Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Synthesis and biological activity of photostable and persistent abscisic acid analogs

Jun Takeuchi, Haruka Asakura, Yuri Ozasa, Motoki Koide, Toshiyuki Ohnishi, and Yasushi Todoroki

Supporting Information

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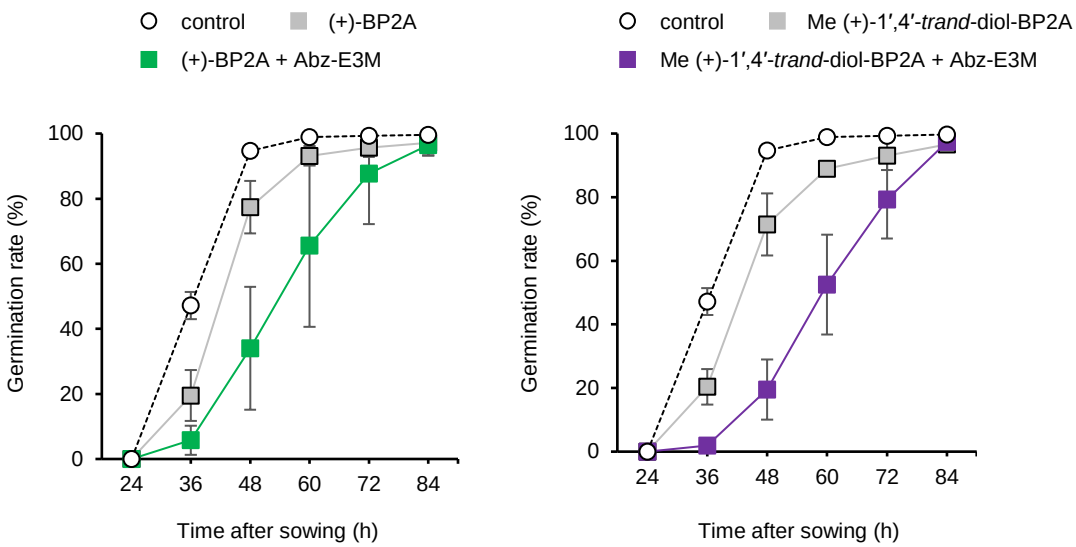
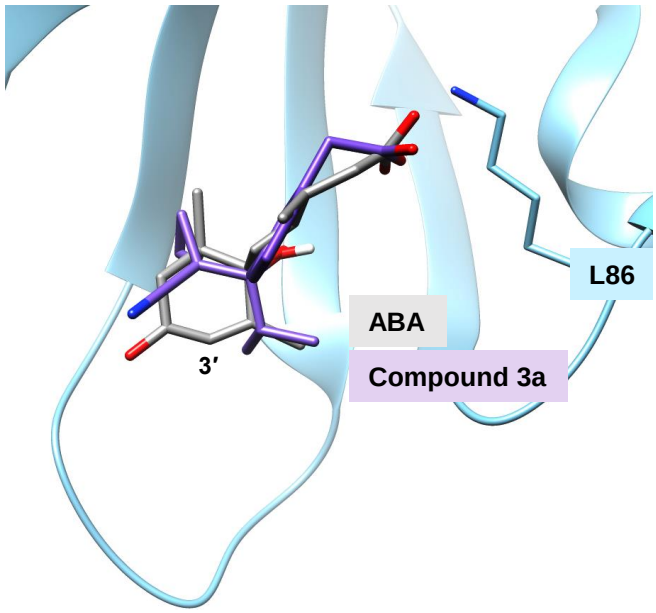
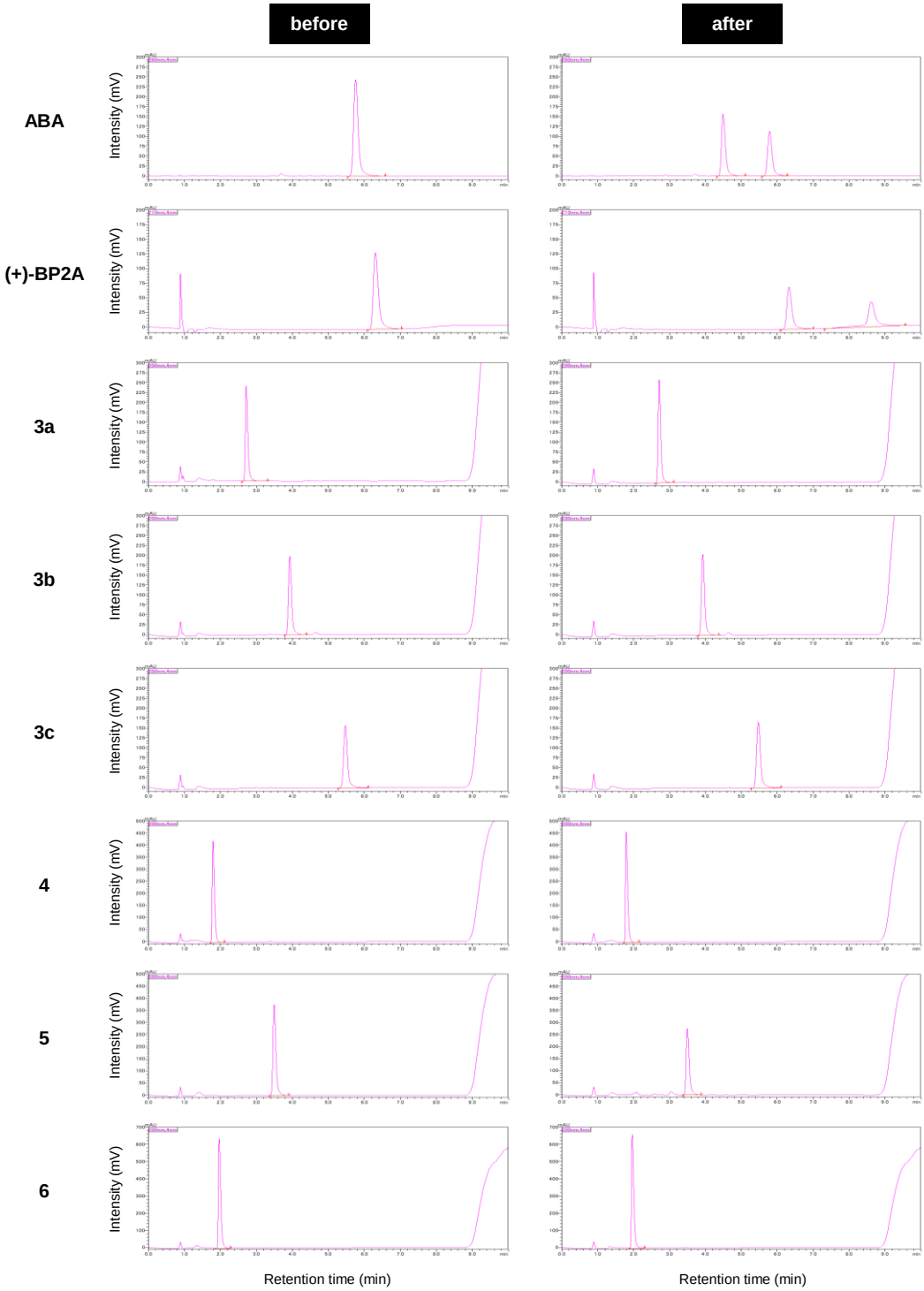


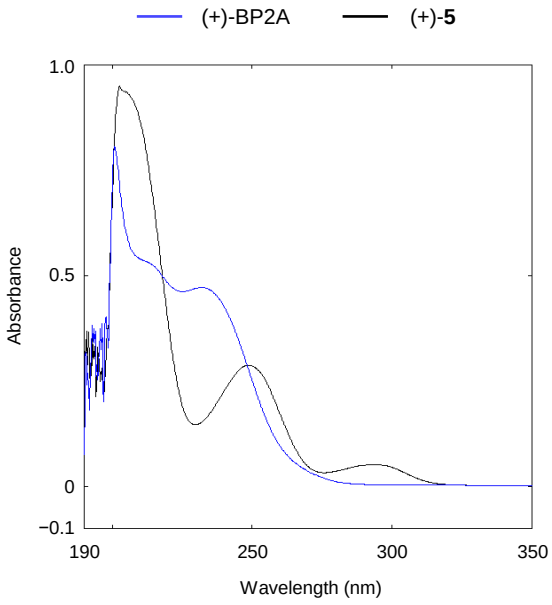
Supplementary Figure 1 *Arabidopsis* seed germination rate in the presence of 0.3 µM (+)-BP2A or Me 1′,4′-*trans*-diol-BP2A and 10 µM Abz-E3M. *n* = 3, error bars represent SDs.



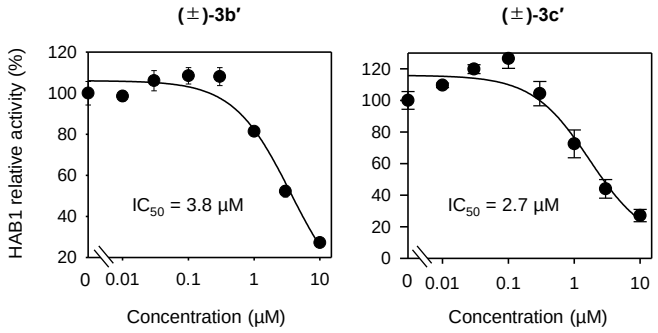
Supplementary Figure 2 Superposition of compound **3a** with ABA in the PYL1-ABA complex (PDB ID: 3JRS). ABA gray sticks and compound 3a purple sticks.



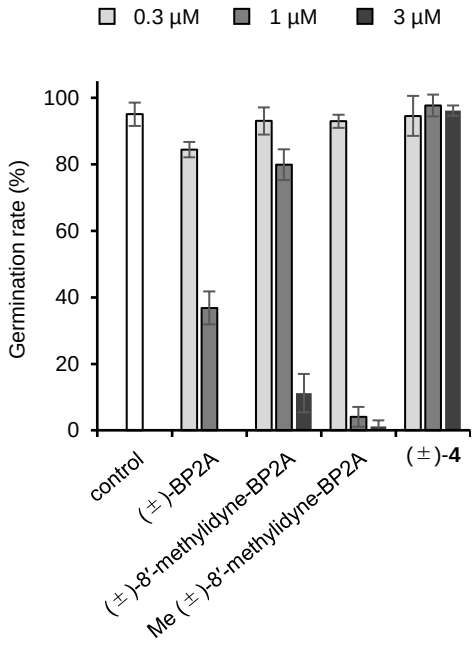
Supplementary Figure 3 Representative HPLC data for sunlight irradiation tests related to Figure 2. The HPLC conditions were as follows: column, Kinetex PS C18 (100 × 4.6 mm, 2.6, μm, Shimadzu GLC Ltd., Tokyo, Japan); solvent, 40% (ABA and BP2A) or 60% (**3a**–**c** and **4**–**6**) MeOH in H_2O containing 0.1% AcOH; flow rate, 1.1 mL min^{-1}; and detection wavelength, 260 (ABA), 210 (BP2A) or 200 (**3a**–**c** and **4**–**6**) nm. The retention times of ABA, (+)-BP2A, **3a**, **3b**, **3c**, **4**, **5** and **6** are 5.8, 6.3, 2.7, 3.9, 5.5, 1.8, 3.5 and 2.0 min, respectively.



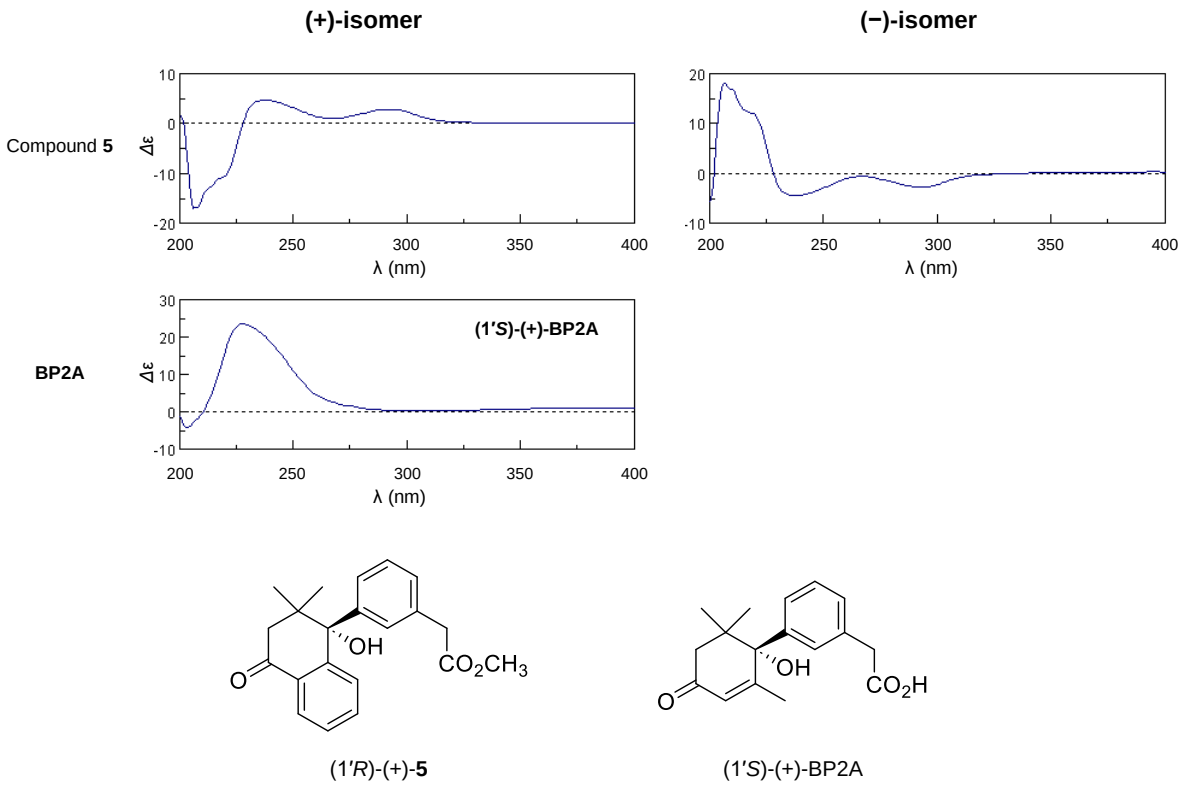
Supplementary Figure 4 UV spectra of (+)-BP2A and (+)-compound **5**.



Supplementary Figure 5 Agonist effects of compounds **3b** and **3c** against *Arabidopsis* ABA receptors, as measured using agonist/receptor-mediated inhibition of HAB1 phosphatase activity. Chemical inhibition of HAB1 by PYL1 in the presence of various concentrations of each test compound. The activity of **3b** and **3c** was measured as the corresponding free carboxylic acids (±)-**3b′** and (±)-**3c′**. The compounds were tested at 0.01, 0.03, 0.1, 0.3, 1, 3 and 10 μM in reactions. The concentration of PYL1 was set at a 2:1 molar ratio to HAB1. The HAB1 phosphatase activity was normalized to a control (DMSO-treated) value of 100% (*n* = 3, error bars represent SDs) and is expressed as relative activity .

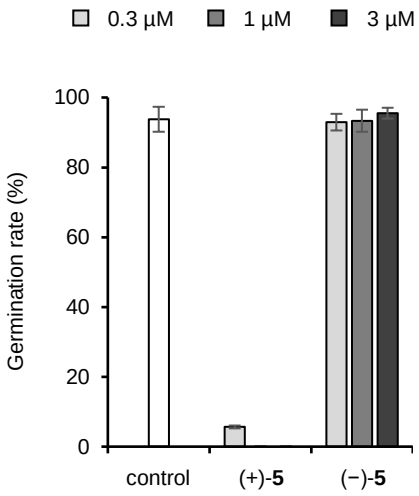


Supplementary Figure 6 Comparison of the activity of (±)-compound **4** and its oxidation form, Me (±)-8′-methylidyne-BP2A and (±)-8′-methylidyne-BP2A. *Arabidopsis* seed germination rate in the presence of 0.3, 1 or 3 μM (±)-4, Me (±)-8′-methylidyne-BP2A and (±)-8′-methylidyne-BP2A at 48 h after stratification (*n* = 3, error bars represent SDs).

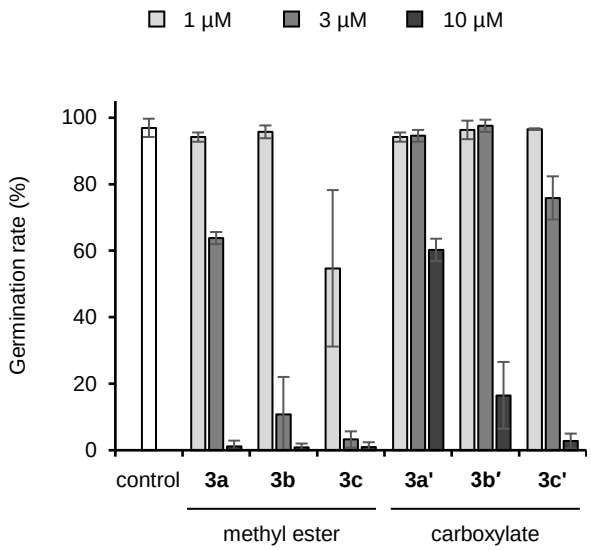


(1′*R*)-(+)-**5** (1′*S*)-(+)-BP2A

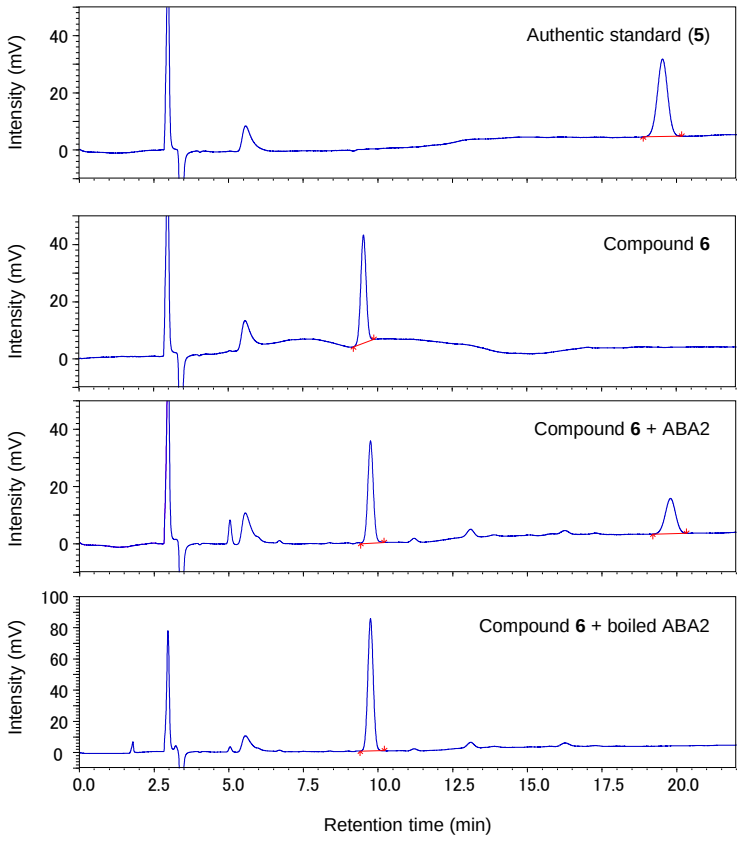
Supplementary Figure 7 Experimental CD spectra of enantiomers of compound **5** and the structures of (1′*R*)-(+)-**5** and (1′*S*)-(+)-BP2A



Supplementary Figure 8 Comparison of the activity of (+)-**5** and its (−)-isomer. *Arabidopsis* seed germination rate in the presence of 0.3, 1 or 3 µM (+)-**5** or (−)-**5** at 60 h after stratification (*n* = 3, error bars represent SDs).



Supplementary Figure 9 Comparison of the activity of **3a–c** to the corresponding free carboxylic acids **3a′–c′**. *Arabidopsis* seed germination rate at 60 h after stratification in the presence of 1, 3 and 10 µM of each compound (*n* = 3, error bars represent SDs).



Supplementary Figure 10 ABA2 metabolized (+)-**6** to (+)-**5** *in vitro*. HPLC conditions were as follows: column: Hydrosphere C18 (150 × 4.6 mm, YMC); solvent: 55% MeOH in water; and detection: 200 nm. The retention times of (+)-**5** and (+)-**6** are 19.5 and 9.6 min.

Experimental

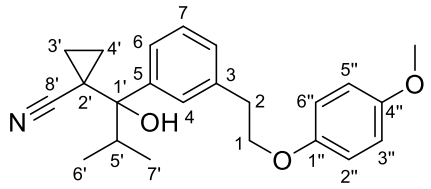
General procedures

ABA was a gift from Dr. Y. Kamuro and Toray Industries Inc., Tokyo, Japan. ^{1}H NMR spectra were recorded with tetramethylsilane as the internal standard using JNM-LA500 (500 MHz) and JNM-ECZ R (500 MHz) NMR spectrometers (JEOL Ltd., Tokyo, Japan). For peak assignments, refer to the numbering of the structures of compounds **10a**, **15** or **22**. High resolution mass spectra were obtained with a JEOL JMS-T100LC AccuTOF mass spectrometer (ESI-TOF, positive mode; JEOL Ltd.). Optical rotations were recorded with a Jasco DIP-1000 digital polarimeter. Circular dichroism spectra were recorded with a Jasco J-820 spectrophotometer. Column chromatography was performed using silica gel (Wakosil C-200, Wako P22ure Chemical Industries, Ltd.).

Synthesis of (±)-BP2A analogs

1-(1-hydroxy-1-(3-(2-(4-methoxyphenoxy)ethyl)phenyl)-2-methylpropyl)cyclopropane-1-carbonitrile (10a)

Bromo-3-(2-(4-methoxyphenoxy)ethyl)benzene (604 mg, 1.97 mmol) in dry THF (6 mL) was cooled to −80 °C under an atmosphere of Ar. *N*, *N*, *N*, *N*-tetramethylenediamine (0.9 mL, 6 mmol) and 1.59 M *n*-Butyllithium (1.9 mL, 3.0 mmol) was then added slowly. After being stirred for 15 min at −80 °C, a solution of **9a**[1] (323 mg, 2.4 mmol) in dry THF (4 mL) was added dropwise to the mixture. The reaction mixture was stirred at 0 °C for 2 h. After quenching with sat. NH_4Cl solution (15 mL), it was extracted with EtOAc (20 mL × 3), washed with brine, and dried over Na_2SO_4, and concentrated *in vacuo*. The residual oil was purified by silica gel chromatography with 15% EtOAc in hexane to obtain **10a** (447 mg, 62%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 0.72 (3H, d, *J*=6.7 Hz, H_3-6′ or 7′), 0.85 (1H, m, H-3′ or 4′), 0.90 (1H, m, H-3′ or 4′), 1.21 (3H, d, *J*=6.7 Hz, H_3-6′ or 7′), 1.23 (1H, m, H-3′ or 4′), 1.52 (1H, m, H-3′ or 4′), 1.54 (1H, s, -O*H*), 2.92 (1H, qq, *J*=6.7 and 6.7 Hz, H-5′), 3.10 (2H, d, *J*=6.1 Hz, H_2-2), 3.76 (3H, s, -O*CH*$_3$), 4.09–4.18 (2H, m, H_2-1), 6.80–6.84 (4H, m, H-2″, 3″, 5″ and 6″), 7.23 (1H, d, *J*=7.6 Hz, H-8), 7.33 (1H, dd, *J*=7.9 and 7.6 Hz, H-7), 7.42 (1H, d, *J*=7.9 Hz, H-6), 7.45 (1H, br s H-4); ^{13}C NMR (126 MHz, $CDCl_3$): δc 9.9, 14.4, 16.6, 17.1, 19.3, 35.1, 36.1, 55.7, 69.4, 75.1, 114.6, 114.6, 115.6, 115.6, 122.9, 123.4, 125.5, 128.0, 128.6, 138.6, 144.7, 152.9, 153.8; HRMS (*m/z*): $[M+Na]^+$ calcd. for $C23H_{27}NO_3Na$, 388.1883; found, 388.1765.



1-(1-hydroxy-1-(3-(2-(4-methoxyphenoxy)ethyl)phenyl)-2,2-dimethylpropyl)cyclopropane-1-carbonitrile (10b)

Bromo-3-(2-(4-methoxyphenoxy)ethyl)benzene (436 mg, 1.4 mmol) in dry THF (5 mL) was cooled to −80 °C under an atmosphere of Ar. *N*, *N*, *N*, *N*-tetramethylenediamine (0.65 mL, 4.4 mmol) and 1.59 M *n*-Butyllithium (1.4 mL, 2.2 mmol) was then added slowly. After being stirred for 15 min at −80 °C, a solution of **9b**[1] (257 mg, 1.7 mmol) in dry THF (3 mL) was added dropwise to the mixture. The reaction mixture was stirred at 0 °C for 2 h. After quenching with sat. NH_4Cl solution (15 mL), it was extracted with EtOAc (20 mL × 3), washed with brine, and dried over Na_2SO_4, and concentrated *in vacuo*. The residual oil was purified by silica gel chromatography with 18% EtOAc in hexane to obtain **10b** (441 mg, 82%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 0.72 (1H, m, H-3′ or 4′), 1.06 (1H, m, H-3′ or 4′), 1.15 (9H, s, H_3-6′, 7′ and 8′), 1.31 (1H, m, H-3′ or 4′), 1.66 (1H, m, H-3′ or 4′), 3.10 (2H, t, *J*=6.7 Hz, H_2-2), 3.76 (3H, s, -O*CH*$_3$), 4.14 (2H, td, *J*=6.7 and 1.2 Hz, H_2-1), 6.82 (4H, m, H-2″, 3″, 5″ and 6″), 7.23 (1H, dt, *J*=7.6 and 1.2 Hz, H-8), 7.31 (1H, td, *J*=7.6 and 1.2 Hz, H-7), 7.66 (2H, m H-4 and 6); ^{13}C NMR (126 MHz, $CDCl_3$): δc 12.6, 15.8, 16.0, 26.6, 26.6, 26.6, 36.1, 40.5, 55.7, 69.3, 78.1, 114.6, 114.6, 115.5, 115.5, 125.1, 126.4, 127.7, 127.7, 128.0, 137.8, 143.7, 152.9, 153.8; HRMS (*m/z*): $[M+Na]^+$ calcd. for $C_{24}H_{29}NO_3Na$, 402.2045; found, 402.2057.

1-(1-hydroxy-1-(3-(2-(4-methoxyphenoxy)ethyl)phenyl)-2,2-dimethylbutyl)cyclopropane-1-carbonitrile (10c)

Bromo-3-(2-(4-methoxyphenoxy)ethyl)benzene (459 mg, 1.5 mmol) in dry THF (5 mL) was cooled to −80 °C under an atmosphere of Ar. *N*, *N*, *N*, *N*-tetramethylenediamine (0.67 mL, 4.5 mmol) and 1.59 M *n*-Butyllithium (1.4 mL, 2.2 mmol) was then added slowly. After being stirred for 15 min at −80 °C, a solution of **9c**[1] (296 mg, 1.8 mmol) in dry THF (3 mL) was added dropwise to the mixture. The reaction mixture was stirred at 0 °C for 2 h. After quenching with sat. NH_4Cl solution (15 mL), it was extracted with EtOAc (20 mL × 3), washed with brine, and dried over Na_2SO_4, and concentrated *in vacuo*. The residual oil was purified by silica gel chromatography with 18% EtOAc in hexane to obtain **10c** (106 mg, 18%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 0.69 (1H, m, H-3′ or H-4′), 0.86 (3H, t, *J*=7.6 Hz, H_3-9′), 1.04 (3H, s, H_3-6′ or 7′), 1.05 (1H, m, H-3′ or H-4′), 1.10 (3H, s, H_3-6′ or 7′), 1.31 (1H, m, H-3′ or H-4′) , 1.54 (1H, m, H-8′), 1.66 (1H, m, H-3′ or H-4′), 1.67 (1H, m, H-8′), 1.78 (1H, d, *J*= 2.4 Hz, -O*H*), 3.10 (2H, t, *J*= 6.7 Hz, H_2-2), 3.75 (3H, s, -O*CH*$_3$), 4.14 (2H, td, *J*=6.7 and 1.2 Hz, H_2-1), 6.82 (4H, m, H-2", 3", 5" and 6"), 7.22 (1H, d, *J*= 7.6 Hz, H-8), 7.31 (1H, t, *J*=7.6 Hz, H-7), 7.64 (1H, s, H-4), 7.65 (1H, d, *J*=7.6 Hz, H-6); ^{13}C NMR (126 MHz, $CDCl_3$): δc 8.7, 12.8, 15.9, 16.3, 21.8, 21.9, 29.3, 36.1, 43.2, 55.7, 69.2, 79.0, 114.6, 114.6, 115.5, 115.5, 125.3, 126.4, 127.6, 127.9, 127.9, 137.7, 143.8, 152.9, 153.8; HRMS (*m/z*): $[M+Na]^+$ calcd. for $C_{25}H_{31}NO_3Na$, 416.2202; found, 416.2223.

1-(1-hydroxy-1-(3-(2-hydroxyethyl)phenyl)-2-methylpropyl)cyclopropane-1-carbonitrile (11a)

To a stirred solution of **10a** (110 mg, 0.3 mmol) in THF (1 mL) was cooled to 0 °C and added an aqueous solution of ammonium cerium nitrate (165 mg, 0.3 mmol). The reaction mixture was stirred for 30 min

at room temperature, and then added water (10 mL) and extracted with EtOAc (15 mL × 3). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residual oil was purified by silica gel chromatography with 40% EtOAc in hexane to obtain **11a** (77.5 mg, 99%) as a brown oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 0.72 (3H, d, *J*=6.7 Hz, H_3-6′ or 7′), 0.85 (1H, m, H-3′ or 4′), 0.92 (1H, m, H-3′ or 4′), 1.21 (3H, d, *J*=6.7 Hz, H_3-6′ or 7′), 1.24 (1H, m, H-3′ or 4′), 1.53 (1H, m, H-3′ or 4′), 1.61 (1H, s, -O*H*), 2.90 (2H, d, *J*=6.1 Hz, H_2-2), 2.94 (1H, qq, *J*=6.7 and 6.7 Hz, H-5′), 3.88 (2H, m, H_2-1), 7.17 (1H, ddd, *J*=7.6, 1.2 and 1.2 Hz, H-8), 7.33 (1H, ddd, *J*=7.6, 7.6 and 1.2 Hz, H-7), 7.42 (1H, br s, H-4), 7.43 (1H, ddd, *J*=7.6, 1.2 and 1.2 Hz, H-6); ^{13}C NMR (126 MHz, $CDCl_3$): δc 9.8, 14.3, 16.6, 17.1, 19.3, 35.0, 39.4, 63.6, 75.1, 123.0, 123.4, 125.5, 128.1, 128.7, 138.7, 144.8; HRMS (*m/z*): $[M+Na]^+$ calcd. for $C_{16}H_{21}NO_2Na$, 282.1470; found, 282.1479.

1-(1-hydroxy-1-(3-(2-hydroxyethyl)phenyl)-2,2-dimethylpropyl)cyclopropane-1-carbonitrile (11b)
To a stirred solution of **10b** (166 mg, 0.44 mmol) in THF (1 mL) was cooled to 0 °C and added an aqueous solution of ammonium cerium nitrate (598 mg, 1.1 mmol). The reaction mixture was stirred for 1 h at room temperature, and then added water (20 mL) and extracted with EtOAc (15 mL × 3). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residual oil was purified by silica gel chromatography with 40% EtOAc in hexane to obtain **11b** (134 mg, quantitative yield) as a brown oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 0.74 (1H, m, H-3′ or 4′), 1.06 (1H, m, H-3′ or 4′), 1.15 (9H, s, H_3-6′, 7′ and 8′), 1.30 (1H, m, H-3′ or 4′), 1.66 (1H, m, H-3′ or 4′), 1.90 (1H, s, -O*H*), 2.90 (2H, d, *J*=6.4 Hz, H_2-2), 2.94 (1H, qq, *J*=6.7 and 6.7 Hz, H-5′), 3.88 (2H, m, H_2-1), 7.17 (1H, ddd, *J*=7.6, 1.2 and 1.2 Hz, H-8), 7.32 (1H, dd, *J*=7.6 and 7.6 Hz, H-7), 7.59 (1H, br s, H-4), 7.67 (1H, ddd, *J*=7.6, 1.2 and 1.2 Hz, H-6); ^{13}C NMR (126 MHz, $CDCl_3$): δc 12.6, 15.8, 16.0, 26.6, 26.6, 26.6, 39.3, 40.5, 63.6, 78.1, 125.2, 126.4, 127.6, 127.8, 128.0, 137.8, 143.9; HRMS (*m/z*): $[M+Na]^+$ calcd. for $C_{17}H_{23}NO_2Na$, 296.1626; found, 296.1598.

1-(1-hydroxy-1-(3-(2-hydroxyethyl)phenyl)-2,2-dimethylbutyl)cyclopropane-1-carbonitrile (11c)
To a stirred solution of **10c** (89.6 mg, 0.23 mmol) in THF (1 mL) was cooled to 0 °C and added an aqueous solution of ammonium cerium nitrate (313 mg, 0.57 mmol). The reaction mixture was stirred for 1.5 h at room temperature, and then added water (10 mL) and extracted with EtOAc (15 mL × 3). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residual oil was purified by silica gel chromatography with 40% EtOAc in hexane to obtain **11c** (36.2 mg, 55%) as a brown oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 0.70 (1H, m, H-3′ or H-4′), 0.87 (3H, t, *J*=7.6 Hz, H_3-9′), 1.04 (3H, s, H_3-6′ or 7′), 1.06 (1H, m, H-3′ or H-4′), 1.10 (3H, s, H_3-6′ or 7′), 1.31 (1H, m, H-3′ or H-4′) , 1.55 (1H, m, H-8′), 1.66 (1H, m, H-3′ or H-4′), 1.67 (1H, m, H-8′), 1.84 (1H, s, -O*H*), 2.91 (2H, t, *J*= 6.4 Hz, H_2-2), 3.88 (2H, m, H_2-1), 7.17 (1H, d, *J*= 7.6 Hz, H-8), 7.32 (1H, dd, *J*=7.6 and 7.6 Hz, H-7), 7.59 (1H, br s, H-4), 7.67 (1H, ddd, *J*=7.6, 1.2 and 1.2 Hz, H-6); ^{13}C NMR (126 MHz, $CDCl_3$): δc 8.7, 12.8, 15.9,

16.3, 21.8, 21.9, 29.3, 39.3, 43.2, 63.7, 78.9, 125.4, 125.6, 127.7, 127.8, 127.9, 137.7, 144.1; HRMS (*m/z*): $[M+Na]^+$ calcd. for $C_{18}H_{25}NO_2Na$, 310.1783; found, 310.1766.

2-(3-(1-(1-cyanocyclopropyl)-1-hydroxy-2-methylpropyl)phenyl)acetic acid (12a)

To a two-phase mixture of **11a** (28 mg, 0.11 mmol) in CH_2Cl_2 (0.5 mL) and 1.0 M sodium acetate buffer (pH 4.0, 0.5 mL) was added $NaClO_2$ (37 mg, 0.33 mmol) and catalytic amount of AZADOL® (0.9 mg, 6 μmol), and the mixture was stirred for 3 h at room temperature. Then the reaction mixture was added 2-methyl-2-butene (3 drops). The pH of the mixture was adjusted to 9 using sat. $NaHCO_3$ solution, it was washed with EtOAc. The aqueous phase was then acidified with 1 M HCl and extracted with EtOAc (15 mL × 3). The organic phase was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residual solid was purified by silica gel chromatography with 50% EtOAc in hexane containing 0.1 % AcOH to obtain **12a** (20.7 mg, 70 %) as a white solid ^1H NMR (500 MHz, CD_3OD): δ_H 0.73 (3H, d, *J*=6.7 Hz, H_3-6′ or 7′), 0.78 (1H, m, H-3′ or 4′), 0.91 (1H, m, H-3′ or 4′), 1.17 (1H, m, H-3′ or 4′), 1.20 (3H, d, *J*=6.7 Hz, H_3-6′ or 7′), 1.59 (1H, m, H-3′ or 4′), 2.81 (1H, qq, *J*=6.7 and 6.7 Hz, H-5′), 3.61 (2H, s, H_2-2), 7.21 (1H, d, *J*=7.6 Hz, H-8), 7.32 (1H, dd, *J*=7.6 and 7.6 Hz, H-7), 7.48 (1H, d, *J*=7.6 Hz, H-6), 7.50 (1H, br s, H-4); ^{13}C NMR (126 MHz, CD_3OD): δc 10.5, 15.1, 17.1, 17.5, 20.4, 36.8, 42.3, 75.9, 124.9, 125.1, 127.5, 129.1, 129.2, 135.9, 147.1, 175.7; HRMS (*m/z*): $[M+Na]^+$ calcd. for $C_{16}H_{19}NO_3Na$, 296.1263; found, 296.1288.

2-(3-(1-(1-cyanocyclopropyl)-1-hydroxy-2,2-dimethylpropyl)phenyl)acetic acid (12b)

To a two-phase mixture of **11b** (122 mg, 0.45 mmol) in CH_2Cl_2 (1 mL) and 1.0 M sodium acetate buffer (pH 4.0, 1 mL) was added $NaClO_2$ (153 mg, 1.34 mmol) and catalytic amount of AZADOL® (3.5 mg, 22 μmol), and the mixture was stirred for 3 h at room temperature. Then the reaction mixture was added 2-methyl-2-butene (5 drops). The pH of the mixture was adjusted to 9 using sat. $NaHCO_3$ solution, it was washed with EtOAc. The aqueous phase was then acidified with 1 M HCl and extracted with EtOAc (15 mL × 3). The organic phase was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residual solid was purified by silica gel chromatography with 50% EtOAc in hexane containing 0.1 % AcOH to obtain **12b** (81 mg, 63 %) as a white solid ^1H NMR (500 MHz, CD_3OD): δ_H 0.83 (1H, m, H-3′ or 4′), 0.99 (1H, m, H-3′ or 4′), 1.11 (9H, s, H_3-6′, 7′ and 8′), 1.22 (1H, m, H-3′ or 4′), 1.71 (1H, m, H-3′ or 4′), 3.62 (2H, s, H_2-2), 7.21 (1H, d, *J*=7.6 Hz, H-8), 7.29 (1H, dd, *J*=7.6 and 7.6 Hz, H-7), 7.67 (1H, dd, *J*=1.2 and 1.2 Hz, H-4), 7.71 (1H, ddd, *J*=7.6, 1.2 and 1.2 Hz, H-6); ^{13}C NMR (126 MHz, CD_3OD): δc 13.1, 16.6, 16.9, 27.2, 27.2, 27.2, 41.4, 42.2, 79.3, 127.2, 128.2, 128.3, 129.1, 129.8, 135.0, 146.0, 175.6; HRMS (*m/z*): $[M+Na]^+$ calcd. for $C_{17}H_{21}NO_3Na$, 310.1419; found, 310.1444.

2-(3-(1-(1-cyanocyclopropyl)-1-hydroxy-2,2-dimethylbutyl)phenyl)acetic acid (12c)

To a two-phase mixture of **11c** (32 mg, 0.11 mmol) in CH_2Cl_2 (0.5 mL) and 1.0 M sodium acetate buffer

(pH 4.0, 0.5 mL) was added $NaClO_2$ (38 mg, 0.34 mmol) and catalytic amount of AZADOL® (0.9 mg, 6 μmol), and the mixture was stirred for 2 h at room temperature. Then the reaction mixture was added 2-methyl-2-butene (3 drops). The pH of the mixture was adjusted to 9 using sat. $NaHCO_3$ solution, it was washed with EtOAc. The aqueous phase was then acidified with 1 M HCl and extracted with EtOAc (15 mL × 3). The organic phase was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residual solid was purified by silica gel chromatography with 45% EtOAc in hexane containing 0.1 % AcOH to obtain **12c** (24 mg, 72 %) as a white solid ^{1}H NMR (500 MHz, CD_3OD): δ_H 0.76 (1H, m, H-3′ or H-4′), 0.79 (3H, t, *J*=7.6 Hz, H_3-9′), 0.94 (1H, m, H-3′ or H-4′), 0.97 (3H, s, H_3-6′ or 7′), 1.02 (3H, s, H_3-6′ or 7′), 1.18 (1H, m, H-3′ or H-4′), 1.48 (1H, m, H-8′), 1.69 (1H, m, H-3′ or H-4′), 1.71 (1H, m, H-8′), 3.58 (2H, br s, H_2-2), 7.16 (1H, d, *J*= 7.6 Hz, H-8), 7.25 (1H, dd, *J*=7.6 and 7.6 Hz, H-7), 7.62 (1H, s, H-4), 7.65 (1H, d, *J*=7.6 Hz, H-6); ^{13}C NMR (126 MHz, CD_3OD): δc 9.0, 13.2, 16.9, 16.9, 22.3, 22.4, 30.3, 42.3, 44.1, 80.2, 127.4, 128.2, 128.3, 1290., 130.0, 135.1, 146.1, 175.8; HRMS (*m/z*): $[M+Na]^+$ calcd. for $C_{18}H_{23}NO_3Na$, 324.1576; found, 324.1566.

methyl 2-(3-(1-(1-cyanocyclopropyl)-1-hydroxy-2-methylpropyl)phenyl)acetate (3a)

To a stirred solution of **12a** (18 mg, 0.065 mmol) in THF (0.6 mL) was cooled to 0 °C and added DMF (4 drops) and oxalyl chloride (15 μL, 0.17 mmol). The reaction mixture was stirred for 1.5 h at room temperature, then MeOH (0.5 mL) was added and the mixture was stirred for 15 min. The pH of the mixture was adjusted to 9 using sat. $NaHCO_3$ solution, it was extracted with EtOAc (10 mL × 3). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residual oil was purified by silica gel chromatography with 20% EtOAc in hexane to obtain **3a** (13.2 mg, 71%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 0.73 (3H, d, *J*=6.7 Hz, H_3-6′ or 7′), 0.86 (1H, m, H-3′ or 4′), 0.91 (1H, m, H-3′ or 4′), 1.21 (3H, d, *J*=6.7 Hz, H_3-6′ or 7′), 1.24 (1H, m, H-3′ or 4′), 1.53 (1H, m, H-3′ or 4′), 1.61 (1H, s, -O*H*), 2.92 (1H, qq, *J*=6.7 and 6.7 Hz, H-5′), 3.66 (2H, s, H_2-2), 3.70 (3H, s, -O*CH₃*), 7.23 (1H, d, *J*=7.6 Hz, H-8), 7.35 (1H, dd, *J*=7.6 and 7.6 Hz, H-7), 7.45 (1H, br s, H-4), 7.48 (1H, d, *J*=7.6 Hz, H-6); HRMS (*m/z*): $[M+Na]^+$ calcd. for $C_{17}H_{21}NO_3Na$, 310.1419; found, 310.1427

methyl 2-(3-(1-(1-cyanocyclopropyl)-1-hydroxy-2,2-dimethylpropyl)phenyl)acetate (3b)

To a stirred solution of **12b** (27 mg, 0.093 mmol) in THF (0.7 mL) was cooled to 0 °C and added DMF (5 drops) and oxalyl chloride (20 μL, 0.23 mmol). The reaction mixture was stirred for 40 min at room temperature, then MeOH (1 mL) was added and the mixture was stirred for 15 min. The pH of the mixture was adjusted to 9 using sat. $NaHCO_3$ solution, it was extracted with EtOAc (10 mL × 3). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residual oil was purified by silica gel chromatography with 40% EtOAc in hexane to obtain **3b** (16.7 mg, 59%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 0.73 (1H, m, H-3′ or 4′), 1.07 (1H, m, H-3′ or 4′), 1.15 (9H, s, H_3-6′, 7′ and 8′), 1.31 (1H, m, H-3′ or 4′), 1.65 (1H, m, H-3′ or 4′), 1.86 (1H, s, -O*H*), 3.64 (2H, s, H_2-2), 3.70 (3H,

s, -O*CH*$_3$), 7.22 (1H, d, *J*=7.6 Hz, H-8), 7.33 (1H, dd, *J*=7.6 and 7.6 Hz, H-7), 7.63 (1H, br s, H-4), 7.72 (1H, d, *J*=7.6 Hz, H-6); HRMS (*m/z*): $[M+Na]^+$ calcd. for $C_{18}H_{23}NO_3Na$, 324.1576; found, 324.1586.

methyl 2-(3-(1-(1-cyanocyclopropyl)-1-hydroxy-2,2-dimethylbutyl)phenyl)acetate (3c)

To a stirred solution of **12c** (21 mg, 0.069 mmol) in THF (0.5 mL) was cooled to 0 °C and added DMF (5 drops) and oxalyl chloride (15 µL, 0.17 mmol). The reaction mixture was stirred for 1.5 h at room temperature, then MeOH (1 mL) was added and the mixture was stirred for 15 min. The pH of the mixture was adjusted to 9 using sat. $NaHCO_3$ solution, it was extracted with EtOAc (10 mL × 3). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residual oil was purified by silica gel chromatography with 25% EtOAc in hexane to obtain **3c** (14.9 mg, 69%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 0.71 (1H, m, H-3′ or H-4′), 0.87 (3H, t, *J*=7.6 Hz, H_3-9′), 1.04 (3H, s, H_3-6′ or 7′), 1.06 (1H, m, H-3′ or H-4′), 1.10 (3H, s, H_3-6′ or 7′), 1.31 (1H, m, H-3′ or H-4′), 1.54 (1H, m, H-8′), 1.65 (1H, m, H-3′ or H-4′), 1.67 (1H, m, H-8′), 1.86 (1H, s, -O*H*), 3.67 (2H, br s, H_2-2), 3.70 (3H, s, -O*CH*$_3$), 7.22 (1H, d, *J*= 7.6 Hz, H-8), 7.32 (1H, dd, *J*=7.6 and 7.6 Hz, H-7), 7.62 (1H, br s, H-4), 7.71 (1H, d, *J*=7.6 Hz, H-6); HRMS (*m/z*): $[M+Na]^+$ calcd. for $C_{19}H_{25}NO_3Na$, 338.1732; found, 338.1722.

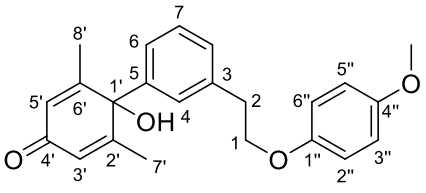
7,9-dimethyl-1,4-dioxaspiro[4.5]deca-6,9-dien-8-one (14)

To a stirred solution of iodobenzene diacetate **13** (16.7 g, 49.1 mmol) in hexane (80 mL) was cooled to 0 °C and added dimethyl phenol (3.0 g, 24.6 mmol) and ethylene glycol (14.0 mL, 246 mmol). The reaction mixture was stirred for 1 h at room temperature, and then added water (80 mL) and extracted with EtOAc (100 mL × 3). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residual oil was purified by silica gel chromatography with 15% EtOAc in hexane to obtain **14** (902 mg, 20%) as a yellow oil. Compound **14** is known, and its spectroscopic data are virtually identical with the reported literature values[2].

1-hydroxy-3'-(2-(4-methoxyphenoxy)ethyl)-2,6-dimethyl-[1,1'-biphenyl]-4(1H)-one (15)

Bromo-3-(2-(4-methoxyphenoxy)ethyl)benzene (1.10 g, 3.6 mmol) in dry THF (5 mL) was cooled to −78 °C under an atmosphere of Ar. *N*, *N*, *N*, *N*-tetramethylenediamine (0.95 mL, 6.1 mmol) and *n*-Butyllithium (3.9 mL, 6.1 mmol) was then added slowly. After being stirred for 15 min at −78 °C, a solution of **14** (902 mg, 5.0 mmol) in dry THF (2.5 mL) was added dropwise to the mixture. The reaction mixture was stirred at 0 °C for 1 h. After quenching with sat. NH_4Cl solution (10 mL), it was extracted with EtOAc (20 mL × 3), washed with brine, and dried over Na_2SO_4, and concentrated *in vacuo*. The residual oil was purified by silica gel chromatography with 35% EtOAc in hexane to obtain **15** and its acetal-protected compound, which was deprotected by 1 M HCl to yield compound **15** (total 1.06 g, 81%) as a pale-yellow oil. ^{1}H NMR (500 MHz, CD_3OD): δ_H 1.74 (3H, s, H_3-7′ or 8′), 1.75 (3H, s, H_3-7′ or 8′),

3.00 (2H, t, *J*=6.3 Hz, H_2-2), 3.71 (3H, s, -O*CH*$_3$), 4.09 (2H, t, *J*=6.3 Hz, H_2-1), 6.05 (2H, br s, H-3′ and 5′), 6.76–6.80 (4H, m, H-2″, 3″, 5″ and 6″), 7.20–7.32 (4H, m, H-4, 6, 7 and 8); ^{13}C NMR (126 MHz, CD_3OD): δc 18.7, 18.7, 36.8, 56.1, 70.3, 76.3, 115.6, 115.6, 116.6, 116.6, 124.3, 125.8, 125.8, 127.0, 129.4, 129.6, 140.7, 140.9, 154.3, 155.4, 166.5, 166.5, 188.9; HRMS (*m/z*): $[M+Na]^+$ calcd. for $C_{23}H_{24}O_4Na$, 387.1572; found, 387.1570.



1-hydroxy-3'-(2-hydroxyethyl)-2,6-dimethyl-[1,1'-biphenyl]-4(1H)-one (16)

To a stirred solution of **15** (1.06 g, 2.9 mmol) in THF (6 mL) was cooled to 0 °C and added an aqueous solution of ammonium cerium nitrate (4.0 g, 7.3 mmol). The reaction mixture was stirred for 1 h at room temperature, and then added water (10 mL) and extracted with EtOAc (30 mL × 3). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residual oil was purified by silica gel chromatography with 40% EtOAc in hexane to obtain **16** (340 mg, 45%) as a brown oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 1.77 (6H, s, H_3-7′ and H_3-8′), 2.81 (2H, t, *J*=6.9 Hz, H_2-2), 3.72 (2H, t, *J*=6.9 Hz, H_2-1), 6.06 (2H, s, H-3′ and 5′), 7.17 (1H, m, H-6 or 8), 7.22 (1H, m, H-6 or 8), 7.27 (1H, dd, *J*=7.5 and 7.5 Hz, H-7), 7.28 (1H, br s, H-4); ^{13}C NMR (126 Hz, CD_3OD): δc 18.6, 18.6, 40.3, 64.1, 76.3, 124.1, 125.8, 125.8, 126.8, 129.4, 129.6, 140.9, 140.9, 166.5, 166.5, 188.9; HRMS (*m/z*): $[M+Na]^+$ calcd. for $C_{16}H_{18}O_3Na$, 281.1154; found, 281.1154.

2-(1'-hydroxy-2',6'-dimethyl-4'-oxo-1',4'-dihydro-[1,1'-biphenyl]-3-yl)acetic acid (17)

To a two-phase mixture of **16** (366 mg, 1.62 mmol) in THF (8 mL) and 1.0 M sodium acetate buffer (pH 4.0, 8 mL) was added $NaClO_2$ (984 mg, 807 mmol) and catalytic amount of AZADOL® (9.1 mg, 0.059 mmol), and the mixture was stirred for 5 h at room temperature. Then the reaction mixture was added 2-methyl-2-butene (1.1 mL). The pH of the mixture was adjusted to 9 using sat. $NaHCO_3$ solution, it was washed with EtOAc. The aqueous phase was then acidified with 1 M HCl and extracted with EtOAc (20 mL × 3). The organic phase was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residual solid was purified by silica gel chromatography with 70% EtOAc in hexane containing 0.1 % AcOH to obtain **17** (331 mg, 86 %) as a white solid ^{1}H NMR (500 MHz, CD_3OD): δ_H 1.77 (6H, s, H_3-7′ and 8′), 3.60 (2H, s, H_2-2), 7.22 (1H, ddd, *J*=7.5, 1.7 and 1.7 Hz, H-6 or 8), 7.27 (1H, d, *J*=7.5 Hz, H-6 or 8), 7.31 (1H, dd, *J*=7.5 and 7.5 Hz, H-7), 7.36 (1H, br s, H-4); ^{13}C NMR (126 MHz, CD_3OD): δc 18.6, 18.6, 42.0, 76.2, 124.9, 125.9, 125.9, 127.3, 129.7, 129.8, 136.6, 141.2, 166.4, 166.4, 175.4, 188.9; HRMS (*m/z*): $[M+Na]^+$ calcd. for $C_{16}H_{14}O_4Na$, 295.0946; found, 295.0952.

methyl 2-(1'-hydroxy-2',6'-dimethyl-4'-oxo-1',4'-dihydro-[1,1'-biphenyl]-3-yl)acetate (18)

To a stirred solution of **17** (331 mg, 1.22 mmol) in THF (11 mL) was cooled to 0 °C and added DMF (10 drops) and oxalyl chloride (1.1 mL, 12.6 mmol). The reaction mixture was stirred for 60 min at room temperature, then MeOH (10 mL) was added and the mixture was stirred for 10 min. The pH of the mixture was adjusted to 9 using sat. $NaHCO_3$ solution, it was extracted with EtOAc (20 mL × 3). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residual oil was purified by silica gel chromatography with 45% EtOAc in hexane to obtain **18** (281 mg, 81%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 1.78 (6H, s, H_3-7′ and 8′), 3.63 (2H, s, H_2-2), 3.69 (3H, s, -O*CH*$_3$), 7.22 (1H, m, H-6 or 8), 7.26 (1H, m, H-6 or 8), 7.31 (1H, dd, *J*=7.5 and 7.5 Hz, H-7), 7.31 (1H, br s, H-4); ^{13}C NMR (126 MHz, $CDCl_3$): δc 18.3, 18.3, 41.0, 52.1, 75.3, 123.8, 125.9, 125.9, 126.1, 128.7, 128.8, 134.4, 139.2, 161.8, 161.8, 171.8, 186.5. HRMS (*m/z*): $[M+Na]^+$ calcd. for $C_{17}H_{18}O_4Na$, 309.1103; found, 309.0859.

methyl 2-((1'*S,2'*R**)-2'-ethynyl-1'-hydroxy-2',6'-dimethyl-4'-oxo-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-3-yl)acetate (19)**

To a stirred solution of 0.5 M ethylmagnesium chloride in THF (10 mL, 5.0 mmol) was cooled to 0 °C and a solution of compound **18** (142 mg, 0.5 mmol) in THF (3 mL) was added slowly. The reaction mixture was stirred at 0 °C for 4 h. After quenching with water (3mL), it was filtered over a bed of Celite® Evaporation of the solvent in vacuo and residual oil was purified by silica gel chromatography with 25% EtOAc in hexane to obtain **19** (47.8 mg, 30%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 1.04 (3H, s, H_3-9′), 1.89 (3H, d, *J*=1.7 Hz, H_3-7′), 2.36 (1H, s, H-10′), 2.45 (1H, d, *J*=16.7 Hz, H-5′), 2.54 (1H, dd, *J*=16.7 and 1.7 Hz, H-5′), 3.04 (1H, s, -O*H*), 3.65 (2H, s, H^2-2), 3.69 (3H, s, -O*CH*$_3$), 6.21 (1H, dq, *J*=1.7 and 1.7 Hz, H-3′), 7.26–7.43 (4H, m, H-4, 6, 7 and 8); ^{13}C NMR (126 MHz, $CDCl_3$): δc 19.6, 23.5, 41.1, 44.4, 47.3, 52.1, 73.6, 79.3, 86.8, 125.9, 128.3, 128.4, 128.6, 129.4, 134.1, 135.6, 163.1, 171.8, 196.3. HRMS $[M+Na]^+$ calcd. for $C_{19}H_{20}O_4Na$, 335.1259; found, 335.1065.

methyl 2-((1'*S,2'*R**,4′*S**)-2'-ethynyl-1',4'-dihydroxy-2',6'-dimethyl-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-3-yl)acetate (4)**

To a stirred solution of **4** (26.6 mg, 0.085 mmol) in MeOH (0.8 mL) was cooled to 0 °C and added cerium (III) chloride heptahydrate (90 mg, 0.24 mmol) and $NaHB_4$ (8 mg, 0.21 mmol). The reaction mixture was stirred for 30 min at 0 °C, and then quenched with sat. NH_4Cl solution and extracted with EtOAc (10 mL × 3). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residual oil was purified by silica gel chromatography with 40% EtOAc in hexane. A portion of the diastereomeric mixture containing Me 8′-methylidyne-1′,4′-diol-BP2A (14.6 mg, colorless oil) was chromatographed on Luna® PFP (2) ODS HPLC column (150×21.2 mm, Phenomenex) and eluted under

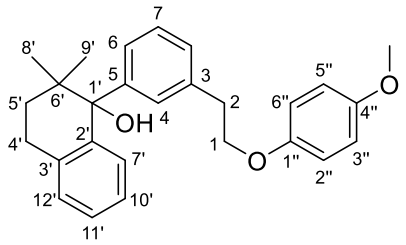
isocratic conditions using 50% MeCN in water at a flow rate of 8.5 mL min^{-1}. The material at t_R 20.2 min were collected to give compound **4** (8.5 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 0.92 (3H, s, H_3-9′), 1.61 (3H, s, H_3-7′), 1.61 (1H, dd, *J*=13.2 and 10.9 Hz, H-5′), 2.05 (1H, ddd, *J*=13.2, 6.3 and 1.7 Hz, H-5′), 2.28 (1H, s, H-10′), 2.79 (1H, s, -O*H*), 3.63 (2H, s, H_2-2), 3.68 (3H, s, -OCH_3), 4.66 (1H, m, H-4′), 5.83 (1H, m, H-3′), 7.19 (1H, dd, *J*=7.5 Hz, H-6 or 8), 7.29 (1H, dd, *J*=7.5 and 7.5 Hz, H-7), 7.37–7.65 (2H, m, H-4 and H-6 or 8); ^{13}C NMR (126 MHz, $CDCl_3$): δ_C 18.6, 24.5, 40.8, 41.0, 42.9, 52.1, 65.9, 71.9, 79.0, 87.6, 126.8, 127.7, 128.4, 129.0, 129.1, 133.1, 138.7, 139.3, 172.2; HRMS (*m/z*): $[M+Na]^+$ calcd. for $C_{19}H_{22}O_4Na$, 337.1410; found, 337.1243.

2,2-dimethyl-3,4-dihydronaphthalen-1(2*H*)-one (21)

To a suspension of NaH (3.0 g, 75 mmol) in dry THF (40 mL) was added 6-methoxy-1-tetralone **20** (2.0 g, 14 mmol) dissolved in THF (30 mL). After stirring the mixture for 10 min at room temperature, methyl iodide (2.6 mL, 41 mmol) was added to the mixture. The mixture was stirred for 1.5 h at 40 °C. After quenching with water, it was then extracted with EtOAc (15 mL × 3), washed with brine, and dried over Na_2SO_4, and concentrated *in vacuo*. The residual oil was purified by silica gel chromatography with 2% EtOAc in hexane to obtain **21** (2.34 g, 98%) as a colorless oil. Compound **21** is known, and its spectroscopic data are virtually identical with the reported literature values[3].

1-(3-(2-(4-methoxyphenoxy)ethyl)phenyl)-2,2-dimethyl-1,2,3,4-tetrahydronaphthalen-1-ol (22)

1-Bromo-3-(2-(4-methoxyphenoxy)ethyl)benzene (1.91 g, 6.2 mmol) in dry THF (18 mL) was cooled to −78 °C under an atmosphere of Ar. *N*, *N*, *N*, *N*-tetramethylenediamine (1.6 mL, 11 mmol) and *n*-Butyllithium (8.0 mL, 13 mmol) was then added slowly. After being stirred for 15 min at −78 °C, a solution of **21** (1.52 g, 8.7 mmol) in dry THF (16 mL) was added dropwise to the mixture. The reaction mixture was stirred at 0 °C for 1 h. After quenching with sat. NH_4Cl solution (40 mL), it was extracted with EtOAc (30 mL × 3). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residual oil was purified by silica gel chromatography with 13% EtOAc in hexane to obtain **22** (1.8 g, 72%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 0.78 (3H, s, H_3-8′ or 9′), 1.03 (3H, s, H_3-8′ or 9′), 1.71 (1H, m, H-5′), 1.79 (1H, m, H-5′), 2.02 (1H, s, -OH), 2.94 (2H, t, *J*=6.9 and 6.9 Hz, H-4′). 3.04 (2H, t, *J*=6.9 and 6.9 Hz, H-2), 3.75 (3H, s, -OCH_3), 4.07 (2H, m, H-1), 6.77–6.81 (4H, m, H-2″, 3″, 5″ and 6″), 7.04–7.25 (8H, m, H-4, 6, 7, 8, 7′, 10′, 11′ and 12′); ^{13}C NMR (126 MHz, $CDCl_3$): δ_C 23.4, 25.0, 26.1, 33.0, 36.0, 37.2, 55.7, 69.5, 80.1, 114.6, 114.6, 115.5, 115.5, 115.5, 126.4, 126.6, 127.0, 127.1, 127.1, 128.5, 128.8, 129.5, 136.5, 142.8, 144.8, 153.0, 153.8; HRMS (*m/z*): $[M+Na]^+$ calcd. for $C_{27}H_{30}O_3Na$, 425.2087; found, 425.2011.



1-(3-(2-hydroxyethyl)phenyl)-2,2-dimethyl-1,2,3,4-tetrahydronaphthalen-1-ol (23)

To a stirred solution of **22** (2.0 g, 4.5 mmol) in THF (10 mL) was cooled to 0 °C and added an aqueous solution of ammonium cerium nitrate (6.81 g, 12.4 mmol). The reaction mixture was stirred for 1 h at room temperature, and then added water (20 mL) and extracted with EtOAc (30 mL × 3). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residual oil was purified by silica gel chromatography with 40% EtOAc in hexane to obtain **23** (656 mg, 45%) as a brown oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 0.78 (3H, s, H_3-8′ or 9′), 1.03 (3H, s, H_3-8′ or 9′), 1.71 (1H, dt, *J*=13.8 and 6.9 Hz, H-5′), 1.80 (1H, dt, *J*=13.8 and 6.9 Hz, H-5′), 2.04 (1H, s, -OH), 2.83 (2H, t, *J*=6.9 Hz, H-4′), 2.95 (2H, td, *J*=6.9 and 1.7 Hz, H_2-2), 3.80 (2H, t, *J*=6.9 Hz, H_2-1), 7.02–7.21 (8H, m, H-4, 6, 7, 8, 7′, 10′, 11′ and 12′): δ_C 23.4, 25.1, 26.1, 33.0, 37.2, 39.3, 63.8, 80.1, 126.4, 126.8, 127.1, 127.2, 127.2, 127.2, 128.6, 128.8, 129.4, 136.5, 142.8, 145.0; HRMS (*m/z*): $[M+Na]^+$ calcd. for $C_{20}H_{24}O_2Na$, 319.1669; found, 319.1430.

3-(3-(1-hydroxy-2,2-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)propanoic acid (24)

To a two-phase mixture of **23** (325 mg, 1.1 mmol) in CH_2Cl_2 (5 mL) and 1.0 M sodium acetate buffer (pH 4.0, 5 mL) was added $NaClO_2$ (372 mg, 3.3 mmol) and catalytic amount of AZADOL® (8.4 mg, 0.055 mmol), and the mixture was stirred for 2 h at room temperature. Then the reaction mixture was added 2-methyl-2-butene (0.14 mL). The pH of the mixture was adjusted to 9 using sat. $NaHCO_3$ solution, it was washed with CH_2Cl_2. The aqueous phase was then acidified with 1 M HCl and extracted with EtOAc (15 mL × 3). The organic phase was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residual solid was purified by silica gel chromatography with 25% EtOAc in hexane containing 0.1 % AcOH to obtain **24** (227 mg, 67 %) as a white solid ^{1}H NMR (500 MHz, CD_3OD): δ_H 0.74 (3H, s, H_3-8′ or 9′), 1.01 (3H, s, H_3-8′ or 9′), 1.67 (1H, dd, *J*=13.8 and 6.9 Hz, H-5′), 1.75 (1H, dd, *J*=13.8 and 6.9 Hz, H-5′), 2.95 (2H, t, *J*=6.9 Hz, H-4′), 3.51 (1H, d, *J*=15.5 Hz, H-2), 3.55 (1H, d, *J*=15.5 Hz, H-2), 7.03–7.21 (8H, m, H-4, 6, 7, 8, 7′, 10′, 11′ and 12′); ^{13}C NMR (126 MHz, CD_3OD): δ_C 24.0, 25.7, 27.1, 34.1, 38.2, 42.2, 81.0, 127.0, 127.5, 127.8, 128.2, 128.8, 129.3, 130.2, 131.0, 134.0, 137.7, 144.1, 147.1, 175.7; HRMS (*m/z*): $[M+Na]^+$ calcd. for $C_{20}H_{22}O_3Na$, 333.1461; found, 333.1279.

Methyl 3-(3-(1-hydroxy-2,2-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)propanoate (25)

To a stirred solution of **24** (550 mg, 1.77 mmol) in THF (15 mL) was cooled to 0 °C and added DMF (15 drops) and oxalyl chloride (0.39 mL, 4.43 mmol). The reaction mixture was stirred for 30 min at room temperature, then MeOH (10 mL) was added and the mixture was stirred for 10 min. The pH of the mixture was adjusted to 9 using sat. $NaHCO_3$ solution, it was extracted with EtOAc (20 mL × 3). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residual oil was purified by silica gel chromatography with 10% EtOAc in hexane to obtain **25** (443 mg, 77%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 0.78 (3H, s, H_3-8′ or 9′), 1.03 (3H, s, H_3-8′ or 9′), 1.70 (1H, m, H-5′), 1.82 (1H, m, H-5′), 2.95 (2H, t, *J*=6.3 and 6.3 Hz, H-4′), 3.57 (1H, d, *J*=14.9 Hz, H-2), 3.62 (1H, d, *J*=14.9 Hz, H-2), 3.65 (3H, s, -O*CH*$_3$), 7.07–7.21 (8H, m, H-4, 6, 7, 8, 7′, 10′, 11′ and 12′); ^{13}C NMR (126 MHz, $CDCl_3$): δ_C 23.4, 24.9, 26.1, 33.0, 37.2, 41.3, 51.9, 80.1, 126.4, 126.7, 127.2, 127.3, 127.7, 128.6, 128.8, 129.7, 132.2, 136.6, 142.7, 144.9, 172.1; HRMS (*m/z*): $[M+Na]^+$ calcd. for $C_{21}H_{24}O_3Na$, 347.1618; found, 347.1435.

Methyl 3-(3-(1-hydroxy-2,2-dimethyl-4-oxo-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)propanoate (5)

To a stirred solution of **25** (388 mg, 1.2 mmol) in acetone (5 mL) was added 70% *tert*-butyl hydroperoxide (1.7 mL, 12 mmol) and $Co(acac)_2$ (15.4 mg, 0.06 mmol). The reaction mixture was stirred for 5 h at room temperature, then water (20 mL) was added and extracted with EtOAc (20 mL × 3). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residual oil was purified by silica gel chromatography with 25% EtOAc in hexane to obtain **5** (119 mg, 29%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 0.93 (3H, s, H_3-8′ or 9′), 1.09 (3H, s, H_3-8′ or 9′), 2.56 (1H, d, *J*=16.6 Hz, H-5′), 2.72 (1H, d, *J*=16.6 Hz, H-5′), 3.59 (1H, d, *J*=14.9 Hz, H-2), 3.62 (1H, d, *J*=14.9 Hz, H-2), 3.66 (3H, s, -O*CH*$_3$), 7.07–7.32 (4H, m, H-4, 6, 7 and 8), 7.39 (1H, d, *J*=8.0 Hz, H-7′), 7.44 (1H, ddd, *J*=8.0, 8.0 and 1.7 Hz, H-10′), 7.56 (1H, ddd, *J*=8.0, 8.0 and 1.7 Hz, H-11′), 8.11 (1H, dd, *J*=8.0 and 1.7 Hz, H-12′); ^{13}C NMR (126 MHz, $CDCl_3$): δ_C 24.0, 25.0, 41.2, 41.4, 49.9, 52.0, 80.1, 126.2, 127.2, 127.4, 127.9, 128.2, 128.2, 129.3, 132.0, 133.1, 134.6, 142.2, 147.5, 171.9, 197.9; HRMS (*m/z*): $[M+Na]^+$ calcd. for $C_{21}H_{22}O_4Na$, 361.1410; found, 361.1254.

A CHIRAL ART Cellulose-SC HPLC column (YMC, 250 × 10 mm i.d.; solvent, 15 % 2-propanol in hexane; flow rate, 2.5 mL min^{-1}; detection, 254 nm) was infected with (±)-Me tetralone-BP2A. The material at t_R 13.6 and 15.5 min were collected to give Me (+)-tetralone-BP2A (15.5 mg) and the (−)-enantiomer (15.1 mg) with an optical purity of 99% and 99%, respectively. Me (+)-tetralone-BP2A: $[\alpha]_D^{20}$ +64.8 (MeOH; *c* 0.095); CD λ_{ext} (MeOH) nm (Δε): 291.0 (2.8), 268.0 (1.0), 238.0 (4.7), 206.0 (−17.1). Me (−)-tetralone-BP2A: $[\alpha]_D^{20}$ −65.9 (MeOH; *c* 0.108); CD λ_{ext} (MeOH) nm (Δε): 293.0 (−2.8), 267.0 (−0.7), 237.0 (−4.5), 207.0 (18.0).

Methyl 3-(3-((1*R,4*S**)-1,4-dihydroxy-2,2-dimethyl-1,2,3,4-tetrahydronaphthalen-1-**

yl)phenyl)propanoate (6)

To a stirred solution of **5** (57.9 mg, 0.17 mmol) in MeOH (1 mL) was cooled to 0 °C and added cerium (III) chloride heptahydrate (180 mg, 0.48 mmol) and $NaHB_4$ (14.2 mg, 0.38 mmol). The reaction mixture was stirred for 30 min at 0 °C, and then quenched with sat. NH_4Cl solution (20 mL) and extracted with EtOAc (20 mL × 3). The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residual oil was purified by silica gel chromatography with 40% EtOAc in hexane to obtain **6** (26.5 mg, 46%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 0.81 (3H, s, H_3-8′ or 9′), 1.10 (3H, s, H_3-8′ or 9′), 1.77 (1H, dd, *J*=13.5 and 9.8 Hz, H-5′ ax.), 1.96 (1H, d, *J*=13.5 and 6.9 Hz, H-5′ eq.), 3.55 (2H, s, H_2-2), 3.65 (3H, s, -O*CH*$_3$), 4.95 (1H, dd, *J*=9.8 and 6.9 Hz, H-4′), 7.07 (1H, d, *J*=7.5 Hz, H-6), 7.10 (1H, br s, H-4), 7.14–7.36 (5H, m, H-7, 8, 7′, 10′ and 11′), 8.11 (1H, *J*=7.5 Hz, H-12′); ^{13}C NMR (126 MHz, $CDCl_3$): δ_C 2.32, 25.7, 39.3, 40.8, 43.4, 52.1, 66.8, 80.3, 127.0, 127.1, 127.2, 127.3, 127.4, 127.7, 128.4, 129.7, 132.2, 138.9, 142.1, 144.8, 172.3; HRMS (*m/z*): $[M+Na]^+$ calcd. for $C_{21}H_{24}O_4Na$, 363.1567; found, 363.1414.

Methyl (1′*R*,4′*S*)-(+)-1′,4′-diol-tetralone-BP2A, (+)-6

Methyl (+)-tetralone-BP2A (10 mg, 29 μmol) was converted to Me (1′*S*,4′*S*)-(+)-1′,4′-diol-tetralone-BP2A (4.3 mg, 13 μmol, 43%) by the same manner. $[\alpha]_D^{23}$ +196 (MeOH; *c* 0.072)

Photolysis of (±)-BP2A analogs by sunlight

0.1 mg/mL aqueous solutions of ABA, (+)-BP2A, and (±)-BP2A analogs were prepared by taking 10 μL of a 10 mg/mL MeOH solution of the compounds into dishes and adding 1 mL distilled water. At this time, it was visually confirmed that all the compounds were dissolved. These aqueous compound solutions were irradiated sunlight for 6 h. The dried sample was then dissolved in 1 mL MeOH, after which a 3-μL aliquot was analyzed by high-performance liquid chromatography (HPLC). The HPLC conditions were as follows: column, Kinetex PS C_{18} (100 × 4.6 mm, 2.6 μm, Shimadzu GLC Ltd., Tokyo, Japan); solvent, 60% MeOH in H_2O containing 0.1% acetic acid (AcOH); flow rate, 1.5 mL min^{-1}; and detection wavelength, 190−350 nm. Data are presented as the averages from three independent experiments.

Seed germination assays

The classic definition of radical emergence was used for seed germination assays. All assays were performed at least three times. *Arabidopsis* (Colombia accession) seeds (25–40) were sterilized by soaking in 70% aqueous ethanol (EtOH, v/v) for 30 min and reagent-grade EtOH for 1 min. Seeds were then soaked in distilled water and incubated in the dark at 4°C for 3 days. The stratified seeds were then soaked in 0.1 mL of a test medium liquid agar containing 1/2 Murashige and Skoog (MS) in 96-well plates and allowed to germinate under continuous illumination at 22 °C.

PP2C enzyme assay

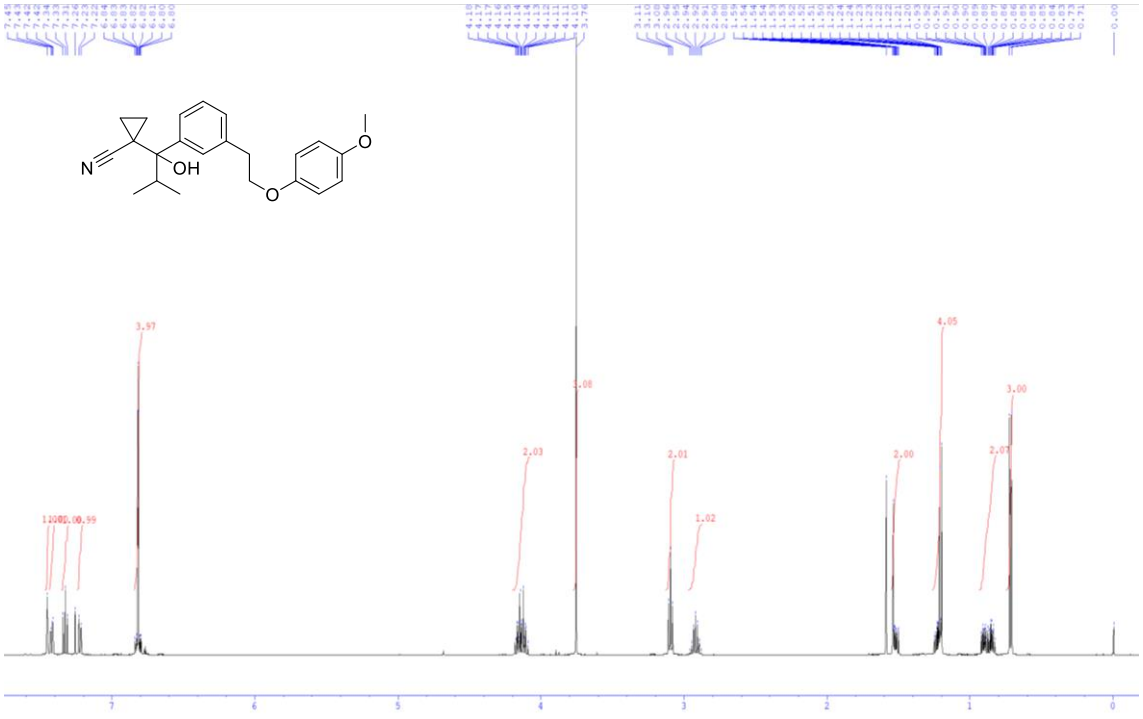
The PP2C phosphatase assays were performed as described previously[4] with some modification. Briefly, PYL1 and HAB1 were expressed in *E. coli* and purified by affinity column chromatography. Purified proteins were preincubated in 80 μL of a buffer containing 1.25 mM $MnCl_2$ and test compound at 22°C for 20 min. After adding 20 μL of substrate buffer (165 mM Tris-acetate, pH 7.9, 330 mM potassium acetate, and 25 mM *p*NPP), reactions were immediately monitored for hydrolysis of *p*NPP at 405 nm. The reactions contained 600 nM HAB1 and 1200 nM PYL1 proteins.

ABA2 enzyme assay

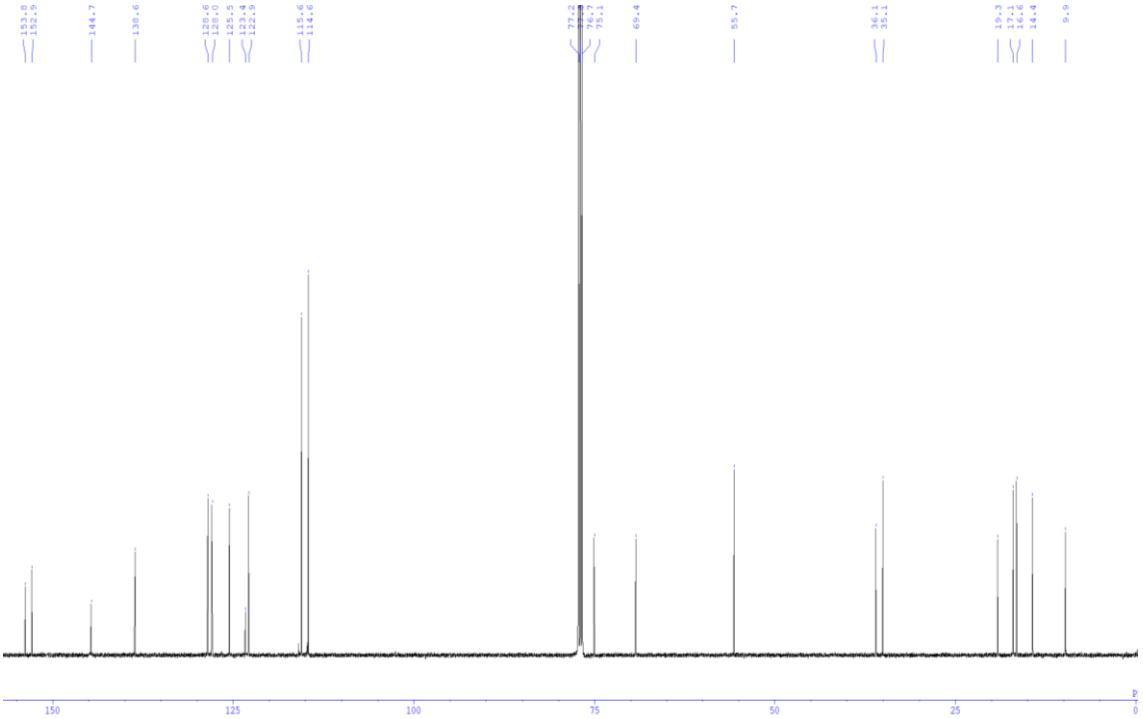
Reaction mixtures, containing 50 μg mL^{-1} of ABA2, 64 μM compound **6**, and 2 mM NAD^+ in potassium phosphate buffer (pH 7.2), were incubated at 30 °C for 30 min. Reactions were initiated by adding NAD^+ and stopped by the addition of 20 μL of 1 M HCl. 1′,4′-*cis*-diol-ABA, as the internal standard, was then added to the reaction product, which was extracted with EtOAc (150 μL ×3). The organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. Each dried sample was then dissolved in 50 μL of MeOH, and a 10-μL volume was subjected to HPLC. The HPLC conditions were as follows: column, Hydrosphere C18 (150 × 6.0 mm, 5 μm, YMC); solvent, 55% MeOH in H_2O containing 0.05% AcOH; flow rate, 1.0 mL min^{-1}; and detection wavelength, 190–350 nm. The chromatograms show representative results obtained from three independent experiments.

3) ^{1}H and ^{13}C NMR Spectrums of Synthesized Compounds

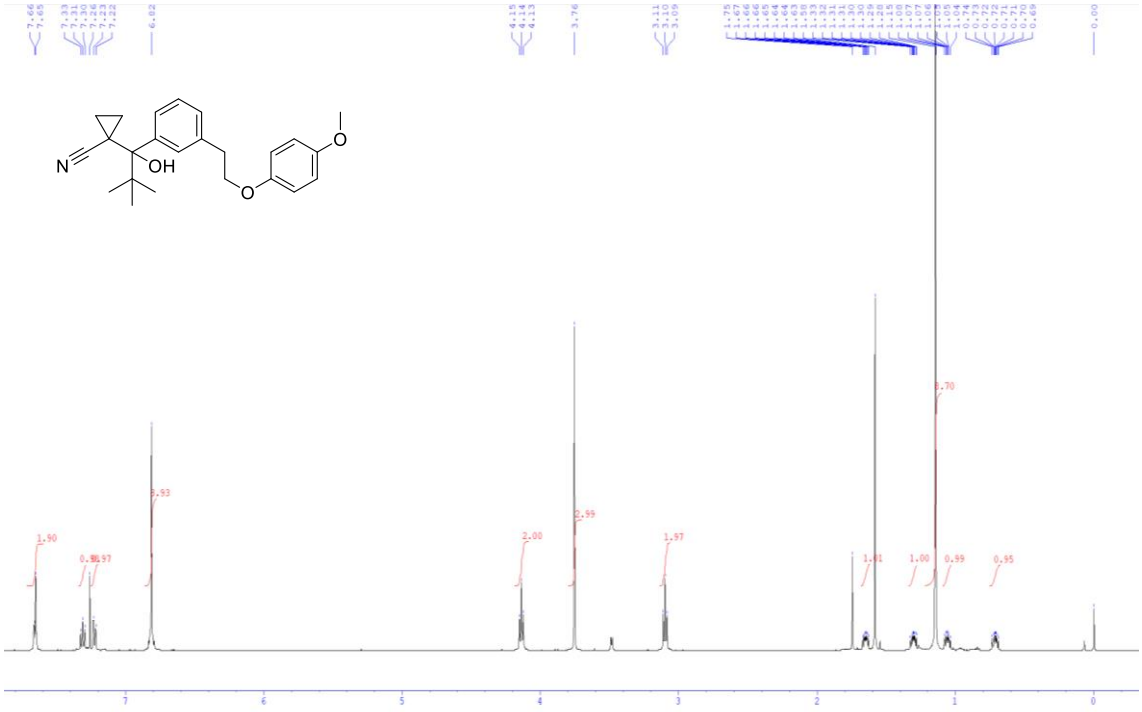
^{1}H NMR spectrum of Compound 10a



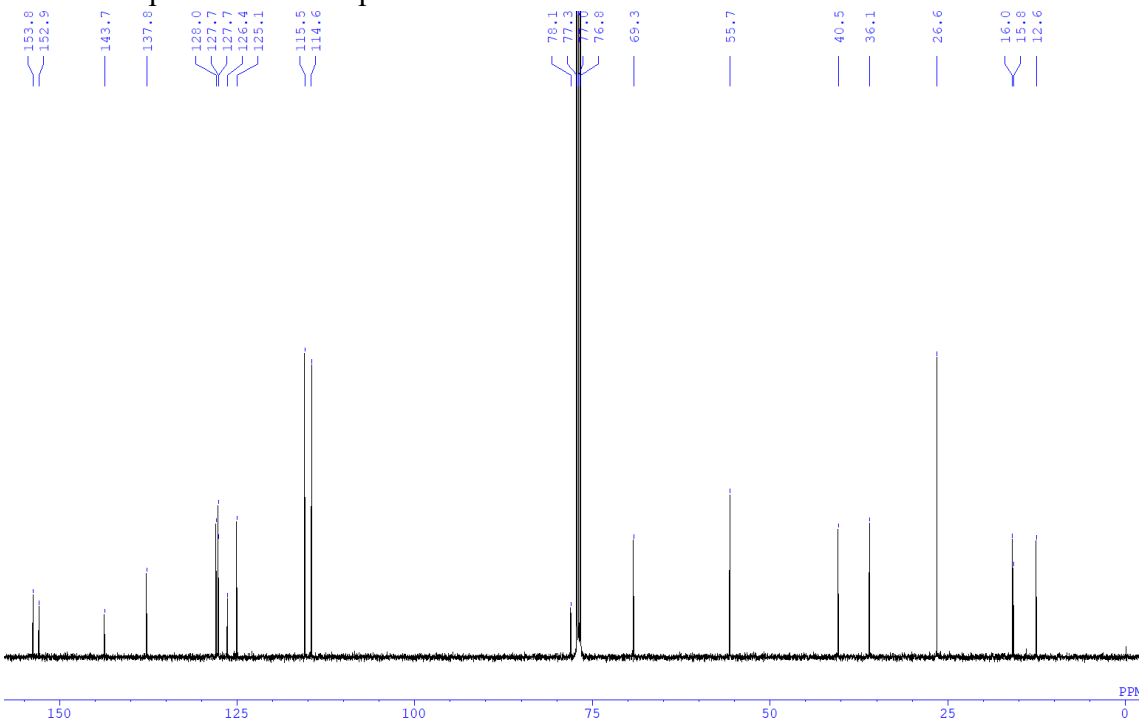
^{13}C NMR spectrum of Compound 10a



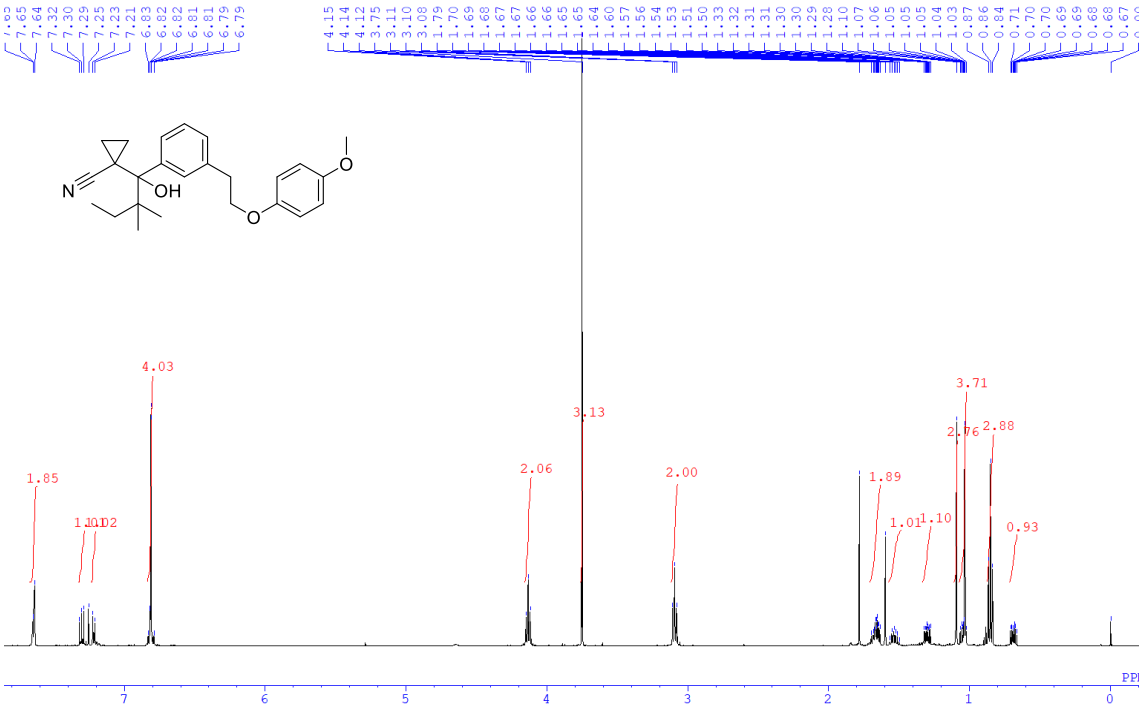
^{1}H NMR spectrum of Compound 10b



^{13}C NMR spectrum of Compound 10b



^{1}H NMR spectrum of Compound 10c



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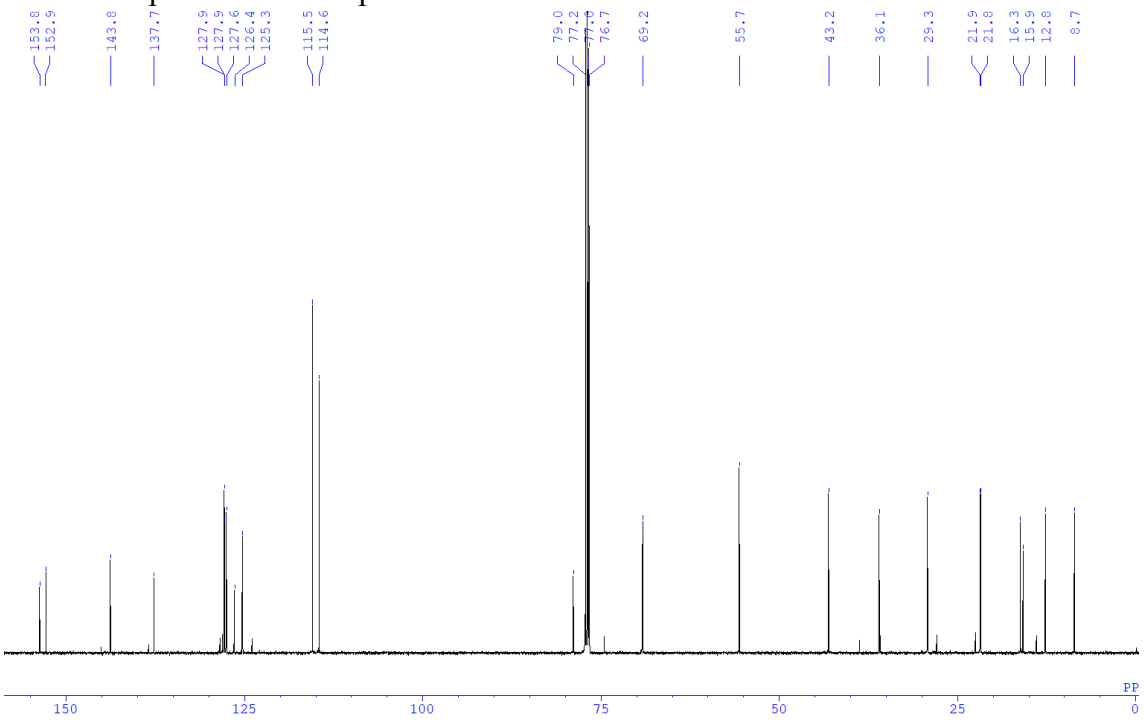
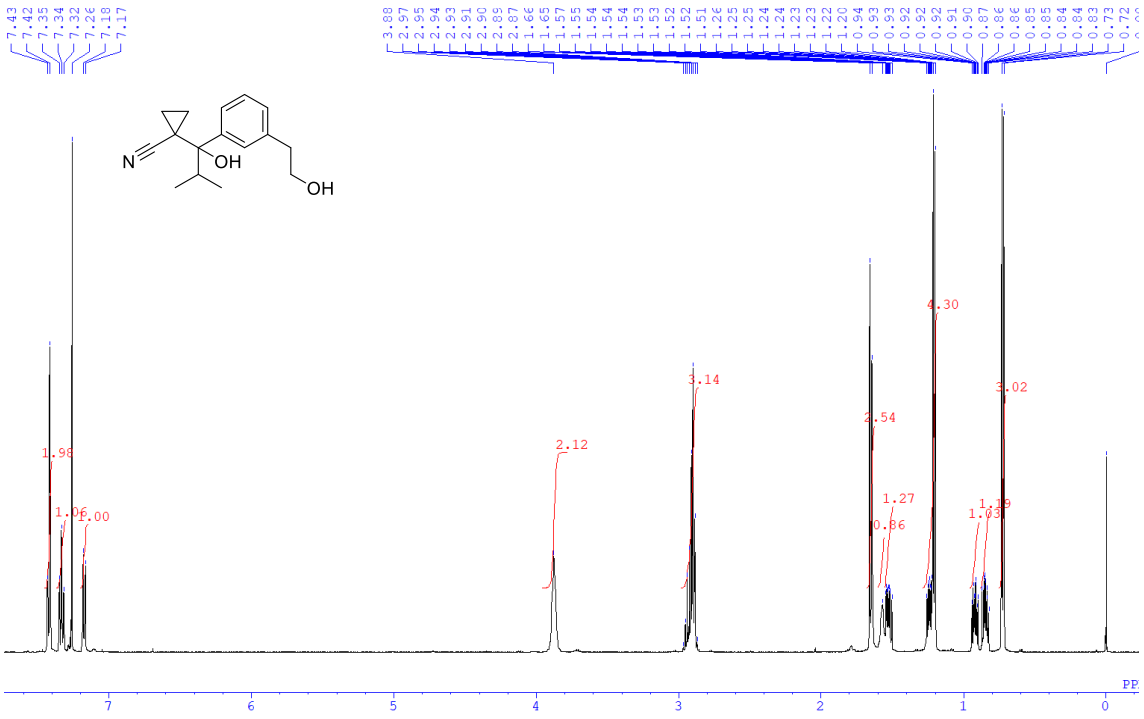
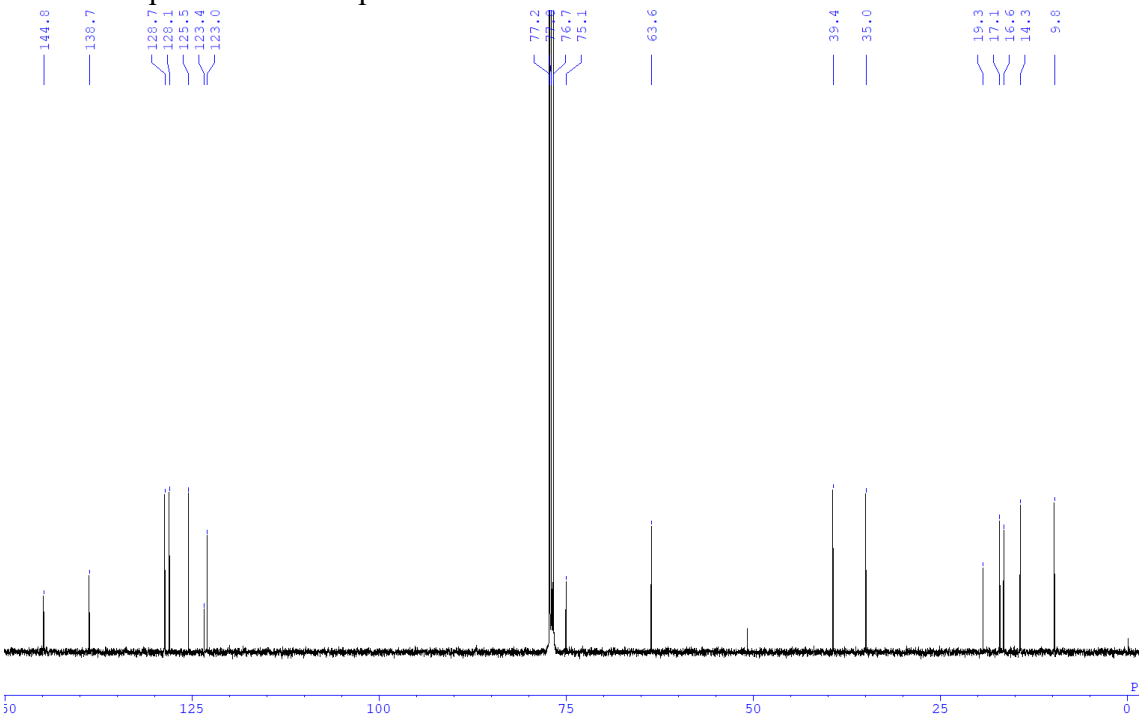


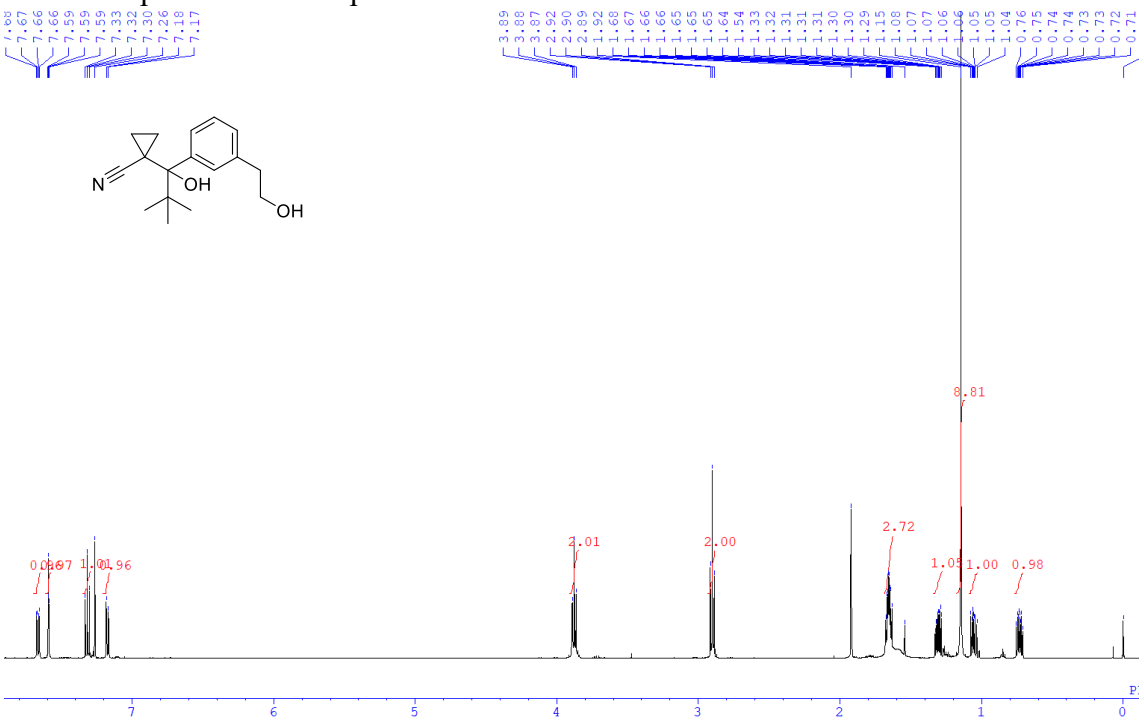
^{1}H NMR spectrum of Compound 11a



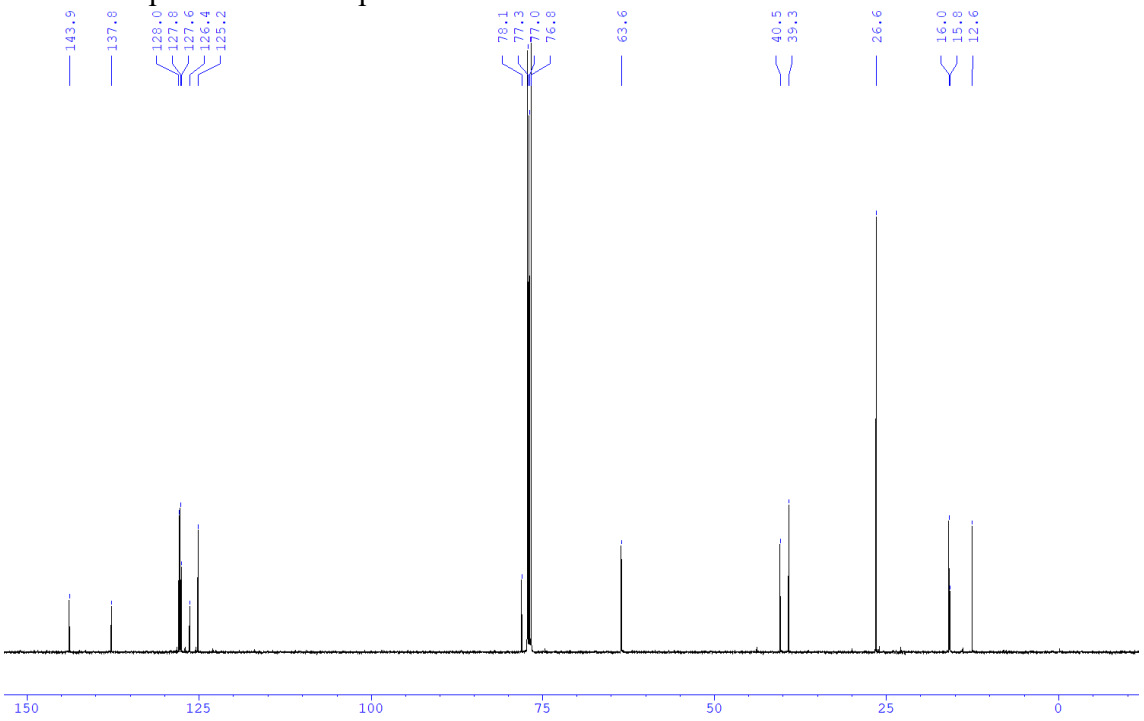
^{13}C NMR spectrum of Compound 11a



^{1}H NMR spectrum of Compound 11b



^{13}C NMR spectrum of Compound 11b



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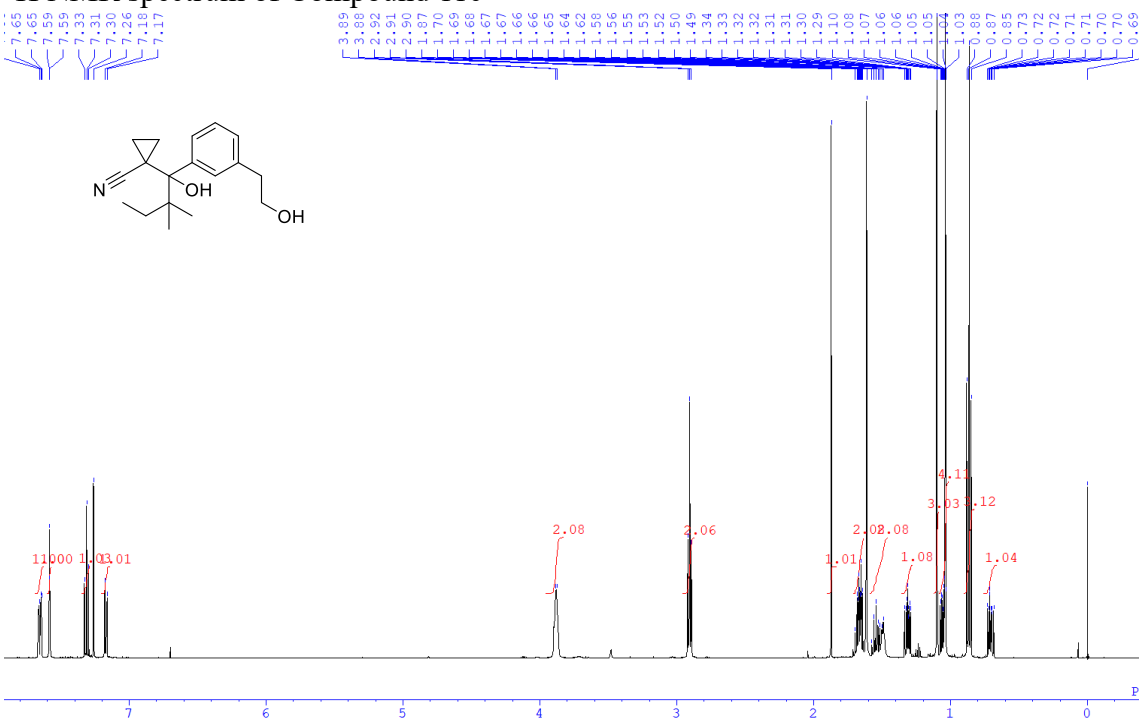
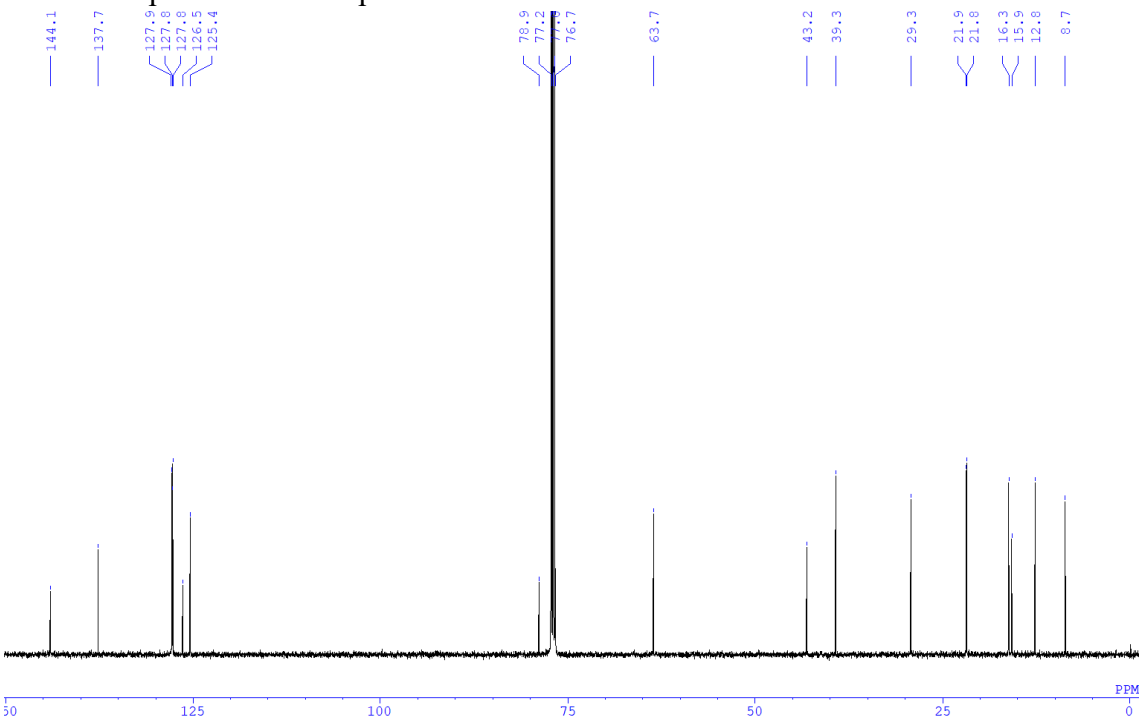
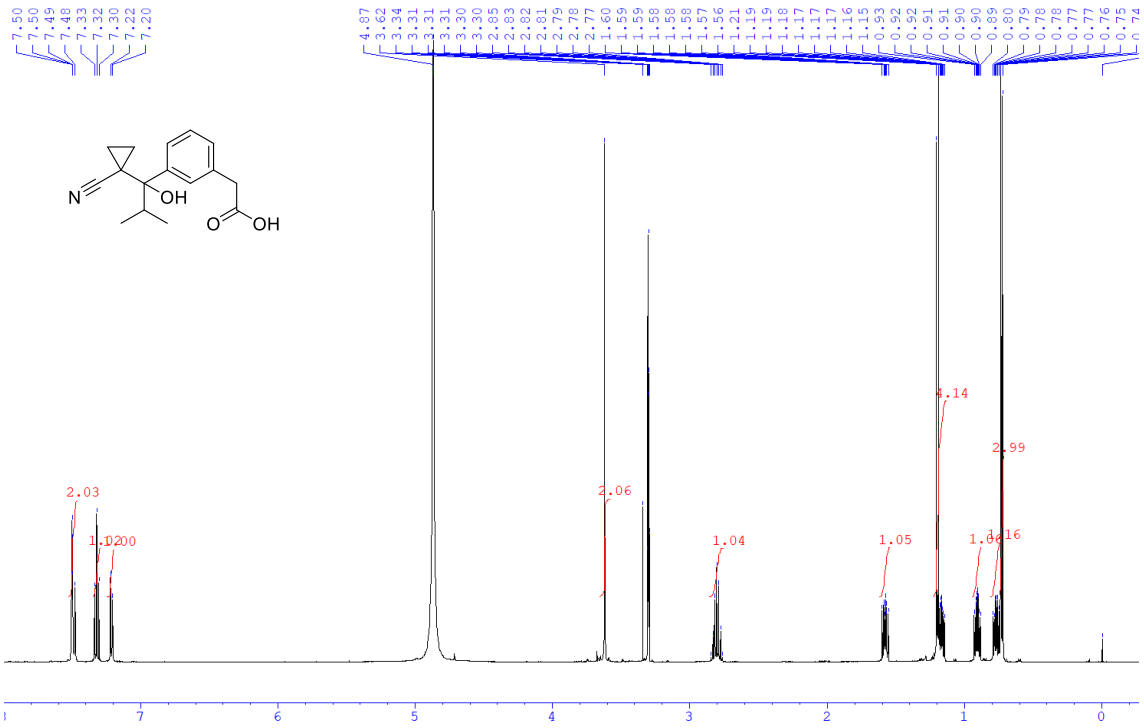


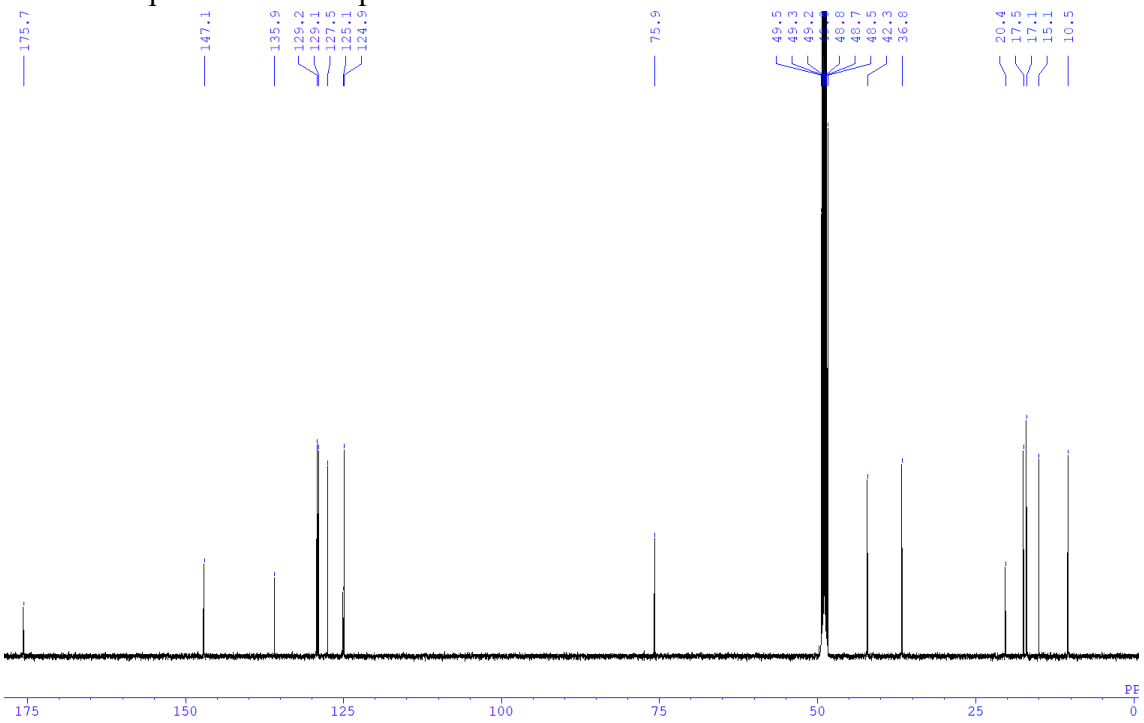
^{13}C NMR spectrum of Compound 11c



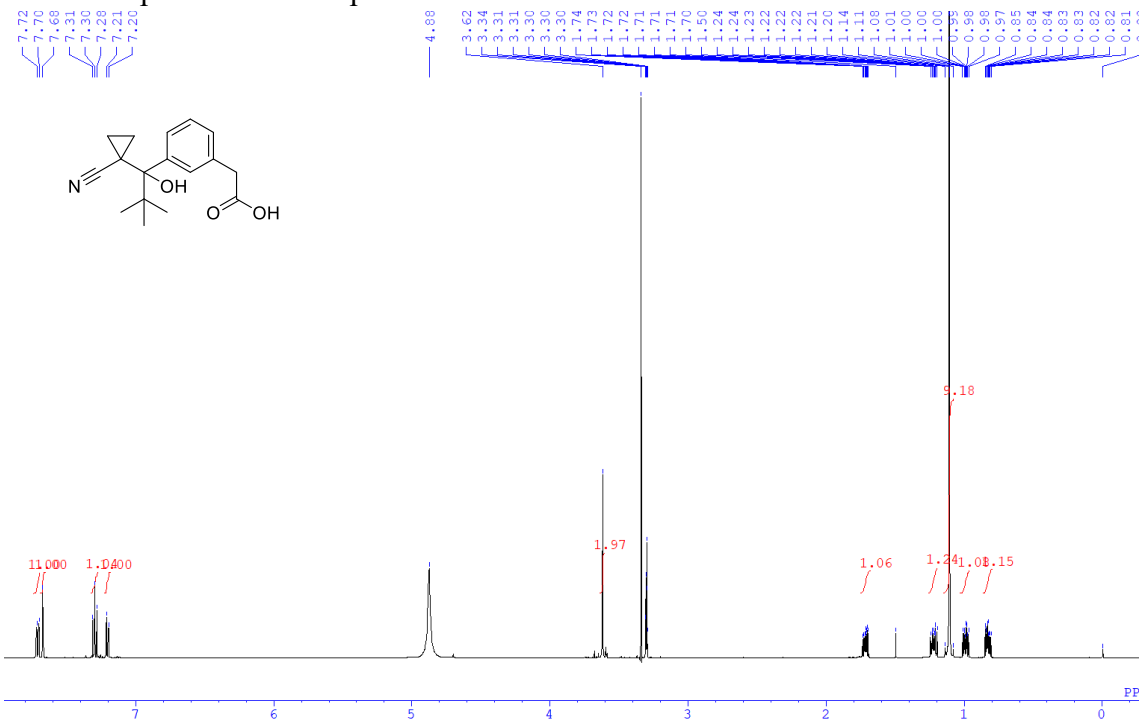
^{1}H NMR spectrum of Compound 12a



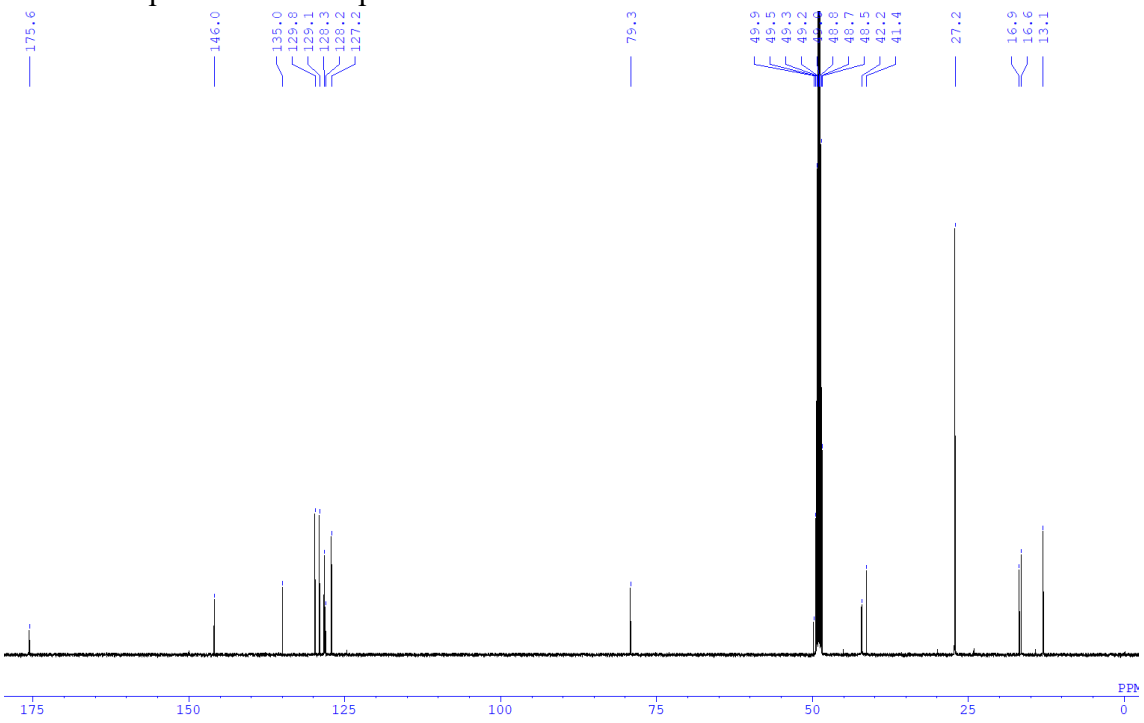
^{13}C NMR spectrum of Compound 12a



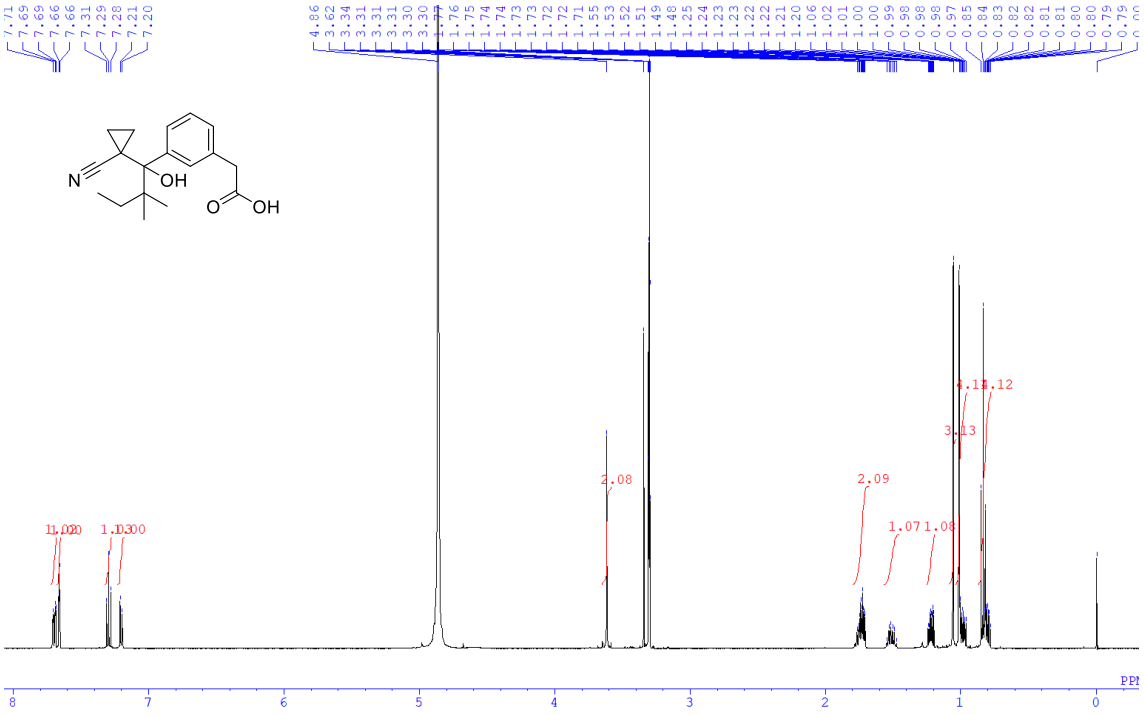
^{1}H NMR spectrum of Compound 12b



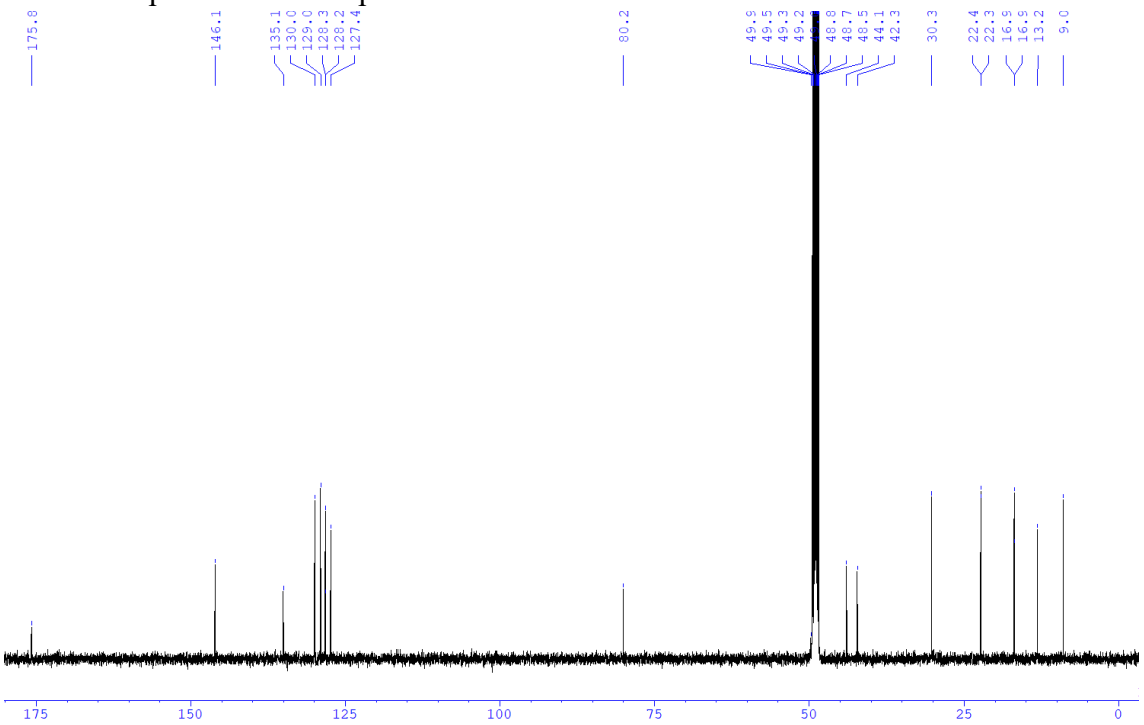
^{13}C NMR spectrum of Compound 12b



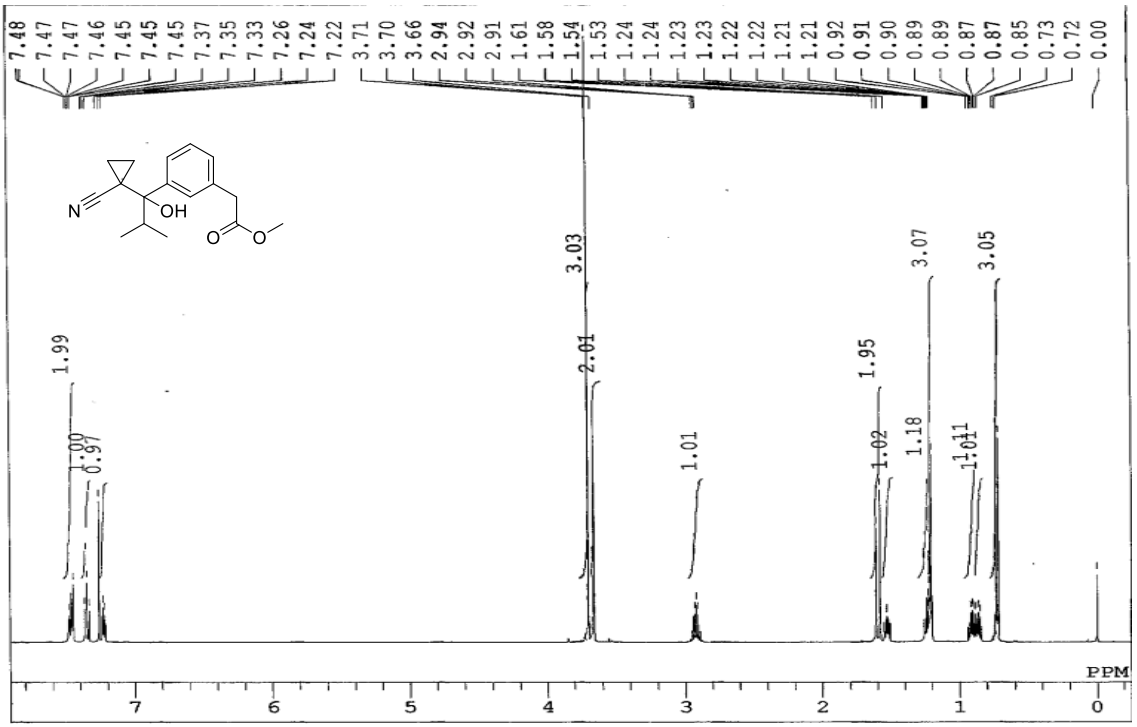
^{1}H NMR spectrum of Compound 12c



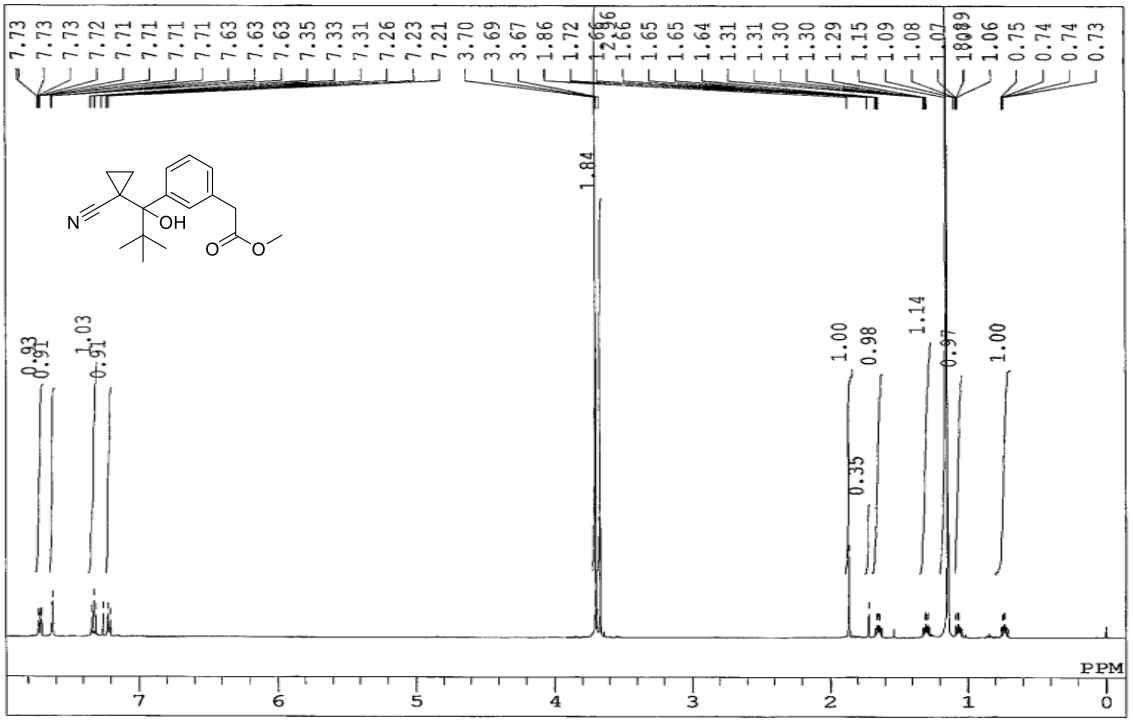
^{13}C NMR spectrum of Compound 12c



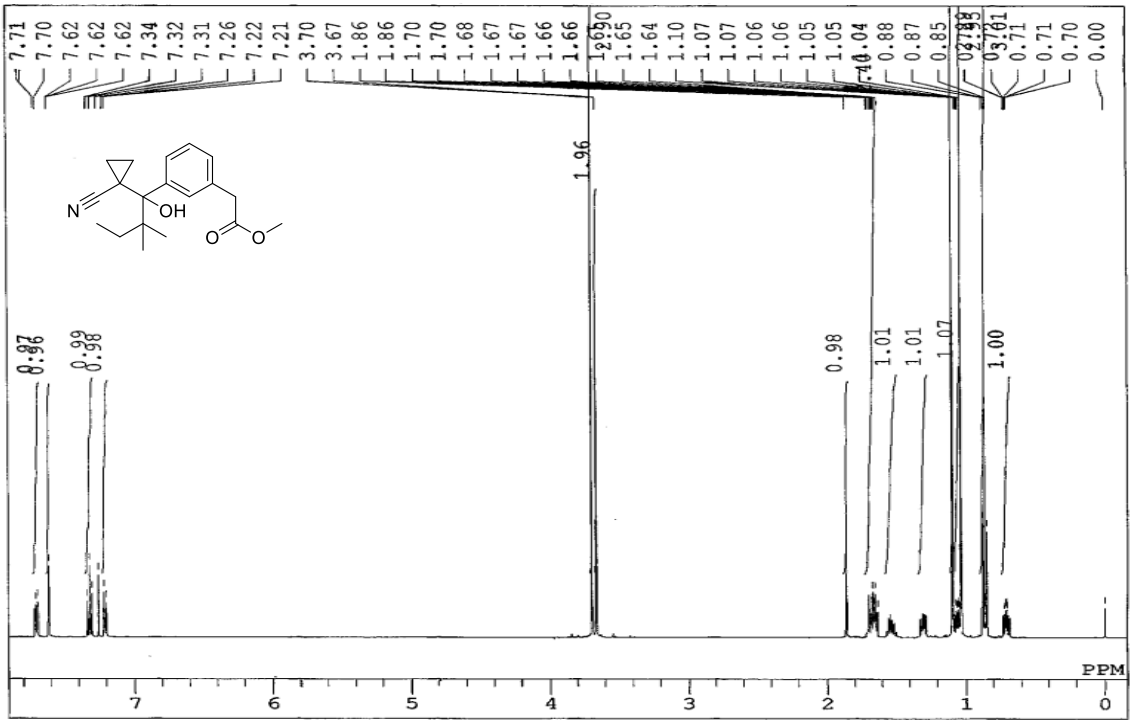
^{1}H NMR spectrum of Compound 3a



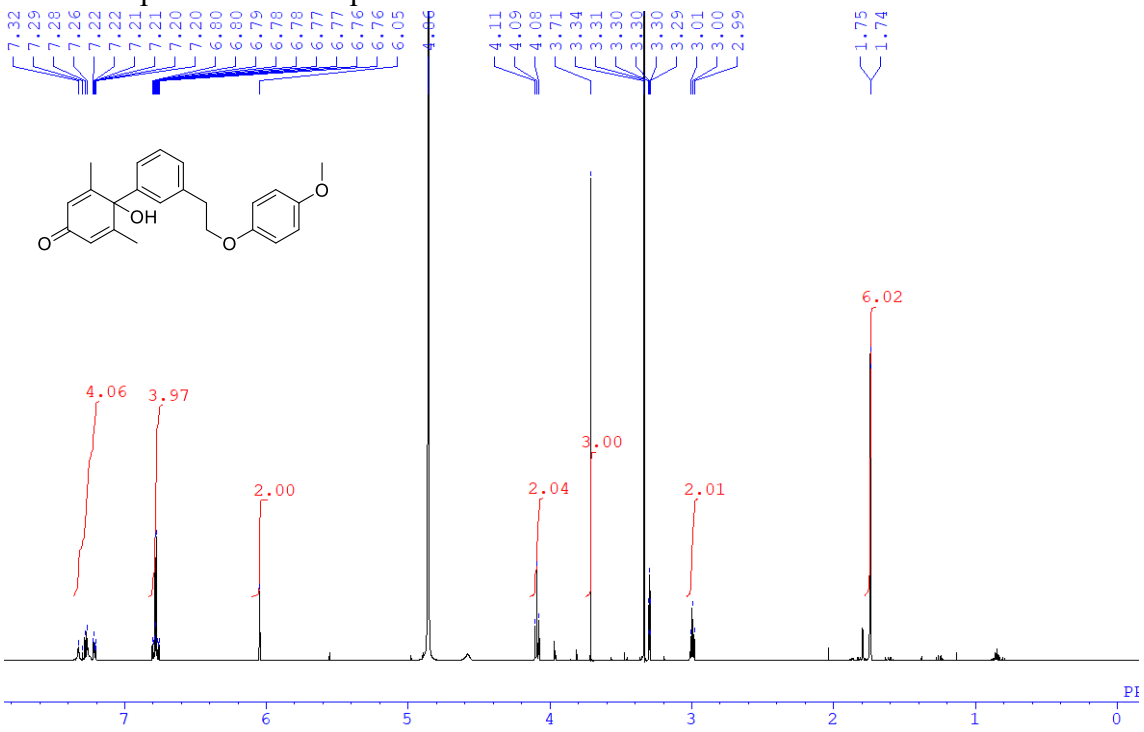
^{1}H NMR spectrum of Compound 3b



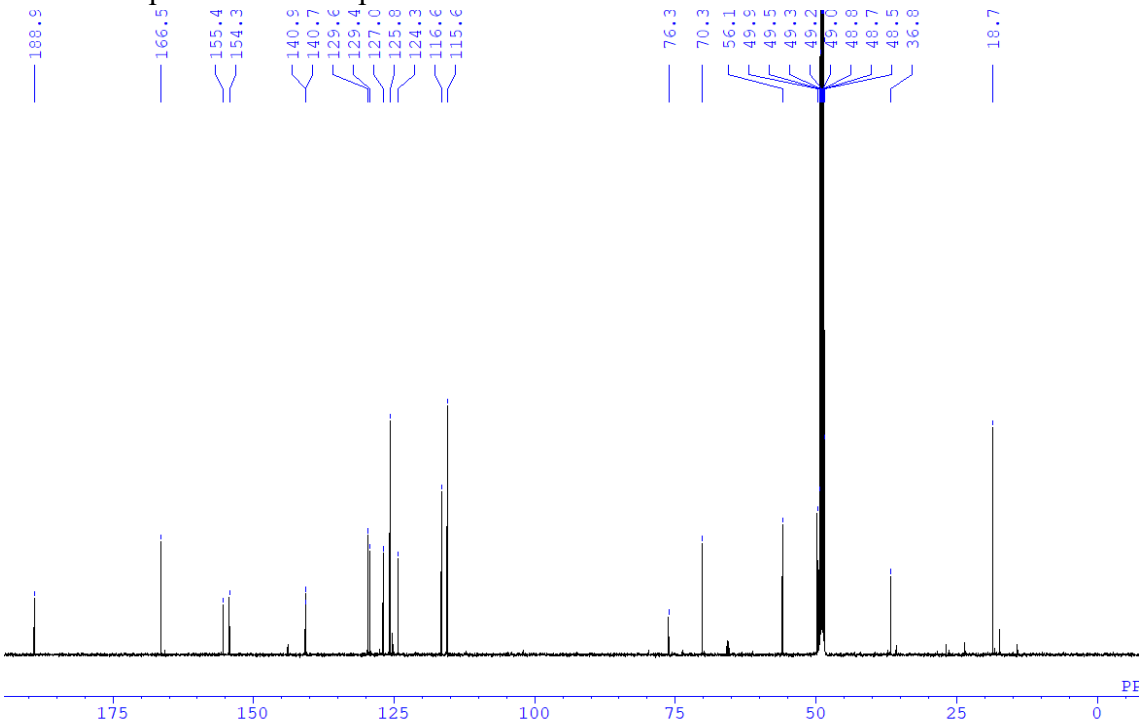
^{1}H NMR spectrum of Compound 3c



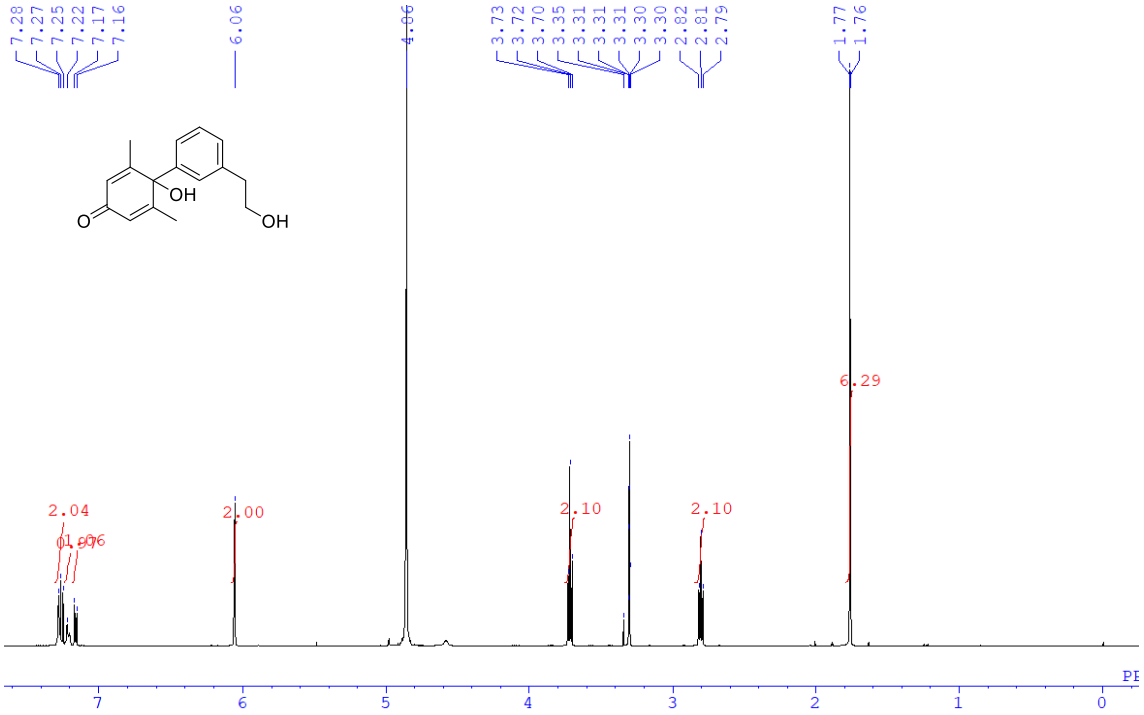
^{1}H NMR spectrum of Compound 15



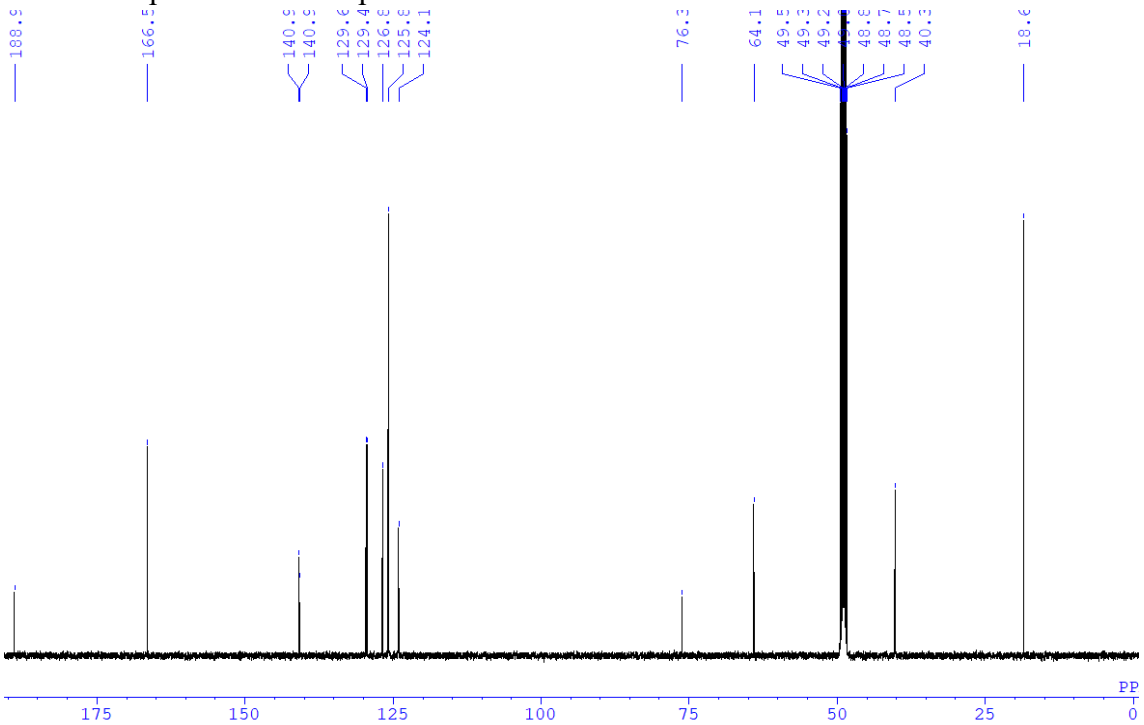
^{13}C NMR spectrum of Compound 15



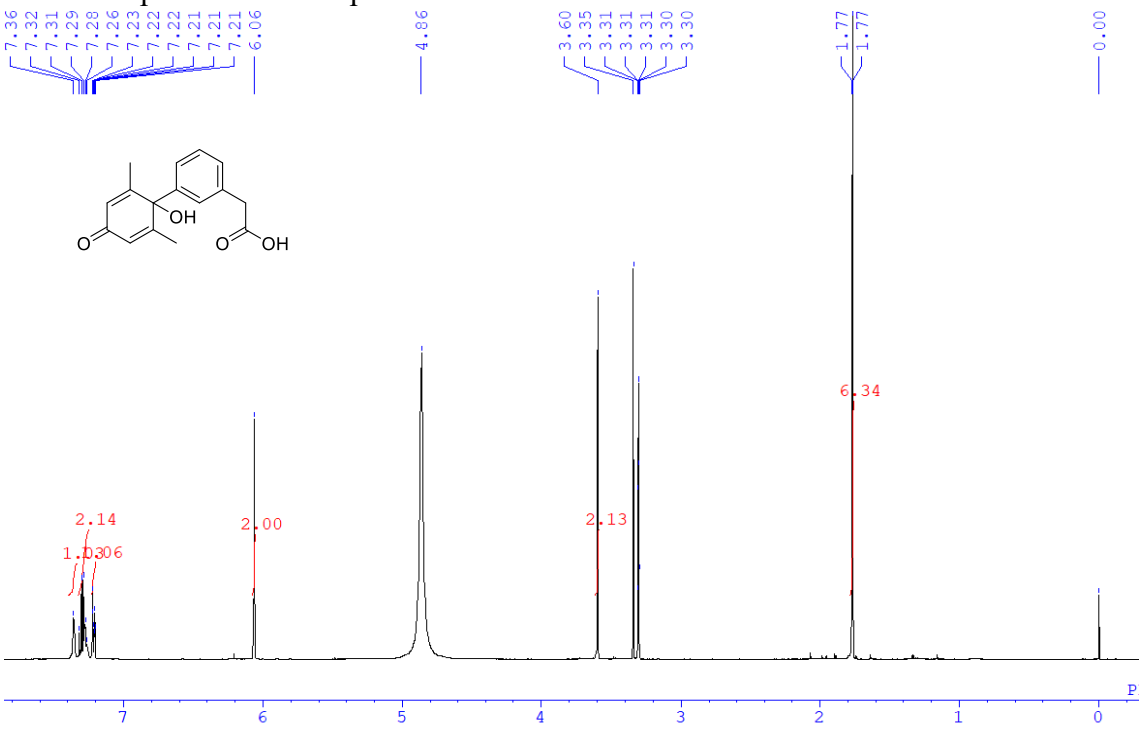
^{1}H NMR spectrum of Compound 16



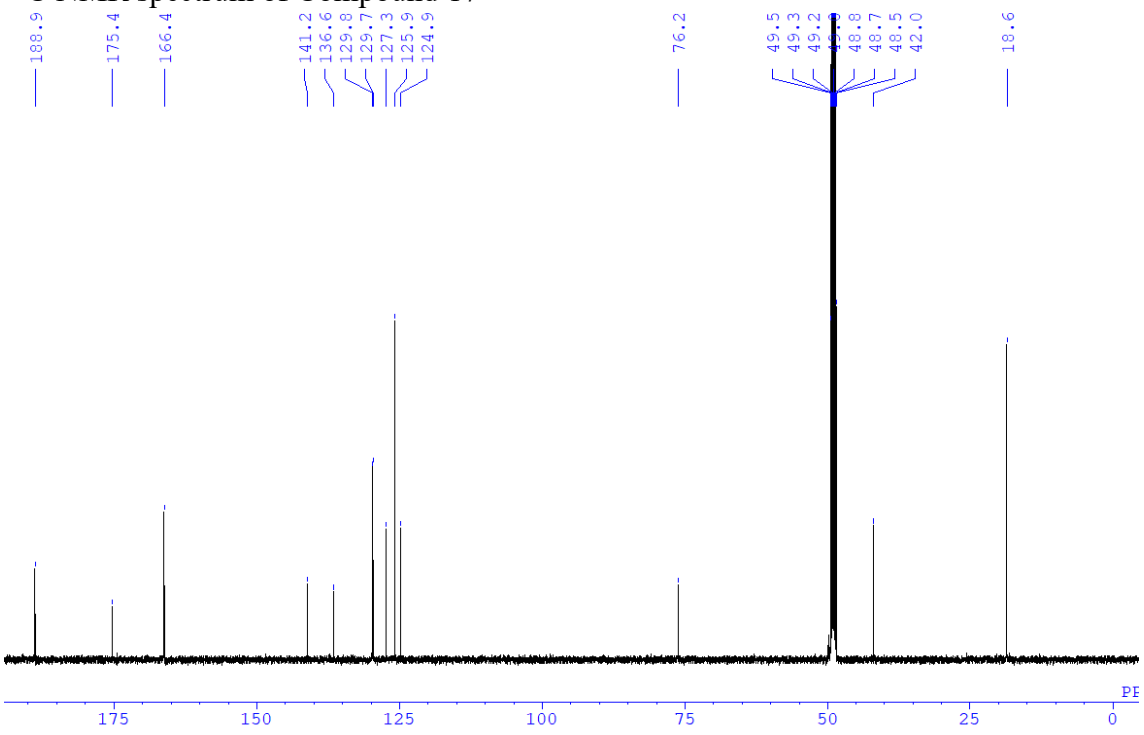
^{13}C NMR spectrum of Compound 16



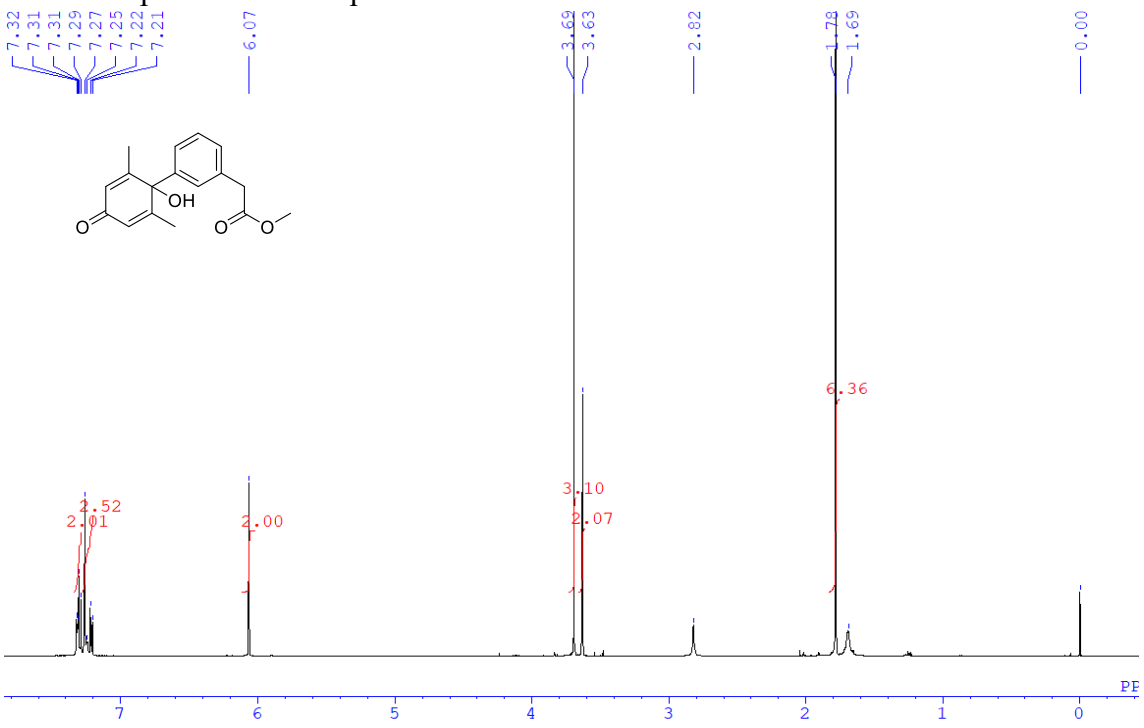
^{1}H NMR spectrum of Compound 17



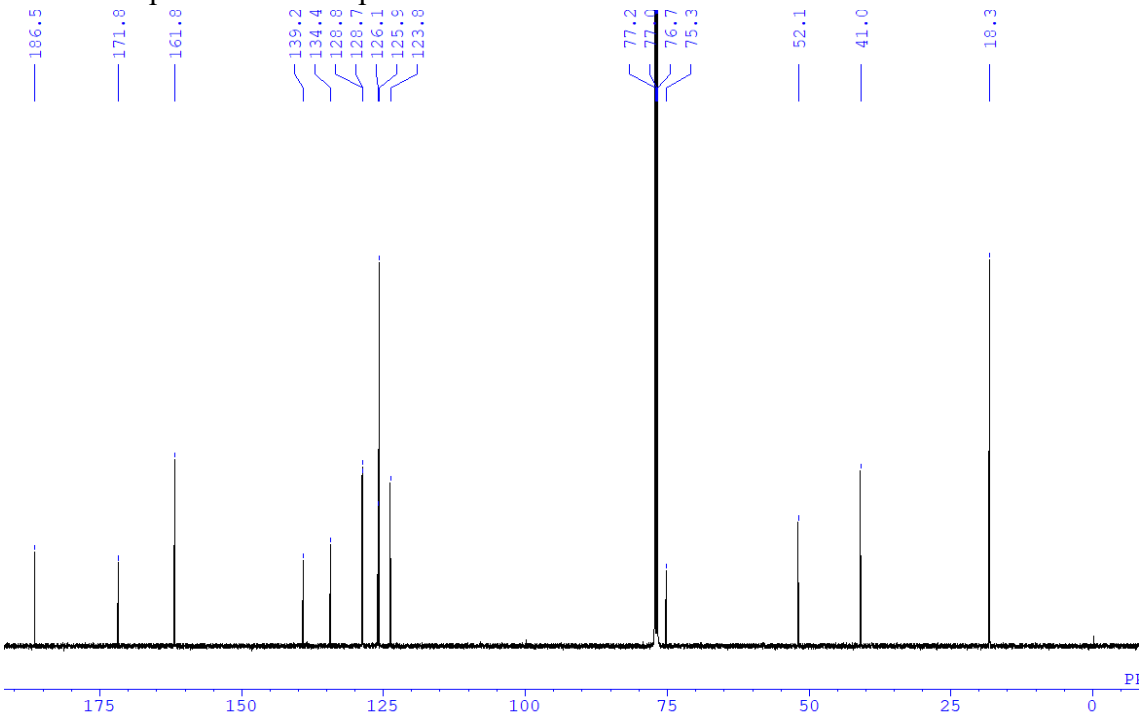
^{13}C NMR spectrum of Compound 17



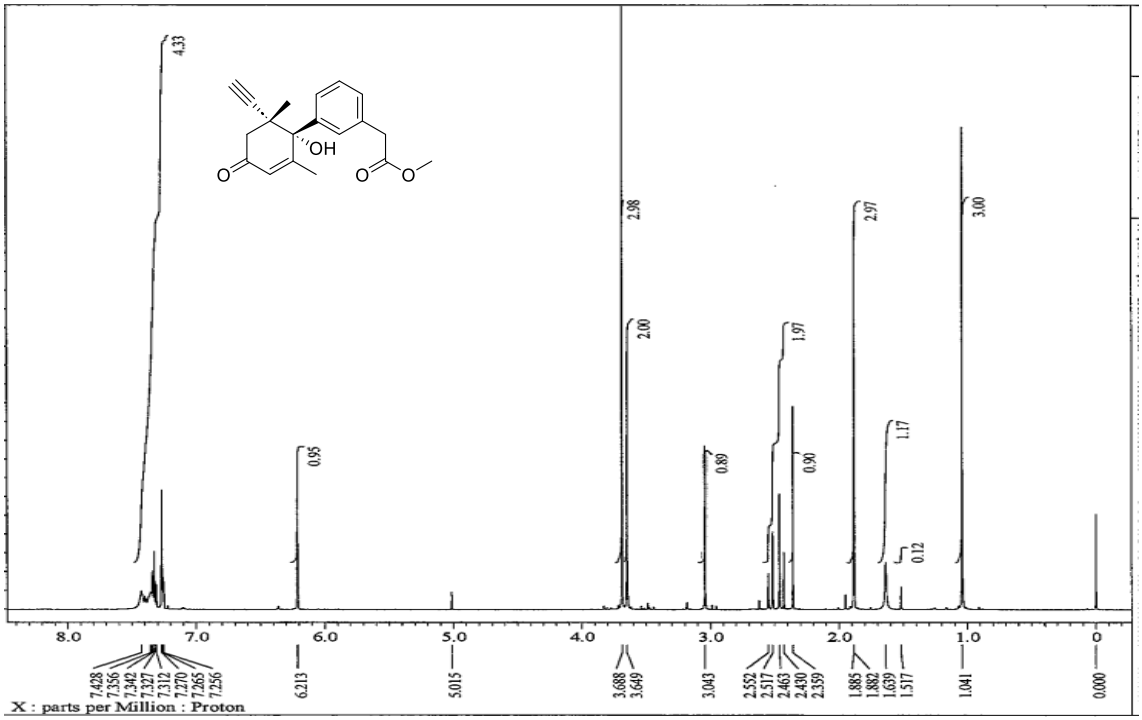
^{1}H NMR spectrum of Compound 18



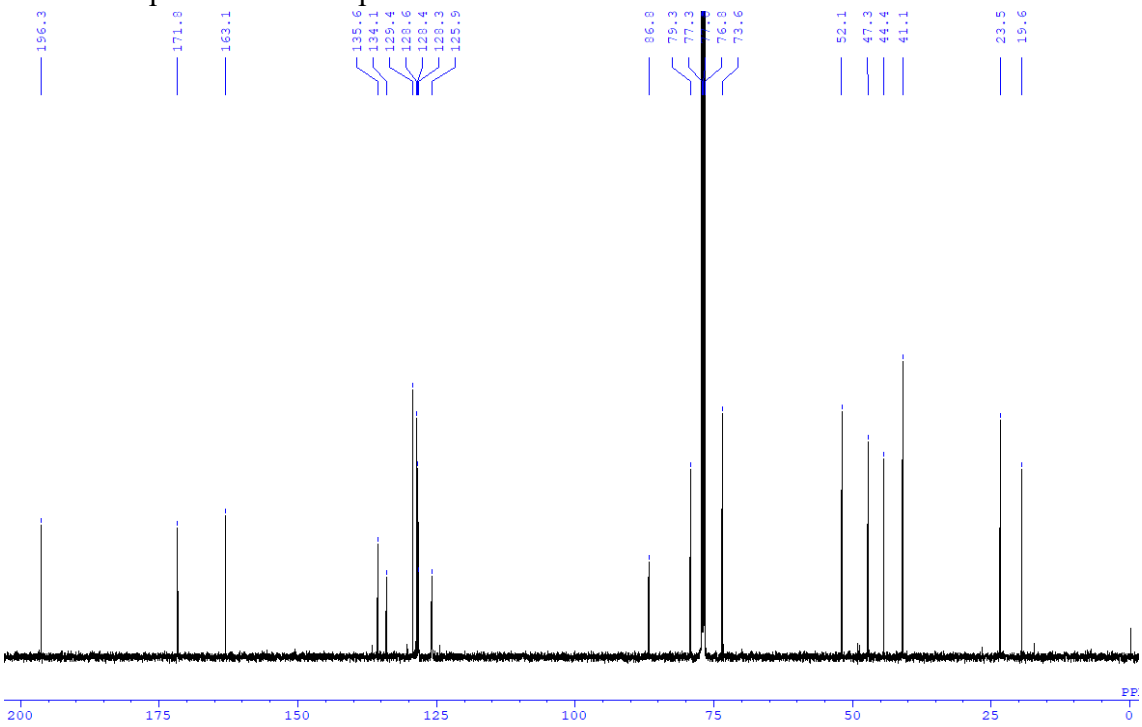
^{13}C NMR spectrum of Compound 18



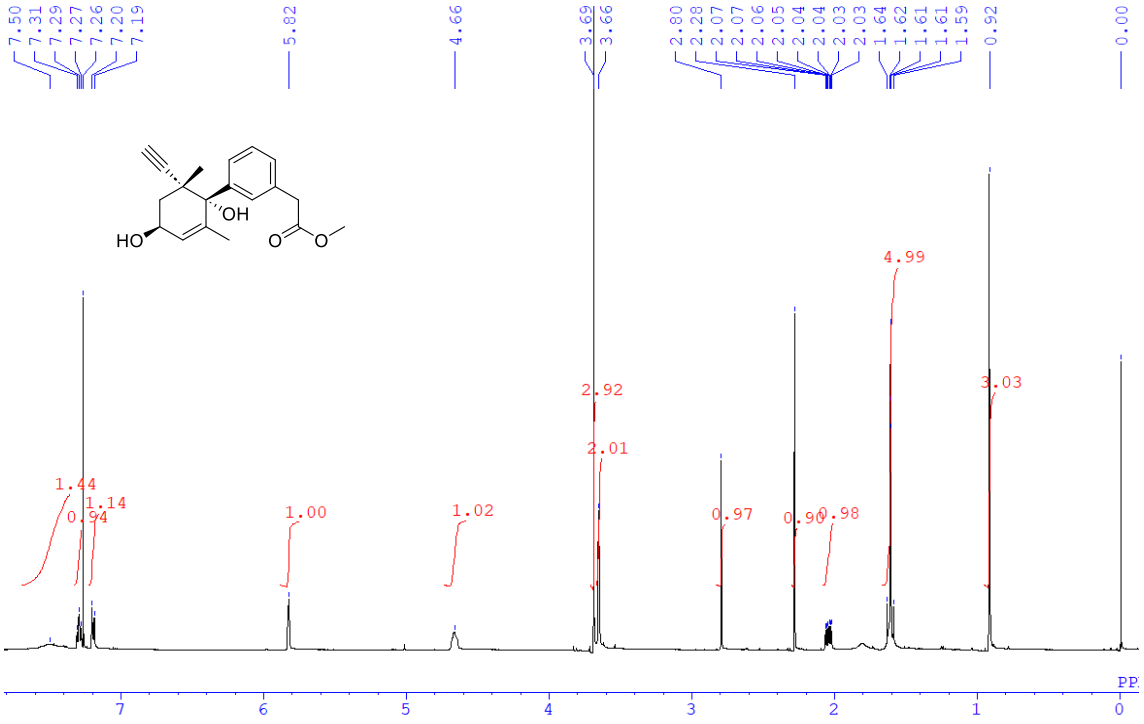
^{1}H NMR spectrum of Compound 19



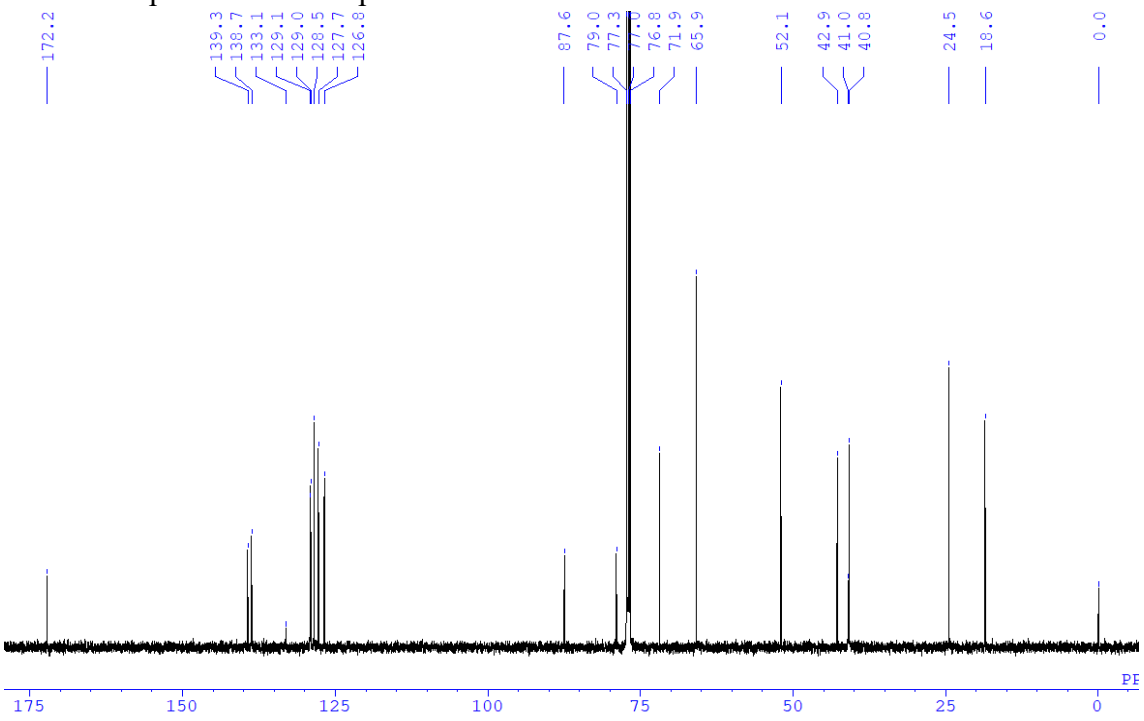
^{13}C NMR spectrum of Compound 19



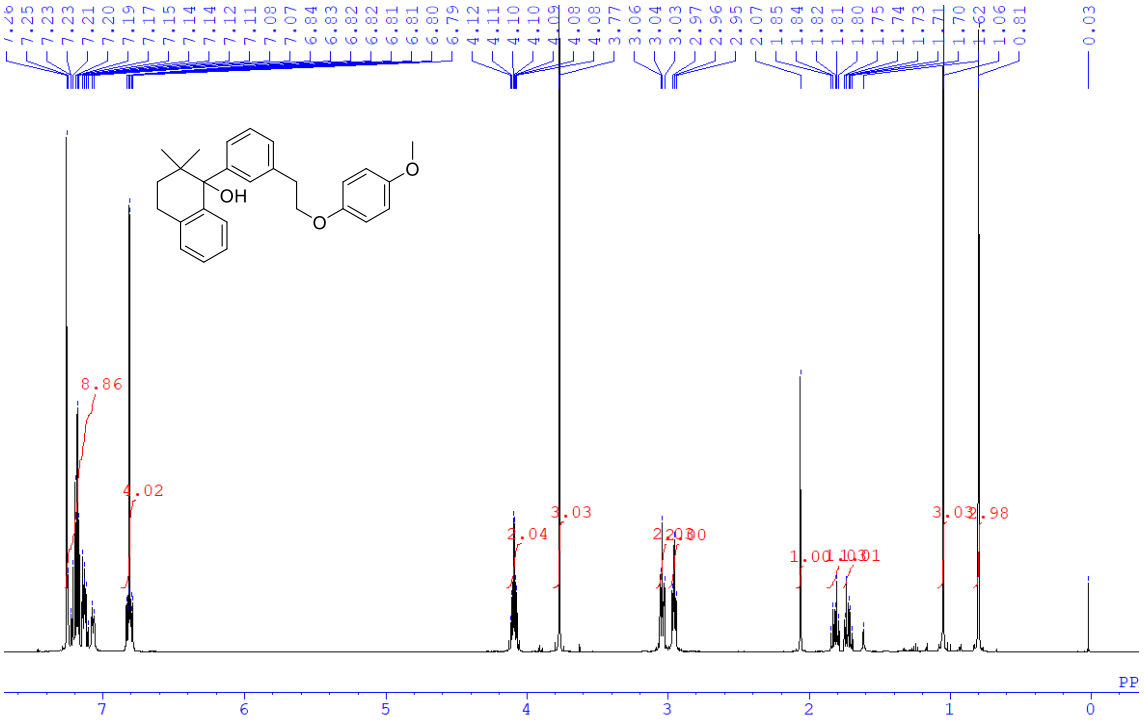
^{1}H NMR spectrum of Compound 4



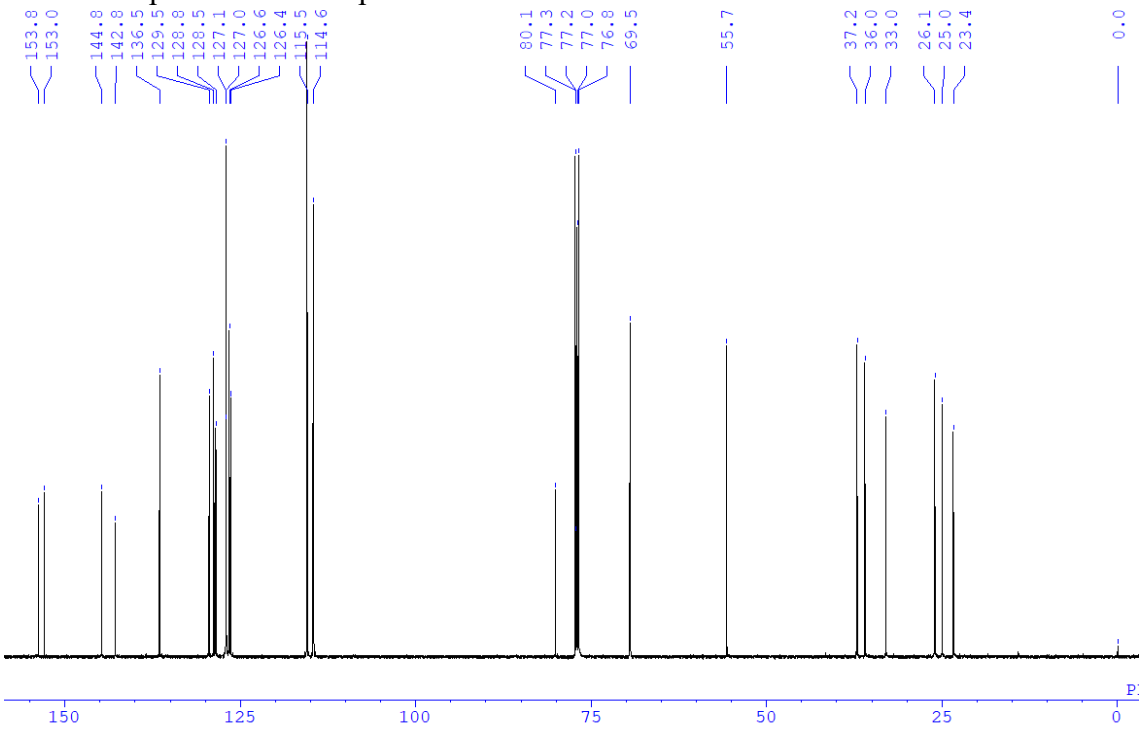
^{13}C NMR spectrum of Compound 4



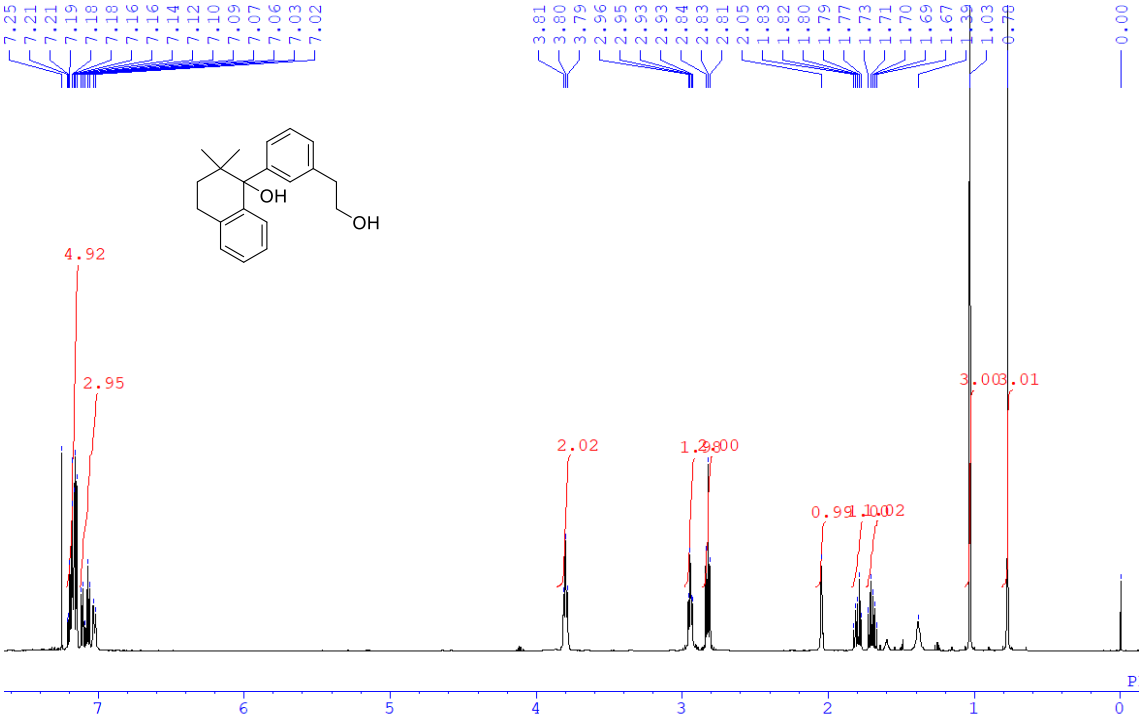
^{1}H NMR spectrum of Compound 22



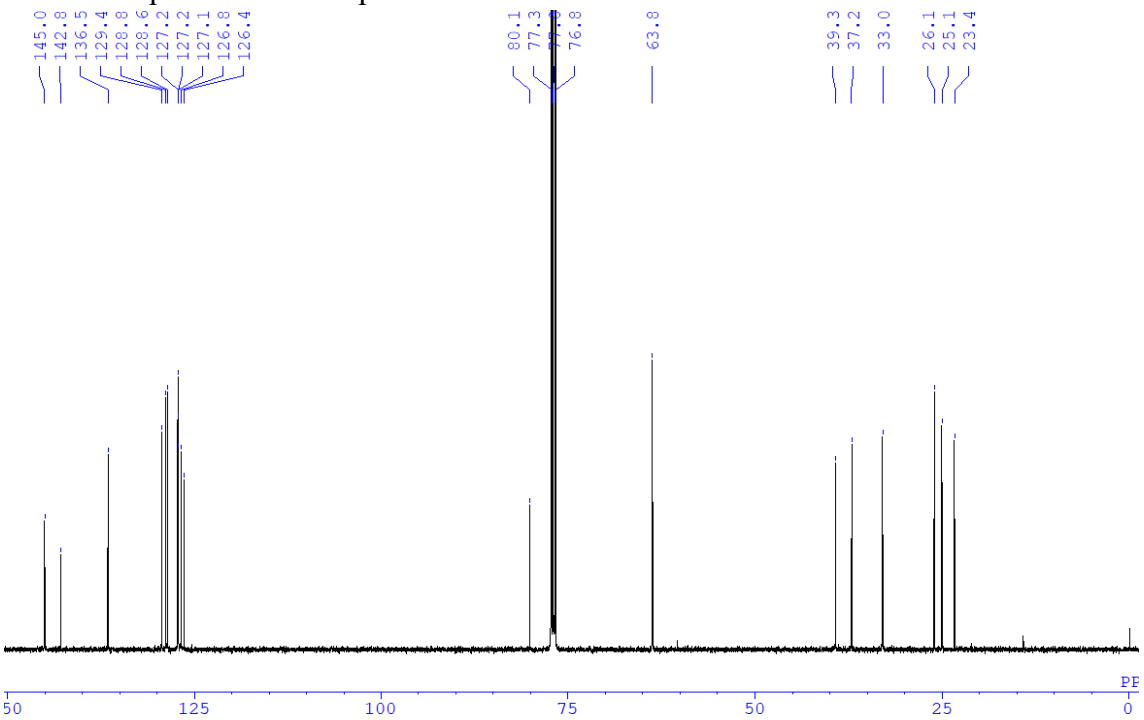
^{13}C NMR spectrum of Compound 22



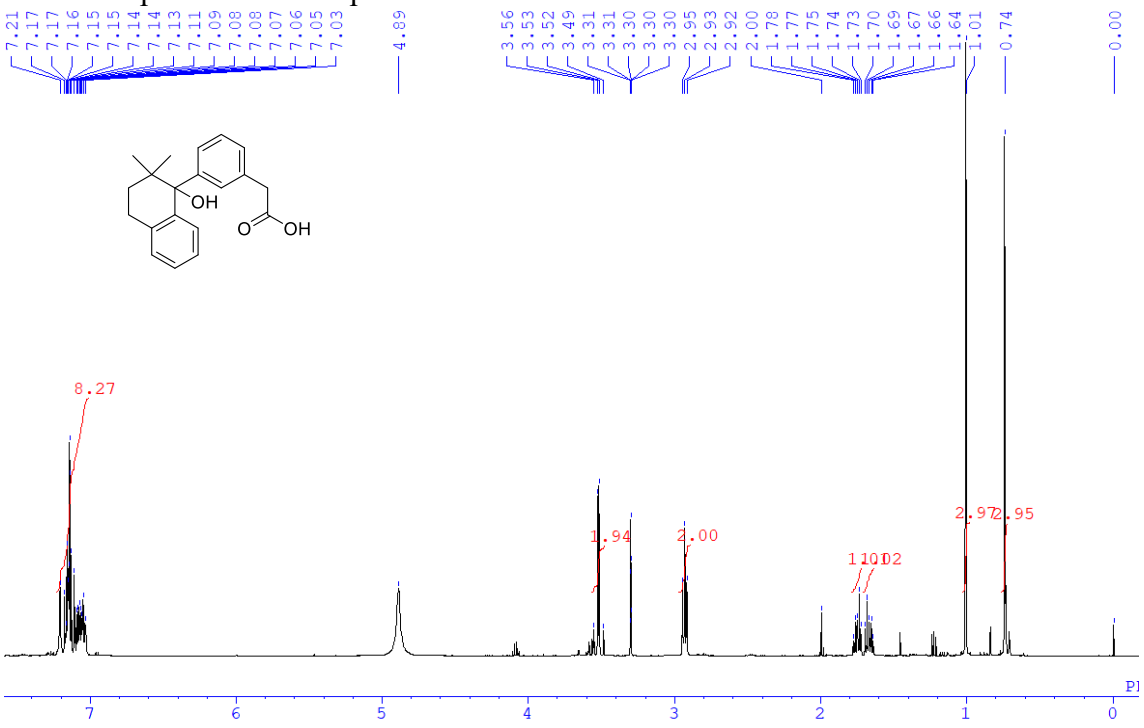
^{1}H NMR spectrum of Compound 23



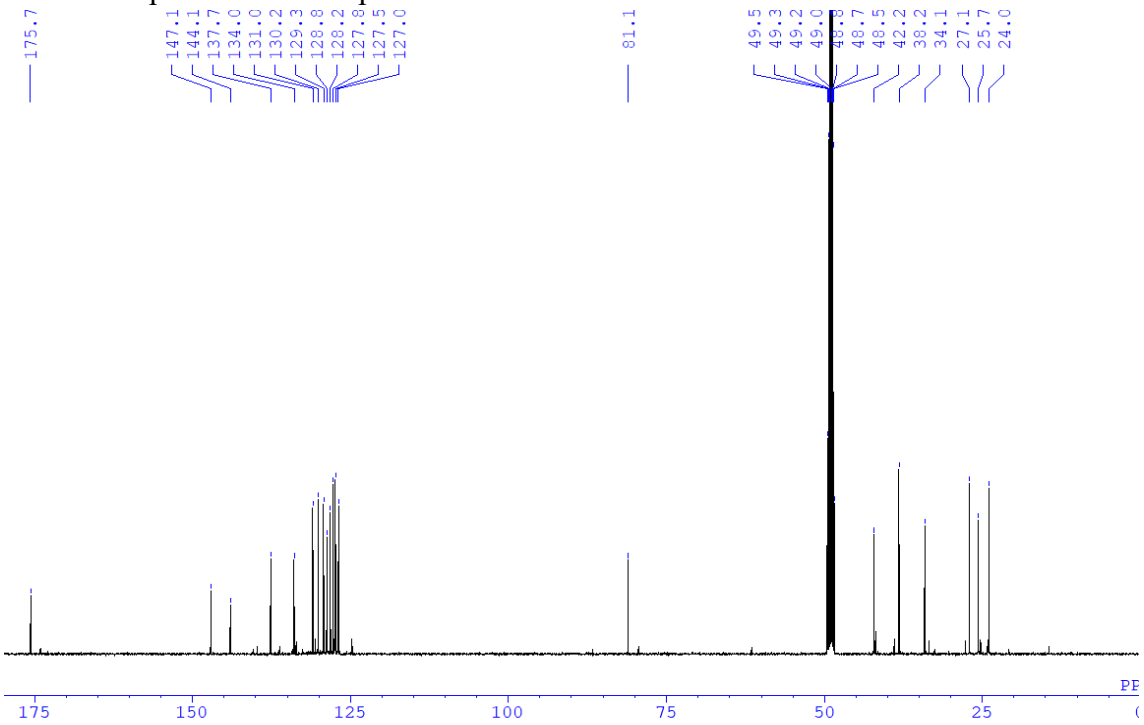
^{13}C NMR spectrum of Compound 23



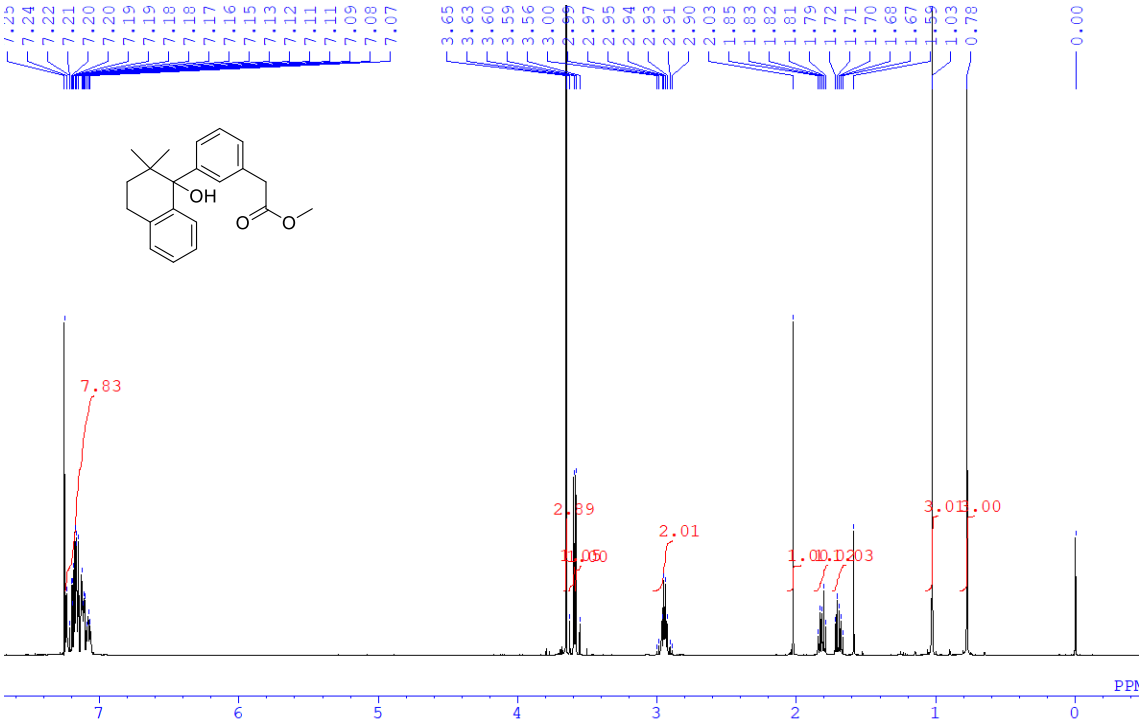
^{1}H NMR spectrum of Compound 24



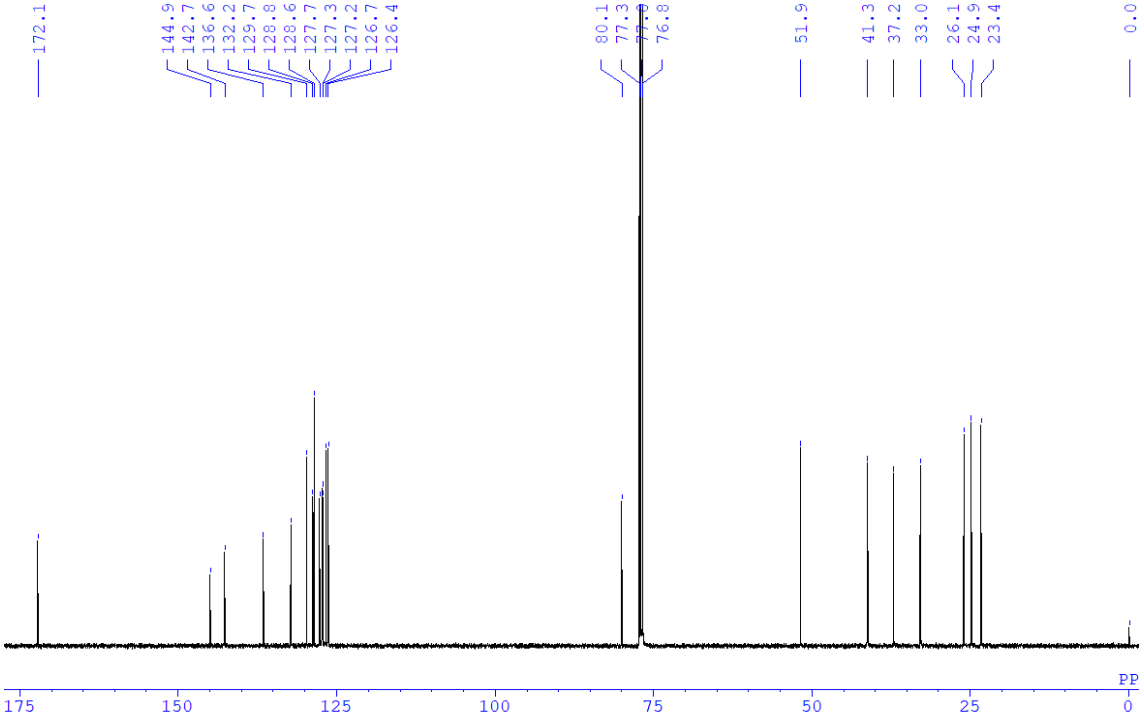
^{13}C NMR spectrum of Compound 24



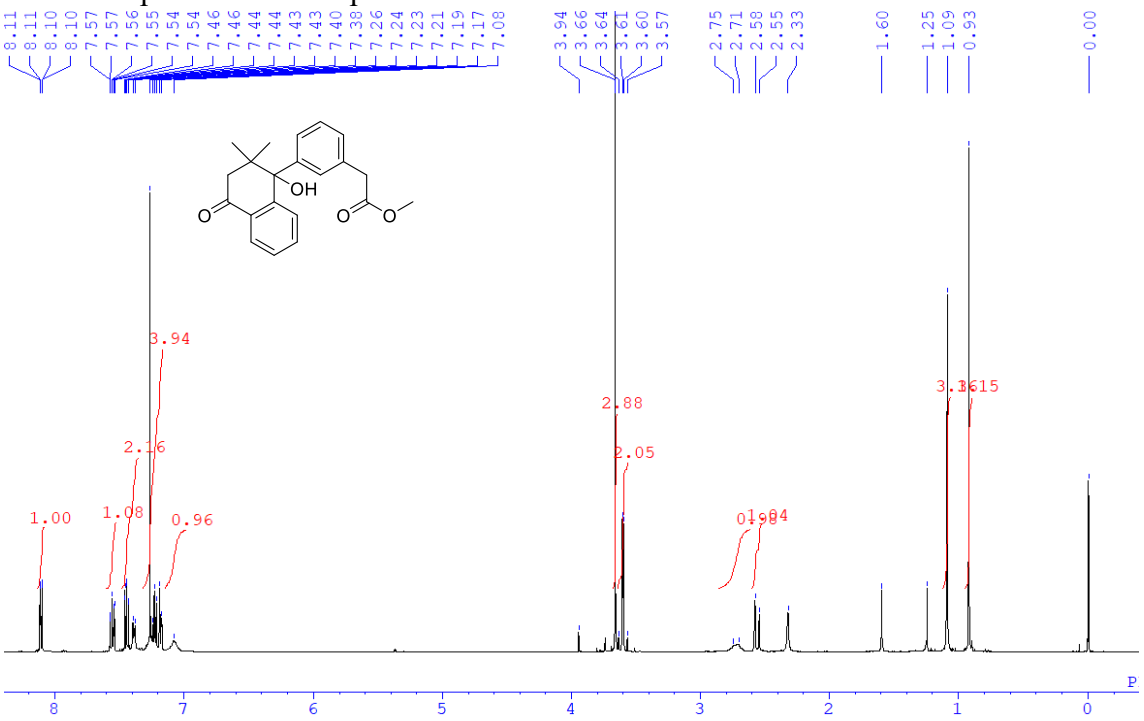
^{1}H NMR spectrum of Compound 25



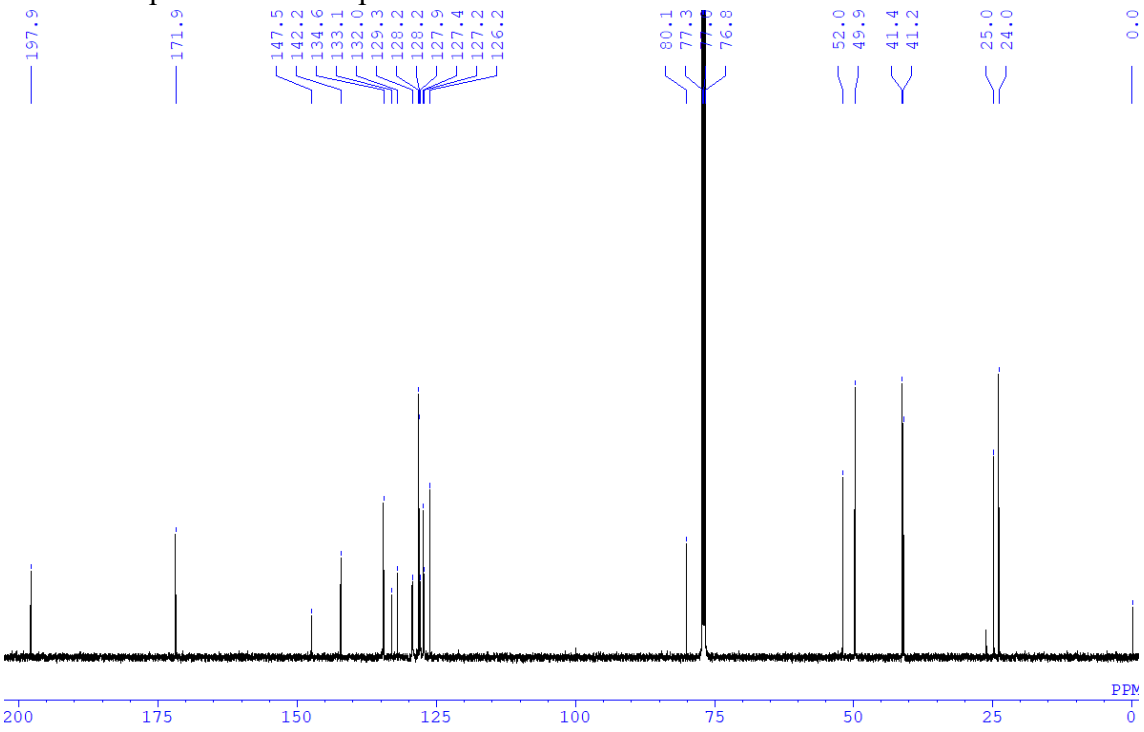
^{13}C NMR spectrum of Compound 25



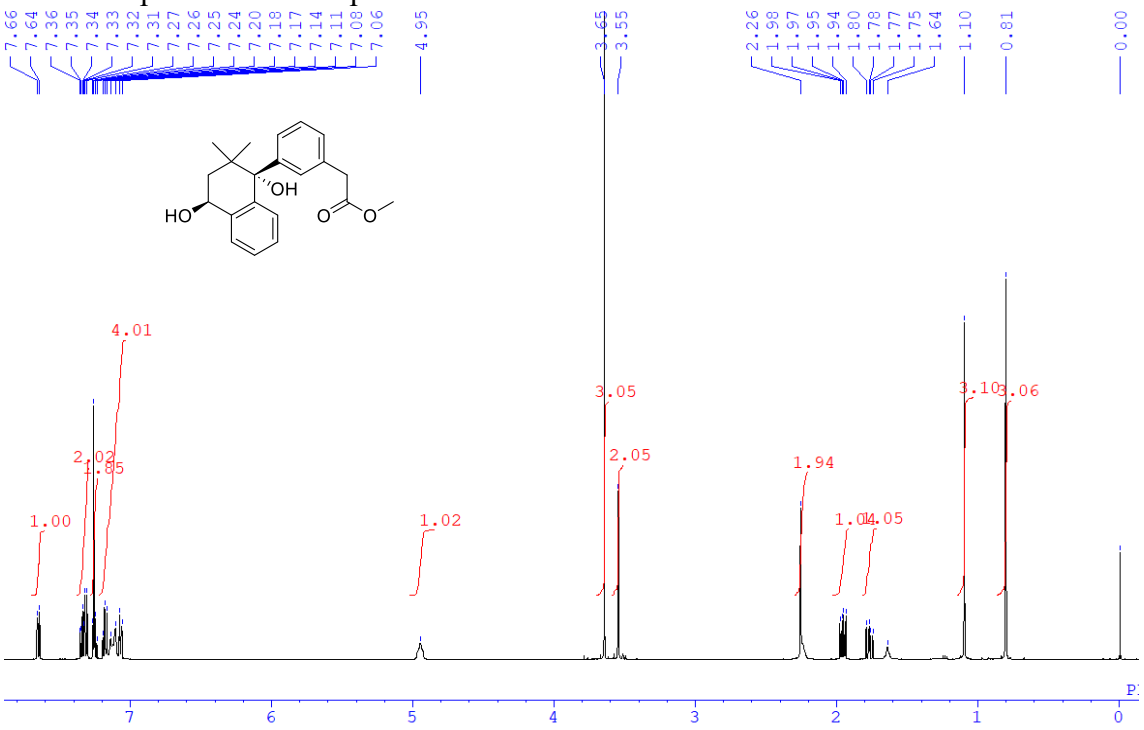
^{1}H NMR spectrum of Compound 5



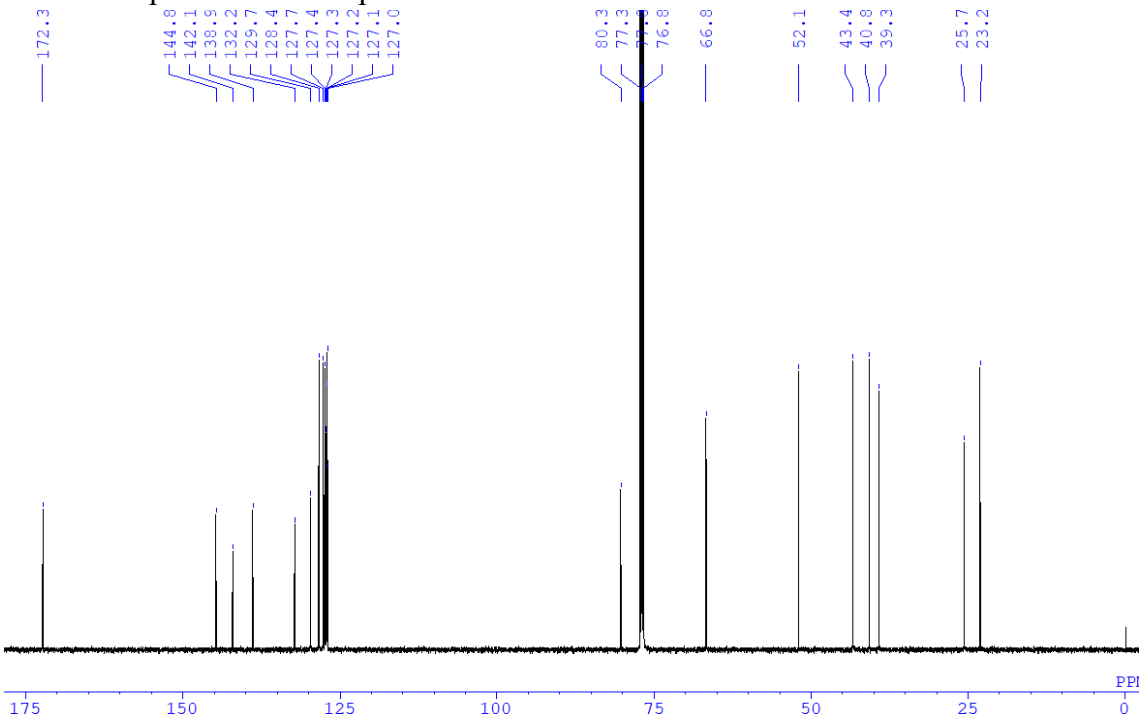
^{13}C NMR spectrum of Compound 5



^{1}H NMR spectrum of Compound 6



^{13}C NMR spectrum of Compound 6



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