Metabolic Stability of [^{18}F]Fluoroalkylbiphenyls

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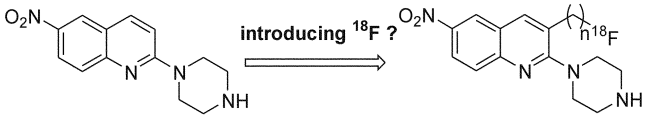
The stability of fluoroalkyl groups as a pendent on the phenyl ring was measured *in vitro* using rat hepatic microsomes and human serum to predict their *in vivo* stabilities. We have prepared three [^{18}F]fluoroalkylbiphenyls as the model compounds of fluoroalkyl aromatic compounds to compare the *in vitro* stabilities. In addition, *in vitro* stabilities were measured separately using rat hepatic microsomes and human serum at 37 °C. Fluoroethylbiphenyl had similar or slightly superior stability to fluoropropylbiphenyl and these two compounds were much more stable than fluoromethylbiphenyl *in vitro*.

Key Words : Metabolism study, Fluoroalkyl, Fluoroalkylaromatics, Fluorine-18, PET tracer

Introduction

Positron-emitting radiopharmaceuticals labeled with [^{18}F]fluorine are being increasingly used in clinical diagnosis.[1] Although [^{18}F]fluorine is the most attractive radionuclide in the preparation of imaging agents for positron emission tomography (PET), there are few chemical processes suitable for introducing [^{18}F]fluorine into organic molecules.[2] Many publications have described an effective approach, including the use of [^{18}F]fluoride ion displacement of good leaving groups at aliphatic[3-7] or aromatic[8] position. Due to the difficulty of [^{18}F]fluorine labeling to aromatic compounds,[9-11] the introduction of a fluoroalkyl group on aromatic ring could be a new way of labeling of fluorine.[12-16] One of the most appropriate methods for the incorporation of [^{18}F]fluorine into organic molecules is an aliphatic nucleophilic substitution reaction of the leaving group, sulfonate group such as mesylate, tosylate, nosylate, or triflate.[3-7,17,18]

The systematic studies for the introduction of a fluoroalkyl group on the aromatic ring have not been extensively studied. Substitution of the hydrogen atom on aromatic ring with fluoro, methyl, fluoromethyl, fluoroethyl, or fluoropropyl group will make the compound more lipophilic. After de Paulis reported the optimization of the chain length for its effect on affinity,[19] the introduction of fluoroalkyl group to aromatic ring was applied to benzamides such as fallypride, a dopamine D_2 receptor ligand.[20-22] The introduction of [^{18}F]fluorine to the aromatic system is not easy except on the system with an electron-withdrawing group at ortho or para position of leaving group. The following Scheme 1 showed



Scheme 1. One Example of the Introduction of a Fluoroalkyl Group to the Aromatic Compound.

one example of the application for the introduction of a fluoroalkyl group to the C3 position of 6-nitroquipazine that has strong binding affinity toward the serotonin transporter.[23]

In this report, we investigated *in vitro* stabilities of fluoroalkyl groups, consequently providing the valuable information on *in vivo* stabilities of compounds which have a fluoroalkyl group. The [^{18}F]fluoroalkylbiphenyls were prepared as the model compounds of fluoroalkyl aromatic compounds and their metabolisms were studied using rat hepatic microsomes to predict their *in vivo* metabolic stabilities.[24]

Results and Discussion

Synthesis of Fluoroalkylbiphenyls. As shown in the Scheme 2, 4-fluoromethylbiphenyl (**3a**), 4-(2-fluoroethyl)biphenyl (**3b**), and 4-(3-fluoropropyl)biphenyl (**3c**) were prepared by conventional homologation from 4-hydroxymethylbiphenyl. Although this homologated synthetic routes were tedious, we could not find other better routes. Recently, vinylation or allylation using trialkylvinyltin or trialkylallyltin from the corresponding bromo or iodoarenes by Stille coupling reaction was reported.[25] The transformations of vinyl or allyl compound to **3b** or **3c** by hydroboration, and mesylation followed by fluorination are expected to give better yields. Three mesylates **2a-c** were the precursors for the radiolabeling.

Mesylation of the alcohol **1a** afforded the mesylate **2a** in high yield. The displacement reaction of the mesylate **2a** with fluoride ion proceeded within 30 min at 110 °C in acetonitrile when an appropriate soluble source of fluoride ion such as *n*-Bu_4NF was used. The introduction of fluorine

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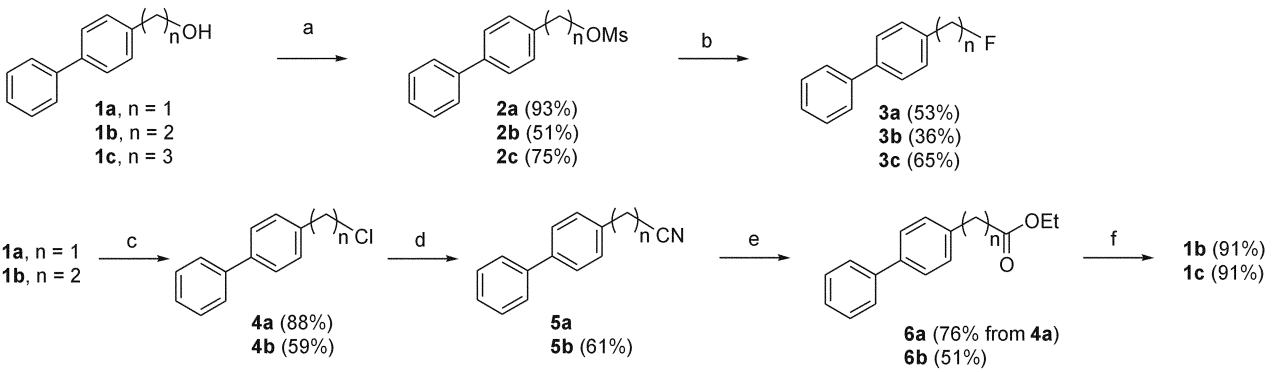


Scheme 2. (a) MsCl, Et_3N, CH_2Cl_2, 0 °C, 30 min; (b) *n*-$Bu_4NF{\cdot}xH_2O$, CH_3CN, 130 °C, 10 min; (c) $SOCl_2$, pyridine, benzene, 70 °C, 24 h; (d) NaCN, DMSO, 90 °C, 2 h; (e) CH_3CH_2OH, H_2SO_4, H_2O, reflux, 7 h; (f) LAH, THF, -30 °C, 30 min.

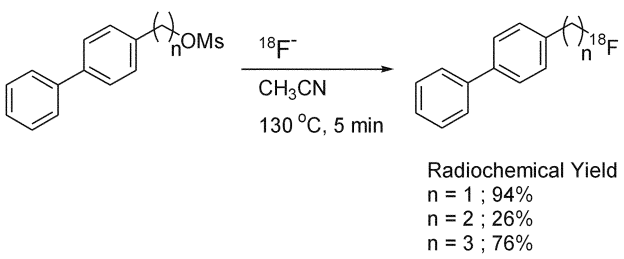
is easily identified by ^{1}H NMR, in which the signal of CH_2F group at 5.43 ppm is a doublet due to typical geminal coupling with fluorine (J = 47.6 Hz).

Homologations to synthesize **3b** and **3c** have been achieved as follows: Treatment of biphenyl methanol (**1a**) with thionyl chloride at 80 °C in benzene provided biphenylmethylchloride **4a** in 88% isolated yield. Treatment of the chloride **4a** with sodium cyanide in DMSO afforded 4-cyanomethylbiphenyl (**5a**). Hydrolysis of **5a** with concentrated sulfuric acid and esterification with ethyl alcohol gave ester **6a** in 76% yield from **4a**. Treatment of the ester **6a** with LAH in dried THF at -30 °C provided alcohol **1b** in 91% isolated yield. Mesylation of the alcohol afforded a mesylate **2b** in 51% yield. Displacement reaction of mesylate **2b** with fluoride ion proceeded within 30 min at 110 °C in acetonitrile. The introduction of fluorine is easily identified by ^{1}H NMR, in which the signals of $C\underline{H}_2F$ and $C\underline{H}_2CH_2F$ group at 4.67 and 3.06 ppm are the doublet-triplet peaks due to geminal and vicinal couplings with fluorine (J = 47.4, 23.0 Hz). However, the synthesis of the fluoroethyl compound **3b** has limitation, since two reactions - elimination and nucleophilic substitution - compete each other during the fluorination reaction of the sulfonate precursor.

Treatment of alcohol **1b** with thionyl chloride at 80 °C in benzene provided chloride **4b** in 59% isolated yield. All modifications from chloride **4b** to 3-fluoropropyl compound **3c** are the same as for the preparation of 4-(2-fluoroethyl)-biphenyl. In ^{1}H NMR, the signals of $C\underline{H}_2F$ and $C\underline{H}_2CH_2F$ group appear at 4.49 (J = 47.2 Hz) and 2.09 (J = 26.8 Hz) ppm as the doublet-triplet peaks.

Synthesis of 4-[^{18}F]Fluoroalkylbiphenyls ([^{18}F]3a-c). [^{18}F]Fluoride ion displacement reactions of each mesylate (**2a-c**) were carried out at 130 °C for 5 min and afforded [^{18}F]fluoroalkylbiphenyls ([^{18}F]**3a-c**) reproducibly in each 94, 26, and 76% isolated yield (Unless noted, all yields are decay-corrected.) under no-carrier-added (NCA) conditions (Scheme 3). Each [^{18}F]fluoroalkylbiphenyl derivative was purified by a short silica gel column chromatography and used for the metabolism studies.

As shown in the Table 1, the metabolic stability of the [^{18}F]fluoroalkylbiphenyls was measured using rat hepatic microsomes. In all cases, the metabolite was generated and



Scheme 3

Table 1. *In vitro* Metabolic Stability of [^{18}F]Fluoroalkyl Compounds in Rat Hepatic Microsomes

Time (min)	[^{18}F]F$^-$ (%)	[^{18}F]**3a** (%)	[^{18}F]F$^-$ (%)	[^{18}F]**3b** (%)	[^{18}F]F$^-$ (%)	[^{18}F]**3c** (%)
2	4.64	92.75	3.38	94.31	5.00	75.25
5	6.12	91.70	4.48	91.05	6.80	77.07
15	10.65	87.10	4.18	89.66	11.98	71.69
30	17.25	80.29	7.41	86.96	13.56	70.91
60	37.31	59.37	15.94	79.67	14.46	69.41

identified as [^{18}F]fluoride ion by comigration with the authentic [^{18}F]fluoride ion on radio-TLC and precipitation with calcium phosphate.[24] The [^{18}F]fluoride ion was generated more rapidly from the [^{18}F]fluoromethylbiphenyl than the others. According to these results, the [^{18}F]fluoroethyl-biphenyl was the most stable *in vitro* (Figure 1).

Proposed Metabolic Pathways of [^{18}F]Fluoroalkylbiphenyl. In 1988, Welch *et al.* showed the difference on the metabolism between [^{18}F]fluoroethyl and [^{18}F]fluoropropyl spiperones.[26] It was proposed that the *N*-[^{18}F]fluoroalkylated compounds on lactam are metabolized by *N*-dealkylation reaction to produce [^{18}F]fluoroaldehydes. The stabilities of [^{18}F]fluoroacetaldehyde and [^{18}F]fluoropropanal are quite different. While [^{18}F]fluoroacetaldehyde is a stable lipophilic metabolite, [^{18}F]fluoropropanal is unstable towards fluoride ion elimination (retro Michael addition) and subsequently oxidized to 3-[^{18}F]fluoropropionic acid.

Another consideration on metabolism of aliphatic hydrocarbon attached to aromatic ring is hydroxylation that is one of the major pathways of biotransformation. As shown in the

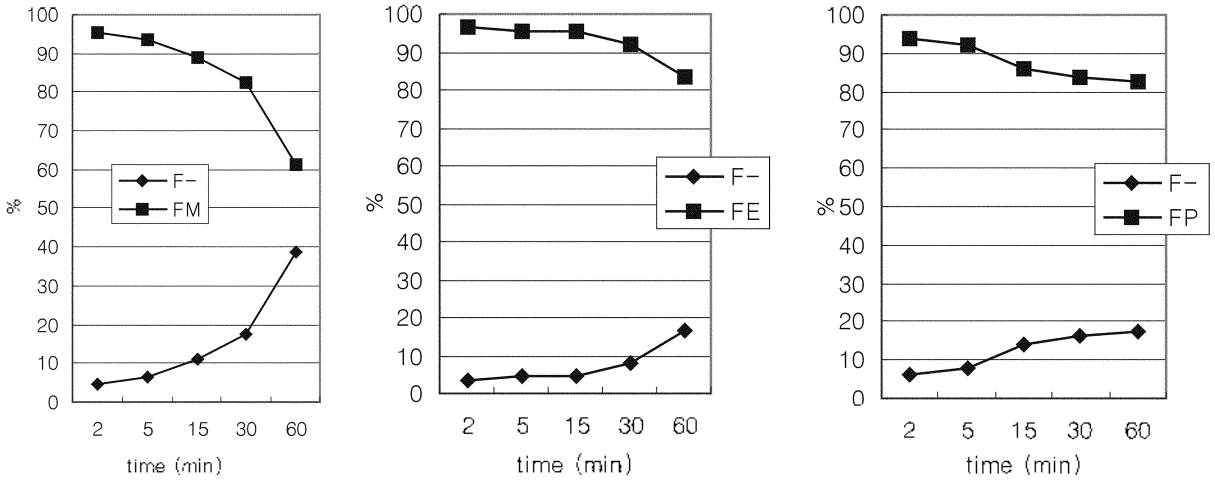
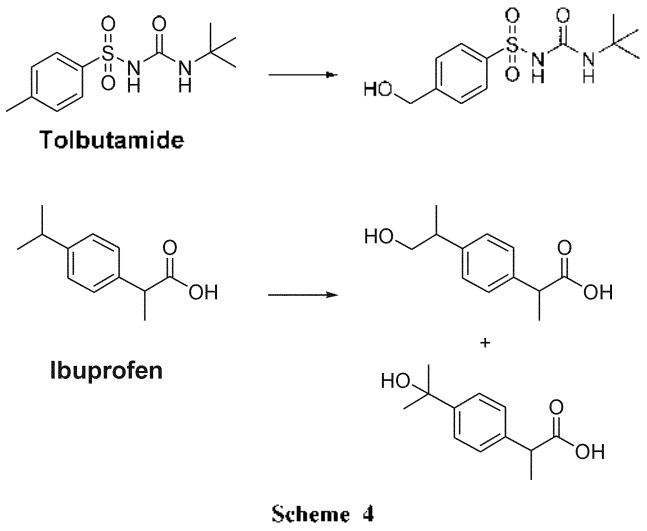


Figure 1. Metabolite analysis of [^{18}F]fluoroalkylbiphenyls (FM = [^{18}F]**3a**, FE = [^{18}F]**3b**, FP = [^{18}F]**3c**).



Scheme 4

Scheme 4, methyl group of tolbutamide is converted into hydroxymethyl group and isopropyl group of ibuprofen is oxidized to both α-carbon hydroxylation and β-carbon hydroxylation.[27]

Figure 2 shows *in vitro* stability of the [^{18}F]fluoroalkylbiphenyls in human serum. [^{18}F]Fluoroethyl and [^{18}F]fluoropropylbiphenyl were shown to be stable with more than 90% retention during the entire duration of the study. In contrast, [^{18}F]fluoromethylbiphenyl was less stable than the others, converting 40-50% of the fraction to [^{18}F]fluoride and an unknown compound which was presumably derived from α-carbon hydroxylation of aliphatic hydrocarbon as shown in Scheme 4.

Based on results of the *in vitro* study of [^{18}F]fluoroalkylbiphenyl in rat hepatic microsomes, the metabolism of [^{18}F]fluoroalkylbiphenyls proceeds by α-carbon hydroxylation followed by oxidation as shown in Scheme 5. While fluoroacetyl is much more stable due to slow α-elimination, fluoropropanone is less stable than fluoroacetyl because β-elimination occurs much faster.[26]

According to the *in vitro* metabolic stability of the [^{18}F]fluoroalkylbiphenyl in rat hepatic microsomes, the stability of the compound was determined by the relative rate of defluorination from the [^{18}F]fluoroalkylbiphenyl. The [^{18}F]fluoromethylbiphenyl underwent defluorination faster than the [^{18}F]fluoroethylbiphenyl or the [^{18}F]fluoropropylbiphenyl, because it is hydroxylated easily at the α-carbon. Moreover, after α-carbon hydroxylation of the [^{18}F]fluoro-

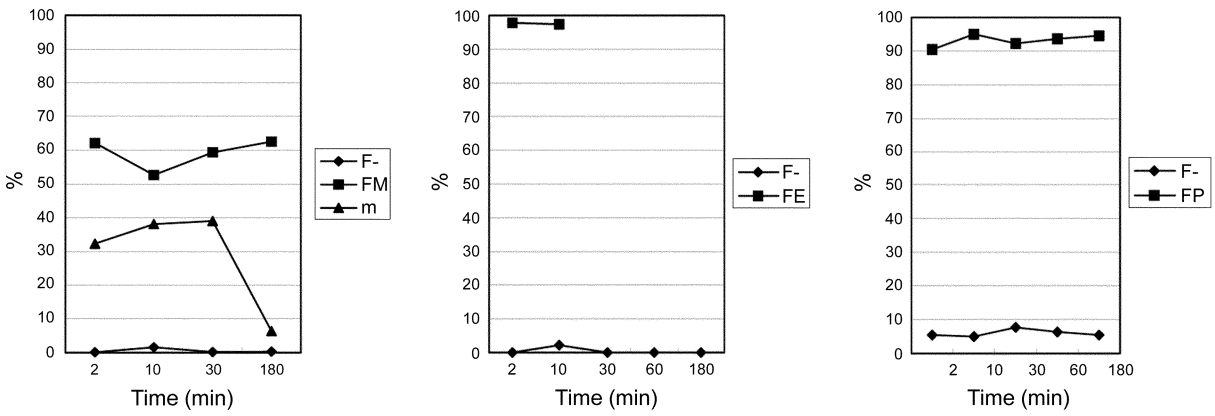
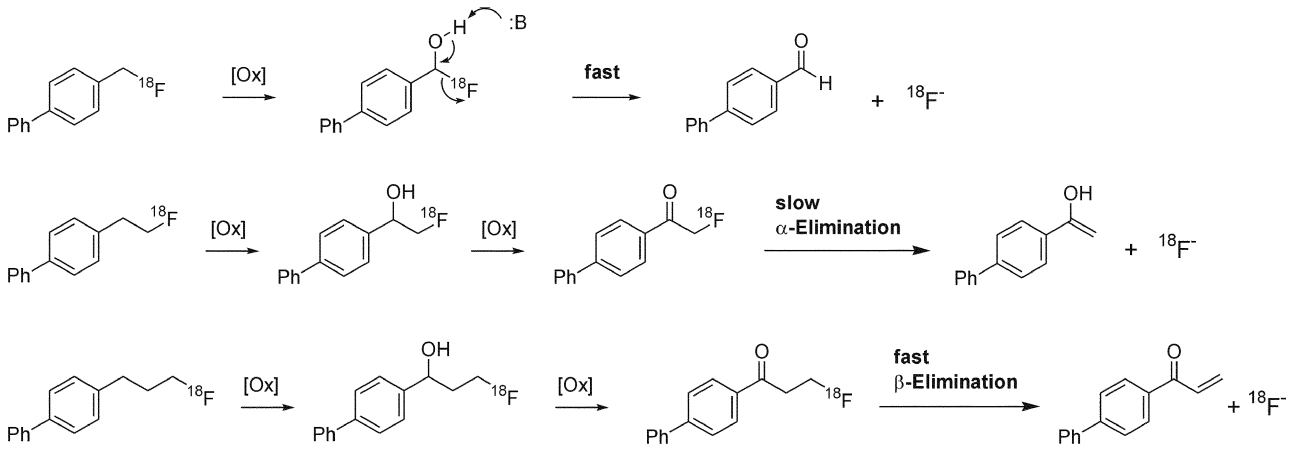


Figure 2. *In vitro* stability in human serum at 37 °C (FM = [^{18}F]**3a**, FE = [^{18}F]**3b**, FP = [^{18}F]**3c**). The notation m in graph of FM is a metabolite of unknown structure.



Scheme 5

ethylbiphenyl and the [^{18}F]fluoropropylbiphenyl, fluoroacetyl of the former is much more stable due to the slow α-elimination, whereas fluoroacetyl of the latter is less stable due to much faster β-elimination. In the *in vitro* stability studies of [^{18}F]fluoroalkylbiphenyl in human serum, [^{18}F]fluoroethylbiphenyl was the most stable and [^{18}F]fluoromethylbiphenyl was the least stable. The degraded product was confirmed as the [^{18}F]fluoride ion in all cases and an unknown product was also observed in the case of [^{18}F]fluoromethylbiphenyl. Interestingly, the product, [^{18}F]fluoride ion and the trend of the stability of [^{18}F]fluoroalkylbiphenyl were consistent in both studies using hepatic microsomes and human serum, although the effect of the former was more profound. This result enabled us to predict the *in vivo* stability as follow: Fluoroethylbiphenyl would have a similar or slightly better stability to fluoropropylbiphenyl and these both compounds were much more stable than fluoromethylbiphenyl *in vivo*.

In conclusion, we prepared three 4-(ω-[^{18}F]fluoroalkyl)biphenyls as model compounds to compare the *in vitro* stabilities. *In vitro* stabilities were measured separately using rat hepatic microsomes and human serum at 37 °C. Fluoroethylbiphenyl had a similar or slightly better stability to fluoropropylbiphenyl and these both compounds were much more stable than fluoromethylbiphenyl *in vitro*. The [^{18}F]fluoroethyl derivatives would be the most suitable for PET imaging studies. Synthesis of the [^{18}F]fluoroethyl compound has some limitations, since two reactions – elimination and nucleophilic substitution – compete each other during [^{18}F]fluorination reaction of the sulfonate precursor, consequently providing low labeling yield (26%). However, as recent new methodology for the synthesis of fluoroethyl group using high pressure or ionic liquid would probably overcome this limitation, applicability of [^{18}F]fluoroethyl moiety to the preparation of radiopharmaceuticals is expected to grow.

Experimental Section

4-(Methanesulfonyloxy)methylbiphenyl (2a). To 4-hydroxymethyl-biphenyl (3.00 g, 16.28 mmol) in dichloromethane (20 mL) was added triethylamine (3.40 mL, 24.42 mmol) and methanesulfonyl chloride (1.51 mL, 19.54 mmol) at 0 °C. After 30 min, the reaction mixture was quenched with H_2O. The reaction mixture was extracted with dichloromethane, and the organic layer was dried (Na_2SO_4) and evaporated. Flash column chromatography (40% EtOAc/hexane) provided **2a** (3.96 g, 93%) as a white solid.

4-Fluoromethylbiphenyl (3a). In 5 mL Reacti-vial® to mesylate **2a** (50 mg, 0.19 mmol) in acetonitrile (1.5 mL) was added tetra-*n*-butylammonium fluoride hydrate (60 mg, 0.19 mmol) and heated at 80 °C for 4 h (or 110 °C for 30 min). The reaction mixture was extracted with ethyl acetate and washed (H_2O, brine) and the organic layer was dried (Na_2SO_4) and evaporated. Flash column chromatography (20% EtOAc/hexane) provided **3a** (19 mg, 53%) as a pale yellow solid: mp 61.0-63.7 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.43 (d, 2H, J = 47.6 Hz), 7.39-7.65 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 83.35 (d, J = 165.35 Hz), 120.18, 126.14, 126.34, 126.51, 126.95, 127.07, 127.80, 133.97; MS (EI) *m/z* 186 (100), 165, 109, 83, 51.

4-[^{18}F]Fluoromethylbiphenyl ([^{18}F]3a). A [^{18}F]fluoride ion displacement reaction of 4-chloromethylbiphenyl or mesylate **2a** (2.0 mg, 9.9 μmol) in CH_3CN (200 μL) was carried out at 130 °C for 5 min and afforded [^{18}F]**3a** reproducibly in 94% isolated yield under NCA conditions (843 mCi F-18 fluoride ion, tetra-*n*-butylammonium hydroxide (40% aq, 5.74 μL, 8.42 μmol), resolubilization yield; 64%, resolubilization time; 6 min). The 4-fluoromethylbiphenyl was purified by a short silica gel column chromatography.

4-Chloromethylbiphenyl (4a). To 4-hydroxymethylbiphenyl (**1a**, 1.00 g, 5.43 mmol) in benzene (10 mL) was added thionyl chloride (792 μL, 10.86 mmol) and pyridine (878 μL, 10.86 mmol) and heated at 80 °C for 24 h. The reaction mixture was poured into water and extracted with benzene and washed (H_2O, brine) and the organic layer was dried (Na_2SO_4) and evaporated. Flash column chromatography (10% EtOAc/hexane) provided **4a** (965 mg, 88%) as a white solid: ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.83 (s, 2H),

7.63-7.85 (m, 9H).

4-Cyanomethylbiphenyl (5a). To dried DMSO (10 mL) was added sodium cyanide (578 mg, 11.80 mmol) and heated at 90 °C and then removed the heating bath. To the reaction mixture was slowly added 4-chloromethylbiphenyl (**4a**, 1.99 g, 9.84 mmol) and stirred for 30 min at 50 °C. The reaction mixture was poured into water and extracted with ethyl acetate and washed (H_2O, brine) and the organic layer was dried (Na_2SO_4) and evaporated. The crude product **5a** was obtained (2.32 g) and used for next reaction without further purification.

4-(Ethoxycarbonylmethyl)biphenyl (6a). To 4-cyanomethylbiphenyl (**5a**) crude product (2.32 g, 13.74 mmol) and conc. H_2SO_4 (1.47 mL) in EtOH (5 mL) was heated at 80 °C for 22 h. The reaction mixture was poured into cool water and extracted with ethyl acetate and washed ($NaHCO_3$, brine) and the organic layer was dried (Na_2SO_4) and evaporated. Flash column chromatography (10% EtOAc/hexane) provided **6a** (2.52 g, 76%) as a white solid: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.36 (t, 3H, J = 7.0 Hz), 3.74 (s, 2H), 4.28 (q, 2H, J = 7.1 Hz), 7.39-7.71 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.68, 39.44, 59.28, 125.50, 125.71, 125.76, 126.08, 126.12, 126.82, 127.28, 127.37, 128.20, 131.80, 138.39, 139.23, 169.85.

4-(2-Hydroxyethyl)biphenyl (1b). To LAH (169 mg, 4.45 mmol) in dried THF at under -30 °C was added ester **6a** (534 mg, 2.23 mmol) and stirred for 30 min at under -30 °C. The reaction mixture was quenched by small amount water and filtered and extracted with ethyl acetate and washed (H_2O, brine) and the organic layer was dried (Na_2SO_4) and evaporated. Flash column chromatography (10% EtOAc/hexane) provided **1b** (403 mg, 91%) as a white solid: ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.91 (t, 2H, J = 6.6 Hz), 3.90 (t, 2H, J = 6.4 Hz), 7.28-7.60 (m, 9H).

4-(2-Methanesulfonyloxyethyl)biphenyl (2b). To alcohol **1b** (360 mg, 1.82 mmol) in dichloromethane (5 mL) was added triethylamine (304 μL, 2.18 mmol) and methanesulfonyl chloride (211 μL, 2.73 mmol) at 0 °C. After 30 min, the reaction mixture was quenched with H_2O. The reaction mixture was extracted with dichloromethane, and the organic layer was dried (Na_2SO_4) and evaporated. Flash column chromatography (40% EtOAc/hexane) provided **2b** (257 mg, 51%) as a white solid: ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.69 (s, 3H), 2.91 (t, 2H, J = 7.0 Hz), 4.27 (t, 2H, J = 7.0 Hz), 7.10-7.46 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 33.52, 25.50, 68.75, 125.31, 125.67, 125.75, 127.23, 127.85, 133.95, 138.18, 138.92.

4-(2-Fluoroethyl)biphenyl (3b). In 5 mL Reacti-vial® to mesylate **2b** (20 mg, 0.07 mmol) in acetonitrile (1 mL) was added tetra-*n*-butylammonium fluoride hydrate (23 mg, 0.07 mmol) and heated at 80 °C for 4 h (or 110 °C for 30 min). The reaction mixture was extracted with ethyl acetate and washed (H_2O, brine) and the organic layer was dried (Na_2SO_4) and evaporated. Flash column chromatography (20% EtOAc/hexane) provided **3b** (5 mg, 36%) as a pale yellow solid: mp 35.9-37.5 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.06 (dt, 2H, J = 23.0, 6.4 Hz), 4.67 (dt, 2H, J = 47.4, 6.6 Hz), 7.26-7.60 (m, 9H); MS(EI) *m/z* 200, 167 (100), 165, 115, 83, 51.

4-(2-[^{18}F]Fluoroethyl)biphenyl ([^{18}F]3b). The [^{18}F]fluoride ion displacement reaction of mesylate **2b** (2.0 mg, 7.2 μmol) in CH_3CN (200 μL) was carried out at 130 °C for 5 min and afforded 4-(2-[^{18}F]fluoroethyl)biphenyl reproducibly in 26% isolated yield under NCA conditions (1.4 mCi F-18 fluoride ion, tetra-*n*-butylammonium hydroxide (40% aq. 4.18 μL, 6.12 μmol), resolubilization yield; 70%, resolubilization time: 8 min). The 4-(2-[^{18}F]fluoroethyl)biphenyl was purified by a short silica gel column chromatography.

4-(2-Chloroethyl)biphenyl (4b). To 4-(2-hydroxyethyl)-biphenyl (**1b**, 403 mg, 2.04 mmol) in benzene (3 mL) was added thionyl chloride (379 μL, 5.19 mmol) and pyridine (420 μL, 5.19 mmol) and heated at 80 °C for 24 h. The reaction mixture was poured into water and extracted with benzene and washed (H_2O, brine) and the organic layer was dried (Na_2SO_4) and evaporated. Flash column chromatography (10% EtOAc/hexane) provided **4b** (245 mg, 59%) as a pale yellow oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.10 (t, 2H, J = 7.3 Hz), 3.74 (t, 2H, J = 7.5 Hz), 7.26-7.59 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 37.25, 43.35, 125.49, 125.75, 127.27, 127.72, 135.61, 138.26, 139.25.

4-(2-Cyanoethyl)biphenyl (5b). To dried DMSO (5 mL) was added sodium cyanide (17 mg, 0.35 mmol) and heated at 90 °C and then removed the heating bath. To the reaction mixture was slowly added 4-(2-chloroethyl)biphenyl (**4b**, 50 mg, 0.23 mmol) and stirred for 30 min at 50 °C. The reaction mixture was poured into water and extracted with ethyl acetate and washed (H_2O, brine) and the organic layer was dried (Na_2SO_4) and evaporated. Flash column chromatography (10% EtOAc/hexane) provided **5b** (30 mg, 61%) as a pale yellow oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.66 (t, 2H, J = 7.3 Hz), 3.00 (t, 2H, J = 7.3 Hz), 7.25-7.60 (m, 9H).

4-(2-Ethoxycarbonylethyl)biphenyl (6b). To 4-(2-cyanoethyl)biphenyl (**5b**, 520 mg, 2.51 mmol) and conc. H_2SO_4 (0.2 mL) in EtOH (1 mL) was heated at 80 °C for 22 h. The reaction mixture was poured into cool water and extracted with ethyl acetate and washed ($NaHCO_3$, brine) and the organic layer was dried (Na_2SO_4) and evaporated. Flash column chromatography (10% EtOAc/hexane) provided **6b** (322 mg, 51%) as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.23 (t, 3H, J = 7.0 Hz), 2.64 (t, 2H, J = 7.6 Hz), 2.99 (t, 2H, J = 7.5 Hz), 4.11 (q, 2H, J = 4.7 Hz), 7.25-7.58 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.60, 28.99, 34.23, 58.78, 125.35, 125.50, 125.56, 127.10, 137.58, 138.07, 139.32, 171.17.

4-(3-Hydroxypropyl)biphenyl (1c). To LAH (96 mg, 2.54 mmol) in dried THF at under -30 °C was added ester **6b** (322 mg, 1.27 mmol) and stirred for 30 min at under -30 °C. The reaction mixture was quenched by small amount water and filtered and extracted with ethyl acetate and washed (H_2O, brine) and the organic layer was dried (Na_2SO_4) and evaporated. Flash column chromatography (10% EtOAc/hexane) provided **1c** (246 mg, 91%) as a white solid: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.94 (q, 2H, J = 6.8 Hz), 2.76 (t, 2H, J = 7.5 Hz), 3.72 (t, 2H, J = 6.4 Hz), 7.26-7.60 (m, 9H);

^{13}C NMR (50 MHz, $CDCl_3$) δ 30.09, 32.54, 60.46, 125.33, 125.40, 125.47, 127.10, 127.23, 137.17, 139.41.

4-(3-Methanesulfonyloxypropyl)biphenyl (2c). To alcohol **1c** (50 mg, 0.24 mmol) in dichloromethane (2 mL) was added triethylamine (49 μL, 0.35 mmol) and methanesulfonyl chloride (18.0 μL, 0.24 mmol) at 0 °C. After 30 min, the reaction mixture was quenched with H_2O. The reaction mixture was extracted with dichloromethane, and the organic layer was dried (Na_2SO_4) and evaporated. Flash column chromatography (40% EtOAc/hexane) provided **2c** (52 mg, 75%) as a white solid: ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.10 (q, 2H, J = 6.9 Hz), 2.79 (t, 2H, J = 7.5 Hz), 2.99 (s, 3H), 4.25 (t, 2H, J = 6.4 Hz), 7.24-7.60 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 28.97, 29.52, 35.68, 67.52, 125.32, 125.53, 125.63, 127.13, 127.24, 137.60, 137.76, 139.18.

4-(3-Fluoropropyl)biphenyl (3c). In 5 mL Reacti-vial® to mesylate **2c** (44 mg, 0.15 mmol) in acetonitrile (1.5 mL) was added tetra-*n*-butylammonium fluoride hydrate (48 mg, 0.15 mmol) and heated at 80 °C for 4 h (or 110 °C for 30 min). The reaction mixture was extracted with ethyl acetate and washed (H_2O, brine) and the organic layer was dried (Na_2SO_4) and evaporated. Flash column chromatography (20% EtOAc/hexane) provided **3c** (21 mg, 65%) as a pale yellow oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.09 (dq, 2H, J = 26.8, 8.4 Hz), 2.79 (t, 2H, J = 7.5 Hz), 4.49 (dt, 2H, J = 47.2, 5.8 Hz), 7.33-7.61 (m, 9H); MS (EI) m/z 214, 167 (100), 165, 115, 51.

4-(3-[^{18}F]Fluoropropyl)biphenyl ([^{18}F]3c). A F-18 fluoride ion displacement reaction of mesylate **2c** (2.0 mg, 6.8 μmol) in CH_3CN (200 μL) was carried out at 130 °C for 5 min and afforded 4-(3-[^{18}F]fluoropropyl)biphenyl reproducibly in 76% isolated yield under NCA conditions (1.52 mCi F-18 fluoride ion, tetra-*n*-butylammonium hydroxide (40% aq, 3.94 μL, 5.78 μmol), resolubilization yield: 67%, resolubilization time: 7 min). The 4-(3-[^{18}F]fluoropropyl)biphenyl was purified on a short silica gel column chromatography.

***In Vitro* Metabolism Study Using Rat Microsomes.** The radiotracer dissolved in a minimal volume of EtOH was preincubated with rat hepatic microsomes (final conc., 1 mg/mL) in phosphate buffer (0.1 M, pH 7.4) at 37 °C for 3 min. The incubation was started by addition of NADPH (0.25 mM) at 37 °C. An aliquot (500 μL) was removed at each time point (5, 15, 30, and 60 min) and filtered through a celite column that was washed with 2 mL of EtOH. The metabolites were analyzed by Radio-TLC. In another set of the incubation, an aliquot (500 μL) was removed from the mouse microsomal reaction mixture and passed through a celite plug (2 cm). The eluant was added to calcium phosphate (10 mg) and incubated at 37 °C for 30 min. The mixture was then centrifuged, and the supernatant was removed and counted.

***In Vitro* Stability in Human Serum.** An aliquot of the radiotracer was added to human serum (1 mL) and incubated at 37 °C, and the solution was analyzed at 2, 10, 30, 60 and 180 min by radio-TLC using 50% EtOAc/hexane as the developing solvents.

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