THESES OF DOCTORAL (PH.D.) DISSERTATION

Correlations between anticancer and solution chemistry properties of polydentate ligands

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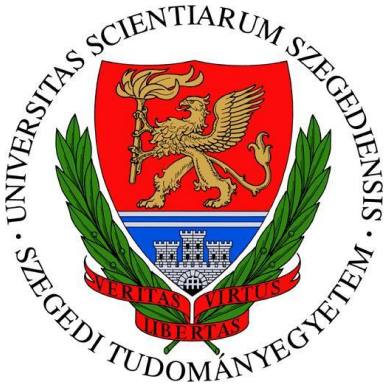

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Faculty of Science and Informatics

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1. INTRODUCTION AND OBJECTIVES

Many people suffer from cancer worldwide. Cancer can appear anywhere in the body, metastasizing, making further treatment difficult. Science is trying to keep up with cancer, but the drugs used have serious side effects, and resistance that could develop during their administration also makes treatment difficult. To solve these problems, new drugs are constantly being developed with the aim to increase selectivity and reduce side effects. The rational way of drug development requires understanding the mechanism of action at the molecular level and to characterize the factors influencing the pharmacokinetic behavior. Metal-containing compounds can undergo significant chemical changes before reaching the site of action. At the same time, many anticancer compounds exert their effect through complexation with metal ions. Therefore, it is necessary to map the behavior of metal complexes in solution, i.e. their stability in aqueous solution, their actual structure and redox properties.

I dedicated my doctoral work to three different families of compounds, the common feature of which is that their anticancer effects are related to their interaction with metal ions. The first group of compounds I investigated are (thio)semicarbazones ((T)SCs). Their best-known analog is triapine, which has already entered clinical phase III trials. It is known from the literature that (T)SCs are able to form complexes with endogenous copper, iron, and zinc ions. In addition, DpC and COTI-2 are other (T)SCs that have already entered clinical trials. Their biological activity can be related to the complexation with copper ions and the redox properties of the formed complexes.

The second group is the 8-hydroxyquinolines. These compounds are also excellent complexing agents for transition metal ions along with significant biological activity that is associated with complex formation (similar to TSCs). While complexes formed with copper(II) ions have a stronger cytotoxic effect in the case of the first two groups, complex formation with iron ions plays a dominant role in the case of the third group. The anticancer VLX600, which has also been in clinical trials, is a triazino indolylhydrazone-type compound, and its derivatives are considered to be iron chelators in the literature. While there is a lot of data available in the literature on the biological activity of the compounds listed above, much less information has been reported on their solution equilibrium properties.

The primary goal of my doctoral thesis is the detailed solution equilibrium characterization of three different families of compounds shown in Figure 1. I have studied the proton dissociation processes of the ligands and their complexation with four endogenous

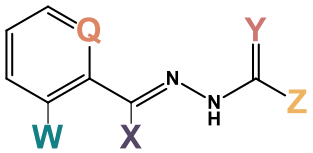
metal ions (copper(II), iron(II), iron(III) and zinc(II) ions) using a combination of different methods. Within each family of compounds, I have investigated how different structural elements (e.g. different coordination modes, methyl groups or other substituents on the ligand scaffold) affect complexation and anticancer activity.

Complex formation significantly affects the solution equilibrium properties. Moreover, it is also important to reveal in what form the ligands and the resulting metal complexes are present in the body. To better understand the structure and coordination mode of the ligands and the complexes formed, it is necessary to prepare single crystals and conduct X-ray crystallographic mesurements on the ligands (and their metal complexes). In the case of complexes formed with different metal ions, the type, number of coordinating donor atoms, and the resulting geometry have to be determined. For all these purposes, we have planned NMR, EPR, and CD spectroscopic titrations. In addition, for a ligand entering the body, it is particularly important to know its solubility, lipophilicity, and how it can penetrate various biological membranes. These properties can notably influence the in vivo applicability of the active ingredient, as well as its subsequent absorption and distribution. Therefore, I have investigated the properties mentioned above in the case of ligands and their complexes with various metal ions.

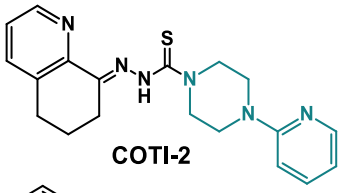
An additional aim was to synthesize the iron chelator VLX600 and its four derivatives substituted differently with the help of our collaborating partners. Similar to the above-listed compound families, a detailed solution chemistry characterization was planned. Besides mapping the anticancer effect, additional biological studies were envisioned such as the production of reactive oxygen species or the induction of apoptosis. I was curious about how structural changes affect biological activity in addition to the solution chemistry properties.

In biofluids, the oxidation state of the metal ion in the complexes formed may also change, or the complexes may interact with different bioligands through ligand exchange or the formation of mixed ligand complexes. The investigation of the redox properties of the complexes formed with redox active endogenous metal ions (copper(II) and iron(III) ions) and the determination of their formal potential values may provide a more precise picture of the mechanism of action. Cyclic voltammetry measurements of the complexes were performed using direct reduction studies with various natural reducing agents, namely: glutathione and ascorbic acid. Interaction of the complexes with different biomolecules (e.g. DNA) may contain valuable information from regarding the mechanism of action and pharmacokinetic behavior. Therefore, this was also investigated in the case of selected compounds.

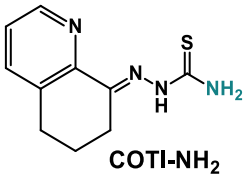
Thiosemicarbazones and semicarbazones



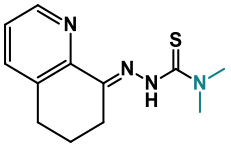
	Q	W	X	Y	Z
3AP	N	NH_2	H	S	NH_2
S-Me-3AP	N	NH_2	H	S-Me	NH_2
O-3AP	N	NH_2	H	O	NH_2
STSC	C-OH	H	H	S	NH_2
SSC	C-OH	H	H	O	NH_2
FTSC	N	H	H	S	NH_2
PTSC	N	H	H	S	N-Me_2
Dp44mT	N	H	pyridil	S	N-Me_2
DpC	N	H	pyridil	S	N-Me-chexyl
H_2NNHMe	N	NH_2	H	S	NH-Me
H_2NNHMe_2	N	NH_2	H	S	N-Me_2
$MeHNNMe_2$	N	NH-Me	H	S	N-Me_2
Me_2NNH_2	N	N-Me_2	H	S	NH_2
Me_2NNHMe	N	N-Me_2	H	S	NH-Me
Me_2NNMe_2	N	N-Me_2	H	S	N-Me_2



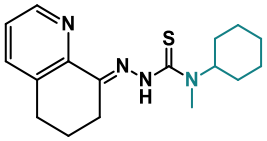
COTI-2



COTI-NH_2

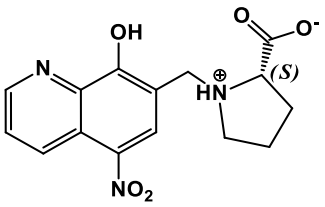


COTI-NMe_2

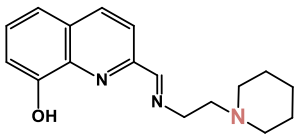


COTI-NMeCy

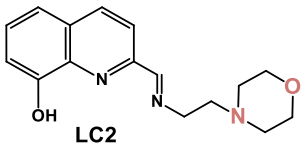
8-hydroxyquinolines



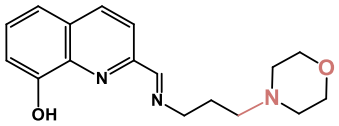
$HQNO_2$-L-Pro



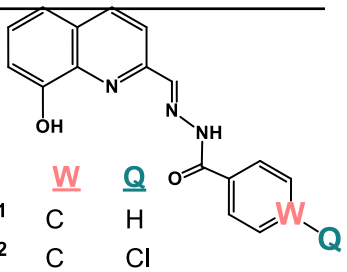
LC1



LC2

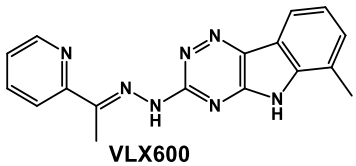


LC3

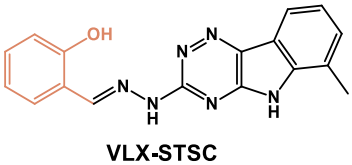


	W	Q
L^1	C	H
L^2	C	Cl
L^3	C	F
L^4	C	Me
L^5	C	O-Me
L^6	C	OH
L^7	C	NH_2
L^8	N	-

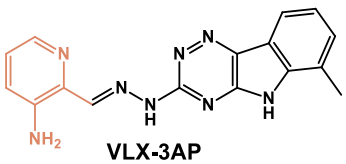
VLX600 derivatives



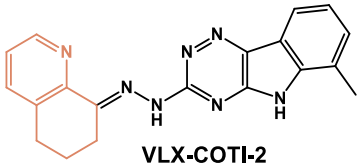
VLX600



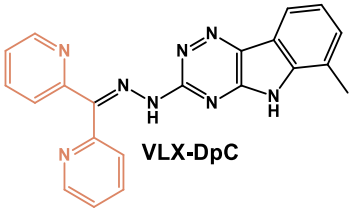
VLX-STSC



VLX-3AP



VLX-COTI-2



VLX-DpC

Figure 1: Structure of the studied ligands.

2. EXPERIMENTAL METHODS

$HQNO_2$-L-Pro, 3AP, O-3AP, SSC, STSC, Dp44mT, and DpC were obtained from Sigma-Aldrich. The following ligands were synthesized by collaborators: COTI-2 derivatives, FTSC, PTSC, H_2NNHMe, H_2NNMe_2, $MeHNNMe_2$, Me_2NNH_2, Me_2NNHMe, Me_2NNMe_2 (Bernhard K. Keppler, Christian R. Kowol, University of Vienna), Schiff base 8-hydroxyquinolines (Isabel Correia, University of Lisbon), 5-nitro-8-hydroxyquinoline (István Szatmári, SZTE, Institute of Pharmaceutical Chemistry). I synthesized the VLX600 analogues in the research group of Christian R. Kowol.

UV-visible spectrophotometry was used to perform several measurements:

• To determine the proton dissociation constants of ligands and to study their interactions with endogenous metal ions;

• To follow ligand displacement reactions with EDTA;

• To study the kinetics of the reduction of copper(II) and iron(III) complexes with ascorbic acid and glutathione under oxygen-free conditions;

• To measure lipophilicity and solubility;

• To study the membrane permeability of ligands and complexes using a pre-coated Corning Gentest plate system;

• During ultrafiltration, where we used a Millipore Amicon Ultra-0.5 membrane filter, and examined the binding of copper(II) complexes to ct-DNA using ethidium bromide displacement measurements

For spectrophotometric measurements, I used Agilent Cary 8454 and Hewlett-Packard 8452A diode array spectrophotometers, Metrohm Dosimat 665 automatic burette, Orion 710A pH meter, and Metrohm 6.0234.100 combined glass electrode. During the investigation of iron(II) complexes, the measurements were performed in a Jacomex laboratory glove box (O_2 ≤ 1ppm). The PSEQUAD program was used to determine the equilibrium constants.

Spectrofluorimetric measurements were carried out to investigate the binding to DNA, where ethidium bromide displacement measurements were also performed using a Fluoromax (Horiba Jobin Yvon) type fluorimeter. During the investigation of the copper(II) complexes, information about the type, number and geometry of the coordinating donor atoms was obtained using **CD spectroscopy** using a JASCO-J-1500 spectrometer.

EPR spectroscopy was used to study copper(II) complexes, during which the spectra were recorded at different pH values and metal ion/ligand ratios with a CW-EPR BRUKER EleXsys E500 spectrometer (9.45 GHz, 13 mW, 5 G, 100 kHz), at room temperature or 77 K, with the assistance of Nóra V. May (HUN-REN TTK, Budapest).

During **^{1}H NMR spectroscopic** titrations, I also determined the proton dissociation constants of the ligands and in some cases their purity of them was also checked by quantitative NMR, using a Bruker Ultrashield 500 Plus (500 MHz) instrument. The PSEQUAD program to calculate the equilibrium constants.

Cyclic voltammetric measurements were performed using a computer-controlled Autolab-PGSTAT 204 electrochemical instrument. Platinum working and auxiliary electrodes and Ag/AgCl/KCl (3 M) reference electrodes were used. In addition to determining redox potentials for copper and iron complex, ***in situ*** **UV-visible spectroelectrochemical** data were gathered using an Avantes spectrometer equipped with an AvaLight-DHc spectroelectrochemical cell kit (AKSTCKIT3) equipped with an AvaSpec-UL2048XL-EVO light source and a Pt-microstructured "honeycomb" working electrode (Pine Research). The spectra were processed further using the AvaSoft 8.1.1 software package.

Cytotoxicity studies were performed using the **MTT method** with the help of Dr. Gabriella Spengler and her colleagues, while in the case of VLX600 and its derivatives, I performed measurements in the laboratory of Dr. Michael Jakupec at the University of Vienna. There I also examined the **induction of** programmed cell death, also known as **apoptosis**, and the **production of reactive oxygen species**.

Additional measurements were carried out by our collaborators: precise structure determination was performed using **X-ray crystallography** from single crystals of the VLX600, LC1-3, and COTI-2 ligands, as well as their complexes with various metal ions (University of Vienna, University of Lisbon). **Elemental analysis** and **mass spectrometry** measurements were conducted at the University of Vienna for VLX600 and its derivatives.

3. NEW SCIENTIFIC RESULTS

T1: As a result of the investigation of various (thio)semicarbazones, I found that Dp44mT showed the strongest, while the O-3AP derivative the weakest copper(II)-binding affinity. Cu(II) binding affinity showed the following trend for the different coordination modes: (N,N,S^-) > (N,N,O^-) > (O^-,N,S^-) > (O^-,N,O^-).

T1.1: Replacing sulfur with oxygen significantly increased the solubility, while replacing the pyridine nitrogen with phenolic-OH slightly decreased it. Under physiological conditions, the solubility trend is as follows: O-3AP > 3AP > SSC > STSC > Dp44mT.

T1.2: The binding strength of copper(II) complexes to DNA showed the following order: O-3AP > 3AP, Dp44mT > SSC > STSC, where the change observed in the case of O-3AP was related to free copper(II) ions released from the complex due to its low stability, while STSC was unable to displace the intercalator ethidium bromide.

T2: Monomethylation of triapine derivatives has only a marginal effect on the determined proton dissociation constants and the stability of the resulting copper(II) complexes. On the other hand, dimethylation at different positions (terminal and amino group of the pyridine ring) increased the stability to a greater extent. I observed that the weaker the copper binding ability of the ligand, the faster the reduction of complexes with glutathione and the lower the cytotoxicity.

T2.1: Methylation of the thioamide sulfur of triapine reduced the stability of the compound. The stock solution of S-Me-3AP prepared in DMSO is not stable, which is related to the elimination of CH_3SH. Moreover, I observed that this process is significantly slower in aqueous solution at physiological pH but becomes faster with increasing pH.

T3: Ascorbic acid and glutathione were able to reduce the iron(III) complexes of COTI-2 and its derivatives. In contrast, first the formation of a mixed-ligand complex with the reducing agent was observed in the case of copper(II) complexes, followed by the slow redox reaction in the case of the N-terminally unsubstituted derivatives (COTI-NH_2). On the other hand, no further changes were observed after the formation of the mixed complex with GSH with the disubstituted ligands. The ABCC1 efflux pump overexpressed in COTI-2-resistant cells is substrate specific for GSH thus, it is able to recognize the formed Cu(II)-ligand-GSH mixed complex and pump it out of the cell in the case of COTI-2 (as well as the other two N-terminally disubstituted derivatives),

which results in drug resistance. In contrast to the COTI-NH_2 ligand, where the ligand is released from the complex during copper(II) complex reduction, which in this form is not recognized by the efflux pump.

T3.1: All ligands form mono- and bis-ligand complexes with iron(II/III) ions and zinc(II), while only mono complexes were identified with Cu(II)ions. The stability of these complexes resulted in the following trend: Fe(II) > Cu(II) > Zn(II) > Fe(III).

T3.2: When examining COTI-2 and its derivatives, the thermodynamic solubility changes in the following order: COTI-2 < COTI-NMeCy << COTI-NMe_2 < COTI-NH_2.

T4: For ligands L^1-L^8, I found that substituents at the distal positions have only a minimal effect on the pK_a values of the aromatic -OH and NH^+ groups. In contrast, the electron-withdrawing chlorine and fluorine substituents decrease the pK_a of the nearby benzohydrazide-NH group, while the electron-donating methyl and methoxy groups increase it. Based on the calculated pCu values, L^1 and L^5 are able to form complexes with Cu(II) ions with similar strength, while L^6 forms complexes with slightly lower stability, suggesting that the benzohydrazide N^2_{im} is not involved in the coordination.

T4.1: Ascorbic acid and glutathione can reduce the copper complexes with L^1, L^5 and L^6 ligands as evidenced by the direct redox reaction experiments. The free ligand was released during the reduction process due to the dissociation of the formed Cu(I)-complex. Thus, a stable Cu(I)-complex was formed with the reducing agent. The redox reaction was faster with glutathione, and the reaction rates showed the following trend: $L^1 \sim L^6 > L^5$.

T5: For the LC1-3 ligands, two pK_a values of the N_qH^+ and -OH groups were found to be lower than those of the reference compound, 8-hydroxyquinoline. These ligands form mono and bis complexes with copper(II) and zinc(II) ions, and it was also found that the copper(II) complexes are significantly more stable than the zinc(II) complexes.

T6: The determined stability products are the largest for Cu(II) and Fe(III) complexes in the case of the HQNO_2-L-Pro ligand, while they are smaller for Fe(II) and Zn(II) complexes. Under physiological conditions, the affinity towards different metal ions is: Cu(II) > Zn(II) > Fe(II) > Fe(III). The proline donor groups are also involved in the coordination in the case of Cu(II) and Zn(II) ions.

T6.1: We observed that reversible redox processes take place in the case of the iron complexes while mapping the redox properties of the complexes. In contrast, the redox process was irreversible in the case of the copper complexes. High formal potential value was determined for the iron complex, indicating a higher affinity towards Fe(II) ion.

T7: I synthesized the iron chelator VLX600 and its four new derivatives inspired by the chemical structure of tridentate thiosemicarbazones. VLX600 is able to reduce the Fe(III) ions in aqueous solution, the forming Fe(II) complex could be crystallized and its structure was determined by SC-XRD. The formation of mono- and bis complexes with Fe(II) and Zn(II) ions was observed, while only mono-ligand complexes were formed with Cu(II) ions.

T7.1: Based on cyclic voltammetry measurements, a high positive formal potential value was determined in the case of the iron complexes of VLX600, which suggests the stronger affinity of the ligand towards Fe(II) ions. On the other hand, relatively smaller values were obtained for the copper complex. This indicates a greater affinity of VLX600 to Cu(II) ions than to Cu(I) ions.

T7.2: I have studied the *in vitro* cytotoxic activity of VLX600 and its derivatives on three different types of human cancer cell lines (A549, CH1/PA-1, SW480). In the case of VLX600, the effect of various endogenous metal ions (Cu(II), Zn(II), and Fe(III)) was also investigated. Both the free ligands and complexes showed strong cytotoxic effect, however, we did not observe any significant differences between the ligands.

T7.3: By flow cytometry, we observed concentration-dependent apoptosis induction for VLX600, but the percentage of apoptotic events was reduced in the presence of Cu(II), Zn(II), and Fe(III) ions.

4. SCIENTIFIC PUBLICATIONS

The Hungarian Scientific Bibliography (MTMT) identifier: 10069341

Full papers related to the dissertation:

1. Sonja Hager, Veronika F.S. Pape, **Vivien Pósa**, Bianca Montsch, Lukas Uhlik, Gergely Szakács, Szilárd Tóth, Nikolett Jabronka, Bernhard K. Keppler, Christian R. Kowol, Éva A. Enyedy,* Petra Heffeter*
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ANTIOXIDANTS & REDOX SIGNALING 33 (2020) 395–414.
D1, IF: 8.401, independent citations: 13

2. Kateryna Ohui, Iryna Stepanenko,* Iuliana Besleaga, Maria V. Babak, Radu Stafi, Denisa Darvasiova, Gerald Giester, **Vivien Pósa**, Éva A. Enyedy, Daniel Vegh, Peter Rapta, Wee Han Ang, Ana Popović-Bijelić, Vladimir B. Arion*
Triapine derivatives act as copper delivery vehicles to induce deadly metal overload in cancer cells
BIOMOLECULES 10 (2020) 1336.
Q2, IF: 4.879, independent citations: 6

3. Julia H. Bormio Nunes, Sonja Hager, Marlene Mathuber, **Vivien Pósa**, Alexander Roller, Éva A. Enyedy, Alessia Stefanelli, Walter Berger, Bernhard K. Keppler, Petra Heffeter*, Christian R. Kowol*
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4. **Vivien Pósa**, Bálint Hajdu, Gábor Tóth, Orsolya Dömötör, Christian R. Kowol, Bernhard K. Keppler, Gabriella Spengler, Béla Gyurcsik, Éva A. Enyedy*
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7. Tamás Pivarcsik, **Vivien Pósa**, Hilda Kovács, Nóra V. May, Gabriella Spengler, Szonja P. Pósa, Szilárd Tóth, Zeinab Nezafat Yazdi, Csilla Özvegy-Laczka, Imre Ugrai, István Szatmári, Gergely Szakács, Éva A. Enyedy*
Metal complexes of a 5-nitro-8-hydroxyquinoline-proline hybrid with enhanced water solubility targeting multidrug resistant cancer cells
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8. Nádia Ribeiro, Ipek Bulut, Baris Sergi, **Vivien Pósa**, Gabriella Spengler, Giuseppe Sciortino, Vânia André, Liliana P. Ferreira, Tarita Biver, Valeria Ugone, Eugenio Garribba, João Costa Pessoa, Éva A. Enyedy,* Ceyda Acilan Ayhan,* Isabel Correia*
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Cu(II) and Zn(II) complexes of new 8-hydroxyquinoline Schiff bases: Investigating their structure, solution speciation and anticancer potential
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10. **Vivien Pósa**, Anja Federa, Klaudia Cseh, Dominik Wenisch, Gabriella Spengler, Nóra V. May, Norbert Lihi, Gergely F. Samu, Michael A. Jakupec, Bernhard K. Keppler, Christian R. Kowol,* Éva A. Enyedy*
A comparative study on complexation of the anticancer iron chelator VLX600 with essential metal ions
INORGANIC CHEMISTRY 63 (2024) 2401-2417.
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ΣIF=51.026

Full papers not related to the dissertation:

1. Teresa Żołek, Éva A. Enyedy, Kinga Ostrowska, **Vivien Pósa**, Dorota Maciejewska*
Drug likeness predictions of 5-hydroxy-substituted coumarins with high affinity to 5-HT1A and 5-HT2A receptors
EUROPEAN JOURNAL OF PHARMACEUTICAL SCIENCES 115 (2018) 25–36.
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Oral presentations and posters related to the dissertation:

1. **Vivien Pósa**, Sonja Hager, Veronika F. S. Pape, Gergely Szakács, Bernhard K. Keppler, Christian R. Kowol, Petra Heffter, Éva A. Enyedy (poster)
Redox properties and solution stability of copper complexes formed with various methylated Triapine derivatives
International Symposium on Metal Complexes, 11–14.06.2019, Hajdúszoboszló/Debrecen, Hungary

2. Éva A. Enyedy, **Vivien Pósa**, Orsolya Dömötör, Nóra V. May, Sonja Hager, Petra Heffeter, Veronika F.S. Pape, Gergely Szakács, Bernhard K. Keppler, Christian R. Kowol (oral presentation)
Impact of structural modifications of the α-N-pyridyl thiosemicarbazone scaffold on solution properties, copper binding and cytotoxicity
International Symposium on Metal Complexes, 11–14.06.2019, Hajdúszoboszló/Debrecen, Hungary

3. **Vivien Pósa**, Julia H. Bormio Nunes, Bernhard K. Keppler, Christian R. Kowol, Éva A. Enyedy (hungarian oral presentation)
A solution chemistry study on COTI-2 and its derivatives: complex formation with iron(III) and Cu(II) ions
XLIII. Chemistry Days, 27–28.10.2020. (online), Szeged, Hungary

4. Sonja Hager, Julia H. Bormio Nunes, Marlene Mathuber, **Vivien Pósa**, Alexander Roller, Éva A. Enyedy, Alessia Stefanelli, Walter Berger, Bernhard K. Keppler, Christian R. Kowol, Petra Heffeter (poster)
Elucidating mechanisms of resistance against the anticancer thiosemicarbazone COTI-2 by structural modifications and metal complex formation
COST Action 17104 (STRATAGEM) WG3, Meeting - International Online Symposium on "New Therapeutic Tools Against Preclinical Models of Multidrug Resistant Tumors", 04.11.2020. (online)

5. **Vivien Pósa**, Nóra V. May, Julia H. Bormio Nunes, Bernhard K. Keppler, Christian R. Kowol, Éva A. Enyedy (poster)
A comparative solution equilibrium study on the interactions of Cu(II), Fe(II/III) and Zn(II) with COTI-2 and its derivatives
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6. **Vivien Pósa,** Bálint Hajdu, Gábor Tóth, Orsolya Dömötör, Christian R. Kowol, Bernhard K. Keppler, Gabriella Spengler, Béla Gyurcsik, Éva A. Enyedy (poster)
Effects of variations in coordination modes of copper(II) complexes of (thio)semicarbazones on solution chemical and biological properties
4th Annual Conference, New diagnostic and therapeutic tools against multidrug resistant tumours, 06–08.09.2021., Prague, Czech Republic

7. Alessia Stefanelli, **Vivien Pósa**, Julia H. Bormio Nunes, Sonja Hager, Marlene Mathuber, Alexander Roller, Nóra V. May, Walter Berger, Bernhard K. Keppler, Chrsitian R. Kowol, Éva A. Enyedy, Petra Heffeter (poster)
Thiosemicarbazone derivatives developed to overcome COTI-2 resistance
4th Annual Conference, New diagnostic and therapeutic tools against multidrug resistant tumours, 06–08.09.2021., Prague, Czech Republic

8. Julia H. Bormio Nunes, Sonja Hager, Marlene Mathuber, **Vivien Pósa**, Alexander Roller, Éva A. Enyedy, Alessia Stefanelli, Walter Berger, Bernhard K. Keppler, Christian R. Kowol, Petra Heffeter (poster)
Resistance against the thiosemicarbazone COTI-2 is based on formation of intracellular copper complex glutathione adducts and ABCC1-mediated efflux
4th Annual Conference, New diagnostic and therapeutic tools against multidrug resistant tumours, 06–08.09.2021., Prague, Czech Republic

9. **Vivien Pósa**, Julia. H. Bormio Nunes, Bernhard K. Keppler, Christian R. Kowol, Nóra V. May, Petra Heffeter Éva A. Enyedy (hungarian oral presentation)
Solution studies on the interaction of the COTI-2 thiosemicarbazone with endogenous metal ions
Meeting of the Coordination Chemistry Working Group of the Hungarian Academy of Sciences, 03.12.2021. (online), Szeged, Hungary

10. **Vivien Pósa,** László Gy. Tusa, Gabriella Spengler, Nóra V. Ma., Christian R. Kowol, Éva A. Enyedy (hungarian oral presentation)
Solution studies on the interaction of the anticancer VLX600 iron chelator with endogenous metal ions
55th Colloquium on Complex Chemistry and Meeting of the Coordination Chemistry Working Group of the Hungarian Academy of Sciencess, 25–27.05.2022., Debrecen, Hungary

11. **Vivien Pósa**, Nóra V. May, Gabriella Spengler, Szonja Pósa, Szilárd Tóth, Gergely Szakács, Imre Ugrai, István Szatmári, Petra Nagy, Éva A. Enyedy (poster)
Investigation of the interaction of a water-soluble 8-hydroxyquinoline amino acid hybrid with essential metal ions
International Symposium on Metal Complexes, 06–08.05.2022., Valencia, Spain

12. **Vivien Pósa**, Alessia Stefanelli, Julia H. Bormio Nunes, Sonja Hager, Marlene Mathuber, Nóra V. May, Walter Berger, Bernhard K. Keppler, Christian R. Kowol, Petra Heffeter, Éva A. Enyedy (poster)
Solution chemistry studies of the interaction of COTI-2 and its derivatives with endogenous metal ions
16th European Biological Inorganic Chemistry Conference, 17–21.07.2022.07., Grenoble, France

13. Nádia Ribeiro, Ipek Bulut, **Vivien Pósa**, Baris Sergi, Éva A. Enyedy, Ceyda Acilan, Tarita Biver, João Costa Pessoa, Isabel Correia (poster)
Characterization and interaction with biomolecules of Cu^{II} and $V^{IV}O$ complexes of new 8-hydroxyquinoline Schiff bases
16th European Biological Inorganic Chemistry Conference, 17–21.07.2022.07., Grenoble, France

14. Éva A. Enyedy, **Vivien Pósa**, Inna Safyanova, János P. Mészáros, Tamás Pivarcsik, Nóra V. May, Gabriella Spengler, Szonja Pósa, Szilárd Tóth, Gergely Szakács, Oszkár Csuvik, István Szatmári (oral presentation)
Water-soluble 8-hydroxyquinoline-amino acid hybrids and their interaction with various metal ions: relationship between solution chemistry and cytotoxicity
16th European Biological Inorganic Chemistry Conference, 17–21.07.2022.07., Grenoble, France

15. **Vivien Pósa**, Leonor Corte-Real, Isabel Romero, Mariana Figueira, Catarina Pinto Reis, Maria M. Gaspar, João Costa Pessoa, Isabel Correia, É.A. Enyedy (poster)
Solution studies on the interaction of three new Schiff base 8-hydroxyquinolines with essential metal ions
3rd European NECTAR Conference, 24–26.08.2022., Ljubljana, Szlovenia

16. Nádia Ribeiro, Ipek Bulut, **Vivien Pósa**, Baris Sergi, Giuseppe Sciortino, João Costa Pessoa, Tarita Biver, Valeria Ugone, Eugenio Garribba. Éva A. Enyedy, Ceyda Acilan, Isabel Correia (poster)
New 8-hydroxyquinoline benzohydrazones: solution behaviour, metal complexation (Cu^{II} and $V^{IV}O$) and anticancer properties
3rd European NECTAR Conference, 24–26.08.2022., Ljubljana, Szlovenia

17. Alessia Stefanelli, **Vivien Pósa**, Julia H. Bormio Nunes, Sonja Hager, Nóra V. May, Walter Berger, Bernhard K. Keppler, Christian R. Kowol, Éva A. Enyedy, Petra Heffeter (poster)
COTI-2 derivatives developed to overcome ABCC1 resistance
9th FEBS Special Meeting on ABC Proteins-ABC2023, 26.02–03.03.2023., Innsbruck, Austria

18. **Vivien Pósa**, Alessia Federa, Klaudia Cseh, Dominik Wenisch, Gabriella Spengler, Nóra V. May, Michael A. Jakupec, Bernhard K. Keppler, Christian R. Kowol, Éva A. Enyedy ((oral presentation)
A comparative study on complexation and biological activity of the anticancer iron chelator VLX600 and its derivatives with essential metal ions
International Symposium on Metal Complexes, 11–14.06.2023., Urbino, Italy

19. Éva A. Enyedy, Tamás Pivarcsik, **Vivien Pósa**, Hilda Kovács, Éva Frank, Isabel Correia, Iztok Turel, Gabriella Spengler (poster)
Modulation of the anticancer and solution chemical properties of 8-hydroxyquinolines and oligopyridines via metal complexation
4th European NECTAR Conference, and Final Action Meeting, 26–27.02.2024., Milazzo, Italy