

Communication

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Posted Date: 6 March 2024

doi: 10.20944/preprints202403.0342.v1

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Communication

# Three-Step Synthesis of *N*-(7-Chloro-4-morpholinoquinolin-2-yl)benzamide from 4,7-Dichloroquinoline

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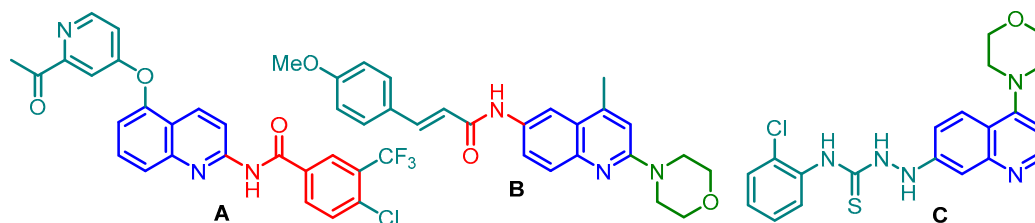
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**Abstract:** The quinoline derivative, *N*-(7-chloro-4-morpholinoquinolin-2-yl)benzamide, was synthesized in a conventional three-step procedure from 4,7-dichloroquinoline using *N*-oxidation reaction/C2-amidation reaction/C4  $S_NAr$  reaction sequence. The structure of the compound was fully characterized by FT-IR,  $^1H$ -,  $^{13}C$ -NMR, DEPT-135°, and ESI-MS techniques. Its physicochemical parameters (Lipinski's descriptors) were also calculated using the online SwissADME database. Such derivatives are relevant therapeutic agents exhibiting potent anticancer, antibacterial, antifungal, and antiparasitic properties.

**Keywords:** 4,7-dichloroquinoline; *N*-oxides; C-H bond functionalization; C2-amidation reaction; C4  $S_NAr$  reaction; *N*-(quinolinyl)morpholines; *N*-(quinolinyl)amides; Lipinski' descriptors

## 1. Introduction

Quinoline and morpholine are favored molecular frameworks for medicinal and advanced materials chemistry [1–6]. (Quinolinyl)amides and *N*-(quinolinyl)morpholines are especially interesting biological active molecules that can serve as useful scaffolds in pharmaceutical research. They can act as human vanilloid receptor type 1 (TRPV1) antagonists and melanin-concentrating hormone 1 receptor (MCH1R) antagonists [7–9], antifungal, antibacterial, and trypanocidal agents [10–13]. In particular, *N*-(quinolin-2-yl)benzamide derivative **A** (Figure 1), designed and synthesized as an anticancer sorafenib congener, presented interesting antiproliferative activity (HCT-116, MCF-7, and SK-BR3 cancer cell lines) [14]. On the other hand, the 4-(6-amidoquinolin-2-yl)morpholine **B** is a potent MCH1R antagonist, implicated in body weight (obesity) regulation, a major contributor to the development of diseases including type 2 diabetes mellitus, coronary heart disease, certain forms of cancer, and osteoarthritis [9], and 4-(quinolin-4-yl)morpholine **C** exhibited some *in vitro* antibacterial activity [15].



**Figure 1.** Representative examples of pharmacological agents based on *N*-(quinolinyl)amide and *N*-(quinolinyl)morpholine scaffolds.

Additionally, pincer palladium complexes, based on the *N*-(quinolin-8-yl)amide ring, have been widely explored for diverse catalytic transformations [16], and 4,7-dichloroquinoline has been

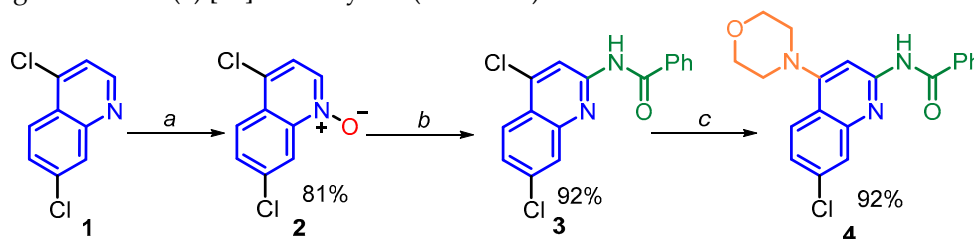
extensively used in drug and functional material research as an affordable chemical intermediate for numerous bioactive functionalized 4-amino-quinoline compounds [17–20].

Due to the paramount significance of the functionalized quinoline core in the search for drug candidates and medicinal chemistry, the development of new synthetic methodologies remains an active area. Among modern methodologies, there is regioselective functionalization of the quinoline ring through C-H activation, especially via *N*-oxide formation, using it as a directing group [21,22]. The latter is considered one of the most powerful and, thus, attractive approaches for synthesizing C-2 and C-8 functionalized quinoline compounds under mild reaction conditions [23–26]. In particular, metal-free deoxygenative 2-amidation of quinoline *N*-oxides is one of the most promising constructions of *N*-acylated 2-aminoquinolines, in which amides and nitriles are used as the amidation reagents in the presence of several promoters, i.e., oxalyl chloride, trifluoroacetic anhydride/2-fluoropyridine mixture, TsOH·H<sub>2</sub>O or selectfluor-methylcarbazate (NH<sub>2</sub>NHCO<sub>2</sub>Me) combination, and under Brønsted acidic ionic liquid (BAIL, [BSmim][OTf]) medium [27–31]. Such approaches constitute a paradigm in diversity-oriented synthesis strategies, permitting the late-stage diversification of key pharmaceutical scaffolds [32].

Considering the above-stated aspects and as a continuation of our efforts to prepare new bioactive 7-chloroquinoline-based molecules [33–38], we designed, prepared, and characterized the above-mentioned *N*-(7-chloro-4-morpholinoquinolin-2-yl)benzamide. Therefore, this work describes a practical, efficient method for synthesizing the title compound through the *N*-oxidation reaction/C2-amidation reaction/C4 S<sub>N</sub>Ar reaction sequence using commercially accessible reagents.

## 2. Results and Discussion

The *N*-(7-chloro-4-morpholinoquinolin-2-yl)benzamide (**4**) was easily prepared through a conventional three-step procedure from commercially available 4,7-dichloroquinoline (**1**), which was oxidized with a 1.2 equivalent of *m*-chloroperbenzoic acid (*m*-CPBA) in CHCl<sub>3</sub> at room temperature for 5 h to give *N*-oxide (**2**) [39] in 81% yield (Scheme 1).



**Scheme 1.** Three-step synthesis of *N*-(7-chloro-4-morpholinoquinolin-2-yl)benzamide (**4**) from commercially available 4,7-dichloroquinoline (**1**): (a) Oxidation step: *m*-CPBA, CHCl<sub>3</sub>, rt, 5 h; (b) C2 functionalization (amidation) process: Ph-C≡N, 97% H<sub>2</sub>SO<sub>4</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 70 °C, 24 h; (c) C4 functionalization (amination) process: Morpholine, K<sub>2</sub>CO<sub>3</sub>, DMF, 120 °C, 24 h.

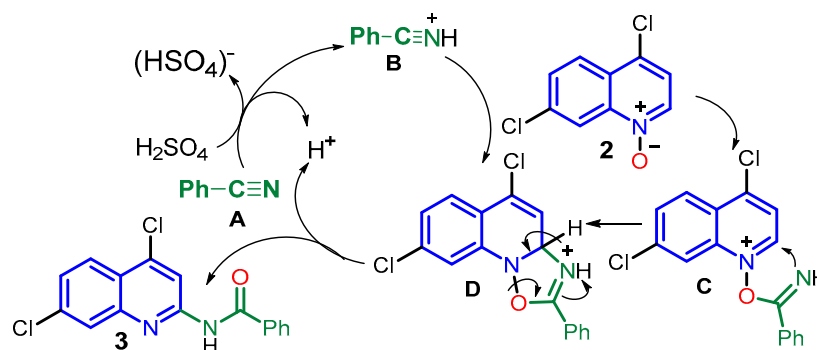
This *N*-oxide was also obtained in 87% yield using acetic acid and 30% hydrogen peroxide mixture [40] as an oxidant reagent at 70 °C for 1 h. The reaction of (**2**) with benzonitrile proceeded in refluxing dichloromethane and conc. sulfuric acid at 70 °C for 24 h with deoxygenation and provided *N*-(quinolin-2-yl)benzamide (**3**) in 92% yield (a key C2 amidation process). Note the conditions reported by Chen et al. in 2018 (TsOH·H<sub>2</sub>O, 150 °C, 12 h) to carry out C-H functionalization via C2 amidation [29] failed in our hands. The final step of the developed method is the nucleophilic aromatic substitution (S<sub>N</sub>Ar) involving the displacement of the C4-chlorine atom in quinoline compound (**3**) to obtain titled quinoline (**4**) in 92% yield. That was achieved through a base-promoted amination [41], easily realized by reacting 4-chloroquinoline derivative (**3**) and morpholine in the presence of K<sub>2</sub>CO<sub>3</sub> in refluxing DMF for 24 h (Scheme 1). This protocol is valuable for industrial applications due to its simplicity of operation, transition metal-free conditions, and scalability.

The structural elucidation of the intermediate (**2**) and final compounds (**3-4**) was achieved based on spectroscopic data, and the results are presented in the experimental section and the electronic supporting information (ESI). Their infrared spectra record the absorption bands associated with the

functional groups present in their structure. Characteristic amide  $\text{-C=O}$  strain vibration appeared in 1693 and 1674  $\text{cm}^{-1}$ , respectively, for (3) and (4), while the band at 1287  $\text{cm}^{-1}$ , corresponding to the tension of the N-O bond of precursor (2), is not present that confirms successful deoxygenated amidation procedure of (2) to form (3) (ESI, Figure S1-S3). This C-2 functionalization process is also indirectly corroborated by the absence of the signal of proton H2 in the  $^1\text{H}$  NMR spectra of quinolines (3-4); meanwhile, the doublet-shaped signal centered at 8.43 ppm with a coupling constant of 6.6 Hz corresponds to the hydrogen that is in position 2 of the quinoline ring is observed in the proton spectra of *N*-oxide (2) (Figure S7, S9, and S11). Each product (3-4) formation was further verified by its mass spectra. The electrospray ionization (ESI) technique in the positive mode of the obtained *N*-(quinolin-2-yl) benzamides (3-4) allowed us to observe the molecular ion peak  $[\text{M}+\text{H}^+]$  at  $m/z$  319.0/317.0 and 370.1/368.1 for  $\text{C}_{16}\text{H}_{10}\text{Cl}_2\text{N}_2\text{O}$  and  $\text{C}_{20}\text{H}_{18}\text{ClN}_3\text{O}_2$  molecular formula, exhibiting the isotopic contribution of  $^{37}\text{Cl}$  in the ratio of ~1:2 and 1:3 ( $^{37}\text{Cl}/^{35}\text{Cl}$ ), respectively Figure S5-S6).

The  $^{13}\text{C}$ -NMR and DEPT-135° spectra, shown in Figures S8, S10, and S12, were analyzed to complete the characterization. Each hydrogen and carbon atom signal is assigned by carefully analyzing the homonuclear and heteronuclear correlation spectra (COSY, HMBC, and HSQC experiments) (Figure S13-S20).

According to previous literature reports [29,42,43], a plausible reaction mechanism of the key C2 amidation process could be proposed. Nitrilium ion **B**, generated *in situ* from benzonitrile **A** with sulfuric acid, could react with *N*-oxide (2) as a dipolarophile via the [3+2]-dipolar cycloaddition to afford the five-membered oxadiazolidine intermediate **D** or as an electrophilic reagent through nucleophilic addition to form the Reissert-type intermediate **C** which is susceptible to intramolecular nucleophilic attack producing the intermediate **D**. The latter undergoes rearomatization with rupture of the bond (N-O) and a loss of a proton to form the stable product (3) (Scheme 2).



**Scheme 2.** Plausible reaction mechanism of C2 amidation of *N*-oxide (2) with  $\text{PhC}\equiv\text{N}$  to form *N*-(quinolin-2-yl) benzamide (3).

However, the low reactivity of such *N*-oxides as a 1,3-dipole in the cycloaddition reaction [43] makes the direct formation of intermediate **D** less possible. Thus, it is believed that its formation via the trapping of highly electrophilic intermediate **B** with weakly nucleophilic *N*-oxide (2) and subsequent intramolecular nucleophilic attack [42] is the more probable.

Due to the pharmacological importance of the obtained quinoline benzamides (3-4), we addressed the SwissADME software [44], which allowed us to rapidly estimate the potential biological activity of newly synthesized molecules. According to the predictions (Table S1), benzamides (3-4) displayed good drug-likeness scores with an acceptable hydrophilic-lipophilic balance (cLogP 3.89 and cLogP 3.16, respectively), obeying Lipinski's rule [45] and presenting the optimal range for each six physicochemical properties (lipophilicity, size, polarity, solubility, flexibility, and saturation) in the hexagon snapshots [46]. Interestingly, introducing the benzamide fragment in the C-2 position of the quinoline ring (1) increased the lipophilicity of the comp. (3), while the second functionalization of carbon C-4 lowered it to ideal parameters (comp. (4)). However, both prepared benzamides could have a good hematoencephalic barrier permeation (the total molecular polar surface area, TPSA < 140 Å<sup>2</sup>) (Table S1, Figure S21). Their ability to permeate the blood-brain



barrier (BBB) is a relevant factor in drug design. Crossing the BBB easily, they could be distributed homogeneously throughout the central nervous system (CNS). Noteworthy that according to the SwissTargetPrediction tools [47], the most achievable macromolecular targets of *N*-(7-chloro-4-morpholinoquinolin-2-yl)benzamide (**4**) would be protein kinase inhibitors (40%) or phosphodiesterase modulator (33%) while these targets are less feasible for *N*-(4,7-dichloroquinolin-2-yl) benzamide (**3**) (33% and 13.3%, respectively) (Figure S22).

### 3. Materials and Methods

#### 3.1. Chemical Analysis

The solvents and reagents employed in the synthesis of the intermediate and final compounds were of purity grade for synthesis. The composition and monitoring of the reactions, as well as the preliminary analysis of the purity of the synthesized compounds, were carried out by thin-layer chromatography (TLC) on Silufol UV254 plates of 0.25 mm thickness, revealed in a UV light chamber of 254 nm or an ethanolic solution of phosphomolybdic-sulfuric acids. The melting points of the products were determined in a Fisher-Johns melting point apparatus and the values were not corrected, reporting the average of three measurements. Infrared spectra (FT-IR) were acquired on a Thermo Scientific Nicolet iS50 FT-IR spectrophotometer with Fourier transform, with attenuated total reflectance (ATR) module, acquisition range: 4000–400  $\text{cm}^{-1}$  (256 scans, resolution of 2  $\text{cm}^{-1}$ ).

Mass spectra were obtained in UltraScan mode using a Hitachi LaChrom Elite HPLC liquid chromatograph coupled to a Bruker Daltonics AmaZon-X mass selective detector equipped with an Apollo-type electrospray ionization or ESI (ElectroSpray Ionization) source in positive mode, and a quadrupole ion trap or QIT (Quadrupole Ion Trap) analyzer. The acquisition of nuclear magnetic resonance spectra  $^1\text{H}$ ,  $^{13}\text{C}$ , and 2D variants was achieved using a Bruker Avance-400 spectrometer (400 MHz for  $^1\text{H}$  and 100 MHz for  $^{13}\text{C}$ ) using deuterated chloroform ( $\text{CDCl}_3$ , 99.8% Merck®) as the solvent. Chemical shift values ( $\delta$ ) are expressed in ppm. In  $^1\text{H}$ -NMR spectra, the scale was adjusted from the residual chloroform signal (7.26 ppm). Similarly, the  $^{13}\text{C}$ -NMR spectra were scaled from the signal characteristic for the solvent ( $\text{CDCl}_3$ ). The coupling constants ( $J$ ) are given in Hz; the multiplicity of signals is expressed by the following abbreviations: (s) singlet, (d) doublet, (t) triplet, (dd) doublet of doublets, and (m) multiplet.

#### 3.2. Step 1: Preparation of 4,7-Dichloroquinoline 1-Oxide (**2**)

In a 10 mL flask, 4,7-dichloroquinoline (**1**) (197 mg, 1 mmol) was dissolved in chloroform (2.5 mL) and stirred for 5 min. Then, *m*-CPBA (206 mg, 1.2 mmol) was added gradually. It was allowed to stir for 5 hours at room temperature. Once the reaction (TLC monitoring) was completed, the reaction mixture was neutralized with a  $\text{NaHCO}_3$  solution, and then the organic phase was extracted with ethyl acetate (3x20 mL). The resulting extracts were dried (anhydrous  $\text{Na}_2\text{SO}_4$ ), and the solvent was removed by distillation. The crude product was purified by column chromatography with silica gel using a mixture of petroleum ether–ethyl acetate (1:3) to obtain 172.5 mg of *N*-oxide (**2**) as a white solid (81% yield).  $R_f$  = 0.41 (petroleum ether–ethyl acetate, 1:3); Mp. 164–166 °C; IR (ATR,  $\nu_{\text{max}}/\text{cm}^{-1}$ ): 3095 and 3043 ( $\nu_{\text{ArC-H}}$ ), 1497–1604 ( $\nu_{\text{ArC=C}}$ ), 1287 ( $\nu_{\text{N-O}}$ ), 1085 ( $\nu_{\text{ArC-Cl}}$ ) 812–886 ( $\nu_{\text{ArC-H}}$ ).  $^1\text{H}$ -NMR (400 MHz,  $\text{CDCl}_3$ ),  $\delta$ (ppm): 8.79 (d,  $J$  = 1.9 Hz, 1H, 8-H), 8.43 (d,  $J$  = 6.6 Hz, 1H, 2-H), 8.16 (d,  $J$  = 9.0 Hz, 1H, 5-H), 7.70 (dd,  $J$  = 9.0, 1.95 Hz, 1H, 6-H), 7.37 (d,  $J$  = 6.55 Hz, 1H, 3-H).  $^{13}\text{C}$ -NMR (101 MHz,  $\text{CDCl}_3$ ),  $\delta$ (ppm): 142.4 (8a-C), 138.3 (7-C), 135.9 (2-C), 130.8 (6-C), 129.8 (4-C), 126.8 (5-C), 126.6 (4a-C), 121.2 (3-C), 120 (8-C).

#### 3.3. Step 2: Synthesis of *N*-(4,7-Dichloroquinolin-2-yl) Benzamide (**3**)

In a 10 mL crimp vial equipped with a magnetic stir, benzonitrile (0.824 mL, 8 mmol) and 97%  $\text{H}_2\text{SO}_4$  (0.107 mL, 2 mmol) were added. It was left stirring for 1 min. at room temperature, then *N*-oxide (**2**) (213 mg, 1 mmol) in  $\text{CH}_2\text{Cl}_2$  (2 mL) was added. The reaction mixture was left stirring for 2 min. at room temperature, the reaction system was sealed and heated to 70 °C in a reflux system for 24 hours. TLC monitored the progress of the reaction. Once the reaction was finished, ethyl acetate

(3x20 mL) and brine were added. The organic phase was separated and dried over anhydrous  $\text{Na}_2\text{SO}_4$ . The solvent was removed by distillation. The crude product was purified by column chromatography with silica gel using a mixture of petroleum ether–ethyl acetate (6:1) to obtain 290.7 mg of benzamide (**3**) as a white solid (92% yield).  $R_f$  = 0.60 (petroleum ether–ethyl acetate, 7:1); Mp. 133–134 °C; IR (ATR,  $\nu_{\text{max}}/\text{cm}^{-1}$ ): 3334 ( $\nu_{\text{N-H}}$ ), 2925 and 2856 ( $\nu_{\text{ArC-H}}$ ), 1693 ( $\nu_{\text{C=O}}$ ), 1576–1393 ( $\nu_{\text{ArC=C}}$ ), 1250 ( $\nu_{\text{C-N}}$ ), 863–759 ( $\gamma_{\text{ArC-H}}$ ).  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ),  $\delta(\text{ppm})$ : 8.82 (s, 1H, N-H, -NH), 8.77 (s, 1H, 3-H), 8.11 (d,  $J$  = 9.0 Hz, 1H, 5-H), 8.00–7.97 (m, 2H, 2'-H/6'-H), 7.83 (d,  $J$  = 2.0 Hz, 1H, 8-H), 7.65–7.59 (m, 1H, 4'-H), 7.54–7.52 (m, 2H, 3'-H/5'-H), 7.49 (dd,  $J$  = 9.0, 2.0 Hz, 1H, 6-H).  $^{13}\text{C-NMR}$  (101 MHz,  $\text{CDCl}_3$ ),  $\delta(\text{ppm})$ : 165.9 (C=O), 151.5 (2-C), 147.6 (8a-C), 144.5 (4-C), 137.1 (7-C), 133.6 (1'-C), 132.8 (4'-C), 129.8 (3'-C/5'-C), 127.4 (2'-C/6'-C), 127 (6-C), 126.7 (8-C), 125.7 (5-C), 123.1 (4a-C), 114.4 (3-C). COSY correlation [ $\delta\text{H}/\delta\text{H}$ ]: 8.11/7.49 [5-H/6-H], 7.97/7.54 [(2'-H/6'-H)/(3'-H/5'-H)], 7.83/7.49 [8-H/6-H], 7.62/7.54 [4'-H/(3'-H/5'-H)]. HSQC correlation [ $\delta\text{H}/\delta\text{C}$ ]: 8.77/114.4 [3-H/3-C], 8.11/125.7 [5-H/5-C], 7.97/127.4 [(2'-H/6'-H)/(2'-C/6'-C)], 7.83/126.7 [8-H/8-C], 7.62/132.8 [4'-H/4'-C], 7.54/129 [(3'-H/5'-H)/(3'-C/5'-C)], 7.49/127 [6-H/6-C]. HMBC correlation [ $\delta\text{H}/\delta\text{C}$ ]: 8.77/123.1/144.5 [3-H/4a-C/4-C], 8.11/137.1/144.5/147.6 [5-H/7-C/4-C/8a-C], 7.97/127.4/132.8/165.9 [(2'-H/6'-H)/(2'-C/6'-C)/4'-C/0'-C], 7.83/123.1/127.1/137.1 [8-H/4a-C/6-C/7-C], 7.62/127.4 [4'-H/(2'-C/6'-C)], 7.54/129/133.6 [(3'-H/5'-H)/(3'-C/5'-C)/1'-C], 7.49/123.1/126.7/137.1 [6-H/4a-C/8-C/7-C]. ESI-MS,  $m/z$  (%): calculated mass for  $\text{C}_{16}\text{H}_{11}\text{Cl}_2\text{N}_2\text{O}_2$ : 318.0 ( $^{37}\text{Cl}$ ), 316.0 ( $^{35}\text{Cl}$ ); found,  $[\text{M}+\text{H}]^+$ : 319.0 (61%), 317.0 (100 %).

#### 3.4. Step 3: Synthesis of *N*-(7-Chloro-4-morpholinoquinolin-2-yl) Benzamide (**4**)

In a 10 mL crimp vial equipped with a magnetic stir, benzamide (**3**) (316 mg, 1 mmol), morpholine (0.346 mL, 4 mmol), and  $\text{K}_2\text{CO}_3$  (413 mg, 3 mmol) in DMF (2.5 mL) were mixed. The reaction system was sealed and heated at 120 °C for 24 hours. TLC monitored the progress of the reaction. Once the reaction was finished, the reaction mixture was treated with brine. The precipitate was obtained from the mother liquor. It was filtered and dried in air to give 337.7 mg of the final product (**4**) as a very light orange solid (92% yield).  $R_f$  = 0.79 (petroleum ether–ethyl acetate, 5:1); Mp. 223–225 °C. IR (ATR,  $\nu_{\text{max}}/\text{cm}^{-1}$ ): 3279 ( $\nu_{\text{N-H}}$ ), 2858 and 2824 ( $\nu_{\text{ArC-H}}$ ), 1674 ( $\nu_{\text{C=O}}$ ), 1577–1398 ( $\nu_{\text{ArC=C}}$ ), 1254 ( $\nu_{\text{C-N}}$ ).  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ),  $\delta(\text{ppm})$ : 8.76 (s, 1H, N-H), 8.17 (s, 1H, 3-H), 7.88 (d,  $J$  = 8.9 Hz, 1H, 5-H), 7.99–7.96 (m, 2H, 2'-H/6'-H), 7.78 (d,  $J$  = 2.0 Hz, 1H, 8-H), 7.62–7.57 (m, 1H, 4'-H), 7.55–7.52 (m, 2H, 3'-H/5'-H), 7.34 (dd,  $J$  = 9.0, 2.1 Hz, 1H, 6-H), 3.99 (t,  $J$  = 4.6 Hz, 4H, 2''-H/6''-H), 3.31 (t,  $J$  = 4.6 Hz, 4H, 3''-H/5''-H).  $^{13}\text{C-NMR}$  (101 MHz,  $\text{CDCl}_3$ ),  $\delta(\text{ppm})$ : 166.1 (C=O), 159 (4-C), 152.8 (2-C), 148.6 (8a-C), 135.6 (7-C), 134.1 (1'-C), 132.5 (4'-C), 129 (3'-C/5'-C), 127.3 (2'-C/6'-C), 127.1 (8-C), 125.1 (5-C), 124.9 (6-C), 120 (4a-C), 101.9 (3-C), 66.8 (3''-C/5''-C), 52.7 (2''-C/6''-C). COSY correlation [ $\delta\text{H}/\delta\text{H}$ ]: 7.99–7.96/7.55–7.52 [(2'-H/6'-H)/(3'-H/5'-H)], 7.88/7.34 [5-H/6-H], 7.78/7.34 [8-H/6-H], 7.62–7.57/7.55–7.52 [4'-H/(3'-H/5'-H)], 3.99/3.31 [(3''-H/5''-H)/(2''-H/6''-H)]. HSQC correlation [ $\delta\text{H}/\delta\text{C}$ ]: 8.17/101.9 [3-H/3-C], 7.99–7.96/127.3 [(2'-H/6'-H)/(2'-C/6'-C)], 7.88/125.1 [5-H/5-C], 7.78/127.1 [8-H/8-C], 7.62–7.57/132.5 [4'-H/4'-C], 7.55–7.52/127.3 [(3'-H/5'-H)/(3'-C/5'-C)], 7.34/124.9 [6-H/6-C], 3.99/66.8 [(3''-H/5''-H)/(3''-C/5''-C)], 3.31/52.7 [(2''-H/6''-H)/(2''-C/6''-C)]. HMBC correlation [ $\delta\text{H}/\delta\text{C}$ ]: 8.17/120 [3-H/4a-C], 7.99–7.96/127.3/132.5/166.1 [(2'-H/6'-H)/(2'-C/6'-C)/4'-C/0'-C], 7.88/135.6/148.6/159 [5-H/7-C/8a-C/4-C], 7.78/120/124.9/135.6 [8-H/4a-C/6-C/7-C], 7.62–7.57/127.3 [4'-H/(2'-C/6'-C)], 7.55–7.52/127.3/129/134.1 [(3'-H/5'-H)/(2'-C/6'-C)/(3'-C/5'-C)/1'-C], 7.49/120/127.1/135.6 [6-H/4a-C/8-C/7-C], 3.99/66.8/52.7 [(3''-H/5''-H)/(3''-C/5''-C)/(2''-C/6''-C)], 3.31/52.7/66.8 [(2''-H/6''-H)/(2''-C/6''-C)/(3''-C/5''-C)]. ESI-MS,  $m/z$  (%): calculated mass for  $\text{C}_{20}\text{H}_{19}\text{ClN}_3\text{O}_2$ : 369.1 ( $^{37}\text{Cl}$ ), 367.1 ( $^{35}\text{Cl}$ ); found,  $(\text{M}+\text{H})^+$ : 370.1 (32.6%), 368.1 (100%); 263.1  $[(\text{M}+\text{H})^+-105, 94.7\%]$ .

## 4. Conclusions

In summary, this communication described a three-step approach for the synthesis of *N*-(7-chloro-4-morpholinoquinolin-2-yl)benzamide from commercially available 4,7-dichloroquinoline through C-H amidation of 4,7-dichloroquinoline-*N*-oxide. The synthetic method is simple and efficient, presenting excellent yields (77–92%). The synthesized *N*-(7-chloro-quinolin-2-yl)benzamides are an interesting biological model for pharmacological agent research, especially

regarding antineoplastic drug design or treatment of central and peripheral nervous system disorders.

**Supplementary Materials:** The following supporting information can be downloaded at the website of this paper posted on Preprints.org. FT-IR,  $^1\text{H}$ -,  $^{13}\text{C}$ -NMR, and 2D variants (COSY, HSQC, and HMBC) for compounds (3) and (4).

**Author Contributions:** D.F.A.A and M.C.O.V. conceived the experiments; V.V.K. designed and wrote the paper. All three authors analyzed and discussed the results and data. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research received no external funding.

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** Not applicable.

**Acknowledgments:** The authors thank Universidad Industrial de Santander. M.C.O.V. thanks to the National Program 727 for her doctoral fellowship.

**Conflicts of Interest:** The authors declare no conflict of interest. The founding sponsors had no role in the study's design, collection, analysis, or interpretation of data, the writing of the manuscript, or the decision to publish the results.

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