”Click-to-chelate”: in vitro and in vivo comparison of a 99mTc(CO)3-labeled N(tau)-histidine folate derivative with its isostructural, clicked 1,2,3-triazole analogue

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A side-by-side comparison of the synthesis, radiolabeling, and in vitro and in vivo characterization of two new and isostructural (99m)Tc-tricarbonyl folic acid radiotracers comprising either a N(tau)-functionalized histidine (His) chelator or a 1,4-bifunctionalized 1,2,3-triazole His analogue is described. The 1,2,3-triazole-containing folic acid derivative was synthesized in approximately 80% yield by a short reaction sequence including application of click chemistry (the Cu(I)-catalyzed cycloaddition of azides and terminal alkynes). The synthesis of the ligand system and the functionalization of the folic acid derivative were accomplished simultaneously, which prompted us to call this approach ”click-to-chelate”. In comparison, the reported regioselective synthesis of the N(tau)-His compound provided the final product in only very low yields (<1%). While the efficiency of the syntheses differs considerably, the two isostructural folate derivatives exhibit virtually identical properties with respect to Tc-99m radiolabeling and in vitro and in vivo characteristics as shown by experiments performed with FR-positive KB cells and xenografted mice bearing folate receptor overexpressing tumors. We have demonstrated herein for the first time that a ligand system known to be an excellent chelator for the stable complexation of the organometallic core [M(CO)3] (+) (M = Tc-99m, Re) can be replaced by an isostructural 1,2,3-triazole analogue without influencing the characteristics of the radiometal conjugate. The ”click-to-chelate” strategy provides a highly efficient and convenient entry to metal conjugates suitable for diagnostic and potentially therapeutic applications. The described procedures should be readily applicable to any azide-functionalized (bio)molecule and, thus, are likely to represent the method of choice for the future development of radiopharmaceuticals radiolabeled with the organometallic precursors [M(CO)3(H2O)3] (+) (M = (99m)Tc, (188)Re).

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