SYNTHESIS AND PRELIMINARY EVALUATION OF TACN BASED BIFUNCTIONAL CHELATORS WITH ORTHOGONAL CONJUGATION REACTIVITY

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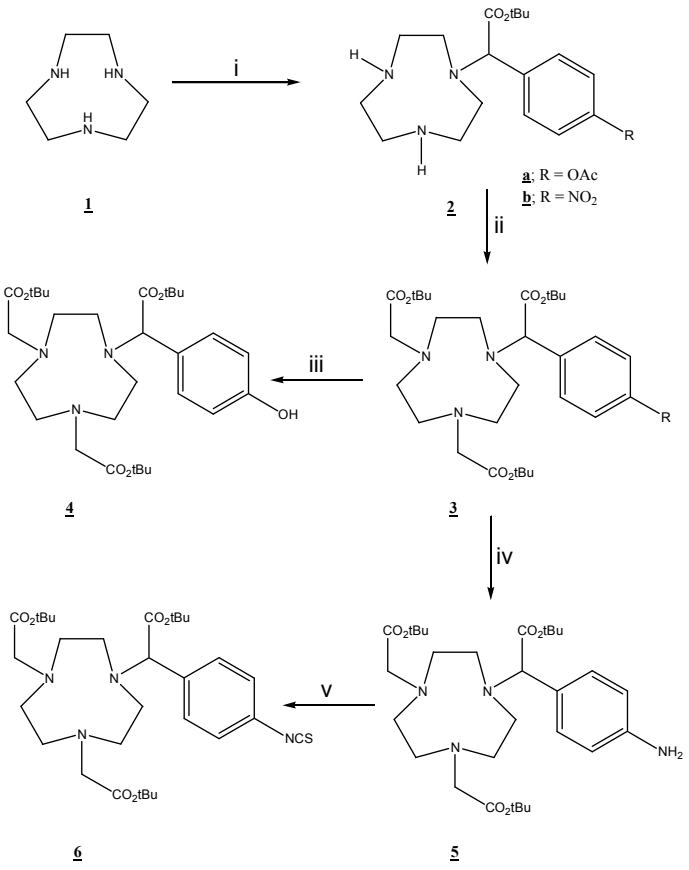
Introduction and aim: Easily available generator derived ^{68}Ga offers a remarkable potential for clinical applications of PET. To reinforce the flow of novel tracer candidates to biological evaluation, a convenient, time efficient route to chelator conjugated targeting vectors (TV) would be desirable. The macrocyclic chelators NOTA and DOTA have emerged as frequently considered alternatives for the introduction of a ^{68}Ga-tag. DOTA remains the most frequently used because of its greater availability and less challenging synthesis, although NOTA and its derivatives usually display higher stabilities and faster labelling kinetics.
Starting from an improved Richman-Atkins-cyclisation to afford high purity 1,4,7-triazacyclononane in 85 % yield, we developed an efficient route to NOTA-analogue bifunctional chelators.



Scheme 1: synthesis route to **4a** and **5**

Experimental: TACN **1** was obtained via a modified protocol of the route of Richman and Atkins[1]. **1** was reacted subsequently with either 2'-bromo-4-nitrophenylacetic acid tert.-butyl ester bromide or 2'-bromo-4-acetoxyphenylacetic acid tert.-butyl ester to obtain **2a-b**. Subsequent reaction with tert.-butyl bromoacetate furnished tert.-butyl protected NOTA analogues **3a-b**. **4** was obtained via deprotection of **2a** using 10% KOH in MeOH in a yield of 68% over 5 steps. Reduction of **3b** following Zinin's procedure or employing Pd/C under alkaline conditions furnished **5**. **5** was reacted thiophosgen to obtain acceptor conjugated chelator **6** in a yield of 57 %.
^{68}Ga labelling of both chelators was performed after deprotection in TFA and purification via ion exchange chromatography. Stability of both chelates was determined in a DTPA-challenge experiment at 40 °C.

Results and discussion: With **4** and **6** two novel bifunctional chelators have been synthesised in convenient yield. Both chelators contain functional groups for orthogonal conjugation of TVs under mild and efficient conditions. ^{68}Ga was incorporated in a yield of 85±8 % at 45 °C in water. Both chelators remained stable for 4 h in a DTPA challenge experiment.

Conclusion: Both novel compounds **4** and **6** 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 very good yield under mild conditions, indicating adequacy as radiolabel.

References:
[1] J. E. Richman and T. J. Atkins, *J. Am. Chem. Soc.*, 1974, **96**, 2268