SYNTHESIS AND IN VITRO AND IN VIVO EVALUATION OF IODINE-131-LABELED FOLATES: POTENTIAL MOLECULAR DIAGNOSTIC AND THERAPEUTIC RADIOPHARMACEUTICALS

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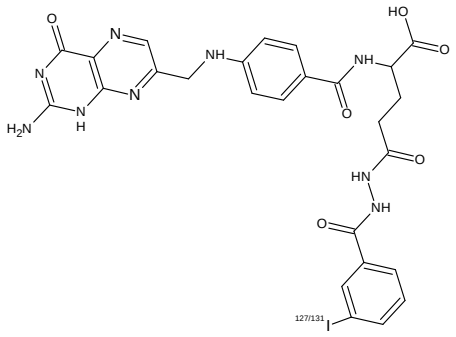
Molecular targeting imaging has a great potential to be able to image molecular changes that are currently defined as predisease states which facilitate earlier detection of cancer and consequently, the greatest chance of cure. Advancement of scintigraphic imaging and radiotherapy is highly determined by development of more specific radiotracers. The Membrane-associated-folic acid receptor is a glycosylphospstidylinositol protein that overexpressed in approximately 100% of serious ovarian adenocarcinomas and various epithelial cancers including cervical, colorectal and renal cancers. Meanwhile, this receptor is highly restricted in most normal tissues which make these tumors as an excellent candidates for molecular targeting imaging and therapy through the folate receptor system. As part of our on-going research effort to develop prosthetic precursors for radiohalogenation of bioactive molecules, we have previously reported the synthesis and biological characterization of [^{18}F]-fluorobenzene and pyridine carbohydrazide-folate conjugates ([^{18}F]-SFB and [^{18}F]-SFP-folates). We here report the synthesis and biological characterization of [^{131}I]-iodobenzenecarbohydrazide-folate conjugate ([^{131}I]-SIB-folate) as a potential therapeutic radiopharmaceutical. The synthetic approaches for preparation of [^{131}I]iodobenzene carbohydrazide-folates ([^{131}I]-SIB-folate, Scheme 1) entailed sequence of reactions. Hydrazide-folate was reacted with N-succinimidyl-m-[^{131}I]-iodobenzoate-carboxylate ([^{131}I]-SIB) to give [^{131}I]-SIB-folate conjugate. Radiochemical yield was greater than 80% and synthesis times were ranging between 40-45 min. Radiochemical purity was also greater than 97% without HPLC purification. These synthetic approaches hold considerable promise as rapid and simple method for the radiohalogenation of folate in high radiochemical yield in short time. In vitro tests on KB cell line has shown that significant amount of the radioconjugate associated with cell fractions and in vivo characterization in normal CBA/J mice revealed rapid blood clearance of this radioconjugate with excretion predominantly by the hepatobiliary system. In vivo tumor targeting capacity of this radioconjugate in athymic mice with folate-recptor-positive human KB cell tumor xenografts is currently in progress.



Scheme 1: m–[^{131}I]-iodobenzenecarbohydrazide-folate conjugate ([^{131}I]-SIB-folate).