Indole, a Privileged Structural Core Motif

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Isaac Giménez Sonsona was born in Zaragoza, Spain, in 1991. He received his B.S. in chemistry at the University of Zaragoza in 2014. He is currently working towards his PhD degree in the Department of Organic Chemistry at the University of Zaragoza under the supervision of Dr. Raquel P. Herrera and Dr. Eugenia Marqués-López. His primary research interest focuses on the enantioselective organocatalytic study of different organic reactions aimed at the asymmetric synthesis of potential biologically active compounds.

Introduction

Indole (1), denominated by some authors as The Lord of the Rings of heterocyclic compounds1 due to its importance in fields like chemistry, biology, and medicine,2 represents the structural core of many natural and non-natural products with a wide range of biological properties, including antiviral3 and anticancer4 activities. An example of this spectrum of utilities is Arbidol (2), which is administered as a drug in Russia and China against influenza and other respiratory viral infections.5 Recent examples of other applications of indole-containing compounds are their potential use in SPECT imaging or detecting Aβ plaques in Alzheimer’s disease, as compound 3,6 or their use as ligands in the synthesis of organometallic complexes with optoelectronic properties and with potential use in the construction of light-emitting devices.7

![Figure 1: Indole-based target compounds](image)

Table 1 Use of Indole, a Privileged Structural Core Motif

(A) N1 Reactivity:
The total synthesis of the monoterpene alkaloid mersicarpine (10) was reported in 2014 by Liang’s group.10 The synthesis involves the nucleophilic attack of the NH of the indole 7 to the activated carboxylic acid 8, giving the corresponding amide intermediate 9. This allows access to indole analogue 10, an unusual seven-membered cyclic imine fused with a δ-lactam with two stereogenic centers.

(B) C2 Activation:
Zhang and co-workers11 reported the synthesis of N-(6-(indol-2-yl)pyridine-3-sulfonamide 13 starting from the substituted indole 11. The mechanism involves the boronic acid intermediate 12.

Preparation

The interest in the synthesis of indole rings from the last century to the present day is due to the important biological activities that compounds with this privileged structural core exhibit. Therefore, many different synthetic approaches have been developed in order to obtain these scaffolds.8 Undoubtedly, the most important method to obtain differently substituted indoles is the Fischer synthesis.9 In this crucial reaction, arylhydrazines 4 react with ketones or aldehydes 5 by heating in the presence of an acid to give the corresponding functionalized indoles 6 with good yield (Scheme 1).
(C) **C3 Reactivity:**
In 2014, McLaughlin’s group\(^{12}\) published the synthesis of the violacein scaffold 17, a microbial pigment with antimicrobial and anticancer activities. Indole derivatives 14 react at the C3 position with the acyl chloride derivative 15 to afford the main product 16, key in the construction of violacein analogues 17.

(D) **C4 Activation:**
Lanke and Prabhu reported the direct functionalization of N-protected indole-3-carbaldehyde derivatives 18 at the C4 position under mild conditions employing ruthenium as a catalyst and with the aldehyde functionality as the directing group.\(^{13}\) This reaction could be crucial in the synthesis of organic targets such as ergot- and related alkaloids.

(E) **C5 Activation:**
In 2013, Liebhold and Li reported the benzylation of tryptophan derivatives 19 at the C5 position of the indole ring using the fungal di-methylallyl transferase FgaPT2 (20).\(^{14}\) This method gives access to pharmaco logically active lipophilic chain containing compounds 21 in moderate yield.

(F) **C6 Reactivity:**
In 2014, Shi and co-workers developed a Brønsted acid organocatalyzed arylation of 3-indolylmethanol derivatives 22, affording a direct method for C6 functionalization of substituted indoles 23, leading to scaffolds 24.\(^{15}\)

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**References**