

Claisen Rearrangement-Based Synthesis of Substituted Naphthofuran Derivatives from *o*-Allylated Dihydroisoxazoles and Their Antimicrobial Evaluation

Saleha Anjum Mohd. Shakeel

Research centre, Department of Chemistry G.S Tompe Arts, Commerce and Science College, Chandur Bazar Dist- Amravati

M.A.Kotak

Research centre, Department of Chemistry G.S Tompe Arts, Commerce and Science College, Chandur Bazar Dist- Amravati

M.M.Kodape

Department of Chemistry, Sant, Gadge Baba Amravati University, Amravati

N.D. Gawhale

Department of Chemistry G.S Tompe Arts, Commerce and Science College, Chandur Bazar Dist- Amravati

Abstract

A convenient synthetic protocol was established for the synthesis of substituted naphthofuran derivatives using a Claisen rearrangement strategy involving *o*-allylated dihydroisoxazole intermediates. Initially, a series of substituted dihydroisoxazoles was prepared and subsequently subjected to *O*-allylation to generate the corresponding allyl ether intermediates. The resulting intermediates were then exposed to Claisen rearrangement conditions, followed by intramolecular cyclization, leading to the formation of the desired substituted naphthofuran derivatives. The synthesized compounds were characterized using ¹H NMR spectroscopy and GC-MS analysis. Their antimicrobial properties were subsequently investigated against selected Gram-positive and Gram-negative bacterial strains as well as fungal strains. The compounds displayed different levels of antimicrobial activity, with the observed responses influenced by the type and substitution pattern of the groups attached to the naphthofuran framework. These findings indicate that the Claisen rearrangement of *o*-allylated dihydroisoxazoles represents an effective approach for constructing structurally varied naphthofuran derivatives and provides a useful platform for further exploration of their antimicrobial properties.

Keywords: Claisen rearrangement; Naphthofuran derivatives; *o*-Allylated dihydroisoxazoles; Heterocyclic synthesis; Antimicrobial activity; ¹H NMR; GC-MS

Introduction

Isioxazole is a five-membered oxygen- and nitrogen-containing heterocyclic system and represents an important structural motif in modern organic and medicinal chemistry. The distinctive electronic properties and structural flexibility of the isioxazole nucleus have contributed to its extensive investigation in medicinal chemistry, materials science, and agrochemical research. A wide range of isioxazole derivatives has been reported to possess diverse pharmacological activities, including antimicrobial, antiviral, antioxidant, anticancer, and anti-inflammatory effects [1–11]. The presence of the isioxazole moiety in biologically active molecules further emphasizes its pharmaceutical relevance. In addition to its medicinal applications, isioxazole-containing compounds have attracted considerable attention in the development of fluorescent materials [12], coordination compounds [13], and organic electronic materials [14]. These diverse applications demonstrate the broad synthetic and functional potential of the isioxazole framework across pharmaceutical, chemical, and materials-related research.

Furans are aromatic five-membered heterocyclic compounds characterized by the presence of an oxygen atom within the ring system. They constitute important structural units in numerous natural products, pharmaceutical compounds, and polymeric materials. Owing to their versatile chemical reactivity, furans also serve as valuable intermediates for the synthesis of structurally diverse and functionally useful molecules. Consequently, considerable attention has been devoted to the development of efficient synthetic methodologies for constructing the furan framework, resulting in a broad range of established synthetic approaches [15].

Fused furan systems, particularly naphthofuran derivatives, have attracted considerable research interest because of their occurrence in both naturally derived and synthetically developed bioactive molecules. Several natural products containing dihydroxynaphthalene (DHN)-related structural motifs have demonstrated diverse biological and pharmacological properties [16]. For instance, furaquinocin A, characterized by a highly oxygenated *p*-quinone moiety, has been reported to exhibit antihypertensive activity along with cytotoxic effects against HeLa S3 and

B16 melanoma cells. It has also demonstrated inhibitory effects on platelet aggregation and blood coagulation. Similarly, (–)-nocardione, which contains an *o*-quinone structural unit, has been identified as an inhibitor of Cdc25B tyrosine phosphatase and has shown moderate antifungal and cytotoxic properties [17]. Rubioncolins A and B represent additional naturally occurring naphthofuran-related compounds that have been isolated in racemic forms from *Rubia oncotricha*. These compounds have also been reported from *Rubia cordifolia*, a medicinal plant traditionally used in Korean medicine for conditions including cough, bladder and kidney stones, joint inflammation, uterine bleeding and uterine inflammation [18].

In view of the structural diversity and reported biological significance of fused furan systems, the present study focuses on the synthesis of substituted naphthofuran derivatives and the investigation of their antimicrobial properties. The study aims to develop an efficient synthetic approach while examining the influence of structural substitution on the biological activity of the resulting naphthofuran compounds.

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 (^1H NMR) spectra were recorded in CDCl_3 on a 500 MHz spectrometer with tetramethylsilane (TMS) serving as the internal standard.

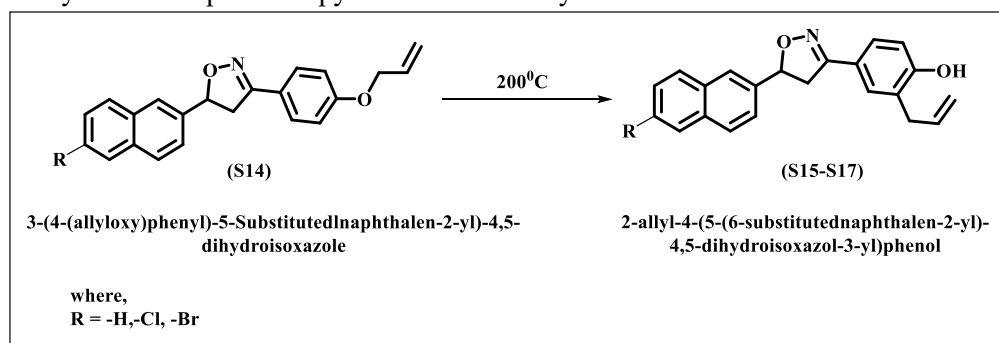
Characterization Techniques

The structure of synthesized compounds was determined by chemical properties elemental analysis and spectral data. ^1H -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

Synthesis of *o*-Allyl substituted Dihydroisoxazoles

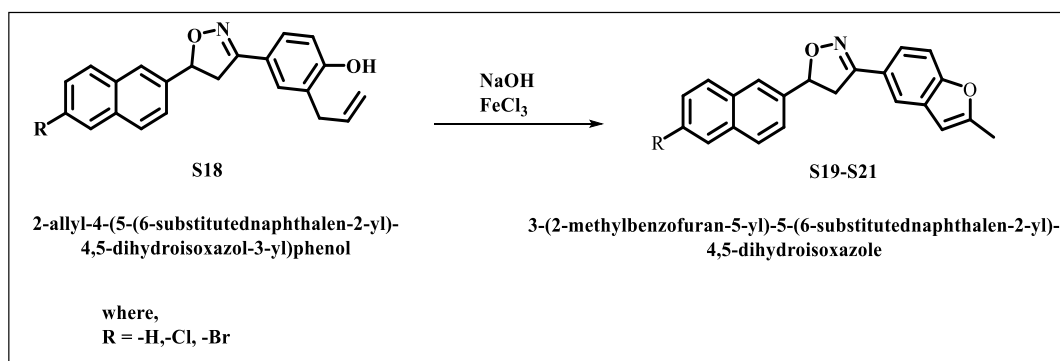
The synthesized *o*-allylated dihydroisoxazole derivative S14 (1.0 mmol) was heated at 200 °C under continuous stirring to facilitate the Claisen rearrangement. The reaction was continued at 200 °C until complete conversion of the starting material, as confirmed by TLC. Upon completion, the reaction mixture was cooled to room temperature and diluted with ethyl acetate. The organic phase was subsequently washed with water followed by brine and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure to obtain the crude product. Purification was carried out by silica-gel column chromatography using an appropriate petroleum ether/ethyl acetate solvent system, furnishing the corresponding substituted naphthofuran derivatives S15–S17. The structures of the isolated products were established by ^1H NMR spectroscopy and GC–MS analysis.



Scheme 1. Synthesis of Allylation of substituted *o*-allyl derivative of dihydroisoxazole

Synthesis of *o*-Allyl substituted Naphthofuran

Well-proportioned reaction mixture of substituted dihydroisoxazole (S18) in presence of catalyst and in solvent at suitable temperature for suitable time will be refluxed (6-8 h). The reaction is monitored by TLC. The rearranged claisen product (S19-S21) is recrystallised by column chromatography.



Scheme 1. Synthesis of substituted naphthofuran

Table 1. Structural Analysis

Sr. No	Structure of Products	Structural analysis by ¹ HNMR and GCMS
1	 (a)	¹ HNMR(500MHz,CDCl ₃):δ 7.90-8.08 (m,5H), 7.71-7.66 (m, 2H), 7.55-7.48 (m, 3H), 6.72(m, 1H), 5.93 (m,1H), 3.85-3.60(dd,2H), 2.30 (s,3H),3.69-3.85 (d, 2H) GCMS: Cal m/z: 327.38 Found m/z: 327.30
2	 (b)	¹ HNMR(500MHz,CDCl ₃):δ 7.91-8.09 (m,5H), 7.73-7.68 (m, 2H), 7.56-7.49 (m, 3H), 6.74(m, 1H), 5.95 (m,1H), 3.87-3.60 (dd,2H), 2.32 (s,3H), GCMS: Cal m/z: 361.83 Found m/z: 361.76
3	 (c)	¹ HNMR(500MHz,CDCl ₃):δ 7.93-8.09 (m,5H), 7.74-7.68 (m, 2H), 7.57-7.49 (m, 3H), 6.75(m, 1H), 5.95 (m,1H), 3.87-3.65(dd,2H), 2.33 (s,3H), GCMS: Cal m/z: 406.28 Found m/z: 406.21

Biological Investigation of substituted naphthofuran

Antimicrobial evaluation

The synthesized substituted naphthofuran derivatives were investigated for their *in vitro* antimicrobial activity against selected bacterial and fungal strains using the agar well diffusion method. Antimicrobial efficacy was determined by measuring the diameter of the inhibition zones produced by the respective compounds and expressed in millimetres. The synthesized derivatives displayed variable levels of activity against the tested microorganisms, suggesting that structural modifications on the naphthofuran framework can significantly influence antimicrobial response. In particular, the incorporation of halogen substituents such as -Cl and -Br resulted in differences in antimicrobial activity, indicating that the electronic and steric characteristics of these groups may affect the interaction of the compounds with microbial cells. The observed activities were compared with those of a standard antimicrobial agent evaluated under the same experimental conditions. Overall, the synthesized naphthofuran derivatives exhibited moderate to promising antimicrobial activity, highlighting the potential of halogen-substituted naphthofuran scaffolds for further investigation in antimicrobial research.

Compound	<i>Staphylococcus aureus</i> (mm)	<i>Escherichia coli</i> (mm)
Naphthofuran S19	18	15
Naphthofuran S20	22	19
Naphthofuran S21	16	14
Standard	25	23

Conclusion

In the present study, a series of substituted naphthofuran derivatives was successfully synthesized and investigated for their antimicrobial properties. The naphthofuran framework represents a valuable structural motif with considerable potential for biological applications. In particular, the introduction of halogen substituents such as chlorine (–Cl) and bromine (–Br) onto the benzo-fused ring produced noticeable variations in antimicrobial activity. These observations suggest that the nature of the substituent can influence the biological response of the naphthofuran scaffold, possibly through changes in its electronic and physicochemical properties. Overall, the findings demonstrate the potential of substituted naphthofuran derivatives as useful structural frameworks for antimicrobial research and provide a basis for further structural modification and investigation toward future antimicrobial drug-design studies.

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

Acknowledgement

The authors are thankful to Author also thank to the Principal, Department of Chemistry, G.S Tompe Arts, Commerce and Science College, Chandur Bazar Dist- Amravati and Department of Chemistry, Sant, Gadge Baba Amravati University, Amravati for providing the necessary laboratory facilities. Authors are very much thankful to the Director, SAIF, Punjab University Chandigarh for providing spectral data.

References

- Kakkar, S.; Narasimhan, B. A Comprehensive Review on Biological Activities of Oxazole Derivatives. *BMC Chem.* 2019, 13, 16.
- Reddy, A.B.; Hymavathi, R.V.; Swamy, G.N. A New Class of Multi-Substituted Oxazole Derivatives: Synthesis and Antimicrobial Activity. *J. Chem. Sci.* 2013, 125, 495–509.
- Chen, J.Y.; Lv, S.Y.; Liu, J.; Yu, Y.L.; Wang, H.; Zhang, H.W. An Overview of Bioactive 1,3-Oxazole-Containing Alkaloids from Marine Organisms. *Pharmaceuticals* 2021, 14, 1274.
- Sternberg, J.A.; Geffken, D.; Adams, J.B.; Pöstages, R.; Sternberg, C.G.; Campbell, C.L.; Moberg, W.K. Famoxadone: The Discovery and Optimisation of a New Agricultural Fungicide. *Pest Manag. Sci.* 2001, 57, 143–152.
- Kachaeva, M.V.; Pilyo, S.G.; Hartline, C.B.; Harden, E.A.; Prichard, M.N.; Zhirnov, V.V.; Brovarets, V.S. In Vitro Activity of Novel Derivatives of 1,3-Oxazole-4-Carboxylate and 1,3-Oxazole-4-Carbonitrile against Human Cytomegalovirus. *Med. Chem. Res.* 2019, 28, 1205–1211.
- Rayan, S.A.; George, R.F.; Said, M.F. Insight on Development of Oxazole and Imidazole Derivatives as COX Inhibitors with Anti-Inflammatory Effects. *J. Mol. Struct.* 2025, 1321, 140148.
- Hawash, M.; Jaradat, N.; Abualhasan, M.; Thaher, M.; Sawalhi, R.; Younes, N.; Shanaa, A.; Nuseirat, M.; Mousa, A. In Vitro and in Vivo Assessment of the Antioxidant Potential of Isoxazole Derivatives. *Sci. Rep.* 2022, 12, 18223.
- Šagud, I.; Škorić, I.; Burćul, F. Naphthoxazoles and Heterobenzoxazoles: Cholinesterase Inhibition And antioxidant Activity. *Turk. J. Chem.* 2019, 43, 118–124.
- Zhang, H.Z.; Zhao, Z.L.; Zhou, C.H. Recent Advance in Oxazole-Based Medicinal Chemistry. *Eur. J. Med. Chem.* 2018, 144, 444–492.

10. Xu, C.; Wang, Y.Z.; Liu, M.; Ma, X.Y.; Wu, J.J. Research progress of isoxazoline insecticide Fluralaner. *J. Technol.* 2024, 24, 167–177.
11. Kokkiligadda, S.B.; Musunuri, S.; Maiti, B.; Rao, M.V.B.; Somaiah, N. Synthesis and Biological Evaluation of Amide Derivatives of Quinazoline-Thiazole-Oxazole as Anticancer Agents. *Chem. Data Collect.* 2023, 48, 101046.
12. Zheng, Y.J.; Chen, L.N.; Du, G.F.; Yang, B. Determination of Fluorescent Brightener 367 and 393 in Cosmetics by LC-MS/MS. *Flavour Fragrance Cosmet.* 2021, 6, 19–26.
13. Mastalarz, H.; Mastalarz, A.; Wietrzyk, J.; Milczarek, M.; Kochel, A.; Regiec, A. Studies on the Complexation of Platinum(II) by Some 4-Nitroisoxazoles and Testing the Cytotoxic Activity of the Resulting Complexes. *Molecules* 2023, 28, 1284.
14. Moran W. J. Rodriguez A. *Org. Prep. Proced. Int.* 2012;44:103–130. doi: 10.1080/00304948.2012.657558.
15. (a) Komiyama K. Funayama S. Anraku Y. Ishibashi M. Takahashi Y. mura S. O. J. Antibiot. 1990;43:247–252. doi: 10.7164/antibiotics.43.247. Panthee S. Takahashi S. Takagi H. Nogawa T. Oowada E. Uramoto M. Osada H. J. Antibiot. 2011;64:509–513. doi: 10.1038/ja.2011.41.
16. Otani T. Sugimoto Y. Aoyagi Y. Igarashi Y. Furumai T. Saito N. Yamada Y. Asao T. Oki T. J. Antibiot. 2000;53:337–344. doi: 10.7164/antibiotics.53.337.
17. Qiao Y. F. Takeya K. Itokawa H. Iitaka Y. *Chem. Pharm. Bull.* 1990;38:2896–2898. doi: 10.1248/cpb.38.2896.
18. Itokawa H. Mihara K. Takeya K. *Chem. Pharm. Bull.* 1983;31:2353–2358. doi: 10.1248/cpb.31.2353.