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A novel series of tetrahydrothieno[2,3-*c*]pyridin-2-yl derivatives: fluorescence spectroscopy and BSA binding, ADMET properties, molecular docking, and DFT studies†

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In this study, a series of substituted tetrahydrothieno[2,3-*c*]pyridin-2-yl (THTP) derivatives, *i.e.*, **C1–C3** and **N1–N3**, was synthesized in one step using 2-amino-5,5,7,7-tetramethyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carbonitrile with two different adjacent chloro- and nitro-substituted groups. Specifically, with a nitrile group on the thiophene structure, six new THTP (**C1–C3** and **N1–N3**)-bearing electron-donating-electron-withdrawing moieties were designed with various pharmacological properties. For the first time in the literature, the synthesis of these target pharmaceutical products was carried out in less steps with high efficiency. Specifically, the notable features of this protocol are its simplicity and high reaction yields. Furthermore, spectroscopic methods were used to verify the structures of all the synthesized compounds (FT-IR, UV, ^{1}H NMR, and ^{13}C NMR). Additionally, the binding properties of the molecules with serum albumin were analyzed as a function of concentration and temperature and in the presence of Mg^{2+}, Zn^{2+}, and Ca^{2+}. Moreover, molecular docking calculations were performed against bovine serum albumin, human leukemia inhibitory factor, and DNA. Also, DFT and TD-DFT computational studies were performed at the B3LYP/6-311G** level for structural and spectroscopic confirmation of compounds **C1–C3** and **N1–N3**, and their possible reactivity features were evaluated *via* FMO "frontier molecular orbital" and NBO "natural bond orbital" analyses. Further, their physicochemical properties such as lipophilicity and water solubility, in addition to ADMET properties were estimated and evaluated. Considering the results obtained from the experiments and computations, it is hoped that this work will be a useful guide for future research on drug design.

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1. Introduction

Structurally, tetrahydrothieno[2,3-*c*]pyridin-2-yl (THTP) derivatives and their congener skeletons have significant biological applications in medicinal chemistry and related areas.[1] In addition to carrying electron-withdrawing and electron-donating groups, the presence of a cyano group attached to thiophene increases the importance of the synthesized compounds.[2] Due to the promising antibacterial activities of the cyanothiophene scaffold, it is a crucial component in novel antibacterial drugs and the development of new synthetic building pathways.[3–7] Accordingly, many synthetic methods have been developed for the construction of these molecules, and they have also attracted interest in medicinal and organic chemistry from a synthetic standpoint.[8–10] Some examples of known biologically active tetrahydrothieno[2,3-*c*]pyridin-2-yl (THTP) derivatives are shown in Scheme 1. Herein, we report the synthesis of the title tetrahydrothieno[2,3-*c*]pyridin-2-yl derivatives *via* a method with improved efficiency.[11–14] Compared to the methods in the literature, this approach is novel and practical with useful starting materials for the development of heterocyclic systems. THTP derivatives have been found to exhibit a broad spectrum of activities in medicinal chemistry.[15,16] They

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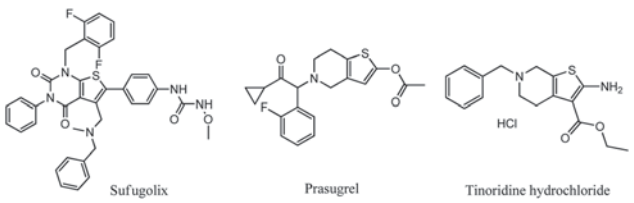

Scheme 1 Structure of tetrahydrothieno[2,3-*c*]pyridin-2-yl (THTP) derivatives based on some drugs.