Synthesis And Biological Evaluation of Substituted Hydroxyl Dihydroisoxazole Derivatives

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***Abstract*—Dihydroisoxazoles are an important class of heterocyclic compounds that have attracted considerable attention due to their diverse biological and pharmacological properties. In the present study, a series of substituted hydroxyl dihydroisoxazole derivatives were synthesized using an efficient and straightforward synthetic methodology. The reactions were performed under optimized conditions, affording the target compounds in good to excellent yields. The structures of the synthesized derivatives were confirmed by spectroscopic techniques, including ^{1}H NMR GC-MS. The synthesized compounds were evaluated for their biological activities using standard in vitro assays. Several derivatives exhibited promising biological activity, indicating that the presence and position of hydroxyl substituents play a crucial role in influencing biological performance. The results of this study suggest that substituted hydroxyl dihydroisoxazole derivatives may serve as potential lead compounds for further pharmacological development.**

***Index Terms*—Dihydroisoxazole derivatives, Hydroxyl-substituted heterocycles, Heterocyclic synthesis, biological evaluation, Structure activity relationship**

I. INTRODUCTION

In medical chemistry, materials science, and agrochemical research, isoxazole a pair of isomers of oxazole has become a crucial scaffold. It is a five-membered heterocyclic ring with one oxygen atom and one nitrogen atom. Numerous biological actions, such as antibacterial, antiviral, antioxidant, anticancer, and anti-inflammatory qualities, are made possible by the structural adaptability of isoxazole derivatives [1-11]. Interestingly, isoxazole motifs are essential to a number of clinically authorized medications, including the anticancer medicine bleomycin and the antibiotic linezolid. In addition to pharmaceuticals, isoxazole-based compounds are used in organic electronics [14], coordination chemistry [13], and fluorescent materials [12], highlighting their multidisciplinary importance [15-19].

The cyclization reaction [20–22] and other traditional synthetic pathways to isoxazole derivatives frequently have drawbacks, such as severe reaction conditions and the requirement for extremely hazardous transition-metal catalysts such copper metals [23]. These disadvantages show how urgently green and sustainable approaches that increase productivity, lower energy use, and lessen environmental effect are needed. In recent decades, ultrasound-assisted synthesis has become a revolutionary tool in organic chemistry [24, 25]. The acoustic cavitation caused by ultrasonic irradiation (20~100 kHz) is the primary source of this method's benefits. This phenomenon causes microbubbles to form and collapse in the reaction medium, producing localized high temperatures (~5000 K) and pressures (~1000 atm). By increasing mass transfer, quickening reaction kinetics, and encouraging the creation of reactive intermediates, this mechanical energy raises yields and lowers side reactions. Importantly, by facilitating reactions in milder environments, lowering solvent quantities, and frequently doing away with the need for hazardous catalysts, sonochemistry adheres to the principles of green chemistry [26,27].

Heterocyclic synthesis is a significant and effective technique in the wide range of applications for ultrasound-assisted organic synthesis [28–30]. For example, sonochemical techniques enable effective cyclization, cross-coupling, and multicomponent processes for the production of isoxazole derivatives. In contrast to conventional thermal approaches, Borthakur *et al.* reported a technique for utilizing an ultrasound-assisted approach to the addition process to synthesize isoxazoline and greatly shorten the reaction time [31]. These developments highlight how ultrasound and isoxazole derivative synthesis work together to optimize reaction paths.

II. MATERIAL AND METHODS

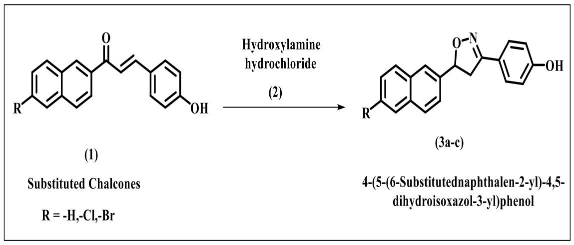
All chemicals used in the experiments were of analytical reagent (AR) grade. Analytical thin-layer chromatography (TLC) was carried out on Merck pre-coated silica gel 60 F254 aluminium sheets. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded in $CDCl_3$ on a 500 MHz spectrometer with 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 4-(5-(6-substitutednaphthalen-2-yl)-4,5-dihydroisoxazol-3-yl) phenol

Hydroxylamine hydrochloride will reflux a well-proportioned reaction mixture of substituted chalcones for nine hours at an appropriate temperature. TLC will keep an eye on the reaction. Ethyl acetate and ethanol will be used in column chromatography to recrystallize the product substituteddihyroisoxazole.



Scheme 1. Synthesis of 4-(5-(6-substitutednaphthalen-2-yl)-4,5-dihydroisoxazol-3-yl) phenol

Table 1. Scope of Hydroxylamine

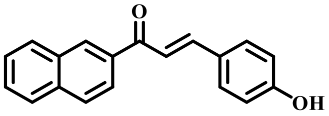
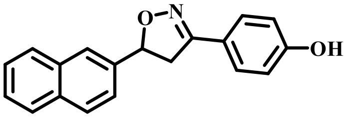
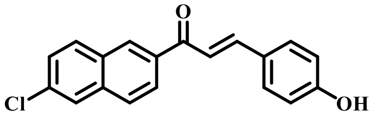
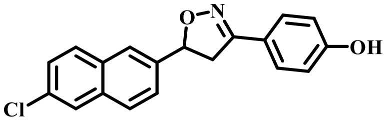
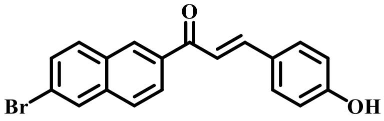
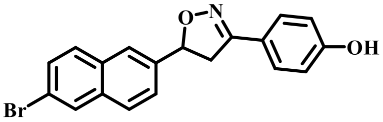
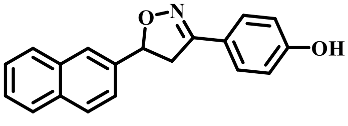
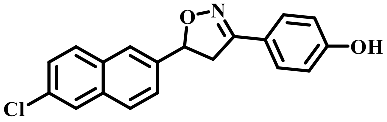
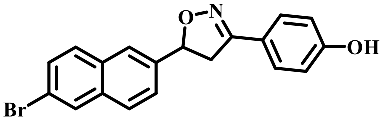
Sr.No	Substrate	Reagent	Product	Time in Hrs.	Yield
1		NH_2-OH		8	81
2		NH_2-OH		8	84
3		NH_2-OH		8	85

Table 2. Structural Analysis

Sr. No	Structure of Products	Structural analysis by ^{1}HNMR and GCMS
1	 (a)	^{1}HNMR (500MHz, $CDCl_3$):δ 9.9 (s,1H), 7.90-7.99 (m, 3H), 7.71-7.74 (m, 3H), 7.45-7.65 (m, 3H), 6.80 (d,2H), 5.93 (d,1H), 3.80-3.85 (dd,2H) GCMS: Cal m/z: 289.33 Found m/z: 289.28
2	 (b)	^{1}HNMR (500MHz, $CDCl_3$):δ 9.96 (s,1H), 7.92-7.98 (m, 3H), 7.74-7.76 (m, 2H), 7.46-7.69 (m, 3H), 6.81 (d,2H), 5.93(d,1H), 3.81-3.84 (dd,2H) GCMS: Cal m/z: 223.78 Found m/z: 223.70
3	 (c)	^{1}HNMR (500MHz, $CDCl_3$):δ 9.94 (s,1H), 7.90-7.96 (m, 3H), 7.71-7.74 (m, 2H), 7.40-7.68 (m, 3H), 6.80 (d,2H), 5.90(d,1H), 3.80-3.84 (dd,2H) GCMS: Cal m/z:368.23 Found m/z: 368.30

Biological Investigation of 4-(5-(6-substitutednaphthalen-2-yl)-4,5-dihydroisoxazol-3-yl) phenol

Method: DPPH Free Radical Scavenging Assay

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

IV. CONCLUSION

In present work, synthesized the series of 4-(5-(6-substitutednaphthalen-2-yl)-4,5-dihydroisoxazol-3-yl) phenol structure is promising moiety that are able to shows the strong biological activity. Furthermore, the benzo ring inflection of the structure intentionally incorporation of chlorine (-Cl) and bromine (-Br) 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.

Conflict of Interest:

Authors have declared that no competing interests exist.

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