Supporting Information

Evaluation of the influence of halogenation on the binding of bisphenol A to the estrogen-related receptor γ

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Materials ad Methods

General Information.

Synthesis of halogenated BPA analogs was carried out by aromatic electrophilic substitution reaction of BPA. All organic reactions were carried out in oven-dried glassware with magnetic stirring. The obtained crude products were purified by silica gel column chromatography. Purity of the products was determined by RP-HPLC (HPLC LC-2000 series, JASCO Corporation, Tokyo, Japan) equipped with an packed column YMC-Pack C8 (4.6 x 150 mm, YMC Co. Ltd., Okayama, Japan) or YMC-Pack Ph (4.6 x 150 mm, YMC Co. Ltd.) at 25°C with a solvent system consisting of a mixture of water containing 0.1% trifluoroacetic acid (TFA) and acetonitrile in a gradient method (40% to 56% acetonitrile in 40 min) (flow rate= 0.6 mL/min). The spectral data of HPLC were monitored and analyzed by chromato integrator CDS plus ver. 5.0 (LAsoft Ltd., Chiba, Japan). A JMS-700 MStation mass spectrometer (JEOL Ltd., Tokyo, Japan) was used to perform the positive ionization FAB mass spectroscopy of BPA-triF.

Synthesis of halogenated BPA analogs.

2-fluoro-4-[1-(4-hydroxyphenyl)-1-methylethyl]phenol (BPA-monoF). To a solution of bisphenol A (1.00 mmol, 0.232 g) in DMF (0.99 mL) was added *N*-fluoro-benzenesulfonimide (1.00 mmol, 0.323 g).[1] The resulting mixture was stirred overnight at 100°C. The mixture was extracted with ethyl acetate. The organic phase was washed with water and brine and dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure and the obtained crude product was purified by silica gel column chromatography using a mixed solvent of petroleum ether and ethyl acetate (3.5:1, v/v). Removal of the solvent from appropriate fractions gave BPA-monoF with 15.0% yield (0.150 mmol, 37.0 mg). ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.09–7.05 (m, 2H, ArH), 6.94-6.86 (m, 3H, ArH), 6.76–6.73 (m, 2H,

ArH), 5.00 (d, 1H, OH), 4.69 (s, 1H, OH) 1.61 (s, 6H, CH_3). ^{13}C NMR (600 MHz, $CDCl_3$): δ 153.4, 150.5 (d, Ar-CF, J = 236.9 Hz), 144.3, 142.6, 141.1, 127.9, 122.8, 116.4, 114.8, 114.1, 41.8, 30.9. ^{19}F NMR (600 MHz, $CDCl_3$): δ -142.0 (ArF).

2,2-bis(3-fluoro-4-hydroxyphenyl)propane (BPA-diF). To a solution of bisphenol A (2.01 mmol, 0.460 g) in a mixed solvent of methanol and acetonitrile (2: 1, v/v, 60 mL) was added selectfluor (4.43 mmol, 1.57 g). The resulting mixture was stirred for 4 h at 70°C. The reaction solvent was removed under reduced pressure, the crude reaction mixture dissolved in 50 mL of dichloromethane. After removal of the insoluble matter by filtration, the filtrate was washed with water and brine and dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure and the obtained crude product was purified by silica gel column chromatography using a mixed solvent of hexane and ethyl acetate (5: 1, v/v). Removal of the solvent from appropriate fractions gave BPA-diF with 5.93% yield (0.119 mmol, 31.5 mg). ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.26–6.86 (m, 6H, ArH), 5.00–4.99 (s, 2H, OH), 1.60 (s, 6H, CH_3). ^{13}C NMR (600 MHz, $CDCl_3$): δ150.6 (d, Ar-CF, J = 235.6 Hz), 143.6, 141.3, 122.8, 116.6, 114.1, 41.9, 30.8. ^{19}F NMR (600 MHz, $CDCl_3$): δ -141.7 (ArF).

2,6-difluoro-4-[1-(3-fluoro-4-hydroxyphenyl)-1-methylethyl]phenol (BPA-triF). To a solution of BPA-triBr-MOM (described later) (0.805 g, 1.46 mmol) in THF (10 mL) at -78°C was slowly added *n*-butyllithium (7.4 mL of 2.5 M in hexanes).[2] The resulting solution was stirred at -78°C for 0.5 h and a solution of N-fluorobenzenesulfonimide (2.296 g, 7.28 mmol) in THF (15 mL) was added. After an additional 2 h at -78 °C, the reaction mixture was warmed to room temperature, poured into water, and extracted with ethyl acetate. The organic phase was washed with water and brine and dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residual product was then added to a mixed solvent of 12 M of HCl and THF (1: 1, v/v, 10 mL) and stirred at 25°C for 24 h to cleave MOM

protection. The resulting mixture was concentrated under reduced pressure. The obtained crude product was purified by silica gel column chromatography using a mixed solvent of hexane and ethyl acetate (15:1, v/v). Removal of the solvent from appropriate fractions gave BPA-triF with 11.1% yield (0.163 mmol, 46.1 mg). ^{1}H-NMR (600 MHz, $CDCl_3$): δ 6.92–6.85 (m, 3H, ArH), 6.77–6.72 (m, 2H, ArH), 5.08 (br, 2H, OH), 1.59 (s, 6H, CH_3). ^{13}C NMR (600 MHz, $CDCl_3$): δ151.4 (d, Ar-CF, J = 242.6 Hz), 150.7 (d, Ar-CF, *J* = 236.9 Hz), 142.8, 124.7, 141.6, 130.6, 122.8, 116.9, 114.2, 110.1, 42.1, 30.7. ^{19}F NMR (600 MHz, $CDCl_3$): δ -136.5, -141.5 (ArF). MS (FAB+) *m*/*z*, calculated for $C_{15}H_{13}F_3O_2$: 282.0868 ($[M]^+$), found 282.0839.

2,2-bis(3,5-difluoro-4-hydroxyphenyl)propane (BPA-tetraF). BPA-tetraF was synthesized and purified by the same method as BPA-triF except for usage of BPA-tetraBr-MOM (described later) as a starting material. BPA-tetraF with 23.0% yield (0.232 mmol, 69.6 mg). ^{1}H-NMR (600 MHz, $CDCl_3$): δ 6.76–6.71 (m, 4H, ArH), 5.20 (br, 2H, OH), 1.57 (s, 6H, CH_3). ^{13}C NMR (600 MHz, $CDCl_3$): δ151.4 (d, Ar-CF, *J* = 242.7 Hz), 141.9, 130.8, 110.1, 42.2, 30.5. ^{19}F NMR (600 MHz, $CDCl_3$): δ -136.7 (ArF).

2-chloro-4-[1-(4-hydroxyphenyl)-1-methylethyl]phenol (BPA-monoCl). To a solution of bisphenol A (2.00 mmol, 0.455 g) in a mixed solvent of dichloromethane and ethyl acetate (10: 1, v/v, 11 mL) was added pyridine (0.200 mmol, 16.0 μL). The mixture was slowly added trichlo-roisocyanuric acid (4.00 mmol, 0.925 g).[4] The resulting mixture was stirred overnight at reflux. The mixture was extracted with ethyl acetate. The organic phase was washed with water and brine and dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure and the obtained crude product was purified by silica gel column chromatography using a mixed solvent of hexane and ethyl acetate (4:1, v/v). Removal of the solvent from appropriate fractions gave BPA-monoCl with 4.55% yield (0.0910 mmol, 23.0 mg). ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.17 (m, 1H, ArH), 7.09–7.06 (m, 2H, ArH), 7.01–6.99

(m, 1H, ArH), 6.91–6.89 (m, 1H, ArH), 6.75–6.73 (m, 2H, ArH), 5.42 (s, 1H, OH), 4.76 (s, H, OH), 1.61 (s, 6H, CH_3). ^{13}C NMR (600 MHz, $CDCl_3$): δ 153.4, 149.4, 144.5, 142.5, 127.9, 127.1, 127.0, 119.3, 115.6, 114.8, 41.8, 30.9.

2,2-bis(3-chloro-4-hydroxyphenyl)propane (BPA-diCl) and 2,6-dichloro-4-(2-(3-chloro-4-hydroxyphenyl)propan-2-yl)phenol (BPA-triCl). To a solution of bisphenol A (2.01 mmol, 0.460 g) in a mixed solvent of dichloromethane and ethyl acetate (5: 1, v/v, 12 mL) was added pyridine (0.200 mmol, 16.0 μL). The mixture was slowly added trichloroisocyanuric acid (1.35 mmol, 0.314 g) at 0℃. The resulting mixture was stirred for 4 h at room temperature. The mixture was extracted with ethyl acetate. The organic phase was washed with water and brine and then dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure and the obtained crude product was purified by silica gel column chromatography using a mixed solvent of hexane and ethyl acetate (5: 1, v/v). Removal of the solvent from appropriate fractions gave BPA-diCl and BPA-triCl.

BPA-diCl with 47.0% yield (0.946 mmol, 281 mg). ^1H-NMR (600 MHz, $CDCl_3$): δ 7.16 (m, 2H, ArH), 7.00–6.99 (m, 2H, ArH), 6.92–6.91 (m, 2H, ArH), 5.42 (s, 2H, OH), 1.60 (s, 6H, CH_3). ^{13}C NMR (600 MHz, $CDCl_3$): δ149.3, 143.7, 127.0, 126.9, 119.4, 115.8, 41.9, 30.8.

BPA-triCl with 13.9% yield (0.28 mmol, 93.2 mg). ^1H-NMR (600 MHz, $CDCl_3$): δ 7.16–7.15 (m, 1H, ArH), 7.08 (s, 2H, ArH), 6.99–6.98 (m, 1H, ArH), 6.94–6.92 (m, 1H, ArH), 5.74 (s, 1H, OH), 5.46 (s, 1H, OH), 1.60 (s, 6H, CH_3). ^{13}C NMR (600 MHz, $CDCl_3$): δ149.5, 145.8, 143.9, 142.8, 127.0, 126.9, 126.7, 120.6, 119.5, 116.0, 42.0, 30.7.

2-bromo-4-[1-(4-hydroxyphenyl)-1-methylethyl]phenol (BPA-monoBr). To a solution of bisphenol A (6.07 mmol, 1.39 g) in acetonitrile (5.0 ml) was added *N*-bromosuccinimide (2.06 mmol, 0.366 g) and methanesulfonic acid (2.00 mmol, 130 μL).[5] The resulting mixture was stirred for 22 h at room temperature. The mixture was extracted with ethyl acetate. The organic

phase was washed with water and brine and then dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure and the obtained crude product was purified by silica gel column chromatography using a mixed solvent of petroleum ether and ethyl acetate (6: 1, v/v). Removal of the solvent from appropriate fractions gave BPA-monoBr with 80.4% yield (1.65 mmol, 508 mg). ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.32–7.31 (d, 1H, ArH), 7.09–7.07 (m, 2H, ArH), 7.05–7.03 (m, 1H, ArH), 6.91–6.90 (m, 1H, ArH), 6.75–6.73 (m, 2H, ArH), 5.38 (s, 1H, OH), 4.70 (s, 1H, OH), 1.61 (s, 6H, CH_3). ^{13}C NMR (600 MHz, $CDCl_3$): δ 153.5, 150.0, 144.9, 142.5, 130.0, 127.9, 127.9, 115.5, 114.9, 109.8, 41.8, 31.0.

2,2-bis(3-bromo-4-hydroxyphenyl)propane (BPA-diBr). To a solution of bisphenol A (2.01 mmol, 0.460 g) in acetonitrile (5.0 mL) was added *N*-bromosuccinimide (4.06 mmol, 0.721 g) and methanesulfonic acid (2.00 mmol, 130 μL). The resulting mixture was stirred for 24 h at room temperature. The mixture was extracted with ethyl acetate. The organic phase was washed with water and brine and then dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure and the obtained crude product was purified by silica gel column chromatography using a mixed solvent of petroleum ether and ethyl acetate (8:1, v/v). Removal of the solvent from appropriate fractions gave BPA-diBr with 68.6% yield (1.38 mmol, 534 mg). ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.31–7.30 (m, 2H, ArH), 7.03–7.02 (m, 2H, ArH), 6.92–6.91 (m, 2H, ArH), 5.42 (s, 2H, OH), 1.60 (s, 6H, CH_3). ^{13}C NMR (600 MHz, $CDCl_3$): δ150.2, 144.1, 130.0, 127.8, 115.7, 110.0, 41.8, 30.9.

2,6-dibromo-4-[1-(3-bromo-4-hydroxyphenyl)-1-methylethyl]phenol (BPA-triBr). To a solution of bisphenol A (4.01 mmol, 0.916 g) in acetonitrile (15 mL) was added *N*-bromosuccinimide (12.1 mmol, 2.148 g), followed by methanesulfonic acid (6.01 mmol, 390 μL). The resulting mixture was stirred for 24 h at room temperature. The mixture was extracted with ethyl acetate. The organic phase was washed with water and brine and then dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure and the obtained

crude product was purified by silica gel column chromatography using a mixed solvent of hexane and ethyl acetate (8: 1, v/v). Removal of the solvent from appropriate fractions gave BPA-triBr with 49.9% yield (2.000 mmol, 930 mg). ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.30 (m, 2H, ArH), 7.26 (s, 2H, ArH), 7.02 (m, 1H, ArH), 6.94–6.92 (m, 1H, ArH), 5.79 (s, 1H, OH), 5.46 (s, 1H, OH), 1.59 (s, 6H, CH_3). ^{13}C NMR (600 MHz, $CDCl_3$): δ 150.4, 147.4, 145.0, 143.3, 130.4, 129.8, 127.7, 115.8, 110.0, 109.6, 41.9, 30.8.

1,3-dibromo-5-{2-[3-bromo-4-(methoxymethoxy)phenyl]propan-2-yl}-2-(methoxymethoxy) benzene (BPA-triBr-MOM).[3] Sodium hydride (60% oil, 0.625 g, 15.6 mmol) was suspended in THF (7.5 mL) at 0°C under N_2. A solution of BPA-triBr (0.893 g, 1.92 mmol) in THF (7.5 mL) was slowly added to NaH suspension. The resulting mixture was stirred for 2 h at 25°C. Chloromethyl methyl ether (1.0 mL, 13.2 mmol) was slowly added to the mixture at 0°C. The reaction mixture was stirred for 20 h at 25°C and extracted with ethyl acetate. The organic phase was washed with water and brine and dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The obtained crude product was purified by silica gel column chromatography using a mixed solvent of hexane and ethyl acetate (15: 1, v/v). Removal of the solvent from appropriate fractions gave BPA-triBr-MOM with 75.8% yield (1.46 mmol, 805 mg). Purified product was used for synthesis of BPA-triF as described above. ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.387–7.402 (m, 1H, ArH), 7.332 (s, 2H, ArH), 7.048–7.072 (m, 1H, ArH), 7.014–7.040 (m, 2H, ArH), 5.230 (s, 2H, CH_2), 5.157 (s, 4H, CH_2), 3.719 (s, 3H, CH_3), 3.525 (s, 3H, CH_3), 1.600 (s, 6H, CH_3).

5,5'-(propane-2,2-diyl)bis[1,3-dibromo-2-(methoxymethoxy)benzene] (BPA-tetraBr-MOM). Sodium hydride (60% oil, 0.962 g, 24.1 mmol) was suspended in THF (10 mL) at 0°C under N_2. A solution of BPA-tetraBr (1.64 g, 3.01 mmol, purchased from Tokyo Chemical Industry Co. Ltd., Tokyo, Japan) in THF (10 mL) was slowly added to NaH suspension. The resulting mixture was stirred for 2 h at 25°C. Chloromethyl methyl ether (1.40 mL, 18.4 mmol)

was slowly added to the mixture at 0°C. The reaction mixture was stirred for 20 h at 25°C and extracted with ethyl acetate. The organic phase was washed with water and brine and dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The obtained crude product was purified by silica gel column chromatography using a mixed solvent of hexane and ethyl acetate (20: 1, v/v). Removal of the solvent from appropriate fractions gave BPA-tetraBr-MOM with 87.4% yield (2.64 mmol, 1668 mg). Purified product was used for synthesis of BPA-tetraF as described above. ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.32 (s, 4H, ArH), 5.17 (s, 4H, CH_2), 3.73 (s, 6H, CH_3), 1.59 (s, 6H, CH_3).

2-iodo-4-[1-(4-hydroxyphenyl)-1-methylethyl]phenol (BPA-monoI). To a solution of Bisphenol A (6.00 mmol, 1.37 g) in acetonitrile (4.5 mL) was added *N*-iodosuccinimide (2.00 mmol, 0.451 g) and methanesulfonic acid (2.00 mmol, 130 μL).[6] The resulting mixture was stirred overnight at room temperature. The mixture was extracted with ethyl acetate. The organic phase was washed with water and brine and dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure and the obtained crude product was purified by silica gel column chromatography using a mixed solvent of dichloromethane and methanol (100:1, v/v). Removal of the solvent from appropriate fractions gave BPA-monoI with 58.0% yield (1.20 mmol, 0.410 g). ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.51–7.50 (m, 1H, ArH), 7.09–7.05 (m, 3H, ArH), 6.88–6.86 (m, 1H, ArH), 6.75–6.73 (m, 2H, ArH), 5.19 (s, 1H, OH), 4.76 (s, 1H, OH), 1.59 (s, 6H, CH_3). ^{13}C NMR (600 MHz, $CDCl_3$): δ 153.4, 152.6, 145.4, 142.5, 136.0, 129.1, 127.9, 114.8, 114.5, 85.5, 41.6, 31.0.

2,2-bis(3-iodo-4-hydroxyphenyl)propane (BPA-diI). To a solution of bisphenol A (1.00 mmol, 0.229 g) in acetonitrile (3.0 mL) was added *N*-iodosuccinimide (2.00 mmol, 0.465 g) and methanesulfonic acid (1.00 mmol, 65.0 μL).[6] The resulting mixture was stirred overnight at room temperature. The mixture was extracted with ethyl acetate. The organic phase was washed with water and brine and dried over Na_2SO_4. After filtration, the filtrate was

concentrated under reduced pressure and the obtained crude product was purified by silica gel column chromatography using a mixed solvent of hexane and ethyl acetate (8:1, v/v). Removal of the solvent from appropriate fractions gave BPA-diI with 47.0% yield (0.470 mmol, 0.230 g). ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.50–7.49 (m, 2H, ArH), 7.04–7.03 (m, 2H, ArH), 6.89–6.87 (d, 2H, ArH), 5.25 (s, 2H, OH), 1.58 (s, 6H, CH_3). ^{13}C NMR (600 MHz, $CDCl_3$): δ152.9, 144.6, 136.0, 130.0, 114.6, 85.6, 41.5, 30.9.

2,6-diiodo-4-[1-(3-iodo-4-hydroxyphenyl)-1-methylethyl]phenol (BPA-triI) and 2,2-bis(3,5-dichloro-4-hydroxyphenyl)propane (BPA-tetraI). To a solution of bisphenol A (2.00 mmol, 0.457 g) in ethanol (15 mL) at 0℃ was slowly added sulfuric acid (2.0 mL), followed by 1,3-diiodo-5,5-dimethylhydantoin (4.206 mmol, 1.598 g). The resulting mixture was stirred for 1 h at room temperature. The mixture was extracted with dichloromethane. The organic phase was washed with 5% $NaHCO_3$ aq., 5% $Na_2S_2O_3$ aq., water and brine and then dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure and the obtained crude product was dissolved by a mixed solvent of dichloromethane and hexane (5: 1, v/v, 60 mL). After standing solution for 24 h, the precipitated solid was filtrated and washed with dichloromethane and methanol to give a pure BPA-tetraI. The filtrate was concentrated under reduced pressure and the obtained crude product was purified by silica gel column chromatography using a mixed solvent of hexane and dichloromethane (1: 1, v/v). Removal of the solvent from appropriate fractions gave BPA-triI.

BPA-triI. 6.53% yield (0.131 mmol, 79.2 mg). ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.48 (m, 1H, ArH), 7.47 (s, 2H, ArH), 7.02–7.01 (m, 1H, ArH), 6.90–6.89 (m, 1H, ArH), 5.63 (br, 1H, OH), 5.20 (br, 1H, OH), 1.57 (s, 6H, CH_3). ^{13}C NMR (600 MHz, $CDCl_3$): δ 153.0, 151.6, 146.5, 143.9, 137.6, 135.8, 129.0, 114.8, 85.7, 82.1, 41.3, 30.9.

BPA-tetraI. 17.8% yield (0.357 mmol, 261 mg). ^{1}H-NMR (600 MHz, DMSO-d_6): δ 9.39 (br, 2H, OH), 7.46 (s, 4H, ArH), 1.48 (s, 6H, CH_3). ^{13}C NMR (600 MHz, DMSO-d_6): δ154.0, 146.2, 137.6, 87.7, 41.0, 30.7.

Receptor protein expression and purification.

Preparation of the receptor protein was carried out essentially as reported previously.[7] The cDNA fragment encoding human ERRγ-LBD (corresponding to amino acid residues 222–458) was generated by PCR, and the amplified product was cloned into the expression vector pGEX 6P-1 (Amersham Biosciences, Piscataway, NJ, USA) to express the product as a glutathione-S-transferase (GST) fusion protein by using *Escherichia coli* BL21.[8] GST was cleaved by PreScission Protease (Amersham Biosciences), and the protein concentration was determined by the Bradford method.[9]

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Supporting Tables.

Table S1. Results of HPLC analyses of halogenated BPA analogs.

Compound	Column	Retention time [min]	Purity
BPA	YMC-Pack C8	10.9	>99%†
BPA-monoF	YMC-Pack C8	13.3	96%
BPA-diF	YMC-Pack C8	14.2	99%
BPA-triF	YMC-Pack C8	15.9	>99%
BPA-tetraF	YMC-Pack C8	18.2	99%
BPA-monoCl	YMC-Pack C8	15.9	>99%
BPA-diCl	YMC-Pack C8	22.3	>99%
BPA-triCl	YMC-Pack C8	28.6	98%
BPA-tetraCl	YMC-Pack C8	35.9	>99%†
BPA-monoBr	YMC-Pack C8	16.7	99%
BPA-diBr	YMC-Pack C8	25.2	>99%
BPA-triBr	YMC-Pack C8	33.5	>99%
BPA-tetraBr	YMC-Pack C8	43.0	>95%†
BPA-monoI	YMC-Pack C8	20.0	>99%
BPA-diI	YMC-Pack C8	31.3	98%
BPA-triI	YMC-Pack C8	41.2	>99%
BPA-tetraI	YMC-Pack Ph	27.9	97%

Purity of the compounds was determined by RP-HPLC at 25°C in a linear gradient of acetonitrile in water (containing 0.1% TFA), 40% to 56% over 45 min. Since BPA-tetraI did not eluted off from YMC-Pack C8 column within 45 min, YMC-Pack Ph column was used for this compound.
†: The provided information from supplier.

Table S2. Effects of ionization of halogenated BPA analogs on docking calculation.

	Δ*G* (Vina) [kcal mol^{-1}]		Δ*G* (VinaXB) [kcal mol^{-1}]	
Compound	un-ionized form	univalent anion	un-ionized form	univalent anion
BPA	-9.7	-9.8	-9.7	-9.8
BPA-monoF	-9.9	-9.9	-9.9	-9.8
BPA-diF	-9.8	-10.1	-9.8	-10.1
BPA-triF	-9.8	-10.1	-9.8	-10.1
BPA-tetraF	-9.6	-9.9	-9.6	-9.9
BPA-monoCl	-9.9	-9.8	-9.8	-9.8
BPA-diCl	-8.7	-9.0	-8.8	-9.0
BPA-triCl	-7.8	-8.1	-7.9	-8.2
BPA-tetraCl	-6.9	-6.9	-6.9	-6.9
BPA-monoBr	-9.7	-9.6	-9.7	-9.6
BPA-diBr	-7.7	-8.0	-7.9	-8.1
BPA-triBr	-6.4	-6.1	-6.4	-6.2
BPA-tetraBr	-4.9	-4.8	-5.0	-5.1
BPA-monoI	-9.1	-9.2	-9.1	-9.2
BPA-diI	-6.1	-6.4	-6.2	-6.5
BPA-triI	-5.8	-5.4	-5.4	-5.6
BPA-tetraI	-4.7	-4.6	-4.9	-4.8

Docking simulations were carried out by using representative X-ray crystal structure of ERRγ (PDB ID: 2E2R) as templates and the lowest binding energy values (*ΔG*) were shown. In the calculation of "univalent anion", the three-dimensional structures of univalent anion of BPA and halogenated BPA analogs, with one deprotonated hydroxyl group, were treated as ligands in the docking calculations.

Table S3. Relationship between hydrophobicity or molecular polarity of halogenated BPA analogs and binding affinity to ERRγ-LBD.

Compound	log *P*	Dipole moment (debye)	IC_{50} (nM)
BPA	3.32	2.0698	6.45 ± 0.52
BPA-monoF	4.11	5.9543	5.30 ± 0.32
BPA-diF	4.21	7.7844	15.1 ± 1.91
BPA-triF	4.31	7.8368	31.5 ± 3.47
BPA-tetraF	4.41	6.7166	282 ± 29.6
BPA-monoCl	4.64	5.1718	5.96 ± 0.88
BPA-diCl	5.26	6.4337	56.6 ± 1.63
BPA-triCl	5.89	6.2801	1.55×10^3 ± 198
BPA-tetraCl	6.52	5.4308	Not Determined
BPA-monoBr	4.70	5.1491	17.9 ± 0.95
BPA-diBr	5.39	6.3544	473 ± 30.5
BPA-triBr	6.08	6.1248	Not Bound
BPA-tetraBr	6.77	5.2171	Not Bound
BPA-monoI	4.66	4.8263	111 ± 12.8
BPA-diI	5.31	5.7983	Not Bound
BPA-triI	5.96	5.5139	Not Bound
BPA-tetraI	6.61	4.7252	Not Bound

The values of Log P were computed by XLogP3 3.0. Dipole moment of each BPA analog was calculated by Gaussian 16 Rev. B.01. The calculations of dipole moment were performed by the Møller-Plesset method second (MP2) with different basis sets; 6-31++G(d, p) basis function was used for hydrogen, carbon, oxygen, fluorine, chlorine, and bromine atoms, whereas LanL2DZ basis set was used for iodine atom.

Supporting Figures.

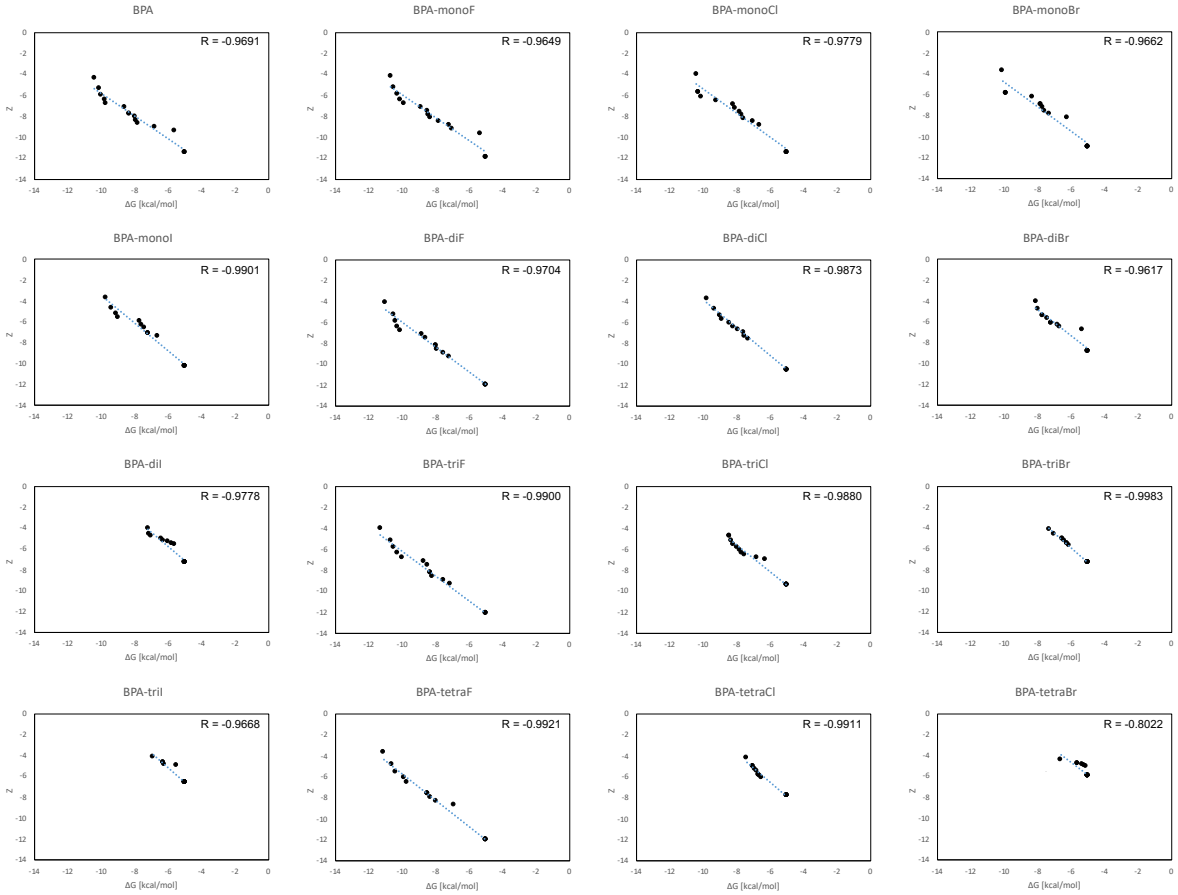

Figure S1. Q-Q plot for estimation of average binding energy ΔG calculated by AutoDock Vina.

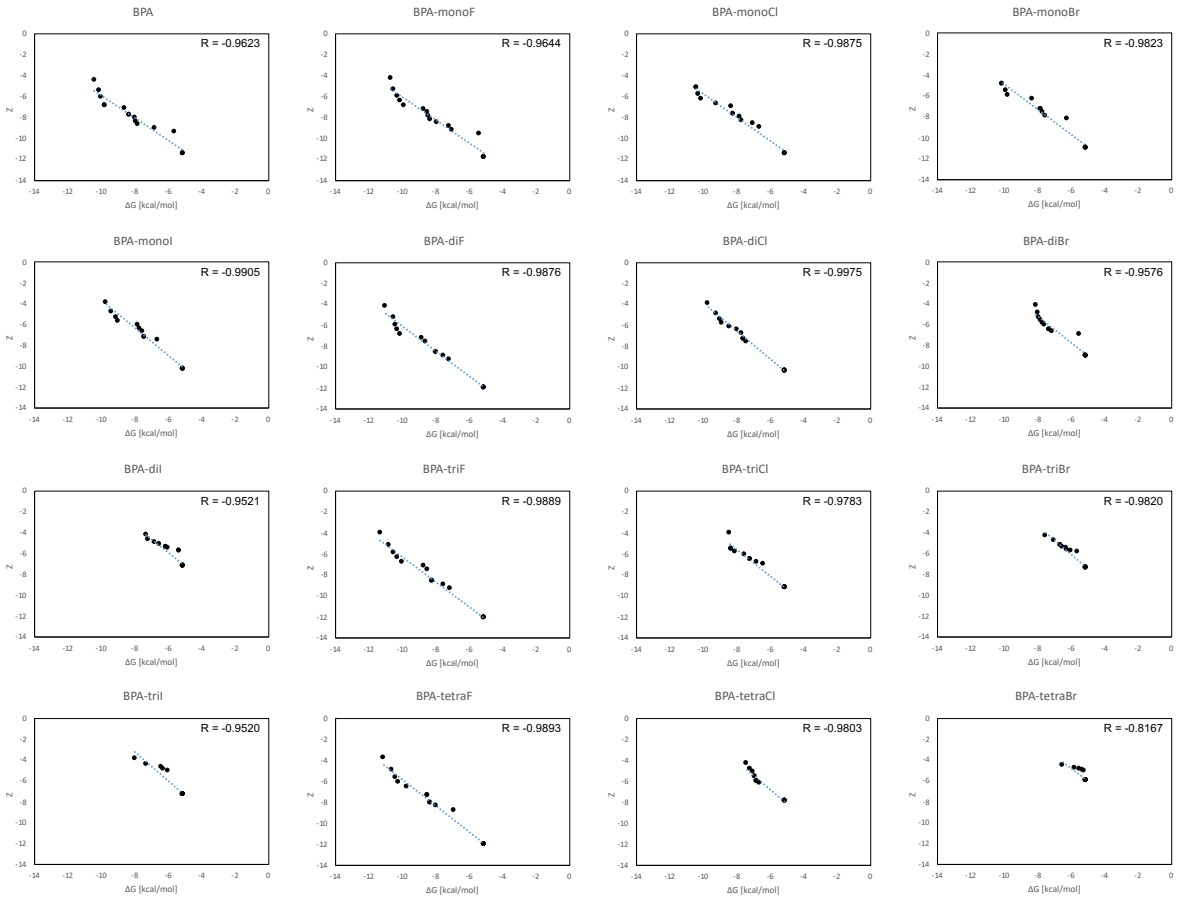

Figure S2. Q-Q plot for estimation of average binding energy ΔG calculated by Vina XB.

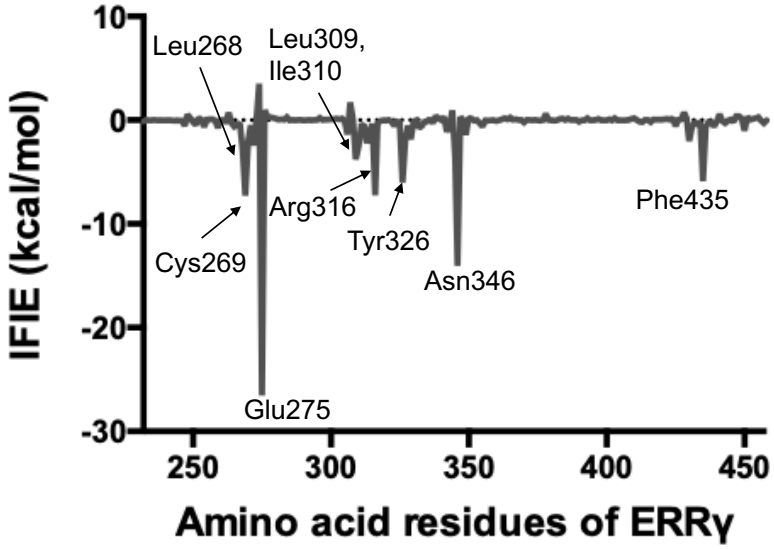

Figure S3. Interaction energies between each amino acid residue of ERRγ-LBD and BPA calculated by FMO calculation.

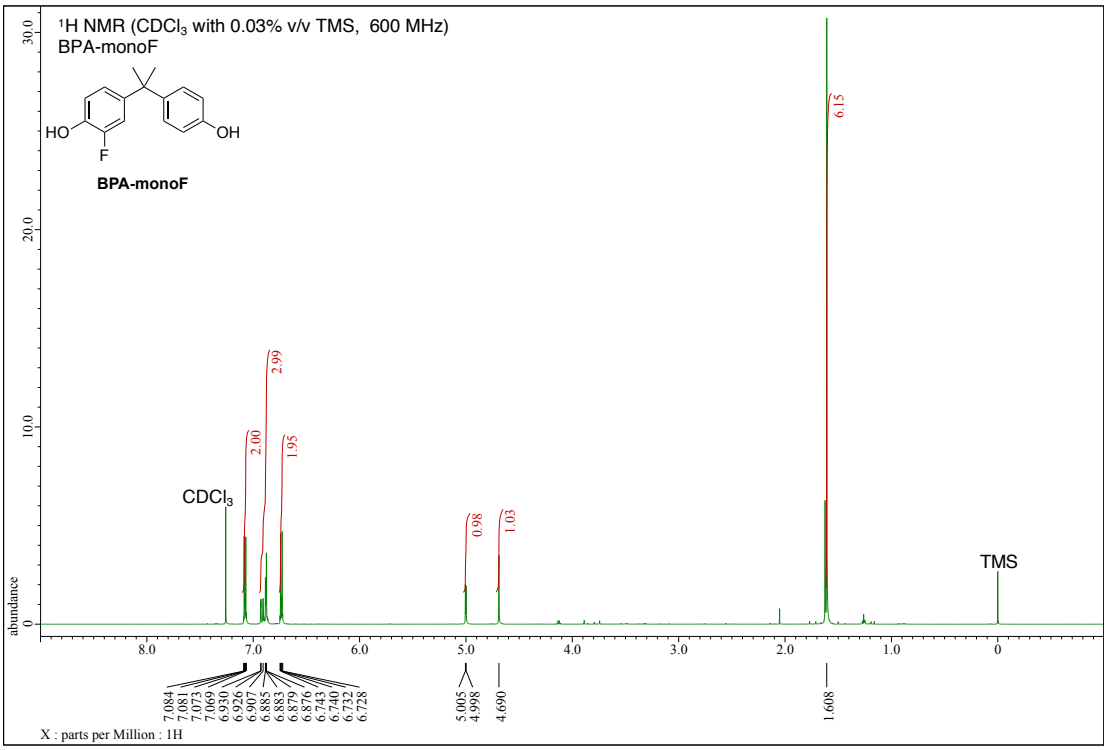

Figure S4. ^{1}H-NMR spectrum of BPA-monoF (600 MHz) in $CDCl_3$.

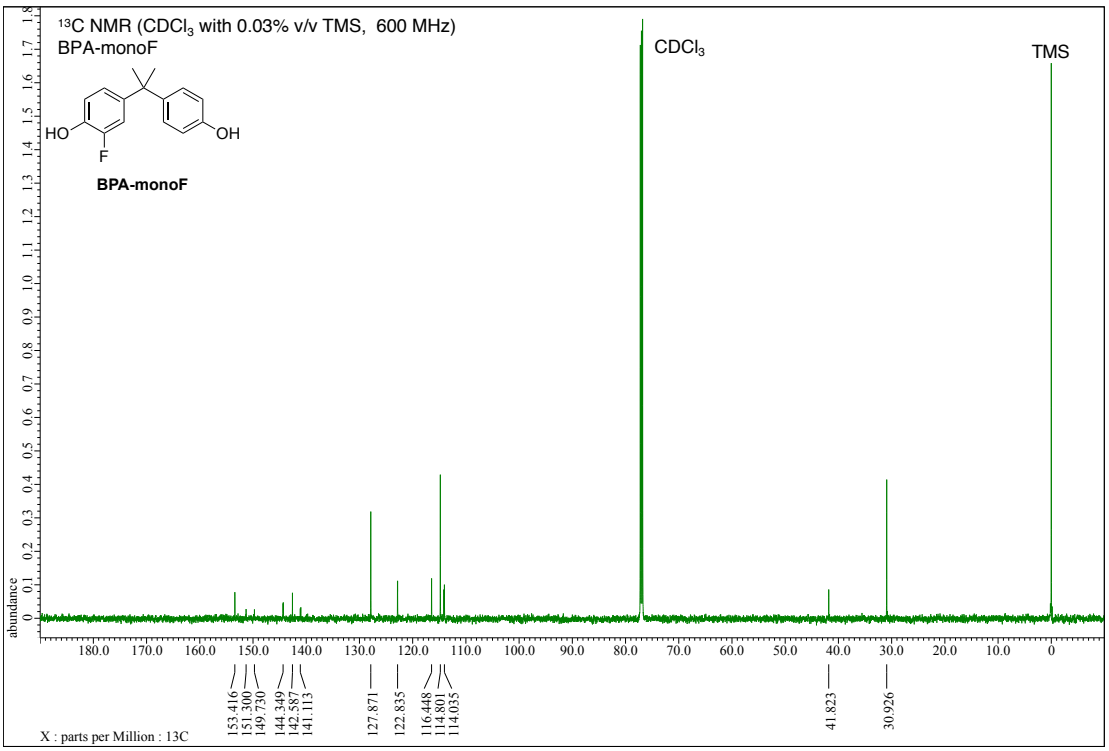

Figure S5. ^{13}C-NMR spectrum of BPA-monoF (600 MHz) in $CDCl_3$.

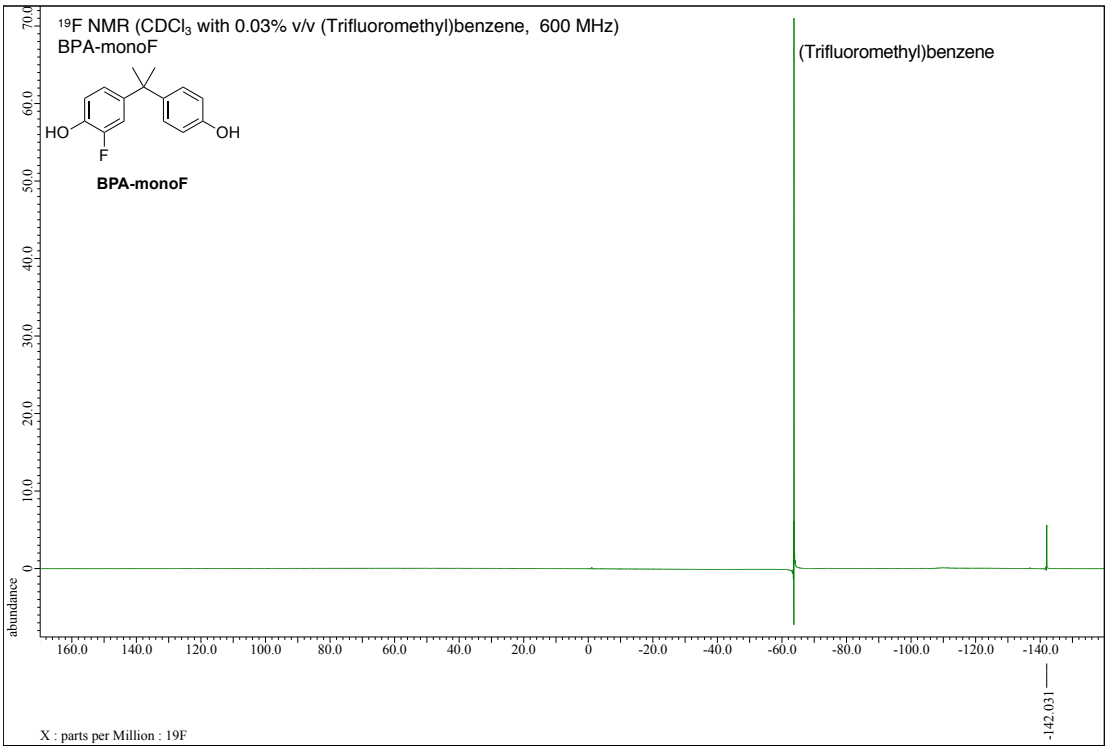

Figure S6. ^{19}F-NMR spectrum of BPA-monoF (600 MHz) in $CDCl_3$.

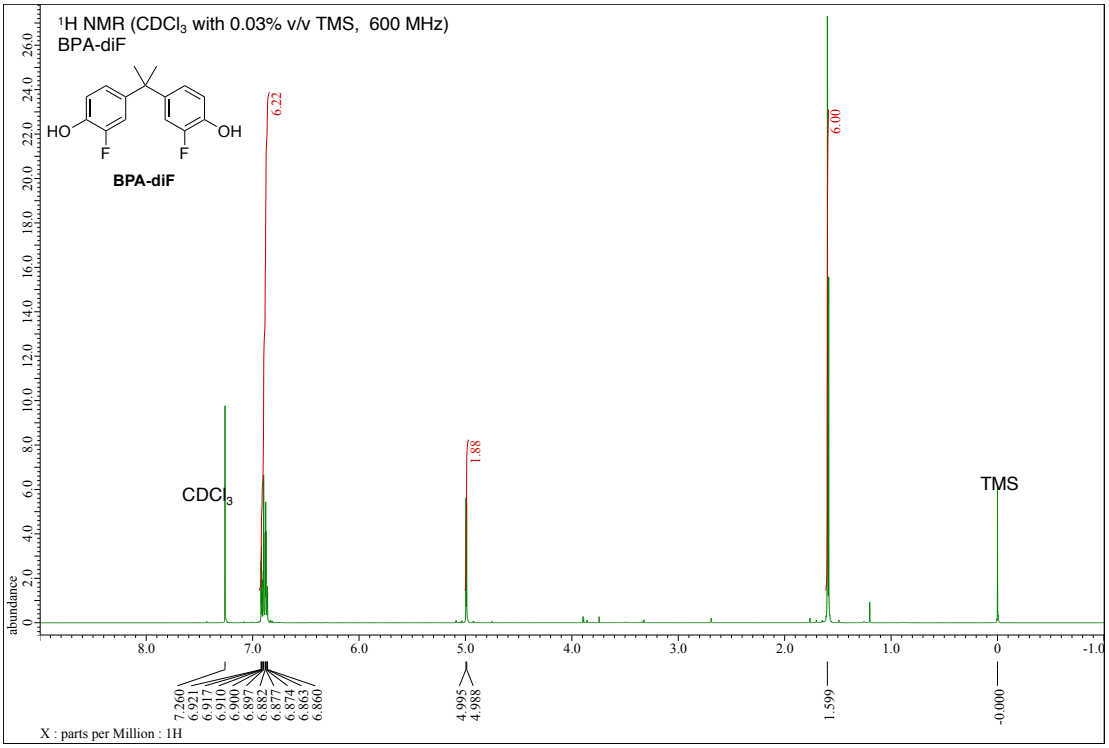

Figure S7. ^{1}H-NMR spectrum of BPA-diF (600 MHz) in $CDCl_3$.

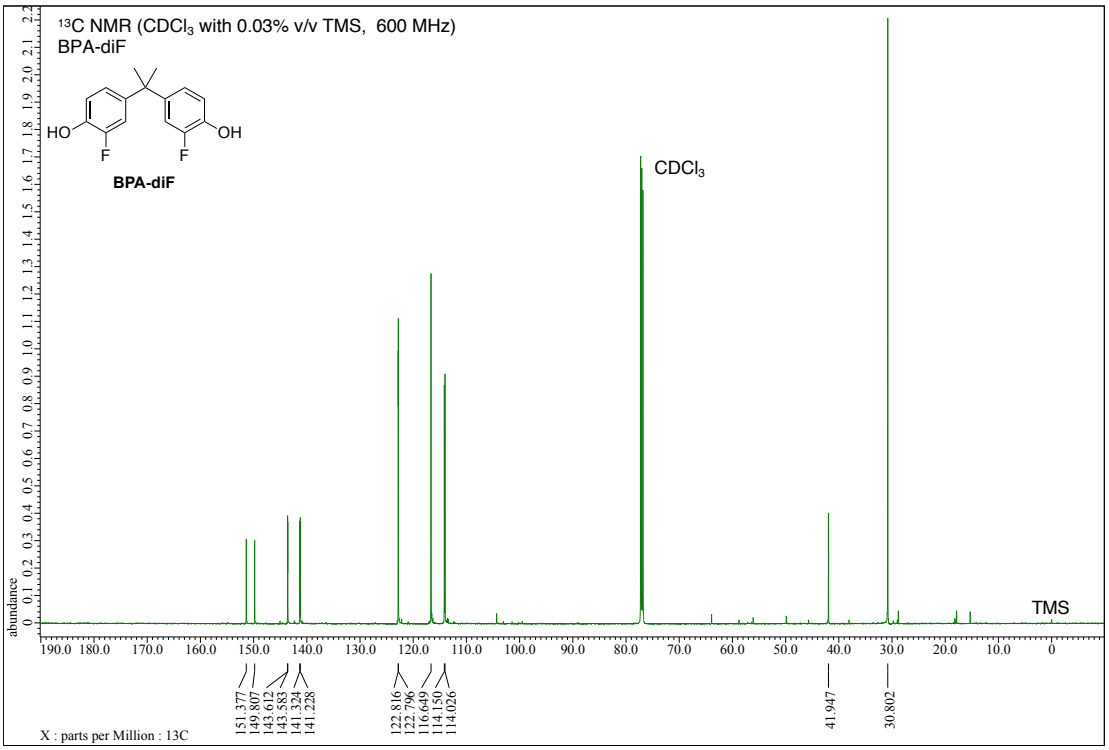

Figure S8. ^{13}C-NMR spectrum of BPA-diF (600 MHz) in $CDCl_3$.

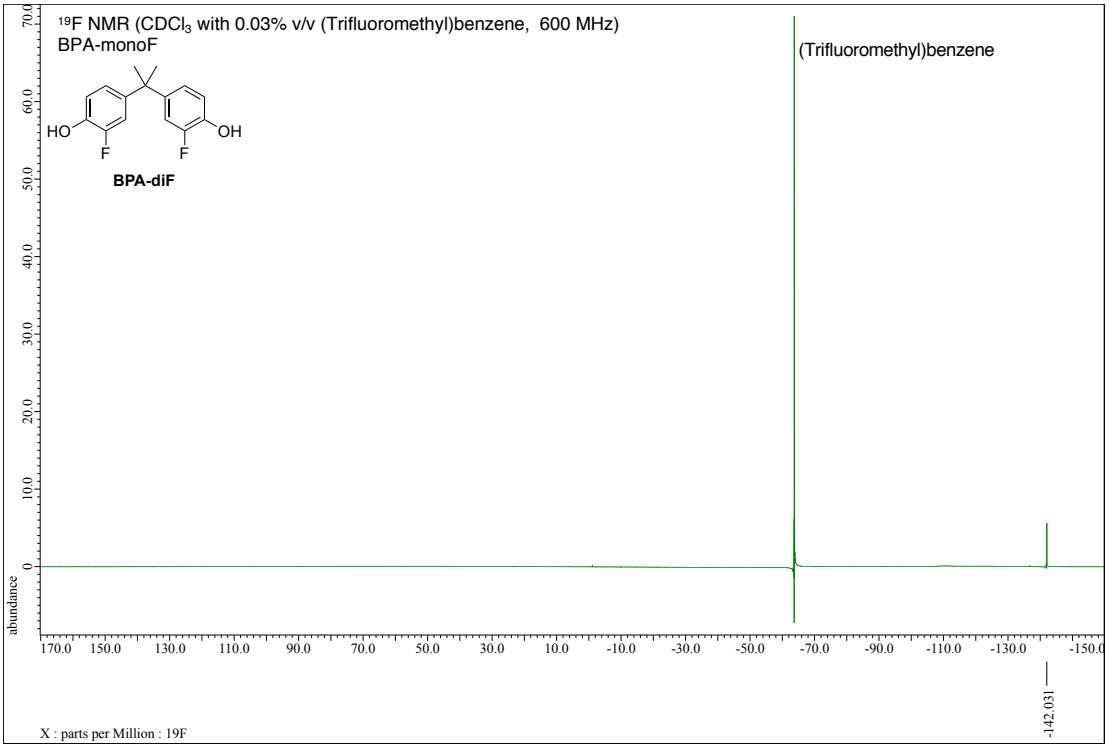

Figure S9. ^{19}F-NMR spectrum of BPA-diF (600 MHz) in $CDCl_3$.

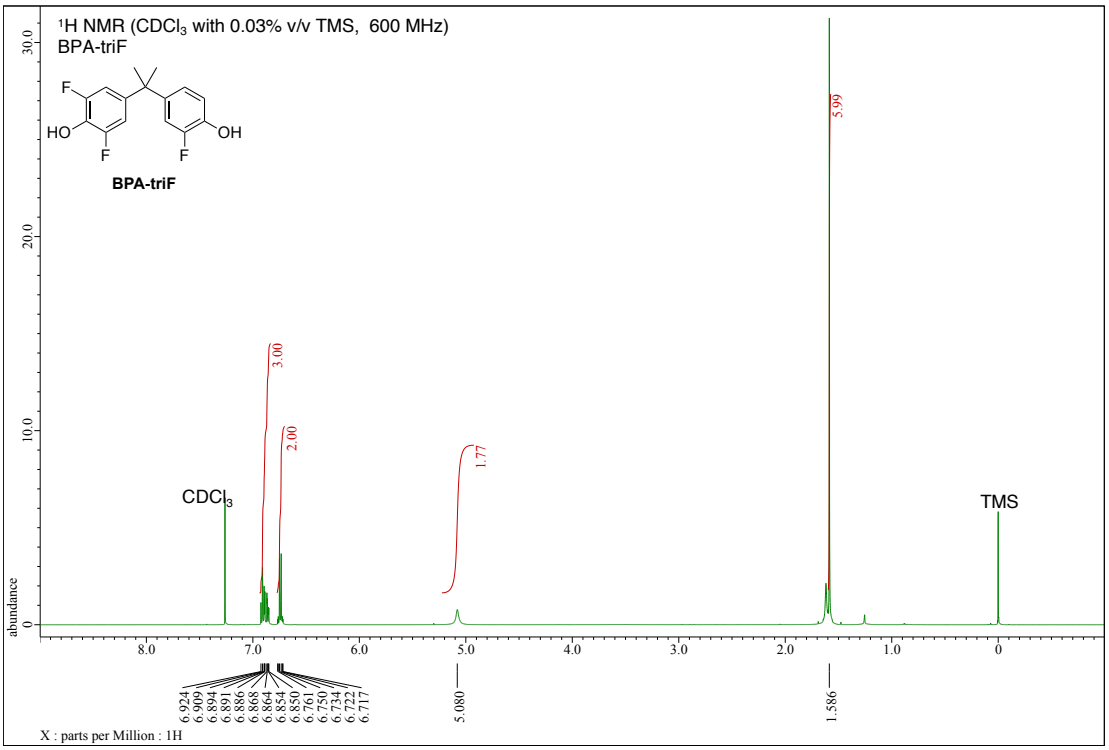

Figure S10. ^{1}H-NMR spectrum of BPA-triF (600 MHz) in $CDCl_3$.

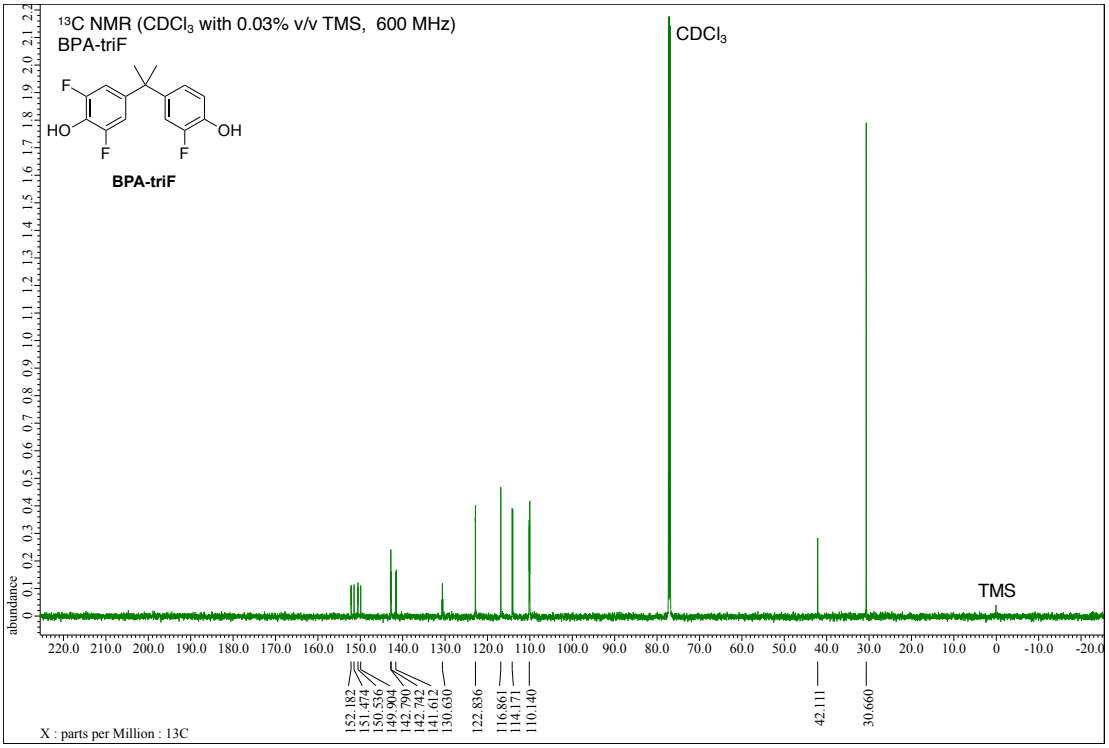

Figure S11. ^{13}C-NMR spectrum of BPA-triF (600 MHz) in $CDCl_3$.

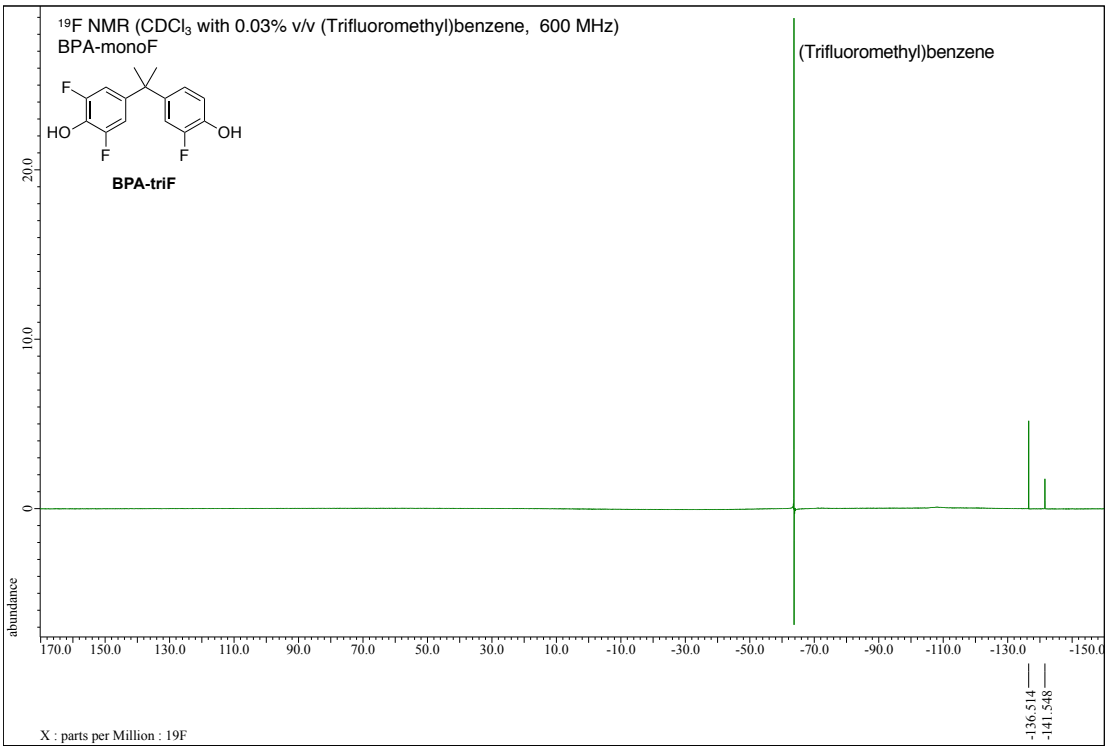

Figure S12. ^{19}F-NMR spectrum of BPA-triF (600 MHz) in $CDCl_3$.

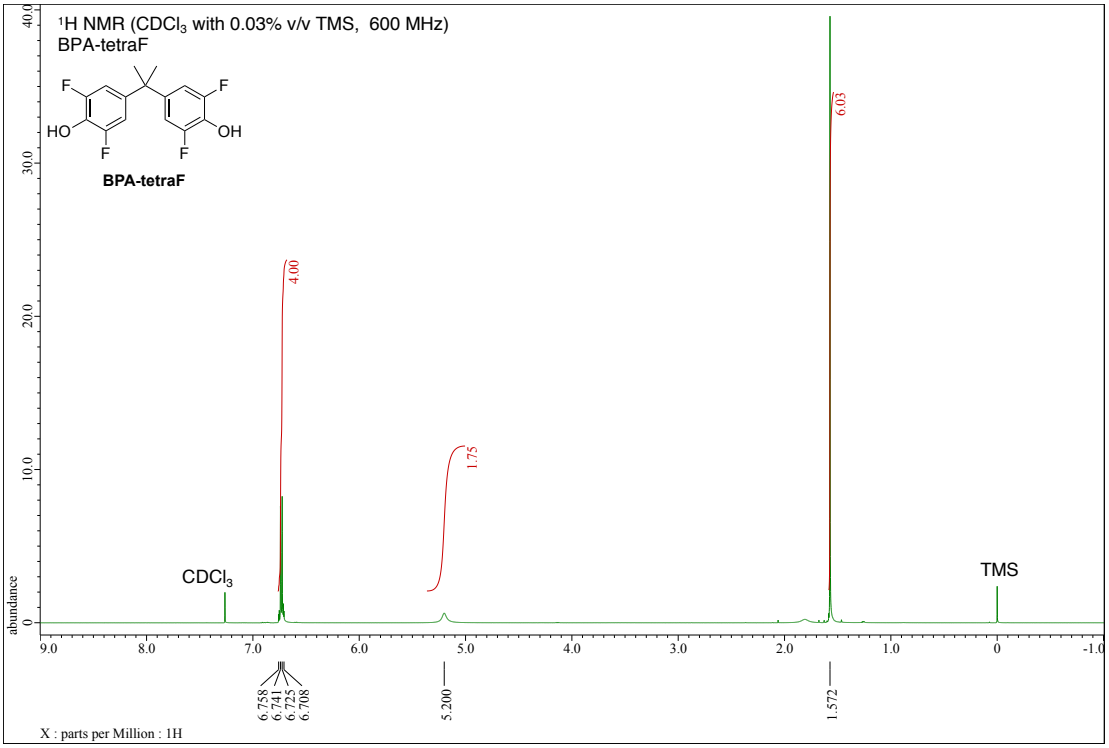

Figure S13. ^{1}H-NMR spectrum of BPA-tetraF (600 MHz) in $CDCl_3$.

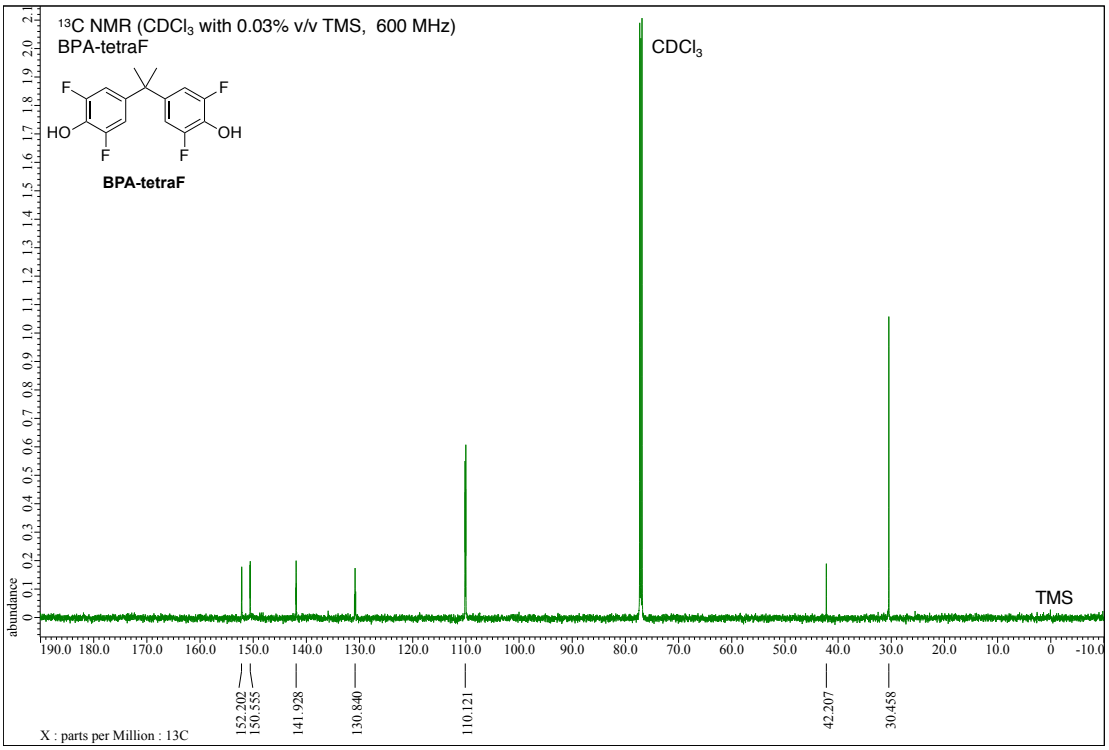

Figure S14. ^{13}C-NMR spectrum of BPA-tetraF (600 MHz) in $CDCl_3$.

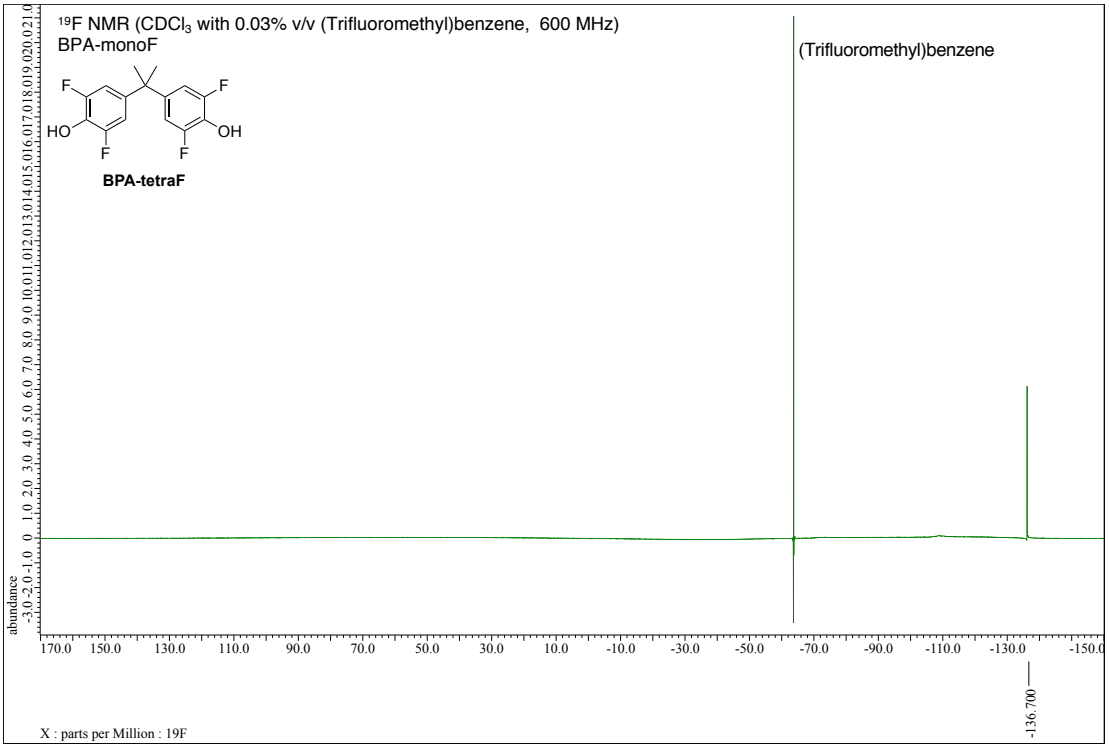

Figure S15. ^{19}F-NMR spectrum of BPA-tetraF (600 MHz) in $CDCl_3$.

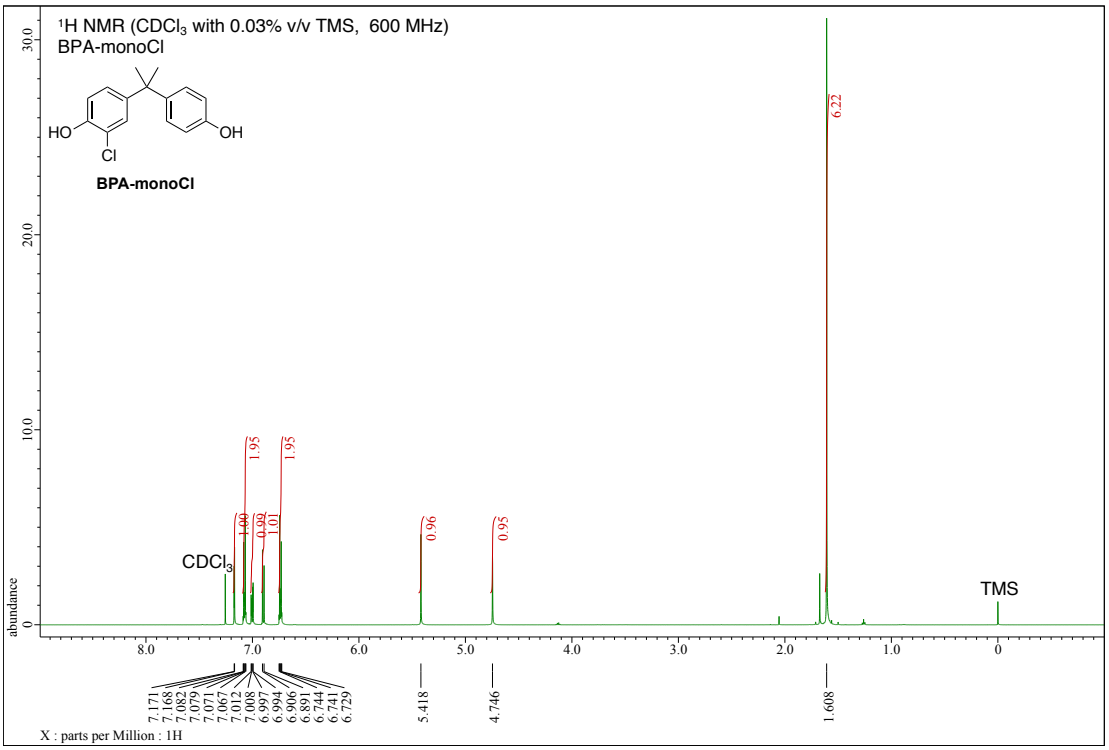

Figure S16. ^{1}H-NMR spectrum of BPA-monoCl (600 MHz) in $CDCl_3$.

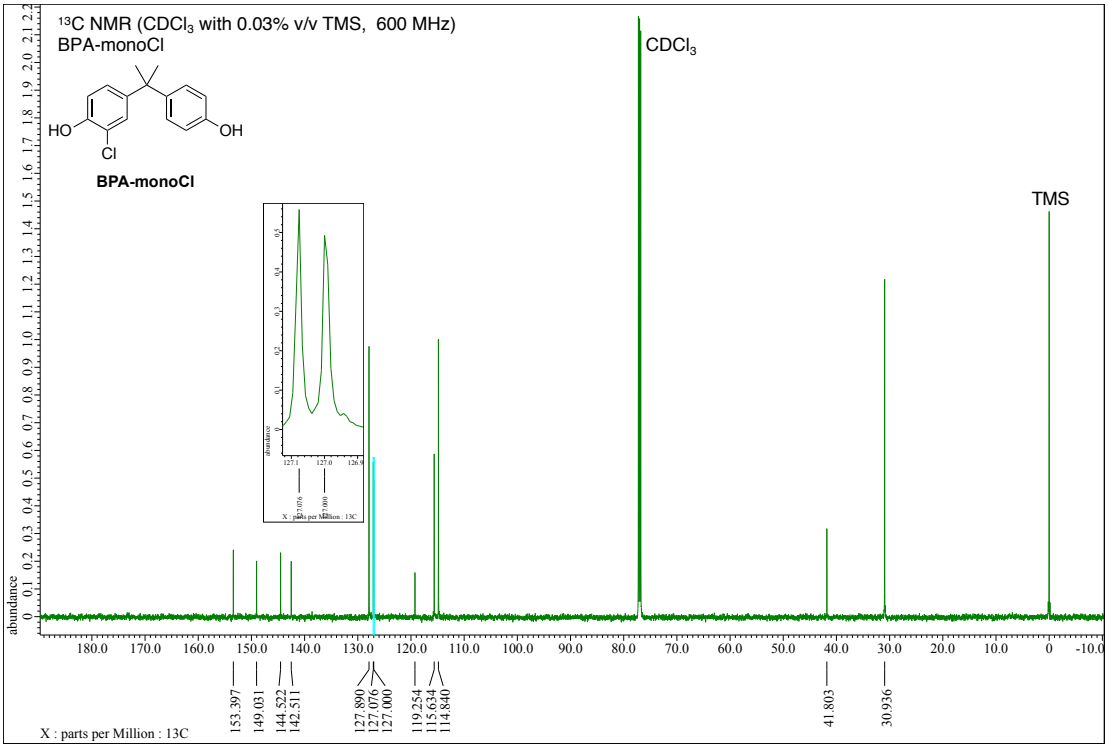

Figure S17. ^{13}C-NMR spectrum of BPA-monoCl (600 MHz) in $CDCl_3$.

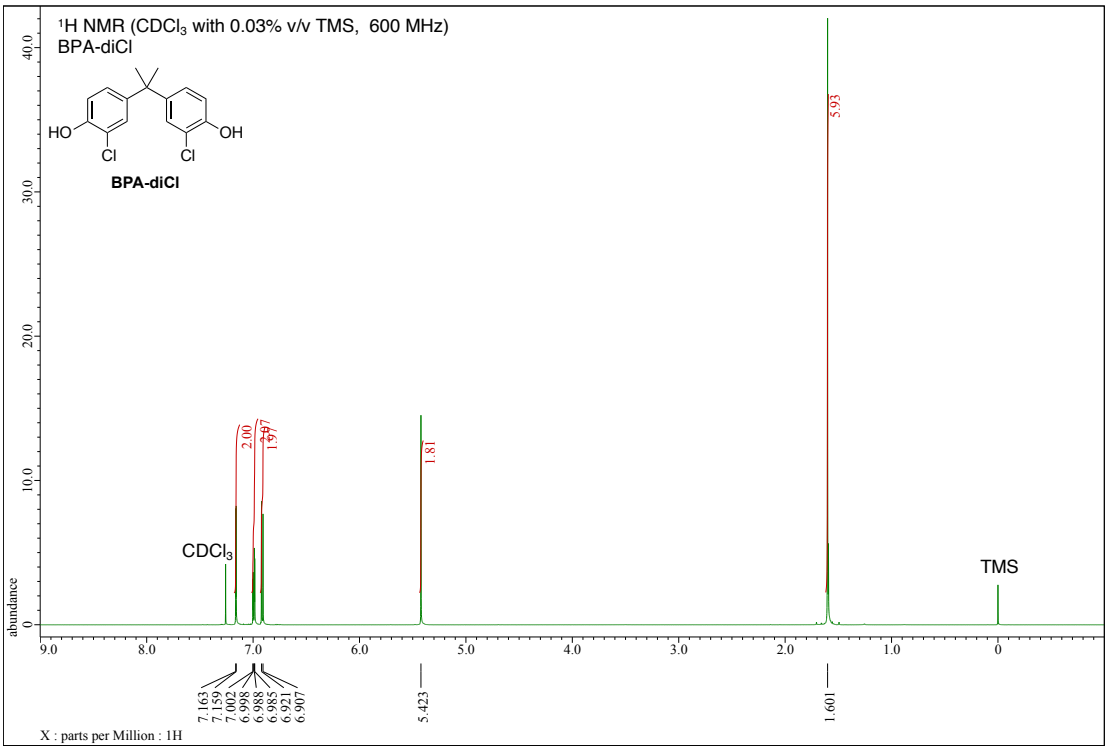

Figure S18. ^{1}H-NMR spectrum of BPA-diCl (600 MHz) in $CDCl_3$.

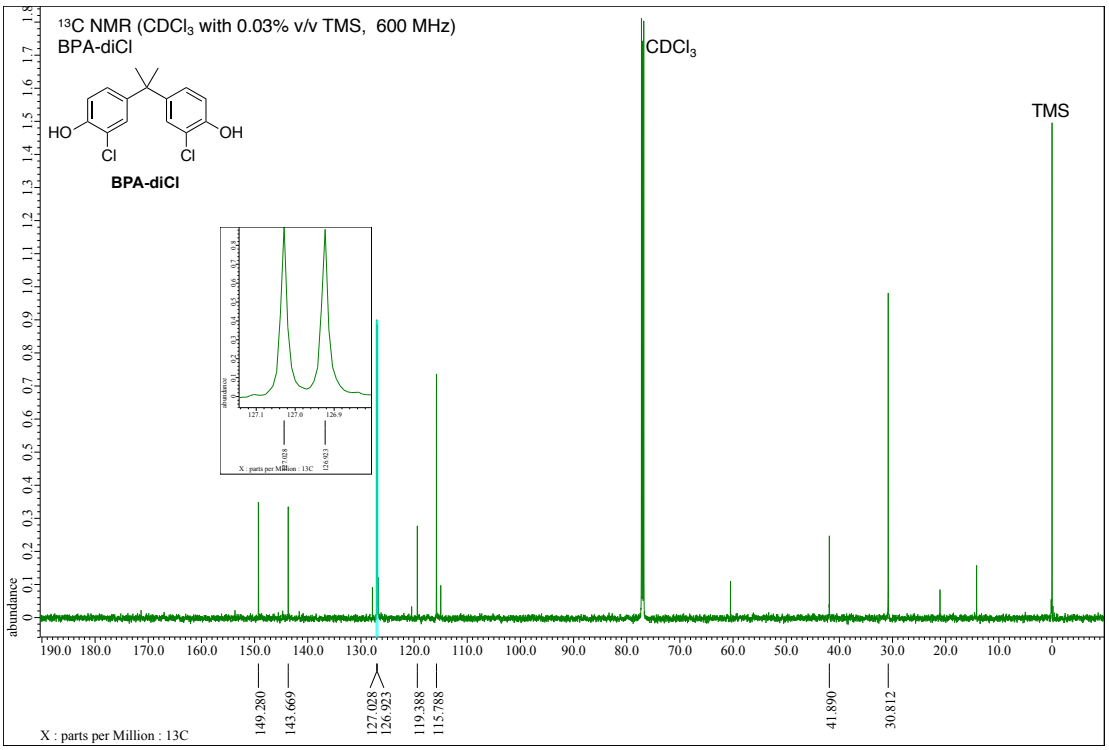

Figure S19. ^{13}C-NMR spectrum of BPA-diCl (600 MHz) in $CDCl_3$.

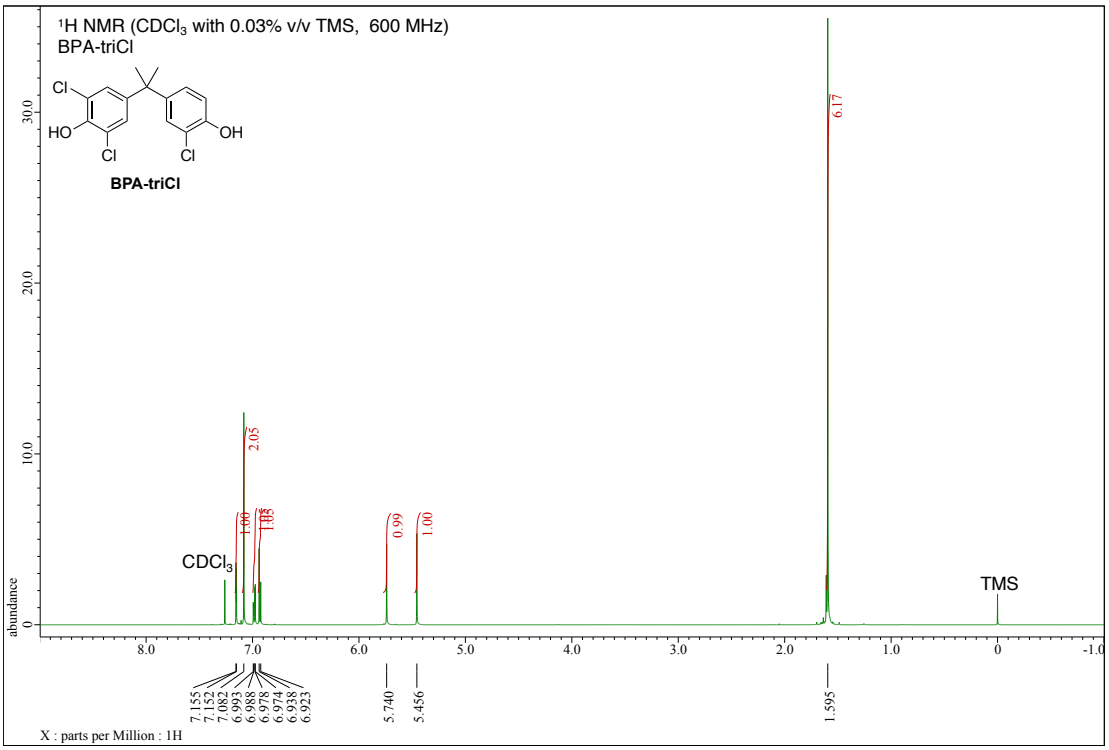

Figure S20. ^{1}H-NMR spectrum of BPA-triCl (600 MHz) in $CDCl_3$.

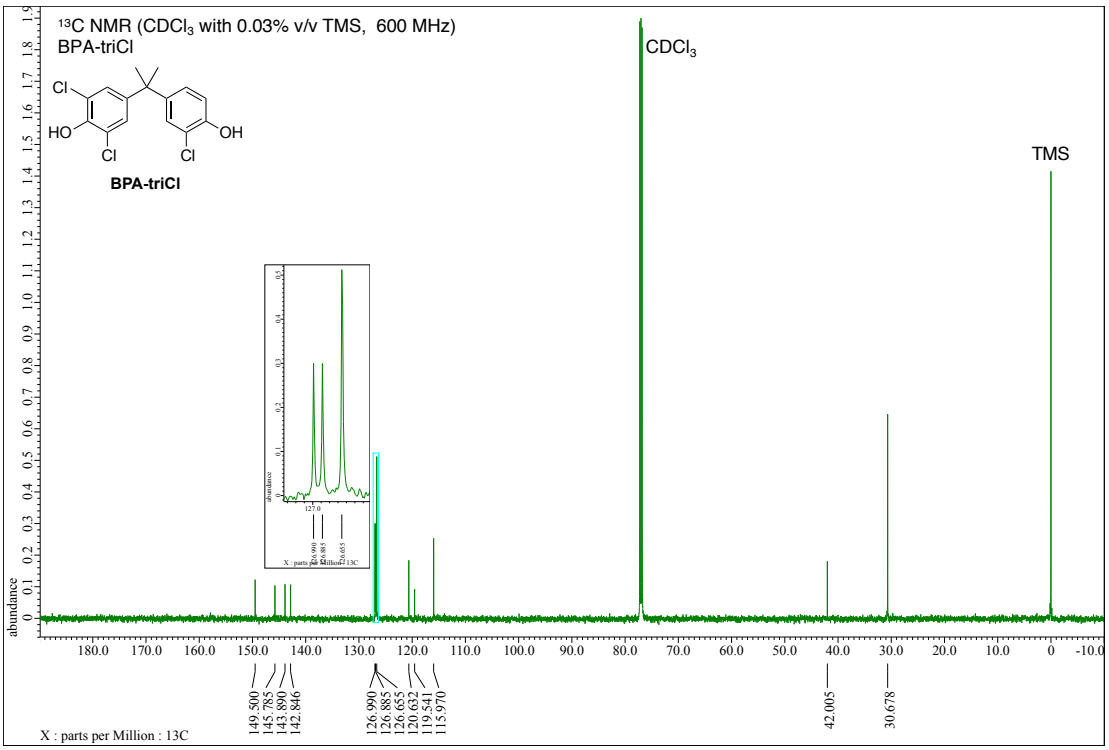

Figure S21. ^{13}C-NMR spectrum of BPA-triCl (600 MHz) in $CDCl_3$.

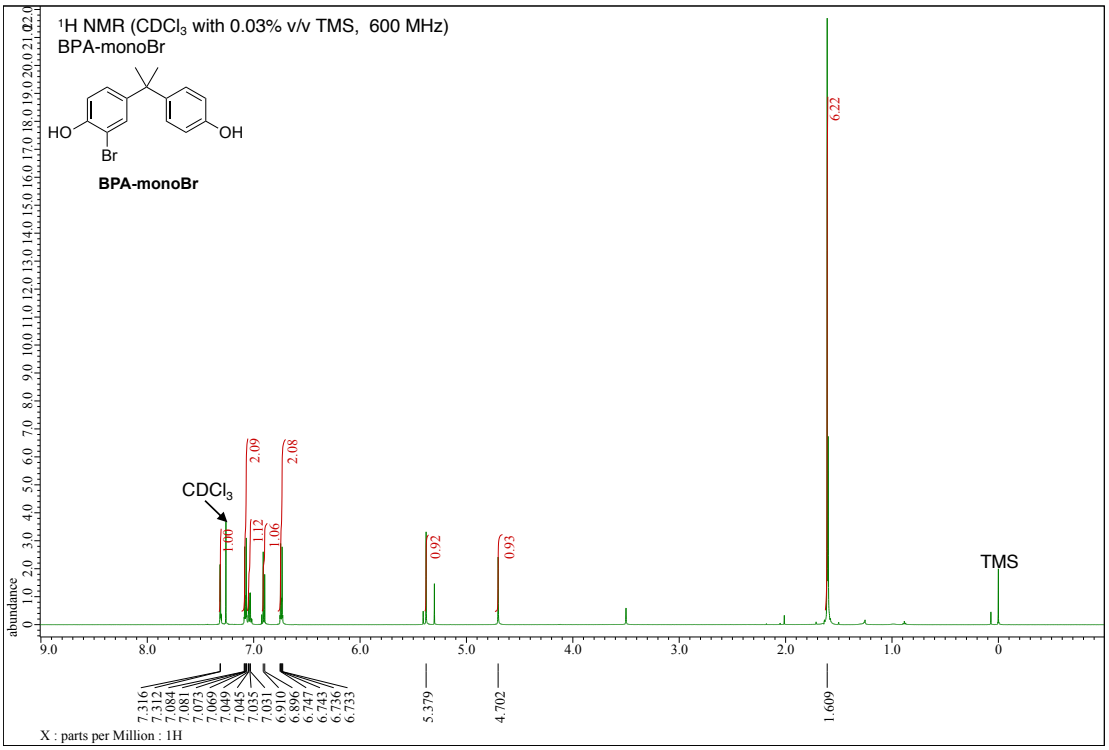

Figure S22. ^{1}H-NMR spectrum of BPA-monoBr (600 MHz) in $CDCl_3$.

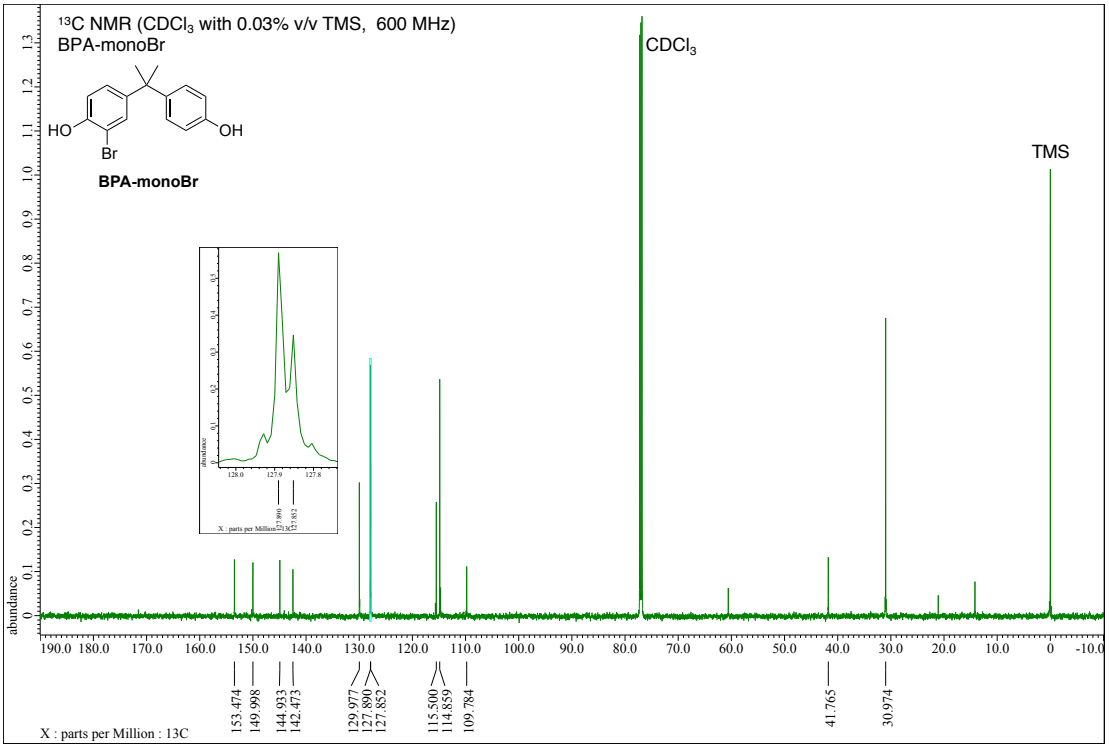

Figure S23. ^{13}C-NMR spectrum of BPA-monoBr (600 MHz) in $CDCl_3$.

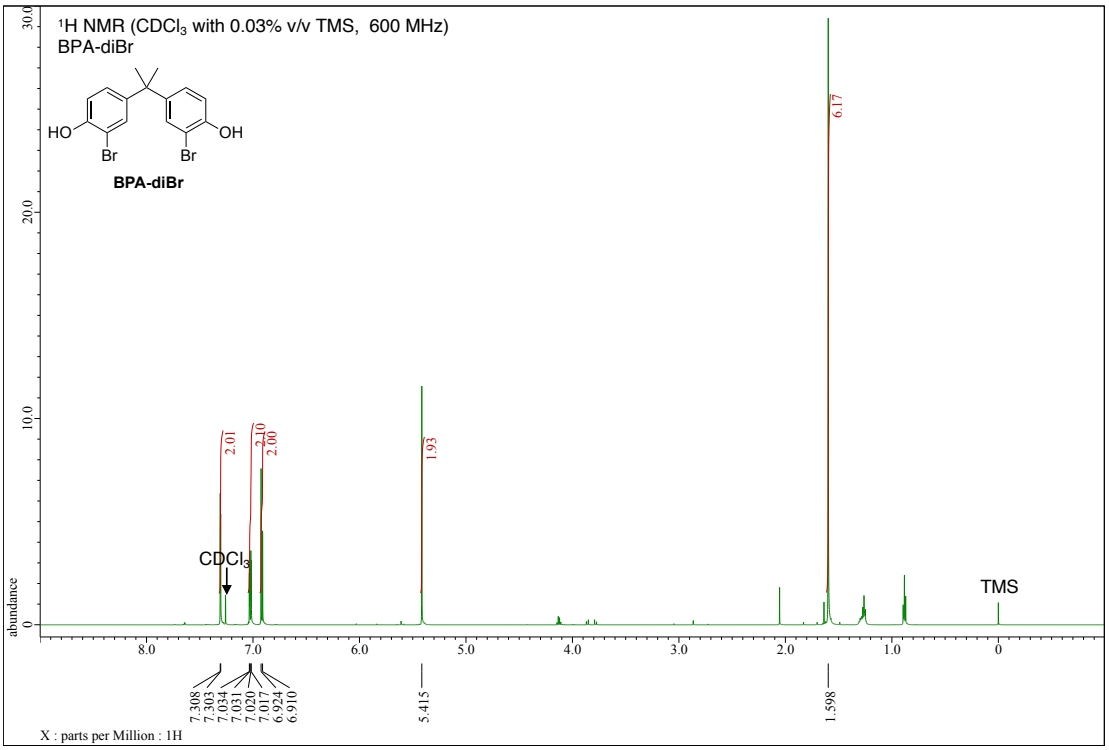

Figure S24. ^{1}H-NMR spectrum of BPA-diBr (600 MHz) in $CDCl_3$.

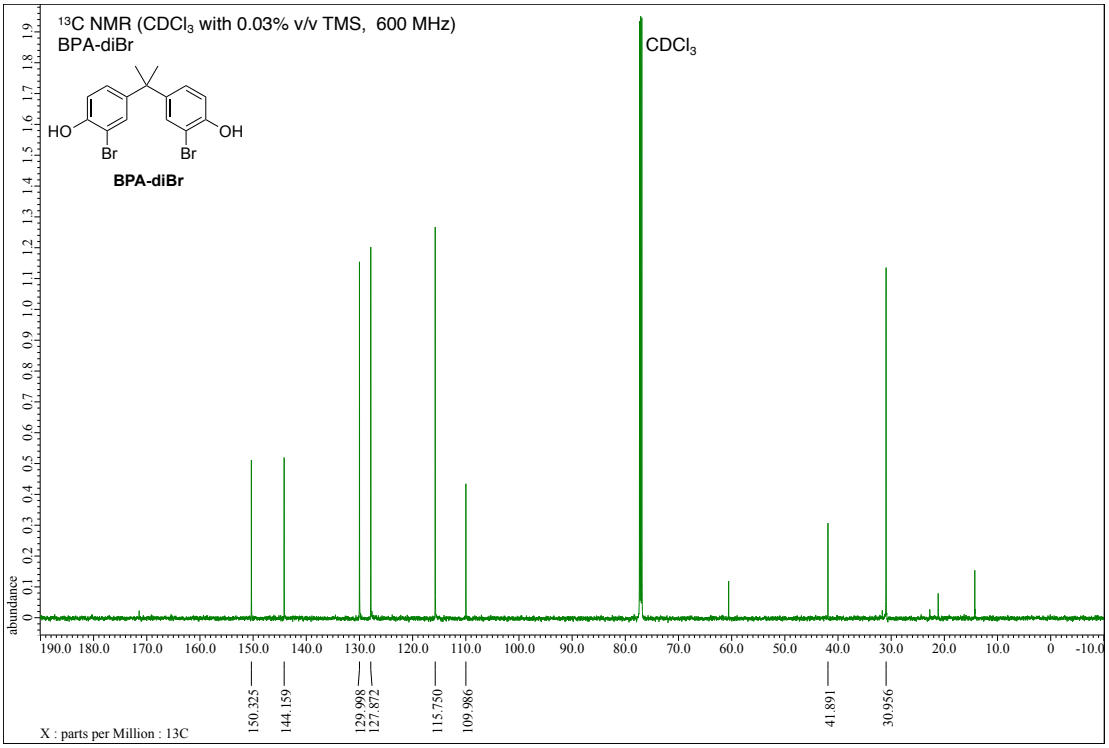

Figure S25. ^{13}C-NMR spectrum of BPA-diBr (600 MHz) in $CDCl_3$.

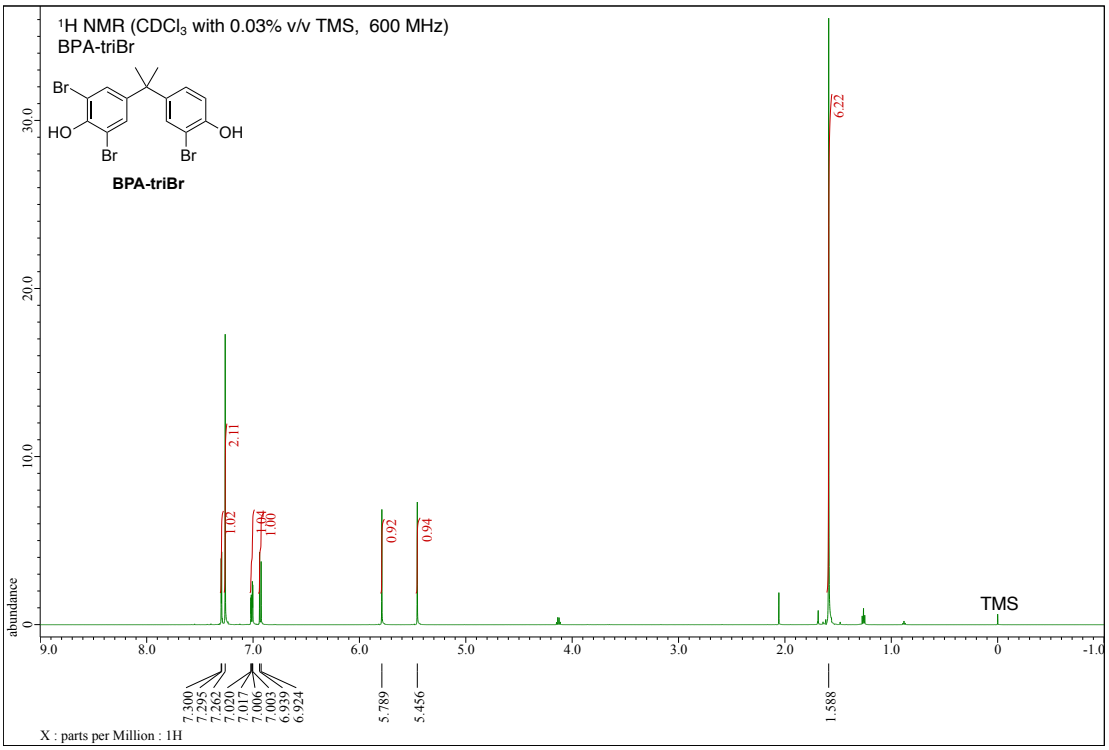

Figure S26. ^{1}H-NMR spectrum of BPA-triBr (600 MHz) in $CDCl_3$.

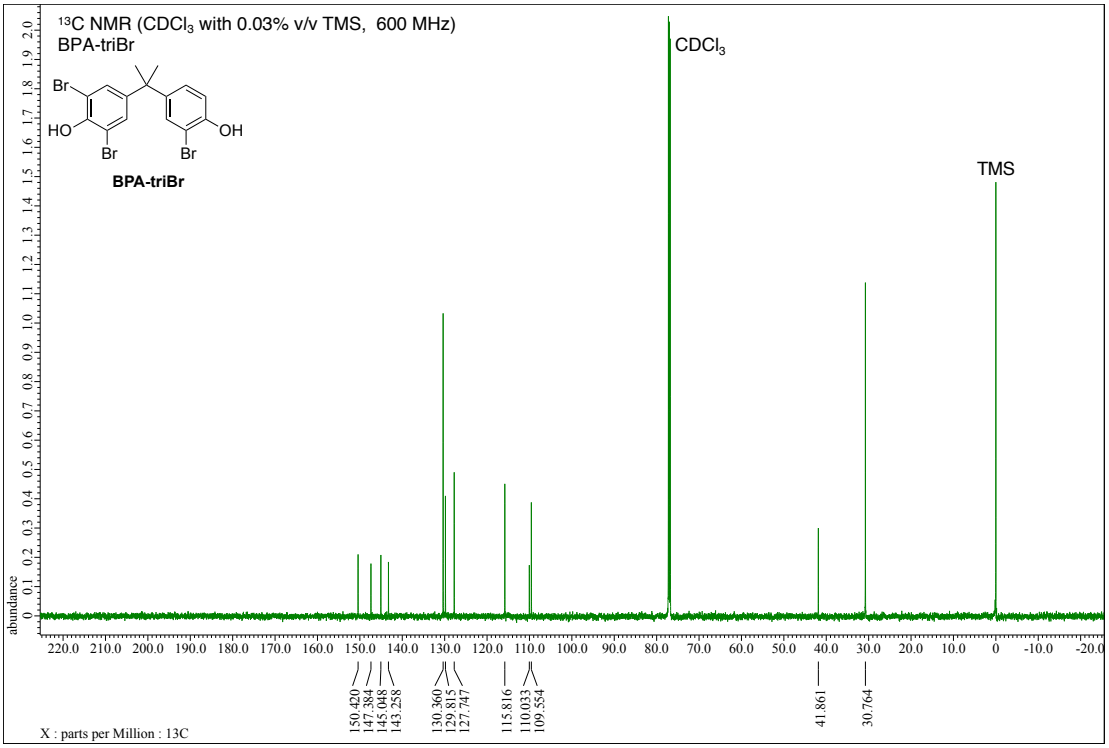

Figure S27. ^{13}C-NMR spectrum of BPA-triBr (600 MHz) in $CDCl_3$.

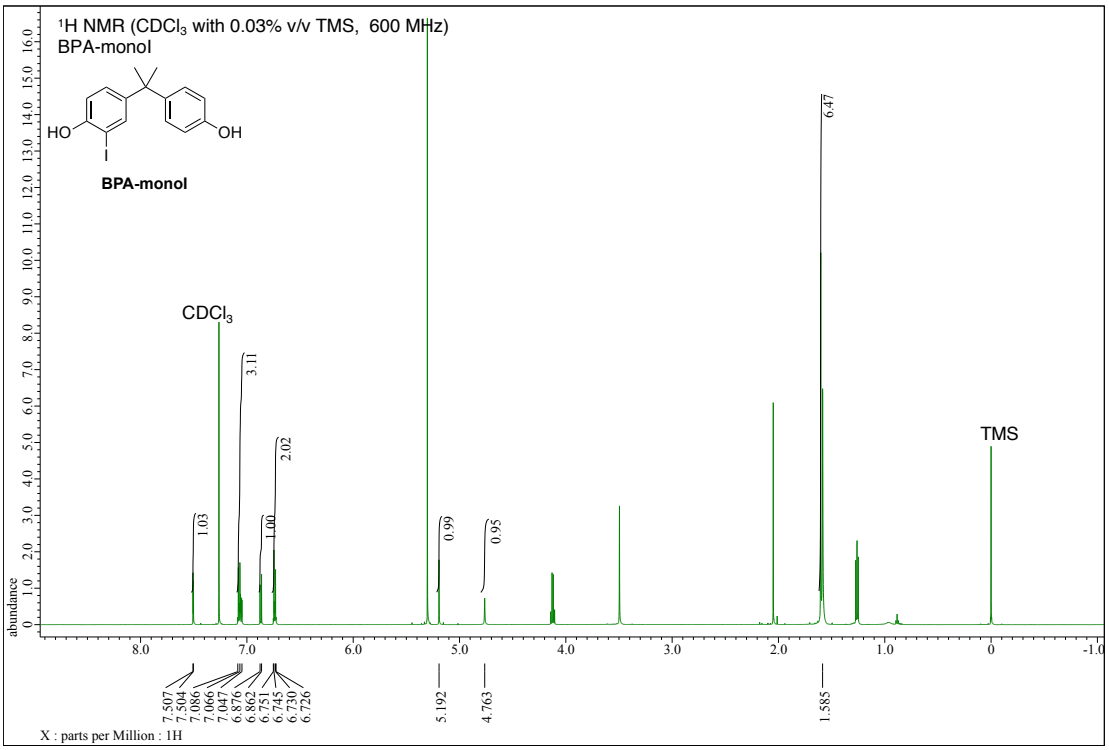

Figure S28. ^{1}H-NMR spectrum of BPA-monoI (600 MHz) in $CDCl_3$.

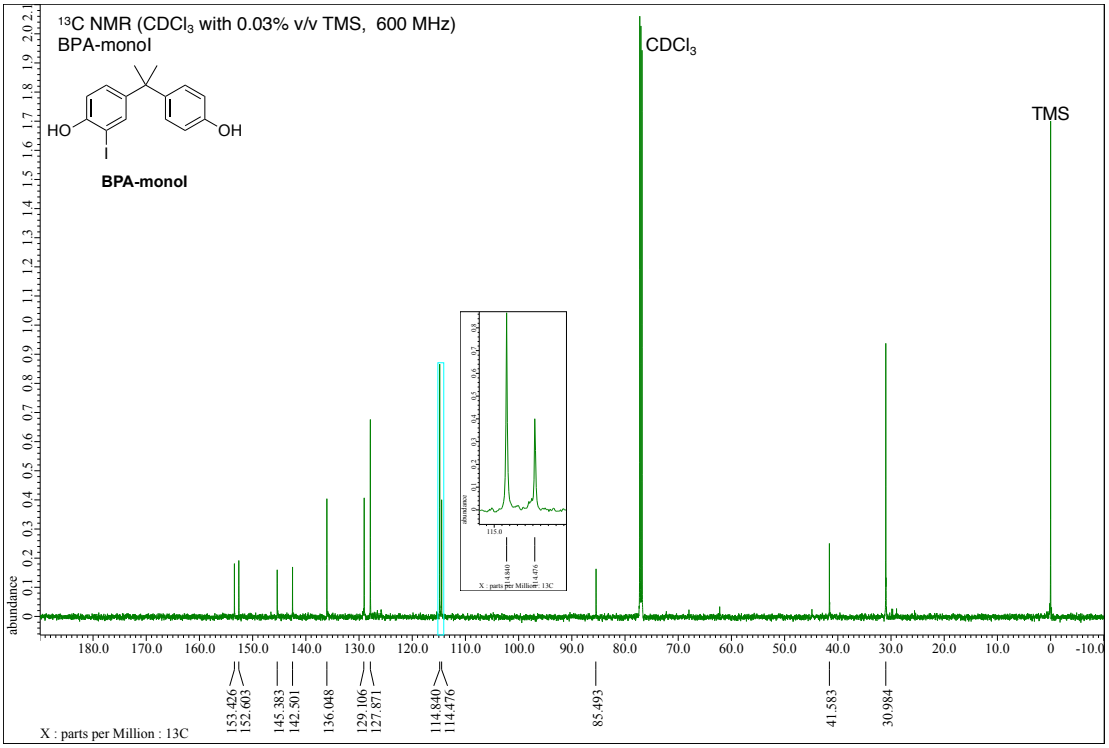

Figure S29. ^{13}C-NMR spectrum of BPA-monoI (600 MHz) in $CDCl_3$.

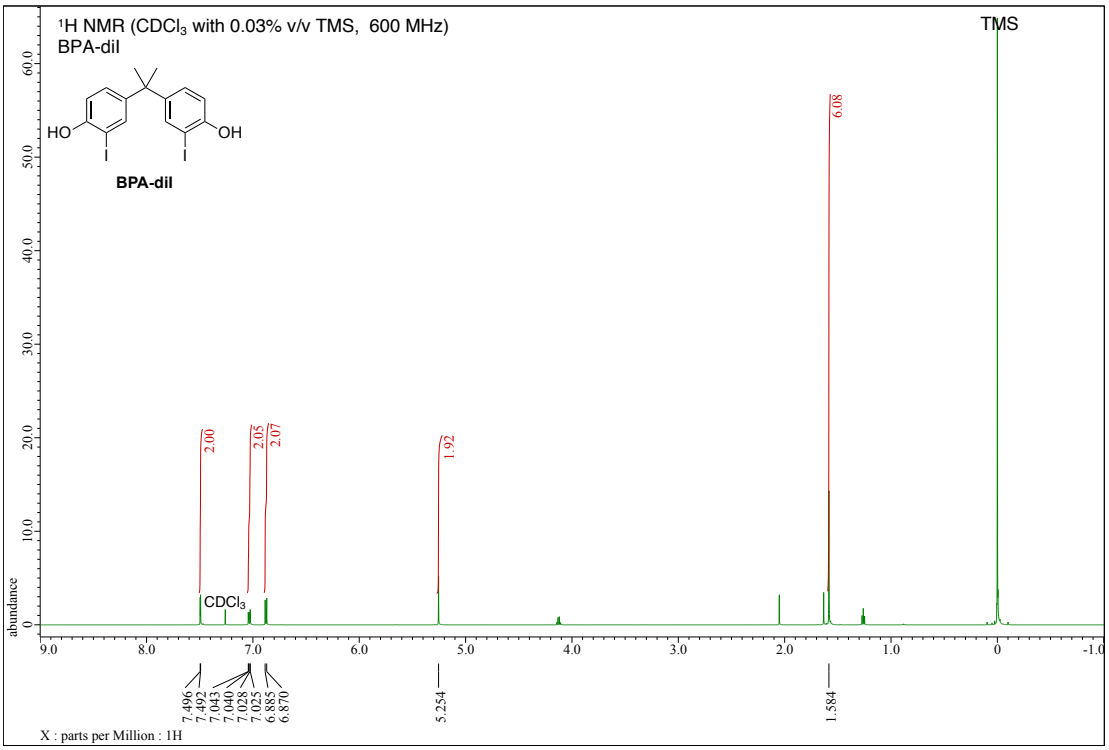

Figure S30. ^{1}H-NMR spectrum of BPA-diI (600 MHz) in $CDCl_3$.

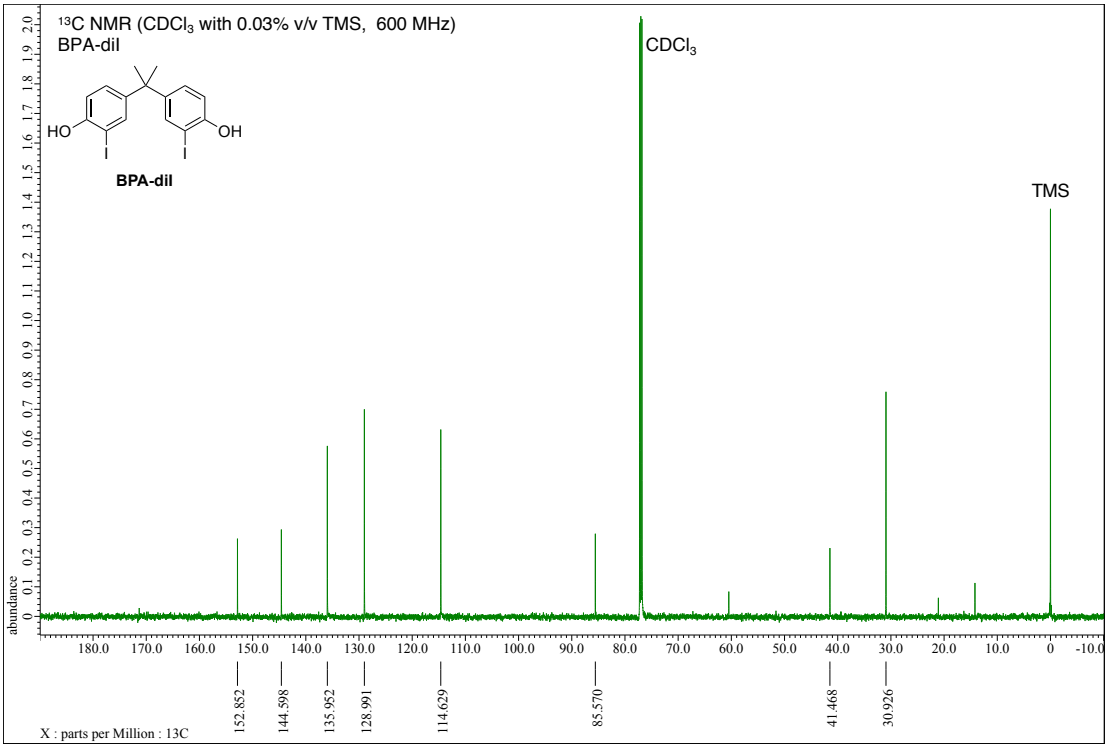

Figure S31. ^{13}C-NMR spectrum of BPA-diI (600 MHz) in $CDCl_3$.

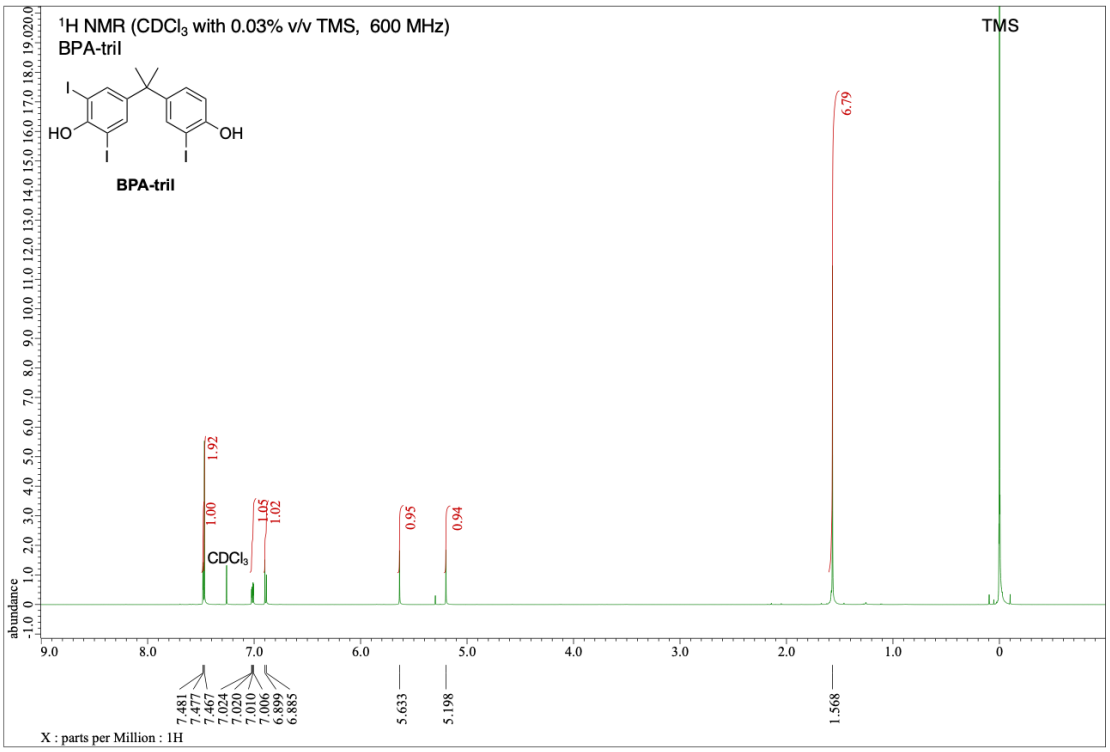

Figure S32. ^{1}H-NMR spectrum of BPA-triI (600 MHz) in $CDCl_3$.

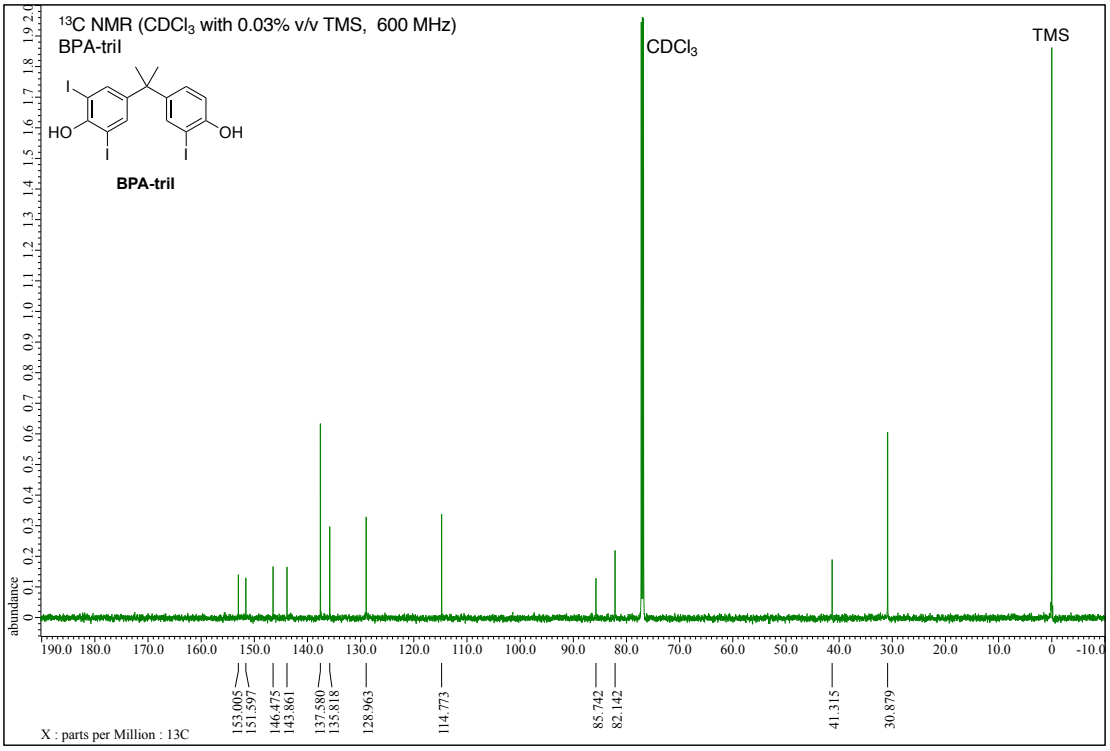

Figure S33. ^{13}C-NMR spectrum of BPA-triI (600 MHz) in $CDCl_3$.

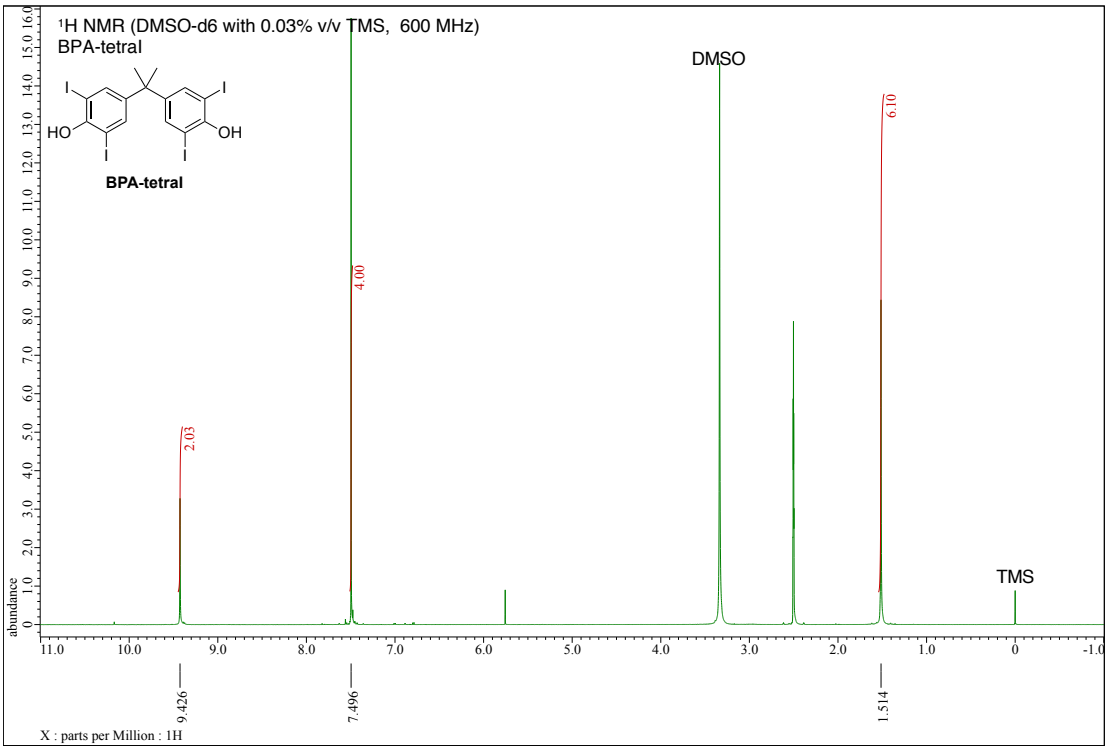

Figure S34. ^{1}H-NMR spectrum of BPA-tetraI (600 MHz) in DMSO-d6.

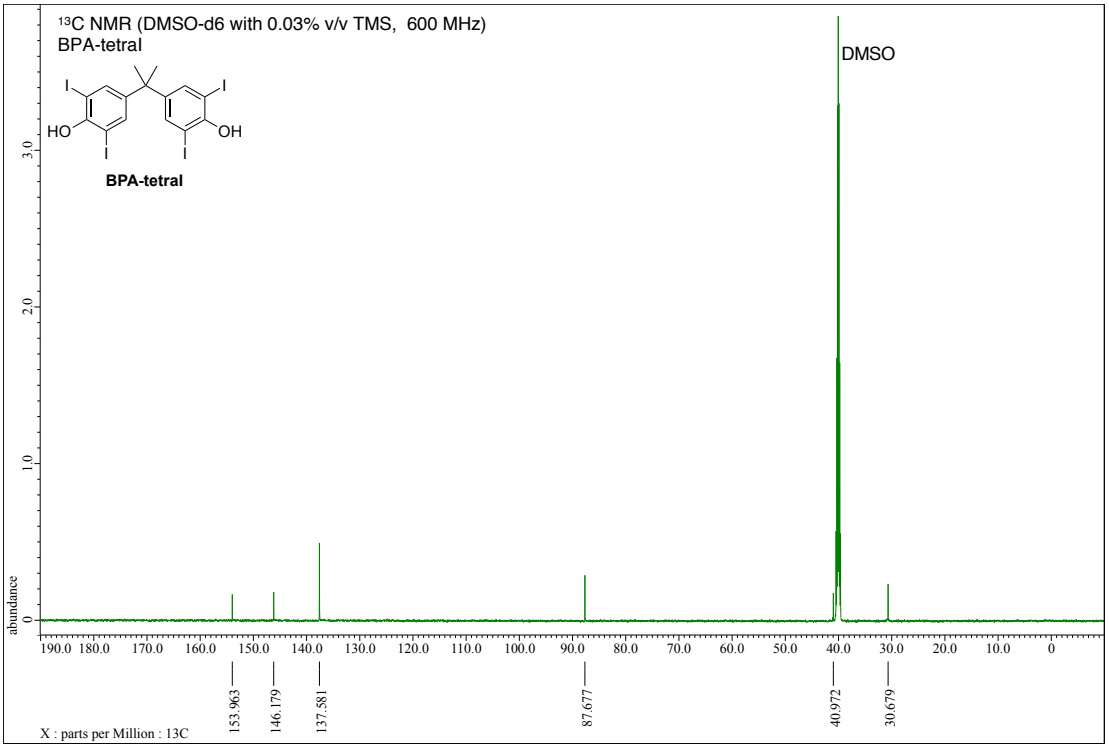

Figure S35. ^{13}C-NMR spectrum of BPA-tetraI (600 MHz) in DMSO-d6.

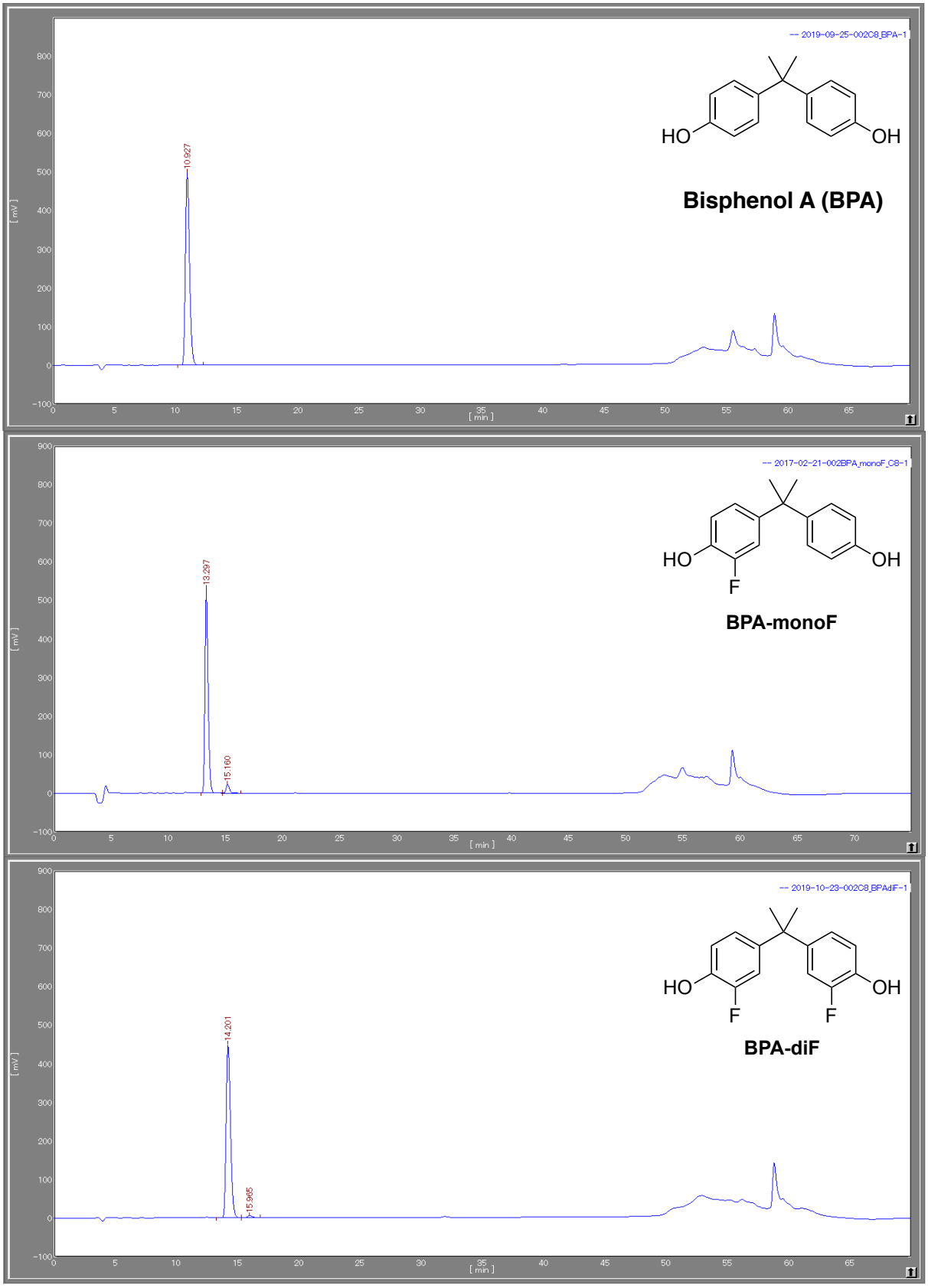

Figure S36. HPLC profiles of synthesized halogenated-BPA analogs (1/6).

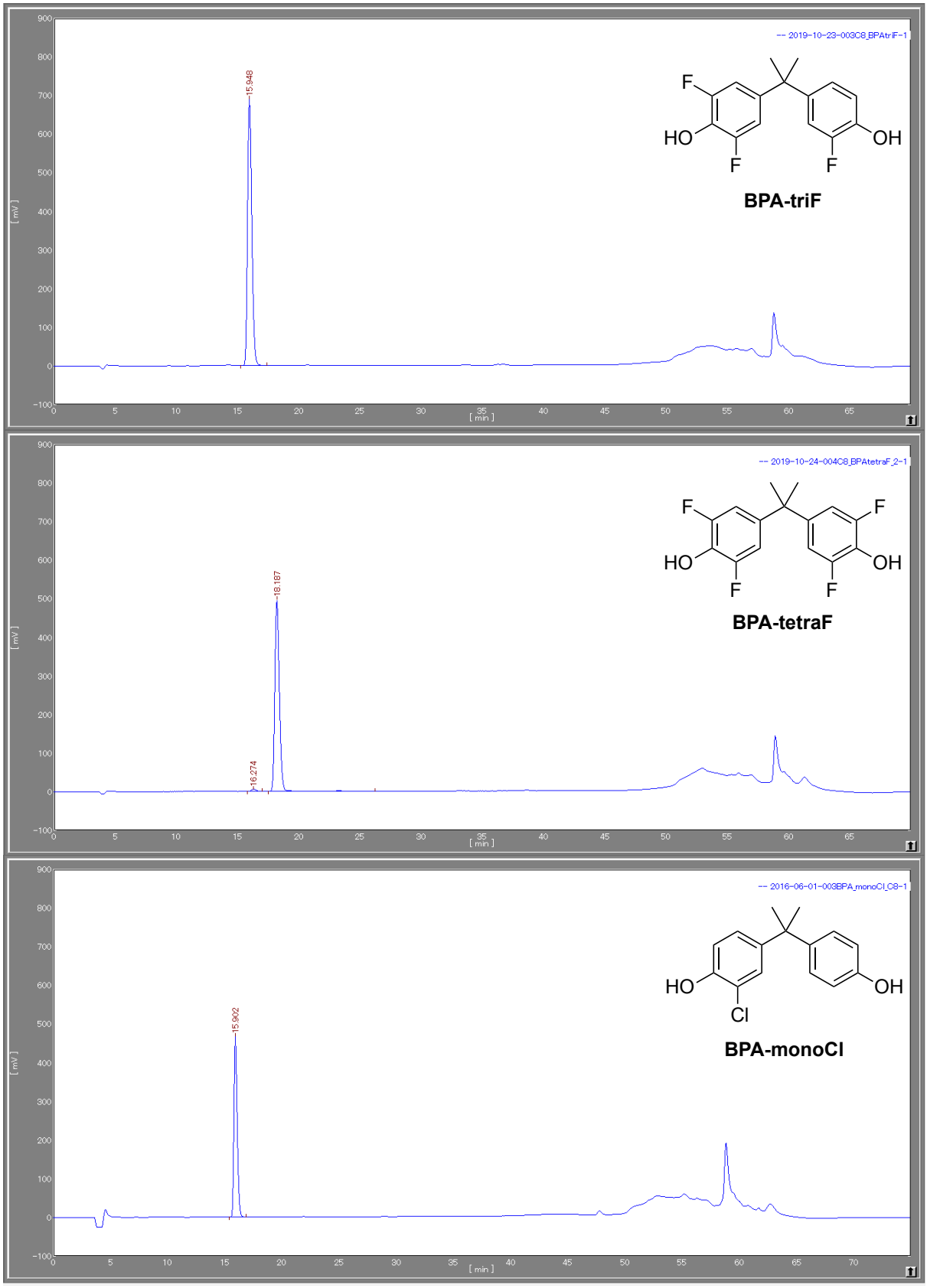

Figure S36. HPLC profiles of synthesized halogenated-BPA analogs (2/6).

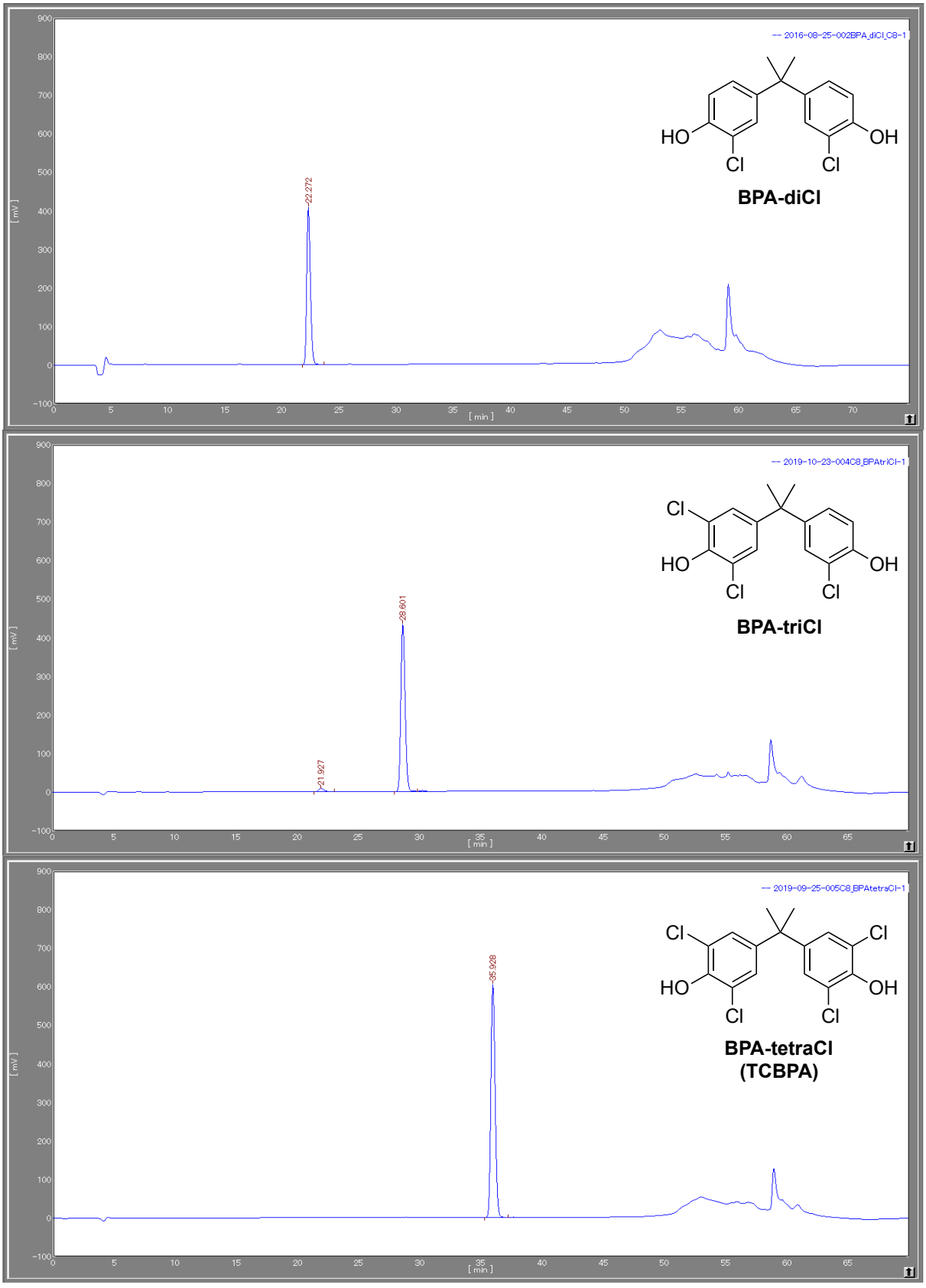

Figure S36. HPLC profiles of synthesized halogenated-BPA analogs (3/6).

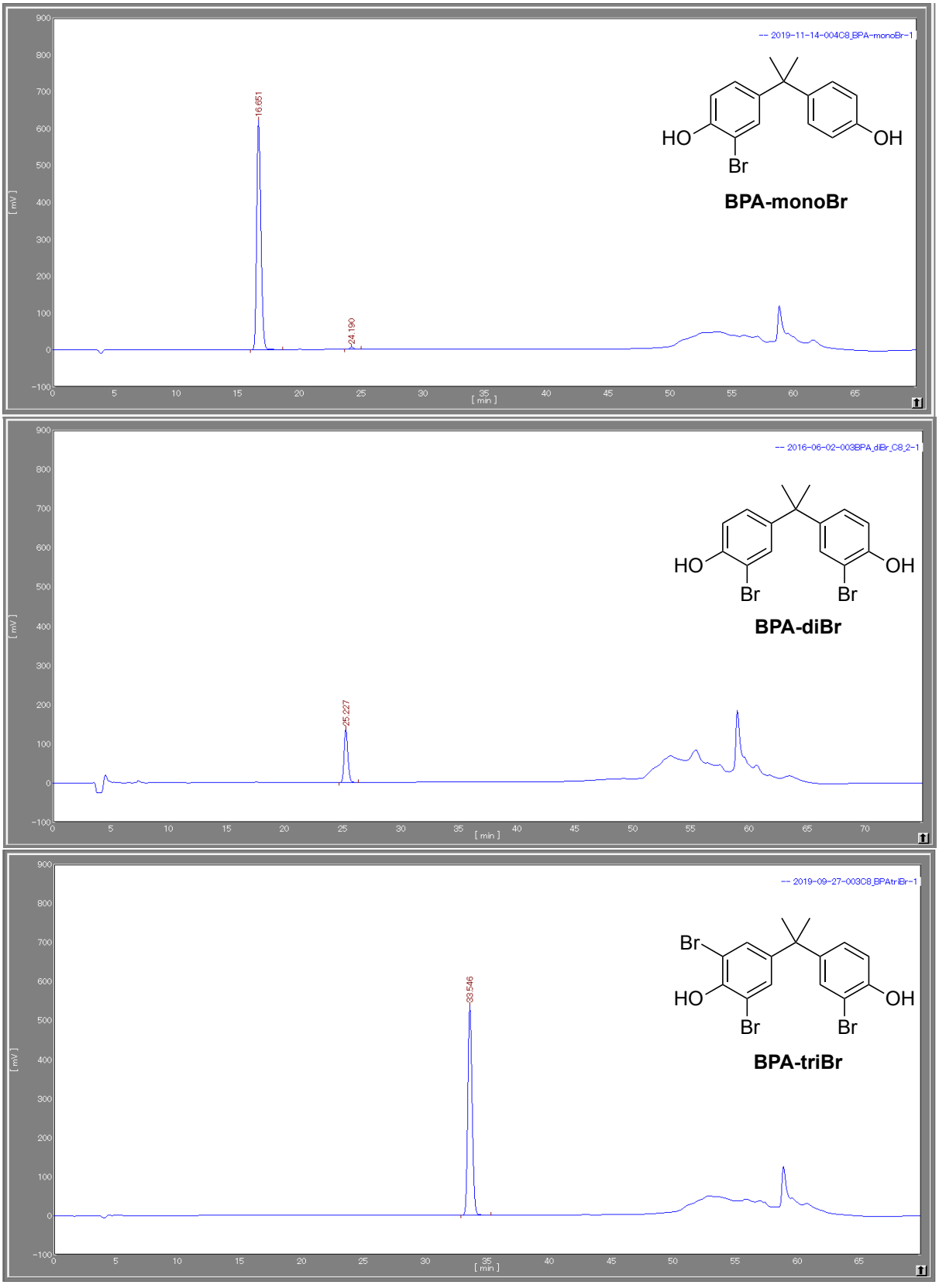

Figure S36. HPLC profiles of synthesized halogenated-BPA analogs (4/6).

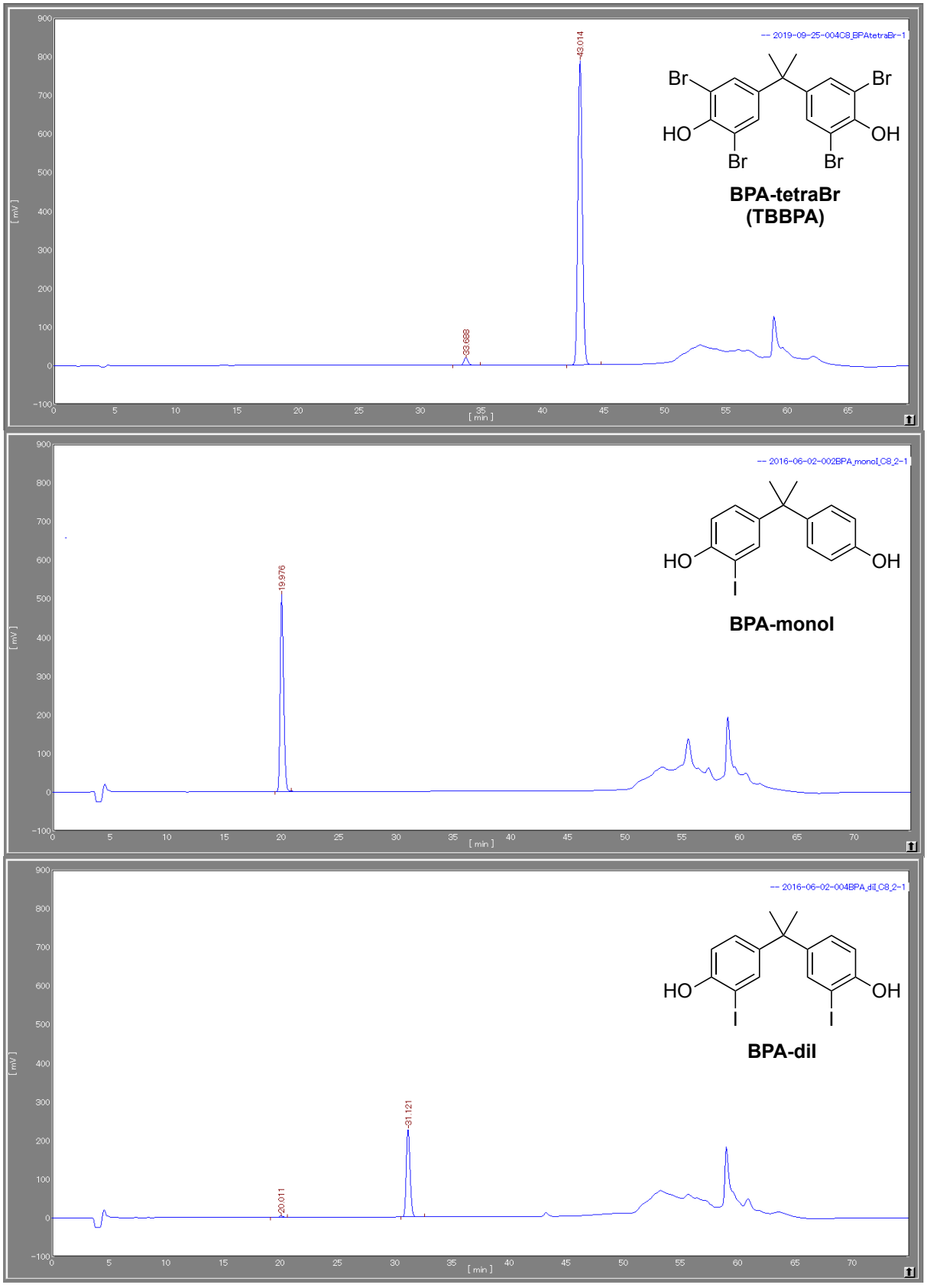

Figure S36. HPLC profiles of synthesized halogenated-BPA analogs (5/6).

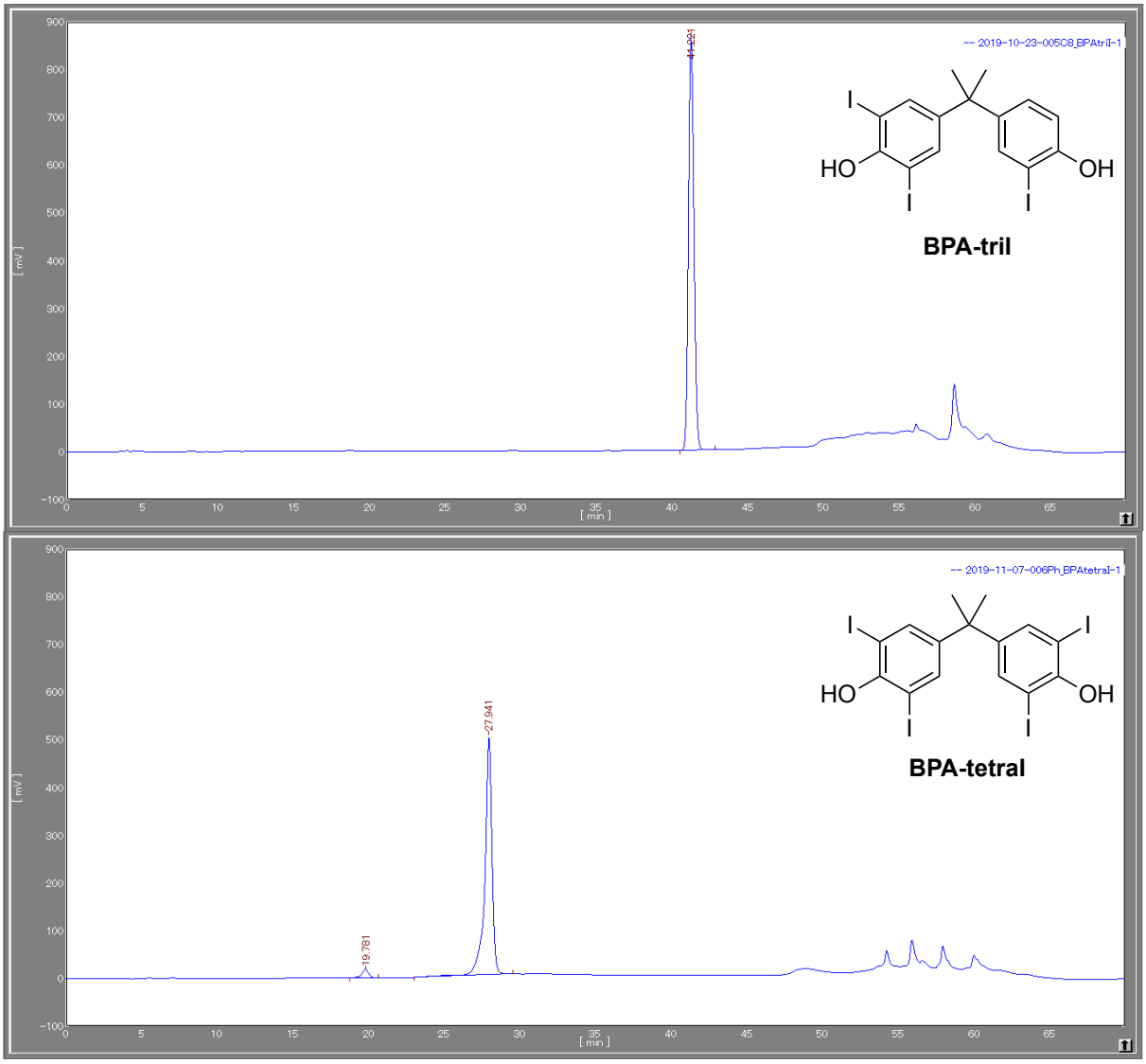

Figure S36. HPLC profiles of synthesized halogenated -BPA analogs (6/6).

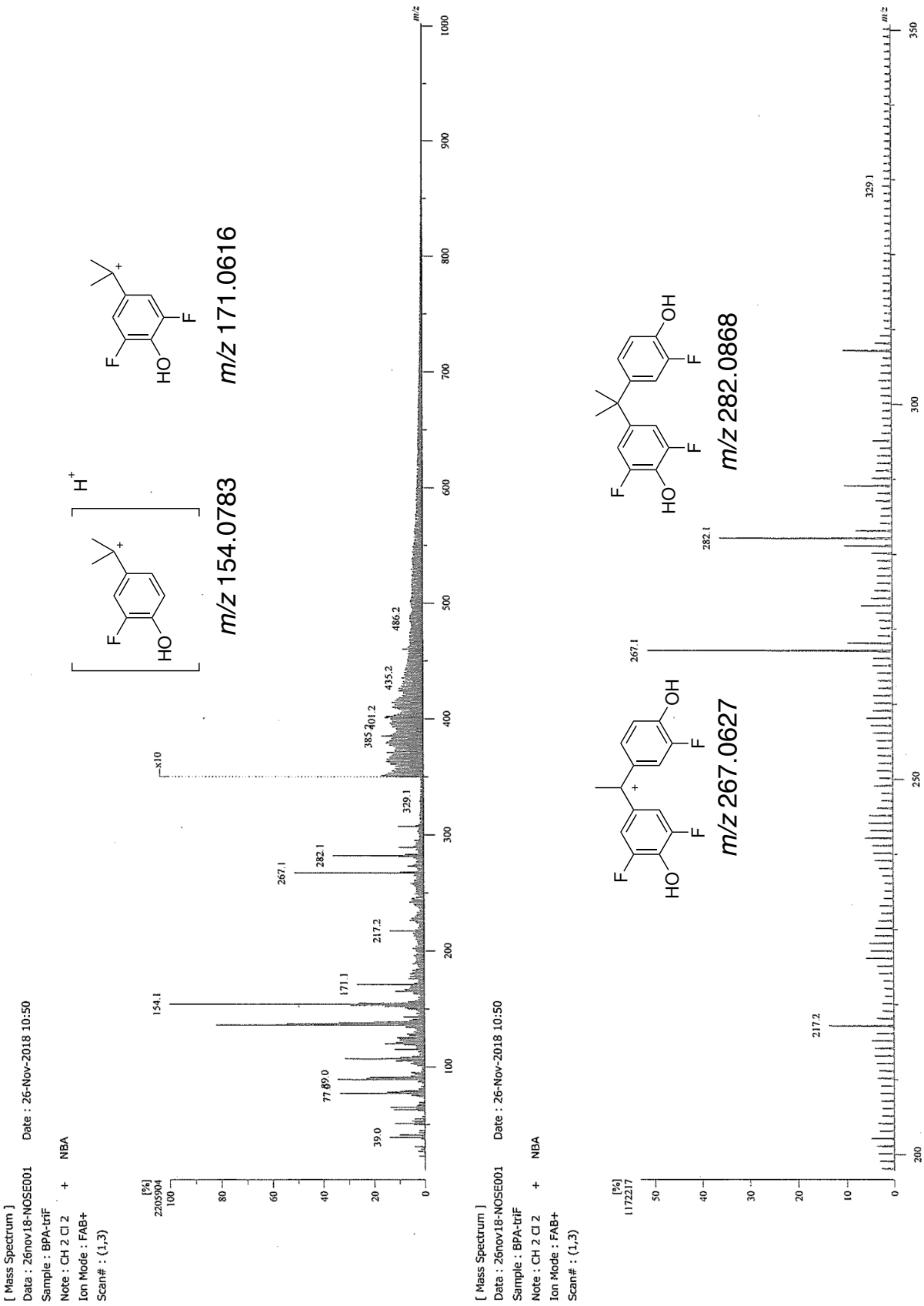

Figure S37. Positive ionization FAB mass spectra of BPA-triF.