Electronic Supplementary Materials

A concise and efficient total synthetic route of active stilbene dimer (±)-*ε*-viniferin†

Qibin Zhu,‡ Binhao Teng,‡ Ying Chen,‡ Fubao Su, Yanqiu Li, Qingyun Yang and Chunsuo Yao*

[a] State Key Laboratory of Bioactive Substance and Function of Natural Medicines, Institute of Materia Medica, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing 100050, P. R. China

*Fax: +86-10-6301-7757; e-mail: yaocs@imm.ac.cn

‡ These authors contributed equally to this work.

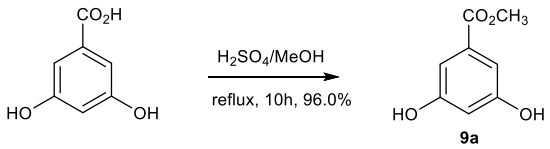
Content

Section 1. General Experimental

Unless otherwise mentioned, solvents and reagents were purchased from commercial sources. All commercially available reagents were used without further purification. Unless otherwise stated, dry solvents were **s**uper dry solvent from commercial sources. Some solvents used in the reactions were dried by different ways. CH_2Cl_2 was dried by $CaSO_4$ or P_2O_5. DMF was dried by $MgSO_4$. HR-MS-ESI and ESI spectra were measured using an AccuToFCS JMST100CS spectrometer (AgilentTechnologies, Ltd, Santa Clara, CA, USA). Column chromatography (CC) was performed with silica gel (200-300 mesh, Qingdao Marine Chemical Inc. Qingdao, China). The reaction progress was detected by TLC. TLC was carried out with glass precoated silica gel GF254 plates (Qingdao Marine Chemical, Inc., Qingdao, China). Spots were visualized under UV light. ^1H and ^{13}C NMR spectra for all compounds were recorded at 400/500/600 and 100/125/150 MHz **(**Bruker Corporation, Karlsruhe, Germany), respectively, and the chemical shifts are reported in ppm. In most of the cases, yields refer to isolated yields after purification.

Section 2. Experimental for the synthesis of (±)-ε-viniferin

Methyl 3,5-dihydroxyl benzoate (9a).

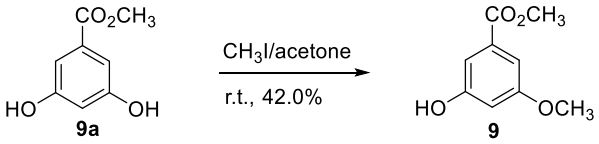


9a

To a solution of 3,5-Dihydroxybenzoic Acid (100.00 g, 64.9 mmol) in methanol (400 mL) was added concentrated sulfuric acid (10 mL in 100 mL methanol), and the solution was allowed to reflux for 10 h. After cooled to ambient temperature, methanol was evaporated under reduced pressure and the residue was dissolved in ethyl acetate (300 mL), which was then washed with saturated $NaHCO_3$ solution and water. The organic layer was dried over anhydrous Na_2SO_4 and ethyl acetate was removed *in vacuo* to afford methyl 3,5-dihydroxyl benzoate **9a** (104.7 g, 96%) as a white powder.

Methyl 3,5-dihydroxyl benzoate, white powder (**9a**), m.p. 165.1 - 168.4 ˚C . ^1H NMR (500 MHz, acetone-d_6): δ 8.54 (s, 2H), 7.00 (d, J = 2.1 Hz, 2H), 6.58 (t, J = 2.1 Hz, 1H), 3.83 (s, 3H). ESI-MS *m/z* 169.0 $[M+H]^+$, 191.0 $[M+Na]^+$.

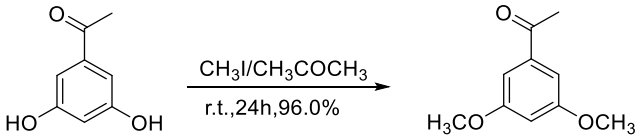
Methyl 5-hydroxyl-3-methoxy benzoate (9)



The acquired methyl 3,5-dihydroxylbenzoate **9a** (53.0 g, 315.5 mmol) was dissolved in acetone (500 mL), and K_2CO_3 (88.4 g, 639.5 mmol) was added to the solution slowly under stirring. Then the mixture was stirred for 30 min at room temperature. Iodomethane (45.5 g, 319.5 mmol) was added and the resulted solution was stirred at room temperature for 18 h. The mixture was filtered through celite and the filter cake was washed with acetone. The solvent was evaporated in vacuo, and the residue was subjected to silica column chromatography (petroleum : acetone = 6 : 1, v/v) to afford compound Methyl 5-hydroxyl-3-methoxy benzoate **9** as a white amorphous powder (24.1 g, 42.0%).

Methyl 5-hydroxyl-3-methoxy benzoate (**9**)： white amorphous powder, ^{1}H NMR (500 MHz, acetone-d_6): δ 8.66 (s, 1H), 7.09 (dd, J = 2.2, 1.3 Hz, 1H), 7.04 (dd, J = 2.2, 1.3 Hz, 1H), 6.64 (t, J = 2.2 Hz, 1H), 3.85 (s, 3H), 3.81 (s, 3H). ESI-MS *m/z* 183.0 $[M+H]^+$, 205.0 $[M+Na]^+$.

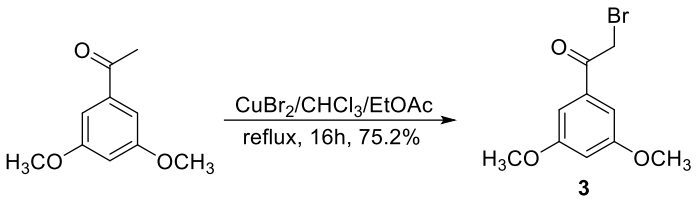
3,5-Dimethoxyacetophenone



K_2CO_3 (91.0 g, 654.6 mmol) was added to a stirred solution of 3',5'-dihydroxyacetophenone (25.0 g, 165 mmol) in 250 mL of acetone, and the mixture was stirred for 15 min before iodomethane (93.3 g, 654.6 mmol) was added in batches. Then the solution was stirred at room temperature for 24 h. The mixture was filtered through celite and the filter cake was washed with acetone. The solvent was evaporated in vacuo to afforded 3,5-dimethoxyacetophenone (30.8 g, 96.0%) quantitatively.

3,5-dimethoxyacetophenone： red block solid, ^{1}H NMR (500 MHz, acetone-d_6): δ 7.10 (d, J = 2.2 Hz, 2H), 6.71 (t, J = 2.2 Hz, 1H), 3.84 (s, 6H), 2.55 (s, 3H). ESI-MS: *m/z* 181.1 $[M+H]^+$, 203.0 $[M+Na]^+$, 219.0 $[M+K]^+$.

2-Bromo-3,5-dimethoxyacetophenone (3)

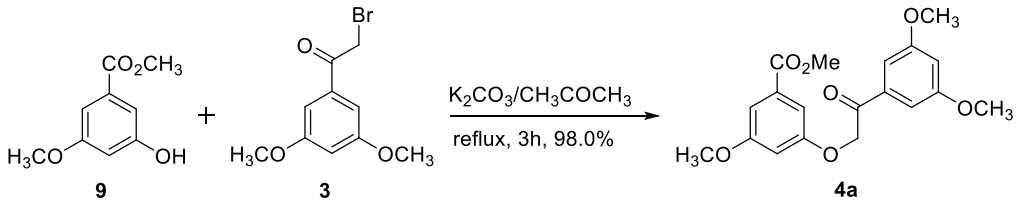


3

The attained 3,5-dimethoxyacetophenone (6.5g, 36 mmo) was dissolved in a solution of chloroform and ethyl acetate (375 mL : 375 mL,v/v). $CuBr_2$ (15.8 g, 72 mmol) was added to the solution, and the mixture was refluxed for 18 h. After cooled to room temperature, the reaction mixture was filtered through celite and washed with ethyl acetate. The organic layer was evaporated *in vacuo* and the resulted residue was purified by silica gel (200-300 mesh) column chromatography (petroleum ether: ethyl acetate: dichloromethane = 90 : 2 : 5) to afford compound **3** as a dark red solid ((7.03 g, 75%).

2-bromo-3,5-dimethoxyacetophenone (**3**): dark red solid, ^{1}H NMR (500 MHz, acetone-d_6): δ 7.13 (d, J = 2.2 Hz, 2H), 6.72 (t, J = 2.2 Hz, 1H), 4.72 (s, 2H), 3.82 (s, 6H). ESI-MS: *m/z* 281.0 $[M+Na]^+$.

Methyl 3-[2-(3,5-dimethoxyphenyl)-2-oxoethoxy]-5-methylbenzoate (4a)

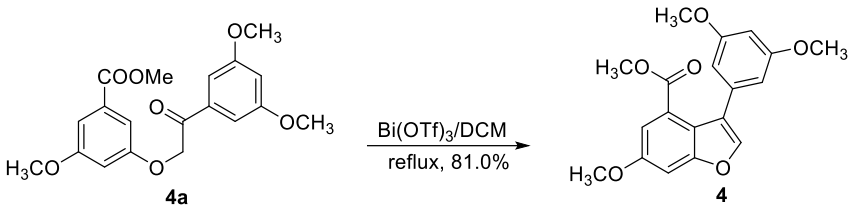


9 **3** **4a**

Powdered K_2CO_3 (7.39 g, 53.5 mmol) was added to a stirred solution of **9** (4.5 g, 26.8 mmol) and **3** (6.9 g, 26.8 mmol) in acetone (150 mL). The mixture was stirred at room temperature for 1h before refluxed for 3 h. Then the mixture was cooled to ambient temperature, filtered through celite and washed with acetone. The organic layer was removed by reduced pressure and the residue was purified by silica gel column chromatography (petroleum ether : ethyl acetate: dichloromethane = 30 : 2 : 5) to afford compound **4a** (8.7g, 98.0%) as a white amorphous powder.

Methyl 3-(2-(3,5-dimethoxyphenyl)-2-oxoethoxy)-5-methylbenzoate (**4a**): white amorphous powder, ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.15 (d, J = 2.5 Hz, 2H), 7.07-7.09 (m, 2H), 6.85 (m, 1H), 6.82 (m, 1H), 5.64 (s, 2H), 3.82 (s, 9H), 3.79 (s, 3H), 3.32 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 193.92, 165.85, 160.70 (2 × C), 160.42, 159.18, 136.14, 131.55, 107.72, 106.92, 106.12, 105.66, 105.60,70.48, 55.59 (3 × C), 52.29. (+)-HRESI-MS: *m/z* 361.1287 $[M+H]^+$ (Calcd for $C_{19}H_{21}O_7$: 361.1282).

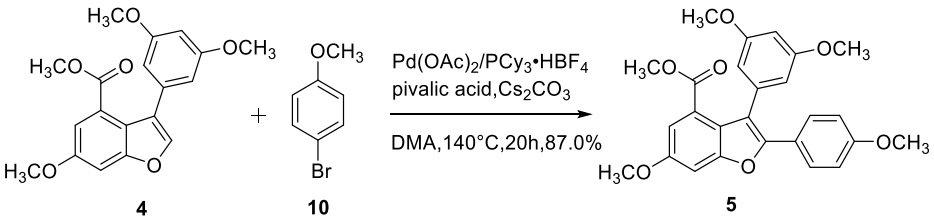
3-(3,5-Dimethoxyphenyl)-6-methoxybenzofuran-4-carboxylic acid methyl ester (4)



$Bi(OTf)_3$ (1.824 g, 2.78 mmol) was slowly added to a stirred solution of **4a** (10.00 g, 27.8 mmo) in dichloromethane (500 mL), and the mixture was stirred at 55 ˚C for 23 h. Then the reaction mixture was cooled to room temperature, washed with saturated $NaHCO_3$ solution and water. The organic layer was combined and dried on anhydrous Na_2SO_4. After removing of the solvent under reduced pressure, the residue was purified by silica gel column chromatography (petroleum ether : ethyl acetate: dichloromethane = 60 : 2 : 5) to afford a off-white amorphous powder **4** (7.70 g, 81.0%).

Methyl 3-(3,5-dimethoxyphenyl)-6-methoxybenzofuran-4-carboxylate (**4**): off-white amorphous powder, ^{1}H NMR (500 MHz, acetone-d_6): δ 7.89 (s, 1H), 7.38 (d, J = 2.2 Hz, 1H), 7.24 (d, J = 2.2 Hz, 1H), 6.50 (s, 3H), 3.93 (s, 3H), 3.81 (s, 6H), 3.30 (s, 3H). ^{13}C NMR (125 MHz, acetone-d_6): δ 168.05, 161.79 (2 × C), 158.60, 157.97, 144.09 (2 × C), 135.81, 127.09, 123.82, 118.81, 113.72, 107.16 (2 × C), 100.17, 100.10, 56.44, 55.69 (2 × C), 51.61. (-)-HRESI-MS: *m/z* 341.1155 $[M-H]^-$ (Calcd for $C_{19}H_{17}O_6$: 341.1148).

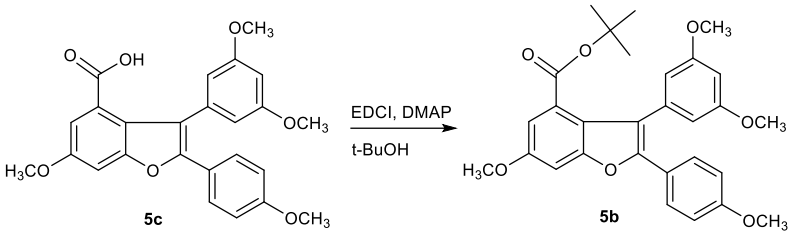
3-(3,5-Dimethoxyphenyl)-6-methoxy-2-(4-methoxyphenyl)-4-benzofurancarboxylic acid methyl ester (5)



Cs_2CO_3 (4.17g, 30.0 mmol), $Pd(OAc)_2$ (500 mg, 2.0 mmol), pivalic acid (6.12g, 60.0 mmol), $PCy_3 \cdot HBF_4$ (1.47g, 4.0 mmol), and 4-bromoanisole **10** (3.7 mL, 30.0 mmol) was added in sequence to a stirred solution of **4** (6.84g, 20.0 mmol) in DMA (250 mL) at room temperature. The mixture was stirred in a sealed tube filled with dry argon at 140℃ for 18 h. Then the mixture was filtered through celite and washed with ethyl acetate. The organic layer was concentrated under reduced pressure, and the residue was recrystallized in acetone to afford a colorless crystal **5** (7.8 g, 87.0%).

Methyl 3-(3,5-dimethoxyphenyl)-6-methoxy-2-(4-methoxyphenyl)-benzofuran-4-carboxylate (**5**)：colorless crystal, ^{1}H NMR (500 MHz, acetone-d_6): δ 7.51 (d, J = 9.0 Hz, 2H), 7.37 (d, J = 2.3 Hz, 1H), 7.17 (d, J = 2.3 Hz, 1H), 6.90 (d, J = 9.0 Hz, 2H), 6.56 (t, J = 2.3 Hz, 1H), 6.49 (d, J = 2.3 Hz, 2H), 3.94 (s, 3H), 3.81 (s, 3H), 3.79 (s, 6H), 3.20 (s, 3H). ^{13}C NMR (125 MHz, acetone-d_6): 167.92, 162.27 (2 × C), 160.90, 158.33, 156.11, 152.23, 137.20, 128.96 (2 × C), 126.78, 123.65, 122.03, 116.86, 114.77 (2 × C), 113.39, 108.54 (2 × C), 100.51, 99.64, 56.43, 55.76 (2 × C), 55.65, 51.60. (+)-HRESI-MS: *m/z* 449.1577 $[M+H]^+$ (Calcd for $C_{26}H_{25}O_7$: 449.1595).

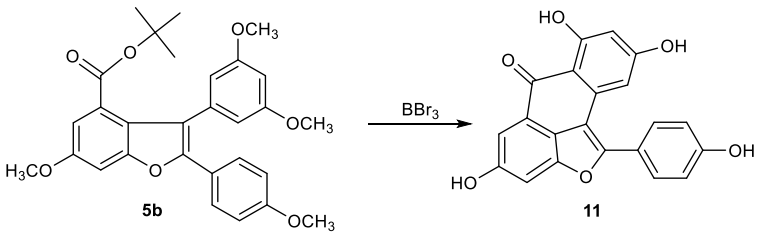
3-(3,5-Dimethoxyphenyl)-6-methoxy-2-(4-methoxyphenyl)benzofuran-4-carboxylic acid *tert*-butyl ester (5b)



EDCI (70.1 mg, 0.28 mmol) and DMAP (33.7 mg, 0.2 mmol) was added in sequence to a stirred solution of **5c** (100 mg, 0.23 mmol) in dichloromethane (20 mL) at room temperature. After 20 min, 75 μL *tert*-butyl alcohol was added, and the reaction mixture was stirred for 26 h. After completion, the mixture was concentrated in vaccuo, and the residue was purified by preparative chromatography (petroleum ether : ethyl acetate : dichloromethane = 5 : 1 : 2, v/v) to afford compound **5b** as a white amorphous powder (51.6 mg, 45.7%).

3-(3,5-dimethoxyphenyl)-6-methoxy-2-(4-methoxyphenyl)benzofuran-4-carboxylic acid tert-butyl ester (**5b**)：white amorphous powder，^{1}H NMR (500 MHz, Chloroform-d) δ 7.48 (d, J = 8.9 Hz, 2H), 7.20 (t, J = 1.9 Hz, 2H), 6.82 (d, J = 8.9 Hz, 2H), 6.52 (d, J = 2.3 Hz, 2H), 6.48 (t, J = 2.3 Hz, 1H), 3.90 (s, 3H), 3.80 (s, 3H), 3.76 (s, 6H), 1.25 (s, 9H). ^{13}C NMR (126 MHz, cdcl$_3$) δ 167.94, 161.23 (2×C), 159.78, 157.29, 155.43, 151.75, 136.47, 128.45 (2×C), 126.11, 123.14, 121.37, 115.84, 113.98 (2×C), 112.24, 107.59 (2×C), 100.37, 99.39, 61.31, 56.20, 55.58 (2×C), 55.42, 29.85 (2×C).

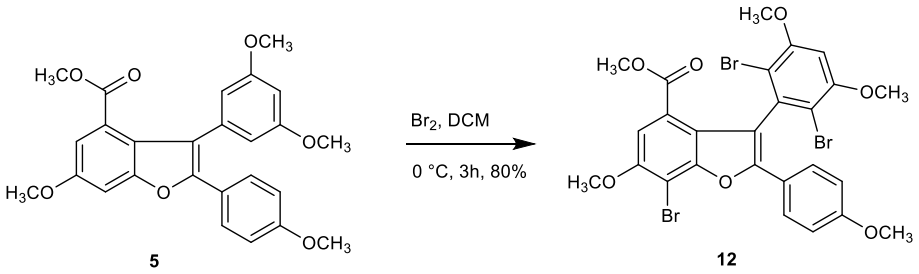
4,7,9-Trihydroxy-1-(4-hydroxyphenyl)-*6H*-anrhra(1,9-bc)furan-6-one (11)



To a solution of compound **5b** (20 mg, 0.04 mmol) in redistilled dichloromethane (10 ml), a solution of BBr3 (0.4 mmol) in redistilled dichloromethane (5 ml) was added dropwise at -45 ℃ within 30 min, and the mixture was stirred for 2 h at the same temperature. Then the mixture was warmed up to -25 ℃, 10 ℃, 0 ℃, and stirred for another 2 h respectively. After stirred overnight at room temperature, methanol (3 ml) was added dropwise at -45 ˚C to quench the reaction. The solution was diluted with 30 ml ethyl acetate, washed with water, dried over anhydrous Na2SO4, and evaporated under reduced pressure to afford a residue, which was then purified through silica gel preparative chromatography (dichloromethane: MeOH 10: 1, v/v) to afford compound **11** as a brown oil (5.2 mg, 35.6%).

4,7,9-trihydroxy-1-(4-hydroxyphenyl)-*6H*-anrhra(1,9-bc)furan-6-one (**11**)：brown oil，^{1}H NMR (500 MHz, Methanol-d_4) δ 7.80 (d, J = 8.7 Hz, 2H), 7.48 (d, J = 1.7 Hz, 1H), 7.26 (d, J = 1.7 Hz, 1H), 7.21 (d, J = 2.4 Hz, 1H), 7.04 (d, J = 8.7 Hz, 2H), 6.32 (d, J = 2.3 Hz, 1H). (+)-HRESI m/z: 359.0563 $[M+H]^+$ (Calcd for $C_{21}H_{11}O_6$: 359.0561).

2-(4-Methoxyphenyl)-3-(2,6-dibromo-3,4-dimethoxyphenyl)-7-bromo-6-methoxy-4-benzofurancarboxylic acid methyl ester (12)

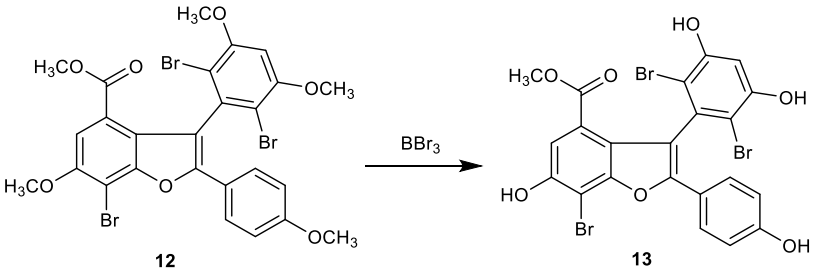


Bromine (356.3 mg, 2.2 mmol) was aded to a stirred solution of **5** (100 mg, 0.22 mmol) in dry dichloromethane (30ml), and the mixture was stirred for 3h at 0 ℃. After completion, the reaction mixture was diluted with EtOAc, washed with brine, dried

over Na_2SO_5, and concentrated under reduced pressure to afford a residue, which was purified by silica gel preparative chromatography (petroleum ether : ethyl acetate : dichloromethane, 5 : 1 : 2, v/v) to afford compound **12** as a white amorphous powder (121.9 mg, 80%).

2-(4-methoxyphenyl)-3-(2,6-dibromo-3,4-dimethoxyphenyl)-7-bromo-6-methoxy-4-benzofurancarboxylic acid methyl ester (**12**)：white amorphous powder，^{1}H NMR (500 MHz, CD_3Cl_3) δ 7.41 (d, J = 8.9 Hz, 2H), 7.20 (s, 1H), 6.83 (d, J = 9.0 Hz, 2H), 6.64 (s, 1H), 3.98 (s, 9H), 3.79 (s, 3H), 3.34 (s, 3H). ^{13}C NMR (126 MHz, CD_3Cl_3) δ 165.66, 160.14, 156.60 (2×C), 153.83, 153.71, 151.81, 135.99, 127.84, 127.34 (2×C), 122.70, 120.16, 114.39 (2×C), 114.22, 113.57, 107.11, 100.97, 97.13, 96.80, 57.14, 56.89, 56.84, 55.40, 51.87. (+)-HRESI *m/z*: 682.8919 $[M+H]^+$ (Calcd for $C_{26}H_{22}O_7Br_3$: 682.8910).

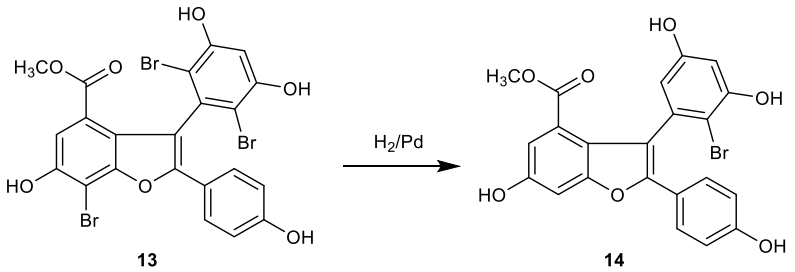
2-(4-Hydroxyphenyl)-3-(2,6-dibromo-3,4-dihydroxyphenyl)-7-bromo-6-hydroxy-4-benzofurancarboxylic acid methyl ester (13)



To a solution of compound **12** (20 mg, 0.029 mmol) in redistilled dichloromethane (20 ml), a solution of BBr3 (0.29 mmol) in redistilled dichloromethane (5 ml) was added dropwise at -45 ℃ within 30 min, and the mixture was stirred for 2 h at the same temperature. Then the mixture was warmed up to -25 ℃, -10 ℃, 0 ℃, and stirred for another 2 h respectively. After stirred overnight at room temperature, methanol (3 ml) was added dropwise at -45 ˚C to quench the reaction. The solution was diluted with 50 ml ethyl acetate, washed with water, dried over anhydrous Na2SO4, and evaporated under reduced pressure to afford a residue. The residue was then purified by silica gel preparative chromatography (dichloromethane: MeOH 10: 1, v/v) to afford compound **13** as a red amorphous powder (7.1 mg, 38.9%).

2-(4-hydroxyphenyl)-3-(2,6-dibromo-3,4-dihydroxyphenyl)-7-bromo-6-hydroxy-4-benzofurancarboxylic acid methyl ester (**13**)：red amorphous powder，^{1}H NMR (500 MHz, acetone-d_6) δ 9.32 (s, 1H), 9.09 (s, 1H), 7.59 (s, 1H), 7.51 (d, J = 8.6 Hz, 2H), 6.99 (d, J = 8.7 Hz, 2H), 6.72 (s, 1H), 4.03 (s, 3H), 3.79 (s, 3H).

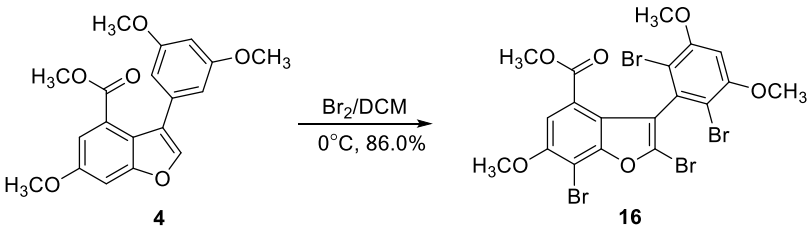
2-(4-Hydroxyphenyl)-3-(2-bromo-3,4-dihydroxyphenyl)-6-hydroxy-4-benzofurancarboxylic acid methyl ester (14)



To a stirred solution of **13** (20 mg, 0.032 mmol) in methanol (10 mL) was added 10% Pd-C (8 mg). The mixture was stirred under hydrogen atmosphere (0.6 MPa) for 16 hours. Subsequently, the reaction mixture was filtered, and the filtrate was reduced in vacuo. The residue was then purified through silica gel column chromatography using dichloromethane : methanol = 10 : 1 as eluent to yield **14** as a colorless oil (11.8 mg, 78.6%).

2-(4-hydroxyphenyl)-3-(2-bromo-3,4-dihydroxyphenyl)-6-hydroxy-4-benzofurancarboxylic acid methyl ester (**14**)：colorless oil，^{1}H NMR (500 MHz, Acetone-d_6) δ 13.10 (s, 1H), 9.19 (s, 1H), 8.60 (s, 1H), 8.04 (s, 1H), 7.12 (d, J = 2.5 Hz, 1H), 6.83 (d, J = 2.6 Hz, 1H), 6.50 – 6.42 (m, 3H), 6.33 (d, J = 2.5 Hz, 1H), 6.26 (d, J = 8.4 Hz, 2H), 3.86 (s, 3H).

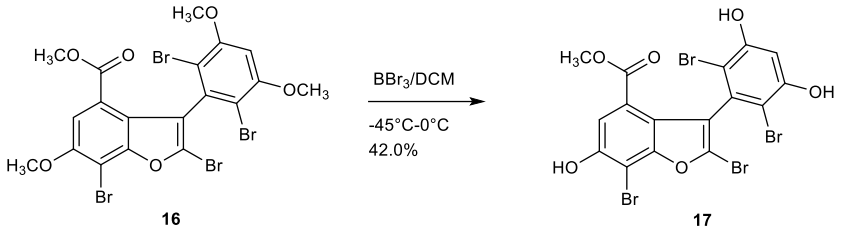
3-(2,6-Dibromo-3,4-dimethoxyphenyl)-2,7-dibromo-6-methoxy-4-benzofuran carboxylic acid methyl ester (16)



A solusion of bromine (4.5 ml) in dichloromethane (100 ml) was aded to a stirred solution of **4** (3.0 g, 10 mmol) in dry dichloromethane (200ml), and the mixture was stirred for 6h at 0 ℃. After completion, the reaction was quenched with ice-water mixture. The mixture was then extracted with dichloromethane, washed with aqueous solusion of 10% $Na_2S_2O_4$, brine, dried over Na_2SO_5, and concentrated under reduced pressure to afford compound **16** as a white amorphous powder (6.6 g, 86.0%).

3-(2,6-dibromo-3,4-dimethoxyphenyl)-2,7-dibromo-6-methoxy-4-benzofurancarboxylic acid methyl ester (**16**)：white amorphous powder, ^{1}H NMR (400 MHz, chloroform-d_1): δ 7.15 (s, 1H), 6.62 (s, 1H), 3.97 (s, 9H), 3.30 (s, 3H). ^{13}C NMR (100 MHz, chloroform-d_1): δ 166.16, 156.83, 156.04 (3 × C), 137.72, 123.85, 121.72, 119.91, 117.37, 114.21, 106.14, 101.09 (2 × C), 96.48, 56.79 (2 × C), 56.13, 51.37. (+)-HRESI-MS: *m/z* 654.7569 $[M + H]^+$(Calcd for $C_{19}H_{15}O_6Br_4$: 654.7597).

3-(2,6-Dibromo-3,4-dihydroxyphenyl)-2,7-dibromo-6-hydroxy-4-benzofuran carboxylic acid methyl ester (17)

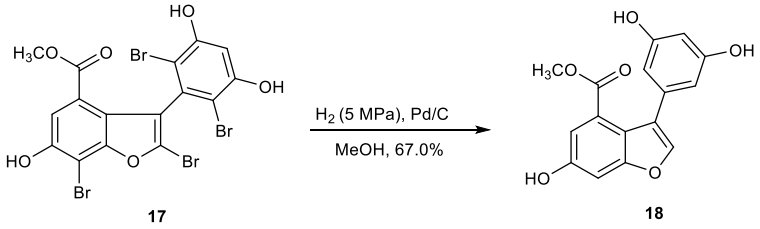


To a solution of compound **16** (200 mg, 0.305mmol) in dichloromethane (100 ml), a solution of BBr_3 (286 μL) in dichloromethane (10 ml) was added dropwise at -45 ℃ within 30 min, and the mixture was stirred for 2 h at the same temperature. Then the mixture was warmed up to -25 ℃, -10 ℃, 0 ℃, and stirred for another 2 h, respectively. After stirred overnight at room temperature, methanol was added dropwise at -45 ˚C to quench the reaction. The solution was diluted with ethyl acetate, washed with water, brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure to afford a residue. The residue was then purified by silica gel column chromatography (dichloromethane: MeOH = 20: 1, v/v) to afford compound **17** as a white amorphous powder (77.5 g, 42.0%).

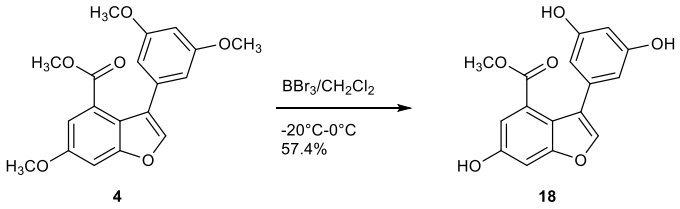
3-(2,6-dibromo-3,4-dihydroxyphenyl)-2,7-dibromo-6-hydroxy-4-benzofurancarboxylic acid methyl ester (**17**)：white amorphous powder, ^{1}H NMR (500

MHz, acetone-d_6): δ 7.34 (s, 1H), 6.89 (s, 1H), 3.27 (s, 3H). ^{13}C NMR (125 MHz, acetone-d_6): δ 165.42, 155.73, 155.16 (2 × C), 152.79, 133.64, 131.95, 129.57, 128.91, 128.85, 121.90, 119.47, 104.94, 104.38, 100.51, 52.02. (-)-HRESI-MS: *m/z* 610.6984 $[M - H]^-$ (Calcd for $C_{16}H_7O_6Br_4$: 610.6982).

3-(3,5-Dihydroxyphenyl)-6-hydroxy-4-benzofurancarboxylic acid methyl ester (18)



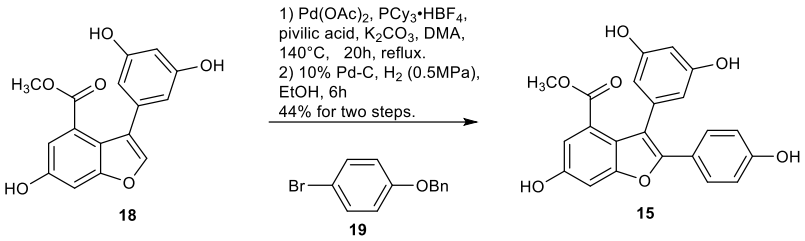
To a stirred solution of **17** (20 mg, 0.0487 mmol) in methanol (5 mL) was added 10% Pd-C (20 mg). The mixture was stirred under hydrogen atmosphere (0.5 MPa) for 6 hours. After completion, the reaction mixture was filtered, and the filtrate was reduced in vacuo. The residue was then purified through silica gel column chromatography using dichloromethane : methanol = 20 : 1 as eluent to yield **18** as a white solid (6.6 mg, 67.0%).



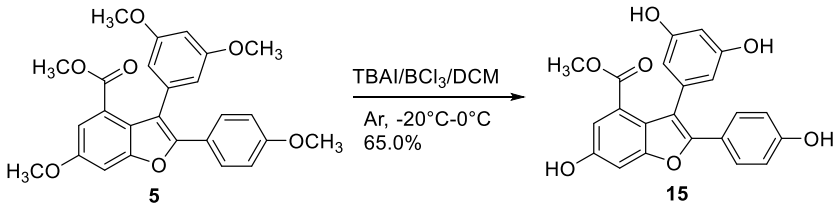
To a solution of compound **4** (50 mg, 0.146 mmol) in dichloromethane (20 ml), a solution of BBr_3 (1.5 mL, 1 mmol/L) in dichloromethane (15 ml) was added dropwise at -20 ℃, and the mixture was stirred for 2 h at the same temperature. Then the mixture was warmed up to -10 ℃ stirred for another 2 h. After stirred overnight at 0 ℃, methanol was added dropwise at 0 ℃ to quench the reaction. The solution was diluted with water, and filtered. The filtrate was then evaporated under reduced pressure. The residue was subsequently purified by silica gel column chromatography (dichloromethane: MeOH = 20: 1, v/v) to afford compound **18** as a white amorphous powder (25.1 mg, 57.4%).

3-(3,5-dihydroxyphenyl)-6-hydroxy-4-benzofurancarboxylic acid methyl ester (**18**)：white amorphous powder, ^{1}H NMR (400 MHz, acetone-d_6): δ 7.75 (s, 1H), 7.20 (d, J = 2.2 Hz, 1H), 7.18 (d, J = 2.2 Hz, 1H), 6.37 (t, J = 2.0 Hz, 1H), 6.32 (d, J = 2.0 Hz, 2H), 3.34 (s, 3H). ^{13}C NMR (100 MHz, acetone-d_6): δ 168.12, 159.30 (2 × C), 157.97, 155.96, 143.40, 135.92, 127.04, 124.01, 118.34, 114.12, 107.86 (2 × C), 102.26, 102.00, 51.48. (+)-HRESI-MS: *m/z* 323.0890 $[M + Na]^+$ (Calcd for $C_{17}H_{16}O_5Na$: 323.0890).

3-(3,5-Dihydroxyphenyl)-6-hydroxy-2-(4-hydroxyphenyl)-4-benzofuran carboxylic acid methyl ester (15)



K_2CO_3 (620 mg, 4.5 mmol), $Pd(OAc)_2$ (34 mg, 0.15 mmol), pivalic acid (62.0mg, 0.6 mmol), $PCy_3 \cdot HBF_4$ (110.4 mg, 0.3 mmol), and 4-bromoanisole **19** (0.93 mL, 7.5 mmol) was added in sequence to a stirred solution of **18** (900 mg, 3.0 mmol) in DMA (50 mL) at room temperature. The mixture was stirred in a sealed tube filled with dry argon at 140℃ for 20 h. The mixture was filtered through celite and washed with ethyl acetate. The organic layer was concentrated under reduced pressure, and the residue was redissolve in 100 ml ethanol. 100 mg 10% Pd/C was then added to the mixture, the mixture was stirred for 6h under hydrogen atmosphere (0.5 Mpa). After completion, the mixture was filtered through celite and washed with ethyl acetate. The organic layer was concentrated in vaccuo, and the residue was subsequently purified by silica gel column chromatography (dichloromethane: MeOH = 20: 1, v/v) to afford compound **15** as a white amorphous powder (516 mg, 44.0%).

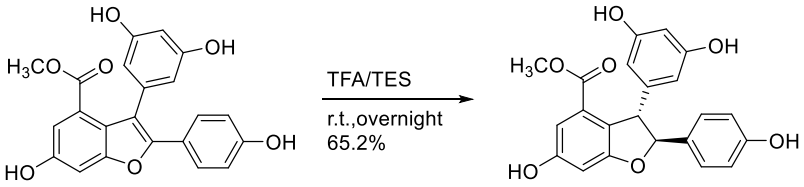


TBAI (7.41 g, 20.07 mmol) was added to a solution of compound **5** (900 mg, 2.007 mmol) in dichloromethane (200 ml), a solution of BCl_3 (32 mL, 1 mmol/L) in

dichloromethane (50 ml) was then added dropwise at -10 ℃, and the mixture was stirred for 12 h at the same temperature under argon atmosphere. Then the mixture was warmed up to 0 ℃ stirred for another 6 h. After completion, methanol was added dropwise at 0 ℃ to quench the reaction. The solution was diluted with water, and filtered. The filtrate was then evaporated under reduced pressure. The residue was subsequently purified by silica gel column chromatography (dichloromethane: methanol = 20: 1, v/v) to afford compound **15** as a white amorphous powder (511mg, 65.0%).

3-(3,5-dihydroxyphenyl)-6-hydroxy-2-(4-hydroxyphenyl)-4-benzofurancarboxylic acid methyl ester (**15**)：white amorphous powder, ^{1}H NMR (400 MHz, Methanol-d_4): δ 7.39 (d, J = 8.96 Hz, 2H), 7.03 (d, J = 2.4 Hz, 1H), 7.02 (d, J = 2.4 Hz, 1H), 6.70 (d, J = 8.96 Hz, 2H), 6.31 (t, J = 2.0 Hz, 1H), 6.23 (d, J = 2.0 Hz, 2H), 3.27 (s, 3H). ^{13}C NMR (100 MHz, Methanol-d_4): δ 167.57, 160.12 (2 × C), 158.99, 156.64, 156.17, 152.55, 138.02, 129.23 (2 × C), 126.38, 123.15, 121.88, 116.72, 116.15 (2 × C), 113.94, 109.34 (2 × C), 102.58, 101.69, 51.92. (+)-HRESI-MS: *m/z* 393.0962 $[M + H]^+$ (Calcd for $C_{22}H_{17}O_7$: 393.0969).

3-(3,5-Dihydroxyphenyl)-2,3-dihydro-6-hydroxy-2-(4-hydroxyphenyl)-4-benzofurancarboxylic acid methyl ester (20)



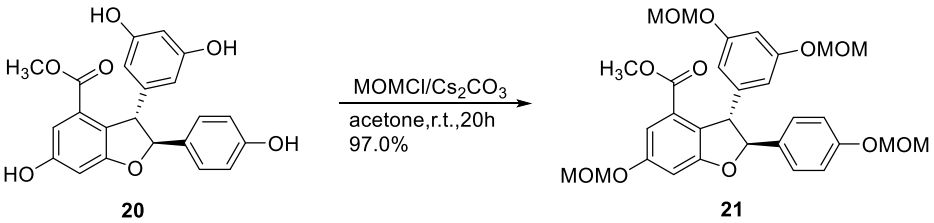
15 **20**

Triethylsilane (3.0 ml, 19.1 mmol) was added to a stirred solution of **15** (500 mg, 1.27 mmol) in trifluoroacetic acid (20 mL). The reaction mixture was allowed to react at room temperature overnight. TLC detection demonstrated a completion of the reaction, the solution was cooled to 0 ˚C. Saturated $NaHCO_3$ solution was slowly added to the reaction solution while vigorously stirring to neutralize the trifluoroacetic acid. The solution was then extracted with ethyl acetate (3 × 60 mL), and the combined organic layer was washed with brine and water. Afterwards, the organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was

chromatographed on silica gel using petroleum ehter : ethyl acetate (10 : 1) as the eluent to afford compound **20** a white amorphous powder (326 mg, 65.2%).

3-(3,5-Dihydroxyphenyl)-2,3-dihydro-6-hydroxy-2-(4-hydroxyphenyl)-4-benzofurancarboxylic acid methyl ester (20): White amorphous powder, ^{1}H NMR (400 MHz, methanol-d_4): δ 7.13 (d, J = 8.50 Hz, 2H), 6.94 (d, J = 2.4 Hz, 1H), 6.78 (d, J = 8.50 Hz, 1H), 6.58 (d, J = 2.4 Hz, 1H), 6.12 (t, J = 2.4 Hz, 1H), 5.98 (d, J = 2.4 Hz, 2H), 5.34 (d, J = 5.2 Hz, 1H), 4.62 (d, J = 5.2 Hz, 1H), 3.56 (s, 3H). ^{13}C NMR (100 MHz, Methanol-d_4): δ 168.15, 163.64, 159.95, 159.74 (2 × C), 158.59, 148.20, 134.03, 129.57, 127.97 (2 × C), 122.92, 116.36 (2 × C), 110.30, 106.66 (2 × C), 102.16, 101.82, 94.75, 58.82, 51.98. (-)-HRESI-MS: *m/z* 393.0962 $[M + H]^+$ (Calcd for $C_{22}H_{17}O_7$: 393.0969).

3-[(3,5-Bbis(methoxymethoxy)phenyl)-2,3-dihydro-6-(methoxymethoxy)-2-(4-methoxymethoxyphenyl)-4-benzofurancarboxylic acid methyl ester (21)

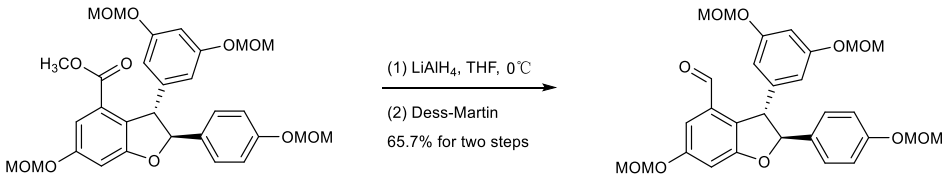


Cs_2CO_3 (830 mg, 2.55 mmol) was added to a solution of **20** (100 mg, 0.255 mmol) in anhydrous acetone (20 mL). After stirring for 10 min, MOMCl liquid (195 μL, 2.55 mmol) was added slowly, and stirred for 20 h at room temperature. After completion, the reaction mixture was filtered through a short pad of celite, washed with acetone (500 mL), and concentrated *in vacuo*. The remaining residue was suspended in water and extracted with EtOAc (20 mL × 3), the combined organic layer was dried over Na_2SO_4, concentrated in vacuo, subjected to silica gel column chromatography to furnish **21** (146.7 mg, 97.0%) as a yellow oil.

3-[(3,5-bis(methoxymethoxy)phenyl)-2,3-dihydro-6-(methoxymethoxy)-2-(4-methoxymethoxyphenyl)-4-benzofurancarboxylic acid methyl ester (**21**)**：** yellow oil, ^{1}H NMR (400 MHz, acetone-d_6): δ 7.30 (d, J = 8.60 Hz, 2H), 7.04 (d, J = 8.60 Hz, 1H), 7.18 (d, J = 2.4 Hz, 1H), 6.90 (d, J = 2.4 Hz, 1H), 6.61 (t, J = 2.4 Hz, 1H), 6.43 (d, J = 2.4 Hz, 2H), 5.54 (d, J = 3.6 Hz, 1H), 5.26 (s, 2H), 5.19 (s, 2H), 5.12 (s, 4H), 4.82 (d, J = 3.6 Hz, 1H), 3.59 (s, 3H), 3.47 (s, 3H), 3.36 (s, 6H), 3.42 (s, 3H). ^{13}C NMR (100 MHz, acetone-d_6): δ 166.24, 162.72, 159.44, 159.41 (2 × C), 158.15, 147.29, 135.54, 129.18, 127.50 (2 × C), 124.59, 117.11 (2 × C), 110.87, 109.35 (2 × C), 103.46, 102.99,

95.29, 95.03 (2 × C), 94.90, 93.32, 57.90, 56.16, 55.98 (2 × C), 55.90, 51.76. (+)-HRESI-MS: *m/z* 593.1998 $[M + Na]^+$ (Calcd for $C_{30}H_{34}O_{11}Na$: 593.1993).

3-[(3,5-Bis(methoxymethoxy)phenyl)]-2,3-dihydro-6-(methoxymethoxy)-2-(4-methoxymethoxyphenyl)-4-benzofurancarboxaldehyde (22)

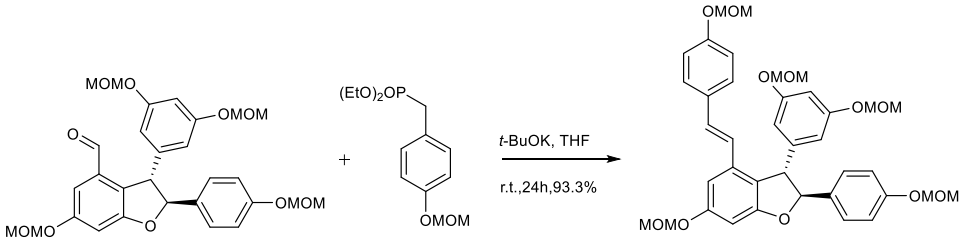


21 **22**

$LiAlH_4$ (4 mg, 0.1 mmol) was added to a stirred solution of compound **21** (20 mg, 0.035 mmol) in freshly redistilled THF (30 mL), and the resulted suspension was allowed to stir at room temperature for 2 h. After TLC detection revealed a completion of the reaction, 1ml EtOAc was added to quench the reaction. The mixture was filtered through celite, the filtrate was dried over anhydrous Na_2SO_4, and evaporated in vacuo to afford a colorless oil. The colorless oil was then redissolved in redistilled dichloromethane (5 mL). Dess-Martin Periodinane (43.3 mg, 0.102 mmol) was added at 0℃, and the reaction mixture was stirred overnight at room temperature. After completion, the solution was washed successively with saturated $NaHCO_3$ solution, saturated NaS_2O_3 solution, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography over silica gel using petroleum ehter and acetone (20 : 1, v/v) as the eluent to afford compound **22** as a colorless oil (12.4 mg，65.7%).

3-[(3,5-Bis(methoxymethoxy)phenyl)]-2,3-dihydro-6-(methoxymethoxy)-2-(4-methoxymethoxyphenyl)-4-benzofurancarboxaldehyde (22)： olorless oil, ^1H NMR (600 MHz, acetone-d_6): δ 9.83 (s, 1H), 7.31 (d, J = 8.60 Hz, 2H), 7.12 (d, J = 3.6 Hz, 1H), 7.05 (d, J = 8.60 Hz, 2H), 6.95 (d, J = 3.6 Hz, 1H), 6.64 (t, J = 3.6 Hz, 1H), 6.52 (d, J = 3.6 Hz, 2H), 5.64 (d, J = 7.8 Hz, 1H), 5.29 (s, 2H), 5.20 (s, 2H), 5.13 (M, 4H), 4.97 (d, J = 7.8 Hz, 1H), 3.48 (s, 3H), 3.42 (s, 3H), 3.39 (s, 6H). ^{13}C NMR (150 MHz, acetone-d_6): δ 190.57, 162.22, 159.29, 158.97 (2 × C), 157.55, 146.19, 134.32, 133.49, 127.02 (2 × C), 124.50, 116.42 (2 × C), 109.05, 108.88 (2 × C), 103.50, 102.97, 94.62, 94.38 (2 × C), 94.21, 93.48, 55.51, 55.34 (2 × C), 55.26, 55.22. (+)-HRESI-MS: *m/z* 541.2080 $[M + H]^+$ (Calcd for $C_{29}H_{33}O_{10}$: 541.2068).

2-(4-Methoxymethoxyphenyl)-3-[(3,5-bis(methoxymethoxy)phenyl)]-4-[(1*E*)-2-(4-methoxymethoxyphenyl)ethenyl]-2,3-dihydro-6-(methoxymethoxy)benzofuran (24)

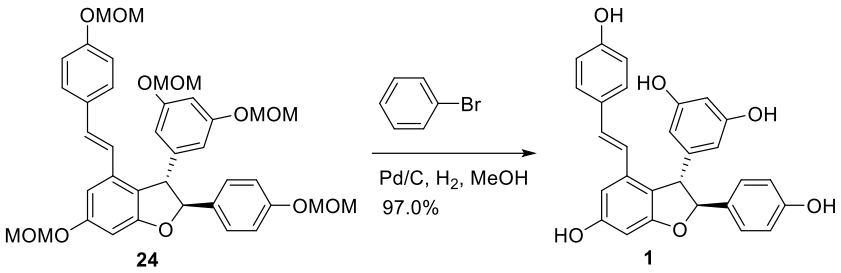


22 23 24

t-BuOK (303 mg, 2.73 mmol) was added to a stirred solution of (4-methoxymethoxyphenyl)methyl phosphonic acid diethyl ester **23** (75 mg, 0.259 mmol) in freshly redistilled THF (15 mL) at -40 ℃, the mixture was stirred at this temperature for 20 min. Subsequently, compound **22** (100 mg, 0.184 mmol) in freshly redistilled THF (20 mL) was added, and the mixture was allowed to warm to room temperature slowly and was stirred for another 24 h. After the solvent was removed under reduced pressure, the mixture was diluted with ethyl acetate, washed with saturated aqueous NaCl and water, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was then purified by column chromatography over silica gel with petroleum and acetone (12 : 1, v/v) as the eluent to afford compound **24** as a light yellow oil (115.9 mg, 93.3%).

2-(4-methoxymethoxyphenyl)-3-[(3,5-bis(methoxymethoxy)phenyl)]-4-[(1*E*)-2-(4-methoxymethoxyphenyl)ethenyl]-2,3-dihydro-6-(methoxymethoxy)benzofuran (**24**)：light yellow oil, ^{1}H NMR (500 MHz, acetone-d_6): δ 7.33 (d, J = 8.50 Hz, 2H), 7.28 (d, J = 8.50 Hz, 2H), 7.06 (d, J = 8.0 Hz, 2H), 7.01 (d, J = 16.0 Hz, H), 6.94 (d, J = 8.0 Hz, 2H), 6.93 (brs,1H), 6.80 (d, J = 16.0 Hz, 1H), 6.65 (brs, 3H), 6.58 (brs, 1H), 5.57 (d, J = 5.0 Hz, 1H), 5.25 (s, 2H), 5.20 (s, 2H), 5.16 (s, 2H), 5.14 (s, 4H), 4.71 (d, J = 5.0 Hz, 1H), 3.43 (s, 3H), 3.42 (s, 3H), 3.40 (s, 3H), 3.33 (s, 6H).^{13}C NMR (125 MHz, acetone-d_6): δ 161.20, 158.98, 158.88 (2 × C), 157.31, 157.18, 143.04, 135.29, 134.76, 131.07, 130.97, 129.42 (2 × C), 128.70, 127.86 (2 × C), 126.94 (2 × C), 123.36, 121.05, 116.22 (2 × C), 109.17 (2 × C), 104.68, 102.94, 97.05, 94.43, 94.26 (2 × C), 94.11, 94.06, 92.65, 64.99, 56.12, 55.26 (2 × C), 55.12. (+)-HRESI-MS: *m/z* 675.2802 $[M + H]^+$ (Calcd for $C_{38}H_{43}O_{11}$: 675.2800).

(±)-*ε*-viniferin (1)



10% Pd/C (2.12g, 0.9 mmol) was added to a solution of 0.5 ml bromobenzene (4.5 mmol) in 10 mL methanol under hydrogen atmosphere (0.1-0.2 MPa), and the mixture were stirred for 15 min at room temperature. After removal of hydrogen, compound **24** (200 mg, 0.3 mmol) were added, the mixture was then allowed to warm to room temperature slowly and was stirred for another 5h.

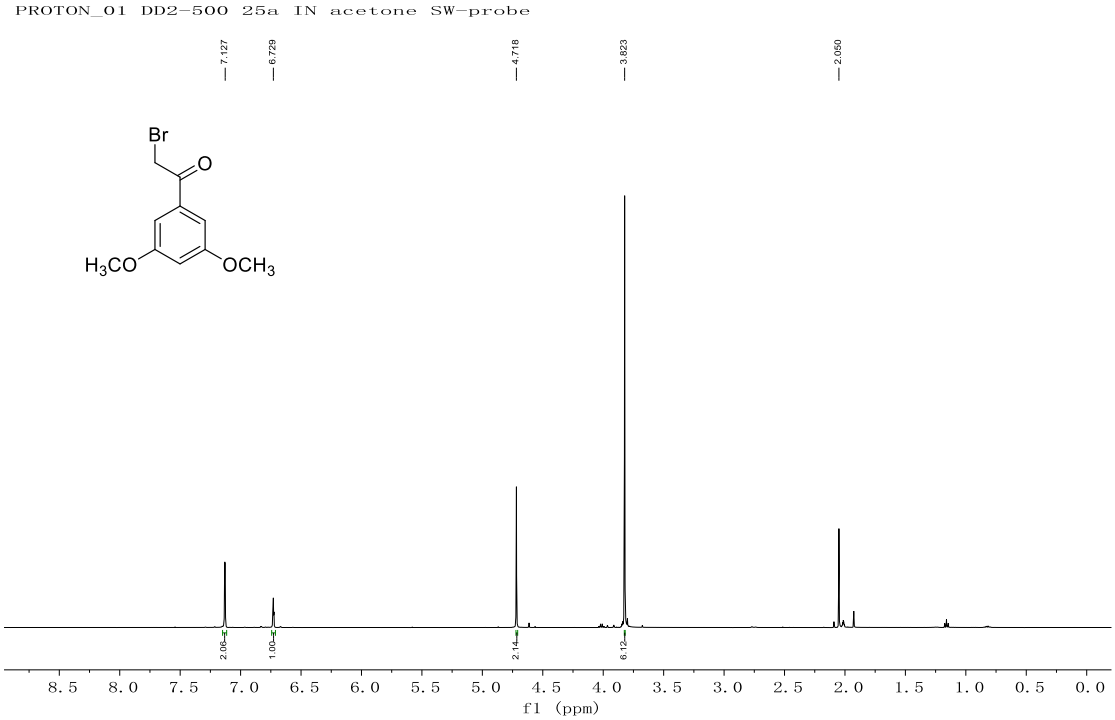
After completion, the reaction mixture was filtered, concentrated *in vacuo*. The residue was subjected to silica gel column chromatography to furnish **1** (130.7 mg, 97.0%) as a reddish-brown solid.

5-[2,3-dihydro-6-hydroxy-2-(4-hydroxyphenyl)-4-[(1*E*)-2-(4-hydroxyphenyl) ethenyl]-3-benzofuranyl]-1,3-benzenediol (**1**)： reddish-brown solid, ^{1}H NMR (500 MHz, Methanol-d_4): δ 7.17 (d, J = 8.0 Hz, 2H), 7.07 (d, J = 8.0 Hz, 2H), 6.84 (d, J = 16.0 Hz, 1H), 6.80 (d, J = 8.0 Hz , 2H), 6.68 (d, J = 8.0 Hz, 2H), 6.65 (brs, 1H), 6.59 (d, J = 16.0 Hz, 1H), 6.27 (brs, 1H), 6.20 (brs, 1H), 6.19 (brs, 2H), 5.38 (d, J = 5.0 Hz, 1H), 4.38 (d, J = 5.0 Hz, 1H). ^{13}C NMR (125 MHz, Methanol-d_4): δ 162.72, 160.02 (2 × C), 159.71, 158.49, 158.35, 147.35, 136.90, 133.89, 130.39, 130.33, 128.76 (3 × C), 128.19 (2 × C), 123.70, 120.05, 116.37 (2 × C), 116.27 (3 × C), 107.49 (2 × C), 104.35, 102.20, 96.85, 94.81, 58.28. (+)-HRESI-MS: *m/z* 455.1500 $[M+H]^+$ (Calcd for $C_{28}H_{23}O_6$: 455.1489).

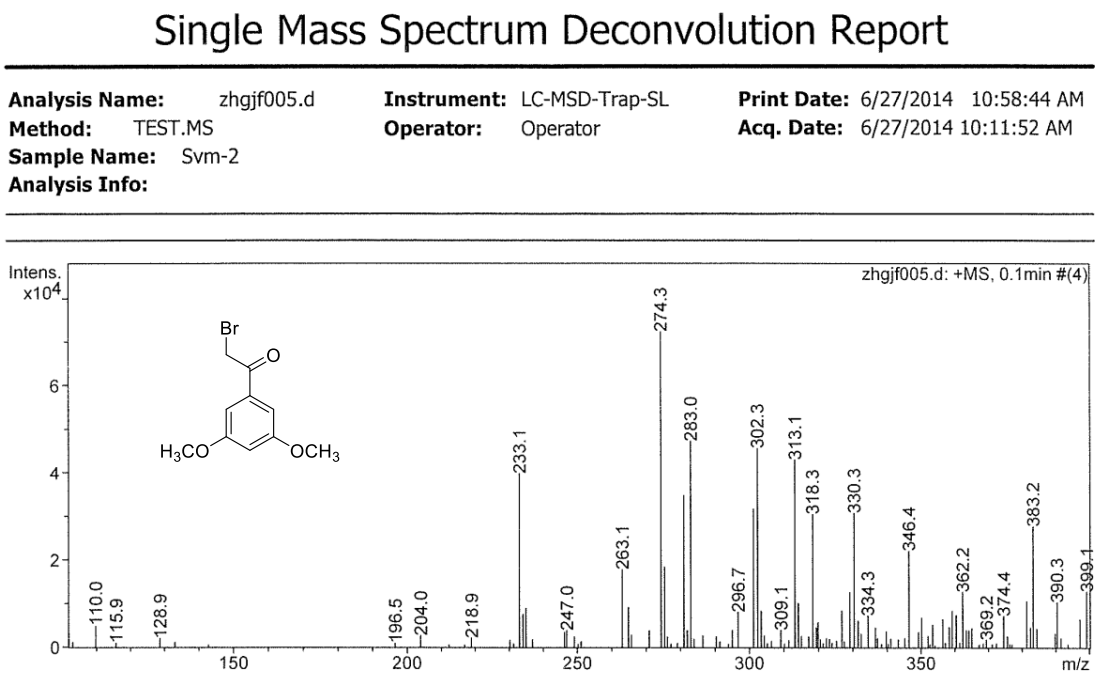
Section 3. Spectra in the total synthesis of (±)-ε-viniferin (1)

3.1 spectra of 3

^{1}H NMR of Compound **3**

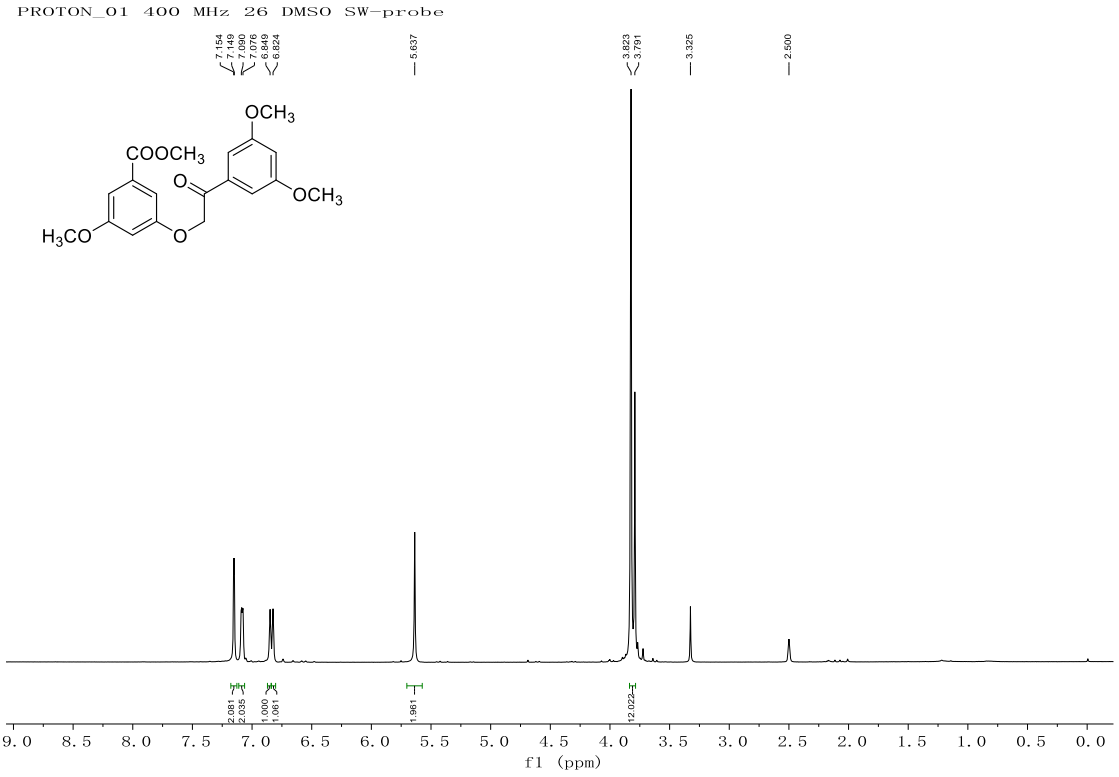


ESI-MS of Compound **3**

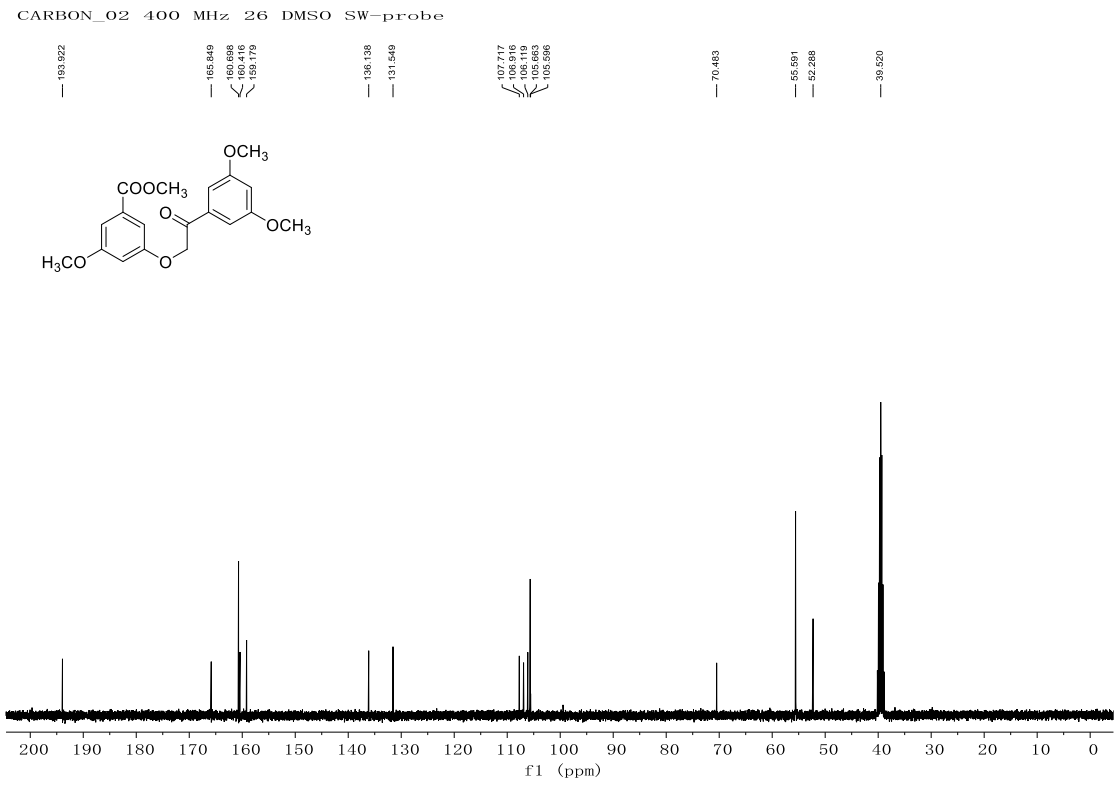


3.2 spectra of 4a

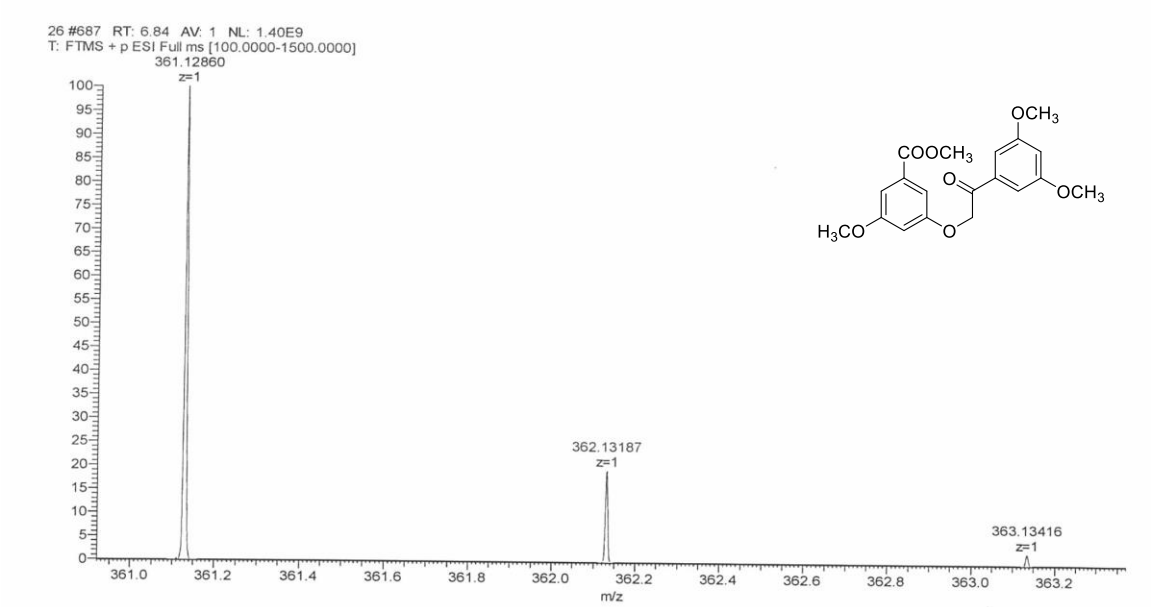
^{1}H NMR of Compound **4a**



^{13}C NMR of Compound **4a**



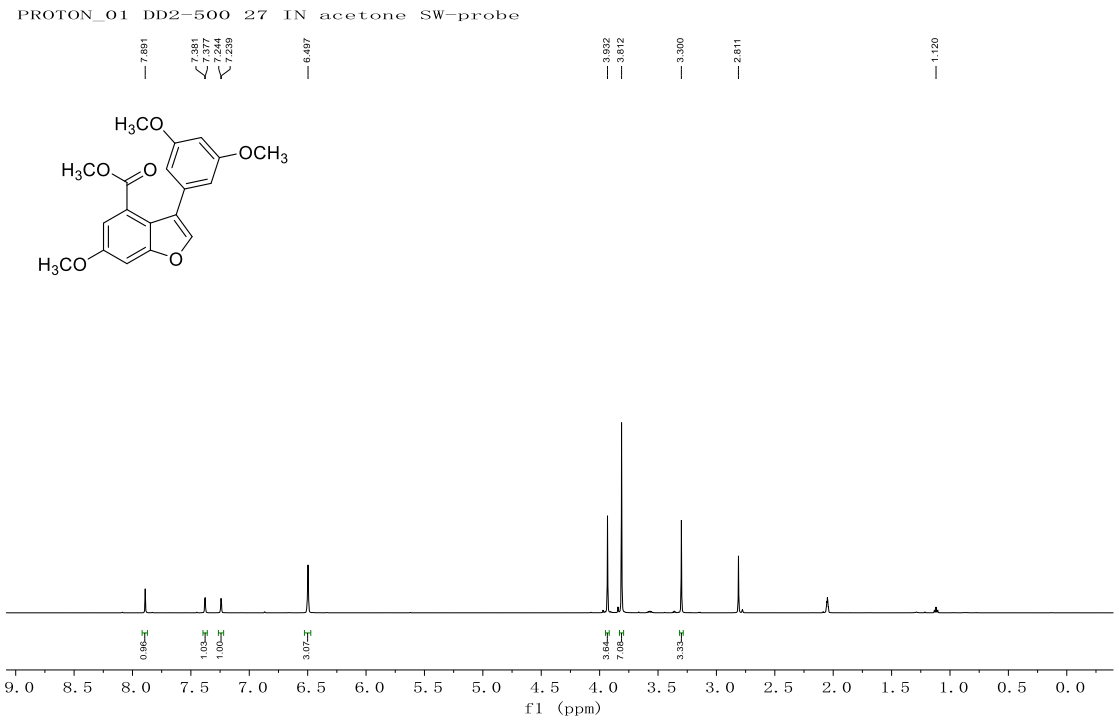
ESI-MS of Compound **4a**



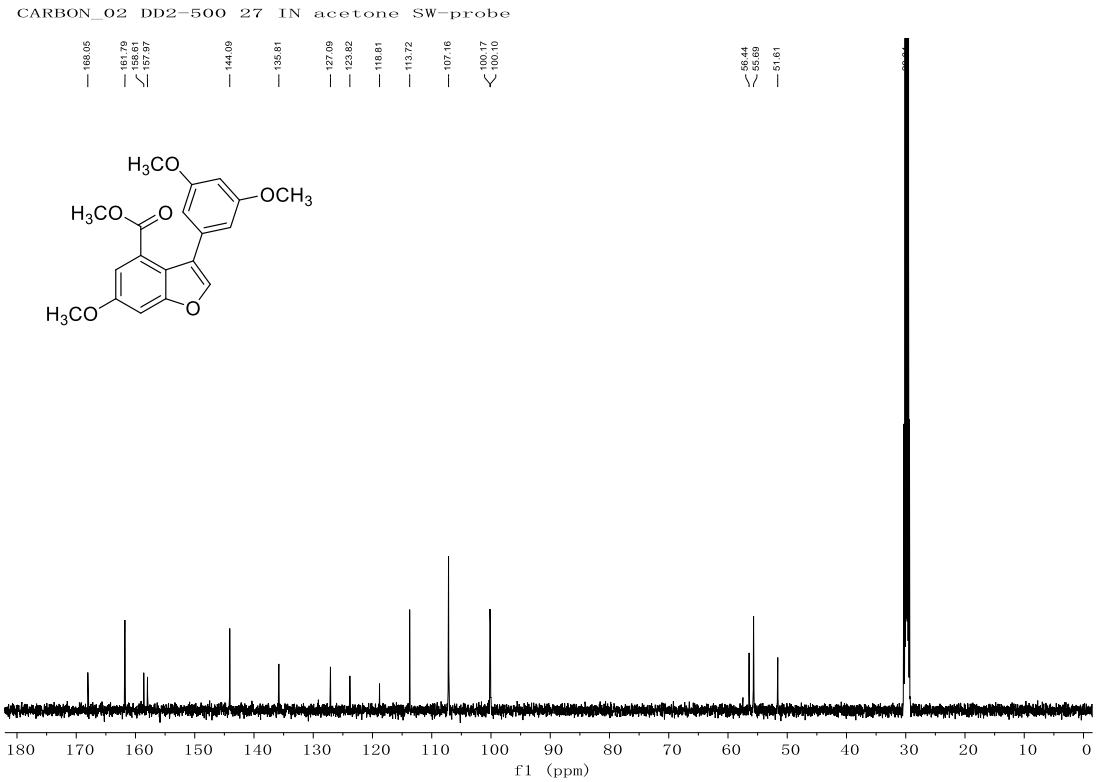
m/z	Theo. Mass	Delta (ppm)	RDB equiv.	Composition	
361.12860	361.12818	1.16	9.5	C19 H21 O7	M+H

3.3 spectra of 4

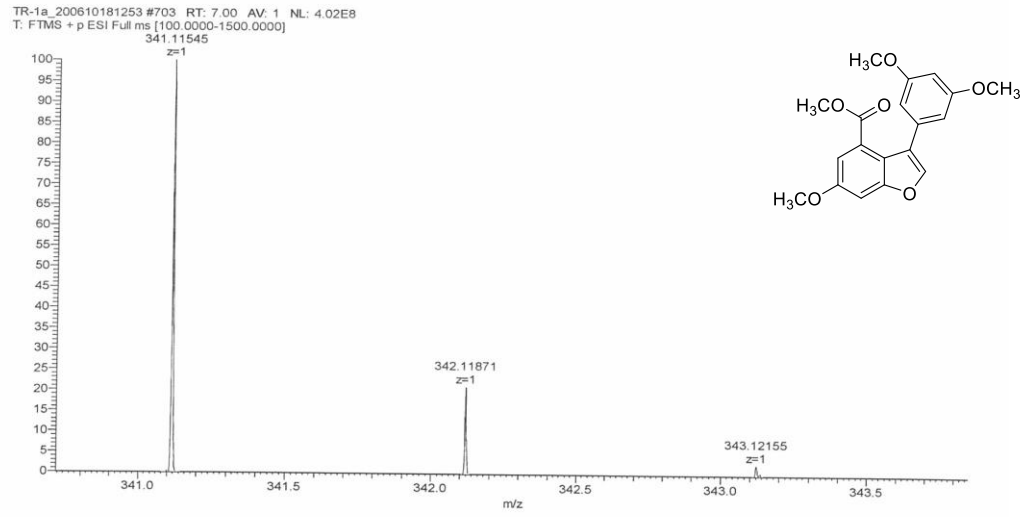
^{1}H NMR of Compound **4**



^{13}C NMR of Compound **4**



ESI-MS of Compound **4**

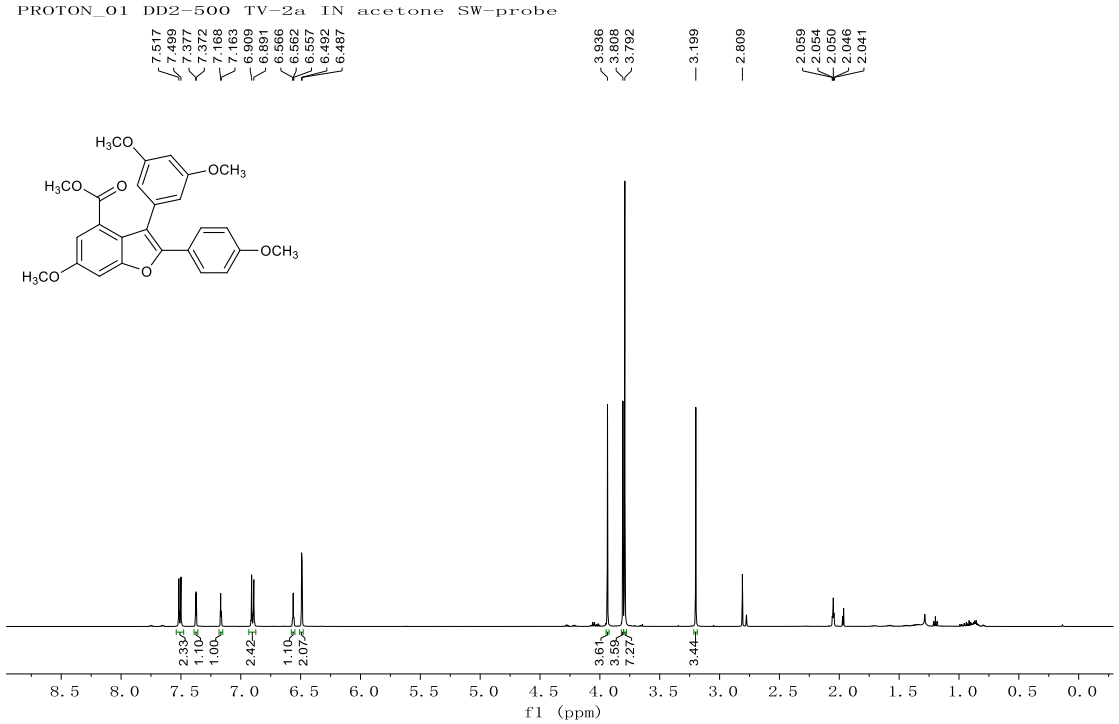


m/z	Theo. Mass	Delta (ppm)	RDB equiv.	Composition	
341.11545	341.11482	1.86	12.5	C21 H18 O3 Na	M+Na

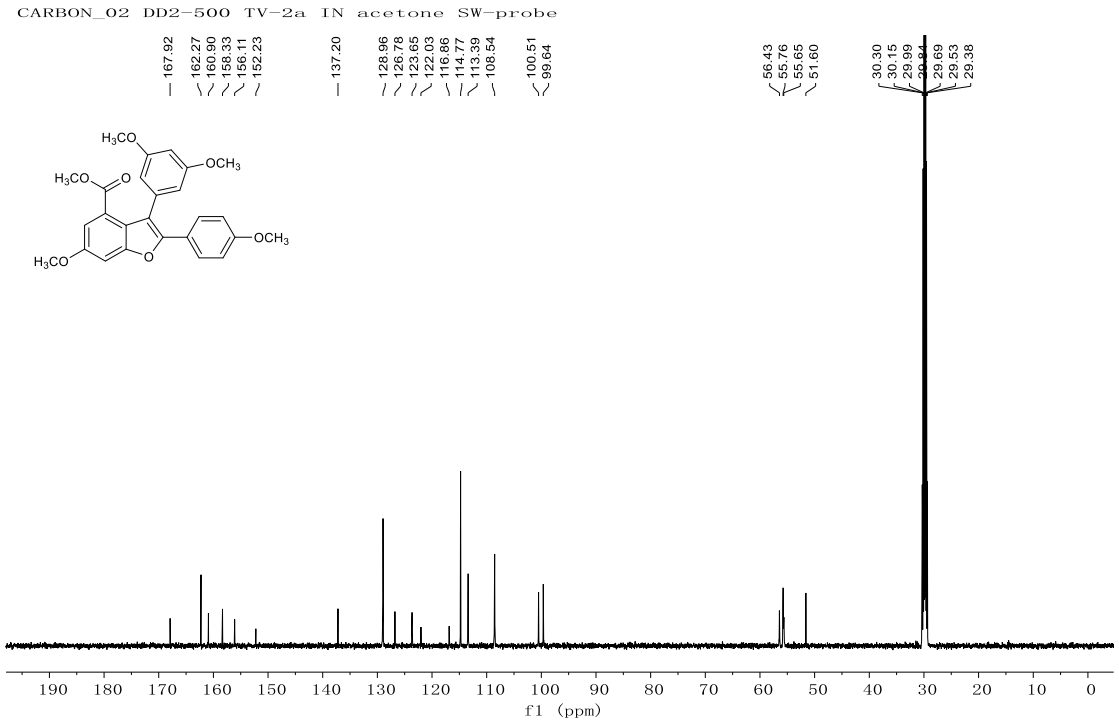
T

3.4 spectra of 5

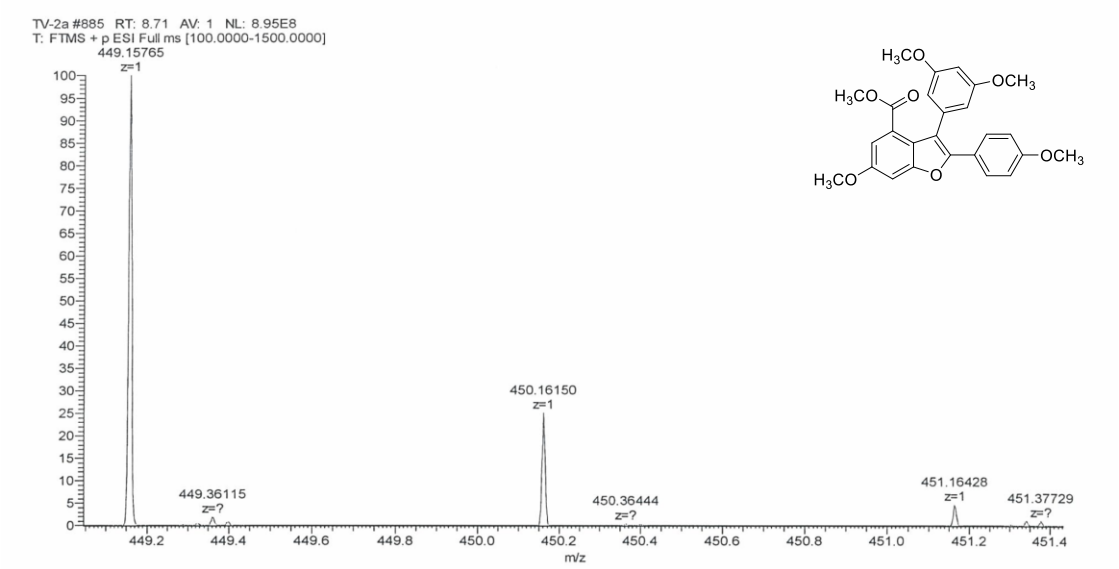
^{1}H NMR of Compound **5**



^{13}C NMR of Compound **5**



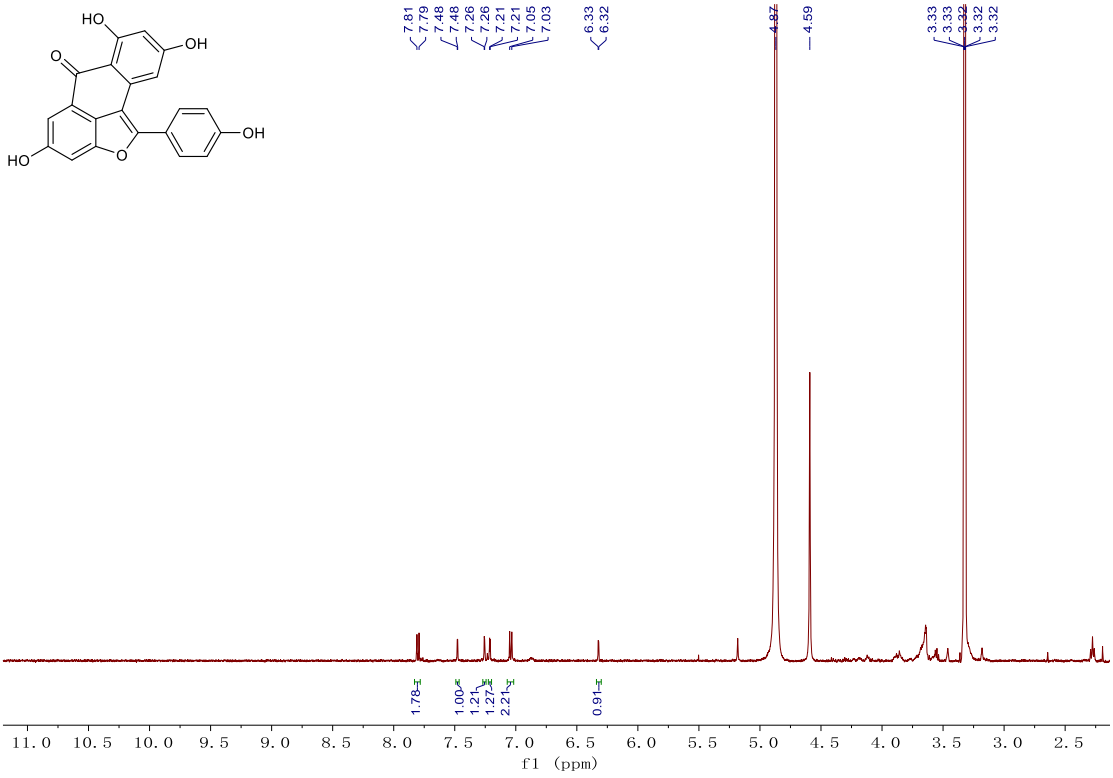
ESI-MS of Compound **5**



m/z	Theo. Mass	Delta (ppm)	RDB equiv.	Composition	
449.15765	449.15948	-4.07	14.5	C26 H25 O7	M+H

3.5 spectra of 11

^{1}H NMR of Compound **11**

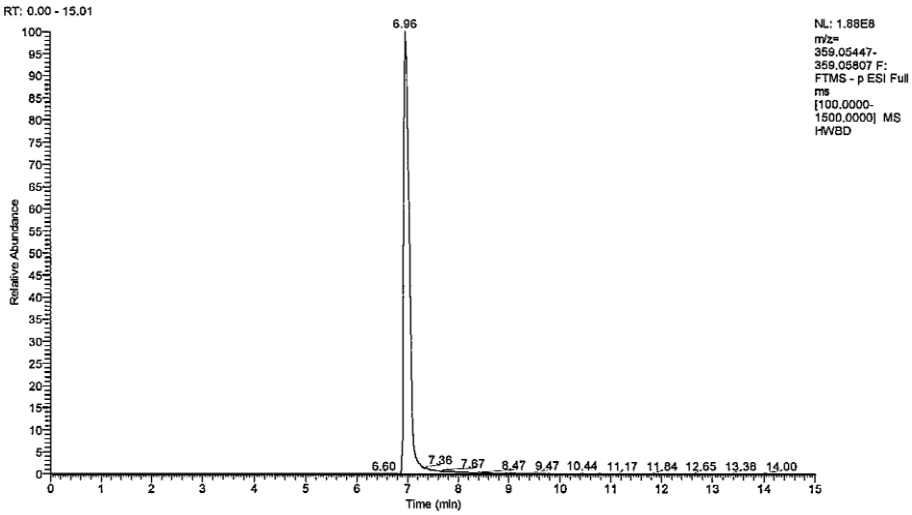


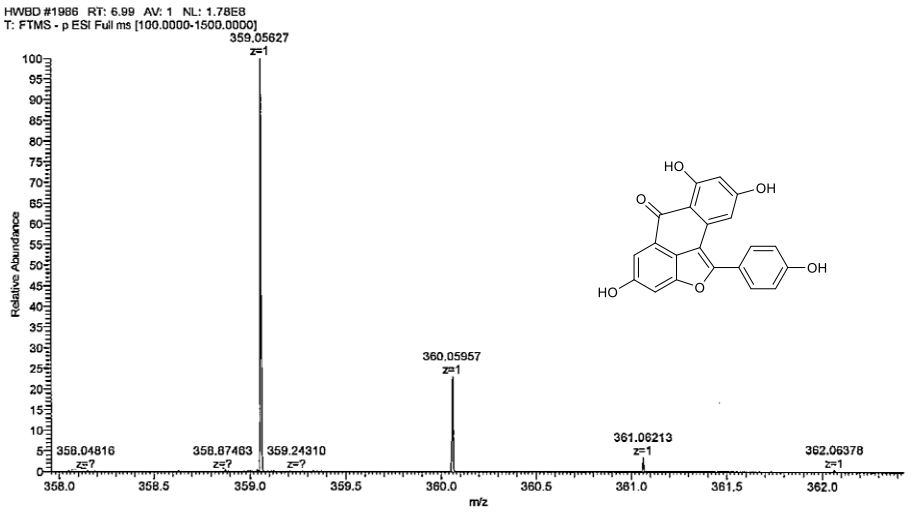
HRESI of Compound **11**

Thermo Qexactive Focus Report

compound NO. : HWBD

Method : LCMS(compound)-low

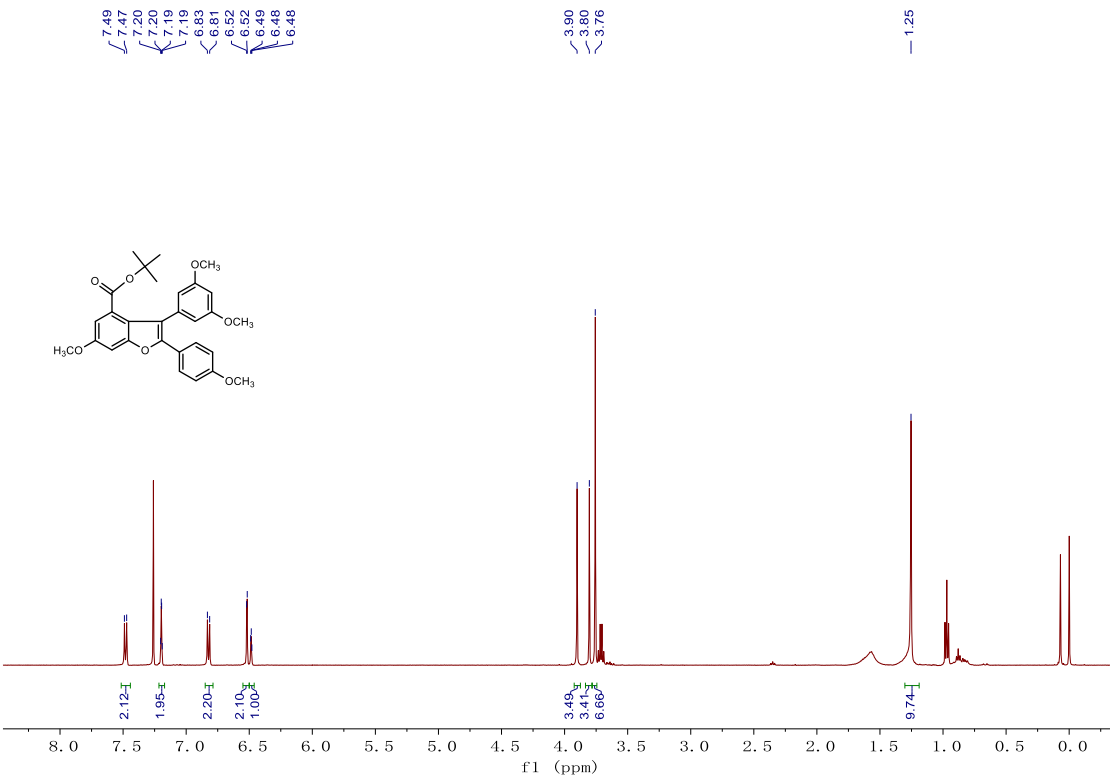




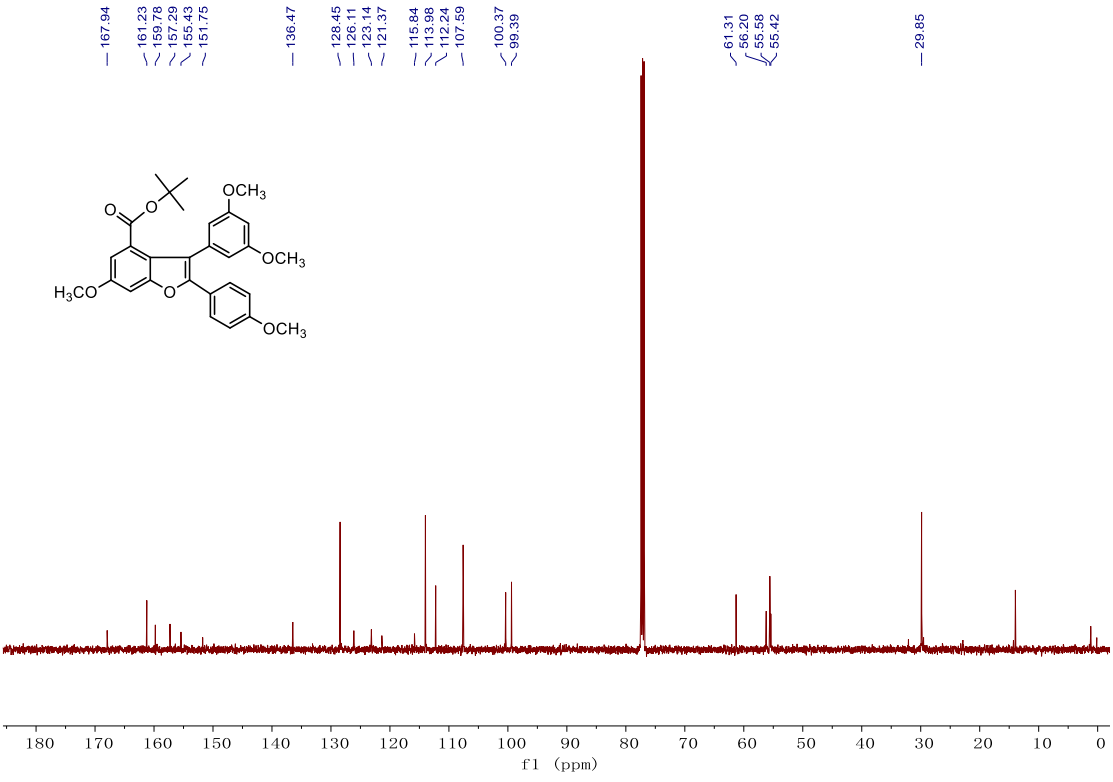
m/z	Theo. Mass	Delta (ppm)	RDB equiv.	Composition	
359.05627	359.05611	0.44	16.5	C21 H11 O6	M-H

3.6 spectra of 5b

^{1}H NMR of Compound **5b**

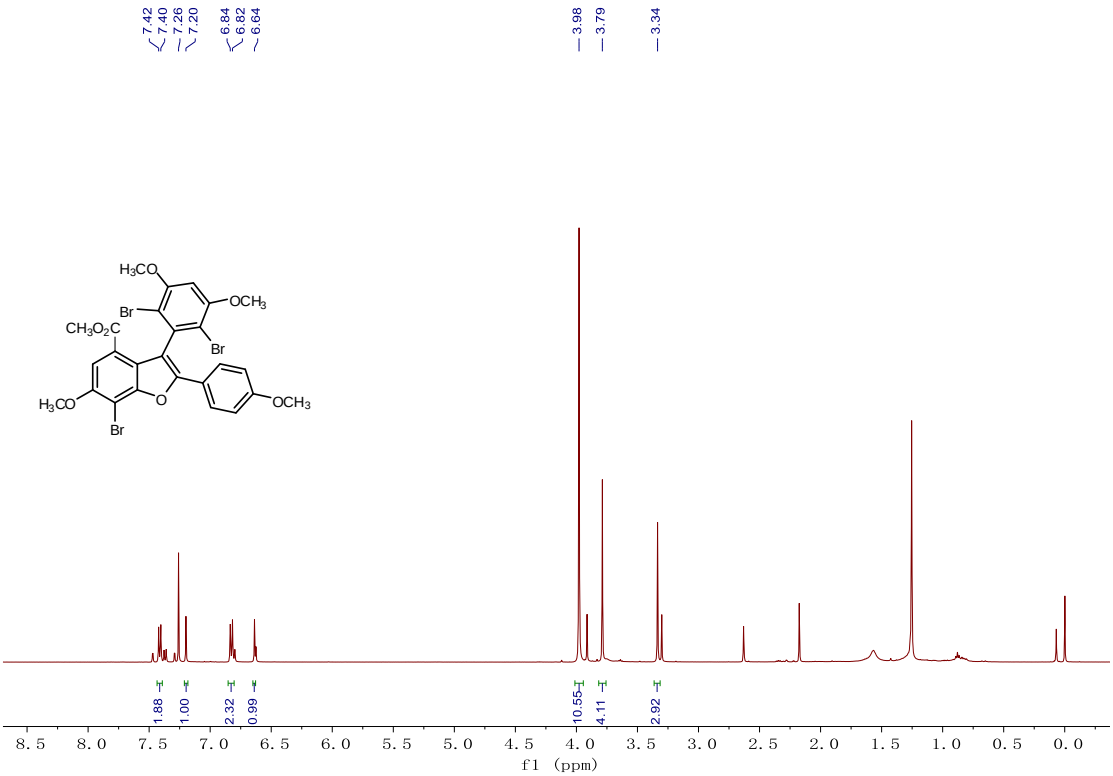


^{13}C NMR of Compound **5b**

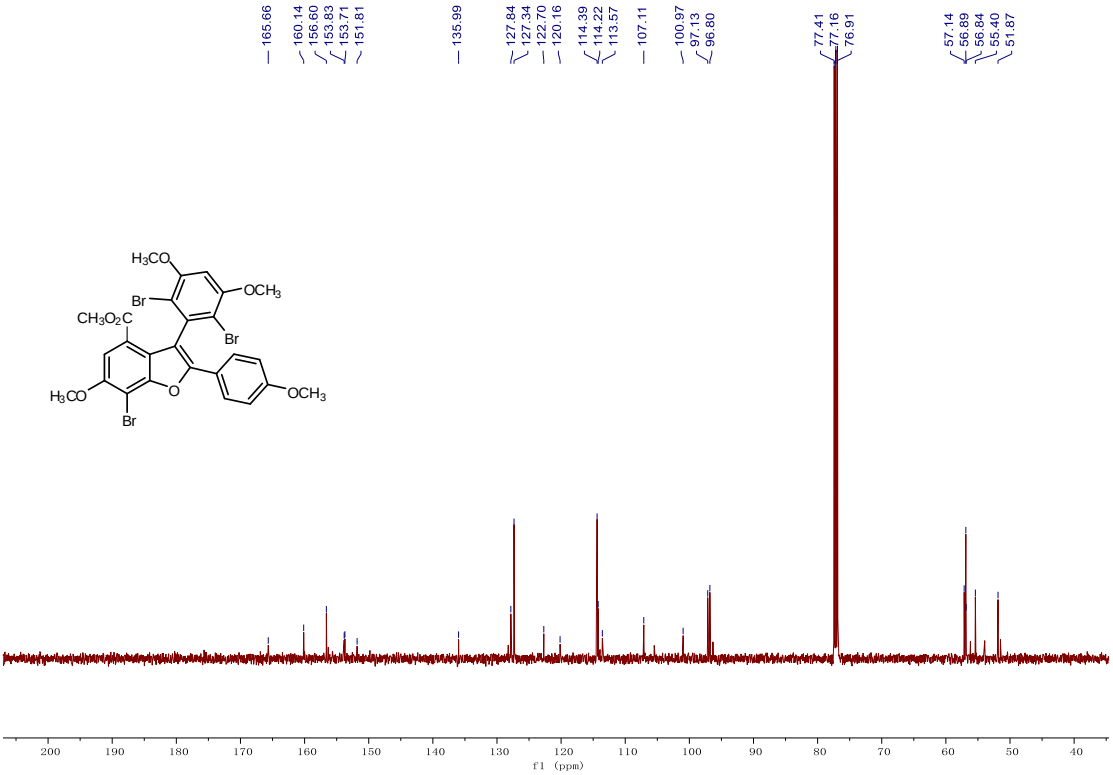


3.7 spectra of 12

^{1}H NMR of Compound **12**



^{13}C NMR of Compound **12**

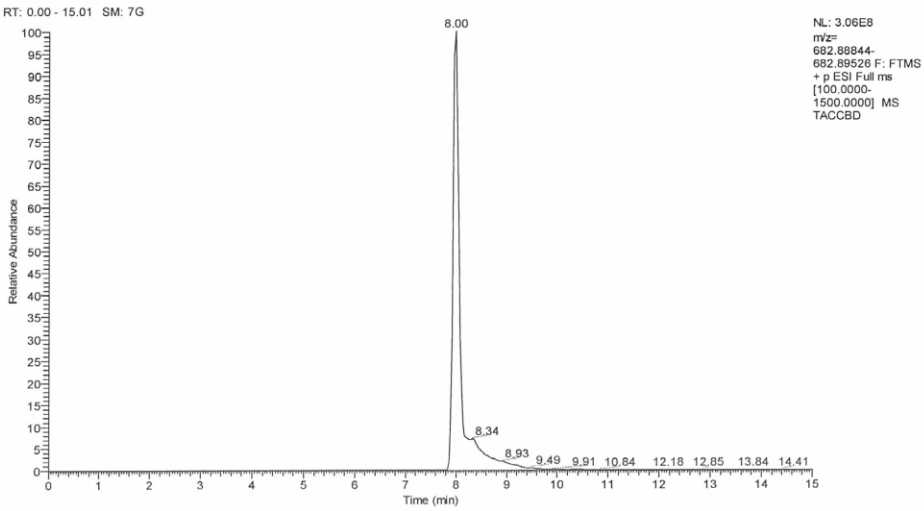


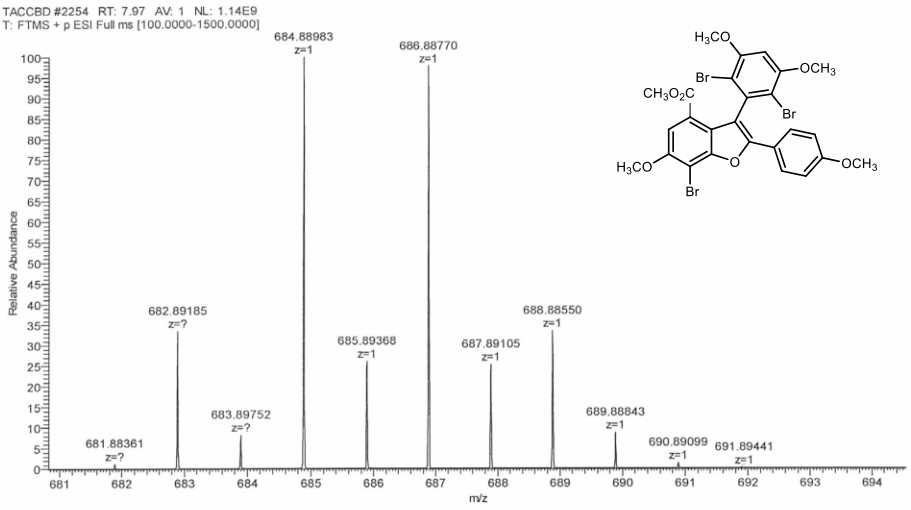
HRESI of Compound **12**

Thermo Qexactive Focus Report

compound NO. : TACCBD

Method : LCMS(compound)-low

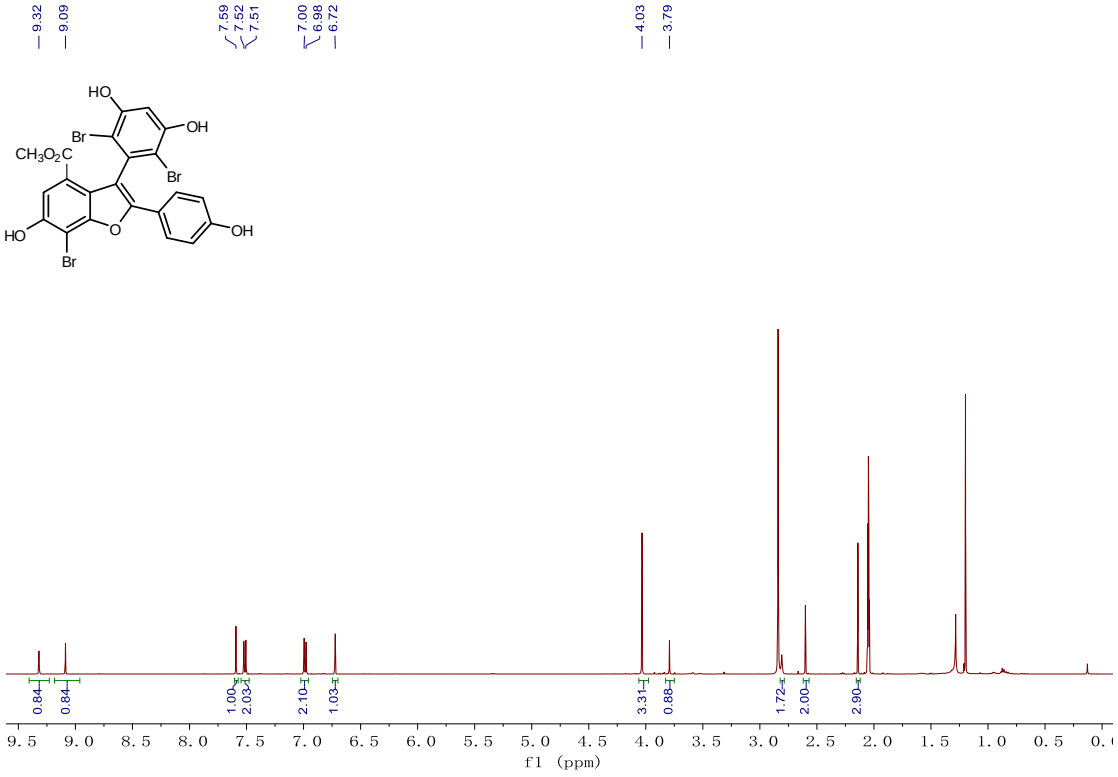


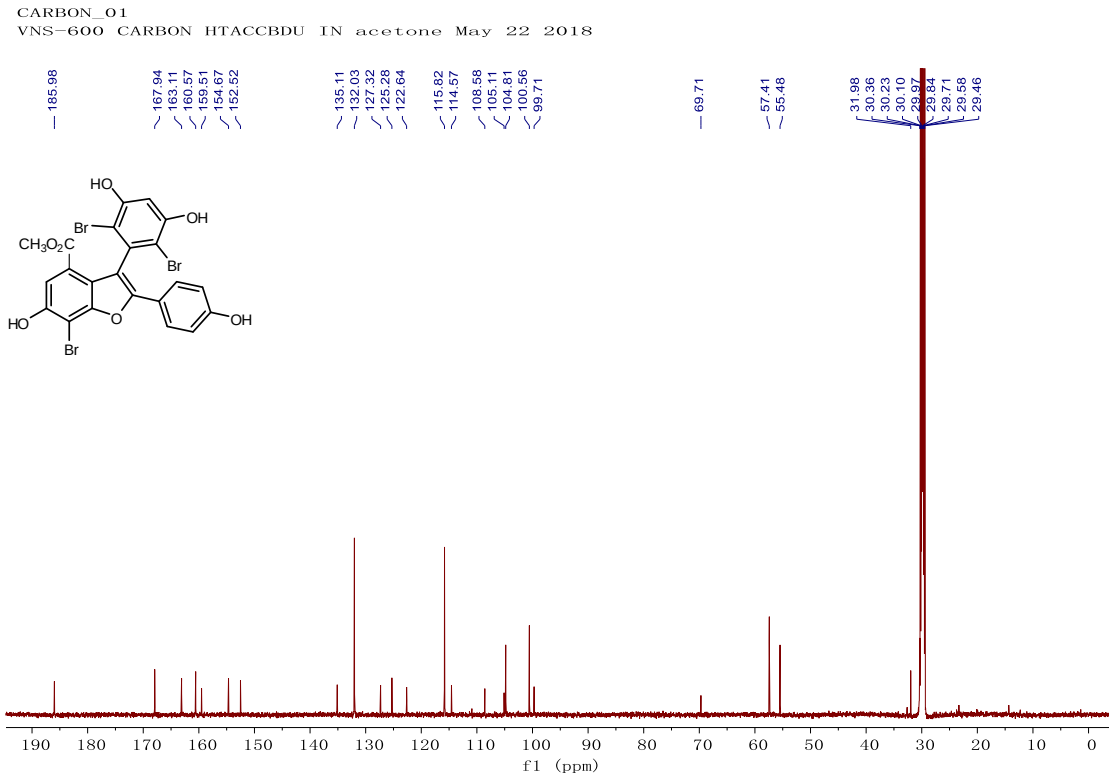


m/z	Theo. Mass	Delta (ppm)	RDB equiv.	Composition	
682.89185	682.89102	1.22	14.5	C26 H22 O7 Br3	M+H

3.8 spectra of 13

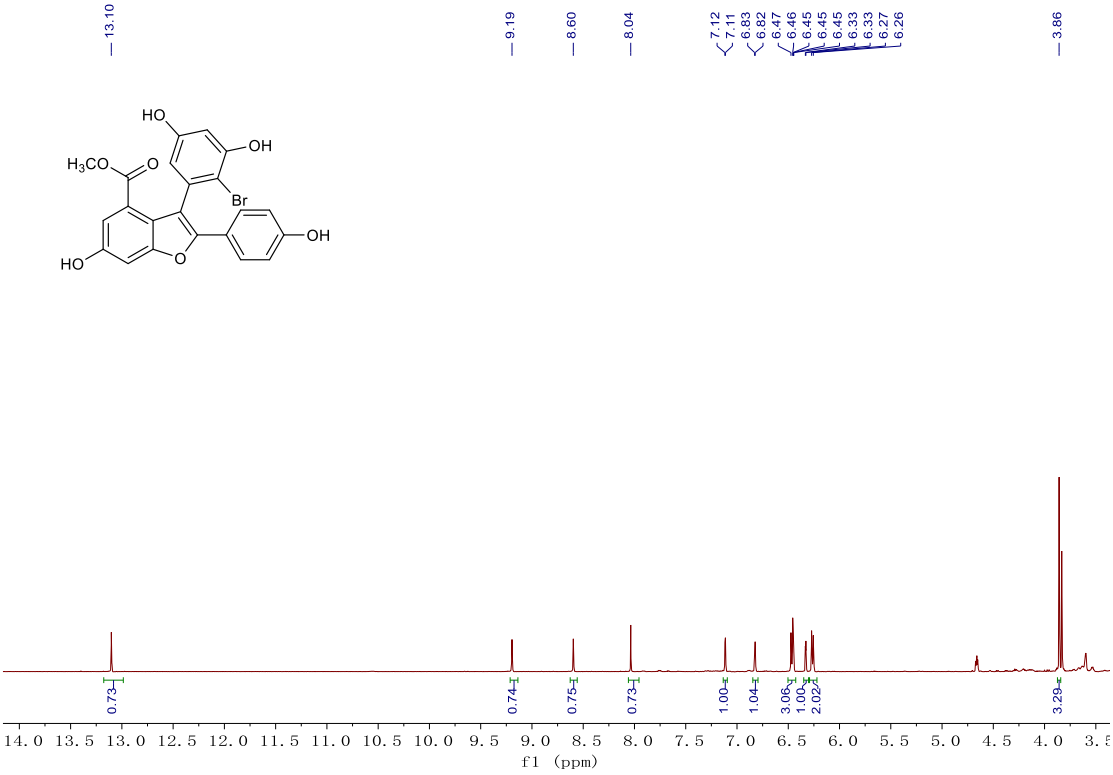
^{1}H NMR of Compound **13**

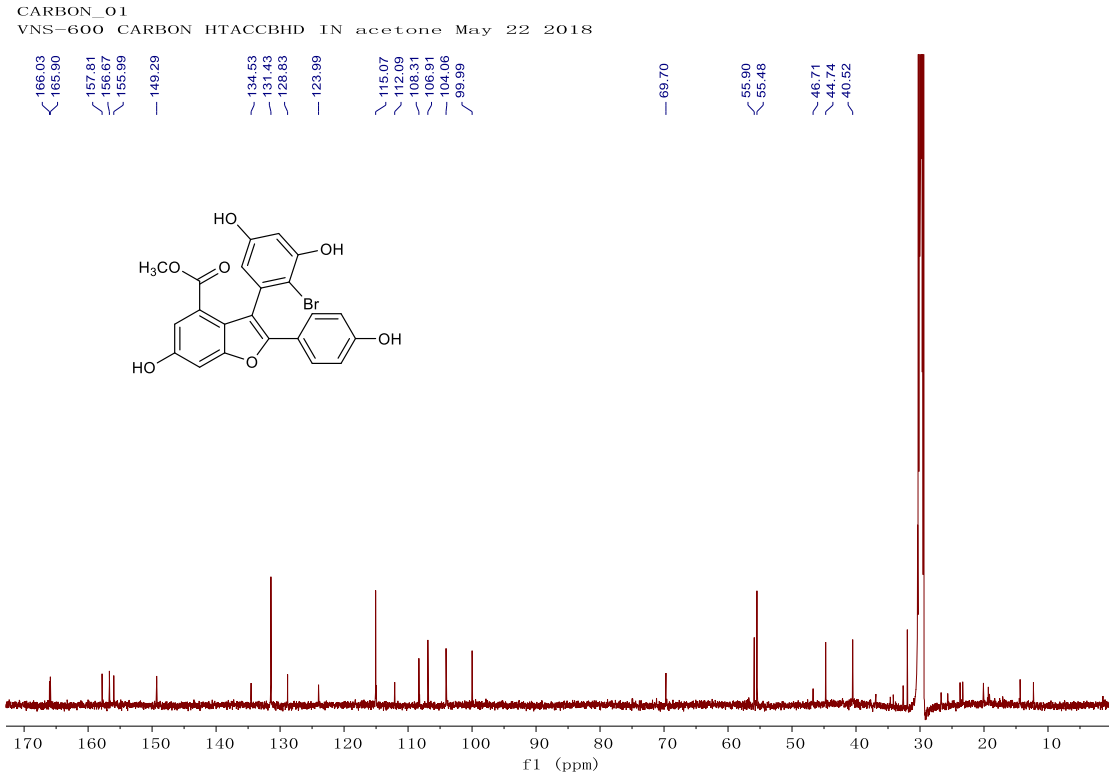




3.9 spectra of 14

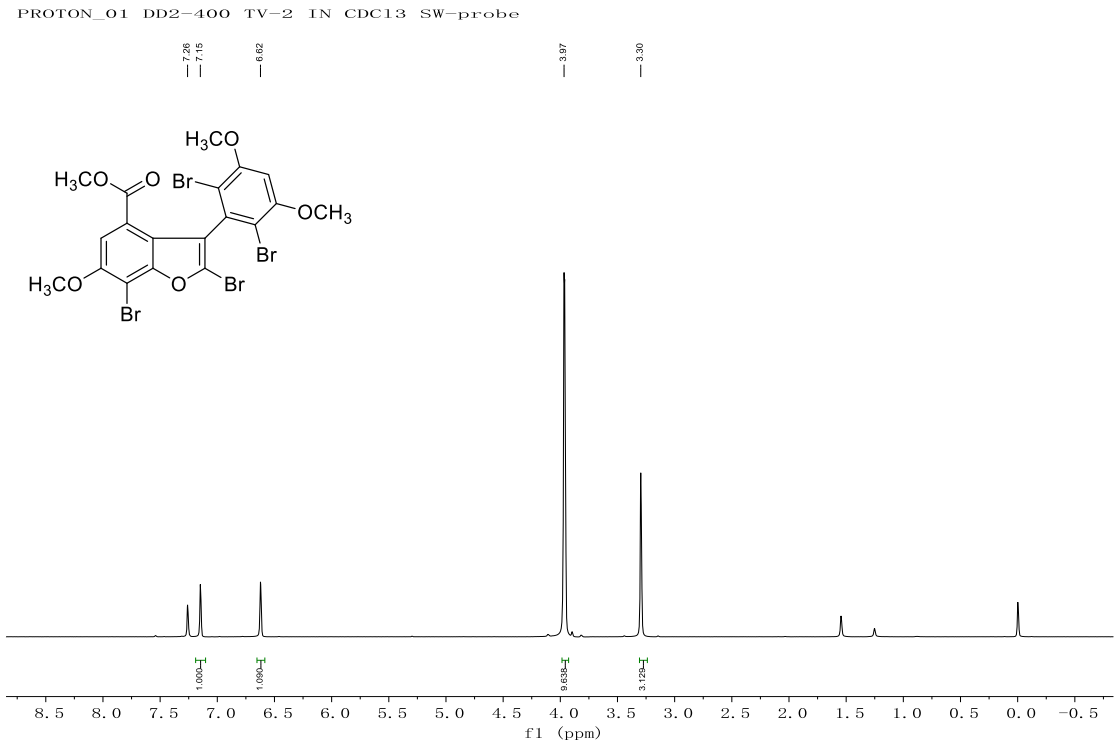
^{1}H NMR of Compound **14**



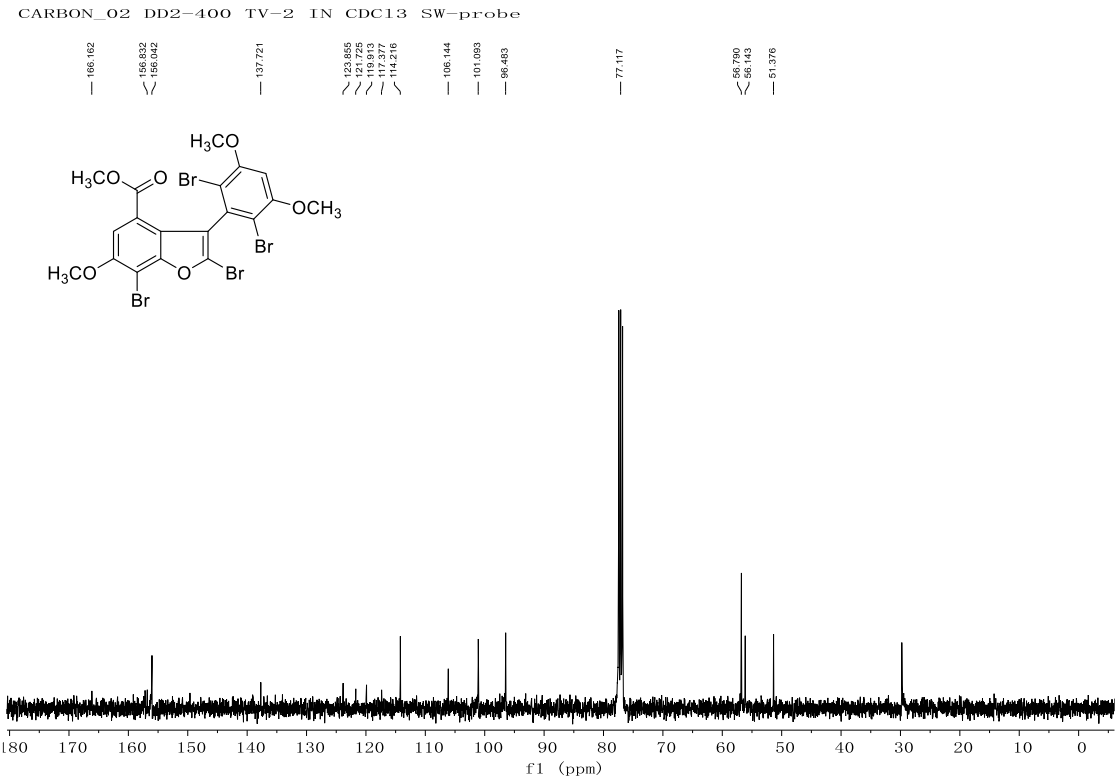


3.10 spectra of 16

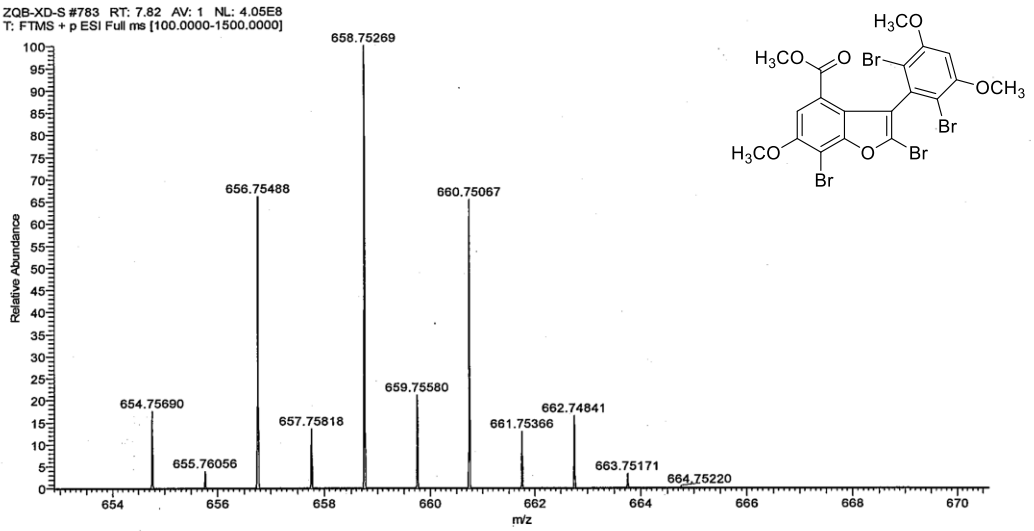
^{1}H NMR of Compound **16**



^{13}C NMR of Compound **16**



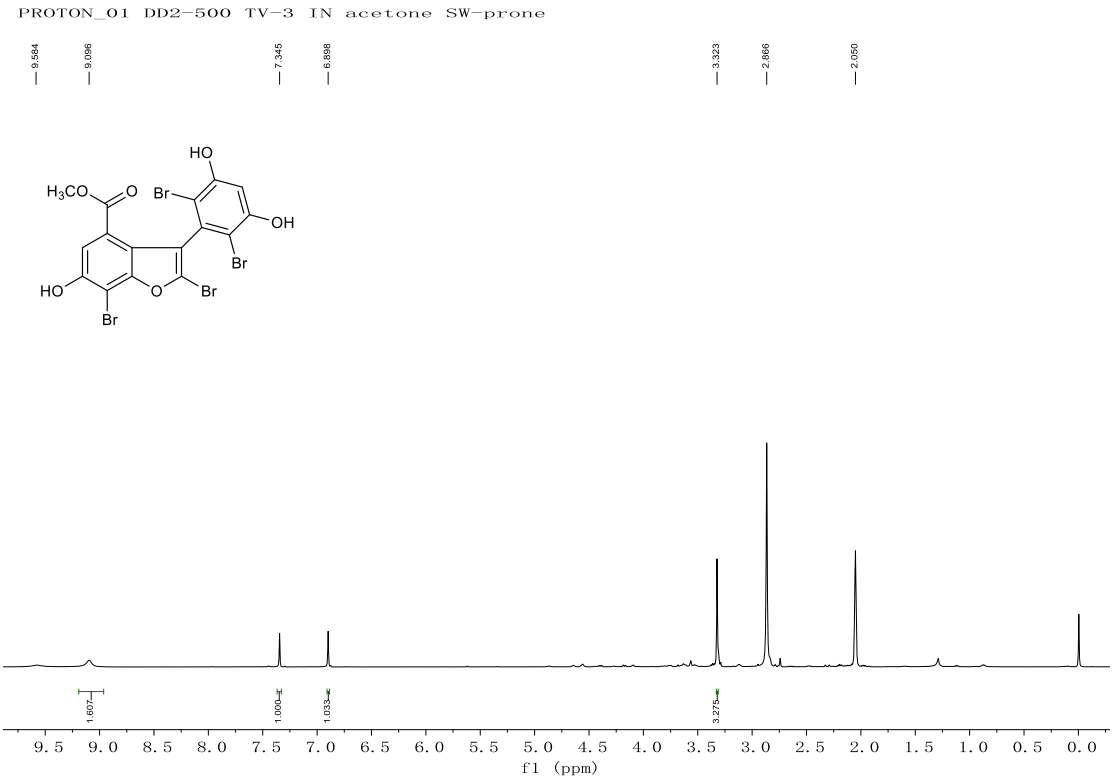
HR-MS (ESI) of Compound **16**



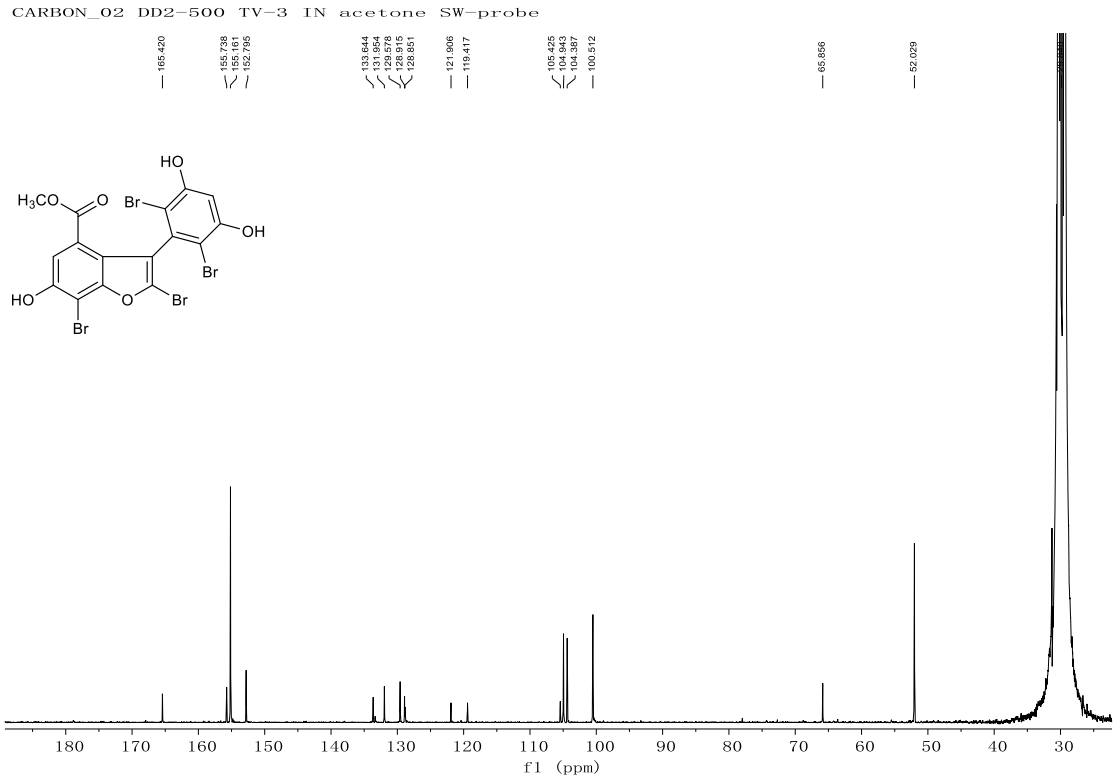
m/z	Theo. Mass	Delta (ppm)	RDB equiv.	Composition	
654.75690	654.75967	-4.22	10.5	C19 H15 O6 Br4	M+H

3.11 spectra of 17

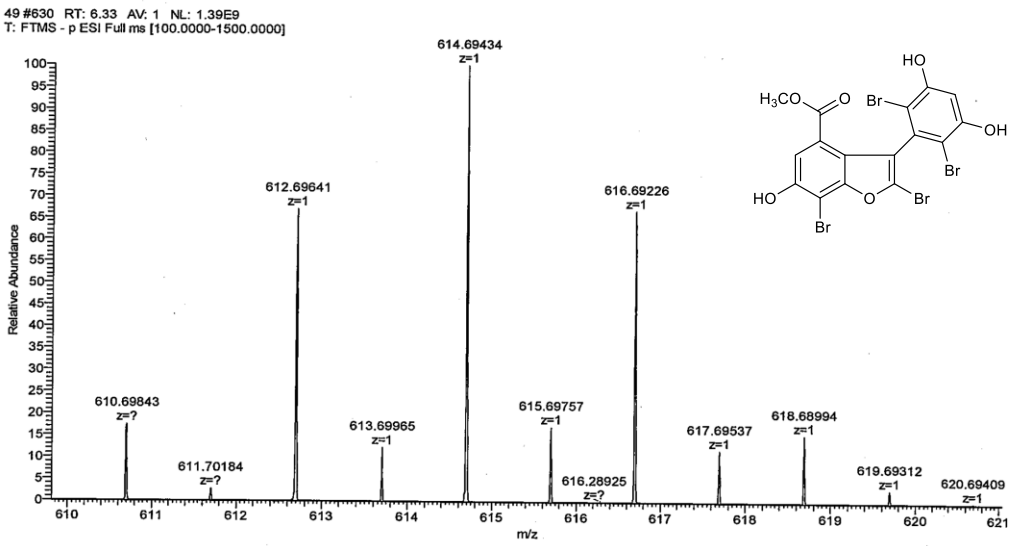
^{1}H NMR of Compound **17**



^{13}C NMR of Compound **17**



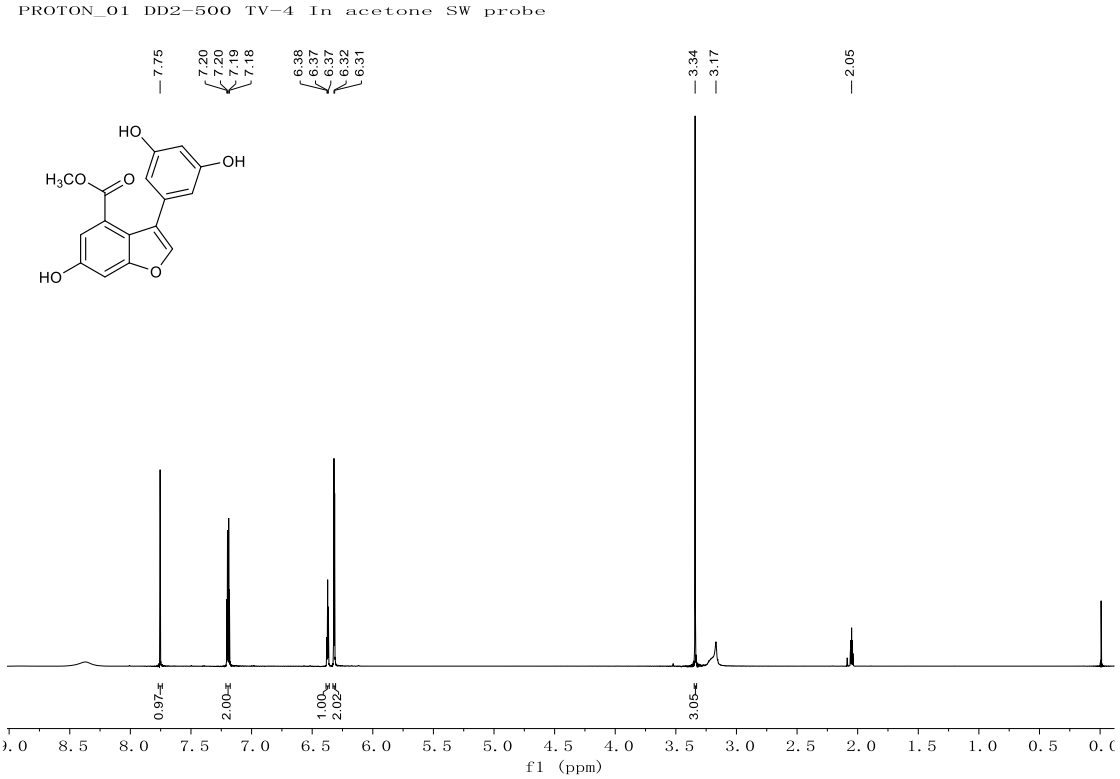
HR-MS (ESI) of Compound **17**



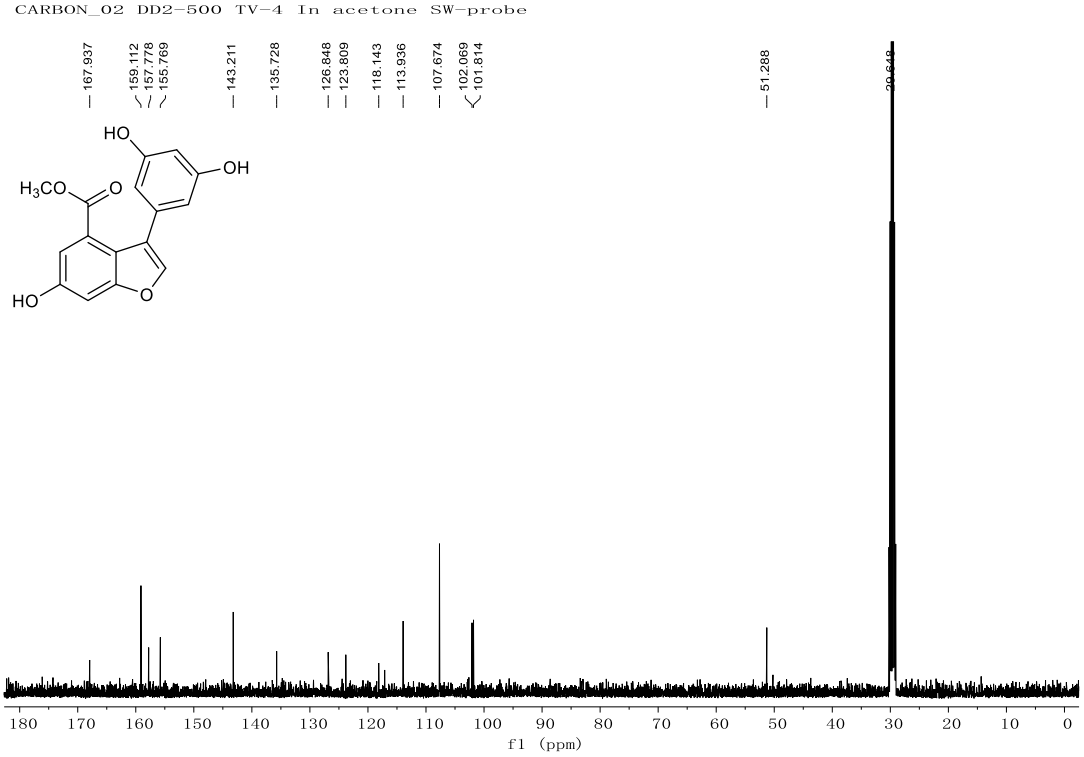
m/z	Theo. Mass	Delta (ppm)	RDB equiv.	Composition	
610.69843	610.69816	0.44	11.5	C16 H7 O6 Br4	M-H

3.12 spectra of 18

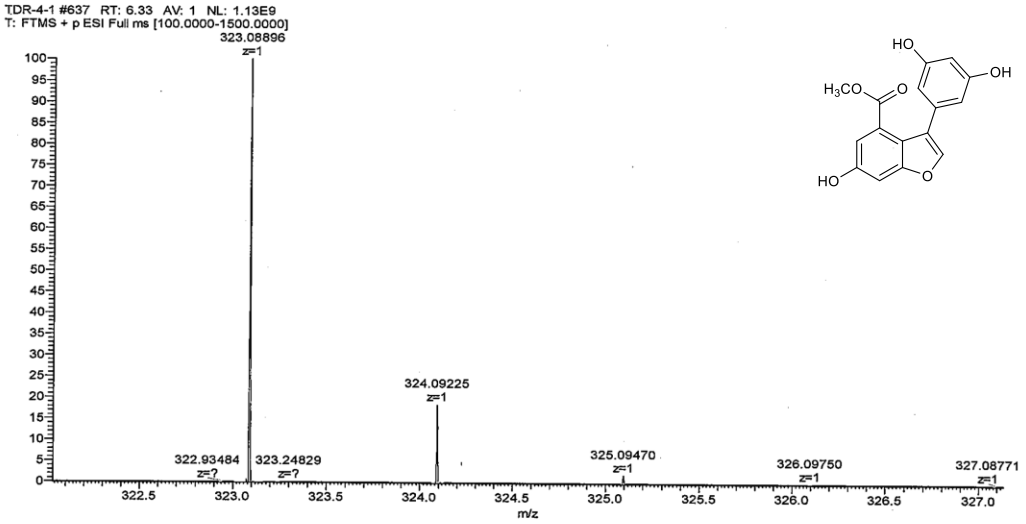
^{1}H NMR of Compound **18**



^{13}C NMR of Compound **18**



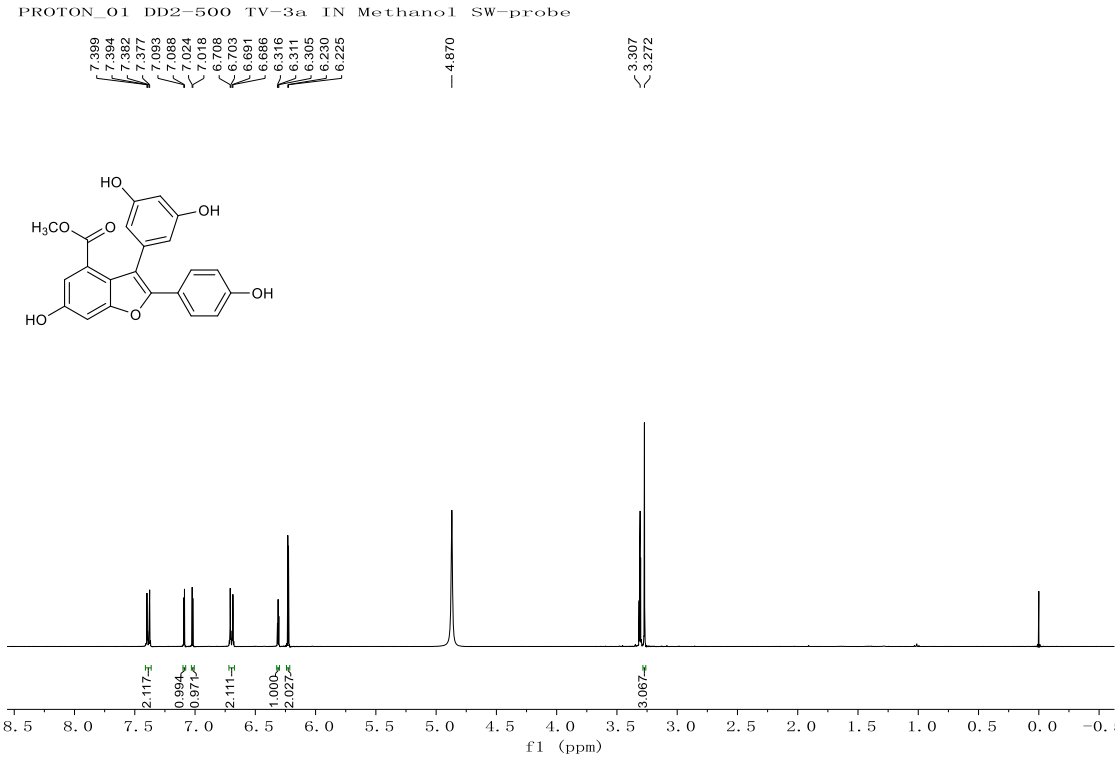
HR-MS (ESI) of Compound **18**



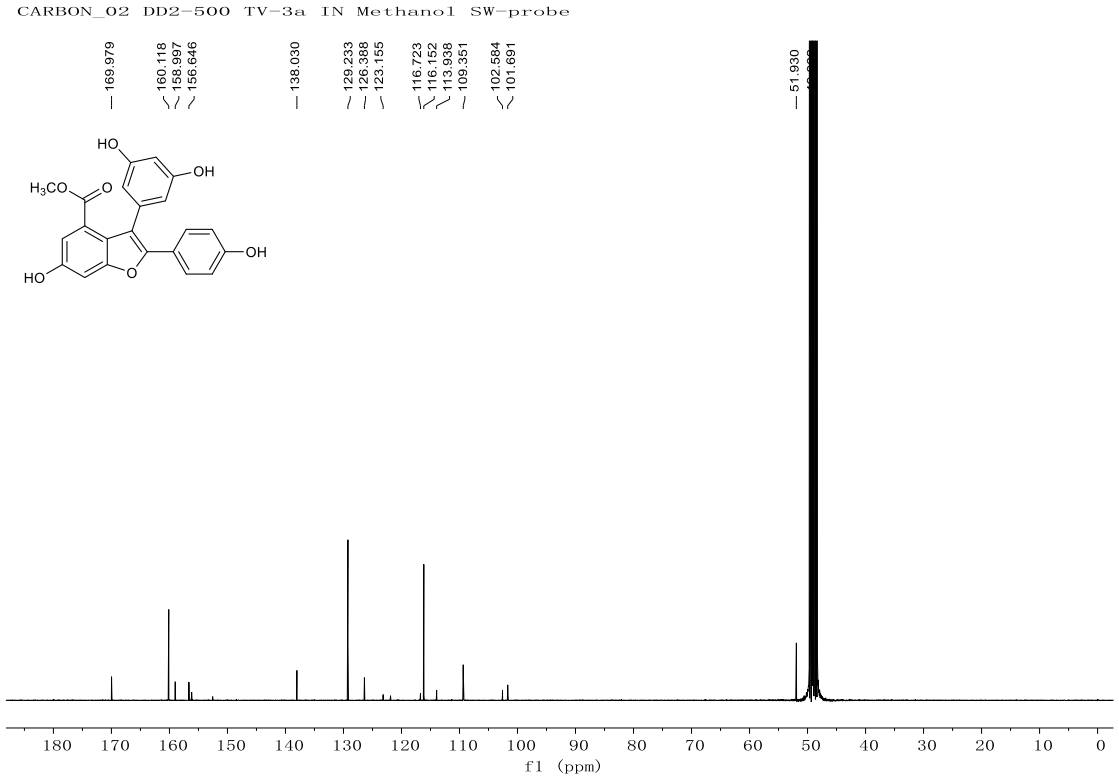
m/z	Theo. Mass	Delta (ppm)	RDB equiv.	Composition	
323.08896	323.08899	-0.11	9.5	C17 H16 O5 Na	M+Na

3.13 spectra of 15

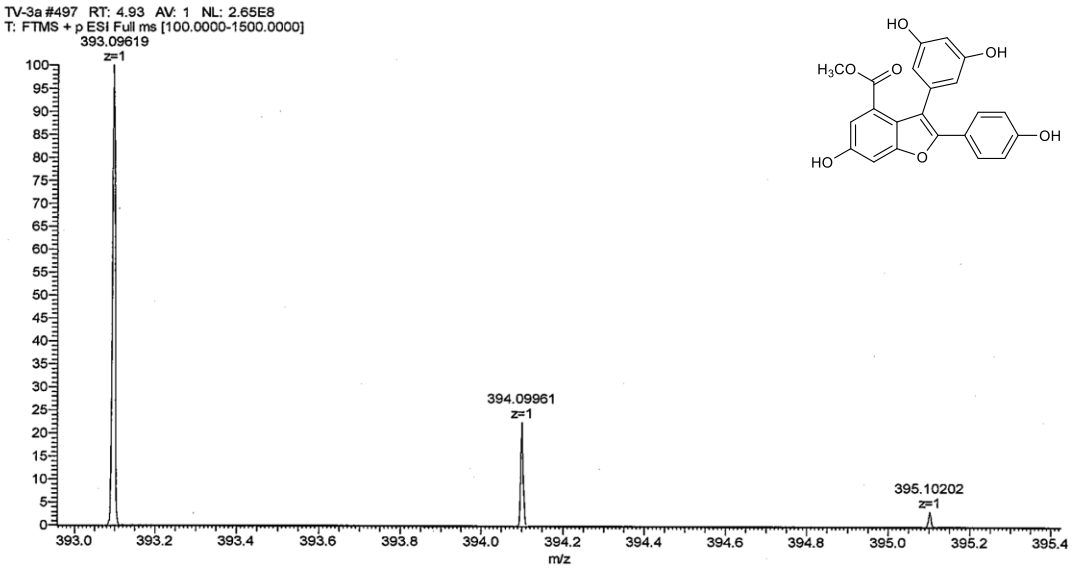
^{1}H NMR of Compound **15**



^{13}C NMR of Compound **15**



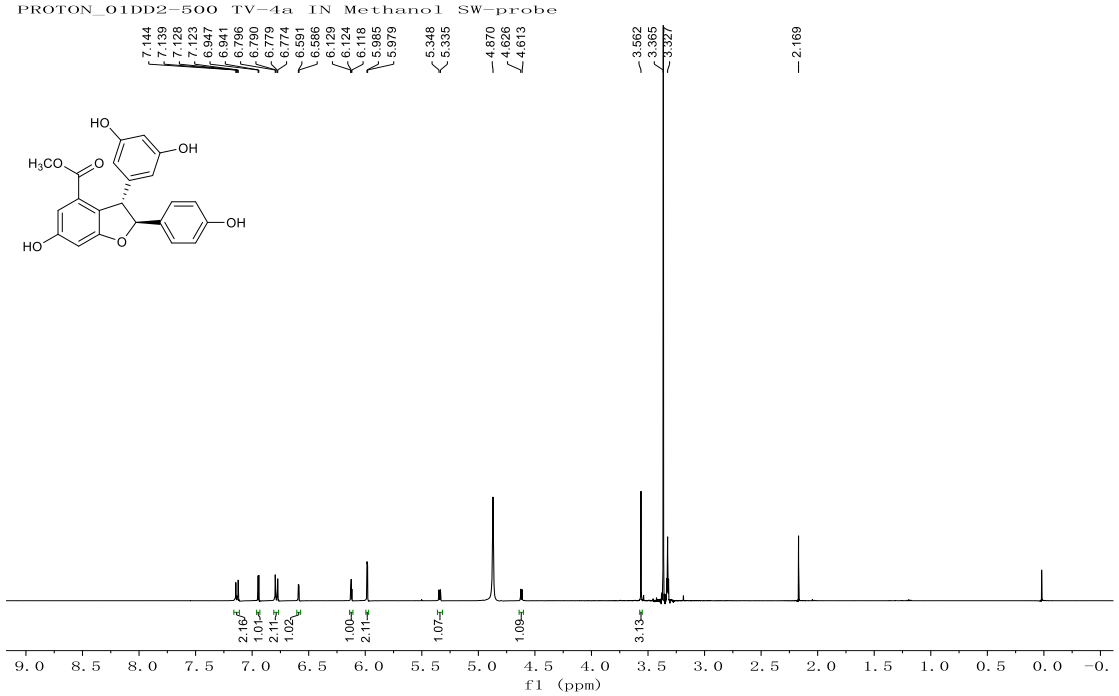
HR-MS (ESI) of Compound **15**



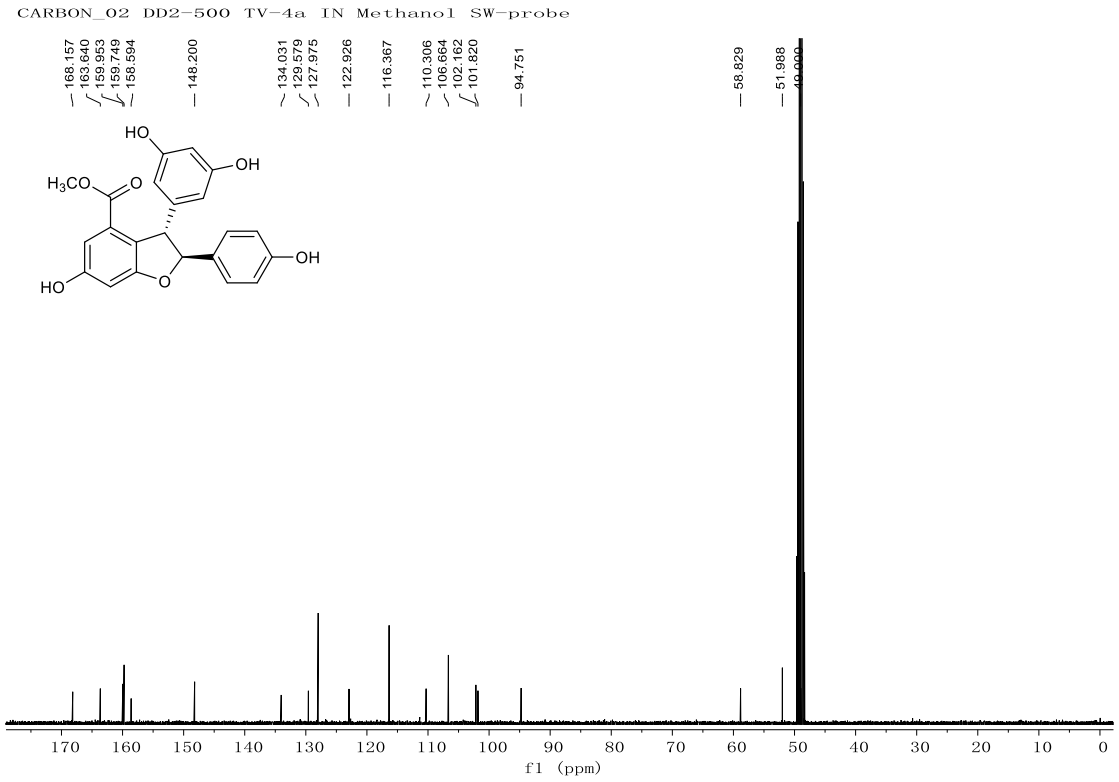
m/z	Theo. Mass	Delta (ppm)	RDB equiv.	Composition	
393.09619	393.09688	-1.75	14.5	C22 H17 O7	M+H

3.14 spectra of 20

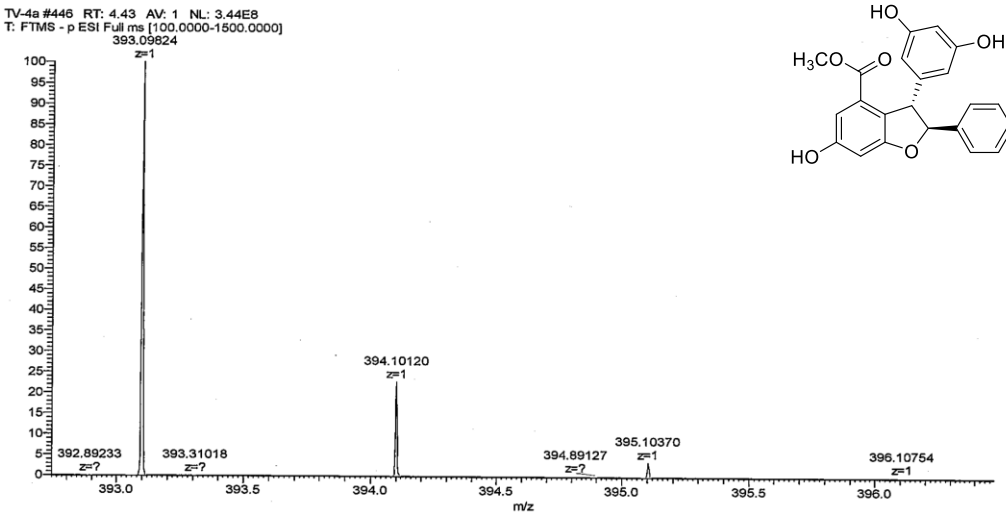
^{1}H NMR of Compound **20**



^{13}C NMR of Compound **20**



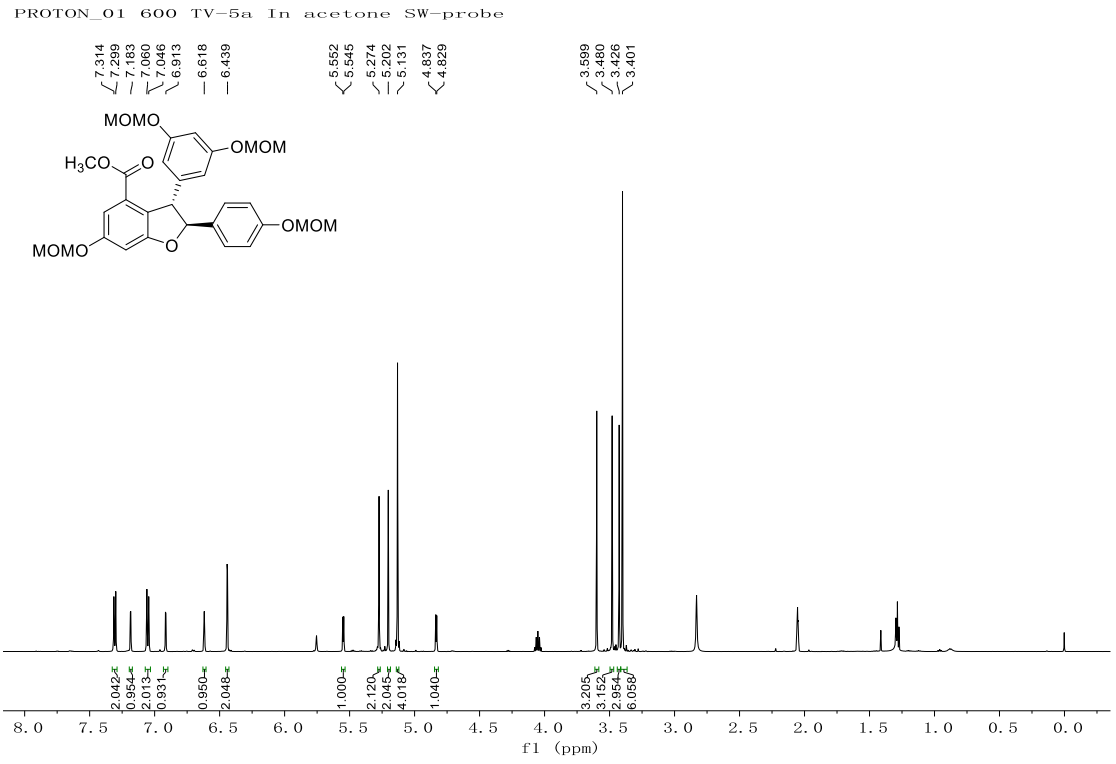
HR-MS (ESI) of Compound **20**



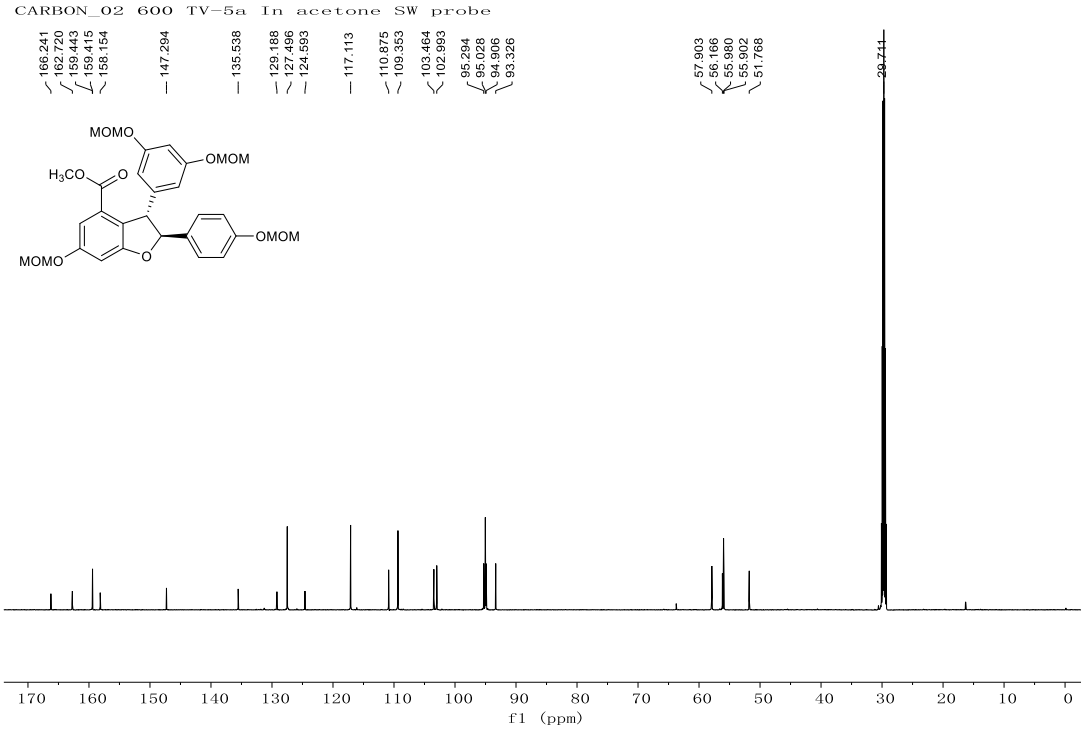
m/z	Theo. Mass	Delta (ppm)	RDB equiv.	Composition	
393.09824	393.09798	0.67	14.5	C22 H17 O7	M-H

3.15 spectra of 21

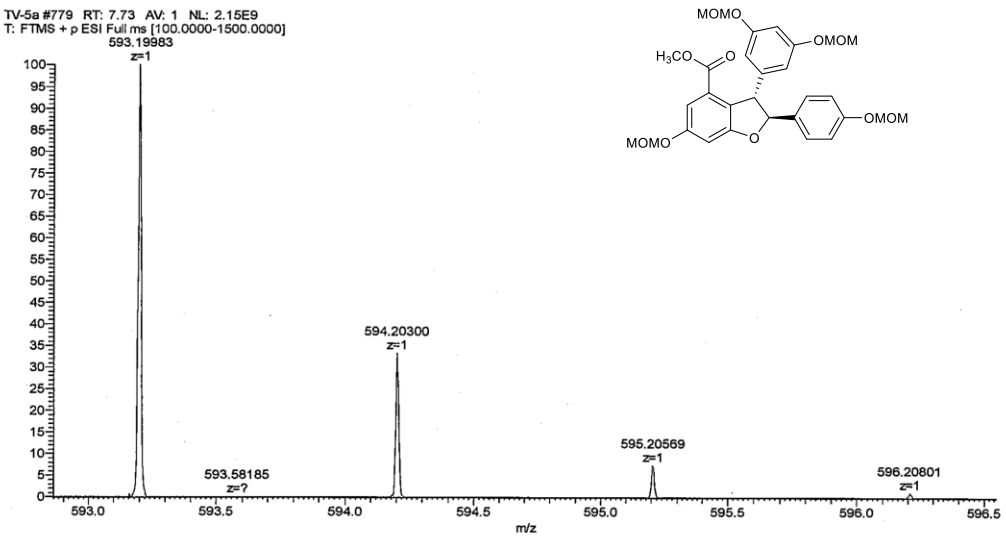
^{1}H NMR of Compound **21**



^{13}C NMR of Compound **21**



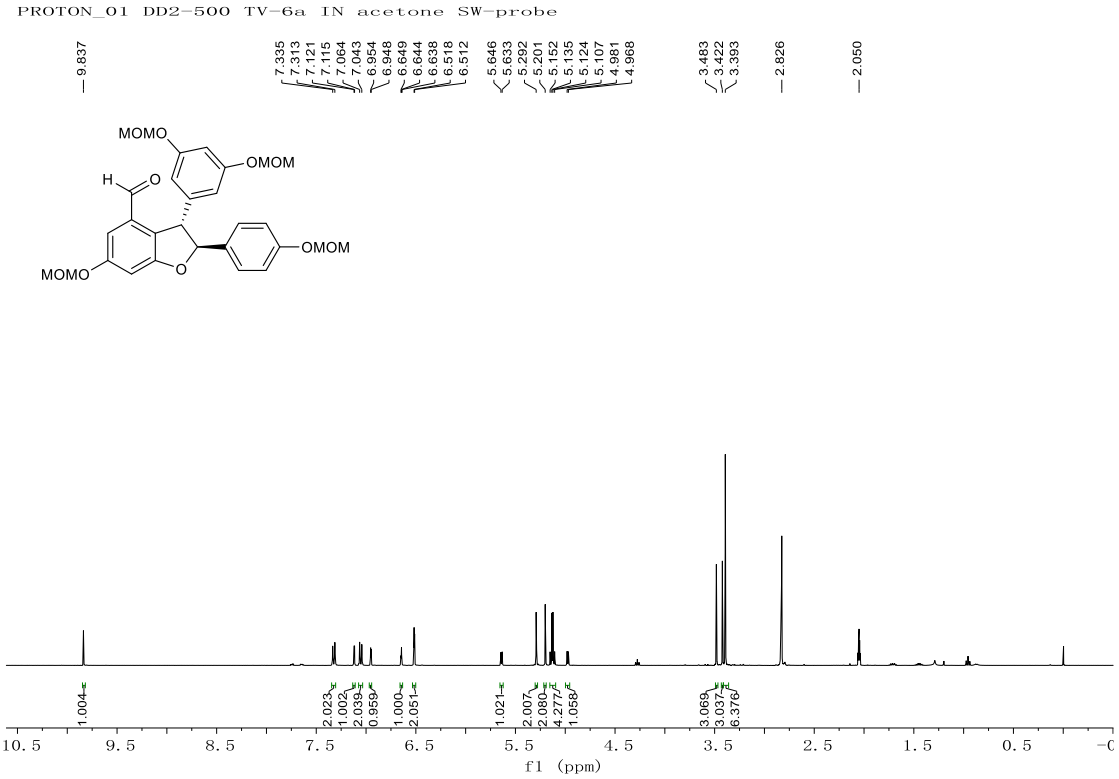
HR-MS (ESI) of Compound **21**



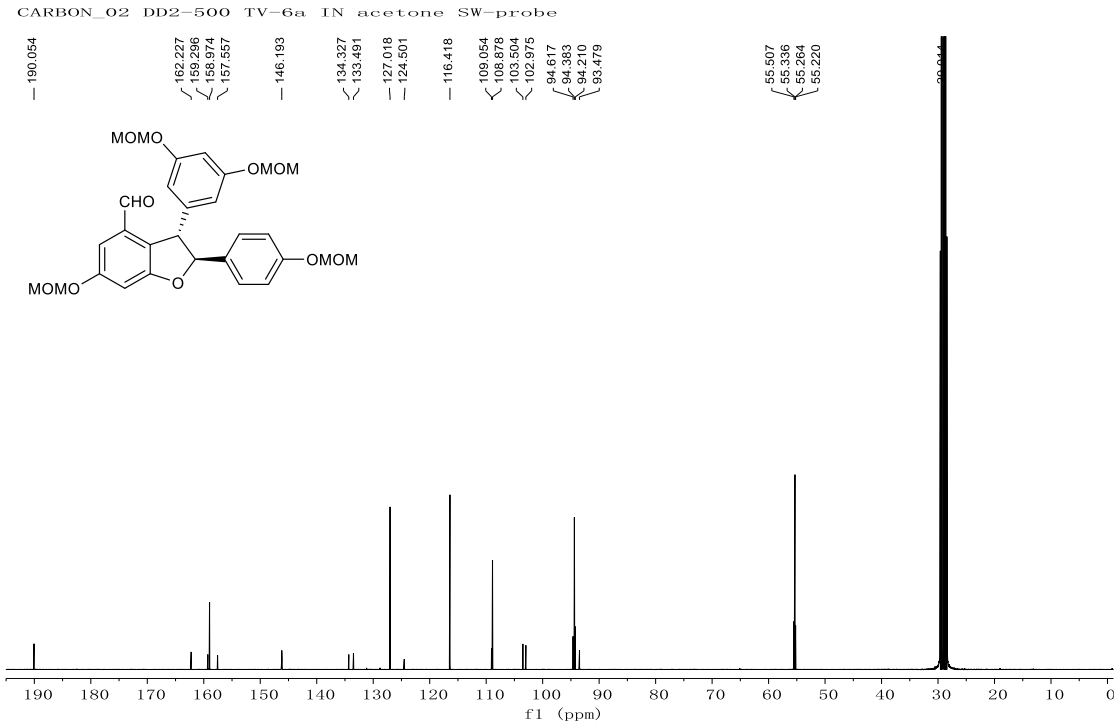
m/z	Theo. Mass	Delta (ppm)	RDB equiv.	Composition	
593.19983	593.19933	0.84	13.5	C30 H34 O11 Na	M+Na

3.16 spectra of 22

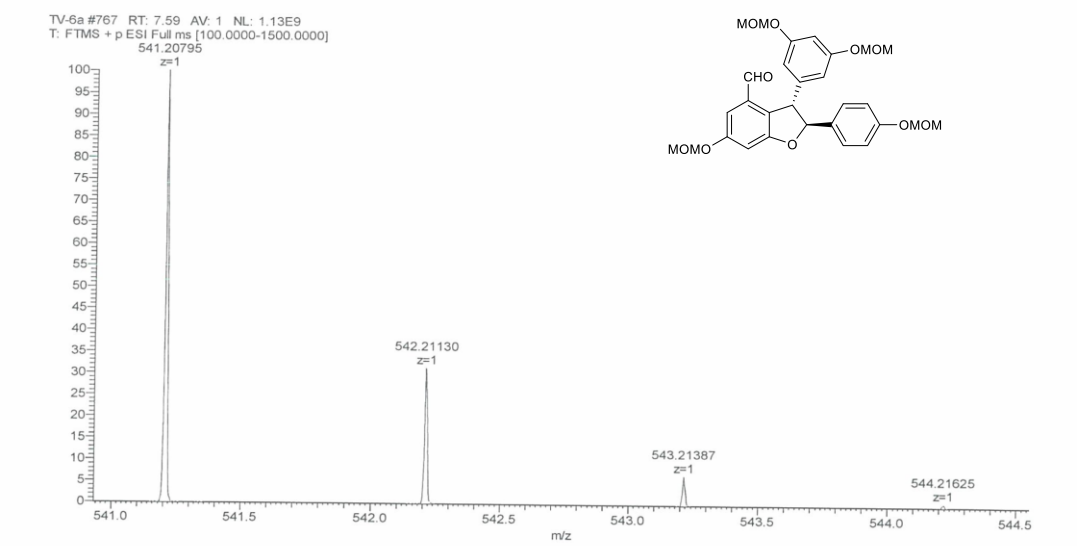
^{1}H NMR of Compound **22**



^{13}C NMR of Compound **22**



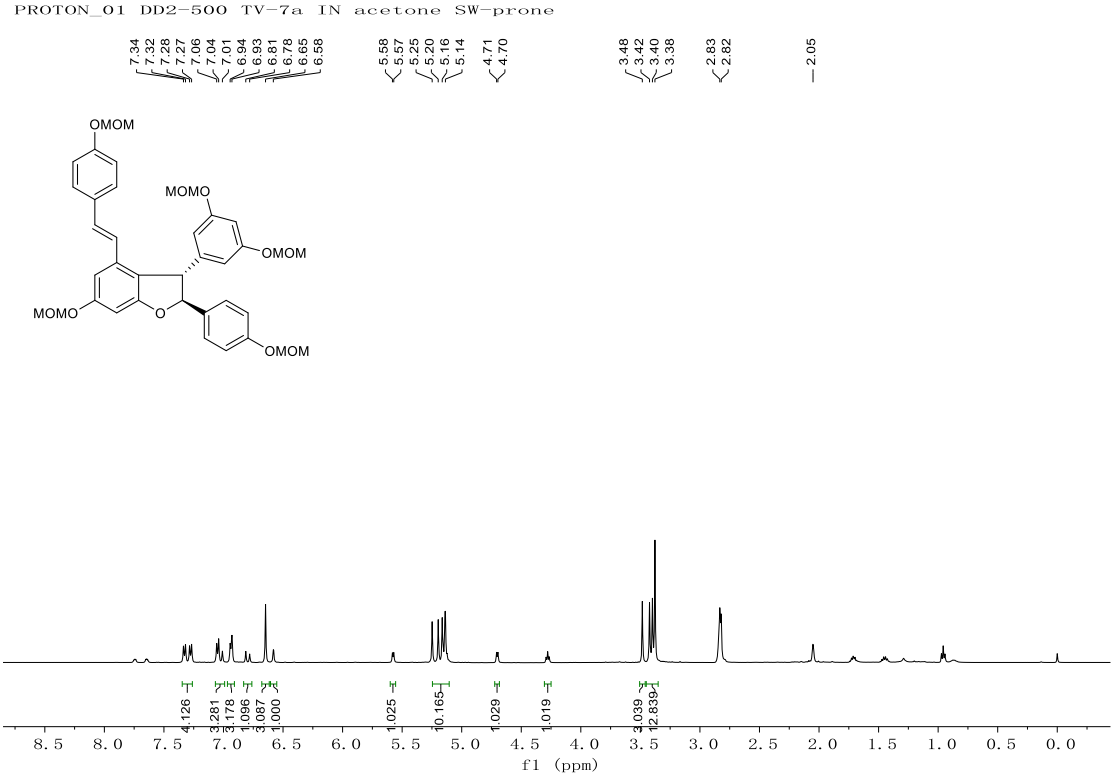
HR-MS (ESI) of Compound **22**



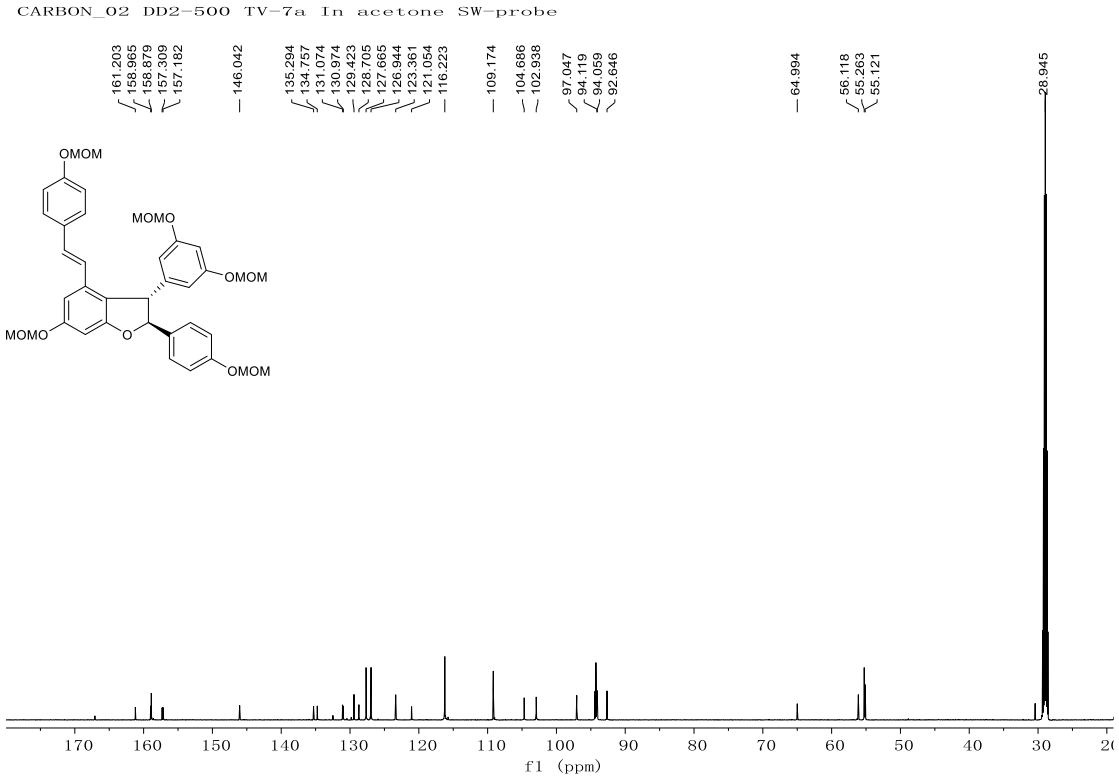
m/z	Theo. Mass	Delta (ppm)	RDB equiv.	Composition	
541.20795	541.20682	2.08	13.5	C29 H33 O10	M+H

3.17 spectra of 24

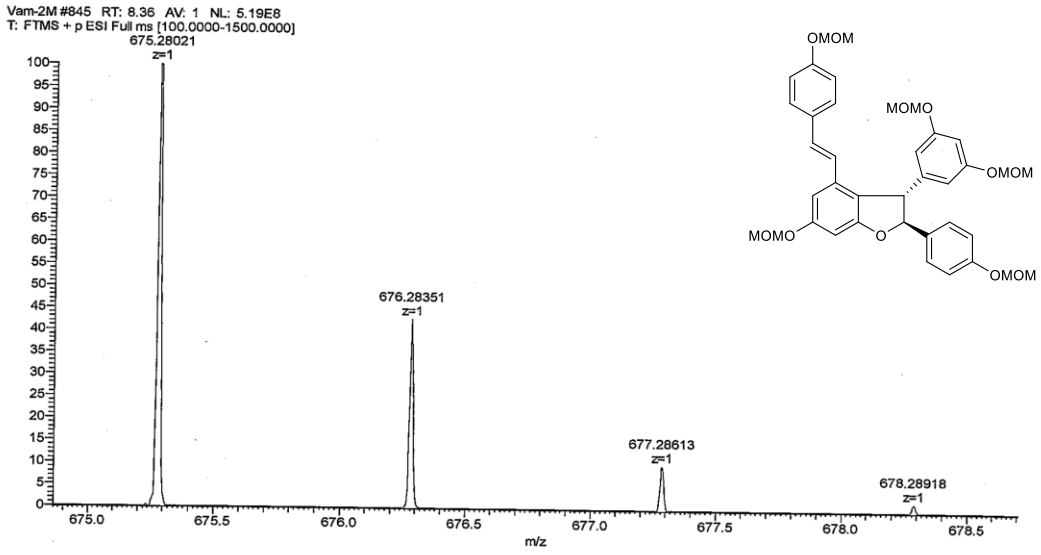
^{1}H NMR of Compound **24**



^{13}C NMR of Compound **24**



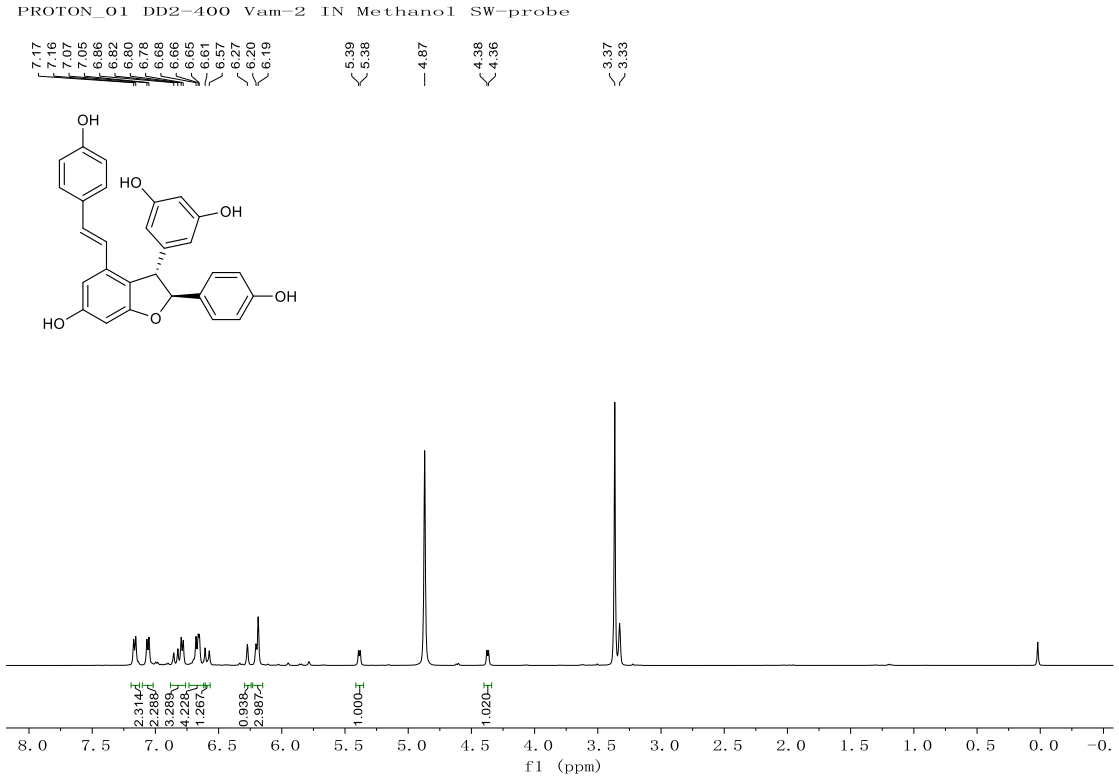
HR-MS (ESI) of Compound **24**



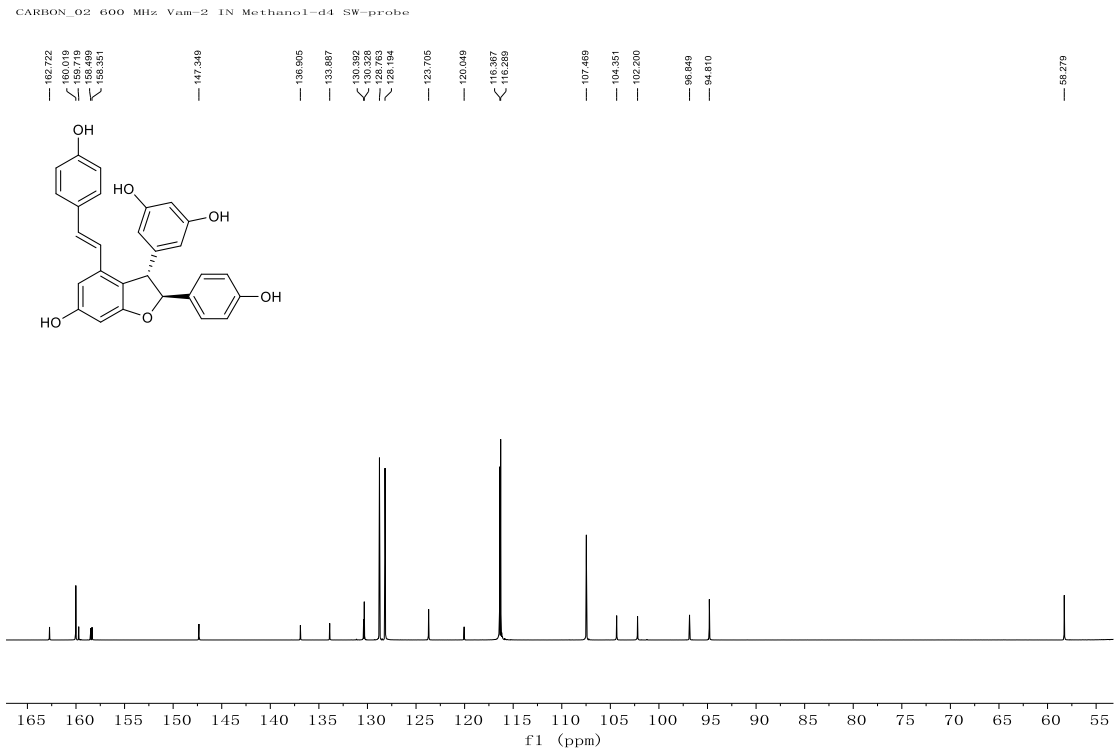
m/z	Theo. Mass	Delta (ppm)	RDB equiv.	Composition	
675.28021	675.27999	0.33	17.5	C38 H43 O11	M+H

3.18 spectra of 1

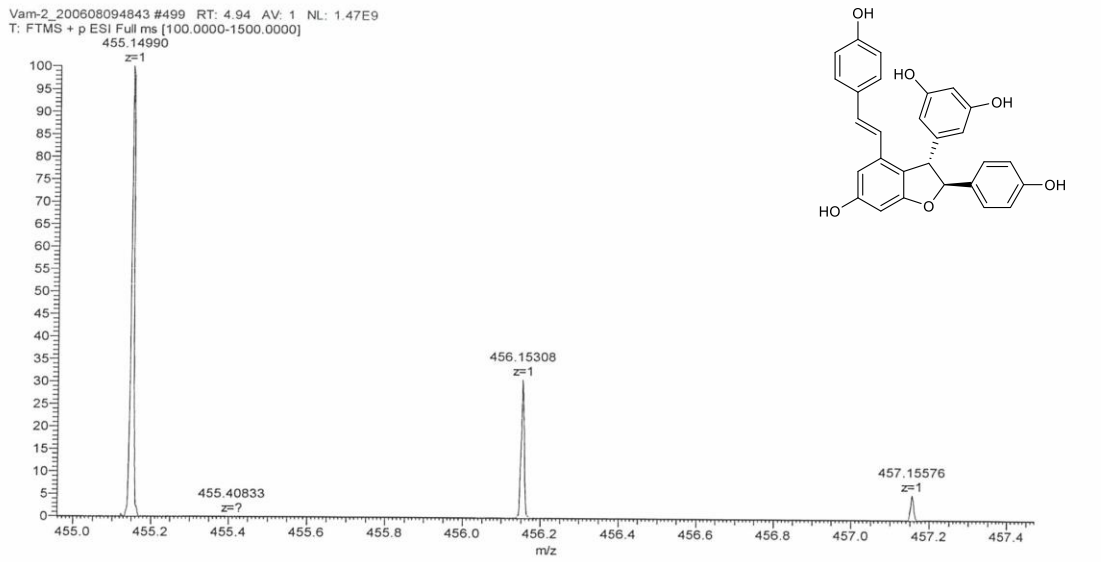
^{1}H NMR of Compound **1**



^{13}C NMR of Compound **1**



ESI-MS of Compound **1**



m/z	Theo. Mass	Delta (ppm)	RDB equiv.	Composition	
455.14990	455.14891	2.16	17.5	C28 H23 O6	M+H