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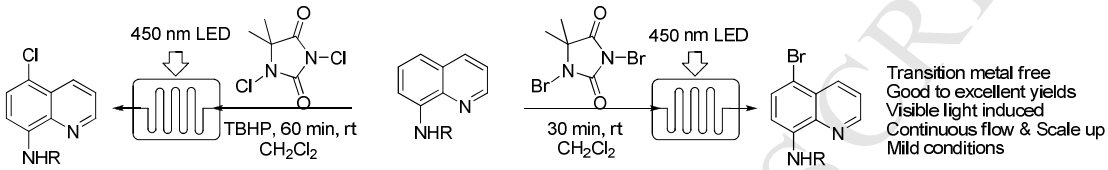

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ABSTRACT

An efficient and convenient method for remote C5 halogenation of 8-aminoquinoline derivatives was developed in continuous flow at room temperature. This method employed inexpensive 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) and 1,3-dichlro-5,5-dimethylhydantoin (DCDMH) as halogenation reagents and visible light to catalyze the reaction. The reaction is scalable to gram-scale and proceeded with air and moisture tolerance, good functional group compatibility, and outstanding site selectivity, providing a new pathway for C5 halogenation of 8-aminoquinolines.

1. Introduction

Quinoline is one of the most privileged structural motifs because of its existence in many natural products[1], drugs[2], and pesticides[3]. There have been a large number of reports on quinolines not only as pharmaceuticals[4], but also as a ligand for various organic synthesis[5]. Moreover, some reports suggested the therapeutic effects of quinoline-based derivatives[6]. In recent years, halogenated quinolines have been constantly found in many natural products and bioactive molecules, which can be used as intermediates in the synthesis of substituted quinolines. Therefore, halogenation of quinolines, especially halogenation at the C5 position, has been becoming an intensive research focus on synthetic chemistry[7]. Some important bioactive molecules with halogenated quinoline unit are shown in Fig 1[8].

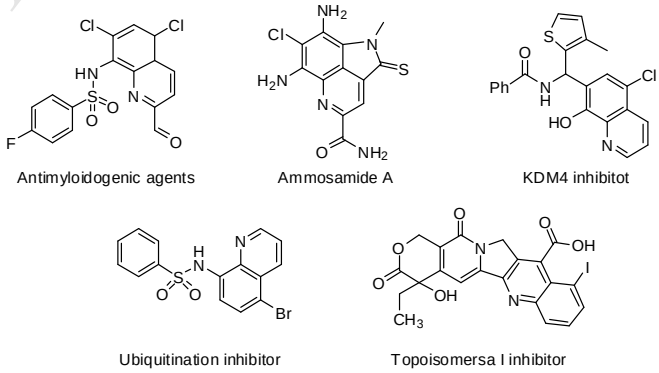

Figure 1. Representative natural products and bioactive molecules.

In 2013, Stahl and co-workers firstly reported Cu(I) catalyzed C5 chlorination of 8-aminoquinoline using LiCl as chlorination reagent and molecular O_2 as an oxidant[9]. Following this work, tremendous interest focused on C5 functionalization of 8-aminoquinolines. The first example of transition-metal-free C5 halogenation of 8-aminoquinoline with NaX (X=Cl, Br) was reported by Li[10]. However, a certain amount of oxone and excess loading of NaX were used in this method. Meanwhile, Wu developed a protocol of transition-metal coupling photoredox catalyst catalyzed C5 halogenation[11]. In 2018, S. C. Ghosh[12] disclosed C5 halogenation by heterogeneous Cu-MnO under visible light irradiation in which NXS(X= Cl, Br, I) were of halogen source. Nevertheless, in most cases, the reaction employed transition-metal and/or oxidant (or additives), which makes the reactions uneconomical and environmentally unfriendly, limiting the practicality for large-scale use. The reactions also involved unfavorable stoichiometric amounts of the halogen source and high temperature. Therefore new method with high regioselectivity by using green reagent under the mild conditions is still thirsted.

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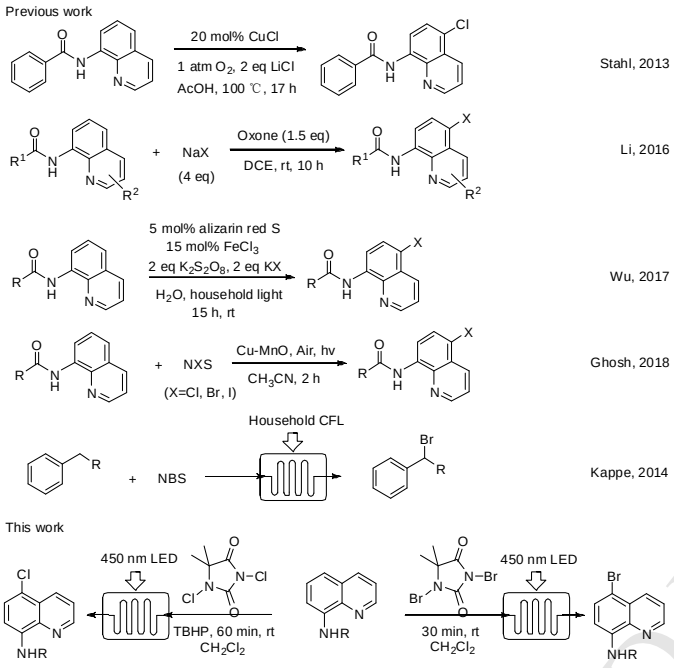
Visible-light catalyzed reactions[13] and continuous flow reactions[14] have captured much attention of academia because of their safety and sustainability. Studies have showed that economic savings can be reached in some cases through transforming batch reaction into a continuous process. Kappe [15] reported a scalable procedure for light-induced benzylic brominations showing the advantages of continuous flow. Herein, we report a mild and environmental-friendly method for visible light induced halogenation of 8-aminoquinolines by using easy-available 1,3-dibromo-5,5-dimethylhydantoin (DBDMH)/1,3-dibromo-5,5-dimethylhydantoin (DCDMH) in continuous flow, in which outstanding regioselectivity and higher yields were obtained in a short period of time.



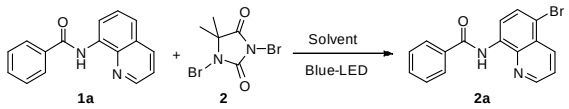
Scheme 1. Remote halogenation of quinoline at C5 position.

2. Results and discussion

Initially, the bromination of *N*-8-quinolinyl-benzamide (**1a**) with DBDMH (**2**) was selected as a model to screen the reaction parameters in batch. When the reaction was carried out at room temperature for 4 h under irradiation of blue-LED using 1,4-dioxane as solvent, only 11% yield of C5 brominated product (**2a**) was obtained (Table 1, entry 1). Solvents were screened firstly since solvent plays an important role in photo-induced reactions. Either tetrahydrofuran (THF) or *N*, *N*-dimethyl formamide (DMF) used as the solvent, resulted in poor remote C5-brominated conversions (Table 1, entries 2, 4). Other solvents such as methanol (CH_3OH), acetonitrile (CH_3CN), and dichloromethane (CH_2Cl_2), however, gave the desired product **2a** in excellent yields of 92-95% (Table 1, entries 3, 5, 6). Considering of the poor solubility of **2a** in CH_3OH and CH_3CN, the CH_2Cl_2 was selected as solvent in the following reactions. For the control experiments, the reactions were carried out in the dark and the yield of **2a** was drastically reduced to 45% (Table 1, entry 7), and with Ar instead of open-air atmosphere there was no significant improvement of the **2a** yield. Transitioning to continuous flow using CH_2Cl_2 as solvent, the residence time and the amount of DBDMH were tested. To our delight, even within 30 minutes of residence time in flow, the reaction went to end and the C5-brominated product **2a** was obtained in a satisfactory yield of 90% (Table 1, entries 9, 10). Keeping the residence time at 30 min at a flow rate of 53 μL • min^{-1}, and increasing the

Table 1

Optimization of the bromination reaction conditions[a,c]



Entry	Solvent	DBDMH/equiv.	Time/min	Yield[c]/%
1	1,4-dioxane	0.5	240	11
2	THF	0.5	240	9
3	CH_3OH	0.5	240	92
4	DMF	0.5	240	18
5	CH_3CN	0.5	240	94
6	CH_2Cl_2	0.5	240	95
7[d]	CH_2Cl_2	0.5	240	45
8[e]	CH_2Cl_2	0.5	240	95
9[b]	CH_2Cl_2	0.5	30	90
10[b]	CH_2Cl_2	0.5	50	90
11[b]	CH_2Cl_2	0.55	30	94
12[b]	CH_2Cl_2	0.6	30	92
13[b]	CH_2Cl_2	0.55	20	76
14[b]	CH_2Cl_2	0.55	40	92

[a]Conditions: **1a**, (0.2 mmol), solvent (2 mL) at r.t. under irradiation of 15 W blue-LED in a batch in air. [b]**1a**, (0.2 mmol), solvent (2 mL) at r.t. under irradiation of 15 W blue LED in continuous flow in air. [c]GC yield. [d]Dark. [e]Ar atmosphere.

amount of DBDMH to 0.55 equivalent, the yield of **2a** reached up to 94% (Table 1, entry 11). Further increasing the loading of DBDMH, however, the yield of brominated product just remains unchanged (Table 1, entry 12). Either prolonged or shorten resident time did not lead to the higher yield (Table 1, entries 13-14). Thus optimized reaction conditions in continuous flow were achieved using 0.55 equivalent of DBDMH in CH_2Cl_2 at ambient temperature for 30 min under irradiation of blue-LED in air.

Having identified the optimal reaction conditions for bromination of **1a** with DBDMH, the substrate scope were then examined in continuous flow (Table 2). Both the electron-donating (CH_3, OCH_3) (**2b–2e**) and electron-withdrawing (F, Cl) (**2f–2h**) substituted benzamides exhibited good reactivity affording the desired products in good to excellent yields. The yields of benzamides bearing electron-donating groups are higher than those bearing electron-withdrawing groups. Moreover, the alkyl amides could also provide the desired brominated products in good yields (**2i-2l**). Furthermore, the heteroaromatic amide was also compatible in this process and delivered corresponding product in good yield (**2m**). Surprisingly, **1n**, which is not easy to halogenate under metal catalyst[8][16] or transition metal free conditions[7c][17], served well under the optimal conditions (**2n**). This methodology was successfully applied to sulfonamide giving the target products in moderate to good yields (**2o-2q**).

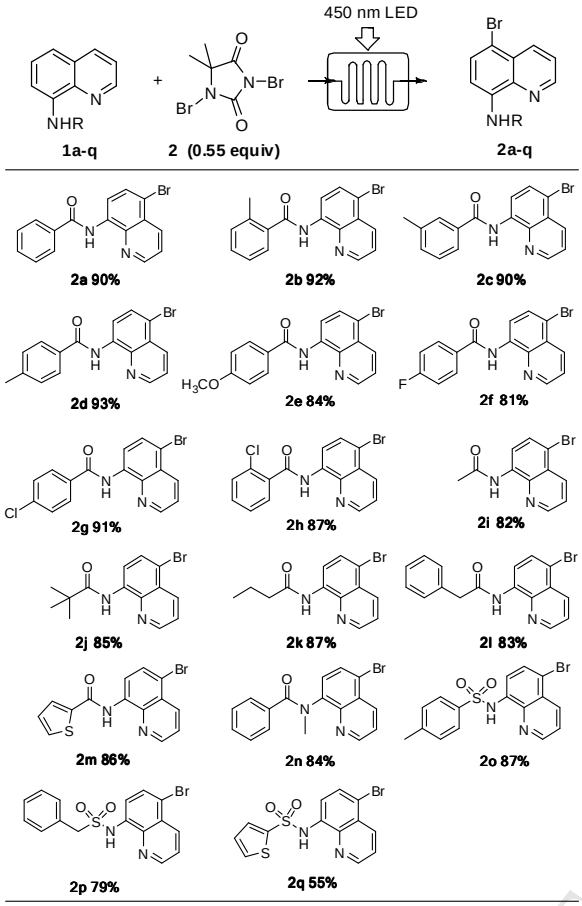
Gram-scale up reaction

One of the advantages of the continuous flow system is that the reaction can be scaled up easily in contrast with batch, where a larger scale requires a corresponding new reactor. To demonstrate the utility of the protocol, *N*-8-quinolinyl-benzamide (5 mmol, 1.240 g) was used under the optimized reaction conditions at 53.3 μL • min^{-1} flow rate in continuous flow where

the desired product **2a** was obtained in 85% yield (1.390 g) after purification on silica gel.

Table 2

Substrate scope of the C5 bromination of quinolines[a,b]



[a]Conditions: Substituted quinolines (0.2 mmol), DBDMH (0.55 equiv.), DCM (2 mL) under irradiation of 15 W blue-LED in continuous flow for 30 min in air. [b]Isolated yields on silica gel column chromatography.

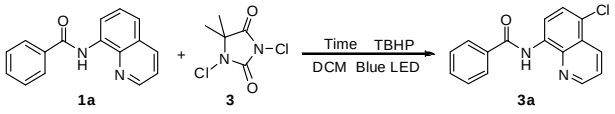
C5 chlorination of 8-aminoquinolines

Encouraged by the good results of bromination reaction, this reaction system was applied to the corresponding chlorination of 8-aminoquinoline derivatives using DCDMH (**3**). Unfortunately, trace C5 chlorination product was detected (Table 3, Entry 17). However, adding 2.1 equivalents of *tert*-butyl hydroperoxide (TBHP), 13% yield of **3a** quinoline chlorination at the C5 position was observed. Then the reaction conditions were further optimized as follows: 1.1 equivalent of DCDMH and 3.5 equivalent of TBHP under irradiation of blue-LED in continuous flow for 1 h in air (Table 3, entry 15).

With the optimized reaction conditions in hand, we set out to investigate the applicability of the present protocol for the scope of acyl motif. A broad range of quinoline substrates readily participated in this mild chlorination with great efficiency (Table 4). Both electron-donating (**3b**) and electron-withdrawing (**3c-3e**) benzamides were well tolerated in the current reaction system and the desired products were obtained in good to excellent yields. The reactants with electron-donating substituents afforded the desired products in higher yields relative to those with electron-withdrawing groups. In addition to good tolerance of different kinds of carboxamide with aromatic substitutions, this reaction was also amenable to heteroaromatic amide (**3f**) and alkyl amides (**3g-i**), giving the target products in good yields.

Table 3

Optimization of the chlorination reaction conditions[a,d]

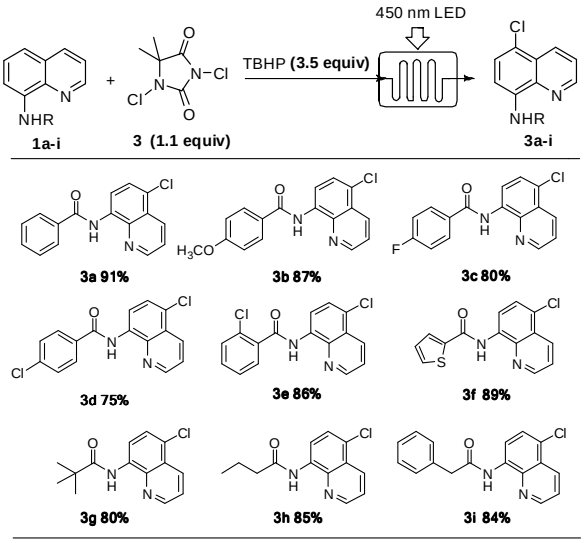


Entry	Solvent	DCDMH/equiv	TBHP/equiv	Time/h	Yield[c]/%
1	CH_2Cl_2	0.55	2.1	4	13
2	CH_2Cl_2	1.1	2.1	4	18
3	CH_2Cl_2	0.55	3.5	4	27
4	CH_2Cl_2	1.1	3.5	4	48
5	CH_2Cl_2	0.55	2.1	8	19
6	CH_2Cl_2	1.1	2.1	8	51
7	CH_2Cl_2	0.55	3.5	8	44
8	CH_2Cl_2	1.1	3.5	8	65
9	CH_2Cl_2	0.55	2.1	12	25
10	CH_2Cl_2	1.1	2.1	12	55
11	CH_2Cl_2	0.55	3.5	12	50
12	CH_2Cl_2	1.1	3.5	12	97
13[c]	CH_2Cl_2	1.1	3.5	12	42
14[b]	CH_2Cl_2	1.1	3.5	0.5	55
15[b]	CH_2Cl_2	1.1	3.5	1	92
16[b]	CH_2Cl_2	1.1	3.5	1.5	90
17	CH_2Cl_2	0.55		4	Trace
18	CH_2Cl_2	1.1		12	35

[a]Conditions: **1a**, (0.2 mmol), TBHP 70 % in water, solvent (2 mL) under irradiation of 15 W blue-LED at r.t. in a batch in air. [b]**1a**, (0.2 mmol), TBHP (70 % in water), solvent (2 mL) under irradiation of 15 W blue LED at room temperature in continuous flow in air. [c]Dark. [d]GC yields.

Table 4

Substrate scope of the C5 chlorination of quinolines[a,b]



[a]Conditions: Substituted quinolines (0.2 mmol), DCDMH (1.1 equiv.), TBHP (70 % in water, 3.5 equiv.), DCM (2 mL) under irradiation of 15 W blue-LED in continuous flow for 1 h in air. [b]Isolated yields on silica gel column chromatography.

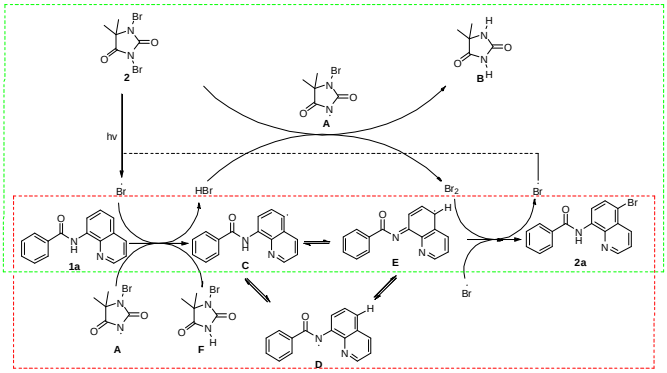
Mechanism studies

To gain more insight into the reaction mechanism, radical capturing experiments were put into effect. When 2.0 equivalents of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) were added

into either bromination or chlorination reaction system, the yield of the desired product decreased sharply to 15% and 13% respectively, implying that the reaction follows a radical pathway.

Based on our experiment and the previous work[17,18], possible reaction mechanism was outlined in Scheme 2. Initially, the active bromine and complex A radical species were created from DBDMH under blue-LED irradiation. In following propagation process, Br radical or A radical react with stable molecules **1a** to form radical intermediate **C** and HBr or complex **F**. Next, **C** could tautomerize to stable intermediates **D** and **E**. Br_2 was generated through combining of HBr and complex **A**, which then underwent a bromination process with intermediate **C** or **E** to give the C5 brominated product **2a**. Beside this process, **2a** could also be obtained through bromine radical and intermediates **C** or **E**.

TBHP could liberate tert-butoxy radical (t-BuO·) under blue-LED irradiation which may promote the formation of chlorine radical or intermediates **C**-**E**. The following chlorination procedure is similar to the bromination process.



Scheme 2. Proposed mechanism for the bromination of quinolines

3. Conclusion

In summary, an efficient visible-light induced, C5 halogenation of 8-aminoquinolines in continuous flow was developed, in which, a smaller amount of low-cost and easy available DBDMH and DCDMH were used as halogenation reagents. The reaction condition of chlorination differs from that of bromination due to the less reactivity of DCDMH. Both chlorination and bromination reaction reveals good functional group tolerance and high reactivity (short reaction time and high yields) under open-air conditions. Gram-scale of the desired product can easily be obtained simply in continuous flow.

4. Experiment

4.1. General information

All the chemicals unless otherwise noted, were obtained commercially and used without further purification. All products were isolated by column chromatography on a silica gel (200-300 mesh). Continuous flow reactor from Syrris Ltd and Corning were used for the continuous flow process. ^{1}H NMR spectra were determined on Bruker instruments with operating frequencies of 400 or 500 MHz spectrometer as solutions in $CDCl_3$. Chemical shifts were expressed in parts per million (δ) and the signals were reported as s (singlet), d (doublet), dd (doublet of doublet), t (triplet), m (multiplet), and coupling constants (J) were given in Hz. ^{13}C NMR spectra were recorded at 101 or 125 MHz in $CDCl_3$ solution. Chemical shifts as internal standard were referenced to $CDCl_3$ (δ = 7.26 for ^{1}H and δ = 77.16 for ^{13}C NMR) as internal standard. GC chromatography with FID detector from Agilent and GC-MS from Thermo were used to record data. High-resolution mass spectrometry data were also recorded in the ESI-TOF.

4.2. General procedure for synthesis of starting amides

The synthesis of starting amides was according to previously reported literature[19]. 5 mmol of 8-aminoquinoline, and 6 mmol of triethylamine were dissolved in 20 mL of CH_2Cl_2, stirred in 100 mL single neck flask at room temperature for 5 minutes, the reaction solution was cooled in an ice bath afterwards. The acid chloride (6 mmol) was added dropwise (if the acid chloride is solid, it was dissolved with 5 mL CH_2Cl_2). The reaction solution was allowed to stir overnight at room temperature. The reaction mixture was washed with CH_2Cl_2, and the organic layer with 1M $NaHCO_3$ (3×15 mL). The organic layer was dried over anhydrous Na_2SO_4, subsequently. The solvent was removed over rotary evaporator. The product was purified by silica gel column chromatography with PE/EtOAc (10 : 1).

4.3. General procedure for synthesis of N-methyl-N-(quinolin-8-yl)benzamide

The synthesis of *N*-methyl-*N*-(quinolin-8-yl)benzamide was according to previously reported literature[20]. To a suspension of sodium hydride (2.0 mmol) in 5 mL of dry dimethylformamide, was added a solution of *N*-8-quinolinyl-benzamide (1.0 mmol) in 5 mL of dry dimethylformamide in an ice bath. The reaction was warmed to room temperature and stirred for another hour. Methyl iodide (1.0 mmol) was added and the reaction mixture was stirred for a further half hour, subsequently. Then the reaction mixture was washed with 30 mL of CH_2Cl_2 and the organic layer was washed with water (3×15 mL). The organic layer was dried over anhydrous Na_2SO_4, and the solvent removed roto-evaporated. The product was purified by column chromatography using CH_2Cl_2 as eluent.

4.4. General procedure for the synthesis of brominated quinolines in continuous flow

0.2 mmol of substituted quinolines and 0.11 mmol of DBDMH in CH_2Cl_2 (2 mL) was injected into the pump, then the reaction mixture entered into the fluorinated ethylene propylene (FEP) tubing convection flow coil reactor (1/32 inner diameter, 1.6 ml inner volume, 53.3 μL • min^{-1} flow rate), which was maintained at room temperature (residence time = 30 min) and under the irradiation of blue-LED. The reaction mixture was collected at a test tube and then concentrated under vacuum. The residue was purified by column chromatography on silica gel (200-300 mesh) with PE/EtOAc (10 : 1) to give the final products.

4.4.1. N-(5-bromoquinolin-8-yl)benzamide (2a):

Obtained as a white solid in 90%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.54 (s, 1H), 8.71 (dd, *J* = 5.0, 3.4 Hz, 2H), 8.35 (dd, *J* = 8.5, 1.6 Hz, 1H), 8.00 (dd, *J* = 5.2, 3.3 Hz, 2H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.56-7.45 (m, 3H), 7.42 (dd, *J* = 8.5, 4.2 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.13 , 148.67, 139.19 , 135.79 , 134.71 , 134.36 , 131.99 , 130.81 , 128.82 , 127.24 , 127.04 , 122.65 , 116.85 , 114.36. GC-MS (EI, m/z): 328 (M^+).

4.4.2. N-(5-bromoquinolin-8-yl)-2-methylbenzamide (2b):

Obtained as a white solid in 92%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.19 (s, 1H), 8.84 (d, *J* = 8.4 Hz, 1H), 8.79 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.54 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.85 (d, *J* = 8.4 Hz, 1H), 7.67 (d, *J* = 7.7 Hz, 1H), 7.55 (dt, *J* = 7.5, 3.7 Hz, 1H), 7.44 – 7.38 (m, 1H), 7.32 (t, *J* = 7.6 Hz, 2H), 2.60 (s, 3H). ^{13}C NMR (101 MHz,

$CDCl_3$) δ 168.14, 148.77, 139.32, 136.82, 136.33, 136.02, 134.67, 130.20, 127.23, 127.21, 122.77, 117.37, 114.92. GC-MS (EI, m/z): 362 (M^+).

131.48, 130.96, 130.52, 127.26, 126.08, 122.74, 117.02, 114.51, 20.25. HRMS (ESI) m/z: $[M+H]^+$ Calcd For $C_{17}H_{14}BrN_2O$ 343.0191; found 343.0292.

4.4.3. N-(5-bromoquinolin-8-yl)-3-methylbenzamide (2c):

Obtained as a white solid in 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.64 (s, 1H), 8.84 (d, *J* = 4.1 Hz, 1H), 8.81 (d, *J* = 8.4 Hz, 1H), 8.51 (d, *J* = 8.5 Hz, 1H), 7.83 (dd, *J* = 14.0, 7.1 Hz, 3H), 7.55 (dd, *J* = 8.5, 4.2 Hz, 1H), 7.45 – 7.36 (m, 2H), 2.47 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.61, 148.76, 139.42, 138.75, 135.99, 134.85, 134.57, 132.80, 130.98, 128.70, 128.06, 127.23, 124.21, 122.72, 117.02, 114.35, 21.51. HRMS (ESI) m/z: $[M+H]^+$ Calcd For $C_{17}H_{14}BrN_2O$ 343.0191; found 343.0295.

4.4.4. N-(5-bromoquinolin-8-yl)-4-methylbenzamide (2d):

Obtained as a white solid in 93%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.58 (s, 1H), 8.77 (dd, *J* = 4.1, 1.3 Hz, 1H), 8.74 (d, *J* = 8.4 Hz, 1H), 8.44 (dd, *J* = 8.5, 1.3 Hz, 1H), 7.88 (d, *J* = 8.1 Hz, 2H), 7.75 (d, *J* = 8.4 Hz, 1H), 7.49 (dd, *J* = 8.5, 4.2 Hz, 1H), 7.26 (d, *J* = 7.9 Hz, 2H), 2.37(s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.34, 147.68, 141.53, 138.41, 134.96, 133.60, 131.01, 129.96, 128.47, 126.26, 121.66, 115.92, 113.19, 20.53. HRMS (ESI) m/z: $[M+H]^+$ Calcd For $C_{17}H_{14}BrN_2O$ 343.0191; found 343.0279.

4.4.5. N-(5-bromoquinolin-8-yl)-4-methoxybenzamide (2e):

Obtained as a white solid in 84%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.65 (s, 1H), 8.88 (dd, J = 4.2, 1.5 Hz, 1H), 8.83 (d, J = 8.4 Hz, 1H), 8.56 (dd, J = 8.5, 1.5 Hz, 1H), 8.07 – 8.03 (m, 2H), 7.85 (d, J = 8.4 Hz, 1H), 7.60 (dd, J = 8.5, 4.2 Hz, 1H), 7.07 – 7.02 (m, 2H), 3.90 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.93, 162.67, 148.67, 139.43, 136.01, 134.71, 131.02, 129.19, 127.25, 127.14, 122.68, 116.87, 114.05, 55.48. GC-MS (EI, m/z): 358 (M^+).

4.4.6. N-(5-bromoquinolin-8-yl)-4-fluorobenzamide (2f):

Obtained as a white solid in 81%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.64 (s, 1H), 8.86 (dd, *J* = 4.2, 1.5 Hz, 1H), 8.79 (d, *J* = 8.4 Hz, 1H), 8.54 (dd, *J* = 8.5, 1.5 Hz, 1H), 8.11 – 8.04 (m, 2H), 7.83 (d, *J* = 8.4 Hz, 1H), 7.59 (dd, *J* = 8.5, 4.2 Hz, 1H), 7.25 – 7.19 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.10 (d, J_{CF} = 252.9 Hz), 164.26, 148.78, 139.35, 136.12, 134.34, 131.04(d, J_{CF} = 3.1 Hz), 130.98, 129.72(d, J_{CF} = 9.1 Hz), 127.28, 122.78, 117.06 , 116.02(d, J_{CF} = 22.0 Hz), 114.56. GC-MS (EI, m/z): 346 (M^+).

4.4.7. N-(5-bromoquinolin-8-yl)-4-chlorobenzamide (2g):

Obtained as a white solid in 91%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.64 (s, 1H), 8.85 (dd, *J* = 4.2, 1.4 Hz, 1H), 8.77 (d, *J* = 8.4 Hz, 1H), 8.53 (dd, *J* = 8.5, 1.4 Hz, 1H), 7.99 (d, *J* = 8.5 Hz, 2H), 7.82 (d, *J* = 8.4 Hz, 1H), 7.58 (dd, *J* = 8.5, 4.2 Hz, 1H), 7.51 (d, *J* = 8.5 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.18 , 148.81 , 139.31 , 138.34 , 136.05 , 134.22 , 133.17 , 130.93 , 129.11 , 128.69 , 127.23 , 122.79 , 117.04 , 114.66. GC-MS (EI, m/z): 362 (M^+).

4.4.8. N-(5-bromoquinolin-8-yl)-2-chlorobenzamide (2h):

Obtained as a white solid in 87%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.50 (s, 1H), 8.88 – 8.79 (m, 2H), 8.54 (d, J = 8.5 Hz, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.82 (dd, J = 7.4, 1.7 Hz, 1H), 7.57 (dd, J = 8.5, 4.2 Hz, 1H), 7.52 – 7.49 (m, 1H), 7.43 (tdd, J = 14.9, 10.5, 4.5 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.79, 148.87, 139.30, 135.93, 135.48, 134.36, 131.70, 131.16, 130.88, 130.58,

4.4.9. N-(5-bromoquinolin-8-yl)acetamide (2i):

Obtained as a white solid in 82%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.71 (s, 1H), 8.76 (dd, J = 4.1, 1.6 Hz, 1H), 8.61 (d, J = 8.4 Hz, 1H), 8.45 (dd, J = 8.5, 1.6 Hz, 1H), 7.73 (d, J = 8.4 Hz, 1H), 7.51 (dd, J = 8.5, 4.2 Hz, 1H), 2.34 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.60, 148.52, 138.80, 135.87, 134.38, 130.83, 127.04, 122.59, 116.81, 114.06, 25.14. GC-MS (EI, m/z):266 (M^+).

4.4.10. N-(5-bromoquinolin-8-yl)pivalamide (2j):

Obtained as a white solid in 85%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.21 (s, 1H), 8.80 (d, *J* = 2.9 Hz, 1H), 8.68 (d, *J* = 8.4 Hz, 1H), 8.47 (d, *J* = 8.4 Hz, 1H), 7.76 (d, *J* = 8.4 Hz, 1H), 7.52 (dd, *J* = 8.4, 4.1 Hz, 1H), 1.42 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.22, 148.66, 139.42, 135.85, 134.62, 130.89, 127.10, 122.55, 116.69, 113.86, 40.38, 27.69. HRMS (ESI) m/z: $[M+H]^+$ Calcd For $C_{14}H_{15}BrN_2ONa$ 329.0368; found 329.0266.

4.4.11. N-(5-bromoquinolin-8-yl)butyramide (2k):

Obtained as a white solid in 87%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.66 (s, 1H), 8.69 (d, *J* = 3.6 Hz, 1H), 8.57 (d, *J* = 8.4 Hz, 1H), 8.38 (d, *J* = 8.5 Hz, 1H), 7.66 (d, *J* = 8.4 Hz, 1H), 7.43 (dd, *J* = 8.4, 4.1 Hz, 1H), 2.45 (t, *J* = 7.5 Hz, 2H), 1.81 – 1.71 (m, 2H), 0.97 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.70, 148.54, 138.96, 135.87, 134.45, 130.89, 127.09, 122.57, 116.83, 113.93, 40.12, 19.04, 13.81. HRMS (ESI) m/z: $[M+H]^+$ Calcd For $C_{13}H_{14}BrN_2O$ 293.0211; found 293.0446.

4.4.12. N-(5-bromoquinolin-8-yl)-2-phenylacetamide (2l):

Obtained as a white solid in 83%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.82 (s, 1H), 8.62 (dd, *J* = 11.3, 6.1 Hz, 2H), 8.39 (d, *J* = 8.4 Hz, 1H), 7.70 (d, *J* = 8.4 Hz, 1H), 7.45 – 7.37 (m, 5H), 7.33 (t, *J* = 6.7 Hz, 1H), 3.86 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.49, 148.60, 139.03, 135.75, 134.48, 134.27, 130.78, 129.56, 129.04, 127.45, 127.02, 122.55, 116.77, 114.27, 45.36. HRMS (ESI) m/z: $[M+H]^+$ Calcd For $C_{17}H_{14}BrN_2O$ 343.0191; found 343.0454.

4.4.13. N-(5-bromoquinolin-8-yl)thiophene-2-carboxamide (2m):

Obtained as a white solid in 86%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.47 (s, 1H), 8.79 (dd, J = 4.2, 1.4 Hz, 1H), 8.66 (d, J = 8.4 Hz, 1H), 8.46 (dd, J = 8.5, 1.4 Hz, 1H), 7.77 – 7.73 (m, 2H), 7.56 – 7.48 (m, 2H), 7.14 – 7.09 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.95, 148.80, 139.78, 139.19, 136.03, 134.27, 131.16, 130.99, 128.59, 127.91, 127.27, 122.77, 116.99, 114.43. HRMS (ESI) m/z: $[M-H]^-$ Calcd For $C_{14}H_8BrN_2OS$ 332.9598; found 332.9536.

4.4.14. N-(5-bromoquinolin-8-yl)-N-methylbenzamide (2n):

Obtained as a white solid in 84%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.99 (dd, J = 4.1, 1.5 Hz, 1H), 8.47 (dd, J = 8.5, 1.5 Hz, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.52 (dd, J = 8.5, 4.1 Hz, 1H), 7.29 (dd, J = 7.7, 3.0 Hz, 3H), 7.11 (t, J = 7.4 Hz, 1H), 7.01 (t, J = 7.6 Hz, 2H), 3.57 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.04, 151.11, 144.54, 142.52, 136.53, 135.82, 129.96, 129.47, 129.28, 128.49, 127.92, 127.53, 122.80, 120.98, 38.59. HRMS (ESI) m/z: $[M+H]^+$ Calcd For $C_{17}H_{14}BrN_2O$ 343.0191; found 343.0261.

4.4.15. N-(5-bromoquinolin-8-yl)-4-methylbenzenesulfonamide (2o):

Obtained as a white solid in 87%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.12 (s, 1H), 8.69 (dd, J = 4.2, 1.5 Hz, 1H), 8.35 (dd, J = 8.5, 1.5 Hz, 1H), 7.71 (d, J = 8.3 Hz, 2H), 7.62 (d, J = 2.3 Hz, 2H),

7.44 (dd, J = 8.5, 4.2 Hz, 1H), 7.09 (d, J = 8.1 Hz, 2H), 2.22 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.19, 143.99, 139.10, 136.22, 135.89, 133.85, 130.35, 129.63, 127.49, 127.23, 123.02, 115.24, 114.88, 21.47. HRMS (ESI) m/z: $[M-H]^-$ Calcd For $C_{16}H_{12}BrN_2O_2S$ 376.9861; found 376.9792.

4.4.16. N-(5-bromoquinolin-8-yl)-1-phenylmethanesulfonamide (2p):

Obtained as a white solid in 79%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.83 (s, 1H), 8.70 (dd, J = 4.2, 1.4 Hz, 1H), 8.48 (dd, J = 8.5, 1.4 Hz, 1H), 7.68 (t, J = 9.9 Hz, 1H), 7.61 (d, J = 8.3 Hz, 1H), 7.55 (dd, J = 8.5, 4.2 Hz, 1H), 7.24 (t, J = 5.4 Hz, 1H), 7.13 (t, J = 7.6 Hz, 2H), 7.08 (d, J = 7.5 Hz, 2H), 4.39 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.15, 138.71, 135.95, 134.33, 130.72, 130.46, 128.81, 128.66, 128.12, 127.53, 123.18, 114.97, 114.86, 58.04. HRMS (ESI) m/z: $[M-H]^-$ Calcd For $C_{16}H_{12}BrN_2O_2S$ 376.9861; found 376.9795.

4.4.17. N-(5-bromoquinolin-8-yl)thiophene-2-sulfonamide (2q):

Obtained as a white solid in 55%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.21 (s, 1H), 8.71 (d, J = 3.9 Hz, 1H), 8.40 (d, J = 8.5 Hz, 1H), 7.71 (dd, J = 20.2, 8.3 Hz, 2H), 7.59 – 7.54 (m, 1H), 7.47 (dd, J = 8.5, 4.2 Hz, 1H), 7.38 (d, J = 4.9 Hz, 1H), 6.87 (t, J = 4.4 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.32, 139.60, 139.26, 135.97, 133.47, 132.84, 132.42, 130.36, 127.54, 127.19, 123.11, 115.81, 115.50. HRMS (ESI) m/z: $[M-H]^-$ Calcd For $C_{13}H_8BrN_2O_2S_2$ 368.9268; found 368.9196.

4.5. General procedure for the synthesis of chlorinated quinolines in continuous flow

A solution of substituted quinolines (0.2 mmol), DCDMH (0.22 mmol) and TBHP (70% in water, 0.7 mmol) in DCM (2 mL) was injected into the pump, then the reaction mixture entered into the fluorinated ethylene propylene (FEP) convection flow coil reactor (1/32 inner diameter, 1.6 ml inner volume, 26.7 μL • min^{-1} flow rate), which was maintained at room temperature (residence time = 60 min) and under the irradiation of blue-LED. The reaction mixture was collected at a test tube and then concentrated under vacuum. The residue was purified by column chromatography on silica gel (200-300 mesh) with PE/EtOAc to give the final products.

4.5.1. N-(5-chloroquinolin-8-yl)benzamide (3a):

Obtained as a white solid in 91%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.53 (s, 1H), 8.75 (dd, J = 5.0, 3.5 Hz, 2H), 8.42 (dd, J = 8.5, 1.5 Hz, 1H), 7.97 – 7.92 (m, 2H), 7.53 – 7.41 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.24, 147.85, 138.17, 133.78, 132.77, 132.31, 130.93, 127.77, 126.38, 126.20, 124.87, 123.38, 121.32, 115.34. HRMS (ESI) m/z: $[M+Na]^+$ Calcd For $C_{16}H_{11}ClN_2ONa$ 307.0428; found 307.0419.

4.5.2. N-(5-chloroquinolin-8-yl)-4-methoxybenzamide (3b):

Obtained as a white solid in 87%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.61 (s, 1H), 8.91 – 8.82 (m, 2H), 8.58 (dd, J = 8.5, 1.5 Hz, 1H), 8.09 – 7.99 (m, 2H), 7.64 (d, J = 8.4 Hz, 1H), 7.58 (dd, J = 8.5, 4.2 Hz, 1H), 7.03 (d, J = 8.8 Hz, 2H), 3.90 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.94, 162.65, 148.67, 139.31, 134.08, 133.44, 129.18, 127.36, 127.17, 126.00, 124.15, 122.36, 116.28, 114.04, 55.49. HRMS (ESI) m/z: $[M+Na]^+$ Calcd For $C_{17}H_{13}ClN_2O_2Na$ 337.0534; found 337.0530.

4.5.3. N-(5-chloroquinolin-8-yl)-4-fluorobenzamide (3c):

Obtained as a white solid in 80%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.50 (s, 1H), 8.77 (dd, J = 4.1, 1.3 Hz, 1H), 8.73 (d, J = 8.4 Hz, 1H), 8.47 (dd, J = 8.5, 1.3 Hz, 1H), 8.00 – 7.93 (m, 2H), 7.53 (d, J = 8.4 Hz, 1H), 7.48 (dd, J = 8.5, 4.2 Hz, 1H), 7.12 (t, J = 8.5 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.08(d, J_{CF} = 252.9 Hz), 164.18, 148.76, 139.21, 134.65, 133.69, 133.46, 131.04(d, J_{CF} = 3.1 Hz), 129.69(d, J_{CF} = 9.0 Hz), 127.26, 125.97, 124.58, 116.42, 115.99(d, J_{CF} = 21.9 Hz). HRMS (ESI) m/z: $[M+Na]^+$ Calcd For $C_{16}H_{10}ClFN_2ONa$ 325.0334; found 325.0331.

4.5.4. 4-chloro-N-(5-chloroquinolin-8-yl)benzamide (3d):

Obtained as a white solid in 75%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.51 (s, 1H), 8.79 – 8.75 (m, 1H), 8.72 (d, J = 8.4 Hz, 1H), 8.48 – 8.44 (m, 1H), 7.89 (d, J = 8.4 Hz, 2H), 7.52 (d, J = 8.4 Hz, 1H), 7.48 (dd, J = 8.5, 4.2 Hz, 1H), 7.41 (d, J = 8.4 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.16, 148.79, 139.19, 138.31, 133.58, 133.47, 133.19, 129.09, 128.67, 127.25, 125.97, 124.70, 122.44, 116.48. HRMS (ESI) m/z: $[M+Na]^+$ Calcd For $C_{16}H_{10}Cl_2N_2ONa$ 341.0039; found 341.0033.

4.5.5. 2-chloro-N-(5-chloroquinolin-8-yl)benzamide (3e):

Obtained as a white solid in 86%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.48 (s, 1H), 8.90 (d, J = 8.4 Hz, 1H), 8.84 (dd, J = 4.2, 1.5 Hz, 1H), 8.59 (dd, J = 8.5, 1.5 Hz, 1H), 7.82 (dd, J = 7.4, 1.9 Hz, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.58 (dd, J = 8.5, 4.2 Hz, 1H), 7.51 (dd, J = 7.8, 1.3 Hz, 1H), 7.43 (dtd, J = 17.3, 7.4, 1.6 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.82, 148.85, 139.21, 135.53, 133.72, 133.44, 131.69, 131.18, 130.58, 130.20, 127.26, 127.21, 126.02, 124.97, 122.44, 116.89. HRMS (ESI) m/z: $[M+Na]^+$ Calcd For $C_{16}H_{10}Cl_2N_2ONa$ 341.0039; found 341.0041.

4.5.6. N-(5-chloroquinolin-8-yl)thiophene-2-carboxamide (3f):

Obtained as a white solid in 89%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.58 – 10.45 (s, 1H), 8.87 (dd, J = 4.2, 1.5 Hz, 1H), 8.76 (d, J = 8.4 Hz, 1H), 8.61 – 8.51 (m, 1H), 7.81 (dd, J = 3.7, 0.8 Hz, 1H), 7.59 (ddd, J = 12.7, 11.0, 6.3 Hz, 3H), 7.18 (dd, J = 4.8, 3.8 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.93, 148.78, 139.77, 139.01, 133.59, 133.43, 131.14, 128.56, 127.91, 127.29, 125.97, 124.49, 122.43, 116.39. HRMS (ESI) m/z: $[M+Na]^+$ Calcd For $C_{14}H_9ClN_2OSNa$ 312.9993; found 312.9988.

4.5.7. N-(5-chloroquinolin-8-yl)pivalamide (3g):

Obtained as a white solid in 80%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.21 (s, 1H), 8.84 (d, *J* = 4.1 Hz, 1H), 8.74 (d, *J* = 8.4 Hz, 1H), 8.53 (d, *J* = 8.5 Hz, 1H), 7.59 – 7.52 (m, 2H), 1.43 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.26, 148.68, 139.31, 133.99, 133.33, 127.25, 125.88, 123.96, 122.25, 116.12, 40.37, 27.71. HRMS (ESI) m/z: $[M+Na]^+$ Calcd For $C_{14}H_{15}ClN_2ONa$ 285.0873; found 285.0771.

4.5.8. N-(5-chloroquinolin-8-yl)butyramide (3h):

Obtained as a white solid in 85%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.65 (s, 1H), 8.74 – 8.70 (m, 1H), 8.62 (d, *J* = 8.4 Hz, 1H), 8.43 (d, *J* = 8.4 Hz, 1H), 7.49 – 7.42 (m, 2H), 2.45 (t, *J* = 7.5 Hz, 2H), 1.81 – 1.72 (m, 2H), 0.97 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.76, 148.52, 138.80, 133.77, 133.33, 127.22, 125.84, 124.04, 122.25, 116.31, 40.10, 19.06, 13.81. HRMS (ESI) m/z: $[M+Na]^+$ Calcd For $C_{13}H_{13}ClN_2ONa$ 271.0716; found 271.0743.

4.5.9. N-(5-chloroquinolin-8-yl)-2-phenylacetamide (3i):

Obtained as a white solid in 84%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.81 (s, 1H), 8.66 (d, *J* = 7.7 Hz, 2H), 8.43 (d, *J* = 8.5 Hz, 1H), 7.50 (d, *J* = 8.4 Hz, 1H), 7.45 – 7.38 (m, 5H), 7.33 (t, *J* = 6.8 Hz, 1H), 3.87 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.49, 148.59, 138.89, 134.51, 133.62, 133.19, 129.56, 129.04,

127.44, 127.11, 125.75, 124.32, 122.22, 116.21, 45.33. HRMS (ESI) m/z: $[M+H]^+$ Calcd For $C_{17}H_{14}ClN_2O$ 297.0716; found 279.0742.

4.6. Procedure for scale-up bromination reaction of N-8-quinolinyl-benzamide

A test tube was filled with 10 mL of CH_2Cl_2, in which N-8-quinolinyl-benzamide (5 mmol, 1.240 g), DBDMH (2.75 mmol, 786.5 mg) were dissolved. The reagent solutions were pumped into PTFE-FEP tubes (1/32 inner diameter) through pump (Syrris Ltd) at a flow rate of 53.3 μL • min^{-1}. The solution then immediately entered a 1.6 mL convection flow coil (CFC) reactor (1/32 inner diameter) at a flow rate of 53.3 μL • min^{-1}, which was maintained at ambient temperature (residence time = 30 min). The flow process was run continuously for 210 min. The product stream exiting the reactor was collected in a test tube and then concentrated under vacuum. After evaporation, the residue was purified by column chromatography on silica gel (200–300 mesh size) using petroleum ether/EtOAc as the eluent to give 1.39 g of the product. This flow process gave a product output of 397 mg • h^{-1}.

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References and notes

1. (a) J. P. Michael, Nat. Prod. Rep. **1999**, 16, 697–709; (b) J. P. Michael, Nat. Prod. Rep. **2003**, 20, 476–493; (c) J. P. Michael, Nat. Prod. Rep. **2004**, 21, 650–668; (d) J. P. Michael, Nat. Prod. Rep. **2008**, 25, 166–187; (e) C. C. Hughes, J. B. MacMillan, S. P. Gaudencio, W. Fenical, J. J. La Clair, Angew. Chem. Int. Ed. **2009**, 48, 728–732; (f) C. C. Hughes, J. B. MacMillan, S. P. Gaudencio, P. R. Jensen, W. Fenical, Angew. Chem. Int. Ed. **2009**, 48, 725–727.
2. (a) S. R. Vippagunta, A. Dorn, H. Matile, J. Med. Chem. **1999**, 42, 4630–4639; (b) P. B. Madrid, J. Sherrill, A. P. Liou, J. L. Weisman, J. L. DeRisib, R. K. Guy, Bioorg. Med. Chem. Lett. **2005**, 15, 1015–1018; (c) S. Bhat, J. S. Shim, F. Zhang, C. R. Chong, J. O. Liu, Org. Biomol. Chem. **2012**, 10, 2979–2992; (d) D. K. Heidary, B. S. Howerton, E. C. Glazer, J. Med. Chem. **2014**, 57, 8936–8946.
3. J. A. Bond, T. W. Walker, Weed Technol. **2012**, 26, 183–188.
4. (a) E. Pan, M. Jamison, M. Yousufuddin, J. B. MacMillan, Org. Lett. **2012**, 14, 2390–2393; (b) S. Tardito, A. Barilli, I. Bassanetti, M. Tegoni, O. Bussolati, R. F. Gazzola, C. Mucchino, L. Marchik, J. Med. Chem. **2012**, 55, 10448–10459; (c) Y. C. Liu, J. H. Wei, Z. F. Chen, M. Liu, Y. Q. Gu, K. B. Huang, Z. Q. Li, H. Liang, Eur. J. Med. Chem. **2013**, 69, 554–563; (d) Y. Abouelhassan, A. T. Garrison, G. M. Burch, W. Wong, V. M. Norwood IV, R. W. Huigens III, Bio. Med. Chem. Lett. **2014**, 24, 5076–5080.
5. (a) V. G. Zaitsev, D. Shabashow, O. Daugulis, J. Am. Chem. Soc. **2005**, 127, 13154–13155; (b) L. D. Tran, I. Popov, O. Daugulis, J. Am. Chem. Soc. **2012**, 134, 18237–18240; (c) L. D. Tran, J. Roane, O. Daugulis, Angew. Chem. Int. Ed. **2013**, 52, 6043–6046; (d) M. Nishino, K. Hirano, T. Satoh, M. Miura, Angew. Chem. Int. Ed. **2013**, 52, 4457–4461; (e) T. Truong, K. Klimovica, O. Daugulis, J. Am. Chem. Soc. **2013**, 135, 9342–9345; (f) J. Roane, O. Daugulis, Org. Lett. **2013**, 15, 5842–5845; (g) M. Corbet, F. D. Campo, Angew. Chem. Int. Ed. **2013**, 52, 9896–9898; (h) J. Dong, F. Wang, J. You, Org. Lett. **2014**, 16, 2884–2887; (i) X. C. Wang, W. Gong, L. Z. Fang, R. Y. Zhu, S. Li, K. M. Engle, J. Q. Yu, Nat. Lett. **2015**, 519, 334–338; (j) V. P. Reddy, R. Qiu, T. Iwasaki, N. Kambe, Org. Biomol. Chem. **2015**, 13, 6803–6813; (k) J. Roane, O. Daugulis, J. Am. Chem. Soc. **2016**, 138, 4601–4607.
6. (a) H. Liu, F. Wu, B. Zhang, C. Tan, Y. Chen, G. Hao, Y. Tan, Y. Jiang, RSC Adv. **2016**, 6, 77508–77514; (b) M. W. Chao, H. L. Huang, W. C. H. Fu, K. C. Hsu, Y. M. Liu, Y. W. Wu, C. F. Lin, Y. L. Chen, M. J. Lai, H. Y. Lee, J. P. Liou, C. M. Teng, C. R. Yang, Oncotarget. **2017**, 8, 27772–27785.
7. (a) B. Khan, H. S. Dutta, D. Koley, Asian J. Org. Chem. 2018, 7, 1270 – 1297. (b) T. Iwai, M. Sawamura, ACS Catal. 2015, 5, 5031-5040. (c) J. Xu, X. Zhu, G. Zhou, B. Ying, P. Ye, L. Su, C. Shen, P. Zhang, Org. Biomol. Chem. **2016**, 14, 3016–3021; (d) X. X. Liu, Z. Y. Wu, X. L. Luo, Y. Q. He, X. Q. Zhou, Y. X. Fan, G. S. Huang, RSC Adv. **2016**, 6, 71485–71488; (e) J. Y. Jiao, Y. J. Mao, A. W. Feng, X. F. Li, M. T. Li, X. H. Zhang, Tetrahedron **2017**, 73, 1482–1488; (f) H. Guo, M. Chen, P. Jiang, J. Chen, L. Pan, M. Wang, C. Xie, Y. Zhang, Tetrahedron **2015**, 71, 70-76; (g) Y. Long, L. Pan, X. Zhou, Molecules **2019**, 24, 535-548.
8. X. He, Y. Xu, L. Kong, H. Wu, D. Ji, Z. Wang, Y. Xu, Q. Zhu, Org. Chem. Front. **2017**, 4, 1046–1050.
9. A. M. Suess, M. Z. Ertem, C. J. Cramer, S. S. Stahl, J. Am. Chem. Soc. **2013**, 135, 9797–9804.
10. Y. Wang, Y. Wang, K. Jiang, Q. Zhang, D. Li, Org. Biomol. Chem. **2016**, 14, 10180–10184.
11. H. Qiao, S. Sun, F. Yang, Y. Zhu, J. Kang, Y. Wu, Y. Wu, Adv. Synth. Catal. **2017**, 359, 1976–1980.
12. H. Singh, C. Sen, T. Sahoo, S. C. Ghosh, Eur. J. Org. Chem. **2018**, 4748–4753.
13. (a) D. M. Schultz, T. P. Yoon, Science, **2014**, 343, 1239176. (b) J. J. Douglas, M. J. Sevrin, C.R. J. Stephenson, Org. Process Res. Dev. **2016**, 20, 1134−1147.
14. (a) S. Mascia, P. L. Heider, H. Zhang, R. Lakerveld, B. Benyahia, P. I. Barton, R. D. Braatz, C. L. Cooney, J. M. B. Evans, T. F. Jamison, K. F. Jensen, A. S. Myerson and B. L. Trout, Angew. Chem. Int. Ed. **2013**, 52, 12359−12363; (b) P. Poechlauer, J. Manley, R. Broxterman, B. Gregertsen and M. Ridemark, Org. Process Res. Dev. **2012**, 16, 1586−1590.
15. D. Cantillo, O. Frutos, J. A. Rincon, C. Mateos, C. O. Kappe, J. Org. Chem. **2014**, 79, 223−229.
16. (a) J. Ding, W. Li, K. Ye, J. Li, ChemistrySelect. **2016**, 1, 5874–5878. (b) Y. Guan, K. Wang, J. Shen, J. Xu, C. Shen, P. Zhang, Catal. Lett. **2017**, 147, 1574−1580.
17. J. Chen, T. Wang, Y. Liu, T. Wang, A. Lin, H. Yao, J. Xu, Org. Chem. Front. **2017**, 4, 622−626.
18. (a) H. Shimojo, K. Moriyama, H. Togo, Synthesis, 2015, 47, 1280-1290. (b) D. Tsuchiya, Y. Kawagoe, K. Moriyama, H. Togo, Org. Lett. **2013**, 15, 4194-4197; (c) S. Shimokawa, Y. Kawagoe, K. Moriyama, H. Togo, Org. Lett. **2016**, 18, 784-787; (d) Y. Li, L. Zhu, X. Cao, C. T. Au, R. Qiu, S. F. Yin, Adv. Synth. Catal. 2017, 359, 2864–2873; (e) D. R. Motati, D. Uredi, E. B. Watkins, Chem. Sci. 2018, 9, 1782–1788.
19. (a) D. Katayev, K. F. Pfister, T. Wendling, L. J. Gooßen, Chem. Eur. J. **2014**, 20, 9902−9905; (b) M. Liu, Y. Niu, Y. F. Wu, X. S. Ye, Org. Lett. **2016**, 18, 1836−1839.
20. Y. Wang, F. Yu, X. Han, M. Li, Y. Tong, J. Ding, H. Hou, Inorg. Chem. **2017**, 56, 5953−5958.