

## Supporting Information

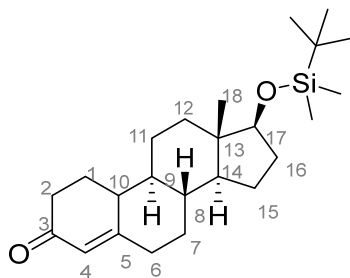
### Aza Analogs of the TRPML1 Inhibitor Estradiol Methyl Ether (EDME)

**Philipp Rühl<sup>1</sup> and Franz Bracher<sup>1,\*</sup>**

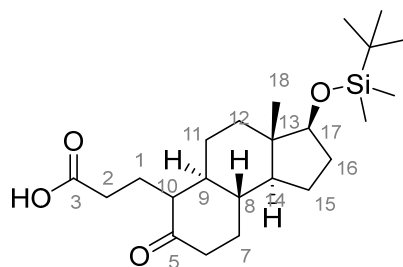
<sup>1</sup> Department of Pharmacy – Center for drug Research, Ludwig-Maximilians University, Munich, Germany; [philipp.ruehl@cup.lmu.de](mailto:philipp.ruehl@cup.lmu.de) (P.R.); [franz.bracher@cup.uni-muenchen.de](mailto:franz.bracher@cup.uni-muenchen.de) (F.B.)

\* Correspondence: [franz.bracher@cup.uni-muenchen.de](mailto:franz.bracher@cup.uni-muenchen.de)

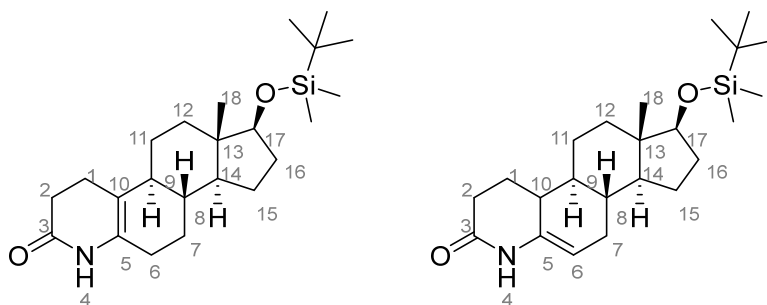
## Additional synthetic procedures



(8*R*,9*S*,13*S*,14*S*,17*S*)-17-((*tert*-Butyldimethylsilyl)oxy)-13-methyl-1,2,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-3*H*-cyclopenta[*a*]phenanthren-3-one (**S1**): 19-Nortestosterone (**3**; 1.92 g, 7.00 mmol, 1.00 eq), *tert*-butyldimethylsilyl chloride (1.32 g, 8.75 mmol, 1.25 eq) and imidazole (1.19 g, 17.5 mmol, 2.50 eq) were combined in a round bottom flask. Dry dimethylformamide (20 mL) was added and the resulting reaction mixture stirred at room temperature for 7 h. It was diluted with diethyl ether (150 mL) and washed with 2M aqueous hydrochloric acid solution (3 x 50 mL), saturated aqueous sodium bicarbonate solution (3 x 50 mL) and water (30 mL). The organic layer was dried over anhydrous sodium sulfate and filtered. After evaporation of the solvent, the crude product was purified by flash column chromatography (isohehexane/ ethyl acetate 4:1) to yield 2.60 g (6.69 mmol, 95.6 %) of the desired compound as a white solid. m.p.: 137 °C. <sup>1</sup>H NMR (400 MHz, CD<sub>2</sub>Cl<sub>2</sub>) δ/ppm = 5.75 (s, 1H, 4-H), 3.59 (dd, *J* = 8.8 Hz, 7.8 Hz, 1H, 17-H), 2.45 (ddd, *J* = 14.5 Hz, 4.0 Hz, 2.4 Hz, 1H, 6-H<sub>a</sub>), 2.34 (m, 1H, 6-H<sub>b</sub>), 2.28 (m, 1H, 2-H<sub>a</sub>), 2.25 (m, 1H, 1-H<sub>a</sub>), 2.22 (m, 1H, 2-H<sub>b</sub>), 2.08 (m, 1H, 10-H), 1.90 (m, 1H, 16-H<sub>a</sub>) 1.85 (m, 1H, 7-H<sub>a</sub> or 15-H<sub>a</sub>), 1.81 (m, 1H, 7-H<sub>a</sub> or 15-H<sub>a</sub>), 1.77 (m, 1H, 12-H<sub>a</sub>), 1.59 (m, 1H, 11-H<sub>a</sub>), 1.51 (m, 1H, 1-H<sub>b</sub>), 1.45 (m, 1H, 16-H<sub>b</sub>), 1.34 (m, 1H, 8-H), 1.29 (m, 1H, 11-H<sub>b</sub>), 1.25 (m, 1H, 15-H<sub>b</sub>), 1.06 (m, 1H, 12-H<sub>b</sub>), 1.02 (m, 1H, 7-H<sub>b</sub>), 0.97 (m, 1H, 9-H), 0.89 (s, 9H, (CH<sub>3</sub>)<sub>3</sub>), 0.82 (m, 1H, 14-H), 0.77 (s, 3H, 18-H) , 0.02 (s, 3H, dimethylsilyl<sub>a</sub>), 0.01 (s, 3H, dimethylsilyl<sub>b</sub>) <sup>13</sup>C NMR (101 MHz, CD<sub>2</sub>Cl<sub>2</sub>) δ/ppm = 199.74 (C-3), 167.24 (C-5), 124.62 (C-4), 82.11 (C-17), 50.20 (C-14), 49.79 (C-9), 43.74 (C-13), 43.00 (C-10), 40.92 (C-8), 37.28 (C-12), 36.96 (C-2), 35.90 (C-6), 31.24 (C-7 or C-16), 31.22 (C-7 or C-16), 27.10 (C-1), 26.62 (C-15), 26.02 ((CH<sub>3</sub>)<sub>3</sub>), 23.69 (C-11), 18.38 (*tert*-butyl, quaternary carbon), 11.50 (C-18), -4.39 (dimethylsilyl<sub>a</sub>), -4.72 (dimethylsilyl<sub>b</sub>) IR (ATR): ν<sub>max</sub>/cm<sup>-1</sup> = 2929, 2856, 1667, 1616, 1457, 1249, 1140, HRMS (ESI): *m/z* = [M+H]<sup>+</sup> calculated for C<sub>24</sub>H<sub>41</sub>O<sub>2</sub>Si<sup>+</sup>: 389.2870; found: 389.2871.



3-((3*S*,3*aS*,5*aS*,6*R*,9*aR*,9*bS*)-3-((*tert*-Butyldimethylsilyl)oxy)-3*a*-methyl-7-oxododecahydro-1*H*-cyclopenta[*a*]naphthalen-6-yl)propanoic acid (**S2**): To a solution of the above compound (2.60 g, 6.70 mmol, 1.00 eq) in 40 mL of *tert*-butanol were added 13.0 mL of a saturated aqueous Na<sub>2</sub>CO<sub>3</sub> solution. The mixture was heated at reflux and a solution of NaIO<sub>4</sub> (14.3 g, 67.0 mmol, 10.00 eq) and KMnO<sub>4</sub> (80.0 mg, 0.500 mmol, 7.50 mol%) in water (40 mL) preheated to 80 °C was added via a dropping funnel over a time period of 30 min. After cooling, the reaction mixture was filtered and the filter cake was washed with 10 mL of water. The filtrate was acidified with 6M HCl to pH 2 and then extracted with dichloromethane (4 × 20 mL). The organic phase was washed with water (20 mL) and dried over anhydrous sodium sulfate. After filtration and removal of the solvent, the crude product was purified by column chromatography to yield a colorless oil (2.37 g, 5.81 mmol, 86.7%) <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ/ppm = 11.98 (s, 1H, COOH), 3.58 (t, *J* = 8.1 Hz, 1H, 17-H), 2.41 (td, *J* = 13.7 Hz, 6.1 Hz, 1H, 6-H<sub>a</sub>), 2.29 (m, 1H, 10-H), 2.20 (m, 1H, 6-H<sub>b</sub>), 2.13 (m, 1H, 2-H<sub>a</sub>), 2.07 (m, 1H, 2-H<sub>b</sub>), 1.90 (m, 1H, 7-H<sub>a</sub> or 16-H<sub>a</sub>), 1.85 (m, 1H, 7-H<sub>b</sub> or 16-H<sub>b</sub>), 1.76 (m, 1H, 1-H<sub>a</sub>), 1.69 (m, 1H, 15-H<sub>a</sub>), 1.65 (m, 1H, 12-H<sub>a</sub>), 1.61 (m, 1H, 1-H<sub>b</sub>), 1.57 (m, 1H, 8-H), 1.51 (m, 1H, 11-H<sub>a</sub>), 1.39 (m, 1H, 7H<sub>b</sub> or 16-H<sub>b</sub>), 1.32 (m, 1H, 15-H<sub>b</sub>), 1.27 (m, 1H, 11-H<sub>b</sub>), 1.15 (m, 1H, 7-H<sub>b</sub> or 16-H<sub>b</sub>), 1.06 (m, 1H, 12-H<sub>b</sub>), 1.01 (m, 1H, 9-H), 0.94 (m, 1H, 14-H), 0.86 (s, 9H, (CH<sub>3</sub>)<sub>3</sub>), 0.74 (s, 3H, 18-H), 0.01 (s, 3H, dimethylsilyl<sub>a</sub>), 0.00 (s, 3H, dimethylsilyl<sub>b</sub>) <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ/ppm = 211.39 (C-5), 174.61 (C-3), 81.01 (C-17), 52.77 (C-10), 49.50 (C-14), 47.40 (C-9), 43.00 (C-13), 41.15 (C-6), 40.15 (C-8), 36.18 (C-12), 30.91 (C-2), 30.70 (C-7 or C-16), 30.40 (C-7 or C-16), 26.50 (C-15), 25.75 ((CH<sub>3</sub>)<sub>3</sub>), 23.01 (C-11), 20.54 (C-1), 17.78 (*tert*-butyl, quaternary carbon), 11.30 (C-18), -4.51 (dimethylsilyl<sub>a</sub>), -4.84 (dimethylsilyl<sub>b</sub>) IR (ATR): ν<sub>max</sub>/cm<sup>-1</sup> = 2927, 2856, 1715, 1558, 1541, 1418, 1249, 1199 HRMS (ESI): *m/z* = (M-H)<sup>-</sup> calculated for C<sub>23</sub>H<sub>39</sub>O<sub>4</sub>Si: 407.2623; found: 407.2625.



(4*bS*,6*aS*,7*S*,9*aS*,9*bR*)-7-((*tert*-Butyldimethylsilyl)oxy)-6*a*-methyl-1,3,4,4*b*,5,6,6*a*,7,8,9,9*a*,9*b*,10,11-tetradecahydro-2*H*-indeno[5,4-*f*]quinolin-2-one (**Δ<sub>5,10</sub> isomer, S3a**) and (4*bS*,6*aS*,7*S*,9*aS*,9*bR*)-7-((*tert*-butyldimethylsilyl)oxy)-6*a*-methyl-1,3,4,4*a*,4*b*,5,6,6*a*,7,8,9,9*a*,9*b*,10-tetradecahydro-2*H*-indeno[5,4-*f*]quinolin-2-one (**Δ<sub>5,6</sub> isomer, S3b**): A mixture of the above ketocarboxylic acid (2.32

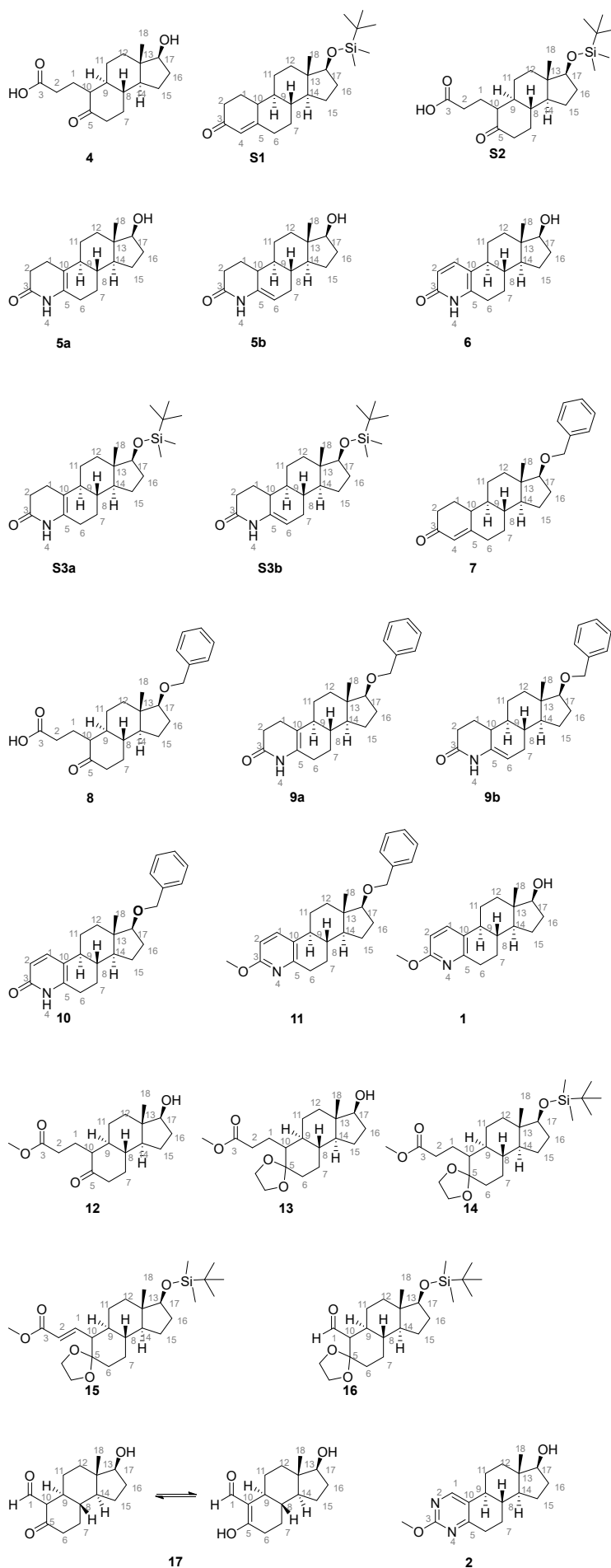
g, 5.70 mmol, 1.00 eq) and ammonium acetate (1.54 g, 19.9 mmol, 3.50 eq) in glacial acetic acid (45 mL) was stirred and heated at reflux for 4 h. After cooling, it was concentrated under reduced pressure and the remaining residue was poured into water. The precipitate was filtered, washed with water (20 mL) and dissolved in dichloromethane (40 mL). The resulting solution was washed with NaOH (1M, 3 x 20 mL), water (20 mL) and brine (20 mL), filtered over a hydrophobic filter and concentrated in vacuo. The crude product was purified by flash column chromatography (isohexane/ ethyl acetate 5:1) to yield 1.59 g (4.08 mmol, 71.6%) of a mixture of the two lactams (ratio:  $\Delta 5,10$  isomer:  $\Delta 5,6$  isomer: 15:85) as a beige solid.

**$\Delta 5,10$  isomer S3a:**  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta/\text{ppm}$  = 3.62 (m, 1H, 17-H), 2.38 (m, 1H, 6- $\text{H}_a$ ), 2.31 (m, 1H, 1- $\text{H}_a$ ), 2.20 (m, 1H, 2- $\text{H}_a$ ), 2.12 (m, 1H, 1- $\text{H}_b$ ), 1.95 (m, 1H, 2- $\text{H}_b$ ), 1.91 (m, 1H, 16- $\text{H}_a$ ), 1.86 (m, 1H, 15- $\text{H}_a$ ), 1.81 (m, 1H, 12- $\text{H}_a$ ), 1.74 (m, 1H, 7- $\text{H}_a$ ), 1.68 (m, 1H, 9-H), 1.57 (m, 1H, 11- $\text{H}_a$ ), 1.50 (m, 1H, 15- $\text{H}_b$ ), 1.43 (m, 1H, 16- $\text{H}_b$ ), 1.36 (m, 1H, 11- $\text{H}_b$ ), 1.30 (m, 1H, 8-H), 1.26 (m, 1H, 6- $\text{H}_b$ ), 1.19 (m, 1H, 7- $\text{H}_b$ ), 1.10 (m, 1H, 14-H), 1.01 (m, 1H, 12- $\text{H}_b$ ), 0.88 (s, 9H,  $(\text{CH}_3)_3$ ), 0.73 (s, 3H, 18-H), 0.02 (2s, 6H, dimethylsilyl)  $^{13}\text{C}$  NMR (126 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta/\text{ppm}$  = 171.05 (C-3), 128.52 (C-5), 113.11 (C-10), 82.08 (C-17), 49.32 (C-14), 44.41 (C-9), 44.38 (C-13), 39.56 (C-8), 37.60 (C-12), 31.38 (C-6 or C-16), 31.10 (C-6 or C-16), 27.39 (C-2), 26.36 (C-7), 26.01 ( $(\text{CH}_3)_3$ ), 25.75 (C-15), 23.45 (C-11), 22.21 (C-1), 18.38 (*tert*-butyl, quaternary carbon), 11.76 (C-18), -4.39 (dimethylsilyl<sub>a</sub>), -4.72 (dimethylsilyl<sub>b</sub>) IR (ATR):  $\nu_{\text{max}}/\text{cm}^{-1}$  = 32145, 2953, 2928, 1695, 1674, 1472, 1387, 1255, 1141, 1094, HRMS (EI):  $m/z$  =  $[\text{M}^{*+}]$  calculated for  $\text{C}_{23}\text{H}_{39}\text{NO}_2\text{Si}^{*+}$ : 389.2745; found: 389.2746.

**$\Delta 5,6$  isomer S3b:**  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta/\text{ppm}$  = 7.58 (NH), 4.88 (dt,  $J$  = 5.1 Hz, 2.3 Hz, 1H, 6-H), 3.60 (t,  $J$  = 8.3 Hz, 1H, 17-H), 2.46 (ddd,  $J$  = 17.3 Hz, 5.0 Hz, 2.0 Hz, 1H, 2- $\text{H}_a$ ), 2.37 (m, 1H, 2- $\text{H}_b$ ), 2.11 (m, 1H, 1- $\text{H}_a$ ), 2.07 (m, 1H, 7- $\text{H}_a$ ), 1.95 (m, 1H, 10-H), 1.91 (m, 1H, 16- $\text{H}_a$ ), 1.89 (m, 1H, 11- $\text{H}_a$ ), 1.78 (m, 1H, 12- $\text{H}_a$ ), 1.64 (m, 1H, 7- $\text{H}_b$ ), 1.56 (m, 1H, 15- $\text{H}_a$ ), 1.44 (m, 1H, 16- $\text{H}_b$ ), 1.40 (m, 1H, 8-H), 1.31 (m, 1H, 1- $\text{H}_b$ ), 1.29 (m, 1H, 15- $\text{H}_b$ ), 1.27 (m, 1H, 11- $\text{H}_b$ ), 1.08 (m, 1H, 12- $\text{H}_b$ ), 1.00 (m, 1H, 9-H), 0.97 (m, 1H, 14-H), 0.88 (s, 9H,  $(\text{CH}_3)_3$ ), 0.74 (s, 3H, 18-H), 0.02 (2s, 6H,  $\text{Si}(\text{CH}_3)_2$ )  $^{13}\text{C}$  NMR (126 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta/\text{ppm}$  = 170.07 (C-3), 136.43 (C-5), 102.77 (C-6), 82.15 (C-17), 50.35 (C-14), 43.91 (C-9), 43.73 (C-13), 39.97 (C-10), 37.15 (C-8), 37.10 (C-12), 32.33 (C-2), 31.20 (C-16), 29.24 (C-7), 26.69 (C-11), 26.01 ( $(\text{CH}_3)_3$ ), 25.27 (C-1), 23.63 (C-15), 18.38 (*tert*-butyl, quaternary carbon), 11.40 (C-18), -4.39 (dimethylsilyl<sub>a</sub>), -4.72 (dimethylsilyl<sub>b</sub>). IR (ATR):  $\nu_{\text{max}}/\text{cm}^{-1}$  = 32145, 2953, 2928, 1695, 1674, 1472, 1387, 1255, 1094 HRMS (EI):  $m/z$  =  $[\text{M}^{*+}]$  calculated for  $\text{C}_{23}\text{H}_{39}\text{NO}_2\text{Si}^{*+}$ : 389.2745; found: 389.2745.

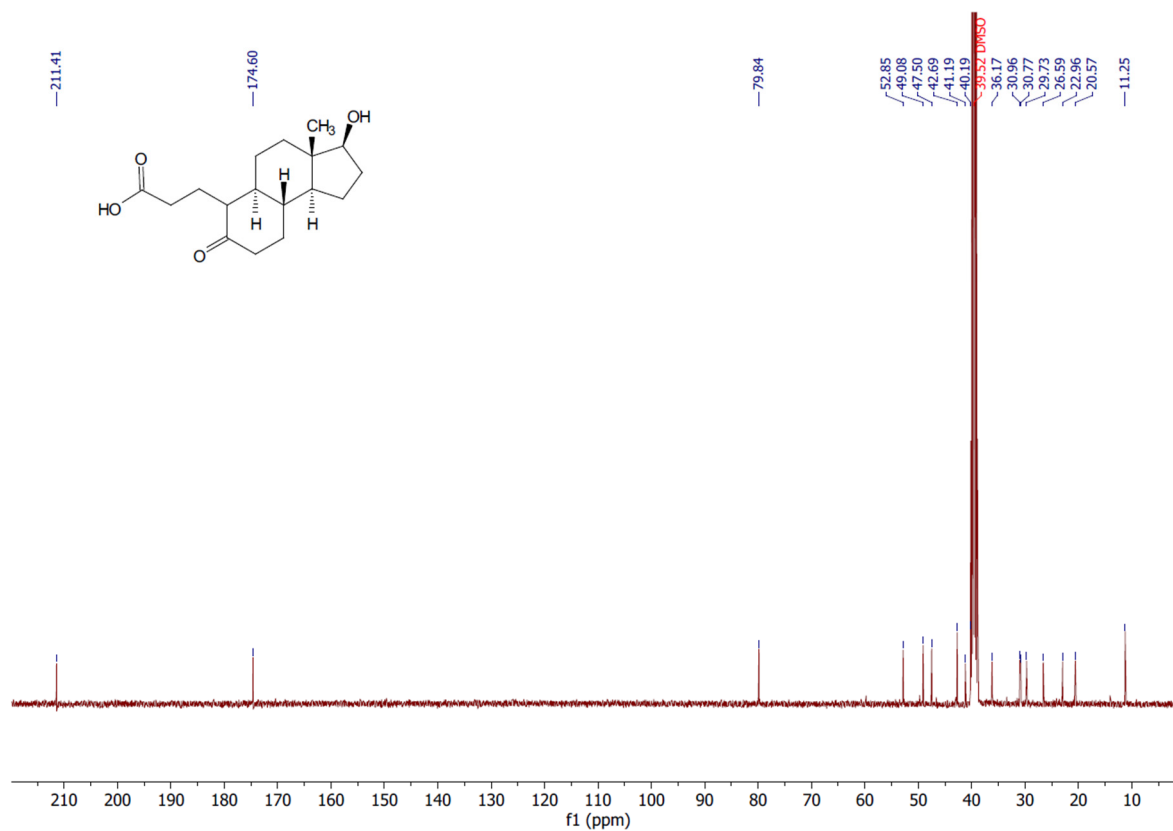
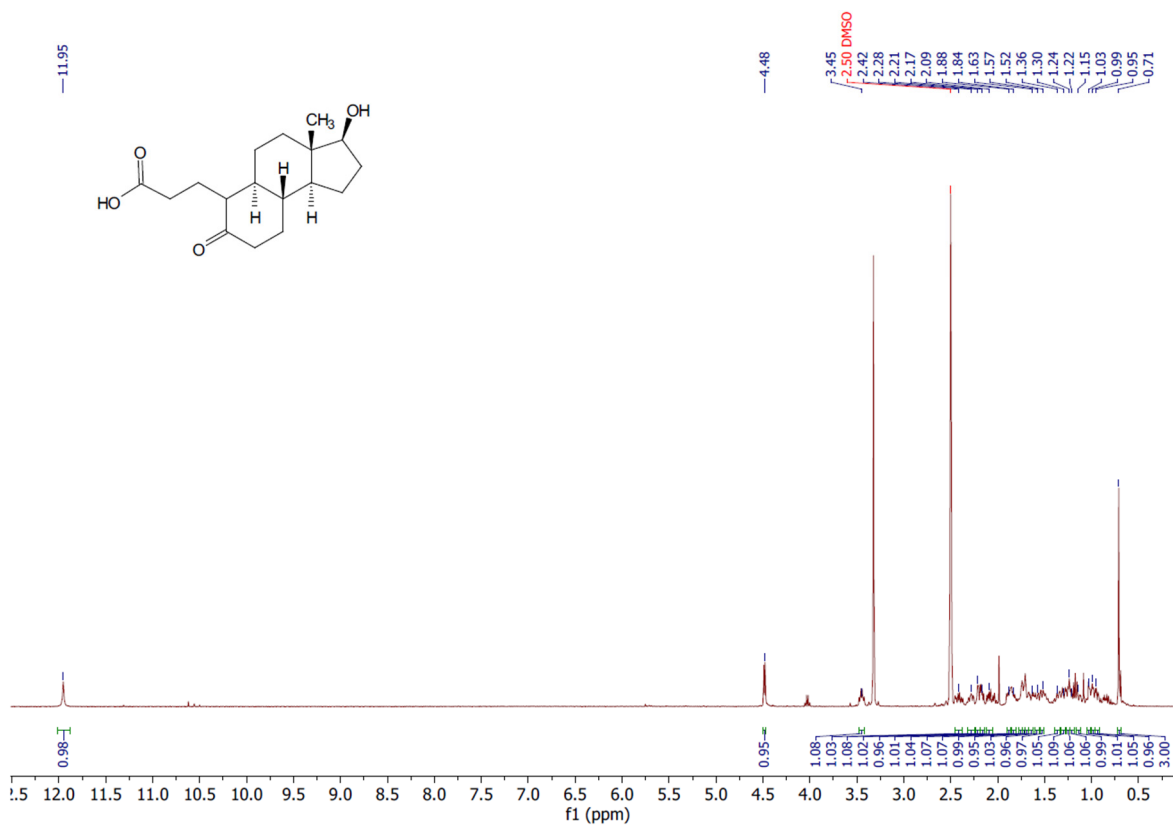


**Figure S1: Numbering of the compounds (for assignment of NMR signals).**

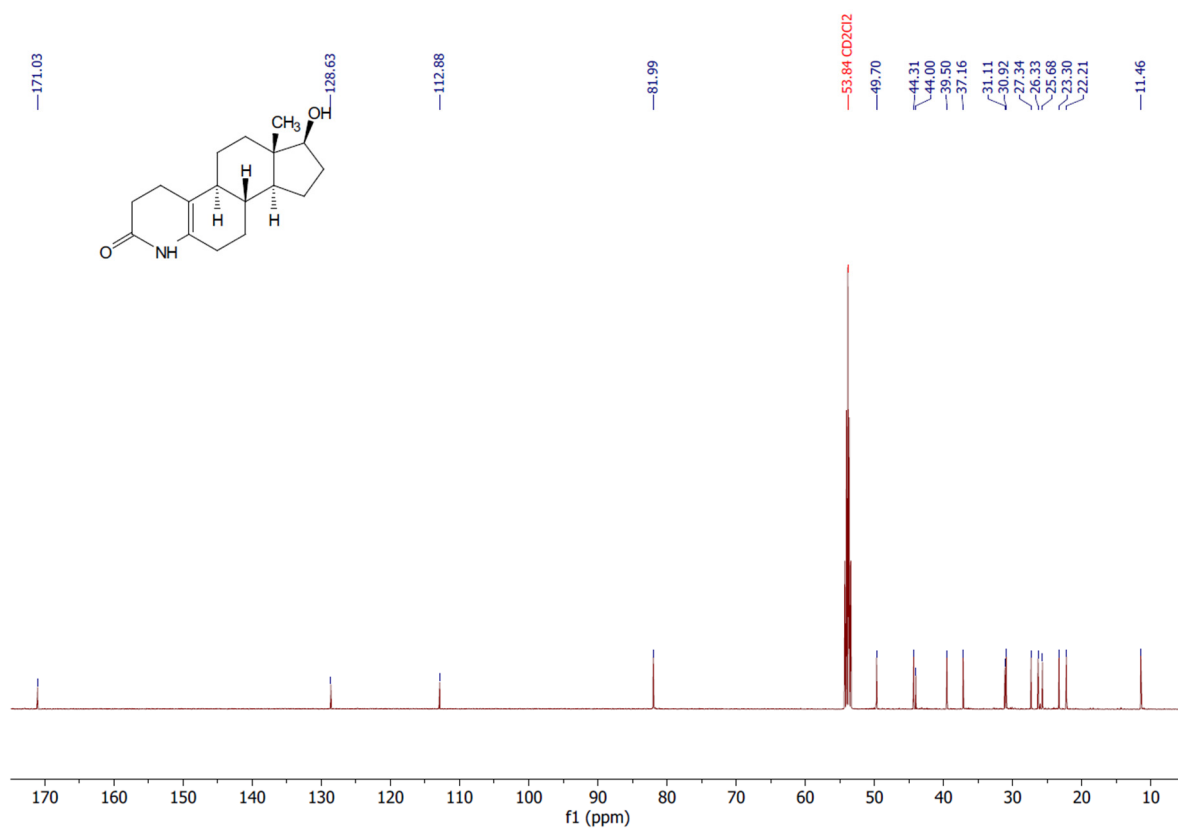
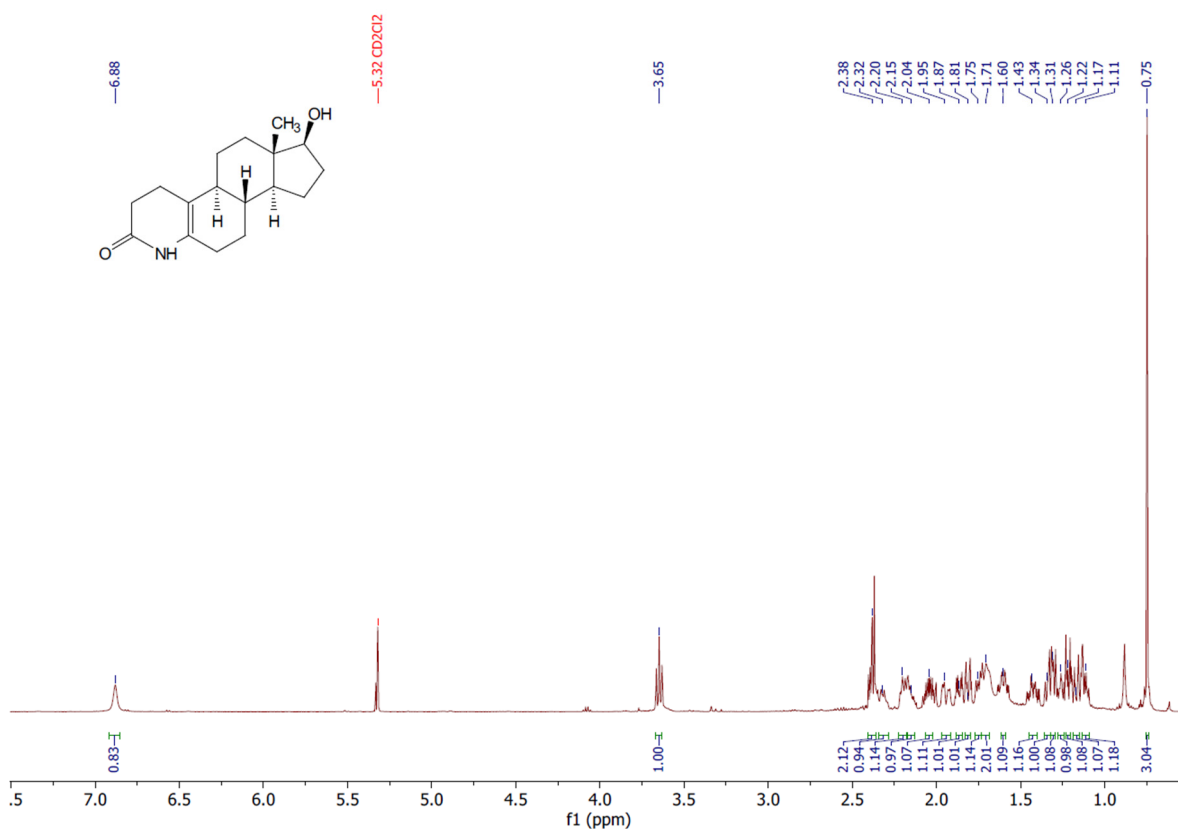


# $^1\text{H}$ - and $^{13}\text{C}$ -NMR spectra

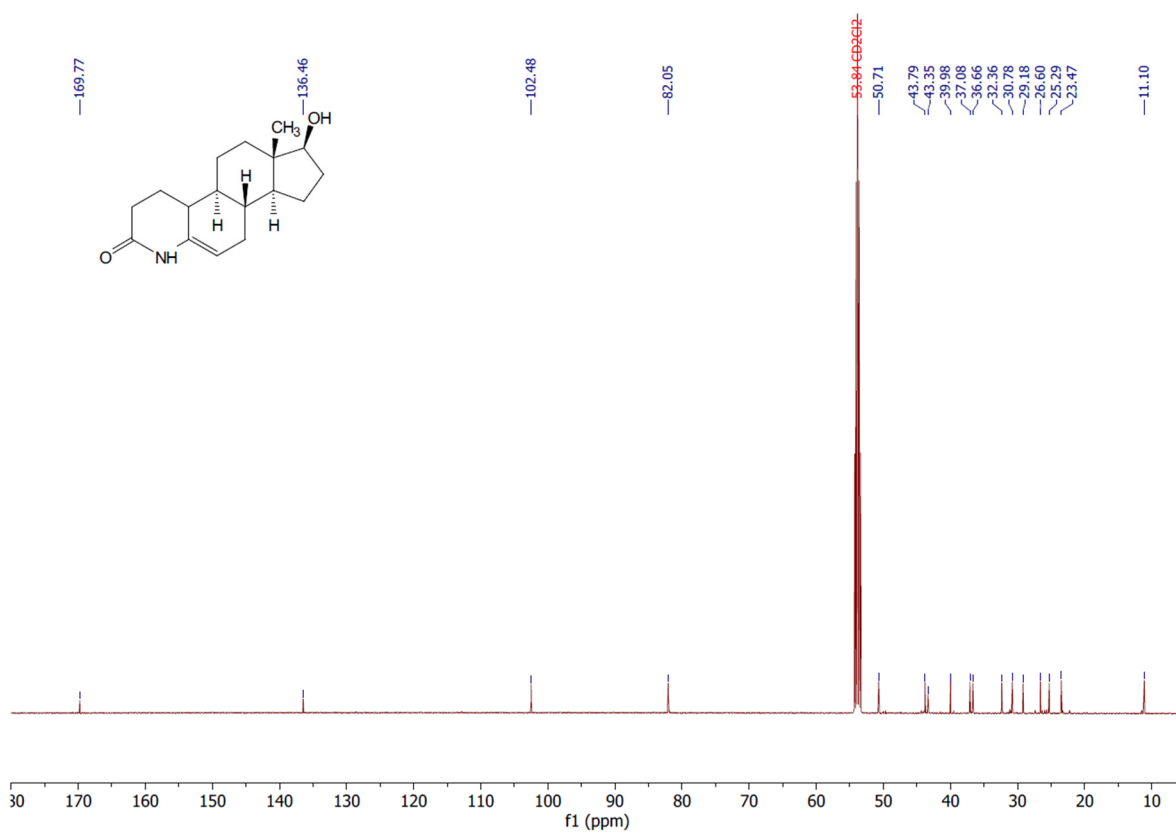
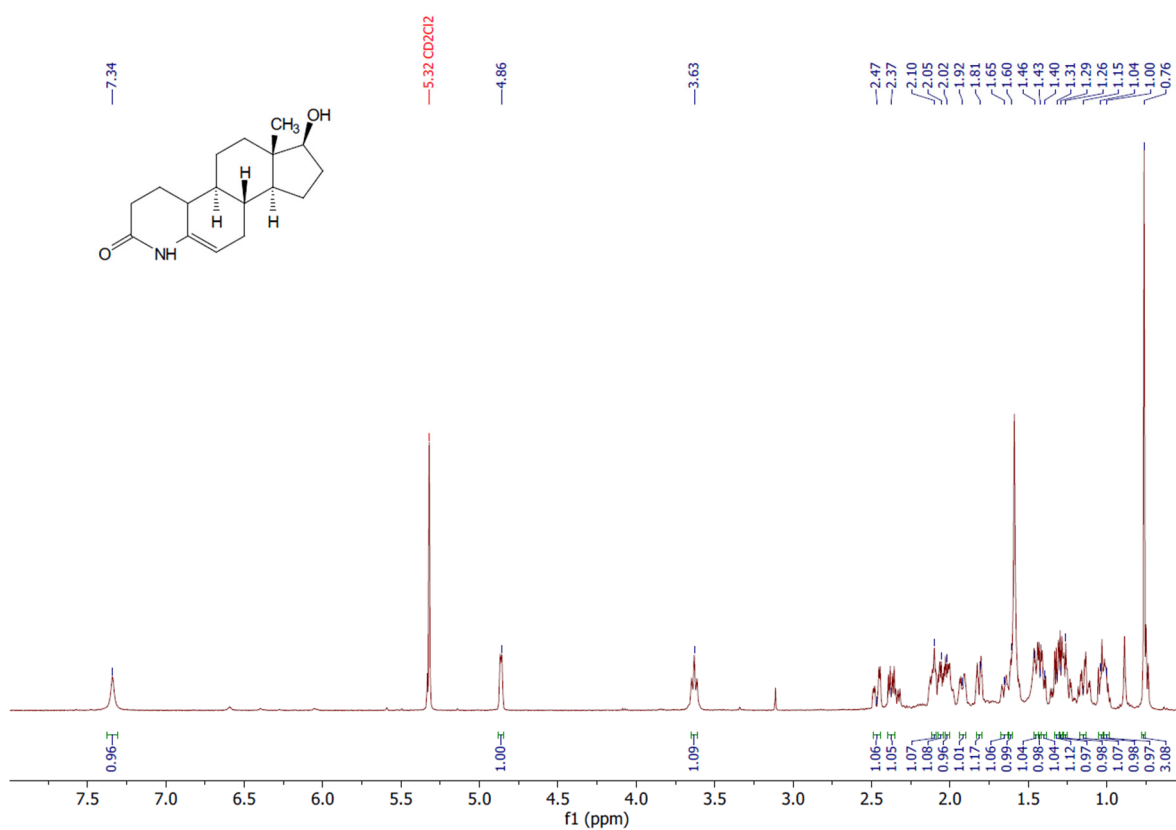
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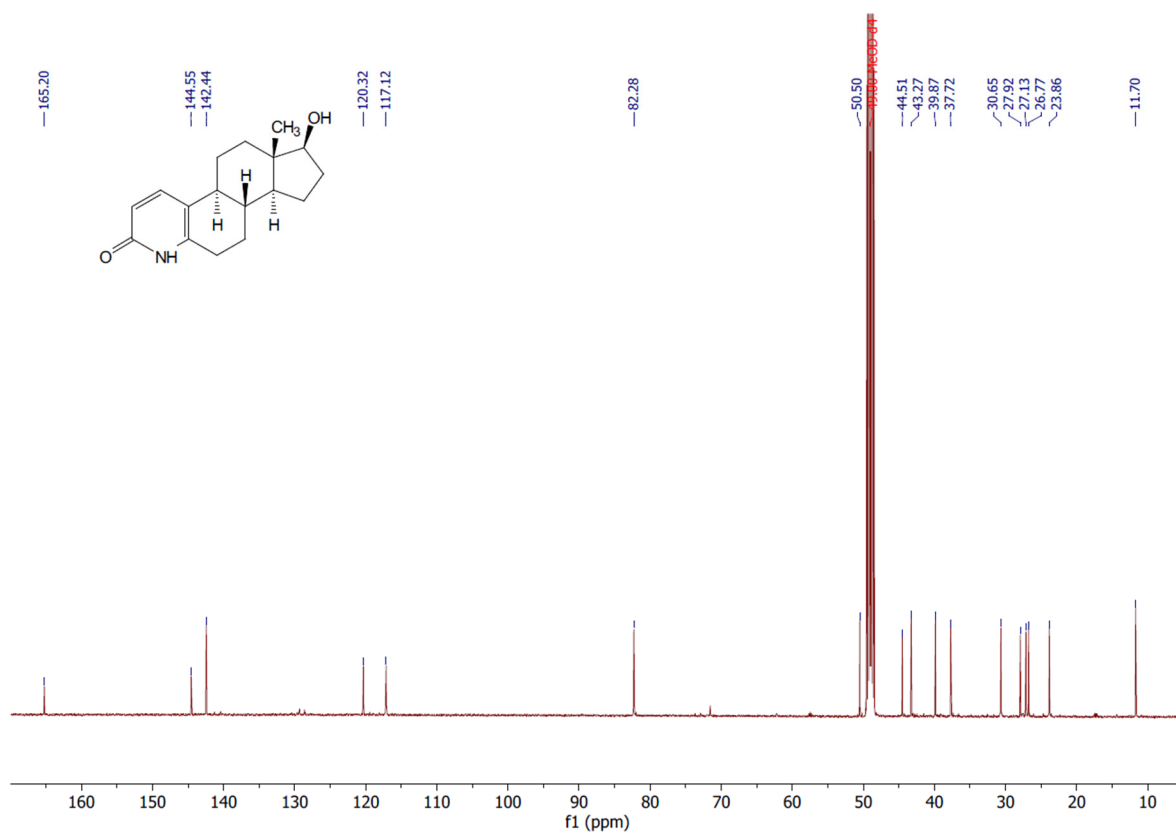
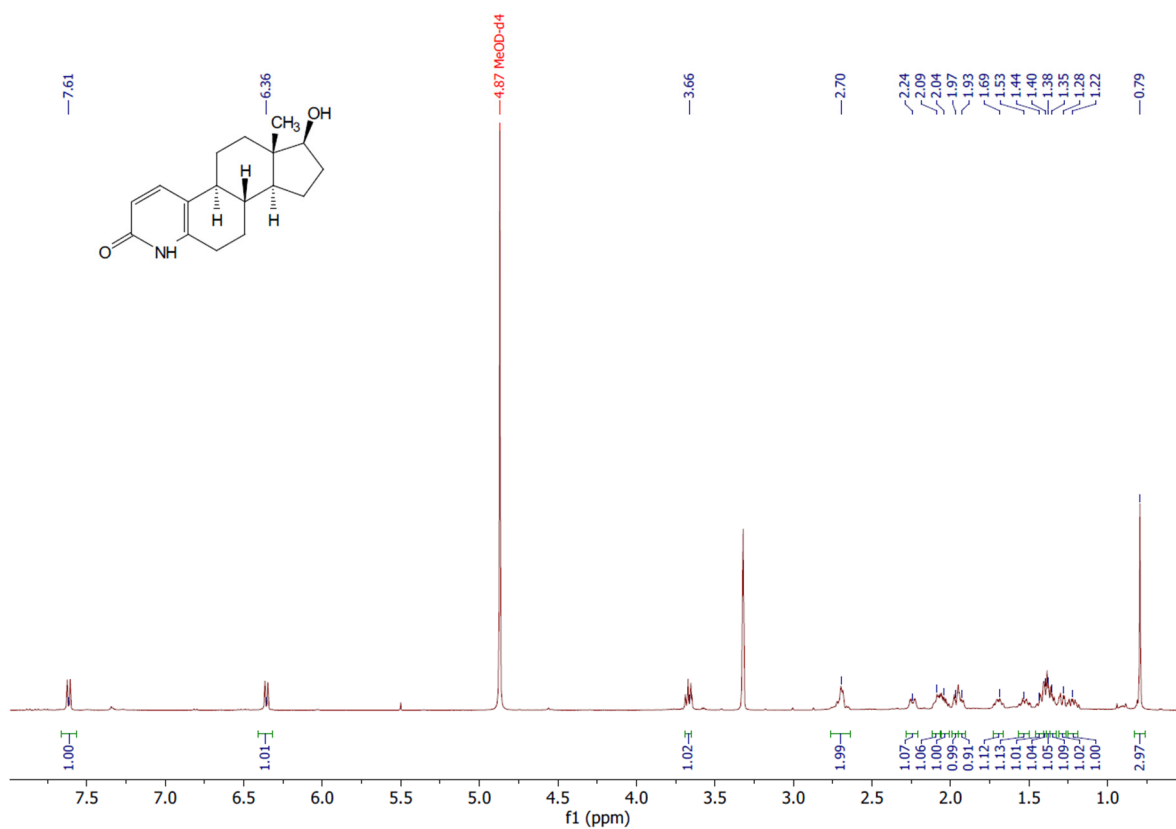
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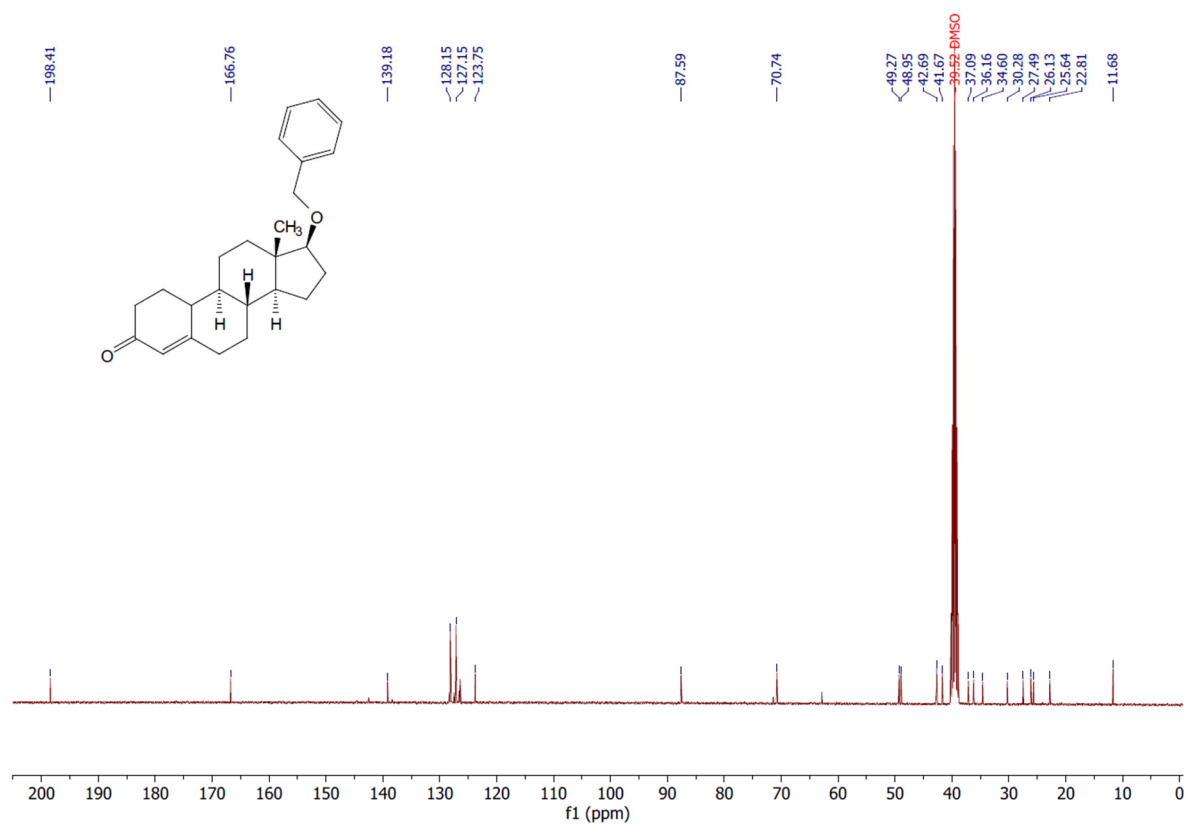
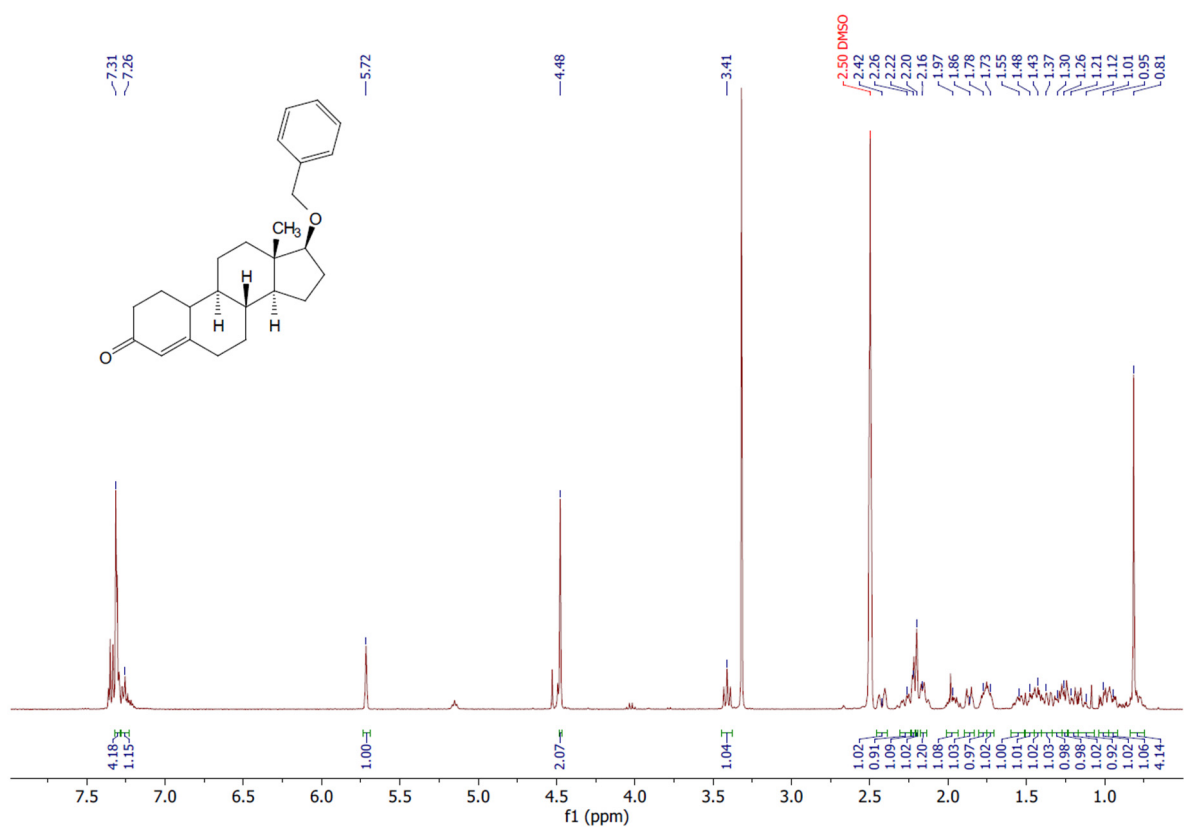
# Compound 5b



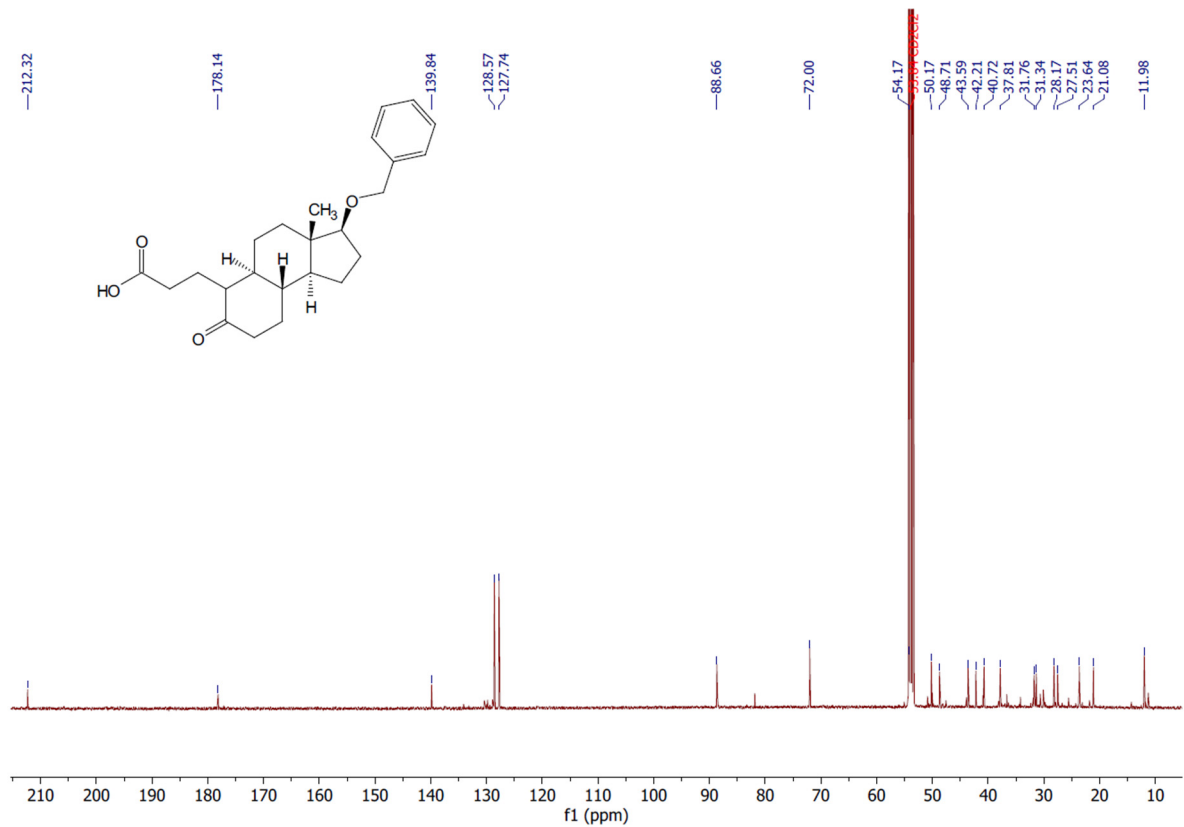
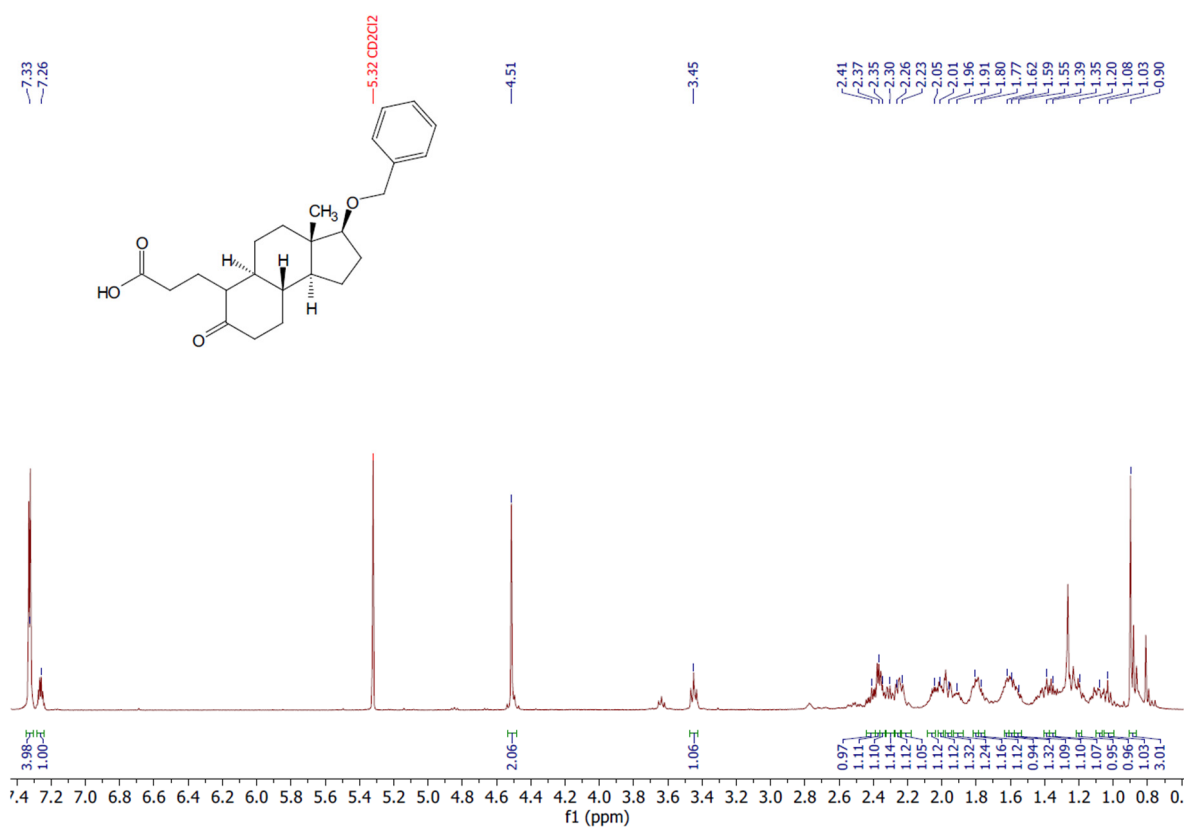
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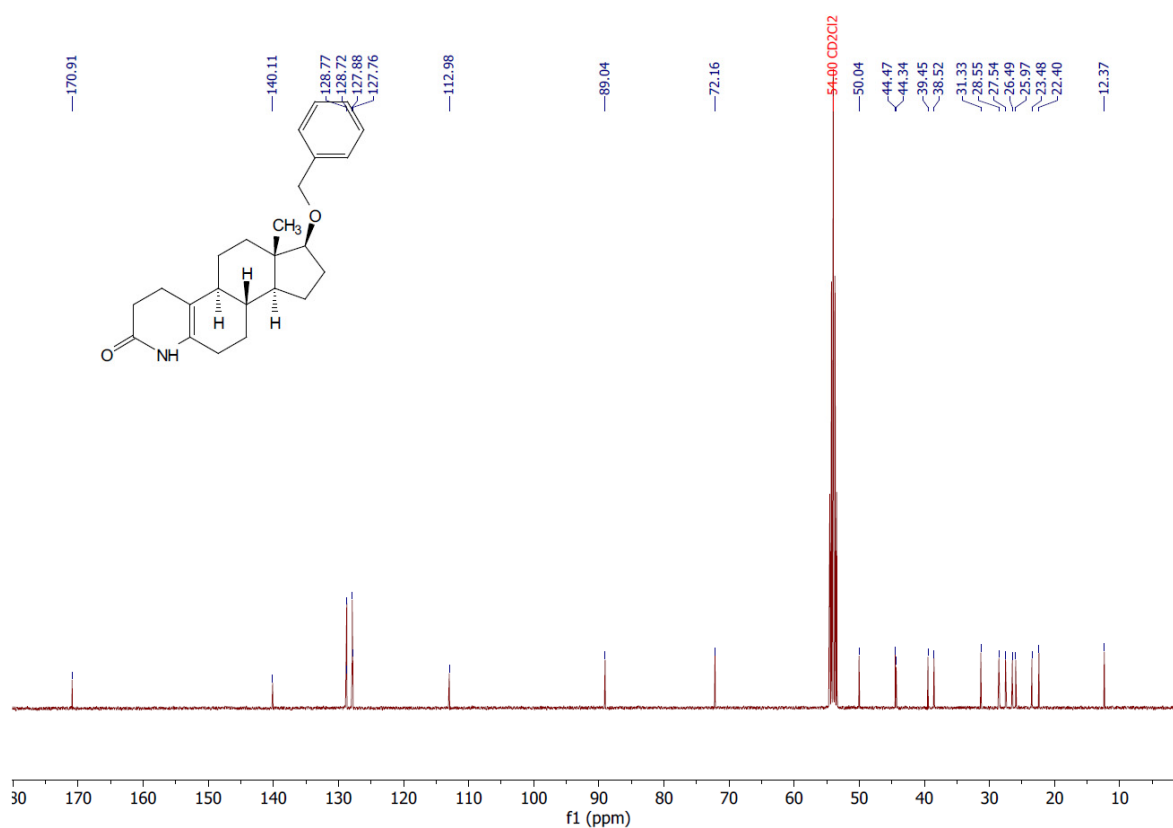
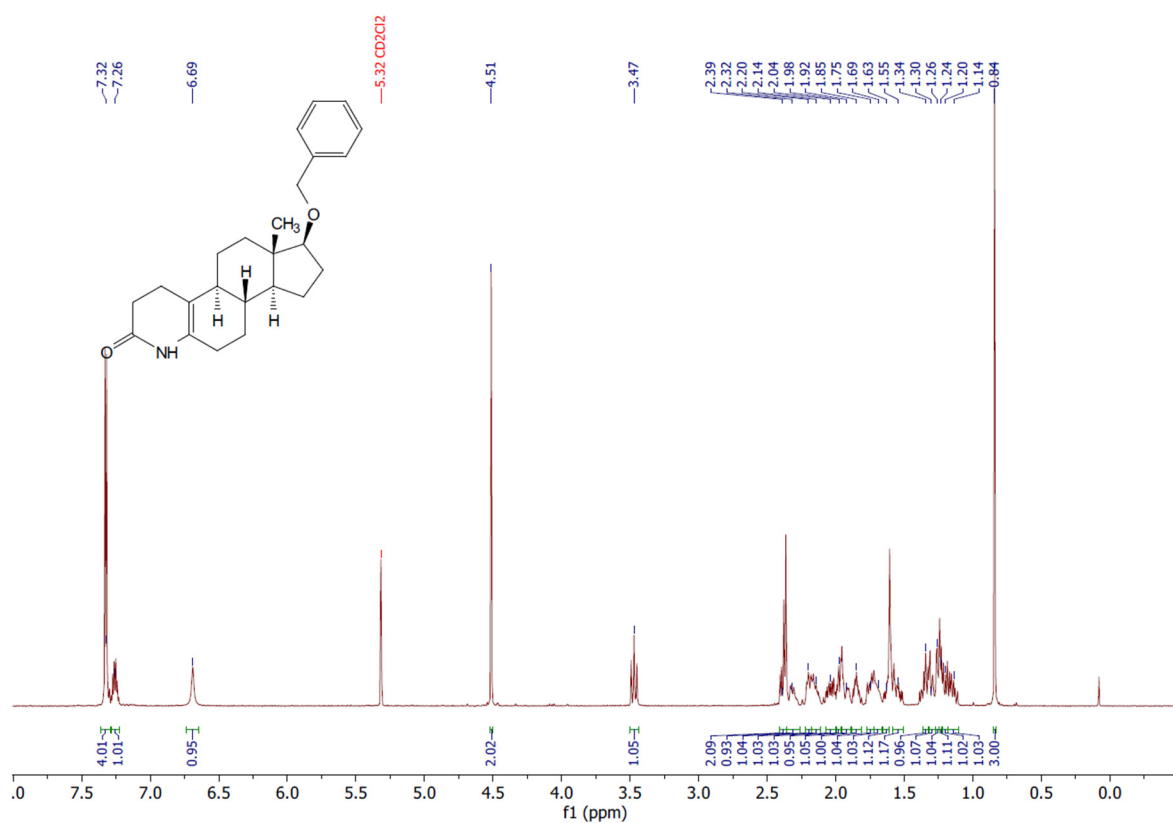
# Compound 7



# Compound 8

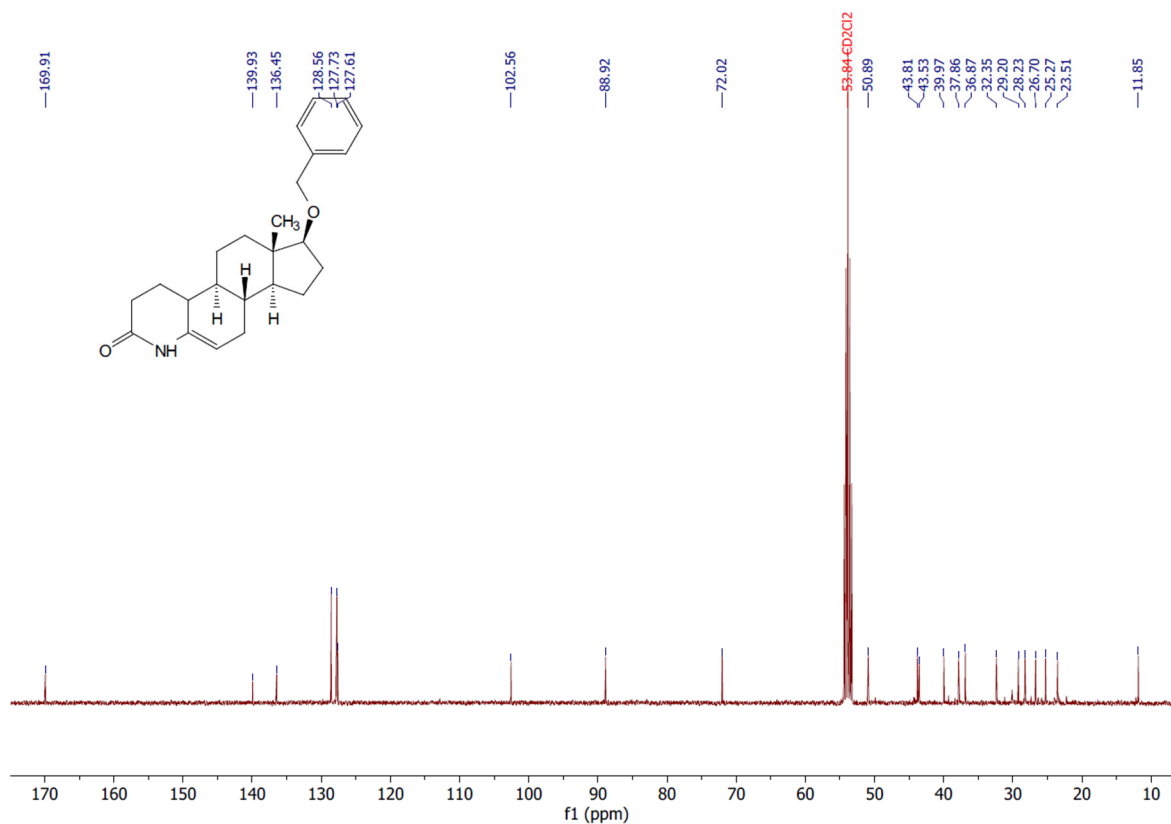
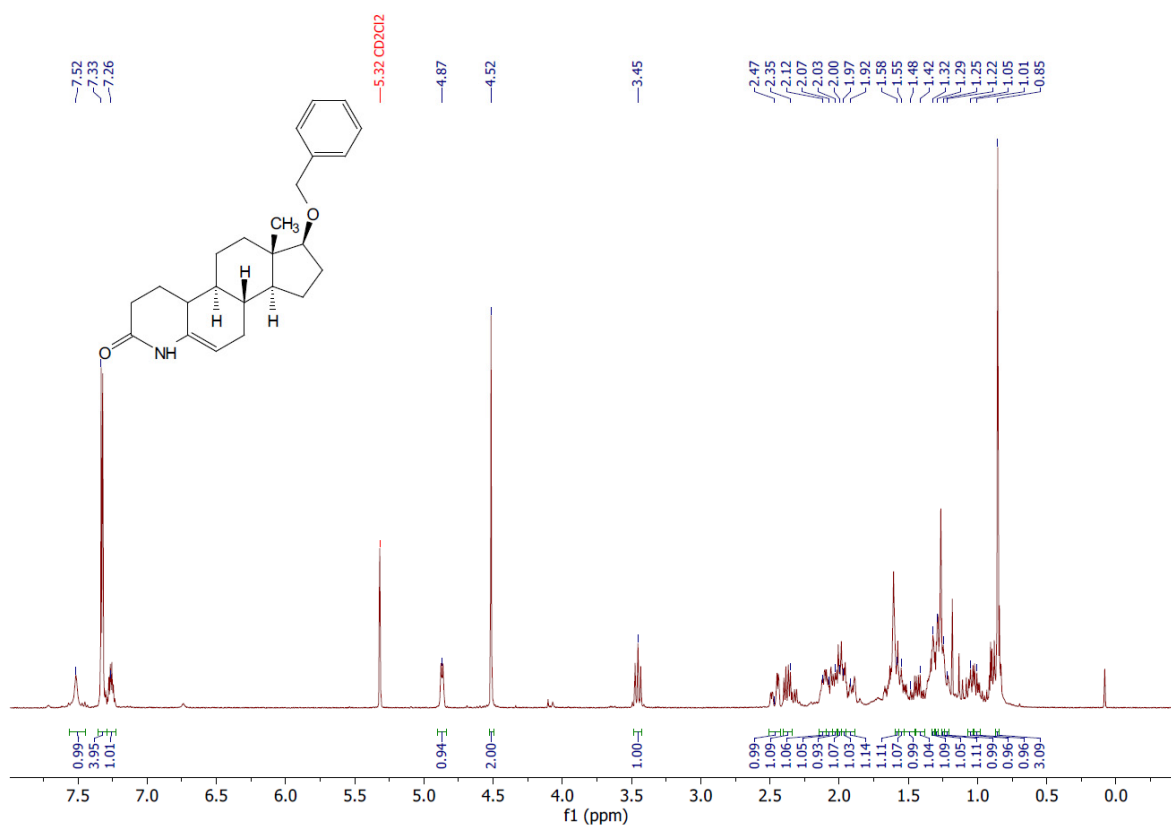


# Compound 9a

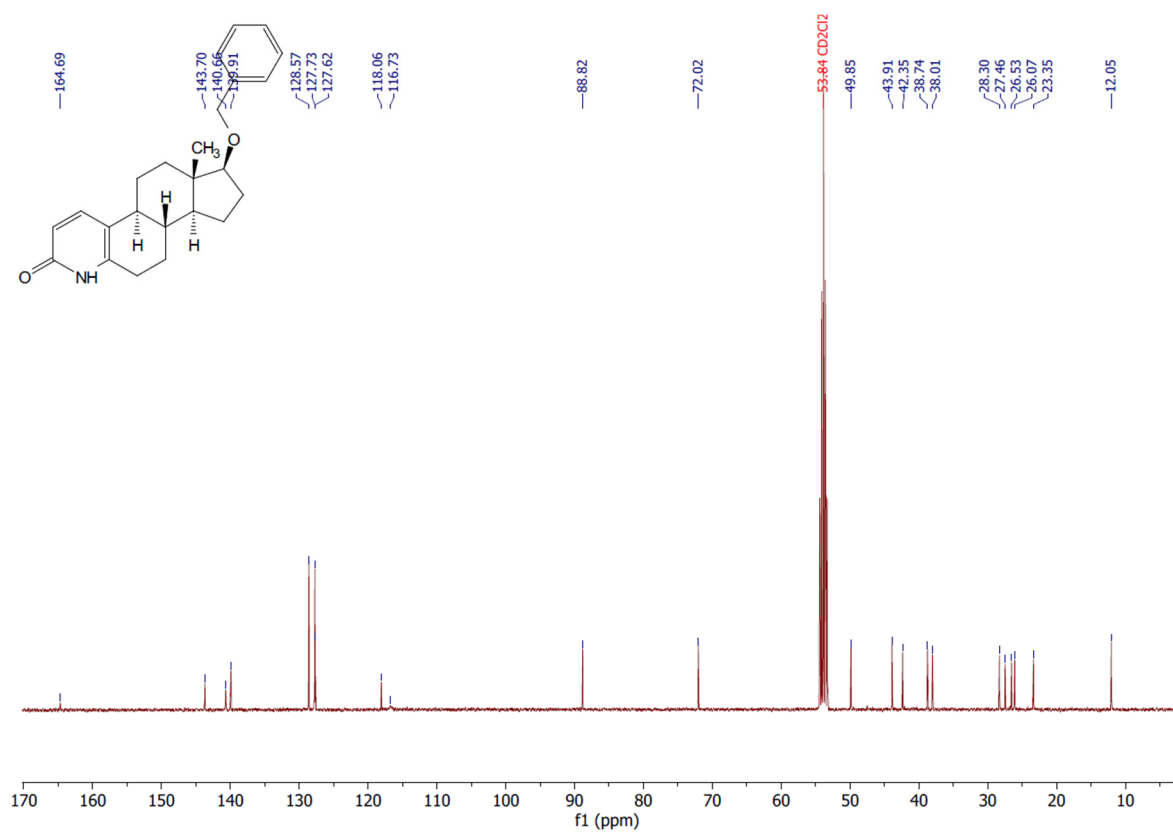
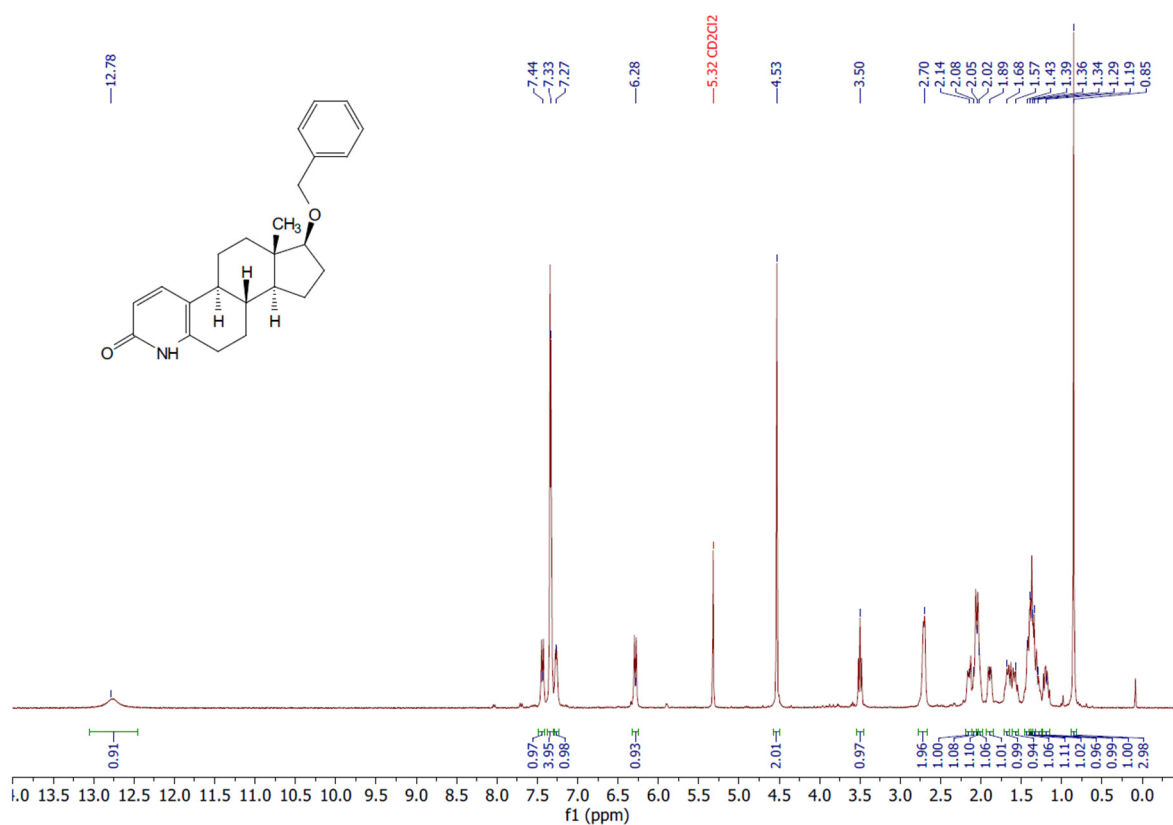




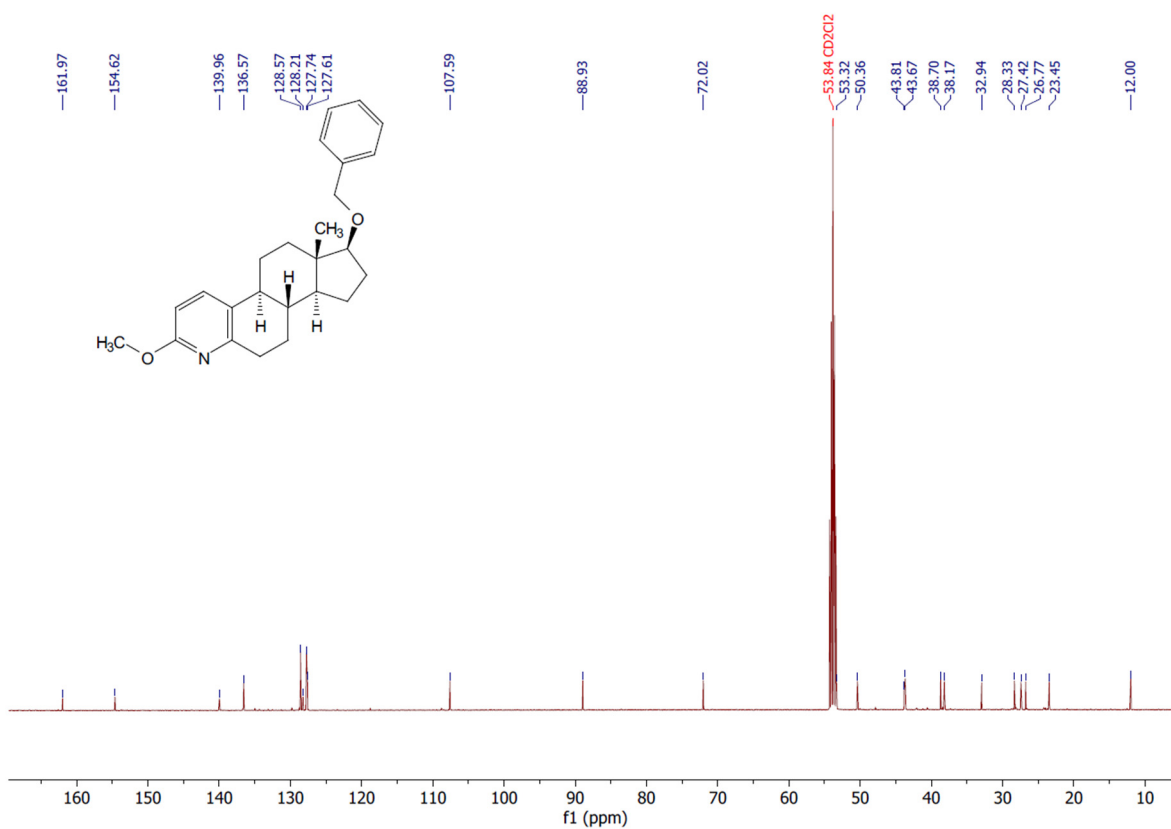
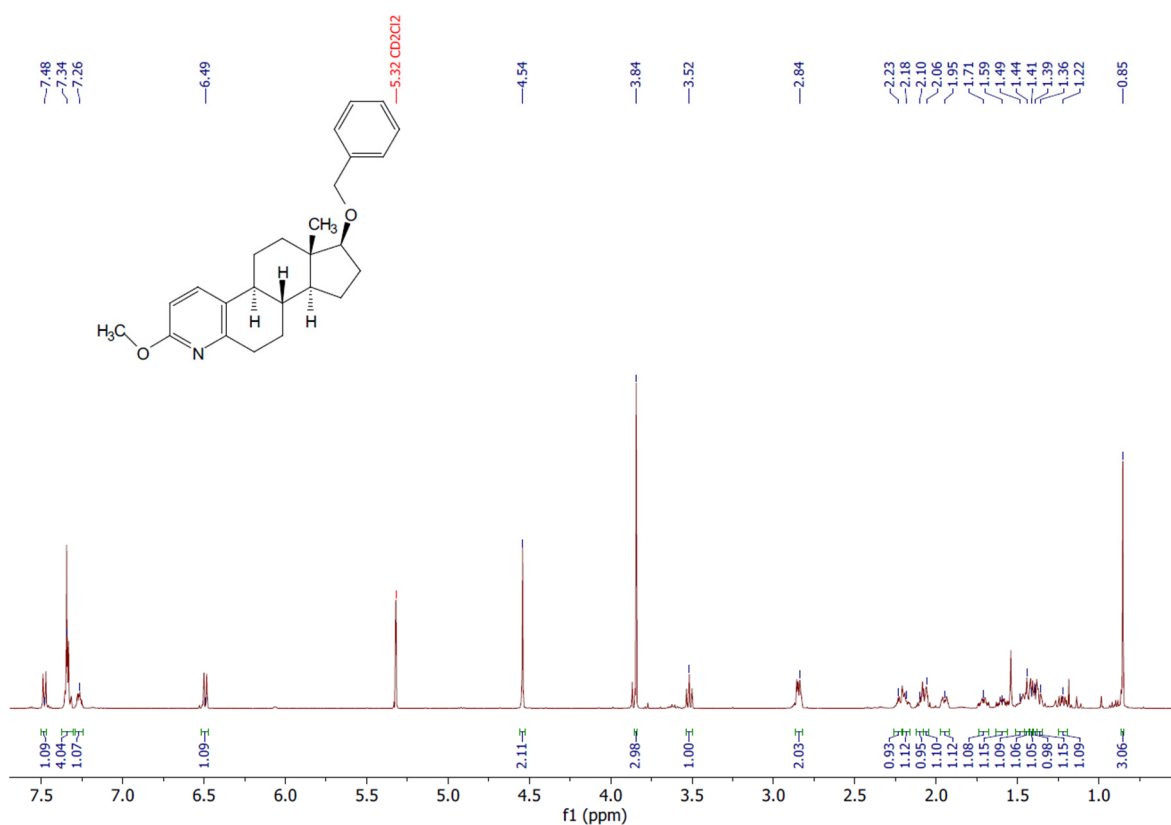
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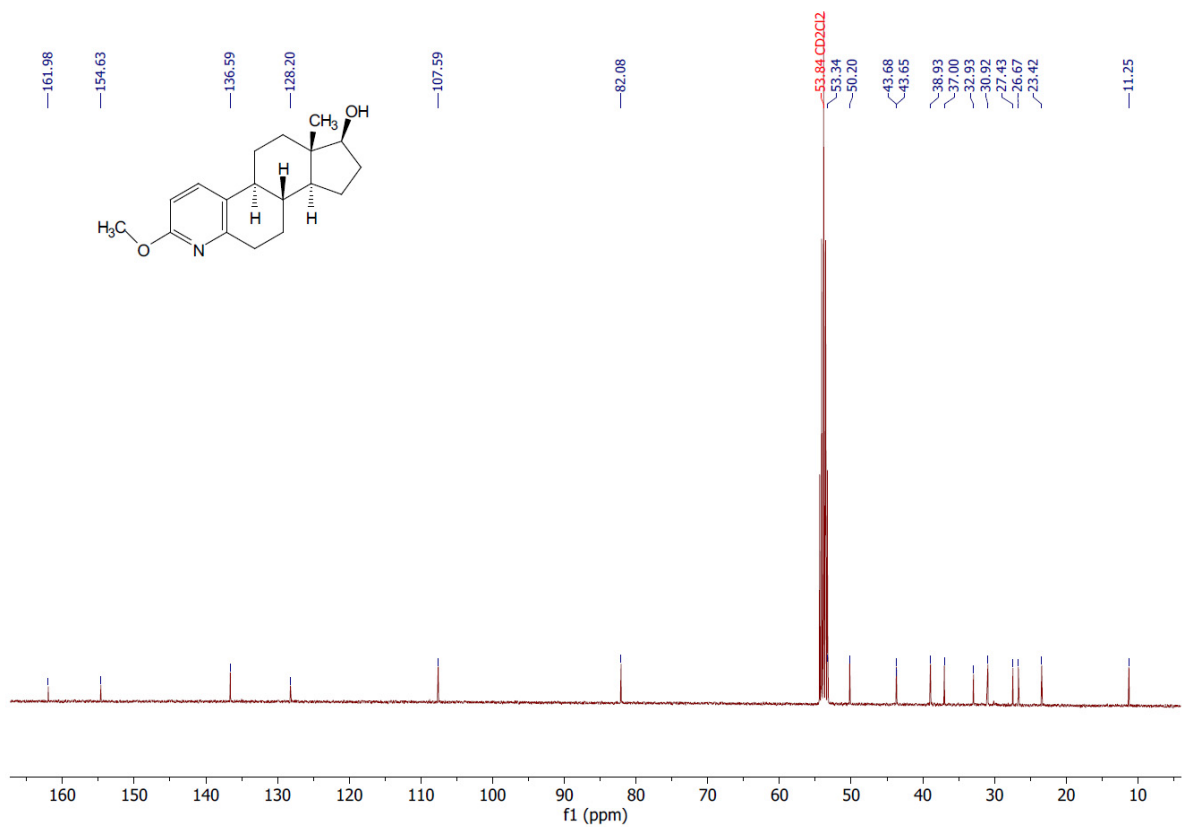
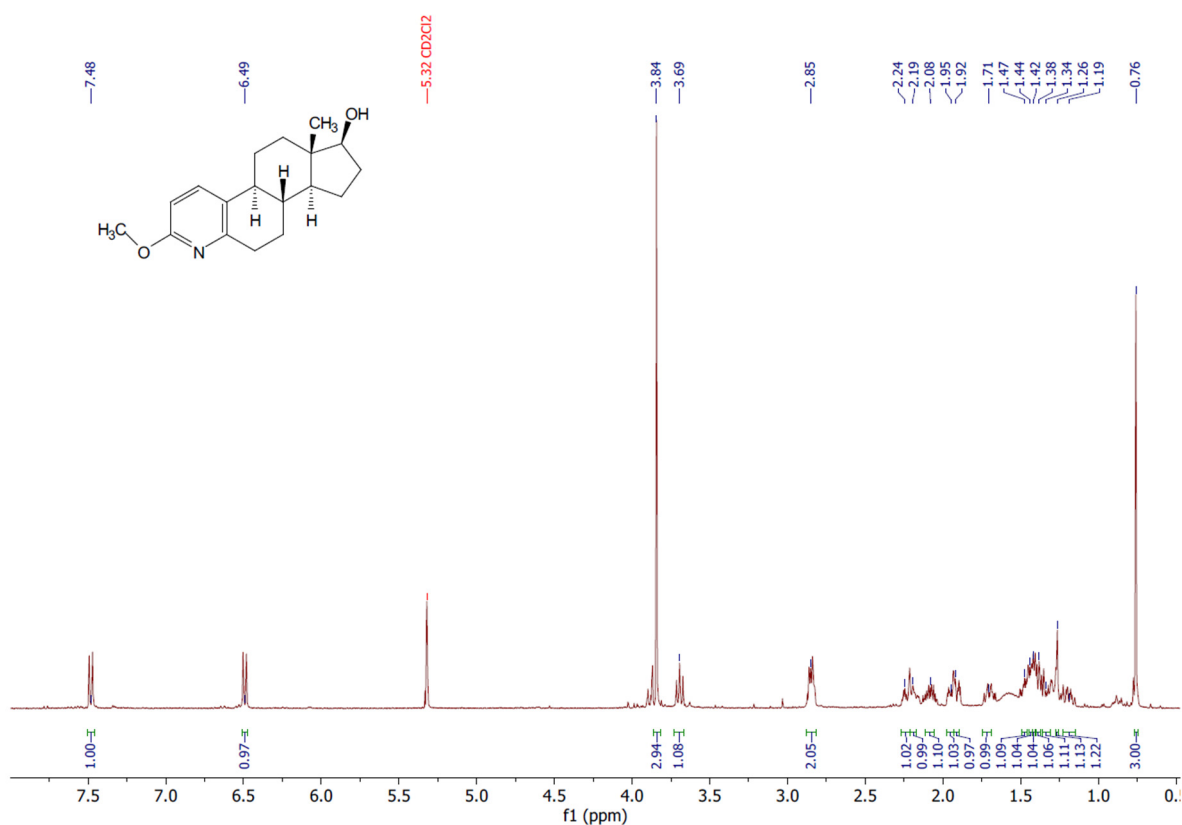
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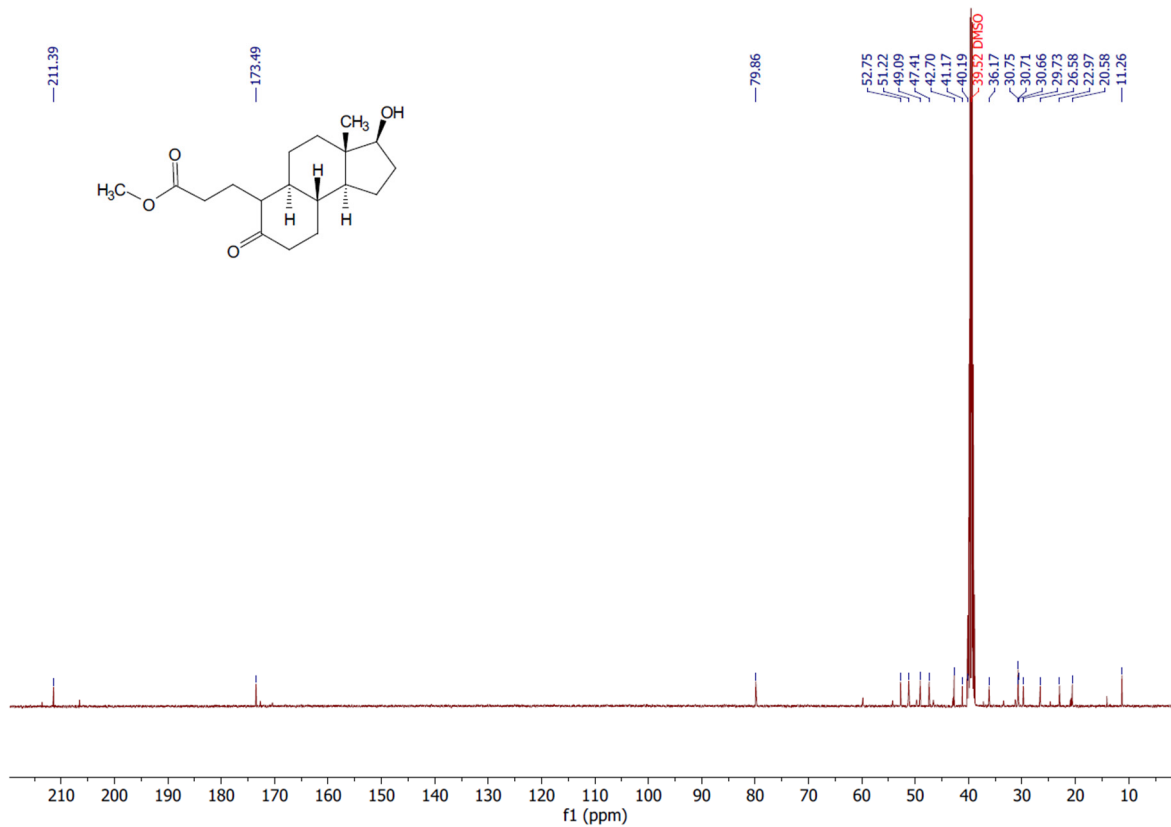
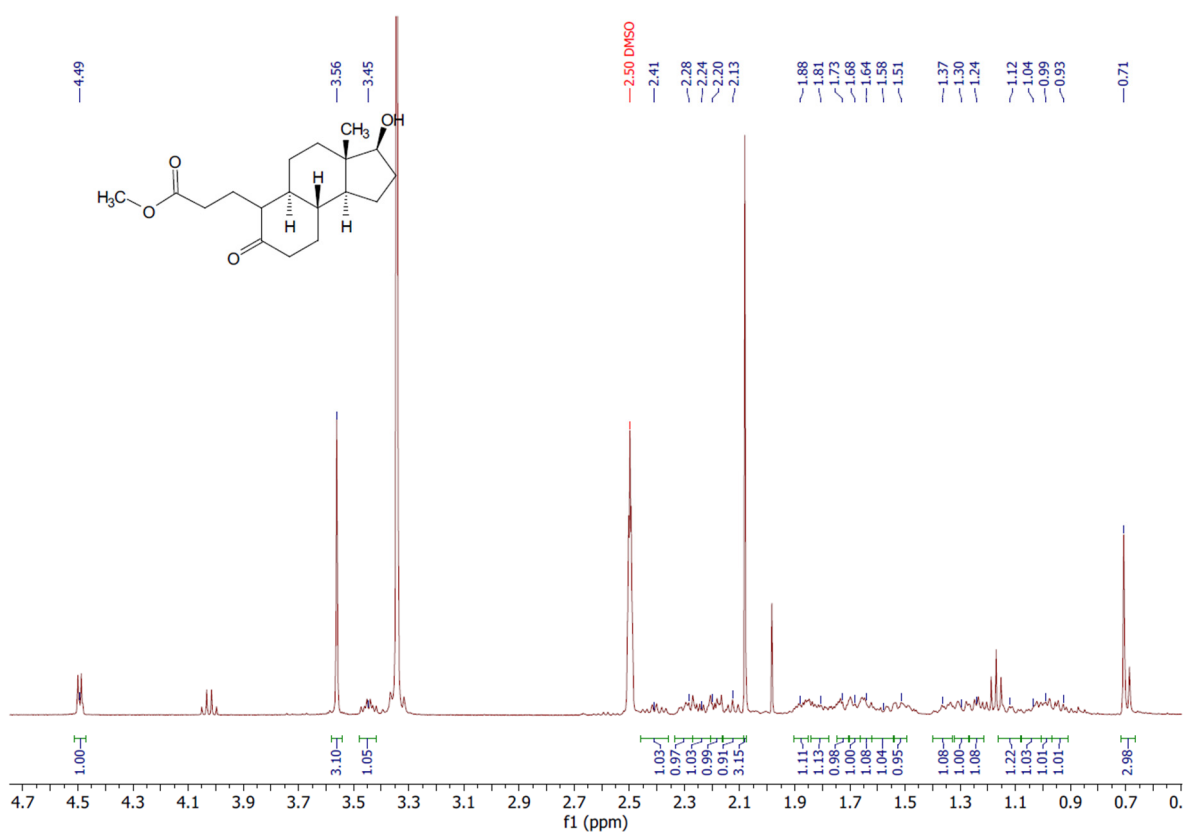
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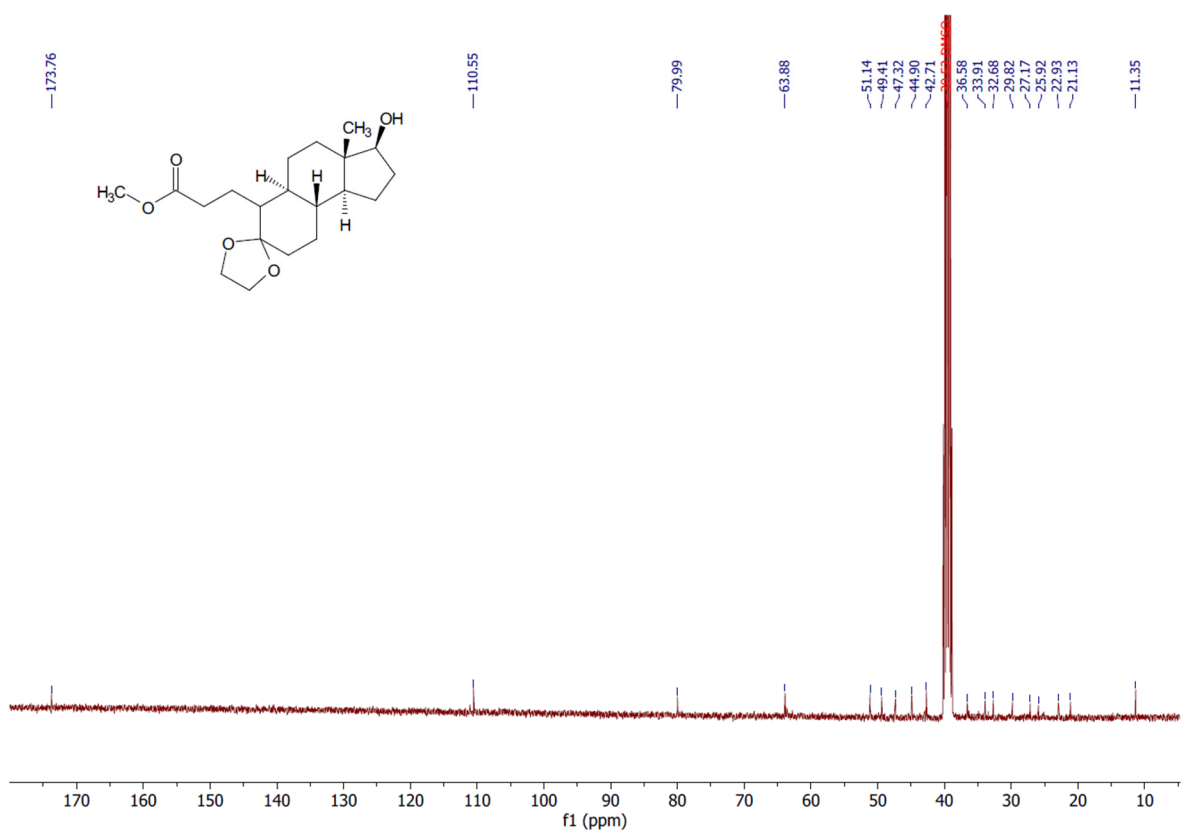
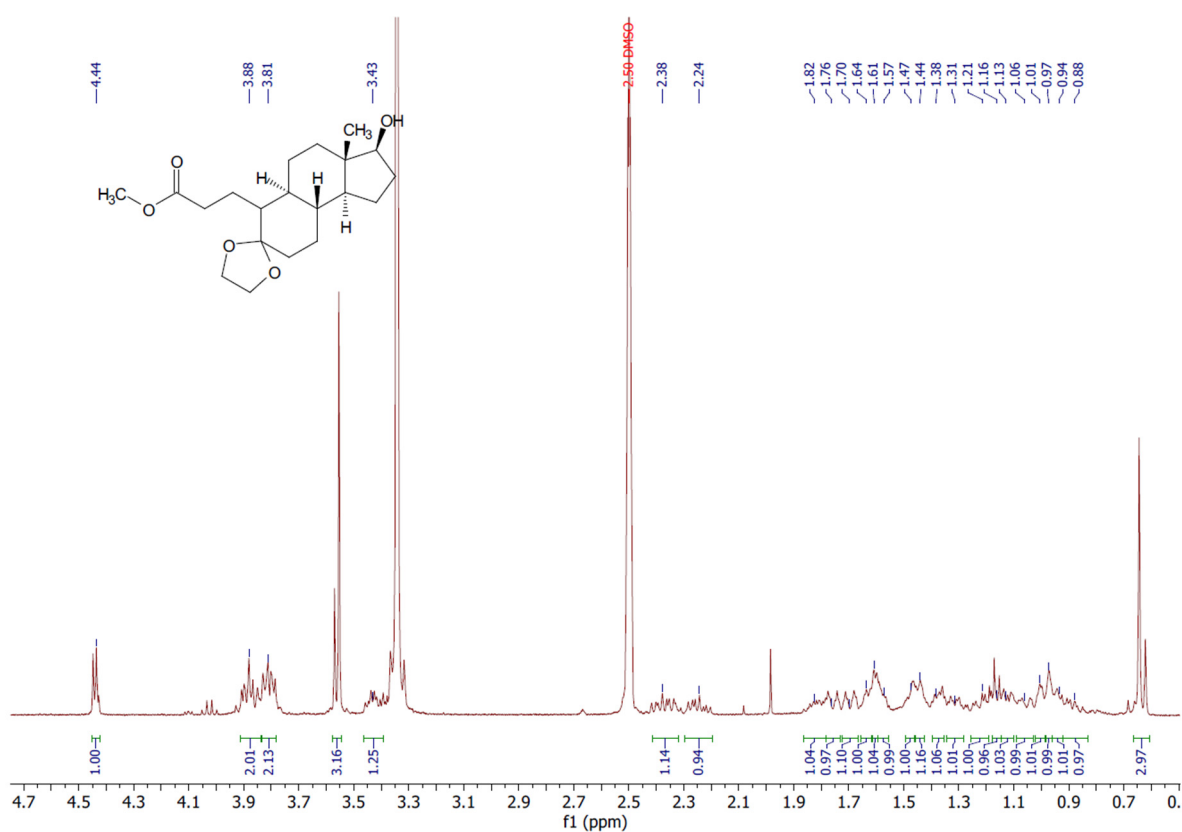
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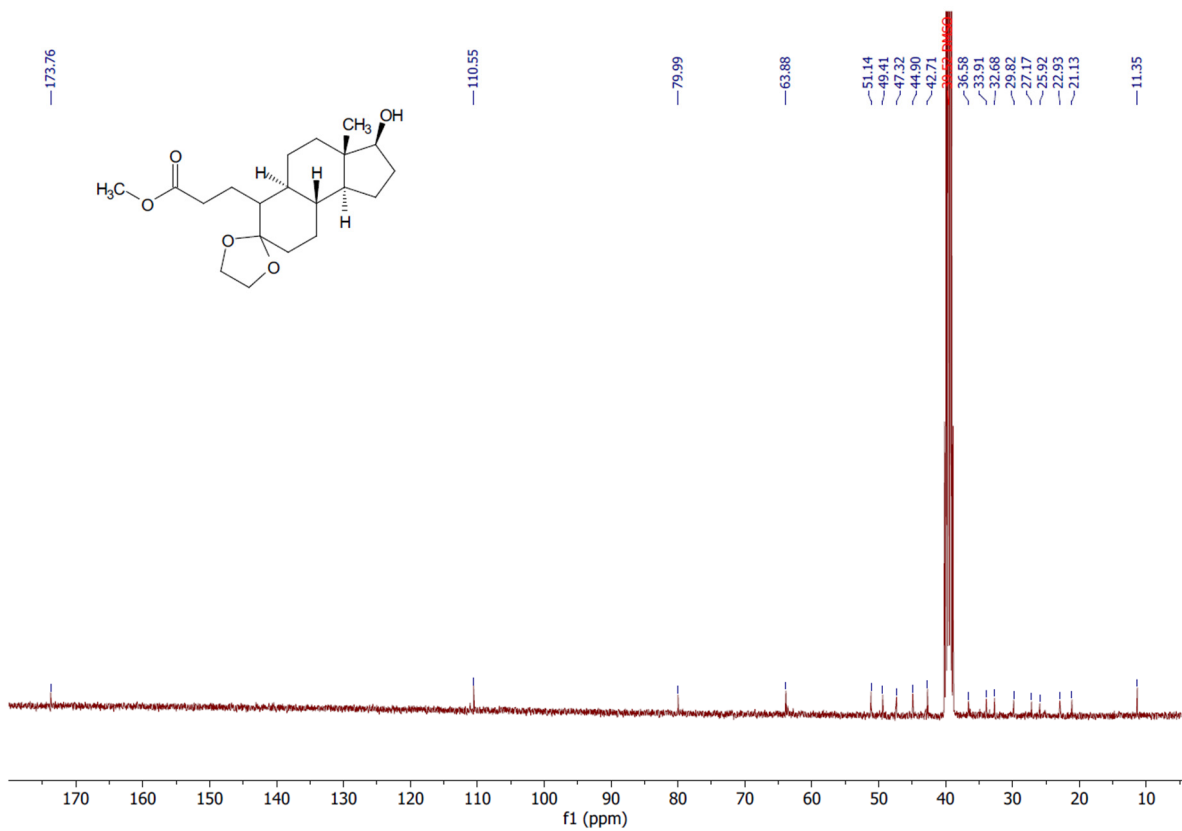
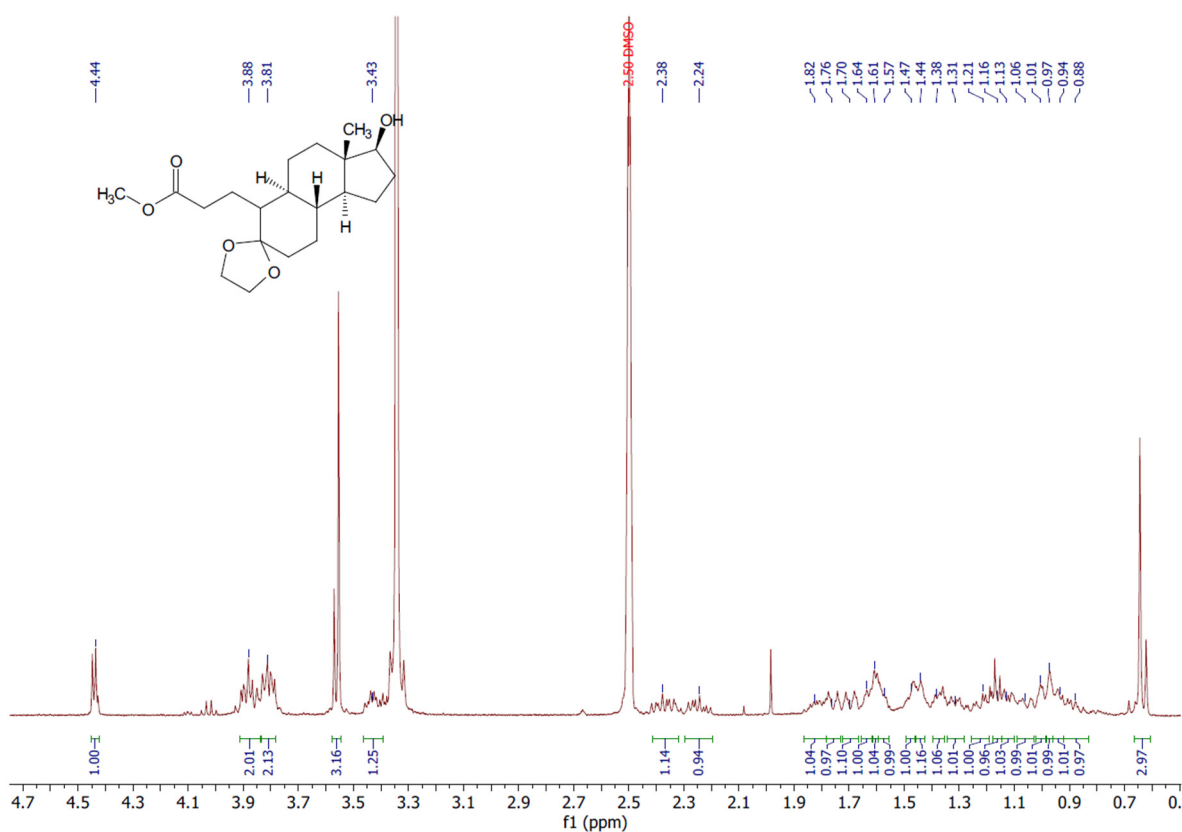
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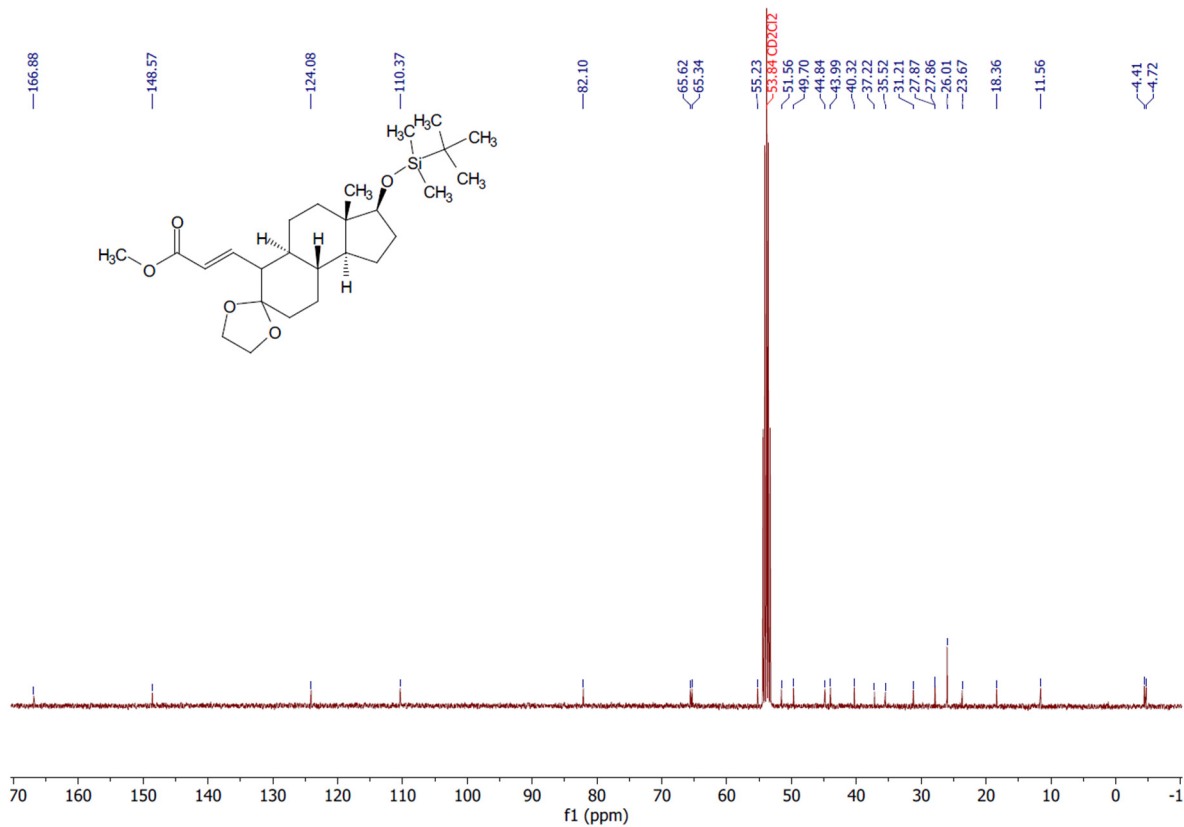
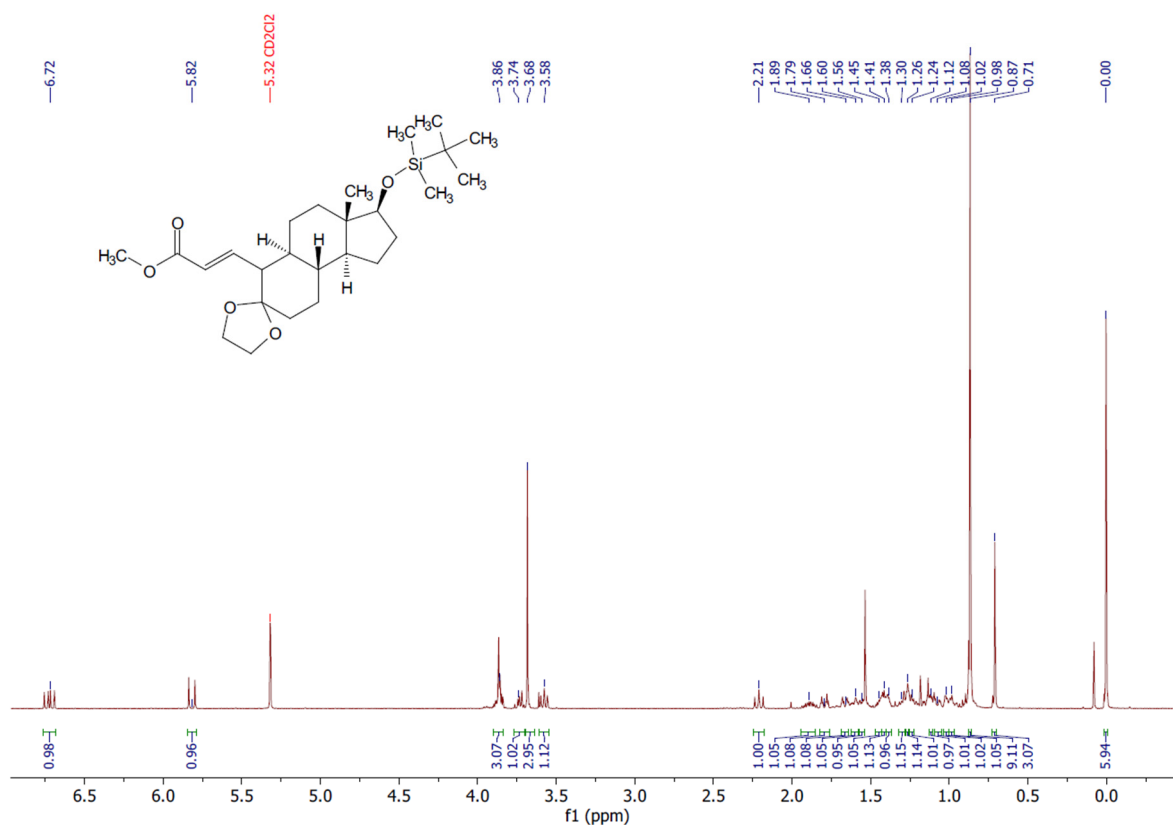
# Compound 13



# Compound 14

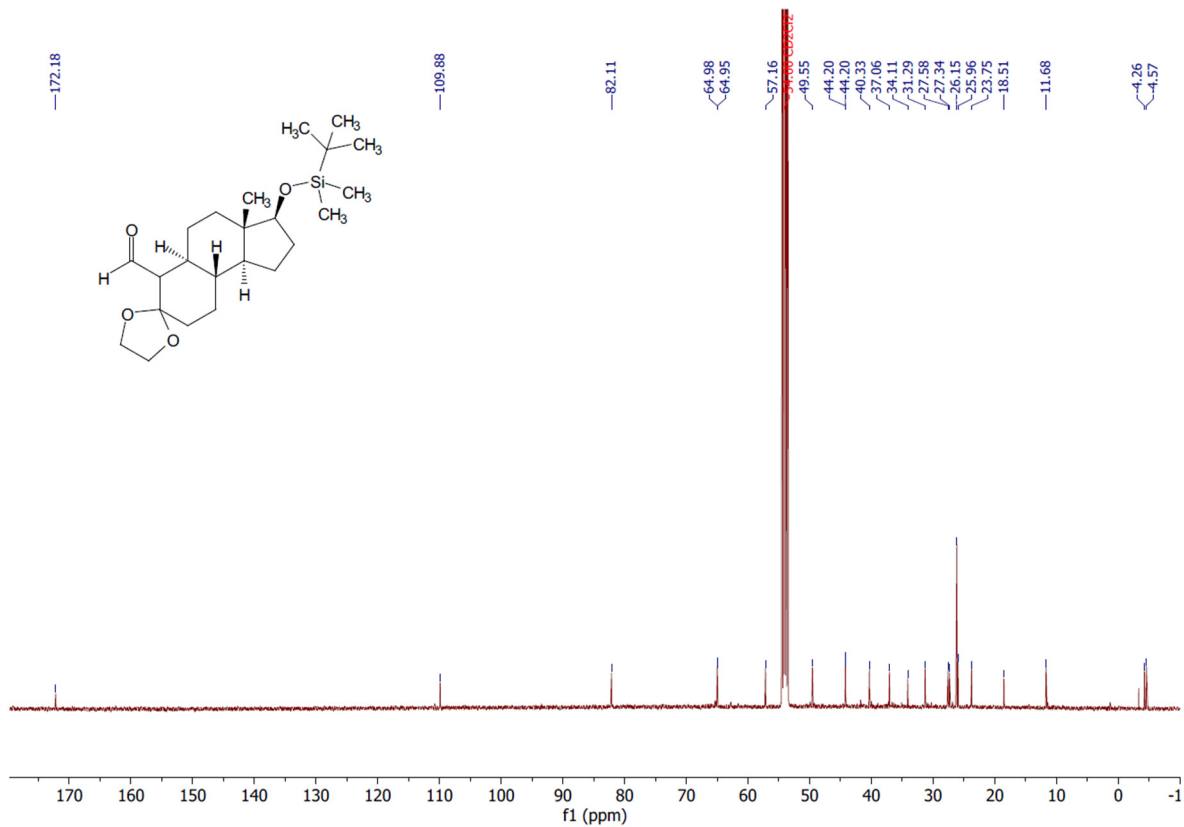
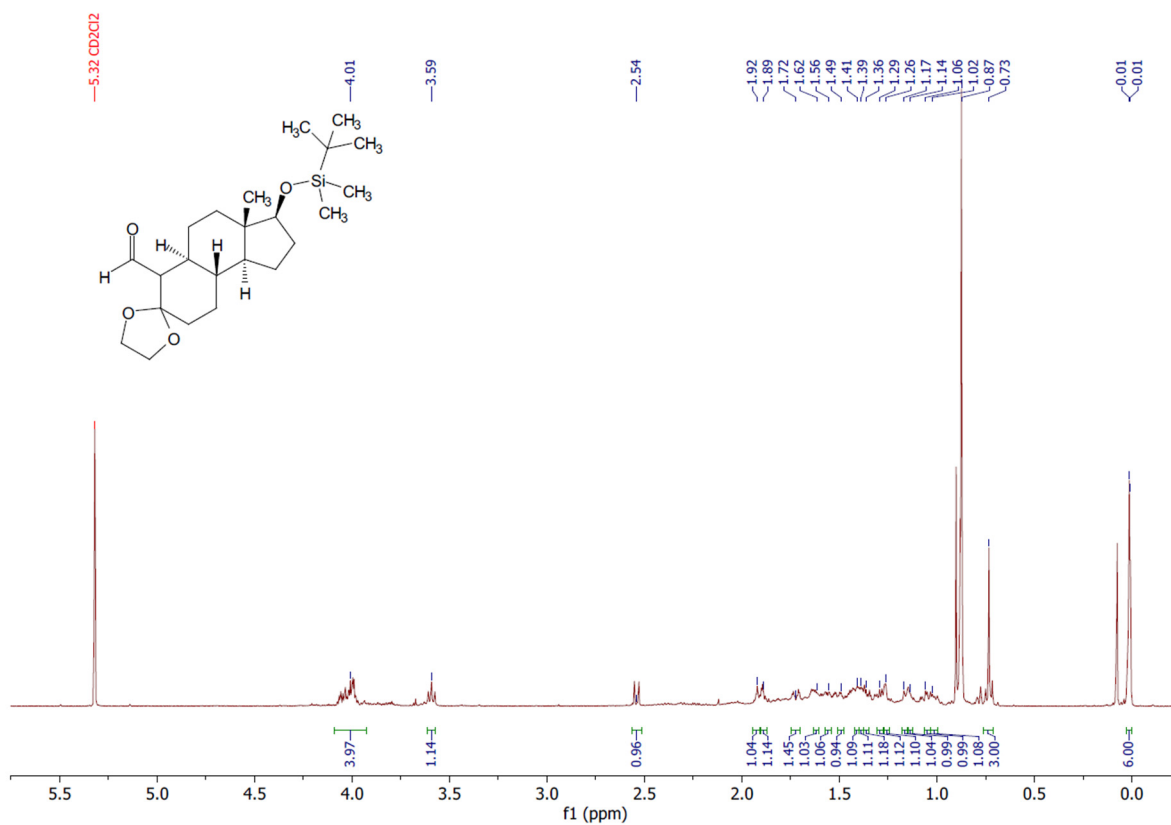


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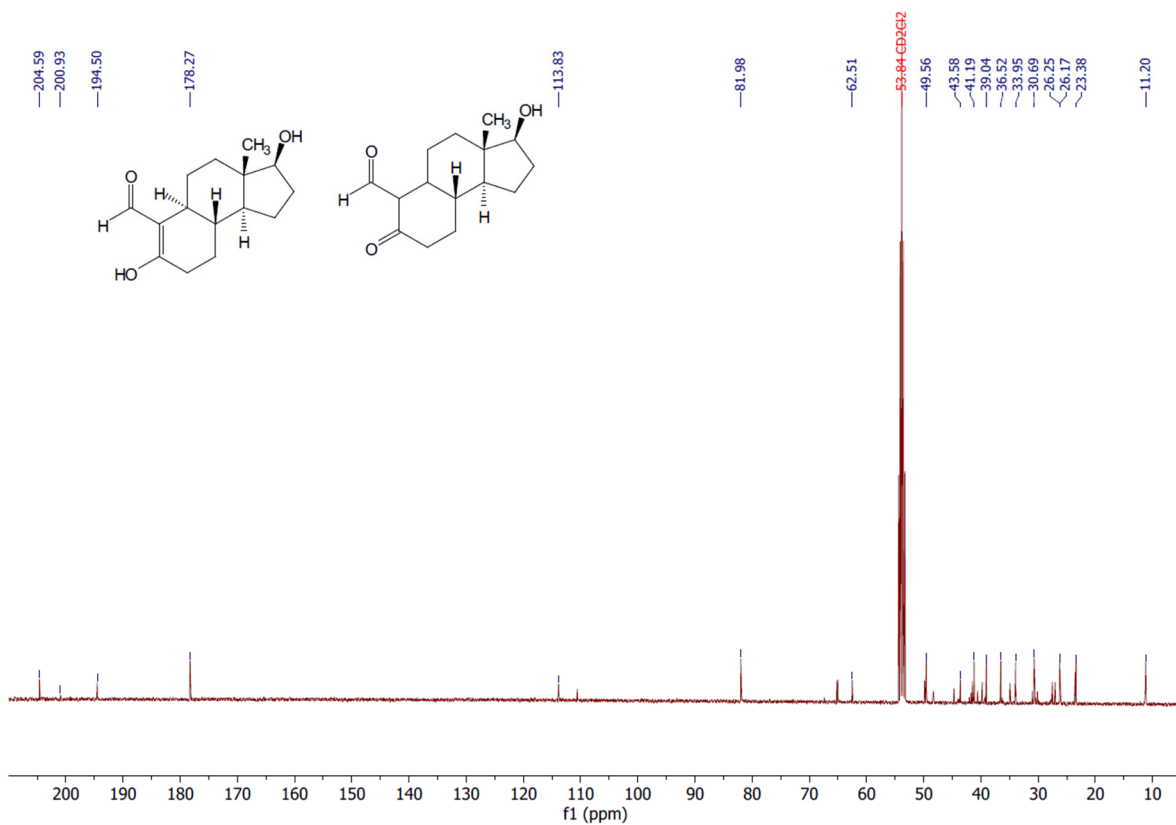
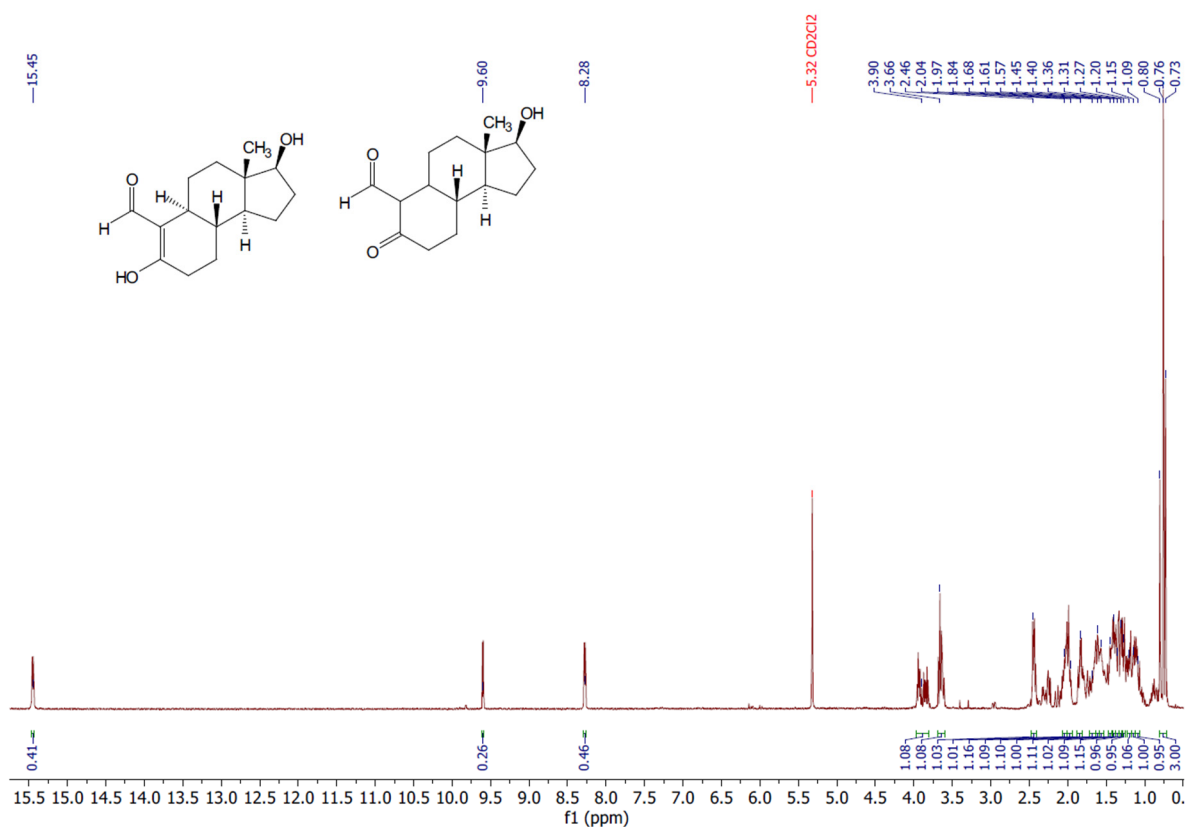




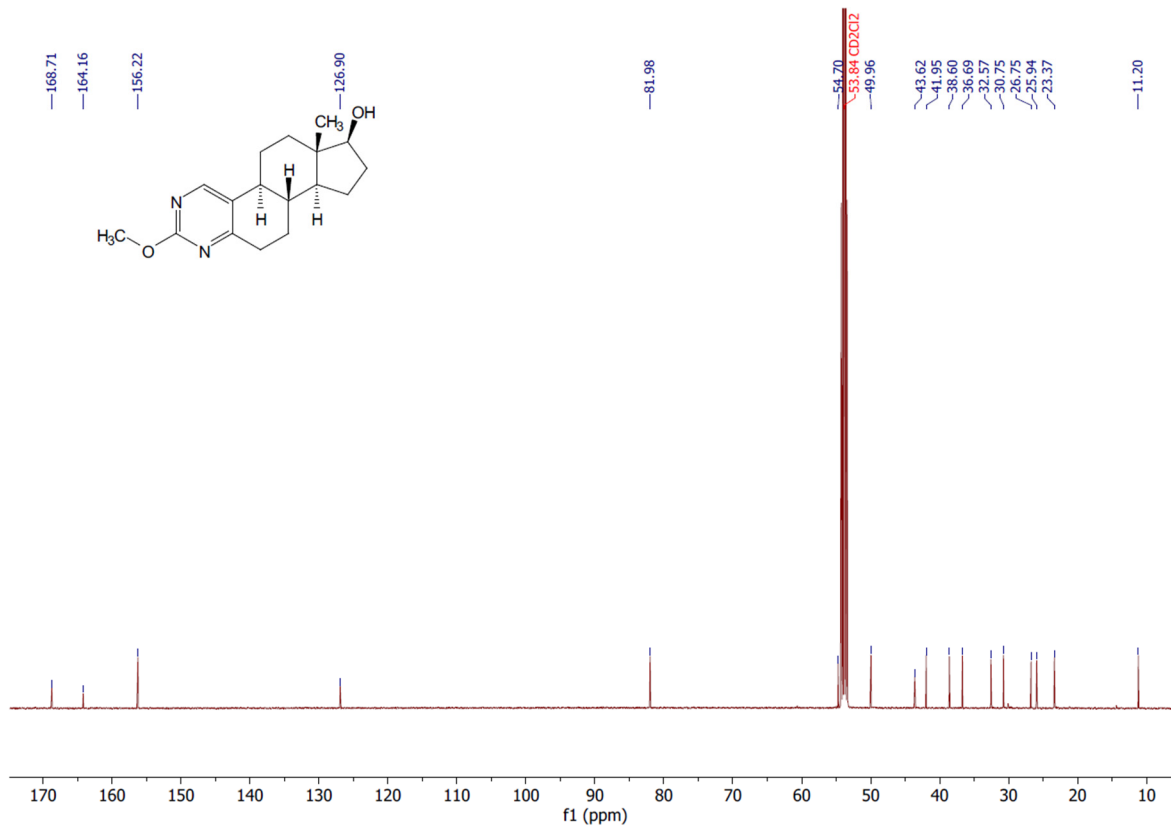
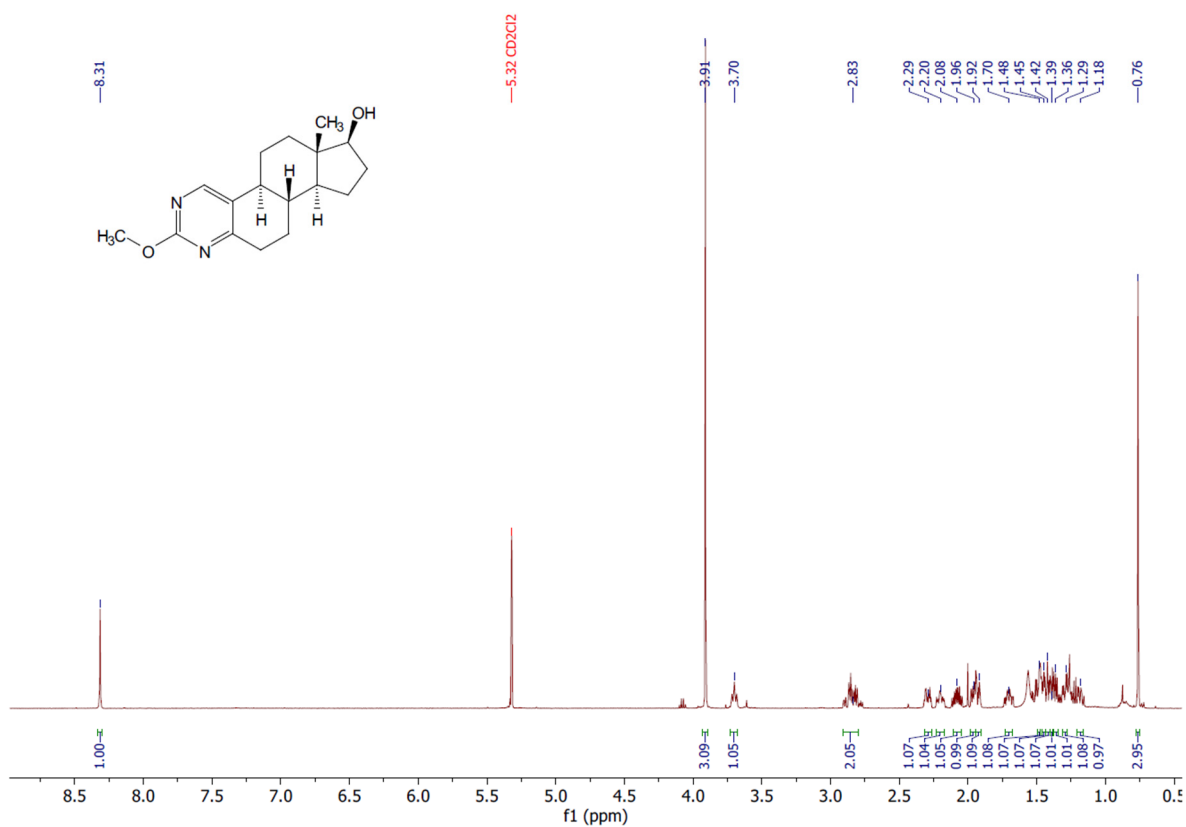
# Compound 16



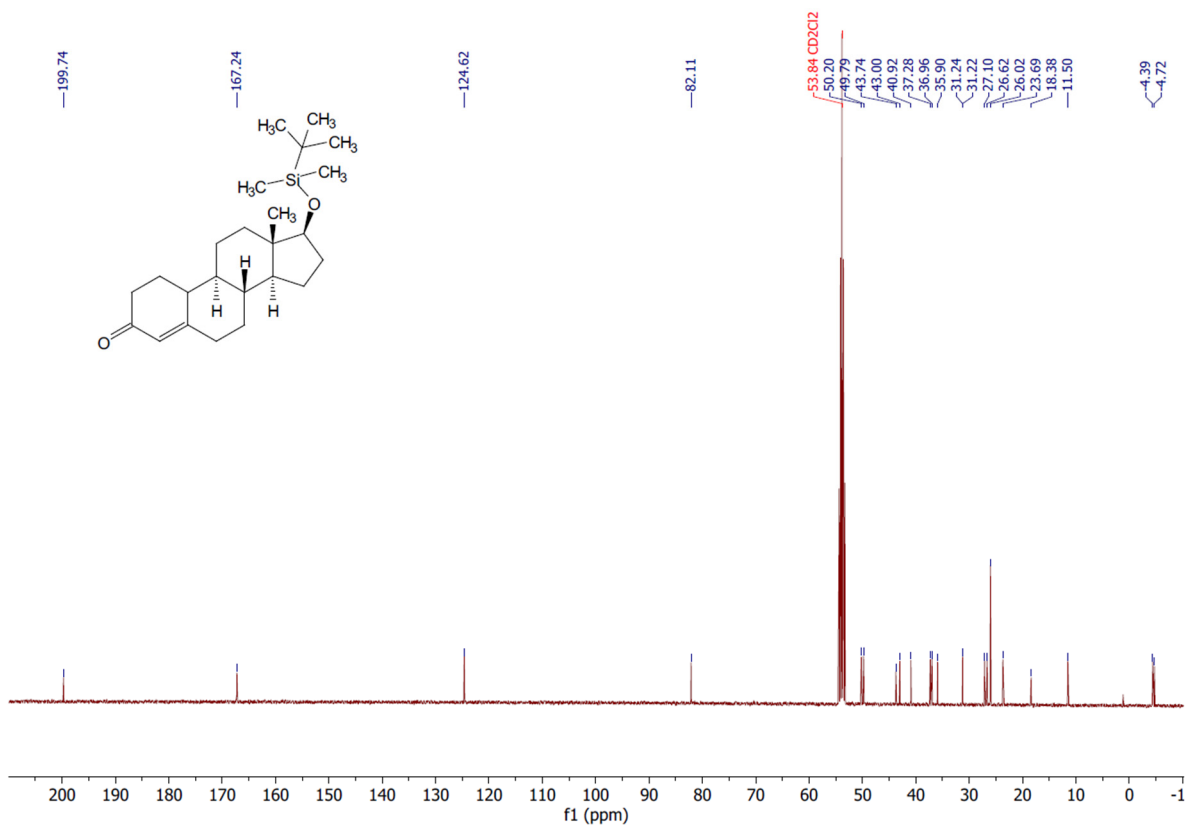
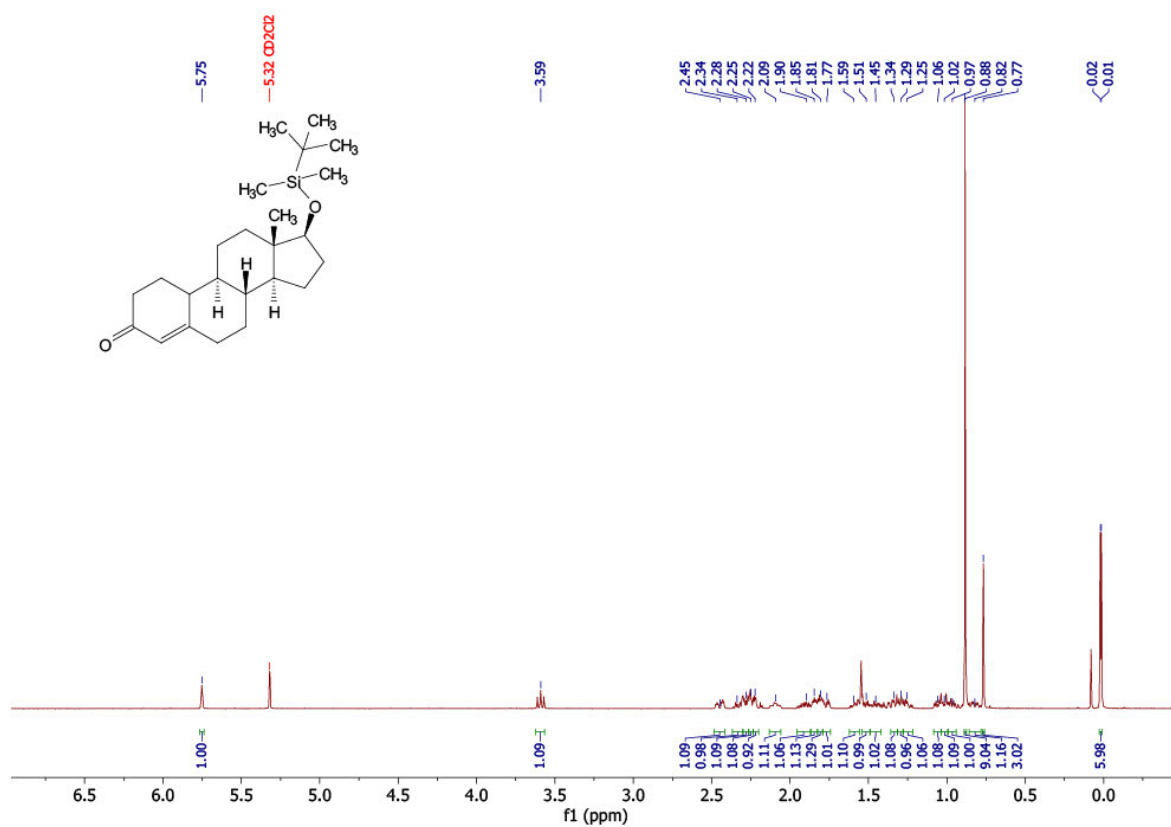
# Compound 17



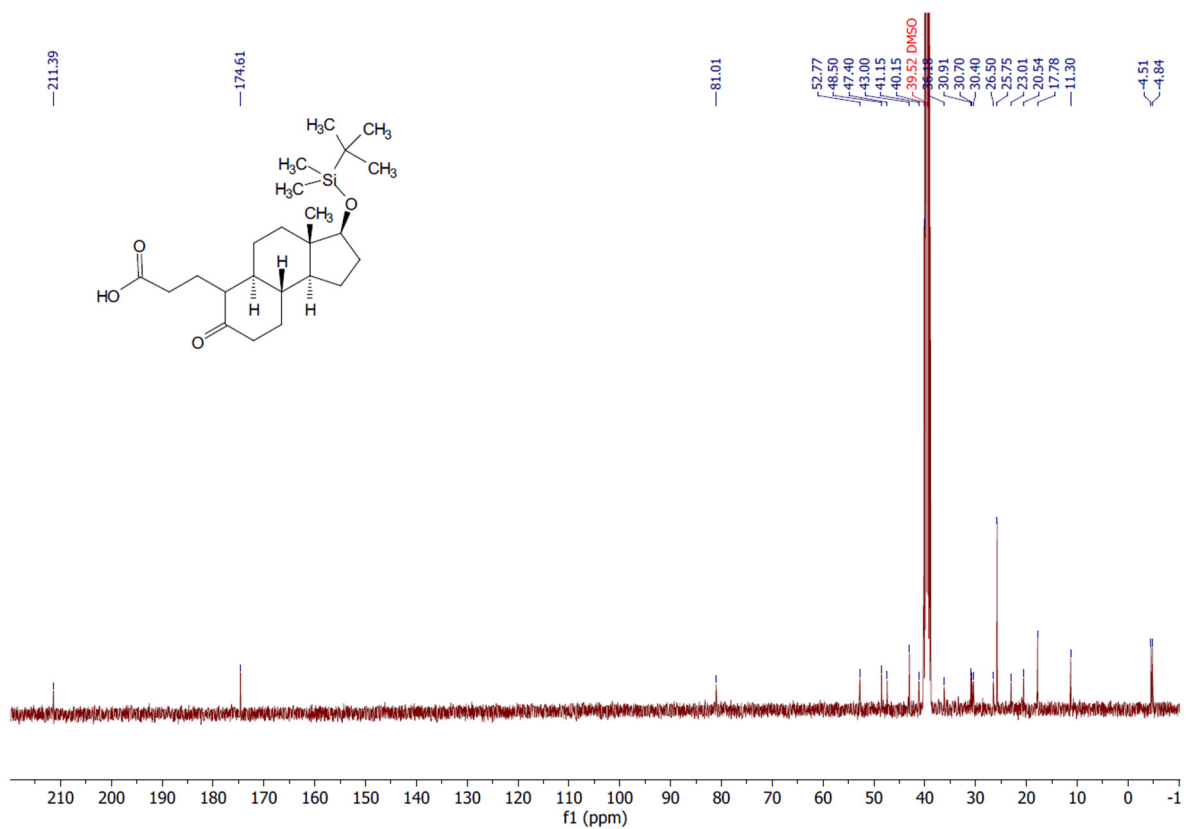
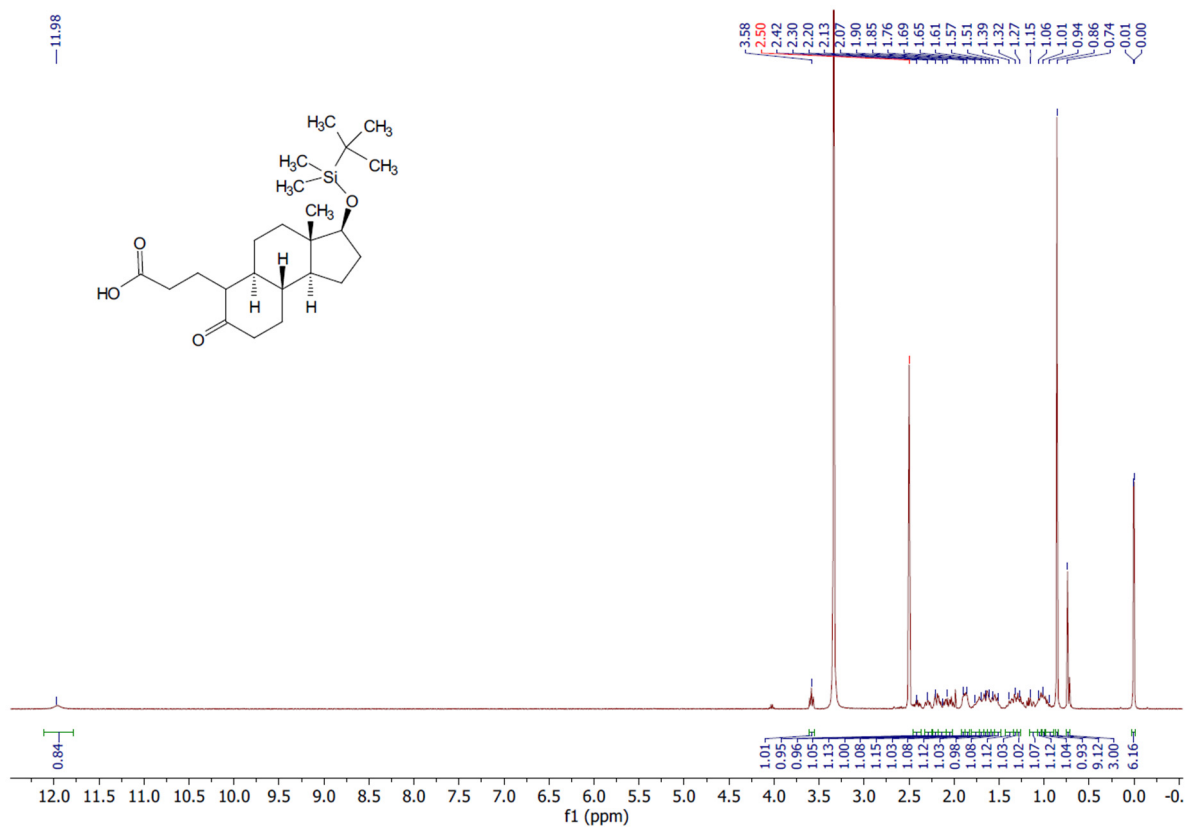
# Compound 2



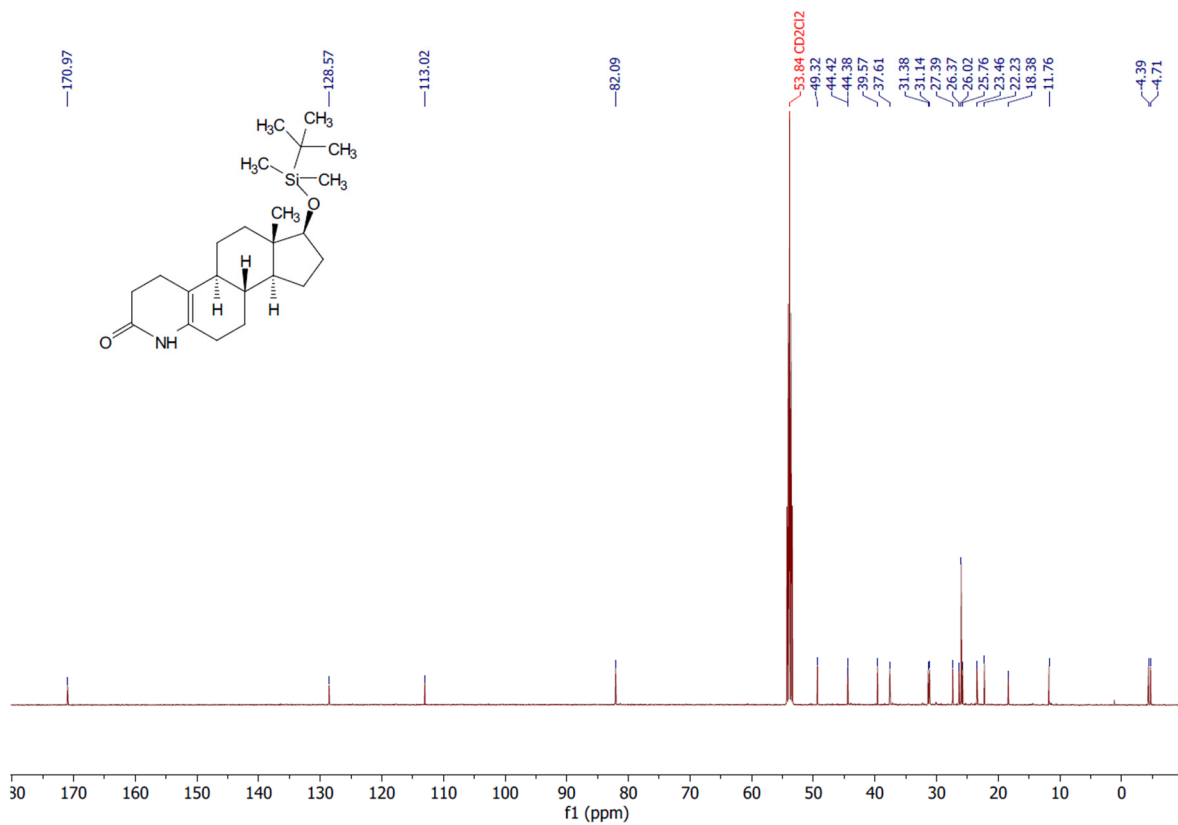
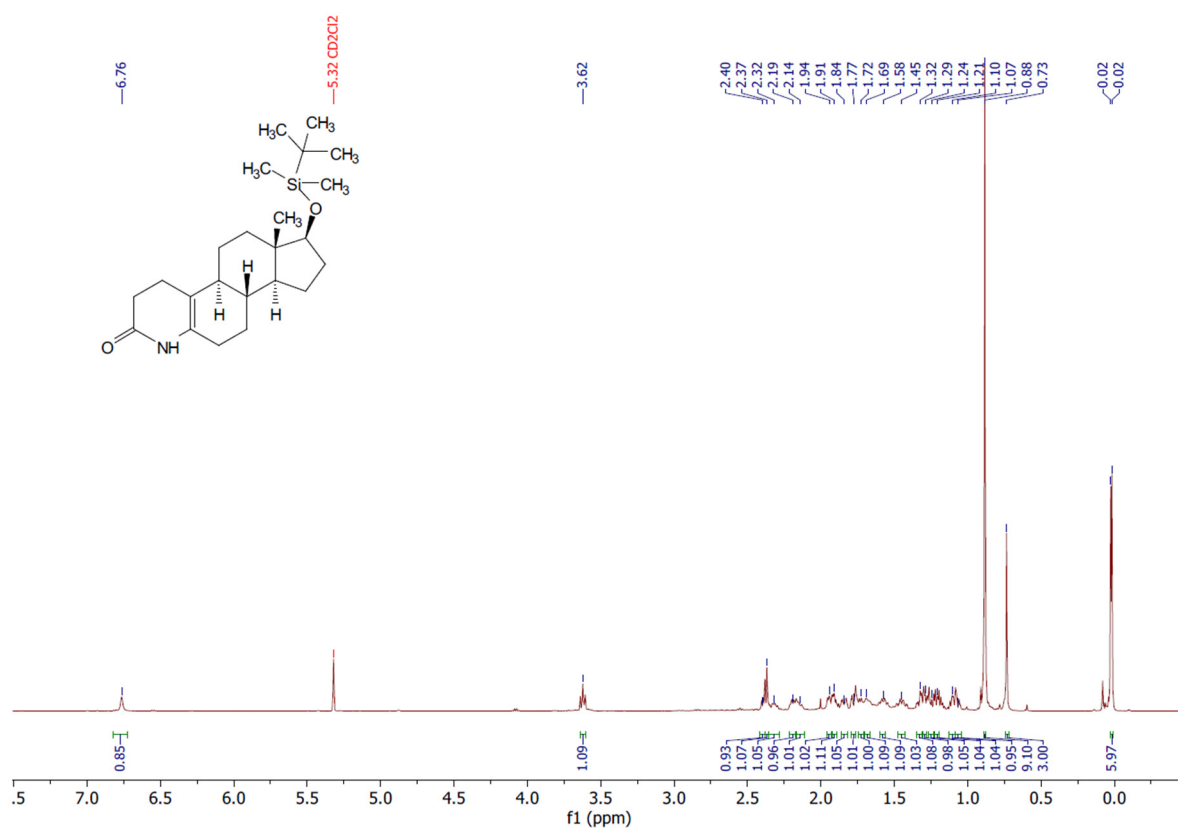
# Compound S1



# Compound S2



# Compound S3a



# Compound S3b

