Spirooxindole

Chemistry, Synthesis, Characterization and Biological Significance

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Chapter 25

Anticancer potential of spirooxindole derivatives

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25.1 Introduction

The intricate structures of spirooxindoles (SOXs), prevalent in numerous alkaloids, contribute significantly to the enhancement of medication efficacy (Lopes et al., 2019). Meticulous strategies were used for the synthesis of chiral SOXs, showcasing a potent level of precision in their design (Zhang et al., 2018). The inherent chirality within spiro-bridged and C-3 sp^3 hybridized spiro-fused heterocyclic scaffold frameworks plays a pivotal role in various carcinomas. In recent years, the emergence of 3-alkenyl-oxindoles as a prominent structural foundation has played a pivotal role in the synthesis of potent SOX derivatives (Akaev et al., 2019). The eco-friendly [3 + 2] and [4 + 2] cycloaddition reactions were also used for the formation of the SOXs, offering promising avenues for the creation of chiral-SOXs (Brandão et al., 2021). Furthermore, synthetic strategies for the formation of new drug like molecules have been conveyed to the broad goal in field of medicinal chemistry. Actually, various synthesized and isolated SOXs from the natural sources are used in the treatment of various carcinomas through the FDA (Food And Drug Administration) and NCI (National Cancer Institute) approval drugs (Mandai et al., 2021). Recognizing this resilience, numerous approaches have been devised, heightened, and proposed for transforming dioxindole (DOX) into a diverse array of spiro-fused heterocyclic compounds (Chen et al., 2022). These advancements underscore the critical role of SOXs in medicinal chemistry and highlight their potential for further exploration in drug development (Wang & Ganesan, 2000).

25.2 Literature survey on the C-3 spirooxindole derivatives

Asif et al. (2023) reported the various strategies for synthesis of SOX derivatives using multicomponent or click chemistry and their anticancer activity (Asif, Alvi, et al., 2023; Asif, Aqil, et al., 2023; Asif, Azaz, et al., 2023; Asif, Saquib, et al., 2023; Hassan et al., 2022; Herlin Shamina et al., 2023; Jeba Reeda et al., 2023; Yu et al., 2015). In the realm of nature, DOXs and SOXs manifest themselves in distinctive plants and animals in the form of alkaloids. Additionally, their synthesis is achievable based on their skeleton-core, exhibiting drug-like properties. Notably, spirotryprostatines (A, B), identified in the *Aspergillus fumigatus* fungus, have been recognized as potent antiproliferative agents. Similarly, specific plants such as *Horsfieldia superba* and *Mitragyna speciosa* harbor compounds like horsifiline and mitraphylline, contributing to the rich array of natural pentacyclic SOXs. Extracted from *Uncaria rhynchophylla*, Pertopodine and Isopteropodine further add to the diversity of these intriguing compounds. Macroline-oxindole, discovered in *Alstonia muelleriana*, showcases robust antimalarial activity, while marcfortine (A) SOX, sourced from *Penicillium roqueforti*, exhibits nematicidal properties against parasitic nematodes. Fungi such as *Penicillium citrinum* and *Penicillium cyclopium* produce citrinadins and cyclopiamines (A and B), respectively, as part of the paraherquamide family, demonstrating versatile bioactivities, i.e., antiproliferative and insecticidal properties (Henneberg et al., 2021).

Strychnofoline, isolated from *Strychnos usambarensis* leaves, has shown promising antimitotic activity against cultures of mouse melanoma and Ehrlich tumor cells (Shakri et al., 2020). Rhynchophylline and Isorhynchophylline, isolated from *U. rhynchophylla*, are active alkaloids with similar biological activities, such as neuroprotection and antihypertension (Fig. 25.1). In the realm of SOX synthesis, the intriguing challenge lies in the inherent chirality present in the spiro-skeleton. Pioneering efforts in green catalysis have been explored, contributing to diverse libraries of SOXs

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