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Palladium-Catalyzed ortho-Selective C−H Chlorination of Benzamide Derivatives under Anodic Oxidation Conditions

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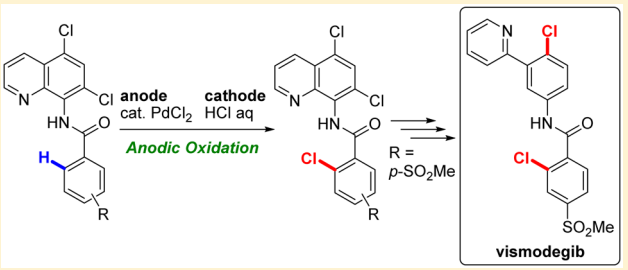
Supporting Information

ABSTRACT: The palladium-catalyzed ortho-selective chlorination of *N*-quinolinylbenzamide derivatives with hydrochloric acid was achieved under anodic oxidation conditions. The use of 5,7-dichloro-8-quinolinyl group as directing group was effective for the selective chlorination, and the reaction was applicable to benzamide derivatives bearing various functional groups. Synthesis of vismodegib was also completed using the palladium-catalyzed electrochemical C−H chlorination in two different steps.



Chloroarenes are an important class of compounds that are found in many molecules of biological and pharmaceutical interest as well as synthetic intermediates. In recent years, transition-metal-catalyzed regioselective C−H chlorination of aromatic compounds has been widely explored because it provides convenient methods for construction of aromatic carbon−chlorine bonds.[1] Our group has reported the palladium-catalyzed ortho-selective chlorination of aromatic C−H bonds under anodic oxidation conditions.[2−5] This method allows us to avoid using stoichiometric oxidative chlorinating reagents or oxidants, because a reactive chlorinating agent is generated in situ by anodic oxidation of a chloride ion. However, only arylpyridines and -pyrimidines have been used as substrates for these reactions.

Here we report that benzamide derivatives containing a bidentate directing group are applicable to the palladium-catalyzed ortho-selective chlorination with hydrochloric acid under anodic oxidation conditions.

We first examined various aromatic carbonyl compounds for the palladium-catalyzed electrochemical C−H chlorination. The desired chlorination did not proceed with simple aromatic carbonyl compounds such as *o*-toluic acid, ethyl benzoate, *N*-phenylbenzamide, *N*-(pentafluorophenyl)-2-methylbenzamide, and *N*,*N*-dimethylbenzamide.[6] We speculated that the low coordinating ability of the directing groups of these substrates may prevent efficient C−H bond cleavage by a palladium center and envisioned that the use of a more strongly coordinating directing group would facilitate the cleavage of the ortho C−H bonds and the catalytic chlorination reaction. Therefore, the reaction was examined using benzamide derivatives having a bidentate directing group.[7] Since the pioneering study by Daugulis group,[8] various C−H functionalization reactions of substrates possessing a bidentate directing group have been extensively studied, and several examples of the use of bidentate directing groups have been reported for ortho C−H chlorination.[9] In 2013, Stahl and co-workers reported on the ortho C−H chlorination of *N*-(8-quinolinyl)benzamide (**1a**) using copper complexes, but the desired ortho chlorination was observed only when a stoichiometric amount of $CuCl_2$ and a base were employed for the reaction.[9a] In the following year, Chen and co-workers reported the catalytic ortho C−H chlorination of benzylamine derivatives having a picolinamide directing group.[9b] Copper- and nickel-catalyzed ortho C−H chlorinations of benzamide derivatives were reported by Shi and co-workers using substrates possessing a 2-(2-pyridinyl)-2-aminopropane moiety.[9c] Catalytic ortho C−H chlorination of *N*-(8-quinolinyl)-benzamides have not been reported, while the corresponding fluorination was developed by Daugulis and co-workers.[10]

When a reaction of benzamide **1a** with aqueous hydrogen chloride was performed in the presence of 10 mol % of palladium chloride with 20 mA electric current using a divided cell at 90 °C for 6 h, ortho-chlorination of the benzoyl group was observed (eq 1). However, considerable amounts of chlorine atoms were also introduced onto the 5- and 7-positions of the 8-quinolinyl group, and chlorination products **2a**, **3a**, and **4a** were isolated in 4, 32, and 11% yields, respectively. The chlorination on the 8-quinolinyl group was also observed by Stahl and co-workers for the attempted oxidative chlorination of **1a** with a copper catalyst.[9a]

To avoid the formation of a complex mixture by the chlorination of the directing group, the reaction of a substrate bearing a 5,7-dichloro-8-quinolinyl group (**5a**) was conducted, and only **2a** and **3a** were observed as products (eq 2).[11] Reduction of the electric current to 5 mA improved the yields of

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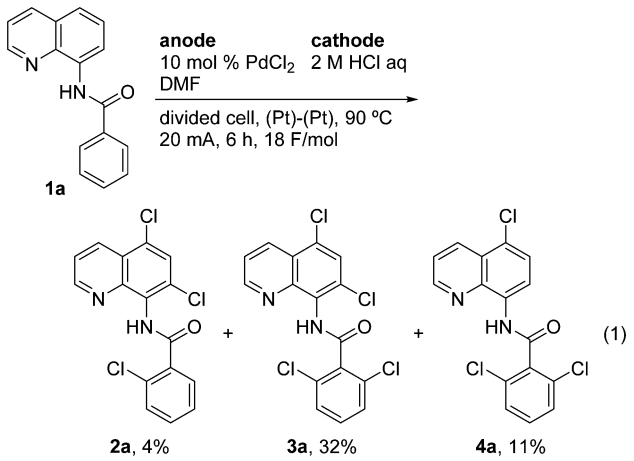
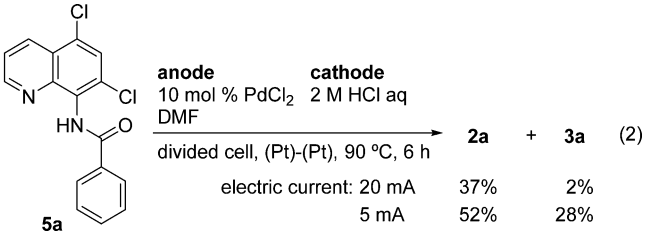
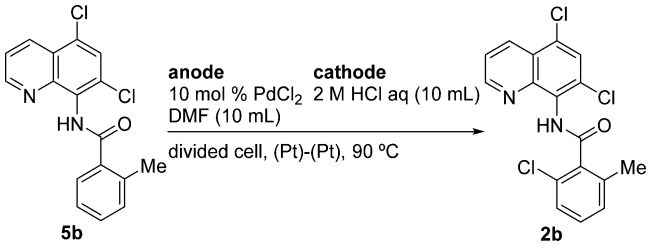


products **2a** and **3a** to 52 and 28%, respectively, due to suppression of product decomposition.[12]



The reaction of *o*-methylbenzamide derivative **5b** was then investigated. The reaction of 0.25 mmol of **5b** using 10 mL of DMF provided the ortho chlorination product **2b** in 51% isolated yield (Table 1, entry 1). Lowering of the substrate concentration

Table 1. Palladium-Catalyzed Electrochemical ortho C−H Chlorination of Benzamide 5b[a]



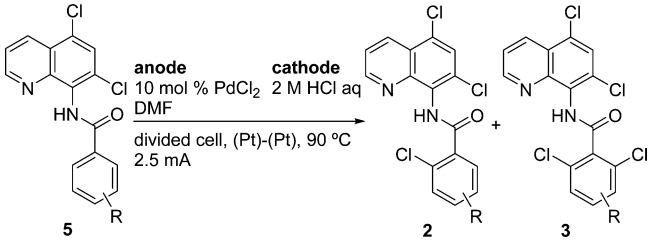
entry	**5b** (mmol)	electric current (mA)	time (h)	F/mol	yield (%)
1	0.25	5	6	4.5	51
2	0.20	5	6	5.6	56
3	0.20	2.5	6	2.8	68
4	0.20	2.5	12	5.6	86

[a]Reaction conditions: **5b**, $PdCl_2$ (10 mol %), DMF (10 mL) [anode], and 2 M HCl aq (10 mL) [cathode] in an H-type divided cell with two platinum electrodes and an anion-exchange membrane, 90 °C.

using 0.20 mmol of **5b** led to a slight increase in the product yield (entry 2). Reduction of the electric current from 5 mA to 2.5 mA further improved the yield of **2b** to 68% (entry 3). Finally, extension of the reaction time to 12 h led to the formation of product **2b** in 86% yield (entry 4).[13]

The ortho C−H chlorination was then performed using *m*- or *p*-substituted benzamide derivatives (Table 2). The reaction of *m*-substituted benzamides took place mainly at the less hindered ortho position of the benzene ring. Substrates possessing

Table 2. Palladium-Catalyzed Electrochemical ortho C−H Chlorination of Various *m*- or *p*-Substituted Benzamides[a]



					yields (%)	
entry	**5**	R	time (h)	F/mol	**2**	**3**
1	**5c**	*m*-OMe	6	2.8	84 (**2c**)	10 (**3c**)
2	**5d**	*m*-Me	6	2.8	78 (**2d**)	11 (**3d**)
3	**5e**	*m*-F	6	2.8	62 (**2e**)	12 (**3e**)
4	**5f**	*m*-Br	6	2.8	77 (**2f**)	nd[b]
5	**5g**	*m*-CF_3	24	11	71 (**2g**)	nd[b]
6	**5h**	*p*-OMe	4.5	2.1	56 (**2h**)	10 (**3h**)
7	**5i**	*p*-^{t}Bu	4.5	2.1	49 (**2i**)	9 (**3i**)
8	**5i**	*p*-^{t}Bu	7	3.3	55 (**2i**)	29 (**3i**)
9	**5j**	*p*-Me	4.5	2.1	58 (**2j**)	11 (**3j**)
10	**5k**	*p*-SO_2Me	9	4.2	75 (**2k**)	8 (**3k**)
11	**5l**	*p*-NO_2	12	5.6	60 (**2l**)	5 (**3l**)

[a]Reaction conditions: **5** (0.2 mmol), $PdCl_2$ (0.02 mmol), DMF (10 mL) [anode], and 2 M HCl aq (10 mL) [cathode] in an H-type divided cell with two platinum electrodes and an anion-exchange membrane, 90 °C, 2.5 mA. [b]Not detected.

electron-donating meta substituents ($\sigma+ < 0$) showed higher reactivity than those with electron-withdrawing groups. The reactions of the benzamide derivatives bearing methoxy, methyl, and fluoro groups (**5c−e**) for 6 h gave monochlorination products **2c−e** in 62−84% yields, but more than 10% yields of dichlorination products **3c−e** were also generated (entries 1−3). On the other hand, the reactions of substrates possessing electron-withdrawing bromo (**5f**) and trifluoromethyl (**5g**) groups at the meta position gave only monochlorination products **2f** and **2g** in high yields (entries 4 and 5), probably because the further decreased electron density of the benzene ring of these substrates by the monochlorination made it difficult for the second chlorination at the hindered position to proceed. These substrates showed relatively low reactivity, and the reaction of **5g** took 24 h to obtain product **2g** in 71% yield (entry 5). A similar trend in reactivity was observed for para-substituted benzamides. Substrates with electron-donating groups **5h−j** exhibited high reactivity, and the reactions gave a mixture of monochlorination products **2** and dichlorination products **3** in high combined yields within 4.5−7 h. The substrates having electron-withdrawing methylsulfonyl (**5k**) and nitro (**5l**) groups at the para position required longer reaction time (9−12 h), but high selectivity for monochlorination over dichlorination was also observed with these para-substituted substrates (entries 10 and 11).

A stoichiometric reaction of benzamide **5i** with $Pd(OAc)_2$ in acetonitrile provided palladacycle **6i**, presumably formed after C−H bond cleavage assisted by the bidentate directing group (Figure 1a). The same reaction of an *N*-(8-quinolinyl)benzamide derivative was reported by Chen and co-workers.[14] The reaction of complex **6i** under the anodic oxidation conditions gave the corresponding C−H monochlorination product **2i** and dichlorination product **3i** in 39 and 48% yields, respectively (Figure 1b).

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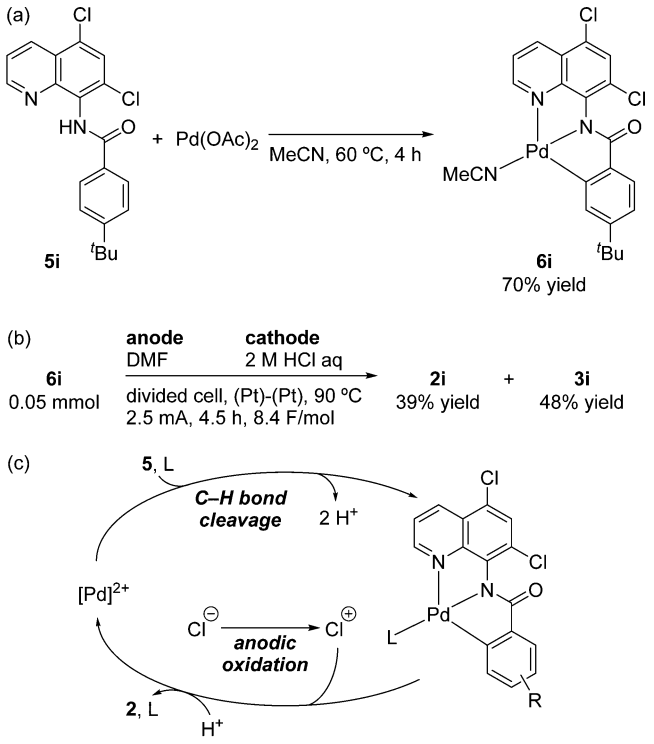
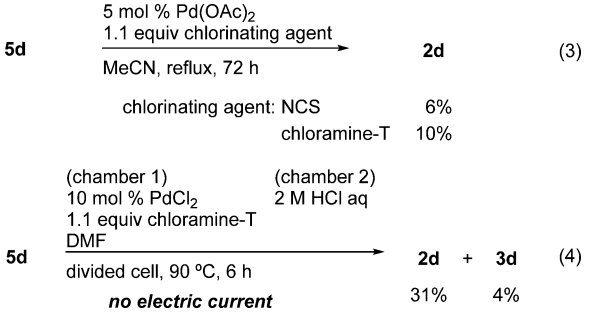


Figure 1. Stoichiometric reactions related to the palladium-catalyzed electrochemical C−H chlorination. (a) Reaction of benzamide **5i** with $Pd(OAc)_2$ to form palladacycle **6i**. (b) Reaction of palladacycle **6i** under the anodic oxidation conditions. (c) A proposed catalytic cycle of the palladium-catalyzed electrochemical C−H chlorination of benzamide **5**.

Based on these results, the palladium-catalyzed electrochemical C−H chlorination is considered to proceed via directed cleavage of the ortho C−H bond of benzamide **5**, followed by the reaction with electrochemically generated chlorinating species (Cl^+ or an equivalent species), as depicted in Figure 1c.

To compare the reaction conditions described here using anodic oxidation with the conventional conditions, the reactions using chlorinating agents were examined. Following Sanford's method for C−H chlorination,[15] benzamide **5d** was reacted with reagents such as NCS and chloramine-T using 5 mol % of $Pd(OAc)_2$ in refluxing MeCN for 72 h. Only monochlorination product **2d** was obtained in low yields (eq 3). The reaction with chloramine-T was also conducted in a divided cell used for the electrochemical reaction without applying an electric current, but products **2d** and **3d** were obtained in 31 and 4% yields, respectively (eq 4), which are much lower than those obtained under the electrochemical reaction conditions (Table 2, entry 2). These results indicate that the chlorinating species generated under the electrochemical conditions is more reactive than these conventional chlorinating agents.



Finally, the palladium-catalyzed C−H chlorination under anodic oxidation conditions was applied to the convergent synthesis of vismodegib, which inhibits the hedgehog signaling pathway and is an FDA-approved drug for treatment of basal cell carcinoma (Figure 2).[16] In this synthesis, the C−H chlorination

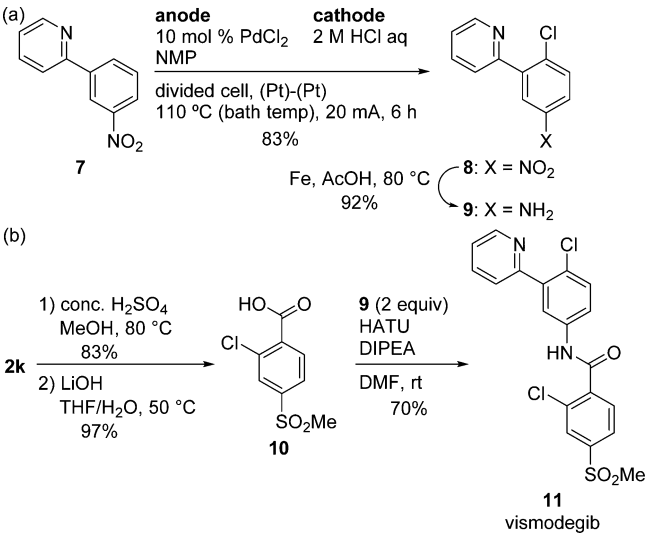


Figure 2. Synthesis of vismodegib using palladium-catalyzed electrochemical C−H chlorination. (a) Synthesis of aniline derivative **9** using C−H chlorination of arylpyridine **7**. (b) Synthesis of vismodegib by coupling of chlorinated carboxylic acid **10** with **9**.

was employed in two independent steps. First, the palladium-catalyzed electrochemical C−H chlorination was performed using arylpyridine **7** as a substrate,[2] and ortho-chlorination product **8** was obtained in 83% yield, even though the substrate has a strongly electron-withdrawing nitro group (Figure 2a). The reduction of the nitro group of **8** with iron in acetic acid gave the corresponding aniline derivative **9**.[16c] The synthesis of vismodegib was achieved by coupling of **9** with carboxylic acid **10** (Figure 2b). Methylsulfonyl-substituted chlorination product **2k**, obtained by palladium-catalyzed electrochemical C−H chlorination in entry 10 of Table 2, was treated with sulfuric acid in methanol[17] to form a methyl ester, which was then hydrolyzed using lithium hydroxide in THF/water[18] to afford **10** in high yield. HATU-mediated amide bond formation[18] using **9** and **10** in the presence of diisopropylethylamine in DMF provided vismodegib **11** in 70% yield.

In conclusion, the palladium-catalyzed electrochemical C−H chlorination of benzamide derivatives was achieved. The use of a bidentate directing group, 5,7-dichloro-8-quinolinyl group was effective in this reaction, and the reaction gave high yields of ortho-chlorination products from benzamide derivatives possessing various electro-donating and -withdrawing substituents. An efficient synthesis of vismodegib was also achieved using the palladium-catalyzed electrochemical C−H chlorination in two different steps.

EXPERIMENTAL SECTION

General Information. ^1H and $^{13}C\{^1H\}$ spectra were recorded on a JEOL ECX-400, AL-400, or ALPHA-400 spectrometer in $CDCl_3$ (using TMS as internal standard), DMSO-d_6, CD_2Cl_2, or acetone-d_6. IR spectra were recorded on a JASCO FT/IR-410 infrared spectrometer. ESI-TOF and DART-TOF MS analyses were performed on a JEOL JMS-T100LCS. Flash column chromatography was carried out with silica gel 60N (Kanto Chemical Co., Inc.) or Chromatorex NH (Fuji Silysia

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J. Org. Chem. XXXX, XXX, XXX−XXX

Chemical Ltd.). Anion-exchange membrane (Neosepta AHA, ASTOM Corporation) was washed with water, MeOH, and acetone before use.

The following starting materials and solvents were obtained from commercial sources and were used without further purification: benzoyl chloride, 2-methylbenzoyl chloride, 3-methoxybenzoyl chloride, 3-methylbenzoyl chloride, 3-fluorobenzoyl chloride, 3-bromobenzoyl chloride, 3-trifluoromethylbenzoyl chloride, 4-methoxylbenzoyl chloride, 4-(*tert*-butyl)benzoyl chloride, 4-methylbenzoyl chloride, 4-nitrobenzoyl chloride, 4-(methylsulfonyl)benzoic acid, thionyl chloride, *N*-chlorosuccinimide (NCS), Chloramine-T, palladium chloride, palladium acetate, triethylamine (Et_3N), hydrochloric acid, sulfuric acid, lithium hydroxide, HATU, *N,N*-diisopropylethylamine (DIPEA), Fe powder, *N,N*-dimethylformamide (DMF), AcOH, *N*-methylpyrrolidone (NMP), MeOH, THF, CH_2Cl_2, and MeCN. 8-Aminoquinoline was used after recrystallization from CH_2Cl_2/hexane. 2-(3-Nitrophenyl)pyridine (**7**) was prepared according to the literature procedure.[19]

Preparation of 5,7-Dichloro-8-quinolinamine. To a solution of 8-aminoquinoline (720 mg, 5.0 mmol) and Et_3N (0.070 mL, 0.50 mmol) in 10 mL of DMF in a 100 mL round-bottom flask was added slowly NCS (2.00 g, 15 mmol), and the mixture was stirred at room temperature for 2 h. The reaction mixture was filtered through a Celite pad and washed with Et_2O. The filtrate was extracted twice with Et_2O. The combined organic layers were washed with an aqueous solution of $Na_2S_2O_3$, an aqueous solution of $NaHCO_3$, water, and brine. The resulting solution was dried over anhydride Na_2SO_4, filtered, and concentrated. Flash column chromatography (silica gel 60 N, 20:1 hexane/AcOEt) of the crude material afforded 432 mg (40% yield) of 5,7-dichloro-8-quinolinamine as a yellow solid. The spectroscopic data of 5,7-dichloro-8-quinolinamine are in good agreement with those reported in literature.[20]

Preparation of *N*-(8-Quinolinyl)benzamide (1a). An oven-dried 100 mL three-necked flask was charged with 8-aminoquinoline (1.50 g, 10 mmol). The flask was evacuated and backfilled with nitrogen three times. Then Et_3N (1.5 mL, 11 mmol) and anhydrous CH_2Cl_2 (10 mL) were added to the flask. The mixture was cooled to 0 °C, and a suspension of benzoyl chloride (1.3 mL, 11 mmol) in anhydrous CH_2Cl_2 (5 mL) was added dropwise to the mixture. The reaction mixture was stirred for 6 h at room temperature. After the reaction, an aqueous solution of $NaHCO_3$ (20 mL) was added to the mixture, which was then extracted with CH_2Cl_2 (3 × 10 mL). The combined organic portions were washed with water (20 mL) and brine (20 mL). The resulting solution was dried over anhydrous Na_2SO_4, filtered, and concentrated. Column chromatography (High flash 3L, 5:1 hexane/AcOEt) using an automated flash chlomatography system (Yamazen Corporation) afforded 2.14 g (83% yield) of benzamide **1a** as a white solid. The spectroscopic data of **1a** are in good agreement with those reported in literature.[21]

General Procedure A for Preparation of *N*-(5,7-Dichloro-8-quinolinyl)benzamide derivatives. An oven-dried 50 mL two-necked flask was charged with 5,7-dichloro-8-quinolinamine (639 mg, 3.0 mmol). The flask was evacuated and backfilled with nitrogen three times. Then Et_3N (0.8 mL, 6.0 mmol) and anhydrous THF (10 mL) were added to the flask. The mixture was cooled to 0 °C, and benzoyl chloride (4.5 mmol) as added dropwise to the mixture. The reaction mixture was stirred at 0 °C for 30 min and then gradually warmed to rt overnight. After the reaction, an aqueous solution of $NaHCO_3$ (20 mL) was added to the resulting mixture, which was then extracted with AcOEt (3 × 10 mL). The combined organic portions were washed with brine (20 mL). The resulting solution was dried over anhydrous Na_2SO_4, filtered, and concentrated. The benzamide derivative was isolated by flash column chromatography and recrystallization.

***N*-(5,7-Dichloro-8-quinolinyl)benzamide (5a).** General procedure A was followed with 853 mg (4.0 mmol) of 5,7-dichloro-8-quinolinamine and 0.70 mL (6.0 mmol) of benzoyl chloride. Column chromatography (silica gel 60 N, 2:1 hexane/AcOEt), followed by recrystallization from $CHCl_3$/hexane afforded 308 mg (24% yield) of benzamide **5a** as a yellow solid: Mp 130−131 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52−7.62 (m, 4H), 7.77 (s, 1H), 8.09 (d, J = 6.8 Hz, 2H), 8.57 (dd, J = 1.6, 8.8 Hz, 1H), 8.89 (dd, J = 1.1, 4.4 Hz, 1H), 9.08 (brs, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 122.3, 125.1, 128.0, 128.5, 128.5, 128.7, 129.7, 131.4, 132.2, 133.3, 133.8, 143.4, 150.5, 165.3; IR (KBr) 3288, 1654, 1603, 1583, 1521, 1507, 1491, 1483, 1281, 950, 877, 785, 710, 687 cm^{-1}; HRMS (ESI-TOF) Calcd for $[M + Na]^+$ ($C_{16}H_{10}Cl_2N_2Na_1O_1$) m/z 339.0068, Found 339.0065.

***N*-(5,7-Dichloro-8-quinolinyl)-2-methylbenzamide (5b).** General procedure A was followed with 640 mg (3.0 mmol) of 5,7-dichloroquinolin-8-amine and 0.60 mL (4.5 mmol) of 2-methylbenzoyl chloride. Column chromatography (silica gel 60 N, 2:1 hexane/AcOEt) and recrystallization from $CHCl_3$/hexane afforded 326 mg (33% yield) of benzamide **5b** as a white solid: Mp 145−146 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.61 (s, 3H), 7.33 (t, J = 7.2 Hz, 2H), 7.42 (t, J = 7.2 Hz, 1H), 7.58 (dd, J = 4.0, 8.8 Hz, 1H), 7.78 (s, 1H), 7.82 (d, J = 6.8 Hz, 1H), 8.58 (dd, J = 1.6, 8.8 Hz, 1H), 8.62 (brs, 1H), 8.91 (dd, J = 1.6, 4.0 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 20.2, 122.3, 125.1, 125.8, 127.7, 128.3, 128.8, 130.0, 130.6, 131.1, 131.3, 133.2, 135.2, 137.6, 143.6, 150.7, 167.7; IR (KBr) 3229, 1665, 1602, 1584, 1512, 1485, 1455, 1389, 1362, 1305, 1287, 1274, 1237, 1139, 1058, 1045, 946, 927, 873, 857, 809, 787, 781 cm^{-1}; HRMS (ESI-TOF) Calcd for $[M + Na]^+$ ($C_{17}H_{12}Cl_2N_2Na_1O_1$) m/z 353.0224, Found 353.0228.

***N*-(5,7-Dichloro-8-quinolinyl)-3-methoxybenzamide (5c).** General procedure A was followed with 1.06 g (5.0 mmol) of 5,7-dichloroquinolin-8-amine and 1.1 mL (7.5 mmol) of 3-methoxybenzoyl chloride. Column chromatography (silica gel 60 N, 2:1 hexane/AcOEt) and recrystallization from CH_2Cl_2/hexane afforded 727 mg (42% yield) of benzamide **5c** as a yellow solid: Mp 131−132 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.90 (s, 3H), 7.15 (dd, J = 2.4, 8.4 Hz, 1H), 7.45 (t, J = 8.0 Hz, 1H), 7.56 (dd, J = 4.4, 8.8 Hz, 1H), 7.62 (s, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.77 (s, 1H), 8.56 (dd, J = 1.6, 8.8 Hz, 1H), 8.89 (dd, J = 1.6, 4.4 Hz, 1H), 9.07 (brs, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 55.4, 112.9, 118.7, 119.9, 122.3, 125.1, 128.5, 128.6, 129.7, 129.8, 131.4, 133.4, 135.2, 143.4, 150.6, 159.8, 165.2; IR (KBr) 3335, 1696, 1607, 1585, 1501, 1477, 1432, 1377, 1292, 1276, 1236, 1227, 1204, 1044, 988, 953, 879, 872, 811, 784, 746, 654 m cm^{-1}; HRMS (ESI-TOF) Calcd for $[M + Na]^+$ ($C_{17}H_{12}Cl_2N_2Na_1O_2$) m/z 369.0174, Found 369.0182.

***N*-(5,7-Dichloro-8-quinolinyl)-3-methylbenzamide (5d).** General procedure A was followed with 1.07 g (5.0 mmol) of 5,7-dichloroquinolin-8-amine and 1.1 mL (9.7 mmol) of 3-methylbenzoyl chloride. Column chromatography (silica gel 60 N, 2:1 hexane/AcOEt) and recrystallization from CH_2Cl_2/hexane afforded 593 mg (36% yield) of benzamide **5d** as a white solid: Mp 144−145 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.47 (s, 3H), 7.42−7.43 (m, 2H), 7.56 (dd, J = 4.4, 8.0 Hz, 1H), 7.76 (s, 1H), 7.87−7.90 (m, 2H), 8.56 (dd, J = 1.6, 8.0 Hz, 1H), 8.89 (dd, J = 1.2, 4.0 Hz, 1H), 9.03 (brs, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 21.4, 122.3, 125.0, 125.1, 128.4, 128.6, 128.6, 128.7, 129.5, 131.5, 133.1, 133.3, 133.9, 138.6, 143.4, 150.6, 165.5; IR (KBr) 1700, 1643, 1603, 1588, 1558, 1507, 1481, 1374, 1303, 1219, 1141, 1091, 1045, 951, 860, 839, 806, 778, 740 w cm^{-1}; HRMS (ESI-TOF) Calcd for $[M + H]^+$ ($C_{17}H_{13}Cl_2N_2O_1$) m/z 331.0405, Found 331.0409.

***N*-(5,7-Dichloro-8-quinolinyl)-3-fluorobenzamide (5e).** General procedure A was followed with 639 mg (3.0 mmol) of 5,7-dichloroquinolin-8-amine and 0.54 mL (4.5 mmol) of 3-fluorobenzoyl chloride. Column chromatography (silica gel 60 N, 5:1 hexane/AcOEt) and recrystallization from CH_2Cl_2/hexane afforded 212 mg (21% yield) of benzamide **5e** as a white solid: Mp 140−141 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (td, J = 2.4, 8.4 Hz, 1H), 7.49−7.59 (m, 2H), 7.77−7.78 (m, 2H), 7.86 (d, J = 7.6 Hz, 1H), 8.56 (dd, J = 0.8, 8.4 Hz, 1H), 8.89 (dd, J = 0.8, 4.4 Hz, 1H), 9.05 (brs, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 115.3 (d, J = 23.1 Hz), 119.4 (d, J = 20.6 Hz), 122.5, 123.5 (d, J = 2.9 Hz), 125.2, 128.6, 128.9, 129.7, 130.5 (d, J = 7.8 Hz), 131.1, 133.5, 136.2 (d, J = 6.6 Hz), 143.4, 150.7, 162.8 (d, J = 247.7 Hz), 164.1 (d, J = 2.4 Hz); IR (KBr) 1692, 1661, 1603, 1589, 1506, 1482, 1439, 1388, 1376, 1362, 1298, 1268, 1223, 1186, 1140, 959, 937, 896, 891, 880, 874, 868, 842, 812, 800, 783, 743 s cm^{-1}; HRMS (ESI-TOF) Calcd for $[M + Na]^+$ ($C_{16}H_9Cl_2F_1N_2Na_1O_1$) m/z 356.9974, Found 356.9973.

3-Bromo-*N*-(5,7-dichloro-8-quinolinyl)benzamide (5f). General procedure A was followed with 633 mg (3.0 mmol) of 5,7-dichloroquinolin-8-amine and 0.59 mL (4.5 mmol) of 3-bromobenzoyl chloride. Column chromatography (silica gel 60 N, 2:1 hexane/AcOEt) and recrystallization from CH_2Cl_2/hexane afforded 679 mg (58% yield)

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J. Org. Chem. XXXX, XXX, XXX−XXX

of benzamide **5f** as a pale brown solid: Mp 154−155 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (t, J = 8.0 Hz, 1H), 7.58 (dd, J = 4.4, 8.0 Hz, 1H), 7.72−7.76 (m, 2H), 8.00 (d, J = 8.0 Hz, 1H), 8.21 (s, 1H), 8.57 (dd, J = 1.2, 8.0 Hz, 1H), 8.90 (dd, J = 1.6, 4.0 Hz, 1H), 9.05 (brs, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 122.4, 122.9, 125.2, 126.5, 128.5, 129.0, 130.1, 130.2, 131.0, 131.2, 133.5, 135.2, 135.7, 143.4, 150.7, 164.0; IR (KBr) 1672, 1567, 1510, 1478, 1467, 1361, 1292, 1258, 1239, 951, 897, 882, 813, 789, 772, 745 s cm^{-1}; HRMS (ESI-TOF) Calcd for $[M + Na]^+$ ($C_{16}H_9Br_1Cl_2N_2Na_1O_1$) m/z 416.9173, Found 416.9191.

***N*-(5,7-Dichloro-8-quinolinyl)-3-(trifluoromethyl)benzamide (5g).** General procedure A was followed with 641 mg (3.0 mmol) of 5,7-dichloroquinolin-8-amine and 0.67 mL (4.5 mmol) of 3-trifluoromethylbenzoyl chloride. Column chromatography (silica gel 60 N, 2:1 hexane/AcOEt) and recrystallization from CH_2Cl_2/hexane afforded 314 mg (27% yield) of benzamide **5g** as a white solid: Mp 159−160 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (dd, J = 4.3, 8.2 Hz, 1H), 7.67 (t, J = 7.8 Hz, 1 H), 7.78 (s, 1H), 7.86 (d, J = 8.2 Hz, 1H), 8.27 (d, J = 7.8 Hz, 1H), 8.34 (s, 1H), 8.57 (dd, J = 1.6, 8.6 Hz, 1H), 8.90 (dd, J = 1.6, 5.5 Hz, 1H), 9.13 (brs, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 122.5, 123.7 (q, J = 272.4 Hz), 125.1 (q, J = 3.7 Hz), 125.3, 128.5, 128.9 (q, J = 3.6 Hz), 129.1, 129.4, 130.1, 131.0, 131.2, 131.3 (q, J = 32.9 Hz), 133.6, 134.7, 143.5, 150.7, 164.1; IR (KBr) 3296, 1660, 1585, 1522, 1507, 1487, 1478, 1334, 1319, 1271, 1176, 1092, 1080, 869, 783 m cm^{-1}; HRMS (ESI-TOF) Calcd for $[M + Na]^+$ ($C_{17}H_9Cl_2F_3N_2Na_1O_1$) m/z 406.9942, Found 406.9944.

***N*-(5,7-Dichloro-8-quinolinyl)-4-methoxybenzamide (5h).** General procedure A was followed with 639 mg (3.0 mmol) of 5,7-dichloroquinolin-8-amine and 0.62 mL (4.6 mmol) of 4-methoxylbenzoyl chloride. Column chromatography (silica gel 60 N, 2:1 hexane/AcOEt) and recrystallization from CH_2Cl_2/hexane afforded 431 mg (41% yield) of benzamide **5h** as a white solid: Mp 161−162 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.90 (s, 3H), 7.02 (d, J = 8.8 Hz, 2H), 7.55 (dd, J = 4.4, 8.8 Hz, 1H), 7.76 (s, 1H), 8.05 (d, J = 8.8 Hz, 2H), 8.55 (dd, J = 1.6, 8.8 Hz, 1H), 8.87 (dd, J = 1.6, 4.4 Hz, 1H), 9.03 (brs, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 55.5, 113.9, 122.3, 125.2, 126.2, 128.2, 128.6, 129.4, 130.0, 131.8, 133.4, 143.4, 150.5, 162.9, 164.9; IR (KBr) 3211, 1647, 1603, 1583, 1525, 1500, 1484, 1462, 1315, 1299, 1176, 1028, 946, 871, 842, 839, 763 cm^{-1}; HRMS (ESI-TOF) Calcd for $[M + Na]^+$ ($C_{17}H_{12}Cl_2N_2Na_1O_2$) m/z 369.0174, Found 369.0179.

4-(*tert*-Butyl)-*N*-(5,7-dichloro-8-quinolinyl)benzamide (5i). General procedure A was followed with 1.06 g (5.0 mmol) of 5,7-dichloroquinolin-8-amine and 1.4 mL (7.5 mmol) of 4-(*tert*-butyl)-benzoyl chloride. Column chromatography (silica gel 60 N, 10:1 hexane/AcOEt) and recrystallization from CH_2Cl_2/hexane afforded 294 mg (16% yield) of benzamide **5i** as a white solid: Mp 202−203 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (s, 9H), 7.54−7.57 (m, 3H), 7.76 (s, 1H), 8.03 (d, J = 8.6 Hz, 2H), 8.55 (dd, J = 1.6, 8.2 Hz, 1H), 8.87 (dd, J = 1.6, 4.3 Hz, 1H), 9.09 (brs, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 31.2, 35.1, 122.3, 125.2, 125.7, 127.9, 128.4, 128.6, 129.5, 131.0, 131.6, 133.4, 143.4, 150.5, 155.9, 165.2; IR (KBr) 2962, 1602, 1527, 1504, 1482, 1386, 1355, 1303, 1276, 947, 924, 872, 857, 811, 786, 758, 716 cm^{-1}; HRMS (ESI-TOF) Calcd for $[M + Na]^+$ ($C_{20}H_{18}Cl_2N_2Na_1O_1$) m/z 395.0694, Found 395.0669.

***N*-(5,7-Dichloro-8-quinolinyl)-4-methylbenzamide (5j).** General procedure A was followed with 639 mg (3.0 mmol) of 5,7-dichloroquinolin-8-amine and 0.51 mL (4.5 mmol) of 4-methylbenzoyl chloride. Column chromatography (silica gel 60 N, 2:1 hexane/AcOEt) and recrystallization from CH_2Cl_2/hexane afforded 230 mg (23% yield) of benzamide **5j** as a white solid: Mp 155−156 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.46 (s, 3H), 7.34 (d, J = 7.6 Hz, 2H), 7.56 (dd, J = 4.4, 8.8 Hz, 1H), 7.76 (s, 1H), 7.98 (d, J = 8.4 Hz, 2H), 8.55 (dd, J = 1.6, 8.4 Hz, 1H), 8.87 (dd, J = 1.6, 4.0 Hz, 1H), 9.03 (brs, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 21.6, 122.3, 125.2, 128.1, 128.4, 128.6, 129.4, 130.1, 131.1, 131.6, 133.4, 142.9, 143.4, 150.6, 165.4; IR (KBr) 3208, 1644, 1610, 1603, 1584, 1518, 1497, 1484, 1453, 1376, 1358, 1298, 1286, 1272, 1180, 1119, 1044, 952, 904, 870, 863, 841, 834, 800, 778, 753 cm^{-1}; HRMS (ESI-TOF) Calcd for $[M + H]^+$ ($C_{17}H_{13}Cl_2N_2O_1$) m/z 331.0405, Found 331.0393.

***N*-(5,7-Dichloro-8-quinolinyl)-4-nitrobenzamide (5l).** General procedure A was followed with 640 mg (3.0 mmol) of 5,7-dichloroquinolin-8-amine and 840 mg (4.5 mmol) of 4-nitrobenzoyl chloride. Column chromatography (silica gel 60 N, 2:1 hexane/AcOEt and Chromatorex NH gel, 10:1 $CHCl_3$/MeOH) afforded 296 mg (27% yield) of benzamide **5l** as a white solid: Mp 215−216 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (dd, J = 4.3, 8.6 Hz, 1H), 7.78 (s, 1H), 8.24 (d, J = 8.2 Hz, 2H), 8.39 (d, J = 8.2 Hz, 2H), 8.58 (dd, J = 1.2, 8.6 Hz, 1H), 8.90 (dd, J = 1.2, 3.9 Hz, 1H), 9.10 (brs, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 122.6, 124.0, 125.3, 128.5, 129.2, 129.4, 129.9, 130.6, 133.6, 139.5, 143.3, 150.1, 150.9, 163.5; IR (KBr) 1650, 1603, 1524, 1481, 1347, 1301, 879, 852, 783, 720 cm^{-1}; HRMS (ESI-TOF) Calcd for $[M + Na]^+$ ($C_{16}H_9Cl_2N_3Na_1O_3$) m/z 383.9919, Found 383.9929.

Preparation of *N*-(5,7-Dichloro-8-quinolinyl)-4-(methylsulfonyl)benzamide (5k).[22] An oven-dried 100 mL three-necked flask was charged with 4-(methylsulfonyl)benzoic acid (200 mg, 1.0 mmol). The flask was evacuated and backfilled with nitrogen three times. Then Et_3N (0.8 mL, 6.0 mmol), DMF (2 drops), and THF (1 mL) were added to the flask. Thionyl chloride (0.29 mL, 3.0 mmol) was added dropwise to the mixture. The reaction mixture was stirred at room temperature for 30 min and then heated to reflux for 30 min. After the resulting mixture was cooled to room temperature, volatile materials were removed in vacuo. The resulting acid chloride was used immediately without further purification.

To a solution of the acid chloride in CH_2Cl_2 (10 mL) was added dropwise at 0 °C a solution of 5,7-dichloro-8-quinolinamine (200 mg, 1.0 mmol) and Et_3N (0.8 mL, 6.0 mmol) in CH_2Cl_2 (10 mL). The resulting mixture was stirred overnight at room temperature. After the reaction, the mixture was quenched with an aqueous solution of $NaHCO_3$ (20 mL), which was then extracted with AcOEt (3 × 10 mL). The combined organic portions were washed with brine (20 mL). The resulting solution was dried over anhydrous Na_2SO_4, filtered, and concentrated. Column chromatography (silica gel 60 N, 2:1 CH_2Cl_2/Et_2O) afforded 106 mg (27% yield) of benzamide **5k** as a white solid: Mp 200−201 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.12 (s, 3H), 7.59 (dd, J = 4.3, 8.6 Hz, 1H), 7.78 (s, 1H), 8.12 (d, J = 8.6 Hz, 2H), 8.27 (d, J = 8.6 Hz, 2H), 8.58 (dd, J = 1.6, 8.6 Hz, 1H), 8.89 (dd, J = 1.6, 4.3 Hz, 1H), 9.11 (brs, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 44.4, 122.6, 125.3, 127.9, 128.5, 129.1, 129.3, 130.0, 130.7, 133.6, 138.8, 143.3, 143.7, 150.9, 163.8; IR (KBr) 1649, 1518, 1480, 1315, 1296, 1155, 1056, 949 m cm^{-1}; HRMS (ESI-TOF) Calcd for $[M + Na]^+$ ($C_{17}H_{12}Cl_2N_2Na_1O_3S_1$) m/z 416.9843, Found 416.9857.

General Procedure B for Palladium-Catalyzed Electrochemical C−H Chlorination of Benzamide Derivatives. The reaction was carried out in an H-type divided cell (anion-exchange membrane) equipped with two platinum electrodes (1.7 × 1.7 cm^2).[23] The anodic chamber was charged with a solution of a benzamide derivative (0.20 mmol) and a catalytic amount of palladium chloride (0.020 mmol, 3.6 mg) in DMF (10 mL). A 2 M aqueous solution (10 mL) of hydrochloric acid was introduced into the cathodic chamber. An electric field was applied at 90 °C under a constant current condition, and the mixture in the anodic chamber was stirred. After the reaction, the mixture was quenched with an aqueous solution of $NaHCO_3$ (20 mL) and was extracted with AcOEt (3 × 10 mL). The combined organic portions were washed with water (5 × 15 mL) and then with brine (20 mL). The resulting solution was dried over anhydride Na_2SO_4, filtered, and concentrated. The chlorination product was isolated by flash column chromatography.

Synthesis of 2,6-Dichloro-*N*-(5-chloro-8-quinolinyl)-benzamide (4a). General procedure B was followed with 62.1 mg (0.25 mmol) of benzamide **1a**, 4.3 mg (0.025 mmol) of palladium chloride. The reaction was carried out under a 20 mA constant current condition for 6 h. Column chromatography (silica gel 60 N, 80:1 CH_2Cl_2/Et_2O) afforded 10.0 mg (11% yield) of 2,6-dichloro-*N*-(5-chloro-8-quinolinyl)benzamide **4a** as a white solid: Mp 256−257 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.43 (m, 3H), 7.59 (dd, J = 4.4, 8.4 Hz, 1H), 7.68 (d, J = 8.8 Hz, 1H), 8.61 (dd, J = 1.2, 8.8 Hz, 1H), 8.83 (dd, J = 1.2, 3.6 Hz, 1H), 8.92 (d, J = 8.4 Hz, 1H), 10.01 (brs, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 117.1, 122.5, 125.4, 126.0, 127.2, 128.3, 131.0, 132.5, 133.2, 133.5, 136.0, 139.0, 148.9, 162.7; IR (KBr) 1679, 1520, 1483, 786, 768, 720 cm^{-1}; HRMS (ESI-TOF) Calcd for $[M + Na]^+$ ($C_{16}H_9Cl_3N_2Na_1O_1$) m/z 372.9678, Found 372.9668.

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J. Org. Chem. XXXX, XXX, XXX−XXX

Electrochemical Chlorination of Benzamide 5a. General procedure B was followed with 79.3 mg (0.25 mmol) of benzamide **5a**, 4.5 mg (0.025 mmol) of palladium chloride. The reaction was carried out under a 5 mA constant current condition for 6 h. Column chromatography (silica gel 60 N, 80:1 CH_2Cl_2/Et_2O) afforded 46.1 mg (52% yield) of 2-chloro-*N*-(5,7-dichloro-8-quinolinyl)benzamide **2a** as a white solid and 27.0 mg (28% yield) of 2,6-dichloro-*N*-(5,7-dichloro-8-quinolinyl)benzamide **3a** as a white solid.

*2-Chloro-N-(5,7-dichloro-8-quinolinyl)benzamide (**2a**).* Mp 143−144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.58 (m, 4 H), 7.76 (s, 1H), 7.92 (d, J = 7.6 Hz, 1H), 8.54 (d, J = 8.0 Hz, 1H), 8.87−8.93 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 122.3, 125.1, 127.0, 128.3, 129.2, 130.3, 130.5, 130.6, 130.7, 131.6, 131.8, 133.2, 134.4, 143.7, 150.9, 164.2; IR (KBr) 1679, 1580, 1501, 1430, 1362, 1295, 1141, 1048, 950, 784, 747 cm^{-1}; HRMS(ESI-TOF) Calcd for $[M + Na]^+$ ($C_{16}H_9Cl_3N_2Na_1O_1$) m/z 372.9678, Found 372.9671.

*2,6-Dichloro-N-(5,7-dichloro-8-quinolinyl)benzamide (**3a**).* Mp 212−213 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.42 (m, 3H), 7.58 (dd, J = 3.6, 8.0 Hz, 1H), 7.78 (s, 1H), 8.56 (dd, J = 1.6, 8.8 Hz, 1H), 8.78 (brs, 1H), 8.93 (dd, J = 1.6, 4.4 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 123.2, 124.8, 127.7, 128.2, 129.3, 131.2, 131.2, 131.7, 131.8, 132.7, 136.3, 144.8, 151.9, 162.0; IR (KBr) 1685, 1577, 1507, 1488, 1429, 1272, 955, 776 cm^{-1}; HRMS(ESI-TOF) Calcd for $[M + Na]^+$ ($C_{16}H_8Cl_4N_2Na_1O_1$) m/z 406.9288, Found 406.9293.

Electrochemical Chlorination of Benzamide 5b. General procedure B was followed with 66.4 mg (0.20 mmol) of benzamide **5b** and 3.8 mg (0.022 mmol) of palladium chloride. The reaction was carried out under a 2.5 mA constant current condition for 12 h. Column chromatography (silica gel 60 N, 5:1 Hexane/AcOEt) afforded 62.9 mg (86% yield) of 2-chloro-*N*-(5,7-dichloro-8-quinolinyl)-6-methylbenzamide **2b** as a white solid: Mp 196−197 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.58 (s, 3H), 7.19 (d, J = 6.8 Hz, 1H), 7.28 (d, J = 6.8 Hz, 2H), 7.57 (dd, J = 4.0, 8.8 Hz, 1H), 7.77 (s, 1H), 8.54−8.59 (m, 2H), 8.91 (dd, J = 1.6, 4.0 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 19.7, 122.4, 125.2, 127.0, 128.5, 128.7, 129.3, 130.1, 130.2, 130.4, 130.9, 133.3, 136.5, 137.8, 143.7, 150.8, 165.1; IR (KBr) 3209, 3170, 1680, 1600, 1581, 1496, 1488, 1457, 1449, 1388, 1375, 1359, 1274, 1177, 1141, 1048, 957, 901, 883, 871, 865, 780 s cm^{-1}; HRMS (ESI-TOF) Calcd for $[M + Na]^+$ ($C_{17}H_{11}Cl_3N_2Na_1O_1$) m/z 386.9835, Found 386.9821.

Electrochemical Chlorination of Benzamide 5c. General procedure B was followed with 69.4 mg (0.20 mmol) of benzamide **5c** and 3.7 mg (0.021 mmol) of palladium chloride. The reaction was carried out under a 2.5 mA constant current condition for 6 h. Column chromatography (silica gel 60 N, 20:1 CH_2Cl_2/Et_2O) afforded 64.1 mg (84% yield) of 2-chloro-*N*-(5,7-dichloro-8-quinolinyl)-5-methoxybenzamide **2c** as a yellow solid and 8.1 mg (10% yield) of 2,6-dichloro-*N*-(5,7-dichloro-8-quinolinyl)-3-methoxybenzamide **3c** as a white solid.

*2-Chloro-N-(5,7-dichloro-8-quinolinyl)-5-methoxybenzamide (**2c**).* Mp 165−166 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.85 (s, 3H), 6.98 (dd, J = 3.1, 9.0 Hz, 1H), 7.38 (d, J = 9.0 Hz, 1H), 7.46 (d, J = 3.1 Hz, 1H), 7.56 (dd, J = 4.3, 8.6 Hz, 1H), 7.76 (s, 1H), 8.55 (dd, J = 1.6, 8.6 Hz, 1H), 8.92−8.97 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 55.8, 115.5, 118.4, 122.4, 122.8, 125.2, 128.4, 129.3, 130.4, 130.8, 131.5, 133.3, 134.8, 143.8, 151.0, 158.4, 163.9; IR (KBr): 1678, 1581, 1502, 1485, 1478, 1462, 1317, 1232, 855, 811 cm^{-1}; HRMS (ESI-TOF) Calcd for $[M + Na]^+$ ($C_{17}H_{11}Cl_3N_2Na_1O_2$) m/z 402.9784, Found 402.9781.

*2,6-Dichloro-N-(5,7-dichloro-8-quinolinyl)-3-methoxybenzamide (**3c**).* Mp 253−254 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.92 (s, 3H), 7.26 (d, J = 9.2 Hz, 1H), 7.51 (d, J = 8.8 Hz, 1H), 7.77 (dd, J = 4.0, 8.4 Hz, 1H), 8.07 (s, 1H), 8.60 (dd, J = 2.0, 8.8 Hz 1H), 9.07 (dd, J = 1.6, 4.0 Hz, 1H), 10.95 (brs, 1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 56.7, 113.7, 119.9, 122.0, 123.2, 124.8, 127.7, 128.7, 129.2, 131.2, 131.8, 132.7, 137.2, 144.8, 151.9, 153.8, 161.9; IR (KBr) 1678, 1579, 1567, 1502, 1463, 1455, 1437, 1295, 1275, 1247, 1049, 954, 802 cm^{-1}; HRMS (ESI-TOF) Calcd for $[M + Na]^+$ ($C_{17}H_{10}Cl_4N_2Na_1O_2$) m/z 436.9394, Found 436.9375.

Electrochemical Chlorination of Benzamide 5d. General procedure B was followed with 66.4 mg (0.20 mmol) of benzamide **5d** and 3.5 mg (0.020 mmol) of palladium chloride. The reaction was carried out under a 2.5 mA constant current condition for 6 h. Column chromatography (silica gel 60 N, 80:1 CH_2Cl_2/Et_2O) afforded 57.3 mg (78% yield) of 2-chloro-*N*-(5,7-dichloro-8-quinolinyl)-5-methylbenzamide **2d** and 8.5 mg (11% yield) of 2,6-dichloro- *N*-(5,7-dichloro-8-quinolinyl)-3-methylbenzamide **3d** as white solids.

*2-Chloro-N-(5,7-dichloro-8-quinolinyl)-5-methylbenzamide (**2d**).* Mp 180−181 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.40 (s, 3H), 7.24 (m, 1H), 7.39 (d, J = 7.6 Hz, 1H), 7.56 (dd, J = 4.4, 8.8 Hz, 1H), 7.73−7.77 (m, 2H), 8.55 (dd, J = 1.6, 8.4 Hz, 1H), 8.90−8.94 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 20.8, 122.3, 125.2, 128.4, 128.5, 129.2, 130.3, 130.4, 130.8, 131.3, 132.7, 133.3, 133.9, 137.2, 143.8, 150.9, 164.3; IR (KBr) 1678, 1653, 1502, 1485, 950, 813, 778 m cm^{-1}; HRMS (ESI-TOF) Calcd for $[M + Na]^+$ ($C_{17}H_{11}Cl_3N_2Na_1O_1$) m/z 386.9835, Found 386.9810.

*2,6-Dichloro-N-(5,7-dichloro-8-quinolinyl)-3-methylbenzamide (**3d**).* Mp 245−246 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.41 (s, 3H), 7.24−7.29 (m, 2H), 7.56 (dd, J = 4.3, 8.6 Hz, 1H), 7.77 (s, 1H), 8.55 (dd, J = 4.3, 8.6 Hz, 1H), 8.83 (brs, 1H), 8.92 (dd, J = 1.6, 4.3 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 20.0, 122.4, 125.1, 127.7, 128.6, 129.2, 129.6, 130.0, 130.3, 132.0, 132.4, 133.3, 135.8, 135.9, 143.5, 150.7, 162.4; IR (KBr) 3145, 2923, 1680, 1581, 1507, 1449, 1380, 1283, 1140, 951, 887, 855, 807 w cm^{-1}; HRMS (ESI-TOF) Calcd for $[M + Na]^+$ ($C_{17}H_{10}Cl_4N_2Na_1O_1$) m/z 420.9445, Found 420.9438.

Electrochemical Chlorination of Benzamide 5e. General procedure B was followed with 67.2 mg (0.20 mmol) of benzamide **5e** and 3.7 mg (0.021 mmol) of palladium chloride. The reaction was carried out under a 2.5 mA constant current condition for 6 h. Column chromatography (silica gel 60 N, 80:1 CH_2Cl_2/Et_2O) afforded 45.7 mg (62% yield) of 2-chloro-*N*-(5,7-dichloro-8-quinolinyl)-5-fluorobenzamide **2e** and 9.9 mg (12% yield) of 2,6-dichloro-*N*-(5,7-dichloro-8-quinolinyl)-3-fluorobenzamide **3e** as white solids.

*2-Chloro-N-(5,7-dichloro-8-quinolinyl)-5-fluorobenzamide (**2e**).* Mp 182−183 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (ddd, J = 3.1, 7.6, 8.8 Hz, 1H), 7.49 (dd, J = 4.8, 8.8 Hz, 1H), 7.58 (dd, J = 4.4, 8.8 Hz, 1H), 7.67 (dd, J = 3.1, 8.4 Hz, 1H), 7.77 (s, 1H), 8.57 (dd, J = 1.6, 8.8 Hz, 1H), 8.80 (brs, 1H), 8.94 (dd, J = 1.6 Hz, 4.4 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 117.9 (d, J = 22.7 Hz), 119.1 (d, J = 22.7 Hz), 122.5, 125.3, 126.6 (d, J = 3.3 Hz), 128.4, 129.6, 130.4, 130.5, 132.2 (d, J = 7.8 Hz), 133.3, 135.9 (d, J = 7.0 Hz), 143.7, 151.1, 161.1 (d, J = 248.6 Hz), 162.9; IR (KBr) 1703, 1477, 1471, 1462, 753 m cm^{-1}; HRMS (ESI-TOF) Calcd for $[M + Na]^+$ ($C_{16}H_8Cl_3F_1N_2Na_1O_1$) m/z 390.9584, Found 390.9583.

*2,6-Dichloro-N-(5,7-dichloro-8-quinolinyl)-3-fluorobenzamide (**3e**).* Mp 259−260 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.57−7.66 (m, 2H), 7.78 (dd, J = 4.3, 9.0 Hz, 1H), 8.09 (s, 1H), 8.62 (d, J = 8.2 Hz, 1H), 9.08 (d, J = 3.1 Hz, 1H), 11.11 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 118.1 (d, J = 22.6 Hz), 119.0 (d, J = 20.2 Hz), 123.3, 124.9, 126.6 (d, J = 3.8 Hz), 127.7, 129.5, 129.7 (d, J = 7.1 Hz), 130.9, 131.8, 132.8, 137.9, 144.7, 152.1, 156.3 (d, J = 247.6 Hz), 160.5 (d, J = 2.4 Hz); IR (KBr) 1685, 1508, 1449, 1284 cm^{-1}; HRMS (ESI-TOF) Calcd for $[M + Na]^+$ ($C_{16}H_7Cl_4F_1N_2Na_1O_1$) m/z 424.9194, Found 424.9173.

Electrochemical Chlorination of Benzamide 5f. General procedure B was followed with 79.1 mg (0.20 mmol) of benzamide **5f** and 3.7 mg (0.021 mmol) of palladium chloride. The reaction was carried out under a 2.5 mA constant current condition for 6 h. Column chromatography (silica gel 60 N, 5:1 hexane/AcOEt) afforded 66.5 mg (77% yield) of 5-bromo-2-chloro-*N*-(5,7-dichloro-8-quinolinyl)-benzamide **2f** as a white solid: Mp 191−192 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, J = 8.6 Hz, 1H), 7.57−7.59 (m, 2H), 7.76 (s, 1H), 8.03 (d, J = 2.4 Hz, 1H), 8.56 (dd, J = 1.6, 8.6 Hz, 1H), 8.84 (brs, 1H), 8.93 (dd, J = 1.6, 3.9 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 120.8, 122.5, 125.2, 128.3, 129.6, 130.4, 130.6, 130.6, 132.0, 133.3, 133.4, 134.7, 136.1, 143.7, 151.1, 162.8; IR (KBr) 1700, 1507, 1491, 1472 cm^{-1}; HRMS(ESI-TOF) Calcd for $[M + H]^+$ ($C_{16}H_9Br_1Cl_3N_2O_1$) m/z 428.8964, Found 428.8982.

Electrochemical Chlorination of Benzamide 5g. General procedure B was followed with 77.0 mg (0.20 mmol) of benzamide **5g** and 3.6 mg (0.020 mmol) of palladium chloride. The reaction was carried out under a 2.5 mA constant current condition for 24 h. Column chromatography (silica gel 60 N, 40:1 CH_2Cl_2/Et_2O) afforded 59.3 mg (71% yield) of 2-chloro-*N*-(5,7-dichloro-8-quinolinyl)-5-

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J. Org. Chem. XXXX, XXX, XXX−XXX

(trifluoromethyl)benzamide **2g** as a white solid: Mp 186−187 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (dd, J = 3.6, 8.0 Hz, 1H), 7.63 (d, J = 8.4 Hz, 1H), 7.70 (d, J = 8.4 Hz, 1H), 7.77 (s, 1H), 8.17 (s, 1H), 8.56 (dd, J = 1.6, 8.8 Hz, 1H), 8.87 (brs, 1H), 8.93 (dd, J = 1.6, 3.6 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, CD_2Cl_2) δ 123.0, 124.1 (q, J = 272.3 Hz), 125.6, 127.7 (q, J = 3.7 Hz), 128.5, 128.7 (q, J = 3.0 Hz), 129.7 (q, J = 33.3 Hz), 130.1, 130.8, 130.9, 131.7, 133.6, 135.8 (q, J = 1.4 Hz), 136.0, 144.1, 151.7, 163.4; IR (KBr) 3219, 1669, 1586, 1517, 1487, 1334, 1262, 1188, 1116, 923, 906, 859, 828, 811, 782 cm^{-1}; HRMS (ESI-TOF) Calcd for $[M + Na]^+$ ($C_{17}H_8Cl_3F_3N_2Na_1O_1$) m/z 440.9552, Found 440.9548.

Electrochemical Chlorination of Benzamide 5h. General procedure B was followed with 69.4 mg (0.20 mmol) of benzamide **5h** and 3.6 mg (0.020 mmol) of palladium chloride. The reaction was carried out under a 2.5 mA constant current condition for 4.5 h. Column chromatography (silica gel 60 N, 80:1 CH_2Cl_2/Et_2O) afforded 43.0 mg (56% yield) of 2-chloro-*N*-(5,7-dichloro-8-quinolinyl)-4-methoxybenzamide **2h** as a yellow solid and 8.1 mg (10% yield) of 2,6-dichloro-*N*-(5,7-dichloro-8-quinolinyl)-4-methoxybenzamide **3h** as a white solid.

*2-Chloro-N-(5,7-dichloro-8-quinolinyl)-4-methoxybenzamide (**2h**).* Mp 141 °C (decompose); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.88 (s, 3H), 6.91 (dd, J = 2.4, 8.6 Hz, 1H), 7.02 (d, J = 2.4 Hz, 1H), 7.56 (dd, J = 4.3, 8.6 Hz, 1H), 7.76 (s, 1H), 7.96 (d, J = 8.2 Hz, 1H), 8.55 (dd, J = 1.6, 8.2 Hz, 1H), 8.92 (dd, J = 1.6, 4.3 Hz, 1H), 9.00 (brs, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 55.8, 113.0, 115.9, 122.3, 125.2, 126.1, 128.4, 129.0, 130.2, 131.2, 132.8, 133.1, 133.2, 143.8, 150.9, 162.0, 163.7; IR (KBr) 1653, 1603, 1563, 1524, 1496, 1484, 1453, 1314, 1296, 1277, 1236, 1138, 1042, 1030, 948, 927, 886, 860, 842, 811, 783 cm^{-1}; HRMS (ESI-TOF) Calcd for $[M + Na]^+$ ($C_{17}H_{11}Cl_3N_2Na_1O_2$) m/z 402.9784, Found 402.9769.

*2,6-Dichloro-N-(5,7-dichloro-8-quinolinyl)-4-methoxybenzamide (**3h**).* Mp 204−206 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.85 (s, 3H), 6.93 (s, 2H), 7.57 (dd, J = 4.4, 8.8 Hz, 1H), 7.77 (s, 1H), 8.55 (dd, J = 1.2, 8.4 Hz, 1H), 8.74 (brs, 1H), 8.92 (dd, J = 1.6, 4.8 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 56.2, 114.0, 123.2, 124.8, 127.7, 129.0, 129.2, 131.4, 131.8, 132.4, 132.7, 144.8, 152.0, 160.0, 162.1; IR (KBr) 1679, 1598, 1557, 1503, 1485, 1468, 1298, 1272, 1247, 1138, 1056, 1037, 957, 883, 866, 824, 816, 781 cm^{-1}; HRMS (ESI-TOF) Calcd for $[M + Na]^+$ ($C_{17}H_{10}Cl_4N_2Na_1O_2$) m/z 436.9394, Found 436.9376.

Electrochemical Chlorination of Benzamide 5i. General procedure B was followed with 74.6 mg (0.20 mmol) of benzamide **5i** and 3.6 mg (0.020 mmol) of palladium chloride. The reaction was carried out under a 2.5 mA constant current condition for 7 h. Column chromatography (silica gel 60 N, 200:1 CH_2Cl_2/Et_2O) afforded 45.0 mg (55% yield) of 4-(*tert*-butyl)-2-chloro-*N*-(5,7-dichloro-8-quinolinyl)-benzamide **2i** and 25.9 mg (29% yield) of 4-(*tert*-butyl)-2,6-dichloro-*N*-(5,7-dichloro-8-quinolinyl)benzamide **3i** as white solids.

*4-(tert-Butyl)-2-chloro-N-(5,7-dichloro-8-quinolinyl)benzamide (**2i**).* Mp 134−135 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (s, 9H), 7.42 (dd, J = 2.0, 8.2 Hz, 1H), 7.50 (d, J = 2.0 Hz, 1H), 7.55 (dd, J = 4.3, 8.6 Hz, 1H), 7.76 (s, 1H), 7.90 (d, J = 7.8 Hz, 1H), 8.55 (dd, J = 1.6, 8.6 Hz, 1H), 8.91 (dd, J = 1.6, 4.3 Hz, 1H), 8.97 (brs, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 31.0, 35.0, 122.3, 124.2, 125.2, 127.8, 128.4, 129.1, 130.3, 130.8, 130.9, 131.2, 131.5, 133.2, 143.7, 150.8, 156.1, 164.1; IR (KBr) 3169, 2964, 2871, 1668, 1605, 1586, 1508, 1481, 1385, 1361, 1309, 1256, 1137, 1041, 946, 930, 883, 859, 837, 794, 778 cm^{-1}; HRMS (ESI-TOF) Calcd for $[M + Na]^+$ ($C_{20}H_{17}Cl_3N_2Na_1O_1$) m/z 429.0304, Found 429.0311.

*4-(tert-Butyl)-2,6-dichloro-N-(5,7-dichloro-8-quinolinyl)-benzamide (**3i**).* Mp 245−246 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (s, 9H), 7.39 (s, 2H), 7.56 (dd, J = 3.9, 8.6 Hz, 1H), 7.77 (s, 1H), 8.55 (dd, J = 1.2, 8.2 Hz, 1H), 8.76 (brs, 1H), 8.92 (dd, J = 1.6, 4.3 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 30.9, 35.2, 122.4, 125.1, 125.5, 128.6, 129.1, 130.1, 130.1, 132.2, 132.9, 133.2, 143.5, 150.7, 155.2, 162.1; IR (KBr) 2965, 1682, 1596, 1578, 1499, 1457, 1375, 1260, 1136, 951, 886, 867 cm^{-1}; HRMS (ESI-TOF) Calcd for $[M + Na]^+$ ($C_{20}H_{16}Cl_4N_2Na_1O_1$) m/z 462.9914, Found 462.9912.

Electrochemical Chlorination of Benzamide 5j. General procedure B was followed with 66.2 mg (0.20 mmol) of benzamide **5i** and 3.6 mg (0.020 mmol) of palladium chloride. The reaction was carried out under a 2.5 mA constant current condition for 4.5 h. Column chromatography (silica gel 60 N, 150:1 CH_2Cl_2/Et_2O) afforded 42.3 mg (58% yield) of 2-chloro-*N*-(5,7-dichloro-8-quinolinyl)-4-methoxybenzamide **2j** and 8.8 mg (11% yield) of 2,6-dichloro-*N*-(5,7-dichloro-8-quinolinyl)-4-methoxybenzamide **3j** as white solids.

*2-Chloro-N-(5,7-dichloro-8-quinolinyl)-4-methylbenzamide (**2j**).* Mp 173−175 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.41 (s, 3H), 7.19 (d, J = 6.8 Hz, 1H), 7.33 (s, 1H), 7.55 (dd, J = 4.0, 8.4 Hz, 1H), 7.76 (s, 1H), 7.85 (d, J = 7.6 Hz, 1H), 8.55 (dd, J = 1.6, 8.8 Hz, 1H), 8.91−8.93 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 21.2, 122.3, 125.2, 127.9, 128.4, 129.1, 130.3, 130.9, 131.0, 131.1, 131.3, 131.5, 133.2, 142.8, 143.7, 150.9, 164.1; IR (KBr) 3201, 3162, 2993, 1656, 1608, 1541, 1524, 1484, 1452, 1389, 1380, 1355, 1311, 1284, 1266, 1150, 1138, 1041, 946, 929, 885, 866, 824, 810, 784, 766 cm^{-1}; HRMS (ESI-TOF) Calcd for $[M + Na]^+$ ($C_{17}H_{11}Cl_3N_2Na_1O_1$) m/z 386.9835, Found 386.9816.

*2,6-Dichloro-N-(5,7-dichloro-8-quinolinyl)-4-methylbenzamide (**3j**).* Mp 225−226 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.37 (s, 3H), 7.18 (s, 2H), 7.57 (dd, J = 4.3, 8.6 Hz, 1H), 7.78 (s, 1H), 7.56 (d, J = 8.2 Hz, 1H), 8.91−8.95 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 20.2, 123.2, 124.8, 127.7, 128.5, 129.3, 131.2, 131.3, 131.8, 132.7, 133.5, 141.6, 144.8, 152.0, 162.2; IR (KBr) 1686, 1597, 1577, 1499, 1459, 1386, 1374, 1273, 1146, 1136, 950, 885, 844, 813, 806, 781 m cm^{-1}; HRMS (ESI-TOF) Calcd for $[M + Na]^+$ ($C_{17}H_{10}Cl_4N_2Na_1O_1$) m/z 420.9445, Found 420.9429.

Electrochemical Chlorination of Benzamide 5k. General procedure B was followed with 79.1 mg (0.20 mmol) of benzamide **5k** and 3.6 mg (0.020 mmol) of palladium chloride. The reaction was carried out under a 2.5 mA constant current condition for 9 h. Column chromatography (silica gel 60 N, 10:1 CH_2Cl_2/Et_2O) afforded 64.4 mg (75% yield) of 2-chloro-*N*-(5,7-dichloro-8-quinolinyl)-4-methylslufonylbenzamide **2k** and 7.2 mg (8% yield) of 2,6-dichloro-*N*-(5,7-dichloro-8-quinolinyl)-4-methylslufonylbenzamide **3k** as white solids.

*2-Chloro-N-(5,7-dichloro-8-quinolinyl)-4-(methylsulfonyl)-benzamide (**2k**).* Mp 213-214 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.11 (s, 3H), 7.59 (dd, J = 4.4, 8.8 Hz, 1H), 7.77 (s, 1H), 7.95 (d, J = 7.6 Hz, 1H), 8.05−8.09 (m, 2H), 8.57 (dd, J = 1.6, 8.8 Hz, 1H), 8.80 (brs, 1H), 8.93 (dd, J = 0.80, 4.0 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 43.2, 123.4, 125.0, 125.8, 127.5, 128.3, 129.8, 130.3, 131.3, 131.4, 132.2, 132.9, 140.7, 143.1, 144.9, 152.4, 164.2; IR (KBr) 3232, 1683, 1524, 1485, 1375, 1305, 1151, 1095, 947, 823, 809, 763 m cm^{-1}; HRMS (ESI) Calcd for $[M + Na]^+$ ($C_{17}H_{11}Cl_3N_2Na_1O_3S_1$) m/z 450.9454, Found 450.9475.

*2,6-Dichloro-N-(5,7-dichloro-8-quinolinyl)-4-(methylsulufonyl)-benzamide (**3k**).* Mp 315−316 °C (decompose); ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.42 (s, 3H), 7.80 (dd, J = 3.9, 8.2 Hz, 1H), 8.10−8.11 (m, 3H), 8.62 (dd, J = 1.6, 8.6 Hz, 1H), 9.09 (dd, J = 1.6, 4.3 Hz, 1H), 11.21 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 42.9, 123.3, 124.9, 126.6, 127.7, 129.6, 130.6, 131.7, 132.8, 132.8, 140.6, 143.2, 144.6, 152.1, 161.0; IR (KBr) 3235, 3201, 1681, 1604, 1589, 1530, 1485, 1380, 1373, 1307, 1292, 1284, 1277, 1161, 1145, 1136, 1110, 978, 972, 953, 908, 878, 860, 832, 811, 757 cm^{-1}; HRMS (DART-TOF) Calcd for $[M + H]^+$ ($C_{17}H_{11}Cl_4N_2O_3S_1$) m/z 462.9245, Found 462.9218.

Electrochemical Chlorination of Benzamide 5l. General procedure B was followed with 72.2 mg (0.20 mmol) of benzamide **5l** and 3.6 mg (0.020 mmol) of palladium chloride. The reaction was carried out under a 2.5 mA constant current condition for 12 h. Column chromatography (silica gel 60 N, 80:1 CH_2Cl_2/Et_2O) afforded 47.2 mg (60% yield) of 2-chloro-*N*-(5,7-dichloro-8-quinolinyl)-4-nitrobenzamide **2l** and 4.3 mg (5% yield) of 2,6-dichloro-*N*-(5,7-dichloro-8-quinolinyl)-4-nitrobenzamide **3l** as white solids.

*2-Chloro-N-(5,7-dichloro-8-quinolinyl)-4-nitrobenzamide (**2l**).* Mp 232−233 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.77 (dd, J = 4.4, 8.8 Hz, 1H), 7.98 (d, J = 6.4 Hz, 1H), 8.10 (s, 1H), 8.35−8.41 (m, 2H), 8.59 (dd, J = 0.80, 8.8 Hz, 1H), 9.10 (dd, J = 1.2, 4.0 Hz, 1H), 10.98 (brs, 1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 122.4, 123.3, 124.8, 125.0, 127.4, 129.8, 130.4, 131.2, 131.5, 132.2, 132.9, 141.8, 144.8, 148.5, 152.4, 163.9; IR (KBr) 1680, 1519, 1347, 952, 886, 875 cm^{-1}; HRMS (ESI-TOF) Calcd for $[M + Na]^+$ ($C_{16}H_8Cl_3N_3Na_1O_3$) m/z 417.9529, Found 417.9518.

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J. Org. Chem. XXXX, XXX, XXX−XXX

*2,6-Dichloro-N-(5,7-dichloro-8-quinolinyl)-4-nitrobenzamide (**3l**).* Mp 266−267 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.80 (dd, J = 4.3, 8.2 Hz, 1H), 8.10 (s, 1H), 8.43 (s, 2H), 8.62 (dd, J = 1.6, 8.2 Hz, 1H), 9.09 (dd, J = 1.2, 4.3 Hz, 1H), 11.28 (brs, 1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 123.4, 123.4, 124.9, 127.7, 129.7, 130.5, 131.8, 132.8, 132.9, 141.7, 144.6, 148.2, 152.2, 160.9; IR (KBr) 2924, 1687, 1539, 1507, 1354, 1269, 954, 896, 885, 874, 813, 741 cm^{-1}; HRMS (DART-TOF) Calcd for $[M + H]^+$ ($C_{16}H_8Cl_4N_3O_3$) m/z 429.9320, Found 429.9295.

Preparation of Palladacycle 6i.[12] An oven-dried 20 mL Schlenk tube was charged with benzamide **5i** (112 mg, 0.30 mmol) and $Pd(OAc)_2$ (67.6 mg, 0.30 mmol). The Schlenk tube was evacuated and backfilled with nitrogen three times. Anhydrous MeCN (1 mL) was added to the flask, and the mixture was stirred at 60 °C for 4 h. After the reaction, the reaction mixture was cooled to room temperature. The resulting yellowish precipitate was washed with 1 mL of MeCN. Removal of the volatile materials in vacuo afforded palladacycle **6i** in 70% yield (108.5 mg) as a yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (s, 9H), 2.25 (s, 3H), 6.93 (d, J = 1.2 Hz, 1H), 7.06 (dd, J = 3.9, 7.8 Hz, 1H), 7.16 (dd, J = 1.6, 7.1 Hz, 1H), 7.46 (d, J = 7.8 Hz, 1H), 7.56 (s, 1H), 8.16 (d, J = 8.2 Hz, 1H), 8.27 (d, J = 3.1 Hz, 1H); Calcd for ($C_{22}H_{19}Cl_2N_3O_1Pd_1$): C 50.94, H 3.69, N 8.10, Found: C 50.59, H 3.66, N 7.93.

Electrochemical Chlorination of Palladacycle 6i. General procedure B was followed with 25.9 mg (0.050 mmol) of palladacycle **6i**. The reaction was carried out under a 2.5 mA constant current condition for 4.5 h. Column chromatography (silica gel 60 N, 50:1 CH_2Cl_2/Et_2O) afforded 7.9 mg (39% yield) of 4-(*tert*-butyl)-2-chloro-*N*-(5,7-dichloro-8-quinolinyl)benzamide **2i** and 10.6 mg (48% yield) of 4-(*tert*-butyl)-2,6-dichloro-*N*-(5,7-dichloro-8-quinolinyl)benzamide **3i** as white solids.

Palladium-Catalyzed C−H Chlorination Using Chlorination Reagents.[14] To a 50 mL round-bottom flask was charged with 66.2 mg (0.20 mmol) of benzamide **5d**, 2.3 mg (0.010 mmol) of $Pd(OAc)_2$, and 1.1 equiv of the chlorination agent (0.22 mmol, 29.5 mg of NCS or 61.9 mg of Chloramine-T) in CH_3CN (7.5 mL). The resulting mixture was heated to reflux for 72 h. After the reaction, the mixture was quenched with an aqueous solution of $NaHCO_3$ and was extracted with AcOEt (3 × 10 mL). The obtained organic portions were washed with brine (20 mL). The resulting solution was dried over anhydrous Na_2SO_4, filtered, and concentrated. The chlorination product was isolated by flash column chromatography (silica gel 60 N, 40:1 CH_2Cl_2/Et_2O), and the crude material afforded chlorination product **2d**. Using NCS, 4.5 mg (6% yield) of benzamide **2d** was obtained, while the reaction using Chloramine-T gave 7.8 mg (10% yield) of **2d**.

Palladium-Catalyzed C−H Chlorination Using Chloramin-T Without Electric Current. The reaction was carried out in an H-type divided cell (anion-exchange membrane) equipped with two platinum electrodes (1.7 × 1.7 cm^2). One chamber was charged with a solution of 66.7 mg (0.20 mmol) of benzamide **5d**, 61.9 mg of Chloramin-T (0.22 mmol), and a catalytic amount of palladium chloride (0.020 mmol, 3.6 mg) in DMF (10 mL). A 2 M aqueous solution (10 mL) of hydrochloric acid was introduced into the other chamber. The resulting mixture was stirred at 90 °C for 6 h with no electric current. After the reaction, the mixture was quenched with an aqueous solution of $NaHCO_3$ (20 mL) and was extracted with AcOEt (3 × 10 mL). The combined organic portions were washed with water (5 × 15 mL) and then with brine (20 mL). The resulting solution was dried over anhydride Na_2SO_4, filtered, and concentrated. Column chromatography (silica gel 60 N, 80:1 CH_2Cl_2/Et_2O) afforded 22.6 mg (31% yield) of **2d** and 3.3 mg (4% yield) of **3d**.

Electrochemical C−H Chlorination of 2-(3-Nitrophenyl)-pyridine. The reaction was carried out in an H-type divided cell (anion-exchange membrane) equipped with two platinum electrodes (1.7 × 1.7 cm^2). The anodic chamber was charged with a solution of 40.0 mg (0.20 mmol) of 2-(3-nitrophenyl)pyridine **7** and 3.6 mg (0.020 mmol) of $PdCl_2$ in NMP (10 mL). A 2 M aqueous solution (10 mL) of hydrochloric acid was introduced into the cathodic chamber. An electric field was applied at 110 °C under a 20 mA constant current condition, and the mixture in the anodic chamber was stirred for 6 h. After the reaction, the mixture was quenched with an aqueous solution of $NaHCO_3$ (20 mL) and was extracted with CH_2Cl_2 (3 × 10 mL). The obtained organic portions were washed with water (5 × 10 mL) and then with brine (20 mL). The resulting solution was dried over anhydrous Na_2SO_4, filtered, and concentrated. Column chromatography (silica gel 60 N, 200:1 CH_2Cl_2/Et_2O) afforded 38.9 mg (83% yield) of 2-(2-chloro-5-nitrophenyl)pyridine **8** as a white solid. The spectroscopic data of **8** are in good agreement with those reported in literature.[24]

Conversion of Nitroarene 8 into Aniline 9[14c]**.** A 50 mL round-bottom flask was charged with 117 mg (0.50 mmol) of 2-(2-chloro-5-nitrophenyl)pyridine **8** and 280 mg (5.0 mmol) of Fe powder, and AcOH (4 mL). The resulting mixture was stirred at 80 °C for 30 min. After cooling to room temperature, the mixture was quenched with H_2O at 0 °C and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic portions were washed with brine (20 mL). The resulting solution was dried over anhydride Na_2SO_4, filtered, and concentrated. Column chromatography (silica gel 60 N, 1:1 CH_2Cl_2/Et_2O) afforded 94.3 mg (92% yield) of 4-chloro-3-(2-pyridyl)aniline **9** as a brown solid. The spectroscopic data of **9** are in good agreement with those reported in literature.[21]

Conversion of Benzamide 2k into Carboxylic Acid 10.[17,18] An oven-dried 10 mL Schlenk tube was charged with 42.9 mg (0.10 mmol) of 2-chloro-*N*-(5,7-dichloro-8-quinolinyl)-4-(methylsulufonyl)-benzamide **2k**. The Schlenk tube was evacuated and backfilled with nitrogen three times. Conc. H_2SO_4 (4 drops) and anhydrous MeOH (2 mL) were added to the flask. The resulting mixture was stirred at 80 °C (reflux) for 48 h. After the reaction, solid $NaHCO_3$ was added to the mixture until the pH became ca. 8, and the mixture was filtered to remove the solid materials. The resulting solution was dried over anhydride Na_2SO_4, filtered, and concentrated. Column chromatography (silica gel 60 N, 80:1 → 1:1 CH_2Cl_2/Et_2O) afforded 20.5 mg (83% yield) of methyl 2-chloro-4-(methylsulfonyl)benzoate as a white solid and 16.9 mg (79% yield) of 5,7-dichloro-8-quinolinamine as a yellow solid. The spectroscopic data of methyl 2-chloro-4-(methylsulfonyl)-benzoate were in good agreement with those reported in literature.[24]

A 20 mL round-bottom flask was charged with 65.6 mg (0.26 mmol) of methyl 2-chloro-4-(methylsulfonyl)benzoate and 12.6 mg (0.52 mmol) of LiOH in THF/H_2O (1.4 mL, 1:1 (v/v)). The resulting mixture was stirred at 50 °C for 5 h. After cooling to room temperature, AcOH was added to the mixture until the pH became ca. 2. The mixture was extracted three times with AcOEt. The combined organic portions were washed with brine. The resulting solution was dried over anhydrous Na_2SO_4, filtered, and concentrated. Removal of the volatile materials in vacuo afforded 59.3 mg (97% yield) of 2-chloro-4-(methylsulfonyl)benzoic acid **10** as a white solid: Mp 194−195 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 3.25 (s, 3H), 7.98−8.10 (m, 3H); ^{13}C{^{1}H} NMR (100 MHz, acetone-d_6) δ 43.9, 126.7, 130.2, 132.7, 134.1, 136.4, 145.4, 165.8; IR (KBr) 3092, 3005, 2924, 2666, 2575, 1702, 1655, 1596, 1560, 1477, 1419, 1369, 1319, 1283, 1154, 1099, 1049, 971, 938, 899, 835, 782, 768 cm^{-1}; HRMS (ESI-TOF) $[M - H]^-$ ($C_8H_6Cl_1O_4S_1$) m/z 232.9675, Found 232.9663.

Condensation of Aniline 9 and Carboxylic Acid 10.[18] An oven-dried 10 mL two-necked flask was charged with carboxylic acid **10** (23.5 mg, 0.10 mmol). The flask was evacuated and backfilled with nitrogen three times. Aniline **9** (40.9 mg, 0.20 mmol), HATU (45.8 mg, 0.12 mmol), DIPEA (26.8 mg, 0.21 mmol), and anhydrous DMF (2 mL) were added to the flask. The solution was stirred for 24 h at room tempureture. After the reaction, the mixture was quenched with an aqueous solution of $NaHCO_3$ (5 mL) and was extracted with AcOEt (3 × 5 mL). The combined organic portions were washed with water (5 × 5 mL) and brine (10 mL). The resulting solution was dried over anhydrous Na_2SO_4, filtered, and concentrated. Column chromatography (silica gel 60 N, 10:1 AcOEt/hexane) afforded 29.6 mg (70% yield) of vismodegib **11** as a white solid. The spectroscopic data of **11** are in good agreement with those reported in literature.[24]

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■ ASSOCIATED CONTENT

Supporting Information

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^{1}H and ^{13}C{^{1}H} NMR spectra of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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