Toward Auger radiotherapy with Rhodium-103m: Bifunctional 16aneS4 chelator synthesis and development of a Rhodium-103m generator

Charlotte B. Magnus[1], Gregory Severin[1,2], Fedor Zhuravlev[1], Ulli Köster[3], Jesper Fonslet[1], Mikael Jensen[1], Andreas I. Jensen[1]*

[1]*Center for Nuclear Technologies (DTU Nutech), Technical University of Denmark, Roskilde.* [2]*Department of Chemistry, Michigan State University, East Lansing, MI, United States.* [3]*Institut Laue-Langevin, Grenoble, France.*

Objective: Auger electron emitters represent an attractive modality for internally targeted radiotherapy. Auger electrons have short ranges of less than a cell diameter and high-energy deposition. Small tumors lesions, such as micro metastases, can therefore be targeted while sparing surrounding healthy tissue. Rhodium-103m (^{103m}Rh, $T_{½}$ = 56.1 min) has been identified as a very promising therapeutic Auger electron emitter due to its high electron-to-photon yield [1]. ^{103m}Rh can be obtained as the decay daughter of Palladium-103 (^{103}Pd, $T_{½}$ = 17 days) [2]. Macrocyclic thioethers have previously been found to form strong chelates with Rhodium [3]. Here, we present our efforts to synthesize a bifunctional macrocyclic chelator for ^{103m}Rh, based on the 16aneS4 ring. Further, we hypothesized that the decay of chelated ^{103}Pd would result in the expulsion of radiochemically pure ^{103m}Rh. We utilized this principle in the development of a radionuclide generator for ^{103m}Rh.

Methods: The macrocyclic thioether 16aneS4-ol **(5)** was synthesized in five consecutive steps (**fig. 1**)**.** The linear diol **(1)** was prepared in quantitative yield. By tosylation and conversion of **(2)**, compound **(3)** was obtained in 97% yield. Finally, deprotection of **(4)** with subsequent ring-closing, gave the macrocyclic thioether-alcohol **(5)** as the final product in excellent purity and 50% yield. Compound **(5)** offered functionality for further modification. The oxo-butanoic acid derivate **(6)** was formed in one-step in 74% yield. Compound **(7)** was formed from octanol mesylate and compound **(5)** in excellent purity and 40% yield. Compound **(6)** was conjugated to human epidermal growth factor (hEGF) using EDC and NHS. [^{103}Pd]Pd was obtained by neutron irradiation of enriched [^{102}Pd]Pd. The targets were dissolved in aqua regia, followed by reconstitution in hydrochloric acid. The [^{103}Pd]Pd was then chelated by compound **(7)** in excess. The chelate was applied to a C18 solid support, which was eluted with hydrochloric acid. Eluates were analyzed by liquid scintillation and X-ray spectrometry.

Results: We synthesized 16aneS4-ol, and this was further functionalized into compound **(6)**. Preliminary studies show that **(6)** has been conjugated to hEGF. hEGF is an internalizing and nucleus-localizing small protein that was recently used in phase I clinical studies [4]. To achieve efficient therapy, Auger decays must occur near the DNA, making internalization paramount. [^{103}Pd]Pd was successfully chelated by compound **(7)** and captured on a C18 solid support. By eluting with aqueous hydrochloric acid (1.0 M), radiochemically pure (RCP: >99%) could be obtained. Maximum effective molar activities were 23 MBq/nmol, decay-corrected to dissolution of the target. Elution yields, as percentage of theoretical maximum, were generally modest at about 5%. It has been previously calculated that recoil energy alone would not be sufficient for Szillard-Chalmers based expulsion (Van Royen 2008). We suggest that transient ionization of the daughter may play a role in the observed expulsion, but that this may not be sufficient to achieve near quantitative elution yields.

Conclusion: We successfully synthesized bifunctional derivatives of the 16aneS4-ol chelator and conjugated these to a nucleus-localizing vector (hEGF). In addition, we developed a practical generator capable of furnishing ^{103m}Rh in high radiochemical purity, although in modest yields. We will continue this work through optimization of both technologies, as well as combining the two into therapeutically effective ^{103m}Rh based Auger radiotherapeutics.

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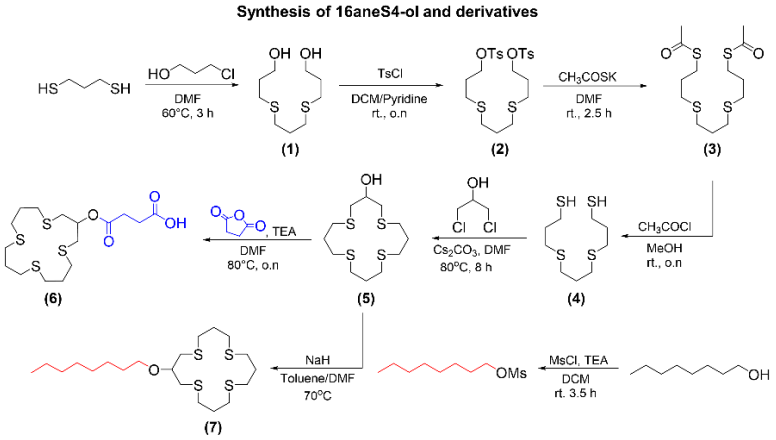

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