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Supplementary Information

Total synthesis of the cyanobacterial metabolite nostodione A: discovery of its antiparasitic activity against *Toxoplasma gondii*†

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General information:

Dichloromethane (DCM) was distilled over calcium hydride. Toluene (PhMe), Tetrahydrofuran (THF) was distilled over sodium metal in the presence of benzophenone indicator. All other solvents including dimethylformamide (DMF) (>99%) was were purchased as sure-seal bottles from Sigma Aldrich.^{1}H and ^{13}C spectra were obtained on a 600 MHz Bruker NMR spectrometer. Chemical shifts are reported in units of δ (ppm) and coupling constants (*J*) are expressed in Hz. Solvent residual peak from $CDCl_3$ (^{1}H = 7.26 ppm, ^{13}C = 77.16 ppm) and DMSO-d6 (^{1}H = 2.50 ppm, ^{13}C = 39.52 ppm) were used as reference peaks for recording the chemical shifts. Mass spectra were run on a Micromass Quattro Ultima spectrometer fitted with a direct injection probe (DIP) with ionization energy set at 70 eV and HRMS (EI) were performed with a Micromass Q-TOF Ultima spectrometer. Thin layer chromatography (TLC) was run using Macherey-Nagel aluminum-backed plates. Melting points were obtained on an Electronic Research Associates Inc. melting point apparatus corrected against an external calibrant. SiliaFlash® P60 [Particle size 40-63 μm (230-400 mesh)] from Silicycle, Canada was used for all the silica gel column chromatography.

Ethyl 1-tosyl-1H-indole-2-carboxylate (8)

Into a flame-dried flask with a stirring bar was added ethyl indole-2-carboxylate (1.0 g, 1.0 equiv, 5.28 mmol). Dimethylformamide (8.0 mL) was added to the flask under inert atmosphere. Sodium hydride (0.32 g, 1.5 equiv, 60% dispersion in mineral oil) was added to the flask in portions while maintaining the temperature at 0 ˚C. The reaction mixture was stirred for 30 min at 0 °C. 4-Toluenesulfonyl chloride (2.01 g, 2.0 equiv, 10.5 mol) was added to the flask slowly in portions. The reaction mixture was stirred for 30 min at 0 °C and then overnight (12 h) at room temperature. Reaction mixture was diluted with excess water and extracted with ethyl acetate (3 X 100 mL). The organic layer was washed with brine and dried over sodium sulfate to give crude product which was purified using silica-gel flash chromatography (10-15% of EtOAc : hexanes, gradient elution) to yield Ethyl 1-tosyl-1H-indole-2-carboxylate. Yield = 93%. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.13 (d, *J* = 8.5 Hz, 1H), 7.95 (d, *J* = 8.4 Hz, 2H), 7.58 (d, *J* = 7.8 Hz, 1H), 7.45 (ddd, *J* = 8.4, 7.3, 1.1 Hz, 1H), 7.32 – 7.25 (m, 3H), 7.17 (s, 1H), 4.44 (q, *J* = 7.1 Hz, 2H), 2.39 (s, 3H), 1.42 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 161.51, 145.02, 138.26, 135.82, 132.04, 129.66, 128.36, 127.52, 127.04, 124.16, 122.55, 116.60, 115.51, 62.06, 21.74, 14.25.

(1-tosyl-1H-indol-2-yl)methanol (9)

Into a flame-dried flask with a stirring bar was added Ethyl 1-tosyl-1H-indole-2-carboxylate (1.0 g, 1.0 equiv, 2.91 mmol). Dichloromethane (8.00 mL) was added to the flask under inert atmosphere. The reaction mixture was cooled to -78 °C whereupon; DIBAL (7.28 mL, 2.5 equiv, 1M solution in cyclohexane) was added drop wise to the flask. The reaction mixture was stirred at -78 °C for additional 2 h. The reaction mixture was then allowed to warm to room temperature and stirred overnight (12 h). The reaction mixture was diluted with diethyl ether and cooled to 0 °C. Slowly water (0.30 mL) was added to the reaction mixture followed by 15% aqueous sodium hydroxide (0.30 mL). Additional water (0.72 mL) was added and then allowed the reaction mixture to warm to room temperature and stir for 15 minutes. Anhydrous magnesium sulphate

was added to the flask and further reaction mixture was stirred for 15 minutes. The reaction mixture was filtered and washed with dichloromethane to remove salts. The fitrate was concentrated to give crude product which was purified using silica-gel flash chromatography (15-30% of EtOAc : hexanes, gradient elution) to yield (1-tosyl-1H-indol-2-yl)methanol.[1] Yield = 96%. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.4 Hz, 1H), 7.71 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 7.7 Hz, 1H), 7.32 – 7.28 (m, 1H), 7.23 (t, *J* = 7.5 Hz, 1H), 7.20 (d, *J* = 8.3 Hz, 2H), 6.64 (s, 1H), 4.91 (s, 2H), 3.31 (brs, 1H), 2.33 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 145.25, 140.31, 137.09, 135.64, 130.06, 129.21, 126.51, 125.06, 123.83, 121.28, 114.45, 111.28, 58.67, 21.63.

2-(chloromethyl)-1-tosyl-1H-indole (10)

Into a flame-dried flask with a stirring bar was added (1-tosyl-1H-indol-2-yl)methanol (1.0 g, 1.0 equiv, 3.31 mmol). Dichloromethane (8.00 mL) was added to the flask under inert atmosphere. The reaction mixture was cooled to 0 °C. Triphenylphosphine (1.74 g, 2.0 equiv, 6.63 mmol) was added to the flask. N-Chlorosuccinimide (0.755 g, 1.7 equiv, 5.64 mmol) was then added slowly to the flask at 0 ˚C. *(The reaction was monitored by using TLC).* The reaction mixture was stirred approximately for 20 min at 0 °C. Upon completion of reaction, the reaction mixture was diluted with water and extracted with ethyl acetate (3 X 100 mL). The organic layer was washed with brine and dried over sodium sulfate to give crude product which was purified using silica-gel flash chromatography (10-15% of EtOAc : hexanes, gradient elution) to yield 2-(chloromethyl)-1-tosyl-1H-indole. Yield = 92%. M.P.: 53-55 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.00 (dd, *J* = 8.5, 0.7 Hz, 1H), 7.69 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 7.8 Hz, 1H), 7.24 (ddd, *J* = 8.5, 7.3, 1.2 Hz, 1H), 7.18 – 7.14 (m, 1H), 7.12 (d, *J* = 8.1 Hz, 2H), 6.71 (d, *J* = 0.5 Hz, 1H), 4.99 (s, 2H), 2.25 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 145.25, 137.35, 136.49, 135.75, 129.96, 128.83, 126.91, 125.53, 123.93, 121.37, 114.83, 113.12, 39.05, 21.69. HRMS: calcd. For $C_{16}H_{14}ClNO_2S$ $[M]^+$ 319.0430; found 319.0434.

Dimethyl (1-tosyl-1H-indol-2-yl)methylphosphonate (11)

Into a 10-20 mL Biotage microwave vial with a stirring bar was added 2-(chloromethyl)-1-tosyl-1H-indole (1.0 g, 1.0 equiv, 3.12 mmol). Trimethyl phosphite (1.94 mL, 5 equiv, 15.6 mmol) was added to the vial. The reaction mixture was sealed and heated to 100 °C overnight (12h). The reaction mixture was diluted with water and extracted with ethyl acetate (3 X 100 mL). The organic layer was washed with brine and dried over sodium sulfate. The solvent was removed using rotary evaporator (*caution! Use proper ventilation*.) to give crude product which was purified using silica-gel flash chromatography (50-90% of EtOAc : hexanes, gradient elution) to yield dimethyl (1-tosyl-1H-indol-2-yl)methylphosphonate. Yield = 92%. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.4 Hz, 1H), 7.62 (d, *J* = 8.4 Hz, 2H), 7.43 (d, *J* = 7.7 Hz, 1H), 7.27 (t, *J* = 7.7 Hz, 1H), 7.23 – 7.19 (m, 1H), 7.17 (d, *J* = 8.1 Hz, 2H), 6.81 (d, *J* = 3.5 Hz, 1H), 3.81 – 3.76 (m, 2H), 3.77 (s, 3H), 3.75 (s, 3H), 2.31 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 145.10, 137.10, 135.69, 130.82 (d, *J* = 5.7 Hz), 129.96, 129.66, 126.51, 124.65, 123.94, 120.78, 115.15, 112.73

(d, J = 6.8 Hz), 53.24, 53.20, 25.42 (d, J = 142.8 Hz), 21.64. ^{31}P NMR (243 MHz, $CDCl_3$) δ 26.50. HRMS: calcd. For $C_{18}H_{20}NO_5PS$ $[M]^+$ 393.0795; found 393.0800.

Dimethyl (1H-indol-2-yl)methylphosphonate (12)

Into a flame-dried flask with a stirring bar was added dimethyl (1-tosyl-1H-indol-2-yl)methylphosphonate (0.200 g, 1.0 equiv, 0.50 mmol). THF (5.0 mL) was added to the flask under inert atmosphere. The reaction mixture was cooled to 0 °C. Tetra-n-butylammonium fluoride (4.06 mL, 8.0 equiv, 4.06 mmol, 1M solution in THF) was added drop wise to the flask. The reaction mixture was then allowed to warm to room temperature and stirred overnight (15 h). The reaction mixture was diluted with excess water and extracted with ethyl acetate (3 X 50 mL). The organic layer was washed with brine and dried over sodium sulfate and evaporated using rotary evaporator to give crude product which was purified using silica-gel flash chromatography (0-3% of MeOH : DCM, gradient elution) to yield dimethyl (1H-indol-2-yl)methylphosphonate. Yield = 76%. M.P.: 112-114 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.97 (s, 1H), 7.54 (d, J = 7.8 Hz, 1H), 7.34 (dd, J = 8.1, 0.6 Hz, 1H), 7.15 (t, J = 7.6 Hz, 1H), 7.10 – 7.06 (m, 1H), 6.36 (s, 1H), 3.72 (s, 3H), 3.70 (s, 3H), 3.37 (d, J = 20.9 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 136.59, 128.44, 128.03 (d, J = 10.5 Hz), 121.93, 120.12, 119.98, 111.09, 102.69 (d, J = 10.7 Hz), 53.35, 53.31, 25.66 (d, J = 140.6 Hz).^{31}P NMR (243 MHz, $CDCl_3$) δ 27.24. HRMS: calcd. For $C_{11}H_{14}NO_3P$ $[M]^+$ 239.0714; found 239.0711.

Methyl 2-(2-((dimethoxyphosphoryl)methyl)-1H-indol-3-yl)-2-oxoacetate (14)

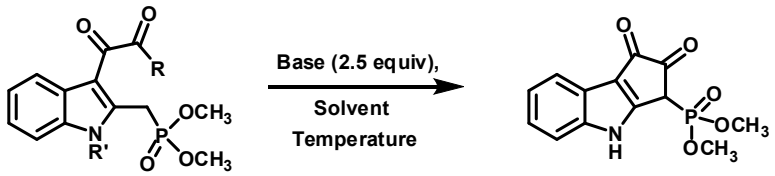
Into a flame-dried flask with a stirring bar was added dimethyl (1H-indol-2-yl)methylphosphonate (0.053 g, 1.0 equiv, 0.22 mmol). Freshly distilled diethyl ether (20.0 mL) was added to the flask under inert atmosphere. The reaction mixture was sonicated for 5 min and then cooled to 0 °C. Oxalyl chloride (0.047 mL, 2.5 equiv, 0.55 mmol) was added drop wise to the flask. The reaction mixture was stirred at 0 °C for additional 2.0 h. Methanol (excess) was added to the flask and then the reaction mixture was then allowed to warm to room temperature and stirred for additional 2.0 h. Diethyl ether was removed under reduced pressure and the crude reaction mixture was purified using silica-gel flash chromatography (0-4% of MeOH : DCM, gradient elution) to yield methyl 2-(2-((dimethoxyphosphoryl)methyl)-1H-indol-3-yl)-2-oxoacetate. Yield = 92%. ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.82 (s, 1H), 7.67 (d, J = 8.0 Hz, 1H), 7.24 – 7.22 (m, 1H), 7.21 – 7.19 (m, 1H), 7.18 – 7.14 (m, 1H), 4.02 (s, 3H), 3.99 (d, J = 21.7 Hz, 2H), 3.79 (s, 3H), 3.77 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 181.92, 166.14, 139.60 (d, J = 9.6 Hz), 135.59, 125.86, 123.85, 123.04, 119.61, 112.08, 110.39, 53.65, 53.60, 52.84, 24.49 (d, J = 136.8 Hz). ^{31}P NMR (243 MHz, $CDCl_3$) δ 26.14. HRMS: calcd. For $C_{14}H_{16}NO_6P$ $[M]^+$ 325.0715; found 325.0711.

Dimethyl 1,2-dioxo-1,2,3,4-tetrahydrocyclopenta[b]indol-3-ylphosphonate (15)

Into a flame-dried two necked round bottom flask with a stirring bar and a reflux condenser was added methyl 2-(2-((dimethoxyphosphoryl)methyl)-1H-indol-3-yl)-2-oxoacetate (0.105 g, 1.0

equiv, 0.32 mmol). Freshly distilled THF (40.0 mL) was added to the flask under inert atmosphere. The reaction mixture was cooled to 0 °C. Sodium hydride (0.031 g, 2.5 equiv, 0.80 mmol, 60% dispersion in mineral oil) was added to the flask. The reaction mixture was heated at reflux approximately 12 h (overnight, check TLC) in oil bath. During this time the solution develops an intense red color. Excess THF was distilled off under reduced pressure and the crude reaction mixture was purified using silica-gel flash chromatography [2-15% of MeOH : DCM, gradient elution (very slow column)] to yield dimethyl 1,2-dioxo-1,2,3,4-tetrahydro-cyclopenta[b]indol-3-ylphosphonate. Yield = 55-60%. ^{1}H NMR (600 MHz, DMSO) δ 12.98 (s, 1H), 7.84 (d, *J* = 7.7 Hz, 1H), 7.64 (d, *J* = 8.1 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.34 (t, *J* = 7.3 Hz, 1H), 5.01 (d, *J* = 26.4 Hz, 1H), 3.79 (d, *J* = 11.2 Hz, 3H), 3.70 (d, *J* = 11.1 Hz, 3H). ^{13}C NMR (151 MHz, DMSO) δ 194.79, 175.44, 158.57 (d, *J* = 9.0 Hz), 140.09, 125.61, 123.62, 123.07 (d, *J* = 5.6 Hz), 120.92, 120.65, 113.72, 53.76 (d, *J* = 6.1 Hz), 53.56 (d, *J* = 6.5 Hz), 43.93 (d, *J* = 136.6 Hz). ^{31}P NMR (243 MHz, DMSO) δ 17.00. HRMS (ES): calcd. For $C_{13}H_{13}NO_5P$ $[M]^+$ 294.0525; found 294.0531.

Table 1S Optimisation of the intramolecular phosphonate acylation.



R = Cl (13),
R = OCH_3 (14),

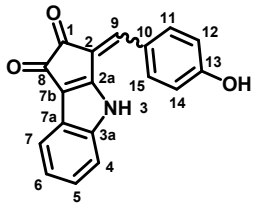
(15)

Entry	R/R'	Base	Solvent	Temperature (^{o}C)	Isolated yield (%)
1	-Cl/H	LHMDS	THF	rt	not clean
2	-Cl/H	NaH	THF	rt	not clean
3	-OCH_3/H	LHMDS	THF	reflux	38
4	-OCH_3/H	LDA	THF	reflux	not clean
5	-OCH_3/H	KO^{t}Bu	THF	reflux	22
6	-OCH_3/H	NaH	THF	reflux	55-60
7	-OCH_3/H	NaH	PhMe	reflux	NR
8	-OCH_3/H	NaH	THF+HMPA(1:1)	rt/reflux	NR
9	-OCH_3/H	NaH	THF+DMF(1:1)	rt/reflux	trace
10	-OCH_3/PMB	NaH/LHMDS /KO^{t}Bu	THF/DMF	rt/ reflux	NR

Nostodione A (1)

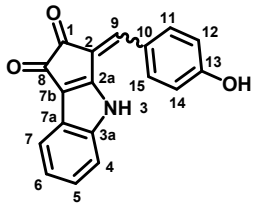
Into a flame-dried two necked round bottom flask with a stirring bar and a reflux condenser was added dimethyl 1,2-dioxo-1,2,3,4-tetrahydrocyclopenta[b]indol-3-ylphosphonate (0.034 g, 1.0 equiv, 0.11 mmol). DMF (3.5 mL) was added to the flask under inert atmosphere. The reaction mixture was cooled to 0 °C. Sodium hydride (0.012 g, 2.5 equiv, 0.29 mmol, 60% dispersion in mineral oil) was added to the flask. The reaction mixture was stirred for 5 min at 0 °C. 4-(tetrahydro-2H-pyran-2-yloxy)benzaldehyde (0.048 g, 2 equiv, 0.23 mmol) was added to the flask. The reaction mixture was then heated at reflux approximately 12 h (overnight) in oil bath. Excess DMF was distilled off under vacuum. The crude reaction mixture was dissolved in dichloromethane and passed through a short packed silica gel bed. Dichloromethane was evaporated under reduced pressure. The crude material was re-dissolved in dry MeOH (5.0 mL) and *p*-toluenesulphonic acid (10 mol%) was added to the flask. The reaction mixture was refluxed for 30 minutes. Methanol was evaporated under reduced pressure and the crude reaction mixture was purified using silica-gel flash chromatography (0-5% of MeOH : DCM, gradient elution) to yield Nostodione A (1).[3] Yield = 68%. M.P.: decompose at >285°C. ^{1}H NMR (600 MHz, DMSO, *Major isomer*) δ 12.21 (s, 1H), 10.26 (br s, 1H), 7.83 (d, *J* = 7.8 Hz, 1H), 7.73 (d, *J* = 8.2 Hz, 2H), 7.66 (d, *J* = 8.1 Hz, 1H), 7.41 (ddd, *J* = 8.1, 7.2, 0.9), 7.33 (ddd, *J* = 8.1, 7.2, 0.9), 7.29 (s, 1H), 6.96 (d, *J* = 8.6 Hz, 2H). ^{13}C NMR (151 MHz, DMSO) δ 193.60, 176.93, 159.85, 158.91, 141.25/140.77, 131.86, 128.71, 126.34, 124.59, 123.84, 123.80, 121.01, 120.74, 119.41/119.06, 116.42, 114.34.

^{1}H NMR (600 MHz, DMSO, *Minor isomer*) δ 12.93 (s, 1H), 10.35 (s, 1H), 8.08 (d, *J* = 8.7 Hz, 2H), 7.76 (d, *J* = 7.8 Hz, 1H), 7.57 (d, *J* = 8.1 Hz, 1H), 7.38 (ddd, *J* = 8.2, 7.2, 1.1), 7.29 (ddd, *J* = 8.0, 7.1, 0.8), 7.23 (s, 1H), 6.90 (d, *J* = 8.7 Hz, 2H). ^{13}C NMR (151 MHz, DMSO) δ 192.53, 175.98, 164.56, 160.47, 141.25/140.77, 134.07, 131.91, 126.01, 125.25, 123.60, 121.65, 121.08, 119.66, 119.41/119.06, 115.70, 113.17. HRMS: calcd. For $C_{18}H_{11}NO_3$ $[M]^+$ 289.0731; found 289.0739.



Comparison of [1]H-NMR and [13]C-NMR signals (δ) between reported[3] (Mårtensson), current synthetic approach and natural[4] Nostodione A (1) in DMSO-d_6 : <u>Major isomer</u>

Position	Synthetic[3]	Current Approach	Natural[4]	Synthetic[3]	Current Approach	Natural[4]
1				193.4	193.60	193.5
2				119.1/119.4	119.06/119.41	119.2
2a				158.6	158.91	158.6
3	12.22 (br s)	12.21 (br s)	12.23 (s)			
3a				140.8/140.9	141.25/140.77	140.9
4	7.67 (dt, *J* = 8.1, 1 Hz)	7.66 (d, *J* = 8.1 Hz)	7.67 (d, *J* = 8.0 Hz)	114.2	114.34	114.3
5[a]	7.40 (ddd, *J* = 8.3, 7.2, 1.3 Hz)	7.41 (ddd, *J* = 8.1, 7.2, 0.9)	7.41 (dd, *J* = 8.0, 7.9 Hz)	126.4	126.34	126.6
6[a]	7.32 (ddd, *J* = 7.9, 7.2, 0.9 Hz)	7.33 (ddd, *J* = 8.1, 7.2, 0.9)	7.33 (dd, *J* = 7.9, 7.8 Hz)	123.9	123.84	124.1
7	7.84 (dt, *J* = 7.8, 1.1 Hz)	7.83 (d, *J* = 7.8 Hz)	7.83 (d, *J* = 7.8 Hz)	120.8	120.74	120.9
7a				120.9	121.01	121.0
7b				123.7	123.80	123.8
8				177.0	176.93	177.2
9	7.31 (s)	7.29 (s)	7.29 (s)	128.9	128.71	129.1
10				124.5	124.59	124.6
11,15	7.70 (AA'XX')	7.73 (d, *J* = 8.2 Hz)	7.69 (d, *J* = 8.7 Hz)	131.8	131.86	131.9
12,14	6.97 (AA'XX')	6.96 (d, *J* = 8.6 Hz)	6.96 (d, *J* = 8.7 Hz)	116.5	116.42	116.7
13				159.9	159.85	160.1
13-OH	10.28 (br s)	10.26 (br s)	10.30 (s)			



Comparison of [1]H-NMR and [13]C-NMR signals (δ) between reported[3] (Mårtensson), current synthetic approach and natural[4] Nostodione A (1) in DMSO-d_6 : Minor isomer

Position	Synthetic[3]	Current Approach	Natural[4]	Synthetic[3]	Current Approach	Natural[4]
1				192.5	192.53	192.7
2				119.1/119.4	119.06/119.41	119.2
2a				164.6	164.56	164.7
3	12.96 (br s)	12.93 (br s)	13.02 (s)			
3a				140.8/140.9	141.25/140.77	140.9
4	7.58 (dt, *J* = 8.1, 1.0 Hz)	7.57 (d, *J* = 8.1 Hz)	7.56 (d, *J* = 8.1 Hz)	113.2	113.17	113.3
5[a]	7.37 (ddd, *J* = 8.2, 7.3, 1.2 Hz)	7.38 (ddd, *J* = 8.2, 7.2, 1.1)	7.37 (dd, *J* = 8.1, 7.9 Hz)	126.0	126.01	126.1
6[b]	7.28 (ddd, *J* = 7.9, 7.3, 0.9 Hz)	7.29 (ddd, *J* = 8.0, 7.1, 0.8)	7.27 (dd, *J* = 7.9, 7.7 Hz)	123.6	123.60	123.7
7	7.76 (dt, *J* = 7.8, 1.0 Hz)	7.76 (d, *J* = 7.8 Hz)	7.76 (d, *J* = 7.7 Hz)	121.1	121.08	121.2
7a				121.7	121.65	121.8
7b				119.5	119.66	119.5
8				176.0	175.98	176.1
9	7.23 (s)	7.23 (s)	7.26 (s)	131.9	131.91	132.1
10				125.3	125.25	125.4
11,15	8.08 (AA'XX')	8.08 (d, *J* = 8.7 Hz)	8.08 (d, *J* = 8.7 Hz)	134.1	134.07	134.2
12,14	6.90 (AA'XX')	6.90 (d, *J* = 8.7 Hz)	6.89 (d, *J* = 8.7 Hz)	115.7	115.70	115.9
13				160.5	160.47	160.6
13-OH	10.35 (br s)	10.35 (br s)	10.35 (s)			

Representative procedure for synthesis of Nostodione A analogues:

Into a flame-dried two necked round bottom flask with a stirring bar and a reflux condenser was added dimethyl 1,2-dioxo-1,2,3,4-tetrahydrocyclopenta[b]indol-3-ylphosphonate (0.040 g, 1.0 equiv, 0.13 mmol). DMF (4.5 mL) was added to the flask under inert atmosphere. The reaction

mixture was cooled to 0 °C. Sodium hydride (0.014 g, 2.5 equiv, 0.34 mmol) was added to the flask. The reaction mixture was stirred for 5 min at 0 °C. Corresponding aldehyde (2 equiv) was added to the flask. The reaction mixture was then heated at reflux approximately 12 h (overnight) in oil bath. Excess DMF was distilled off under vacuum. The crude reaction mixture was purified using silica-gel flash chromatography (MeOH : DCM, gradient elution) to yield corresponding analogue.

3-(4-chlorobenzylidene)cyclopenta[b]indole-1,2(3H,4H)-dione (17)

Isomeric ratio: 83:17. M.P.: decomposes at >290 °C. Major isomer: ^{1}H NMR (600 MHz, DMSO) δ 12.20 (s, 1H), 7.87 (d, *J* = 7.8 Hz, 1H), 7.82 (d, *J* = 8.3 Hz, 2H), 7.65 (d, *J* = 8.3 Hz, 1H), 7.63 (d, *J* = 8.5 Hz, 2H), 7.47 – 7.43 (m, 1H), 7.38 (s, 1H), 7.37-7.33 (m, 1H). Minor isomer: ^{1}H NMR (600 MHz, DMSO) δ 13.08 (s, 1H), 8.08 (d, *J* = 8.6 Hz, 2H), 7.82 (d, *J* = 8.3 Hz, 1H, overlap with major isomer), 7.63 (d, *J* = 8.5 Hz, 1H, overlap with major isomer), 7.57 (d, *J* = 8.6 Hz, 2H), 7.45 – 7.42 (m, 1H), 7.34-7.31 (m, 1H), 7.29 (s, 1H). ^{13}C NMR (151 MHz, DMSO) δ 193.01(major), 192.28(minor), 176.90(major), 175.96(minor), 162.77, 157.33, 140.89, 140.86, 135.01, 134.53, 132.84(minor), 132.76, 132.42, 130.96(major), 129.52(major), 129.00(minor), 128.63(minor), 127.02(major), 126.71(minor), 126.37(major), 125.35, 124.06(major), 123.79(minor), 123.08, 121.43(minor), 121.34, 121.06(major), 120.70, 114.19(major), 113.40(minor). HRMS: calcd. For $C_{18}H_{10}ClNO_2$ $[M]^+$ 307.0403; found 307.0400.

3-(4-(benzyloxy)benzylidene)cyclopenta[b]indole-1,2(3H,4H)-dione (18)

Isomeric ratio: 94:06. M.P.: decomposes at > 247 °C. Major isomer: ^{1}H NMR (600 MHz, DMSO) δ 12.25 (s, 1H), 7.85 (d, *J* = 7.8 Hz, 1H), 7.79 (d, *J* = 8.6 Hz, 2H), 7.66 (d, *J* = 8.2 Hz, 1H), 7.50 (d, *J* = 7.3 Hz, 2H), 7.45 – 7.42 (m, 2H), 7.44-7.40 (m, 1H), 7.38 – 7.35 (m, 1H), 7.34 (s, 1H), 7.33-7.32 (m, 1H), 7.22 (d, *J* = 8.6 Hz, 2H), 5.23 (s, 2H). Major isomer: ^{13}C NMR (151 MHz, DMSO) δ 193.24, 177.01, 160.09, 158.16, 140.73, 136.66, 131.47, 128.53, 128.14, 128.03, 127.81, 126.60, 126.32, 124.15, 123.98, 120.84, 120.80, 120.43, 115.80, 114.16, 69.51. HRMS: calcd. For $C_{25}H_{17}NO_3$ $[M]^+$ 379.1203; found 379.1208.

3-(4-methoxybenzylidene)cyclopenta[b]indole-1,2(3H,4H)-dione (19):

Isomeric ratio: 94:06. M.P.: decomposes with melt at 290-294 °C. Major isomer: ^{1}H NMR (600 MHz, DMSO) δ 12.22 (s, 1H), 7.84 (d, *J* = 7.8 Hz, 1H), 7.79 (d, *J* = 8.6 Hz, 2H), 7.66 (d, *J* = 8.2 Hz, 1H), 7.44 – 7.39 (m, 1H), 7.34-7.31 (m, 2H) *including the olefinic -H*, 7.14 (d, J = 8.8 Hz, 2H), 3.88 (s, 3H). ^{13}C NMR (151 MHz, DMSO) δ 193.27, 176.99, 160.97, 158.24, 140.80, 131.44, 128.17, 126.56, 126.13, 124.12, 123.94, 120.81, 120.41, 115.01, 114.17, 55.47. HRMS: calcd. For $C_{19}H_{13}NO_3$ $[M]^+$ 303.0907; found 303.0895.

3-(4-methylbenzylidene)cyclopenta[b]indole-1,2(3H,4H)-dione (20)

Isomeric ratio: 88:12. M.P.: decomposes with melt > 308-310 °C. Major isomer: ^{1}H NMR (600 MHz, DMSO) δ 12.20 (s, 1H), 7.85 (d, *J* = 7.8 Hz, 1H), 7.70 (d, *J* = 8.0 Hz, 2H), 7.67 (d, *J* = 8.2 Hz, 1H), 7.45 – 7.41 (m, 1H), 7.39 (d, *J* = 7.9 Hz, 2H), 7.36 – 7.32 (m, 2H) *including the olefinic -H*, 3.33 (s, 1H). ^{13}C NMR (151 MHz, DMSO) δ 193.19, 176.95, 157.78, 140.78, 140.21, 130.94, 130.10, 129.35, 128.07, 126.74, 124.69, 123.98, 121.63, 120.91, 120.73, 114.24, 21.18. HRMS: calcd. For $C_{19}H_{13}NO_2$ $[M]^+$ 287.0946; found 287.0946.

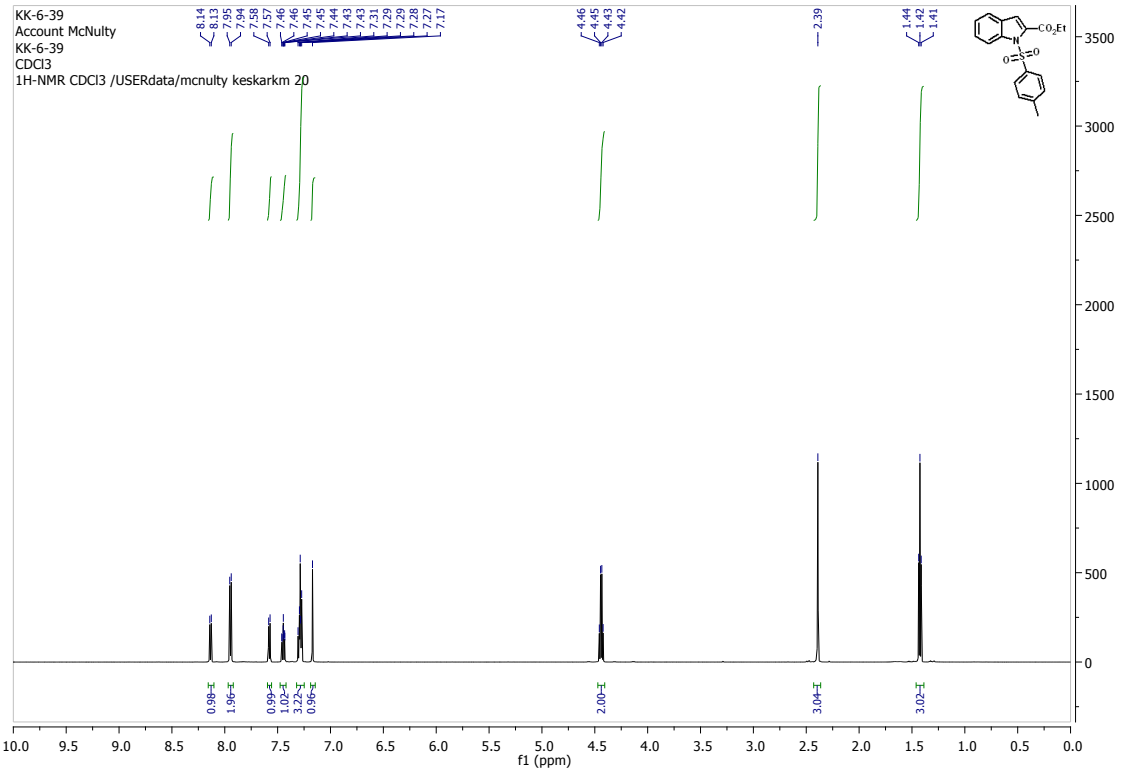
3-(benzo[d][1,3]dioxol-5-ylmethylene)cyclopenta[b]indole-1,2(3H,4H)-dione (21)

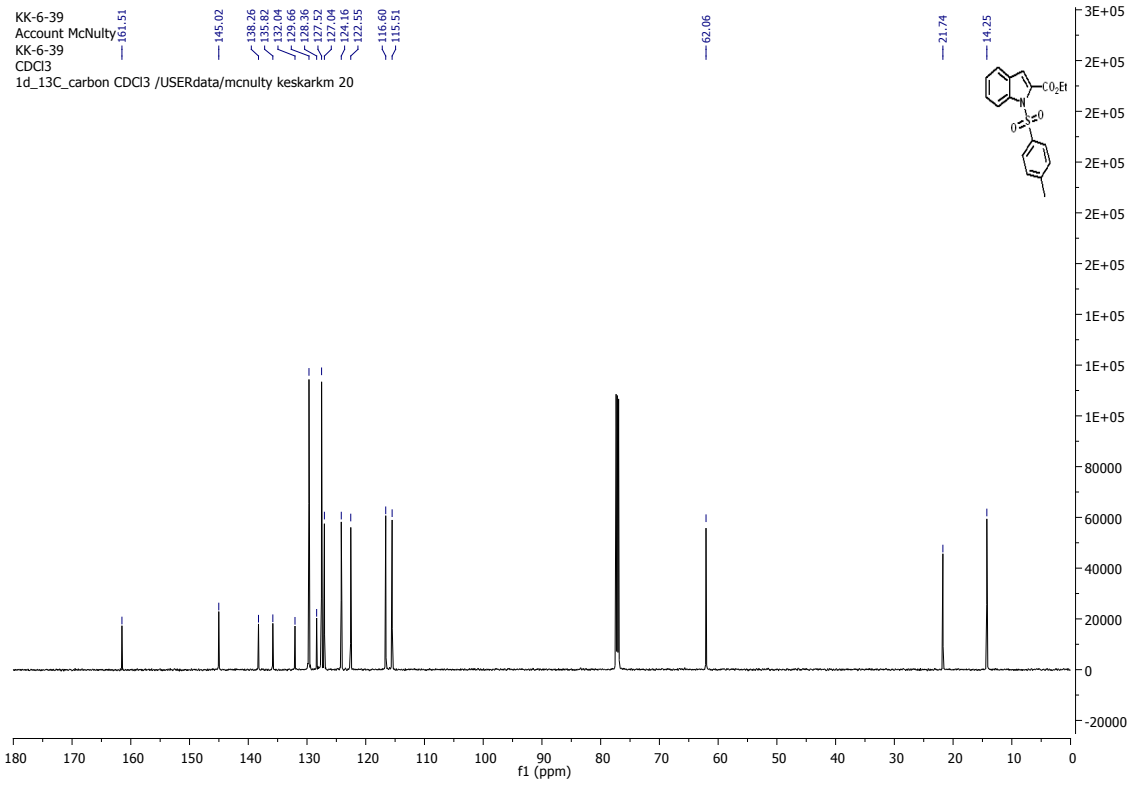
Isomeric ratio: 95:05. M.P.: decomposes with melt > 320 °C. Major isomer: ^{1}H NMR (600 MHz, DMSO) δ 12.25 (s, 1H), 7.84 (d, *J* = 7.8 Hz, 1H), 7.66 (d, *J* = 8.2 Hz, 1H), 7.42 (t, *J* = 7.7 Hz, 1H), 7.38-7.35 (m, 2H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.30 (s, 1H), 7.11 (d, *J* = 7.9 Hz, 1H), 6.16 (s, 2H). ^{13}C NMR (151 MHz, DMSO) δ 193.21, 176.94, 158.09, 149.21, 148.06, 140.82, 128.18, 127.78, 126.64, 124.96, 124.35, 123.95, 120.97, 120.87, 120.81, 114.15, 109.31, 108.92, 101.80. HRMS: calcd. For $C_{19}H_{11}NO_4$ $[M]^+$ 317.0685; found 317.0688.

3-(4-nitrobenzylidene)cyclopenta[b]indole-1,2(3H,4H)-dione (22)

Reaction carried out at room temperature. Isomeric ratio: >98: 02. M.P.: decomposes with melt > 300 °C. Major isomer: ^{1}H NMR (600 MHz, DMSO) δ 12.21 (s, 1H), 8.39 (d, *J* = 8.7 Hz, 2H), 8.05 (d, *J* = 8.6 Hz, 2H), 7.90 (d, *J* = 7.8 Hz, 1H), 7.65 (d, *J* = 8.2 Hz, 1H), 7.50 – 7.44 (m, 2H)) *including the olefinic -H*, 7.36 (t, *J* = 7.6 Hz, 1H). ^{13}C NMR (151 MHz, DMSO) δ 192.81, 176.83, 156.77, 147.54, 141.24, 140.83, 130.31, 127.41, 126.46, 125.28, 124.68, 124.48, 124.14, 123.48, 121.26, 120.68, 114.28. HRMS: calcd. For $C_{18}H_{10}N_2O_4$ $[M]^+$ 318.0645; found 318.0641.

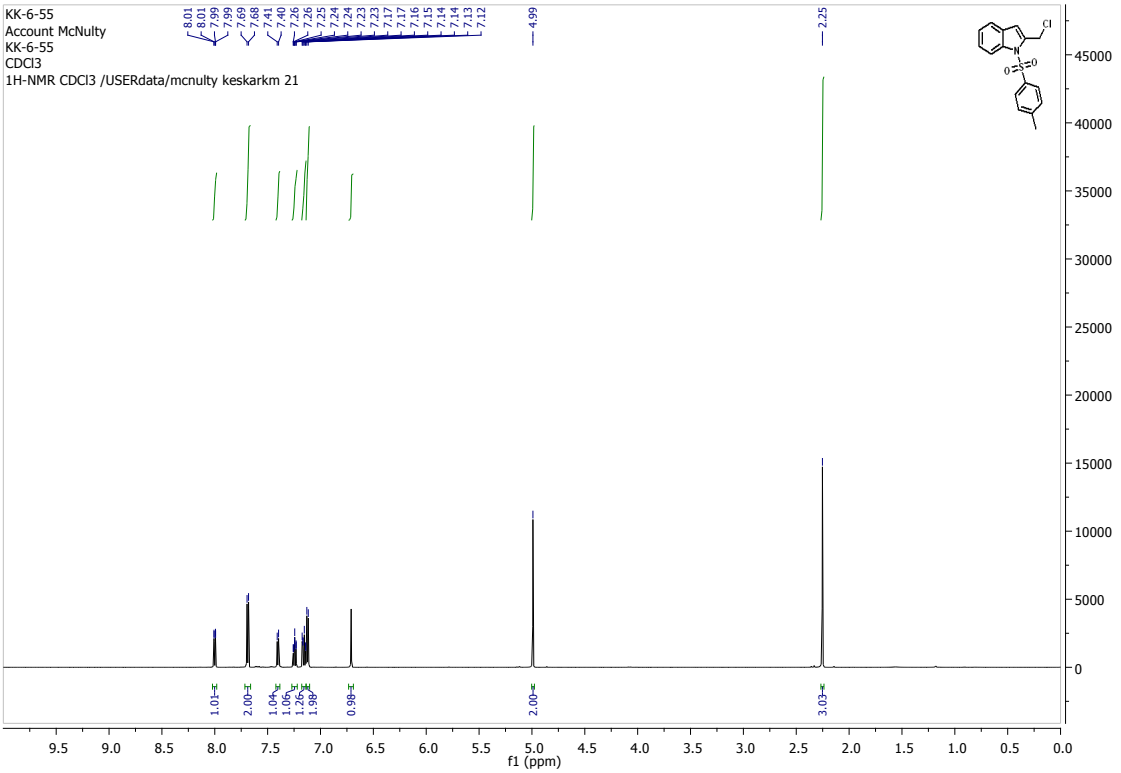
Ethyl 1-tosyl-1H-indole-2-carboxylate: (8)

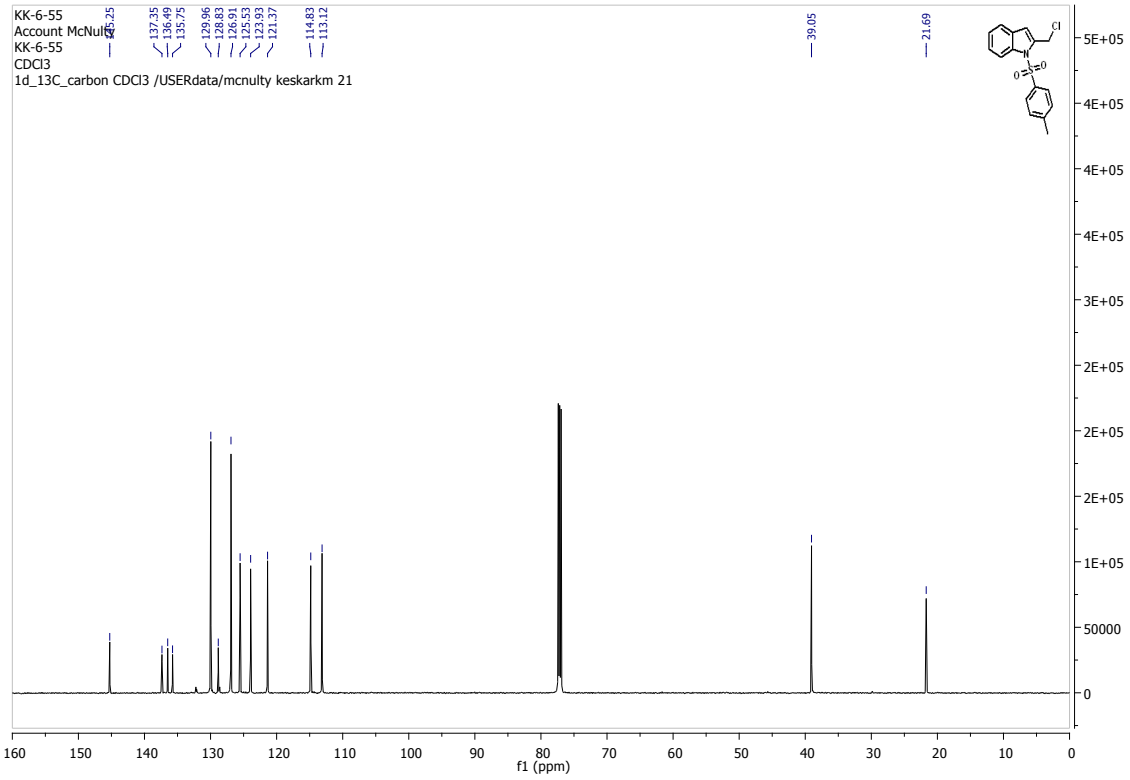




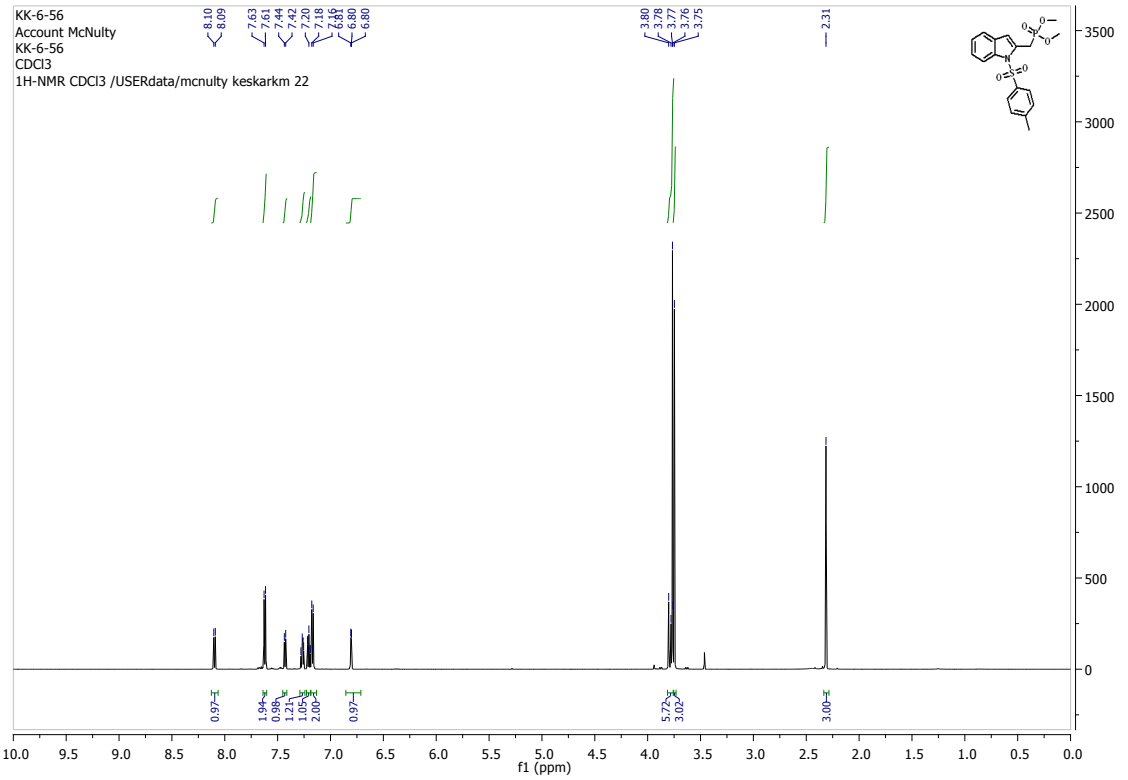
(1-tosyl-1H-indol-2-yl)methanol: (9) See spectra in ref 2

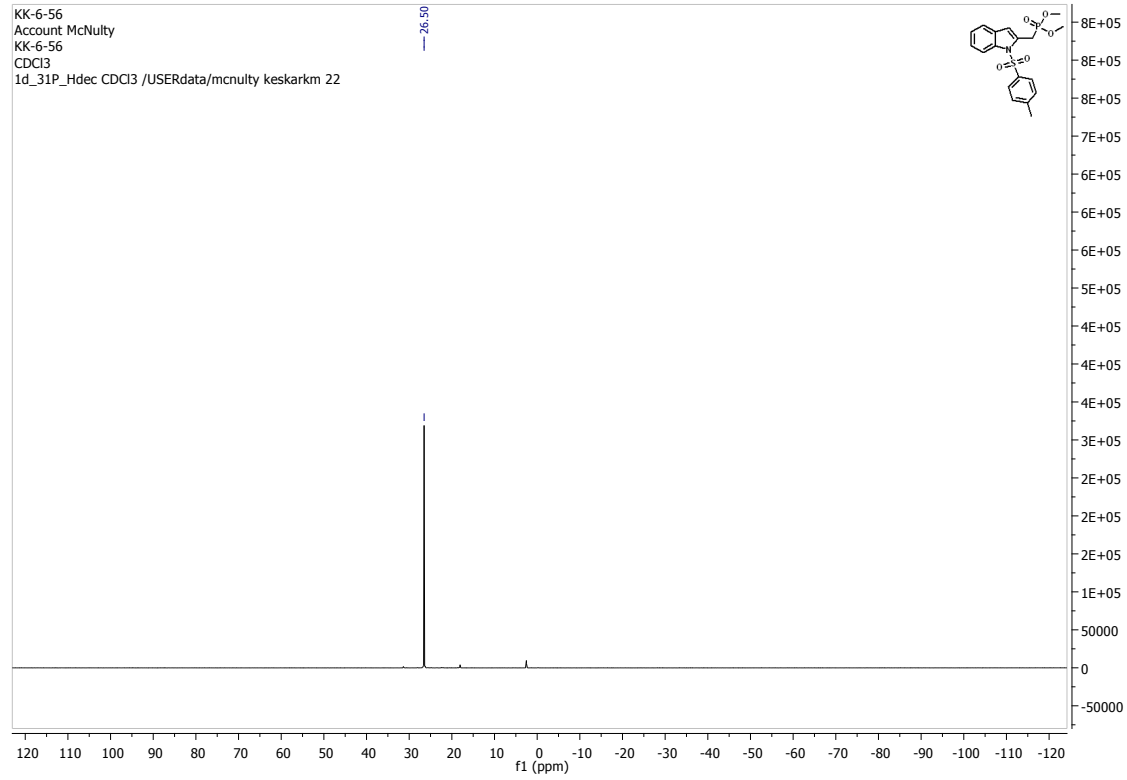
2-(chloromethyl)-1-tosyl-1H-indole: (10)

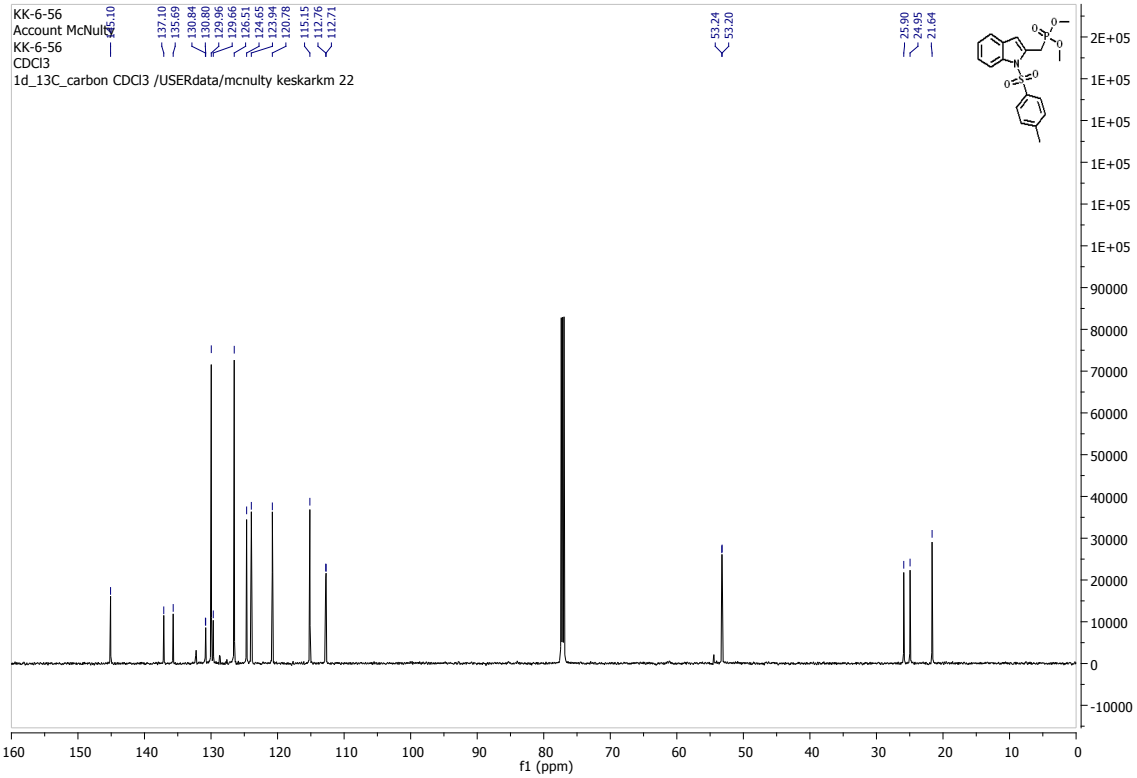




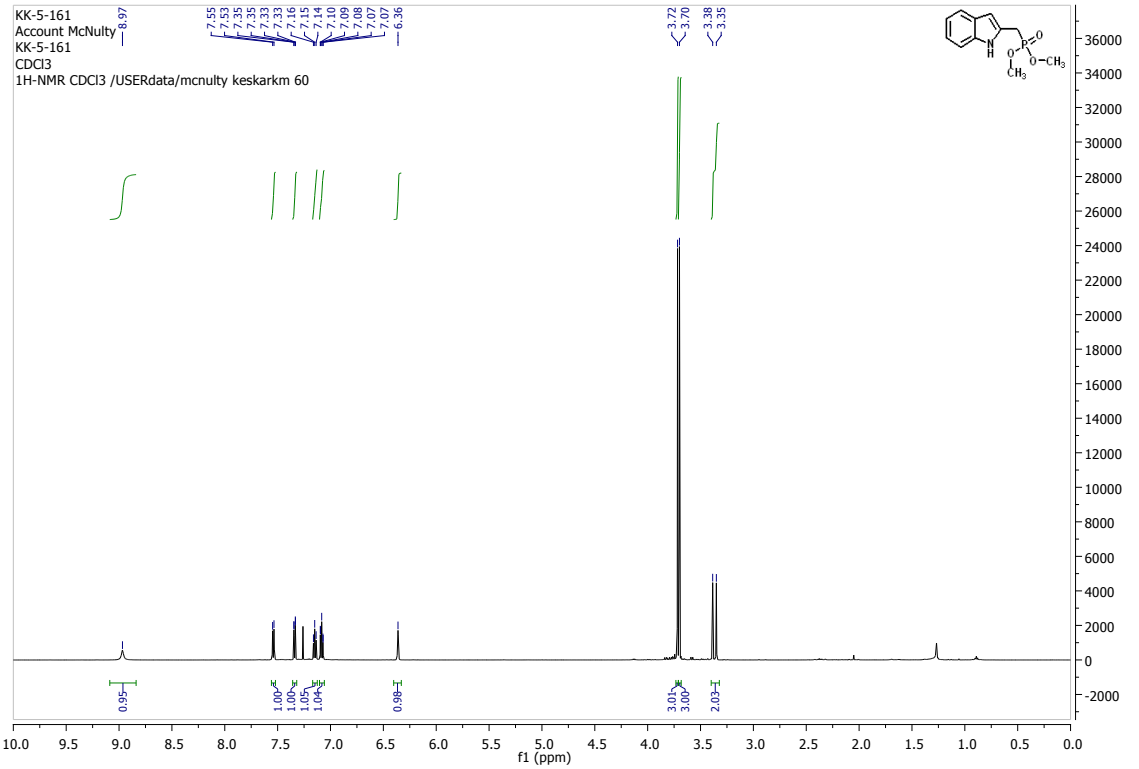
Dimethyl (1-tosyl-1H-indol-2-yl)methylphosphonate: (11)

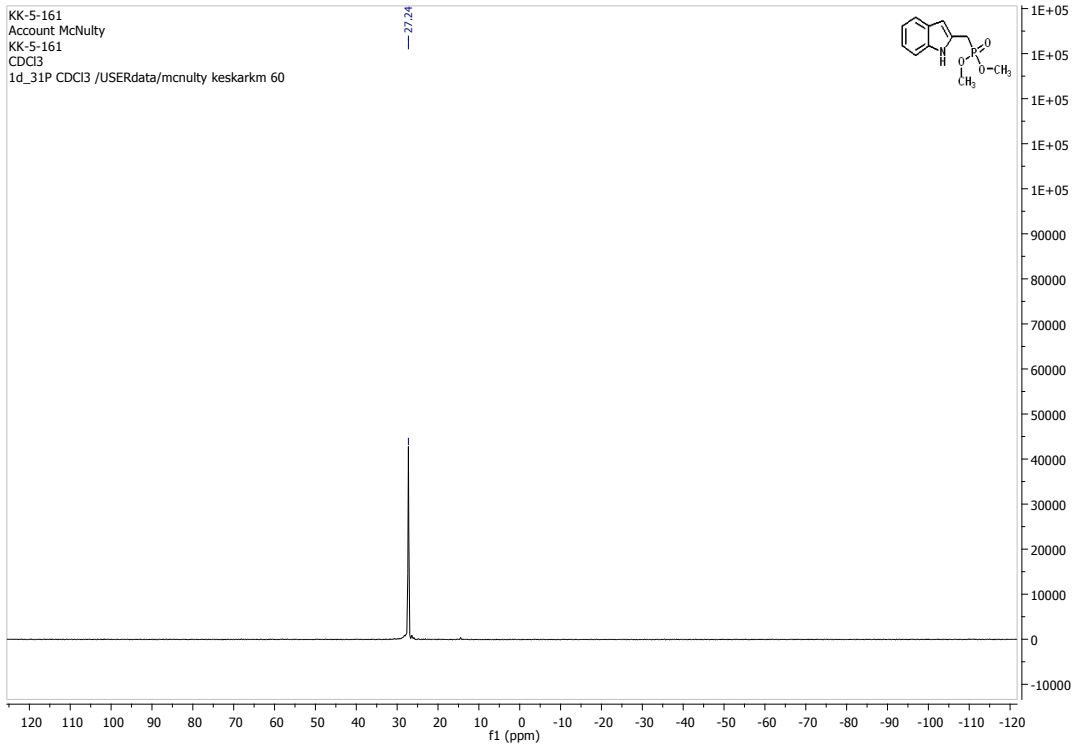






Dimethyl (1H-indol-2-yl)methylphosphonate: (12)

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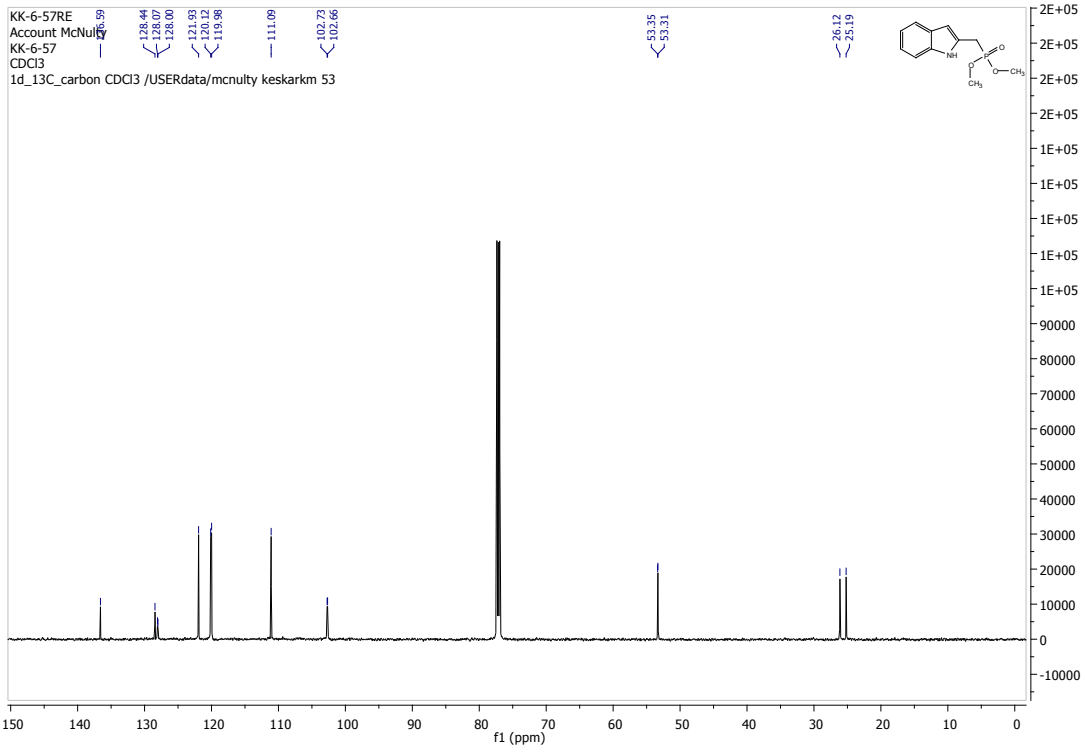
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119.98
111.09
102.73
102.66
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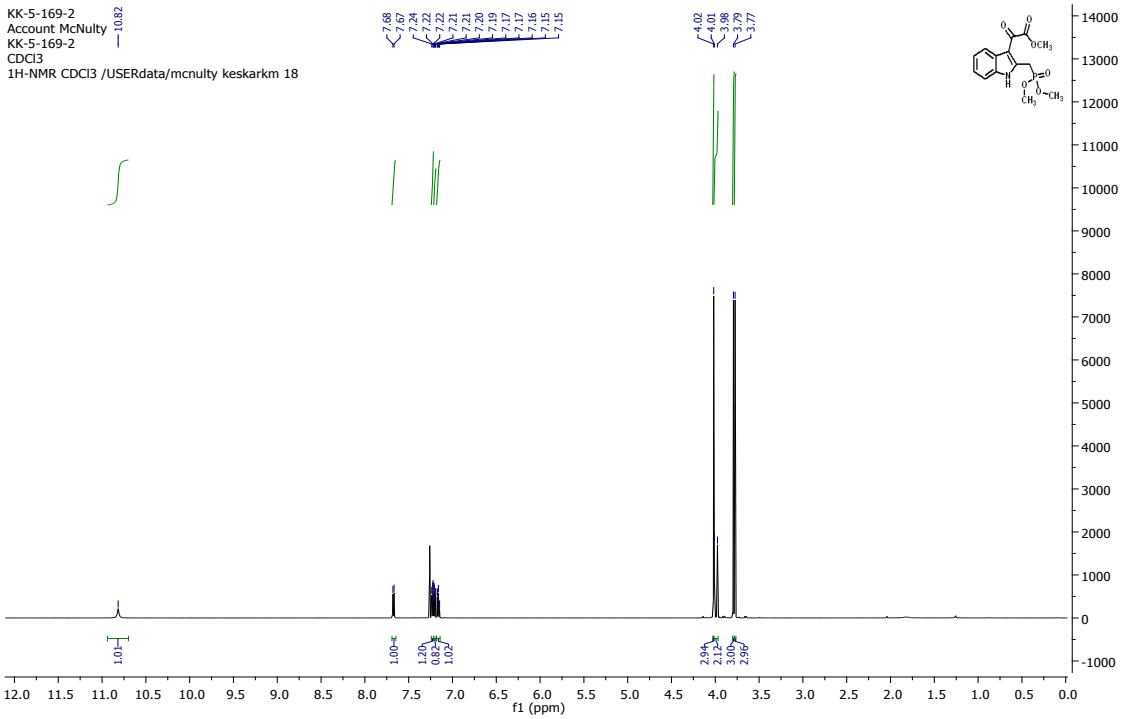
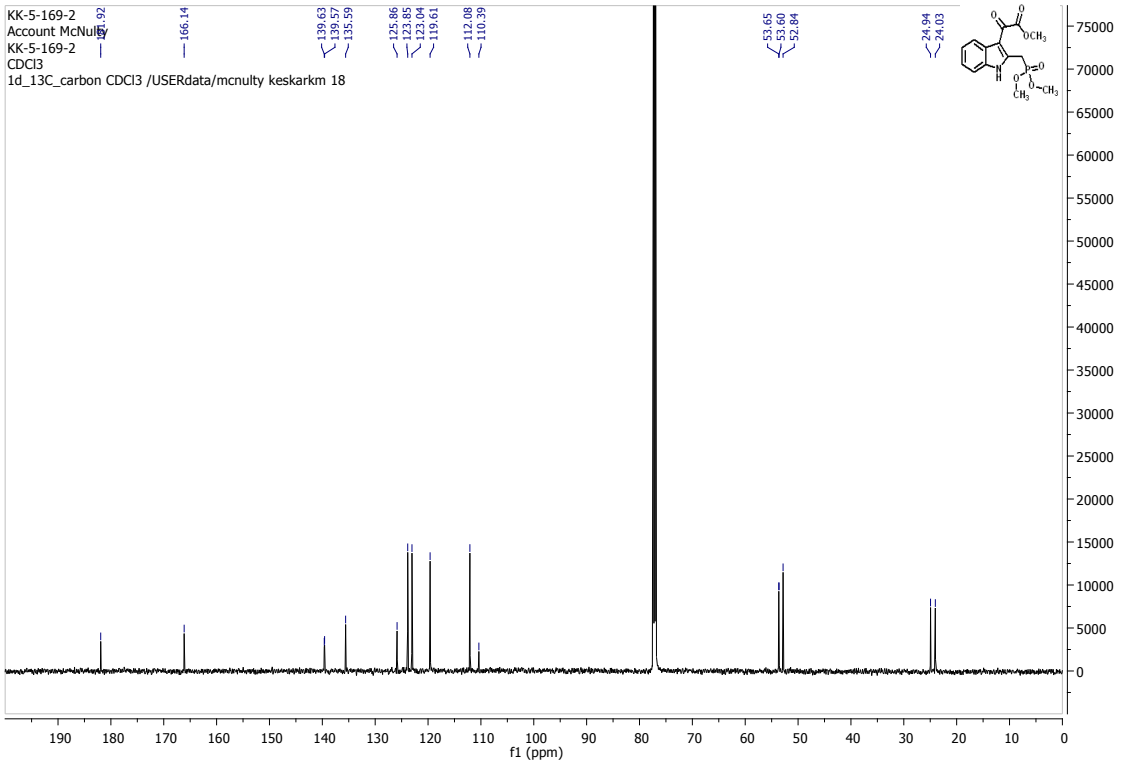
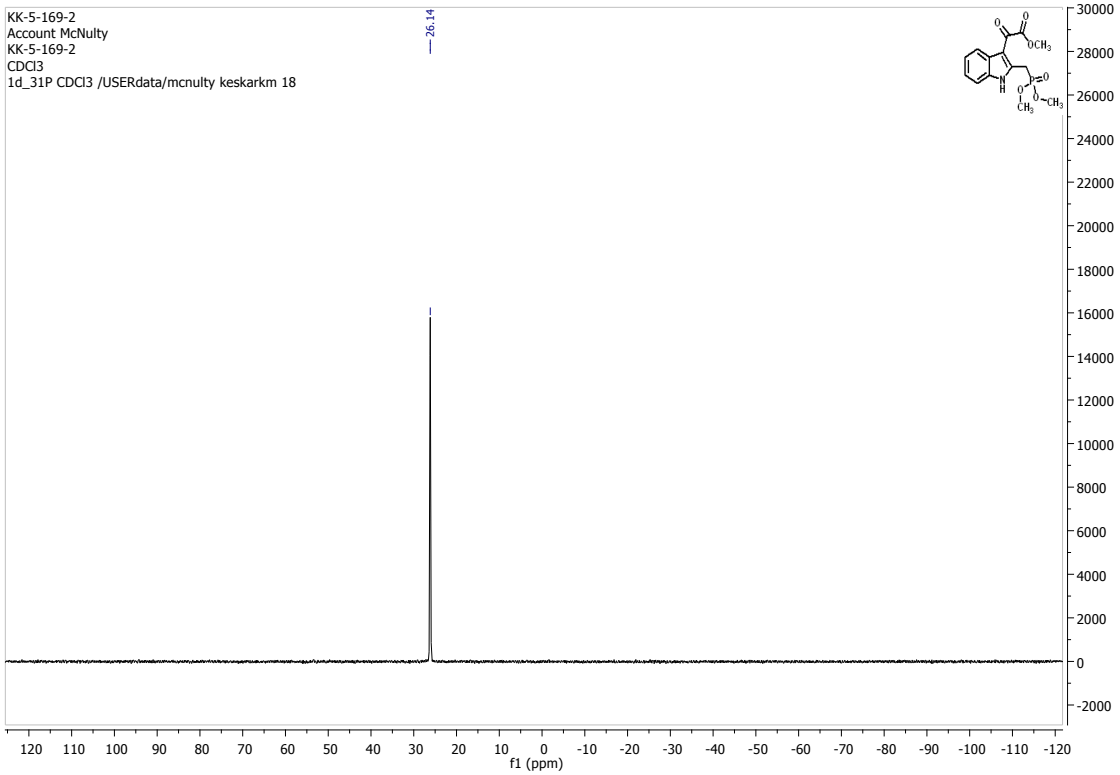
f1 (ppm)

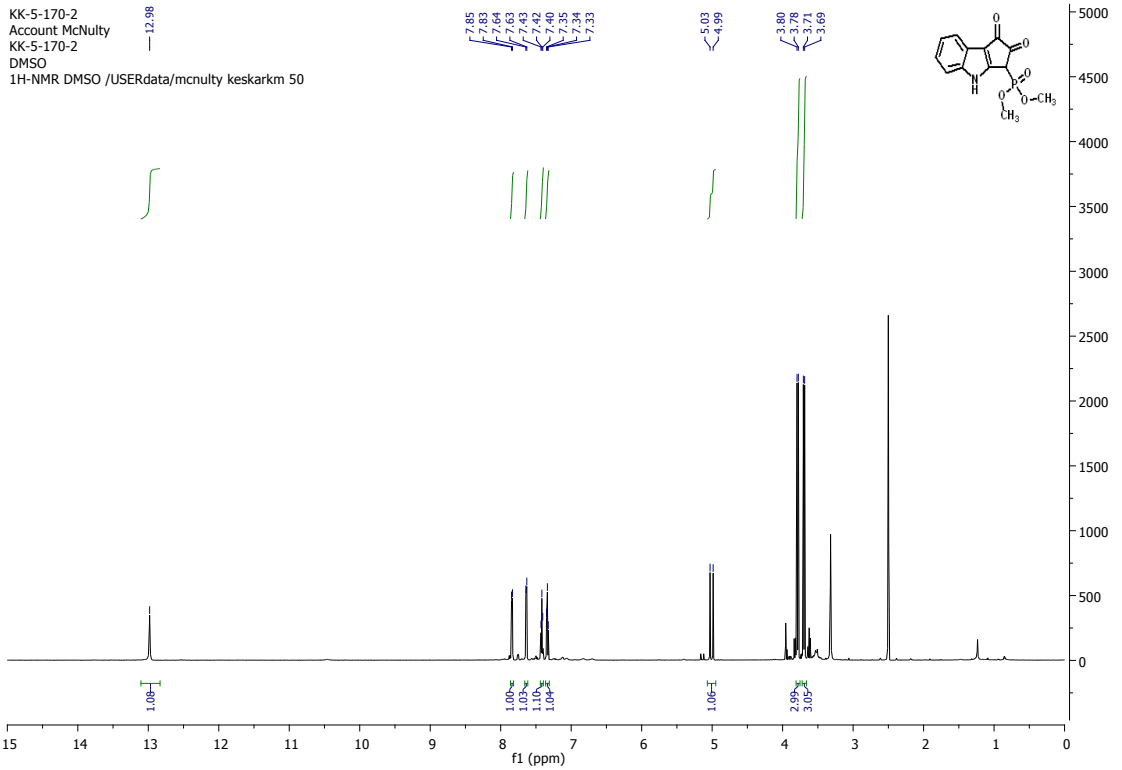
Methyl 2-(2-((dimethoxyphosphoryl)methyl)-1H-indol-3-yl)-2-oxoacetate: (14)

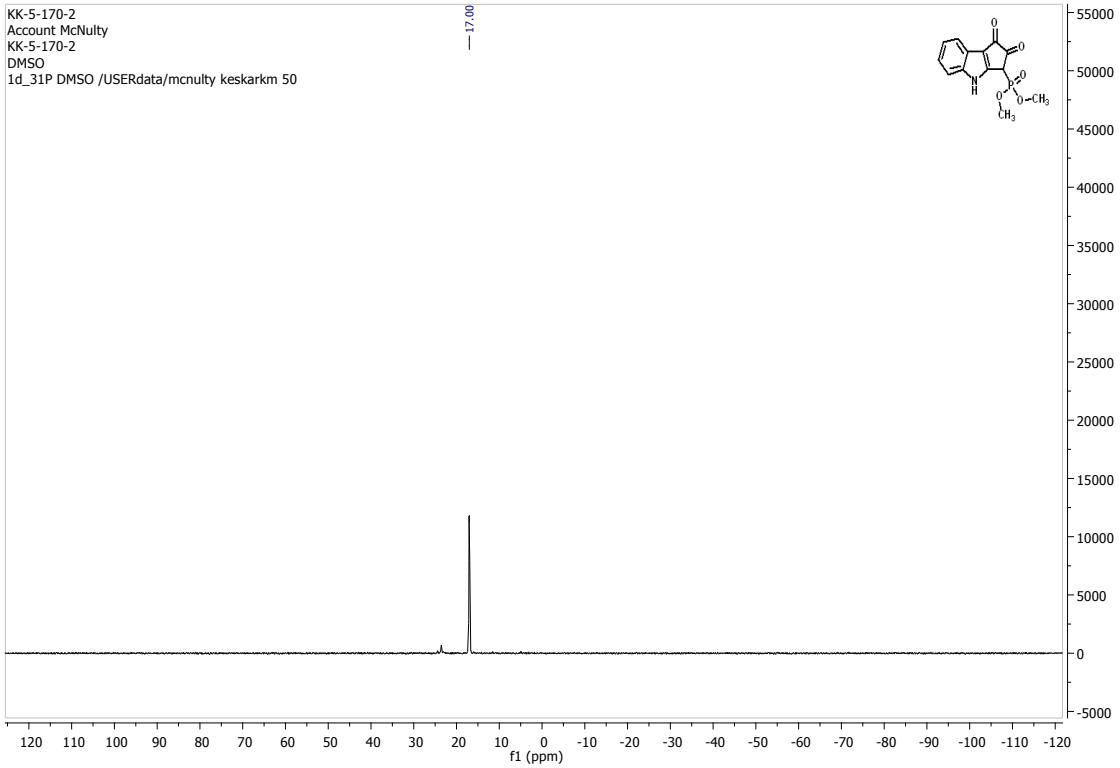






Dimethyl 1,2-dioxo-1,2,3,4-tetrahydrocyclopenta[b]indol-3-ylphosphonate: (15)

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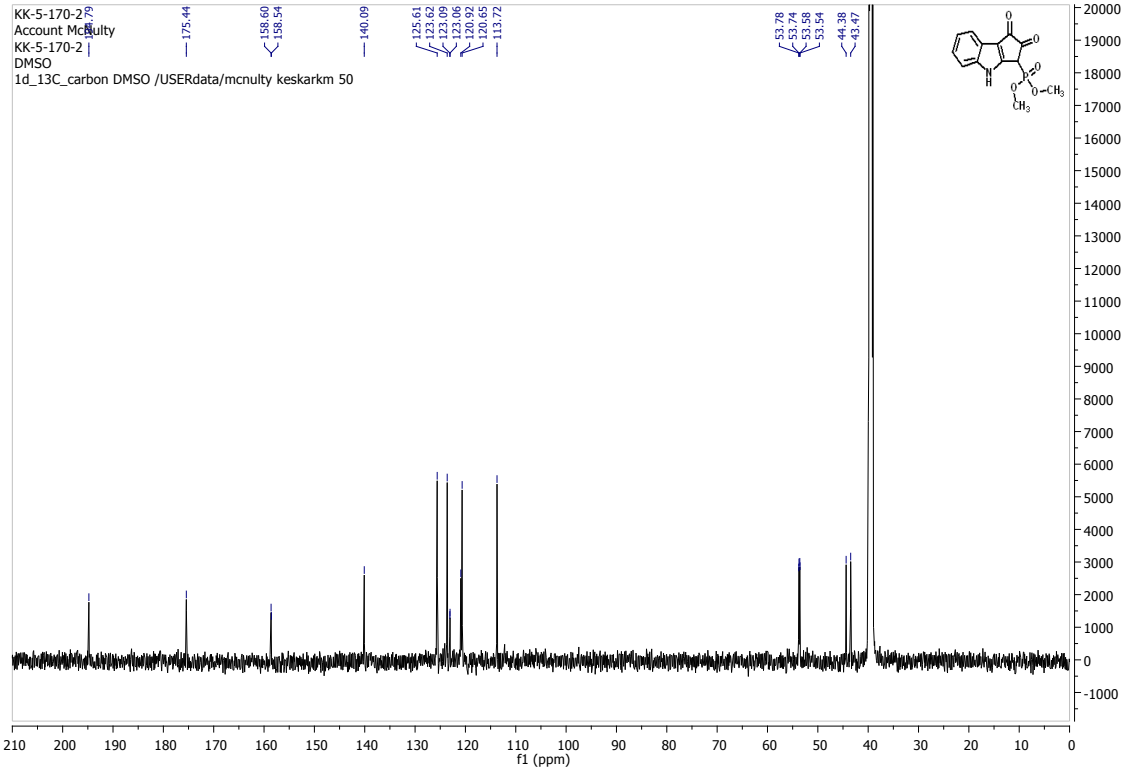
f1 (ppm)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123.09
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53.78
53.74
53.58
53.54
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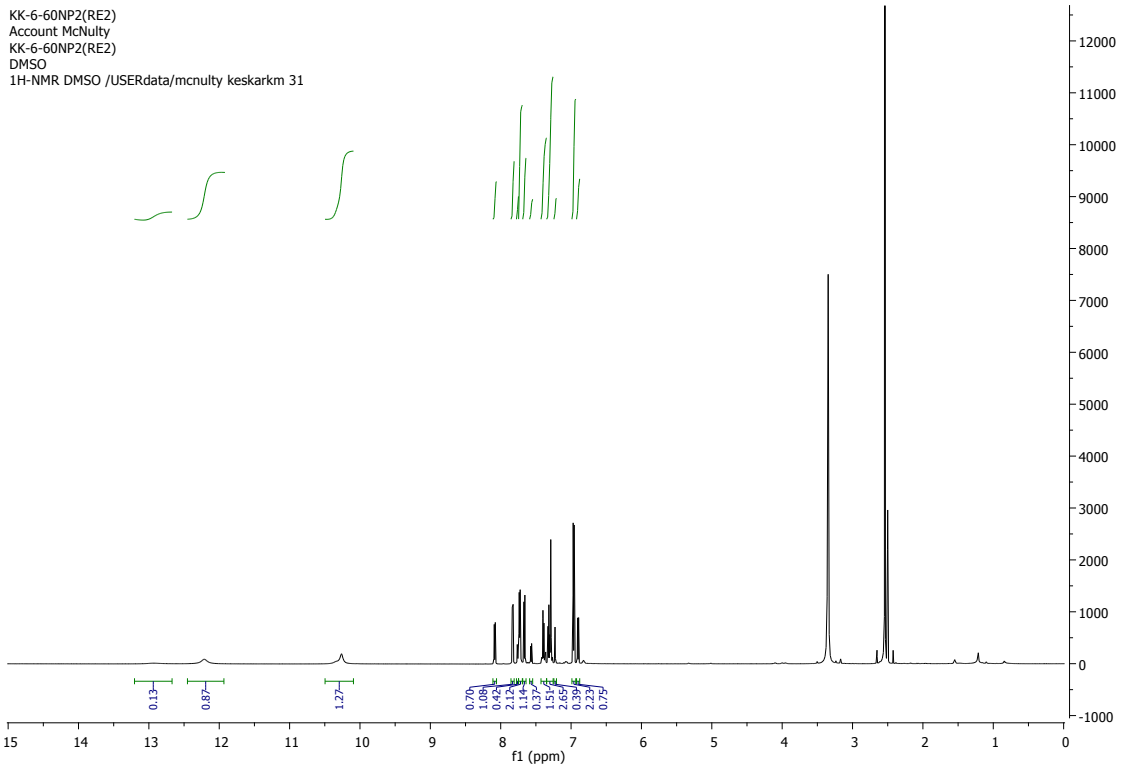
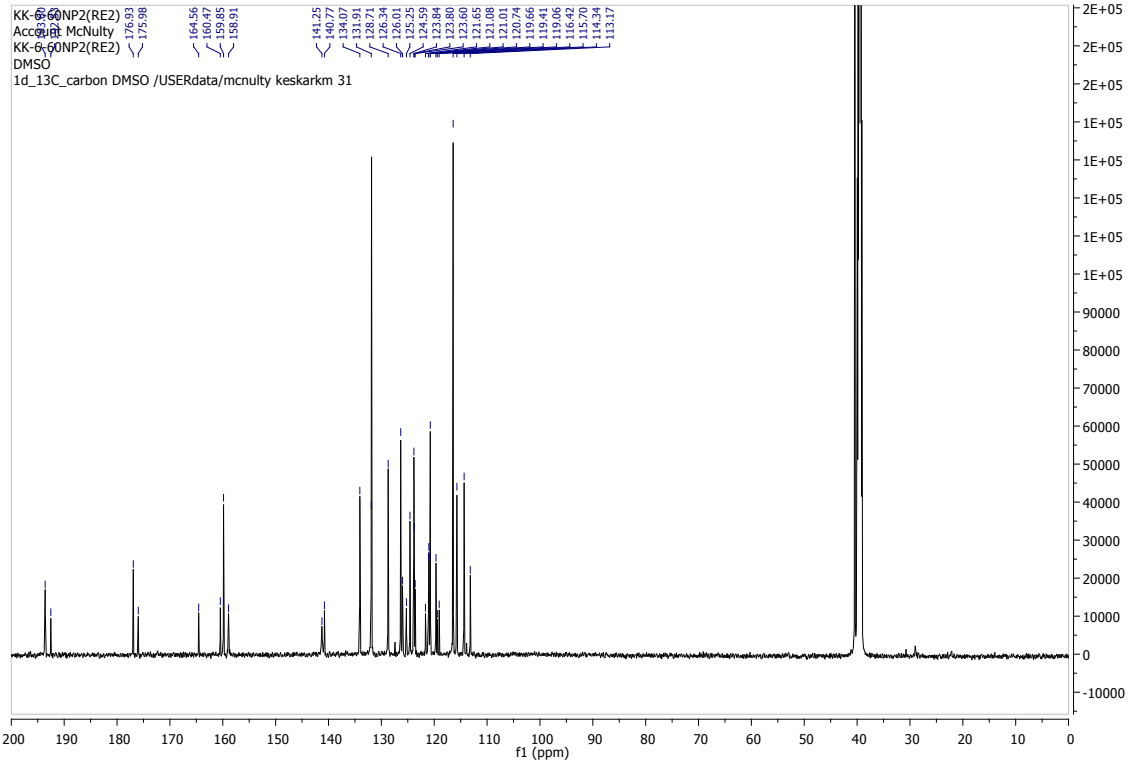
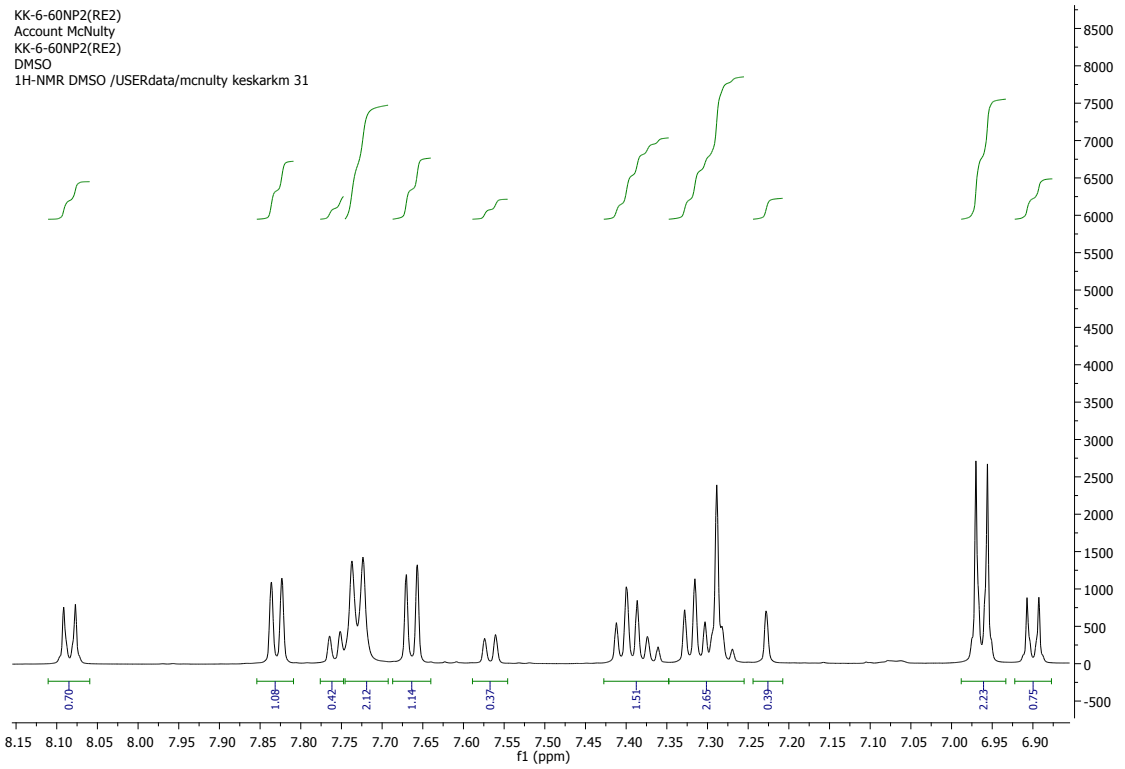
43.47
f1 (ppm)

Nostodione A: (1)

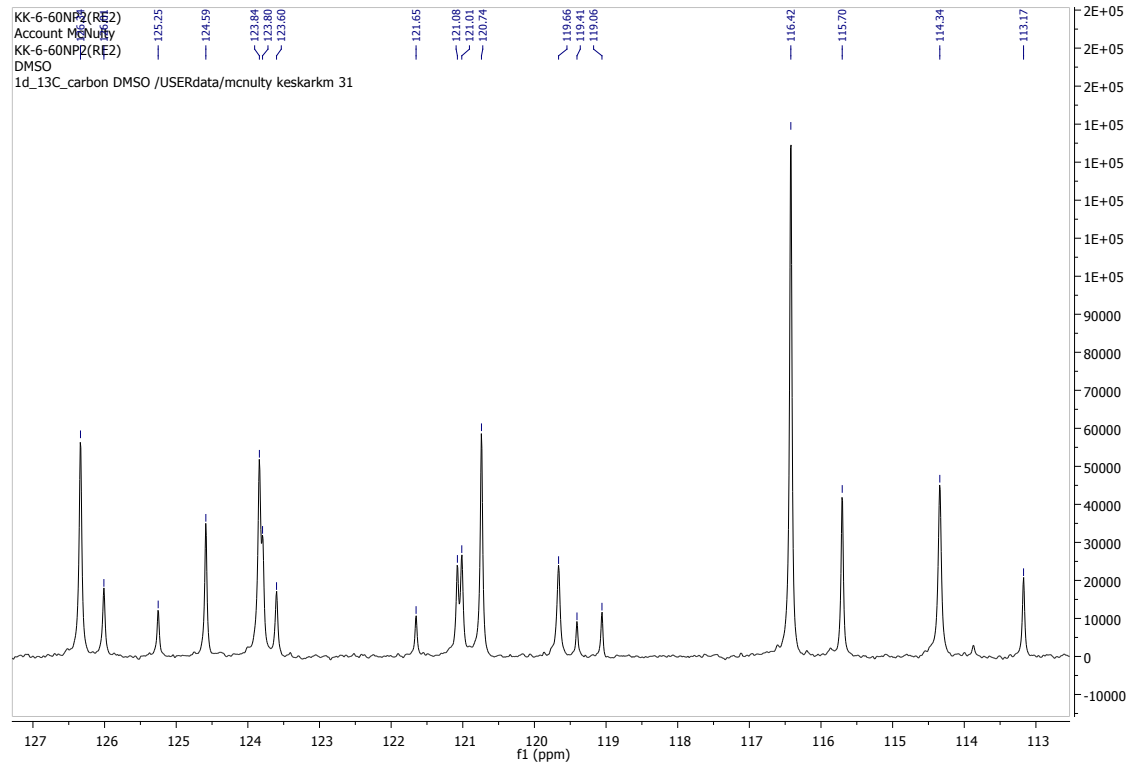




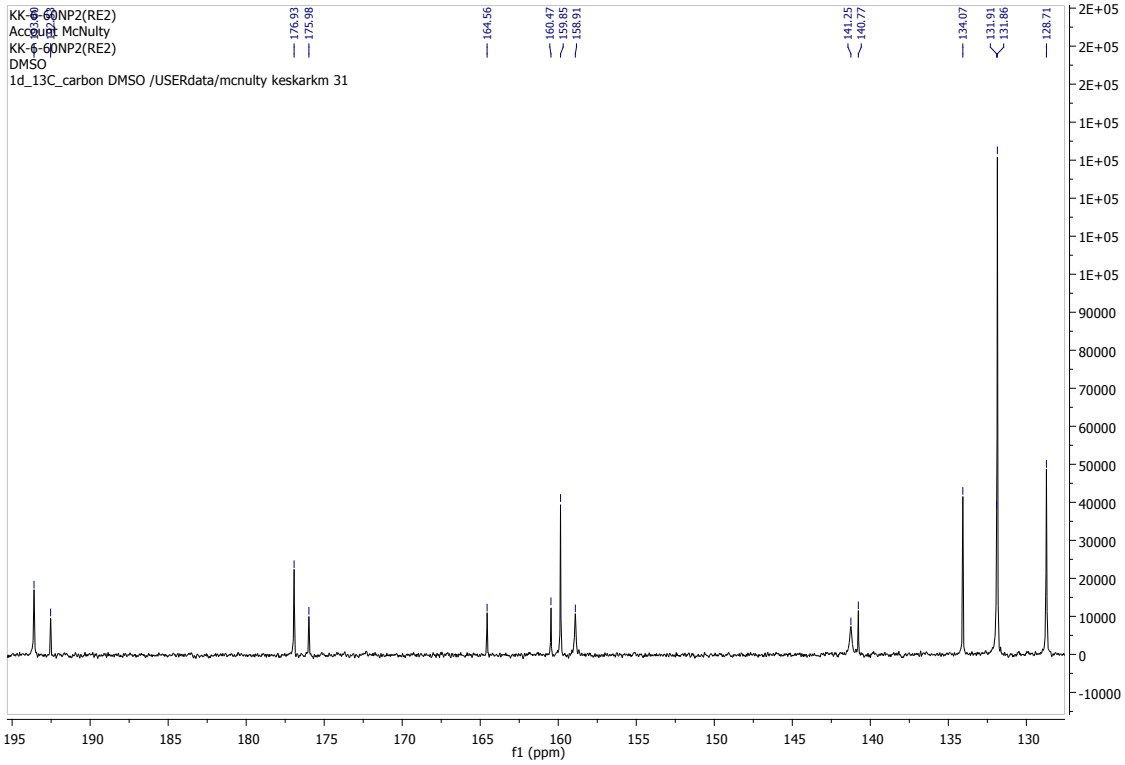
Nostodione A: (1) *(Aromatic Region zoomed - ^{1}H-NMR)*



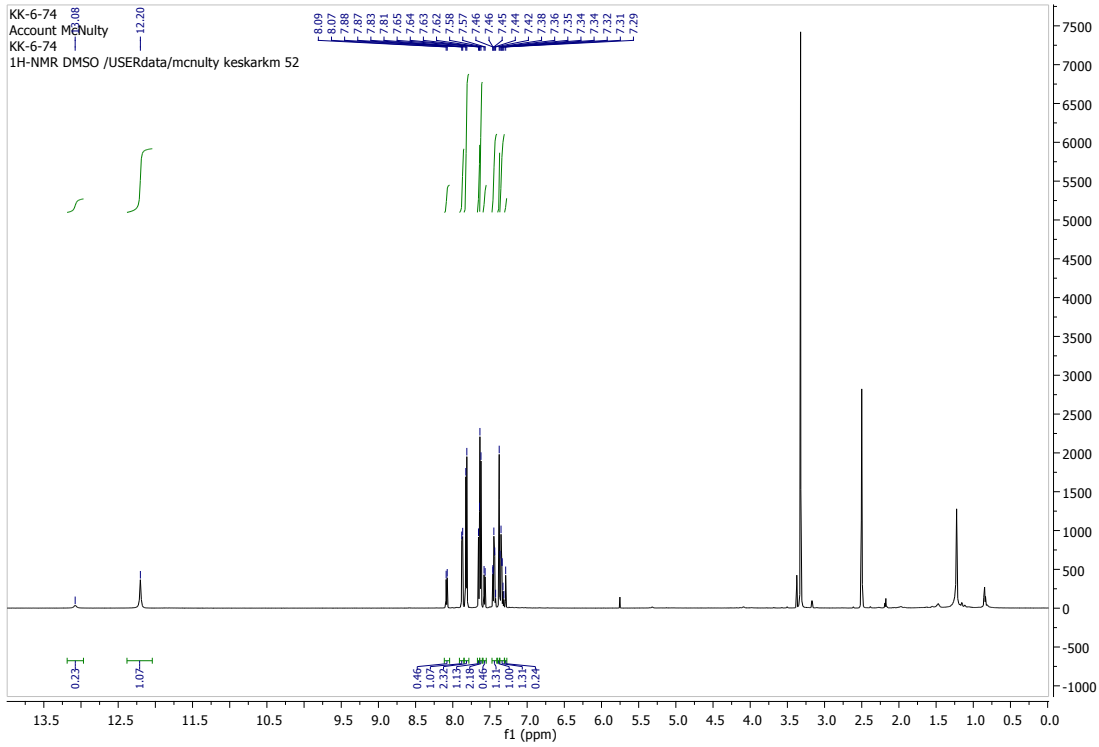
Nostodione A: (1) *(127 ppm-112 ppm zoomed - ^{13}C-NMR)*

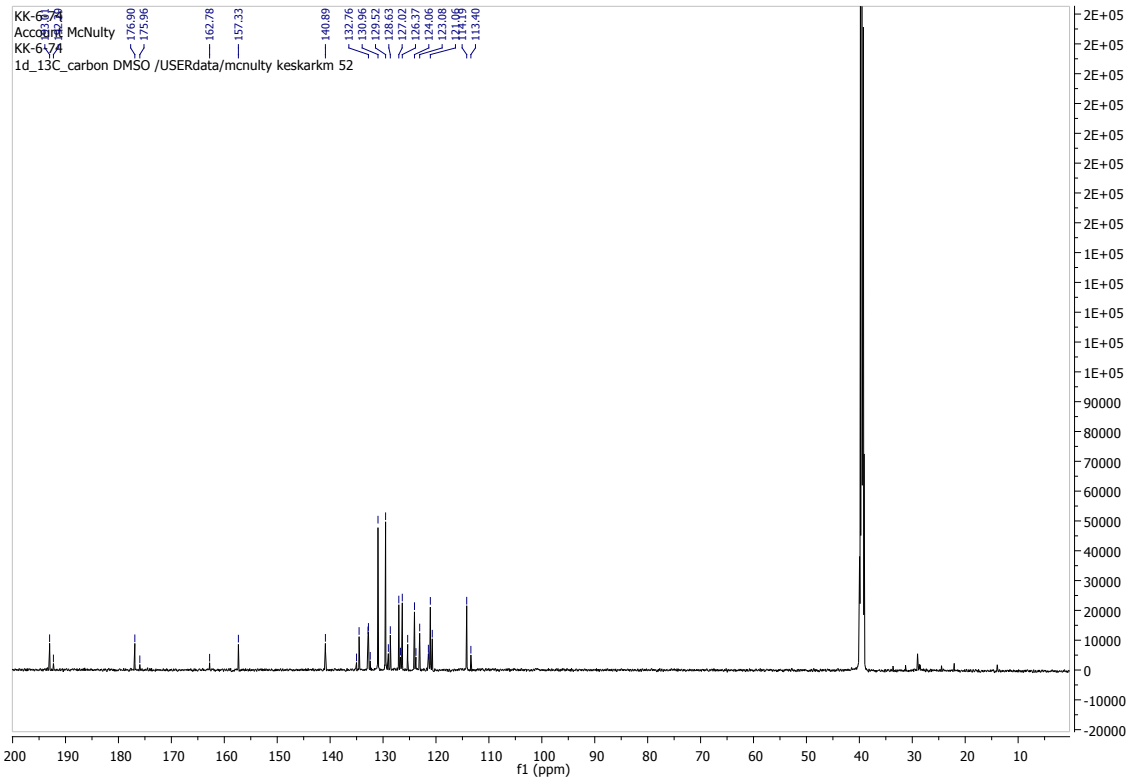


Nostodione A: (1) *(195 ppm-128 ppm zoomed - ^{13}C-NMR)*



3-(4-chlorobenzylidene)cyclopenta[b]indole-1,2(3H,4H)-dione: (17)

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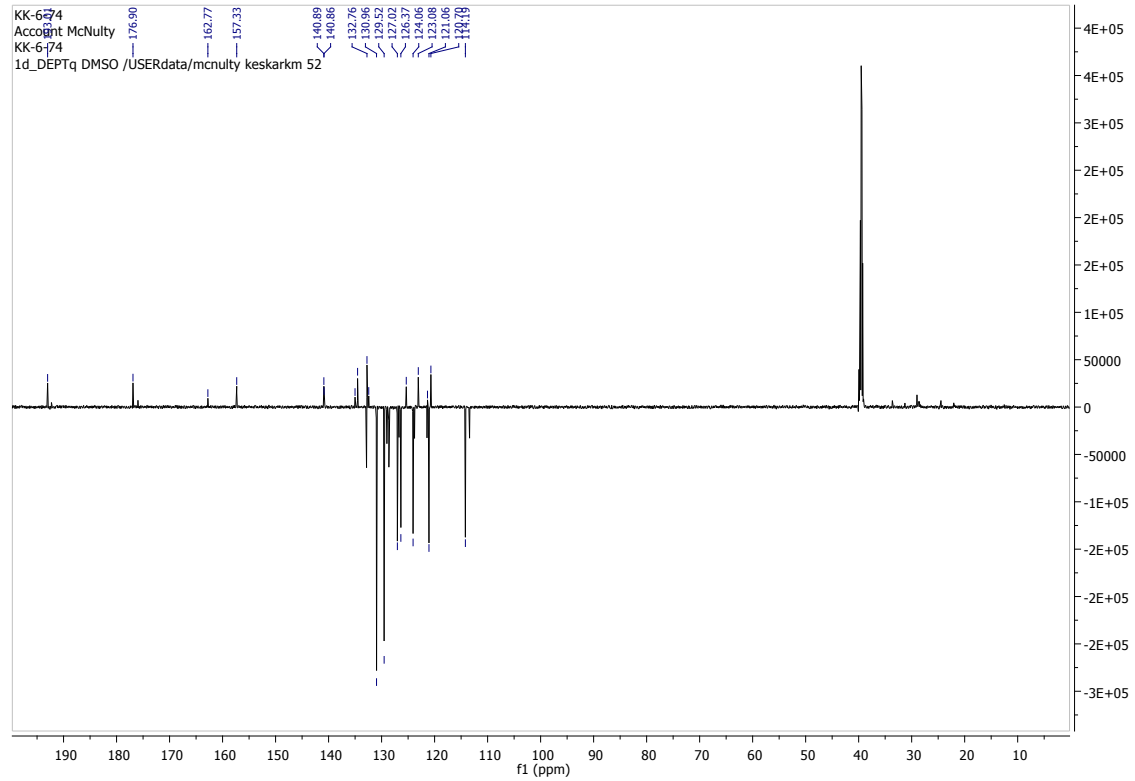
123.08
113.40
f1 (ppm)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157.33
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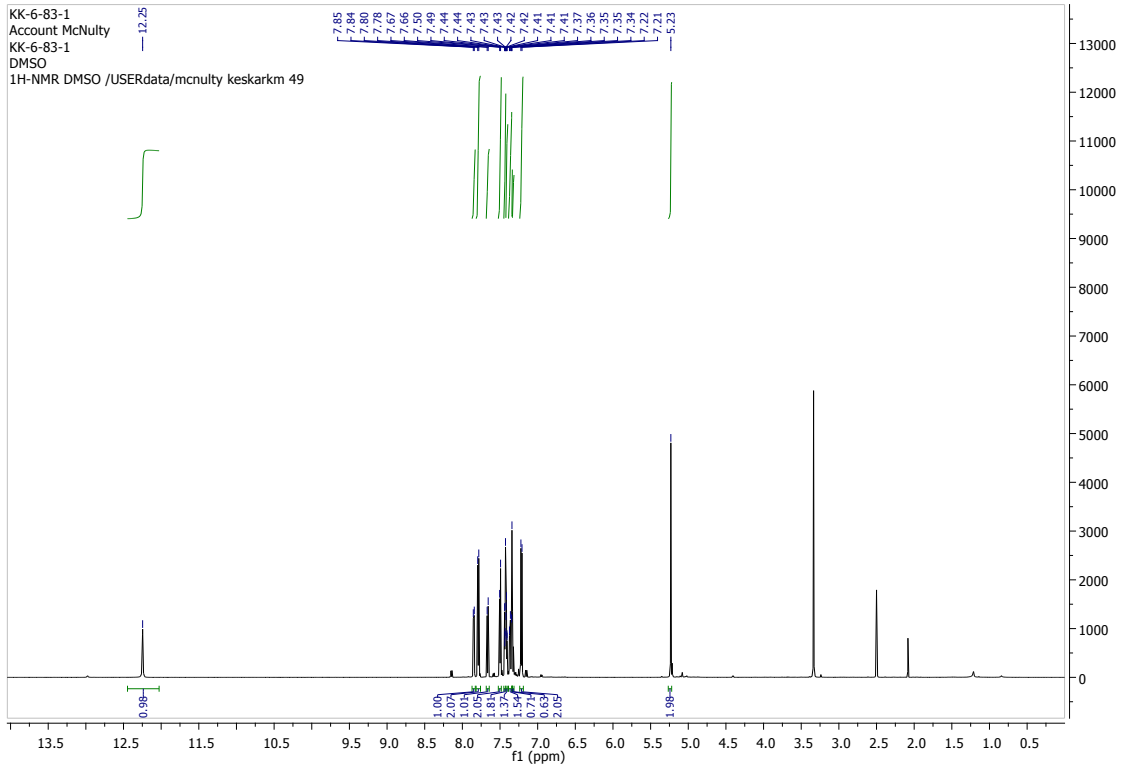
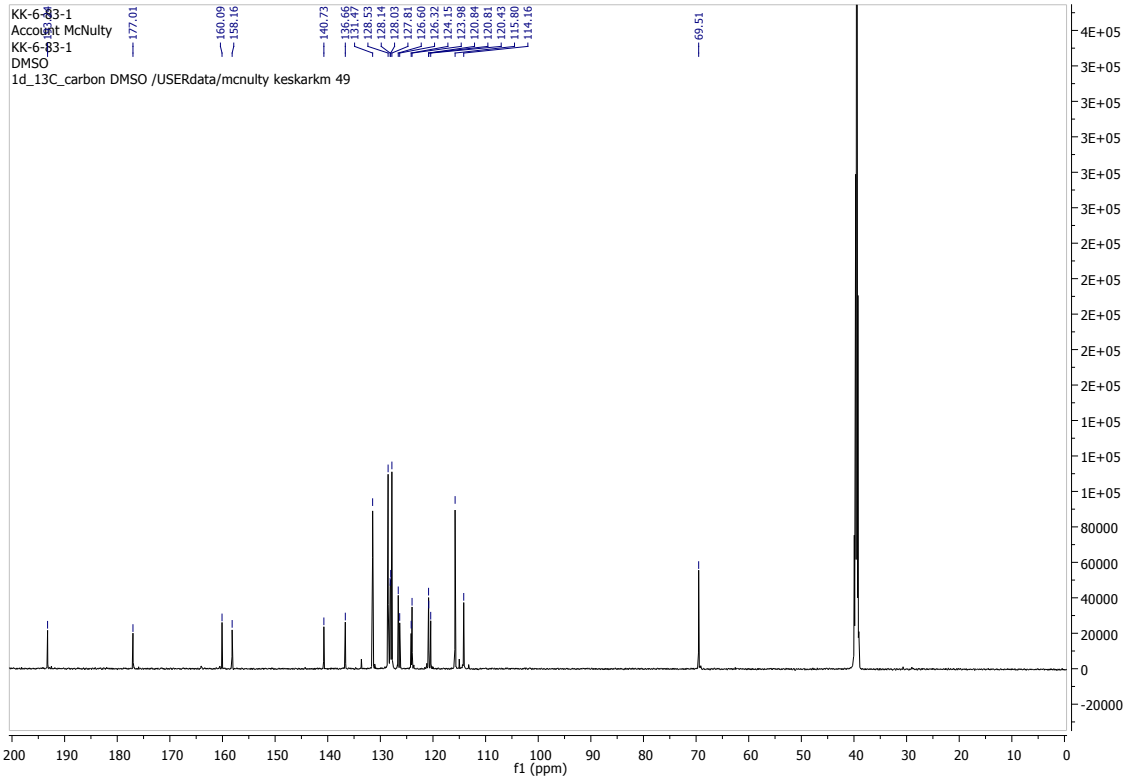
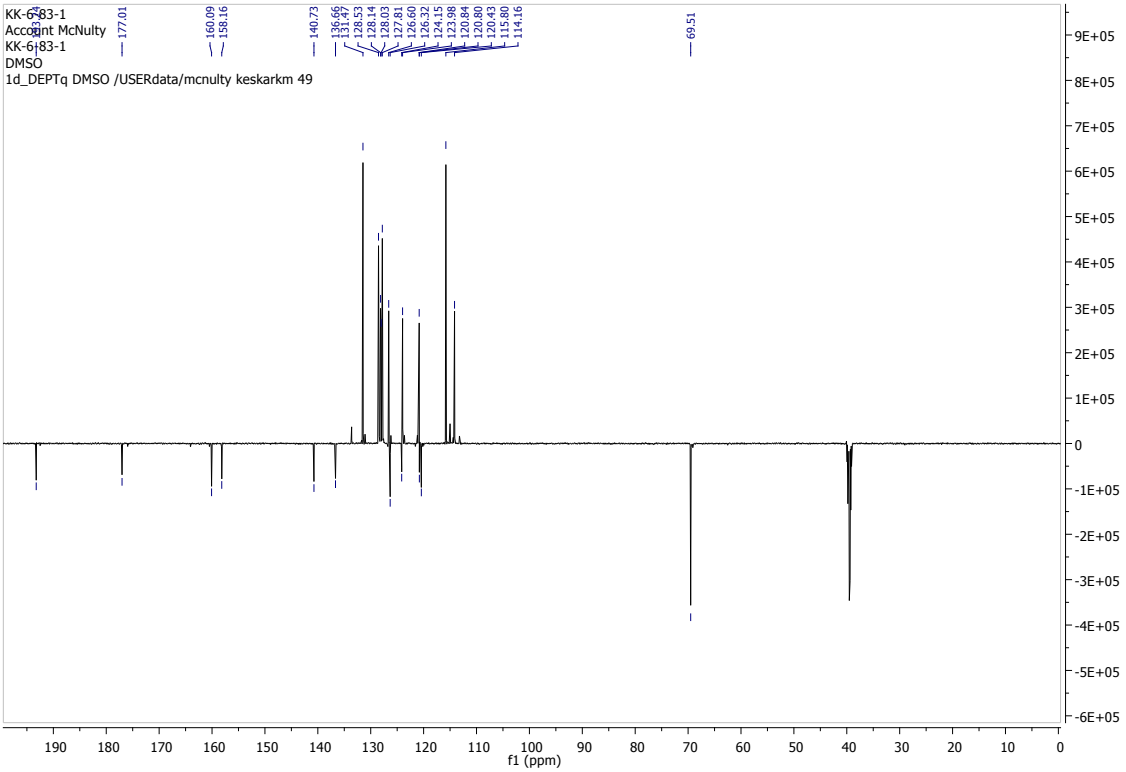
132.76
130.96
129.52
127.02
126.37
124.06
123.08
121.06
f1 (ppm)

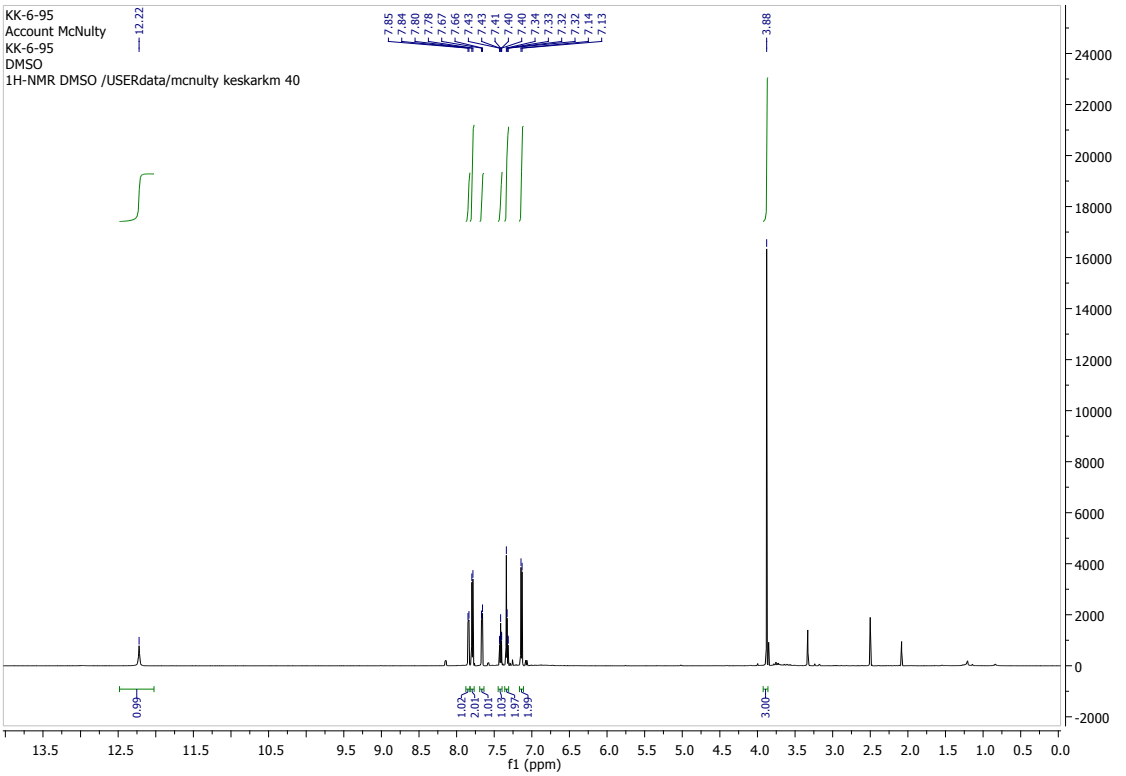
3-(4-(benzyloxy)benzylidene)cyclopenta[b]indole-1,2(3H,4H)-dione: (18)

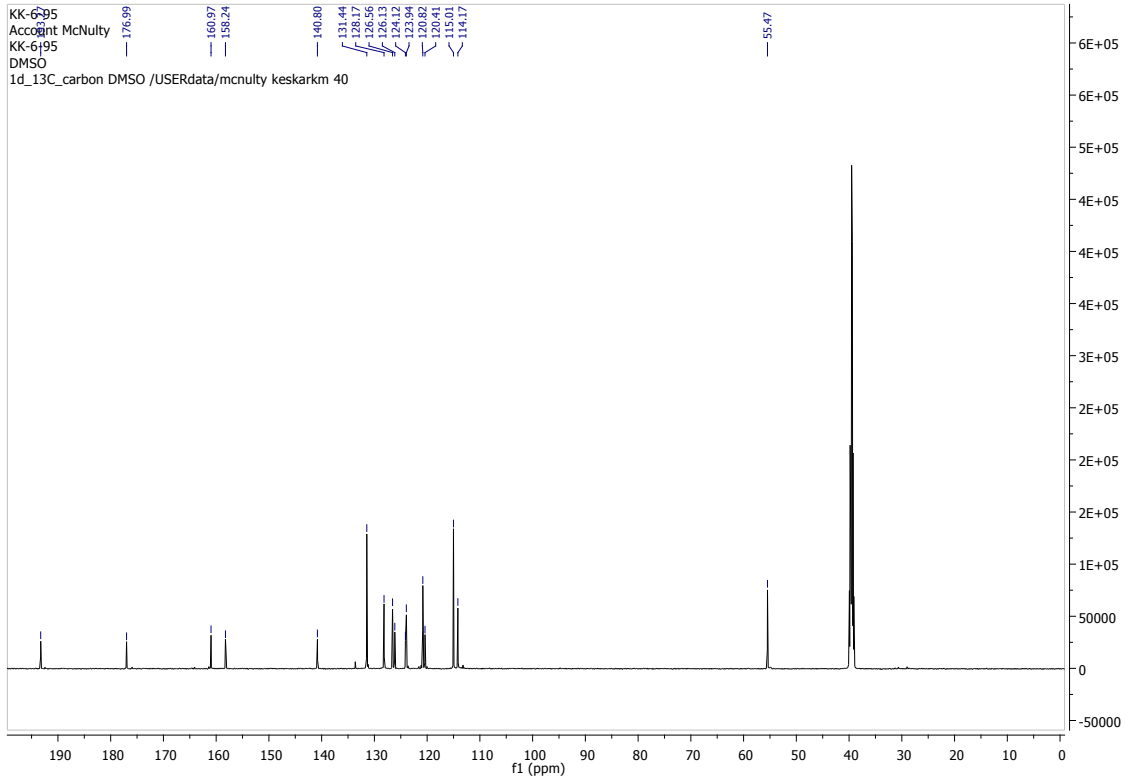






3-(4-methoxybenzylidene)cyclopenta[b]indole-1,2(3H,4H)-dione: (19)

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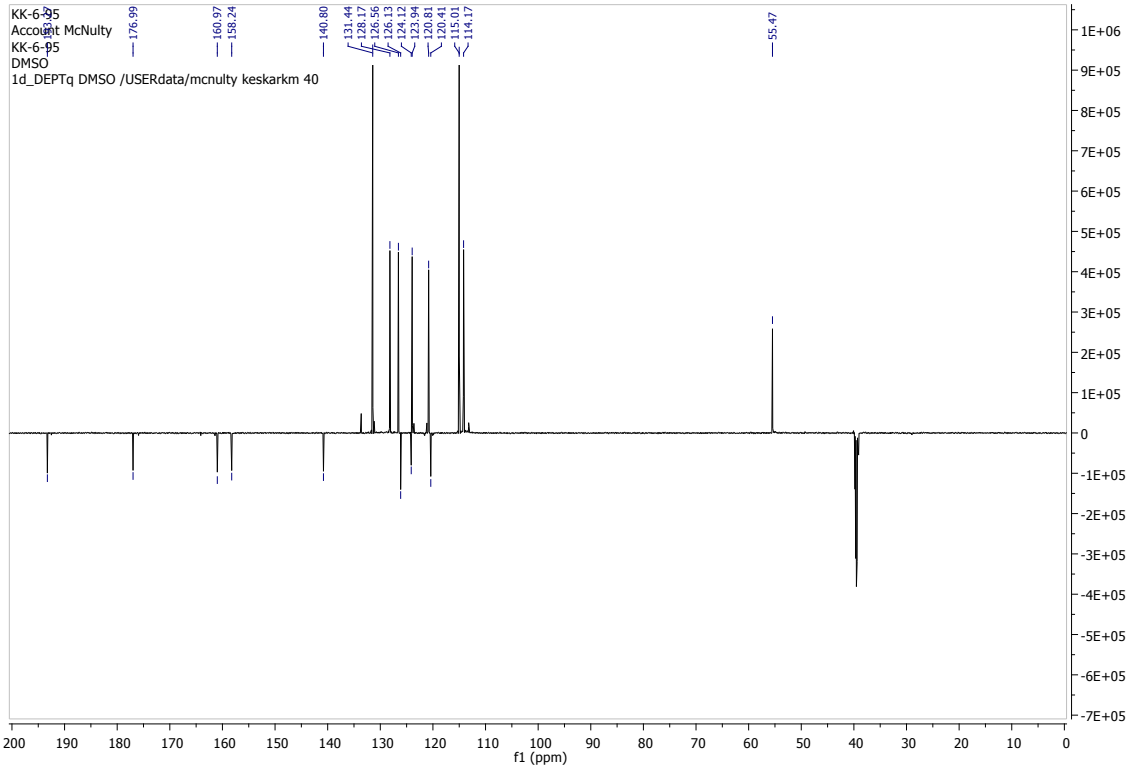
55.47
f1 (ppm)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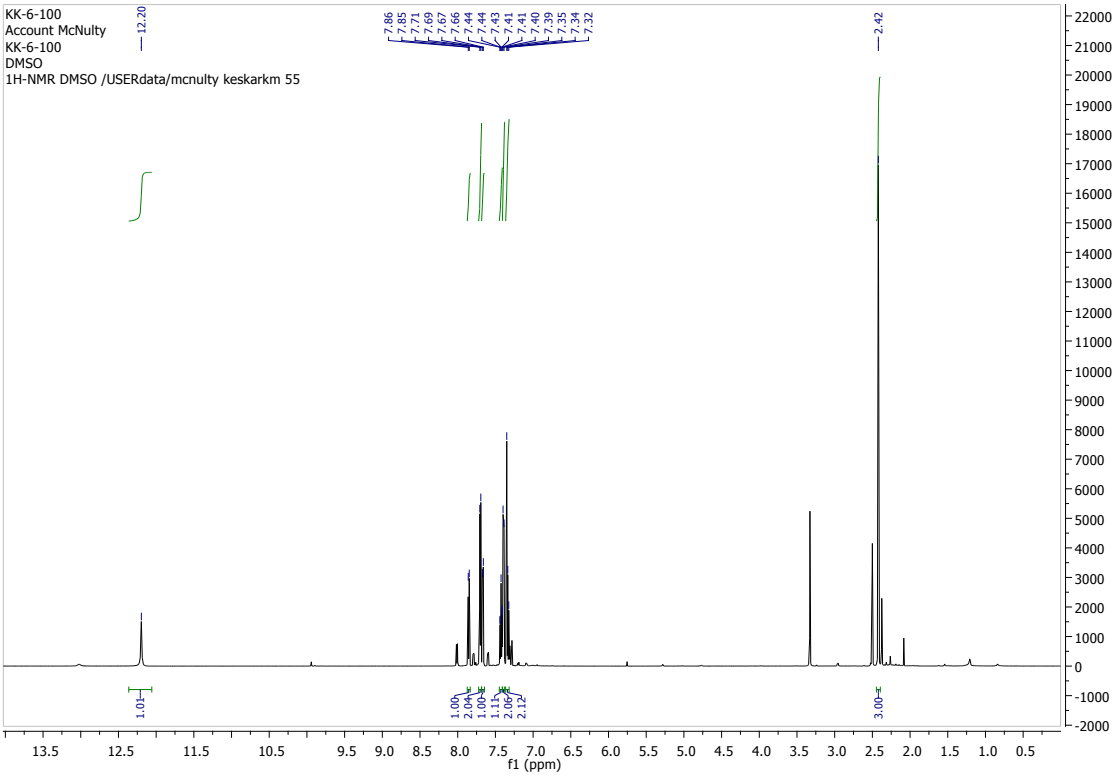
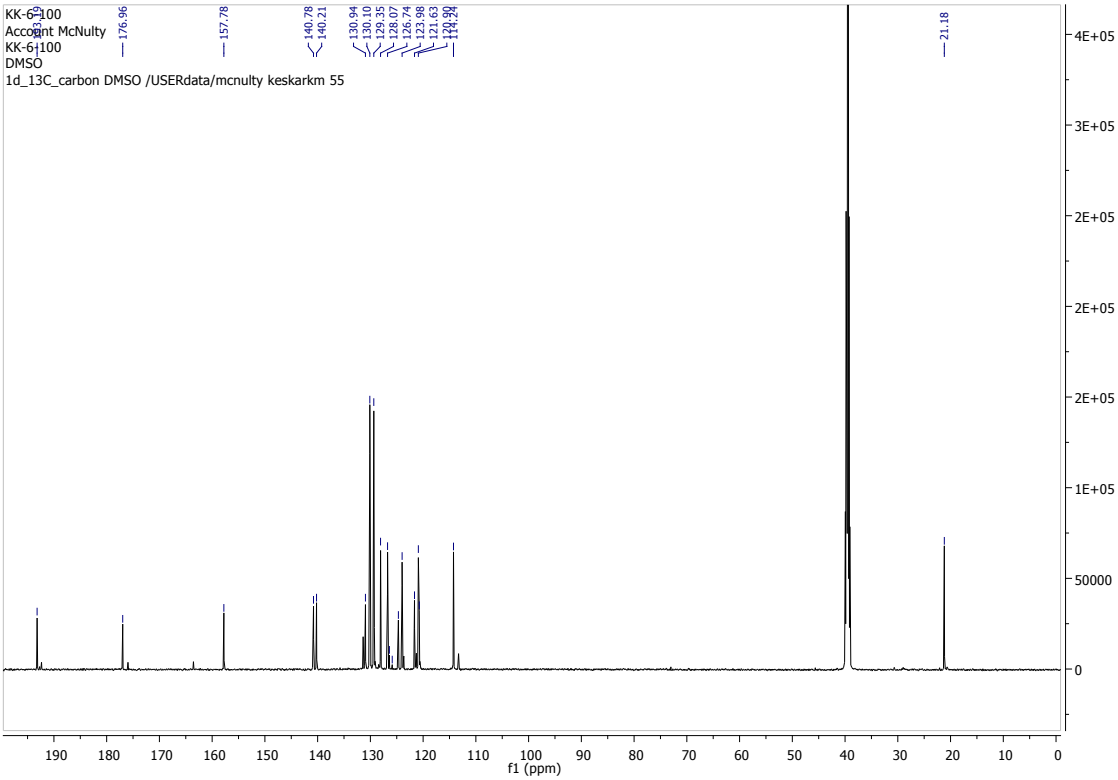
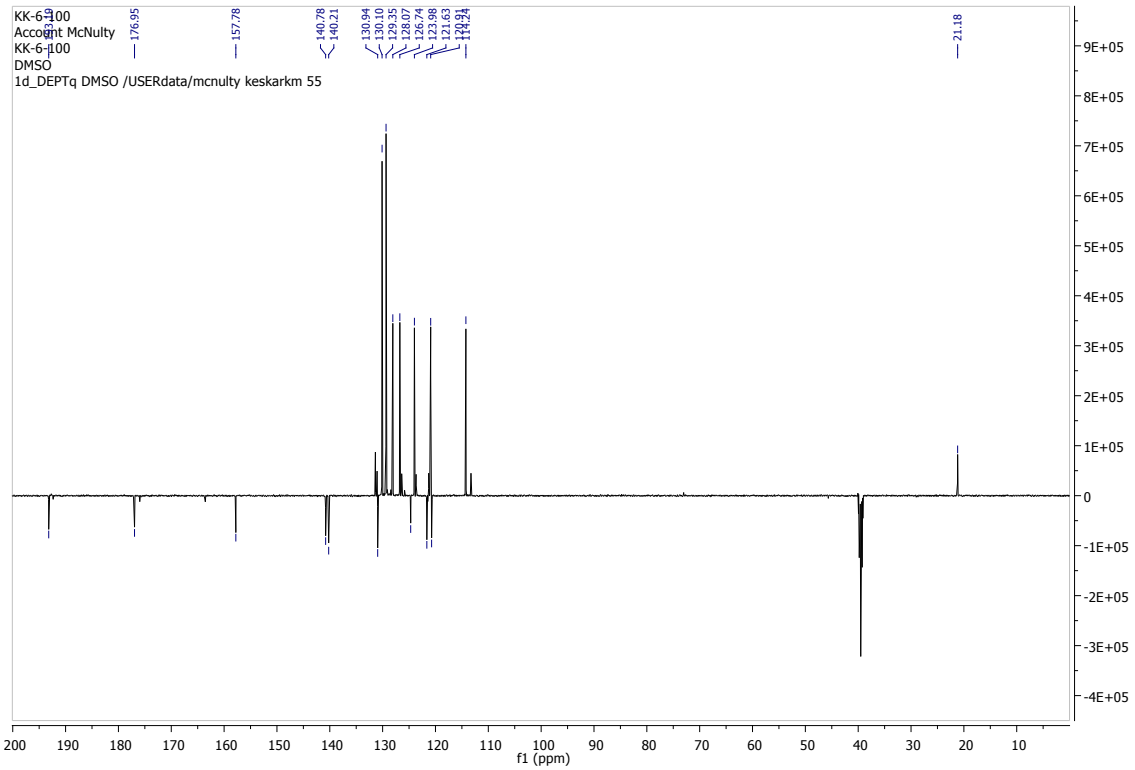
131.44
128.17
126.56
126.13
124.12
123.94
120.81
120.41
115.01
114.17
55.47
f1 (ppm)

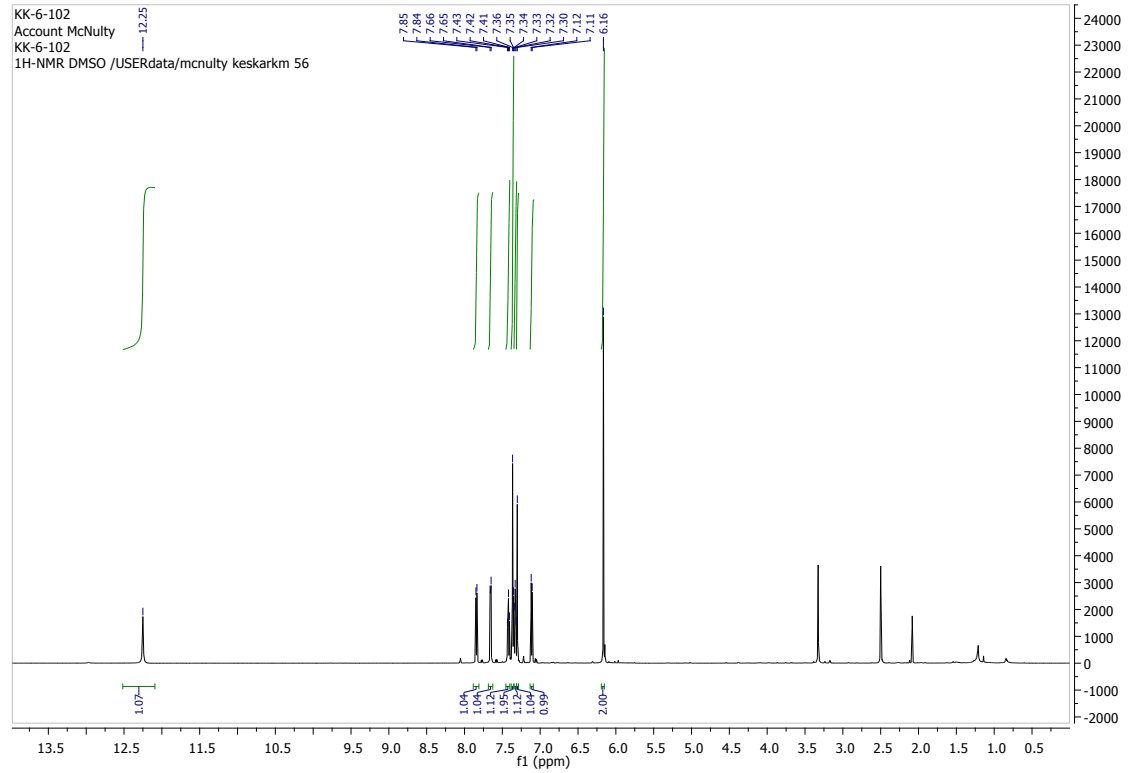
3-(4-methylbenzylidene)cyclopenta[b]indole-1,2(3H,4H)-dione: (20)

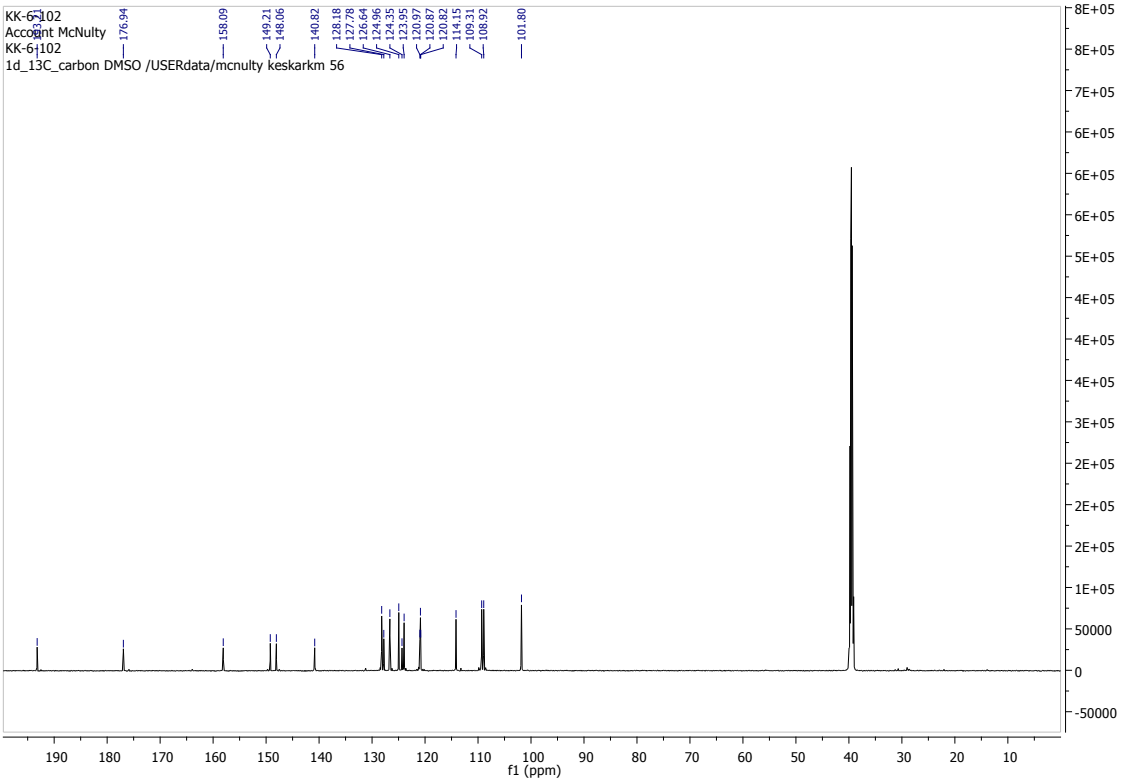


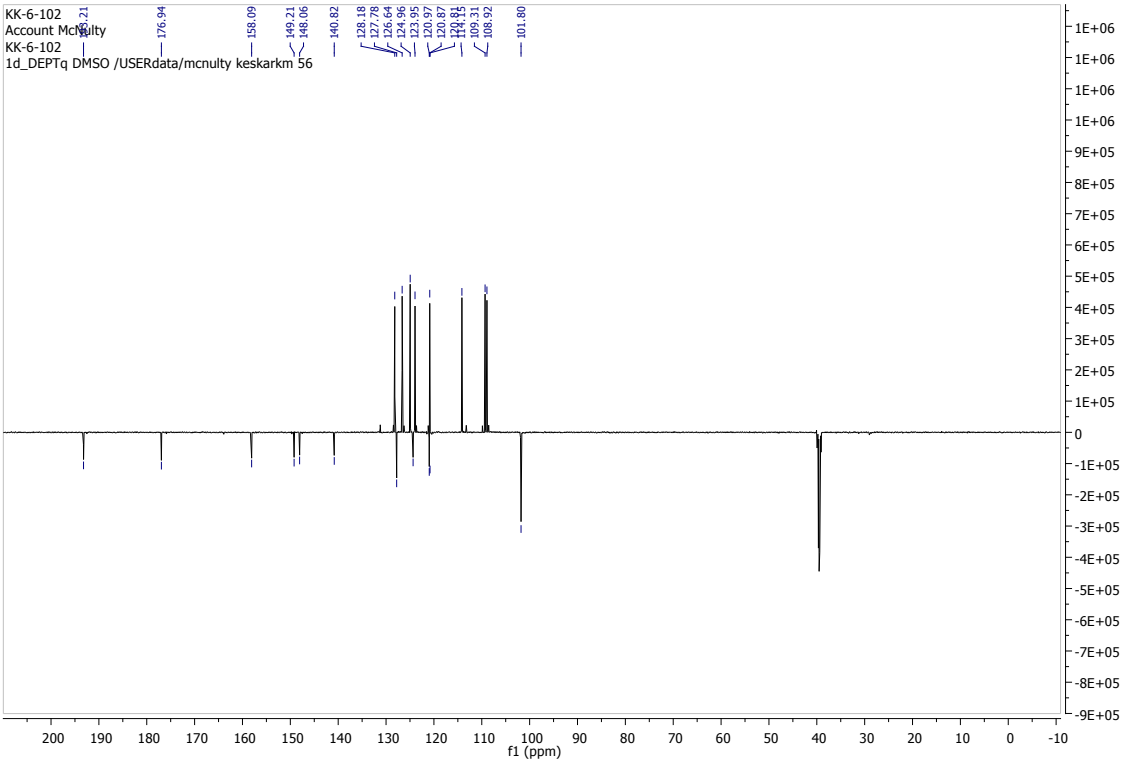




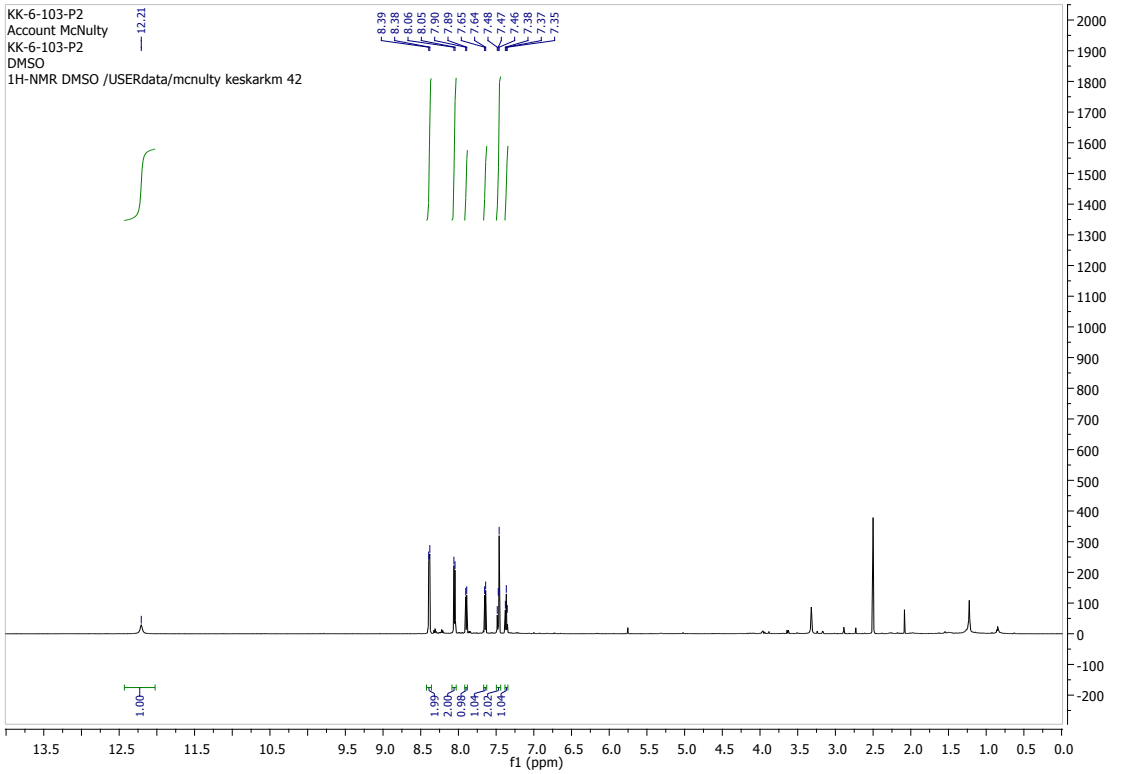
3-(benzo[d][1,3]dioxol-5-ylmethylene)cyclopenta[b]indole-1,2(3H,4H)-dione: (21)

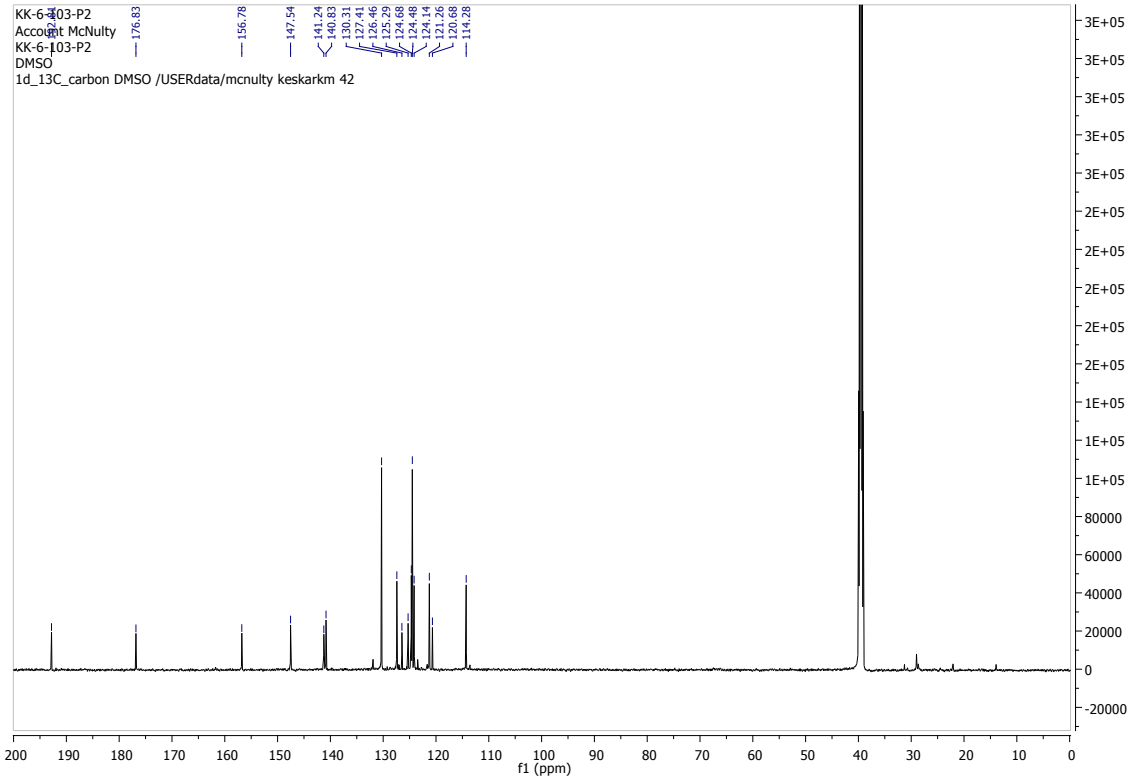


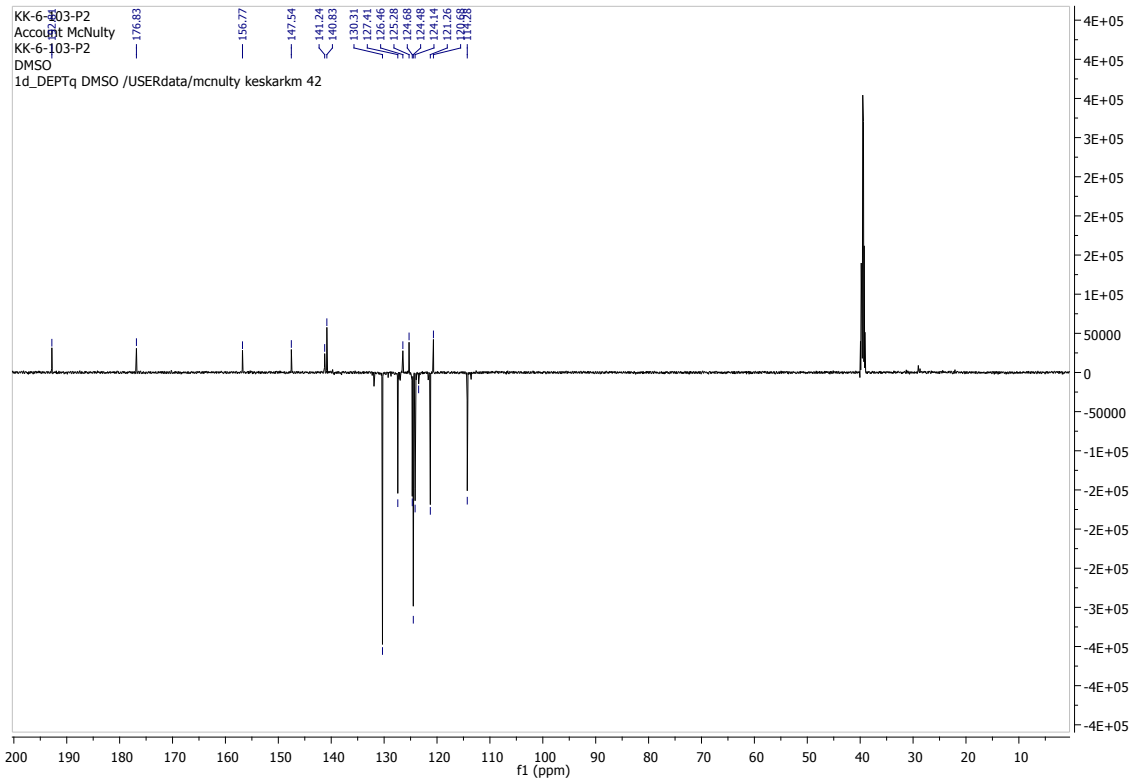

KK-6-102
Account McNulty
KK-6-102
1d_13C_carbon DMSO /USERdata/mcnulty keskarkm 56
176.94
158.09
149.21
148.06
140.82
128.18
127.78
126.64
124.96
124.35
123.95
120.97
120.87
120.82
114.15
109.31
108.92
101.80
f1 (ppm)


KK-6-102
Account McNulty
KK-6-102
1d_DEPTq DMSO /USERdata/mcnulty keskarkm 56
176.94
158.09
149.21
148.06
140.82
128.18
127.78
126.64
124.96
123.95
120.97
120.87
120.81
114.15
109.31
108.92
101.80
f1 (ppm)

3-(4-nitrobenzylidene)cyclopenta[b]indole-1,2(3H,4H)-dione: (22)







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