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Chalcone-Mediated Synthesis of Substituted Oxazepine Derivatives: Characterization and In Vitro Antimicrobial Evaluation

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Abstract
The synthesis, characterization and antibacterial assessment of new oxazepine derivatives are described in this paper. Through appropriate cyclization processes, a number of substituted chalcones were utilized as essential precursors for the synthesis of oxazepines. Spectroscopic methods such as mass spectrometry and ^{1}H NMR were used to purify and characterize the produced molecules. Using a suitable in vitro test, their antimicrobial properties were assessed against certain strains of bacteria and fungi that were both Gram-positive and Gram-negative. Depending on the kind and location of the substituents, the produced oxazepine derivatives exhibited differing levels of antibacterial activity. The oxazepine scaffold is highlighted in the paper as a helpful structural foundation for the creation of possible antibacterial drugs.

Keywords: *Oxazepines, Bioactive heterocyclic scaffolds, Heterocyclic frameworks, In vitro bioactivity*

Introduction

The primary goal of organic synthesis is to offer a simple process for producing frequently used organic molecules from easily available chemicals. The relevance of nitrogen heterocyclic compounds as both natural and manmade materials makes them intriguing [1]. Numerous of these substances have important biological connections, which makes them viable options for creating novel therapies for neurodegenerative diseases like epilepsy and pain [2]. Furthermore, the effective one-step synthesis of heterocyclic derivatives may aid in the development of new treatment strategies. The biological effects of several Schiff bases with aryl groups or heterocyclic residues have attracted a lot of attention in recent years [3]. Because of their seven-membered ring structure, which combines nitrogen and oxygen atoms, 1,3-oxazepine-4,7-dione derivatives have become a distinct class of heterocyclic compounds [4]. Strong interactions with a variety of biological targets and increased pharmacological activity are made possible by this scaffold's exceptional adaptability. Oxazepines are less studied than other heterocycles like pyrazoles, triazoles, or quinolines, but they have shown better bioactivity profiles in antibacterial, anticancer, and anti-inflammatory applications [5]. Their promise as lead compounds in medicinal chemistry is expanded by their structural flexibility, which permits functionalization at various locations [6].

Oxazepine analogs can function as protease inhibitors, kinase modulators, and antimicrobial agents with advantageous cytotoxic properties against cancer cell lines and resistant bacterial strains, according to recent research. One crucial type of organic molecules is heterocyclic compounds. The presence of rings in their molecular structure, where at least one element is not carbon (C), is what sets them apart [7]. The prefix "hetero" denotes the noncarbon atoms, or heteroatoms, in the ring, whereas the phrase "heterocyclic" denotes the presence of at least one ring structure. However, heteroatoms provide heterocyclic compounds distinct physical and chemical characteristics that are very different from those of their all carbon ring counterparts [8]. Many essential biological components required for maintaining life are included in heterocyclic compounds.

For example, long chains of heterocyclic units joined by other chemicals make up nucleic acids, chemical substances that carry genetic information that governs inheritance [9]. Many naturally occurring colors, vitamins, medications, and hallucinogens contain heterocyclic molecules. Because of their diverse biological functions and possible therapeutic uses, 1,3-oxazepine-4,7-dione derivatives have attracted interest in medicinal chemistry. These heterocyclic compounds are important drug discovery intermediates, especially when developing anti-inflammatory, anti-

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cancer, and antibacterial medicines. Their distinct seven-membered ring structure, which contains nitrogen and oxygen, allows them to interact with a variety of biological targets, increasing their pharmacological potency. Certain 1,3-oxazepine-4,7-dione variations have demonstrated favorable cytotoxic capabilities against cancer cell lines by encouraging cell death and inhibiting cell proliferation. Additionally, the design of enzyme inhibitors has been investigated using their structural framework [10].

Synthesizing the derivatives of substituted oxazepine is the next step. The synthesis of substituted [1,4] oxazepine and a knowledge of substituted molecules with interesting biological properties are the goals of this study. It might result in the synthesis of novel therapeutic approaches in the future.

Material and Methods

All chemicals used in the experiments were of analytical reagent (AR) grade. Analytical thin-layer chromatography (TLC) was carried out on Merck pre-coated silica gel 60 F254 aluminium sheets. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded in $CDCl_3$ on a 500 MHz spectrometer with tetramethylsilane (TMS) serving as the internal standard.

Characterization Techniques

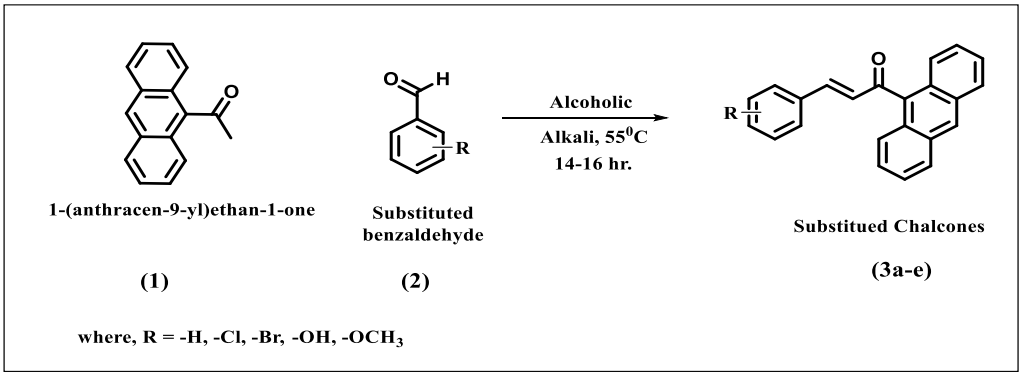
The structure of synthesized compounds was determined by chemical properties elemental analysis and spectral data. ^{1}H-NMR spectra were recorded on Bruker Avance Neo 500 MHz spectrometer using $CDCl_3$ solvent and TMS as internal standards at SAIF, Punjab University, Chandigarh (India). Chemical shifts are expressed in ppm. Mass spectrums were recorded on Thermo Scientific TSQ 8000 Gas Chromatogram.

Experimental

General Reaction for synthesis of substituted chalcones

The Claisen–Schmidt condensation is a simple and effective method for chalcone synthesis [11], involving equimolar acetophenone and benzaldehyde derivatives in aqueous alcoholic alkali. The alkali concentration generally ranges from 10–60%, with reactions carried out at approximately 55 °C for 14–16 h or at room temperature for about one week. However, the Cannizzaro reaction may occur under these conditions, lowering chalcone yields. Benzylidene-diacetate has therefore been suggested as an alternative aldehyde substrate to minimize aldehyde disproportionation. (Scheme 1.)

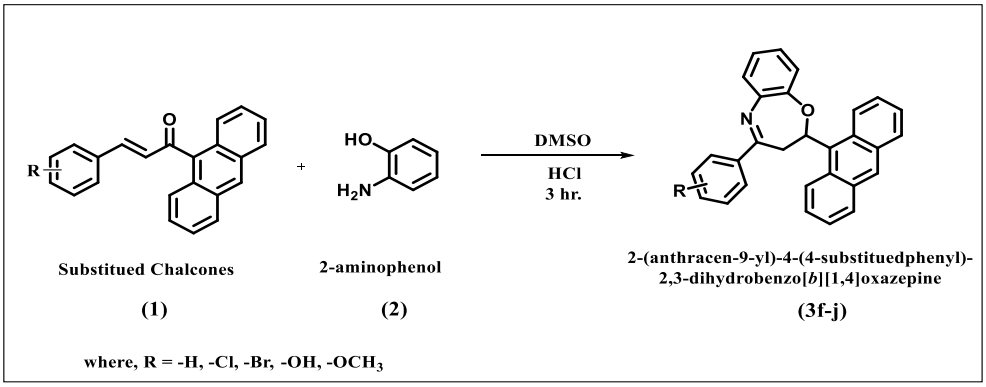
By applying similar procedure to all other synthesized derivatives of substituted chalcones



Scheme 1. Synthesis of substituted chalcones

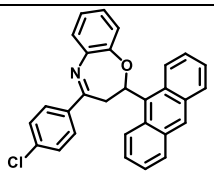
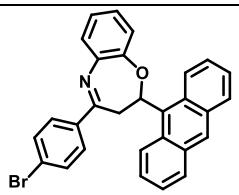
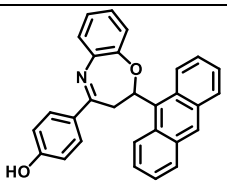
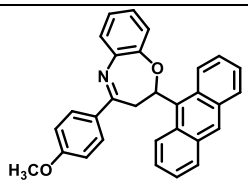
General Reaction for synthesis of Substituted Oxazepine

One of the major moieties in heterocycles containing nitrogen and oxygen is the [1,4] oxazepine ring, which has been utilized extensively as a fundamental building block for both pharmacological drugs and physiologically active molecules. The most widely used method for synthesizing 1,4-benzothiazepines is the cyclocondensation reaction of α-aminophenol with α,β-unsaturated ketones (chalcones) in HCl conditions for three hours in DMSO solvent [12]. (Scheme-2)



Scheme 1. General reaction for synthesis of substituted oxazepines

Table 1. Structural Analysis (Compound 3g-j)

Sr. No	Structure of Products	Structural analysis by ^{1}HNMR and GCMS
1	 **(g)**	**^{1}HNMR(500MHz,$CDCl_3$)**:δ 8.37(s,1H), 8.25(dd,2H),7.94-8.03 (m,4H),7.48-7.56 (m,6H), 7.35(m,1H), 7.06-7.10 (d, 2H),6.57(dd,1H), 5.00 (d,2H), 2.95-2.70(dd,2H) **GCMS: Cal m/z:** 433.12, Found m/z:433.10
2	 **(h)**	**^{1}HNMR(500MHz,$CDCl_3$)**:δ 8.34(s,1H), 8.23(dd,2H),7.92-8.01 (m,4H),7.46-7.55 (m,6H), 7.33(m,1H), 7.02-7.8 (d, 2H),6.56(dd,1H), 5.00 (d,2H), 2.94-2.68(dd,2H) **GCMS:** Cal m/z: 477.07, Found m/z: 477.01
3	 **(i)**	**^{1}HNMR(500MHz,$CDCl_3$)**:δ 9.70 (s,1H), 8.34(s,1H), 8.23(dd,2H),7.92-8.01 (m,4H),7.46-7.55 (m,6H), 7.33(m,1H), 7.02-7.8 (d, 2H),6.56(dd,1H), 5.00 (d,2H), 2.94-2.68(dd,2H) **GCMS:** Cal m/z: 415.16, Found m/z: 415.10
4	 **(j)**	**^{1}HNMR(500MHz,$CDCl_3$)**:8.32(s,1H), 8.24(dd,2H),7.90-8.00 (m,4H),7.45-7.54 (m,6H), 7.32(m,1H), 7.0-7.8 (d, 2H),6.51(dd,1H), 5.00 (d,2H), 3.81 (s,3H), 2.92-2.69(dd,2H) **GCMS:** Cal m/z: 429.17, Found m/z: 429.12

Biological Investigation of substituted[1,4]oxazepine (compound 3g-j)

Antimicrobial Evaluation

Using an appropriate antimicrobial assay, the synthesized substituted oxazepine derivatives were assessed for their in vitro antibacterial activity against specific Gram-positive (*S. aureus*) and Gram-negative (*E. coli*) bacterial and fungus strains. The type and location of substituents on the oxazepine ring may have an impact on the compounds' differing levels of antibacterial activity. The observed results suggest that the antibacterial potential of the oxazepine scaffold may be impacted by structural change.

The antimicrobial screening results of the synthesized derivatives are summarized in **Table 2**.

Compound	Substituent (R)	Gram-positive bacteria (*S. aureus*)	Gram-negative bacteria (*E. coli*)	Fungal strain	Activity
g	4-Cl	+	+	+	Moderate
h	4-Br	++	+	++	Good
I	4-OH	++	++	+	Good
J	4-OCH_3	+++	++	++	Significant

Conclusion

In present work, synthesized the series of substituted[1,4]oxazepine (compound 3g-j) structure is promising moiety that are able to shows the strong biological activity. Furthermore, the benzo ring inflection of the structure intentionally incorporation of chloro (-Cl), bromo (-Br), hydroxyl (-OH) and methoxy (-OCH_3) group over the ring. Which shows the promising and the strong biological activities. As a conclusion, our results revels and participate significantly to create a structural moiety and interactive relationship shows strong activity against bacteria. Which is useful in drug design strategy in future.

Conflict of Interest: Authors have declared that no competing interests exist.

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