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NKFI-128201

Novel coordination compounds of selected non-transition metal heavy elements: preparation and chemical characterization

Final report

The project has been completed in 66 months instead of 48 stated originally in the contract. The extensions of the term were based on the difficulties connected to the COVID19 pandemic. The working team was basically identical with the planned group, only a few new students (several undergraduates and two PhD students) joined for the extension period. The research plan has been followed in the sense of basic aims. The publication list contains 26 units. 17 papers are published in international journals, 2 book-chapters, 2 PhD-thesis (the third is under preparation) and 2 BSc-thesis, 3 abstract (related to incomplete research subprojects) are listed. The name of the principal investigator (I.T.) is listed in 18 items as author or supervisor. In the other 8 items, senior researchers (Z. Baranyai, F. Kálmán and G. Tircsó) are the corresponding authors, indicating their high-level intellectual contribution to the project. The large number of publications can obviously be attributed to the intensive cooperation with our international partners, first at all Z. Baranyai at the Bracco Imaging, Triest, Italy; U. Kortz at Constructor University, Bremen, Germany; and E. Tóth at CNRS, Orleans, France.

The title of the project uses the high-sounding although poorly defined phrase “non-transition metal heavy elements”. In fact, we focused on metallic elements with high atomic numbers like In, Sb, Pt, Tl, Bi with Z= 49, 51, 78, 81 and 83, respectively. However, Pt (although not as central ion) was typically transition metal. Others, like Sc and Ga with Z= 21 and 31 are not real heavy elements, moreover Sc was a transition metal, although it had no d-electrons in its +3 oxidation state. Independently from these “cheatings”, in all systems we studied well defined metal-ligand complexes, the ligands were either organic, open chain- or cyclic amino-polycarboxylates and their derivatives, or inorganic polyoxopalladates (POPs). We usually determined the stability constants, the structure in solid and/or in solution, kinetics of formation and/or decomposition. These basic chemical data were analysed in order to decide if the compounds could be recommended for medical imaging, mostly for PET or SPECT as radiolabelled compounds, or for the targeted alfa therapy in case of Bi(III) chelates. Some of the compounds were tested as anticancer or antibacterial agents by our partners. Some paramagnetic complexes as MRI contrast agents were also discussed in several papers (Publication List (**PL**) **PL6, PL8, PL14**, **PL17**)but in those particular cases the newly prepared ligands, partly financed from this project, meant the primer interest. In addition to the 17 primary publications, we wrote three invited reviews (**PL5, PL13, PL18**).

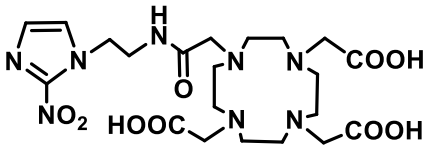
The number of publications together with the reputation of journals (D1 and Q1) may support my self-evaluation: I consider that my very last project in OTKA/NKFI (as PI) was successful. Among the valuable papers, I note, that the two defended high quality PhD theses, i.e. the works of two young scientists, Edit Farkas and Tibor Csupász (and partly two active students, Dániel Szűcs and Bayar Wahab), were financed from this fund.

The majority of the results was published in public journals; therefore, I just shortly summarize the highlights and refer to the number of the given paper in the **PL**. Other results are documented in

the theses of two BSc and two PhD students, and included in the **PL**. As an obvious way to organise the results, I follow the increasing atomic number of the central metal (ion)

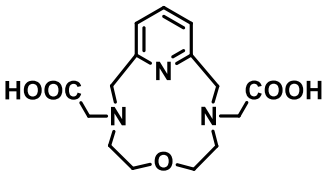
Scandium (Z = 21)

"Smart**" hypoxia sensitive PET Probe** was developed based on **a tetraaza-macrocyclic ligand**, DO3AM-NI, where the biological vector capable of taxiing the molecule to the diseased tissue was the nitro-imidazol (NI). The DOTA derivative ligand designed and obtained appeared to be an excellent **Sc(III)-binder**, the inertness of its Sc(III) chelate was especially good. The tumor-to muscle ratio of the [44Sc]Sc(DO3AM-NI in KB tumor bearing SCID mice was 10-15 higher compared to similar 68Ga-labelled agent (**PL15**).



DO3AM-NI

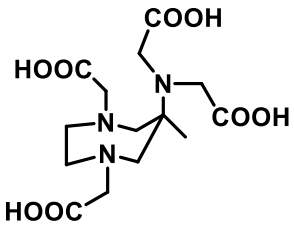
The rigid OPC2A ligand (known as a good primary Mn(II)-binder, see **PL19** and **PL23**), was studied for by Sc(III) ion complexation. The Sc(OPC2A) complex was remarkably stable and outstanding in inertness. Moreover, a stable Sc(OPC2A)F mixed ligand complex was also detected (**PL21**) and characterized**.** The labelling experiments (both [^{18}F] and [^{44}Sc]) was suggested to develop a "dual" PET probe. (Additional results on [^{44}Sc]–probes are in **PL22** and are going to be summarized in a forthcoming PhD-thesis of D. Szűcs.)



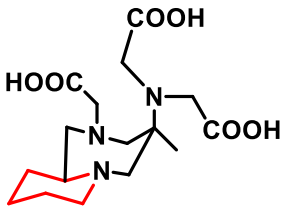
3,9-OPC2A

Gallium (Z = 31)

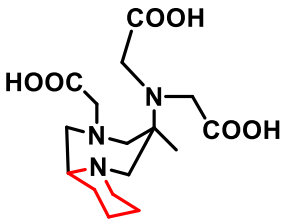
Two structurally constrained **chelators based on a fused bicyclic scaffold**, [(4*R**,10a*S**)-PIDAZTA (L1) and (4*R**,10a*R**)-PIDAZTA (**L2**)], were designed for the preparation of **Ga(III)-based radiopharmaceuticals.** The stereochemistry of the ligand scaffold has a deep impact on the properties of the complexes, with unexpected [Ga(L2)OH] species being superior in terms of both thermodynamic stability and inertness. Fast and efficient formation of the Ga(III) chelates at room temperature was observed at pH values between 7 and 8, which enables ^{68}Ga radiolabelling under mild, truly physiological conditions (pH 7.4) (**PL2**).



AAZTA



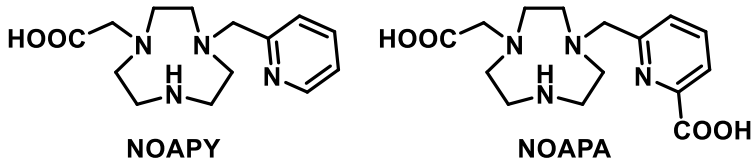
(4*R,10a*S**) PIDAZTA (L1)**



(4*R,10a*R**) PIDAZTA (L2)**

We synthesized two **1,4,7-triazacyclononane derivatives containing an acetate arm and either a methylpyridine or a picolinic acid group**, respectively, Hnoapy and H_2noapa, as new Ga^{3+}

chelators for potential use in nuclear medicine. The $[Ga(noapy)]^{2+}$ complex exists in solution as two diasteroisomeric pairs of enantiomers, while for $[Ga(noapa)]^{+}$ a single species is present in solution. ^{67}Ga radiolabeling studies were performed in order to demonstrate the potential of these chelators for [$^{67/68}Ga$]-based radiopharmaceuticals. Both complexes displayed nota like complexation properties towards Ga^{3+} ions with **no significant decomplexation of $[^{67}Ga][Ga(noapy)]^{2+}$ and $[^{67}Ga][Ga(noapa)]^{+}$** (**PL20**).



Quite stable **Ga(OPC2A) complex** compared to the Sc(OPC2A) was detected in wide pH-range by ^{71}Ga-, ^{1}H-NMR and pH-potentiometry (**PL21**).

Three **gallium(III)**- and ***thallium(III)***-containing **polyoxopalladates** (POPs) have been synthesized and structurally characterized in the solid state and in solution, namely, the phosphate-capped 12-palladate nanocubes $[XPd_{12}O_8(PO_4)8]_{13}^{-}$ (X = Ga(III), Tl(III), and the 23-palladate double-cube $[Tl_2Pd_{23}P_{14}O_70(OH)_2]^{20-}$ ($Tl_2Pd_{23}P_{14}$). The cuboid POPs, $GaPd_{12}P_8$ and $TlPd_{12}P_8$, are solution stable as verified by the respective ^{31}P, ^{71}Ga, and ^{205}Tl nuclear magnetic resonance (NMR) spectra. Of prime interest, the spin–spin coupling schemes allowed for an intimate study of the solution behavior of the Tl(III)-containing POPs via a combination of ^{31}P and ^{205}Tl NMR, including the stoichiometry of the major fragments of $Tl_2Pd_{23}P_{14}$. Moreover, biological studies demonstrated the **antitumor and antiviral activity** of $GaPd_{12}P_8$ and $TlPd_{12}P_8$, which were validated to be as efficient as cis-platinum against human melanoma and acute promyelocytic leukemia cells. Furthermore, $GaPd_{12}P_8$ and $TlPd_{12}P8$ exerted inhibitory activity against two herpetic viruses, HSV-2 and HCMV, in a dose–response manner (**PL26**).

Indium (Z = 49)

We have prepared the **indium(III)-centered**, all-acetate-capped polyoxopalladate(II) **nanocube** $[InPd_{12}O_8(OAc)_{16}]^{5-}$ (**InPd12Ac16**), which can be further used as precursor to form the phosphate-capped (i) **double-cube** $[In_2Pd_{23}O_{17}(OH)(PO_4)_{12}(PO_3OH)]^{21-}$ (**In2Pd23P13**) and (ii) **monocube** $[InPd_{12}O_8(PO_4)_8]^{13-}$ (**InPd12P8**). All three novel polyoxopalladates (POPs) were characterized in the solid state (single-crystal XRD, IR, elemental analysis), in solution (^{115}In, ^{31}P, and ^{13}C NMR), and in the gas phase (ESI-MS). The T_1- relaxation time of ^{115}In nuclei is very sensitive to the symmetry **(PL3)**.

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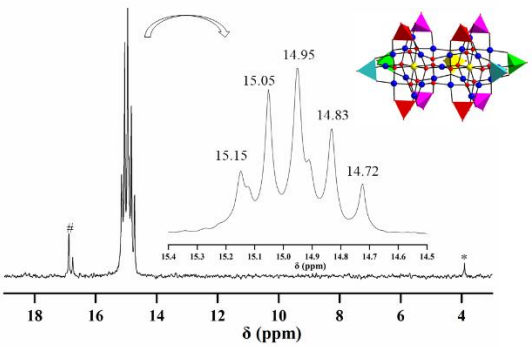
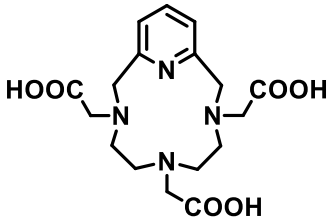


^{31}P NMR spectrum of **$In_2Pd_{23}P_{13}$** in D_2O/H_2O at room temperature. The star indicates free phosphate impurity and the hashtag an unknown impurity.

Antimony (Z = 51)

We reported a detailed study on **[Sb(PCTA)]** (PCTA: 3,6,9,15-tetraazabicyclo[9.3.1]pentadeca-1(15),11,13-triene-3,6,9-triacetic acid), a macrocyclic aminopolycarboxylate type complex of antimony(III). The formation of [Sb(PCTA)] was confirmed by NMR and ESI-MS measurements in solution, furthermore the structure of [Sb(PCTA)]·NaCl·3H_2O and [Sb(PCTA)]·HCl·3H_2O was described by X-ray diffraction and DFT calculations. The [Sb(PCTA)] is the first, thermodynamically stable antimony(III) complex bearing formed by a macrocyclic polyamino-polycarboxylate platform, whose [^{119}Sb] labelled form could be a suitable low-energy electron (Auger) emitter **for targeted radiotherapy (PL11)**.

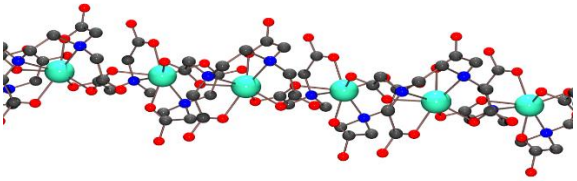


PCTA

hallium (Z = 81)

Thallium(III)-containing polyoxopalladates (POPs) has been discussed in the **Gallium** section **(PL26)**.

Thallium APC complexes: We managed to get **suitable single crystals of guadinium-Tl(III)edta** for X-ray analysis (following numerous failed attempts during the last twenty years) (**PL4**).



The infinite chain of $Tledta^-$ in the crystal. (Color code: large light blue Tl(III); dark blue N, black C, red O.)

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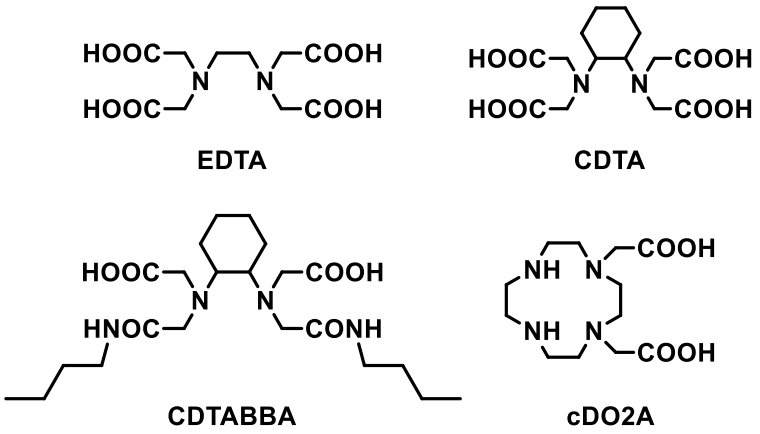


Studied ligands in Tl(III) – Ligand – iodide systems

We studied potential **iodide-carrier Tl(III)APK complexes (APK = aminopoly carboxylate type)**. The stability constants of $[Tl(EDTA)I]^{2-}$, $[Tl(CDTA)I]^{2-}$, [Tl(CDTABBA)I] and [Tl(cDO2A)I] mixed-ligand complexes were 5.69(9), 5.02(4), 6.90(1) and 4.39(7), respectively as determined by ^{205}Tl NMR titrations. The chemical shifts of the Tl(III)APK complexes were in the range of 2300-2500 ppm, while for the mixed-iodo complexes those were between 850-950 ppm. The NMR signals indicated the existence of isomers in solution for the Tl(III)-CDTABBA and Tl(III)-CDTABBA-I^- complexes, suggesting inert ternary comlexes. However, further improvement might be required for theragnostic application **(PL1).** Recent results indicated formation of **very stable Tl(III)(OPC2A)X (**X=Cl and I) **ternary** complexes, those X-ray structures were also solved **(PL21)**.

The research on the **Tl-containing chiral compound** was already classified in the application as "high risk for failing", therefore undergraduate students of the PI instead of PhD students were dominantly involved in this subproject. Although the less experienced students made several mistakes resulting difficulties in reproducibility, the basic aim was (finally) reached. We prepared several $[(CN)_5Pt\text{-}Tl(Ligand)]$ adducts and measured the ^{205}Tl NMR parameters with different denticity of the ligand **(PL7)**.

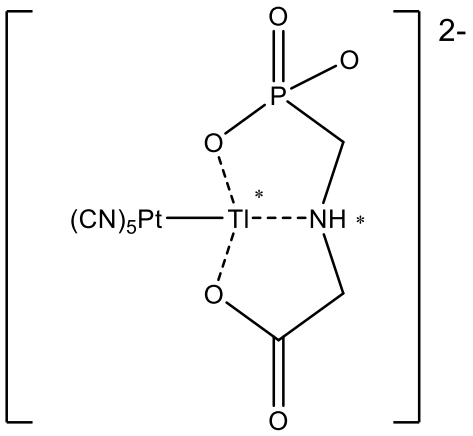
We verified the formation of $[(CN)_5Pt\text{-}Tl(HGLY)]^{2-}$ complex (H_3GLY = *N*-(phosphonomethyl)glycine; GLY^{3-} = glyphosate) based on ^{1}H, ^{205}Tl, ^{31}P NMR and mass spectrometry, where two chiral centers, the Tl and N of the GLY ligand were formed. Two signal groups could be detected. Slightly different $^1J_{Pt\text{-}Tl}$ coupling constants of the order of 50 kHz in ^{205}Tl NMR showed the persistence of the Pt-Tl metal-metal bond, while the $^2J_{Tl\text{-}P}$ spin-spin coupling constants of about 400 Hz in ^{31}P NMR showed the binding of the GLY ligand. The intensity ratios of the two signal groups measured on both nuclei were ~ 75:25, and their presence was interpreted as the formation of stereoisomers. The two anomeric centers represented 4 isomers (RR; SS; RS; SR), with **NMR spectra likely showing diastereomeric pairs**. No time remained for optical studies and for chiral separation (**PL4 and PL7**). (*Additional work and publication could be strongly recommended for our research group.*)

NMR chemical shifts and coupling constants of $[(CN)_5Pt\text{-}Tl(Ligand)]$ adducts

Ref.	WP(ligand)	Coordination number of Tl center	δ_{Tl} (ppm)	$^1J_{Pt\text{-}Tl}$ (kHz)	$^2J_{P\text{-}Tl}$ (Hz)
M. Maliarik	$(CN)_5PtTl(H_2O)_x$	?	786	71.1	—

R. Jószai	$(CN)_5PtTl(edta)^{4-}$		?	1351	58.7	—
	$(CN)_5PtTl(nta)^{3-}$		[a]6	1267	65.9	—
	$(CN)_5PtTl(mimda)^{2-}$		4?	1358	57.6	—
PL4	$(CN)_5PtTl(imda)^{2-}$		4?	1287	57.6	—
G. Ma	$(CN)_5Pt\text{-}Tl(bipy)(dmso)_3$		[a]6	1016	64.9	—
	$(CN)_5Pt\text{-}Tl(bipy)_2$		[a]5	—	—	—
	$[(^{13}CN)_5Pt\text{-}Tl(en)_2]$		[a]5	1885	48.0	—
	$[(CN)_5Pt\text{-}Tl(en)(dmso)_y]$		4?	1448	55.0	—
PL7	[b]$(CN)_5PtTl(CAPA)^{2-}$		4?	1680	54.6	—
	$(CN)_5PtTl(glyphosate)^{2-}$	25% isomer A	4	1897	49.0	402
		75% isomer B	4	1844	49.6	427

[a]The X-ray crystal structure is known in solid state. [b]CAPA: (R)-2-((*N*-carboxymethyl)-*N*-(methyl)amino)propionate



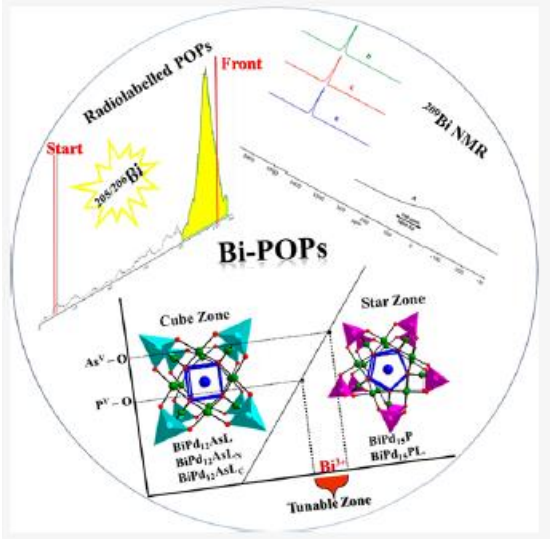
Simplified structure of the $[(CN)_5Pt\text{-}Tl(GLY)]^{2-}$ complex

Upon the dissolution of **$Tl(CF_3SO_3)_3$ and $Tl(CF_3COO)_3$** salts**, in dimethylsulfoxide (dmso) or tetramethylurea (tmu), intensely red-colored complexes were formed.** This red thallium complex was stable for years in dmso, while it was reduced fairly rapidly to thallium(I) in tmu in a few hours. ^{205}Tl NMR spectroscopy indicates Tl^+ and Tl^{3+} at 1:1 ratio in dmso as a result of partial reduction of Tl(III). EXAFS showed 3.49 Å Tl – Tl atomic distance. The strong electrostatic repulsion at this remarkable short distance between the cations might be balanced by the solvate molecules in bridging position. The structure of this unusual adduct has been supported by DFT calculations **(PL25)**.

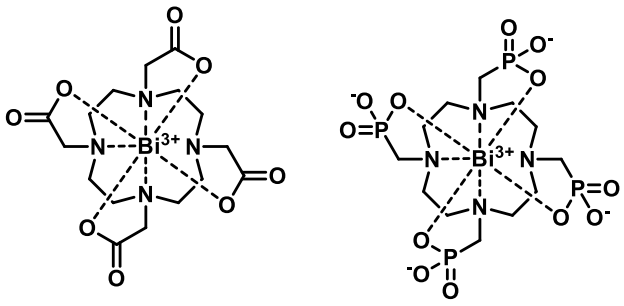
Bismuth (Z = 83)

Five bismuth(III)-containing polyoxopalladates (POPs) were synthetized in collaboration with our German-partners: the cube-shaped $[BiPd_{12}O_{32}(AsPh)8]^{5-}$ (BiPd12AsL), $[BiPd_{12}O_{32}(AsC_6H_4N_3)_8]^{5-}$

(BiPd12AsLN), and [BiPd12O32(AsC6H4COO)8]13− (BiPd12AsLC) as well as the star-shaped $[BiPd_{15}O_{40}(PO)_{10}H_6]^{11-}$ (BiPd15P) and $[BiPd_{15}O_{40}(PPh)_{10}]^{7-}$ (BiPd15PL), respectively. The organically modified capping groups phenylarsonate, p-azidophenylarsonate, and p-carboxyphenylarsonate were chosen as the azido (−N3) and carboxyl (−COOH) groups **allows for the covalent conjugation** (via click reaction, amide coupling, etc.) **with targeting vector molcules**. Our contribution was substantial in NMR, MS and radiochemistry. The ^{209}Bi NMR (I = 9/2) spectra of cubic BiPOPs revealed narrow peaks ($\nu_{1/2}$ ~ 200 Hz) at 5470 ppm with a longitudinal relaxation time in the millisecond range (at 8.46 T). The absence of a quadrupole relaxation contribution could be attributed to the allocation of Bi(III) in the highly symmetrical cuboid POP host cage. Similar peaks were absent in the ^{209}Bi-NMR spectra of the star-shaped POPs due to the lower symmetry. [205/206Bi]-radiolabelled POPs have been synthesized by incorporating a $^{205/206}$Bi(III) ion in the POP structures. Carrier-free $^{205/206}$Bi radioisotopes (as surrogates of α-emitting ^{213}Bi) were incorporated into four BiPOPs. The radiochemical yield was complete (>99%) in 10 min. **(PL9, PL12).**



A thorough study of the thermodynamics and kinetics of formation of **Bi(III)-DOTP** including radio-labelling and the comparison with the congener Bi(III)-DOTA was undertaken. The Bi(III)-DOTP complex was characterised by a fast formation kinetics (kBi(H_2DOTP) = 0.33 s^{-1}), an outstanding thermodynamic stability (log $K_{Bi(DOTP)}$ = 38.67) and an impressive kinetic inertness ($t_{1/2\ at\ pH=3}$ = 47 600 h). The results clearly demonstrated that DOTP was a better chelating agent for Bi(III) both in terms of thermodynamic stability and kinetics compared to Bi(DOTA) **(PL10)**.



[Bi(DOTA)]⁻ **[Bi(DOTP)]$^{5-}$**

We have demonstrated that the mesocyclic chelator **AAZTA quickly coordinates Bi(III)** at room temperature, leading to a robust complex. A comprehensive study of the structural, thermodynamic and kinetic properties of [Bi(AAZTA)]⁻ is reported, along with bifunctional [Bi(AAZTA-C4-COO−)]2− and the targeted agent [Bi(AAZTA-C4-TATE)]⁻, which incorporates the SSR agonist Tyr3-octreotate. An unexpected increase in the stability and kinetic inertness of the metal chelate was observed for the

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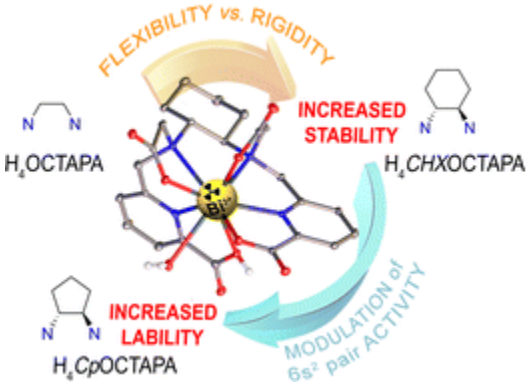
bifunctional derivative and was maintained for the peptide conjugate. A cyclotron-produced $^{205/206}$Bi mixture was used as a model of ^{213}Bi in labelling, stability, and biodistribution experiments, allowing for the estimation of the efficiency of [^{213}Bi(AAZTA-C4-TATE)]$^-$ **High accumulation in AR42J tumors and reduced kidney uptake were observed with respect to the macrocyclic [^{213}Bi(DOTA-TATE)]$^-$ chelate (PL16).**

Octadentate ligands containing ethyl (H_4OCTAPA), cyclohexyl (H_4*CHX*OCTAPA) or cyclopentyl (H_4*Cp*OCTAPA) spacers were assessed **as chelators for Bi(III)-based radiopharmaceuticals.** The H_4*CHX*OCTAPA chelator displays excellent properties, including $^{205/206}$Bi-nuclide radiolabelling under mild conditions, excellent stability in serum and in the presence of competing cations or H_5DTPA. The poor performance of H_4*Cp*OCTAPA could be related to the stereochemical activity of the Bi(III) lone pair **(PL24)**.



Debrecen, April 30, 2024.

Imre Tóth

principal investigator

Appendix: Structure of the ligands mentioned in the text

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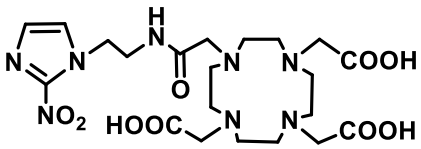
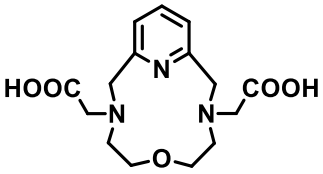
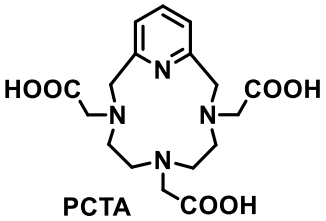


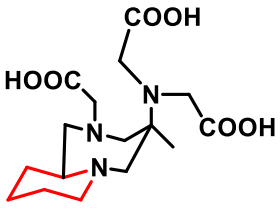
DO3AM-NI



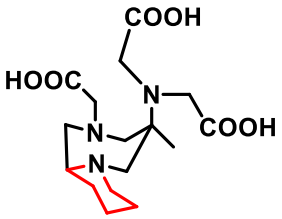
3,9-OPC2A



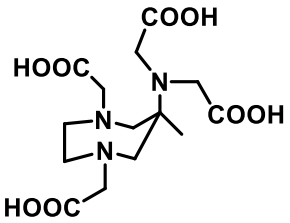
PCTA



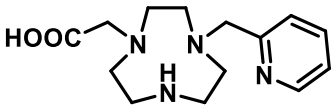
(4*R**,10a*S**) PIDAZTA (L1)



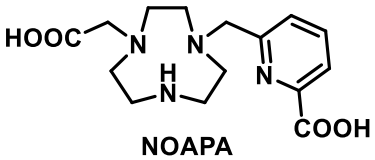
(4*R**,10a*R**) PIDAZTA (L2)



AAZTA



NOAPY



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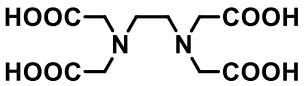

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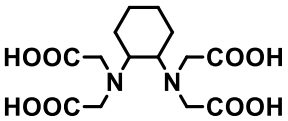

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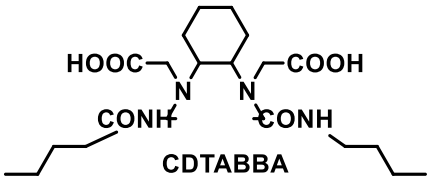

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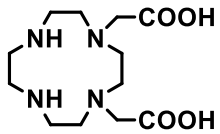

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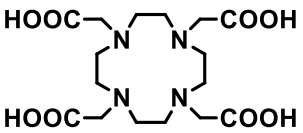

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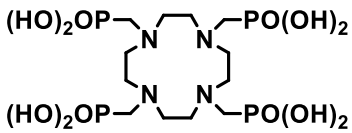

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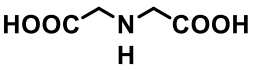

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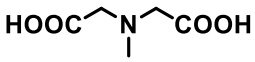

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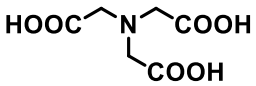

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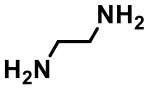

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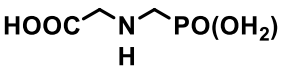

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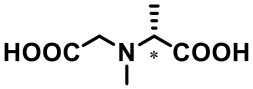

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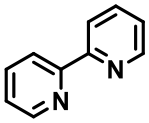

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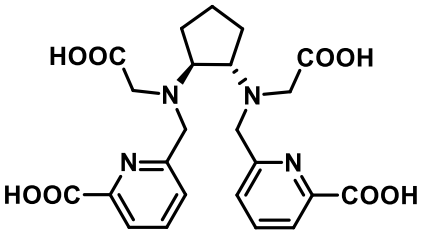

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