SYNTHESIS OF OF TWO CYCLEN BASED BIFUNCTIONAL ^{68}Ga CHELATORS WITH ORTHOGONAL CONJUGATION REACTIVITY

P J Riß[1], C Kroll[1], O Koehler[1], S Anderhub[1], J Peters[2] and F Roesch[1]

[1]Institute of Nuclear Chemistry, Mainz University, Fritz Strassmann-Weg 2, 55128 Mainz, Germany;
[2]Institute of Organic Chemistry und Catalysis, TU Delft, Julianalaan 136, 2628 BL Delft, The Netherlands

Introduction and aim: Easily available generator derived ^{68}Ga offers a remarkable potential for clinical applications of PET. To reinforce the flow of novel tracer candidates to biological evaluation, a convenient, time efficient route to chelator conjugated potential targeting vectors would be desirable. The macrocyclic chelators NOTA and DOTA have emerged as frequently considered alternatives for the introduction of a ^{68}Ga-tag. Although both have been conjugated to a variety of targeting vectors (TV), eight-coordinate DOTA remains the most frequently used. Making use of two redundant pendant arms in six coordinate Ga(III)-DOTA complexes, we developed an approach towards dimeric conjugates, assembled from two targeting vectors and one Chelator unit.

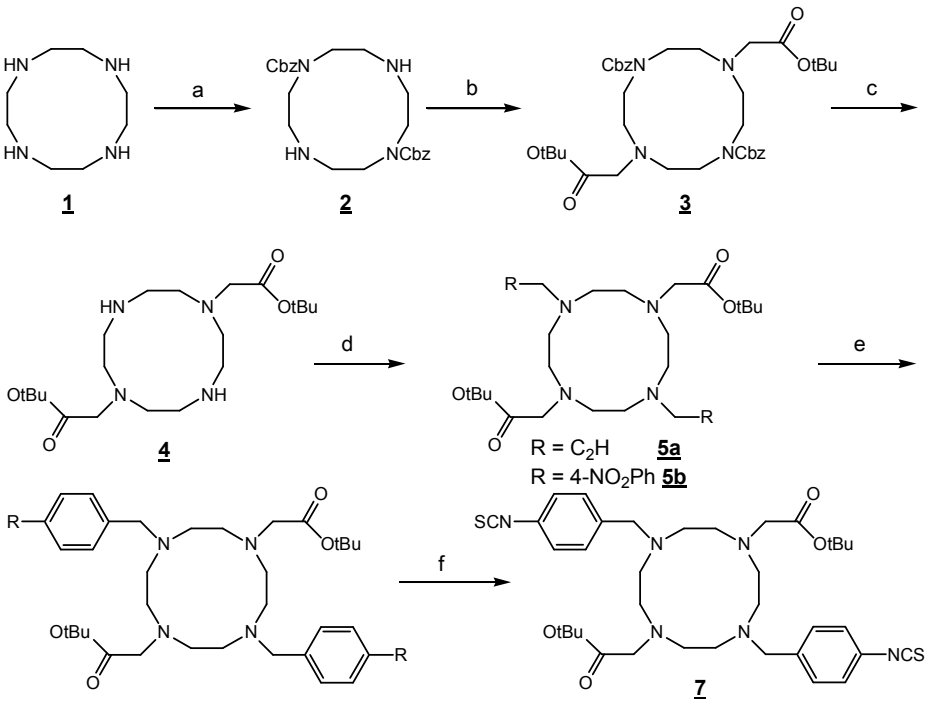
Experimental: 1,7-tBu-DO2A **4** was synthesised in 86% yield via the route of Kovacs et al.[1]. **4** was reacted subsequently with either 4-nitrobenzyl bromide or propargyl chloride to obtain **5a-b**. Reduction of **5b** following Zinin's procedure or employing Pd/C under alkaline conditions furnished **6b**. **6b** was reacted subsequently with 2 eq. of thiophosgen to obtain acceptor conjugated chelator **7** in a yield of 47 % over 6 steps. ^{68}Ga labelling of both chelators was performed after deprotection in TFA and purification via ion exchange chromatography. Stability of both chelators was determined in a DTPA challenge experiment at 40°C.

Results and Discussion: With 1,7-bis-tert-butoxycarbonylmethyl-4,10-bis-(propargylyl)-1,4,7,10-tetraaza-cyclododecane **6a** and 1,7-bis-tert-butoxycarbonylmethyl-4,10-bis-(4-isothiocyanato-benzyl)-1,4,7,10-tetraaza-cyclododecane **7** two novel bifunctional chelators have been synthesised in acceptable yield. Both chelators contain functional groups for orthogonal conjugation of TVs under mild and efficient conditions. ^{68}Ga was incorporated in a yield of 65 ±7 % at 90 °C in water. Both chelates remained stable for 2 h in a DTPA challenge experiment.

Conclusion: Both novel compounds **5a** and **7** can be employed as building blocks in a convergent approach to large tables of chelator-[spacer]-TV conjugates. ^{68}Ga-labelled chelators were obtained in good yield under standard conditions, indicating adequacy as radiolabel.

References:

[1] Kovacs, Zoltan; Sherry, A. Dean; J. Chem. Soc. Chem. Comm. (1995), (2), 185 f.



Scheme 1: Synthetic route to **5a** and **7**