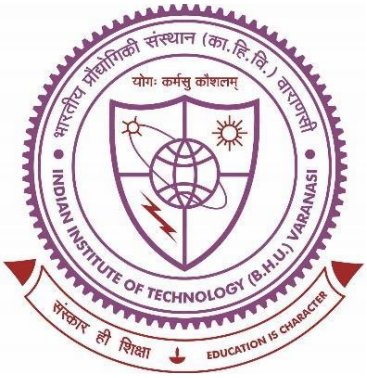
Advancement in Synthesis and Functionalization of Biologically Relevant Heterocyclic Scaffolds



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Award of Degree

Doctor of Philosophy

By

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Chapter-7

Summary and Future Prospects

7. Summary and Future Prospects

The thesis entitled “Advancement in Synthesis and Functionalization of Biologically Relevant Scaffolds” embodies the environmentally benign methods for synthesizing and functionalizing biologically important heterocyclic compounds containing nitrogen and oxygen atoms. The research involves the design of alternative economically efficient for the construction and functionalization of various biologically relevant scaffolds, such as diindolylmethanes (DIMs), imidazopyridines, coumarins, and quinazoline-based vasicine.

Different analytical methods have been used to characterize the synthesized compounds. ^{1}H & ^{13}C-NMR, FT-IR, and Mass spectrometry. The total content of the thesis has been divided into six chapters.

Chapter 1 gives a brief introduction and literature review of the existing synthetic protocols for the construction and functionalization of some of the major classes of nitrogen and oxygen-containing heterocyclic compounds and further application of these methodologies in synthesizing various medicinally active molecules.

Chapter 2 demonstrates the synthesis of diindolylmethanes (DIMs), which are a therapeutically significant class of indole alkaloids, by coupling of alcohols with indoles in presence of potassium persulfate ($K_2S_2O_8$) as the oxidant. In this method, $K_2S_2O_8$ is activated by glucose in water at room temperature which facilitates the conversion of alcohols to aldehydes, followed by coupling with indoles to form DIMs. This method is metal-free, eco-friendly alternative of DIM synthesis with high yield outputs and a broad substrate scope, that includes various benzyl and aliphatic alcohols. Moreover, the methodology shows robustness due to its gram scale transition, producing the desired product in decent yields.

In **Chapter 3,** we illustrate another pathway of synthesizing DIMs by coupling arylacetic acids with indoles, mediated by $K_2S_2O_8$, in the presence of glucose in water at ambient temperature conditions. This green synthetic protocol provides another economically efficient suitable alternative to DIM synthesis, along with the benefits of high product yields and good substrate tolerability of both substituted arylacetic acids and indoles. This method also helps to generate biologically active DIMs in gram scale levels.

Chapter 4 outlines the importance of C-3 formylated imidazo[1,2-a]pyridines (IMPs) as a key intermediate in the synthesis of sedative and anxiolytic drugs, like alpidem and zolpidem and encompasses a green synthetic route for easy formylation of IMPs. The traditional approach for the formylation of IMP often involves harsh conditions and low yields. We have developed a method for the C-3 formylation of IMP using glyoxylic acid and $K_2S_2O_8$. The optimized reaction methodology results in high yields and regioselective formylation. This synthetic approach is scalable to gram-scale, confirming its practical application in producing key intermediates in the synthesis of alpidem and zolpidem.

Chapter 5 provides an insight into the significance of coumarins as one of the major natural product scaffolds with diverse therapeutic applications. Amongst these coumarins, 7-aminocoumarins are mention-worthy due to their excellent photophysical properties. However, the existing synthetic routes for the construction of 7-aminocoumarins are mostly reliant on the use of transition metal catalysts. This segment introduces a transition-metal-free C–N cross-coupling method using a multifunctional reagent to synthesize 7-aryl/alkyl-aminocoumarin derivatives. This approach addresses the limitations of conventional methods by offering a more sustainable and efficient pathway for constructing coumarin-based compounds. Further, we have shown the applicability of our method in the gram-scale synthesis of coumarin-based fluorescent molecules.

In **Chapter 6**, we have demonstrated *tert*-butyl nitrite (TBN) mediated conversion of alcohols to amides and showed its application in synthesizing anti-Alzheimer compounds. The transformation of alcohols to amides requires a variety of metal-based catalysts. This TBN-mediated method provides a straightforward and efficient synthesis route. We have shown the application of our developed method in synthesis of vasicine analogues reported for anti-Alzheimer's activity. Also, we have performed gram-scale synthesis of bioactive compounds using our optimized method.

In conclusion, the research has successfully developed several green and efficient synthetic methodologies for the functionalization and synthesis of biologically relevant scaffolds. The research achieves versatile and scalable synthetic routes by utilizing environmentally safe oxidants like potassium persulfate and *tert*-butyl nitrite. These methods not only deliver high yields and broad substrate scopes but also emphasize the sustainability and practicability of large-scale applications.

Adopting green chemistry principles and metal-free synthetic methods exemplifies the potential to transform the field of medicinal chemistry, offering both environment-friendly and economically viable pathways. This research contributes valuable insights and practical techniques, paving the way for more sustainable pharmaceutical development practices. This opens new avenues for the design of alternative green synthetic routes for developing other synthetically challenging but medicinally important small molecules and marine compounds. This also allows for the exploration of innovative and efficient cost-effective methodologies in the design of customized heterocyclic scaffolds.

List of Publications

1. **Indurthi, H. K.**; Das, S.; Kumari, A.; Sharma, D. K. $K_2S_2O_8$-Glucose Mediated Oxidative Coupling of Alcohols with Indoles for Synthesis of Bis(Indolyl)Methanes in Water. *New J. Chem.* **2022**, *46*, 13924–13930.

2. **Indurthi, H. K**.; Das, S.; Saha, P.; Sharma, D. K. $K_2S_2O_8$-Mediated C-3 Formylation of Imidazopyridines Using Glyoxylic Acid. *Eur. J. Org. Chem.* **2023**, *26*, e202300829.

3. **Indurthi, H. K**.; Das, S.; Saha, P.; Sharma, D. K. A Metal-Free System for Conversion of Alcohols to Amides Using *Tert* -Butyl Nitrite. *Asian J Org Chem* **2024**, *13*, e202300576.

4. **Indurthi, H. K**.; Das, S.; Saha, P.; Koli, S. N.; Sharma, D. K. Potassium Persulfate-Glucose Mediated Synthesis of 3, 3′-Bis (Indolyl) Methanes from Arylacetic Acid and Indoles in Water. *J. Mol. Struct.* **2024**, *1307*, 137959.