Supplementary Information

Highly Efficient Enantioselective Synthesis of 1,3-Disubstituted 2,5-DKP Derivatives via Microwave Irradiation

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General Information

All chemicals were reagent grade and used as purchased. Reactions were monitored by TLC analysis using Merck silica gel 60 F-254 thin layer plates for solution-phase synthesis. Microwave reactions were conducted by microwave synthesizer (Biotage Initiator+). Flash column chromatography was carried out on Merck silica gel 60 (230-400 mesh). Optical rotation value was checked by polarimeter (Rudolph Autopol V). An ATR-IR spectrometer (Smiths detection) and automatic melting-point apparatus (Stuart SMP40) were used. ^{1}H NMR and ^{13}C NMR spectra were recorded in δ (ppm) units relative to deuterated solvent ($CDCl_3$, DMSO-d_6) as an internal reference using a 500-MHz NMR instrument (Bruker). Liquid chromatography tandem mass spectrometry (Agilent 6460 Triple Quad LC/MS) analysis was performed using an electrospray ionization (ESI) mass spectrometer with a photodiode-array detector (PDA). High-resolution mass spectrometry spectra were obtained using a TOF LC/MS system (Agilent 6550 iFunnel Q-TOF LC/MS). Reaction monitoring and analysis of enantiomers were carried out with High Performance Liquid chromatography (Agilent 1260 infinity series HPLC). Agilent ZORBAX Eclipse Plus C18 4.6 x 250 mm LC column and Daicel Chiralpak IA 4.6 x 250 mm (CSP A), Agilent Chiradex 4.0 x 250 mm (CSP B) LC column cartridge were used.

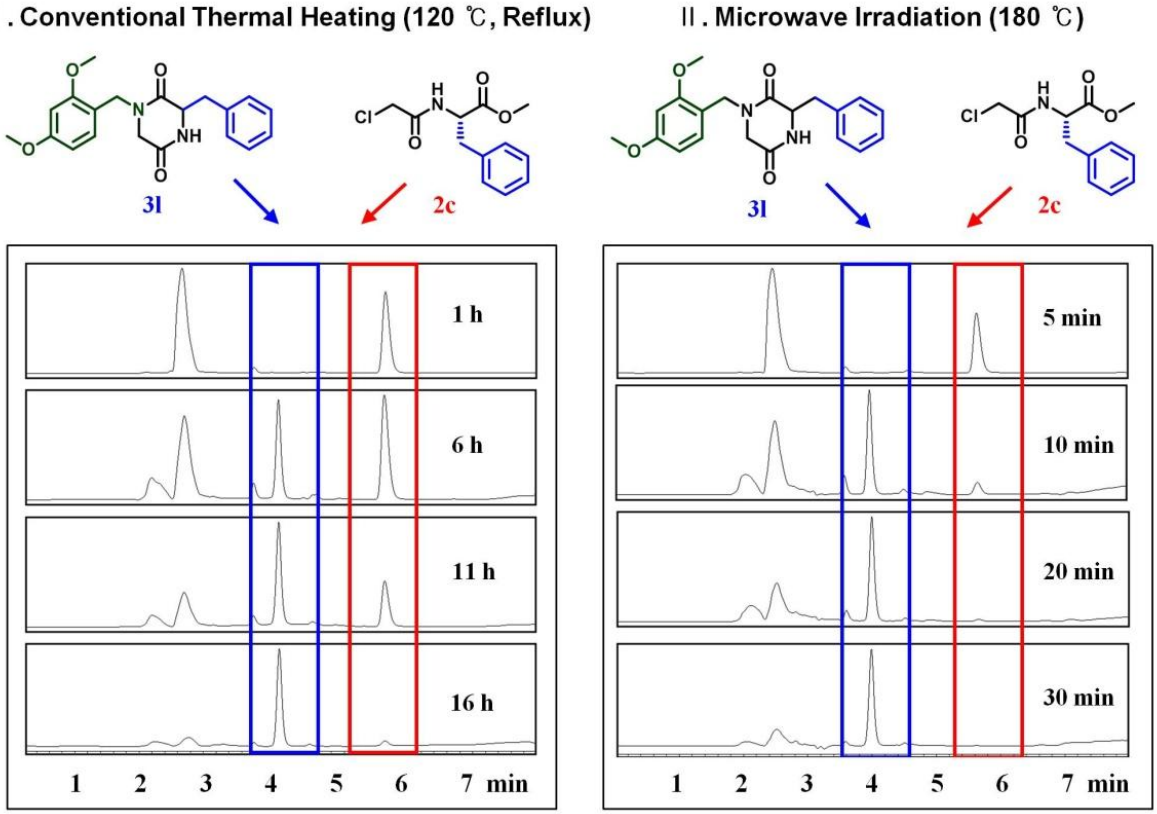


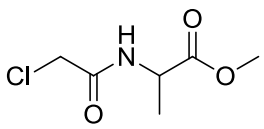
Figure S1. HPLC spectra comparison between conventional thermal heating and microwave radiation heating

1. Full analytical data of all synthesized compounds

Representative Procedure for the Preparation of Compounds 2

To a suspension of L-amino methyl ester hydrochloride **1** (30.0 mmol, 1.0 eq.) in CH_2Cl_2 (400 mL), Et_3N (8.363 mL, 60.0 mmol, 2.0 eq.) and diluted 2-chloro acetyl chloride (2.390 mL, 30.0 mmol, 1.0 eq. with CH_2Cl_2) were added slowly at 0°C. The reaction mixture was stirred for 2 h at r.t. and then washed with H_2O, neutralized to *p*H 7 with a saturated aqueous $NaHCO_3$ solution. The organic layer was separated, dried with anhydrous Na_2SO_4, and evaporated under reduced pressure. The crude mixture was purified by column chromatography (eluent: *n*-Hexane / Ethyl acetate) on silica gel to afford the desired product **2**.

(S)-methyl 2-(2-chloroacetamido)propanoate (2a) [22]



Colorless solid; yield: 5.093 g (95%); purity: 100% (checked by LC-MS, 254 nm); mp: 76.0-77.4 ℃; R_f: 0.5 (*n*-Hexane/Ethyl acetate = 3:1).

ATR-IR (neat): 3324 (N-H, amide), 2941 (sp^3 C-H), 1727 (C=O, ester), 1644 (C=O, amide), 1224, 1154 (C-O, ester), 987, 696 cm^{-1}.

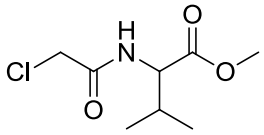
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.18 (s, 1H), 4.63 – 4.58 (m, 1H), 4.07 (s, 2H), 3.78 (s, 3H), 1.46 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 172.76, 165.58, 52.63, 48.37, 42.38, 18.17.

LC-MS (ESI, 60 eV): m/z = 180.1 $[M + H]^+$.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_6H_{11}ClNO_3$: 180.0422; found : 180.0421.

(S)-methyl 2-(2-chloroacetamido)-3-methylbutanoate (2b)



Colorless solid; yield: 6.018 g (97%); purity: 100% (checked by LC-MS, 254 nm); mp: 46.8-48.5 ℃; R_f: 0.682 (*n*-Hexane/Ethyl acetate = 3:1).

ATR-IR (neat): 3323 (N-H, amide), 2968, 2931, 2876 (sp^3 C-H), 1739 (C=O, ester), 1641 (C=O, amide), 1198, 1146 (C-O, ester), 987, 772 cm^{-1}.

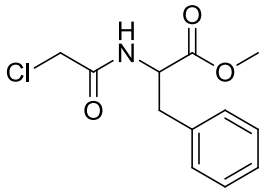
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.04 (d, *J* = 6.0 Hz, 1H), 4.55 (dd, *J* = 8.8, 4.9 Hz, 1H), 4.10 (d, *J* = 1.1 Hz, 2H), 3.77 (s, 3H), 2.22 (tt, *J* = 11.8, 3.4 Hz, 1H), 0.96 (dd, *J* = 11.1, 6.9 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 171.73, 165.89, 57.37, 52.29, 42.55, 31.24, 18.86, 17.70.

LC-MS (ESI, 60 eV): m/z = 208.2 $[M + H]^+$.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_8H_{15}ClNO_3$: 208.0735; found : 208.0735.

(S)-methyl 2-(2-chloroacetamido)-3-phenylpropanoate (2c) [22]



Colorless solid; yield: 7.525 g (98%); purity: 100% (checked by LC-MS, 254 nm); mp: 41.9-43.2 ℃; R_f: 0.386 (*n*-Hexane/Ethyl acetate = 3:1).

ATR-IR (neat): 3286 (N-H, amide), 3068 (sp^2 C-H), 3001, 2953 (sp^3 C-H), 1736 (C=O, ester), 1649 (C=O, amide), 1545, 1454 (C=C, aromatic), 1217, 1141 (C-O, ester), 973, 782 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.28 (dd, *J* = 15.0, 7.3 Hz, 3H), 7.12 (d, *J* = 7.3 Hz, 2H), 6.98 (d, *J* = 6.7 Hz, 1H), 4.87 (dd, *J* = 13.7, 5.9 Hz, 1H), 4.02 (d, *J* = 1.3 Hz, 2H), 3.74 (s, 3H), 3.14 (dt, *J* = 13.9, 6.8 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 171.27, 165.59, 135.36, 129.24, 128.73, 127.38, 53.41, 52.52, 42.41, 37.80.

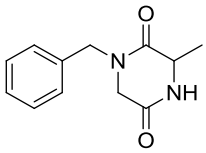
LC-MS (ESI, 60 eV): m/z = 256.1 $[M + H]^+$.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{12}H_{15}ClNO_3$: 256.0735; found : 256.0735.

Representative Procedure for the Preparation of Compounds 3

In a 10-mL sealed microwave reactor vessel, a mixture of *N*-α-chloroacetyl amino methyl ester **2** (3.0 mmol, 1.0 eq.), primary amine (3.6 mmol, 1.2 eq.), Et_3N (1.254 mL, 9.0 mmol, 3.0 eq.) in *n*-BuOH (1.5 mL) was stirred with irradiation at 180℃ for 30 min. After cooling to r.t., the resulting mixture was evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2. The organic phase was washed with H_2O and a saturated aqueous solution of citric acid and $NaHCO_3$. The organic layer was separated, dried with anhydrous Na_2SO_4, and evaporated. The obtained crude oil was purified by column chromatography (eluent: CH_2Cl_2 / MeOH) on silica gel and triturated with diethyl ether to afford the desired product **3**.

1-benzyl-3-methylpiperazine-2,5-dione (3a) [22]



White solid; yield: 481 mg (74%); purity: 100% (checked by LC-MS, 254 nm); mp: 119.7-122.7 ℃; R_f: 0.26 (CH_2Cl_2/MeOH = 20:1); optical rotation α: -2.8° (c=1, MeOH, enantiomeric mixture).

ATR-IR (neat): 3240 (N-H, amide), 3061 (sp^2 C-H), 3029, 2976, 2928 (sp^3 C-H), 1651(C=O, amide), 1452 (C=C, aromatic) cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.31 (s, 1H), 7.36 (t, *J* = 7.3 Hz, 2H), 7.29 (t, *J* = 7.3 Hz, 1H), 7.25 (d, *J* = 8.2 Hz, 2H), 4.55 – 4.48 (m, 2H), 4.08 – 3.99 (m, 1H), 3.79 (d, *J* = 17.4 Hz, 2H), 1.33 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 167.78, 165.96, 136.89, 129.12, 128.20, 127.92, 50.43, 49.72, 48.85, 19.50.

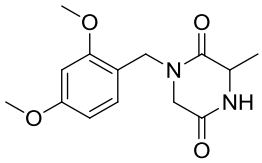
LC-MS (ESI, 60 eV): m/z = 219.1 $[M + H]^+$.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{12}H_{15}N_2O_2$: 219.1128; found : 219.1129.

CSP-HPLC A (210 nm, Daicel Chiralpak IA 4.6 x 250 mm, *n*-Hexane/EtOH = 80 : 20, r.t., 0.5 mL/min): t_R = 34.318 min (78.5%, major), t_R = 36.371 min (21.5%, minor).

CSP-HPLC B (210 nm, Agilent Chiradex 4.0 x 250 mm, ACN / MeOH / 5 mM Ammonium formate buffer = 2.5 : 2.5 : 95, r.t., 0.8 mL/min): t_R = 22.802 min (78.7%, major), t_R = 24.608 min (21.3%, minor).

1-(2,4-dimethoxybenzyl)-3-methylpiperazine-2,5-dione (3b)



Ivory solid; yield: 729 mg (87%); purity: 100% (checked by LC-MS, 254 nm); mp: 121.8-122.0 ℃; R_f: 0.217 (CH_2Cl_2/MeOH = 20:1); optical rotation α: 4.5° (c=1, MeOH).

ATR-IR (neat): 3194 (N-H, amide), 3064, 3001 (sp^2 C-H), 2941, 2893, 2843 (sp^3 C-H), 1653 (C=O, amide), 1507, 1457 (C=C, aromatic), 1207, 1155, 1038 (C-O, Ph-O-Me) cm^{-1}.

^{1}H NMR (500 MHz, DMSO): δ = 8.28 (s, 1H), 7.05 (d, *J* = 8.3 Hz, 1H), 6.58 (d, *J* = 2.3 Hz, 1H), 6.50 (dd, *J* = 8.3, 2.4 Hz, 1H), 4.39 (dd, *J* = 31.9, 14.7 Hz, 2H), 3.97 (q, *J* = 6.6 Hz, 1H), 3.80 – 3.74 (m, 8H), 1.30 (d, *J* = 7.0 Hz, 3H).

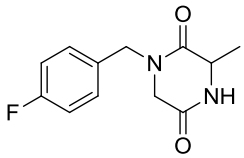
^{13}C NMR (126 MHz, DMSO): δ = 167.51, 166.11, 160.60, 158.72, 130.24, 116.40, 105.24, 98.88, 55.94, 55.67, 50.48, 49.87, 43.88, 19.56.

LC-MS (ESI, 60 eV): m/z = 279.1 $[M + H]^+$.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{14}H_{19}N_2O_4$: 279.1339; found : 279.1339.

CSP-HPLC A (254 nm, Daicel Chiralpak IA 4.6 x 250 mm, *n*-Hexane/THF = 30 : 70, r.t., 0.5 mL/min): t_R = 12.363 min (87.4%, major), t_R = 13.635 min (12.6%, minor).

1-(4-fluorobenzyl)-3-methylpiperazine-2,5-dione (3c)



White solid; yield: 501 mg (71%); purity: 100% (checked by LC-MS, 254 nm); mp: 138.6-140.1 ℃; R_f: 0.239 (CH_2Cl_2/MeOH = 20:1).

ATR-IR (neat): 3234 (N-H, amide), 3071 (sp^2 C-H), 2988, 2941 (sp^3 C-H), 1651 (C=O, amide), 1510, 1449 (C=C, aromatic) cm^{-1}.

^{1}H NMR (500 MHz, DMSO): δ = 8.31 (s, 1H), 7.31 (dd, *J* = 8.5, 5.6 Hz, 2H), 7.18 (t, *J* = 8.8 Hz, 2H), 4.57 – 4.41 (m, 2H), 4.02 (q, *J* = 6.6 Hz, 1H), 3.83 (s, 2H), 1.32 (d, *J* = 7.0 Hz, 3H).

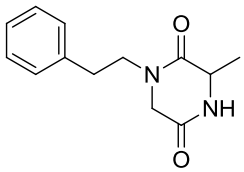
^{13}C NMR (126 MHz, DMSO): δ = 167.80, 165.95, 162.98, 161.05, 133.16, 133.14, 130.40, 130.34, 115.96, 115.79, 50.42, 49.68, 48.18, 19.45.

LC-MS (ESI, 60 eV): m/z = 237.1 $[M + H]^+$.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{12}H_{14}FN_2O_2$: 237.1034; found : 237.1039.

CSP-HPLC A (210 nm, Daicel Chiralpak IA 4.6 x 250 mm, *n*-Hexane/THF = 40 : 60, r.t., 0.5 mL/min): t_R = 15.594 min (76.3%, major), t_R = 7.648 min (23.7%, minor).

3-methyl-1-phenethylpiperazine-2,5-dione (3d)



White solid; yield: 628 mg (90%); purity: 100% (checked by LC-MS, 254 nm); mp: 150.1-151.1 ℃; R_f: 0.239 (CH_2Cl_2/MeOH = 20:1); optical rotation α: -1.1° (c=1, MeOH).

ATR-IR (neat): 3248 (N-H, amide), 3076, 3023 (sp^2 C-H), 2963, 2926, 2868 (sp^3 C-H), 1654 (C=O, amide), 1448 (C=C, aromatic) cm^{-1}.

^{1}H NMR (500 MHz, DMSO): δ = 8.24 (s, 1H), 7.29 (t, *J* = 7.4 Hz, 2H), 7.21 (dd, *J* = 15.3, 7.2 Hz, 3H), 3.92 – 3.81 (m, 3H), 3.58 – 3.50 (m, 1H), 3.47 – 3.40 (m, 1H), 2.78 (t, *J* = 7.5 Hz, 2H), 1.23 (d, *J* = 6.9 Hz, 3H).

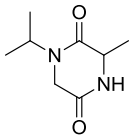
^{13}C NMR (126 MHz, DMSO): δ = 167.28, 165.97, 139.21, 129.19, 128.85, 126.74, 50.46, 50.23, 47.42, 32.84, 19.72.

LC-MS (ESI, 60 eV): m/z = 233.1 $[M + H]^+$.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{13}H_{17}N_2O_2$: 233.1285; found : 233.1285.

CSP-HPLC A (210 nm, Daicel Chiralpak IA 4.6 x 250 mm, *n*-Hexane/THF = 20 : 80, r.t., 0.5 mL/min): t_R = 10.125 min (88.3%, major), t_R = 11.251 min (11.7%, minor).

1-isopropyl-3-methylpiperazine-2,5-dione (3e)



White solid; yield: 302 mg (59%); purity: 100% (checked by LC-MS, 210 nm); mp: 122.2-124.4 ℃; R_f: 0.196 (CH_2Cl_2/MeOH = 20:1).

ATR-IR (neat): 3207 (N-H, amide), 3079 (sp^2 C-H), 2975, 2873 (sp^3 C-H), 1654 (C=O, amide), 1465 (C=C, aromatic) cm^{-1}.

^{1}H NMR (500 MHz, DMSO): δ = 8.25 (s, 1H), 4.56 (hept, *J* = 6.8 Hz, 1H), 3.89 (q, *J* = 6.9 Hz, 1H), 3.83 – 3.69 (m, 2H), 1.27 (d, *J* = 7.0 Hz, 3H), 1.05 (dd, *J* = 6.9, 1.3 Hz, 6H).

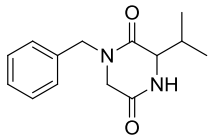
^{13}C NMR (126 MHz, DMSO): δ = 167.02, 166.61, 50.58, 43.94, 43.89, 19.24, 19.17, 19.10.

LC-MS (ESI, 60 eV): m/z = 171.1 $[M + H]^+$.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_8H_{15}N_2O_2$: 171.1128; found : 171.1128.

CSP-HPLC A (210 nm, Daicel Chiralpak IA 4.6 x 250 mm, *n*-Hexane/*i*-PrOH = 70 : 30, r.t., 0.5 mL/min): t_R = 11.310 min (68.7%, major), t_R = 12.933 min (31.3%, minor).

1-benzyl-3-isopropylpiperazine-2,5-dione (3f)



White solid; yield: 528 mg (72%); purity: 97% (checked by LC-MS, 254 nm); mp: 143.1-145.7 ℃; R_f: 0.435 (CH_2Cl_2/MeOH = 20:1).

ATR-IR (neat): 3246 (N-H, amide), 3089, 3029 (sp^2 C-H), 2962, 2936, 2908, 2873 (sp^3 C-H), 1648 (C=O, amide), 1466 (C=C, aromatic) cm^{-1}.

^{1}H NMR (500 MHz, DMSO): δ = 8.37 (s, 1H), 7.36 (t, *J* = 7.2 Hz, 2H), 7.32 – 7.24 (m, 3H), 4.66 (d, *J* = 14.5 Hz, 1H), 4.40 (d, *J* = 14.5 Hz, 1H), 3.86 – 3.70 (m, 3H), 2.21 – 2.12 (m, 1H), 0.92 (d, *J* = 7.0 Hz, 3H), 0.81 (d, *J* = 6.8 Hz, 3H).

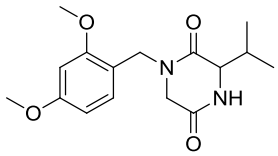
^{13}C NMR (126 MHz, DMSO): δ = 166.16, 165.78, 136.86, 129.12, 128.52, 128.04, 60.35, 49.23, 48.92, 33.29, 19.11, 17.37.

LC-MS (ESI, 60 eV): m/z = 247.2 $[M + H]^+$.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{14}H_{19}N_2O_2$: 247.1441; found : 247.1441.

CSP-HPLC A (210 nm, Daicel Chiralpak IA 4.6 x 250 mm, *n*-Hexane/*i*-PrOH = 75 : 25, r.t., 0.5 mL/min): t_R = 14.068 min (93.7%, major), t_R = 15.323 min (6.3%, minor).

1-(2,4-dimethoxybenzyl)-3-isopropylpiperazine-2,5-dione (3g)



White solid; yield: 774 mg (84%); purity: 100% (checked by LC-MS, 254 nm); mp: 124.4-126.4 ℃; R_f: 0.391 (CH_2Cl_2/MeOH = 20:1).

ATR-IR (neat): 3187 (N-H, amide), 3051 (sp^2 C-H), 2973, 2956, 2928, 2891, 2833 (sp^3 C-H), 1653 (C=O, amide), 1509, 1465 (C=C, aromatic), 1213, 1158, 1032 (C-O, Ph-O-Me) cm^{-1}.

^{1}H NMR (500 MHz, DMSO): δ = 8.32 (s, 1H), 7.10 (d, *J* = 8.3 Hz, 1H), 6.57 (d, *J* = 2.3 Hz, 1H), 6.50 (dd, *J* = 8.3, 2.4 Hz, 1H), 4.57 (d, *J* = 14.4 Hz, 1H), 4.27 (d, *J* = 14.4 Hz, 1H), 3.77 (t, *J* = 10.1 Hz, 7H), 3.69 – 3.63 (m, 2H), 2.17 – 2.09 (m, 1H), 0.90 (d, *J* = 7.0 Hz, 3H), 0.80 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (126 MHz, DMSO): δ = 165.96, 165.79, 160.72, 158.77, 130.95, 116.29, 105.21, 98.81, 60.45, 55.91, 55.67, 49.35, 43.76, 33.28, 19.06, 17.30.

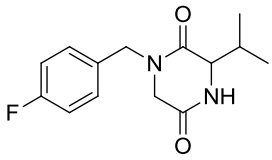
LC-MS (ESI, 60 eV): m/z = 307.2 $[M + H]^+$.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{16}H_{23}N_2O_4$: 307.1652; found : 307.1652.

CSP-HPLC A (210 nm, Daicel Chiralpak IA 4.6 x 250 mm, *n*-Hexane/*i*-PrOH = 75 : 25, r.t., 0.5 mL/min): t_R = 18.304 min (74.1%, major), t_R = 20.523 min (25.9%, minor).

CSP-HPLC B (254 nm, Agilent Chiradex 4.0 x 250 mm, ACN / MeOH / 5 mM Ammonium formate buffer = 5 : 5 : 90, r.t., 0.8 mL/min): t_R = 10.866 min (25.4%, minor), t_R = 12.099 min (74.6%, major).

1-(4-fluorobenzyl)-3-isopropylpiperazine-2,5-dione (3h)



White solid; yield: 556 mg (70%); purity: 98% (checked by LC-MS, 254 nm); mp: 120.3-121.4 ℃; R_f: 0.413 (CH_2Cl_2/MeOH = 20:1).

ATR-IR (neat): 3249 (N-H, amide), 3094, 3049 (sp^2 C-H), 2969, 2938, 2911, 2878 (sp^3 C-H), 1647 (C=O, amide), 1509, 1459 (C=C, aromatic) cm^{-1}.

^{1}H NMR (500 MHz, DMSO): δ = 8.36 (s, 1H), 7.34 (dd, *J* = 8.5, 5.6 Hz, 2H), 7.19 (t, *J* = 8.9 Hz, 2H), 4.64 (d, *J* = 14.5 Hz, 1H), 4.38 (d, *J* = 14.5 Hz, 1H), 3.79 (dd, *J* = 52.6, 17.5 Hz, 2H), 3.71 (t, *J* = 3.5 Hz, 1H), 2.16 (dtd, *J* = 13.8, 6.9, 4.2 Hz, 1H), 0.91 (d, *J* = 7.0 Hz, 3H), 0.79 (d, *J* = 6.8 Hz, 3H).

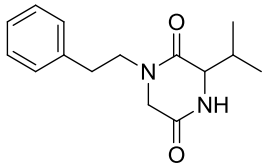
^{13}C NMR (126 MHz, DMSO): δ = 166.19, 165.76, 163.03, 161.09, 133.16, 133.13, 130.74, 130.67, 115.97, 115.80, 60.31, 49.20, 48.22, 33.29, 19.08, 17.34.

LC-MS (ESI, 60 eV): m/z = 265.1 $[M + H]^+$.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{14}H_{18}FN_2O_2$: 265.1347; found : 265.1348.

CSP-HPLC A (210 nm, Daicel Chiralpak IA 4.6 x 250 mm, *n*-Hexane/THF = 40 : 60, r.t., 0.5 mL/min): t_R = 12.329 min (94.4%, major), t_R = 14.951 min (5.6%, minor).

3-isopropyl-1-phenethylpiperazine-2,5-dione (3i)



White solid; yield: 690 mg (88%); purity: 100% (checked by LC-MS, 254 nm); mp: 155.1-157.6 ℃; R_f: 0.413 (CH_2Cl_2/MeOH = 20:1); optical rotation α: -12.3° (c=1, MeOH).

ATR-IR (neat): 3247 (N-H, amide), 3089, 3066, 3023 (sp^2 C-H), 2966, 2933, 2873, 2462 (sp^3 C-H), 1640 (C=O, amide), 1462 (C=C, aromatic) cm^{-1}.

^{1}H NMR (500 MHz, DMSO): δ = 8.29 (s, 1H), 7.29 (t, *J* = 7.4 Hz, 2H), 7.24 (d, *J* = 6.9 Hz, 2H), 7.20 (t, *J* = 7.1 Hz, 1H), 3.94 (d, *J* = 17.6 Hz, 1H), 3.79 – 3.71 (m, 2H), 3.57 (t, *J* = 3.4 Hz, 1H), 3.34 – 3.26 (m, 1H), 2.84 – 2.75 (m, 2H), 2.04 (qd, *J* = 11.1, 6.8 Hz, 1H), 0.84 (d, *J* = 7.0 Hz, 3H), 0.74 (d, *J* = 6.8 Hz, 3H).

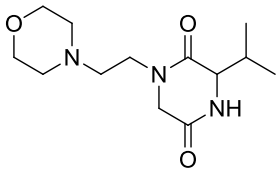
^{13}C NMR (126 MHz, DMSO): δ = 165.93, 165.73, 139.13, 129.16, 128.84, 126.75, 60.40, 49.81, 47.25, 33.16, 32.69, 19.04, 17.34.

LC-MS (ESI, 60 eV): m/z = 261.2 $[M + H]^+$.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{15}H_{21}N_2O_2$: 261.1598; found : 261.1598.

CSP-HPLC A (210 nm, Daicel Chiralpak IA 4.6 x 250 mm, *n*-Hexane/THF = 30 : 70, r.t., 0.5 mL/min): t_R = 10.273 min (98.5%, major), t_R = 12.548 min (1.5%, minor).

3-isopropyl-1-(2-morpholinoethyl)piperazine-2,5-dione (3j)



Ivory solid; yield: 608 mg (75%); purity: 100% (checked by LC-MS, 220 nm); mp: 182.4-184.5 ℃; R_f: 0.217 (CH_2Cl_2/MeOH = 20:1); optical rotation α: 4.6° (c=1, MeOH).

ATR-IR (neat): 3241 (N-H, amide), 3091, 3014 (sp^2 C-H), 2960, 2901, 2851, 2800 (sp^3 C-H), 1644 (C=O, amide), 1463 (C=C, aromatic), 1115 (C-O) cm^{-1}.

^{1}H NMR (500 MHz, DMSO): δ = 8.30 (s, 1H), 4.07 (d, *J* = 17.6 Hz, 1H), 3.86 – 3.79 (m, 2H), 3.60 (t, *J* = 3.4 Hz, 1H), 3.52 (s, 4H), 3.05 (dt, *J* = 13.7, 5.6 Hz, 1H), 2.50 – 2.46 (m, 1H), 2.45 – 2.25 (m, 5H), 2.11 (dtd, *J* = 13.8, 6.9, 3.9 Hz, 1H), 0.93 (d, *J* = 7.0 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H).

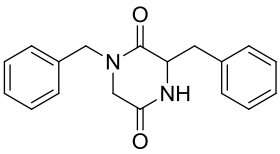
^{13}C NMR (126 MHz, DMSO): δ = 166.07, 165.88, 66.70, 60.50, 55.15, 53.62, 49.97, 42.28, 33.61, 19.10, 17.25.

LC-MS (ESI, 60 eV): m/z = 270.2 $[M+H]^+$.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{13}H_{24}N_3O_3$: 270.1812; found : 270.1812.

CSP-HPLC A (210 nm, Daicel Chiralpak IA 4.6 x 250 mm, *n*-Hexane/THF = 30 : 70, r.t., 0.5 mL/min): t_R = 13.722 min (97.8%, major), t_R = 17.435 min (2.2%, minor).

1,3-dibenzylpiperazine-2,5-dione (3k) [22]



White solid; yield: 572 mg (76%); purity: 100% (checked by LC-MS, 254 nm); mp: 170.6-172.8 ℃; R_f: 0.239 (CH_2Cl_2/MeOH = 20:1); optical rotation α: 12.0° (c=1, MeOH, enantiomeric mixture).

ATR-IR (neat): 3252 (N-H, amide), 3056, 3029 (sp^2 C-H), 2936, 2888 (sp^3 C-H), 1651 (C=O, amide), 1453 (C=C, aromatic) cm^{-1}.

^{1}H NMR (500 MHz, DMSO): δ = 8.35 (s, 1H), 7.35 – 7.27 (m, 3H), 7.19 (t, *J* = 7.2 Hz, 1H), 7.12 (t, *J* = 6.4 Hz, 4H), 7.06 (d, *J* = 7.4 Hz, 2H), 4.59 (d, *J* = 14.4 Hz, 1H), 4.27 (d, *J* = 2.3 Hz, 1H), 4.17 (d, *J* = 14.4 Hz, 1H), 3.45 (d, *J* = 17.2 Hz, 1H), 3.16 (dd, *J* = 13.4, 3.9 Hz, 1H), 2.89 (dd, *J* = 13.4, 4.8 Hz, 1H), 2.64 (d, *J* = 17.2 Hz, 1H).

^{13}C NMR (126 MHz, DMSO): δ = 164.76, 164.25, 135.09, 134.90, 129.45, 127.85, 127.66, 127.43, 126.87, 126.12, 54.91, 47.77, 47.60, 38.56.

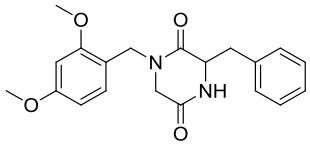
LC-MS (ESI, 60 eV): m/z = 295.2 $[M+H]^+$.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{18}H_{19}N_2O_2$: 295.1441; found : 295.1441.

CSP-HPLC A (210 nm, Daicel Chiralpak IA 4.6 x 250 mm, *n*-Hexane/*i*-PrOH = 60 : 40, r.t., 0.5 mL/min): t_R = 11.985 min (73.4%, major), t_R = 13.575 min (26.6%, minor).

CSP-HPLC B (210 nm, Agilent Chiradex 4.0 x 250 mm, ACN / MeOH / 5 mM Ammonium formate buffer = 30 : 5 : 65, r.t., 0.8 mL/min): t_R = 5.434 min (26.0%, minor), t_R = 5.949 min (74.0%, major).

3-benzyl-1-(2,4-dimethoxybenzyl)piperazine-2,5-dione (3l)



White solid; yield: 862 mg (81%); purity: 100% (checked by LC-MS, 254 nm); mp: 138.3-140.8 ℃; R_f: 0.196 (CH_2Cl_2/MeOH = 20:1); optical rotation α: 1.4° (c=1, MeOH, enantiomeric mixture).

ATR-IR (neat): 3124 (N-H, amide), 3084, 3026 (sp^2 C-H), 2963, 2946, 2891, 2833 (sp^3 C-H), 1628 (C=O, amide), 1510, 1435 (C=C, aromatic), 1264, 1031 (C-O, Ph-O-Me) cm^{-1}.

^{1}H NMR (500 MHz, DMSO): δ = 8.30 (s, 1H), 7.21 (t, *J* = 7.0 Hz, 1H), 7.14 (t, *J* = 7.2 Hz, 2H), 7.03 (d, *J* = 7.2 Hz, 2H), 6.95 (d, *J* = 8.2 Hz, 1H), 6.55 (s, 1H), 6.47 (d, *J* = 8.0 Hz, 1H), 4.34 (d, *J* = 14.4 Hz, 1H), 4.18 (d, *J* = 14.8 Hz, 2H), 3.76 (s, 3H), 3.72 (s, 3H), 3.39 (d, *J* = 17.4 Hz, 1H), 3.13 (dd, *J* = 13.2, 3.2 Hz, 1H), 2.87 (dd, *J* = 13.3, 4.3 Hz, 1H), 2.66 (d, *J* = 17.4 Hz, 1H).

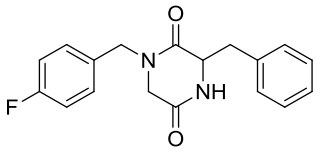
^{13}C NMR (126 MHz, DMSO): δ = 165.77, 165.57, 160.65, 158.73, 136.04, 131.04, 130.51, 128.50, 127.19, 116.01, 105.14, 98.68, 56.02, 55.85, 55.71, 49.14, 43.69, 39.74.

LC-MS (ESI, 60 eV): m/z = 355.2 $[M + H]^+$.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{20}H_{23}N_2O_4$: 355.1652; found : 355.1651.

CSP-HPLC A (210 nm, Daicel Chiralpak IA 4.6 x 250 mm, *n*-Hexane/*i*-PrOH = 60 : 40, r.t., 0.5 mL/min): t_R = 12.507 min (52.6%, major), t_R = 15.677 min (47.4%, minor).

3-benzyl-1-(4-fluorobenzyl)piperazine-2,5-dione (3m)



White solid; yield: 780 mg (83%); purity: 98% (checked by LC-MS, 254 nm); mp: 180.2-182.7 ℃; R_f: 0.217 (CH_2Cl_2/MeOH = 20:1); optical rotation α: 9.6° (c=1, MeOH, enantiomeric mixture).

ATR-IR (neat): 3249 (N-H, amide), 3069, 3031 (sp^2 C-H), 2933, 2896 (sp^3 C-H), 1649 (C=O, amide), 1509, 1467 (C=C, aromatic) cm^{-1}.

^{1}H NMR (500 MHz, DMSO:) δ = 8.35 (s, 1H), 7.26 – 7.07 (m, 7H), 7.04 (d, *J* = 7.1 Hz, 2H), 4.60 (d, *J* = 14.4 Hz, 1H), 4.26 (dd, *J* = 6.7, 4.0 Hz, 1H), 4.12 (d, *J* = 14.4 Hz, 1H), 3.47 (d, *J* = 17.2 Hz, 1H), 3.15 (dd, *J* = 13.4, 3.9 Hz, 1H), 2.88 (dd, *J* = 13.4, 4.8 Hz, 1H), 2.61 (d, *J* = 17.2 Hz, 1H).

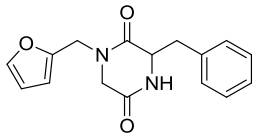
^{13}C NMR (126 MHz, DMSO): δ = 165.88, 165.33, 163.02, 161.09, 135.95, 132.49, 132.47, 130.99, 130.92, 130.52, 128.49, 127.25, 115.76, 115.59, 55.96, 48.63, 48.14, 39.82.

LC-MS (ESI, 60 eV): m/z = 313.2 $[M + H]^+$.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{18}H_{18}FN_2O_2$: 313.1347; found : 313.1347.

CSP-HPLC A (210 nm, Daicel Chiralpak IA 4.6 x 250 mm, *n*-Hexane/*i*-PrOH = 60 : 40, r.t., 0.5 mL/min): t_R = 12.502 min (74.0%, major), t_R = 13.668 min (26.0%, minor).

3-benzyl-1-(furan-2-ylmethyl)piperazine-2,5-dione (3n)



Ivory solid; yield: 683 mg (80%); purity: 100% (checked by LC-MS, 254 nm); mp: 135.5-137.2 ℃; R_f: 0.217 (CH_2Cl_2/MeOH = 20:1); optical rotation α: 32.0° (c=1, MeOH, enantiomeric mixture).

ATR-IR (neat): 3242 (N-H, amide), 3056, 3026 (sp^2 C-H), 2953, 2926, 2888 (sp^3 C-H), 1653 (C=O, amide), 1466 (C=C, aromatic) cm^{-1}.

^{1}H NMR (500 MHz, DMSO): δ = 8.30 (s, 1H), 7.64 (s, 1H), 7.16 (dt, *J* = 23.6, 7.1 Hz, 3H), 7.02 (d, *J* = 7.1 Hz, 2H), 6.42 (s, 1H), 6.29 (d, *J* = 2.8 Hz, 1H), 4.64 (d, *J* = 15.1 Hz, 1H), 4.19 (dd, *J* = 18.6, 8.3 Hz, 2H), 3.45 (d, *J* = 17.1 Hz, 1H), 3.13 (dd, *J* = 13.4, 3.4 Hz, 1H), 2.85 (dd, *J* = 13.4, 4.9 Hz, 1H), 2.57 (d, *J* = 17.1 Hz, 1H).

^{13}C NMR (126 MHz, DMSO): δ = 165.76, 165.38, 149.71, 143.47, 135.80, 130.47, 128.51, 127.16, 110.88, 109.81, 55.93, 48.66, 41.56, 39.82.

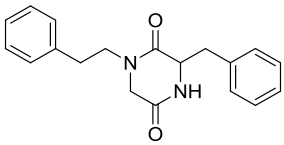
LC-MS (ESI, 60 eV): m/z = 285.3 $[M+H]^+$.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{16}H_{17}N_2O_3$: 285.1234; found : 285.1234.

CSP-HPLC A (210 nm, Daicel Chiralpak IA 4.6 x 250 mm, *n*-Hexane/*i*-PrOH = 60 : 40, r.t., 0.5 mL/min): t_R = 11.955 min (78.8%, major), t_R = 13.922 min (21.2%, minor).

CSP-HPLC B (210 nm, Agilent Chiradex 4.0 x 250 mm, ACN / 5 mM Ammonium formate buffer = 30 : 70, r.t., 0.8 mL/min): t_R = 5.124 min (18.7%, minor), t_R = 5.765 min (81.3%, major).

3-benzyl-1-phenethylpiperazine-2,5-dione (3o)



Ivory solid; yield: 788 mg (85%); purity: 100% (checked by LC-MS, 254 nm); mp: 173.8-175.7 ℃; R_f: 0.239 (CH_2Cl_2/MeOH = 20:1); optical rotation α: -17.5° (c=1, MeOH, enantiomeric mixture).

ATR-IR (neat): 3242 (N-H, amide), 3084, 3029 (sp^2 C-H), 2928, 2893, 2860 (sp^3 C-H), 1653 (C=O, amide), 1467 (C=C, aromatic) cm^{-1}.

^{1}H NMR (500 MHz, DMSO): δ = 8.29 (s, 1H), 7.27 (t, *J* = 7.3 Hz, 5H), 7.20 (d, *J* = 7.3 Hz, 1H), 7.16 (d, *J* = 7.2 Hz, 2H), 7.14 – 7.08 (m, 2H), 4.15 (d, *J* = 2.6 Hz, 1H), 3.52 – 3.41 (m, 2H), 3.23 (ddd, *J* = 13.2, 9.6, 6.1 Hz, 1H), 3.11 (dd, *J* = 13.4, 4.2 Hz, 1H), 2.86 (dd, *J* = 13.5, 4.7 Hz, 1H), 2.77 (d, *J* = 17.3 Hz, 1H), 2.66 (ddd, *J* = 15.3, 9.6, 5.9 Hz, 1H), 2.55 (ddd, *J* = 13.4, 9.8, 6.1 Hz, 1H).

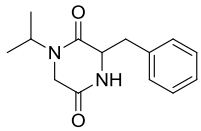
^{13}C NMR (126 MHz, DMSO): δ = 165.64, 165.50, 139.17, 136.16, 130.59, 129.08, 128.86, 128.64, 127.37, 126.74, 56.00, 49.42, 47.56, 39.82, 32.61.

LC-MS (ESI, 60 eV): m/z = 309.2 $[M+H]^+$.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{19}H_{21}N_2O_2$: 309.1598; found : 309.1598.

CSP-HPLC A (210 nm, Daicel Chiralpak IA 4.6 x 250 mm, *n*-Hexane/*i*-PrOH = 60 : 40, r.t., 0.5 mL/min): t_R = 11.074 min (79.8%, major), t_R = 13.221 min (20.2%, minor).

3-benzyl-1-isopropylpiperazine-2,5-dione (3p)



White solid; yield: 437 mg (59%); purity: 96% (checked by LC-MS, 254 nm); mp: 153.3-155.1 ℃; R_f: 0.217 (CH_2Cl_2/MeOH = 20:1); optical rotation α: 18.5° (c=1, MeOH, enantiomeric mixture).

ATR-IR (neat): 3267 (N-H, amide), 3026 (sp^2 C-H), 2978, 2921, 2878 (sp^3 C-H), 1646 (C=O, amide), 1460 (C=C, aromatic) cm^{-1}.

^{1}H NMR (500 MHz, DMSO): δ = 8.30 (s, 1H), 7.27 (dd, *J* = 4.7, 1.5 Hz, 3H), 7.11 (dd, *J* = 6.5, 2.8 Hz, 2H), 4.53 (dt, *J* = 13.7, 6.8 Hz, 1H), 4.13 (dd, *J* = 7.1, 3.9 Hz, 1H), 3.35 (s, 1H), 3.12 (dd, *J* = 13.4, 4.1 Hz, 1H), 2.86 (dd, *J* = 13.4, 4.7 Hz, 1H), 2.46 (d, *J* = 17.2 Hz, 1H), 0.96 (d, *J* = 6.8 Hz, 3H), 0.80 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (126 MHz, DMSO): δ = 165.79, 165.03, 136.11, 130.59, 128.62, 127.37, 56.19, 43.84, 42.85, 39.81, 18.92, 18.52.

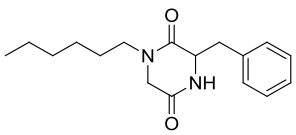
LC-MS (ESI, 60 eV): m/z = 247.2 $[M + H]^+$.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{14}H_{19}N_2O_2$: 247.1441; found : 247.1441.

CSP-HPLC A (210 nm, Daicel Chiralpak IA 4.6 x 250 mm, *n*-Hexane/*i*-PrOH = 60 : 40, r.t., 0.5 mL/min): t_R = 8.830 min (63.7%, major), t_R = 10.114 min (36.3%, minor).

CSP-HPLC B (210 nm, Agilent Chiradex 4.0 x 250 mm, ACN / 5 mM Ammonium formate buffer = 15 : 85, r.t., 0.8 mL/min): t_R = 9.132 min (35.2%, minor), t_R = 10.255 min (64.8%, major).

3-benzyl-1-hexylpiperazine-2,5-dione (3q)



White solid; yield: 549 mg (64%); purity: 99% (checked by LC-MS, 254 nm); mp: 105.5-107.3 ℃; R_f: 0.283 (CH_2Cl_2/MeOH = 20:1); optical rotation α: 5.0° (c=1, MeOH, enantiomeric mixture).

ATR-IR (neat): 3237 (N-H, amide), 3064, 3029 (sp^2 C-H), 2965, 2925, 2866 (sp^3 C-H), 1652 (C=O, amide), 1467 (C=C, aromatic) cm^{-1}.

^{1}H NMR (500 MHz, DMSO): δ = 8.28 (s, 1H), 7.30 – 7.21 (m, 3H), 7.15 – 7.07 (m, 2H), 4.14 (dd, *J* = 6.8, 4.0 Hz, 1H), 3.47 (d, *J* = 17.3 Hz, 1H), 3.30 – 3.23 (m, 1H), 3.11 (dd, *J* = 13.4, 4.2 Hz, 1H), 3.00 – 2.93 (m, 1H), 2.86 (dd, *J* = 13.4, 4.8 Hz, 1H), 2.77 (d, *J* = 17.3 Hz, 1H), 1.33 – 1.18 (m, 6H), 1.10 (dt, *J* = 8.6, 7.2 Hz, 2H), 0.86 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (126 MHz, DMSO): δ = 165.61, 165.50, 136.17, 130.56, 128.56, 127.31, 56.04, 49.10, 45.85, 39.77, 31.39, 26.34, 26.23, 22.46, 14.39.

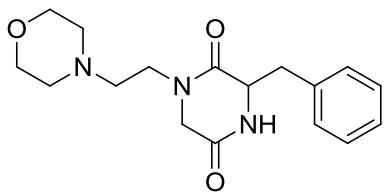
LC-MS (ESI, 60 eV): m/z = 289.3 $[M + H]^+$.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{17}H_{25}N_2O_2$: 289.1911; found : 289.1911.

CSP-HPLC A (210 nm, Daicel Chiralpak IA 4.6 x 250 mm, *n*-Hexane/*i*-PrOH = 60 : 40, r.t., 0.5 mL/min): t_R = 11.955 min (78.8%, major), t_R = 13.922 min (21.2%, minor).

CSP-HPLC B (210 nm, Agilent Chiradex 4.0 x 250 mm, ACN / 5 mM Ammonium formate buffer = 30 : 70, r.t., 0.8 mL/min): t_R = 5.124 min (18.7%, minor), t_R = 5.765 min (81.3%, major).

3-benzyl-1-(2-morpholinoethyl)piperazine-2,5-dione (3r)



Ivory solid; yield: 698 mg (73%); purity: 100% (checked by LC-MS, 254 nm); mp: 149.8-150.4 ℃; R_f: 0.065 (CH_2Cl_2/MeOH = 20:1); optical rotation α: 7.2° (c=1, MeOH, enantiomeric mixture).

ATR-IR (neat): 3242 (N-H, amide), 3061, 3026 (sp^2 C-H), 2951, 2933, 2893, 2858, 2805 (sp^3 C-H), 1646 (C=O, amide), 1464 (C=C, aromatic), 1175 (C-O) cm^{-1}.

^{1}H NMR (500 MHz, DMSO): δ = 8.27 (s, 1H), 7.26 (dd, *J* = 5.5, 4.7 Hz, 3H), 7.14 (dd, *J* = 7.1, 1.9 Hz, 2H), 4.15 (d, *J* = 2.7 Hz, 1H), 3.59 (d, *J* = 17.3 Hz, 1H), 3.50 (t, *J* = 4.1 Hz, 4H), 3.45 – 3.39 (m, 1H), 3.18 – 3.08 (m, 2H), 3.00 (d, *J* = 17.3 Hz, 1H), 2.87 (dd, *J* = 13.5, 4.8 Hz, 1H), 2.41 – 2.17 (m, 6H).

^{13}C NMR (126 MHz, DMSO): δ = 165.73, 165.63, 136.23, 130.53, 128.62, 127.27, 66.66, 55.99, 55.58, 53.65, 49.89, 42.67.

LC-MS (ESI, 60 eV): m/z = 318.4 $[M + H]^+$.

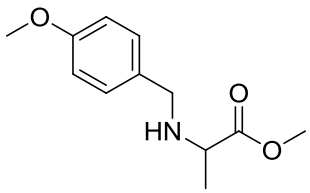
HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{17}H_{24}N_3O_3$: 318.1812; found : 318.1813.

CSP-HPLC B (210 nm, Agilent Chiradex 4.0 x 250 mm, ACN / 5 mM Ammonium formate buffer = 10 : 90, r.t., 0.8 mL/min): t_R = 21.072 min (85.2%, major), t_R = 24.897 min (14.8%, minor).

Representative Procedure for the Preparation of Compounds 4

Et_3N (4.182 mL, 30.0 mmol, 1.0 eq.) and p-methoxybenzaldehyde (4.376 mL, 36.0 mmol, 1.2 eq.) were slowly added successively to L-amino methyl ester hydrochloride **1** (30.0 mmol, 1.0 eq.) in MeOH (300 mL). The reaction mixture was stirred for 1 h at r.t. and monitored by TLC. When the starting material had completely disappeared, $NaBH_4$ (2.270 g, 60.0 mmol, 2.0 eq.) was added carefully at 0°C and stirred for 1 h at r.t.. MeOH was removed under reduced pressure. The reaction mixture was extracted with CH_2Cl_2 and H_2O and neutralized with a saturated aqueous solution of citric acid and $NaHCO_3$. The organic residue was separated, washed with brine, and dried over anhydrous Na_2SO_4. The crude mixture was purified by column chromatography (eluent: *n*-Hexane / Ethyl acetate) to yield the desired product **4**.

(S)-methyl 2-((4-methoxybenzyl)amino)propanoate (4a)



Transparent oil; yield: 6.035 g (90%); purity: 93% (checked by LC-MS, 254 nm); R_f: 0.182 (*n*-Hexane/Ethyl acetate = 5:1).

ATR-IR (neat): 3330 (N-H, amine), 3001 (sp^2 C-H), 2998, 2953, 2903, 2838 (sp^3 C-H), 1734 (C=O, ester), 1512, 1455 (C=C, aromatic), 1247, 1175, 1035 (C-O, Ph-O-Me, ester) cm^{-1}.

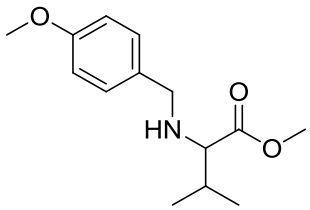
^{1}H NMR (500 MHz, DMSO): δ = 7.21 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 3.72 (s, 3H), 3.64 (d, *J* = 12.4 Hz, 4H), 3.50 (d, *J* = 13.1 Hz, 1H), 3.24 (q, *J* = 6.9 Hz, 1H), 2.34 (s, 1H), 1.18 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (126 MHz, DMSO): δ = 175.95, 158.57, 132.64, 129.56, 113.98, 55.45, 51.86, 50.64, 19.05.

LC-MS (ESI, 60 eV): m/z = 224.1 $[M + H]^+$.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{12}H_{18}NO_3$: 224.1281; found : 224.1282.

(S)-methyl 2-((4-methoxybenzyl)amino)-3-methylbutanoate (4b) [25]



Transparent oil; yield: 6.808 g (90%); purity: 91% (checked by LC-MS, 254 nm); R_f: 0.410 (*n*-Hexane/Ethyl acetate = 5:1).

ATR-IR (neat): 3330 (N-H, amine), 3009 (sp^2 C-H), 2994, 2859, 2876, 2835 (sp^3 C-H), 1733 (C=O, ester), 1512, 1464 (C=C, aromatic), 1247, 1178, 1036 (C-O, Ph-O-Me, ester) cm^{-1}.

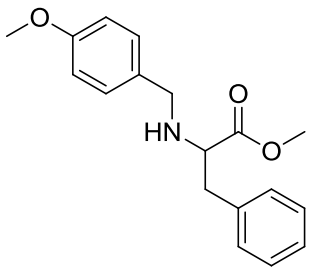
^{1}H NMR (500 MHz, DMSO): δ = 7.21 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 3.73 (s, 3H), 3.68 (d, *J* = 13.3 Hz, 1H), 3.63 (s, 3H), 3.42 (d, *J* = 13.3 Hz, 1H), 2.87 (d, *J* = 6.4 Hz, 1H), 2.22 (s, 1H), 1.81 (dq, *J* = 13.5, 6.7 Hz, 1H), 0.89 (d, *J* = 6.8 Hz, 3H), 0.84 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (126 MHz, DMSO): δ = 175.46, 158.59, 132.62, 129.53, 113.96, 66.21, 55.43, 51.60, 51.22, 31.43, 19.67, 19.22.

LC-MS (ESI, 60 eV): m/z = 252.1 $[M + H]^+$.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{14}H_{22}NO_3$: 252.1594; found : 252.1594.

(S)-methyl 2-((4-methoxybenzyl)amino)-3-phenylpropanoate (4c)



Transparent oil; yield: 8.272 g (92%); purity: 94% (checked by LC-MS, 254 nm); R_f: 0.227 (*n*-Hexane/Ethyl acetate = 5:1).

ATR-IR (neat): 3322 (N-H, amine), 3064 (sp^2 C-H), 3031, 3001, 2951, 2835 (sp^3 C-H), 1734 (C=O, ester), 1512, 1455 (C=C, aromatic), 1247, 1171, 1034 (C-O, Ph-O-Me, ester) cm^{-1}.

^{1}H NMR (500 MHz, DMSO): δ = 7.26 (t, *J* = 7.3 Hz, 2H), 7.20 (t, *J* = 7.3 Hz, 1H), 7.17 – 7.08 (m, 4H), 6.83 (d, *J* = 8.6 Hz, 2H), 3.71 (s, 3H), 3.66 (d, *J* = 13.3 Hz, 1H), 3.55 (s, 3H), 3.50 (d, *J* = 13.3 Hz, 1H), 3.40 (t, *J* = 6.6 Hz, 1H), 2.91 – 2.80 (m, 2H), 2.36 (s, 1H).

^{13}C NMR (126 MHz, DMSO): δ = 174.86, 158.58, 138.28, 132.41, 129.60, 129.47, 128.56, 126.77, 113.95, 62.11, 55.44, 51.70, 50.67, 39.20.

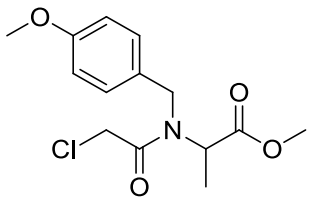
LC-MS (ESI, 60 eV): m/z = 300.2 $[M + H]^+$.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{18}H_{22}NO_3$: 300.1594; found : 300.1594.

Representative Procedure for the Preparation of Compounds 5

To a mixture of *N*-PMB-amino methyl ester **4** (21.0 mmol, 1.0 eq.) in CH_2Cl_2 (210 mL), Et_3N (3.220 mL, 23.1 mmol, 1.1 eq.) and diluted 2-chloro acetyl chloride (1.840 mL, 23.1 mmol, 1.1 eq. with CH_2Cl_2) were added slowly at 0°C. The reaction mixture was stirred for 1 h at r.t. and then washed with H_2O, neutralized to *p*H 7 with a saturated aqueous solution of $NaHCO_3$. The organic layer was dried with anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude mixture was purified by column chromatography (eluent: *n*-Hexane / Ethyl acetate) to afford the desired product **5**.

(S)-methyl 2-(2-chloro-*N*-(4-methoxybenzyl)acetamido)propanoate (5a)



Pale yellow oil; yield: 5.915 g (94%); purity: 99% (checked by LC-MS, 254 nm); R_f: 0.318 (*n*-Hexane/Ethyl acetate = 3:1).

ATR-IR (neat): 3010 (sp^2 C-H), 2996, 2952, 2911, 2835 (sp^3 C-H), 1740 (C=O, ester), 1656 (C=O, amide), 1513, 1455 (C=C, aromatic), 1248, 1176, 1031 (C-O, Ph-O-Me, ester) cm^{-1}.

Ratio of Rotational Isomers (Rotamers) = 3 (Major Rotamer) : 1 (Minor Rotamer),

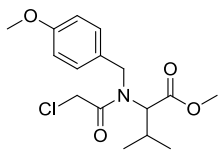
^{1}H NMR (500 MHz, DMSO): Major Rotamer δ = 7.32 (d, *J* = 8.6 Hz, 2H), 6.94 (d, *J* = 8.7 Hz, 2H), 4.62 – 4.52 (m, 2H), 4.47 (d, *J* = 13.7 Hz, 1H), 4.34 (d, *J* = 13.7 Hz, 1H), 4.18 (t, *J* = 7.0 Hz, 1H), 3.75 (s, 3H), 3.57 (s, 3H), 1.22 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (126 MHz, DMSO): Major Rotamer δ = 171.50, 166.44, 159.16, 129.23, 128.81, 114.41, 113.95, 55.54, 52.27, 50.98, 42.71, 14.62.

LC-MS (ESI, 60 eV): m/z = 300.0 $[M + H]^+$.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{14}H_{19}ClNO_4$: 300.0997; found : 300.0997.

(S)-methyl 2-(2-chloro-*N*-(4-methoxybenzyl)acetamido)-3-methylbutanoate (5b) [22]



Pale yellow oil; yield: 6.217 g (90%); purity: 100% (checked by LC-MS, 254 nm); R_f: 0.568 (*n*-Hexane/Ethyl acetate = 3:1).

ATR-IR (neat): 3019 (sp^2 C-H), 2962, 2913, 2878, 2835 (sp^3 C-H), 1740 (C=O, ester), 1662 (C=O, amide), 1513, 1462 (C=C, aromatic), 1249, 1177, 1033 (C-O, Ph-O-Me, ester) cm^{-1}.

Ratio of Rotational Isomers (Rotamers) = 5 (Major Rotamer) : 2 (Minor Rotamer),

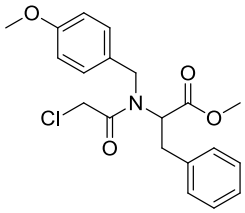
^{1}H NMR (500 MHz, DMSO): Major Rotamer δ = 7.17 (d, *J* = 8.5 Hz, 2H), 6.93 (d, *J* = 8.6 Hz, 2H), 4.60 (d, *J* = 31.7 Hz, 2H), 4.40 (dd, *J* = 14.4, 12.0 Hz, 2H), 4.24 (d, *J* = 13.7 Hz, 1H), 3.74 (s, 3H), 3.43 (s, 3H), 2.30 (d, *J* = 10.0 Hz, 1H), 0.92 (d, *J* = 6.5 Hz, 3H), 0.78 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (126 MHz, DMSO): Major Rotamer δ = 170.48, 167.43, 159.01, 129.27, 128.49, 114.40, 63.34, 55.53, 52.02, 49.23, 42.73, 27.76, 20.60, 18.93.

LC-MS (ESI, 60 eV): m/z = 328.2 $[M + H]^+$.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{16}H_{23}ClNO_4$: 328.1310; found : 328.1310.

(S)-methyl 2-(2-chloro-*N*-(4-methoxybenzyl)acetamido)-3-phenylpropanoate (5c)



Pale yellow oil; yield: 7.786 g (99%); purity: 97% (checked by LC-MS, 254 nm); R_f: 0.386 (*n*-Hexane/Ethyl acetate = 3:1).

ATR-IR (neat): 3029 (sp^2 C-H), 2998, 2950, 2835 (sp^3 C-H), 1739 (C=O, ester), 1654 (C=O, amide), 1513, 1454 (C=C, aromatic), 1248, 1177, 1031 (C-O, Ph-O-Me, ester) cm^{-1}.

Ratio of Rotational Isomers (Rotamers) = 5 (Major Rotamer) : 1 (Minor Rotamer),

^{1}H NMR (500 MHz, DMSO): Major Rotamer δ = 7.28 (d, *J* = 6.9 Hz, 2H), 7.23 (d, *J* = 7.0 Hz, 1H), 7.11 (dd, *J* = 10.3, 8.0 Hz, 4H), 6.86 (d, *J* = 8.6 Hz, 2H), 4.41 (dd, *J* = 14.9, 5.9 Hz, 2H), 4.29 (dd, *J* = 16.2, 9.7 Hz, 2H), 3.84 (d, *J* = 16.2 Hz, 1H), 3.73 (s, 3H), 3.53 (s, 3H), 3.27 (dd, *J* = 13.8, 5.7 Hz, 1H), 3.03 (dd, *J* = 13.7, 9.0 Hz, 1H).

^{13}C NMR (126 MHz, DMSO): Major Rotamer δ = 170.46, 166.81, 159.20, 138.37, 129.73, 129.66, 128.80, 128.03, 126.95, 114.26, 61.32, 55.53, 52.28, 52.22, 42.57, 34.82.

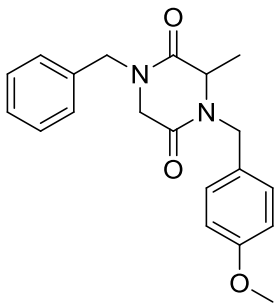
LC-MS (ESI, 60 eV): m/z = 376.1 $[M + H]^+$.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{20}H_{23}ClNO_4$: 376.1310; found : 376.1310.

Representative Procedure for the Preparation of Compounds 6

In a 10-mL sealed microwave reactor vessel, a suspension of *N*-PMB-α-chloroacetyl amino methyl ester **5** (1.5 mmol, 1.0 eq.), primary amine (1.8 mmol, 1.2 eq.), Et_3N (4.5 mmol, 3.0 eq.) in *n*-BuOH (0.75 mL) was stirred with irradiation at 180℃ for 30 min. After cooling to r.t., the reaction mixture was evaporated. The crude mixture was washed with H_2O and neutralized with a saturated aqueous solution of citric acid and $NaHCO_3$. The precipitate was formed, then filtered and dried under high vacuum. The crude product was triturated with diethyl ether, *n*-Hexane, and a small portion of MeOH to yield the desired product **6**.

(S)-1-benzyl-4-(4-methoxybenzyl)-3-methylpiperazine-2,5-dione (6a)



White solid; yield: 418 mg (90%); purity: 99% (checked by LC-MS, 254 nm); mp: 136.3-137.5 ℃; R_f: 0.25 (*n*-Hexane/Ethyl acetate = 1:1).

ATR-IR (neat): 3006 (sp^2 C-H), 2978, 2933, 2938 (sp^3 C-H), 1653 (C=O, amide), 1612, 1513, 1470 (C=C, aromatic), 1249, 1172, 1031 (C-O, Ph-O-Me) cm^{-1}.

^{1}H NMR (500 MHz, DMSO): δ = 7.36 (t, *J* = 7.3 Hz, 2H), 7.30 (t, *J* = 7.3 Hz, 1H), 7.27 – 7.18 (m, 4H), 6.91 (d, *J* = 8.6 Hz, 2H), 4.84 (d, *J* = 14.7 Hz, 1H), 4.57 (d, *J* = 14.8 Hz, 1H), 4.45 (d, *J* = 14.8 Hz, 1H), 4.15 (dd, *J* = 15.8, 13.4 Hz, 2H), 3.87 (q, *J* = 7.0 Hz, 1H), 3.81 (d, *J* = 17.2 Hz, 1H), 3.74 (s, 3H), 1.33 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (126 MHz, DMSO): δ = 167.58, 164.46, 159.16, 136.79, 129.79, 129.24, 129.19, 128.08, 128.00, 114.50, 55.77, 55.54, 49.36, 48.69, 46.09, 17.62.

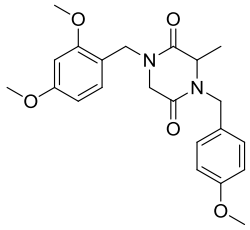
LC-MS (ESI, 60 eV): m/z = 339.2 $[M + H]^+$.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{20}H_{23}N_2O_3$: 339.1703; found : 339.1703.

CSP-HPLC A (210 nm, Daicel Chiralpak IA 4.6 x 250 mm, *n*-Hexane/*i*-PrOH = 30 : 70, r.t., 0.5 mL/min): t_R = 24.150 min (100%, chiral pure compound).

CSP-HPLC B (210 nm, Agilent Chiradex 4.0 x 250 mm, ACN / 5 mM Ammonium formate buffer = 20 : 80, r.t., 0.8 mL/min): t_R = 17.197 min (98.9%, chiral pure compound).

(S)-1-(2,4-dimethoxybenzyl)-4-(4-methoxybenzyl)-3-methylpiperazine-2,5-dione (6b)



Orange oil; yield: 527 mg (88%); purity: 100% (checked by LC-MS, 254 nm); R_f: 0.227 (*n*-Hexane/Ethyl acetate = 1:1).

ATR-IR (neat): 3001 (sp^2 C-H), 2965, 2931, 2835 (sp^3 C-H), 1655 (C=O, amide), 1610, 1508, 1459 (C=C, aromatic), 1243, 1207, 1157, 1029 (C-O, Ph-O-Me) cm^{-1}.

^{1}H NMR (500 MHz, DMSO): δ = 7.21 (d, *J* = 8.6 Hz, 2H), 7.04 (d, *J* = 8.3 Hz, 1H), 6.91 (d, *J* = 8.6 Hz, 2H), 6.59 (d, *J* = 2.3 Hz, 1H), 6.51 (dd, *J* = 8.3, 2.3 Hz, 1H), 4.86 (d, *J* = 14.8 Hz, 1H), 4.41 (dd, *J* = 33.5, 14.7 Hz, 2H), 4.11 (dd, *J* = 16.0, 8.7 Hz, 2H), 3.82 (q, *J* = 7.0 Hz, 1H), 3.75 (dd, *J* = 14.5, 4.7 Hz, 10H), 1.32 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (126 MHz, DMSO): δ = 167.20, 164.59, 160.74, 159.16, 158.79, 130.45, 129.76, 129.25, 116.19, 114.48, 105.18, 98.93, 55.92, 55.83, 55.65, 55.50, 49.34, 46.02, 43.94, 17.56.

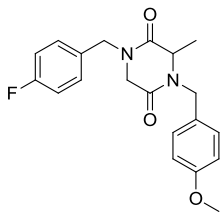
LC-MS (ESI, 60 eV): m/z = 399.2 $[M + H]^+$.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{22}H_{26}N_2O_5$: 399.1914; found : 399.1914.

CSP-HPLC A (254 nm, Daicel Chiralpak IA 4.6 x 250 mm, *n*-Hexane/*i*-PrOH = 30 : 70, r.t., 0.5 mL/min): t_R = 27.458 min (100%, chiral pure compound).

CSP-HPLC B (254 nm, Agilent Chiradex 4.0 x 250 mm, ACN / 5 mM Ammonium formate buffer = 20 : 80, r.t., 0.8 mL/min): t_R = 7.061 min (100%, chiral pure compound).

(S)-1-(4-fluorobenzyl)-4-(4-methoxybenzyl)-3-methylpiperazine-2,5-dione (6c)



Ivory solid; yield: 512 mg (96%); purity: 100% (checked by LC-MS, 254 nm); mp: 133.1-134.9 ℃; R_f: 0.250 (*n*-Hexane/Ethyl acetate = 1:1).

ATR-IR (neat): 3049 (sp^2 C-H), 2981, 2956, 2923, 2835 (sp^3 C-H), 1655 (C=O, amide), 1615, 1510, 1476 (C=C, aromatic), 1243, 1175, 1031 (C-O, Ph-O-Me) cm^{-1}.

^{1}H NMR (500 MHz, DMSO): δ = 7.29 (dd, *J* = 8.1, 5.8 Hz, 2H), 7.24 – 7.17 (m, 4H), 6.91 (d, *J* = 8.5 Hz, 2H), 4.84 (d, *J* = 14.7 Hz, 1H), 4.59 (d, *J* = 14.7 Hz, 1H), 4.41 (d, *J* = 14.7 Hz, 1H), 4.15 (dd, *J* = 15.9, 9.5 Hz, 2H), 3.89 – 3.82 (m, 2H), 3.74 (s, 3H), 1.32 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (126 MHz, DMSO): δ = 167.59, 164.44, 163.02, 161.09, 159.16, 133.08, 133.06, 130.33, 130.27, 129.79, 129.22, 116.05, 115.88, 114.50, 55.75, 55.53, 49.31, 48.02, 46.10, 17.59.

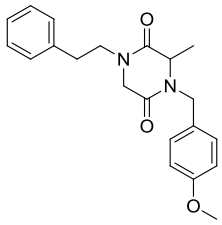
LC-MS (ESI, 60 eV): m/z = 357.2 $[M + H]^+$.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{20}H_{22}FN_2O_3$: 357.1609; found : 357.1609.

CSP-HPLC A (210 nm, Daicel Chiralpak IA 4.6 x 250 mm, *n*-Hexane/*i*-PrOH = 30 : 70, r.t., 0.5 mL/min): t_R = 19.931 min (100%, chiral pure compound).

CSP-HPLC B (254 nm, Agilent Chiradex 4.0 x 250 mm, ACN / 5 mM Ammonium formate buffer = 20 : 80, r.t., 0.8 mL/min): t_R = 9.408 min (100%, chiral pure compound).

(S)-4-(4-methoxybenzyl)-3-methyl-1-phenethylpiperazine-2,5-dione (6d)



White solid; yield: 489 mg (93%); purity: 100% (checked by LC-MS, 254 nm); mp: 131.7-133.1 ℃; R_f: 0.250 (*n*-Hexane/Ethyl acetate = 1:1).

ATR-IR (neat): 3061, 3031, 3006 (sp^2 C-H), 2968, 2938, 2838 (sp^3 C-H), 1656 (C=O, amide), 1607, 1509, 1465 (C=C, aromatic), 1237, 1167, 1025 (C-O, Ph-O-Me) cm^{-1}.

^{1}H NMR (500 MHz, DMSO): δ = 7.30 – 7.25 (m, 2H), 7.19 (dd, *J* = 17.2, 7.7 Hz, 5H), 6.90 (d, *J* = 8.6 Hz, 2H), 4.85 (d, *J* = 14.7 Hz, 1H), 4.11 (d, *J* = 17.2 Hz, 1H), 4.04 (d, *J* = 14.7 Hz, 1H), 3.85 (d, *J* = 17.3 Hz, 1H), 3.74 (s, 3H), 3.69 (q, *J* = 7.0 Hz, 1H), 3.65 – 3.59 (m, 1H), 3.45 – 3.38 (m, 1H), 2.84 – 2.72 (m, 2H), 1.20 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (126 MHz, DMSO): δ = 167.10, 164.45, 159.14, 138.99, 129.77, 129.23, 129.18, 128.81, 126.76, 114.48, 55.55, 55.53, 49.74, 46.90, 45.81, 32.81, 17.56.

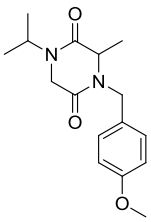
LC-MS (ESI, 60 eV): m/z = 353.2 $[M + H]^+$.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{21}H_{25}N_2O_3$: 353.1860; found : 353.1860.

CSP-HPLC A (210 nm, Daicel Chiralpak IA 4.6 x 250 mm, *n*-Hexane/*i*-PrOH = 30 : 70, r.t., 0.5 mL/min): t_R = 19.446 min (100%, chiral pure compound).

CSP-HPLC B (254 nm, Agilent Chiradex 4.0 x 250 mm, ACN / 5 mM Ammonium formate buffer = 20 : 80, r.t., 0.8 mL/min): t_R = 10.973 min (100%, chiral pure compound).

(S)-1-isopropyl-4-(4-methoxybenzyl)-3-methylpiperazine-2,5-dione (6e)



White solid; yield: 282 mg (65%); purity: 98% (checked by LC-MS, 254 nm); mp: 136.9-139.1 °C; R_f: 0.182 (*n*-Hexane/Ethyl acetate = 1:1).

ATR-IR (neat): 3061, 3009 (sp^2 C-H), 2966, 2933, 2878, 2843 (sp^3 C-H), 1656 (C=O, amide), 1611, 1508, 1464 (C=C, aromatic), 1245, 1180, 1032 (C-O, Ph-O-Me) cm^{-1}.

^{1}H NMR (500 MHz, DMSO): δ = 7.21 (d, *J* = 8.5 Hz, 2H), 6.90 (d, *J* = 8.5 Hz, 2H), 4.81 (d, *J* = 14.7 Hz, 1H), 4.54 – 4.43 (m, 1H), 4.14 (d, *J* = 14.7 Hz, 1H), 4.06 (d, *J* = 17.2 Hz, 1H), 3.83 (d, *J* = 17.2 Hz, 1H), 3.79 – 3.75 (m, 1H), 3.73 (s, 3H), 1.27 (d, *J* = 7.0 Hz, 3H), 1.11 – 1.01 (m, 6H).

^{13}C NMR (126 MHz, DMSO): δ = 166.79, 164.87, 159.14, 129.81, 129.27, 114.50, 55.93, 55.52, 46.02, 44.05, 43.60, 19.17, 19.11, 17.33.

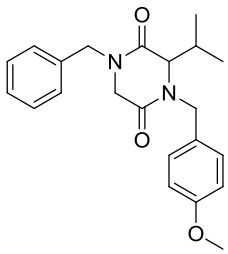
LC-MS (ESI, 60 eV): m/z = 291.3 $[M+H]^+$.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{16}H_{23}N_2O_3$: 291.1703; found : 291.1703.

CSP-HPLC A (210 nm, Daicel Chiralpak IA 4.6 x 250 mm, *n*-Hexane/*i*-PrOH = 30 : 70, r.t., 0.5 mL/min): t_R = 13.127 min (100%, chiral pure compound).

CSP-HPLC B (254 nm, Agilent Chiradex 4.0 x 250 mm, ACN / 5 mM Ammonium formate buffer = 20 : 80, r.t., 0.8 mL/min): t_R = 6.467 min (100%, chiral pure compound).

(S)-1-benzyl-3-isopropyl-4-(4-methoxybenzyl)piperazine-2,5-dione (6f)



Orange oil; yield: 443 mg (81%); purity: 100% (checked by LC-MS, 254 nm); R_f: 0.523 (*n*-Hexane/Ethyl acetate = 1:1).

ATR-IR (neat): 3061, 3036 (sp^2 C-H), 2965, 2928, 2878, 2833 (sp^3 C-H), 1655 (C=O, amide), 1611, 1512, 1452 (C=C, aromatic), 1244, 1171, 1030 (C-O, Ph-O-Me) cm^{-1}.

^{1}H NMR (500 MHz, DMSO): δ = 7.36 (t, *J* = 7.3 Hz, 2H), 7.30 (t, *J* = 7.3 Hz, 1H), 7.24 (d, *J* = 7.0 Hz, 2H), 7.18 (d, *J* = 8.6 Hz, 2H), 6.95 – 6.87 (m, 2H), 5.06 (d, *J* = 14.8 Hz, 1H), 4.67 (d, *J* = 14.6 Hz, 1H), 4.39 (d, *J* = 14.6 Hz, 1H), 4.08 (d, *J* = 17.6 Hz, 1H), 3.99 (d, *J* = 14.8 Hz, 1H), 3.82 (d, *J* = 17.6 Hz, 1H), 3.75 (s, 3H), 3.64 (d, *J* = 5.9 Hz, 1H), 2.19 (dp, *J* = 13.5, 6.8 Hz, 1H), 1.01 (d, *J* = 6.9 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (126 MHz, DMSO): δ = 165.43, 164.82, 159.14, 136.90, 129.60, 129.14, 129.13, 128.43, 128.11, 114.47, 65.23, 55.53, 49.79, 48.79, 47.61, 31.97, 20.25, 18.14.

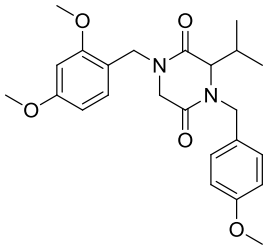
LC-MS (ESI, 60 eV): m/z = 367.3 $[M+H]^+$.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{22}H_{27}N_2O_3$: 367.2016; found : 367.2016.

CSP-HPLC A (210 nm, Daicel Chiralpak IA 4.6 x 250 mm, *n*-Hexane/*i*-PrOH = 30 : 70, r.t., 0.5 mL/min): t_R = 17.672 min (100%, chiral pure compound).

CSP-HPLC B (254 nm, Agilent Chiradex 4.0 x 250 mm, ACN / 5 mM Ammonium formate buffer = 20 : 80, r.t., 0.8 mL/min): t_R = 13.406 min (100%, chiral pure compound).

(S)-1-(2,4-dimethoxybenzyl)-3-isopropyl-4-(4-methoxybenzyl)piperazine-2,5-dione (6g)



Orange oil; yield: 513 mg (80%); purity: 100% (checked by LC-MS, 254 nm); R_f: 0.386 (*n*-Hexane/Ethyl acetate = 1:1).

ATR-IR (neat): 3076 (sp^2 C-H), 2996, 2961, 2931, 2836 (sp^3 C-H), 1655 (C=O, amide), 1611, 1509, 1459 (C=C, aromatic), 1245, 1208, 1157, 1030 (C-O, Ph-O-Me) cm^{-1}.

^{1}H NMR (500 MHz, DMSO): δ = 7.17 (d, *J* = 8.6 Hz, 2H), 7.07 (d, *J* = 8.3 Hz, 1H), 6.90 (d, *J* = 8.7 Hz, 2H), 6.57 (d, *J* = 2.3 Hz, 1H), 6.49 (dd, *J* = 8.3, 2.4 Hz, 1H), 5.06 (d, *J* = 14.8 Hz, 1H), 4.60 (d, *J* = 14.3 Hz, 1H), 4.24 (d, *J* = 14.3 Hz, 1H), 3.99 (d, *J* = 5.6 Hz, 1H), 3.95 (d, *J* = 2.6 Hz, 1H), 3.76 (s, 6H), 3.73 (d, *J* = 8.4 Hz, 4H), 3.59 (d, *J* = 5.7 Hz, 1H), 2.16 (dq, *J* = 13.5, 6.8 Hz, 1H), 0.99 (d, *J* = 6.9 Hz, 3H), 0.82 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (126 MHz, DMSO): δ = 164.95, 164.85, 160.82, 159.12, 158.80, 131.17, 129.59, 129.15, 116.24, 114.46, 105.09, 98.82, 65.25, 55.87, 55.65, 55.51, 49.84, 47.42, 43.83, 31.91, 20.20, 17.92.

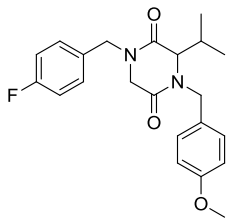
LC-MS (ESI, 60 eV): m/z = 427.3 $[M + H]^+$.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{24}H_{31}N_2O_5$: 427.2227; found : 427.2227.

CSP-HPLC A (210 nm, Daicel Chiralpak IA 4.6 x 250 mm, *n*-Hexane/*i*-PrOH = 30 : 70, r.t., 0.5 mL/min): t_R = 20.212 min (100%, chiral pure compound).

CSP-HPLC B (254 nm, Agilent Chiradex 4.0 x 250 mm, ACN / 5 mM Ammonium formate buffer = 20 : 80, r.t., 0.8 mL/min): t_R = 6.874 min (100%, chiral pure compound).

(S)-1-(4-fluorobenzyl)-3-isopropyl-4-(4-methoxybenzyl)piperazine-2,5-dione (6h)



White solid; yield: 473 mg (82%); purity: 100% (checked by LC-MS, 254 nm); mp: 105.1-107.3 ℃; R_f: 0.5 (*n*-Hexane/Ethyl acetate = 1:1).

ATR-IR (neat): 3079, 3011 (sp^2 C-H), 2973, 2938, 2913, 2880, 2833 (sp^3 C-H), 1655 (C=O, amide), 1611, 1508, 1474 (C=C, aromatic), 1246, 1173, 1035 (C-O, Ph-O-Me) cm^{-1}.

^{1}H NMR (500 MHz, DMSO): δ = 7.30 (dd, *J* = 8.5, 5.6 Hz, 2H), 7.19 (dd, *J* = 17.4, 8.7 Hz, 4H), 6.91 (d, *J* = 8.6 Hz, 2H), 5.05 (d, *J* = 14.8 Hz, 1H), 4.68 (d, *J* = 14.5 Hz, 1H), 4.33 (d, *J* = 14.5 Hz, 1H), 4.08 (d, *J* = 17.6 Hz, 1H), 3.98 (d, *J* = 14.8 Hz, 1H), 3.85 (d, *J* = 17.6 Hz, 1H), 3.75 (s, 3H), 3.63 (d, *J* = 5.8 Hz, 1H), 2.17 (dq, *J* = 13.4, 6.7 Hz, 1H), 0.99 (d, *J* = 6.9 Hz, 3H), 0.81 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (126 MHz, DMSO): δ = 165.42, 164.78, 163.06, 161.12, 159.14, 133.22, 133.20, 130.68, 130.62, 129.59, 129.12, 116.01, 115.84, 114.48, 65.17, 55.53, 49.74, 48.09, 47.57, 31.95, 20.26, 18.08.

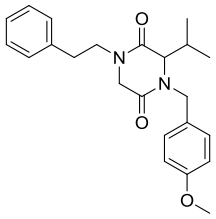
LC-MS (ESI, 60 eV): m/z = 385.3 $[M + H]^+$.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{22}H_{26}FN_2O_3$: 385.1922; found : 385.1922.

CSP-HPLC A (210 nm, Daicel Chiralpak IA 4.6 x 250 mm, *n*-Hexane/*i*-PrOH = 30 : 70, r.t., 0.5 mL/min): t_R = 16.400 min (100%, chiral pure compound).

CSP-HPLC B (254 nm, Agilent Chiradex 4.0 x 250 mm, ACN / 5 mM Ammonium formate buffer = 20 : 80, r.t., 0.8 mL/min): t_R = 11.367 min (100%, chiral pure compound).

(S)-3-isopropyl-4-(4-methoxybenzyl)-1-phenethylpiperazine-2,5-dione (6i)



Orange oil; yield: 481 mg (84%); purity: 100% (checked by LC-MS, 254 nm); R_f: 0.455 (*n*-Hexane/Ethyl acetate = 1:1).

ATR-IR (neat): 3026 (sp^2 C-H), 2966, 2936, 2911, 2876, 2855, 2835 (sp^3 C-H), 1649 (C=O, amide), 1612, 1531, 1471 (C=C, aromatic), 1247, 1176, 1031 (C-O, Ph-O-Me) cm^{-1}.

^{1}H NMR (500 MHz, DMSO): δ = 7.30 – 7.26 (m, 2H), 7.23 (d, *J* = 7.0 Hz, 2H), 7.21 (s, 1H), 7.17 (d, *J* = 8.6 Hz, 2H), 6.91 (d, *J* = 8.7 Hz, 2H), 5.07 (d, *J* = 14.8 Hz, 1H), 4.14 (d, *J* = 17.6 Hz, 1H), 3.94 (d, *J* = 14.8 Hz, 1H), 3.88 – 3.79 (m, 2H), 3.74 (s, 3H), 3.52 (d, *J* = 5.6 Hz, 1H), 3.38 – 3.32 (m, 1H), 2.86 – 2.74 (m, 2H), 2.08 (dq, *J* = 13.5, 6.8 Hz, 1H), 0.94 (d, *J* = 6.9 Hz, 3H), 0.72 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (126 MHz, DMSO): δ = 164.84, 164.80, 159.13, 138.93, 129.67, 129.18, 129.07, 128.81, 126.76, 114.46, 64.96, 55.50, 50.23, 47.23, 46.77, 32.84, 31.73, 20.19, 17.91.

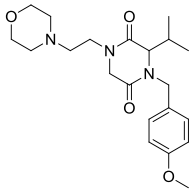
LC-MS (ESI, 60 eV): m/z = 381.3 $[M + H]^+$.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{23}H_{29}N_2O_3$: 381.2173; found : 381.2173.

CSP-HPLC A (210 nm, Daicel Chiralpak IA 4.6 x 250 mm, *n*-Hexane/*i*-PrOH = 30 : 70, r.t., 0.5 mL/min): t_R = 16.219 min (100%, chiral pure compound).

CSP-HPLC B (254 nm, Agilent Chiradex 4.0 x 250 mm, ACN / 5 mM Ammonium formate buffer = 20 : 80, r.t., 0.8 mL/min): t_R = 12.731 min (100%, chiral pure compound).

(S)-3-isopropyl-4-(4-methoxybenzyl)-1-(2-morpholinoethyl)piperazine-2,5-dione (6j)



White solid; yield: 409 mg (78%); purity: 100% (checked by LC-MS, 254 nm); mp: 107-109.7 °C; R_f: 0.114 (*n*-Hexane/Ethyl acetate = 1:1).

ATR-IR (neat): 3009 (sp^2 C-H), 2962, 2933, 2853, 2820, 2795 (sp^3 C-H), 1648 (C=O, amide), 1611, 1513, 1462 (C=C, aromatic), 1241, 1115, 1036 (C-O, Ph-O-Me) cm^{-1}.

^{1}H NMR (500 MHz, DMSO): δ = 7.19 (d, *J* = 8.6 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 5.06 (d, *J* = 14.8 Hz, 1H), 4.25 (d, *J* = 17.6 Hz, 1H), 3.98 (d, *J* = 14.8 Hz, 1H), 3.94 – 3.86 (m, 2H), 3.73 (s, 3H), 3.57 (d, *J* = 5.1 Hz, 1H), 3.52 (s, 4H), 3.00 (dt, *J* = 13.8, 5.2 Hz, 1H), 2.50 – 2.45 (m, 1H), 2.45 – 2.28 (m, 5H), 2.23 – 2.17 (m, 1H), 1.00 (d, *J* = 6.9 Hz, 3H), 0.94 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (126 MHz, DMSO): δ = 165.00, 164.90, 159.12, 129.69, 129.18, 114.46, 66.67, 65.00, 55.52, 55.19, 53.57, 50.44, 47.06, 42.08, 31.94, 20.20, 17.87.

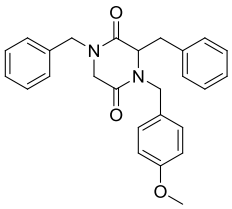
LC-MS (ESI, 60 eV): m/z = 390.3 $[M + H]^+$.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{21}H_{32}N_3O_4$: 390.2387; found : 390.2387.

CSP-HPLC A (210 nm, Daicel Chiralpak IA 4.6 x 250 mm, *n*-Hexane/*i*-PrOH = 30 : 70, r.t., 0.5 mL/min): t_R = 22.382 min (100%, chiral pure compound).

CSP-HPLC B (254 nm, Agilent Chiradex 4.0 x 250 mm, ACN / 5 mM Ammonium formate buffer = 20 : 80, r.t., 0.8 mL/min): t_R = 9.927 min (100%, chiral pure compound).

(S)-1,3-dibenzyl-4-(4-methoxybenzyl)piperazine-2,5-dione (6k)



White solid; yield: 553 mg (89%); purity: 99% (checked by LC-MS, 254 nm); mp: 176.5-177.9 °C; R_f: 0.455 (*n*-Hexane/Ethyl acetate = 1:1).

ATR-IR (neat): 3059, 3026, 3009 (sp^2 C-H), 2961, 2936, 2835 (sp^3 C-H), 1650 (C=O, amide), 1611, 1510, 1468 (C=C, aromatic), 1251, 1175, 1034 (C-O, Ph-O-Me) cm^{-1}.

^{1}H NMR (500 MHz, DMSO): δ = 7.40 – 7.31 (m, 3H), 7.25 (d, *J* = 8.3 Hz, 2H), 7.21 (d, *J* = 7.0 Hz, 2H), 7.16 (t, *J* = 7.3 Hz, 1H), 7.00 (t, *J* = 7.4 Hz, 2H), 6.93 (dd, *J* = 11.4, 8.1 Hz, 4H), 5.08 (d, *J* = 14.6 Hz, 1H), 4.61 (d, *J* = 14.2 Hz, 1H), 4.18 – 4.07 (m, 2H), 4.03 (d, *J* = 14.7 Hz, 1H), 3.75 (s, 3H), 3.50 (d, *J* = 17.1 Hz, 1H), 3.22 (dd, *J* = 13.7, 5.1 Hz, 1H), 3.04 (dd, *J* = 13.7, 3.3 Hz, 1H), 2.35 (d, *J* = 17.1 Hz, 1H).

^{13}C NMR (126 MHz, DMSO): δ = 165.88, 164.46, 159.28, 136.00, 135.47, 130.27, 130.14, 129.25, 128.98, 128.83, 128.63, 128.16, 127.52, 114.58, 60.15, 55.56, 48.98, 48.63, 45.79, 36.64.

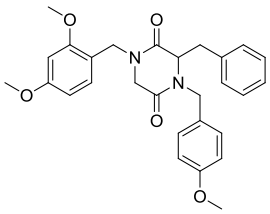
LC-MS (ESI, 60 eV): m/z = 415.2 $[M + H]^+$.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{26}H_{27}N_2O_3$: 415.2016; found : 415.2016.

CSP-HPLC A (210 nm, Daicel Chiralpak IA 4.6 x 250 mm, *n*-Hexane/*i*-PrOH = 30 : 70, r.t., 0.5 mL/min): t_R = 21.633 min (100%, chiral pure compound).

CSP-HPLC B (210 nm, Agilent Chiradex 4.0 x 250 mm, ACN / 5 mM Ammonium formate buffer = 20 : 80, r.t., 0.8 mL/min): t_R = 11.775 min (100%, chiral pure compound).

(S)-3-benzyl-1-(2,4-dimethoxybenzyl)-4-(4-methoxybenzyl)piperazine-2,5-dione (6l)



Orange oil; yield: 635 mg (89%); purity: 100% (checked by LC-MS, 254 nm); R_f: 0.341 (*n*-Hexane/Ethyl acetate = 1:1).

ATR-IR (neat): 3029, 3001 (sp^2 C-H), 2961, 2936, 2905, 2836 (sp^3 C-H), 1655 (C=O, amide), 1610, 1509, 1458 (C=C, aromatic), 1245, 1207, 1174, 1156, 1030 (C-O, Ph-O-Me) cm^{-1}.

^{1}H NMR (500 MHz, DMSO): δ = 7.23 (dd, *J* = 16.5, 8.0 Hz, 3H), 7.08 (dd, *J* = 15.5, 7.9 Hz, 3H), 6.95 – 6.90 (m, 4H), 6.57 (d, *J* = 2.3 Hz, 1H), 6.52 (dd, *J* = 8.3, 2.4 Hz, 1H), 5.09 (d, *J* = 14.6 Hz, 1H), 4.33 (d, *J* = 14.2 Hz, 1H), 4.17 (d, *J* = 14.2 Hz, 1H), 4.05 (t, *J* = 4.4 Hz, 1H), 4.01 (d, *J* = 14.7 Hz, 1H), 3.78 (s, 3H), 3.75 (s, 3H), 3.71 (s, 3H), 3.40 (d, *J* = 17.3 Hz, 1H), 3.20 (dd, *J* = 13.7, 5.1 Hz, 1H), 3.01 (dd, *J* = 13.7, 3.6 Hz, 1H), 2.37 (d, *J* = 17.2 Hz, 1H).

^{13}C NMR (126 MHz, DMSO): δ = 165.66, 164.60, 160.87, 159.26, 158.87, 135.57, 131.93, 130.27, 130.09, 128.85, 128.64, 127.51, 115.99, 114.56, 105.09, 98.73, 60.13, 55.81, 55.73, 55.54, 49.12, 45.73, 43.80, 36.71.

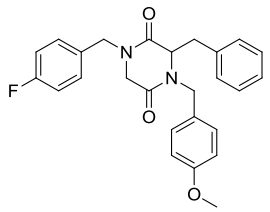
LC-MS (ESI, 60 eV): m/z = 475.3 $[M + H]^+$.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{28}H_{31}N_2O_5$: 475.2227; found : 475.2227.

CSP-HPLC A (210 nm, Daicel Chiralpak IA 4.6 x 250 mm, *n*-Hexane/*i*-PrOH = 30 : 70, r.t., 0.5 mL/min): t_R = 27.711 min (100%, chiral pure compound).

CSP-HPLC B (254 nm, Agilent Chiradex 4.0 x 250 mm, ACN / 5 mM Ammonium formate buffer = 20 : 80, r.t., 0.8 mL/min): t_R = 14.135 min (98.7%, chiral pure compound).

(S)-3-benzyl-1-(4-fluorobenzyl)-4-(4-methoxybenzyl)piperazine-2,5-dione (6m)



Ivory solid; yield: 599 mg (92%); purity: 94% (checked by LC-MS, 254 nm); mp: 157.7-160 ℃; R_f: 0.432 (*n*-Hexane/Ethyl acetate = 1:1).

ATR-IR (neat): 3069, 3031 (sp^2 C-H), 2998, 2936, 2893, 2835 (sp^3 C-H), 1648 (C=O, amide), 1605, 1509, 1467 (C=C, aromatic), 1247, 1178, 1031 (C-O, Ph-O-Me) cm^{-1}.

^{1}H NMR (500 MHz, DMSO): δ = 7.29 – 7.24 (m, 4H), 7.19 (dt, *J* = 11.4, 8.2 Hz, 3H), 7.01 (t, *J* = 7.6 Hz, 2H), 6.92 (dd, *J* = 18.8, 7.9 Hz, 4H), 5.09 (d, *J* = 14.6 Hz, 1H), 4.64 (d, *J* = 14.2 Hz, 1H), 4.10 (t, *J* = 4.3 Hz, 1H), 4.04 (d, *J* = 14.4 Hz, 2H), 3.75 (s, 3H), 3.53 (d, *J* = 17.0 Hz, 1H), 3.22 (dd, *J* = 13.7, 5.2 Hz, 1H), 3.03 (dd, *J* = 13.7, 3.5 Hz, 1H), 2.31 (d, *J* = 17.0 Hz, 1H).

^{13}C NMR (126 MHz, DMSO): δ = 165.91, 164.44, 163.17, 161.23, 159.28, 135.44, 132.34, 132.32, 131.49, 131.43, 130.26, 130.15, 128.82, 128.59, 127.57, 115.81, 115.64, 114.58, 60.09, 55.55, 48.56, 48.23, 45.78, 36.61.

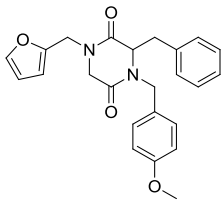
LC-MS (ESI, 60 eV): m/z = 433.2 $[M + H]^+$.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{26}H_{26}FN_2O_3$: 433.1922; found : 433.1922.

CSP-HPLC A (210 nm, Daicel Chiralpak IA 4.6 x 250 mm, *n*-Hexane/*i*-PrOH = 30 : 70, r.t., 0.5 mL/min): t_R = 23.161 min (100%, chiral pure compound).

CSP-HPLC B (210 nm, Agilent Chiradex 4.0 x 250 mm, ACN / 5 mM Ammonium formate buffer = 20 : 80, r.t., 0.8 mL/min): t_R = 20.106 min (100%, chiral pure compound).

(S)-3-benzyl-1-(furan-2-ylmethyl)-4-(4-methoxybenzyl)piperazine-2,5-dione (6n)



Beige solid; yield: 506 mg (83%); purity: 100% (checked by LC-MS, 254 nm); mp: 138.8-141.3 °C; R_f: 0.41 (*n*-Hexane/Ethyl acetate = 1:1).

ATR-IR (neat): 3064, 3009 (sp^2 C-H), 2966, 2931, 2908, 2835 (sp^3 C-H), 1654 (C=O, amide), 1612, 1511, 1467 (C=C, aromatic), 1250, 1176, 1035 (C-O, Ph-O-Me) cm^{-1}.

^{1}H NMR (500 MHz, DMSO): δ = 7.68 (d, *J* = 1.0 Hz, 1H), 7.27 (d, *J* = 8.6 Hz, 2H), 7.20 (t, *J* = 7.4 Hz, 1H), 7.10 (t, *J* = 7.6 Hz, 2H), 6.93 (dd, *J* = 7.7, 5.9 Hz, 4H), 6.44 (dd, *J* = 3.0, 1.9 Hz, 1H), 6.33 (d, *J* = 3.1 Hz, 1H), 5.09 (d, *J* = 14.6 Hz, 1H), 4.73 (d, *J* = 15.1 Hz, 1H), 4.09 (d, *J* = 8.3 Hz, 2H), 4.05 (s, 1H), 3.75 (s, 3H), 3.52 (d, *J* = 17.0 Hz, 1H), 3.22 (dd, *J* = 13.7, 5.3 Hz, 1H), 3.03 (dd, *J* = 13.7, 3.1 Hz, 1H), 2.27 (d, *J* = 17.0 Hz, 1H).

^{13}C NMR (126 MHz, DMSO): δ = 165.65, 164.30, 159.28, 149.53, 143.57, 135.33, 130.23, 130.21, 128.81, 128.65, 127.51, 114.57, 110.93, 110.12, 59.97, 55.54, 48.60, 45.72, 41.39, 36.60.

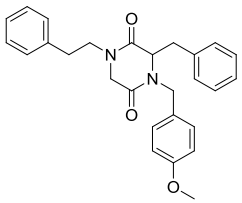
LC-MS (ESI, 60 eV): m/z = 405.2 $[M + H]^+$.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{24}H_{25}N_2O_4$: 405.1809; found : 405.1809.

CSP-HPLC A (210 nm, Daicel Chiralpak IA 4.6 x 250 mm, *n*-Hexane/*i*-PrOH = 30 : 70, r.t., 0.5 mL/min): t_R = 24.450 min (100%, chiral pure compound).

CSP-HPLC B (210 nm, Agilent Chiradex 4.0 x 250 mm, ACN / 5 mM Ammonium formate buffer = 20 : 80, r.t., 0.8 mL/min): t_R = 15.183 min (100%, chiral pure compound).

(S)-3-benzyl-4-(4-methoxybenzyl)-1-phenethylpiperazine-2,5-dione (6o)



White solid; yield: 602 mg (94%); purity: 96% (checked by LC-MS, 254 nm); mp: 151.4-153.4 ℃; R_f: 0.432 (*n*-Hexane/Ethyl acetate = 1:1).

ATR-IR (neat): 3036 (sp^2 C-H), 2951, 2928, 2898, 2835 (sp^3 C-H), 1652 (C=O, amide), 1611, 1515, 1470 (C=C, aromatic), 1245, 1182, 1031 (C-O, Ph-O-Me) cm^{-1}.

^{1}H NMR (500 MHz, DMSO): δ = 7.29 (dt, *J* = 14.6, 6.0 Hz, 5H), 7.22 – 7.15 (m, 5H), 7.06 (dd, *J* = 7.2, 1.7 Hz, 2H), 6.93 (d, *J* = 8.6 Hz, 2H), 5.09 (d, *J* = 14.7 Hz, 1H), 3.98 (dd, *J* = 9.8, 5.1 Hz, 2H), 3.75 (s, 3H), 3.49 (d, *J* = 17.1 Hz, 1H), 3.34 (ddd, *J* = 15.4, 8.2, 5.0 Hz, 2H), 3.19 (dd, *J* = 13.7, 5.1 Hz, 1H), 3.01 (dd, *J* = 13.7, 3.9 Hz, 1H), 2.68 (ddd, *J* = 15.4, 9.3, 6.3 Hz, 1H), 2.56 (dt, *J* = 13.2, 5.9 Hz, 2H).

^{13}C NMR (126 MHz, DMSO): δ = 165.62, 164.42, 159.25, 138.97, 135.80, 130.41, 130.05, 129.10, 128.87, 128.85, 128.81, 127.80, 126.77, 114.56, 60.11, 55.56, 49.08, 47.09, 45.69, 36.78, 32.51.

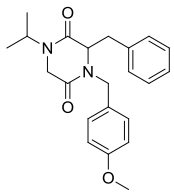
LC-MS (ESI, 60 eV): m/z = 429.3 $[M + H]^+$.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{27}H_{29}N_2O_3$: 429.2173; found : 429.2173.

CSP-HPLC A (210 nm, Daicel Chiralpak IA 4.6 x 250 mm, *n*-Hexane/*i*-PrOH = 30 : 70, r.t., 0.5 mL/min): t_R = 23.384 min (100%, chiral pure compound).

CSP-HPLC B (210 nm, Agilent Chiradex 4.0 x 250 mm, ACN / 5 mM Ammonium formate buffer = 20 : 80, r.t., 0.8 mL/min): t_R = 13.249 min (100%, chiral pure compound).

(S)-3-benzyl-1-isopropyl-4-(4-methoxybenzyl)piperazine-2,5-dione (6p)



Pale yellow solid; yield: 335 mg (61%); purity: 100% (checked by LC-MS, 254 nm); mp: 116.7-118 ℃; R_f: 0.364 (*n*-Hexane/Ethyl acetate = 1:1).

ATR-IR (neat): 3031 (sp^2 C-H), 2983, 2941, 2833 (sp^3 C-H), 1649 (C=O, amide), 1612, 1512, 1463 (C=C, aromatic), 1246, 1181, 1030 (C-O, Ph-O-Me) cm^{-1}.

^{1}H NMR (500 MHz, DMSO): δ = 7.28 (ddd, *J* = 20.0, 12.9, 7.4 Hz, 5H), 7.04 (d, *J* = 6.1 Hz, 2H), 6.93 (d, *J* = 8.5 Hz, 2H), 5.08 (d, *J* = 14.6 Hz, 1H), 4.47 (dt, *J* = 13.6, 6.8 Hz, 1H), 4.09 (d, *J* = 14.6 Hz, 1H), 4.02 (t, *J* = 4.1 Hz, 1H), 3.74 (s, 3H), 3.42 (d, *J* = 17.1 Hz, 1H), 3.21 (dd, *J* = 13.7, 4.9 Hz, 1H), 3.01 (dd, *J* = 13.7, 3.5 Hz, 1H), 2.22 (d, *J* = 17.1 Hz, 1H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.82 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (126 MHz, DMSO): δ = 165.00, 164.67, 159.25, 135.78, 130.45, 130.17, 128.85, 127.78, 114.59, 60.28, 55.55, 45.74, 43.98, 42.91, 36.59, 19.13, 18.46.

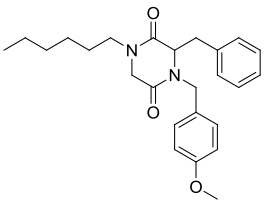
LC-MS (ESI, 60 eV): m/z = 367.3 $[M + H]^+$.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{22}H_{27}N_2O_3$: 367.2016; found : 367.2016.

CSP-HPLC A (210 nm, Daicel Chiralpak IA 4.6 x 250 mm, *n*-Hexane/*i*-PrOH = 30 : 70, r.t., 0.5 mL/min): t_R = 14.744 min (100%, chiral pure compound).

CSP-HPLC B (210 nm, Agilent Chiradex 4.0 x 250 mm, ACN / 5 mM Ammonium formate buffer = 20 : 80, r.t., 0.8 mL/min): t_R = 9.829 min (95.8%, chiral pure compound).

(S)-3-benzyl-1-hexyl-4-(4-methoxybenzyl)piperazine-2,5-dione (6q)



White solid; yield: 471 mg (77%); purity: 98% (checked by LC-MS, 254 nm); mp: 76.5-78.4 ℃; R_f: 0.568 (*n*-Hexane/Ethyl acetate = 1:1).

ATR-IR (neat): 3049, 3009 (sp^2 C-H), 2953, 2931, 2853 (sp^3 C-H), 1655 (C=O, amide), 1614, 1512, 1472 (C=C, aromatic), 1248, 1183, 1037 (C-O, Ph-O-Me) cm^{-1}.

^{1}H NMR (500 MHz, DMSO): δ = 7.34 – 7.26 (m, 3H), 7.23 (d, *J* = 8.6 Hz, 2H), 7.08 – 7.03 (m, 2H), 6.92 (d, *J* = 8.7 Hz, 2H), 5.09 (d, *J* = 14.6 Hz, 1H), 4.00 (dd, *J* = 9.4, 5.0 Hz, 2H), 3.74 (s, 3H), 3.49 (d, *J* = 17.1 Hz, 1H), 3.28 – 3.18 (m, 2H), 3.04 – 2.92 (m, 2H), 2.54 (s, 1H), 1.35 – 1.19 (m, 6H), 1.11 (ddt, *J* = 19.9, 13.2, 6.7 Hz, 2H), 0.85 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (126 MHz, DMSO): δ = 165.49, 164.56, 159.25, 135.82, 130.41, 130.11, 128.88, 128.80, 127.76, 114.55, 60.19, 55.55, 48.95, 45.74, 36.69, 31.34, 26.38, 26.29, 22.46, 14.36.

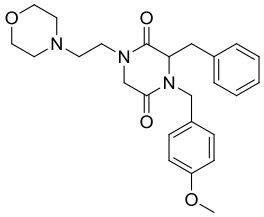
LC-MS (ESI, 60 eV): m/z = 409.3 $[M + H]^+$.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{25}H_{33}N_2O_3$: 409.2486; found : 409.2486.

CSP-HPLC A (210 nm, Daicel Chiralpak IA 4.6 x 250 mm, *n*-Hexane/*i*-PrOH = 30 : 70, r.t., 0.5 mL/min): t_R = 14.744 min (100%, chiral pure compound).

CSP-HPLC B (210 nm, Agilent Chiradex 4.0 x 250 mm, ACN / 5 mM Ammonium formate buffer = 20 : 80, r.t., 0.8 mL/min): t_R = 9.829 min (95.8%, chiral pure compound).

(S)-3-benzyl-4-(4-methoxybenzyl)-1-(2-morpholinoethyl)piperazine-2,5-dione (6r)



Beige solid; yield: 526 mg (80%); purity: 98% (checked by LC-MS, 254 nm); mp: 138.8-141.3 °C; R_f: 0.045 (*n*-Hexane/Ethyl acetate = 1:1).

ATR-IR (neat): 3064, 3016 (sp^2 C-H), 2973, 2933, 2845, 2810 (sp^3 C-H), 1649 (C=O, amide), 1611, 1509, 1468 (C=C, aromatic), 1242, 1116, 1030 (C-O, Ph-O-Me) cm^{-1}.

^{1}H NMR (500 MHz, DMSO): δ = 7.29 (dd, *J* = 10.5, 5.1 Hz, 3H), 7.22 (d, *J* = 8.5 Hz, 2H), 7.14 – 7.07 (m, 2H), 6.91 (d, *J* = 8.6 Hz, 2H), 5.09 (d, *J* = 14.6 Hz, 1H), 4.00 (t, *J* = 4.5 Hz, 1H), 3.94 (d, *J* = 14.7 Hz, 1H), 3.74 (s, 3H), 3.61 (d, *J* = 17.2 Hz, 1H), 3.51 (s, 4H), 3.43 (dd, *J* = 13.5, 6.6 Hz, 1H), 3.22 (dd, *J* = 13.7, 5.2 Hz, 1H), 3.17 – 3.10 (m, 1H), 3.02 (dd, *J* = 13.7, 3.9 Hz, 1H), 2.78 (d, *J* = 17.2 Hz, 1H), 2.42 – 2.18 (m, 6H).

^{13}C NMR (126 MHz, DMSO): δ = 165.76, 164.62, 159.24, 135.89, 130.37, 130.04, 128.86, 128.85, 127.70, 114.54, 66.68, 60.20, 55.55, 55.41, 53.65, 49.67, 45.75, 42.52, 36.77.

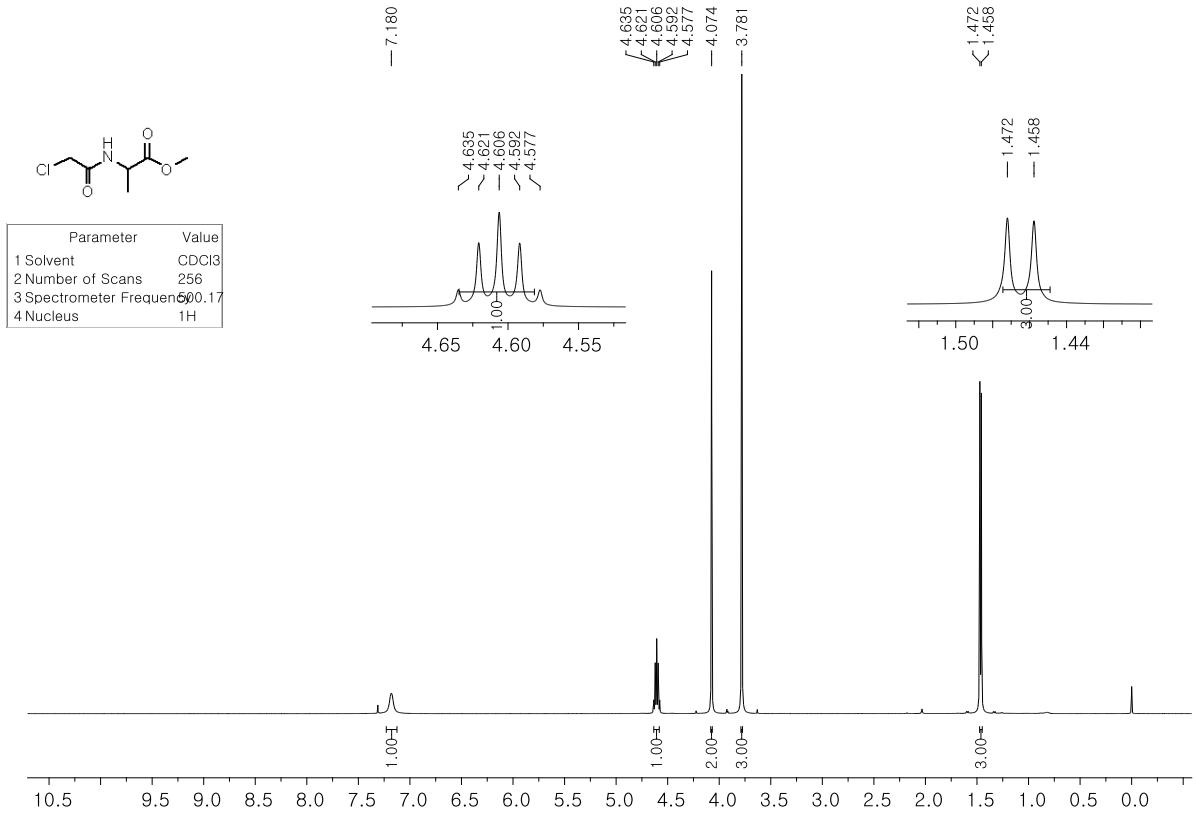
LC-MS (ESI, 60 eV): m/z = 438.3 $[M + H]^+$.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{25}H_{32}N_3O_4$: 438.2387; found : 438.2387.

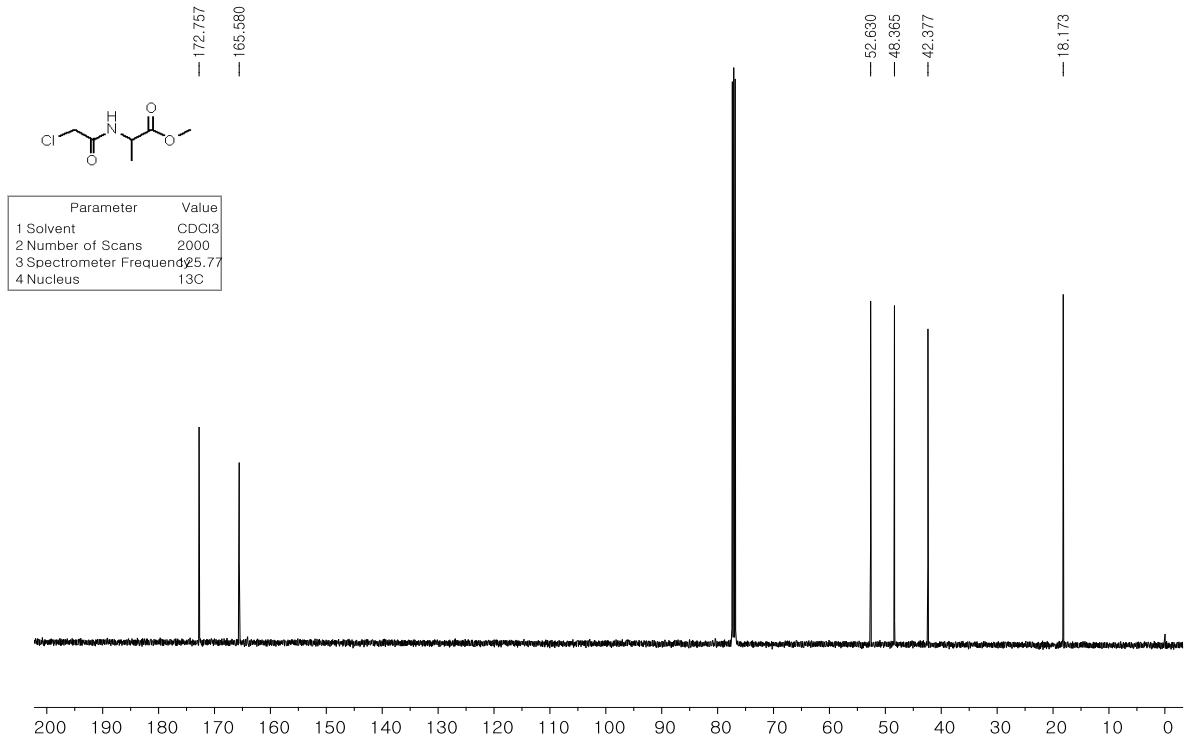
CSP-HPLC A (210 nm, Daicel Chiralpak IA 4.6 x 250 mm, *n*-Hexane/*i*-PrOH = 30 : 70, r.t., 0.5 mL/min): t_R = 29.290 min (100%, chiral pure compound).

CSP-HPLC B (210 nm, Agilent Chiradex 4.0 x 250 mm, ACN / 5 mM Ammonium formate buffer = 20 : 80, r.t., 0.8 mL/min): t_R = 10.650 min (100%, chiral pure compound).

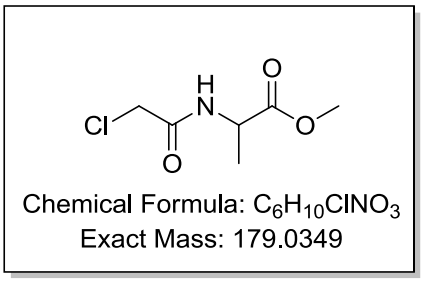
2. ^{1}H NMR, ^{13}C NMR, LC/MS and HRMS spectra of compounds 2

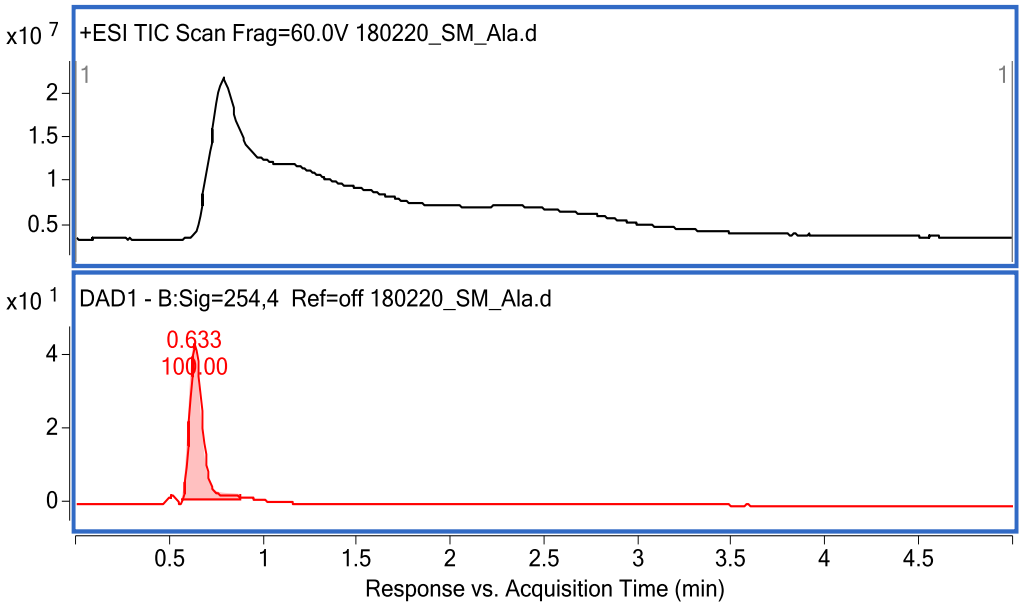


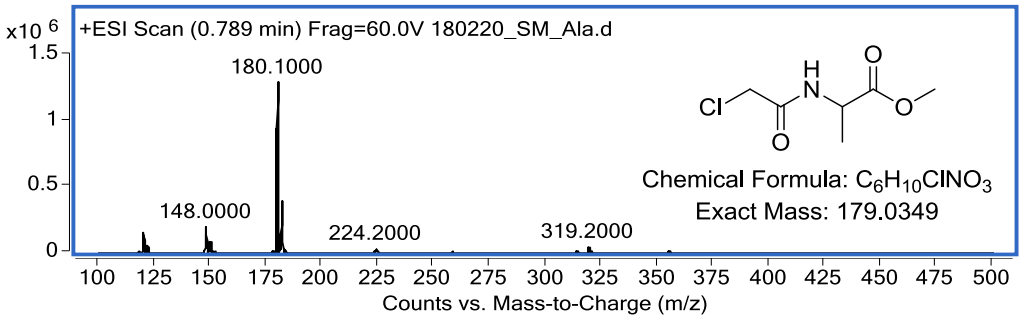
^{1}H NMR – 2a



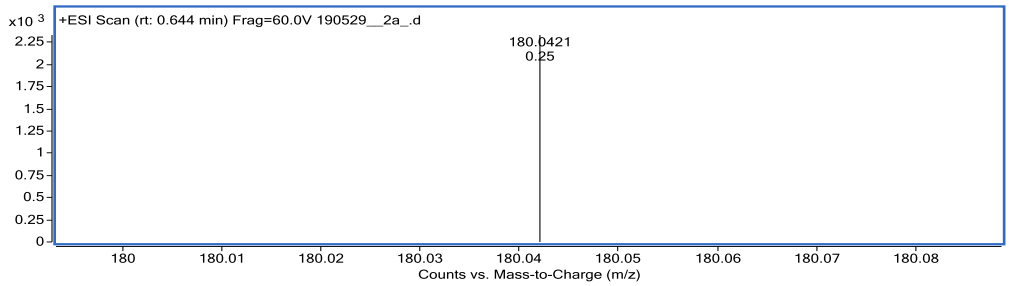
^{13}C NMR – 2a



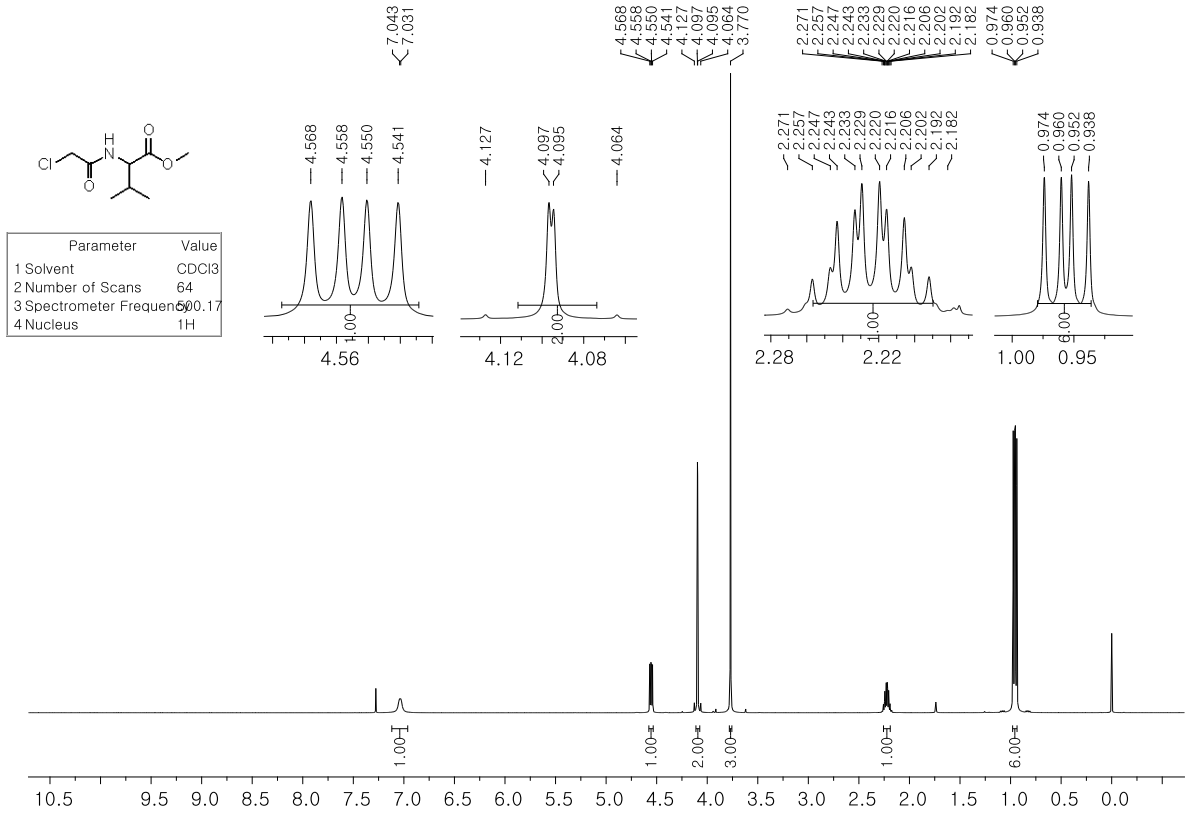




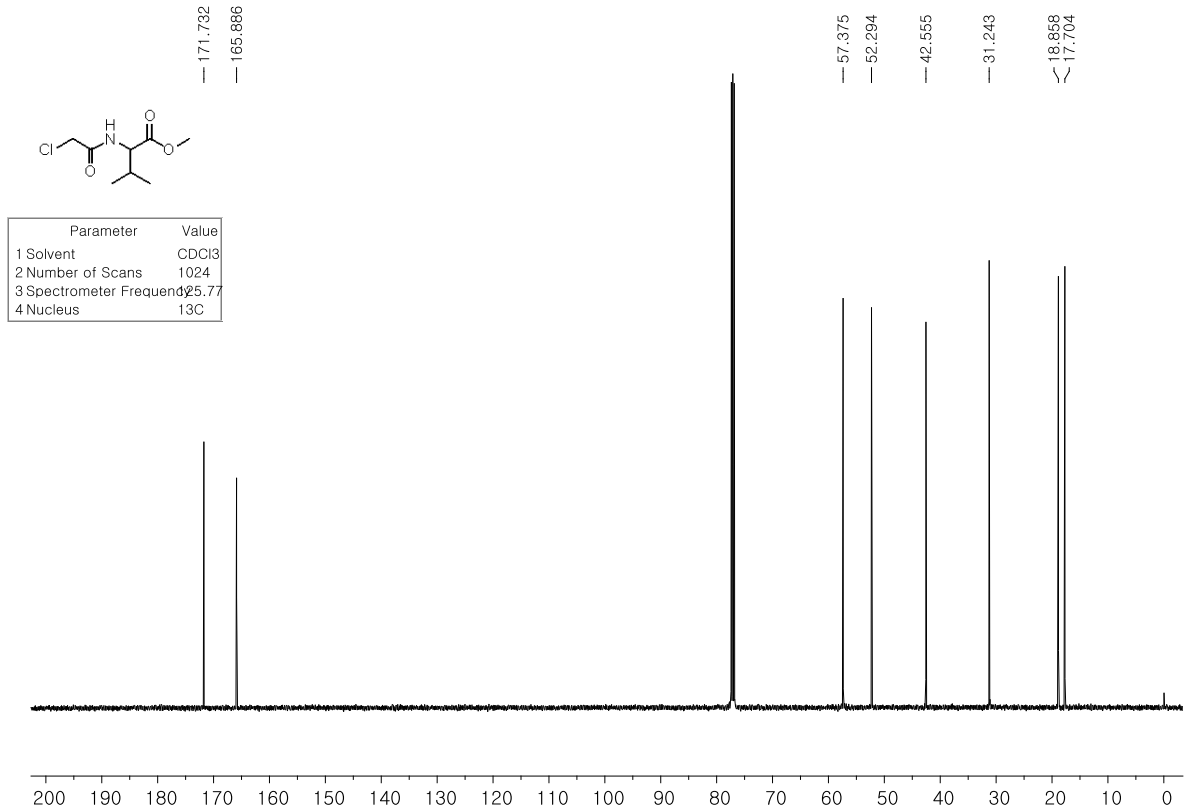
LC/MS – 2a



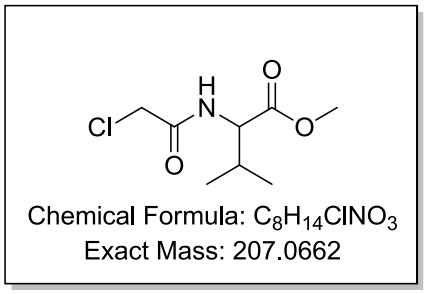
HRMS – 2a

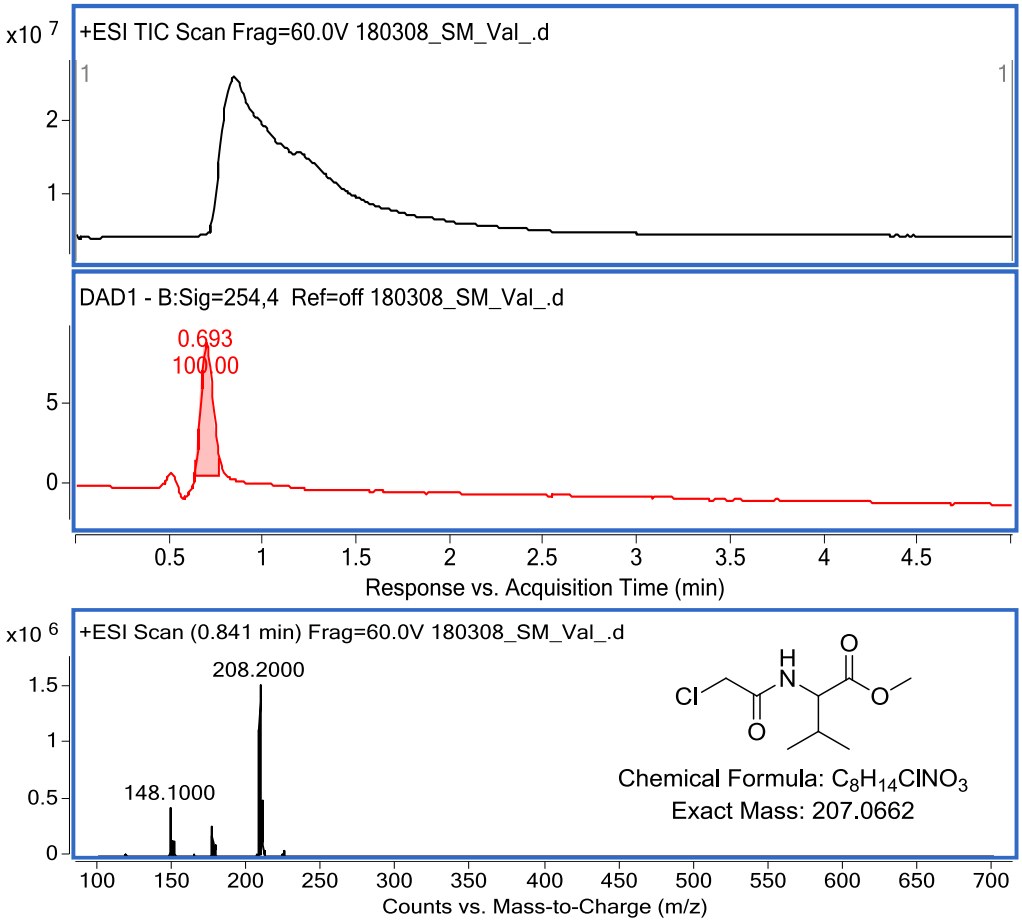


^{1}H NMR – 2b

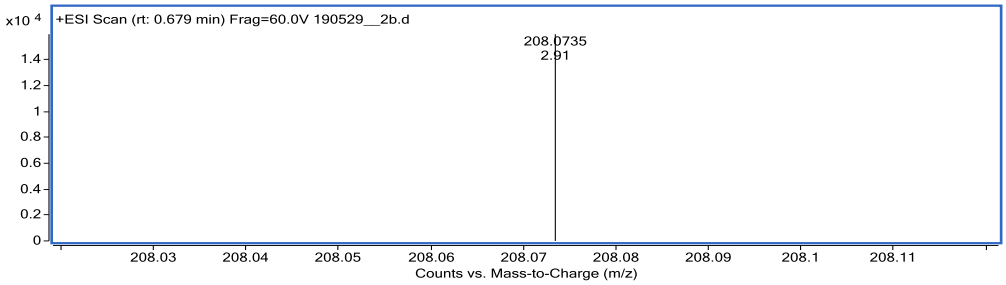


^{13}C NMR – 2b

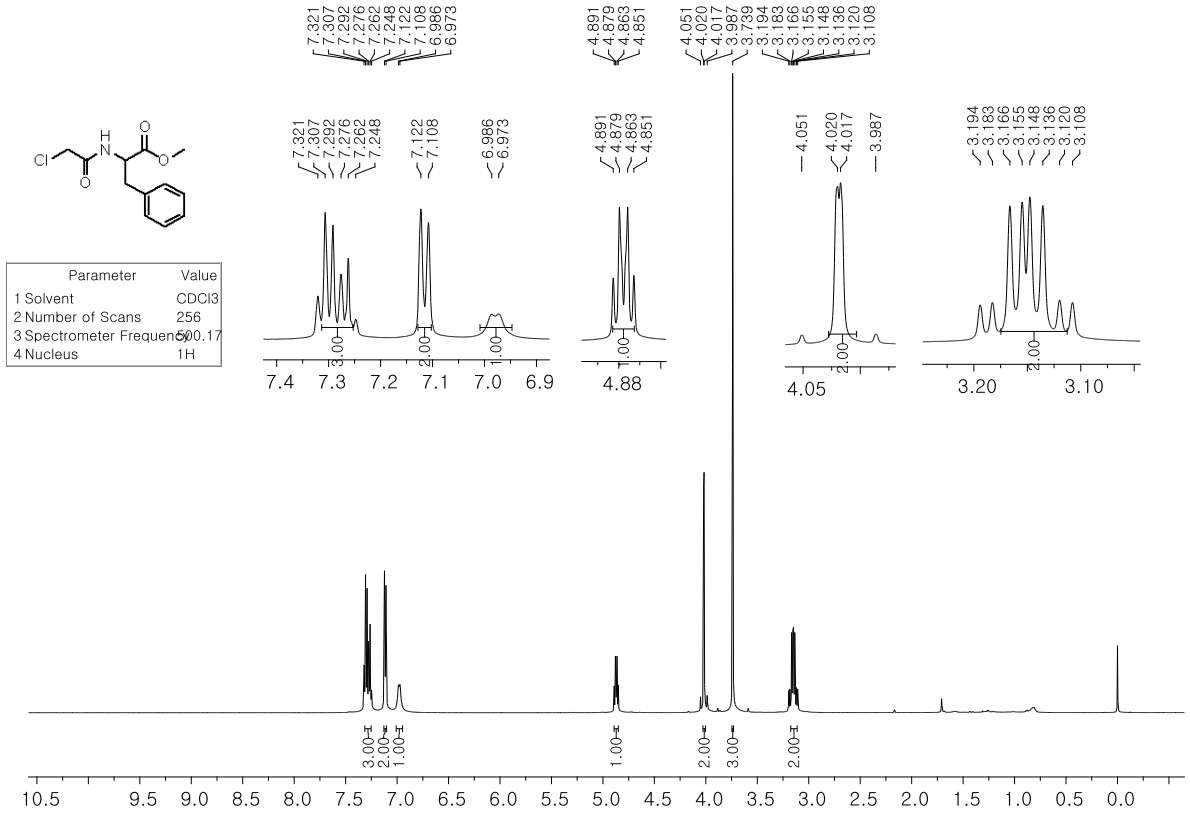




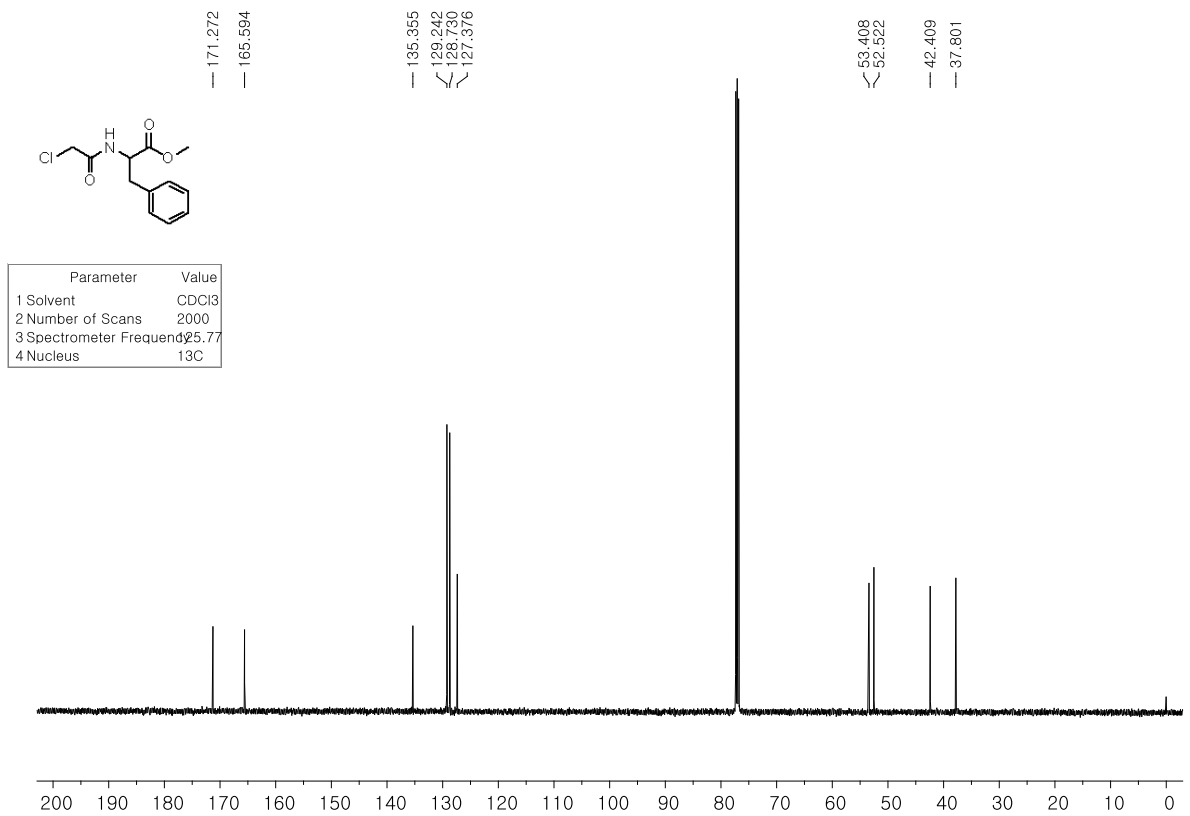
LC/MS – 2b



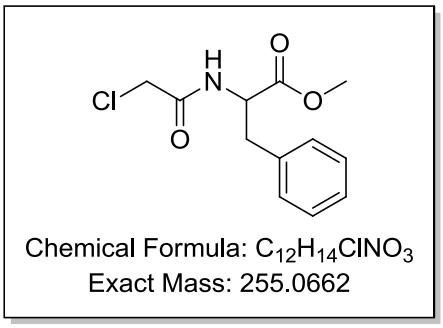
HRMS – 2b

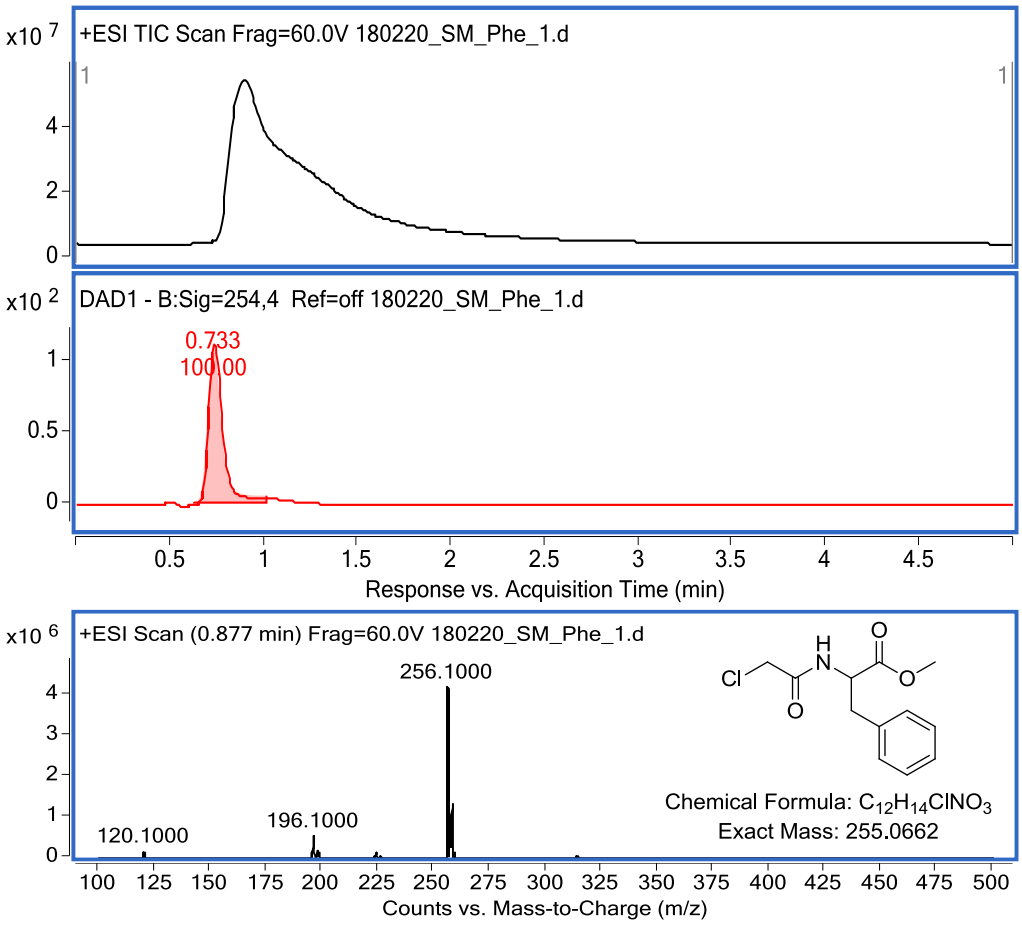


^{1}H NMR – 2c

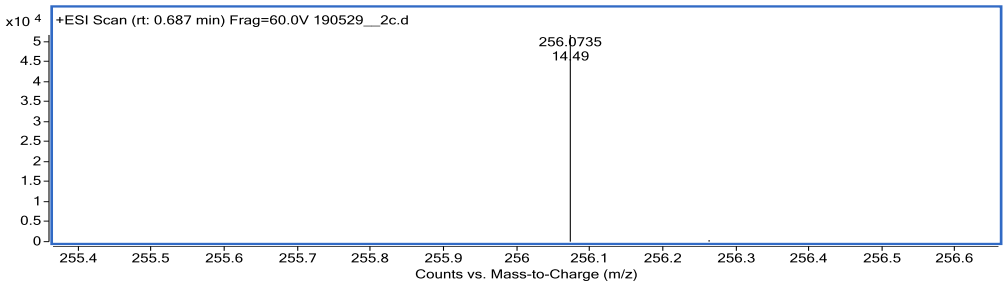


^{13}C NMR – 2c



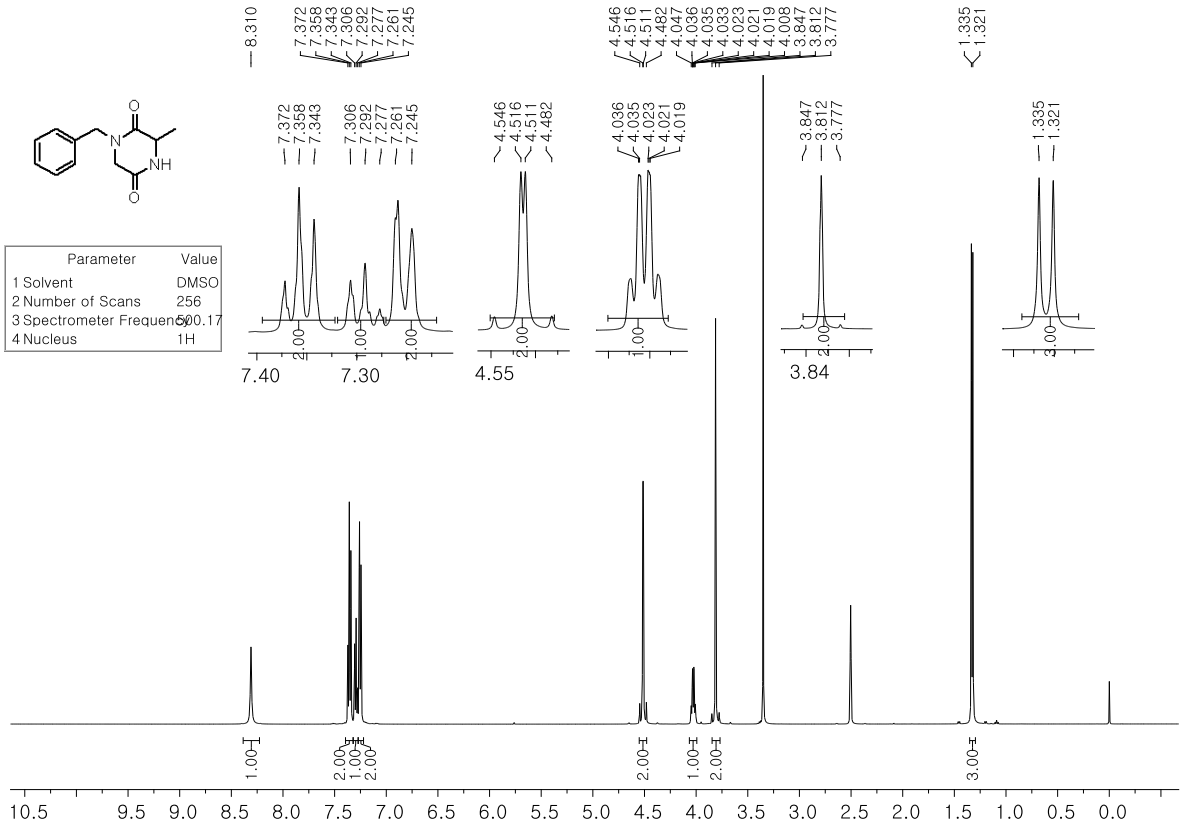


LC/MS – 2c

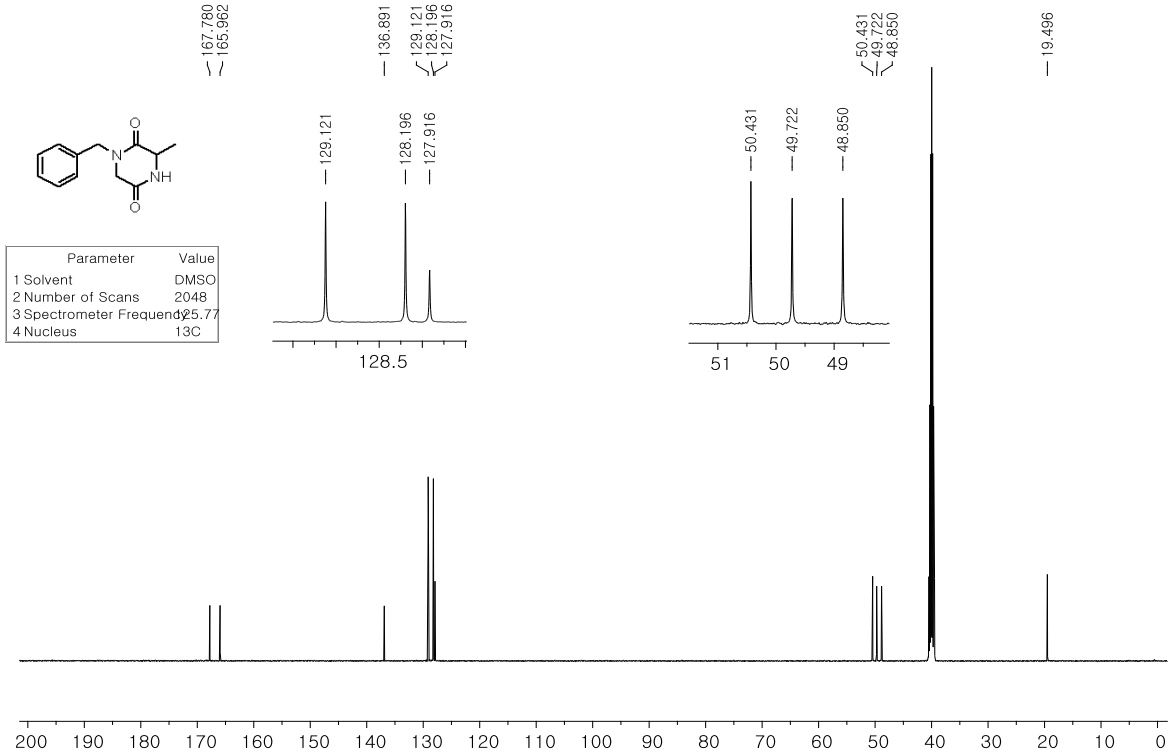


HRMS – 2c

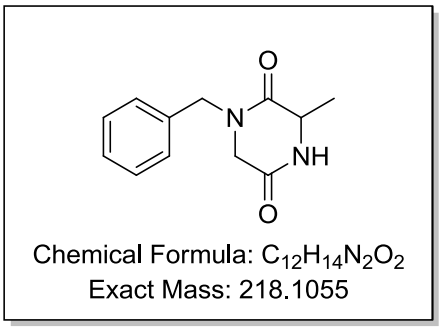
3. ^{1}H NMR, ^{13}C NMR, LC/MS and HRMS spectra of compounds 3

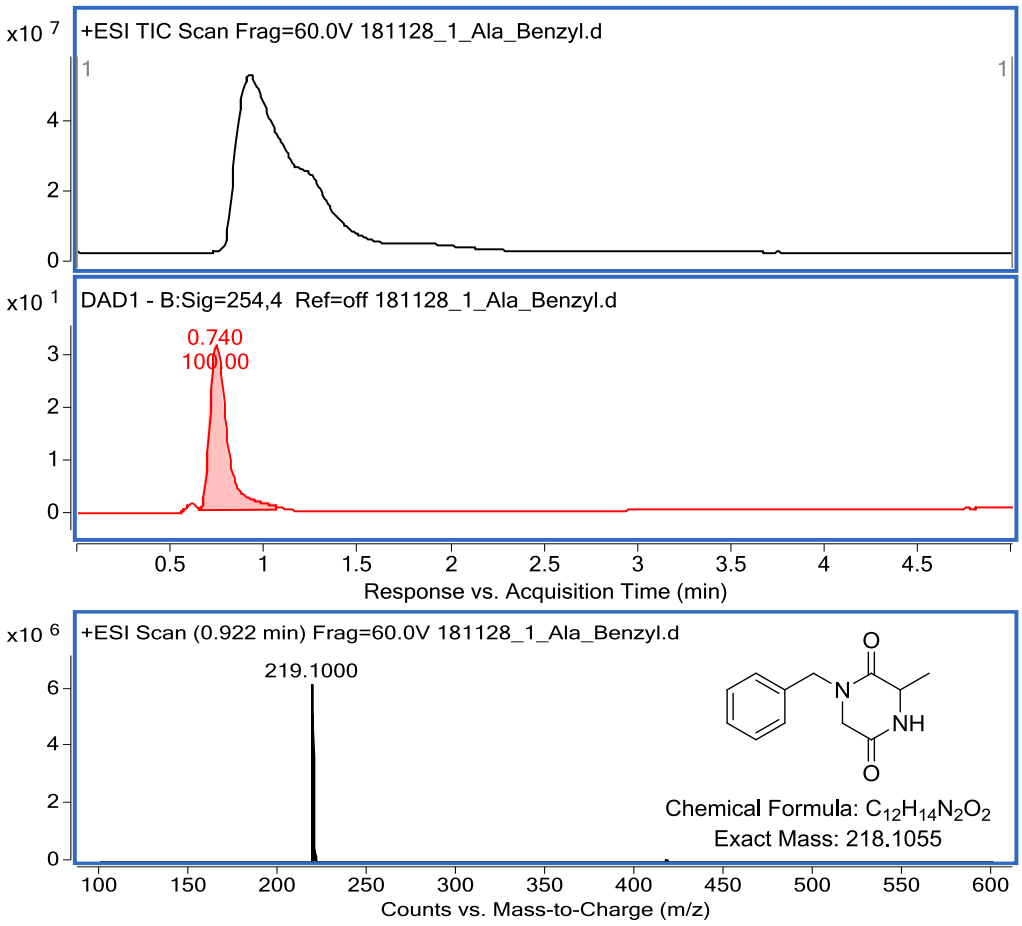


^{1}H NMR – 3a

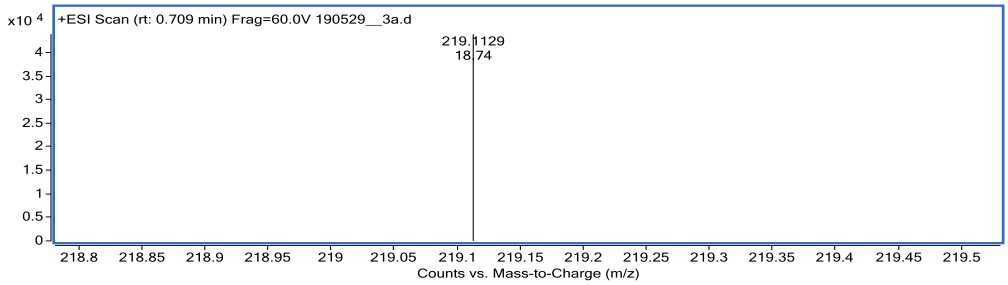


^{13}C NMR – 3a





LC/MS – 3a



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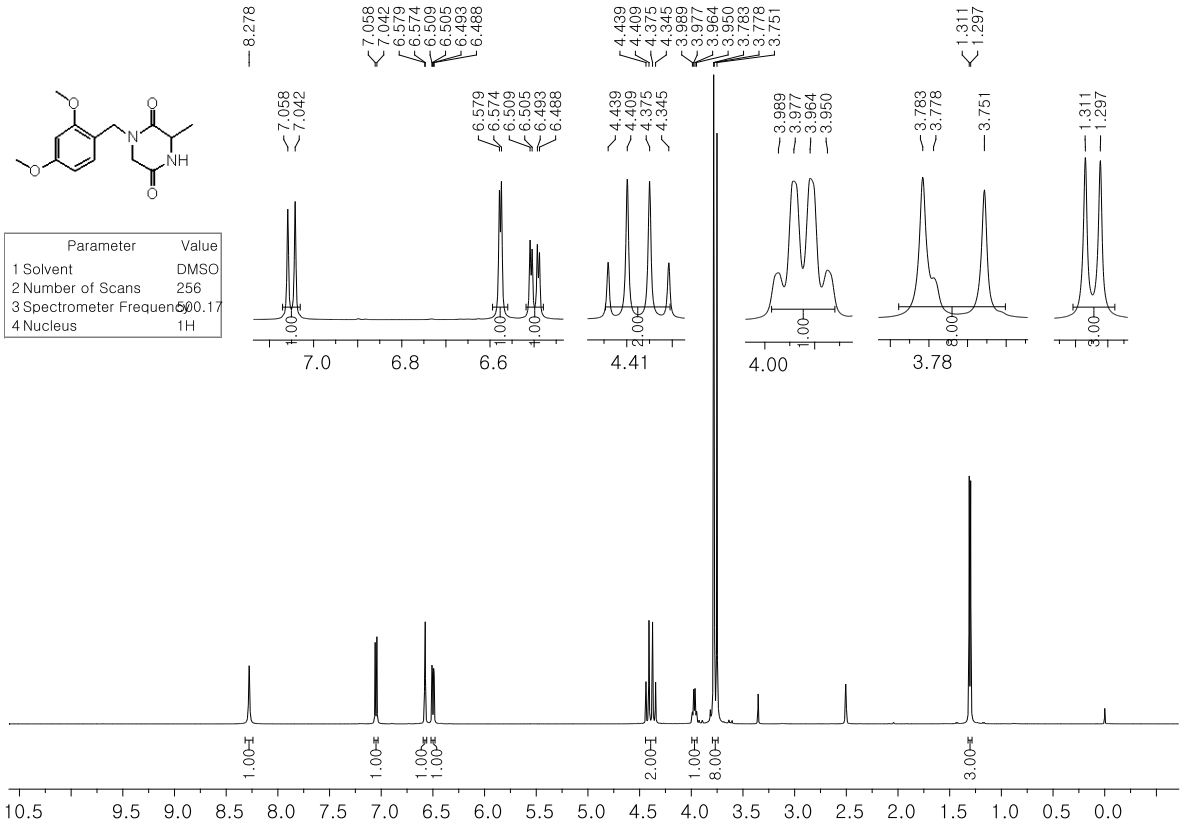
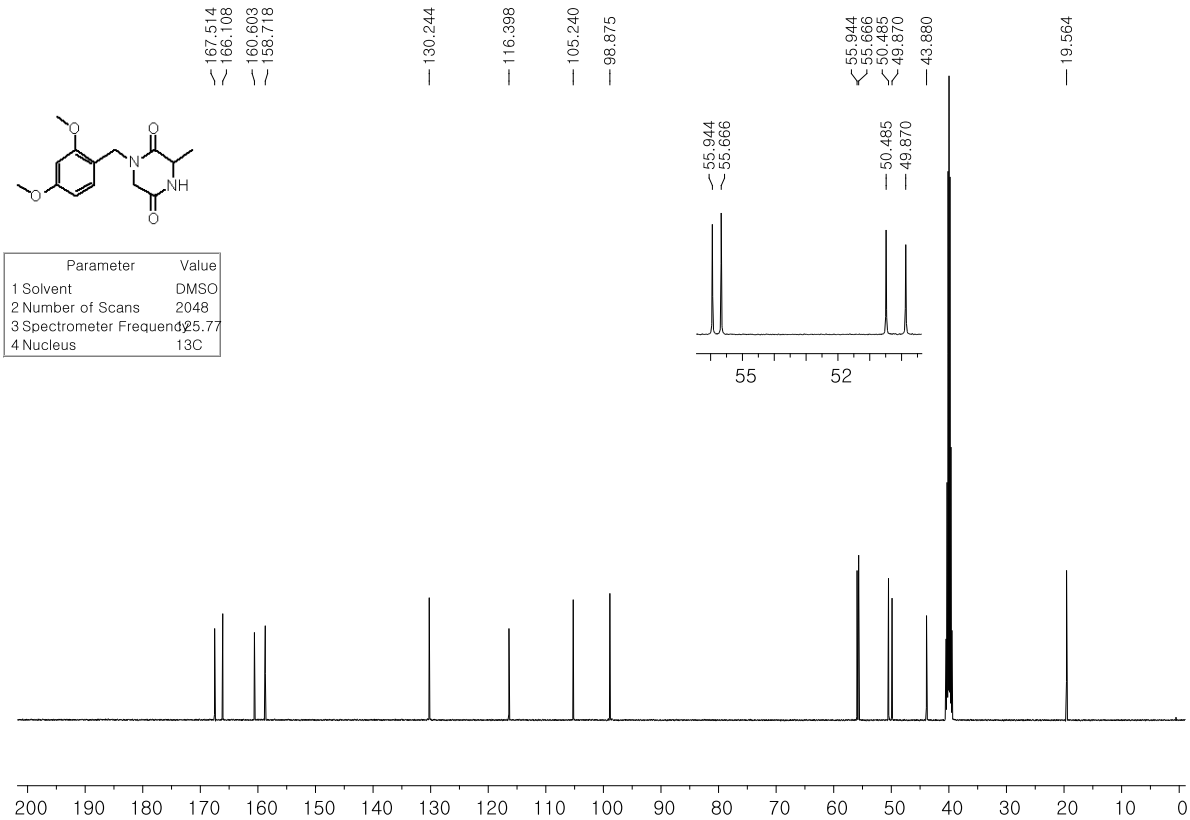
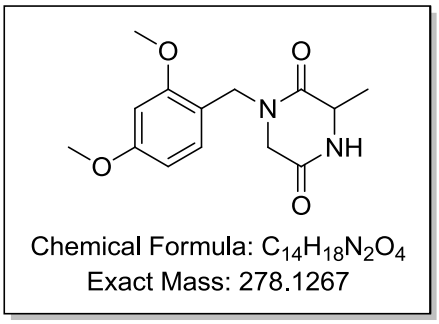
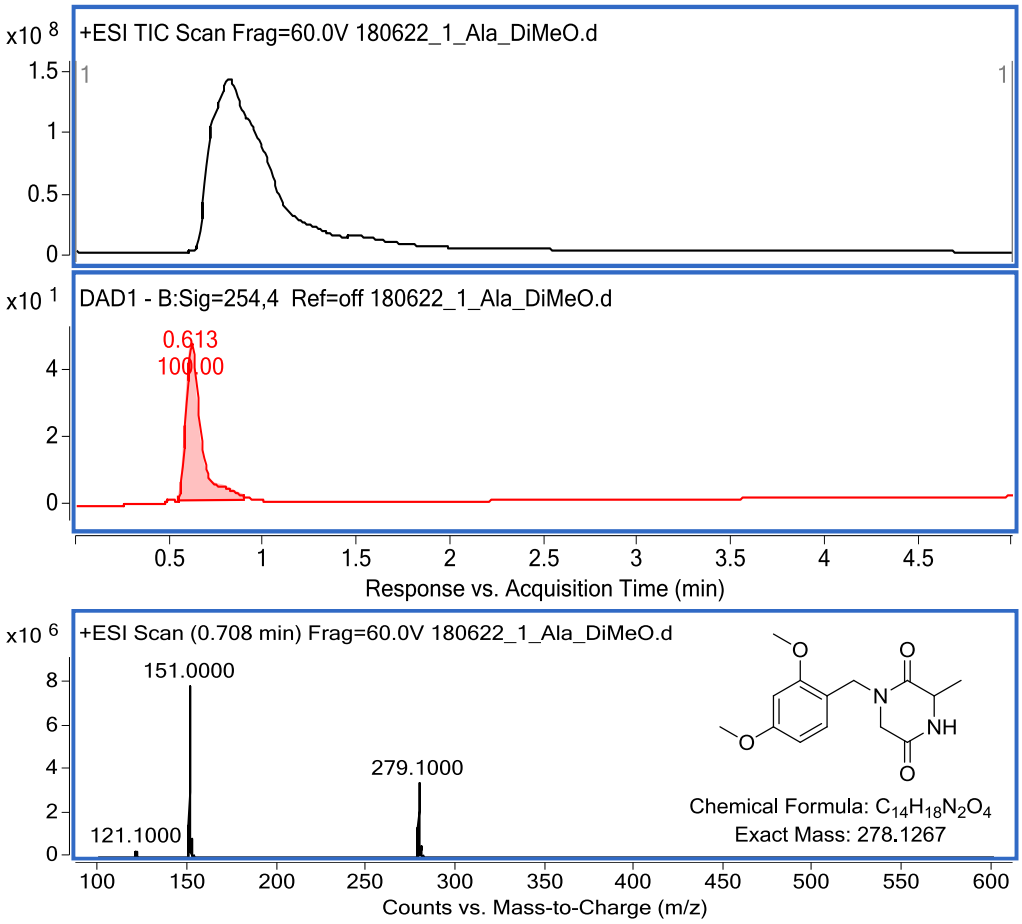


^{1}H NMR – 3b

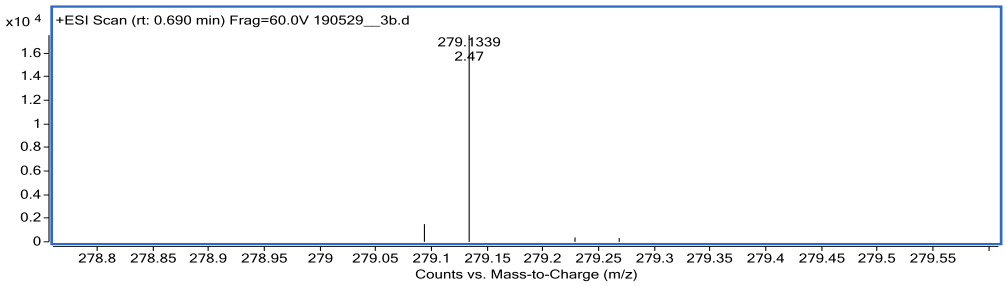


^{13}C NMR – 3b

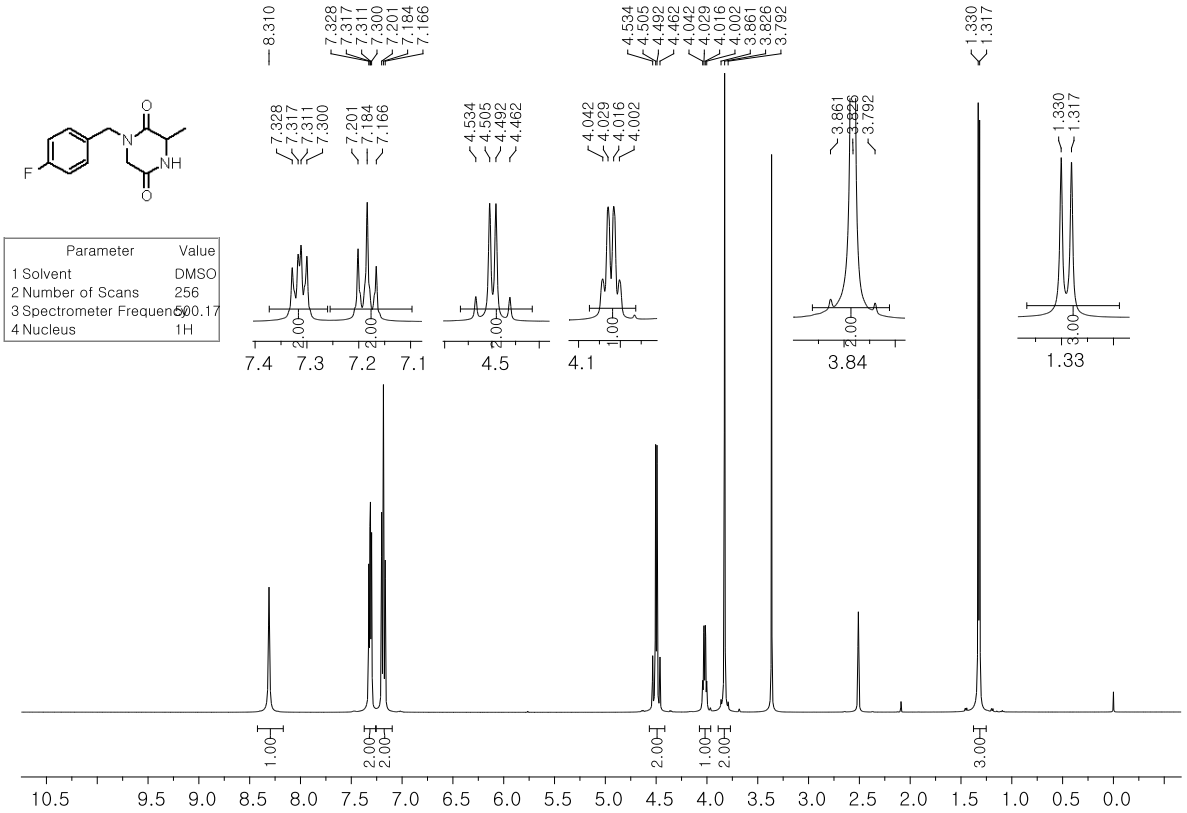




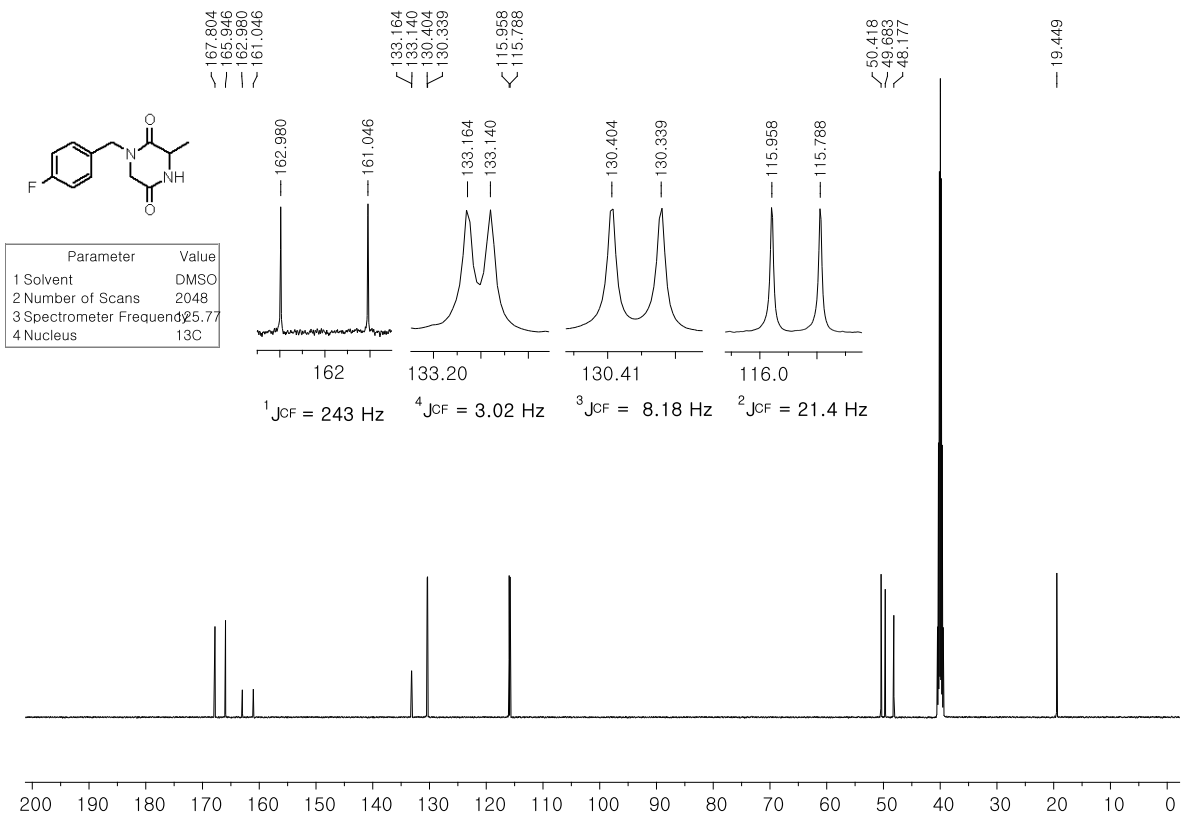
LC/MS – 3b



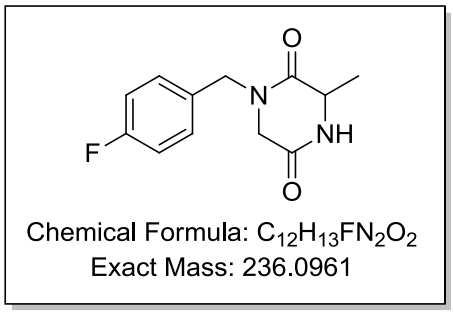
HRMS – 3b

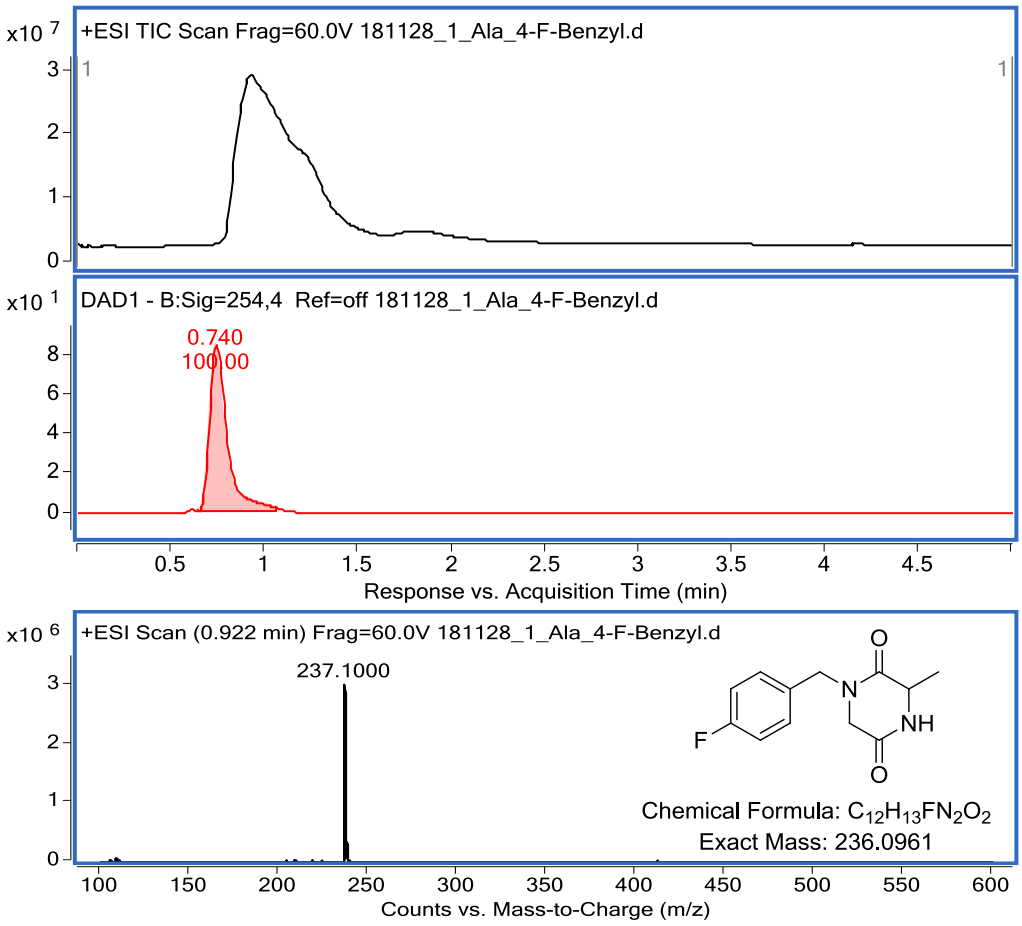


^{1}H NMR – 3c

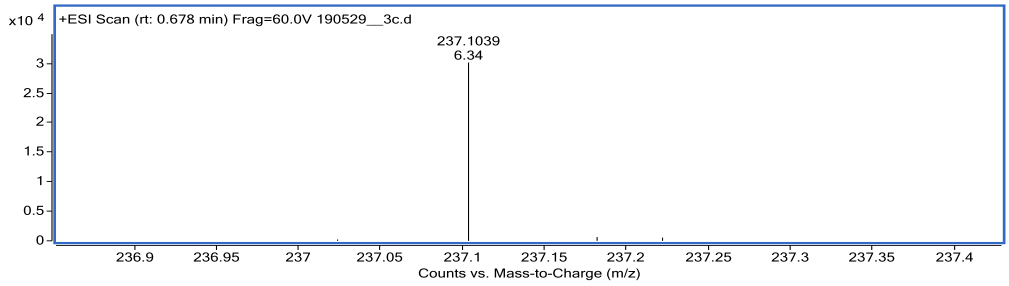


^{13}C NMR – 3c

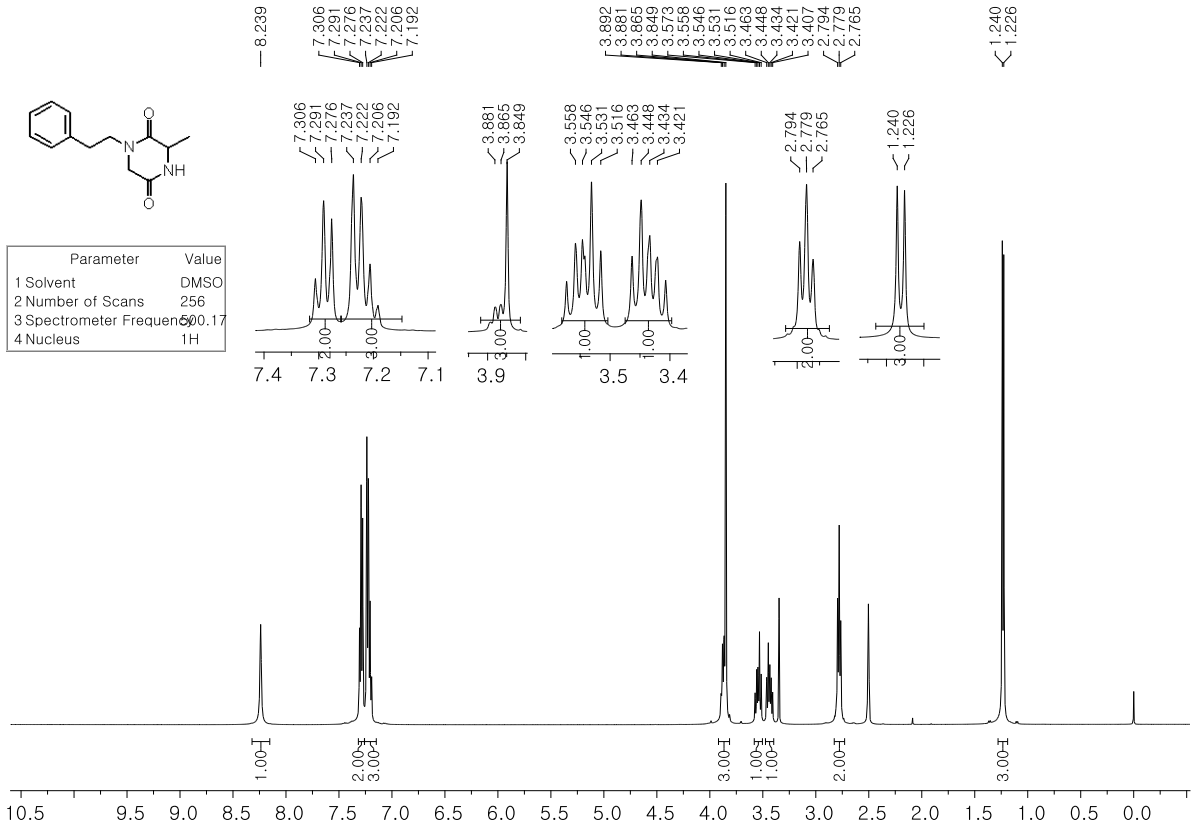




LC/MS – 3c



HRMS – 3c



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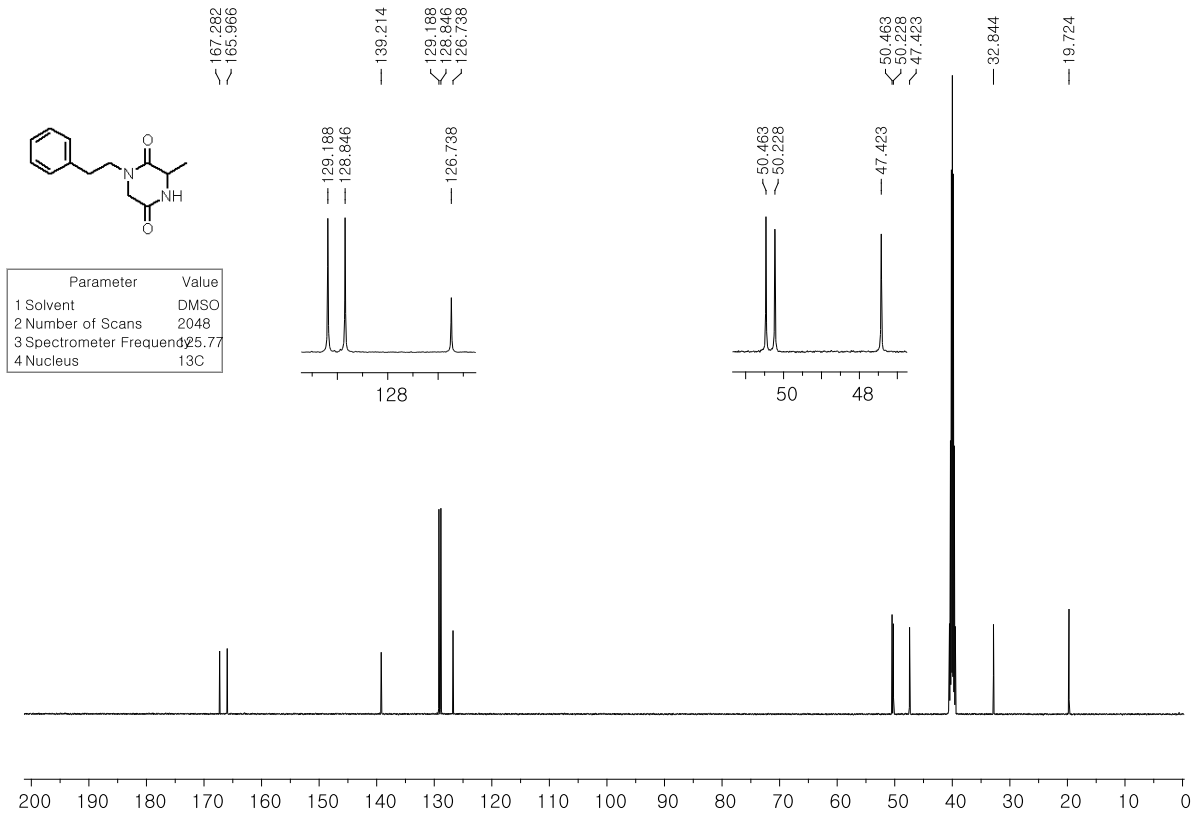
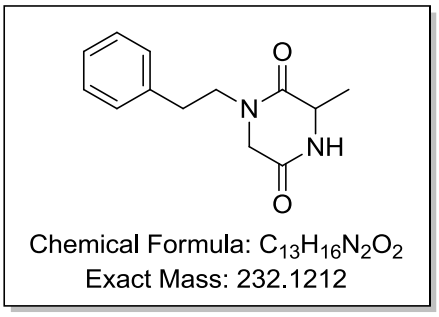
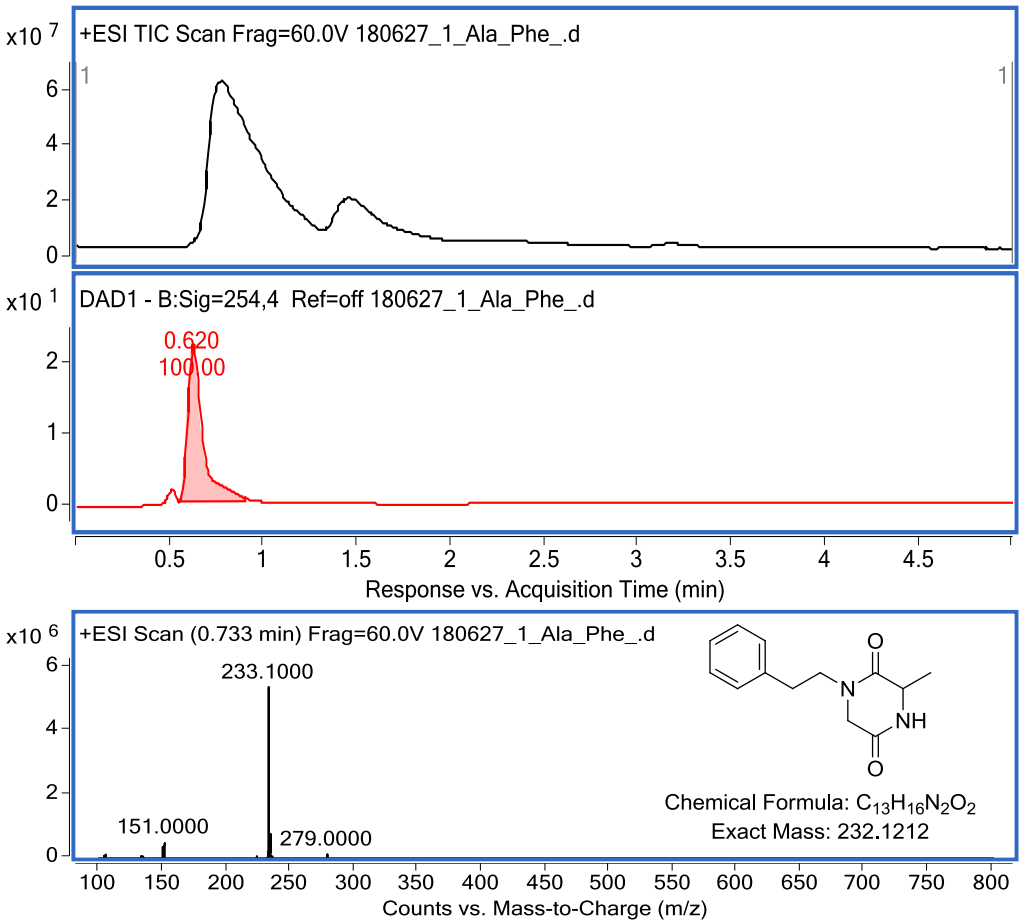
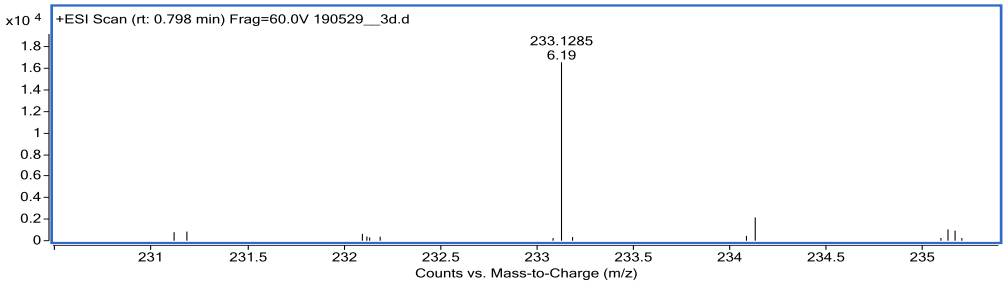


^{13}C NMR – 3d

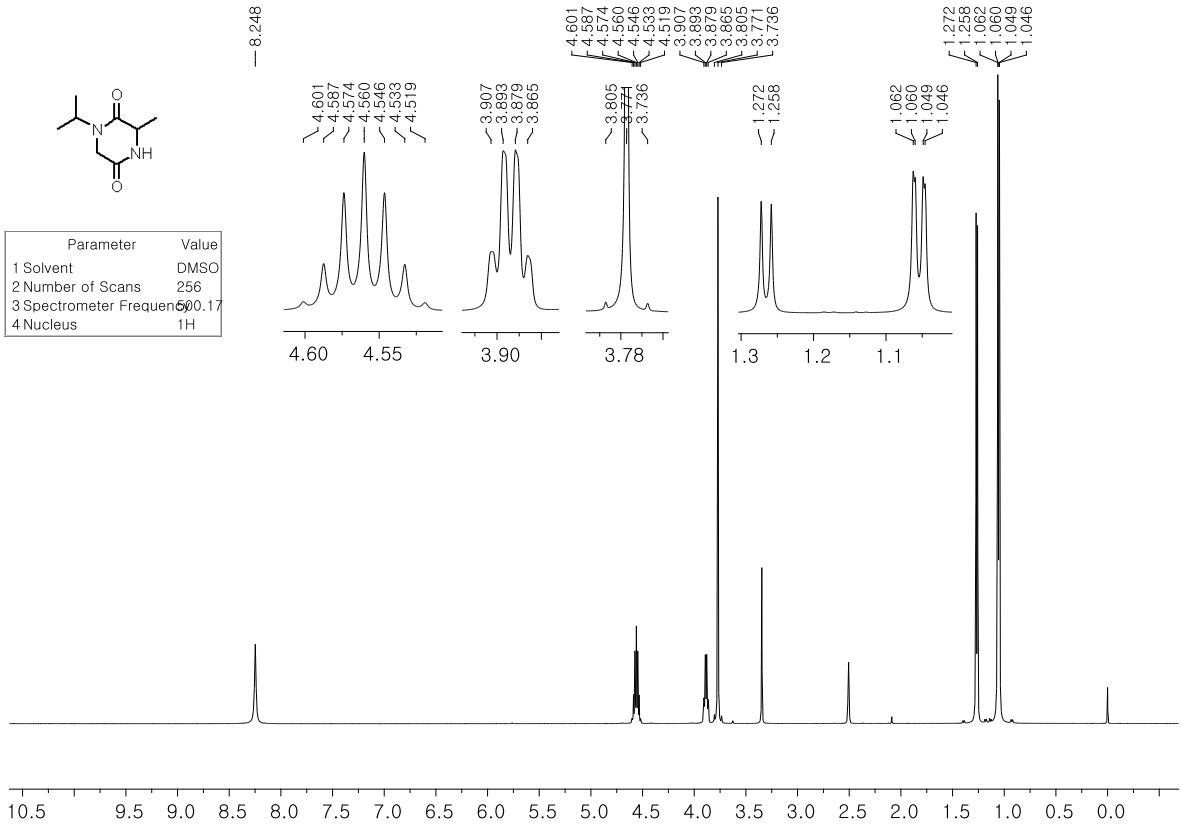




LC/MS – 3d



HRMS – 3d



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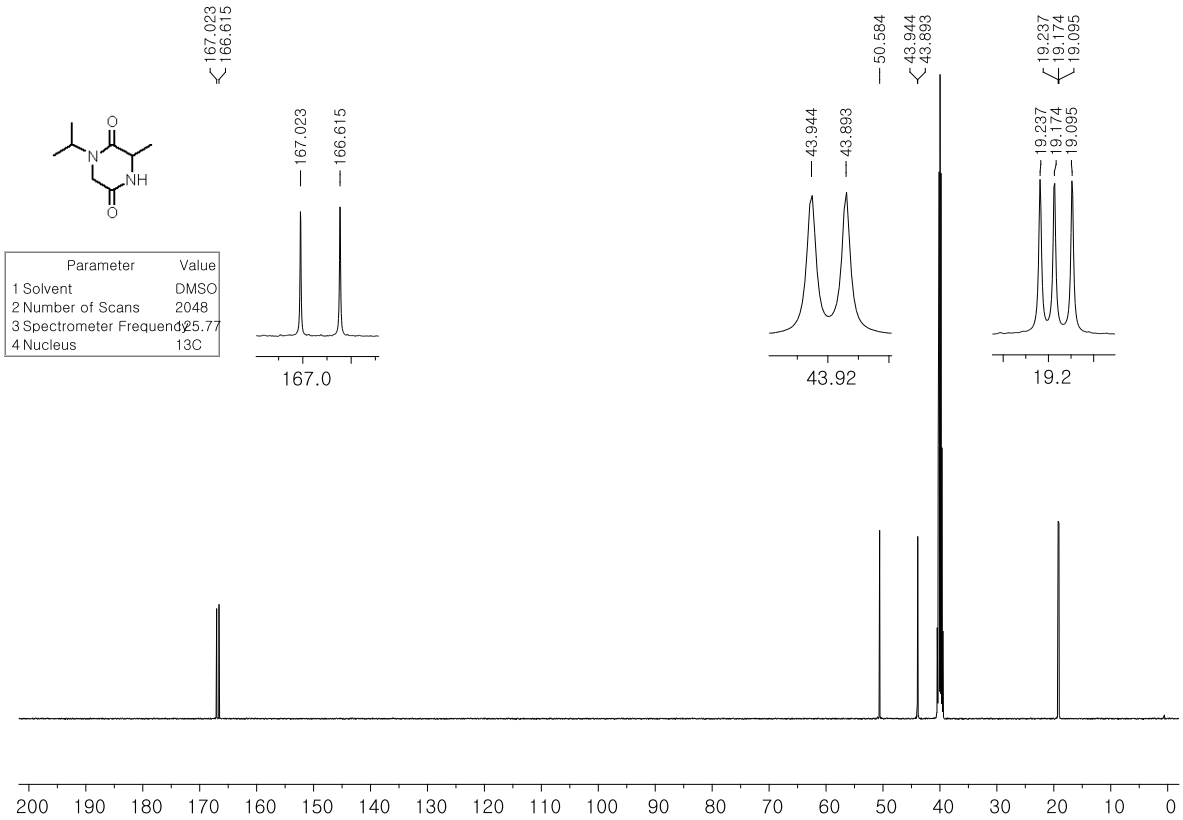

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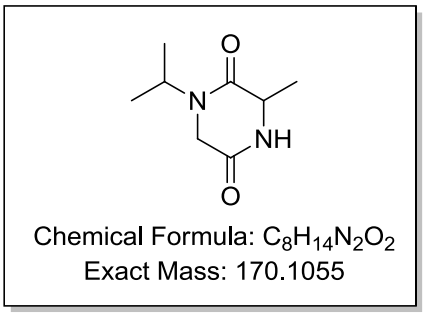

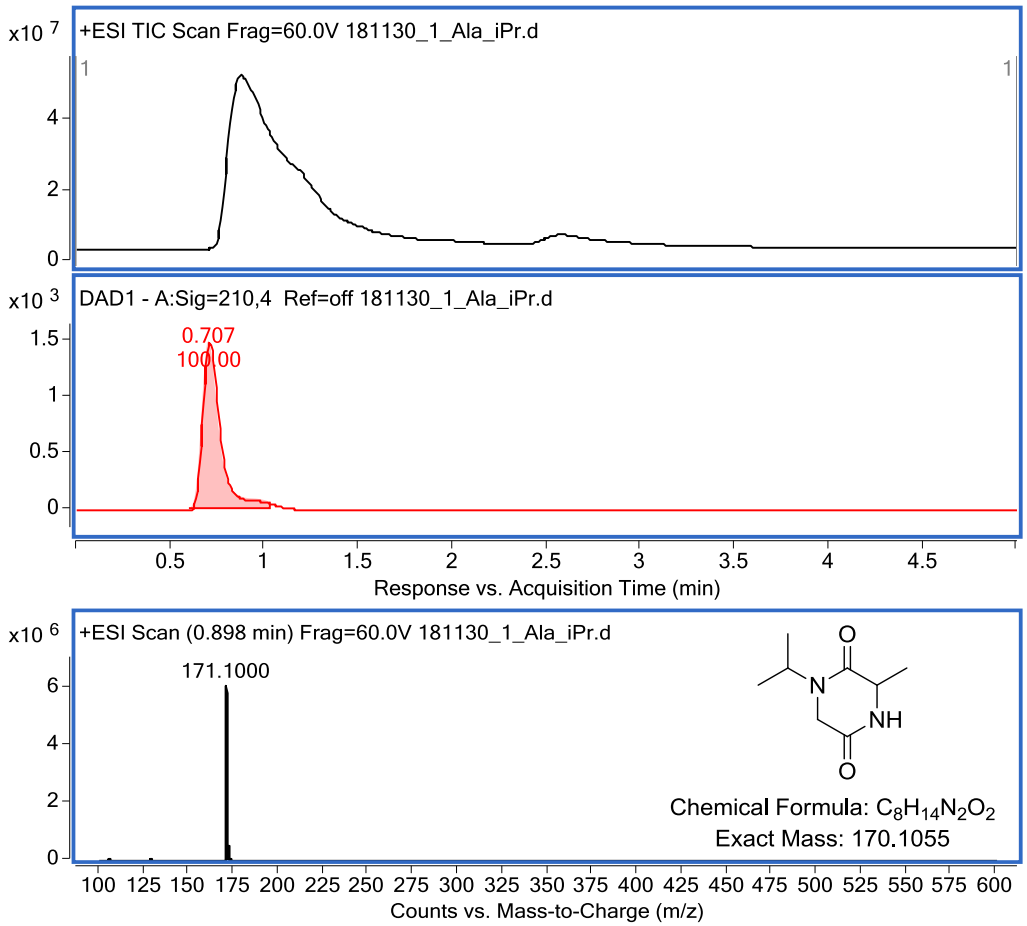

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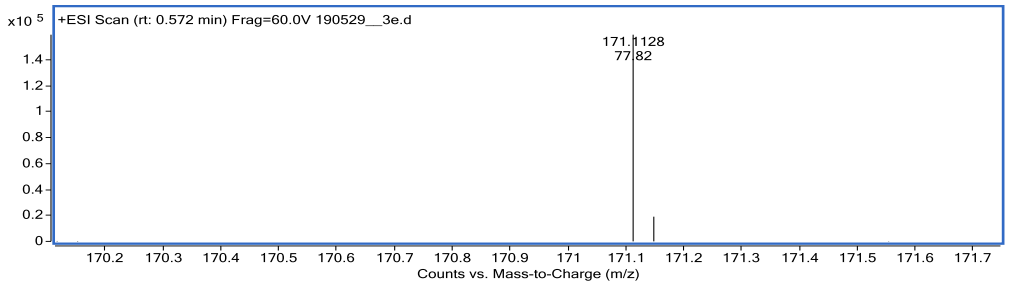
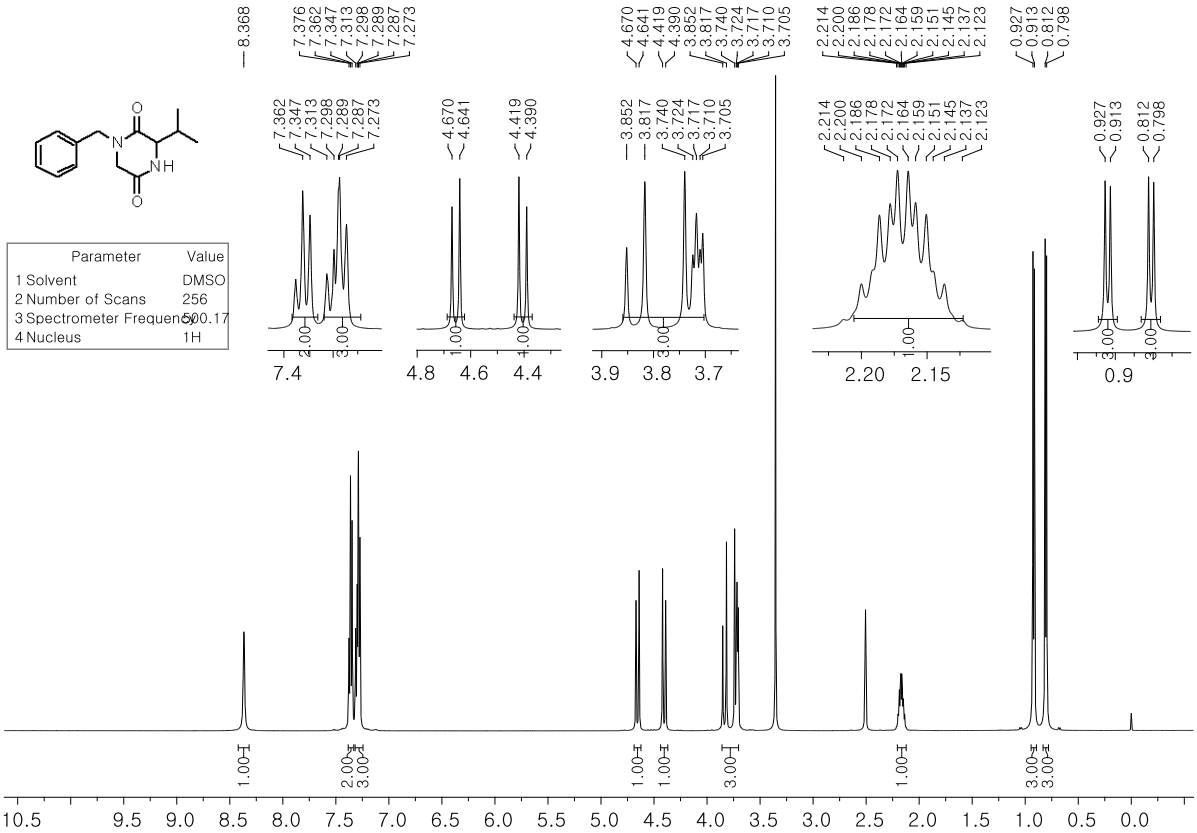
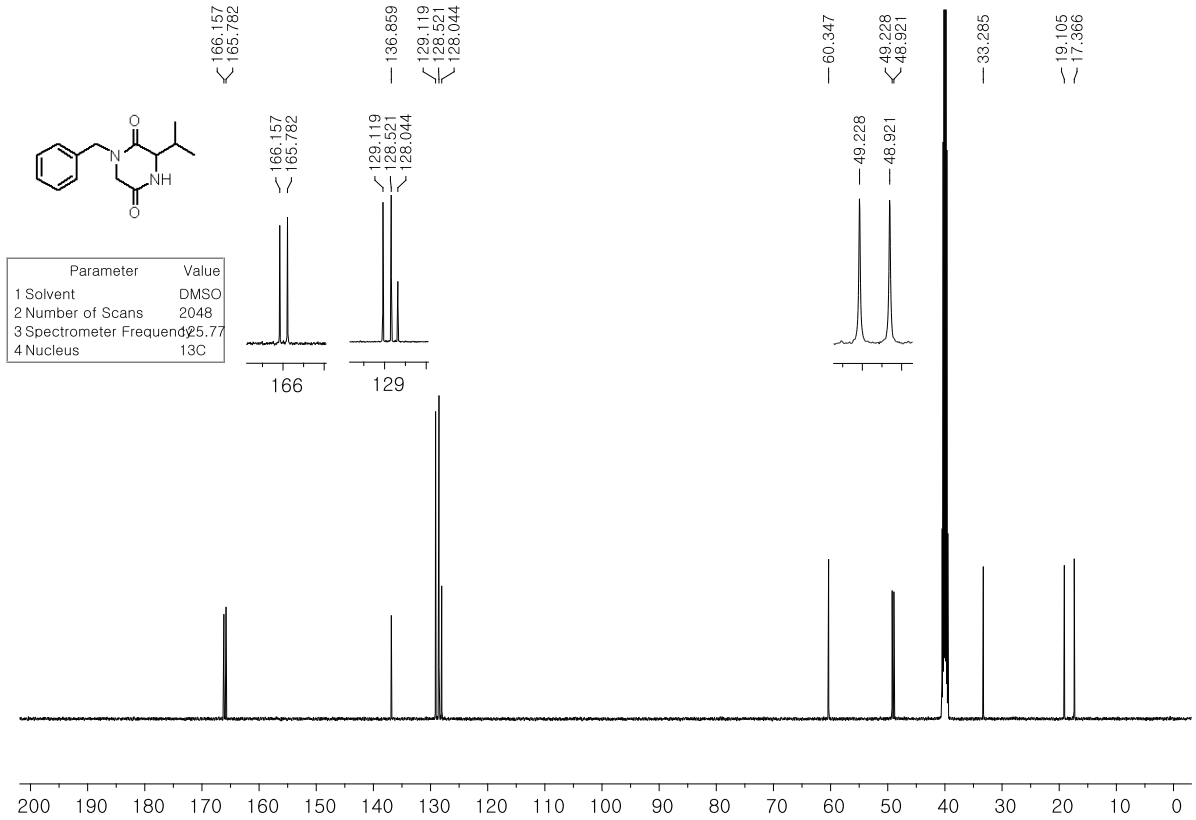


HRMS – 3e



^{1}H NMR – 3f



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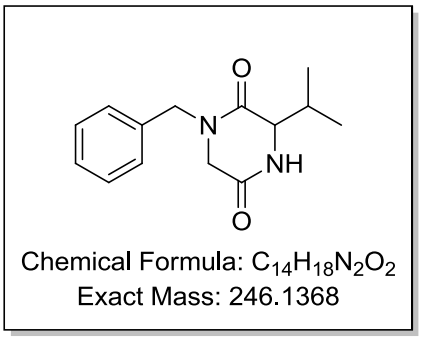

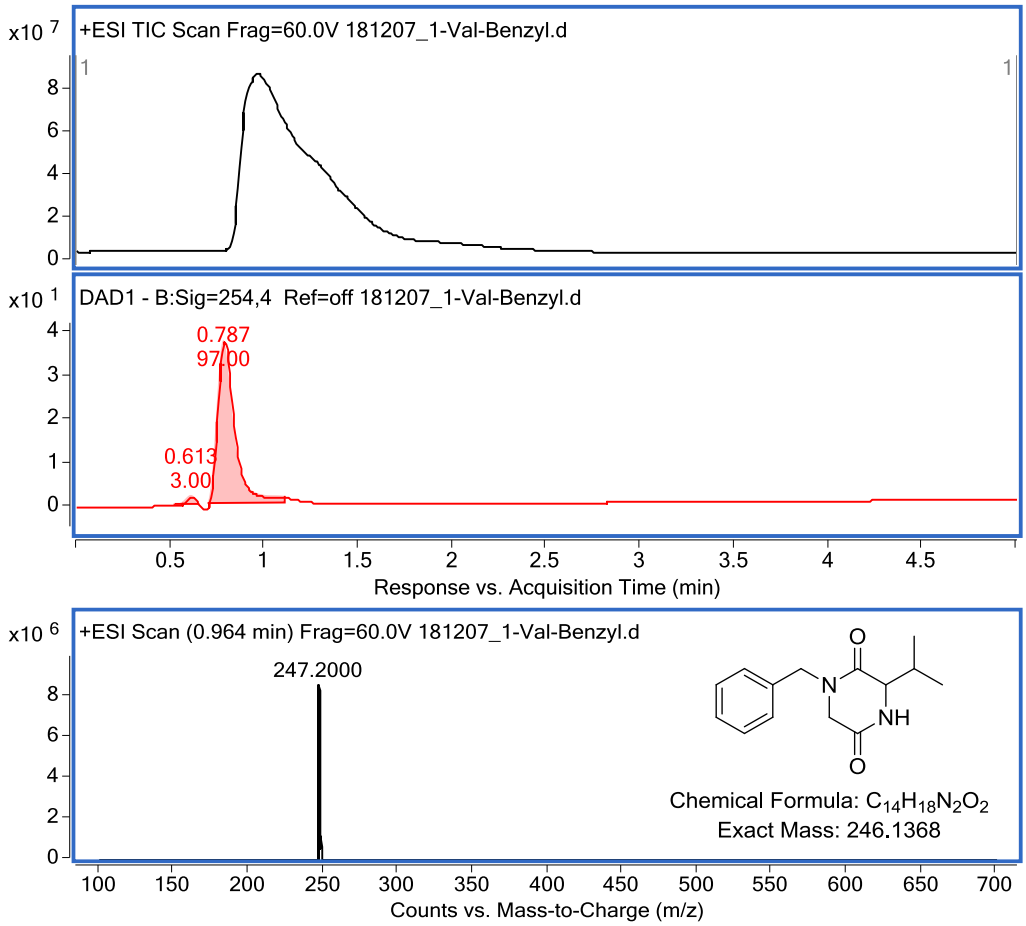

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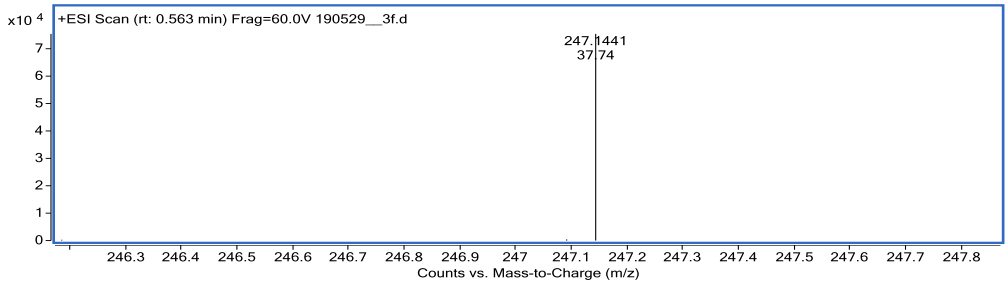

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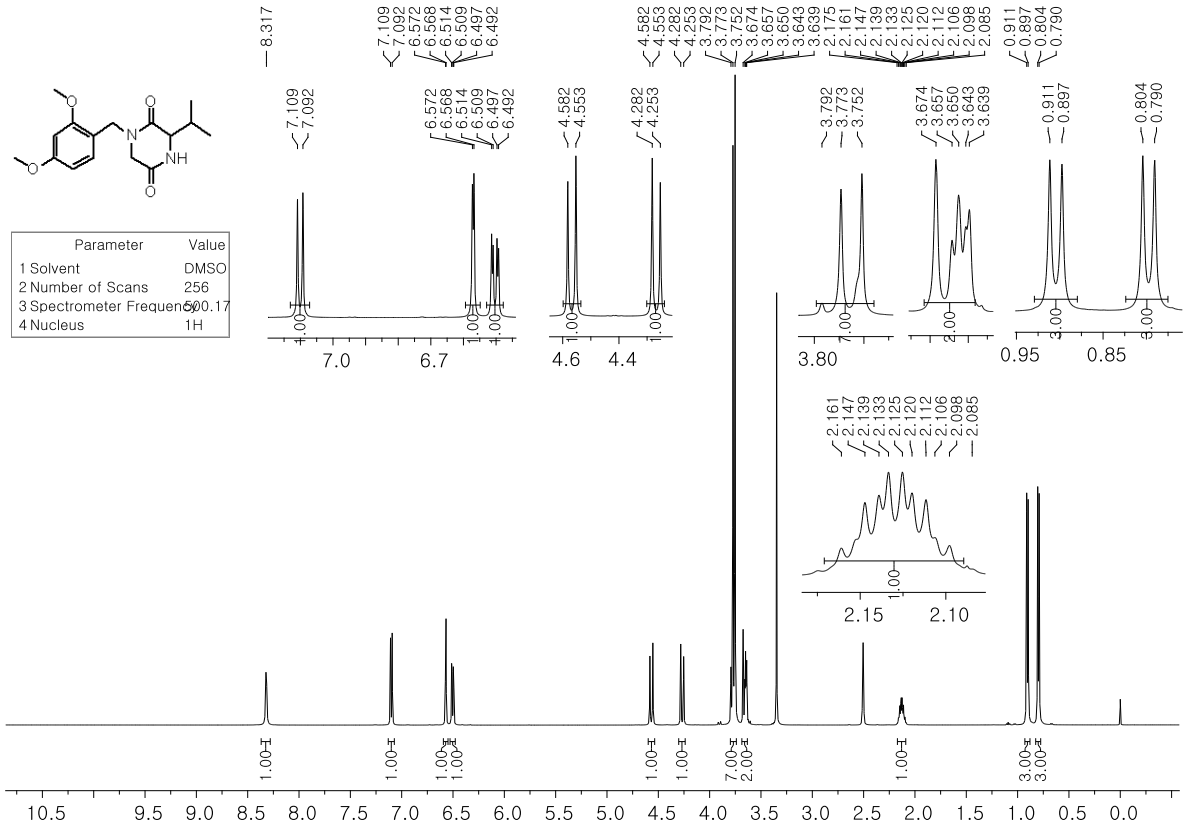

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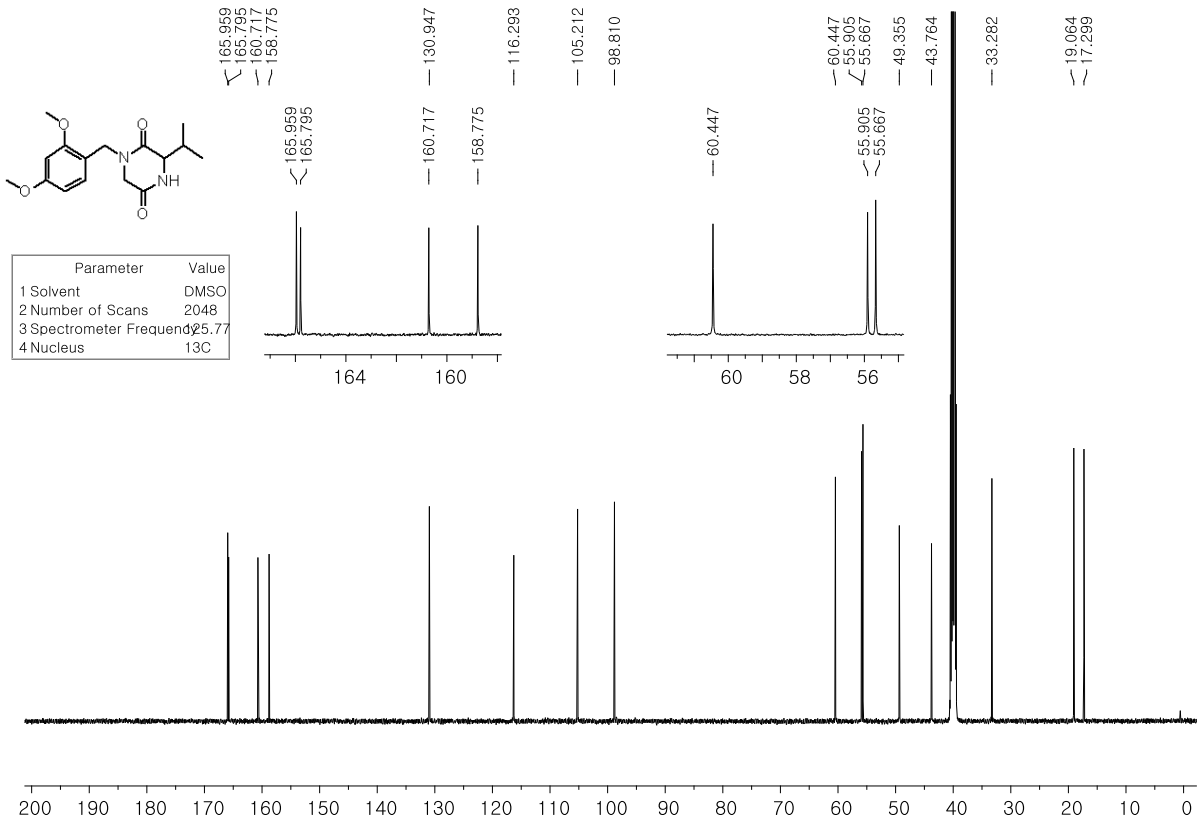

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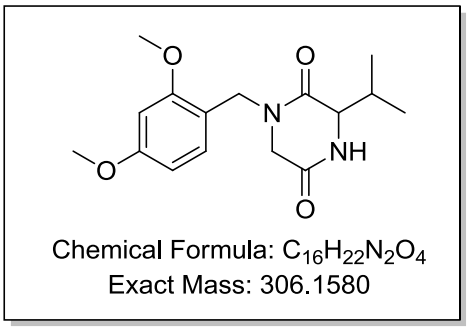

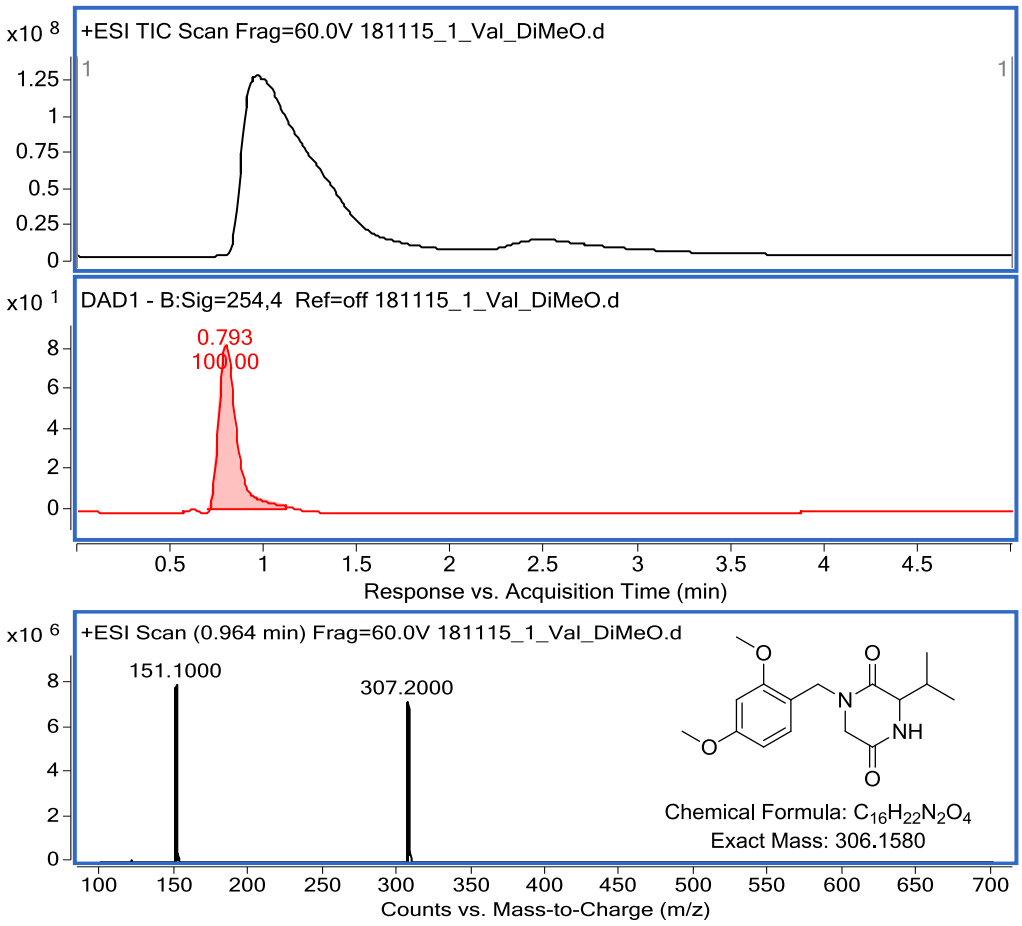

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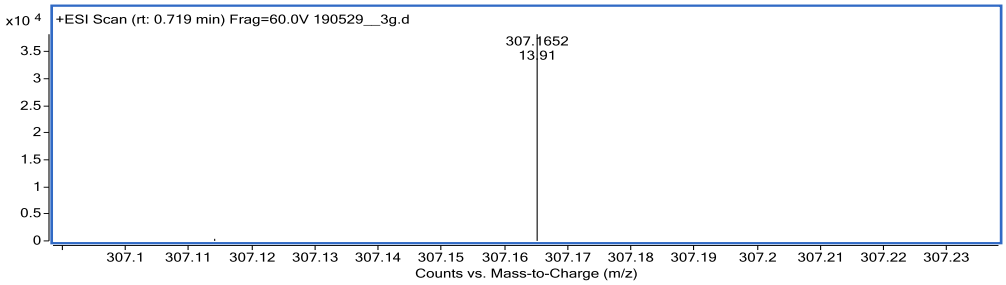

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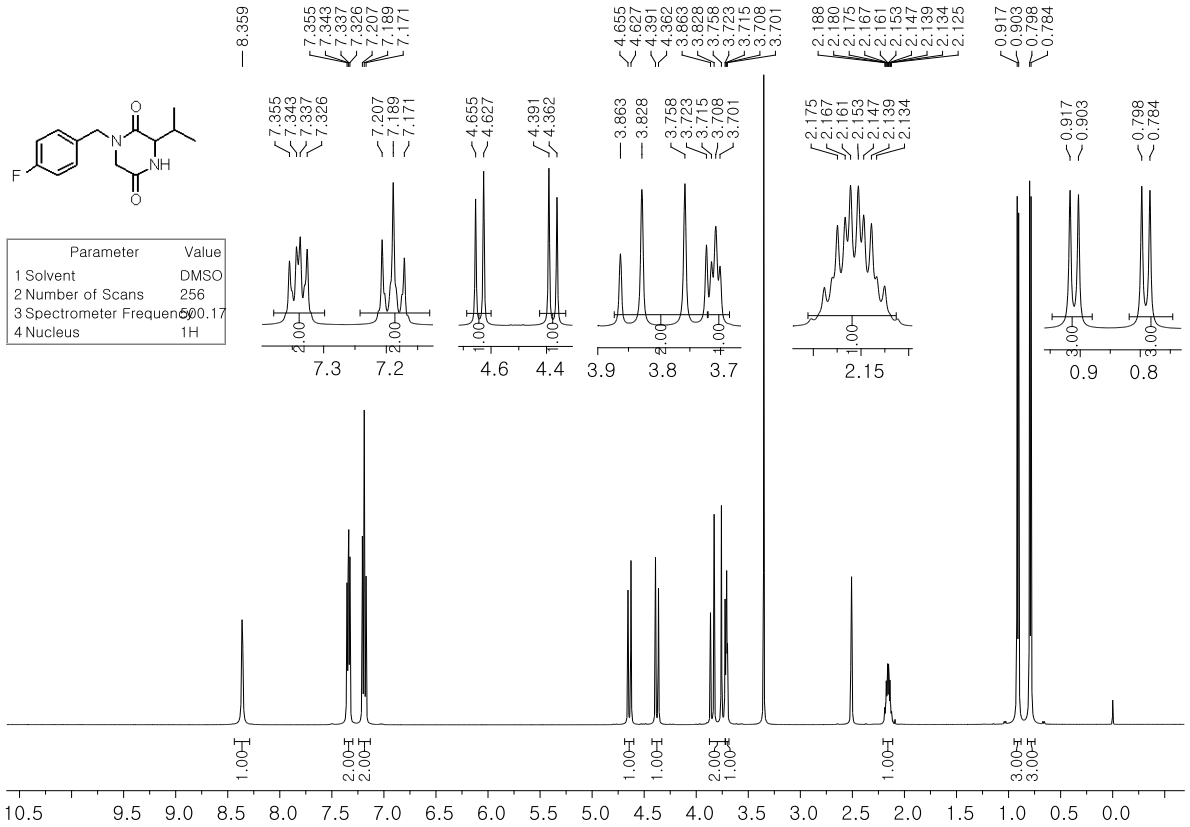
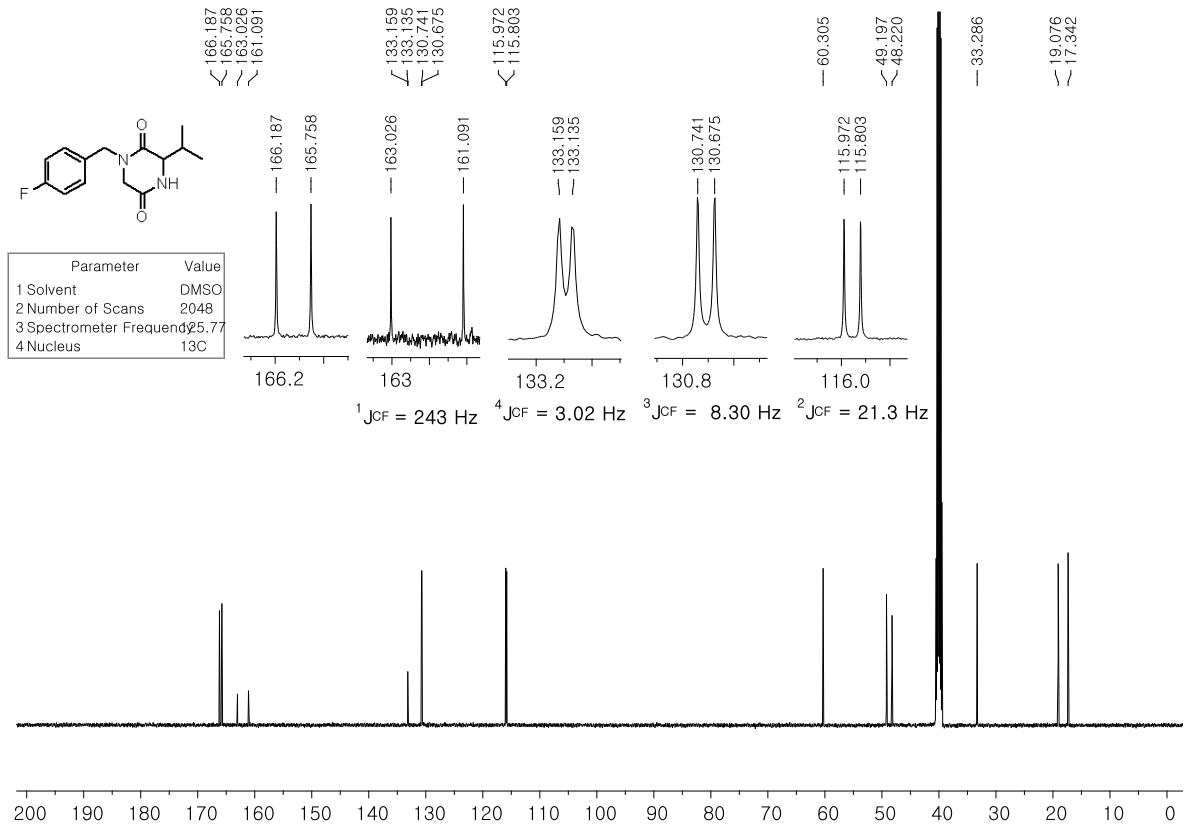


^{1}H NMR – 3h



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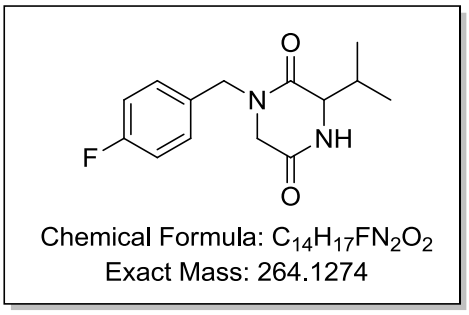
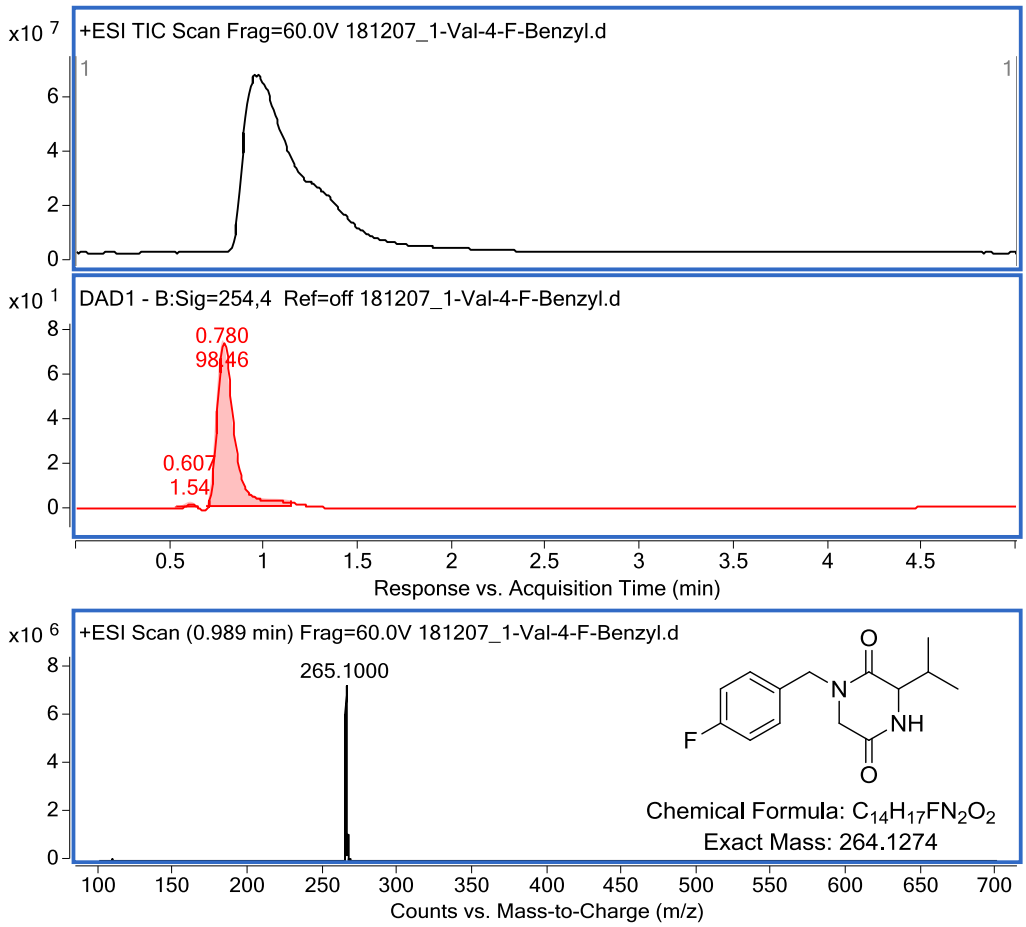
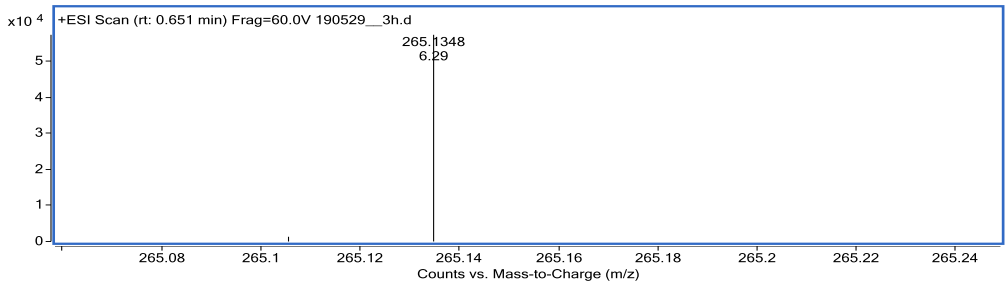
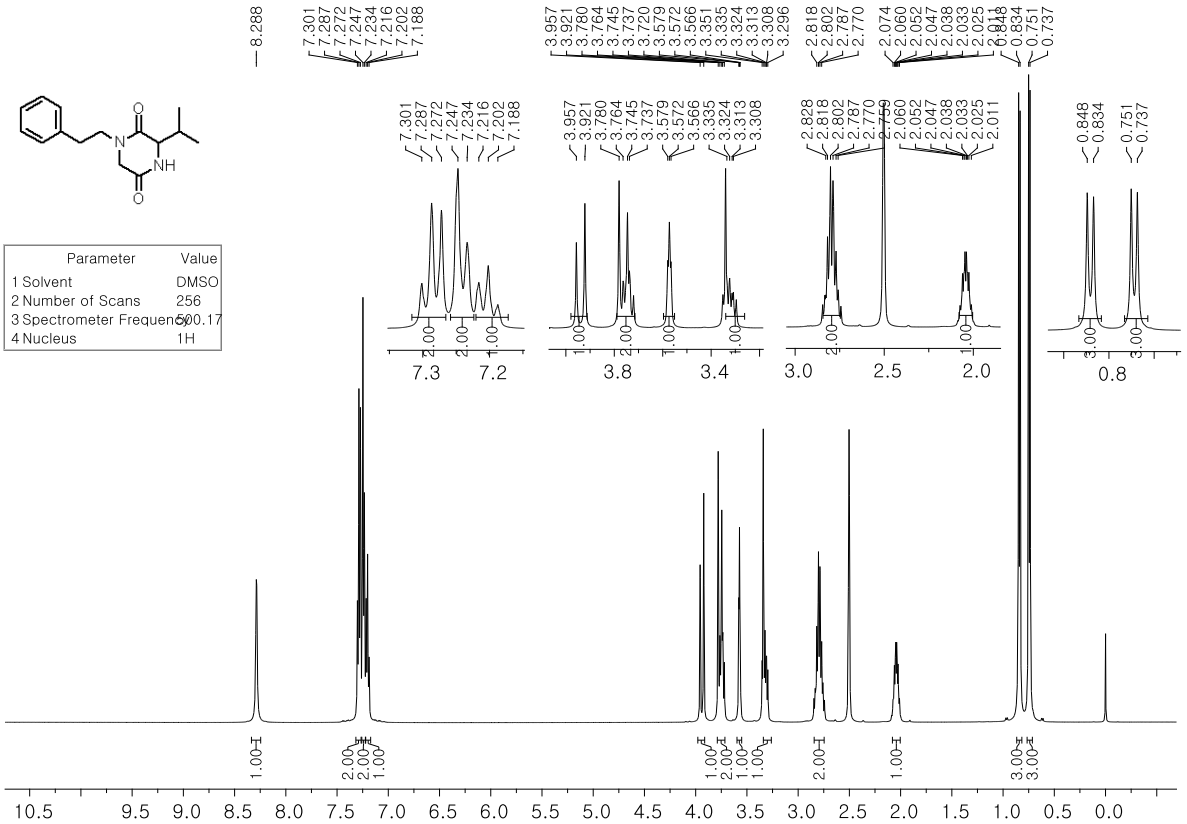




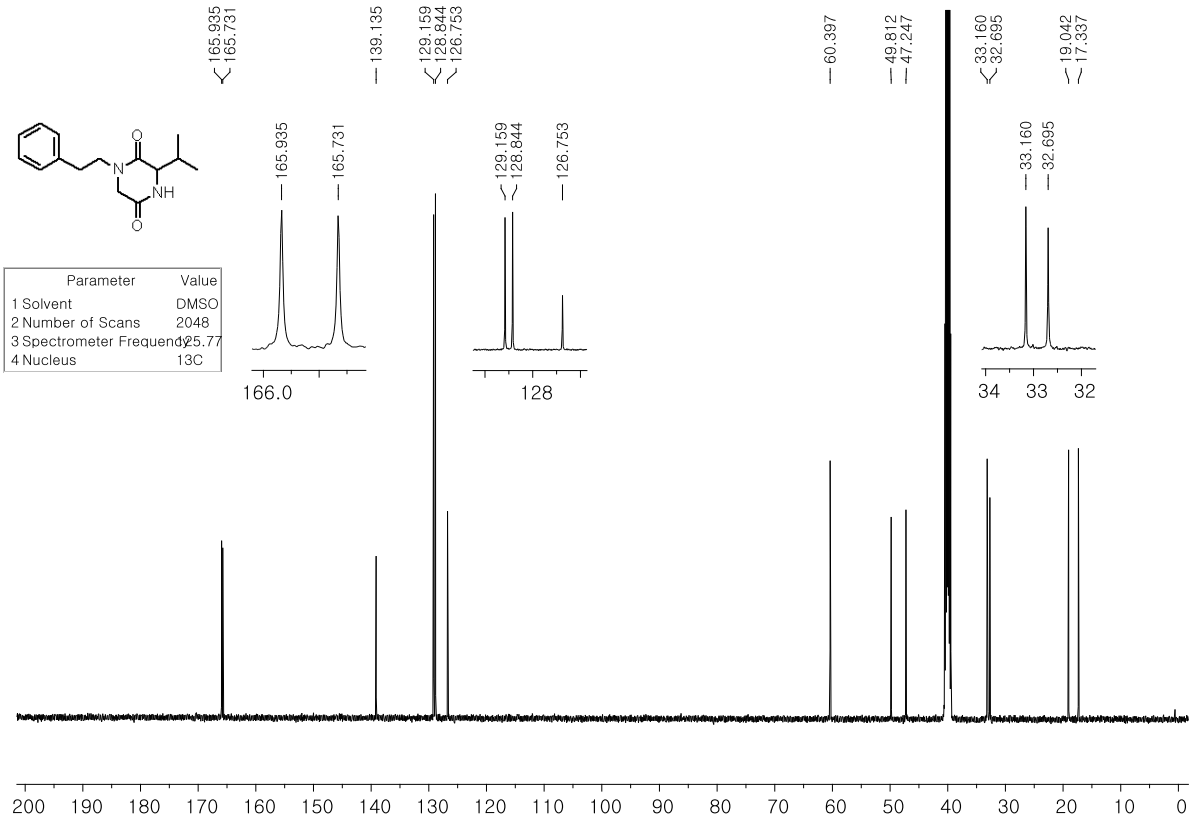
LC/MS – 3h



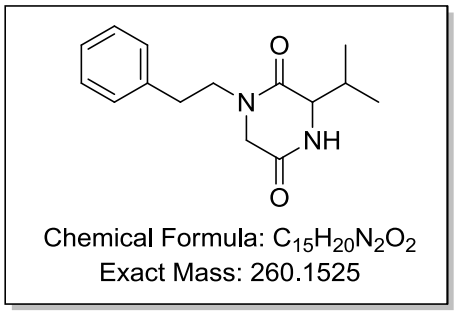
HRMS – 3h

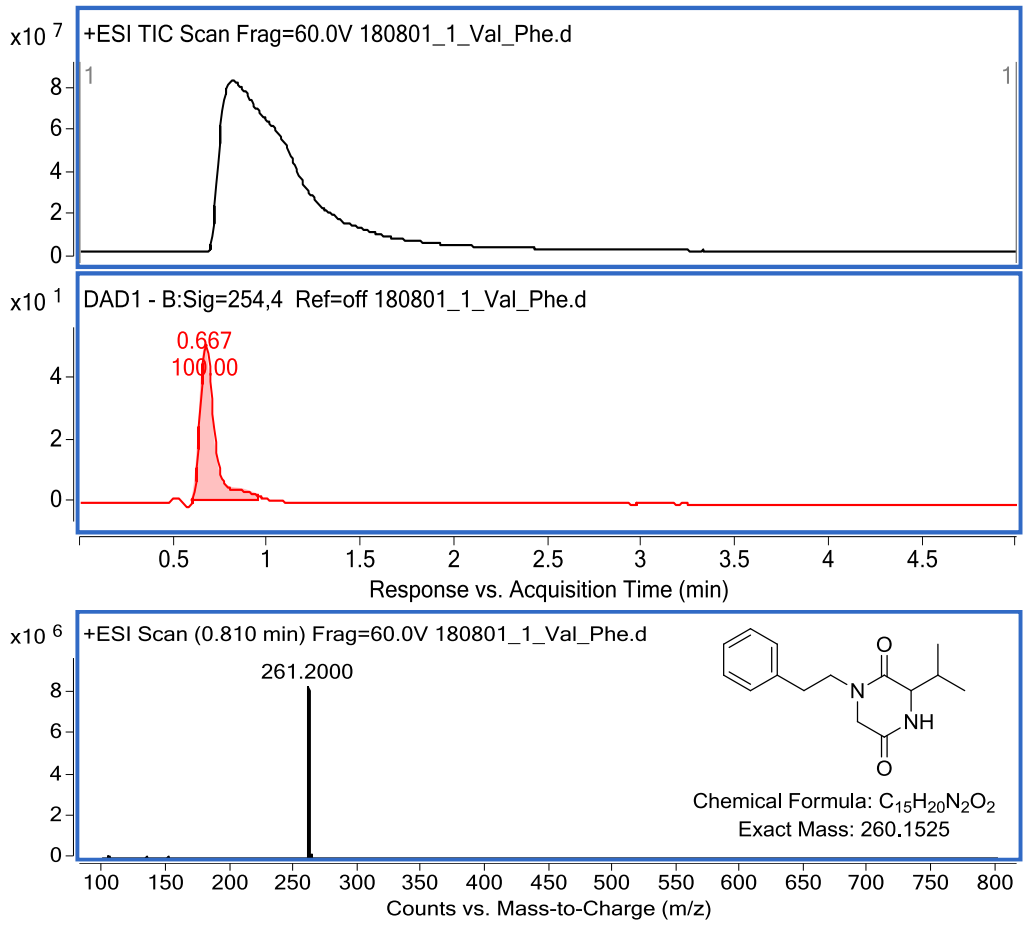


^{1}H NMR – 3i

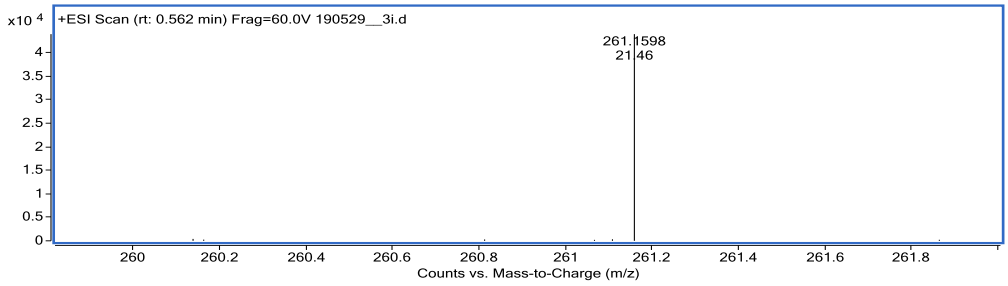


^{13}C NMR – 3i





LC/MS – 3i



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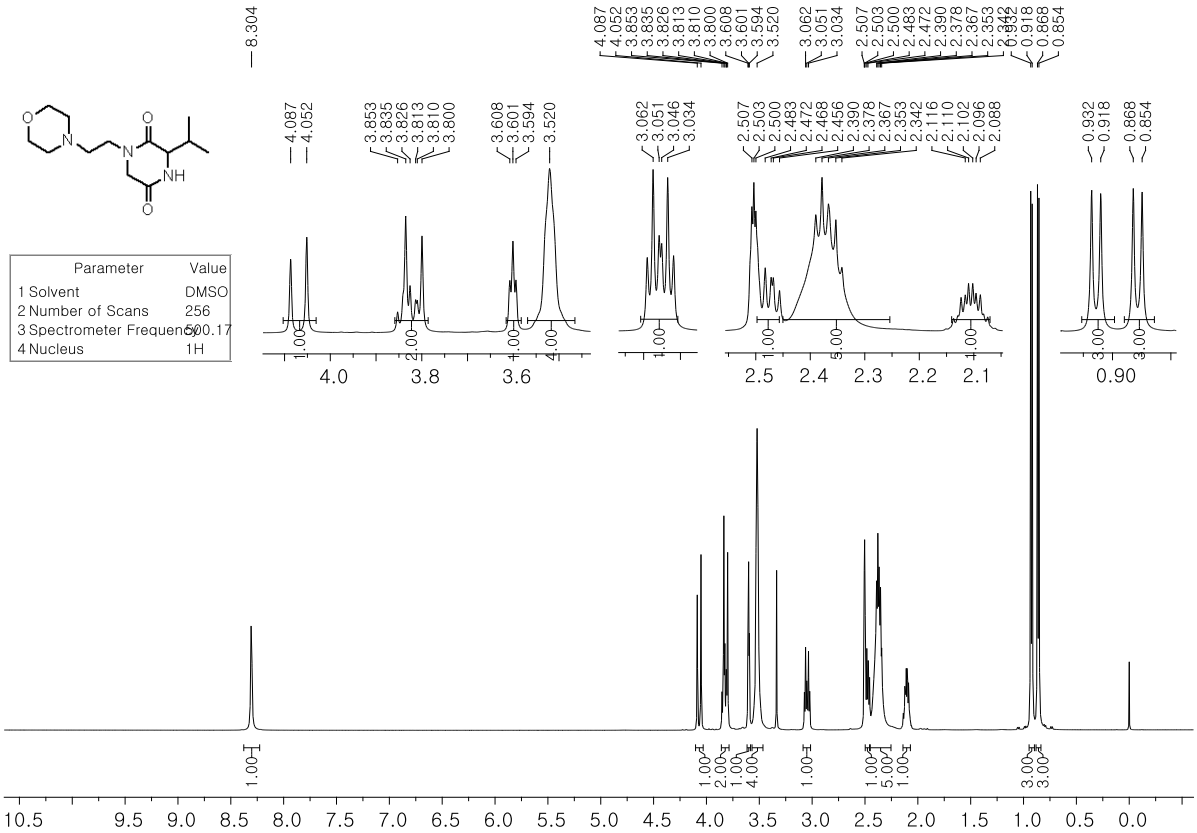

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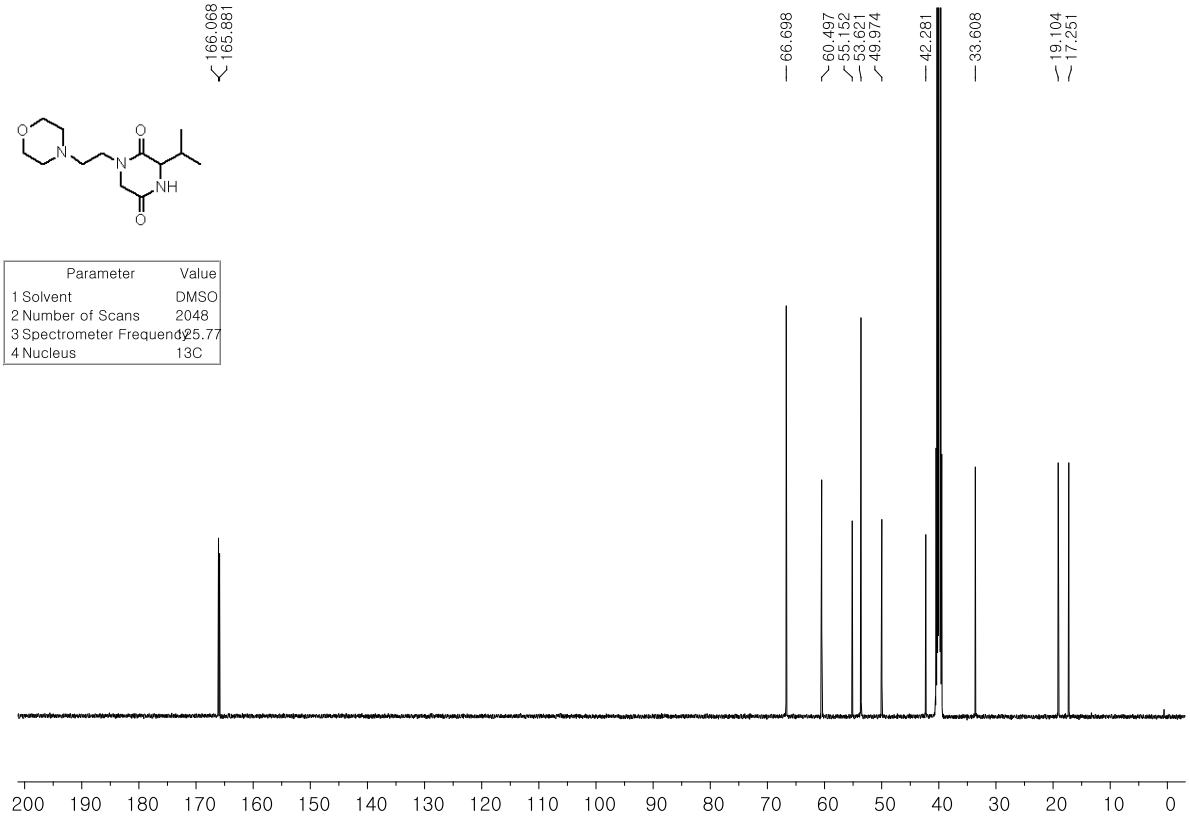
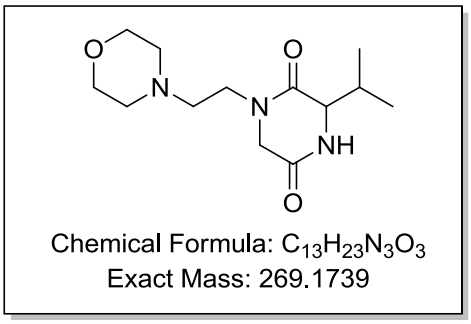
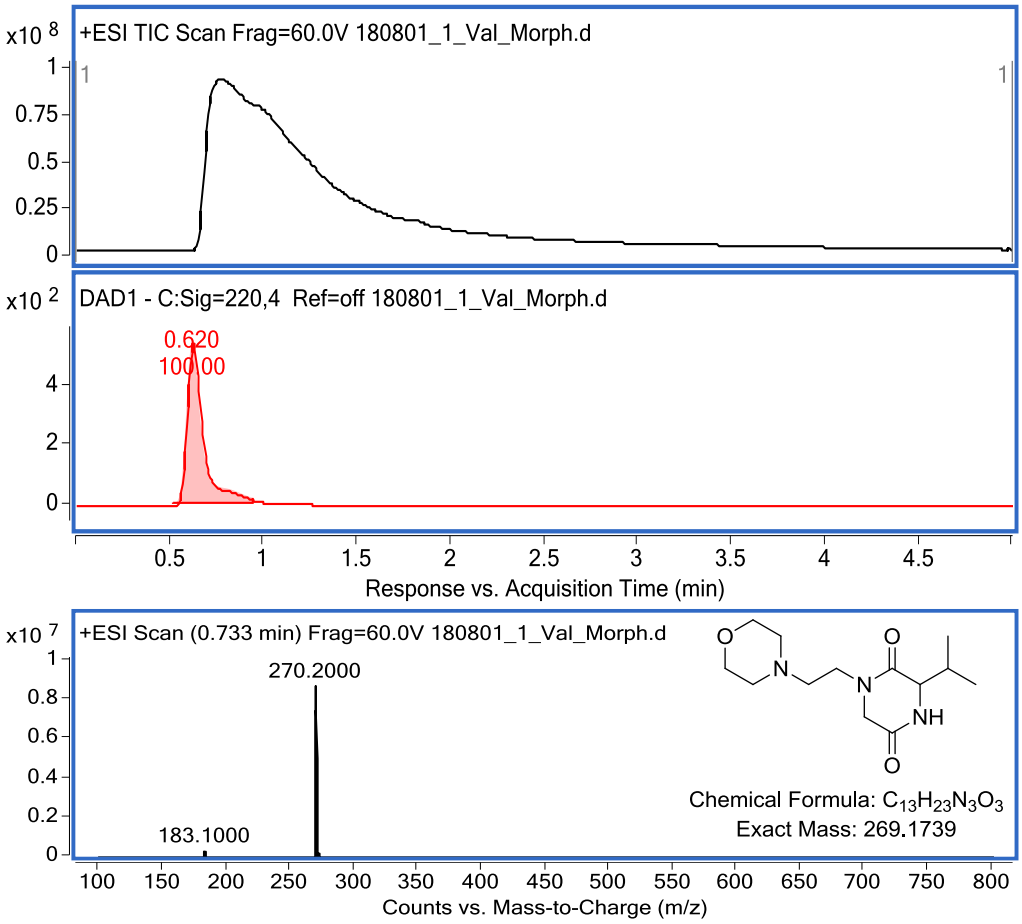
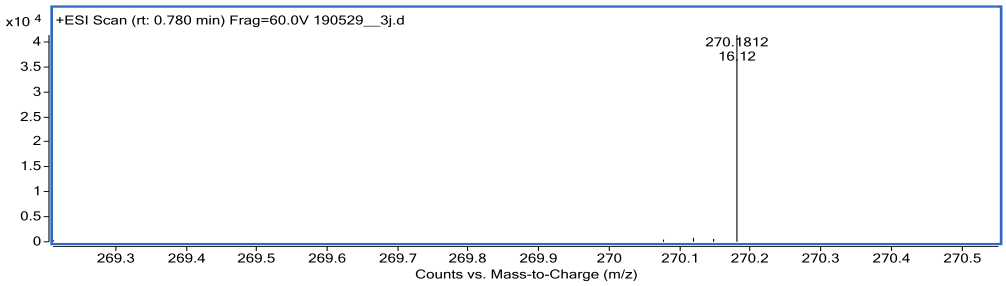


^{13}C NMR – 3j





LC/MS – 3j



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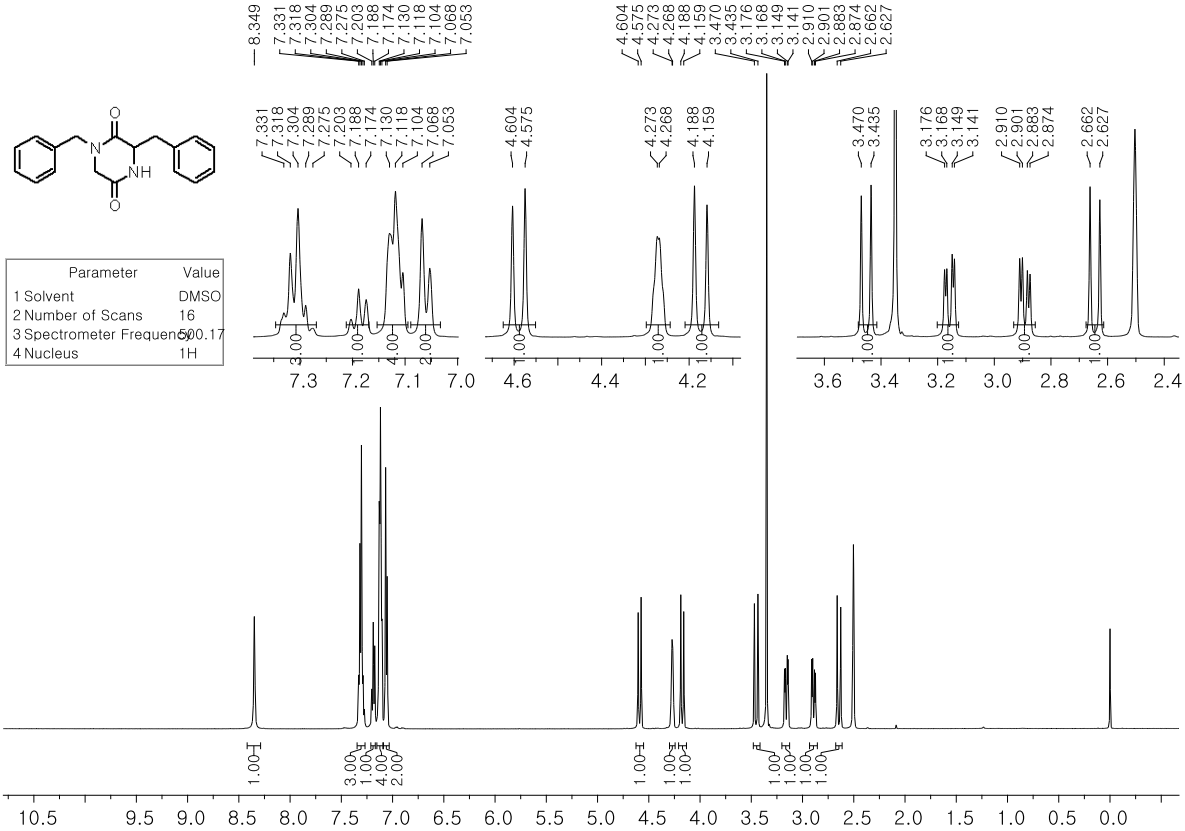
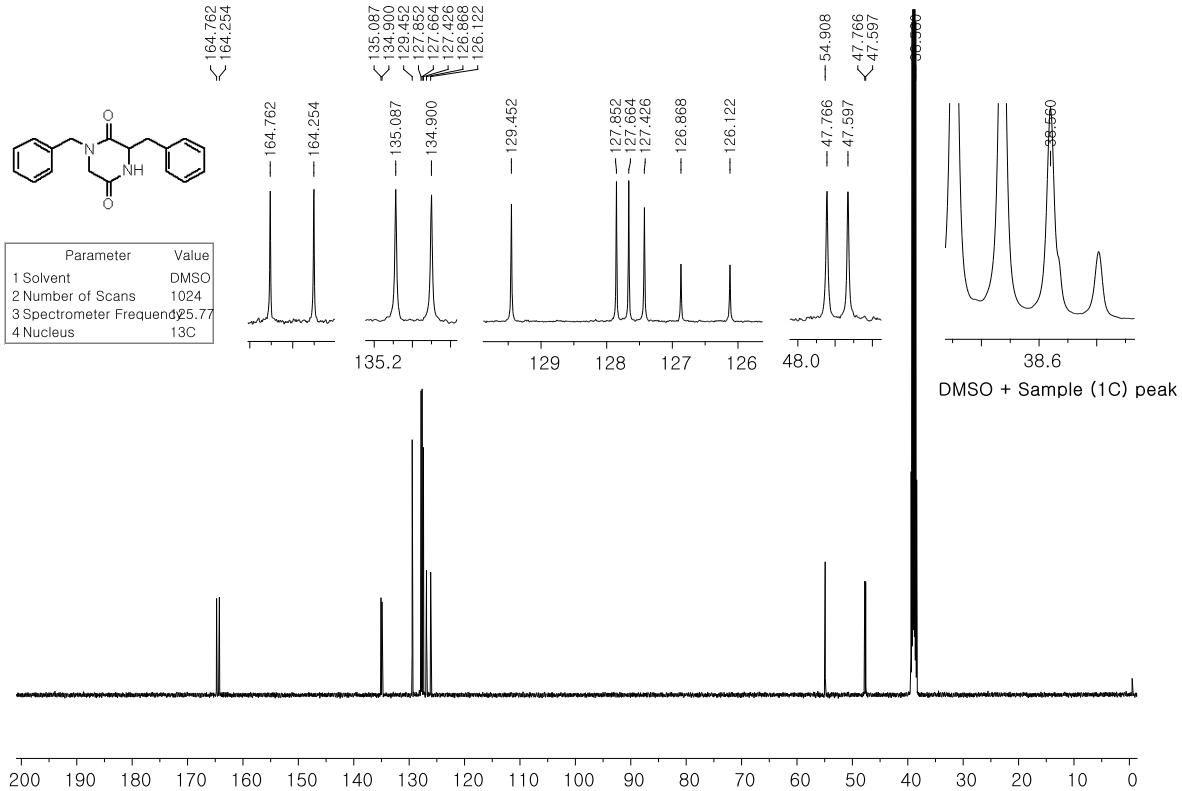
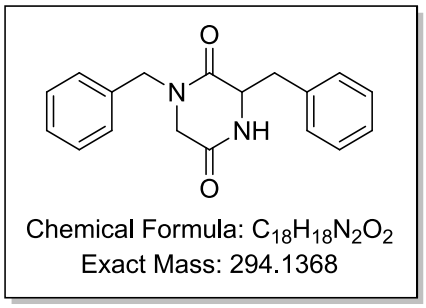
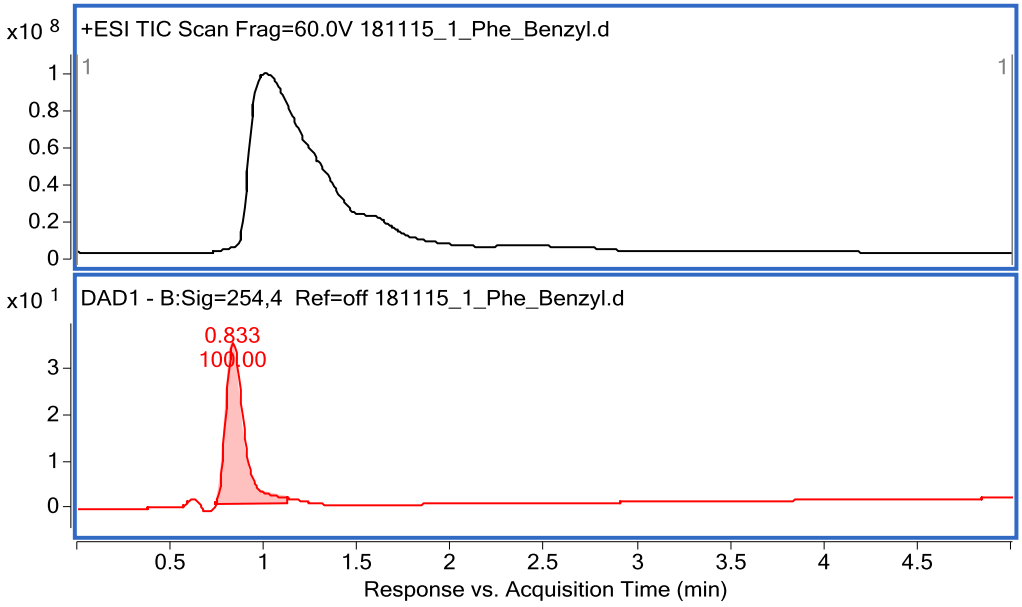


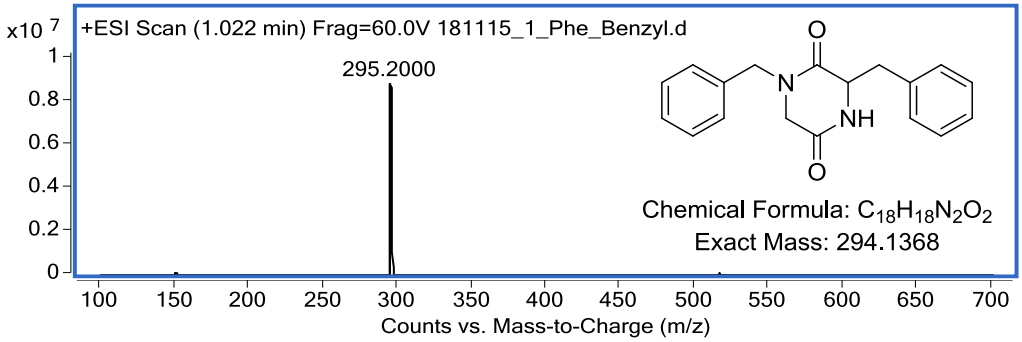
^{1}H NMR – 3k



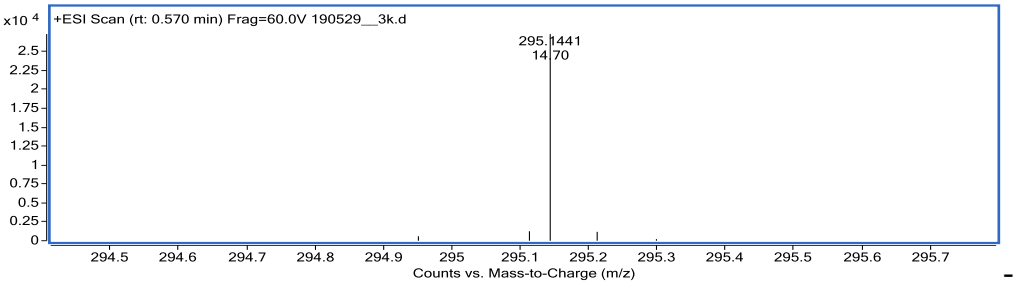
^{13}C NMR – 3k



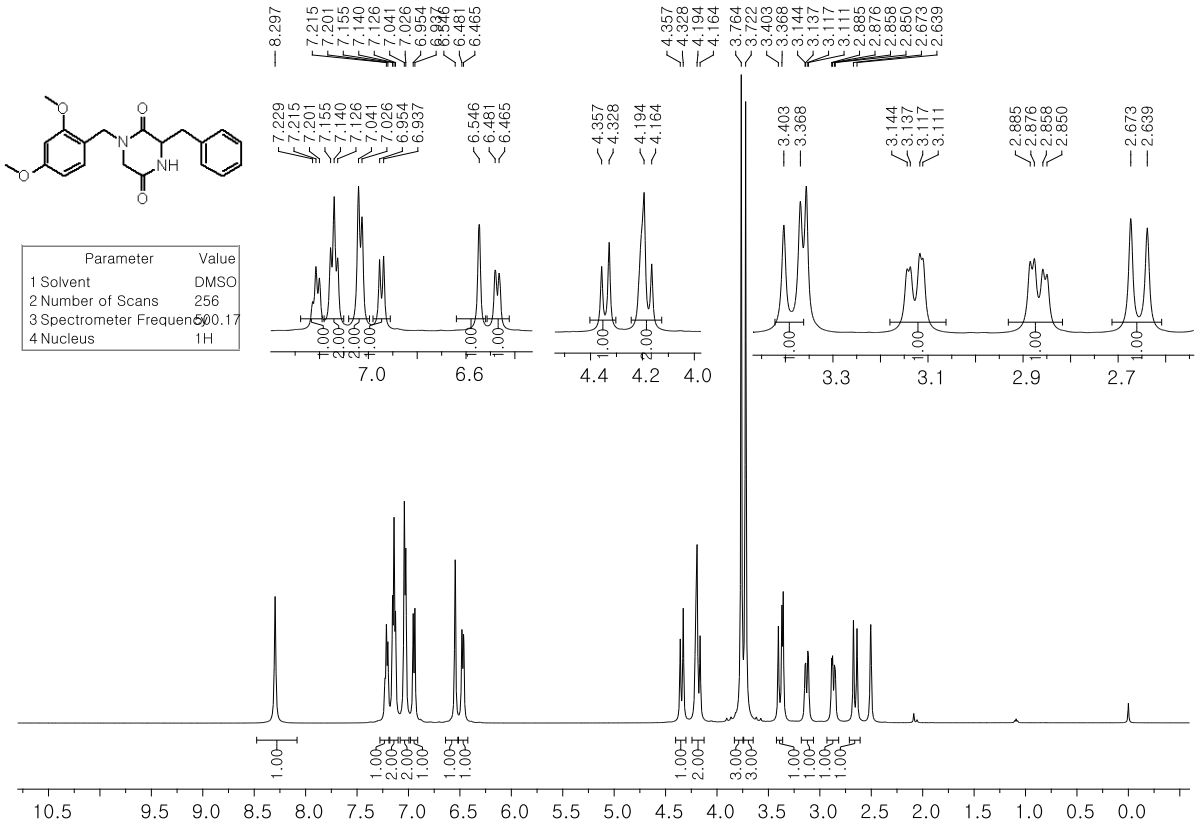




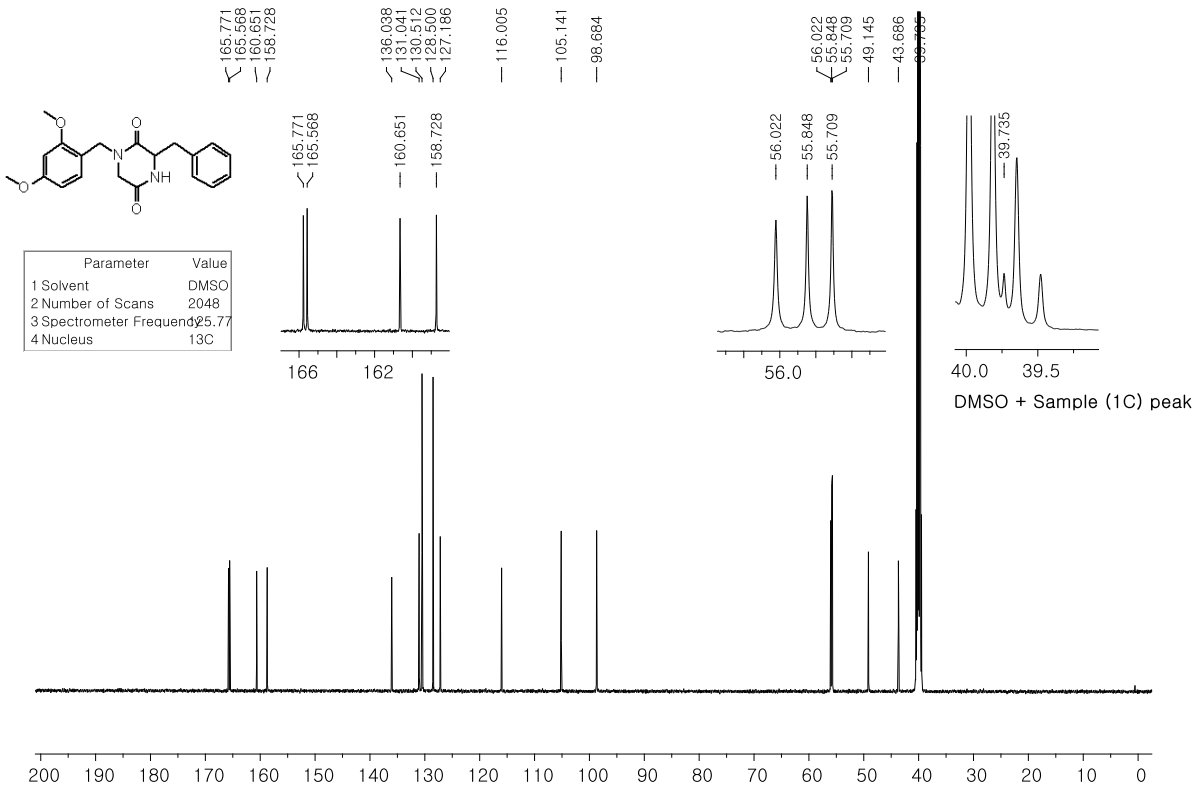
LC/MS – 3k



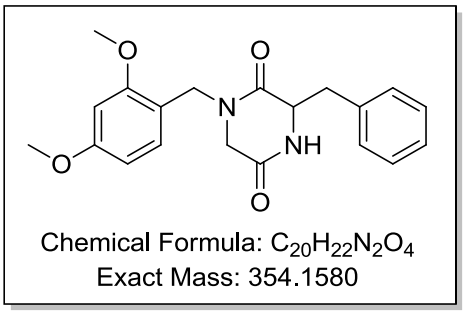
HRMS – 3k

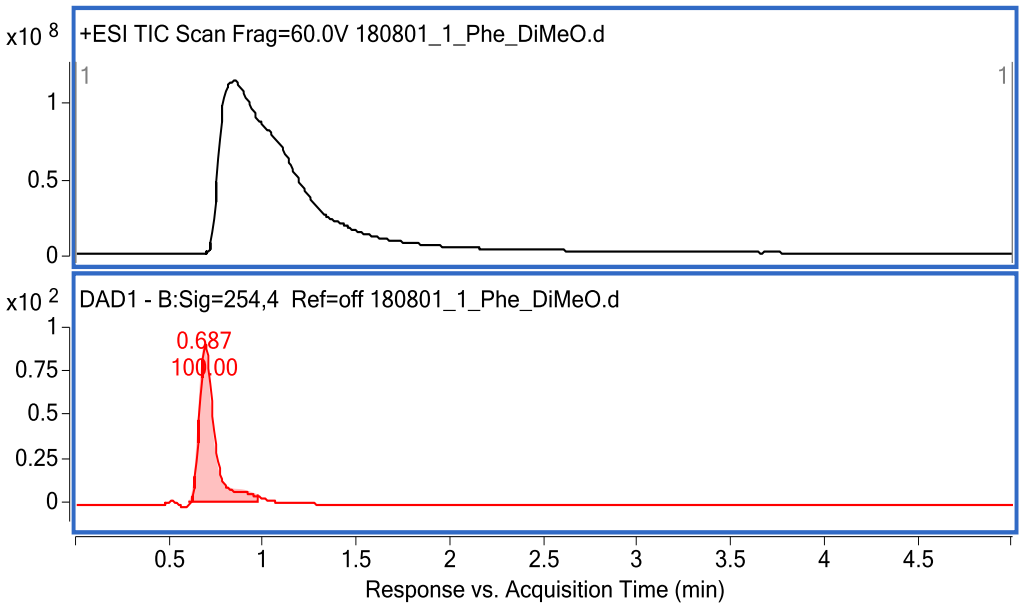


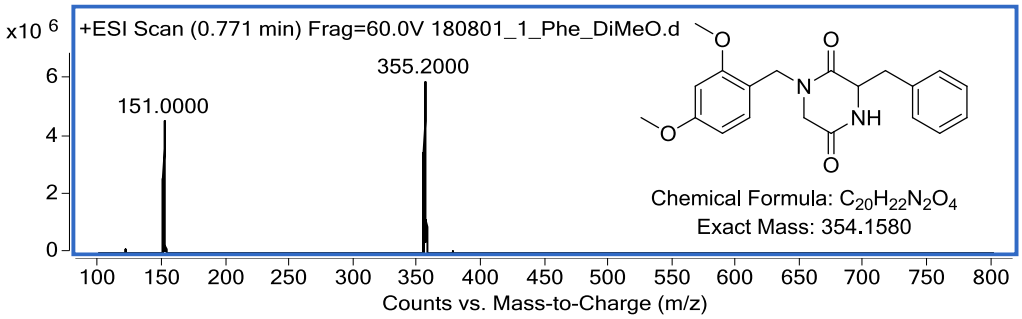
^{1}H NMR – 3l



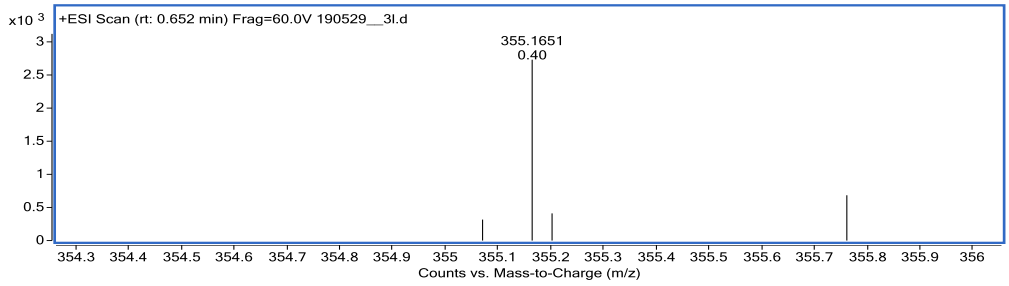
^{13}C NMR – 3l



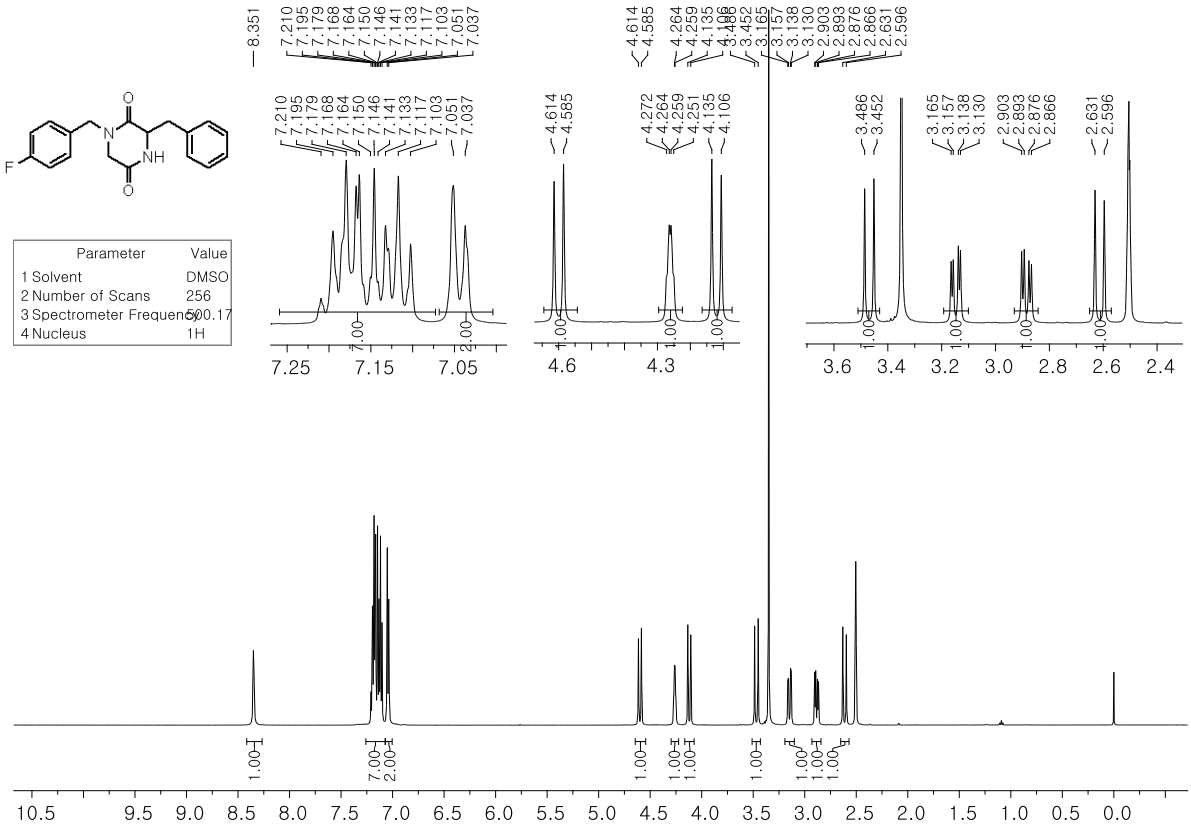




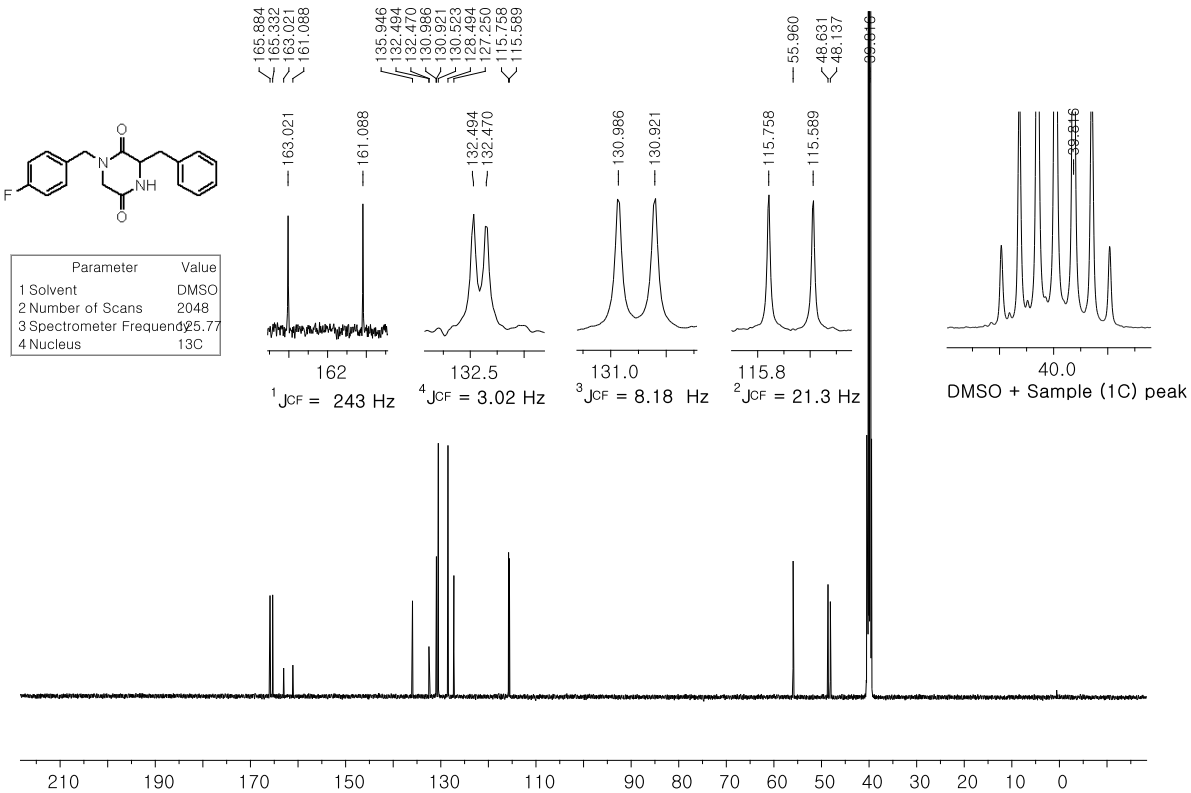
LC/MS – 3l



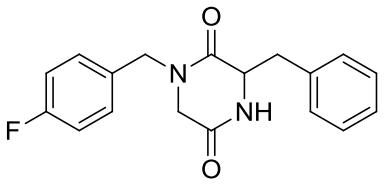
HRMS – 3l



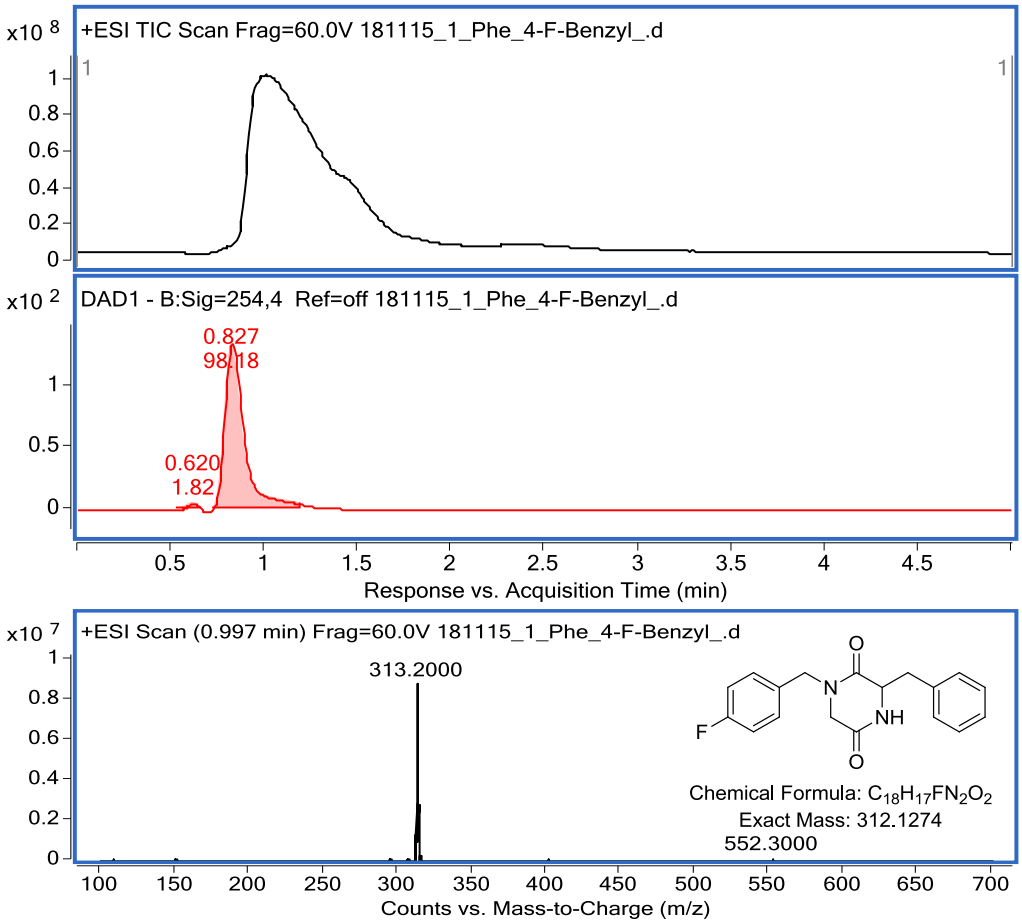
^{1}H NMR – 3m



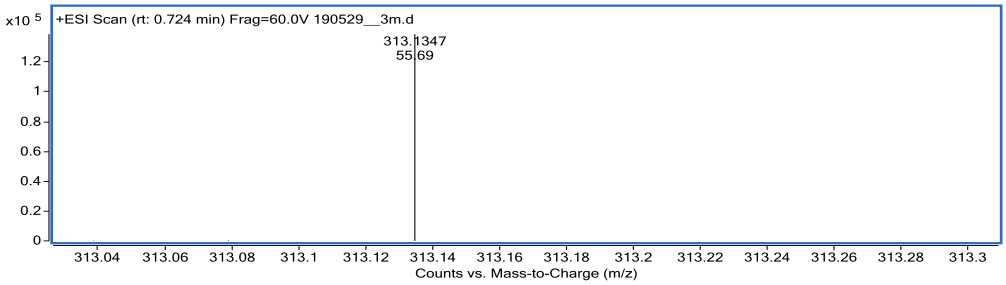
^{13}C NMR – 3m



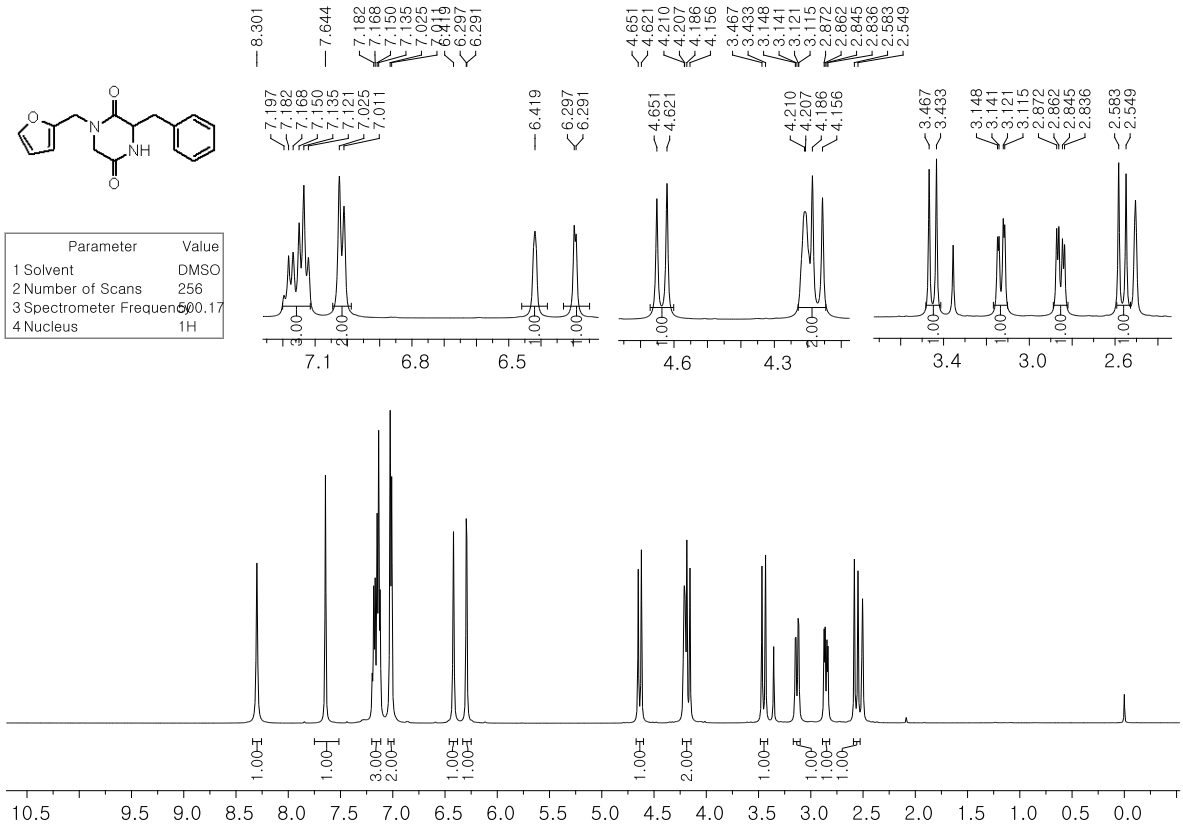
Chemical Formula: $C_{18}H_{17}FN_2O_2$
Exact Mass: 312.1274



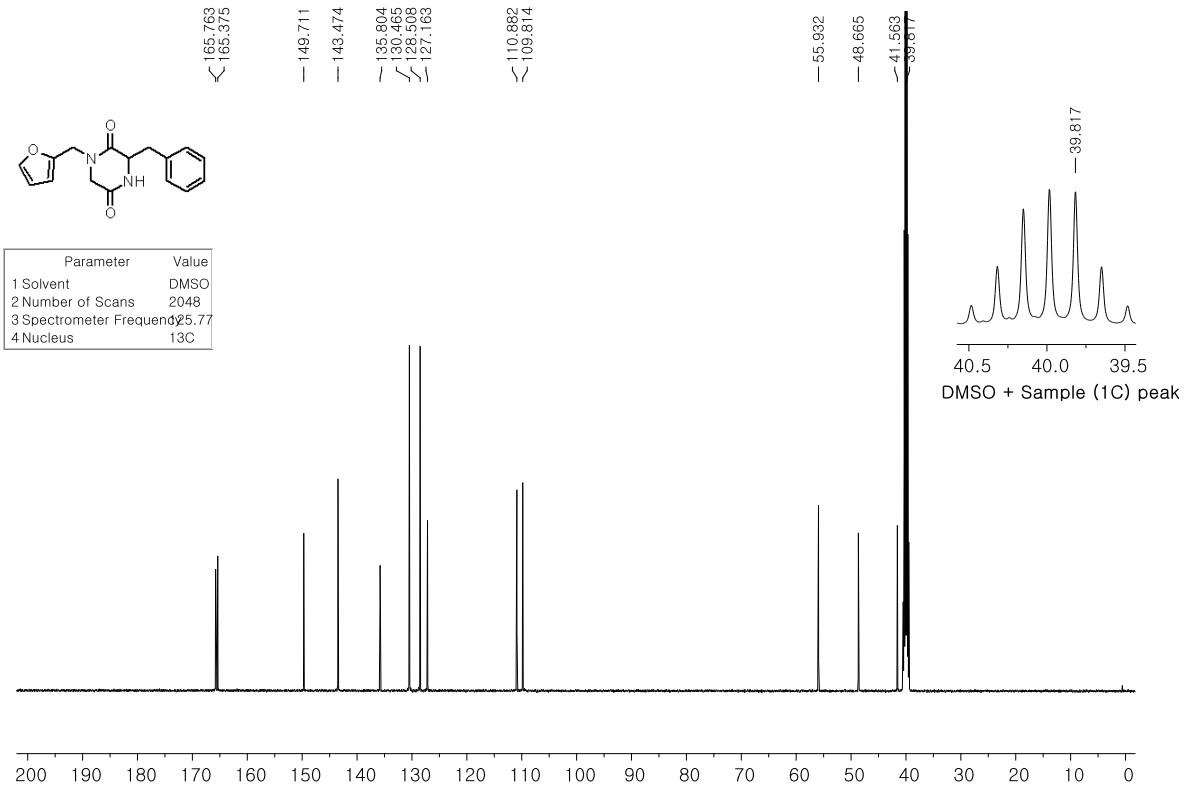
LC/MS – 3m



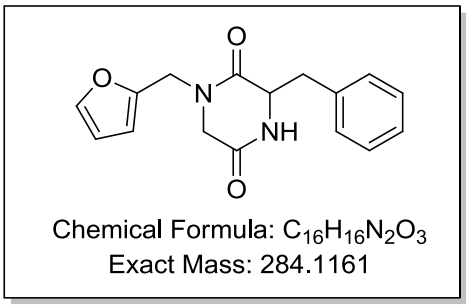
HRMS – 3m

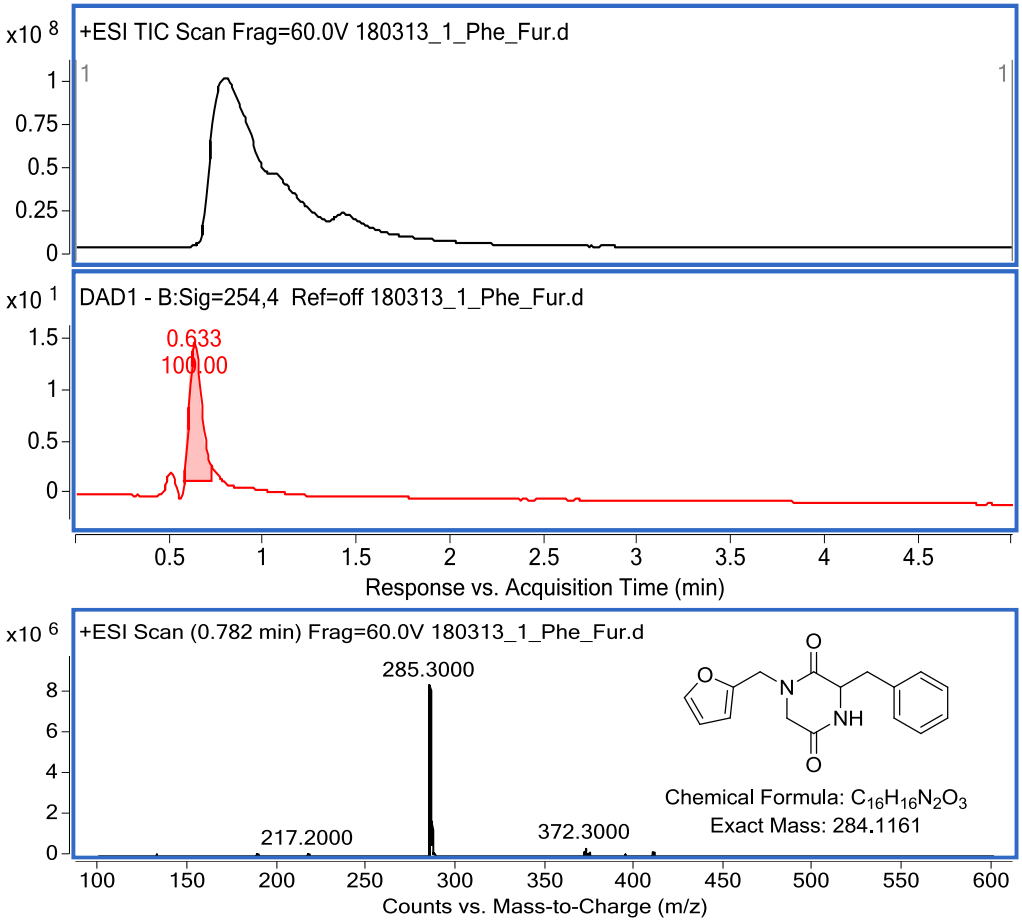


^{1}H NMR – 3n

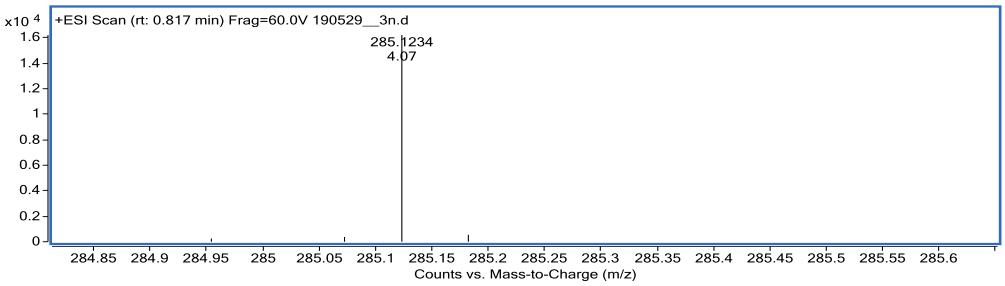


^{13}C NMR – 3n

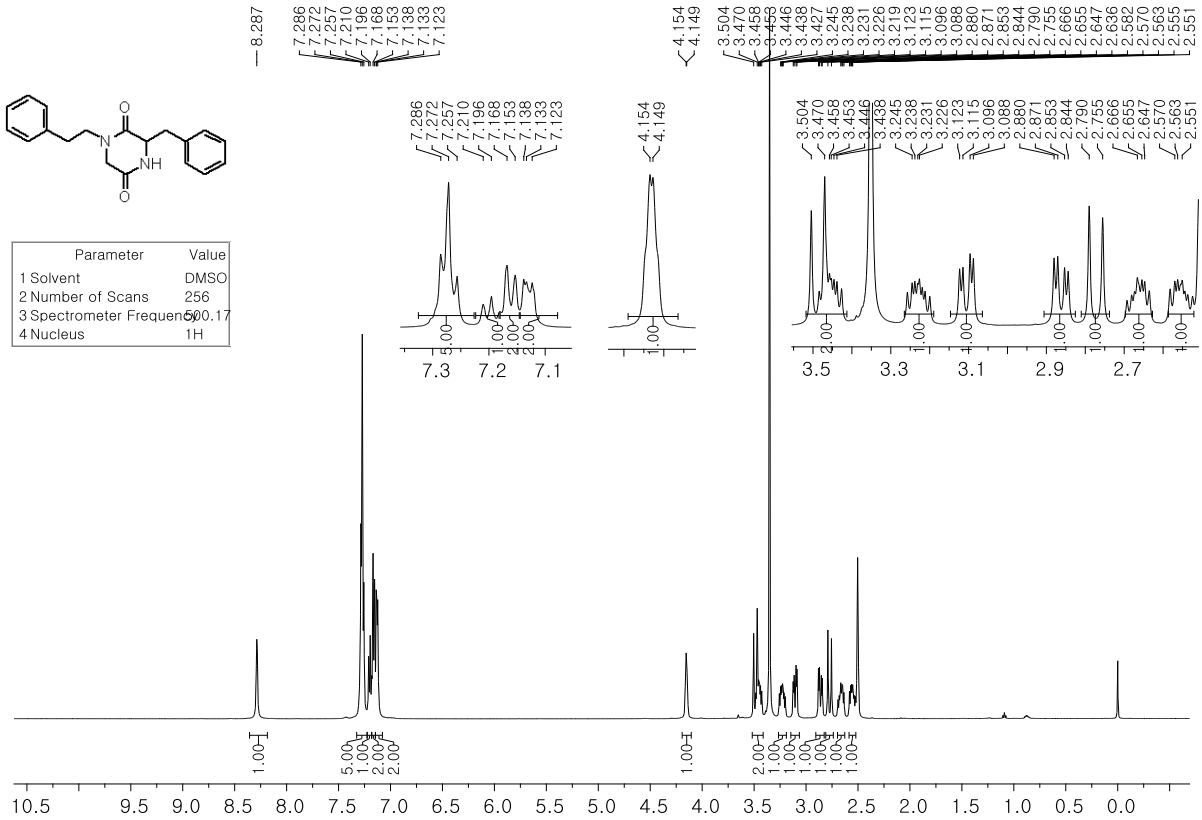




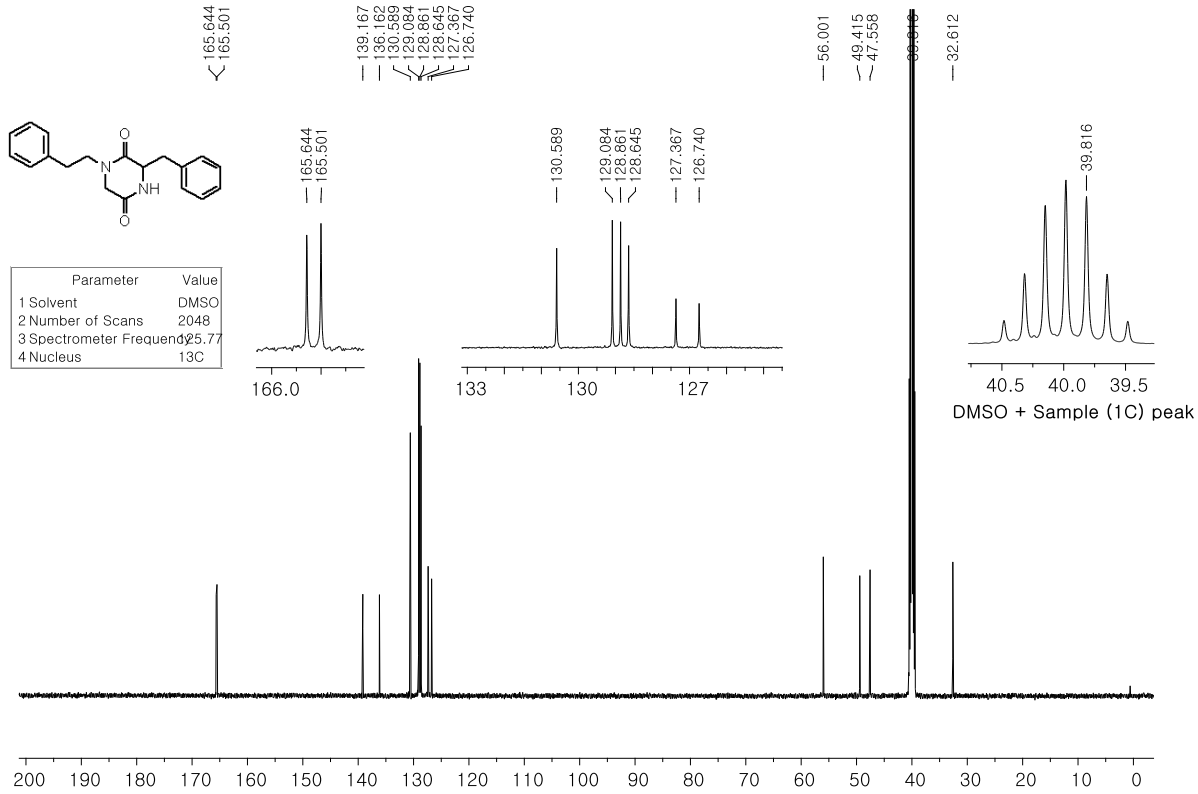
LC/MS – 3n



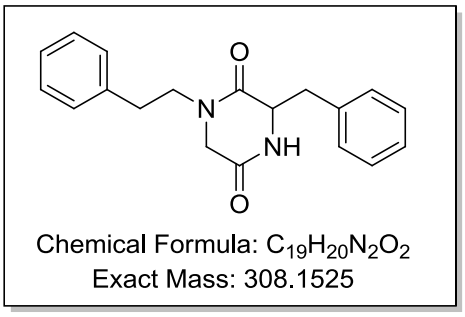
HRMS – 3n

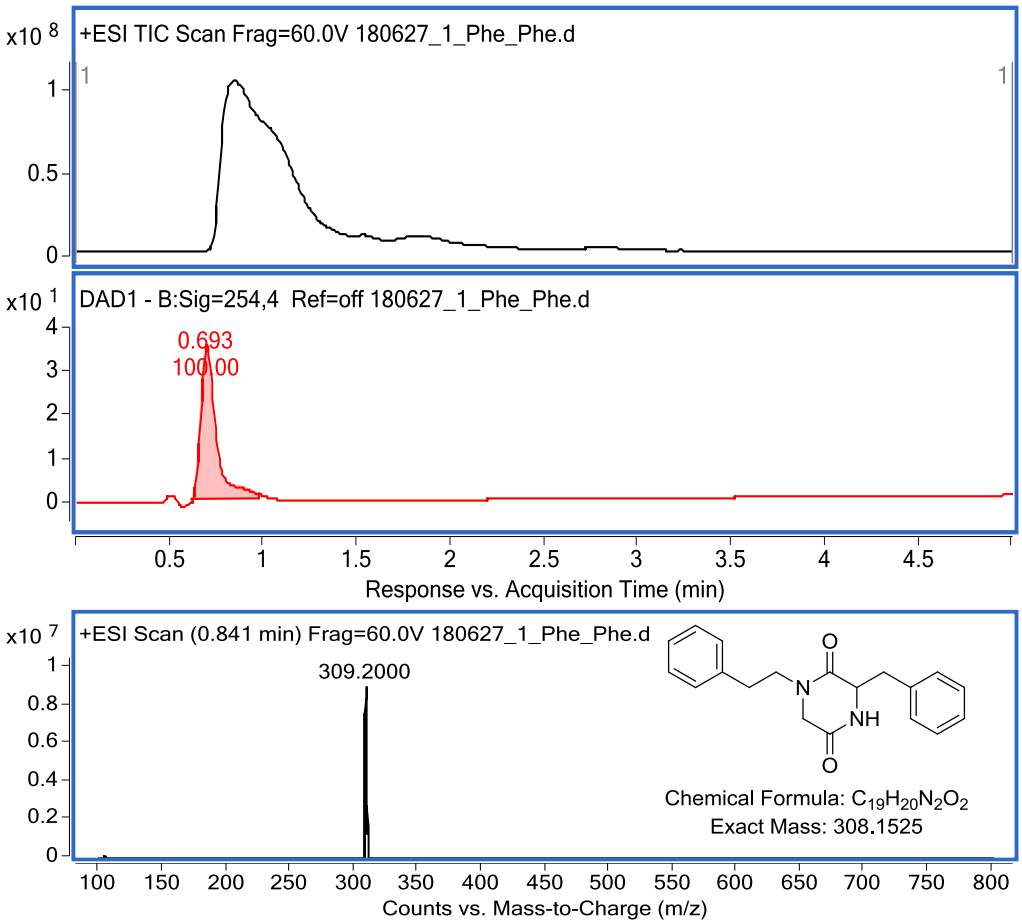


^{1}H NMR – 3o

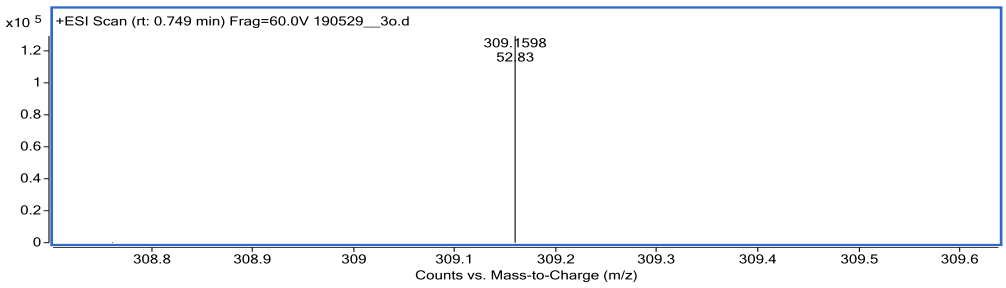


^{13}C NMR – 3o

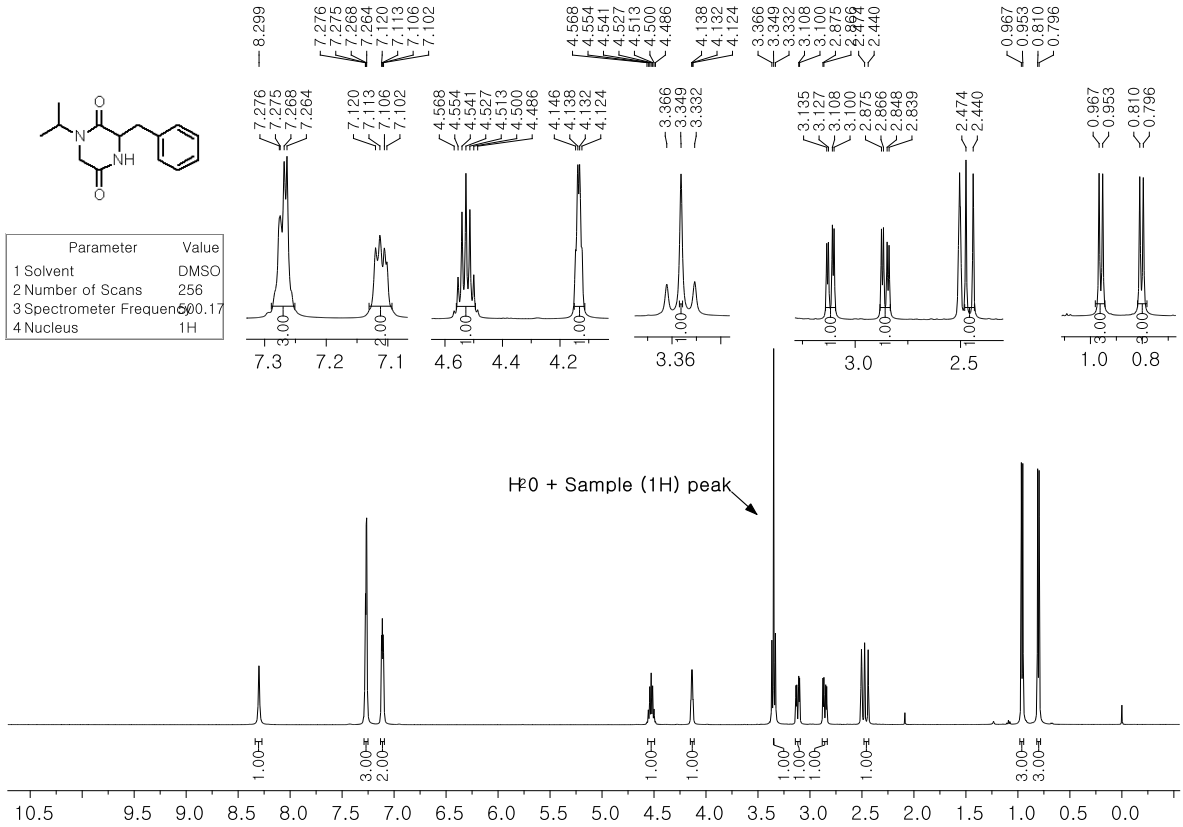




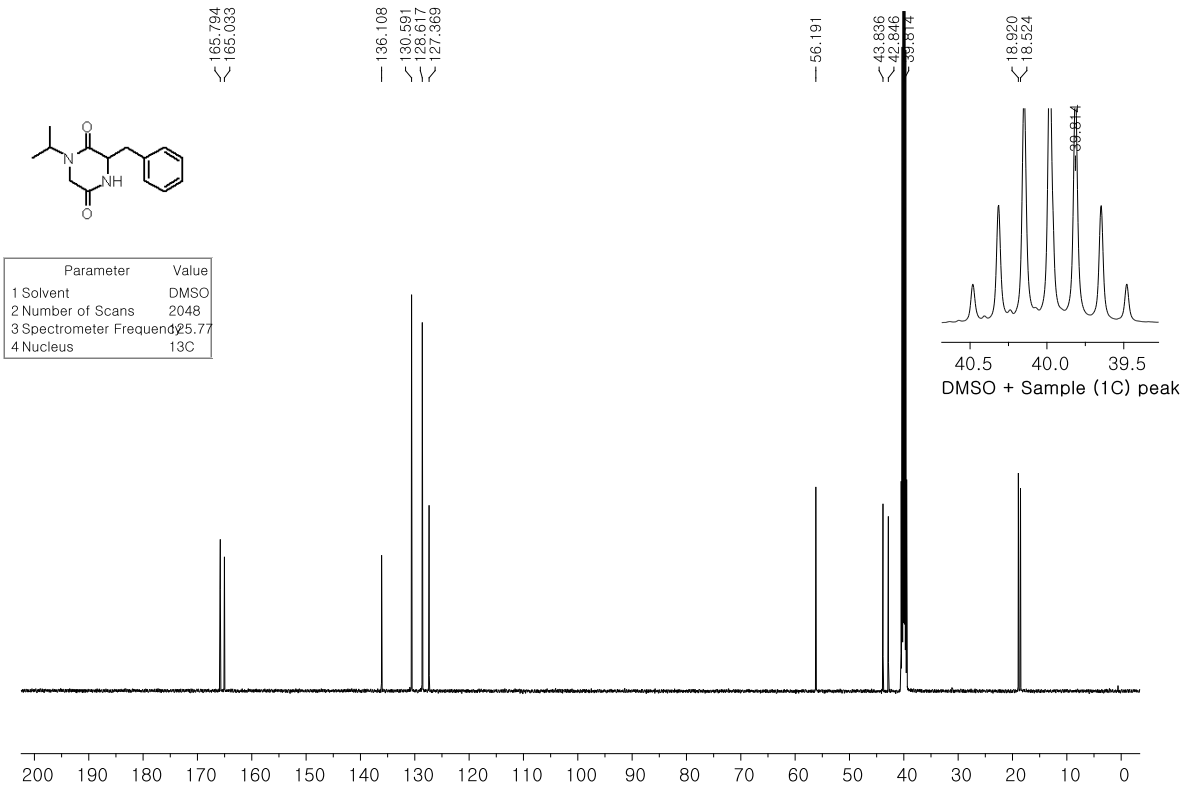
LC/MS – 3o



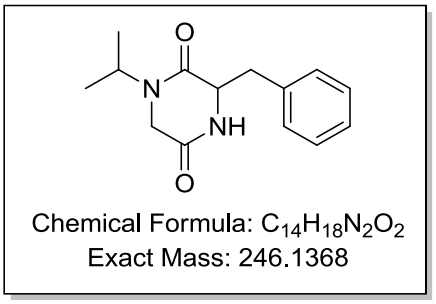
HRMS – 3o

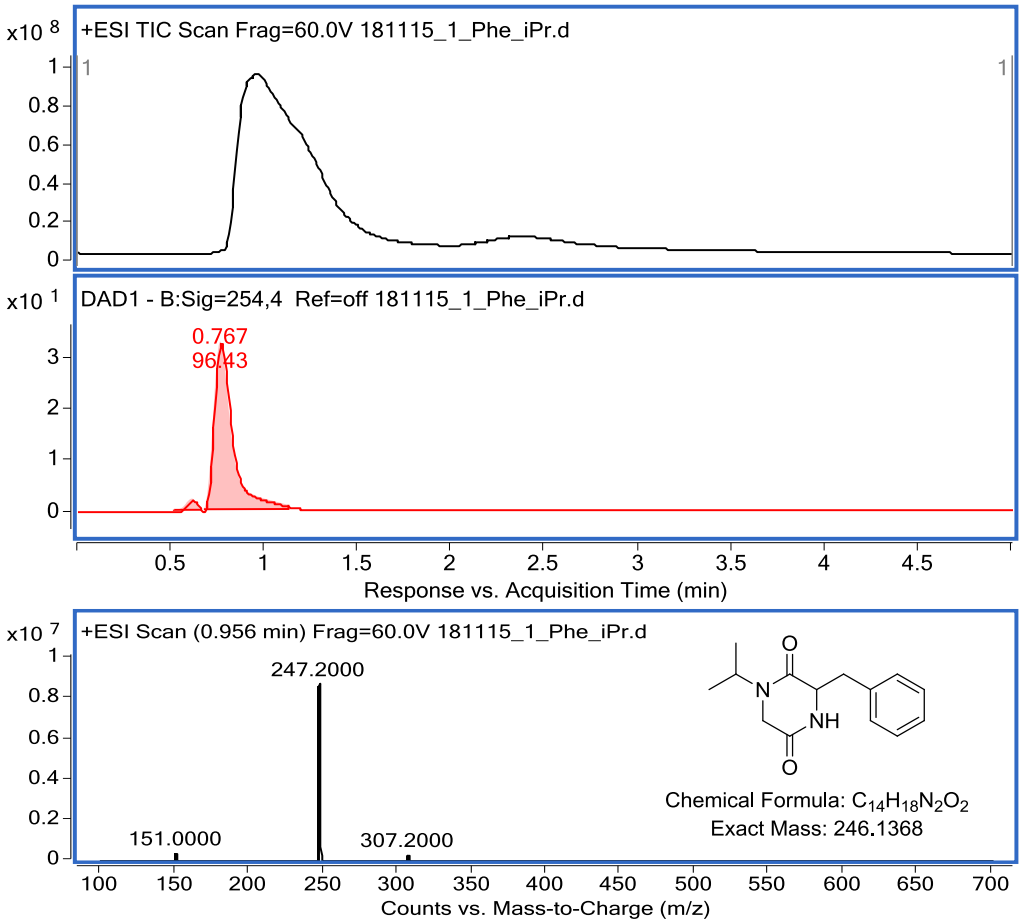


^{1}H NMR – 3p

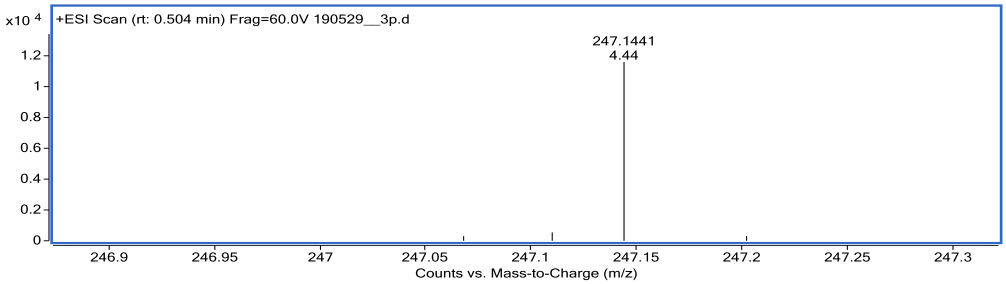


^{13}C NMR – 3p

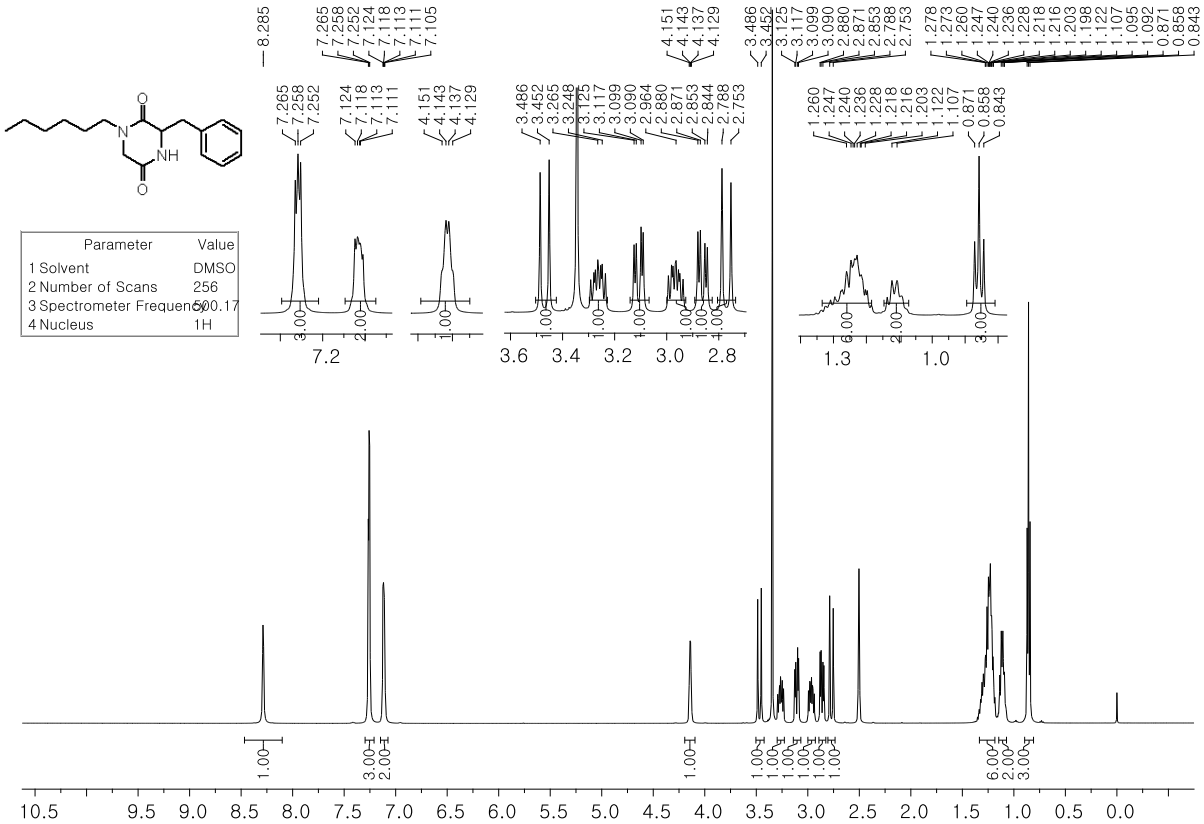




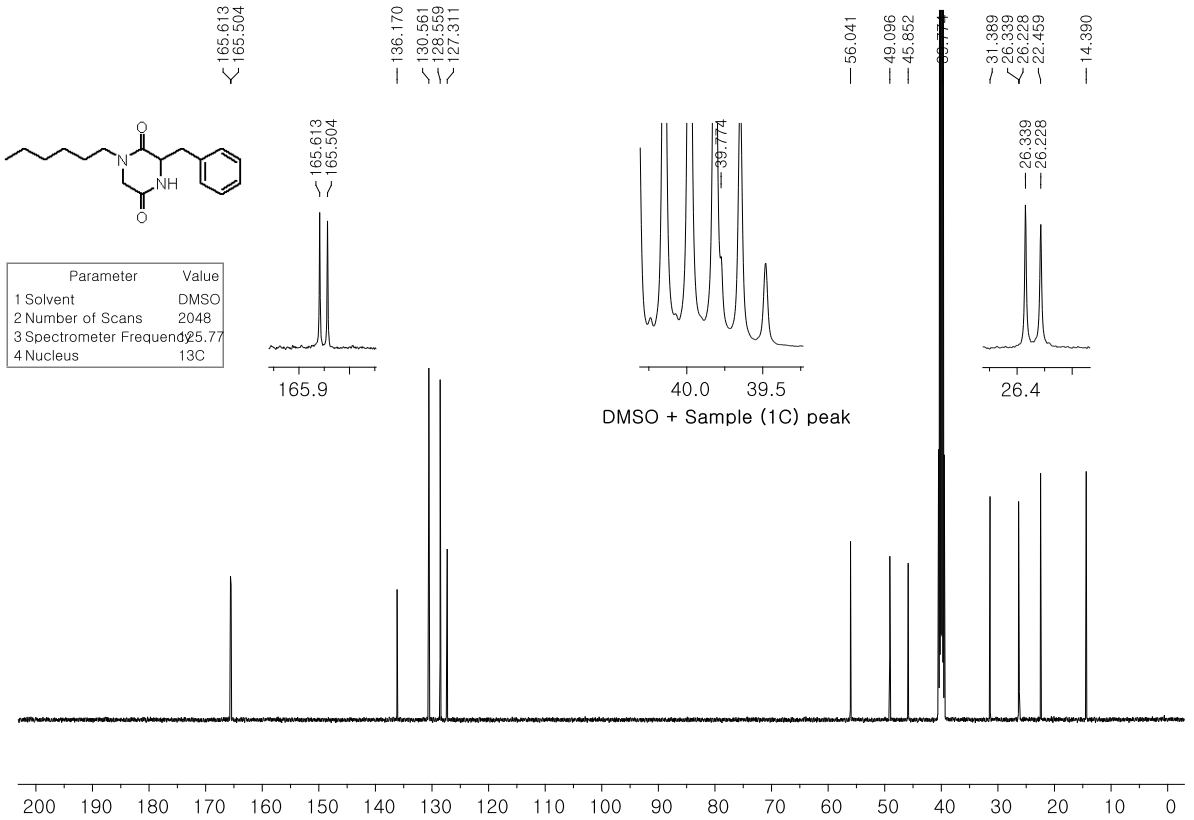
LC/MS – 3p



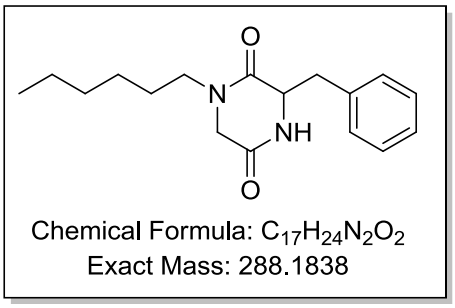
HRMS – 3p

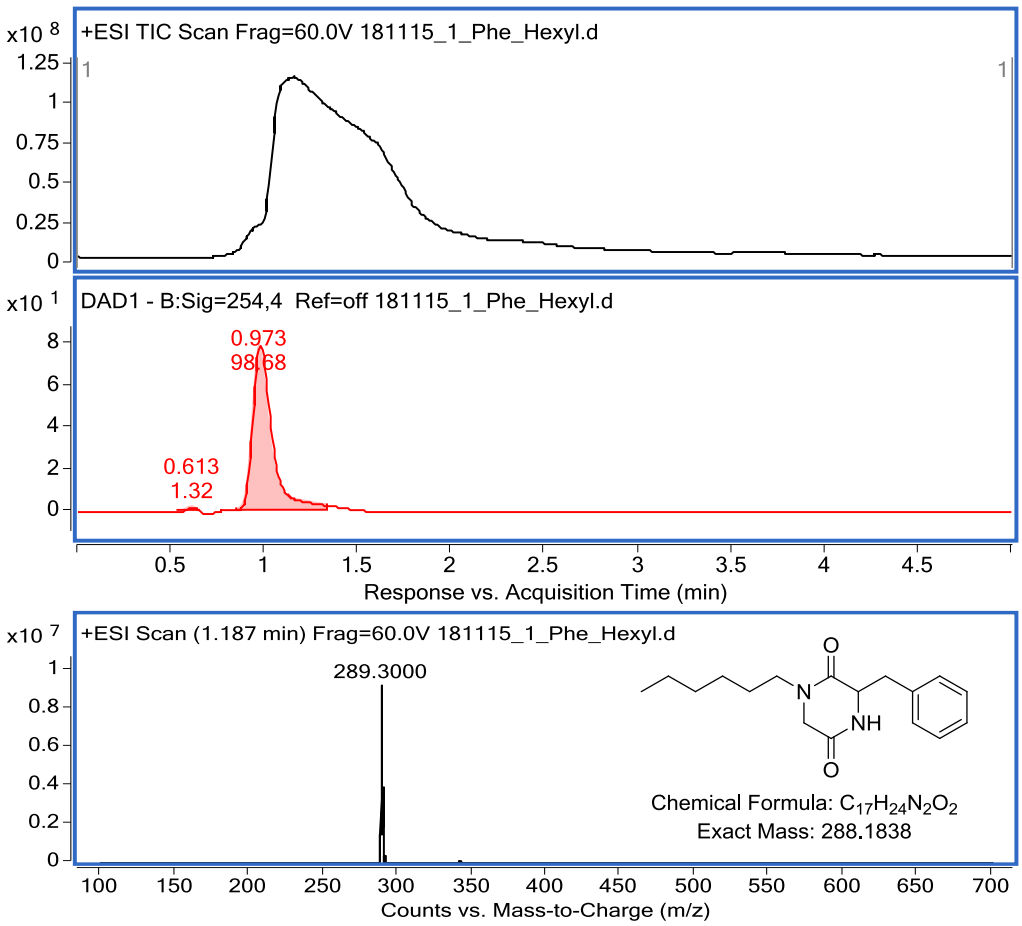


^{1}H NMR – 3q

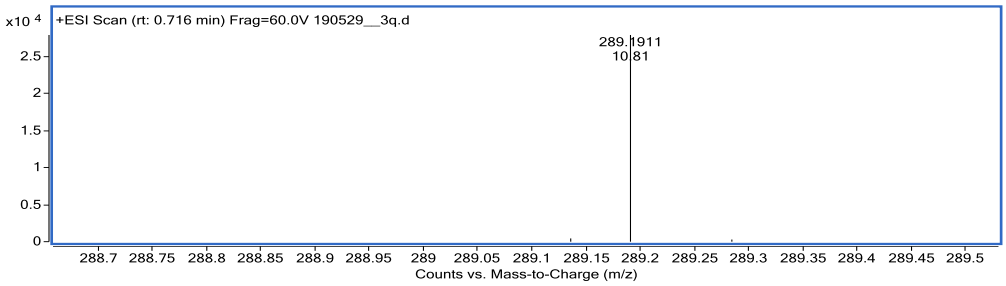


^{13}C NMR – 3q

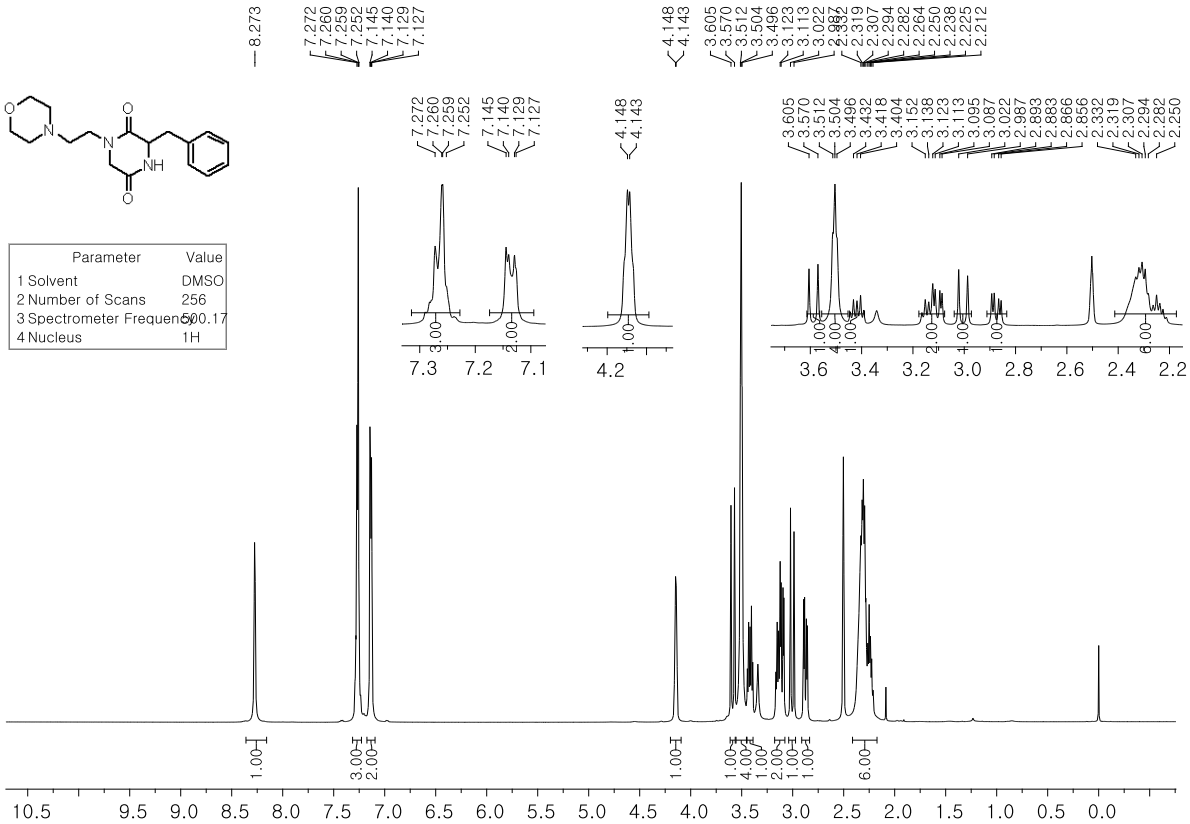




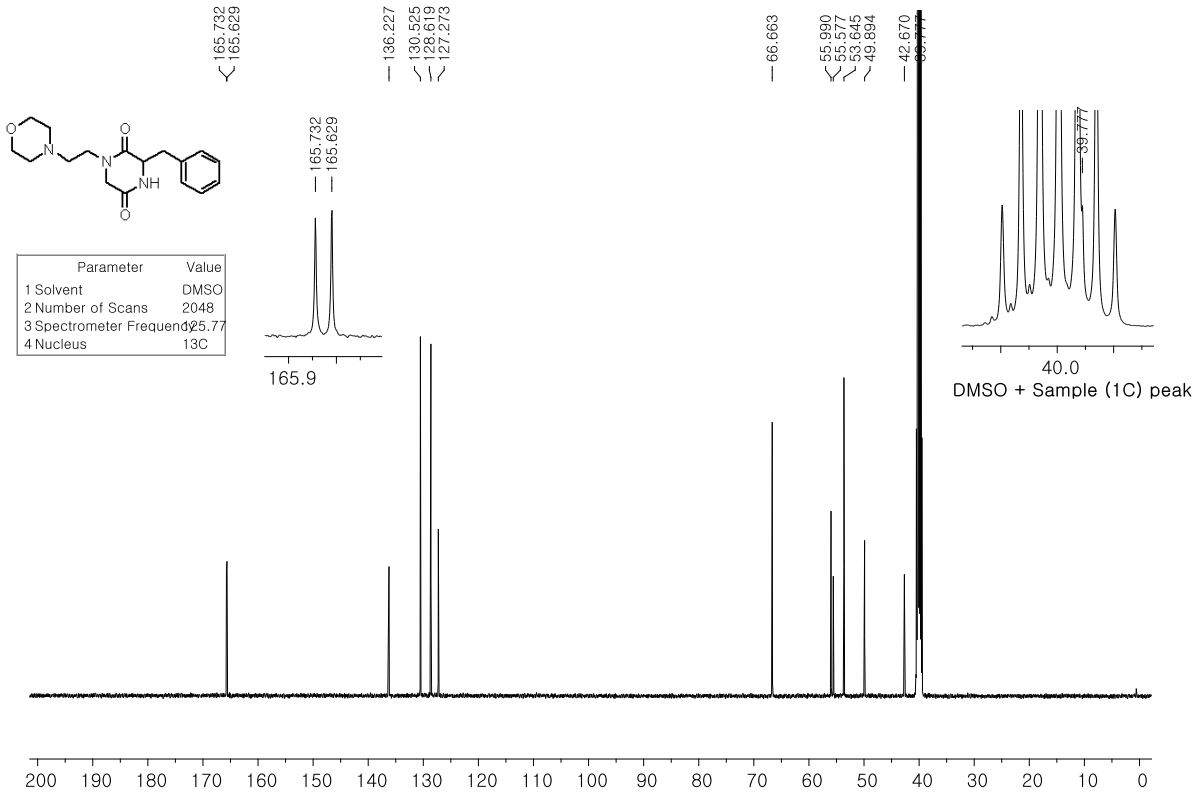
LC/MS – 3q



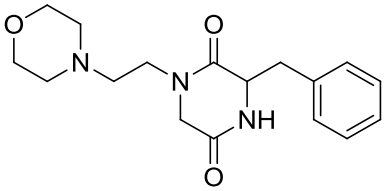
HRMS – 3q



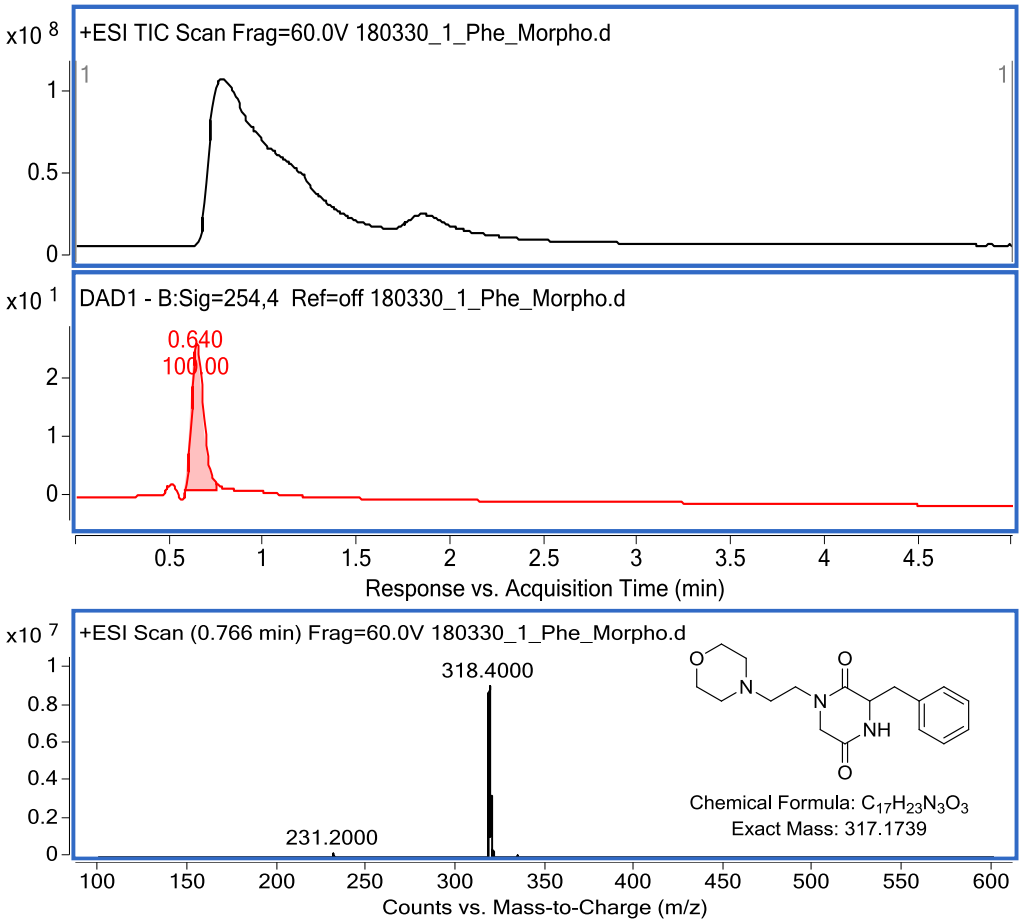
^{1}H NMR – 3r



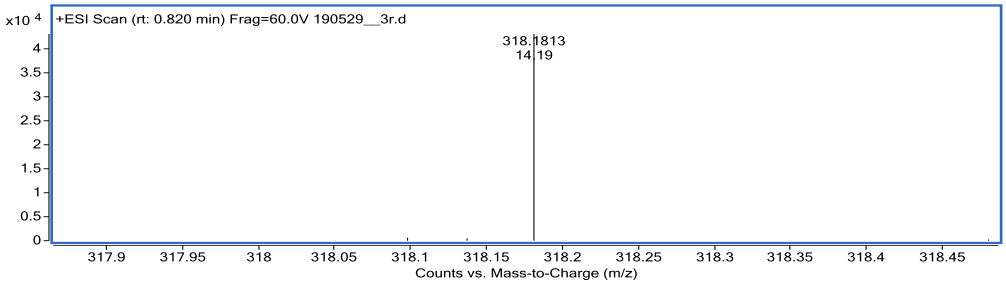
^{13}C NMR – 3r



Chemical Formula: $C_{17}H_{23}N_3O_3$
Exact Mass: 317.1739

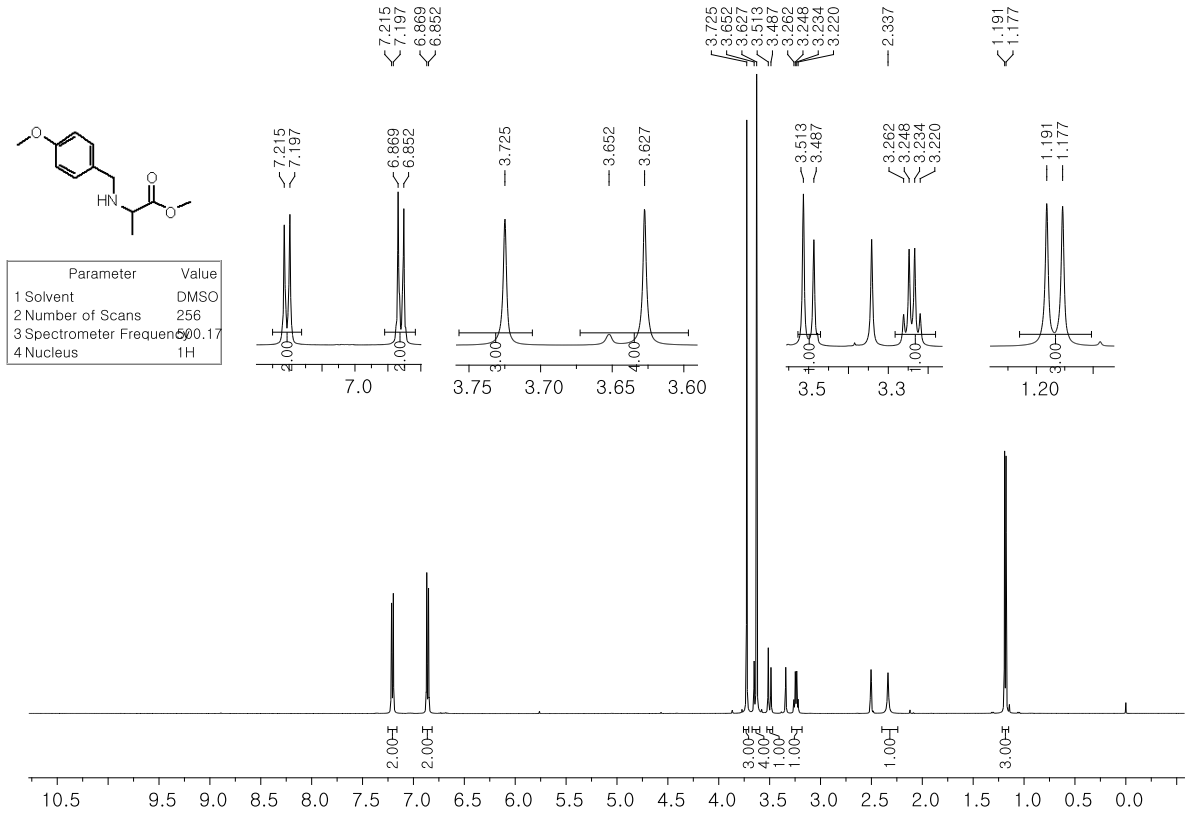


LC/MS – 3r

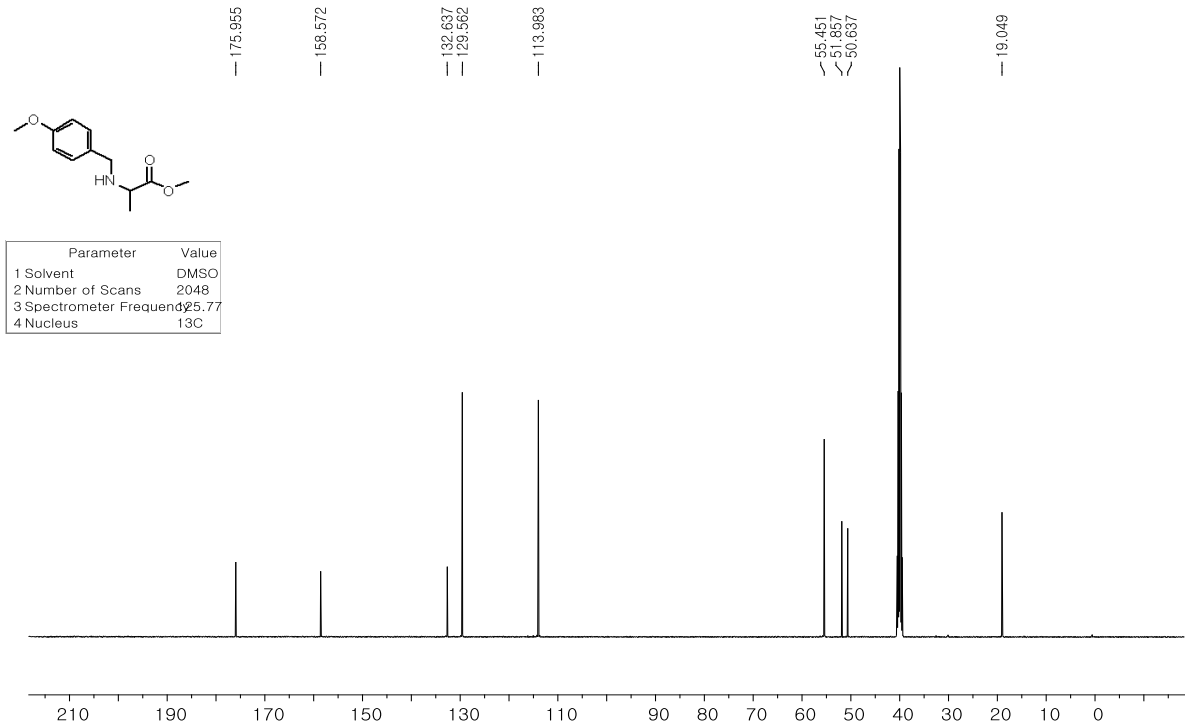


HRMS – 3r

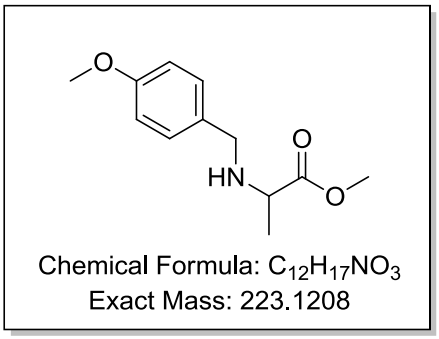
4. ^{1}H NMR, ^{13}C NMR, LC/MS and HRMS spectra of compounds 4

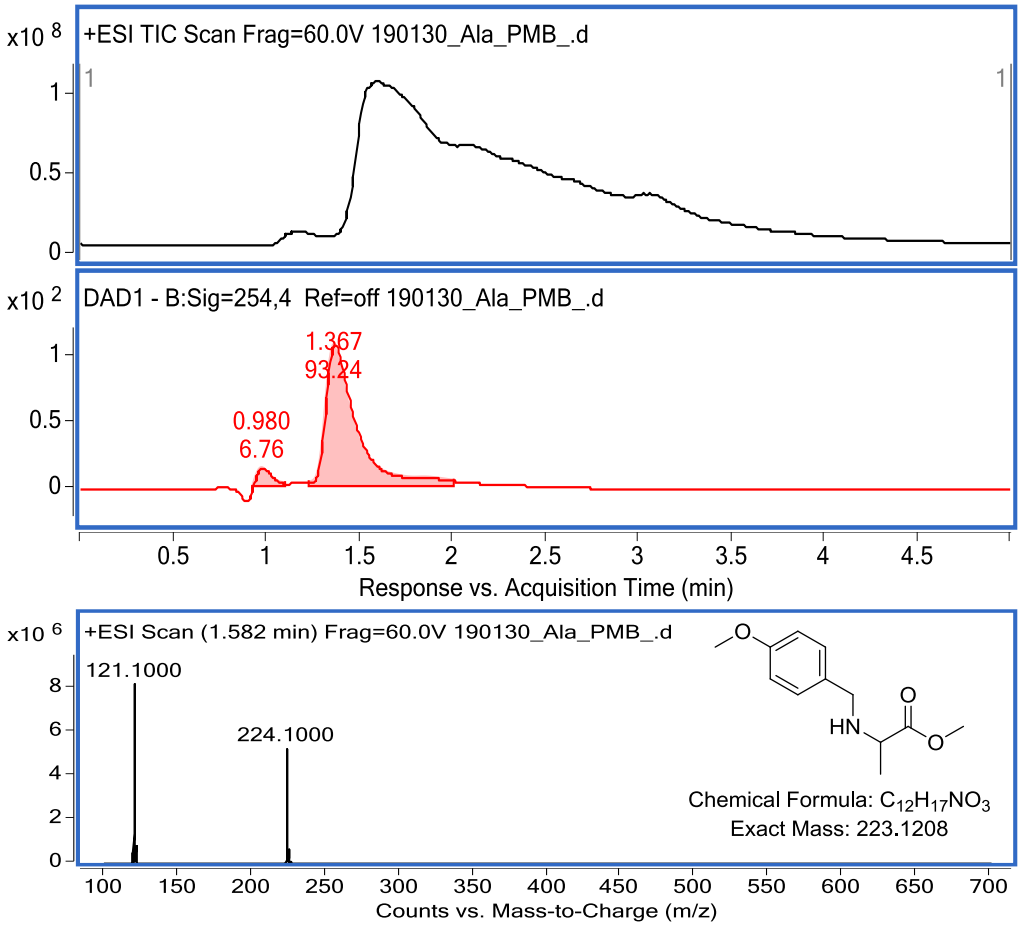


^{1}H NMR – 4a

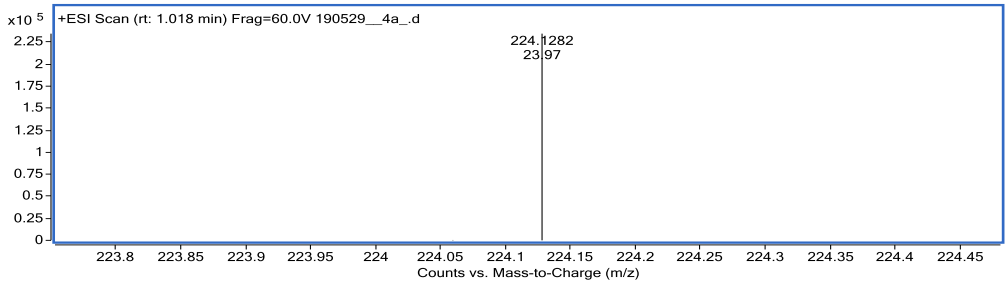


^{13}C NMR – 4a

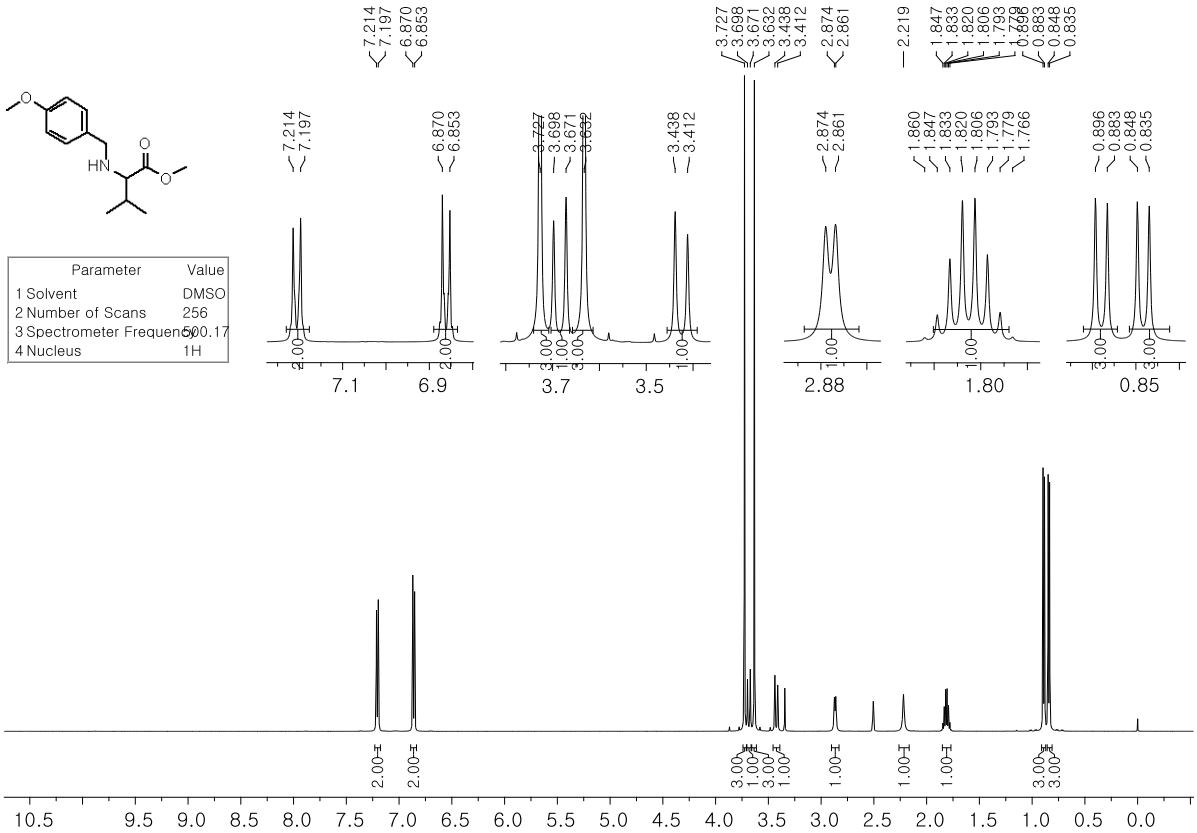




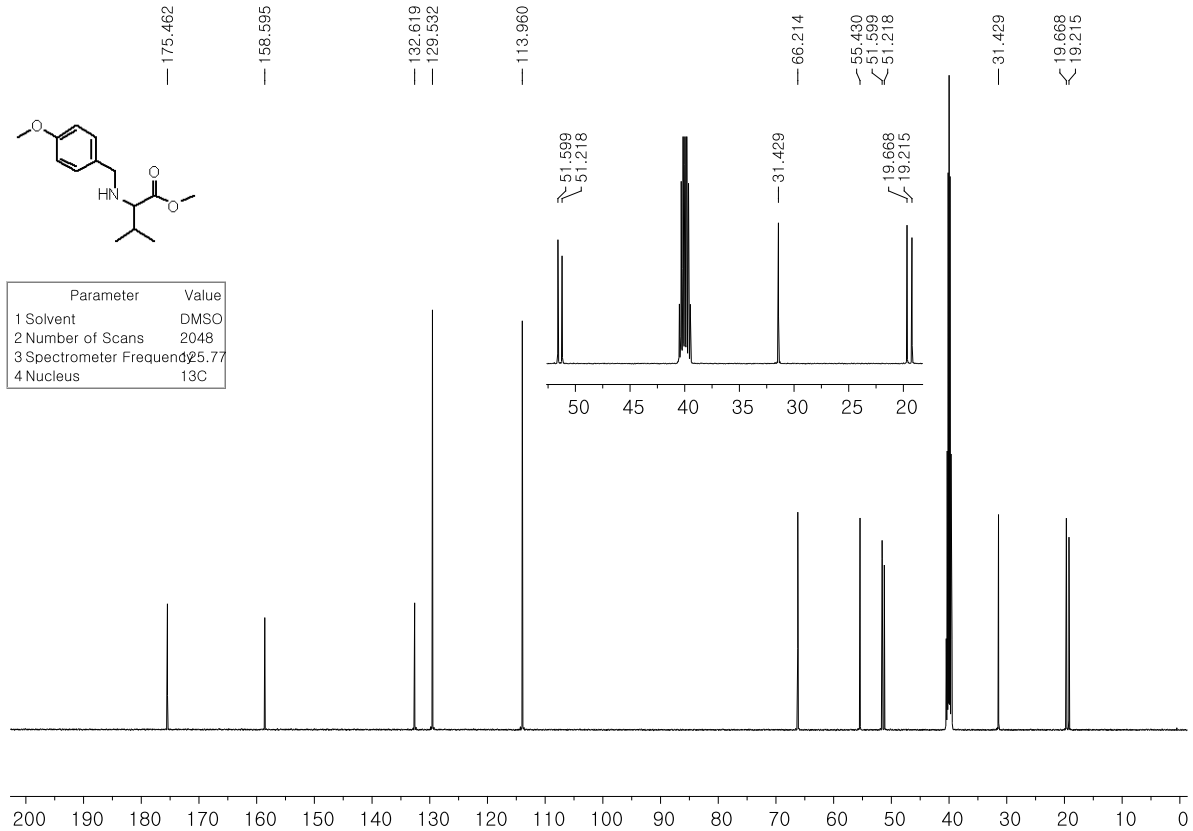
LC/MS – 4a



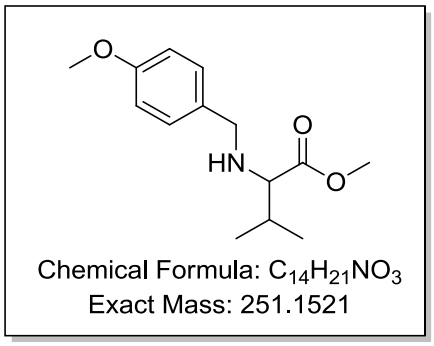
HRMS – 4a

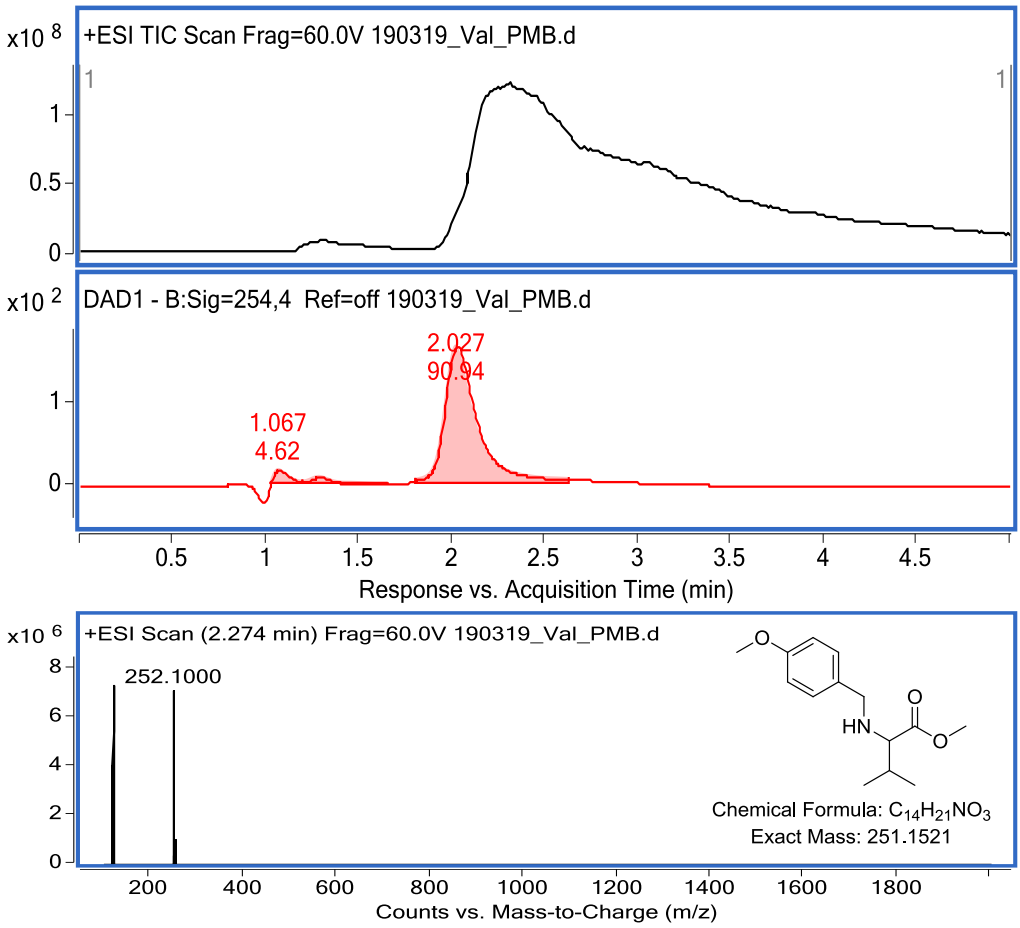


^{1}H NMR – 4b

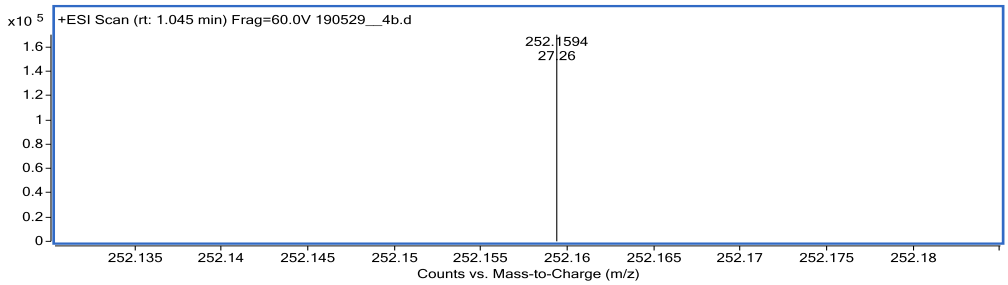


^{13}C NMR – 4b

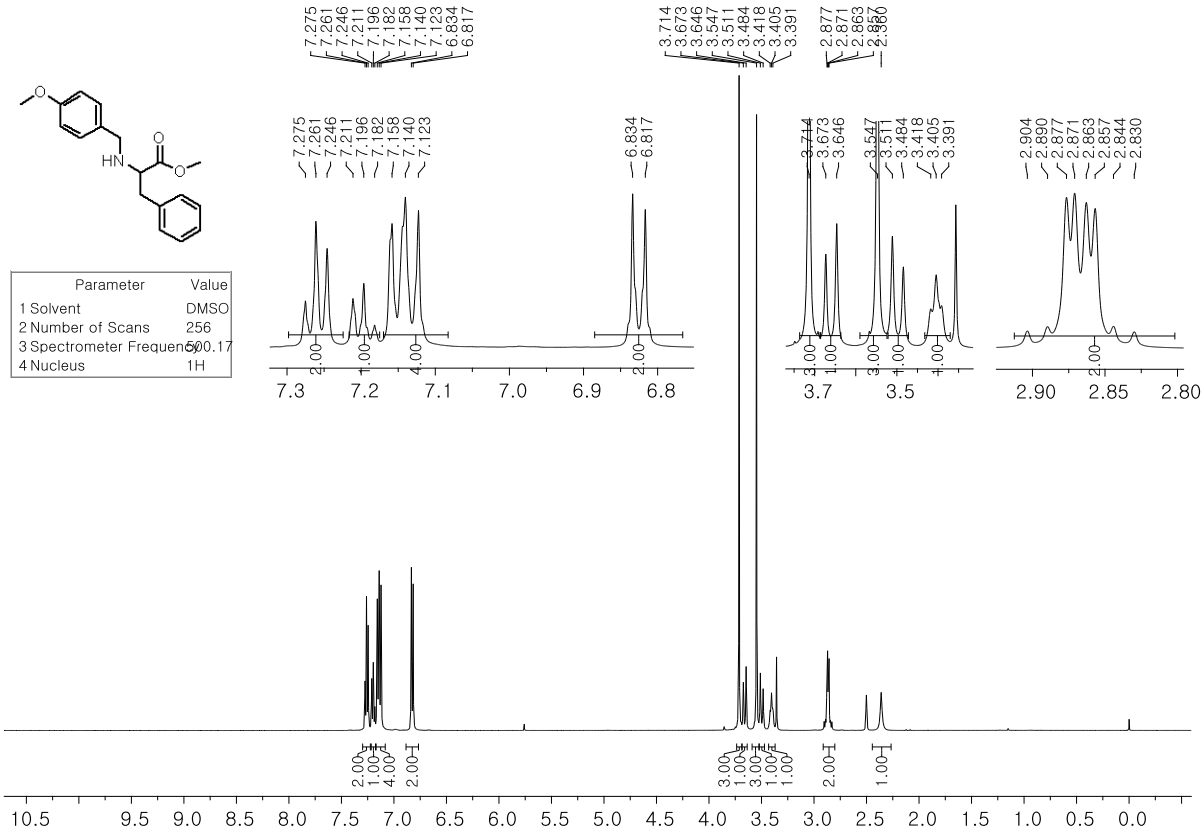




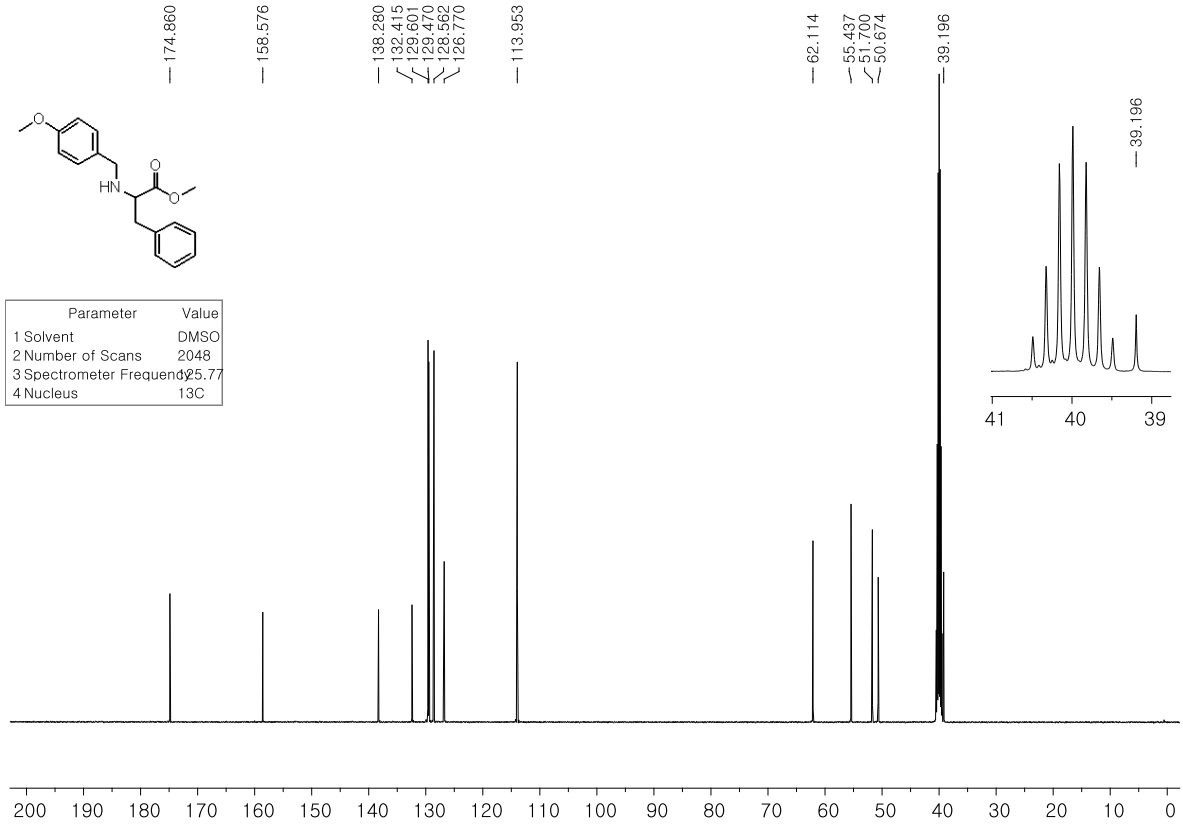
LC/MS – 4b



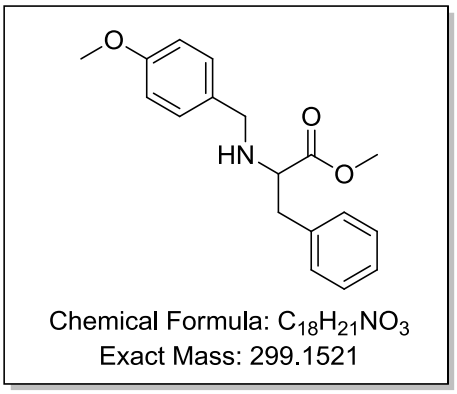
HRMS – 4b

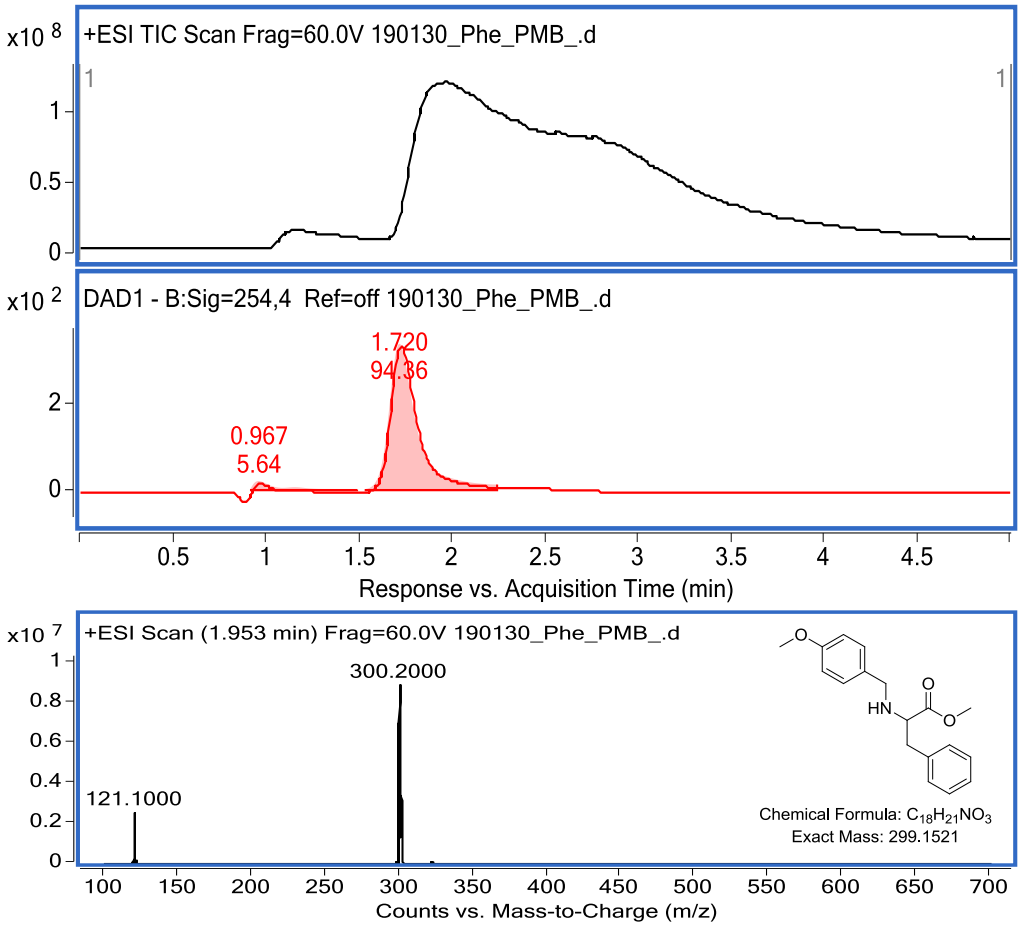


^{1}H NMR – 4c

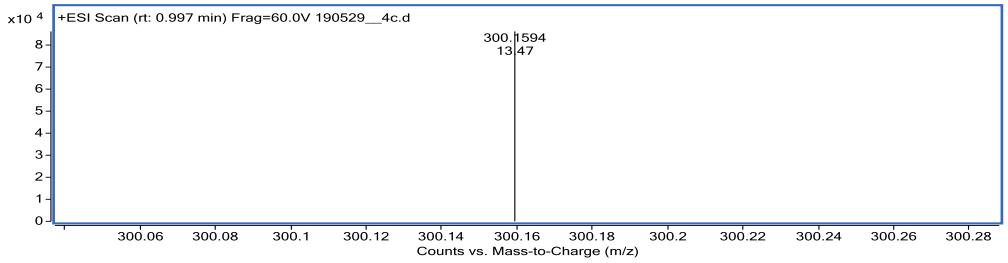


^{13}C NMR – 4c



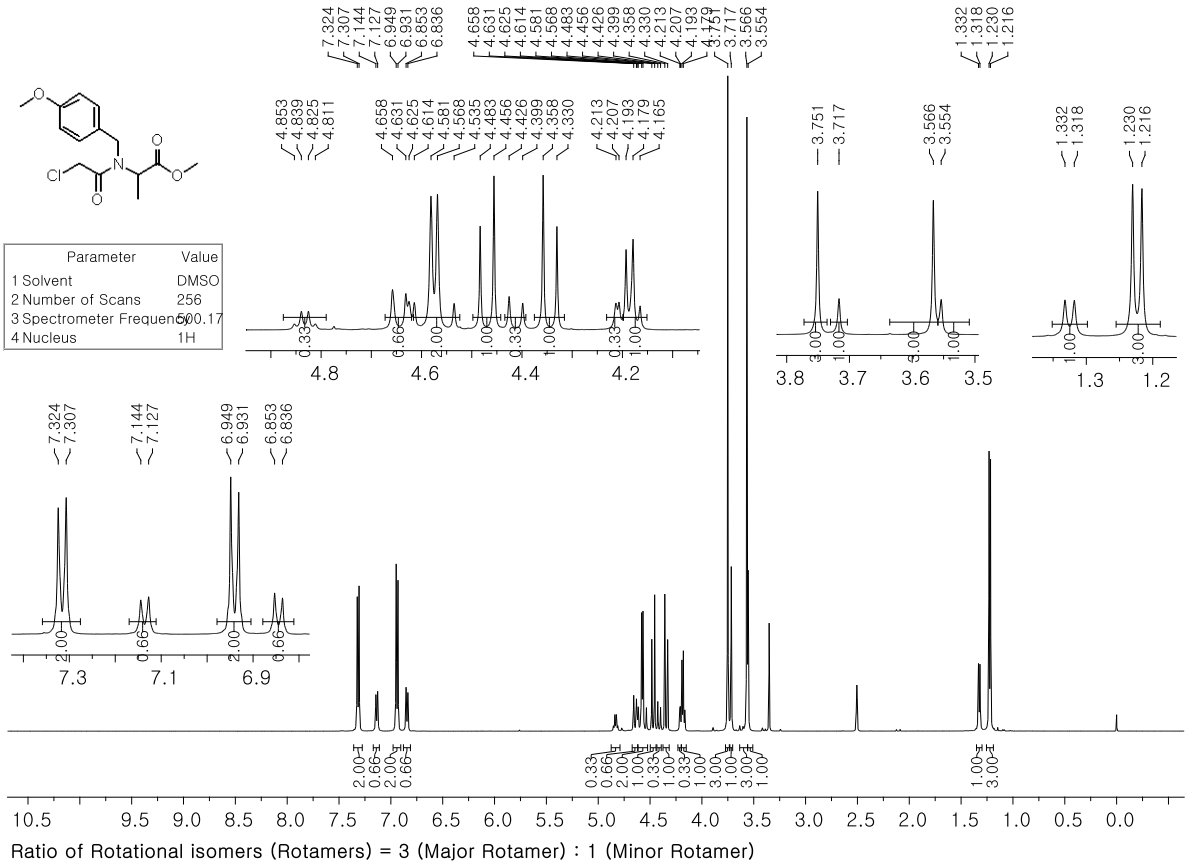


LC/MS – 4c

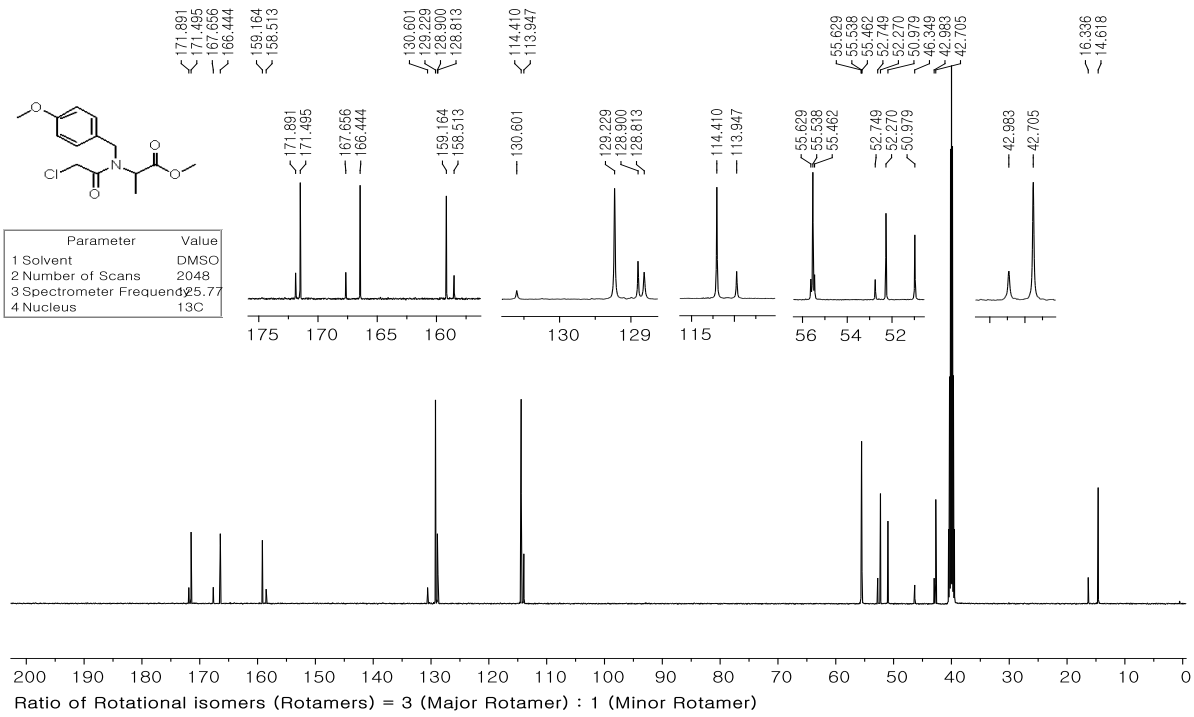


HRMS – 4c

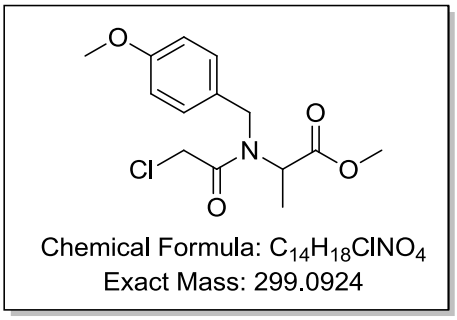
5. ^{1}H NMR, ^{13}C NMR, LC/MS and HRMS spectra of compounds 5

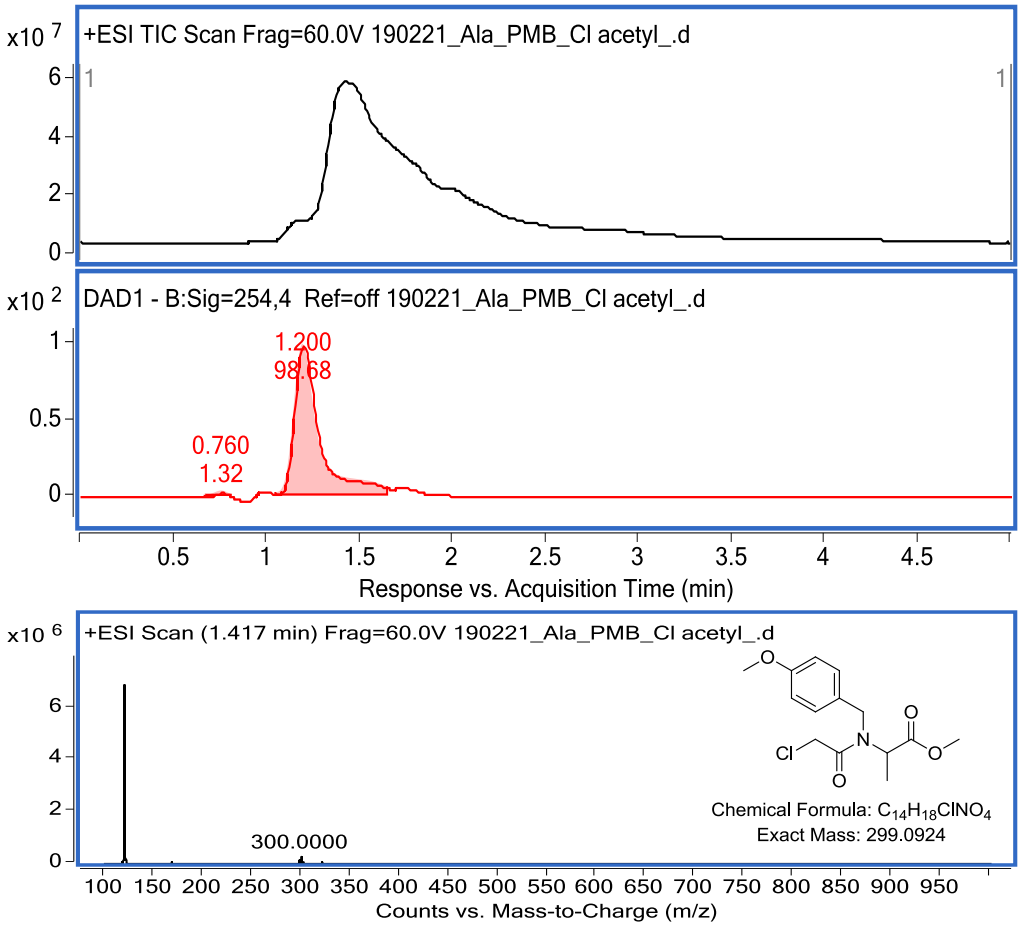


^{1}H NMR – 5a



^{13}C NMR – 5a





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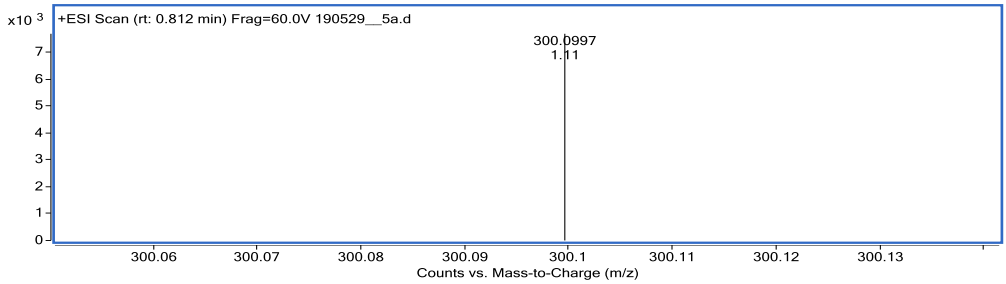
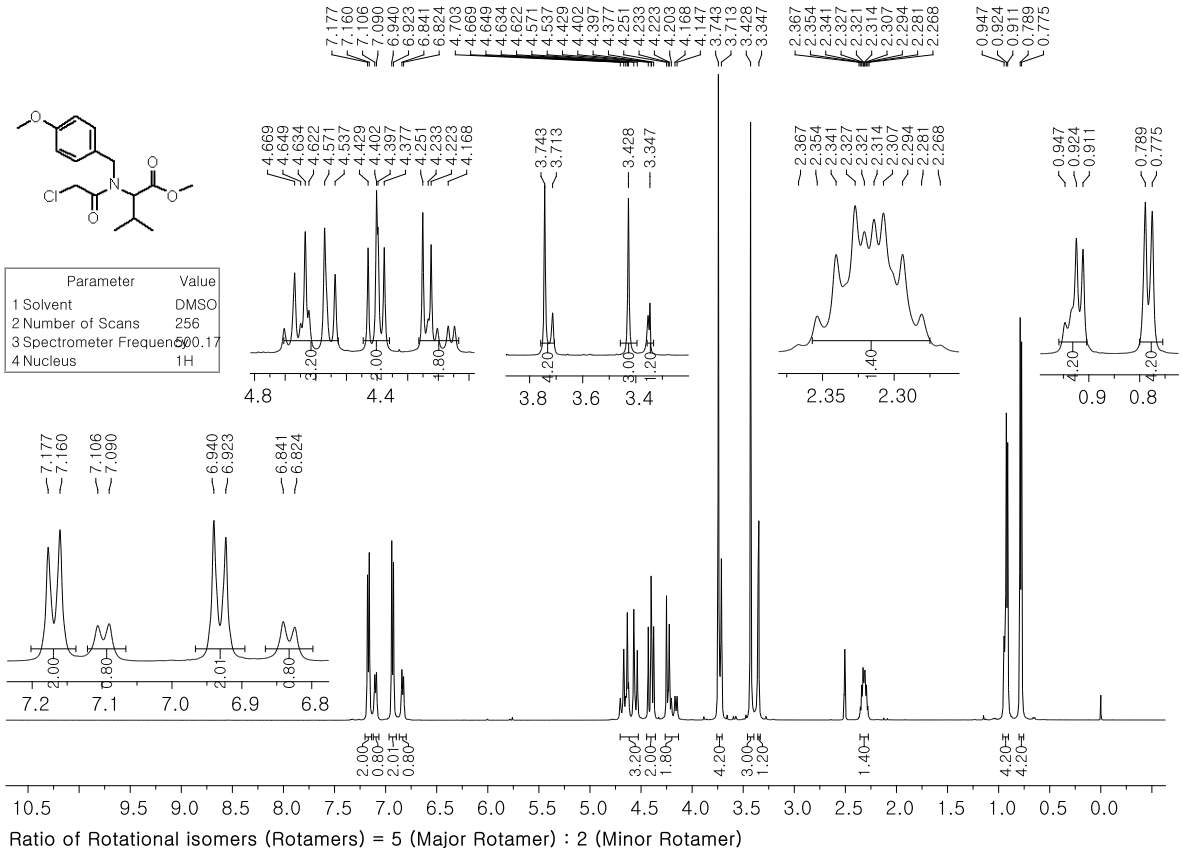
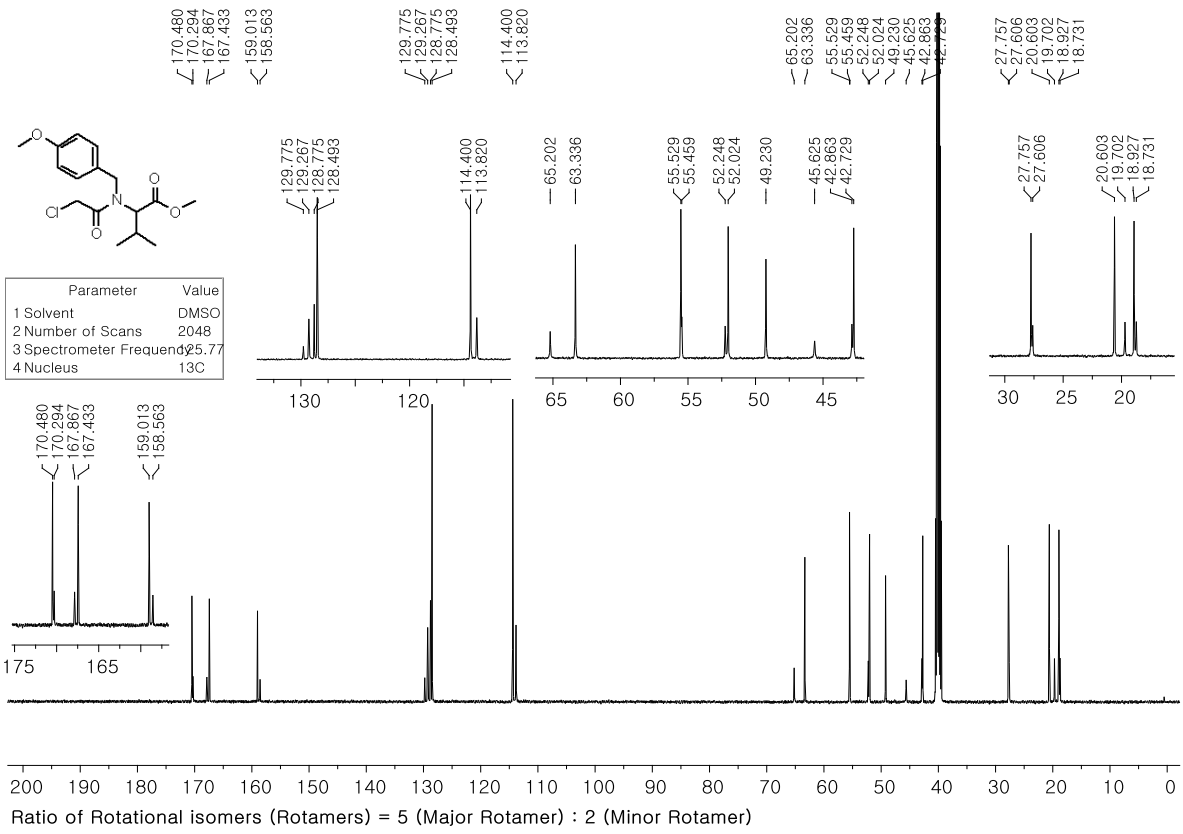


HRMS – 5a



^{1}H NMR – 5b



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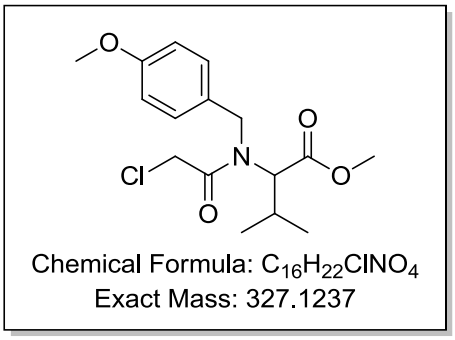

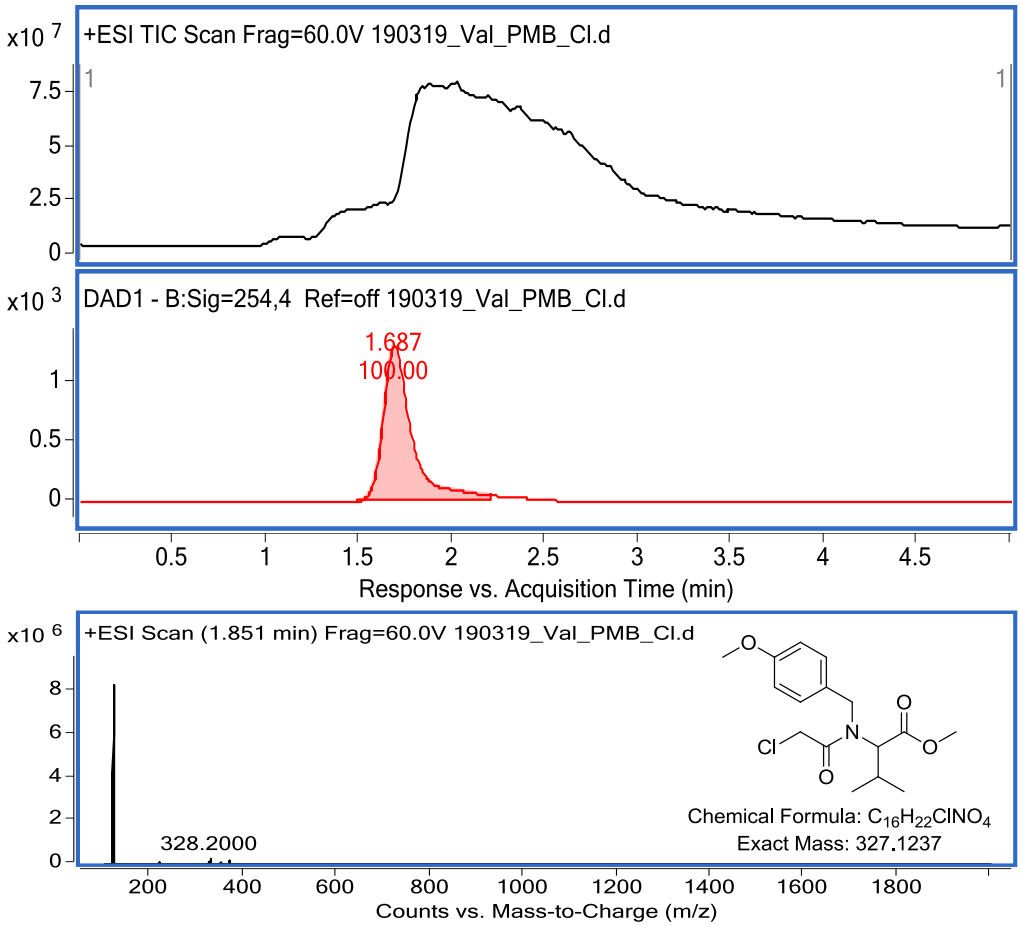

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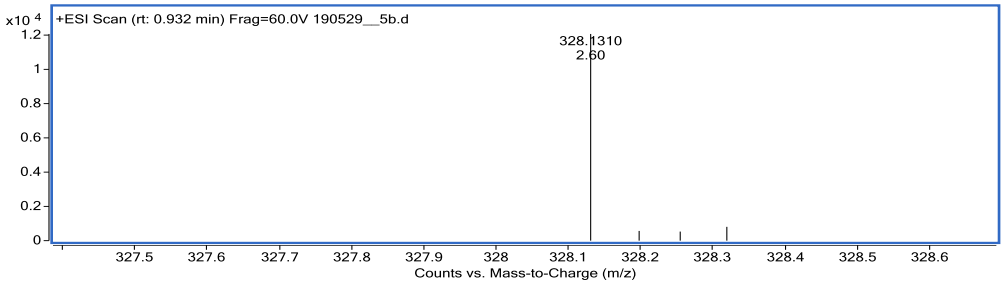

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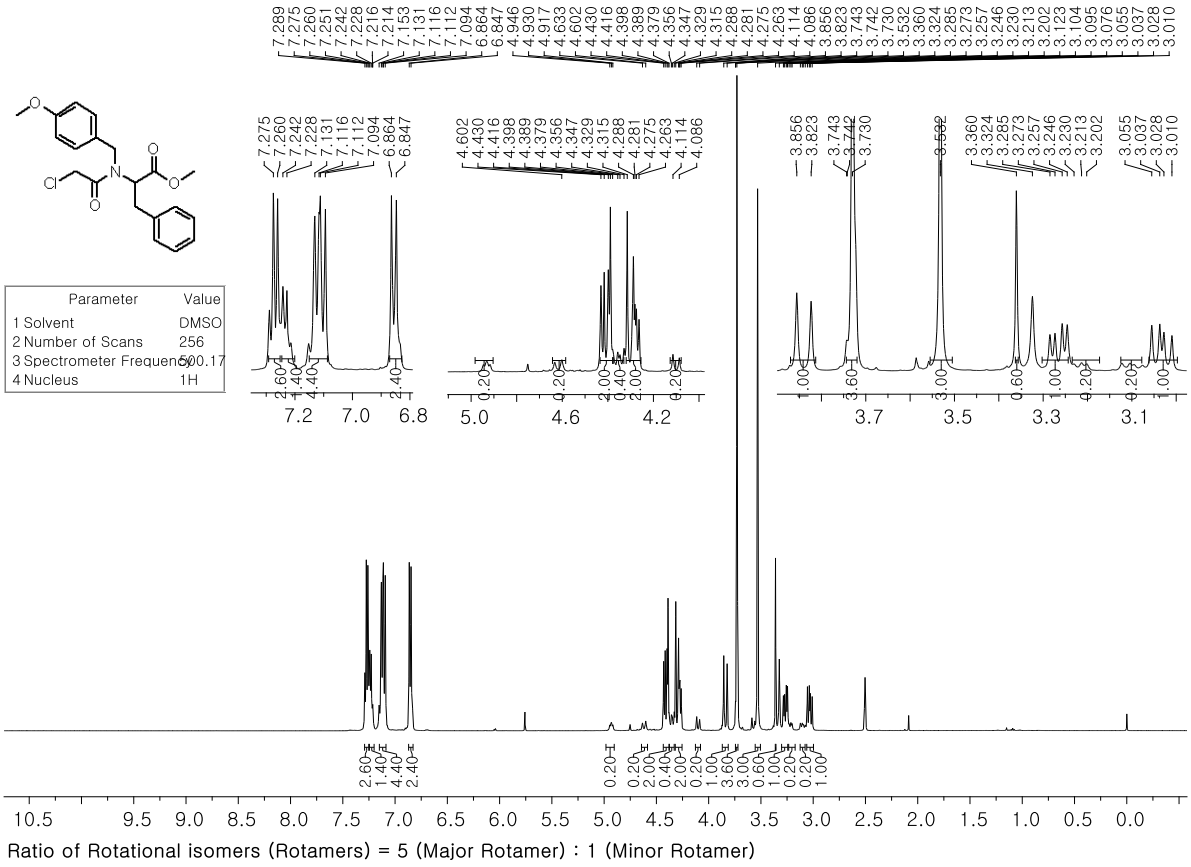
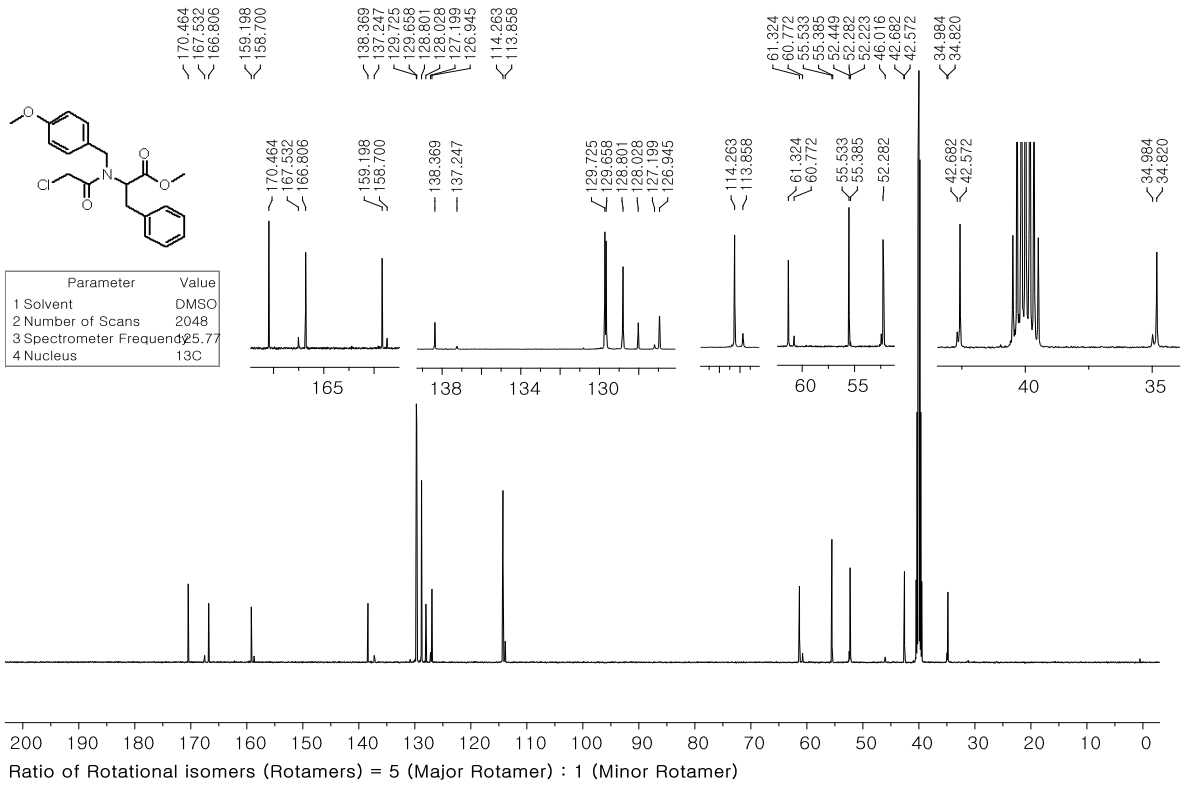
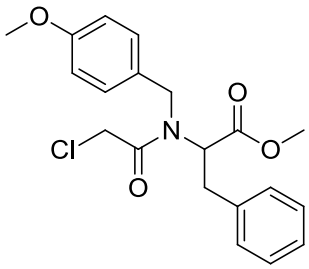


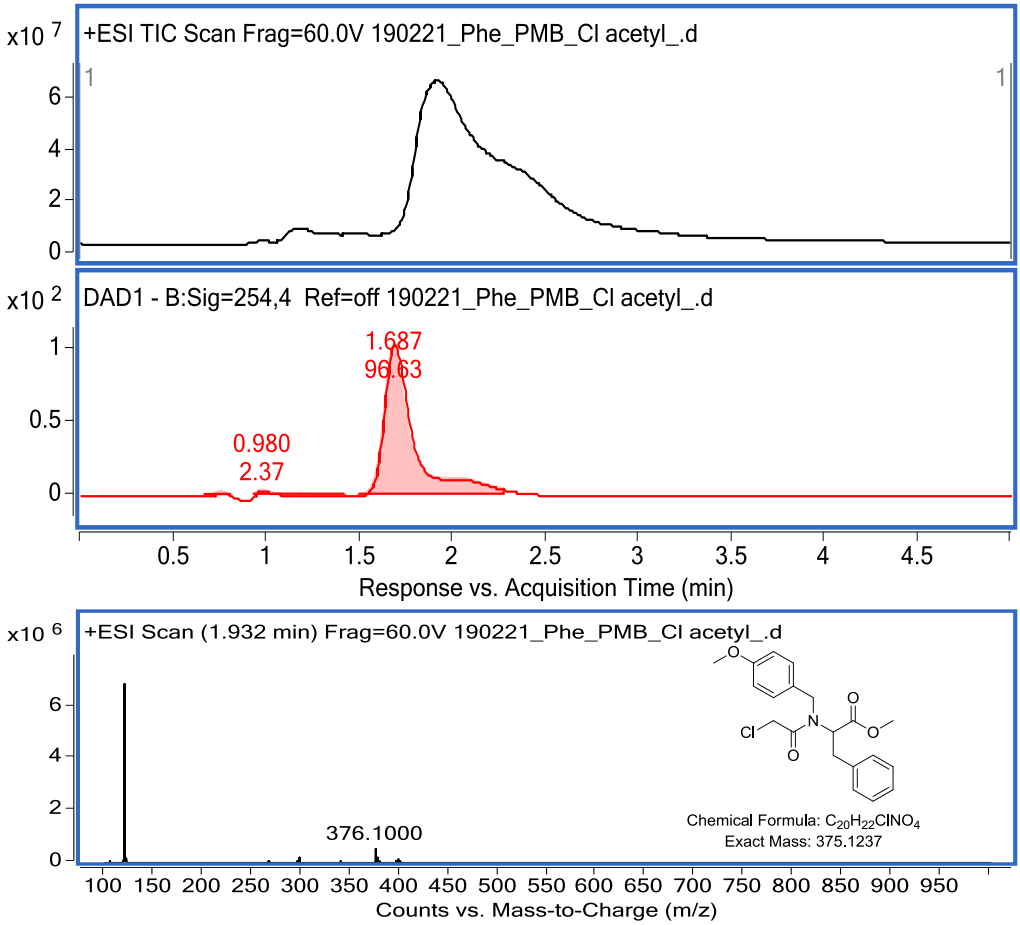
^{1}H NMR – 5c



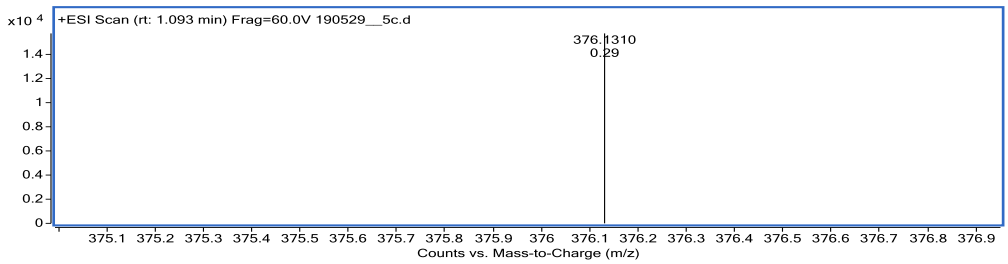
^{13}C NMR – 5c



Chemical Formula: $C_{20}H_{22}ClNO_4$
Exact Mass: 375.1237

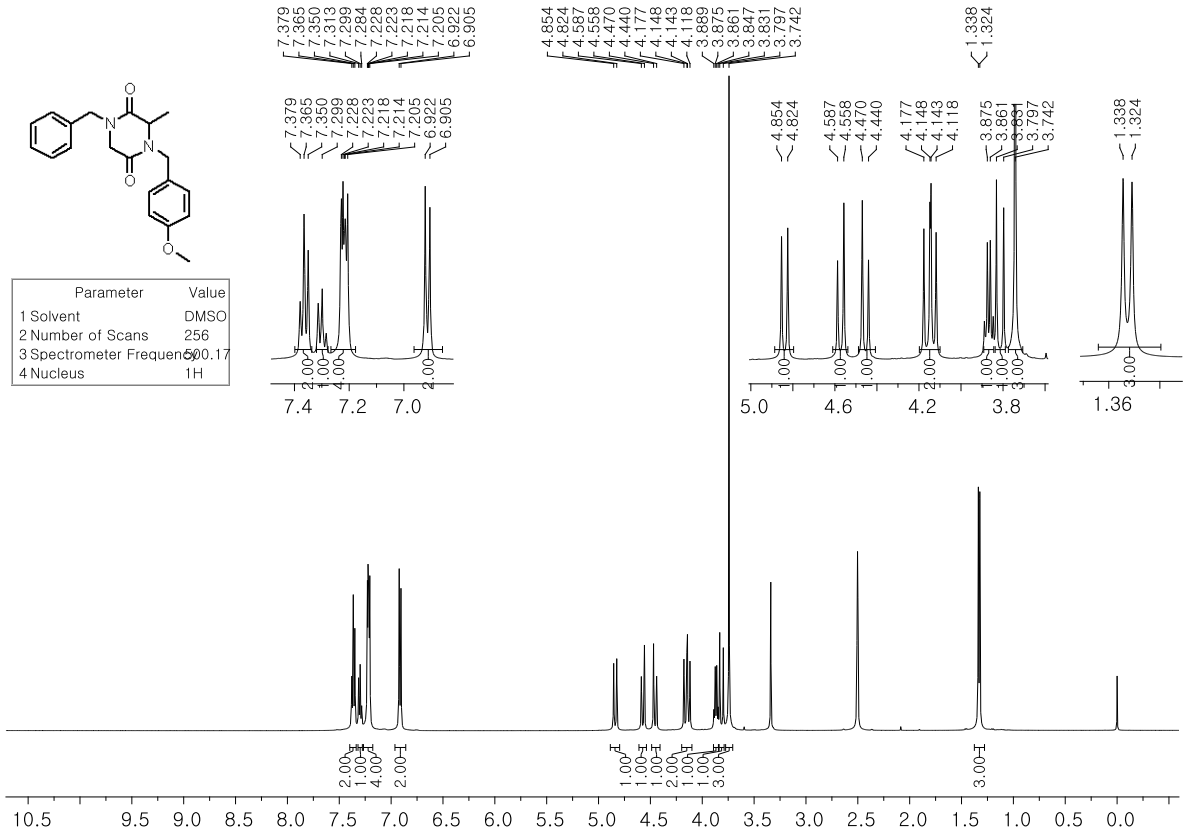


LC/MS – 5c

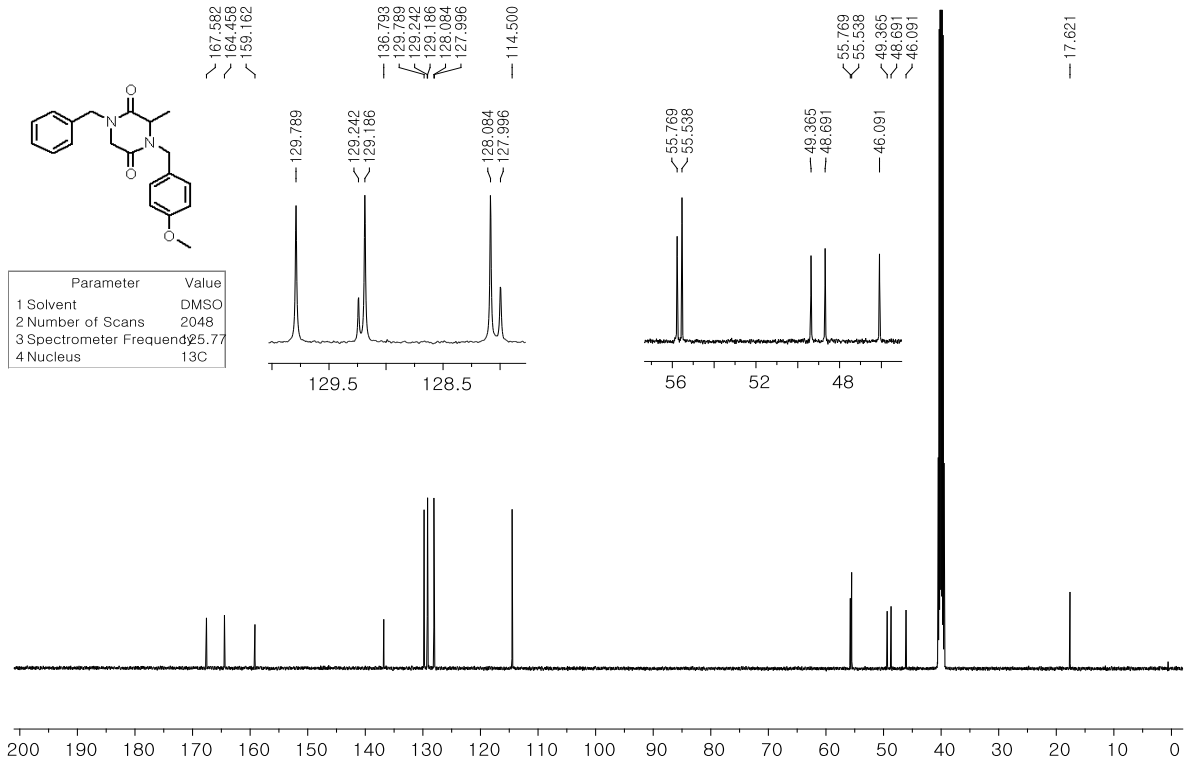


HRMS – 5c

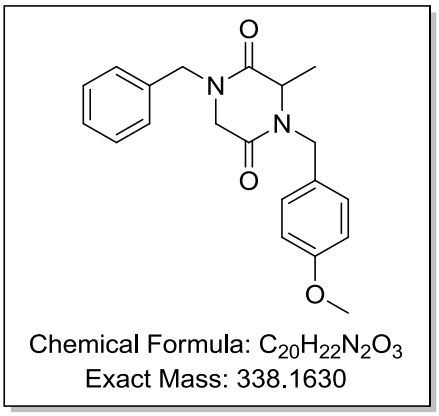
6. ^{1}H NMR, ^{13}C NMR, LC/MS and HRMS spectra of compounds 6

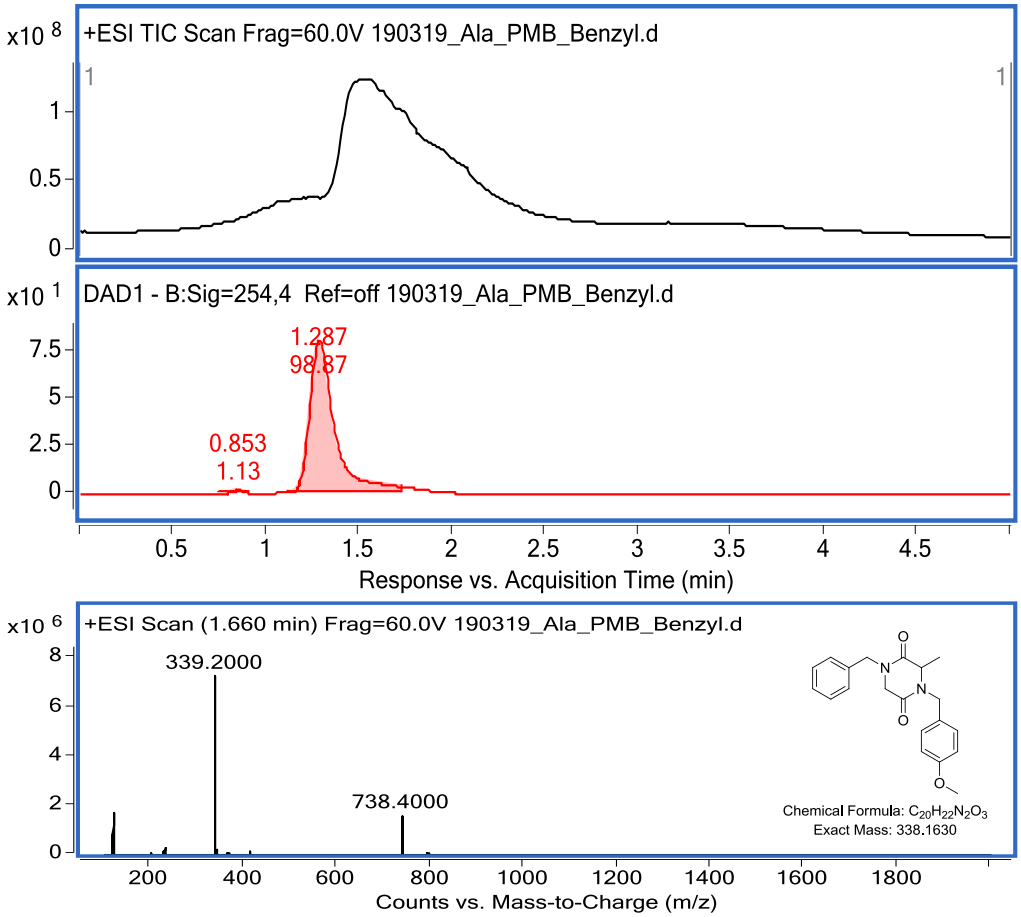


^{1}H NMR – 6a

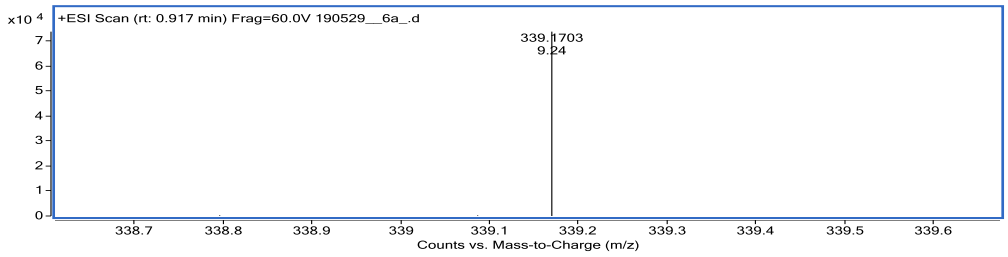


^{13}C NMR – 6a

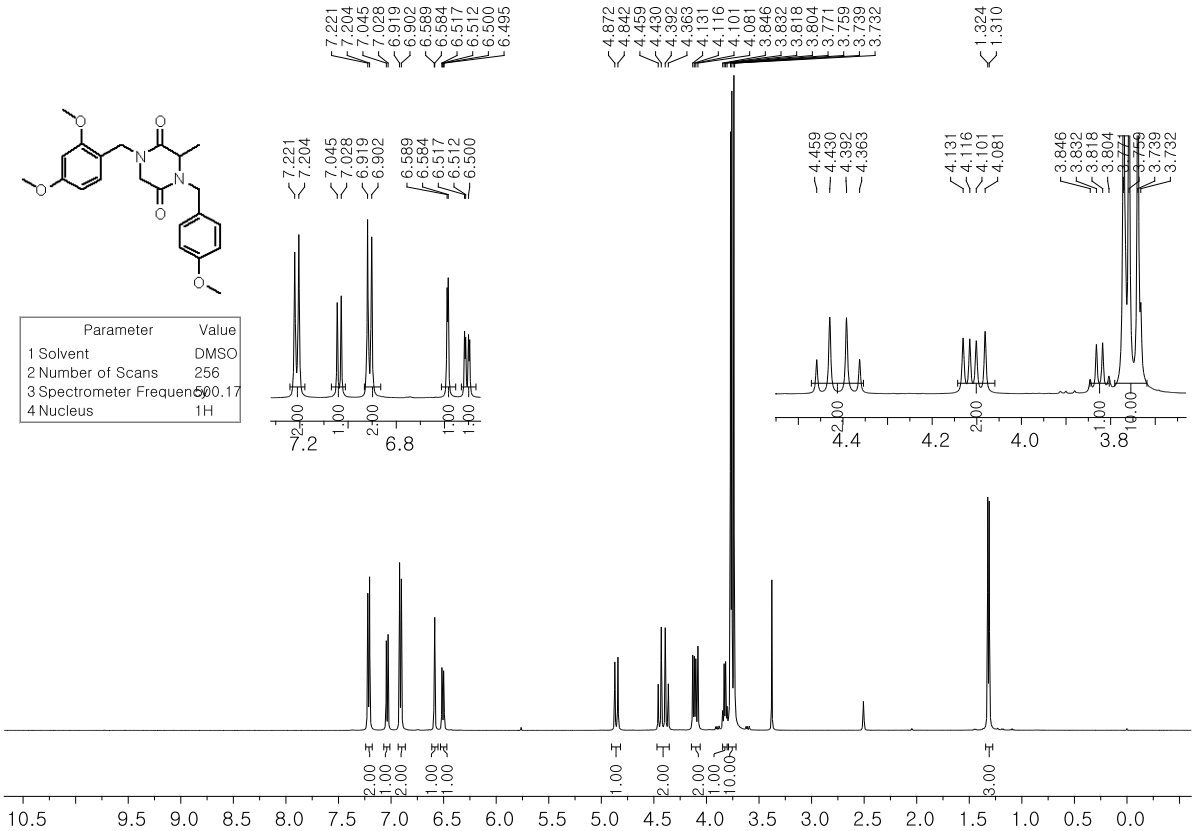




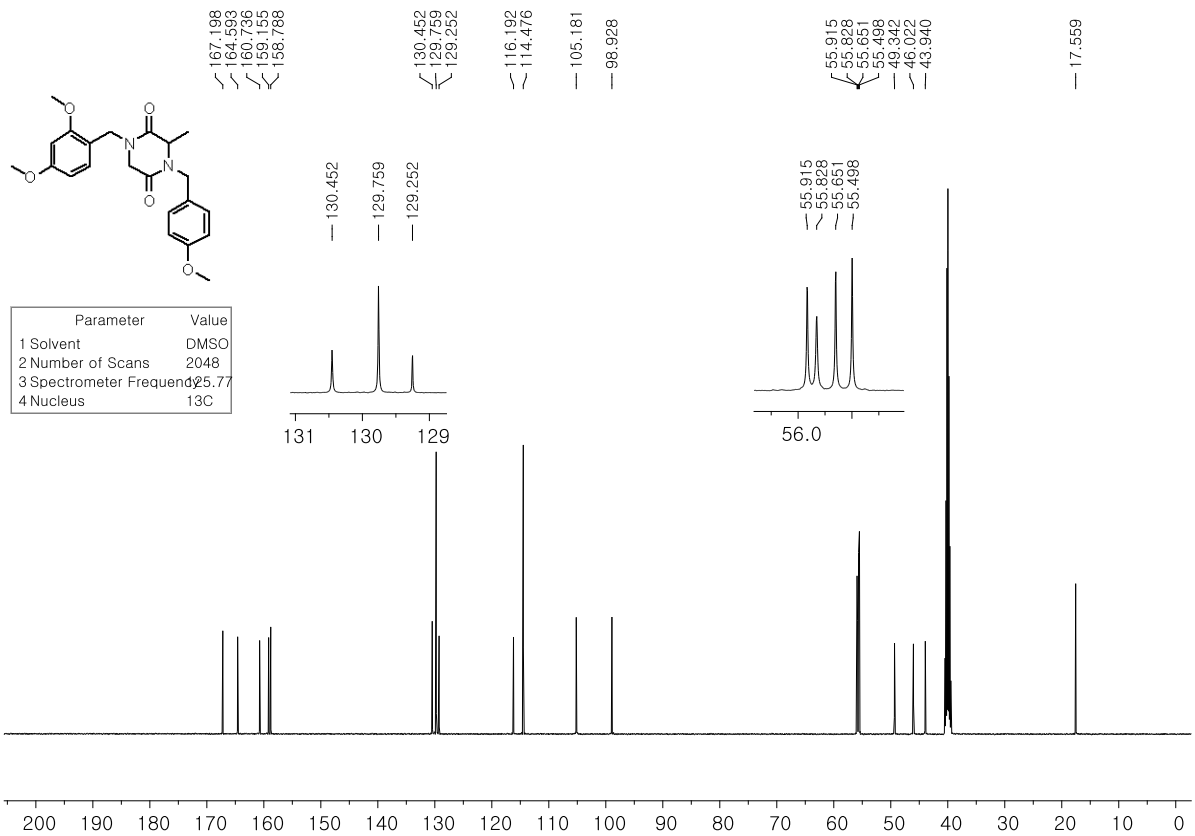
LC/MS – 6a



HRMS – 6a



^{1}H NMR – 6b



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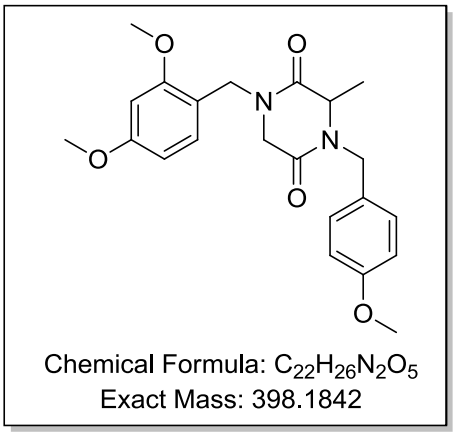

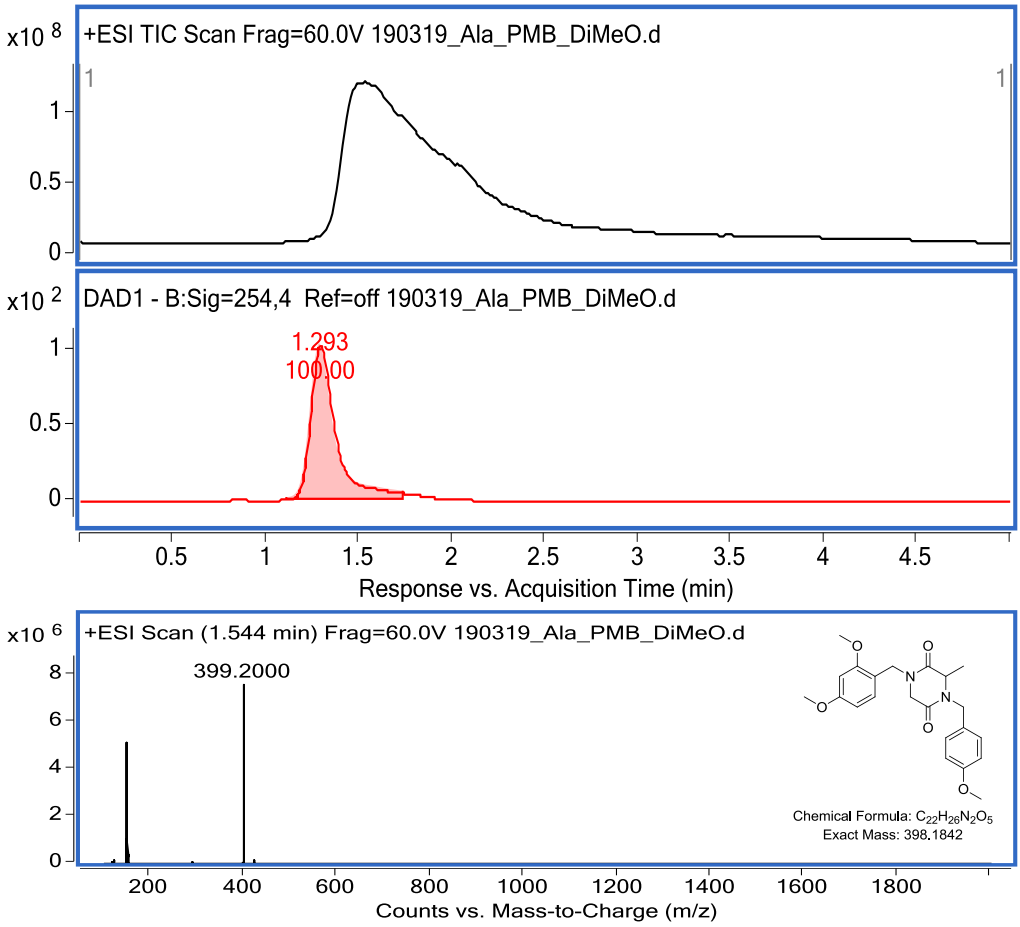

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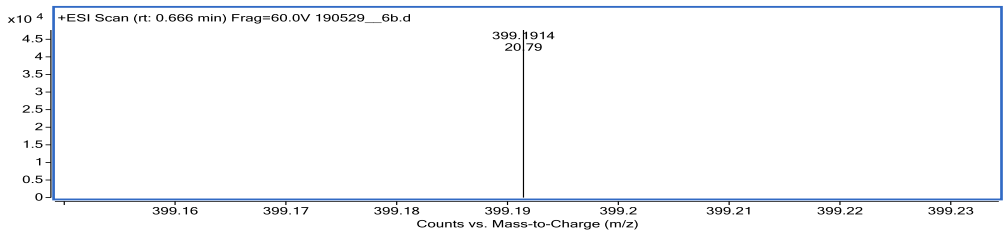
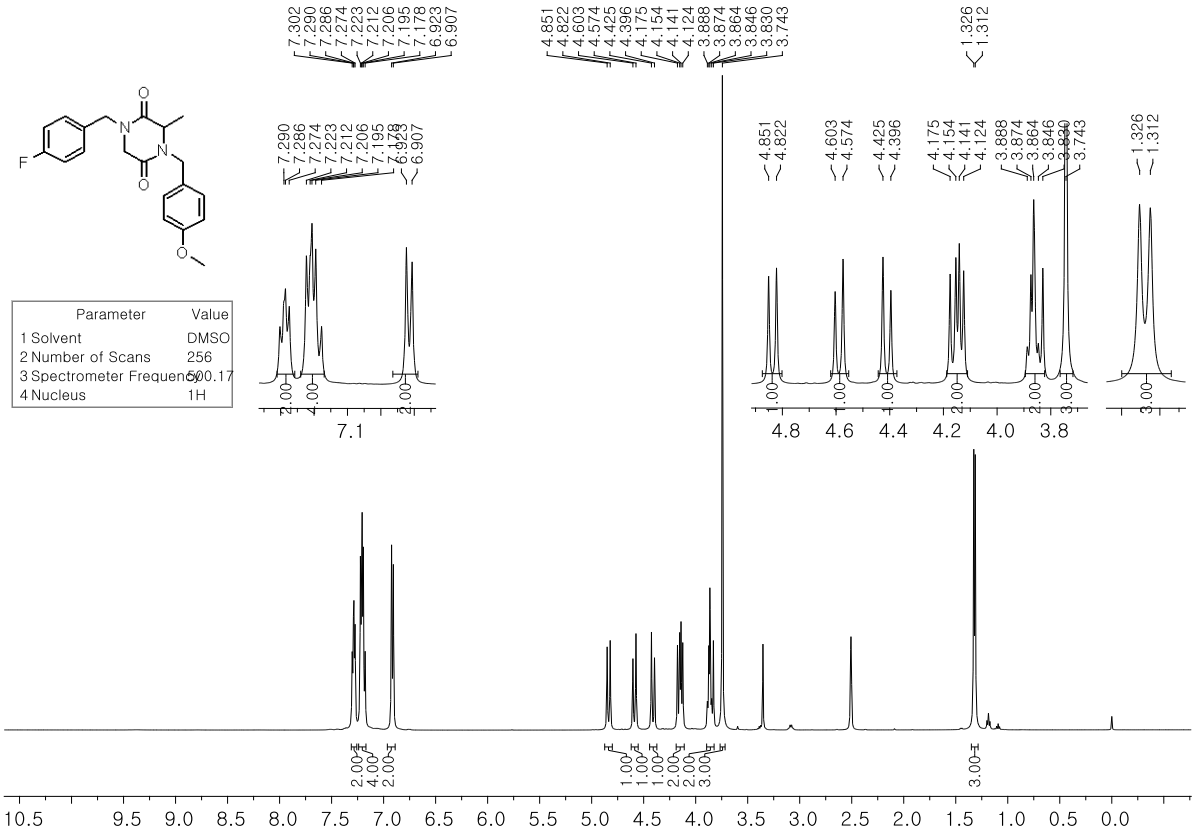
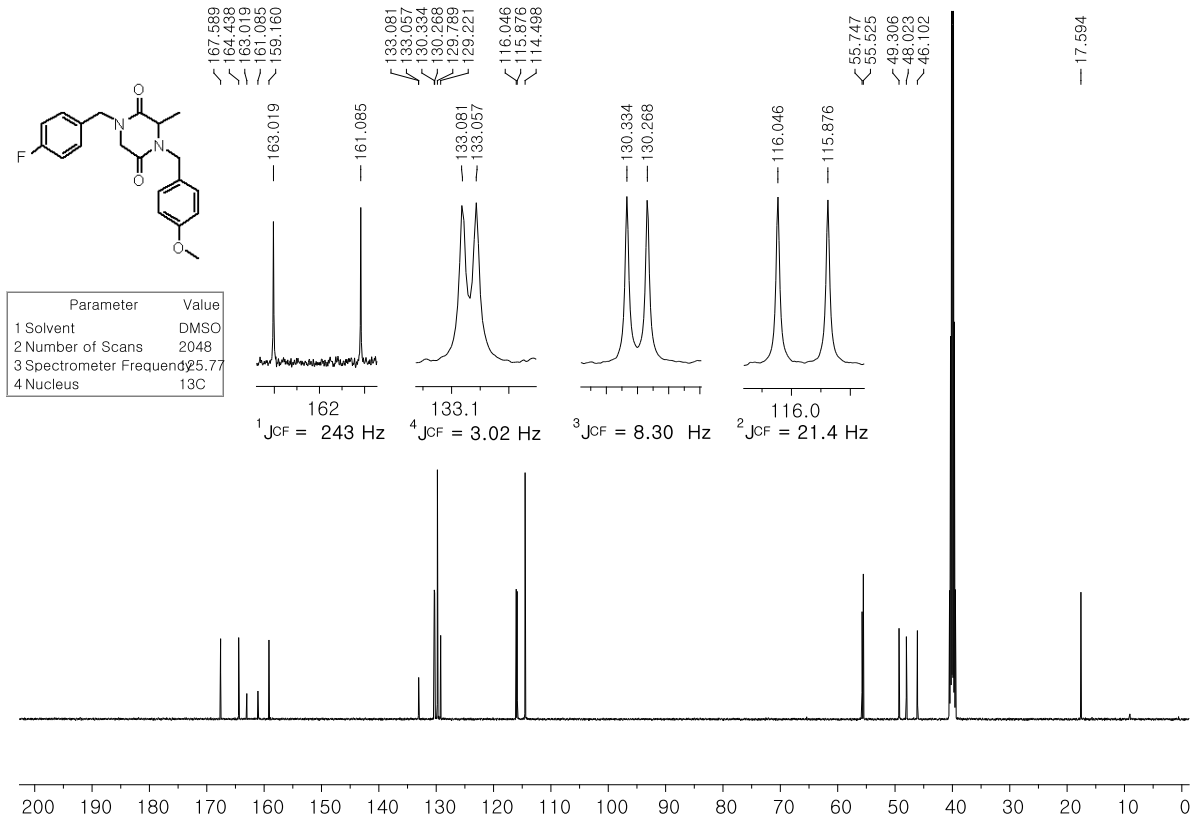


HRMS – 6b



^{1}H NMR – 6c



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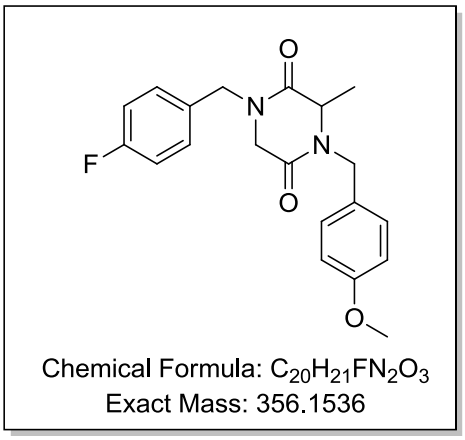

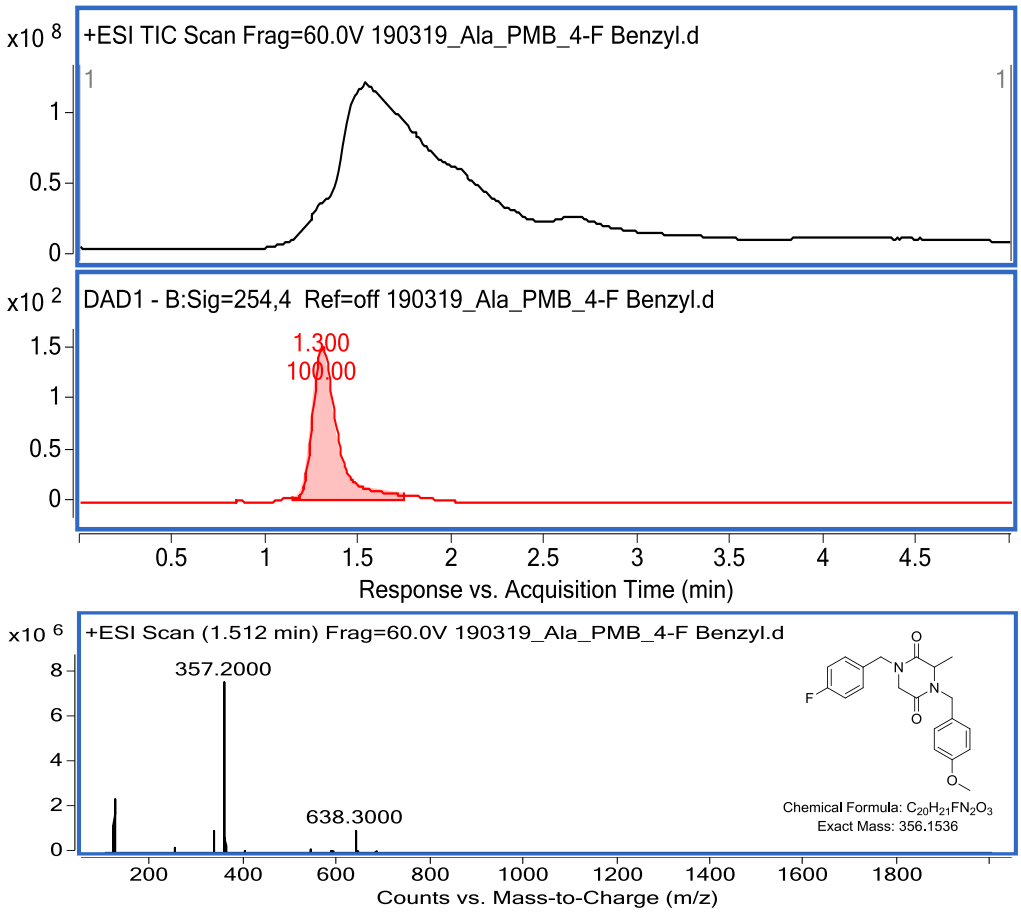

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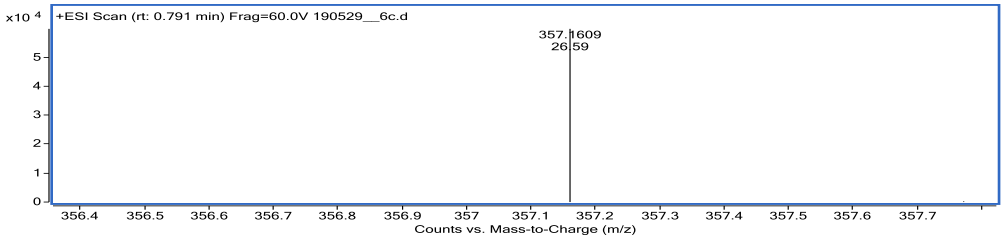

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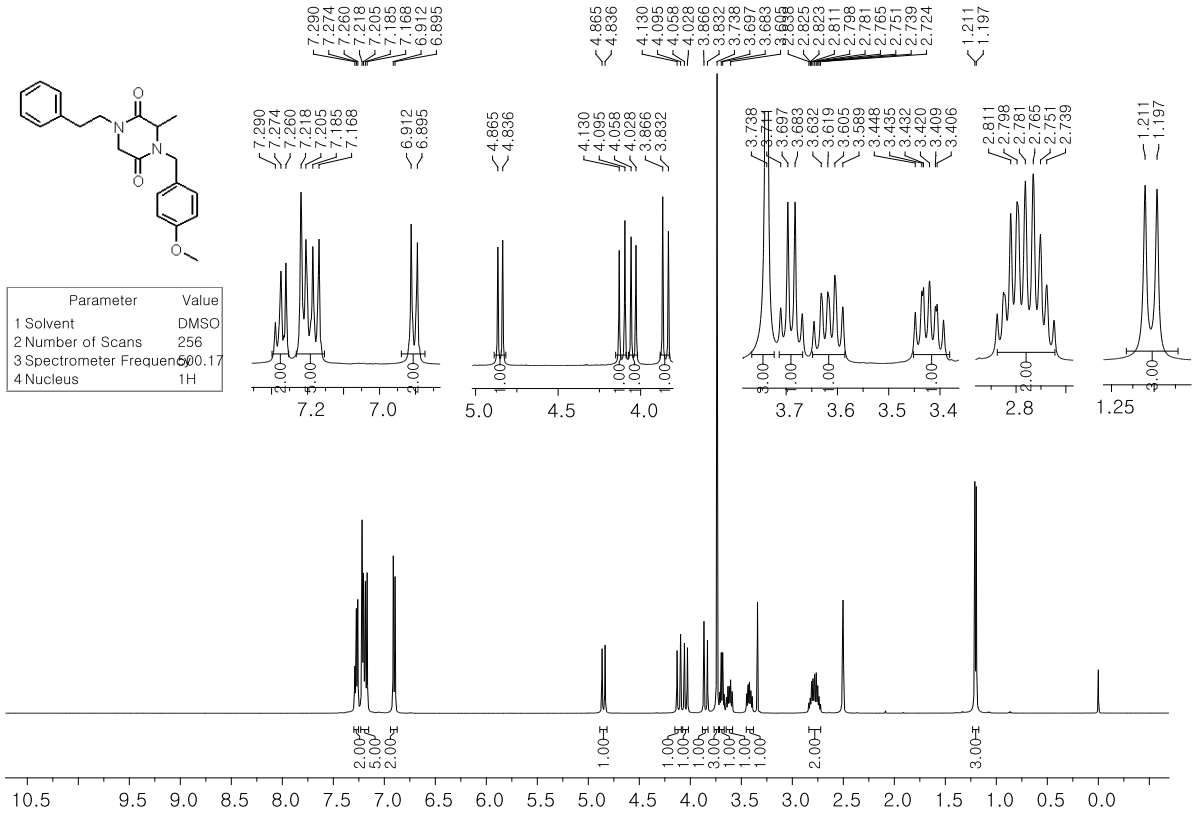
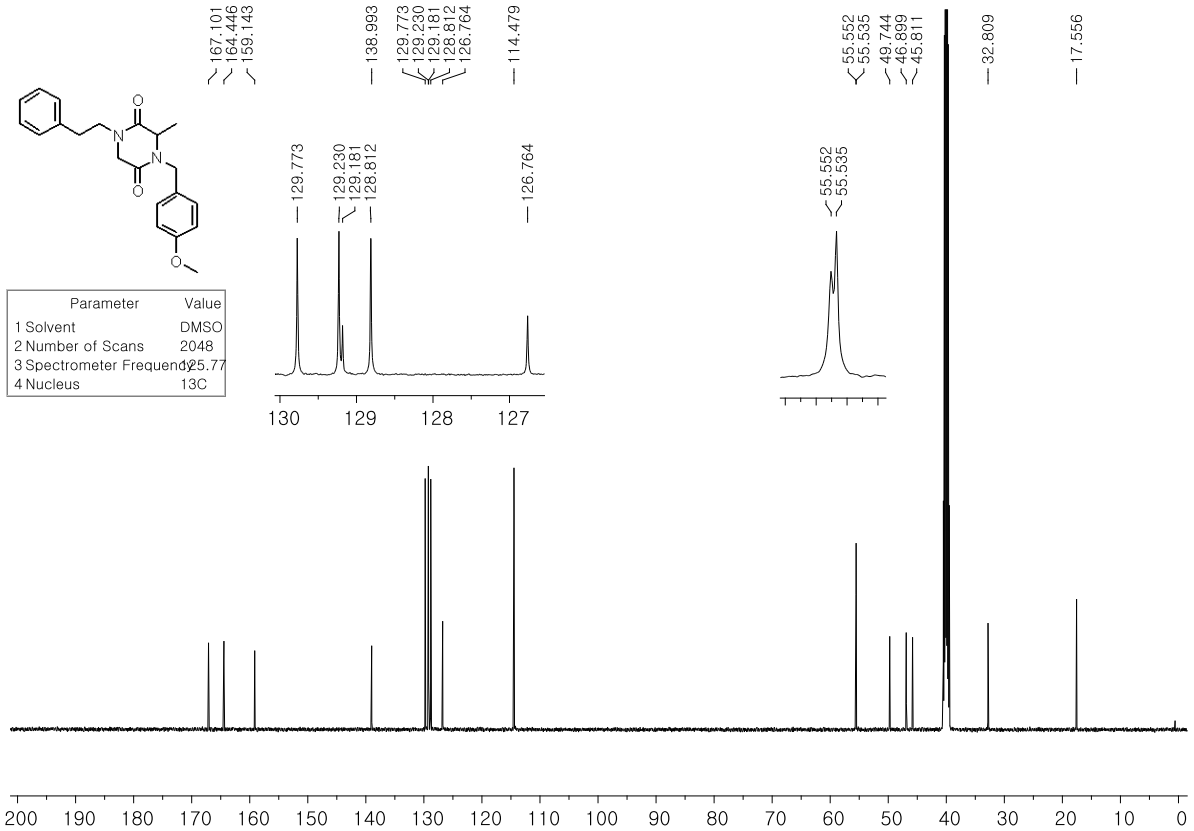
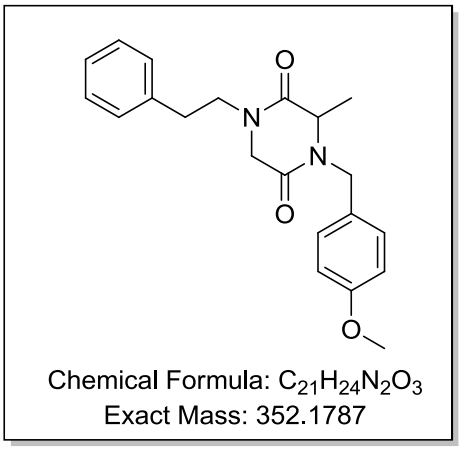
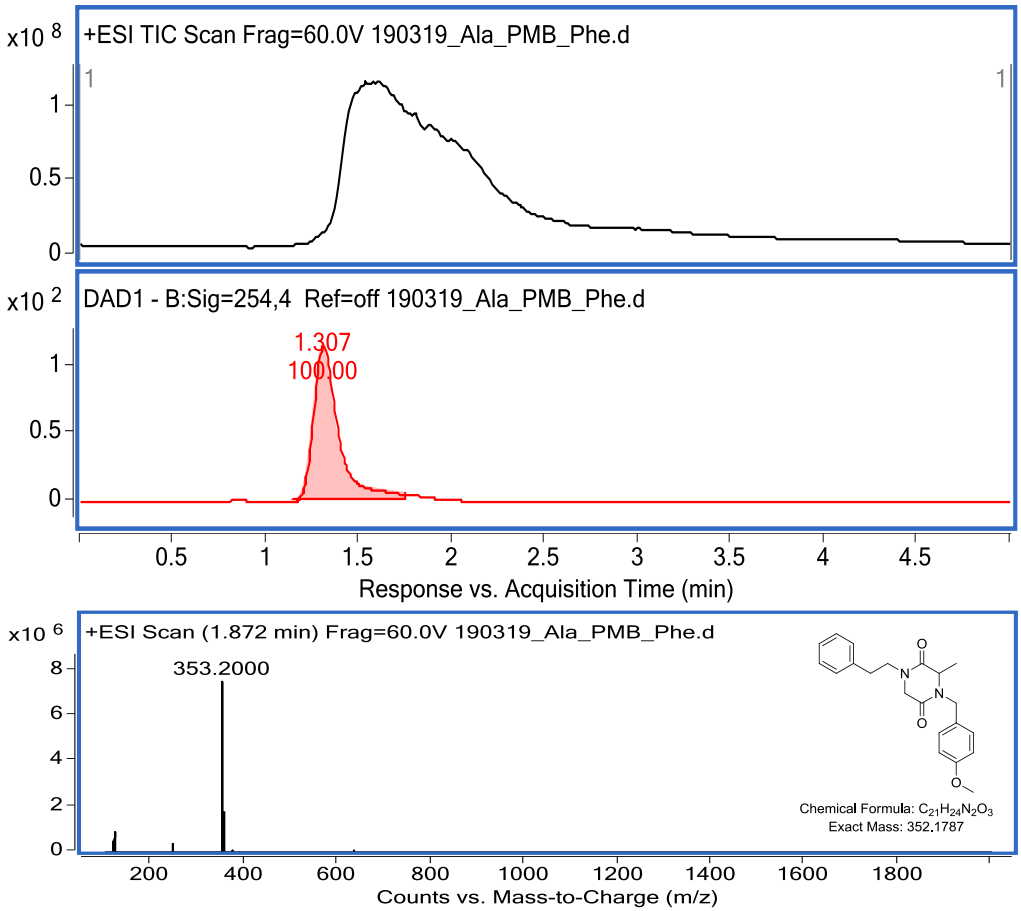


^{1}H NMR – 6d



^{13}C NMR – 6d





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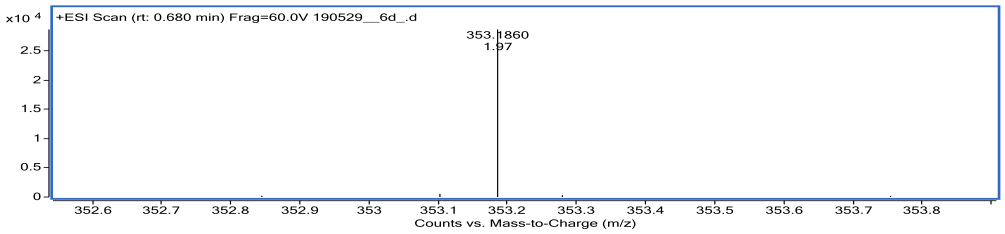

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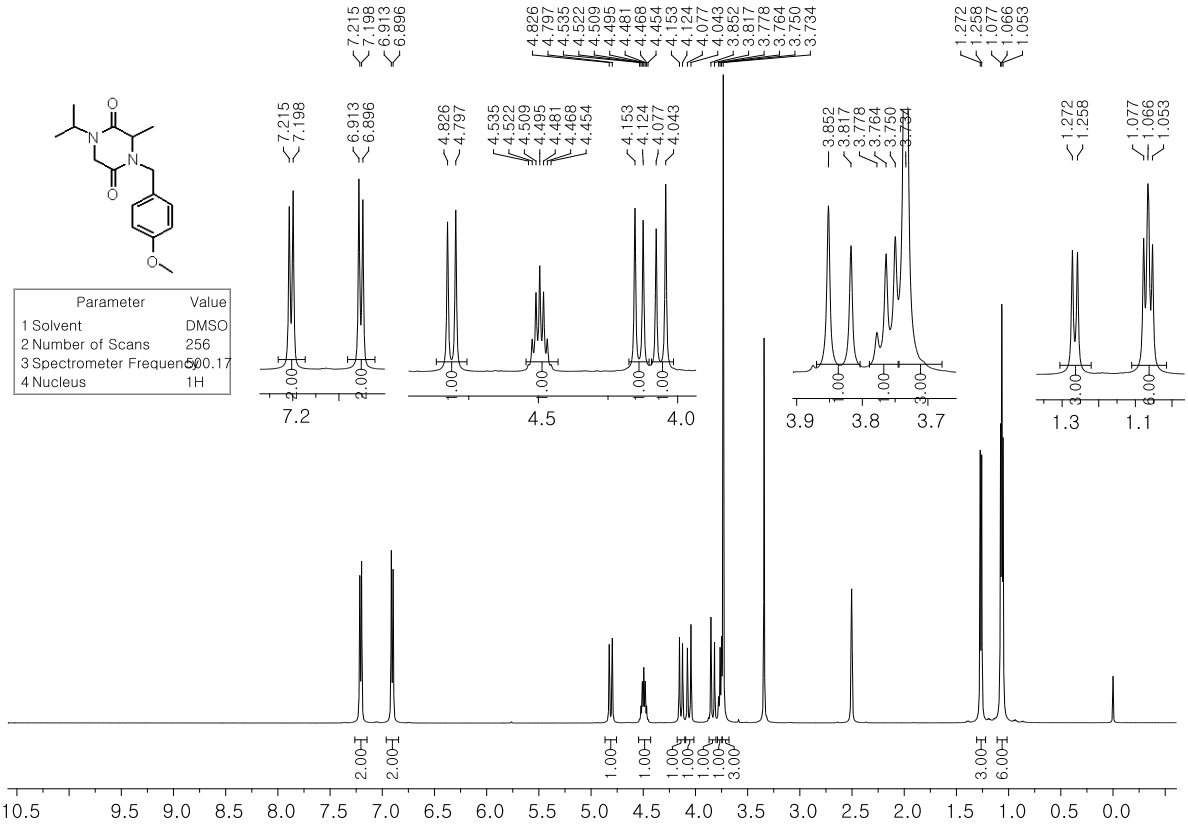

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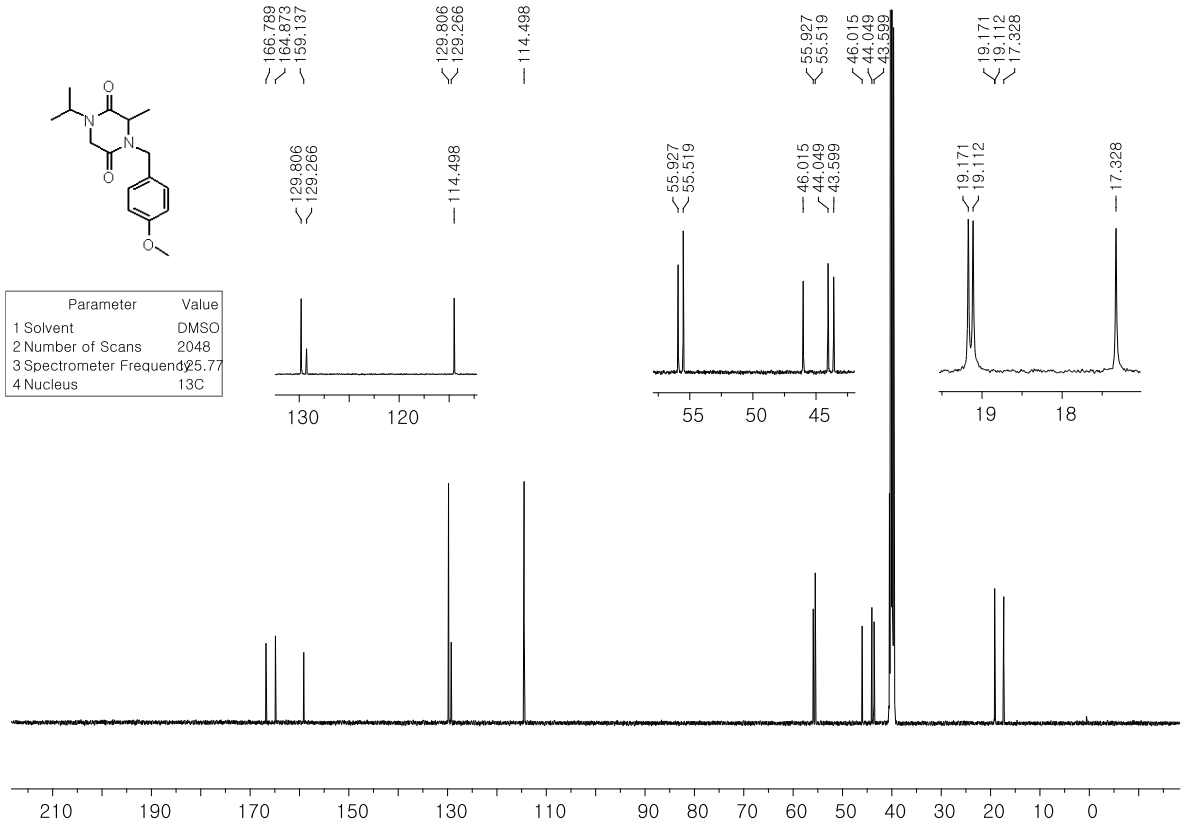

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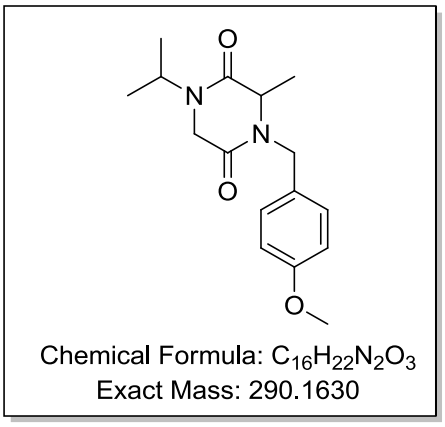

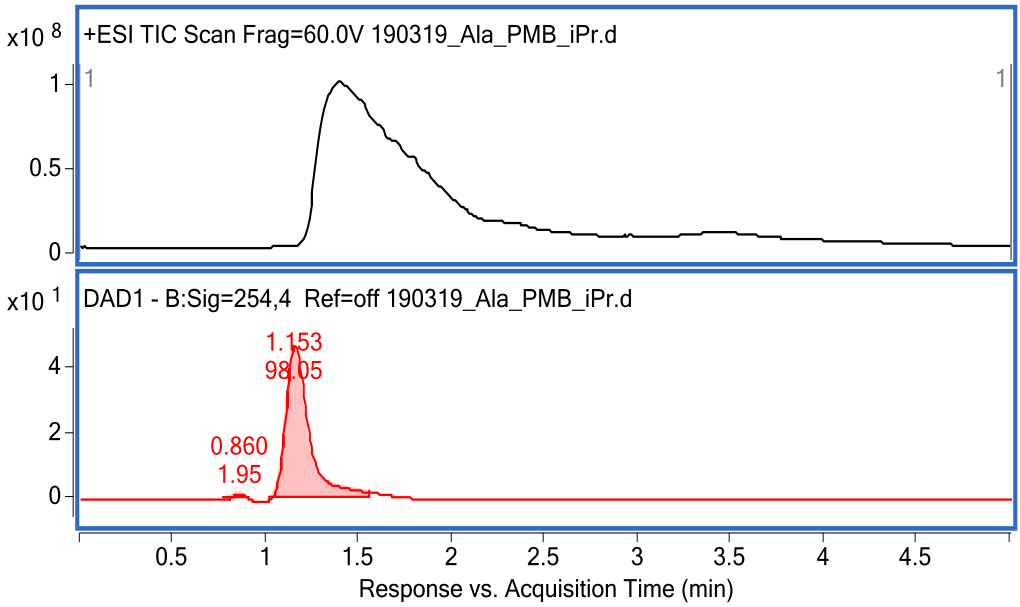

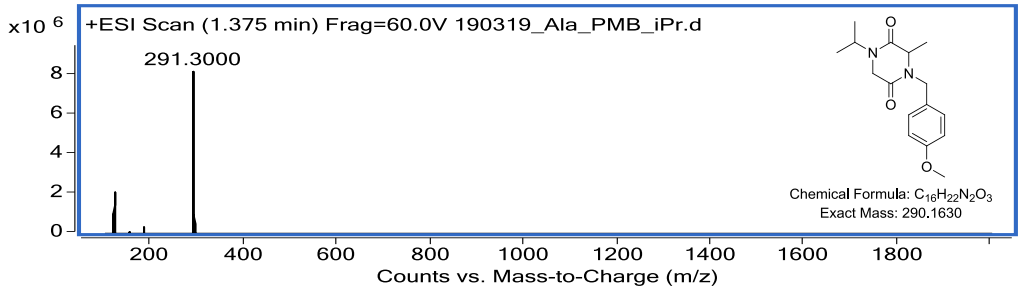

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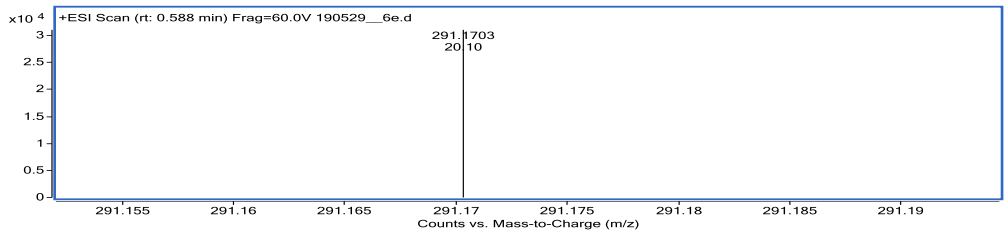

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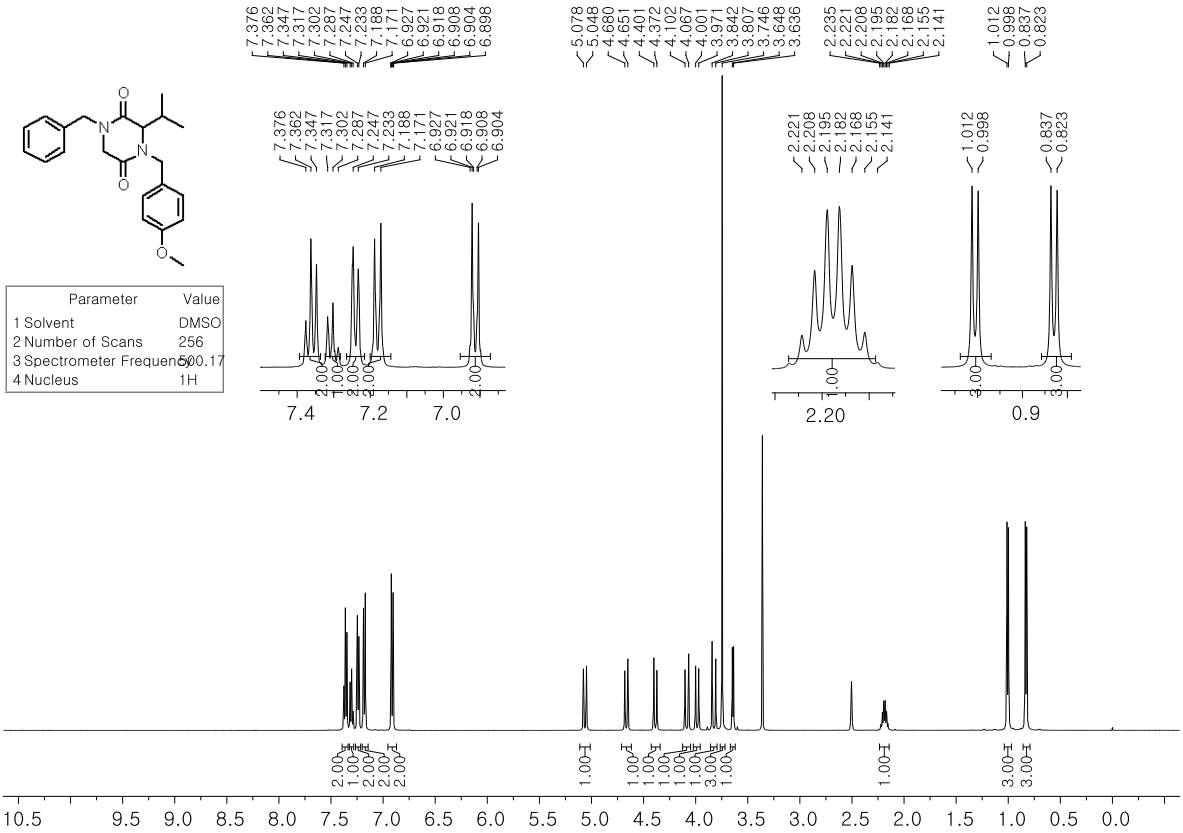
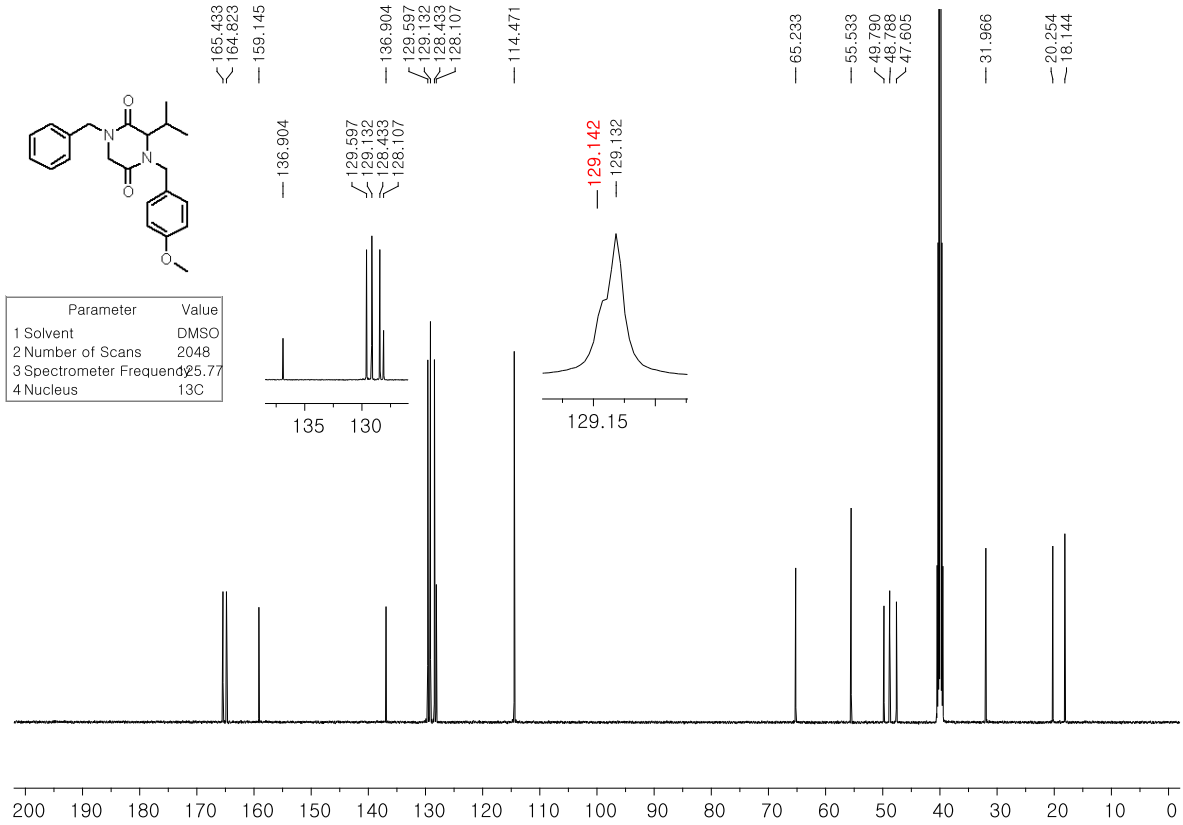


^{1}H NMR – 6f



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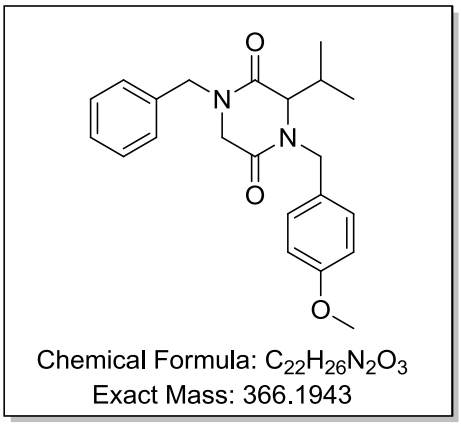

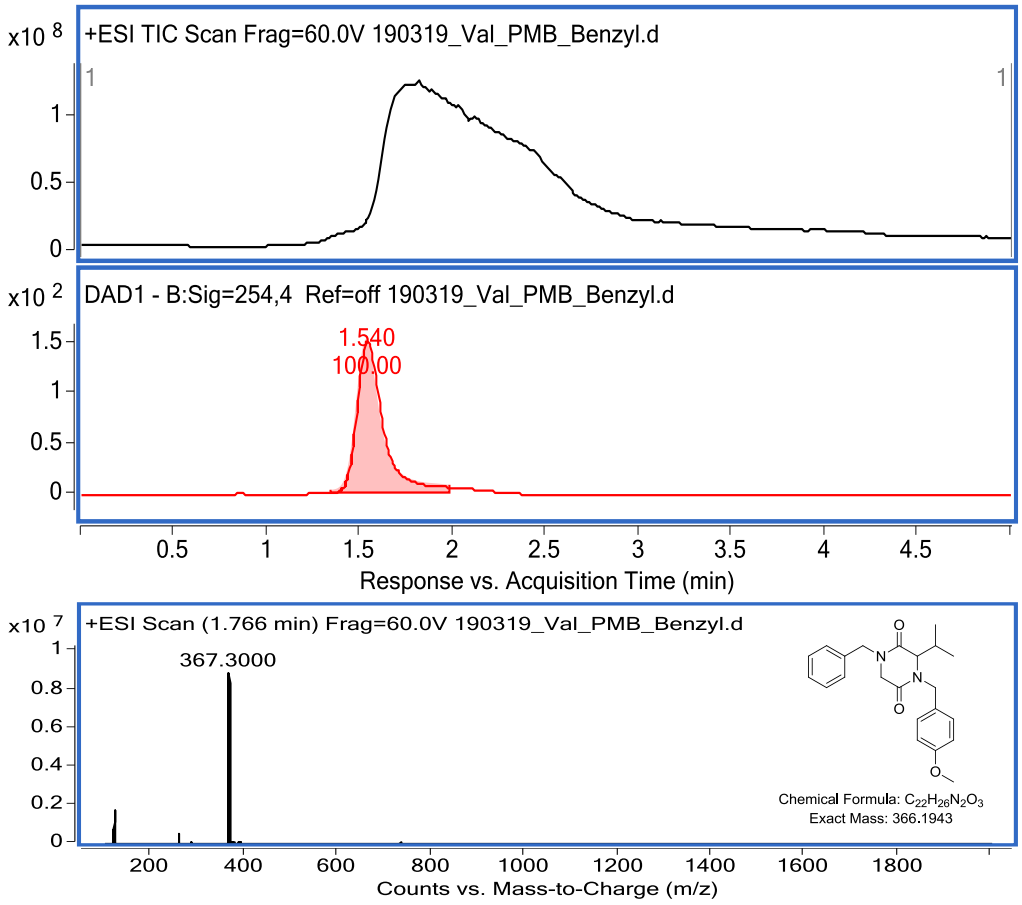

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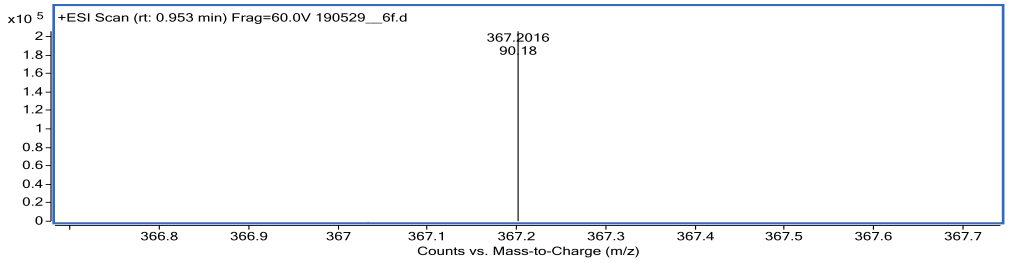

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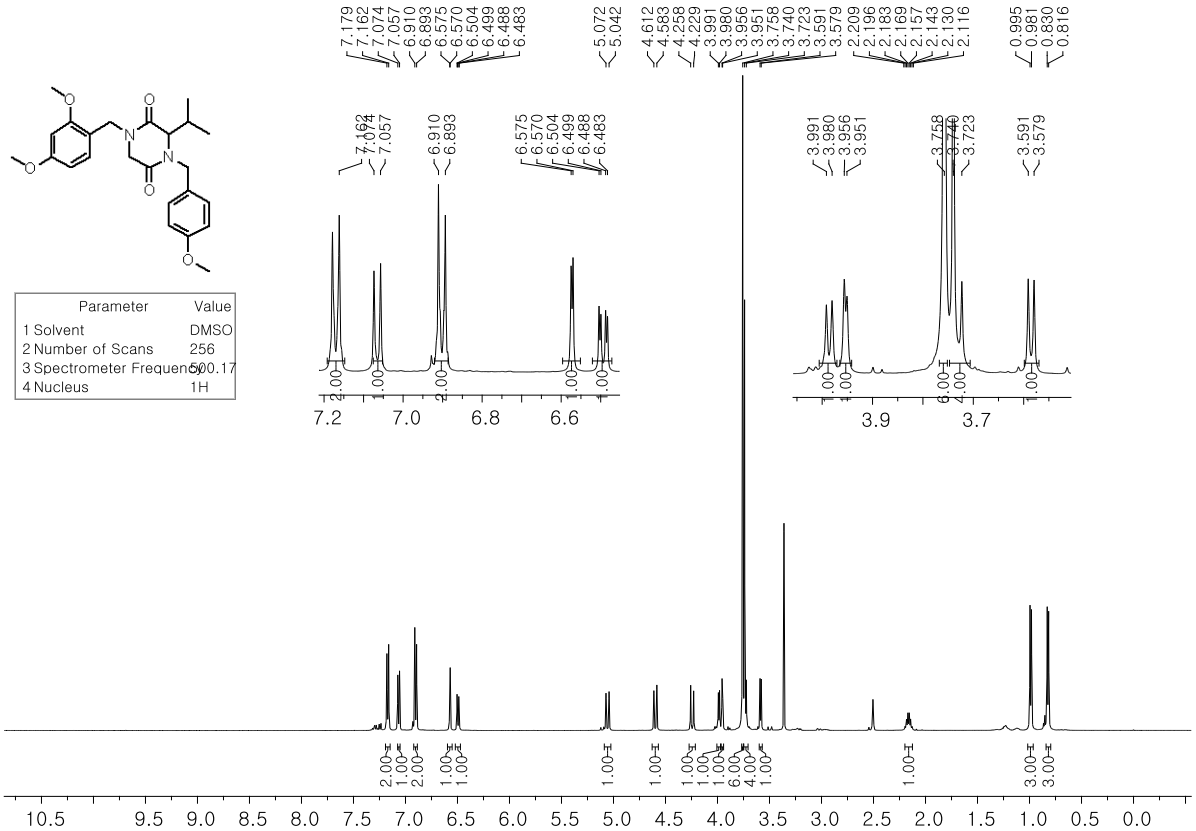
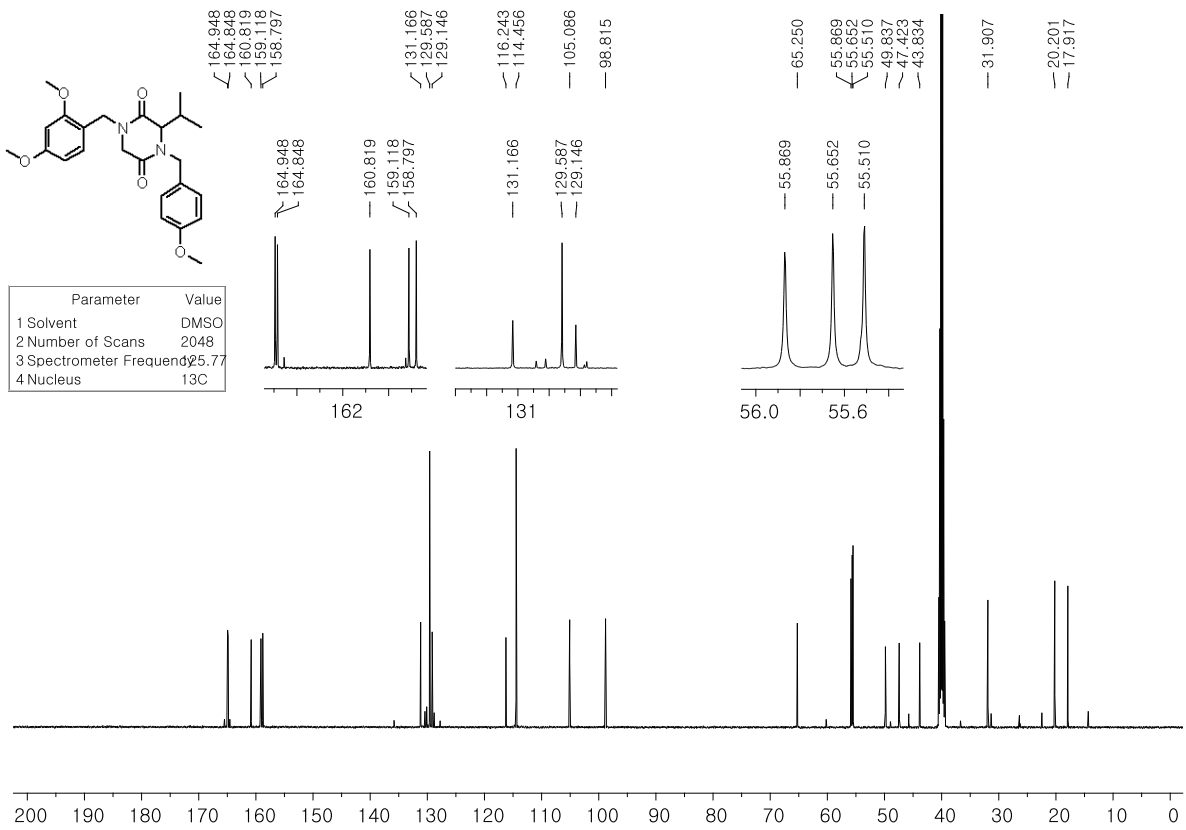
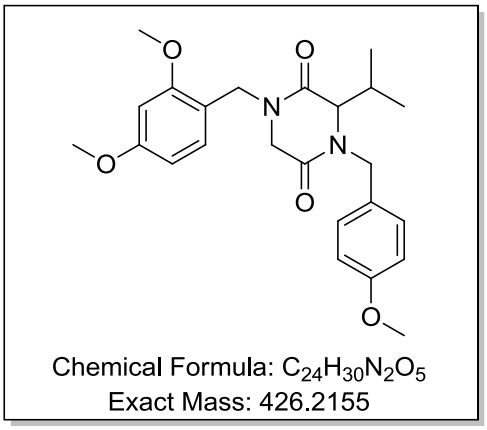
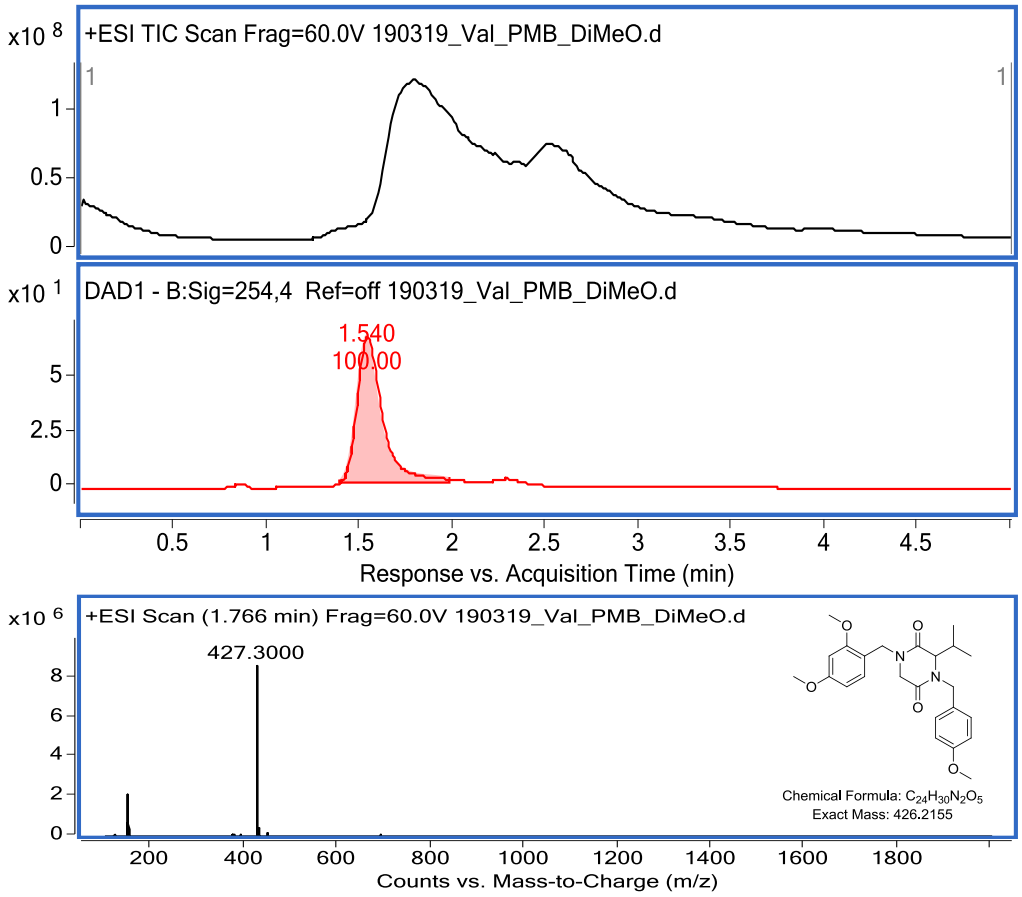


^{1}H NMR – 6g



^{13}C NMR – 6g





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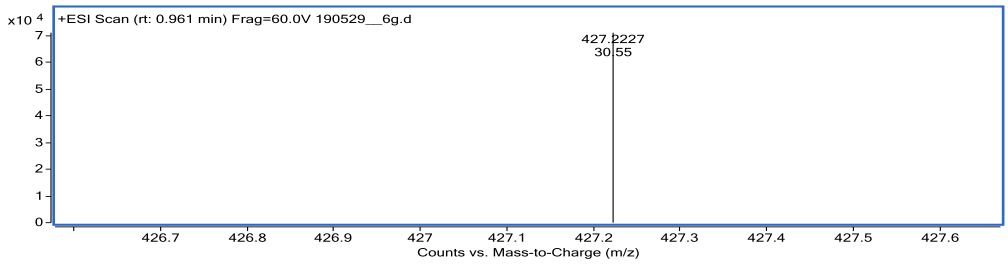

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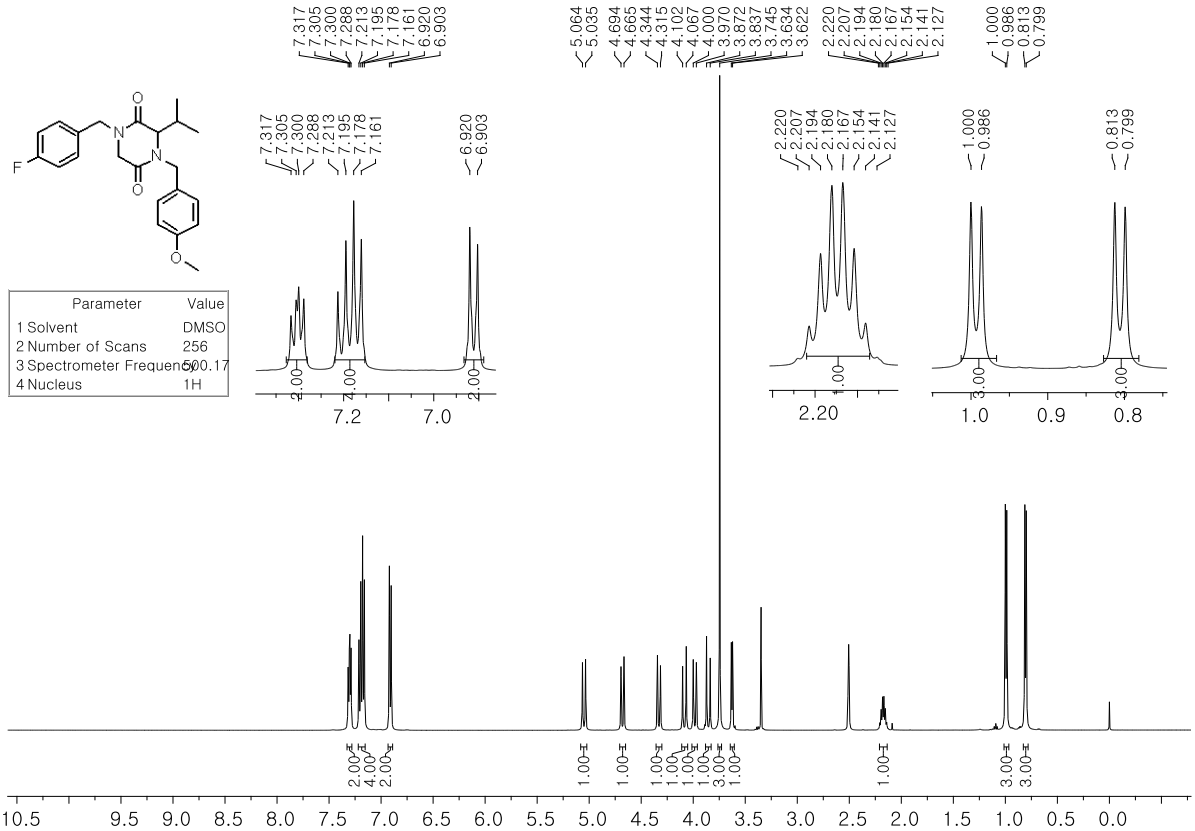

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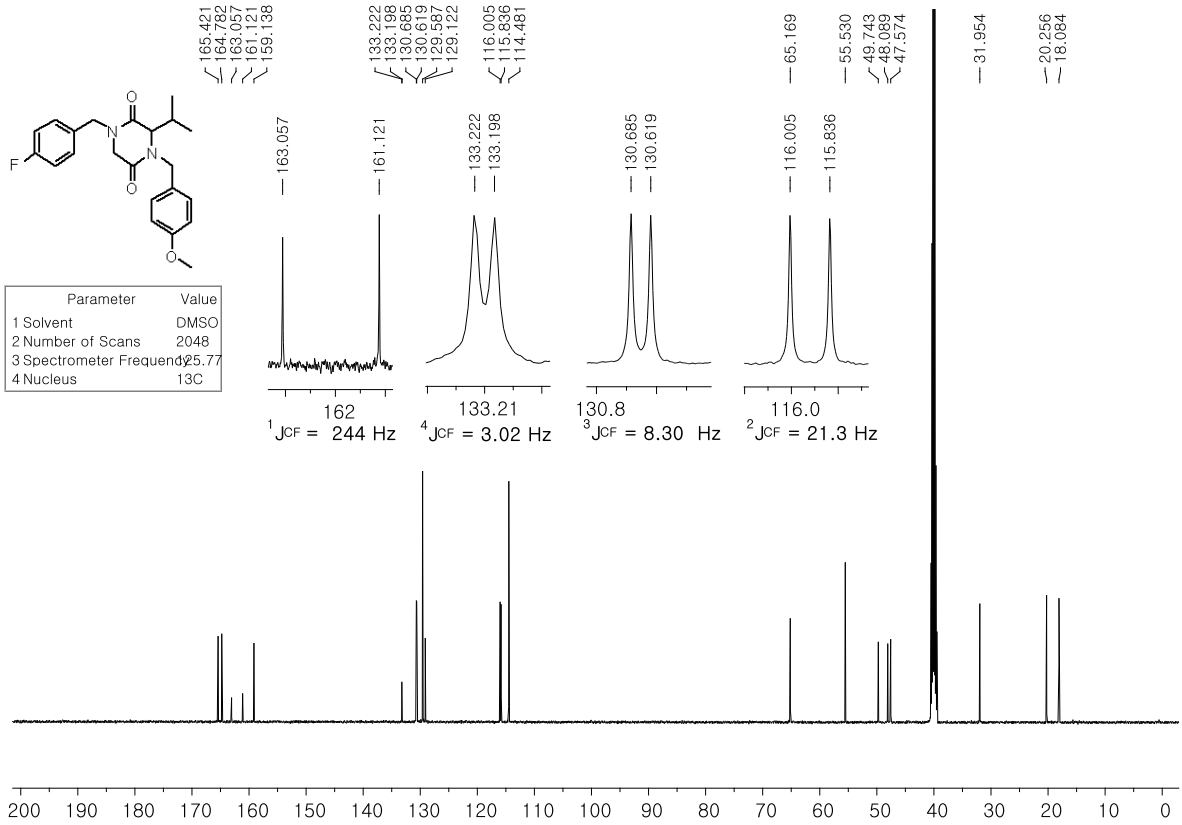

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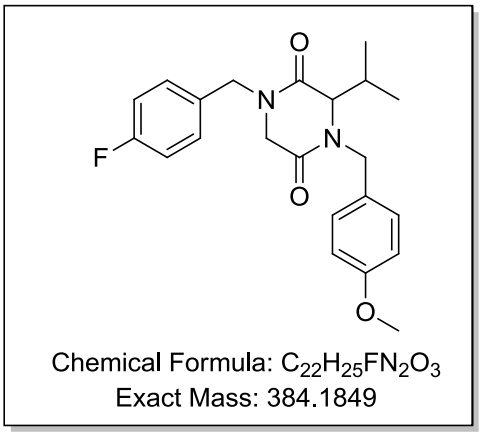
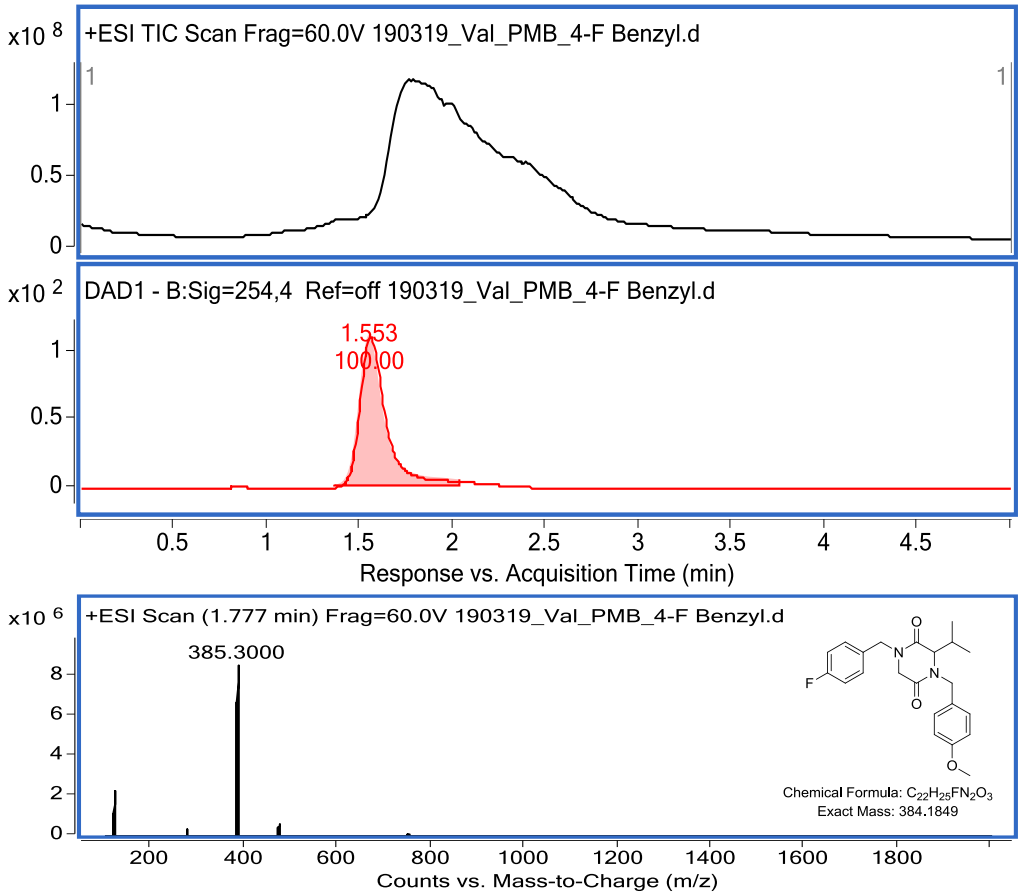
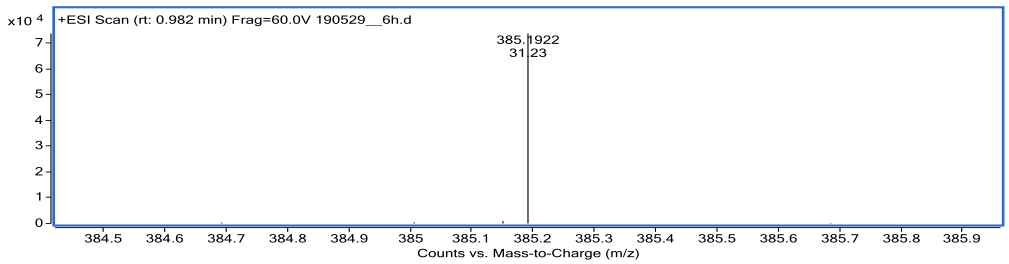
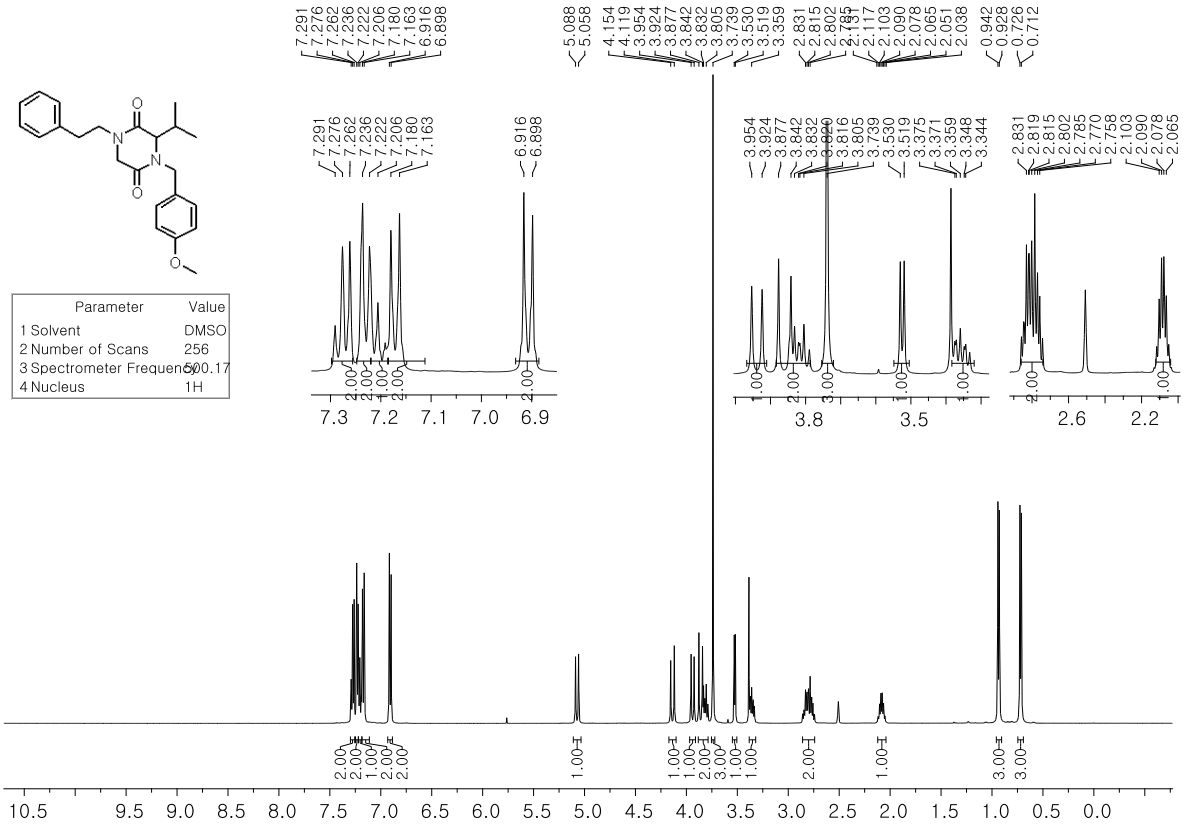




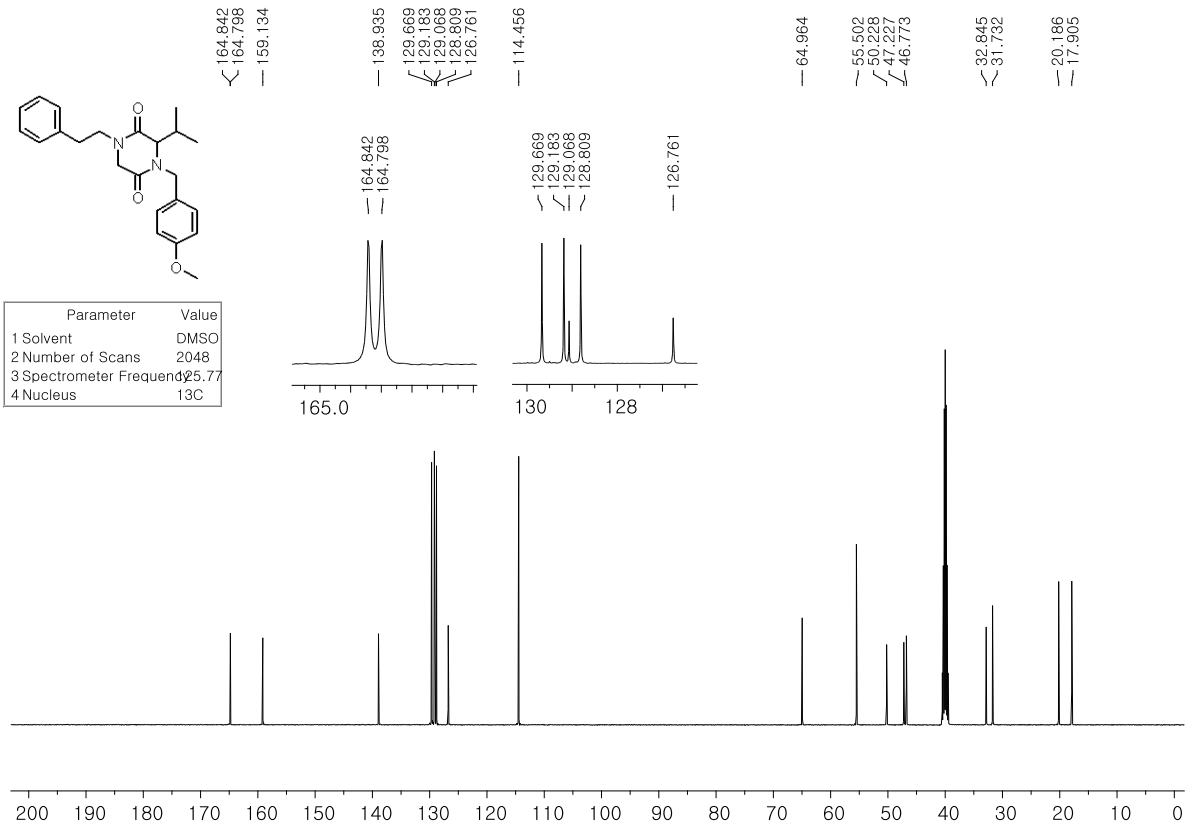
LC/MS – 6h



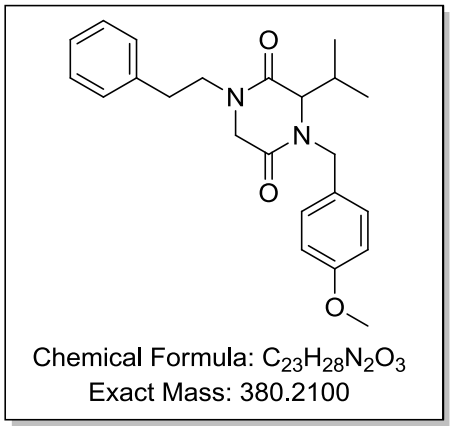
HRMS – 6h

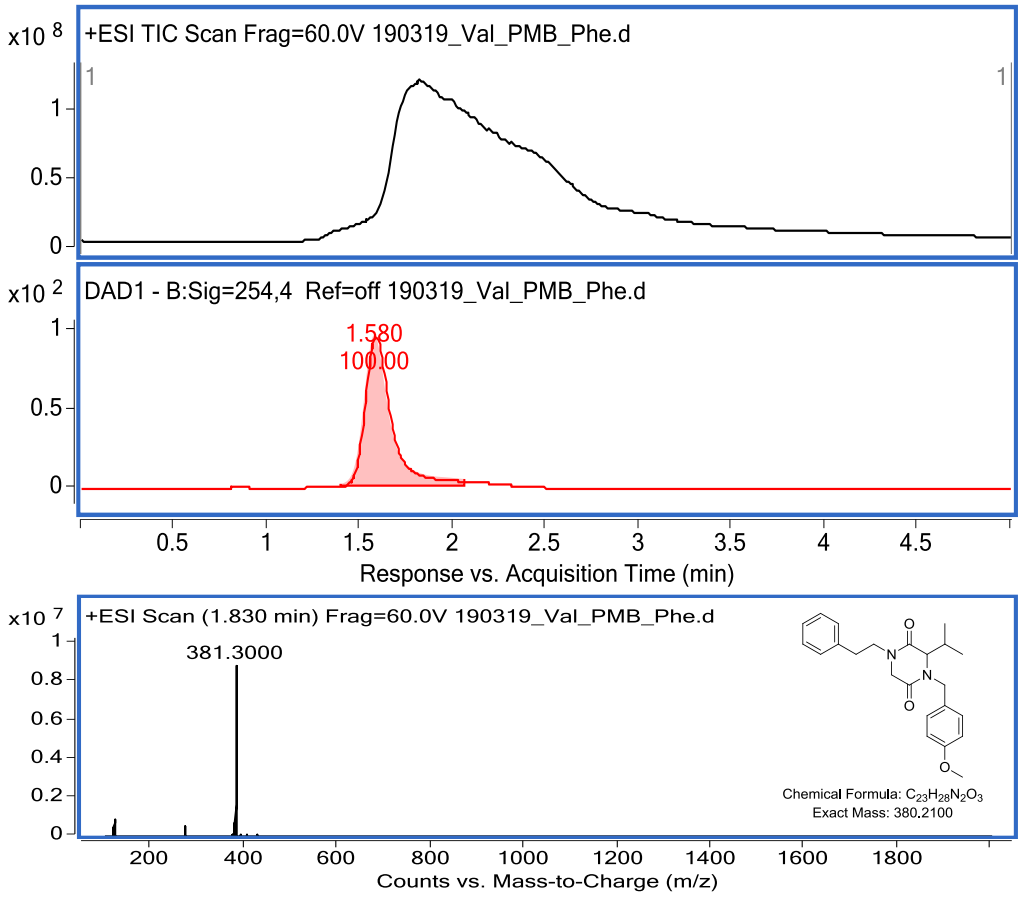


^{1}H NMR – 6i

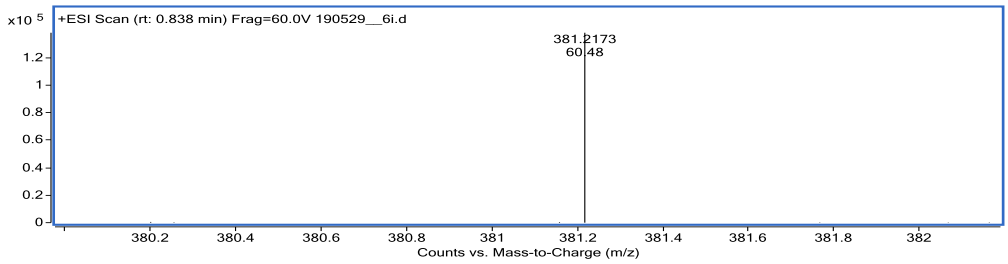


^{13}C NMR – 6i

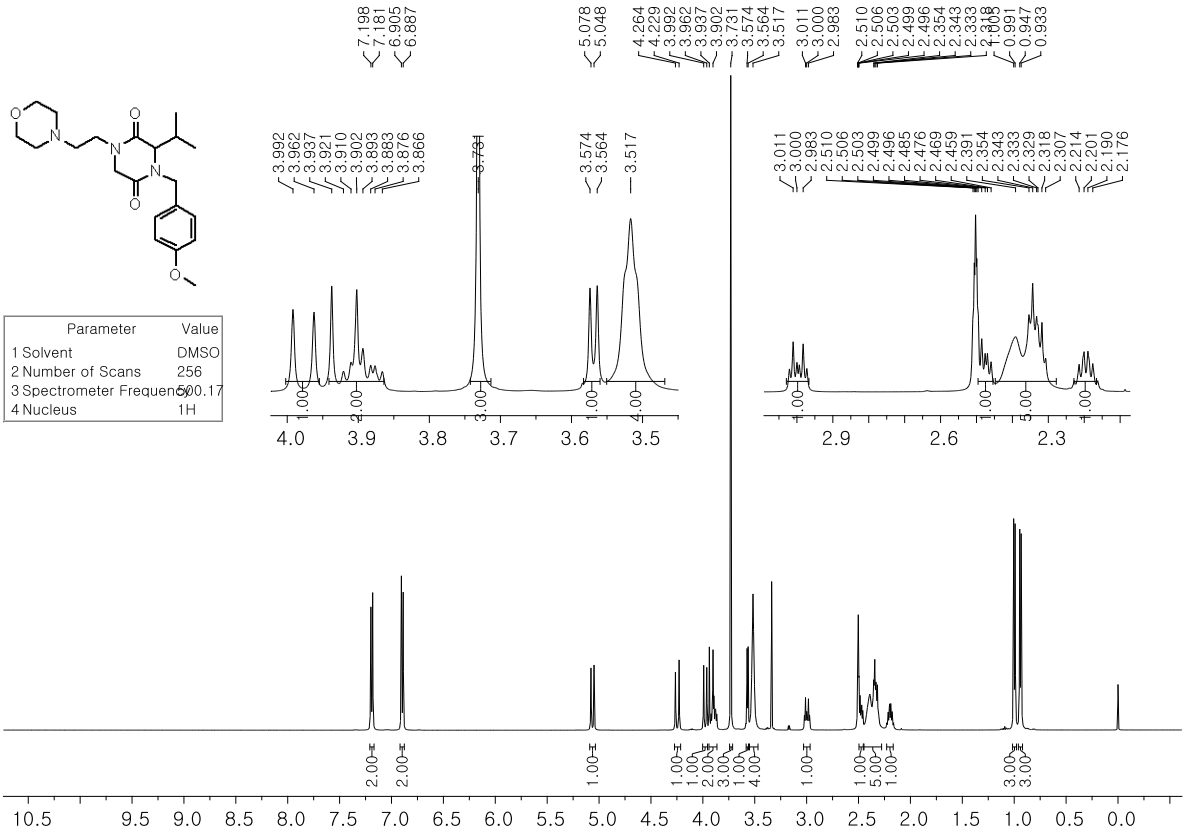




LC/MS – 6i



HRMS – 6i



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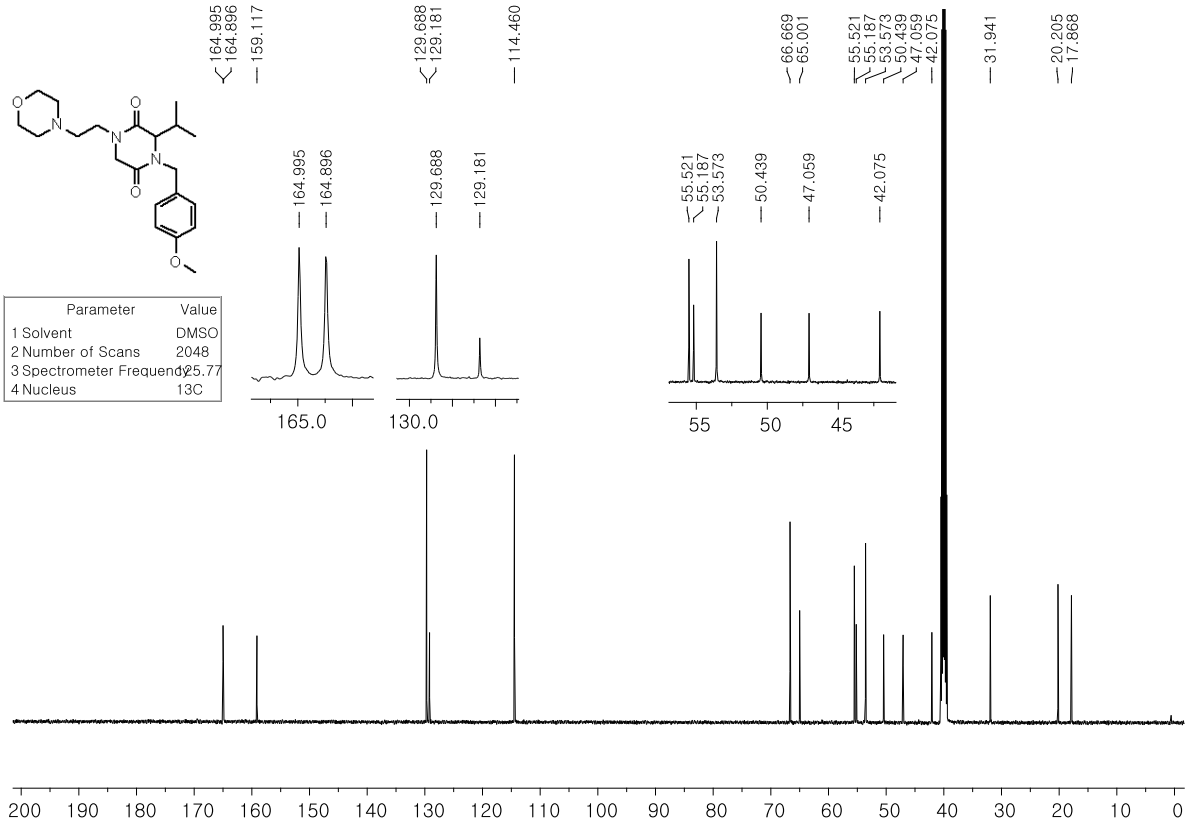

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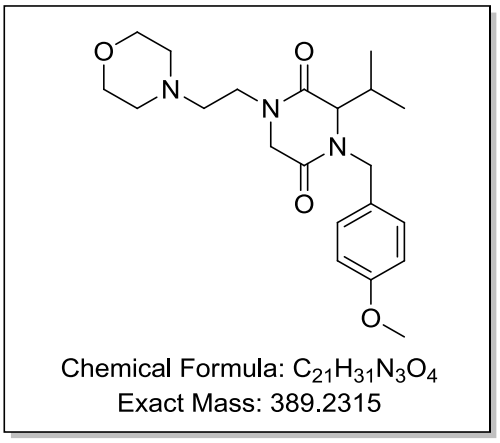
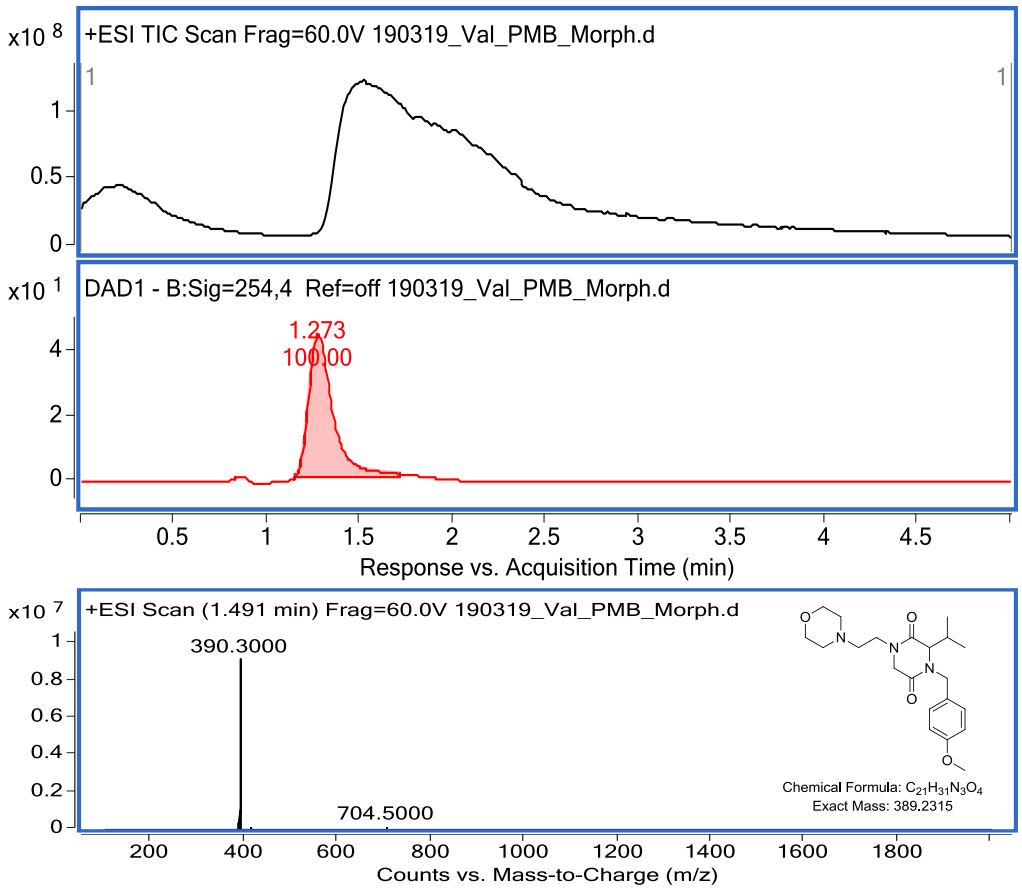
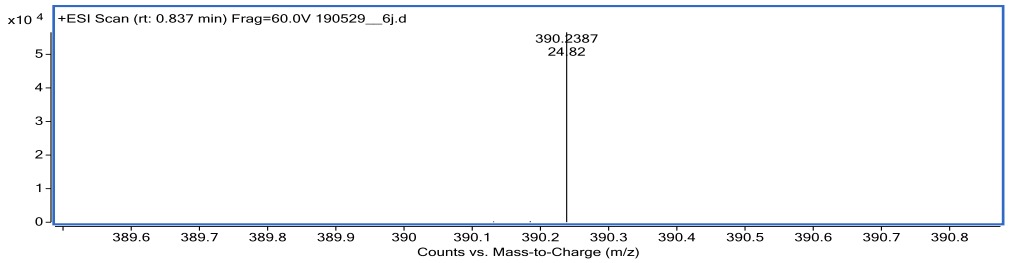




LC/MS – 6j



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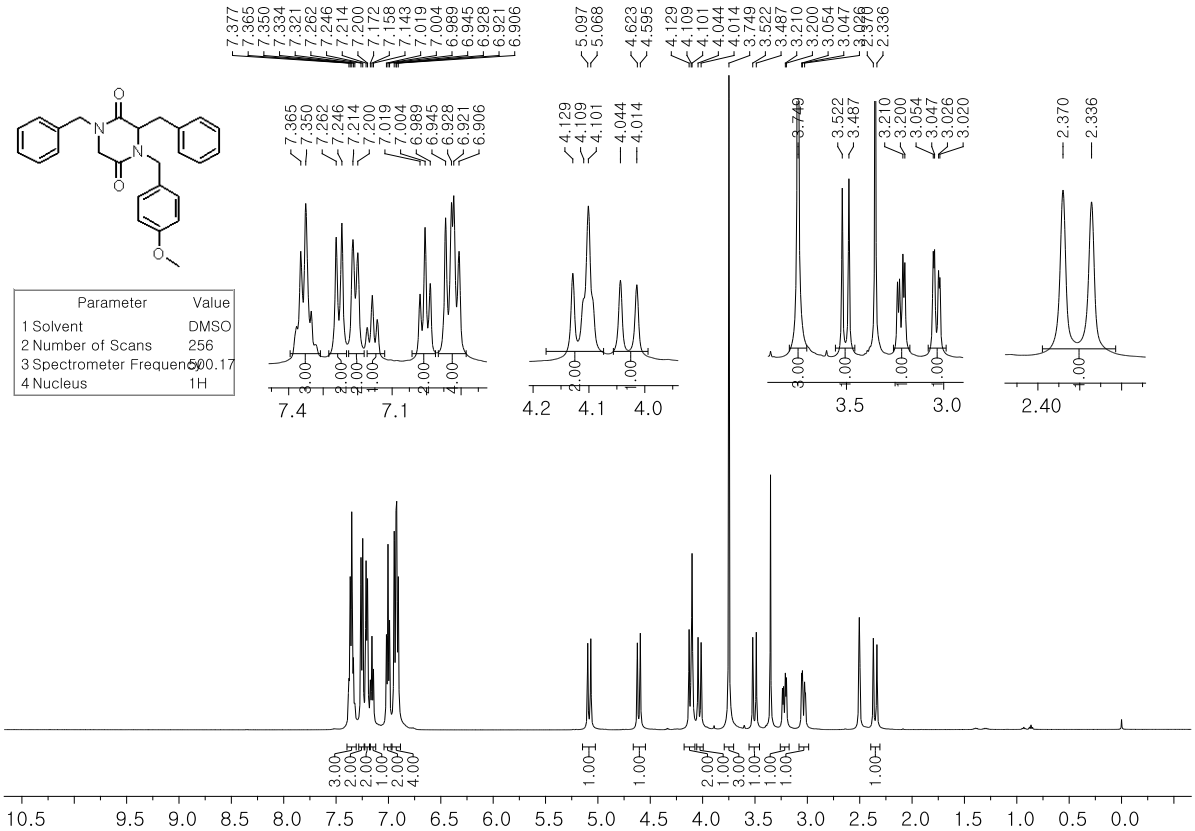

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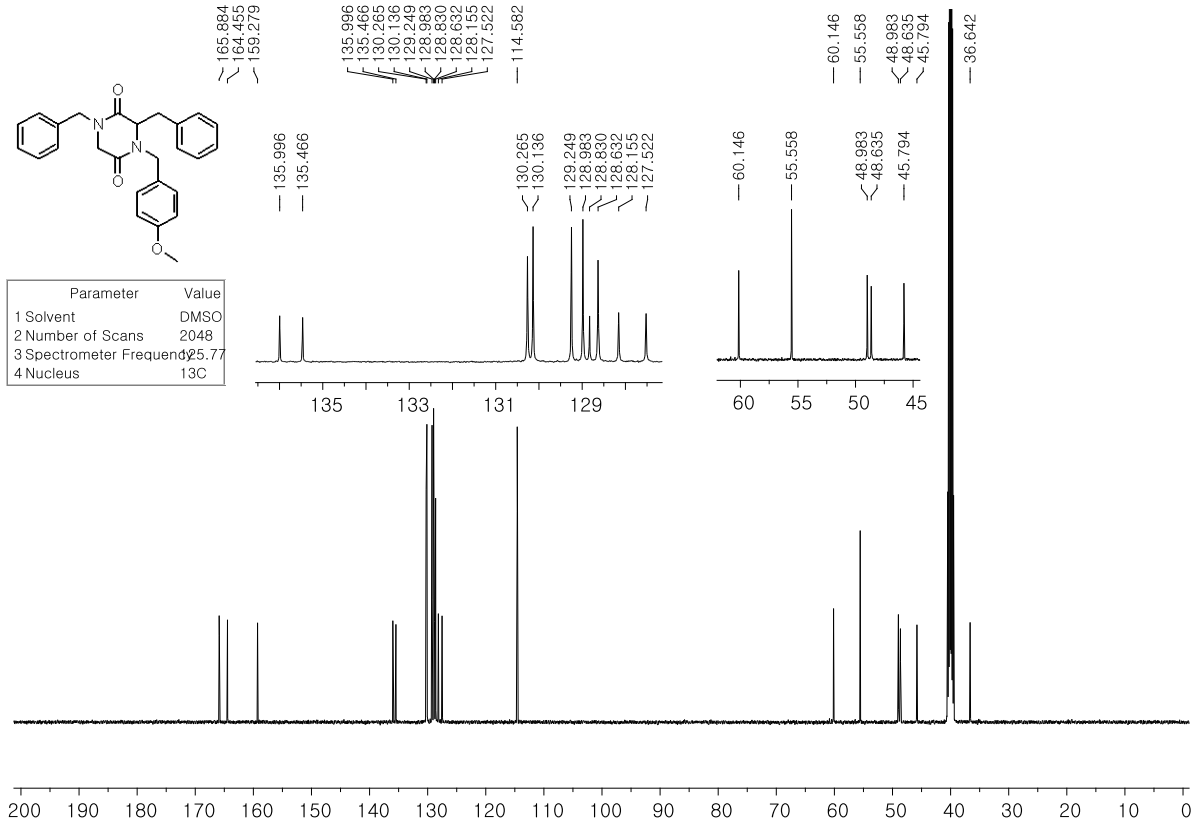

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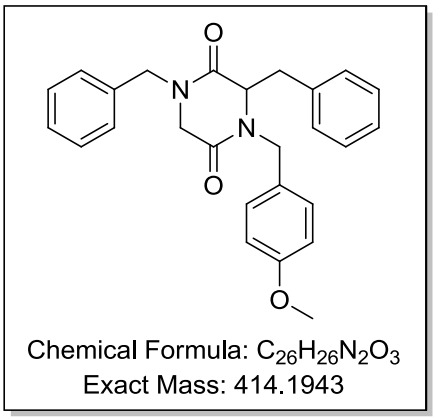
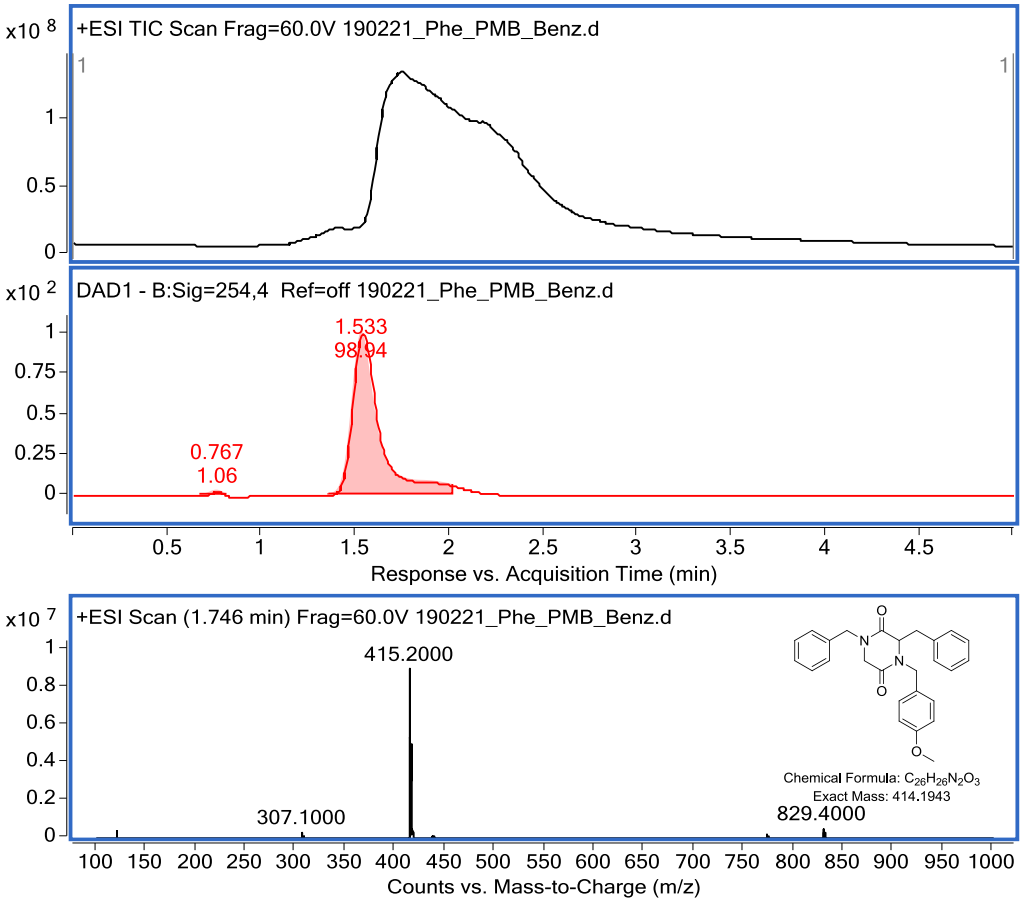
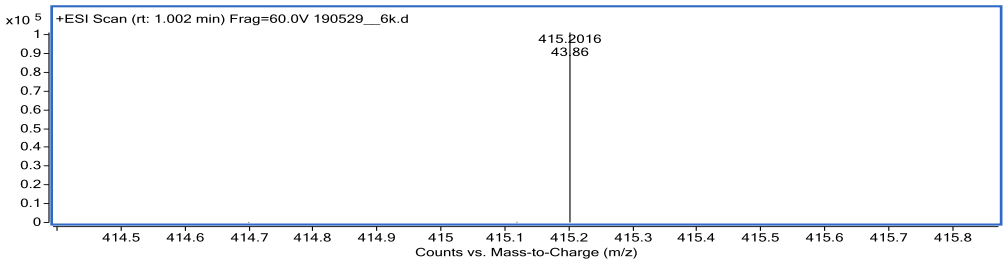




LC/MS – 6k



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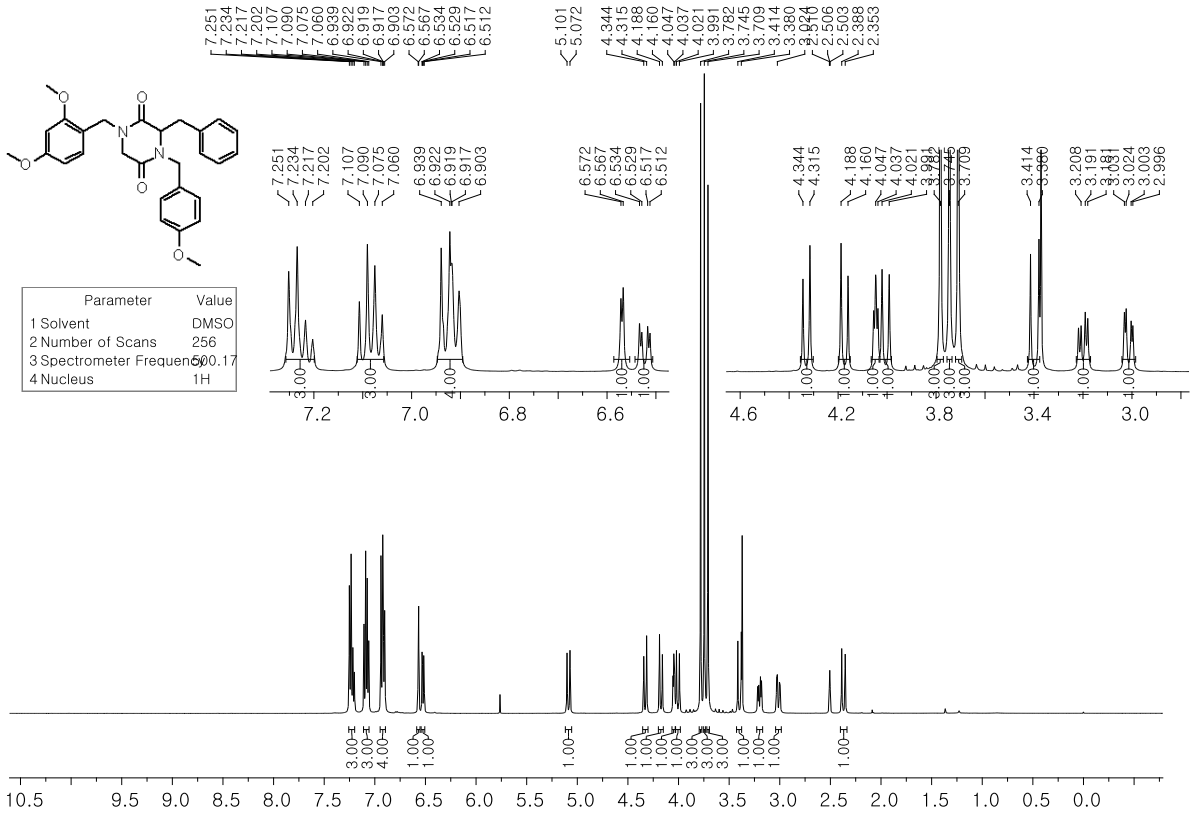

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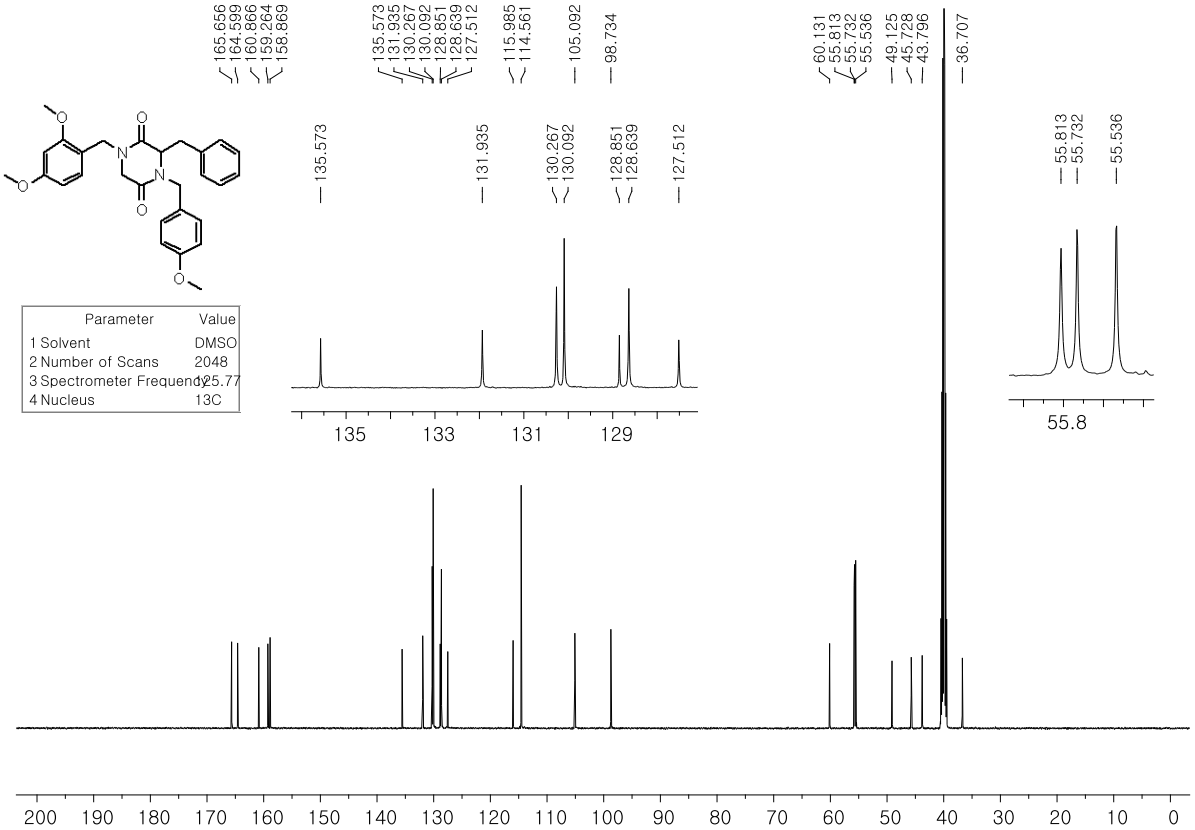
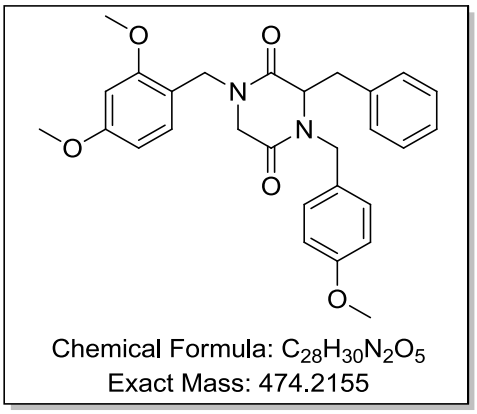
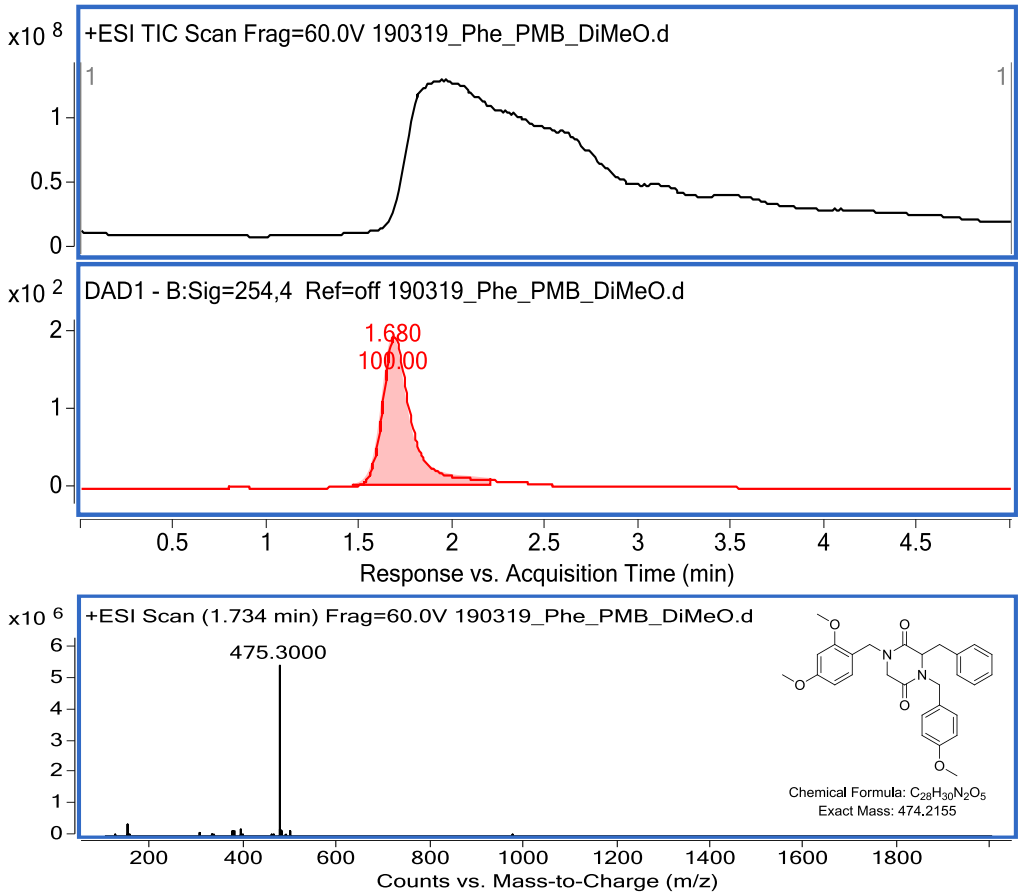
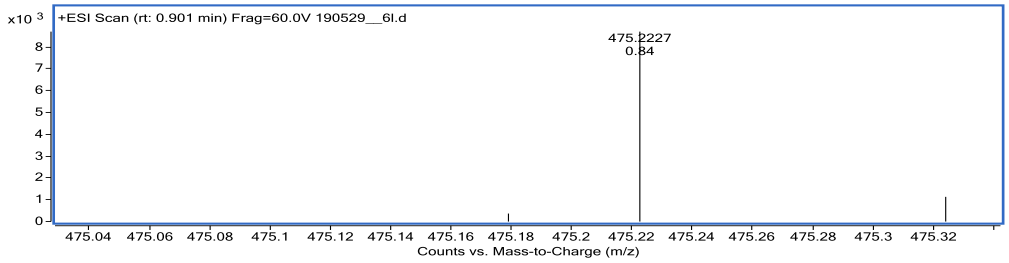


^{13}C NMR – 6l





LC/MS – 6l



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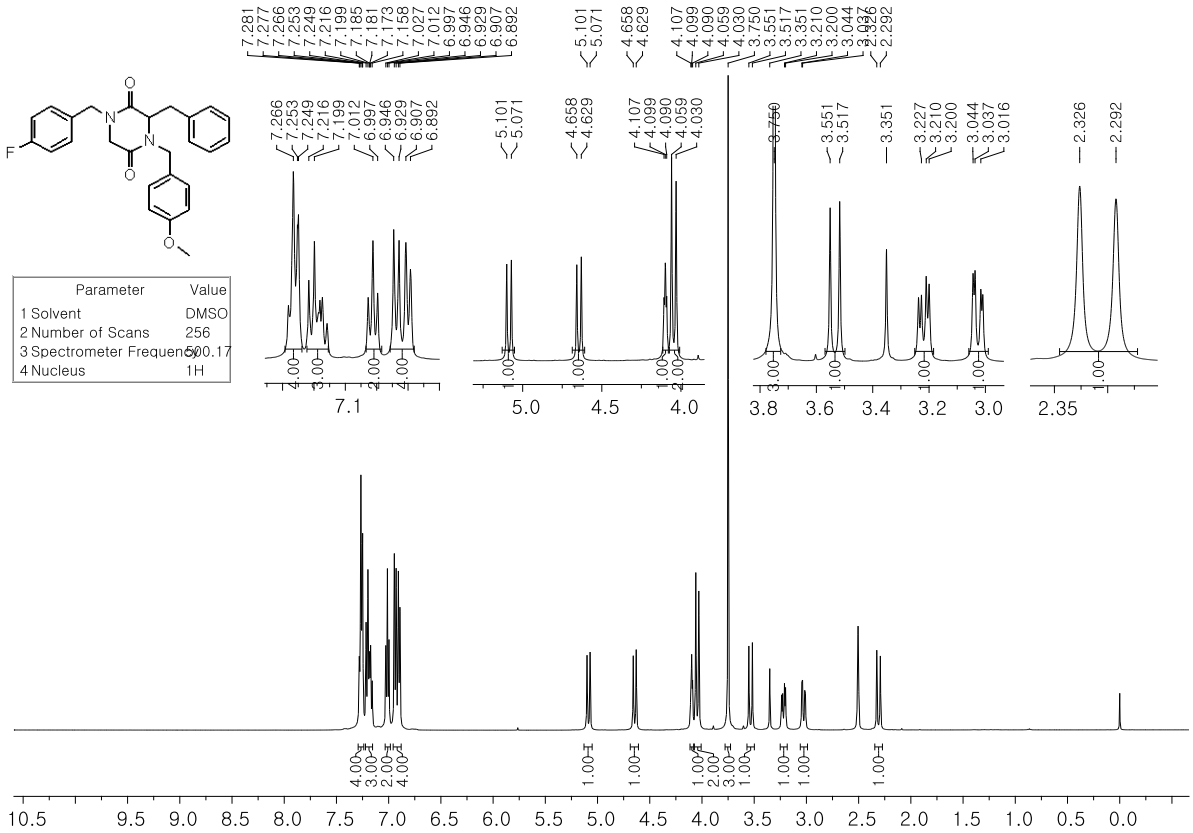

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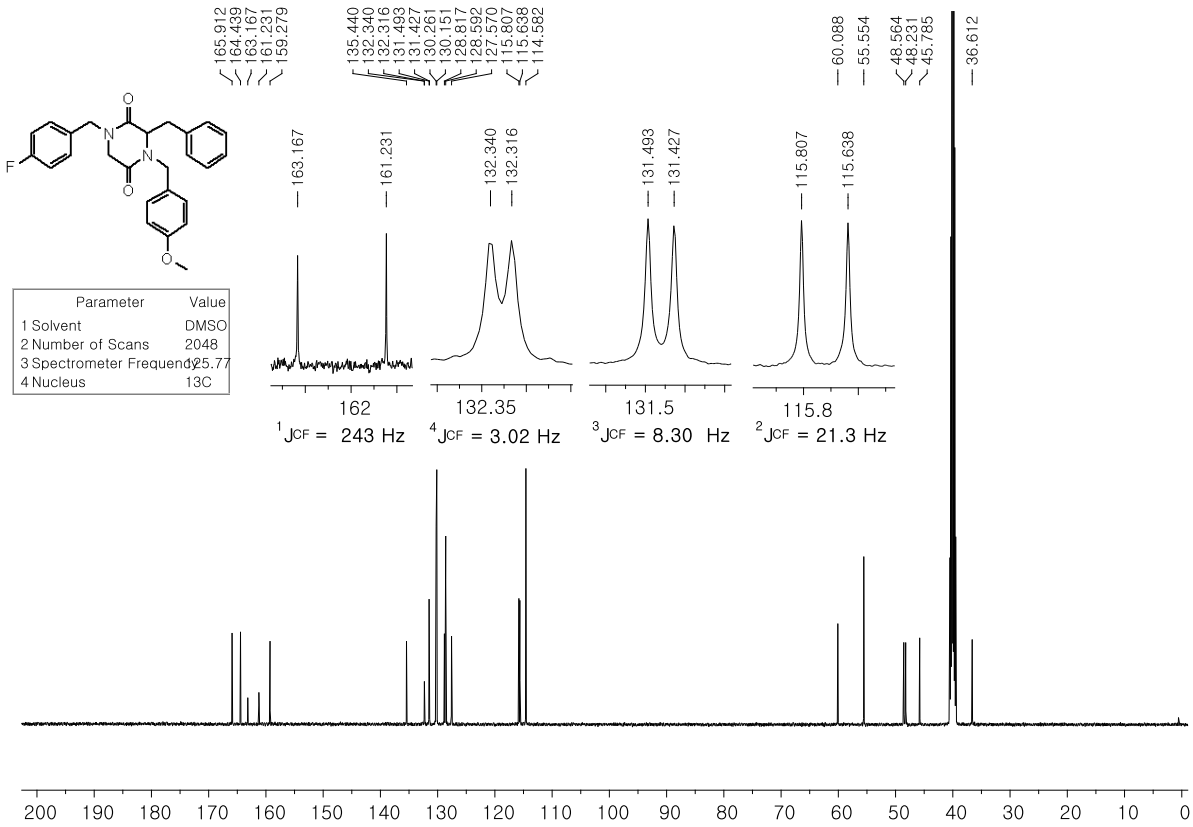
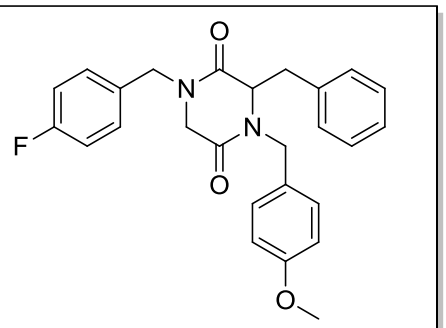
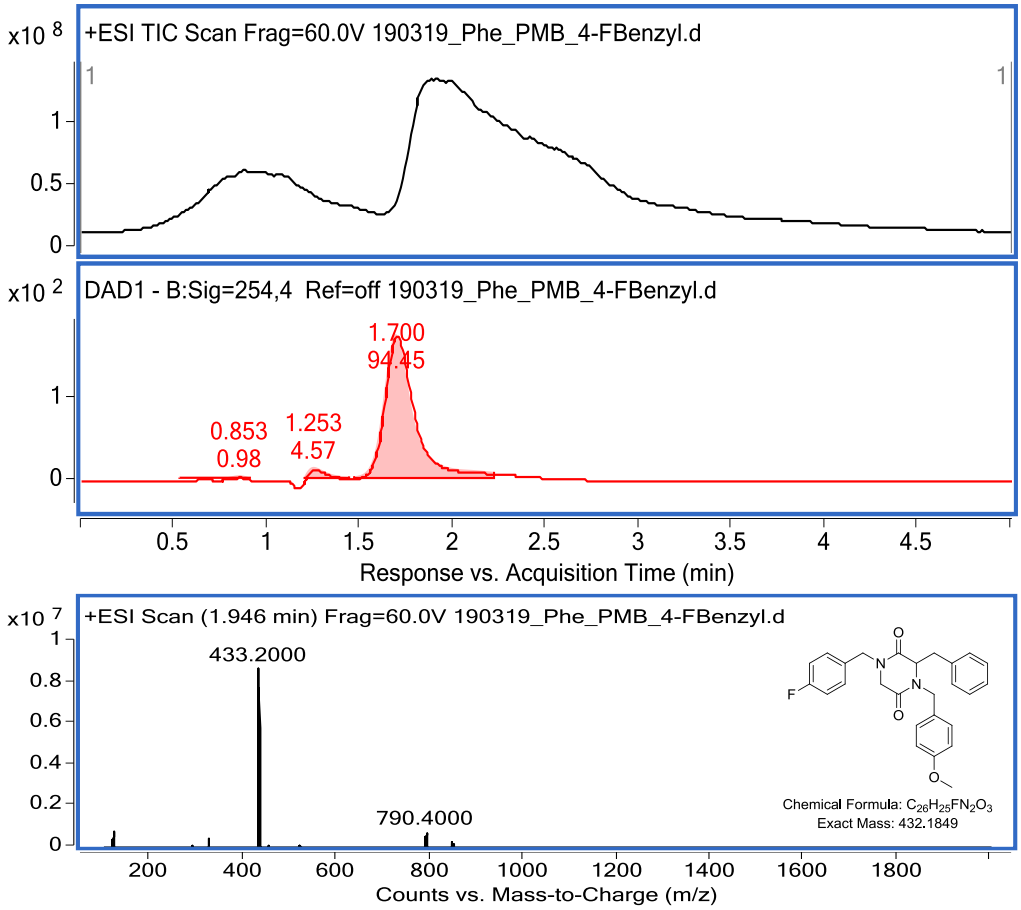


^{13}C NMR – 6m



Chemical Formula: $C_{26}H_{25}FN_2O_3$
Exact Mass: 432.1849



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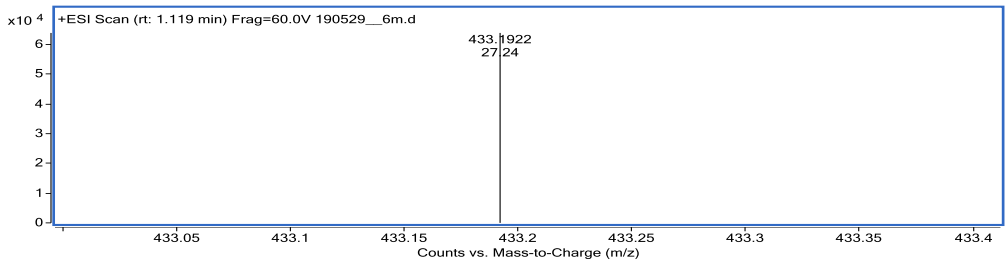

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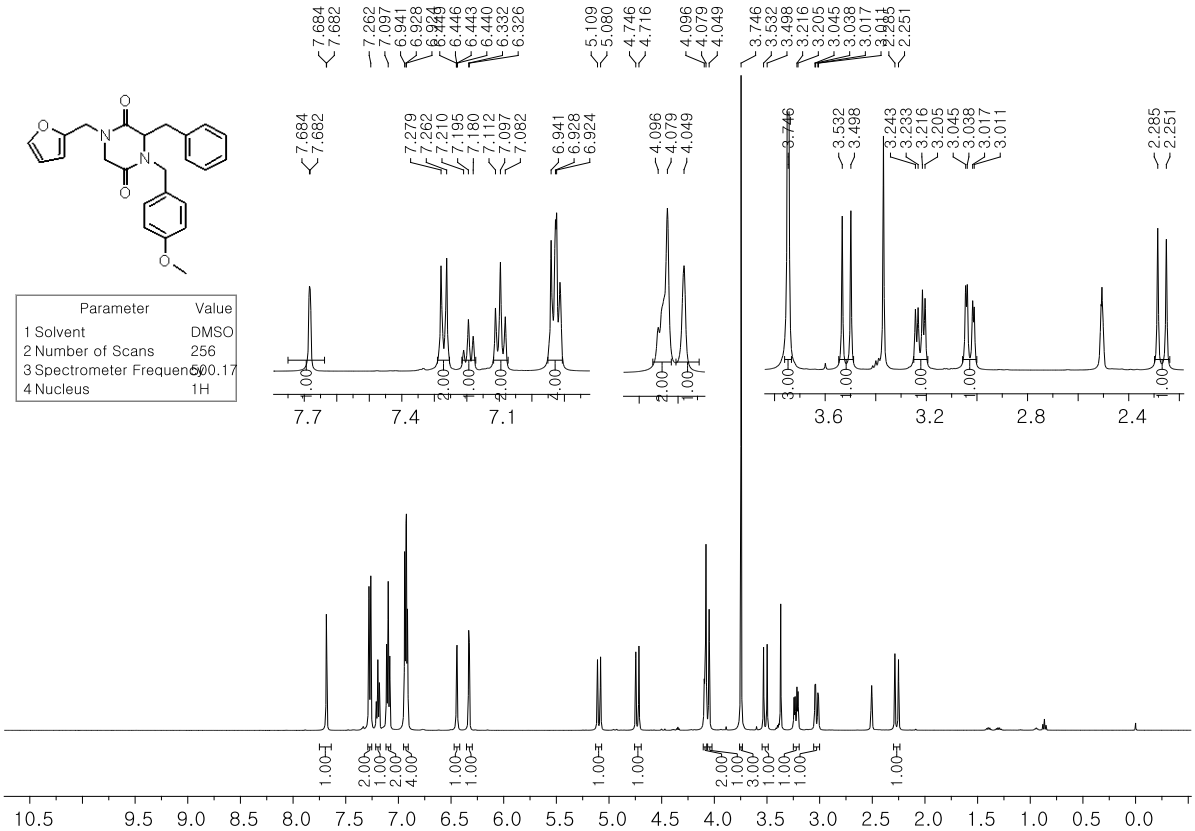

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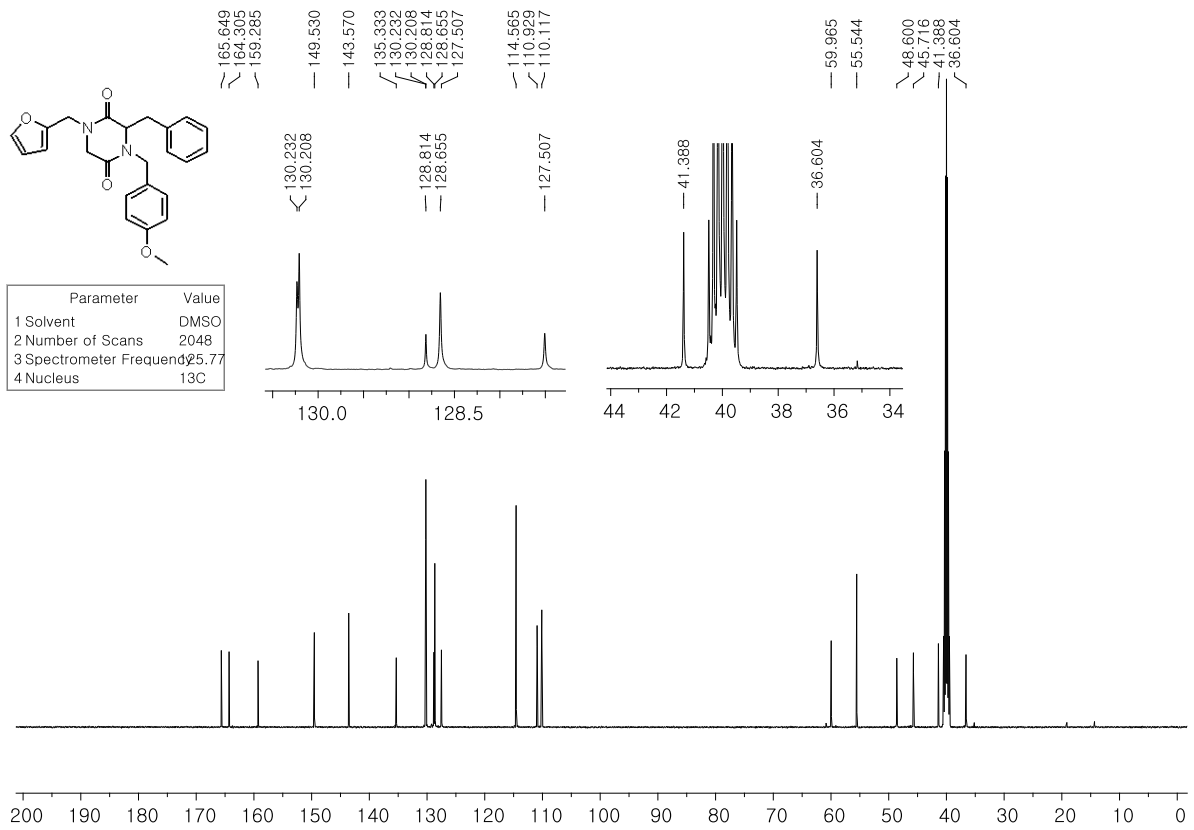

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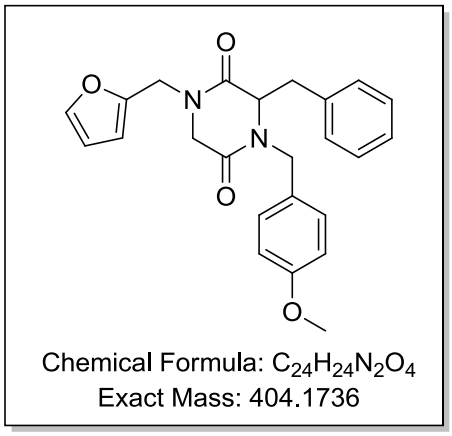

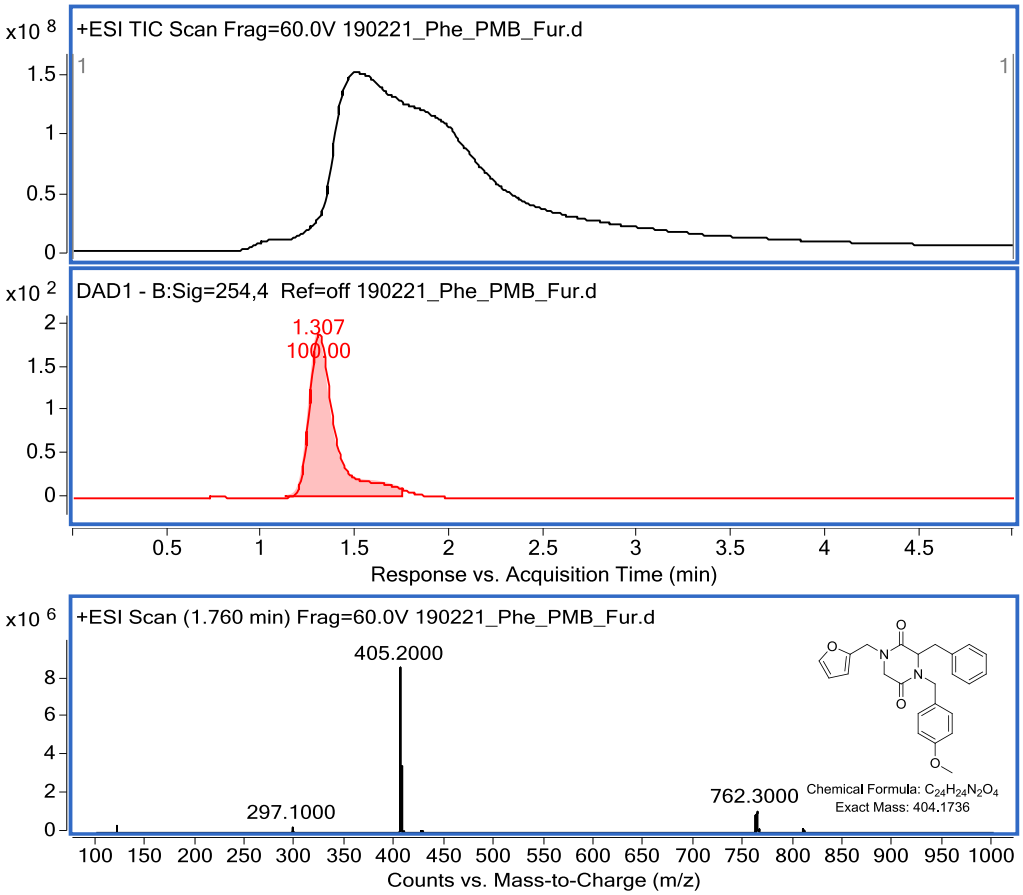

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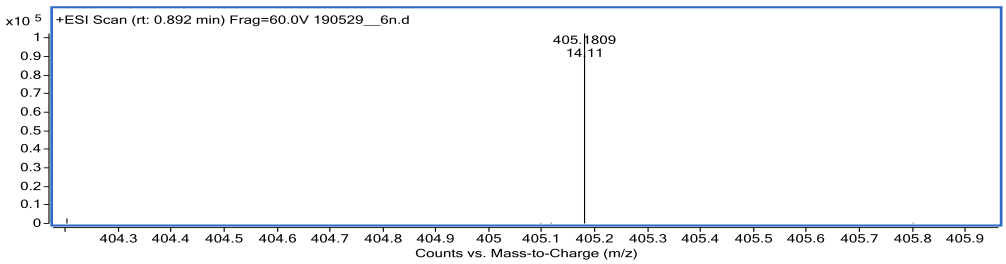

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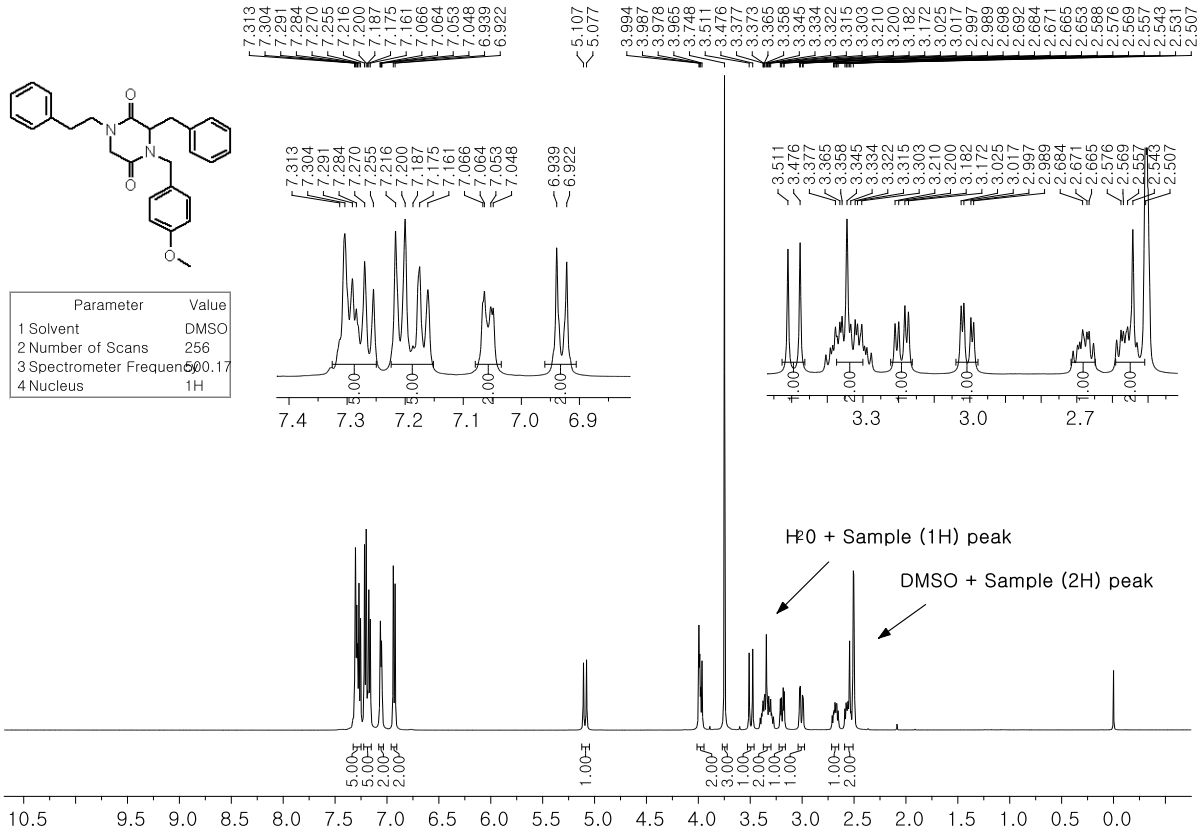
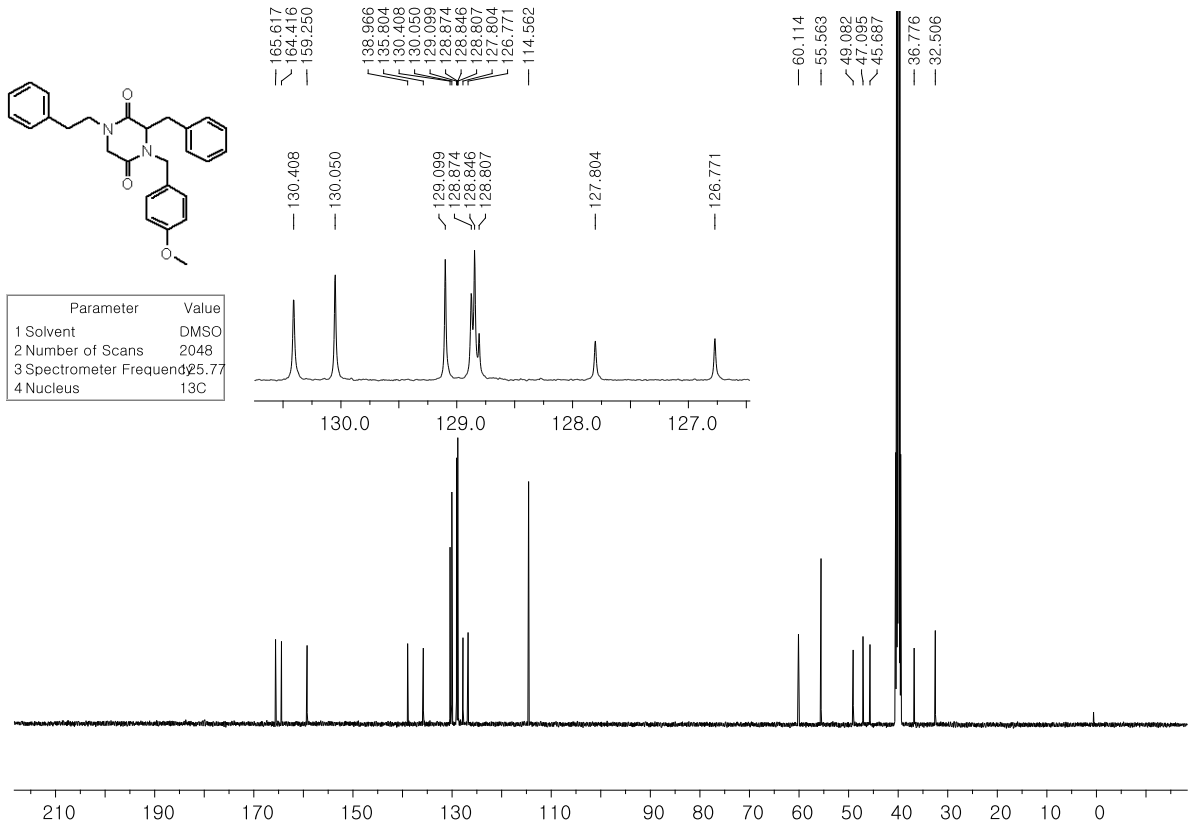


^{1}H NMR – 6o



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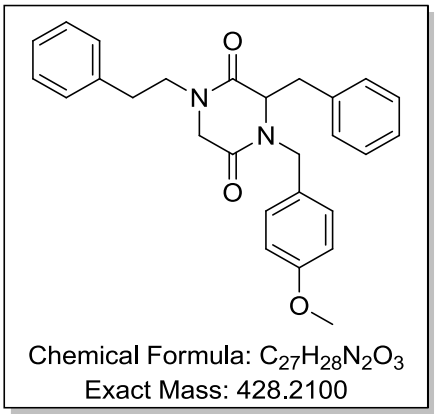

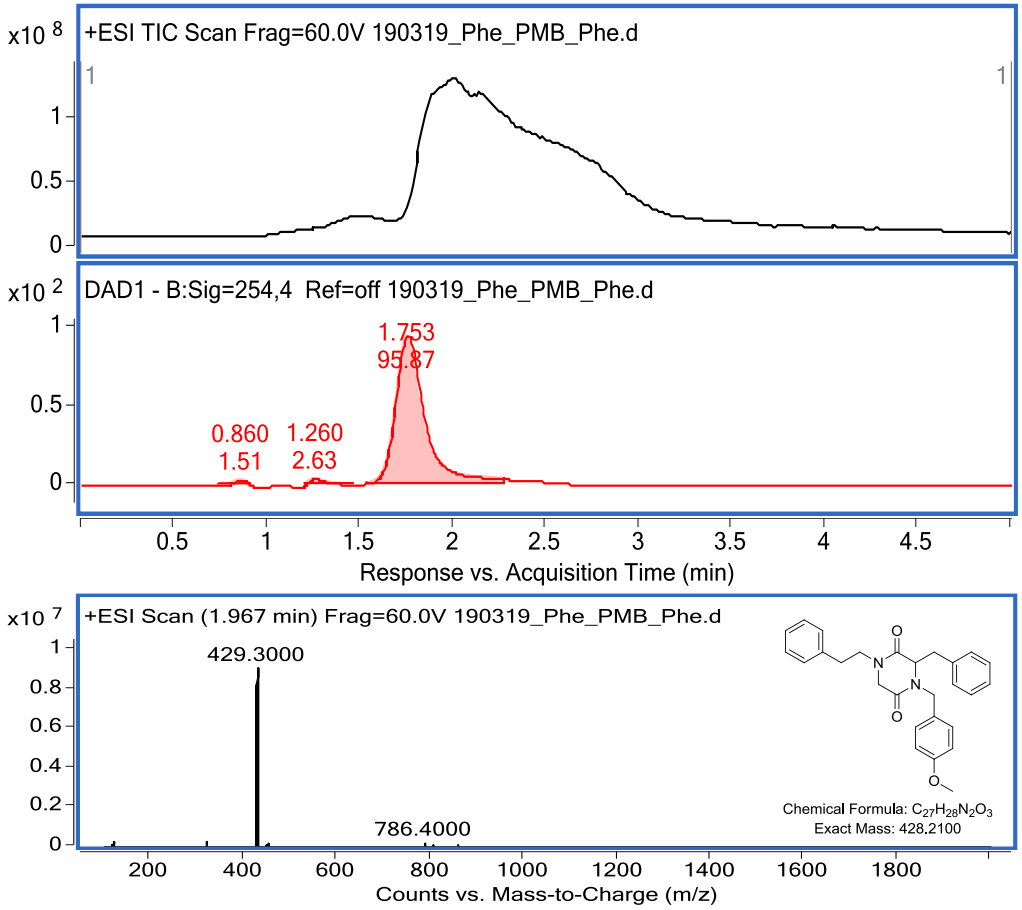

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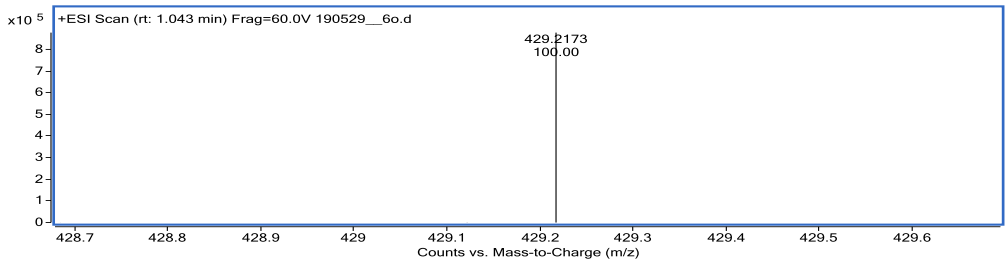
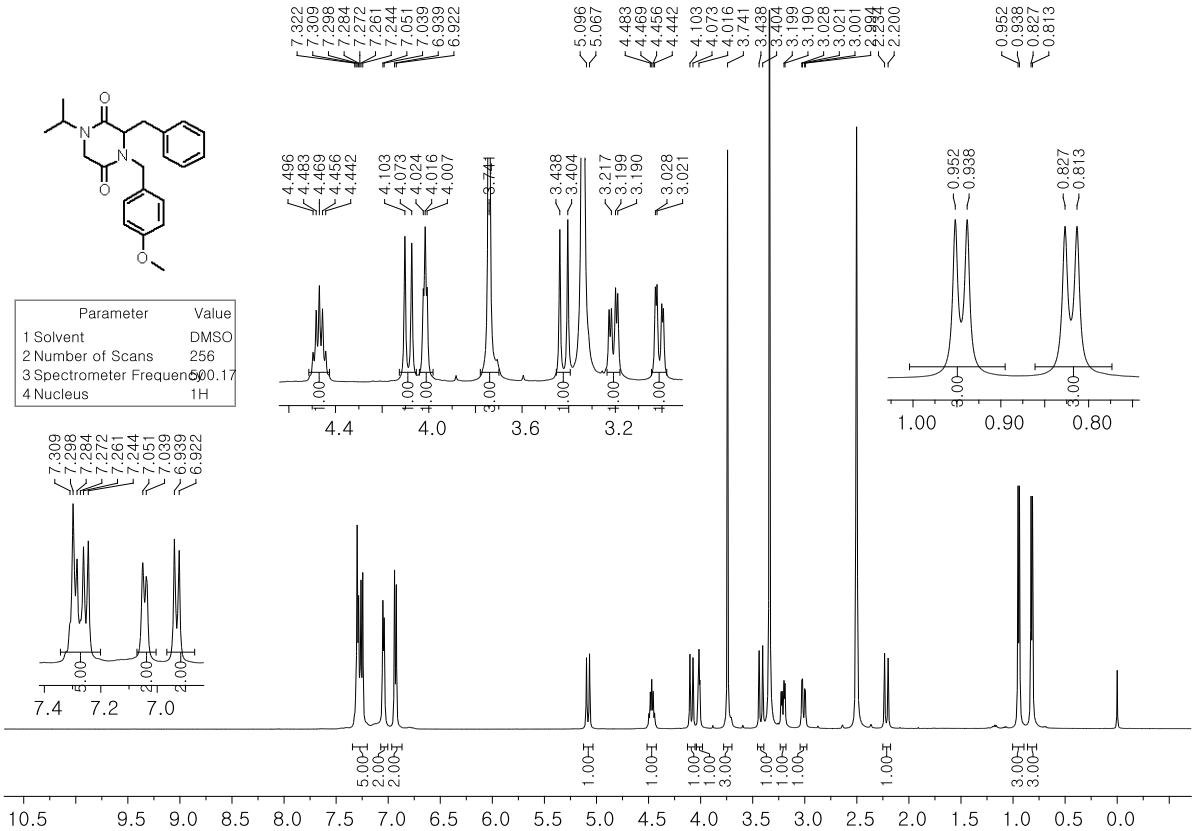
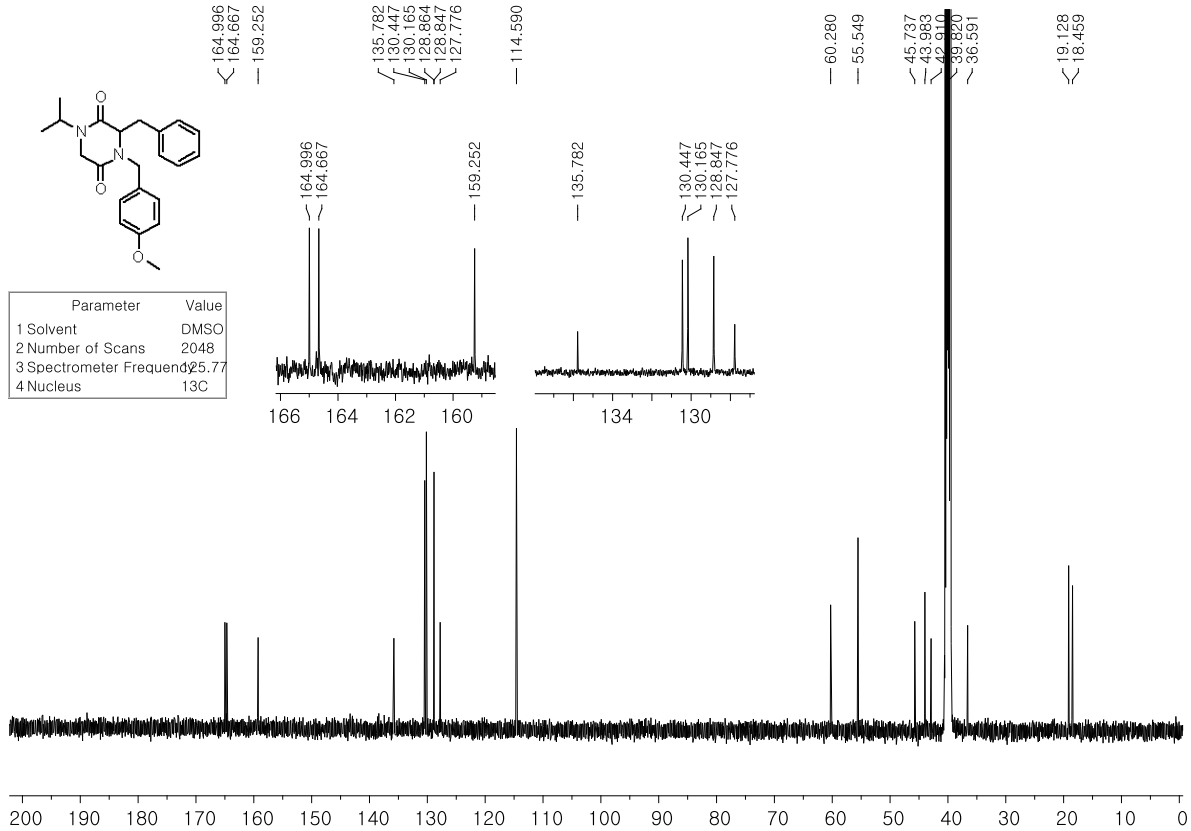


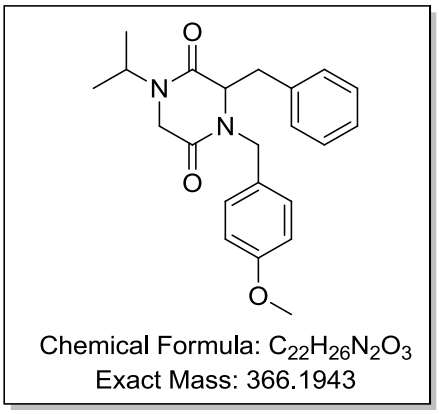
HRMS – 6o

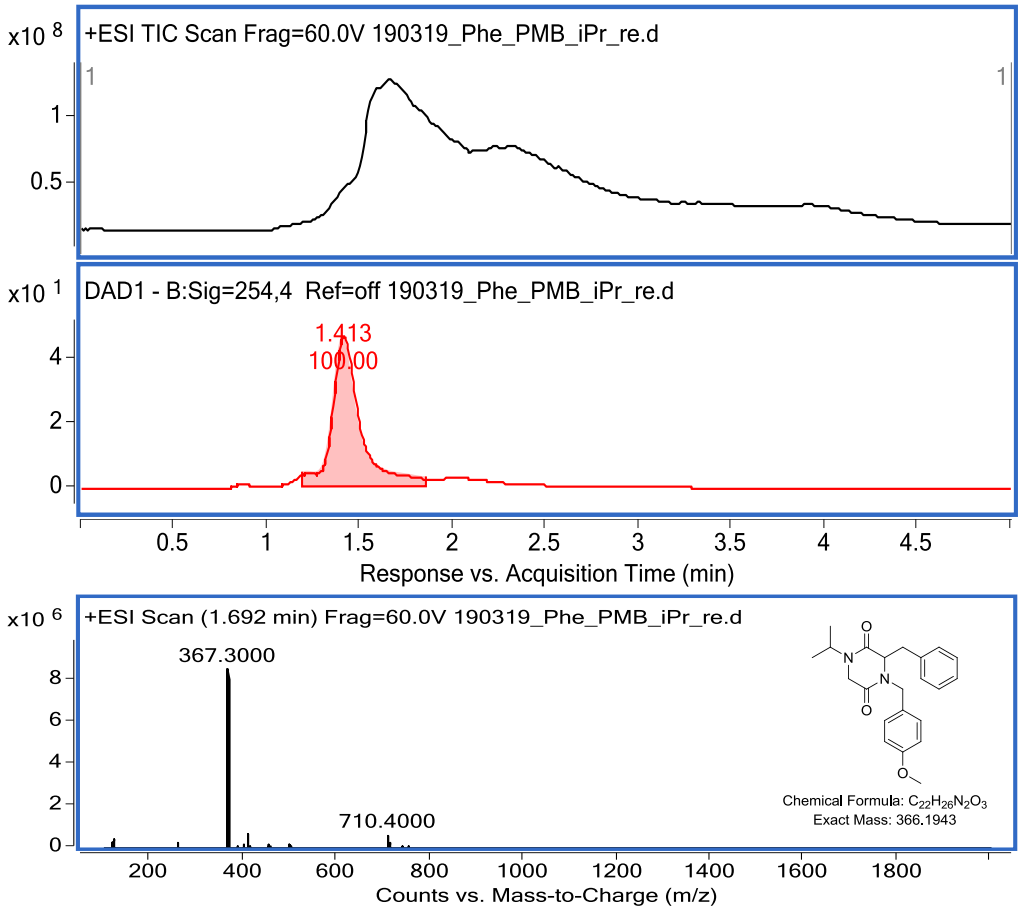


^{1}H NMR – 6p

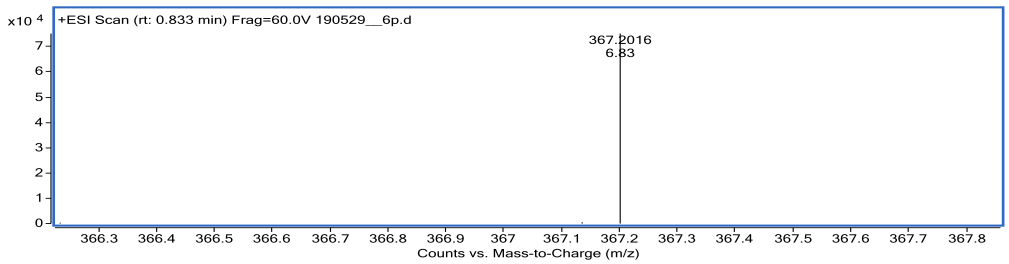


^{13}C NMR – 6p





LC/MS – 6p



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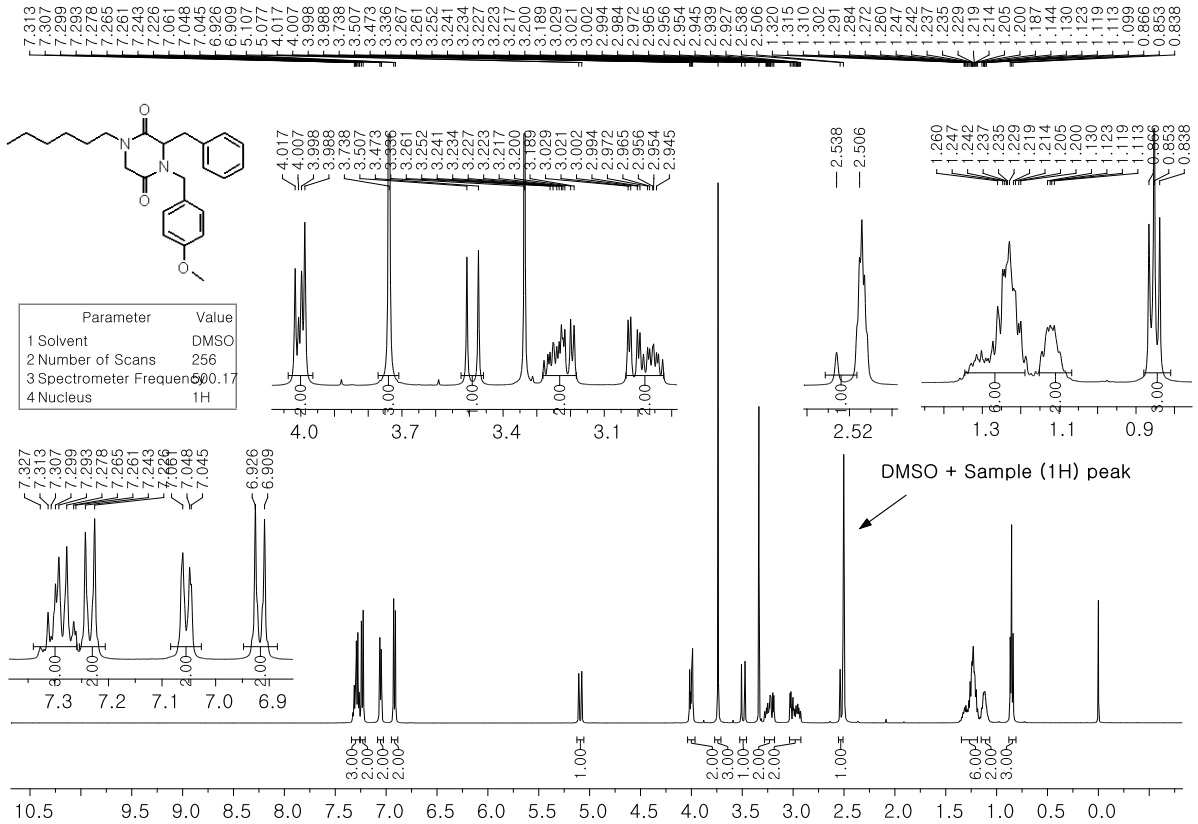
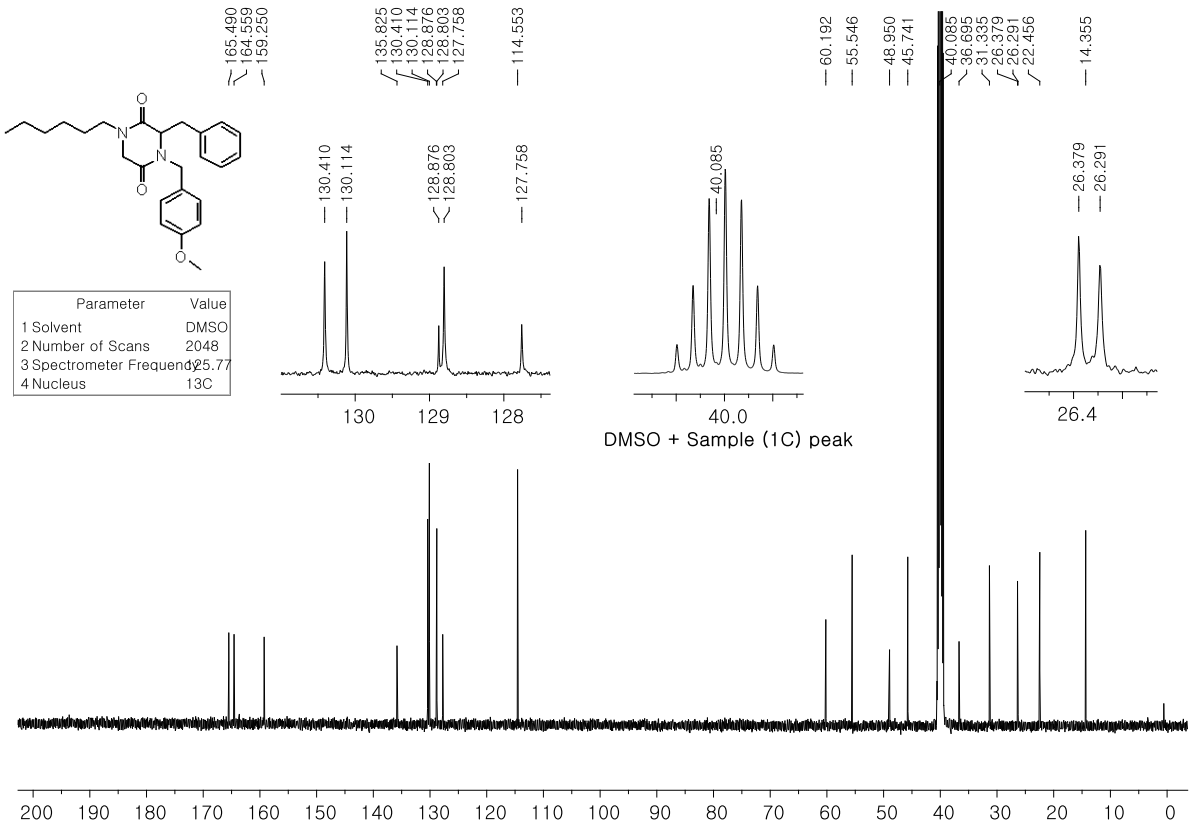


^{1}H NMR – 6q



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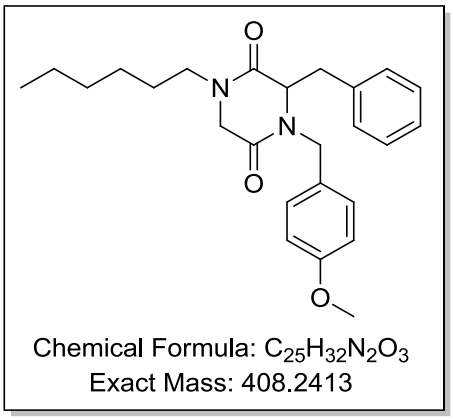

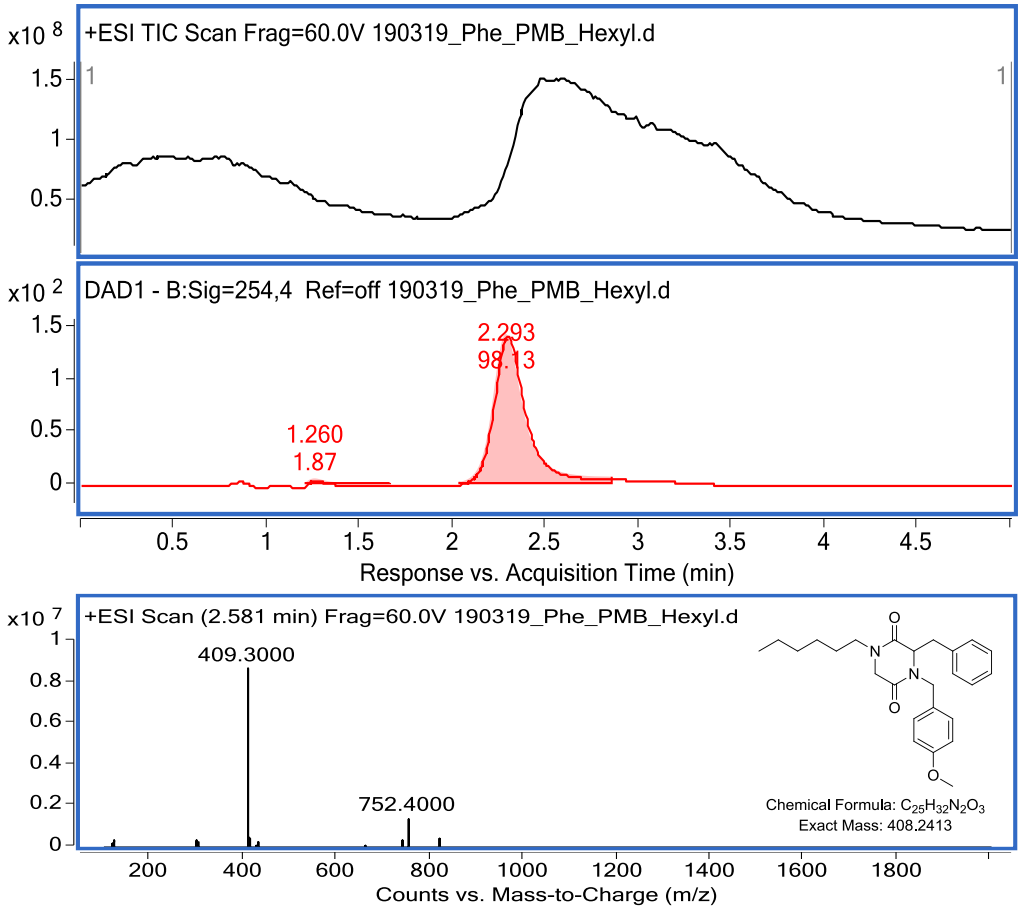

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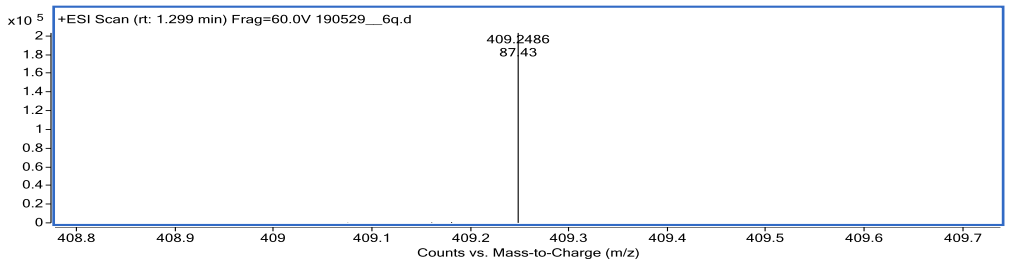
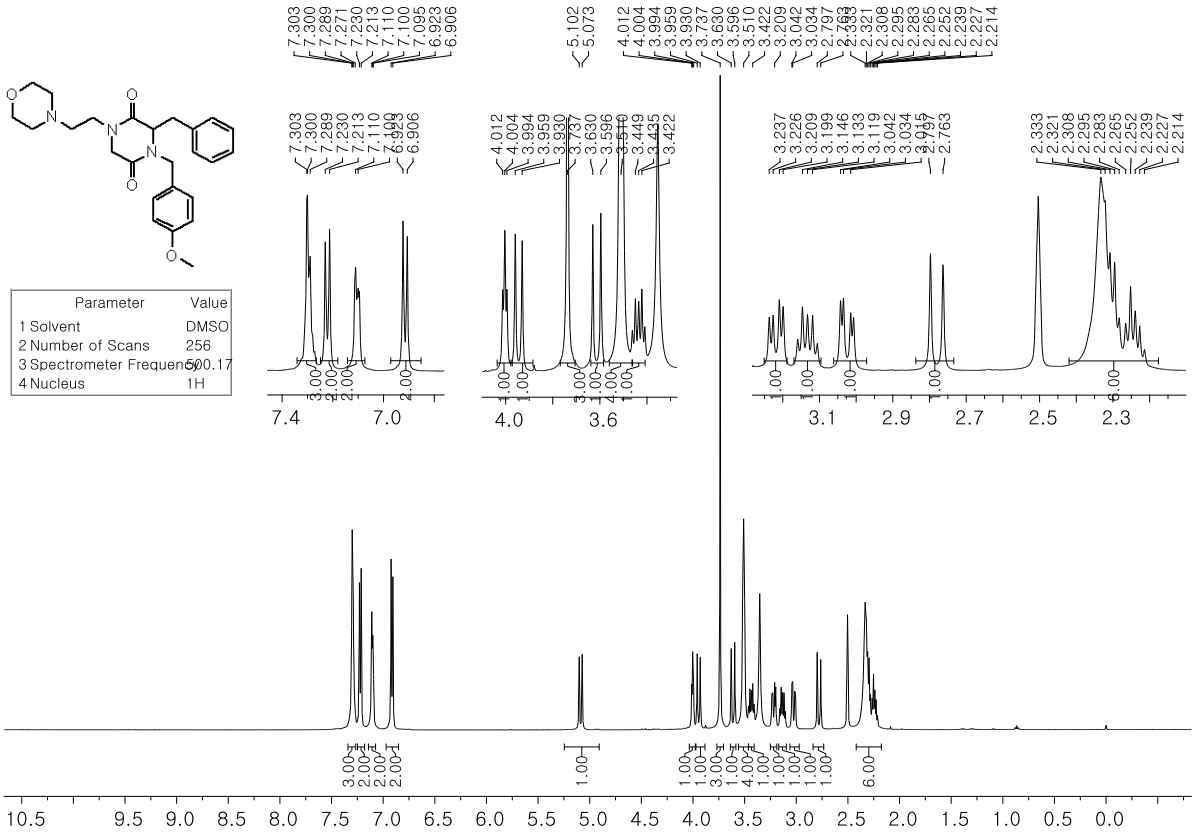
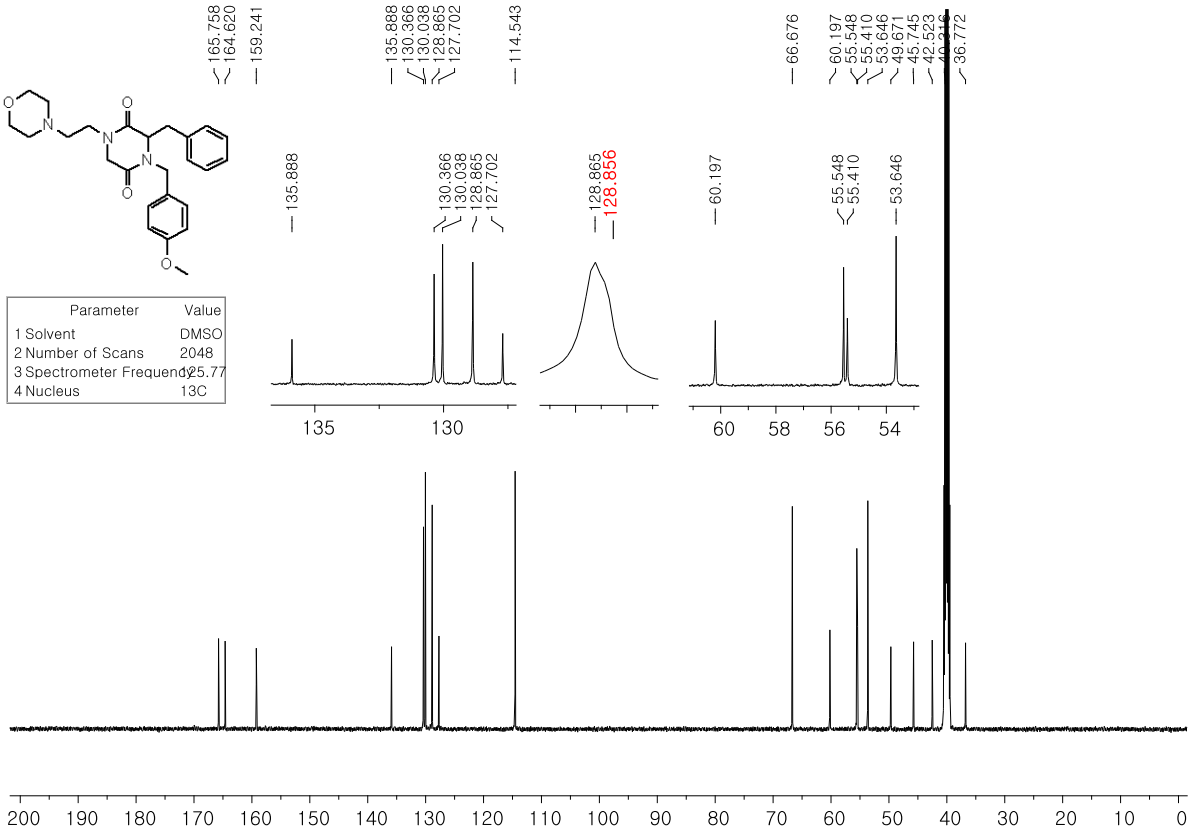


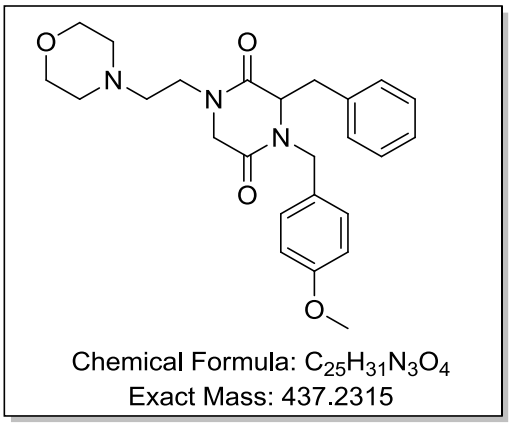
HRMS – 6q

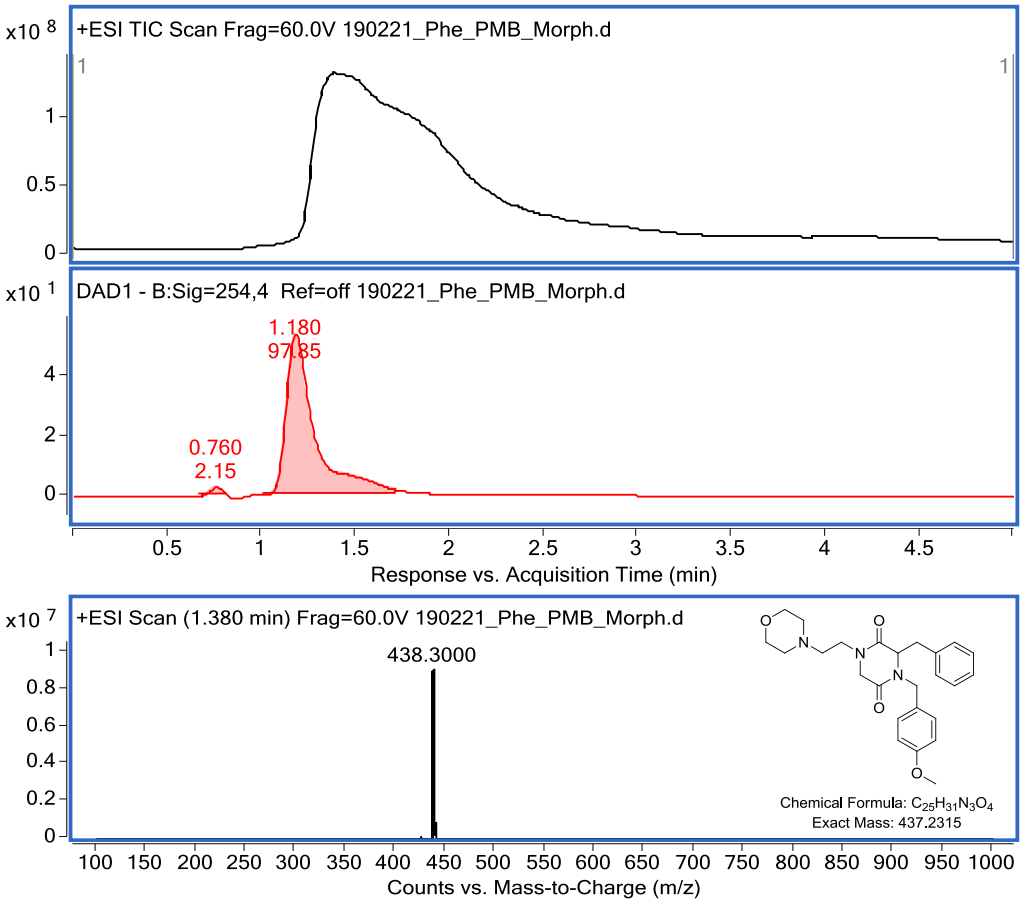


^{1}H NMR – 6r

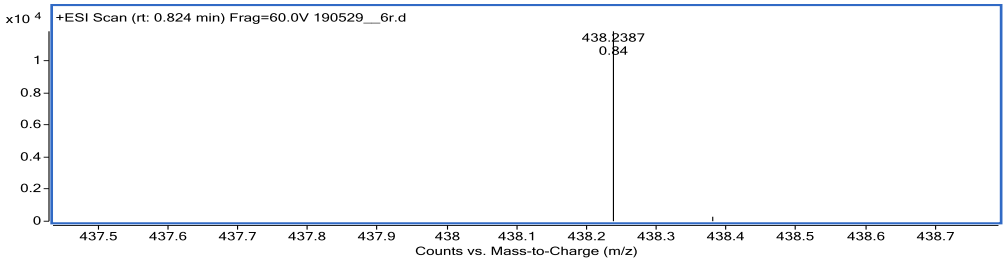


^{13}C NMR – 6r



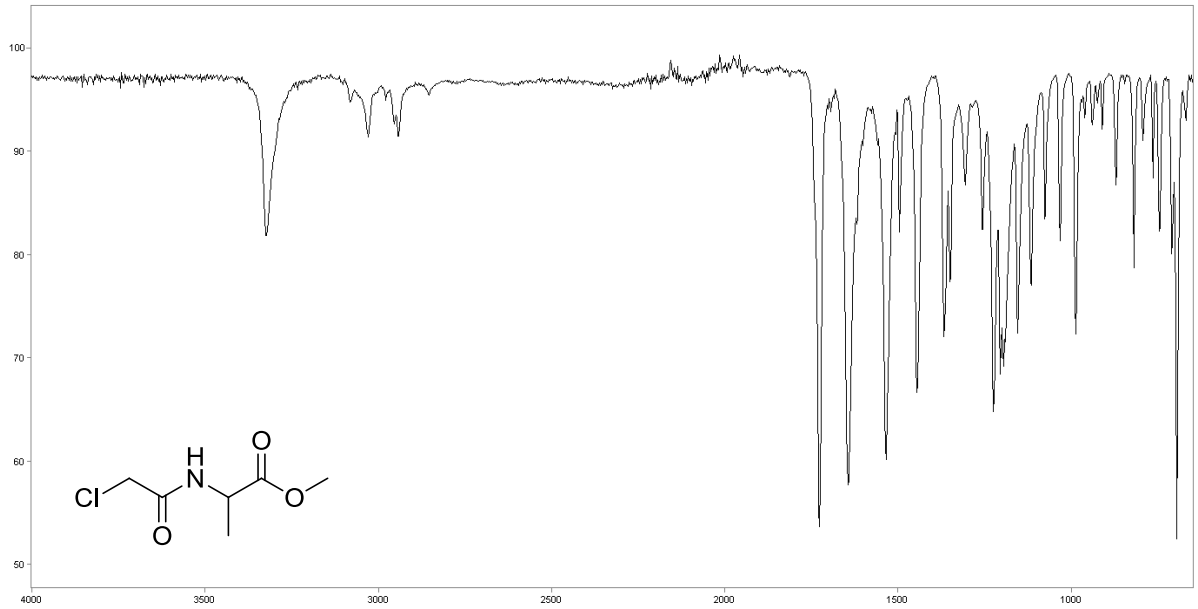


LC/MS – 6r

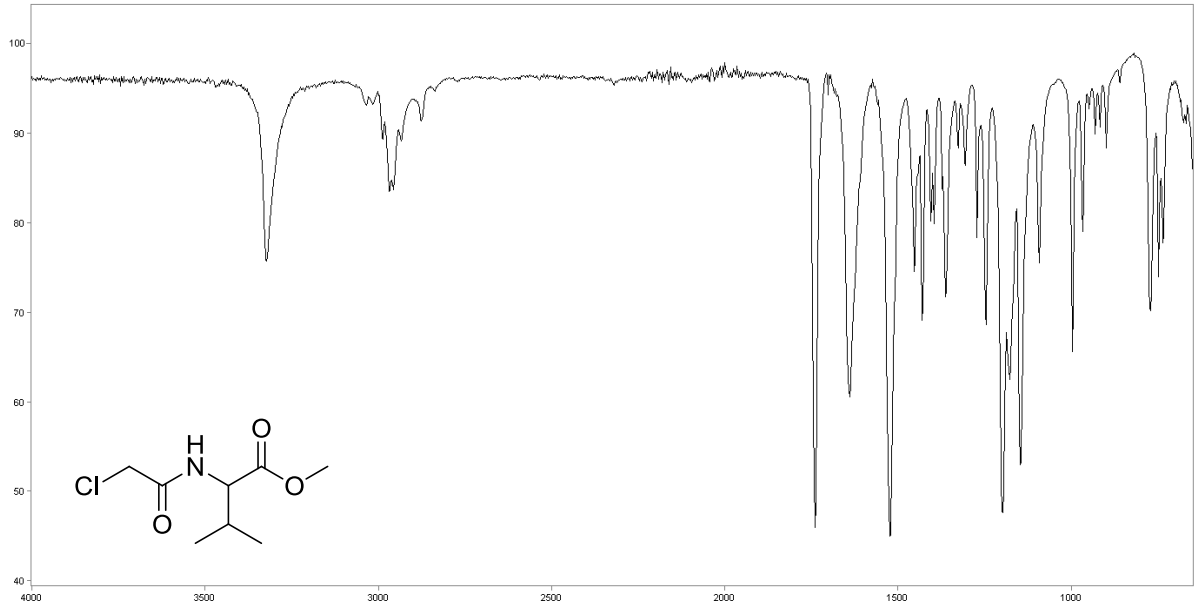


HRMS – 6r

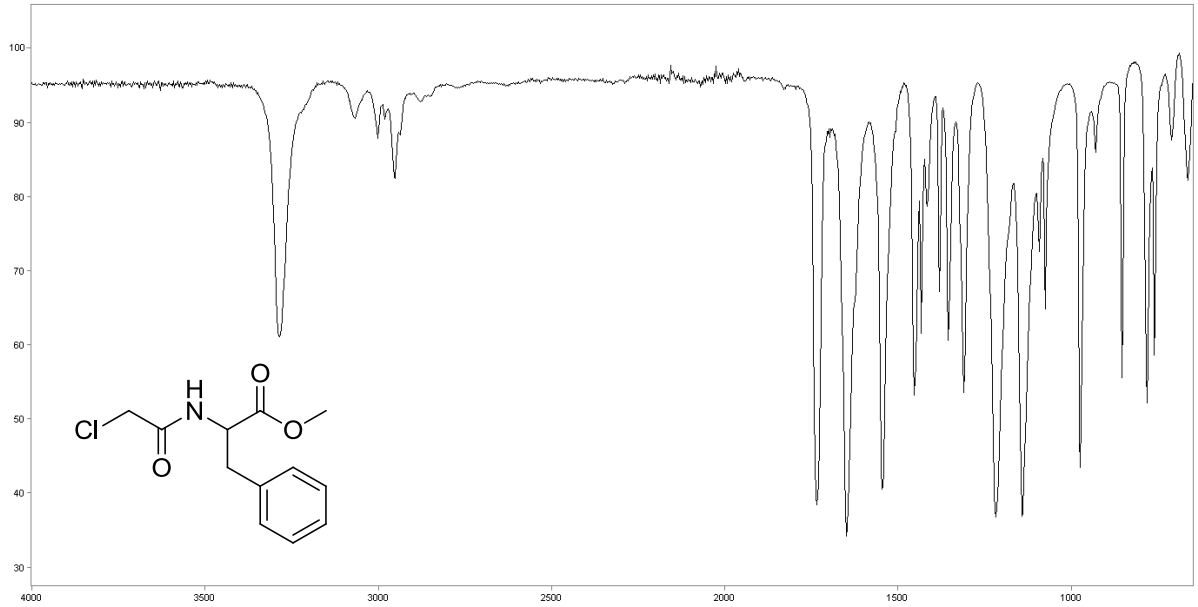
7. IR spectra of compounds 2



IR – 2a

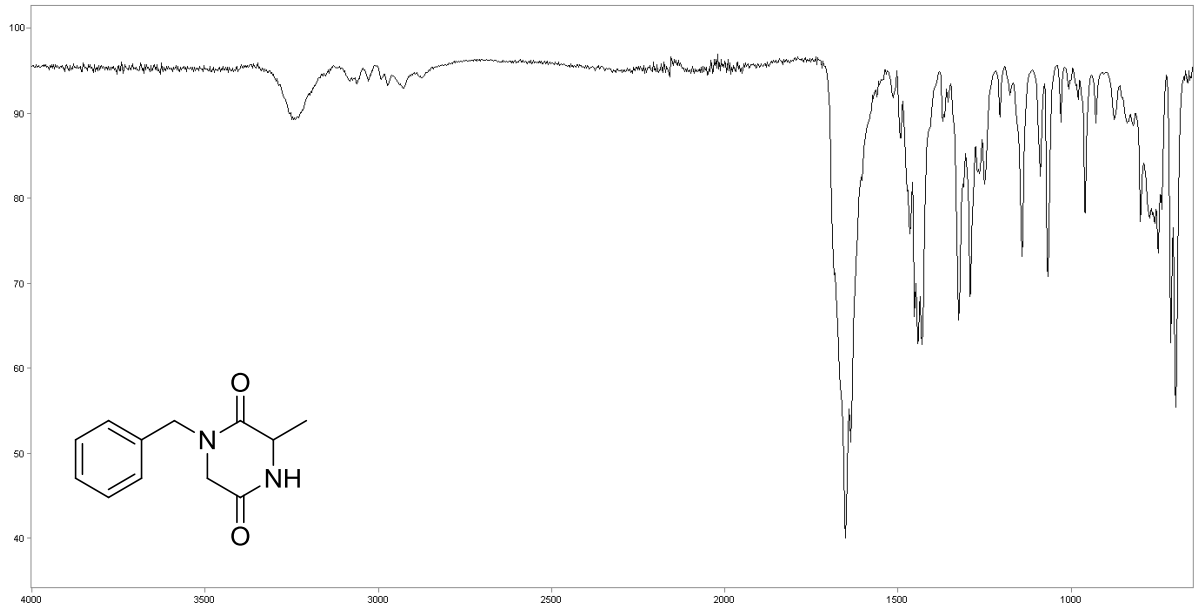


IR – 2b

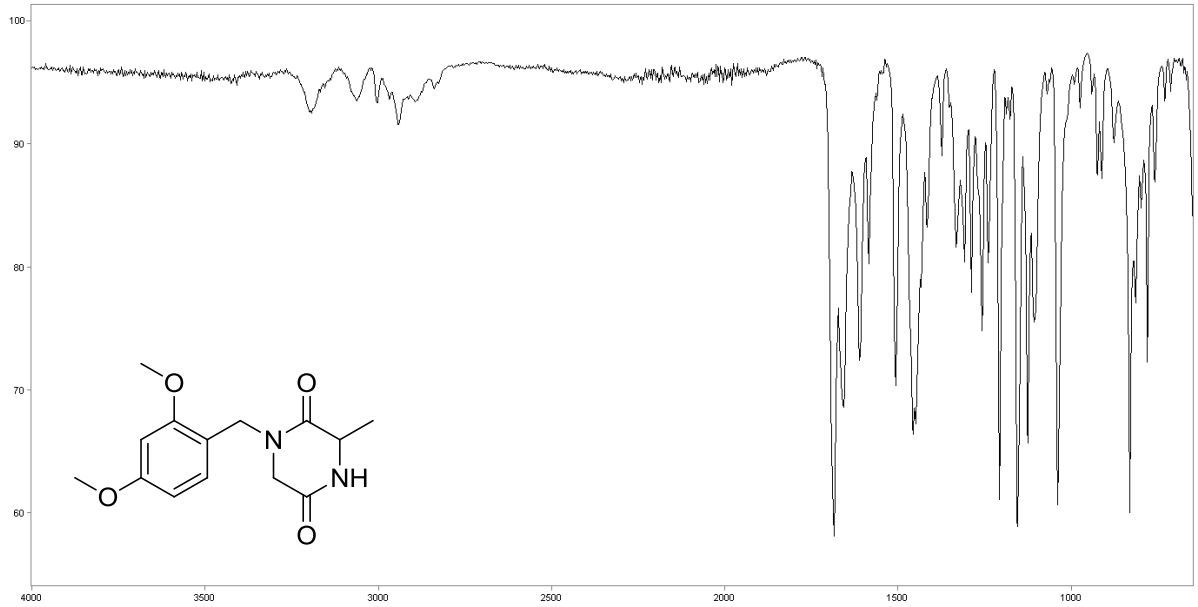


IR-2c

8. IR spectra of compounds 3



IR-3a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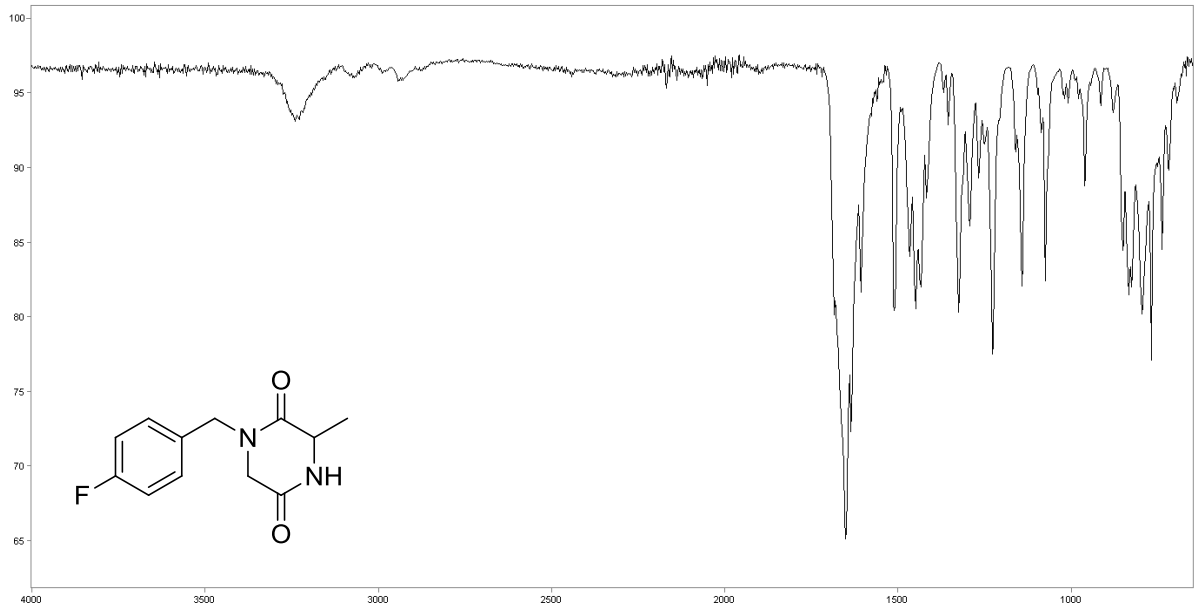
IR-3b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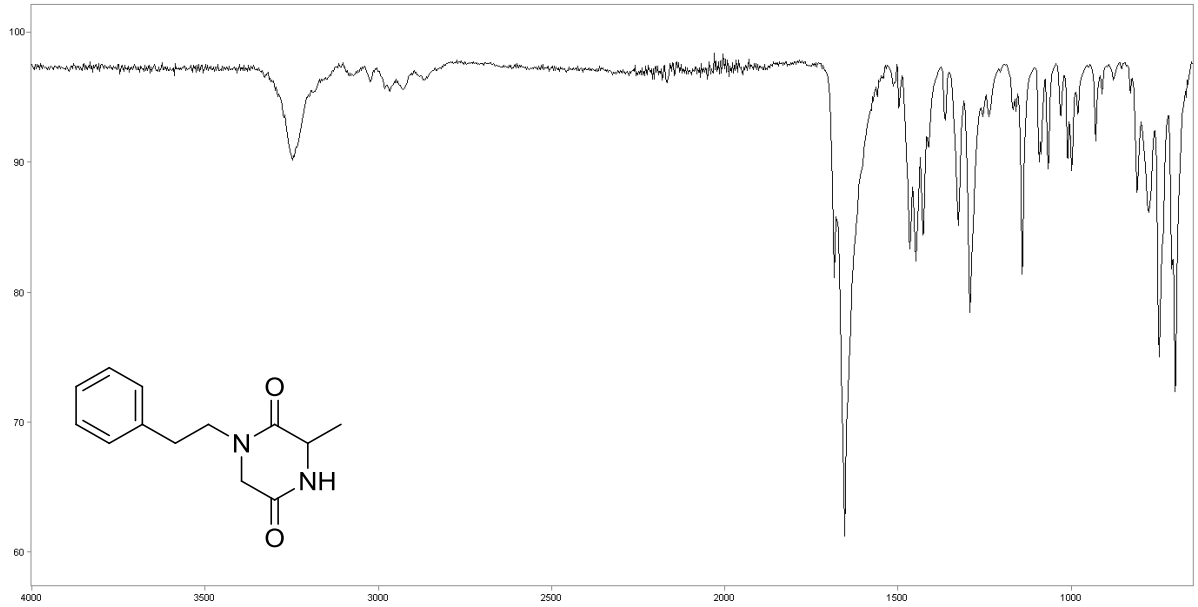
IR-3c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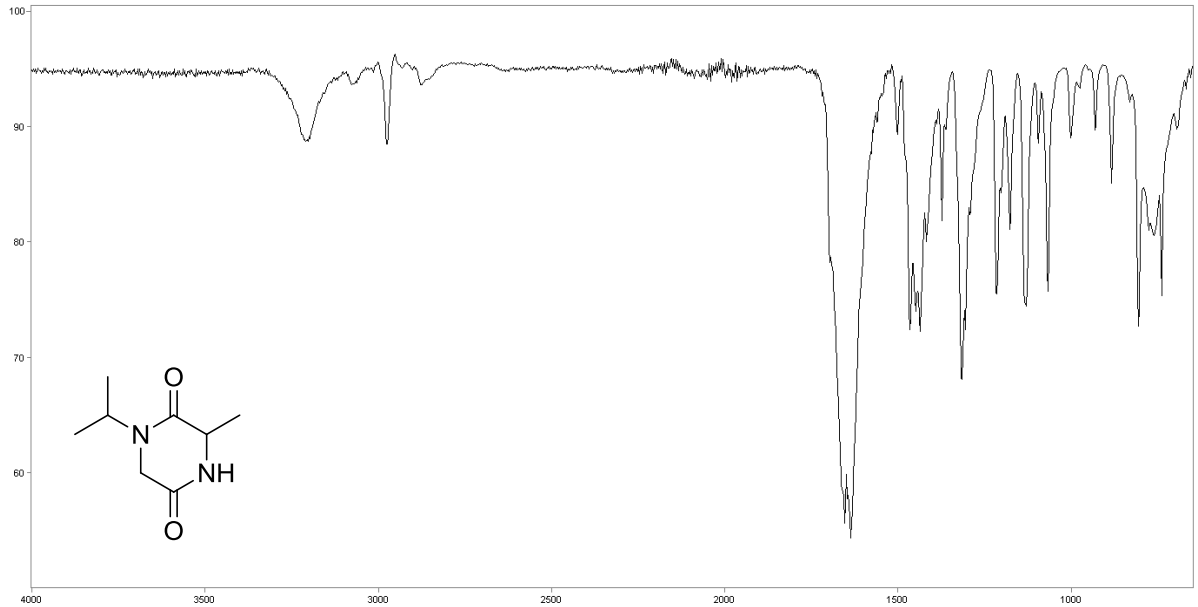
IR-3d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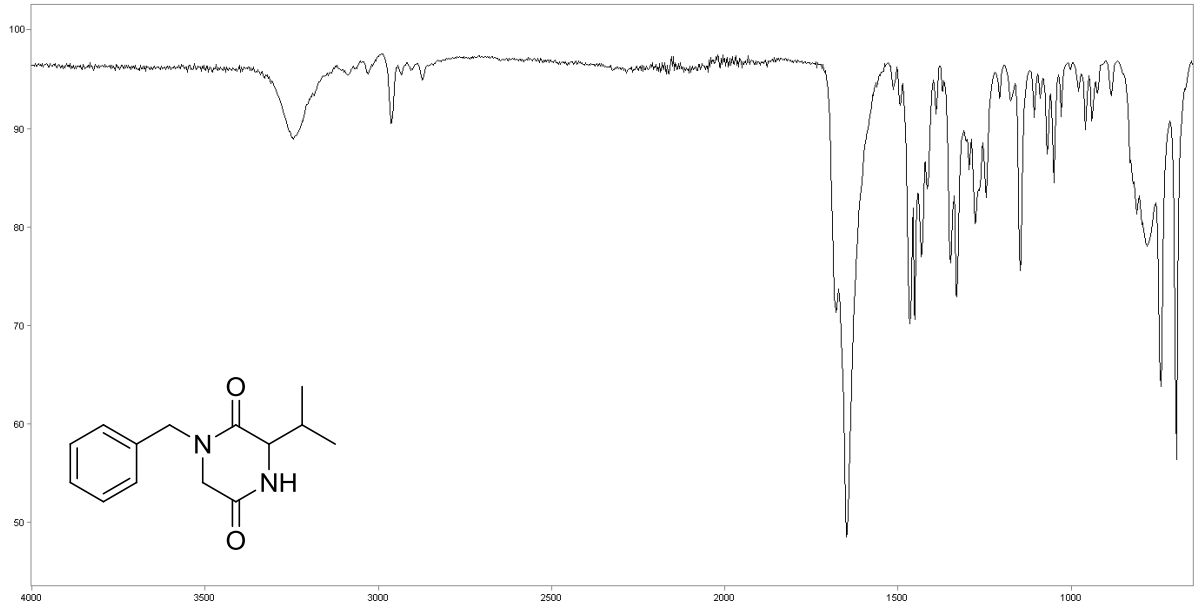
IR-3e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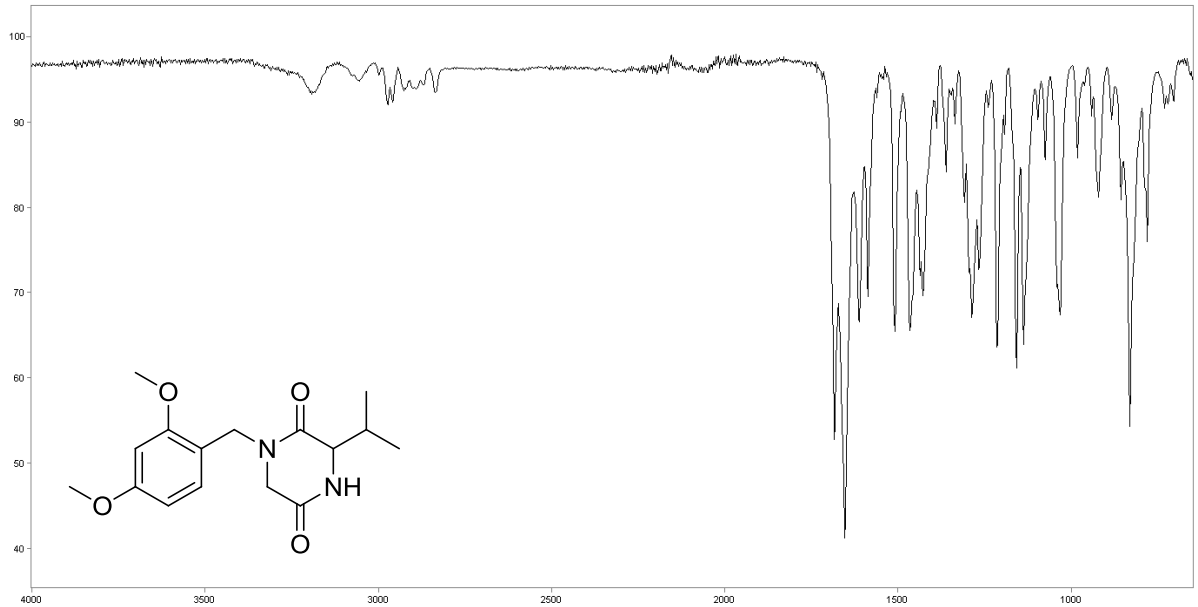
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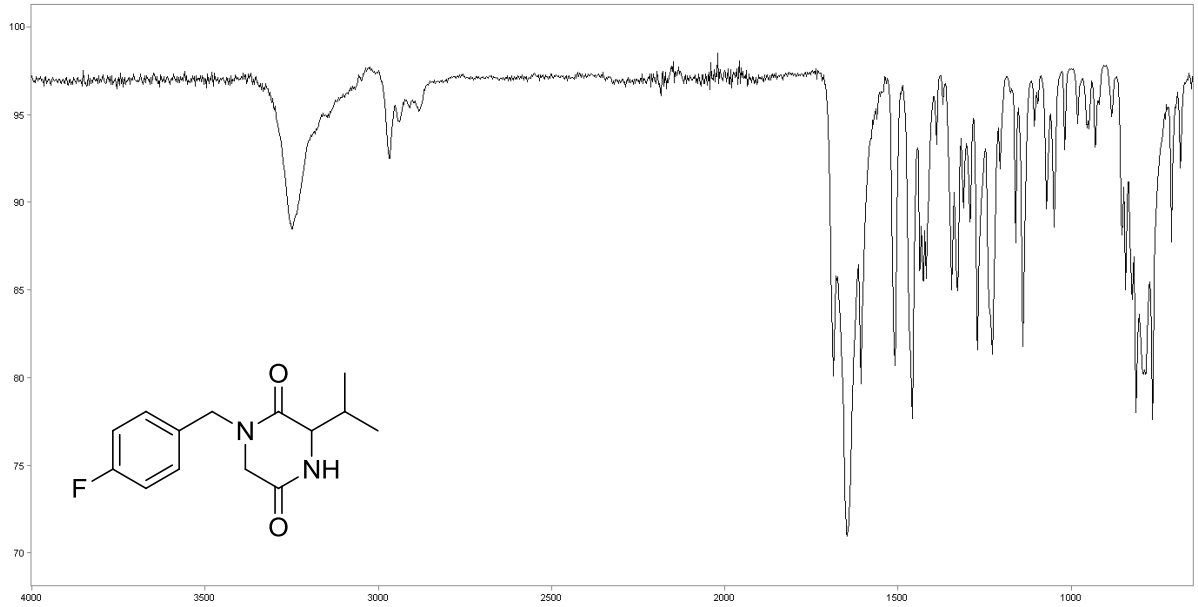
IR-3g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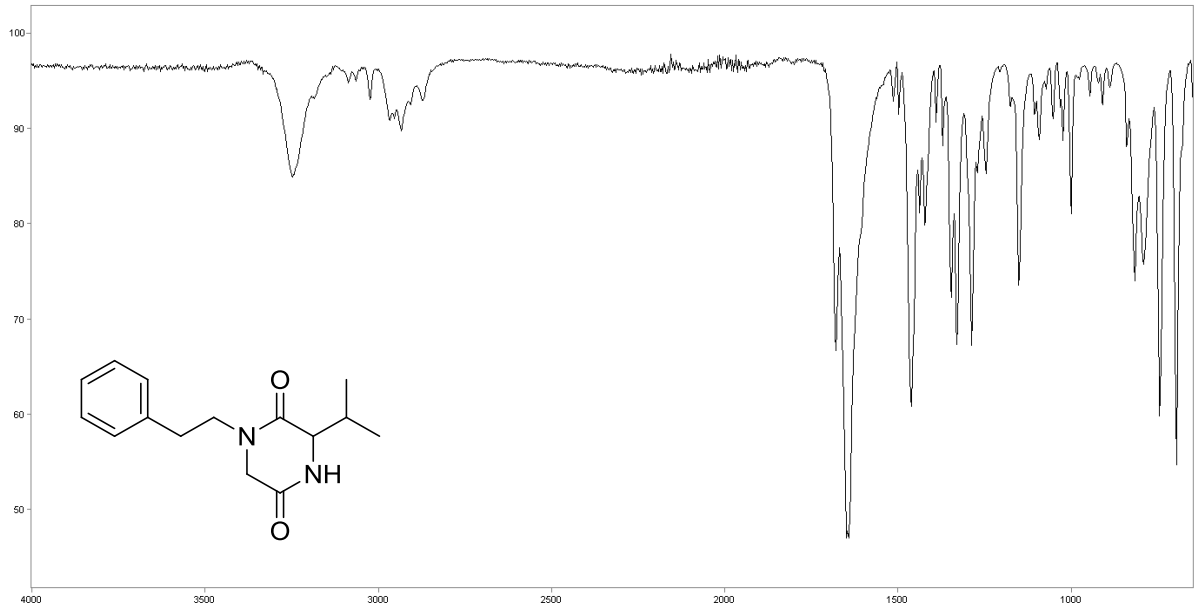
IR-3h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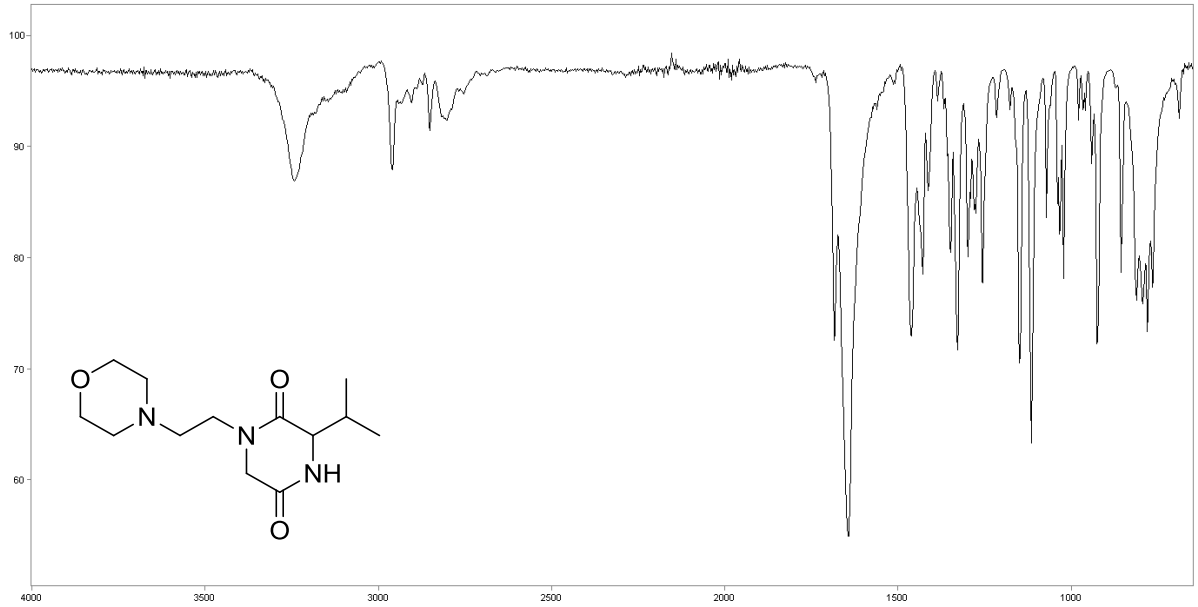
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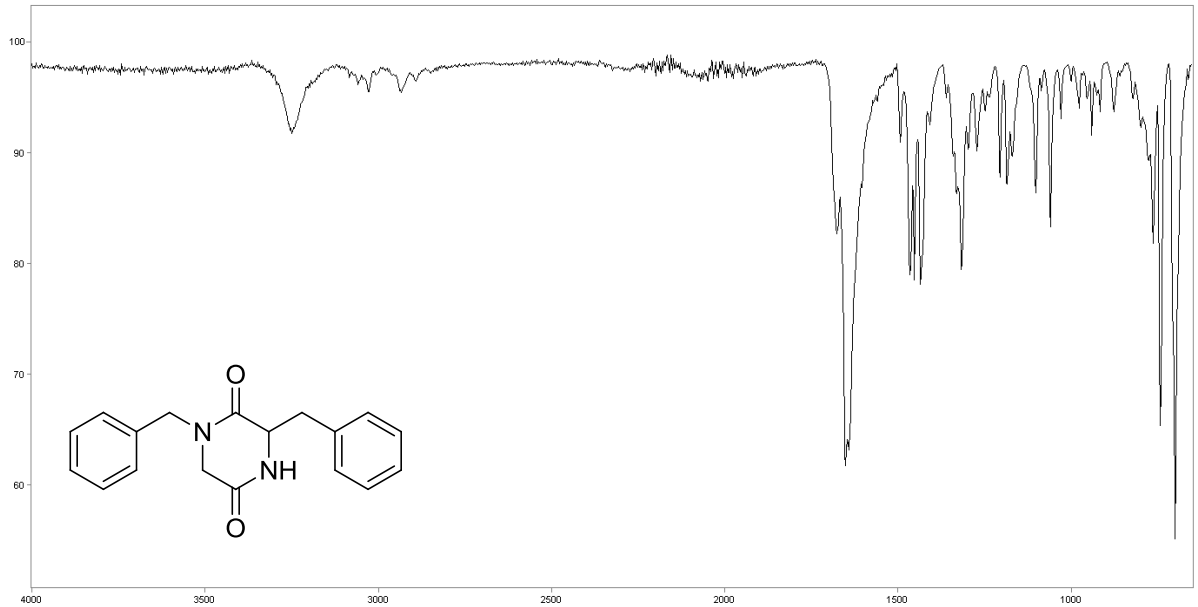
IR-3j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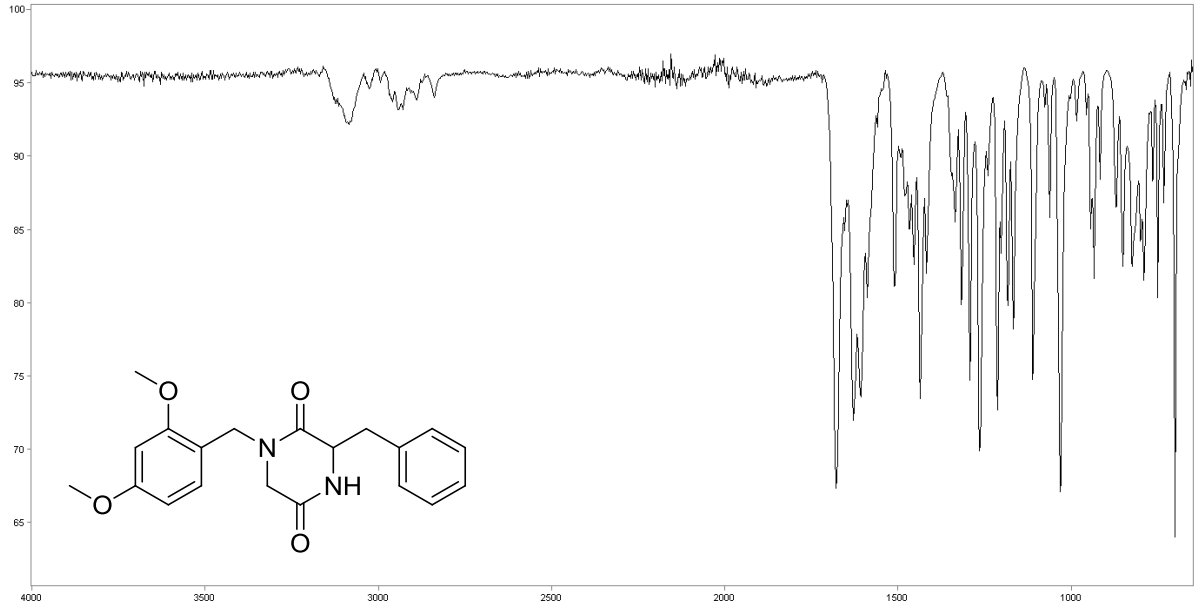
IR-3k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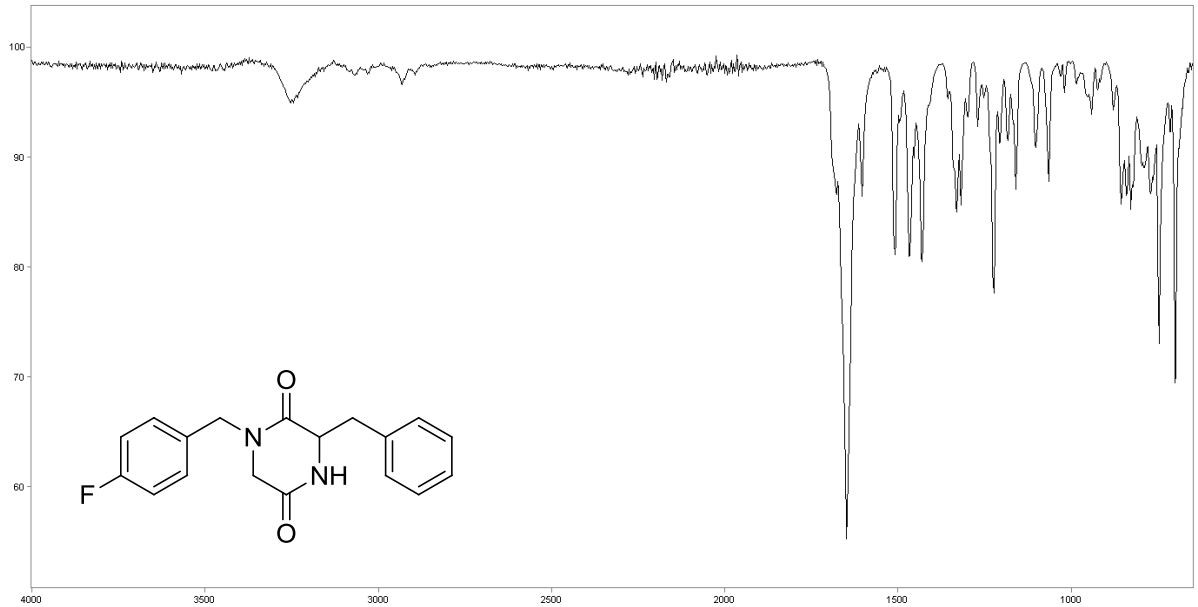
IR-3l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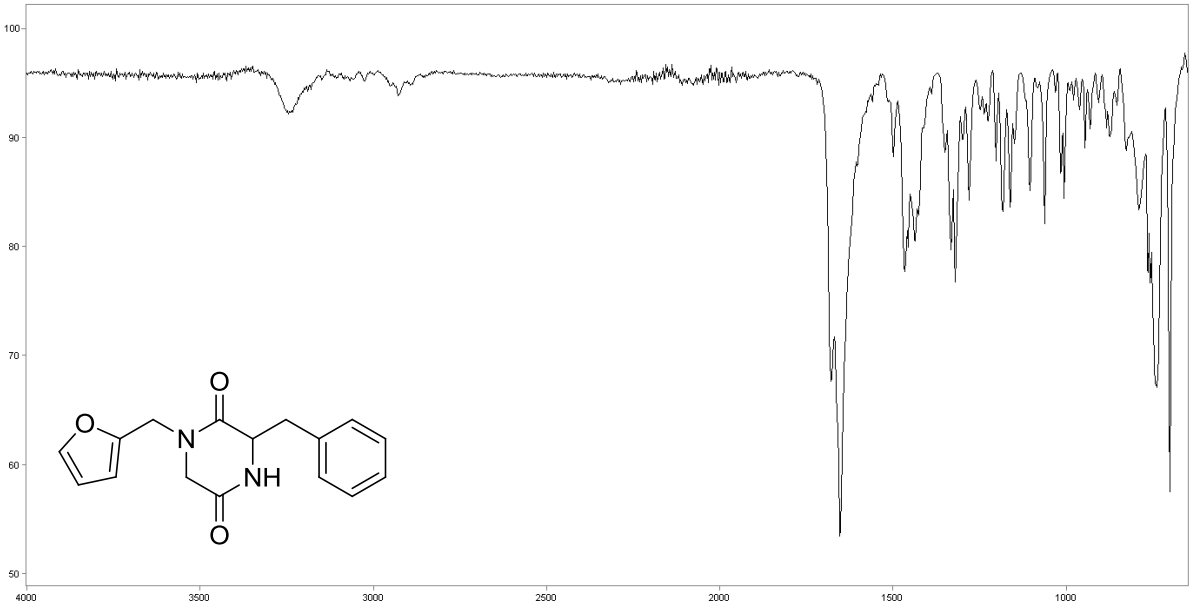
IR-3m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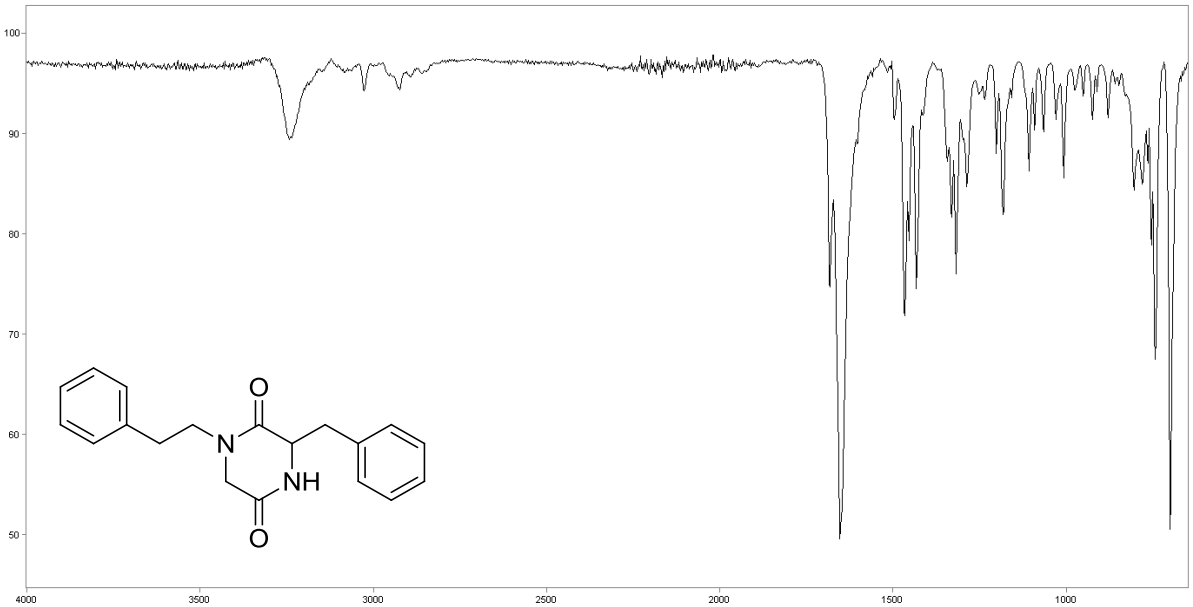
IR-3n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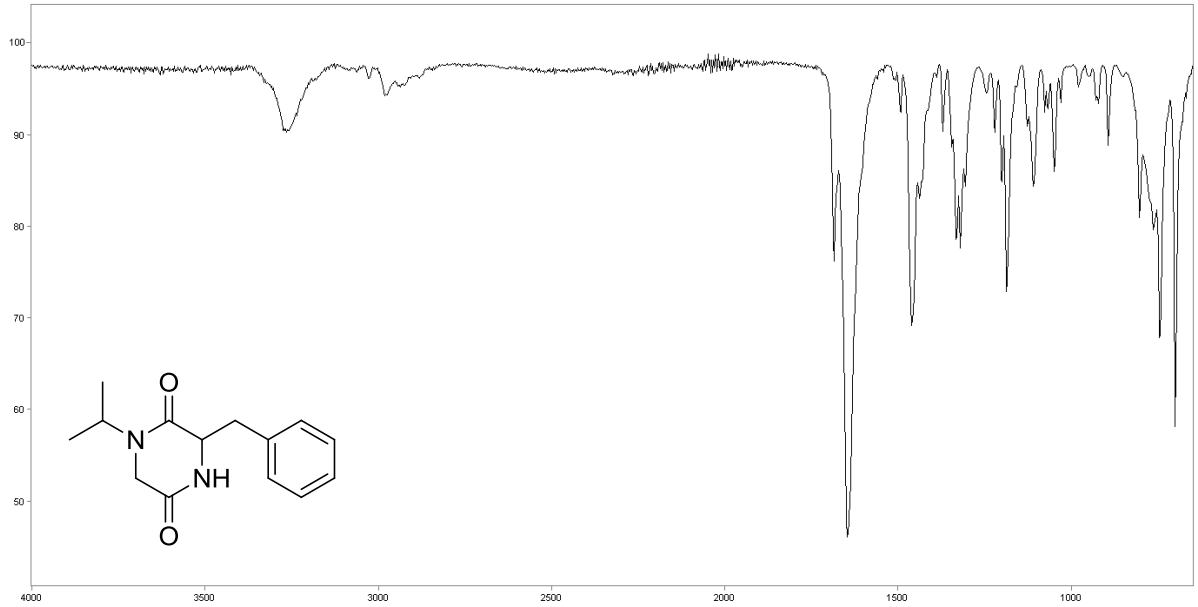
IR-3o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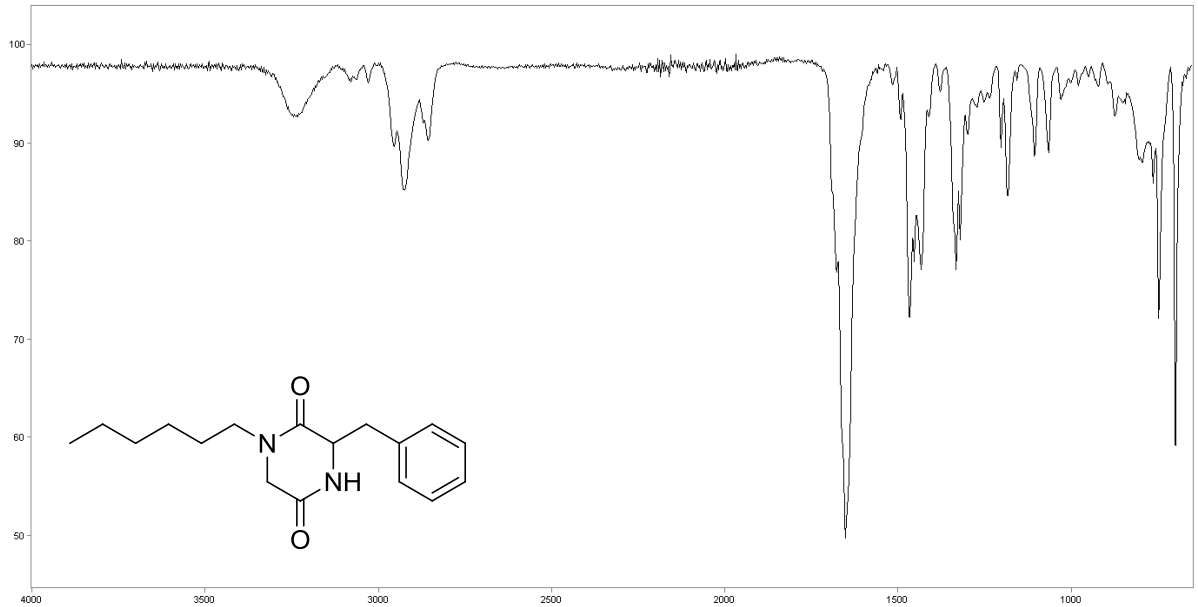
IR-3p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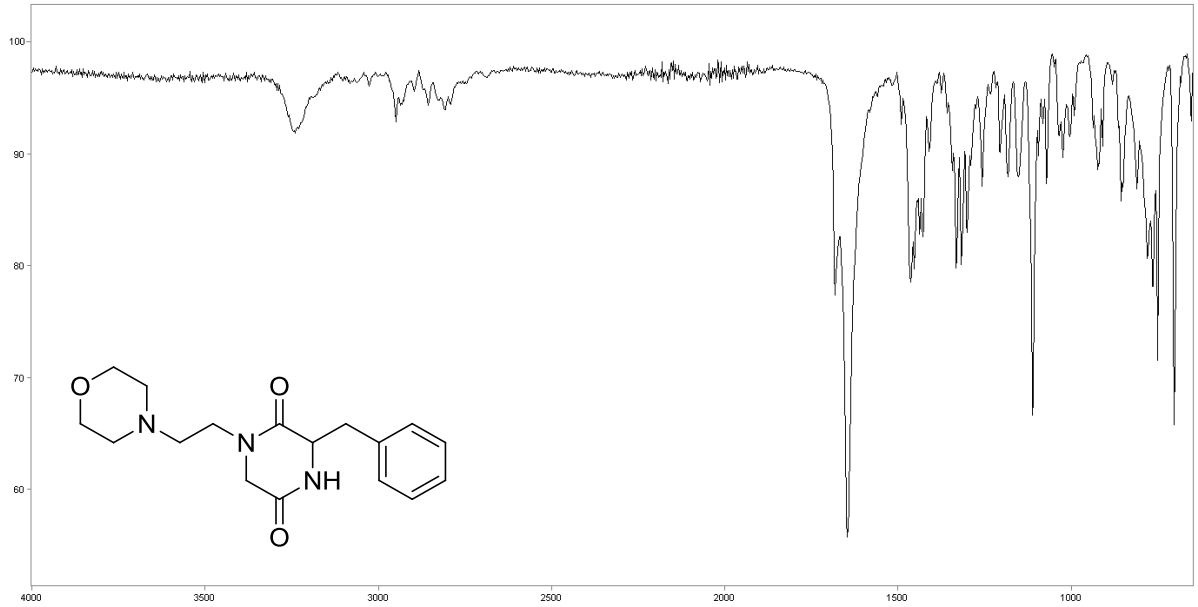
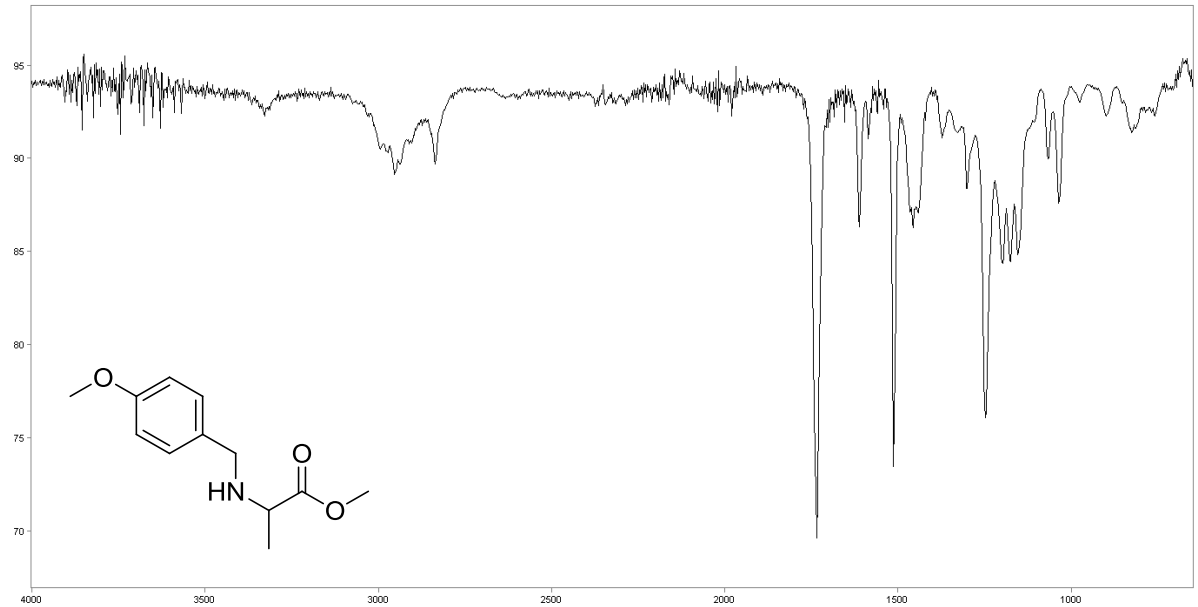
IR-3q

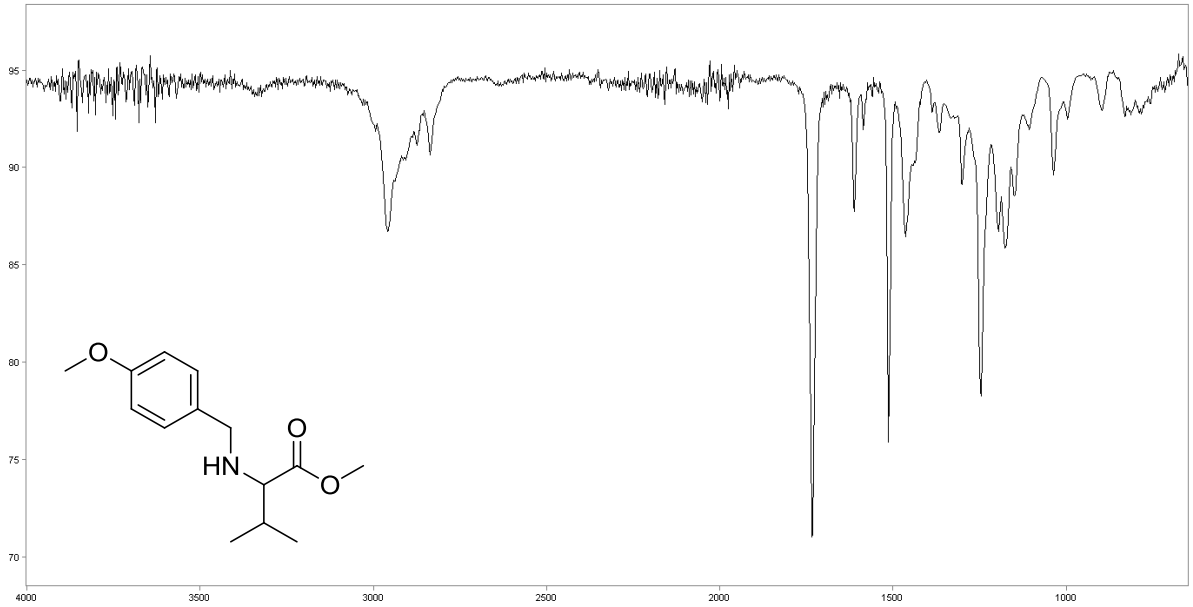


IR-3r

9. IR spectra of compounds 4



IR-4a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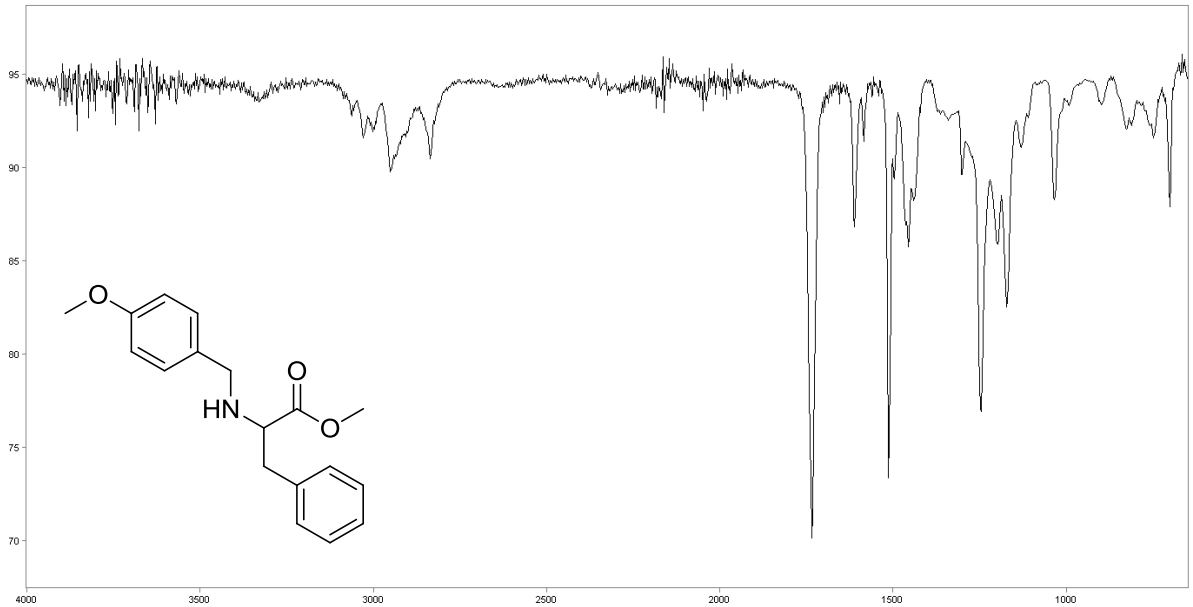
IR-4b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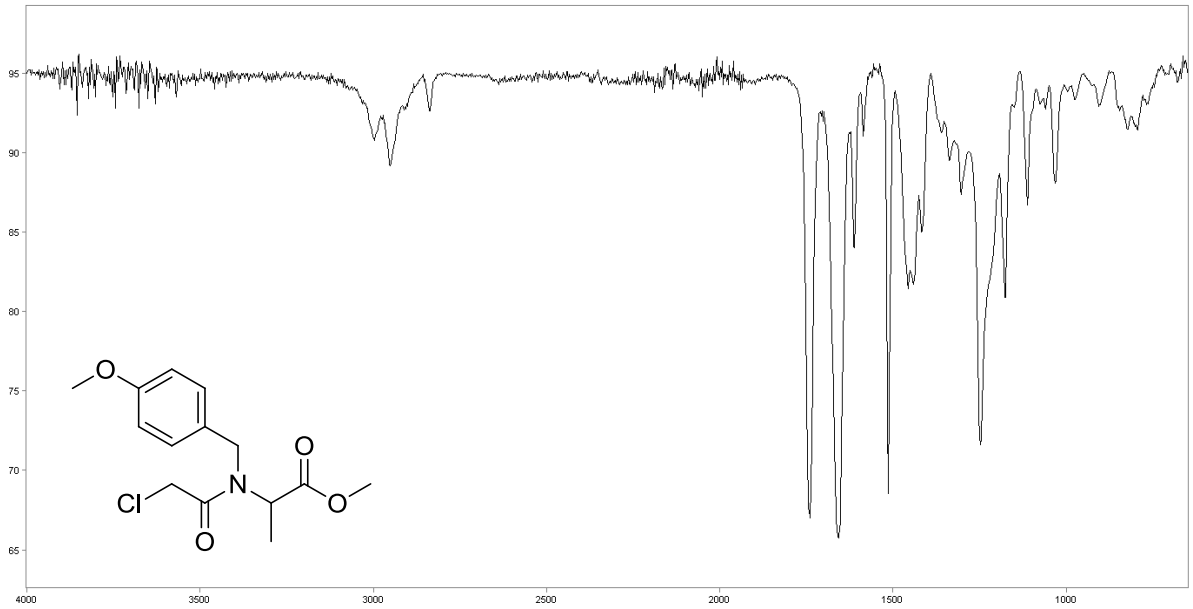
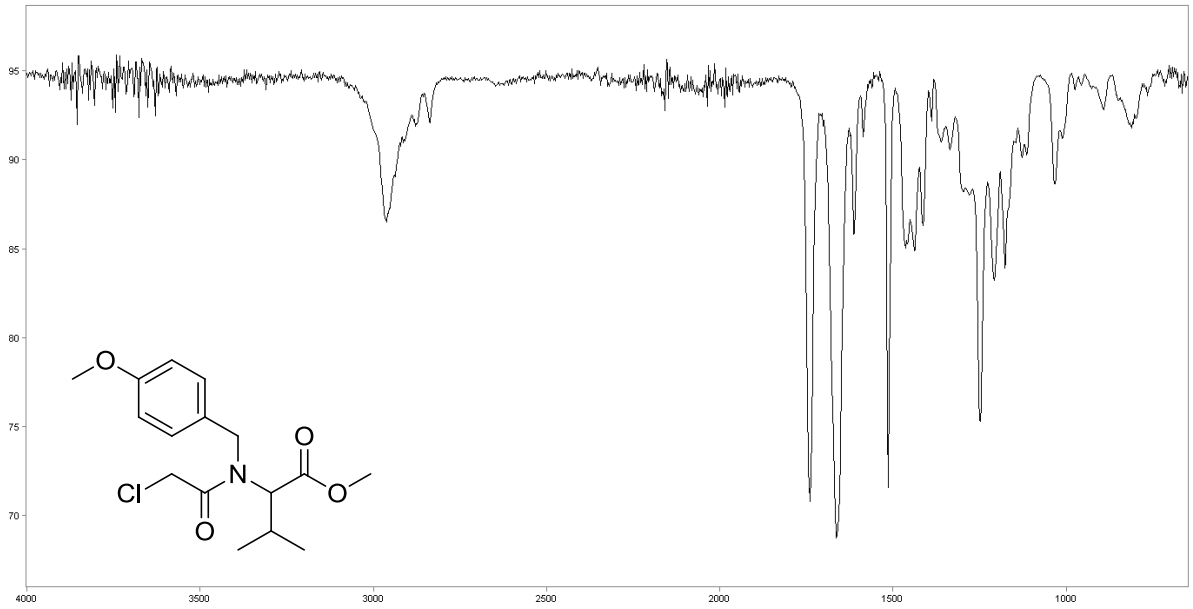
IR-4c

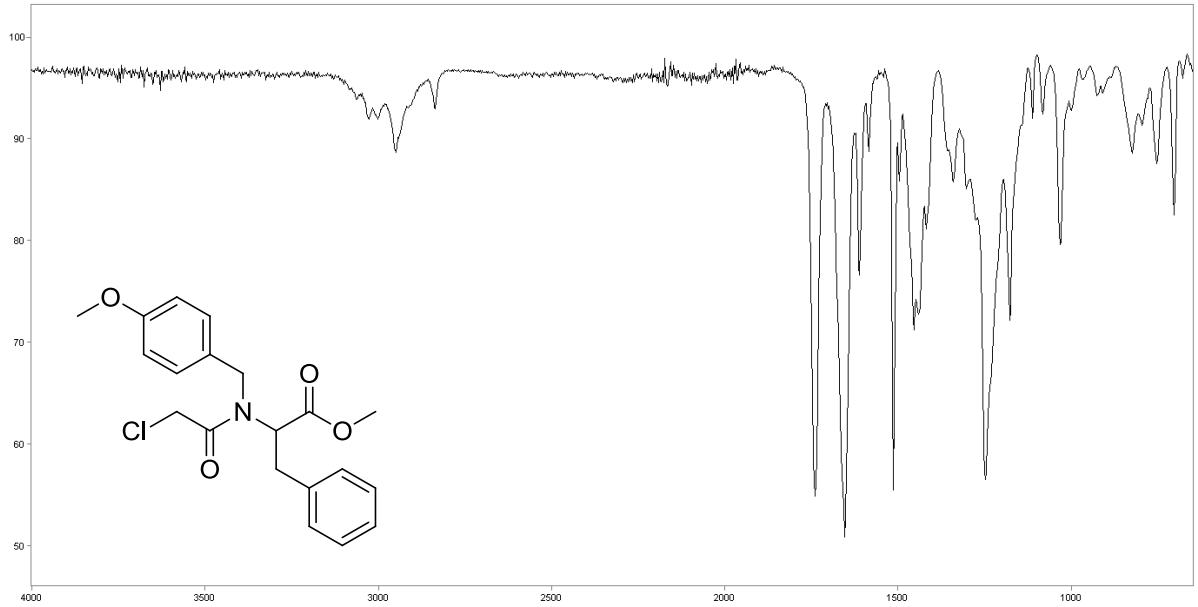
10. IR spectra of compounds 5



IR-5a

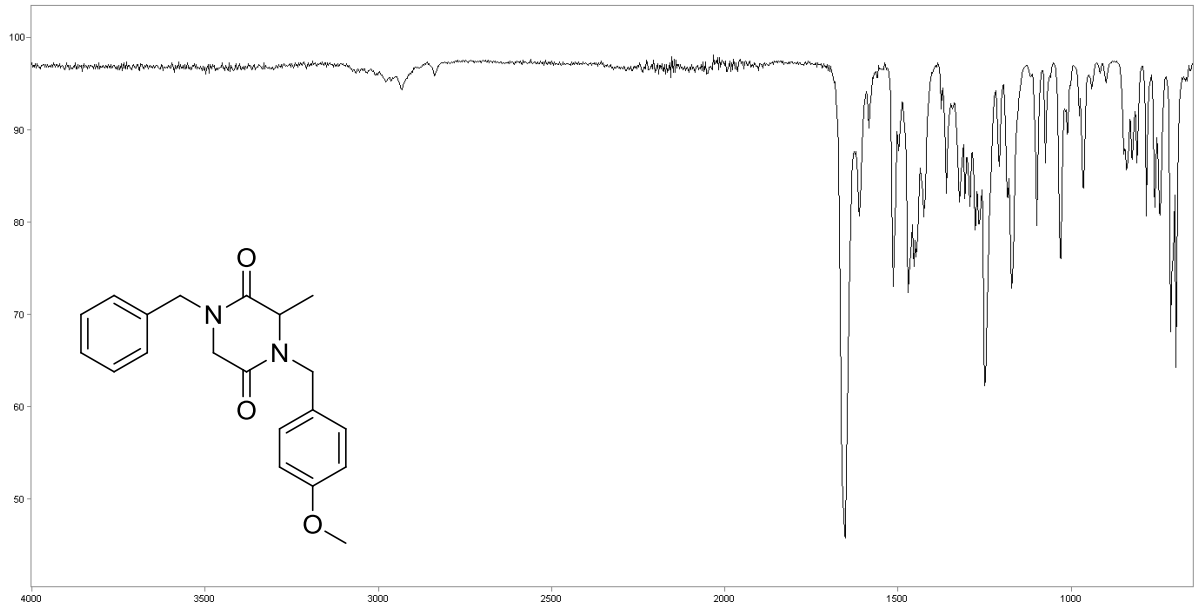


IR-5b

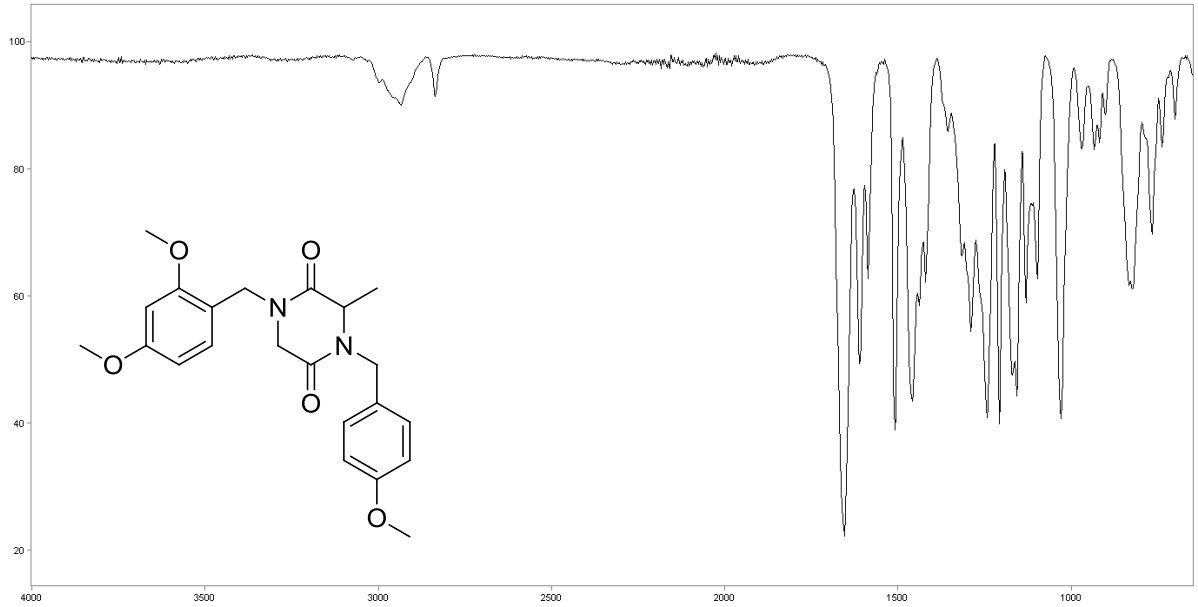


IR-5c

11. IR spectra of compounds 6



IR-6a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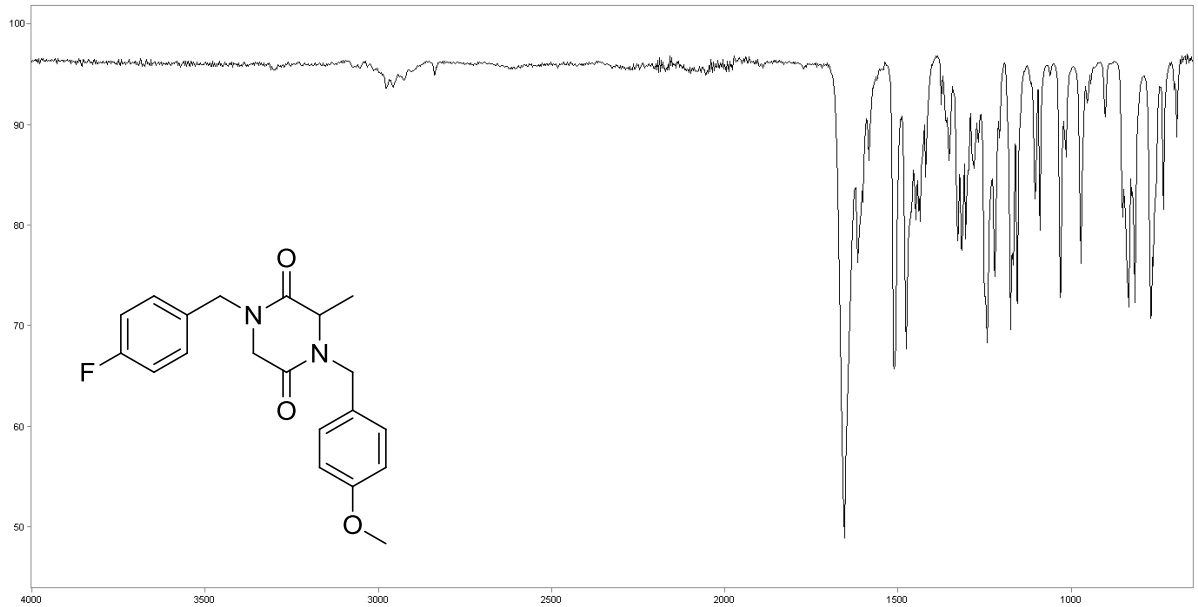
IR-6b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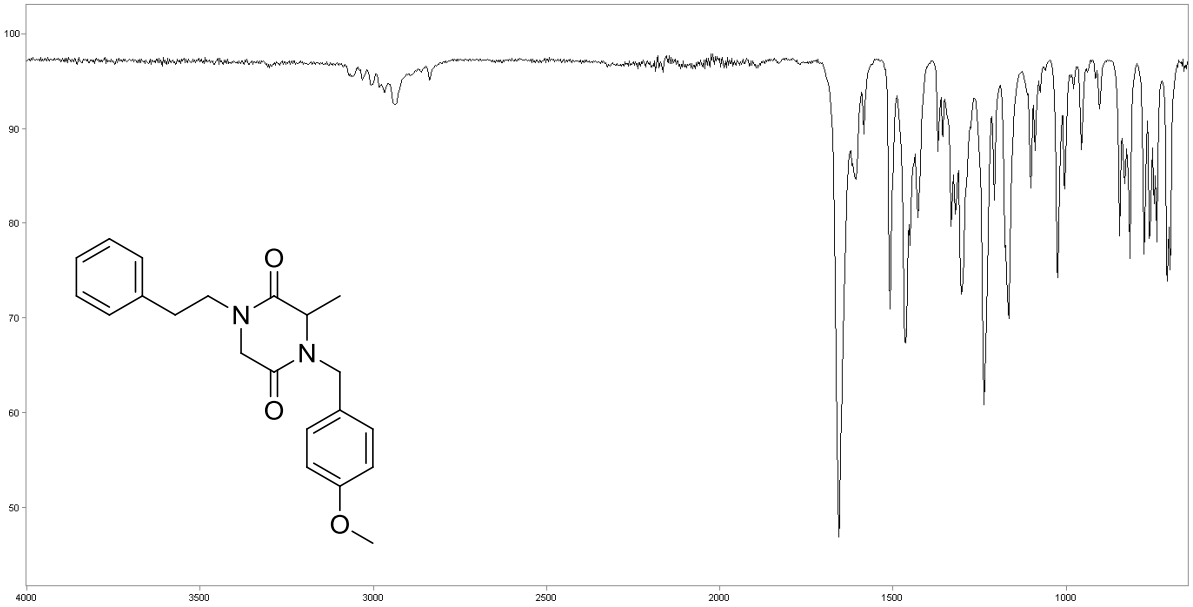
IR-6c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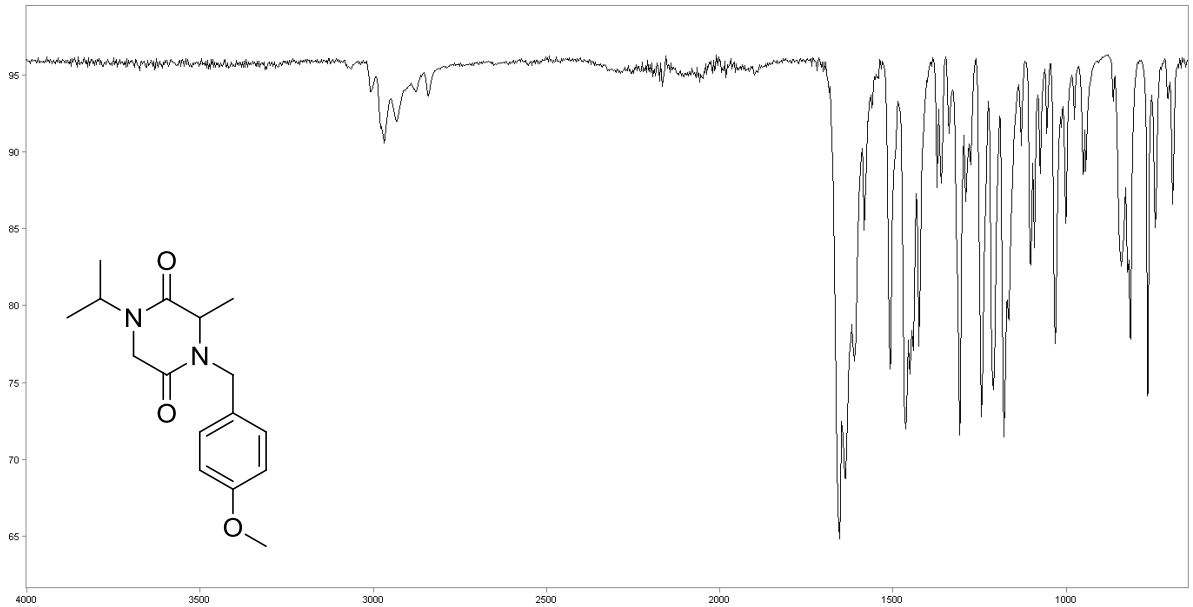
IR-6d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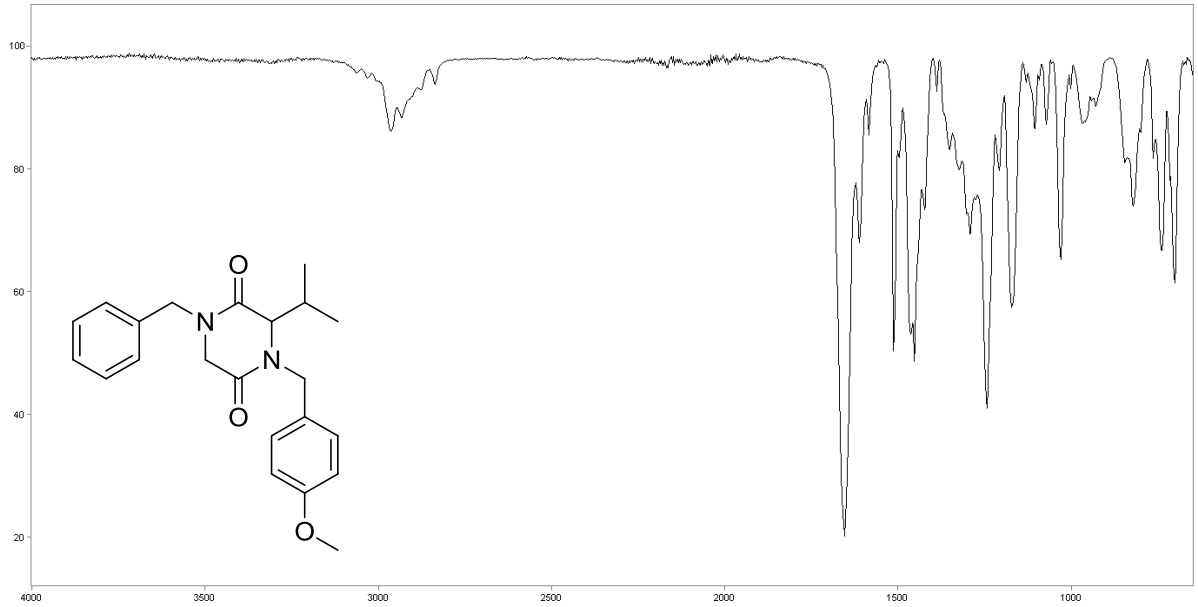
IR-6e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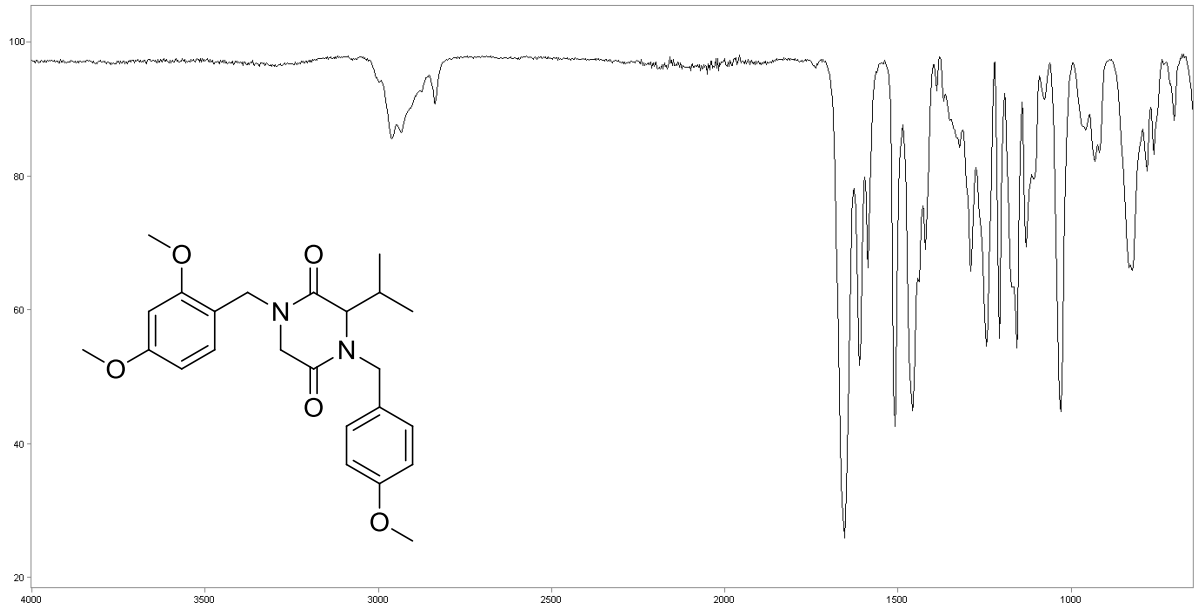
IR-6f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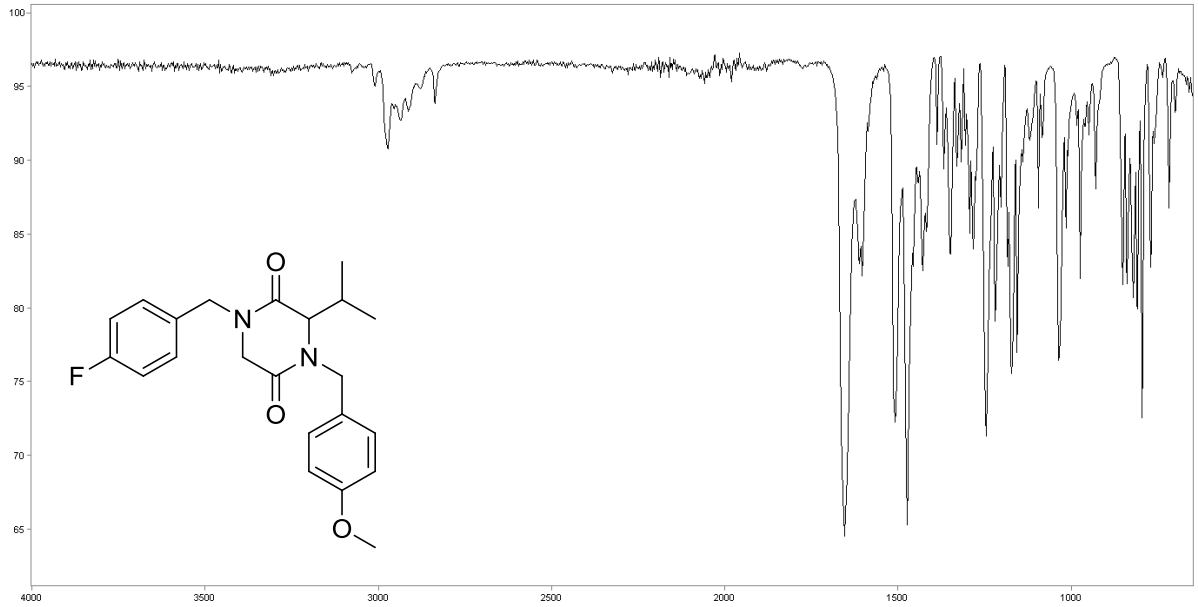
IR-6g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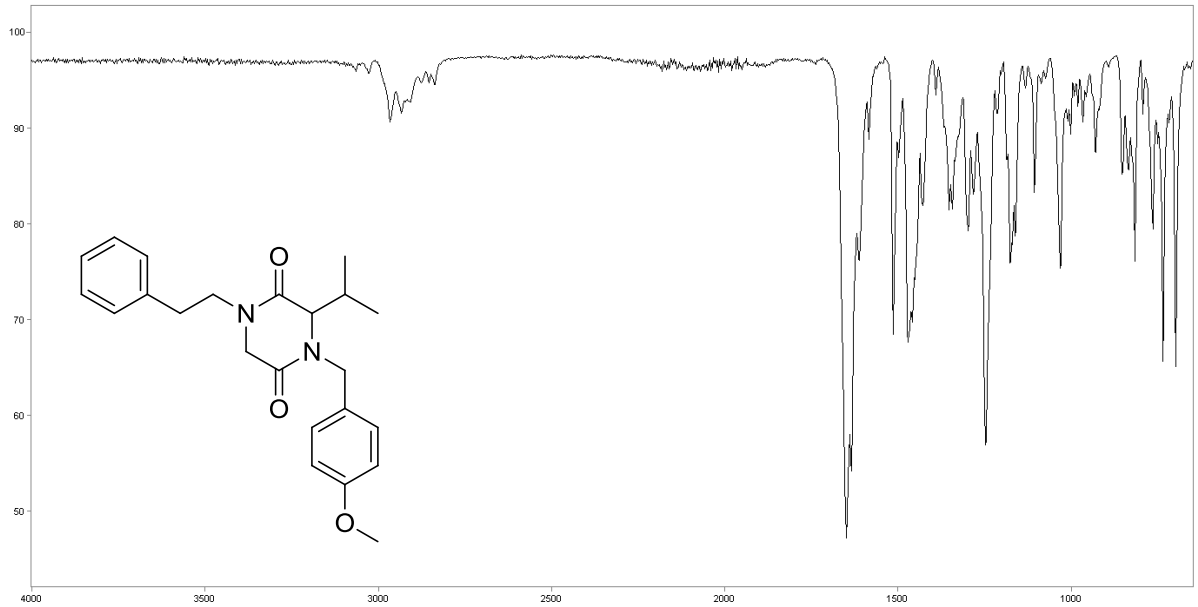
IR-6h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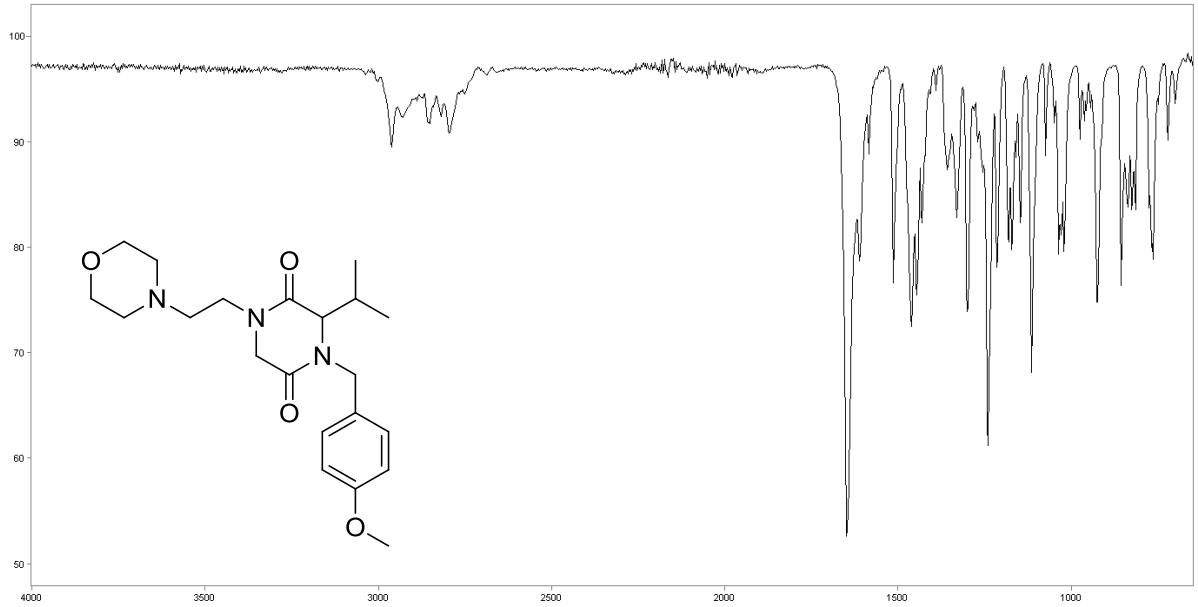
IR-6i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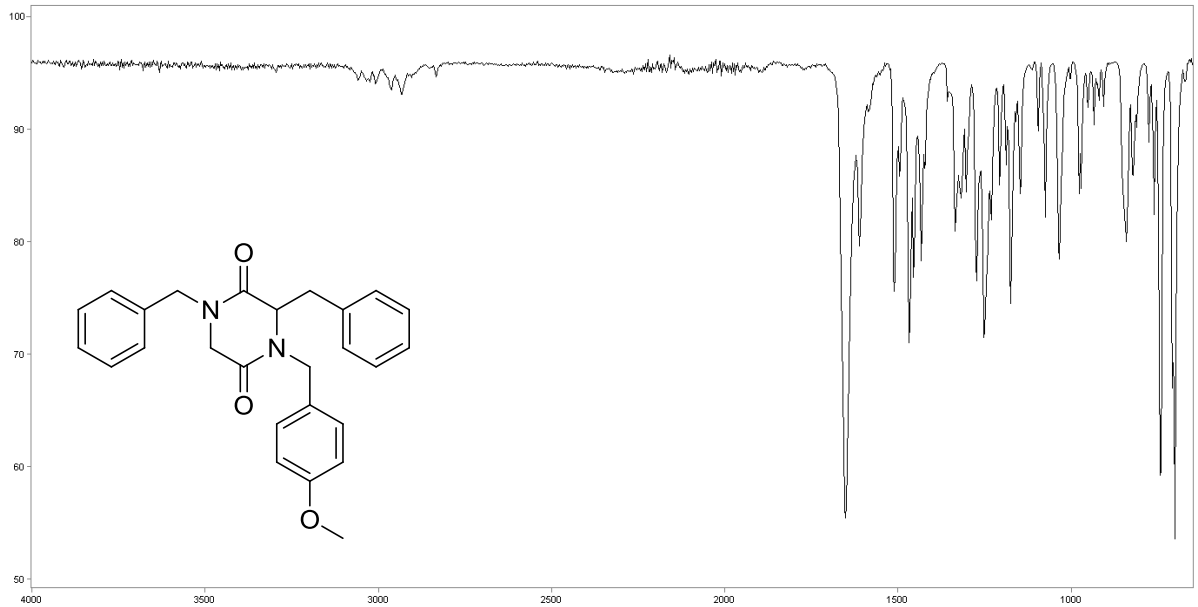
IR-6j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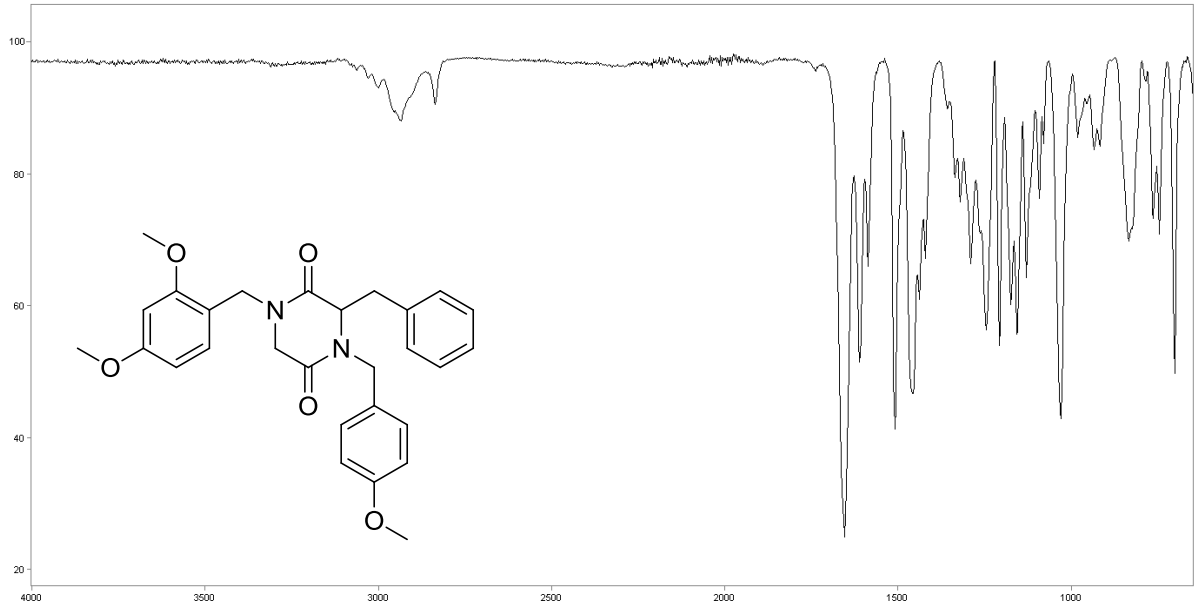
IR-6k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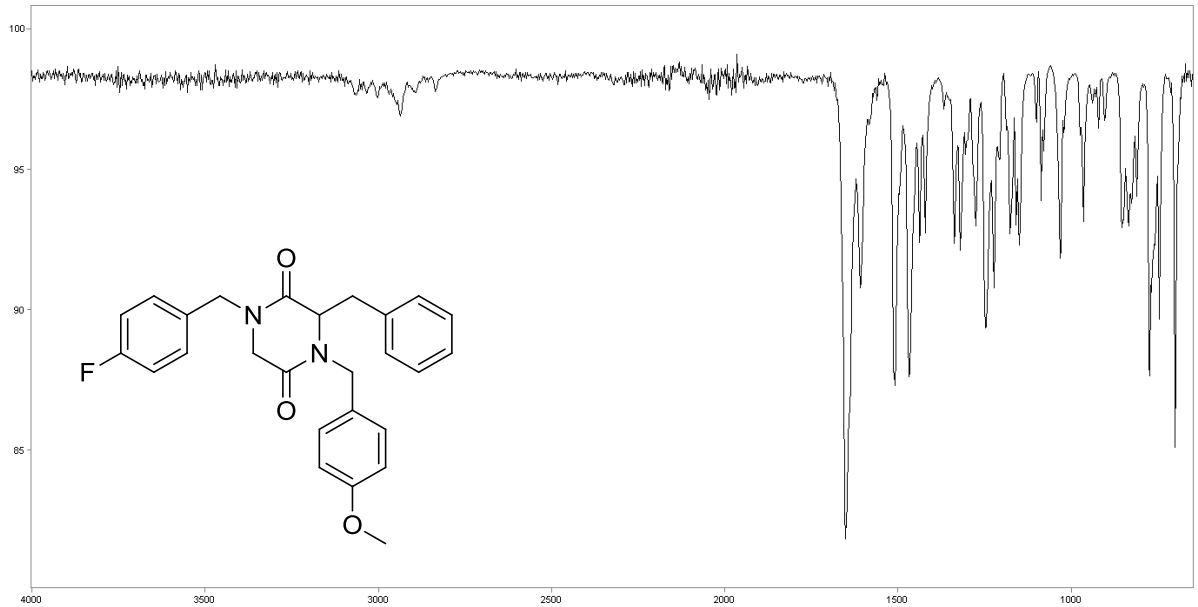
IR-6l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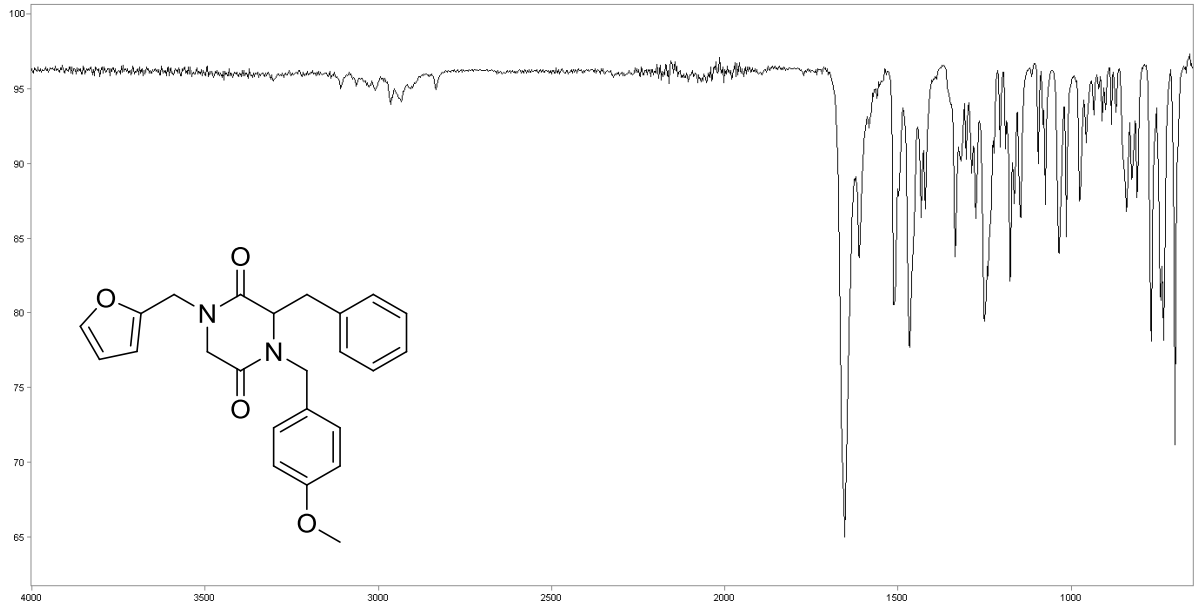
IR-6m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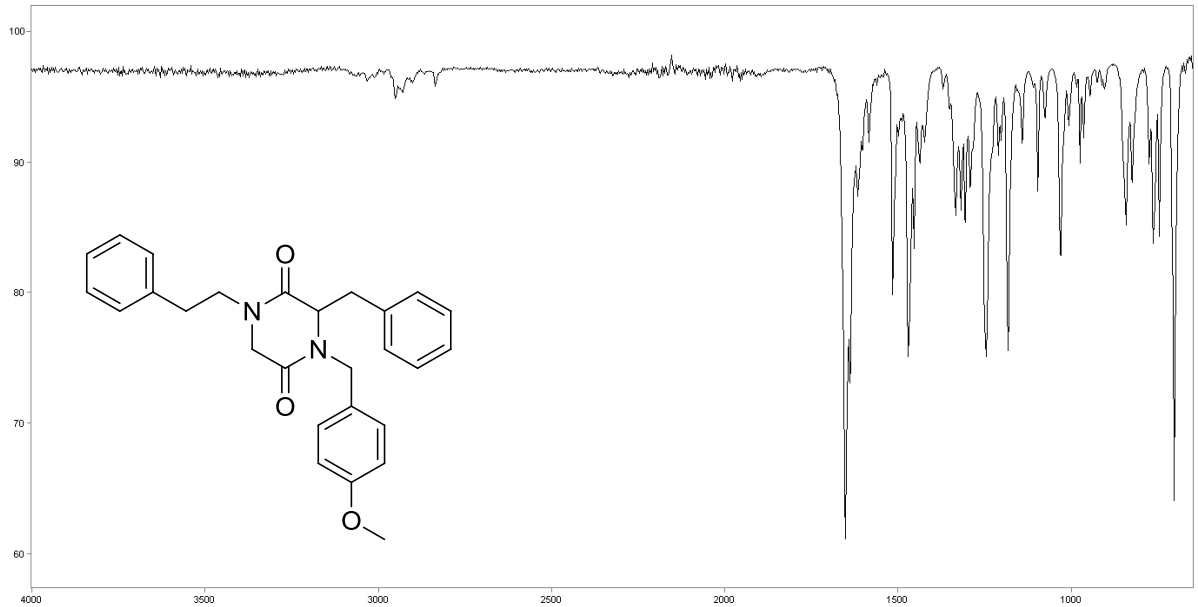
IR-6n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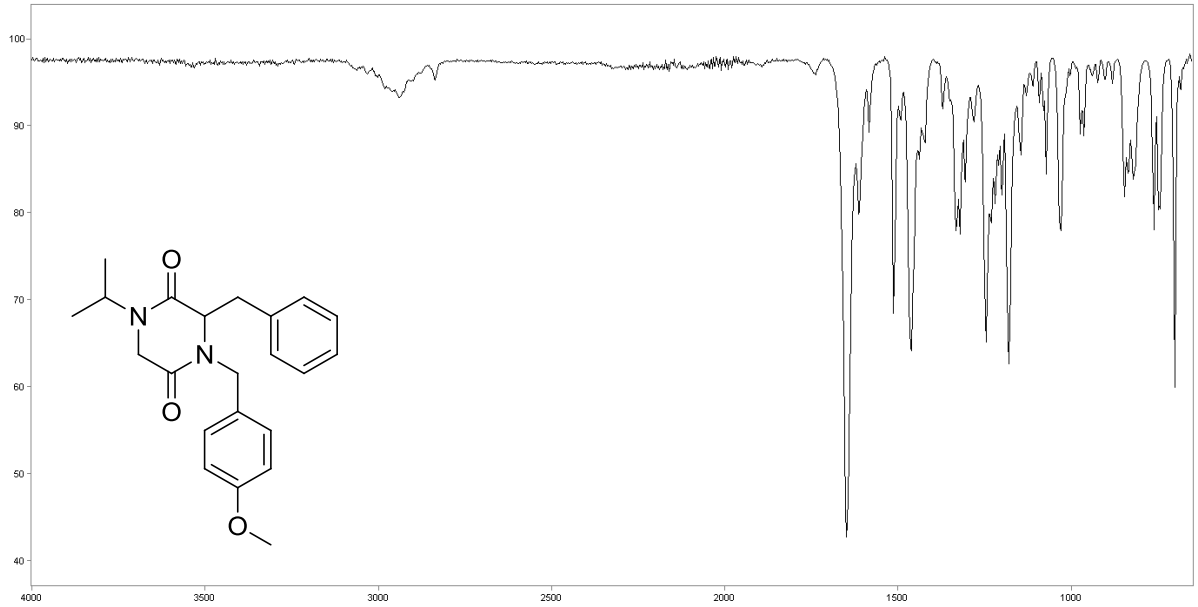
IR-6o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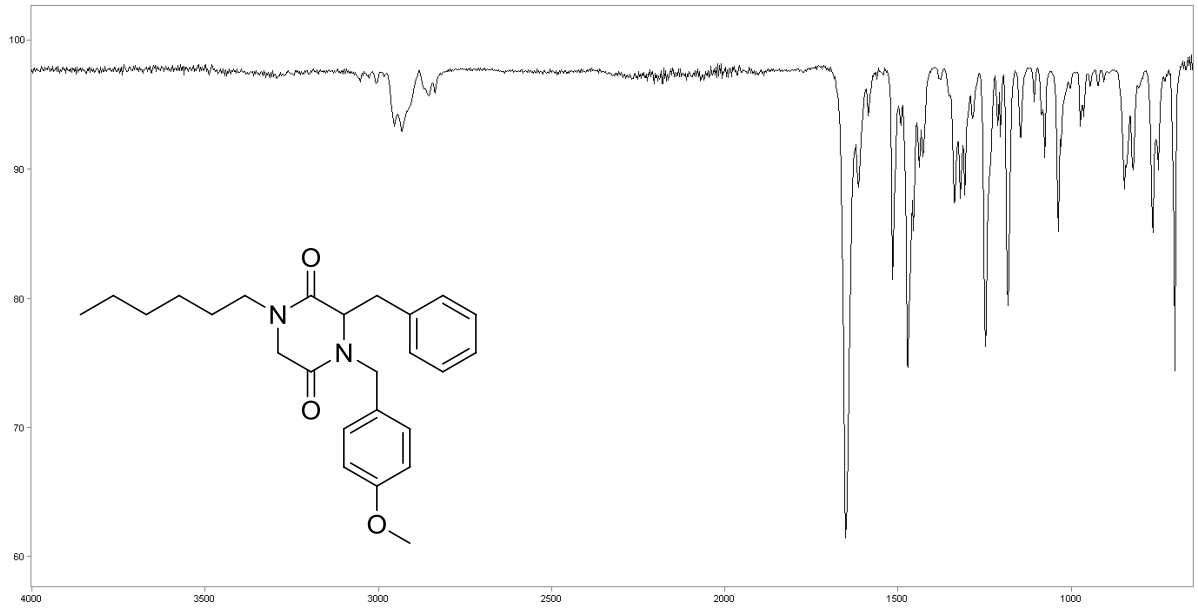
IR-6p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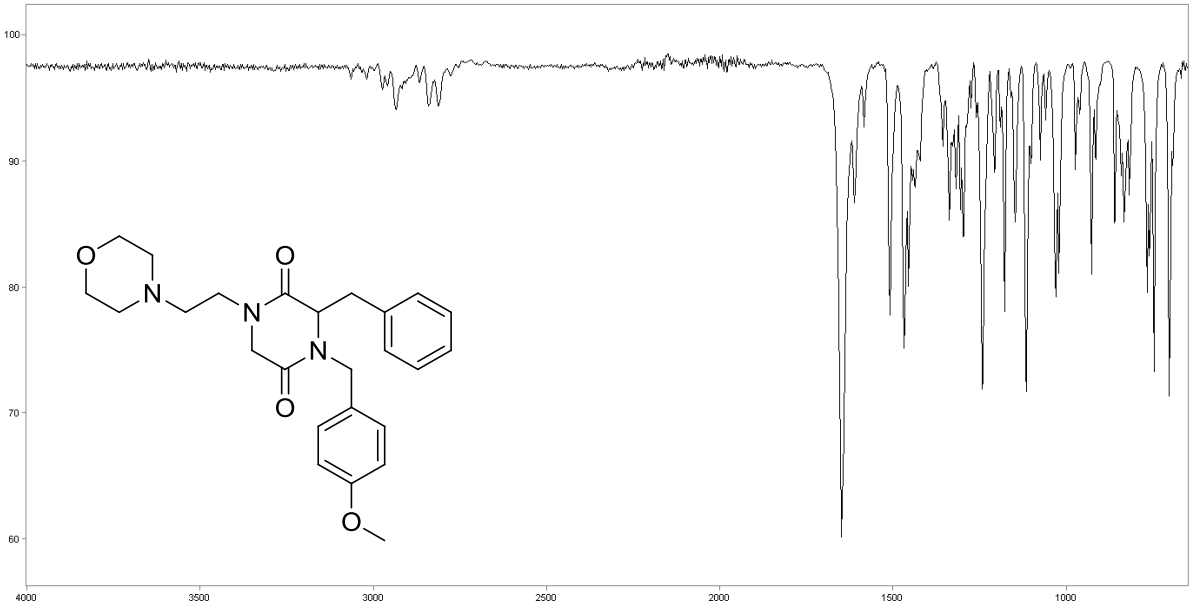
IR-6q



IR-6r

112. Chiral HPLC spectra of compounds 3

Column Type:

a) Daicel Chiralpak IA 4.6 x 250 mm (Normal phase)

b) Agilent Chiradex 4.0 x 250 mm LC column (Reverse phase)

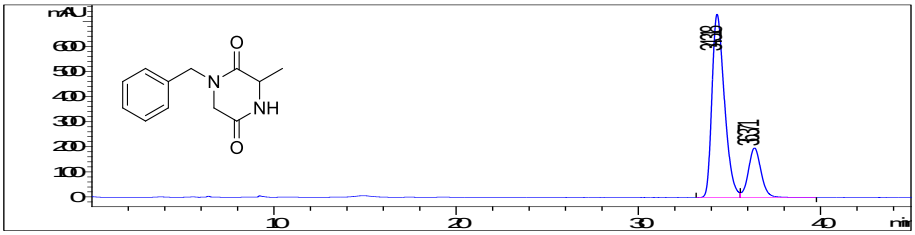
Eluent: (It depends on sample.)

a) *n*-Hexane / *i*-PrOH (210, 254 nm UV Detection)

b) ACN / MeOH / 5 mM Ammonium Formate Buffer (210, 254 nm UV Detection)

Chiral HPLC spectra of 3a

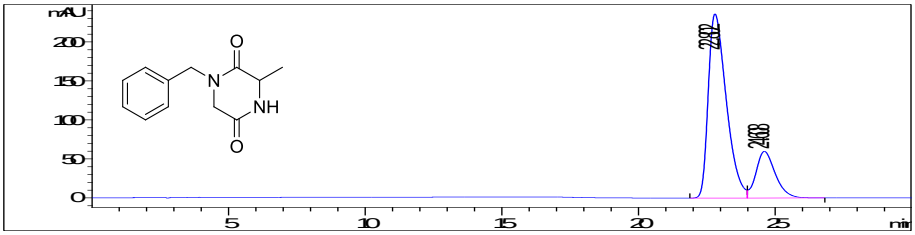
a)



78.5% (t_R = 34.318 min), 21.5% (t_R = 36.371 min)

Eluent: *n*-Hexane 80.0% / EtOH 20.0% (210 nm UV Detection)

b)



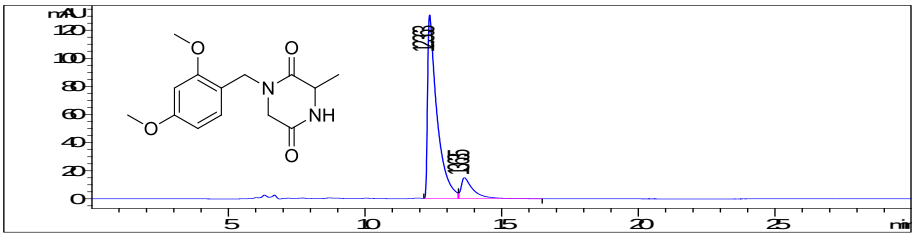
78.7% (t_R = 22.802 min), 21.3% (t_R = 24.608 min)

Eluent: ACN 2.5% / MeOH 2.5% / 5mM Ammonium Formate Buffer 95.0%

(210 nm UV Detection)

Chiral HPLC spectra of 3b

a)

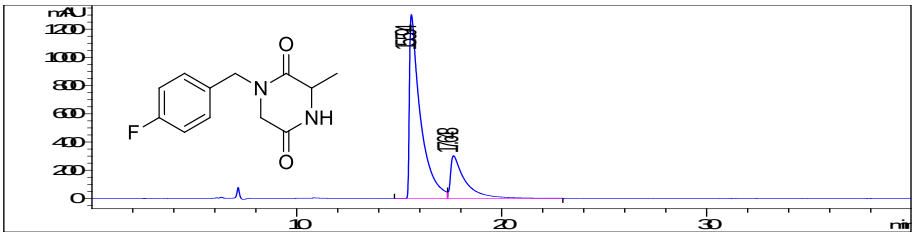


87.4% (t_R = 12.363 min), 12.6% (t_R = 13.635 min)

Eluent: *n*-Hexane 30.0% / THF 70.0% (254 nm UV Detection)

Chiral HPLC spectra of 3c

a)

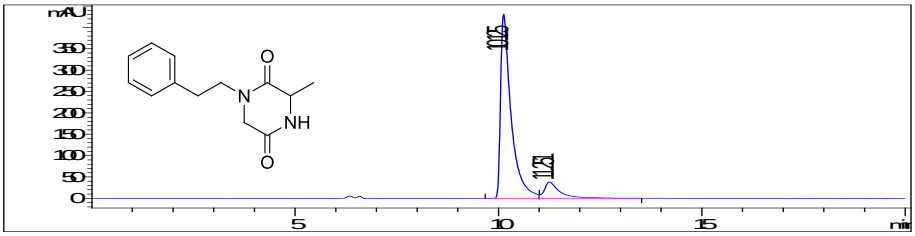


76.3% (t_R = 15.594 min), 23.7% (t_R = 17.648 min)

Eluent: *n*-Hexane 40.0% / THF 60.0% (210 nm UV Detection)

Chiral HPLC spectra of 3d

a)

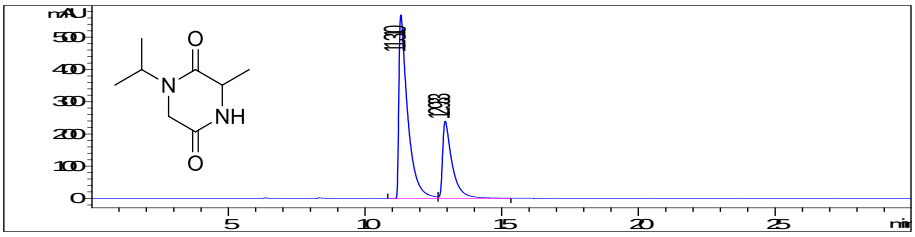


88.3% (t_R = 10.125 min), 11.7% (t_R = 11.251 min)

Eluent: *n*-Hexane 20.0% / THF 80.0% (210 nm UV Detection)

Chiral HPLC spectra of 3e

a)

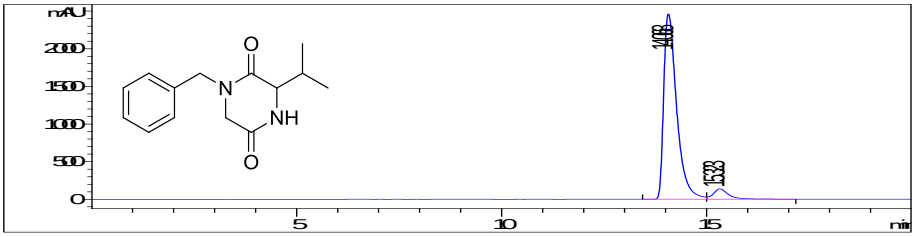


68.7% (t_R = 11.310 min), 31.3% (t_R = 12.933 min)

Eluent: *n*-Hexane 70.0% / *i*-PrOH 30.0% (210 nm UV Detection)

Chiral HPLC spectra of 3f

a)

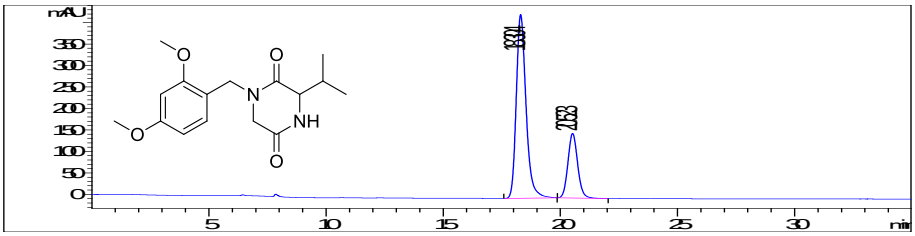


93.7% (t_R = 14.068 min), 6.3% (t_R = 15.323 min)

Eluent: *n*-Hexane 75.0% / *i*-PrOH 25.0% (210 nm UV Detection)

Chiral HPLC spectra of 3g

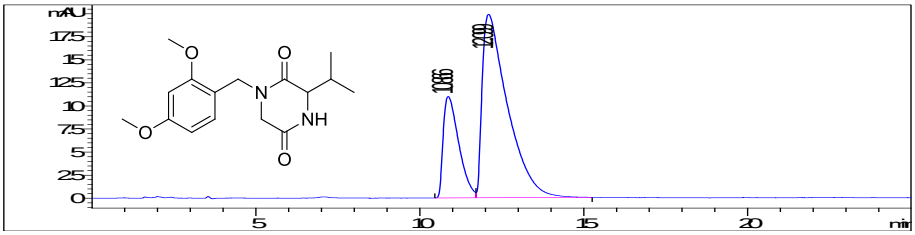
a)



74.1% (t_R = 18.304 min), 25.9% (t_R = 20.523 min)

Eluent: *n*-Hexane 75.0% / *i*-PrOH 25.0% (210 nm UV Detection)

b)



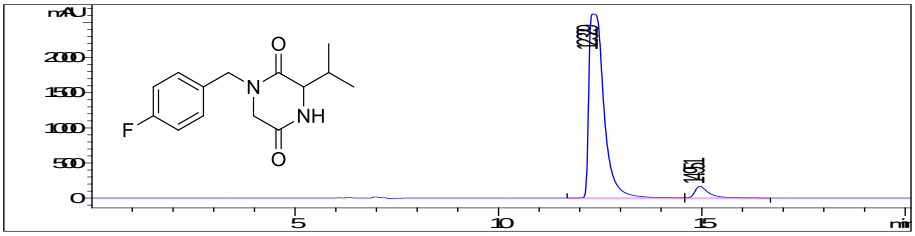
25.4% (t_R = 10.866 min), 74.6% (t_R = 12.099 min)

Eluent: ACN 5.0% / MeOH 5.0% / 5mM Ammonium Formate Buffer 90.0%

(254 nm UV Detection)

Chiral HPLC spectra of 3h

a)

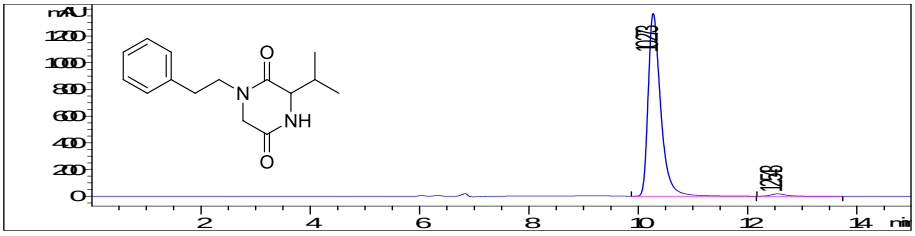


94.4% (t_R = 12.329 min), 5.6% (t_R = 14.951 min)

Eluent: *n*-Hexane 40.0% / THF 60.0% (210 nm UV Detection)

Chiral HPLC spectra of 3i

a)

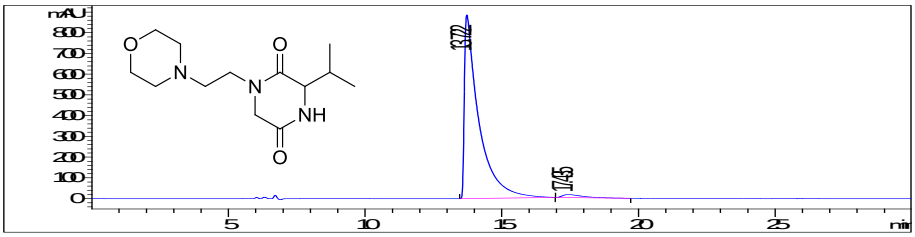


98.5% (t_R = 10.273 min), 1.5% (t_R = 12.548 min)

Eluent: *n*-Hexane 30.0% / THF 70.0% (210 nm UV Detection)

Chiral HPLC spectra of 3j

a)

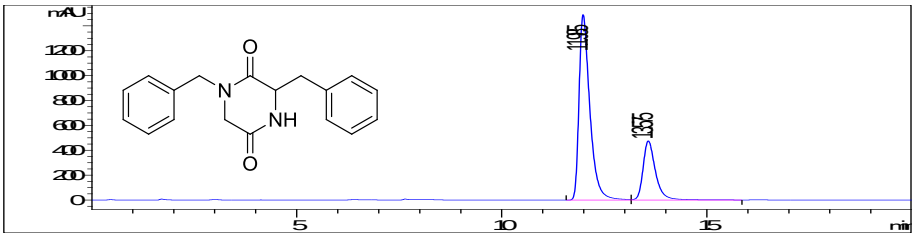


97.8% (t_R = 13.722 min), 2.2% (t_R = 17.435 min)

Eluent: *n*-Hexane 30.0% / THF 70.0% (210 nm UV Detection)

Chiral HPLC spectra of 3k

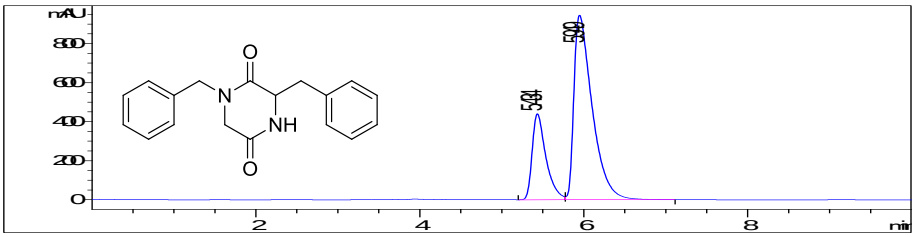
a)



73.4% (t_R = 11.985 min), 26.6% (t_R = 13.575 min)

Eluent: *n*-Hexane 60.0% / *i*-PrOH 40.0% (210 nm UV Detection)

b)



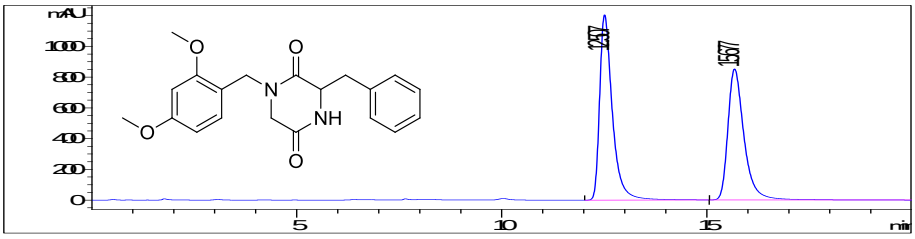
26.0% (t_R = 5.434 min), 74.0% (t_R = 5.949 min)

Eluent: ACN 30.0% / MeOH 5.0% / 5mM Ammonium Formate Buffer 65.0%

(210 nm UV Detection)

Chiral HPLC spectra of 3l

a)

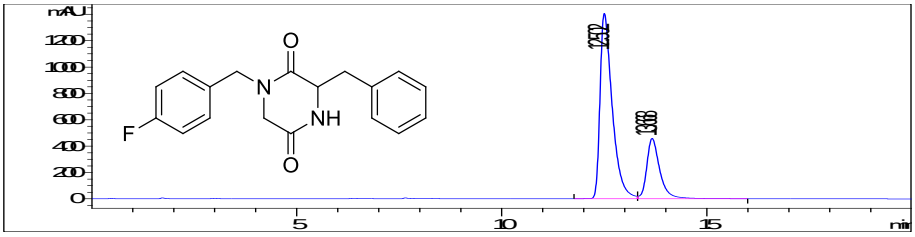


52.6% (t_R = 12.507 min), 47.4% (t_R = 15.677 min)

Eluent: *n*-Hexane 60.0% / *i*-PrOH 40.0% (210 nm UV Detection)

Chiral HPLC spectra of 3m

a)

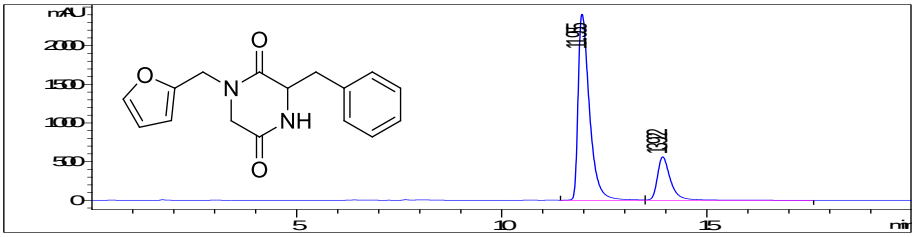


74.0% (t_R = 12.502 min), 26.0% (t_R = 13.668 min)

Eluent: *n*-Hexane 60.0% / *i*-PrOH 40.0% (210 nm UV Detection)

Chiral HPLC spectra of 3n

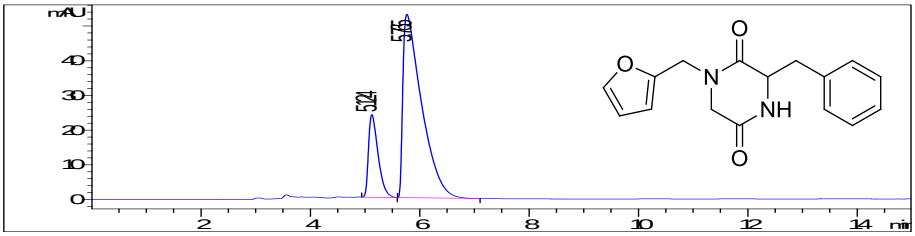
a)



78.8% (t_R = 11.955 min), 21.2% (t_R = 13.922 min)

Eluent: *n*-Hexane 60.0% / *i*-PrOH 40.0% (210 nm UV Detection)

b)

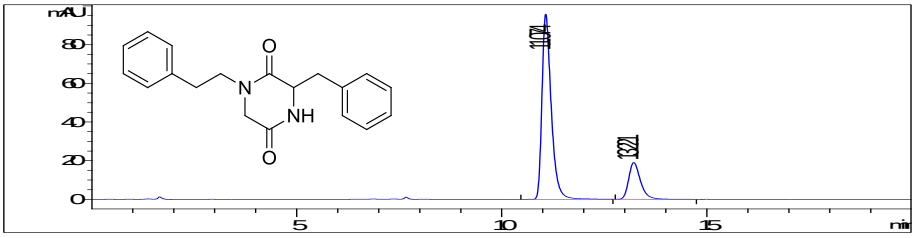


18.7% (t_R = 5.124 min), 81.3% (t_R = 5.765 min)

Eluent: ACN 30.0% / 5mM Ammonium Formate Buffer 70.0% (254 nm UV Detection)

Chiral HPLC spectra of 3o

a)

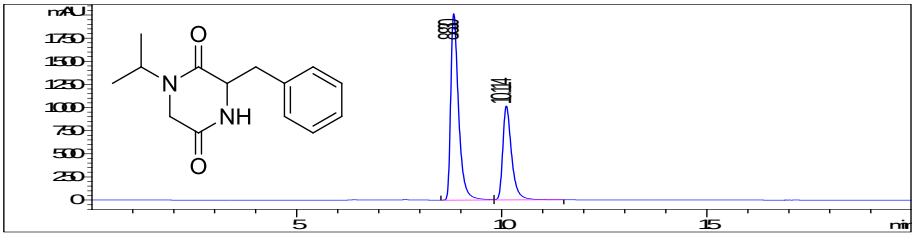


79.8% (t_R = 11.074 min), 20.2% (t_R = 13.221 min)

Eluent: *n*-Hexane 60.0% / *i*-PrOH 40.0% (210 nm UV Detection)

Chiral HPLC spectra of 3p

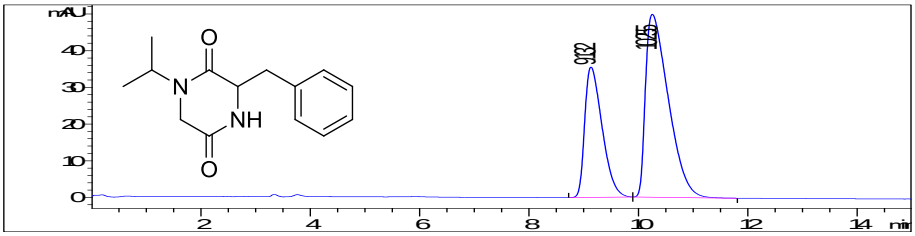
a)



63.7% (t_R = 8.830 min), 36.3% (t_R = 10.114 min)

Eluent: *n*-Hexane 60.0% / *i*-PrOH 40.0% (210 nm UV Detection)

b)

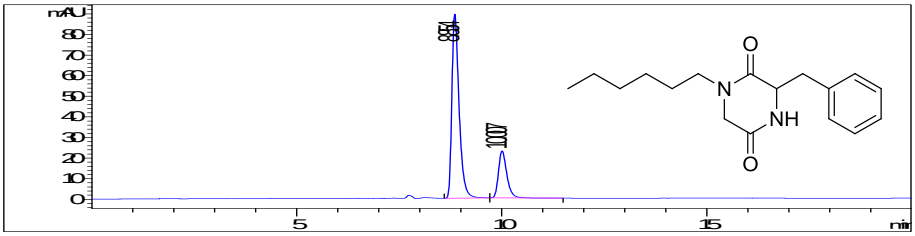


35.2% (t_R = 9.132 min), 64.8% (t_R = 10.255 min)

Eluent: ACN 15.0% / 5mM Ammonium Formate Buffer 85.0% (254 nm UV Detection)

Chiral HPLC spectra of 3q

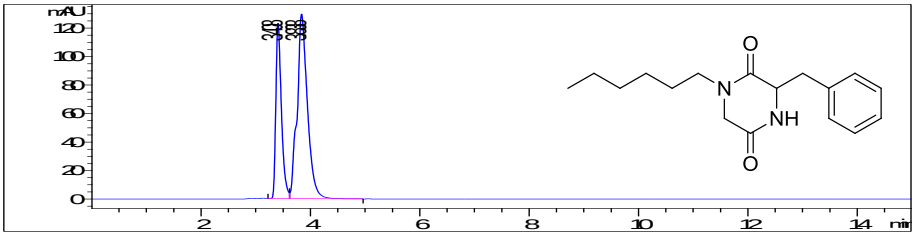
a)



77.1% (t_R = 8.854 min), 22.9% (t_R = 10.007 min)

Eluent: *n*-Hexane 60.0% / *i*-PrOH 40.0% (210 nm UV Detection)

b)

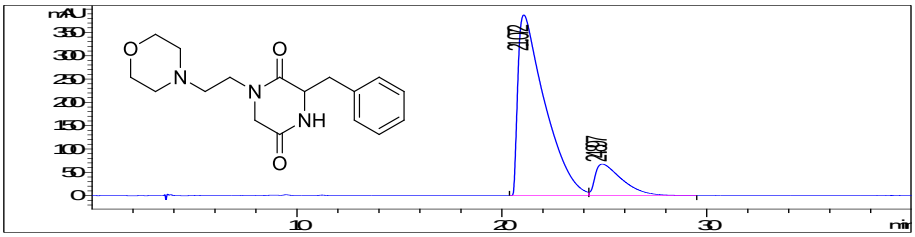


25.0% (t_R = 3.408 min), 75.0% (t_R = 3.838 min)

Eluent: ACN 50.0% / 5mM Ammonium Formate Buffer 50.0% (210 nm UV Detection)

Chiral HPLC spectra of 3r

b)



85.2% (t_R = 21.072 min), 14.8% (t_R = 24.897 min)

Eluent: ACN 10.0% / 5mM Ammonium Formate Buffer 90.0% (210 nm UV Detection)

13. Chiral HPLC spectra of compounds 6 (Only (S)-enantiomers)

Column Type:

a) Daicel Chiralpak IA 4.6 x 250 mm (Normal phase)

b) Agilent Chiradex 4.0 x 250 mm LC column (Reverse phase)

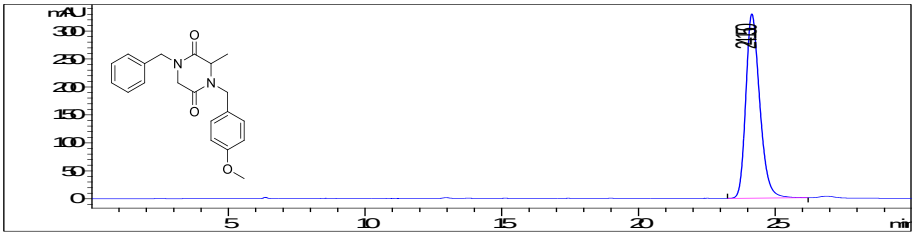
Eluent:

a) *n*-Hexane 30.0% / *i*-PrOH 70.0% (210, 254 nm UV Detection)

b) ACN 20.0% / 5 mM Ammonium Formate Buffer 80.0% (210, 254 nm UV Detection)

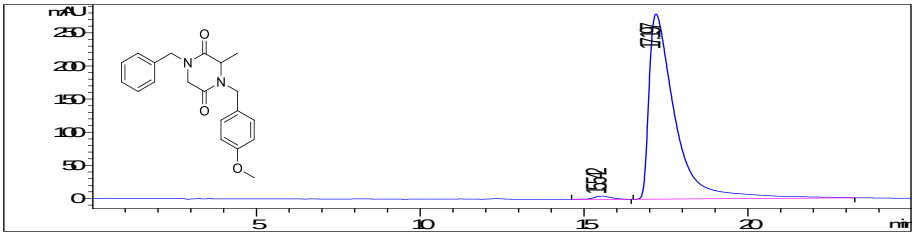
Chiral HPLC spectra of 6a

a)



100.0% (t_R = 24.150 min) (210 nm UV Detection)

b)

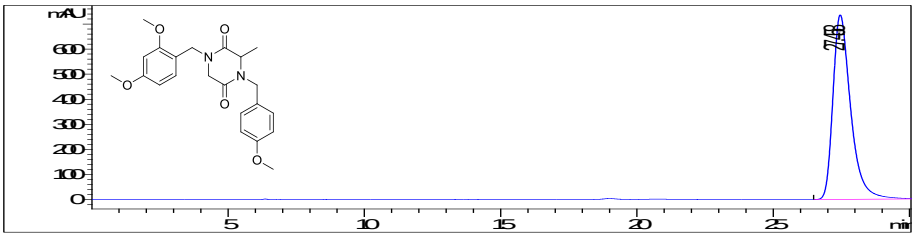


1.1% (t_R = 15.542 min) (reaction byproduct, not enantiomer), 98.9% (t_R = 17.197 min)

(210 nm UV Detection)

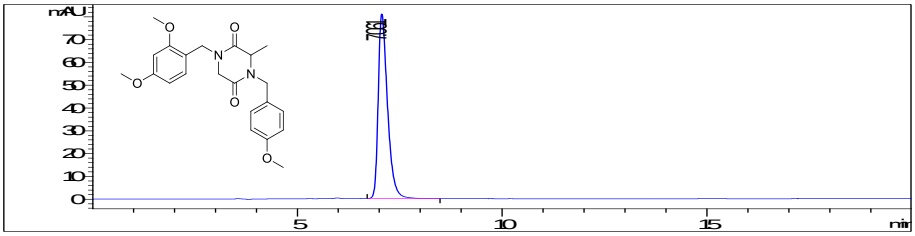
Chiral HPLC spectra of 6b

a)



100.0% (t_R = 27.458 min) (254 nm UV Detection)

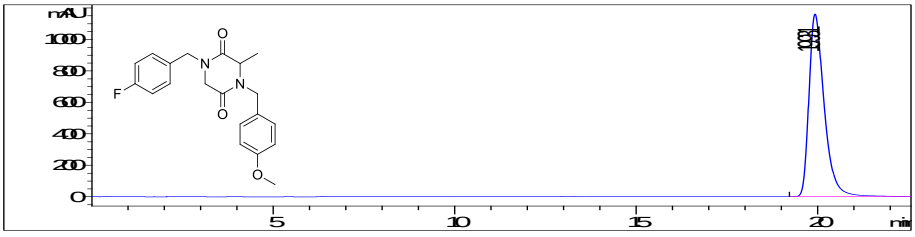
b)



100.0% (t_R = 7.061 min) (254 nm UV Detection)

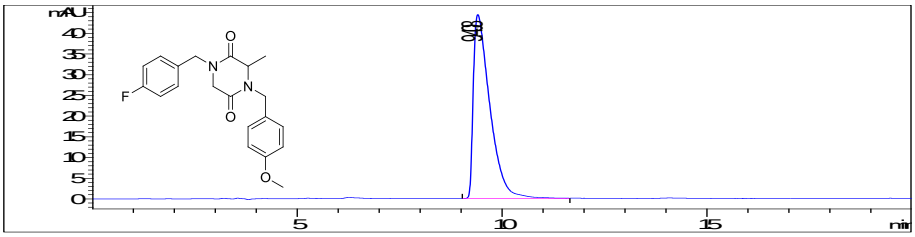
Chiral HPLC spectra of 6c

a)



100.0% (t_R = 19.931 min) (210 nm UV Detection)

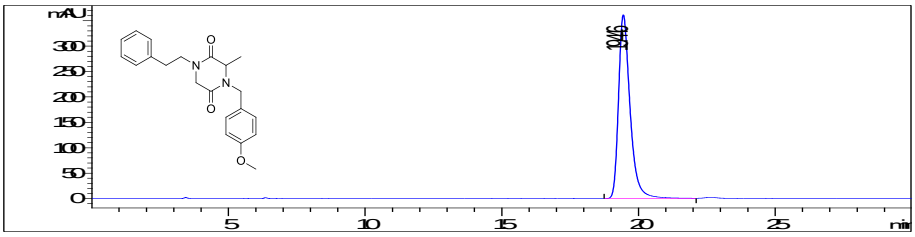
b)



100.0% (t_R = 9.408 min) (254 nm UV Detection)

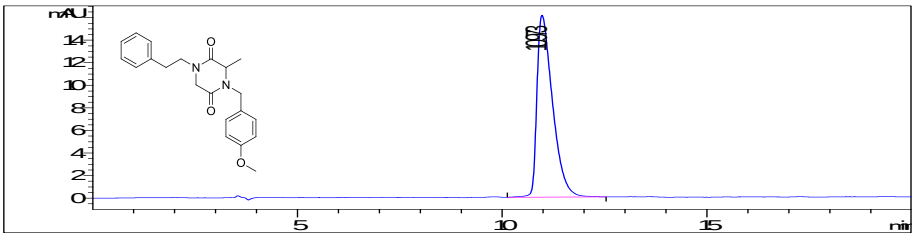
Chiral HPLC spectra of 6d

a)



100.0% (t_R = 19.446 min) (210 nm UV Detection)

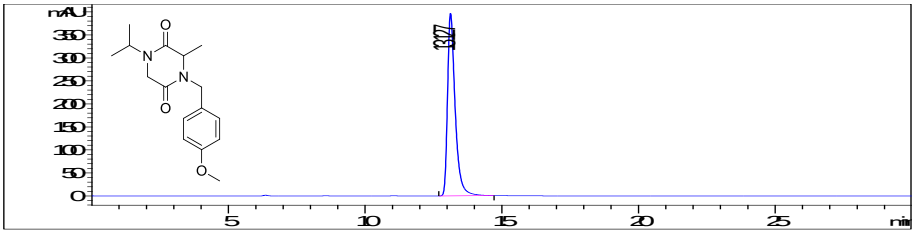
b)



100.0% (t_R = 10.973 min) (254 nm UV Detection)

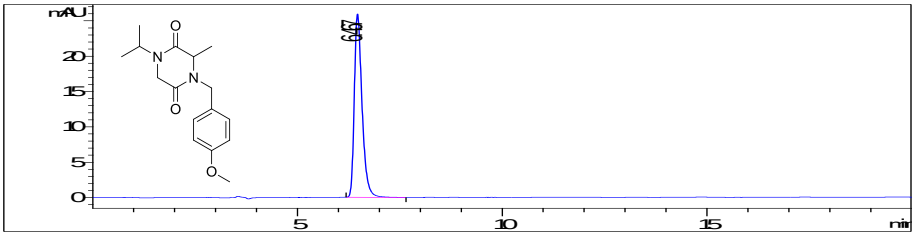
Chiral HPLC spectra of 6e

a)



100.0% (t_R = 13.127 min) (210 nm UV Detection)

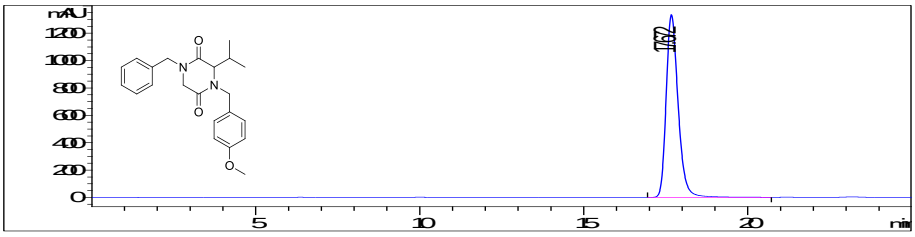
b)



100.0% (t_R = 6.467 min) (254 nm UV Detection)

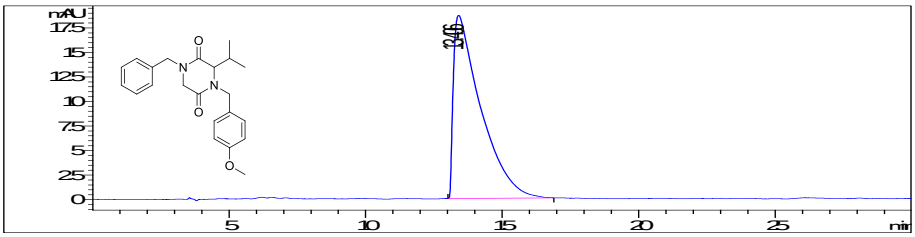
Chiral HPLC spectra of 6f

a)



100.0% (t_R = 17.672 min) (210 nm UV Detection)

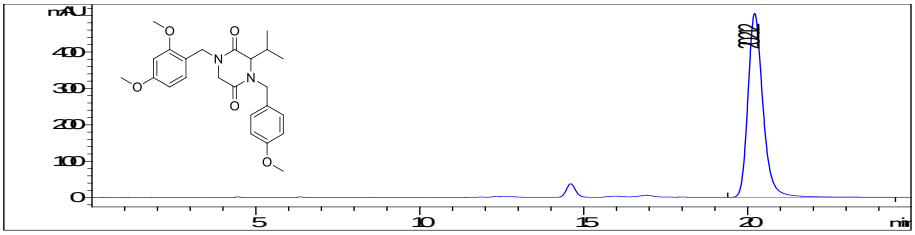
b)



100.0% (t_R = 13.406 min) (254 nm UV Detection)

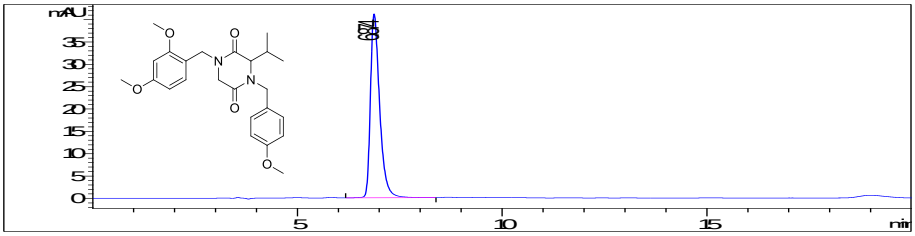
Chiral HPLC spectra of 6g

a)



100.0% (t_R = 20.212 min) (210 nm UV Detection)

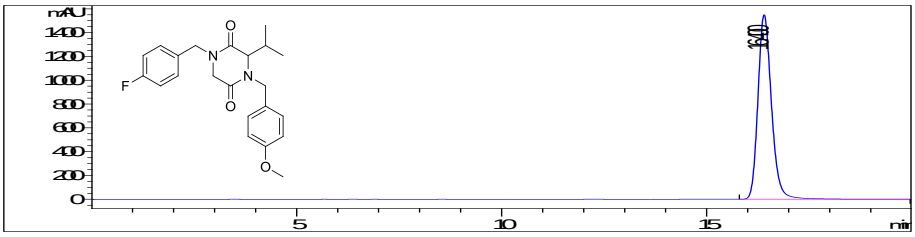
b)



100.0% (t_R = 6.874 min) (254 nm UV Detection)

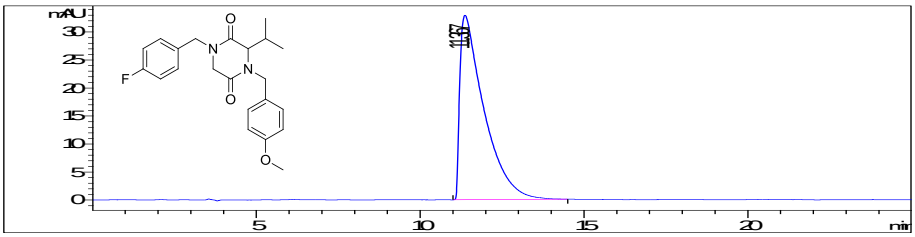
Chiral HPLC spectra of 6h

a)



100.0% (t_R = 16.400 min) (210 nm UV Detection)

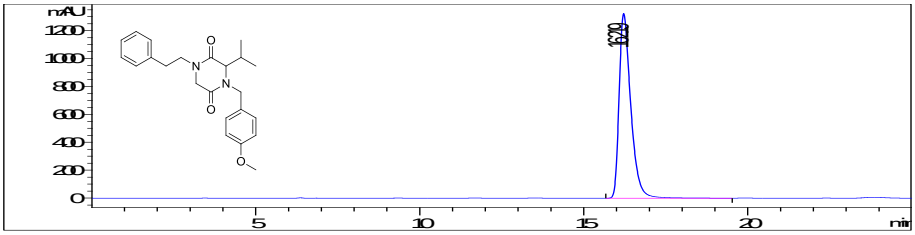
b)



100.0% (t_R = 11.367 min) (254 nm UV Detection)

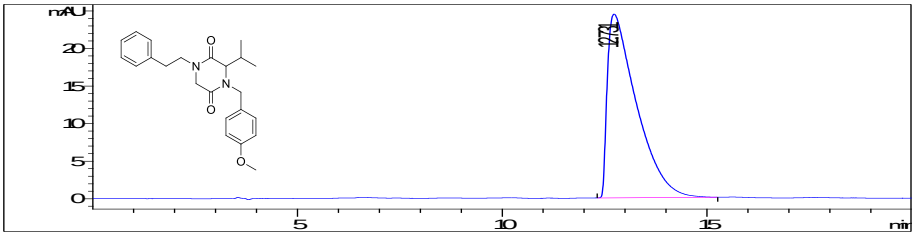
Chiral HPLC spectra of 6i

a)



100.0% (t_R = 16.219 min) (210 nm UV Detection)

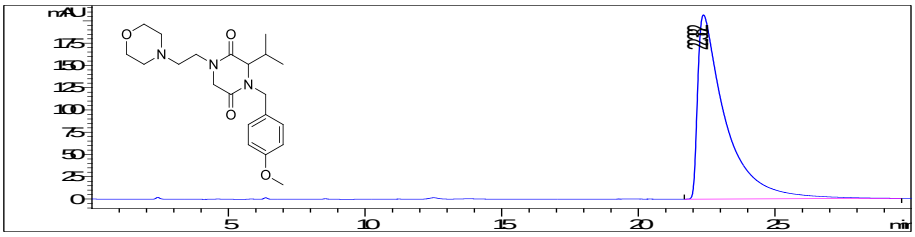
b)



100.0% (t_R = 12.731 min) (254 nm UV Detection)

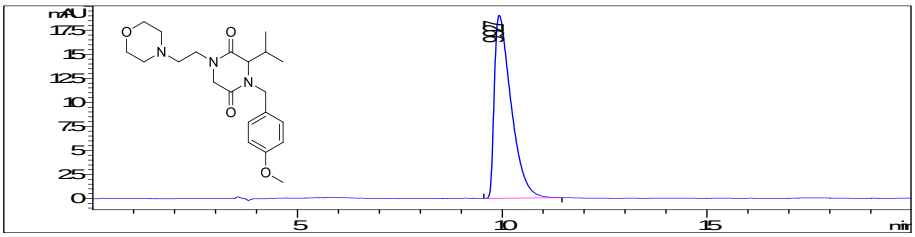
Chiral HPLC spectra of 6j

a)



100.0% (t_R = 22.382 min) (210 nm UV Detection)

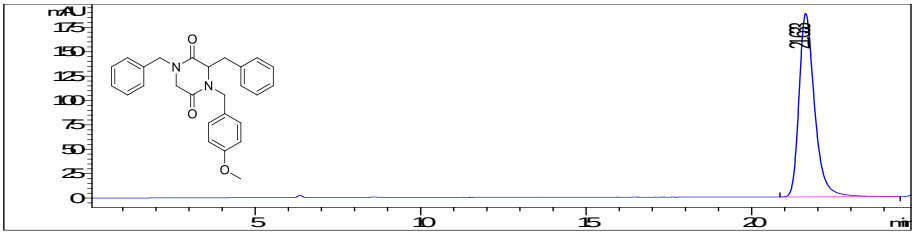
b)



100.0% (t_R = 9.927 min) (254 nm UV Detection)

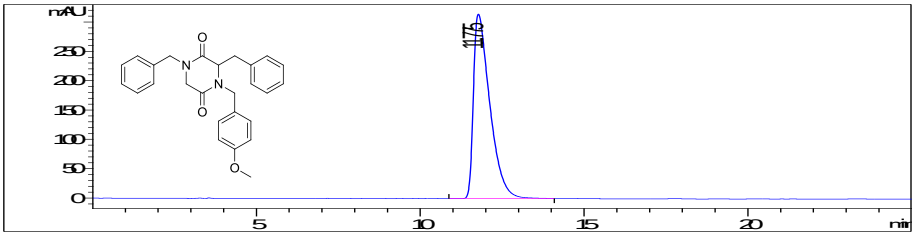
Chiral HPLC spectra of 6k

a)



100.0% (t_R = 21.633 min) (210 nm UV Detection)

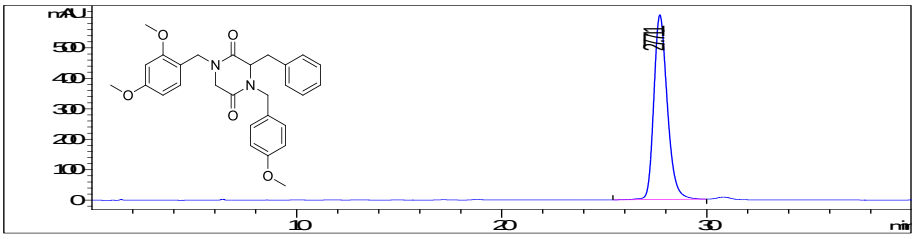
b)



100.0% (t_R = 11.775 min) (210 nm UV Detection)

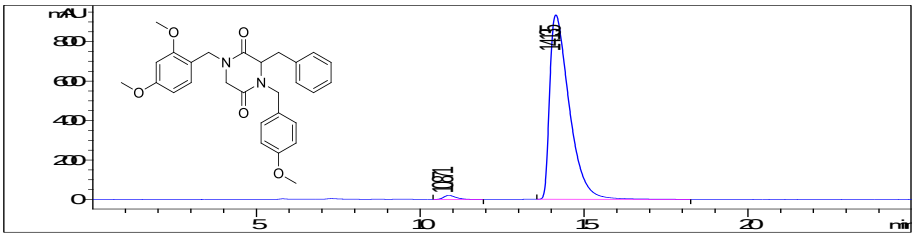
Chiral HPLC spectra of 6l

a)



100.0% (t_R = 27.711 min) (210 nm UV Detection)

b)

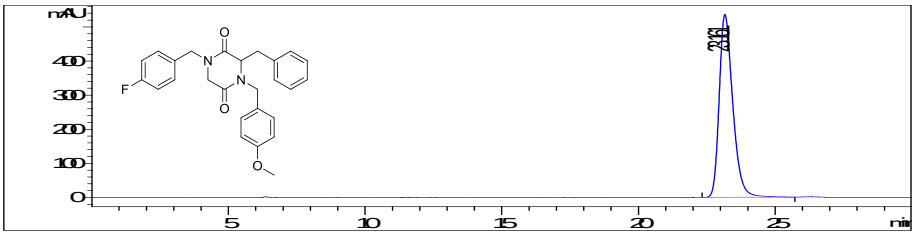


1.3% (t_R = 10.871 min) (reaction byproduct, not enantiomer), 98.7% (t_R = 14.135 min)

(210 nm UV Detection)

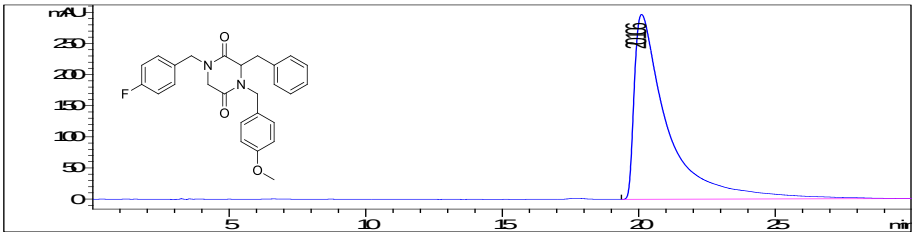
Chiral HPLC spectra of 6m

a)



100.0% (t_R = 23.161 min) (210 nm UV Detection)

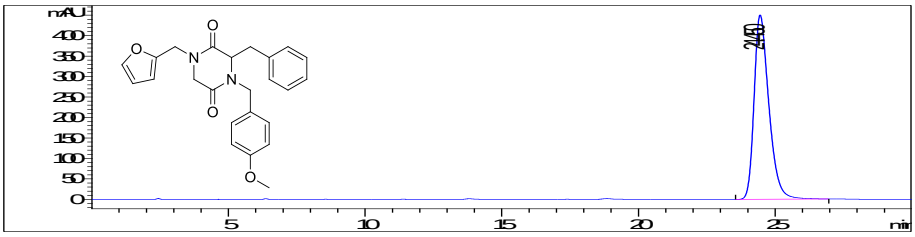
b)



100.0% (t_R = 20.106 min) (210 nm UV Detection)

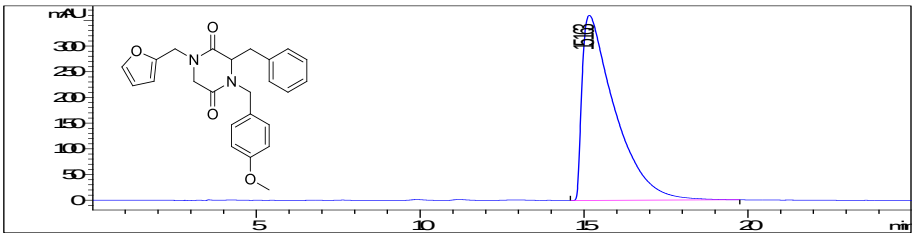
Chiral HPLC spectra of 6n

a)



100.0% (t_R = 24.450 min) (210 nm UV Detection)

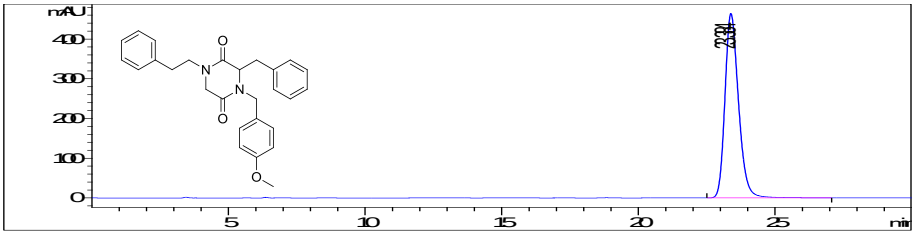
b)



100.0% (t_R = 15.183 min) (210 nm UV Detection)

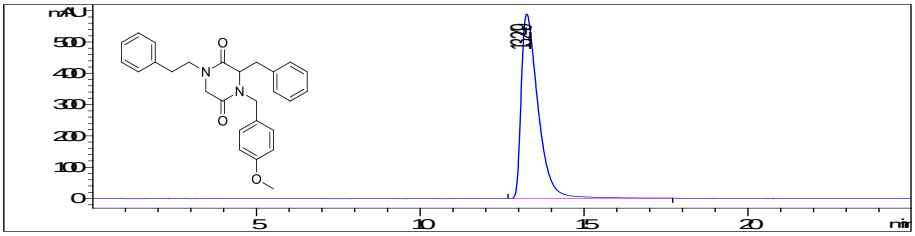
Chiral HPLC spectra of 6o

a)



100.0% (t_R = 23.384 min) (210 nm UV Detection)

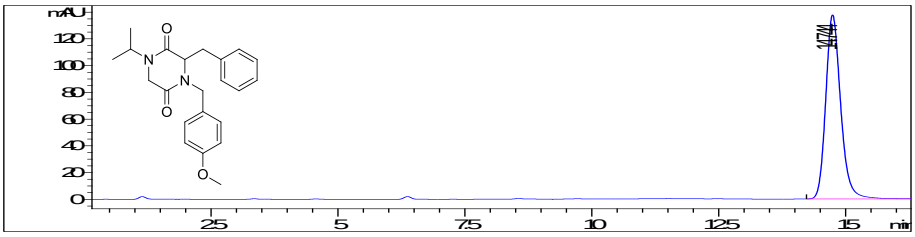
b)



100.0% (t_R = 13.249 min) (210 nm UV Detection)

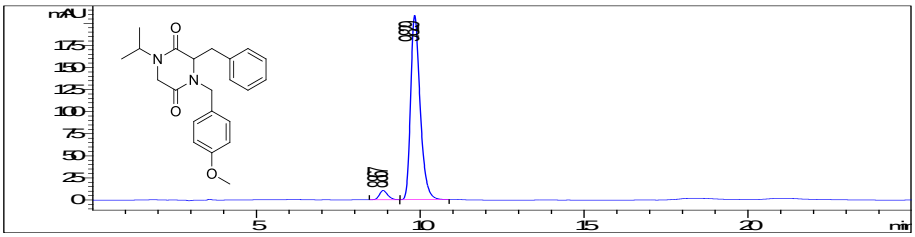
Chiral HPLC spectra of 6p

a)



100.0% (t_R = 14.744 min) (210 nm UV Detection)

b)

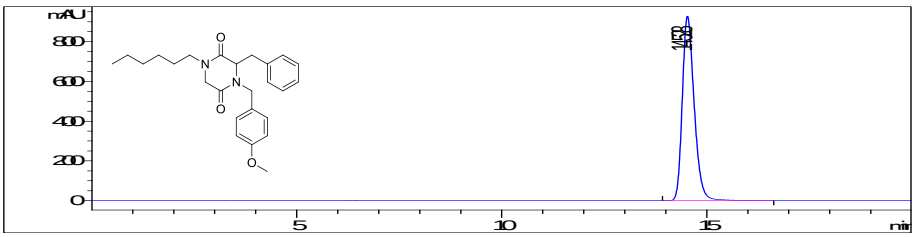


4.2% (t_R = 8.867 min) (reaction byproduct, not enantiomer), 95.8% (t_R = 9.829 min)

(210 nm UV Detection)

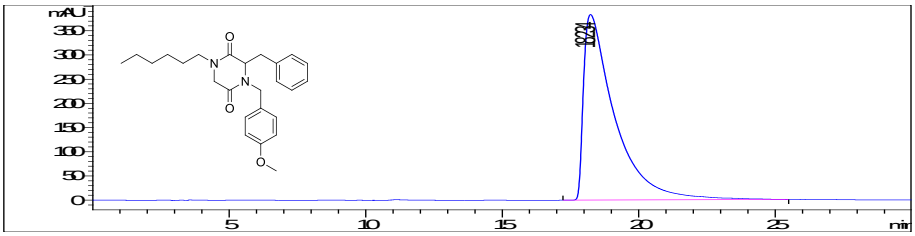
Chiral HPLC spectra of 6q

a)



100.0% (t_R = 14.7528 min) (210 nm UV Detection)

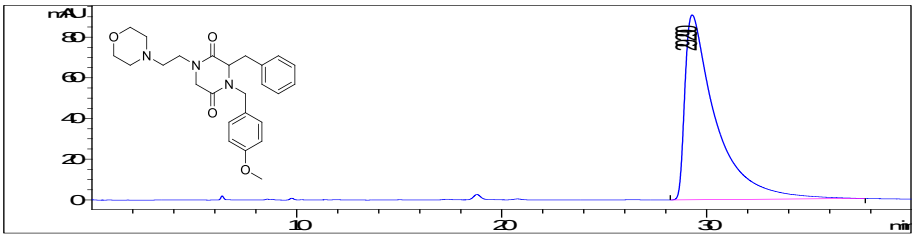
b)



100.0% (t_R = 18.234 min) (210 nm UV Detection)

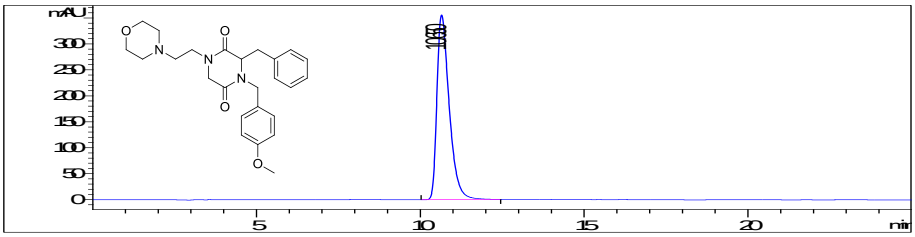
Chiral HPLC spectra of 6r

a)



100.0% (t_R = 29.290 min) (210 nm UV Detection)

b)



100.0% (t_R = 10.650 min) (210 nm UV Detection)