Novel ^{99m}Tc(I)-labeled bone-seeking molecules for bone imaging

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Several malignant tumors, especially breast and prostate cancers, have high tendency to metastasize to bone. Moreover, the development and progression of bone metastases have a high impact in the quality of life of patients, causing drastic complications such as bone pain, pathologic fractures, hypercalcemia and spinal cord compression. Bisphosphonates (BPs) are a class of compounds with high affinity for the bone mineral matrix, binding strongly to the hydroxyapatite (HA) crystals and accumulate in areas of high bone metabolism such as metastases. Consequently, BPs are being extensively explored for the treatment of several bone diseases and as molecular imaging probes. In fact, complexes of ^{99m}Tc with BPs such as methylene diphosphonate (^{99m}Tc-MDP) and hydroxymethylene diphosphonate (^{99m}Tc-HMDP) are widely used as radiopharmaceuticals for the assessment of bone metastases. Despite their proven clinical success these radiopharmaceuticals present several limitations, namely low specificity, uncertainty in the radiopharmaceutical's molecular structure and long acquisition time after injection. Consequently, there is a need for rational design of novel ^{99m}Tc-bisphosphonates based radiopharmaceuticals with improved chemical and biological properties.

Aiming to find novel bone-seeking radiotracers, we have successfully synthesized and characterized a set of novel organometallic compounds of the type *fac*-[M(CO)$_3$(k^3-Pz-BP)] which contain a bisphosphonate unit (bone seeking agent), and the metal fragment *fac*-[M(CO)$_3$] (M = ^{99m}Tc, Re). The stable radioactive complexes were obtained with high yield and radiochemical purity (>95%) and have been characterized by comparing their chromatographic HPLC gamma-traces with the UV-vis traces of the respective Re surrogates. In vitro hydroxiapatite binding studies revealed that the complexes presented bone seeking potential. Herein, we will also present the biodistribution studies in Balb-c mice and compare their biological properties (e.g. bone-targeting properties) with ^{99m}Tc-MDP studied in the same conditions. The best complexes presented fast blood clearance and high bone uptake. Notably, the target to non-target ratios are considerably higher than the ones obtained for ^{99m}Tc-MDP, the gold standard for bone imaging in nuclear medicine.

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