Efficient Synthesis and Biological Evaluation of Substituted Oxazepine Derivatives

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***Abstract*—Oxazepines constitute an important class of heterocyclic compounds due to their wide range of biological and pharmacological activities. In the present study, an efficient and convenient synthetic route for a series of substituted oxazepine derivatives has been developed. The target compounds were synthesized using readily available starting materials under optimized reaction conditions, affording good to excellent yields. The structures of the synthesized oxazepine derivatives were confirmed by spectroscopic techniques including ^{1}H NMR and GC-MS. The synthesized compounds were further evaluated for their biological activities using standard in vitro assays. Several derivatives exhibited promising biological activity, indicating that substitution patterns on the oxazepine ring play a significant role in modulating their activity. The results suggest that these substituted oxazepine derivatives may serve as potential candidates for further pharmacological investigation.**

***Index Terms*—Oxazepines, Bioactive heterocycles, Heterocyclic compounds, in vitro biological activity**

I. INTRODUCTION

One of the most significant and varied types of organic molecules, heterocyclic compounds have several uses in the fields of medicine and pharmacology. Seven-membered heterocycles, such as oxazepines, have attracted special attention because of their complex structures and diverse biological activities. The most prevalent of these compounds have a heterocyclic framework with nitrogens and oxygens, which enhances their extensive pharmacological potential [1]. Over the past few decades, this class of chemicals has been studied as possible antibacterial agents, anticancer agents, and neurological disease modulators [2]. In addition to providing a foundation for future investigations into novel derivatives with enhanced potential to evade recognized types of microbial resistance and to produce more potent therapeutic results, appropriate functional replacements produce structural diversity [3]. Put differently, oxazepine molecules exhibit a wide range of biological actions, including antibacterial, anti-inflammatory, and antioxidant properties. Numerous investigations have demonstrated that subamination on oxazepine rings can change pharmacological action [4].

In example, pyrrolo-based oxazepines have demonstrated strong antibacterial action and have been suggested as possible opioid analgesics and antihypertensive drugs. Even while these findings are encouraging, it is still unclear how the chemical change and biological activity are related, especially when it comes to derivatives made via sublimation [5]. These emphasize the necessity of systematic experimental research to show their structural stability and bioactivity. The review of the literature reveals that a large number of oxazepine basics rely on limited biological assays and conventional syntheses. However, more recent efforts have rendered comparable molecules functional, making them appear more stable, soluble, and to have a longer therapeutic index [6].

Nevertheless, broad-spectrum in vitro antibacterial evaluation against Gram-positive and Gram-negative organisms is not integrated with spectroscopic characterisation. Furthermore, the direct therapeutic potential of newly synthesized oxazepines is uncertain due to the lack of comparisons with clinically validated antibiotics such as ciprofloxacin [7]. In order to close this gap, the current study will use

condensation of the reaction of 2-aminophenol with various chalcones to synthesize and describe novel oxazepine derivatives.

Heptameric compounds known as oxazepines are referred to as oxazepines when they are unsaturated and oxazepines when they are saturated [8,9]. Two heteroatoms and five carbon atoms make up their composition [10]. isomers, based on where the nitrogen and oxygen atoms are located within the heptameric structure [11]. Oxazepines have numerous medical and pharmacological uses, and numerous studies have demonstrated that they can cure a variety of illnesses, including psychiatric problems [12]. Additionally, they have antioxidant, anticancer, and antimicrobial properties [13,14].

In continuation, synthesizing the derivatives of 2-(anthracen-9-yl)-4-(4-substituedphenyl)-2,3-dihydrobenzo[b] [1,4] oxazepine. This study aims to synthesized substituted [1,4] thiazepine and [1,4] oxazepine, understanding of substituted compounds as has promising biological properties. In future it may leads to synthesized new drug strategies.

II. MATERIAL AND METHODS

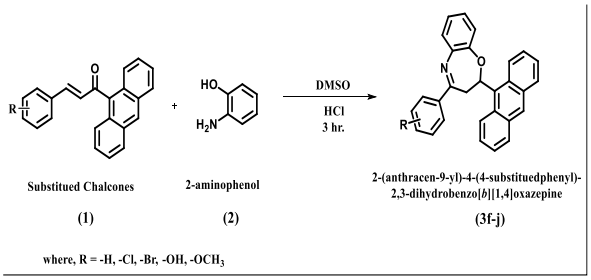
All chemicals used in the experiments were of analytical reagent (AR) grade. Analytical thin-layer chromatography (TLC) was carried out on Merck pre-coated silica gel 60 F254 aluminium sheets. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded in $CDCl_3$ on a 500 MHz spectrometer with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

III. 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.

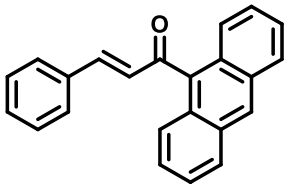
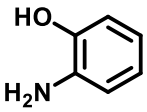
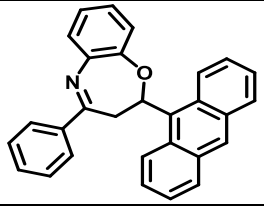
General Reaction for synthesis of 2-(anthracen-9-yl)-4-(4-substituedphenyl)-2,3-dihydrobenzo[b] [1,4] oxazepane.

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. () (Scheme-1)



Scheme 1. General reaction for synthesis of 2-(anthracen-9-yl)-4-(4-substituedphenyl)-2,3-dihydrobenzo[b][1,4]oxazepine

Table 1. Scope of 2-aminophenol

Sr.No	Substrate	Reagent	Product	Time in Hrs.	Yield
1				3	79

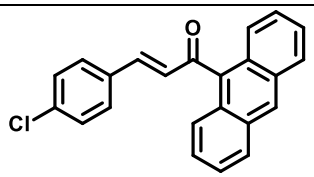
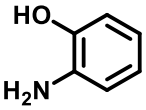
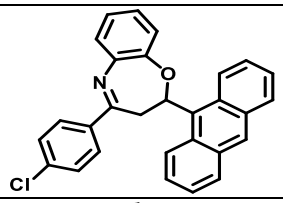
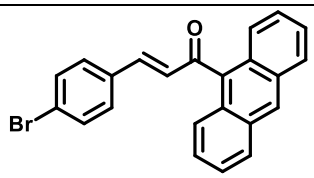
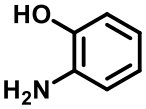
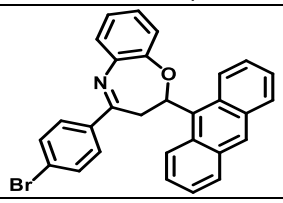
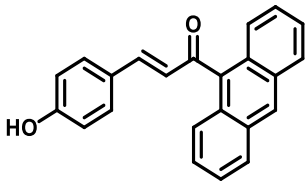
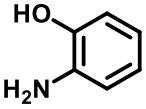
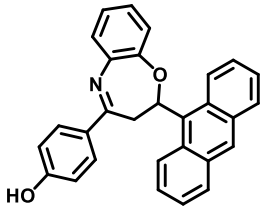
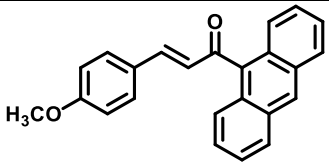
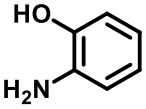
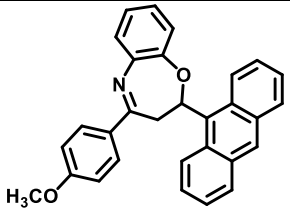
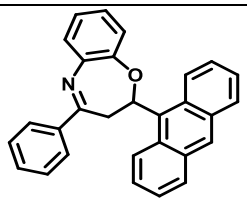
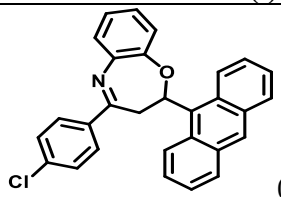
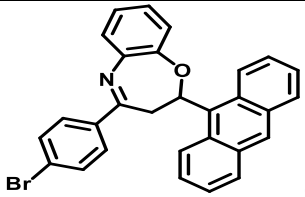
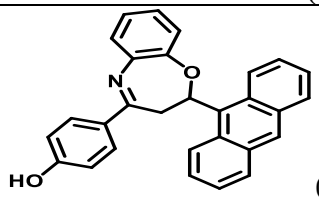
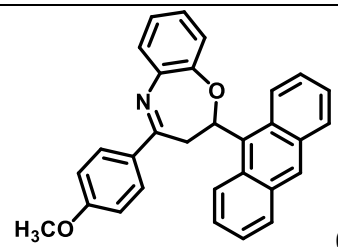
2				3	82
3				3	85
4				3	86
5				3	87

Table 2. Structural Analysis (Compound 3f-j)

Sr. No	Structure of Products	Structural analysis by ^{1}HNMR and GCMS
1	 (f)	^{1}HNMR (500MHz, $CDCl_3$):δ 8.35(s,1H), 8.23(dd,2H),7.93-8.00 (m,4H),7.47-7.55 (m,7H), 7.33(m,1H), 7.04-7.14 (d, 2H),6.56(dd,1H), 4.99 (d,2H), 2.96-2.72(dd,2H) GCMS: Cal m/z: 399.16, Found m/z: 399.10
2	 (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
3	 (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
4	 (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

5	 (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 2-(anthracen-9-yl)-4-(4-substituedphenyl)-2,3-dihydrobenzo[b][1,4]oxazepine (compound 3f-j)

Antioxidant activity

An antioxidant may be defined as "any substance that when present at low concentration, compared with those of the oxidizable substrate significantly delays or inhibits oxidation of that substrate."

Method: DPPH Free Radical Scavenging Assay

Preparation of Sample:

The free-radical scavenging activity was estimated by DPPH assay. The reaction mixture contained 10 µl of test sample and positive control ascorbic acid with 10 mg concentration and 190 µl of methanolic solution of 0.1 mM DPPH radical. The mixture was then shaken vigorously and incubated at 38 °C for 6 min. The absorbance was measured at 518 nm on ELISA plate reader indicated higher free radical scavenging activity, which was calculated using the following equation:

("%")"Free radical scavenging effect"

$$= \frac{[\text{Absorbance of control (Ac)- Absorbance of sample(As)}]}{\text{Absorbance of control (Ac)}} \times 100$$

Antioxidant Potential of synthetic compounds

The antioxidant activities was successfully performed 2-(anthracen-9-yl)-4-(4-substituedphenyl)-2,3-dihydrobenzo[b] [1,4] oxazepine (compound 3f-j), free radical scavenging assay. The results are shown in the picture and table below;

Antioxidant activity of 2-(anthracen-9-yl)-4-(4-substituedphenyl)-2,3-dihydrobenzo[b] [1,4] oxazepine (compound 3f-j)

Table 3. % Antioxidant Potential Using DPPH Assay Method (Conc. used 1 mg)

Compound Code	Antioxidant Potential (%) (Mean±SD)	
	R	
f	-H	31.262±1.31
g	4-Cl	19.551±1.54
h	4-Br	31.2.02±2.12
i	4-OH	19.062±0.59
j	4-OCH_3	35.546±1.22
Standard	88.79±2.14	

IV. CONCLUSION

In present work, synthesized the series of 2-(anthracen-9-yl)-4-(4-substituedphenyl)-2,3-dihydrobenzo[b][1,4]oxazepine (compound 3f-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 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 microbes. Which is useful in drug design strategy in future.

V. CONFLICT OF INTEREST

Authors have declared that no competing interests exist.

VI. AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Mr. Varun. A. Mahale, Ms. Khushbu S. Jaiswal and Prof. N.D. Gawhale. The first draft of manuscript is written Mr. Varun. A. Mahale, Khushbu S. Jaiswal and Prof. N.D. Gawhale

contributed to data analysis and interpretation. The resources, are supervised by and Prof. N.D. Gawhale. and All authors read and approved the final manuscript. All authors are aware of the submission and agree to its publication.

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