Preliminary evaluation of TACD-TM: A novel candidate as bifunctional Chelator for ^{68}Ga

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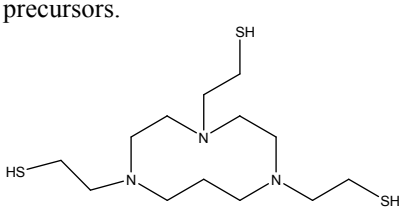
Introduction and aim: Easily available generator derived ^{68}Ga offers a remarkable potential for clinical applications of PET. Macrocyclic chelators have emerged as most frequently uttered ligands for the introduction of a ^{68}Ga-tag. DOTA remains the most frequently used because of its greater availability and less challenging synthesis, although NOTA and its derivatives display higher stabilities and faster labelling kinetics. Unfortunately, the carboxylate donors of NOTA and DOTA lead to non-lipophilic Ga-chelator complexes. From our experience a less polar donor function might increase the lipophilicity of the complexes obtained with gallium to some extend, to enable passage of the blood-brain-barrier, as well as increase passive diffusion into cells. TACN-TM has already been prepared and characterised [1]. We focussed our effort on the novel TACD-TM chelator 1,4,7-tris-mercaptoethyl-1,4,7-triazacyclodecane, obtained via Mitsunobu cyclisation from common precursors.



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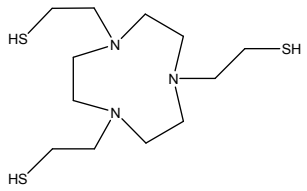

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Scheme 1: 1,4,7-trismercaptoethyl-1,4,7-triaza-cyclodecane TACD-TM **1** and 1,4,7-trismercaptoethyl-1,4,7-triazacyclononane TACN-TM **2**

The synthetic approach to TACD facilitates the introduction of a chain branch in position 2 of the propylene moiety. Various side chains may be incorporated to generate a bifunctional chelator. In the present study, the stability of [^{68}Ga]TACD-TM has been examined and compared to [^{68}Ga]TACD-TM.

Experimental: TACD was obtained via a modified protocol of the route of Richman and Atkins [2]. **1** was obtained via alkylation with 2-tritylthioethyl bromide followed by deprotection in TFA under cation trapping conditions and purification via ion exchange chromatography. ^{68}Ga was incorporated in aqeous hydrochloric acid at 75 °C. Stability of both [^{68}Ga]TACD-TM and [^{68}Ga]TACD-TM.was determined in a challenge experiment at 25 °C. The octanol water distribution coefficient log $P_{7.4}$ of the Ga-ligand complexes was determined via an HPLC-method.

Results and Discussion:
With **1** a lipophilic ^{68}Ga-chelate has been synthesised. At least 70 % of the gallium-chelate remained stable for 3 h in a challenge experiment using substoichiometric and stoichiometric amounts of a macrocyclic as well as an open chain Ga-chelator at 40 °C.

Table 1: results of challenge experiments

	DOTA 23 nmol (1:1)			DOTA 2,3 nmol (0,1:1)		
t / min	TACD	DOTA	Free ^{68}Ga	TACD	DOTA	Free ^{68}Ga
15	88.5	8.2	3.2	87.9	8.7	3.5
30	87.7	8.8	3.5	88.7	8.1	3.2
60	84.5	12.3	3.2	88.1	8.9	2.9
120	80.8	16	3.2	87.7	9.5	2.7
180	78	18.7	3.4	88.6	7.6	3.8
	EDTA 23 nmol (1:1)			EDTA 2,3 nmol (0,1:1)		
t / min	TACD	EDTA	Free ^{68}Ga	TACD	EDTA	Free ^{68}Ga
15	86.4	10	3.6	88.1	8.6	3.2
30	86.3	10.5	3.2	88.2	8.6	3.2
60	82.9	14.2	2.9	87.8	9.5	2.7
120	75.1	22.1	2.9	85.4	11.6	3
180	70.9	26.2	2.8	85.9	10.6	3.5

Conclusion: Bifunctional derivatives of compounds **1** and **2** can be employed as building blocks in the synthesis of lipophilic chelator-spacer-TV conjugates. ^{68}Ga-labelled chelates were obtained in very good yield under mild conditions, both remained stable for several hours indicating adequacy as radiolabel.

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