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Calixarene based ligands for Radium and Barium

Objectives

Due to their high biological effectiveness and suitable half-lives, there is increased interest in using the radionuclides radium-223 and radium-224 for radiopharmaceutical applications [1]. Xofigo ([223Ra]radium chloride) is a bone-seeking, alpha-emitting radiopharmaceutical with EMA and FDA approval. It is used to treat bone metastasis of castrate-resistant prostate cancer. To expand the possible applications for these promising radionuclides, it is necessary to stably bind the radionuclide within a chelator. Therefore, calixarene-based ligands have been synthesized, which show encouraging affinities to radium ions. In our recent studies, we have already presented the high potential of these ligands [2,3]. Since radium and barium have similar chemistry, and therefore comparable affinities to our ligands, it is possible to create a matched pair for theragnostic approaches. The radionuclide barium-131 has a suitable physical half-life for therapeutic applications and the potential of being a SPECT nuclide.

Methods

A series of ten calixarene derivatives, functionalized with a crown ether bridge, has been synthesized. To form a neutral complex, two deprotonable moieties have been attached to the calixarene backbone, consisting of perfluorinated sulfone amides. A variety of different sulfone amides has been compared to investigate their influence on the stability of the formed metal-complex. The complexation behavior of these ligands was studied with non-radioactive barium via UV/Vis and NMR spectroscopy. Radiolabeling was performed with barium-133 (for test labeling instead of barium-131, due to its longer half-life) and radium-224 in a simple chloroform/water-two-phase extraction for one hour at room temperature. The ion extraction potential and logK values were determined from the radioactivity distribution equilibrium. In a second step, re-extraction experiments were performed to determine the radiometal release in presence of competing metal ions like Ca2+.

Results

All synthesized calixarene derivatives showed strong interactions with barium ions in initial UV/Vis and NMR measurements. Stability constants in a range of logK=5 7 were obtained for the complexation of [133Ba]Ba2+ and [224Ra]Ra2+ via the radioactivity distribution equilibrium. Depending on the functionalization of the ligand, different amounts of radioactivity release (5-30%) were obtained in the competitive extraction studies. The complexation of radioactive [133Ba]Ba2+ ions was verified by HPLC as well.

Conclusions

Calixarene derivatives, modified with perfluorinated sulfone amides, are suitable ligands for the complexation of heavy alkaline earth metal ions. Ongoing research is concentrating on the functionalization of these ligands, regarding their water solubility and biocompatibility. Furthermore, a biological targeting unit will be attached and first biological studies will be performed.

References:

[1] M. Gott et al., *The Radiochemical and Radiopharmaceutical Applications of Radium*, Open Chem. 2016, **14**, 118-129.
[2] Steinberg, J., et al., *Modified Calix[4]crowns as Molecular Receptors for Barium.* ChemistryOpen, 2018, **7**, 432.
[3] Bauer, D., et al., *Chelation of heavy group 2 (radio)metals by p-tert-butylcalix[4]arene-1,3-crown-6 and logK determination via NMR.* Spectrochim Acta A Mol Biomol Spectrosc, 2018, **199**, 50.

Email Address

d.bauer@hzdr.de

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Primary author: Mr BAUER, David (Dresden)

Co-authors: Dr MAMAT, Constantin (Helmholtz-Zentrum Dresden-Rossendorf, Institute of Radiopharmaceutical Cancer Research); Mr REISSIG, Falco (Helmholtz-Zentrum Dresden-Rossendorf, Institute of Radiopharmaceutical Cancer Research); Dr PIETZSCH, Hans-Jürgen (Helmholtz-Zentrum Dresden-Rossendorf, Institute of Radiopharmaceutical Cancer Research); Prof. STEINBACH, Jörg (Helmholtz-Zentrum Dresden-Rossendorf, Institute of Radiopharmaceutical Cancer Research)

Presenter: Mr BAUER, David (Dresden)