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NEW DINUCLEAR CYANIDO COMPLEXES WITH AMINE ALCOHOL LIGAND: SYNTHESIS, CHARACTERIZATION AND BIOTECHNOLOGICAL APPLICATION POTENTIAL

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In this study, the cyanido complexes given by the formula $[Ni(Abut)Ni(CN)_4]$ - $8H_2O$ (C1), $[Cu(Abut)_2Ni(CN)_4]$ - $7H_2O$ (C2), $[Zn(Abut)Ni(CN)_4]$ - $8H_2O$ (C3) and $[Cd(Abut)Ni(CN)_4]$ - $7H_2O$ (C4) were obtained by microwave synthesis method. The powder forms of the complexes were characterized by elemental, FT-IR spectroscopy, and thermal analysis. And also antibacterial, antibiofilm and anticancer activities were investigated. The splitting stretching bands of cyanido groups in the FT-IR spectra of C1-C4 indicated the assets of terminal and end cyanido groups. The antibacterial activities of C1-C4 were tested with nine Gram negative and six Gram positive bacteria. The most efficient antibacterial activity of complexes was observed at $1000 \, \mu \text{g/ml}^{-1}$ concentration. Anticancer activity was tested using HeLa cell line and MTT test. The studied cyanide complexes have been shown to decrease the viability of HeLa cells with IC_{50} values 14.86, 6.5, 7.2 and 19.2 $\mu \text{g/ml}$ for C1, C2, C3 and C4 complex, respectively.

Keywords: cyanido complexes, antimicrobial, anticancer activity, HeLa cells.

he cyanido complexes, which are still up to date in coordination chemistry and organometallic chemistry, are among the first coordination compounds that have been synthesized, characterized, and used [1,2]. These complexes exhibit different structures due to the ability of cyanido ligand to bind the transition metal atoms in different ways. Cyanido is one of the strong ligands after carbonyl in the spectrochemical series used in the synthesis of 1D, 2D and 3D cyanido complexes. The four-electron donor cyanido is a bidentate ligand with potentially reactive nitrogen and carbon atoms and exhibit σ -donor (C \rightarrow M, N \rightarrow M') and β -acceptor

(M→C, M'→N) features. The cyanido complexes have different structural properties, allowing for a wide use in the field of chemistry, biology, and material chemistry [2]. The applications of these complexes have been focused on catalysis [3], nonlinear optics, ion exchange materials, gas storage [4], molecular magnets [5-9], molecular sieves [10], enzymatic [11], antibacterial [13] and anticancer activities [5, 12, 13] and thermally stable materials [14-17]. Homoleptic tetracyanidonickelate(II) building block has been extensively used for the synthesis and design of different dimensional networks [18-21]. Cyanido complexes exhibit different structures due to

the ability of the cyanido ligand to bind differently to the second metal atoms such as Hg^{II} [22], Mn^{II} [23], Co^{II} [24], Cd^{II} [25,26], Cu^{II} [27-29] and Zn^{II} [30-33].

The 2-amino-1-butanol (*Abut*) ligand is a bidentate neutral ligand that can coordinate with a metal atom with nitrogen and oxygen and can form different complex structures originating from its geometry. Although many examples of cyanido complexes were found in the literature review, complexes using this ligand could not be found. This research aimed at synthesizing four cyanido complexes having general formulas ($[M(Abut)_n Ni(CN)_4]$, ($M=Ni^{II}$, Cu^{II} , Zn^{II} , Cd^{II} ; Abut: 2-amino-1-butanol; n=1 or 2) and their spectroscopic (IR) and thermal properties, antibacterial properties on 16 different human disease-causing bacteria and antibiofilm activity.

Materials and Methods

Materials and instrumentation. In this study, all chemicals NiCl₂·6H₂O, CuCl₂·2H₂O, ZnCl₂, CdSO₄·8/3H₂O and 2-amino-1-butanol (*Abut*, C₄H₁₁NO) were obtained commercially and used without further purification. The IR spectra of **C1-C4** were recorded at room temperature in powder form between 400-4000 cm⁻¹ using a FT-IR spectrophotometer (Jasco Spectra Manager V.2). Thermal analysis of C1-C4 containing tetracyanidonickelate were done. The TG, DTG and DTA (DSC) curves were recorded simultaneously in a Pt crucible using 5-10 mg of sample, in a nitrogen atmosphere, at a heating rate of 10°C/min in the temperature area 25-860°C on a Hitachi / STA 7300 thermal analyzer.

Synthesis of complexes. [$Ni(C_AH_{11}NO)$] Ni(CN)₄]-8H,O (C1): At room temperature, NiCl₂·6H₂O (0.30 g; 1.41 mmol) was dissolved in 20 cm3 of water-alcohol solution (1:1; v/v) and KCN (0.19 g; 1.45 mmol) was added to this solution, forming a cloudy light blue one. The second metal salt (NiCl₂·6H₂O, 0.35 g; 1.47 mmol) was added to this solution to form a light blue solution. Abut ligand (0.22 g; 1.48 mmol), which was prepared by dissolving in 15 cm³ of ethanol, was added to the resulting solution to give a clear lilac solution. The result solution was transferred to microwave synthesizer (MW) and the reaction medium was applied at 100°C, 500W and 25 min synthesis program. The cloudy light green solution was filtered after MW synthesis program and allowed to stand at room temperature and undergo slow evaporation whereupon powder product was obtained.

The procedure for the synthesis of **C1** was similar to that of **C2**, **C3** and **C4** complexes using CuCl₂·2H₂O (0.18 g; 1.06 mmol), ZnCl₂ (0.35 g; 2.56 mmol) and CdSO₄·8/3H₂O (0.45 g; 1.7 mmol) instead of second metal salt NiCl₂·6H₂O, respectively.

[Ni(C4H11NO)Ni(CN)4]-8H2O (**C1**): calcd. %: C 21.13; H 5.98; N 15.40 %; found %: C 21.22; H 5.01; N 15.11 %. MW:454.71g/mol. Colour: Cream. Yield: 61%. IR spectrum (cm⁻¹): $3601\nu_{\text{(O-H)}}$, 3337, 3270 $\nu_{\text{(N-H)}}$, 2964, 2932, 2881 $\nu_{\text{(C-H)}}$, 2168, 2129 $\nu_{\text{(C=N)}}$, 1615 $\delta_{\text{(N-H)}}$, 1460 $\delta_{\text{(CH2)}}$, 1114 $\nu_{\text{(C-N)}}$, 1031 $\nu_{\text{(C-O)}}$.

[Cu(C₄H₁₁NO)₂Ni(CN)₄]·7H₂O (**C2**): calcd. %: C 27.16; H 6.84; N 15.84 %; found %: C 27.39; H 5.99; N 15.94 %. MW:530.69 g/mol. Colour: Navy blue. Yield: 32%. IR spectrum (cm⁻¹):3600 $v_{\text{(O-H)}}$, 3314, 3123 $v_{\text{(N-H)}}$), 2968, 2920, 2877, 2853 $v_{\text{(C-H)}}$, 2170, 2115 $v_{\text{(C=N)}}$, 1615, 1591 $\delta_{\text{(N-H)}}$, 1460 $\delta_{\text{(CH2)}}$, 1118 $v_{\text{(C-N)}}$, 1055 $v_{\text{(C-O)}}$.

[Zn(C₄H₁₁NO)Ni(CN)₄]·8H₂O (**C3**): calcd. %: C 20.82; H 5.90; N 15.18 %; found %: C 19.80; H 4.82; N 15.99 %. MW:461.43 g/mol. Colour: Blue. Yield: 59%. IR spectrum (cm⁻¹): $3596\nu_{\text{(O-H)}}$, $33213250\nu_{\text{(N-H)}}$, 2964, 2936, 2877 $\nu_{\text{(C-H)}}$, 2190, 2130 $\nu_{\text{(C=N)}}$, 1511 $\delta_{\text{(N-H)}}$, 1456 $\delta_{\text{(CM)}}$, 1118 $\nu_{\text{(CN)}}$, 1031 $\nu_{\text{(CO)}}$.

Antibacterial activity. To determine antibacterial characteristic of complexes (C1, C2, C3 and C4), nine Gram (-) (E. aerogenes ATCC 13048, S. infantis, K. pneumoniae, P. aeruginosa DSMZ 50071, S. kentucky, S. enteritidis ATCC 13075, S. typhimurium, E. coli ATCC 25922, S. marrescens ATCC 13048) six Gram (+) (E. faecalis ATCC 29212, L. innocua, E. durans, S. aureus ATCC 25923, S. epidermidis DSMZ 20044, B. subtilis DSMZ 1971) were analyzed. All bacteria strains were supplied by Department of Molecular Biology and Genetic at Bartın University (Bartın, Turkey). The minimum inhibition concentration (MIC) of the complex were identified based on method applied by Andrews [34]. All bacteria were inoculated into Luria Bertani broth (LB) and bacterial growth were standardized to 0.5 Mc Farland turbidity (1.5×108 CFU/ml). The concentration of complexes was serially diluted, and the mixture was incubated at 37°C during overnight. By UV-visible spectrum at 600 nm, MIC value was

designated regarding bacterial growth turbidity. The suspected wells were inoculated into petri dishes and were incubated at 37°C. The minimum bactericidal concentration (MBC) was detected the lowest concentration that killed microorganisms.

Antibiofilm activity. Antibiofilm activity against six bacteria (E. coli ATCC 25922, E. aerogenes ATCC 13048, S. infantis, B. subtilis DSMZ 1971, S. aureus ATCC 25923, S. epidermidis DSMZ 20044) was examined by using complexes (C1, C2, C3 and C4). The mixture complexes and bacteria culture and were incubated within a 96-well microplate at 37°C for 48 h. After incubation, all wells were rinsed and desiccated at room temperature. Methanol (95%) was added for fixation for about fifteen minutes and all wells were stained with 0.1% crystal violet. Gram (+) and (-) respectively were treated 33% glacial acetic acid and 95% ethyl alcohol and then the wells were measured by UV spectrophotometer. Eventually, the percentage of antibiofilm activity was calculated by formula:

%Inhibition = (Control OD₆₀₀ – Sample OD₆₀₀)/ Control OD₆₀₀×100 [35].

Anticancer studies. The anti-cancer activity of complexes (C1, C2, C3 and C4) was tested using human cervical cancer cell line HeLa obtained from the American Type Culture Collection (ATCC). Cells were cultured in DMEM containing 10% bovine fetal serum (FBS-12A, Capricorn, South America), 1% penicillin/ streptomycin and 1% glutamine (15140148, Thermo) in a 75 cm² culture flask at 5% CO₂ in incubator at 37°C. The cytotoxicity of Ag-NWs was evaluated by MTT assay using HeLa cell lines. At 5 mg/mL concentration, MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) was prepared. 100 µL of MTT was added and incubated for 4 h. The crystals of purple colored formazone were formed and then dissolved with 200 μl of di-methyl sulphoxide (DMSO). Complexes (C1, C2, C3 and C4 (0.5 to 64 μ g/ml) including DMEM solution were added into 96-well plates and 2×10⁴ cells and were inoculated into wells. MTT assays were applied and OD values were measured using a microplate reader (SPECTROstar Nano, BMG) at 570 nm after 24 h after incubation.

Results and Discussion

IR spectra. The characteristic peaks of Abut ligand were observed with the shifts in their positions in the IR spectra of complexes C1-C4 (Fig. 1). The stretching vibrations of the OH-groups in alcohol-

derived compounds were observed in the IR spectrum in the range of 3700-3500 cm⁻¹ [36, 37]. Therefore, the stretching vibration of OH-group of **C1**, **C2**, **C3** and **C4** was observed at 3601, 3600, 3596 and 3603 cm⁻¹, respectively. The NH2 group of the abut ligand was observed in the range of 3155-3373 cm⁻¹ with wide weak interpreted as the result of overlapping of the OH-groups of lattice water in their structures. The CH₂ groups of the ligand that has different sphere were observed as a multi peaks in the range of 2849-2968 cm⁻¹.

The most characteristic and distinctive peak in cyanido complexes was the sharp cyanido peak observed in the 2200-2000 cm⁻¹ range. The M-C≡N-M' bridged type cyanido group stretching vibration shifts to a higher frequency than the end cyanido group. Therefore, the presence of both bridges and end cyanido groups in the structure could be observed by splitting of cyanido peaks [38]. Based on this information, the peaks observed at 2168, 2129 cm⁻¹ (C1), 2170, 2115 cm⁻¹ (C2) and 2190, 2130 cm⁻¹ (C3) indicated the presence of bridged and end cyanido groups in the structures. The single peak observed at 2170 cm⁻¹ (C4) was attributed to all cyanido groups bridged in the complex structure or end cyanido groups involved in weak HB interactions. In the fingerprint region of the spectrum the $\delta_{\text{(N-H)}},~\delta_{\text{(CH2)}},~\upsilon_{\text{(C-N)}}$ and $\upsilon_{\text{(C-O)}}$ were observed in the range of 1621-1012 cm⁻¹. In addition, it was estimated that the small intense peaks in the 600-400 cm⁻¹ range were due to the bonds of Ni-C, Ni-N and Ni-O.

Thermal analyses. To assess the thermal stability of C1-C4, thermal gravimetric experiments were carried out. The TGA results indicate that the C1-C4 complexes were stable at room temperature. The first weight loss of 30.74% (calc: 31.66%) in the range 89-250°C was corresponded to the removal of eight water molecule (Fig. 2). The second weight loss in the range of 250-346°C was shown a loss of 20.86%, indicating the removal of neutral Abut ligand (calc: 19.60%). The continuous and last weight loss in the range 480-840°C was shown a mass loss of 22.07%, indicating the removal of four cyanido ligands (calc: 22.87%), which was followed by decomposition of the framework. The remaining weight percentage of 26.33% (calc: 25.87%) at 840°C is in agreement with the theoretical value of a mixture of Ni+Ni. Thermal decomposition of C2 consists of three degradation stages from 80°C to 211°C, 211°C to 410°C and 410°C to 865°C corresponding to release of seven water molecule, two Abut ligand and four cyanido,

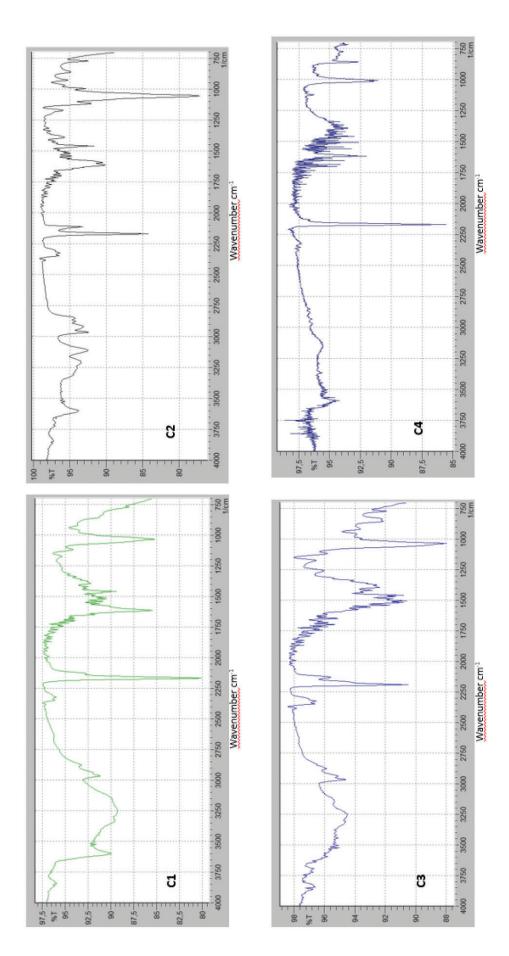


Fig. 1. IR spectra of C1-C4

respectively. The remaining mass loss of **C2** was pointed to Ni+Cu as end product (found: 24.09%; calc: 23.08%). The **C3** and **C4** decomposed similarly at 75-840°C (**C3**) and 80-190°C (**C4**) in two stages with *Abut* and four cyanido groups were liberated at 410-840°C for **C3** and 190-840 for **C4**. Thermal

analyses data for **C1-C4** complexes were given in Table 1. The TG and DTA curves of **C1-C4** complexes were shown in Fig. 2.

Antibacterial activity. Almost all complex synthesis whose antibacterial activities were studied indicated an antibacterial effect. However, no bacte-

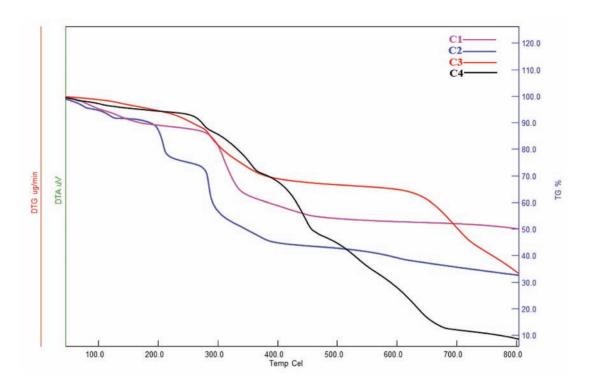


Fig. 2. The TG curves of C1-C4

Table 1. The thermal analysis data of C1-C4 complexes

Complex	Step	Temperature range (°C)	Mass loss, Δm (%)		Total mass loss, Δm (%)		Leaving
			Exp.	Calc.	Exp.	Calc.	group
[Ni(Abut)Ni(CN) ₄]·8H ₂ O	1	89-250	30.74	31.66	30.74	31.66	8H ₂ O
MA:454.71 C ₈ H ₂₇ N ₅ O ₉ Ni ₂ (C1)	2	250-346	20.86	19.60	51.60	51.26	Abut
	3	480-840	22.07	22.87	73.67	74.13	4CN
[Cu(Abut) ₂ Ni(CN) ₄]-7H ₂ O MA:530.69 C ₁₂ H ₃₆ N ₆ O ₉ NiCu (C2)	1	80-211	23.01	23.74	23.01	23.74	7H ₂ O
	2	211-410	32.89	33.59	55.90	57.33	2Abut
	3	410-865	20.01	19.59	75.91	76.92	4CN
[Zn(Abut)Ni(CN) ₄]·8H ₂ O MA:461.40 C ₈ H ₂₇ N ₅ O ₉ NiZn (C3)	1	75-410	31.00	31.20	31.00	31.20	8H ₂ O
	2	410-840	40.71	41.85	50.56	50.51	Abut+4CN
[Cd(Abut)Ni(CN) ₄]·7H ₂ O	1	80-190	24.91	25.66	24.91	25.66	7H ₂ O
MA:491.01 C ₈ H ₂₅ N ₅ O ₈ NiCd (C4)	2	190-840	38.75	39.81	64.72	64.41	Abut+4CN

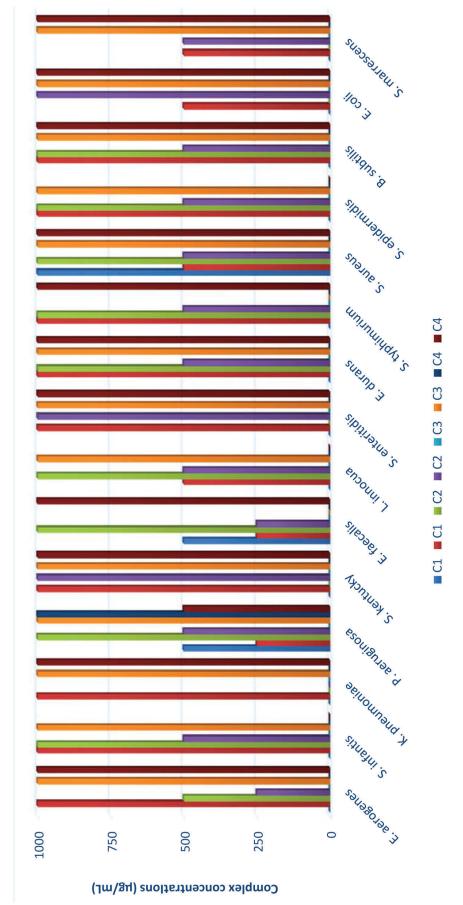


Fig. 3. Antibacterial activity of CI-C4 complexes concentrations (mg/ml)

ricidal effect was observed against *K. pneumoniae*, *S. kentucky*, *S. enteritidis*, *E. coli* and *S. marrescens*. According to the results (Fig. 3), it was observed that **C2** complex both inhibits bacterial growth and showed a bactericidal effect even at low concentrations. Metal ions act as chelators and due to some important factors, such as ion coordination area, hydrophilicity and binuclear structure, bimetallic complexes have critical effects on the antibacterial activity on bacteria. Metal ions bind to enzymes, proteins, and DNA, and investigate antibacterial properties on bacteria [39]. The presence of metal ions also changes the biological activity because of changing the solubility and conductivity of substances. In addition, metal ions affect the permeability

of cell membranes. By connecting metal ions to cell membranes, they can damage bacterial membranes or by binding to lipids on the membrane, increasing membrane permeability. As a result, it alters the amount of complex-synthesis up taken into the cell, leading to increased intracellular toxicity and bacterial death or inhibition of bacterial growth [12, 40-42]. (C1) analyzed the antibacterial effects of their complex-synthesis and used *B. subtilis*, *S. aureus*, *E. coli*, *E. aerogenes*, *P. aureginosa* and *S. enteridis* bacteria strains was used in present study. Compared to the complex syntheses in this study with C1 and C4 complex-synthesis containing Ni-CN bridge synthesized by both, they were shown antibacterial effect against tested bacteria.

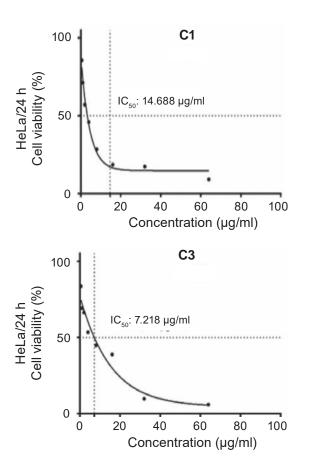
Table 2. Inhibition percentages of the formation of complex-syntheses biofilm layer

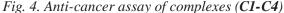
		Bacteria									
Con., μg/ml		E. coli ATCC 25922	E. aerogenes ATCC 13048	S. infantis	B. subtilis DSMZ 1971	S. aureus ATCC 25923	S. epidermidis DSMZ 20044				
C 1	1000	57	55	70	53	67	42				
	500	11	17	1	0	47	3				
	250	0	0	0	0	0	8				
	125	0	0	5	0	0	0				
	62.5	0	4	4	0	0	9				
	31.25	0	3	0	0	0	0				
C2	1000	58	55	66	32	63	22				
	500	29	3	1	7	57	0				
	250	7,5	0	0	0	0	8				
	125	7	0	0	0	3	0				
	62.5	4	0	1	6	1	0				
	31.25	5	0	2	6	0	0				
С3	1000	44.3	46.8	71.2	57	57.5	28.8				
	500	40.1	17.1	60.8	38.2	36	5				
	250	8.7	0	1	0	18.4	0				
	125	6.5	6.9	3.1	0	15.5	7.5				
	62.5	8.7	0	10.4	17.4	20.8	0				
	31.25	6	3.1	13.2	28.5	16.8	0				
C4	1000	24.3	26.6	30.8	13.3	53.2	0				
	500	0	0	0	0	0	0				
	250	1.3	0	0	0	0	0				
	125	1.9	8.2	0	0	8.3	0				
	62.5	8.4	0	0.5	7	6.9	0				
	31.25	4.6	5.4	8.2	0	6.5	0				

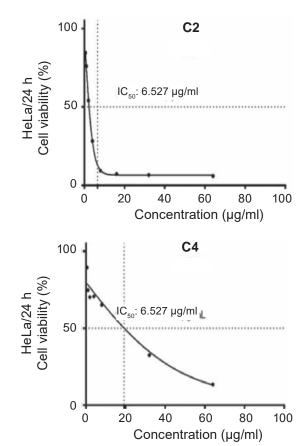
Antibiofilm activity. The biofilm layer is a collection of cells that are attached to a living or inanimate surface of bacteria, embedded in the extracellular and self-produced polymer matrix. Biofilm layer can occur on different surfaces such as glass, plastic, wood, metal, soil, medical implants, food product and tissue [43, 44]. The most efficient biofilm inhibition activity for all complexes was observed at 1000 µg·ml⁻¹, the highest concentration. Considering the results obtained in the study, it was noticed that the highest percentage of biofilm inhibition was obtained by C3 complex-synthesis with a concentration of 1000 μg·ml⁻¹, with a 71.2% against S. infantis. Only C4 complex synthesis did not act an antibiofilm effect against the S. epidermis strain at all concentrations. The cell membranes of Gram (-) bacteria contain a thinner polysaccharide layer, and the polysaccharide layer of Gram (+) bacteria is thicker and contains teicoic acid. According to the results, it was determined that the percentage of Gram (-) bacteria biofilm inhibition was higher than other.

Anticancer activity. C1-C4 complexes were investigated for anticancer activity on HeLa cell lines. After 24 h incubation with different doses of prepared complexes C1-C4 (0.5, 1, 2, 4, 8, 16, 32, 64 μg/ml), they showed cytotoxic activity at high doses HeLa cell lines. The increasing concentration of complexes C1-C4 decreased cell viability, as expected. Therefore, as shown in Figure 4 the anticancer activity of the complexes C1-C4 was dosedependent in confluent cultures, and the IC₅₀ values were 14.856 μg/ml, 6.527 μg/ml, 7.218 μg/ml and 19.250 μg/ml for HeLa cell line (Fig. 4).

Conclusions. In this paper, we synthesized four cyanido complexes by using tetracyanidonickelate anion and Abut ligand. All of them were in powder form and characterized by IR spectroscopy, elemental, and thermal analysis. The characteristic peak of cyanido ligand was seen in the 2115-2190 cm⁻¹ range as expected. As a general trend from the thermal analysis curves of complexes, first hydrate water, then neutral Abut ligand and finally anionic cyanido ligands were away from the structure. At the end of







thermal decomposition, Ni+Ni, Ni+Cu, Ni+Zn and Ni+Cd metal mixtures were obtained. The complex syntheses analyzed in current study were found to demonstrate antibacterial properties at low concentrations. In literature, cyanido-bridged bimetallic complex-syntheses have been studied in many areas such as antibacterial, antifungal, anticancer. The type of biofilm inhibition test applied in this study had not been performed in the earlier studies and it was observed that the results provided inhibition of biofilm layer at very low concentrations. The cyanido complexes C1-C4 had anticancer activity against service cancer cell line HeLa. These cyanido complexes showed activity in the concentrations of 0.5 to 64 µg/ml.

Conflict of interest. Authors have completed the Unified Conflicts of Interest form at http://ukrbiochemjournal.org/wp-content/uploads/2018/12/coi_disclosure.pdf and declare no conflict of interest.

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НОВІ ДВОЯДЕРНІ КОМПЛЕКСИ ЦІАНІДІВ ІЗ ГИДРОКСИАМІНОВИМ ЛІГАНДОМ: СИНТЕЗ, ХАРАКТЕРИСТИКА ТА МОЖЛИВОСТІ ЗАСТОСУВАННЯ

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Метою цієї роботи було синтезувати комплекси ціанідів $[Ni(Abut)Ni(CN)_4]\cdot 8H_2O$ (C1), $[Cu(Abut)_2Ni(CN)_4]\cdot 7H_2O$ (C2), $[Zn(Abut)Ni(CN)_4]\cdot 8H_2O$ (C3) та $[Cd(Abut)Ni(CN)_4]\cdot 7H_2O$ (C4) та дослідити їх антибактеріальну та цитотоксичну дію. Одержані комплекси вивчали методом мікрохвильового синтезу з використанням

ІЧ- Фур'є спектроскопії та термічного аналізу. Досліджено антибактеріальну та цитотоксічну активність синтезованих комплексів. Встановлено, що розщеплення смуг коливання ціанідогруп в ІЧ-Фур'є спектрах С1-С4 вказує на наявність ціаногруп. Антибактеріальну кінцевих активність С1-С4 вивчали на дев'яти видах грамнегативних та шести грам-позитивних бактеріях. антибактеріальну Найбільшу активність комплексів спостерігали за концентрації 1000 мкг/мл. Цитотоксичну активність оцінювали з використанням клітинної лінії Не La та МТТтесту. Виявлено, що досліджувані ціанідні комплекси знижують життєздатність клітин HeLa зі значеннями IC_{50} 14,86; 6,5; 7,2 та 19,2 мкг/мл для комплексів С1, С2, С3 та С4, відповідно.

Ключові слова: комплекси цианідів, антибактеріальна, цитотоксична активність, клітини HeLa.

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