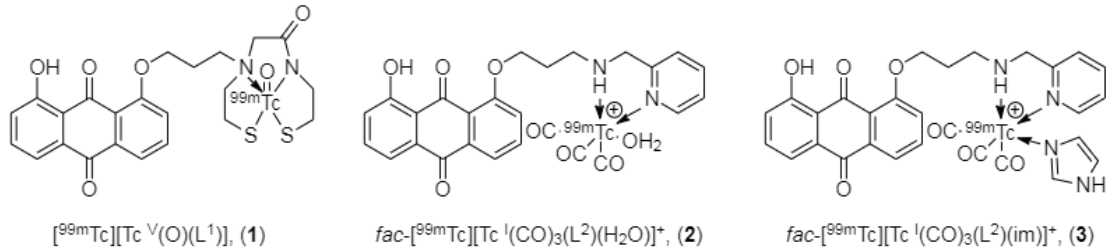
SYNTHESIS AND EVALUATION OF ^{99m}Tc-ANTHRAQUINONE COMPLEXES AS TUMOR IMAGING AGENTS

Migkos Theofanis Matthaios*, Akrivou Melpomeni**, Vizirianakis Ioannis**, Papagiannopoulou Dionysia*

*Laboratory of Pharmaceutical Chemistry, **Laboratory of Pharmacology, School of Pharmacy, Faculty of Health Sciences, Aristotle University of Thessaloniki, 54124, Thessaloniki

Anthraquinones are biologically active molecules that can act as DNA intercalators and topoisomerase IIa inhibitors.[1] The development of anthraquinone-based diagnostic radiopharmaceuticals may be useful in tumor patients. In this work, the design and synthesis of 3 new radiotracers of technetium-99m is described, based on 1,8-dihydroxyanthraquinone pharmacophore conjugated to the tetradentate monoamino monoamido dithiol (MAMA) chelator for oxotechnetium(V) labeling and picolylamine bidentate chelator for technetium(I)-tricarbonyl labeling, by employing the "2+1" mixed ligand approach with imidazole as monodentate co-ligand.[2]

The synthesis of the ligands was achieved by reaction of 1-(3-bromopropoxy)-8-hydroxyanthracene-9,10-dione with bis-S-trityl-N-(2-mercaptoethyl)-2-((2-mercaptoethyl)amino)acetamide for the preparation of L^1 or with 2-picolylamine for the preparation of L^2. The rhenium reference compounds, $[Re^{V}O(L^1)]$ and *fac*-$[Re^{I}(CO)_3(L^2)(MeOH)]^+$ and *fac*-$[Re^{I}(CO)_3(L^2)(im)]^+$, with imidazole (im) as co-ligand were synthesized and characterized by spectroscopic methods. The radiotracer technetium-99m complexes, $[^{99m}Tc][Tc^{V}O(L^1)]$ (**1**), *fac*-$[^{99m}Tc][Tc^{I}(CO)_3(L^2)(H_2O)]^+$ (**2**) and *fac*-$[^{99m}Tc][Tc^{I}(CO)_3(L^2)(im)]^+$(**3**) were prepared and characterized by standard methods. The purified radiotracers displayed high stability ≥ 90% after 24 h in 1mM L-cysteine, 1mM L-histidine or rat plasma. All tracers exhibited fast blood clearance after *iv* administration in mice (% Injected Dose/g-Blood (ID/g), **1**: 1.09±0.61, **2**: 2.62±1.14, **3**: 0.47±0.31 at 2 h post injection, *p.i.*). The tracers **2** and **3** were evaluated *in vitro* in CT26 murine adenocarcinoma cells and their uptake was 4.31±1.13 and 0.37±0.04 at 4 h, respectively. Tracer **3** exhibited higher tumor/blood and tumor/muscle ratios in tumor-bearing mice (2.3±0.61 and 2.42±0.42, respectively at 2 h *p.i.).*



$[^{99m}Tc][Tc^{V}(O)(L^1)]$, (**1**) *fac*-$[^{99m}Tc][Tc^{I}(CO)_3(L^2)(H_2O)]^+$, (**2**) *fac*-$[^{99m}Tc][Tc^{I}(CO)_3(L^2)(im)]^+$, (**3**)

Figure 1: *Structures of ^{99m}Tc – complexes of L^1 and L^2*

[1] Malik, E.M. and Müller, C.E. (2016). Med. Res. Rev., 36: 705-748
[2] Papagiannopoulou, D. (2017). J. Label. Compd. Radiopharm., 60: 502-520