Development of Radiolabeled Compounds Directed Against Platelet-Derived Growth Factor Receptor Beta (PDGFRβ) for Tumor Imaging

学位論文要旨

Platelet-derived growth factor receptor β (PDGFRβ) belongs to a subfamily of receptor tyrosine kinases (RTKs). The PDGFRs are a family of growth factor ligands PDGF AA, AB, BB, CC, and DD additionally, PDGFRα and PDGFRβ are two types of PDGFRs. It possesses an outer membrane with a PDGF ligand binding site and an inner membrane tyrosine kinase (TK) domain with an adenosine triphosphate (ATP) binding site. Binding of PDGF ligands to the extracellular binding domain triggers PDGFRβ dimerization, thus inducing phosphorylation in intracellular domain. This is followed by the activation of signaling pathways that regulate important cellular functions. Upregulation of PDGFRβ in numerous human tumors and its relationship with tumor progression features such as cell migration, metastasis, angiogenesis, and proliferation, have been reported. PDGFRβ expression in normal cells is highly restricted; however, its upregulation was found in the various malignant tumor. Therefore, PDGFRβs can be an attarctive target not only for cancer therapy but also for developing tumor-imaging agents.

Nuclear medicine is a revolutionized invention not only in cancer research but also in drug development, which can be utilized to investigate disease noninvasively as well as facilitate monitoring disease progression or response to therapy repeatedly. Quantification of receptor density is meaningful because it allows disease diagnosis as well as monitoring the effectiveness of therapy. Single photon emission computed tomography (SPECT) and positron emission tomography (PET) are molecular imaging modalities which allow expression assessment of molecular targets within living organism. Although PET has better sensitivity and spatial resolution, SPECT has advantages such as more available, widely used, and cheaper than PET.

1-{2-[5-(2-Methoxyethoxy)-1*H*-benzo[*d*]imidazol-1-yl]quinolin-8-yl}piperidin-4-amine (CP-673451, IQP) (Fig. 1), is a derivative of benzimidazole. It is a potent PDGFRβ inhibitor which inhibits phosphorylation of cells with high selectivity relative to many other subfamilies of receptor tyrosine kinases (IC_{50} = 1.0 nM). IQP targeted ATP binding site as tumor therapeutic target. Using this scaffold to develop PDGFRβ imaging agents might be meaningful to visualize intracellular part of the molecular target.

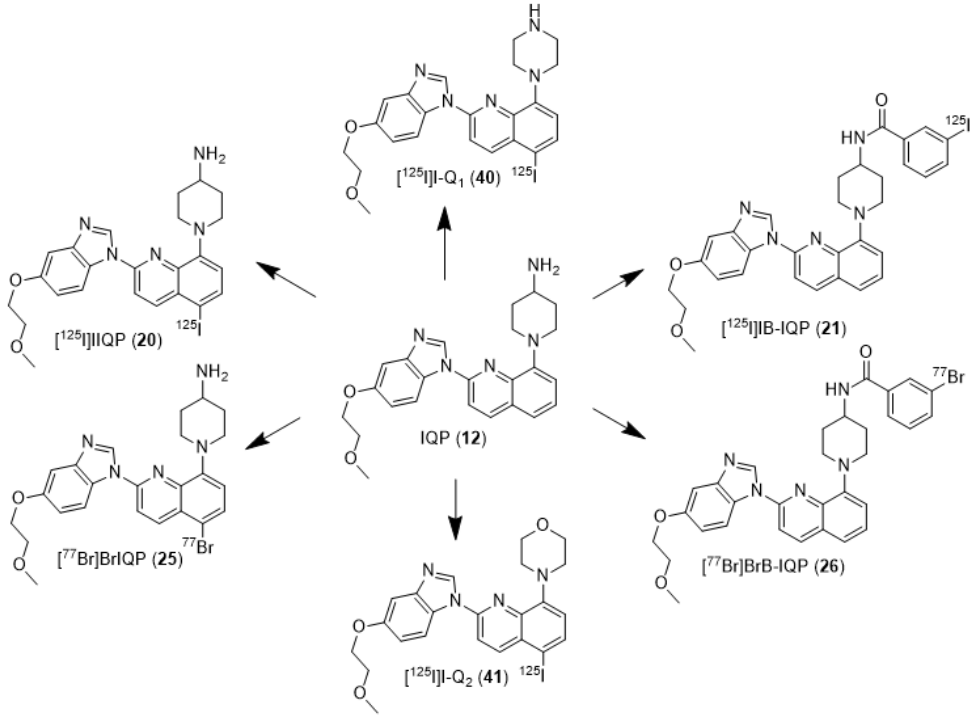

Figure 1. Chemical structures of IQP (**12**) and its radiolabeled derivatives [^{125}I]IIQP (**20**), [^{125}I]IB-IQP (**21**), [^{77}Br]BrIQP (**25**), [^{77}Br]BrB-IQP(**26**), [^{125}I]I-Q$_1$ (**40**), and [^{125}I]I-Q$_2$ (**41**).

The purpose of this study was to develop the radiohalogenated derivatives of IQP as new radiotracers for imaging of the PDGFRβ expressing tumors.

This manuscript is divided into three chapters. Chapter 1 described the synthesis and evaluation of radioiodinated 1-{2-[5-(2-methoxyethoxy)-1*H*-benzo[*d*]imidazol-1-yl]quinolin-8-yl}piperidin-4-amine derivatives for PDGFRβ imaging. Iodine was introduced into IQP scaffold directly at the C-5 of quinoline core of IQP and indirectly by conjugation wherein amine group of piperidine was linked with 3-iodobenzoyl group using ATE (*N*-succinimidyl-3-iodobenzoate). Radioiodinated compounds [^{125}I]IIQP and [^{125}I]IB-IQP were synthesized using tin precursors under non-carrier added condition and *N*-chlorosuccinimide (NCS) as an oxidizing agent. In this study, ^{125}I was used as an alternative radionuclide instead of ^{123}I and ^{124}I, which are radionuclide for SPECT and PET, respectively. Chapter 2 described Synthesis and evaluation of radiobrominated benzimidazole-quinoline derivatives as new candidate PET probes for PDGFRβ. Not only radioiodination, but also radiobromination of IQP scaffold have been achieved using ^{77}Br. In this initial study, ^{77}Br was utilized because it has relatively long half-life compared to ^{76}Br, which is a radionuclide for PET. Chapter 3 described the synthesis and preliminary biological evaluation of radioiodinated benzimidazole-quinoline derivatives as PDGFRβ imaging probes. In an effort to modify the scaffold structure of benzimidazole-quinoline, nine new compounds were designed in which a variety of side chain was introduced into C-8 of quinoline core instead of piperidine group in IQP. Hereafter, iodinated compounds were synthesized in order to assess their feasibility as imaging agents using iodine as radionuclide.

Evaluation of these compounds by *in vitro* stability, *in vitro* cellular uptake, blocking studies, competitive binding assay, and biodistribution studies in mice were performed.

審査結果の要旨

Platelet-derived growth factor receptor beta (PDGFRβ)は、チロシンキナーゼ活性を有する膜受容体 PDGFR ファミリーのメンバーであり、そのチロシンキナーゼ部位は癌分子標的薬剤の標的となっている。つまり、PDGFRβ を非侵襲的にイメージングにより定量評価することが可能であれば、癌治療の治療方針に有益な情報を与える。そこで、本研究では、PDGFRβ イメージングプローブの開発を目的に、PDGFRβ の阻害剤である 1-(2-(5-(2-methoxyethoxy)-1*H*-benzo[*d*]imidazol-1-yl)quinolin-8-yl)piperidin-4-amine (CP-673451, IQP)をリード化合物として、誘導体を設計、合成した。次いで、放射標識を行い、標識体の有用性を評価した。その結果、in vitro、in vivo において、放射標識 IQP 誘導体は、PDGFRβ 発現癌細胞に高く取り込まれ、その取込は過剰量の IQP により阻害された。つまり、本プローブが PDGFRβ イメージングに有用である可能性が示された。これまでに PDGFRβ チロシンキナーゼ部位を標的としたイメージングプローブは開発されておらず、本研究の新規性は高く、受容体チロシンキナーゼイメージングプローブ開発に有益な情報を与えるものである。以上より、本論文は博士（学術）に値すると判断される。