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ARTICLE

One-Pot Synthesis of Polyfunctionalized Quinolines *via* a Copper-Catalyzed Tandem Cyclization†

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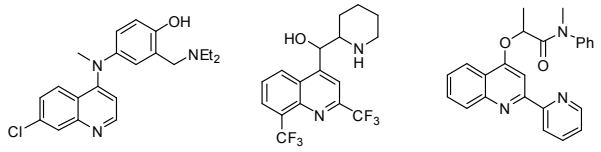
An efficient one-pot approach for the synthesis of polyfunctionalized quinolines was developed *via* a sequence of copper-catalyzed coupling reaction /propargyl-allenyl isomerization/aza-electrocyclization. Easily available starting materials, mild conditions, and a wide substrate scope make this approach potentially useful.

Introduction

Quinoline derivatives represent an important group of heterocycles due to their privileged scaffold motifs of physicochemical properties, biological activities, and pharmacological value.[1-3] Many famous molecules in the quinoline family, especially for the 4-substituted quinolines, have attracted much more attention for the widely application in medicinal chemistry (Figure. 1). As a 4-aminoquinoline compound, Amodiaquine is used to treat malaria.[4] Mefloquine possesses significant anti-inflammatory and antiasthmatic activities.[5] TSPO is a recognized biomarker of neuroinflammation, with high affinity and human genotype insensitivity.[6]

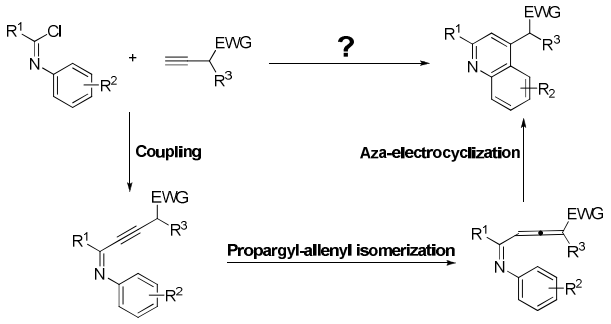


Amodiaquine Mefloquine TSPO

Figure. 1 Bioactive quinoline derivatives quinolines

Classical methods for the synthesis of quinolines have been frequently employed, such as Combes,[7] Doebner-von Miller[8] and Skraup reactions[9]. Although these methods are efficient, harsh reaction conditions and poor tolerance of functional groups may limit the synthetic applications in some cases. Accordingly, developing new and effective approach for the construction of polyfunctionalized quinolines remains a formidable challenge.

Tandem cyclizations, in which multistep reactions are combined into one synthetic operation, have emerged as a powerful tool for the rapid construction of complex molecular skeletons.[10] Since Müller pioneered the coupling-isomerization reactions, continuous efforts have been devoted to this area.[11] During our research on the *in situ* propargyl-allenyl isomerization,[12] we found that alkynyl imides equipped with electron-withdrawing groups could offer corresponding allenes in the presence of appropriate base.[13] Herein, we wish to report a sequence of copper-catalyzed coupling reaction /propargyl-allenyl isomerization/aza-electrocyclization by one-pot, yielding polyfunctionalized quinolines, which are difficult to prepare by other methods (Scheme 1).



Scheme 1 Proposal for the construction of polyfunctionalized quinolines

Results and discussion

Stimulated by this proposal, we chose (*Z*)-*N*-phenylbenzimidoyl chloride (**1a**) and *tert*-butyl 1-(4-chlorophenyl)prop-2-ynyl carbonate (**2a**) as the starting material. Our study was initiated by testing the reaction of **1a** and **2a** in the presence of CuI and triethylamine (TEA) in THF at -78 °C followed by warming to room temperature. To our delight, this set of conditions afforded the expected *tert*-butyl (4-chlorophenyl)(2-phenylquinolin-4-yl)methyl carbonate (**3a**) in 62% yield (Table 1, entry 1). Then we began to optimize the reaction with

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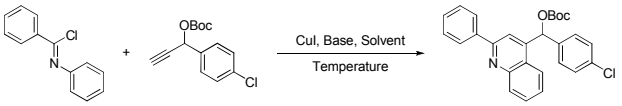
respect to different bases, solvents, and temperatures. Replacing TEA by DIPEA (*N*,*N*-diisopropylethylamine) or the stronger organic base DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) gave similar yields (Table 1, entries 2-3). Inorganic bases, such as Na_2CO_3, K_2CO_3 and *t*-BuOK, showed poor reactivity and gave **3a** in 17-28% yields (Table 1, entries 4-6). Whereas subsequent screening of other common solvents, such as acetonitrile, 1,4-dioxane and toluene, did not improve the yield obviously, DCE (1,2-dichloroethane) was found to be an appropriate solvent for this reaction that afforded the product in 87% yield (Table 1, entries 7-10). In addition, increasing the reaction temperature to 60 °C led to a low yield (Table 1, entry 11), and keeping the reaction temperature at 80 °C offered an unidentified mixture (Table 1, entry 12). Thus, the optimized reaction conditions were chosen as follows: **1a** (0.5 mmol), **2a** (0.6 mmol), CuI (10 mol %) and TEA (1.5 equiv) in 2 mL of DCE were stirred at -78 °C followed by warming to room temperature.

Table 1 Optimization of the reaction conditions[a]



1a **2a** **3a**

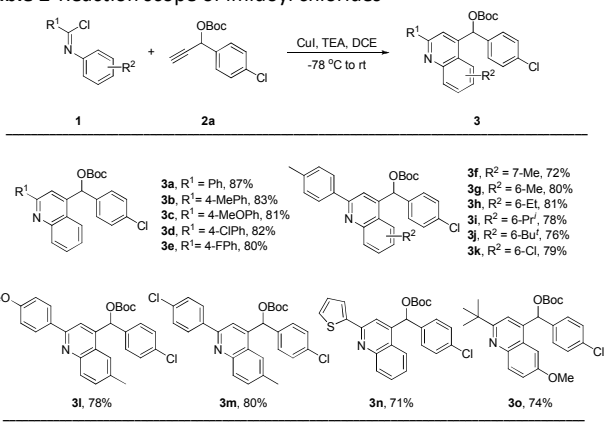
Entry	Base (equiv)	Solvent	Temperature (°C)	Yield (%)[b]
1	TEA (1.5)	THF	-78 to rt	62
2	DIPEA (1.5)	THF	-78 to rt	60
3	DBU (1.5)	THF	-78 to rt	57
4	Na_2CO_3 (1.5)	THF	-78 to rt	28
5	K_2CO_3 (1.5)	THF	-78 to rt	25
6	*t*-BuOK (1.5)	THF	-78 to rt	17
7	TEA (1.5)	CH_3CN	-78 to rt	52
8	TEA (1.5)	dioxane	-78 to rt	70
9	TEA (1.5)	toluene	-78 to rt	41
10	**TEA (1.5)**	**DCE**	**-78 to rt**	**87**
11	TEA (1.5)	DCE	-78 to 60	23
12	TEA (1.5)	DCE	-78 to 80	Complex

[a] Conditions: **1a** (0.5 mmol), **2a** (0.6 mmol), CuI (10 mol %) and TEA (1.5 equiv) in 2 mL of DCE were stirred at -78 °C followed by warming to room temperature under a N_2 atmosphere. [b] Isolated yield based on **1a**.

With the optimized conditions in hand, the scope of this reaction was investigated further. As shown in Table 2, various functional groups could be tolerated. The R^1 and R^2 could be phenyl groups optionally substituted with an electron-donating or an electron-withdrawing group, and the yields were satisfactory. Moreover, the reaction could proceed smoothly when the R^1 was thienyl (Table 2, **3n**) or alkyl (Table 2, **3o**).

Then we turned our attention to explore the scope of the alkyne partners. As shown in Table 3, a series of polyfunctionalized quinolines were synthesized in good yields.

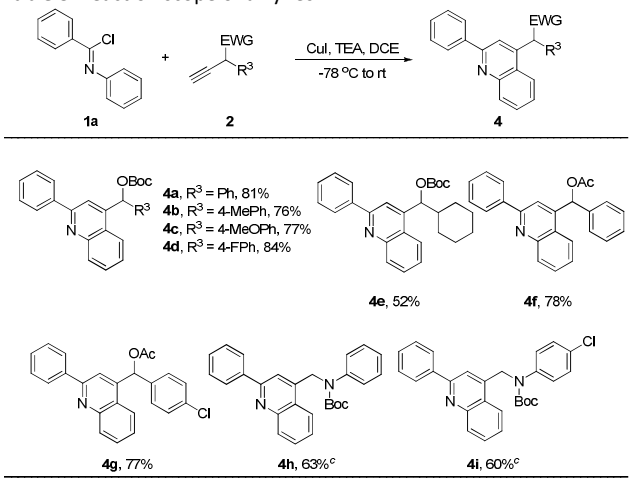
Table 2 Reaction scope of imidoyl chlorides[a,b]



[a] Conditions: **1** (0.5 mmol), **2a** (0.6 mmol), CuI (10 mol %) and TEA (1.5 equiv) in 2 mL of DCE were stirred at -78 °C followed by warming to room temperature under a N_2 atmosphere. [b] Isolated yield based on **1**.

It was noteworthy that DBU was used to trigger the reaction due to the weak acidity of protons adjacent to the nitrogen atom (Table 3, **4h**, **4i**). Furthermore, the yield decreased greatly when the R^3 was alkyl (Table 3, **4e**) or hydrogen (Table 3, **4h**, **4i**). We hypothesized that allene intermediates might be more stable and the occurrence of aza-electrocyclization could be more easy-going when the R^3 was aryl.

Table 3 Reaction scope of alkynes[a,b]



[a] Conditions: **1** (0.5 mmol), **2a** (0.6 mmol), CuI (10 mol %) and TEA (1.5 equiv) in 2 mL of DCE were stirred at -78 °C followed by warming to room temperature under a N_2 atmosphere. [b] Isolated yield based on **1**. [c] DBU was used as the base instead of TEA.

Compounds containing the 4-substituted quinoline moiety are always present in pharmacology. To demonstrate the scalability of this carbonylation protocol, a gram-scale reaction of imidoyl chloride (**1a**) and alkyne (**2a**) was carried out under standard conditions. As shown in Scheme 2, the corresponding **3a** was obtained in 85% yield.

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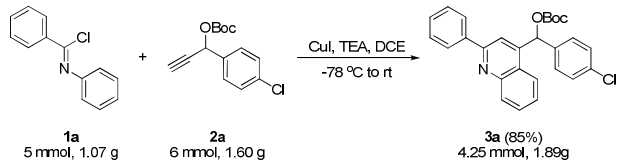
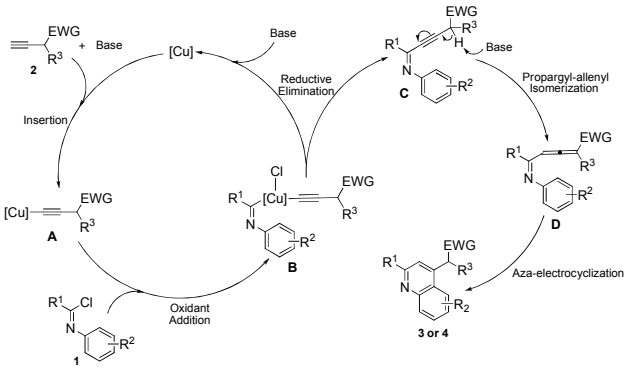


Scheme 2 Gram-scale reaction of **1a** with **2a**

We proposed a plausible pathway as shown in Scheme 3. Intermediate **A** was formed through the insertion of copper species with alkyne **2**. Then an imidoyl chloride **1** insertion would be involved to afford the intermediate **B** by oxidant addition. After reductive elimination, intermediate **C** was generated. Subsequently, Intermediate **D** was offered by propargyl-allenyl isomerisation, which underwent aza-electrocyclization reaction to give product **3** or **4**. The copper species was able to fulfill the catalytic cycle in the presence of base.[14]



Scheme 3 Plausible mechanism

Conclusions

In summary, we have developed an approach for the synthesis of polyfunctionalized quinolines *via* a sequence of copper-catalyzed coupling reaction/propargyl-allenyl isomerization/aza-electrocyclization by one-pot. Easily available starting materials, mild conditions, and a wide substrate scope make this protocol potentially very useful. Further applications of this tandem cyclization to the synthesis of diverse nitrogen heterocycles are currently underway.

Experimental

General methods and materials

Unless stated otherwise, reactions were conducted in dried glassware. Commercially available reagents and solvents were used as received. 300-400 Mesh silica gel was used for flash column chromatography. Visualization on TLC was achieved by the use of UV light (254 nm). 400 MHz and 100 MHz were used for the record of ^{1}H NMR and ^{13}C NMR spectra. Chemical shifts (δ ppm) were reported in parts per million referring to either the internal standard of TMS or the residue of the deuterated solvents. Splitting pattern was described as follows: s for singlet, d for doublet, t for triplet, q for quartet, and m for multiplet. Coupling constants were reported in Hz. The high-resolution mass spectrum (HRMS) was performed on Waters Xevo G2-S QTof mass spectrometer.

General procedure for the reaction

Under nitrogen condition, CuI (0.05 mmol) was successively added to a 25mL vial equipped with a stir bar at -78 °C. A solution of the imidoyl chloride **1** (0.5 mmol) in DCE (2 mL) was added using a syringe. Then, the corresponding alkyne **2** (0.6 mmol) was added to the mixture. TEA (0.75 mmol) was added at last. The reaction was stirred for 30 minutes at -78 °C, and stirred for another 12 hours (monitored by TLC) at room temperature. Solvent was removed in vacuo to leave a crude mixture, which is purified by silica gel column chromatography to afford pure product **3** or **4**.

***tert*-butyl (4-chlorophenyl)(2-phenylquinolin-4-yl)methyl carbonate (3a):** Pale white solid, 193mg, 87% yield; Mp: 183-185 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23–8.17 (m, 3H), 8.07 (s, 1H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.69 (m, 1H), 7.57–7.52 (m, 2H), 7.51–7.45 (m, 2H), 7.37 (m, 3H), 7.32–7.29 (m, 2H), 1.49 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.2, 152.7, 148.7, 144.9, 139.5, 136.7, 134.7, 130.7, 129.6, 129.5, 129.2, 129.1, 128.9, 127.7, 126.8, 124.2, 123.2, 116.4, 83.4, 75.5, 27.8; IR (neat) 2927, 1866, 1390cm^{-1}; HRMS (EI-TOF) calcd for $C_{27}H_{24}ClNO_3$ 445.1445, found 445.1446.

***tert*-butyl (4-chlorophenyl)(2-*p*-tolylquinolin-4-yl)methyl carbonate (3b):** Pale white solid, 190mg, 83% yield; Mp: 164-166 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.0 Hz, 1H), 8.09 (d, *J* = 8.0 Hz, 2H), 8.05 (s, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.71–7.65 (m, 1H), 7.48–7.43 (m, 1H), 7.36 (m, 3H), 7.33 (s, 2H), 7.31 (s, 1H), 7.31–7.28 (m, 1H), 2.45 (s, 3H), 1.49 (s, 9H); ^{13}C NMR (100 MHz, CDCl3) δ 157.2, 152.7, 148.7, 144.7, 139.7, 136.7, 134.7, 130.6, 129.6, 129.5, 129.3, 129.0, 127.5, 126.6, 124.1, 123.2, 116.2, 83.4, 75.6, 27.8, 21.4; IR (neat) 2946, 1857, 1384cm^{-1}; HRMS (EI-TOF) calcd for $C_{28}H_{26}ClNO_3$ 459.1601, found 459.1603.

***tert*-butyl (4-chlorophenyl)(2-(4-methoxyphenyl)quinolin-4-yl)methyl carbonate (3c):** Pale yellow solid, 192mg, 81% yield; Mp: 142-144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 7.0 Hz, 3H), 8.03 (s, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.66 (t, *J* = 8.0 Hz, 1H), 7.43 (t, *J* = 8.0 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.31 (t, *J* = 9.0 Hz, 3H), 7.06 (d, *J* = 9.0 Hz, 2H), 3.89 (s, 3H), 1.49 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.0, 156.7, 152.7, 148.8, 144.7, 136.7, 134.7, 132.0, 130.5, 129.5, 129.3, 129.1, 129.0, 126.4, 123.9, 123.2, 115.9, 114.3, 83.4, 75.6, 55.4, 27.8; IR (neat) 1690, 1473, 1366cm^{-1}; HRMS (EI-TOF) calcd for $C_{28}H_{26}ClNO_4$ 475.1550, found 475.1547.

***tert*-butyl (4-chlorophenyl)(2-(4-chlorophenyl)quinolin-4-yl)methyl carbonate (3d):** Pale white solid, 196mg, 82% yield; Mp: 199-201 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.0 Hz, 1H), 7.73–7.67 (m, 1H), 7.51 (d, *J* = 9.0 Hz, 2H), 7.50–7.45 (m, 1H), 7.35 (t, *J* = 6.0 Hz, 3H), 7.31 (d, *J* = 9.0 Hz, 2H), 1.49 (s, 9H); ^{13}C NMR (100

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MHz, $CDCl_3$) δ 155.8, 152.6, 148.7, 145.2, 137.8, 136.6, 135.8, 134.8, 130.7, 129.8, 129.2, 129.1, 128.9, 127.0, 124.2, 123.3, 115.9, 83.5, 75.5, 27.8; IR (neat) 1658, 1510, 1443cm^{-1}; HRMS (EI-TOF) calcd for $C_{27}H_{23}Cl_2NO_3$ 479.1055, found 479.1056.

***tert*-butyl (4-chlorophenyl)(2-(4-fluorophenyl)quinolin-4-yl)methyl carbonate (3e):** Pale white solid, 185mg, 80% yield; Mp: 181-183 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23–8.15 (m, 3H), 8.03 (s, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.73–7.66 (m, 1H), 7.50–7.44 (m, 1H), 7.36 (t, *J* = 7.0 Hz, 3H), 7.32–7.29 (m, 2H), 7.25 (t, *J* = 3.0 Hz, 1H), 7.20 (d, *J* = 2.0 Hz, 1H), 1.49 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.0 ($J_{C\text{-}F}$ = 248 Hz), 156.0, 152.6, 148.7, 145.1, 136.6, 135.6 ($J_{C\text{-}F}$ = 3 Hz), 134.8, 130.6, 129.7, 129.5 ($J_{C\text{-}F}$ = 16 Hz), 129.2, 129.1, 126.8, 124.1, 123.3, 115.9 ($J_{C\text{-}F}$ = 2 Hz), 115.7, 83.5, 75.5, 27.8; IR (neat) 1256, 1011, 790cm^{-1}; HRMS (EI-TOF) calcd for $C_{27}H_{23}ClFNO_3$ 463.1350, found 463.1349.

***tert*-butyl (4-chlorophenyl)(7-methyl-2-*p*-tolylquinolin-4-yl)methyl carbonate (3f):** Pale white solid, 170mg, 72% yield; Mp: 173-175 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.0 Hz, 2H), 7.97 (d, *J* = 4.0 Hz, 2H), 7.75 (d, *J* = 9.0 Hz, 1H), 7.35 (dd, *J* = 8.0, 7.0 Hz, 4H), 7.31–7.27 (m, 4H), 2.52 (s, 3H), 2.44 (s, 3H), 1.48 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.1, 152.7, 149.0, 144.5, 139.8, 139.6, 136.8, 134.6, 129.7, 129.6, 129.2, 129.0, 128.8, 127.5, 122.9, 122.1, 115.4, 83.3, 75.6, 27.8, 21.7, 21.4; IR (neat) 1715, 1602, 1369cm$^{-1;}$ HRMS (EI-TOF) calcd for $C_{29}H_{28}ClNO_3$ 473.1758, found 473.1761.

***tert*-butyl (4-chlorophenyl)(6-methyl-2-*p*-tolylquinolin-4-yl)methyl carbonate (3g):** Pale yellow solid, 189mg, 80% yield; 164-166 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (dd, *J* = 8.0, 2.0 Hz, 3H), 7.99 (s, 1H), 7.62 (s, 1H), 7.50 (dd, *J* = 9.0, 1.0 Hz, 1H), 7.37 (d, *J* = 9.0 Hz, 2H), 7.32 (t, *J* = 8.0 Hz, 5H), 2.47 (s, 3H), 2.42 (s, 3H), 1.48 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 152.7, 147.3, 144.0, 139.5, 136.8, 136.7, 136.5, 134.7, 131.8, 130.3, 129.6, 129.3, 129.0, 127.4, 124.1, 122.1, 116.1, 83.4, 75.4, 27.8, 22.1, 21.4; IR (neat) 1688, 1497, 1320cm^{-1}; HRMS (EI-TOF) calcd for $C_{29}H_{28}ClNO_3$ 473.1758, found 473.1757.

***tert*-butyl (4-chlorophenyl)(6-ethyl-2-*p*-tolylquinolin-4-yl)methyl carbonate (3h):** Pale yellow solid, 197mg, 81% yield; Mp: 129-131 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (dd, *J* = 14.0, 8.0 Hz, 3H), 7.98 (s, 1H), 7.63 (s, 1H), 7.55 (d, *J* = 9.0 Hz, 1H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.32 (t, *J* = 8.0 Hz, 5H), 2.77 (q, *J* = 7.0 Hz, 2H), 2.43 (s, 3H), 1.49 (s, 9H), 1.27 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 152.7, 147.5, 144.2, 142.6, 139.4, 136.9, 136.7, 134.7, 130.7, 130.4, 129.6, 129.3, 129.0, 127.4, 124.1, 120.7, 116.1, 83.3, 75.5, 29.2, 27.8, 21.4, 15.3; IR (neat) 1687, 1472, 1323cm^{-1}; HRMS (EI-TOF) calcd for $C_{30}H_{30}ClNO_3$ 487.1914, found 487.1917.

***tert*-butyl (4-chlorophenyl)(6-isopropyl-2-*p*-tolylquinolin-4-yl)methyl carbonate (3i):** Pale yellow solid, 195mg, 78% yield; Mp: 112-114 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 9.0 Hz, 1H), 8.05 (d, *J* = 8.0 Hz, 2H), 7.97 (s, 1H), 7.65 (s, 1H), 7.59 (dd, *J* = 9.0, 2.0 Hz, 1H), 7.39 (d, *J* = 9.0 Hz, 2H), 7.36–7.29 (m, 5H), 3.09–2.97 (m, 1H), 2.43 (s, 3H), 1.49 (s, 9H), 1.28 (t, *J* = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 152.7, 147.6, 147.1, 144.3, 139.4, 136.9, 136.7, 134.6, 130.4, 129.6, 129.4, 129.3, 129.0, 127.4, 124.0, 119.4, 116.0, 83.3, 75.5, 34.3, 27.8, 23.9, 23.7, 21.4; IR (neat) 1706, 1603, 1369cm^{-1}; HRMS (EI-TOF) calcd for $C_{31}H_{32}ClNO_3$ 501.2071, found 501.2075.

***tert*-butyl (6-*tert*-butyl-2-*p*-tolylquinolin-4-yl)(4-chlorophenyl)methyl carbonate (3j):** Pale yellow solid, 195mg, 76% yield; Mp: 96-98 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 9.0 Hz, 1H), 8.05 (d, *J* = 8.0 Hz, 2H), 7.98 (s, 1H), 7.79–7.74 (m, 2H), 7.41 (d, *J* = 9.0 Hz, 2H), 7.35–7.32 (m, 4H), 7.31 (d, *J* = 2.0 Hz, 1H), 2.44 (s, 3H), 1.49 (s, 9H), 1.34 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5, 152.7, 149.3, 147.2, 144.5, 139.4, 136.9, 136.7, 134.7, 130.1, 129.6, 129.4, 129.0, 128.3, 127.4, 123.6, 118.3, 115.9, 83.3, 75.7, 35.2, 31.2, 27.8, 21.4; IR (neat) 1690, 1478, 1368cm^{-1}; HRMS (EI-TOF) calcd for $C_{32}H_{34}ClNO_3$ 515.2227, found 515.2230.

***tert*-butyl (6-chloro-2-*p*-tolylquinolin-4-yl)(4-chlorophenyl)methyl carbonate (3k):** Pale white solid, 194mg, 79% yield; Mp: 172-174 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12–8.02 (m, 4H), 7.84 (s, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.34 (d, *J* = 5.0 Hz, 6H), 7.24 (s, 1H), 2.43 (s, 3H), 1.49 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.3, 152.6, 147.2, 144.1, 140.0, 136.2, 136.1, 134.9, 132.4, 132.1, 130.5, 129.7, 129.2, 129.1, 127.5, 124.8, 122.4, 117.0, 83.6, 75.3, 27.8, 21.4; IR (neat) 1689, 1487, 1356cm^{-1}; HRMS (EI-TOF) calcd for $C_{28}H_{25}Cl_2NO_3$ 493.1211, found 493.1210.

***tert*-butyl (4-chlorophenyl)(2-(4-methoxyphenyl)-6-methylquinolin-4-yl)methyl carbonate (3l):** Pale yellow solid, 190mg, 78% yield; Mp: 135-137 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 9.0 Hz, 1H), 8.04 (d, *J* = 8.0 Hz, 2H), 7.97 (s, 1H), 7.38 (d, *J* = 9.0 Hz, 2H), 7.35–7.31 (m, 5H), 7.26 (s, 1H), 7.08 (d, *J* = 3.0 Hz, 1H), 3.82 (s, 3H), 2.43 (s, 3H), 1.49 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 154.8, 152.7, 144.8, 143.2, 139.2, 136.8, 136.6, 134.7, 132.0, 129.6, 129.2, 129.0, 127.2, 125.0, 121.8, 116.6, 101.7, 83.4, 75.7, 55.4, 27.8, 21.3; IR (neat) 1689, 1490, 1368cm^{-1}; HRMS (EI-TOF) calcd for $C_{29}H_{28}ClNO_4S$ 489.1707, found 489.1705.

***tert*-butyl (4-chlorophenyl)(2-(4-chlorophenyl)-6-methylquinolin-4-yl)methyl carbonate (3m):** Pale white solid, 197mg, 80% yield; Mp: 156-158 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.0 Hz, 2H), 8.07 (d, *J* = 9.0 Hz, 1H), 7.97 (s, 1H), 7.63 (s, 1H), 7.53 (dd, *J* = 9.0, 2.0 Hz, 1H), 7.51–7.48 (m, 2H), 7.38–7.35 (m, 2H), 7.32 (t, *J* = 7.0 Hz, 3H), 2.48 (s, 3H), 1.49 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 152.7, 147.2, 144.5, 137.9, 137.1, 136.6, 135.6, 134.8, 132.1, 130.3, 129.2, 129.1, 129.0, 128.8, 124.2, 122.1, 115.8, 83.5, 75.3, 27.8, 22.1; IR (neat) 1693, 1482, 1354cm^{-1}; HRMS (EI-TOF) calcd for $C_{28}H_{25}Cl_2NO_3$ 493.1211, found 493.1214.

***tert*-butyl (4-chlorophenyl)(2-(thiophen-2-yl)quinolin-4-yl)methyl carbonate (3n):** Pale yellow solid, 160mg, 71% yield; Mp: 132-135 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.0 Hz, 1H), 7.99 (s, 1H), 7.79 (t, *J* = 5.0 Hz, 2H), 7.65 (t, *J* = 8.0 Hz, 1H), 7.49 (d, *J* = 5.0 Hz, 1H), 7.42 (t, *J* = 8.0 Hz, 1H), 7.35 (d, *J* = 9.0 Hz, 2H), 7.30 (d, *J* = 7.0 Hz, 3H), 7.17 (dd, *J* = 5.0, 4.0 Hz, 1H), 1.49 (s, 9H); ^{13}C NMR (100

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MHz, $CDCl_3$) δ 152.6, 152.2, 148.5, 145.3, 144.8, 136.5, 134.8, 130.2, 129.7, 129.3, 129.1, 128.9, 128.1, 126.5, 126.2, 124.2, 123.3, 114.9, 83.5, 75.4, 27.8; IR (neat) 1689, 1485, 1302cm^{-1}; HRMS (EI-TOF) calcd for $C_{25}H_{22}ClNO_3S$ 451.1009, found 451.1006.

***tert*-butyl (2-*tert*-butyl-6-methoxyquinolin-4-yl)(4-chlorophenyl)methyl carbonate (3o):** Gum, 168mg, 74% yield; ^1H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 9.0 Hz, 1H), 7.60 (s, 1H), 7.31 (s, 4H), 7.28 (dd, *J* = 9.0, 3.0 Hz, 1H), 7.18 (s, 1H), 7.01 (s, 1H), 3.78 (s, 3H), 1.48 (s, 9H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 157.3, 152.7, 143.9, 142.4, 136.5, 134.6, 131.7, 129.3, 129.0, 124.3, 121.1, 115.6, 101.5, 83.2, 76.0, 55.4, 38.0, 30.2, 27.8; IR (neat) 1677, 1490, 1321cm^{-1}; HRMS (EI-TOF) calcd for $C_{26}H_{30}ClNO_4$ 455.1863, found 455.1866.

***tert*-butyl phenyl(2-phenylquinolin-4-yl)methyl carbonate (4a):** Pale white solid, 166mg, 81% yield; Mp: 152-154 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.22–8.16 (m, 3H), 8.09 (s, 1H), 7.94 (d, *J* = 8.0 Hz, 1H), 7.69 (dd, *J* = 11.0, 4.0 Hz, 1H), 7.54 (t, *J* = 7.0 Hz, 2H), 7.46 (m, 4H), 7.39 (s, 1H), 7.34 (m, 3H), 1.49 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.2, 152.8, 148.7, 145.5, 139.6, 138.0, 130.6, 129.5, 128.9, 128.8, 128.7, 127.9, 127.7, 126.6, 124.4, 123.4, 116.4, 83.2, 76.3, 27.8; IR (neat) 1608, 1511, 1386cm^{-1}; HRMS (EI-TOF) calcd for $C_{27}H_{25}NO_3$ 411.1843, found 411.1848.

***tert*-butyl (2-phenylquinolin-4-yl)(*p*-tolyl)methyl carbonate (4b):** Pale white solid, 161mg, 76% yield; Mp: 166-168 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.22–8.15 (m, 3H), 8.10 (s, 1H), 7.93 (d, *J* = 8.0 Hz, 1H), 7.71–7.64 (m, 1H), 7.54 (t, *J* = 7.0 Hz, 2H), 7.46 (m, 2H), 7.36 (s, 1H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.13 (d, *J* = 8.0 Hz, 2H), 2.31 (s, 3H), 1.48 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.2, 152.8, 148.7, 145.7, 139.7, 138.7, 135.1, 130.6, 129.5, 129.4, 128.9, 127.9, 127.7, 126.6, 124.4, 123.4, 116.1, 83.1, 76.2, 27.8, 21.2; IR (neat) 1658, 1523, 1437cm^{-1}; HRMS (EI-TOF) calcd for $C_{28}H_{27}NO_3$ 425.1991, found 425.1990.

***tert*-butyl (4-methoxyphenyl)(2-phenylquinolin-4-yl)methyl carbonate (4c):** Pale yellow solid, 170mg, 77% yield; Mp: 133-135 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.18–8.13 (m, 3H), 8.05 (s, 1H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.68–7.62 (m, 1H), 7.45–7.40 (m, 3H), 7.38 (s, 1H), 7.36–7.28 (m, 3H), 7.05 (d, *J* = 9.0 Hz, 2H), 3.88 (s, 3H), 1.48 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.0, 156.7, 152.8, 148.7, 145.2, 138.1, 132.2, 130.4, 129.4, 129.0, 128.8, 128.7, 127.9, 126.3, 124.1, 123.4, 115.9, 114.3, 83.1, 76.3, 55.4, 27.8; IR (neat) 1660, 1532, 1438cm^{-1}; HRMS (EI-TOF) calcd for $C_{28}H_{27}NO_4$ 441.1940, found 441.1937.

***tert*-butyl (4-fluorophenyl)(2-phenylquinolin-4-yl)methyl carbonate (4d):** Pale white solid, 180mg, 84% yield; Mp: 176-178 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.24–8.16 (m, 3H), 8.09 (s, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.72–7.66 (m, 1H), 7.55 (t, *J* = 7.0 Hz, 2H), 7.51–7.44 (m, 2H), 7.44–7.38 (m, 2H), 7.36 (s, 1H), 7.02 (t, *J* = 9.0 Hz, 2H), 1.49 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8 (J_{C-F} = 247 Hz), 157.2, 152.7, 148.7, 145.2, 139.5, 134.0, 130.7, 129.9 (J_{C-F} = 8 Hz), 129.6, 128.9, 127.7, 126.7, 124.2, 123.3, 116.0 (J_{C-F} = 23 Hz), 115.7, 83.3, 75.6, 27.8; IR (neat) 1664, 1538, 1421cm^{-1}; HRMS (EI-TOF) calcd for $C_{27}H_{24}FNO_3$ 429.1740, found 429.1742.

***tert*-butyl cyclohexyl(2-phenylquinolin-4-yl)methyl carbonate (4e):** Light yellow oil, 108mg, 52% yield; ^1H NMR (400 MHz, $CDCl_3$) δ 8.14 (m, 4H), 7.90 (s, 1H), 7.73 (s, 1H), 7.51 (m, 4H), 6.10 (d, *J* = 5.0 Hz, 1H), 1.93 (m, 2H), 1.70 (m, 3H), 1.42 (s, 9H), 1.21 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 153.3, 148.6, 146.3, 139.7, 130.7, 129.4, 128.8, 127.6, 126.4, 125.1, 123.2, 116.4, 82.6, 78.9, 43.2, 29.6, 28.5, 27.8, 26.1, 26.0, 25.8; IR (neat) 1660, 1546, 1427cm^{-1}; HRMS (EI-TOF) calcd for $C_{27}H_{31}NO_3$ 417.2304, found 417.2302.

phenyl(2-phenylquinolin-4-yl)methyl acetate (4f): Light yellow oil, 138mg, 78% yield; ^1H NMR (400 MHz, $CDCl_3$) δ 8.22–8.14 (m, 3H), 8.03 (s, 1H), 7.94 (d, *J* = 8.0 Hz, 1H), 7.68 (m, 1H), 7.62 (s, 1H), 7.57–7.51 (m, 2H), 7.51–7.43 (m, 2H), 7.41 (dd, *J* = 8.0, 2.0 Hz, 2H), 7.37–7.28 (m, 3H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 157.1, 148.8, 145.3, 139.7, 138.4, 130.6, 129.5, 129.4, 128.9, 128.8, 128.7, 127.8, 127.6, 126.7, 124.5, 123.6, 116.8, 73.5, 21.3; IR (neat) 1672, 1488, 1370cm^{-1}; HRMS (EI-TOF) calcd for $C_{24}H_{19}NO_2$ 353.1416, found 353.1418.

(4-chlorophenyl)(2-phenylquinolin-4-yl)methyl acetate (4g): Light yellow oil, 149mg, 77% yield; ^1H NMR (400 MHz, $CDCl_3$) δ 8.23–8.15 (m, 3H), 8.02 (s, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.69 (m, 1H), 7.59–7.52 (m, 3H), 7.51–7.43 (m, 2H), 7.36–7.29 (m, 4H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 157.2, 148.8, 144.8, 139.5, 136.9, 134.7, 130.7, 129.6, 129.6, 129.2, 129.1, 128.9, 127.6, 126.8, 124.3, 123.4, 116.8, 72.9, 21.2; IR (neat) 1672, 1490, 1375cm^{-1}; HRMS (EI-TOF) calcd for $C_{24}H_{18}ClNO_2$ 387.1026, found 387.1027.

***tert*-butyl phenyl((2-phenylquinolin-4-yl)methyl)carbamate (4h):** Gum, 129mg, 63% yield; ^1H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.0 Hz, 1H), 8.08 (d, *J* = 7.0 Hz, 2H), 8.00 (d, *J* = 8.0 Hz, 1H), 7.78–7.69 (m, 2H), 7.56–7.42 (m, 4H), 7.27 (d, *J* = 8.0 Hz, 1H), 7.25–7.11 (m, 4H), 5.38 (s, 2H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.0, 154.6, 148.4, 144.2, 142.4, 139.7, 130.6, 129.5, 129.4, 128.9, 127.5, 126.4, 126.1, 126.0, 125.3, 122.7, 81.2, 51.3, 28.3; IR (neat) 1689, 1494, 1366cm^{-1}; HRMS (EI-TOF) calcd for $C_{27}H_{26}N_2O_2$ 410.1994, found 410.1987.

***tert*-butyl 4-chlorophenyl((2-phenylquinolin-4-yl)methyl)carbamate (4i):** Gum, 133mg, 60% yield; ^1H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, *J* = 8.0 Hz, 1H), 8.10–8.05 (m, 2H), 7.98 (d, *J* = 8.0 Hz, 1H), 7.73 (m, 2H), 7.56–7.44 (m, 4H), 7.21 (d, *J* = 9.0 Hz, 2H), 7.12 (d, *J* = 7.0 Hz, 2H), 5.35 (s, 2H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.0, 154.3, 148.5, 143.8, 140.9, 139.5, 131.6, 130.6, 129.6, 129.5, 129.0, 128.9, 127.5, 127.2, 126.6, 125.2, 122.7, 81.6, 51.1, 28.2; IR (neat) 1688, 1490, 1368cm^{-1}; HRMS (EI-TOF) calcd for $C_{27}H_{25}ClN_2O_2$ 444.1605, found 444.1608.

Conflicts of interest

We declare no conflicts of interest.

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