

Synthesis, Characterization and Antimicrobial Screening of Ni(II), Cu(II) and Co(II) Complexes of Some Schiff Base Ligands Derived from 5-Aminouracil

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ABSTRACT

The synthesis, spectroscopic and biological activity studies of Ni(II), Cu(II) and Co(II) complexes of Schiff base ligands derived from 5-aminouracil, 2-hydroxy-1-naphthaldehyde, 2,4-dihydroxybenzaldehyde and salicylaldehyde are reported. In all cases, the complexes appear to be monomeric. The ligands coordinate in bidentate fashion to Ni(II) and Co(II) but in a tridentate fashion to Cu(II) by coordinating to the carbonyl oxygen atom in the 4th position of uracil ring. The biological activities of the Schiff bases and metal complexes have been tested *in vitro* against a number of bacteria and a fungus. Ni(II) complexes derived from the salicylaldehyde Schiff base ligand showed good antimicrobial activity whereas a Co(II) complex derived from the same ligand showed good anticandidal activity.

Key Words: 5-aminouracil, Schiff base, biological activity.

1. INTRODUCTION

Schiff base ligands are considered “privileged ligands” because they are easily prepared by the condensation between aldehydes and amines. Schiff base ligands are able to coordinate many different metals [1,2] and to stabilize them in various oxidation states. Structure-activity relationship of Schiff base compounds are studied due to their antitumor, antimicrobial and antiviral activities [3-5]. In recent years, because of new interesting applications found in the field of pesticides and medicine, the metal complexes with tridentate O, N, N types of alternative structures have attracted the attention of chemist. Various metal complexes with bi- and tridentate Schiff bases containing nitrogen and oxygen donor atoms play important role in biological systems [6-8]. Schiff base complexes incorporating phenolic group as chelating moieties in the ligand are considered as models for executing important biological reactions and mimic the catalytic activities of metalloenzymes [9].

In the present paper, 5-aminouracil has been selected for use as the amine moiety in the preparation of Schiff base ligands. This is because it has a close structural relationship with naturally-occurring nucleobases and so the products can be expected to be of interest from a biological point of view. For example, certain naturally occurring uracil derivatives are known to participate in an intracellular mechanism regulating pyrimidine, while a number of synthetic 5-substituted uracil derivatives are of value as chemotherapeutic agents [10, 11]. The synthesis, spectroscopic and biological studies of Co(II), Ni(II), Cu(II), Zn(II), Cd(II), Au(III) and Hg(II) complexes of the Schiff base derived from the 1:2 condensation of 2,6-diformyl-4-methylphenol and 5-aminouracil were reported by Huesco-Urena et. al.[12] (Figure 1). The Schiff base complexes have been reported to show significant growth inhibitory activity against *Aspergillus niger*, *Candida albicans*, *Pseudomonas aurenosa* and *Bacillus cirroflagellosus*.

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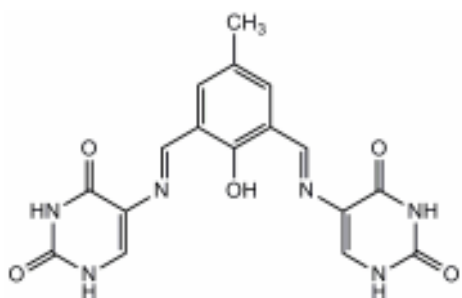


Figure 1. Schiff base ligand of 5-aminouracil reported by Huesco-Urena et. al.

In order to further understand the chemistry and biological activity of uracil containing Schiff bases, we synthesized a series of Schiff base ligands and their novel metal complexes with Ni(II), Cu(II) and Co(II) metal ions and screened their antimicrobial and antifungal activities.

2. EXPERIMENTAL

All the reagents used were chemically pure grade. All the solvents were distilled before use. ^1H NMR and ^{13}C NMR spectra were carried out using a 400 MHz Varian NMR spectrometer. IR spectra were recorded using a Mattson FTIR 1000 spectrometer. Melting points were recorded with an electro thermal digital melting point apparatus.

2.1. Synthesis of Schiff Bases

Schiff base reactions were performed in refluxing ethanol. 5-aminouracil (0.074g, 0.58 mmol) and the appropriate aldehyde (0.58 mmol) in the required mole ratios were placed in a flask with 20 ml ethanol and a few drops of glacial acetic acid. This mixture was refluxed for several hours. Then the precipitate was filtered off, washed with hot ethanol and ether and air dried.

5-[(1E)-(2-hydroxy-1-naptyl)methylene]amino]pyrimidine-2,4-(1H,3H)-dione(1)

Orange solid. Yield 87%. IR (KBr) 1623 (-CH=N), 1715-1661 (C=O) cm^{-1} ; ^1H NMR (DMSO) δ (ppm) 6.9 (d, J=2 Hz, 1H), 7.3-7.5 (t, 1H), 7.7-7.8 (d, 1H), 8.3 (d, 1H), 8.1 (s, 1H), 8.2 (d, J=2Hz, 1H), 9.8(s, 1H), 11.3-11.5 (bs, 2H). ^{13}C NMR (DMSO) 109.57, 119.75, 120.74, 122.11, 124.03, 127.52, 128.58, 129.67, 133.50, 133.82, 136.25, 150.90, 155.56, 161.61, 168.08. UV-Vis (DMSO) λ (nm) 269, 331, 379. Anal. Calcd for $\text{C}_{15}\text{H}_{11}\text{N}_3\text{O}_3$: C, 64.05; H, 3.97; N, 14.93. Found: C, 65.33; H, 4.02; N, 14.33.

5-[(1E)-(2,4-dihydroxyphenyl)methylene]amino]pyrimidine-2,4-(1H,3H)-dione (2)

Yellow solid. Yield 86%. IR (KBr) 1622 (-CH=N), 1715-1646 (C=O) cm^{-1} . ^1H NMR (DMSO) δ (ppm) 6.28 (s, J=2Hz, 1H), 6.3 (dd, J=8.1Hz, 1H), 7.4 (d, J=8.1Hz, 1H), 7.7 (s, 1H), 9.2 (s, 1H), 10-11 (bs, 2H), 11-13 (s, 2H). ^{13}C NMR (DMSO) 103.15, 108.29, 112.92, 121.53, 134.37, 135.19, 150.84, 161.95, 162.47, 163.06. UV-Vis (DMSO) λ (nm) 346. Anal. Calcd. for $\text{C}_{11}\text{H}_9\text{N}_3\text{O}_4$: C, 57.13; H, 3.92; N, 18.17. Found: C, 58.10; H, 4.02; N, 17.53.

5-[(2-hydroxybenzylidene)amino]pyrimidine-2,4(1H,3H)-dione (3)

Yellow solid. Yield 88%. IR (KBr) 1631 (-CH=N), 1677-1715 (C=O) cm^{-1} . ^1H NMR (DMSO) δ (ppm) 6.88 (d, J=8.2Hz, 1H), 6.90 (t, J=7.4Hz, 1H), 7.32 (td, J=7.8Hz, 1H), 7.46 (dd, J=7.8Hz, 1H), 7.57 (s, 1H), 7.83 (s, 1H), 9.29 (s, 1H), 11.08 (bs, 2H). ^{13}C NMR (DMSO) 117.24, 119.71, 120.36, 120.95, 132.52, 133.11, 137.45, 150.79, 160.48, 161.83, 161.91. UV-Vis (DMSO) λ (nm) 283, 345, 415. Anal. Calcd for $\text{C}_{11}\text{H}_9\text{N}_3\text{O}_3$: C, 57.15; H, 3.92; N, 18.17. Found: C, 56.89; H, 4.08; N, 17.62.

2.2. Synthesis of Complexes

Preparation of complex 4 from Schiff Base 1 and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$

A solution of $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (0.011g, 0.053 mmol) in MeOH (15 ml) was added to a suspension of the Schiff base 1 (0.015 g, 0.053 mmol) in DMF. The mixture was stirred and heated at 70°C for 5 hours. The precipitated complex was filtered and washed with cold DMF and MeOH, then air dried to afford a dark yellow solid (0.011g, 48%). IR (KBr) 1607 (-CH=N), 1661 (C=O) cm^{-1} . UV-Vis (DMSO) λ (nm) 282, 346, 445, 468. Anal. Calcd for $\text{C}_{17}\text{H}_{15}\text{CuN}_3\text{O}_6$: C, 48.51; H, 3.59; N, 9.98. Found: C, 48.83; H, 3.56; N, 10.35.

Preparation of complex 5 from Schiff Base 1 and $\text{Cu}(\text{Cl})_2 \cdot 2\text{H}_2\text{O}$

A solution of KOH (0.016 g, 0.281 mmol) in MeOH (10 ml) was added to a solution of Schiff base 1 (0.02 mg, 0.071 mmol) in DMF (10 ml) then a solution of $\text{CuCl}_2 \cdot \text{H}_2\text{O}$ (0.009 g, 0.071 mmol) in MeOH (10ml) was added. The mixture was stirred and heated at 60°C for 1 hour. The precipitated complex was filtered and washed with MeOH, then air dried to afford a dark blue solid (0.021g, 90%). IR(KBr) 1607 (-CH=N), 1661 (C=O) cm^{-1} . UV-Vis (DMSO) λ (nm) 259, 335, 435, 473. Anal. Calcd for $\text{C}_{15}\text{H}_{12}\text{CuClN}_3\text{O}_4$: C, 45.35; H, 3.04; N, 10.57. Found: C, 45.87; H, 2.40; N, 10.34.

Preparation of complex 6 from Schiff Base 2 and $\text{Ni}(\text{Cl})_2 \cdot 6\text{H}_2\text{O}$

The procedure was the same as described above for the preparation of complex 5. A green solid was obtained in 57% yield. IR (KBr) 1607 (-CH=N), 1715, 1646 (C=O) cm^{-1} . UV-Vis (DMSO) λ (nm) 265, 331, 435. Anal. Calcd for $\text{C}_{11}\text{H}_{14}\text{ClNiN}_3\text{O}_7$: C, 33.49; H, 3.57; N, 10.65. Found: C, 32.66; H, 3.14; N, 9.44.

Preparation of complex 7 from Schiff Base 3 and $\text{Ni}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$

The procedure was the same as described above for the preparation of complex 4. A green solid was obtained in 88% yield. IR (KBr) 1615 (-CH=N), 1669, 1708 (C=O) cm^{-1} . UV-Vis(DMSO) λ (nm) 290, 325, 465. Anal. Calcd for $\text{C}_{13}\text{H}_{17}\text{NiN}_3\text{O}_8$: C, 38.84; H, 4.20; N, 10.45. Found: C, 39.07; H, 3.97; N, 11.13.

Preparation of complex 8 from Schiff Base 3 and $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$

The procedure was the same as described above for the preparation of complex 5. A green solid was obtained in 67% yield. IR (KBr) 1608 (-CH=N), 1646, 1708 (C=O)

cm^{-1} . UV-Vis(DMSO) $\lambda(\text{nm})$ 307, 343, 440. Anal. Calcd for $\text{C}_{11}\text{H}_{14}\text{NiN}_3\text{O}_6\text{Cl}$: C, 34.92; H, 3.73; N, 11.11. Found: C, 34.93; H, 4.19; N, 10.25.

Preparation of complex 9 from Schiff Base 3 and $\text{Co}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$

The preparation was the same as described above for the Schiff base 3 with $\text{Ni}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$. An orange solid was obtained in 59% yield. IR (KBr) 1608 (-CH=N), 1662, 1715 (-C=O) cm^{-1} . UV-Vis(DMSO) $\lambda(\text{nm})$ 293, 343, 439. Anal. Calcd for $\text{C}_{13}\text{H}_{17}\text{CoN}_3\text{O}_8$: C, 38.82; H, 4.30; N, 10.45. Found: C, 38.29; H, 3.18; N, 11.09.

Preparation of complex 10 from Schiff Base 3 and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$

The preparation was the same as described above for the preparation of complex 4. A green solid was obtained in 76% yield. IR(KBr) 1608 (-CH=N), 1669 (-C=O) cm^{-1} . UV-Vis(DMSO) $\lambda(\text{nm})$ 305, 340, 450. Anal. Calcd for $\text{C}_{13}\text{H}_{13}\text{CuN}_3\text{O}_6$: C, 42.11 ; H, 3.53; N, 11.33. Found: C, 42.23 ; H, 3.06 ; N, 13.20.

2.3. Antimicrobial activity

The antimicrobial activity of the newly synthesized compounds was evaluated *in vitro* against an assortment of two Gram-positive and three Gram-negative bacteria, and one fungus. Gentamycin and clotrimazole were used as standard antibacterial and antifungal agents respectively. All test microorganisms were obtained from Ege University Faculty of Science, Basic and Industrial Microbiology Department, Izmir-Turkey. Test organisms included: *Staphylococcus aureus* ATCC6538-P and *Bacillus subtilis* ATCC 6633 as Gram-positive bacteria, *Salmonella typhimurium* CCM 5445, *Escherichia coli* ATCC 12228 and *Proteus vulgaris* AATC6897. as Gram-negative bacteria and *Candida albicans* ATCC 10239 as yeast-like fungus. The bacteria were grown in nutrient agar (Oxoid) at 37°C and maintained on nutrient agar slants at 4°C. *Candida albicans* was grown at 37 °C and maintained on Sabouraud-dextrose agar slants at 4°C (Oxoid).

The minimum inhibitory concentrations (MICs) of compounds and reference antibiotics were determined by microdilution techniques in Mueller-Hinton broth (Oxoid) for bacteria and Sabouraud-dextrose Broth (Oxoid) for fungus. Briefly, all compounds were first

dissolved at a concentration of 25 mM in DMSO. Reference antibiotics were initially tested using a concentration of 0.40 mg/ml for gentamycin in distilled water and 0.50 mg/ml for clotrimazole in ethanol. Then two-fold dilutions of each compound were performed. Inocula for assays were prepared from activated cultures in broth media by dilution in growth medium to give a final viable cell count of $4.0\text{-}5.5 \times 10^5$ CFU/ml. Each compound solution (25 μl) and inoculum of microorganism (25 μl) was added into each well of a flat-bottom, 96-well microtiter plate pre-filled with 200 μl of medium to give a total volume of 250 μl . Microtiter plates were incubated at 37 °C for 24 h for bacteria and 48–72 h for *C. albicans*. The solvents, DMSO and ethanol, were used as a negative control for all experiments. After incubation, MIC values were determined by adding 50 μl of 0.5% TTC (Triphenyl tetrazolium chloride, Merck) aqueous solution [13]. MIC was defined as the lowest concentration of extract that inhibited visible growth as indicated by TTC reduction. In the presence of bacterial growth by reduction reactions, TTC changes the color of microbial cells from colorless to red. This provided clearly defined and easily readable endpoints. All tests were repeated three times to confirm the results.

3. RESULTS AND DISCUSSION

The preparative method used to prepare the Schiff base ligands can be seen in Scheme 1 and the ligands are shown in Figure 2. The products were obtained by refluxing a mixture of 5-aminouracil and aldehyde for several hours in ethanol, and then filtering off the solid that was remaining when reaction was completed. All three Schiff bases were obtained in good yields. The Schiff bases, similar to 5-aminouracil, were found to be sparingly soluble in common organic solvents such as dichloromethane, methanol, ethanol and diethyl ether.

The obtained Schiff base ligands were then reacted with metal salts to give the corresponding complexes. First, the Schiff base ligands were suspended in DMF, and then a solution of the appropriate metal salt in methanol was added at 60°C to the reaction mixture. In some cases, KOH (1 equivalent) was also added to the reaction and it was stirred for several hours. Ni(II)

Table 1. Analytical data for Schiff base metal complexes

Complex No	Ar	MX ₂	Complex	Yield (%)	Found (calc. %) for the complex		
					C	H	N
4	2-hydroxynaphthaldehyde	Cu(OAc) ₂ .H ₂ O	Cu(L)OAc.H ₂ O	49	48.83(48.51)	3.56(3.59)	10.35(9.98)
5	2-hydroxynaphthaldehyde	CuCl ₂ .2H ₂ O	Cu(L)Cl.H ₂ O	90	45.87(45.35)	2.40(3.04)	10.34(10.57)
6	2,4-dihydroxybenzaldehyde	NiCl ₂ .6H ₂ O	Ni(L)Cl.3H ₂ O	60	32.66(33.49)	3.14(3.57)	9.44(10.65)
7	salicylaldehyde	Ni(OAc) ₂ .4H ₂ O	Ni(L)(OAc).3H ₂ O	88	39.07(38.84)	3.97(4.20)	11.13(10.45)
8	salicylaldehyde	NiCl ₂ .6H ₂ O	Ni(L)Cl.3H ₂ O	67	34.93(34.92)	4.19(3.73)	10.25(11.11)
9	salicylaldehyde	Co(OAc) ₂ .4H ₂ O	Co(L)OAc.3H ₂ O	59	38.29(38.82)	3.18(4.30)	11.09(10.45)
10	salicylaldehyde	Cu(OAc) ₂ .H ₂ O	Cu(L)OAc.H ₂ O	76	42.23(42.11)	3.06(3.53)	13.20(11.33)

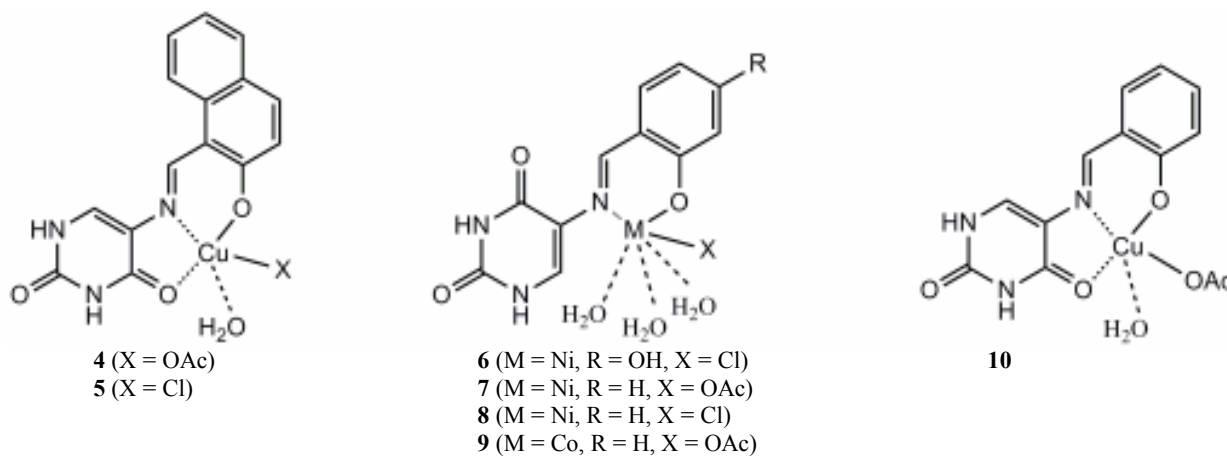


Figure 3. Proposed structures of the metal complexes

3.1. Antimicrobial Analysis Results

The evaluation of the activity of the Schiff base ligands and their metal complexes against both gram positive and gram negative bacteria and *Candida albicans*, yeast like fungus, using the micro dilution technique are given in Table 2. Of these 10 compounds tested, the naphthaldehyde free Schiff base **1** and the Ni(II) complexes derived from the salicylaldehyde Schiff base, **7** and **8** showed *in vitro* a good antimicrobial activity with MIC values of 6.25 - 0,312 mM against all microorganisms tested. The similar activity of complexes **7** and **8** appears to indicate that the nature of the counter ion ($X = OAc^-$ or Cl^- respectively) is not important. For

the three acetate-containing salicylaldehyde derived Schiff base metal complexes (**7**, $M=Ni$; **9**, $M=Co$; **10**, $M=Cu$), better biological activity was observed for the Ni(II) and Co(II) complexes than the Cu(II) complex. This suggests that complexation of the metal to a uracil ring carbonyl oxygen may be detrimental to the biological activity of the complex. MIC values of compounds showing anticandidal activity ranged from 6.25 mM to 0.19 mM. The most active compounds were free Schiff base **1** and the Co complex derived from the salicylaldehyde Schiff base, **9**. This finding suggests that **1** and **9** could be potential anticandidal agents. However, compound **6** which displayed a MIC value greater than 6.25 mM is considered to be inactive.

Table 2. Antimicrobial activities of Schiff bases and the complexes

Minimum inhibitory concentration (MIC ,mM)	Bacillus cereus CCM 99	Proteus vulgaris ATCC 6897	Escherichia coli ATCC 12228	Staphylococcus aureus ATCC 6538-P	Salmonella thyphimirium CCM 5445	Candida albicans ATCC 10239
1	1.56	3.12	0.39	3.12	1.56	0.39
2	3.12	3.12	3.12	-	6.25	1.56
3	-	6.25	-	-	6.25	1.25
4	6.25	6.25	6.25	-	-	1.56
5	-	6.25	-	-	-	6.25
6	6.25	3.12	6.25	-	3.12	-
7	3.12	6.25	3.12	3.12	3.12	1.56
8	6.25	6.25	3.12	6.25	6.25	3.12
9	0.78	3.12	3.12	-	3.12	0.19
10	6.25	3.12	6.25	-	-	3.12
Gentamycin(μ g/ml)*	1.25	1.25	1.25	1.25	1.25	n.t
Clotrimazole(μ g/ml)*	n.t	n.t	n.t	n.t	n.t	0,78

n.t: not tested

*reference antibiotic

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