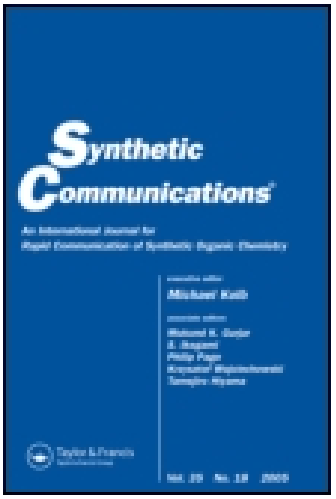

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Practical Synthesis of FEt-penta-cyclofenil and Its Derivatives for Potential PET Imaging

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PRACTICAL SYNTHESIS OF FEt-PENTA-CYCLOFENIL AND ITS DERIVATIVES FOR POTENTIAL PET IMAGING

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Generally, FEt-penta-cyclofenil and its derivatives have greater relative binding affinity to estradiol receptors than estradiol. (4-Fluoroethoxyphenyl)–(4′-hydroxyphenyl) methylenecyclopentane and its derivatives were synthesized for potential radioactive image agents, and their structures were characterized by ultraviolet, infrared, ^{1}H NMR, ^{19}F NMR, and high-resolution mass spectrometry.

Keywords: Cyclofenil; PET imaging agent; radiolabeling

INTRODUCTION

Early detection and accurate staging is very important for cancer treatment. For breast cancer, proper staging includes the determination of estradiol receptor (ER) status, which is overexpressed in many cases.[1] A number of estradiol (E_2) derivatives labeled with fluorine,[2,3] bromine,[4,5] and iodine[6] have been developed as positron emission tomography (PET) imaging agents. Selective ER modulators have been investigated more for steroidal estrogens, and only a few for nonsteroidal estrogens or antiestrogens.[7–10]

The ER displays a remarkable capacity for binding nonsteroidal ligands with high affinity.[11] There are two structurally similar subtypes, ERα and ERβ, and they have different biological properties.[12,13] It is notable that in breast cancer the level of ERβ relative to ERα declines with cancer progression.[14–16] Seo et al. proposed the structure model with greater relative binding affinity (RBA) to ER.[17] Cyclofenil derivatives, distinguished greatly in RBA value, generally have greater binding

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affinity than E_2.[18] Introducing fluorine in the structure of cyclofenil derivatives greatly improved the RBA to ER.[19] ^{18}F-labeled fluoro-cyclofenils' analog 4-[^{18}F] fluoro [bis (4-hydoroxyphenyl) methylene] cyclohexane ([^{18}F]-FCF) and ^{11}C-labeled cyclofenil-ester [^{11}C]methyl-2-{4-[bis(4-hydroxyphenyl) methylene] cyclohexyl}-acetate ([^{11}C]-CCFE) have been synthesized and investigated as potential PET agents. Unfortunately, these ligands with high affinity for the ER failed to show receptor-mediated uptake into the uterus.[20,21] In the structure's modifications for cyclofenil derivatives, at least one phenol hydroxyl must be kept free.[22,23]

Herein we report our preliminary result for the synthesis of these compounds for evaluation as potential radioactive PET imaging agents.

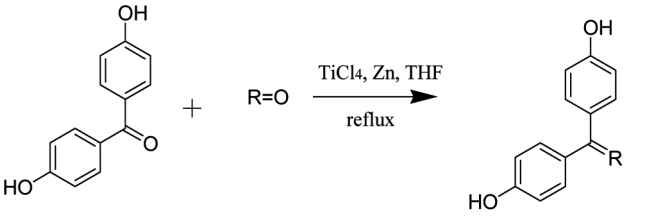
RESULTS AND DISCUSSION

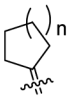
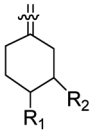
Synthesis of Cyclofenil 2–4

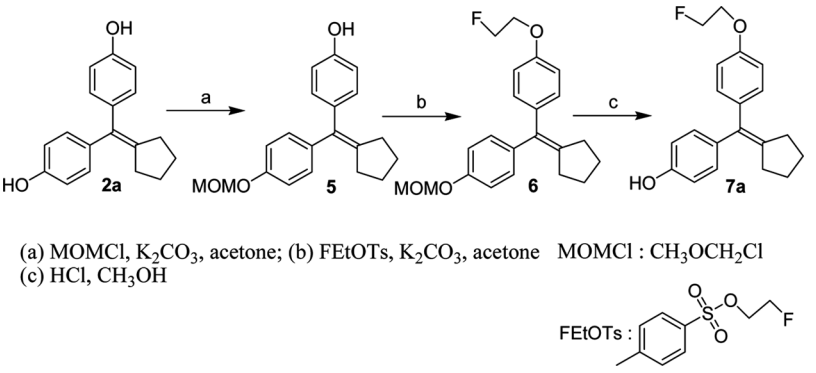
The synthetic procedure for cyclofenil and its analogs **2**–**4** is shown in Table 1.

The cyclofenil and its analogs were prepared via a McMurry coupling reaction between 4,4′-dihydroxybenzophenone **1** and ketone.[24,25] The low-valent titanium was formed by reaction of $TiCl_4$ with zinc power in absolute tetrahydrofuran (THF) at 100 °C. A mixture of **1** and ketone dissolved in absolute THF was injected into the flask by syringe, followed by refluxing for 2 h. Under the optimized conditions, all of the reactions gave reasonable yields of 78–85%, which is much greater than that literature reported.

Table 1. Synthesis of cyclofenil **2–4**



Entry	R			Product	Yield (%)
1		n=1		2a	81
2		n=2		2b	78
3		n=3		2c	83
4		R_1=H	R_2=CH_3	3a	83
5		R_1=CH_3	R_2=H	3b	78
6				4	85



Scheme 1. Three-step synthesis of **7a**.

Rapid and Separation-Free Synthesis of FEt-Cyclofenil

The synthetic procedure of FEt-penta-cyclofenil **7a** is for developing a potential radioactive fluorine-labeling method (Scheme 1).

Compound **2a** was dissolved in acetone, and potassium carbonate was added under an N_2 atmosphere. The mixture was cooled to $-5\,^{\circ}C$, and methoxymethyl chloride (MOMCl) was added dropwise. The mixture was stirred about 2 h to give mono-substituted product MOM-penta-cyclofenil **5**. This experiment must be performed below $0\,^{\circ}C$ because MOMCl is very active.

The synthesis of FEt-MOM-penta-cyclofenil **6** started from fluoroethyltosylate (FEtOTs), followed by adding compound **5** in acetone under basic conditions. The mixture was stirred at $65\,^{\circ}C$ for 50 min. The reaction time was controlled within 1 h with yield of more than 95%.

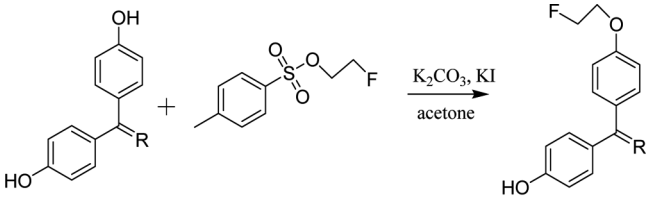
The general method to remove the MOM group is to overnight at room temperature. For radioactive labeling synthesis, the reaction temperature was kept at $60\,^{\circ}C$, and compound **7a** was formed quantitatively from **6** within 10 min. The high yield and short reaction time make it a potential radioactive labeling method.

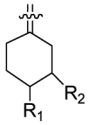
One-Step Synthesis of FEt-Cyclofenil

In this method, although the reaction time was controlled within 1 h, the two-step procedure is still not convenient for radiolabeling, so a one-step synthetic procedure for fluorinated cyclofenil (**7**–**9**) was developed as shown in Table 2.

Take FEt-penta-cyclofenil **7a** as an example: compound **2a** was dissolved in acetone, and then FEtOTs, potassium carbonate (K_2CO_3), and potassium iodide (KI) were added to the flask separately under a nitrogen atmosphere. The temperature was controlled at $60\,^{\circ}C$ and stirred for 1 h. After purification by flash chromatography, the pure compound **7a** was given with up to 85% yield. It is notable that this reaction's temperature is extremely important and should be controlled between 59 and $61\,^{\circ}C$.

Table 2. One-step synthesis of FEt-cyclofenil **7–9**



Entry	R		Product	Yield (%)
1		n=1	7a	85
2		n=2	7b	61
3		n=3	7c	66
4		R_1=H R_2=CH_3	8a	77
5		R_1=CH_3 R_2=H	8b	69
6			9	69

CONCLUSION

Cyclofenil and its analogs were synthesized for evaluation as potential radioactive PET image agents. Under controlled conditions, the reaction time for both of them is 1 h. The three-step method for the reaction is very clear and can be used directly without further purification in animal experiments. For the one-step method, a little by-product was formed in the reaction; however, in a radioactive labeling reaction, if the labeling yield can be kept at 85%, the method will be more practical.

EXPERIMENTAL

General Experimental Procedures

Melting points (mp) were determined on a WRS-1A melting-point apparatus and were uncorrected. ^{1}H and ^{19}F NMR spectra were recorded on a Bruker AC-300 (300-MHz) instrument with Me_4Si and $CFCl_3$ as internal standards in the indicated solution. Chemical shifts were reported in δ values in parts per million (ppm) downfield from Me_4Si (δ = 0) for proton and upfield from $CFCl_3$ (δ = 0) for fluorine NMR. Electrospray ionization high-resolution mass spectra electron (ESI-HRMS) were obtained on a Micromass GCTTM. Infrared spectra (IR) were recorded on an Avatar 370 Fourier transform FT–IR (Thermo Nicolet) as KBr disc. Ultraviolet spectra (UV) were recorded on a Shimadzu UV-240 spectrophotometer.

Synthesis of Cyclofenil and Its Analogs 2–4

A two-necked flask containing zinc powder (2.4 g, 37.0 mmol) was fitted with a reflux condenser, and charged with N_2. After THF (15 mL) was added, the reaction mixture was cooled in an ice bath (0 °C), and then titanium(IV) chloride (3.28 g, 17.24 mmol) was slowly added. The reaction was refluxed for 1 h at 100 °C and then cooled to room temperature. A solution of **1** (1.00 g, 4.66 mmol) and each ketone (aldehyde) (5.3 mmol) dissolved in THF (15 mL) was injected by syringe and refluxed for 2 h. The cooled reaction mixture was slowly poured into a $NaHCO_3$ solution (50 mL) and then filtered through celite. After the organic layer was decanted and saved, the aqueous layer was extracted with additional CH_2Cl_2 (100 mL). The combined organic layer was dried over $MgSO_4$ and concentrated. Flash-column chromatography or recrystallization from hexane/dichloromethane (DCM) gave a white solid.

Selected Data

Bis(4-hydroxyphenyl)methylenecyclopentane (2a). Yield 81.0%, white solid, mp 193–194 °C; IR (KBr): ν 3280, 2949, 1613, 1592, 1429, 1332, 840, 562 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 9.25 (s, 2H, -OH), 6.91 (d, 4H, aromatic, $J = 8.6$ Hz), 6.66 (d, 4H, aromatic, $J = 8.6$ Hz), 2.28 (t, 4H, C_2-H, $J = 6.8$ Hz), 1.61 (dt, 4H, C_3-H, $^2J_{H\text{-}H} = 6.6$ Hz, $^3J_{H\text{-}H} = 2.7$ Hz).

Bis(4-hydroxyphenyl)methylenecyclohexane (2b). Yield 78.0%, white solid, mp 235.1–237.0 °C; IR (KBr): ν 3276, 2929, 1605, 1507, 1429, 1225, 1168, 833, 563 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 9.25 (2H, s, -OH), 6.81 (4H, d, $J = 8.6$ Hz, aromatic), 6.64 (4H, d, $J = 7.6$ Hz, aromatic), 2.14 (4H, s, C_2-H), 1.49–1.60 (6H, m, $C_{3,4}$-H).

Bis(4-hydroxyphenyl)methylenecycloheptane (2c). Yield 83.0%, white solid, mp 195–198 °C; IR (KBr): ν 3248, 2933, 1609, 1503, 1230, 829, 567 cm^{-1}; ^1H NMR (acetone-d_6) δ: 6.95 (4H, d, $J = 7.3$ Hz, aromatic), 6.74 (4H, d, $J = 7.3$ Hz, aromatic), 2.26 (4H, t, $J = 6.0$ Hz, C_2-H), 1.50–1.70 (m, 8H, $C_{3,4}$-H).

4-Methyl[bis(4-hydroxyphenyl)methylene]cyclohexane (3a). Yield 82.7%, white solid, mp 183–184 °C; IR (KBr): ν 3249, 2924, 1608, 1509, 1235, 827, 569 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 6.80 (4H, d, $J = 8.4$ Hz, aromatic), 6.74 (4H, d, $J = 8.1$ Hz, aromatic), 4.67 (2H, s, -OH), 2.57 (2H, bd, $J = 13.2$ Hz, C_2-H), 1.94 (2H, td, $J = 13$ Hz, C_2-H), 1.70–1.80 (2H, m, C_3-H), 1.55–1.65 (1H, m, C_4-H), 0.93–1.1 (2H, m, C_3-H), 0.92 (3H, d, $J = 8.0$ Hz, -CH_3).

3-Methyl[bis(4-hydroxyphenyl)methylene]cyclohexane (3b). Yield 78.0%, white solid, mp 172.2–172.7 °C; IR (KBr): ν 3238, 2930, 1612, 1506, 1231, 831, 565 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 6.80 (4H, dd, $^2J_{H\text{-}H} = 6.39$ Hz, $^3J_{H\text{-}H} = 2.24$ Hz, aromatic), 6.72 (4H, dd, $^2J_{H\text{-}H} = 5.93$ Hz, $^3J_{H\text{-}H} = 2.96$ Hz, aromatic), 4.67 (2H, s, -OH), 2.51 (2H, bd, $J = 12.3$ Hz, C_2-H), 1.77 (2H, td, $C_{2'}$-H, $J = 11.6$ Hz), 1.50–1.70 (4H, m, $C_{3',4}$-H), 1.30–1.40 (1H, m, C_3-H), 0.87 (3H, d, $J = 6.19$ Hz, -CH_3).

Iso-[bis(4-hydroxyphenyl)methylene]butane (4). Yield 85.0%, white solid, mp 168.4–170.4 °C; IR (KBr): ν 3314, 2958, 1607, 1513, 1223, 835, 595 cm^{-1}; ^1H NMR

($CDCl_3$) δ: 7.09 (2H, d, $J = 8.7$ Hz, aromatic), 7.04 (2H, d, $J = 8.7$ Hz, aromatic), 6.82 (2H, d, $J = 8.7$ Hz, aromatic), 6.71 (2H, d, $J = 8.7$ Hz, aromatic), 5.72 (1H, d, $J = 10.3$ Hz, alkene-H), 4.88 (2H, s, -OH), 2.42 (1H, m, C-H), 1.00 (6H, d, $J = 6.9$ Hz, $-CH_3$).

Synthesis of (4-Methoxymethylphenyl)-(4′-hydroxyphenyl) methylenecycloheptane (5)

Two-necked flask containing **2a** (800 mg, 3.0 mmol) and K_2CO_3 (960 mg, 6.9 mmol) was charged with N_2. After acetone (10 mL) was added, it was stirred and cooled to −5 °C, and MOMCl (0.27 ml, 3.3 mmol) dissolved in another 10 mL acetone was dropped into the mixture and then reacted for 2 h below zero. The reaction stopped, the solvent was filtered, and the filtrate was evaporated under reduced pressure and purified by column chromatography. The desired product, straw yellow oil, was obtained in 37.3% yield (350 mg). IR (KBr): ν 3320, 2941, 1610, 1585, 1214, 1165, 1018, 916, 766 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.09 (2H, d, $J = 8.7$ Hz, aromatic), 7.04 (2H, d, $J = 7.8$ Hz, aromatic), 6.94 (2H, d, $J = 8.7$ Hz, aromatic), 6.84 (2H, d, $J = 8.6$ Hz, aromatic), 5.18 (2H, s, $-OCH_2O-$), 3.49 (3H, s, $-OCH_3$), 2.37–2.38 (4H, m, C_2-H), 1.60–1.70 (4H, m, C_3-H).

Synthesis of (4-Fluoroethoxyphenyl)-(4′-methoxymethylphenyl) methylenecycloheptane (6)

A flask containing **5** (300 mg, 0.97 mmol) and K_2CO_3 (200 mg, 1.45 mmol) was fitted with a reflux condenser and charged with nitrogen gas. After acetone (15 mL) was added, stirred, and heated to 60 °C, FEtOTs (400 mg, 1.83 mmol) dissolved in another 10 mL acetone was dropped into the mixture and then reacted for 1 h at 65 °C. The reaction stopped, the solvent was filtered while hot, the filtrate was evaporated under reduced pressure, and water was added to remove the inorganic salt. Then the residue was filtered, rinsed with water, extracted with additional CH_2Cl_2 (10 mL), and concentrated without further purification. The desired product, yellow oil, was obtained in 93.3% yield (317 mg). UV (EtOH): λ 205, 232 nm; IR (KBr): ν 2954, 1607, 1508, 1241, 1175, 1008, 924, 775 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.05–7.15 (4H, m, aromatic), 6.94 (2H, d, $J = 8.7$ Hz, aromatic), 6.84 (2H, d, $J = 8.6$ Hz, aromatic), 5.16 (2H, s, $-OCH_2O-$), 4.74 (2H, dt, $^2J_{H\text{-}F} = 47.36$ Hz, $^2J_{H\text{-}H} = 4.18$ Hz, $-CH_2F$), 4.20 (2H, dt, $^3J_{H\text{-}F} = 27.65$ Hz, $^2J_{H\text{-}H} = 4.17$ Hz, $-OCH_2-$), 3.49 (3H, s, $-OCH_3$), 2.36–2.38 (4H, m, C_2-H), 1.62–1.72 (4H, m, C_3-H); ^{19}F NMR ($CDCl_3$) δ: −223.09 (1 F, tt, $^2J_{F\text{-}H} = 50.10$ Hz, $^3J_{F\text{-}H} = 23.08$ Hz).

Synthesis of (4-Fluoroethoxyphenyl)-(4′-hydroxyphenyl) methylenecycloheptane (7a)

Two-necked flask containing **6** (100 mg, 0.28 mmol) was fitted with a reflux condenser and charged with N_2. Concentrated HCl (0.4 mL) dissolved in 10 ml CH_3OH was injected by syringe. The reaction mixture was stirred at room temperature for 12 h, rinsed with saturation $NaHCO_3$, then extracted with additional CH_2Cl_2, and concentrated without further purification. Desired product, straw yellow oil, was obtained in about 99% yield (86.7 mg). It also can be obtained by

stirring at 60 °C for 10 min to get about 95% yield. UV (EtOH): λ 208, 225, 265 nm; IR (KBr): ν 3350, 2953, 2864, 1605, 1164, 829, 575 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.09 (2H, d, $J = 8.3$ Hz, aromatic), 7.03 (2H, d, $J = 8.2$ Hz, aromatic), 6.84 (2H, d, $J = 8.3$ Hz, aromatic), 6.74 (2H, d, $J = 8.4$ Hz, aromatic), 4.7 (2H, dt, $^2J_{H\text{-}F} = 47.44$ Hz, $^2J_{H\text{-}H} = 3.88$ Hz, -CH_2F), 4.39 (2H, dt, $^3J_{H\text{-}F} = 27.79$ Hz, $^2J_{H\text{-}H} = 5.98$ Hz, -OCH_2-), 2.40–2.45 (4H, m, C_2-H), 1.60–1.70 (4H, m, C_3-H); ^{19}F NMR ($CDCl_3$) δ: −223.83 (1 F, tt, $^2J_{F\text{-}H} = 50.55$ Hz, $^3J_{F\text{-}H} = 24.45$ Hz); ESI-HRMS calcd. for $C_{20}H_{22}O_2F$ $[M+1]^+$ 313.1604; found 313.1604.

One-Step Synthesis of FEt-Cyclofenil and Its Analogs 7–9

A flask containing cyclofenil (1.0 mmol), 2-fluoroethyl tosylate (305 mg, 1.4 mmol), K_2CO_3 (205 mg, 1.5 mmol), and KI (17 mg, 0.2 mmol) was fitted with a reflux condenser and charged with nitrogen gas. After acetone (10 mL) was added, the mixture was stirred and heated to 60 °C for 6 h. The reaction stopped, the solvent was filtered while hot, the filtrate was evaporated under reduced pressure, and water was added to remove the inorganic salt. Then the residue was filtered, rinsed with water, and purified by column chromatography.

Selected Data

(4-Fluoroethoxyphenyl)-(4′-hydroxyphenyl)methylenecyclopentane (7a). Yield 85.0%, characterized previously.

(4-Fluoroethoxyphenl)-(4′-hydroxyphenyl)methylenecyclohexane (7b). Yield 61.0%, white solid, mp 73.5–75.5 α; UV (EtOH): λ 207, 253 nm; IR (KBr): ν 3259, 2921, 1707, 1609, 1169, 833, 575 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.01 (2H, d, $J = 8.9$ Hz, aromatic), 6.92 (2H, d, $J = 8.9$ Hz, aromatic), 6.83 (2H, d, $J = 7.4$ Hz, aromatic), 6.73 (2H, d, $J = 7.3$ Hz, aromatic), 4.7 (2H, dt, $^2J_{H\text{-}F} = 47.46$ Hz, $^2J_{H\text{-}H} = 2.66$ Hz, -CH_2F), 4.18 (2H, dt, $^3J_{H\text{-}F} = 27.72$ Hz, $^2J_{H\text{-}H} = 2.84$ Hz, -OCH_2-), 2.10–2.25 (4H, m, C_2-H), 1.50–1.70 (6H, m, $C_{3,4}$-H); ^{19}F NMR ($CDCl_3$) δ: −223.03 (tt, 1F, $^2J_{F\text{-}H} = 49.35$ Hz, $^3J_{F\text{-}H} = 24.55$ Hz); ESI-HRMS calcd. for $C_{21}H_{24}O_2F$ $[M+1]^+$ 327.1760; found 327.1765.

(4-Fluoroethoxyphenyl)-(4′-hydroxyphenyl)methylenecyclopentane (7c). Yield 66.4%, yellow oil; UV (EtOH): λ 209, 225 nm; IR (KBr): ν 3293, 2913, 1605, 1507, 1180, 608 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.06 (2H, d, $J = 8.6$ Hz, aromatic), 7.00 (2H, d, $J = 8.4$ Hz, aromatic), 6.83 (2H, d, $J = 8.5$ Hz, aromatic), 6.72 (2H, d, $J = 8.4$ Hz, aromatic), 4.72 (2H, dt, $^2J_{H\text{-}F} = 47.37$ Hz, $^2J_{H\text{-}H} = 4.13$ Hz, -CH_2F), 4.18 (2H, dt, $^3J_{H\text{-}F} = 27.65$ Hz, $^2J_{H\text{-}H} = 4.1$ Hz, -OCH_2-), 2.30–2.45 (4H, m, C_2-H), 1.50–1.70 (8H, m, $C_{3,4}$-H); ^{19}F NMR ($CDCl_3$) δ: −223.16 (1F, tt, $^2J_{F\text{-}H} = 50.55$ Hz, $^3J_{F\text{-}H} = 23.03$ Hz); ESI-HRMS calcd. for $C_{22}H_{26}O_2F$ $[M+1]^+$ 341.1917; found 341.1928.

4-Methyl-[(4-fluoroethoxyphenyl)-(4′-hydroxyphenyl)methylene]-cyclohexane (8a). Yield 77.1%, straw yellow oil; UV (EtOH): λ 225 nm; IR (KBr): ν 3270, 2810, 1599, 1359, 1178, 922, 555 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.02 (2H, d, $J = 8.7$ Hz, aromatic), 6.96 (2H, d, $J = 8.4$ Hz, aromatic), 6.83 (2H, d, $J = 8.7$ Hz,

aromatic), 6.72 (2H, d, $J = 8.1$ Hz, aromatic), 4.81 (2H, dt, $^2J_{H\text{-}F} = 47.1$ Hz, $^2J_{H\text{-}H} = 4.42$ Hz, -CH_2F), 4.18 (2H, dt, $^3J_{H\text{-}F} = 27.6$ Hz, $^2J_{H\text{-}H} = 4.1$ Hz, -OCH_2-), 2.54 (2H, bd, $J = 15.2$ Hz, C_2-H), 1.93 (2H, td, $J = 13.0$ Hz, C_2-H), 1.70–1.80 (2H, m, C_3-H), 1.55–1.65 (1H, m, C_4-H), 0.99–1.1 (2H, m, C_3-H), 0.93 (3H, d, $J = 8.0$ Hz, -CH_3); ^{19}F NMR ($CDCl_3$) δ: −223.09 (1F, tt, $^2J_{F\text{-}H} = 50.40$ Hz, $^3J_{F\text{-}H} = 25.90$ Hz); ESI-HRMS calcd. for $C_{22}H_{26}O_2F$ $[M + 1]^+$ 341.1917; found 341.1911.

3-Methyl-(4-fluoroethoxyphenyl)-(4′-hydroxyphenyl)methylenecyclohexane (8b). Yield 68.9%, colorless oil. UV (EtOH): λ 225 nm; IR (KBr): ν 3245, 2958, 1598, 1359, 1177, 921, 554 cm^{-1};^{1}H NMR ($CDCl_3$) δ: 7.02 (2H, d, $J = 7.5$ Hz, aromatic), 6.96 (2H, d, $J = 8.4$ Hz, aromatic), 6.83 (2H, d, $J = 7.5$ Hz, aromatic), 6.73 (2H, d, $J = 6.9$ Hz, aromatic), 4.76 (2H, dt, $^2J_{H\text{-}F} = 47.2$ Hz, $^2J_{H\text{-}H} = 4.1$ Hz, -CH_2F,), 4.20 (2H, dt, $^3J_{H\text{-}F} = 27.1$ Hz, $^2J_{H\text{-}H} = 4.1$ Hz, -OCH_2), 2.52 (2H, bd, $J = 11.1$ Hz, C_2-H), 1.77 (2H, bd, $J = 14.4$ Hz, $C_{2'}$-H), 1.40–1.70 (4H, m, $C_{3',4}$-H), 1.20–1.30 (1H, m, C_3-H), 0.87 (3H, d, $J = 5.7$ Hz, -CH_3); ^{19}F NMR ($CDCl_3$) δ: −223.74 (1F, tt, $^2J_{F\text{-}H} = 50.25$ Hz, $^3J_{F\text{-}H} = 23.50$ Hz); ESI-HRMS calcd. for $C_{22}H_{26}O_2F$ $[M + 1]^+$ 341.1917; found 341.1892.

Iso-(4-fluoroethoxyphenyl)-(4′-hydroxyphenyl)methylenebutane (9). Yield 68.9%, straw yellow oil. UV (EtOH): λ 224, 265 nm; IR (KBr): ν 3212, 2955, 1519, 1269, 1169, 918, 552 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 7.15 (2H, d, $J = 8.7$ Hz, aromatic), 7.04 (2H, d, $J = 8.4$ Hz, aromatic), 6.93 (2H, d, $J = 8.7$ Hz, aromatic), 6.72 (2H, d, $J = 8.4$ Hz aromatic), 5.76 (1H, d, $J = 10.2$ Hz, alkene-H), 4.73 (2H, dt, $^2J_{H\text{-}F} = 47.1$ Hz, $^2J_{H\text{-}H} = 2.1$ Hz, -CH_2F), 4.20 (2H, dt, $^3J_{H\text{-}F} = 28.2$ Hz, $^2J_{H\text{-}H} = 3.45$ Hz, -OCH_2-), 2.42 (1H, m, C-H), 1.00 (6H, d, $J = 6.9$ Hz, -CH_3); ^{19}F NMR ($CDCl_3$) δ: −223.03 (1F, tt, $^2J_{F\text{-}H} = 50.55$ Hz, $^3J_{F\text{-}H} = 23.65$ Hz); ESI-HRMS calcd. for $C_{19}H_{22}O_2F$ $[M + 1]^+$ 301.1604; found 301.1616.

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