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ARTICLE

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Synthesis of substituted quinolines via $B(C_6F_5)_3$-catalyzed aniline-aldehyde-pyruvate oxidative annulation

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Abstract

A metal-free method to construct quinoline derivatives via $B(C_6F_5)_3$-catalyzed cyclization of anilines with aldehyde derivatives and pyruvates is described. This three-component cascade reaction provides an efficient approach for the easy access to various substituted quinoline-4-carboxylic esters with 71% to 92% yield. The utility of this methodology was further demonstrated by gram-scale formal synthesis of the antimalarial drug DDD107498.

1 | INTRODUCTION

Quinoline is an important *N*-heterocycle, existing in numerous drugs and natural products (Figure 1).[1–4] Particularly, quinoline-4-carboxylic esters represent a class of versatile scaffolds, widely used in catalyst design and drug discovery. For example, quinine isolated from *Rubiaceae plant Cinchona*, acted as a powerful organocatalyst in a plenty of asymmetric reactions.[5–12] Moreover, DDD107498 showed excellent inhibition against 3D7 parasites, with the EC50 value of 1.0nM.[13–15] Due to this great importance, a deal of effort has been devoted to develop new and efficient synthetic methods for these structures.[16–22] Particularly, the aniline-aldehyde-pyruvate reaction (also recognized as the A^3 reaction) represents one of the most powerful and efficient methods for the direct synthesis of 4-esteryl quinolines owing to its readily available starting materials, mild reaction conditions, and product diversity. In this context, the Hu group reported a $CuBr_2$-catalyzed simple one-pot reaction of aromatic amines, glyoxylic ester, and pyruvate, leading to a variety of quinoline-2,4-dicarboxyl derivatives (Scheme 1a).[23] Moreover, Gao and coworkers achieved 4-esteryl quinolines in high yields by using an elegant triple zirconocene/brønsted acid/CuO cooperative catalysis system (Scheme 1b).[24] Recently, Wu's group discovered a highly efficient I_2-catalyzed Povarov-type reaction of structure. Methyl ketones, arylamines, and α-ketoesters to form versatile quinolines (Scheme 1c).[25] Despite their unarguable efficiency, the use of metal catalysts[23,24] or harsh conditions[25] limited their further application in pharmaceuticals. As a consequence, there is an urgent demand to develop efficient and practical methodologies to access quinoline-4-carboxylic esters.

$B(C_6F_5)_3$, reported[26] in 1964, re-emerged as a paradigm for small molecule activation in the past decade,

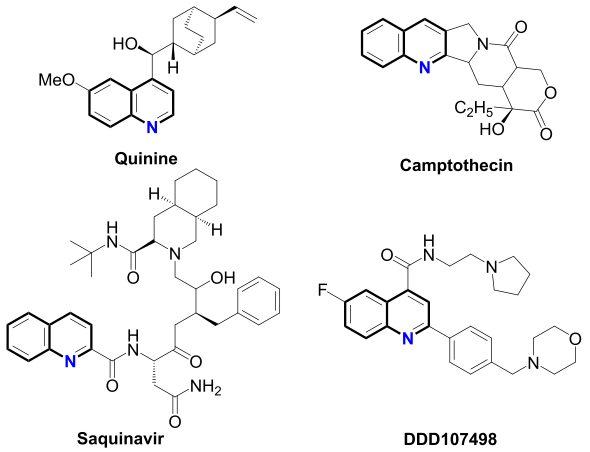


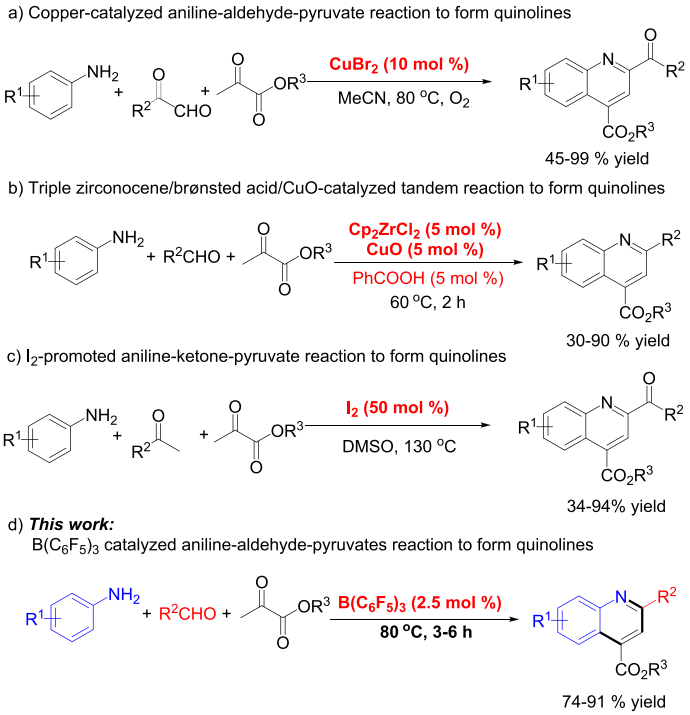
FIGURE 1 Drugs and nature products containing quinoline structure [Color figure can be viewed at wileyonlinelibrary.com]

especially as a component in frustrated Lewis pairs (FLPs) chemistry.[27–32] Moreover, $B(C_6F_5)_3$ has been successfully employed in various other transformations.[33–40] One of the research hotspots is the borane-catalyzed multicomponent reactions (MCRs). Recently, a remarkable work made by Ingleson and coworkers covered a $B(C_6F_5)_3$-initiated aldehyde-aniline-alkyne reaction, which enabled the synthesis of various functionalized quinolines.[41] However, the high catalyst loading (20 mol %) and the utility of expensive alkynes limited its practicability to some degree. Very recently, our group have devoted much efforts to $B(C_6F_5)_3$-catalyzed MCRs, furnishing versatile 2,4,6-triarylpyridines and bis(indolyl)alkanes in high yields.[42–44] Inspired by our previous work, herein, we reported our studies on B$(C_6F_5)_3$-catalyzed aniline-aldehyde-pyruvate annulation reaction for the synthesis of substituted 4-esteryl quinoline derivatives (Scheme 1d).

2 | RESULT AND DISCUSSION

Our initial attempt to realize this transformation was conducted with the reaction of aniline (**1a**), 4-chlorobenzaldehyde (**2a**), and methyl pyruvate (**3a**), using 10 mol % of $B(C_6F_5)_3$. Delightfully, the desired quinoline **4a** was obtained in a yield of 47% when stirring the solution of **1a**, **2a**, and **3a** with a ratio of 1.2:1.1:1 in toluene at 100°C for 2 hours in the presence of $B(C_6F_5)_3$ (Scheme 2). Interestingly, a by-product *N*-(4-chlorobenzyl)aniline (**5a**) was also produced in 42% yield. A possible explanation for the formation of **5a** is that a transfer hydrogenation process occurred in the oxidation step to form the quinoline where the imine acts as a hydrogen acceptor.[41]

Next, the optimization of the reaction conditions was firstly studied on the ratio of the substrates. As expected, raising the ratio of both **1a** and **2a** (Table 1, entries 1-3) improved the reaction yield significantly. The best yield of 78% was accomplished by using 3.6:3.3:1 of **1a**:**2a**:**3a**, further, increasing the ratio did not benefit the reaction outcomes. In addition, the effect of reaction temperature was investigated (Table 1, entries 3 and 4). The results indicated that lowering reaction temperature from 100°C to 80°C did not affect the reaction efficiency, while a



SCHEME 1 Preparation of quinoline-4-carboxylic esters via the A^3 reactions [Color figure can be viewed at wileyonlinelibrary.com]

SCHEME 2 The initial attempt of B$(C_6F_5)_3$-catalyzed aniline-aldehyde-pyruvate reaction [Color figure can be viewed at wileyonlinelibrary.com]

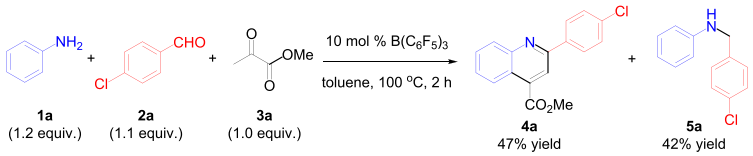
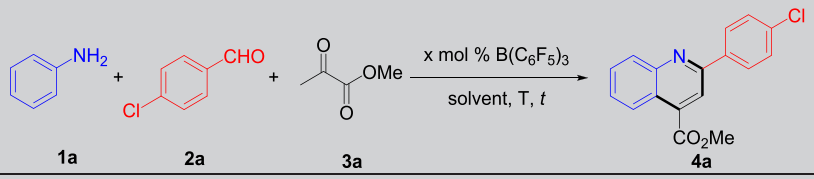


TABLE 1 Optimization of reaction conditions[a]



Entry	1a/2a/3a	x	T, °C	Solvent	*t*, h	Yield of 4a,[b] %
1	2.4/2.2/1.0	10	100	Toluene	2	73
2	3.6/3.3/1.0	10	100	Toluene	2	78
3	4.8/4.4/1.0	10	100	Toluene	2	78
4	3.6/3.3/1.0	10	80	Toluene	4	77
5	3.6/3.3/1.0	10	60	Toluene	8	71
6	3.6/3.3/1.0	10	80	$CHCl_3$	5	69
7	3.6/3.3/1.0	10	80	Hexane	12	61
8	3.6/3.3/1.0	10	80	THF	9	32
9	3.6/3.3/1.0	10	80	EtOH	12	48
10	3.6/3.3/1.0	5	80	Toluene	2	77
11	***3.6/3.3/1.0***	***2.5***	***80***	***Toluene***	***3***	***77***
12	3.6/3.3/1.0	1	80	Toluene	6	62
13	3.6/3.3/1.0	0	80	Toluene	6	Trace

The data in bold and italic represents the optimal reaction conditions.

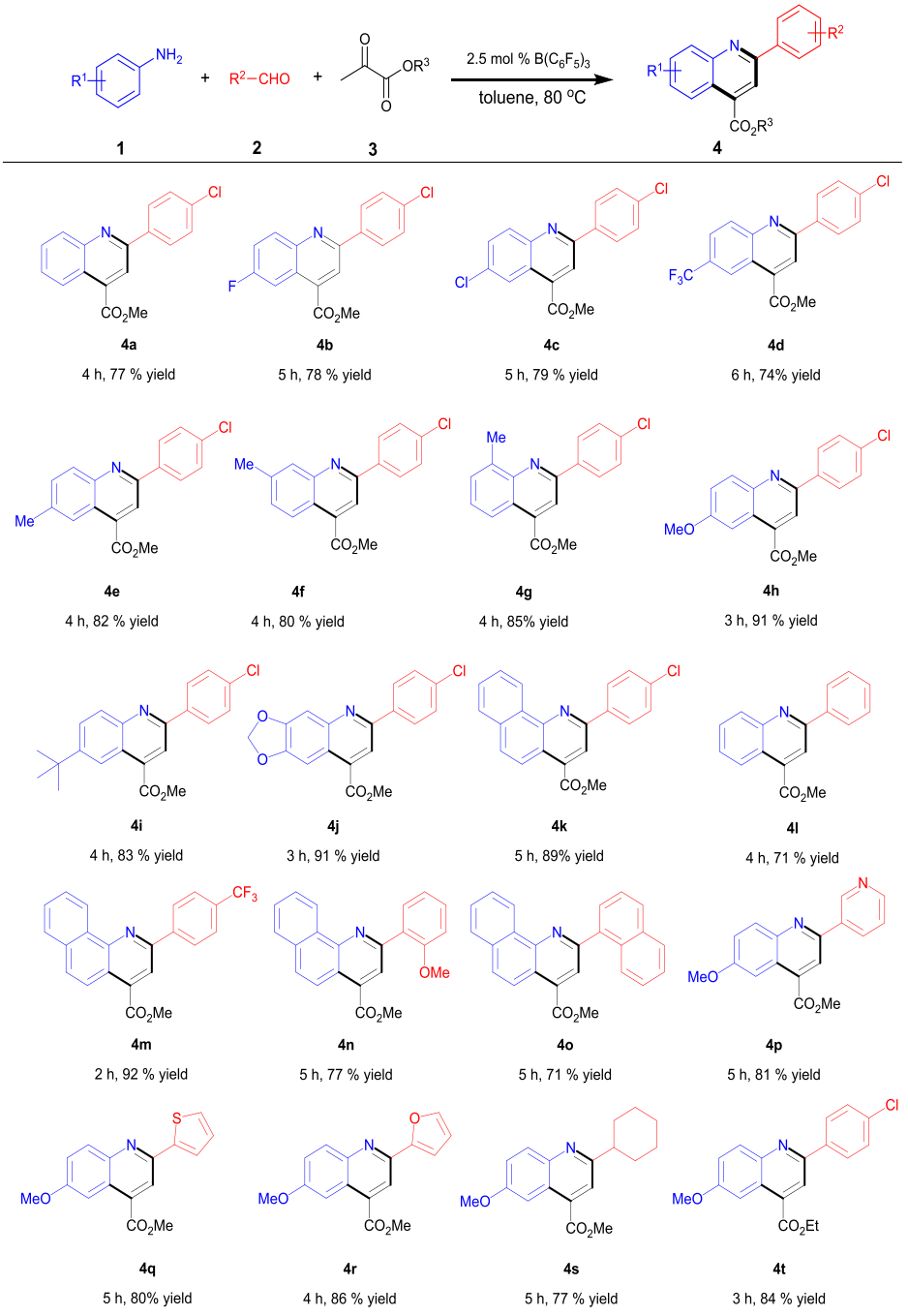
[a]*Note*. Reaction conditions: **1a**, **2a**, **3a**, and B$(C_6F_5)_3$ in solvent for 2 to 12 h under air.

[b]Isolated yields based on **3a**.

drop on yield of **4a** from 78% to 71% was observed when the reaction was conducted at 60°C, even

after 8 hours. Notably, the reaction solvents had great impact on this transformation, and toluene still turned out to be the best medium (Table 1, entries 6-9). Satisfyingly, this process proceeded smoothly without loss of efficiency in yield even with the reduced catalyst loading from 10 to 2.5 mol % (Table 1, entry 11), while no product **4a** was obtained in the absence of B$(C_6F_5)_3$ (Table 1, entry 13). With the optimal reaction conditions in hand, we set out to expand the generality and scope of B$(C_6F_5)_3$ catalyzed three-component cascade reaction (Scheme 3). The substrate scope of this reaction was initially explored with a range of aromatic amines **1** with 4-chlorobenzaldehyde (**2a**) and methyl 2-oxopropanoate (**3a**). Variation of R^1 showed that benzene rings with an electron-donating group (–Me, –OMe, or –*t*-Bu) gave better yields than those with an electron-withdrawing group (–F, –Cl, or –CF_3). Moreover, the substitution pattern had no impact on this transformation, leading to the meta-product **4f** and ortho-product **4 g** in 80% and 85% yields, respectively. Notably, other aromatic amines were also compatible with this reaction, affording the corresponding products **4j** and **4k** in excellent yields.

Subsequently, the scope of this reaction with respect to the aldehydes **2** was studied, and the desired products were achieved in 71% to 92% yield. Aldehyde with an electron-donating group (–OMe) produced the expected product in lower yield (**4n**, 77%) than that with an electron-withdrawing group (–CF_3, **4m**, 92%). Delightfully, hetero-aromatic aldehydeslike 3-pyridylaldehyde (**2p**), 2-thenaldehyde (**2q**), and furaldehyde (**2r**) were also tolerated in this reaction, affording the corresponding products **4p-4r** in excellent yields. As expected, treating

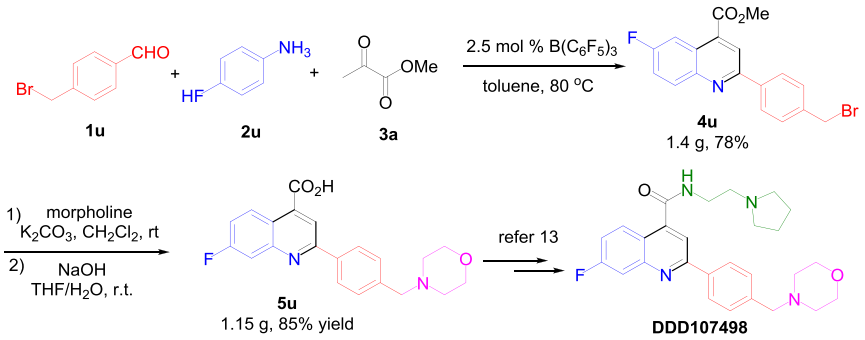


SCHEME 3 Substrate scope of $B(C_6F_5)_3$-catalyzed aniline-aldehyde-pyruvate reaction [Color figure can be viewed at wileyonlinelibrary.com]

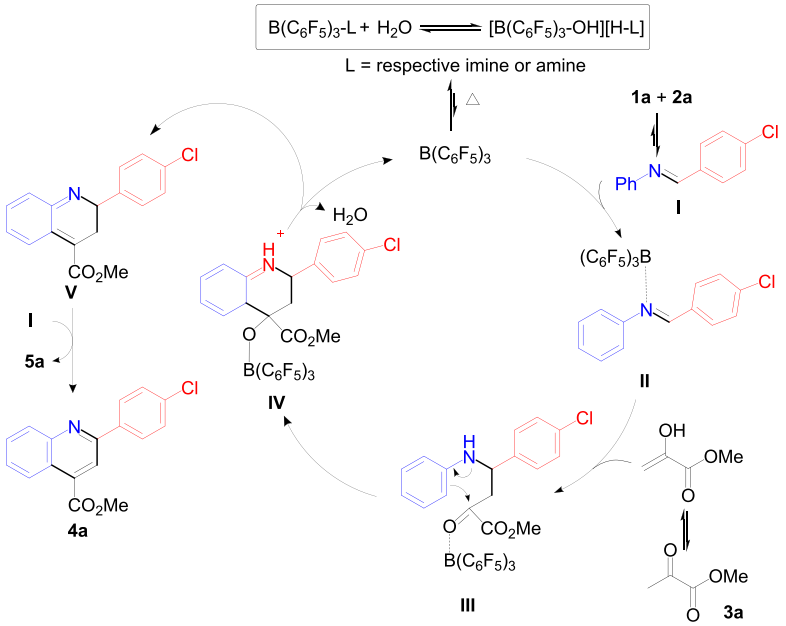
ethyl pyruvate with 4-methoxyaniline and 4-chlorobenzaldehyde under standard conditions furnished the desired substituted quinoline **4t** in 84% yield.

To demonstrate the scalability and utility of this method, we applied it in the formal synthesis of DDD107498 on a gram scale (Scheme 4). Initially, the B $(C_6F_5)_3$-catalyzed A^3 reaction of 4-fluoroaniline, 4-(bromomethyl)benzaldehyde, and methyl pyruvate was conducted to afford the targeted product **4u** in 1.40 g, 78% yield. Then, nucleophilic attack of **4u** by morpholine, followed by hydrolysis of the ester group resulted in the formation of 4-carboxyl quinoline **5u** in 1.15 g, 85% yield over two steps. Finally, **5u** could be converted into DDD107498 according to the literature.[45]

Based on our findings and the related references,[33–44] a plausible reaction mechanism for the present $B(C_6F_5)_3$-catalyzed aniline-aldehyde-pyruvate annulation reaction is depicted in Scheme 5. Upon heating, $B(C_6F_5)_3$ is



SCHEME 4 Gram-scale synthesis of the key intermediate **5u** of DDD107498 [Color figure can be viewed at wileyonlinelibrary.com]



SCHEME 5 Proposed mechanism [Color figure can be viewed at wileyonlinelibrary.com]

generated from a Lewis adduct or the hydroxy borate to activate the imine **I** derived from aniline **1a** and aldehyde **2a**, which then undergoes nucleophilic

addition of pyruvate **3a** to form the intermediate **III**. Subsequently, the electron-rich benzene ring attacked the keto-carbonyl group to afford the species **IV**. Then, the release of $B(C_6F_5)_3$ and H_2O from **IV** resulted the dihydroquinoline **V**. Finally, the oxidation of the dihydroquinoline **V** by an equivalent of imine **I** to furnish the product **4a**, accompanied by the formation of by-product **5a**.

3 | CONCLUSIONS

In conclusion, we have presented a $B(C_6F_5)_3$-catalyzed cyclization of anilines with aldehydes and pyruvates to afford various substituted quinoline-4-carboxylic esters in high yields (71%-92%). The three-component cascade reaction has a broad substrate scope covering a wide range of aryl and alkyl aldehydes, functional group tolerance, and low catalyst loading. The utility of this method was further demonstrated by the formal synthesis of the antimalarial drug DDD107498 on a gram scale.

4 | EXPERIMENTAL

4.1 | General information

All starting materials and reagents were purchased from commercial sources and used as received unless otherwise noted. Reactions were monitored using thin-layer chromatography (TLC) on commercial silica gel plates. Visualization of the developed plates was performed under UV light (254 nm). Flash column chromatography was performed on silica gel. NMR spectra were recorded on a Bruke Avance III spectrometer, operating at 400 MHz (^{1}H) and 100 MHz (^{13}C) respectively. Chemical shifts (δ) were reported in parts per million (ppm) downfield from TMS (=0) or relative to $CHCl_3$ (7.254 ppm) for ^{1}H NMR. For ^{13}C NMR, chemical shifts were reported in

the scale relative to $CHCl_3$ (77.16 ppm) as an internal reference. Multiplicities are abbreviated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and br, broad. The coupling constants are expressed in Hz. Melting points were determined with a Büchi B-540 capillary melting point apparatus and are uncorrected.

4.2 | Preparation method for the synthesis of compound 4

4.2.1 | Methyl-2-(4-chlorophenyl) quinoline-4-carboxylate (4a)

White solid; 229 mg, 77% yield; m.p. 85.1°C-87.8°C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.76 (d, J = 8.4 Hz, 1H), 8.37 (s, 1H), 8.21 (t, J = 12.6 Hz, 1H), 8.18 (d, J = 8.4 Hz, 2H), 7.79 (t, J = 7.8 Hz, 1H), 7.71-7.62 (m, 1H), 7.53 (d, J = 8.4 Hz, 2H), 4.10 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.7, 155.3, 149.2, 137.1, 136.0, 135.7, 130.3, 130.1, 129.1 (2C), 128.7 (2C), 128.0, 125.5, 124.0, 119.9, 52.8. HRMS-ESI (*m/z*) calcd for $C_{17}H_{13}ClNO_2$ $[M + H]^+$: 298.0629 found: 298.0621.

4.2.2 | Methyl2-(4-chlorophenyl)-6-fluoroquinoline-4-carboxylate (4b)

White solid; 246 mg, 78% yield; m.p. 112.3°C-113.9°C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.53 (d, J = 10.8 Hz, 1H), 8.47 (s, 1H), 8.28-8.20 (m, 1H), 8.17 (d, J = 8.0 Hz, 2H), 7.59 (d, J = 8.4 Hz, 1H), 7.54 (d, J = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.3, 162.8 ($J_{C\text{-}F}$ = 240 Hz) 154.7, 146.5, 136.8, 136.1, 134.9 ($J_{C\text{-}F}$ = 5.9 Hz), 132.7 (d, J = 9.3 Hz), 129.2 (2C), 128.6, 125.0 (d, J = 11.3 Hz), 120.8, 120.5 (d, J = 26.0 Hz), 109.6 (d, J = 25.1 Hz), 52.9. HRMS-ESI (*m/z*) calcd for $C_{17}H_{12}ClFNO_2$ $[M + H]^+$: 316.0535, found: 316.0528.

4.2.3 | Methyl6-chloro-2-(4-chlorophenyl) quinoline-4-carboxylate (4c)

White solid; 262 mg, 79% yield; m.p. 121.5°C-122.9°C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.84 (d, J = 2.4 Hz, 1H), 8.43 (s, 1H), 8.19-8.16 (m, 2H), 8.14 (d, J = 8.8 Hz, 1H), 7.73 (dd, J = 8.8, 2.4 Hz, 1H), 7.56-7.51 (m, 2H), δ 4.11 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.2, 155.5, 147.7, 136.7, 136.3, 134.6, 134.2, 131.7, 131.1, 129.2 (2C), 128.7 (2C), 124.6 (2C), 120.7, 53.0. HRMS-ESI (*m/z*) calcd for $C_{17}H_{12}Cl_2NO_2$ $[M + H]^+$: 332.0240, found: 332.0243.

4.2.4 | Methyl2-(4-chlorophenyl)-6-(trifluoromethyl)quinoline-4-carboxylate (4d)

White solid; 270 mg, 74% yield; m.p. 135.8°C-136.9°C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.53 (d, J = 10.8 Hz, 1H), 8.47 (s, 1H), 8.26-8.20 (m, 1H), 8.17 (d, J = 8.0 Hz, 2H), 7.59 (d, J = 8.4 Hz, 1H), 7.54 (d, J = 8.0 Hz, 2H), 4.10 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.0, 157.4, 150.1, 136.8, 136.4, 136.2, 131.3 (2C), 129.3 (2C), 128.9 (2C), 125.8 (d, J = 3.1 Hz), 123.8 (d, J = 4.6 Hz), 123.2, 121.0 (2C), 53.1. HRMS-ESI (*m/z*) calcd for $C_{18}H_{12}ClF_3NO_2$ $[M + H]^+$: 366.0503, found: 366.0521.

4.2.5 | Methyl2-(4-chlorophenyl)-6-methylquinoline-4-carboxylate (4e)

White solid; 256 mg, 82% yield; m.p. 119.7°C-121.2°C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.50 (s, 1H), 8.28 (s, 1H), 8.15-8.10 (m, 2H), 8.07 (d, J = 8.4 Hz, 1H), 7.59 (dd, J = 8.4, 1.6 Hz, 1H), 7.50-7.46 (m, 3H), 4.07 (s, 2H), 2.58 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.8, 154.2, 147.8, 138.2, 137.2, 135.7, 134.8, 132.3, 129.9, 129.0 (2C), 128.5 (2C), 124.2, 124.0, 119.7, 52.7, 22.2. HRMS-ESI (*m/z*) calcd for $C_{18}H_{15}ClNO_2$ $[M + H]^+$: 312.0786, found: 312.0790.

4.2.6 | Methyl2-(4-chlorophenyl)-7-methylquinoline-4-carboxylate (4f)

White solid; 249 mg, 80% yield; m.p. 116.7°C-118.6°C; ^{1}H NMR (600 MHz, $CDCl_3$, ppm) δ 8.63 (d, J = 8.8 Hz, 1H), 8.27 (s, 1H), 8.16-8.09 (m, 2H), 7.97 (s, 1H), 7.52-7.48 (m, 2H), 7.46 (dd, J = 8.8, 1.6 Hz, 1H), 4.07 (s, 3H), 2.58 (d, J = 1.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.7, 155.1, 149.4, 140.4, 137.2, 135.8, 135.3, 130.3, 129.2, 129.0 (2C), 128.6 (2C), 125.1, 122.1, 118.9, 52.7, 21.7. HRMS-ESI (*m/z*) calcd for $C_{18}H_{15}ClNO_2$ $[M + H]^+$: 312.0786, found: 312.0780.

4.2.7 | Methyl2-(4-chlorophenyl)-8-methylquinoline-4-carboxylate (4g)

White solid; 265 mg, white solid, 85% yield; m.p. 92.1°C-93.2°C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.56 (d, J = 8.4 Hz, 1H), 8.34 (s, 1H), 8.21 (d, J = 8.4 Hz, 2H), 7.62 (d, J = 6.8 Hz, 1H), 7.52 (t, J = 8.4 Hz, 3H), 4.08 (s, 3H), 2.90 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 167.0, 153.4, 148.0, 138.1, 137.3, 136.0, 135.8, 130.2, 129.0 (2C), 128.5 (2C), 127.7, 124.0, 123.0, 119.0, 52.8,

18.5. HRMS-ESI (*m/z*) calcd for $C_{18}H_{15}ClNO_2$ $[M + H]^+$: 312.0786, found: 312.0795.

4.2.8 | Methyl2-(4-chlorophenyl)-6-methoxyquinoline-4-carboxylate (4h)

White solid; 298 mg, white solid, 91% yield; m.p. 102.1°C-103.5°C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.37 (s, 1H), 8.21 (s, 1H), 8.11 (t, *J* = 10.4 Hz, 3H), 7.50 (d, *J* = 8.0 Hz, 2H), 7.43 (d, *J* = 9.2 Hz, 1H), 4.65-4.49 (m, 2H), 3.99 (s, 3H), 1.53 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.4, 159.1, 152.7, 145.6, 137.3, 135.4, 133.9, 131.6, 129.0 (2C), 128.4, 125.6, 123.0, 120.2, 103.3, 61.8, 55.6, 14.4. HRMS-ESI (*m/z*) calcd for $C_{18}H_{15}ClNO_3$ $[M + H]^+$: 328.0735, found: 328.0741.

4.2.9 | Methyl6-(tert-butyl)-2-(4-chlorophenyl)quinoline-4-carboxylate (4i)

White solid; 293 mg, 83% yield; m.p. 133.5°C-135.1°C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.43 (s, 1H), 8.24 (s, 1H), 8.18-8.08 (m, 3H), 7.58 (d, *J* = 7.8 Hz, 2H), 7.44 (d, *J* = 9.1 Hz, 1H), 4.08 (s, 3H), 4.00 (s, 3H), 1.41 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 167.0, 158.9, 154.2, 152.5, 145.7, 136.2, 133.2, 131.7, 126.9 (2C), 125.9 (2C), 125.4, 122.7, 120.7 (2C), 103.3, 55.6, 52.6, 34.8, 31.3. HRMS-ESI (*m/z*) calcd for $C_{21}H_{21}ClNO_2$ $[M + H]^+$: 354.1255, found: 354.1265.

4.2.10 | Methyl6-(4-chlorophenyl)-[1,3]dioxolo[4,5-g]quinoline-8-carboxylate (4j)

White solid; 311 mg, 91% yield; m.p. 190.2°C-191.8°C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.24 (s, 1H), 8.16 (s, 1H), 8.14-8.09 (m, 2H), 7.53-7.46 (m, 3H), 6.17 (s, 2H), 4.06 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.9, 153.2, 150.9, 149.5, 148.1, 137.2, 135.5, 134.1, 129.0 (2C), 128.4 (2C), 121.7, 118.0, 106.4, 102.1, 101.2, 52.7. HRMS-ESI (*m/z*) calcd for $C_{18}H_{13}ClNO_4$ $[M + H]^+$: 342.0528, found: 342.0522.

4.2.11 | Methyl2-(4-chlorophenyl)benzo[h]quinoline-4-carboxylate (4k)

White solid; 309 mg, 89% yield; m.p. 133.1°C-135.9°C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.43 (s, 1H), 8.66-8.55 (m, 1H), 8.41 (d, *J* = 6.0 Hz, 1H), 8.29 (s, 2H), 7.89 (d, *J* = 12.4 Hz, 2H), 7.76 (s, 2H), 7.54 (d, *J* = 7.2 Hz, 2H), 4.10 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 167.0, 153.4, 147.4, 137.2, 135.8, 135.6, 133.5, 131.5, 129.3, 129.1 (2C), 128.7 (2C), 128.5, 127.7, 127.2, 125.1, 122.7, 122.3, 119.2, 52.8. HRMS-ESI (*m/z*) calcd for $C_{21}H_{15}ClNO_2$ $[M + H]^+$: 348.0786, found: 348.0781.

4.2.12 | Methyl 2-phenylquinoline-4-carboxylate (4l)

White solid; 187 mg, 71% yield; m.p. 50.5°C-51.6°C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.78 (dd, *J* = 8.4, 1.2 Hz, 1H), 8.43 (s, 1H), 8.27 (d, *J* = 8.4 Hz, 1H), 8.26-8.22 (m, 2H), 7.80 (dd, *J* = 8.4, 6.8 Hz, 1H), 7.65 (dd, *J* = 8.4, 6.8 Hz, 1H), 7.57 (dd, *J* = 8.0, 6.8 Hz, 2H), 7.54-7.50 (m, 1H), 4.09 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.8, 156.7, 149.2, 149.2, 135.6, 130.3, 130.3, 129.9, 129.8, 129.0 (2C), 127.8, 127.5, 125.4, 124.0, 120.4, 52.8. HRMS-ESI (*m/z*) calcd for $C_{17}H_{14}NO_2$ $[M + H]^+$: 264.1019, found: 264.1010.

4.2.13 | Methyl2-(4-(trifluoromethyl)phenyl)benzo[h]quinoline-4-carboxylate (4 m)

White solid; 351 mg, 92% yield; m.p. 141.0°C-142.3°C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.46-9.39 (m, 1H), 8.61 (d, *J* = 9.2 Hz, 1H), 8.42 (d, *J* = 9.2 Hz, 3H), 7.90 (t, *J* = 8.8 Hz, 2H), 7.85-7.72 (m, 4H), 4.11 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.8, 152.9, 147.4, 142.0, 135.6, 133.4, 131.4, 129.6, 128.8, 127.7 (2C), 127.5 (2C), 127.3 (2C), 125.87-125.67 (m), 125.0, 123.0, 122.1 (2C), 119.5, 52.8. HRMS-ESI (*m/z*) calcd for $C_{22}H_{15}F_3NO_2$ $[M + H]^+$: 383.1049, found: 383.1053.

4.2.14 | Methyl2-(2-methoxyphenyl)benzo[h]quinoline-4-carboxylate (4n)

White solid; 265 mg, 77% yield; m.p. 134.9°C-135.8°C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.51 (dd, *J* = 7.8, 1.6 Hz, 1H), 8.75-8.62 (m, 2H), 8.25 (dt, *J* = 7.8, 1.6 Hz, 1H), 7.98-7.89 (m, 2H), 7.76 (pd, *J* = 7.2, 1.6 Hz, 2H), 7.55-7.45 (m, 1H), 7.25 (q, *J* = 7.8 Hz, 1H), 7.10 (d, *J* = 8.3 Hz, 1H), 4.11 (s, 3H), 3.96 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 167.5, 157.6, 154.4, 147.3, 134.4, 133.3, 132.0, 132.7, 130.7, 128.9, 128.8, 128.4, 127.6, 127.1, 125.2, 124.5, 122.4, 122.2, 121.3, 111.6, 55.8, 52.7. HRMS-ESI (*m/z*) calcd for $C_{22}H_{18}NO_3$ $[M + H]^+$: 344.1281, found: 344.1270.

4.2.15 | Methyl2-(naphthalen-1-yl)benzo[h]quinoline-4-carboxylate (4o)

White solid; 258 mg, 71% yield; m.p. 169.1°C-170.4°C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.50-9.41 (m, 1H), 8.76 (d, *J* = 9.2 Hz, 1H), 8.54-8.45 (m, 1H), 8.39 (s, 1H), 8.07-7.95 (m, 4H), 7.89 (d, *J* = 6.8 Hz, 1H), 7.80-7.73 (m,

2H), 7.68 (t, J = 7.6 Hz, 1H), 7.59 (dd, J = 7.2, 4.0 Hz, 2H), 4.11 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 167.1, 157.4, 147.4, 138.1, 135.3, 134.2, 133.5, 131.7, 131.3, 129.5, 129.4, 128.7, 128.5, 128.5, 127.7, 127.3, 126.8, 126.1, 125.9, 125.4, 125.4, 124.2, 122.4, 122.3, 52.8. HRMS-ESI (m/z) calcd for $C_{25}H_{18}NO_2$ $[M + H]^+$: 364.1332, found: 364.1326.

4.2.16 | Methyl6-methoxy-2-(pyridin-3-yl) quinoline-4-carboxylate (4p)

White solid; 239 mg, 81% yield; m.p. 121.3°C-122.5°C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.12 (s, 1H), 8.78 (d, J = 4.4 Hz, 1H), 8.65 (d, J = 8.0 Hz, 1H), 8.31 (d, J = 2.4 Hz, 1H), 8.15 (d, J = 9.2 Hz, 1H), 7.91 (t, J = 7.6 Hz, 1H), 7.46 (dd, J = 9.2, 2.4 Hz, 1H), 7.44-7.37 (m, 1H), 4.08 (s, 3H), 4.02 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 167.0, 159.6, 155.7, 153.0, 149.1, 145.3, 137.1, 133.3, 131.8, 126.8, 124.0, 122.9, 121.4, 120.8, 103.3, 55.7, 52.5. HRMS-ESI (m/z) calcd for $C_{17}H_{15}N_2O_3$ $[M + H]^+$: 295.1077, found: 295.1068.

4.2.17 | Methyl6-methoxy-2-(thiophen-2-yl)quinoline-4-carboxylate (4q)

White solid; 240 mg, 80% yield; m.p. 123.2°C-124.9°C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.33 (s, 1H), 8.19 (s, 1H), 8.05 (d, J = 9.2 Hz, 1H), 7.75 (s, 1H), 7.47 (d, J = 4.8 Hz, 1H), 7.41 (d, J = 9.2 Hz, 1H), 7.22-7.14 (m, 1H), 4.07 (s, 3H), 3.99 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.7, 158.9, 149.4, 145.4, 144.7, 133.1, 131.2, 128.3, 128.1, 125.5, 125.5, 122.9, 119.6, 103.5, 55.6, 52.7. HRMS-ESI (m/z) calcd for $C_{16}H_{14}NO_3S$ $[M + H]^+$: 300.0689, found: 300.0693.

4.2.18 | Methyl2-(furan-2-yl)-6-methoxyquinoline-4-carboxylate (4r)

White solid; 256 mg, 86% yield; m.p. 87.8°C-89.9°C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.37 (s, 1H), 8.22 (d, J = 2.7 Hz, 1H), 8.09 (d, J = 9.2 Hz, 1H), 7.64 (s, 1H), 7.42 (dd, J = 9.2, 2.8 Hz, 1H), 7.23 (d, J = 3.2 Hz, 1H), 6.61 (dd, J = 2.8, 1.6 Hz, 1H), 4.07 (s, 3H), 3.99 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.7, 159.0, 153.2, 146.2, 145.4, 143.9, 133.2, 131.3 (2C), 125.5, 123.0, 119.4, 112.3, 109.6, 103.5, 55.6, 52.6. HRMS-ESI (m/z) calcd for $C_{16}H_{14}NO_4$ $[M + H]^+$: 284.0917, found: 284.0915.

4.2.19 | Methyl2-cyclohexyl-6-methoxyquinoline-4-carboxylate (4s)

White solid; 231 mg, 77% yield; m.p. 122.3°C-123.5°C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.18 (d, J = 2.8 Hz, 1H), 8.00 (d, J = 9.2 Hz, 1H), 7.87 (s, 1H), 7.39 (dd, J = 9.2, 2.8 Hz, 1H), 4.04 (s, 3H), 3.97 (s, 3H), 3.00-2.85 (m, 1H), 2.09-2.01 (m, 2H), 1.95-1.88 (m, 2H), 1.81 (d, J = 12.4 Hz, 1H), 1.65 (dd, J = 12.4, 3.2 Hz, 2H), 1.49 (dt, J = 12.8, 2.8 Hz, 2H), 1.36 (d, J = 4.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 167.1, 163.5, 158.5, 145.1, 133.0, 130.9 (2C), 125.2, 122.3, 121.5, 103.3, 55.5, 52.5, 47.1, 32.8, 29.7, 26.5, 26.0. HRMS-ESI (m/z) calcd for $C_{18}H_{22}NO_3$ $[M + H]^+$: 300.1594, found: 300.1591.

4.2.20 | Ethyl2-(4-chlorophenyl)-6-methoxyquinoline-4-carboxylate (4t)

White solid; 287 mg, 84% yield; m.p. 129.1°C-130.9°C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.37 (s, 1H), 8.21 (s, 1H), 8.11 (t, J = 10.4 Hz, 3H), 7.50 (d, J = 8.0 Hz, 2H), 7.43 (d, J = 9.2 Hz, 1H), 4.64-4.49 (m, 2H), 3.99 (s, 3H), 1.53 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.4, 159.1, 152.7, 145.6, 137.3, 135.4, 133.9, 131.6, 129.0 (2C), 128.4 (2C), 125.6, 123.0, 120.2, 103.3, 61.8, 55.6, 14.4. HRMS-ESI (m/z) calcd for $C_{19}H_{17}ClNO_3$ $[M + H]^+$: 342.0925, found: 342.0917.

4.3 | Gram-scale synthesis of the intermediate 5u

4.3.1 | The procedure for the preparation of 4u

4-(Bromomethyl)benzaldehyde (3.3 g, 16.5 mmol), 4-fluoroaniline (2.0 g, 18 mmol), methyl pyruvate (510 mg, 5.0 mmol), and $B(C_6F_5)_3$ (64 mg, 0.125 mmol) were dissolved in toluene (25 mL) under ambient atmosphere. The mixture was stirred at 80°C for 4 hours monitored by TLC. Subsequently, the mixture was concentrated in vacuo, and the crude residue was purified by column chromatography to afford **4u** in 78% yield.

Methyl2-(4-(bromomethyl)phenyl)-6-fluoroquinoline-4-carboxylate (4u)

White solid; 1.4 g, 78% yield; m.p. 124.4°C-126.1°C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.53 (dd, J = 10.8, 2.4 Hz, 1H), 8.48 (s, 1H), 8.26-8.21 (m, 1H), 8.19 (d, J = 8.4 Hz, 2H), 7.57 (dd, J = 15.6, 5.2 Hz, 3H), 4.60 (s, 2H), 4.10 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.3, 162.8, 160.3, 155.2 (d, J = 2.9 Hz), 146.5, 139.4, 138.4, 134.7 (d, J = 5.9 Hz), 132.7 (d, J = 9.4 Hz), 129.6,

129.2, 127.7 (d, J = 6.6 Hz), 125.0 (d, J = 11.1 Hz), 121.0, 120.3 (d, J = 26.0 Hz), 109.5 (d, J = 25.1 Hz), 52.8, 32.9. HRMS-ESI (m/z) calcd for $C_{18}H_{14}BrFNO_2$ $[M + H]^+$: 374.0186, found 374.0172.

4.3.2 | The procedure for the preparation of 5u

A mixture of **4u** (1.4 g, 3.9 mmol), morpholine (508 mg, 5.9 mmol), and dry CH_2Cl_2 (10 mL) was added K_2CO_3 (1.1 g, 7.8 mmol) under ambient atmosphere. The reaction mixture was stirred at room temperature for additional 1 hour monitored by TLC. Subsequently, the mixture was concentrated in vacuo, and the crude product was used for the next step without further purification. The crude product obtained from the above was dissolved in 10 mL of sodium hydroxide (2M) and 10 mL THF. The reaction mixture was stirred at room temperature for additional 2 hours monitored by TLC. Subsequently, the THF was removed in vacuo, and the residue solution was adjusted to pH 7 to 8 with 10% HCl. The resulting precipitate was filtered and washed with water (10 mL) and ethyl acetate (10 mL) to obtain the desired product **5u** as white solid in 85% yield.

6-Fluoro-2-(4-(morpholinomethyl)phenyl))quinoline-4-carboxylic acid (5u)

White solid; 468 mg, 85% yield; m.p. 132.1°C-133.4°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.54-8.44 (m, 2H), 8.28-8.16 (m, 3H), 7.77 (td, J = 8.8, 2.9 Hz, 1H), 7.53 (d, J = 8.2 Hz, 2H), 3.65-3.58 (t, J = 4.4 Hz, 4H), 2.53-2.50 (m, 6H). MS (ESI): m/z = 367.1 $[M + H]^+$.

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