NODAPA-OH and NODAPA-NCS: Mono- and multimeric six-coordinate Ga-chelators

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Introduction: The commercially available $^{68}Ge/^{68}Ga$ radionuclide generator systems and its recent improvement concerning on-line processing and labelling,[1] may provide a beneficial complement to nuclear imaging with established, cyclotron produced PET nuclides like ^{11}C and ^{18}F. ^{68}Ga provides a high positron abundance of 89 % and an intermediate positron maximum energy. With its half-life (1.13 h) lying perfectly in between the half-lives of the most frequently used ^{11}C (0.33 h) and ^{18}F (1.82 h), it provides excellent decay characteristics as a PET-radiolabel. On the other hand, the main group metal rapidly forms chelate-complexes with hard donor functions of four to six coordinating chelators. Adequate radioligand precursors meeting the coordination chemistry of gallium(III) with versatile conjugation possibilities are of high interest. The macrocyclic chelators DOTA and NOTA (Fig. 1) are established as frequently considered routes for the introduction of a ^{68}Ga-tag. Compared to open chain acyclic analogues, both provide complexes of superior kinetic and thermodynamic stability since gallium is irreversibly complexed at room temperature. DOTA remains the most frequently used chelator because of its better commercial availability and less challenging synthesis, although its six-coordinate nine-ring analogue NOTA displays higher stabilities and faster incorporation of Ga(III) at lower temperatures. Thus, we were interested in a time-saving and cost-effective access to a NOTA based versatile gallium chelator allowing convenient conjugation to various targeting molecules.

Experimental: Chelators 1-3 were synthesised from 4-substituted phenylacetic acids and TACN. To analyse whether the chain branch in one pendant arm affects the kinetic and themodynamic characteristics of [^{68}Ga]NOTA-complex formation, labelling of NODAPA-OH, NODAPA-NCS, NODAPA-NCS_2 and NODAPA-NO_2 with generator produced and purified Gallium-68 was carried out in aqueuous solution at pH = 2.8. Quality control was performed using an Agilent Zorbax C 8 column using 50 mM phosphate buffer and MeOH as eluent at 0.5 ml/min. The stability of the novel ^{68}Ga chelates was determined in a DTPA-challenge study at 25 °C and 37 °C employing 1 mM, 10 mM and 100 mM solutions of DTPA in water.

Plasma protein binding and transchelation to serum proteins *in vitro* was examined under physiological conditions in rat plasma. 4 MBq of [^{68}Ga]NODAPA-OH were incubated in 300 µL of rat plasma from male adult Wistar rats, obtained via centrifugation of full blood. Samples of 50 µL were withdrawn after 1, 30, 60, 90 and 180 min and analysed by radio-TLC.

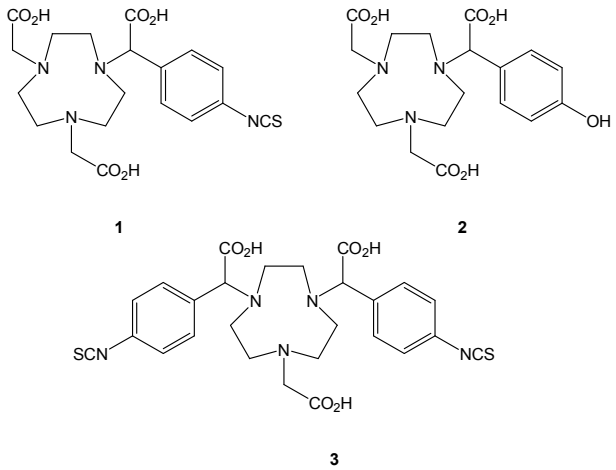

Figure 1. Novel NOTA-derived bifunctional chelators NODAPA-NCS (**1**), NODAPA-OH (**2**) and NODAPA-$(NCS)_2$ (**3**)

Results: Chelators **1-3** were obtained in 22 ± 6 % overall yield. Yields for ^{68}Ga(III) complex formation were very high (85±5 % already at 1 min) and comparable to those achieved for NOTA (Fig. 3).

The DTPA challenge experiment indicated >94% complex stability, in a similar range as the congener NOTA. In correlation to the DTPA-challenge, less than 2 % of non-[^{68}Ga]NODAPA-OH radioactivity was observed in rat plasma after 3 h.

Conclusion: Three novel NOTA-based bifunctional chelators have been obtained via a simple and efficient synthesis route. Compounds 1-3 provide excellent ^{68}Ga labeling and stability parameters. While offering –NCS and –OH functionalities, covalent coupling to various potential targeting vectors is possible.

References

[1] P. J. Riß, C. Kroll, V. Nagel, F. Roesch, *Bioorganic Medicinal Chemistry Letters* **2008,** *18***,** 5364-7

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