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Metal-Catalyzed Indole-Based Macrocyclization Methods

Mintau Porele*

Department of Chemistry, Indian Institute of Technology Palakkad, Palakkad 678557, India

Introduction

This review focuses on the various types of macrocycles synthesized with indole units in their architecture using metal-catalyzed strategies. The advancement of new macrocyclization approaches has remained an active area of study. Macrocycles contain a wide range of molecules, and heteroaryl motifs are valuable constituents that add an appealing feature to macrocyclic systems. Indole is a privileged pharmacophore against a wide range of targets with diverse biological applications. Among nitrogen-based heterocycles, indole is widely used in organic synthesis, medicinal chemistry, pharmaceuticals, natural product synthesis, agrochemicals, dye and fragrance synthesis, and drug design. These scaffolds are found in a variety of bioactive natural products and synthetic macrocycles designed to target a specific biochemical target, as well as the most common constituents of naturally occurring molecules.

Description

Because of its significance, the development of novel approaches for the synthesis of indole-based scaffolds has been steadily increasing. The macrolactamization and macrolactonization processes, as well as the C-C bond macrocyclization process described by metal-catalyzed ring-closing metathesis and coupling reactions, are responsible for the majority of macrocycle synthesis. Metal-catalyzed macrocyclizations are regarded as one of the most powerful tools for synthetic chemists in the design of a wide range of macrocycles. This review aims to provide a thorough understanding of the synthesis of various macrocycles with indole scaffolds catalysed by various transition metals that have emerged in the literature over the last two decades. We hope that this review will encourage synthetic chemists to look for new strategies for C-C bond macrocyclization using metal-catalyzed protocols.

Macrocycles are versatile motifs that have piqued the interest of synthetic chemists, particularly those involved in natural product synthesis, over the last several decades. Because of their enormous impact on bioactive natural products, chemical biology, polymers, drug design and development, bioorganic chemistry, supramolecular chemistry, pharmaceutics, and medicinal chemistry, the interest in the synthesis of macrocyclic compounds has grown steadily. Macrocycles are cyclic chemical entities composed of 12-membered or more atoms with larger rings. These are very important common privileged scaffolds for drug design, and there is a growing interest in their study.

In supramolecular chemistry, some macrocycles containing heteroatoms serve as hosts and act as selective complexing agents and catalysts. Macrocycles' structural topography provides excellent molecular recognition as well as useful molecular carriers for delivering drug molecules and therapeutic biomolecules. Macrocyclic scaffolds containing heteroatoms are valuable compounds with a wide range of medicinal and pharmacological activities. Some macrocyclic motifs are used as probes or drugs to target protein-protein interactions, increase metabolic activity, and improve selectivity and binding affinity. In general, these are found in nature, and the structure of these macrocycles performs some degree of conformational pre-organization due to restricted rotation.

Natural products with macrocyclic skeletons have a wide range of pharmacological properties, and their biochemical functions have led to drug development. These macrocyclic scaffolds are conformationally pre-organized and provide distinct functionality and stereo chemical complexity in their architecture, resulting in improved affinity and selectivity for protein targets. Macrocycles have numerous advantages, especially when compared to their linear counterparts. Designing and developing drug-like macrocycles is always an exciting area of research in medicinal chemistry, and it has piqued the interest of many organic chemists in recent years. The macro cyclization strategy is promising for drug design because it reduces entropic loss associated with the ligand through conformational adaptation, which may lead to improved potency and selectivity.

Nitrogen-bearing heterocycles have long been regarded as a desirable target for the synthetic community due to their promising biological activities. Because of their unique ability to bind a wide range of receptors, N-based heterocycles have piqued the interest of synthetic chemists and chemical biologists over the last several decades, and they are found in a wide range of natural products and medicinally relevant substances. Among the various heterocyclic scaffolds, indole is a distinct core known as a privileged pharmacophore found in a variety of biologically active scaffolds. Some indole units can be found in natural and synthetic macrocycles with important biological functions, and it is a key synthon in a variety of clinically important drugs for the treatment of cancer, circulatory disease, Alzheimer's disease, and neuro disorders [1-5].

Conclusion

Finally, the metal-catalysed approaches described here enable the synthesis of a wide range of heteroaryl macrocycles containing indole units with a high structural diversity and complexity. Because of the importance of macrocyclic frameworks containing heteroaryl systems in a variety of fields of research, there has been a surge in interest in recent years. Furthermore, indole scaffold derivatives are widely distributed in a wide range of biologically relevant molecules and play an important role as key synthons in the synthesis of medicinally important small molecule drugs, natural products, and pharmaceuticals. As a result, novel approaches to achieving indole-based macrocycles are still needed in synthetic organic chemistry. Because of their unique structures, easy functionalization, and diverse applications in a variety of fields, macrocyclic indole frameworks have emerged as appealing synthetic targets.

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***Address for Correspondence:** Mintau Porele, Department of Chemistry, Indian Institute of Technology Palakkad, Palakkad 678557, India, E-mail: mintauporele@gmail.com*

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