

Bimodal nanoparticles for MRI and optical imaging based on polymer vesicles (polymersomes) for image-guided drug delivery

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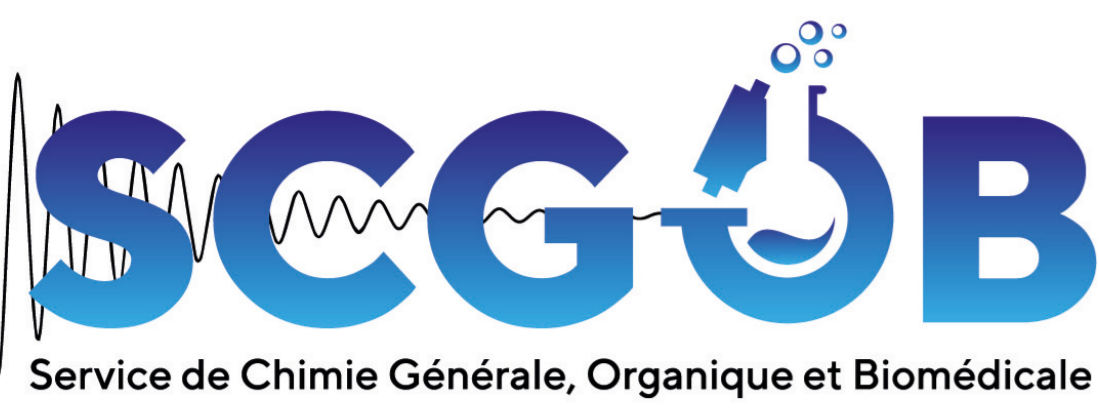
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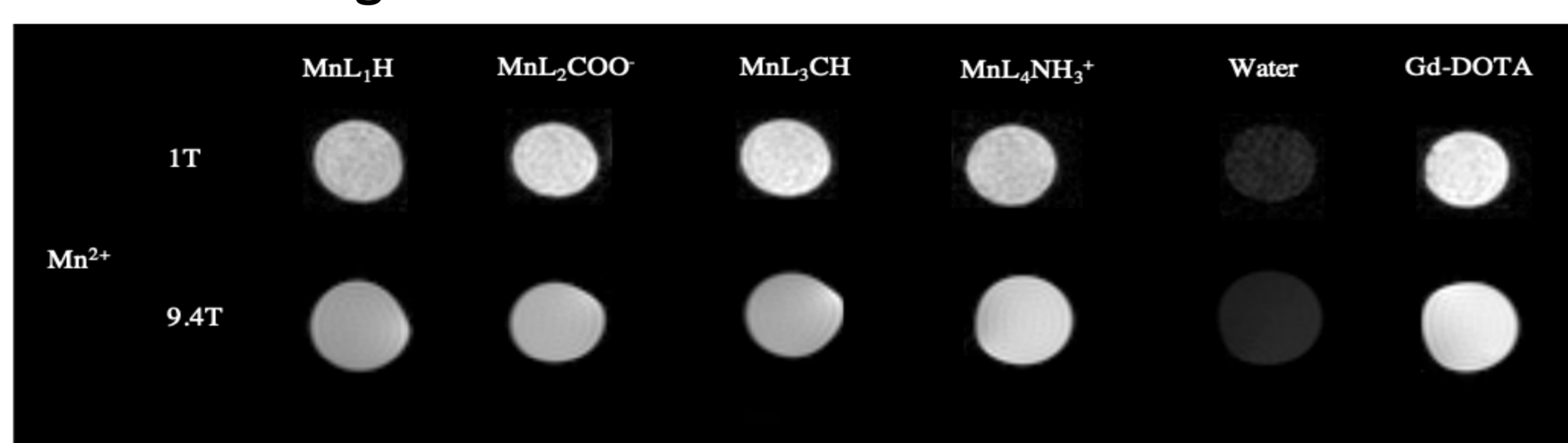


1. Introduction

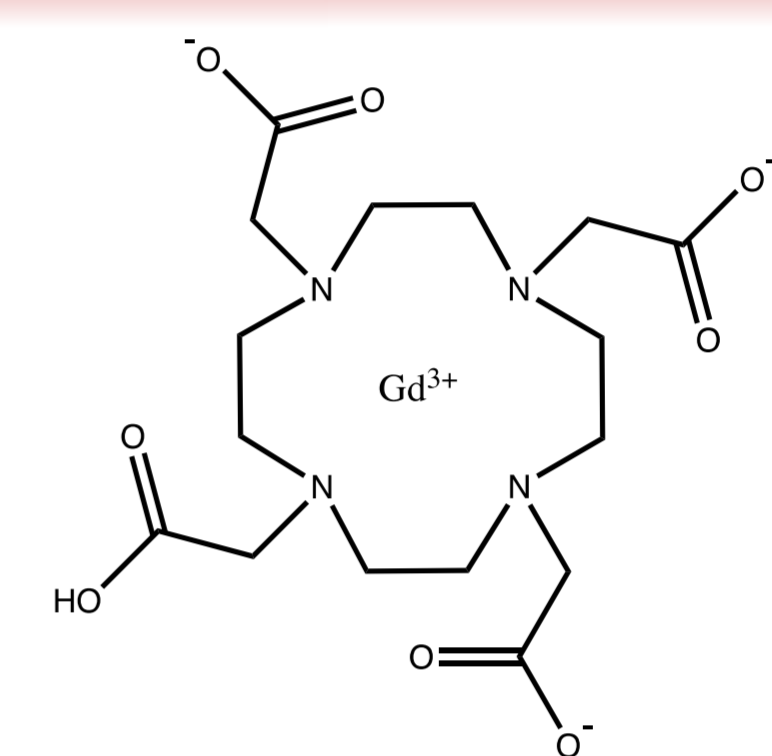
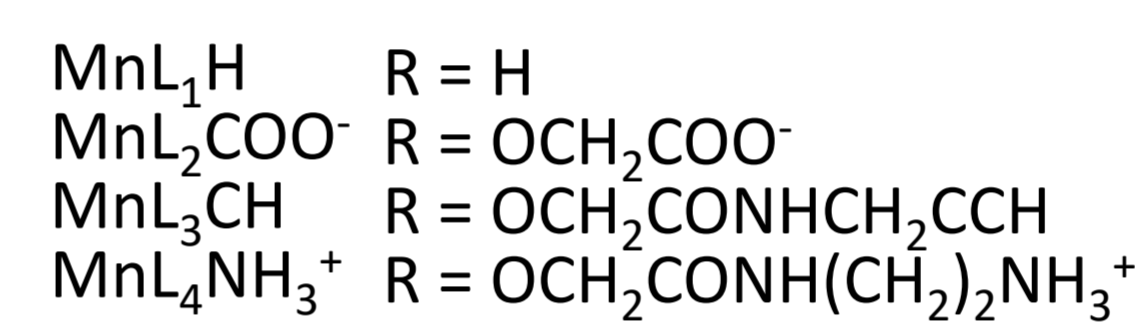
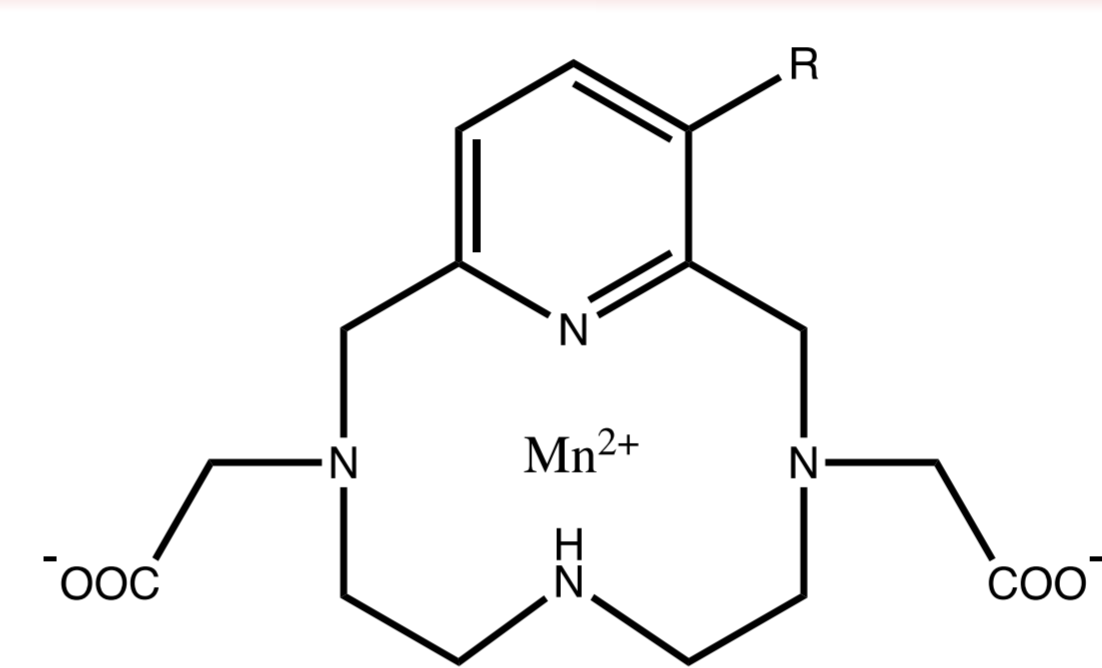
In modern medicine, bioimaging acquired a leading place in the diagnosis setting. This is why researches are continually carrying out to improve the available techniques. One of the most used techniques to obtain anatomical information is magnetic resonance imaging (MRI). Although it is a highly resolutive technique, it has low sensitivity, which needs to be enhanced by a contrast agent. However, the commercially available contrast agents are based on gadolinium complexes, which can lead to nephrogenic systemic fibrosis. That is why the synthesis of new complexes based on another magnetic cation, such as manganese (Mn^{2+}), is interesting. Manganese ions are indeed potentially less toxic since they are naturally present in the body. This study shows the interest of pyclen derivatives complexed with Mn^{2+} ions. Further improvement will consist in the relaxometric study of the macrocyclic complexes grafted on polymer nano-vesicles, also called "polymersomes", made of a pH-sensitive polyester shell encapsulating doxorubicin and ZW800-1 in order to obtain a controlled release of the drug in the acidic tumoral environment which could be monitored by MRI and optical imaging.

2. Pyclen based manganese complexes

Phantom images

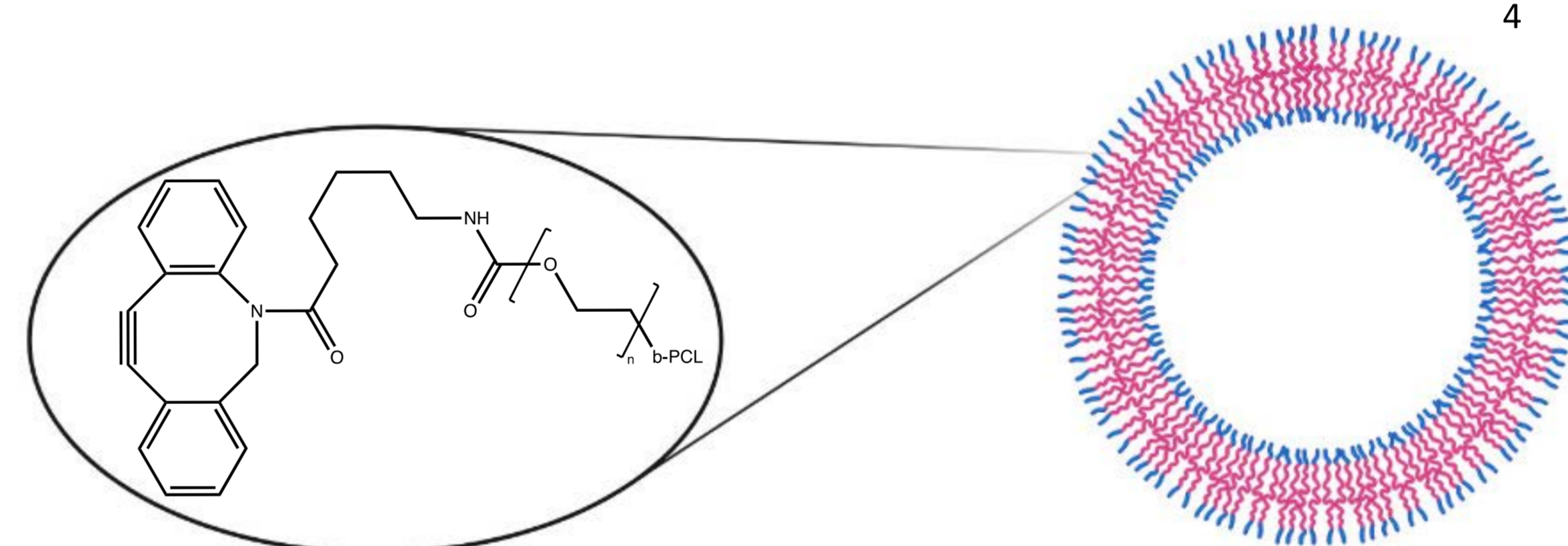
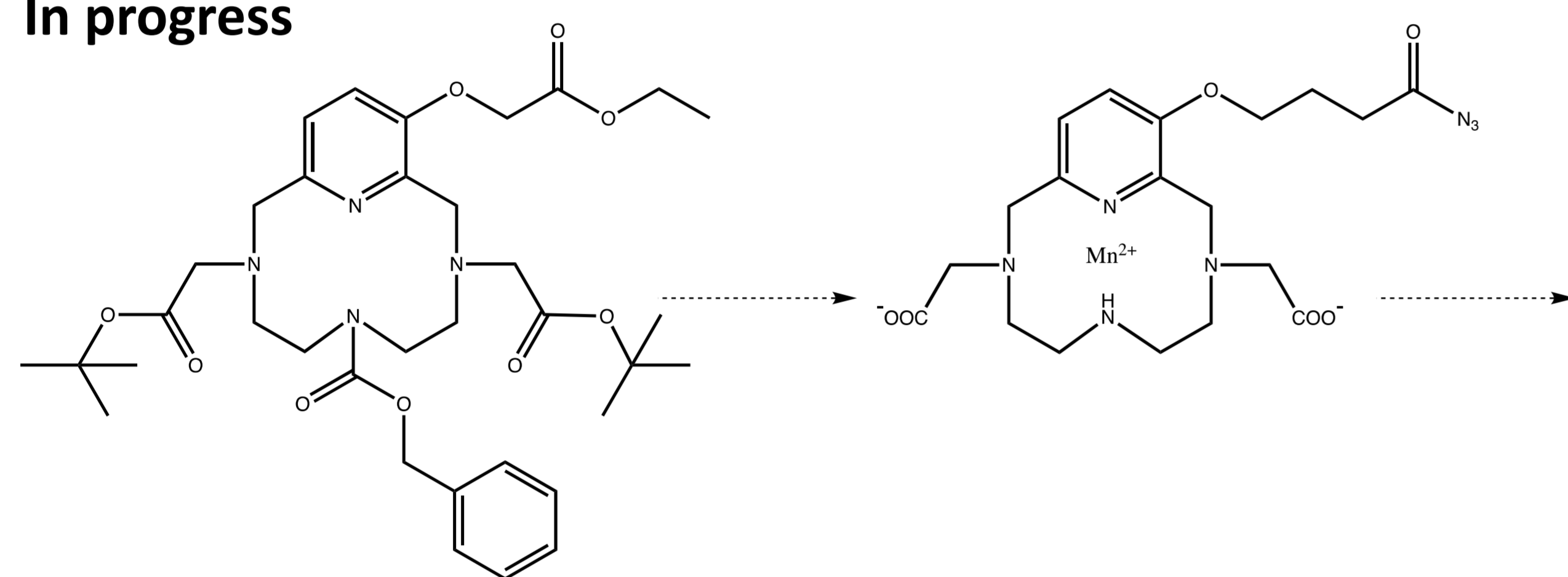


	MnL ₁ H	MnL ₂ COO ⁻	MnL ₃ CH	MnL ₄ NH ₃ ⁺	Gd-DOTA ¹
r_1 (s ⁻¹ ·mM ⁻¹)	2.8 ± 0.1	2.7 ± 0.1	3.1 ± 0.1	2.95 ± 0.1	3.2 ± 0.1
9.4T, 37°C					



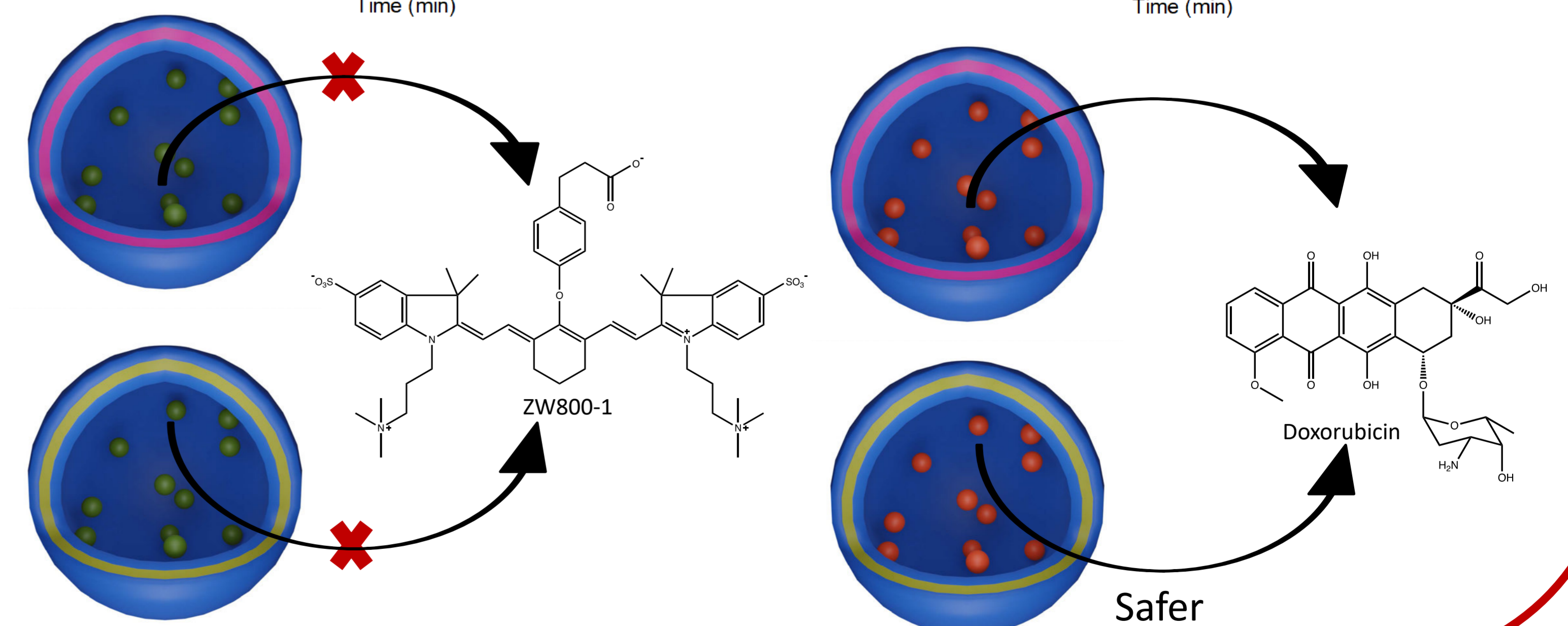
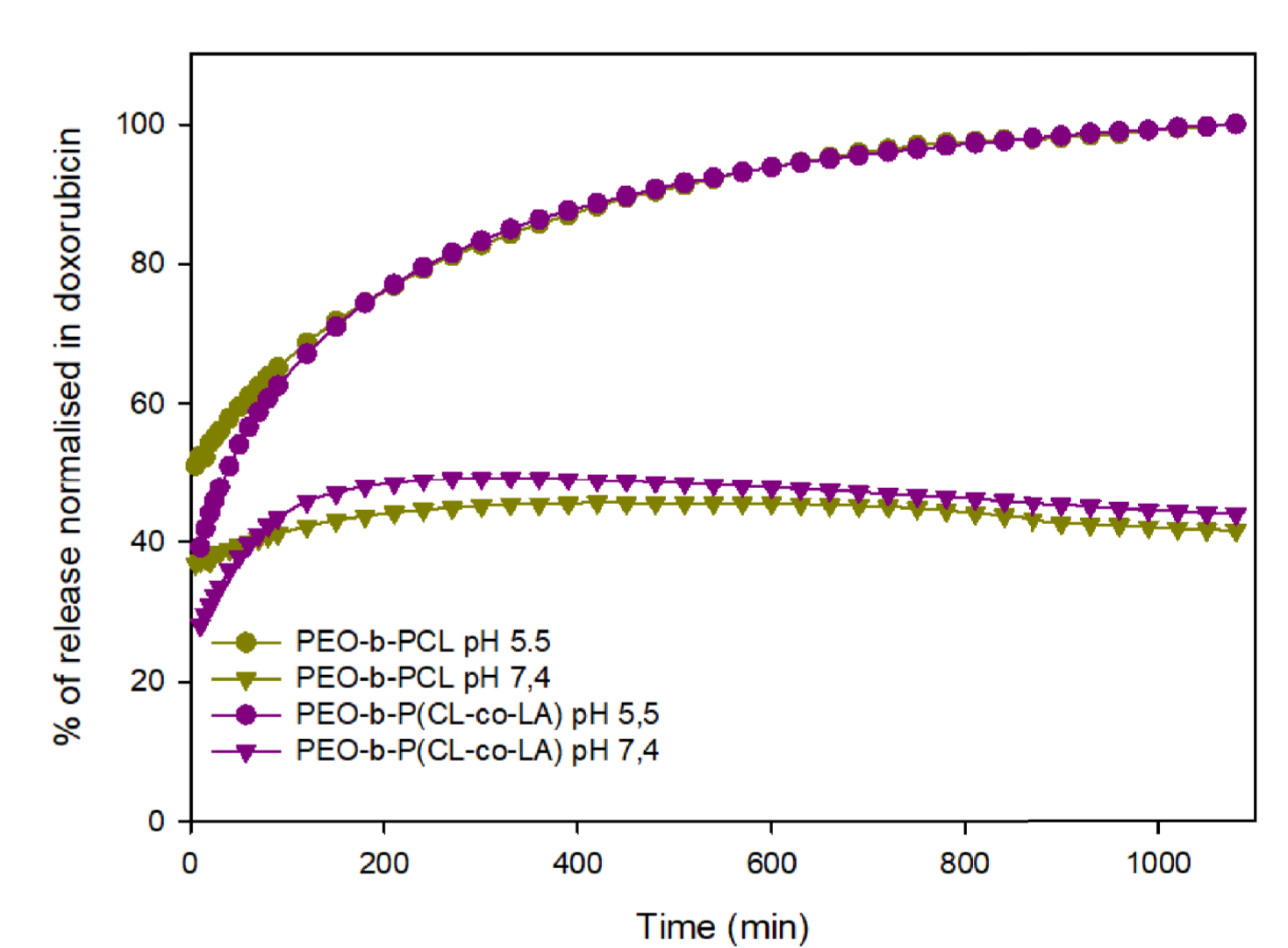
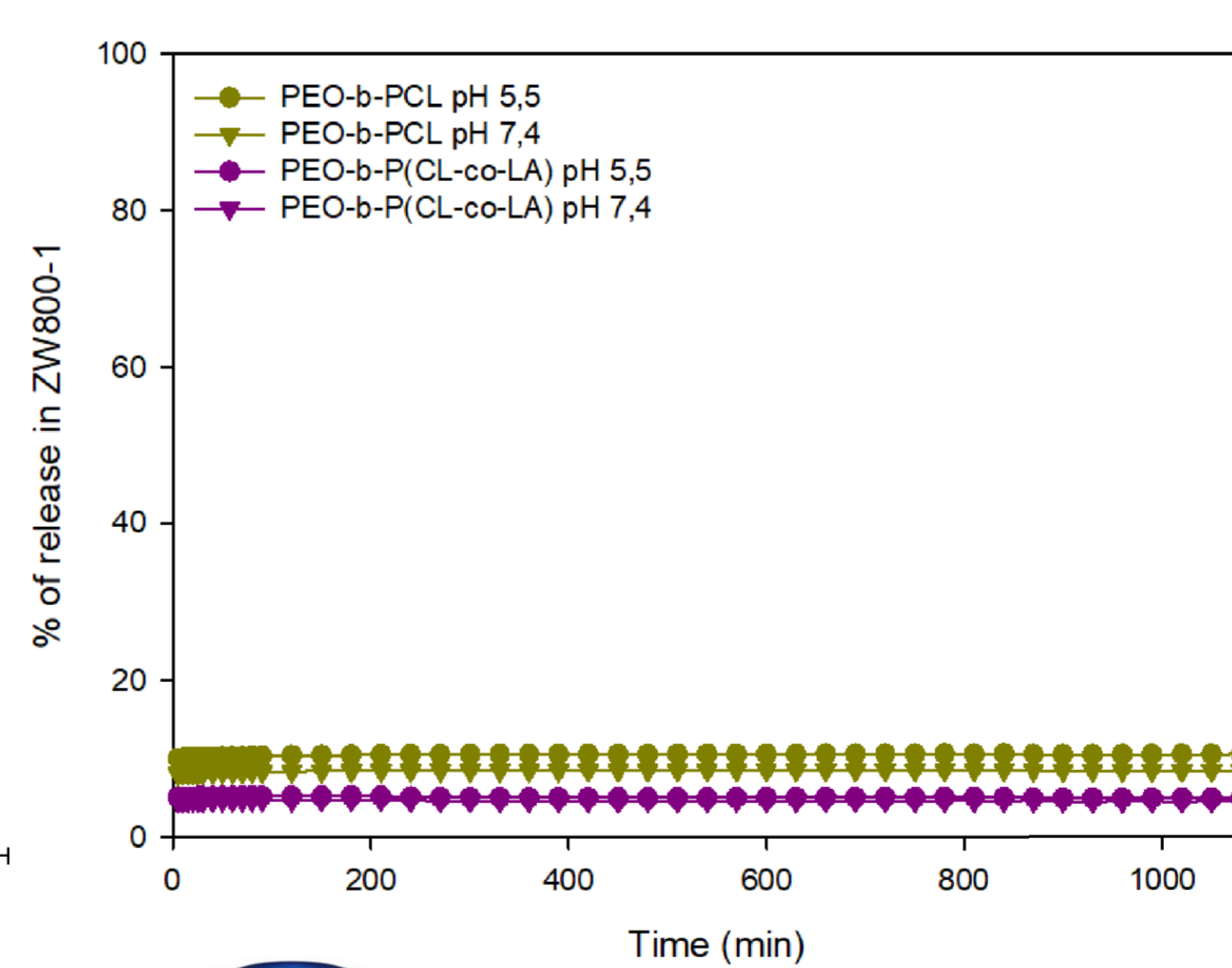
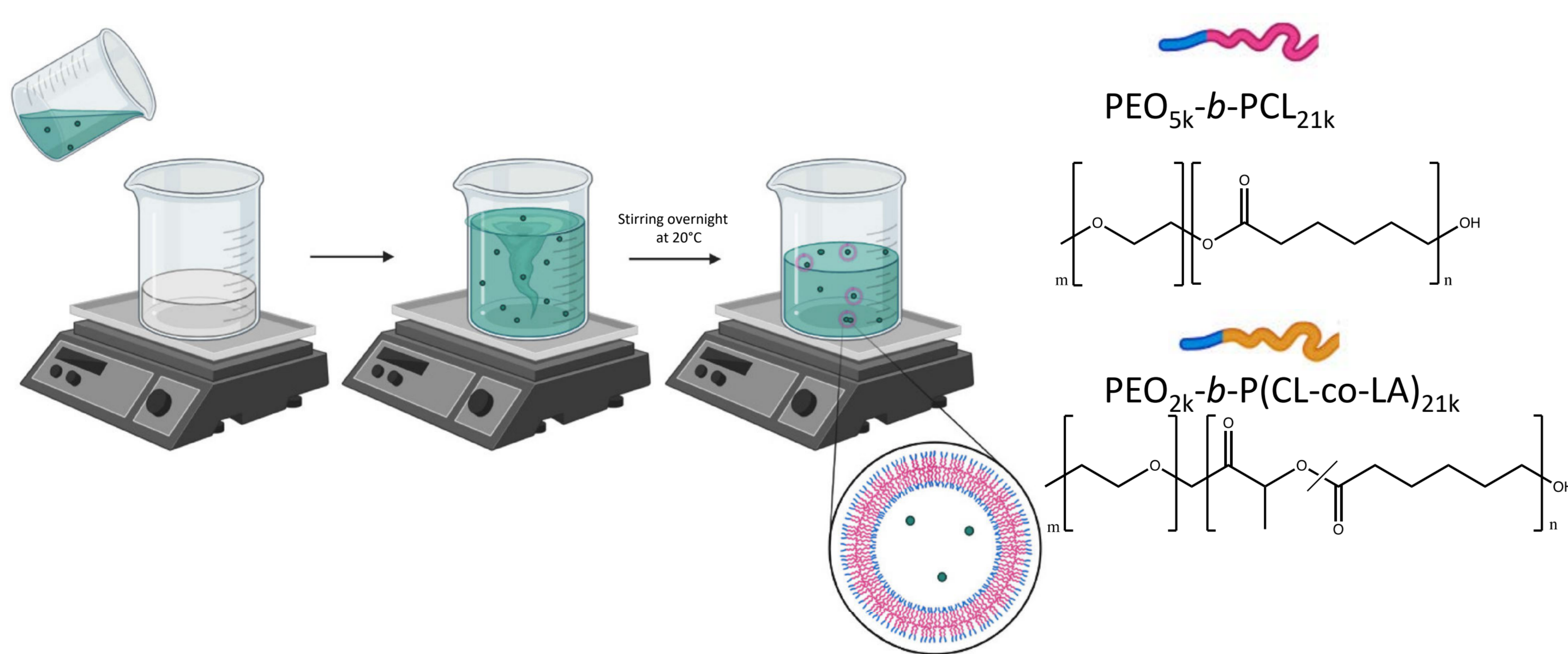
Gd-DOTA

In progress



3. Polymersomes vesicles

Nanoprecipitation of copolymers to prepare polymersomes



Cumulative release assay by automated dissolution apparatus (SOTAX® USP-4)³:

Doxorubicin release curves were detected from UV-Vis absorbance at 483 nm in flow-through conditions at 37°C and at two pH : in acidic medium (pH 5.5) to mimic tumoral micro-environment and at physiological medium (pH 7.4). Compared to control, a burst of drug release is observed within the 1st two hours instead of the ZW800-1 that show no release at 769 nm.

4. Conclusions and perspectives

This study shows that these four manganese-pyclen derivatives are promising T₁ MRI contrast agents to palliate adverse effects of gadolinium complexes. Moreover, different functions can be conjugated to obtain a functionalized pyclen that can be grafted onto the polymersomes surface to improve relaxivity and bring pH-sensitivity to the MR signal. The release of doxorubicin is currently being optimized to afford a more sustained drug release under acidic conditions in addition to the observed burst at the beginning of the test.

5. Acknowledgements

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