A New Amphiphilic Host Molecule for ^{99m}Tc. Specific Imaging of the Hepatobiliary System in a Rabbit Model

Yvette B. J. Aldenhoff,[a,b] Marinus J. P. G. van Kroonenburgh,[b] Sandra V. M. Zimny,[b] Paul P. C. A. Menheere[b] and Leo H. Koole*[a]

[a] *Biomaterials and Polymer Research Institute Maastricht-Eindhoven, University of Limburg PO Box 616, 6200 MD Maastricht, The Netherlands*

[b] *Department of Nuclear Medicine, Maastricht Academic Hospital, Maastricht, The Netherlands*

A new amphiphilic derivative of DTPA, compound **1**, readily includes ^{99m}Tc; the complex shows biological characteristics suitable for scintigraphic imaging of the hepatobiliary system.

Development of radiopharmaceuticals, drugs containing a γ-emitting radioactive element, is currently receiving much interest. It is by virtue of radiopharmaceuticals that detailed *in vivo* monitoring of biochemical and physiological functions is possible. The images, routinely measured with a so-called γ-camera, constitute a powerful means to evaluate normal or pathological status of a patient.

Modern diagnostic nuclear medicine is largely based on the use of ^{99m}Tc, which has ideal nuclear properties: halflife 6.02 h, E_γ = 140 keV, relatively low cost as it is readily available from a ^{99}Mo/^{99m}Tc generator, no β-emission, and emission of only low-energy Auger electrons.[1] ^{99m}Tc normally acts as the guest in a guest–organic host inclusion complex. The molecular architecture of the host determines the biodistribution, and the pharmacological properties of the drug. Several ^{99m}Tc-based drugs have now received FDA approval, *e.g.* as cerebral perfusion imaging agents, as renal imaging agents, as myocardial perfusion imaging agents, for the evaluation of kidney function and as bone imaging agents.[2,3] It is widely anticipated that sophisticated design and synthesis of new host molecules will lead to improved and more selective imaging techniques in the coming years.

Herein, we report preliminary results of a study with a new host molecule, **1**. Compound **1** is a new amphiphilic derivative of diethylenetriaminopentaacetic acid (DTPA), a well-known host structure for ^{99m}Tc. Compound **1** was prepared in only two essential synthetic steps from cheap basic chemicals (DTPA dianhydride, triethylene glycol, and trityl chloride).† The product, a white amorphous powder, was obtained in pure form through preparative reversed-phase HPLC and lyophilisation. Free **1** dissolves in basic solution (pH 10–11), thereby displaying a marked surface activity ('soapy' character), which is in agreement with the molecular structure. Purity was assessed through analytical reversed-phase HPLC and high resolution ^{1}H NMR (400 MHz).‡ In a rabbit model, the 1 : 1 complex§ of **1** and ^{99m}Tc shows biological characteristics suitable for imaging of the hepatobiliary system [liver, gall bladder, bile duct, intestines; *viz.* Fig. 1(*B*)]. The 1 : 1 complex of ^{99m}Tc and native DTPA, on the other hand, is not taken up by the hepatobiliary system, but rapidly cleared *via* the kidneys [*viz.* Fig. 1(*A*)].

Based on these observations, we believe that compound **1** has the potential to become an attractive alternative for the rather complex and expensive so-called HIDA agents (HIDA = hepatobiliary iminodiacetic acid).[5,6]

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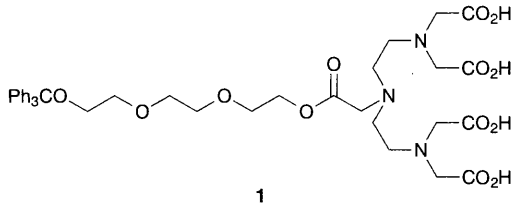

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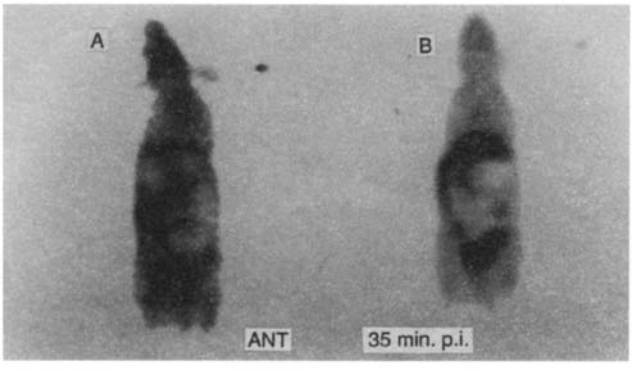

Fig. 1 (A) Scintigraphic image of the rabbit, 35 min post injection (p.i) with the complex ^{99m}Tc DTPA. Both kidneys and the bladder are clearly visible. Note the spot of injection in the right ear. (B) Scintigraphic image of the same rabbit (two weeks later), 35 min p.i. with the complex ^{99m}Tc–compound **1**. Now, the liver and the bile duct, as well as the bladder, are clearly visible. The marked differences between A and B must be ascribed to the physico-chemical differences of the host molecules (hydrophilic DTPA *vs.* amphiphilic **1**). Reproducibility of A and B was verified in several independent experiments.

Footnotes

† **1**: Step 1: Monotritylation of triethylene glycol through reaction of trityl chloride with an eightfold excess of triethylene glycol in dry pyridine. Pure product (89%) was obtained after an extraction step, and silicagel column chromatography.

Step 2: Coupling of monotrityl-triethylene glycol with diethylenetriamine pentaacetic dianhydride in dry CH_2Cl_2 according to the BOP-Cl method (ref. 4). Upon complete conversion, aqueous $NaHCO_3$ was added and CO_2 was seen to evolve. The aqueous phase was subjected to preparative reversed-phase HPLC. Fractions containing pure compound **1** were pooled, treated with a mildly acid ion-exchange resin, and lyophilised.

‡ ^{1}H NMR [$(CD_3)_2SO$]: δ, 7.42–7.18 (15 H, m, CPh_3), 4.10 [2H, s, $CH_2OC(O)$], 3.9–2.6 (28 H, CH_2 groups). IR (KBr), cm^{-1}: 3650–3090, 1730, 1590 and 1420, 1230–1000.

§ Labelling of compound **1** with ^{99m}Tc was carried out according to a standard procedure.[7–9] Compound **1** (17.8 mg) and NaCl (13.3 mg) were dissolved in 0.5 ml 0.1 mol dm^{-3} NaOH solution. Then water was added until the final mass was 0.83 g and the pH was adjusted to 4. Nitrogen was purged through the solution for 30 min, and 1 ml aqueous $SnCl_2$-solution (a tenfold excess was used; 460 mg/100 ml) was added. The mixture was filtered through a 0.2 μm Millipore filter into a sterile 10 ml vial. To 1 ml of the solution of compound **1** (Sn) was added 5 ml ^{99m}Tc-eluate so that an activity was reached of approximately 1 mCi/ml; 2 ml of this sterile solution was used for injection. Significantly, no detritylation was observed during or after the labelling procedure, implying that the trityl group is stable at pH 4.

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