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Syntheses of F-18 labeled fluoroalkyltyrosine derivatives and their biological evaluation in rat bearing 9L tumor

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Abstract—We hereby report the synthesis of four fluorine-18 labeled tyrosine derivatives, 3-(2-[^{18}F]fluoroethyl)tyrosine ([^{18}F]**1**, [^{18}F]*ortho*-FET), 3-(3-[^{18}F]fluoropropyl)tyrosine ([^{18}F]**2**, [^{18}F]*ortho*-FPT) *O*-methyl-[3-(2-[^{18}F]fluoroethyl)]tyrosine ([^{18}F]**3**, [^{18}F]MFET), and *O*-methyl-[3-(3-[^{18}F]fluoropropyl)]tyrosine ([^{18}F]**4**, [^{18}F]MFPT). The fluorine-18 labeled tyrosine derivatives were prepared by the displacement reaction of the ethyl and propyl tosylates with K[^{18}F]/K2.2.2 in acetonitrile under no-carrier-added (NCA) conditions, followed by hydrolysis with 4 N HCl. The biological properties of labeled compounds were evaluated in rats bearing 9L tumor after an intravenous injection and PET image was obtained. The tumor/blood and tumor/brain ratios were 2.06, 2.92 for [^{18}F]**1**, 2.25, 4.05 for [^{18}F]**2**, 2.88, 1.90 for [^{18}F]**3**, and 2.00, 2.60 for [^{18}F]**4** at 60 min post injection, respectively. The PET image showed localized accumulation of PET tracers in 9L glioma of the rat.

Of all nuclear medicine imaging modalities, positron emission tomography (PET) offers the highest resolution and allows the tracer concentration in tissues to be quantified.[1] One of the PET tracers, 2-[^{18}F]fluorodeoxyglucose (FDG) as a parameter of the glucose metabolism, has been used widely in PET for oncology, neurology, and psychiatry, as well as for treatment evaluation.[2] However, [^{18}F]FDG images of solid tumors are often complicated by the high uptake in both the tumor and nonmalignant, inflammatory tissue. Therefore, so far, there has been considerable research into the development of new oncologic PET tracers.[3] For more than 40 years, labeled amino acids such as [^{11}C-*methyl*]methionine (MET),[4] 3-[^{18}F]fluoro-α-methyltyrosine (FMT),[5] [^{18}F]fluoro-L-phenylalanine,[6] 1-amino-3-[^{18}F]fluorocyclobutane-1-carboxylic acid,[7] [^{18}F]fluoro-L-proline,[8] [^{11}C-*methyl*]-α-aminoisobutyric acid,[9] 4-borono-2-[^{18}F]fluoro-L-phenylalanine (FBPA),[10] and L-3-[^{123}I]iodo-α-methyltyrosine[11] have been developed and evaluated for their potential use in oncology, particularly for tumors of the brain, lung, and breast. In general, radiolabeled amino acids can be categorized in two—natural and non-natural amino acids analogues labeled with various radionuclides.[12] Radiolabeled natural amino acid analogues have been extensively investigated for humans to detect tumors such as brain and systemic tumors. However, they are readily metabolized through multiple pathways, giving rise to several radioactive metabolites. Such susceptibility makes pharmacokinetic study in living substances hard to be obtained for given time period. On the other hand, radiolabeled non-natural amino acid analogues provide some considerable advantages. As they are slowly or differently metabolized, the pharmacokinetic analysis after post injection of radiotracers becomes quite simple. Therefore, recent efforts have focused on the development of radiolabeled non-natural amino acids.

Recently, among new structurally similar amino acid analogues, *O*-(2-[^{18}F]fluoroethyl)-L-tyrosine ([^{18}F]FET),[13,14] *O*-(3-[^{18}F]fluoropropyl)-L-tyrosine ([^{18}F]FPT)[15] have

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been developed and evaluated. [^{18}F]FET has a low uptake in activated inflammatory cells in an experimental acute abscess model and in inflammation within lymph nodes.[16,17] [^{18}F]FPT is superior to FDG and has a slight advantage over FET in being able to differentiate a tumor from inflammation, and like [^{18}F]FET, it appears to be a potential amino acid tracer for tumor imaging with PET.[15]

Radiopharmaceuticals labeled with fluorine-18 are being used increasingly in clinical diagnoses. Although fluorine-18 is the most attractive radionuclide for the preparation of imaging agents for PET, the labeling of amino acids with fluorine-18 is often difficult, particularly in aromatic positions. An alternative way of labeling aromatic systems with fluorine-18 involves the introduction of a fluoroalkyl group to an aromatic position, rather than by direct labeling with a fluorine atom.[18] Lee et al. reported the in vitro biological stability of fluoroalkyl groups, such as fluoromethyl, fluoroethyl, and fluoropropyl, using rat hepatic microsomes and human serum.[19] In the current study, fluoroethyl and fluoropropyl groups were introduced at the R1 position and OCH3 was introduced at the R2 position. The main reason for fluoroalkyl groups in R1 position is just synthetically easy on introduce the fluoroalkyl group at R1 position which is *ortho*-position of phenol. And if we protected phenol by methylation, the compounds **3** and **4** would be more lipophilic than the corresponding compounds **1** and **2** with a similar effect to FET (Fig. 1). We report the synthesis and biological evaluation of four novel non-natural fluorine-substituted tyrosine derivatives for tumor imaging, 3-(2-[^{18}F]fluoroethyl)tyrosine ([^{18}F]**1**, [^{18}F]*ortho*-FET), 3-(3-[^{18}F]fluoropropyl)tyrosine ([^{18}F]**2**, [^{18}F]*ortho*-FPT), *O*-methyl[3-(2-[^{18}F]fluoroethyl)]tyrosine ([^{18}F]**3**, [^{18}F]MFET), and *O*-methyl[3-(3-[^{18}F]fluoropropyl)]tyrosine ([^{18}F]**4**, [^{18}F]MFPT). The biological properties of these new radiotracers were evaluated using in vivo uptake assays in rats bearing 9L (glioma) and PET image.

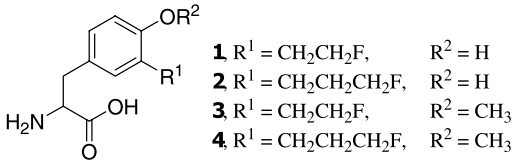
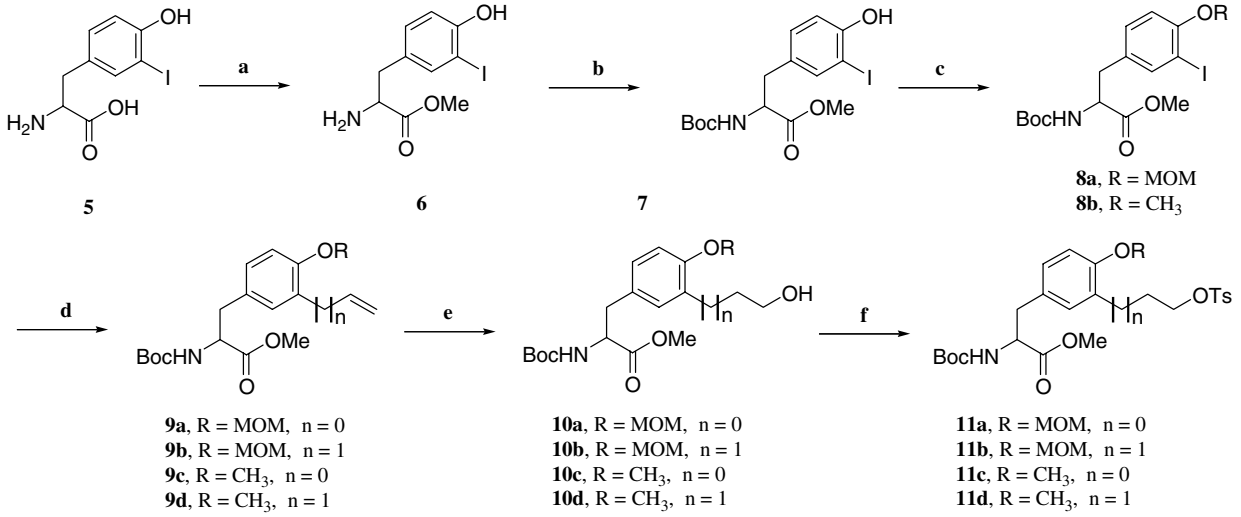


Figure 1. Structure of the tyrosine derivatives used in this study.

The precursors for **1** (*ortho*-FET), **2** (*ortho*-FPT), **3** (MFET), and **4** (MFPT) were prepared in six steps from 3-iodotyrosine (**5**) as shown in Scheme 1. 3-Iodotyrosine methyl ester (**6**) was synthesized by the reaction with 3.0 equiv of trimethylsilyl chloride (TMSCl) in MeOH at rt for 24 h, followed by removal of TMSCl and MeOH by evaporation and isolation by flash column chromatography. *N*-(*tert*-butoxycarbonyl)-3-iodo-L-tyrosine methyl ester (**7**) was prepared by the reaction of $(Boc)_2O$ with triethylamine (TEA) at rt for 2 h in 70% yield. MOM protected *N*-(*tert*-butoxycarbonyl)-3-iodo-L-tyrosine methyl ester (**8a**) was synthesized using MOMCl and NaH in dry THF at 0–70 °C for 1 h in 65% yield. Introduction of methyl moiety (**8b**) was obtained through a reaction with CH_3I and K_2CO_3 in DMSO at rt for 2 h in 75% yield. Treatment of the R group-protected **8a** or **8b** with allyl (or vinyl) tributylstannane and $Pd(PPh_3)_4$ in anhydrous 1,4-dioxane at 90 °C for 1 h afforded the R group induced 3-allyl (or vinyl) tyrosine **9a**–**9d** in 50–60% yields. Hydroboration of alkenes **9a**–**9d** using a borane–THF complex in THF at 0 °C for 2 h and subsequent oxidation with alkaline peroxide gave the aliphatic alcohols **10a**–**10d** in 45–60% yields. The tosylation of the alcohol afforded the tosylates **11a**–**11d** in 75–85% yields. The authentic compounds **1**, **2**, **3**, and **4** were synthesized from the tosylated compounds using TBAF·3H$_2$O followed by deprotection of MOM and Boc groups with 4 N HCl and then purified with reverse-phase semi-HPLC (see a Ref. 20: structure analysis data).



Scheme 1. Reagents and conditions: (a) TMSCl, MeOH, rt, 24 h, 75%; (b) $(Boc)_2O$, TEA, MeOH, rt, 2 h, 70%; (c) NaH, MOMCl, THF, 0–70 °C, 1 h, 65% for R = MOM; CH_3I, K_2CO_3, DMSO, rt, 2 h, 75% for R = CH_3; (d) allyl (or vinyl) tributylstannane, $Pd(PPh_3)_4$, 1,4-dioxane, 90 °C, 1 h, 50–60%; (e) i—BH_3–THF complex, THF, 0 °C, 2 h, ii—4 N NaOH, 30% H_2O_2, 45–60%; (f) TsCl, TEA, CH_2Cl_2, rt, 2 h, 75–85%.