Canadian Radiotheranostics Leaders' Summit 2025

Abstract Submission

Title: Development of triaza-18-crown-6 chelators for radiotheranostic metals

Authors and institutional affiliation:
Fiaccabrino D, University of British Columbia - TRIUMF Life Sciences Jaraquemada-Pelaez M, University of British Columbia
Orvig C, University of British Columbia Schaffer P, TRIUMF Life Sciences

Email of submitting/first author:
dfiaccabrino@triumf.ca **(Desiree Fiaccabrino)**

Training program first author is enrolled in:
PhD in Chemistry

Year of training:
PhD Y5

Abstract:

Purpose: Alpha-particle emitters such as 225Ac, 227Th, 212Pb, and 213Bi offer exceptional therapeutic potential in nuclear medicine due to their high linear energy transfer and submillimeter tissue range, which maximize tumor cell cytotoxicity while minimizing off-target damage. However, the lack of chemically matched companion diagnostics for many α-emitters underscores the need for versatile chelators capable of forming kinetically inert complexes with both large actinide ions and smaller hard metal ions used in imaging. Herein, we report the design, synthesis, and comprehensive characterization of three novel macrocyclic chelators based on a triaza-18-crown-6 scaffold: H3tripa (three picolinic acid arms), H3trica (three carboxylic acid arms), and H3trihopo (three 1-hydroxypyridin-2-one arms).

Methods: Ligands were synthesized in high yield and purity, and characterized by 1H/13C NMR spectroscopy, high-resolution mass spectrometry, and elemental analysis. Metal complexation studies with nonradioactive La3+, Th4+, Zr4+, Bi3+, In3+, and Pb2+ were evaluated with NMR spectroscopy and potentiometric-UV thermodynamic solution titrations. Radiolabeling experiments with [225Ac]Ac3+, [213Bi]Bi3+, [227Th]Th4+, and [203Pb]Pb2+ were conducted at physiological pH and ambient temperature. Radiochemical

conversion was measured by radio-TLC after 10-30 minutes. Radiometal complexes stability was assessed in human serum over one radionuclide half-life.

Results: All three chelators formed robust complexes with each nonradioactive metal, exhibiting high stability constants. Radiolabeling achieved >95% RCC within 30 minutes at ligand concentrations sub micromolar concentrations under mild conditions. Selected radiometal complexes maintained >90% integrity in human serum for durations surpassing one half-life of the radionuclide. Conclusion: These results demonstrate that the triaza-18-crown-6 scaffold supports efficient, mild radiolabeling and forms stable complexes across a spectrum of diagnostic and therapeutic radionuclides. The chelators presented here represent a promising platform for the streamlined development of next-generation theranostic radiopharmaceuticals, enabling matched diagnostic-therapeutic pairs for α-particle therapy..