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Copper(II) triflate-catalyzed reactions for the synthesis of novel and diverse quinoline carboxylates†

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An efficient one-pot synthesis of a variety of quinoline carboxylates was accomplished by $Cu(OTf)_2$-catalyzed reactions of Michael addition/cyclization/aromatization between 2-aminoaryl carbonyls and alkynyl carboxylates. This methodology offers several significant advantages, namely, ease of handling, mild reaction conditions, enhanced reaction rates, and use of an effective and non-toxic catalyst. The synthesized compounds were further transformed into highly functionalized novel quinoline carboxylates bearing aromatic rings on the quinoline skeleton using the Suzuki reaction.

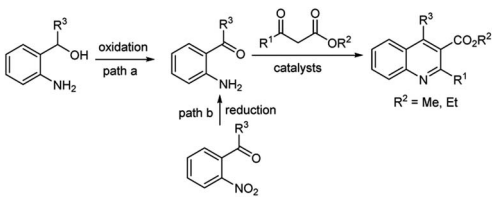
Introduction

Quinolines and their derivatives are prevalent structural motifs and are found in a wide variety of natural products with important pharmacological activities.[1] These compounds have been shown to possess various biological properties, such as antimalarial, antimicrobial, antitumor, anti-inflammatory, antiasthmatic, and antihypertensive activities.[2] In addition, some isolated from marine organisms have been shown to have other properties, such as, the inhibitions of phosphoinositide-dependent protein 1 (PDK-1), which is involved in the progression of some cancers,[3] and tyro-kinase PDGF-RTK.[4] Due to their interesting activities, a number of classical methods, including the Skraup,[5] Doebner-von Miller,[6] Doebner,[7] Combes,[8] Pfitzinger,[9] and Friedländer[10] protocols, have been used to synthesize the quinoline core. Among these, Friedländer annulation has been widely used to synthesize substituted 3-quinolinecarboxylic esters (Scheme 1).[10] Reactions between 2-aminoaryl carbonyl compounds, generated *in situ* by oxidation of 2-aminobenzylic alcohols (path a)[10a] or by reduction of nitro compounds (path b),[10b] and β-keto esters in the presence of various catalysts lead to the formation of 3-quinolinecarboxylic esters *via* cyclocondensation. The usefulness of quinoline moiety has driven the attention of synthetic chemists towards the discovery of exceptionally convenient strategies in designing and synthesis of exclusive quinoline skeleton. Consequently numerous methods dealing with catalytic activity of Brønsted acids (polyphosphoric sulfamic or *p*-TsOH)[11] and Lewis acids ($AuCl_3$, $Y(OTf)_3$, $ZnCl_2$, $Ag_3PW_{12}O_{40}$, $FeCl_3$, $Mg(ClO_4)_2$, $RuCl_2(dmso)_4$, CuI or Ag(OTf))[12] has been explored.

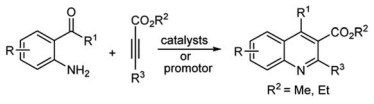
Other useful methods have been described for the synthesis of quinoline carboxylates, such as, cycloaddition between 2-amino carbonyl compounds and dialkyl acetylenedicarboxylates or alkyl acetylenecarboxylates, in which $AuCl(PPh_3)$/AgOTf,[13] β-cyclodextrin (β-CD),[14] or pyridine[15] were used as catalysts, and PPh_3 (ref. 16) as a promoter (Scheme 2).

Recently, other methods of synthesizing quinoline dicarboxylate were reported based on the photo-Fries rearrangement of *p*-substituted anilides[17] and the $[Cp^*Fe(CO_2)]_2$-catalyzed reductive cyclization of *o*-nitro Baylis–Hillman acetates.[18] Despite a few methods devised to synthesize quinoline dicarboxylate,[13–16] which is limited in the use of propiolates, there is still a demand for simpler, less toxic, more effective, milder catalysts. In particular, the reported methods have been widely used for the synthesis of quinoline methylcarboxylates and ethylcarboxylates.

Development of new methods for functionalized quinoline has always been a challenge since the installation of particular



Scheme 1 Typical method for the synthesis of quinoline carboxylates from aminocarbonyls and 1,3-ketoesters.



Scheme 2 General methods for the synthesis of quinoline carboxylates from aminocarbonyls and dialkyl acetylene dicarboxylates.

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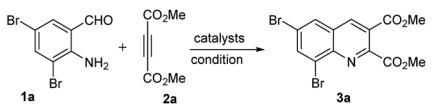
functionality in the moiety often requires tactful handling of vulnerable function in the reaction. Our on-going studies on mild and efficient synthetic methods for producing functionalized quinoline carboxylates and dicarboxylates led to examine potentially more convenient and safe catalysts. Of those examined, $Cu(OTf)_2$ was found to provide a viable alternative, because of its availability, ease of handling, enhanced reaction rates, greater selectivity, and simple requirements.[19] Here, we describe the copper triflate-catalyzed synthesis of biologically interesting novel and diverse quinoline carboxylates bearing methyl, ethyl, prenyl, phenylpropyl, phenoxyethyl, benzyl, 1-naphthyl, and phenyl groups. We also report on the synthesis of functionalized quinoline dicarboxylates with various substituents such as dibromo, methyl, phenyl, and 4-bromophenyl on the quinoline ring.

Results and discussion

To synthesize 6,8-dibromo-2,3-dimethylquinoline dicarboxylate (**3a**), we first investigated reactions between 2-amino-3,5-dibromobenzaldehyde (**1a**) and dimethyl acetylenedicarboxylate (DMAD, **2a**) using different catalysts and solvents. Results are depicted in Table 1. Reaction between **1a** and **2a** in the presence of $InCl_3$ (10 mol%) or $Yb(OTf)_3$ (both Lewis catalysts) in refluxing methylene chloride for 12 h provided the desired product **3a** in 78 and 81% yield, respectively. When CuCl (10 mol%) was used, **3a** was obtained in 66% yield. Interestingly, when $Cu(OTf)_2$ was used as a catalyst, a significant increase in yield occurred. Treatment of **1a** with **2a** in the presence of 10 mol% of $Cu(OTf)_2$ in refluxing methylene for 12 h afforded **3a** in 90% yield. When the temperature was raised to 83 °C using 1,2-dichloroethane, the yield improved to 96%. Despite the use of high boiling solvents at their reflux, reactions in toluene, ethanol, and water did not improve the yield. Compound **3a** was easily separated by column chromatography and identified by analyzing spectroscopic data. In the ^1H NMR spectrum of **3a**, the two *m*-protons on the benzene ring appeared at δ 8.21 (d, $J = 2.0$ Hz) and δ 7.99 (d, $J = 2.0$ Hz) ppm due to a long range coupling, whereas one proton on the pyridinyl ring exhibited at δ 8.60 ppm as a singlet. In order to compare with reported work, further reactions were carried out. For examples, reaction of **1a** with **2a** in the presence of 10 mol% of pyridine in refluxing 1,2-dichloroethane for 12 h provided **3a** in 68% yield, whereas that in 10 mol% of PPh_3 for 12 h afforded **3a** in 50% yield.

Table 1 Effects of catalysts and solvents for the synthesis of 2,3-quinoline dicarboxylate **3a**



Catalyst	Solvent	Condition	Yield (%)
$InCl_3$ (10 mol%)	CH_2Cl_2	Reflux, 12 h	78
$Yb(OTf)_3$ (10 mol%)	CH_2Cl_2	Reflux, 12 h	81
CuCl (10 mol%)	CH_2Cl_2	Reflux, 12 h	66
$Cu(OTf)_2$ (10 mol%)	CH_2Cl_2	Reflux, 12 h	90
$Cu(OTf)_2$ (10 mol%)	$ClCH_2CH_2Cl$	Reflux, 6 h	96
$Cu(OTf)_2$ (10 mol%)	Toluene	Reflux, 12 h	89
$Cu(OTf)_2$ (20 mol%)	EtOH	Reflux, 12 h	82
$Cu(OTf)_2$ (20 mol%)	H_2O	Reflux, 12 h	75

Several methods for the synthesis of quinoline carboxylates starting from 2-amino carbonyl compounds have been reported.[13–16] These known methods mostly employed internal acetylene carboxylates such as dialkyl acetylenedicarboxylates and ethyl 3-phenylpropiolate as reactants, which provided quinoline dicarboxylates.[13–16] To explore the generality and scope of our method, additional reactions between 2-aminoaryl carbonyl compounds **1a–1d** and various internal/terminal acetylene carboxylates **2b–2l** were carried out in the presence of 10 mol% of $Cu(OTf)_2$ under optimized reaction conditions. In particular, a number of synthesized terminal alkylpropiolates bearing prenyl, 3-phenylpropyl, 2-phenoxyethyl, benzyl, naphthalen-1-ylmethyl, and phenyl group were used. Results are summarized in Table 2. Reaction between 2-amino-3,5-dibromobenzaldehyde (**1a**) and diethyl acetylenedicarboxylate (**2b**) in the presence of 10 mol% of $Cu(OTf)_2$ in 1,2-dichloroethane under reflux for 6 h furnished 6,8-dibromo-2,3-diethylquinoline dicarboxylate (**3b**) in 85% yield (Table 2, entry 1). Treatment of **1a** with methyl propiolate (**2c**) or ethyl propiolate (**2d**) afforded the expected products **3c** and **3d** at yields of 92 and 90%, respectively (Table 2, entries 2–3). Further reactions between **1a** and other propiolates **2e–2j** were also successful. Treatment of **1a** with propiolates **2e–2g** bearing a prenyl, 3-phenylpropyl, or 2-phenoxyethyl group provided the desired products **3e–3g** at yields of 86, 80, and 73%, respectively (entries 4–6), whereas treatment of **1a** with **2h–2j** bearing benzyl, naphthalene-1-yl methyl, or phenyl group afforded products **3h–3j** in 80, 78, and 81% yield (entries 7–9). Importantly, all terminal acetylenic carboxylates **2e–2j** provided the directionality to afford 3-quinoline carboxylates as single isomers and no regioisomeric 2-substituted quinoline carboxylates were observed in the process. The reactions of 2-amino acetophenone (**1b**), 2-amino benzophenone (**1c**), and 2-amino-4′-bromobenzophenone (**1d**) were also successful. Conversion of **1b–1d** into the corresponding products **3k–3p** took slightly more time (12 h), but at satisfactory yields of 75–82% (entries 10–15). In addition, treatment of **1a** with ethyl 3-phenylpropiolate (**2k**) for 12 h afforded **3q** in 30% yield and starting material **1a** (50%) was recovered (entry 16). However, reaction with ethyl 3-methylpropiolate (**2l**) for 12 h did not provide the desired product **3r**, instead almost of starting material was recovered (entry 17).

The formation of **3k** could be explained by the putative mechanism shown in Scheme 3. Dimethyl acetylenedicarboxylate forms a carbonyl–copper complex in the presence of $Cu(OTf)_2$, and this complex is attacked by 2-amino acetophenone (**1b**) to produce intermediate **4** *via* Michael reaction. Proton transfer of **4** followed by isomerization of **5** gives intermediate **6**, which then forms a complex with $Cu(OTf)_2$ to afford **7**. Intramolecular cyclization of **7** furnishes **8**, which on aromatization yields the final product **3k**. As an evidence of this

Table 2 $Cu(OTf)_2$-catalyzed synthesis of a variety of quinoline carboxylates in refluxing 1,2-dichloroethane

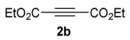
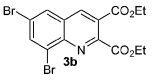
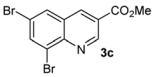
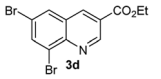
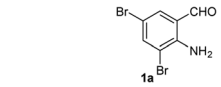
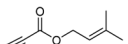
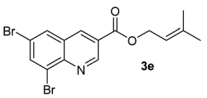
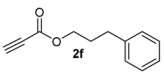
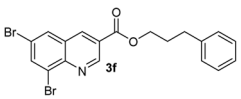
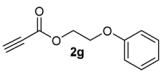
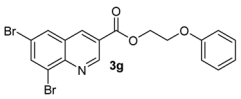
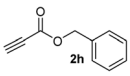
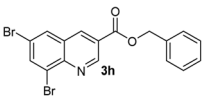
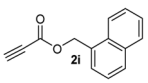
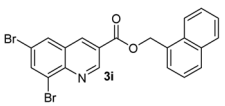
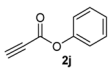
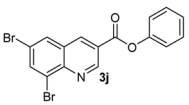
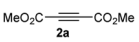
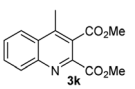
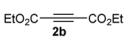
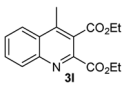
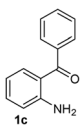
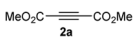
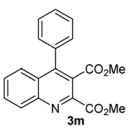
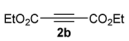
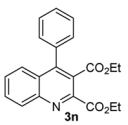
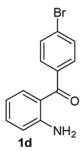
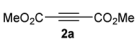
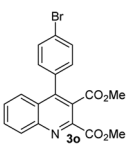
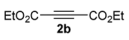
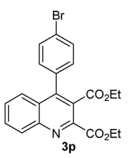
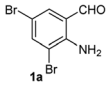
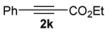
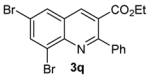
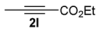
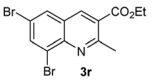
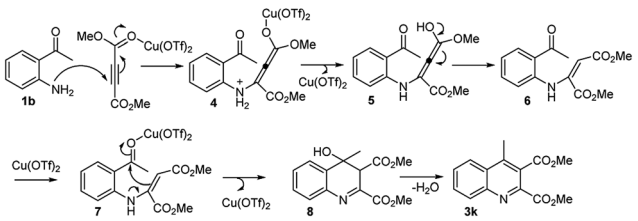
Entry	Starting material	Acetylene carboxylate	Time (h)	Product	Yield (%)
1		 2b	6	 3b	85
2		 2c	6	 3c	92
3		 2d	6	 3d	90
4	 1a	 2e	7	 3e	86
5		 2f	7	 3f	80
6		 2g	7	 3g	73
7		 2h	7	 3h	80
8		 2i	7	 3i	78
9		 2j	7	 3j	81
10	 1b	 2a	12	 3k	76
11		 2b	12	 3l	75
12	 1c	 2a	12	 3m	80
13		 2b	12	 3n	76
14	 1d	 2a	12	 3o	82
15		 2b	12	 3p	80

Table 2 (*Contd.*)

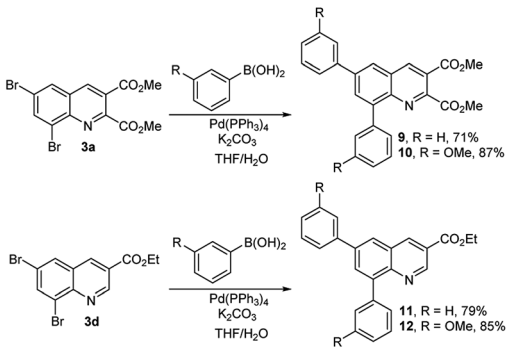
Entry	Starting material	Acetylene carboxylate	Time (h)	Product	Yield (%)
16			12		30
17			12		0



Scheme 3 The possible mechanism for the formation of **3k**.

mechanism, the Michael adduct **6** was isolated from a reaction mixture after 5 h and characterized by NMR spectroscopy, but underwent complete conversion into the final product in a prolonged reaction time (12 h).

As an application of this methodology, we attempted the conversion of synthesized compound **3a** to other interesting novel molecules using Suzuki reactions, as shown in Scheme 4. Reaction of **3a** with phenylboronic acid in the presence of $Pd(PPh_3)_4$ in refluxing aqueous THF for 5 h gave **9** in 71% yield, whereas reaction with 3-methoxyphenylboronic acid for 3 h provided **10** in 87% yield. Similarly, the Suzuki coupling of ethyl 6,8-dibromoquinoline-3-carboxylate (**3d**) with phenylboronic acid or 3-methoxyphenylboronic acid furnished **11** and **12** in 79 and 85% yield, respectively. We expect that these synthetic routes will be widely used to synthesize novel and diverse polysubstituted quinoline carboxylates bearing aromatic rings on the quinoline skeleton.



Scheme 4 Transformation to poly substituted quinoline carboxylates using Suzuki coupling.

Conclusions

In summary, we have synthesized a variety of quinoline carboxylates through reactions between 2-aminoaryl carbonyl compounds and acetylene dicarboxylates or propiolates. The key strategy involves $Cu(OTf)_2$-catalyzed cascade reactions *via* Michael addition/cyclization/aromatization. The synthesized compounds were further transformed into novel and interesting polysubstituted quinoline carboxylates bearing aromatic rings on the quinoline skeleton using Suzuki reactions.

Experimental

All the experiments were carried out under nitrogen atmosphere. Merck precoated silica gel plates (Art. 5554) with fluorescent indicator were used for analytical TLC. Flash column chromatography was performed using silica gel 9385 (Merck). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian VNS (300 and 75 or 150 MHz, respectively) spectrometer in $CDCl_3$ using δ = 7.24 and 77.0 ppm as solvent chemical shifts. Multiplicities were abbreviated as s = singlet, d = doublet, t = triplet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets. IR spectra were recorded on a FTIR (BIO-RAD), and HRMS were carried out at the Korean Basic Science Institute.

General procedure for the synthesis of quinoline carboxylates

To a solution of 2-aminoaryl carbonyl (0.5 mmol) and acetylene carboxylate (0.6 mmol) in 1,2-dichloroethane (5 mL) was added $Cu(OTf)_2$ (18 mg, 10 mol%) and the reaction mixture was refluxed for 6–12 h. After completion of reaction as indicated by TLC, the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel using hexane–EtOAc (10 : 1) to give the product.

Dimethyl 6,8-dibromoquinoline-2,3-dicarboxylate (3a). White solid, (192 mg, 96%), mp 165–166 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.60 (s, 1H), 8.21 (d, J = 2.0 Hz, 1H), 7.99 (d, J = 2.0 Hz, 1H), 3.99 (s, 3H), 3.92 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.6, 164.8, 151.5, 144.3, 139.1, 138.9, 130.4, 129.0, 126.6, 124.0, 122.4, 53.4, 53.3; FT-IR (KBr) 3069, 1727, 1272, 1144 cm^{-1}; HRMS (EI) m/z (M^+) calcd for $C_{13}H_9Br_2NO_4$: 400.8898. Found: 400.8897.

Diethyl 6,8-dibromoquinoline-2,3-dicarboxylate (3b). White solid, (182 mg, 85%), mp 160–162 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.65 (s, 1H), 8.24 (s, 1H), 8.04 (s, 1H), 4.50 (q, J = 7.5

Hz, 2H), 4.42 (q, $J = 7.2$ Hz, 2H), 1.44–1.37 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.1, 164.3, 151.8, 144.1, 139.0, 138.6, 130.3, 128.8, 126.4, 124.0, 122.1, 62.5, 62.4, 14.2, 14.1; FT-IR (KBr) 2982, 1732, 1275, 1063 cm^{-1}; HRMS (EI) m/z (M^+) calcd for $C_{15}H_{13}Br_2NO_4$: 428.9211. Found: 428.9211.

Methyl 6,8-dibromoquinoline-3-carboxylate (3c). White solid, (157 mg, 92%), mp 124–126 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.52 (s, 1H), 8.74 (s, 1H), 8.25 (s, 1H), 8.06 (s, 1H), 4.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.1, 151.1, 145.7, 138.3, 138.2, 130.9, 128.9, 126.1, 124.7, 121.1, 53.0; FT-IR (KBr) 3074, 1713, 1276, 1108 cm^{-1}; HRMS (EI) m/z (M^+) calcd for $C_{11}H_7Br_2NO_2$: 342.8844. Found: 342.8842.

Ethyl 6,8-dibromoquinoline-3-carboxylate (3d). White solid, (160 mg, 90%), mp 121–123 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.49 (s, 1H), 8.69 (s, 1H), 8.20 (s, 1H), 8.02 (s, 1H), 4.46 (q, $J = 7.2$ Hz, 2H), 1.43 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.5, 151.1, 145.6, 138.1, 138.0, 130.8, 128.8, 126.1, 125.0, 120.9, 62.0, 14.4; FT-IR (KBr) 2985, 1721, 1261, 1109 cm^{-1}; HRMS (EI) m/z (M^+) calcd for $C_{12}H_9Br_2NO_2$: 356.9000. Found: 356.8997.

3-Methylbut-2-enyl 6,8-dibromoquinoline-3-carboxylate (3e). White solid, (170 mg, 86%), mp 98–100 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.51 (d, $J = 1.5$ Hz, 1H), 8.71 (d, $J = 1.5$ Hz, 1H), 8.22 (d, $J = 2.1$ Hz, 1H), 8.04 (d, $J = 2.1$ Hz, 1H), 5.48 (t, $J = 7.2$ Hz, 1H), 4.90 (d, $J = 7.2$ Hz, 2H), 1.79 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.5, 151.1, 145.5, 140.3, 138.0, 137.9, 130.8, 128.8, 126.0, 125.0, 120.8, 118.1, 62.8, 25.9, 18.3; FT-IR (KBr) 2972, 1713, 1245, 1106, 926 cm^{-1}; HRMS (EI) m/z (M^+) calcd for $C_{15}H_{13}Br_2NO_2$: 396.9313. Found: 396.9312.

3-Phenylpropyl 6,8-dibromoquinoline-3-carboxylate (3f). White solid, (178 mg, 80%), mp 75–76 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.53 (s, 1H), 8.64 (d, $J = 2.0$ Hz, 1H), 8.25 (d, $J = 2.0$ Hz, 1H), 8.06 (d, $J = 1.5$ Hz, 1H), 7.31–7.18 (m, 5H), 4.43 (t, $J = 6.3$ Hz, 2H), 2.80 (t, $J = 7.8$ Hz, 2H), 2.20–2.10 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 164.2, 150.7, 145.3, 140.6, 137.9, 137.8, 130.5, 128.6, 128.3, 128.3, 128.2, 128.2, 125.9, 125.7, 124.5, 120.6, 65.0, 32.1, 29.8; FT-IR (KBr) 3055, 1720, 1240, 1100 cm^{-1}; HRMS (EI) m/z (M^+) calcd for $C_{19}H_{15}Br_2NO_2$: 446.9470. Found: 446.9469.

2-Phenoxyethyl 6,8-dibromoquinoline-3-carboxylate (3g). White solid, (164 mg, 73%), mp 100–102 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.53 (d, $J = 2.0$ Hz, 1H), 8.71 (d, $J = 2.0$ Hz, 1H), 8.24 (d, $J = 2.1$ Hz, 1H), 8.05 (d, $J = 2.1$ Hz, 1H), 7.32–7.27 (m, 2H), 7.00–6.95 (m, 3H), 4.76 (t, $J = 4.5$ Hz, 2H), 4.35 (t, $J = 4.5$ Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 164.4, 158.3, 151.0, 145.7, 138.3, 138.1, 130.8, 129.6, 129.6, 128.7, 126.0, 124.3, 121.4, 120.9, 114.6, 114.6, 65.6, 64.2; FT-IR (KBr) 3060, 1715, 1247, 1105 cm^{-1}; HRMS (EI) m/z (M^+) calcd for $C_{18}H_{13}Br_2NO_3$: 448.9262. Found: 448.9262.

Benzyl 6,8-dibromoquinoline-3-carboxylate (3h). White solid, (167 mg, 80%), mp 145–146 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.55 (s, 1H), 8.73 (d, $J = 2.0$ Hz, 1H), 8.23 (d, $J = 2.0$ Hz, 1H), 8.04 (s, 1H), 7.45–7.38 (m, 5H), 5.44 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.3, 151.1, 145.7, 138.2, 138.1, 135.4, 130.8, 128.9, 128.9, 128.9, 128.8, 128.5, 128.5, 126.1, 124.7, 121.0, 67.6; FT-IR (KBr) 3066, 1713, 1245, 1109 cm^{-1}; HRMS (EI) m/z (M^+) calcd for $C_{17}H_{11}Br_2NO_2$: 418.9157. Found: 418.9156.

Naphthalen-1-ylmethyl 6,8-dibromoquinoline-3-carboxylate (3i). White solid, (183 mg, 78%), mp 181–182 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.53 (d, $J = 1.5$ Hz, 1H), 8.68 (d, $J = 1.5$ Hz, 1H), 8.21 (d, $J = 1.5$ Hz, 1H), 8.12 (d, $J = 8.1$ Hz, 1H), 7.99 (d, $J = 1.8$ Hz, 1H), 7.91–7.87 (m, 2H), 7.65 (d, $J = 6.9$ Hz, 1H), 7.60–7.45 (m, 3H), 5.90 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 164.3, 151.0, 145.5, 138.2, 138.0, 133.7, 131.7, 130.7, 130.6, 129.8, 128.8, 128.7, 127.9, 126.8, 126.1, 125.9, 125.2, 124.5, 123.3, 120.8, 65.9; FT-IR (KBr) 3058, 2928, 1716, 1251, 1108, 784 cm^{-1}; HRMS (EI) m/z (M^+) calcd for $C_{21}H_{13}Br_2NO_2$: 468.9313; found: 468.9314.

Phenyl 6,8-dibromoquinoline-3-carboxylate (3j). White solid, (164 mg, 81%), mp 193–195 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.60 (s, 1H), 8.84 (d, $J = 1.5$ Hz, 1H), 8.22 (d, $J = 1.5$ Hz, 1H), 8.04 (s, 1H), 7.44–7.38 (m, 2H), 7.28–7.21 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.2, 151.2, 150.6, 146.0, 139.0, 138.6, 131.0, 129.8, 129.8, 128.9, 126.6, 126.3, 124.4, 121.6, 121.6, 121.3; FT-IR (KBr) 3053, 1725, 1473, 1207, 1095 cm^{-1}; HRMS (EI) m/z (M^+) calcd for $C_{16}H_9Br_2NO_2$: 404.9000. Found: 404.8998.

Dimethyl 4-methylquinoline-2,3-dicarboxylate (3k).[17] Yellow solid, (99 mg, 76%), mp 80 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.24 (d, $J = 8.1$ Hz, 1H), 8.06 (d, $J = 8.1$ Hz, 1H), 7.79 (dd, $J = 9.3$, 7.2 Hz, 1H), 7.67 (dd, $J = 6.9$, 6.9 Hz, 1H), 4.02 (s, 3H), 3.98 (s, 3H), 2.71 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 168.2, 165.4, 146.1, 144.7, 143.7, 130.9, 130.7, 128.9, 127.8, 127.0, 123.9, 53.2, 52.7, 15.4; FT-IR (KBr) 3007, 2953, 1726, 1568, 1443, 1244, 1058, 770 cm^{-1}.

Diethyl 4-methylquinoline-2,3-dicarboxylate (3l). Yellow solid, (107 mg, 75%), mp 63–64 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.23 (d, $J = 8.1$ Hz, 1H), 8.06 (d, $J = 8.1$ Hz, 1H), 7.77 (dd, $J = 8.1$, 6.9 Hz, 1H), 7.66 (dd, $J = 7.5$, 7.1 Hz, 1H), 4.52–4.41 (m, 4H), 2.72 (s, 3H), 1.45–1.36 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.9, 165.4, 146.4, 145.9, 143.9, 131.1, 130.8, 129.0, 128.0, 127.1. 124.1, 62.5, 62.0, 15.5, 14.2, 14.1; FT-IR (KBr) 2982, 1730, 1239, 1182 cm^{-1}; HRMS (EI) m/z (M^+) calcd for $C_{16}H_{17}NO_4$: 287.1158. Found: 287.1157.

Dimethyl 4-phenylquinoline-2,3-dicarboxylate (3m).[16] Yellow solid, (128 mg, 80%), mp 79–80 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.30 (d, $J = 8.4$ Hz, 1H), 7.82–7.76 (m, 1H), 7.62–7.52 (m, 2H), 7.48–7.46 (m, 3H), 7.34–7.31 (m, 2H), 4.04 (s, 3H), 3.60 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.6, 165.5, 148.0, 147.0, 144.8, 134.4, 131.0, 130.6, 129.3, 129.3, 129.2, 128.8, 128.3, 128.3, 127.5, 127.2, 126.6, 53.4, 52.4; FT-IR (KBr) 3050, 2995, 1725, 1245, 1180 cm^{-1}.

Diethyl 4-phenylquinoline-2,3-dicarboxylate (3n).[16] Yellow solid, (133 mg, 76%), mp 60–61 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.30 (d, $J = 7.8$ Hz, 1H), 7.81–7.76 (m, 1H), 7.62–7.52 (m, 2H), 7.48–7.46 (m, 3H), 7.35–7.32 (m, 2H), 4.51 (q, $J = 7.2$ Hz, 2H), 4.09 (q, $J = 7.2$ Hz, 2H), 1.43 (t, $J = 7.2$ Hz, 3H), 0.96 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.1, 165.2, 147.9, 147.0, 145.8, 134.7, 130.9, 130.6, 129.4. 129.4, 129.1, 128.7, 128.2, 128.2, 127.5, 127.0, 126.6, 62.6, 61.5, 14.2, 13.6; FT-IR (KBr) 3030, 1985, 1728, 1240, 1179 cm^{-1}.

Dimethyl 4-(4-bromophenyl)quinoline-2,3-dicarboxylate (3o). White solid, (164 mg, 82%), mp 162–163 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.28 (d, $J = 8.4$ Hz, 1H), 7.80–7.74 (m, 1H), 7.60–7.50 (m, 4H), 7.18 (d, $J = 7.8$ Hz, 2H), 4.00 (s, 3H), 3.61 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.3, 165.4, 147.0, 146.7,

144.9, 133.37, 131.6, 131.6, 131.2, 131.0, 131.0, 130.7, 129.5, 127.2, 127.0, 126.2, 123.4, 53.5, 52.6; FT-IR (KBr) 3066, 2948, 1731, 1231, 1052, 774 cm^{-1}; HRMS (EI) *m/z* (M^+) calcd for $C_{19}H_{14}BrNO_4$: 399.0106. Found: 399.0105.

Diethyl 4-(4-bromophenyl)quinoline-2,3-dicarboxylate (3p). White solid, (170 mg, 80%), mp 100–101 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 8.25 (d, $J = 8.4$ Hz, 1H), 7.77–7.72 (m, 1H), 7.59–7.48 (m, 4H), 7.18 (d, $J = 8.4$ Hz, 2H), 4.46 (q, $J = 7.2$ Hz, 2H), 4.06 (q, $J = 7.2$ Hz, 2H), 1.38 (t, $J = 7.2$ Hz, 3H), 0.99 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.0, 165.3, 147.2, 146.8, 146.1, 133.8, 131.7, 131.7, 131.3, 131.3, 131.2, 130.9, 129.4, 127.3, 127.1, 126.4, 123.4, 62.8, 61.8, 14.3, 13.8; FT-IR (KBr) 2978, 1725, 1213, 1044, 771 cm^{-1}; HRMS (EI) *m/z* (M^+) calcd for $C_{21}H_{18}BrNO_4$: 427.0419. Found: 427.0422.

Ethyl 6,8-dibromo-2-phenylquinoline-3-carboxylate (3q). White solid, (129 mg, 30%), mp 80–82 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 8.44 (s, 1H), 8.19 (d, $J = 1.8$ Hz, 1H), 7.99 (d, $J = 1.8$ Hz, 1H), 7.74–7.71 (m, 2H), 7.46–7.44 (m, 3H), 4.20 (q, $J = 7.2$ Hz, 2H), 1.08 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.6, 158.4, 143.9, 139.4, 138.1, 137.5, 129.7, 129.2, 129.0, 129.0, 128.2, 128.2, 127.4, 127.2, 126.2, 120.2, 61.9, 13.6; FT-IR (KBr) 3060, 1710, 1583, 1438, 1250, 1105, 696 cm^{-1}; HRMS (EI) *m/z* (M^+) calcd for $C_{18}H_{13}Br_2NO_2$: 432.9313. Found: 432.9315.

Dimethyl 2-(2-acetylphenylamino)maleate (6). Yellow solid, mp 82–84 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 11.92 (s, NH, 1H), 7.80 (d, $J = 9.6$ Hz, 1H), 7.36–7.24 (m, 1H), 7.01–6.96 (m, 1H), 6.62 (d, $J = 8.4$ Hz, 1H), 5.59 (s, 1H), 3.76 (s, 3H), 3.72 (s, 3H), 2.63 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.6, 167.9, 165.5, 144.3, 142.0, 133.4, 131.7, 124.0, 121.3, 118.6, 100.3, 53.0, 51.6, 28.3; FT-IR (KBr) 3455, 3290, 1733, 1669, 1594, 1440, 1272, 1199, 768 cm^{-1}; HRMS (EI) *m/z* (M^+) calcd for $C_{14}H_{15}NO_5$: 277.0950. Found: 277.0947.

General procedure for Suzuki coupling

Dimethyl 6,8-diphenylquinoline-2,3-dicarboxylate (9). To a mixture of phenylboronic acid (181 mg, 1.5 mmol), **3a** (200 mg, 0.5 mmol), and K_2CO_3 (207 mg, 1.5 mmol) in THF–H_2O (1 : 1) (5 mL) was added $Pd(PPh_3)_4$ (29 mg, 5 mol%) under N_2 and the mixture was heated at 60 °C for 5 h. The reaction mixture was quenched with saturated NH_4Cl solution (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined layers were washed with water (10 mL), dried ($MgSO_4$), and evaporated under reduced pressure. Flash chromatography on silica gel using hexane–ethyl acetate (5 : 1) afforded **9** (281 mg, 71%) as yellow solid, mp 115–117 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 8.82 (s, 1H), 8.15 (d, $J = 2.0$ Hz, 1H), 8.05 (d, $J = 2.0$ Hz, 1H), 7.80–7.71 (m, 4H), 7.52–7.39 (m, 6H), 3.97 (s, 3H), 3.96 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.1, 165.4, 149.8, 144.8, 141.3, 140.9, 139.7, 139.2, 138.0, 132.7, 130.8, 130.8, 129.0, 129.0, 128.2, 127.8, 127.8, 127.7, 127.6, 127.3, 127.3, 125.4, 122.0, 52.8, 52.7; FT-IR (KBr) 2952, 2919, 1728, 1574, 1265, 1194, 1142, 1061, 762, 695 cm^{-1}; HRMS *m/z* (M^+) calcd for $C_{25}H_{19}NO_4$: 397.1314. Found: 397.1312.

Dimethyl 6,8-bis(3-methoxyphenyl)quinoline-2,3-dicarboxylate (10). To a mixture of 3-methoxyphenylboronic acid (226 mg, 1.5 mmol), **3a** (200 mg, 0.5 mmol), and K_2CO_3 (207 mg, 1.5 mmol) in THF–H_2O (1 : 1) (5 mL) was added $Pd(PPh_3)_4$ (29 mg, 5 mol%) under N_2 and the mixture was heated at 60 °C for 3 h. The reaction mixture was quenched with saturated NH_4Cl solution (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined layers were washed with water (10 mL), dried ($MgSO_4$), and evaporated under reduced pressure. Flash chromatography on silica gel using hexane–ethyl acetate (4 : 1) afforded **10** (397 mg, 87%) as an oil; ^1H NMR (300 MHz, $CDCl_3$): δ 8.69 (s, 1H), 8.05 (d, $J = 2.1$ Hz, 1H), 7.92 (d, $J = 2.1$ Hz, 1H), 7.31–7.30 (m, 1H), 7.28 (d, $J = 2.7$ Hz, 1H), 7.26 (d, $J = 2.4$ Hz, 1H), 7.24–7.23 (m, 1H), 7.21–7.16 (m, 1H), 7.14–7.12 (m, 1H), 6.89–6.83 (m, 2H), 3.86 (s, 6H), 3.76 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.0, 165.4, 160.0, 159.0, 149.7, 144.8, 141.0, 140.8, 140.7, 139.7, 139.2, 132.6, 130.0, 128.8, 127.7, 125.5, 123.0, 122.2, 119.8, 116.2, 114.0, 113.5, 113.1, 55.2, 55.1, 52.7, 52.7; FT-IR (neat) 2951, 2838, 1732, 1594, 1449, 1391, 1284, 1143, 1049, 785, 697 cm^{-1}; HRMS *m/z* (M^+) calcd for $C_{27}H_{23}NO_6$: 457.1525. Found: 457.1522.

Ethyl 6,8-diphenylquinoline-3-carboxylate (11). To a mixture of phenylboronic acid (181 mg, 1.5 mmol), **3d** (180 mg, 0.5 mmol), and K_2CO_3 (207 mg, 1.5 mmol) in THF–H_2O (1 : 1) (5 mL) was added $Pd(PPh_3)_4$ (29 mg, 5 mol%) under N_2 and the mixture was heated at 60 °C for 3 h. The reaction mixture was quenched with saturated NH_4Cl solution (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined layers were washed with water (10 mL), dried ($MgSO_4$), and evaporated under reduced pressure. Flash chromatography on silica gel using hexane–ethyl acetate (5 : 1) afforded **11** (278 mg, 79%) as an off-white solid, mp 60–62 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 9.34 (d, $J = 2.1$ Hz, 1H), 8.79 (d, $J = 2.1$ Hz, 1H), 7.98 (d, $J = 2.0$ Hz, 1H), 7.96 (d, $J = 2.0$ Hz, 1H), 7.63–7.62 (m, 2H), 7.61–7.59 (m, 2H), 7.41–7.35 (m, 4H), 7.33–7.29 (m, 2H), 4.36 (q, $J = 6.9$ Hz, 2H), 1.33 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.3, 156.0, 149.5, 146.6, 141.3, 139.7, 139.5, 139.1, 138.7, 132.3, 130.5, 129.3, 128.9, 128.0, 128.0, 127.7, 127.6, 127.3, 126.0, 123.3, 120.0, 115.2, 61.5, 14.2; FT-IR (KBr) 3049, 2983, 1717, 1599, 1478, 1256, 1107, 1020, 762, 695 cm^{-1}; HRMS *m/z* (M^+) calcd for $C_{24}H_{19}NO_2$: 353.1416. Found: 353.1414.

Ethyl 6,8-bis(3-methoxyphenyl)quinoline-3-carboxylate (12). To a mixture of 3-methoxyphenylboronic acid (226 mg, 1.5 mmol), **3d** (180 mg, 0.5 mmol), and K_2CO_3 (207 mg, 1.5 mmol) in THF–H_2O (1 : 1) (5 mL) was added $Pd(PPh_3)_4$ (29 mg, 5 mol%) under N_2 and the mixture was heated at 60 °C for 3 h. The reaction mixture was quenched with saturated NH_4Cl solution (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined layers were washed with water (10 mL), dried ($MgSO_4$), and evaporated under reduced pressure. Flash chromatography on silica gel using hexane–ethyl acetate (3 : 1) afforded **12** (351 mg, 85%) as an off-white solid, mp 123–125 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 9.46 (d, $J = 2.1$ Hz, 1H), 8.89 (d, $J = 2.1$ Hz, 1H), 8.09 (d, $J = 2.1$ Hz, 1H), 8.07 (d, $J = 2.1$ Hz, 1H), 7.45–7.37 (m, 2H), 7.32–7.25 (m, 4H), 7.01–6.93 (m, 2H), 4.47 (q, $J = 7.2$ Hz, 2H), 3.87 (s, 3H), 3.86 (s, 3H), 1.45 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.2, 160.0, 159.2, 149.6, 146.8, 141.1, 141.0, 140.1, 139.5, 138.8, 132.1, 130.0, 128.9, 127.5, 126.1, 123.3, 123.0, 119.8, 116.3, 113.3, 113.2, 113.0, 61.4, 55.2, 55.2, 14.2; FT-IR (KBr) 3055, 2975, 1713, 1594, 1481, 1373, 1232,

1034, 782, 696 cm^{-1}; HRMS *m*/*z* (M^+) calcd for $C_{26}H_{23}NO_4$: 413.1627. Found: 413.1624.

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