# Synthesis, Evaluation, and Characterization of Lanthanum-132/135 and Actinium-225 Chelators for Radiopharmaceuticals

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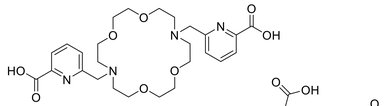
## Background

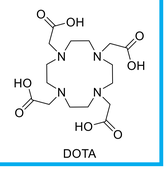
Theranostic radiopharmaceuticals allow clinicians to noninvasively visualize tumor biology and deliver personalized treatment directly to cancer cells while minimizing damage to surrounding healthy tissue. Various radionuclides can be harnessed for both therapeutic and diagnostic applications through the unique emissions produced during their radioactive decay.

$^{135}$La can be exploited as a cancer therapeutic through Meitner-Auger electron emissions that can be used to deliver localized radiation to cancer sites. Additionally, $^{132}$La emits positrons to provide diagnostic information through PET imaging. [1]

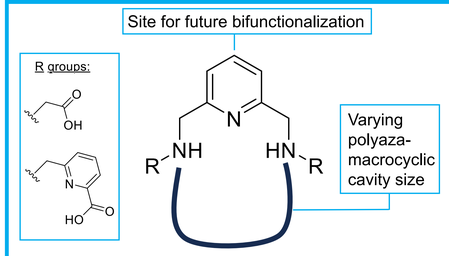
The highly promising alpha-emitting therapeutic agent $^{225}$Ac lacks a suitable diagnostic counterpart; lanthanum-132 could serve as an imaging surrogate due to its similar ionic radius and coordination chemistry. [2]


However, existing chelators for lanthanum and actinium radioisotopes lack the kinetic inertness required for *in vivo* applications (DOTA) or are synthetically difficult to bifunctionalize (Macropa), motivating the design of new chelators for these theranostic pairs. [3]



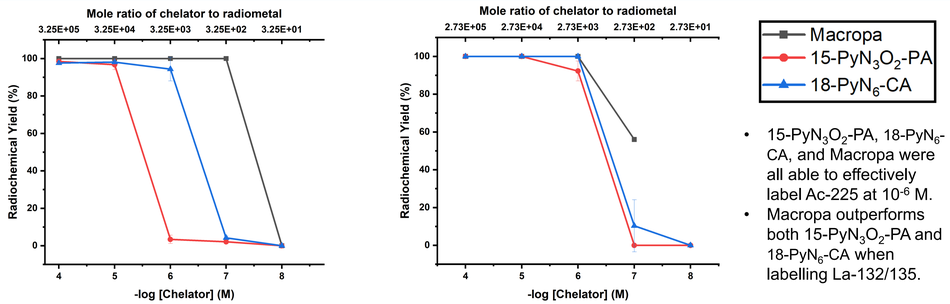




## Aim




- Design a chelator by varying type of pendant arm and backbone size for preferential lanthanum and actinium binding
- Resulting metal complexes should have high kinetic inertness and site for easy bifunctionalization

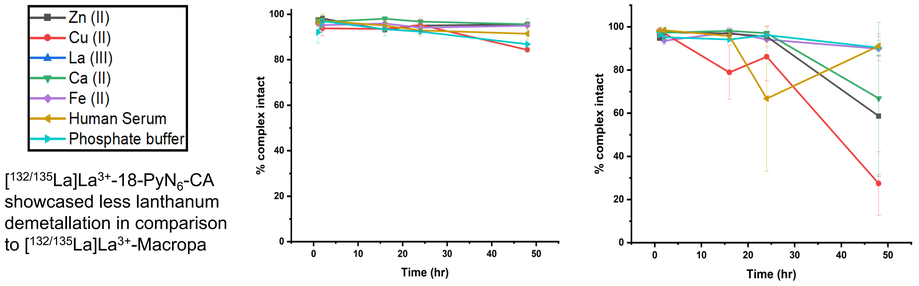
## Concentration-dependent Radiolabelling Data




- 15-Py$N_3O_2$-PA, 18-Py$N_6$-CA, and Macropa were all able to effectively label Ac-225 at $10^{-6}$ M.
- Macropa outperforms both 15-Py$N_3O_2$-PA and 18-Py$N_6$-CA when labelling La-132/135.

**Figure 1**. Radiochemical yield of chelators radiolabelled with lanthanum-132/135 (left) and actinium-225 (right) after 1 hour. Reactions conditions using 0.1 M $NH_4OAc$ (buffer) at pH 7 under ambient temperature. n = 3

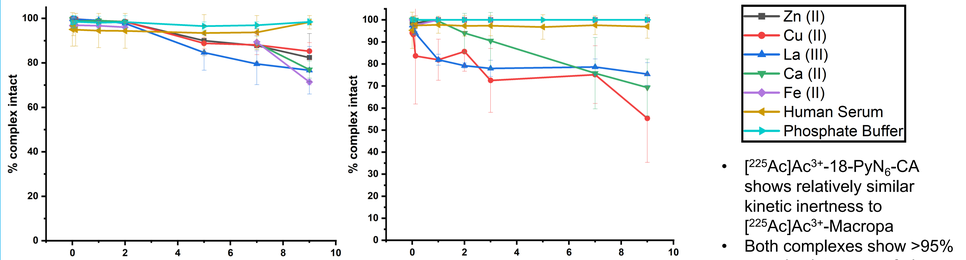
## *In vitro* Stability Challenge Assays with $^{132/135}$La Complexes




- [$^{132/135}$La]$La^{3+}$-18-Py$N_6$-CA showcased less lanthanum demetallation in comparison to [$^{132/135}$La]$La^{3+}$-Macropa

**Figure 2**. Percentage of [$^{132/135}$La] radiometal complex intact, [$^{132/135}$La]$La^{3+}$-18-Py$N_6$-CA (left) and [$^{132/135}$La]$La^{3+}$-Macropa (right), after 48 hours in various stability challenge assays. [Metal] to [Chelator] ratio was 100:1. % v/v 1:1 for human serum/phosphate buffer solution to reaction solution. Reactions were kept at 37 °C with 0.1 M $NH_4OAc$ (buffer) pH 7 and [Chelator] was $10^{-6}$ M. n = 3

## *In vitro* Stability Challenge Assays with $^{225}$Ac Complexes




- [$^{225}$Ac]$Ac^{3+}$-18-Py$N_6$-CA shows relatively similar kinetic inertness to [$^{225}$Ac]$Ac^{3+}$-Macropa
- Both complexes show >95% complex intact over 9 days

**Figure 3.** Percentage of [$^{225}$Ac] radiometal complex intact, [$^{225}$Ac]$Ac^{3+}$-18-Py$N_6$-CA (left) and [$^{225}$Ac]$Ac^{3+}$-Macropa (right), after 9 days in various stability challenge assays. [Metal] to [chelator] ratio was 100:1. % v/v 1:1 for human serum/phosphate buffer solution to reaction solution. Reactions were kept at 37 °C with 0.1 M $NH_4OAc$ (buffer) pH 7 and [Chelator] was $10^{-6}$ M. n = 3

## Radio-HPLC Chromatogram of 18-Py$N_6$-CA Radiometal Complex

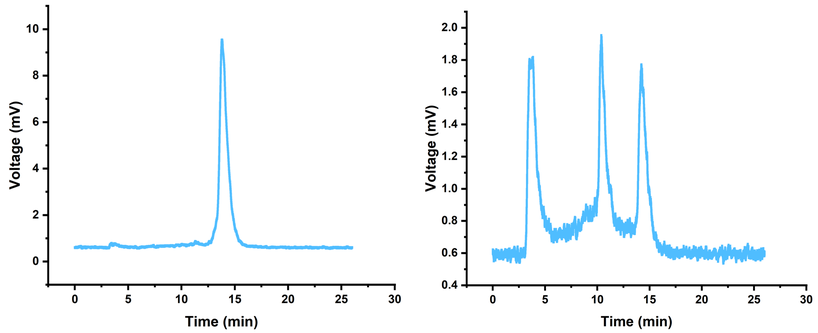



**Figure 4.** Radio-HPLC chromatogram of $^{132/135}$La-18-Py$N_6$-CA (left) and $^{225}$Ac-18-Py$N_6$-CA (right) using standard gradient of 100% $H_2O$ + 0.1% formic acid to 100% Acetonitrile + 0.1% formic acid on Luna 5 µm C18 100 Å LC Column 100 × 4.6 mm. The [$^{132/135}$La]$La^{3+}$-18-Py$N_6$-CA complex retention time match closely with that of the [$^{225}$Ac]$Ac^{3+}$-18-Py$N_6$-CA complex.

## Conclusion

- Tested two chelators, 15-Py$N_3O_2$-PA and 18-Py$N_6$-CA, at different concentrations for radiolabelling Ac-225 and La-132/135.
- At 1 hour, Macropa was able to radiolabel La-132/135 at a $10^{-7}$ M whereas 15-Py$N_3O_2$-PA only labels at $10^{-5}$ M and 18-Py$N_6$-CA at $10^{-6}$ M.
- The [$^{132/135}$La]$La^{3+}$-18-Py$N_6$-CA showed excellent kinetic inertness when challenged with excess metal solutions, phosphate buffer solution, and human serum solution.
- In a similar manner, [$^{225}$Ac]$Ac^{3+}$-18-Py$N_6$-CA showed comparable in vitro complex stability to [$^{225}$Ac]$Ac^{3+}$-Macropa.
- Comparing the radio-HPLC chromatograms of [$^{132/135}$La]$La^{3+}$-18-Py$N_6$-CA and [$^{225}$Ac]$Ac^{3+}$- 18-Py$N_6$-CA we see that the peak at 14.9 minutes corresponds to the lanthanum/actinium complexation. The [$^{225}$Ac]$Ac^{3+}$-18-Py$N_6$-CA chromatogram shows an additional complex ($Bi^{3+}$-18-Py$N_6$-CA) presence.
- Based on the *in vitro* stability results 18-Py$N_6$-CA looks to be a promising chelator candidate for La-132/135 and Ac-225 theranostic applications.

## References

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[2] Nelson, B. J.; Wilson, J.; Andersson, J. D.; Wuest, F. Theranostic Imaging Surrogates for Targeted Alpha Therapy: Progress in Production, Purification, and Applications. *Pharmaceuticals* **2023**, *16* (11), 1622. DOI:10.3390/ph16111622.

[3] Kadassery, K. J.; King, A. P.; Fayn, S.; Baidoo, K. E.; MacMillan, S. N.; Escorcia, F. E.; Wilson, J. J. H2Bzmacropa-NCS: A Bifunctional Chelator for Actinium-225 Targeted Alpha Therapy. *Bioconjugate Chemistry* **2022**, *33* (6), 1222–1231. DOI:10.1021/acs.bioconjchem.2c00190.