THESES OF PH.D. DISSERTATION

ANTITUMOR GALLIUM AND PLATINUM-GROUP METAL COMPLEXES: SOLUTION CHEMISTRY AND INTERACTION WITH BLOOD SERUM PROTEINS AND DNA

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I. INTRODUCTION

One of the largest medical challenges of the 20th and present centuries is the treatment of tumor diseases. In point of fact these clinical aspects show both in progression and in appearance various pictures, accordingly various treatment strategies are required. Surgical resection, radiotherapy, medication or their combination are available depending on the type, progression and localization of a tumor. Chemo-, and hormone therapeutics and the more and more successful immunotherapeutics belong to the latest group. Cisplatin (*cis*-[Pt(II)$Cl_2(NH_3)_2$]) is used in chemotherapy since almost 40 years. It is highly effective against testicular-, ovarian- and head-neck cancers. The use of cisplatin is however severely limited by its serious side effects and intrinsic or acquired resistance accompanying the therapy. Two other Pt-containing derivatives carboplatin and oxaliplatin (*cis*-[Pt(II)(ciclobutan-1,1-dicarboxylate)$(NH_3)_2$] and [Pt(II)((1R,2R)-1,2-ciklohexanediamin)oxalate]) are also in clinical use so far. These complexes have partly improved side effect profile and different spectrum of toxicity, but cross resistance still exists between these compounds. This has prompted chemists to employ various strategies in the development of new metal-based anticancer agents with different mechanisms of action.

In this context, complexes of the neighboring transition metals such as Ru, Au and group 13 metal Ga have received considerable attention as possible alternatives to Pt anticancer agents; their anticancer activity was tested *in vitro* and/or *in vivo*. Recently Ru(III)-based complexes such as KP1019 (HInd *trans*-[Ru(III)$Cl_4(Ind)_2$]; Ind = indazole) (and its sodium salt KP1339) and NAMI-A (HIm *trans*-[Ru(III)Cl_4(Im)(DMSO)]; Im = imidazole; DMSO = dimethyl sulfoxide) are promising in clinical aspect as well. The former complex showed in phase I/II clinical studies outstanding activity against colorectal tumors and exhibited low general toxicity. NAMI-A was ineffective in *in vitro* experiments but its antimetastatic activity was proven in clinical trials. Ruthenium complexes were developed originally as functional analogs of cisplatin, hence DNA was supposed to be as their primary target for a long time. Now the co-existence of protein targets of these complexes is more likely.

Gallium complexes KP46 ([*tris*-(8-hydroxyquinolinato)Ga(III)]) and [*tris*-maltolato-Ga(III)] (maltol = 3-hydroxy-2-methyl-4H-piran-4-on) are tested in clinical trials as well and their supposed targets are proteins exclusively. Ribonucleotide reductase is considered as the primary target, which catalyzes the reduction of ribonucleotides to deoxyribonucleotides required for DNA synthesis and its level is often elevated in malignant tumor cells. Like in case of Ru(III)-complexes the role of serum proteins is also assumed as other reason for tumor selectivity. The selective cellular uptake of Ga(III) species can be achieved via transferrin (Tf), which is the main iron transporter protein in blood serum and efficient carrier for other metal ions.

The selectivity is guaranteed by the overexpression of Tf receptors on tumor cells as a cause of high iron demand of quick proliferating tumor tissues. The other important transport protein is the human serum albumin (HSA). According to the results of recent studies, this protein is able to accumulate selectively in tumor tissues as well owing to the enhanced retention and permeability. Besides active transport mechanisms through vascular endothel are presented close to cancer tissues. Furthermore transport proteins can facilitate the sustained presence of a drug in blood flow and can delay its premature excretion from the body. Nowadays special chemical moieties are built on drugs in several cases that support the binding to serum proteins, thus the targeting.

II. AIMS AND OBJECTIVES

It is important to clarify the following questions in order to understand comprehensively the effect of an agent with bioactivity: (i) what the actual chemical form is in certain compartments; (ii) exactly where and how it exerts the effect; (iii) how much time it spends in human body and than (iv) by which organs it is excreted. This kind of experiments is of special importance in case of metal complexes that may undergo more extreme changes compared to traditional organic drugs. Only incomplete and limited information is available in the field of metallodrugs regarding to the above mentioned mechanisms. Traditional solution equilibrium studies are considerably useful tools in terms of various pharmacokinetic questions. Investigations of the interactions with serum proteins can promote the wider understanding of distribution and biotransfer processes. Further important step is the exploration of probable targets.

Our goal was to characterize the chosen metal complexes with the aid of traditional solution equilibrium techniques, and studies on their interactions with serum proteins human serum albumin and human transferrin are also involved. In certain cases interactions with DNA as possible target were investigated as well. Since literature data are fairly incomplete in this research area our approaches were selected according to the former works on the chosen metal complexes in order to complete and/or confirm and/or traverse the previously published results.

Consequently the experiments carried out are the followings (for the abbreviations see figure 1):

1. Solution equilibrium studies
    a.) of $[Rh(\eta^5\text{-}Cp^*)]^{2+}$ cation and its complexes formed with (O,O), (O,N), and (O,S) donor ligands;
    b.) and in case of Ga(III) complexes of 8HQ (8-hydroxyquinoline), 8HQS (8-hydroxyquinoline-5-sulfonate), maltol and thiomaltol.

2. We investigated the interaction between HSA and:
   a.) [Rh(η^5-Cp*)]-dhp and -picolinic acid complexes;
   b.) Ga(III) *tris*-ligand complexes of 8HQ and maltol and
   c.) some Pt(IV)/(II) complexes;
   d.) some Ru(III)/(II)- and Os(II) complexes.
3. Furthermore in case of chosen Ga(III) complexes interaction with Tf was studied as well.
4. Interaction with DNA was investigated in case of Ru(III)-salan and Ru(II)-phenantroline complexes.
5. The binding reaction of cytotoxic reduced Schiff-base coumarin ligands towards HSA was used to test the fluorometric method and the possibility for computational evaluation with PSEQUAD program.

III. EXPERIMENTAL METHODS

Traditional solution equilibrium experiments were carried out in case of [Rh(η^5-Cp*)]- and Ga(III) complexes and coumarin ligands. The applied conditions in the experiments with proteins or DNA were chosen depending on the chemical systems, the pH corresponded always to the physiological value of the blood serum (pH = 7.40).

pH-potentiometry

pH-potentiometric titrations were used for [Rh(η^5-Cp*)]- and Ga(III) complexes in aqueous solution at 25 °C using mainly 0.20 M KCl as background electrolyte. Additionally measurements in 30, and 60% (m/m) DMSO/water mixtures were performed in case of Ga(III)–maltol, –8HQ and –8HQS systems as well. Ligand deprotonation constants (pK_a) and overall stability constants (logβ) of the metal complexes were determined using the computer programs HYPERQUAD and PSEQUAD, respectively.

^{1}H NMR spectroscopy

First of all ^{1}H NMR spectroscopy was used to confirm the speciation in course of experiments with [Rh(η^5-Cp*)]- and Ga(III) complexes. Interactions between HSA or apoTf and Pt(II)-, [Rh(η^5-Cp*)]-, and Ga(III) complexes were studied using ^{1}H NMR and STD (*saturation transfer difference*) techniques. The samples contained 10% (v/v) D_2O and 4,4-dimethyl-4-silapentane-1-sulfonic acid (DSS) as inner standard, and WATERGATE water suppression pulse sequence was used in all cases. Since KP46 has quite low water solubility the ^{1}H and STD NMR spectra were

recorded at 20 μM concentration by a 600 MHz spectrometer equipped with a cryo probe. For quantitative evaluations PSEQUAD program were used.

UV-vis spectrophotometry

This technique was used for traditional solution equilibrium studies on [Rh(η^5-Cp*)]- and Ga(III) complexes and coumarin ligands. Depending on the chemical systems metal-to-ligand charge transfer bands and/or ligand bands were monitored. Based on the pH-dependent spectral changes stability constants of the metal complexes and/or ligand proton dissociation constants were calculated with the computer program PSEQUAD. Additionally hydrolytic behavior of Pt(II)-, Pt(IV)-, *bis*-indazole-Ru(III)- and Ru/Os(II)-nitrosyl complexes were followed with spectrophotometry. In certain cases (in)direct information could be obtained referring the interactions with proteins. Binding to Cys34 on HSA in case of Pt(IV) complexes was studied indirectly with the aid of 2,2'-dithiodipyridine (DTDP).

Spectrofluorometry

Interactions between macromolecules and metal complexes or ligands were followed mainly by spectrofluorometric methods. Accordingly the following experiments were carried out: Trp quenching measurements at site I of HSA, Tyr quenching measurements at iron(III) binding site of apoTf, and fluorescent markers were used as well. These are in case of HSA: warfarin (WF, site I), dansylglycine (DG, site II) and bilirubin (BR, site I). Interactions with DNA were followed with the help of: ethidium bromide (EB, DNA intercalator) and 4',6-diamidino-2-phenylindole (DAPI, DNA minor groove binder). Ru(II)-phen complexes and KP46 possess intrinsic fluorescence which allowed us to monitor the changes of their emission spectra in certain experiments. The pH-dependent complex formation process could be followed in case of Ga(III)-8HQ system via fluorometry, and stability constants were evaluated. In course of our fluorometric studies steady-state and time resolved (using time correlated single photon counting method) measurements were carried out. The measurements were evaluated usually with PSEQUAD program.

Ultrafiltration

In the case of the ultrafiltration measurements the high- (macromolecule and the bound small molecules) and low- (free small molecules) molecular mass fractions were separated after sufficient incubation time using a membrane filter unit. The protein free (LMM) fractions were studied by spectrophotometric-, fluorometric- or ICP-MS techniques.

Capillary zone electrophoresis (CZE)

The interaction of HSA with *bis*-indazole-Ru(III)- and [Rh(η^5-Cp*)] complexes were studied using this method as well. The electrophoretic mobility of HSA and the

protein-bound metal complexes differs from the mobility of unbound complexes (or in case of ternary systems from the mobility of the site marker). The peak height or integral values of the non-bound metal complex, ligand, or site marker were used in order to obtain quantitative information.

The chemical structures and abbreviations of the investigated metal complexes and ligands are shown in figure 1.

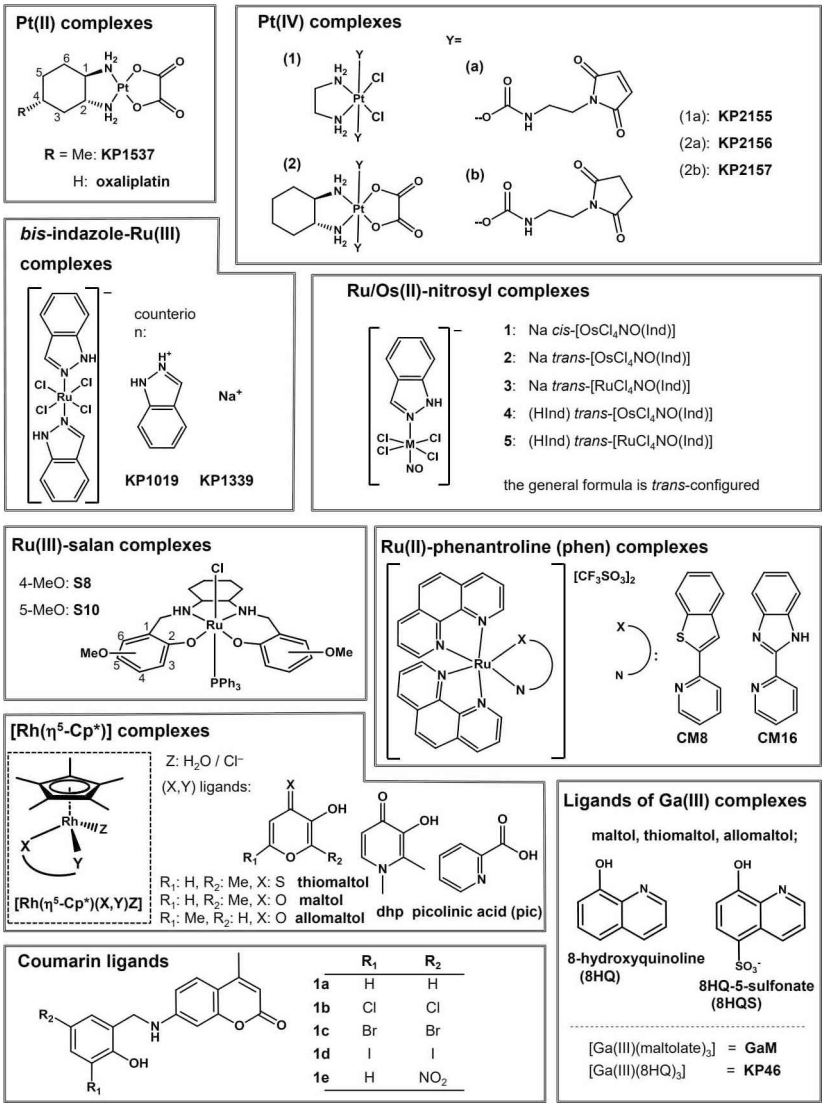

Figure 1. Chemical structures and abbreviations of the investigated metal complexes and ligands.

IV. NEW SCIENTIFIC RESULTS

1. Oxaliplatin and KP1537

1.1. Hydrolytic behavior of KP1537 and oxaliplatin was monitored by UV spectrophotometric measurements at physiological pH at 25 and 37 °C and in the presence of 100 mM, 23 mM, and 0 mM NaCl; the impact of 13 mM $NaHCO_3$ was tested as well. Decomposition of the original complexes in presence of chloride ions is faster than in pure aqueous media, however the hydrolysis of samples containing 100 mM chloride is still a slow process (> 4 days).

- In the solution of KP1537 precipitate as yellow needles appeared in the presence of chloride ions as a result of the low water solubility of the formed *di*chlorido complex.
- Apart from this, the hydrolytic behavior of the two metal complexes is rather similar in terms of the kinetics.

1.2. Their interaction with HSA was followed by STD NMR, ultrafiltration–ICP-MS and fluorometric methods.

- The reaction of both metal complexes with HSA was found to be fairly slow since the equilibrium could not be reached during 48 h.
- The level of binding towards HSA was increased with increasing concentration of chloride ions.
- The two Pt complexes are bound to HSA in similar extent with moderate affinity.
- The hydrophobic binding pockets, sites I and II on HSA are not involved in the binding event towards the protein.
- The role of other serum proteins – referring those Pt(II)-complexes binding ability – is feasible, one of those may the often referred γ-globulins.

1.3. According to our results the different profile of KP1537 in its biological action (regarding the side effect) compared to oxaliplatin can not be explained by altered hydrolytic- or serum protein binding properties.

2. Interaction of maleimide-functionalized Pt(IV) complexes with HSA

2.1. In our work it was investigated whether KP2155 and KP2156 complexes are able to bind to the free Cys34 on HSA through their maleimide functional group or not. The binding was monitored using an indirect spectrophotometric technique [3].

- Prior to the measurements with HSA reliable experimental method has been developed to determine the accessible portion of Cys thiol(ate) groups on HSA.
- It was ascertained that HSA interacts with the DTDP reagent in only one-step reaction unlike small thiol-models (GSH and Cys). The applied temperature and pH conditions have been also optimized.

2.2. Subsequently we estimated indirectly the 1-to-1 adduct formation between KP2155 or KP2156 and HSA, the binding took place practically in a quantitative manner [3].

2.3. Coupling to the protein can assure the prolonged presence of these Pt(IV) complexes in the blood flow [3].

3. Ruthenium and osmium complexes

3.1. Binding of KP1019 and KP1339 towards HSA

3.1.1. The aim of this part of my work was to study the fast binding process of these complexes by secondary interactions towards albumin using spectrofluorometry, ultrafiltration–UV-Vis and CZE techniques [2].

- The binding event was found to be rather fast, it occurred in few minutes. Both KP1019 and KP1339 are able to bind to both hydrophobic sites on HSA (site I and II) with moderately strong affinity and no significant differences were found in the binding ability at these binding sites on the basis of the spectrofluorometric binding constants.
- The two complexes showed rather similar affinity towards each binding site, thus the counter ion does not affect the binding of *trans*-[tetrachlorido*bis*(1H-indazole)ruthenate(III)] anions to HSA.
- CZE–UV–vis and ultrafiltration–UV–vis measurements also confirmed the results of the spectrofluorometric experiments. Direct ultrafiltration studies showed the binding of two equivalent metal complexes on HSA.
- A result of clinical relevance is the finding that KP1339 and KP1019 are able to compete with BR (an endogenous metabolite) for its binding site under physiological conditions and may adversely affect the treatment of patients with elevated BR levels.

3.1.2. Our investigations pointed out, that prior to the relatively slow formation of the adducts via coordinative bonds on the protein a fast secondary interaction occurs, that may be suitable to avoid the premature excretion of the complexes from blood serum [2].

3.2. *Ru(II)-, Os(II)-nitrosyl complexes: interaction with HSA*

3.2.1. The interaction with HSA in case of structurally analogous Ru(II)- and Os(II)-nitrosyl complexes of KP1019 was studied as well.

- No significant differences could be observed between the binding affinities of the studied metal complexes (**1**-**5**) to HSA. Only complex **5** showed somewhat lower affinity towards the protein.
- Experiments with human serum pointed out the primary role of HSA in the transport process of the complexes.
- Striking difference between these complexes and KP1019 was found, namely the displacement constants calculated for site I and II are about one order of magnitude lower in case of the nitrosyl complexes, at the same time ultrafiltration studies showed no such kind of differences. Therefore existence of further – for nitrosyl complexes available – binding sites on HSA is feasible.

4. Ru(III)-salan and Ru(II)-phenantroline complexes: binding towards DNA

4.1. One of our main goals was to characterize quantitatively the interactions of these complexes with DNA, therefore fluorometric steady-state and time resolved measurements were carried out.

- A fluorometric method was elaborated to determine the binding site size (expressed in number of nucleotides) and binding affinity towards DNA of the well known DNA marker molecules such as EB and DAPI. It should be noted that calculated binding site size reflects not only the real space demand of a marker but the occurence of the preferred base sequence within the nucleotide chain as well. [8].

4.2. In case of Ru(III)-salan complexes (S8, S10) [8]:

- intercalative binding mode of the complexes was found, and intercalation takes place most probably from the minor groove.
- The displacement was confirmed by fluorescence lifetime measurements.
- Differences found in cytotoxicity do not seem to originate from the distinct mode of binding to DNA.

4.3. Ru(II)-phen complexes (CM8, CM16):

- showed relatively high binding affinity and binding frequency into the minor groove of DNA.
- The two coordinated phenantroline ligands of the complexes fit most probably via extra helical stacking into the minor groove, but the third ligand is not sufficiently extended for actual intercalation.

4.4. Displacement constants for both Ru(III)-salan and Ru(II)-phenantroline complexes were calculated, however these values are based on the site size of the given markers, and the site size (or binding frequency) of the complexes is most probably not identical with those [8].

5. [Rh(η^5-Cp*)] complexes

5.1. The primary goal for [Rh(η^5-Cp*)] complexes was to describe the solution equilibria of [Rh(η^5-Cp*)Z_3] (Z = H_2O/Cl^-) and its complexes with various (O,O), (O,N) and (O,S) bidentate ligands (see figure 1.) in pure aqueous phase [5,9].

- Chloride ions are possible coordinating ligands in solution and are able to shift the hydrolysis of [Rh(η^5-Cp*)Z_3] to higher pH values.
- Exclusive formation of the *mono*-ligand complexes [MLZ] and [MLH_{-1}] (=[ML(OH)]) in case of (O,O) donor maltol, allomaltol and dhp and (O,N) donor pic ligands were detected.
- pK_a-s of the [MLZ] complexes are relatively high values (9.32-11.90).
- *Bis*-ligand complex formation ([ML_2H], [ML_2]) with the (O,S) donor thiomaltol could be observed in the presence of ligand excess.
- The general stability trend for complexes [MLZ] is: (O,O) < (O,N) < (O,S).
- Chloride ions act as competitive ligands and are able to shift the formation of complex [MLZ] to more basic pH values.
- The *mono*-complex of thiomaltol is stable only at acidic pH values and formation of mixed hydroxido oligomer species is probable at physiological pH.
- Based on model calculations only complexes [MLZ] formed with dhp and pic show sufficient stability at physiological pH at micromolar concentration range among the studied (O,O) and (O,N) donor ligands.
- The aquation of complexes [MLCl] takes place to different extents which may have impact on their biological activities.

5.2. As a second step to explore the distribution in blood serum, interaction of Rh(η^5-Cp*)Z_3] and its dhp- and pic complexes with HSA was studied by ^{1}H NMR, ultrafiltration, fluorometry and CZE measurements.

- Relative high binding affinity of [Rh(η^5-Cp*)Z_3] and its dhp- and pic complexes towards HSA was found.
- Binding to albumin is partialy followed by displacement of the coordinated ligands. Dissociation of the original metal complexes in case of dhp possessing lower stability is more pronounced compared to pic. Consequently binding on HSA has mostly coordinative nature.

- $[Rh(\eta^5\text{-}Cp^*)Z_3]$ and its dhp- and pic complexes are able to bind to sites I and II as well, however pic complex binds to both sites with lower affinity compared to the former two species.

6. Ga(III) complexes

6.1. The stoichiometry and stability constants of the Ga(III) complexes of maltol, thiomaltol, 8HQ and 8HQS were determined by means of traditional solution equilibrium studies. Our primary goal was to characterize the stability of the *tris*-ligand complexes KP46 and GaM undergoing clinical trials [1,6].

- Owing to the poor water solubility of 8HQ complexes, their stability constants were determined in 30 and 60% (m/m) DMSO-water mixtures by pH-potentiometry. $\log\beta$ values in pure aqueous phase were extrapolated from the former measurements and with the help of the constants of 8HQS calculated in all three media.
- Stability constants for complexes formed with 8HQ were calculated based on fluorometric titrations as well due to their fluorescent features.
- Calculated stability constants obtained by both methods mentioned above are in good agreement with UV spectrophotometric results measured in highly diluted samples.
- *Tris*-ligand complex GaM predominates in the millimolar concentration range, while KP46 is stable in the micromolar range at physiological pH. The stability of GaM is much lower than that of KP46.

6.2. At rather diluted (but physiological relevant, low micromolar) concentration range 8HQ is able to preserve the original entity of the *tris*-complex, however GaM dissociates partly. Accordingly different biodistribution and ligand exchange processes are presumable in the presence of high- and low molecular mass components of human serum [1,6].

6.3. This assumption was confirmed by experiments performed with HSA and apoTf by the aid of ^{1}H NMR, ultrafiltration, UV-Vis, spectrofluorometry and computational docking calculations [6,7].

- According to our measurements and model calculations GaM complex mainly dissociates at therapeutically relevant concentration range and Ga(III) ion is transported mostly by Tf.
- The GaM complex does not bind to HSA only the free maltol itself.
- On the contrary the role of the competitor Tf is not pronounced in case of KP46 owing to the high stability of the metal complex.
- Although binding to HSA does not alter the original coordination mode in the complex, and KP46 is bound mainly to this protein.

6.4. Thus, while GaM is largely dissociated KP46 is transported in its original form in blood serum [6,7].

7. Interaction of anticancer reduced Schiff base coumarin derivatives with HSA

7.1. Our studies on reduced Schiff-base coumarin ligands (**1a-1e**) were used to test the fluorometric method and the possibility for computational evaluation with PSEQUAD program [4].

- Proton dissociation constants of the ligands were determined by UV-Vis spectrophotometry beforehand.
- The simulated emission curves determined from the HSA binding constants are in fairly good agreement with those obtained by experimental data.
- The computer program PSEQUAD can operate with the whole recorded spectra and numerous emitting compounds can be taken into consideration at the same time.
- Coumarin derivatives were bound with rather high affinity at site I of HSA, and this is their primary binding site.
- According to docking calculations derivatives with partly deprotonated phenolic OH-group (**1b**, **1c**, **1d**, **1e**) at physiological pH are bound to HSA at higher extent compared to the completely protonated **1a**.

V. OUTLOOK

The general aim of our work is to point out the necessity of solution equilibrium studies in case of biologically relevant systems. Interactions with macromolecules such as HSA, apoTf and DNA were characterized in both qualitative and quantitative manners, which allowed us the mathematical and chemical modeling of the behavior of the metal complexes in the presence of bioligands at biologically relevant (but experimentally often impractical) concentrations or conditions. The results of this kind of *in vitro* investigations can be used hardly for living organisms in a direct manner, but still can explain the in vivo pharmacokinetic behavior of metal complexes, and it may be possible to propose the synthesis of compounds with improved pharmacokinetic parameters.

9. PUBLICATION LIST

Publications related to the dissertation **ΣIF: 21.66**

[1] É.A. Enyedy*, **O. Dömötör,** E. Varga, T. Kiss, R. Trondl, C.G. Hartinger, B.K. Keppler; **Comparative solution equilibrium studies of anticancer gallium(III) complexes of 8-hydoxyquinoline and hydroxy(thio)pyrone ligands**
J. Inorg. Biochem. 117 (2012) 189-197. IF: 3.197
Independent citations: 7

[2] **O. Dömötör**, C.G. Hartinger*, A.K. Bytzek, T. Kiss, B.K. Keppler, É.A. Enyedy*; **Characterization of the binding sites of the anticancer ruthenium(III) complexes KP1019 and KP1339 on human serum albumin via competition studies**
J. Biol. Inorg. Chem. 18 (2013) 9-17. IF: 3.164
Independent citations: 11

[3] V. Pichler, J. Mayr, P. Heffeter*, **O. Dömötör**, É.A. Enyedy, G. Hermann, D. Groza, G. Köllensperger, M. Galanski, W. Berger, B.K. Keppler, C.R. Kowol*; **Maleimide-functionalised platinum(IV) complexes as a synthetic platform for targeted drug delivery**
Chem. Comm. 49 (2013) 2249-2251. IF: 6.718
Independent citations: 1

[4] **O. Dömötör**, T. Tuccinardi, D. Karcz, M. Walsh, B.S. Creaven, É.A. Enyedy*; **Interaction of anticancer reduced Schiff base coumarin derivatives with human serum albumin investigated by fluorescence quenching and molecular modeling**
Bioorg. Chem. 52(52) (2014) 16-23. IF: 2.141
Independent citations: 1

[5] **O. Dömötör**, S. Aicher, M. Schmidlehner, M.S. Novak, A. Roller, M.A. Jakupec, W. Kandioller, C.G. Hartinger, B.K. Keppler, É.A. Enyedy*; **Antitumor Pentamethylcyclopentadienyl Rhodium Complexes of Maltol and Allomaltol: Synthesis, Solution Speciation and Bioactivity**
J. Inorg. Biochem. 134 (2014) 57-65. IF: 3.274
Independent citations: -

[6] **O. Dömötör**, K. Bali, A. Hetényi, É.A. Enyedy*; **Rákellenes gallium(III)komplexek oldategyensúlyi jellemzése és szérum-fehérjékkel való kölcsönhatásuk vizsgálata,** (Hungarian), (Solution studies of antitumor gallium(III) complexes and their interactions with human serum proteins)
Magyar Kémiai Folyóirat (*Hungarian Journal of Chemistry*)120(2-3) (2014) 127-131. IF: -
Independent citations: -

[7] É.A. Enyedy*, **O. Dömötör**, K. Bali, A. Hetényi, T. Tuccinardi, B.K. Keppler; **Interaction of the anticancer gallium(III) complexes of 8-hydroxyquinoline and maltol with human serum proteins**
J. Biol. Inorg. Chem. (DOI: 10.1007/s00775-014-1211-9) IF: 3.164

[8] **O. Dömötör**, L. Côrte-Real, R.F. M. de Almeida, C.P. Matos, F. Marques, P. Adão, C. Real, É.A. Enyedy, M.H. Garcia, A.I. Tomaz*; **On the mechanism of action of anti-tumoral aminophenolate ruthenium(III) complexes**
Chem. Bio. Chem (prepared for submission, IF: 4,097)

[9] É.A. Enyedy*, **O. Dömötör**, C.M. Hackl, M. Novak, M.A. Jakupec, B.K. Keppler, W. Kandioller; **Solution equilibria and antitumor activity of pentamethylcyclopentadienyl rhodium complexes of picolinic acid and deferiprone**
J. Coord. Chem. (submitted manuscript, IF: 2,212)

Publications related to the topic of the dissertation **ΣIF: 12.94**

1. É.A. Enyedy*, E. Farkas, **O. Dömötör**, M.A. Santos;
Interaction of folic acid and some matrix metalloproteinase (MMP) inhibitor folate-γ-hydroxamate derivatives with Zn(II) and human serum albumin
J. Inorg. Biochem. 105 (2011) 444–453. IF: 3.354
Independent citations: 3

2. A. Rathgeb, A. Böhm, M.S. Novak, A. Gavriluta, **O. Dömötör**, J.B. Tommasino, É.A. Enyedy, S. Shova, S. Meier, M.A. Jakupec, D. Luneau*, V.B. Arion*;
Ruthenium-Nitrosyl Complexes with Glycine, L-Alanine, L-Valine, L-Proline, D-Proline, L-Serine, L-Threonine and L-Tyrosine: Synthesis, X-ray Diffraction Structures, Spectroscopic and Electrochemical Properties and Antiproliferative Activity
Inorg. Chem. 52(5) (2014) 2718–2729. IF: 4.794
Independent citations: 1

3. F. Bacher, **O. Dömötör**, M. Kaltenbrunner, M. Mojović, A. Popović-Bijelić, A. Gräslund, G. Novitchi, A. Ozarowski, L. Filipovic, S. Radulović, É.A. Enyedy*, V.B. Arion*;
Effects of Terminal Dimethylation and Metal Coordination of Proline-2-Formylpyridine Thiosemicarbazone Hybrids on Lipophilicity, Anti-proliferative Activity and hR2 RNR inhibition
Inorg. Chem. 53 (2014) 12595–609. IF: 4.794
Independent citations: -

Oral and poster conference presentations

1. **Dömötör O**., Enyedy É.A., Kiss T. (oral presentation, Hungarian)
Interaction between [bis-indazole-ruthenate(III)]complexes with antitumor activity and human serum albumin with the help of site markers
XXXIII. Chemistry days,2010.10.25-27., Szeged, Hungary.

2. **O. Dömötör**, É.A. Enyedy, T. Kiss, A.K. Bytzek, C.G. Hartinger, B.K. Keppler (poster)
Interaction of the anticancer ruthenium(III) complexes KP1019 and KP1339 with human serum albumin via competition studies
4th European Conference on Chemistry for Life Sciences, 2011.08.31-09.03., Budapest, Hungary.

3. **O.Dömötör.**, E. Varga., C.G. Hartinger, B.K. Keppler, T. Kiss, É.A. Enyedy (oral presentation, Hungarian)
Solution equilibria of antitumor gallium(III) complexes
46. Colloquium on Complex Chemistry,.2012.05.21-23., Mátrafüred, Hungary.

4. **O. Dömötör**, E. Varga, K. Bali, C.G. Hartinger, B.K. Keppler, T. Kiss, É.A. Enyedy (poster)
Solution studies on antitumor gallium(III) complexes and their interactions with human serum proteins
International Symposium on Metal Complexes, 2012.06.18-22., Lisbon, Portugal.
Proceeding in: *Acta of the International Symposia on Metal Complexes*: ISMEC Group Series, Series, 2 (2012) 165-166, (ISSN:2239-2459).

5. É.A. Enyedy, **O. Dömötör,** É. Sija, T. Jakusch, C.G. Hartinger, B.K. Keppler, T. Kiss, (poster)
Comparative solution equilibrium study on $[Rh(III)(\eta^5\text{-}Cp^*)]^{2+}$ and $[Ru(II)(\eta^6\text{-}p\text{-}cymene)]^{2+}$ ternary complexes formed with various bidentate ligands
11th European Biological Inorganic Chemistry Conference, 11, 2012.09.12-16., Granada, Spain.

6. **O. Dömötör**, K. Bali, A. Hetényi, É.A. Enyedy (oral presentation, Hungarian)
Interaction of antitumor Ga(III) complexes with blood serum proteins
47. Colloquium on Complex Chemistry,2013.05.29-31., Mátraháza, Hungary.

7. **O. Dömötör**, R.F.M. de Almeida, C.P. Matos, É.A. Enyedy, A.I. Tomaz (poster)
Interaction of new polydentate Ru(III)-salan complexes with DNA using time resolved and steady state fluorescence spectroscopy
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8. **O. Dömötör,** G. Kiss, J.P. Mészáros, É.A. Enyedy (oral presentation, Hungarian)
Solution equilibria of Rh(III)(η5-Cp*) complexes formed with bidentate N/O/S-donor ligands and their interaction with albumin
48. Colloquium on Complex Chemistry,2014.05.28-30., Siófok, Hungary.

9. É.A. Enyedy, **O. Dömötör**, W. Kandioller, B.K. Keppler (poster)
Solution equilibria of analogous Rh(III)(η^5-Cp*) and Ru(II)(η^6-p-cymene) complexes formed with various bidentate ligands
7th International Symposium on Bioorganometallic Chemistry, 2014.07.22-25., Vienna, Austria.

10. **O. Dömötör**, G. Kiss, J.P. Mészáros, W. Kandioller, B.K. Keppler, É.A. Enyedy (poster)
Complexes of Rh(III)(η^5-Cp*) with N/O-donor bidentate ligands: solution equilibrium and interaction with human serum albumin
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11. J. Mayr, V. Pichler, P. Heffeter, **O. Dömötör**, É.A. Enyedy, G. Hermann, D. Groza, G. Kollensperger, M. Galanski, W. Berger, B.K. Keppler, C.R. Kowol (poster)
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12th European Biological Inorganic Chemistry Conference, 2014.08.24-28., Zurich, Switzerland.
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13. **O. Dömötör O.** (oral presentation, Hungarian)
Solution studies on antitumor gallium(III) complexes and their interactions with human serum proteins
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