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TOWARD HIGHLY STABLE [$^{212/203}$Pb]Pb^{2+} COMPLEXES: RIGIDIFIED HEXADENTATE LIGAND DESIGN

Jennifer Storchi,[1] Matteo Mari,[1] Filippo Bonini,[1] Francesco Faglioni,[1] Marianna Tosato,[2,3] Simona Mastroianni,[2,3] Caterina F. Ramogida,[2,3] Mattia Asti,[4] Sofia Gama,[5] and Erika Ferrari[1]

[1]Department of Chemical and Geological Sciences, University of Modena and Reggio Emilia, 41125, Modena, Italy
[2] Department of Chemistry , Simon Fraser University, Burnaby, BC V5A 1S6, Canada
[3] Life Sciences, TRIUMF, Vancouver, BC V6T 2A3, Canada
[4] RACHEL, Nuclear Medicine Unit, AUSL-IRCCS Reggio Emilia, 42122, Reggio Emilia, Italy
[5] C2TN, Instituto Superior Tecnico, 7 2695-066 Bobadela, Universidade de Lisboa, Portugal
erika.ferrari@unimore.it

Aim/Introduction: The *theranostic* approach exploits the same drug delivery system with either diagnostic or therapeutic radionuclide, allowing an accurate prediction of the therapeutic biodistribution. Lead-203 (^{203}Pb, $t_{1/2}$ 51.9 h, γ, 80.94 %) and lead-212 (^{212}Pb, $t_{1/2}$ = 10.6 h, β^-, 100% followed by a decay chain including α-emission) are one example of a *true theranostic pair* [1]. This study reports two hexadentate acyclic chelators based on a rigid *trans*-diaminocyclohexane (DACH) scaffold [**Figure 1**] to improve both thermodynamic stability and kinetic intertness of the Pb^{2+} complexes.

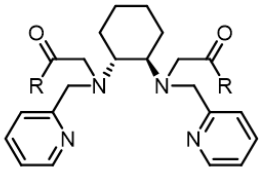

Figure 1. *Structure of the investigated DACH-based ligands. R = OH (**H_2bpcd**); NH_2 (**NH_2bpcd**).*

Materials and Methods: Thermodynamic and kinetic studies were performed combining potentiometry, UV-Vis and ^{1}H NMR spectroscopy. ^{203}Pb was produced via the ^{203}Tl (p,n)^{203}Pb reaction at TRIUMF's TR13 cyclotron. Concentration-, time-, temperature-dependent radiolabelling with ^{203}Pb were conducted at pH 6 (0.1 M NH_4OAc). The radiochemical yields (RCYs) were determined by radio-TLC. The *in vitro* stability of the preformed ^{203}Pb complex was assessed in human serum over 48 h by radio-TLC.

Results: H_2bpcd and NH_2bpcd combine pyridine and carboxylate/carboxamide donor groups creating an N_4O_2 coordination environment. NMR complexation studies with $^{nat}Pb^{2+}$ show that both ligands have good affinity for Pb^{2+}, revealing rapid complex formation and high stability in acidic conditions (pH ~1). However, the two complexes differ in the isomerization profiles: H_2bpcd forms one dominant species in solution, while NH_2bpcd yields two isomers. These results are further confirmed by DFT calculations. Thermodynamic studies reveal a significantly higher thermodynamic stability of H_2bpcd compared to NH_2bpcd, with the former establishing a new benchmark among acyclic ligands for Pb^{2+} (pPb^{2+} 15.9 *vs* 9.7 for DTPAm and 14.8 for H_2ampa). [^{203}Pb]Pb^{2+} radiolabeling experiments show that only H_2bpcd can incorporate the radiometal (RCY% > 95%, [H_2bpcd] = 10^{-5} M, pH 6, 15 min, RT/80°C) while NH_2bpcd shows poor radiolabeling efficiency.

Conclusions: This study pinpoints H_2bpcd as a promising scaffold capable of forming highly stable $^{nat}Pb^{2+}$ complexes and efficiently binding [^{203}Pb]Pb^{2+}. These findings provide strong support for further (pre)clinical translation of $^{212/203}$Pb-labelled radiotracers.

[1] A. Ingham, T. I. Kostelnik, B. L. McNeil, N. Choudhary, B. O. Patrick, M. de Guadalupe Jaraquemada-Peláez and C. Orvig, *Dalton Trans.*, **2021**, *50*, 11579