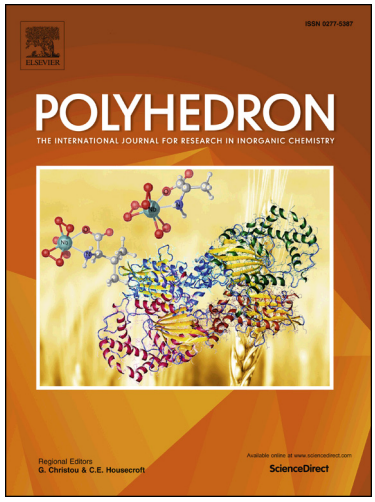


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# Synthesis, Characterization, and Cytotoxicity of Binuclear Copper(II) Complexes with Tetradentate Nitrogen-Containing Ligands bis-5-(2-Pyridylmethylidene)-3,5-dihydro-4H-imidazol-4-ones

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**Abstract**

A treatment of the $N_4$-type organic ligands containing two 5-(2-pyridylmethylidene)-2-thio-3,5-dihydro-4*H*-imidazol-4-one fragments linked by $(CH_2)_2$ bridges between the sulfur atoms with $CuCl_2$ affords to binuclear copper(II) complexes of corresponding ligands. A series of copper complexes with $L(CuCl_2)_2$ composition were isolated and characterized by elemental analysis, UV-vis spectra and cyclic voltammetry; the X-ray crystal structures of four synthesized complexes showed the distored tetrahedral environment of both copper atoms; Cu-Cu distances is about 4.5 Å, which is confirming the absence of interaction between copper ions. Electrochemical studies of complexes demonstrated the simultaneous reduction of each of the coordinated copper atoms at a potential of +0.39–+0.43 V.

**Keywords:** 2-alkylthio-3,5-dihydro-4H-imidazole-4-ones; binuclear copper(II) complexes; X-ray diffraction, cyclic voltammetry.

## Introduction

The design and synthesis of complexes featuring two copper centers held in close proximity has received considerable attention because of the potential application of such complexes as catalysts that function through the concerted action of multiple metal centres (see, for example, [1-3]), magnetic material due to possibility of magnetic exchange interactions between paramagnetic metal centres [4-6], as selective receptors for different substrates [7-10] and also as low-molecular models of metalloenzyme [11, 12]. Metalloproteins, requiring a metal ion for their activity, are one of the most important class of enzymes. A specialized group of the metalloproteins is the binuclear metalloenzymes, containing two closely spaced metals ions (≤4 Å apart) that are attached to the polypeptide scaffold. Binuclear copper complexes have some features that make them favorable targets for drug design and discovery. Firstly, the metals are highly charged; therefore strong ionic attractions to an inhibitor are feasible. Secondly,

metalloenzymes constitutes much less than one percent of an organism's complete proteome; this reduced risk the of off-target inhibition [13].

Copper is an essential element for all organisms living in oxygen-containing environment. This redox active metal easily converts oxidation state from a Cu(I) to Cu(II), and vice versa, as in chemical reactions and in physiological conditions [14]. Copper is essential for the function of several enzymes and proteins, such as cytochrome oxidase, Zn, Cu-superoxide dismutase, lysyl oxidase, tyrosinase, and dopamine-b-monooxygenase [14-16].

During the past decades copper complexes have gained a growing interest as pharmaceuticals for the use as diagnostic agents or as chemotherapeutic drugs. Copper, as an essential cofactor in a number of enzymes and physiological processes, may be less toxic than non essential metals, such as platinum. At the current time, two copper complexes have reached clinical assay, which paves the road to the first copper-based anticancer therapeutics [17]. Most of the investigated anti-cancer copper coordination compounds belong to the family of copper(II) complexes showing either five-coordinate environments comprising distorted square pyramidal and trigonal bipyramidal geometries or distorted six-coordinate octahedral arrays. The majority of these agents are mononuclear species, but there are few distinctive examples of dimeric compounds exhibiting remarkable antitumor activity [18]. The anoxic character of cancer cells promotes the reduction of Cu(II) to Cu(I), which is not possible in normal cells and thus provides a therapeutic opportunity to target tumors [19]. The synthesis, design, and development of copper complexes as anticancer agents have been presented in several reviews over the last decade [18, 20-24].

We have recently synthesized and investigated a series of binuclear mixed valence Cu(I,II) complexes containing substituted bis-5-(2-pyridylmethylidene)-3,5-dihydro-4H-imidazol-4-ones as $N_4$-coordinating ligands. These complexes are high cytotoxic for various cell lines. We have found that these compounds did not intercalate DNA, inhibited number of polymerases (telomerase predominantly), accumulated in the cell nucleus, and caused DNA degradation [25]. In the work we describe the synthesis of new binuclear bis-5-(pyridylmethylene)-2-thiohydantoin complexes Cu(II,II) complexes with isolated copper atoms formed as the results of there ligand interaction with copper(II) chloride.

**Experimental**

All common reagents were purchased from commercial suppliers and used as received. The melting points are uncorrected. $^1$H NMR spectra were recorded on a Bruker Avance recorder (400 MHz for $^1$H) in DMSO-$d_6$ or $CDCl_3$. Chemical shifts are reported in parts per million relative to the residual solvent signal. The IR spectra in nujol were recorded on a Perkin-Elmer

1430 spectrophotometer. Electronic spectra in $10^{-3}$ M DMF solution were obtained on a U2900 Hitachi UV–Vis spectrophotometer. High resolution mass spectra (HRMS) were recorded on an Orbitrap Elite (Thermo Scientific) mass spectrometer with an IRET. To inject solutions with a concentration of 0.1 to 9 μg/mL (in 1% formic acid in acetonitrile), direct injection into the ion source using a syringe pump (5 μl/min) was used. The spray voltage was ± 3.5 kV, the temperature of the capillary was 275ºC. Electrochemical measurements were performed on a IPC Pro M potentiostat. Glassy-carbon (d = 2 mm) disks were used as the working electrodes, a 0.1 M $Bu_4NClO_4$ solution in DMF served as the supporting electrolyte, and Ag/AgCl/KCl(satur.) was used as the reference electrode. The potential scan rates were 100 mV $s^{-1}$ All measurements were carried out under argon. The samples were dissolved in the pre-deaerated solvent. Dimethylformamide (high purity grade) was purified by refluxing followed by successive vacuum distillation over anhydrous $CuSO_4$ and $P_2O_5$.

For single-crystal measurements of **4a**, **4d**, a suitable crystals was selected and tip-mounted on a Bruker SMART diffractometer, Mo Kα radiation (0.71073 Å) platform with an Apex 2-detector at 100 K. For compounds **4f**, **4g** the X-ray data was collected by using STOE diffractometer Pilatus100K detector, focusing mirror collimation Cu Kα (1.54086 Å) radiation, rotation method mode. STOE X-AREA software was used for cells refinement and data reduction. Data collection and image processing was performed with X-Area 1.67 (STOE & Cie GmbH, Darmstadt, Germany, 2013). Intensity data were scaled with LANA (part of X-Area) in order to minimize differences of intensities of symmetry-equivalent reflections (multi-scan method). The structures were solved and refined with SHELX program [26]. The non-hydrogen atoms were refined by using the anisotropic full matrix least-square procedure. Molecular geometry calculations were performed with the SHELX program, and the molecular graphics were prepared by using DIAMOND software [27]. The crystal data one can see in the Table 1S in Supplementary Information.

**Synthesis of 3-substituted 2-thioxotetrahydro-4H-imidazol-4-ones (1) from glycine and isothiocyanate (typical procedure).** Glycine (1 eq.) was dissolved in a 1:1 water-pyridine mixture. Then a 2 M sodium hydroxide solution was added to pH 9, and this pH was maintained until the reaction was completed. The reaction mixture was warmed to 55 °C. At this temperature, isothiocyanate (1.1 eq.) was added. The reaction mixture was stirred at 55 °C for 1 h, pH being monitored from time to time. Pyridine and excess of isothiocyanate were removed by extraction with the same volume of toluene. Concentrated hydrochloric acid was added to the aqueous phase to pH = 6-7 and the resulting solution was boiled 2.5 hours. The reaction mixture

was evaporated to half volume under reduced pressure and cooled to room temperature. The formed precipitate was filtered off and recrystallized from methanol.

Synthesis of compounds **1-4e** were described previously [28-31].

**3-(But-2-yl)-2-thioxotetrahydro-4H-imidazol-4-one (1a).** As a result of the reaction of glycine (0.97 g, 7.9 mmol) and 2-butyl isothiocyanate (1 g, 1.1 mL, 8.7 mmol) 0.67 g (72%) of compound **1a** was obtained. M.p. 103 °C. $^1$H NMR (400 MHz, DMSO-$d_6$, δ, ppm): 10.16 (bs, 1H, NH), 4.85 (m, 1H, -$CH_3C\underline{H}CH_2CH_3$), 4.05 (m, -$CH_2$-), 1.95 (m, 1H, -$CH_3C\underline{H}CH_2CH_3$), 1.67 (m, 1H, -$CH_3CHC\underline{H}_2CH_3$), 1.35 (d, 3H, J = 6.91 Hz, $C\underline{H}_3CH_2CH_2CH_3$), 0.79 (t, 3H, J = 7.08 Hz, $C\underline{H}_3CH_2CH_2CH_3$). IR (cm$^{-1}$): 3180 (NH), 1730 (C=O). Calculated C, 48.83%; H, 6.97%; N, 16.27%; S-18.6%. $C_7H_{12}N_2OS$. Found C, 48.79%; H. 6.91%; N. 15.88%; S, 18.95%.

**(2-Methylbut-1-yl)-2-thioxotetrahydro-4H-imidazol-4-one (1b)**. As a result of the reaction of glycine (0.528 g, 7 mmol) and (2-methylbutyl) isothiocyanate (1 g, 7.7 mmol) 1.1 g (90%) of compound **1b** was obtained. M.p. 116 °C. $^1$H NMR (400 MHz, DMSO-$d_6$, δ, ppm): 10.15 (bs, 1H, NH), 4.15 (s, 2H, $CH_2$), 3.49 (m, 2H, HCN), 1.95 (m, 1H, $C\underline{H}_2CH_3$), 1.35 (m, 1H, $C\underline{H}_2CH_3$), 1.05 (t, J = 7.45 Hz, 3H, $CH_3$), 0.80 (d, J = 6.55 Hz, 3H, $CH_3$). IR (cm$^{-1}$): 3280 (NH), 1750 (C=O) Calculated C, 51.61; H, 7.52%; N, 15.05%; S, 17.2%. $C_7H_{12}N_2OS$. Found C, 51.45%; H, 7.44%; N, 15.00%; S, 16.88%.

**3-Benzyl-2-thioxotetrahydro-4H-imidazol-4-one (1c)**. As a result of the reaction of glycine (0.46 g, 6.1 mmol) and benzyl isothiocyanate (1 g, 0.9 mL, 6.7 mmol) 0.15 g (92%) of compound **1c** was obtained. M.p. 138 °C. $^1$H NMR (400 MHz, DMSO-$d_6$, δ, ppm): 10.25 (bs, 1H, NH), 7.20-7.30 (m, 5H, Ph), 4.88 (s, 2H, HCN), 4.20 (s, 2H, $CH_2$). IR (cm$^{-1}$): 3280 (NH), 1750 (C=O). Calculated C, 58.25%; H, 4.85%; N, 13.59%; S, 15.56%. $C_{10}H_{10}N_2OS$. Found C, 58.44%; H, 4.8%; N, 13.39%; S, 15.30%.

**3-(2-Phenylethyl)-2-thioxotetrahydro-4H-imidazol-4-one (1d)**. As a result of the reaction of glycine (0.44 g, 5.8 mmol) and 2-phenylethyl isothiocyanate (0.96 g, 6.2 mmol) 0.96 g (76%) of compound **1d** was obtained. M.p. 126 °C. $^1$H NMR (400 MHz, DMSO-$d_6$, δ, ppm): 10.25 (bs, 1H, NH), 7.31 (d, 2H, J = 6.72 Hz, Ph), 7.20-7.25 (m, 3H, Ph), 4.11 (s, 2H, $CH_2$), 3.85 (t, 2H, J = 7.34Hz, HCN), 2.86 (t, 2H, J = 7.41Hz, $C\underline{H}_2$-Ph). IR (cm$^{-1}$): 3280 (NH), 1750 (C=O). Calculated C, 60.0%; H, 5.45%; N, 12.72%; S,14.54%. $C_{11}H_{12}N_2OS$. Found C, 60.31%; H, 5.61%; N, 12.81%; S, 14.49%.

**3-Substituted 5-((*Z*)-2-pyridylmethylidene)-2-thiohydantoins 2a-e (typical procedure)**. 3-Substituted 2-thiohydantoin **1a-d** (1 eq.) was dissolved in a 2% ethanolic solution of KOH (1.2 eq.) with vigorous stirring. After complete dissolution of 2-thiohydantoin, (1 eq.) was added dropwise and the reaction mixture was stirred for 12 h. The precipitate was filtered off and

dissolved in water. The solution was neutralized with vigorous stirring with dilute HCl to pH 7. The formed precipitate was filtered off and washed with ethanol and then diethyl ether.

**3-(2-Butyl)-5-((*Z*)-2-pyridylmethylidene)-2-thioxotetrahydro-4H-imidazol-4-one (2a).** As a result of the reaction of thiohydantoin **1a (**0.5 g, 2.9 mmol) and 2-pyridinecarbaldehyde ( 0.34 g, 3.19 mmol) 0.96 g (76%) of compound **1d** was obtained. M.p. 116 °C. $^1$H NMR (400 MHz, DMSO-$d_6$, δ, ppm):: 11.61 (bs, 1H, NH), 8.73 (d, 1H, J = 5.48 Hz, $H_α$-Py), 7.90 (t, 1H, J = 7.68 Hz, $H_β$-Py), 7.75 (d, 1H, J = 6.16 Hz, $H_{β'}$-Py), 7.39 (t, 1H, J = 6.28 Hz, $H_γ$-Py), 6.67 (s, 1H, =CH), 4.63 (m, 1H, $CH_3$-CH-$CH_2$-$CH_3$), 2.03(m, 1H, $CH_3$-CH-$CH_2$-$CH_3$), 1.72 (m, 1H, $CH_3$-CH- $CH_2$-$CH_3$), 1.41 (d, 3H, J = 5.89 Hz, $CH_3$-CH- $CH_2$-$CH_3$), 0.76(t, 3H, J = 7.52 Hz, $CH_3$-CH-$CH_2$-$CH_3$). IR ($cm^{-1}$): 3280 (NH), 1750 (C=O), 1600 (C=C). Calculated C, 59.77%; H, 5.74%; N, 16.09%; S 12.26%. $C_{13}H_{15}N_3OS$. Found C, 66.10%; H, 4.69%; N, 13.45%; S, 10.50%.

**3-(2-Methylbutyl)-5-((*Z*)-2-pyridylmethylidene)-2-thioxotetrahydro-4H-imidazol-4-one (2b)**. **1b (**0.2 g, 1.1 mmol) and 2-pyridinecarbaldehyde ( 0.129 g, 1.2 mmol) 0.26 g (85%) of compound **2b** was obtained. M.p. 158 °C. $^1$H NMR (400 MHz, DMSO-$d_6$, δ, ppm): 11.52 (bs, 1H, NH), 8.55 (m, Hα-Py), 7.90 (t, 1H, J = 7.79 Hz, H-Py), 7.78 (m, 1H, Hβ-Py), 7.38 (m, 1H, Hγ-Py), 6.72 (s, 1H, =CH), 3.56 (m, 2H, $CH_2$-$CH(CH_3)CH_2CH_3$), 1.94 (m, 1H, $CH_2$-$CH(CH_3)CH_2CH_3$), 1.31 (m, 1H, $CH_2$-$CH(CH_3)CH_2CH_3$), 1.07 (m, 1H, $CH_2$-$CH(CH_3)CH_2CH_3$), 0.81 (m, 6H, $CH_2$-$CH(CH_3)CH_2CH_3$). IR ($cm^{-1}$): 3290 (NH), 1750 (C=O), 1600 (C=C). Calculated C, 61.09; H, 6.18%; N, 15.27%, S, 11.63. $C_{14}H_{17}N_3OS$. Found C, 60.76%; H, 5.98%; N, 15.04%; S, 11.57%.

**3-Benzyl-5-((*Z*)-2-pyridylmethyidene)-2-thioxotetrahydro-4H-imidazol-4-one (2c)**. As a result of the reaction of thiohydantoin **1c (**0.3 g, 1.45 mmol) and 2-pyridinecarbaldehyde (0.171 g, 1.6 mmol) 0.4 g (95%) of compound **2c** was obtained. M.p. 133 °C. $^1$H NMR (400 MHz, DMSO-$d_6$, δ, ppm): 11.81 (bs, 1H, NH) 8.77 (d, 1H, J = 4.38 Hz, Hα'-Py), 7.91 (td, 1H, $J_1$ = 7.75 Hz, $J_2$ = 1.46 Hz, Hβ-Py), 7.77 (d, 1H, J = 7.75 Hz, Hβ'-Py), 7.41 (dd, 1H, $J_1$ = 4.79 Hz, $J_2$ = 1.10 Hz, Hγ-Py), 7.34 (m, 3H, Ph), 7.29 (m, 2H, Ph) 6.76 (s, 1H, CH=), 5.03 (s, 2H, -$CH_2$-Ph). Calculated C, 65.08; H, 4.40%; N, 14.23%; S, 10.84. $C_{16}H_{13}N_3OS$. Found C, 60.03%; H, 4. 55%; N, 14.01%; S, 11.62%.

3-**Phenylethyl-5-((*Z*)-2-pyridylmethylidene)-2-thioxotetrahydro-4H-imidazol-4-one (2d).** As a result of reaction of thiohydantoin **1d (**0.185 g, 0.84 mmol) and 2-pyridinecarbaldehyde (0.098 g, 0.92 mmol) 0.33 g (90%) of compound **2d** was obtained. M.p. 143 °C (dec.) $^1$H NMR (400 MHz, DMSO-$d_6$, δ, ppm): 11.47 (bs, 1H, NH) 8.69 (d, 1H, J = 4.14 Hz, Hα'-Py), 7.76 (td, 1H, $J_1$ = 7.96 Hz, $J_2$ = 1.56 Hz, Hβ '), 3.42 (t, 2H, J = 7.69Hz, $CH_2$), 3.06 (t, J = 7.70 Hz, 2H, $CH_2$). Calculated C, 66.01%; H, 4.85%; N, 13.59%; S, 10.35%. $C_{17}H_{15}N_3OS$. Found C, 66.10%; H, 4.69%; N, 13.45%; S, 10.50%.

**3-(4-Ethoxyphenyl)-5-((*Z*)-2-pyridylmethylidene)-2-thioxotetrahydro-4H-imidazol-4-one (2f).** This compound was synthesized without isolation of thiohydantoins **1f**. To a solution of 4-ethoxyaniline **(**0.174 g, 1.27 mmol) in diethyl ether, ethyl isothiocyanatoacetate (0.184 g, 1.27 mmol) was added dropwise. Yhe resulting mixture was vigorously stirred overnight to obtain white solid. The solid was filtered off, dried under reduced pressure and dissolved in 2% KOH ethanol solution, than pyridine 2-carboxaldehyde (0.145 g, 1.35 mmol) was added dropwise. After 3h stirring at room temperature the reaction mixture was diluted with water 1:1 and acidified to pH 6 with 1M hydrochloric acid to give yellow precipitate. The yellow precipitate was filtered off, washed with water, ethanol and diethyl ether. 0.305 g (74%) of Compound **2f** was obtained. M.p. 215 °C (dec.). HRMS: calculated for $C_{17}H_{14}O_3N_3S$ $(M-H)^-$ 340.0756, found 340.0760; calculated for $C_{17}H_{16}O_3N_3S^+$ $(M+H)^+$ 342.0912, found 342.0909. $^1$H NMR (400 MHz, DMSO-$d_6$, δ, ppm): 8.75 (m, 1H, Hα'-Py) 7.88 (td, 1H, $J_1$ = 1.65 Hz, $J_2$ = 7.52 Hz, Hβ'-Py), 7.74 (d, 1H, $J_1$ = 7.89 Hz, Hγ-Py), 7.38 (m, 1H, Hβ-Py), 7.26 (m, 2H, Hα, Hα'-Ph), 7.00 (m, 2H, Hβ, Hβ'-Ph), 6.76 (s, 1H, CH=), 4.05 (q, 2H, J = 6.97 Hz, $CH_2$), 1.32 (t, 3H, J = 6.97 Hz, $CH_3$). Calculated C, 62.75%; H, 4.65%; N, 12.91%; S, 9.85%. $C_{17}H_{15}N_3O_2S$. Found C, 63.00%; H, 4.50%; N, 13.08%; S, 9.88%.

**3-(3,4-Dimethoxyphenyl)-5-((*Z*)-2-pyridylmethylidene)-2-thioxotetrahydro-4H-imidazol-4-one (2g).** This compound was obtained by a procedure analogous to **2f.** As a result of reaction of 3,4-dimethoxyaniline **(**0.182 g, 1.19 mmol), ethyl isocyanatoacetate (0.172 g, 1.19 mmol) and 2-pyridinecarbaldehyde (0.136 g, 1.27 mmol) 0.364 g (89%) of compound **2g** was obtained. M.p. 206 °C. 2f: HRMS: calculated for $C_{17}H_{14}O_2N_3S$ $(M-H)^-$ 324.0807, found 324.0812; calculated for $C_{17}H_{16}O_2N_3S$ $(M+H)^+$ 326.0963, found 326.0960. $^1$H NMR (400 MHz, $CDCl_3$, δ, ppm): 8.70 (d, 1H, J = 4.95 Hz, Hα'-Py) 7.78 (td, 1H, $J_1$ = 1.65 Hz, $J_2$ = 7.70 Hz, Hβ'-Py), 7.44 (d, 1H, $J_1$ = 7.89 Hz, Hγ-Py), 7.28 (m, 1H, Hβ-Py), 6.95 (m, 2H, Hα, Hα'-Ph), 6.85 (m, 1H, Hβ-Ph), 6.60 (s, 1H, CH=), 3.91 (s, 3H, m-$CH_3$), 3.89 (s, 3H, p-$CH_3$). Calculated C, 59.81%; H, 4.43%; N, 12.31%; S, 9.35%. $C_{17}H_{15}N_3O_3S$. Found C, 59.38%; H, 4.18%; N, 12.33%; S, 9.29%.

**Reactions of 5-((*Z*)-2-pyridylmethylidene)-2-thiohydantoins 2a-g witb dibromoethane (typical procedure)**. 1,2-Dibromoethane (1 eq.) was added for 5 min with stirring to a mixture of compound **2a-g** (2 eq.) and dry $K_2CO_3$ (> 2 eq.) in DMF (10-15 mL) at –10 °C. The reaction mixture was stirred for 2 h at –10 °C and then for 2 h at room temperature. Water (50 mL) was added to the mixture. A formed precipitate was filtered off, washed with water, and recrystallized from ethyl acetate.

(**5*Z*,5´*Z*)-2,2´-(Ethane-1,2-diyldisulfanyldiyl)bis(3-(but-2-yl)-5-(2-pyridylmethylidene)-3,5-dihydro-4H-imidazol-4-one) (3a**), As a result of the reaction of thiohydantoin **2a (**0.2 g, 0.76

mmol) with 0.033 mL (0.072 g, 0.14 mmol) of 1,2-dibromoethane and 0.16 g (1.1 mmol) of $K_2CO_3$ 0.25 g (61%) of compound **3a** was obtained. M.p. 173 °C. $^1$H NMR (400 MHz, DMSO-$d_6$, δ, ppm): 8.75 (bs, 2H, Hα'-Py) 8.65 (d, 2H, J = 7.85 Hz, Hβ'-Py), 7.73 (m, 2 H, Hβ-Py), 7.26 (m, 2H, Hγ-Py), 7.07 (s, 2H, CH=), 3.96 (m, 6H), 1.98 (m, 4H), 1.50 (d, 6H, J = 6.87 Hz, $C\underline{H}_3CHCH_2CH_3$), 0.93 (t, 6H, J = 7.13 Hz, $CH_3CHCH_2C\underline{H}_3$). IR (cm$^{-1}$): 3400-3300 (OH), 1710 (C=O), 1670 (C=N), 1640 (C=C). Calculated C, 59.36%; H, 6.00%; N, 14.84%; S, 11.3%. $C_{36}H_{32}N_6O_2S_2{\cdot}H_2O$. Found C, 58.91%; H, 5.85%; N, 14.28%; S, 10.7%.

**(5*Z*,5´*Z*)-2,2´-(Ethane-1,2-diyldisulfanyldiyl)bis(3-(2-methylbuthyl)-5-(2-pyridylmethylidene)-3,5-dihydro-4H-imidazol-4-one) (3b)**. As a result of the reaction of thiohydantoin **2b (**0.2 g, 0.76 mmol) with 0.033 mL (0.072 g, 0.38 mmol) of 1,2-dibromoethane and 0.31 g (2.3 mmol) of $K_2CO_3$, 0.54 g (56%) of compound **2b** was obtained. M.p. 103° C. $^1$H NMR (400 MHz, DMSO-$d_6$, δ, ppm): 8.69 (m, 4H, Py), 7.68 (t, 2H, Py), 7.23 (t, 1H, J = 7.64Hz, Py) , 7.12 (s, 1H, CH =), 3.94 (s, 1H, $CH_2$), 3.49 (s, 4H, HCS), 1.93 (m, 2H), 1.45 (m, 2H), 1.22 (m, 2H), 0.94 (m, 12H, $CH_2$-CH($C\underline{H}_3$)$CH_2C\underline{H}_3$). IR (cm$^{-1}$): 1710 (C=O), 1670 (C=N), 1640 (C=C). Calculated C, 62.5%; H, 6.25%; N, 14.58%. $C_{30}H_{36}N_6O_2S_2$. Found C, 62.40%; H, 6.36%; N, 14.32%.

**(5*Z*,5´*Z*)-2,2´-(Ethane-1,2-diyldisulfanyldiyl)bis(3-benzyl-5-(2-pyridylmethylidene)-3,5-dihydro-4H-imidazol-4-one) (3c).** As a result of the reaction of thiohydantoin **2c** (0.15 g, 0.52 mmol) with 0.023 mL (0.048 g, 0.26 mmol) of 1,2-dibromoethane and 0.21 g (1.5 mmol) of $K_2CO_3$, 0.2 g (61%) of compound **3c** was obtained. M.p. 173 °C. $^1$H NMR (400 MHz, $CDCl_3$, δ, ppm): 8.65 (m, 4H, Hα'Hβ'-Py) 7.57 (td, 2H, $J_1$ = 7.64 Hz, $J_2$ = 1.67 Hz, Hβ-Py) 7.35 (m, 10H, Ph), 7.19 (t, 2H, J = 4.66 Hz, Hγ-Py), 7.16 (s, 2H, CH=), 4.81 (s, 4H, HCS), 3.83 (s, 4H, $CH_2$Ph). IR (cm$^{-1}$): 3450-3250 (OH), 1710 (C=O), 1670 (C=N), 1640 (C=C). Calculated C, 64.35%; H, 4.41%; N, 13.24%; S, 10.09%. $C_{34}H_{30}N_6O_3S_2{\cdot}H_2O$. Found C, 64.52%; H, 4.49%; N, 12.84%; S, 9.59%.

**(5*Z*,5´*Z*)-2,2´-(Ethane-1,2-diyldisulfanyldiyl)bis(3-(2-phenylethyl)-5-(2-pyridylmethylidene)-3,5-dihydro-4H-imidazol-4-one) (3d).** As a result of the reaction of 0.1 g (0.28 mmol) of thiohydantoin **2d** with 0.012 mL (0.027 g, 0.14 mmol) of 1,2-dibromoethane and 0.06 g (0.42 mmol) of $K_2CO_3$, 0.05 g (54%) of compound **3d** was obtained. M.p. 175 °C (dec.). $^1$H NMR (400 MHz, $CDCl_3$, δ, ppm): 8.82 (d, 2H, J = 8.12 Hz, Hα'-Py), 8.45 (d, 2H, J = 8.0 Hz, Hβ-Py), 7.71 (td, 2H, $J_1$ = 8.03 Hz, $J_2$ = 1.58 Hz, Hβ '), 7.26 (m, 8H, Ph), 7.20 (t, 2H, J = 7.24 Hz, Hγ-Ph), 7.10 (t, 2H, J = 6.10 Hz, Hγ-Py), 6.67 (s, 2H, CH=), 4.02 (t, 4H, J = 4.51 Hz, HCN), 3.81 (s, 4H, HCS), 2.91 (t, J = 2.81Hz, 4H, $CH_2$-Ph). IR (cm$^{-1}$): 3450-3250 (OH), 1710 (C=O), 1670 (C=N), 1640 (C=C). Calculated C, 64.38%; H, 5.21%; N, 12.51%; S, 9.13%. $C_{36}H_{32}N_6O_2S_2{\cdot}1.5H_2O$. Found C, 64.38%; H, 5.21%; N, 12.51%; S, 8.88%.

(**5*Z*,5´*Z*)-2,2´-(Ethane-1,2-diyldisulfanyldiyl)bis(3-(4-ethoxyphenyl)-5-(2-pyridylmethylidene)-3,5-dihydro-4H-imidazol-4-one) (3f).** As a result of the reaction of 0.1 g (0.30 mmol) of thiohydantoin **2f** with 0.013 mL (0.028 g, 0.15 mmol) of 1,2-dibromoethane and 0.06 g (0.42 mmol) of $K_2CO_3$, 0.054 g (53%) of compound **3f** was obtained. M.p. 198 °C. HRMS: calculated for $C_36H_{33}O_4N_6S_2$ $(M+H)^+$ 677.2005, found 677.1998. $^1$H NMR (400 MHz, $CDCl_3$, δ, ppm): 8.70 (d, 2H, J = 7.83 Hz, Hα'-Py), 8.64 (d, 2H, J = 3.91 Hz, Hβ-Py), 7.57 (t, 2H, J = 7.83 Hz, Hβ '-Py), 7.15-7.25 (m, 8H, Ph), 6.99 (m, 4H, CH=, Hγ-Py), 4.08 (q, 4H, $CH_2$), 3.82 (s, 4H, $CH_2CH_2$), 1.46 (t, 6H, J = 6.85 Hz,$CH_3$). UV-vis (λ, nm/ε, l mol$^{-1}$ cm$^{-1}$): 434/19336, 379/19336, 266/21289. Calculated C, 63.89%; H, 4.77%; N, 12.42%; S, 9.48%. $C_{36}H_{32}N_6O_4S_2$. Found C, 64.18%; H, 5.01%; N, 12.51%; S, 9.88%,

(**5*Z*,5´*Z*)-2,2´-(Ethane-1,2-diyldisulfanyldiyl)bis(3-(3,4-dimethoxyphenyl)-5-(2-pyridylmethylidene)-3,5-dihydro-4H-imidazol-4-one) (3g).** As a result of the reaction of 0.1 g (0.29 mmol) of thiohydantoin **2g** with 0.012 mL (0.027 g, 0.14 mmol) of 1,2-dibromoethane and 0.06 g (0.42 mmol) of $K_2CO_3$, 0.053 g (53%) of compound **3g** was obtained. M.p. 241 °C (dec.). HRMS: calculated for $C_{36}H_{33}O_6N_6S_2$ $(M+H)^+$ 709.1903, found 709.1896. H NMR (400 MHz, $CDCl_3$, δ, ppm): 8.70 (d, 2H, J = 7.83 Hz, Hα'-Py), 8.65 (d, 2H, J = 3.91 Hz, Hβ-Py), 7.59 (t, 2H, J = 7.82 Hz, Hβ '-Py), 7.20 (m, 2H, Ph), 6.87-6.97 (m, 4H, Ph), 6.80 (s, 2H, CH=), 3.95 (s, 6H, p-$CH_3$), 3.90 (s, 6H, m-$CH_3$), 3.84 (s, 4H,$CH_2CH_2$). UV-vis (λ, nm/ε, l mol$^{-1}$ cm$^{-1}$): 362/10936, 277/7574. Calculated C, 61.00%; H, 4.55%; N, 11.86%; S, 9.05%. $C_{36}H_{32}N_6O_6S_2$. Found C, 60.83%; H, 4.25%; N, 12.00%; S, 8.84%,

**Coordination compounds of ligands 3a-g with copper(II) (typical procedure)**. To a solution of ligand **3a-g** (concentration ~$10^{-5}$ M) in 1 mL of dichloromethane 0.1 mL of *n*-butanol was added carefully to obtain two-phase system. A solution of copper(II) chloride dihydrate of the same concentration in 1 mL of butanol was slowly added. The reaction mixture was sealed tightly and left to precipitate.

[(**5*Z*,5´*Z*)-2,2´-(Ethane-1,2-diyldisulfanyldiyl)bis(3-(but-2-yl)-5-(2-pyridylmethylidene)-3,5-dihydro-4H-imidazol-4-one)]dicopper(II) tetrachloride (4a**). From 0.012 g (0.021 mmol) of ligand **3a** and 0.0075 g (0.044 mmol) of $CuCl_2$•$2H_2O$, 0.0073 g (41%) of complex **4a** was obtained as black crystals. M.p. 180 °C. UV-vis (λ, nm/ε, L mol$^{-1}$ cm$^{-1}$): 371/9550, 281/5390. Calculated C, 41.07%; H, 3.91%; N, 10.26%; S, 7.82%. $C_{28}H_{32}N_6O_2S_2Cu_2Cl_4$. Found C, 41.08%; H, 4.11%; N, 9.97%; S, 7.89%.

[(**5*Z*,5´*Z*)-2,2´-(Ethane-1,2-diyldisulfanyldiyl)bis(3-(2-methylbutyl)-5-(2-pyridylmethylidene)-3,5-dihydro-4H-imidazol-4-one)]dicopper(II) tetrachloride (4b**). From

0.03 g (0.052 mmol) of ligand **3b** and 0.018 g (0.1 mmol) of $CuCl_2 \cdot 2H_2O$, 0.0097 g (54%) of complex **4b** was obtained as black crystals. M.p 165 °C. Calculated C, 42.55%; H, 4.25%; N, 9.92%. $C_{30}H_{36}N_6O_2S_2Cu_2Cl_4$. Found C, 43.45%; H, 4.05%; N, 9.62%.

[(**5*Z*,5´*Z*)-2,2´-(Ethane-1,2-diyldisulfanyldiyl)bis(3-benzyl-5-(2-pyridylmethylidene)-3,5-dihydro-4H-imidazol-4-one)]dicopper(II) tetrachloride (4c**). From 0.0135 g (0.021 mmol) of ligand **3c** and 0.0075 g (0.044 mmol) of $CuCl_2 \cdot 2H_2O$, 0.01 g (54%) of complex **4c** was obtained as black crystals. M.p. 186 °C. Calculated C, 46.04%; H, 3.16%; N, 9.48%. $C_{34}H_{28}N_6O_2S_2Cu_2Cl_4$. Found C, 45.97%; H, 3.05%; N, 9.76%.

[(**5*Z*,5´*Z*)-2,2´-(Ethane-1,2-diyldisulfanyldiyl)bis(3-phenylethyl-5-(2-pyridylmethylidene)-3,5-dihydro-4H-imidazol-4-one)]dicopper(II) tetrachloride (4d**). From 0.014 g (0.022 mmol) of ligand **4d** and 0.0075 g (0.044 mmol) of $CuCl_2 \cdot 2H_2O$, 0.0062 g (32%) complex **4d** was obtained as black crystals. M.p. = 205 $^oC$. UV-vis (λ, nm/ε, L $mol^{-1}$ $cm^{-1}$): 370/13490. 279/6890. Calculated C, 47.26%; H, 4.59%; N, 9.19%; S, 7.00%. $C_{36}H_{32}N_6O_2S_2Cu_2Cl_4$. Found C.47.26%; H, 4.19%; N, 8.86%; S, 7.45%.

[(**5*Z*,5´*Z*)-2,2´-(Ethane-1,2-diyldisulfanyldiyl)bis(3-(4-ethoxyphenyl)-5-(2-pyridylmethylidene)-3,5-dihydro-4H-imidazol-4-one)]dicopper(II) tetrachloride (4f**). From 0.015 g (0.022 mmol) of ligand **3f** and 0.0075 g (0.044 mmol) of $CuCl_2 \cdot 2H_2O$, 0.0053 g (26%) complex **4f** was obtained as black crystals. M.p. = 224 $^oC$ (dec). UV-vis (λ, nm/ε, l $mol^{-1}$ $cm^{-1}$): 431/23828, 388/60351, 273/19140.

[(**5*Z*,5´*Z*)-2,2´-(Ethane-1,2-diyldisulfanyldiyl)bis(3-(3,4-dimethoxyphenyl)-5-(2-pyridylmethylidene)-3,5-dihydro-4H-imidazol-4-one)]dicopper(II) tetrachloride (4g.**). From 0.015 g (0.021 mmol) of ligand **3g** and 0.0072 g (0.042 mmol) of $CuCl_2 \cdot 2H_2O$, 0.0061 g (30%) complex **4g** was obtained as black crystals. M.p. = 215 $^oC$ (dec). UV-vis (λ, nm/ε, l $mol^{-1}$ $cm^{-1}$): 351/7617, 274/19276.

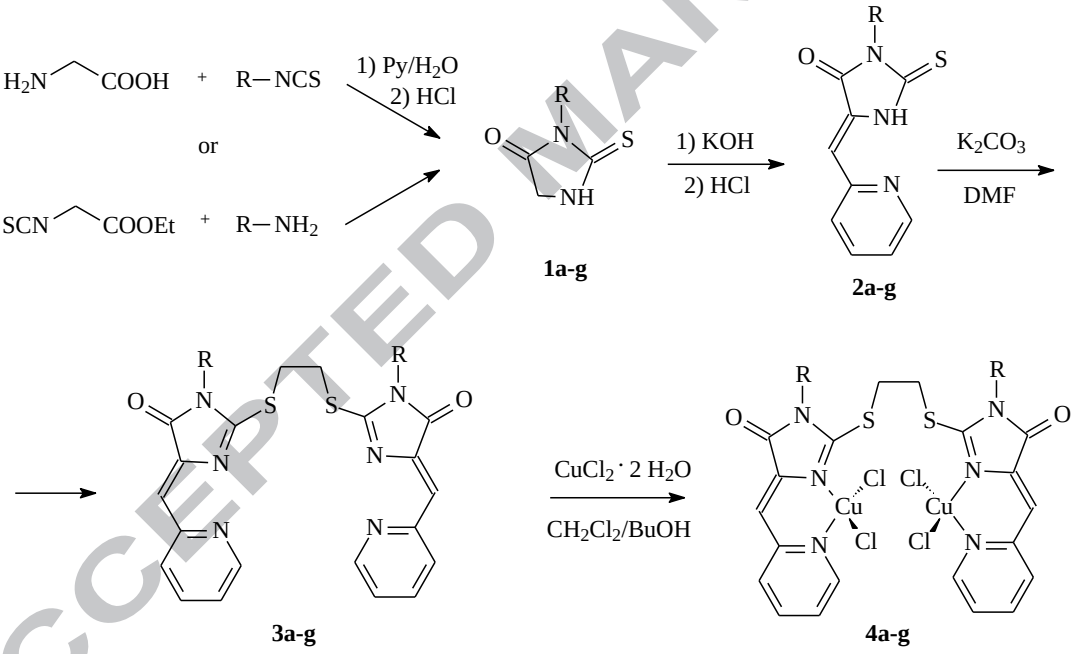
## Results and discussion

*Synthesis of ligands and copmplexes*

The tetradentate $N_4$ ligands **3a-g** were synthesized by the three-step sequence of reactions shown in Scheme 1. At the first step, 3-substituted 2-thiohydantoins **1a-g** was synthesized using one of two manners: reaction of the isothiocyanate with glycine or ethyl isothiocyanatoacetate with an amine; the choice of the method was determined by the availability of corresponding amines or isothiocyanates. Compounds **1a-e** were isolated and characterized by $^1H$ NMR, IR spectroscopy and elemental analysis; thiohydantoins **1f**, **1g** were used into the following reaction without further purification. The condensation of thiohydantoins **1a-g** with 2-pyridine carbaldehyde gave 5-pyridylmethylene-substituted derivatives **2a-g**. All of these compounds

were obtained as single geometrical isomers which can in general be *Z* or *E*. It was shown earlier [32] that the shifts of the vinyl protons in the $^1$H NMR spectrum of the *Z* and *E* isomers of 5-arylidene-2-thiohydantoins are 6.40-6.85 and 6.10-6.35 ppm, respectively. Based on these data, compounds **2a-g** are the *Z* isomers. This fact was later confirmed by the X-ray diffraction study of complexes **4a, d, f, g**. The preferential generation of *Z* isomers for these compounds may be the result of the formation of an intramolecular hydrogen bond between the pyridine nitrogen atom and the N–H fragment of the thiohydantoin cycle.

Tetradentate ligands **3a-g** were synthesized by the alkylation of thiohydantoins **2a-g** with 1,2-dibromoethane in DMF solution, using $K_2CO_3$ as a base (Scheme 1). Coordination compounds **4a-g** were synthesized by the slow diffusion of copper(II) chloride dehydrate in *n*-butanol into a ligand solution in $CH_2Cl_2$ (Scheme 2).




R = *sec*-Bu (**a**), 2-Me-$C_4H_8$ (**b**), Bn (**c**), $CH_2CH_2Ph$ (**d**), Ph (**e**), 4-EtO-$C_6H_4$ (**f**), 3,4-$(MeO)_2$-$C_6H_3$ (**g**)

Scheme 1. Synthesis of ligand and complexes.

All copper complexes were isolated as very dark green (near black) crystals with moderate yields (26-54%). The UV-Vis spectra of coordination compounds contain intensive broad adsorption bands in the UV region, which are similar to those in the UV spectrum of corresponding ligands and refer, most likely, to the π—π* and n—π* transitions in the organic fragment [33-35]. The peaks in the spectra of complexes are slightly shifted relatively to the corresponding peaks of the free ligands, but their intensity changes significantly: the intensity of

the shorter-wave peaks increases, while the intensity of peaks at 340-400 nm decreases (Figure 1). The spectra of the complexes contain also very low-intensive absorption bands of d-d transitions in the visible spectral region at ~ 700–850 nm. Such electronic spectra agree with the tetrahedral or distorted tetrahedral coordination environment of copper(II) ions [36] and are consistent with the previous data for the compounds of the same series [26, 37].

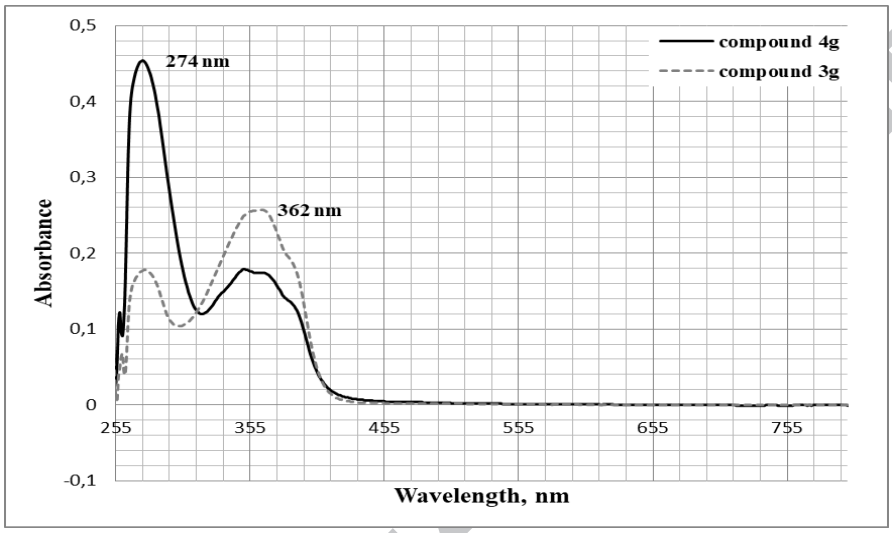



Figure 1. Electronic spectra of coordination compound **4g** and corresponding ligand **3g** in DMF, $2.35 \cdot 10^{-6}$M.

*X-ray crystallography*

The structure of complexes **4a,d,f,g** were established by X-ray diffraction. The molecular structures of complexes are shown in Figure 2. The most important bond lengths and angles are given in Table 1. The crystallographic data and refinement parameters are shown in the Supplementary information Crystals available for structural investigation were obtained by slow diffusion of the ethanolic solution of $CuCl_2$ $2H_2O$ to the solution of corresponding ligand **3** in $CH_2Cl_2$; if there was no crystal formation, the diethyl ether vapor was diffused into the resulting solution.

Summarizing the results of X-ray structural studies for binuclear copper complexes with bis-5-(2-pyridylmethylidene)-3,5-dihydro-4H-imidazol-4-ones the several typical features can be noticed.

1. The complexes contain two structurally equivalent or almost equivalent copper cations.

2. The coordination polyhedron of the copper atom is $N_4$ type, has a distorted tetrahedral shape and is formed by two donor nitrogen atoms of pyridine and imidazolone fragments of organic ligand and two chloride anions.

3. The Cu-Cu distances in complexes are about 4.5-4.6 Å, which is greater than the sum of van der Waals radii. Thus, two copper atoms are not directly connected to one another.

4. The conjugated thiohydantoin and pyridine rings in organic ligand fragments are planar and are virtually coplanar. Six-membered chelate rings of coordination polyhedra are virtually coplanar. In molecules **3f** and **3g**, the carbon atoms of the benzene ring at the N(3) atom deviate from the plane of the five-membered ring of the ligand; the angle of deviation is ~90°.

5. Aromatic fragments of the two "halves" of the ligand are arranged parallel or close to parallel one above the other with a slight shift. The distance between centroids of pyridine rings is approximately 3.5 A.

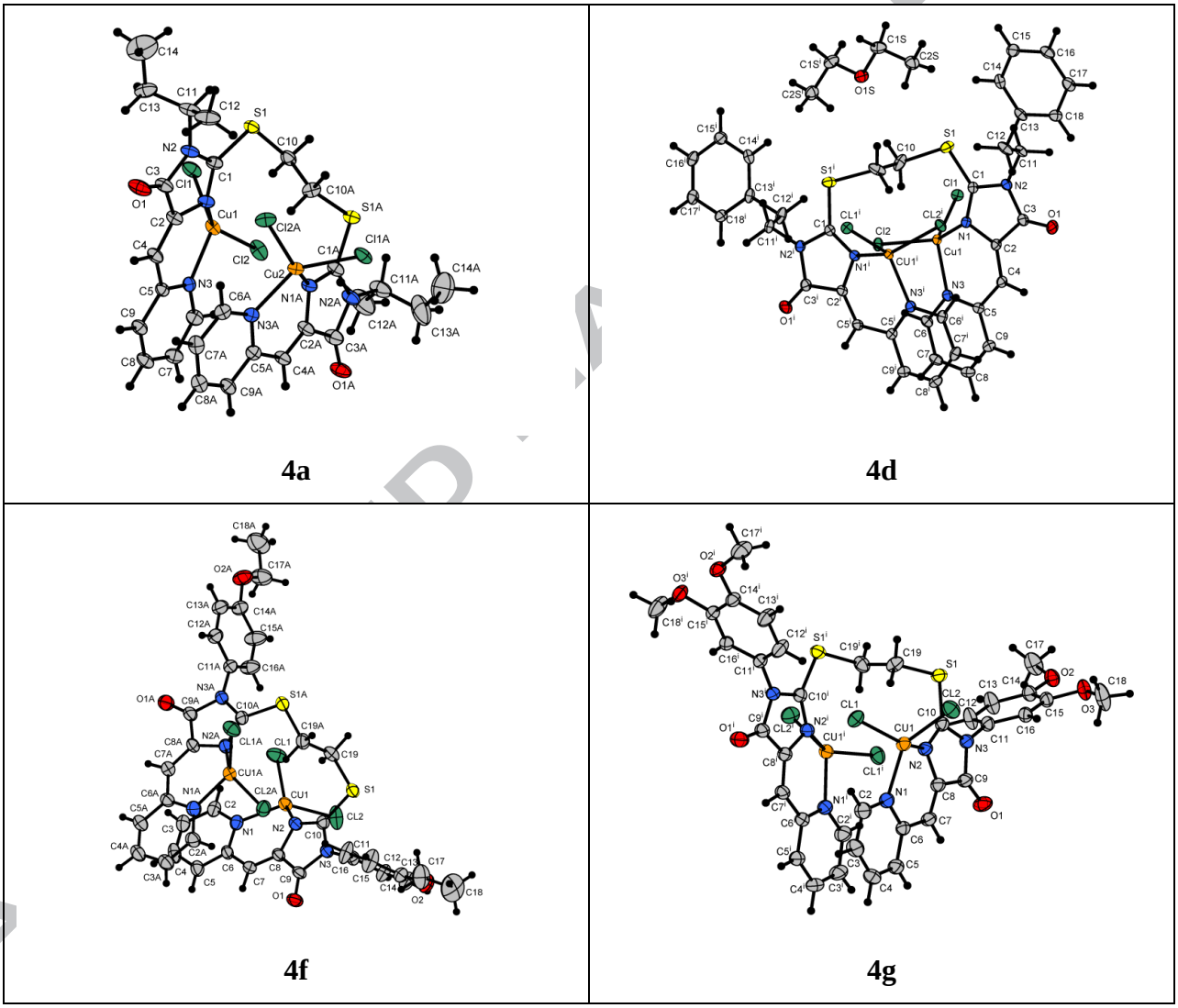



Figure 2. The molecular structures of **4a**, **4d**, **4f**, **4g**, showing the atom-numbering schemes. Displacement ellipsoids are drawn at the 30% probability level. In (4f) two disordered solvate molecules of $CH_2Cl_2$ have been omitted, for clarity. Symmetry related atoms in 4d, 4g are labeled as $N^i$ , symmetry code i= 1-x,y,1.5-z and 2-x,y,1.5-z for 4g, 4d respectively.

Table 1. Selected interatomic distances and bond angles for compounds **4a**, **4d**, **4f** and **4g**.

| **Atoms** | **Distance (Å) or angle (°)** |
|---|---|

| | Complex 4a | Complex 4d | Complex 4f | Complex 4g |
|---|---|---|---|---|
| **Cu-Cu** | 4.546 | 4.559 | 4.610 | 4.536 |
| **Cu(1)-N(1)** | 1.972(5) | 1.9699(17) | 1.999(6) | 1.992(2) |
| **Cu(1)-N(2)** | 2.042(5) | 2.0413(19) | 2.034(7) | 2.064(2) |
| **Cu(1)-Cl(1)** | 2.2030(19) | 2.2218(5) | 2.205(3) | 2.2111(8) |
| **Cu(1)-Cl(2)** | 2.2334(19) | 2.2266(6) | 2.212(2) | 2.2143(7) |
| **N(1)-Cu(1)-N(3)** | 93.5(2) | 93.16(17) | 94.2(3) | 95.86(7) |
| **N(1)-Cu(1)-Cl(2)** | 145.14(17) | 141.84(5) | 142.8(2) | 142.94(7) |
| **N(3)-Cu(1)-Cl(2)** | 98.30(15) | 99.44(5) | 98.5(2) | 97.98(6) |
| **N(1)-Cu(1)-Cl(1)** | 94.95(16) | 96.29(6) | 93.6(2) | 94.95(16) |
| **N(3)-Cu(1)-Cl(1)** | 138.84(15) | 138.00(5) | 138.28(19) | 136.07(7) |
| **Cl(1)-Cu-Cl(2)** | 97.32(8) | 97.91(2) | 98.5(2) | 99.00(3) |

*Electrochemistry*

Ligands **3e-f** and their complexes **4e-f** were studied by cyclic voltammetry (CV) and rotating disk electrode (RDE) voltammetry in DMF in the presence of 0.05 M $Bu_4NClO_4$ as the supporting electrolyte. The electrochemical results and the experimental conditions are given in Table 2 and Supplementary Information. The typical cyclic voltammograms of the complexes and ligands are shown in Figure 6. Ligands undergo a two- of three step reduction at -1.19–-1.23 V and -1.76–-2.06 V (see Table 2); they oxidize in one irreversible step at 1.12-1.51 V. Our previous calculations [30] suggest that both oxidation and reduction occur primarily at the thiohydantoin moiety of the ligands (the orbital of the sulfur lone pair makes the major contribution to HOMO, whereas the cross-conjugated methylidenehydantoin π-system O=CC(=C)N=C makes the major contribution to LUMO).

Copper complexes **4** undergoes a quasi-reversible two-electron cathodic redox transition at the potentials +0.39–+0.43 V; this processes are apparently copper based and correspond to $Cu^{II} \rightarrow Cu^{I}$ reduction. Thus, in dinuclear complexes **4**, both copper ions are reduced simultaneously at the same potential. This is additional evidence that both copper ions in these complexes are not bound to each other. The subsequent peaks in cathodic region at -0.85–-2.25 V apparently correspond to the reduction of organic ligand fragment, not copper(I). In favor of this fact is the absence of peaks of $Cu^0$ reductive desorption during the reverse anodic scans after the potential of second and third cathodic peaks. In addition, there was no copper precipitation on the electrode surface. These observations indicate that the reduced forms of complexes does not break down with the release of $Cu^0$. Note also, that the reduction of the organic fragment in complexes occurs at less negative potentials that those for the free ligands, similar observed

earlier for copper coordination compounds, in which the ligand fragment reduction preceded the reduction of copper(I). This is an additional argument in favor of the fact that the reduced organic ligand remains attached to the positively charged metallic atoms [38].

Note, that for copper-containing complexes the peaks of the reduction of coordinated ligand fragment are doubled (see Figure 3, *right* and Table 2). In our opinion, this may be due to the formation of binuclear copper(I)-containing complexes with Cu-Cu bonding, analogous to [28], under the first reduction stage. The pyridylmethylene-imidazolone fragments of these intermediates, being bound to the conjugated via copper atoms, are reduced further stepwise and one-electronically. A proposed scheme of the first steps of electrochemical reduction of complexes 4 is shown on Scheme 2.

$$[L]Cu^{II}_2 \xrightarrow{+\,2e} [L]Cu^{I}_2 \xrightarrow{+\,1e} [L^{-}]Cu^{I}_2 \xrightarrow{+\,1e} [L^{2-}]Cu^{I}_2$$

Scheme 2. The proposed sequence of the first steps of compounds **4** electrochemical reduction

The oxidation of complexes **4** takes place initially at 1.16–1.17 V, at potentials corresponding to the oxidation all of the coordinated chloride anions at once. The subsequent oxidation peak corresponds to oxidation of the organic ligand fragments (Figure 3).

Thus, during the initial reduction of complexes **4**, both copper ions are reduced simultaneously, during the initial oxidation all four chloride ions are also oxidized simultaneously. As to further reduction, two symmetrical conjugate fragments of the ligand moiety are reduced in stages, whereas they are oxidized at the same potential.

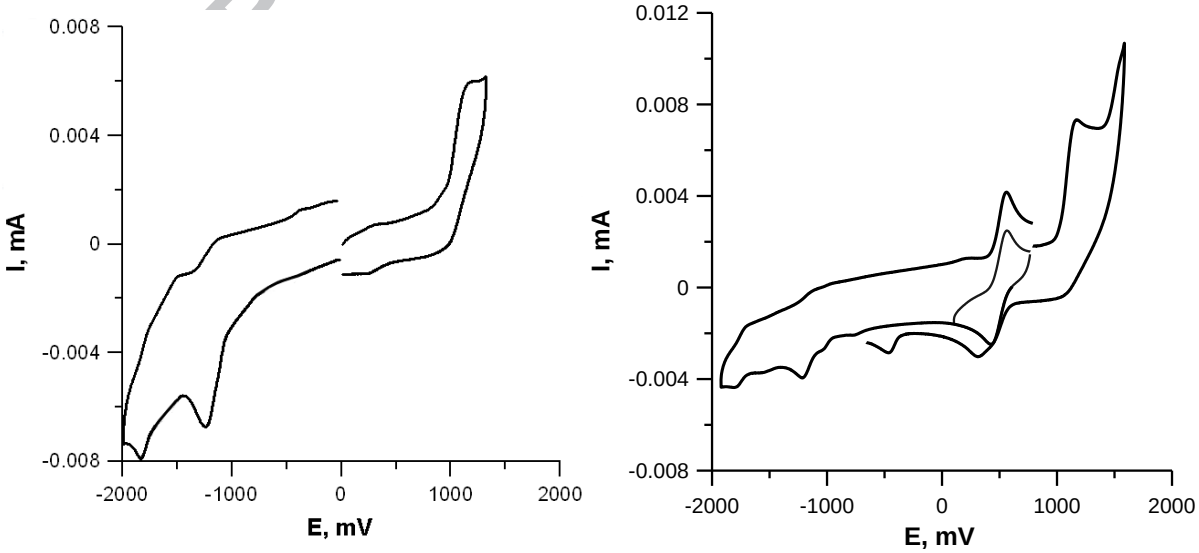



Figure 3. Cyclic voltammograms for ligand **3f** (*left*) and its complex **4f** (*right*). GC electrode, DMF, $5 \cdot 10^{-4}$ M, $Bu_4NClO_4$.

Table 2. The electrochemical potentials (vs. Ag /AgCl /KCl (aq.,sat.)) of the compounds **3e-g**, **4e-g** in DMF in presence 0.1 M $Bu_4NClO_4$ at a GC electrode; potential scan rate 100 mV $s^{-1}$

| **Compound** | **$E_{pc}$, V** | **$E_{pa}$, V** |
|---|---|---|
| Ligand **3e** | -1.19<br>-1.76<br>-2.06 | 1.43 |
| Complex **4e** | +0.39/0.51<br>-0.85<br>-1.14<br>-2.25 | 1.16<br>1.48 |
| Ligand **3f** | -1.23<br>-1.56<br>-1.82 | 1.12 |
| Complex **4f** | +0.43/0.55<br>-1.03<br>-1.21<br>-1.55<br>-1.79 | 1.16<br>1.54 |
| Ligand **3g** | -1.23<br>-1.84 | 1.51 |
| Complex **4g** | +0.40/0.57<br>-1.01<br>-1.19<br>-1.51<br>-1.76 | 1.17<br>1.52 |

*Cytotoxicity*

Ligands **3a,d,g** and their copper complexes **4a,d,g** were tested in terms of their *in vitro* cytotoxicity against cell cancer cells lines, including human lung cancer (A549), breast adenocarcinoma (MCF-7) and human embryonic kidney (HEK293) cells using a standard MTT assay [39]. The results of this assay are shown in Table 4 together with the results obtained for the clinically used drugs cisplatin and doxorubicin, which have been given for comparison.

Table 4. Cytotoxicity of ligands and complexes against A549, MCF7 and HEK293T cell lines measured by MTT-assay (μM)

| **Compound** | **HEK293T, μM** | **MCF7, μM** | **A549, μM** |
|---|---|---|---|
| **3a** | >100 | 18.2±0.9 | |
| **4a** | 2.06±0.8 | 1.34±0.18 | |
| **3d** | 59.5±9 | 34.7±6 | >100 |
| **4d** | 1.27±0.8 | 0.66±0.3 | 1.38±0.13 |
| **3g** | 18.7±6.4 | 54.4±20.6 | 101.9±47 |
| **4g** | 3.4±0.5 | 8.1±0.9 | 19.3±2.5 |
| Doxorubicin [a] | 2.0±0.8 | 2.1±0.8 | 1.1±0.1 |
| Cisplatin [b] | >30 | 64.13±3.9 | 12.4±3.9 |
| $CuCl_2 \cdot 2H_2O$ | >100 | >100 | >100 |

[a] according to [25].

[b] according to [40].

Based on the obtained data, the cytotoxicity of the free ligands were much higher than those of the corresponding copper complexes. The nature of the substituent at the N(3) position of the imidazolone ring had some impact on the cytotoxicity. All tested complexes demonstrate significant cytotoxicity comparable to doxorubicine and greater than cisplatin. Note also that the cytotoxicity of the investigated binuclear coordination compounds of copper(II) is higher than the cytotoxicity of the previously studied binuclear mixed-valence (Cu(II)/Cu(I)) complexes of the same ligands [25].

## Conclusion

The present study involved the synthesis of binuclear copper(II) complexes obtained as a results of (5Z,5´Z)-(2,2´-ethane-1,2-diyldisulfanyldiyl)bis(5-(2-pyridylmethylidene)-3,5-dihydro-4H-imidazol-4-ones) interaction with $CuCl_2 \cdot 2H_2O$. These complexes were characterized by UV-vis spectroscopy, X-ray diffraction and cyclic voltammetry. Based on X-ray data complexes contain two structurally equivalent and unconnected with each other copper atoms. Both copper ions are electrochemically reduced simultaneously at the same potential. The cytotoxicities of the copper containing complexes against MCF7, A549 and HEK293T cells were comparable to those of doxorubicin and greater than those of cisplatin.

## Appendix A. Supplementary data

CCDC entries: 1826604 (**4a**), 1826603 (**4d**), 1826602 (**4f**), 1826644 (**4g**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk.

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