Journal of Molecular Structure 1274 (2023) 134437

Contents lists available at ScienceDirect

Journal of Molecular Structure

journal homepage: www.elsevier.com/locate/molstr

Design, synthesis, characterization, antioxidant, antiproliferative activity and molecular docking studies of new transition metal complexes of 1,2,4-triazole as combretastatin A-4 analogues

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ARTICLE INFO

Article history:
Received 11 September 2022
Revised 24 October 2022
Accepted 26 October 2022

Keywords:
Transition metals
Triazole
Schiff base
Combretastatin A-4
Anti-cancer

ABSTRACT

In the present work, we introduce new transition metal complexes. The complexes are designed to have 3,4,5-trimethoxyphenyl and 2–hydroxy-4-methoxyphenyl groups connected by 1,2,4-triazole ring and imine linkage to be proper analogues for the anti-tubulin agent combretastatin A-4. FT-IR, ^{1}H NMR, ^{13}C NMR, mass spectrometry, CHNS, thermal gravimetric analysis (TGA-DSC), magnetic susceptibility, conductivity measurements, UV–Vis spectrophotometry, and flame atomic absorption spectroscopy have been used for the characterization of the synthesized compounds. The observed analytical and spectral data confirmed the octahedral environment around cobalt(II), platinum(IV) and square planar around nickel(II), copper(II) and palladium(II) ions. The antioxidant activity of the synthesized complexes was assessed by the DPPH assay, the obtained results showed that **C4** is the most active one, with a scavenging capacity of 87.6% in comparison with ascorbic acid as a reference antioxidant agent at 50 µg/mL. The new metal complexes were screened for anticancer activity by the MTT assay against the breast cancer cell line MCF-7 and normal cell line WRL-68. The obtained results revealed that the lowest IC_{50} 24.38 µM was recorded for palladium complex (**C4**) against the cancer cell line MCF-7,and an IC_{50} value of 90.2 µM against the normal cell line WRL-68. The synthesized compounds were also subjected to theoretical DFT studies, the obtained results came in agreement with the experimental results. The new ligand and its metal complexes were subjected to molecular docking studies, the structures were docked with the colchicine binding site (PDB: 1SA0), and good docking scores were recorded.

1. Introduction

The nucleus of the 1,2,4-triazole is involved in the structures of a variety of compounds with a wide range of bioactivities, including antimicrobial [1], antituberculous [2], anticonvulsant [3], anti-inflammatory [4], analgesic [5], antiasthmatic [6], antidepressant [7], insecticide and plant growth regulators [8]. This nucleus is also used in the development of a variety of anticancer agents [9–11]. Nucleoside-based anti-cancer agents, kinase inhibitors, tubulin modulators, aromatase and sulfatase inhibitors, and metal complex-based antitumor agents with this nucleus have been reported in the literature [12]. Combretastatin A-4 (C A-4) was found to have effective anticancer efficacy against several cancer cell lines, including multidrug-resistant (MDR) cancer cells [13]. According to the experimental and structure-activity relationship (SAR) studies, 3,4,5-trimethoxy, *para*–methoxy groups, and the *cis*-configuration of the double bond are the structural requirements for the significant anti-tubulin activity of C A-4 [14]. Several strategies have been proposed to maintain the *cis*-configuration of CA-4 necessary for bioactivity, one of which is based on the incorporation of the double bond in a five-member aromatic heterocyclic ring, and triazole is one of those rings [15]. The presence of the -SH group enhances the biological activity of the 1,2,4-triazole derivatives [16]. Due to the biological activity, many Schiff base compounds derived from 1,2,4-triazole have been reported [17]. This could be attributed to the presence of both the triazole ring and the imine linkage in the structure of these compounds, 1,2,4-triazole-based complexes with different metals have also been explored for their antitumor

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https://doi.org/10.1016/j.molstruc.2022.134437
0022-2860/