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New Biologically Active Transition Metal Complexes Of 2-Mercapto-4,6-Diamino-5-Hydroxypyrimidine

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ABSTRACT

The reaction of 2-mercapto-4,6-diamino-5-hydroxypyrimidine(HMDAHP) with Fe(III), Ni(II), Ag(I),$[Ru^{II}(PPh_3)_3Cl_2]$ and$[Ag^{I}(phen)(H_2O)(NO_3)]$ is described. IR, ^1H NMR and mass spectra, conductivity, magnetic and thermal measurements of the complexes reported and their structures discussed. In all complexes, HMDAHP behaves as a bidentate forming four-membered cyclic nitrogen-sulfur chelate without any participation of the pendant amino or hydroxy groups in complexation. The biological activity of Ag(I) complexes against bacteria(*S.aureus* and *P.aeruginosa*) and fungi(*A.niger* and *C. albicans*) was also discussed.

KEYWORDS

HMDAHP;
Complexes;
Spectra;
Bacteria;
Fungi

INTRODUCTION

The coordination chemistry of sulphur derivatives of nucleic bases has received sporadic attention due to their interest in metal-based drugs[1]. Many studies reported that 2-mercaptopyrimidine and 4-amino-2-mercaptopyrimidine are similar to 2-mercaptopy rimidine in nucleotides[2-4]. Furthermore, they are able to inhibit the synthesis of *t*RNA[5] and act as valuable substrates in the synthesis of antibacterial, antifungal and antitumour chemothera peutic agents[6-8]. The coordination chemistry of 4-amino-2-mercaptopy rimidine has been explored with a number of transition metals[9-13]. In addition, substituted 2-mercapto pyrimidines have N-C-S moiety offer the possibility of forming homo- or hetero-binuclear complexes[14]. The weak acid substituted 2-mercap topyrimidine exists in two tautomeric(thione and thiol) forms. The thione form is thought to be predominant as the spectral data confirm[14,15].

We have reported the interaction of 5,6-diamino-2,4-dihydroxypyrimidine with some transition metal ions[16]. The complexes obtained from the reaction of 2-mercapto-4,6-diamino-5-hydroxypyrimidine (HMDAHP) with Fe(III), Ni(II), Ru(II) and Ag(I) are discussed below. Also, the Ag(I) complexes have been tested as growth inhibitors against bacteria (*S.aureus* and *P.aeruginosa*) and fungi(*A.niger* and *C.albicans*) microorganisms.

EXPERIMENTAL

Materials and methods

All manipulations were performed under aerobic conditions using 2-mercapto-4,6-diamino-5-hydroxy pyrimidine(HMDAHP) and all other reagents(Merck) as received.$[Ru(PPh_3)_3Cl_2]$ was prepared by the literature method[17].

Synthesis of complexes

$[Fe(MDAHP)_3]\cdot 4H_2O$

A suspension of HMDAHP(0.24g, 1.5mmol) in 0.1m NaOH(15cm^3) was mixed with $Fe(NO_3)_3.9H_2O$ (0.202g, 0.5mmol). The reaction mixture was warmed and stirred for 3h and a purple complex was isolated. It was filtered off, washed with methanol, diethyl ether and dried in vacuo. Conductivity data(10^{-3}m in DMSO): Λ_M=11.0ohm^{-1} cm^2 mol^{-1}. Elemental Anal. Calc. for $C_{12}H_{23}N_{12}O_7S_3Fe$: C, 24.05; H, 3.85; N, 28.05; S, 16.03. Found C, 24.22; H, 3.88; N, 28.12; S, 15.98.

$[Ni(MDAHP)_2(H_2O)_2]\cdot 2H_2O$

Hydrated nickel chloride(0.12g, 0.5mmol) was added to a suspension of HMDAHP(0.12g, 0.75 mmol) in ethanol. The reaction mixture was stirred and heated under reflux for 5h. The brown precipitate was filtered off during hot, washed with ethanol, diethyl ether and dried in vacuo. Conductivity data(10^{-3}m in DMSO): Λ_M=3.0ohm^{-1}cm^2 mol^{-1}. Elemental Anal.Calc.for $C_8H_{18}N_8O_6S_2Ni$: C, 21.59; H, 4.05; N, 25.17; S, 14.38. Found C, 21.50; H, 4.10; N, 25.06; S, 14.31.

$[Ru(PPh_3)_2(HMDAHP)Cl_2]$

The complex$[Ru(PPh_3)_3Cl_2]$(0.25g, 0.25mmol) was added to methanolic solutions of HMDAHP (0.063g, 0.4mmol) and Et_3N(0.05cm^3, 0.03mmol) was added to the reaction mixture. The mixture was refluxed for 2.5h during which shiny blue micro crystals were isolated, washed with methanol, diethyl ether and dried in vacuo. Conductivity data(10^{-3}m in DMSO): Λ_M=9.0ohm^{-1} cm^{2}mol^{-1}. Elemental Anal. Calc. for $C_{40}Cl_2H_{36}N_4OSP_2Ru$: C, 56.20; H, 4.21; N, 6.56; S, 3.75; Cl, 8.31. Found C, 55.71; H, 4.32; N, 6.39; S, 3.45; Cl, 8.20.

$[Ag(HMDAHP)_2]NO_3$

Silver nitrate(0.087g, 0.5mmol) in water(2cm^3) was added to HMDAHP(0.16g, 1mmol) in ethanol. The reaction mixture was stirred and warmed at 40^0 in the dark for 5h to produce a pale red-brown solid. It was filtered off, washed with little water, methanol, diethyl ether and dried in vacuo. Conductivity data (10^{-3}m in DMF): Λ_M=55.0ohm^{-1} cm^2 mol^{-1}. Elemental Anal. Calc. for $C_8H_{12}N_9O_5S_2Ag$: C,19.76; H, 2.47; N, 25.93; S, 13.17. Found C, 19.65; H, 2.56; N, 25.37; S, 13.05.

$[Ag(phen)(HMDAHP)]NO_3$

Silver nitrate(0.087g, 0.5mmol) in water(2cm^3) was added to phen(0.09g, 0.5mmol) inmethanol (35cm^3) to produce a colourless solution of$[Ag(phen)(H_2O)(NO_3)]$, to which HMDAHP(0.08g, 0.5mmol) was added. The reaction mixture was stirred in dark for 3h to produce a pale brown solid. It was filtered off, washed with little water, methanol, diethyl ether and dried in vacuo. Conductivity data(10^{-3}m in DMF): Λ_M=52.0ohm^{-1} cm^2 mol^{-1}. Elemental Anal. Calc. for $C_{16}H_{14}N_7O_4SAg$: C, 37.80; H, 2.76; N, 19.29; S, 6.30. Found C, 37.54; H, 2.86; N, 18.96; S, 6.24.

Instrumentations

Microanalyses were determined by the micro analytical unit of the chemistry department, Ioannina university, Greece. Magnetic moments at 25^{0}C were recorded using a Johnson Matthey magnetic susceptibility balance with $Hg[Co(SCN)_4]$ as calibrant. Electronic spectra were recorded using a Unicam $UV_{2\text{-}100}$ U.V.-vis. Spectrometer. IR spectra were measured as KBr discs on a Matson 5000 FT-IR spectrometer. ^{1}H NMR spectra were measured on a Varian Gemini WM-200 spectrometer(Laser centre, cairo university). Thermal analysis measurements were made in the 20-00^{0}C arnge at the heating rate of 10^{0}C in^{-1}, using α-Al_2O_3 as a reference, on a shimadzu thermogravimetric analyzer TGA-50. Conductometric measurements were carried out at room temperature on a YSI model 32 conductivity bridge. Mass spectra were recorded on a Matson MS 5988 spectrometer. Antimicrobial measurements were carried out in The microbiology department (Micro analytical unit, cairo university).

Anti-microbial activity

The bacterial strains(*S.aureus* and *P.aeruginosa*) were grown in nutrient agar slants and the fungal strains(*A.niger* and *C.albicans*) were grown in sabouraud dextrose agar slants. The viable bacterial cells were

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TABLE 1: Spectral data of HMDAHP and its complexes

Complexes	ν(OH)	ν^{s}(NH$_2$)	IR spectral ν^{as}(NH$_2$)	data δ(NH)	ν(C=C) ν(C=N)	ν(NCS)	ν(CN), ν(NCS), ν(CS)	ν(M-O)	ν(M-N)
[Fe(MDAHP)$_3$].4H$_2$O	--	3390 3360	3175	1632	1563	1462	1376 1266 1169	530	413
[Ni(MDAHP)$_2$(H$_2$O)$_2$].2H$_2$O	--	3390 3355	3165	1630	1564	1457	1377 1250 1160	512	432
[Ru(PPh$_3$)$_2$(HMDAHP)Cl$_2$]	3308	3399	3178	1650	1555	1484	1389 1288 1210	-- 390[a]	420 340[b] 290[b]
[Ag(HMDAHP)$_2$]NO$_3$	3307	3398	3170	1645	1544	1487	1380 1285 1198	--	390[a]
[Ag(phen)(HMDAHP)]NO$_3$	3308	3396	3171	1650	1543	1479	1396 1277 1207	--	372[a]

[a]ν(M-S), [b]ν(Ru-Cl)

swabbed onto nutrient agar plates while the fungal spores onto sabouraud dextrose agar plates. HMDAHP was dissolved in dimethylsulfoxide while[Ag (HMDAHP)$_2$]$^+$ and[Ag(phen) (HMDAHP)]$^+$ in water with 10, 20, 50 and 100mg/ml concentrations. The baterial and fungal plated were incubated for 36 and 72h, respectively, and the activity of the compounds was detected by measuring the diameter of the inhibition zone around the respective zoon[18].

RESULTS AND DISCUSSION

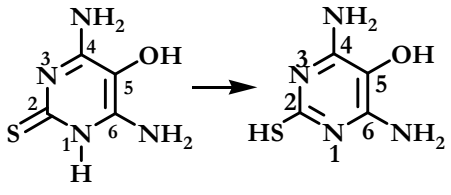
TABLE 1 lists new complexes of 2-mercapto-4,6-diamino-5-hydroxypyrimidine(HMDAHP). The elemental analyses of the isolated complexes, listed in the experimental section, agree with the assigned formulae. The molar conductivities(Λ_M) in DMF or DMSO at room temperature showed non-electrolytic character of the reported complexes except[Ag (HMDAHP)$_2$]NO$_3$ and[Ag(phen)(HMDAHP)] NO$_3$[19]. The complex[Ni(MDAHP)$_2$(H$_2$O)$_2$] was prepared from NiCl$_2$ and HMDAHP in water-ethanol. The complex[Fe(MDAHP)$_3$] was formed from the reaction of HMDAHP with Fe(NO$_3$)$_3$ in aqueous base. [Ru(PPh$_3$)$_2$(HMDAHP)Cl$_2$] was made from [Ru(PPh$_3$)$_3$Cl$_2$] and HMDAHP in basic methanolic medium. The complexes[Ag(HMDAHP)$_2$]$^+$ and [Ag (phen)(HMDAHP)]$^+$ were prepared from AgNO$_3$ or[Ag(phen)(H$_2$O)(NO$_3$)] and HMDAHP in methanol, respectively.

The complexes are microcrystalline or powder-like, stable in the normal laboratory atmosphere and soluble in DMF or DMSO.

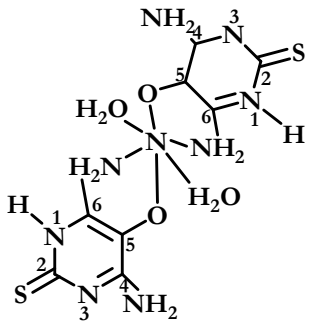
Vibrational spectra

The characteristic IR bands observed and vibration assignments of 2-mercapto-4,6-diamino-5-hydroxy pyrimidine(HMDAHP) complexes are reported in TABLE 1. The spectrum of HMDAHP supports the preponderance of the thione form in the solid phase(SCHEME 1). This is due to the presence of ν(NH) stretch at 2970cm^{-1}[14], the absence of ν(SH) near 2600cm^{-1} and the formation of the characteristic thioamide bands due to extensive coupling of δ(NH), ν(C=N), ν(NCS) and ν(C=S) at 1652, 1562, 1455 and(1375, 1268, 1177)cm^{-1}, respectively[20-22]. The presence of ν(C=C)+ν(C=N) stretches near 1560cm^{-1} attributed to strong non-aromatic character[23].

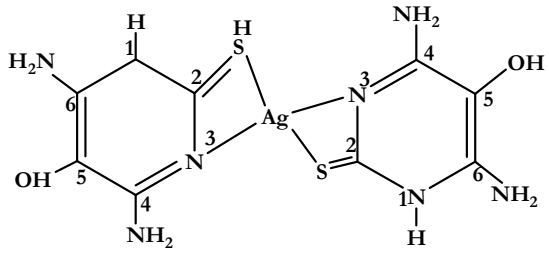
In the spectra of the complexes,[Fe(HMDAHP)$_3$] and[Ni(HMDAHP)$_2$(H$_2$O)$_2$], the stretching vibration ν(OH) at 3305cm^3 in the free ligand is missing in the



SCHEME 1: Structure of HMDAHP



SCHEME 2 : Structure of$[Ni(MDAHP)_2(H_2O)_2]$



SCHEME 3: Structure of$[Ag(HMDAHP)_2]^+$

complexes[24]. The bands at 3390 and 3185cm^{-1} arising from $\nu^s(NH_2)$ and $\nu^{as}(NH_2)$, respectively[24,25], in the free ligand are shifted to lower wave numbers upon coordination[15,24]. The bands arising from ν(C=N), ν(NCS) and ν(C=S) are not affected while the bands arising from both ν(NH) and δ(NH) stretches are shifted slightly to lower wave number in the complexes. This means that HMDAHP acts as a bidentate ligand, chelating the metal ion through the deprotonated hydroxy and amino N(6)H_2 groups, without any participation of the thione sulphur or cyclic nitrogen atoms in coordination[16]. This feature is further supported by the observation of a band near 1178cm^{-1} arises from ν(C=S) stretch, remains unchanged[20]. SCHEME 2 shows the structure of$[Ni(MDAHP)_2(H_2O)_2]$.

The vibration spectra of$[Ru(PPh_3)_2$ (HMDAHP) $Cl_2]$,$[Ag(HMDAHP)_2]NO_3$ and[Ag(phen)(HMDAHP)] NO_3 contains $\nu(NH_2)$ stretching bands in the 3400-3165cm^{-1} and a broad band near 3310cm^{-1} assigned to ν(OH) which is not appreciably shifted from the free ligand value suggesting that the coordination does not occur through oxygen[10]. The participation of the thiocarbonyl and the cyclic N(3) in the coordination is suggested due to the positive shift observed in the ν(C=S) and ν(N-C=S) stretching vibrations(SCHEME 2 shows the structure of[Ag $(HMDAHP)_2]^+$). This suggestion is supported by the slight shift of ν(NH) and δ(NH) to lower wave number with the existence of $\nu^s(NH_2)$, $\nu^{as}(NH_2)$ and ν(OH) stretches more or less in the same position as in the free ligand[26].

In the spectrum of$[Ag(phen)(HMDAHP)]^+$, the bands of the free phen near 740cm^{-1} are shifted to higher frequencies in the complexes(775cm^{-1})[27,28].

The region of the complexes spectra between 550-200cm^{-1} contains several weak bands, this would indicate ν(M-O), ν(M-N), ν(M-S) and ν(M-Cl) stret chesnear 500, 420, 350 and 260, respectively[29,30]. The spectrum of$[Ru(PPh_3)_2(Hdahmp)Cl_2]$ exhibits two extra sharp stretches at 340 and 290cm^{-1}, correspond to ν(Ru-Cl), indicating a cis-$RuCl_2$ arrangement[31].

The spectra of the complexes $[Ag(HMDAHP)_2]$ NO_3 and$[Ag(phen)(HMDAHP)]NO_3$ show new strong band near 1370cm^{-1} assigned to the ionic uncoordi nated NO_3^-[20].

Electronic spectra and magnetic measurements

The electronic spectra(200-900nm) in DMSO and magnetic moments for some complexes are reported. The electronic spectrum of$[Ni(MDAHP)_2$ $(H_2O)_2]$ can be interpreted in a terms of a distorted octahedral stereochemistry around the nickel centre. The $^3A_{2g}\rightarrow{}^3T_{1g}(F)$ transition appears at 870 and 805nm, likely causes by a distortion from regular octahedral while the strong band at 415nm can assign to a combination of $^3A_{2g}\rightarrow{}^3T_{1g}(P)$ and charge transfer transitions[32,33]. The magnetic moment of 3.12 B. M. lies within the range reported for octahedral Ni(II) complexes[34]. The electronic spectrum of the diamagnetic Ru(II) complex, $[Ru(PPh_3)_2(HMDAHP)$ $Cl_2]$, show several intense absorptions in the visible and ultraviolet region at 555, 428, 314 and 262nm. The absorptions in the ultraviolet region are assignable to the transitions involving ligand orbitals. In the visible region, the transition with the lowest energies is much weaker in intensity and assigned to $^1A_{1g}\rightarrow{}^1T_{1g}$ and the other probably due to $^1A_{1g}\rightarrow{}^1T_{2g}$ transition at higher energies[35]. The magnetic moment of$[Fe(MDAHP)_3]$ is 4.20 B.M., this value indicates anti-ferromagnetic exchange interaction. The electronic spectrum of this complex shows an absor

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TABLE 2 : ^{1}HNMR spectral data of HMDAHP and its complexes

Compounds	N(1)H	N(4)H$_2$	O(5)H	N(6)H
HMDAHP	7.43	6.07	9.13	6.18
[Ru(PPh$_3$)$_2$(HMDAHP)$_2$Cl$_2$]	--[a]	6.04	9.10	6.20
[Ag(HMDAHP)$_2$]$^+$	7.51	6.10	9.18	6.21
[Ag(phen)(HMDAHP)]$^+$	--[a]	6.16	9.20	6.24

[a]Signal interefered with Ph or phen protons

ption band at 470 nm may arise from $^6A_{1g} \rightarrow {}^4T_{2g}$ transi tion in octahedral geometry around Fe(III)[36]. The electronic spectra of silver(I) complexes show two bands near 470 and 390nm indicating the presence of Ag(I) in a square planar configuration[27].

^{1}H-NMR spectra

The ^{1}H NMR spectra of some of the reported complexes can give information on the coordination mode of HMDAHP. The ^{1}H NMR spectrum of HMDAHP in d_6-DMSO shows two singlets at δ 6.07 and 6.18ppm arising from N(4)H$_2$ and N(6)H$_2$, respectively(see SCHEME 1 for numbering SCHEME). The proton of the hydroxy group O(5)H appears as a broad singlet at δ 9.13ppm and the N(1)H proton gives a singlet at δ 7.43ppm. The ^{1}H NMR spectra of some of the reported complexes (TABLE 2) can give information on the coordination mode and chelate ring conformation that HMDAHP adopts, supporting data obtained from the vibration spectra. The ^{1}H NMR spectra of[Ag(HMDAHP)$_2$]$^+$, [Ag(phen(HMDAHP)]$^+$ and [Ru(PPh$_3$)$_2$(HMDAHP) Cl$_2$] confirm the neutral bidentate behaviour of HMDAHP through the thione sulfur and the cyclic N(3) centre, as there is a slight shift from the free ligand spectrum. This is probably due to the decrease in the electron density caused by the withdrawing of electrons by the metal ions from the pyrimidine ring coordination centres[13,16,37].

In the^{1}H-NMR spectrum of[Ag(phen) (HMD AHP)]$^+$, the phen shows upfield shifts as compared with[Ag(phen)(H$_2$O)(NO$_3$)]. This is interpreted in terms of strong binding of MDAHP$^-$ to Ag(I) in comparison to binding of nitrate ion[38].

Mass spectra

The mass spectra of[Fe(MDAHP)$_3$]·4H$_2$O and [Ru(PPh$_3$)$_2$(HMDAHP)Cl$_2$] are reported and their molecular ion peaks are in agreement with their assigned formulae. The mass spectrum of [Fe (MDAHP)$_3$]·4H$_2$O shows fragmentation patterns corresponding to the successive degradation of the molecule. The first signal at m/e 596(Calcd. 595.85), represents the molecular ion peaks of the complex with 3.8% abundance. The spectrum exhibits signals indicate step-wise ligand loss at m/e 522, 366 and 211 corresponding to [Fe(MDAHP)$_3$]$^+$[Fe(MDAHP)$_2$]$^+$ and[Fe(MDAHP)]$^+$ fragments, respectively[37]. The mass spectrum of[Ru(PPh$_3$)$_2$(HMDAHP)Cl$_2$] shows a signal at m/ e 855(Cacld.854.1) with 23.6% abundance. The spectrum shows signals at 782, 625 and 361 corresponding to[Ru(PPh$_3$)$_2$ (HMDAHP)]$^+$, [Ru (PPh$_3$)$_2$]$^+$,[Ru(PPh$_3$)]$^+$fragments, respectively[37].

Thermal measurements

The thermal decomposition of[Ru(PPh$_3$)$_2$ (HMDAHP)Cl$_2$] and[Ag(phen)(HMDAHP)]NO$_3$ complexes was studied using thermogravimetry(TG) technique. The TG data for[Ru(PPh$_3$)$_2$(HMDAHP) Cl$_2$] shows the first weight loss step(Cacld. 44.37, Found 45.07%) between 192 and 320^{0}C may be attributed to the elimination of Cl$_2$ and four Ph groups(C$_{24}$H$_{20}$) fragments. The second decomposition step occurs between 321-364^{0}C(Calcd. 8.20, found 8.10%) due to the release of C$_3$H$_6$N$_2$ species. The third TG inflection lies in the 465-523^{0}C range and may arise from the release of CS, N$_2$ and two PPh fragments(Calcd. 33.72, found 34.05%), followed by a residue of Ruthenium oxides(Found 14.50%)[39]. The thermogram of[Ag(phen)(HMDAHP)]NO$_3$ shows the first step weight loss of 9.33% between 214 and 2650C, Which corresponds to the release of NO$_2$ species(Calcd.9.06%). The second decom position step occurs between 266 and 342^{0}C, this weight loss is attributed the loss of C$_3$H$_6$N$_2$O fragment(Calcd. 16.93, Found 17.02%). There is one more TG inflection between 412-511^{0}C, may arise from the elimination of phen, CS, N$_2$ and half O$_2$ species(Calcd. 51.18, Found 51.26%), leaving Ag$_2$O representing(Calcd. 22.86, Found 23.00%)[39,40].

Anti-microbial activity

The metal-free HMDAHP and its complexes, [Ag(HMDAHP)$_2$]$^+$ and[Ag(phen)(HMDAHP)]$^+$, were

TABLE 3 : Diameters(mm/mg) of growth inhibition zones antibacterial activity of HMDAHP and its Ag(I) complexes

Compound	Bateria							
	S.aureus (mg/cm³)				*P.aeruginosa* (mg/cm³)			
	10	20	50	100	10	20	50	100
HMDAHP	5	11	28	58	4	10	30	55
[Ag(phen)(HMDAHP)]$^+$	15	25	61	95	12	21	49	92
[Ag(HMDAHP)$_2$]$^+$	11	18	45	89	10	17	42	80

TABLE 4 : Diameters(mm/mg) of growth inhibition zones antifungal activity of HMDAHP and its Ag(I) complexes

Compound	Fungi							
	A.niger (mg/cm³)				*C.albicans* (mg/cm³)			
	10	20	50	100	10	20	50	100
HMDAHP	5	12	23	44	6	9	34	55
[Ag(phen)(HMDAHP)]$^+$	20	33	67	100	19	31	54	97
[Ag(HMDAHP)$_2$]$^+$	18	26	45	86	20	29	51	88
Nystatin[a]	17	19	36	65	20	26	42	79

[a]**Nystatin is antifungal drug**

assayed in *vitro* for antimicrobial activity against two bacterial(*S.aureus* and *P.aeruginosa*) and two fungal (*A.niger* and *C.albicans*) cultures. The hole plate diffusion method was adopted for the activity measurements[18]. The antibacterial and antifungal activity results of HMDAHP and its Ag(I) complexes are listed in TABLES 3 and 4, respectively, with the currently prescribed, antifungal, nystatin.

The silver complexes were found to be more active than HMDAHP at the measured concentrations. The water-soluble[Ag(phen)(HMDAHP)]$^+$ complex was found to be the more active against the pathogens under study, followed by[Ag(HMDAHP)$_2$]$^+$ and rather than currently prescribed, antifungal, nystatin, in all concentrations reported in this study. There are reports that 2,2'-bipyridyl base adducts of copper are less toxic in biological systems than their free ligands[41,42]. The activity of phen complex is believed to be related to the abstraction by the phen chelated Ag(I) present on a trace amount in the growth media, and Ag-phen species is responsible for the high antimicrobial activity[43]. The inhibition activity of the silver(I) complexes may attribute to their inhibition of the replication of microorganisms DNA by interacting with enzyme prosthetic group, altering the microbial metabolism and their ability to form hydrogen bonds with the cell wall and cell constituents[42,44]. Also, it is reported that, the substituted 2-mercaptopyri midines inhibits the synthesis of tRNA in *E.coli*[16,13,26]. Thus, it is expected that, the high biological activity of[Ag(phen) (HMDAHP)]$^+$ is high due to the presence of both phen and 2-mercaptopyrimidine rings in the complex. It is clear that, as the complex concentration increases, the antimicrobial activity becomes higher[44,45].

In order to detect the influence of the solvent in the antimicrobial activity of HMDAHP,[Ag (HMDAHP)$_2$]$^+$ and[Ag(phen)(HMDAHP)]$^+$. As expected, the water-soluble[Ag(HMDAHP)$_2$]$^+$ and [Ag(phen)(HMDAHP)]$^+$complexes have less side effect on the kidney and act on DNA by a mechanism different from DMSO soluble HMDAHP[40].

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