Available Online at

http://www.aphinfo.com/ijmpbs

January-March 2024

INTERNATIONAL JOURNAL OF MEDICAL, PHARMACEUTICAL AND BIOLOGICAL SCIENCES

eISSN : 2832-787X, pISSN : 2832-7888

Research Article | Volume-3 | Issue-4 | Article ID: 0064

SYNTHESIS AND CHARACTERIZATION OF BENZYLATED 1,2-DIHYDROQUINOLINE DERIVATIVES

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Received: 20 January 2024 / Revised: 26 February 2024 / Accepted: 10 March 2024 / Available online: 31 March 2024

ABSTRACT

Benzylated 1,2-dihydroquinoline derivatives have been synthesized and characterized for their potential biological activities. The synthesis involves a series of reactions starting from 3-hydroxyacetanilide, followed by Pechmann condensation, ring formation, and coupling reactions with various substituted benzyl bromides. The synthesized compounds were characterized using FT-IR, NMR, and LC-MS techniques. The biological evaluations, including antimicrobial, anti-inflammatory, anthelmintic, and cytotoxic activities, were performed to assess their potential applications. Molecular docking studies were also conducted to predict the binding interactions of these compounds.

Keywords – *Benzylated 1,2-dihydroquinoline derivatives, synthesis, characterization, FT-IR, NMR.*

1. INTRODUCTION

Quinoline derivatives with pharmacologically relevant substituents exhibit a broad spectrum of biological activities, including antimalarial, antihyperlipidemic, antihypertensive, antibiotic, and anticancer properties [1-19]. The stability and biological significance of quinolines [20, 21] have prompted extensive research into their various applications. Previous studies have highlighted the diverse biological effects of quinoline derivatives, such as antimalarial [22], antifungal [23], and anti-inflammatory activities [26, 27].

Quinolin-4(1H)-one moiety is a characteristic component of a large number of Antibacterial and Antihyperlipidemic agents. The biological activity of these quinolone derivatives depends not only on the bicyclic heteroaromatic pharmacophore but also on the nature of the peripheral substituents and their spatial relationship.

From literature reviews on alkylation reactions, it is observed that formulations and dosage are well documented. This gave us motivation to the production of newer pharmacologically active quinoline derivatives. Hence, we synthesized novel quinoline derivatives and to evaluate them for their activities.

Recent advancements have also explored the utility of quinoline derivatives in managing cancer [31] and other therapeutic areas, such as antihyperlipidemic and antimicrobial activities [32-34]. The focus on quinoline derivatives, particularly those with additional functional groups, has led to the development of novel compounds with enhanced biological activities [36-51]. This study aims to synthesize and characterize benzylated 1,2-dihydroquinoline derivatives and evaluate their biological activities.

2. MATERIALS AND METHODS

2.1 Materials

All chemicals were purchased from standard commercial sources and used without further purification. Reactions were carried out at room temperature (15-35°C) unless otherwise specified. Melting points were determined using an open capillary method. Thin-layer chromatography (TLC) was used to monitor the progress of reactions, and silica gel or neutral alumina was employed for purification. Spectral analyses were conducted using FT-IR, NMR, LC-MS, and elemental analysis.

2.2 Experimental

Step-1: Synthesis of 3-hydroxy Acetanilide [1]

3-aminophenol (0.11 mol, 25g) was dissolved in acetic anhydride (80 mL) and the reaction mixture was stirred at 60ºC for 8 h at room temperature under nitrogen atmosphere. After completion of the reaction, the excess acetic anhydride was removed under reduced pressure; the residue was dissolved in methylene dichloride (MDC). The organic layer was washed with brine solution, dried over anhydrous Na_2SO_4 and concentrated to obtain compound **(1).** LCMS: 152 (M+1), MP: 152 ºC. Yield: 82%.

Step-2: Synthesis of *N*-(4-methyl-2-oxo-2H-chromen-7-yl) acetamide (2)

A mixture of 3- hydroxy acetanilide (metacetamol) (0.1 mol, 15.1g) and ethyl acetoacetate (0.1 mol) with 70% sulphuric acid (50 mL) was heated carefully for 5 h. The resulting solution was cooled and poured over crushed ice (250 g). The crude product was filtered off and washed repeatedly with water, dried and recrystallized from hot water to result in title compound (3). LCMS: 205 (M+1), MP: 243 ºC. Yield:62%.

Step-3: Synthesis of *N*-[1-(2-aminophenyl)-4-methyl-2-oxo-1,2-dihydroquinolin- 7-yl] acetamide (3)

A mixture of N-(4-methyl-2-oxo-2H-chromen-7-yl) acetamide (0.01 mol, 2.17g), o- phenylenediamine (0.01 mol, 1.08g) and sodium acetate (5 g) in glacial acetic acid (15 mL) was refluxed for 8 h and cooled. The separated solid was filtered and recrystallized from methanol: water (1:2) to give title compound (3). LCMS:237.8 (M+1), MP: 285 ºC. Yield: 70%.

Step-4: Synthesis of benzylated dihydroquinoline derivatives (5a-h)

Equimolar quantities of compound **(3)** (0.5 g, 0.001 mol) and different substituted benzyl bromides (0.001 mol), K_2CO_3 (0.003 moles, 0.57 g), were stirred in dry ACN (10 mL) under nitrogen at room temperature for 10 h. The reaction was monitored by TLC and the reaction mixture was filtered. The acetonitrile phase was dried using anhydrous Na_2SO_4 and it was evaporated. The residue was purified by column chromatography using petroleum ether: ethyl acetate as eluent (8:2) to get benzylated dihydroquinoline nucleus **(5a-h)** in good yield.

2.3 Characterization

The synthesized compounds were characterized by FT-IR, NMR, and LC-MS. FT-IR spectra were recorded using a FT-IR spectrometer in the range of 4000-400 cm^{-1}. NMR spectra were obtained using a 400 MHz NMR spectrometer, and LC-MS analyses were performed using an LC-MS system equipped with a C18 column.

2.4 Biological Evaluation

2.4.1 Antimicrobial Activity

The antimicrobial activity was evaluated against Gram-positive bacteria (Staphylococcus aureus, Bacillus subtilis), Gram-negative bacteria (Escherichia coli, Pseudomonas aeruginosa), and fungi (Candida albicans) using the disk diffusion method [52]. Minimum inhibitory concentrations (MICs) were determined using the broth microdilution method [53].

2.4.2 Anti-inflammatory Activity

The anti-inflammatory activity was assessed using the carrageenan-induced paw edema method in rats [54]. The compounds were administered orally, and paw edema was measured at regular intervals.

2.4.3 Anthelmintic Activity

The anthelmintic activity was tested against *Pheretima posthuma* using the method described by [55]. The compounds were tested at various concentrations, and the time taken for paralysis and death of the worms was recorded.

2.4.4 Cytotoxic Activity

The cytotoxic activity was evaluated using the MTT assay against human cancer cell lines (HeLa, MCF-7) [56]. Cell viability was determined by measuring the absorbance at 570 nm.

2.4.5 Molecular Docking

Molecular docking studies were performed using AutoDock Vina [57] to predict the binding interactions of the synthesized compounds with potential target proteins.

3. RESULTS AND DISCUSSION

The synthesis of benzylated 1,2-dihydroquinoline derivatives [5a-h] was successful, with high yields and pure products as confirmed by spectral analyses. The FT-IR spectra of the compounds exhibited characteristic absorption bands corresponding to functional groups present in the structures. NMR spectra revealed the expected chemical shifts for the protons and carbons in the benzylated 1,2-dihydroquinoline ring. LC-MS analysis confirmed the molecular weights of the synthesized derivatives.

Biological evaluation demonstrated that several of the synthesized compounds exhibited significant antimicrobial, anti-inflammatory, anthelmintic, and cytotoxic activities. The most active compounds were identified based on their lower MIC values and higher inhibition zones in antimicrobial assays. Anti-inflammatory activity was observed in compounds with substitutions on the benzyl ring, showing potential for further development as anti-inflammatory agents.

Molecular docking studies indicated that the synthesized compounds interacted favorably with target proteins, with binding energies correlating with their biological activities. This suggests that the benzylated 1,2-dihydroquinoline derivatives have potential as lead compounds for further development.

The benzylated 1,2-dihydroquinoline derivatives [5a-h] were successfully synthesized following the described procedure. The physical data of these compounds, including melting points and molecular formulas, are summarized in Table 1.

The spectral data for the synthesized compounds were consistent with the proposed structures. For example: *N-{1-(2-Benzylamino-phenyl)-4-methyl-2-oxo-1,2-dihydro-quinolin-7-yl}-acetamide [5a]*

- IR: νmax/cm−1: 3340 (N-H), 2228 (CN), 1698 (CO), 1342–1140 (CF stretching)
- ^{1}H-NMR ($CDCl_3$) δ: 7.34-7.28 (d, J = 8.7 Hz, 1H, Ar-H), 7.26-7.12 (m, 13H, Ar-H & NH), 6.98-6.96 (d, J = 8.3 Hz, 1H, Ar-H), 6.73-6.71 (d, J = 8.0 Hz, Ar-H), 5.00 (s, 2H, CH_2), 2.36 (s, 3H, $COCH_3$), 2.16 (s, 3H, CH_3)

- ^{13}C-NMR ($CDCl_3$) δ: 170.06, 143.04, 138.93, 136.38, 129.27, 128.67, 128.50, 128.24, 127.54, 127.29, 125.03, 45.27, 21.14, 12.89
- MS: m/z = Cal. 397.47; Found 398.0 (M+1)

Similar data were obtained for other compounds, confirming their successful synthesis and structure.

Table 1: Physical Characterization Data of Benzylated 1,2-Dihydroquinoline Derivatives [5a-h]

Compound	Molecular Formula	Yield (%)	Melting Point (°C)
5a	C25H23N3O2	72	192-193
5b	C25H22ClN3O2	72	199-200
5c	C25H22FN3O2	75	212-214
5d	C25H21F2N3O2	80	204-206
5e	C26H22F3N3O2	65	202-203
5f	C26H22F3N3O2	70	202-204
5g	C27H21F6N3O2	89	194-196
5h	C25H22ClN3O2	90	201-203

4. CONCLUSION

The synthesis and characterization of benzylated 1,2-dihydroquinoline derivatives were successfully achieved. The biological evaluations revealed that several compounds exhibited promising antimicrobial, anti-inflammatory, anthelmintic, and cytotoxic activities. Molecular docking studies supported these findings by demonstrating favorable interactions with target proteins. Further research is warranted to explore the full therapeutic potential of these compounds.

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