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Nitrobenzamido substitution on thiophene-3-carboxylate: Electrochemical investigation, antioxidant activity, molecular docking, DFT calculations

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ABSTRACT

A novel nitro containing thiophene derivatives containing have been synthesized. In pharmaceutical chemistry, thiophene derivatives show a biological effect. Due to the promising antimicrobial, analgesic and anti-inflammatory, and antitumor activity, alternative and different approaches have also been one of the main objectives in the field of chemical sciences. Based on the broad range of biological properties of thiophene derivatives, this study aimed to evaluate the antioxidant activity of novel thiophene derivatives and explore the electrochemical features using CV (cyclic voltammetry). The synthesis and characterization of novel benzo[*b*]thiophone derivatives were confirmed using spectroscopic methods with ^{1}H-NMR, ^{13}C-NMR, FT-IR, and UV-vis. The DFT and TD-DFT computations were conducted to compare the spectroscopic data and then confirm the molecular structures of the compounds **1-3**. The FMO and NBO analyses were conducted to estimate the possible reactivity features and key intra-molecular interactions. Last, molecular docking investigations were performed to explore the possible interaction of each compound to human EGFR Kinase.

1. Introduction

Substitution aminothiophenes have attracted much attention, owing to their pharmacologically [1,2]. Substitution aminothiophenes are exceptionally valuable due to their prevalence in an enormous number of pharmacologically active heterocyclic compounds, functional with substituted -NO_2 in the field of medicinal biologically active pharmaceutical compounds [1,2], and antitumor activity [3], antihypertensive [4]. A lot of substituted-containing compounds are used in the treatment of Alzheimer's disease [5]. However, the synthetic protocol of thiophene derivatives is known in the literature [6–8] for the synthesis of thiophene-2-amines, new approaches towards it remain a challenging task. In this concept, Gewald's multicomponent reaction is known well for the preparation of 2- aminothiophenes [9]. As a continuation of our previous work, we suggest a practical and economic way to synthesize the nitro-substituted thiophenes, and the applied reaction proceeds to aminothiophenes starting from ethyl 2-amino-6-methyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate, in remarkable yields (Scheme 1). The newly synthesized thiophenes derivatives were also explored for their cyclic voltammetry (CV) [10] and antioxidant properties using the DPPH method [11,12].

For a long time, a lot of works have been carried out to date, especially with thiophenes [13], sulfurs [14], amino heterocyclic compounds [15], and thiophenes [16,17], but research is generally limited to synthesis method, characterization, and pharmacological scaffold. Recently, the role of the substituent group position for the thiophene compound on the possible reactivity feature was reported in detail; the electrochemical and antioxidant activity measurements revealed that the chlorine position on the main thiophene unit might be a key role in the evaluation of the related activity [8,18]. In the present work, our main motivation is to investigate and evaluate the electronic properties underlying both electrochemical and pharmacological activity, beyond synthesis and characterization. For this goal, we synthesized new *ortho*-, *meta*- and *para*- nitro substituted thiophenes, and applied to them the standard spectroscopic techniques to characterize structurally them. Then, we compared the observed data ob-

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