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Study on the compounds containing ^{19}F and ^{10}B atoms in a single molecule for the application to MRI and BNCT

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Abstract—Magnetic resonance imaging (MRI) and boron-neutron capture therapy (BNCT) are quite attractive techniques for diagnosis and treatment of cancer, respectively. In order to progress the study on both MRI and BNCT, the novel compounds containing ^{19}F and ^{10}B atoms in a single molecule were designed and synthesized. In the present paper, the syntheses and the internalization rates into tumor cells of these compounds are elucidated.

1. Introduction

Magnetic resonance imaging (MRI) is commonly used as a technique for diagnosis of cancer. Recently, MRI based on the measurement of ^{19}F atom attracts the attention to the field of diagnostics.[1] According to our preliminary elucidation, dipeptides containing 3-(4-fluorophenyl)alanine [Phe(F)] (**1**) seem to be transferred into some kinds of tumor cells through the oligopeptide transporter. Furthermore, dipeptide containing 3-(pentafluorophenyl)alanine [Phe(F_5)] (**2**) was certified to be detectable by ^{19}F NMR up to μM order concentration.[2] These facts suggest that MRI based on ^{19}F NMR measurement of the Phe(F_5)-containing peptides internalized into the tumor cells may be accessible as a promising means for diagnosis of cancer.

From the standpoint of the treatment of brain cancer or melanoma, the boron-neutron capture therapy (BNCT) based on the interaction of ^{10}B isotope and neutron has been highly noted in recent years.[3] At present β-[4-(^{10}B)boronophenyl]alanine (^{10}Bpa)[4] (**3**) and β-[4-(^{10}B)boronophenyl]alaninol (^{10}Bpa-ol)[5] (**4**) seem to be good candidates as the ^{10}B carrier for BNCT.

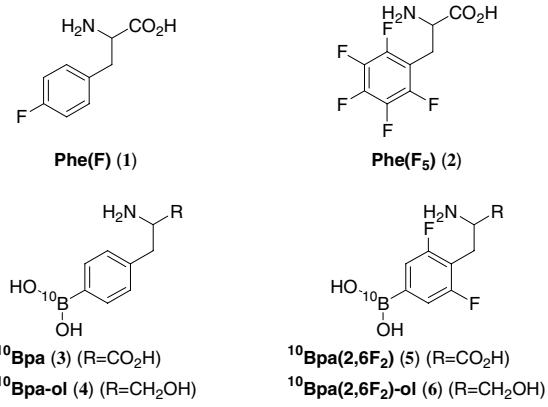

Figure 1. Amino acids and their related compounds containing fluorine and/or boron-10.

In order to create novel materials to use practically for diagnosis and treatment of cancer by means of MRI and BNCT, respectively, we designed and synthesized the compounds containing both fluorine and boron-10 atoms in a single molecule such as β-[4-(^{10}B)borono-2,6-difluorophenyl]alanine [$^{10}Bpa(2,6F_2)$] (**5**) or β-[4-(^{10}B)borono-2,6-difluoropheny 1]alaninol [$^{10}Bpa(2,6F_2)$-ol] (**6**) (Fig. 1). In the present paper, we elucidated the syntheses and internalization rates into tumor cells of these compounds.

Keywords: Magnetic resonance imaging; Boron-neutron capture therapy; β-[4-(^{10}B)Borono-2,6-difluorophenyl]-alanine; β-[4-(^{10}B)Borono-2,6-difluorophenyl]alaninol.
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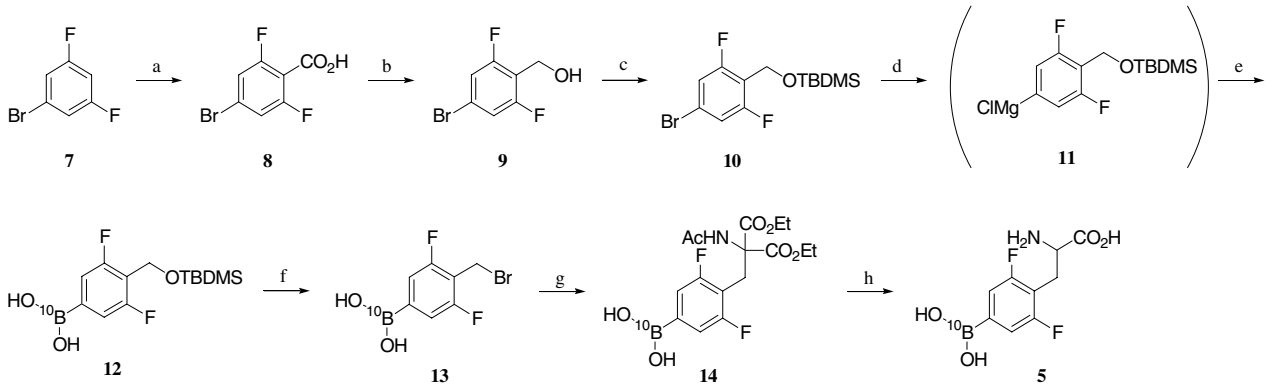


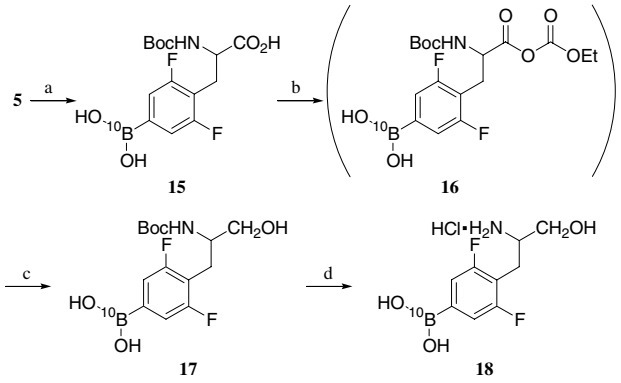
Scheme 1. Reagents and conditions: (a) 1—LDA, THF, −78 °C, 2 h; (2)—CO_2, −78 °C, 30 min, 86.8%. (b) 1— $ClCO_2CH(CH_3)_2$, Et_3N, THF, 1.5 h, −10 °C; (2)— $NaBH_4$, H_2O, 0 °C, 4 h, 94.8%. (c) TBDMS-Cl, *H*-imidazole, DMF, rt, 6 h, 90.4%. (d) *i*PrMgCl, THF, 0 °C, 1 h. (e) $^{10}B(OMe)_3$, rt, 24 h, 93.7%. (f) 1—66% AcOH aq, rt, 8 h; 2—PBr_3, Et_2O, 0 °C, 4 h, 94.2%. (g) Diethyl acetamidomalonate, 60% NaH, THF, 0 °C then reflux, 3 h, 92.7%. (h)1—3 M HCl, 80 °C, 27 h; (2)—propylene oxide, *i*PrOH, rt, 6 h, 73.7%.

2. Chemistry

The synthesis of **5** was first carried out by the conventional method based on the reaction of alkyl halide with diethyl acetamidomalonate as shown in Scheme 1.

1-Bromo-3,5-difluorobenzene (**7**) was reacted with lithium diisopropyl amide (LDA) and then CO_2 to give 4-bromo-2,6-difluorobenzoic acid (**8**).[6] The benzoic acid derivative **8** was converted into the benzylalcohol derivative **9**, and then the alcohol group was protected with the TBDMS group to give the silyl ether derivative **10**. In the next step, the preparation of phenylboric acid derivative **12** was first carried out by lithiation of **10** with *n*BuLi and TMEDA, followed by addition of $^{10}B(OMe)_3$. Although this reaction gave mainly *m*-boronated and *m*,*m*′-diboronated compounds rather than *p*-boronated one, the halogen-metal exchange reaction[7] between **10** and isopropyl-magnesium chloride produced **12** in excellent yield.

Treatment of **12** with 66% aqueous AcOH cleaved the TBDMS group, and the alcohol derivative thus obtained was brominated[8] with PBr_3 to give the benzylbromide derivative **13**. The coupling of **13** with diethyl acetamidomalonate proceeded appreciably using 60% NaH, instead of NaOEt, as base. Acid hydrolysis of the reaction product **14** gave $^{10}Bpa(2,6F_2)$ (**5**).



Scheme 2. Reagents and conditions: (a) $(Boc)_2O$, Na_2CO_3, acetone, H_2O, rt, 7 h, 97.3%. (b) $ClCO_2Et$, NMM, THF, −10 °C, 10 min. (c) $NaBH_4$, MeOH, 0 °C, 1 h, 80.1%. (d) 4 M HCl/AcOEt, rt, 30 min, 92.6%.

The amino acid **5** was then converted into the alcohol derivative **17** as shown in Scheme 2. The α-amino group of **5** was protected with the Boc group, and the carboxyl group was reduced to the alcohol derivative **17** through the mixed acid anhydride (**16**).[9] The Boc group was cleaved by 4 M HCl/AcOEt to give $^{10}Bpa(2,6F_2)$-ol (**18**) as HCl salt.

3. Results and discussion

Incorporation amount and cytotoxicity of $^{10}Bpa(2,6F_2)$ and $^{10}Bpa(2,6F_2)$-ol were examined using three kinds of cancer cells, C6 (rat glioma), HeLa (human epithelioma), and KB (human squamous cell carcinoma).

Boron concentration incorporated into three cancer cells was shown in Figure 2. In C6 cell, the amount of both

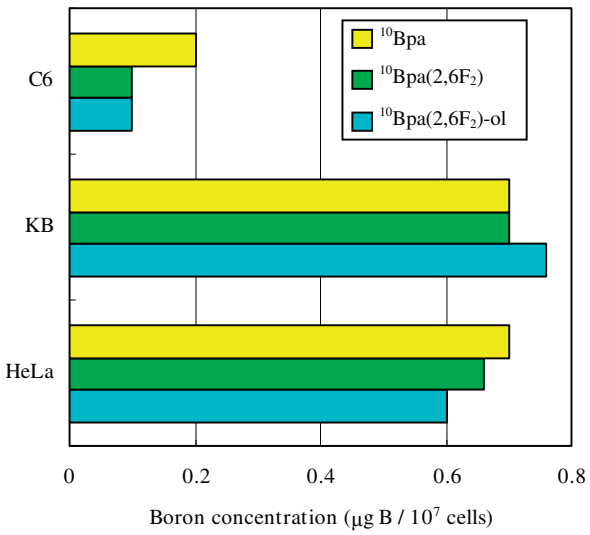


Figure 2. Boron concentration in tumor cells which internalized Bpa, $^{10}Bpa(2,6F_2)$, and $^{10}Bpa(F_2)$-ol.

^{10}Bpa(2,6F$_2$) and ^{10}Bpa(2,6F$_2$)-ol was half of that of ^{10}Bpa. In KB and HeLa, however, the accumulation amount of these compounds was almost the same as that of ^{10}Bpa, respectively.

Cytotoxicity of these compounds toward C6 cell was not observed in the range of 1–20 mM concentration (data not shown). These results suggest that the cytotoxicity of these compounds might almost be equal to that of ^{10}Bpa and also useful for a ^{10}B carrier of BNCT.

4. Experimental

4.1. General

Silica-gel column chromatography was carried out with silica gel PSQ100B (Fuji Silysia, Aichi, Japan). ^{1}H NMR and ^{19}F NMR spectra were measured on a Varian Mercury 300 [300 MHz (^{1}H) and 282 MHz (^{19}F), Varian Co., Ltd., USA] spectrometer. The chemical shifts in ^{1}H NMR are given in δ values from TMS and those in ^{19}F NMR from TFA used as the internal standard, respectively. Matrix-assisted laser desorption ionization time-of-flight mass spectra (MALDI-TOF MS) were obtained on a KRATOS KOMPACT MALDI IV mass spectrometer (Shimadzu Co. Ltd., Kyoto, Japan). Measurement of high resolution mass was carried out by fast-atom bombardment mass spectrometry (FAB-MS) using a JEOL JMS-700 TKM mass spectrometer (JEOL Co. Ltd., Tokyo, Japan). ^{10}B(OMe)$_3$ was given by Stella Chemifa Corporation (Osaka, Japan).

4.2. Synthesis

4.2.1. 4-Bromo-2,6-difluorobenzoic acid (8). To a solution of diisopropylamine (4.82 g, 25.0 mmol) in anhydrous THF (35 mL) was consecutively added a solution of 1.60 M *n*BuLi in hexane (15.6 mL, 25.0 mmol) and **7** (2.53 g, 25.0 mmol) under Ar atmosphere at −78 °C. After stirring for 2 h at −78 °C, CO_2 gas (0.02 MPa) was bubbled into the reaction mixture for 30 min under cooling at −78 °C. After evaporation of the solvent, the residue was dissolved in water (50 mL), and the solution was washed with Et_2O (20 mL × 3). The aqueous layer was acidified with concd HCl to pH 1 and extracted with CH_2Cl_2 (20 mL × 3). The combined extracts were dried over anhydrous $MgSO_4$ and concentrated in vacuo. The crystalline residue was recrystallized from benzene and hexane to give **8** as yellow crystals (5.15 g, 86.8%): mp 195–197 °C. ^{1}H NMR ($CDCl_3$) δ 7.28–7.42 (m, 2H); Anal. Calcd for $C_7H_3BrF_2O_2$: C, 35.47; H, 1.28. Found: C, 35.49; H, 1.50.

4.2.2. 4-Bromo-2,6-difluorobenzyl alcohol (9). To a solution of **8** (2.00 g, 12.7 mmol) and Et_3N (1.93 g, 19.1 mmol) in anhydrous THF (100 mL) was added $ClCO_2CH(CH_3)_2$ (2.34 g, 19.1 mmol) dropwise for 10 min at −20 °C. After stirring for 1.5 h at −10 °C, to the reaction mixture was added water (50 mL) at −10 °C, and then to the solution was added slowly $NaBH_4$ (1.83 g, 50.8 mmol) at 0 °C. After stirring for 4 h at room temperature, the reaction mixture was acidified with citric acid and diluted with H_2O (50 mL) to dissolve precipitated inorganic materials. After evaporation of THF, the aqueous solution was extracted with AcOEt (40 mL × 3). The combined extracts were washed with sat. $NaHCO_3$ aq (30 mL × 3) and brine (30 mL × 3), and dried over anhydrous $MgSO_4$. The solution was concentrated in vacuo, and the residue was purified by silica-gel column chromatography (silica gel: 60 g, hexane/AcOEt = 9:1) to give **9** as a colorless crystals (1.79 g, 94.8%): mp 38–40 °C. ^{1}H NMR ($CDCl_3$) δ 1.95 (t, 1H, *J* = 6.0 Hz), 4.73 (d, 2H, *J* = 6.0 Hz), 7.11 (d, 2H, *J* = 15.9 Hz); Anal. Calcd for $C_7H_5BrF_2O$: C, 37.70; H, 2.26. Found: C, 37.40; H, 2.34.

4.2.3. 4-Bromo-2,6-difluorobenzyl alcohol *t*-butyldi-methylsilyl ether (10). To a solution of **9** (1.14 g, 7.89 mmol) in DMF (10 mL) were added 1*H*-imidazole (644 mg, 9.47 mmol) and TBDMS-Cl (1.31 g, 8.68 mmol), and the reaction mixture was stirred for 1 h. After evaporation of the solvent, the residue was dissolved in Et_2O (50 mL). The solution was washed with H_2O (20 mL × 3), and brine (20 mL × 3), and dried over anhydrous $MgSO_4$. The solution was concentrated in vacuo, and the residue was purified by silica-gel column chromatography (silica gel: 40 g, hexane) to give **10** as colorless oil (1.89 g, 92.6%): ^{1}H NMR ($CDCl_3$) δ 0.10 (s, 6H), 0.88 (s, 9H), 4.77 (s, 2H), 7.11 (d, 2H, *J* = 15.9 Hz).

4.2.4. 4-(^{10}B)Borono-2,6-difluorobenzyl alcohol *t*-butyl-dimethylsilyl ether (12). To a solution of **10** (6.87 g, 20.4 mmol) in anhydrous THF (40 mL) was added a solution of 2.00 M *i*PrMgCl in THF (10.2 mL, 20.4 mmol) at 0 °C under Ar atmosphere. After stirring for 1 h at 0 °C, to the reaction mixture was added ^{10}B(OMe)$_3$ (1.62 g , 15.7 mmol), and the solution was stirred for 24 h. The reaction mixture was acidified with 10% aqueous citric acid, and THF was removed by evaporation in vacuo. The aqueous solution was extracted with Et_2O (60 mL × 3), and the extract was dried over anhydrous $MgSO_4$. The solution was concentrated in vacuo, and the residue was purified by silica-gel column chromatography (silica gel: 180 g, hexane/AcOEt = 1:1) to give **12** as colorless oil (5.77 g, 93.7%): ^{1}H NMR (CD_3COCD_3) δ 0.10 (s, 6H), 0.88 (s, 9H), 4.77 (s, 2H), 6.95 (d, 2H, *J* = 15.9 Hz), 7.62 (s, 2H).

4.2.5. 4-(^{10}B)Borono-2,6-difluorobenzyl bromide (13). A solution of **12** (1.59 g, 5.26 mmol) in 66% AcOH (100 mL) was stirred for 8 h. The reaction mixture was concentrated in vacuo, and the residue was dissolved in Et_2O (100 mL). To the solution was added PBr_3 (1 mL) slowly at 0 °C, and the mixture was stirred for 4 h at 0 °C. To the reaction mixture was added ice-cooled water (50 mL), and the solution was extracted with Et_2O (40 mL × 3). The combined extracts were washed with water (50 mL × 3) and brine (50 mL × 3), and dried over anhydrous $MgSO_4$. The solution was concentrated in vacuo, and the residue was purified by silica-gel column chromatography (silica gel: 50 g, $CHCl_3$/Me0H = 9:1) to give **13** as colorless crystals (1.24 g, 94.2%): mp 60–65 °C. ^{1}H NMR (CD_3COCD_3) δ 4.64 (s, 2H), 7.43 (d, 2H, *J* = 8.4 Hz); Anal. Calcd for C_7H_6 ^{10}BBrF_2O_2: C, 33.63; H, 2.42. Found: C, 33.97; H, 2.77.

4.2.6. 2-Acetylamino-2-[4-(^{10}B)borono-2,6-difluoro)]-phenylmethylmalonic acid diethyl ester (14). To a suspension of 60% NaH (122 mg, 3.65 mmol) in anhydrous THF (5 mL) was added a solution of diethyl acetamido-malonate (693 mg, 3.19 mmol) in anhydrous THF (5 mL) at 0 °C under Ar atmosphere. After stirring for 1 h, to the reaction mixture was added **13** (762 mg, 3.04 mmol) at 0 °C, and the suspension was refluxed for 3 h. The reaction mixture was acidified with 1 M HCl and THF was removed by evaporation in vacuo. The residual aqueous solution was extracted with AcOEt (30 mL × 3), and the combined extracts were washed with 10% aqueous citric acid (20 mL × 3), saturated $NaHCO_3$ (20 mL × 3) and brine (20 mL × 3). The organic layer was dried over anhydrous $MgSO_4$, and the solution was concentrated in vacuo. The residue was purified by silica-gel column chromatography (silica gel: 50 g, benzene/acetone = 3:1) to give **13** as colorless crystals (1.09 g, 92.7%): mp 131–134 °C. ^{1}H NMR (CD_3COCD_3) δ 1.23 (t, 6H, J = 6.9 Hz), 1.94 (s, 3H), 3.67 (s, 2H), 3.73–4.27 (m, 4H), 7.32 (d, 2H, J = 8.4 Hz), 7.50 (br, 2H); Anal. Calcd for C_9H_{10} $^{10}BF_2NO_4$: C, 38.58; H, 5.04; N, 5.00. Found: C, 38.27; H, 4.96; N 4.87.

4.2.7. β-[4-(^{10}B)Borono-2,6-difluorophenyl]alanine (5). A solution of **14** (3.00 g, 7.77 mmol) in 3 M HCl (2 L) was stirred for 27 h at 100 °C. The reaction mixture was concentrated in vacuo, and the residual solid was dissolved in 3 M HCl (500 mL). The solution was washed with Et_2O (100 mL × 3) and concentrated in vacuo. The residual solid was dissolved in *i*PrOH and to the solution was added propylene oxide (900 mg, 15.5 mmol). After stirring for 6 h, the reaction mixture was concentrated in vacuo. The crystalline residue was recrystallized from water to give **5** as colorless crystals (1.40 g, 73.7%): mp 292–297 °C (dec). ^{1}H NMR (D_2O) δ 3.09–3.27 (m, 2H), 4.12 (t, 1H, J = 6.9 Hz), 7.12 (dd, 2H, J = 6.6 Hz, 4.8 Hz); ^{19}F NMR (D_2O) δ-119; MALDI-TOF MS: found *m/z* 246.5 $[M+H]^+$ (calcd for C_9H_{10} $^{10}BF_2NO_4$+H: 246.1); Anal. Calcd for C_9H_{10} $^{10}BF_2NO_4 \cdot 2H_2O$: C, 38.58; H, 5.04; N, 5.00. Found: C, 38.27; H, 4.96; N 4.87.

4.2.8. N^{α}-*t*-Butoxycarbonyl-β-[4-(^{10}B)borono-2,6-di-fluorophenyl]alanine (15). To a solution of **5** (1.00 g, 4.10 mmol) in water (50 mL) and acetone (50 mL) were added Na_2CO_3 (478 mg, 4.51 mmol) and Boc_2O (984 mg, 4.51 mmol), and the reaction mixture was stirred for 8 h. The reaction mixture was acidified with 10% aqueous citric acid, and acetone was removed by evaporation in vacuo. The aqueous solution was extracted with AcOEt (40 mL × 3), and the combined extracts were washed with 10% aqueous citric acid (30 mL × 3) and brine (30 mL × 3). The organic layer was dried over anhydrous $MgSO_4$, and the solution was concentrated in vacuo. The crystalline residue was recrystallized from AcOEt and hexane to give **15** as colorless crystals (1.37 g, 97.2%): mp 280–296 °C (dec). ^{1}H NMR (CD_3COCD_3) δ 1.29 (s, 9H), 3.06–3.30 (m, 2H), 4.24–4.33 (m, 1H), 7.42 (d, 2H, J = 9.3 Hz); Anal. Calcd for $C_{14}H_{18}$ $^{10}BF_2NO_6$: C, 48.84; H, 5.27; N, 4.07. Found: C, 48.08; H, 5.39; N 3.91.

4.2.9. N^{α}-*t*-Butoxycarbonyl-y3-[4-(^{10}B)borono-2,6-di-fluorophenyl]alaninol (17). To a solution of **15** (1.25 g, 3.63 mmol) in anhydrous THF (50 mL) were added *N*-methylmorpholine (511 mg, 5.45 mmol) and $ClCO_2Et$ (591 mg, 5.45 mmol) at −10 °C. After stirring for 10 min at −10 °C, to the reaction mixture were added $NaBH_4$ (412 mg, 10.9 mmol) and MeOH (5 mL) at −10 °C, and the mixture was stirred for 1 h at room temperature. After evaporation of organic solvents in vacuo, the residual aqueous solution was extracted with AcOEt (40 mL × 3). The combined extracts were washed with 10% aqueous citric acid (15 mL × 3) and brine (15 mL × 3), and dried over anhydrous $MgSO_4$. The solution was concentrated in vacuo, and the residue was purified by silica-gel column chromatography (silica gel; 70 g, $CHCl_3$:MeOH = 9:1) to give **17** as a colorless amorphous solid (961 mg, 80.1%): ^{1}H NMR (CD_3COCD_3) δ 1.27 (s, 9H), 2.85–3.07 (m, 2H), 3.49–3.75 (m, 2H), 3.91–4.09 (m, 1H), 7.41 (d,2H,J = 9.0 Hz).

4.2.10. β-[4-(^{10}B)Borono-2,6-difluorophenyl]alaninol hydrochloride (18). The compound **17** (900 mg, 2.72 mmol) was dissolved in 4 M HCl/AcOEt (10 mL) and the reaction mixture was stirred for 10 min. The solution was concentrated in vacuo, and the residue was dissolved in H_2O (20 mL). The aqueous solution was washed with Et_2O (10 mL × 3) and concentrated in vacuo. The crystalline residue was recrystallized from MeOH to give **17** as colorless crystals (671 mg, 92.6%): mp 225–243 °C (dec). ^{1}H NMR (D_2O) δ 2.83–2.97 (m, 2H), 3.52–3.49 (m, 2H), 3.62–3.70 (m, 1H), 7.13 (dd, 2H, J = 7.5 Hz, 5.1 Hz; ^{19}F NMR (D_2O) δ-119; MALDI-TOF MS: found *m/z* 231.7 $[M+H]^+$ (calcd for C_9H_{12} $^{10}BF_2NO_3$+H: 232.1); Anal. Calcd for C_9H_{13} $^{10}BClF_2NO_3$: C, 40.54; H, 4.91; N, 5.25. Found: C, 40.42; H, 5.00; N 5.40.

4.3. Cells and cell culture

HeLa (human adenocarcinoma) cell, KB (human epidermal carcinoma) cell, and C6 (rat glioma) cell lines were used in the boron incorporation study. Cells were cultured in Dulbecco's minimum essential medium (DMEM) supplemented with 10% fetal bovine serum, 2 mM glutamine, and 24 mM sodium bicarbonate at 37.C in a 5% CO_2 atmosphere.

Cells in monolayer were harvested with 0.25% trypsin/0.02% EDTA in Ca^{2+}-free phosphate-buffered saline (PBS).

4.4. In vitro boron incorporation into cultured tumor cells

Cultures were inoculated with 5×10^6 cells/dish, and cells were grown for 24 h in DMEM. The medium was replaced with each medium containing boron compounds such as ^{10}Bpa(2,6F_2), ^{10}Bpa(2,6F_2)-ol, and ^{10}Bpa (final concentration was 1.0 mM in each case). The cells were cultured for 24 h, and the medium was removed by aspiration. Cells were washed three times with PBS, harvested by trypsinization, and cell number was counted. Each sample containing 1×10^7 cells was added to a mixture consisting of $HClO_4$ (60%, 0.3 ml) and H_2O_2 (31%, 0.6 ml), and then the mixture was heated at 75 °C for 1 h. After filtration of the mixture through membrane filter (Millipore, 0.45 μm), boron concentration in the filtrate was measured by ICP-AES.

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