned well in K_2CO_3/DMF in an excellent yield (entries 8–12 in Table 1). However, compound **10f** and **10g** were obtained in moderate yield even with BuLi as the base (entries 13 and 14 in Table 1).



Scheme 1. Synthesis of **6** and **7** from 3,4-difluoroaniline.



Scheme 2. When X=O, (A) NaH, THF, reflux, 6 h; (B) K_2CO_3, DMF, 100 °C, 16 h; (C) NaH, DMSO, 100 °C, 12 h. When X=S, (A) NaH, THF, ice bath, 4 h; (B) K_2CO_3, DMF, 50 °C, 16 h; (C) NaH, DMSO, 130 °C, 24 h. When X=NCH_3, (A) BuLi, THF, ice bath, 2 h. (B) BuLi, THF, r.t., 4 h.

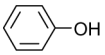
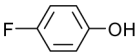
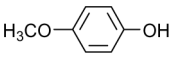
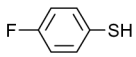
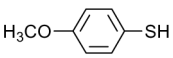
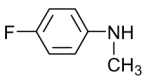
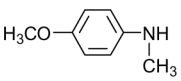
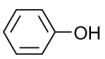
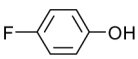
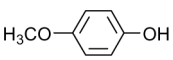
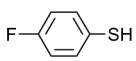
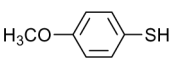
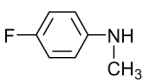
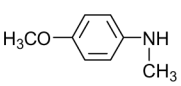
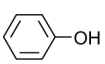
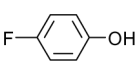
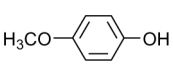
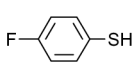
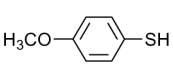
It is difficult to prepare 4,6,7-trisubstituted products. For phenols and thiophenols, the ardent reaction conditions such as NaH and DMSO were employed, while the yields were only 30–50% when the amounts of nucleophile and base were increased to 3.5 or 4 equivalents (entries 15–19), and it was failed to get the 4,6,7-tri-(*N*-methylphenylamino) products although many tests were tried.

Encouraged by the above results, we investigated the S_NAr reaction with **7** as the substrate. It was showed that the 4-monosubstitutions with three series of nucleophilic agents might go in the same condition as the subtract **6**. The disubstitution gave 4,5-disubstituted products in the lower yield, indicating that in compound **7**,5-fluoro was a better leaving group than the 6-fluoro, but the leaving ability was not as good as the 7-fluoro in compound **6** (Scheme 3).

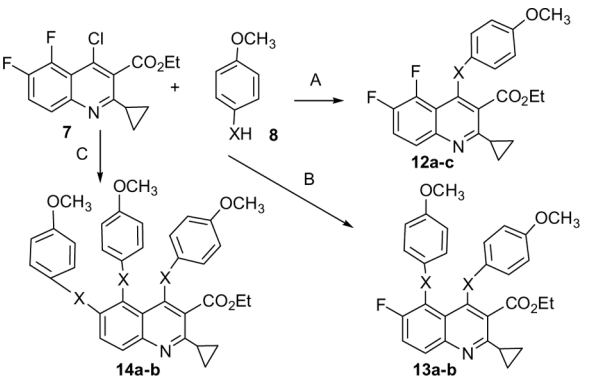
The ^{1}H NMR data (in $CDCl_3$, 400 MHz) were very helpful to identify the 4-substituted, 4,6,7-trisubstituted, 4,5-disubstituted and 4,5,6-trisubstituted products. For example, in the ^{1}H NMR spectrum of **9b**, the double double peak at 7.68 ppm was assigned to 8-H at quinoline ring and the coupling constants of $J_{H\text{-}F\ (o)}$, $J_{H\text{-}F(m)}$ were calculated as 11.2 Hz and 7.2 Hz, respectively, another double double peak at 7.56 ppm was assigned to 5-H with the coupling constants of $J_{H\text{-}F\ (o)}$, $J_{H\text{-}F(m)}$ 10.4 Hz and 8.4 Hz. In the spectrum of **11b**, the two sharp single peaks at 7.26 and 7.16 could be assigned to be the signal of 8-H and 5-H, respectively, indicating the absence of fluorine at position 6 and 7. In the spectrum of **13a**, the triple peak at 7.57 could be assigned to be the signal of 7-H, indicating the presence of fluorine at position 6. In the spectrum of **14a**, the two double peaks at 7.85 and 7.38 could be assigned to be the signal of 7-H and 8-H, indicating the absence of fluorine at position 5 and 6. It was difficult to identify 4,7-disubstituted or 4,6-disubstituted products only by the ^{1}H NMR and MS. The structure of **10a** was confirmed by X-ray crystallography and the data (Figure 1) shows that it was a 4,7-disubstituted product.[7]

In summary, we have shown a systematic study on the S_NAr reaction of ethyl 4-chloro-2-cyclopropyl-6,7-difluoro-quinoline-3-carboxylate or ethyl 4-chloro-2-cyclopropyl-5,6-difluoro-quinoline-3-carboxylate with phenols, thiophenols or

Table 1. Substitutions of **6**

Entry	Nucleophile **8**	Product	Ratio of **8** to **6**	Base	Sovent	Time/h	Temp./°C	Yield (%)*	Mp/°C
1		**9a**	1.1	NaH	THF	6	67	91	110–2
2		**9b**	1.1	NaH	THF	6	67	88	120–2
3		**9c**	1.1	NaH	THF	6	67	88	86–88
4		**9d**	1.1	NaH	THF	4	0∼5	89	114–6
5		**9e**	1.1	NaH	THF	4	0∼5	87	110–2
6		**9f**	1.1	BuLi	THF	2	0∼5	79	139–40
7		**9g**	1.1	BuLi	THF	2	0∼5	80	100–2
8		**10a**	2.1	K_2CO_3	DMF	16	100	87	102–4
9		**10b**	2.1	K_2CO_3	DMF	16	100	85	143–5
10		**10c**	2.1	K_2CO_3	DMF	16	100	92	oil
11		**10d**	2.1	K_2CO_3	DMF	16	50	93	oil
12		**10e**	2.1	K_2CO_3	DMF	16	50	94	oil
13		**10f**	3	BuLi	THF	4	25	42	177–9
14		**10g**	3	BuLi	THF	4	25	56	oil
15		**11a**	3.5	NaH	DMSO	12	100	42	72–4
16		**11b**	3.5	NaH	DMSO	12	100	50	oil
17		**11c**	3.5	NaH	DMSO	12	100	39	150–2
18		**11d**	4	NaH	DMSO	24	130	36	166–8
19		**11e**	4	NaH	DMSO	24	130	31	170–2

*The products **9a–10b** were recrystallized from n-hexane; **10c–11e** were isolated by flash chromatography.



Scheme 3. When X=O, (A) NaH, THF, reflux, 6 h; (B) K_2CO_3, DMF, 100 °C, 16 h; (C) NaH, DMSO, 100 °C, 10 h. When X=S, (A) NaH, THF, ice bath, 4 h; (B) K_2CO_3, DMF, 50 °C, 16 h; (C) NaH, DMSO, 130 °C, 24 h. When X=NCH_3, (A) BuLi, THF, ice bath, 2 h.

N-methylanilines, revealing that the substitution is highly regioselective, which would afford 4-monosubstituted, 4,7-disubstituted, 4,5-disubstituted, 4,6,7-trisubstituted or 4,5,6-trisubstituted quinoline-3-carboxylates by controlling the reaction temperature, the type of the base, the solvents as well as the ratio of the substrate to the nucleophile.

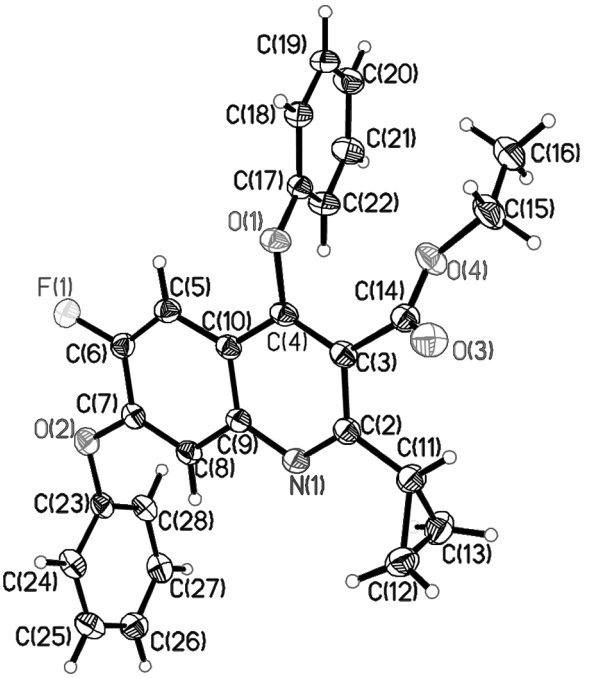


Figure 1. X-ray crystallographic structure of compound **10a**.

EXPERIMENTAL

Melting points were determined on an Electrothermal Melting Point Apparatus and were uncorrected. ^{1}H NMR spectra were recorded at 400 MHz on a Varian Inova-400 spectrometer in deuterated chloroform or deuterated dimethylsulfoxide with chemical shifts (δ) given in ppm relative to TMS as an internal standard. High-resolution mass spectra (HRMS) were recorded on an Agilent 6210 TOF instrument. X-Ray crystallography data were collected on a SMART APEX-II diffractometer with CCD detector using Cu-Kα radiation (λ = 1.54178 Å).

Preparation of Diethyl[cyclopropyl(3,4-difluorophenylamino) methylene]malonate (3)

A mixture of **1** (31.0 g, 0.24 mol), **2** (49.4 g, 0.2 mol), anhydrous K_2CO_3 (33.1 g, 0.24 mol), and DMF (300 ml) was stirred at 100 °C (oil bath temperature) for 16 h. When it was cooled to room temperature, the inorganic material was removed by filtration and washed with ethyl acetate. The resulting solution was transferred to a separatory funnel, and ethyl acetate and water were added. The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated to give yellow oil (61.0 g, yield 90%) which was used for the next step without further purification. It was purified by silica gel chromatography (petroleum ether—ethyl acetate, 10:1) to provide **3** as an analytical sample: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.96 (s, 1H), 7.13–6.84 (m, 3H), 4.26 (q, J = 7.2 Hz, 2H), 4.18 (q, J = 7.2 Hz, 2H), 1.92–1.84 (m, 1H), 1.33 (t, J = 7.2 Hz, 3H), 1.28 (q, J = 7.2 Hz, 3H), 0.77–0.72 (m, 2H), 0.47–0.43 (m, 2H).

Preparation of Ethyl 2-Cyclopropyl-6,7-difluoro-4-hydroxyquinoline-3-carboxylate (4)

The crude **3** (60 g, 0.18 mol) was added to diphenyl ether (500 ml) and heated at 220 °C for 0.5 h. After the solution cooled, the precipitate was filtered off, washed with petroleum ether, and dried. The obtained solid (47.4 g, 91.4%) was used for the next step without further purification. It was recrystallized from 95% ethanol to give **4** as an analytical sample: Colorless crystal, mp 280–282 °C; ^{1}H NMR (400 MHz, $CDCl_3 + D_2O$): δ 7.99 (dd, J = 10.8, 8.8 Hz, 1H), 7.53 (dd, J = 10.8, 6.8 Hz, 1H), 4.37 (q, J = 7.2 Hz, 2H), 2.23–1.99 (m, 1H), 1.37 (t, J = 7.2 Hz, 3H), 1.10–1.06 (m, 4H).

Preparation of Ethyl 4-Chloro-2-cyclopropyl-6,7-difluoroquinoline-3-carboxylate (6) and Ethyl 4-Chloro-2-cyclopropyl-5,6-difluoroquinoline-3-carboxylate (7)

Phosphorus oxychloride (26.0 ml, 0.28 mol) was added to a suspension of crude **4** (46.0 g, 0.16 mol) in acetonitrile (400 ml) and the mixture was heated at 75 °C for 6 h. The resulting light brown solution was poured into the aqueous solution saturated with sodium bicarbonate (500 ml); the suspension was extracted with ethyl acetate twice. The organic extracts were dried over Na_2SO_4 and concentrated to dryness to

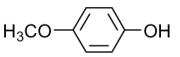
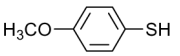
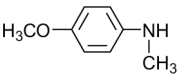
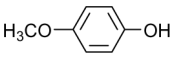
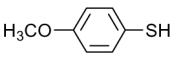
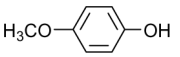
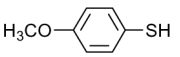
give an off-white solid, which was purified by silica gel chromatography (petroleum ether–ethyl acetate, 100:1) to give **6** (32.5 g, 66.5%) and **7** (4.4 g, 9.6%). **6**: white solid, mp 68–70 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (dd, $J = 10.8$, 8.4 Hz, 1H), 7.68 (dd, $J = 11.2$, 7.6 Hz, 1H), 4.53 (q, $J = 7.2$ Hz, 2H), 2.10–2.06 (m, 1H), 1.45 (t, $J = 7.2$ Hz, 3H), 1.31–1.27 (m, 2H), 1.09–1.04 (m, 2H). MS (ESI): m/z = 312, 314 $(M+H)^+$. HRMS: m/z calcd. for $C_{15}H_{13}ClF_2NO_2$ $(M+H)^+$ 312.0603, found: 312.0623. **7**: white solid, mp 88–90 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78–7.74 (m, 1H), 7.61–7.54 (m, 1H), 4.57 (q, $J = 7.2$ Hz, 2H), 2.11–2.05 (m, 1H), 1.49 (t, $J = 7.2$ Hz, 3H), 1.34–1.31 (m, 2H), 1.11–1.07 (m, 2H). MS (ESI): m/z = 312, 314 $(M + H)^+$.

S_NAr of 6 or 7 Ethyl 2-Cyclopropyl-6,7-difluoro-4-phenoxyquinoline-3-carboxylate (9a)

Phenol (0.66 g, 7.0 mmol) was added to a mixture of NaH (60%, 0.28 g, 7.0 mmol) in THF (20 ml) at 0 °C. The resulting mixture was stirred at 0 °C for 0.5 h, and then **6** (2.0 g, 6.4 mmol) was added. The mixture was refluxed for 6 h. the reaction mixture was transferred to a separatory funnel, then ethyl acetate and water were added. The organic layer were separated, washed with brine, dried over Na_2SO_4 and concentrated to dryness to give a white solid, which was recrystallized from n-hexane to give **9a** (2.16 g, 91%) as a colorless powder. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (dd, $J = 11.2$, 7.2 Hz, 1H), 7.59 (dd, $J = 10.4$, 8.8 Hz, 1H), 7.32–7.27 (m, 2H), 7.09 (t, $J = 7.6$ Hz, 1H), 6.92–6.89 (m, 2H), 4.16 (q, $J = 7.2$ Hz, 2H), 2.26–2.20 (m, 1H), 1.36–1.32 (m, 2H), 1.14 (t, $J = 7.2$ Hz, 3H), 1.09–1.05 (m, 2H).

Compounds **9b–9e** and **12a–12b** were prepared in the similar manner otherwise the reaction temperature mentioned in Tables 1 and 2.

Table 2. Substitutions of **7**

Entry	Product	Nucleophiles **8**	Ratio of **8** to **7**	Base	Sovent	Time/h	Temp./°C	Yield (%)*	Mp/°C
1	**12a**		1.1	NaH	THF	6	67	83	105–7
2	**12b**		1.1	NaH	THF	4	0∼5	88	123–5
3	**12c**		1.1	BuLi	THF	2	ice bath	88	137–9
4	**13a**		2.1	K_2CO_3	DMF	16	100	58	oil
5	**13b**		2.1	K_2CO_3	DMF	16	100	39	oil
6	**14a**		4	NaH	DMSO	24	130	38	101–3
7	**14b**		4	NaH	DMSO	24	130	32	163–5

*The products **12a–c** were recrystallized from n-hexane; **13a–14b** were isolated by flash chromatography.

Ethyl 2-Cyclopropyl-6,7-difluoro-4-(4-fluorophenyloxy)quinoline-3-carboxylate (9b)

Colorless powder, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (dd, $J = 11.2$, 7.2 Hz, 1H), 7.56 (dd, $J = 10.4$, 8.4 Hz, 1H), 7.0–6.96 (m, 2H), 6.87–6.84 (m, 2H), 4.17 (q, $J = 7.2$ Hz, 2H), 2.21–2.17 (m, 1H), 1.34–1.30 (m, 2H), 1.16 (t, $J = 7.2$ Hz, 3H), 1.08–1.03 (m, 2H).

Ethyl 2-Cyclopropyl-6,7-difluoro-4-(4-methoxyphenyloxy)quinoline-3-carboxylate (9c)

Colorless powder, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69–7.59 (m, 2H), 6.86–6.90 (m, 4H), 4.14 (q, $J = 7.2$ Hz, 2H), 3.77 (s, 3H), 2.20–2.16 (m, 1H), 1.33–1.29 (m, 2H), 1.17 (t, $J = 7.2$ Hz, 3H), 1.06–1.02 (m, 2H).

Ethyl 2-Cyclopropyl-6,7-difluoro-4-(4-fluorophenylthio)quinoline-3-carboxylate (9d)

Lightly yellow powder. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (dd, $J = 11.6$, 8.4 Hz, 1H), 7.69 (dd, $J = 11.2$, 8.0 Hz, 1H), 7.26–7.22 (m, 2H), 6.96–6.92 (m, 2H), 4.46 (q, $J = 7.2$ Hz, 2H), 2.13–2.08 (m, 1H), 1.36 (t, $J = 7.2$ Hz, 3H), 1.38–1.31 (m, 2H), 1.12–1.07 (m, 2H).

Ethyl 2-Cyclopropyl-6,7-difluoro-4-(4-methoxyphenylthio)quinoline-3-carboxylate (9e)

Lightly yellow powder. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (dd, $J = 11.6$, 8.8 Hz, 1H), 7.59 (dd, $J = 11.2$, 7.6 Hz, 1H), 7.22–7.18 (m, 2H), 6.73–6.70 (m, 2H), 4.39 (q, $J = 7.2$ Hz, 2H), 3.68 (s, 3H), 2.05–2.01 (m, 1H), 1.32 (t, $J = 7.2$ Hz, 3H), 1.27–1.23 (m, 2H), 1.03–0.98 (m, 2H).

Ethyl 2-Cyclopropyl-5,6-difluoro-4-(4-methoxyphenyloxy)quinoline-3-carboxylate (12a)

Colorless powder. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78–7.74 (m, 1H), 7.56–7.51 (m, 1H), 6.83–6.81 (m, 4H), 4.26 (q, $J = 7.2$ Hz, 2H), 3.78 (s, 3H), 2.21–2.17 (m, 1H), 1.38–1.34 (m, 2H), 1.19 (t, $J = 7.2$ Hz, 3H), 1.12–1.07 (m, 2H).

Ethyl 2-Cyclopropyl-5,6-difluoro-4-(4-methyloxyphenylthio)quinoline-3-carboxylate (12b)

Lightly yellow powder. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74–7.72 (m, 1H), 7.50–7.46 (m, 1H), 7.34–7.32 (m, 2H), 6.80–6.78 (m, 2H), 4.50 (q, $J = 7.2$ Hz, 2H), 3.77 (s, 3H), 2.13–2.10 (m, 1H), 1.42 (t, $J = 7.2$ Hz, 3H), 1.36–1.32 (m, 2H), 1.13–1.09 (m, 2H).

Ethyl 2-Cyclopropyl-6,7-difluoro-4-(*N*-methyl-4-fluorophenylamino)-quinoline-3-carboxylate (9f)

BuLi (2.7 mol/L, 1.25 mL, 3.37 mmol) was added to a mixture of *N*-methyl-4-fluoroaniline (0.41 g, 3.27 mmol) in THF (15 ml) at 0 °C. The resulting mixture was stirred at 0 °C for 0.5 h, and then **6** (1.0 g, 3.21 mmol) was added. The mixture was stirred for 2 h below 5 °C. The reaction mixture was transferred to a separatory funnel, then ethyl acetate and water were added. The organic layer were separated, washed with brine, dried over Na_2SO_4 and concentrated to dryness to give a yellow solid, which was recrystallized from n-hexane to give **9f** (1.01 g, 79%) as a yellow powder. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86–7.81 (m, 1H), 7.47 (dd, $J = 10.4$, 8.8 Hz, 1H), 6.95–6.90 (m, 2H), 6.61–6.57 (m, 2H), 4.15 (q, $J = 7.2$ Hz, 2H), 3.34 (s, 3H), 2.19–2.14 (m, 1H), 1.15 (t, $J = 7.2$ Hz, 3H), 1.39–1.36 (m, 2H), 1.14–1.07 (m, 2H).

Compounds **9g**, **10f**, **10g**, and **12c** were prepared in the similar manner otherwise the reaction temperature and the molecular ratio mentioned in Tables 1 and 2.

Ethyl 2-Cyclopropyl-6,7-difluoro-4-(*N*-methyl-4-methyloxyphenylamino)quinoline-3-carboxylate (9g)

Yellow powder. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79–7.76 (m, 1H), 7.48 (dd, $J = 10.8$, 8.8 Hz, 1H), 6.79–6.76 (m, 2H), 6.62–6.59 (m, 2H), 4.11 (q, $J = 7.2$ Hz, 2H), 3.75 (s, 3H), 3.31 (s, 3H), 2.17–2.13 (m, 1H), 1.15 (t, $J = 7.2$ Hz, 3H), 1.35–1.32 (m, 2H), 1.07–1.03 (m, 2H).

Ethyl 2-Cyclopropyl-6-difluoro-4,7-di-(*N*-methyl-4-fluorophenylamino)quinoline-3-carboxylate (10f)

Yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (b, 1H), 7.30–7.27 (m, 1H), 7.01–6.57 (m, 8H), 4.12 (q, $J = 7.2$ Hz, 2H), 3.45 (s, 3H), 3.35 (s, 3H), 2.20 (b, 1H), 1.20 (t, $J = 7.2$ Hz, 3H), 1.35 (m, 2H), 1.12–1.08 (m, 2H).

Ethyl 2-Cyclopropyl-6difluoro-4,7-(*N*-methyl-4-methyloxyphenylamino)quinoline-3-carboxylate (10g)

Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (b, 1H), 7.26 (d, $J = 9.2$ Hz, 1H), 7.01–6.60 (m, 8H), 4.08 (q, $J = 7.2$ Hz, 2H), 3.79 (s, 3H), 3.74 (s, 3H), 3.38 (s, 3H), 3.30 (s, 3H), 2.19–2.17 (m, 1H), 1.14 (t, $J = 7.2$ Hz, 3H), 1.29–1.26 (m, 2H), 1.02–0.98 (m, 2H).

Ethyl 2-Cyclopropyl-5,6-difluoro-4-(*N*-methyl-4-methyloxyphenylamino)quinoline-3-carboxylate (12c)

Yellow powder. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84–7.80 (m, 1H), 7.56–7.49 (m, 1H), 6.81–6.77 (m, 2H), 6.56–6.53 (m, 2H), 4.20 (q, $J = 7.2$ Hz, 2H), 3.76 (s, 3H), 3.28 (s, 3H), 2.16–2.12 (m, 1H), 1.17 (t, $J = 7.2$ Hz, 3H), 1.38–1.36 (m, 2H), 1.11–1.08 (m, 2H).

Ethyl 2-Cyclopropyl-6-fluoro-4,7-diphenyloxyquinoline-3-carboxylate (10a)

A mixture of phenol (0.95 g, 10.1 mmol), **6** (1.5 g, 4.81 mmol), anhydrous K_2CO_3 (1.39 g, 10.1 mmol), and DMF (15 ml) was stirred at 100 °C for 16 h. When it was cooled to room temperature, the solid was isolated by filtration and washed with ethyl acetate. The resulting mixture was transferred to a separatory funnel, and ethyl acetate and water were added. The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated to dryness to give an off-white solid, which was recrystallized from n-hexane to give **10a** (1.85 g, 87%) as a colorless powder. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (d, $J = 11.6$ Hz, 1H), 7.44–6.89 (m, 11H), 4.17–4.12 (m, 2H), 2.24–2.18 (m, 1H), 1.25–1.20 (m, 2H), 1.12 (td, $J = 7.2$, 1.2 Hz, 3H), 1.02–0.97 (m, 2H). HRMS: m/z calcd for $C_{27}H_{23}FNO_4$ $(M + H)^+$ 444.1611, found: 444.1613.

Compounds **10b**–**10e** and **13a–b** were prepared in the similar manner otherwise the reaction temperature mentioned in Tables 1 and 2.

Ethyl 2-Cyclopropyl-6-fluoro-4,7-di-(4-fluorophenyloxy)quinoline-3-carboxylate (10b)

Colorless powder. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, $J = 11.2$ Hz, 1H), 7.25 (d, $J = 7.6$ Hz, 1H), 7.12–7.10 (m, 4H), 7.01–6.96 (m, 2H), 6.88–6.84 (m, 2H), 4.17 (q, $J = 7.2$ Hz, 2H), 2.20–2.16 (m, 1H), 1.26–1.21 (m, 2H), 1.15 (t, $J = 7.2$ Hz, 3H), 1.03–0.99 (m, 2H).

Ethyl 2-Cyclopropyl-6-fluoro-4,7-di-(4-methoxyphenyloxy) quinoline-3-carboxylate (10c)

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (d, $J = 10.8$ Hz, 1H), 7.19 (d, $J = 8.4$ Hz, 1H), 7.10–7.08 (m, 2H), 6.96–6.94 (m, 2H), 6.86–6.80 (m, 4H), 4.18 (q, $J = 7.2$ Hz, 2H), 3.84 (s, 3H), 3.77 (s, 3H), 2.18–2.16 (m, 1H), 1.26–1.19 (m, 2H), 1.16 (t, $J = 7.2$ Hz, 3H), 1.00–0.96 (m, 2H).

Ethyl 2-Cyclopropyl-6-fluoro-4,7-di-(4-fluorophenylthio)quinoline-3-carboxylate (10d)

Lightly yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, $J = 10.8$ Hz, 1H), 7.58–7.54 (m, 2H), 7.43 (d, $J = 7.2$, Hz, 1H), 7.28–7.24 (m, 2H), 7.19–7.15 (m, 2H), 6.98–6.93 (m, 2H), 4.45 (q, $J = 7.2$ Hz, 2H), 2.11–2.07 (m, 1H), 1.37 (t, $J = 7.2$ Hz, 3H), 1.29–1.25 (m, 2H), 1.07–1.02 (m, 2H).

Ethyl 2-Cyclopropyl-6-fluoro-4,7-di-(4-methoxyphenylthio)quinoline-3-carboxylate (10e)

Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, $J = 10.8$ Hz, 1H), 7.49 (d, $J = 8.8$ Hz, 2H), 7.27–7.22 (m, 3H), 6.97 (d, $J = 9.2$ Hz, 2H), 6.75 (d, $J = 9.2$ Hz, 2H), 4.42 (q, $J = 7.2$ Hz, 2H), 3.86 (s, 3H), 3.74 (s, 3H), 2.05–2.03 (m, 1H), 1.37 (t, $J = 7.2$ Hz, 3H), 1.20–1.17 (m, 2H), 0.99–0.96 (m, 2H). MS (ESI): $m/z = 536(M + H)^+$.

Ethyl 2-Cyclopropyl-6-fluoro-4,5-di-(4-methoxyphenoxy)quinoline-3-carboxylate (13a)

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (dd, $J = 9.2$, 4.4 Hz, 1H), 7.57 (t, $J = 9.6$ Hz, 1H), 6.83–6.54 (m, 8H), 4.16 (q, $J = 7.2$ Hz, 2H), 3.79 (s, 3H), 3.76 (s, 3H), 2.20–2.17 (m, 1H), 1.43–1.40 (m, 2H), 1.12–1.08 (m, 5H).

Ethyl 2-Cyclopropyl-6-fluoro-4,5-di-(4-methoxyphenylthio)-quinoline-3-carboxylate (13b)

Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08–8.04 (m, 1H), 7.41 (t, $J = 8.8$ Hz, 1H), 7.08–6.69 (m, 8H), 4.33 (q, $J = 7.2$ Hz, 2H), 3.75 (s, 3H), 3.74 (s, 3H), 2.14–2.09 (m, 1H), 1.28 (t, $J = 7.2$ Hz, 3H), 1.40–1.35 (m, 2H), 1.12–1.07 (m, 2H).

Ethyl 2-Cyclopropyl-4,6,7-triphenoxyquinoline-3-carboxylate (11a)

Phenol (2.12 g, 22.5 mmol) was added to a mixture of NaH (60%, 0.85 g, 21.2 mmol) in DMSO (20 ml) at room temperature. The resulting mixture was stirred at room temperature for 0.5 h after which, **6** (2.0 g, 6.42 mmol) was added. The mixture was stirred at 100 °C for 12 h. When TLC indicated that the reaction was complete, the reaction mixture was transferred to a separatory funnel, then ethyl acetate and water were added. The organic layer were separated, washed with brine, dried over Na_2SO_4 and concentrated to dryness. The residue was purified by silica gel column chromatography (petroleum ether—ethyl acetate, 80:1) to provide **11a** (1.4 g, 42.2%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38–7.33 (m, 4H), 7.25–7.15 (m, 5H), 7.06–7.00 (m, 4H), 6.87–6.80 (m, 4H), 4.15 (q, $J = 7.2$ Hz, 2H), 2.23–2.19 (m, 1H), 1.26–1.22 (m, 2H), 1.12 (t, $J = 7.2$ Hz, 3H), 1.01–0.96 (m, 2H).

Compounds **11b** and **11c** were prepared in the manner analogous to the method described above. Compounds **11d**, **11e**, **14a**, and **14b** were prepared in the above method, but the reaction temperature were raised up to 130 °C and reacted for 24 h.

Ethyl 2-Cyclopropyl-4,6,7-tri-(4-fluorophenoxy)quinoline-3-carboxylate (11b)

White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 (s, 1H), 7.16 (s, 1H), 7.10–7.01 (m, 4H), 6.97–6.89 (m, 4H), 6.86–6.82 (m, 2H), 6.78–6.74 (m, 2H), 4.21 (q, $J = 7.2$ Hz, 2H), 2.21–2.16 (m, 1H), 1.25–1.21 (m, 2H), 1.16 (t, $J = 7.2$ Hz, 3H), 1.02–0.97 (m, 2H). HRMS: m/z calcd for $C_{33}H_{25}F_3NO_5$ $(M + H)^+$ 572.1685, found: 572.1688.

Ethyl 2-Cyclopropyl-4,6,7-tri-(4-methoxyphenoxy)quinoline-3-carboxylate (11c)

White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (s, 1H), 7.19 (s, 1H), 7.10–7.07 (m, 2H), 6.97–6.94 (m, 2H), 6.90–6.87 (m, 2H), 6.82–6.80 (m, 2H), 6.76 (s, 4H), 4.20 (q, $J = 7.2$ Hz, 2H), 3.86 (s, 3H), 3.83 (s, 3H), 3.80 (s, 3H), 2.21–2.18 (m, 1H), 1.25–1.22 (m, 2H), 1.20 (t, $J = 7.2$ Hz, 3H), 1.01–0.98 (m, 2H).

Ethyl 2-Cyclopropyl-4,6,7-tri-(4-fluorophenylthio)quinoline-3-carboxylate (11d)

Lightly yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (s, 1H), 7.54–7.49 (m, 3H), 7.32–7.28 (m, 2H), 7.18–7.14 (m, 2H), 7.06–7.02 (m, 2H), 7.00–7.97 (m, 2H), 7.89–6.84 (m, 2H), 4.44 (q, $J = 7.2$ Hz, 2H), 2.10–2.06 (m, 1H), 1.35 (t, $J = 7.2$ Hz, 3H), 1.33–1.28 (m, 2H), 1.08–1.03 (m, 2H).

Ethyl 2-Cyclopropyl-4,6,7-tri-(4-methoxyphenylthio)quinoline-3-carboxylate (11e)

Yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (s, 1H), 7.49–7.47 (m, 2H), 7.35–7.32 (m, 2H), 7.26 (s, 1H), 6.99–6.90 (m, 6H), 6.67–6.64 (m, 2H), 4.42 (q, $J = 7.2$ Hz, 2H), 3.87 (s, 3H), 3.86 (s, 3H), 3.74 (s, 3H), 2.04–2.01 (m, 1H), 1.35 (t, $J = 7.2$ Hz, 3H), 1.21–1.16 (m, 2H), 0.98–0.94 (m, 2H). MS (ESI): $m/z = 656$ $(M + H)^+$.

Ethyl 2-Cyclopropyl-4,5,6-tri-(4-methoxyphenoxy)quinoline-3-carboxylate (14a)

White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, $J = 8.8$ Hz, 1H), 7.38 (t, $J = 9.2$ Hz, 1H), 6.79–6.47 (m, 12H), 4.16 (q, $J = 7.2$ Hz, 2H), 3.77 (s, 3H), 3.75 (s, 3H), 3.74 (s, 3H), 2.19–2.16 (m, 1H), 1.39–1.35 (m, 2H), 1.11–1.06 (m, 5H).

Ethyl 2-Cyclopropyl-4,6,7-tri-(4-methoxyphenylthio)quinoline-3-carboxylate (14b)

Yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (b, 1H), 7.39–7.36 (m, 2H), 7.07 (d, $J = 9.2$ Hz, 1H), 7.05–7.03 (m, 2H), 6.97–6.72 (m, 8H), 4.25 (q, $J = 7.2$ Hz, 2H), 3.87 (s, 3H), 3.76 (s, 6H), 2.08–2.06 (m, 1H), 1.25 (t, $J = 7.2$ Hz, 3H), 1.34–1.31 (m, 2H), 1.07–1.03 (m, 2H).

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7. The crystallographic data for molecule **8a** have been deposited with the Cambridge Crystallographic Data Centre, 12 Union Road, CB2 1EZ, UK (e-mail: deposit@ccdc.cam.ac.uk) and are available on request quoting the deposition mumbers CCDC 732271 for **8a**.