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SYNTHESIS OF NOVEL QUINOLINE DERIVATIVES: A VERSATILE PLATFORM FOR ADVANCED ORGANIC AND MEDICINAL CHEMISTRY

DAMIÁN CASTILLO-RÍOS [a], IGNACIO ALEJANDRO GONZÁLEZ-GUTIÉRREZ [b],
AND JUAN PABLO GONZÁLEZ-GUTIÉRREZ [a]*

[a]*Instituto de Ciencias Aplicadas, Facultad de Ingeniería, Universidad Autónoma de Chile, Talca 3467987, Chile.*
[b]*Interno de Medicina, Facultad de Medicina y Ciencias de la salud, Universidad Mayor, Huechuraba 8580000, Chile.*

ABSTRACT

Quinolines are heterocyclic compounds with significant therapeutic potential, initially recognized for their role in treating malaria. Their structural versatility has led to the development of derivatives used in the treatment of various diseases, including Alzheimer's and Parkinson's. Found primarily in plants of the Rutaceae and Rubiaceae families, quinoline derivatives target key enzymes and receptors in the central nervous system. Recent advances focus on enhancing their pharmacokinetic properties to improve efficacy and selectivity in treating neurodegenerative disorders.

Keywords: Heterocyclic compounds, organic synthesis, quinoline.

1. INTRODUCTION

Quinolines, a class of heterocyclic aromatic compounds characterized by a fused benzene and pyridine ring system, have played a pivotal role in medicinal chemistry due to their diverse biological activities[1],[2]. Historically, quinoline alkaloids such as quinine, isolated from the bark of the *Cinchona* tree in 1820 (Figure 1), were instrumental in the treatment of malaria, marking one of the earliest uses of natural products in therapeutic applications[3]–[5]. The discovery of quinine (Figure 1) revolutionized malaria treatment, providing a foundation for the development of quinoline derivatives as scaffolds for modern drug discovery[6],[7]. This includes the development of antimalarial agents such as chloroquine and mefloquine (Figure 1), which have also been investigated for their broad-spectrum efficacy against other diseases[8]–[10].

These compounds are predominantly found in various plant species, particularly within the Rutaceae and Rubiaceae families, where they act as defense mechanisms against herbivores and pathogens[11]–[13]. The ability of quinoline alkaloids to inhibit microbial growth and disrupt enzymatic functions in pests further highlights their biological significance[14],[15]. As such, quinolines are a key example of how natural products can serve as templates for drug design[14]–[16].

The quinoline scaffold's structural versatility makes it a highly effective pharmacophore in medicinal chemistry, facilitating the synthesis of numerous biologically active molecules[17].

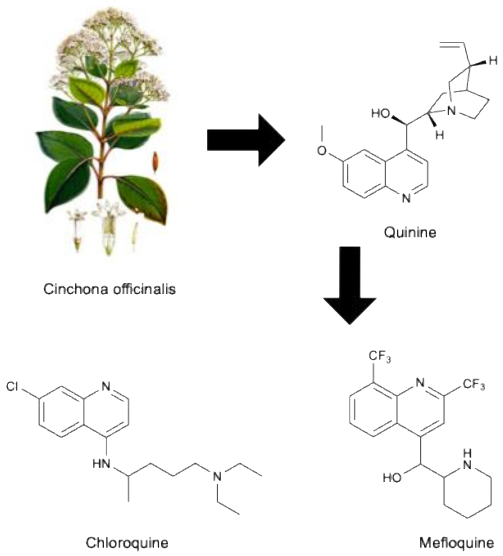

Figure 1. Cinchona officinalis and chemical structure of quinoline derivatives used in the treatment of malaria.

This versatility has been especially important in the development of drugs targeting central nervous system (CNS) disorders, with quinoline derivatives being explored for conditions such as neuroinflammation and Alzheimer's disease[18]–[20]. For example, chloroquine, initially developed as an antimalarial, has been repurposed to treat CNS-related conditions due to its ability to modulate neuroinflammatory responses and influence autophagy pathways in neurodegenerative diseases[21],[22].

The quinoline scaffold's ability to engage with diverse biological targets, such as enzymes, receptors, and ion channels, makes it a valuable pharmacophore for CNS-active compounds[23],[24]. Notably, quinoline derivatives have been shown to interact with acetylcholinesterase, an enzyme critical for acetylcholine degradation[19],[25]. Acetylcholine is a key neurotransmitter in Alzheimer's disease, and its degradation contributes to cognitive dysfunction[26],[27]. Inhibition of acetylcholinesterase by quinoline-based molecules enhances cholinergic transmission, offering a therapeutic strategy for Alzheimer's disease[28]. Similarly, quinoline analogs targeting monoamine oxidase, an enzyme involved in the breakdown of neurotransmitters like dopamine and serotonin, have shown potential in the treatment of Parkinson's disease and depression[29].

Recent advances in medicinal chemistry have focused on optimizing the pharmacokinetic and pharmacodynamic properties of quinoline derivatives to improve their efficacy and selectivity[2]. Structural modifications, such as the introduction of electron-donating or withdrawing groups at specific positions on the quinoline ring, have been explored to enhance blood-brain barrier penetration, improve metabolic stability, and increase receptor-binding affinity[30]. Furthermore, quinoline-based molecules have demonstrated dual activities, such as antioxidant and neuroprotective effects, making them promising candidates for the treatment of multifactorial CNS disorders like Alzheimer's and Parkinson's[31].

Finally, the rich history, natural abundance, and structural adaptability of quinolines highlight their significance in the ongoing development of therapeutic agents for CNS disorders. Their ability to interact with various biological targets and their versatility as pharmacophores continue to drive innovation in the design of novel CNS-active drugs. Given the wide-ranging applications of quinolines in the design of molecules for therapeutic purposes, we present the synthesis of novel quinoline derivatives (Figure 2).

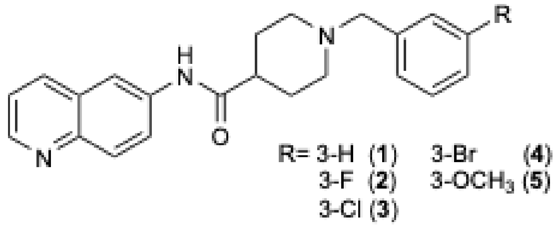

Figure 2. General chemical structure of novel quinoline derivatives.

*Corresponding author email: juan.gonzalez01@uautonoma.cl

2. RESULTS AND DISCUSSION

2.1 Chemistry

For the synthesis of **A** as described in procedure 3.1.1 (Figure 3), it is important to emphasize that, after the reaction is completed, dichloromethane should be removed using a rotary evaporator. Then ethyl ether should be added to precipitate pyridine as pyridinium salt (a white solid), which can be separated from the reaction crude by filtration. Due to the high reactivity of **A** and its good reaction yield (94% yield). Due to the reactivity of this compound, it was not characterized by NMR spectroscopy and was immediately used for the next reaction.

For the synthesis of **B** as described in procedure 3.1.2 (Figure 3), the reaction between **A** and 6-aminoqunoline occurs with a 99% yield, and no further purification is required after the compound extraction. The reaction was monitored by TLC using ethyl acetate as the mobile phase.

This compound was characterized by ^{1}H-NMR (supplementary figure 1), showing the following characteristic signals: a signal at δ 8.79 ppm indicating the presence of NH protons in the amide group, five signals between δ 8.62 – 7.43 ppm of quinoline moiety, and a signal at δ 1.46 ppm corresponding to the three CH_3 groups of N-boc-piperidine.

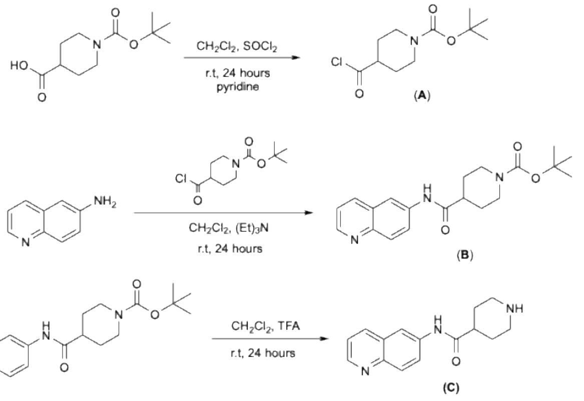

Figure 3. General synthetic route for the preparation of compounds A, B and C.

Compound **C** was synthesized according to the described procedure 3.1.3 (Figure 3), with a yield of 76.0%. For the extraction of this compound, it is important to adjust the pH to 10 with NaOH after neutralizing trifluoroacetic acid with K_2CO_3. The characterization of this compound was performed using ^{1}H-NMR (supplementary figure 2), showing the following characteristic signals: five signals between δ 9.02 – 8.03 ppm of quinoline moiety. The signal the proton of CH_3 disappear after the removal of the N-Boc protecting group. The N-H amine of piperidine and the N-H amide group are not present due to an isotopic exchange between the hydrogen atoms of these groups and the deuterium of the D_2O solvent.

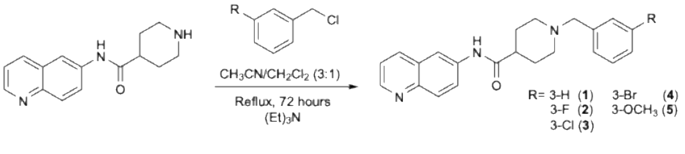

Figure 4. General synthetic route for the preparation of quinoline derivatives (1-5).

The compounds (**1-5**) were synthesized according to procedures 3.1.4 (Figure 4), with a yield between 31.6 – 40.2%. All the synthesized compounds **(1-5)**, which were fully characterized spectroscopically by FT-IR, ^{1}H-NMR, ^{13}C-NMR, and HRMS, observing the following signs:

In ^{1}H-NMR analysis (supplementary figure 3-7), all compounds (**1–5**) exhibited a single signal integrating for one hydrogen between 9.51 and 8.82 ppm, corresponding to the amide group located between the quinoline and piperidine portions. Additionally, seven aromatic signals were observed, originating from the quinoline aromatic ring and the benzyl group, with chemical shifts ranging from 9.42 to 7.06 ppm. These signals, depending on the substitution pattern of the benzyl group, integrated for 11 to 12 hydrogens. Furthermore, six signals attributed to the piperidine group were detected, with chemical shifts ranging from 4.76 to 2.02 ppm, integrating for nine hydrogens. Regarding compounds (**1-5**), they showed a signal between δ 3.81 to 3.64 ppm, integrating for two hydrogens from the methylene of the alkyl chain between piperidine and the phenyl group (N-**C**H_2-Ph).

In the ^{13}C-NMR analysis (supplementary figure 8-12), compounds (**1–5**) exhibited the following signals: one in the range of δ 173.43–173.09 ppm, corresponding to the carbonyl carbon of the amide group; signals in the range of δ 144.85–115.31 ppm, attributed to the aromatic carbons of the quinoline and benzyl groups; and a signal in the range δ 59.31–58.43 ppm, originating from the methylene group (N-**C**H_2-Ph) portion. Additionally, signals were observed in the range of δ 51.15–25.82 ppm, corresponding to the carbons of the piperidine ring.

Furthermore, in IR spectroscopy, all compounds (**1-5**) exhibited the following characteristics: an N-H amide absorption stretching band between 3422 and 3402 cm^{-1}, an aromatic C-H absorption stretching band between 3065 and 3045 cm^{-1}, an aliphatic C-H absorption stretching band to 2977 cm^{-1}, an absorption stretching band for the amide carbonyl group between 1699 and 1679 cm^{-1}, a C-N absorption stretching band between 1243 and 1226 cm^{-1}.

For high-resolution mass spectroscopy, molar masses found by this technique of all compounds were compared with that calculated theoretically.

3. MATERIALS AND METHODS

All the reagents and solvents used for the synthesis of these compounds were obtained commercially and used without further purification. The 6-aminoquinoline, N-Boc-Isonipecotic acid and benzyl chloride derivatives obtained from Ak Scientific Inc. (CA, USA) and, thionyl chloride, acetone, diethyl ether, dichloromethane, methanol, ethyl acetate, isopropyl alcohol obtained from Merck Millipore (Santiago, Chile).

3.1 Synthesis.

3.1.1 Procedures for the synthesis of tert-butyl 4-(chlorocarbonyl)piperidine-1-carboxylate (**A**):

The N-Boc-isonipecotic acid (4.3 mmol, 1.0 g) was reacted with pyridine (4.3 mmol, 0.35 mL) and $SOCl_2$ (4.3 mmol, 0.3 mL) in 50 mL of CH_2Cl_2 at room temperature with constant stirring for 24 hours. After the reaction was completed, the crude reaction mixture was concentrated under reduced pressure, and then diethyl ether was added, resulting in the formation of a white precipitate, which was filtered and discarded. The product dissolved in diethyl ether was concentrated under reduced pressure and used for the next reaction. Yield 94.0%.

3.1.2 Procedures for the synthesis of *tert*-butyl 4-(6-quinolinylcarbamoyl)piperidine-1-carboxylate (**B**):

The previous tert-butyl 4-(chlorocarbonyl)piperidine-1-carboxylate (8.07 mmol, 2.0 g) was reacted with 6-aminoquinoline (8.07 mmol, 1.56 g) and a spoonful of $NaHCO_3$ in 50 mL of CH_2Cl_2 at room temperature with constant stirring for 24 hours. Then, a 10% $NaHCO_3$ solution was added to the reaction mixture, and the mixture was transferred to a separatory funnel. The compound was extracted using 3 portions of 30 mL of CH_2Cl_2, and anhydrous sodium sulfate was added to the organic phase. Finally, the solution was concentrated under reduced pressure, resulting in the formation of a white solid. Yield 99.0%.

3.1.3 Procedures for the synthesis of N-(quinolin-6-yl)piperidine-4-carboxamide (**C**):

The tert-butyl 4-(6-quinolinylcarbamoyl)piperidine-1-carboxylate (4.95 mmol, 2.0 g) was reacted with 5 mL of trifluoroacetic acid in 100 mL of CH_2Cl_2 at room temperature with constant stirring for 24 hours. After the reaction time, the reaction was neutralized with a concentrated K_2CO_3 solution and brought to pH 10 with 10% NaOH solution. The biphasic solution was transferred to a separatory funnel, and the compound was extracted using 5 portions of 30 mL of CH_2Cl_2. After the extraction, anhydrous sodium sulfate was added to the organic solvent, and it was concentrated under reduced pressure, yielding a white solid. Yield 76.0%.

3.1.4 General procedures for the synthesis of 1-benzyl-*N*-(quinolin-6-yl)piperidine-4-carboxamide derivatives (**1-5**):

The N-(quinolin-6-yl)piperidine-4-carboxamide (1.27 mmol, 0.386 g) was reacted with previously synthesized benzyl chloride derivatives (1.27 mmol) and $(Et)_3N$ in a mixture of CH_3CN/CH_2Cl_2 (3:1) under reflux and constant stirring for 72 hours. After the reaction time, the reaction mixture was concentrated under reduced pressure, transferred to a separatory funnel, and a 10% K_2CO_3 solution was added. The organic compound was then extracted with 3 portions of 30 mL of CH_2Cl_2, and anhydrous sodium sulfate was added to the organic phase. The organic phase was concentrated under reduced pressure, yielding a pale-yellow oil, which was further purified by column chromatography using ethyl acetate as the mobile phase, resulting in a colorless oil. Finally, the hydrochloride salts of the compounds were obtained using a 7.4% w/v HCl solution in isopropanol. Yield 40.2 - 30.0%.

3.2 Chemical characterization.

Melting points were determined with a RY-1 Melting Point Tester. The IR spectra were recorded on an FT-IR IRSpirit Shimadzu and wavenumbers were reported in cm^{-1}. ^{1}H-NMR and ^{13}C-NMR spectra were recorded using a Bruker AMX 400 spectrometer at 400 MHz. Chemical shifts are reported relative to TMS (δ= 0.00) and coupling constants (J) are given in Hz. High-resolution mass spectra (HRMS) were recorded using a Bruker compact QTOF MS with direct injection. Reactions and product mixtures were routinely monitored by thin-layer chromatography (TLC) on silica gel pre-coated F_{254} Merck plates, and the compounds obtained were purified by column chromatography using ethyl acetate as the mobile phase.

3.2.1 *Tert*-butyl 4-(6-quinolinylcarbamoyl)piperidine-1-carboxylate (**B**):

Compound was prepared as described in procedures section 3.1.2. Obtained as a white solid, yield 99.0%. ($C_{20}H_{25}N_3O_3$): ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.79 (dd, *J* = 4.4, 1.7 Hz, 1H), 8.62 (s, 1H), 8.52 (d, *J* = 2.3 Hz, 1H), 8.18 (dt, *J* = 8.4, 1.2 Hz, 1H), 8.09 (d, *J* = 9.1 Hz, 1H), 7.69 (dd, *J* = 9.1, 2.4 Hz, 1H), 7.43 (dd, *J* = 8.3, 4.4 Hz, 1H), 4.16 (d, *J* = 13.1 Hz, 2H), 2.82 – 2.72 (m, 2H), 2.54 (dt, *J* = 11.4, 3.8 Hz, 1H), 1.96 – 1.87 (m, 2H), 1.85 – 1.70 (m, 2H), 1.46 (s, 9H).

3.2.2 N-(quinolin-6-yl)piperidine-4-carboxamide (**C**):

Compound was prepared as described in procedures section 3.1.3. Obtained as a white solid, yield 76.0% ($C_{15}H_{17}N_3O$): ^{1}H-NMR (400 MHz, D_2O) δ 9.02 (d, J = 6.8 Hz, 2H), 8.48 (d, J = 2.2 Hz, 1H), 8.22 – 8.14 (m, 1H), 8.15 – 8.08 (m, 1H), 8.07 – 7.99 (m, 1H), 3.66 – 3.56 (m, 2H), 3.26 – 3.14 (m, 2H), 3.02 – 2.90 (m, 1H), 2.32 – 2.21 (m, 2H), 2.13 – 1.97 (m, 2H).

3.2.3 benzyl-*N*-(6-quinolinyl)piperidine-4-carboxamide (**1**):

Compound was prepared as described in procedures section 3.1.4. Obtained as a white solid, yield 37.8% ($C_{22}H_{23}N_3O$): ^{1}H-NMR (400 MHz, D_2O) δ 8.79 (s, 1H), 8.39 – 8.31 (m, 1H), 8.11 – 8.05 (m, 1H), 8.03 – 7.94 (m, 1H), 7.78 – 7.70 (m, 1H), 7.61 – 7.51 (m, 5H), 7.30 (s, 1H), 7.06 (s, 1H), 4.40 – 4.34 (m, 2H), 3.66 – 3.62 (m, 2H), 3.18 – 3.14 (m, 2H), 2.85 – 2.81 (m, 1H), 2.23 – 2.18 (m, 2H), 2.02 (s, 2H). ^{13}C-NMR (101 MHz, DMSO) δ 173.43, 144.81, 143.82, 139.97, 135.81, 132.01, 130.26, 129.87, 129.19, 127.96, 122.74, 115.32, 59.31, 50.91, 40.66, 40.60, 40.39, 40.18, 39.97, 39.76, 39.56, 39.35, 25.82. IR (cm^{-1}): 3411, 3065, 2977, 2833, 1696, 1243. HRMS m/z calcd. for $C_{22}H_{24}N_3OCl$ (M-H), 380.1524; found, 380.1535.

3.2.4 3-fluorobenzyl-*N*-(6-quinolinyl)piperidine-4-carboxamide (**2**):

Compound was prepared as described in procedures section 3.1.4. Obtained as a white solid, yield 40.2% ($C_{22}H_{22}FN_3O$): ^{1}H-NMR (400 MHz, D_2O) δ 8.82 (s, 1H), 8.48 – 8.38 (m, 1H), 8.13 (d, *J* = 13.1 Hz, 1H), 8.06 – 7.95 (m, 1H), 7.84 – 7.73 (m, 1H), 7.70 – 7.55 (m, 2H), 7.41 – 7.27 (m, 3H), 7.18 – 7.03 (m, 1H), 4.39 (t, *J* = 13.1 Hz, 2H), 3.68 – 3.64 (m, 2H), 3.22 – 3.17 (m, 2H), 2.89 – 2.83 (m, 1H), 2.36 – 2.12 (m, 2H), 2.08 – 2.03 (m, 2H). ^{13}C-NMR (101 MHz, DMSO) δ 173.40, 163.59, 161.16, 144.85, 143.82, 139.97, 135.80, 132.92, 132.84, 131.27, 131.19, 129.87, 128.17, 127.99, 122.77, 122.73, 118.87, 118.65, 116.95, 116.75, 115.34, 58.50, 51.02, 40.61, 40.40, 40.19, 39.99, 39.78, 39.57, 39.36, 25.80. IR (cm^{-1}): 3402, 3065, 2977, 1699, 1243. HRMS m/z calcd. for $C_{22}H_{23}FN_3OCl$ (M-H), 398.1430; found, 398.1435.

3.2.5 3-chlorobenzyl-*N*-(6-quinolinyl)piperidine-4-carboxamide (**3**):

Compound was prepared as described in procedures section 3.1.4. Obtained as a white solid, yield 31.6% ($C_{22}H_{22}ClN_3O$): ^{1}H-NMR (400 MHz, DMSO) δ 8.92 (s, 1H), 8.63 – 8.53 (m, 2H), 8.13 (d, *J* = 9.2 Hz, 1H), 8.05 (d, *J* = 9.5 Hz, 1H), 7.82 (s, 1H), 7.73 – 7.61 (m, 2H), 7.55 – 7.44 (m, 2H), 4.35 (s, 2H), 3.43 – 3.36 (m, 2H), 3.03 – 2.97 (m, 2H), 2.87 – 2.75 (m, 1H), 2.18 – 2.03 (m, 4H). ^{13}C-NMR (101 MHz, DMSO) δ 173.09, 146.79, 140.74, 140.08, 138.68, 133.72, 132.66, 131.78, 131.02, 130.73, 129.89, 129.26, 126.52, 125.77, 122.44, 115.39, 58.46, 51.10, 40.61, 40.41, 40.20, 39.99, 39.78, 39.58, 39.37, 25.89. IR (cm^{-1}): 3416, 3045, 2977, 1679, 1226. HRMS m/z calcd. for $C_{22}H_{23}N_3OCl_2$ (M+H), 380.1524; found, 380.1521.

3.2.6 3-bromobenzyl-*N*-(6-quinolinyl)piperidine-4-carboxamide (**4**):

Compound was prepared as described in procedures section 3.1.4. Obtained as a white solid, yield 31.6% ($C_{22}H_{22}BrN_3O$): ^{1}H-NMR (400 MHz, DMSO) δ 9.09 (d, *J* = 5.1 Hz, 1H), 9.00 (d, *J* = 8.4 Hz, 1H), 8.74 (s, 1H), 8.34 (d, *J* = 8.8 Hz, 1H), 8.21 (d, *J* = 9.4 Hz, 1H), 8.01 – 7.86 (m, 3H), 7.67 (t, *J* = 7.7 Hz, 2H), 7.43 (t, *J* = 7.8 Hz, 1H), 4.33 (s, 2H), 3.39 (d, *J* = 12.1 Hz, 2H), 3.06 – 2.92 (m, 2H), 2.88 – 2.76 (m, 1H), 2.14 – 1.98 (m, 4H). ^{13}C-NMR (101 MHz, DMSO) δ 173.38, 144.60, 144.06, 139.88, 136.12, 134.62, 132.90, 132.81, 131.29, 131.12, 129.85, 127.87, 123.04, 122.72, 122.31, 115.37, 58.43, 51.06, 40.61, 40.40, 40.19, 39.98, 39.77, 39.57, 39.35, 25.84. IR (cm^{-1}): 3422, 3045, 2977, 1691, 1240. HRMS m/z calcd. for $C_{22}H_{23}BrN_3OCl$ (M-H), 426.1001; found, 426.1000.

3.2.7 3-methoxybenzyl-*N*-(6-quinolinyl)piperidine-4-carboxamide (**5**):

Compound was prepared as described in procedures section 3.1.4. Obtained as a white solid, yield 30.0% ($C_{23}H_{25}N_3O_2$): ^{1}H-NMR (400 MHz, DMSO) δ 9.08 (s, 1H), 8.97 (d, *J* = 8.4 Hz, 1H), 8.74 (s, 1H), 8.39 – 8.31 (m, 1H), 8.29 – 8.19 (m, 1H), 7.97 – 7.88 (m, 1H), 7.42 – 7.37 (m, 1H), 7.37 – 7.30 (m, 2H), 7.21 – 7.13 (m, 1H), 6.99 (t, *J* = 7.6 Hz, 2H), 4.28 (s, 2H), 3.79 (s, 3H), 3.37 (d, *J* = 12.0 Hz, 2H), 3.05 – 2.93 (m, 2H), 2.93 – 2.80 (m, 1H), 2.15 – 2.05 (m, 4H). ^{13}C-NMR (101 MHz) δ 173.42, 159.79, 144.07, 139.89, 131.73, 130.23, 129.82, 127.74, 123.92, 123.85, 123.13, 122.70, 117.33, 117.26, 115.53, 115.31, 59.28, 55.69, 51.15, 50.96, 40.69, 32.82. IR (cm^{-1}): 3410, 3065, 2977, 1697, 1240. HRMS m/z calcd. for $C_{23}H_{26}N_3O_2Cl$ (M+H), 376.2020; found, 376.2026.

CONCLUSIONS.

In this work, the successful synthesis of a series of quinoline derivatives was achieved through organic chemistry strategies aimed at the selective functionalization of the quinoline scaffold. Structural characterization using spectroscopic techniques such as ^{1}H-NMR, ^{13}C-NMR, IR, and HRMS confirmed the identity and integrity of the obtained products.

The introduced chemical modifications, including the incorporation of protecting groups and the formation of amide and N-benzylated bonds, highlight the versatility of quinoline as a synthetic platform. These results lay the groundwork for future structural optimizations and reactivity studies, expanding the chemical diversity of these compounds in the search for new applications in medicinal chemistry.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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SUPPORTING INFORMATION:

Supporting Information on the chemical characterization of all compounds by means of ^{1}H-NMR, IR and ^{13}C-NMR is available in this section.

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