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Synthesis, spectroscopic characterizations, TD/DFT calculations, colorimetric metal ions, and molecular docking studies of a novel 3-acetylpyridine 2-hyrdoxyphenyl thiosemicarbazone

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ABSTRACT

A novel thiosemicarbazone scaffold, namely 3-acetylpyridine-2-hydroxyphenyl thiosemicarbazone (3APHT), which contains π-conjugated heterocyclic and phenyl rings, was successfully synthesized and characterized experimentally and theoretically. Through TD/DFT calculations, it was found that the new compound has 14 signals in ^{13}CNMR spectroscopy, 96 types of vibrations for vibration analysis, and *n*-π* and π-π* electronic transitions that lead to an 87.12 % HOMO-LUMO excitation. The vibrations follow 3N-6 degrees of freedom for a non-linear compound. Based on the global reactivity parameter and other results, it has been shown that 3APHT has potential applications in metal ion detection and as an inhibitor for the overexpressed receptor of breast cancer caused by copper ions pollution. The novel APHT was optimized as a colorimetric metal ions recognition using UV–Vis analysis. Suitable conditions for 3APHT to act as a colorimetric metal ion recognition was detected in DMSO/water (8:2 v/v, pH 7). The change of test strips from colorless to yellowish revealed the presence of Cu^{2+} ions in the water. The selectivity toward the Cu^{2+} ion did not interfere with other metal ions. The potential of 3APHT to inhibit the upregulation of apoptotic genes caused by copper ions in BCL-2 family proteins—the main cause of breast cancer—was determined using an *in-silico* approach. The results showed strong binding of 3APHT with BCL-2, BCL-W, MCL-1, and ER-α through hydrogen bonds and electrostatic interactions at -6.35, -6.31, -8.05, and -7.05 kcal/mol, respectively. The physicochemical through ADME analysis showed that the compound has a structure that presents good absorption properties, therefore permeability across the cell membrane, and good theoretical oral bioavailability.

1. Introduction

The common thiosemicarbazone ligand is bidentate and binds to metal ions through the azomethine nitrogen (C=N) and thiocarbonyl sulfur (C=S) atoms. Furthermore, the ligand can bind in a multidentate fashion when the N1 position of the thiosemicarbazone moiety is substituted at the α-carbon with an aldehyde or ketone group possessing atoms of different electronegativities. The unique structure of the thiosemicarbazone scaffold, containing various electronegative atoms (N and S), makes the compound suitable as a colorimetric sensor for metal ion detection and also for pharmacological industries [1]. In this study, a novel compound (3-acetylpyridine-2-hydroxyphenyl thiosemicarbazone (3APHT)) was synthesized and characterized through spectroscopy. Theoretical approaches were also applied to elucidate the formation mechanism of the compound and characterize its chemical properties. Because this compound shows unique properties (e.g., it contains various binding sites), it was optimized as a selective and sensitive colorimetric chemosensor toward Cu ions.

Copper is frequently used in the production of wires and pipes, as well as in agriculture. Agriculture, industrial waste, mining, and

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