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Synthesis, spectroscopic properties, molecular docking, anti-colon cancer and anti-microbial studies of some novel metal complexes for 2-amino-4-phenylthiazole derivative



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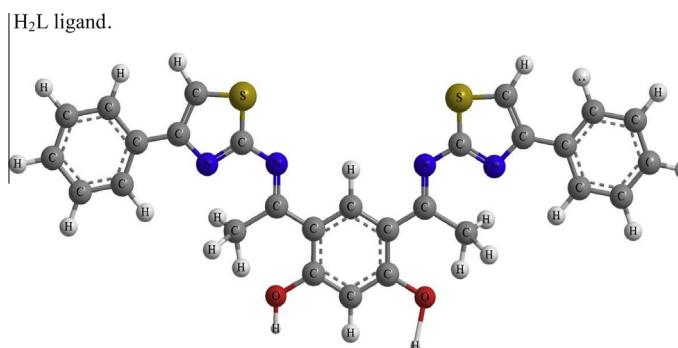
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HIGHLIGHTS

- A novel bidentate NO Schiff base ligand was synthesized and characterized.
- The Schiff base ligand was allowed to react with a variety of transition metal ions.
- Binuclear complexes were synthesized and characterized.
- The ligand and its metal complexes showed variable antimicrobial activity.
- Molecular docking of the compounds showed various interactions with the active sites of dihydrofolate reductase enzyme.

GRAPHICAL ABSTRACT



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ABSTRACT

This article describes the synthesis of novel bidentate Schiff base (H₂L) from condensation of 2-amino-4-phenylthiazole (APT) with 4,6-diacetylresorcinol (DAR) in the molar ratio 2:1. We studied interaction of ligand (H₂L) with transition metal ions such as Cr(III), Fe(III), Cu(II), Zn(II) and Cd(II). The ligand (H₂L) has two bidentate sets of (N–O) units which can coordinate with two metal ions to afford novel binuclear metal complexes. The directions of coordinate bonds are from nitrogen atoms of azomethine groups and oxygen atoms of the phenolic groups. Structures of the newly synthesized complexes were confirmed by elemental analysis, IR, UV, ¹H NMR, ESR, TGA and mass spectral data. All of the newly synthesized complexes were evaluated for their antibacterial and anti-fungal activities. They were also evaluated for their *in vitro* anticancer activity against human colon carcinoma cells (HCT-116) and mammalian cells of African green monkey kidney (VERO). The Cu(II) complex with selectivity index (S.I.) = 21.26 exhibited better activity than methotrexate (MTX) as a reference drug with S.I. value = 13.30, while Zn(II) complex with S.I. value = 10.24 was found to be nearly as active as MTX. Molecular docking studies further helped in understanding the mode of action of the compounds through their various interactions with active sites of dihydrofolate reductase (DHFR) enzyme. The observed activity of Fe(III) and Cu(II) complexes gave rise to the conclusion that they might exert their action through inhibition of the DHFR enzyme.

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Introduction

In recent years, one of the key goals of medicinal chemistry has been the development of new antimicrobial and anticancer therapeutic agents. There currently exist several complex problems in cancer therapy such as cytotoxicity of anticancer drugs to normal cells. Death of normal cells results from the use of anticancer drugs which are strong enough to kill tumor cells, and this can lead to many side effects that limits treatment efficacy. Regarding antibiotics, therapeutic problems can likewise occur due to pathogens developing resistance to treatment. Consequently, scientists have focused on developing both antimicrobial and anticancer agents which can avoid such side effects.

Schiff base ligands play a central role as chelating ligands in main group and transition metal coordination chemistry [1–3]. Transition metal complexes of multidentate Schiff base ligands find application as model analogs of certain metal enzymes [4], catalysts in oxidative addition reactions [5–9], and modifiers for selective electrodes, as well as through different uses in material chemistry [10–12]. A bimetallic core is versatile at the active site of many metalloenzymes and plays an essential role in biological systems via the interplay of a pair of metal ions [13].

In the past decade, a large number of bimetallic Schiff base complexes of different structural types have been synthesized and characterized [14,15]. These complexes vary in their new applications, donating types, structures [16,17] and biological activities [18–22]. In terms of new applications, their use can be extended to include the synthesis of novel multidentate binuclear Schiff base complexes, which could then be put to numerous uses.

2-Amino-4-phenylthiazole (APT) and its Schiff base derivatives, which are formed by condensation reaction with aldehydes and ketones show significant antibacterial and antifungal activities [23–26]. Additionally, the same behaviors where also identified in transition metal complexes of 2-amino-4-phenylthiazole derivatives [27–30].

In the present study, the ligand was prepared by condensation of 4,6-diacetylresorcinol (DAR), as starting material, with 2-amino-4-phenylthiazole (APT) providing the corresponding Schiff base, H₂L, ligand. Reactions of this ligand with chromium(III), iron(III), copper(II), zinc(II) and cadmium(II) ions, in the 1:2 M ratio (ligand:metal ion) were studied. The newly prepared metal complexes of this ligand were identified by different physicochemical and spectroscopic techniques.

Schiff base, H₂L, ligand and its metal complexes were investigated for antibacterial and antifungal properties. Eight pathogenic microorganisms were used for this investigation. Gram-positive bacteria used were *Staphylococcus aureus* (RCMB 010027), *Streptococcus pneumoniae* (RCMB 010010) and *Bacillus subtilis* (RCMB 010067). Gram-negative bacteria were *Pseudomonas aeruginosa* (RCMB 010043), *Klebsiella pneumoniae* (RCMB 0010093) and *Escherichia coli* (RCMB 010052). Two fungi, *Aspergillus fumigatus* (RCMB 02568) and *Candida albicans* (RCMB 05036), were also utilized. H₂L ligand showed significant activity, while the metal complexes each showed moderate activity, against the organisms.

Currently, colorectal cancer is the third most commonly diagnosed cancer in males worldwide and the fourth most common

in females. In Kingdom of Saudi Arabia, colorectal cancer (CRC) is actually the most common cancer in males and third most common in females. Thiazole Schiff base ligands and their metal complexes are one of the drugs involved in the cytotoxicity of anticancer. Therefore, this present work is considered an assessment where the transition metal complexes of Schiff base containing sulfur derived from (ATP) and (DAR) is overcoming the human cancer colon carcinoma HCT-116 cell line.

Experimental

Materials

4,6-Diacetylresorcinol (DAR) and 2-amino-4-phenylthiazole (APT) were synthesized according to the methods specified in the literature [22,24]. Chromium(III), iron(III), copper(II), zinc(II) and cadmium(II) ions were used as nitrate salts and were Merck or BDH. Organic solvents (absolute ethanol, methanol, diethylether and dimethylformamide) were obtained from Sigma–Aldrich and were used as supplied.

Synthesis of Schiff base ligand

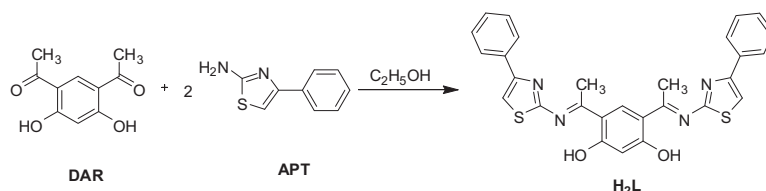
The ligand was synthesized by adding 4,6-diacetylresorcinol (DAR) (3.88 g, 20 mmol) dissolved in hot absolute ethanol (30 mL) to 2-amino-4-phenylthiazole (APT) (7.04 g, 40 mmol) in absolute ethanol (30 mL). The reaction mixture was heated to reflux for 4 h. Yellow crystals were filtered off and washed with a few amount of ethanol then ether and air dried. Fine crystals were obtained by recrystallization from ethanol. The ligand was kept in a desiccator until used. The yield was 7.98 g (78.2%), m.p. 212–213 °C. Schiff base, H₂L, ligand was characterized by elemental analyses, ¹H-NMR and electronic spectra in dimethylformamide (DMF) solution and in the solid state by IR and mass spectra. The formation of H₂L ligand is illustrated in Scheme 1.

Synthesis of transition metal complexes of the Schiff base (H₂L) ligand

The mixtures of the H₂L ligand (2.55 g; 5.0 mmol) with metal salts (10 mmol) in (50 mL) ethanol, were stirred on cold for 30 min, and then heated to reflux, for 3 h. The resulting precipitates were formed on cold after evaporation until near dryness. The products were filtered off, washed with ethanol and ether, and then air dried. The complexes are soluble in most common solvents. The following detailed preparation is given as an example and the other complexes were obtained similarly.

Synthesis of Cu(II) complex (3)

A solution of H₂L ligand (2.55 g, 5.0 mmol) in ethanol (25 mL) was added gradually with constant stirring to Cu(NO₃)₂·2.5H₂O, (2.326 g, 10 mmol) in ethanol (25 mL). The pH of the mixture was 2.2. The mixture was stirred on cold for 30 min and then was heated to reflux for 3 h. A greenish blue precipitate was formed on cold after evaporation of the solvent on a water bath near dryness. The yield was 3.01 g (66.7%), m.p. 163–164 °C.



Scheme 1. Formation of the H₂L Schiff base ligand.

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