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Efficient synthesis of chromeno[2,3-*b*]pyridine derivatives using Zn $(OTf)_2$ as a catalyst: DFT computations, molecular docking and ADME studies

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ABSTRACT

An efficient method was developed for the synthesis of chromeno[2,3-*b*]pyridine derivatives by using Zn $(OTf)_2$ (Zinc trifluoromethanesulfonate) *via* one-pot [3 + 3] cascade annulation methods using 2-amino-4*H*-chromen-4-one with a different substituted group (**1**–**6**) and *trans*-chalcone. This strategy offers the pharmacological importance of 2-amino-4H-chromen-4-one derivatives in reaction time and good yields. This approach also brings a different perspective to the literature as an intramolecular cyclization pathway. All computational works were performed at the B3LYP/6–311++G** level of theory. After confirming the optimized structures and comparing the calculated spectroscopic data with corresponding experimental data, the intramolecular interactions were evaluated on the basis of NBO "Natural Bond Orbital" theory. The quantum chemical reactivity features and FMO "Frontier Molecular Orbital" analyses were conducted at the same level of theory. The solvent effect on the reactivity behaviors was also investigated by using the results that were determined by obtaining the different solvent environments. Molecular docking was employed to explore the binding affinities of the compounds against AChE (Acetylcholinesterase), BuChE (Butyrylcholinesterase), and HSA (Human serum albümin). Also, the bioavailability and drug-likeness properties of compounds **1**–**6** were determined to explore the possible usage in further drug design works.

1. Introduction

Chromene and its derivatives have caught the fascinating classes of synthetic chemists due to diverse pharmaceutical activities and the privileged scaffolds of their members [1–4]. Due to their interesting biological properties, various synthesis methods have been developed for chromone derivatives by many working groups [5–10]. In recent work, Hu and coworkers reported exhibiting a anti-rotavirus activity of two chromeno[3,2-*c*]pyridin derivatives extracted from *the Thalictrum finetii* plant [10]. Also, the polycondensed naphthyridine derivatives obtained from oxidative cyclization of 5H-Chromeno[2,3-*b*]pyridines were suggested as a promising material for using OLED technology [11]. Syntheses of the chromone heterocycles are somehow based on the chromeno [2,3-*b*]pyridin skeleton, the key element heterocyclic building block of azaxanthones type-structure [12–15]. Some examples of known biologically active chromeno[2,3-*b*]pyridine are shown in Scheme 1. Among these synthetic approaches, Friedel Crafts cyclization, [4 + 2], [3 + 2], and [3 + 3] annulation reactions [16,17] have been commonly used. Compounds **1**, **2**, **3**, and **5** are known-well compounds [18], but in this work, these compounds are synthesized using different types of catalysts and reagents with a new method as well as a proposal for a different mechanism. In this respect, Soares and coworkers reported a novel route on the basis of DABCO-catalyzed [3 + 3] annulation to chromeno[3,4-*b*] pyridine derivatives [19]. In one of them, the multi-component synthesis of the chromeno[2,3-*b*]pyridine, in a one-step, has been quite promising research to save energy and time [20]. In recent work, a novel catalyst GO/*N*-Ligand-Cu nanocomposites were reported due to the capability the catalyze the multi-component reactions (MCRs) to get chromeno[2,3-*b*]pyridine; it was remarkable for the green and economic synthesis of the chromeno[2,3-*b*]pyridine [21]. Furthermore, a smooth synthetic protocol has been reported to get bis(chromeno[3,4-*c*]pyridine) derivatives via

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