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Synthesis, characterization of 1,2,4-triazole Schiff base derived *3d*-metal complexes: Induces cytotoxicity in HepG2, MCF-7 cell line, BSA binding fluorescence and DFT study

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ABSTRACT

Two novel Schiff base ligands $\mathbf{H_2L^1}$ and $\mathbf{H_2L^2}$ have been synthesized by condensation reaction of amine derivative of 1,2,4-triazole moiety with 2-hydroxy-4-methoxybenzaldehyde. Co(II), Ni(II), Cu(II) and Zn(II) of the synthesized Schiff bases were prepared by using a molar ratio of ligand:metal as 1:1. The structure of the Schiff bases and synthesized metal complexes were established by ^{1}H NMR, UV–Vis, IR, Mass spectrometry and molar conductivity. The thermal stability of the complexes was study by TGA. Fluorescence quenching mechanism of metal complexes 1–4 show that Zn(II) and Cu(II) complex binds more strongly to BSA. In DFT studies the geometries of Schiff bases and metal complexes were fully optimized with respect to the energy using the 6-31 + g(d,p) basis set. The spectral data shows that the ligands behaves as binegative tridentate. On the basis of the spectral studies, TGA and DFT data an octahedral geometry has been assigned for Co(II), Ni(II), square planar for Cu(II) and tetrahedral for Zn(II) complexes. The anticancer activity were screened against human breast cancer cell line (MCF-7) and human hepatocellular liver carcinoma cell line (Hep-G2). Result indicates that metal complexes shows increase cytotoxicity in proliferation to cell lines as compared to free ligand.

1. Introduction

There is a considerable increase in the use of metal complexes for cancer treatment after the accidental discovery of the biological activity of platinum complex, cisplatin, in 1965 by Rosenburg [1]. In recent years, many studies associated with metal-based drugs show promising biological activity and are of great interest in chemistry and biology [2]. Literature survey revealed that substituted heterocyclic upon reaction with transition metal salts form complexes that show enhanced physiochemical and pharmacological properties [3–6]. Heteroaromatic moiety on combination with a positive charged metal centre leads to complexes that show well defined geometries, which can easily interact with biomolecules [7].

Transition metal complexes of 1,2,4-triazole substituted moiety have acknowledged considerable interest because of their brilliant coordination potential and diverse pharmacological properties, notable for antibacterial, antifungal, antitumor activities [8–12]. A number of commercially available drugs having 1,2,4-triazole moiety like Vorozole, Letrozole and Anastrozole (Fig. 1) are used for the treatment of breast cancer [13]. Other includes, Fluconazole, a very well-known antifungal drug and Trazodone is known for their antidepressant properties (Fig. 1) [14,15].

Similarly, the phenolic aldehyde compound like vanillin is very well known. Valen Schiff bases are well known in literature and represents a class of molecule which show extensive biological properties [16–18]. In contrary, a very little work has been published on Schiff base derived from another isomer of vanillin *i.e.* 2-hydroxy-4-methoxybenzaldeyde [19]. An added advantage of using 2-hydroxy-4-methoxybenzaldehyde over vanillin is the position of —OH group. The —OH group present at the ortho position can easily deprotonate and coordinate with metal centre.

Metals like cobalt, nickel and copper have great affinity for coordination because of their smaller size, higher nuclear charge. To the best of our knowledge no work has been reported on the synthesis of metal complexes of Schiff bases derived from 1,2,4-triazole amine derivatives and 2-hydroxy-4-methoxybenzaldehyde. Two novel Schiff base ligands $\mathbf{H_2L^1}$ and $\mathbf{H_2L^2}$ and their metal complexes were synthesized and characterized by ^{1}H NMR, Mass, IR and analytical data. The synthesized complexes were screened for their *in vitro* anticancer activity against cell line MCF-7 and HepG2.

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2. Experimental

2.1. Materials and methods

All the chemicals were used of Anala R grade and received from Sigma-Aldrich and Fluka. Metal salts were purchased from E. Merck and used as received. MTT (3-(4,5-dimethylthiazole-2-yl)-2,5-diphenyl tetrazolium bromide) and 0.25% trypsin and 0.02% EDTA mixture was purchased from Himedia (India). Fetal bovine serum (FBS) was purchased from Biowest (USA).

2.2. General procedure for the synthesis of ligands H_2L^1–H_2L^2

Intermediate **3a**–**3b** were synthesized from starting compounds (**1a**–**1b**) (Scheme 1) as per the method reported in literature [13–14]. First the hydrazides (**1a**–**1b**) were treated with carbon disulphide and potassium hydroxide in absolute ethanol and are converted to their potassium salts (**2a**–**2b**). On reaction with hydrazine hydrate the potassium salt undergoes ring closure to yield the amine, **3a**–**3b**. For the synthesis of ligand $\mathbf{H_2L^1}$ equimolar quantity (10 mmol) of **3a** and 2-hydroxy-4-methoxybenzaldehyde (10 mmol) were dissolved in 30 ml of acetic acid. The resultant solution was refluxed for 6 h under constant stirring. After completion of the reaction the solution was poured into crushed ice.

The separated product was filtered, washed with ice cold water, and recrystallized with a 1:1 solution of DMF & methanol. Similar method was used for the synthesis of ligand $\mathbf{H_2L^2}$. The structure of the synthesized Schiff bases were supported by ^{1}H NMR, IR and Mass spectra.

2.2.1. 2-(((3-Mercapto-5-(pyridin-4-yl)-4H-1,2,4-triazol-4-yl)imino)methyl)-4-methoxyphenol $\boldsymbol{H_2L^1}$

Yield: 74(%). Color (pale-yellow). M.p. >260 °C. IR (KBr, cm^{-1}): 1598 ν(HC═N), 2704 ν(—SH), 3230 ν(—OH). ^{1}H NMR (DMSO-d_6, δ, ppm) 3.80 (s, 3H, —OCH_3), 6.82–6.83 (m, 2H, Ar—H), 7.81–7.87 (m, 1H, Ar—H), 8.12 (d, 2H, J = 6.92 Hz, Ar—H), 8.75–8.82 (m, 2H, Ar—H), 9.79 (s, 1H, N═CH), 11.57 (s, 1H, —OH), 14.45 (s, 1H, triazole —SH). Anal. Calcd. for $C_{15}H_{13}N_5O_2S$ (327.36): C: 55.04; H: 4.00; N: 21.39; Found: C: 55.0; H: 4.02; N: 21.35%. Mass spectrum (ESI) $[M + H]^+ = 328.01$.

2.2.2. 2-(((3-Mercapto-5-(pyridin-3-yl)-4H-1,2,4-triazol-4-yl)imino)methyl)-4-methoxyphenol $\boldsymbol{H_2L^2}$

Yield: 69(%). Color (yellow). M.p. >260 °C. IR (KBr, cm^{-1}): 1598 ν(HC═N), 2698 ν(−SH), 3213 ν(−OH). ^{1}H NMR (DMSO-d_6, δ, ppm): 3.89 (s, 3H, –OCH_3), 6.72 (d, 1H, J = 7.92 Hz, Ar—H), 6.89–6.93 (m, 1H, Ar —H), 7.89–7.93 (m, 2H, Ar—H), 8.73–8.79 (m, 2H, Ar —H), 9.37 (d, 1H, J = 7.32 Hz, Ar—H), 9.93 (s, 1H, N═CH), 11.69 (s, 1H, —OH), 14.39 (s, 1H, triazole –SH). Anal. Calcd. for $C_{15}H_{13}N_5O_2S$ (327.36): C: 55.04; H: 4.00; N: 21.39; Found: C: 55.12; H: 3.98; N: 21.36%. Mass spectrum (ESI) $[M + H]^+ = 328.13$.

2.3. General procedure for the synthesis of metal complexes 1–8

Schiff base metal(II) complexes (**1**–**4**) of ligand $\mathbf{H_2L^1}$ were synthesized from $\mathbf{H_2L^1}$ (0.34 g, 1 mmol) in (DMF:Methanol in 1:1) (20 ml) with corresponding metal(II) salts {chloride of Co(II) (0.24 g, 1 mmol), Ni(II) (0.24 g, 1 mmol), Cu(II) (0.17 g, 1 mmol) and Zn(II) (0.14 g, 1 mmol)} in methanol (20 ml) in 1:1 ratio (Scheme 1). The solution was refluxed for 10–16 h. The resulting solution was reduced to half volume on a water bath and kept aside overnight. The solid product separated out, which was *vacuum* filtered, washed with cold ethanol, diethyl ether and dried under *vacuum* over anhydrous $CaCl_2$ (Yield: 58–72%). Similarly, Schiff base metal(II) (5–8) complexes of Schiff base $\mathbf{H_2L^2}$ were prepared. Physical, analytical and spectral data of ligands and metal complexes are given in Table 1. Attempt to grow the single crystal of the metal complexes was not successful. To have a understanding of the molecular and electronic structure of the synthesized metal complexes, their DFT study is done. The stability of the proposed geometry is also confirmed by the binding energies values.

2.4. Analysis

The carbon and hydrogen were analyzed on Carlo-Erba 1106 elemental analyzer. The nitrogen content of the complexes was determined using Kjeldahl's method. Molar conductance was measured on the ELICO (CM82T) conductivity bridge. ESI-MS spectra were obtained using a VG Biotech Quattro mass spectrometer equipped with an electrospray ionisation source in the mass range of m/z 100 to m/z 1000. IR spectra (CsBr) were recorded on FTIR BX-II spectrophotometer. NMR spectra were recorded with a model Bruker Advance DPX-300 spectrometer operating at 400 MHz using DMSO-d_6 as a solvent and TMS as internal standard. The electronic spectra were recorded in DMSO on Shimadzu UV mini-1240 spectrophotometer. Thermogravimetric analysis (TGA) was carried out in dynamic nitrogen atmosphere (30 ml/min) with a heating rate of 10 °C/min using a Schimadzu TGA-50H thermal analyzer. EPR spectra of the Cu(II) complexes were recorded as polycrystalline sample at room temperature on E4-EPR spectrometer using the DPPH as the g-marker. Fluorescence spectra was recorded on

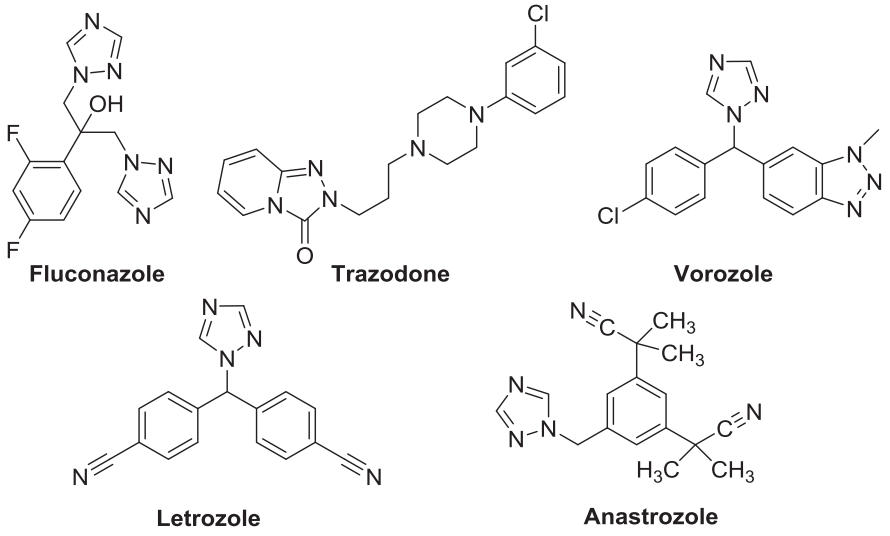

Fig. 1. Some triazole based market available drugs.