Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Supporting Information

The Piancatelli Rearrangement of Non-Symmetrical Furan-2,5-dicarbinols for the Synthesis of Highly Functionalized Cyclopente-nones

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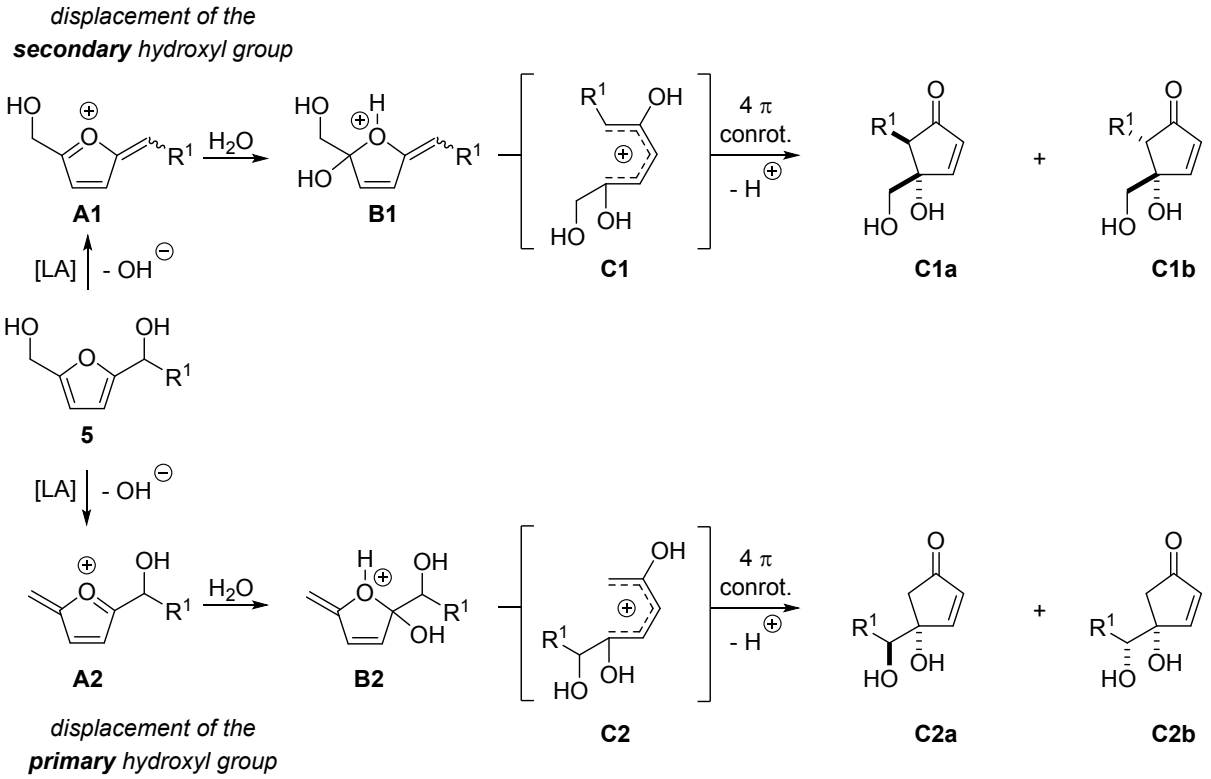
I. Mechanistic Considerations:

Since substrates **5** possess two different furfuryl alcohol moieties, the Piancatelli rearrangement can occur by two pathways (Scheme 5). The displacement of the secondary hydroxyl group leads to furanoxonium ion intermediate **A1**, which undergoes an addition of water and ring opening to reveal a pentadienyl cation equivalent **C1**. This latter species can deliver the desired diastereoisomeric substituted cyclopentenones **C1a** and **C1b** through a 4π-conroratory electrocyclisation. On the other hand, the displacement of the primary hydroxyl group leads to furanoxonium ion intermediate **A2** and, in a similar pathway, the diastereoisomeric substituted cyclopentenones **C2a** and **C2b** could be obtained.



Scheme S1. Proposed intermediates in the Piancatelli rearrangement and an overview of different potential products from non-symmetrical 2,5-bis(carbinol)furan 5

II. General information:

Reactions were performed using oven dried glasswares under an atmosphere of argon. All separations were carried out under flash-chromatographic conditions on silica gel (Redi Sep prepacked column, 230–400 mesh) at medium pressure (20 psi) with use of a CombiFlash Companion or preparative HPLC. Reactions were monitored by thin-layer chromatography on Merck silica gel plates (60 F254 aluminum sheets) which were rendered visible by ultraviolet and spraying with vanillin (15%) + sulfuric acid (2.5%) in EtOH followed by heating. Reagent-grade chemicals were obtained from diverse commercial suppliers and used as received.

Microwave-assisted reactions were performed in a Monowave 300 microwave reactor, using borosilicate glass standard vials G10. Sealed reaction vessels were used. The reaction temperature was monitored with an external surface sensor and was maintained in each experiment.

^{1}H NMR (500 or 300 MHz) and ^{13}C NMR (125 or 75 MHz) spectra were recorded on Brüker Avance spectrometers at 298 K unless otherwise stated. Chemical shifts are given in ppm (δ) and are referenced to the internal solvent signal. Multiplicities are declared as follow: s (singlet), brs (broad singlet), d (doublet), t (triplet), q (quadruplet), dd (doublet of doublet), m (multiplet). Coupling constants *J* are given in Hz. Carbon multiplicities were determined by DEPT135 experiment.

Infrared spectra (IR) were recorded on a Perkin-Elmer FT-IR system using diamond window Dura SamplIR II and the data are reported in reciprocal centimeters (cm^{-1}).

High-resolution mass spectrometry (HRMS) was performed using electrospray ionization (ESI) and time-of-flight (TOF) analyzer, in positive-ion or negative-ion detection mode.

III. Experimental procedures:

Synthesis of (5-(hydroxymethyl)furan-2-yl)(aryl)methanol substrates 5a-j.

General procedure A.

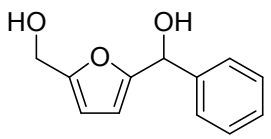
To a solution of 5-(hydroxymethyl)furfural (1.0 eq.) in anhydrous THF (0.25 M), was added at 0 °C a solution of arylmagnesium bromide in Et_2O (3.0 M*,* 2.5 eq). The reaction mixture was stirred for 2 h from 0 °C to room temperature. Then the mixture was quenched with a 0.1 *M* solution of hydrogen chloride. The aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated to dryness under vacuum. The residue was purified by flash chromatography on silica gel (10 to 60% EtOAc/heptane) to afford compounds **5.**

General procedure B.

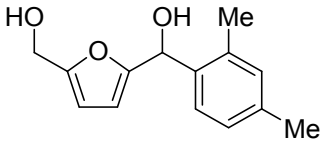
To a suspension of magnesium (6.0 eq) in anhydrous THF (0.20 M) were added a few drops of 1-bromoaryl substrate and 1,2-dibromoethane under argon. The reaction mixture was warmed up for 2 minutes to initiate the reaction and 1-bromo-aryl (4.0 eq) was added dropwise. After refluxing for 2 h under argon, the mixture was cooled to 0 °C and a solution of 5-(hydroxymethyl)furfural (1.0 eq) in THF was added dropwise. After stirring for 2 h from 0 °C to room temperature, the reaction was quenched with a saturated solution of NH_4Cl. The aqueous layer was extracted thrice with ethyl acetate. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated to dryness under vacuum. The residue was purified by flash chromatography on silica gel (10 to 60% EtOAc/heptane) to afford compounds **5**.

General procedure C.

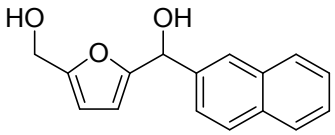
To a solution of 2-bromoaryl (1.0 eq) in anhydrous THF (0.15 M) at -78 °C, was added *n*-BuLi 1.6 *M* in hexanes (1.1 eq). The reaction mixture was stirred at -78 °C for 15 min and 5-(hydroxymethyl)furfural (1.05 eq) was added. The reaction mixture was then stirred 2 h at -78 °C. The mixture was quenched with a saturated solution of NH_4Cl. The aqueous layer was extracted thrice with ethyl acetate. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated to dryness under vacuum. The residue was purified by flash chromatography on silica gel (10 to 60% EtOAc/heptane) to afford compounds **5**.



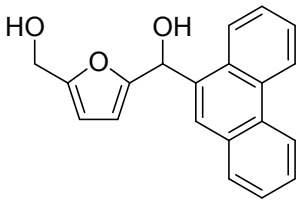
III.1. (5-(Hydroxymethyl)furan-2-yl)(phenyl)methanol (5a). This product was synthesized according to General Procedure A. Pale yellow oil, 1.25 g, 77% yield. R_f 0.24 (50% EtOAc/heptane); **^{1}H-NMR (Acetone-d_6, 300 MHz)** δ 7.48-7.44 (m, 2H), 7.37-7.28 (m, 3H), 6.16 (d, 1H, *J* = 3.0 Hz), 6.03 (d, 1H, *J* = 3.0 Hz), 5.75 (d, 1H, *J* = 4.8 Hz), 4.88 (d, *J* = 4.8 Hz, 1H), 4.45 (d, *J* = 5.8 Hz, 2H), 4.11 (t, *J* = 5.8 Hz, 1H); **^{13}C-NMR (Acetone-d_6, 75 MHz)** δ 157.8 (C), 156.0 (C), 143.5 (C), 128.9 (CH), 128.2 (CH), 127.5 (CH), 108.2 (CH), 108.0 (CH), 70.3 (CH), 57.4 (CH_2); **IR (ν/cm^{-1})** 3351, 2866, 1494, 1452, 1365, 1189, 1012, 791, 745, 699; **HRMS (ESI)** *m/z* = 187.0757, calcd. for $C_{12}H_{11}O_2$ $[M\text{-}H_2O+H]^+$: 187.0759.

III.2. (2,4-Dimethylphenyl)(5-(hydroxymethyl)furan-2-yl)methanol (5b). 

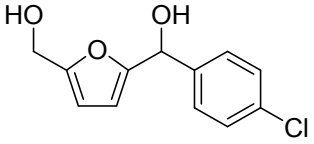
This product was synthesized according to General Procedure B. Yellow oil, 920 mg, 99% yield. R_f 0.45 (70% EtOAc/heptane); **^{1}H-NMR (Acetone-d_6, 300 MHz)** δ 7.44 (d, *J* = 8.0 Hz, 1H), 7.01 (d, *J* = 8.0 Hz, 1H), 6.95 (s, 1H), 6.15 (d, *J* = 2.9 Hz, 1H), 5.93 (d, *J* = 2.9 Hz, 1H), 5.89 (d, *J* = 5.0 Hz, 1H), 4.76 (d, *J* = 5.0 Hz, 1H), 4.45 (d, *J* = 5.8 Hz, 2H), 4.16 (t, *J* = 5.8 Hz, 1H), 2.27 (s, 3H), 2.22 (s, 3H); **^{13}C-NMR (Acetone-d_6, 75 MHz)** δ 157.5 (C), 155.8 (C), 138.4 (C), 137.3 (C), 135.7 (C), 131.6 (CH), 127.4 (CH), 127.2 (CH), 108.2 (CH), 108.0 (CH), 67.3 (CH), 57.4 (CH_2), 21.0 (CH_3), 19.1 (CH_3); **IR (ν/cm^{-1})** 3379, 2921, 1667, 1614, 1499, 1451, 1196, 1014, 909, 796, 730; **HRMS (ESI)**: *m/z* = 215.1075, calcd. for $C_{14}H_{15}O_2$ $[M\text{-}H_2O+H]^+$: 215.1072.

III.3. (5-(Hydroxymethyl)furan-2-yl)(naphthalen-2-yl)methanol (5c). 

This product was synthesized according to General Procedure C. Yellow solid, 249 mg, 34% yield. R_f 0.48 (70% EtOAc/heptane); Mp: 106 - 108 °C; **^{1}H-NMR (Acetone-d_6, 300 MHz)** δ 7.98 (s, 1H), 7.91-7.85 (m, 3H), 7.58 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.51-7.47 (m, 2H), 6.19 (d, *J* = 3.0 Hz, 1H), 6.10 (d, *J* = 3.0 Hz, 1H), 5.94 (d, *J* = 4.8 Hz, 1H), 5.05 (d, *J* = 4.8 Hz, 1H), 4.45 (d, *J* = 6.0 Hz, 2H), 4.12 (t, *J* = 6.0 Hz, 1H); **^{13}C-NMR (Acetone-d_6, 75 MHz)** δ 157.7 (C), 155.9 (C), 140.8 (C), 134.4 (C), 133.9 (C), 128.8 (CH), 128.5 (CH), 128.4 (CH), 126.9 (CH), 126.7 (CH), 126.0 (CH), 108.2 (CH), 108.1 (CH), 70.4 (CH), 57.4 (CH_2); **IR (ν/cm^{-1})** 3350, 2931, 2870, 1665, 1190, 1122, 1013, 965, 861, 785; **HRMS (ESI)**: *m/z* = 237.0914, calcd. for $C_{16}H_{13}O_2$ $[M\text{-}H_2O+H]^+$: 237.0916.

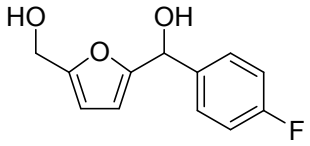
III.4. (5-(Hydroxymethyl)furan-2-yl)(phenanthren-9-yl)methanol (5d). 

This product was synthesized according to General Procedure B. Yellow solid, 94 mg, 16% yield. R_f 0.24 (70% EtOAc/heptane); Mp: 148 - 150 °C; **^{1}H-NMR (CD_3OD, 300 MHz)** δ 8.78 (d, *J* = 8.4 Hz, 1H), 8.73 (d, *J* = 8.4 Hz, 1H), 8.08-8.02 (m, 2H), 7.93-7.90 (m, 1H), 7.66-7.53 (m, 4H), 6.49 (s, 1H), 6.21 (d, *J* = 3.0 Hz, 1H), 6.04 (d, *J* = 3.0 Hz, 1H), 4.48 (s, 2H); **^{13}C-NMR (CD_3OD, 75 MHz)** δ 157.5 (C), 155.7 (C), 136.6 (C), 132.8 (C), 132.0 (C), 131.6 (C), 131.1 (C), 129.9 (CH), 127.9 (CH), 127.8 (CH), 127.5 (CH), 127.3 (CH), 126.2 (CH), 125.6 (CH), 124.2 (CH), 123.6 (CH), 109.6 (CH), 109.3 (CH), 68.3 (CH), 57.5 (CH_2); **IR (ν/cm^{-1})** 3350, 1497, 1449, 1247, 1067, 1012, 793, 747, 725; **HRMS (ESI)**: *m/z* = 287.1061, calcd. for $C_{20}H_{15}O_2$ $[M\text{-}H_2O+H]^+$: 287.1072.

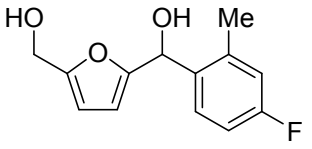
III.5. (4-Chlorophenyl)(5-(hydroxymethyl)furan-2-yl)methanol (5e). 

This product was synthesized according to General Procedure A. Pale yellow solid, 773 mg, 82% yield. R_f 0.31 (50% EtOAc/heptane); Mp: 78 - 81°C; **^{1}H-NMR (Acetone-d_6, 300 MHz)** δ 7.47 (d, *J* = 8.0 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 6.18 (d, *J* = 3.0 Hz, 1H), 6.07 (d, *J* = 3.0 Hz, 1H), 5.78 (d, *J* = 4.6 Hz, 1H), 5.09 (d, *J* = 4.6 Hz, 1H), 4.45 (d, *J* = 6.0 Hz, 2H), 4.20 (t, *J* = 6.0 Hz, 1H); **^{13}C-NMR (Acetone-d_6, 75 MHz)** δ 157.2 (C), 156.2 (C), 142.4 (C), 133.4 (C), 129.2 (CH), 128.9 (CH), 108.3 (CH), 108.2 (CH), 69.6 (CH), 57.3 (CH_2); **IR (ν/cm^{-1})** 3350, 2871, 1666, 1490, 1408, 1189, 1089, 1013, 843, 799, 774; **HRMS (ESI)**: *m/z* = 221.0364, calcd. for $C_{12}H_{10}O_2Cl$ $[M\text{-}H_2O+H]^+$: 221.0369.

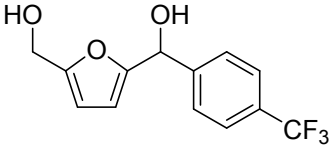
III.6. (4-Fluorophenyl)(5-(hydroxymethyl)furan-2-yl)methanol (5f). This product was synthesized according to General Procedure A. Pale yellow solid, 766 mg, 97% yield. R_f 0.46 (60% EtOAc/heptane); Mp: 95 - 98 °C; **^{1}H-NMR (Acetone-d_6, 300 MHz)** δ 7.51-7.47 (m, 2H), 7.13-7.07 (m, 2H), 6.18 (d, *J* = 3.2 Hz, 1H), 6.06 (d, *J* = 3.2 Hz, 1H), 5.78 (d, *J* = 4.8 Hz, 1H), 5.02 (d, *J* = 4.8 Hz, 1H), 4.45 (d, *J* = 6.0 Hz, 2H), 4.19 (t, *J* = 6.0 Hz, 1H); **^{13}C-NMR (Acetone-d_6, 75 MHz)** δ 163.0 (d, J_{CF} = 240 Hz, C), 157.5 (C), 156.0 (CH), 139.6 (CH) , 129.4 (d, J_{CF} = 9 Hz, CH), 115.5 (d, J_{CF} = 21 Hz, CH), 108.2 (CH), 108.1 (CH), 69.6 (CH), 57.3 (CH_2); **^{19}F-NMR (Acetone-d_6, 282 MHz)** 60.4; **IR (ν/cm^{-1})** 3324, 1604, 1508, 1414, 1221, 1185, 1157, 1011, 843, 800, 777; **HRMS (ESI)**: *m/z* = 205.0655, calcd. for $C_{12}H_{10}O_2F$ $[M-H_2O+H]^+$: 205.0665.



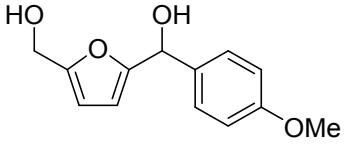
III.7. (4-Fluoro-2-methylphenyl)(5-(hydroxymethyl)furan-2-yl)methanol (5g). This product was synthesized according to General Procedure B. Yellow oil, 773 mg, 82% yield. R_f 0.29 (50% EtOAc/heptane); **^{1}H-NMR (Acetone-d_6, 300 MHz)** δ 7.62-7.57 (m, 1H), 7.00-6.90 (m, 2H), 6.17 (d, *J* = 3.0 Hz, 1H), 5.96 (d, *J* = 3.0 Hz, 1H), 5.92 (d, *J* = 4.6 Hz, 1H), 4.95 (d, *J* = 4.6 Hz, 1H), 4.46 (d, *J* = 6.0 Hz, 2H), 4.21 (t, *J* = 6.0 Hz, 1H), 2.27 (s, 3H); **^{13}C-NMR (Acetone-d_6, 75 MHz)** δ 162.7 (d, J_{CF} = 241 Hz, C), 156.9 (C), 156.0 (C), 138.7 (d, J_{CF} = 9 Hz, C), 137.4 (C), 129.3 (d, J_{CF} = 9 Hz, CH), 117.2 (d, J_{CF} = 22 Hz, CH), 112.9 (d, J_{CF} = 22 Hz, CH), 108.2 (CH), 66.8 (CH), 57.3 (CH_2), 19.0 (CH_3); **IR (ν/cm^{-1})** 3318, 1615, 1591, 1496, 1449, 1246, 1176, 1097, 1011, 952, 864, 783; **HRMS (ESI)**: *m/z* = 219.0819., calcd. for $C_{13}H_{12}O_2F$ $[M-H_2O+H]^+$: 219.0821.



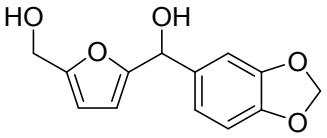
III.8. ((5-(Hydroxymethyl)furan-2-yl)(4-(trifluoromethyl)phenyl) methanol (5h). This product was synthesized according to General Procedure B. Yellow solid, 765 mg, 87% yield. R_f 0.25 (50% EtOAc/heptane); Mp: 90 - 92 °C; **^{1}H-NMR (Acetone-d_6, 300 MHz)** δ 7.70 (bs, 4H), 6.19 (d, *J* = 3.0 Hz, 1H), 6.11 (d, *J* = 3.0 Hz, 1H), 5.89 (d, *J* = 4.8 Hz, 1H), 5.19 (d, *J* = 4.8 Hz, 1H), 4.45 (d, *J* = 6.0 Hz, 2H), 4.15 (t, *J* = 6.0 Hz, 1H); **^{13}C-NMR (Acetone-d_6, 75 MHz)** δ 156.8 (C), 156.4 (C), 148.0 (C), 129.8 (q, J_{CF} = 35 Hz, C), 128.1 (CH), 125.8 (q, J_{CF} = 4 Hz, CH), 125.4 (q, J_{CF} = 267 Hz, C), 108.4 (CH), 108.3 (CH), 69.6 (CH), 57.3 (CH_2); **^{19}F-NMR (Acetone-d_6, 282 MHz)** 114.6; **IR (ν/cm^{-1})** 3327, 1620, 1416, 1325, 1164, 1123, 1067, 1016, 855, 801, 783; **HRMS (ESI)**: *m/z* = 255.0626, calcd. for $C_{13}H_{10}O_2F_3$ $[M-H_2O+H]^+$: 255.0633.



III.9. (5-(Hydroxymethyl)furan-2-yl)(4-methoxyphenyl) methanol (5i). This product was synthesized according to General Procedure C. Pale yellow oil, 1.12 g, 99% yield. R_f 0.47 (70% EtOAc/heptane); **^{1}H-NMR (Acetone-d_6, 300 MHz)** δ 7.35 (d, *J* = 8.4 Hz, 2H), 6.89 (d, *J* = 8.4 Hz, 2H), 6.16 (d, *J* = 3.0 Hz, 1H), 6.03 (d, *J* = 3.0 Hz, 1H), 5.70 (d, *J* = 4.8 Hz, 1H), 4.81 (d, *J* = 4.8 Hz, 1H), 4.44 (d, *J* = 6.0 Hz, 2H), 4.16 (t, *J* = 6.0 Hz, 1H), 3.78 (s, 3H); **^{13}C-NMR (Acetone-d_6, 75 MHz)** δ 160.0 (C), 158.1 (C), 155.8 (C), 135.6 (C), 128.7 (CH), 114.2 (CH), 108.1 (CH), 107.7 (CH), 70.0 (CH), 57.4 (CH_2), 55.5 (CH_3); **IR (ν/cm^{-1})** 3356, 1611, 1512, 1463, 1303, 1247, 1173, 1012, 838, 800, 781; **HRMS (ESI)**: *m/z* = 217.0863, calcd. for $C_{13}H_{13}O_3$ $[M-H_2O+H]^+$: 217.0865.



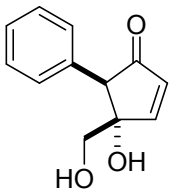
III.10. Benzo[d][1,3]dioxol-5-yl(5-(hydroxymethyl)furan-2-yl) methanol (5j). This product was synthesized according to General Procedure C. Yellow solid, 262 mg, 33% yield. R_f 0.24 (50% EtOAc/heptane); Mp: 89.6 - 91.5 °C; **^{1}H-NMR (Acetone-d_6, 300 MHz)** δ 6.96 (d, *J* = 1.5 Hz, 1H), 6.93 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.79 (d, *J* = 8.0 Hz, 1H), 6.17 (d, *J* = 3.0 Hz, 1H), 6.07 (d, *J* = 3.0 Hz, 1H), 5.97 (s, 2H), 5.68 (d, *J* = 4.6 Hz, 1H), 4.86 (d, *J* = 4.6 Hz, 1H), 4.45 (d, *J* = 6.0 Hz, 2H), 4.14 (t, *J* = 6.0 Hz, 1H); **^{13}C-NMR (Acetone-d_6, 75 MHz)** δ 157.8 (C), 155.9 (C), 148.5 (C), 147.8 (C), 137.6 (C), 120.9 (CH), 108.5 (CH), 108.2 (CH), 108.0 (CH), 107.7 (CH), 101.9 (CH_2), 70.1 (CH), 57.3 (CH_2); **IR (ν/cm^{-1})** 3329, 1502, 1488, 1443, 1242, 1095, 1036, 1011, 928, 868, 776; **HRMS (ESI)**: *m/z* = 231.0665, calcd. for $C_{13}H_{11}O_4$ $[M\text{-}H_2O+H]^+$: 231.0657.



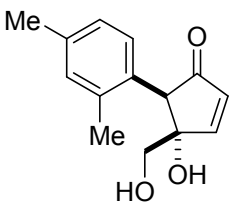
General Procedure D for the synthesis of the cyclopentenone compounds 6a-j.

To a solution a furan derivative **5** (1 eq.) in a mixture of *t*-BuOH/H_2O 5:1 (0.1 *M*), was added $DyCl_3$ (10 mol %). The reaction mixture was heated under MW irradiation for 1.5 h at 100 °C. After cooling to room temperature, the mixture was quenched with a saturated solution of $NaHCO_3$. The aqueous layer was extracted thrice with ethyl acetate. The combined organic layers were washed with brine dried over magnesium sulfate, filtered and concentrated to dryness under vacuum. The residue was purified by flash chromatography on silica gel (heptane/ethyl acetate) to afford the cyclopentenone derivatives **6**.

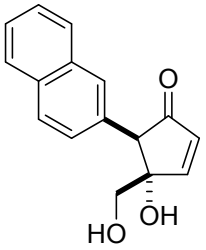
III.11. 4-Hydroxy-4-(hydroxymethyl)-5-phenylcyclopent-2-en-1-one (6a). This compound was prepared according to the General Procedure D using 50 mg of **5a** (0.25 mmol) and 6.6 mg of dysprosium chloride (0.02 mmol). **6a** (26 mg, 51% yield, dr > 95:5) was obtained as a pale yellow oil after flash chromatography (toluene/acetone: 80:20 to 70:30). R_f 0.39 (40% acetone/toluene); **^{1}H-NMR ($CDCl_3$, 300 MHz)** δ 7.53 (d, *J* = 5.8 Hz, 1H), 7.39-7.30 (m, 3H), 7.22-7.16 (m, 2H), 6.40 (d, *J* = 5.8 Hz, 1H), 3.85 (s, 1H), 3.42-3.33 (m, 2H); **^{13}C-NMR ($CDCl_3$, 75 MHz)** δ 205.2 (C), 162.2 (CH), 134.9 (CH), 134.2 (C), 129.7 (CH), 129.3 (CH), 128.1 (CH), 82.1 (C), 66.9 (CH_2), 63.6 (CH); **IR (ν/cm^{-1})** 3401, 2924, 1699, 1497, 1453, 1338, 1170, 1079, 1033, 925, 814, 739, 699; **HRMS (ESI)**: *m/z* = 205.0876, calcd. for $C_{12}H_{13}O_3$ $[M+H]^+$: 205.0865.



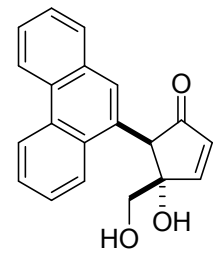
III.12. 5-(2,4-Dimethylphenyl)-4-hydroxy-4-(hydroxymethyl)cyclopent-2-en-1-one (6b). This compound was prepared according to the General Procedure D using 70 mg of **5b** (0.30 mmol) and 7.2 mg of dysprosium chloride (0.03 mmol). **6b** (33 mg, 47% yield, dr > 95:5) was obtained as an orange oil after flash chromatography (heptane/ethyl acetate: 100:0 to 20:80). R_f 0.46 (70% EtOAc/heptane); **^{1}H-NMR (Acetone-d_6, 300 MHz)** δ 7.72 (d, *J* = 5.8 Hz, 1H), 7.01 (bs, 1H), 6.90 (d, *J* = 8.1 Hz, 1H), 6.78 (d, *J* = 8.1 Hz, 1H), 6.30 (d, *J* = 5.8 Hz, 1H), 4.68 (bs, 1H), 3.93 (s, 1H), 3.80 (bs, 1H), 3.23-3.15 (m, 2H), 2.37 (s, 3H), 2.26 (s, 3H); **^{13}C-NMR (Acetone-d_6, 75 MHz)** δ 206.8 (C), 165.1 (CH), 139.0 (C), 137.0 (C), 133.8 (CH), 132.2 (C), 131.5 (CH), 130.5 (CH), 126.9 (CH), 83.4 (C), 67.5 (CH_2), 60.2 (CH), 21.0 (CH_3), 20.5 (CH_3); **IR (ν/cm^{-1})** 3418, 2922, 1699, 1505, 1376, 1217, 1082, 1026, 908, 809, 727; **HRMS (ESI)**: *m/z* = 233.1163, calcd. for $C_{14}H_{17}O_3$ $[M+H]^+$: 233.1178.



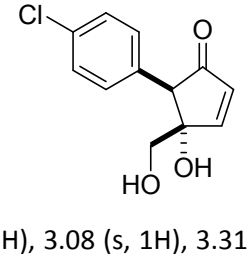
III.13. 4-Hydroxy-4-(hydroxymethyl)-5-(naphthalen-2-yl)cyclopent-2-en-1-one (6c). This compound was prepared according to the General Procedure D using 50 mg of **5c** (0.20 mmol) and 5.3 mg of dysprosium chloride (0.02 mmol). **6c** (40 mg, 80% yield, dr > 95:5) was obtained as an orange oil after flash chromatography (heptane/ethyl acetate: 100:0 to 20:80). R_f 0.25 (70% EtOAC/heptane); **^{1}H-NMR ($CDCl_3$, 300 MHz)** δ 7.85 -7.74 (m, 3H), 7.65 (s, 1H), 7.55 (d, *J* = 6.0 Hz, 1H), 7.51-7.46 (m, 2H), 7.21 (dd, *J* =8.4, 1.4 Hz, 1H), 6.41 (d, *J* = 5.8 Hz, 1H), 3.98 (s, 1H), 3.39 (s, 2H); **^{13}C-NMR ($CDCl_3$, 75 MHz)** δ 205.4 (C), 162.6 (CH), 134.7 (CH), 133.5 (C), 132.8 (C), 131.6 (C), 129.1 (CH), 128.8 (CH), 128.0 (CH), 127.8 (CH), 127.1 (CH), 126.6 (CH), 126.5 (CH), 82.3 (C), 66.9 (CH_2), 63.4 (CH); **IR (ν/cm^{-1})** 3416, 2925, 1704, 1508, 1337, 1084, 1034, 860, 810, 747; **HRMS (ESI)**: *m/z* = 237.0914, calcd. for $C_{16}H_{13}O_2$ $[M\text{-}H_2O+H]^+$: 237.0916.



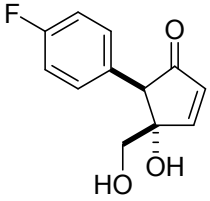
III.14. 4-Hydroxy-4-(hydroxymethyl)-5-(phenanthren-9-yl)cyclopent-2-en-1-one (6d). This compound was prepared according to the General Procedure D using 50 mg of **5d** (0.20 mmol) and 5.2 mg of dysprosium chloride (0.02 mmol). **6d** (20 mg, 40% yield, dr > 95:5) was obtained as a beige crystalline solid (mp: 148-150 °C) after flash chromatography (heptane/ethyl acetate: 100:0 to 40:60). R_f 0.20 (50% EtOAc/heptane; Mp: 114-116 °C; **^{1}H-NMR (Acetone-d_6, 300 MHz)** δ 8.87 (dd, *J* = 7.2, 2.1 Hz, 1H), 8.80 (d, *J* = 8.1 Hz, 1H), 7.90-7.83 (m, 2H), 7.72-7.54 (m, 6H), 6.47 (d, *J* = 6.0 Hz, 1H), 4.55 (s, 1H), 3.34-3.22 (m, 2H); **^{13}C-NMR (Acetone-d_6, 75 MHz)** δ 206.3 (C), 165.1 (CH), 134.0 (CH), 132.3 (C), 131.5 (C), 131.4 (C), 130.7 (C), 129.5 (CH), 127.6 (CH), 127.4 (CH), 127.3 (C), 126.3 (CH), 124.0 (CH), 123.4 (CH), 83.5 (C), 66.9 (CH_2), 59.4 (CH); **IR (ν/cm^{-1})** 3404, 2925, 1698, 1451, 1336, 1186, 1086, 1037, 1016, 748, 724; **HRMS (ESI)**: *m/z* = 305.1187, calcd. for $C_{20}H_{17}O_3$ $[M+H]^+$: 305.1178.



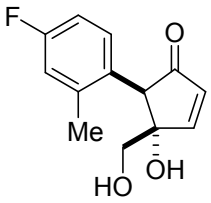
III.15. 5-(4-Chlorophenyl)-4-hydroxy-4-(hydroxymethyl)cyclopent-2-en-1-one (6e). This compound was prepared according to the General Procedure D using 50 mg of **5e** (0.2 mmol) and 5.6 mg of dysprosium chloride (0.02 mmol). **6e** (24.6 mg, 49% yield, dr = 95:5) was obtained as a beige solid after flash chromatography (heptane/ethyl acetate: 100:0 to 20:80). R_f 0.30 (70% EtOAc/heptane); Mp: 109 - 111 °C; **^{1}H-NMR ($CDCl_3$, 300 MHz)** δ 7.56 (d, *J* = 5.8 Hz, 1H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.11 (d, *J* = 8.4 Hz, 2H), 6.38 (d, *J* = 5.8 Hz, 1H), 3.08 (s, 1H), 3.31 (bs, 2H); **^{13}C-NMR ($CDCl_3$, 75 MHz)** δ 204.7 (C), 162.6 (CH), 134.5 (CH), 134.0 (C), 132.5 (C), 131.1 (CH), 129.2 (CH), 82.0 (C), 66.8 (CH_2), 62.6 (CH); **IR (ν/cm^{-1})** 3404, 2976, 1702, 1592, 1493, 1339, 1091, 1034, 1016, 834, 810, 774; **HRMS (ESI)**: *m/z* = 239.0479, calcd. for $C_{12}H_{12}ClO_3$ $[M+H]^+$: 239.0475.



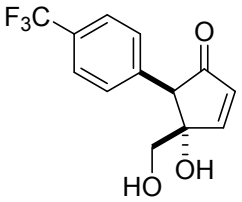
III.16. (5-(4-Fluorophenyl)-4-hydroxy-4-(hydroxymethyl)cyclopent-2-en-1-one (6f). This compound was prepared according to the General Procedure D using 60 mg of **5f** (0.3 mmol) and 7.2 mg of dysprosium chloride (0.03 mmol). **6f** (34 mg, 57% yield, dr = 90:10) was obtained as a white solid after flash chromatography (heptane/ethyl acetate: 100:0 to 20:80). R_f 0.31 (60% EtOAc/heptane; Mp: 111 - 113°C; **^{1}H-NMR (Acetone-$d_6$300 MHz)** δ 7.57 (d, *J* = 5.9 Hz, 1H), 7.32-7.27 (m, 2H), 7.10-7.03 (m, 2H), 6.31 (d, *J* = 5.9 Hz, 1H), 4.80 (s, 1H), 3.81 (dd, *J* = 6.3,



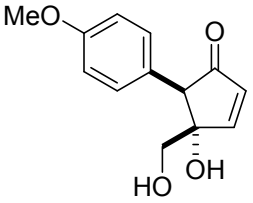
4.8 Hz, 1H), 3.77 (s, 1H), 3.30 (dd, *J* = 10.8, 4.8 Hz, 1H), 3.16 (dd, *J* = 10.8, 6.3 Hz, 1H); **^{13}C-NMR (Acetone-*d*$_6$, 75 MHz)** δ 204.3 (C), 163.7 (CH), 162.7 (d, J_{CF} = 241 Hz, C), 134.1 (CH), 133.1 (d, J_{CF} = 9 Hz, CH), 132.0 (C), 115.3 (d, J_{CF} = 21 Hz, CH), 83.3 (C), 66.1 (CH_2), 63.8 (CH); **^{19}F-NMR (Acetone-*d*$_6$, 282 MHz)** 60.0; **IR (ν/cm^{-1})** 3418, 2919, 1704, 1606, 1510, 1225, 1162, 1035, 841, 812; **HRMS (ESI)**: *m/z* = 223.0764, calcd. for $C_{12}H_{12}FO_3$ $[M+H]^+$: 223.0770.



III.17. 5-(4-Fluoro-2-methylphenyl)-4-hydroxy-4-(hydroxymethyl)cyclopent-2-en-1-one (6g). This compound was prepared according to the General Procedure D using 71 mg of **5g** (0.30 mmol) and 8.0 mg of dysprosium chloride (0.03 mmol). **6g** (28 mg, 39% yield, dr > 95:5) was obtained as a white solid after flash chromatography (heptane/ethyl acetate: 40:60 to 30:70). R_f 0.29 (50% EtOAc/heptane); Mp: 180 - 182 °C; **^{1}H-NMR (Acetone-*d*$_6$, 300 MHz)** δ 7.68 (d, *J* = 6.0 Hz, 1H), 7.01-6.96 (m, 2H), 6.88-6.82 (m, 1H), 6.32 (d, *J* = 6.0 Hz, 1H), 4.77 (s, 1H), 3.97 (s, 1H), 3.88 (t, *J* = 5.3 Hz, 1H), 3.21 (d, *J* = 5.3 Hz, 2H), 2.44 (s, 3H); **^{13}C-NMR (Acetone-*d*$_6$, 75 MHz)** δ 205.9 (C), 164.8 (CH), 162.3 (d, J_{CF} = 241 Hz, C), 134.1 (d, J_{CF} = 10 Hz, C), 134.0 (CH), 132.6 (d, J_{CF} = 8 Hz, CH), 131.2 (C), 117.1 (d, J_{CF}= 21 Hz, CH), 112.6 (d, J_{CF}= 21 Hz, CH), 83.6 (C), 67.0 (CH_2), 60.0 (CH), 20.6 (CH_3); **^{19}F-NMR (Acetone-*d*$_6$, 282 MHz)** 59.6; **IR (ν/cm^{-1})** 3406, 1699, 1612, 1590, 1499, 1255, 1169, 1028, 957, 866, 811, 778, 691; **HRMS (ESI)**: *m/z* = 237.0924, calcd. for $C_{13}H_{14}O_3F$ $[M+H]^+$: 237.0927.

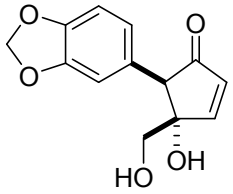


III.18. 4-Hydroxy-4-(hydroxymethyl)-5-(4-(trifluoromethyl)phenyl) cyclopent-2-en-1-one (6h). This compound was prepared according to the General Procedure D using 80 mg of **5h** (0.30 mmol) and 8.0 mg of dysprosium chloride (0.03 mmol). **6h** (39 mg, 49% yield, dr = 90:10) was obtained as an orange oil after flash chromatography (heptane/ethyl acetate: 100:0 to 20:80). R_f 0.36 (70% EtOAc/heptane; **^{1}H-NMR (Acetone-*d*$_6$, 300 MHz)** δ 7.66 (d, *J* = 8.2 Hz, 2H), 7.58 (d, *J* = 6.0 Hz, 1H), 7.52 (d, *J* = 8.2 Hz, 2H), 6.35 (d, *J* = 6.0 Hz, 1H), 4.94 (s, 1H), 3.88-3.85 (m, 2H), 3.33 (dd, *J* = 10.5, 4.1 Hz, 1H), 3.15 (dd, *J* = 10.5, 5.8 Hz, 1H); **^{13}C-NMR (Acetone-*d*$_6$, 75 MHz)** δ 203.6 (C), 163.7 (CH), 134.3 (CH), 132.4 (C), 132.1 (CH), 129.3 (q, J_{CF} = 32 Hz, C), 125.4 (q, J_{CF} = 273 Hz, C), 125.3 (q, J_{CF} = 4.3 Hz, CH), 83.6 (C), 65.6 (CH_2), 64.2 (CH); **^{19}F-NMR (Acetone-*d*$_6$, 282 MHz)** 114.6; **IR (ν/cm^{-1})** 3407, 1704, 1419, 1325, 1164, 1111, 1069, 1021, 847, 768; **HRMS (ESI)**: *m/z* = 255.0640, calcd. for $C_{13}H_{10}F_3O_2$ $[M-H_2O+H]^+$: 255.0633.



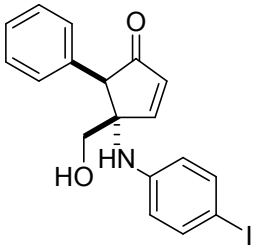
III.19. 4-Hydroxy-4-(hydroxymethyl)-5-(4-methoxyphenyl)cyclopent-2-en-1-one (6i). This compound was prepared according to the General Procedure D using 70 mg of **5i** (0.3 mmol) and 8.0 mg of dysprosium chloride (0.03 mmol). **6i** (32 mg, 46% yield, dr > 95:5) was obtained as a pale yellow solid after flash chromatography (heptane/ethyl acetate: 100:0 to 20:80). R_f 0.37 (70% EtOAc/heptane); Mp: 134 - 136 °C; **^{1}H-NMR ($CDCl_3$, 300 MHz)** δ 7.51 (d, *J* = 5.9 Hz, 1H), 7.07 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 6.36 (d, *J* = 5.9 Hz, 1H), 3.79 (s, 3H), 3.77 (s, 1H), 3.38-3.29 (m, 2H); **^{13}C-NMR ($CDCl_3$, 75 MHz)** δ 205.7 (C), 162.4 (CH), 159.3 (C), 134.7 (CH), 130.8 (CH), 125.9 (C), 114.7 (CH), 82.1 (C), 66.9 (CH_2), 62.8 (CH), 55.4 (CH_3); **IR (ν/cm^{-1})** 3411, 2934, 1703, 1612, 1514, 1250, 1180, 1087, 1033, 836; **HRMS (ESI)**: *m/z* = 235.0972, calcd. for $C_{13}H_{15}O_4$ $[M+H]^+$: 235.0970.

III.20. 5-(Benzo[d][1,3]dioxol-5-yl)-4-hydroxy-4-(hydroxymethyl)cyclopent-2-en-1-one (6j). This compound was prepared according to the General Procedure D using 74.4 mg of **5j** (0.30 mmol) and 8.0 mg of dysprosium chloride (0.03 mmol). **6j** (40.4 mg, 54% yield, dr > 95:5) was obtained as a brown oil after flash chromatography (heptane/ethyl acetate: 40:60 to 30:70). R_f 0.29 (50% EtOAc/heptane); **^{1}H-NMR ($CDCl_3$, 300 MHz)** δ 7.52 (d, *J* = 5.8 Hz, 1H), 6.76 (d, *J* = 8.1 Hz, 1H), 6.62 (d, *J* = 8.1 Hz, 1H), 6.60 (s, 1H), 6.33 (d, *J* = 5.8 Hz, 1H), 5.93 (s, 2H), 3.72 (s, 1H), 3.38-3.28 (m, 2H); **^{13}C-NMR ($CDCl_3$, 75 MHz)** δ 205.5 (C), 162.8 (CH), 148.1 (C), 147.3 (C), 134.3 (CH), 127.4 (C), 123.3 (CH), 109.8 (CH), 108.8 (CH), 101.3 (CH_2), 82.0 (C), 66.9 (CH_2), 63.0 (CH); **IR (ν/cm^{-1})** 3411, 2898, 1700, 1504, 1489, 1442, 1234, 1035, 929, 806, 733; **HRMS (ESI)**: *m/z* = 249.0759, calcd. for $C_{13}H_{13}O_5$ $[M+H]^+$: 249.0763.

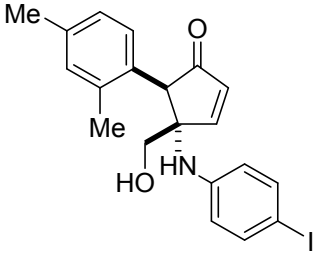


General Procedure E for the synthesis of the 4-aminocyclopentenone compounds 8a-c. To a solution a furan derivative **5** (1 eq.) and anilines **7** (1 eq.) in *t*-BuOH (0.08 *M*), was added $DyCl_3$ (10 mol %). The reaction mixture was heated under MW irradiation for 30-60 min at 80 °C. After cooling to room temperature, the mixture was quenched with a saturated solution of $NaHCO_3$. The aqueous layer was extracted thrice with ethyl acetate. The combined organic layers were washed with brine dried over magnesium sulfate, filtered and concentrated to dryness under vacuum. The residue was purified by flash chromatography on silica gel (heptane/ethyl acetate) to afford the 4-aminocyclopentenone derivatives **8**.

III.21. 4-(Hydroxymethyl)-4-((4-iodophenyl)amino)-5-phenylcyclopent-2-en-1-one (8a). This compound was prepared according to the General Procedure E using 41 mg of **5a** (0.20 mmol), 44 mg of *p*-iodoaniline (0.20 mmol) and 5.4 mg of dysprosium chloride (0.02 mmol). **8a** (27.2 mg, 33% yield, dr > 95:5) was obtained as a brown oil after flash chromatography (heptane/ethyl acetate: 100:0 to 40:60). R_f 0.30 (50% EtOAc/heptane; **^{1}H-NMR ($CDCl_3$, 300 MHz)** δ 7.62 (d, *J* = 5.8 Hz, 1H), 7.48 (d, *J* = 8.8 Hz, 2H), 7.41-7.33 (m, 3H), 7.14-7.11 (m, 2H), 6.57 (d, *J* = 8.8 Hz, 2H), 6.52 (d, *J* = 5.8 Hz, 1H), 4.30 (s, 1H), 3.49-3.43 (m, 2H); **^{13}C-NMR ($CDCl_3$, 75 MHz)** δ 203.9 (C), 164.6 (CH), 145.0 (CH), 138.5 (CH), 135.3 (CH), 133.7 (C), 129.6 (CH), 129.5 (CH), 128.2 (CH), 117.6 (CH), 81.2 (C), 69.1 (C), 67.5 (CH_2), 56.7 (CH); **IR (ν/cm^{-1})** 3375, 2925, 1700, 1588, 1486, 1253, 1075, 907, 812, 731, 701; **HRMS (ESI)**: *m/z* = 406.0321, calcd. for $C_{18}H_{17}INO_2$ $[M+H]^+$: 406.0304.

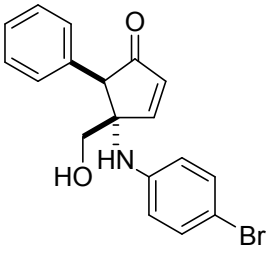


III.22. 5-(2,4-Dimethylphenyl)-4-(hydroxymethyl)-4-((4-iodophenyl) amino)cyclopent-2-en-1-one (8b). This compound was prepared according to the General Procedure E using 70 mg of **5b** (0.30 mmol), 66 mg, of *p*-iodoaniline (0.30 mmol), and 8.1 mg of dysprosium chloride (0.02 mmol). **8b** (32.5 mg, 25% yield, dr > 95:5) was obtained as a brown oil after flash chromatography (heptane/ethyl acetate: 80:20 to 60:40). R_f 0.51 (50% EtOAc/heptane); **^{1}H-NMR ($CDCl_3$, 300 MHz)** δ 7.60 (d, *J* = 5.9 Hz, 1H), 7.42 (d, *J* = 8.8 Hz, 2H), 7.05-6.96 (m, 3H), 6.54 (d, *J* = 5.9 Hz, 1H), 6.48 (d, *J* = 8.8 Hz, 2H), 4.50 (s, 1H), 3.57 (bs, 2H), 2.29 (s, 3H), 2.02 (s, 3H); **^{13}C-NMR ($CDCl_3$, 75 MHz)** δ 205.7 (C),



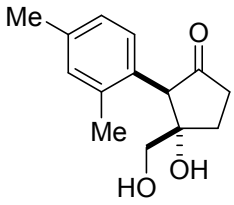
166.1 (CH), 144.9 (C), 138.3 (CH), 137.9 (C), 135.4 (CH), 131.9 (CH), 129.9 (C), 128.9 (CH), 127.7 (CH), 116.2 (CH), 79.8 (C), 68.8 (C), 67.7 (CH_2), 52.9 (CH), 21.0 (CH_3), 19.8 (CH_3); **IR (ν/cm^{-1})** 3383, 2922, 1697, 1589, 1485, 1295, 1073, 1029, 906, 810, 728; **HRMS (ESI)**: *m/z* = 434.0612, calcd. for $C_{20}H_{21}INO_2$ $[M+H]^+$: 434.0617.

III.23. 4-((4-Bromophenyl)amino)-4-(hydroxymethyl)-5-phenylcyclopent-2-en-1-one (8c). This compound was prepared according to the General Procedure E using 15 mg of **5a** (0.07 mmol), 12 mg of *p*-bromoaniline (0.07 mmol) and 2.1 mg of dysprosium chloride (0.01 mmol). **8c** (10.2 mg, 38% yield, dr > 95:5) was obtained as a brown oil after flash chromatography (heptane/ethyl acetate: 100:0 to 40:60). R_f 0.45 (50% EtOAc/heptane); **^{1}H-NMR ($CDCl_3$, 300 MHz)** δ 7.65 (d, *J* = 5.8 Hz, 1H), 7.41-7.32 (m, 5H), 7.13 (d, *J* = 8.2 Hz, 2H), 6.75 (d, *J* = 8.2 Hz, 2H), 6.54 (d, *J* = 5.8 Hz, 1H), 4.29 (s, 1H), 3.51 (s, 2H); **^{13}C-NMR ($CDCl_3$, 75 MHz)** δ 203.9 (C), 164.0 (CH), 143.3 (C), 135.7 (CH), 133.7 (C), 132.7 (CH), 129.7 (CH), 129.5 (CH), 128.3 (CH), 118.0 (CH), 69.7 (C), 67.2 (CH_2), 56.6 (CH); **IR (ν/cm^{-1})** 3359, 1701, 1590, 1489, 1306, 1253, 1074, 906, 814, 729, 700; **HRMS (ESI)**: *m/z* = 358.0461, calcd. for $C_{18}H_{17}BrNO_2$ $[M+H]^+$: 358.0443.

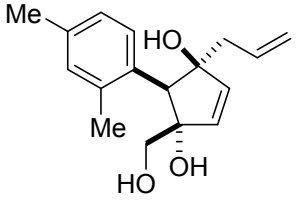


Derivatization of Piancatelli rearrangement product 6b.

III.24. 2-(2,4-Dimethylphenyl)-3-hydroxy-3-(hydroxymethyl)cyclopentan-1-one (9). To a degassed solution of **6b** (30 mg, 0.13 mmol) in EtOAc (2 mL), was added 5% Pd/C (10 mg). The resulting mixture was stirred under 1 atm H_2 gaz for 4 h. Upon completion, the mixture was filtered through a plug of Celite and solvents were removed under vacuum to afford **9** (24.6 mg, 81% yield) as a pale yellow oil. R_f 0.46 (70% EtOAc/heptane); **^{1}H-NMR ($CDCl_3$, 300 MHz)** δ 7.01 (bs, 1H), 6.95 (d, *J* = 8.0 Hz, 1H), 6.70 (d, *J* = 8.0 Hz, 1H), 3.87 (s, 1H), 3.43 (d, *J* = 11.1 Hz, 1H), 3.36 (d, *J* = 11.1 Hz, 1H), 2.78-2.66 (m, 1H), 2.47-2.37 (m, 1H), 2.35 (s, 3H), 2.28 (s, 3H), 2.28-2.15 (m, 2H); **^{13}C-NMR ($CDCl_3$, 75 MHz)** δ 217.2 (C), 138.1 (C), 137.4 (C), 131.9 (CH), 130.5 (C), 128.1 (CH), 127.2 (CH), 81.7 (C), 66.1 (CH_2), 61.4 (CH), 37.2 (CH_2), 31.7 (CH_2), 21.1 (CH_3), 20.4 (CH_3); **IR (ν/cm^{-1})** 3416, 2923, 1737, 1687, 1454, 1193, 1143, 1052, 1029, 914, 817, 733; **HRMS (ESI)**: *m/z* = 217.1243, calcd. for $C_{14}H_{17}O_2$ $[M-H_2O+H]^+$: 217.1229.

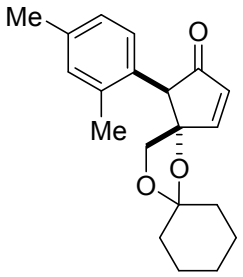


III.25. 1-allyl-2-(2,4-Dimethylphenyl)-3-(hydroxymethyl)cyclopent-4-ene-1,3-diol (10). To a solution of **6b** (30 mg, 0.13 mmol) in anhydrous THF (3 mL), were added at 0 °C a solution of allylmagnesium bromide 1M in Et_2O (520 μL, 0.52 mmol). The reaction mixture was stirred 2 h from 0 °C to room temperature. Then, a saturated aqueous solution of NH_4Cl (5 ml) was added and the aqueous layer was extracted thrice with ethyl acetate (3 x 10 mL). The combined organic layers were washed with brine (20 mL), dried over magnesium sulfate, filtered and concentrated to dryness under vacuum. The residue was purified by chromatography on silica gel (heptane/ethyl acetate: 90:10 to 20:80) to afford **10** (21 mg, 59% yield,

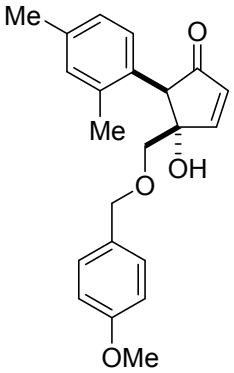


dr = 80:20) as an orange oil. R_f 0.40 (50% EtOAc/heptane); **^{1}H-NMR ($CDCl_3$, 300 MHz,** major diastereoisomer**)** δ 7.50 (d, *J* = 8.0 Hz, 1H), 7.04-6.96 (m, 2H), 6.14 (d, *J* = 5.7 Hz, 1H), 5.99 (d, *J* = 5.7 Hz, 1H), 5.84-5.70 (m, 1H), 5.15-5.09 (m, 1H), 5.09-5.06 (m, 1H), 3.62 (s, 1H), 3.60 (d, *J* = 11.1 Hz, 1H), 3.52 (d, *J* = 11.1 Hz, 1H), 2.44-2.40 (m, 2H), 2.37 (s, 3H), 2.29 (s, 3H); **^{13}C-NMR ($CDCl_3$, 75 MHz)** δ 139.8 (CH), 137.6 (CH), 136.9 (C), 134.8 (C), 133.7 (CH), 132.0 (CH), 131.2 (C), 129.5 (CH), 127.0 (CH), 119.2 (CH_2), 87.3 (C), 84.1 (C), 65.5 (CH_2), 56.7 (CH), 45.2 (CH_2), 21.3 (CH_3), 21.1 (CH_3); **IR (ν/cm^{-1})** 3370, 2923, 1702, 1503, 1377, 1030, 915, 814, 778, 731; **HRMS (ESI)**: *m/z* = 257.1540, calcd. for $C_{17}H_{21}O_2$ $[M\text{-}H_2O+H]^+$: 257.1542.

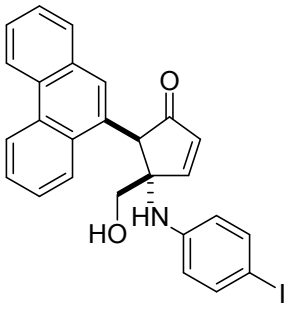
III.26. 1-(2,4-Dimethylphenyl)-6,13-dioxadispiro[4.1.57.25]tetradec-3-en-2-one (11). To a solution of **6b** (25 mg, 0.11 mmol) in anhydrous DCM (2 mL), were added cyclohexanone diethyl ketal (25 μL, 0.13 mmol), and CSA (2 mg, 0.01 mmol). The reaction mixture was stirred at room temperature for 2 h. Then, it was quenched with a saturated aqueous solution of $NaHCO_3$ (5 mL) and the aqueous layer was extracted thrice with dichloromethane (3 x 10 mL). The combined organic layers were washed with brine (20 mL), dried over magnesium sulfate, filtered and concentrated to dryness under vacuum. The residue was purified on a preparative TLC (heptane/ethyl acetate: 70:30) to afford **11** (16 mg, 48% yield) as a pale yellow oil. R_f 0.28 (30% EtOAc/heptane); **^{1}H-NMR ($CDCl_3$, 300 MHz)** δ 7.58 (d, *J* = 5.8 Hz, 1H), 7.04 (s, 1H), 6.93 (d, *J* = 7.6 Hz, 1H), 6.51 (d, *J* = 7.6 Hz, 1H), 6.36 (d, *J* = 5.8 Hz, 1H), 4.22 (s, 1H), 3.72 (d, *J* = 9.7 Hz, 1H), 3.48 (d, *J* = 9.7 Hz, 1H), 2.39 (s, 3H), 2.28 (s, 3H), 1.73-1.40 (m, 10 H); **^{13}C-NMR ($CDCl_3$, 75 MHz)** δ 207.2 (C), 163.6 (CH), 137.9 (C), 137.5 (C), 133.8 (CH), 131.7 (CH), 128.0 (CH), 127.3 (CH), 110.7 (C), 88.6 (C), 69.0 (CH_2), 55.7 (CH), 37.6 (CH_2), 35.3 (CH_2), 24.0 (CH_2), 23.9 (CH_2), 21.2 (CH_3), 20.1 (CH_3); **IR (ν/cm^{-1})** 2934, 2860, 1716, 1448, 1367, 1335, 1285, 1158, 1096, 1069, 1029, 928, 828, 810, 732; **HRMS (ESI)**: *m/z* = 313.1807, calcd. for $C_{20}H_{25}O_3$ $[M+H]^+$: 313.1804.



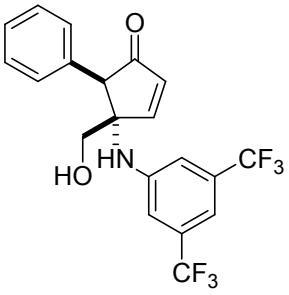
III.27. 5-(2,4-Dimethylphenyl)-4-hydroxy-4-(((4-methoxybenzyl)oxy)methyl) cyclopent-2-en-1-one (12). To a degassed solution of **6b** (25 mg, 0.11 mmol) in DCM (3 mL) were added at 0 °C 4-methoxybenzyl-2,2,2-trichloroacetimidate (30.4 mg, 0.11 mmol, 1 eq), and PPTS (1.3 mg, 0.01 mmol, 0.05 eq). The reaction mixture was stirred from 0 °C to room temperature for 12 h. The volatiles were evaporated under vacuum and the crude mixture was purified by chromatography on silica gel (heptane/ethyl acetate: 70:30 to 60:40), to afford **13** (22 mg, 61% yield) as a pale yellow oil. R_f 0.40 (50% EtOAc/heptane); **^{1}H-NMR ($CDCl_3$, 500 MHz)** δ 7.63 (d, *J* = 5.8 Hz, 1H), 7.29 (d, *J* = 8.2 Hz, 1H), 7.09 (d, *J* = 8.2 Hz, 2H), 7.02 (s, 1H), 6.93-6.89 (m, 1H), 6.85 (d, *J* = 8.2 Hz, 2H), 6.34 (d, *J* = 5.8 Hz, 1H), 4.24 (s, 2H), 4.01 (s, 1H), 3.81 (s, 3H), 3.20 (d, *J* = 9.8 Hz, 1H), 3.05 (d, *J* = 9.8 Hz, 1H), 2.37 (s, 3H), 2.30 (s, 3H); **^{13}C-NMR ($CDCl_3$, 75 MHz)** δ 207.3 (C), 163.8 (CH), 159.4 (C), 138.4 (C), 137.1 (C), 133.8 (C), 133.6 (CH), 131.3 (CH), 130.3 (C), 129.3 (CH), 128.6 (CH), 126.5 (CH), 113.9 (CH), 81.7 (C), 74.3 (CH_2), 73.3 (CH_2), 58.4 (CH), 55.3 (CH_3), 21.0 (CH_3), 20.3 (CH_3); **IR (ν/cm^{-1})** 3422, 1702, 1611, 1512, 1302, 1245, 1173, 1092, 1032, 821, 729; **HRMS (ESI)**: *m/z* = 353.1754, calcd. for $C_{22}H_{25}O_4$ $[M+H]^+$: 353.1753.



Additional Experiments:

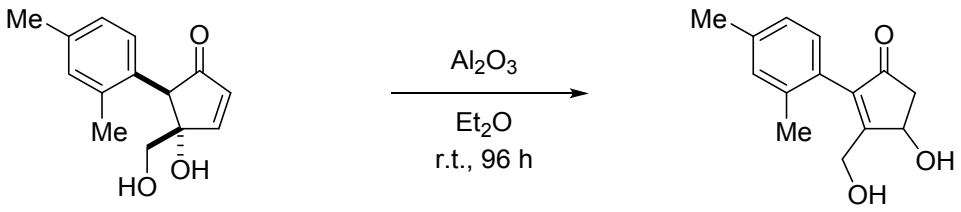


III.28. 4-(Hydroxymethyl)-4-((4-iodophenyl)amino)-5-(phenanthren-9-yl)cyclopent-2-en-1-one (8d). This compound was prepared according to the General Procedure E using 46 mg of **5d** (0.20 mmol), 44 mg of *p*-iodoaniline (0.20 mmol) and 5.4 mg of dysprosium chloride (0.02 mmol). **8d** (14 mg, 14% yield, dr > 95:5) was obtained as a yellow oil after flash chromatography (heptane/ethyl acetate: 100:0 to 30:70). R_f 0.47 (50% EtOAc/heptane); **^{1}H-NMR ($CDCl_3$, 300 MHz)** δ 8.73 (d, *J* = 8.2 Hz, 1H), 8.66 (d, *J* = 8.2 Hz, 1H), 7.83 (d, *J* = 7.5 Hz, 1H), 7.75 (d, *J* = 5.9 Hz, 1H), 7.70-7.57 (m, 5H), 7.54 (d, *J* = 8.8 Hz, 2H), 7.43-7.38 (m, 1H), 6.67 (d, *J* = 5.9 Hz, 1H), 6.61 (d, *J* = 8.8 Hz, 2H), 5.04 (s, 1H), 3.52 (bs, 2H); **^{13}C-NMR ($CDCl_3$, 75 MHz)** δ 205.2 (C), 166.1 (CH), 145.2 (C), 138.6 (CH), 135.6 (CH), 131.7 (C), 131.2 (C), 130.7 (C), 130.1 (C), 129.8 (C), 129.0 (CH), 128.8 (CH), 127.5 (CH), 127.2 (CH), 127.1 (CH), 124.5 (CH), 123.5 (CH), 122.6 (CH), 116.8 (CH), 80.5 (C), 69.5 (C), 68.0 (CH_2), 52.3 (CH); **IR (ν/cm^{-1})** 3384, 1705, 1588, 1486, 1372, 1315, 1250, 1043, 812, 790, 748, 723; **HRMS (ESI)**: *m/z* = 506.0626, calcd. for $C_{26}H_{21}INO_2$ $[M+H]^+$: 506.0617.



III.29. 4-((3,5-Bis(trifluoromethyl)phenyl)amino)-4-(hydroxymethyl)-5-phenylcyclopent-2-en-1-one (8e). This compound was prepared according to the General Procedure E using 11 mg of **5a** (0.05 mmol), 12 mg of 3,5-bis(trifluoromethyl)aniline (0.05 mmol) and 1.4 mg of dysprosium chloride (0.01 mmol). **8e** (3.3 mg, 15% yield, dr = 80:20) was obtained as a brown oil after a preparative TLC (heptane/ethyl acetate: 70:30). R_f 0.1 (30% EtOAc/heptane); **^{1}H-NMR ($CDCl_3$, 300 MHz**, major diastereoisomer**)** δ 7.64 (d, *J* = 6.0 Hz, 1H), 7.43-7.38 (m, 3H), 7.29 (s, 1H), 7.16-7.13 (m, 4H), 6.63 (d, *J* = 6.0 Hz, 1H), 4.29 (s, 1H), 3.57-3.51 (m, 2H); **^{13}C-NMR ($CDCl_3$, 75 MHz)** δ 202.9 (C), 163.5 (CH), 146.3 (C), 136.2 (CH), 133.3 (C), 132.7 (C), 129.7 (CH), 129.6 (CH), 128.6 (CH), 123.4 ($J_{C\text{-}F}$ = 307 Hz, C), 113.9 (CH), 112.5 (CH), 68.6 (C), 67.5 (CH_2), 56.9 (CH); **IR (ν/cm^{-1})** 3362, 1708, 1622, 1474, 1393, 1277, 1173, 1130, 700, 681; **HRMS (ESI)**: *m/z* = 416.1080, calcd. for $C_{20}H_{16}F_6NO_2$ $[M+H]^+$: 416.1085.

III.30. 2-(2,4-Dimethylphenyl)-4-hydroxy-3-(hydroxymethyl)cyclopent-2-en-1-one (14).
The more thermodynamically stable cyclopentenone **14** was obtained under basic conditions.[1]



6b **14**

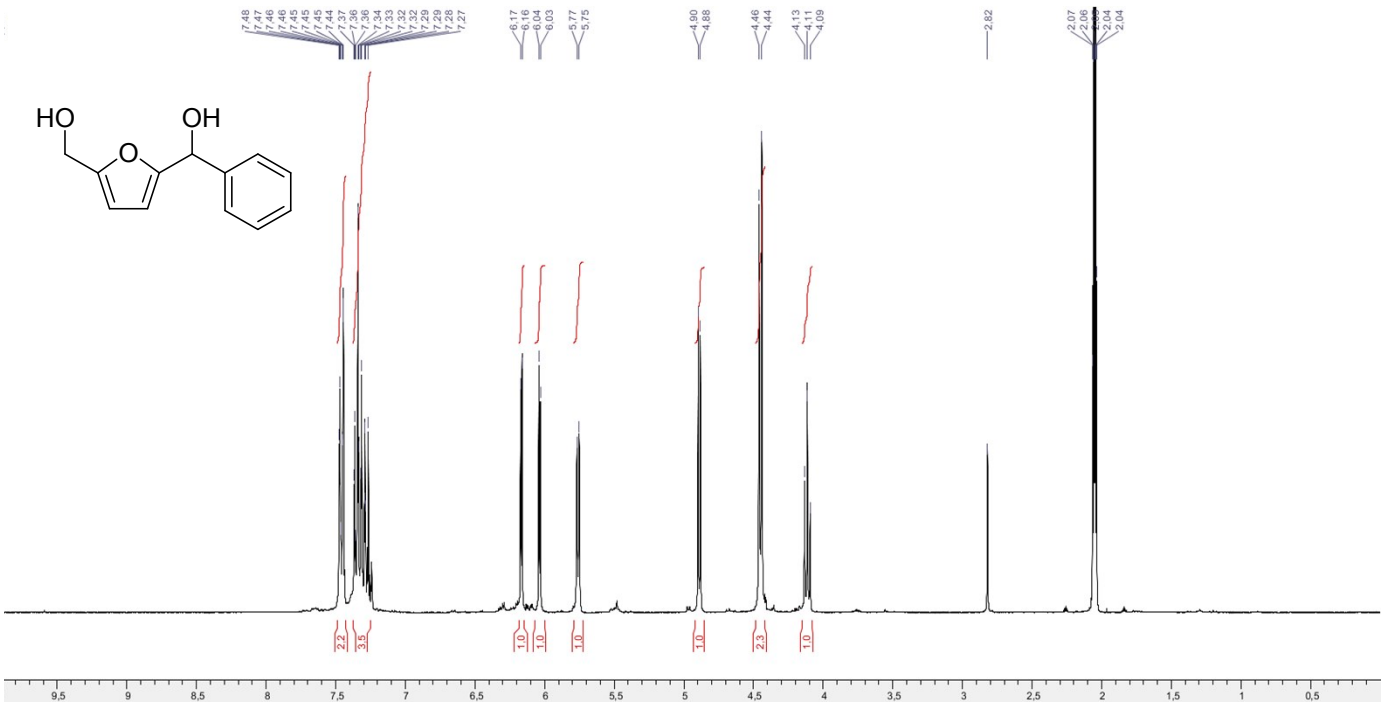
To a solution of **6b** (25 mg, 0.11 mmol in Et_2O (0.4 mL) and water (15 μL) was added activated Al_2O_3 (350 mg). The reaction mixture was stirred at room temperature for 96 h. Then, the mixture was

1 Scettri, A.; Piancatelli, G.; D'Auria, M.; David, G. *Tetrahedron* **1979**, *35*, 135-138. Roche, S. P.; Aitken, D. J. *Eur. J. Org. Chem.* **2010**, 5339-5358.

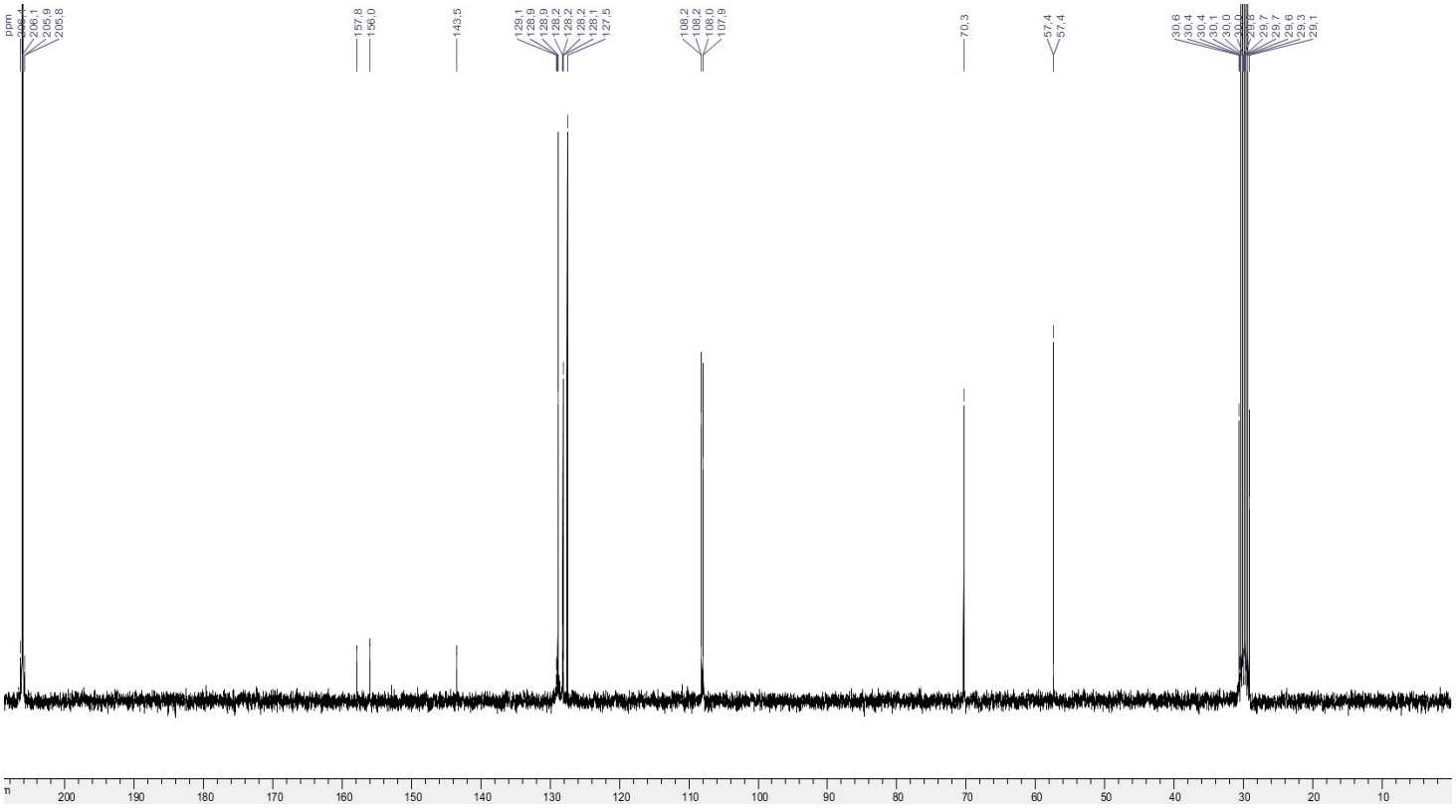
filtered off on a pad of Celite. The crude was purified on a preparative TLC (heptane/ethyl acetate: 20:80) to afford **9d** (5.3 mg, 21% yield) as a colorless oil. R_f 0.15 (80% EtOAc/heptane); **^{1}H-NMR ($CDCl_3$, 300 MHz)** δ 7.06 (d, *J* = 6.6 Hz, 1H), 7.02 (t, *J* = 6.6 Hz, 1H), 6.85 (dd, *J* = 46.5, 6.6 Hz, 1H), 5.32-5.28 (m, 1H), 4.69-4.53 (m, 2H), 2.99-2.93 (m, 1H), 2.56-2.51 (m, 1H), 2.32 (s, 3H), 2.10 (d, J = 35.5 Hz, 3H); **^{13}C-NMR ($CDCl_3$, 75 MHz)** δ 176.8, 161.3, 131.4, 131.3, 129.3, 129.1, 129.0, 126.7 , 70.0, 60.7, 44.2, 21.3, 19.8; **IR (ν/cm^{-1})** 3419, 2922, 2860, 1698, 1611, 1232, 1066, 1038, 815, 743; **HRMS (ESI)**: *m/z* = 233.1172, calcd. for $C_{14}H_{17}O_3$ $[M+H]^+$: 233.1178.

IV. NMR Spectra (^{1}H and ^{13}C NMR):

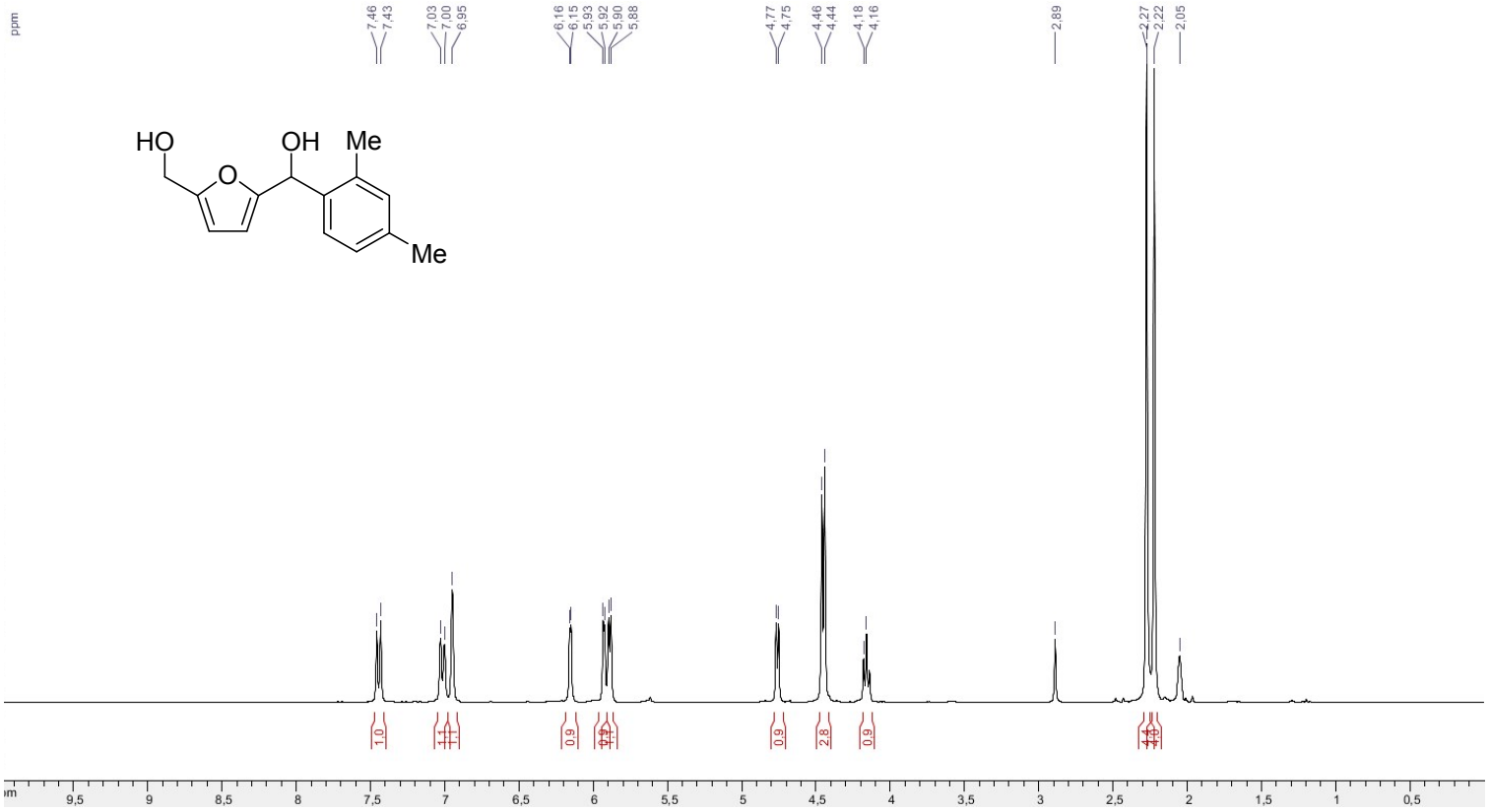
IV.1. ^{1}H NMR (Acetone-d_6, 300 MHz) (**5a**)



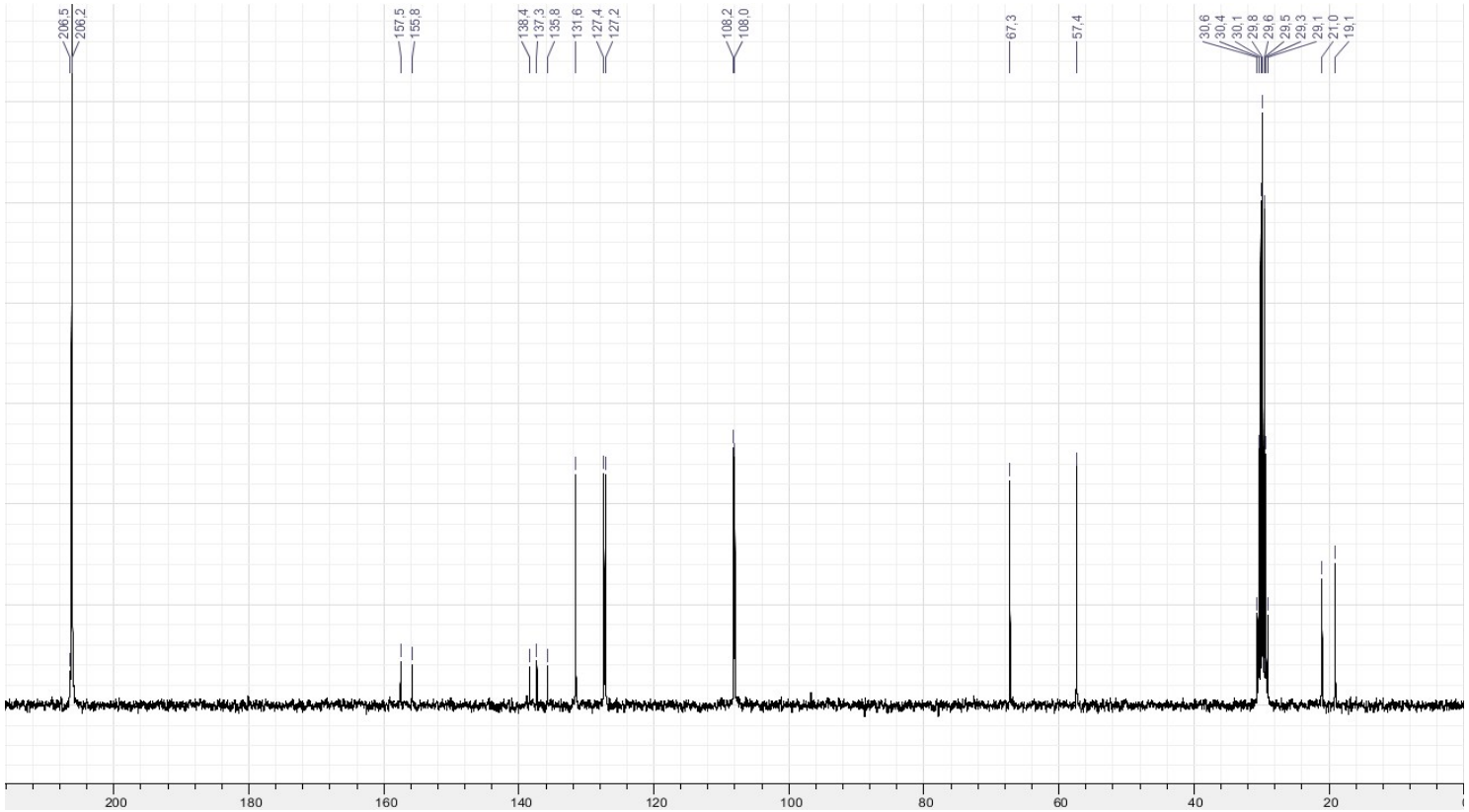
^{13}C NMR (Acetone-d_6, 75 MHz)



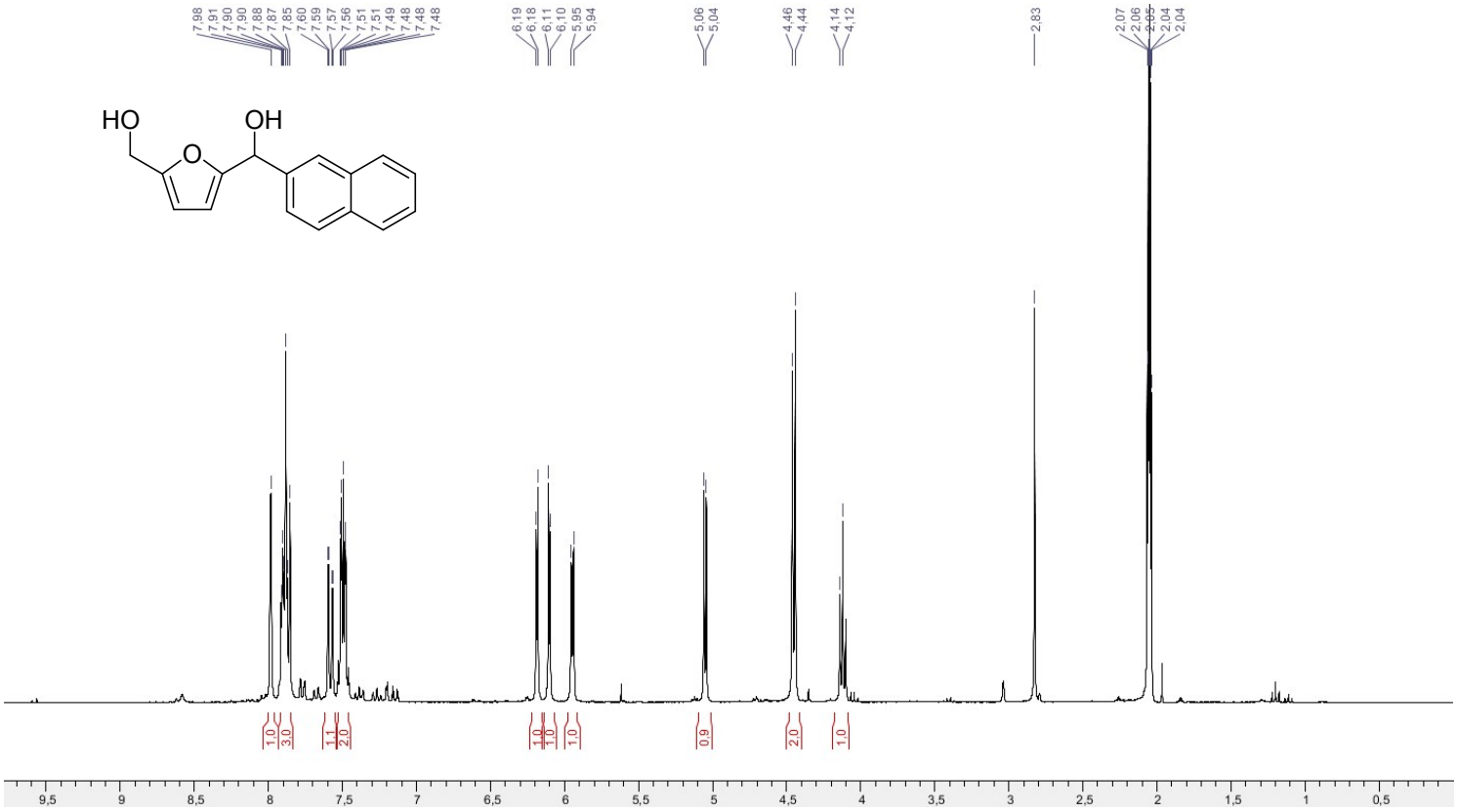
IV.2. ^{1}H NMR (Acetone-d_6, 300 MHz) (**5b**)



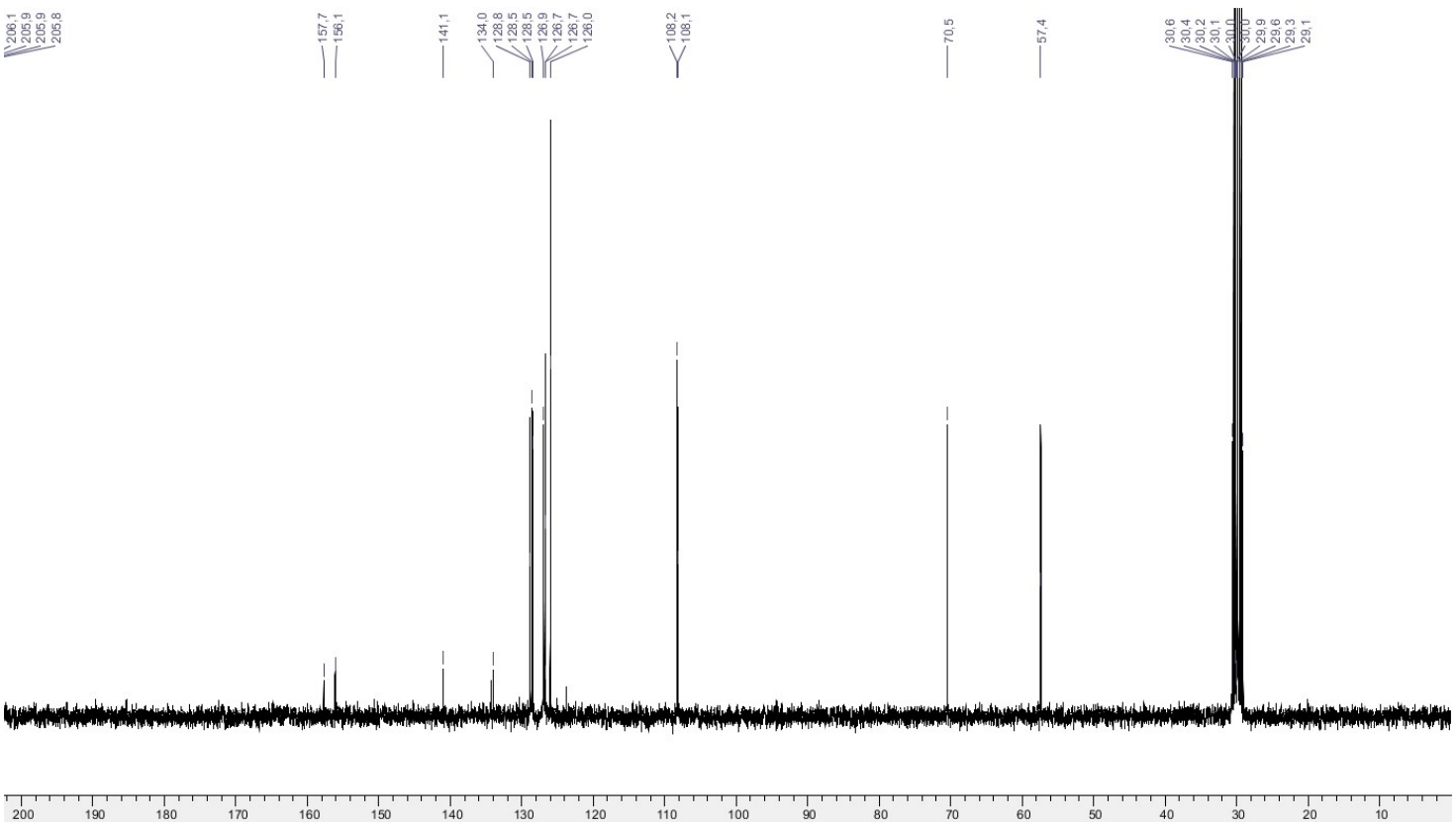
^{13}C NMR (Acetone-d_6, 75 MHz)



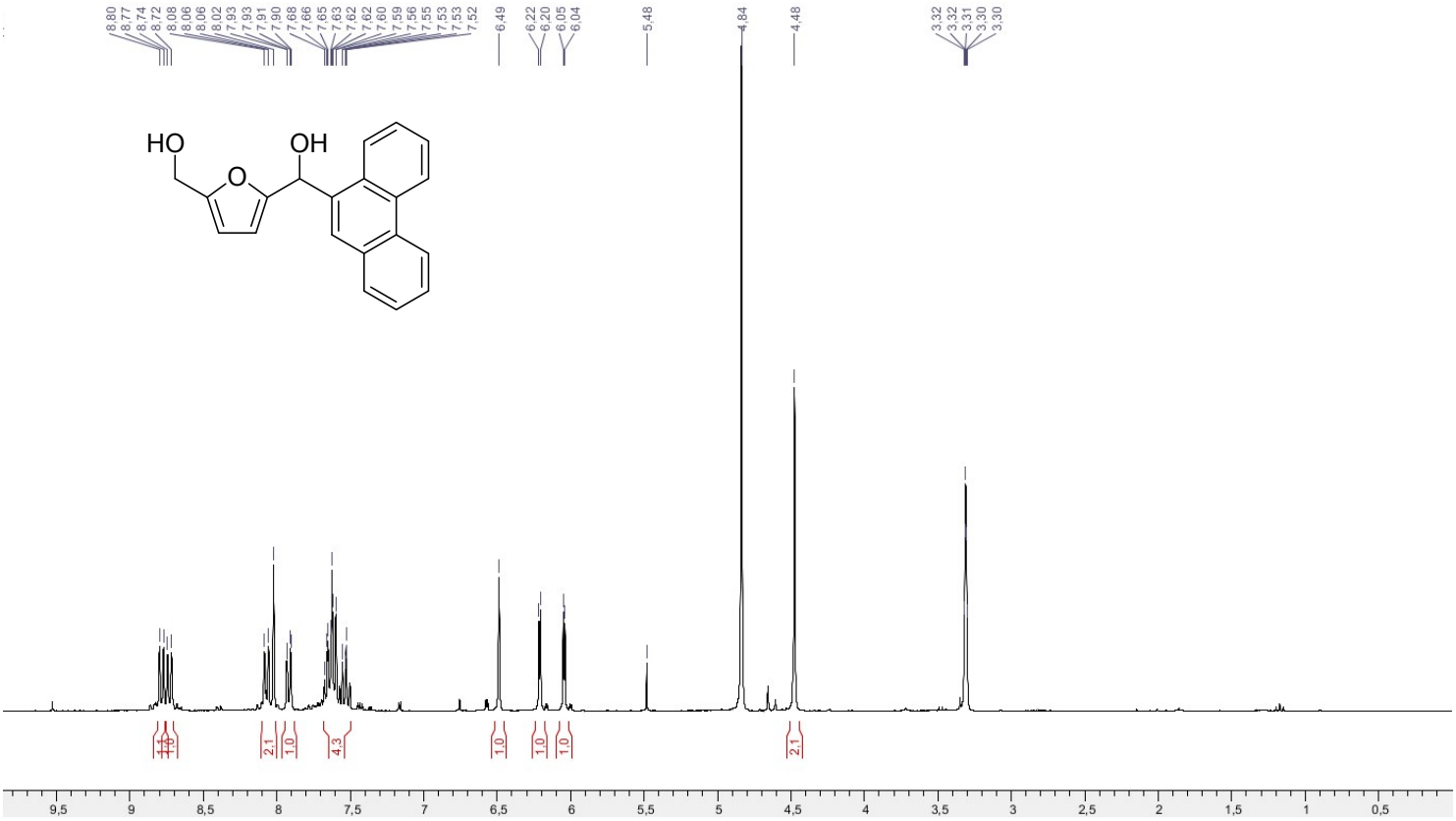
IV.3. ^{1}H NMR (Acetone-d_6, 300 MHz) (**5c**)

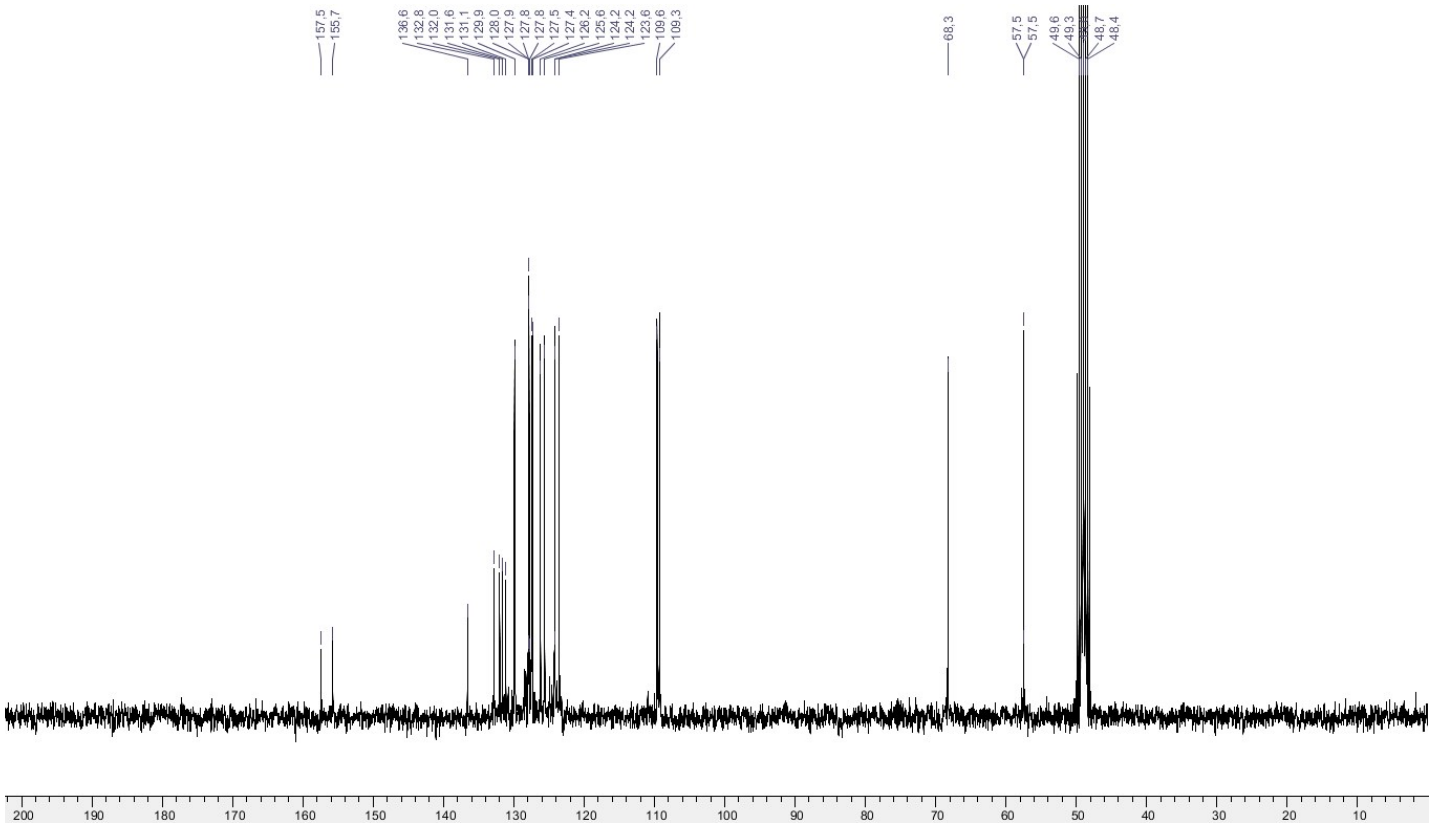


^{13}C NMR (Acetone-d_6, 75 MHz)

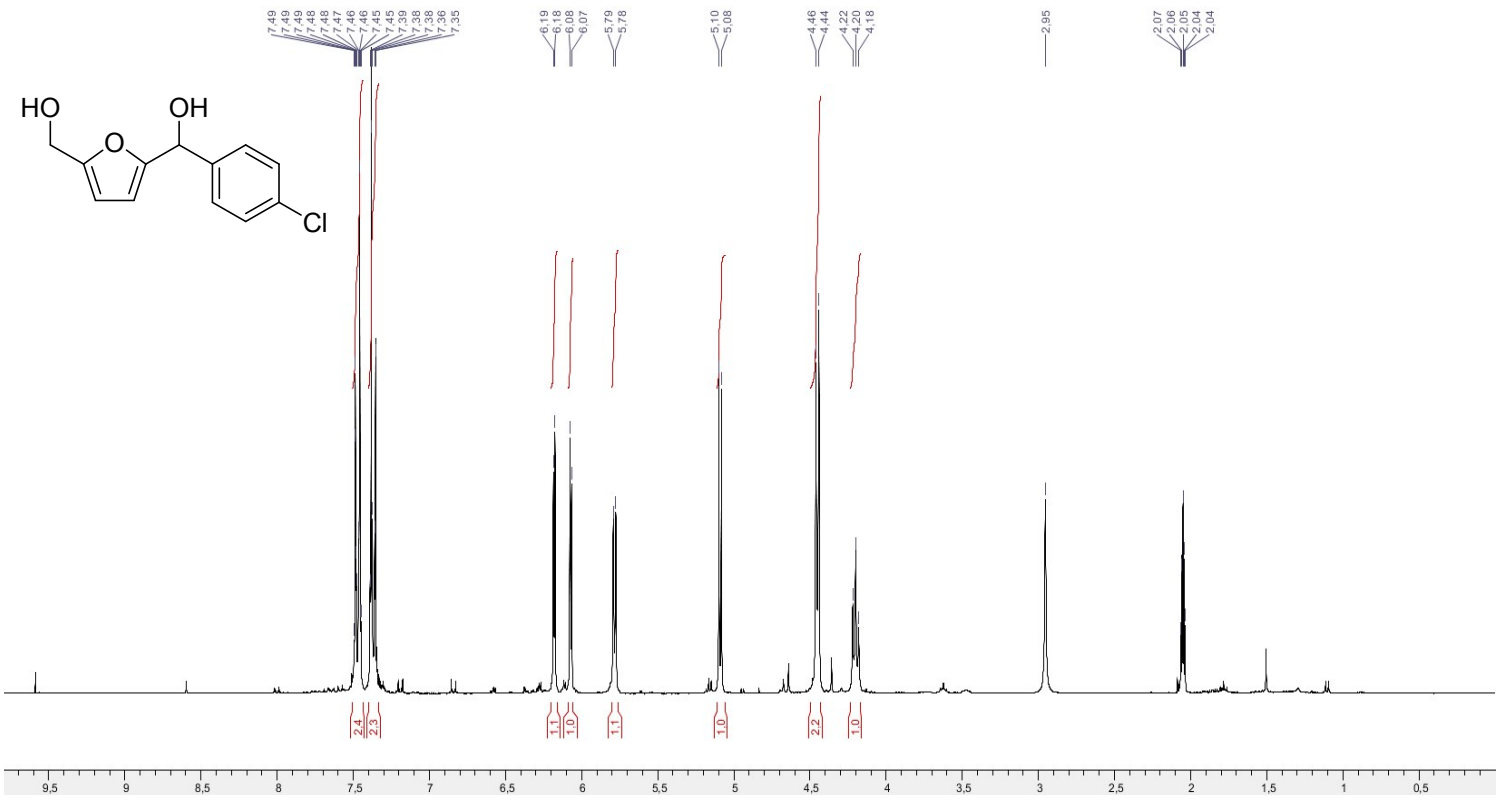


IV.4. ^{1}H NMR (CD_3OD, 300 MHz) (**5d**)

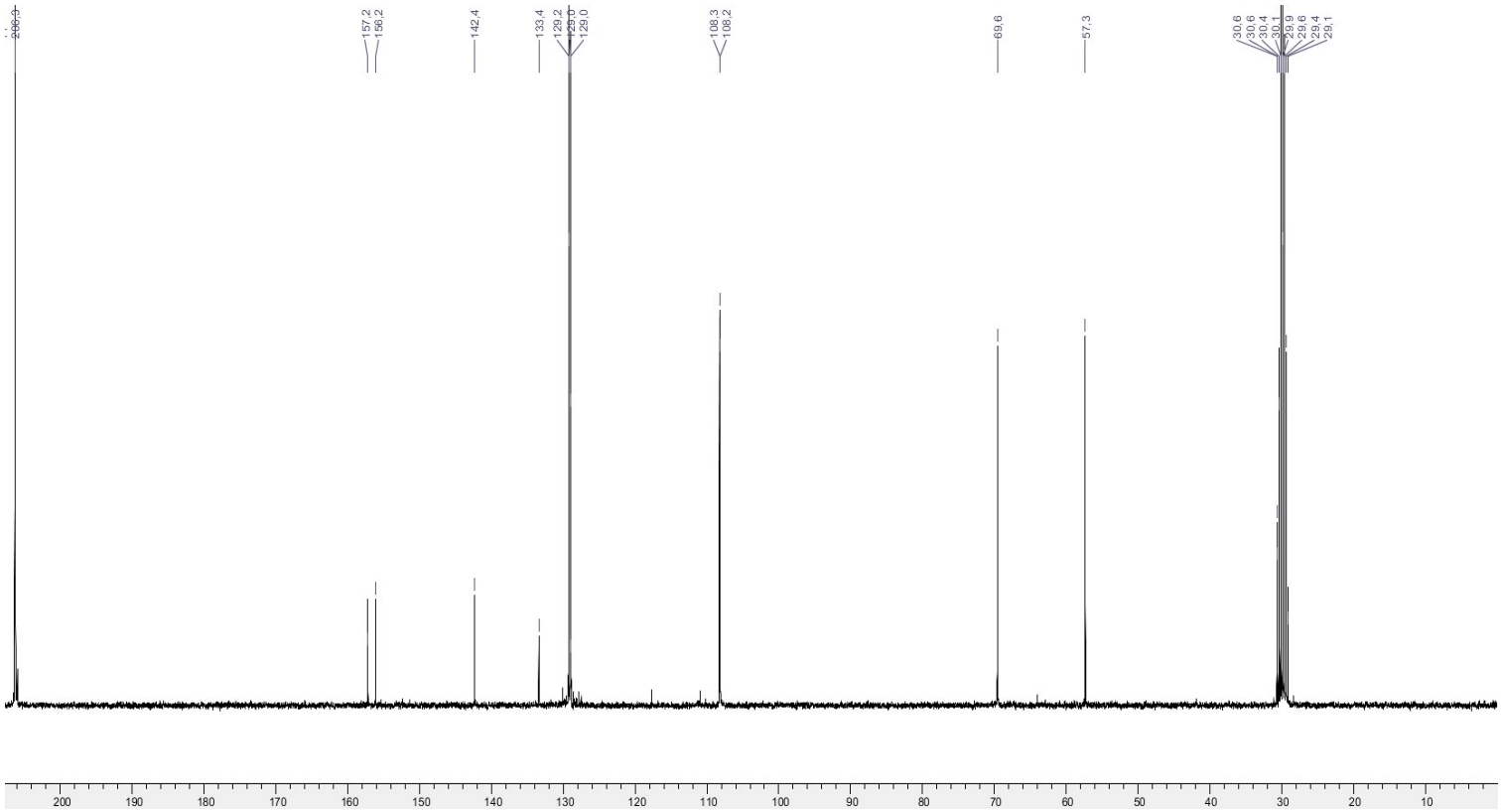




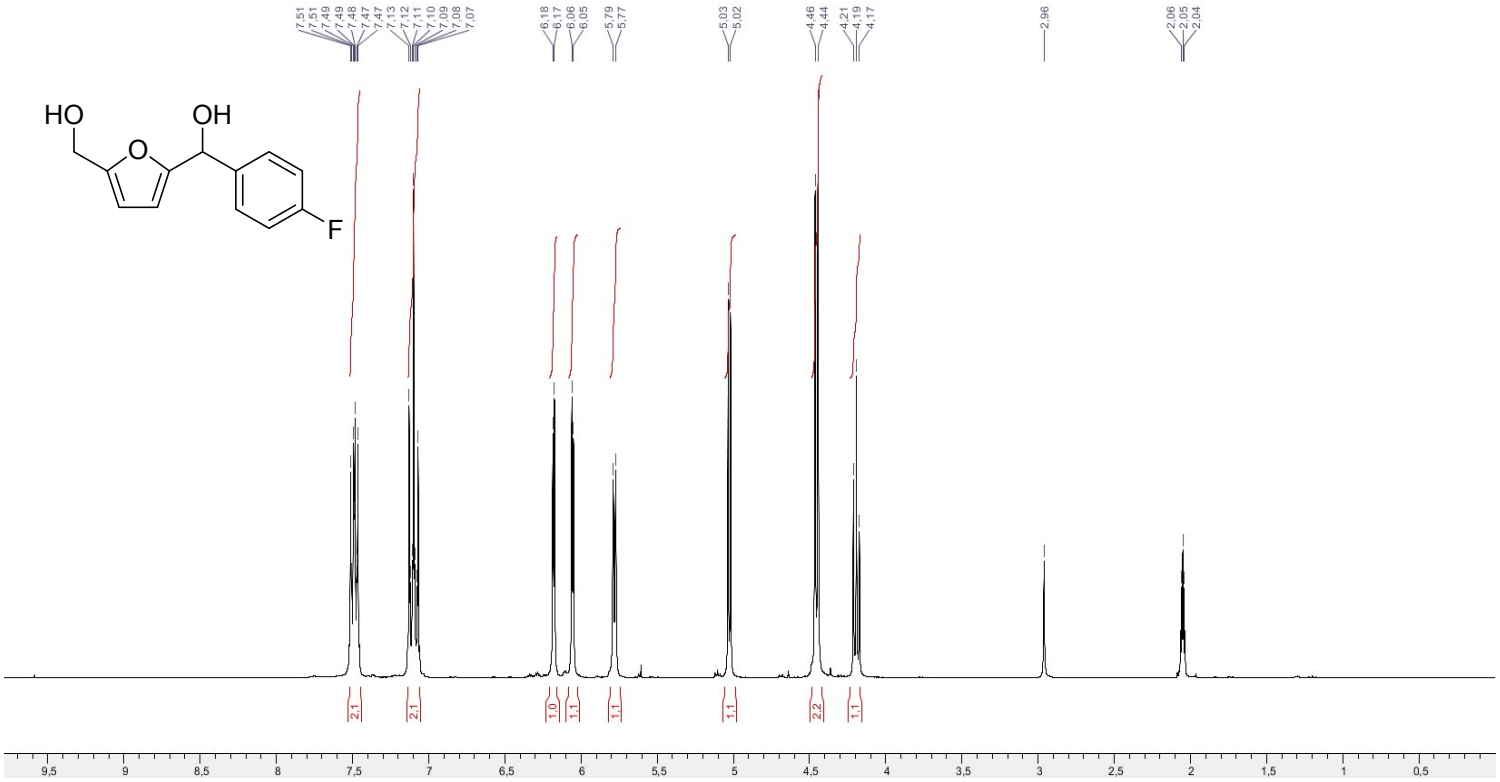
IV.5. ^{1}H NMR (Acetone-d_6, 300 MHz) (**5e**)



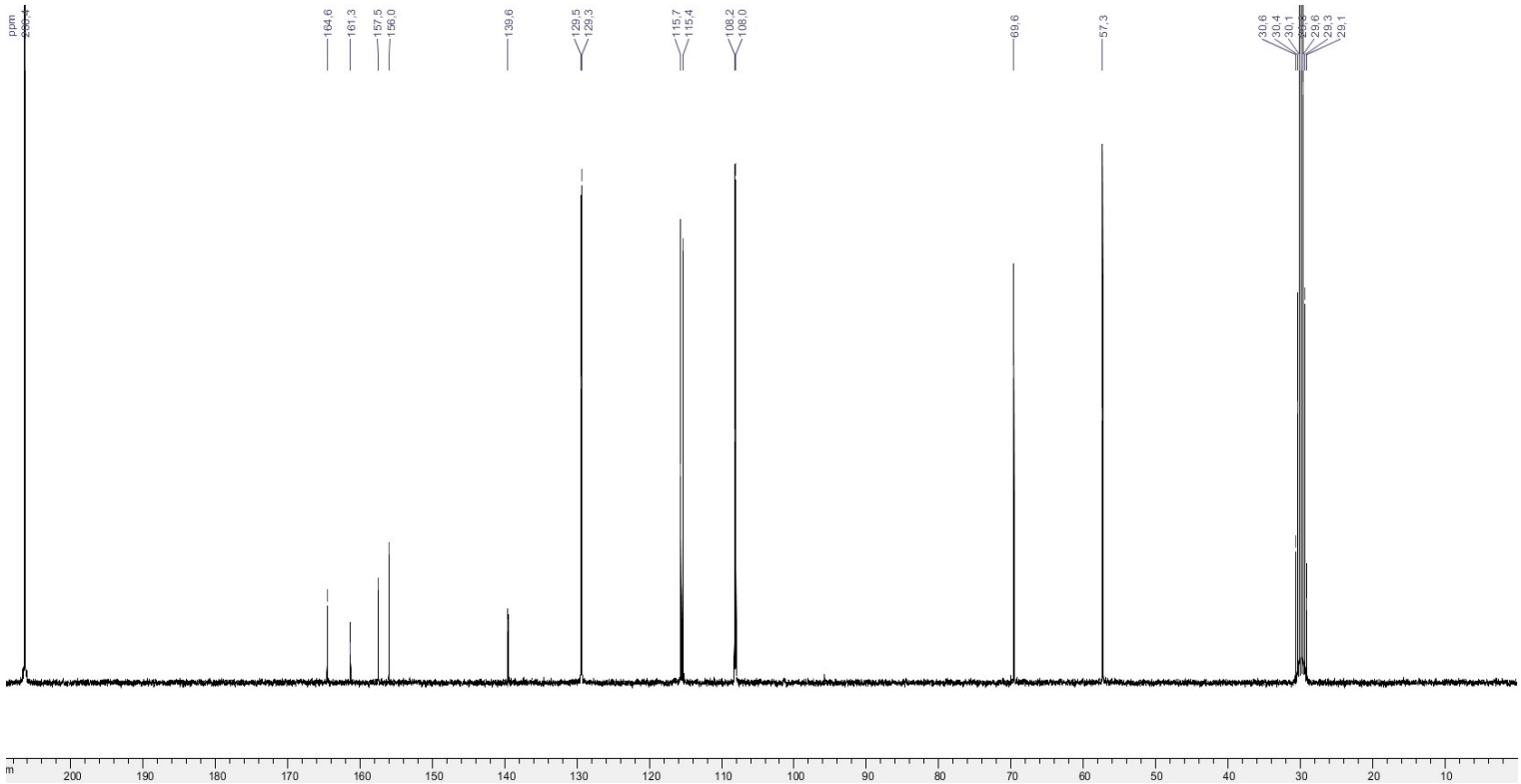
^{13}C NMR (Acetone-d_6, 75 MHz)



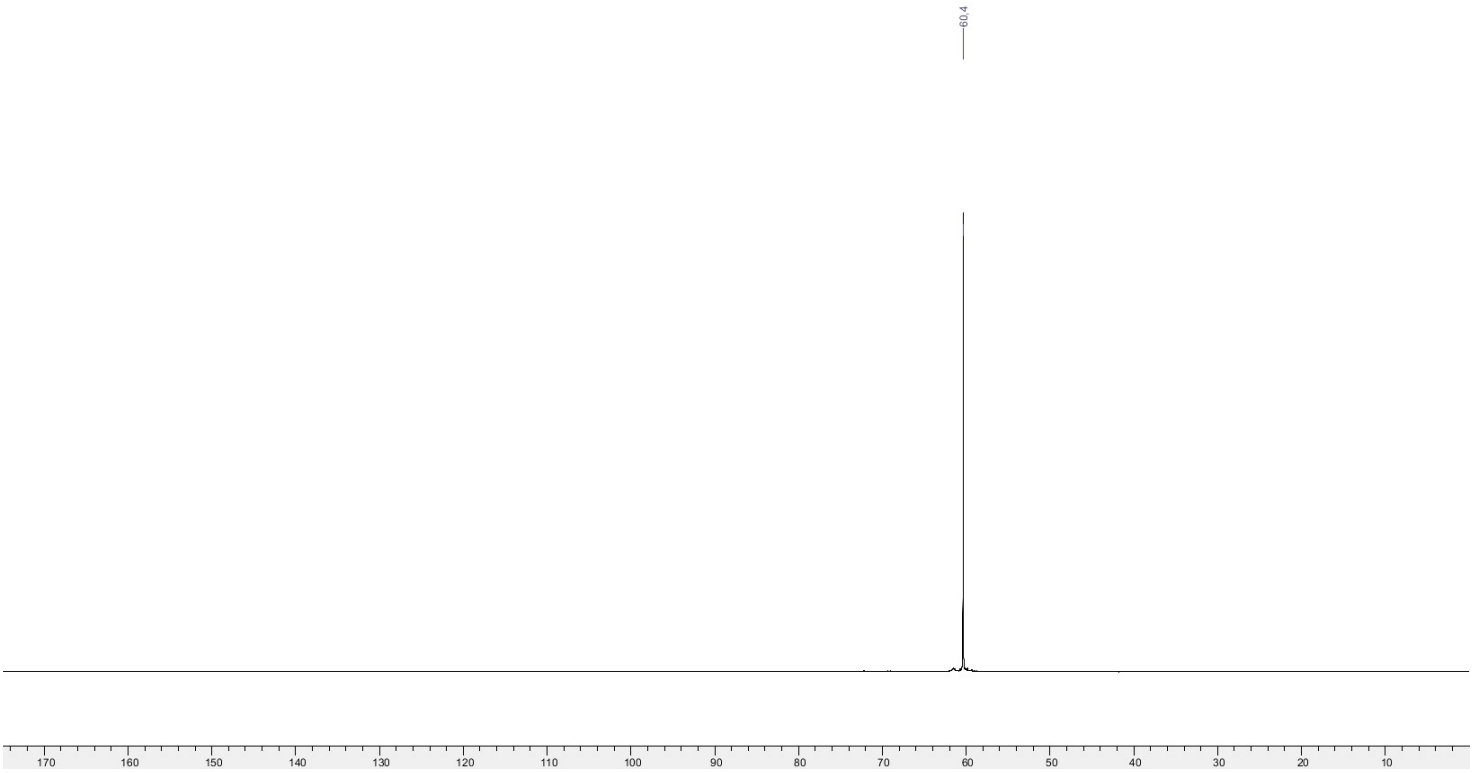
IV.6. ^{1}H NMR (Acetone-d_6, 300 MHz) (**5f**)



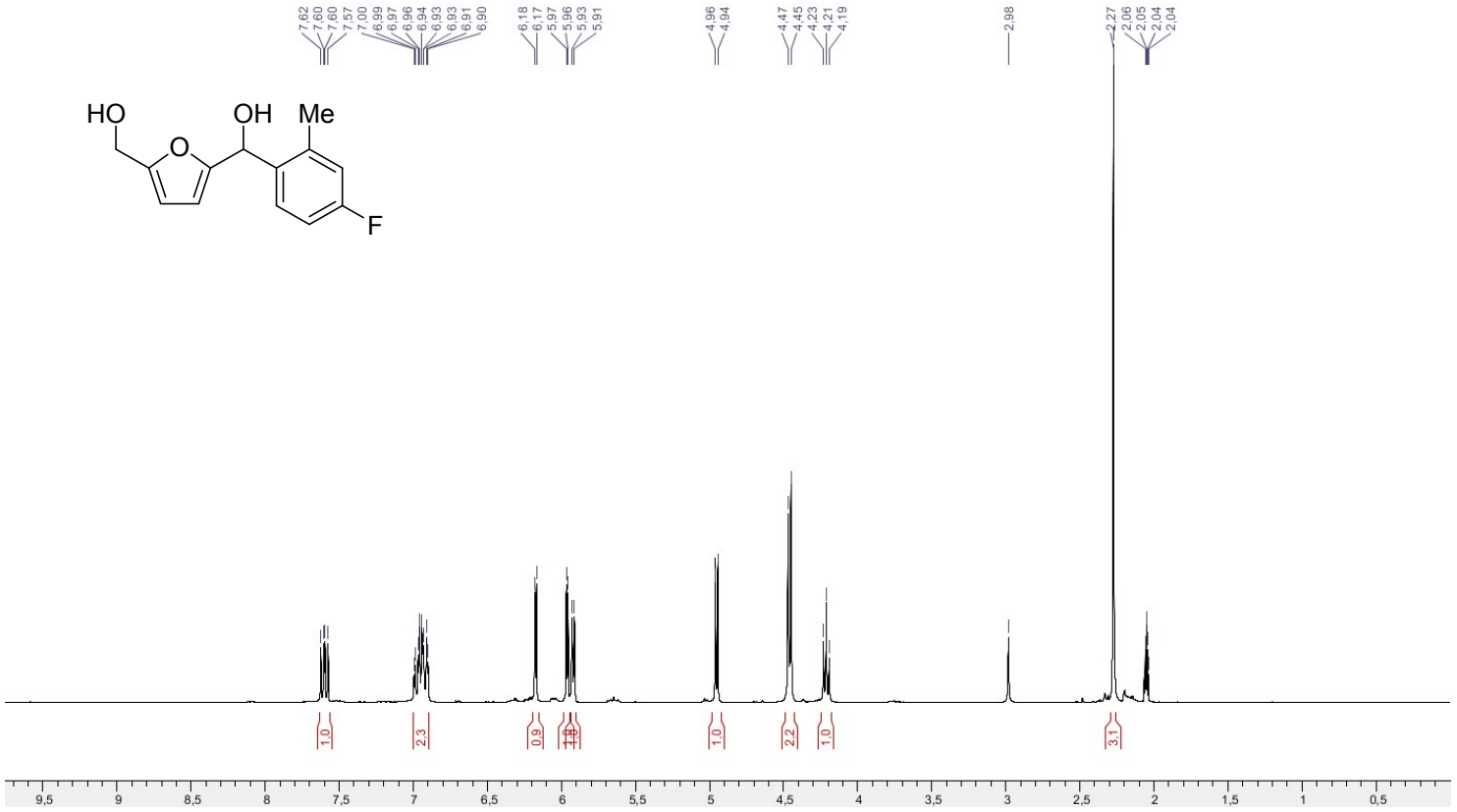
^{13}C NMR (Acetone-d_6, 75 MHz)



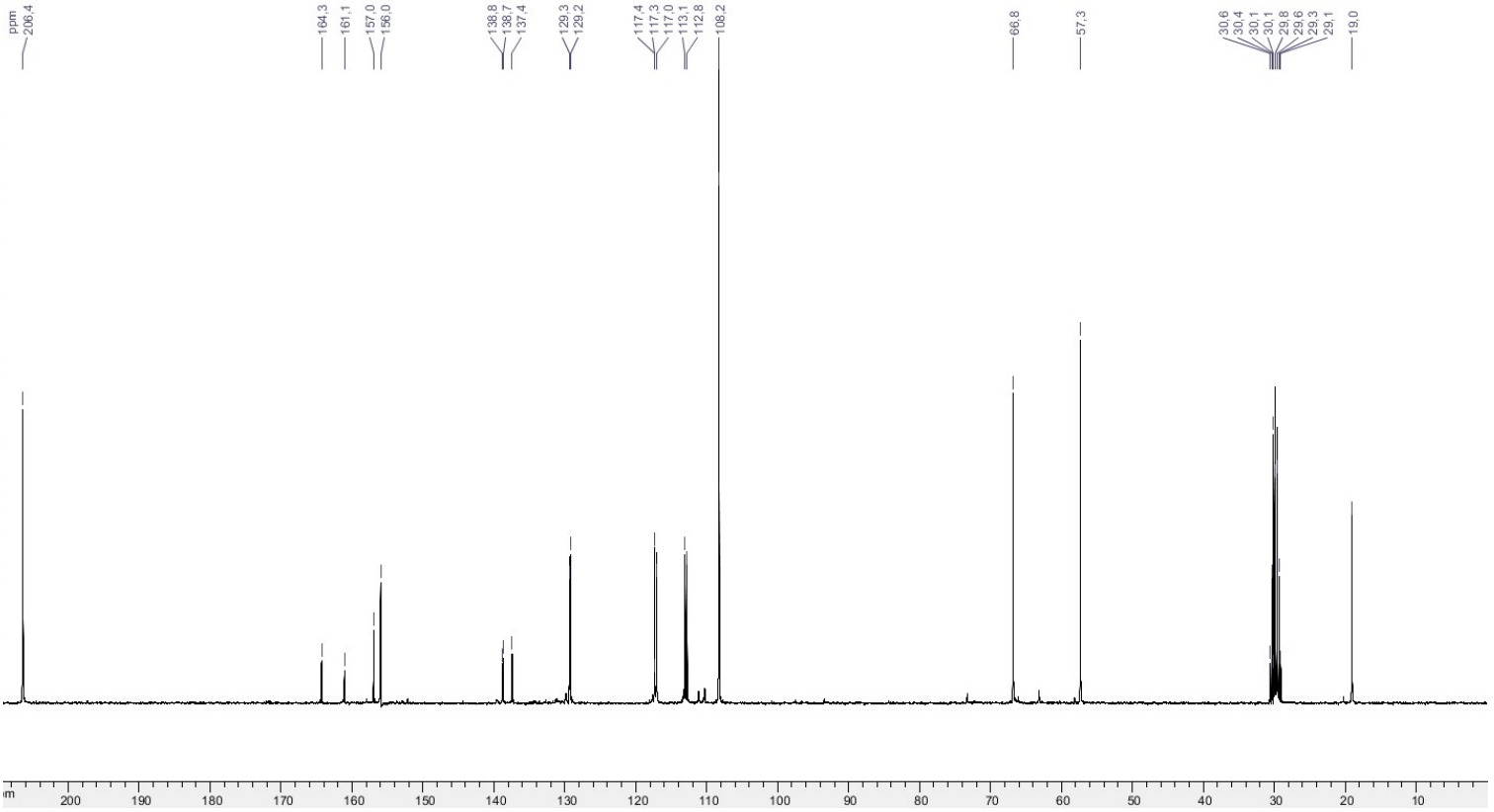
^{19}F-NMR (Acetone-d_6, 282 MHz)


60.4
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

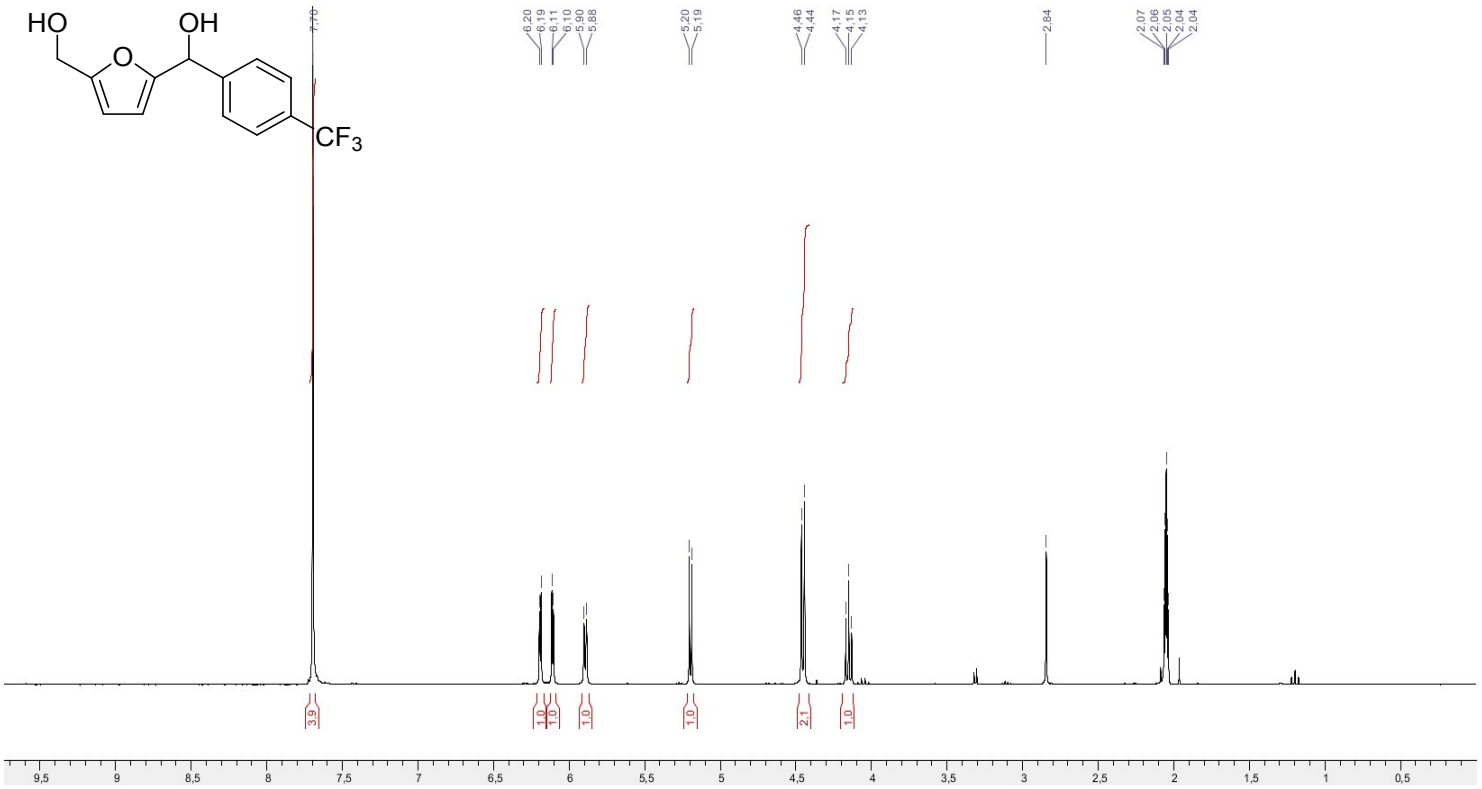
IV.7. ^{1}H NMR (Acetone-d_6, 300 MHz) (**5g**)



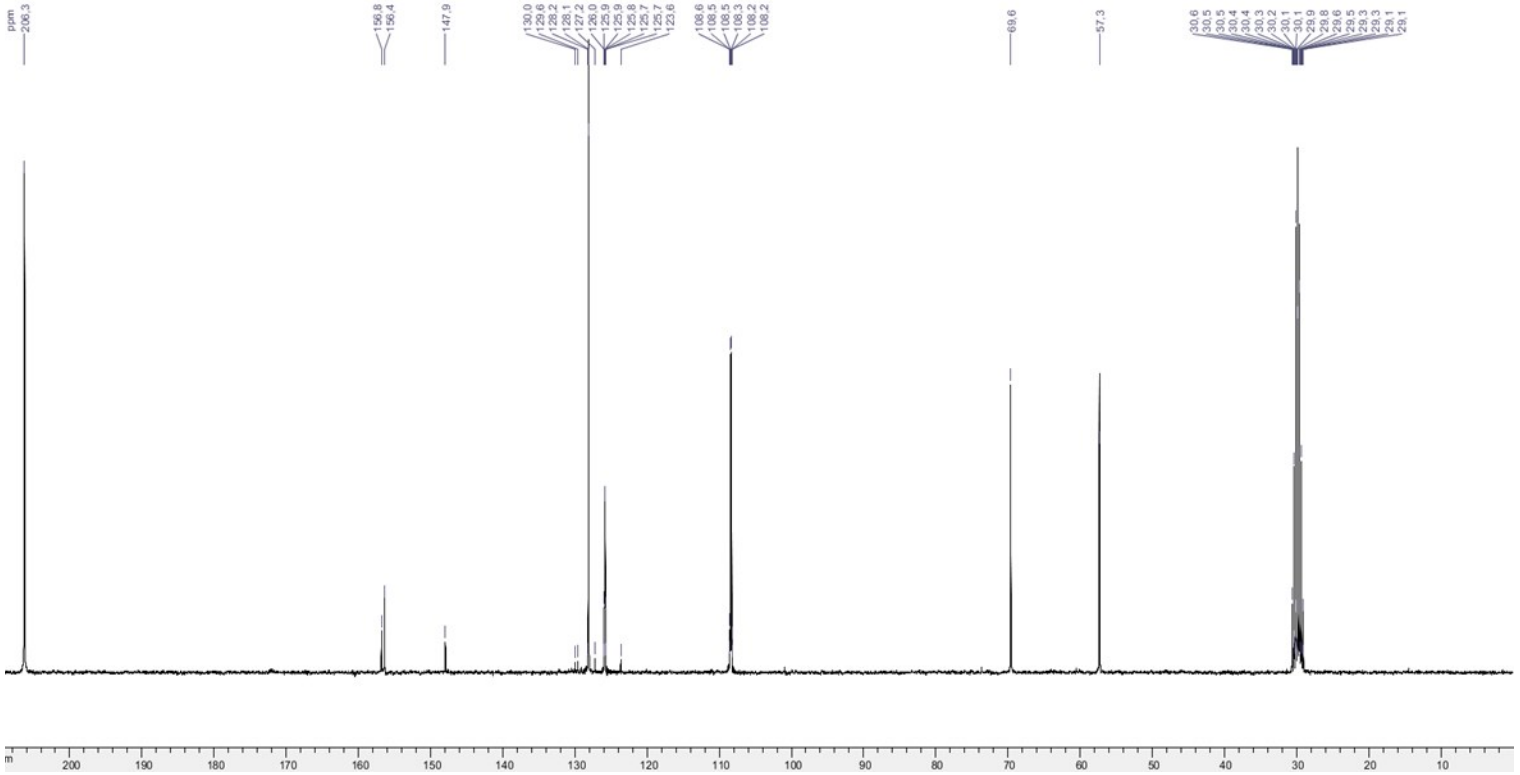
^{13}C NMR (Acetone-d_6, 75 MHz)



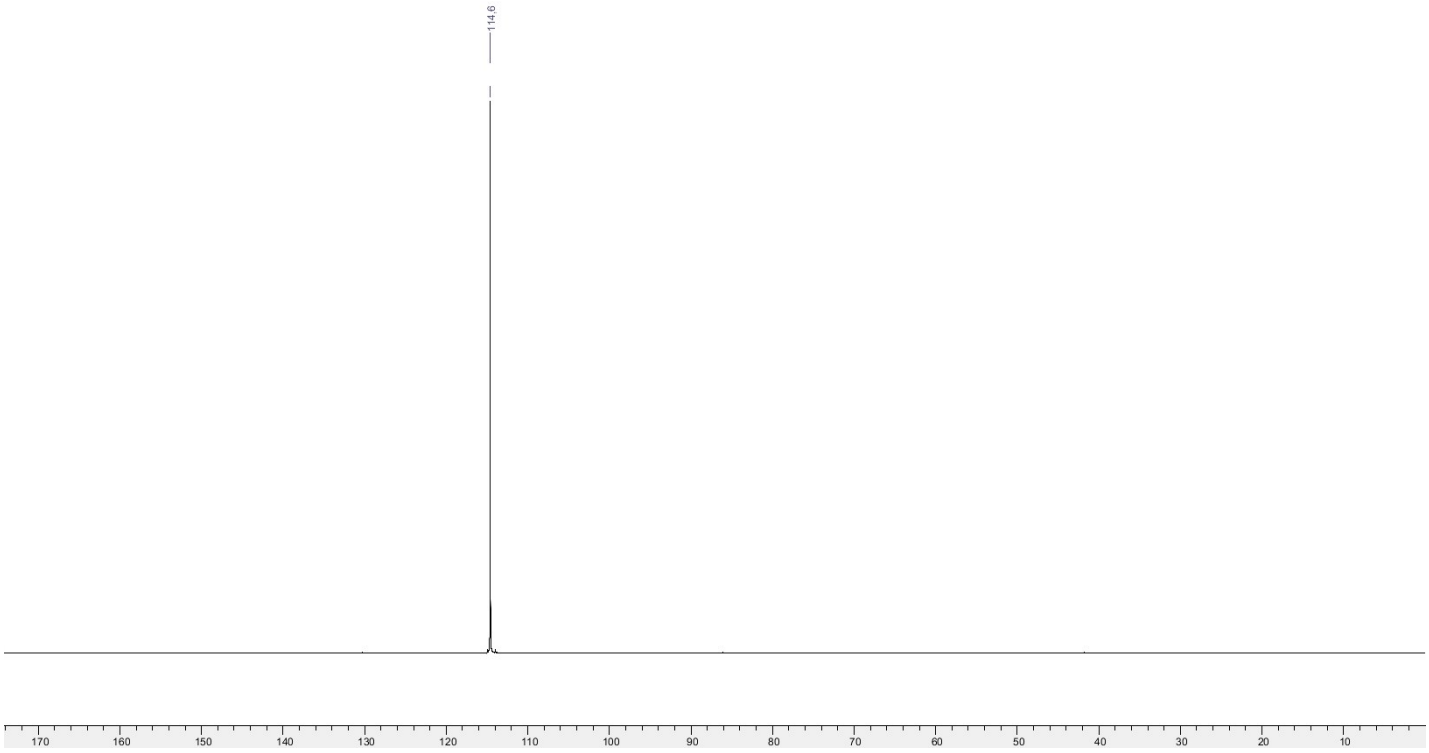
IV.8. ^{1}H NMR (Acetone-d_6, 300 MHz) (**5h**)



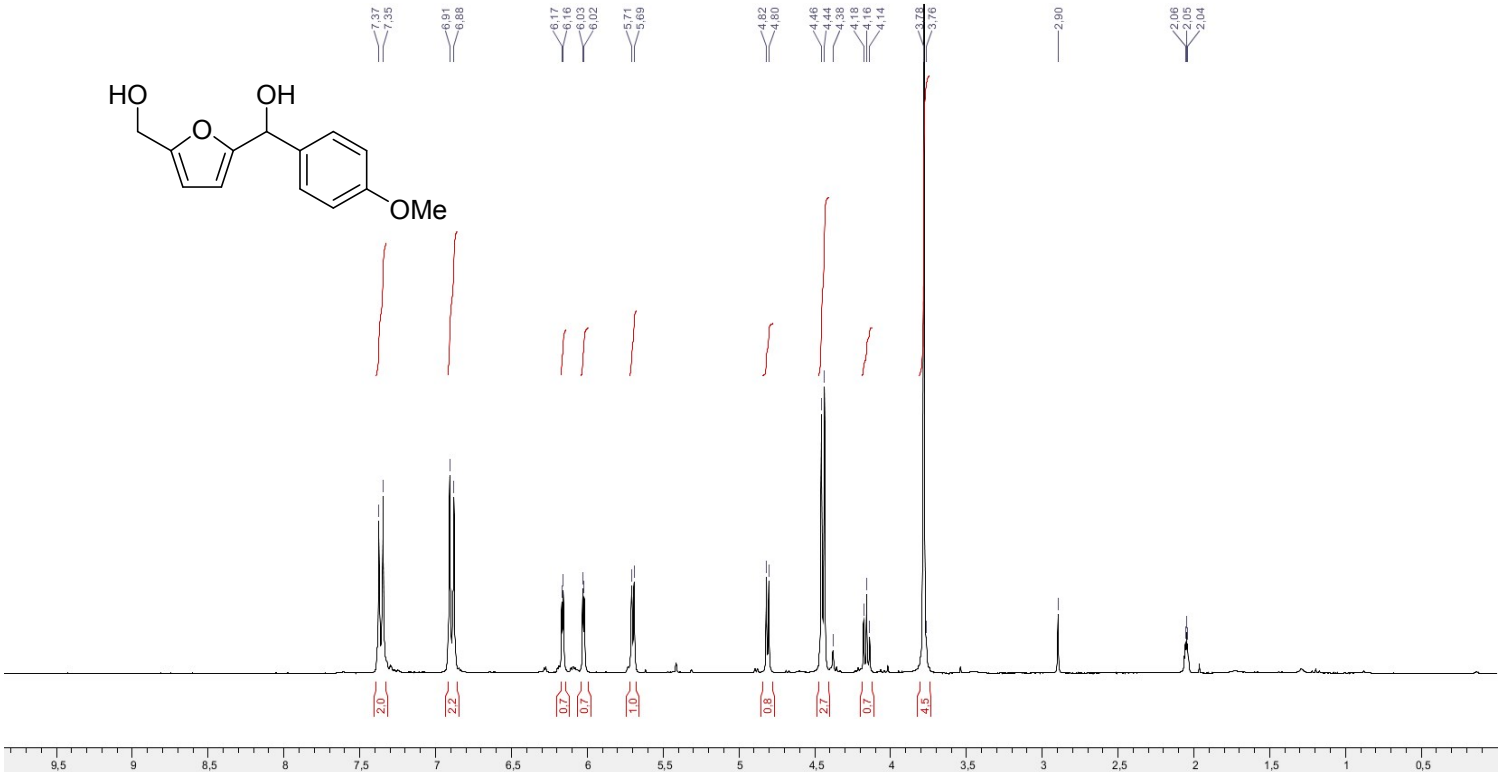
^{13}C NMR (Acetone-d_6, 75 MHz)



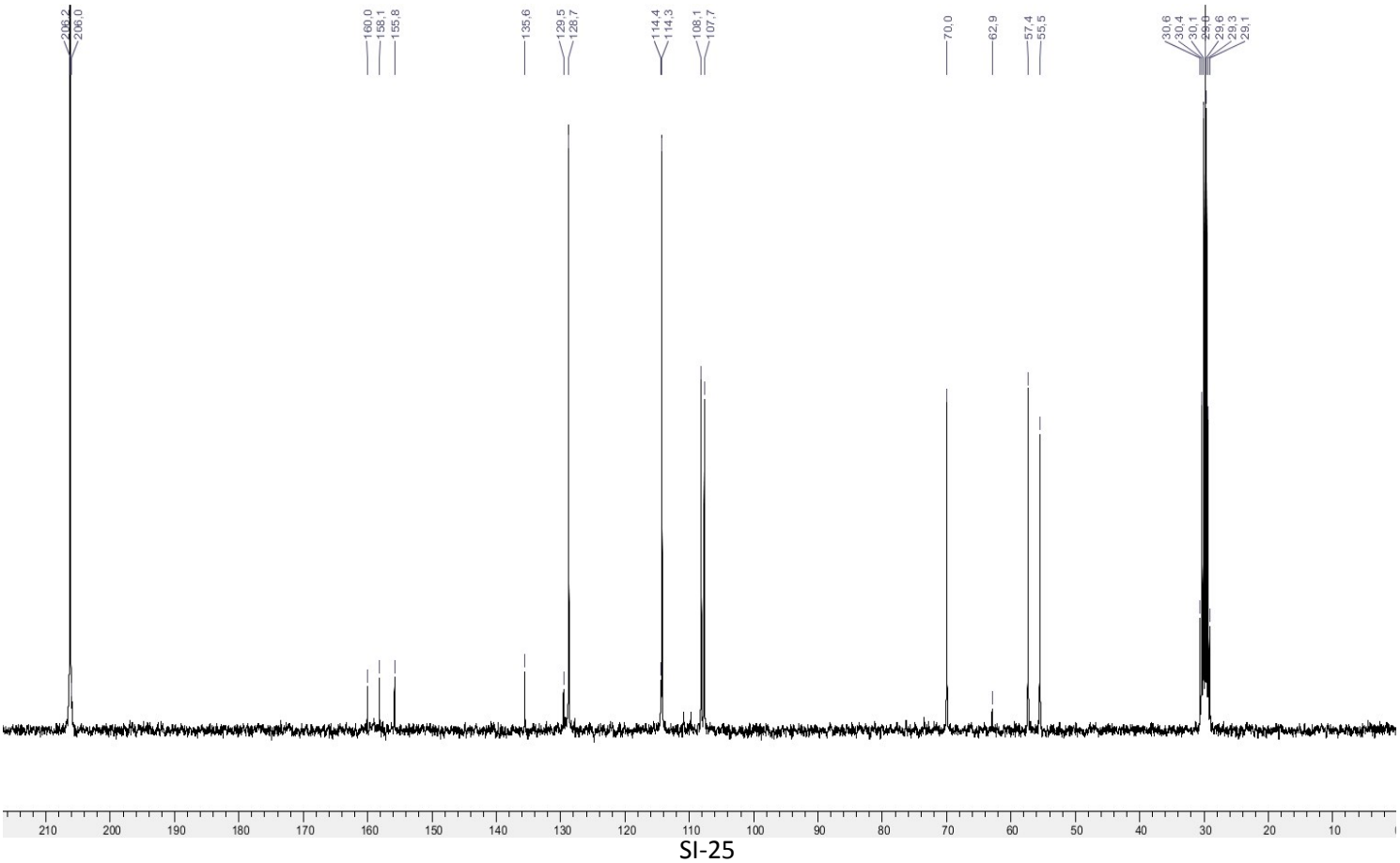
^{19}F-NMR (Acetone-d_6, 282 MHz)



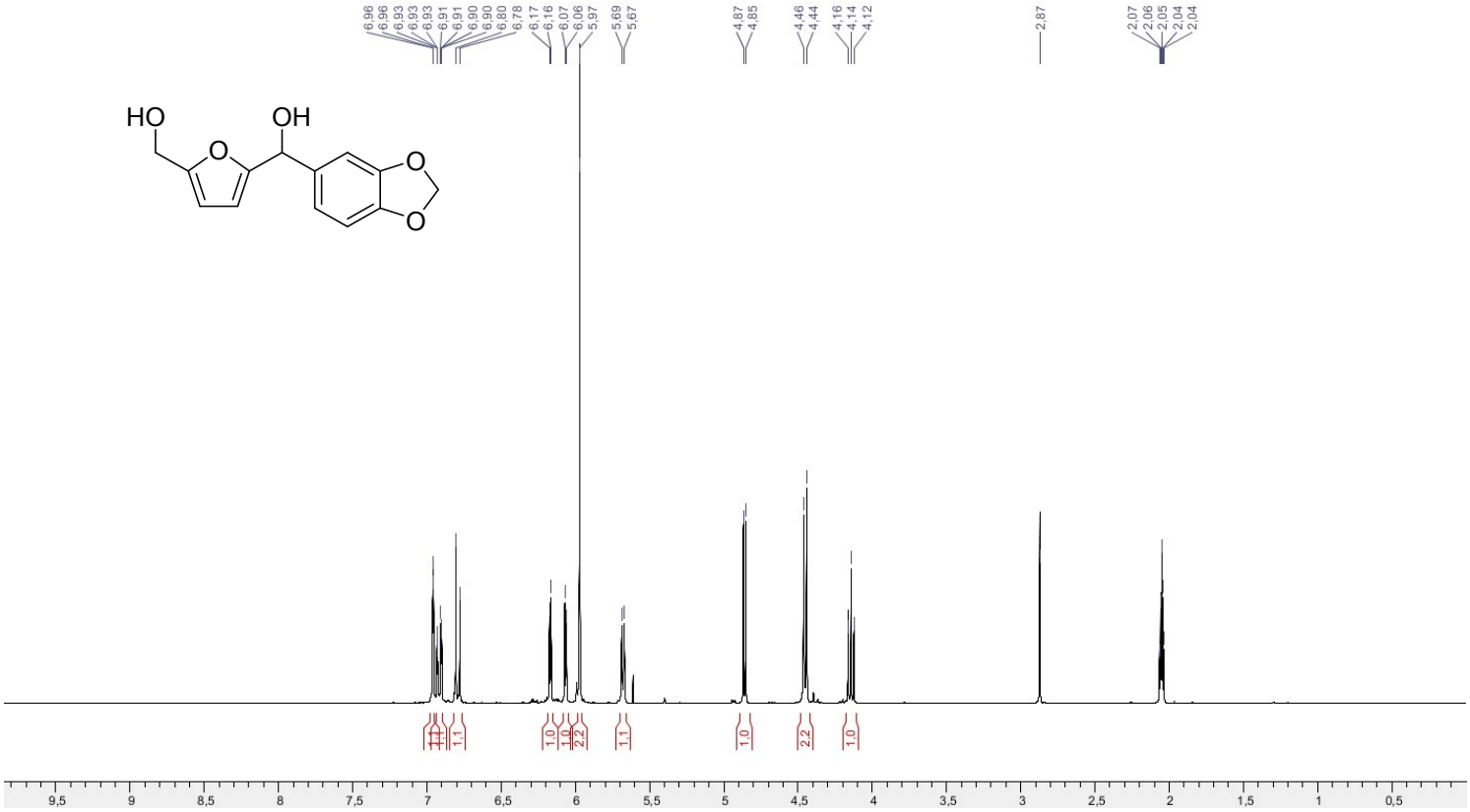
IV.9. ^{1}H NMR (Acetone-d_6, 300 MHz) (**5i**)



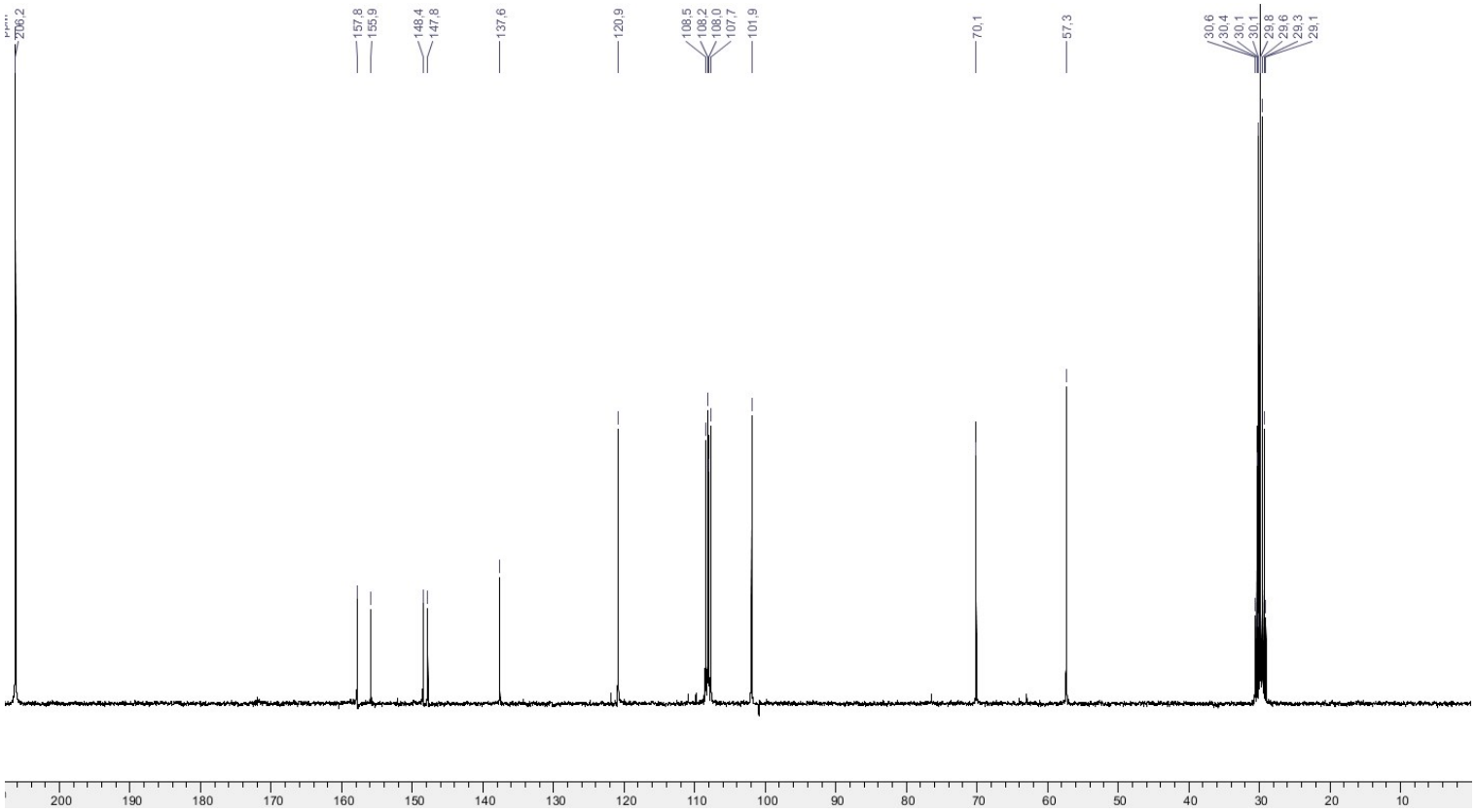
^{13}C NMR (Acetone-d_6, 75 MHz)



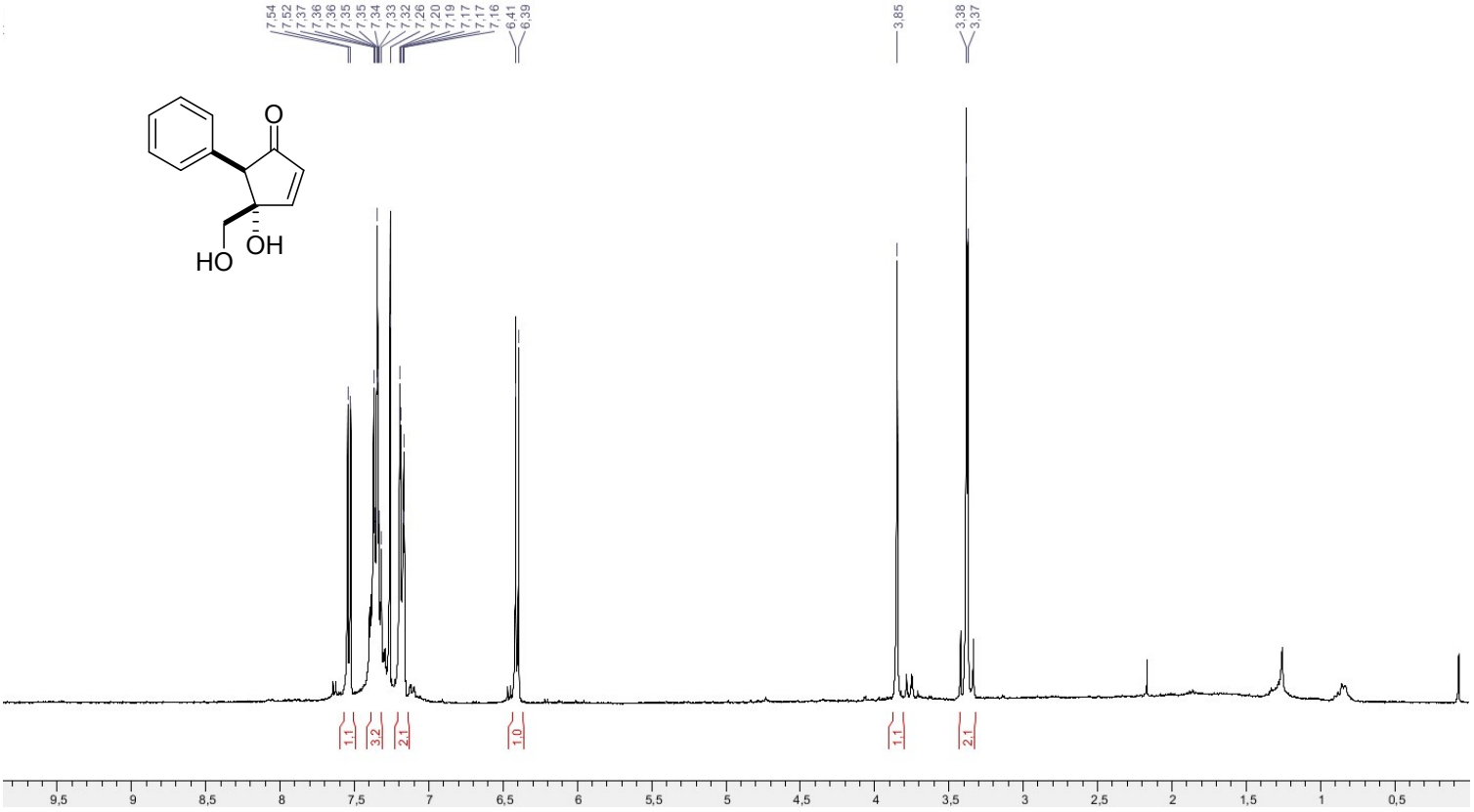
IV.10. ^{1}H NMR (Acetone-d_6, 300 MHz) (**5j**)



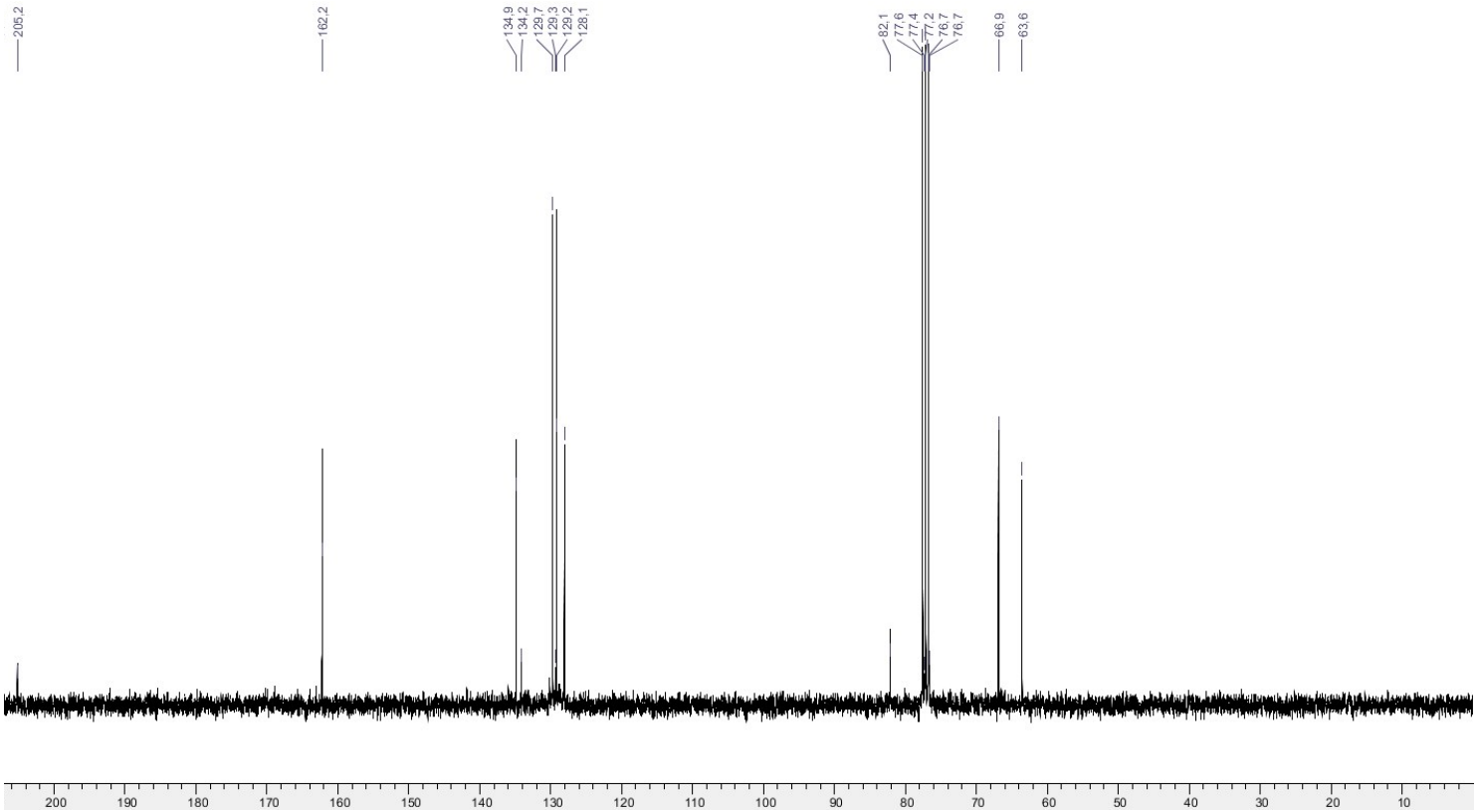
^{13}C NMR (Acetone-d_6, 75 MHz)



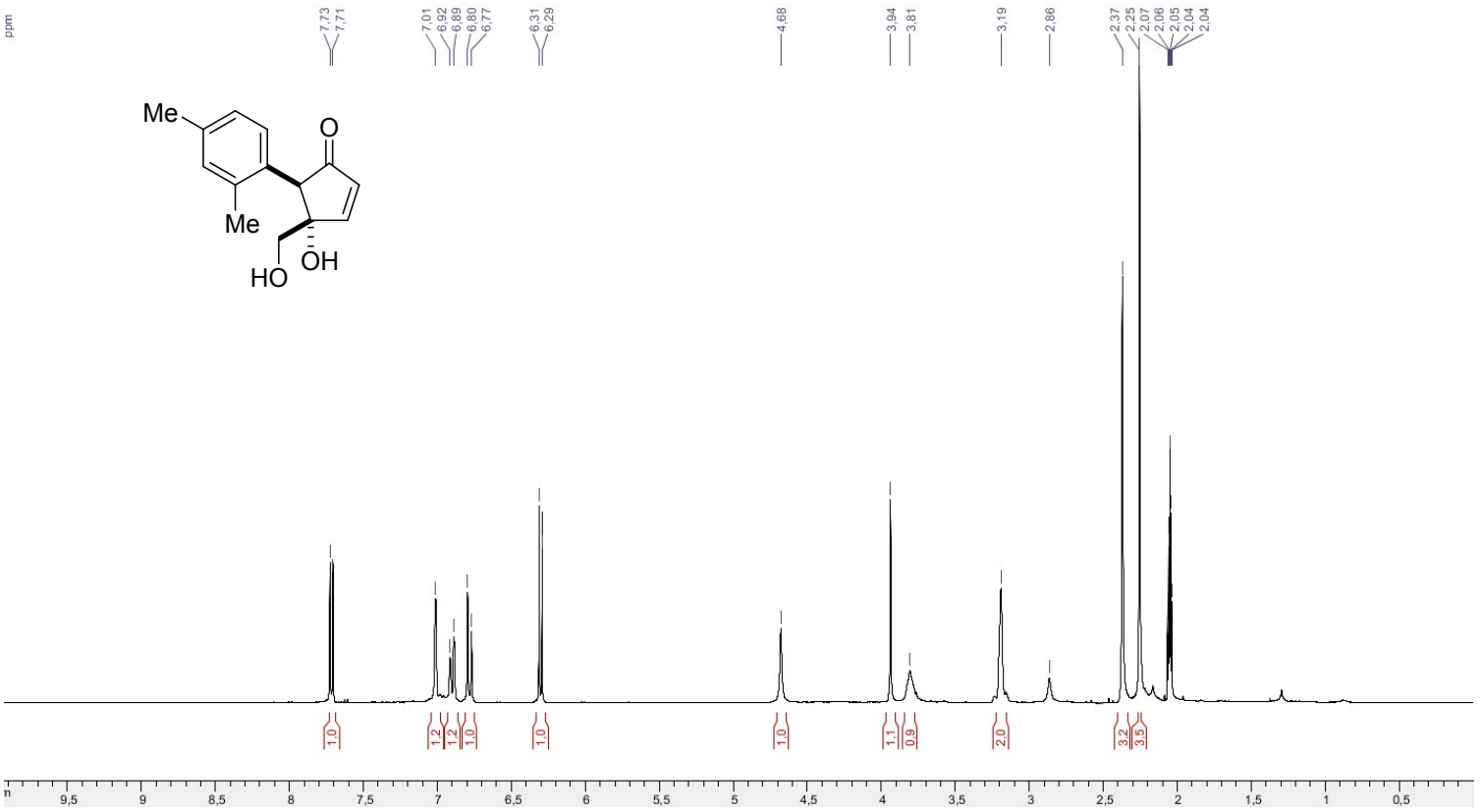
IV.11. ^{1}H NMR ($CDCl_3$, 300 MHz) (**6a**)



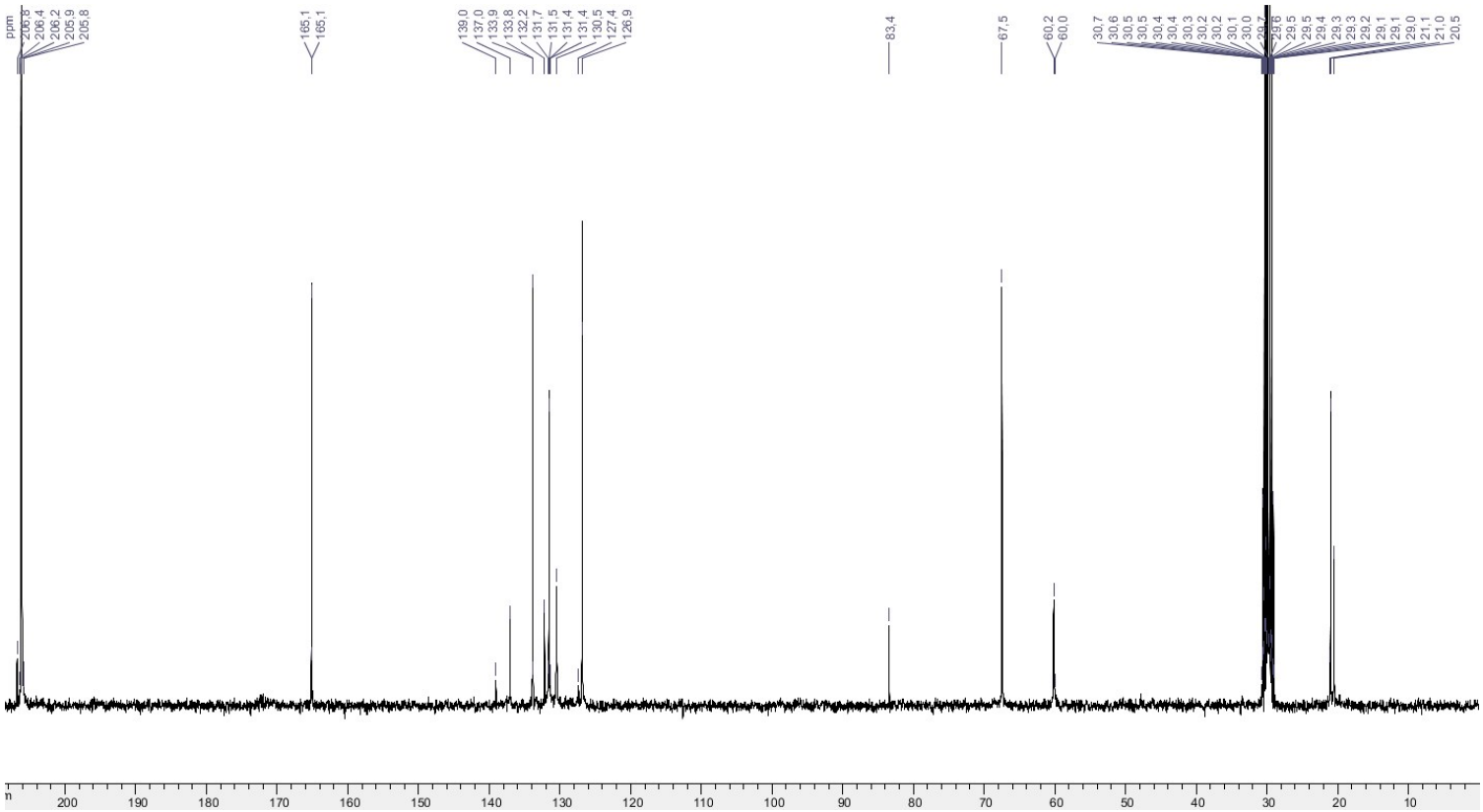
^{13}C NMR ($CDCl_3$, 75 MHz)



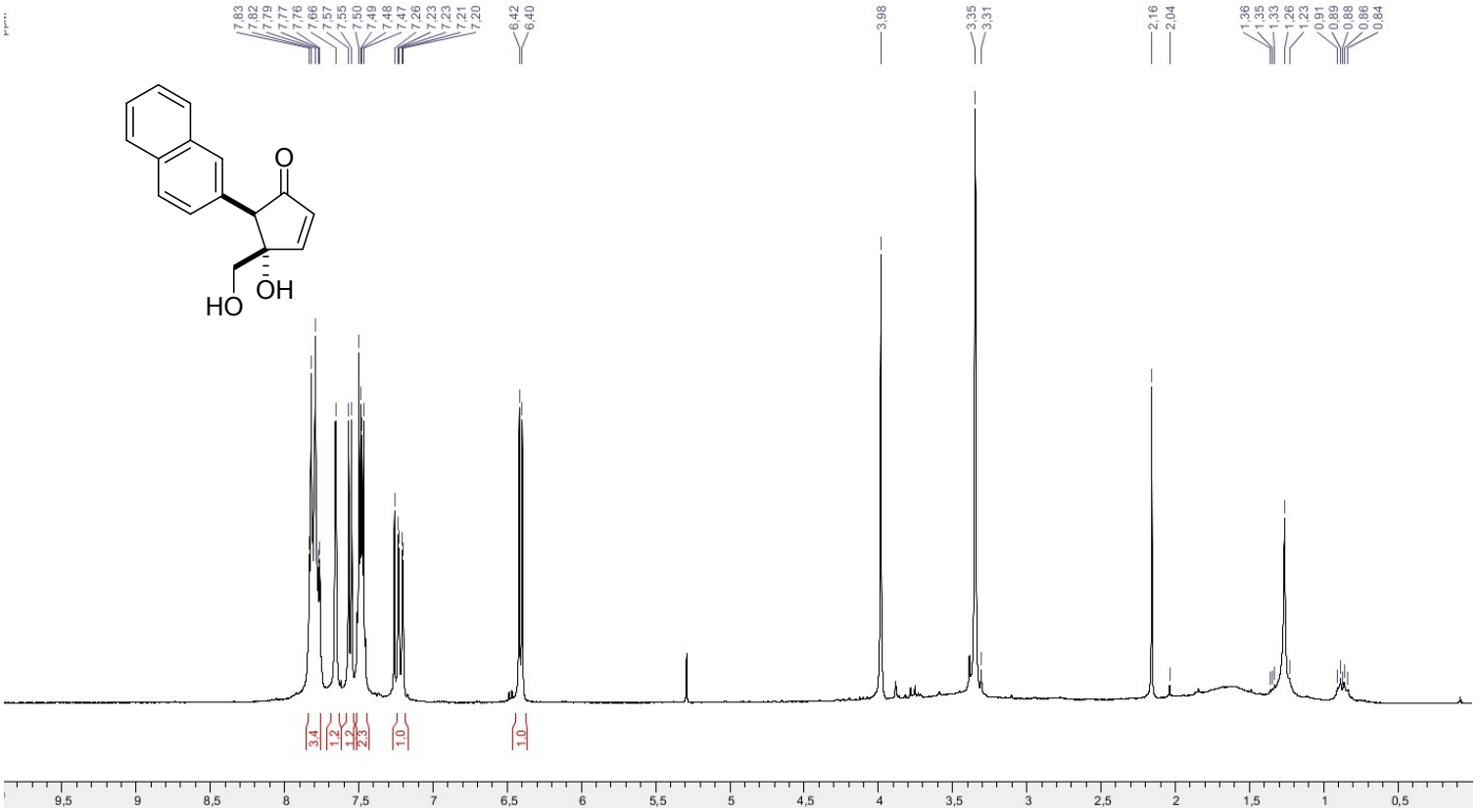
IV.12. ^{1}H NMR (Acetone-d_6, 300 MHz) (**6b**)



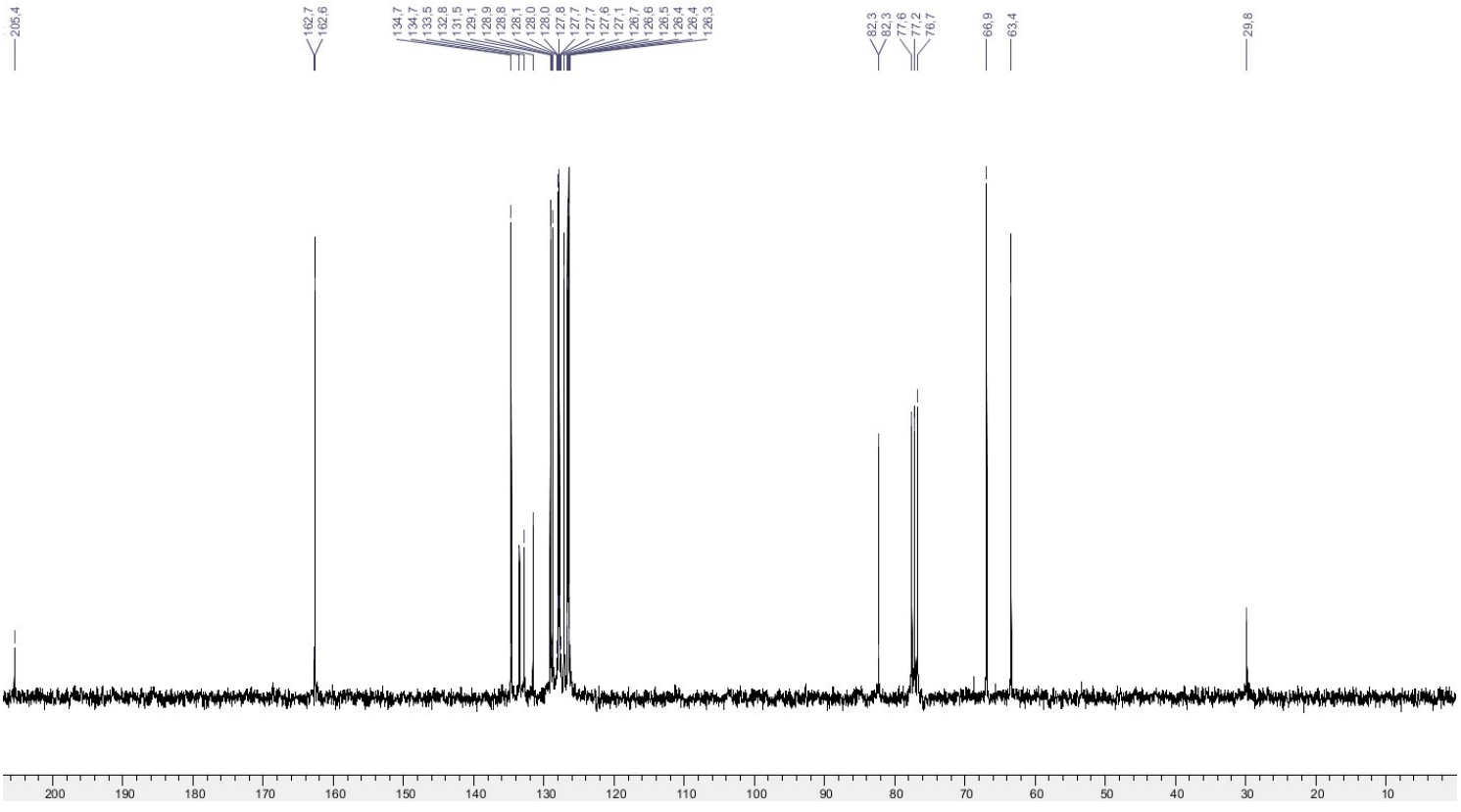
^{13}C NMR (Acetone-d_6, 75 MHz)



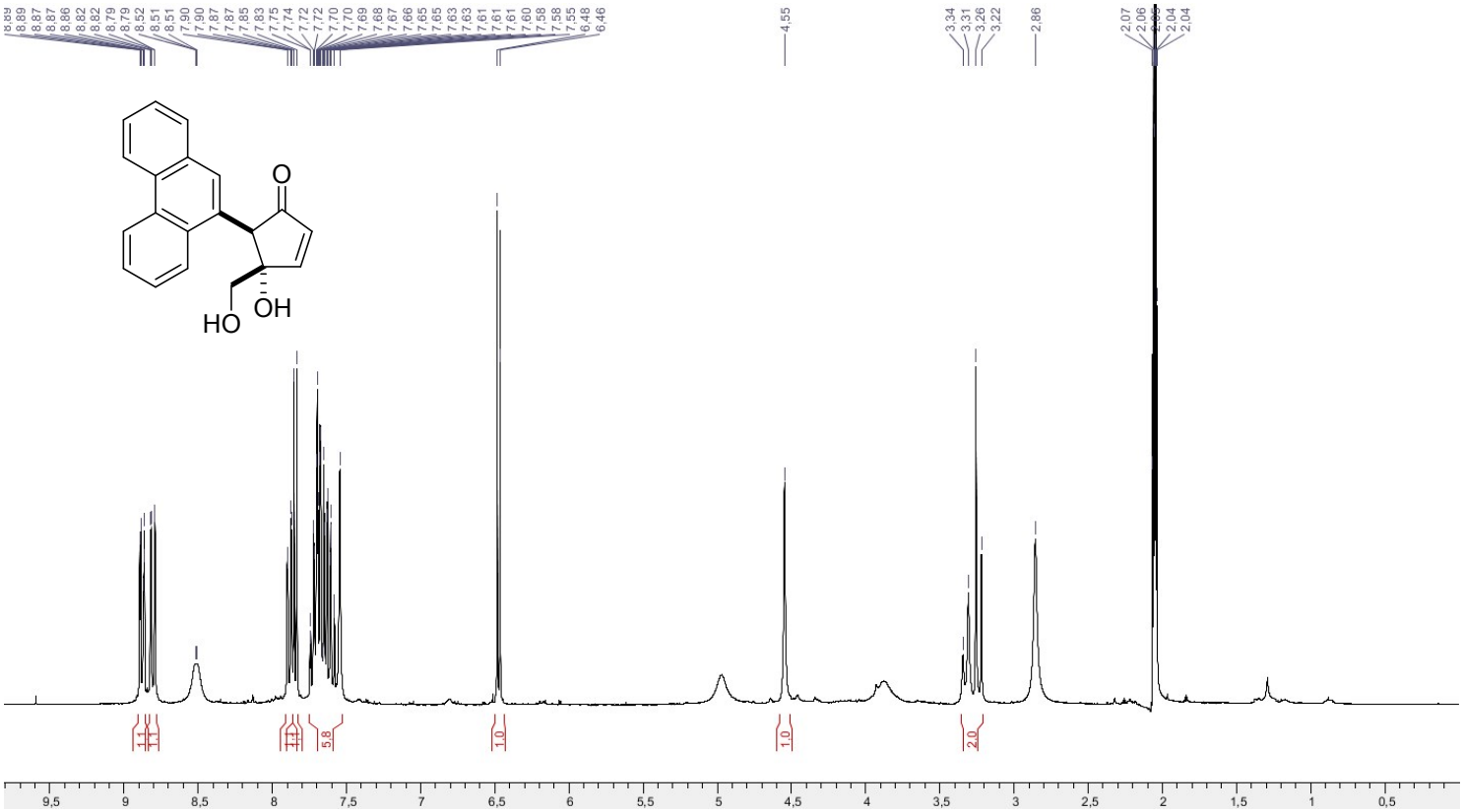
IV.13. ^{1}H NMR ($CDCl_3$, 300 MHz) (**6c**)



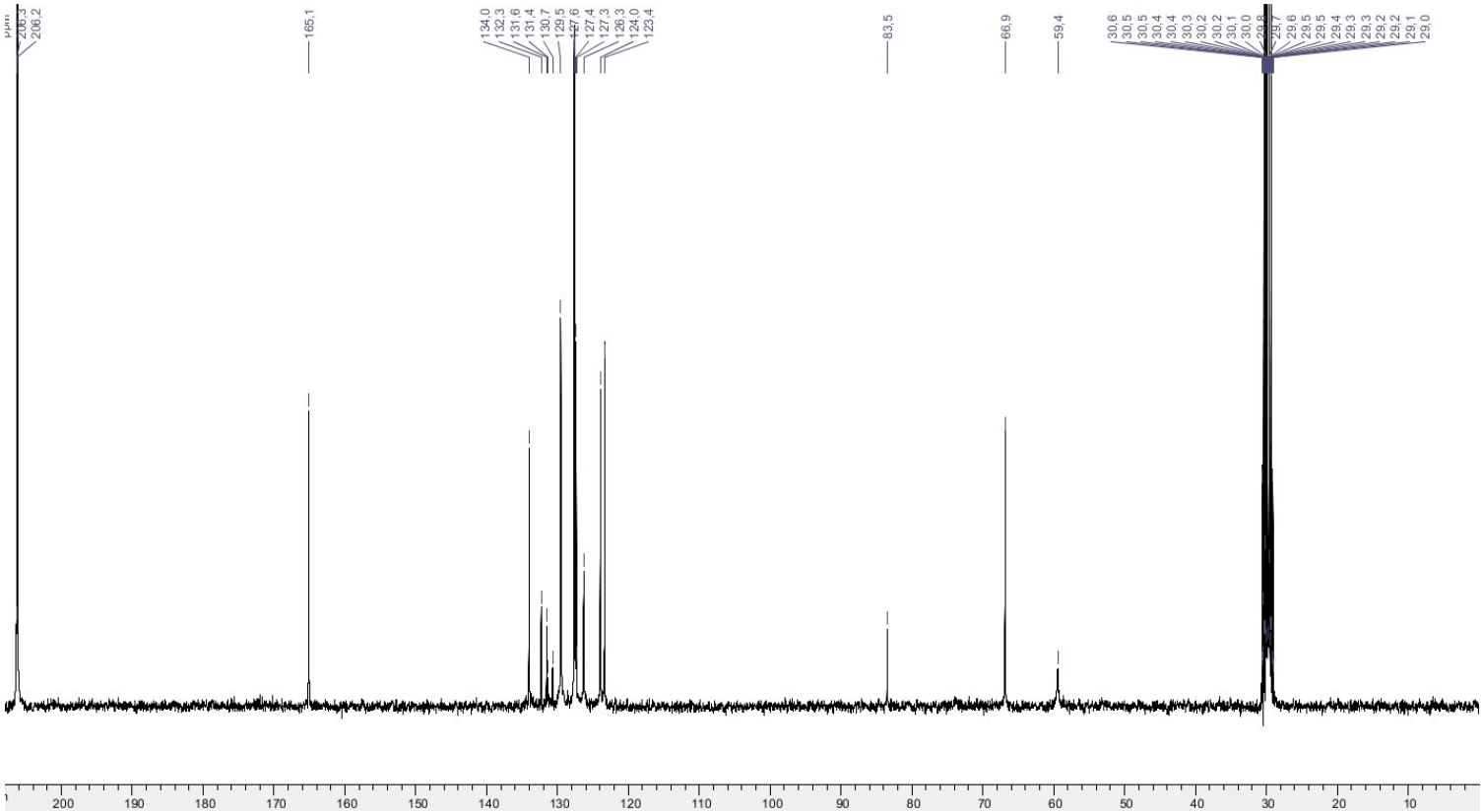
^{13}C NMR ($CDCl_3$, 75 MHz)



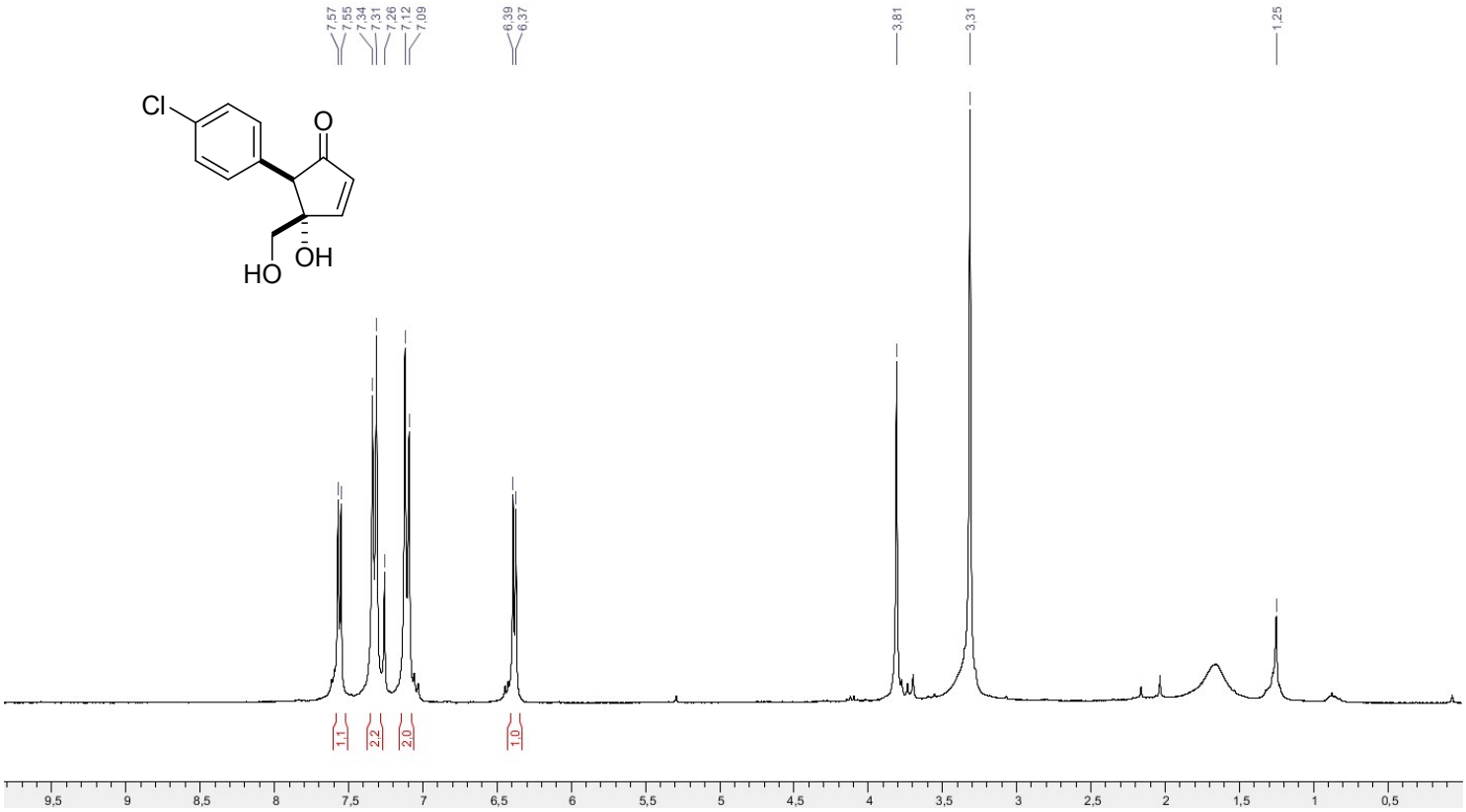
IV.14. ^{1}H NMR (Acetone-d_6, 300 MHz) (**6d**)



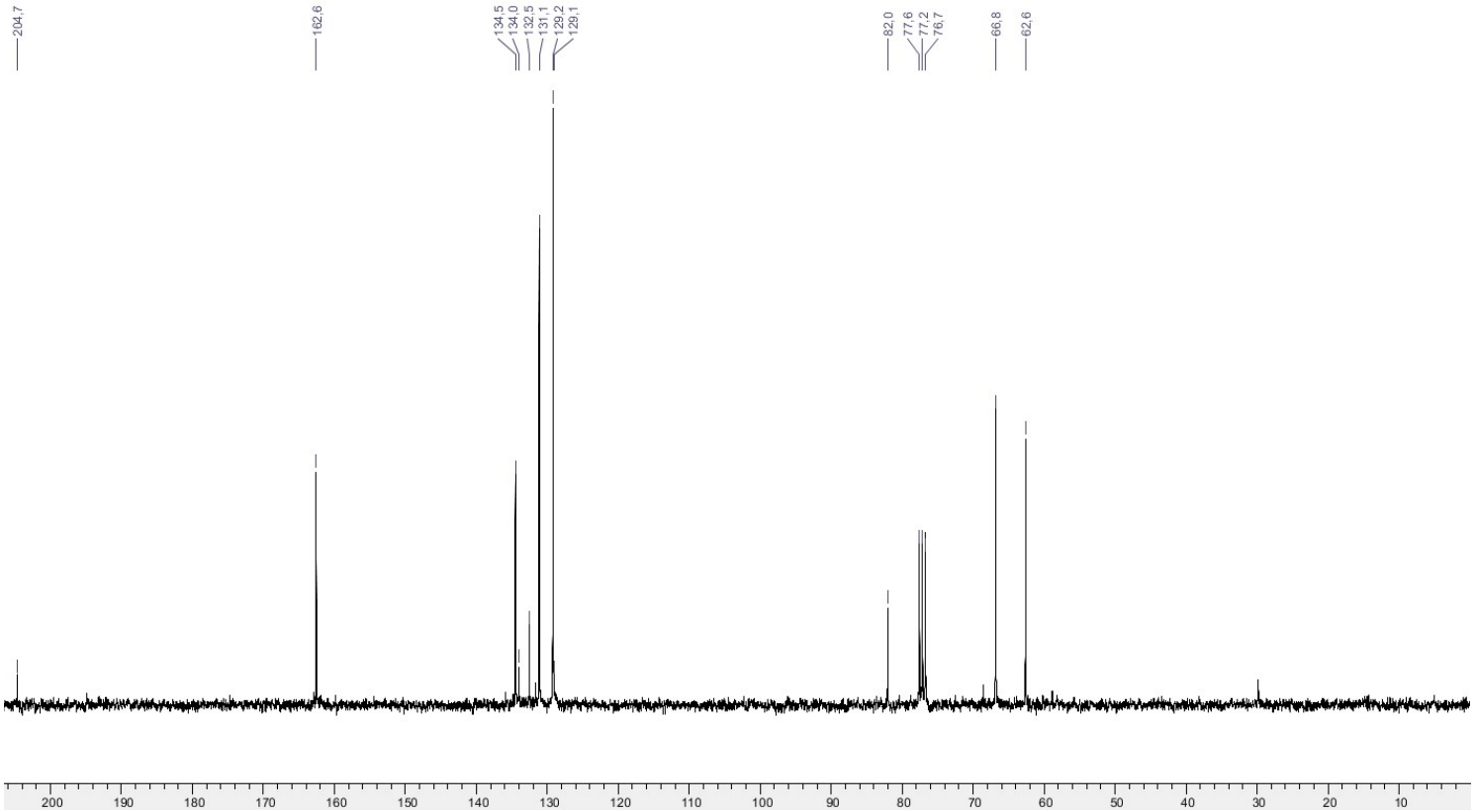
^{13}C NMR (Acetone-d_6, 75 MHz)



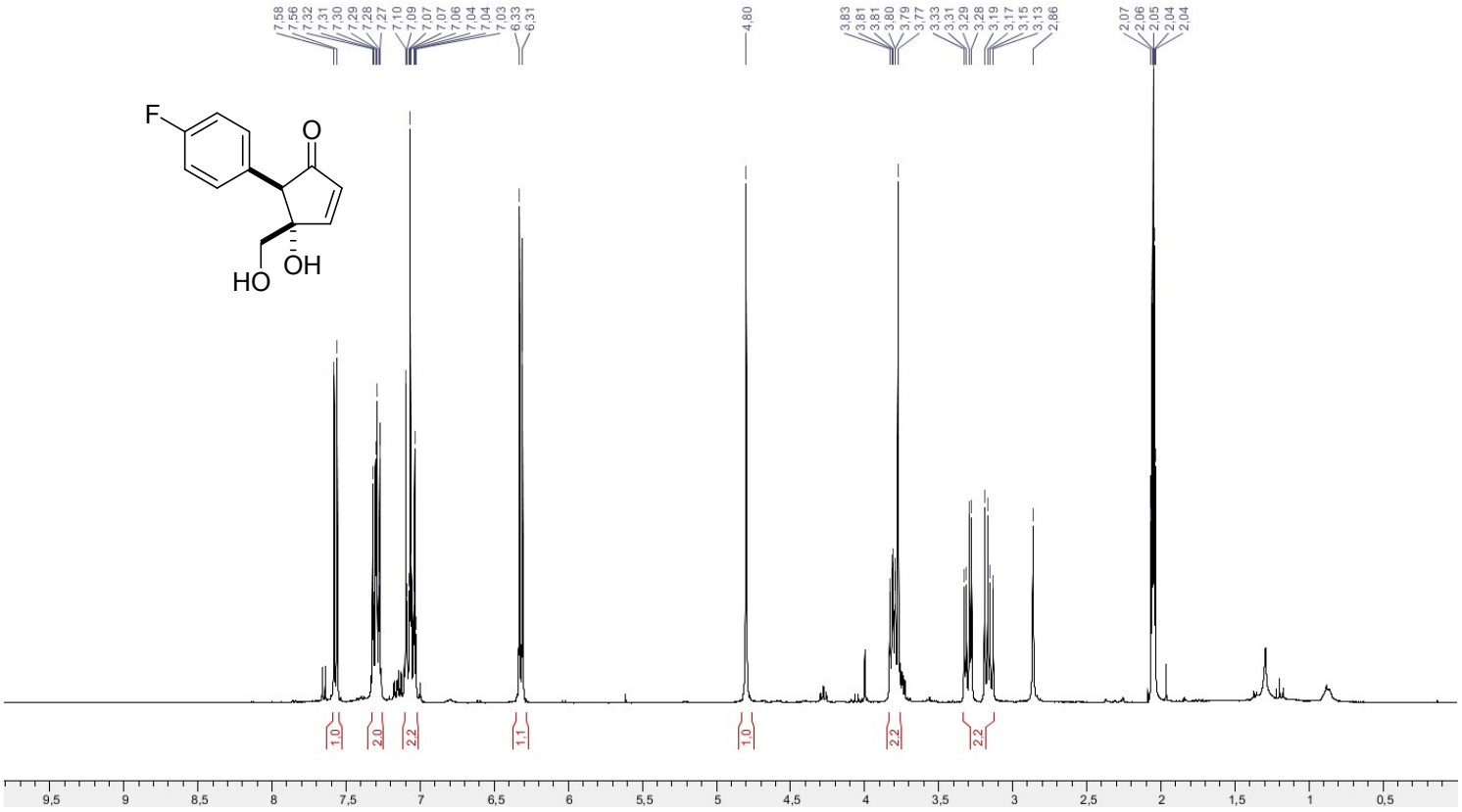
IV.15. ^{1}H NMR ($CDCl_3$, 300 MHz) (**6e**)



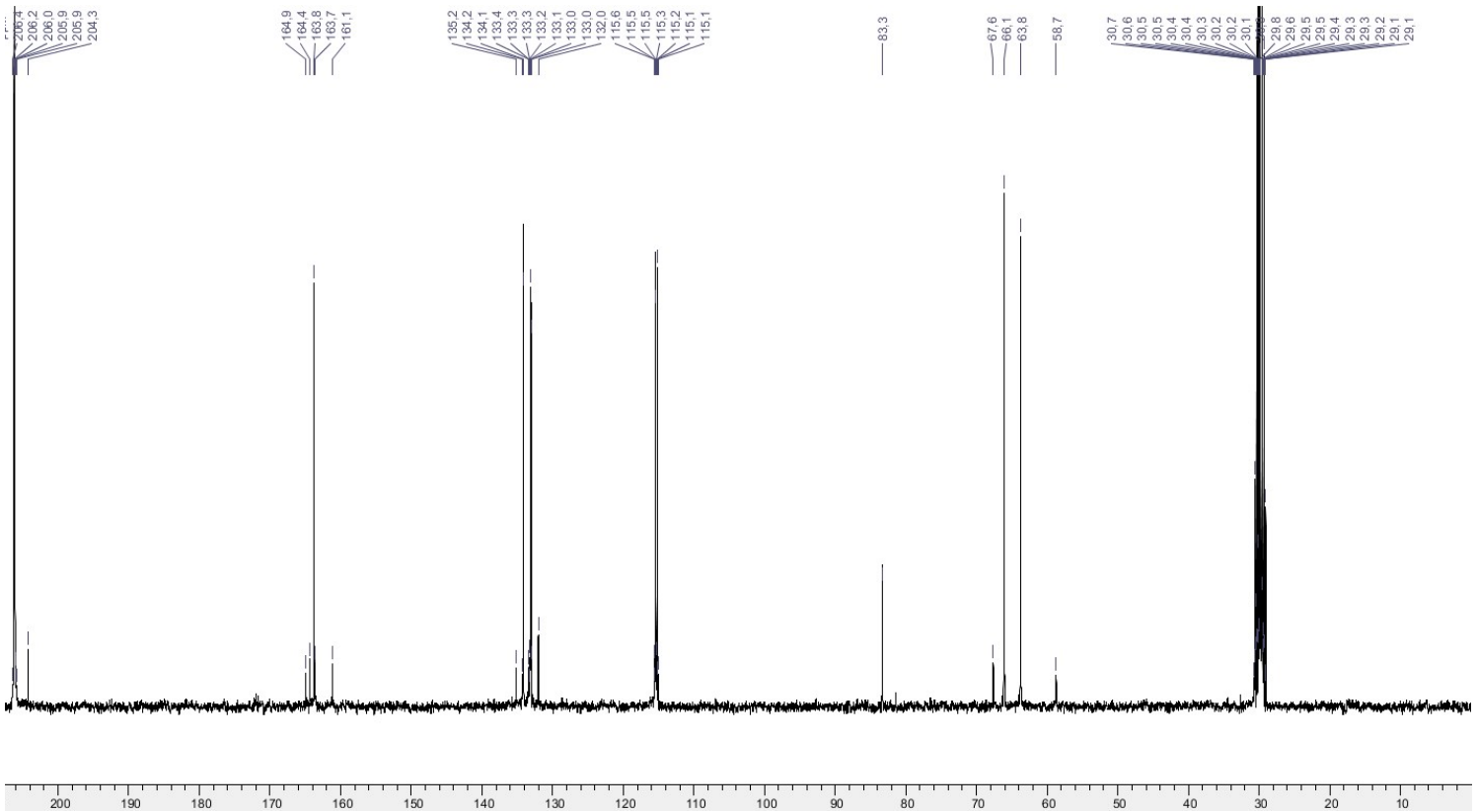
^{13}C NMR ($CDCl_3$, 75 MHz)



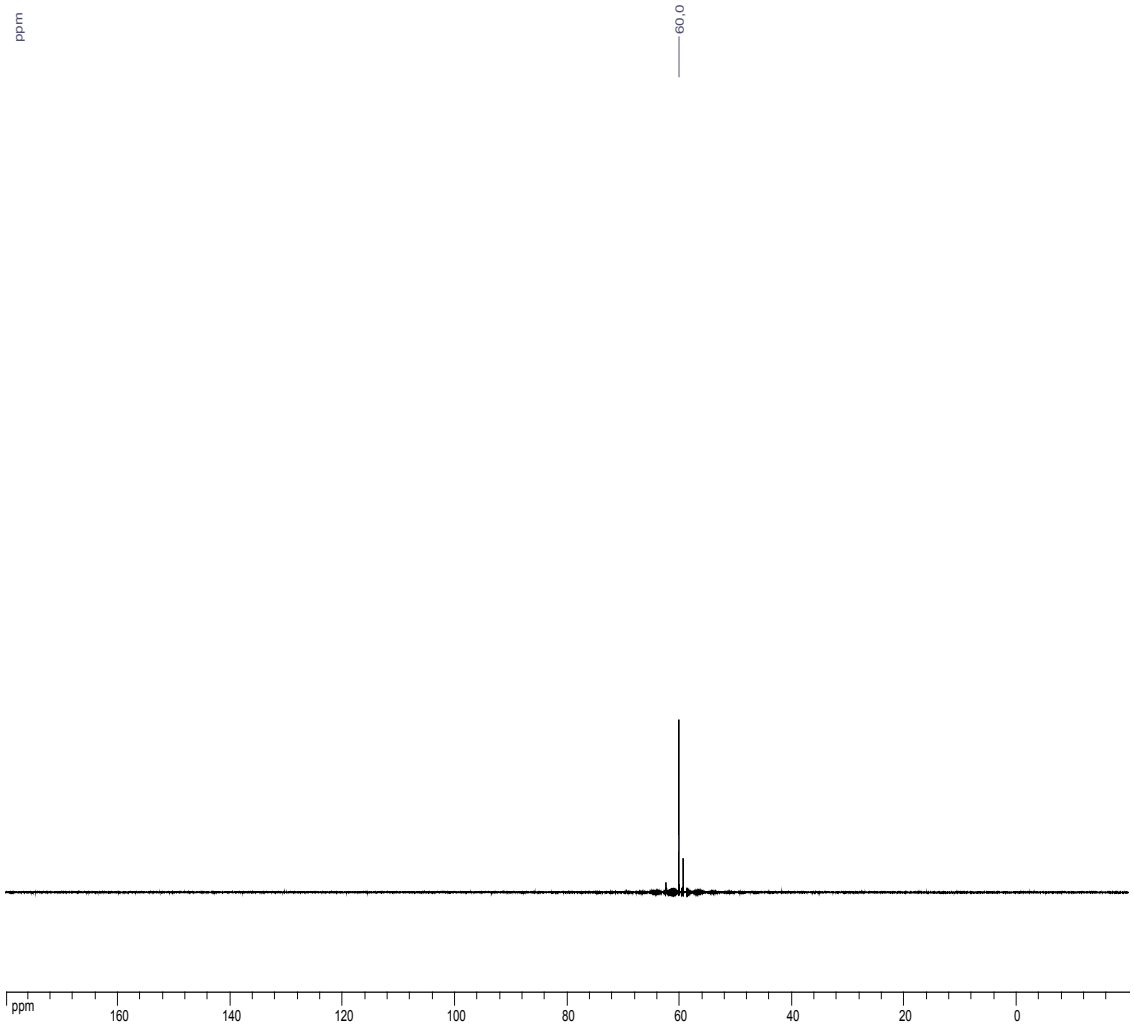
IV.16. ^{1}H NMR (Acetone-d_6, 300 MHz) (**6f**)



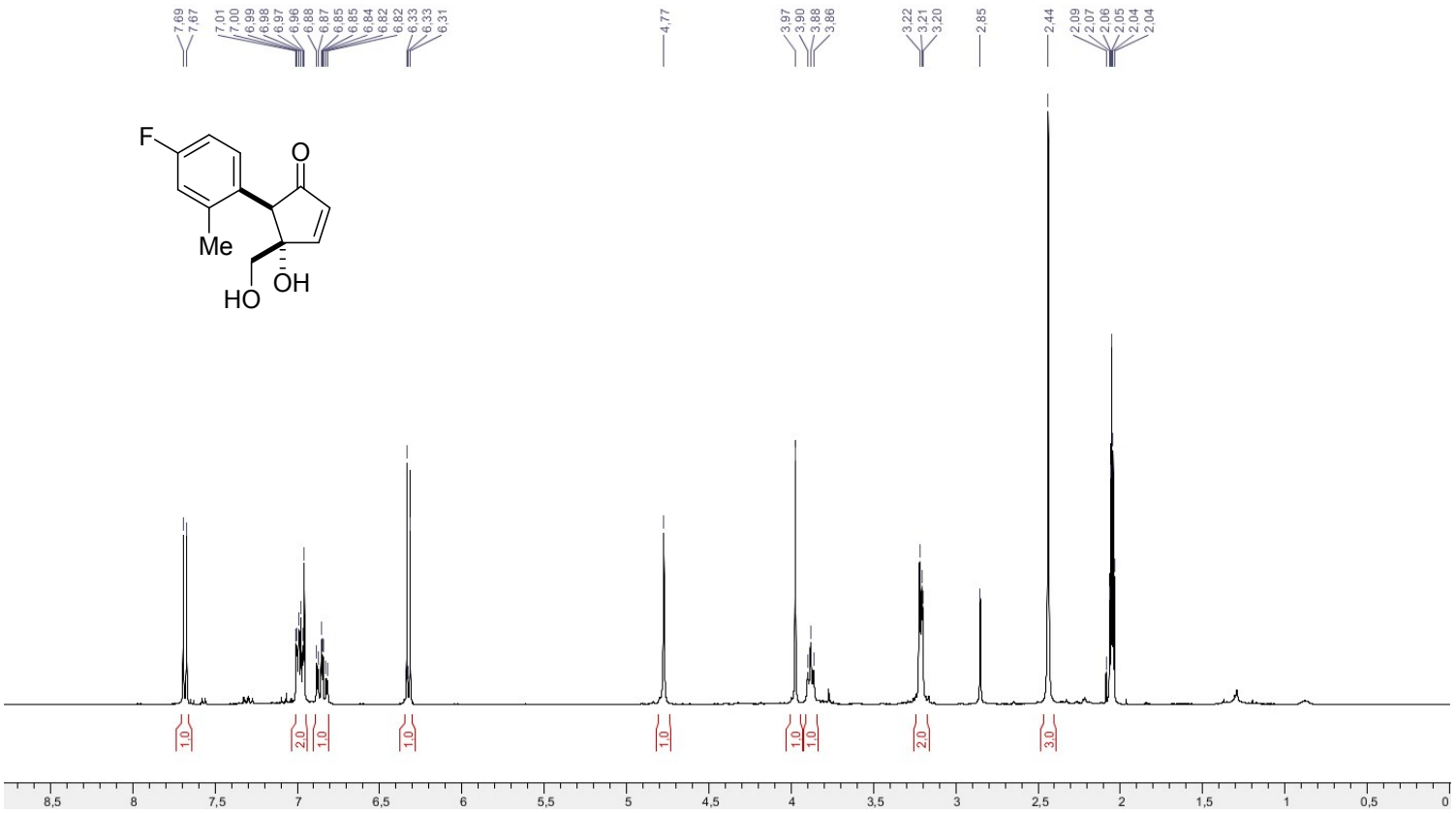
^{13}C NMR (Acetone-d_6, 75 MHz)



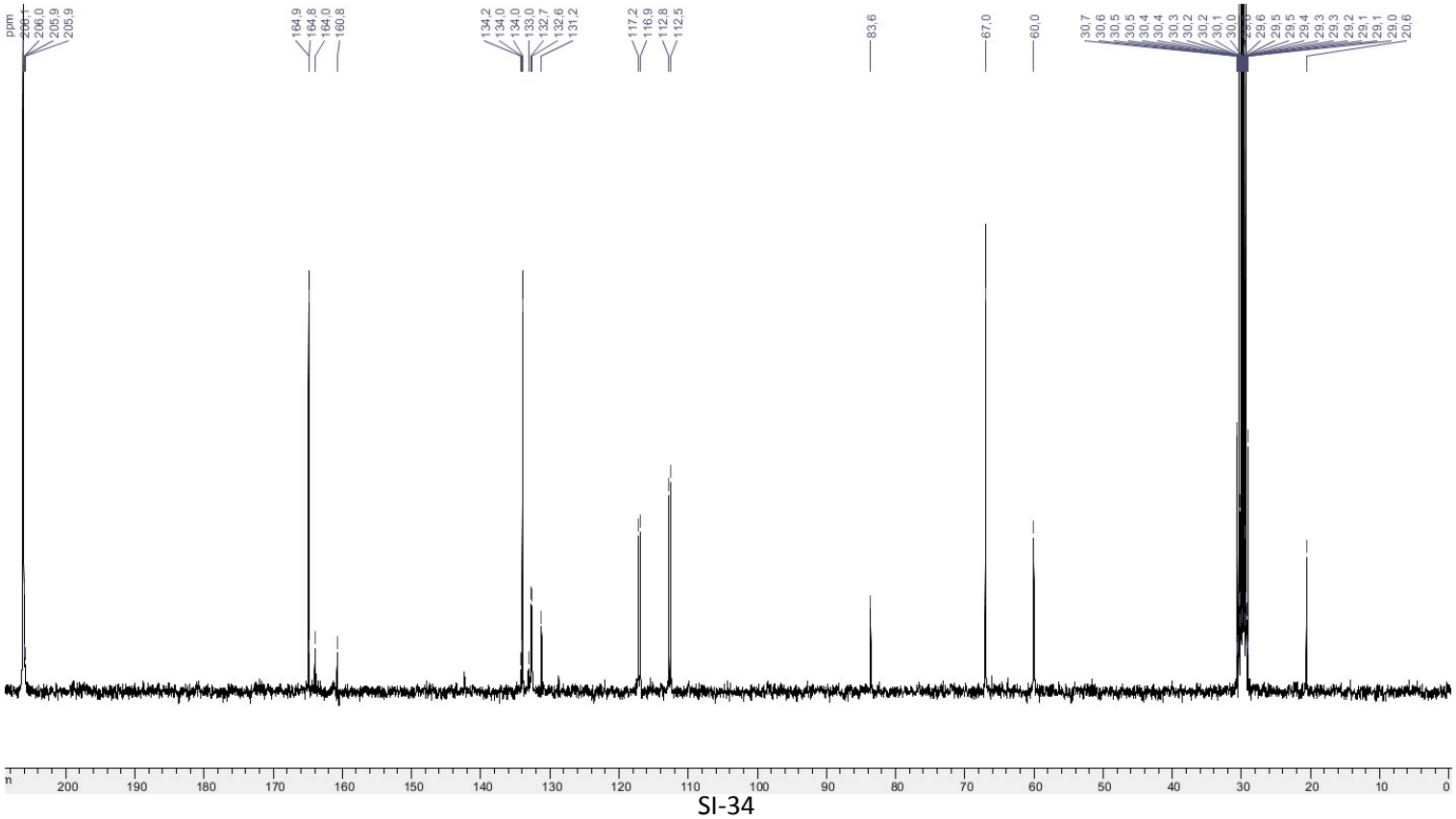
^{19}F-NMR (Acetone-d_6, 282 MHz)



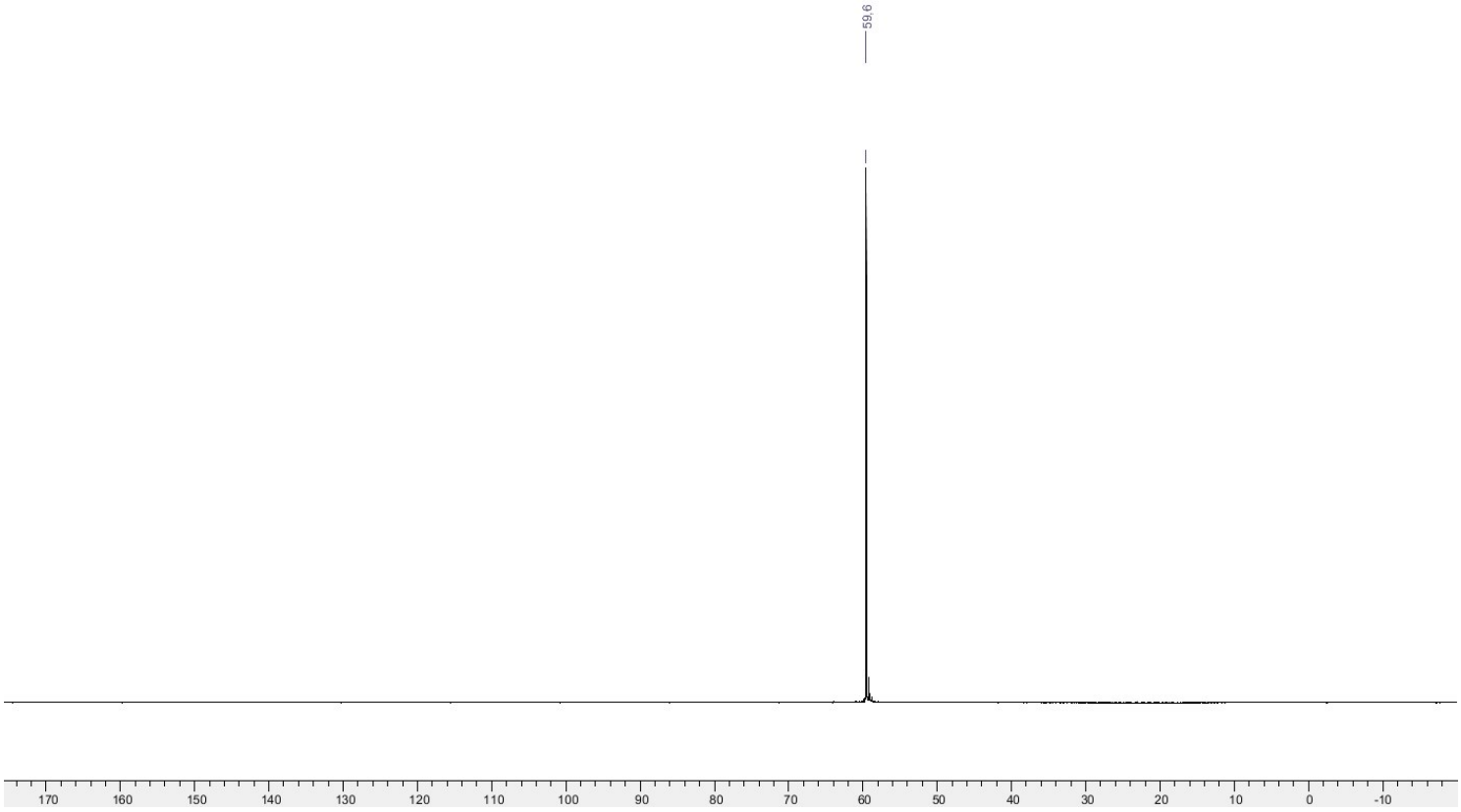
IV.17. ^{1}H NMR (Acetone-d_6, 300 MHz) (**6g**)



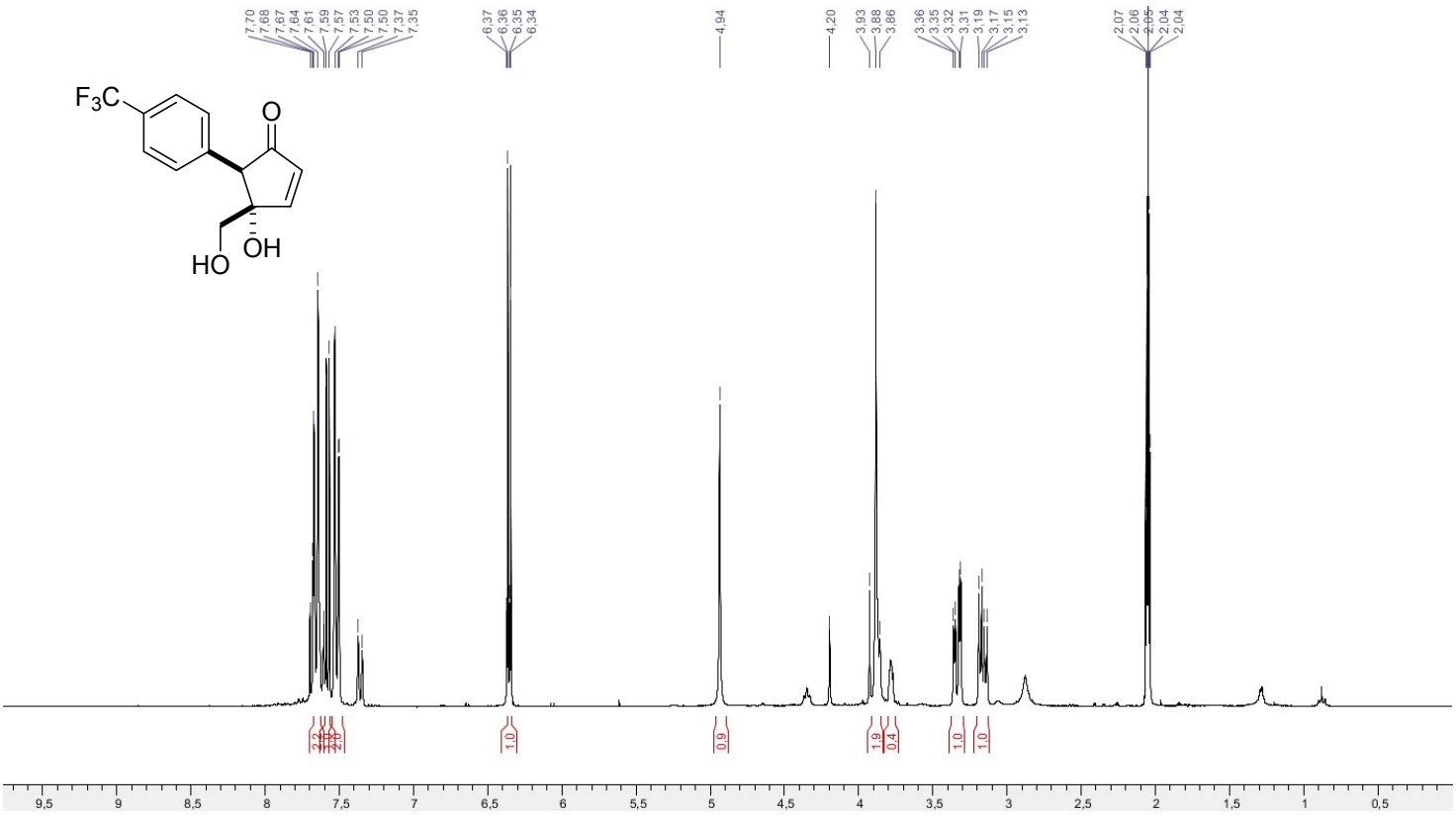
^{13}C NMR (Acetone-d_6, 75 MHz)



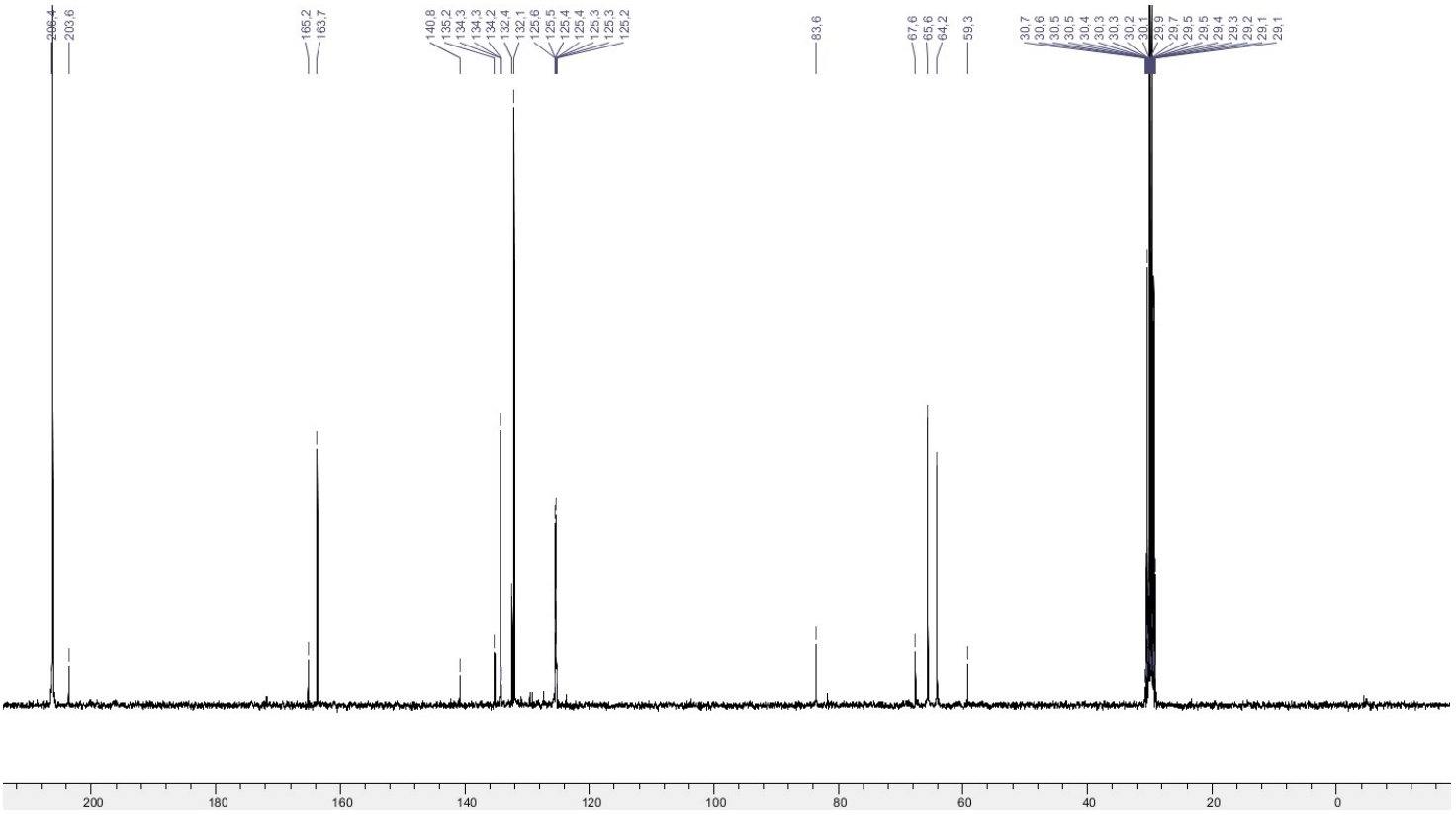
^{19}F-NMR (Acetone-d_6, 282 MHz)



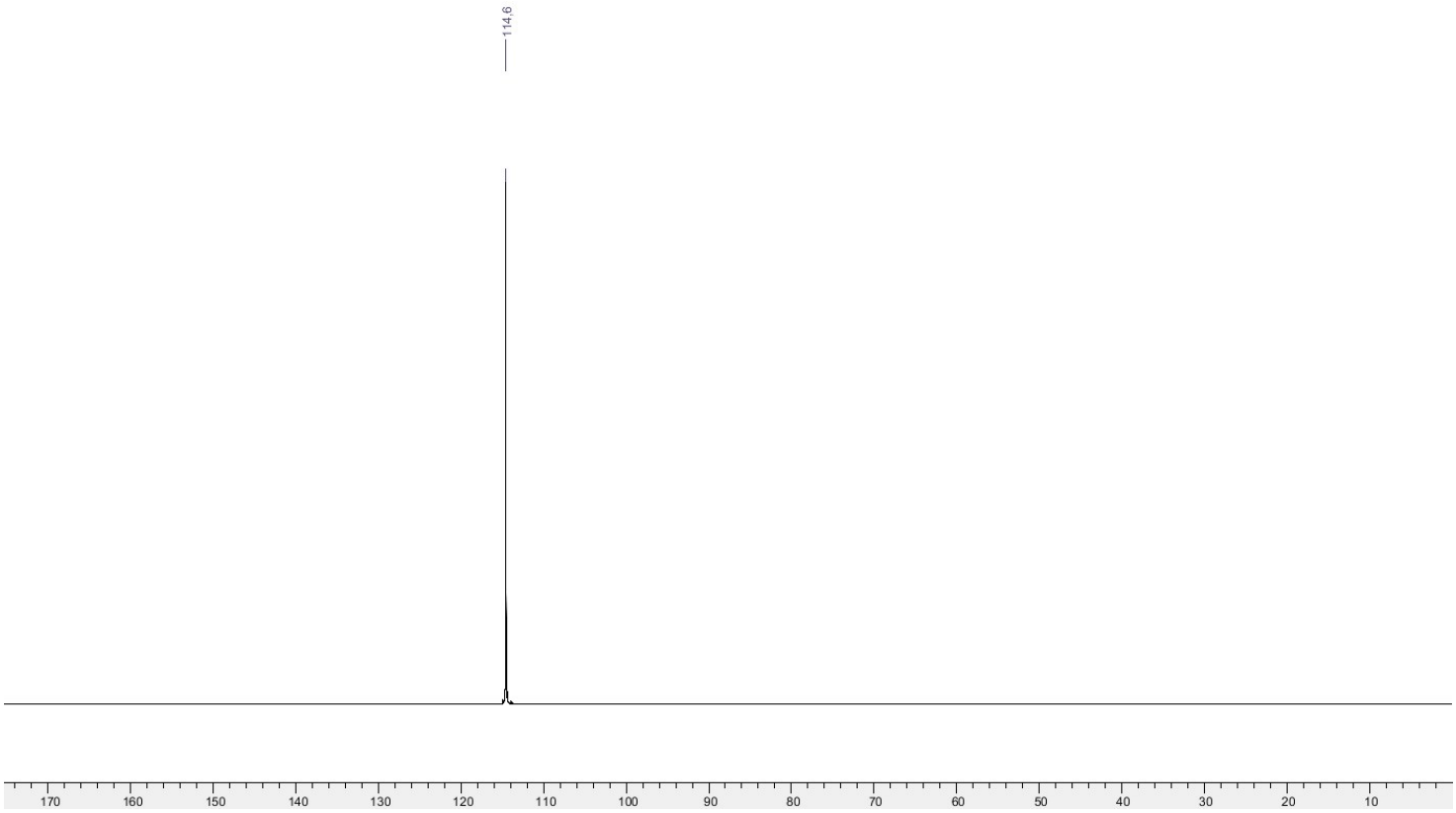
IV.18. ^{1}H NMR (Acetone-d_6, 300 MHz) (**6h**)



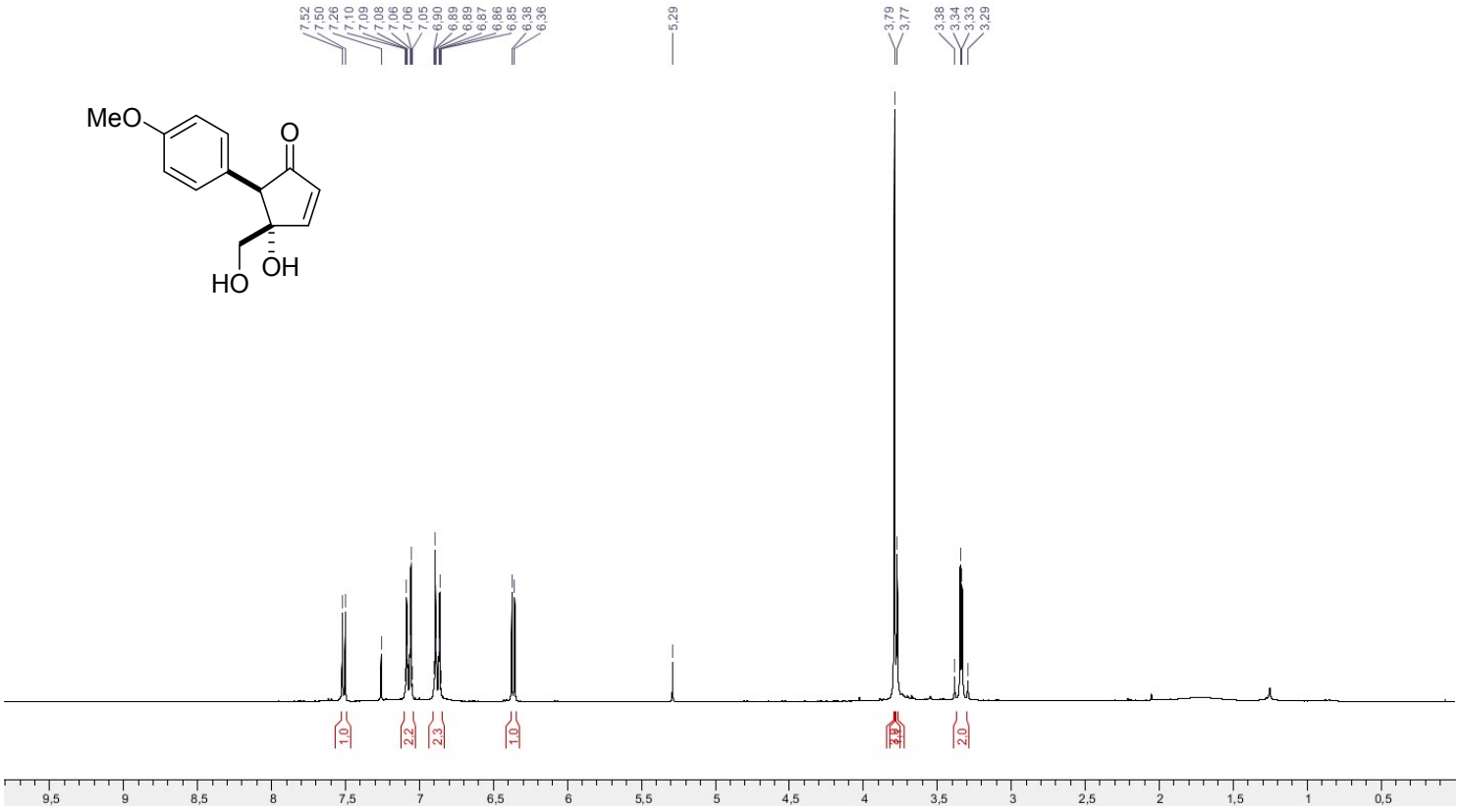
^{13}C NMR (Acetone-d_6, 75 MHz)



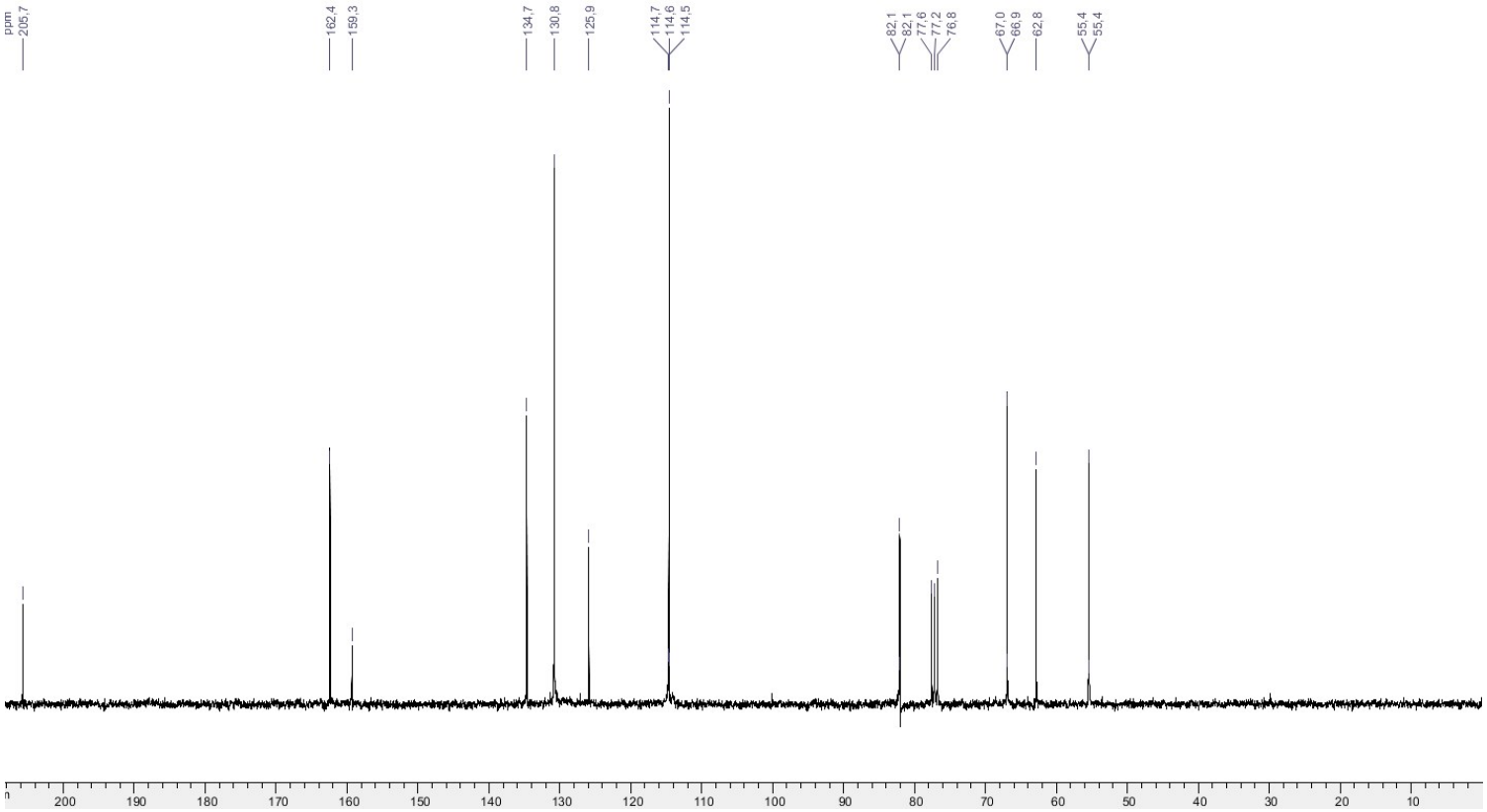
^{19}F-NMR (Acetone-d_6, 282 MHz)



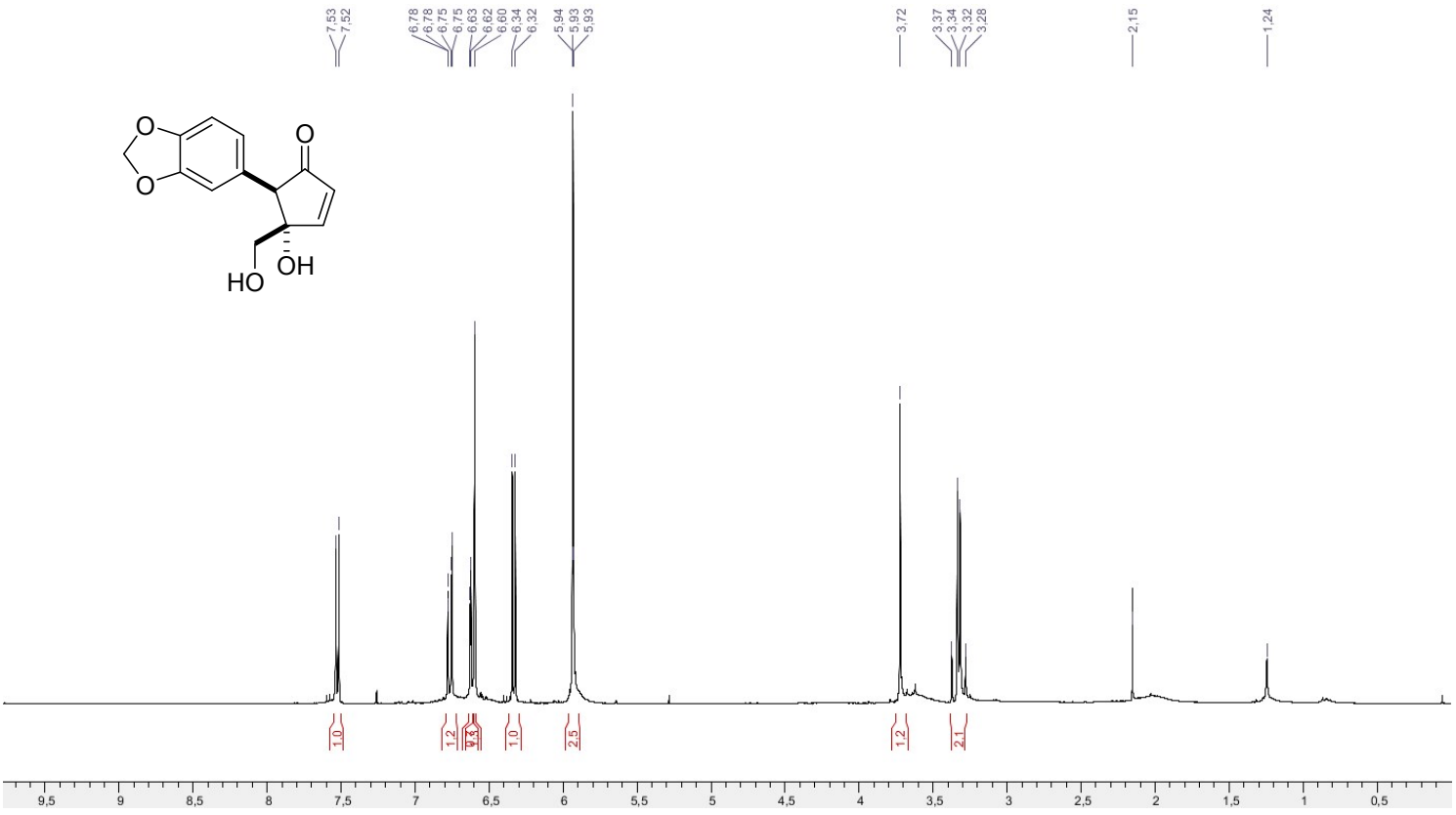
IV.19. ^{1}H NMR ($CDCl_3$, 300 MHz) (**6i**)



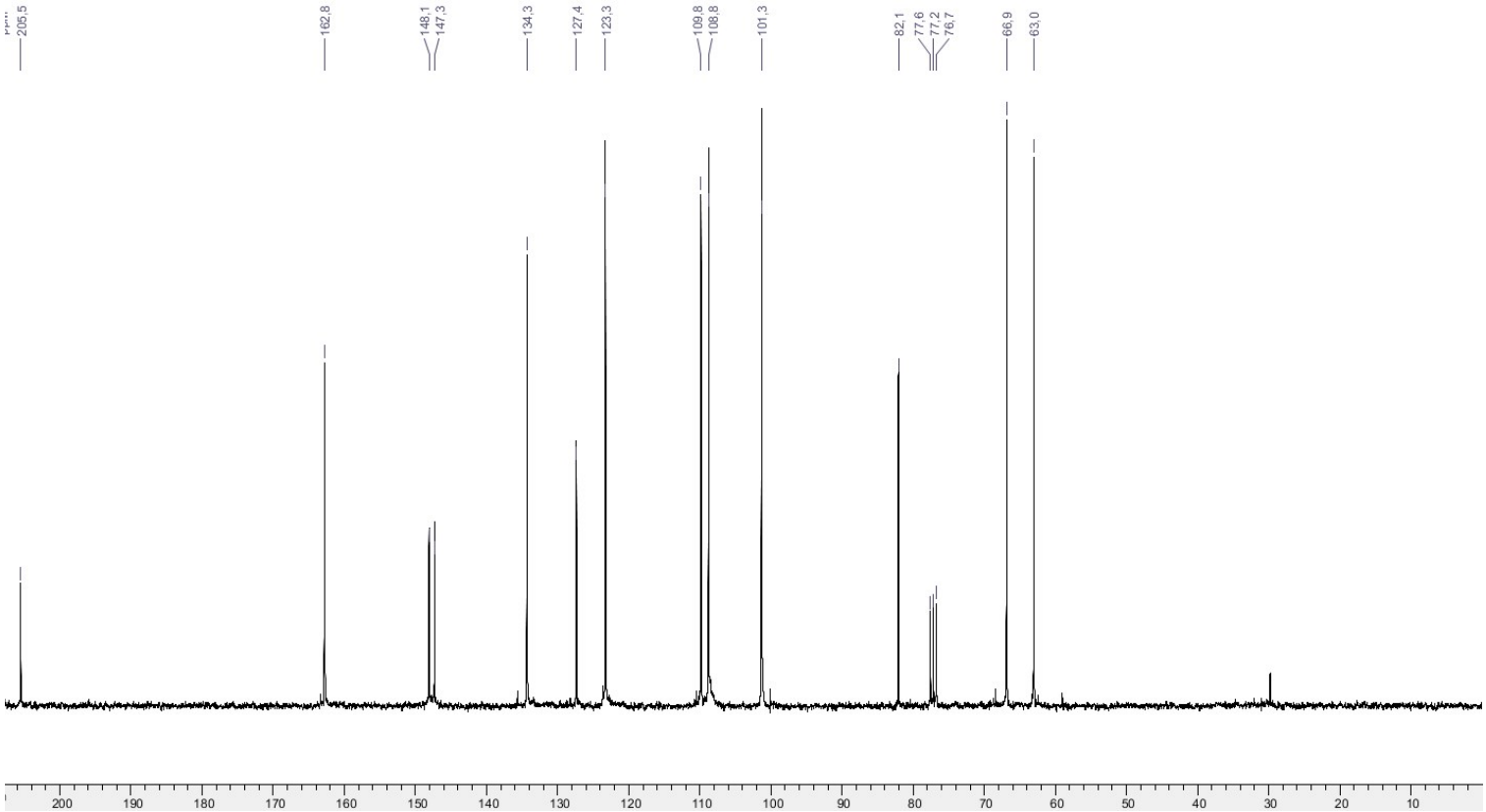
^{13}C NMR ($CDCl_3$, 75 MHz)



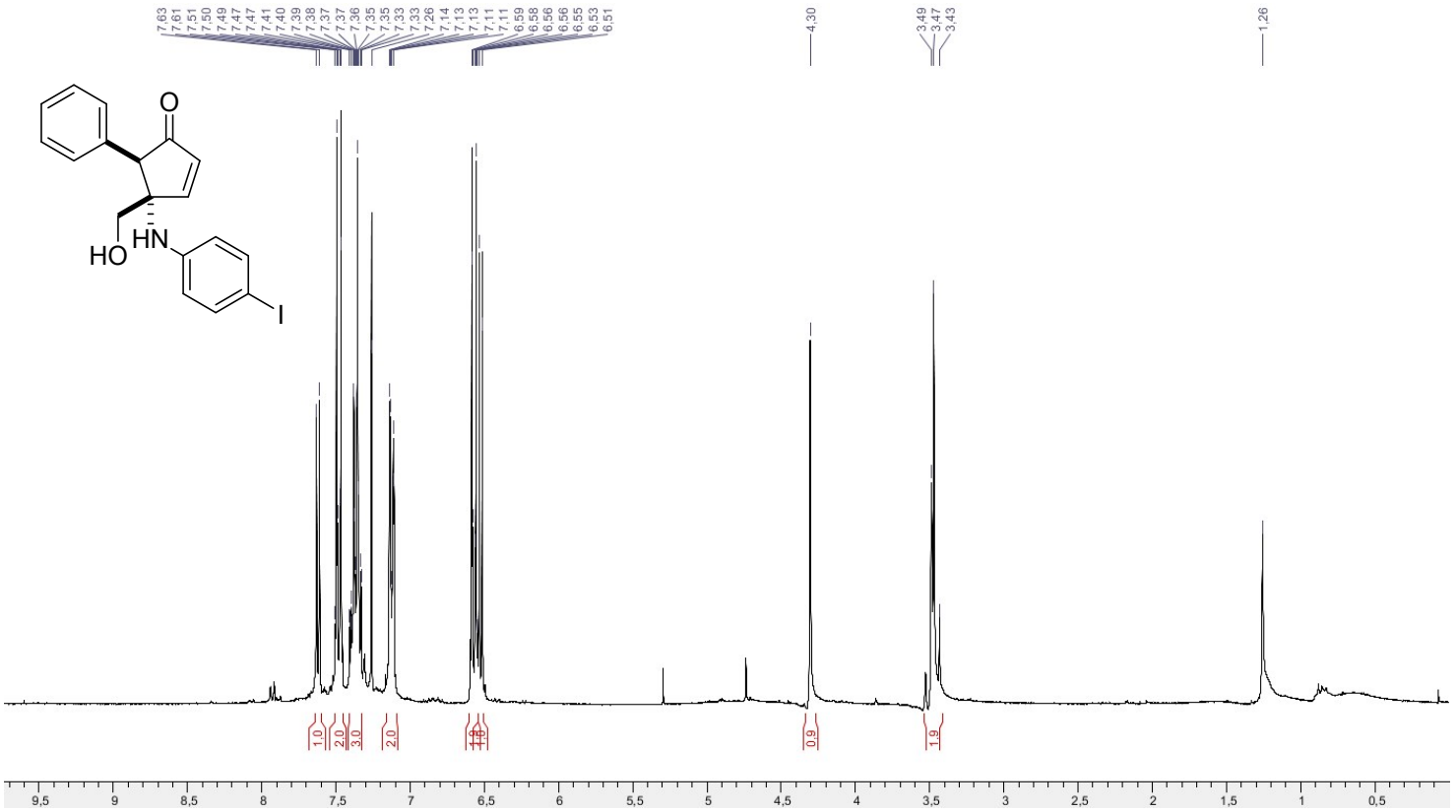
IV.20. ^{1}H NMR ($CDCl_3$, 300 MHz) (**6j**)



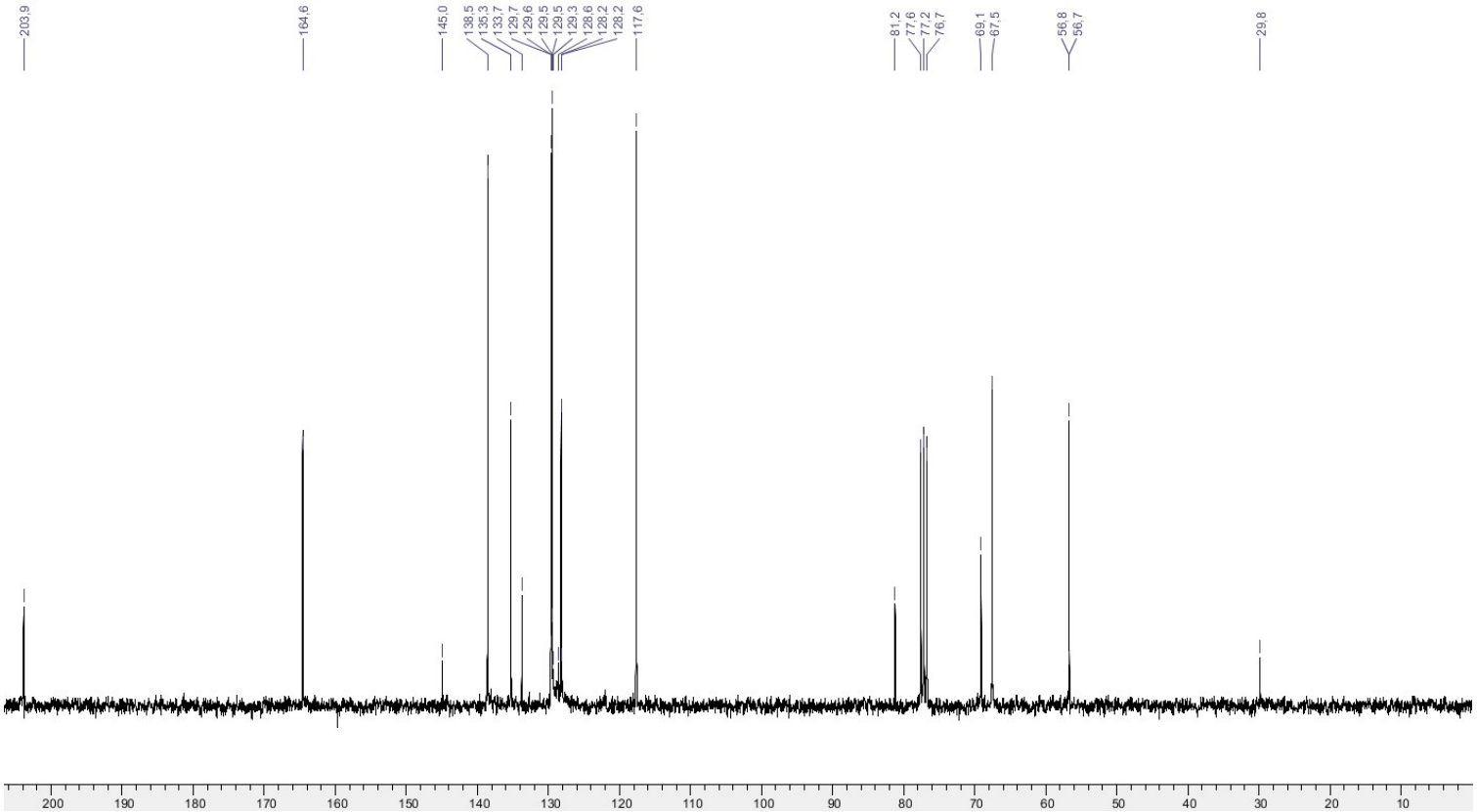
^{13}C NMR ($CDCl_3$, 75 MHz)



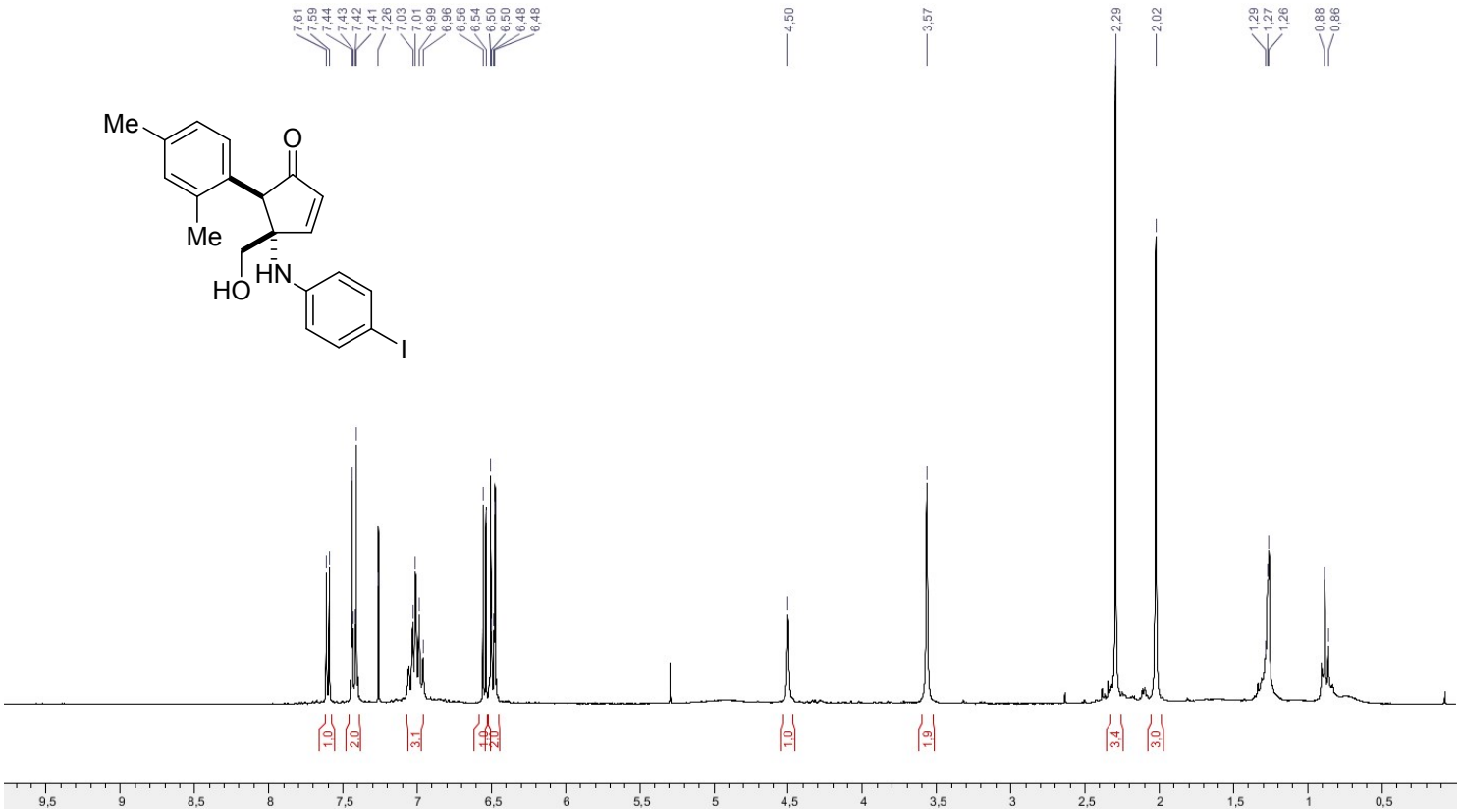
IV.21. ^{1}H NMR ($CDCl_3$, 300 MHz) (**8a**)



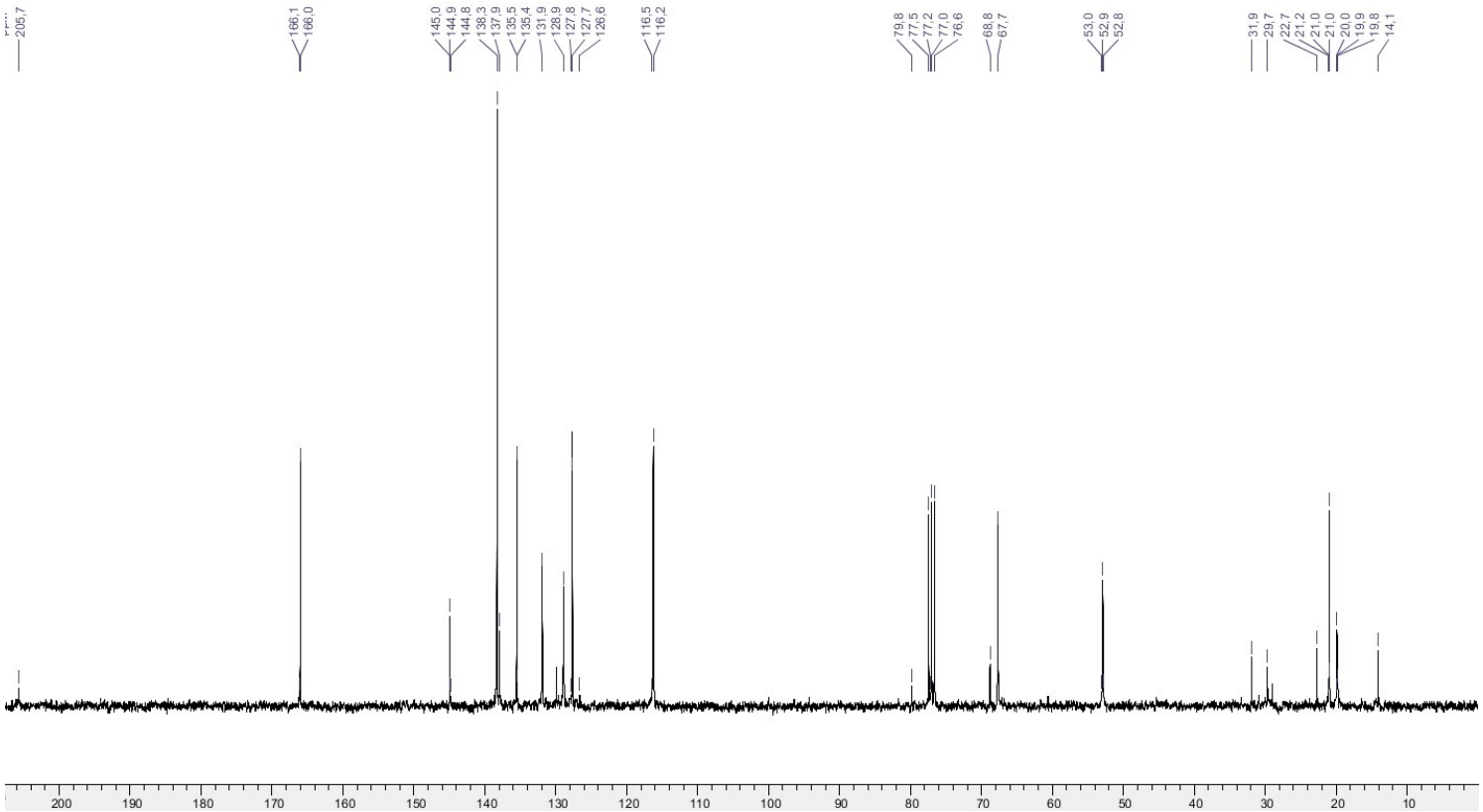
^{13}C NMR ($CDCl_3$, 75 MHz)



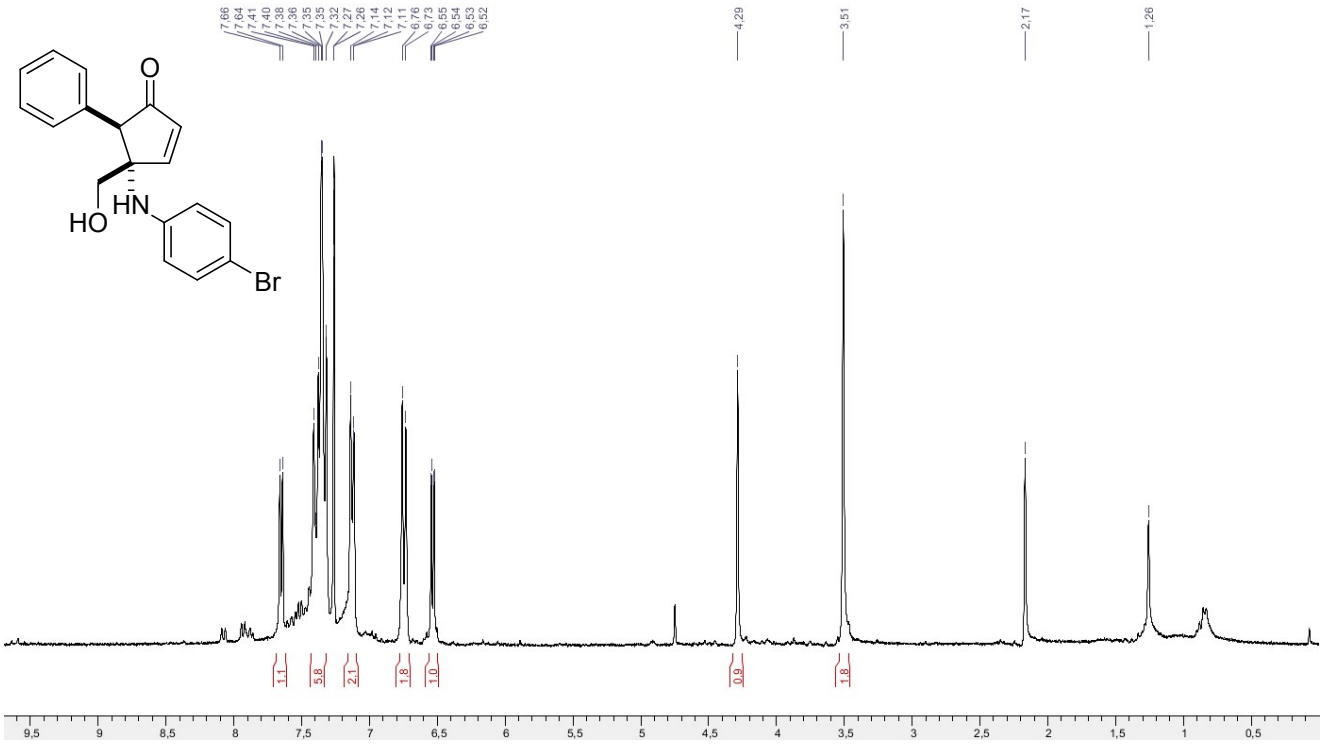
IV.22. ^{1}H NMR ($CDCl_3$, 300 MHz) (**8b**)



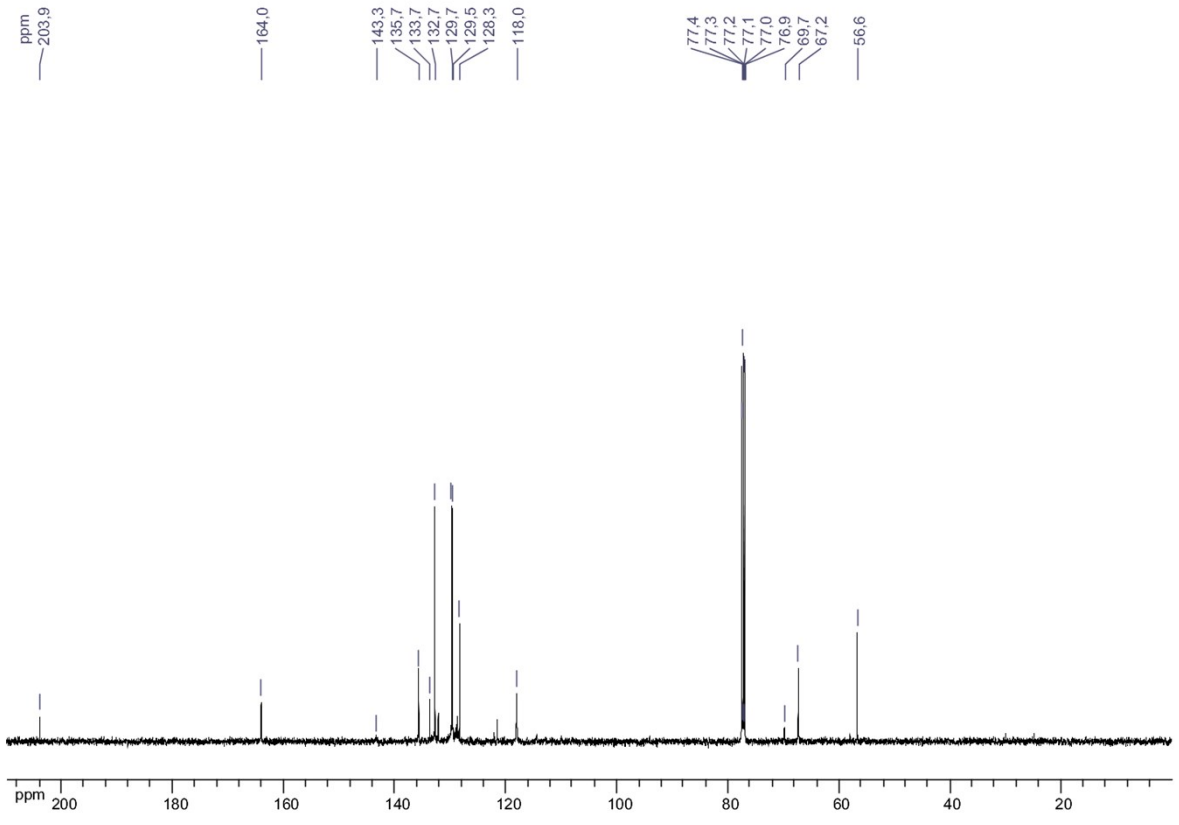
^{13}C NMR ($CDCl_3$, 75 MHz)



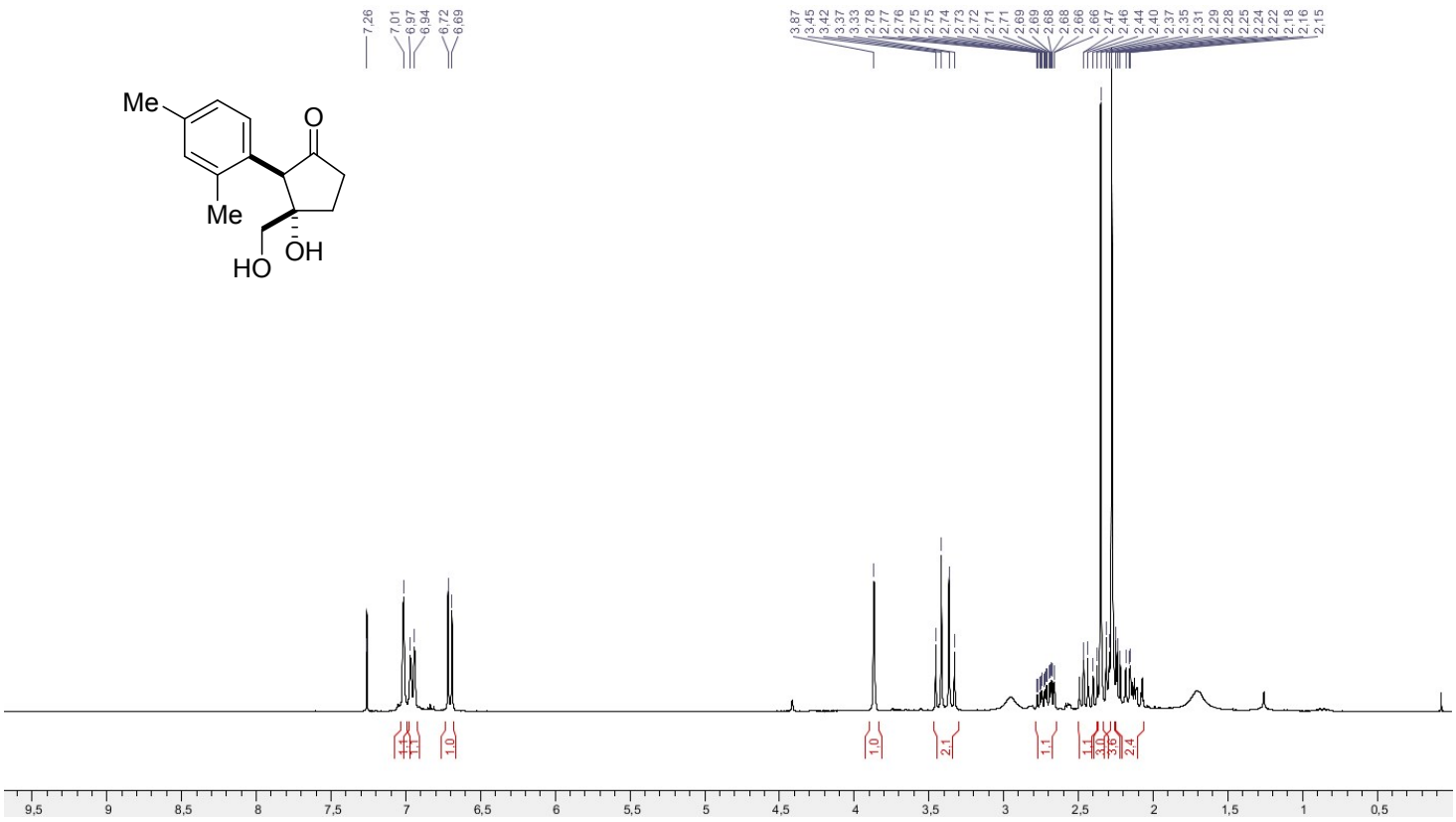
IV.23. ^{1}H NMR ($CDCl_3$, 300 MHz) (**8c**)



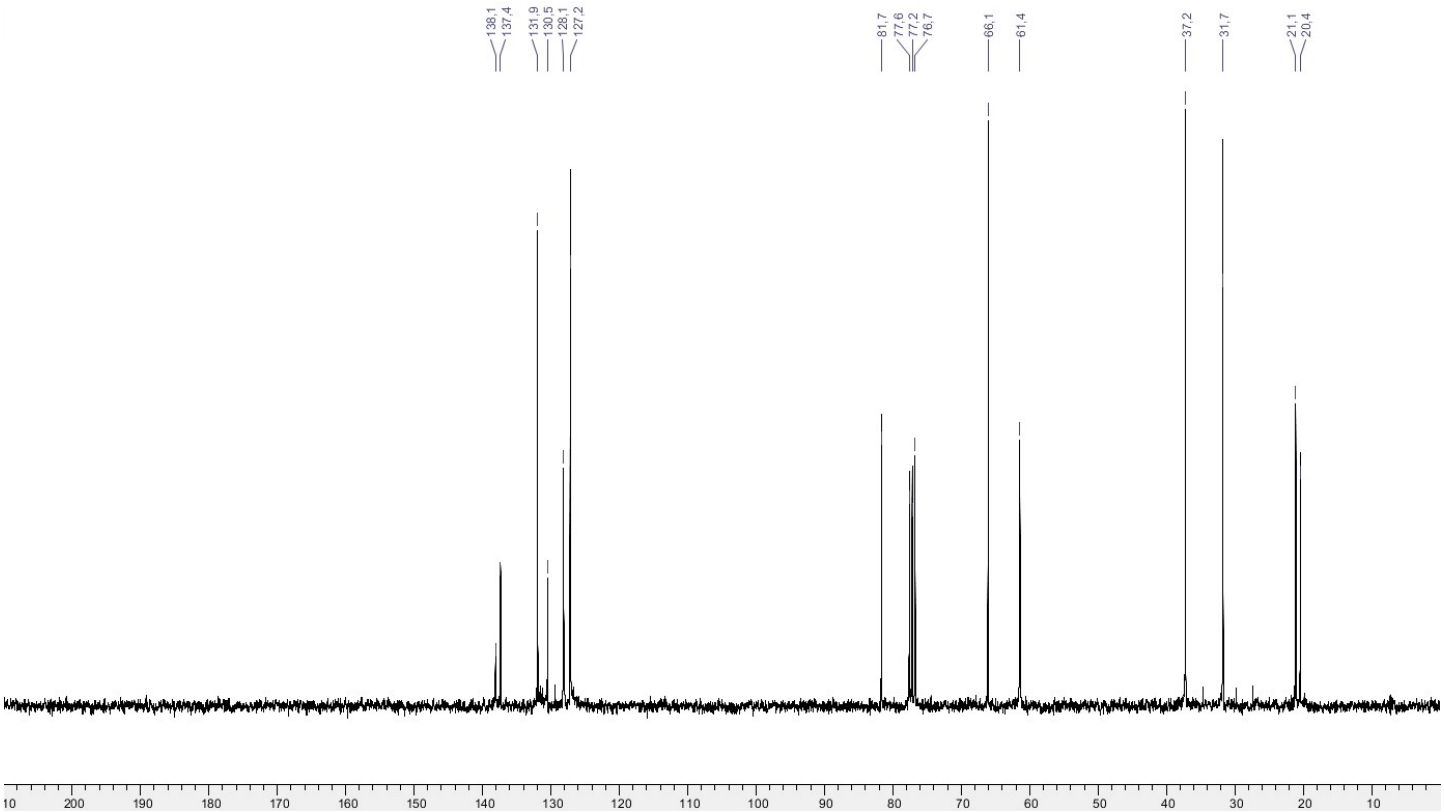
^{13}C NMR ($CDCl_3$, 75 MHz)



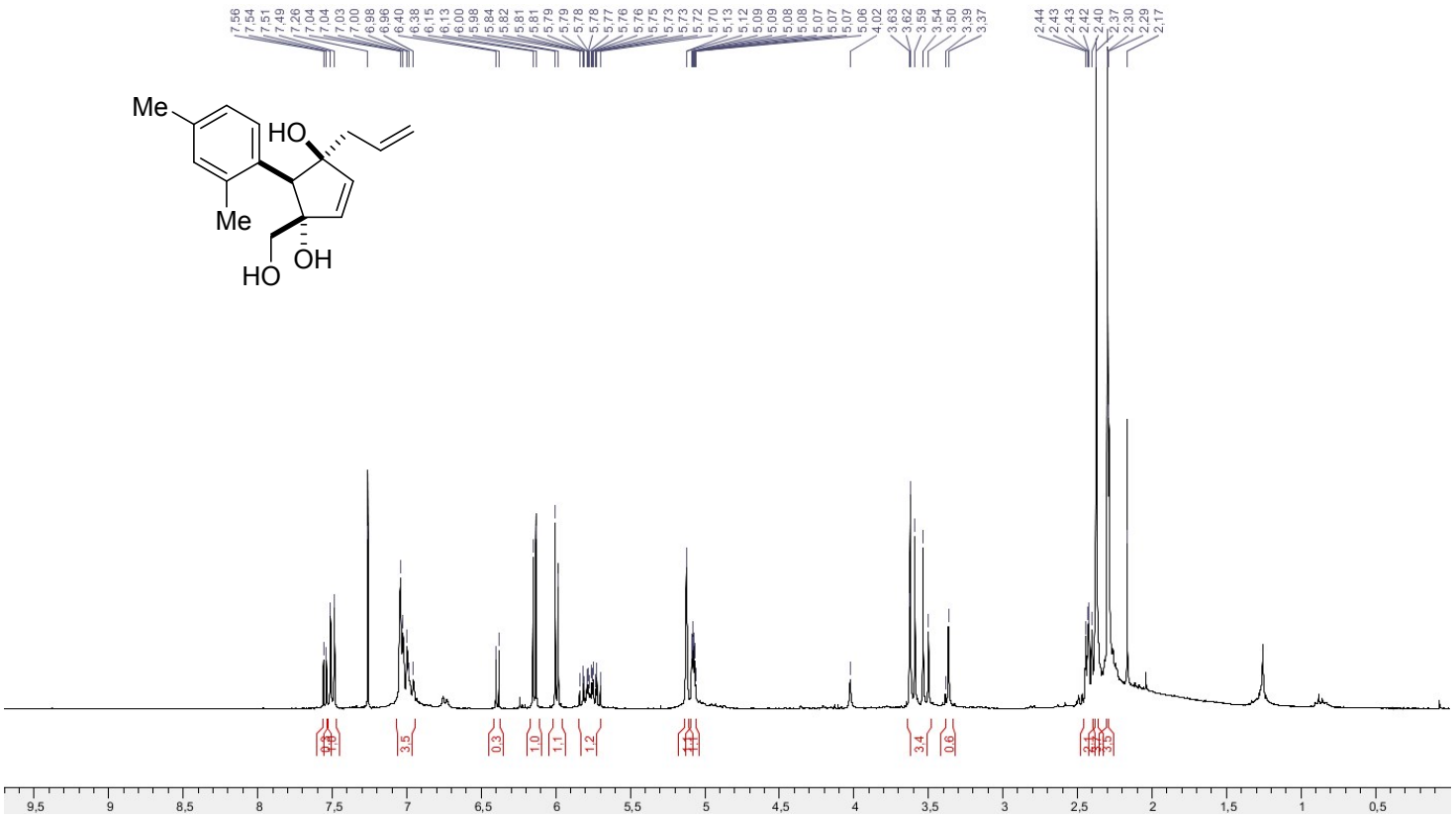
IV.24. ^{1}H NMR ($CDCl_3$, 300 MHz) (**9**)



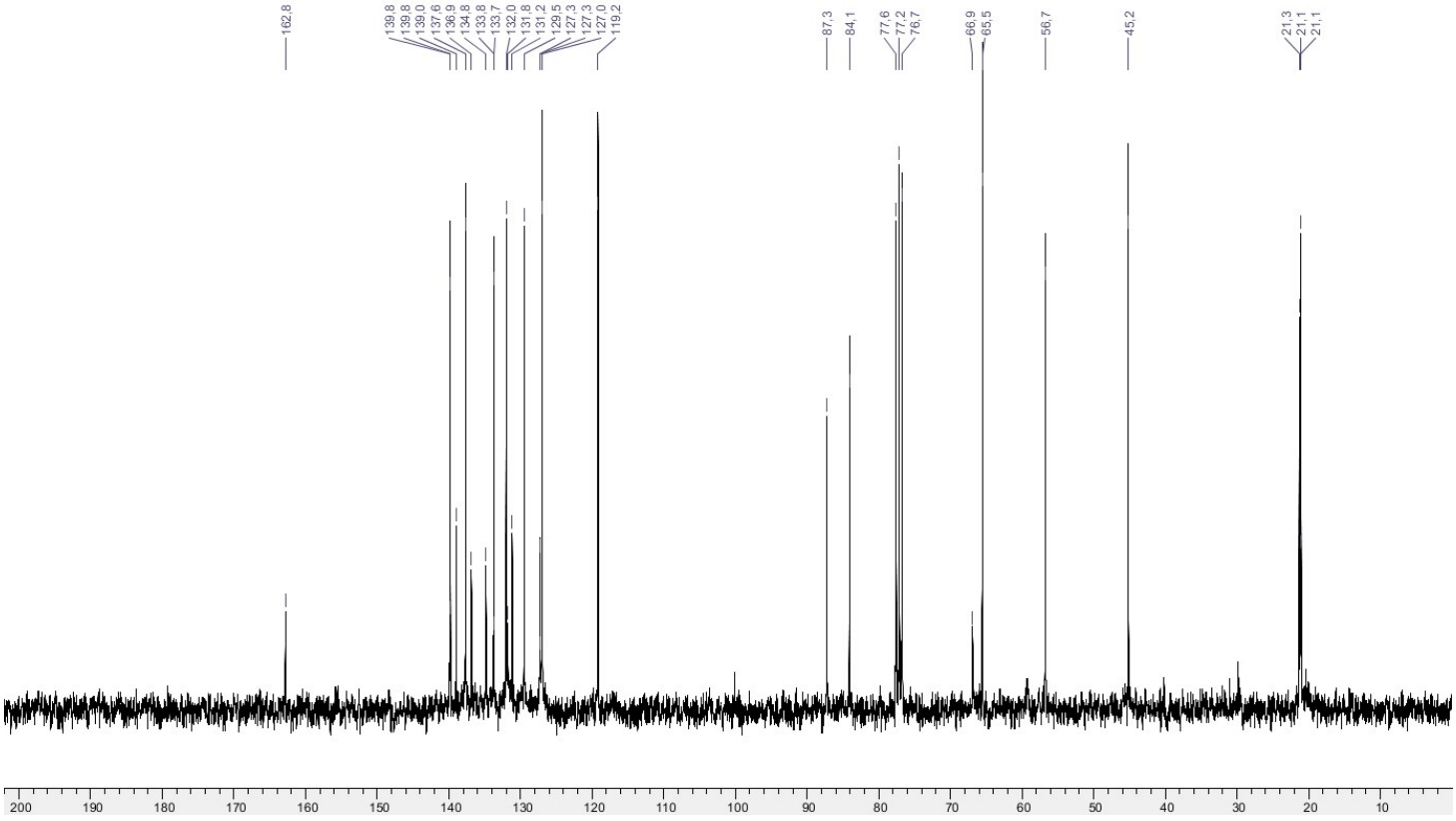
^{13}C NMR ($CDCl_3$, 75 MHz)

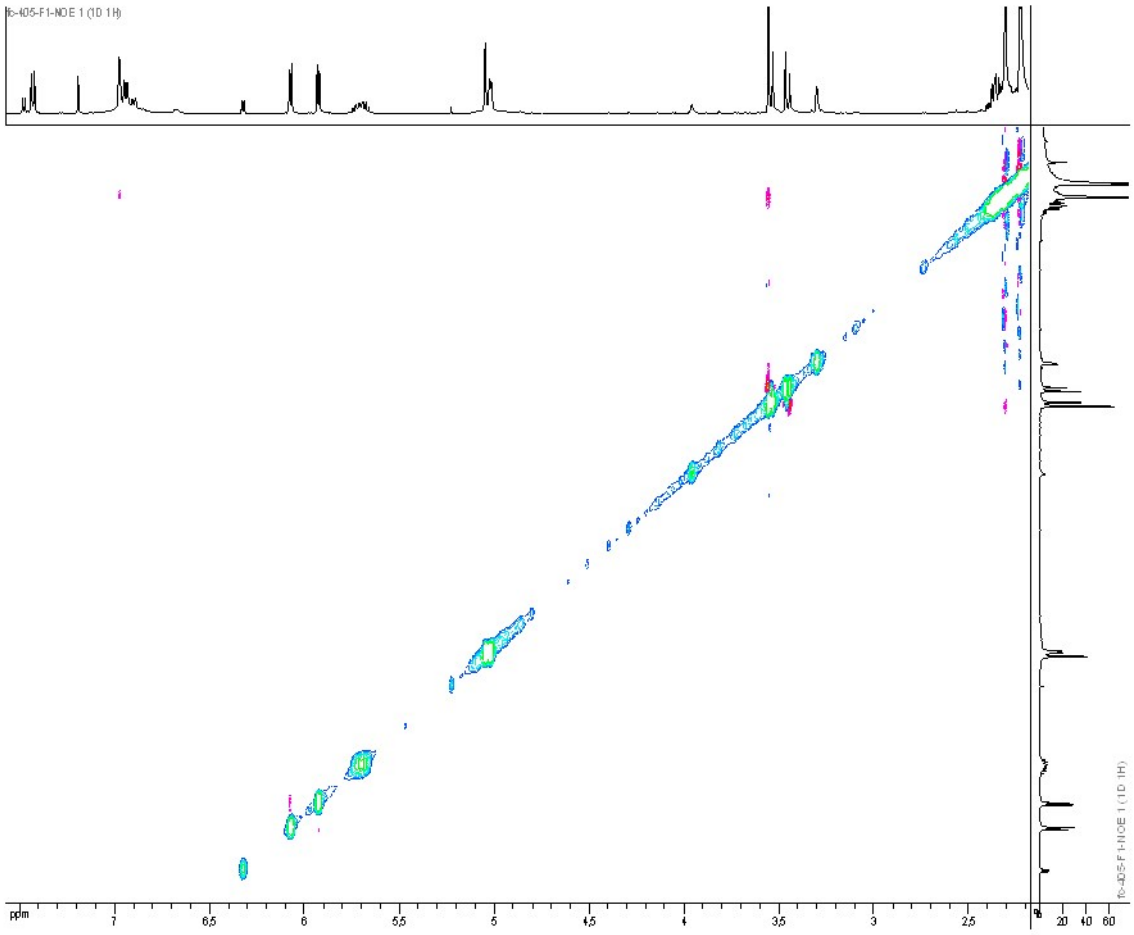


IV.25. ^{1}H NMR ($CDCl_3$, 300 MHz) (**10**)

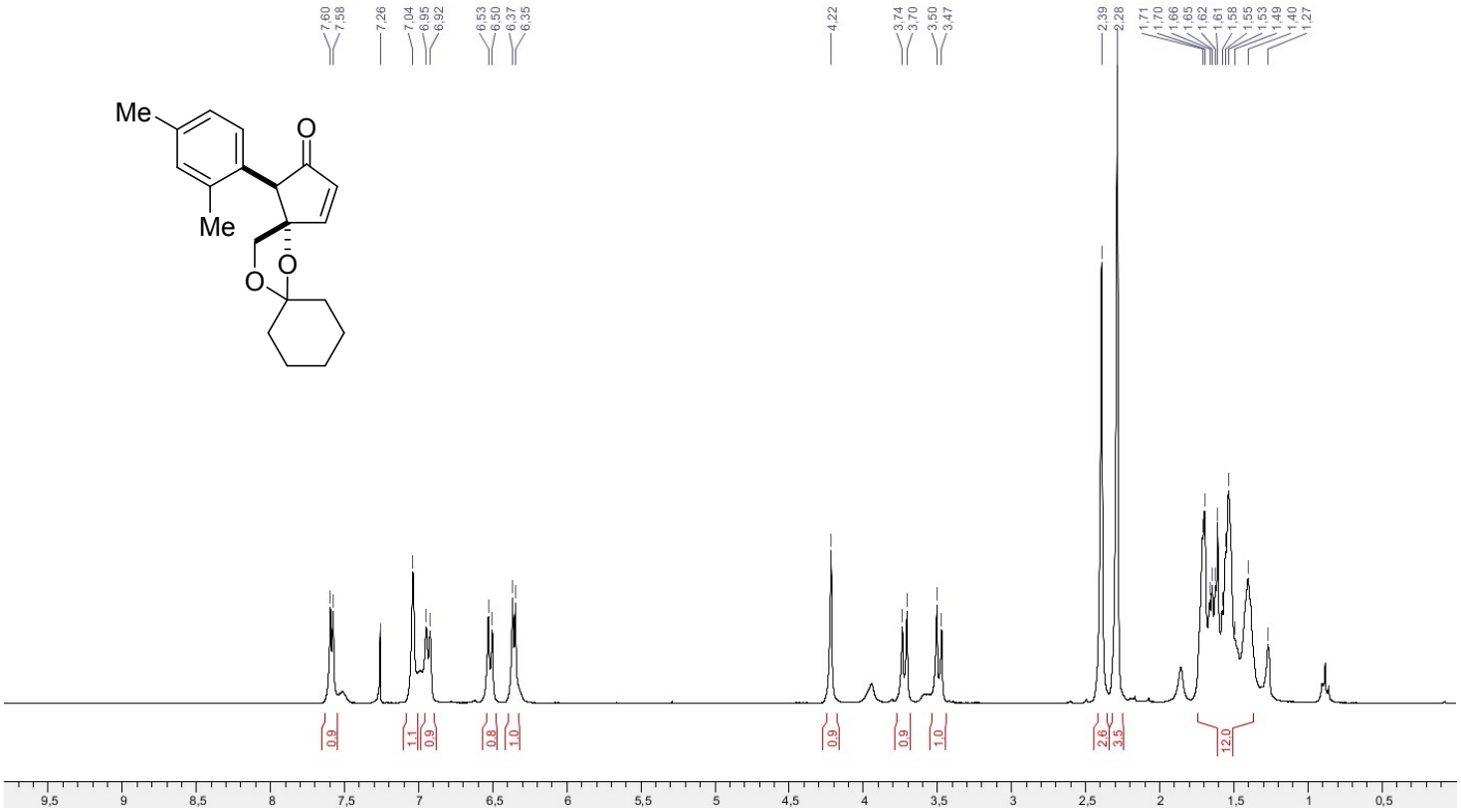


^{13}C NMR ($CDCl_3$, 75 MHz)

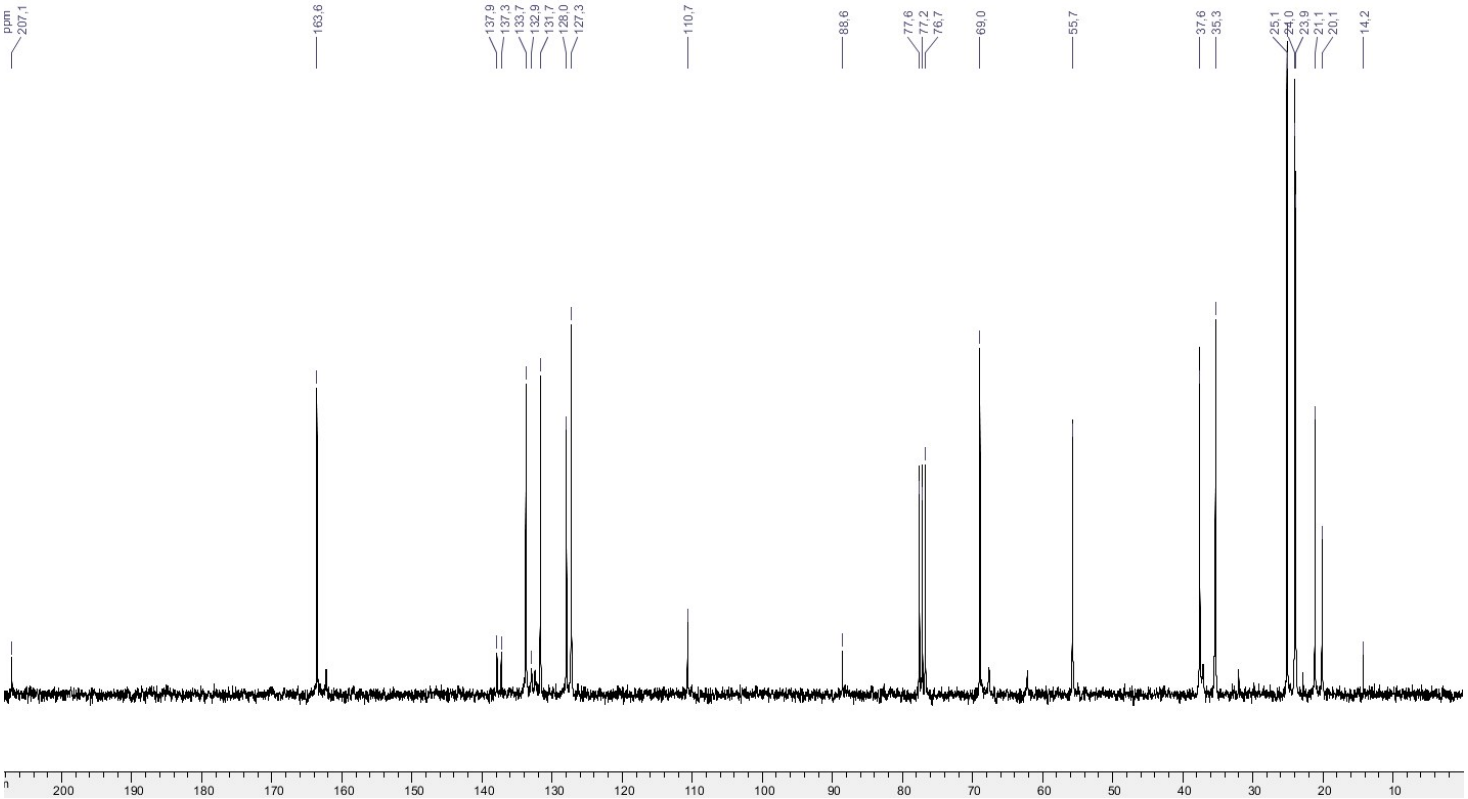



fs-405-F1-NOE 1 (1D 1H)
ppm
7
6,5
6
5,5
5
4,5
4
3,5
3
2,5
20
40
60
fs-405-F1-NOE 1 (1D 1H)

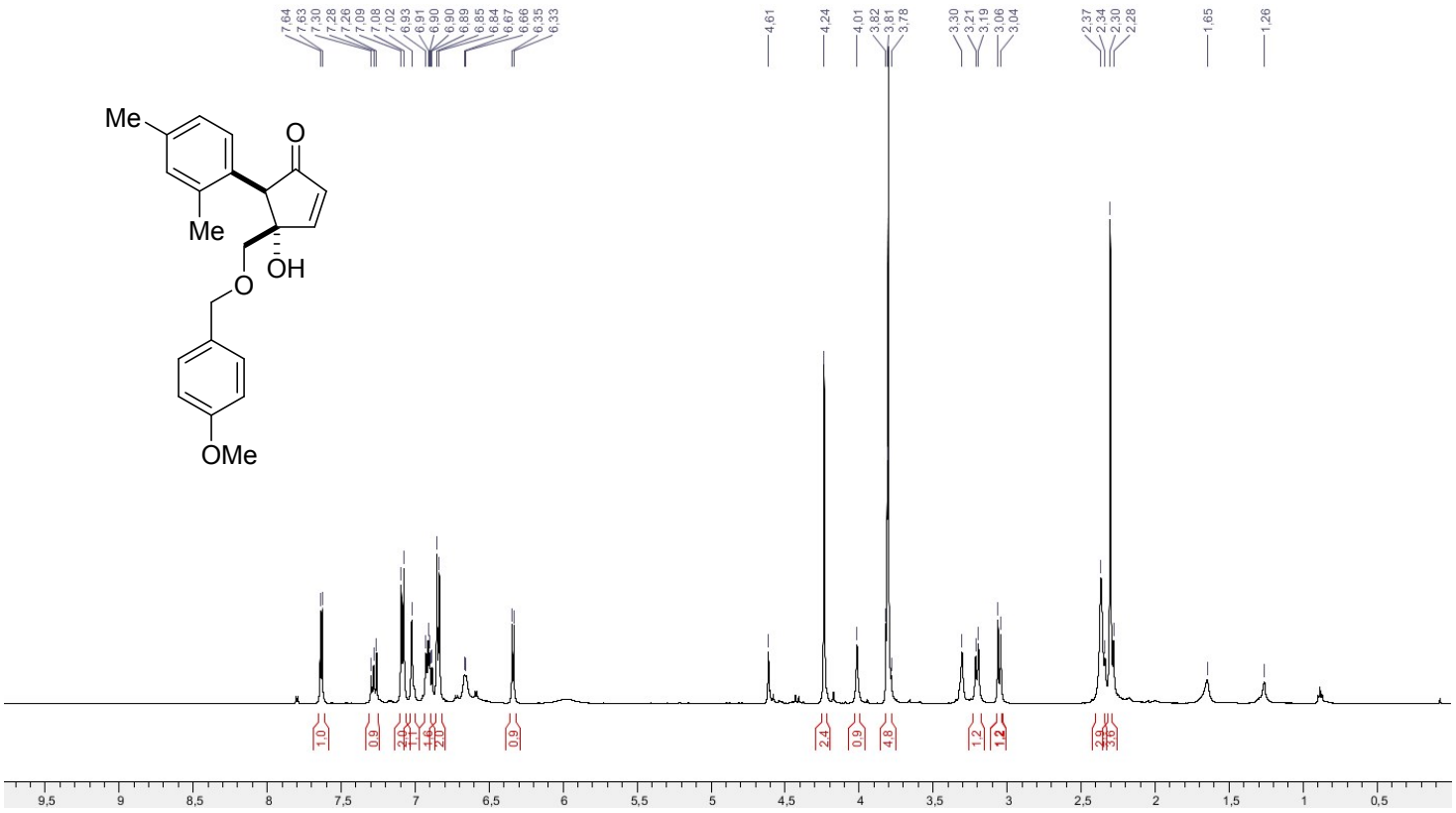
IV.26. ^{1}H NMR ($CDCl_3$, 300 MHz) (**11**)



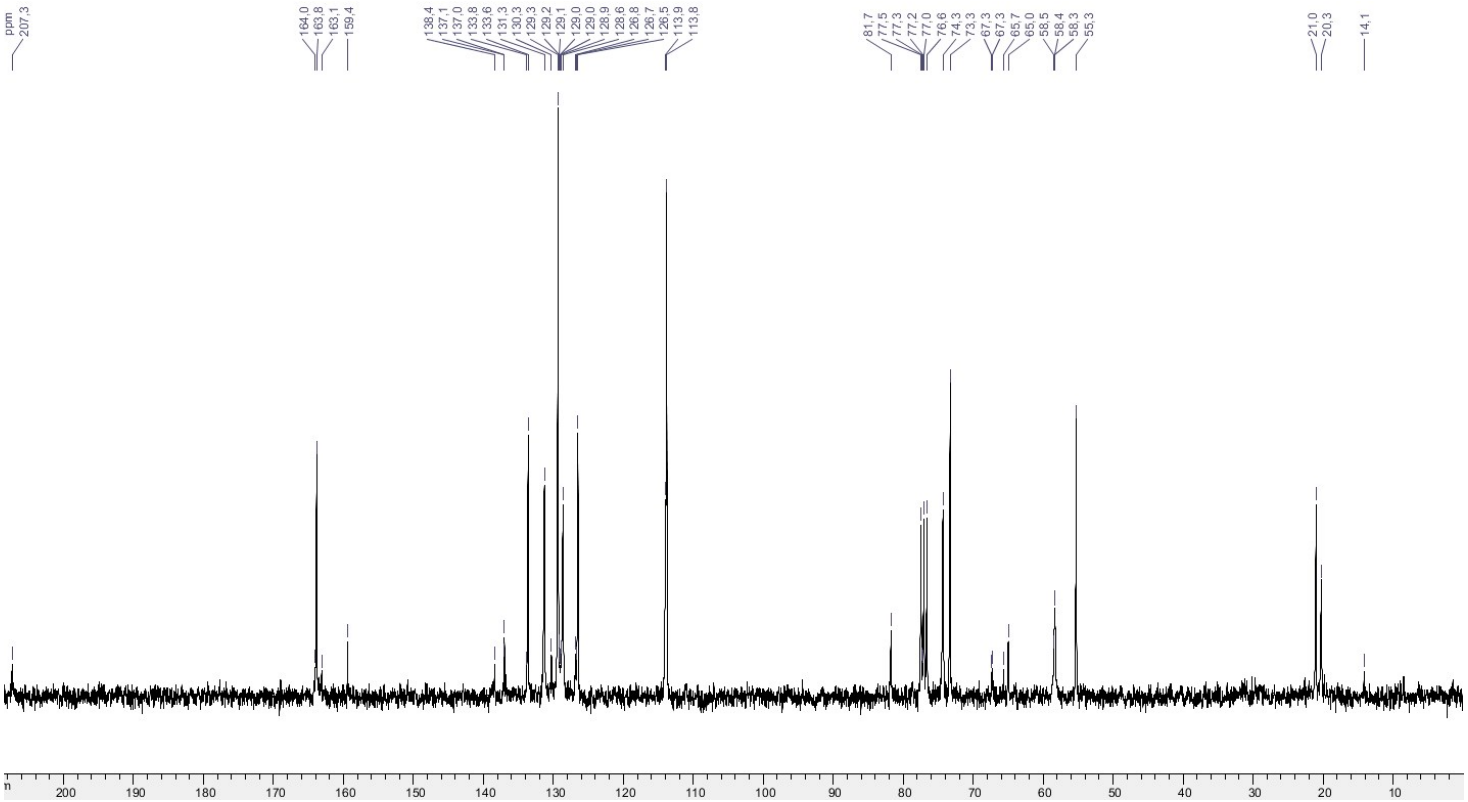
^{13}C NMR ($CDCl_3$, 75 MHz)



IV.27. ^{1}H NMR ($CDCl_3$, 300 MHz) (**12**)



^{13}C NMR ($CDCl_3$, 75 MHz)



V. X-ray diffraction analysis of compound 6d.

A colourless thick plate suitable to single crystal X-Ray Diffraction analysis grew by *slow evaporation* from a mixture of methanol/water solution. XRD experiment was performed on a Rigaku MM007 HF rotating-anode diffractometer, using Cu-Kα radiation (λ =1.54187 Å) delivered through Osmic CMF optics and detected by a Rapid II curved Image Plate at room temperature. Data reduction and scaling were carried out with an empirical absorption correction, including a treatment for Lorentz and polarization effects, using the program *Fs_Process*[1] as implemented into CrystalClear 2.0 software.[1] The structure was solved by Intrinsic Phasing methods,[2] then refined by full matrix least squares on F^2 using the SHELXL-2017/1.[3] Anisotropic thermal parameters were used for all non-hydrogen atoms and even if the H atoms were located in residual maps in vicinity of the molecule of interest, they all were refined as riding, with U_{eq} values set at 1.2U_{eq} (parent atom) (1.5 for the methyl groups or hydroxyl oxygen atoms). Regard to the water molecule that develops a complex network of h-bonds (figure S1) forming hydrophilic layers parallel to (0 0 1) at z = 0 and ½ sandwiched by hydrophobic phenantrene layers (figure S2), bond distances between hydrogen and oxygen atoms were restrained to 0.82 Å with sd 0.02.

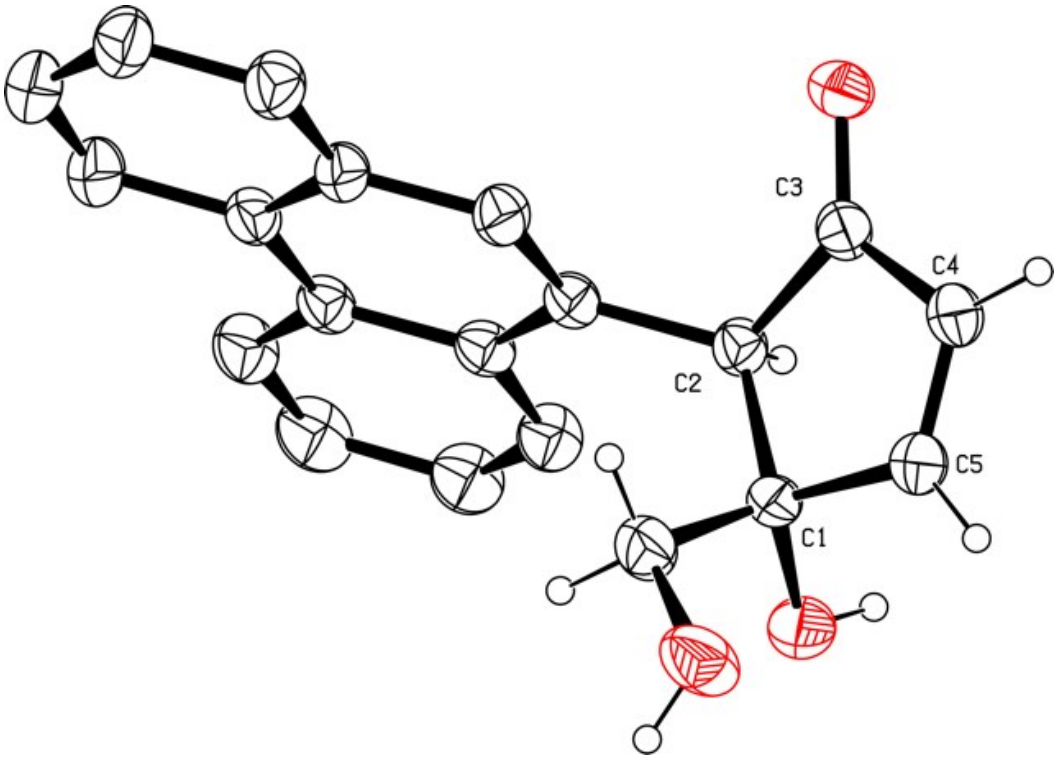


Figure S1: ORTEP view of compound **6d**.

Crystal data and structure refinement for **Compound 6d**.

Identification code	**6c**	
Empirical formula	$C_{20}H_{16}O_3 + [H_2O]$	
Formula weight	322.34	
Temperature	293(2) K	
Wavelength	1.54187 Å	
Crystal system	Monoclinic	
Space group	$P2_1/n$	
Unit cell dimensions	a = 10.8748(4) Å	α= 90°.
	b = 6.9108(2) Å	β= 90.181(6)°.
	c = 42.592(3) Å	γ = 90°.
Volume	3200.9(3) $Å^3$	
Z	8	
Density (calculated)	1.338 Mg/m^3	
Absorption coefficient	0.756 mm^{-1}	
F(000)	1360	
Crystal size	0.42 x 0.38 x 0.12 mm^3	
θ range for data collection	4.152 to 68.267°.	
Index ranges	$-11 \le h \le 13$, $-5 \le k \le 8$, $-51 \le l \le 51$	
Reflections collected	20575	
Independent reflections	5711 [R(int) = 0.0476]	
Completeness to θ = 67.687°	97.4 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.000 and 0.713	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5705 / 4 / 449	
Goodness-of-fit on F^2	1.090	
Final R indices [$I>2\sigma(I)$]	R1 = 0.0537, wR2 = 0.1251	
R indices (all data)	R1 = 0.0885, wR2 = 0.1611	
Largest diff. peak and hole	0.189 and -0.264 $e.Å^{-3}$	

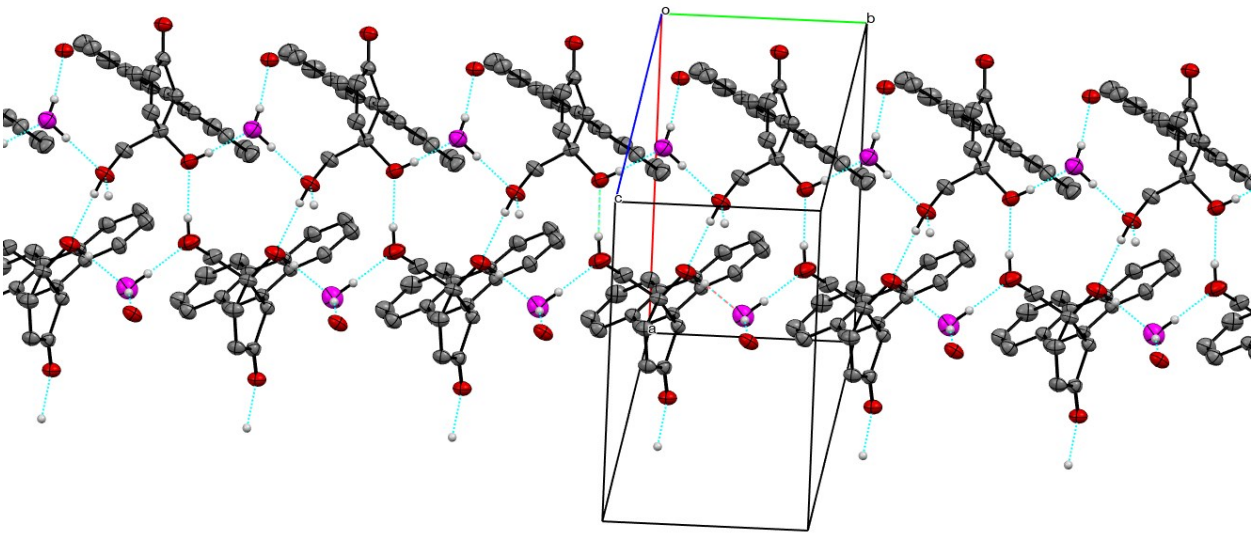


Figure S2: highlight of the h-bond (in dashed cyan) network viewed down the ***c*** axis of the crystal. Water molecules are coloured in magenta.

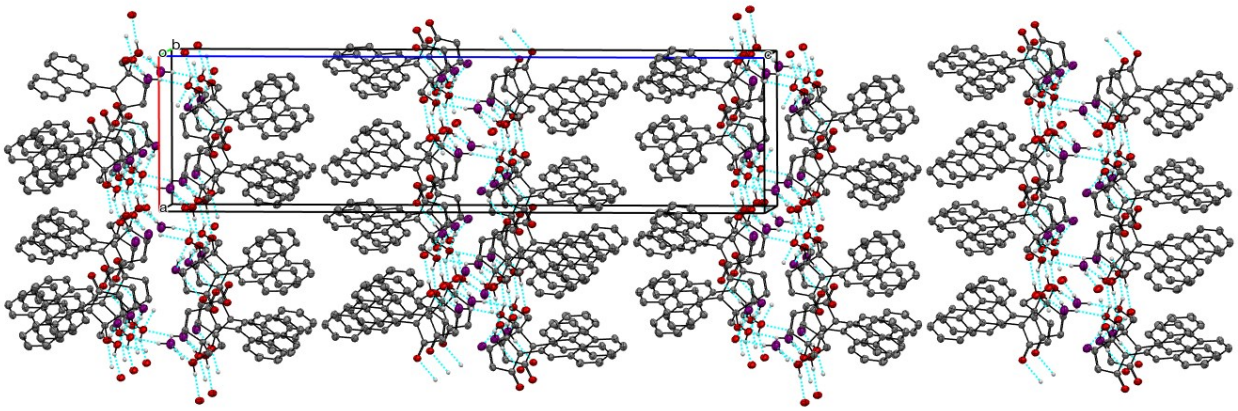


Figure S3: partial view of the crystalline packing down the ***b*** axis, showing the bilayers parallel to the (0 0 1) plane.

Crystallographic data for this compound have been deposited at the CCDC, Cambridge, UK, with the deposit number 1589305. The supplementary crystallographic data can be obtained free of charge from The Cambridge Crystallographic Data Centre via URL www.ccdc.cam.ac.uk/data_request/cif.

VI. Bioassays for cytotoxicity activities of compounds 6a , 6f, 6i and 6j

Cell culture and proliferation assay. Cancer cell lines were obtained from the American type Culture Collection (Rockville, USA) and were cultured according to the supplier's instructions. Briefly, human U87-MG cells were grown in Dulbecco minimal essential medium (DMEM) containing 4.5 g/L glucose supplemented with 10% FCS and 1% glutamine. Human K562 and K562R (Doxo-resistant), HCT116, A549, PC3, HL60 and MCF7 cells were grown in RPMI 1640 containing 10% FCS and 1% glutamine. The doxorubicin-resistant variant of the K562 leukemic cell line was a generous gift from Pr. J.-P. Marie (Paris, France). All cell lines were maintained at 37 °C in a humidified atmosphere containing 5% CO_2. Cell growth inhibition was determined by an MTS assay according to the manufacturer's instructions (Promega, Madison, WI, USA). Briefly, the cells were seeded in 96-well plates (2.5×10^3 cells/well) containing 100 μL of growth medium. After 24 h of culture, the cells were treated with the tested compounds at 10 different final concentrations. After 72 h of incubation, 20 μL of CellTiter 96® AQ_{ueous} One Solution Reagent was added for 2 h before recording absorbance at 490 nm with a spectrophotometric plate reader. The dose-response curves were plotted with Graph Prism software and the IC_{50} values were calculated using the Graph Prism software from polynomial curves (four or five-parameter logistic equations).

Apoptosis assay. Apoptosis of the treated HL60 cells was also assessed by flow cytometry using propidium iodide (PI) and an Annexin-V-FITC apoptosis detection kit (BD Biosciences, San Jose, CA, USA) according to the manufacturer's instructions. FITC-conjugated Annexin V has been used to detect the externalization of phosphatidylserine that occurs at an early stage of apoptosis. PI is currently used as a marker for necrosis due to cell membrane destruction.

Cell cycle analysis. Exponentially growing HL60 cancer cells were incubated with tested compound or DMSO for 24 h. Cell-cycle profiles were determined by flow cytometry on a FC500 flow cytometer (Beckman-Coulter, Villepinte, France) as described previously.[1]

[1] Venot, C.; Maratrat, M.; Dureuil, C.; Conseiller, E.; Bracco, L.; Debussche, L. The requirement for the p53 proline-rich functional domain for mediation of apoptosis is correlated with specific PIG3 gene transactivation and with transcriptional repression *The EMBO Journal* **1998**, *17*, 4668-4679.

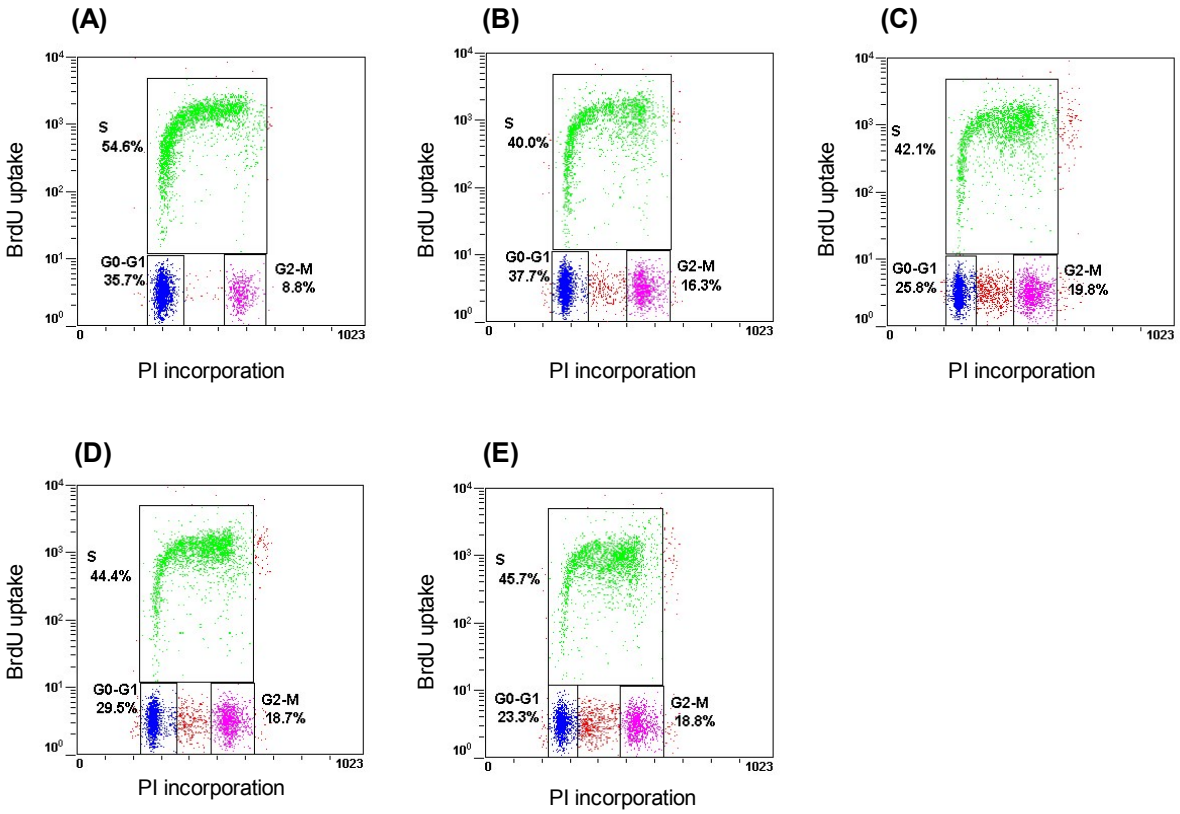


Figure S4: Cell cycle distribution, measured by bromodeoxyuridine (BrdU) uptake and propidium iodide (PI) staining of HL60 cells (control, A) and HL60 cells treated with compounds **6a** at 10 μM (B), **6f** at 10 μM (C) for 24 h, **6i** at 10 μM (D), **6j** at 10 μM (E) for 24 h.