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Metallodrug Cu(II) and Ru(η^6-toluene) complexes and their ligands in solid phase – coordination modes and supramolecular structures

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THESES OF PHD DISSERTATION

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1. Introduction and goals

Small biomolecules and their metal complexes are frequently used as bioactive compounds, such as drugs, imaging agents, or chelators in metal-accumulating diseases (e.g., Alzheimer's disease, Wilson's disease) and also in many other fields of clinical practices. In addition to biological activity these compounds must meet a number of strict physico-chemical requirements (e.g., solubility, stability), which are largely determined by their chemical structure. The clarification of the structure – property and structure – biological activity relationships requires the exploration of the solid-phase structures. The structures of the organic molecules and their complexes are determined at atomic resolution level by single crystal X-ray diffraction (SXRD). Applying this method on the selected crystals, we can study the composition, constitution, conformation, and configuration of the compounds, as well as we learn how the crystals are constructed from the molecules, how the content of the asymmetric unit is organised by the space group symmetries to construct a lattice, and also the kinds of supramolecular interactions occur among the molecules are revealed. A better understanding of intermolecular interactions is essential in both drug formulation and revealing the biological activity.

The aim of my PhD research project was to study the structure of biologically active organic molecules, as well as a commercially available but structurally undiscovered drug, and their transition metal complexes. These studies require the growth of single crystals from the biomolecules themselves which then act as ligands in their complexes. The single crystal growth is frequently the bottleneck of the application of the SXRD method. Therefore, my goal was to grow single crystals from the mostly hardly crystallizing compounds and then to optimize the crystallization conditions. Preparation of the series of crystals, polymorphs, and solvatomorphs enables us to perform the systematic structural studies to reveal the principles that determine the steric and electrostatic effects that drive the arrangement of the molecules and their complexes, as well as the conformation of molecules and complexes in these self-assembled crystals. The results contribute to the development of new chelating agents for medical use, of new biologically active compounds that have the desired properties, as well as to a better understanding of the mechanism of action of the active pharmaceutical ingredients.

The dissertation covers three biologically significant areas: i.) I have investigated a series of hydroxypyridinecarboxylic acids (HPCs) and their complexes with Cu(II), which have been proposed as chelating agents for Fe(III) and Al(III) metal ions, hence copper(II) acts as a primary competitor. ii.) Platinum-containing compounds are widely used in cancer therapy, however, these drugs are not sufficiently selective and specific. Therefore, I have investigated new non-platinum anticancer Cu(II) complexes of 8-hydroxyquinoline-derivative ligands, as well as “piano-stool” type Ru(II) complexes with differently substituted picolinic acids in order to better understand the relationships between structure and biological activity. iii.) I have determined the structure of Clopamide by SXRD. It is a commercially available drug which has not been previously reported. Since the therapeutic use of

Clopamide reduces the level of essential metal ions in the blood, such as zinc and copper as a side effect, presumably due to its complexing properties, my further aim was to investigate the structure of the complexes of Clopamide with Cu(II) ions.

2. New scientific results

2.1. Structures of hydroxypyridinecarboxylate (HPC) derivatives proposed for chelation therapy

Four of the five hydroxypyridinecarboxylic acid (HPC) derivatives (Fig. 1.a) proposed for chelation therapy were crystallized successfully (**P-1** – **P-4**), and their structures were determined by single crystal X-ray diffraction. It is revealed that the hydrogen of the OH group is in an intramolecular hydrogen bond with the oxygen of the COO^- group in all four structures. I also proved that out of the oxo-enol tautomeric forms, the enol form is stabilized in the crystals of the 3HPC derivatives, while the oxo form is present in the crystals of 4HPC derivatives, based on the position of the hydrogen atom and the measured bond distances. The order of the p*K* values of the proton in the hydrogen bond measured by pH potentiometry agrees well with the O-H bond distances obtained from the solid phase structures, thus the deprotonation is shifted towards higher pHs in the case of the enol forms.

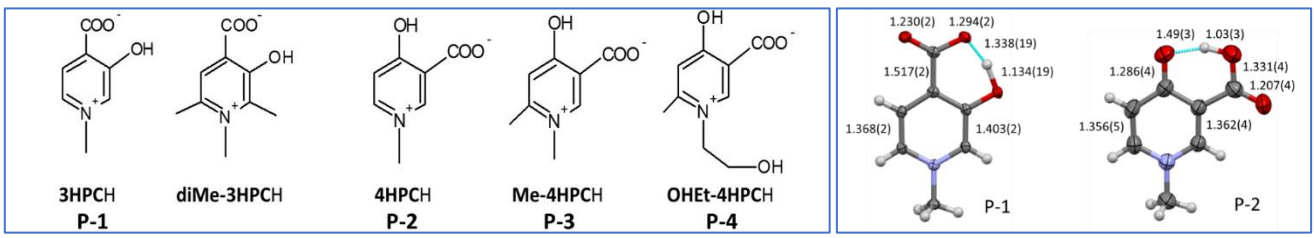

*Fig. 1 a., The formulae diagrams of the investigated HPC molecules in their zwitterionic form with compound assignation b., ORTEP presentations of the **P-1** and **P-2** ligands, as well as some selected bond distances for comparison (Å). Displacement ellipsoids are drawn at 50% probability level.*

2.2. Structures of the complexes of HPC ligands with copper(II) proposed for chelation therapy

I successfully crystallized and determined the structure of the *bis*-complexes of five HPC ligands with copper(II): $[Cu(\mathbf{3HPC})_2.(H_2O)].3(H_2O)$ (**P-5**), $[Cu_2(\mathbf{diMe\text{-}3HPC})_4].12H_2O$ (**P-6**), $[Cu_2(\mathbf{4HPC})_4].4H_2O$ (**P-7**), $[Cu(\mathbf{Me\text{-}4HPC})_2]_n.3H_2O$ (**P-8**) and $[Cu_3(\mathbf{OHEt\text{-}4HPC})_6].18H_2O$ (**P-9**). Although $[O^-_{carb},O^-][O^-_{carb},O^-]$ ligand coordination is realized in the equatorial plane in all Cu(II) complexes, there is a difference in the *cis*/*trans* coordination of the ligands, and in the occupancy of the axial coordination site. In the 3HPC complexes only *cis*, while in the 4HPC complexes only *trans* ligand configurations occur in the solid state. In the **P-5** crystal a monomer complex is present by the axial coordination of a water molecule. In the **P-6** and **P-7** crystals (Fig. 2.) cyclic dimeric structures are formed with the oxygen of the ligand of an adjacent complex molecule. However, while in the case of **P-6** the piridinolate-O^- plays this role,

it is replaced by the carboxylate-O^- in the case of **P-7**. Coordination environment similar to **P-7** is formed around the copper centre in **P-8**, anyhow, the steric hindrance prevents the formation of cyclic dimers resulting in the formation of a 1D polymer chain. In **P-9** the OH groups on the ligand side chains coordinate axially to the adjacent copper cation, resulting in a trimer complex, which contains three copper centres with 5-, 6-, and 5-coordination, respectively. The differences in the electron distribution of the potential drug molecules can be well used to interpret the differences found in the complexes, namely the oxygen atoms with higher electron density creates the bridge between the metal centres.

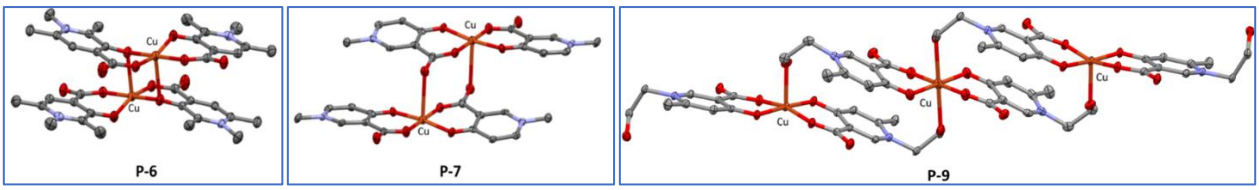

*Fig. 2., ORTEP presentations of the cis-arranged [Cu_2(**diMe-3HPC**)$_4$] (**P-6**) and trans-arranged [Cu_2(**4HPC**)$_4$] (**P-7**) complexes, as well as the [Cu_2(**4HPC**)$_4$] (**P-9**)trimer complex. Displacement ellipsoids are drawn at 30% (**P-6**) and 50 % probability level (**P-7** and **P-9**).*

2.3. Structures of 8-hydroxyquinoline derivatives and their Cu(II) complexes with anticancer activity

Three 8-hydroxyquinoline derivatives were investigated with different antitumor activities, as well as their copper(II) complexes in order to reveal the relation between their chemical structure and biological activity. I successfully crystallized two 8-hydroxyquinoline derivatives and three of their complexes: **Q-1 – Q6** (Fig. 3). Intramolecular hydrogen bond is found in both organic crystals: between the hydroxyl-OH hydrogen atom and the piperidine nitrogen atom in **Q-1**, and between one of the NH_2^+ side chain hydrogen atoms and the hydroxyl-OH oxygen in **Q-2**. In the copper(II) complexes the ligands are in *trans* positions in square planar arrangement with [N,O^-] coordination, similar to that of [Cu(**8HQ**)$_2$] (CUQUIN) known from the literature. In the case of **Q-4**, similar to **P-6,** cyclic dimeric structure is observed, owing to the bridging role of the hydroxylate oxygen atom. A methanol molecule coordinates axially to the copper(II) ion in **Q-6**. The hydroxyl groups of the ligands are deprotonated because of the metal coordination, while the nitrogen groups of the side chains are protonated, resulting in zwitterionic structure of the ligands. No direct link was discovered between the structure of the complexes and the degree of their biological activity. Based on other analyses, the different extent of their biological activity is presumably due to other parameters such as the lipophilicity and pK_a(OH) values of the complexes.

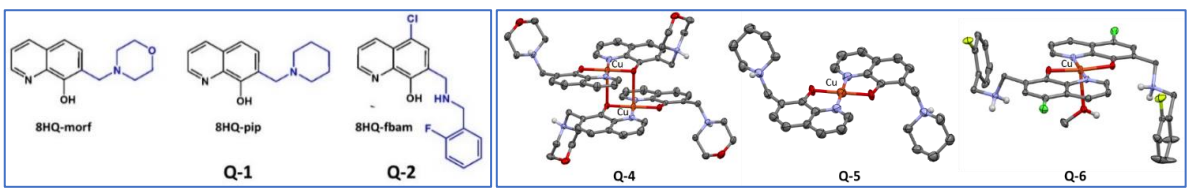

*Fig. 3. a., Formulae diagrams of the 8HQ derivatives in their neutral forms b., Structures of the **Q-4 – Q-6** complexes. Displacement ellipsoids are drawn at 30% probability level.*

2.4. Structure of complexes of Ru(η^6-toluene) with picolinate derivative ligands showing anticancer activity

The structure of four different picolinate derivative complexes with Ru were revealed: [Ru(η^6-toluene)(**pic**)Cl] (**R-1**), [Ru(η^6-toluene)(**3-Me-pic**)Cl].H_2O (**R-2**), [Ru(η^6-toluene)(**5-Br-pic**)Cl] (**R-3**) and [Ru(η^6-toluene)(**2,5-dipic**H)Cl] (**R-4**) (Fig. 4.a). I have determined, that in the half-sandwich complexes there are a η^6 coordinated toluene, a chloride ion and the picolinate derivative ligand coordinated bidentately via its [N,O^-_{carb}] atoms to the metal center (Fig. 4.b). I discovered, that the presence of electron-withdrawing groups (bromo- and carboxylate-) attached to the picolinate decreases the Ru-Cl and increases the Ru-O distances, while the electron-donating group (methyl-) has the opposite effect. The main secondary interactions are of C-H…O and C-H…Cl types in **R-1** and **R-2** crystals. In the crystals of the picolinate complexes containing electron-withdrawing groups (**R-3** and **R-4**) the molecules are arranged by π…π interactions parallel to their picolinate rings. According to the solution equilibrium studies the chloride ion is exchanging to a water molecule when the solid complexes are dissolved in water, and the higher exchange rate results in higher biological activity. Based on our structural study we propose to apply electron-donating substituents on the picoline to increase the anti-cancer activity.

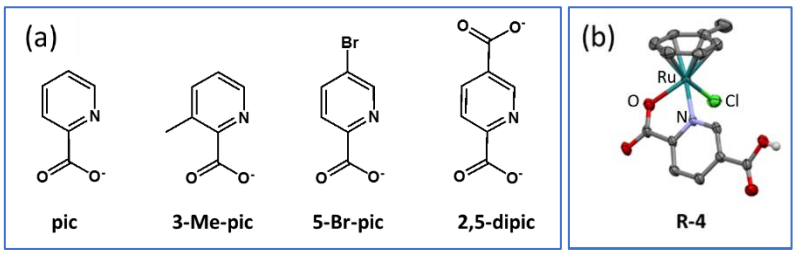

*Fig 4.a., Formulae diagrams of the picolinate derivative compounds. b.,. The structure of the half-sandwich picolinate complexes in the crystal of [Ru(η^6- toluol)(**2,5-dipic**H)Cl] (**R-4**).* Displacement ellipsoids are drawn at 50% probability level.

2.5. Structures of the anhydrate and hemihydrate crystals of the diuretic Clopamide

The SXRD structure of the commercially available diuretic Clopamide (**Clop**H) (Fig. 5.a) was previously unknown, most likely due to the difficulties of the single crystal growth. I successfully crystallized the anhydrate (**C-1**, $P2_1/n$) and hemihydrate (**C-2**, $C2/c$) forms of this drug compound. Dimers are formed in both crystals by N-H… O type hydrogen bonds between the sulfonamide groups of the molecules, which are organised into layers with additional hydrogen bonds. The water molecules act as spacers among the layers and improve the symmetry of the crystal: the pseudo 2-fold axis present in the anhydrate form becomes a real symmetry element lowering the value of Z' from 2 to 1. Intramolecular halogen bond, defined by the IUPAC in 2016, was discovered in both anhydrate and hemihydrate crystals between the chlorine and one of the sulfonamide group oxygens (Fig. 5.b).

Chalcogen bond – which was defined at the end of 2019 – was found in the anhydrate form of Clopamide between the sulfoxy oxygen (donor) and the lone electron pair of the carbonyl oxygen (acceptor) of the adjacent molecules.

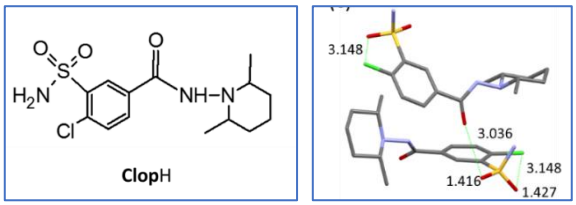

Fig. 5.a., Formulae diagram of Clopamide b., Halogen and chalcogen bonds in the Clopamide anhydrate crystal, some bond distances are indicated (Å).

2. 6. Structures of copper(II) complexes of the diuretic Clopamide

The copper(II) complexes of the Clopamide (Fig. 6.a) were crystallized from a homologous series of alcohols. Four isostructural crystal structures were determined: [Cu(**Clop**)$_2$].2MeOH.2H$_2$O (**C-3**), [Cu(**Clop**)$_2$].2EtOH.2H$_2$O (**C-4**), [Cu(**Clop**)2].2PrOH.2H$_2$O (**C-5**), [Cu(**Clop**)$_2$].2iPrOH.2H$_2$O (**C-6**). Three more solvent-free polymorphs ([Cu(**Clop**)$_2$] Form I (**C-7**), [Cu(**Clop**)$_2$] Form II (**C-8**), [Cu(**Clop**)$_2$] Form III (**C-9**)) and one dichloromethane clathrate ([Cu(**Clop**)$_2$].2CH$_2$Cl$_2$ (**C-10**)) were crystallized from organic solvents. I found, that following the deprotonation of the hydrazine nitrogen *trans* aligned square planar complexes are formed by a bidentate coordination of the piperidine nitrogen and the oxo group of the ligand in all cases. The axial coordination is sterically hindered due to the methyl groups of the piperidine ring. The two different arrangements of the piperidine ring in chair conformation, as well as the differences in the angle between the sulfamoylbenzamide ring and the equatorial coordination plane describe the conformational differences of the complexes observed in the polymorphic and solvatomorphic crystals (Fig. 6. b). In the **C-8** polymorphic form the angle between the equatorial coordination planes of the neighbouring molecules is close to 60^o surrounding a pseudo-threefold axis. It becomes a real C$_3$ rotation axis in the *R*-3 space group in the **C-9** polymorph. With the inclusion of dichloromethane in crystal **C-10** the secondary interactions remain analogous to those in the solvate-free polymorphs, but the parallelism of the chains terminate.

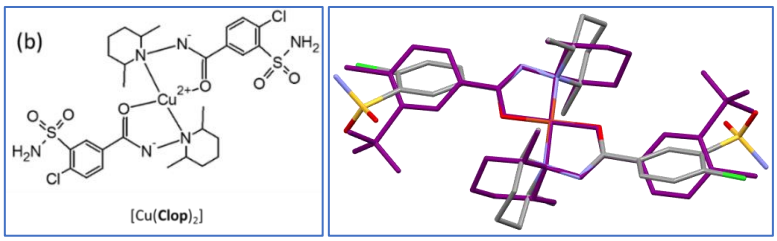

*Fig. 6. a., Formulae diagram of the Clopamide [Cu(**Clop**)$_2$] complex. b., Conformational differences of copper(II) complexes of Clopamide (**C-3** coloured by elements, **C-9** purple).*

3. Experimental

The HPC derivatives were provided by Valerio di Marco (University of Padua) as part of a research collaboration. Single crystals of the compounds suitable for SXRD measurements were grown from solvent mixtures by slow evaporation: from ethanol/methanol (**P-1** and **P-4)**, from toluene/methanol **(P-2)**, as well as from water/methanol mixture **(P-3)**. Cu(II) *bis*-complexes were crystallized from aqueous solution containing $CuCl_2$ and the ligands in two-fold excess. The pH was adjusted to 7 using NaOH solution in order to facilitate the formation of a deprotonated form of the ligand capable for coordination.

The 8HQ-s (**Q-1**, **Q-2**) were crystallized by slow evaporation from methanol solution at room temperature. During the crystallization process of **Q-2**, the solution contained $CuCl_2$ too. The **Q-4** and **Q-5** Cu(II) complexes were crystallized from methanol solution containing $CuCl_2$ and the ligands in two-fold excess by vapor diffusion method applying diethyl ether as antisolvent. The **Q-6** did not crystallize under similar conditions, however, if $ZnCl_2$ was present in the solution, single crystals could be obtained.

The Ru(η^6-toluene)-picolinate complexes were grown by the MTA-SZTE "Lendület" Functional Metal Complexes Research Group. The pure compounds were isolated from methanol or 2-propanol, then the **R-1**, **R-2**, **R-3** and **R-4** complexes were crystallized by slow evaporation of the solvent.

The pharmaceutical company EGIS provided us the powder of Clopamide diuretic drug. Slow evaporation of the solvent was performed to grow the **C-1** and **C-2** crystals from their methanol solutions. The Clopamide anhydride crystals were obtained from a solution, which contained $CuSO_4$ too. Clopamide copper(II) *bis*-complexes (methanol (**C-3**), ethanol (**C-4**), 1-propanol (**C5**) and 2-propanol (**C-6**)) were grown from the homologous series of alcoholic solutions containing $CuCl_2$ and the ligand in two-fold excess by slow evaporation of the solvent. I ensured the deprotonation of the nitrogen atom of the hydrazine unit and the formation of the copper(II) *bis*-complex by setting an alkaline pH using NaOH solution. **C-7** (Form I) and **C-8** (Form II) solvent-free polymorphs were obtained from methanol solutions containing $CuSO_4$ and the ligand in different excess after a year. My aim was to investigate the stability and possible polymorphic transformations of the obtained crystals. The brown single crystals of the **C-9** (Form III) polymorph were grown by slow solvent evaporation technique following its separation from an aqueous solution containing $CuCl_2$ and the ligand by extraction with ethyl acetate. The **C-10** single crystals were grown similarly to **C-9**, where dichloromethane was used instead of ethyl acetate.

The structures of the reported compounds were determined by single crystal X-ray diffraction, the data were collected on a Rigaku RAXIS-RAPID II diffractometer using Mo-Kα or Cu-Kα radiation. Numerical or multi-scan absorption corrections were carried out on the data. The structures were solved by direct methods. The models were refined on full-matrix by least squares calculations on F^2. The anisotropic displacement parameters of the non-hydrogen atoms were refined. Hydrogen atomic positions were located in the difference Fourier maps and then hydrogens were placed into geometric positions, except the -OH, -COOH and H_2O hydrogens, their positions were refined.

Conclusions

Structural analysis of three different biologically active compound families, therapeutic agents and their metal complexes was performed and is reported. These compounds are the hydroxypyridinecarboxylic acid derivatives and their Cu(II) complexes (P-1 – P-9) recommended for chelation therapy, the derivatives of 8-hydroxyquinoline and their Cu(II) complexes (Q-1 – Q-6) and the complexes of picolinate derivatives with Ru(□6-toluene) (R-1 – R-4) both having antitumor activity, as well as the Clopamide, a commercially available marketed diuretic (C-1 – C-10). The aim of the structural analyses was the fine-tuning of physico-chemical properties and the understanding of the structural aspects influencing the biological activity of the free ligands and their Cu(II) or Ru(II) complexes. The projects were completed with several analytical investigations, like ESR spectroscopy, UV-VIS spectrometry, pH potentiometry, as well as with cytotoxicity studies and biological activity measurements; these results can be found in the publications attached. These results complete the research projects but they do not belong to the topic of this PhD dissertation.

The structures were determined by single crystal X-ray diffraction. The advantage of this method that it reveals small structural differences caused by ligand conformation or the electron-donating or electron-withdrawing effects of the substituents. The bottleneck of the method is the growth of the single crystal. It requires careful and often time consuming experimental work. It explains why the investigated compounds' structures have still been unknown at atomic resolution, in spite of the fact that for example Clopamide has been marketed for many years known as Brinaldix (EGIS).

In case of the hydroxypyridinecarboxylate derivatives proposed for chelation therapy I have proved, that out of the oxo-enol tautomeric forms the enol form is stabilized in the crystals of the *p*-carboxylate derivatives, while the oxo form is present in the crystals of the *m*-carboxylate derivatives. Although, $[O^-_{carb},O^-][O^-_{carb},O^-]$ ligand coordination is realized in the equatorial plane of their Cu(II) complexes, there is a difference in the *cis/trans* coordination of the ligands and in the occupancy of the axial coordination site. A wide range of monomer, cyclic dimer, 1D polymer chain, and trimer complexes are formed in the crystals.

Cyclic dimers are formed and the ligands are in zwitterionic states in the copper(II) complexes of the 8-hydroxyquinoline derivatives having antitumor activity. A square planar arrangement emerges with *trans* ligand positions. In the complexes of the half-sandwich type Ru(η^6-toluene) with picolinate derivatives, with antitumor effects, too, the electron-withdrawing groups reduce the Ru-Cl bond distance. Dissolving the solid phase complexes in water the coordinated chloride ion is exchanging for a water molecule: the higher the exchange rate the greater is the biological activity. Based on the structural results we propose the use of electron-donating substituents to boost the anti-cancer activity.

I have successfully crystallized and determined the structure of the anhydrate and hemihydrate crystal forms of the diuretic Clopamide. It made possible to interpret the role of the incorporating water molecule

in the crystal lattice. Two newly defined secondary bond types: an intramolecular halogen bond and an intermolecular chalcogen bond were recognized and described. Four isostructural crystals using a homologous series of alcohols, three solvent-free polymorphic forms and one dichloromethane-containing solvatomorphic form of the Cu(II) complexes of Clopamide were crystallized and characterized. The conformational differences were revealed in the crystals.

During my PhD research work I performed the systematic change of the secondary interactions during the non-covalent syntheses in the studied compound families. I described the steric and electrostatic effects which direct the molecular arrangements in the investigated isostructural, solvatomorphic, and polymorphic crystal structures. The same type of secondary interactions can occasionally also be identified in the crystals of the organic molecules and in the crystals of the concerning complexes, what is changed when the crystal lattice of the complex contain guest solvent molecules. The newly gained structural information contributes to the ability of the production of new compounds with requested biological activity. With the deeper understanding of the crystal engineering principles we will be able to form new synthons and to reach the final aim to prepare new materials with desired properties (solubility, stability, melting point, bioavailability, etc.).

Papers on which the dissertation is based:

1. J. M. Poljarević, **Gál G. T.**, May N. V., G. Spengler, Dömötör O., A. R. Savić, S. Grgurić-Šipka, Enyedy É. A., „Comparative solution equilibrium and structural studies of half-sandwich ruthenium(II)(η6-toluene) complexes of picolinate derivatives" *J. Inorg. Biochem.*, **2018**, 181, 74-85. (IF:3,224)

2. May N. V., **Gál G. T.**, Szentendrei Z., Korecz L., May Z., M. G. Ferlin, A. Dean, Bombicz P. és V. B. Di Marco, „Relationship between Solid State Structural Variety and Solution Stability of Copper(II) - hydroxypyridinecarboxylic Acid Complexes", *New J. Chem.*, **2019**, 43, 10699-10710. (IF:3,288)

3. **Gál G. T.**, May N. V., Trif L., Mihály J., Bombicz P., „Solvatomorph and Polymorph Screening of Clopamide Drug and Its Copper(II) Complex Crystals", *CrystEngComm*, **2021**, 23, 7425-7441.

DOI: 10.1039/D1CE00995H (IF: 3,545)

Other publications:

1. May N. V., **Gál G. T.**, Rapi Z., Bakó P., „Crystal structure of diethyl-2-acetoxy-2-(3-(4-nitrophenyl)3-oxo-1-phenylpropyl)malonate „ *Acta Cryst.*, **2016**, E72, 257-260

2. **Gál G. T.**, May N. V., Bombicz P., „Crystal structure of levomepromazine maleate" *Acta Cryst.*, **2016**, E72, 612-615

3. V. F.S. Pape, May N. V., **Gál G. T.**, Szatmári I., Szeri F., Fülöp F., Szakács G., Enyedy É. A., "Impact of copper and iron binding properties on the anticancer activity of 8-hydroxyquinoline derived Mannich bases" *Dalton Trans.*, **2018**, 47, 17032-17045, 14 p.

4. Mészáros J., J. M. Poljarević, **Gál G. T.,** May N. V., G. Spengler, Enyedy É. A., „Comparative solution and structural studies of half-sandwich rhodium and ruthenium complexes bearing curcumin and acetylacetone" *Journal of Inorg. Biochem.*, **2019**, 195, 91-100. , 10 p.

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6. Tuba R., Nagyházi M., Turczel G., Balla Á., Szálas G., Tóth I., **Gál G. T.,** Bombicz P., P. T. Anastas, „Towards Sustainable Catalysis - Highly Efficient Olefin Metathesis in Protic Media Using Phase Labelled Cyclic Alkyl Amino Carbene (CAAC) Ruthenium Catalysts" *Chem. Cat. Chem.*, **2020**, 12 : 7 pp. 1953-1957. , 6 p.

7. Dömötör O., Kiss M. A., **Gál G. T.,** May N. V., G. Spengler, Nové M., A. Č. Gašparović, Frank É., Enyedy É. A., „Solution equilibrium, structural and cytotoxicity studies on Ru(η6-p-cymene) and copper complexes of pyrazolyl thiosemicarbazones" *J. Inorg. Biochem.*, **2020**, 202 Paper: 110883 , 13 p.

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1. Bombicz P., **Gál G. T.**, Lovász Á., May N. V., Holczbauer T., "Intermolecular interactions of benzimidazole derivatives", 29th European Crystallographic Meeting, 23-28, August 2015, Rovinj, Croatia

2. **Gál G. T.**, Bombicz P., V. B. Di Marco, May N. V., "Effect of alkyl and carboxyl substitution to the molecular arrangement in the crystals of 4-hydroxy-3-pyridinecarboxylic acid derivatives", 4th European Crystallographic School, 02-07, July 2017, Warsaw, Poland

3. May N. V., **Gál G. T.**, V. Di Marco, Bombicz P., "The structure of copper(II)-hydroxypiridinecarboxylic acid derivatives in both solid and solution phases „ 31st European Crystallographic Meeting, Oviedo, Spain 22-27 August 2018, lecture, MS36-O5

4. **Gál G. T.**, May N. V., Bombicz P., "Structural investigation of diuretic Clopamide and its copper(II) complexes under different conditions „ International Symposium on Metal Complexes, 11-14, June 2019, Hajdúszoboszló, Hungary

5. **Gál G. T.**, May N. V., Bombicz P., "Effect of crystallization conditions on diuretic Clopamide and its copper(II) complexes" 32nd European Crystallographic Meeting, 18-23, August 2019, Vienna, Austria, ***IUCr Journals Poster Prize is Structural Chemistry.***

6. May N. V., **Gál G. T.**, Bombicz P., „Structural study of Clopamide drug and copper (II) complexes under different crystallization conditions" 25th Congress of the International Union of Crystallography 14-22 Augustus 2021, Prague, Checz Republic, Acta Cryst. (2021). **A76**

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