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Electrochemical properties of some gold(III) complexes with (*S*,*S*)-R_2edda-type ligands

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Oxidation-reduction properties of eleven gold(III) complexes with (*S*,*S*)-R_2edda-type ligands was studied by cyclic and differential pulse voltammetry in DMSO. Series **I**: $[AuCl_2\{(S,S)\text{-}R_2\text{eddip}\}]PF_6$, (*S*,*S*)-eddip = (*S*,*S*)-ethylenediamine-*N*,*N'*-di-2-propanoate, R = *n*-butyl, *n*-pentyl, isobutyl, isoamyl, cyclopentyl, **1**–**5**; **II**: $[AuCl_2\{(S,S)\text{-}R_2\text{eddch}\}]PF_6$, (*S*,*S*)-eddch = (*S*,*S*)-ethylenediamine-*N*,*N'*-di-2-(3-cyclohexyl)propanoate, R = methyl, ethyl, *n*-propyl, *n*-butyl, isobutyl, isoamyl, **6**–**11**. Voltammograms in DMSO showed two successive irreversible reduction steps, where Au^I species were the final reduction product. Reduction potential values are in range from 116 to 156 mV (Ep_1) and –520 to –572 mV (Ep_2) for Series **I** and from 148 to 228 mV (Ep_1) and –569 to –638 mV (Ep_2) for Series **II**. In general, slightly easier reduction of complexes belonging to Series **I** (higher cytotoxicity) could be due to less steric hindrance around the gold center. Reduction potentials and anticancer activity are not in correlation.

Keywords: gold(III) complexes; R_2edda-type ligands; anticancer activity; reduction potential; voltammetry.

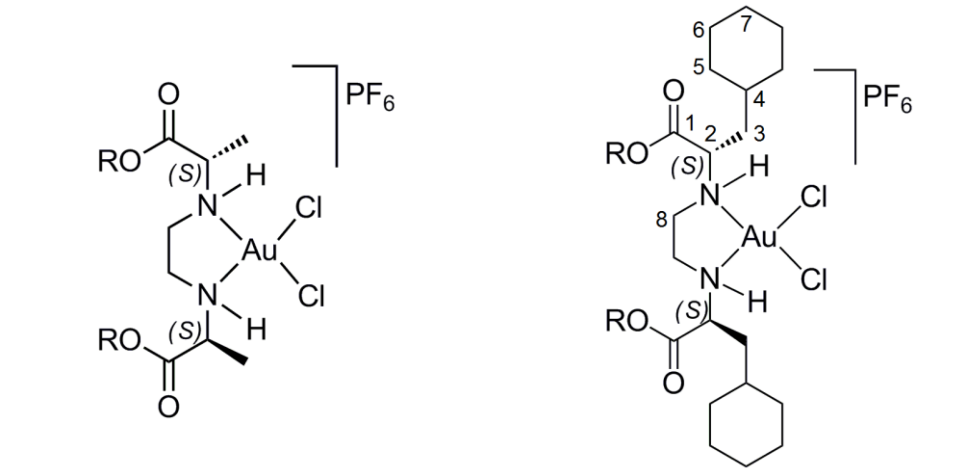
1. INTRODUCTION

The therapeutic value of metal-based drugs has been well established [1-5]. The first metal-based anticancer drug discovered is cisplatin [6]. Its anticancer effect might be due to covalently binding to DNA forming adducts that interfere with transcription and DNA replication, and thereby

triggers programmed cell death [7-9]. However, severe side effects such as nephrotoxicity, ototoxicity and neurotoxicity, and the development of resistance are drawbacks which lead to increased motivation for alternative chemotherapeutic strategies [10-14].

Due to the structural similarity of gold(III) and platinum(II) complexes, it was believed that the mechanism of action for gold(III) compounds might also be DNA binding and disruption of DNA replication [15,16]. However, recent findings by Messori *et al.* showed that most of the cytotoxic gold(III) complexes have a weaker binding affinity for DNA than cisplatin [17-19]. Subsequent studies have suggested that the therapeutic effect of gold compounds may arise from interactions with different proteins [17,18] such as the mitochondrial enzyme thioredoxin reductase (TrxR) [20], the proteasome [21], cystein proteases [22] as well as human serum albumin (HSA), human glutathione reductase and protein tyrosine phosphatases [23]. Moreover, gold(III) complexes were found to be responsible for inhibition of zinc finger PARP-1-protein (PARP = poly(adenosine diphosphate-ribose) polymerase [24].

It is important to note that for almost all known active gold(III) complexes, the active metabolites could be gold(I) species produced by gold(III) reduction *in vivo* [25]. Reduction potential values are an unavoidable parameter in establishing the mode of action since most metallopharmaceuticals are activated by *in vivo* electron transfer [26].



I: 1—5

R = *n*-Bu, *n*-Pe, *i*-Bu, *i*-Am, *c*Pe

II: 6—11

R = Me, Et, *n*-Pr, *n*-Bu, *i*-Bu, *i*-Am

Figure 1. Structure formulae of the studied gold(III) complexes.

In this paper, the aim is to contribute to structure-activity relationships, and as a part of our investigations of the physical and structural parameters of gold(III) complexes, we have studied the electrochemical behavior of eleven gold(III) complexes within two Series of (*S,S*)-R_2edda-type ligands: **I** - [$AuCl_2${(*S,S*)-R_2eddip}]PF_6, ((*S,S*)-eddip = (*S,S*)-ethylenediamine-*N,N*'-di-2-propanoate, R = *n*-butyl (*n*-Bu), *n*-pentyl (*n*-Pe), isobutyl (*i*-Bu), isoamyl (*i*-Am) and cyclopentyl (*c*Pe); **1**–**5**, respectively) and **II** - [$AuCl_2${(*S,S*)-R_2eddch}]PF_6, ((*S,S*)-eddch = (*S,S*)-ethylenediamine-*N,N'*-di-2-(3-cyclohexyl)propanoate, R = methyl (Me), ethyl (Et), *n*-propyl (*n*-Pr), *n*-butyl (*n*-Bu), isobutyl

(*i*-Bu) and isoamyl(*i*-Am); **6**–**11**, respectively) shown in Figure 1. The electrochemical data may be helpful in constructing structure-activity relationships. The synthesis, characterization and biological activity of these gold(III) complexes have recently been published [27,28].

2. EXPERIMENTAL

2.1. Materials and methods

Dimethyl sulfoxide (DMSO) and $LiClO_4$ were purchased (Aldrich, USA) and used without further purification. All complexes (**1−11**) were dissolved in DMSO in the concentration of 1.0 mM, followed by addition of 0.01 M $LiClO_4$ as a supporting electrolyte.

Electrochemical measurements were performed at ambient temperature using CHI-760B potentiostat (CHI Instruments, USA) for cyclic voltammetry and differential pulse voltammetry. The voltammetric measurements were performed in a three-electrode cell containing a platinum working electrode (Model 6.1204.120), a non-aqueous Ag/AgCl reference electrode (Model CHI 112) and a platinum wire as counter electrode (model CHI 115). Reduction potentials of all compounds were determined by differential pulse voltammetry. The obtained electrochemical data are shown in Table 1.

2.2. Complexes

Complexes **1−11** were synthesized and fully characterized in our recent publications [27,28]. Explicitly, gold(III) complexes **1−5** were synthesized in the reaction of $Na[AuCl_4]$ with equimolar amount of corresponding ligand hydrochlorides, *n*-butyl, *n*-pentyl, isobutyl, isoamyl and cyclopentyl diesters of (*S*,*S*)-ethylenediamine-*N*,*N'*-di-2-propanoic acid, respectively [27]. Gold(III) complexes **6−11** were synthesized in the reaction of $Na[AuCl_4]$ with an equimolar amount of corresponding ligand hydrochlorides, methyl, ethyl, *n*-propyl, *n*-butyl, isobutyl and isoamyl diesters of (*S*,*S*)-ethylenediamine-*N*,*N'*-di-2-(3-cyclohexyl)propanoic acid respectively [28]. Each ligand was suspended in methanol, deprotonated with $LiOH{\cdot}H_2O$ and after stirring of 1h, a solution of $Na[AuCl_4]{\cdot}2H_2O$ in methanol was added. The desired complexes were obtained after addition of ammonium hexafluorophosphate. Purity and constitution of the obtained products were confirmed with elemental analysis, ^1H and ^{13}C NMR as well as UV/Vis spectroscopies and mass spectrometry. As examples for Series **I** and **II** analytical and spectroscopic data for complexes **4** and **11** are provided.

*2.3. Characterization of complexes **4** and **11***

Complex **4** [27]: [Yield 55 mg, 57%] Analysis: Calculated for $C_{18}H_{36}N_2O_4AuCl_2PF_6{\cdot}H_2O$: C, 27.88; H, 4.94; N, 3.61. Found: C, 27.44; H, 4.84; N, 3.43. ^1H NMR (200 MHz, DMSO-d_6): 0.92 (d, 12H, $(CH_3)_2CHCH_2CH_2{-}OOC{-}$), 1.61 (m, 10H, $(CH_3)_2CHCH_2CH_2{-}OOC{-}$, CH_3), 1.73 (m, 2H, $(CH_3)_2CHCH_2CH_2{-}OOC{-}$), 3.76 (d, 4H, CH_2-(en)), 3.82 (s, 2H, N*H*), 4.11 (d, 2H, C*H*), 4.31 (m, 4H, $(CH_3)_2CHCH_2CH_2{-}OOC{-}$). ^{13}C NMR (50 MHz, DMSO-d_6): 14.9 $(CH_3)_2CHCH_2CH_2{-}OOC{-}$), 16.2

(*C*H_3), 22.3 $(CH_3)_2$*C*HCH_2CH_2−OOC−), 24.9 $(CH_3)_2$CH*C*H_2CH_2−OOC−), 36.8 (*C*H_2-(en)), 56.1 (*C*H), 66.3 $(CH_3)_2CHCH_2$*C*H_2−OOC−), 169.5 $(CH_3)_2CHCH_2CH_2$−OO*C*−). ESI–MS in CH_3CN: *m/z* 612.17 $[M]^+$. IR / cm^{-1} (ATR): 2961m, 2873m, 1739vs, 1461s, 1227s, 849w, (vs, very strong; s, strong; m, medium; w, weak).. UV-visible in $CHCl_3$ [λ_{max}/nm]: 322.

Complex **11** [28]: [Yield 66 mg, 57%] Analysis: Calculated for $C_{30}H_{56}N_2O_4AuCl_2PF_6$: C, 39.09; H, 6.12; N, 3.04. Found: C, 38.98; H, 6.13; N, 3.11. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.95 (d, $(CH_3)_2CHCH_2CH_2$–OOC–, 12H; m, C^7H_2, 4H), 1.24 (m, $C^{5,6}H_2$, 8H), 1.50-1.90 (m, C^3H_2, C^4H, $C^{5,6}H_2$, $(CH_3)_2CHCH_2CH_2$–OOC– and $(CH_3)_2CHCH_2CH_2$–OOC–, 20H), 3.43 (m, C^8H_2, 4H), 3.92 (m, C^2H, 2H), 4.30 (m, $(CH_3)_2CHCH_2CH_2$–OOC–, 4H), 4.71 (s, N*H*, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 11.1 ($(CH_3)_2CHCH_2CH_2$–OOC–), 16.3 ($(CH_3)_2CHCH_2CH_2$–OOC–), 22.3 ($(CH_3)_2CHCH_2CH_2$–OOC–), 25.9 (C^6), 32.4 (C^4), 33.1 (C^7), 33.8 (C^5), 36.9 (C^3), 44.5 (C^8), 59.2 (C^2), 65.8 ($(CH_3)_2CHCH_2$–OOC–), 171.0 (C^1). ESI–MS in CH_3CN: *m/z* 775.33 $[M]^+$, 776.33 $[M + H]^+$. IR / cm^{-1} (ATR): ν_{max} = 2929m, 2854m, 1731vs, 1453s, 1260s, 1212s, 851w (vs, very strong; s, strong; m, medium; w, weak). UV-visible in $CHCl_3$ [λ_{max}/nm (ε/ M^{-1} cm^{-1})]: 320 (6630).

3. RESULTS AND DISCUSSION

3.1. Electrochemical behavior

*3.1.1. Gold(III) complexes with (S,S)-R$_2$eddip ligands, Series **I**: **1−5***

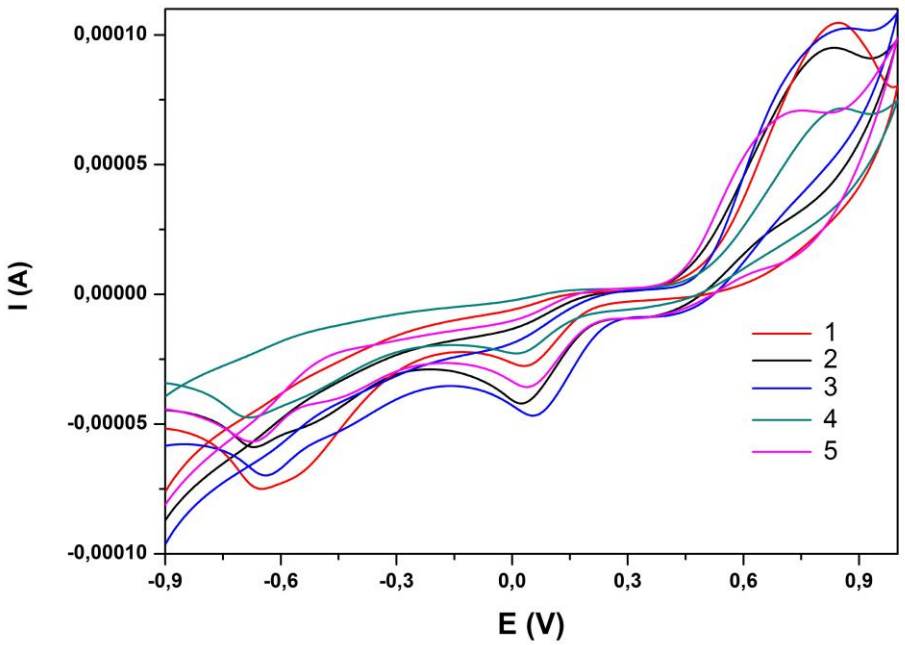


Figure 2. Cyclic voltammograms of 1.0 mM solutions of **1**−**5** in DMSO with $LiClO_4$. Scan rate 0.1 V/s.

The inherent electrochemical properties of the investigated gold(III) complexes with (*S,S*)-R_2eddip ligands were studied by cyclic voltammetry immediately after dissolution (Figure 2). On a clean platinum surface, in DMSO, complexes **1**−**5**, exhibit two successive irreversible reduction steps accompanied by the loss of chlorido ligands. The reduction potential values are in the range from 116 to 156 mV (Ep_1) and from − 520 to − 572 mV (Ep_2). The first step is probably a one-electron process, $[NN\text{'-}AuCl_2]^+ + e^- \rightarrow [NN\text{'-}AuCl]^+ + Cl^-$, whereas the second is $[NN\text{'-}AuCl]^+ + e^- \rightarrow [NN\text{'-}Au]^+ + Cl^-$ (*NN*' presents ligand) . For all complexes the two peaks imply a short-living Au^{II} intermediate in the reduction, whose exact chemical composition (either $AuCl^+$ as given above or some dimer) is not clear at this stage [29]. Due to the absence of metallic gold at the platinum working electrode, we can conclude that overall reduction does not lead to Au^0 but rather to Au^I species. This observation was also confirmed by potentiostatic reduction at –0.8 V vs. Ag/AgCl ref. electrode for 15 min.

There is no strong correlation between reduction potential and the length of the alkyl ester chains in complexes **1**–**5**. Furthermore, the potential differences between the first and second reduction peak remain approx. constant and this might demonstrate the same reduction pathway/mechanism.

Two peaks of similar height with the potentials of around 0.12 V *vs*. Ag/AgCl and around −0.57 V *vs*. Ag/AgCl can be spotted using differential pulse voltammetry (Figure 3.). The length of alkyl chain in ligand didn't significantly influence the reduction potential value.

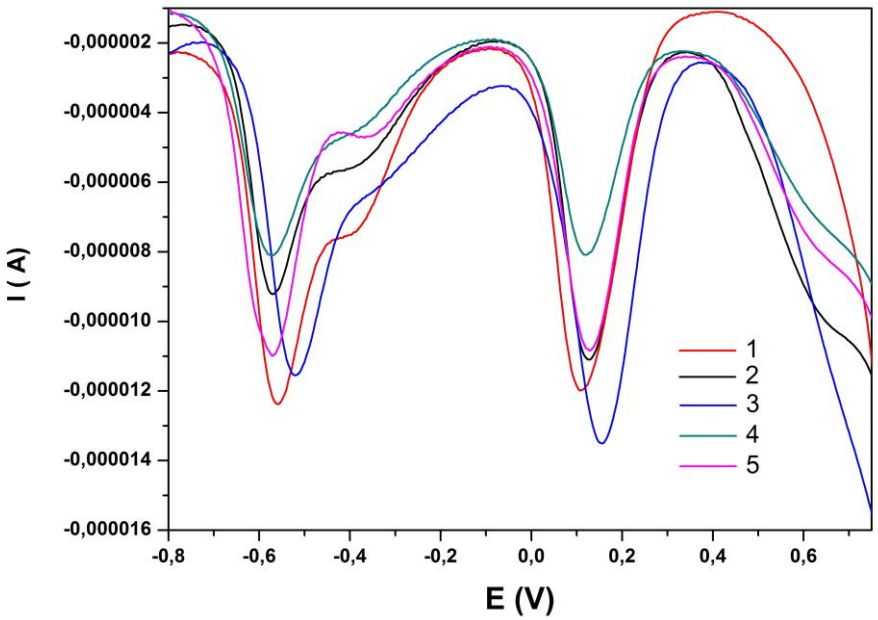


Figure 3. Differential pulse voltammograms of 1.0 mM solutions of **1**−**5** complexes in DMSO with $LiClO_4$. Modulation amplitude 0.05 V, modulation time 0.04 s.

3.1.2. Gold(III) complexes with (S,S)-R_2eddch ligands, Series **II**: **6**−**11**

As observed for **1**−**5**, Au^{III}/Au^I reduction of complexes **6**−**11** is also a two-step process (Figure 4). In DMSO at the platinum electrode complexes have shown a reduction peak in the range from 148

to 228 mV (Ep_1) and from −569 to −638 mV (Ep_2). An irreversible two-electron process followed by the loss of the chlorido ligands is found as for Series **I**, but in this case the reduction process is more difficult (Figure 5). The main reason for this behavior could be found in the steric surrounding of the gold center, which is more pronounced in Series II than in I due to the presence of cyclohexyl moiety. The occurrence of the Au^{III}/Au^0 reduction is rejected due to lack of elemental gold at the platinum electrode.

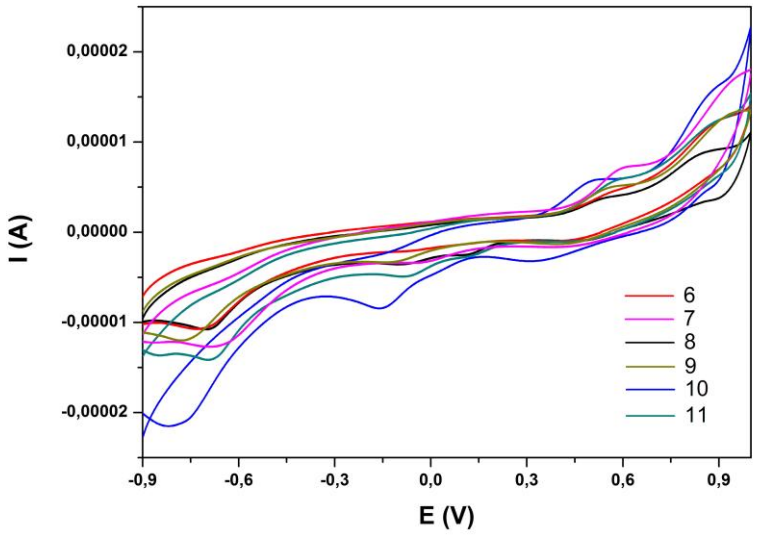


Figure 4. Cyclic voltammograms of 1.0 mM solutions of **6**−**11** in DMSO with $LiClO_4$ at the scan rate of 0.1 V/s.

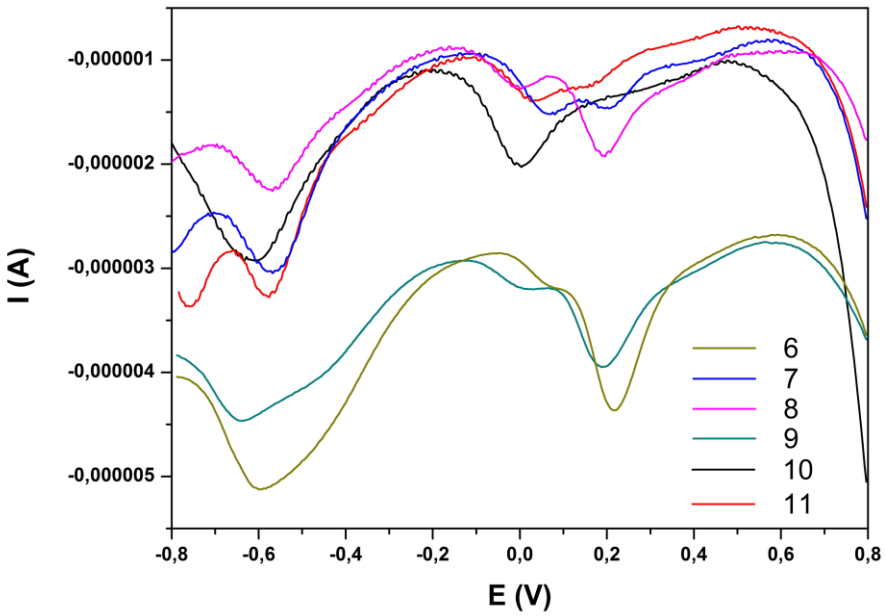


Figure 5. Differential pulse voltammograms of 1.0 mM solutions of **6**−**11** complexes in DMSO with $LiClO_4$. Modulation amplitude 0.05 V, modulation time 0.04 s.

In the cyclic voltammograms of **10**, the observed signals originate from the oxidation/reduction process of the corresponding complex. At the experimental conditions, three reduction and two oxidation peaks were recorded, which all have good linearity of peak current with the square root of ascending scan rate (Figure 6). Shifts in peak potential were not significant. This phenomenon indicates diffusion controlled process of soluble species rather than adsorption to the electrode surface [30,31].

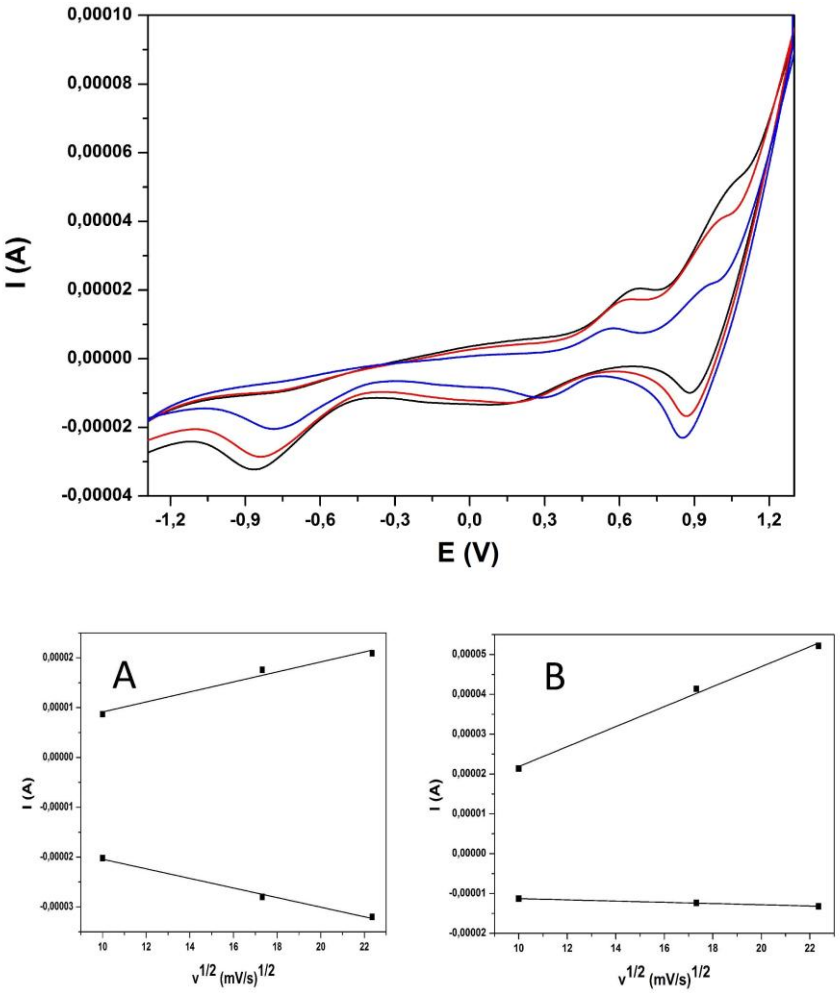


Figure 6. Cyclic voltammograms of 1.0 mM solutions of 10 in DMSO with $LiClO_4$ at the scan rates of 0.1, 0.3, 0.5 V/s using platinum electrode. A) and B) figures present dependence of the peak currents from the square root of the scan rate for the cathodic and anodic peaks.

3.2. Correlation between redox potentials and biological activity

Gold(III) complexes have high reduction potentials and fast rates of hydrolysis, thus they might be unstable under physiological conditions, which is opposite to platinum(II) analogues [32].

When polydentate ligands were used, the reduction potential of the metal center was lowered which led to reporting a large number of gold(III) complexes that are quite stable in physiological

medium, and manifest very promising antitumor activity against different human tumor cell lines, both *in vitro* and *in vivo* [33-36]. Even though mechanistic studies show that apoptosis is induced in tumor cells by the majority of cytotoxic gold complexes, the actual modes of action are still not completely identified.

As it can be seen in Table 1, the most active gold(III) complexes toward HeLa (cervix adenocarcinoma), K562 (myelogenous leukemia) cell lines are those with less bulky ligands, i.e. Series **I**. Gold(III) complexes from both Series, **I** and **II**, have very similar Ep values, and are easily reduced to gold(I) species, thus could be good candidates for further investigations, especially complex **2**. In our study, a correlation between reduction potentials and biological activity was not detected. Reduction potentials do not play crucial role in modulation of the anticancer activity of gold(III) complexes within Series **I** and **II**, and in accordance to previous results with platinum(IV) and similar ligand systems [37], no relationship between reduction potential and IC_{50} values is observed. But in literature these investigations gave some results, and for platinum complexes it was found that the lower IC_{50} values were, the easier the reduction of the examined class of compounds was (and also an increase of the reduction potential as the electron-withdrawing power of the axial ligands rises) [38,39]. In this case, most probably, the activity magnitude is related to the substituents in both ester moieties as well as in the side chain of aminocarboxylato backbone.

Table 1. Comparative biological and electrochemical data

Compound	***IC_{50}/ μM[a]***		***Ep_1/mV[b]***	***Ep_2/mV[b]***
	HeLa	***K562***		
1	2.07[c]	2.97[c]	124	-544
2	1.61[c]	1.45[c]	128	-568
3	1.99[c]	4.41[c]	156	-520
4	2.14[c]	5.01[c]	116	-572
5	1.72[c]	5.54[c]	127	-570
6	29.03[d]	15.03[d]	218	-595
7	16.76[d]	8.35[d]	198	-569
8	20.34[d]	7.77[d]	191	-569
9	16.97[d]	12.05[d]	187	-638
10	17.74[d]	10.73[d]	228	-608
11	26.35[d]	3.76[d]	148	-578
cisplatin	4.47	5.77	-	-

[a]IC_{50} is the *in vitro* cytotoxic activity against HeLa (cervix adenocarcinoma) and K562 (myelogenous leukemia) cell lines in μM.

[b]Ep are reduction potential values determined using differential potential voltammetry.

[c]See literature [27]

[d]See lirerature [28]

4. CONCLUSIONS

Eleven gold(III) complexes, Series **I**: $[AuCl_2\{(S,S)\text{-}R_2eddip\}]PF_6$, Series **II**: $[AuCl_2\{(S,S)\text{-}R_2eddch\}]PF_6$, with (*S,S*)-$R_2$edda-type ester ligands are investigated by cyclic voltammetry and differential pulse voltammetry in DMSO. For both Series, **I** and **II**, the following is found

- Reduction to Au^I species in two steps and through Au^{II} short-living intermediates occur. The two one-electron processes are accompanied with loss of chlorido ligands.

- No elemental gold deposition at the platinum working electrode also indicates reduction to Au^I compounds.

- Complexes from Series **I** have less bulky surroundings of the gold center, and are, in general, slightly easier to reduce.

- Reduction potentials are not in dependence of the number of carbon atoms in ester chains.

- No correlation of reduction potential and anticancer activity is found.

Reduction potentials do not play crucial role in modulation of the anticancer activity of these gold(III) complexes.

SUPPLEMENTARY INFORMATION (SI)
There is NO supplementary information. Characterization (NMR, IR, ESI-MS, elemental analysis, UV-vis) is already published, see literature [27,28].

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