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Synthesis, characterization and antitumor activity of Cu(II), Co(II), Zn(II) and Mn(II) complex compounds with aminothiazole acetate derivative

Research Article

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Abstract: This paper presents the synthesis of complex compounds of type $[M(L1)_2]$, where M(II)= Cu (1), Co (2), Zn (3), L1= 2-aminothiazole-4-acetate and $[Mn(L1)_2(H_2O)]$ (4) using ethyl 2-(2-aminothiazole-4-yl) acetate (L), and characterization by elemental analysis, magnetic susceptibilities, IR, 1H-NMR, UV-Vis spectroscopy and for $[Mn(L1)_2(H_2O)]$ also by X-ray diffraction. In vitro cytotoxicity studies were performed on human cervix adenocarcinoma, HeLa cells. The antitumor selectivity was assessed using normal human peripheral blood mononuclear cells, PBMC as control.

Keywords: *Aminothiazole • Cytotoxicity • HeLa • PBMC*

1. Introduction

Naturally occurring and synthetic thiazole derivatives find applications as antioxidants [1], antibacterial drugs [2-4] and fungicidal treatment [5,6]. Anti-inflammatory, analgesic and antipyretic activities are known for some thiazolyl and benzothiazolyl derivatives [7-9]. These compounds are able to block cartilage destruction during the inflammatory process and thus are a promising class of anti-inflammatory compounds [10].

The use of 2-aminothiazole derivatives as inhibitors of human cancer and Alzheimer's disease was studied and developed [11-15]. 2-Aminothiazole-5-carboxylates are an important class of heterocycles in organic chemistry, especially in the preparation of biologically and medicinally useful agents such as angiotensin II antagonists, DNA minor groove binding analogs of netropsin [16]. The antitumor activity of some thiazole derivatives for example thiazole nucleoside tiazofurin, distamycin, netropsin, thia-netropsin- with binding properties to DNA and the thiazole containing antitumor agent bleomycin was reported. Ethyl 2-substituted-aminothiazole-4-carboxylate analogs were tested for their in vitro antitumor activity against human tumor cell lines. Ethyl 2-[3(diethylamino)propanamido]-thiazole-4-carboxylate exhibited remarkable activity against RPMI-8226 leukemia cell line [17].

Only few studies have been published related to complex compounds with 2-aminothiazole derivatives which presented coordination geometry of the metal ion of tetrahedral type for Zn(II), Co(II) [18,19], Cd(II) [20], and octahedral type for Co(II) [21]. The complex of Ru(III) with ethyl 2-amino-4-phenyl-5-thiazolecarboxylate showed significant antileukaemic activity on various human cells [22] and also Keppler-type ruthenium(III)

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complexes like 2-aminothiazolium[*trans*-tetrachlorobis(2-aminothiazole)ruthenate(III)] exhibit promising antitumor properties [23].

In this work, we synthesized and characterized four new complex compounds of Cu(II), Co(II), Zn(II) and Mn(II), respectively with thiazole derivative L1 (2-aminothiazole-4-acetate) obtained from ethyl 2-(2-aminothiazole-4-yl)acetate, L which hydrolyzed during the synthesis. Cytotoxicity of L as well as $[Cu(L1)_2]$ (**1**) and $[Mn(L1)_2(H_2O)]$ (**4**) on HeLa cells and on PBMC have also been determined.

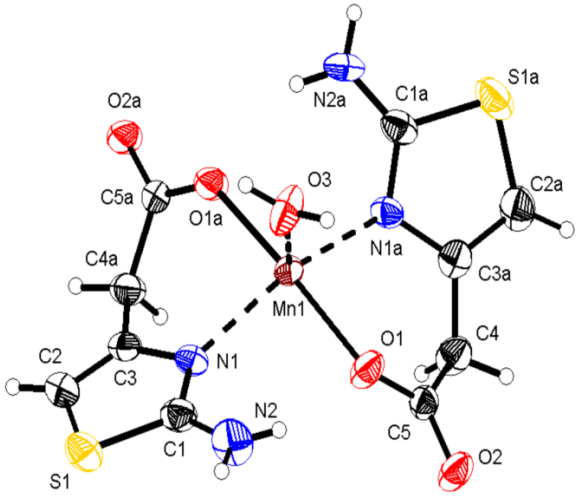

Figure 1. X-ray structure of $[Mn(L1)_2(H_2O)]$

2. Experimental Procedure

All reagents and solvents (Sigma-Aldrich), were of analytical grade and used without further purification. Complete medium for cell growth and the reagents for cytotoxicity studies were purchased from Sigma-Aldrich (Taufkirchen, Germany).

Synthesis of L1: NaOH and L, molar ratio 1,5:1 were mixed in water-ethanol as solvent and kept under reflux for 5 h. The solvent was evaporated and the precipitate resulted was recrystallized from water.

Synthesis of complex (**1**): 0.372 g (2 mmoles) of L dissolved in EtOH were added to an aqueous solution of 0.17 g (1 mmole) $CuCl_2 \cdot 2H_2O$. The solution was kept under stirring at 50^{0}C for 2 h. The brown precipitate was filtered off, washed with EtOH and dried under vacuum. Yield: 55%. *Anal* Found (%): Cu, 16.52; C, 32.10; H, 2.60; N, 15.06. Calculated for $CuC_{10}H_{10}N_4O_4S_2$ (%): Cu, 16.82; C, 31.78; H, 2.65; N, 14.83. σ (μS cm^{-1}): 34, non-electrolyte.

Synthesis of complex (**2**) and complex (**3**): The complexes were prepared as described for complex (**1**), using 0.372 g L and 0.238, and 0.24 g of $CoCl_2 \cdot 6H_2O$ and $ZnCl_2$, respectively.

The complex (**2**) was obtained as a light pink solid. Yield: 60%. *Anal* Found (%): Co, 15.14; C, 32.31; H, 3.02; N, 15.12. Calculated for $CoC_{10}H_{10}N_4O_4S_2$ (%): Co, 15.81; C, 32.17; H, 2.68; N, 15.01. σ (μS cm^{-1}): 42, non-electrolyte.

The complex (**3**) was isolated as a white solid. Yield: 56%. *Anal* Found (%): Zn, 17.06; C, 31.50; H,

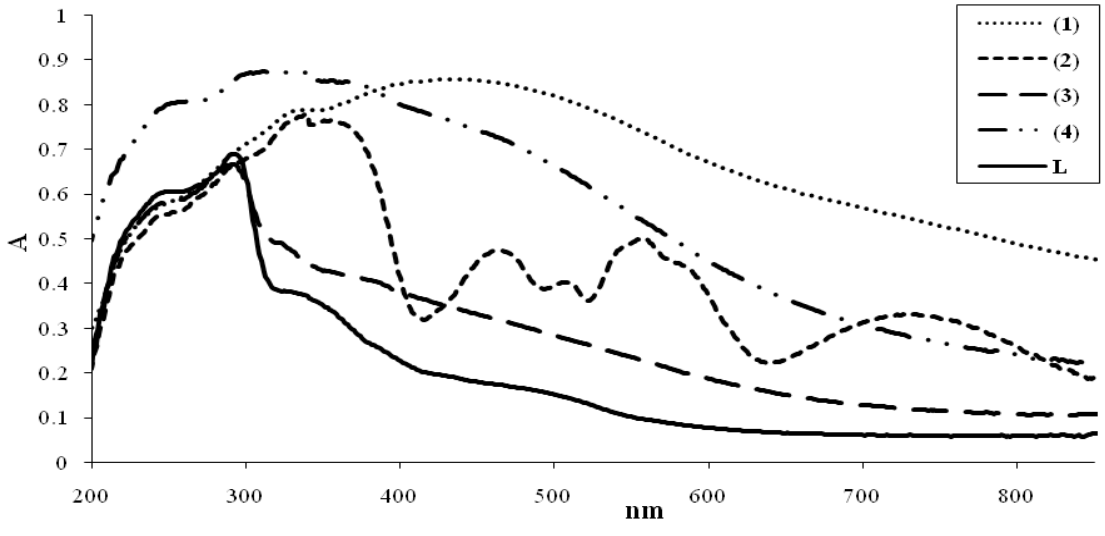

Figure 2. UV-VIS spectra for L, (1), (2), (3) and (4)

2.87; N, 14.23. Calculated for $ZnC_{10}H_{10}N_4O_4S_2$ (%): Zn, 17.15; C, 31.66; H, 2.64; N, 14.77. σ (μS cm^{-1}): 28, non-electrolyte.

Synthesis of complex (**4**): 0.372 g (2 mmoles) of L dissolved in EtOH was added to an aqueous solution of 0.24 g (1 mmole) of $Mn(CH_3COO)_2 \cdot 2H_2O$. The solution was kept under stirring at 50 ^{0}C for 2 h. The light brown precipitate was filtered off, washed with EtOH and dried under vacuum. Yield: 53%. *Anal* Found (%): Mn, 14.15; C, 30.93; H, 3.41; N, 14.65. Calculated for $MnC_{10}H_{12}N_4O_5S_2$ (%): Mn, 14.21; C, 31.01; H, 3.10; N, 14.47. σ (μS cm^{-1}): 46, non-electrolyte.

The elemental analysis was performed on a Perkin-Elmer Series II CHNS/ O Analyser 2400. ^{1}H-NMR spectra were recorded on a Gemini 300 BB operating at 300 MHz in DMSO-d6 using TMS as internal standard. UV-Vis reflectance spectra were recorded on Jasco V-560 spectrophotometer and IR spectra on a FT-IR Bruker VERTEX 70 equipped with a diamond ATR. Electrical molar conductivities were measured in N,N-dimethylformamide (10^{-3} M solution) on OK-114 RADELKIS Conductometer at 25^{0}C. Magnetic measurements were carried out with a Faraday balance at room temperature using Mohr salt as standard. X-ray diffraction measurements were performed on a STOE-IPDS II diffractometer. The structures were solved (SHELXS-97) by direct methods and refined (SHELXL-97) by full matrix least-square procedures on *F*2 [25]. Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 755831.

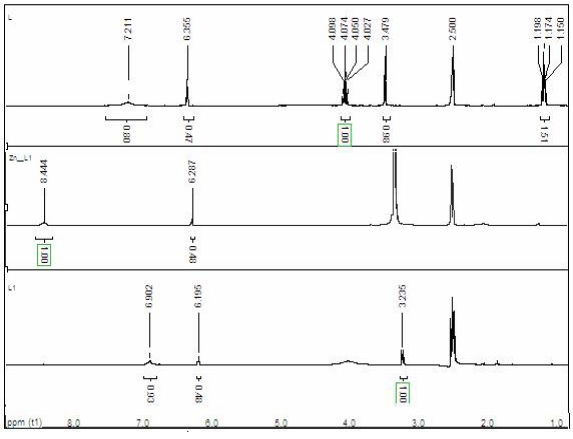

Figure 3. 1H-NMR spectra of L, $[Zn(L1)_2]$ and L1

Table 1. Crystal data and structure refinement for $[Mn(L1)_2(H_2O)]$

Formula weight	386.31
Temperature	297(2) K
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, C2/c
Unit cell dimensions	a = 12.1567(17) Å alpha = 90 deg.
	b = 9.4915(13) Å beta = 94.556(2)deg.
	c = 12.7295(18) Å gamma = 90 deg.
Volume	1464.2(4) Å^3
Z, Calculated density	4, 1.752 g cm^{-3}
Absorption coefficient	1.215 mm^{-1}
F(000)	784
Crystal size	0.52×0.16×0.15 mm
Theta range for data collection	2.73 to 24.99 deg.
Limiting indices	-14<=h<=14, -11<=k<=11, -15<=l<=15
Reflections collected / unique	6785 / 1285 [R(int) = 0.0471]
Completeness to theta = 24.99	99.9%
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.8388 and 0.5707
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1285 / 2 / 110
Goodness-of-fit on F2	1.272
Final R indices [I>2sigma(I)]	R1 = 0.0630, wR2 = 0.1135
R indices (all data)	R1 = 0.0695, wR2 = 0.1163

2.1. Cytotoxicity assays on HeLa cells

(HeLa cells (human cervical carcinoma cell line) were cultured in triplicate in a 96-well plate at 37°C under 5% CO_2 in 100 μL of growth medium, RPMI 1640 (Sigma-Aldrich, Taufkirchen, Germany) supplemented with 10 % fetal calf serum (FCS) (Sigma-Aldrich), 2 mM glutamine (Sigma-Aldrich), 100 IU mL^{-1} penicillin and 100 IU mL^{-1} streptomycin (Sigma-Aldrich). The Hela cells were seeded as 2000 cells/well and after 24 h, serial dilutions of the compounds are added. The ligand and the complex compounds (**1**) and (**4**) were dissolved in DMSO and the solutions were diluted by nutrient medium, RPMI 1640, containing 10% FCS.

After allowing cells to adhere to the plate for 24 h, the medium was removed and the compounds were added to the wells at different concentrations in the range 0,01-100 μM for the ligand and 0,001-10 μM for compound (**1**) and 0,5-500 μM for compound (**4**). For the compounds to take effect freshly prepared compounds solutions were incubated for 24 h at 37°C under 5% CO_2. Cytotoxicity was evaluated using MTT assay (Sigma-Aldrich). A solution of MTT 5mg ml^{-1} in phosphate buffered saline (PBS) was added to each well and mixed with the suspensions followed by incubation to allow the metabolization of MTT. After the incubation,

Table 2. Hydrogen bonds for (4) (Åand deg.)

D–H···A	d(D–H)	d(H···A)	d(D···A)	(DHA)	Symmetry transformations
O(3)–H(3)···O(2)	0.82	1.88	2.654 (5)	157	½+x, ½+y, z
N(2)–H(10)···O(2)	0.85 (4)	2.02 (4)	2.849 (6)	168 (4)	3/2-x, 1/2-y,1-z
N(2)–H(11)···O(1)	0.85 (5)	2.13 (4)	2.916(6)	153 (6)	

the medium was removed and the formazan (MTT metabolic product) resuspended and thoroughly mixed in 100 µL DMSO. The optical densities were read at 540 nm and the background substracted at 670 nm using an Elisa microreader. The measure of the cytotoxicity of the compounds both in PHA/PBMC and HeLa cells is an IC_{50} value (calculated as the concentration of the tested compound needed to reduce cell viability for 50% when compared to the control cells).

2.2. Preparation and treatment of PBMC

Peripheral blood mononuclear cells (PBMCs) were isolated from a healthy donor by Ficoll (Amersham Biosciences) density gradient centrifugation. PBMCs (2×10^5) were cultured in duplicates in 96-well Nunclone plates in 200 µL of RPMI 1640 medium supplemented with 10% fetal calf serum (FCS) (Sigma-Aldrich), 2 mM glutamine (Sigma-Aldrich), 50 µM *β*-mercaptoethanol (Sigma-Aldrich), 25 µg mL^{-1} gentamicin, 100 IU mL^{-1} penicillin and 100 IU mL^{-1} streptomycin (Sigma-Aldrich) at 37°C and 5% CO_2 in a humidified atmosphere. Cells were stimulated with a mitogen, phytohaemaglutinin (PHA) (0.5 µg/mL). The final concentrations of the compounds in cell suspension ranged between 0,001-100 µM (L) 0,0001-10 µM (**1**), 0,5-500 µM for (**4**). Cell survival was determined by MTT test [26-28].

PHA/PBMC cultures with serial dilutions of the compounds were incubated for 76 h in a humidified atmosphere at 37°C, before addition of the MTT reagent. The MTT metabolic product, formazan, solubilizes in DMSO and absorbs at 540 nm. Optical density was read at 540 nm and background subtracted at 670 nm using an Elisa microplate reader.

3. Results and Discussion

The complex compound was synthesized from aqueous solutions of metal salts $MCl_2 \cdot xH_2O$, where M(II)= Cu, Co, Zn, x= 2, 6, 0 and $Mn(CH_3COO)_2 \cdot 4H_2O$ which was mixed with methanol solutions of L (1: 2, metal: ligand ratio).

Ethyl 2-(2-aminothiazole-4-yl)acetate, L, hydrolyzed in the aqueous solutions and in the presence of metal ions, conditions in which ligand L1 was generated. Thus the complex compounds contain L1 that was synthesized and characterized independently. The hydrolysis of the ester group from L was recently noticed by Zhang *et al*. [24].

3.1. X-ray crystallography

X-ray structure was determined for complex compound (**4**), $[Mn(L1)_2(H_2O)]$, (Fig. 1) which crystallizes in the centrosymmetric space group C2/c with a R value of 0.06. Crystal data and structure refinement details are given in Table 1. Mn atom has distorted square pyramidal coordination geometry water molecule in axial position and two ligand molecules in equatorial plane coordinating through N1, N1a, O1, O1a atoms. Interatomic distances are Mn(1)–N(1) 2.175(4), Mn(1)–O(1) 2.106(3) and Mn(1)-O(3) 2.081(5) Å. The packing of the structure is based on intermolecular hydrogen bonding between the unit cells. Hydrogen bond lengths and angles are presented in Table 2. Also, the distance (3,566(3) Å) between the mean planes suggests the existence *of π-π* stacking interactions between the neighboring thiazole rings.

Table 3. FTIR bands and assignments

L	L1	(1)	(2)	(3)	(4)	Assignment
3277	3256	3294	3291	3289	3289	$\nu_{sim}NH_2$
3115	3079	3096	3095	3094	3094	ν_{simCH} (thiazole)
2990						$\nu_{asim}CH_3$
2903						$\nu_{sim}CH_3$
1711						$\nu_{C=O}$
	1591	1574	1578	1579	1578	$\nu_{asimCOO-}$
1621	1619	1634	1632	1634	1634	$\nu_{C=N}$
1521	1515	1511	1511	1514	1514	$\delta_{thiazole}$
	1391	1398	1410	1411	1399	$\nu_{simCOO-}$
1312	1323	1358	1364	1365	1365	δ_{C-H}
1245	1291	1289	1290	1288	1288	ν_{C-O}
1126	1119	1127	1129	1130	1130	ν_{C-N}
977	973	940	943	940	941	ν_{S-C}
		431	434	435	436	$_{\nu M-N}$, M (II)= Cu, Co, Zn, Mn

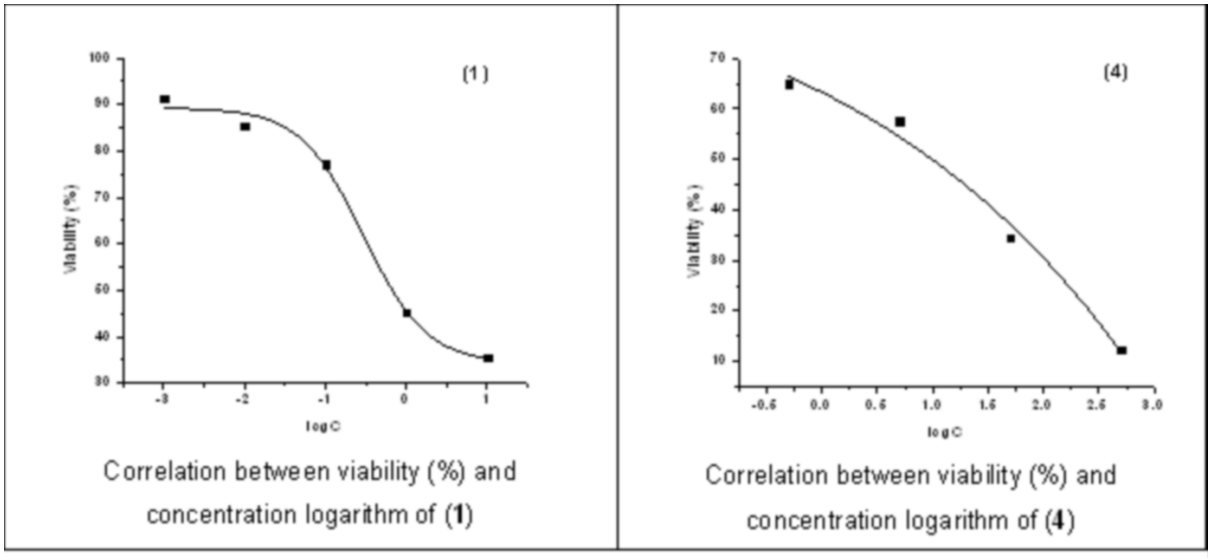

Figure 4. Representative graphs showing survival of tumor cells HeLa grown for 48 h in the presence of increasing concentrations of the complexes (1) and (4) determined by MTT test

Table 4. Magnetic moments of the compounds

Compound	Magnetic susceptibility $10^{6*}\ _{x_g}$, $cm^3\ g^{-1}$	Magnetic moment, μB	Theoretical magnetic moment, μB
(1)	2,6	1,92	1,73
(2)	16	4,39	3,87
(3)	<0	≈0	0
(4)	32	6,42	5,92

3.2. UV-Vis spectroscopy

UV-Vis spectra of the solid powders of L and complex compounds (**1**), (**2**), (**3**), (**4**) are shown in Fig. 2. UV-Vis spectrum of compound (**1**) shows a wide LMCT type band at 470 nm. The bands at 450 nm and 550 nm of compound (**2**) can be assigned to $^4T_{1g} \leftarrow {}^4T_{1g}(P)$ (v2) and $^4T_{1g} \leftarrow {}^4A_{2g}$ (v3) *d-d* transitions, characteristic for Co(II) in tetrahedral symmetry. The UV-Vis spectrum for compound (**4**) contains a large band at 370 nm assigned to LMCT process.

3.3. IR spectroscopy

IR spectra were recorded for the ligand and the complexes in order to determine the coordination manner. The assignments of the IR bands are presented in Table 3. Disappearance of vibration band C=O (ester group) from the IR spectra of L1 and of complex compounds (**1**)- (**4**) which appeared at 1711 cm^{-1} in the IR spectrum of L, confirm the hydrolysis of L. Also the asymmetric and symmetric vibration bands of carboxyl group present in the IR spectrum of L1 at 1591 cm^{-1}, 1391 cm^{-1} respectively, and in the IR spectra of the complex compounds at 1574, 1398 cm^{-1} (**1**), 1578, 1410 cm^{-1} (**2**), 1579, 1411 cm^{-1} (**3**) and 1578, 1399 cm^{-1} (**4**) demonstrates the hydrolysis of L1. A significant difference between IR spectra of the ligand L1 and the coordination compounds is the position of C=N vibration band which is shifted from 1619 cm^{-1} (L1) to higher frequencies 1634 cm^{-1} (**1**), 1632 cm^{-1} (**2**), 1634 cm^{-1} (**3**), 1634 cm^{-1} (**4**), due to the coordination of the endo-N atom to the metal ions.

3.4. ^{1}H- NMR spectroscopy

Aliphatic proton signals from the ester group are shown only in the ^{1}H-NMR spectrum of L as opposed to ^{1}H-NMR spectra of L1 and (**3**) due to ethyl 2-(2-aminothiazole-4-yl)acetate, L, hydrolysis. Another important difference between ^{1}H-NMR spectra of L, L1 and the complex compound is the shift of amino protons

Table 5. EC_{50} values for L, (1) and (4)

EC_{50} (μM)	L	$[Cu(L1)_2]$	$[Mn(H_2O)(L1)_2]$
HeLa	84	0,67	9,85
PBMC	>100	22	51

signals from 7,21 ppm (L), 6,90 ppm (L1) to 8,44 ppm (**3**). Also the signal of aromatic proton from the thiazole ring from L1 suffers a small displacement from 6,19 ppm (L1) to 6,28 ppm for the complex compound $[Zn(L1)_2]$, Fig. 3.

3.5. Magnetic measurements

The values of the experimental magnetic moments are very close to theoretical values (Table 4). The values of the magnetic moments of the (**2**) and (**4**) support the high spin tetrahedral distorted configurations which are in accordance with the appearance of UV-Vis spectra. Compound (**3**) displays diamagnetic behaviour.

3.6.Viability assessments

The EC_{50} values were determined by extrapolation from cell viability curves. Fig. 4 contains two representative graphs for cytotoxic activity of (**1**) and (**4**) on HeLa cella. The EC_{50} values are presented in Table 5.

The viability increases along with the decrease of the concentration of the compounds. The ligand (L) does not show high cytotoxicity in any of the cultures tested. The presence of the metal ions in coordination compounds (**1**) and (**4**) greatly increased its cytotoxicity in comparison with the ligand, especially on HeLa cells.

The values obtained for compounds (**1**) and (**4**) in the assay performed on human PBMC show less toxic effects than those obtained in human cervix adenocarcinoma cell lines. The selectivity in cytotoxic effect on HeLa and PBMC is especially pronounced for complex compound (**4**) that exhibited high selectivity on HeLa cells and a very low EC_{50} value.

4. Conclusions

Four new coordination compounds of type $[M(L1)_2]$, where M(II)= Cu(II), Co(II), Zn(II) and $[Mn(L1)_2(H_2O)]$ were synthesized starting from ethyl 2-(2-aminothiazole-4-yl)acetate which hydrolyzed leading to coordinated ligand L1, 2-aminothiazole-4-acetate. The complexes were characterized by UV-Vis, IR, NMR spectroscopy and magnetic susceptibilities. The structure of complex (**4**) was solved by X-ray structure analysis. The cytotoxic activity of L and of complex compounds (**1**) and (**4**) on HeLa and PBMC was evaluated. The results of the cytotoxicity tests indicate that L exhibits high viability on PBMC and HeLa cells, but when involved in coordination bonding with 3*d* metals the cytotoxicity increases consistently. Coordination compounds (**1**) and (**4**) exhibit promising antitumor activity against cancerous cells (HeLa) and moderate to low toxicity on PBMC.

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