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Synthesis of thiophene derivatives: Substituent effect, antioxidant activity, cyclic voltammetry, molecular docking, DFT, and TD-DFT calculations

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ABSTRACT

The efficient pathway 6-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate derivatives have been synthesized. Due to the promising biochemical reactivity, the bioactive agent synthesis in the frame of the thiophene moiety is one of the main objectives of the contemporary scientific disciplines. The structures of all the presently synthesized compounds were confirmed using spectroscopic methods (UV–vis, FT-IR, ^{1}H NMR, ^{13}C NMR). The cyclic voltammetry (CV) of three compounds (1-3) was performed using a bare ITO electrode and a Nafion modified ITO (Indium Tin Oxide) electrode. The antioxidant properties of these compounds were explored by the CUPRAC method and TEAC (Trolox equivalent total antioxidant capacity) coefficients revealed that the antioxidant capacity of the compounds was ranking as follows: compound 2 (C-2) > compound 3 (C-3) > compound 1 (C-1). The docking studies displayed that compound 1 was the most active compound against Escherichia coli thymidylate synthase (TS). The TD-DFT calculations displayed that two observed peaks on the UV–vis spectra of the thiophenes were related to the n→ π^* and $\pi\rightarrow\pi^*$ transitions. Also, NBO (Natural Bond Orbital) analysis indicated that the resonance interactions (n→ π^* and $\pi\rightarrow\pi^*$) in the ground state of all compounds had an essential role in the decreasing of the stabilization energy. The antioxidant activity and molecular docking results were supported by the electrodonating power and hardness indexes in addition to the NBO results.

1. Introduction

The thiophene ring is fused with cycloalkyl ring important material. The substituted 2-aminothiophene-3-carboxy group are versatile building blocks for the synthesis and have demonstrated a broad spectrum of uses including agrochemicals, dyes, and pharmacologically active compounds [1–3]. These compounds that most effectively decrease the minimum inhibitory concentrations of ciprofloxic were reported [4]. Since 1961 when the first report on the Gewald reaction was reported, several methods [5–8] were reported in the literature for the preparation of these materials [9]. These compounds became a universal method for the synthesis of aminothiophenes and have gained prominence in recent times.

Due to the importance of the indole-based compounds, especially in bio-medicinal applications [10,11], detailed computational works on these kinds of compounds were reported in past, including the solvent effect, basis set, and the computational method effect on the possible reactivity [12–14]. Also, the computational studies combined with the experiments were performed [15,16] on the thiophene derivatives, to evaluate the structure-activity relationship. In continuation of our studies on the synthesis of heterocyclic compounds [17–20] and because of the versatile biological properties of thiophene derivatives, we now report the synthesis of some novel 6-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-

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