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

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Anthraquinones and anthrapyrazoles are biologically active molecules that can act as DNA intercalators and topoisomerase IIa inhibitors. In this work, the development of technetium-99m radiotracers was pursued via the technetium-tricarbonyl "2+1" mixed ligand approach, *fac*-[^{99m}Tc][Tc^{I}(CO)$_3$(NN)(N)]$^+$, with an (N,N) bidentate chelator and an N co-ligand. In one approach, the ligands used were bipyridine and N-functionalized-imidazole, where imidazole was conjugated to an anthraquinone moiety. In the other approach, 2-picolylamine and imidazole were used as the mixed ligand system, where picolylamine was conjugated to an anthrapyrazole moiety.

The synthesis of the N-functionalized-imidazole ligand (**PG1**) was achieved by reaction of 1-(3-bromopropoxy)-8-hydroxyanthracene-9,10-dione with imidazole for the preparation of **PG1** and the synthesis of the 2-picolylamine chelator **GP1** was achieved by reaction with 2-(10-methoxy-6-oxodibenzo[cd,g]indazol-2(6H)-yl)ethyl methanesulfonate. The rhenium reference compounds, *fac*-[Re^{I}(CO)$_3$(bipy)(PG1)]$^+$ with bipyridine (bipy) as bidentate chelator and *fac*-[Re^{I}(CO)$_3$(GP1)(im)]$^+$, with imidazole (im) as co-ligand were synthesized and characterized by spectroscopic methods. The radiotracer technetium-99m complexes (Fig. 1), *fac*-[^{99m}Tc][Tc(CO)$_3$(bipy)(PG1)]$^+$ (**Tc-PG1**) and *fac*-[^{99m}Tc][Tc(CO)$_3$(GP1)(im)]$^+$ (**Tc-GP1**) were prepared and characterized by standard methods. The purified radiotracers displayed high stability ≥ 90% after 24 h in 1mM L-histidine or rat plasma. Tracer **Tc-GP1** exhibited in two isomers with a ratio of 7:3, similar as the Re-analogue. The tracers' cell uptake was evaluated *in vitro* in CT-26 cells and their pharmacokinetic properties and tumor uptake were evaluated *in vivo* in CT26-tumor bearing mice.

The "2+1" technetium-tricarbonyl approach leads to *in vitro* stable tracers and the anthraquinone/anthrapyrazole moiety can be well-tolerated either on the N-substituted imidazole as co-ligand or on the N-substituted-2-picolylamine bidentate chelator.

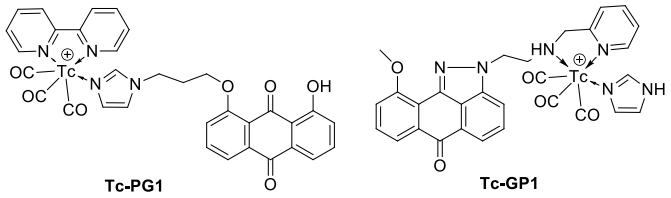

Figure 1: *Structures of "2+1" technetium-99m tracers*