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New Complexes based on Sulfathiazole; Synthesis, Characterization and Toxicity Assessment against Chlorella Vulgaris Microchlorophyte

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ABSTRACT

The reactions between sulfathiazole (Hst) and Ni(II), Zn(II), Pd(II), and Ag(I) in presence and absence of N,N-donors (2,2'-bipyridyl or 2-aminopyrimidine) were reported. Their structures were noted by using spectral {IR, NMR (1H, 13C), UV–Vis, and EI- and muldy-mass} and physical (elemental analyses, molar conductivities and TGA behaviour) measurements. Hst coordinates to the metal ions through (i) the deprotonated N-thiazole atom in mono-negative monodentate manner or (ii) the deprotonated N-thiazole and SO_2-O atoms as mono negative bidentate ligand. The stoichiometries and the formation constants of Hst complexes in solution were calculated spectrophotometrically using molar ratio and Job's methods. Moreover, the toxicity of Hst and its complexes against the microchlorophyte (Chlorella vulgaris) have been measured and assessed in comparison to the free metal ions .

Keywords: *Complexes, Sulfathiazole, Spectra, Stoichiometry, Chlorella vulgaris*

INTRODUCTION

Sulfonamides were considered as effective chemotherapeutic agents that employed systematically for the prevention and cure of bacterial infections in humans [1, 2]. Their antibacterial mechanism of action based on the competitive inhibition of dihydropterase synthetase enzyme towards the substrate *p*-aminobenzoate [3]. Neutral sulfonamides are poor ligands due to the withdrawal of the electron density from N-atom onto the electronegative O-atoms; i.e., sulfonamide N-atom tends a dissociable hydrogen atom, which increases its acidity (deprotonation) and efficacy as donor ligands [4].

Sulfathiazole (4-amino-N-2-thiazolylbencenosulfonamide; Hst (Fig. 1), is one of the most used clinical antibacterial [5]. The synthesis and characterization of metal complexes of sulfathiazole have been reported [6-8]. Sulfathiazole metal complexes possess special antibacterial activity, as well as diuretic, anti glaucoma and antiepileptic drugs [7-12], which in many cases, much better than the free sulfathiazole. Moreover, the X-ray structures of the octahedral sulfathiazole (HST)-Co(II) complexes, $[CoII(ST)_2(H_2O)_4]$ and $[CoII(ST)_2(H_2O)_3]_n$ have been determined. They show antibacterial activity against Aspergillus fumigatus and Aspergillus flavus [13].Zinc (II) sulfadiazine and silver (I) silvadene-(2-sulfanilamido pyrimidine complexes have been used to prevent bacterial infection in burned animal, and for the treatment of topical burn, respectively [14, 15].

Moreover, short- and long-term toxicity of Pb(II) ions exposure on *Chlorella vulgaris* (*C. vulgaris*) and *Chlorella protothecoides* (*C. protothecoides*) have been screened. High level of Pb(II) (50 or 80 mg L^{-1}) could significantly inhibit the growth and chlorophyll synthesis of both algae. The EC_{50} values indicated limited short-term toxicity[16]. Freshwater microalga Chlorella vulgaris was applied to investigate the degree of toxicity induced by silver nanoparticles (AgNPs), which were able to interact directly with the *Chlorella vulgaris* cells surface. AgNPs have negative effect on *C. vulgaris* due to the decrease in chlorophyll content, viable algal cells, increased ROS formation and lipids peroxidation [17]. In addition, two sets of substituted nitrobenzene have been used to examine the toxicity to Chlorella vulgaris, in which one- or two-descriptor models provide useful correlations [18]. Continued interest in the evaluation of biologically active transition metal complexes, the preparation and structure determination of new Ni(II), Zn(II), Pd(II) and Ag(I) complexes of sulfathiazole are reported in this article. Moreover, our interest here is to cover the stoichiometries and stability constants of the complexes in solution based on the spectroscopic measurements in order to testing their toxicity against the microchlorophyte (Chlorella *vulgaris*) algae.

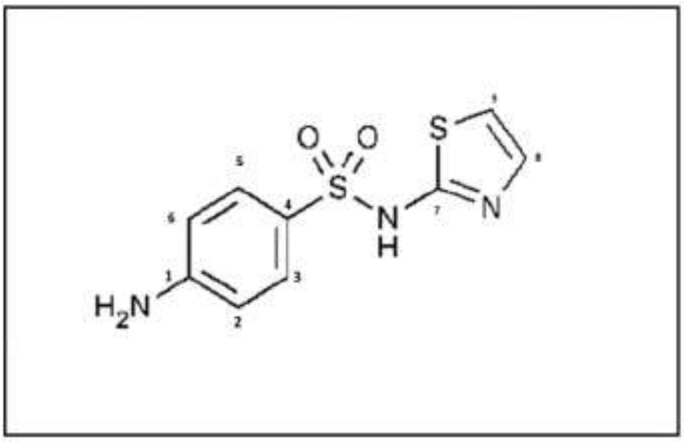


Fig1. *Structure of Sulfathiazole (Hst)*

EXPERIMENTAL

Materials and Methods

All reagents and solvents were purchased from Alfa/Aesar and Sigma-Aldrich, and were used as received. All manipulations were performed under aerobic conditions. DMSO-d_6 was used for the NMR measurements, referenced against TMS. The starting complex, $[Pd(bpy)Cl_2]$, [19] was prepared as we have early reported. Green algae; *Chlorella vulgaris* was provided as a gift from Phycology Lab, Faculty of Science, Mansoura University. It was grown on BG-11 nutrient medium [20].

Instrumentation

Elemental analyses (C, H, N, S) were performed by the Micro analytical Unit, Cairo University. Infrared spectra were recorded on a Nicolet 6700 Diamond ATR spectrometer in the 4000–200 cm^{-1} range. NMR spectra were performed in the Department of Chemistry, McGill University, Montreal, Canada, on Varian Mercury 200-, 300- and 500-MHz spectrometers, in DMSO-d_6 solutions using TMS as the reference. Mass spectra (ESI-muldy) were recorded using LCQ Duo and double-focusing MS25RFA instruments.

Electronic spectra were recorded in DMF using a Hewlett-Packard 8453 spectrophotometer. Thermal analysis measurements were made in the 20–1000^{o} C range at a heating rate of 20^{o} C min^{-1}, using Ni and NiCo as references, on a model Q500Analyzer TGA-50 instrument. Molar conductivity measurements were performed at room temperature on a YSI Model 32 conductivity bridge. Magnetic susceptibilities were measured at room temperature using a Johnson Matthey balance standardized with Hg $[Co(NCS)_4]$; the molar susceptibilities were corrected for the core diamagnetism of the constituent atoms using Pascal's constants.

Preparation of Complexes

$[Ni(st)_2(H_2O)_2].3H_2O$

$Ni(NO_3)_2.6H_2O$ (0.145 g, 0.5 mmol) in water (5 mL) was added drop wise to a basic solution of Hst (0.1275 g, 0.5 mmol) containing NaOH (0.02 g, 0.5 mmol) in water (10 mL). The reaction mixture was heated under reflux for 24 h. The green precipitate was filtered off, washed with water and air-dried. Elemental *Anal*. Calcd. For ($C_{18}H_{26}N_6NiS_4O_9$): C, 32.93; H, 3.96; N, 12.80; S, 19.51; Ni, 8.84; Found: C, 33.14; H, 3.69; N, 12.82; S, 20.38; Ni, 9.02 %. Conductivity data (10^{-3} M in DMF): $\Lambda m = 17.09$ $ohm^{-1}cm^2mol^{-1}$. IR (cm^{-1}): $\nu_{as}(NH_2)$, 3455; $\nu_s(NH_2)$, 3354; ν(C=N), 1626, 1563; $\nu_{as}(SO_2)$, 1297; $\nu_s(SO_2)$, 1127; ν(Ni-O), 544; ν(Ni-N), 433. MS (m/z): 567.81 (Calcd. 566.00) and 313.24 (Calcd. 312.00).

$[Zn(st)_2]$

$ZnCl_2$ (0.068 g, 0.5 mmol) in water (5 mL) was added to basic solution of Hst (0.127 g, 0.5 mmol) containing KOH (0.028 g, 0.5 mmol;

10mL). The mixture was stirred under reflux for 4 h, and the white precipitate was washed with water, EtOH, Et_2O and air-dried. Elemental *Anal*. Calcd. For ($C_{18}H_{16}N_6S_4O_4Zn$): C, 37.66; H, 2.79; N, 14.65; S, 22.32; Zn, 11.42; Found: C, 37.44; H, 2.69; N, 14.52; S, 22.30; Zn, 11.71 %. Conductivity data (10^{-3} M in DMF): Λm = 19.11 $ohm^{-1}cm^2mol^{-1}$. IR (cm^{-1}): $\nu_{as}(NH_2)$, 3474; $\nu_s(NH_2)$, 3377; ν(C=N), 1596, 1565; $\nu_{as}(SO_2)$, 1289; $\nu_s(SO_2)$, 1129; ν(Zn-O), 537; ν(Ni-N), 413. ^{1}HNMR δ (ppm): H(3,5) , 7.66; H(9), 7.19; H(8), 6.77; H(2,6), 6.60. MS (m/z): 575.09 (Calcd. 573.50) and 319.60 (Calcd. 319.50).

[Pd(st)2(H2O)2]

Solid $PdCl_2$ (0.088 g, 0.5 mmol) was added to Hst (0.1275 g, 0.5 mmol) in DMF (15 mL). the reaction mixture was heated under reflux for 24 h. Upon reducing the volume of the brown solution, a deep brown precipitate was obtained. It was filtered off, washed with DMF, Et_2O and dried in vacuo. Elemental *Anal*. Calcd. For ($C_{18}H_{20}N_6S_4O_6Pd$): C, 33.21; H, 3.07; N, 12.92; S, 19.68; Pd, 16.36; Found: C, 33.04; H, 2.89; N, 12.58; S, 20.03; Pd, 16.22 %. Conductivity data (10^{-3} M in DMF): Λm = 12.63 $ohm^{-1}cm^2mol^{-1}$. IR (cm^{-1}): $\nu_{as}(NH_2)$, 3462; $\nu_s(NH_2)$, 3376; ν(C=N), 1594; $\nu_{as}(SO_2)$, 1322; $\nu_s(SO_2)$, 1136; ν(Pd-N), 428. ^{1}HNMR δ (ppm): H(3,5), 7.47; H(9), 7.18; H(8), 6.82; H(2,6), 6.61. MS (m/z): 1228.81 (Calcd. 1228.80), 974.61 (calcd. 974.80) and 614.41 (calcd. 614.40).

[Pd(st)Cl(H_2O)]

An aqueous solution ofK_2PdCl_4 (0.163 g, 0.5 mmol; 5 mL) was added to Hst (0.127 g, 0.5 mmol) in aqueous KOH (0.028 g, 0.5 mmol; 15 mL). The reaction mixture was stirred for 30 h. Upon reducing the reaction solution volume, a deep brown precipitate was obtained, washed with water and air-dried. Elemental *Anal*. Calcd. For ($C_9H_{10}ClN_3S_2O_3Pd$): C, 26.09; H, 2.42; Cl, 8.58; N, 10.15; S, 15.46; Pd, 25.71; Found: C, 26.02; H, 2.32; Cl, 8.21; N, 9.97; S, 15.31; Pd, 25.70 %. Conductivity data (10^{-3} M in DMF): Λm = 11.73 $ohm^{-1}cm^2mol^{-1}$. IR (cm^{-1}): $\nu_{as}(NH_2)$, 3455; $\nu_s(NH_2)$, 3372; ν(C=N), 1596, 1562; $\nu_{as}(SO_2)$, 1299; $\nu_s(SO_2)$, 1114; ν(Pd-O), 529; ν(Pd-N), 423. ^{1}HNMR δ (ppm): H(3,5), 7.62; H(9), 7.20; H(8), 6.81; H(2,6), 6.60. MS (m/z): 722.01 (Calcd, 720.80) and 360.89 (Calcd 360.40).

[Pd(bpy)(st)]Cl

Solid [Pd (bpy)Cl_2] (0.166 g, 0.5 mmol) was added to Hst (0.127 g, 0.5 mmol) in ETOH (8 mL) containing KOH (0.028 g, 0.5 mmol). The obtained mixture was stirred under reflux for 24 h. The yellow precipitate was isolated, washed with EtOH, Et_2O and air-dried. Elemental *Anal*. Calcd. For ($C_{19}H_{16}ClN_5S_2O_2Pd$): C, 41.31; H, 2.90; Cl, 6.43; N, 12.68; S, 11.60; Pd, 19.28; Found: C, 41.62; H, 2.85; Cl, 6.26; N, 13.27; S, 11.28; Pd, 19.21%. Conductivity data (10^{-3} M in DMF): Λm = 8.97 $ohm^{-1}cm^2mol^{-1}$. IR (cm^{-1}): $\nu_{as}(NH_2)$, 3439; $\nu_s(NH_2)$, 3348; ν(C=N), 1641, 1597, 1567; $\nu_{as}(SO_2)$, 1312; $\nu_s(SO_2)$, 1120; ν(Pd-O), 531; ν(Pd-N), 421. ^{1}HNMR δ (ppm): H(3,5), 7.64; H(9), 7.17; H(8), 6.85; H(2,6), 6.63. MS (m/z): 517.16 (Calcd. 516.40) and 426.27 (Calcd. 425.40).

[Ag_2(st)$_2$]

In the dark, an aqueous solution of $AgClO_4$ (0.103 g, 0.5 mmol; 15 mL) was added to Hst (0.127 g, 0.5 mmol) in water (15 mL). The reaction mixture was stirred for 4 h and during which a white precipitate was obtained. It was filtered off, washed was water and air-dried. Elemental *Anal*. Calcd. For ($Ag_2C_{18}H_{16}N_6S_4O_4$): C, 29.83; H, 2.21; N, 11.60; S, 17.68; Ag, 29.83; Found: C, 30.04; H, 2.05; N, 11.23; S, 17.32; Ag, 19.28%. Conductivity data (10^{-3} M in DMF): Λm = 8.95 $ohm^{-1}cm^2mol^{-1}$. IR (cm^{-1}): $\nu_{as}(NH_2)$, 3446; $\nu_s(NH_2)$, 3345; ν(C=N), 1592; $\nu_{as}(SO_2)$, 1322; $\nu_s(SO_2)$, 1135; ν(Ag-N), 451. ^{1}HNMR δ (ppm): H(3,5),7.48; H(9), 7.20; H(8), 6.78; H(2,6), 6.62. MS (m/z): 980.03 (calcd. 979.00), 725.21 (calcd. 724.00) and 471.07 (calcd. 740.00).

[Ag(st)(apy)]

In the dark, $AgNO_3$ (0.084 g, 0.5 mmol) in water (2 mL) was added to a mixture of Hst (0.127 g, 0.5 mmol) and 2-aminopyrimidine (0.047 g, 0.5 mmol) in DMF (8 mL). The mixture was stirred under reflux for 24 h. Upon reducing the volume, the white precipitate was filtered off, washed with water, DMF, Et_2O and dried in vacuo.

Elemental *Anal*. Calcd. For ($AgC_{13}H_{13}N_6S_2O_2$): C, 34.14; H, 2.84; N, 18.38; S, 14.00; Ag, 23.63; Found: C, 34.11; H, 2.60; N, 18.05; S, 15.78; Ag, 23.43%. Conductivity data (10^{-3} M in DMF): Λm = 8.75 $ohm^{-1}cm^2mol^{-1}$. IR (cm^{-1}): $\nu_{as}(NH_2)$, 3438; $\nu_s(NH_2)$, 3349; ν(C=N), 1636, 1595; $\nu_{as}(SO_2)$, 1323; $\nu_s(SO_2)$, 1133; ν(Ag-N), 422. ^{1}HNMR δ (ppm): H (3,5), 7.46; H(9), 7.21; H(8), 6.82; H(2,6), 6.62. MS (m/z): 712.60 (Calcd. 712.00), 457.45 (Calcd. 457.00) and 366.32 (Calcd. 366.0).

Determination of the Stoichiometry of Hst Complexes in Solution Spectro photometrically

The stoichiometry and the stability constants of Co(II), Ni(II), Cu(II), Zn(II), Pd(II) and Ag(I) complexes with Hst in solution were calculated by applying both molar ratio [21] and Job's (continuous variation) methods [22].

Molar Ratio Method

Solutions containing a constant concentration of $CoCl_2.6H_2O$, $NiCl_2.6H_2O$, $CuCl_2.2H_2O$, $Zn(ClO_4)_2.6H_2O$, $AgClO_4$ and $K_2[PdCl_4]$ and various concentrations of Hst were prepared. Absorbances at the maximum wavelength (λ_{max}) were measured spectro photometrically.

Job's (Continuous Variation) Method

The solutions were prepared containing different mole fractions of the two components, the metal complex, $CoCl_2.6H_2O$, $NiCl_2.6H_2O$, $CuCl_2.2H_2O$, $Zn(ClO_4)_2.6H_2O$, $AgClO_4$ and $K_2[PdCl_4]$, and Hst, while maintaining the total concentration constant. The λ_{max} absorbance values of the resulting solutions were then measured.

Toxicity Assessment against the Microchlorophyte (Chlorella Vulgaris)

The assessment of the toxicity of some of the prepared complexes were quantified following the standard instructions of the microalgae growth inhibition test according to OECD guideline for testing of chemicals No. 201 [23]. The growth inhibition test using *Chlorella vulgaris* (test alga was grown on BG-11 nutrient medium [24]) at light intensity equivalent to 4200 Lux using cool white uniform fluorescent illumination for 72 h incubation with 24 h sampling interval.

The growth was determined by manual-cell counting using standard hemocytometer; i.e., it was illustrated as cell yield at the end of the incubation period, logarithmic cell number along the incubation period (24 hr. interval) as well as the relative cell count along incubation period for estimating IC_{50} for each treatment. The variables affecting the growth of *Chlorella vulgaris* were discussed by calculating The average specific growth rate ® using eq. 1,

$$\mathbf{r} = \frac{\ln N_l - \ln N_0}{t_l - t_0} \qquad \textbf{(1)}$$

where, r is the growth rate, T_0 and T_L are start test time and the end of the time interval, respectively. $N_0$and N_L are the nominal initial cell density and the measured cell density at time t_L, respectively.

The inhibition percentage (I) according to eq. 2,

$$\mathbf{I\% = (1 - N/N_0) \times 100} \qquad \textbf{(2)}$$

where, N_0 and N are the cell densities (cells per milliliters) in the control and treated cultures, respectively.

The relative cell number (RCN; eq. 3)

$$\mathbf{RCN=[N_{72}/ N_0] \times 100} \qquad \textbf{(3)}$$

where, N_{72} and N_0 are the cell densities in the treated cultures after 72h and the control, respectively.

The 50% effective concentration (EC_{50}) of the treated samples, which is the concentration corresponding to the point where I is 50% on the inhibition curve.

The toxic unit (eq. 4):

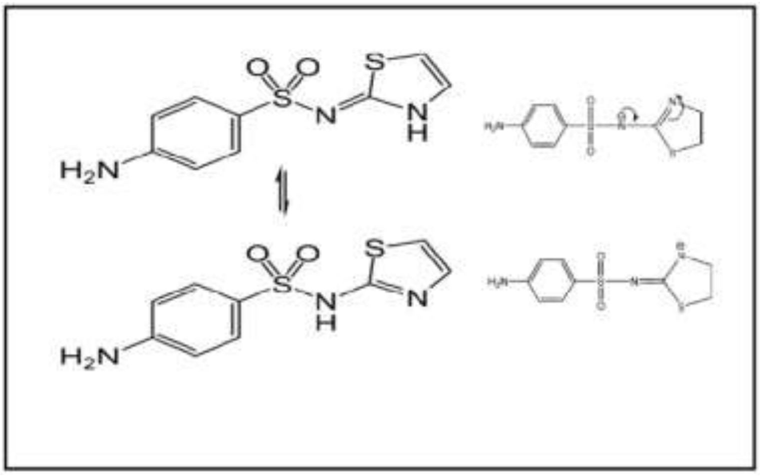
$$\mathbf{TU= [1/ EC_{50}] \times 100} \qquad \textbf{(4)}$$

RESULTS AND DISCUSSION

New complexes of sulphathiazole (Hst; Fig. 1) with Zn(II), Ni(II), Pd(II) and Ag(I) were synthesized and their structures investigated. C, H, N, S and M-analyses are in great agreement with their assigned formulae. Their molar conductivities (Λ_M) in DMF at room temperature indicate the electrolytic nature of [Pd (bpy)(st)]Cl (1:1), while the others are non-electrolytes [25,26]. The complexes are microcrystalline or powder-like, stable under general laboratory conditions and soluble in water (electrolytes), DMF and DMSO.

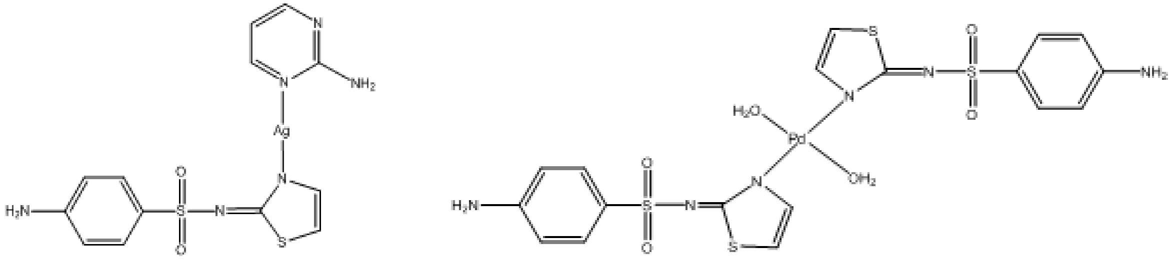
IR Spectra

Sulfathiazole (Hst) is a sulfanilamide derivative, in which the deprotonation of the sulfonamidic nitrogen atom does not imply, necessarily, thatit coordinates to the metal atom, since the two heteroatomsat the five member ring are equidistant and the negative charge can be shifted to the nitrogen atom of the thiazolering (Scheme 1)[13,27]. Selected IR spectral data of Hst and its complexes are reported in The Experimental Section. The spectrum of Hst shows characteristic bands at 3349, 3318, 3091 and 1574 cm^{-1} due to $\nu_{as}(NH_2)$, $\nu_s(NH_2)$, $\nu(NH)$ and $\nu(C=N)$ stretches, respectively [12,13,28]. The amino group bands are shifted by *ca.* 100 cm^{-1} towards lower energies and overlapped with the $\nu(CH)$ stretches, may be attributed to the participation in weak H-bonding [29-32], which disappeared in the complexes.This fact is supported by the shift of these bands to higher wave numbers [33]. The strong bands at 1531 and 929 cm^{-1} assigned to the thiazole ring and ν(SCN) vibrations, respectively. The other bands located at 1325 and 1137 cm^{-1} were due to $\nu_{as}(SO_2)$ and $\nu_s(SO_2)$ vibrations, respectively [13,28].



Scheme1. *Tautomeric forms of Hst*

Since sulfonamide N-atom tends a dissociable hydrogen atom, which increases its acidity and efficacy in coordination [4], in the complexes, [Ag(st)(apy)] and $[Pd(st)_2(H_2O)_2]$ (Fig. 2), the thiazole ring vibration shifted to lower frequencies. This fact is due to the interaction through the N-thiazole center [27,32]. This fact is supported by the missing of ν(NH) stretch with the expected reduction on the electron density in the azomethine link and the shift of ν(C=N) stretch [12,32,33]. The bands attributed to the NH_2 and SO_2 vibrations remain unaltered, suggesting that they are playing no role in interaction with the metal ion. Furthermore, the $\nu_s(SO_2)$ stretch intensity is increased, may be due to the infer of N-thiazole atoms, which might be site of coordination of the metal ion; i.e, sulfathiazole to anions in mononegative monodentate manner. This feature is consistent with the sulfathiazole complexes reported in the literature [4,12,13,27,32–38].



(a) **(b)**

Fig2. *Structures of [Ag(st)(apy)] (a) and $[Pd(st)_2(H_2O)_2]$ (b)*

The complexes, $[Ni(st)_2(H_2O)_2]$, [Pd(bpy)(st)]Cl (Fig. 3), $[Pd(st)Cl(H_2O)]$ and $[Zn(st)_2]$, were prepared in basic media. The pH of Kst was found to be 12.33 and reduced to ~7.00 upon adding the metal ion. In these complexes, the ν(C=N) band is shifted to lower wave number (~ 1560 cm^{-1}) in comparison to the above reported complexes. In addition, $\nu_{as}(SO_2)$ and $\nu_s(SO_2)$ stretches was shifted to a lower wave number, while *v*(SCN) shifted to a higher wave number, with change of the thiazoleN-C–N moiety with deprotonation of the thiazole-N atom (Fig. 5) [12,32,33]; i.e., St$^-$ acts as a mononegative bidentate ligand coordinating Zn(II) or Pd(II) ion through the N-thiazole and SO_2-O centers, forming a six-membered ring (Fig. 6).The binuclear complex, $[Ag_2(st)_2]$, is of particular interest as two st$^-$ units coordinate two Ag(I) ions in mono negative bidentate fashion, through the thiazole-N and imine-N atoms [29,39]. The IR spectrum of [Pd(bpy)(st)] Cl (Fig. 3) shows bands at 855, 842, 751 and 728 cm^{-1}, attributed to the (CH) vibrations of the coordinated bpy [40]. These bands are at higher wave numbers compared with those for the free bpy indicating chelation through N,N-atoms

[41,42]. In the complex, [Ag(apy)(st)], additional band was observed at 1641 cm^{-1} attributed to ν(C=N) stretch of apymoiety, corresponding to the participation of onecyclic-N atom in coordination to Ag(I) ion [41]. Finally, the IR spectra of the complexes display several bands near 540 and420 cm^{-1}, due to ν(M–O) and ν(M–N) stretches, respectively [32,33,40-43].

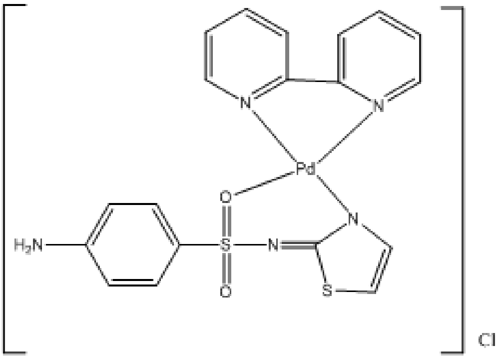


Fig3. *Structure of [Pd(st)(bpy)]Cl*

NMR Spectra

The ^{1}HNMR spectrum of Hst(reported in the Experimental Section; see Fig. 1 for numbering Scheme) shows sharp singlets at δ 12.34 and 5.79 ppm due to NH and NH_2 protons, respectively. A group of doublets at δ 7.45, 7.18, 6.74 and 6.58 ppm are attributed to the rings protons,H(3,5), H(9), H(8) and H(2,6), respectively [33,44,45].

In the complexes, the NH proton is missed, while slight shift on NH_2 and the rings protons was observed,with clear downfield shift on H(8) (δ 6.74 to 6.83 ppm), indicating the coordination *via*the thiazole-N after deprotonation [33,42,45]. Moreover, H(3,5) signal is shifted clearly downfield (~ δ 7.65 ppm) on the spectra of the complexes, [Pd(bpy)(st)]Cl, [Pd(st)$_2$Cl(H_2O)] and [Zn(st)$_2$], indicating the complexation the deprotonated thiazole-N and SO_2-O atoms in mononegative bidentate manner [33,42,45].

The ^{13}C NMR spectrum of Hst shows resonances at δ167.89 (C-7), 152.19 (C-1), 128.02 (C-4), 127.76 (C-3,5), 124.33 (C-8), 112.57 (C-2,6), 107.72 (C-9). In the complexes, the carbon atoms adjacent to the coordination sites, (C-8) and (C-7) are shifted downfield relative to their positions in free Hst [40,41]; i.e., large deshielding observed for (C-8) with very little shift for the other sulfonamide carbon atoms, confirming the participation of thiazole-N atom in coordination, after deprotonation [33,45]. In case of [Pd(bpy)(st)]Cl, [Pd(st)$_2$Cl (H_2O)] and [Zn(st)$_2$], the downfield shift is also observed in C-3,5 resonance, due tothe coordination through thiazole-N$^-$ and SO_2-O in mononegative bidentate manner (Table 1) [**46**].

Table1. *^{13}C-NMR spectra of Hst and its complexes*

Compound	(C-1)	(C-2,6)	(C-3,5)	(C-4) δ(ppm)	(C-7)	(C-8)	(C-9)
Hst	152.19	112.57	127.76	128.02	167.89	124.33	107.72
[Pd(at)$_2$(H_2O)$_2$]	152.25	112.66	127.78	128.57	170.26	125.47	108.07
[Pd(st)Cl(H_2O)]	152.43	112.92	129.15	128.43	171.20	125.25	107.75
[Pd(st)(bpy)]Cl	152.51	112.63	128.97	128.62	170.03	126.15	108.25
[Zn(st)$_2$]	152.25	112.64	129.17	128.05	170.84	124.97	107.97
[Ag$_2$(st)$_2$]	152.68	113.01	127.97	128.08	170.21	124.99	107.59

UV-Visible Spectra and Magnetic Measurements

The electronic spectrum of [Ni(st)$_2$(H_2O)$_2$] shows bands at 867 and 802 nm are probably due to $^3A_{2g}\rightarrow{}^3T_{1g}$ (F) transition, which may be caused by a distortion from regular octahedral around Ni(II) ion. The strong band at 418 nm can be assigned to a combination of $^3A_{2g}\rightarrow{}^3T_{1g}$ (P) and charge transfer transitions [43]. The magnetic moment of 3.04 B. M. lies within the range reported for octahedral Ni(II) complexes [43]. The diamagnetic tetrahedral complex, [Zn(st)$_2$], displays band near 270 nm, may be assigned to π-π* transitions [47].The ligand field spectra of Pd(II) complexes, [Pd(st)Cl(H_2O)], [Pd(st)$_2$(H_2O)$_2$] and [Pd(bpy)(st)]Cl complexes are typical of a square-planargeometry around Pd(II) ion. The bands near 475, 370 and 320 nmare assigned to $^1A_{1g}\rightarrow{}^1A_{2g}$, $^1A_{1g}\rightarrow{}^1E_g$ and

$^1A_{1g}\rightarrow^1B_{1g}$ transitions, respectively [48]. The absorption band near 370 nm is assigned to the combination of charge transfer transition from Pd (d-orbital) to p- orbital of bpy and d–d bands [39-41].

Mass Spectra

The EI- and muldy-mass spectra of Hst complexes were measured, and the molecular ion peaks agreed with their assigned formulae and the fragmentation patterns corresponding to the successive degradation of the complex [19,40]. The EI-mass spectrum of $[Pd(st)_2(H_2O)_2]$ shows the first peak at *m/z*1228.81 (Calcd. 1228.80) with 21.08% abundance, corresponding to the dimeric $[Pd(st)_2]_2^+$ molecular ion. Two more peaks observed at 974.61 and 614.41are due to $[Pd_2(st)_3]^+$ (calcd. 974.80) and $[Pd(st)_2]^+$(calcd. 614.40), indicating stepwise ligand loss [39,40].The spectrum of $[Pd(st)Cl(H_2O)]$ shows peaks at *m/z* 722.01 (Calcd, 720.80) with 60.4% abundance, indicating also the dimeric $[Pd(st)]_2^+$ species. One more peak characteristic of $[Pd(st)]^+$ is present at 360.89 (Calcd 360.40) [76,77].The EI-mass spectrum of [Pd(st)(bpy)]Cl shows a peak at *m/z* 517.16 (Calcd. 516.40) with 8.0% abundance, corresponding to $[Pd(st)(bpy)]^+$ ion, while the peak due to $[Pd(st-C_6H_6N)(bpy)]^+$ is observed at 426.27 (Calcd. 425.40) [29,40].

The muldymass spectra of Ag(I) complexes were measured. The complex $[Ag_2(st)_2]$ shows peak at *m/z*980.03 with 100% abundance, due to the dimeric $[Ag_2(st)_2(Hst)]^+$ species (calcd. 979.00). The peaks at 725.21 (calcd. 724.00) and 471.07 (calcd. 740.00) correspond to the $[Ag_2(st)_2]^+$and $[Ag_2(st)]^+$ species, respectively [29].The spectrum of [Ag(apy)(st)] has a peak at *m/z* 712.60 (Calcd. 712.00), corresponding to $[Ag(apy)(st)(Hst)]^+$ ion.

The peaks at 457.45, (Calcd. 457.00) and 366.32 (Calcd. 366.0) are assigned to $[Ag(apy)(st)]^+$ and $[Ag(apy)(st-C_6H_6N)]^+$, respectively [40]. The spectrum of $[Zn(st)_2]$ shows a peak at *m/z*575.09 (Calcd. 573.50), assigned to $[Zn(st)_2]^+$ ion, while the other peak at 319.60 (Calcd. 319.50) is associated with $[Zn(st)]^+$ species [47].

TGA Measurements

TGA technique was applied to study the thermal stability and degradation behavior of some the reported complexes. The decomposition of st$^-$ moiety was taken place through the break-down of the hetero C-N or C-S bonds; i.e., low bond break energy [48].

The TGA thermogram of $[Pd(st)_2(H_2O)_2]$ shows three weight loss in 100-220, 221-382 and 383-400° C region, arise from the release of two coordinated water molecules(Calcd. 5.54, Found 5.80%), two$C_6H_6N_2O_2S$ (Calcd. 52.27, Found 52.89%) and CS(Calcd. 13.53, Found 13.42%) (Calcd. 34.59, Found 35.04%) species, respectively, leaving Pd(II) nitride and carbide residue [39,49]. The thermogram of [Pd(st)(bpy)]Cl exhibits three decomposition steps corresponding to the release of ½ Cl_2 molecule (Calcd. 6.43, Found 5.98%; 154-226° C), ½ bpy and C_6H_6N species (Calcd. 30.80 Found 31.08%; 227-388° C)}, and {½ bpy and $C_3H_2NS_2$ fragments (Calcd. 35.15, Found 36.12; 389- 778° C), leaving a residue of PdO and nitride [39,49,50].The complex, [Ag(st)(apy)] shows decomposition step between 200-415° C, which may be assigned to loss of $C_4H_5N_2$ and C_6H_6NSO fragments (Calcd. 48.36; Found 49.04%). The complex exhibits one more decomposition step (416-720° C), corresponding to C_3H_2NSO fragment (Calcd. 21.88; Found 22.01%), leaving Ag(I) oxide and nitride residue [50]. The thermogram of $[Zn(st)_2]$ shows two decomposition steps in the 226-550 and 551-631° C regions due to the loss of two C_6H_6N and SO_2(Calcd. 43.24; Found 43.87%), andtwo $C_3H_2NS_2$ and ½ SO_2 species (Calcd. 37.67; Found 38.11%), leaving a residue of ZnO(14.21%) [40,49].

The TGA thermogram of $[Ni(st)_2(H_2O)_2].3H_2O$ shows three decomposition steps in the 34-155, 156-471 and 472-591° C regions due to the release of three lattice water molecules (Calcd. 8.23; Found 8.39%), two water of coordination and two C_6H_6N (Calcd. 33.54; Found 33.76%), andtwo C_3H_2NS and SO species (Calcd. 32.92; Found 32.87%), leaving a residue of Ni(II) oxide, sulfide and nitride (25.27%) [41].

Stoichiometry and Stability Constants of Hst Complexes in Solution

The complexes in this study were dissolved in DMSO-Saline solutions for the growth inhibition of algae experiments, thus, the stoichiometries and stability constants of these complexes were tested in DMSO and saline solution (0.9% NaCl). No changes were observed in the UV-visible spectra with increasing time intervals (0 - 24 and 240 h) thus indicating the stable nature of the complexes in solution.

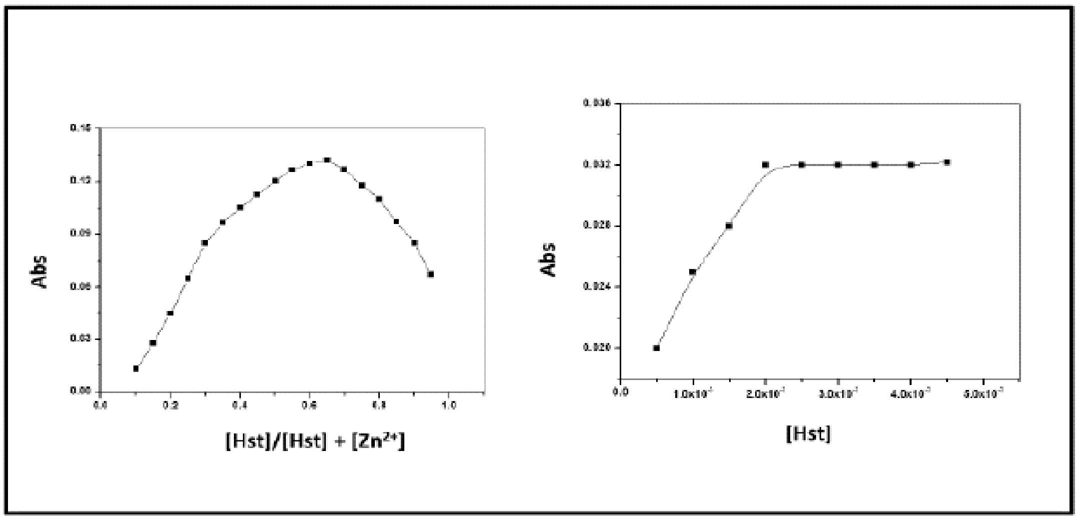
Both the molar ratio [21] and Job's [22] method was applied to study the stoichiometries and stability constants of Co(II), Ni(II), Cu(II), Zn(II), Pd(II) and Ag(I) in DMSO-Saline (1:9 V/V) media.For complexes of a type [ML] and [ML_2], the formation constants (K_f) are calculated using eqs. 1 and 2, respectively

$$K_f = A/A_m\,(1-A/A_m)^2\,C \qquad (1)$$

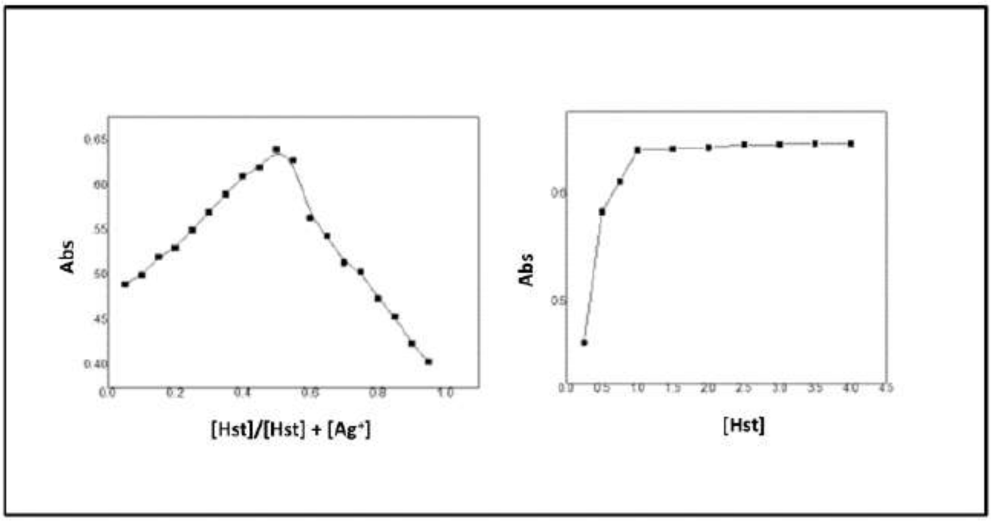
$$K_f = A/Am\;4C^2\,(1-A/A_m)^3 \qquad (2)$$

where A is the arbitrarily chosen absorbance, A_m is the absorbance at the maximum formation of the complex, and C is the initial concentration of the metal. Table 2 and Fig. 4 report the ratios, compositions and stability constants for the complexes. The stability constants increased in the first 30 min and, after that, they become stable for up to 240 h. The stability constants of the complexes, K_f, were determined after 120 min. The composition and the stability constants of the complexes were determined from the curves obtained for equimolar solutions of the metal ions and the ligands in DMSO-saline (1:9 V/V) solutions (Fig. 4). The maxima obtained indicate the formation of the complexes with formulae, [$M(st)_2$] (M = Co, Ni, Cu, Zn) and [M'(st)] (M' = Pd, Ag) [41,47].

The complexes showedstability constants in the range of K_f = 5.5 x 10^8 – 2.5 x 10^6.As expected and on the bases of Irving and Williams order, the stability constants for the first row transition elements complexes with Hst decreased in the order Cu(II) > Ni(II) > Co(II) [41,47]. In addition, the stability constant of Ag(I) >Pd(II) > Cu(II) in agreement with the early reported complexes of 4-hydroxysalicylidene-2-aminopyrimidine Schiff-base [41].



(a)



(b)

Fig4. *Job's method and molar ratio for Hst-Zn(II) (a) and Hst-Ag(I) (b) complexes (5 x 10^{-4} M) in DMSO-Saline (1:9 V/V) at 298 K*

Table 2. *Composition and stability constants of Hst complexes by Job' and molar ratio methods*

Metal ion Salt	Ligand	Ratio	Composition	Stability constant
$CoCl_2$	Hst	0.66	1:2	2.58×10^6
$NiCl_2$	Hst	0.69	1:2	3.00×10^6
$CuCl_2$	Hst	0.71	1:2	3.54×10^6
$Zn(ClO_4)_2$	Hst	0.70	1:2	1.12×10^6
$K_2[PdCl_4]$	Hst	0.50	1:1	2.78×10^7
$AgClO_4$	Hst	0.49	1:1	5.51×10^8

Toxicity Assessment of Hst and its Complexes against the Microchlorophyte (Chlorella Vulgaris)

Microalgae are sensitive indicators of environmental change and are widely used in the assessment of risk and development of environmental regulations for metal ions [51]. The toxic effects of metal ions on different species of algae have been investigated [52-57].

Heavy metal ions constitute an important factor for many microbes, based on their concentrations. Although some of metal ions are required for cell growth, high concentrations show toxicity on the metabolic machinery of algae [58-63].Thus, the aim of this study was to evaluate the effect of some metal ions and their Hst complexes on the growth inhibition of *Chlorella vulgaris*.

Growth Inhibitory

It is well known that algal cells exposed to metal ions may cause morphology and biochemical alterations [64]. In addition, the inhibitory and stimulatory effects of these metal ions are depending on their concentration [65].Moreover, algae are known to be able to accumulate heavy metals. They are able to eliminate metal ions from aquatic solutions in a short time by biosorption in uncomplicated systems, without any problems of toxicity. It is an important biochemical function of algae in the shaping of proper ecological relationships and interactions between organisms in the aquatic environment [65].

The effects of Hst, $NiCl_2.6H_2O$, $Zn(ClO_4)_2$, K_2PdCl_4, $AgNO_3$, $[Ni(st)_2(H_2O)_2]$, $[Zn(st)_2]$, $[Pd(st)Cl(H_2O)]$,$[Ag_2(st)_2]$ and [Ag(apy)(st)] on the growth of green alga microchlorophyte (Chlorella *vulgaris*)after 72 h incubationwere screened(Fig. 5). Free Hst shows slight effect in ecotoxicity; i.e., encourage alga growth. This feature may be attributed to the inter- and intra-H bonds, present between Hst active sites (–NH_2, O=S=O, C-S and C=N), which make it not easy to release [29-32,66]. On the other hand, K_2PdCl_4 and $AgNO_3$show high ecotoxicity; i.e., they are inhibiting the algae growth, in agreement with the effect of Co(II), Cu(II) and Zn(II) ions on Chlorella *vulgaris*, Calothrix *fusca*and Nosto c*muscorum*[52,53].

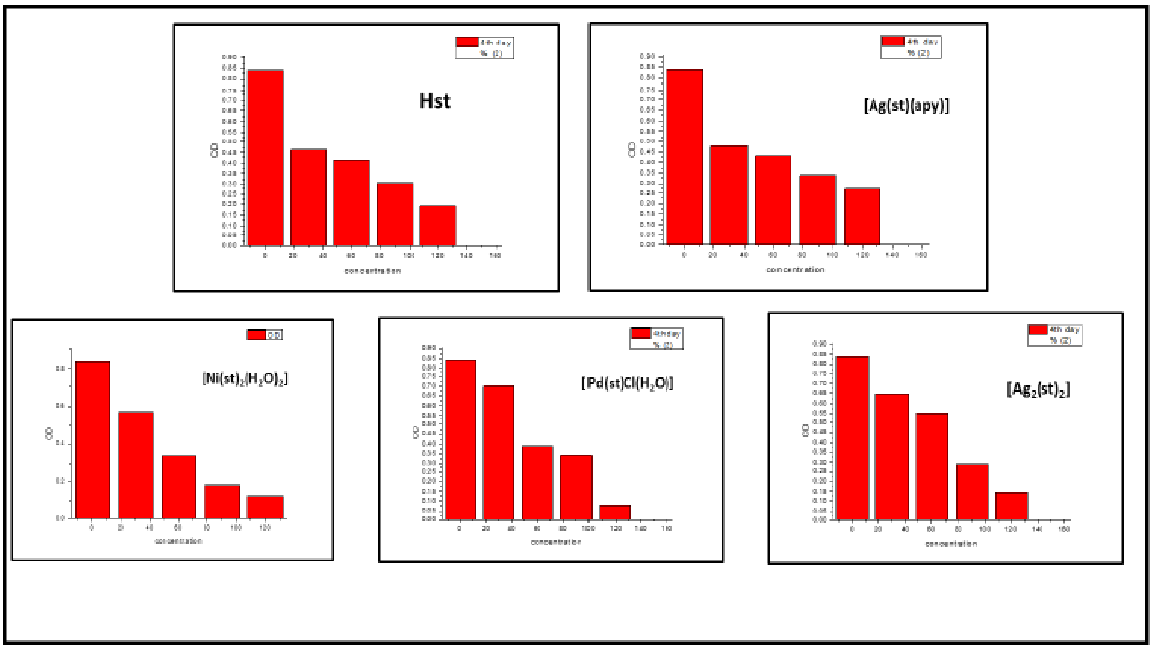


Fig5. *The Inhibitory effects of Hst $[Ni(st)_2(H_2O)_2]$, $[Pd(st)Cl(H_2O)]$, $[Ag_2(st)_2]$ and [Ag(apy)(st)] on the growth of green alga microchlorophyte (Chlorella vulgaris)after 72 h incubation*

At low concentration (30 ppm), the inhibitory effect of the complexes is increasing in the order, Hst<[Ag(apy)(st)] <$[Ni(st)_2(H_2O)_2]$ ≅$[Zn(st)_2]$ <$[Ag_2(st)_2]$< $[Pd(st)Cl(H_2O)]$.The growth of control culture was progressively increased as the incubation period reaching its maximum value after 72 h. These facts were supported by El-Naggar et al [67]who evaluated the stimulated growth of Nostoc*muscorum* at low concentration of Co(II) (0.01 ppm), while on Calothrix *fusca* non-significant growth was observed. However, at high concentration of Co(II), both organisms showed inhibition growth.

Growth Inhibition Percentage

The growth kinetics of the studied complexes exhibit pronounced specific growth rate values. The inhibitory effects are proportional to the concentration (Fig. 5). As the cultures supplemented with different concentrations of the metal ions, Hst and the complexes, $[Ni(st)_2(H_2O)_2]$, $[Zn(st)_2]$, $[Pd(st)Cl(H_2O)]$, $[Ag_2(st)_2]$ and [Ag(apy)(st)],the growth rates decreased with increasing metals ions, Hst or the complexes concentration.

The effect of concentration of $NiCl_2.6H_2O$, $Zn(ClO_4)_2$, K_2PdCl_4, $AgNO_3$, Hst and their complexes (30, 60, 90 and 120 ppm) on the growth inhibition of *C. vulgaris* cultures was calculated, and their microalgae detoxification were estimated, based on the calculation of EC_{50} value (index of toxicity; Fig. 6) [68]; it is the concentration the tested compounds that reduce the growth of algal culture to 50%. The growth inhibition of *C. vulgaris* follows the order;$[Ni(st)_2(H_2O)_2]$≅Hst>[Ag(apy)(st)]>$[Pd(st)Cl(H_2O)]$> $[Ag_2(st)_2]$ (Table 3).

Table3. *Effect of concentration of Hstand their complexes in the toxicity unites of C. vulgaris cultures*

Treatments	**Hst**	**$[Ni(st)_2(H_2O)_2]$**	**$[Pd(st)Cl(H_2O)]$**	**$[Ag_2(st)_2]$**	**[Ag(st)(apy)]**
Ec_{50} (mg/L)	49.99	49.87	69.89	90.00	57.86
Unites Toxicity	2.00 toxic	1.90 toxic	1.40 toxic	1.11 Toxic	1.69 toxic

The growth inhibition % of *C. volgaris* with free Hst is notably high in comparison to the reported complexes. [69]. Moreover, Hst and its complexes, $[Zn(st)_2]$, $[Ni(st)_2(H_2O)_2]$, [Ag(apy)(st)], $[Pd(st)Cl(H_2O)]$ and $[Ag_2(st)_2]$ show toxicity. Generally, the concentration, (30-120 ppm) of the tested metal ions and their complexes, the inhibition is depending on the type of the metal ion, oxidation state, geometry of the complex and the active sites [40,70].

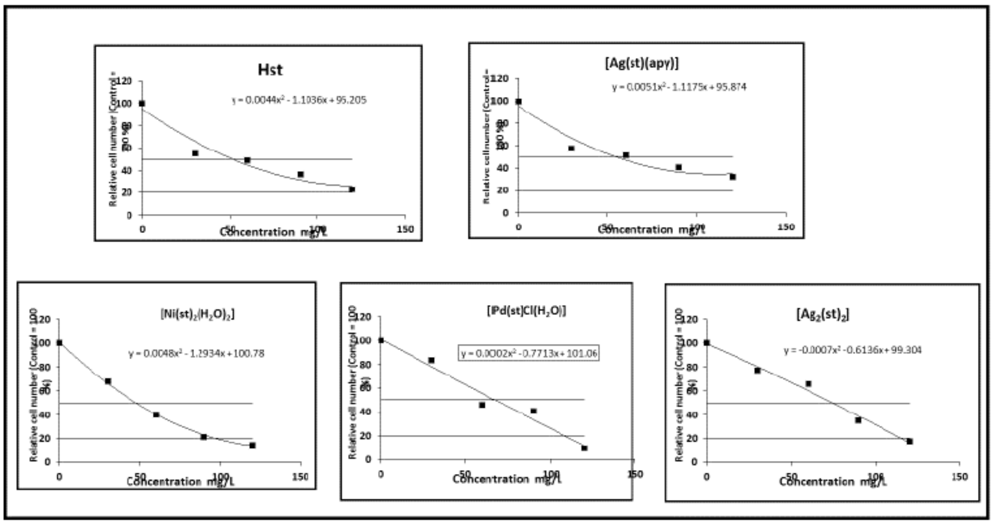


Fig6. *EC50 values of Hst [Ni(st)2(H2O)2], [Pd(st)Cl(H2O)], [Ag2(st)2] and [Ag(apy)(st)] on the growth of green alga microchlorophyte (Chlorella vulgaris)*

In addition, the degree of hydrolysis of the complexes in the applied media may affect their structures and thus the degree of interaction with DNA through the reaction with the phosphate residues with the production of macro-chelates. This may be attributed to the destructor effect on the microtubules and cytoskeletal proteins present in the cells. These microtubules (which found in all eukaryotes) play essential role in the cell division (mitosis). Thus, the action of benzimidazoles is due to the inhibition of the polymerization of α- and β-tubulin subunits by disrupting microtubule role in the algae growth [71]. In addition, the data showed that the bioaccumulation factors of the tested metals ions, $NiCl_2$, $Zn(ClO_4)_2$, K_2PdCl_4, $AgNO_3$, were parallel to the increase in the concentrations in the culture medium. The bio-accumulation factor of Pd(II) and Ag(I) are higher than those of Ni(II) and Zn(II). Metal ions accumulation by *Chlorella vulgaris* were shown in the order of Pd(II) > Ag(I) > Ni(II) > Zn(II). Thus, the ability of microalgae to accumulate metal ions from aqueous solution was early reported [61]. The phenomenon of metal ions accumulation by microbial cells is quite complex and the principal mechanisms of adsorption onto the surface of the cell with slower active uptake into the cytoplasm. As passive biosorption mainly depends on binding to functional surface of the cell wall, which is very important for rapid metal ion uptake [54,72].

CONCLUSION

The new Ni(II), Zn(II), Pd(II) and Ag(I) complexes of sulfathiazole(Hst) have been synthesised. The structures of the complexes were investigated using IR, NMR (^{1}H, ^{13}C), UV–Vis, and EI and maldi-mass spectra, elemental analyses, molar conductivities and TGA measurements. Hst coordinates to the metal ions in a mono-negative monodentate or mononegative bidentate manner *via* the deprotonated thiazole-N or SO_2-O and deprotonated thiazole-N atoms. The composition of the complexes by applying both Job' and molar ratio methods have been calculated based on UV-vis spectroscopy. The toxicity of some metal ions, Hst and its complexes against *Chlorella vulgaris*, were screened.

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