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Ultrasound-Assisted Cascade Condensation of Isatin, Malononitrile, and β-Keto Esters: An Efficient One-Pot Synthesis of Novel Spirooxindole Derivatives with Expected Anti-Esophageal Cancer Activity

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Abstract—A green and facile one-pot synthesis of novel oxospiro[indole-3,4′-pyran] derivatives via a three-component reaction of isatin, malononitrile, and various β-keto esters in the presence of triethylamine under ultrasonic irradiation is reported. This protocol offers several ecological benefits including simple methodology, good to excellent yields, clean reaction, higher atom economy, shorter reaction time, and environmental friendliness. Molecular docking of the synthesized spirooxindole derivatives was performed to evaluate their anti-esophageal cancer activity.

Keywords: ultrasonic irradiation, multicomponent reactions, oxospirooxindoles, molecular docking, anti-esophageal cancer activity

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INTRODUCTION

Efficient, simple, and non-polluting synthetic methodologies encourage environmental chemists to provide equipment of their arsenal. One route to reach this demand involves employing sonochemical strategy [1]. Ultrasound strategy or sonochemical techniques are employed for enhancing various chemical reactions [2]. The importance of ultrasonic irradiation in carrying out most organic reactions is due to the cavitation process [3]. This process induces high local temperature and pressure inside the bubbles (hot spots or cavities) that facilitate mass transfer in the micro-environment and accelerate chemical reactions [4]. Sonochemical strategy offers several benefits compared with conventional methods in terms of precise control, improved yield, shorter reaction time, reduced energy consumption and waste formation [5], and improved selectivity and provides additional expediency in the field of bioorganic chemistry [6, 7]. Multicomponent reactions (MCRs) as a precise method are extensively utilized in organic chemistry due to their unique capability to construct highly functionalized organic compounds in a one-pot reaction [8–13]. The investment of the advantages of MCRs and ultrasonic technique provides an efficient tool to accelerate organic reactions [14].

Spirooxindole ring system is an important heterocyclic structure which is found in numerous cytostatic alkaloids and pharmacological compounds. Spirooxindole structure as a privileged pharmacophore which offers a wide range of biological activities [15]. Examples of biologically active spirooxindole compounds include alkaloids such as spirotryprostatin A which acts as an inhibitor toward mammalian cell cycle [16], gastrin/CCK-B receptor antagonist [17], as well as mitraphylline and rhynchophylline that are currently studied as anticancer agents against human brain cancer (Fig. 1) [18, 19].

A number of synthetic procedures for spirooxindoles fused with various heterocycles have been reported [20]. Also, a wide range of catalysts have been used in the synthesis of spirooxindole derivatives, in-