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Studies towards the development of lipophilic bifunctional N_3S_3 chelators for ^{68}Ga

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Summary. The present study is concerned with a concept of charge-neutral, lipophilic, macrocyclic bifunctional chelators, suitable for the introduction of a gallium-68 label into small molecules. The synthesis of a novel bifunctional N_3S_3-type chelator, derived from 1,4,7-triazacyclononane, initial ^{68}Ga-radiolabelling and the determination of stability and calculated lipophilicity of the compound are described. The ^{68}Ga-labelled chelate was obtained in a maximum radiochemical yield of 93 ± 5% after a reaction time of 2 min. It remained intact over 3 h in a DTPA-challenge and a transferrin challenge experiment, indicating sufficient stability for PET studies.

1. Introduction

In recent years, the positron emitter ^{68}Ga is undergoing a renaissance as a generator-derived PET-nuclide for clinical routine. This is due to recent improvements in the performance of commercially available ^{68}Ge/^{68}Ga generator systems and post-processing of generator eluents [1–3]. The latter includes purification of the cationic [^{68}Ga]Ga^{III} by separation of metal contaminants as well as eluate concentration for labelling purpose [1]. Apart from one exception, bifunctional chelates suitable for complexation of [^{67,68}Ga]Ga^{III} are very hydrophilic compounds which lead to highly polar, sometimes charged complexes. Due to beneficial permeative properties and the potential crossing of the blood-brain-barrier, more lipophilic bifunctional chelators present a milestone in ^{68}Ga-PET. For this reason, several groups elucidated the synthesis [4–12], stability [10, 11] and biological properties [12] of less hydrophilic chelators [4–12].

Luyt and Katzenellenbogen have described a bifunctional chelator based on a tripodal NS_3-chelator (Fig. 1) [5]. Despite the value of the ligand for the intended use as labelling agent for peptides and proteins, the high molecular weight and the particular requirements for conjugation utilising the included aniline-NH_2 donor function limit the value of this compound for labelling of small molecules [5, 24].

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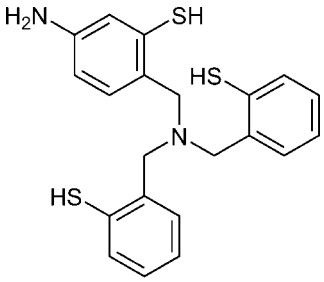
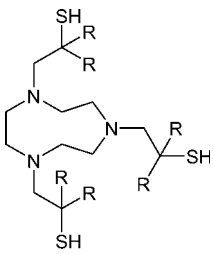


Fig. 1. Tripodal, bifunctional NS_3-type chelator **1** [5].

Less weighty aliphatic chelators were derived from the macrocyclic polyamine 1,4,7-triazacyclononane (TACN) using mercaptoethyl pendant arms. Moore and coworkers have introduced a corresponding compound **2a** [7, 8] (Table 1). The more lipophilic analogue **2b** was studied in rats with regard to a potential application as radiogallium labelled tracer for hepatobiliary imaging by John *et al.* [12]. Those authors generally claimed "lipophilicity" and the available biological properties support this claim. For example, the ^{67}Ga-chelate of **2b** is mainly excreted *via* the liver, which is a general hint on lipophilicity. Nevertheless, the compound did not show any uptake into the brain [7, 8, 12]. Being aware that high liver uptake of [^{67,68}Ga]Ga^{III} labelled compounds might also originate from

Table 1. Hexadentate N_3S_3-type chelators based on 1,4,7-triazacyclononane.



2a-b

Entry	R	Reference
2a	H	[7, 8]
2b	CH_3	[12]

[^{67,68}Ga]Ga^{III}, bound to transferrin, we decided to investigate the stability of a bifunctional derivative of **2a**. In addition, no bifunctional derivatives of **2a** have been described in the literature so far, although these are highly promising candidates for the synthesis of small molecule ^{68}Ga brain imaging agents.

2. Results and discussion

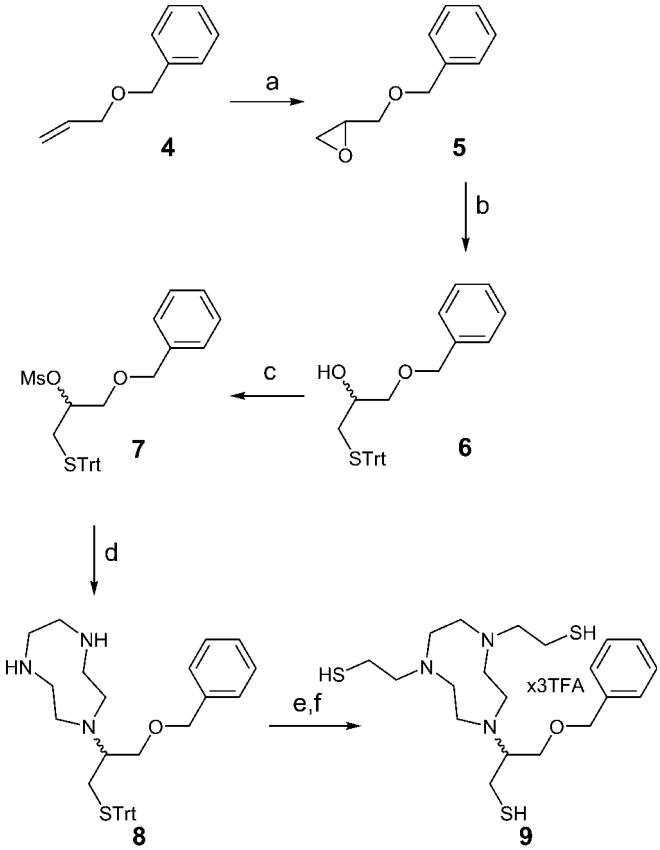
The present work elucidates a charge-neutral, macrocyclic bifunctional chelator derived from compound **2a**. The corresponding gallium chelate should possess a reasonably low molecular weight, a low tendency to form intermolecular hydrogen bonds, kinetic inertness and sufficient thermodynamic stability to facilitate PET-imaging. The kinetic inertness of the complex containing a chain branch in one pendant arm is verified. Furthermore, the claim of lipophilicity of the corresponding bifunctional complex is investigated. Therefore, a bifunctional derivative of compound **2a** was synthesised, labelled with generator-derived ^{68}Ga, tested for stability and the octanol-water partition coefficient was determined at pH 7.4 *via* HPLC.

The synthesis of the bifunctional pendant arms was straightforward from commercially available starting materials. For further functionalisation of the chelator, an asymmetric alkylation approach was chosen, wherein one pendant arm was branched with an adjacent hydroxymethyl substituent. Thereby, various donor and acceptor functions can be incorporated by interconversion of the versatile hydroxyl-group.

To get an estimate on the feasibility of the synthesis and an estimate on the properties of a potential bio-molecule conjugated 1,4,7-trismercaptoethyl-1,4,7-triazacyclononane (TACN-TM, **2a**), model compound **9** was synthesised. 1,4,7-triazacyclononane (**3**) was synthesized *via* the common route described by Richman *et al.* [13, 14]. Deprotection and work up was slightly modified to result in a reproducible yield of 83 ± 5%. The reaction time for deprotection in concentrated sulphuric acid was reduced to 120 min at 110 °C. The conversion of the protected polyamino macrocycle was monitored using the method of Raßhofer and Voegtle [23]. The sulphuric acid was removed by two subsequent precipitations in Et_2O and MeOH. The obtained colourless slurry was taken up in water and made alkaline to pH 12, prior to the extraction with n-butanol to obtain compound **3** as colourless crystals of sufficient purity for all further reactions.

The synthesis of **9** was performed as shown in Scheme 1. Allyl-benzyl ether (**4**) was epoxidised as described previously to obtain **5** in 95% yield [15, 17]. Subsequent ring-opening with lithium triphenylmethyl mercaptate afforded compound **6** in 88% yield [16]. Mesylation of alcohol **6** under standard conditions gave sulphide **7** in 97% yield [17]. Compound **8** was obtained in 33% yield by mono-alkylation of **3** in dichloromethane [22].

The final chelator **9** was obtained from **8** in 55% yield *via* alkylation of the remaining secondary amines with ethylene sulphide followed by immediate deprotection of the mono-thiol-protected intermediate [12, 18], resulting in an overall yield of 15%.



Scheme 1. Synthesis of racemic model compound **9**; (a) mCPBA, $CHCl_3$, r.t., 14 h; (b) 1. *n*-BuLi, heptane, THF, TrtSH, 0 °C, 30 min, 2. THF, **5**, 0 °C to r.t.; (c) MsCl, NEt_3, CH_2Cl_2, 0 °C, 15–30 min; (d) N_2, **3**, MeCN, reflux 3 d; (e) 1. N_2, C_2H_4S, C_6H_6, 50 °C, 2 h, 2. MeCN, anisole, TFA, Et_3SiH, −20 °C to 0 °C, 15 min.

All initial labelling and stability experiments were carried out with model compound **9** bearing a benzyl ether at the intended coupling moiety.

Compound **9** was labelled with ^{68}Ga in anhydrous chloroform as described previously, isolated by solid phase extraction and analysed by HPLC and TLC [21]. Fig. 2 gives a potential structure of the final complex **10**.

The time dependence of the radiochemical yield is shown in Fig. 3. Precursor solution **9** (10 µl, 13 nmol) was added to the reaction mixture and the reaction was conducted under conventional heating (Fig. 3). Alternatively, using microwave irradiation (CEM discover focussed microwave, 300 W, 2 min), the product **10** was obtained in 93 ± 5% yield. The chloroform was evaporated and the product was taken up in purified water and passed through a strong cation exchanger (Merck Lichrolut® SCX, 200 mg)[1].

The product was formulated in DPBS, filtered through a Millex® sterile filter and analysed for radiochemical purity and specific radioactivity by radio-HPLC (Merck LiChroSorb® RP-18, 7μ, 150 × 4.6 mm, 25% MeOH in PBS at pH 7.4) and radio-TLC (silica-gel 60, 0.1 M citrate solution pH 4 or 30% EtOH in 5% NaCl). The radiochemical purity of the product exceeded 98% and the specific activity of the product was ≥ 7 GBq/µmol.

[1] Notably, the trapped non-reacted gallium can be eluted from the cartridge with 15% HCL in Acetone solution and the non-reacted precursor can be recovered by alkaline elution to some extend.

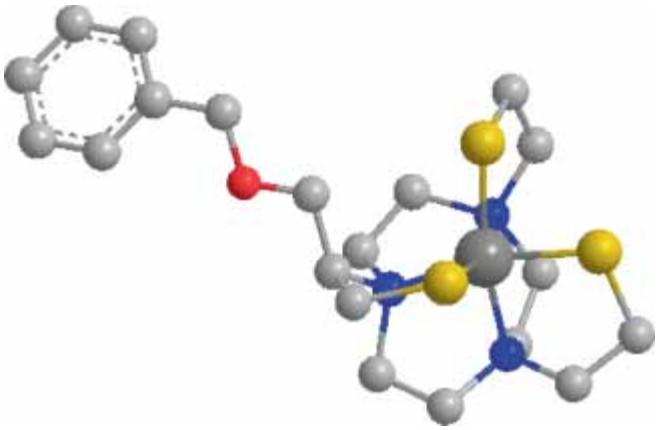


Fig. 2. Potential structure of the gallium complex **10**. Minimised energy conformation from molecular mechanics calculation.

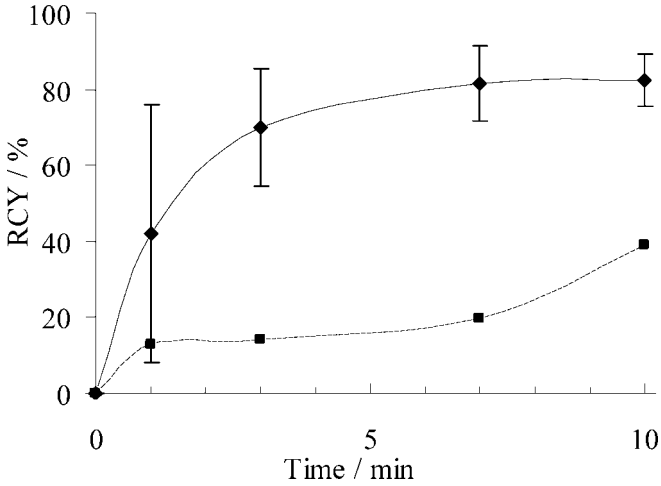


Fig. 3. ^{68}Ga labelling of chelator **9** at two different temperatures. Diamonds: 10 μg **9** at 90 °C; squares: 10 μg **9** at 40 °C. Values are mean ±1 SD from three independent determinations.

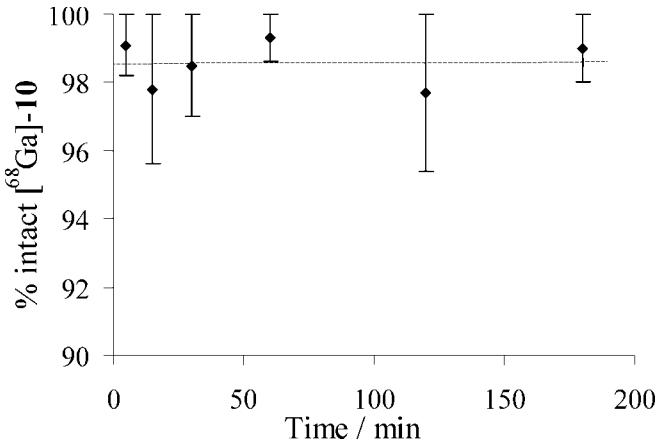


Fig. 4. Results of DTPA challenge experiment using [^{68}Ga]**10**: exemplified for 100 nM DTPA in PBS. 100 μl (10 MBq) of [^{68}Ga]**10** at pH 7.4; incubation at 37 °C for 180 min (errors are 1 SD, $n = 4$).

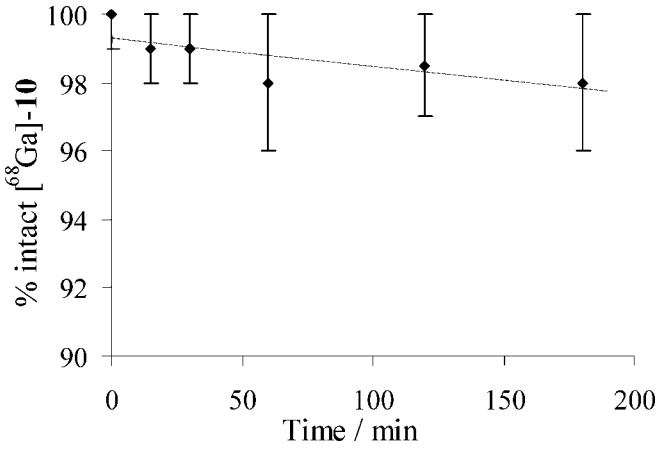


Fig. 5. Results of *apo*-transferrin transchelation experiment using [^{68}Ga]**10**. 10 mg apo-transferrin in 5 ml of PBS; 100 μl (10 MBq) of [^{68}Ga]**10** at pH 7.4; incubation at 37 °C for 180 min (errors are 1 SD, $n = 3$).

The stability of product [^{68}Ga]**10** was determined *via apo*-transferrin transchelation and DTPA-challenge experiments [22]. Therefore, aliquots of the radioactive product were added to 1 nM, 10 nM, 100 nM and 1 μM concentrations of DTPA and 10 mg *apo*-transferrin in PBS (5 ml) at pH 7.4 and incubated at 37 °C for 180 min. Samples were withdrawn from the solutions after 5 min, 15 min, 30 min, 60 min, 120 min and 180 min. The percentage of intact complex [^{68}Ga]**10** was determined by TLC.

It was found that practically no transchelation occurred between [^{68}Ga]**10** and DTPA or *apo*-transferrin, indicating that the known high stability for the non-modified 1,4,7-trismercaptoethyl-1,4-7-triazacyclo-nonane was retained, despite the introduction of the pendant arm branch (Figs. 4 and 5).

The octanol-water partition coefficient of Ga**10** was calculated using Cambridgesoft® ChemBioDraw/ChemBio3D 2007. A log *P* value of 5.36 was obtained for the charge-free octahedral complex shown in Fig. 2. Most of the bioactive molecules suitable for conjugation with an appropriate radiolabel are less lipophilic than the simple aromatic hydrocarbon used as model. Therefore, representative values obtained for the model conjugate are expected to be higher than those obtained with real targeting vectors. However, the high theoretical value for the model compound supports the utility of **10** as a moiety suitable for the synthesis of lipophilic small molecules. Furthermore, the complex [^{68}Ga]**10** shows reasonable kinetic inertness towards transchelation, which is not negatively affected by the pendant arm branch.

3. Conclusion

In conclusion, [^{68}Ga]**10** is a highly promising candidate bifunctional chelator for the synthesis of lipophilic ^{68}Ga imaging agents. Its synthesis is straight forward concerning the labelling precursor **9**, and ^{68}Ga labelling reactions proceed fast and efficient. The compound remains stable *in vitro* over the duration of a typical PET examination. It provides a lipophilic *c* log *P* which indicates suitability for the synthesis of lipophilic imaging agents.

4. Experimental

NMR-spectra were recorded with a Bruker AC 200 FT-NMR-spectrometer, *J* values are given in Hertz, chemical shifts are reported downfield from TMS ($\delta = 0$ ppm) referred to the solvent residual signal ^{1}H NMR (300 MHz,

$CHCl_3$ 7.224 ppm). Field desorption (FD) mass spectra were recorded on a Finnigan MAT90 FD spectrometer. All chemicals were obtained in commercial quality from Acros Organics, Sigma Aldrich, VWR, TCI or STREM and used without further purification unless otherwise stated. TLC was conducted on self-cut Merck silica gel 60 covered aluminium plates. Detection and staining was performed either using iodine on silica gel, potassium permanganate solution, UV fluorescence or vanillin–sulfuric acid. Column chromatography was performed on Acros silica gel 60, 0.063–0.200 mesh, p. a. solvents for chromatography were washed with aqueous acid and base and distilled once, prior to use.

1-(benzyloxy)-3-(tritylthio)-propan-2-ol (**6**): Triphenylmethanethiol (2.76 g, 10 mmol) in THF (25 ml) were added dropwise to a stirred solution of C_4H_9Li in Heptane (1.6 M, 6 ml, 0.96 equiv.) cooled to −17 °C. After effervescence ceased, benzyl glycidyl ether (1.64 g, 10 mmol) dissolved in THF (10 ml) was added to the dark red slurry in one portion. The reaction mixture was allowed to warm to RT over 90 min and stirred unless the epoxide had been consumed (monitored by TLC). The reaction was quenched *via* the addition of saturated ammonium chloride solution (25 ml). Water was added (25 ml) and the aqueous phase was extracted with diethylether (3 × 25 ml) and CH_2Cl_2 (25 ml). The organic layers were combined, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexanes-ethylacetate, 6 : 4) to obtain the title compound as colourless, viscous oil (3.88 g, 8.8 mmol). Rf = 0.4; ^{1}H-NMR (300 MHz, $CDCl_3$) δ in ppm: 7.412 (brd, J = 7.4 Hz, 6 H, Ar*H*), 7.36–7.15 (m, 14 H, Ar*H*), 4.52 (s, 2 H, ArCH_2), 3.51 (“p”, J = 6.6 Hz, 1 H, C*H*), 3.38 (dd, J = 3.3 Hz, J = 10.3 Hz, 1 H, CH_2-O), 3.27 (dd, J = 6.6 Hz, J = 10 Hz, 1 H, CH_2-O), 2.40 (dd, J = 6.6 Hz, J = 12.5 Hz, 1 H, CH_2-S), 2.33 (dd, J = 6.3 Hz, J = 12.5 Hz, 1 H, CH_2-S). MS (FD) = 440.2 (100), $C_{29}H_{28}O_2S$ requires 440.18.

1-(benzyloxy)-3-(tritylthio)-prop-2-yl mesylate (**7**): 1-(benzyloxy)-3-(tritylthio)-propan-2-ol (**6**) (2.2 g, 5 mmol) and triethylamine (501 mg) were dissolved in anhydrous dichloromethane (5 ml) and cooled to 0 °C. After stirring for 10 min, neat methanesulfonyl chloride (507 mg, 5 mmol) was added dropwise with stirring. Stirring at 0 °C was continued for 10 min and the reaction was quenched *via* the addition of ice water (15 ml). CH_2Cl_2 (15 ml) was added and the phases were separated. The aqueous phase was washed with CH_2Cl_2 (15 ml) and the combined organic phases were washed with cold HCl solution (1 M, 15 ml) and cold sodium carbonate solution (1 M, 15 ml). The organic phase was dried (K_2CO_3) and concentrated *in vacuo* to obtain the title compound as viscous opaque oil (2.51 g, 4.85 mmol, 97%). Rf = 0.9 (MeOH-$CHCl_3$, 1 : 9); 7.51–7.37 (m, 6 H, Ar*H*), 7.36–7.15 (m, 14 H, Ar*H*), 4.57 (s, 2 H, ArCH_2), 3.68 (dd, J = 6.6 Hz, J = 10.6 Hz, 1 H, CH_2-O), 3.48 (dd, J = 7 Hz, J = 11 Hz, 1 H, CH_2-O), 3.22 (“p”, J = 6.6 Hz, 1 H, C*H*), 2.51 (brd, J = 6.6 Hz, 1 H, CH_2-S), 2.20 (brd, J = 6 Hz, 1 H, CH_2-S). MS (FD) = 518.2 (100), $C_{30}H_{30}O_4S_2$ requires 518.16.

1-(1-(benzyloxy)-3-(tritylthio)propan-2-yl)-1,4,7-triazonane (**8**): 1-(benzyloxy)-3-(tritylthio)-prop-2-yl mesylate (**7**) (1.55 g, 3 mmol) in anhydrous CH_2Cl_2 (40 ml) were added dropwise to a mixture of K_2CO_3 (1.25 g, 9.05 mmol) and TACN (**3**) (1.03 g, 7.8 mmol) in anhydrous CH_2Cl_2 (40 ml) under nitrogen over 2 h at r.t. Stirring was continued under inert atmosphere at r.t. for approximately 3 d. The solids were filtered off and the reaction mixture was concentrated in vacuo. The residue was purified *via* flash chromatography on silica gel (MeOH-$CHCl_3$; 1 : 6, 2% NH_4OH_{aq}) to obtain the title compound (**8**) as a colourless waxy solid (550 mg, 1 mmol, 33%). Rf = 0.55 (MeOH-$CHCl_3$, 1 : 6, 2% NH_4OH); 7.52 (brd, J = 7.7 Hz, 6 H, Ar*H*), 7.29–7.11 (m, 14 H, Ar*H*), 4.70 (s, 2 H, ArCH_2), 3.59 (dd, J = 4 Hz, J = 13 Hz, 1 H, CH_2-O), 3.54 (dd, J = 4 Hz, J = 11 Hz, 1 H, CH_2-O), 3.22 (“p”, J = 7 Hz, 1 H, C*H*), 3.0–2.78 (m, 12 H, NCH_2), 1.91 (dd, J = 4 Hz, J = 11 Hz, 1 H, CH_2-S), 1.86 (dd, J = 2.5 Hz, J = 12.5 Hz, 1 H, CH_2-S). MS (ESI) = 551.26 (100) $[M]^+$, $C_{35}H_{41}OS$ requires 551.30.

2,2′-(7-(1-(benzyloxy)-3-mercaptopropan-2-yl)-1,4,7-triazonane-1,4-diyl)diethanethiol (**9**): 1-(1-(benzyloxy)-3-(tritylthio)propan-2-yl)-1,4,7-triazonane (**8**) (80 mg, 0.15 mmol) was dissolved in 1.7 ml CH_3CN at r.t. under argon. Thiirane (17.76 mg, 0.296 mmol, 1.95 equiv.) was added and the mixture was stirred under inert atmosphere unless the thiirane had been consumed (monitored by TLC). The solvent was removed under high vacuum with stirring and the flask was filled with Argon. The residue was re-dissolved in anhydrous anisole (1 ml), the mixture was cooled to 0 °C and TFA (2 ml) was added. After stirring at 0–5 °C for 5 min, the yellow mixture was triturated with $(C_2H_5)SiH$ unless a clear, colourless solution was obtained. The mixture was concentrated to dryness in vacuo, the residue was taken up in hydrochloric acid (0.1 M, 2 ml) and purified using a Waters® C_{18} SPE cartridge and a Merck LiChroLut® SCX cartridge. Yield: 34 mg, 55%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ (in ppm) = 7.05–7.2 (m, 5 H, Ar*H*), 4.5 (s, 2 H, ArCH_2-O), 3.58–3.46 (m, 1 H, OCH_2), 3.38–3.24 (m, 2 H, OCH_2, NC-*H*), 3.1–2.7 (m, 22 H, CH_2-S, NCH_2), 1.8 (brs, CH_2SH). MS(ESI) = 430.21 (100) $[M+H]^+$ $C_{20}H_{35}N_3OS_3$ requires 429.1942.

Preparation of [^{68}Ga]Ga(acac)$_3$ as reported recently [21]: Briefly, the hydrochloric acid (0.1 M) containing [^{68}Ga]Ga^{III} was passed through the Biorad AG 50 W8 cation exchanger resin to trap the $^{68}Ga^{3+}$. The resin was subsequently eluted with HCl (0.1 M) in acetone (1 ml) followed by air to remove the non-gallium metal contamination. The n.c.a. radionuclide was eluted in a mixture of 2% acetylacetonate and 5 mg of gentisic acid in acetone, directly into a round-bottom, pressure-tight glass vial. Evaporation of the volatiles followed by reconditioning in dry chloroform (5 ml) afforded n.c.a. [^{68}Ga]Ga(acac)$_3$.

Radiolabelling under conventional heating in chloroform: Chelator **9** was dissolved in acetonitrile (1 mg/ml) and used for radio-labelling without further purification. Labelling precursor stock solution (10 µl) was added to [^{68}Ga]Ga(acac)$_3$ in $CHCl_3$ (20 MBq, 5 ml) and the mixture was heated to 40 or 90 °C. To monitor reaction progress, aliquots were removed from the reactions mixture after 1, 3, 7 or 10 min, analysed by radio-HPLC (Merck LiChroSorb® RP-18, 7μ, 150 × 4.6 mm, 25% MeOH in PBS at pH 7.4) and radio-TLC (silica-gel 60, 0.1 M citrate solution pH 4 or 30% EtOH in 5% NaCl).

Radiolabelling under microwave irradiation in chloroform: Labelling precursor stock solution (10 µl) was added

to [^{68}Ga]Ga(acac)$_3$ in $CHCl_3$ (100 MBq, 5 ml) in a pressure tight microwave reaction vial and irradiated in a CEM discover® focussed microwave reactor for 1, 2 or 5 min at 300 W. The solvent was removed with heating in a stream of nitrogen and the residue was taken up in purified water. The slightly acidic solution was passed through a strong cation exchanger (Merck Lichrolut® SCX, 200 mg) and formulated in PBS solution (1 ml).

Stability determination *via* DTPA and *apo*-transferrin challenge: Aliquots of the radioactive product in PBS (100 µl) were added to 1 nM, 10 nM, 100 nM and 1 µM concentrations of DTPA or 10 mg *apo*-transferrin in PBS (5 ml) at pH 7.4 and incubated for 180 min. Samples were withdrawn from the solutions after 5 min, 15 min, 30 min, 60 min, 120 min and 180 min. The percentage of intact complex [^{68}Ga]**10** was determined by TLC.

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