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FULL PAPER

Acid-promoted Cascade Reaction of 4-Chloroquinolin-3-yl Carbamates with Amines: One-Pot Assembly of Imidazo[4,5-*c*]quinolin-2-ones

Xiao Lu,[a] Myunghoon Kim,[a] Meghan J. Orr,[a] Hao Li,[a] and Wenwei Huang*[a]

Abstract: An acid-promoted cascade reaction of 4-chloroquinolin-3-yl carbamates with amines is described. This method achieves the formation of two new C-N bonds through an intermolecular amination/intramolecular cyclization reaction sequence. In combination with subsequent Suzuki coupling, this three-component telescopic procedure provides rapid access to various bioactive imidazo[4,5-*c*]quinolin-2-one derivatives.

Introduction

Over the past decade, imidazo[4,5-*c*]quinolin-2-ones have shown promising biological activities, resulting in significant interest in this class of compounds. NVP-BEZ235, NVP-BGT226, and LY3023414, three dual PI3K/mTOR inhibitors, have been evaluated as anti-cancer agents in clinical trials.[1] I-BET151, a novel BET bromodomain inhibitor, has shown promising results in preclinical cancer models.[2] AZD0156, a potent and selective ATM kinase inhibitor, has recently been approved for clinical study for advanced solid tumors (Figure 1).[3] We and other groups reported that NVP-BEZ235, NVP-BGT226, and their analogs exhibited potent anti-parasitic activities against *Plasmodium falciparum*,[4] *Trypanosoma cruzi*,[5] *Trypanosoma brucei*,[5b, 6] *Leishmania major,* and *Leishmania donovani*.[5b]

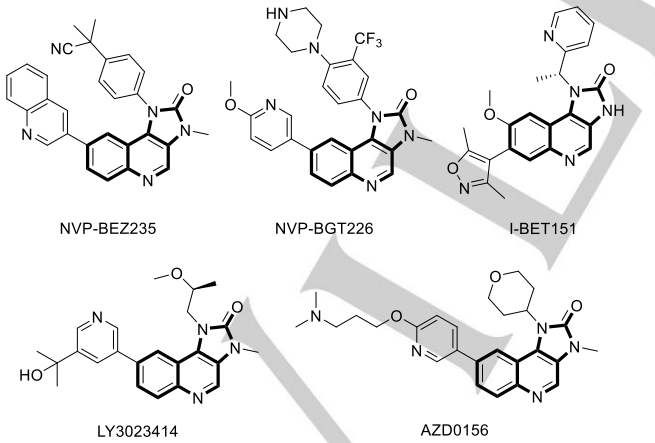

Figure 1. Selected Bioactive Imidazo[4,5-*c*]quinolin-2-ones.

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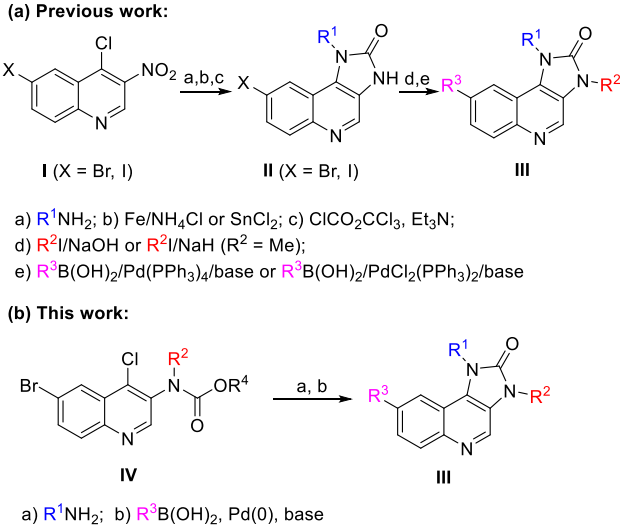
Despite their biological significance, synthetic routes to this class of molecules remain underdeveloped. Previously described syntheses of imidazo[4,5-*c*]quinolin-2-ones **III** usually require a linear multi-step procedure. The reported preparation of NVP-BEZ235 and its analogs followed a reaction sequence including nitroquinoline amination, nitro group reduction, imidazolidinone ring formation and Suzuki coupling (**Scheme 1a**).[4b, 6-7] Introduction of the R^1 substituent in the first step, however, would result in synthetic inefficiencies if analogs with different R^1 substituents were desired. Herein we report a one-pot convergent synthesis of imidazo[4,5-*c*]quinolin-2-ones **III.** The process uses an acid-promoted amination-cyclization cascade, converting carbamates **IV** to the imidazo[4,5-*c*]quinolin-2-one core, and a telescopic Suzuki coupling, forming the desired analogs (**Scheme 1b**).

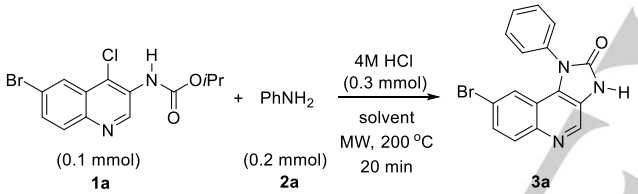
Scheme 1. Preparation of Imidazo[4,5-*c*]quinolin-2-ones **III**.



Results and Discussion

Although some literature examples exist of palladium catalyzed one-pot strategies to construct imidazo[4,5-*b*]pyridine-2-ones or imidazo[4,5-*c*]pyridine-2-ones,[8] we chose to focus on non-metal catalyzed assembly of the imidazolidinone ring in order to avoid a potential selectivity issue (4-Cl vs 6-Br) in the C-N cross-coupling step on 6-bromo-4-chloro-3-aminoquinoline.[9] The reaction was initially explored by treating *N*-H carbamate **1a** with 2 equivalents of aniline **2a** in 2-propanol. After microwave heating at 150 °C for 20 min, no reaction was observed. However, formation of the cyclic product **3a** was observed when HCl was added to facilitate the amination. The reaction temperature was further increased to 200 °C to achieve full conversion (**Table 1**, entry 2). A quick solvent screen showed that acetonitrile, toluene, 1-butanol, dimethylacetamide (DMA), and *N*-methyl-2-pyrrolidone (NMP) gave only fair to poor yields of **3a** (**Table 1,** entries 1, 3, 5, 6 and 7).

Table 1. Optimization Studies: the Effect of Solvents.



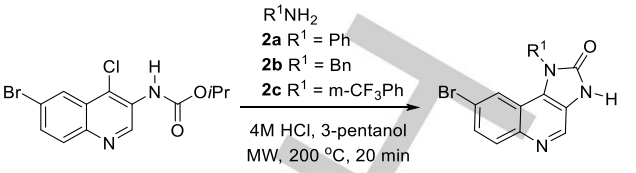
(0.1 mmol) **1a** (0.2 mmol) **2a** **3a**

Entry	Solvent	b.p. (°C)	Conversion[a]	Yield[b]
1	MeCN	82	>99%	61%
2	2-propanol	83	>99%	84%
3	PhMe	111	56%	44%
4	3-pentanol	115	>99%	87%
5	1-butanol	118	>99%	63%
6	DMA	165	>99%	37%
7	NMP	202	>99%	71%

[a] Determined by LC-MS. [b] Isolated yield.

Although both 2-propanol and 3-pentanol gave comparable yields (**Table 1,** entries 2 and 4), we selected 3-pentanol as the solvent of choice to avoid excessive pressure (>20 bar) buildup under microwave irradiation at high temperature. Treatment of **1a** with two equivalents of **2a-c** and three equivalents of HCl in 3-pentanol at 200 °C for 20 min gave **3a-c** in 62-87% isolated yields (**Scheme 2**). Other carbamates including *i*-Bu carbamate and Et carbamate gave similar results (data not shown).

Scheme 2. Investigation on *N*-H *i*-Pr Carbamate **1a**[a].



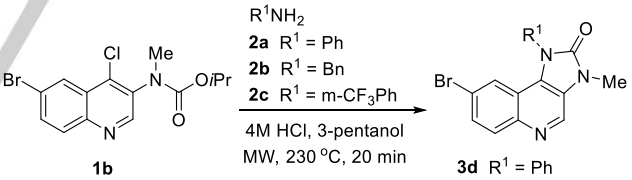
1a

3a R^1 = Ph, 87%[b]
3b R^1 = Bn, 62%[b]
3c R^1 = m-CF_3Ph, 67%[b]

[a] Reaction conditions: **1a** (0.1 mmol), **2** (0.2 mmol) and HCl (0.3 mmol, 4.0 M in 1,4-dioxane) in 3-pentanol (1 mL). [b] Isolated yields.

Encouraged by these results, we subsequently examined *N*-Me carbamate **1b** and found that a higher reaction temperature was needed to achieve good conversion presumably due to the steric effect of the *N*-Me group in **1b**. Treatment of carbamate **1b** with two equivalents of **2a** and three equivalents of HCl at 230 °C gave **3d** in 79% isolated yield (**Table 2**, entry 3). It is worth noting that smaller amounts of HCl used in the reaction gave lower conversions (**Table 2**, entries 1 and 2). Reaction of **1b** with benzylamine (**2b**) went well to afford **3e** in 60% yield (**Table 2**, entry 4). We also found that electron-deficient anilines displayed lower reactivity (**Table 2**, entry 5). Nonetheless, the reaction with aniline **2c** went successfully with four equivalents of aniline and five equivalents of HCl, providing **3f** in 79% yield (**Table 2**, entry 6).

Table 2. Optimization of Ring Closure of **1b**.



1b

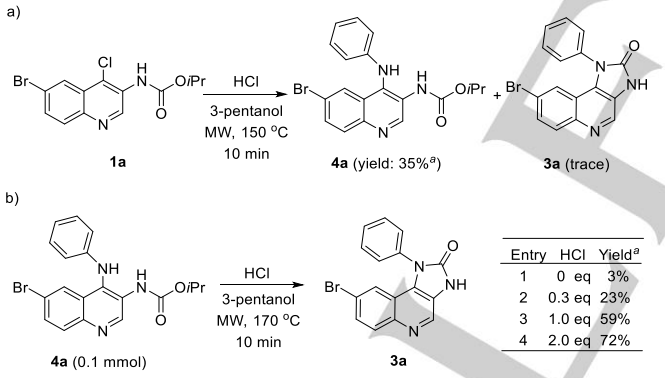
3d R^1 = Ph
3e R^1 = Bn
3f R^1 = m-CF_3Ph

Entry	**2**	Molar ratio (**1**:**2**:HCl)	**3**	Conversion[a]	Yield[b]
1	**2a**	1:2:0.5	**3d**	63%	ND[c]
2	**2a**	1:2:1	**3d**	75%	ND[c]
3	**2a**	1:2:3	**3d**	94%	79%
4	**2b**	1:2:3	**3e**	86%	60%
5	**2c**	1:2:3	**3f**	67%	ND[c]
6	**2c**	1:4:5	**3f**	96%	79%

[a] Determined by LC-MS. [b] Isolated yield. [c] Not determined.

To gain insight into the acid-promoted imidazolidinone formation, two independent reactions were performed (**Scheme 3**). Besides the cyclic end product **3a** and unreacted starting material **1a**, treatment of carbamate **1a** with aniline **2a** and HCl in 3-pentanol at 150 °C for 10 min produced aminated intermediate **4a** (**Scheme 3a**). Notably, heating **4a** in 3-pentanol at 170 °C in the presence of different amounts of HCl showed that the ring closure step was also promoted by HCl (**Scheme 3b**). These results indicate that HCl played a prominent role not only in the amination step of **1a** to produce **4a**, but also in the final cyclization step of **4a** to form **3a**. To the best of our knowledge, this is the first report of a non-metal catalyzed acid-promoted cascade imidazolidinone ring formation method. Amination of HCl-activated quinoline 4-Cl with aniline **2**,[10] was followed by subsequent intramolecular cyclization, involving carbamate aminolysis and concomitant alcohol release to yield the cyclic imidazo[4,5-*c*]quinolin-2-one product. Interestingly, reaction of carbamate **1b** and 4 equivalents of phenylethylamine provided the desired cyclic imidazolidinone after microwave heating at 230 °C without the addition of acid, possibly due to the greater nucleophilicity of an alkyl amine versus aniline.

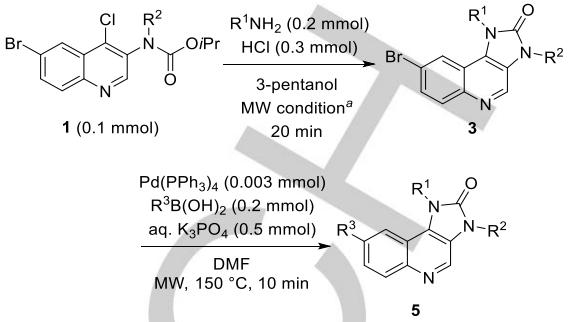
Scheme 3. Synthesis of **3a** from **4a**.

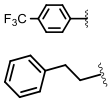


[a] Isolated yield.

The employment of HCl in the amination/intramolecular cyclization synthetic sequence makes this two-step imidazolidinone procedure a suitable candidate for a one-pot synthesis [11] of R^1, R^2, R^3-trisubstituted imidazo[4,5-*c*]quinolin-2-ones. With the optimal ring closure conditions in hand, we tested a telescoped amination-cyclization-coupling strategy by using a microwave-assisted Suzuki protocol that has been previously studied under a variety of conditions by our group.[12] Reaction of

Table 3. Synthesis of Imidazo[4,5-*c*]quinolin-2-ones *via* One-pot Protocol.



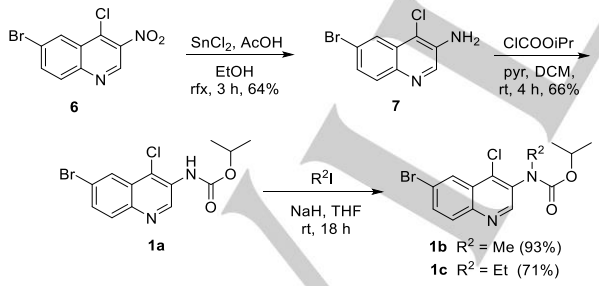
Entry	R^1	R^2	R^3	5	Yield (%)[b]
1		Me		**5a**	51
2		H		**5b**	71
3		Me		**5c**	62
4		Et		**5d**	46
5		Me		**5e**	67
6		Me		**5f**	63
7		Me		**5g**	55
8		Me		**5h**	32
9		Me		**5i**	80
10		Me		**5j**	51
11		Me		**5k**	59
12		Me		**5l**	34
13		Me		**5m**	67
14		Me		**5n**	52
15		Me		**5o**	64[c]
16		Me		**5p**	61[c]
17		Me		**5q**	55[c]
18		Me		**5r**	50[c]
19		Me		**5s**	42
20		Me		**5t**	52

[a] 230 °C for reaction when R^1 is Me or Et, 200 °C for reaction when R^1 is H. [b] Isolated yield. [c] Reagents and conditions: **1** (0.1 mmol), R^1NH_2 (0.4 mmol), HCl (0.5 mmol), 3-pentanol, MW, 230 °C, 20 min; then $Pd(PPh_3)_4$ (0.003 mmol), $R^3B(OH)_2$ (0.2 mmol), aq. K_3PO_4 (0.7 mmol), DMF, MW, 150 °C, 10 min.

1b with aniline **2a** in the presence of HCl in a microwave reactor at 230 °C for 20 min followed by addition of 2 equivalents of phenylboronic acid, 5 equivalents of K_3PO_4 and 0.03 equivalents of $Pd(PPh_3)_4$ gave **5a** in 51% isolated yield (**Table 3**, entry 1). Similarly, treatment of **1a** (R^2 = H) or **1b** (R^2 = Me) with aniline **2a** followed by coupling with 3-pyridylboronic acid generated the desired **5b** and **5c** in 71% and 62% yields, respectively (**Table 3**, entries 2-3). In comparison, a sterically more hindered *N*-Et carbamate (R^2 = Et) provided **5d** in a lower yield (**Table 3**, entry 4). A diverse set of R^1 and R^3 substituents was tested for this one-pot synthesis (**Table 3**, entries 5-20). Boronic acids/esters containing various functional groups including hydroxyl, amino, aldehyde, and cyano were well tolerated. Both alkyl and aryl amines could be incorporated into the R^1 position, although sterically hindered anilines (**Table 3**, entries 8 and 12) and anilines containing electron-withdrawing groups (**Table 3**, entries 15-18) gave slightly lower yields.

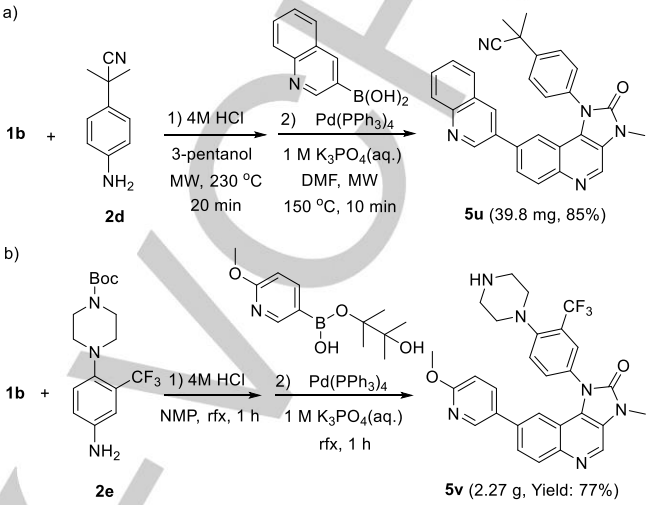
This is the first example of a pot, step economic synthesis [13] of tri-substituted imidazo[4,5-*c*]quinolin-2-ones. The present method would greatly facilitate analog synthesis for structure–activity and structure–property relationship (SAR and SPR) studies. *N*-Methyl and *N*-ethyl isopropyl carbamate (**1b** and **1c**) can be easily made from commercially available 6-bromo-4-chloro-3-nitroquinoline (**6**) in three steps: stannous chloride mediated reduction, carbamate synthesis and subsequent alkylation, providing products **1b** and **1c** in good overall yield (**Scheme 4**).

Scheme 4. Syntheses of *N*-H Isopropyl Carbamate **1a,** *N*-Methyl Isopropyl Carbamate **1b**, and *N*-Ethyl Isopropyl Carbamate **1c**.



To demonstrate the effectiveness of this consolidated methodology, NVP-BEZ235, a clinically investigated imidazo[4,5-*c*]quinolin-2-one, was prepared. Reaction of carbamate **1b** and aniline **2d** in a microwave reactor at 230 °C for 20 min, followed by a microwave assisted Suzuki coupling reaction with 3-quinioline boronic acid at 150 °C for 10 min, gave NVP-BEZ235 **5u** in 85% isolated yield (**Scheme 5a**).

Scheme 5. Syntheses of NVP-BEZ235 and NVP-BGT226.



A more conventional heating method was also attempted to prepare **5v**. To our delight, the amination-cyclization reaction of **1b** with aniline **2e** proceed well in refluxing NMP. It was also noted that the reaction of **1b** with **2c** produced only the aminated intermediate after refluxing for 12 hours in 2-propanol, and a trace amount of the desired cyclized product **3f** in 3-pentanol. Taking advantage of higher volume as compared to microwave assisted procedure, the conventional heating procedure produced 2.27 g of desired product **5v** in 77% yield[14] (**Scheme 5b**).

Conclusions

In summary, we have developed an efficient one-pot two-step three-component synthesis of imidazo[4,5-*c*]quinolin-2-ones **5** using both microwave and conventional heating. The synthesis demonstrates broad substrate scope and excellent functional group tolerance and pot/step economy. This new methodology can be expanded to synthesize a diverse set of biologically interesting imidazopyridin-2-ones/7,9-dihydro-8*H*-purin-8-ones and the result will be reported in due course.

Experimental Section

General Information.

All solvents and reagents were used as received from commercial suppliers without further purification. Microwave reactions were performed in a Biotage® Initiator+ microwave reactor. ^{1}H NMR spectra were acquired on a Varian spectrometer at 400 MHz. ^{13}C NMR spectra were recorded on a Varian spectrometer at 100 MHz. All chemical shifts (δ) were reported in ppm relative to residual solvent signals. The following abbreviations were used to report spectral data: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. LC-MS was conducted on an Agilent 1200 series mass spectrometer with ES+ ionization. High resolution mass spectra (HRMS) were recorded on an Agilent ESI-TOF mass spectrometer. Conversion of carbamate **1** in Table 1 and Table 2 was calculated by the equation as:

Conversion = (amount of **1** converted / amount of **1** used) x 100%

The amount of **1** was determined by the value of AUC (area under curve) in LC-MS using a standard curve.

Procedure for the synthesis of 6-bromo-4-chloroquinolin-3-amine (7). To a 1 L RBF charged with 25 g (85 mmol) of starting material **6**, 500 mL of EtOH, and 75 mL of AcOH was added 98 g (435 mmol) $SnCl_2$ dihydrate as one portion. The reaction mixture was refluxed for 3 hours. Then at 0 °C saturated aqueous $NaHCO_3$ was added with stirring until pH > 7. The solution was extracted with EtOAc (1 L × 3). The EtOAc layers were combined, dried over $MgSO_4$, filtered, and concentrated. The resulting solid was triturated with Et_2O (100 mL × 3), providing final product **7** as a pale-yellow solid (14.3 g, 64%): LC-MS m/z = 257 $[M+H]^+$, $C_9H_6BrClN_2$, requires 256.

Procedure for the synthesis of isopropyl (6-bromo-4-chloroquinolin-3-yl)carbamate (1a). To a stirred solution of 6-bromo-4-chloroquinolin-3-amine **7** (7.98 g, 31 mmol) in anhydrous DCM (140 mL) was added pyridine (37.2 mmol), followed by dropwise addition of isopropyl chloroformate (34.1 mmol, 1M solution in PhMe) at 0 °C under an inert atmosphere. The solution was stirred at 0 °C for 15 min before the ice bath was removed and the stirring was continued at rt for 4 hours. After cooling to 0 °C, 200 mL of DCM was added, followed by addition of an equal volume of saturated aqueous $NaHCO_3$, and several drops of MeOH. The solution was extracted with DCM (200 mL × 3). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated. The resulting orange red mixture was triturated with Et_2O (100 mL × 3), providing **1a** as a pale-orange solid (7.0 g, 66%): *Rf* = 0.43 (3:1 *n*-hexanes:EtOAc); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.69 (s, 1H), 9.08 (s, 1H), 8.31 (d, *J* = 2.2 Hz, 1H), 8.02 (d, *J* = 8.9 Hz, 1H), 7.94 (dd, *J* = 2.2, 8.9 Hz, 1H), 4.94 (p, *J* = 6.2 Hz, 1H), 1.30 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 153.7, 149.2, 143.8, 132.5, 131.5, 130.4, 126.9, 125.4, 121.8, 68.8, 21.8; LC-MS m/z = 343 $[M+H]^+$, $C_{13}H_{12}BrClN_2O_2$, requires 342.

General procedure for the syntheses of isopropyl (6-bromo-4-chloroquinolin-3-yl)(methyl)carbamate (1b) and isopropyl (6-bromo-4-chloroquinolin-3-yl)(ethyl)carbamate (1c). To an ice-bath cooled stirred solution of **1a** (7 g, 20.3 mmol) in anhydrous THF (100 mL) was added portionwise NaH (1.63 g, 40.7 mmol, 60% dispersion in mineral oil) under an inert atmosphere. After 15 min, iodomethane (3.8 mL, 61.1 mmol) or iodoethane was added dropwise. The resulting mixture was stirred at 0 °C for 60 min and then at rt for 18 hours. After cooling to 0 °C, 200 mL saturated aqueous NH_4Cl was added. The solution was extracted with EtOAc (200 mL × 3). EtOAc layers were combined, dried over $MgSO_4$, filtered, and concentrated. The residual mixture was then passed through a silica gel column, and the product eluted with DCM and MeOH.

Isopropyl (6-bromo-4-chloroquinolin-3-yl)(methyl)carbamate (1b). Prepared on a 20.3 mmol scale as a pale yellow solid (6.7 g, 93%): *Rf* = 0.30 (3:1 *n*-hexanes:EtOAc); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.96 (s, 1H), 8.38 (dd, *J* = 0.6, 2.1 Hz, 1H), 8.07 (dd, *J* = 0.7, 8.9 Hz, 1H), 8.03 (dd, *J* = 2.1, 9.0 Hz, 1H), 4.82 (p, *J* = 6.2 Hz, 1H), 3.23 (s, 3H), 1.31 (m, 1.5H), 1.04 (m, 4.5H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.0, 151.8, 145.5, 134.6, 133.9, 131.7, 127.0, 126.0, 122.0, 69.3, 36.4, 21.7; LC-MS m/z = 357 $[M+H]^+$, $C_{14}H_{14}BrClN_2O_2$, requires 356.

Isopropyl (6-bromo-4-chloroquinolin-3-yl)(ethyl)carbamate (1c). Prepared on a 1 mmol scale as a white solid (263 mg, 71%): *Rf* = 0.37 (3:1 *n*-hexanes:EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.43 (d, *J* = 2.2 Hz, 1H), 8.00 (d, *J* = 8.9 Hz, 1H), 7.85 (dd, *J* = 2.1, 9.0 Hz, 1H), 5.06 – 4.91 (m, 1H), 3.92 (dq, *J* = 7.0, 14.3 Hz, 1H), 3.65 (dq, *J* = 7.3, 14.5 Hz, 1H), 1.37 – 1.06 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 151.8, 146.2, 139.1, 133.9, 133.4, 131.5, 127.9, 127.0, 122.5, 69.8, 44.6, 22.0, 13.7; LC-MS m/z = 371 $[M+H]^+$, $C_{15}H_{16}BrClN_2O_2$, requires 370.

General procedure A for the synthesis of imidazo[4,5-*c*]quinolin-one analog (5a-5n, 5s-5u). To a 0.5 mL-2.0 mL conical shaped microwave reaction vial charged with *N*-H carbamate **1a** or *N*-methyl carbamate **1b** (36 mg, 0.1 mmol) was added 1.0 mL of 3-pentanol. With occasional shaking, the vial was heated until the solid is completely dissolved. After cooling to room temperature, the orange solution was added aniline **2** (0.2 mmol), followed by HCl (0.3 mmol, 4.0 M in dioxane). The mixture was homogenized and heated by microwave at 200 °C or 230 °C at high absorption level for 20 min. After cooling to room temperature, the mixture was added 0.5 mL DMF and 0.5 mL 1M K_3PO_4 (106 mg K_3PO_4 in 0.5 mL H_2O). The reaction mixture was degassed with N_2. Then boronic acid/ester (0.2 mmol) was added, followed by $Pd(PPh_3)_4$ (0.003 mmol). The mixture was homogenized and heated by microwave at 150 °C at normal absorption level for 10 min. After cooling to room temperature, 5 mL of saturated aqueous $NaHCO_3$ was added. The solution was extracted with DCM (7 mL × 3). DCM layers were combined, dried over $MgSO_4$, filtered, and concentrated. The residual mixture was then passed through a silica gel column, and the product eluted with DCM and MeOH.

General procedure B for the synthesis of imidazo[4,5-*c*]quinolin-one analog (5o-5r). To a 0.5 mL-2.0 mL conical shaped microwave reaction vial charged with *N*-methyl carbamate **1b** (36 mg, 0.1 mmol) was added 1.0 mL of 3-pentanol. With occasional shaking, the vial was heated until the solid is completely dissolved. After cooling to room temperature, the orange solution was added aniline **2** (0.4 mmol), followed by HCl (0.5 mmol, 4.0 M in dioxane). The mixture was homogenized and heated by microwave at 230 °C at high absorption level for 20 min. After cooling to room temperature, the mixture was added 0.5 mL DMF and 0.7 mL 1M K_3PO_4 (150 mg K_3PO_4 in 0.7 mL H_2O). The reaction mixture was degassed with N_2. Then boronic acid/ester (0.2 mmol) was added, followed by $Pd(PPh_3)_4$ (0.003 mmol). The mixture was homogenized and heated by microwave at 150 °C at normal absorption level for 10 min. After cooling to room temperature, 5 mL of saturated aqueous $NaHCO_3$ was added. The solution was extracted with DCM (7 mL × 3). DCM layers were combined, dried over $MgSO_4$, filtered, and concentrated.

The residual mixture was then passed through a silica gel column, and the product eluted with DCM and MeOH.

General procedure C using conventional heating for the synthesis of imidazo[4,5-*c*]quinolin-one analog (5v). To a 250 mL RBF charged with *N*-methyl carbamate **1b** (6 mmol), aniline (12 mmol) and 100 mL of NMP was added HCl (42 mmol, 4.0 M in dioxnae). The mixture was heated at 230 °C for 1 hour (or until reaction was complete). After cooling to room temperature, the mixture was added 50 mL of H_2O and K_3PO_4 (108 mmol). The reaction mixture was degassed with N_2. Then boronic ester (12 mmol) was added, followed by $Pd(PPh_3)_4$ (0.18 mmol). The mixture was homogenized and refluxed for 1 hour. After cooling to room temperature, 300 mL of saturated aqueous $NaHCO_3$ was added. The solution was extracted with DCM (300 mL × 3). DCM layers were combined, dried over $MgSO_4$, filtered, and concentrated. The residual mixture was then passed through a silica gel column, and the product eluted with DCM and MeOH.

3-Methyl-1,8-diphenyl-1,3-dihydro-2*H*-imidazo[4,5-*c*]quinolin-2-one (5a). Prepared by following the general procedure A as a white solid (17.9 mg, 51%): *Rf* = 0.43 (20:1 DCM:MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (s, 1H), 8.26 (d, *J* = 8.9 Hz, 1H), 7.87 – 7.84 (m, 1H), 7.66 – 7.63 (m, 3H), 7.57 – 7.54 (m, 2H), 7.37 – 7.31 (m, 6H), 3.69 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.7, 144.0, 139.7, 138.7, 135.3, 131.6, 130.2, 129.9, 129.0, 128.7, 128.7, 127.9, 127.0, 127.0, 123.2, 118.3, 115.5, 28.0; HRMS (ESI, $[M+H]^+$) calcd for $C_{23}H_{18}N_3O$ 352.1444, found 352.1435.

1-Phenyl-8-(pyridin-3-yl)-1,3-dihydro-2*H*-imidazo[4,5-*c*]quinolin-2-one (5b). Prepared by following the general procedure A as a white solid (24.0 mg, 71%): *Rf* = 0.43 (20:1 DCM:MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.78 (s, 1H), 8.79 (s, 1H), 8.54 – 8.48 (m, 2H), 8.12 – 8.09 (m, 1H), 7.91 (dd, *J* = 2.1, 8.9 Hz, 1H), 7.76 (ddd, *J* = 1.6, 2.4, 8.0 Hz, 1H), 7.73 – 7.64 (m, 5H), 7.43 (ddd, *J* = 0.9, 4.7, 7.9 Hz, 1H), 7.20 (dd, *J* = 0.6, 2.1 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 153.6, 148.8, 147.2, 143.6, 135.4, 134.7, 134.4, 134.0, 133.9, 130.9, 130.1, 130.0, 129.7, 129.1, 125.5, 124.0, 122.1, 117.9, 115.1; HRMS (ESI, $[M+H]^+$) calcd for $C_{21}H_{15}N_4O$ 339.1240, found 339.1251.

3-Methyl-1-phenyl-8-(pyridin-3-yl)-1,3-dihydro-2*H*-imidazo[4,5-*c*]quinolin-2-one (5c). Prepared by following the general procedure A as a pale yellow solid (21.8 mg, 62%): *Rf* = 0.35 (20:1 DCM:MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (d, *J* = 1.2 Hz, 1H), 8.57 – 8.52 (m, 2H), 8.20 (dt, *J* = 0.8, 8.8 Hz, 1H), 7.77 (ddd, *J* = 1.0, 2.1, 8.8 Hz, 1H), 7.63 (tdd, *J* = 1.3, 2.3, 4.1 Hz, 4H), 7.57 – 7.53 (m, 2H), 7.33 (dd, *J* = 0.7, 2.2 Hz, 1H), 7.29 (ddd, *J* = 0.9, 4.8, 7.9 Hz, 1H), 3.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8, 148.9, 148.2, 144.9, 135.5, 135.4, 135.1, 134.1, 132.8, 131.6, 130.2, 130.1, 129.7, 128.7, 126.0, 123.7, 123.4, 118.7, 115.5, 28.0; HRMS (ESI, $[M+H]^+$) calcd for $C_{22}H_{17}N_4O$ 353.1397, found 353.1391.

3-Ethyl-1-phenyl-8-(pyridin-3-yl)-1,3-dihydro-2*H*-imidazo[4,5-*c*]quinolin-2-one (5d). Prepared by following the general procedure A as a white solid (16.8 mg, 46%): *Rf* = 0.41 (20:1 DCM:MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (s, 1H), 8.57 – 8.53 (m, 2H), 8.20 (dd, *J* = 0.7, 8.9 Hz, 1H), 7.77 (dd, *J* = 2.1, 8.9 Hz, 1H), 7.66 – 7.62 (m, 4H), 7.59 – 7.55 (m, 2H), 7.34 (dd, *J* = 0.8, 2.2 Hz, 1H), 7.29 (ddd, *J* = 0.9, 4.8, 7.9 Hz, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 1.53 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2, 148.9, 148.2, 144.8, 135.6, 135.4, 135.1, 134.1, 132.9, 131.6, 130.2, 130.0, 129.8, 128.7, 126.0, 123.7, 122.6, 118.7, 115.7, 36.9, 14.3; HRMS (ESI, $[M+H]^+$) calcd for $C_{23}H_{19}N_4O$ 367.1553, found 367.1570.

8-(3-Aminophenyl)-3-methyl-1-(*p*-tolyl)-1,3-dihydro-2*H*-imidazo[4,5-*c*]quinolin-2-one (5e). Prepared by following the general procedure A as an off-white solid (25.5 mg, 67%): *Rf* = 0.58 (20:1 DCM:MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (s, 1H), 8.12 (dd, *J* = 0.7, 8.9 Hz, 1H), 7.79 (dd, *J* = 2.2, 8.9 Hz, 1H), 7.47 – 7.41 (m, 4H), 7.32 (dd, *J* = 0.6, 2.1 Hz, 1H), 7.14 (td, *J* = 0.6, 7.7 Hz, 1H), 6.74 (ddd, *J* = 0.9, 1.8, 7.6 Hz, 1H), 6.68 – 6.63 (m, 2H), 3.68 (s, 3H), 2.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.9, 147.0, 144.8, 141.1, 140.0, 138.4, 132.9, 132.3, 130.8, 130.8, 129.9, 129.9, 128.6, 126.5, 123.1, 118.4, 117.4, 115.5, 114.6, 113.7, 28.0, 21.5; HRMS (ESI, $[M+H]^+$) calcd for $C_{24}H_{21}N_4O$ 381.1710, found 381.1721.

3-Methyl-8-(pyridin-3-yl)-1-(*m*-tolyl)-1,3-dihydro-2*H*-imidazo[4,5-*c*]quinolin-2-one (5f). Prepared by following the general procedure A as a pale yellow solid (23.1 mg, 63%): *Rf* = 0.40 (20:1 DCM:MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (d, *J* = 1.2 Hz, 1H), 8.57 – 8.53 (m, 2H), 8.18 (dt, *J* = 0.7, 8.9 Hz, 1H), 7.77 (ddd, *J* = 1.1, 2.2, 8.9 Hz, 1H), 7.67 – 7.63 (m, 1H), 7.52 (t, *J* = 7.7 Hz, 1H), 7.45 – 7.41 (m, 1H), 7.39 – 7.31 (m, 3H), 7.29 (ddd, *J* = 1.1, 4.8, 7.9 Hz, 1H), 3.67 (d, *J* = 1.1 Hz, 3H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8, 148.9, 148.1, 144.9, 140.5, 135.6, 135.2, 135.0, 134.1, 132.8, 131.5, 130.8, 129.9, 129.7, 129.2, 125.9, 125.6, 123.7, 123.3, 118.8, 115.5, 28.0, 21.4; HRMS (ESI, $[M+H]^+$) calcd for $C_{23}H_{19}N_4O$ 367.1553, found 367.1559.

5-(1-(3-Ethylphenyl)-3-methyl-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*c*]quinolin-8-yl)picolinaldehyde (5g). Prepared by following the general procedure A as a yellow solid (22.4 mg, 55%): *Rf* = 0.42 (20:1 DCM:MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.09 (m, 1H), 8.85 (m, 1H), 8.72 (m, 1H), 8.27 (dd, *J* = 1.8, 8.9 Hz, 1H), 7.96 (dq, *J* = 0.9, 8.1 Hz, 1H), 7.83 (ddt, *J* = 0.9, 2.1, 9.0 Hz, 1H), 7.78 (m, *J* = 0.9, 1.9, 8.1 Hz, 1H), 7.60 – 7.55 (m, 1H), 7.52 – 7.49 (m, 1H), 7.41 (d, *J* = 2.1 Hz, 1H), 7.37 (dd, *J* = 1.7, 7.2 Hz, 2H), 3.73 – 3.68 (m, 3H), 2.76 (q, *J* = 7.6 Hz, 2H), 1.23 (t, 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.0, 153.7, 151.8, 148.5, 147.1, 144.7, 139.5, 135.1, 135.0, 133.8, 132.9, 131.5, 130.3, 130.3, 129.9, 128.0, 125.9, 125.9, 123.5, 121.9, 119.8, 115.5, 28.8, 28.1, 15.6; HRMS (ESI, $[M+H]^+$) calcd for $C_{25}H_{21}N_4O_2$ 409.1659, found 409.1653.

4-(3-Methyl-2-oxo-1-(*o*-tolyl)-2,3-dihydro-1*H*-imidazo[4,5-*c*]quinolin-8-yl)benzenesulfonamide (5h). Prepared by following the general procedure A as an off-white solid (14.2 mg, 32%): *Rf* = 0.46 (20:1 DCM:MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.05 (s, 1H), 8.14 (dd, *J* = 0.6, 8.9 Hz, 1H), 7.93 (dd, *J* = 2.1, 8.9 Hz, 1H), 7.84 – 7.80 (m, 2H), 7.65 – 7.62 (m, 2H), 7.60 – 7.52 (m, 2H), 7.49 – 7.45 (m, 2H), 7.41 (s, 2H), 7.08 (dd, *J* = 0.6, 2.1 Hz, 1H), 3.64 (s, 3H), 2.09 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 152.4, 143.9, 143.3, 142.2, 137.0, 135.7, 134.3, 134.0, 131.3, 130.9, 130.2, 129.4, 128.4, 127.7, 126.8, 126.3, 125.6, 123.4, 117.4, 114.8, 27.7, 17.0; HRMS (ESI, $[M+H]^+$) calcd for $C_{24}H_{21}N_4O_3S$ 445.1329, found 445.1347.

1-(4-Methoxyphenyl)-3-methyl-8-(thiophen-3-yl)-1,3-dihydro-2*H*-imidazo[4,5-*c*]quinolin-2-one (5i). Prepared by following the general procedure A as an off-white solid (30.9 mg, 80%): *Rf* = 0.57 (20:1 DCM:MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (d, *J* = 0.9 Hz, 1H), 8.10 (dd, *J* = 0.7, 8.9 Hz, 1H), 7.81 (dd, *J* = 2.1, 8.9

Hz, 1H), 7.48 – 7.43 (m, 2H), 7.38 (dd, *J* = 0.7, 2.1 Hz, 1H), 7.34 – 7.31 (m, 1H), 7.29 (dd, *J* = 1.4, 2.9 Hz, 1H), 7.18 – 7.14 (m, 2H), 7.04 (dt, *J* = 1.1, 5.1 Hz, 1H), 3.94 (s, 3H), 3.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.5, 153.9, 144.5, 141.2, 132.9, 132.0, 130.9, 129.9, 129.7, 127.8, 126.6, 125.9, 125.7, 123.0, 120.9, 117.1, 115.5, 115.3, 55.8, 27.9; HRMS (ESI, $[M+H]^+$) calcd for $C_{22}H_{18}N_3O_2S$ 388.1114, found 388.1106.

1-(3-Methoxyphenyl)-3-methyl-8-(pyridin-3-yl)-1,3-dihydro-2*H*-imidazo[4,5-*c*]quinolin-2-one (5j). Prepared by following the general procedure A as an off-white solid (19.5 mg, 51%): *Rf* = 0.42 (20:1 DCM:MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.02 (s, 1H), 8.54 (dt, *J* = 1.5, 3.9 Hz, 2H), 8.13 (dd, *J* = 0.6, 8.9 Hz, 1H), 7.93 (dd, *J* = 2.1, 8.9 Hz, 1H), 7.80 (ddd, *J* = 1.6, 2.4, 7.9 Hz, 1H), 7.62 (ddd, *J* = 0.6, 7.7, 8.2 Hz, 1H), 7.45 (ddd, *J* = 0.9, 4.8, 8.0 Hz, 1H), 7.31 – 7.23 (m, 4H), 3.81 (s, 3H), 3.61 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.8, 153.3, 149.3, 147.7, 144.4, 136.9, 135.1, 134.4, 134.3, 134.2, 131.5, 131.2, 129.2, 125.9, 124.4, 123.7, 121.4, 118.4, 115.9, 115.2, 115.1, 56.1, 28.1; HRMS (ESI, $[M+H]^+$) calcd for $C_{23}H_{19}N_4O_2$ 383.1503, found 383.1513.

1-(3-Hydroxyphenyl)-3-methyl-8-(pyridin-3-yl)-1,3-dihydro-2*H*-imidazo[4,5-*c*]quinolin-2-one (5k). Prepared by following the general procedure A as a yellow solid (21.6 mg, 59%): *Rf* = 0.37 (20:1 DCM:MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (d, *J* = 1.0 Hz, 1H), 8.57 (d, *J* = 2.5 Hz, 1H), 8.51 (dd, *J* = 1.6, 4.9 Hz, 1H), 8.18 (dd, *J* = 1.0, 8.9 Hz, 1H), 7.82 (ddd, *J* = 1.5, 2.4, 8.0 Hz, 1H), 7.75 (dd, *J* = 2.2, 8.9 Hz, 1H), 7.52 (d, *J* = 2.1 Hz, 1H), 7.43 (t, *J* = 8.0 Hz, 1H), 7.38 – 7.34 (m, 1H), 7.09 – 7.00 (m, 3H), 3.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 153.9, 148.1, 147.4, 144.9, 136.0, 134.9, 134.7, 132.9, 131.4, 131.0, 129.9, 126.0, 124.2, 123.3, 119.5, 119.1, 117.8, 116.4, 115.5, 28.1; HRMS (ESI, $[M+H]^+$) calcd for $C_{22}H_{17}N_4O_2$ 369.1346, found 369.1358.

3-(1-(2-Hydroxyphenyl)-3-methyl-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*c*]quinolin-8-yl)benzonitrile (5l). Prepared by following the general procedure A as a tan solid (13.2 mg, 34%): *Rf* = 0.46 (20:1 DCM:MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.17 (s, 1H), 8.99 (s, 1H), 8.10 (dd, *J* = 0.6, 8.9 Hz, 1H), 7.95 (dd, *J* = 2.2, 8.9 Hz, 1H), 7.81 (dt, *J* = 1.3, 7.6 Hz, 1H), 7.73 (td, *J* = 0.7, 1.9 Hz, 1H), 7.70 (ddd, *J* = 1.2, 2.0, 7.9 Hz, 1H), 7.62 (td, *J* = 0.7, 7.9 Hz, 1H), 7.55 – 7.48 (m, 2H), 7.33 (dd, *J* = 0.7, 2.2 Hz, 1H), 7.21 – 7.16 (m, 1H), 7.09 (td, *J* = 1.4, 7.6 Hz, 1H), 3.61 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.6, 152.9, 143.8, 140.2, 134.6, 133.8, 131.3, 131.1, 130.9, 130.7, 130.7, 130.3, 129.8, 129.2, 125.1, 123.3, 122.4, 119.9, 118.4, 117.7, 116.8, 115.1, 112.3, 27.6; HRMS (ESI, $[M+H]^+$) calcd for $C_{24}H_{17}N_4O_2$ 393.1346, found 393.1351.

1-(4-Fluorophenyl)-8-(furan-3-yl)-3-methyl-1,3-dihydro-2*H*-imidazo[4,5-*c*]quinolin-2-one (5m). Prepared by following the general procedure A as a yellow solid (24.0 mg, 67%): *Rf* = 0.80 (20:1 DCM:MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (s, 1H), 8.09 (dd, *J* = 0.6, 8.9 Hz, 1H), 7.68 (dd, *J* = 2.0, 8.9 Hz, 1H), 7.59 (dd, *J* = 0.9, 1.6 Hz, 1H), 7.57 – 7.52 (m, 2H), 7.44 (t, *J* = 1.7 Hz, 1H), 7.39 – 7.34 (m, 2H), 7.20 (dd, *J* = 0.6, 2.0 Hz, 1H), 6.28 (dd, *J* = 0.9, 1.9 Hz, 1H), 3.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 153.8, 144.7, 144.3, 139.2, 132.1, 131.6, 131.3, 130.9, 130.8, 130.3, 129.1, 125.8, 125.6, 123.3, 117.3, 117.0, 116.2, 115.6, 108.2, 28.0; HRMS (ESI, $[M+H]^+$) calcd for $C_{21}H_{15}FN_3O_2$ 360.1143, found 360.1136.

1-(3-Chlorophenyl)-3-methyl-8-(pyridin-3-yl)-1,3-dihydro-2*H*-imidazo[4,5-*c*]quinolin-2-one (5n). Prepared by following the general procedure A as an off-white solid (20.0 mg, 52%): *Rf* = 0.38 (20:1 DCM:MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (d, *J* = 1.4 Hz, 1H), 8.63 (s, 1H), 8.60 – 8.55 (m, 1H), 8.22 (dt, *J* = 0.7, 8.9 Hz, 1H), 7.79 (ddd, *J* = 1.0, 1.8, 8.4 Hz, 1H), 7.70 (ddd, *J* = 1.7, 2.4, 7.9 Hz, 1H), 7.63 – 7.55 (m, 3H), 7.50 – 7.46 (m, 1H), 7.42 – 7.39 (m, 1H), 7.33 (ddd, *J* = 0.8, 4.8, 7.8 Hz, 1H), 3.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.5, 149.1, 148.2, 144.9, 136.4, 135.7, 135.7, 135.6, 134.3, 132.9, 131.7, 131.1, 130.2, 129.1, 129.0, 126.8, 126.4, 123.8, 123.5, 118.6, 115.4, 28.1; HRMS (ESI, $[M+H]^+$) calcd for $C_{22}H_{16}ClN_4O$ 387.1007, found 387.1000.

3-Methyl-8-(pyridin-3-yl)-1-(3-(trifluoromethyl)phenyl)-1,3-dihydro-2*H*-imidazo[4,5-*c*]quinolin-2-one (5o). Prepared by following the general procedure B as an off-white solid (26.9 mg, 64%): *Rf* = 0.33 (20:1 DCM:MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (s, 1H), 8.61 – 8.54 (m, 2H), 8.24 (dd, *J* = 0.6, 8.8 Hz, 1H), 7.92 – 7.86 (m, 2H), 7.83 – 7.77 (m, 3H), 7.62 (ddd, *J* = 1.7, 2.4, 7.9 Hz, 1H), 7.33 – 7.28 (m, 2H), 3.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.5, 149.2, 148.2, 144.9, 136.0, 135.9, 135.6, 134.3, 133.0, 132.9, 132.6, 132.2, 131.9, 130.9, 128.9, 126.7, 126.5, 125.6, 123.8, 123.6, 118.4, 115.4, 28.1; HRMS (ESI, $[M+H]^+$) calcd for $C_{23}H_{16}F_3N_4O$ 421.1271, found 421.1281.

8-(6-Aminopyridin-3-yl)-3-methyl-1-(3-(trifluoromethyl)phenyl)-1,3-dihydro-2*H*-imidazo[4,5-*c*]quinolin-2-one (5p). Prepared by following the general procedure B as an off-white solid (26.5 mg, 61%): *Rf* = 0.33 (20:1 DCM:MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.92 (s, 1H), 8.19 – 8.15 (m, 1H), 8.08 – 7.98 (m, 3H), 7.96 – 7.90 (m, 1H), 7.86 (dd, *J* = 0.8, 2.6 Hz, 1H), 7.78 (dd, *J* = 2.1, 8.9 Hz, 1H), 7.33 (dd, *J* = 2.6, 8.7 Hz, 1H), 6.98 – 6.93 (m, 1H), 6.41 (dd, *J* = 0.8, 8.7 Hz, 1H), 6.17 (s, 2H), 3.56 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.9, 153.4, 146.0, 143.8, 136.9, 135.8, 135.3, 133.9, 133.4, 131.7, 131.3, 130.9, 128.4, 126.7, 126.5, 125.4, 123.7, 123.1, 122.8, 115.3, 115.1, 108.4, 28.1; HRMS (ESI, $[M+Na]^+$) calcd for $C_{23}H_{16}F_3N_5NaO$ 458.1199, found 458.1220.

8-(6-Hydroxypyridin-3-yl)-3-methyl-1-(3-(trifluoromethyl)phenyl)-1,3-dihydro-2*H*-imidazo[4,5-*c*]quinolin-2-one (5q). Prepared by following the general procedure B as an off-white solid (23.9 mg, 55%): *Rf* = 0.23 (20:1 DCM:MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.98 (s, 1H), 8.17 (d, *J* = 2.2 Hz, 1H), 8.09 – 8.01 (m, 3H), 7.96 (d, *J* = 7.8 Hz, 1H), 7.81 (dd, *J* = 2.2, 9.0 Hz, 1H), 7.50 (d, *J* = 2.8 Hz, 1H), 7.26 (dd, *J* = 2.8, 9.6 Hz, 1H), 6.92 (d, *J* = 2.1 Hz, 1H), 6.32 (d, *J* = 9.6 Hz, 1H), 3.60 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.5, 152.9, 143.4, 138.7, 136.3, 133.5, 133.4, 133.2, 131.2, 130.9, 130.7, 130.4, 128.0, 126.3, 126.0, 126.0, 125.0, 124.6, 123.4, 122.2, 115.0, 114.7, 27.7; HRMS (ESI, $[M+H]^+$) calcd for $C_{23}H_{16}F_3N_4O_2$ 437.1220, found 437.1217.

3-(3-Methyl-2-oxo-1-(4-(trifluoromethyl)phenyl)-2,3-dihydro-1*H*-imidazo[4,5-*c*]quinolin-8-yl)benzonitrile (5r). Prepared by following the general procedure B as a white solid (22.1 mg, 50%): *Rf* = 0.58 (20:1 DCM:MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (d, *J* = 1.1 Hz, 1H), 8.23 (dd, *J* = 1.1, 8.9 Hz, 1H), 7.98 – 7.94 (m, 2H), 7.81 – 7.77 (m, 1H), 7.73 (dt, *J* = 1.0, 8.8 Hz, 2H), 7.67 – 7.65 (m, 1H), 7.61 (s, 1H), 7.48 – 7.42 (m, 2H), 7.23 (d, *J* = 2.1 Hz, 1H), 3.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4, 145.1, 141.2, 138.7, 136.6, 133.2, 132.1, 132.0, 131.5, 131.0, 130.5, 130.0, 129.3, 129.0, 127.3, 127.3, 127.3, 126.1, 123.7, 118.6, 118.4, 115.3, 113.6, 28.2; HRMS (ESI, $[M+H]^+$) calcd for $C_{25}H_{16}F_3N_4O$ 445.1271, found 445.1280.

8-(6-Methoxypyridin-3-yl)-3-methyl-1-phenethyl-1,3-dihydro-2*H*-imidazo[4,5-*c*]quinolin-2-one (5s). Prepared by following the general procedure A as a white solid (17.2 mg, 42%): *Rf* = 0.63 (20:1 DCM:MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (s, 1H), 8.52 (dd, *J* = 0.8, 2.6 Hz, 1H), 8.26 (dd, *J* = 0.6, 2.0 Hz, 1H), 8.23 (dd, *J* = 0.6, 8.9 Hz, 1H), 7.86 (dd, *J* = 2.6, 8.6 Hz, 1H), 7.82 (dd, *J* = 2.0, 8.9 Hz, 1H), 7.26 – 7.20 (m, 5H), 6.88 (dd, *J* = 0.8, 8.6 Hz, 1H), 4.66 – 4.60 (m, 2H), 4.04 (s, 3H), 3.62 (s, 3H), 3.23 – 3.18 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2, 154.0, 145.6, 144.6, 137.7, 137.3, 136.4, 132.5, 131.9, 129.4, 129.2, 129.0, 128.9, 127.2, 126.3, 123.2, 117.7, 116.0, 111.3, 53.9, 44.9, 35.8, 27.9; HRMS (ESI, $[M+H]^+$) calcd for $C_{25}H_{23}N_4O_2$ 411.1816, found 411.1802.

1-Benzyl-3-methyl-8-(pyridin-3-yl)-1,3-dihydro-2*H*-imidazo[4,5-*c*]quinolin-2-one (5t). Prepared by following the general procedure A as an off-white solid (19.0 mg, 52%): *Rf* = 0.45 (20:1 DCM:MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (s, 1H), 8.61 – 8.58 (m, 1H), 8.56 – 8.52 (m, 1H), 8.17 (dd, *J* = 0.6, 8.9 Hz, 1H), 7.99 (dd, *J* = 0.7, 2.1 Hz, 1H), 7.72 (dd, *J* = 2.0, 8.8 Hz, 1H), 7.56 (ddd, *J* = 1.6, 2.4, 7.9 Hz, 1H), 7.40 – 7.35 (m, 2H), 7.32 (ddd, *J* = 1.4, 3.4, 7.9 Hz, 2H), 7.28 (dd, *J* = 0.7, 1.5 Hz, 1H), 7.26 (d, *J* = 1.2 Hz, 1H), 5.61 (s, 2H), 3.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 149.0, 148.5, 144.8, 136.2, 135.9, 134.6, 132.8, 131.5, 129.8, 129.4, 128.1, 126.2, 126.1, 123.6, 123.3, 119.6, 115.7, 46.8, 28.1; HRMS (ESI, $[M+H]^+$) calcd for $C_{23}H_{19}N_4O$ 367.1553, found 367.1548.

2-Methyl-2-(4-(3-methyl-2-oxo-8-(quinolin-3-yl)-2,3-dihydro-1*H*-imidazo[4,5-*c*]quinolin-1-yl)phenyl)propanenitrile (5u). Prepared by following the general procedure A as a white solid (39.8 mg, 85%): *Rf* = 0.33 (20:1 DCM:MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (d, *J* = 2.3 Hz, 1H), 8.84 (s, 1H), 8.26 (d, *J* = 8.8 Hz, 1H), 8.11 – 8.05 (m, 2H), 7.93 (dd, *J* = 2.1, 8.8 Hz, 1H), 7.84 (dd, *J* = 1.6, 8.2 Hz, 1H), 7.80 (d, *J* = 2.1 Hz, 1H), 7.79 (d, *J* = 2.2 Hz, 1H), 7.72 (ddd, *J* = 1.5, 6.9, 8.4 Hz, 1H), 7.66 – 7.62 (m, 2H), 7.58 (ddd, *J* = 1.3, 6.8, 8.1 Hz, 1H), 7.39 (d, *J* = 1.7 Hz, 1H), 3.71 (s, 3H), 1.81 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.7, 149.4, 147.6, 144.9, 143.8, 135.6, 135.0, 133.3, 133.0, 132.8, 131.8, 129.9, 129.4, 129.4, 129.4, 128.1, 127.9, 127.4, 127.0, 126.4, 124.0, 123.5, 119.0, 115.5, 37.6, 29.5, 28.1; HRMS (ESI, $[M+H]^+$) calcd for $C_{30}H_{24}N_5O$ 470.1975, found 470.1980.

8-(6-methoxypyridin-3-yl)-3-methyl-1-(4-(piperazin-1-yl)-3-(trifluoromethyl)phenyl)-1,3-dihydro-2H-imidazo[4,5-c]quinolin-2-one (5v). Prepared by following the general procedure C as a pale yellow solid (2.27 g, 77%): *Rf* = 0.17 (20:1 DCM:MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (s, 1H), 8.19 – 8.14 (m, 2H), 7.83 (d, *J* = 2.5 Hz, 1H), 7.75 (dd, *J* = 2.1, 8.9 Hz, 1H), 7.74 – 7.70 (m, 1H), 7.62 – 7.59 (m, 1H), 7.49 (dd, *J* = 2.6, 8.7 Hz, 1H), 7.12 (dd, *J* = 0.6, 2.1 Hz, 1H), 6.69 (dd, *J* = 0.8, 8.6 Hz, 1H), 3.93 (s, 3H), 3.69 (s, 3H), 3.11 – 3.06 (m, 4H), 3.03 (dt, *J* = 3.5, 5.2 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.0, 154.5, 153.6, 145.1, 144.7, 137.0, 135.7, 133.3, 132.6, 131.6, 131.5, 129.1, 129.0, 128.8, 128.7, 128.1, 126.0, 125.9, 123.3, 117.4, 115.4, 111.0, 54.9, 53.6, 46.5, 28.1; HRMS (ESI, $[M+H]^+$) calcd for $C_{28}H_{26}F_3N_6O_2$ 535.2064, found 535.2042.

General procedure D for the synthesis of imidazo[4,5-*c*]quinolin-one analog (3). To a 0.5 mL-2.0 mL conical shaped microwave reaction vial charged with *N*-H carbamate **1a** or *N*-methyl carbamate **1b** (36 mg, 0.1 mmol) was added 1.0 mL of 3-pentanol. With occasional shaking, the vial was heated until the solid is completely dissolved. After cooling to room temperature, the orange solution was added aniline **2** (0.2 mmol), followed by HCl (0.3 mmol, 4.0 M in dioxane). The mixture was homogenized and heated by microwave at 200 °C or 230 °C at high absorption level for 20 min. After cooling to room temperature, 5 mL of saturated aqueous $NaHCO_3$ was added. The solution was extracted with DCM (7 mL × 3). DCM layers were combined, dried over $MgSO_4$, filtered, and concentrated. The residual mixture was then passed through a silica gel column, and the product eluted with DCM and MeOH.

8-Bromo-1-phenyl-1,3-dihydro-2*H*-imidazo[4,5-*c*]quinolin-2-one (3a). Prepared by following the general procedure D at 200 °C as an off-white solid (29.5 mg, 87%): *Rf* = 0.20 (20:1 DCM:MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.81 (s, 1H), 8.79 (s, 1H), 7.93 (d, *J* = 9.1 Hz, 1H), 7.68 (dd, *J* = 2.1, 5.0 Hz, 3H), 7.65 – 7.59 (m, 3H), 7.05 (d, *J* = 2.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 153.4, 142.6, 134.9, 134.6, 132.3, 129.9, 129.7, 129.4, 128.8, 128.6, 122.3, 122.1, 118.7, 116.0; LC-MS m/z = 340 $[M+H]^+$, $C_{16}H_{10}BrN_3O$, requires 339.

1-Benzyl-8-bromo-1,3-dihydro-2*H*-imidazo[4,5-*c*]quinolin-2-one (3b). Prepared by following the general procedure D at 200 °C as an off-white solid (21.9 mg, 62%): *Rf* = 0.20 (20:1 DCM:MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.77 (s, 1H), 8.06 (d, *J* = 2.1 Hz, 1H), 7.90 (d, *J* = 9.0 Hz, 1H), 7.63 (dd, *J* = 2.2, 9.0 Hz, 1H), 7.38 – 7.31 (m, 2H), 7.29 – 7.22 (m, 3H), 5.53 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.3, 142.5, 136.6, 134.6, 132.1, 129.6, 129.0, 128.6, 127.6, 126.0, 123.3, 122.2, 119.1, 116.1, 44.7; LC-MS m/z = 354 $[M+H]^+$, $C_{17}H_{12}BrN_3O$, requires 353.

8-Bromo-1-(3-(trifluoromethyl)phenyl)-1,3-dihydro-2*H*-imidazo[4,5-*c*]quinolin-2-one (3c). Prepared by following the general procedure D at 200 °C as a pale yellow solid (27.2 mg, 67%): *Rf* = 0.20 (20:1 DCM:MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.80 (s, 1H), 8.15 (ddt, *J* = 0.6, 1.3, 2.0 Hz, 1H), 8.06 (dtt, *J* = 0.6, 1.3, 7.6 Hz, 1H), 8.02 – 7.98 (m, 1H), 7.96 – 7.91 (m, 2H), 7.65 (dd, *J* = 2.2, 9.0 Hz, 1H), 7.02 (dd, *J* = 0.4, 2.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 153.4, 142.6, 135.8, 134.7, 133.2, 132.4, 131.2, 130.8, 130.4, 129.6, 128.4, 126.4, 126.0, 122.5, 122.4, 122.0, 116.0; LC-MS m/z = 408 $[M+H]^+$, $C_{17}H_9BrF_3N_3O$, requires 407.

8-Bromo-3-methyl-1-phenyl-1,3-dihydro-2*H*-imidazo[4,5-*c*]quinolin-2-one (3d). Prepared by following the general procedure D at 230 °C as an off-white solid (27.9 mg, 79%): *Rf* = 0.35 (20:1 DCM:MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (s, 1H), 7.95 (d, *J* = 9.1 Hz, 1H), 7.67 – 7.62 (m, 3H), 7.57 (dd, *J* = 2.2, 9.0 Hz, 1H), 7.51 – 7.46 (m, 2H), 7.23 (d, *J* = 2.2 Hz, 1H), 3.66 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.7, 143.9, 134.9, 132.8, 132.3, 130.6, 130.3, 130.1, 128.5, 128.4, 123.5, 123.1, 120.4, 116.4, 28.0; LC-MS m/z = 354 $[M+H]^+$, $C_{17}H_{12}BrN_3O$, requires 353.

1-Benzyl-8-bromo-3-methyl-1,3-dihydro-2*H*-imidazo[4,5-*c*]quinolin-2-one (3e). Prepared by following the general procedure D at 230 °C as an off-white solid (22.0 mg, 60%): *Rf* = 0.37 (20:1 DCM:MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (s, 1H), 8.07 (d, *J* = 2.1 Hz, 1H), 7.93 (d, *J* = 9.1 Hz, 1H), 7.57 (dd, *J* = 2.2, 9.1 Hz, 1H), 7.36 – 7.32 (m, 2H), 7.30 – 7.26 (m, 3H), 5.53 (s, 2H), 3.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 143.8, 135.8, 132.7, 132.4, 130.5, 129.3, 128.6, 128.2, 126.5, 123.4, 123.4, 120.7, 116.5, 46.8, 28.1; LC-MS m/z = 368 $[M+H]^+$, $C_{18}H_{14}BrN_3O$, requires 367.

8-Bromo-3-methyl-1-(3-(trifluoromethyl)phenyl)-1,3-dihydro-2*H*-imidazo[4,5-*c*]quinolin-2-one (3f). Prepared by following the general procedure D by heating the mixture of *N*-H carbamate **1a** (0.1 mmol), aniline **2a** (0.4 mmol) and HCl (0.5 mmol) in 3-pentanol (1 mL) at 230 °C, as a white solid (33.3 mg, 79%): *Rf* = 0.42 (20:1 DCM:MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (s, 1H), 7.98 (d, *J* = 9.1 Hz, 1H), 7.92 – 7.87 (m, 1H), 7.83 – 7.77 (m, 2H), 7.76 – 7.71 (m, 1H), 7.61 (dd, *J* = 2.2, 9.1 Hz, 1H), 7.23 (dd, *J* = 0.4, 2.2 Hz, 1H), 3.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4, 144.0, 135.5, 133.0, 132.6, 131.8, 130.9, 130.8, 127.7, 126.7, 125.5, 124.8, 123.7, 122.7, 122.1, 120.8, 116.2, 28.1; LC-MS m/z = 422 $[M+H]^+$, $C_{18}H_{11}BrF_3N_3O$, requires 421.

Isopropyl (6-bromo-4-(phenylamino)quinolin-3-yl)carbamate (4a). Prepared by following the general procedure C by heating the mixture of *N*-H carbamate **1a** (0.1 mmol), aniline **2a** (0.15 mmol) and HCl (0.09 mmol) in 3-pentanol (1 mL) at 150 °C for 10 minutes, as a white solid (14.5 mg, 35%): *Rf* = 0.51 (20:1 DCM:MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.22 (s, 1H), 7.95 (d, *J* = 2.2 Hz, 1H), 7.90 (d, *J* = 8.9 Hz, 1H), 7.64 (dd, *J* = 2.2, 8.9 Hz, 1H), 7.20 (dd, *J* = 7.4, 8.6 Hz, 2H), 6.96 (s, 1H), 6.95 – 6.90 (m, 1H), 6.69 – 6.65 (m, 2H), 6.41 (s, 1H), 4.99 (p, *J* = 6.3 Hz, 1H), 1.25 (s, 3H), 1.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.0, 147.5, 145.2, 143.3, 133.9, 132.0, 131.6, 129.7, 126.1, 126.0, 125.3, 121.4, 121.0, 116.1, 70.0, 22.1; LC-MS m/z = 400 $[M+H]^+$, $C_{19}H_{18}BrN_3O_2$, requires 399.

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[14] Only trace amount of **5v** was formed under microwave-assisted conditions, possibly due to poor solubility of **2e** in 3-pentanol.

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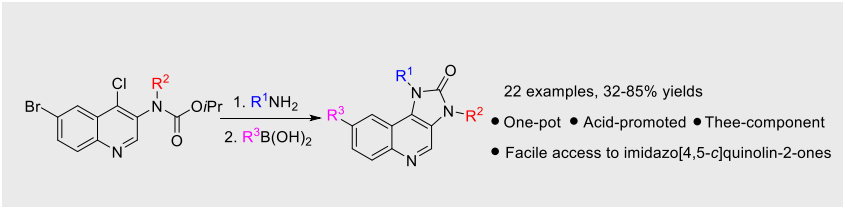

A novel acid-promoted two-step synthesis of imidazo[4,5-*c*]quinolin-2-ones from carbamate and amines was developed. In combination with subsequent Suzuki coupling, this three-component one-pot procedure provides rapid access to various bioactive imidazo[4,5-*c*]quinolin-2-one derivatives.

*One-pot synthesis

Key Topic*

*Xiao Lu, Myunghoon Kim, Meghan J. Orr, Hao Li, and Wenwei Huang**

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Efficient One-Pot Synthesis of Imidazo[4,5-*c*]quinolin-2-ones

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