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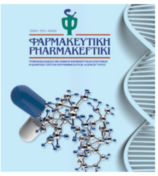

PHARMAKEFTIKI, 37, 2S, 2025 | 164-167 RESEARCH

https://doi.org/10.60988/p.v37i2S.166

Synthesis, characterization, and biological evaluation of new cyclic oxazepine derivatives as potential antibacterial and antifungal agents

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KEY WORDS:
Schiff bases; oxazepine; antibacterial; antifungal; synthesis

ABSTRACT

In this study, Bis(4,4'-diaminophenoxy)ethane (compound C1) was synthesized *via* the reaction of *p*-hydroxyaniline with 1,2-dibromoethane. Schiff bases (compounds C2–C4) were subsequently obtained by condensing compound C1 with various aromatic aldehydes. These intermediates were further reacted with different anhydrides – namely phthalic anhydride and maleic anhydride – in order to yield the final derivatives (compounds C5–C10). All obtained compounds were characterized by using infrared spectroscopy and proton nuclear magnetic resonance, as well as through an assessment of their physical properties. Antimicrobial evaluation was conducted on some of the generated compounds using two bacterial strains (*Escherichia coli* and *Staphylococcus aureus*) and one fungal strain (*Candida albicans*), selected for their clinical relevance as causative agents of diverse human diseases.

ARTICLE INFO:
Received: November 09, 2024
Revised: January 17, 2025
Accepted: February 06, 2025
Available online: October 10, 2025

1. Introduction

The development of synthetic routes to widely used organic compounds using readily available reagents remains a central goal of organic synthesis. Schiff bases constitute an important class of organic compounds due to their broad spectrum of biological activities, including antimalarial, anticancer, antiviral, antifungal, antibacterial, antioxidant, antiproliferative, and anti-inflammatory effects[1]. Schiff bases are condensation products formed from primary amines and carbonyl compounds (aldehydes or ketones)[2]. First reported by the German chemist Hugo Schiff in 1864, these compounds are also known as azomethines or

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imines[3]. Structurally, they consist of an imine group (R-CH=N-R'), where the substituents R and R' may be cycloalkyl, alkyl, heterocyclic, or aryl groups[4].

Heterocyclic compounds play a prominent role in drug synthesis. One notable example is the 1,3-oxazepine; a seven-membered ring containing two heteroatoms: oxygen and nitrogen[5]. Oxazepines exhibit diverse pharmacological activities and have been employed as antibiotics, enzyme inhibitors, and antidepressants. Over time, their synthesis has been extensively documented and investigated. These compounds are typically prepared *via* the reaction of Schiff bases or hydrazones with various anhydrides[6].

In this study, we sought to convert selected Schiff bases into oxazepine derivatives through cyclization of the azomethine bond using maleic anhydride and phthalic anhydride[7]. Oxazepine derivatives are known to exhibit significant variations in biological activities, including antibacterial, anticonvulsant, antiviral, and antifungal properties, among other applications[9].

2. Methodology

2.1. Chemicals and equipment

All chemicals were obtained from various suppliers (e.g., Thomas Baker, Merck, BDH, GCC, and Scharlau) and were used without further purification. Melting points were determined using an electrothermal melting point apparatus (Stuart, Germany) and are reported uncorrected. Purity and reaction completion of all compounds were assessed *via* thin-layer chromatography (TLC) on aluminum-coated silica plates (TLC 60 F_{254}, E. Merck), with absolute ethanol as the mobile phase and visualization under iodine vapor.

Infrared spectra were recorded as KBr disks within the range of 400–4000 cm^{-1} using a Shimadzu FTIR spectrometer (Japan). Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded for the synthesized compounds on a Bruker DMX-500 spectrophotometer (500 MHz) using DMSO-d_6 as the solvent.

2.2. Synthesis of Bis(4,4'-diaminophenoxy)ethane (compound C1)

Alcoholic sodium hydroxide (8 g, 0.2 mol) was added to 20 mL of absolute ethanol containing *p*-hydroxyaniline (0.02 mol, 2.91 g). The mixture was stirred until complete dissolution of the solids, followed by the addition of 1,2-dibromoethane (0.01 mol, 0.64 mL). The reaction mixture was refluxed for 4 h, and progress was monitored by TLC. Upon completion, the solution was poured into ice-cold distilled water, precipitating a violet solid. The crude product was filtered and purified using absolute ethanol[9]. Compound C1 was obtained as a violet precipitate (MP: 200°C–202°C).

2.3. Synthesis of Schiff bases (compounds C2–C4)

A mixture of compound C1 (2 g, 0.008 mol) and various aldehydes (benzaldehyde, 4-chlorobenzaldehyde, 4-bromobenzaldehyde) (0.016 mol) was dissolved in 20 mL of absolute ethanol along with a few drops of glacial acetic acid. The reaction mixture was refluxed for 8–10 h. The resulting solids were filtered and purified using absolute ethanol[8]. Compound C2 was obtained as a dark red precipitate (MP: 184°C–186°C), compound C3 was obtained as a violet precipitate (MP: 118°C–120°C), and compound C4 was obtained as a violet precipitate (MP: 166°C–168°C).

2.4. Synthesis of (oxazepine) compounds C5–C10

Compounds C2–C4 (0.001 mol) were individually dissolved in 10 mL of dry benzene, then reacted with either phthalic anhydride or maleic anhydride (0.002 mol) under reflux for 5 h. TLC was used in order to monitor the reaction completion. Upon cooling, the reaction mixture was filtered and the crude products were purified using ethanol[6]. Compound C5 was obtained as a red precipitate (MP: 190°C–192°C), compound C6 was obtained as a brown precipitate (MP: 173°C–175°C), compound C7 was obtained as a pale brown precipitate (MP: 181°C–182°C), compound C8 was obtained as a red precipitate (MP: 175°C–177°C), compound C9 was obtained as a brown precipitate (MP: 160°C–162°C), and compound C10 was obtained as a dark brown precipitate (MP: 130°C–132°C).

2.5. Antibacterial and antifungal activity

Antimicrobial activities of selected compounds (i.e., compounds C2, C3, C4, C5, C8, and C10) and of amoxicillin were assessed *via* the agar well diffusion method[10]. Tests were conducted against two bacterial strains – *Staphylococcus aureus* (Gram-positive) and *Escherichia coli* (Gram-negative) – and one fungal strain (*Candida albicans*). Wells of 6-mm diameter were created on agar plates using a sterile cork borer. Each well was filled with 0.2 mL of microbial suspension, evenly spread using a sterile cotton swab. Test compounds and amoxicillin were introduced at a concentration of 0.2 mL per well *via* a micropipette. Plates were incubated at 37°C for 24 h, after which inhibition zone diameters were measured with a ruler.

3. Results and Discussion

Compound C1 was synthesized by reacting *p*-hydroxyaniline with 1,2-dibromoethane in the presence of sodium hydroxide in ethanol. Its structure was confirmed by Fourier transform infrared (FT-IR) spectroscopy, which showed the disappearance of the characteristic stretching vibration of the hydroxyl (-OH) group. A new band corresponding to the C-O-C stretching vibration was observed at 1234 cm^{-1}. Additionally, absorption bands at 3417 and 3375 cm^{-1} were attributed to asymmetric and symmetric $N\text{-}H_2$ stretching vibrations, respectively.

Refluxing compound C1 with equimolar amounts of various carbonyl compounds in absolute ethanol, in the presence of a few drops of glacial acetic acid, resulted in the formation of a new series of Schiff bases (compounds C2–C4). The FT-IR spectra of these compounds indicated the disappearance of $N\text{-}H_2$ bands at 3417 and 3375 cm^{-1}, alongside the appearance of a new band corresponding to the imine (-CH=N) group, thereby confirming Schiff base formation. The resulting Schiff bases were then reacted with different anhydrides in order to yield oxazepine derivatives (compounds C5–C10). The FT-IR characterization of compound C5 revealed key vibrational bands associated with the oxazepine ring: a signal at 1739 cm^{-1} indicating ring vibration, and a band at 1651 cm^{-1} attributed to the carbonyl stretching of lactone and lactam functionalities.

Further structural confirmation was obtained for compound C7 *via* ^1H-NMR spectroscopy, which showed: (i) δ 8.9 ppm (s, 2H, -CH=N), (ii) δ 6.5–7.7 ppm (m, 16H, aromatic protons), (iii) δ 3.69–4.42 ppm (t, 4H, methylene $-CH_2-$), and (iv) δ 2.97–3.06 ppm (multiplet, 2H, additional $-CH_2-$ units).

The antimicrobial efficacy of the synthesized compounds was evaluated against *Staphylococcus aureus*, *Escherichia coli*, and *Candida albicans* using the agar well diffusion method. Bacterial strains were incubated at 37°C for 24 h, while fungal cultures were maintained at 28°C for 3–5 days. Multiple compounds demonstrated significant inhibitory activity when compared to the control antibiotic amoxicillin. Compound C10 exhibited the most pronounced activity, with inhibition zones measuring: (i) 24 mm against *Staphylococcus aureus*, (ii) 22 mm against *Escherichia coli*, and (iii) 20 mm against *Candida albicans*. Notably, compound C10 outperformed amoxicillin in terms of antifungal activity, thereby suggesting a broad-spectrum antimicrobial effect and underscoring its potential as a lead candidate for further development.

4. Conclusion

This study provides meaningful contributions to antibacterial and antifungal research through the synthesis and evaluation of novel heterocyclic compounds. Structural characterization has offered key insights into the chemical profiles of the synthesized derivatives, while biological assays have highlighted their potential antimicrobial activity. Although most compounds displayed moderate antibacterial efficacy relative to amoxicillin, compound C10 exhibited notably strong inhibitory effects against *Staphylococcus aureus*, *Escherichia coli*, and *Candida albicans*. These findings suggest that compound C10 possesses broad-spectrum antimicrobial properties and merits further investigation for its potential as an alternative therapeutic agent, particularly in the fight against drug-resistant infections.

Acknowledgements

The authors gratefully acknowledge the College of Science for Women of the University of Baghdad, for generously providing the chemicals and research facilities necessary to conduct this study.

Conflicts of interest

None exist.

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HOW TO CITE:
Alsahib S.A., Kadhim E.A., Mahmood G.H., Abdulghani R.H. Synthesis, characterization, and biological evaluation of new cyclic oxazepine derivatives as potential antibacterial and antifungal agents. *Pharmakeftiki* 37(2s), 164-167, 2025. https://doi.org/ 10.60988/p.v37i2S.166