Evaluation of the Effect of Macrocyclic Ring Size on Pb(II) Selectivity and Complex Stability in Pyridyl Containing Chelators

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Background

- Targeted radionuclide therapy (TRT) couples a radionuclide to a chelator linked to a cancer-seeking targeting vector to deliver a radioactive payload directly to cancer cells[1] (Fig. 1)
- Depending on the type of decay the radionuclide undergoes, it is compatible with imaging or therapy[1]
- ^{203}Pb ($t_{1/2}$= 51.9 h), a gamma-emitting diagnostic isotope, and ^{212}Pb ($t_{1/2}$ = 10.6 h), an alpha-emitting therapeutic isotope, form a chemically matched theranostic pair

Chelators

- Form coordinate bonds with metals to produce a complex
- Ideally should: 1) Complex rapidly in mild conditions and low concentrations[1]
  2) Be kinetically inert and thermodynamically stable[1]
  3) Be metal selective[1]

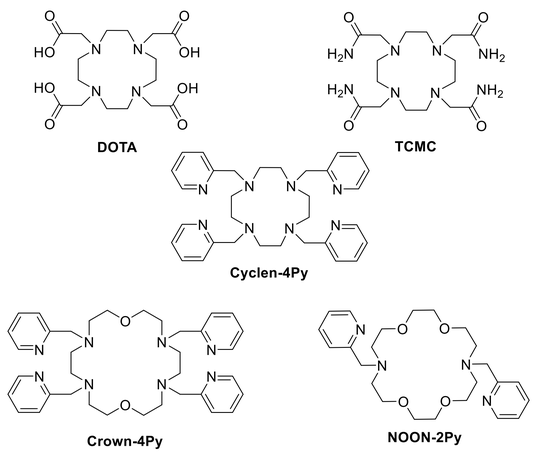


Figure 2. Structures of the chelators investigated in this study for ^{203}Pb radiolabelling.

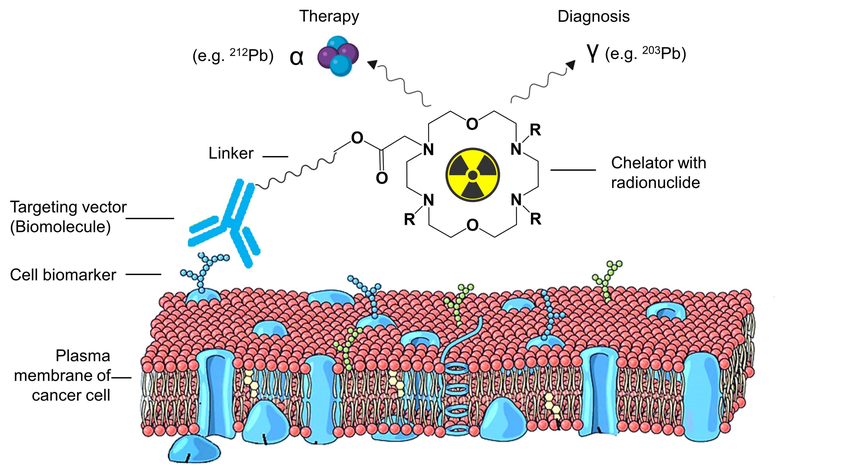


Figure 1. Structure of bifunctional chelator labeled radiopharmaceutical for theranostic purposes.

Radiolabeling

- Conditions: 0.1 M NH_4OAc
  pH 7, 25°C
  60 minutes
- TLC conditions: Glass microfiber chromatography paper impregnated with silicic acid developed with 50 mM EDTA (pH 5)

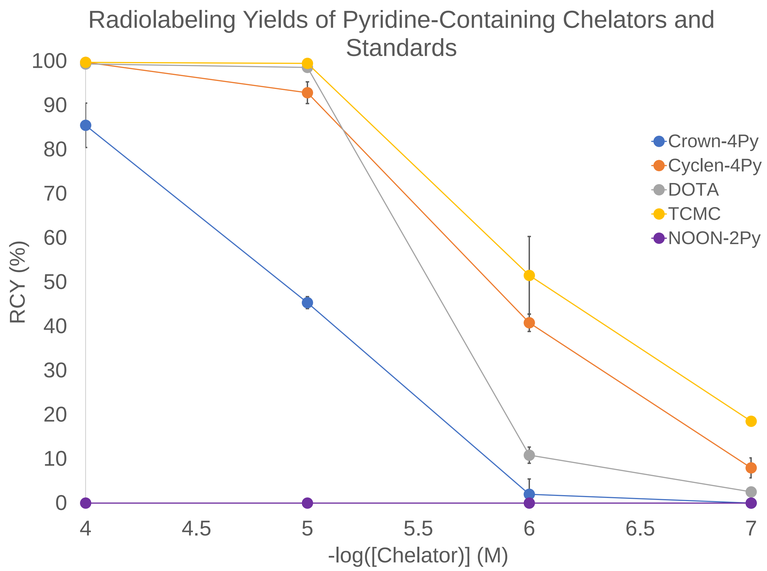
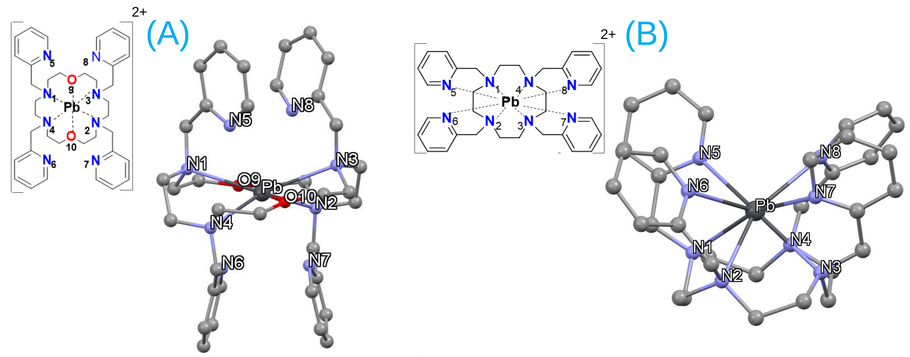


Figure 3. ^{203}Pb radiolabeling yields (n=3) of tested chelators.

Crystal Structures



(C)

Bond	Crown-4Py Average Length (Å)	Cyclen-4Py Average Length (Å)
Pb-$N_{pyridine}$	3.015	2.773

(D)

Bond	Crown-4Py Average Angle (°)	Cyclen-4Py Average Angle (°)
N_{ring}-Pb-$N_{pyridine}$	56.82	62.89

Figure 4. Crystal structures of (A) $[Pb(Crown\text{-}4Py)]^{2+}$ and (B) $[Pb(Cyclen\text{-}4Py)]^{2+}$. Hydrogens and perchlorate counterions have been removed for clarity. (C) Average Pb-$N_{pyridine}$ bond lengths in the crystal structures. (D) Average N_{ring}-Pb-$N_{pyridine}$ bond angles.

Hypotheses

- With sterically hindered donor arms, stable complexation occurs when Pb is accessible for coordination (e.g. Cyclen-4Py)
- NOON-2Py undergoes hemi-directed coordination, thus the large gap in the complex may cause incompatibility with stable coordination[2]
- With larger backbones (ex: N_4O_2 of crown-4Py), harder donor atoms may be needed to increase thermodynamic stability[3]

Future Work

- Potentiometric titrations to determine thermodynamic stability constants
- Perform *in vivo* biodistribution studies with bifunctional cyclen-4Py

References

[1]Price, E.; & Orvig, C. Chem. Soc. Rev. 2013, 43, 260-290.
[2]Hu, A. *et al*. J. Am. Chem. Soc. 2020, 142*(31)*, 13500 – 13506.
[3]Ferreiros-Martiniez, R. et al. Inorg. Chem. 2011, 50, 3772 – 3784.

Discovery, accelerated