

Supporting Information

for

The first Pd-catalyzed Buchwald–Hartwig aminations at C-2 or C-4 in the estrone series

Ildikó Bacsa¹, Dávid Szemerédi¹, János Wölfling¹, Gyula Schneider¹, Lilla Fekete², Erzsébet Mernyák^{*,1}

Address: ¹Department of Organic Chemistry, University of Szeged, Dóm tér 8, H-6720 Szeged, Hungary and ²Department of Medicinal Chemistry, University of Szeged, Dóm tér 8, H-6720 Szeged, Hungary

Email: Erzsébet Mernyák - bobe@chem.u-szeged.hu

*Corresponding author

Experimental procedures for compounds 5–13, their ¹H, ¹³C NMR, MS, elemental analysis data and the copies of their ¹H and ¹³C NMR spectra

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Experimental

General

Melting points (mp) were determined with a Kofler hot-stage apparatus and are uncorrected. Elemental analyses were performed with a Perkin-Elmer CHN analyzer model 2400. Thin-layer chromatography: silica gel 60 F₂₅₄; layer thickness 0.2 mm (Merck); eluent: 30% EtOAc/hexane if otherwise not stated, detection with I₂ or UV (365 nm) after spraying with 5% phosphomolybdic acid in 50% aqueous phosphoric acid and heating at 100–120 °C for 10 min. Flash chromatography: silica gel 60, 40–63 μ m (Merck). Reactions under microwave irradiation were carried out with a CEM Corporation focused microwave system, Model Discover SP. The maximum power of irradiation was 200 W. ¹H NMR spectra were recorded in DMSO-*d*₆, CDCl₃ solution with a Bruker DRX-500 instrument at 500 MHz, with Me₄Si as

internal standard. ^{13}C NMR spectra were recorded with the same instrument at 125 MHz under the same conditions. The full names of certain chemicals used:

$\text{Pd}_2(\text{dba})_3$: *Tris(dibenzylideneacetone)dipalladium(0)* X-Phos: *2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl* BINAP: *(R)-(+)-(1,1'-Binaphthalene-2,2'-diyl)bis(diphenylphosphine)* DBU: 1,8-Diazabicyclo[5.4.0]undec-7-ene

Mass spectrometry: Full scan mass spectra of the compounds were acquired in the range of 50 to 1000 m/z with a Finnigan TSQ-7000 triple quadrupole mass spectrometer (Finnigan-MAT, San Jose, CA) equipped with a Finnigan electrospray ionization source. Analyses were performed in positive ion mode using flow injection mass spectrometry with a mobile phase of 50% aqueous acetonitrile containing 0.1 v/v% formic acid. The flow rate was 0.3 ml/min. A five μl aliquot of the samples were loaded into the flow. The ESI capillary was adjusted to 4.5 kV and N_2 was used as a nebulizer gas.

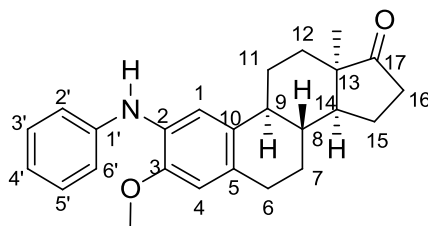
General procedure for microwave-assisted Pd-catalyzed amination of bromoestrone derivatives (1–4)

Palladium acetate (5.6 mg, 0.025 mmol, 10 mol %), potassium *tert*-butoxide (56 mg, 0.5 mmol, 2 equiv), X-Phos (12 mg, 0.025 mmol, 10 mol%), aniline (0.30 mmol, 1.2 equiv) and toluene (5 ml) were added into a 10 ml Pyrex pressure vessel (CEM, Part #: 908035) with silicone cap (CEM, Part #: 909210) under nitrogen atmosphere. The mixture was stirred at 60 °C for 5 min and cooled to rt. Then, the 2- or 4-bromoestrone 3-methyl ether (**1** or **3**, 91 mg, 0.25 mmol) or 2- or 4-bromoestrone 3-benzyl ether (**2** or **4**, 110 mg, 0.25 mmol) was charged into the tube, purged with nitrogen and the mixture was heated in a CEM microwave reactor at 100 °C for 10 min under stirring. The solvent was evaporated in vacuo and the residue was purified by flash chromatography with 15% ethyl acetate/85% hexane as eluent.

General procedure for Pd-catalyzed amination of bromoestrone derivatives (1–4) by thermal heating

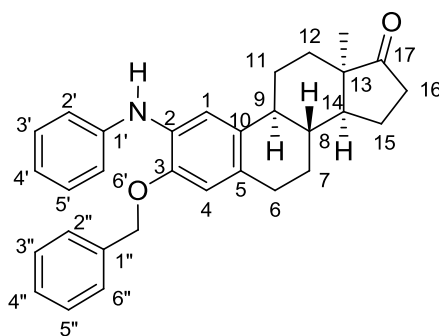
Palladium acetate (5.6 mg, 0.025 mmol, 10 mol %), potassium *tert*-butoxide (56 mg, 0.5 mmol, 2 equiv.), X-Phos (12 mg, 0.025 mmol, 10 mol %), aniline (0.30 mmol, 1.2 equiv.) and toluene (5 ml) were mixed under nitrogen. The mixture was stirred at 60 °C for 5 min and cooled to rt. Then, the 2- or 4-bromoestrone 3-methyl ether (**1** or **3**, 91 mg, 0.25 mmol) or 2- or 4-bromoestrone 3-benzyl ether (**2** or **4**, 110 mg, 0.25 mmol) was added, and the mixture

was stirred at reflux temperature for 24 h under nitrogen atmosphere. The solvent was evaporated in vacuo and the residue was purified by flash chromatography with 15% ethyl acetate/85% hexane as eluent.



3-Methoxy-2-(N-phenylamino)-13α-estra-1,3,5(10)-trien-17-one (5)

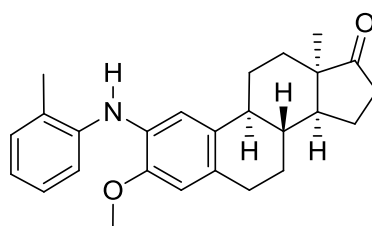
As described above bromo compound **1** (91 mg, 0.25 mmol) was reacted with aniline (27 μ l, 0.30 mmol). After purification by flash chromatography compound **5** was obtained as a white solid (79 mg, 85%, Mp.: 174–176°C, R_f = 0.67). Anal calcd. for $C_{25}H_{29}NO_2$: C, 79.96; H, 7.78. Found: C, 80.05; H, 7.62. M_r : 375.22. 1H NMR (500 MHz, DMSO- d_6) δ ppm :0.96(s, 3H, 18- H_3); 2.74(s, 2H, 6- H_2); 3.73(s, 3H, 3-OCH $_3$); 6.67(s; 1H, 4-H); 6.69(t, 1H, 4'-H); 6.88(d, 2H, 2'-H, 6'-H); 7.08(s, 1H, 1-H); 7.12(d, 2H, 3'-H, 5'-H); 7.14(s, 1H, NH); ^{13}C NMR (DMSO- d_6) δ ppm : 20.4; 24.5(C-18); 27.8; 28.2; 29.4; 31.6; 32.8; 40.7; 40.8; 48.4; 49.4(C-13); 55.3(3-OCH $_3$); 111.5(C-4); 115.4(2C: C-2', C-6'); 116.6(C-1) 118.3(C-4'); 128.8(2C: C-3', C-5'); 129.0(C-2); 129.9 and 131.0(C-5, C-10); 144.8(C-1'); 148.6(C-3); 220.6(C-17). MS m/z (%): 376 (100, $[M + H]^+$).



3-Benzoyloxy-2-(N-phenylamino)-13α-estra-1,3,5(10)-trien-17-one (6)

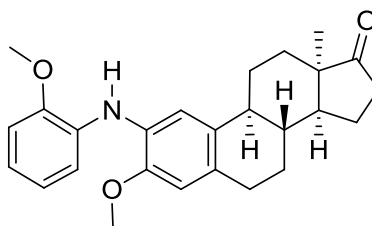
As described above bromo compound **2** (110 mg, 0.25 mmol) was reacted with aniline (27 μ l, 0.30 mmol). After purification by flash chromatography compound **6** was obtained as a white solid (97 mg, 86%, Mp.: 75–77°C, R_f =0.64). Anal calcd. for $C_{31}H_{33}NO_2$: C, 82.45; H, 7.37. Found: C, 82.73; H, 7.25. M_r : 451.25 1H NMR (500 MHz, DMSO- d_6) δ ppm :0.96(s, 3H, 18-

H₃); 2.71(m, 2H, 6-H₂); 5.07(s, 2H, 3-OCH₂); 6.71(t, *J* = 7.2 Hz, 1H, 4'-H); 6.76(s, 1H, 4-H); 6.88(d, *J* = 7.7 Hz, 2H, 2'-H, 6'-H); 7.10(s, 1H, 1-H); 7.13-7.16(overlapping multiplets, 2H, 3'-H, 5'-H, NH); 7.26(m, 1H, 4''-H); 7.31(t, *J* = 7.2 Hz, 2H, 2''-H, 6''-H); 7.36(d, *J* = 7.2 Hz, 2H, 3''-H, 5''-H); ¹³C NMR (DMSO-d₆) δ ppm: 20.4; 24.5(C-18); 27.8; 29.3; 31.5; 32.8; 40.7; 40.8; 48.4; 49.4(C-13); 69.4(OCH₂); 113.2(C-4); 115.5(2C: C-2', C-6'); 117.6(C-1); 118.3(C-4'); 127.1(2C: C-3'', C-5''); 127.4(C-4''); 128.1(2C: C-2'', C-6''); 128.7(2C: C-3', C-5'); 129.4 and 130.3(C-2 and C-10); 131.5(C-5); 137.3(C-1''); 145.0(C-1'); 147.8(C-3); 220.6(C-17). MS *m/z* (%): 452 (100, [M + H]⁺).



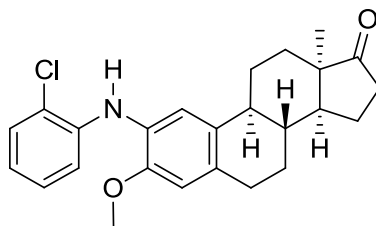
3-Methoxy-2-(N-2'-methylphenylamino)-13α-estra-1,3,5(10)-trien-17-one (7a)

As described above bromo compound **1** (91 mg, 0.25 mmol) was reacted with 2-methylaniline (33 μl, 0.30 mmol). After purification by flash chromatography compound **7a** was obtained as a white solid (78 mg, 80%, Mp.: 168–170°C, R_f = 0.71). Anal calcd. for C₂₆H₃₁NO₂: C, 80.17; H, 8.02. Found: C, 80.37; H, 7.95. M_r: 389.24 ¹H NMR (500 MHz, DMSO-d₆) δ ppm : 0.95(s, 3H, 18-H₃); 2.15(s, 3H, 2'-Me); 2.75(m, 2H, 6-H₂); 3.75(s, 3H, 3- OCH₃); 6.30(s, 1H, NH); 6.66(s, 1H, 4-H); 6.76(s, 1H, 1-H); 6.80(t, 1H, *J*=7.5 Hz, 5'-H); 6.82(d, 1H, *J*=7.3 Hz, 3 6'-H); 7.04(t, 1H, *J*=7.5 Hz, 4'-H); 7.13(d, 1H, *J*=7.3 Hz, 3'-H); ¹³C NMR (DMSO-d₆) δ ppm : 17.7(2'-CH₃); 20.4; 24.5(C-18); 27.9; 28.2; 29.3; 30.3; 31.5; 32.8; 40.8; 48.4; 49.4(C-13); 55.4(OCH₃); 111.2(C-4); 115.3(C-1); 117.3(C-6'); 120.3(C-5'); 126.3(C-4') 127.2(C-1'); 129.0(C-2); 130.3(C-3'); 130.4(C-10); 131.0(C-5); 142.3(C-2'); 147.8(C-3); 220.6(C-17). MS *m/z* (%): 390 (100, [M + H]⁺).



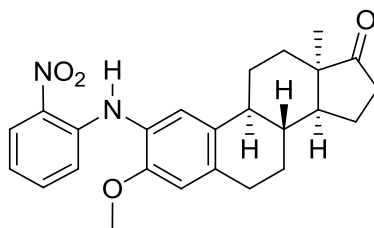
3-Methoxy-2-(N-2'-methoxyphenylamino)-13 α -estra-1,3,5(10)-trien-17-one (7b)

As described above bromo compound **1** (91 mg, 0.25 mmol) was reacted with 2-methoxyaniline (34 μ l, 0.30 mmol). After purification by flash chromatography compound **7b** was obtained as a white solid (95 mg, 94%, Mp.: 132–134°C, R_f = 0.53). Anal calcd. for $C_{26}H_{31}NO_3$: C, 77.01; H, 7.71. Found: C, 69.93; H, 7.88. M_r : 405.23 1H NMR (500 MHz, DMSO- d_6) δ ppm :0.96(s, 3H, 18- H_3); 2.73(m, 2H, 6- H_2); 3.76(s, 3H, 3-OCH $_3$); 3.82(s, 3H, 3'-OCH $_3$); 6.37(s; 1H, NH); 6.67(s, 1H, 4-H); 6.77(t, 1H, J =7.2 Hz, 4'-H); 6.83(t, 1H, J =7.2 Hz, 5'-H); 6.95(d, 1H, J =7.9 Hz, 3'-H); 7.02(d, 1H, J =7.9 Hz, 6'-H); 7.11(s, 1H, 1-H); ^{13}C NMR (DMSO- d_6) δ ppm : 20.4; 24.5(C-18); 27.8; 28.2; 29.4; 31.6; 32.8; 40.8; 40.9; 48.4; 49.4; 55.5(2C: 3-OCH $_3$ and 4'-OCH $_3$); 110.7(C-3'); 111.1(C-4); 113.3(C-6'); 114.5(C-1); 119.1(C-4'); 120.6(C-5'); 128.8(C-10); 129.2(C-2); 131.0(C-5); 132.7(C-1'); 147.3(C-3); 147.8(C-2'); 220.7(C-17). MS m/z (%): 406 (100, $[M + H]^+$).



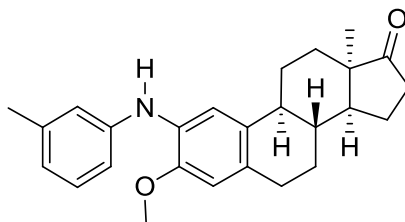
2-(N-2'-Chlorophenylamino)-3-methoxy-13 α -estra-1,3,5(10)-trien-17-one (7c)

As described above bromo compound **1** (91 mg, 0.25 mmol) was reacted with 2-chloroaniline (32 μ l, 0.30 mmol). After purification by flash chromatography compound **7c** was obtained as a white solid (89 mg, 87%, Mp.: 70–72°C, R_f = 0.67). Anal calcd. for $C_{25}H_{28}ClNO_2$: C, 73.25; H, 6.88. Found: C, 73.51; H, 6.94. M_r : 409.18 1H NMR (500 MHz, DMSO- d_6) δ ppm :0.96(s, 3H, 18- H_3); 2.77(m, 2H, 6- H_2); 3.73(s, 3H, 3-OCH $_3$); 6.64(s; 1H, 4-H); 6.73(s; 1H, NH); 6.74 and 7.12(2t, 2x1H, J =7.7 Hz, 4'-H and 5'-H); 6.85 and 7.35(2d, 2x1H, J =7.9 Hz, 3'-H and 6'-H); 7.06(s; 1H, 1-H); ^{13}C NMR (CDCl $_3$) δ ppm : 20.1; 25.1(C-18); 28.4; 28.5; 30.1; 32.1; 33.5; 41.6; 41.6; 49.2; 50.2(C-13); 55.7(3-OCH $_3$); 111.2 and 115.2 and 116.4 and 119.9(C-1 and C-4 and C-4' and C-6'); 121.9(C-10); 127.4(C-5'); 128.6(C-5); 129.6(C-3'); 130.6 and 131.6(C-2 and C-2'); 140.5(C-1'); 148.4(C-3); 221.7(C-17). MS m/z (%): 394 (100); 410 (5, $[M + H]^+$).



3-Methoxy-2-(N-2'-nitrophenylamino)-13α-estra-1,3,5(10)-trien-17-one (7d)

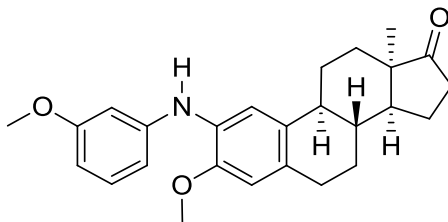
As described above bromo compound **1** (91 mg, 0.25 mmol) was reacted with 2-nitroaniline (41 mg, 0.30 mmol). After purification by flash chromatography compound **7d** was obtained as a yellow solid (101 mg, 96%, Mp.: 106–108°C, R_f = 0.55). Anal calcd. for $C_{25}H_{28}N_2O_4$: C, 71.41; H, 6.71. Found: C, 71.32; H, 6.85. M_r : 420.20 1H NMR (500 MHz, $CDCl_3$) δ ppm : 1.06(s, 3H, 18- H_3); 2.86(m, 2H, 6- H_2); 3.80(s, 3H, 3-OCH $_3$); 6.67(s, 1H, 4-H); 6.72(t, 1H, J = 7.1 Hz, 4'-H); 7.11(d, 1H, J = 7.9 Hz, 6'-H); 7.34(t, 1H, J = 7.1 Hz, 5'-H); 8.18(d, 1H, J = 7.9 Hz, 3'-H); 7.25(s, 1H, 1-H); 9.35(s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ ppm : 21.0; 25.0(C-18); 28.3; 28.4; 30.2; 32.0; 33.4; 41.4; 41.4; 49.2; 50.2(C-13); 55.7(3-OCH $_3$); 111.7(C-4); 116.0(C-6'); 117.0(C-4'); 122.1(C-1); 125.2(C-2); 126.6(C-5'); 132.0(C-10); 133.3(C-2'); 134.8(C-5); 135.5(C-5'); 143.2(C-1'); 151.0(C-3); 221.5(C-17). MS m/z (%): 421 (100, $[M + H]^+$).



3-Methoxy-2-(N-3'-methylphenylamino)-13α-estra-1,3,5(10)-trien-17-one (8a)

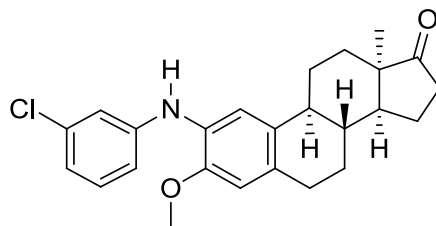
As described above bromo compound **1** (91 mg, 0.25 mmol) was reacted with 3-methylaniline (32 μ l, 0.30 mmol). After purification by flash chromatography compound **8a** was obtained as a white solid (77 mg, 79%, Mp.: 106–107°C, R_f = 0.69). Anal calcd. for $C_{26}H_{31}NO_2$: C, 80.17; H, 8.02. Found: C, 80.38; H, 7.91. M_r : 389.24 1H NMR (500 MHz, DMSO- d_6) δ ppm : 0.96(s, 3H, 18- H_3); 2.18(s, 3H, 3'-CH $_3$); 2.74(m, 2H, 6- H_2); 3.73(s, 3H, 3-OCH $_3$); 6.51(d, 1H, J =7.4 Hz, 4'-H); 6.67(s, 1H, 4-H); 6.69(d, 1H, J =7.4 Hz, 6'-H); 6.68(s, 1H, 2'-H); 7.01(t, 1H, J =7.7 Hz, 5'-H); 7.04(s, 1H, NH); 7.07(s, 1H, 1-H); ^{13}C NMR (DMSO- d_6) δ ppm : 20.4; 21.2(3'-CH $_3$); 24.5(C-18); 27.8; 28.2; 29.4; 31.6; 32.8; 40.7; 40.8 48.4; 49.4(C-13); 55.3(3-

OCH₃); 111.5(C-4); 112.5(C-6'); 116.2(C-2'); 116.9(C-1); 119.1(C-4'); and 128.6(C-5'); 129.1(C-10); 129.9(C-5); 131.0(C-2); 137.8(C-3'); 144.8(C-1'); 148.6(C-3); 220.6(C-17). MS m/z (%): 390 (100, [M + H]⁺).



3-Methoxy-2-(N-3'-methoxyphenylamino)-13α-estra-1,3,5(10)-trien-17-one (8b)

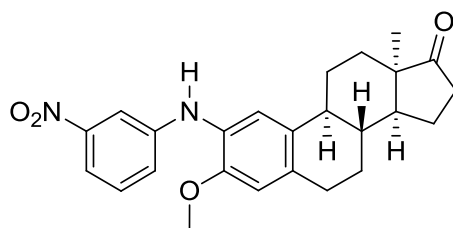
As described above bromo compound **1** (91 mg, 0.25 mmol) was reacted with 3-methoxyaniline (34 μl, 0.30 mmol). After purification by flash chromatography compound **8b** was obtained as a white solid (93 mg, 92%, Mp.: 135–137°C, R_f = 0.51). Anal calcd. for C₂₆H₃₁NO₃: C, 77.01; H, 7.71. Found: C, 69.94; H, 7.85. M_r: 405.23 ¹H NMR (500 MHz, DMSO-d₆) δ ppm : 0.96(s, 3H, 18-H₃); 2.74(m, 2H, 6-H₂); 3.65(s, 3H, 3-OCH₃); 3.73(s, 3H, 3'-OCH₃); 6.27(m, 1H, 1-H, 4'-H); 6.47(m, 2H, 2'-H, 6'-H); 6.50(s, 1H, 4'-H); 6.67(s, 1H, 4-H); 7.03(t, 1H, J=7.9 Hz, 5'-H); 7.11(s, 1H, 1-H); 7.17(s, 1H, NH); ¹³C NMR (DMSO-d₆) δ ppm : 20.4; 24.5(C-18); 27.8; 28.3; 29.4; 31.6; 32.8; 40.7; 40.8; 48.4; 49.4(C-13); 54.6 and 55.3(3-OCH₃ and 3'-OCH₃); 100.8(C-2'); 103.8(C-4'); 107.9(C-6'); 111.5(C-4); 117.1(C-1); 128.8(C-2); 129.5(C-5'); 130.1(C-10); 131.0(C-5); 146.2(C-1'); 148.6(C-3); 160.0(C-3'); 220.7(C-17). MS m/z (%): 406 (100, [M + H]⁺).



2-(N-3'-Chlorophenylamino)-3-methoxy-13α-estra-1,3,5(10)-trien-17-one (8c)

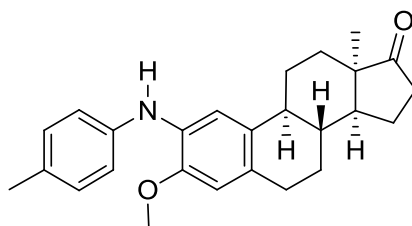
As described above bromo compound **1** (91 mg, 0.25 mmol) was reacted with 3-chloroaniline (32 μl, 0.30 mmol). After purification by flash chromatography compound **8c** was obtained as a white solid (86 mg, 84%, Mp.: 72–74°C, R_f = 0.51). Anal calcd. for C₂₅H₂₈ClNO₂: C, 73.25; H, 6.88. Found: C, 73.46; H, 6.94. M_r: 409.18 ¹H NMR (500 MHz, DMSO-d₆) δ ppm : 0.96(s, 3H, 18-H₃); 2.76(m, 2H, 6-H₂); 3.72(s, 3H, 3-OCH₃); 6.65 and 6.74(2d, 2x1H, J=6.8 Hz, 4'-

H, 6'-H); 6.71(s; 1H, 4-H); 6.77(s; 1H, 2'-H); 7.07(s, 1H, 1-H); 7.11(t, 1H, $J=8.0$ Hz, 5'-H); 7.55(s, 1H, NH); ^{13}C NMR (DMSO- d_6) δ ppm: 20.4; 24.4(C-18); 27.7; 28.2; 29.4; 31.6; 32.8; 40.7; 40.7; 48.4(C-13); 55.3(3-OCH $_3$); 111.8(C-4); 112.7(C-6'); 113.7(C-2'); 117.0(C-1); 119.4(C-4'); 127.5(C-2); 130.2(C-5'); 131.3(C-10); 131.9(C-5); 133.3(C-3') 147.2(C-1'); 149.7(C-3); 220.6(C-17). MS m/z (%): 493 (100); 451 (67, $[\text{M} + \text{MeCN} + \text{H}]^+$); 410 (40, $[\text{M} + \text{H}]^+$).



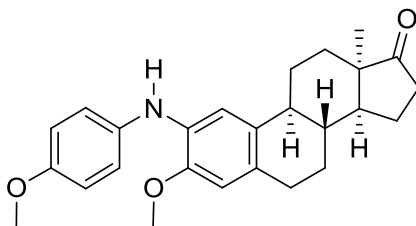
3-Methoxy-2-(N-3'-nitrophenylamino)-13 α -estra-1,3,5(10)-trien-17-one (8d)

As described above bromo compound **1** (91 mg, 0.25 mmol) was reacted with 3-nitroaniline (41 mg, 0.30 mmol). After purification by flash chromatography compound **8d** was obtained as a yellow solid (98 mg, 93%, Mp.: 52–54°C, $R_f = 0.47$). Anal calcd. for $\text{C}_{25}\text{H}_{28}\text{N}_2\text{O}_4$: C, 71.41; H, 6.71. Found: C, 71.33; H, 6.85. M_r : 420.20 ^1H NMR (500 MHz, CDCl_3) δ ppm :1.06(s, 3H, 18-H $_3$); 2.83(m, 2H, 6-H $_2$); 3.82(s, 3H, 3-OCH $_3$); 6.62(s; 1H, 4-H) 7.22(s; 1H, 1-H); 7.30 and 7.60(2d, 2x1H, $J = 7.8$ Hz, 4'-H and 6'-H); 7.34(t, 1H, $J = 8.1$ Hz, 5'-H); 7.78(s; 1H, NH); ^{13}C NMR (CDCl_3) δ ppm : 21.0; 25.1(C-18); 28.3; 28.5; 30.1; 32.0; 33.4; 41.5; 41.6; 49.2; 50.2(C-13); 55.6(3-OCH $_3$); 110.3 and 111.3 and 114.2 and 116.8 and 121.3(C-1 and C-4 and C-2' and C-4' and C-6'); 127.9(C-10); 129.8(C-5'); 131.6(C-5); 131.9(C-2); 145.5(C-1'); 148.4(C-3); 149.3(C-3'); 221.6(C-17). MS m/z (%): 421 (10, $[\text{M} + \text{H}]^+$); 453 (100, $[\text{M} + \text{MeOH} + \text{H}]^+$).



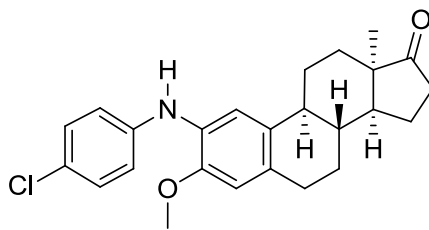
3-Methoxy-2-(N-4'-methylphenylamino)-13 α -estra-1,3,5(10)-trien-17-one (9a)

As described above bromo compound **1** (91 mg, 0.25 mmol) was reacted with 4-methylaniline (32 mg, 0.30 mmol). After purification by flash chromatography compound **9a** was obtained as a white solid (79 mg, 81%, Mp.: 145–147°C, R_f = 0.73). Anal calcd. for $C_{26}H_{31}NO_2$: C, 80.17; H, 8.02. Found: C, 79.88; H, 8.25. M_r : 389.24 1H NMR (500 MHz, DMSO- d_6) δ ppm : 0.95(s, 3H, 18- H_3); 2.18(s, 3H, 4'- CH_3); 2.72(m, 2H, 6- H_2); 3.73(s, 3H, 3-O CH_3); 6.63(s, 1H, 4-H); 6.84(d, 2H, J = 8.9 Hz, 2'-H, 6'-H); 6.95(s, 1H, NH); 6.97(d, 2H, J =8.9 Hz, 3'-H, 5'-H); 6.95(s, 1H, NH); 7.03(s, 1H, 1-H); ^{13}C NMR (DMSO- d_6) δ ppm : 20.1(4'- CH_3); 20.4; 24.5(C-18); 27.9; 28.2; 29.3; 31.5; 32.8; 40.8; 40.9; 48.4; 49.4(C-13); 55.3(O CH_3); 111.3(C-4); 114.8(C-1); 116.4(2C: C-2', C-6'); 129.2(2C: C-3', C-5'); 127.4(C-1'); 128.9(C-10); 129.8(C-2); 131.0(C-5); 141.8(C-4'); 147.8(C-3); 220.6(C-17). MS m/z (%): 390 (100, $[M + H]^+$).



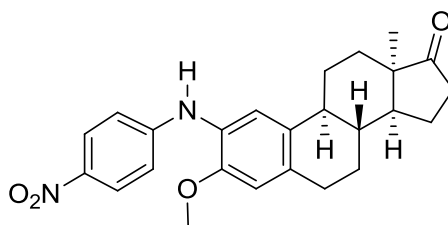
3-Methoxy-2-(N-4'-methoxyphenylamino)-13 α -estra-1,3,5(10)-trien-17-one (9b)

As described above bromo compound **1** (91 mg, 0.25 mmol) was reacted with 4-methoxyaniline (35 μ l, 0.30 mmol). After purification by flash chromatography compound **9b** was obtained as a white solid (95 mg, 94%, Mp.: 83–85°C, R_f = 0.60). Anal calcd. for $C_{26}H_{31}NO_3$: C, 77.01; H, 7.71. Found: C, 69.85; H, 7.93. M_r : 405.23 1H NMR (500 MHz, DMSO- d_6) δ ppm : 0.95(s, 3H, 18- H_3); 2.70(m, 2H, 6- H_2); 3.68(s, 3H, 3-O CH_3); 3.74(s, 3H, 3'-O CH_3); 6.61(s, 1H, 4-H); 6.79(s, 1H, NH); 6.80 (d, 2H, J = 8.8 Hz, 3'-H, 5'-H); 6.92(s, 1H, 1-H); 6.93(d, 2H, J = 8.8 Hz, 2'-H, 6'-H); ^{13}C NMR ($CDCl_3$) δ ppm : 20.4; 24.5(C-18); 27.9; 28.3; 29.3; 31.5; 32.8; 40.8; 40.9; 48.4; 49.4; 55.1 and 55.3(3-O CH_3 and 4'-O CH_3); 111.2(C-4); 112.7(C-1); 114.3(2C: C-3', C-5'); 119.1(2C: C-2', C-6'); 127.7(C-1'); 130.9(C-10); 131.0(C-5); 137.1(C-2); 147.0(C-3); 153.0(C-4'); 220.7(C-17). MS m/z (%): 406 (100, $[M + H]^+$).



2-(*N*-4'-Chlorophenylamino)-3-methoxy-13 α -estra-1,3,5(10)-trien-17-one (9c**)**

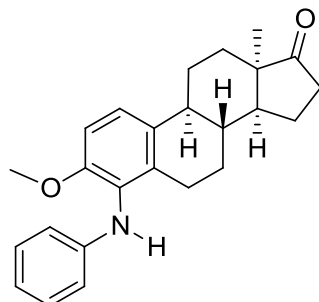
As described above bromo compound **1** (91 mg, 0.25 mmol) was reacted with 4-chloroaniline (38 mg, 0.30 mmol). After purification by flash chromatography compound **9c** was obtained as a white solid (89 mg, 87%, Mp.: 188–190°C, R_f = 0.51). Anal calcd. for $C_{25}H_{28}ClNO_2$: C, 73.25; H, 6.88. Found: C, 73.47; H, 7.03. M_r : 409.18 1H NMR (500 MHz, DMSO- d_6) δ ppm : 0.96(s, 3H, 18- H_3); 2.76(m, 2H, 6- H_2); 3.73(s, 3H, 3-OMe); 6.69(s, 1H, 4-H); 6.83(d, 2H, J = 8.7 Hz, 2'-H, 6'-H); and 7.14(d, 2H, J = 8.7 Hz, 3'-H, 5'-H); 7.06(s, 1H, 1-H); 7.41(s, 1H, NH); ^{13}C NMR (DMSO- d_6) δ ppm : 20.4; 24.5(C-18); 27.8; 28.2; 29.4; 31.6; 32.8; 40.7; 40.8; 48.4; 49.4; 55.3(OCH $_3$); 111.7(C-4); 116.3(2C: C-2', C-6'); 117.8(C-1); 121.0(C-4'); 128.3(C-2); 128.5(2C: C-3', C-5'); 131.0(C-10); 131.2(C-5); 144.2(C-1'); 149.1(C-3); 220.6(C-17). MS m/z (%): 451 (100, $[M + MeCN + H]^+$); 410 (51, $[M + H]^+$).



3-Methoxy-2-(*N*-4'-nitrophenylamino)-13 α -estra-1,3,5(10)-trien-17-one (9d**)**

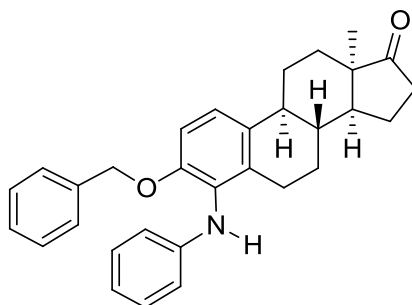
As described above bromo compound **1** (91 mg, 0.25 mmol) was reacted with 4-nitroaniline (41 mg, 0.30 mmol). After purification by flash chromatography compound **9d** was obtained as a yellow solid (100 mg, 95%, Mp.: 112–114°C, R_f = 0.35). Anal calcd. for $C_{25}H_{28}N_2O_4$: C, 71.41; H, 6.71. Found: C, 71.58; H, 6.55. M_r : 420.20 1H NMR (500 MHz, DMSO- d_6) δ ppm : 0.96(s, 3H, 18- H_3); 2.80(m, 2H, 6- H_2); 3.72(s, 3H, 3-OCH $_3$); 6.71(d, 2H, J = 9.2 Hz, 2'-H, 6'-H); 6.80(s, 1H, 4-H); 7.11(s, 1H, 1-H); 8.00(d, 2H, J = 9.2 Hz, 3'-H, 5'-H); 8.72(s, 1H, NH); ^{13}C NMR (DMSO- d_6) δ ppm : 20.4; 24.5(C-18); 27.7; 28.0; 29.5; 31.5; 32.8; 40.6; 40.7; 48.4; 49.4(C-13); 55.3(OCH $_3$); 112.1(C-4); 112.4(2C: C-2' and C-6'); 122.5(C-1); 125.2(C-

2); 125.9(2C: C-3' and C-5'); 131.7(C-10); 134.9(C-5); 136.8(C-4'); 151.0(C-1'); 152.6(C-3); 220.6(C-17). MS m/z (%): 421 (7, [M + H]⁺); 493 (100, [M + MeCN + MeOH + H]⁺).



3-Methoxy-4-(N-phenylamino)-13α-estra-1,3,5(10)-trien-17-one (10)

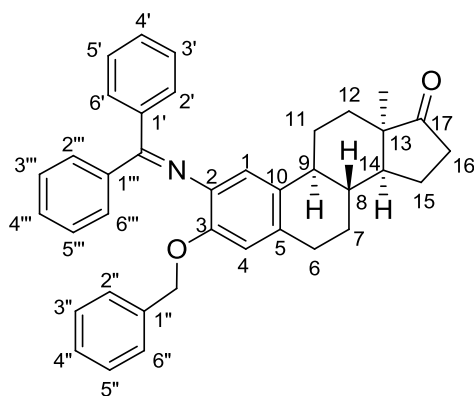
As described above bromo compound **3** (91 mg, 0.25 mmol) was reacted with aniline (27 μl, 0.30 mmol). After purification by flash chromatography compound **10** was obtained as a white solid (80 mg, 85%, Mp.:180–182°C, R_f=0.60). Anal calcd. for C₂₅H₂₉NO₂: C, 79.96; H, 7.78. Found: C, 80.12; H, 7.93. M_r: 375.22 ¹H NMR (500 MHz, CDCl₃) δ ppm :1.06(s, 3H, 18-H₃); 2.47 and 2.81(2xm, 2H, 6-H₂); 3.77(s, 3H, 3-OMe); 6.65(d, 2H, J= 8.3 Hz, 2'-H and 6'-H), 6.79(d, 1H, J= 8.6 Hz, 2-H); 6.83(t, 1H, J=7.9 Hz, 4'-H); 7.12(d, 1H, J=8.6 Hz, 1-H); 7.19(t, 2H, J=7.4 Hz, 3'-H and 5'-H); ¹³C NMR (CDCl₃) δ ppm: 20.9; 25.0(C-18); 26.1; 27.9; 28.6; 32.2; 33.4; 41.1; 41.8; 49.4; 50.2(C-13); 55.8(OCH₃); 108.7(C-2); 115.6(2C: C-2', C-6'); 119.6(C-4'); 123.0(C-1); 127.8(C-4); 129.0(2C: C-3', C-5'); 133.2(C-10); 134.5(C-5); 145.5(C-1'); 151.9(C-3); 221.8(C-17). MS m/z (%): 376 (100, [M + H]⁺).



3-Benzyloxy-4-(N-phenylamino)-13α-estra-1,3,5(10)-trien-17-one (11)

As described above bromo compound **4** (110 mg, 0.25 mmol) was reacted with aniline (27 μl, 0.30 mmol). After purification by flash chromatography compound **11** was obtained as a

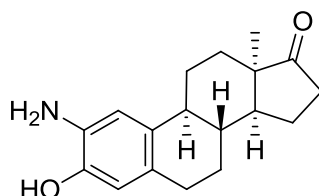
white solid (95 mg, 84%, Mp.: 56–58°C, R_f = 0.62). Anal calcd. for $C_{31}H_{33}NO_2$: C, 82.45; H, 7.37. Found: C, 82.63; H, 7.51. M_r : 451.25 1H NMR (500 MHz, DMSO- d_6) δ ppm :0.97(s, 3H, 18- H_3); 2.30 and 2.75(2xm, 2H, 6- H_2); 5.02(s, 2H, 3-OCH $_2$);); 6.47(d, 2H, J = 7.7 Hz, 2'-H, 6'-H), 6.58(t, 1H, J = 7.2 Hz, 4'-H); 6.80(d, 1H, J = 8.6 Hz, 2-H); 6.98(s, 1H, NH); 7.05(t, 2H, J = 7.7 Hz, 3'-H, 5'-H); 7.08(d, 1H, J = 8.6 Hz, 1-H); 7.19-7.24(overlapping multiplets, 5H, 2''-H, 3''-H, 4''-H, 5''-H, 6''-H); ^{13}C NMR (DMSO- d_6) δ ppm: 20.4; 24.4(C-18); 25.5; 27.4; 28.1; 31.6; 32.7; 40.3; 41.1; 48.5; 49.3(C-13); 69.2(OCH $_2$); 110.9(C-2); 113.1(2C: C-2', C-6'); 116.5(C-4'); 123.0(C-1); 126.9(2C: C-2'', C-6''); 127.3(C-4''); 127.8(C-4); 128.0(2C: C-3'', C-5''); 128.5(2C: C-3', C-5'); 132.8(C-10); 135.5(C-5); 137.3(C-1''); 147.0(C-1'); 151.8(C-3); 220.6(C-17). MS m/z (%): 452 (100, $[M + H]^+$).



Synthesis of 3-benzyloxy-2-(N-diphenylmethylideneamino)-13 α -estra-1,3,5(10)-trien-17-one (12)

Palladium acetate (5.6 mg, 0.025 mmol, 10 mol %), potassium *tert*-butoxide (56 mg, 0.5 mmol, 2 equiv.), X-Phos (12 mg, 0.025 mmol, 10 mol %), benzophenone-imine (50 μ l, 0.30 mmol) and toluene (5 ml) were added into a 10 mL Pyrex pressure vessel (CEM, Part #: 908035) with silicone cap (CEM, Part #: 909210) under nitrogen atmosphere. The mixture was stirred at 60 °C for 5 min and cooled to rt. Then, the 3-benzyloxy-2-bromo-13 α -estra-1,3,5(10)-trien-17-one (**2**) (110 mg, 0.25 mmol) was charged into the tube, purged with nitrogen and the mixture was heated in a CEM microwave reactor at 100 °C for 30 min under stirring. The solvent was evaporated in vacuo and the residue was purified by flash chromatography with 15% ethyl acetate/85% hexane as eluent. yielding 110 mg (81%) of compound **12**. After purification by flash chromatography compound **12** was obtained as a yellow solid (110 mg, 81 %, Mp.: 60–62°C, R_f = 0.58). Anal calcd. for $C_{38}H_{37}NO_2$, C, 84.57; H, 6.91. Found: C, 84.67; H, 7.08. M_r : 539.28 1H NMR (500 MHz, DMSO- d_6) δ ppm :0.93(s,

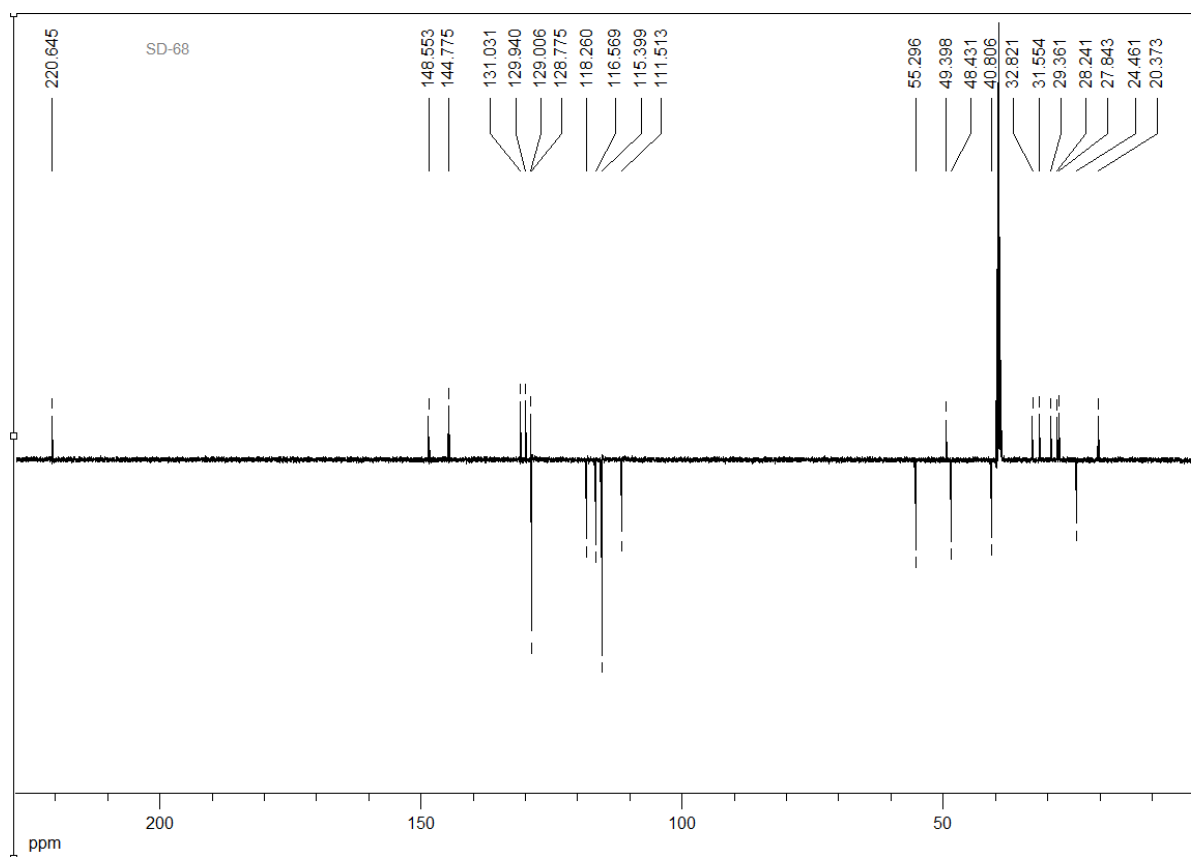
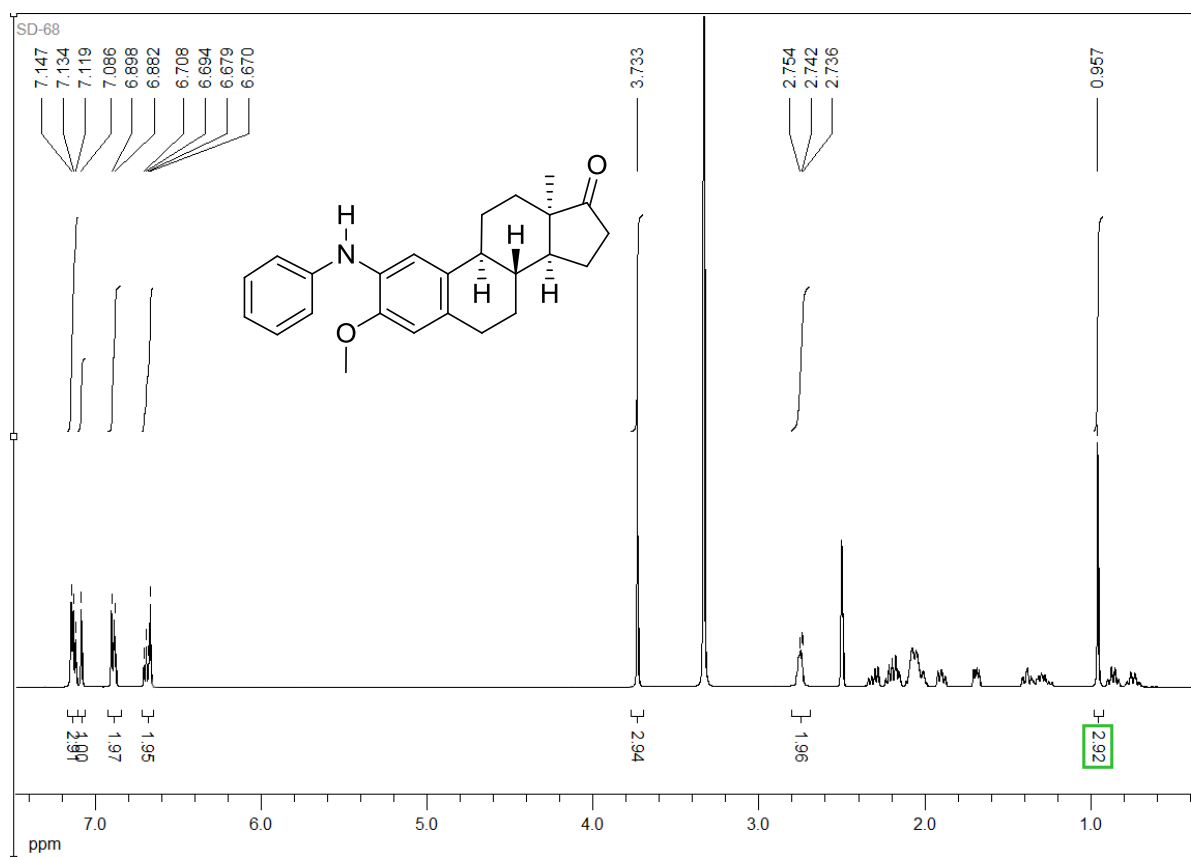
3H, 18-H₃); 2.62(m, 2H, 6-H₂); 4.97(s, 2H, 3-OCH₂); 6.45(s, 1H, 1-H); 6.58(s, 1H, 4-H); 7.07-7.62(overlapping multiplets, 15H, 2'-H, 3'-H, 4'-H, 5'-H, 6'-H; 2''-H, 3''-H, 4''-H, 5''-H, 6''-H; 2'''-H, 3'''-H, 4'''-H, 5'''-H, 6'''-H); ¹³C NMR (DMSO-d₆) δ ppm: 20.8; 24.9(C-18); 28.1; 28.5; 29.8; 32.1; 33.3; 41.3; 48.8; 49.9(C-13); 69.8(OCH₂); 113.7(C-4); 118.7(C-1); 127.5(2C) and 128.0 and 128.4(2C) and 128.6(2C) and 128.8(3C) and 128.9 and 129.1(2C) and 130.1 and 131.2(C-2', C-3', C-4', C-5', C-6', C-2'', C-3'', C-4'', C-5'', C-6'', C-2''', C-3''', C-4''', C-5''', C-6'''); 131.8 and 132.2 and 137.0 and 138.1 and 139.1 and 139.4(C-2, C-5, C-10, C-1', C-1'', C-1'''); 146.5(C-3); 168.4(C=N); 221.2(C-17). MS m/z (%): 540 (100, [M + H]⁺).

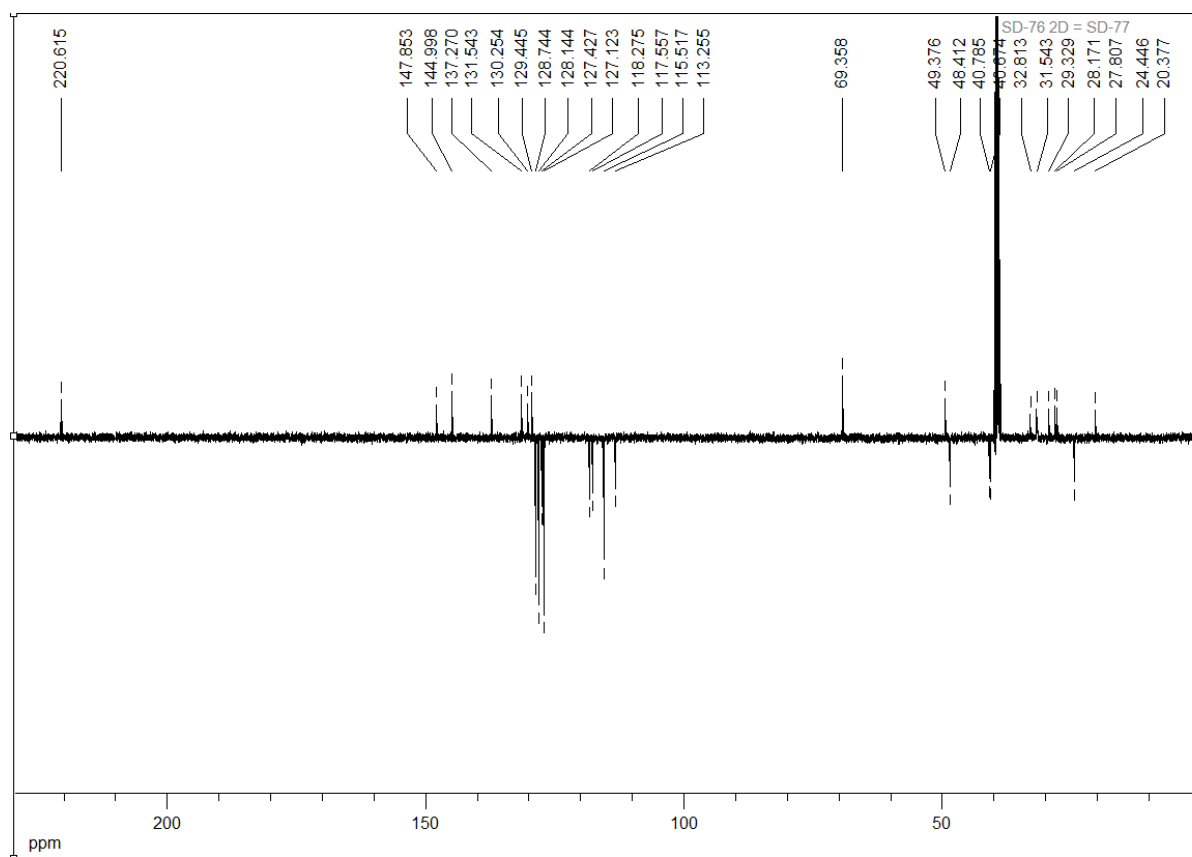
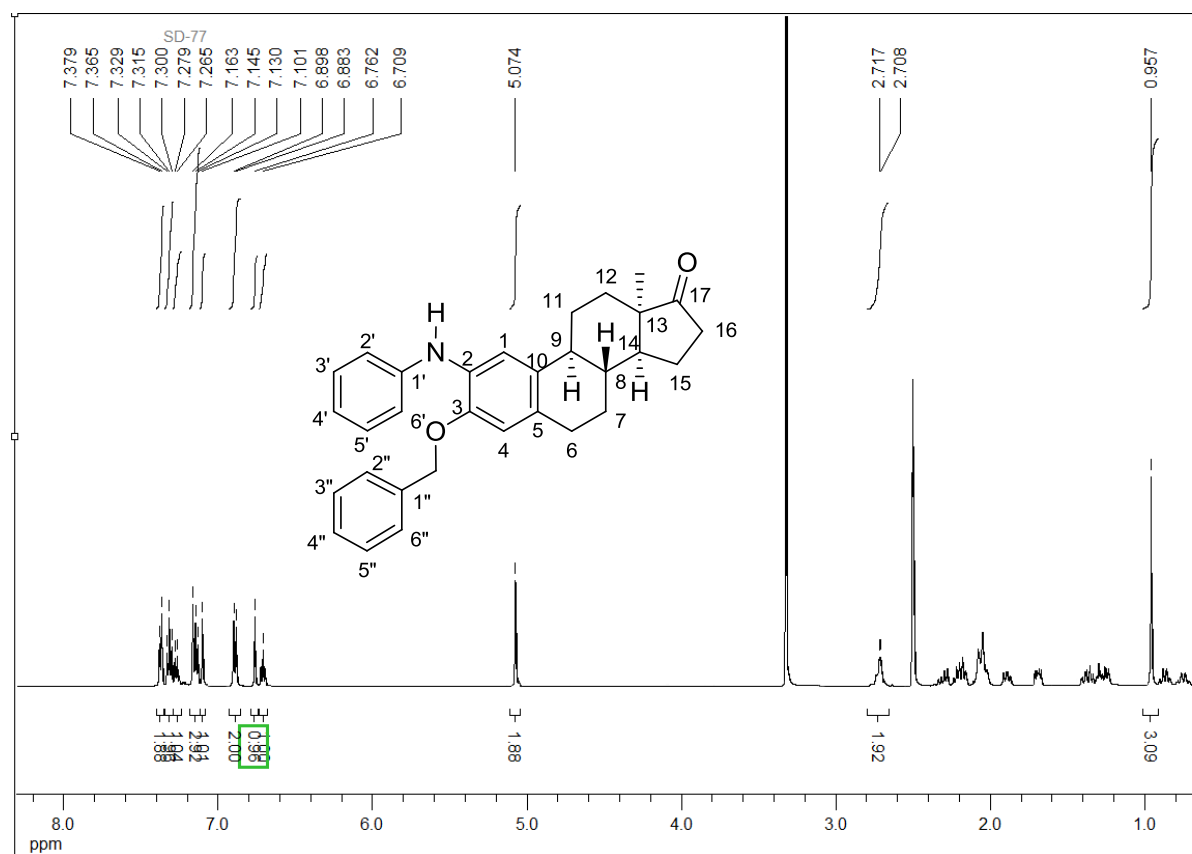


Synthesis of 2-amino-13α-estra-1,3,5(10)-trien-17-one (13)

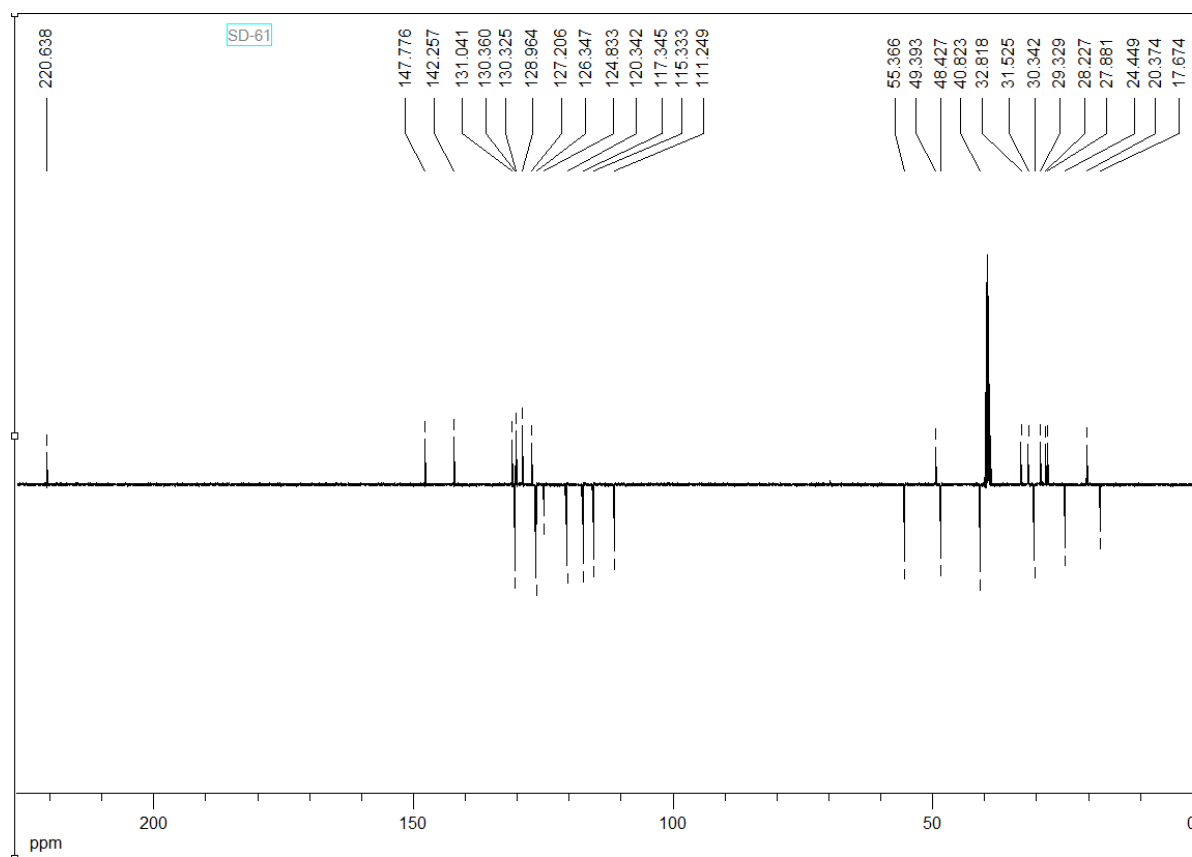
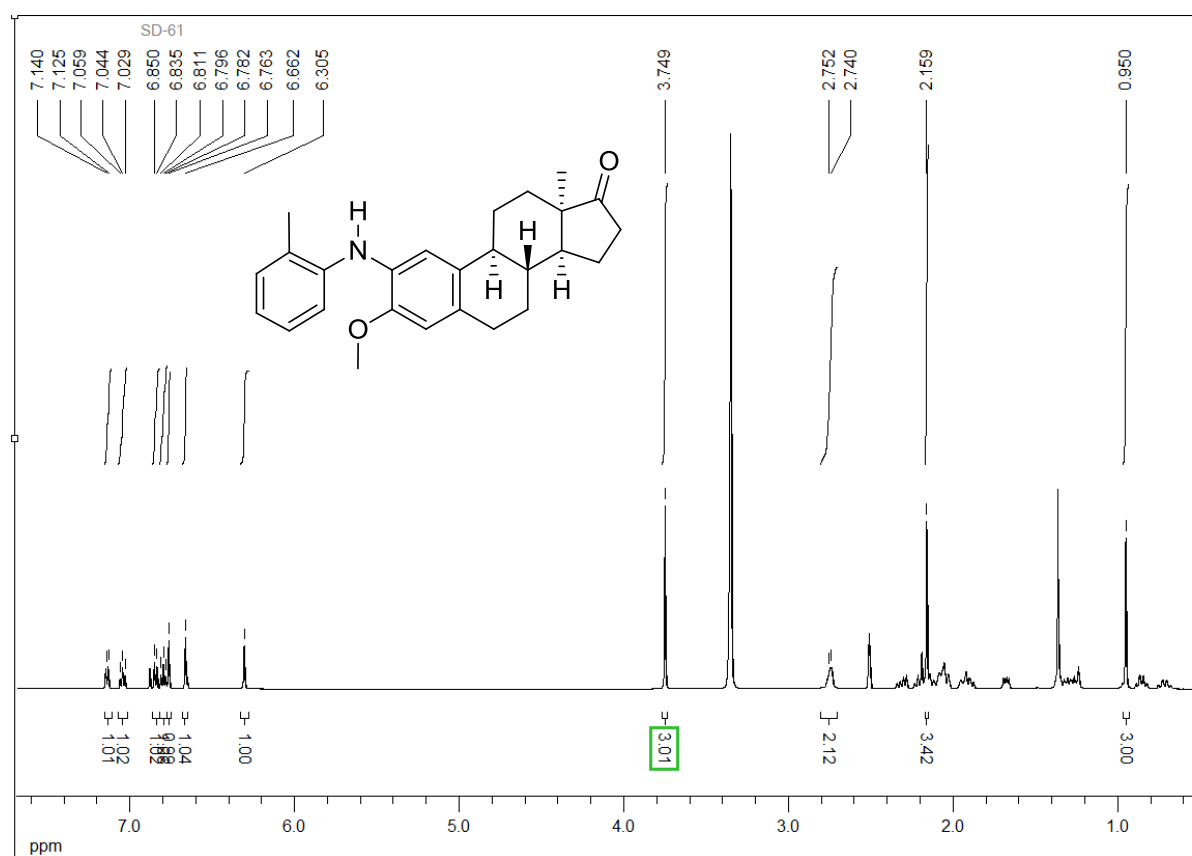
A suspension of **12** (100 mg, 0.185 mmol) and Pd/C (0.35 g, 10%) in EtOAc (20 ml) was subjected to 20 bar of H₂ at room temperature for 3 h. The catalyst was then removed by filtration through a short pad of silica gel. After evaporation of the solvent in vacuo, the crude product was subjected to column chromatography with 15% ethyl acetate/85% hexane as eluent to afford compound **13** in 79% yield (53 mg, Mp.: 208–210 °C, R_f = 0.55 (70% EtOAc/hexane)). Anal calcd. for C₁₈H₂₃NO₂: C, 75.76; H, 8.12. Found: C, 75.58; H, 8.23. M_r: 285.17. ¹H NMR (500 MHz, DMSO-d₆) δ ppm : 0.95(s, 3H, 18-H₃); 2.55(m, 2H, 6-H₂); 4.20(broad s, 2H, 2-NH₂); 6.29(s; 1H, 4-H); 6.49(s, 1H, 1-H); 8.66(s, 1H, OH). ¹³C NMR (DMSO-d₆) δ ppm : 20.4; 24.5(C-18); 28.1; 28.3; 28.9; 31.7; 32.8; 40.9; 41.1; 48.5; 49.4; 111.9 and 114.1 (C-1 and C-4); 124.1 and 129.7(C-5 and C-10); 134.0(C-2); 142.2(C-3); 220.7(C-17). MS m/z (%): 286 (100, [M + H]⁺).

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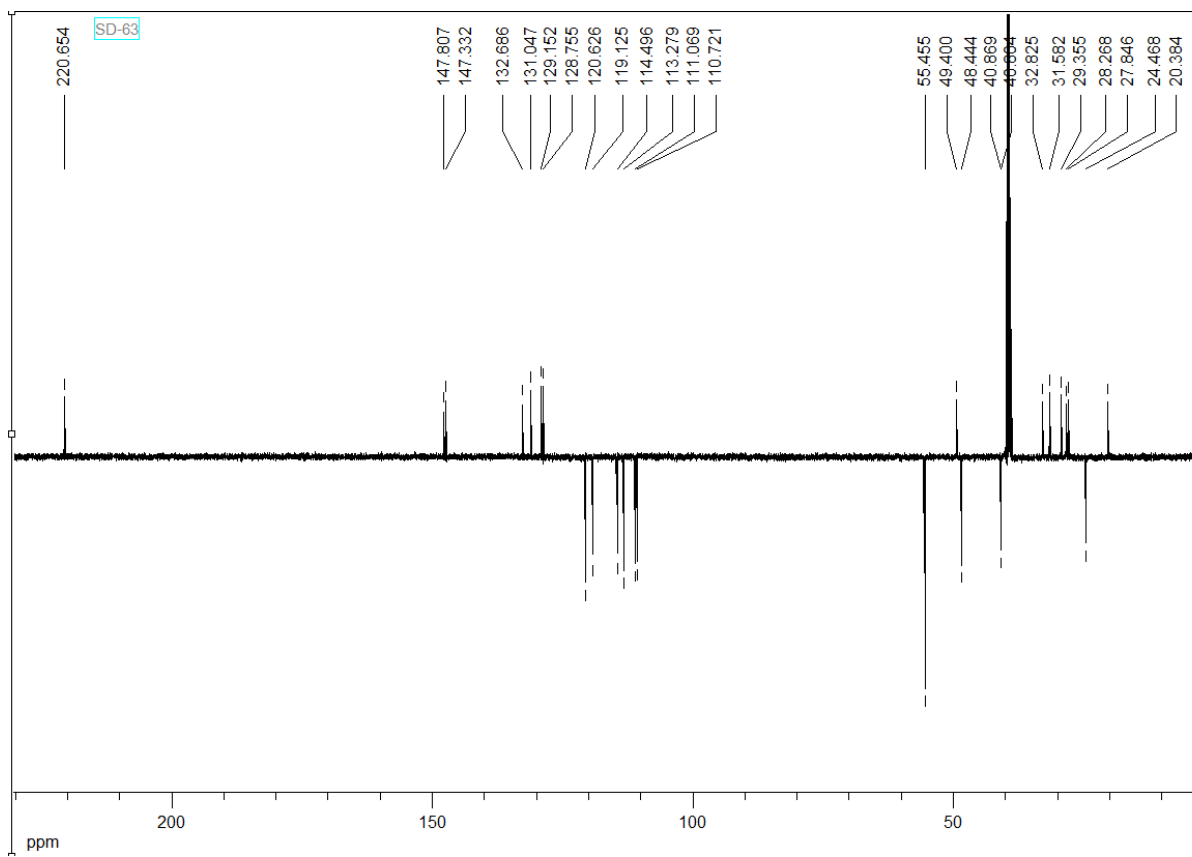
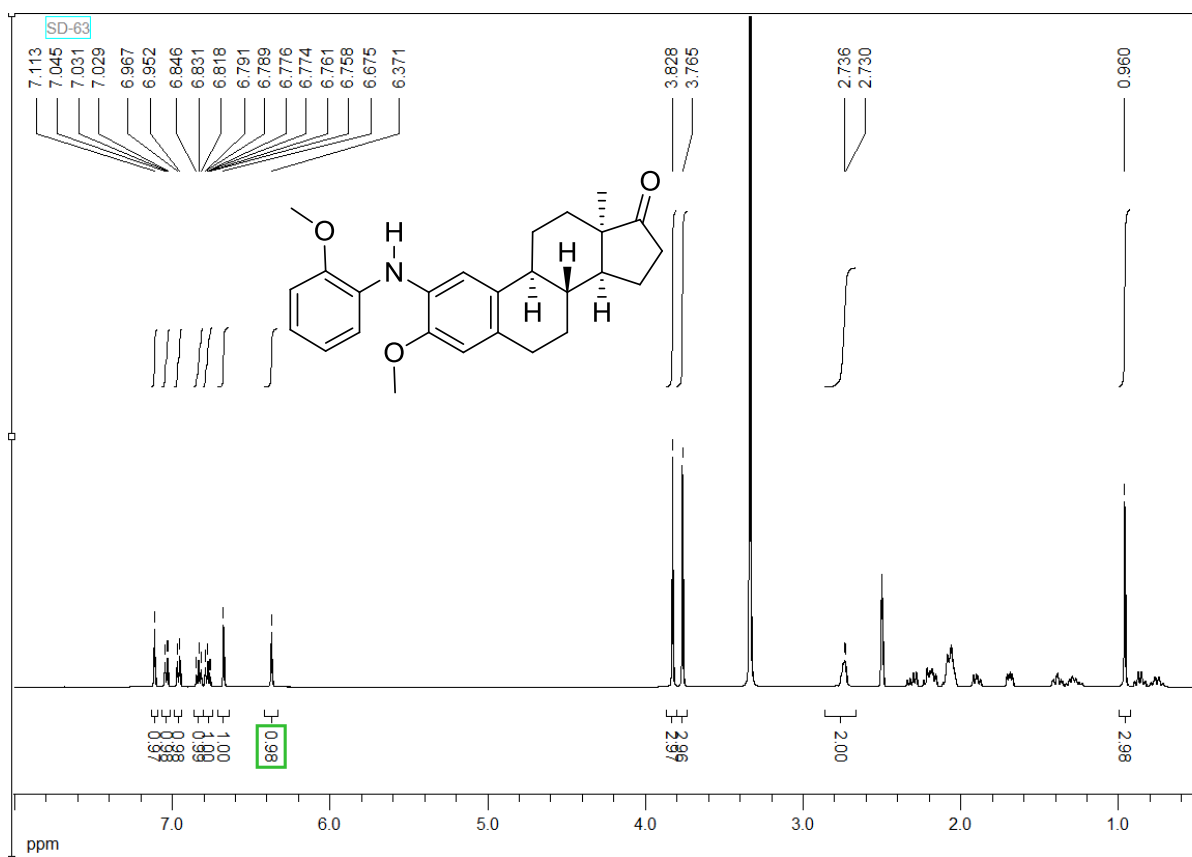




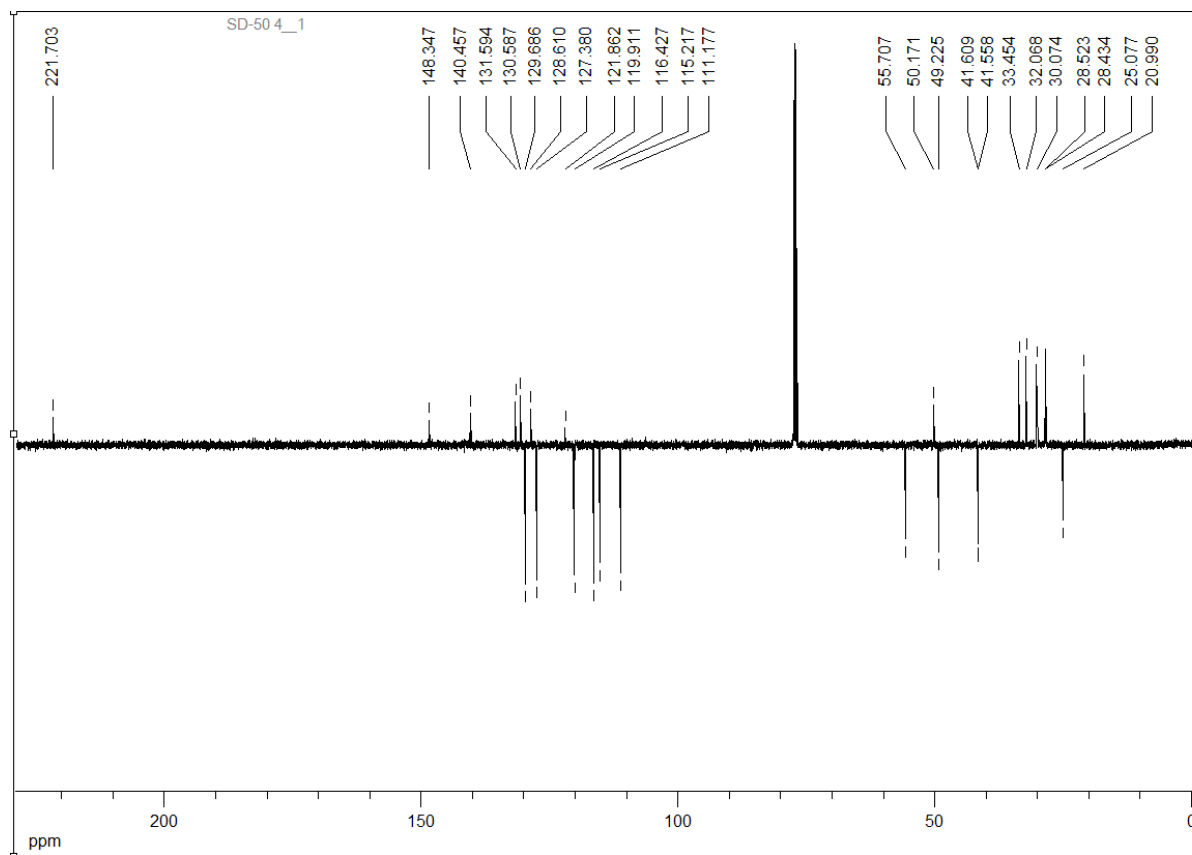
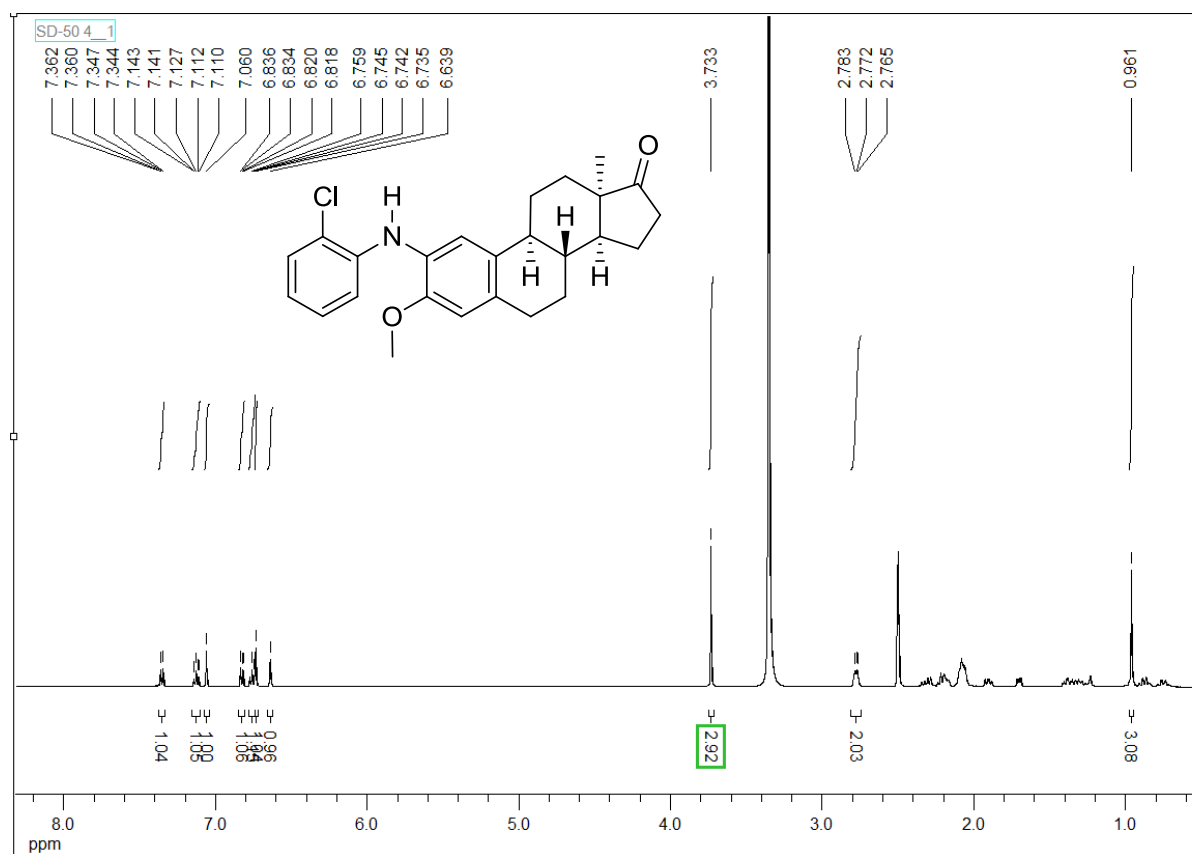
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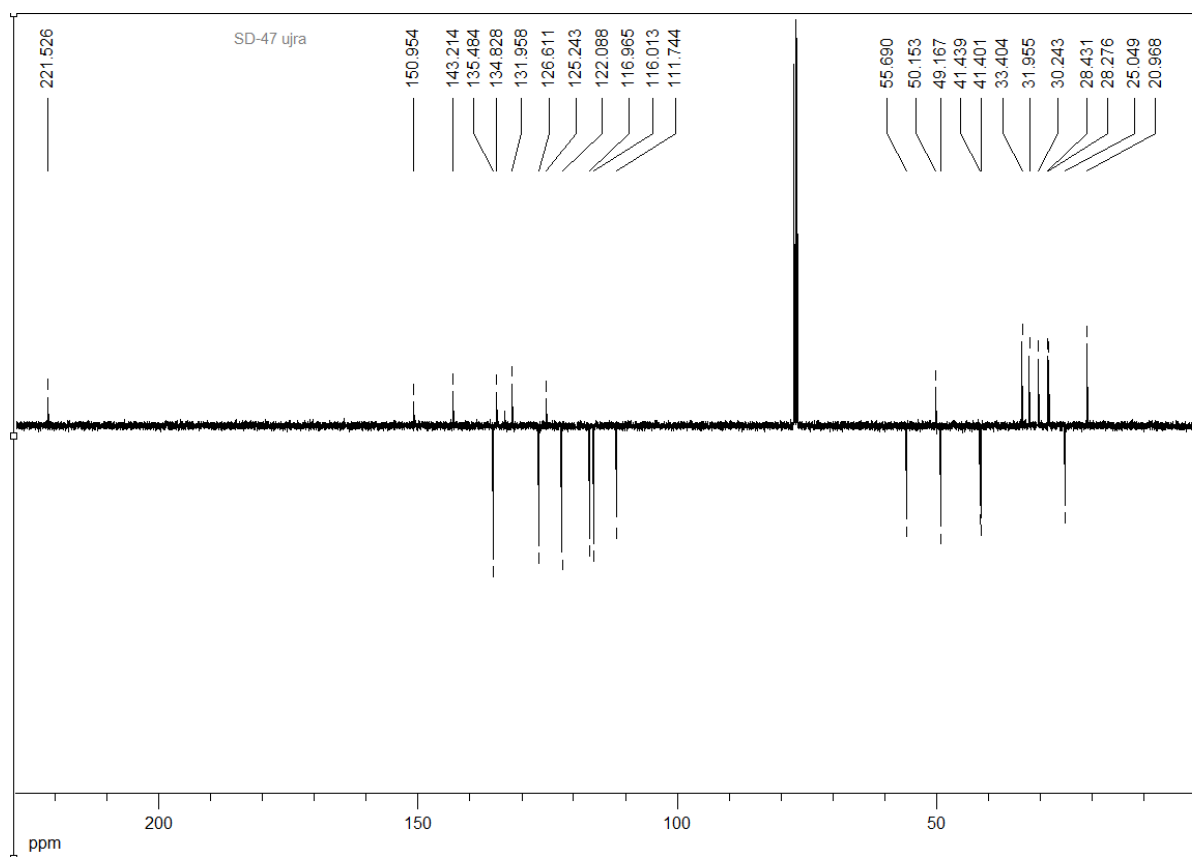
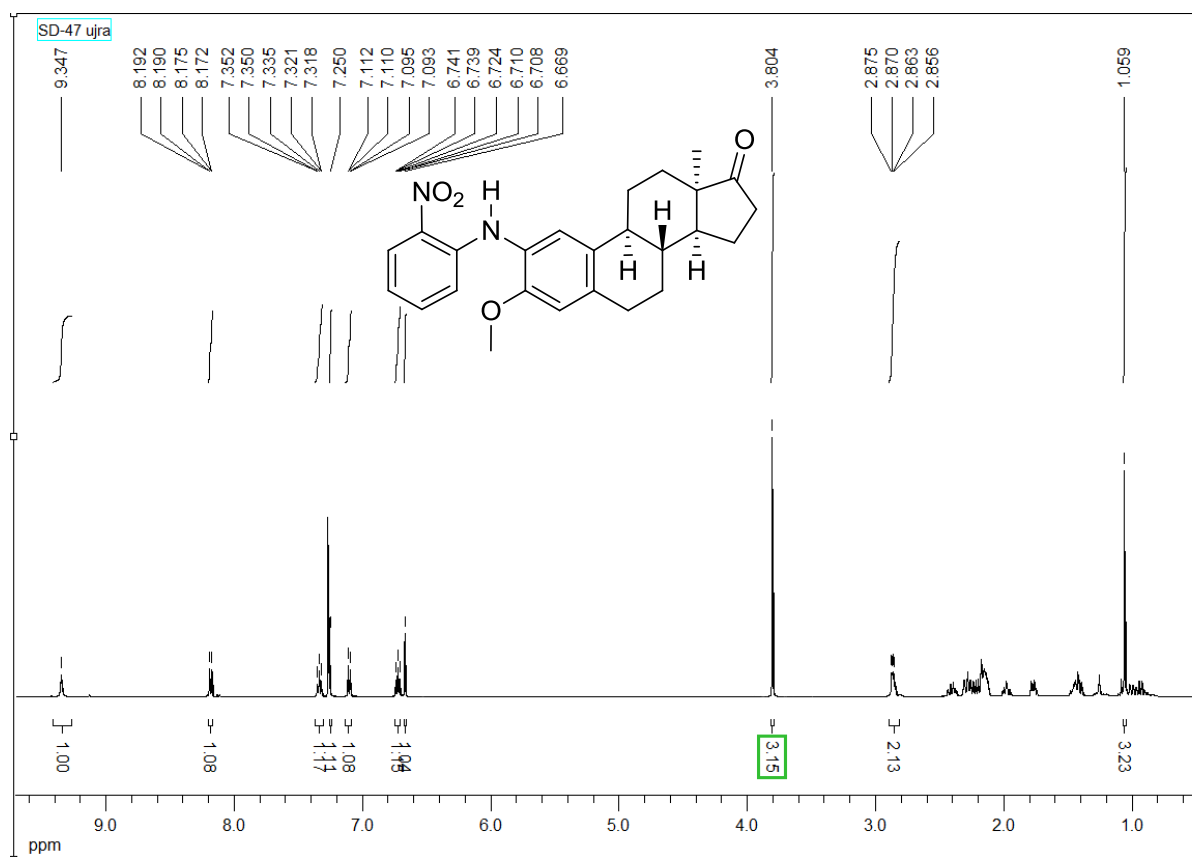
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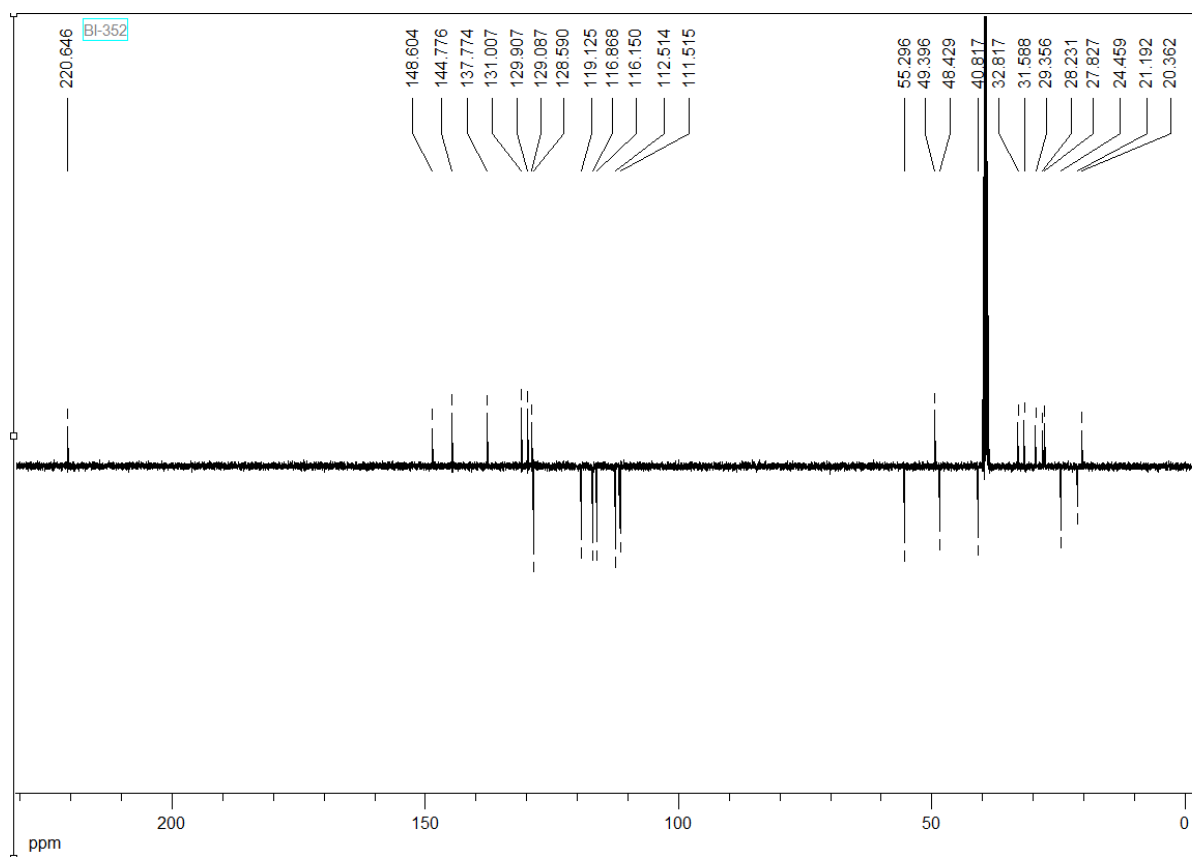
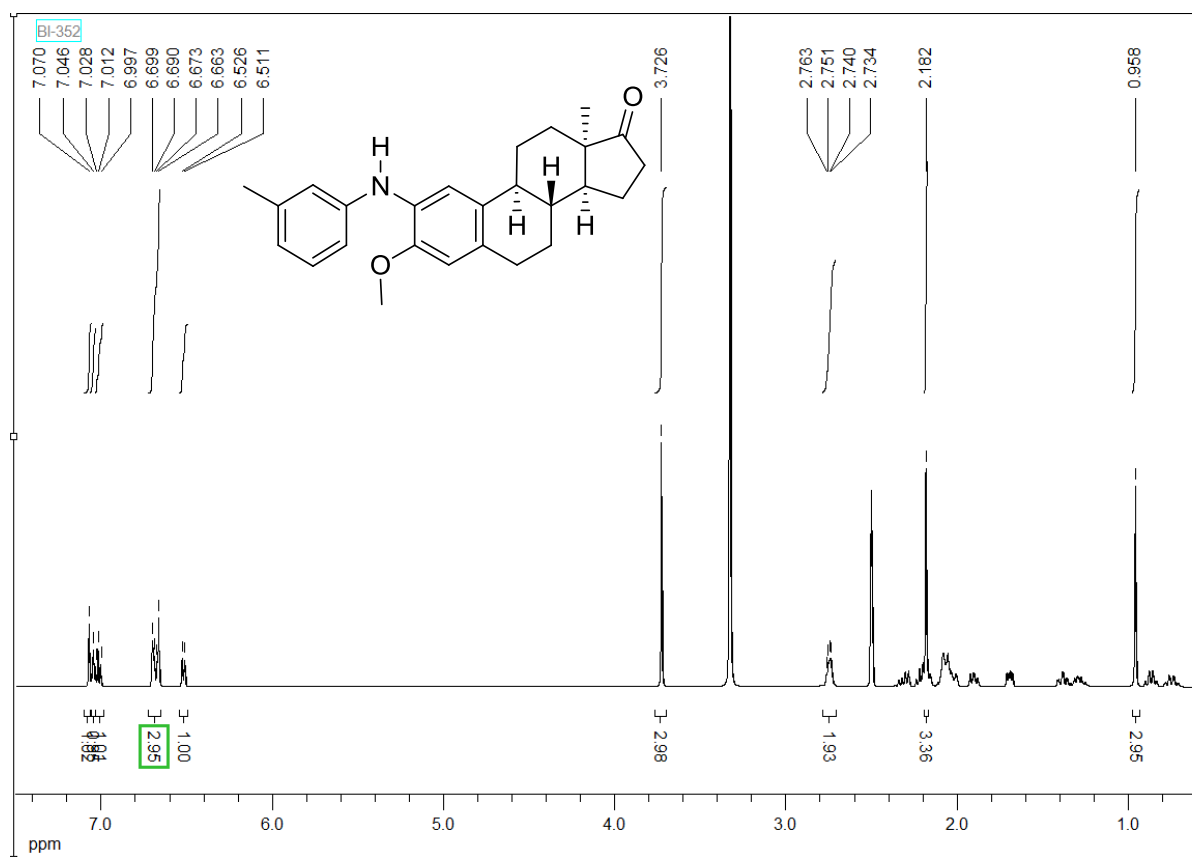
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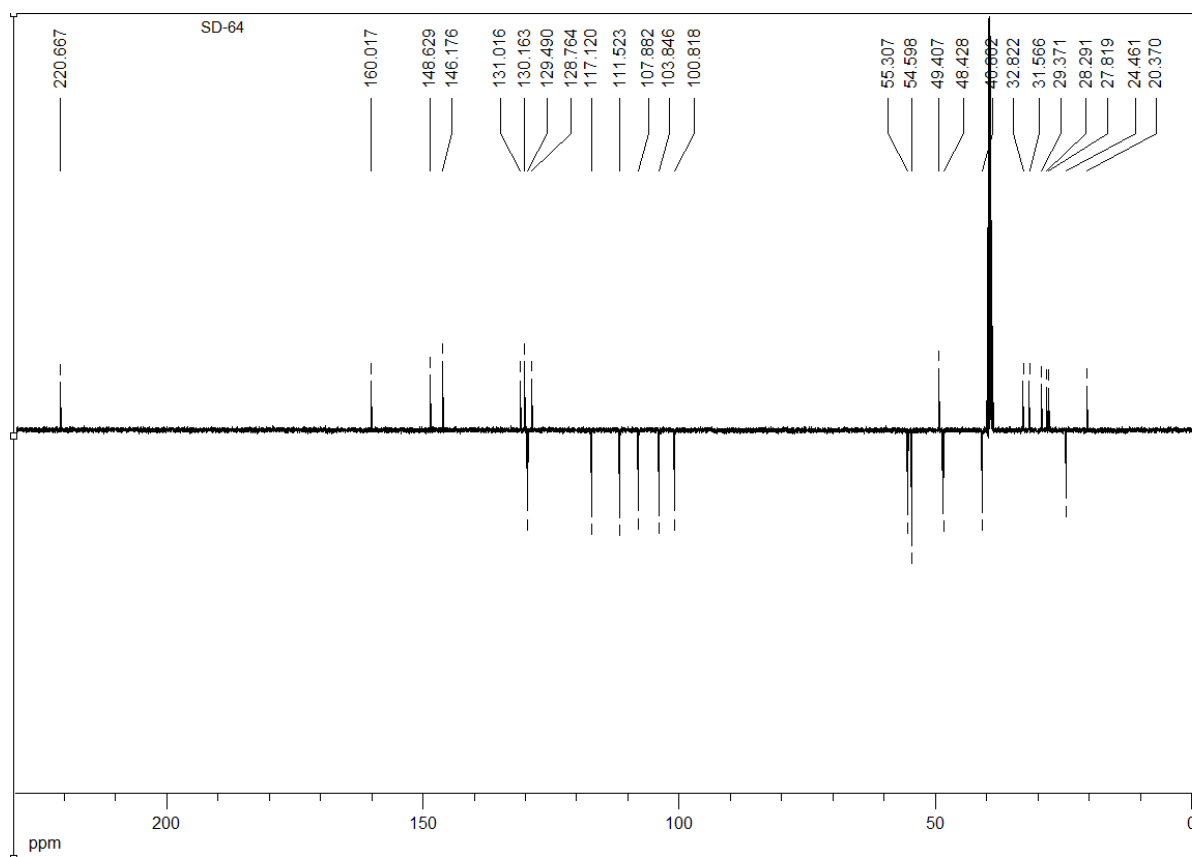
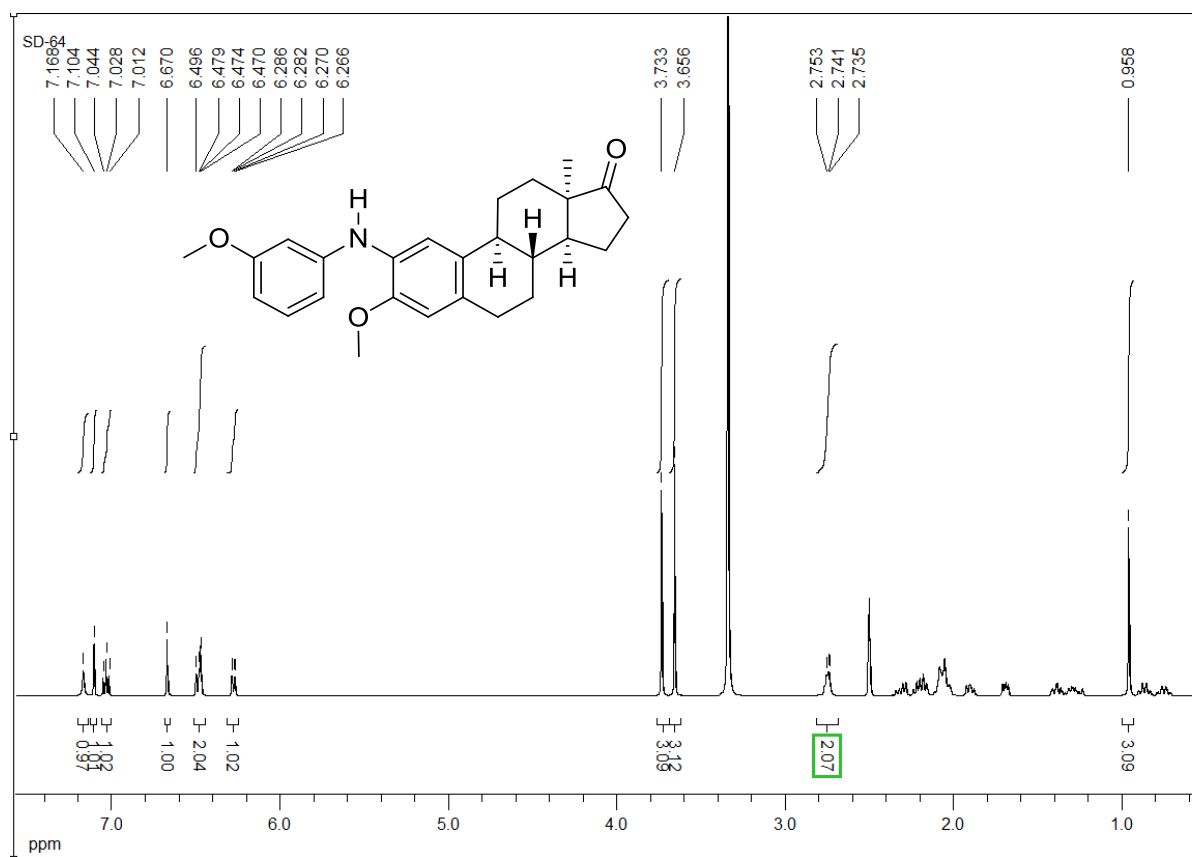
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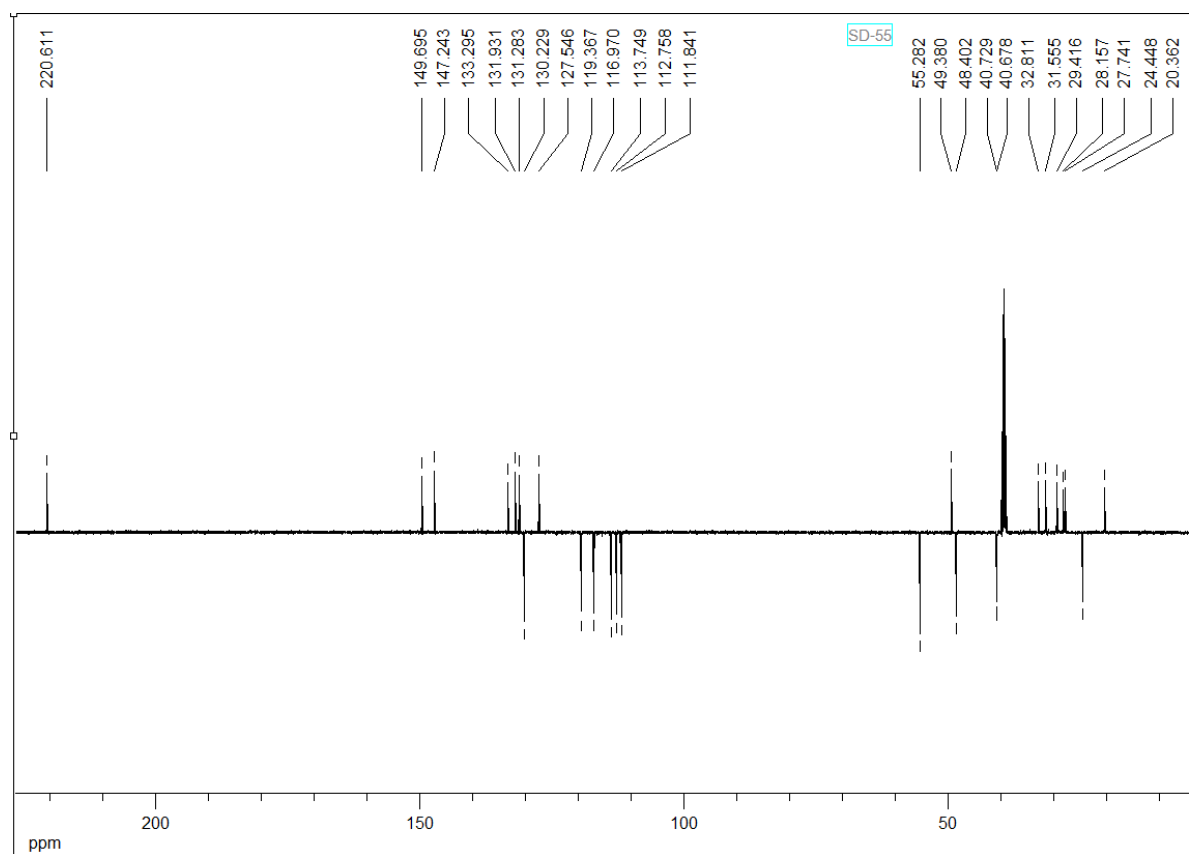
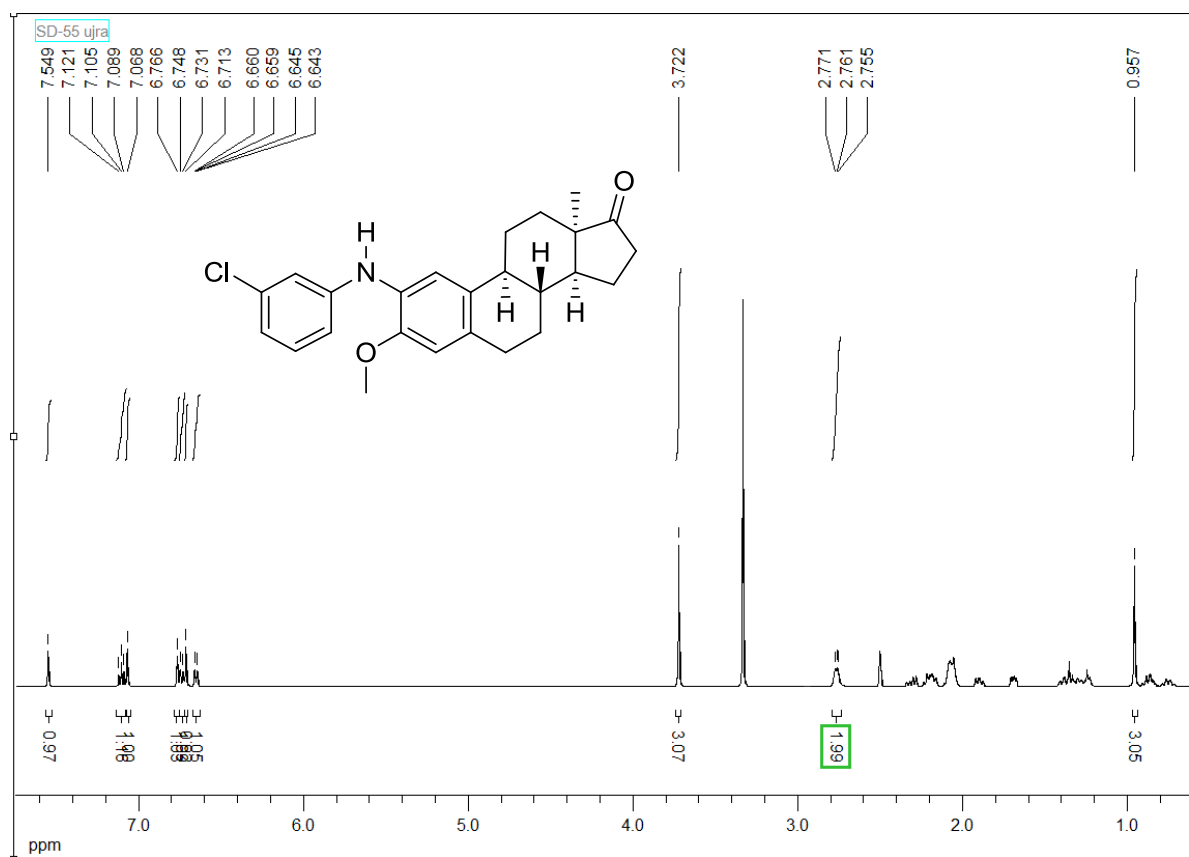
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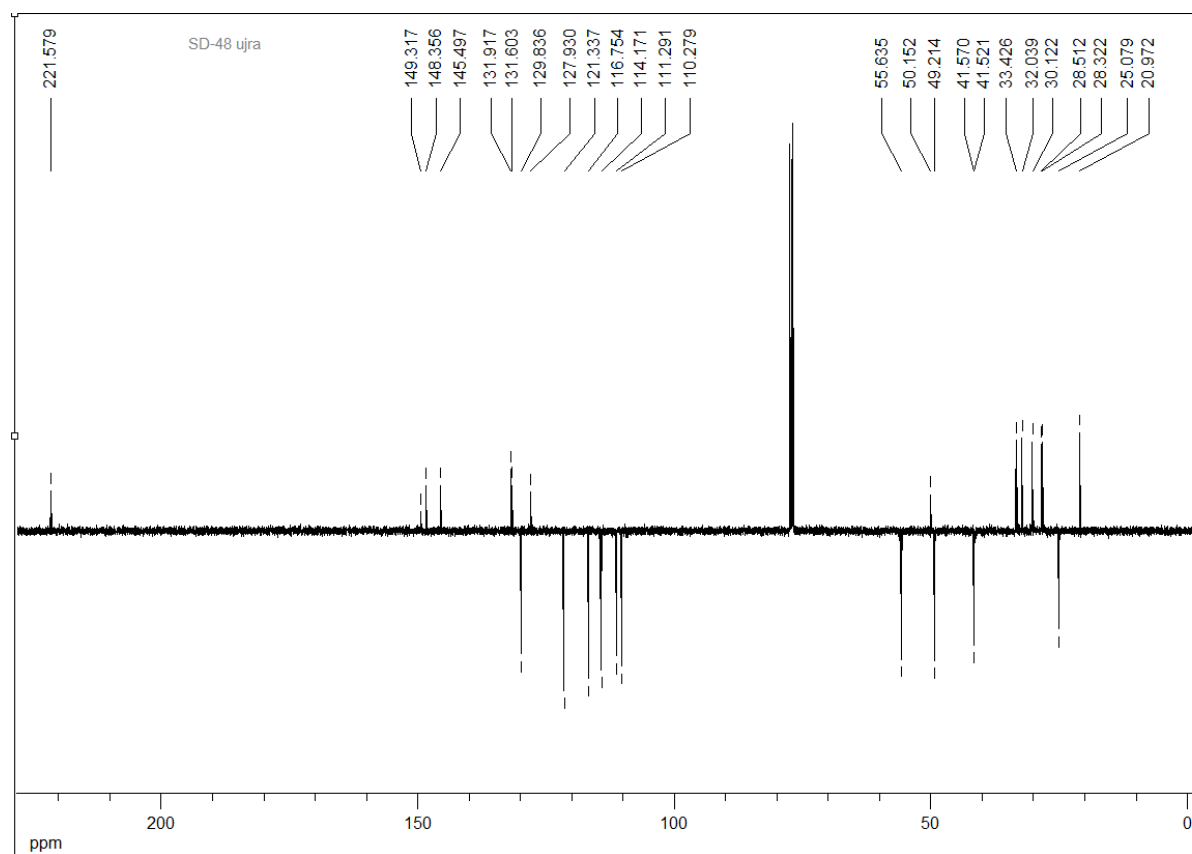
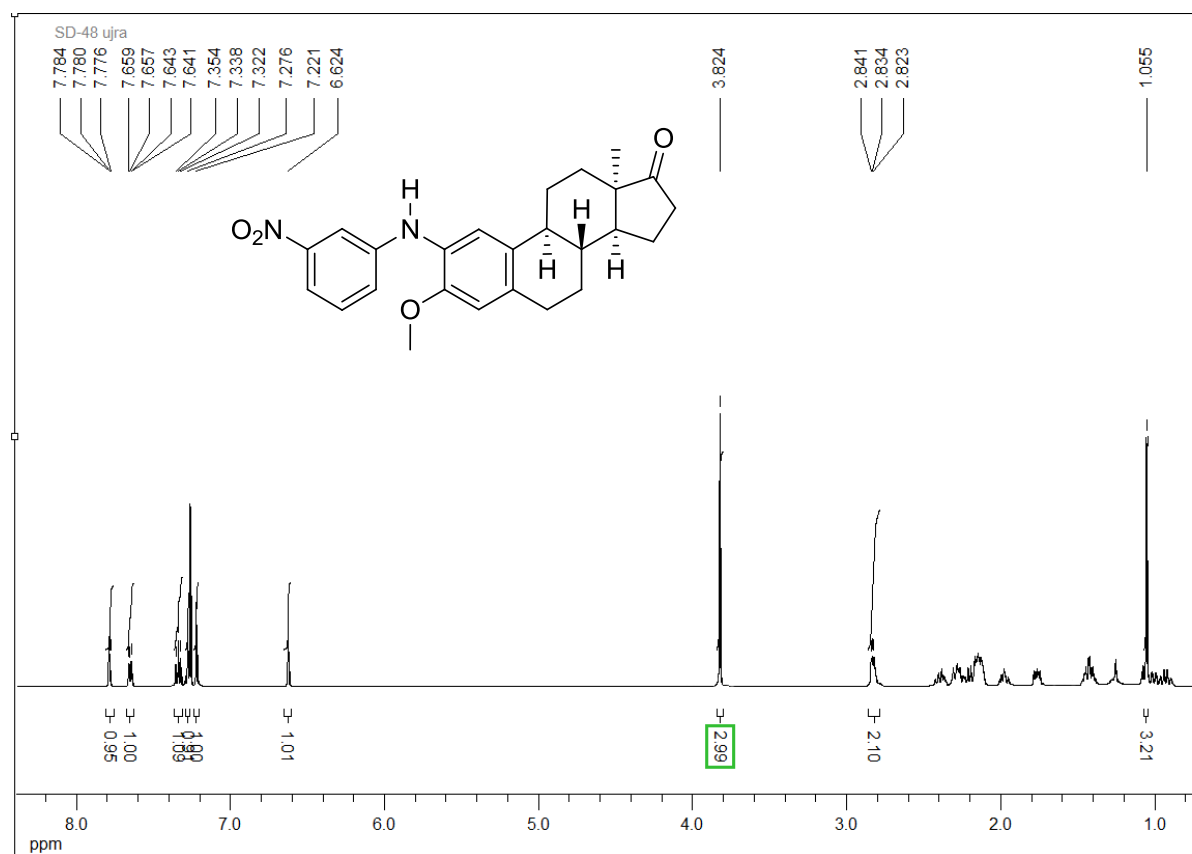
8b



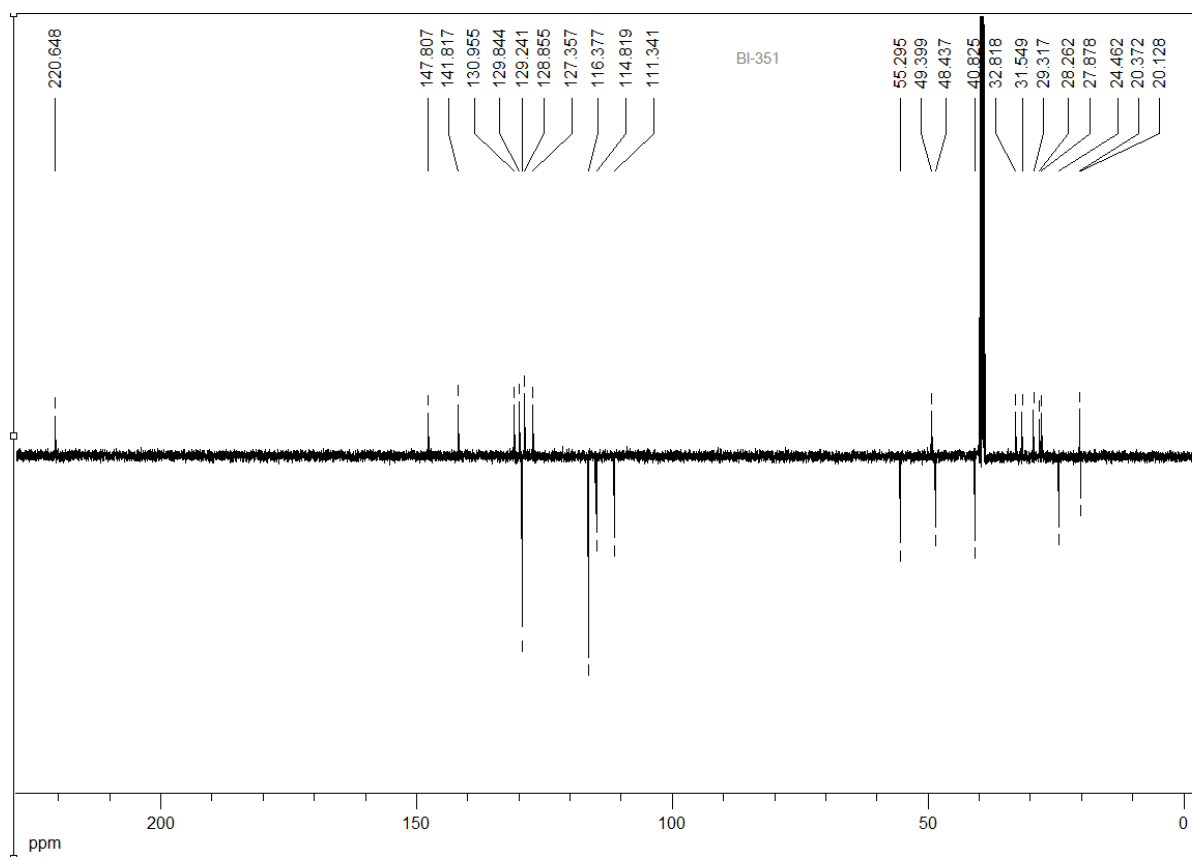
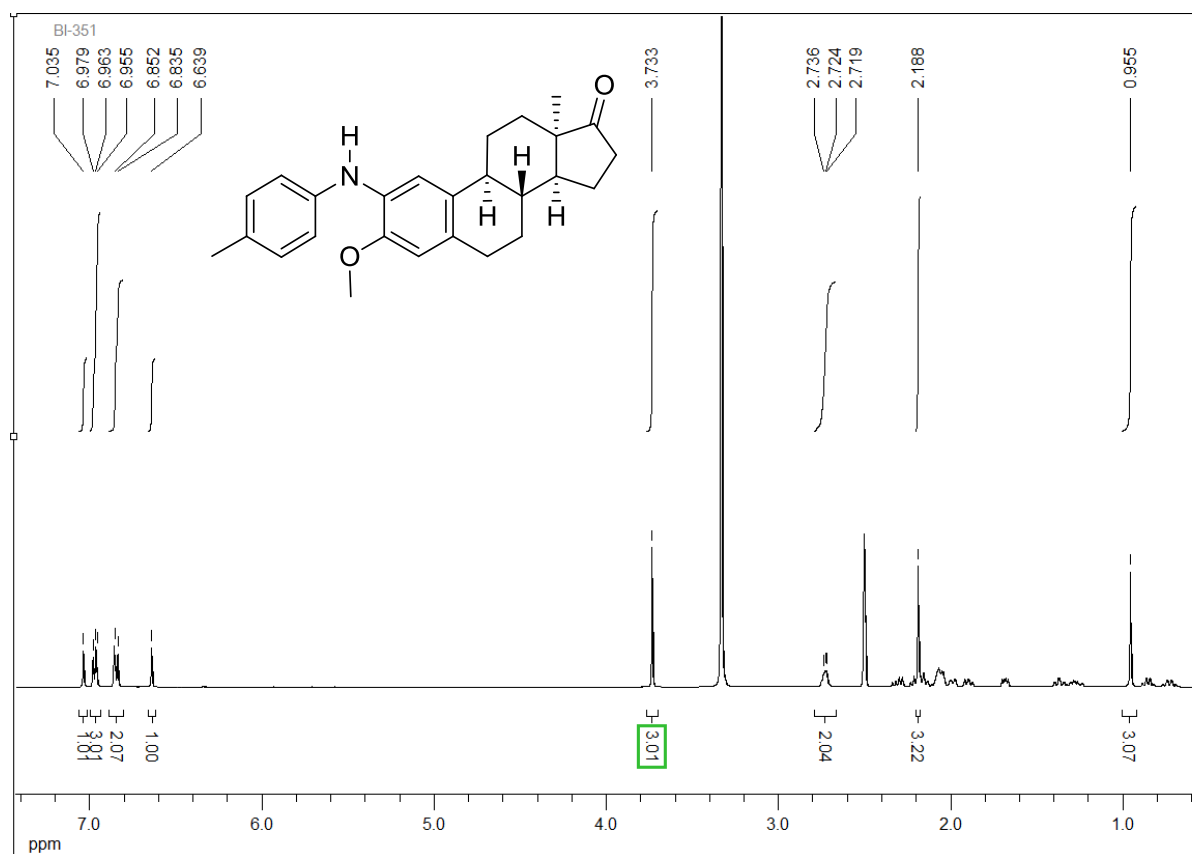
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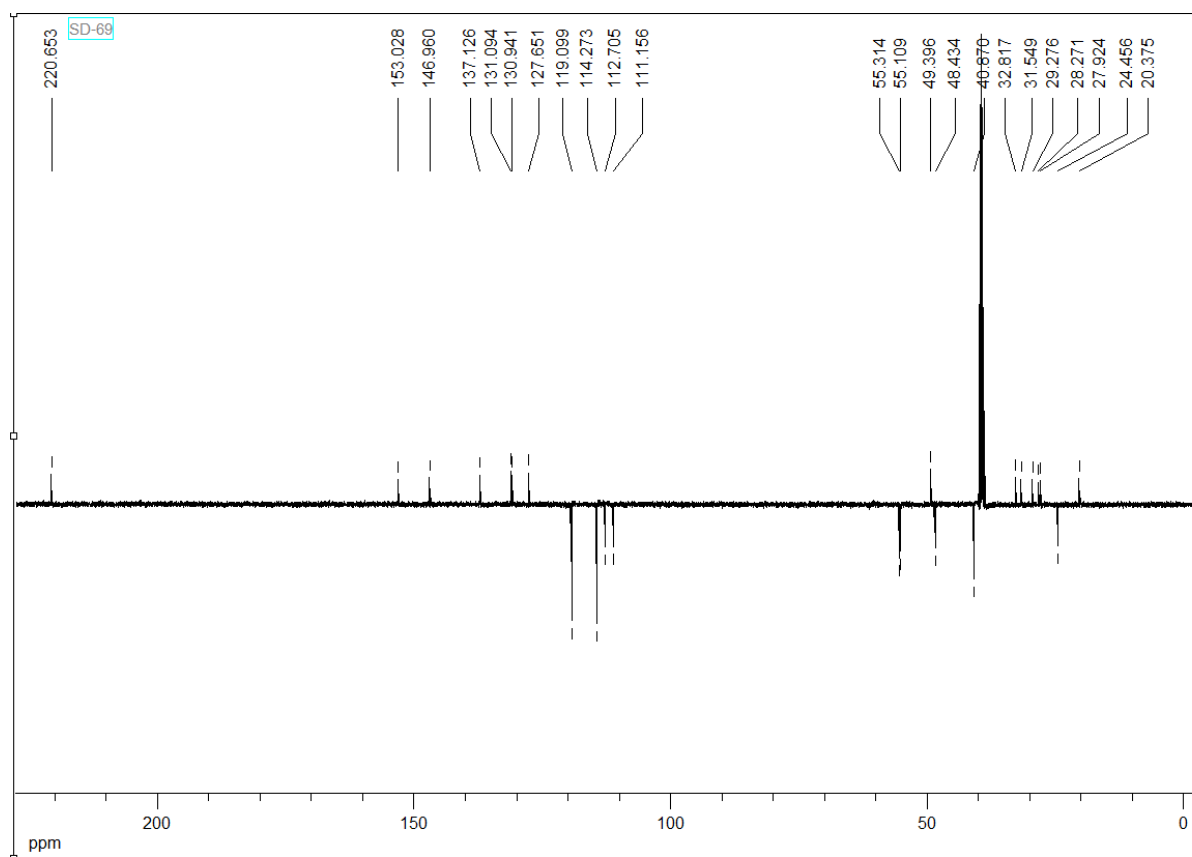
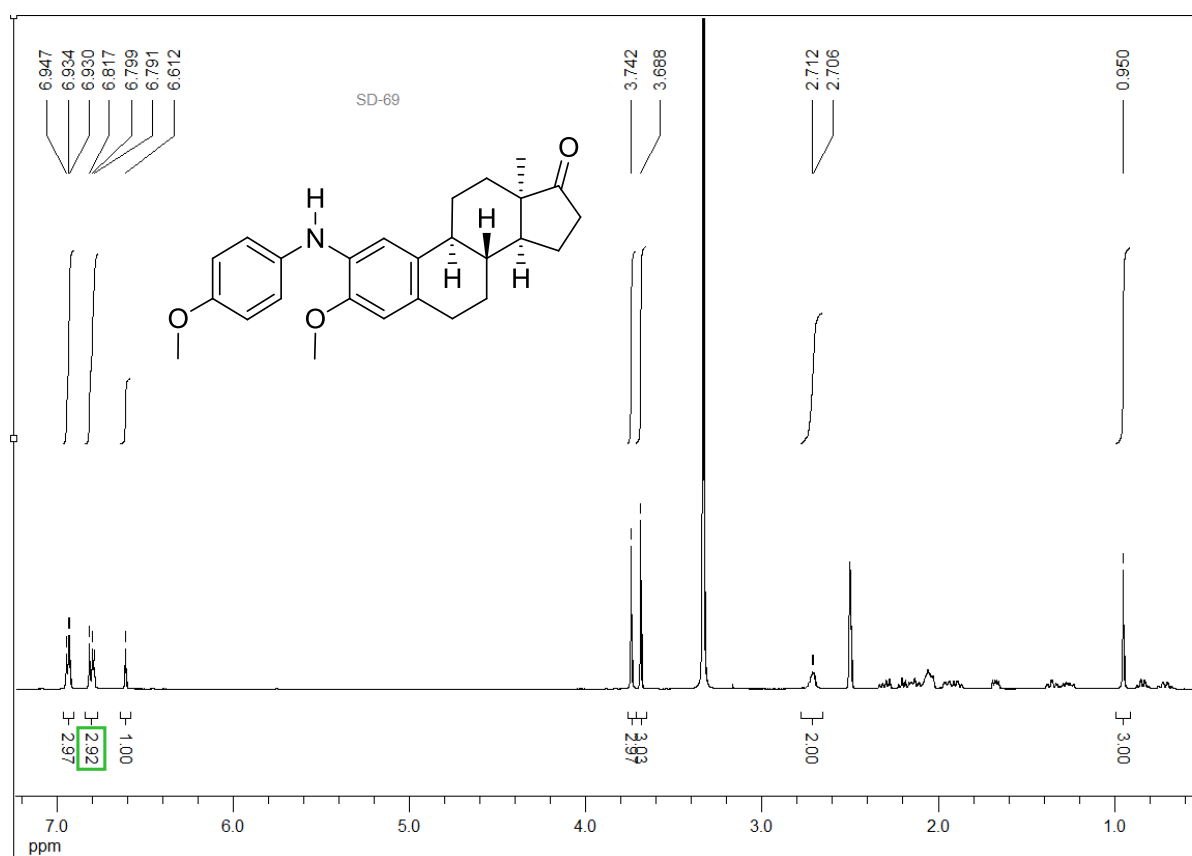
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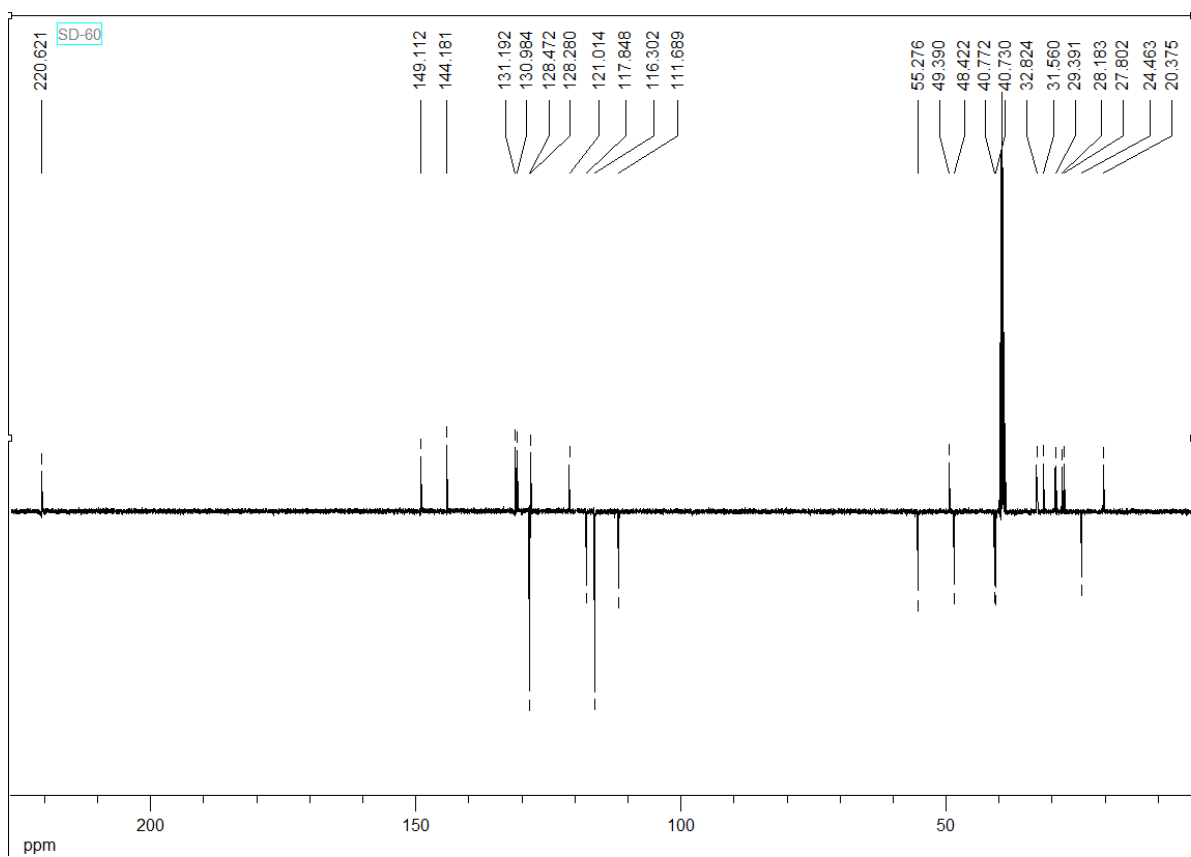
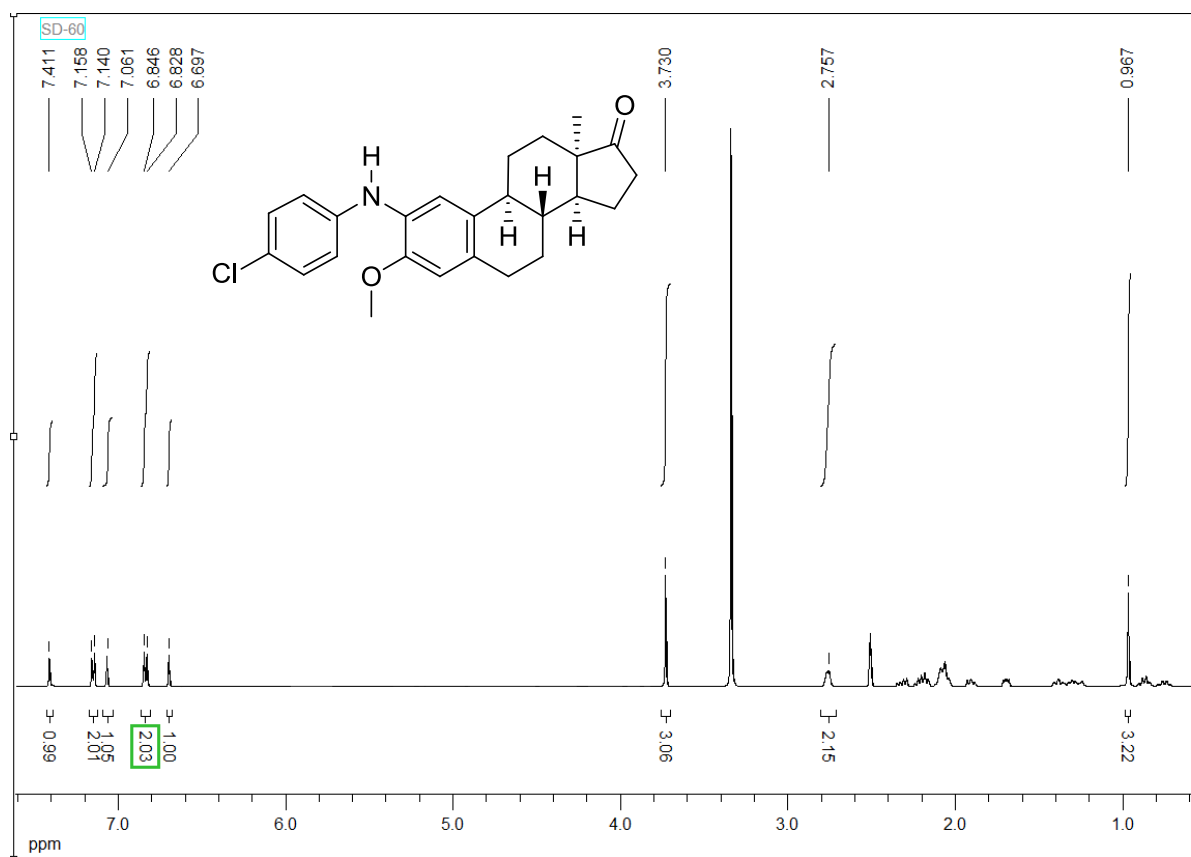
9a



9b



9c



9d

