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Original article

Synthesis, spectroscopic and biological studies on the new symmetric Schiff base derived from 2,6-diformyl-4-methylphenol with N-aminopyrimidine

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ABSTRACT

A phenol based novel Schiff base polydentate symmetric ligand was prepared. The complexes were prepared by reacting ligand and the metal chlorides of Cu (II), Ni(II), Co(II) and Fe(II) in methanol to get a series of mononuclear complexes. The complexes were characterized by elemental analyses, conductivity measurements, magnetic susceptibility data, IR, UV–Vis, NMR and API-ES mass spectral data. The mononuclear structure of the complexes was confirmed on the basis of elemental analyses, magnetic susceptibility and API-ES mass spectral data. The ligand and all the metal complexes were evaluated for their antimicrobial activity against four Gram-positive bacteria (*Staphylococcus aureus* ATCC 6538, *S. aureus* ATCC 25923, *Bacillus cereus* ATCC 7064 and *Micrococcus luteus* ATCC 9345), one Gram-negative bacterium (*Escherichia coli* ATCC 4230), and three yeast (*Candida albicans* ATCC 14053, *Candida krusei* ATCC 6258 and *Candida parapsilosis* ATCC 22019) strains. Therefore, newly synthesized the ligand and two complexes [(Cu(II) and Co(II)] showed good biological activity against all tested bacteria and yeast strains.

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1. Introduction

2,6-Diformyl-4-methylphenol (dfp) is a well-known molecule in coordination chemistry, being employed as a starting material for the synthesis of various compartmental ligands [1–3]. One of the synthetic approaches for obtaining dissymmetric ligands starts from dfp [4]. Many binuclear metal complexes have been studied extensively. First row transition metal Schiff base complexes of dfp with N_2O_2, NON and NOO coordination sites are well characterized. Though many phenoxo bridged acyclic and macrocyclic complexes of dfp are known [5] but symmetric acyclic metal complexes of Schiff base containing both pyrimidine moieties by condensation of dfp are rare [6]. On the other hand, purines and pyrimidines and their derivatives are known for growth factor analogs and they have been used for treatment of bacterial, viral and fungal infections. In recent years, several studies were reported that metal complexes with Schiff bases are extremely important due to their considerable antifungal, antibacterial and antitumor activities [7–9]. A number of previous studies proposed that pyrimidines and their complexes displayed effective and selective antimicrobial activity against bacteria, fungi and virus [10–12].

In view of these observations, we reported synthesis, characterization and biological activity of a novel acyclic symmetric Schiff base ligand obtained by 2 + 1 condensation of dfp with N-aminopyrimidine and its metal complexes.

2. Chemistry

2.1. Materials

All chemicals used in this study were obtained commercially and used without purification. 1-amino-5-benzoyl-4-phenyl-1*H*-pyrimidine-2-one (*N*-AP) [13] and 2,6-diformyl-4-methylphenol [14] were prepared according to the literature method.

2.2. Physical measurements

The Elemental analyses (C, H, N, S) were performed by using Leco CHNS model 932 elemental analyzer. IR spectra were obtained using KBr pellets (4000–400 cm^{-1}) on Bio-Rad-Win-IR Spectrophotometer. The electronic spectra in the 200–900 nm range were recorded in DMF on Unicam UV2-100 UV–Vis spectrophotometer. Magnetic measurements were carried out by Gouy method using $Hg[Co(SCN)_4]$ as a calibrant. Molar conductance of the Schiff base ligand and its transition metal complexes were determined in DMF

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at room temperature by using Jenway model 4070 conductivitymeter. The ^{1}H NMR and ^{13}C NMR spectra of the Schiff base were carried out using Bruker 300 MHz Ultrashield TM NMR instrument. LC/MS-API-ES mass spectra were recorded with Agilent model 1100 MSD mass spectrophotometer.

2.3. Synthesis of the ligand (HL)

The ligand (HL) was prepared by condensation between *N*-aminopyrimidine and dfp. The hot ethanolic solution (25 mL) of dfp (0.164 g, 1 mmol) and *hot* ethanolic solution (25 m*L)* of *N*-aminopyrimidine (0.582 g, 2 mmol) were mixed slowly with a constant stirring. *Then the* mixture was refluxed *for* 3 h. A yellow precipitate *was* formed. The isolated solid precipitate was filtered off, washed with hot ethanol and diethyl ether and then dried in vacuum over P_2O_5.

(0.462 g, 65%); mp: 273 °C. Anal. Calc. for $C_{43}H_{30}N_6O_5$ (710): C, 72.67; H, 4.25; N, 11.82. Found: C, 72.20; H, 4.36; N, 11.66 %. Selected IR data, (ν, cm^{-1}): 3400 (OH), 1687 (–C═O)$_{pyrimidine}$ 1652 (Ph-CO-), 1608 (HC═N); ^{1}H NMR (d6-DMSO, ppm), δ 11.33 (s, 1H, OH), 9.54 (s, 1H, HC═N), 8.85 (s, 1H, C(6)H, 7.31–7.88 (m, 7H, Harm); 2.35 (s, 3H, CH_3); ^{13}C NMR (d6-DMSO, ppm), δ 192.06 (OC-Ar), 179.31 (C═O, pyrimidine), 163.64 (–C6, pyrimidine ring), 157.38 (HC═N), 151.54-116.20 (C, aromatic), 20.22 (CH_3). UV–Vis (in DMF, nm): 276, 302, 347, 363, 396, 483, 549. LC-MS, m/z 711.1 [M + 1].

2.4. Synthesis of the complexes (**1–4**)

0.5 mmol (0.355 g) of the ligand HL was dissolved *in chloroform* and methanol mixture (50 mL; 1:1, v/v) and a solution of 0.5 mmol of $MCl_2 \cdot nH_2O$ in 15 mL methanol was added drop-wise with continuous stirring. The mixture was stirred for 1 h at 60 °C. The precipitated compound was removed by filtration, washed with diethyl ether and cold methanol and dried in vacuum desiccators. The complexes $[CuLCl] \cdot 2H_2O$, $[FeLCl] \cdot 5H_2O$, $[CoL_2] \cdot 4H_2O$ and $[NiL_2] \cdot 2H_2O$ were synthesized by following the above procedure using $CuCl_2 \cdot 2H_2O$ (0.5 mmol, 0.085 g), $FeCl_2 \cdot 4H_2O$ (0.5 mmol, 0.100 g), $CoCl_2 \cdot 6H_2O$ (0.5 mmol, 0.120 g), $NiCl_2 \cdot 6H_2O$ (0.5 mmol, 0.120 g).

2.4.1. Synthesis of $[CuLCl] \cdot 2H_2O$ complex

Cu(II) complex was synthesized according to the procedure as given. Pale green color compound. Yield: 0.290 g (69%); mp: 300 °C. Anal. Calc. for $C_{43}H_{33}ClCuN_6O_7$ (843.93): C, 65.75; H, 4.48; N, 10.46. Found: C, 66.10; H, 4.52; N, 10.40 %. Selected IR data (ν, cm^{-1}): 3332–3400 ν(OH/H_2O), 1659 ν(Ph-CO), 1618 ν(HC═N). μ_{eff}: 1.57 BM. Λ_M (10^{-3} M, in DMF, S cm^2 mol^{-1}): 37. UV–Vis (in DMF, nm): 261, 279, 291, 350, 448, 617. API-ES, m/z: 845.0 [M + $2H_2O$ + 1] (^{64}Cu isotope).

2.4.2. Synthesis of $[FeLCl] \cdot 5H_2O$ complex

Fe(II) complex was synthesized according to the procedure as given. Light brown color compound. Yield: 0.190 g (43%); mp: 225 °C. Anal. Calc. for $C_{43}H_{39}ClFeN_6O_{10}$ (890): C, 57.96; H, 4.41; N, 9.43. Found: C, 58.57; H, 3.93; N, 9.31 %. Selected IR data (ν, cm^{-1}), 3340 ν(OH/H_2O), 1657 ν(Ph-CO), 1617 ν(HC═N). μ_{eff}: 4.60 BM. Λ_M (10^{-3} M, in DMF, S cm^2 mol^{-1}): 46. UV–Vis (in DMF, nm): 236, 285, 330, 372, 407, 526, 652. API-ES, *m/z*: 889 $[M + 5H_2O]^+$ (^{57}Fe isotope).

2.4.3. Synthesis of $[NiL_2] \cdot 2H_2O$ complex

Ni(II) complex was synthesized according to the procedure as given. Red color compound. Yield: 0.997 g (66 %); mp: 145 °C decompose. Anal. Calc. for $C_{86}H_{62}N_{12}NiO_{12}$ (1512.7): C, 68.22; H, 4.10; N, 11.10. Found: C, 68.39; H, 4.34; N, 11.00 %. Selected IR data (ν, cm^{-1}): 3390 ν(OH/H_2O), 1657 ν(Ph-CO), 1602 ν(C═N). μ_{eff}: 1.59 BM. Λ_M (10^{-3} M, in DMF, S cm^2 mol^{-1}): 10.9. UV–Vis (in DMF, nm): 277, 298, 340, 379, 474, 674. API-ES, *m/z*: 1514 [M + $2H_2O$ + 1] (^{58}Ni isotope).

2.4.4. Synthesis of $[CoL_2] \cdot 4H_2O$ complex

Co(II) complex was synthesized according to the procedure as given. Red-brown color compound. Yield: 0.880 g (57%); mp: 186 °C decompose. Anal. Calc. for $C_{86}H_{66}CoN_{12}O_{14}$ (1549): C, 66.62; H, 4.26; N, 10.84. Found: C, 66.27; H, 4.32; N, 10.52. %. Selected IR data (ν, cm^{-1}): 3320 (OH/H_2O), 1654 ν(Ph-CO), 1618 ν(C═N). μ_{eff}:: 3.35 BM. Λ_M (10^{-3} M, in DMF, S cm^2 mol^{-1}): 7.5. UV–Vis (in DMF, nm): 203, 281, 356, 464, 677. API-ES, *m/z*: 1550 [M + $4H_2O$ + 1] (^{59}Co isotope).

3. Biological assay

3.1. Compounds

Test compounds were dissolved in DMSO (12.5%) at an initial concentration 1280 $\mu g\,mL^{-1}$ and then were serially diluted in culture medium.

3.2. Cells

Bacterial strains were supplied from American Types Culture Collection. *Candida* strains were obtained from Refik Saydam Hifsisihha Research Institute, Ankara, Turkey.

3.3. Antibacterial assay

Newly synthesized compounds were screened for their antibacterial activity against four Gram-positive (*Staphylococcus aureus* ATCC 6538, *S. aureus* ATCC 25923, *Bacillus cereus* ATCC 7064 and *Micrococcus luteus* ATCC 9345) and one Gram-negative (*Escherichia coli* ATCC 4230) bacteria as described by the guidelines in NCCLS approved standard document M7-A4 using the microdilution broth procedure [15]. Ampicillin trihydrate was used as reference antibacterial agent. Solutions of the compounds and reference drug were dissolved in DMSO at a concentration of 2560 $\mu g\,mL^{-1}$. The two-fold dilution of compounds and reference drug were prepared (1280, 640, 320, 160, 80, 40, 20, 10, $5 > \mu g\,mL^{-1}$). Antibacterial activities of the new synthesized compounds were performed in Mueller-Hinton broth (Difco) medium at pH 7.2 with an inoculum of $(1–2) \times 10^3$ cells mL^{-1} by spectrophotometric method and an aliquot of 100 µL was added to each tube of serial dilution. The chemical compounds-broth medium serial tube dilutions inoculated with each bacterium were incubated on a rotary shaker at 37 °C for 18 h at 150 rpm. The minimum inhibitory concentrations (MICs) of each chemical compounds were recorded as the lowest concentration of each chemical compounds in the tubes with no growth (i.e. no turbidity) of inoculated bacteria.

3.4. Antifungal assay

The antifungal activities of newly synthesized compounds were tested against three yeast (*Candida albicans* ATCC 14053, *C. krusei* ATCC 6258 and *C. parapsilosis* ATCC 22019) strains according to the guidelines in NCCLS approved standard document M27-A2 using the microdilution broth procedure [16]. Fluconazole was used as reference antifungal agent. Solution of the test compounds and reference drug were dissolved in DMSO at a concentration of 2560 $\mu g\,mL^{-1}$. The two-fold dilution of the compounds and reference drug were prepared (1280, 640, 320, 160, 80, 40, 20, 10,

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