User project report

Novel Macrocycles for Stabilizing Radium-223: Advancing Targeted Alpha Therapy

Federica Battistin

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101008571 (PRISMAP). This document reflects only the view of the author(s). The Agency is not responsible for any use that may be made of the information it contains.

1. Authors

Lead participant
Dr Federica Battistin
Postdoctoral researcher
University of Brest
UMR CNRS 6521 - Département de Chimie
29200
Brest
France
federica.battistin@univ-brest.fr
0298016165
Now:
Research Assistant
University of Trieste
Department of chemical and pharmaceutical science
federica.battistin@units.it

Participant 2
Prof Raphaël Tripier
Group Leader
University of Brest
UMR CNRS 6521 - Département de Chimie
France
raphael.tripier@univ-brest.fr

Participant 3
Dr Nicolas Lepareur
radiochemist
Centre Eugene Marquis
Department of Pharmacy
France
n.lepareur@rennes.unicancer.fr

Participant 4
Dr Clarisse Brossard
radiochemist
Centre Eugene Marquis
Department of Pharmacy
France
c.brossard@rennes.unicancer.fr

2. Context of the project

Targeted alpha therapy is a cutting-edge form of radiotherapy that uses alpha particles, which are highly effective in destroying cancer cells. A key element is radium-223, a radioactive isotope that emits alpha particles and has shown promise in treating certain cancers, such as prostate cancer. A major challenge is ensuring that radium-223 remains securely bound to the delivery compound, preventing it from harming healthy tissues. The goal of this research is to design new macrocycles that can tightly hold radium-223, ensuring it is delivered safely to cancer cells without harming healthy tissues. The current gold-standard chelator, macropa, faces stability issues when linked to vectors—molecules that guide the treatment to the cancer cells— leading to the release of radium in the body.

3. Results and discussion

Radiolabelling of ligands in Fig 1 with radium-223 was evaluated at various T, reaction times, and pH conditions, using macropa as reference.

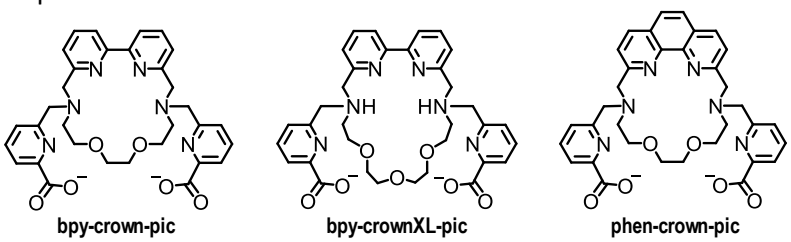

Fig 1. Structure of the proposed ligands.

Optimal conditions were identified at 40°C for 30 min with a final ligand concentration of 6.7×10^{-4} M, and RCY around 95% for all 3 ligands. Macropa demonstrated better performance, maintaining RCY above 95% even at 6.7×10^{-5} M at 20°C.

Stability studies in EDTA medium and human serum revealed that all ligands exhibited lower stability than ^{223}Ra-Macropa, with radiochemical purity decreasing by more than half after one day in EDTA, suggesting radium exchange over time (Fig 2 and 3).

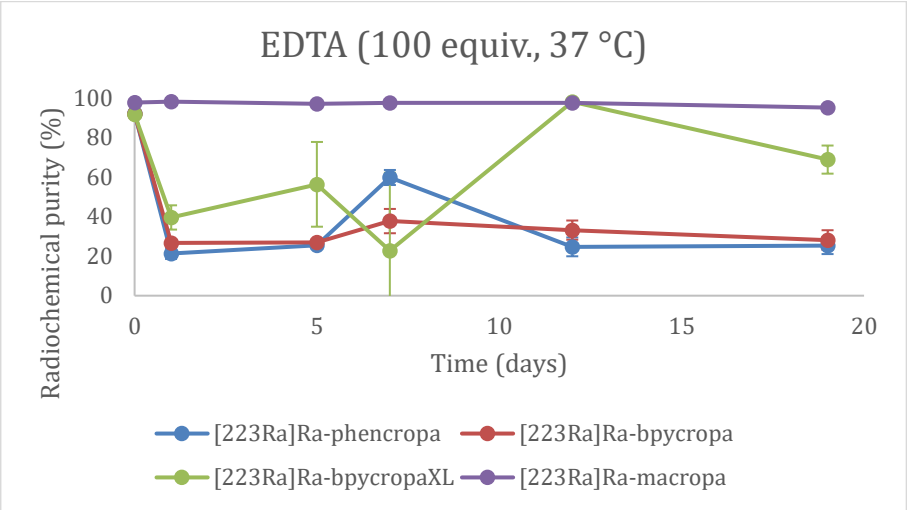

Fig 1. Stability studies in EDTA medium.

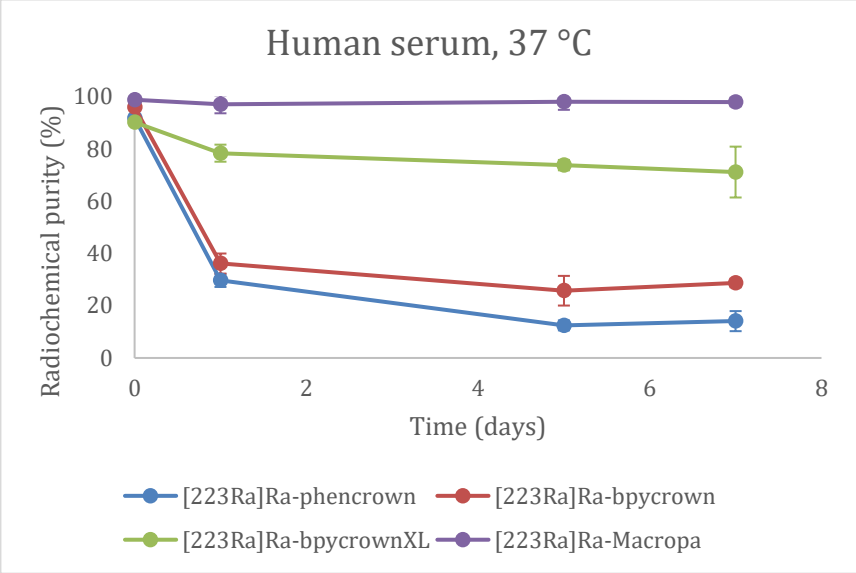

Fig 2. Stability studies in human serum.

Table 1. octanol/water partition coefficient LogD(7.4)

Radiocomplex	**LogD(7.4)**
^{223}Ra-phencropa	0.29 ± 0.01
^{223}Ra-bpycropa	-0.56 ± 0.04
^{223}Ra-bpycropaXL	0.26 ± 0.03
^{223}Ra-Macropa	-1.86 ± 0.01

4. Conclusions

For radium-223 radiolabeling, ligands in Fig 1 performed less effectively than macropa. The 3 ligands achieved radiochemical yields around 95% at 6.7×10^{-4} M and 40°C, whereas macropa reached similar RCY at a ten-fold lower concentration (6.7×10^{-5} M) and room temperature.

Stability studies in EDTA medium and human serum demonstrated that of the three novel ligands were unstable over time, unlike the highly stable [^{223}Ra]Ra-macropa. These results suggest that these macrocycles may not be optimal for radium chelation and stabilization, limiting their potential for therapeutic applications.

5. Involvement of the PRISMAP services

Through PRISMAP services, we received two shipments of radium-223 spaced one month apart, enabling comprehensive optimization of radiolabelling conditions for three novel ligands and direct comparison with the macropa standard. The first delivery allowed us to establish optimal reaction parameters for all ligands. The second shipment enabled stability studies in EDTA medium and human serum over extended periods, providing crucial data on radiocomplex performance. This access to radium-223 was essential for evaluating the potential of these new chelators for therapeutic applications.

6. Feedback to PRISMAP

Communication with PRISMAP was consistently clear and timely throughout the project, particularly regarding radionuclide delivery coordination. The application process was straightforward, and logistical aspects were handled professionally. The team demonstrated excellent responsiveness and provided comprehensive support from initiation to completion. Scheduling and delivery of the two radium-223 shipments were executed flawlessly, enabling efficient experiment planning. Our experience with PRISMAP services has been exceptionally positive.

7. Publications and other dissemination activities (conferences etc.)

A manuscript summarizing the complete radiolabelling optimization and stability studies is currently in preparation for submission to a peer-reviewed journal. We also plan to present the full dataset at upcoming international conferences in nuclear medicine and radiopharmaceutical chemistry. In all cases, we will follow PRISMAP dissemination rules prior to any submission.