THESES OF DOCTORAL (Ph.D.) DISSERTATION

# Comparative solution and structural studies on anticancer copper complexes of thiosemicarbazones and 2-substituted sterane-based compounds

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# I. Introduction and objectives

The pharmaceutical industry usually focuses on organic-based synthetic drugs or biologically derived compounds, although there are some examples of metal complexes in the clinical use. The main advantage of metal complexes over organic drugs is the potential to change redox state, geometry and coordination number. Moreover, metal ions can modulate the biological activity of organic compounds by complex formation. In spite of the interest in metal-based compounds greatly increased by the discovery and successful clinical applications of the Pt(II)-containing anticancer drug like cisplatin, metal-based compounds cover just a few percentage of existing drugs. However, cisplatin has serious side effects, such as nephrotoxicity, bone-marrow suppression and nausea. Furthermore, cisplatin-resistance can be developed during the treatment, which is responsible for the cross-resistance to other compounds. Based on these problems, the development of other novel metal-based anticancer compounds is an important field of drug discovery and the major goals are to find more effective and selective compounds.

Besides the development of new metal complexes, the characterization of their physico-chemical properties and stability in solution are crucial tasks for understanding better the mechanisms of action and establishing structure-activity relationships. Accordingly, detailed solution equilibrium studies can help in the structure optimization, specific targeting of bioactive compounds and successful development of future drugs.

The main objective of my PhD thesis was to investigate the behaviour of anticancer (thio)semicarbazones ((T)SCs), 2-substituted sterane-based compounds and their Cu(II) complexes in aqueous solution, namely:

• Synthesis and characterization of Cu(II) complexes with (thio)semicarbazones and aminophenols bearing (N,N,S), (O,N,S), (O,N,O) and (N,O) donor atoms (**Figure 1**), especially imidazole-TSCs, (T)SCs with tetrahydronaphthalene backbone, 2-substituted sterane-based (T)SCs and 2-aminophenols. Growing of single crystals of Cu(II) complexes suitable for determination by X-ray crystallographic measurements.

• Performing comprehensive solution equilibrium studies for ligands and their Cu(II) complexes with the combined use of different methods such as ultraviolet-visible (UV-vis) spectrophotometry, pH-potentiometry, fluorimetry and $^{1}H$ nuclear magnetic spectroscopy (NMR). Namely, determination of proton dissociation constants of the ligands, the formation constants of the metal complexes, lipophilicity, membrane permeability, the stoichiometry of the formed species and the most plausible chemical forms of the ligands and their Cu(II) complexes at physiological pH under biologically relevant conditions.

• Investigation of the redox properties of some selected Cu(II)-(T)SC complexes and their interaction with physiological reductants, such as glutathione (GSH) and ascorbic acid (AA), in order to understand better their mechanisms of action. Characterization of antioxidant activity using an antioxidant ('DPPH') assay.

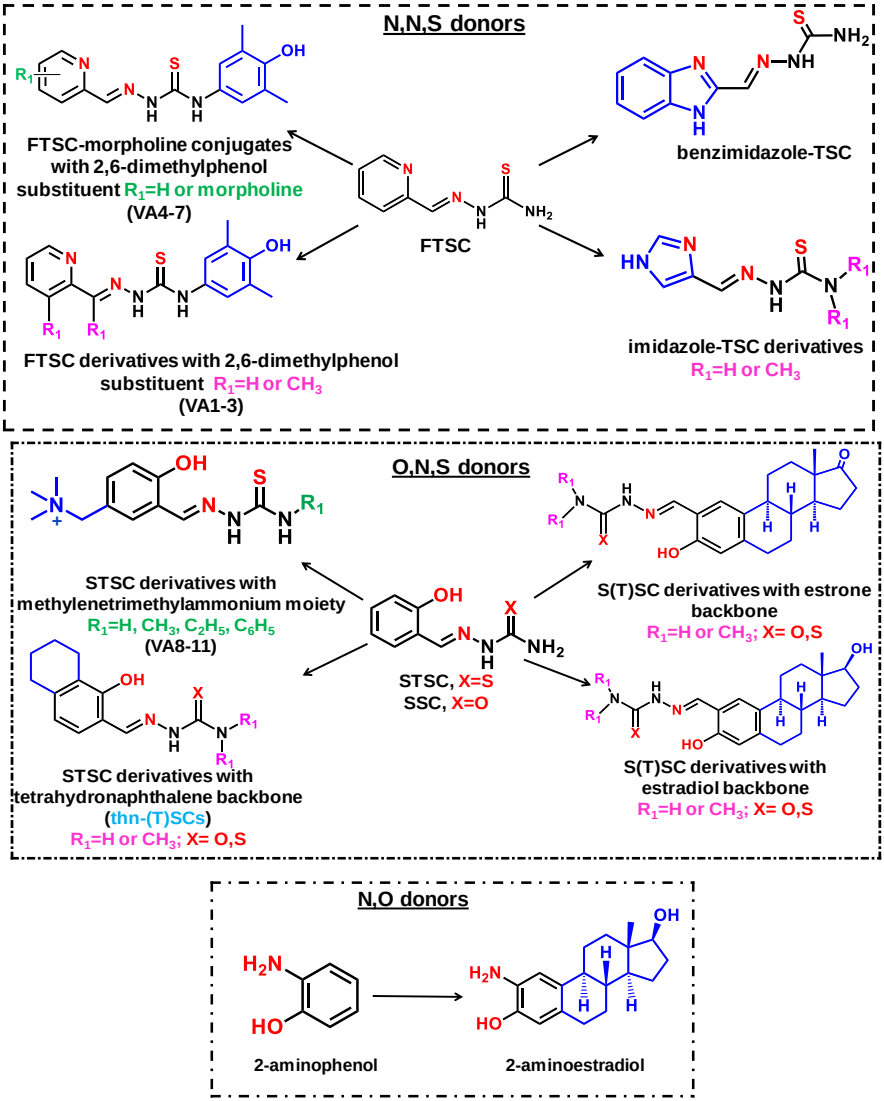


**Figure 1.** Chemical structures and name of class of compounds which were studied in this thesis.

## II. Synthesis of metal complexes and experimental methods

FTSC derivatives with 2,6-dimethylphenol and morpholine conjugates, and STSC derivatives with methylenetrimethylammonium moiety and their Cu(II) complexes were developed in the laboratory of Prof. Vladimir B. Arion (Institute of Inorganic Chemistry of the University of Vienna). Benzimidazole-TSC, imidazole-TSCs, (T)SC derivatives with tetrahydronaphthalene backbone, sterane-based TSCs and aminophenols were produced in the laboratory of Dr. Éva Frank (Department of Molecular and Analytical Chemistry, University of Szeged). Cu(II) complexes were obtained by the reaction between the given ligand and $CuCl_2$ in 1:1 ratio in methanol and were stirred under reflux. In some cases, HEPES buffer was applied for adjusting the pH. The formed precipitation was then decanted, washed four times with water and dried overnight at 50 °C. The Cu(II) complexes were characterized by ESI-MS, UV-vis spectrophotometry and elemental analysis. Single-crystals were grown usually in methanol/$H_2O$ solvent system by slow evaporation of the solvent.

The stock solutions of the tested compounds were prepared on a weight-in-volume basis dissolved in DMSO or $H_2O$. The concentration of these compounds was determined by pH-potentiometric titrations or calculated based on their molecular mass obtained by elemental analysis. $CuCl_2$ stock solution was made by the dissolution of anhydrous $CuCl_2$ in water and its exact concentration was determined by complexometry using EDTA.

**pH-potentiometry**

The pH-potentiometric measurements were carried out at 25.0 ± 0.1°C in water and/or in DMSO/$H_2O$ solvent mixtures (30:70 and/or 60:40 *v/v*) at an ionic strength of 0.10 M (KCl) in order to determine the proton dissociation constants of the ligands and the overall stability constants of the metal complexes. pH values were measured by an Orion 710A pH meter equipped with a Metrohm combined electrode (type 6.0234.100), and a Metrohm 665 Dosimat burette was used for the pH-potentiometric measurements. The proton dissociation constants of the ligands, the stoichiometry and overall stability constants of the complexes were determined with the computer program Hyperquad2013.

**UV-vis spectrophotometry**

Herein, UV-vis spectrophotometry was used for the determination of the proton dissociation constants of the ligands and the overall stability constants of the Cu(II) complexes, and for the characterization of investigated ligands and their Cu(II) complexes. For that purpose, an Agilent Cary 8454 diode array spectrophotometer was used to record the UV-vis spectra at a wavelength range of 200–1100 nm. The path length was varied between 0.5-2 cm. Spectrophotometric titrations were performed under the same conditions, which was applied for pH-potentiometry. Proton dissociation constants ($K_a$) of the tested ligands, the overall stability constants ($\beta$) of the Cu(II) complexes and

the molar absorption spectra of the individual species were calculated by the computer program PSEQUAD. Moreover, this technique was also used for the following redox reaction of the Cu(II) complexes with GSH and ascorbic acid at 25.0 ± 0.1 °C, at pH 7.40 (10 mM HEPES with 0.1 M KCl) and the DPPH free radical scavenging capacity, which was also studied at 25.0 ± 0.1 °C on an Agilent Cary 3500 spectrophotometer. Distribution coefficients ($D_{7.4}$) of the ligands and the complexes were determined by the traditional shake-flask method in *n*-octanol/buffered aqueous solution at pH 7.40, and parallel artificial membrane permeability assay (PAMPA) was applied for the ligands and complexes and evaluated by UV-vis spectrophotometry.

**Fluorescence spectroscopy**

In this work fluorescence spectroscopy was used for recording three-dimensional spectra for selected ligands and in the case of fluorescent ligands, the deprotonation processes were also followed. The emission fluorescence spectra were recorded for ligands on a Hitachi-4500 spectrofluorometer. The fluorometric titrations were performed by the same way as used for the UV-vis titrations. Proton dissociation constants ($K_a$) of the ligands were calculated by the computer program PSEQUAD.

**Nuclear magnetic resonance spectroscopy**

pH-dependent $^1$H NMR spectra were recorded on a Bruker Avance III HD instrument in order to determine proton dissociation constants ($K_a$) of the ligands using the PSEQUAD program. All spectra were recorded with the WATERGATE water suppression pulse scheme using sodium trimethylsilylpropanesulfonate (DSS) internal standard. Samples usually contained 1 mM concentration of the ligand in a 10% (*v/v*) $D_2O/H_2O$, 30% or 60% (*v/v*) $d_6$-DMSO/$H_2O$ mixture and were titrated at 25.0°C, at $I$ = 0.10 M (KCl).

**Cyclic voltammetric and spectroelectrochemical studies**

Cyclic voltammetry was used in combination with UV-vis spectrophotometry, which can provide comprehensive information about the chemical processes driven by the electron transfer for investigation the redox properties of Cu(II) complexes. Cyclic voltammograms of Cu(II) complexes were recorded at 25.0 ± 0.1 °C. Tetrabutylammonium hexafluorophosphate ($n$-$Bu_4NPF_6$) was used as supporting electrolyte and measurements were performed at different pH values on a conventional three-electrode system under argon atmosphere using an Autolab PGSTAT 204 potentiostat/galvanostat monitored with Metrohm's Nova software. Redox potentials were obtained at different scan rates between 10-100 mV/s in the range of −1.3 to +1.0 V. *In situ* UV-vis spectroelectrochemical measurements were performed on a system including a spectrometer (Avantes AvaLight-DHc light source equipped with AvaSpec-UL2048XL-EVO detector), the spectroelectrochemical cell kit (AKSTCKIT3) with the Pt-microstructured honeycomb working electrode. The spectra were processed using the AvaSoft 8.1.1 software package. Measurements and data evaluation for Cu(II) complexes of imidazole-derived thiosemicarbazones were done with the help of Prof. Peter Rapta

(Slovak University of Technology, Institute of Physical Chemistry and Chemical Physics, Bratislava, Slovakia).

Other experiments performed by our partners: single-crystal X-ray crystallography and **electron paramagnetic resonance (EPR) spectroscopy** (Dr. Nóra V. May, Research Centre for Natural Sciences, Budapest, Hungary), **elemental analysis** (Mr. Johannes Theiner, Institute of Inorganic Chemistry, University of Vienna, Vienna, Austria), **ESI-MS** (Dr. Zoltán Kele, Institute of Medicinal Chemistry, University of Szeged and the Mass Spectrometry Centre, University of Vienna, Austria), **antibacterial** and **anticancer activity** (Dr. Gabriella Spengler, Department of Medical Microbiology, Albert Szent-Györgyi Health Center and Albert Szent-Györgyi Medical School, University of Szeged), **anticancer activity** (Dr. Mónika Kiricsi, Department of Biochemistry and Molecular Biology, University of Szeged; Dr. Gergely Szakács (Medical University of Vienna)), **anticancer activity on 3D spheroids** (Dr. Debora Wernitznig, Institute of Inorganic Chemistry, University of Vienna, Vienna, Austria).

## III. New scientific results

**T1. It was shown that the attachment of a redox-active phenolic moiety at the terminal nitrogen atom of triapine derivatives (VA1-3) could significantly change the physico-chemical properties in solution and enhance anticancer activity of ligands and their Cu(II) complexes. However, further functionalization of compounds by connection to *N*-pyridyl scaffold morpholine moiety (VA4-7) has a minor effect on lipophilicity [4].**

T1.1 The obtained p$K_a$ values of pyridinium-$NH^+$ were much higher (*ca.* one and half units) for the set of VA1-3 compounds than for VA4-7. That can be explained by the electron withdrawing effect of the methyl-morpholine group [4].

T1.2 Introduction of a redox-active phenolic substituent at the terminal nitrogen atom increases lipophilicity ($\log D_{7.4} > +2$) and the attachment of the positively charged protonated morpholine moiety does not make compounds more hydrophilic at pH 7.4 [4].

T1.3 The stability of Cu(II) complexes with VA1-7 ligands in solution was higher than for the Cu(II)-triapine complex based on the obtained conditional stability constants [4].

**T2. We found that exchange of the α-*N*-pyridyl moiety to imidazole and benzimidazole units undoubtedly affects the lipophilicity and E/Z isomer distribution in aqueous solution and the complex formation with Cu(II) ions.**

T2.1 Based on $^1$H NMR spectra the Z isomer was found predominant in the aqueous solution of imidazole-TSC derivatives, whereas the E form is preferred in case of α-*N*-pyridyl-TSCs.

T2.2 Imidazole-TSCs are more hydrophilic than the corresponding α-*N*-pyridyl-TSCs.

T2.3 Interaction of imidazole-TSCs with Cu(II) ions showed the formation of mostly mono complexes in different protonation states ($[CuLH]^{2+}$, $[CuL]^+$ and $[CuLH_{-2}]^-$), where the ligand is tridentately coordinated. Although, tetrameric species $[Cu_4L_4H_{-4}]$ was found predominant in the pH range 5 – 9 (also including the physiological pH).

T2.4 *N*-terminal substitution did not significantly increase the stability of Cu(II) complexes.

**T3. Attachment of a positively-charged trimethylammonium group to the aromatic unit of STSC derivatives (VA8-11) could remarkably increase aqueous solubility, whereas *N*-terminal substitution, in the case of methyl and ethyl groups, has a slight contribution [6].**

T3.1 The trimethylammonium group significantly decreases the p$K_a$ value of phenolic OH group (by more than 1 order of magnitude) compared to STSC, due to the electron-withdrawing effect of the attached group [6].

T3.2 *N*-terminal substitution by phenyl group could enhance Cu(II) binding ability [6].

**T4. The conjugation by estrone/estradiol moiety of S(T)SC and *N*-terminal dimethylation increases the stability of Cu(II) complexes [1,3,5,7].**

T4.1 It was found that molecular hybridization of STSC with estrone/estradiol moiety increases p$K_a$ values, and the studied SCs have higher p$K_a$ values by *ca*. half logarithmic units in comparison to the corresponding TSCs [1,3,5,7].

T4.2 The determined stability constants indicate a significant difference in the Cu(II) binding ability between the tested SCs and TSCs, where the latter ones showed the formation of complexes with much higher stability in solution [1,3,5,7].

**T5. We demonstrated that chemical modification of 2-aminophenol to 2-aminoestradiol could make the compound less sensitive for oxidation and also enhance the cytotoxic effect [2].**

T5.1 The obtained p$K_a$ values in three different media ($H_2O$, 30 and in 60% (*v/v*) DMSO/$H_2O$) confirm that the DMSO content has an effect on proton dissociation constants: p$K_1$ becomes lower and p$K_2$ values are higher by the increasing DMSO content [2].

T5.2 Complexation with Cu(II) ions showed low complex stability for both 2-aminophenol and 2-aminoestradiol based on the determined stability constants [2].

**T6. Interaction with GSH plays a crucial role in the mechanism of action of the studied Cu(II)-TSCs, which was demonstrated by the redox reaction occurring between them [1,3,4,5,6,7].**

T6.1 Significant difference was noticed in the reaction rates for Cu-TSCs and Cu(II)-SCs with GSH. It can be explained by the formal redox potential of Cu(II)-TSC complexes, which is usually much higher than that of Cu(II)-SCs, accordingly the latter can be reduced faster by GSH [1,5].

T6.2 We observed that the higher the stability of complexes the slower the reduction by GSH. The *N*-terminal substitution by dimethyl groups results in an outstanding affinity towards Cu(II) ions [1,3,4,5,6,7].

T6.3 Cu(II) complexes with *N*-terminal substitution by dimethyl groups demonstrated the highest anticancer effect and the activity of their Cu(II) complexes even exceeded those of the ligands [1,3,6].

**T7. Antioxidant activity of some selected ligands and their Cu(II) complexes were determined by DPPH assays. Based the on obtained data, 2-aminophenol showed the highest potential to act as an antioxidant agent, since it was more active than the reference compound trolox, while 2-aminoestradiol and some tested (T)SCs showed a somewhat lower antioxidant activity compared to it. In the case of 2-**

**aminophenols, the presence of Cu(II) ions could increase the antioxidant activity, although for (T)SCs the opposite effect was observed [1,2].**

**T8. Based on our results the anticancer activity often can be tuned by complexation with Cu(II) ions. For triapine analogues anticancer effect was increased by the attachment of a redox-active phenolic moiety at the terminal nitrogen atom. In the case of STSC derivatives and 2-aminophenol cytotoxicity was improved by sterane-based conjugation. It should be underlined that *N*-terminal dimethylation of TSCs significantly enhances anticancer activity of their Cu(II) complexes [1-7].**

## IV. Possible applications of the results

In this dissertation a comprehensive study was performed on the solution behaviour of anticancer (thio)semicarbazones, 2-substituted sterane-based compounds and their Cu(II) complexes. Different modifications were presented here, *i.e*. substitution, conjugation and interaction with Cu(II) ions of the (T)SCs and 2-substituted sterane-based compounds. We investigated the effect of these modifications on the physico-chemical properties, such as p$K_a$ values, lipophilicity, stability of Cu(II) complexes in solution, crystal structure data, redox potential values, interaction with some biomolecules (GSH and AA) and cytotoxicity data. The correlation analysis of these thermodynamic, kinetic and biological data contributes to a better understanding of the mechanisms of action and the possible side effects, and helps in the optimization and development of promising drug molecules in the future.

## V. Scientific publications

MTMT ID: 10069622

Papers related to the dissertation:

[1] **Tatsiana V. Petrasheuskaya**, Ferenc Kovács, Nóra Igaz, Andrea Rónavári, Bálint Hajdu, Laura Bereczki, Nóra V. May, Gabriella Spengler, Béla Gyurcsik, Mónika Kiricsi, Éva Frank, Éva A. Enyedy*

*Estradiol-based salicylaldehyde (thio)semicarbazones and their copper complexes with anticancer, antibacterial and antioxidant activities*

MOLECULES 28 (2023) 54., IF: 4.6, Q1, DOI: 10.3390/molecules28010054

Independent citation: 1

[2] **Tatsiana V. Petrasheuskaya**, Ferenc Kovács, Gabriella Spengler, Nóra V. May, Éva Frank, Éva A. Enyedy*

*A comparative study on the complex formation of 2-aminoestradiol and 2-aminophenol with divalent metal ions: solution chemistry and anticancer activity*

JOURNAL OF MOLECULAR STRUCTURE 1261 (2022) 132858., IF: 3.8, Q2, DOI: 10.1016/j.molstruc.2022.132858

Independent citation: 1

[3] **Tatsiana V. Petrasheuskaya**, Debora Wernitznig, Márton A. Kiss, Nóra V. May, Dominik Wenisch, Bernhard K. Keppler, Éva Frank, Éva A. Enyedy*

*Estrone-salicylaldehyde N-methylated thiosemicarbazone hybrids and their copper complexes: solution structure, stability and anticancer activity in tumor spheroids*

JOURNAL OF BIOLOGICAL INORGANIC CHEMISTRY 26 (2021) 775-791., IF: 3.862, Q1, DOI: 10.1007/s00775-021-01891-7

Independent citations: 2

[4] Juliana Besleaga, Iryna Stepanenko, **Tatsiana V. Petrasheuskaya**, Denisa Darvasiova, Martin Breza, Marta Hammerstad, Małgorzata A. Marć, Alexander Prado-Roller, Gabriella Spengler, Ana Popović-Bijelić, Eva A. Enyedy,* Peter Rapta,* Anatoly Shutalev,* Vladimir B. Arion*

*Triapine analogues and their copper(II) complexes: synthesis, characterization, solution speciation, redox activity, cytotoxicity and mR2 RNR inhibition*

INORGANIC CHEMISTRY 60 (2021) 11297-11319., IF: 5.436, Q1. DOI: 10.1021/acs.inorgchem.1c01275

Independent citations: 6

[5] Éva A. Enyedy,* **Tatsiana V. Petrasheuskaya**, Márton A. Kiss, Debora Wernitznig, Dominik Wenisch, Bernhard K. Keppler, Gabriella Spengler, Nóra V. May, Éva Frank, Orsolya Dömötör

*Complex formation of an estrone-salicylaldehyde semicarbazone hybrid with copper(II) and gallium(III): solution equilibria and biological activity*

JOURNAL OF INORGANIC BIOCHEMISTRY 220 (2021) 111468., IF: 4.336, Q2, DOI: 10.1016/j.jinorgbio.2021.111468
Independent citations: 5

[6] Miljan N.M. Milunović,* Oleg Palamarciuc, Angela Sirbu, Sergiu Shova, Dan Dumitrescu, Dana Dvoranová, Peter Rapta, **Tatsiana V. Petrasheuskaya**, Éva A. Enyedy, Gabriella Spengler, Marija Ilic, Harald H. Sitte, Gert Lubec, Vladimir B. Arion*
*Insight into the anticancer activity of copper(II) 5-methylenetrimethylammonium-thiosemicarbazonates and their interaction with organic cation transporters*
BIOMOLECULES 10 (2020) 1213., IF: 4.879, Q2, DOI: 10.3390/biom10091213
Independent citations: 7

[7] **Tatsiana V. Petrasheuskaya**, Márton A. Kiss, Orsolya Dömötör, Tamás Holczbauer, Nóra V. May, Gabriella Spengler, Annamária Kincses, Ana Čipak Gašparović, Éva Frank, Éva A. Enyedy*
*Salicylaldehyde thiosemicarbazone copper complexes: impact of hybridization with estrone on cytotoxicity, solution stability and redox activity*
NEW JOURNAL OF CHEMISTRY 44 (2020) 12154-12168., IF: 3.591, Q1, DOI: 10.1039/D0NJ01070G
Independent citations: 8

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Oral presentations and posters related to the dissertation:

1. **Tatsiana V. Petrasheuskaya**, Márton A. Kiss, Ferenc Kovács, Nóra V. May, Gabriella Spengler, Debora Wernitzing, Nóra Igaz, Mónika Kiricsi, Éva Frank, Éva A. Enyedy (oral lecture)
*Comparative studies of sterane-based thiosemicarbazones and their Cu(II) complexes: synthesis, solution stability, redox properties and biological activity*
MTA Steroid and Terpenoid Chemistry working group meeting, 28.11.2022, Szeged, Hungary

2. **Tatsiana V. Petrasheuskaya**, Gerda T. Gátszegi, Gabriella Spelgler, Peter Rapta, Miljan N. M. Milunovic, Vladimir B. Arion, Éva A. Enyedy (poster)
*Anticancer methylenetrimethylammonium-thiosemicarbazonates and their copper(II) complexes: solution chemistry, redox properties and cytotoxicity*
3rd European NECTAR Conference, 24-26.08.2022, Ljubljana, Slovenia

3. **Tatsiana V. Petrasheuskaya**, Márton A. Kiss, Nóra V. May, Gabriella Spengler, Peter Rapta, Éva Frank, Éva A. Enyedy (poster)

*Comparative solution study on the interactions of Cu(II), Fe(II/III) and Ni(II) with imidazole-derived thiosemicarbazones: impact of methylation, redox and anticancer activity*
16th European Biological Inorganic Chemistry Conference (EuroBIC-16), 17-21.07.2022, Grenoble, France

4. **Tatsiana V. Petrasheuskaya**, Ferenc Kovács, Nóra V. May, Andrea Rónavári, Mónika Kiricsi, Gabriella Spengler, Éva Frank, Éva A. Enyedy (poster)
*Estradiol-based salicylaldehyde (thio)semicarbazones and their copper complexes with anticancer, antibacterial and antioxidant activities*
International Symposium on Metal Complexes (ISMEC 2022), 5-8.06.2022, Valencia, Spain

5. **Tatsiana V. Petrasheuskaya**, Márton A. Kiss, Debora Wernitzing, Dominik Wenisch, Bernard K. Keppler, Nóra V. May, Éva Frank, Éva A. Enyedy (poster)
*Estrone-salicylaldehyde N-methylated-thiosemicarbazone hybrids and their copper complexes: solution study and anticancer activity in tumor spheroids*
International Symposium Thermodynamics of Metal Complexes (ISMEC 2021), 16-18.06.2021, online, Białystok, Poland

6. **Tatsiana V. Petrasheuskaya**, Márton A. Kiss, Orsolya Dömötör, Gabriella Spengler, Debora Wernitzing, Bernard K. Keppler, Nóra V. May, Éva Frank, Éva A. Enyedy (lecture, Hungarian)
*Antitumor thiosemicarbazone-estrone hybrids and their copper complexes*
54th Colloquium on Complex Chemistry and Meeting of the Coordination Chemistry Working Group of the Hungarian Academy of Sciences, 26-27.05. 2021, online, Hungary

7. **Tatsiana V. Petrasheuskaya**, Debora Wernitznig, Márton A. Kiss, Nóra V. May, Dominik Wenisch, Bernhard K. Keppler, Éva Frank, Éva A. Enyedy (poster)
*Effects of stepwise terminal $NH_2$-methylation of estrone-salicylaldehyde–thiosemicarbazone and copper coordination, solution speciation, anticancer activity and redox activity*
26th International Symposium on Analytical and Environmental Problems, 23-24.11.2020, online, Szeged, Hungary

8. **Tatsiana V. Petrasheuskaya**, Márton A. Kiss, Orsolya Dömötör, Debora Wernitznig, Dominik Wenisch, Gabriella Spengler, Annamária Kincses, Nóra V. May, Bernhard K. Keppler, Éva Frank, Éva A. Enyedy (oral lecture)
*Comparative solution study on estrone salicyladehyde (thio)semicarbazones and their copper complexes: impact of hybridization and methylation*
XLIII. Chemistry Days, 27-28.10.2020, Szeged, Hungary

9. **Tatsiana V. Petrasheuskaya**, Márton A. Kiss, Orsolya Dömötör, Gabriella Spengler, Annamária Kincses, Nóra V. May, Éva Frank, Éva A. Enyedy (oral lecture)
*Synthesis, solution stability and anticancer activity of copper complexes formed with salicylaldehyde thiosemicarbazone-estrone conjugates*
MTA Steroid and Terpenoid Chemistry working group meeting, 22.11.2019, Szeged, Hungary

10. **Tatsiana V. Petrasheuskaya**, Orsolya Dömötör, Gabriella Spengler, Annamária Kincses, Nóra V. May, Márton A. Kiss, Éva Frank, Éva A. Enyedy (oral lecture)
*Antitumor copper complexes of salicylaldehydethiosemicarbazones: Solution chemistry and biological acitivity*
XLII. Chemistry Days, 28-30.10.2019, Szeged, Hungary

11. **Tatsiana V. Petrasheuskaya**, Orsolya Dömötör, Gabriella Spengler, Annamária Kincses, Márton A. Kiss, Éva Frank, Éva A. Enyedy (poster)
*Copper(II) complexes of salicylaldehyde thiosemicarbazone and its structurally-related analogs: solution stability, redox properties and cytotoxicity*
International Symposium on Metal Complexes (ISMEC 2019), 11-14.06.2019, Hajdúszoboszló/Debrecen, Hungary

12. Dömötör Orsolya, **Tatsiana V. Petrasheuskaya**, Gál G. Tamás, May Nóra V., Nové Márta, Kincses Annamária, Spengler Gabriella, Ana Čipak Gašparović, Kiss Márton A., Frank Éva, Enyedy Éva A. (lecture, Hungarian)
*Cu(II) and Ru(II)(p-cymene) complexes of pyrazolo- and salicyladehyde thiosemicarbazones: synthesis, antitumor activity, stability and structure*
53rd Colloquium on Complex Chemistry, 21-23.05.2019, Velence, Hungary