Synthesis of bifunctional derivatives of TACN-TM: Novel lipophilic chelators for ^{68}Ga

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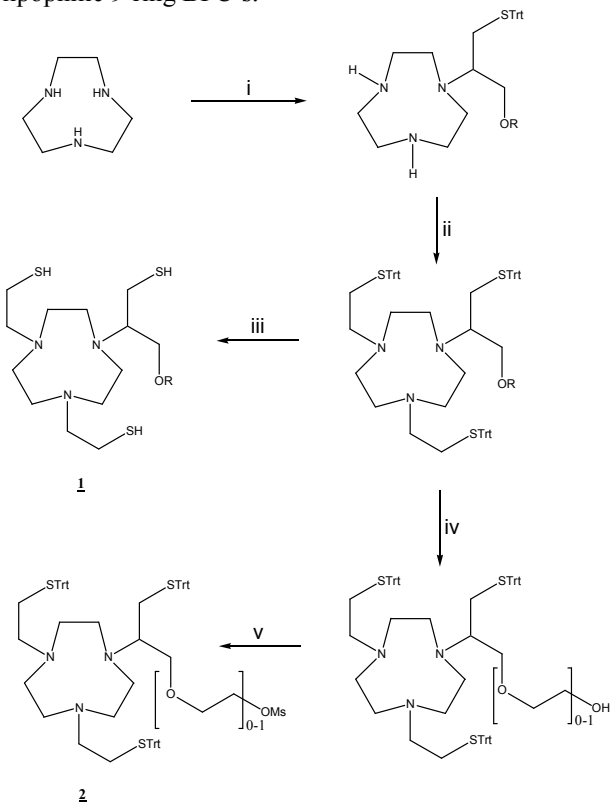
Introduction and aim: Easily available generator derived ^{68}Ga offers a remarkable potential for clinical applications of PET. At present the application of a Ga-radiolabel is limited mainly to non-lipophilic environment. Ga-bifunctional chelator (BFC)-complexes of macrocyclic chelators like NOTA and DOTA remain the most frequently considered method for the introduction of a ^{68}Ga-tag. Unfortunately, the carboxylate donors of NOTA and DOTA lead to non-lipophilic Ga-chelates. From our experience a less polar donor function might increase lipophilicity of the chelates obtained with gallium to some extend, to facilitate passage of the blood brain barrier, as well as passive diffusion into cells. An advantageous effect on general biodistribution and clearance is also possible. TACN-TM has already been prepared and characterised [1].
We focussed our effort on the next generation of TACN-based bifunctional chelators. Herein we introduce the TACN-TM-MZ chelator concept for lipophilic 9-ring BFC´s.



1

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Scheme 1: 1,4,7-trismercaptoethyl-1,4,7-triazacyclononane TACN-TM. The synthetic approach to TACN-TM facilitates the introduction of a conjugation reactivity. Various side chains may be incorporated to generate a bifunctional chelator, cf. Fig. 2.

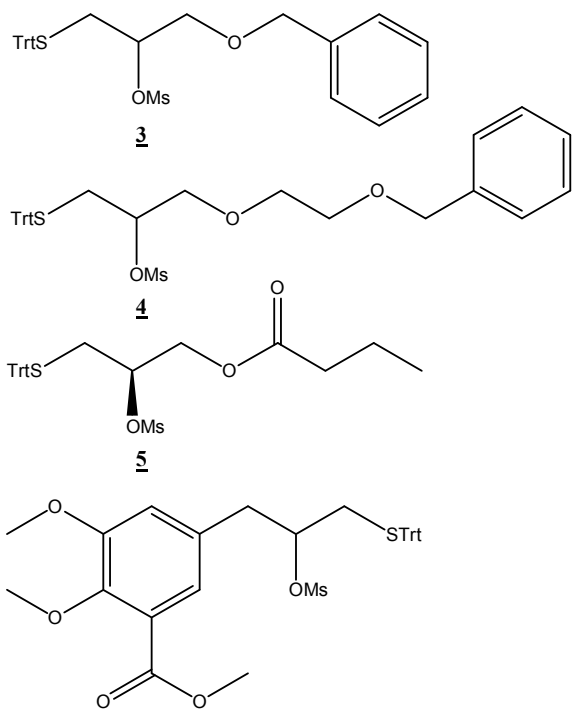

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Figure 2: Reactants for the introduction of a linking-group

Experimental: TACN was obtained via a modified protocol of the route of Richman and Atkins [2]. **1** was obtained via alkylation with 1-benzyloxy-2-mesyloxy-3-tritylthiopropane **3** followed by tritylthioethyl bromide. The chelator was obtained by deprotection in TFA under cation trapping conditions and purification via ion exchange chromatography.

Results and Discussion: With **1** and its derivatives lipophilic chelators for ^{68}Ga coordination have been synthesised as building blocks. These chelators can now be employed in the synthesis of lipophilic Gallium labelled radioligands for PET.

Conclusion: Bifunctional derivatives of compounds **1** and **2** can be employed as building blocks in the synthesis of lipophilic chelator-spacer-TV conjugates. The corresponding ^{68}Ga-labelled chelates can be obtained in good yield under mild conditions.

References

[1] Rong Ma, Michael J. Welch, J. Reibenspies and Arthur E. Martell; Inorganica Chimica Acta**;** Volume 236, Issues 1-2, August 1995, Pages 75-82
[2]. J. E. Richman and T. J. Atkins, *J. Am. Chem. Soc.*, 1974, **96**, 2268