SFU SIMON FRASER UNIVERSITY

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Cryptand Radiometal Complexes as Diagnostic and Therapeutic Radiopharmaceuticals

Novel bifunctional [2.2.2]Cryptand that can be used as a chelator for radiometals and developed into a new class of radiopharmaceuticals

Request an introduction

Reference: 2021-001

Header image is purely illustrative. Source: Trsakaoe, stock.adobe.com/uk/246602810, stock.adobe.com

IP Status

Patent application submitted, Patented

Seeking

Development partner

Background

Use of radiometals in nuclear oncology is a rapidly growing field that uses the properties of radioactive atoms to create radiopharmaceuticals that treat and diagnose cancer. These radiopharmaceuticals can be broken down into four components containing a radiometal, chelator, linker and bioconjugate/targeting vector. Each component has a specific function, where the radiometal provides the diagnosis/treatment, the bioconjugate/targeting vector ensures accumulation of the drug at the point of infection, while the chelator and linker (defined as bifunctional chelator (BFC)) integrate these two components together. The present invention proposes bifunctional [2.2.2]Cryptand chelators could potentially lead to new ligands that bind radiometals under radiopharmaceutical conditions (*vide supra*) to form exceptionally thermodynamically stable and kinetically inert complexes *in vivo*. One challenge would be making the cryptand bifunctional by employing a reproducible synthetic route that could be implemented.

Tech Overview

SFU researchers have synthesized and characterized novel [2.2.2]Cryptand BFCs. The synthesis is convenient, high yielding and gives access to three distinct bifunctional handles (azide (-N_3), isothiocyanate (-NCS), and tetrazine (-Tz)) that can enable the construction of radioimmunoconjugates for targeted and pre-targeted therapy. Proof-of-principle CRYPT radiolabeling was successful, after optimization, with lead-203 ([^{203}Pb]Pb^{2+}) and demonstrated superior complexation efficiency to DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid), and comparable efficiency to the current industry standard DOTAM (aka TCMC, 1,4,7,10-tetraaza-1,4,7,10-tetra-(2-carbamoylmethyl)-cyclododecane). *In vitro* human serum stability assays demonstrated excellent [^{203}Pb]Pb-CRYPT stability over 72 h (91.7 ± 0.56%; n = 3). [^{203}Pb]Pb-CRYPT-radioimmunoconjugates were synthesised from the corresponding CRYPT-immunoconjugate or by conjugating [^{203}Pb]Pb-Tz-CRYPT to transcyclooctene modified trastuzumab (TCO-trastuzumab) via the inverse electron-demand Diels-Alder (IEEDA) reaction.

The modular assembly of the BFC method developed by SFU researchers allows for a vast and quickly advancing field of treatments that are patient specific. With new biomarkers, radiometals, and chelating strategies available, there is now a plethora of combinations available for radiopharmaceutical design. The BFC method is particularly attractive because all steps of the long synthetic manipulation of the chelate, linker, and biomolecule is executed before the radionuclide is added in the last step (Figure 1), saving many half-lives of radioactivity.

Further Details

https://pubs.rsc.org/en/content/articlelanding/2013/CC/c3cc41554f

Benefits

- The cryptand can bind the radiometal under radiopharmaceutical conditions (mild temperatures, sub-micromolar ligand concentrations, fast reaction times)
- Superior complexation efficiency to DOTA, and comparable efficiency to the current industry standard DOTAM
- Convenient synthesis, high yielding
- The complexes formed are kinetically inert and stable to transchelation *in vitro*

Applications

The CRYPT ligands have the potential to become new industry standards for therapeutic and diagnostic radiometals and in turn will lead to new radiopharmaceuticals to treat and diagnose cancer.

Patents

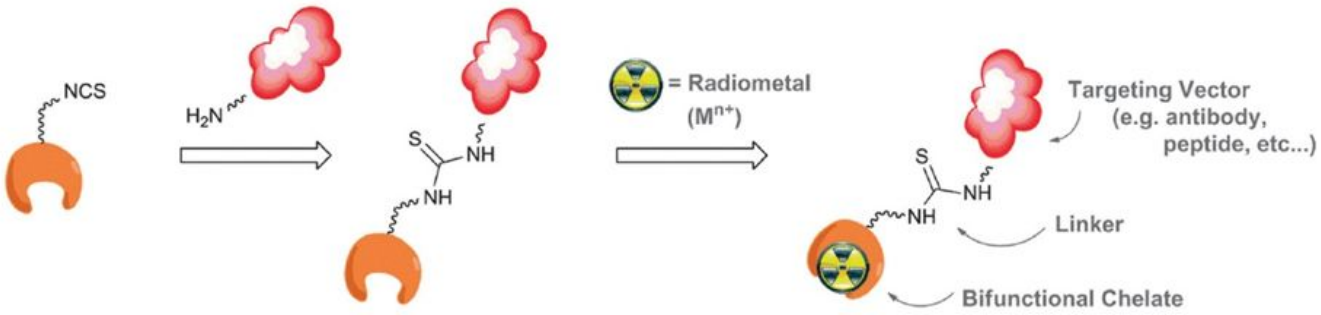
- Provisional application 63/212305, Patented

Appendix 1

Figure 1

Example of the bifunctional chelate (BFC) method employed in metal-based radiopharmaceuticals.

Ramogida et al., Chem. Commun., Vol. 49, 4720—4739 (2013)



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