SOLUTION EQUILIBRIUM CHEMISTRY OF LIGANDS AND METAL COMPLEXES AS POSSIBLE THERAPEUTIC AGENTS IN CANCER AND ALZHEIMER'S DISEASES

Ph.D. Theses

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1. Introduction

In the last few decades numbers of metal complexes have developed for therapeutic or diagnostic purposes or conversely chelation ligands are used as a treatment for toxic metal or overload of essential metal ions from the body. Since the 90' years various studies have been providing evidence that metal ions are critically involved in the pathogenesis of Alzheimer's disease. Elevated levels or imbalance of Fe(III), Al(III), Cu(II) or Zn(II) metal ions can promote the formation of misfolded *β*-amyloids, toxic oligomers and then aggregation as plaque deposits in the brain. The aggregation processes can be changed to reversible by suitable chelating agents. Metal-induced oligomerization or aggregation processes of *β*-amyloids can be reversed by chelation. In this work we focus on a class of ligands, hydroxyl-pyridinecarboxylic acids. The interactions of Cu(II), Zn(II), Fe(III) and Al(III) with 4-hydroxy-3-pyridinecarboxylic acids and 3-hydroxy-4-pyridinecarboxylic acids, as possible chelating agents in Alzheimer's disease, were investigated in aqueous solution.

Transition metal complexes play a crucial role in antitumor therapy. In the last decade, numerous organometallic ruthenium(II)-η^6-arene complexes mainly with piano-stool structure were synthesized and tested by *in vitro* assays regarding their bioactivity. In these Ru(II) complexes the facial arene moiety results in the protection of the metal centre against oxidation. This half-sandwich complex has three available coordination sites to interact with different ligands (Fig. 1.). The type of the chelating ligands has a distinct influence on the stability of the complex formed and the ligand can prevent the hydrolysis of Ru(II)-η^6-*p*-cymene organometallic fragment. A large number of [(Ru(II)-η^6-*p*-cymene)(XY)Cl]-type compounds was prepared, where XY is an (O,O), (O,S), (O,N), (N,N) or (N,S) bidentate ligand.

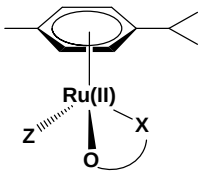


Fig 1. Structure of [Ru(II)-η^6-*p*-cymene]
(X = N,O,or S; Z = H_2O, Cl^- or OH^-)

2. Main goals of the work

At the beginning of my work several goals have been set out. They are as follows:

- determining pK_a values of some hydroxy-pyridinecarboxylic acids and studying the deprotonation processes by ^1H NMR spectroscopy to give a more complete picture about the acid-base properties than the previously published ones,

- investigating the interactions of hydroxy-pyridinecarboxylic acid ligands with Fe(III), Al(III), Cu(II) and Zn(II), calculating the stability constants of the metal complexes formed in order to establish which ligands are able to compete against the β-amyloid peptides for the metal ions, and prevent the formation of toxic oligomers,

- investigating the stoichiometry and stability of the [Ru(II)-η^6-p-cymene] complexes of bidentate
    - (O,O) type hydroxypyrones ligands (2-ethyl-3-hydroxy-4-pyranone (ethyl maltol), 5-hydroxy-2-methyl-4H-pyran-4-one (allomaltol))
    - (O,N) type picolinic acid (pik) and its derivatives as 6-methylpicolinic acid (6-Mepik) and pyridine-2,6-dicarboxylic acid (dipik)
    - (O,S) type hydroxythiopyrone (5-hydroxy-2-methyl-4-thiopyrone (thioallomaltol)

  in order to establish *structure-stability-biological activity* relationships,

- monitoring the chlorido/aqua co-ligand exchange reaction in the [Ru(II)-η^6-*p*-cymene(L)(Cl)] species and determining the stability constants of the complexes in the presence and in the absence of chloride ion since chloride ion is a coordinative ligand for ruthenium(II) in aqueous solution,

- investigating the interaction of hydroxy-pyridinecarboxylic acids, [Ru(II)-η^6-p-cymene] and its some complexes with human serum albumin which is the most important non-specific transport vehicle for the transport in the blood plasma.

3. Experimental

The pH-potentiometric measurements for determination of the protonation constants of the ligands and the overall stability constants of the metal complexes were carried out at 25 °C in water and at an ionic strength of 0.20 M KCl or KNO_3 in order to keep the activity coefficients constant. The titrations were performed with carbonate-free KOH solution. The protonation constants of the ligands were determined with the computer program HYPERQUAD. The computer program PSEQUAD was utilized to establish the stoichiometry of the complexes and to calculate the overall stability constants.

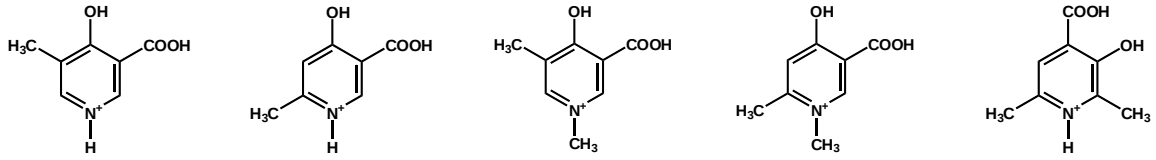
EPR measurements were also carried out for Cu(II)-DQ715 solutions in order to obtain structural information on the complexes.

The spectrophotometric and ^1H NMR pH dependent titrations were performed on samples of the ligands alone or with metal ions at various ratios. The ^1H NMR spectra were recorded to study the H_2O/Cl^- exchange processes in the [Ru(II)-η^6-*p*-cymene(L)Z] complexes at constant pH in dependence of the Cl^- concentration. UV-Vis measurements under pH 2 were carried out at 1:1 metal-to-ligand ratio by preparing individual samples in which KCl (or KNO_3) was partially or completely replaced by HCl (or HNO_3) and pH values varying in the range ca. 0.9–2.0 were calculated from the strong acid content.

In the protein-ligand interaction studies ultrafiltration/UV-Vis and fluorescence spectroscopic measurements were performed.

4. Results

The molecular structures of the studied hydroxy-pyridinecarboxylic acid ligands in completely protonated forms are shown in Fig 2.



4-hydroxy-5-methyl-3-pydidinecarboxylic acid (DQ5)	4- hydroxy-6-methyl-3-pydidinecarboxylic acid (DQ6)	1,5-dimethyl-4-hydroxy-3-pydidinecarboxylic acid (DQ715)	1,6-dimethyl-4-hydroxy-3-pydidinecarboxylic acid (DQ716)	2,6-dimethyl-3-hydroxy -4-pydidinecarboxylic acid (DT726)

Fig 2.: Molecular structures of studied hydroxy-pyridinecarboxylic acids

1. Besides determining pK_a values of DQ5 and DQ715 ligands, the deprotonation processes were studied by ^{1}HNMR spectroscopy and we could provide a more complete picture about their acid-base properties than the previously published ones.

In case of N-methylated DQ715 the existence of the chinoidic and aromatic isomeric forms of L^- was supported by ^{1}H NMR measurements. An unequivocal assignment of the pK_2 and pK_3 values of DQ5 is not possible either, because 4-hydroxy-3-pyridinecarboxylic acid derivatives can adopt a chinoid electronic configuration in tautomeric equilibrium with the corresponding aromatic form. In case of DQ5 three kinds of HL^- forms can exist (Fig. 3.). The chinoidic and the aromatic forms are in a fast exchange for both ligands.

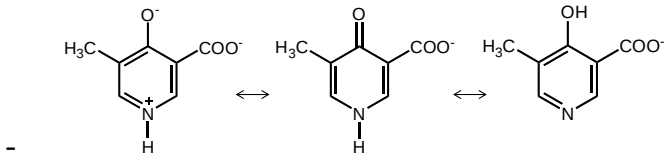


Fig.3.: Possible molecular structures of the HL- form for DQ5 ligand

2. The hydroxy-pyridinecarboxylic acids form mono, bis and tris complexes with Al(III) and Fe(III). With Cu(II) the predominant species are mono- and bis complexes. The Zn(II) binding affinity of the ligands is very low. In most cases with Zn(II) no evidence was found for the presence of any tris complex because of the low stability complexes and precipitation of solid compounds at low pH values.

The hydroxy-pyridinecarboxylic acids form mono, bis and tris complexes with Al(III) and Fe(III). The stability of the complexes was not high enough to prevent the hydrolysis of Fe(III) in most cases, only four studied ligands (DT1, DT712, DQ716 and DQ715 (studied by me)) were able to keep the Fe(III) dissolved in physiological pH range. However the Al(III) binding ability of these ligands is reasonable – all ligands can prevent the formation of $Al(OH)_3$ – but unfortunately not so efficiently as deferiprone or desferrioxamine. The coordination strength is significantly increased when methyl substituents are present in position 5 or 6 at the pyridine ring.

Due to the hard character of the donor atoms of these studied ligands the complex stability is lower with the borderline Zn(II) and Cu(II) ions than that of Fe(III) and Al(III). On basis of the overall stability constants dissociation constants (K_D values) have been calculated for the complexes at pH 7.4. We have found that among the studied ligands only the DQ716 can form sufficiently high stability complexes with Cu(II) and can retrieve the Cu(II) from the β-amyloid aggregates and prevent the oligomerisation and aggregation processes. The Zn(II)

binding ability of the ligands is very low, therefore these ligands most probably do not affect the zinc homeostasis *in vivo*.

3. DQ ligands do not exhibit a measurable tendency to interact with HSA. Only ligand DT726 – one of 3-hydroxy-4-pyridinecarboxylic derivatives is able to bind to the albumin. The interactions of some ligands with human serum albumin (HSA) were studied by ultrafiltration/UV-Vis and fluorescence spectroscopy. From our measurements, we could conclude that up to four DT726 molecules can bind to HSA with high affinity at pH 7.40.

pH-potentiometric, UV-Vis spectrophotometric and ^{1}H NMR spectroscopic measurements were performed to investigate the stoichiometry and stability of the [Ru(II)-η^6-*p*-cymene] complexes in order to establish structure–stability–biological activity relationships the characterization of the stability of these complexes.

4. The studied (O,O) type hydroxypyrone ligands form [ML] complex with [Ru(II)-η^6-*p*-cymene] in a bidentate way. In [ML] the third coordination site is most probably occupied by a water molecule or chloride ion in dependence of chloride ion concentration. In basic solution mixed hydroxido species [ML(OH)] and in overlapping dissociation process $[Ru_2(\eta^6\text{-}p\text{-cymene})_2(OH)_3]^+$ were formed.

The complex formation processes of ethyl maltol and allomaltol with [Ru(II)-η^6-*p*-cymene] studied. The stability constant of the [ML] complex was determined by pH-potentiometry and by UV-Vis spectrometry. The ^{1}H NMR spectral changes clearly show that two overlapping processes take place at pH > 8, namely the formation of a mixed hydroxido species [Ru(II)-η^6-*p*-cymene(L)(OH)] resulting in a significant upfield shift of the peaks and ii) the dissociation of the complex $[ML]^+$ according to

$$2\ [\text{Ru(II)-}\eta^6\text{-}p\text{-cymene(L)(Z)}] + 3\ H_2O \rightleftharpoons [Ru_2(\eta^6\text{-}p\text{-cymene})_2(OH)_3]^+ + 2\ L^- + 3\ H^+ + 2\ Z$$

$$(Z = H_2O \text{ or } Cl^-)$$

equation. The latter process was found to be relatively slow and could not accurately be followed by pH-potentiometry as the real equilibrium could not be reached during the time-scale of this method. The pK_a value for the deprotonation of the species [ML] was estimated on the basis of the pH-dependence of the signals of the C*H*(Ar) cymene protons in the ^{1}H NMR spectra. Chloride ions are coordinative ligands for ruthenium(II) in aqueous solution.

The aquation of the [Ru(II)-η^6-*p*-cymene(L)(Cl)] has a strong impact on the bioactivity, therefore the Cl^-/H_2O co-ligand exchange process was also studied by ^1H NMR spectroscopy. The spectral changes of the [Ru(II)-η^6-*p*-cymene(L)(H_2O)]$^+$ were followed at various chloride concentrations at constant pH at which the species [ML] predominate. A small, but well-defined shift of the NMR signals was observed related to the coordination of Cl^- to the Ru centre. Based on the changes of chemical shifts, the stepwise stability constants could be estimated for the H_2O/Cl^- co-ligand exchange equilibria. Based on these equilibrium constants the ratio of chlorido/aqua complex can be calculated for the complexes [ML] at various chloride concentrations.

The equilibrium of ethyl maltol with [Ru(II)-η^6-*p*-ymene] was studied in the presence and absence of chloride ion. We found that the presence of chloride ions decreases the stability via the competition with the chelating ligand.

5. The complexation of pik and 6-Mepik with [Ru(II)-η^6-*p*-cymene] is very similar to complex equilibriaof (O,O) ligands. (O,N) ligands, however, form complexes [ML] with higher stability and they can protect the complex against the dissociation in basic solution. In case of dipik due the presence of the second carboxyl group on the pyridine ring there is the possibility to form [MLH] complex in acidic pH, wherein the non-coordinating carboxyl group is protonated.

Analysis of the pH-potentiometric titration curves in [Ru(II)-η^6-*p*-cymene]-pik system indicates that complex formation is almost completed at the beginning of the titration (pH ~2). Therefore, the stability constant of complex [ML] was determined by pH-dependent UV-Vis measurements in the pH 0.8–11 range. Individual samples were prepared at pH < 2. Then this logβ value of species [ML] was kept constant during the calculation of the stability constant of complex [MLH_{-1}] (= [ML(OH)]) from the pH-potentiometric data. On the other hand UV-Vis spectra were collected between pH 2 and 11 and logβ value of species [MLH_{-1}] was also calculated from the spectral changes.

The partial decomposition of the complexes [ML]$^+$ and [MLH_{-1}] formed in the [Ru(II)-η^6-*p*-cymene]-pik system would be expected at high pH values, although the ^1H NMR spectra clearly show the lack of the formation of the trihydroxido dimeric complex [$M_2(OH)_3$]$^+$ or the non-bound ligand in the basic pH range even after 24 h waiting. The slow dissociation of the complex [ML]$^+$ has presumably kinetic reason.

6-Mepik forms lower, while dipik does somewhat higher stability complexes compared to pik. Besides species [ML] of dipik formation of its protonated form [MLH] was also found in the strongly acidic pH range. The stability constant of [MLH] could be fitted together with that of [ML] based on the UV-Vis spectra.

Comparing the ^{1}H NMR spectra of the Ru(II)-η^6-*p*-cymene-pik system recorded in the presence and absence of chloride ions it is seen that the spectra in the KCl milieu are more complicated since additional peaks appear. Signals belonging to the complex [ML] turn up in a double set with higher and lower intensities. Careful analysis of the spectra recorded at various chloride concentrations revealed that these signals belong to the aqua and to the chlorido complexes with [Ru(II)-η^6-*p*-cymene(L)(H_2O)] and [Ru(II)-η^6-*p*-cymene(L)(Cl)] compositions respectively, which are in slow exchange processes with respect to the NMR time scale.

The chlorido/aqua co-ligand exchange processes were investigated in detail by ^{1}H NMR spectroscopy. The spectral changes of the species [Ru(II)-η^6-*p*-cymene(L)(H_2O)]$^+$ were followed at various chloride concentrations at carefully chosen pH values at which the species [ML] predominates. Due to the well-separated ^{1}H NMR signals of the protons belonging to the aqua and chlorido complexes the integrated areas of the corresponding peaks could be calculated and converted to molar fractions. Based on the molar fractions logK* values were obtained for the following equilibrium:

$$[\text{Ru(II)-}\eta^6\text{-}p\text{-cymene(L)}(H_2O)] + Cl^- \rightleftharpoons [\text{Ru(II)-}\eta^6\text{-}p\text{-cymene(L)(Cl)}] + H_2O$$

Based on these equilibrium constants (logK*) concentration distribution curves can be calculated for the complexes [ML] at various chloride concentrations.

The equilibrium processes of pik with [Ru(II)-η^6-*p*-ymene] were studied in the presence and absence of chloride ion. Similar trend was observed in the case of the complex of ethyl maltol: the presence of chloride ions decreases the stability via the competition with the chelating ligand.

6. With (O,S) thioallomaltol the complex formation is completed at pH 0.8. The hydrolysis of the thioallomaltol complex at pH > 6 was found to be more complicated most probably due to the formation of mixed hydroxido oligomers with limited water solubility. At excess of ligand thioallomaltol formation of bis complexes were found.

The pH-potentiometric titration curves recorded at 1:1 metal-to-ligand ratio show the complete proton displacement by the metal ion already at the starting pH value (*i.e.* pH 2), which hampers the determination of the stability constant of the mono-ligand complex formed

under these conditions. It was also observed that a slow process starts resulting in proton liberation at pH > 6, which finally leads to the appearance of precipitate. In addition, UV-Vis spectra of the [Ru(II)-η^6-p-cymene]-thioallomaltol systems at 1:1 metal-to-ligand ratio were recorded in the pH range 2.0–11.5, and complemented by studies with samples. The spectra recorded in the pH 0.9–6.0 range were found to be identical, but are unambiguously different from the spectra of the metal-free ligand or the non-bound Ru(II)-η^6-*p*-cymene moiety. This finding strongly suggests the formation of one kind of species, most probably complex [ML]; however its stability constant cannot be calculated, since it predominates at pH 0.7-6.0 and no complex dissociation seems to take place by decreasing the pH. Therefore, only a threshold limit could be estimated for the logβ of complex [ML]

The speciation in the [Ru(II)-η^6-*p*-cymene]-hydroxythiopyr(id)one systems was found to be different and more complicated at ligand excess. The pH-potentiometric titrations clearly showed that an excess of ligand is able to protect the metal ion against the hydrolysis up to pH 10. Careful analysis of the ^{1}H NMR spectra recorded at various metal-to-ligand ratios at pH 3 and 9 reveals in all cases formation of bis-ligand complexes besides the respective species [ML]. The most probable composition of this complex is [ML_2H] at pH 3.0. The [ML_2H] species can be deprotonated at higher pH values resulting in the formation of [ML_2] and the p*K* value of [ML_2H] was also calculated based on ^{1}H NMR titrations at 1:2 metal-to-ligand ratios and pH-potentiometric measurement (pK [ML_2H] = 5.7).

7. Comparing the stabilities of [(Ru(II)-η^6-*p*-cymene)] complexes formed the stability trend corresponds well to the order of their biological activity.

Complexes of hydroxypyrones with lower stability show only moderate cytotoxicity on various cancer cell lines. The [Ru(II)-η^6-*p*-cymene] binding ability of the picolinate ligands represents the following order: 6-Mepik < pik < dipik. The increased stability of the complex of pik compared to that of the (O,O) donor hydroxypyrones may be related to its higher biological activity. The complex of dipik possesses *ca*. one order of magnitude lower logK* value than pik does resulting in less favourable formation of the chlorido [(Ru(II)-η^6-*p*-cymene)(L)(Cl)] complex. The coordination of the negatively charged chloride ions to the neutral [(Ru(II)-η^6-*p*-cymene)(L)(H_2O)] of dipik with the non-coordinated COO^- moiety seems to be less pronounced than to the positively charged aqua complex of pik and 6-Mepik. This finding may contribute to the explanation of the lower biological activity of complex dipik compared with that of pik. The readiness of the dipik complex for the aquation may lead

to an easier interaction with blood serum components via replacing the coordinated water molecule, while the neutral complex [(Ru(II)-η^6-*p*-cymene)(L)(Cl)] of pik can remain more intact during the transport processes facilitating its absorption across the cancer cell membranes. The hydroxythiopyr(id)one ligands form complexes of significantly higher stability compared with the hydroxypyrones correlated with their biologically more active cytotoxicity.

8. Fluorescence measurements were also performed on the binding properties of a [Ru(II)-η^6-*p*-cymene], a [Ru(II)-η^6-*p*-cymene]-picolinate and [Ru(II)-η^6-*p*-cymene]-ethyl maltolate towards HSA to the drug binding site I. and we found the the [Ru^{II}-η^6-*p*-cymene] can bind the HSA.

The fluorescence data indicates the presence of pik with strong binding ability to the [Ru(II)-η^6-*p*-cymene] hinders the formation of [Ru(II)-η^6-*p*-cymene]-protein adduct. The binding of [Ru(II)-η^6-*p*-cymene] (without ligands) to HSA is a relatively slow process, and the equilibrium is not complete after 2 hours incubation time while in case of the ethyl-maltolato complex the interaction is rather fast. After 24 h incubation the effect of increasing concentration of [Ru(II)-η^6-*p*-cymene] and its ethyl-maltolato complex on the protein fluorescence, namely the quenching of the fluorescence emission intensity is quite similar. We have concluded that the coordination of ethyl maltol facilitates the formation of the [Ru(II)-η^6-*p*-cymene]-albumin adduct. Probably the HSA can displace the ethyl maltol bound moderately , while without coordinating ligand the [Ru(II)-η^6-*p*-cymene] exists in the form [$M_2(OH)_3$], and as its dissociation process is slow the formation of the [Ru(II)-η^6-*p*-cymene]-albumin adduct needs more time.

5. Practical applications of the results

In our research we determined the composition and stability of anticancer [Ru(II)-η^6-*p*-cymene] complexes and different hydroxy-pyridincarboxylic acid derivatives with metal ions which can play important role of the Alzheimer's disease. In order to establish structure–stability–activity relationships the characterization of the stability of these complexes, the knowledge of the speciation and the most plausible chemical forms in aqueous solution is mandatory. Equilibrium solution studies are the first approach to characterize their properties in water so the predominant complex formed in physiological conditions is predictable. We

studied the interaction of the ligands, metal ions and their complexes with a blood serum protein (human serum albumin), which interaction can influence the pharmacokinetics properties of the drugs.

6. Publications

6.1. Papers related to the Theses published in refereed journals

É. Sija, N. V. Nagy, V. Gandin, C. Marzano, T. Jakusch, A. Dean, V. B. Di Marco, T. Kiss

Hydroxypyridinecarboxylic Acid Derivatives Influencing Metal Ion Levels in the Brain: Equilibrium Complexation with Cu(II) and Zn(II).

Polyhedron

accepted IF: 1.813

É. Sija, Christian G. Hartinger, Bernhard K. Keppler, Tamás Kiss, Éva A. Enyedy

Solution Equilibrium Studies of Anticancer Ruthenium(II)-η6-p-cymene Complexes of Pyridinecarboxylic Acids

Polyhedron

67 (2014) 51–58 IF: 1.813

É. A. Enyedy, **É. Sija,** T. Jakusch, C. G. Hartinger, W. Kandioller, B. K. Keppler, T. Kiss

Solution Equilibria of Anticancer Ruthenium(II)-(eta6-p-Cymene)-Hydroxy(thio)pyr(id)-one Complexes: Impact of Sulfur vs. Oxygen Donor Systems on the Speciation and Bioactivity

Journal of Inorganic Biochemistry

127 (2013) 161–168 IF: 3.197

A. Dean, **É. Sija,** É. Zsigó, M. G. Ferlin, D. Marton, V. Gandin, C. Marzano, P. Pastore, D. Badocco, A. Venzoe, R. Bertani, T. Kiss, V. B. Di Marco

New possible chelating agents for Iron and Aluminium: 4-hydroxy-5-methyl-3-pyridinecarboxylic acid and 1,5-dimethyl-4-hydroxy-3- pyridinecarboxylic acid

European Journal of Inorganic Chemistry

2013 (2013) 1310–1318 IF: 3.120

É. Sija, A. Dean, T. Jakusch, V. B. Di Marco, A. Venzo, T. Kiss

Interactions of pyridinecarboxylic acid chelators with brain metal ions: Cu(II), Zn(II) and Al(III)

Monatshefte für Chemie-Chemical Monthly

2011 (142) 399–410 IF: 1.532

6.2. Book chapter related to the Theses

É. Sija, A. Dean, T. Jakusch, V. B. Di Marco, A. Venzo, T. Kiss

Interactions of pyridinecarboxylic acid chelators with brain metal ions: Cu(II), Zn(II), and Al(III)

Wolfgang Linert, Henryk Kozlowski (szerk.) Metal Ions in Neurological Systems Wien: Springer,

2012. pp. 199–210. (ISBN: 978-3-7091-1000-3)

6.3. Other paper published in refereed journal

T. Kiss, T. Jakusch, B. Gyurcsik, A. Lakatos, É. A. Enyedy, **É. Sija**

Application of modelling calculations in the description of metal ion distribution of bioactive compounds in biological systems
Coordination Chemistry Reviews

2012 (256) 125–132 IF: 11.016

7. Conference presentations

Sija É., A. Dean, Kiss T.

Hidroxi-piridin-karbonsavak, mint lehetséges fémion-kelátorok a neurodegeneratív betegségek kezelésében,

45. Komplex Kémiai Kollokvium, 2010, Mátraháza, Hungary (oral presentation)

Sija É., A. Dean, Jakusch T., V. B. Di Marco, Kiss T.

Hidroxi-piridin-karbonsavak, mint lehetséges fémion-kelátorok a neurodegeneratív betegségek kezelésében

Kémiai Előadói Napok, 2010, Szeged, Hungary (oral presentation)

Éva Sija, A. Dean, T. Kiss

Hydroxypyridinecarboxylic acids as possible chelating agents in the therapy of neurodegenerative disorders

5th Central European Conference – Chemistry towards Biology, 2010, Primosten, Croatia (poster presentation)

Sija É., Enyedy É. A., Jakusch T., C. G. Hartinger, B. Keppler, Kiss T.

Antitumor hatású Ru(eta6-p-cimol)-pir(idin)on típusú komplexek oldategyensúlyi vizsgálata

MKE 1. Nemzeti Konferencia, 2011, Sopron, Hungary (poster presentation)

Jakusch T., Enyedy É. A., **Sija É.,** Kiss T.

Rákellenes ruténiumkomplexek oldatkémiája

MKE 1. Nemzeti Konferencia, 2011, Sopron, Hungary (oral presentation)

É. Sija, É. A. Enyedy, T. Jakusch, C. G. Hartinger, B. K. Keppler, T. Kiss

Speciation Charachterization of Antitumor Ru(II)-Complexes

Workshop, METAL CONTAINING DRUGS, Meeting of the Inorganic Chemistry Committee of the Szeged Branch of HAS, (4th ECCLS) University of Szeged, Hungary (oral presentation)

É. Sija, É. A. Enyedy, T. Jakusch, C. G. Hartinger, B. K. Keppler, T. Kiss

Solution Equilibrium Studies of Ru(eta6-p-cymene)-(thio)pyr(id)one Complexes with Anticancer Activity; The Characterization of Anticancer Drug Candidate Ru(II) Complexes in Aqueous Solution

4th Europan Conference on Chemistry for Life Sciences, 2011, Budapest, Hungary (poster presentation)

A. Dean, É. Zsigó, **É. Sija,** M.G. Ferlin, D. Badocco, P. Pastore, A. Venzo, R. Bertani, T. Kiss, V. B. Di Marco

Chemical evaluation of hydroxypyridinecarboxylic acids as new possible chelating agents for iron and aluminium,

4th Europan Conference on Chemistry for Life Sciences, 2011, Budapest, Hungary (poster presentation)

T. Jakusch, **É. Sija,** É. A. Enyedy, C.G. Hartinger, B.K. Keppler, T. Kiss

Solution Equilibrium Studies of Ternary Complexes Formed Between Bidentate (O,O; O,N; O,S) Ligands and RuIIIEDTA or RuII(eta6-p- cymene); The Characterization of Anticancer Drug Candidate (RuII/III) Complexes in Aqueous Solution

4th Europan Conference on Chemistry for Life Sciences, 2011, Budapest, Hungary (oral presentation)

T. Kiss, T Jakusch, **É. Sija,** É. A. Enyedy, C. G. Hartinger, B. K. Keppler

Characterization of Anticancer Ru(II, III) Compounds in Aqueous Solution

11th ISABC, International Symposium on Applied Bioinorganic Chemistry, 2011, Barcelona, Spain (poster presentation)

T. Kiss, T. Jakusch, **É. Sija,** É. A. Enyedy, C. G. Hartinger, B. K. Keppler

Biospeciation of Anticancer Ru(II, III) Compounds

12th Eurasian Conference on Chemical Sciences, 2012, Corfu, Greece (poster presentation)

Sija É., Jakusch T., C.G. Hartinger, B.K. Keppler, Kiss T., Enyedy É.A.

Rákellenes hatású Ru(eta6-p-cimol)-pir(idin)on típusú komplexek oldategyensúlyi vizsgálata

46. Komplex Kémiai Kollokvium, 2012, Mátrafüred, Hungary (oral presentation)

É. A. Enyedy, O. Dömötör, **É. Sija,** T. Jakusch, C. G. Hartinger, B. K Keppler, T Kiss

Comparative solution equilibrium study on $[Rh(III)(eta5\text{-}Cp^{*})]^{2+}$ and $[Ru(II)(eta6\text{-}p\text{-}cymene)]^{2+}$ ternary complexes formed with various bidentate ligands

EUROBIC 11, 2012, Granada, Spain (poster presentation)

T. Kiss, T. Jakusch, **É. Sija,** É. A. Enyedy, C. G. Hartinger, B. K. Keppler

Bioequilibria of anticancer Ru(II,III) compounds

EUROBIC 11, 2012, Granada, Spain (oral presentation)

T. Jakusch, **É. Sija,** É. A. Enyedy, T. Kiss, C. G. Hartinger, B. K. Keppler

Bioequilibria of anticancer Ru(II,III) compounds

40th International Conference on Coordination Chemistry (ICCC40), 2012, Valencia, Spain (poster presentation)

É. Sija, V.B. Di Marco, T. Jakusch, A. Dean, A. Venzo, T. Kiss

Complexation of Al(III) with hydroxipyridine(di)carboxylic acids, as a new possible chelating agents in neurodegenerative disorders

The Tenth Anniversary Keele Meeting on Aluminium, 2013 Winchester, England (poster presentation – poster awards)

Sija É., Jakusch T., V. B. Di Marco, A. Dean, Kiss T.

Hidroxi-piridinkarbonsavak, mint lehetséges fémkelátorok az Alzheimer-kór terápiájában

47. Komplexkémiai Kollokvium, 2013, Mátraháza, Hungary (oral presentation)

É Sija, T. Jakusch, V. Di Marco, A. Dean, T. Kiss

Hydroxy-pyridine-(di)carboxylic acids as new possible metal chelating agents in neurodegenerative disorders

International Conference on Coordination and Bioinorganic Chemistry (ICCBIC), 2013, Smolenice, Slovakia (oral presentation)

Full journal papers, total: 6
related to the topic of the Theses: 5
cumulative impact factor, total: 22.491
related to the topic of the Theses: 11.475