Short thesis for the degree of doctor of philosophy (PhD)

Investigation of the physicochemical properties of Bi(III)-complexes formed with triaza and tetraaza ligands for the purpose of developing radiopharmaceuticals

by Dávid Horváth

Supervisors: Dr. Zsolt Baranyai
Dr. Gyula Tircsó

UNIVERSITY OF DEBRECEN

Doctoral School of Chemistry

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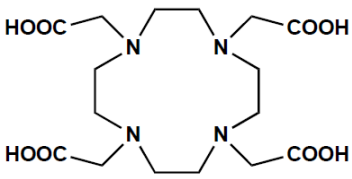
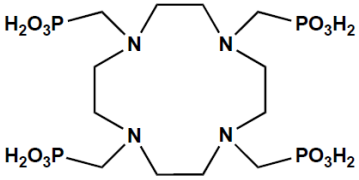
1. Introduction:

Nowadays, modern medicine more and more rely on the application of radioactive isotope containing agents as diagnostics and therapeutics. Among the diagnostic (imaging) modalities Positron Emission Tomography (PET) considered to be the most sensitive imaging technique which require the application of positron emitting isotopes (^{11}C, ^{13}N, ^{18}F, ^{44}Sc, ^{64}Cu, ^{68}Ga). During the PET experiments, a β^+ emitting isotope labelled molecule is administered to the patient via intravenous injection. The emitted positron is annihilates when meets an electron results in the creation of two high energy gamma photons that travel approximately 180 degrees from one another being detected by gamma cameras simultaneously. Another imaging procedure applied in nuclear medicine is Single Photon Emission Computed Tomography (SPECT), in which γ-photon emitting isotopes (^{67}Ga, ^{99m}Tc, ^{111}In, $^{123/131}$I) with γ-energy greater than 70 keV are used. Nearby the diagnostic applications α and β^- emitting isotopes (pl. ^{90}Y, ^{177}Lu, ^{149}Tb, ^{211}At, $^{223/224}$Ra, ^{225}Ac, $^{226/227}$Th) are proposed for the therapy of different diseases and tumors. Bismuth has two α emitting isotopes ^{212}Bi are ^{213}Bi which are being used in **T**argeted **A**lpha **T**herapy of different cancers. The TAT application of $^{212/213}$Bi isotopes is propagated by their accessibility from ^{212}Pb/^{212}Bi and ^{225}Ac/^{213}Bi generators. The *in vivo* use of $^{212/213}$Bi isotopes is possible only in the form of thermodynamically stabile and kinetically inert Bi(III) complexes. Based on the literature data, such Bi(III) complexes are formed with the macrocyclic DOTA and the open-chain DTPA ligands and their derivatives. Our work is related to the above-mentioned topic, with a special emphasis on the following goals:

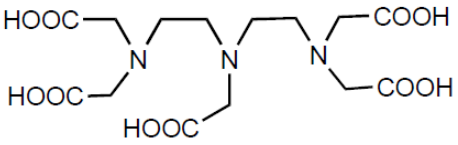
- Characterization of equilibrium, formation and dissociation kinetic properties of the $[Bi(DOTA)]^-$ and $[Bi(DOTP)]^{5-}$ complexes.
- Study of structural features of the $[Bi(DOTP)]^{5-}$ complex in solution
- Optimization of the radiolabeling procedure of H_4DOTA with $^{213}Bi(III)$ isotope.
- Exploring the thermodynamic and kinetic properties of the $[Bi(AAZTA)]^-$, $[Bi(AAZTA\text{-}C4\text{-}COO^-)]^{2-}$ and $[Bi(AAZTA\text{-}C4\text{-}TATE)]^-$ complexes.
- Investigation of the structural properties of the $[Bi(AAZTA)]^-$ and $[Bi(AAZTA\text{-}C4\text{-}COO^-)]^{2-}$ complexes in solution and in solid state.
- Radiolabeling of AAZTA-C4-TATE with $^{205/206}Bi$
- *Ex vivo* and *in vitro* biodistribution studies of the $[^{205/206}Bi][Bi(AAZTA\text{-}C4\text{-}TATE)]^-$ conjugate in animal models using AR42J cell line.



DOTA



DOTP



DTPA

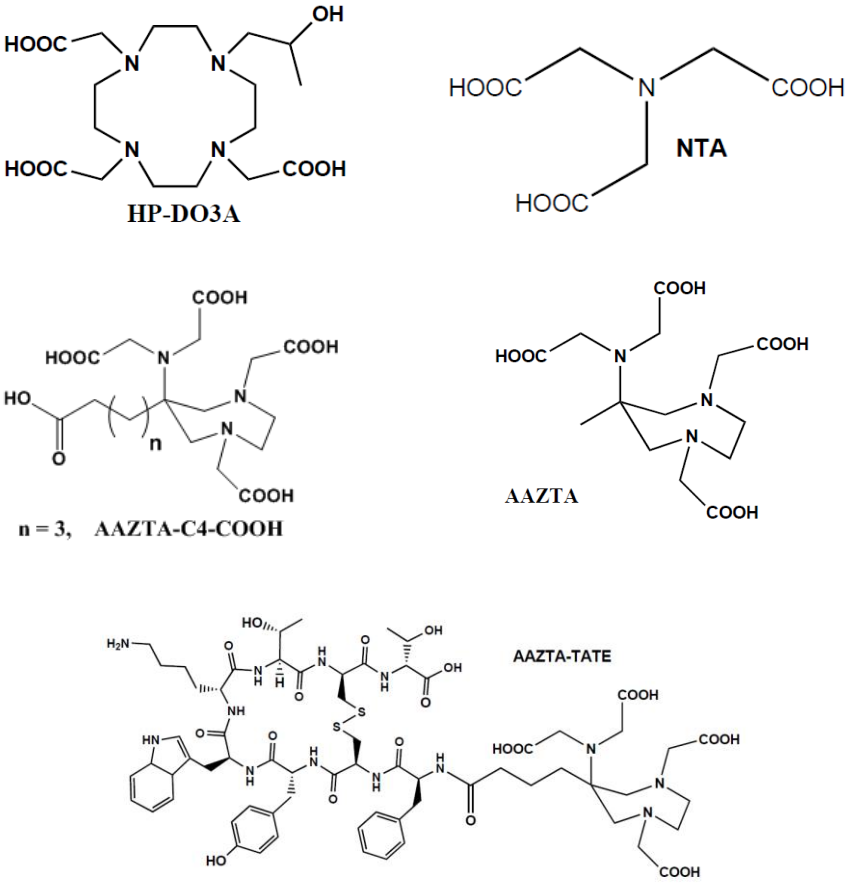


Figure 1. Structure of the studied ligands

2. Materials and methods:

H_4DOTA, H_5DTPA and H_3NTA ligands were obtained from commercial sources (Sigma), while H_8DOTP, H_4AAZTA, H_5AAZTA-C4, H_4AAZTA-C4-TATE and H_3HP-DO3A were provided by Bracco Imaging

Spa.. The $Bi(ClO_4)_3$ stock solution was prepared by dissolving Bi_2O_3 in 6 M perchloric acid and its concentration was determined complexometric titration with Na_2H_2EDTA using xilenolorange as an indicator at pH=1. The H^+ concentration of the $Bi(ClO_4)_3$ stock solution was determined by pH-potentiometric titration in the presence of two-fold Na_2H_2EDTA excess. Bi(III) complexes were prepared by mixing $Bi(ClO_4)_3$ and ligand at 1:1 metal-to-ligand ratio. During the preparation of the Bi(III) complexes $Bi(ClO_4)_3$ solution was added dropwise to solution of the ligands being stirred vigorously. The pH of the solution was set to 5.0-7.0 by the addition of concentrated NaOH solution. The protonation constants of the ligands and Bi(III) complexes were **determined by pH-potentiometric titration** with the Metrohm *888 Titrando* automatic titrator and a *Metrohm-6.0234.110* combined glass electrode. The titrations were carried out with a 0.2 M NaOH in 6 cm^3 solutions. The solutions were stirred, and N_2 was bubbled through them in order to avoid the absorption of CO_2. Titrations were performed at constant temperature (25±0.1°C) and ionic strength (0.15 M $NaClO_4$). 0.2 M NaOH solution was standardized by titrating known amount of 0.0500 M KH-phthalate solution. For the two-point calibration of the pH meter, 0.0500 M KH-phthalate buffer (pH = 4.005) and 0.0100 M borax buffer kept under a N_2 atmosphere (pH = 9.180) were used. To calculate the $[H^+]$ from the measured pH values, the method proposed by *Irving* et al. was used. The stability and protonation constants were calculated from the V_{base}-pH data pairs by using the PSEQUAD program.

Spectrophotometric measurements were performed with a *PerkinElmer Lambda 365* UV-Vis spectrophotometer at 0 and 25°C, in the 240-310 nm range in 1.0 cm cuvette.

A *Hewlett-Packard HP*^{3D} device was used for **the capillary zone electrophoresis (CZE) measurements**. A bare fused-silica capillary (*Agilent*) 64 cm x 50 μm (i.d.) was used during the separations (with an effective length of 56 cm). Prior to its first use, the capillary was washed with 1 M NaOH (15 min), 0.1 M NaOH (30 min) and buffer solution (30 min). During the measurements, the sample solutions were introduced on the anodic side of the capillary with hydrodynamic injection (50 mbar, 6 s). Before the experiments, the capillary was preconditioned with a 150 mM disodium hydrogen phosphate solution, pH=7.4 (for 3 minutes). The separation was carried out at 10°C using a voltage of 20 kV. After separation the capillary was flushed by 0.1 M NaOH (3 min) and buffer (3 min) solution to remove all possible adsorbed material from the capillary. For each measurement, 5 mM DMSO was used as an internal standard to correct the migration time of the components in the electropherogram. The detection was carried out by column DAD measurement at 200 nm. The electropherograms were recorded and processed with the ChemStation B.04.02 computer program (*Agilent*).

The effect of pH, temperature and ligand concentration on the labeling of the AAZTA-C4-TATE and DOTA-TATE ligands with the $^{205/206}$Bi isotope were investigated by **radio thin layer chromatography (TLC).** The stability of [$^{205/206}$Bi][Bi(AAZTA-C4-TATE)] was investigated in PBS buffer, in 0.01 M DTPA solution at room temperature and in human plasma at 37°C by Dr. Adrienn Vágner and Dr. Gábor Nagy at Scanomed Kft. and Dr. Dezső Szikra at the Department of Nuclear Medicine of the University of Debrecen. The affinity of [$^{205/206}$Bi][Bi(AAZTA-C4-TATE)] and [$^{205/206}$Bi][Bi(DOTA-TATE)] to somatostatin receptor was investigated *in vitro* on the AR42J cell line. The efficacy of [^{213}Bi][Bi(AAZTA-C4-TATE)] as a TAT agent for the treatment of

neuroendocrine tumors was evaluated by monitoring the *ex vivo* relative cumulative dose (%ID/g) of [$^{205/206}$Bi][Bi(AAZTA-C4-TATE)]$^{-}$ at 15, 60 and 90 min in AR42J tumor-bearing mice (n=9). The localization of the dissociated $^{205/206}$Bi isotope was determined by examining the *ex vivo* biological distribution of free $^{205/206}$Bi in healthy control mice (n=3). Radioactivity was measured using a calibrated gamma counter (Perkin-Elmer Packard Cobra, Waltham, MA, USA). The *in vitro* and *ex vivo* tests were performed by Dr. György Trencsényi at the Department of Nuclear Medicine, University of Debrecen.

The ^{1}H-, ^{13}C-, and ^{31}P-NMR spectroscopic measurements were performed with a Bruker Avance III (9.4 T) spectrometer equipped by a 5 mm BB inverse z gradient probe and a Bruker cooling unit (BCU).

Single-crystal X-ray diffraction studies of the [Bi(*H*AAZTA)(H_2O)]·3H_2O and ([Bi(*H*AAZTA)]) complexes were performed by Dr. Nicola Dimitri in Elettra Synchrotron, Trieste.

3. New scientific results

3.1 A ligand competition method with the use of NTA was developed and **the stability constant of [Bi(DOTA)]$^{-}$ (log K_{BiL} = 30.86 (7)) and [Bi(DOTP)]$^{5-}$ (log K_{BiL} = 38.67(2)) complexes were determined**. By comparing the stability of [Bi(DOTA)]$^{-}$ and [Bi(DOTP)]$^{5-}$ complexes with those of other trivalent metal ions (e.g.: In(III), Fe(III)) it was observed that the stability of Bi(III) complexes are higher, which can be interpreted by the stronger interaction between the "soft" Bi(III) ion and N donor atoms of the macrocyclic ring.

3.2 The formation rates of the [Bi(DOTA)]$^{-}$ and [Bi(DOTP)]$^{5-}$ complexes were determined in the presence and absence of citrate as an auxiliary ligand to avoid

hydrolysis of Bi(III) ion. **The formation rate of $[Bi(DOTP)]^{5-}$ is very high** and the reaction can be followed by conventional photometry at 0 °C only. The formation rate of $[Bi(DOTP)]^{5-}$ is more than ten times higher that of $[Bi(DOTA)]^{-}$ under identical conditions. For both Bi(III) complexes the formation of the diprotonated intermediate $*[Bi(H_2DOTA)]^{+}$ and $*[Bi(H_2DOTP)]^{3-}$ was observed in which the Bi(III) ion is located outside of the coordination cavity and coordinated by the pendant arms only, while the two opposite macrocyclic ring nitrogen atoms remained protonated. The significant difference between the formation rates of the two Bi(III) complexes can be interpreted by the notably higher stability of the kinetically active diprotonated $*[Bi(H_2DOTP)]^{3-}$ intermediates ($\log K_{Bi(H2DOTA)}$ = 11.6(3), $\log K_{Bi(H2DOTP)}$ = 21.8 (1)) resulted in the faster formation of $[Bi(DOTP)]^{5-}$. In the presence of citrate ion, the formation rate of $[Bi(DOTP)]^{5-}$ decreases with the increase of the citrate concentration due to the formation of the [Bi(Cit)] and $[Bi(Cit)_2]^{3-}$ complexes and the dissociation of the kinetically active $*[Bi(H_2DOTP)]^{3-}$ intermediate. The presence of the citrate ion increase the formation of the $[Bi(DOTA)]^{-}$ by almost ten times owing to the formation of a $*[Bi(H_2DOTA)(Cit)]^{2-}$ intermediate.

3.3 The $[Bi(DOTA)]^{-}$ and $[Bi(DOTP)]^{5-}$ complexes are characterized by high inertness in both acidic or in alkaline media. **The half-lives of dissociation of $Bi(DOTA)]^{-}$ at pH= 3 is $t_{1/2} = 3.1 \times 10^3$ h while at pH= 11 $t_{1/2} = 2.5 \times 10^5$ h. For $[Bi(DOTP)]^{5-}$ at pH= 3 a half-life value of $t_{1/2} = 4.8 \times 10^4$ h was calculated. The dissociation of $[Bi(DOTP)]^{5-}$ can not be evidenced at pH= 11 even after weeks.**

3.4 The labelling efficiency of H_4DOTA ligand with ^{213}Bi isotope have been examined in a collaboration with Prof. J. Notni in Technical University of

Munich. **The labelling efficiency of H_4DOTA ligand with ^{213}Bi isotope was improved by about** 3-4% **in the presence of** 100 μM DOTA and 0.1-10 μM **citrate at pH=5.0.** Interestingly, the presence of acetate buffer slowed down the rates of labelling of the DOTA ligand with ^{213}Bi isotope under the same conditions.

3.5 Based on the results of the 1D and 2D multinuclear NMR studies, **the structure of the** $[Bi(DOTP)]^{5-}$ **complex in solution can be the best described as a twisted square antiprism (TSAP). The activation parameters** characterizing the ring inversion process of the $[Bi(DOTP)]^{5-}$ complex are $\Delta H^{\ddagger}$**= 64 ± 1 kJ·mol^{-1},** $\Delta S^{\ddagger}$**= -14± 2 J·mol^{-1}K^{-1}, and** $\Delta G^{\ddagger}_{298}$**=68 kJ·mol^{-1}.** The obtained activation enthalpy and entropy values are higher than those of $[Bi(DOTA)]^{-}$, which **can be interpreted by the stronger interaction between the Bi(III) ion and the ring nitrogen atoms**.

3.6 We have determined the stability and apparent stability constants of the $[Bi(AAZTA)]^{-}$, $[Bi(AAZTA\text{-}C4\text{-}COO^{-})]^{2-}$ and $[Bi(AAZTA\text{-}C4\text{-}TATE)]^{-}$ complexes at pH=7.4 and 25°C in 0.15 M $NaClO_4$ solution (**log $K_{[Bi(AAZTA)]^-}$= 26.45(6) and log $K_{[Bi(AAZTA\text{-}C4\text{-}COO\text{-})]2-}$= 28.75(8) which translates into log $K_{[Bi(AAZTA)]^-}{}^{cond}$ = 23.5; log $K_{[Bi(AAZTA\text{-}C4\text{-}COO\text{-})]2-}{}^{cond}$ = 25.6 and log $K_{[Bi(AAZTA\text{-}C4\text{-}TATE)]^-}{}^{cond}$ = 24.3(2)).**

3.7 The $[Bi(AAZTA)]^{-}$, $[Bi(AAZTA\text{-}C4\text{-}COO\text{-})]^{2-}$, $[Bi(AAZTA\text{-}C4\text{-}TATE)]^{-}$ and $[Bi(DTPA)]^{2-}$ complexes are characterized by high kinetic inertness. The dissociation half-lives of $Bi(AAZTA)]^{-}$, $[Bi(AAZTA\text{-}C4\text{-}COO\text{-})]^{2-}$, $[Bi(AAZTA\text{-}C4\text{-}TATE)]^{-}$ and $[Bi(DTPA)]^{2-}$ are 4.8; 50.4; 43.4; 12.6 days, respectively at pH=9.0 and 25°C.

3.8 ^{1}H- and ^{13}C-NMR spectra of $[Bi(AAZTA)]^{-}$ and $[Bi(AAZTA\text{-}C4\text{-}COO^{-})]^{2-}$ contain a single set of signals with practically constant halfwidth in the temperature range of 273–333 K. **Bi(III) complexes with AAZTA and AAZTA-C4-COO^{-} ligands are characterized by C_s symmetry in the entire temperature range.** Interestingly, the ^{1}H-NMR signal of the exocyclic carboxylate methylene protons in $[Bi(AAZTA)]^{-}$ and $[Bi(AAZTA\text{-}C4\text{-}COO^{-})]^{2-}$ is a singlet and AB doublet, respectively, revealing a higher structural rigidity of $[Bi(AAZTA\text{-}C4\text{-}COO^{-})]^{2-}$ with respect to the parent $[Bi(AAZTA)]^{-}$.

3.9 X-ray diffraction studies of the single crystals with formula **$[Bi(HAAZTA)(H_2O)]\cdot 3H_2O$ and $\{[C(NH_2)_3][Bi(AAZTA)]\}\cdot 3.5H_2O$ indicates that the coordination polyhedron around the Bi(III) ion can be best described by an irregular dodecahedron defined by a 1:4:3 stack with the apical ligand (H_2O molecule in $[Bi(HAAZTA)(H_2O)]$ and a carboxylate oxygen in $[Bi(AAZTA)]^{-}$, respectively).**

3.10 In cooperation with Scanomed Ltd. and Department of Nuclear Medicine, University of Debrecen labelling of the AAZTA-C4-TATE and DOTA-TATE ligands with the $^{205/206}$Bi isotope were performed. **Optimal labelling conditions (RCY>95%) for the AAZTA-C4-TATE ligand are: pH=3 at 25°C as well as 95°C, 1 μM ligand concentration and 5 min reaction time, while for DOTA-TATE: pH=6 at 95° C, 30 μM ligand concentration and 15 min reaction time.** Based on these results, the AAZTA-C4-TATE can be considered as a better platform for Bi(III) than DOTA-TATE. The $[^{205/206}Bi][Bi(AAZTAC4\text{-}TATE)]$ was stable for at least 21 hours at pH=7.4 at room temperature in 0.01M DTPA solution, in PBS buffer at 37°C in human serum.

3.11 In collaboration with Scanomed Ltd. and Department of Nuclear Medicine, University of Debrecen, the *in vitro* and *ex vivo* properties of [$^{205/206}$Bi][Bi(AAZTA-C4-TATE)] was investigated. *In vitro* data reveal that [$^{205/206}$Bi][Bi(AAZTA-C4-TATE)]$^{-}$ has higher somatostatin receptor affinity than [^{213}Bi][Bi(DOTA-TATE)]$^{-}$. Based on the results of the *ex vivo* studies, **the relative tumor uptake of [$^{205/206}$Bi][Bi(AAZTA-C4-TATE)] is 1.5 times higher than that of [^{213}Bi][Bi(DOTA-TATE)] in** AR42J tumor-bearing mice**. The significantly lower %ID/g values obtained in kidneys and blood indicate a faster clearance of [$^{205/206}$Bi][Bi(AAZTA-C4-TATE)]$^{-}$ than that of [^{213}Bi][Bi(DOTA-TATE)]$^{-}$. Based on the larger tumor uptake, the tumor dose of [$^{205/206}$Bi][Bi(AAZTA-C4-TATE)]$^{-}$ is expected to be higher than that observed for [^{213}Bi][Bi(DOTA-TATE)]$^{-}$ indicating a higher efficiency of [^{213}Bi][Bi(AAZTA-C4-TATE)]$^{-}$ in the TAT of neuroendocrine tumors.**

4. Possibile utilization of the the results:

Our results presented in this PhD thesis are related to the studies of the equilibrium, kinetic and structural properties of open-chain (DTPA), cyclic (AAZTA) and macrocyclic (DOTA and DOTP) aminopolycarboxylate complexes of Bi(III) ion, and are therefore mainly of basic research character. Our investigations aim to determine how changes in the donor atoms and structure of ligands affect the properties of the Bi(III) complexes formed, i.e. how to produce more stable, inert and rapidly forming $^{212/213}$Bi(III) complexes. Based on these results, new structures are currently being designed with our foreign partners, taking into account patentability and their possible applications in TAT.

As it was shown The AAZTA ligand and its derivatives have potential applications in nuclear medicine, as they form stable and innert complexes Ga(III), Sc(III) and Cu(II) ions in addition to Bi(III). Preclinical studies of ligand complexes with ^{68}Ga(III) and ^{44}Sc(III) isotopes labelled with AAZTA coupled to biologically active proteins are ongoing under a research contract between Scanomed and Bracco Imaging S.p.a. Moreover, the *in vivo* and *ex vivo* trials of some new ^{68}Ga(III)-, ^{44}Sc(III)- és $^{205/206}$Bi(III) complexes have also been carried out in collaboration between the Department of Nuclear Medicine, University of Debrecen and Bracco Imaging S.p.a. with an aim of development $^{212/213}$Bi / ^{68}Ga and $^{212/213}$Bi / ^{44}Sc based theranostic agents.

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Candidate: Dávid Horváth
Doctoral School: Doctoral School of Chemistry
MTMT ID: 10066304

List of publications related to the dissertation

Foreign language scientific articles in international journals (2)

1. **Horváth, D.**, Vágner, A., Szikra, D. P., Trencsényi, G., Demitri, N., Guidolin, N., Maiocchi, A., Ghiani, S., Travagin, F., Giovenzana, G. B., Baranyai, Z.: Boosting Bismuth(III) Complexation for Targeted [alfa]-Therapy (TAT) Applications with the Mesocyclic Chelating Agent AAZTA. *Angew. Chem.-Int. Edit. 61* (43), 1-9, 2022. ISSN: 1433-7851.
   DOI: http://dx.doi.org/10.1002/anie.202207120
   IF: 16.823 (2021)

2. **Horváth, D.**, Travagin, F., Guidolin, N., Buonsanti, F., Tircsó, G., Tóth, I., Bruchertseifer, F., Morgenstern, A., Notni, J., Giovenzana, G. B., Baranyai, Z.: Towards 213 Bi alpha-therapeutics and beyond: unravelling the foundations of efficient Bi III complexation by DOTP.
   Inorg. Chem. Front. 8 (16), 3893-3904, 2021. ISSN: 2052-1553.
   DOI: http://dx.doi.org/10.1039/D1QI00559F
   IF: 7.779

List of other publications

Foreign language scientific articles in international journals (5)

3. Lucio-Martínez, F., Esteban-Gómez, D., Laura, V., **Horváth, D.**, Szücs, D., Fekete, A., Szikra, D. P., Tircsó, G., Platas-Iglesias, C.: Rigid H4OCTAPA derivatives as model chelators for the development of Bi(III)-based radiopharmaceuticals.
   Chem. Commun. 23, 1-5, 2023. ISSN: 1359-7345.
   DOI: http://dx.doi.org/10.1039/D2CC06876A
   IF: 6.065 (2021)

4. Martinelli, J., Boccalon, M., **Horváth, D.**, Esteban-Gómez, D., Platas-Iglesias, C., Baranyai, Z., Tei, L.: The critical role of ligand topology: strikingly different properties of Gd(III) complexes with regioisomeric AAZTA derivatives.
Inorg. Chem. Front. 9 (10), 2271-2283, 2022. ISSN: 2052-1553.
DOI: http://dx.doi.org/10.1039/D2QI00451H
IF: 7.779 (2021)

5. Baranyai, Z., Carniato, F., Nucera, A., **Horváth, D.**, Tei, L., Platas-Iglesias, C., Botta, M.: Defining the conditions for the development of the emerging class of Fe III-based MRI contrast agents.
Chem. Sci. 12 (33), 11138-11145, 2021. ISSN: 2041-6520.
DOI: http://dx.doi.org/10.1039/D1SC02200H
IF: 9.969

6. Lattuada, L., **Horváth, D.**, Colombo, S. S., Fringuello Mingo, A., Minazzi, P., Bényei, A., Forgács, A., Fedeli, F., Gianolio, E., Aime, S., Giovenzana, G. B., Baranyai, Z.: Enhanced relaxivity of Gd III-complexes with HP-DO3A-like ligands upon the activation of the intramolecular catalysis of the prototropic exchange.
Inorg. Chem. Front. 8 (6), 1500-1510, 2021. ISSN: 2052-1553.
DOI: http://dx.doi.org/10.1039/D0QI01333A
IF: 7.779

7. Wurzer, A., Vágner, A., **Horváth, D.**, Fellegi, F., Wester, H. J., Kálmán, F. K., Notni, J.: Synthesis of Symmetrical Tetrameric Conjugates of the Radiolanthanide Chelator DOTPI for Application in Endoradiotherapy by Means of Click Chemistry.
Front. Chem. 6, 1-11, 2018. EISSN: 2296-2646.
DOI: http://dx.doi.org/10.3389/fchem.2018.00107
IF: 3.782

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The Candidate's publication data submitted to the iDEa Tudóstér have been validated by DEENK on the basis of the Journal Citation Report (Impact Factor) database.

25 April, 2023

Conference presentation:

1. Horváth Dávid, Dr. Baranyai Zsolt, Dr. Tircsó Gyula és Prof. Dr. Tóth Imre, [Bi(DOTA)]$^{-}$- és [Bi(DOTP)]$^{5-}$-komplexek kémiai jellemzése, orvosdiagnosztikai és terápiás célú felhasználásukhoz.
XXVII. Nemzetközi Vegyészkonferencia 2021, október, 29, Online

2. Horváth Dávid, Dr. Baranyai Zsolt, Dr. Tircsó Gyula és Prof. Dr. Tóth Imre, [Bi(DOTA)]$^{-}$- és [Bi(DOTP)]$^{5-}$-komplexek kémiai jellemzése, targetált alfa terápiában való felhasználásukhoz.
II. FKF Szimpózium 2021, június, 16-28, Online, ISBN: 978-615-6018-05-2

3. Horváth Dávid, Dr. Baranyai Zsolt, Dr. Tircsó Gyula és Prof. Dr. Tóth Imre, Bi(III)-komplexek kémiai jellemzése, orvosdiagnosztikai és terápiás célú felhasználásukhoz.
54. Komplexkémiai Kollokvium 2021, május, 26-27, Online