Tuning Pharmacokinetic Properties of Sulfur-Rich Macrocyclic Chelators for Complexation of Theranostic Meitner-Auger Electron Emitter $^{197m/g}$Hg

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Introduction

- The rapidly growing field of radiopharmaceuticals for treatment of cancer contains two main categories: therapeutics and diagnostics. **Therapeutic** agents incorporate radionuclides with decays that damage cancer cells while **diagnostic** agents make use of decay modes compatible with imaging (see **Figure 1**). The combination of these techniques into one pharmaceutical has been coined **theranostics**.

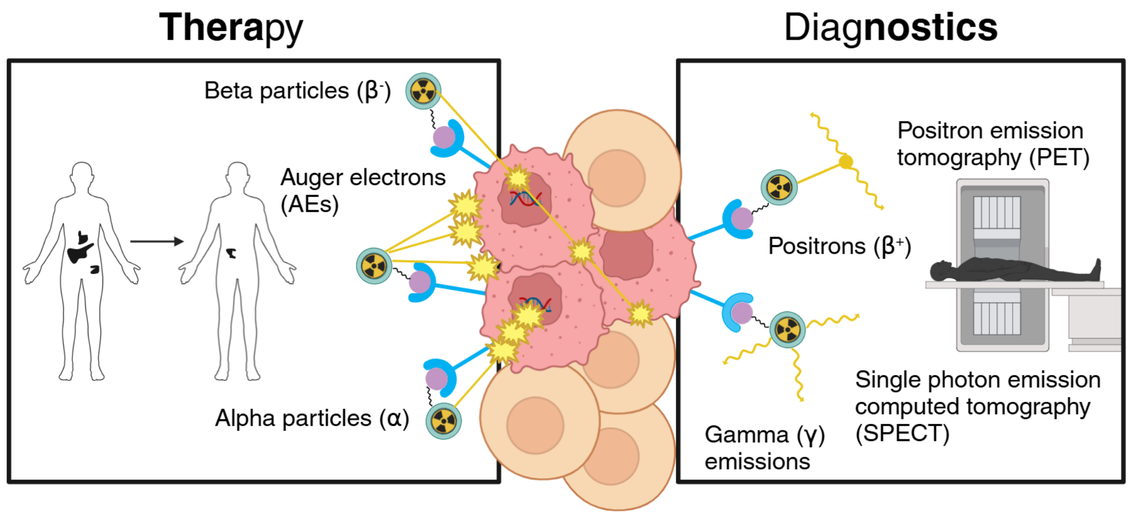

Figure 1. Types of radioactive decays utilized in therapeutic agents and diagnostic agents respectively.

- **Mercury-197m/g** ^{197m}Hg ($t_{1/2}$ = 23.8 h, IT (91%)) and ^{197g}Hg ($t_{1/2}$ = 64.14 h, EC (100 %)) has only recently been investigated for use in **theranostic radiopharmaceuticals** and presents a promising pair of radioactive isomers to be used in a chemically matched theranostic drug, exploiting the SPECT-compatible gamma ray emissions and cytocidal Meitner-Auger electrons.[1]

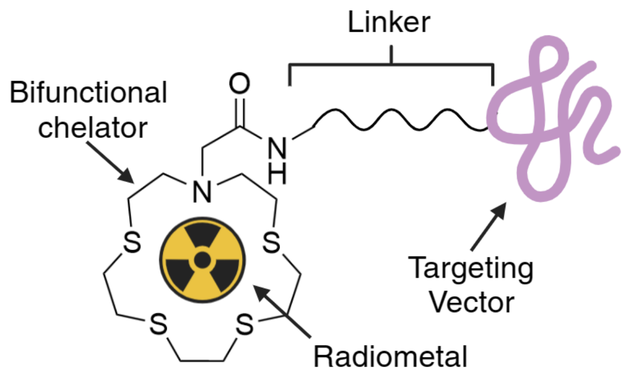

Figure 2. Structure of an inorganic radiopharmaceutical incorporating the NS_4 chelator backbone.

- Our group has previously developed a suitable chelator backbone, NS_4 (see **Figure 2**),that **selectively** forms **stable** $^{197m/g}$Hg complexes for radiolabeling purposes.

- While selective and stable, bifunctional derivatives of this chelator are highly lipophilic, resulting in solubility issues and high liver uptake during *in vivo* studies.[1]

Hypothesis: lipophilicity of NS_4 chelator can be tuned with polar linkers while providing position for conjugation of a targeting vector.

Novel Bifunctional Chelators

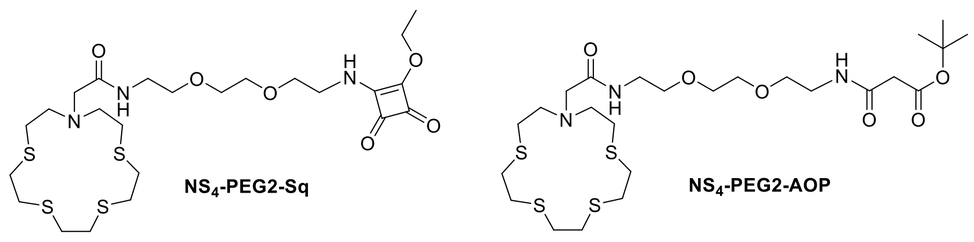

Figure 3. Chemical structures NS_4 chelators bearing first generation linker modifications.

- Two novel bifunctional chelators (BFCs) (**Figure 3**) were designed by the integration of a polyethylene glycol (PEG2) linker chain and two bifunctional handles for the targeting vector.

- The PEG2 chain, squarmine ester (Sq) and protected amino oxopropanoic acid (AOP) are all highly polar.

- The Sq and AOP groups can both be easily deprotected and coupled to exposed lysine residues on a targeting vector. [2]

Novel BFC Synthesis

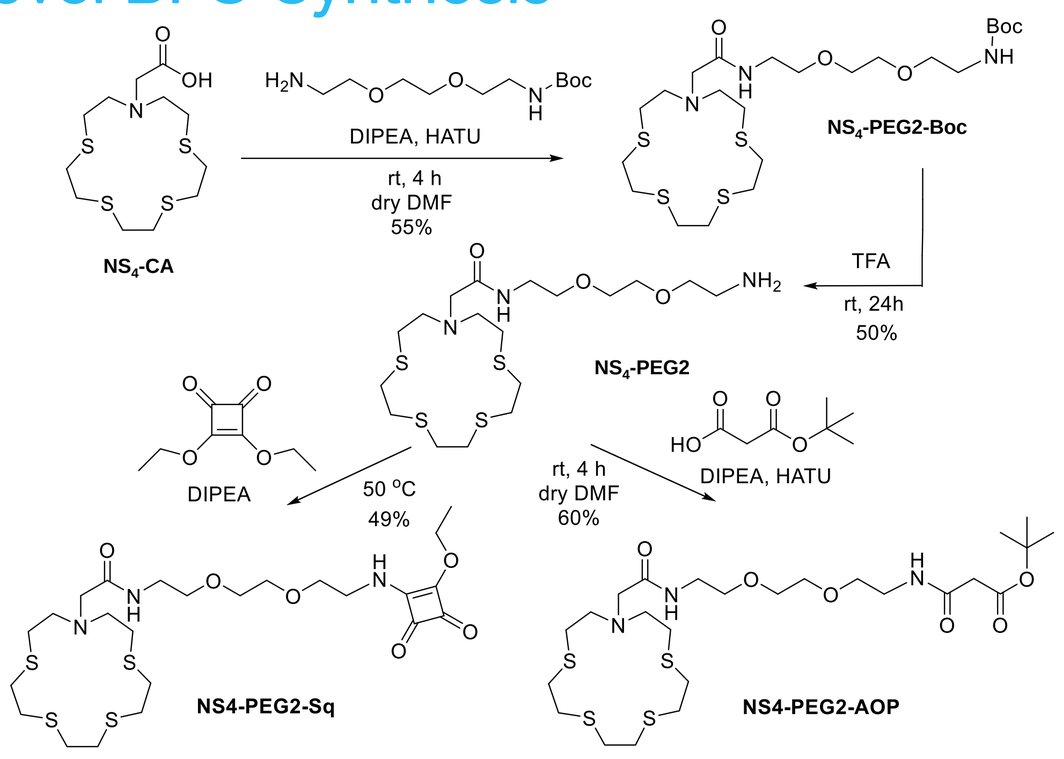

Figure 4. Synthetic route for NS_4-PEG2-(Sq/AOP).[2]

- Both NS_4-PEG2-(Sq/AOP) have been successfully synthesized and characterized.

Non-Radioactive Mercury Study

- Noting the shared methyl acetamide (MA) moiety included in all proposed BFCs, a representative compound, NS_4-MA, was synthesized and characterized.

- A complexation study with non-radioactive Hg was then conducted to investigate the ability of the chelator to complex Hg.

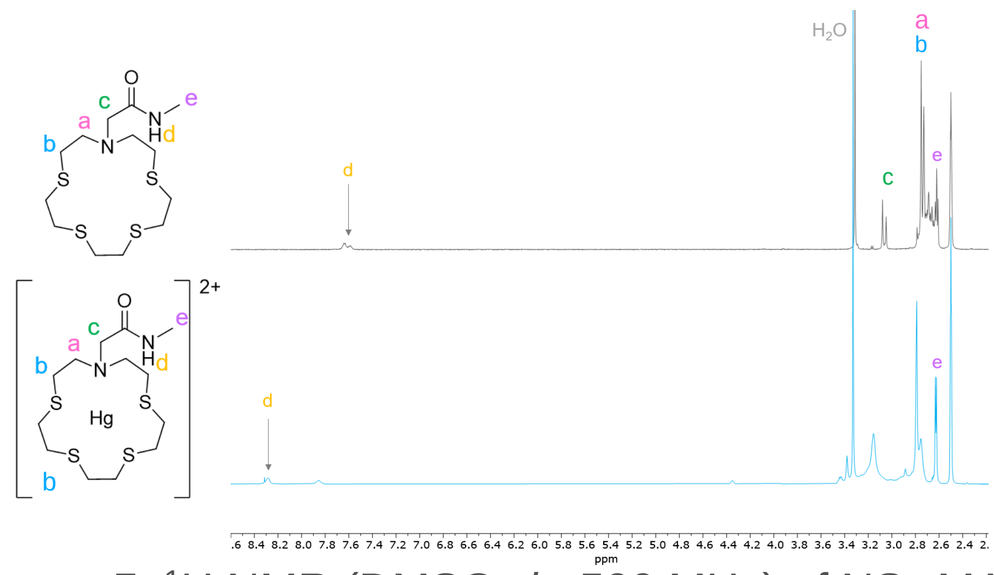

Figure 5. ^{1}H NMR (DMSO-d_6, 500 MHz) of NS_4-MA and $[Hg(NS_4\text{-MA})]^{2+}$.

- Shifting of amide proton (d) while methyl protons (e) remain unchanged is indicative of the carbonyl oxygen acting as a donor atom for Hg complexation; further corroboration (via DFT or crystallography) is required.

Future Work

1. Conduct $^{197m/g}$Hg radiolabeling studies with both BFCs, evaluate the stability of the formed complexes via incubation in biologically relevant media (i.e., glutathione and human serum) and determine the log$D_{7.4}$ of radiometal-complexes to assess the lipophilicity.

2. *In vivo* animal studies to evaluate impact on biodistribution.

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References

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Discovery, accelerated