Volume 4, Issue 3, 2026

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

DESIGN, SYNTHESIS AND EVALUATION OF CLIOQUINOL DERIVATIVES

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DOI: https://doi.org/10.5281/zenodo.21508149

Keywords

Clioquinol, Alzheimer's disease, Therapeutic Application, Synthesis of Compounds

Article History

Received: 30 January 2026
Accepted: 15 March 2026
Published: 31 March 2026

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Abstract

Clioquinol, a significant drug in biological and coordination chemistry, has potential therapeutic applications in central nervous system disorders and has antibacterial, antimicrobial, and anti-inflammatory properties. Clioquinol and its derivatives are effective pharmacological compounds with clean work-up, reduced reaction time, and effective yield. (3a–3l) were synthesized and characterized, highlighting their structural variety and their therapeutic uses.

Introduction

Clioquinol, a halogenated 8-hydroxyquinoline, was used orally for treating intestinal amebiasis between 1950 and 1970. However, it was discontinued in the 1970s due to neurotoxicity claims from Japanese patients (1).

Clioquinol is quickly absorbed in various animals and has a half-life of 11-14 hours. It functions as a chelator for copper and zinc, which are implicated in Alzheimer's disease (AD). Metal chelation is a potential treatment approach, as it lowers oxidation and the amyloid burden, potentially having anticancer properties (2).

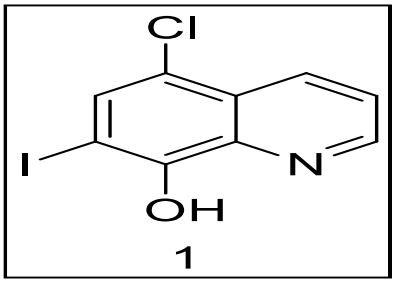

Figure 1: Structural diagram of Clioquinol

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ISSN: (e) 3007-1607 (p) 3007-1593

For wound treatment and preoperative skin preparation, clioquinol-containing creams, ointments, and lotions are applied directly to the skin (3). It is a crucial tool in clinical practice because of its topical application, broad-spectrum antibacterial action, and favorable safety profile (4). Alzheimer's disease is a neurological condition characterized by cognitive and intellectual decline and memory loss (5). With 1.52 billion people globally affected by the condition by 2050, the number is expected to treble. Aβ, a byproduct of amyloid metabolism, is the main component of AD plaques (6). The creation of novel flurbiprofen-clioquinol hybrids as multipurpose medications for the treatment of AD.

Material & Methods

2.1 Typical Information

The following in addition to ethyl acetate, analytical-grade solvents such as methanol, DMF, n-hexane, acetonitrile, sulfuric acid, and hydrochloric acid were employed. For thin layer chromatography, Fluka's pre-coated PolyGram plates were utilized. To measure the 1H-NMR spectra, A type AV-400 nuclear magnetic resonance spectrometer running at 500 MHz was used. At a frequency of 100 MHz, 13C-NMR spectra were also measured using a nuclear magnetic resonance spectrometer (model AV500).

General Procedure

0.1g of clioquinol was put to a 50 mL round-bottom flask that had been cleaned and rinsed. Reaction mixture was then agitated with 5 ml of DCM. One equivalent of substituted carboxylic acid was incorporated into this reaction mixture, and it was agitated for ten minutes to produce a clear solution. 0.045 mL of pyridine was then added to the mixture. After covering the flask with solution shift reflux for four hours, it was covered with aluminum foil and stirred for nearly twenty-four hours (7).

Biological evaluation

Every newly made derivative has its hemolytic activity assessed and the hemolysis percentage explained. This table illustrates how harmful each derivative is to red blood cells. Certain compounds are extremely toxic, whereas others are not. All forms of aczema and AD were examined in relation to the Clioquinol derivatives 3a–l. The respective infected Dulbecco's Modified Eagle's Medium (DMEM) supplemented with fetal bovine serum (FBS) was used to culture the cells at 37°C. They were tested for cell viability using the standard MTT assay (3-(4,5-dimethylthiazole-2-yl)-2,5-diphenyl tetrazolium bromide) (8).

DMSO was used to dilute the produced chemicals. For 48 hours, cells infected with arthritis were treated with a final dose of 0.05% DMSO. In these tests, these DMSO-treated cells acted as the control. After adding 500 µg/ml of MTT reagent, the cell was stored at 37°C for four hours. Investigations were conducted into the derivative solution's absorbance in DMSO. The thermos scientific microplate reader was used to detect absorbance at 575 nm in order to calculate cell viability as a percentage (9).

Characterization of Compounds (NMR & FT-IR)

Organic chemists employ NMR spectroscopy as a vital analytical tool to study compounds by observing their interaction with radiofrequency radiation in a high magnetic field. It helps reveal molecule structure, concentration, and purity, particularly in proton (1H) NMR. Fourier Transform FTIR Spectroscopy (FTIR Analysis) is a method used to identify organic, polymeric, and inorganic materials using infrared light scanning. It is a crucial quality control method for industrial materials, detecting changes in absorption bands and contamination. FTIR microanalysis helps identify product issues, analyzing both larger surface regions and smaller particles.

Statistical analysis

Every experiment was conducted three times, and Microsoft Excel 2010 was used to do the statistical analysis. The cell viability results are shown as mean ± SD.

Results

This study aims to prepare aryl hydroxyl equivalents using novel techniques and evaluate their biological impact. Aryl hydroxy derivatives are effective pharmacological compounds with clean work-up, reduced reaction time, and effective yield.

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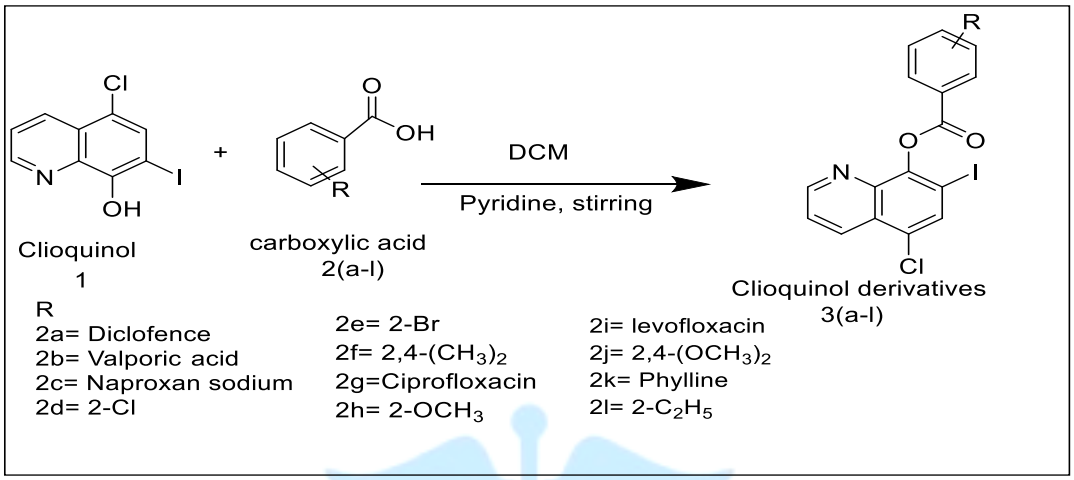
Ciprofloxacin (CQ) was once used for skin infections and diarrhea, but was removed from the market due to SMON in Japan. CQ is now used as a topical Antibiotic under Vioform® and repurposed for cancer and Alzheimer's disease.

4.1 General Outline: Synthesis of Compound

General procedure to produce aryl- hydroxy derivative is given below



Scheme 1: Scheme Outlining the General Process for Producing Analogs of Aryl-hydroxTable 1: Spectral characterization of compounds

Compound	M.P. (°C)	Yield (%)	FT-IR (cm^{-1})ν_{max} / ^{1}HNMR , C^{13}NMR (500 MHz, $CDCl_3$)/ MS (EI) (m/z)
3a	576.75	85	1750 (C=O), 1323(C-N), / 3.91(2H, $OCCH_2$), 6.76 (s,1H, quinoline, Ar-H), 7.18 (d, 3H, Ar-H), 7.29-7.37, (d, 3H, Ar-H), 7.47 (t,1H, Pyridine), 7.82 (d, 1H, quinolone), 8.74 (s, 1H,pyridine), 8.89 (d, 1H, pyridine)/ 35.5, 87.5,120, 124, 128.9, 134, 135, 154, 156.1,171/ 581.92
3b	273.23	80	1650 (C=O), 3400 (N-H)/ 0.89 (t, 6H, $(CH_3)_2$, 1.30 (m,4H, $(CH_2)_2$, 2.13 (q, 2H, CH_2), 3.73(m, 2H, H-Ar), 5.92(t,1H, H-Ar), 6.82(s, 1H, H-Ar), 6.92 (d, 1H, N-H), 7.02 (d, 1H, H-Ar)/ 0.89, 19.9, 34.8, 43.7, 124.01, 125.5, 135.2, 142.9, 154.9, 156.1, 76.9/ 430.1
3c	465.24	65	1725 (C=O), 1250 (C-O), 808 (C-N),/ 1.64 (d,3H CH_3), 3.71 (q, 1H H-Ar), 3.81 (d, 3H CH_3), 7.06 (d,1H H-Ar), 7.23 (d,1H H-Ar), 7.34 (m, 1H H-Ar), 7.48-7.49 (d,2H, H-Ar), 7.73-7.82 (s, 3H, quinoline), 8.74 (d, 1H, H-Ar), 8.89 (d,1H, N-H)/ 13.7, 40.4, 55.8, 87.5, 105.4, 124, 126.7, 128.5, 132.5, 133.5, 134.9, 135.2, 154.9, 156.1, 170.0/ 516.99
3d	363.82	80	1650 (C=O), 808 (C-N),/ 7.43-7.45 (t,2H H-Ar), 7.65-7.73 (m, 3H, H-Ar), 8.12 (d,1H, H-Ar), 8.83 (d,1H, H-Ar), 8.97 (d,1H, N-H)/ 78.2, 124.1, 126.7, 130, 131.7, 131.8, 133.9, 134, 135.4, 140.5,154.8, 161, 165.2/ 422.90
3e	412.57	78	1675 (C=O), 808 (C-N),/ 4.14 (s,2H, $COCH_2$), 7.47 (m,1H, H-Ar), 7.61-7.79 (d,5H, H-Ar), 8.85(d,1H, H-Ar), 8.96 (d,1H, N-H)/ 78.2 121.4, 124.1, 125.7, 126.7, 127.6, 130, 131.8, 133, 134, 135.4, 140.5,154.8, 161, 165.2/ 484.87

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ISSN: (e) 3007-1607 (p) 3007-1593

3f	368.96	75	1735 (C=O), 1250 (C-O), 808 (C-N), 700 (C-Cl)/ 2.30 (s, 3H, H-CH_3), 2.48 (s, 3H, Me), 7.22 – 7.27 (d, 2H ,H-Ar), 7.65-7.69 (d, 2H, H-quinoline), 8.08 (d, 1H, H-Ar), 8.83 (d, 1H, H-Ar), 8.97 (d, 1H, C-N, quinoline)/ 21.6, 21.7 78.2, 124.1s, 125.7, 128.7, 130.8, 134.0, 134,135.4, 139.8, 140.5, 143, 154, 161, 165.2/ 436.97
3g	778.9	70	1740 (C=O), 1250 (C-O), 808 (C-N), 1100(C-Fl)/ 1.07 (m, 1H, N-H), 1.33 (m, 4H, $(CH_2)_2$), 2.78 (t, 4H, $(CH_2)_2$), 3.46 (t, 2H, CH_2), 4.12 (q, 1H, cyclopropane), 6.01 (d, 1H, H-Ar), 7.65-7.69 (q, 2H, H-Ar), 8.01 (d, 1H, H-Ar), 8.09 (s, 1H, H-Ar), 8.83 (d, 1H, H-Ar), 8.97 (d, 1H, C-N)/ 7.7, 35.8, 45.8, 51.3, 78.2, 102.5, 109.3, 112.2, 124.1, 125.7, 130.5, 134, 135.4, 136.8, 140.5, 146.9, 152.5, 154.8, 161,162, 176.4/ 618.03
3h	367	85	1735 (C=O), 1250 (C-O), 808 (C-N)/ 7.22 (d, 1H, H-Ar), 7.57-7.60 (m, 2H, H-Ar), 7.65-7.69 (m, 2H, quinoline), 8.25 (d, 1H, H-Ar), 8.83 (d, 1H, H-Ar), 8. 97 (d, 1H, H-Ar)/ 55.8, 78.2, 114.2, 120.9, 124.1, 125.7,130, 131.3, 134,134.9, 140.5, 154.8, 158.5, 161, 169.1/ 438.95
3i	520.9	80	1735, 1750 (C=O), 1250 (C-O), 808 (C-N)/ 1.9 (d, 3H, Me), 2.21 (s, 3H, Me), 2.35 (t, 4H H-Ar), 3.23 (t, 2H, CH_2), 3.44 (s, 4H, H-Ar), 3.99-4.24 (t, 2H, H_2C-O), 7.69 (d, 1H, H-Ar) 8.66 (s, 1H,H-Ar), 14.93 (t, 1H, OH)/ 17.9, 46.6, 57.2, 59.4, 65.9, 71.1, 103.8, 109.3, 123.4, 126, 132.6, 143.1, 146.9, 158.2, 166.2, 170.4/ 361.14
3j	454.5	70	1635 (C=O), 1250 (C-O)$_2$, 808 (C-N)/ 3. 84- 3.90 (s, 6H, $(OCH_3)_2$), 5.70 (s, 2H, CH_2), 6.72-6.75 (d, 2H, H-Ar), 7.60, 7.62, 7.65 (m, 3H, H-Ar), 8.70 (d, 1H, H-Ar), 8.85 (d, 1H, HC-N)/ 55.8, 73.1, 74.1, 96.8, 106.5, 112.5, 123.9, 129.5, 130.8, 133.7, 135.3, 141.7, 153.6, 162.2, 164,168, 198.3/ 482.97
3k	450	75	1650 (C=O), 1250 (C-O), 808 (C-N)/ 3.32 (s, 3H, CH_3), 7.65, 7.69 (t, 2H, H-Ar), 8.83 (d, 1H, quinoline) 8.97 (d, 1H, H-Ar) 9.24 (s, 1H, imidazole) 13.0 (d, 1H, N-H, imidazole)/ 30.7,78.2, 124.7, 129, 130, 134, 135.4, 140.5,149, 150.8,154.8, 161, 162.8/ 468.94
3l	397.5	80	1700 (C=O), 1200 (C-O), 808 (C-N)/1.18 (t, 1H, 3H, CH_3), 2.71 (q, 2H, CH_2), 5.70 (s, 2H, OCH_2), 7.33 (q, 1H, H-Ar), 7.60- 7.62 (t, 3H, H-Ar), 7.80 (d, 2H, H-Ar), 7.96 (q, 1H, H-Ar), 8.70 (d, 1H, H-Ar), 8.85 (d, 1H, H-Ar)/ 74.1, 27.3, 73.1, 74.1, 123.9, 124.5,127.5, 127.6,129.4, 133, 133.7, 135.5, 135.7,141.7, 143.5, 153.6, 164.8, 198.3/ 450.98

4.2 Discussion

The study successfully synthesized Clioquinol derivatives (3a–3l) with varying yields, melting points, and structural characteristics, as evidenced by the provided spectroscopic data (10). These compounds demonstrated high pharmacological potential due to their functional group diversity and aromatic framework, which could be tailored for specific therapeutic applications. **3a** displayed peaks corresponding to quinoline and pyridine aromatic protons, reflecting its polyaromatic nature, which could be relevant in antimicrobial or anticancer activities. **3g** featured a cyclopropane moiety (δ 4.12), enhancing its rigidity and potential selectivity as a drug molecule. **3k** exhibited imidazole-related signals (δ 9.24 and 13.0), suggesting applications in enzyme modulation or anti-inflammatory properties.

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ISSN: (e) 3007-1607 (p) 3007-1593

Derivatives	%ageof hemolysis	%age of thrombolysis
3a	2.66 ± 0.123	7.5 ± 0.088
3b	1.53 ± 0.006	6.3 ± 0.083
3c	2.80 ± 0.003	10.5 ± 0.007
3d	4.7 ± 0.044	9.9 ± 0.086
3e	1.7 ± 0.008	3.8 ± 0.082
3f	5.90 ± 0.005	10.9 ± 0.084
3g	0.8 ± 0.009	10.3 ± 0.081
3h	0.2 ± 0.006	5.5 ± 0.086
3i	0.3 ± 0.005	8..9 ± 0.086
3j	0.7 ± 0.004	9.5 ± 0.086
3k	0.4 ± 0.003	7.7 ± 0.086
3l	0.8 ± 0.002	6.9 ± 0.086

Conclusion

Clioquinol and its derivatives are effective pharmacological compounds with clean work-up, reduced reaction time, and effective yield. (3a–3l) were synthesized and characterized, highlighting their structural variety and their therapeutic uses. Important functional groups that may affect their biological activity and target selectivity, like imidazole (3k), cyclopropane (3g), and polyaromatic systems (3a), were successfully introduced, according to the spectral analysis. With their unique quinoline and imidazole characteristics, compounds such as 3a and 3k exhibit promise for use in antibacterial, anticancer, and enzyme-modulatory processes. According to these results, the synthesized compounds show promise as subjects for additional pharmacological and therapeutic research. To confirm their effectiveness and enhance their functional qualities, future research should investigate their biological activities both in vitro and in vivo.

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