^{114m}In(III) complexes with 2-acetylpyridine-derived thiosemicarbazones as prototypes of targeted radionuclide therapeutic agents

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Despite significant progress in early diagnosis and treatment, resistance to conventional chemotherapy remains an important challenge for effective therapy of breast cancer. Targeted radionuclide therapy (TRT) can be an alternative way to improve the toxicity and specificity of antitumoral drugs and consists of damaging or destroying the cells through the selective deposition of ionizing radiation from radionuclides linked to specific biomolecules. TRT has shown great advantages over external beam radiotherapy. Neutronic activation of indium-based complexes may be a good strategy in the development of new compounds for the treatment of cancer.[1] Although ^{111}In radiopharmaceuticals for imaging are the main applications of In(III) complexes in medicine,[2] research on indium-based therapeutic drug candidates or their radiolabeled forms remains practically unexplored. Complexes [In(2Ac*N*(4)*p*FPh)Cl_2(MeOH)] (**1a**), [In(2Ac*N*(4)*oCl*Ph)Cl_2(MeOH)] (**1b**) [In(2Ac*N*(4)*p*FPh)$_2$]NO_3 (**2a**), and [In(2Ac*N*(4)*o*ClPh)$_2$]NO_3 (**2b**) with 2-acetylpyridine-*N*(4)-*para*-fluor-phenylthiosemicarbazone (H2Ac4*p*FPh) and 2-acetylpyridine-*N*(4)-*ortho*-chloro-phenylthiosemicarbazone (H2Ac4*o*ClPh) were obtained and their *in vitro* cytotoxic activities were investigated against MCF-7 (breast cancer) and Vero (non-malignant) cells. The cytotoxicities of the ^{114m}In analogs were also evaluated. Unlike the In(III) salts, the non-radioactive In(III) complexes were cytotoxic in sub-micromolar doses with selectivity indexes (SI = $IC_{50\ Vero}/IC_{50\ tumor\ cell}$) higher than 21. The radioactive ^{114m}In-thiosemicarbazone complexes and ^{114m}In salts were produced by neutron activation for 4h in the TRIGA MARK-I IPR-RI CDTN research reactor, with high radiochemical purity (> 90%). The Auger electron emitter ^{114m}In-complexes were around 1,000 fold more potent than their non-radioactive counterparts (Fig. 1), whereas the radioactive ^{114m}In salts proved to be inactive. The combined pharmacological effects of the In(III)-thiosemicarbazone complexes and Auger electrons may result in compounds with potential applications in the treatment of breast cancer.

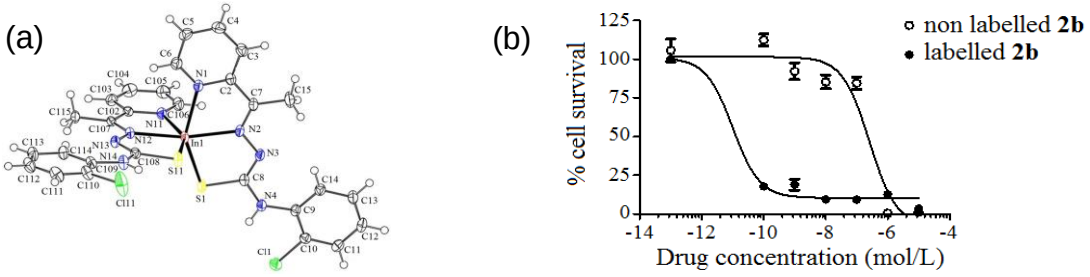

Figure 1. (a) Molecular plot of [In(2Ac*N*(4)*o*ClPh)$_2$]NO_3 (**2b**); (b) Comparison of the cytotoxicity of labelled and non labelled In(III) complex **2b** on MCF-7 lineage

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