



Synthesis, Antibacterial Screening and ADME Prediction of Novel Ester Derivatives of 6-Substituted-2-chloroquinoline-3-carbaldehyde

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In this research, a series of novel 2-chloroquinoline-3-carbaldehyde analogues (**4a-f**) were successfully synthesized by employing several acetanilides in combination with hydrazides and acyl chlorides. The methodology yielded compounds with distinct substitutions, thus expanding the chemical diversity of this class of compounds. Characterization through FT-IR, ¹H NMR, ¹³C NMR and mass spectral analysis confirmed the structural integrity of the synthesized derivatives. The ADME study indicates that the synthesized compounds were found to be possessing reliable ADME properties. The antimicrobial properties were tested against bacterial species with ciprofloxacin as standard drug. These newly synthesized compounds hold promise for further exploration of their biological activities and pharmacological profiles, making them valuable candidates for future research in the quest for novel therapeutic agents.

Keywords: Acetanilide, 2-Chloroquinoline-3-carbaldehyde, Vilsmeier-Haack reaction, Acyl chloride, Hydrazide.

INTRODUCTION

Among this heterogeneous class, quinoline, a distinctive heterocyclic compound, serves as an intriguing scaffold, prevalent in various therapeutic agents [1]. This versatile quinoline framework occurs prolifically within the structures of pharmaceutical compounds and is linked to a wide array of therapeutic effects, including analgesic [2], antibacterial [3], antioxidant [4], antimalarial [5], antifungal [6], anti-inflammatory [7,8], anticancer [9], anthelmintic [10], anti-hypertensive [11], antiviral [12,13], cardiovascular [14], central nervous system activity [15], antidiabetic [16] and anti-HIV activities [17]. The manifold pharmacological attributes of heterocyclic compounds bearing the quinoline ring underscore their critical role in medicinal chemistry, sustaining an enduring fascination with their synthesis and exploration.

Based on these observations, there exists a compelling rationale to engage in the synthesis and comprehensive characterization of a series of novel derivatives derived from 2-chloroquinoline-3-carbaldehyde. The chemical attributes of 2-chloroquinoline-3-carbaldehyde have engendered substantial global research interest, owing to its multifaceted applications in both

biological and industrial domains. The scientific literature offers an extensive array of methodologies for the synthesis of quinoline compounds [18]. Notably, derivatives stemming from 2-chloroquinoline-3-carbaldehyde play a pivotal role as essential intermediates in the synthesis of crucial heterocyclic compounds [19,20]. These intermediates serve as linchpins in the intricate assembly of various heterocyclic structures, with profound implications for medicinal chemistry and industrial processes. The pursuit of novel derivatives of 2-chloroquinoline-3-carbaldehyde promises to elucidate novel synthetic pathways and expand the repertoire of available compounds, with far-reaching implications for diverse applications.

In this work, a series of quinoline derivatives (**4a-f**) were synthesized, characterized and evaluated for their antimicrobial activity. Furthermore, *in silico* ADME study of the synthesized compounds were also examined and found to comply with the ADME properties, demonstrating their usefulness for drug development.

EXPERIMENTAL

Initially, the synthesis of 2-chloroquinoline-3-carbaldehyde and its derivatives was accomplished *via* Vilsmeier-Haack

reaction [21-23]. Analytically pure chemicals procured from reputable commercial sources such as Alfa Aesar, S.D. Fine Chem. and Spectrochem Ltd. were employed throughout the synthetic process. The determination of melting points was conducted utilizing an open capillary tube and an electrical melting point apparatus and found to be uncorrected. The progress of the chemical reactions, thin-layer chromatography (TLC) was executed on silica gel-G plates having a thickness of 0.5 mm. Visualization of spots was achieved through the application of iodine vapours and ultraviolet light. Infrared (IR) spectra were recorded using the KBr pellet method on an FT/IR-4100 instrument and mass spectra were acquired on a Bruker-ESI-MS model. ¹H NMR spectra were obtained in CDCl₃ solvent, utilizing a Bruker 500 MHz spectrometer with TMS as internal standard. Similarly, ¹³C NMR spectra were recorded in DMSO solution on a Bruker Avance Neo 500 MHz NMR spectrometer.

General procedure for the synthesis of substituted 2-chloroquinoline-3-carbaldehyde (2a-d): Dimethylformamide (9.6 mL, 0.125 mol) was cooled to 0 °C within a flask equipped with a desiccant drying tube. Phosphoryl chloride (POCl₃, 32.2 mL, 0.35 mol) was subsequently added dropwise under continuous stirring. To this solution, the acetanilide derivative (0.05 mol) was introduced and after a 5 min interval, the solution was subjected to reflux conditions for an appropriate duration, ranging from 6 to 17 h, at 70-80 °C. Following the reflux period, the reaction mixture was allowed to cool to room temperature and then carefully poured into ice-cold water (200-300 mL). The resulting crude product was isolated through filtration and subsequently subjected to a drying process. The purification of the compound was achieved by recrystallization, utilizing ethyl acetate as recrystallization solvent.

2-Chloro-6-methylquinoline-3-carbaldehyde (2a): Yellow solid; yield 65%; m.p.: 120-122 °C. IR (KBr, ν_{\max} , cm⁻¹): 3432 (NH *str.*), 2874 (CH aldehyde *str.*), 1690 (C=O *str.*), 1580 (C=N *str.*) 1452-1424 (C-C aromatic *str.*), 820 (C-Cl *str.*). ¹H NMR (500 MHz, CHCl₃-d₆) δ ppm: 10.30 (s, 1H), 7.2-8.6 (arom. H), 2.38 (s, 3H). ¹³C NMR (500 MHz, DMSO-d₆) δ ppm: 21.29, 126.69, 126.80, 127.12, 127.48, 130.62, 134.48, 136.38, 147.65, 149.28, 189.28. ESI-MS (*m/z*): 206.13. (M+H)⁺ (calcd. mass for C₁₁H₈ClNO is 205.64); R_f: 0.61, *n*-hexane:ethyl acetate (2:8).

2-Chloro-6-methoxy-quinoline-3-carbaldehyde (2d): Yellow solid; yield 55%; m.p.: 230-233 °C. IR (KBr, ν_{\max} , cm⁻¹): 2928 (CH aldehyde *str.*), 1681 (C=O *str.*), 1450-1649 (C-C arom. *str.*), 1384 (C=N), 861 (C-Cl *str.*). ¹H NMR (500 MHz, CHCl₃-d₆) δ ppm: 10.38 (s, 1H), 7.32-8.47 (arom. H), 3.84 (s, 3H). ¹³C NMR (500 MHz, DMSO-d₆) δ ppm: 21.97, 22.33, 25.07, 32.20, 55.34, 106.39, 122.89, 126.34, 127.60, 129.03, 138.23, 145.67, 147.71, 158.53, 189.29. ESI-MS (*m/z*): 222.06 (M+H)⁺ (calcd. mass for C₁₁H₈ClNO₂ is 221.63); R_f: 0.62, *n*-hexane:ethyl acetate (2:8).

General procedure for the synthesis of 2-chloroquinoline-3-carbaldehyde hydrazide derivative (3a-d): A mixture comprising 2-chloroquinoline-3-carbaldehyde (**2**, 1 mmol) and 4-hydroxybenzoic acid hydrazide (1.1 mmol) was stirring in absolute ethanol (20 mL) at room temperature for a period of

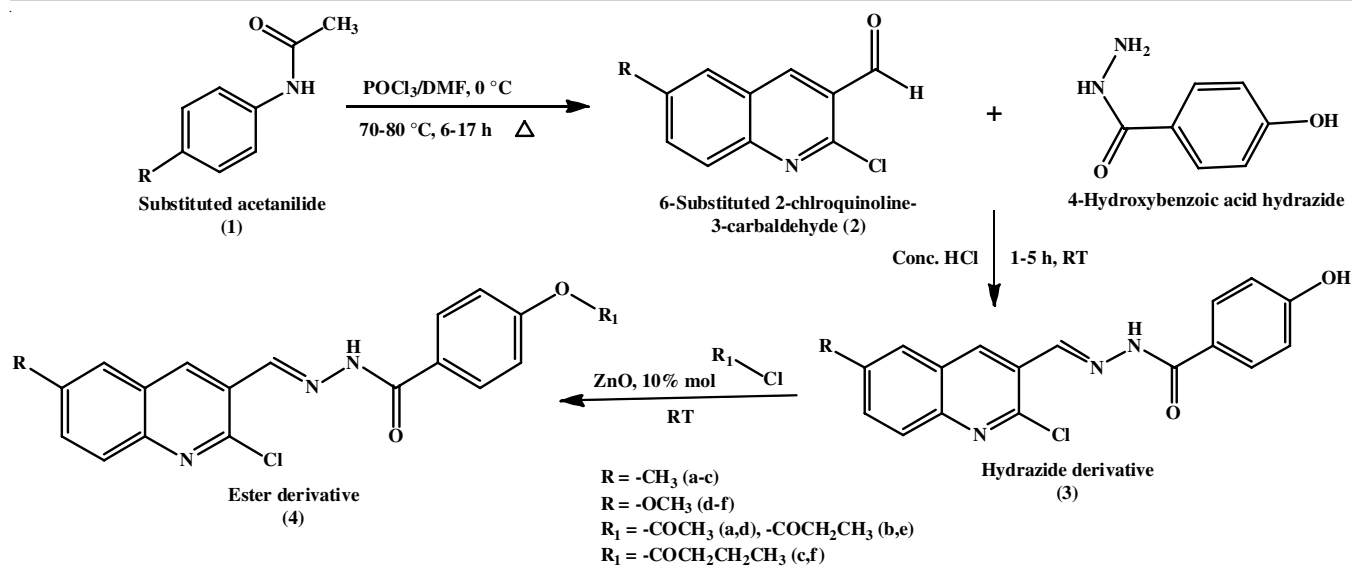
1 to 5 h, facilitated by the addition of 2 drops of HCl, which acted as catalyst. The completion of the reaction was monitored using thin-layer chromatography (TLC) and upon reaching the desired endpoint, neutralization was executed by introducing a 10% aqueous solution of Na₂CO₃. The resulting precipitate was isolated *via* filtration, followed by a thorough washing with 20 mL of water. Subsequently, the compound was purified through recrystallization, utilizing ethanol as recrystallization solvent.

N'-(2-Chloro-6-methylquinolin-3-yl)methylidene]-4-hydroxybenzohydrazide (3a): Yellow solid; yield 32%; m.p.: 167-168 °C. IR (KBr, ν_{\max} , cm⁻¹): 3431 (OH *str.*), 1631 (C=O *str.*), 1515-1458 (C-C arom. *str.*), 1382 (C=N), 847 (C-Cl *str.*). ¹H NMR (500 MHz, CHCl₃-d₆) δ ppm: 12.10 (s, 1H), 9.63 (s, 1H), 7.4-8.6 (aromatic H), 3.48 (s, 3H). ¹³C NMR (500 MHz, DMSO-d₆) δ ppm: 21.29, 115.63, 126.42, 126.69, 126.79, 127.03, 127.46, 129.69, 130.20, 130.60, 134.42, 142.24, 146.95, 147.76, 160.46, 162.61. ESI-MS (*m/z*): 340.09 (M+H)⁺ (calcd. mass for C₁₈H₁₄ClN₃O₂ is 339.77). R_f: 0.70, *n*-hexane:ethyl acetate (2:8).

N'-(2-Chloro-6-methoxyquinolin-3-yl)methylidene]-4-hydroxybenzohydrazide (3d): Yellow solid; yield: 40%; m.p.: 276-278 °C. IR (KBr, ν_{\max} , cm⁻¹): 3432 (OH *str.*), 1627 (C=O *str.*), 1452-1383 (C-C arom. *str.*) 1343 (C=N), 832 (C-Cl *str.*). ¹H NMR (500 MHz, CHCl₃-d₆) δ ppm: 12.11 (s, 1H), 9.68 (s, 1H), 6.86-8.6 (arom.-H), 2.48 (s, 3H). ¹³C NMR (500 MHz, DMSO-d₆) δ ppm: 55.34, 107.34, 115.63, 122.90, 126.42, 126.92, 127.53, 129.02, 129.69, 129.87, 142.42, 145.35, 147.22, 158.53, 160.46, 162.61. ESI-MS (*m/z*): *m/z* 356.02 (M+H)⁺ (calcd. mass for C₁₈H₁₄ClN₃O₃ is 355.77). R_f: 0.72, *n*-hexane:ethyl acetate (2:8).

General procedure for the synthesis of ester derivative (4a-f): A mixture containing compound **3** (10 mmol) and 10 mol% of ZnO was prepared. To this mixture, acyl chlorides (12 mmol) were added and the reaction was initiated with stirring at room temperature. The progression of the reaction was tracked using TLC. Once the reaction had reached completion, the resulting mixture was subjected to extraction using ethyl acetate (2 × 5 mL) and ZnO was removed by filtration. The organic layer was subsequently washed with 10% NaHCO₃ solution and water, followed by drying using Na₂SO₄. The concentrated organic layer yielded the desired product. Alternatively, the product could also be obtained by adding a 10% NaHCO₃ solution and water to the reaction mixture, leading to the separation of the organic layer. This organic layer was then dried with Na₂SO₄ to afford the final product (**Scheme-I**).

4-{2-[(2-Chloro-6-methylquinolin-3-yl)methylidene]-hydrazine carbonyl}phenyl acetate (4a): Yellow solid; yield: 60%; m.p.: 251-254 °C. IR (KBr, ν_{\max} , cm⁻¹): 3250 (NH *str.*), 1620 (C=O *str.*), 1580 (C=N *str.*). ¹H NMR (500 MHz, CHCl₃-d₆) δ ppm: 12.21 (s, 1H), 8.56 (s, 1H), 7.13-8.28 (arom.-H), 2.38 (s, 3H), 2.37 (s, 3H). ¹³C NMR (500 MHz, DMSO-d₆) δ ppm: 21.06, 21.29, 122.52, 126.69, 126.76, 126.79, 127.03, 127.46, 129.92, 130.20, 130.60, 134.42, 142.24, 146.95, 147.76, 153.34, 162.61, 169.22. ESI-MS (*m/z*): (M+H)⁺ (calcd. mass for C₂₀H₁₆ClN₃O₃ is 381.81). R_f: 0.62, *n*-hexane:ethyl acetate (2:8).



Scheme-I: Synthesis of 2-chloroquinoline-3-carbaldehyde derivatives

4-{2-[(2-Chloro-6-methylquinolin-3-yl)methylidene]hydrazine carbonyl}phenyl propionate (4b): Yellow solid; yield: 62%; m.p.: 268-270 °C. IR (KBr, ν_{\max} , cm^{-1}): 3260 (NH *str.*), 1620 (C=O *str.*), 1490 (C=N *str.*). ¹H NMR (500 MHz, CHCl₃-d₆) δ ppm: 12.12 (s, 1H), 8.62 (s, 1H), 7.18-8.55 (arom.-H), 2.72 (s, 3H), 2.52 (q, 2H), 1.38 (s, 3H). ¹³C NMR (500 MHz, DMSO-d₆) δ ppm: 9.08, 21.29, 27.45, 121.93, 126.69, 126.76, 126.79, 127.03, 127.46, 129.91, 130.20, 130.60, 134.42, 142.24, 146.95, 147.76, 153.85, 162.61, 172.53. ESI-MS (*m/z*): 396.11 (M+H)⁺ (calcd. mass for C₂₁H₁₈ClN₃O₃ is 395.83). R_f: 0.71, *n*-hexane:ethyl acetate (2:8).

4-{2-[(2-Chloro-6-methylquinolin-3-yl)methylidene]hydrazine carbonyl}phenyl butanoate (4c): Yellow solid; yield: 53%; m.p.: 275-276 °C. IR (KBr, ν_{\max} , cm^{-1}): 3200 (NH *str.*), 1650 (C=O *str.*), 1500 (C=N *str.*). ¹H NMR (500 MHz, CHCl₃-d₆) δ ppm: 12.01 (s, 1H), 8.68 (s, 1H), 7.15-8.64 (arom.-H), 2.60 (s, 3H), 2.49 (t, 3H), 1.98 (m, 2H), 0.93 (s, 3H). ¹³C NMR (500 MHz, DMSO-d₆) δ ppm: 13.65, 18.40, 21.29, 39.58, 121.93, 126.69, 126.76, 126.79, 127.03, 127.46, 129.91, 130.20, 130.60, 134.42, 142.24, 146.95, 147.76, 153.21, 162.61, 171.94. ESI-MS (*m/z*): 410.16 (M+H)⁺ (calcd. mass for C₂₂H₂₀ClN₃O₃ is 406.86). R_f: 0.61, *n*-hexane:ethyl acetate (2:8).

4-{2-[(2-Chloro-6-methoxyquinolin-3-yl)methylidene]hydrazine carbonyl}phenyl acetate (4d): Yellow solid; yield: 70%; m.p.: 280-282 °C. IR (KBr, ν_{\max} , cm^{-1}): 3150 (NH *str.*), 1680 (C=O *str.*), 1520 (C=N *str.*). ¹H NMR (500 MHz, CHCl₃-d₆) δ ppm: 12.11 (s, 1H), 8.68 (s, 1H), 7.12-5.67 (arom.-H), 3.89 (s, 3H), 2.38 (s, 3H). ¹³C NMR (75 MHz, DMSO-d₆) δ ppm: 21.06, 55.34, 107.34, 122.52, 122.90, 126.76, 126.92, 127.53, 129.02, 129.86, 129.92, 142.42, 145.35, 147.22, 153.34, 158.53, 162.61, 169.22. ESI-MS (*m/z*): 398.08. (M+H)⁺ (calcd. mass for C₂₀H₁₆ClN₃O₄ is 397.81). R_f: 0.60, *n*-hexane:ethyl acetate (2:8).

4-{2-[(2-Chloro-6-methoxyquinolin-3-yl)methylidene]hydrazine carbonyl}phenyl propionate (4e): Yellow solid; yield: 65%; m.p.: 235-237 °C. IR (KBr, ν_{\max} , cm^{-1}): 3210 (NH *str.*), 1650 (C=O *str.*), 1550 (C=N *str.*). ¹H NMR (500 MHz, CHCl₃-

d₆) δ ppm: 12.10 (s, 1H), 8.74 (s, 1H), 7.10-8.69 (arom.H), 3.92 (s, 3H), 2.66 (q, 2H), 1.28 (t, 3H). ¹³C NMR (75 MHz, DMSO-d₆) δ ppm: 9.08, 27.45, 55.34, 107.34, 121.93, 122.90, 126.76, 126.92, 127.53, 129.02, 129.90, 129.91, 142.42, 145.35, 147.22, 153.85, 158.53, 162.61, 172.53; ESI-MS (*m/z*): 412.07 (M+H)⁺ (calcd. mass for C₂₁H₁₈ClN₃O₄ is 411.83). R_f: 0.70, *n*-hexane:ethyl acetate (2:8).

4-{2-[(2-Chloro-6-methoxyquinolin-3-yl)methylidene]hydrazine carbonyl}phenyl butanoate (4f): Yellow solid; yield: 70%; m.p.: 270-273 °C. IR (KBr, ν_{\max} , cm^{-1}): 3150 (NH *str.*), 1620 (C=O *str.*), 1480 (C=N *str.*). ¹H NMR (500 MHz, CHCl₃-d₆) δ ppm: 12.10 (s, 1H), 8.69 (s, 1H), 7.11-8.68 (arom.-H), 3.86 (s, 3H), 2.59 (t, 2H), 1.78 (m, 2H), 1.18 (s, 3H). ¹³C NMR (75 MHz, DMSO-d₆) δ ppm: 13.65, 18.40, 36.20, 55.34, 107.34, 121.93, 122.90, 126.76, 126.92, 127.53, 129.02, 129.86, 129.91, 142.42, 145.35, 147.22, 153.21, 158.53, 162.61, 171.94. ESI-MS (*m/z*): 426.14 (M+H)⁺ (calcd. mass for C₂₂H₂₀ClN₃O₄ is 425.86). R_f: 0.63, *n*-hexane:ethyl acetate (2:8).

Antibacterial activity: The antibacterial activity of synthesized compounds **4a-f** was assessed *in vitro* using the broth microdilution method [24]. Minimum inhibitory concentration (MIC) values were determined to evaluate their antibacterial efficacy. Test microorganisms included Gram-positive strains *Bacillus subtilis* (ATCC 6633) and *Staphylococcus aureus* (ATCC 12598), as well as Gram-negative strains *Klebsiella pneumoniae* (ATCC 29665) and *Escherichia coli* (ATCC 25922). Ciprofloxacin served as the standard drug.

Prediction of ADME properties: The pharmacokinetic parameters of the synthesized compounds were predicted using SwissADME, an online software tool designed for this purpose. The drug likeliness of the compounds was estimated by adhering to Lipinski's rule of five, which serves as a guideline for evaluating the oral bioavailability of chemical entities. The structures of the synthesized compounds **4a-f** were converted into their canonical Simplified Molecular-Input Line-Entry System (SMILES) notation and submitted to SwissADME [25].

RESULTS AND DISCUSSION

Acetanilide derivatives (**1a-d**) were treated with Vilsmeier Haack reagent prepared from DMF and POCl_3 resulted in the formation of substituted 2-chloroquinoline-3-carbaldehyde (**2a-d**) showing a proton singlet between δ 10.305-10387 ppm in the NMR spectrum for CHO and the FTIR for C=O absorption of aldehyde appeared between 1690-1680 cm^{-1} . The CH aldehyde absorption band was observed between 2930-2870 cm^{-1} region.

The study involved the synthesis and characterization of ester derivatives of quinoline **4a-f** obtained by treating compounds **3a-d** with acyl chlorides. The characterization of these derivatives revealed significant structural changes and provided insights into their potential biological activities. In the NMR spectra of ester derivatives **4a-f**, the presence of protons in the δ 1-4 ppm range indicated the formation of side chains and substitutions at the C-6 position. The signals at δ 9.639-9.685 ppm corresponding to the -OH group observed in compounds **3a-d** disappeared in the spectra of ester derivatives **4a-f**. These observations confirmed the successful formation of the desired ester derivatives. Additionally, the FTIR spectra displayed a distinctive absorption band at 1680-1620 cm^{-1} , corresponding to the C=O group in the ester functionality. The appearance of an absorption band between 3250-3150 cm^{-1} indicated the presence of -NH groups, while another absorption band in the range of 1580-1480 cm^{-1} confirmed the presence of C=N groups in the compounds. Mass spectral analysis further supported the formation of the ester derivatives as evidenced by the presence of molecular ion peaks M+1 corresponding to the mass of the compounds. This unequivocally demonstrated the successful synthesis of the targeted ester compounds.

Antibacterial activity: The results of the antibacterial activity, presented in Table-1, illustrate the minimum inhibitory concentrations (MIC) for the synthesized compounds. The MIC values represent the lowest concentration of a compound required to inhibit bacterial growth. The findings of this study suggest that the ester derivatives **4a-f** possess antibacterial properties, as evidenced by their MIC values.

Prediction of ADME properties: The ADME properties of synthesized hybrid molecules were predicted using Swiss-ADME software and the representative results are presented in Table-2. All six molecules, **4a-f** adhered to the Lipinski's rule of five, indicating no violations. This rule serves as a funda-

TABLE-1
ANTIMICROBIAL ACTIVITY RESULT

Sample	MIC ($\mu\text{g/mL}$)			
	Gram-positive		Gram-negative	
	<i>S. aureus</i>	<i>B. subtilis</i>	<i>K. pneumoniae</i>	<i>E. coli</i>
a	6.25	6.25	50	100
b	12.50	12.50	50	100
c	6.25	12.50	50	100
d	25.00	12.50	25	100
e	12.5	12.50	25	100
f	25.00	12.50	25	100
Ciprofloxacin	2	2	1	2

Compound **a** demonstrated good activity *S. aureus*, *B. subtilis*, *K. pneumoniae*, Compound **c** showed good activity against *S. aureus*, *K. pneumoniae*, compounds **d**, **e** and **f** showed very good activity against *K. pneumoniae*.

mental guideline to evaluate drug likeliness, suggesting that these compounds may have favourable pharmacokinetic profiles. The compliance of molecules with this rule underscores their potential suitability for oral administration, given their predicted favourable absorption and distribution characteristics. The number of rotatable bonds (6-9) in these molecules suggests a degree of molecular flexibility that can enhance binding interactions with biological targets without compromising structural integrity or leading to undesirable metabolic instability.

The prediction of high gastrointestinal (GI) absorption for all molecules suggests a promising bioavailability profile, which is critical for oral drug efficacy. Conversely, the absence of blood-brain barrier (BBB) permeation for these compounds indicates specificity in targeting peripheral sites without central nervous system effects. This attribute is particularly advantageous for drugs intended for systemic but not central actions, reducing the risk of central side effects. The analysis revealed that none of the molecules are substrates for P-glycoprotein (pgp), a transporter protein that can lead to drug resistance by effluxing drugs out of cells. This characteristic is beneficial for maintaining therapeutic concentrations at target sites. The consensus log P values, ranging from 3.4 to 4.3, fall within an optimal range that balances solubility and permeability, further affirming the compounds' drug likeliness. Molar refractivity values between 104 and 115, along with 6-9 rotatable bonds, suggest an appropriate balance of molecular flexibility and spatial occupancy, enhancing the likelihood of effective receptor interaction. The synthetic accessibility scores ranged from 2.7

TABLE-2
PHYSICO-CHEMICAL PROPERTIES PREDICTED FOR SYNTHESIZED COMPOUNDS **4a-f** USING SWISSADME

Properties*	4a	4b	4c	4d	4e	4f
Num. rotatable bonds	6	7	8	7	8	9
Num. H-bond acceptors	5	5	5	6	6	6
Num. H-bond donors	1	1	1	1	1	1
Consensus Log Po/w	3.71	4.06	4.36	3.43	3.71	4.04
Molar refractivity	104.39	109.19	114	105.91	110.72	115.53
Bioavailability score	0.55	0.55	0.55	0.55	0.55	0.55
Drug likeliness	Yes	Yes	Yes	Yes	Yes	Yes
Lipinski	0 Violation	0 Violation	0 Violation	0 Violation	0 Violation	0 Violation
Log S (ESOL) (solubility)	-4.88	-5.18	-5.42	-4.65	-4.95	-5.91
Synthetic accessibility	2.79	2.89	3.01	2.83	2.93	3.05s

*Few representative properties are listed in the table.

to 3.0, indicating that these molecules are relatively easy to synthesize, which is favourable for drug development processes. The uniform bioavailability score of 0.55 across all compounds, coupled with their ADME characteristics, predicts a moderate likelihood of success in the preclinical development stages. These findings justify further experimental validation and exploration of these compounds as potential therapeutic agents, laying the groundwork for subsequent *in vitro* and *in vivo* pharmacological studies.

Conclusion

This study successfully synthesized a series of ester derivatives using 6-substituted 2-chloroquinoline-3-carbaldehyde as a pivotal precursor. A thorough characterization spectroscopic techniques affirmed the successful incorporation of ester moieties. Moreover, the evaluation of antibacterial activity against both Gram-positive and Gram-negative bacteria provided valuable insights into the potential pharmaceutical applications. The MIC determination revealed the antibacterial potency of compounds, establishing a foundation for further investigations into their mechanisms of action and therapeutic potential. These ester derivatives represent a valuable expansion of chemical synthesis possibilities, holding implications for medicinal chemistry and drug development.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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