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Supporting Information

Synthesis of the cyanobacterial metabolite nostodione A, structural studies and potent 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

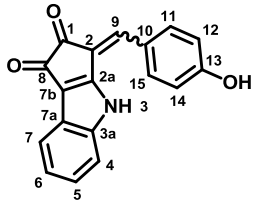
equiv, 0.32 mmol). Freshly distilled THF (40.0 mL) was added to the flask under inert atmosphere. The reaction mixture was cooled to 0 °C. Sodium hydride (0.031 g, 2.5 equiv, 0.80 mmol, 60% dispersion in mineral oil) was added to the flask. The reaction mixture was heated at reflux approximately 12 h (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.

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.

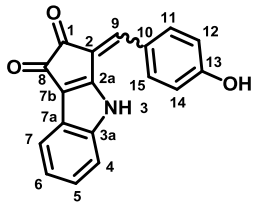
^{1}H NMR (600 MHz, DMSO, *Minor isomer*) δ 12.93 (s, 1H), 10.35 (s, 1H), 8.08 (d, *J* = 8.7 Hz, 2H), 7.76 (d, *J* = 7.8 Hz, 1H), 7.57 (d, *J* = 8.1 Hz, 1H), 7.38 (ddd, *J* = 8.2, 7.2, 1.1), 7.29 (ddd, *J* = 8.0, 7.1, 0.8), 7.23 (s, 1H), 6.90 (d, *J* = 8.7 Hz, 2H). ^{13}C NMR (151 MHz, DMSO) δ 192.53, 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 : <u>Minor isomer</u>

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.

3-(4-(4-(trifluoromethoxy)phenoxy)benzylidene)cyclopenta[b]indole-1,2(3H,4H)-dione (23):

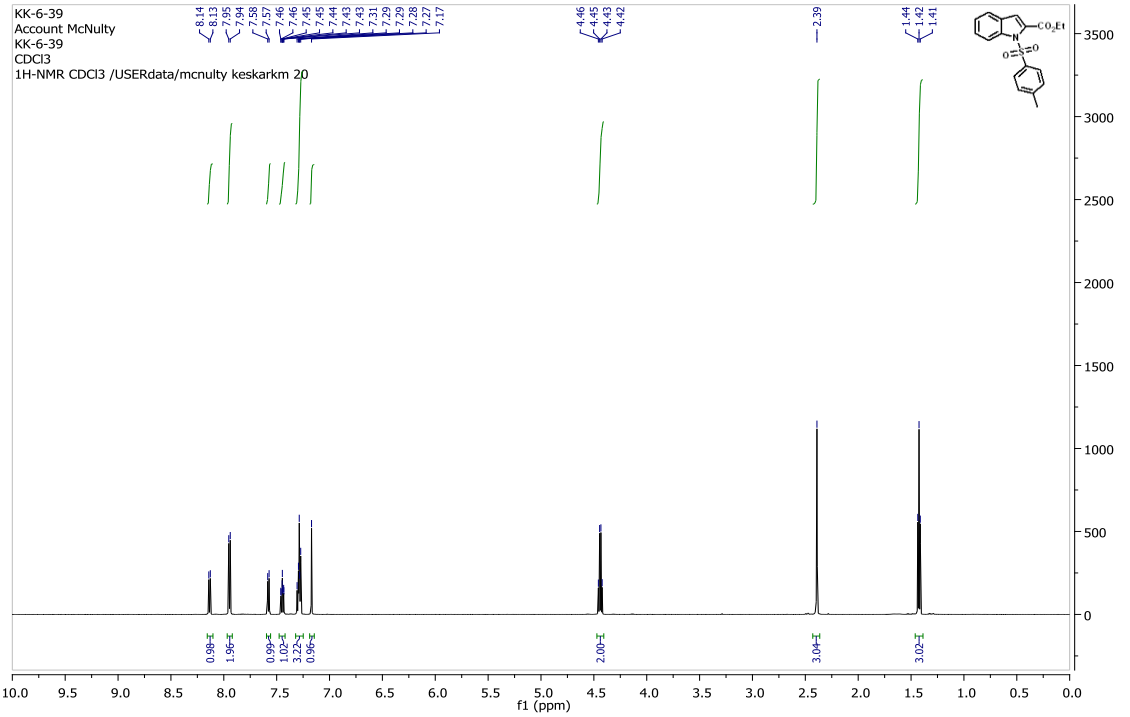
Isomeric ratio: 95:05. M.P.: 350-355 °C. Major isomer: ^{1}H NMR (600 MHz, DMSO) δ 12.27 (s, 1H), 7.92 (d, *J* = 8.6 Hz, 2H), 7.86 (d, *J* = 7.8 Hz, 1H), 7.65 (d, *J* = 8.2 Hz, 1H), 7.53 (d, *J* = 8.3 Hz, 2H), 7.44 (t, *J* = 7.7 Hz, 1H), 7.38 (s, 1H), 7.34 (t, *J* = 7.5 Hz, 1H). ^{13}C NMR (151 MHz, DMSO) δ 193.00, 176.86, 157.19, 149.12, 140.91, 133.00, 131.37, 127.05, 126.01, 125.52, 124.06, 123.11, 121.69, 121.09, 120.70, 120.08 (q, *J* = 257.31 Hz), 114.19. HRMS(EI$^+$): calcd. For $C_{19}H_{10}F_3NO_3$ $[M]^+$ 357.0617; found 357.0613.

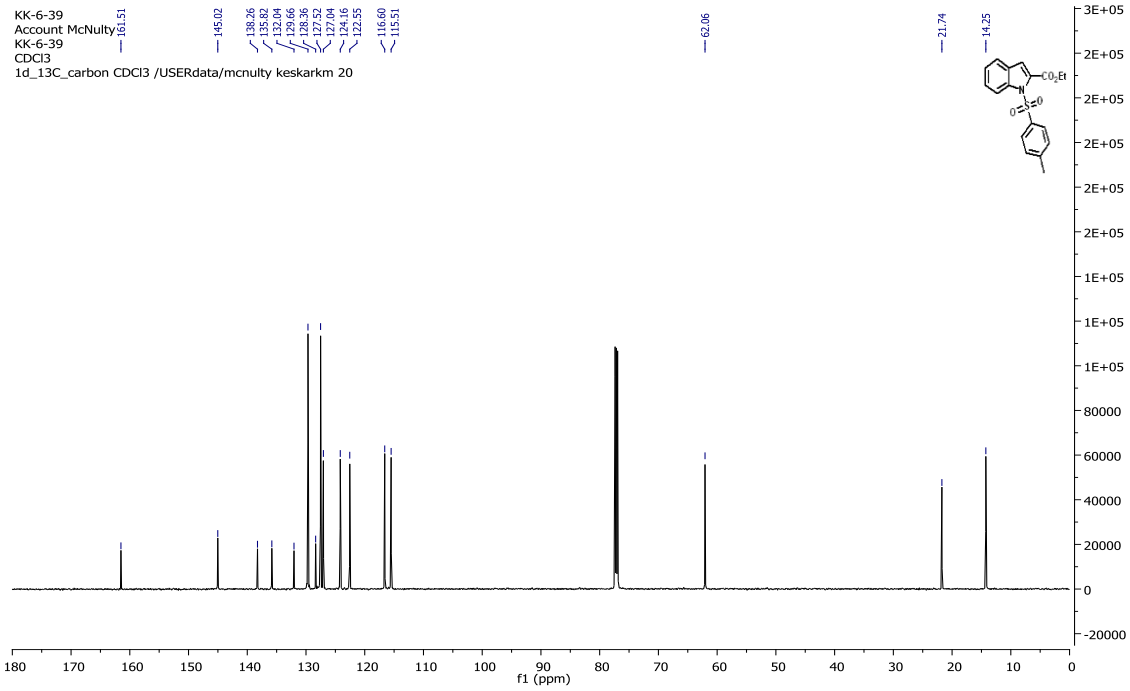
3-(4-(trifluoromethoxy)benzylidene)cyclopenta[b]indole-1,2(3H,4H)-dione (24):

Isomeric ratio: 90:10. M.P.: decomposes with melt at 305-310 °C. Major isomer: ^{1}H NMR (700 MHz, DMSO) δ 12.21 (s, 1H), 7.87-7.83 (m, 3H), 7.65 (d, *J* = 8.2 Hz, 1H), 7.48 (d, *J* = 8.6 Hz, 2H), 7.44 – 7.41 (m, 1H), 7.36 (s, 1H), 7.35-7.31 (m, 1H), 7.28 (d, *J* = 9.0 Hz, 2H), 7.18 (d, *J* =

8.6 Hz, 2H). ^{13}C NMR (176 MHz, DMSO) δ 193.17, 176.92, 158.12, 157.75, 154.41, 144.40, 140.84, 131.65, 129.04, 127.24, 126.78, 124.77, 124.00, 123.20, 121.61, 121.10, 120.94, 120.76, 120.11(q, J = 256 Hz), 118.87, 114.19. HRMS(EI$^+$): calcd. For $C_{25}H_{14}F_3NO_4$ $[M]^+$ 449.0850; found 449.0875. (*4-trifluoromethoxyaryloxy benzaldehyde was prepared via Cu-mediated cross-coupling of 4-bromobenzaldehyde and trifluoromethoxyphenol, using a reported procedure.*[5])

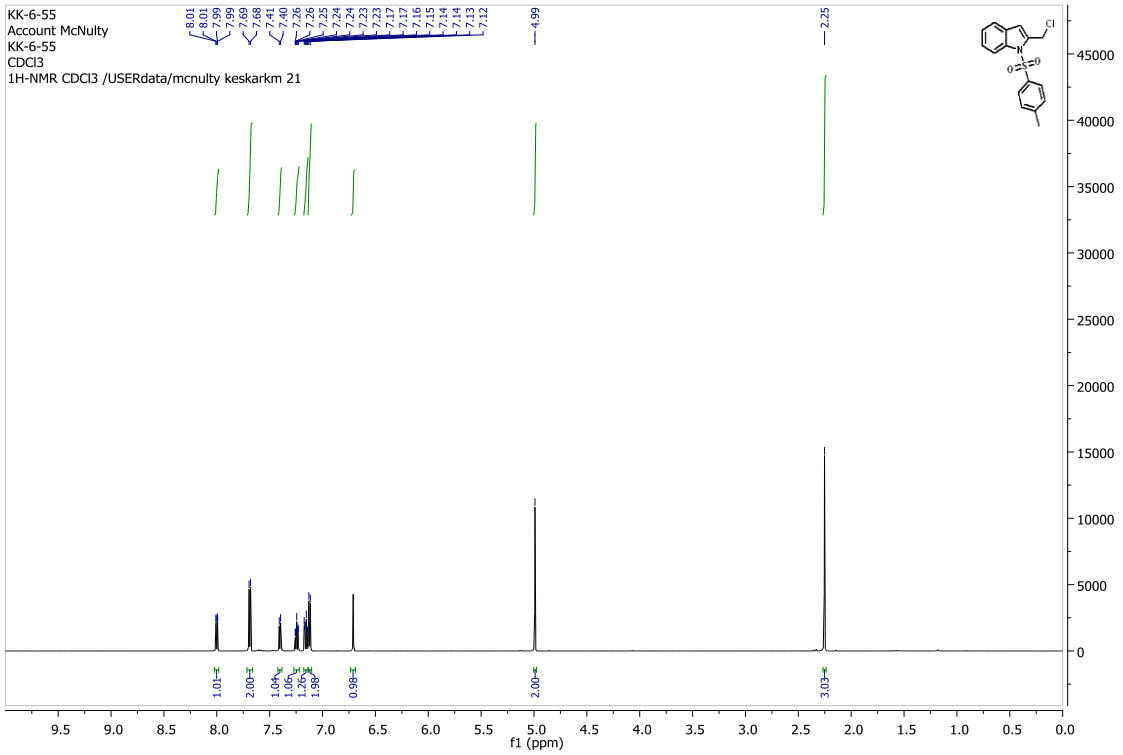
Ethyl 1-tosyl-1H-indole-2-carboxylate: (8)

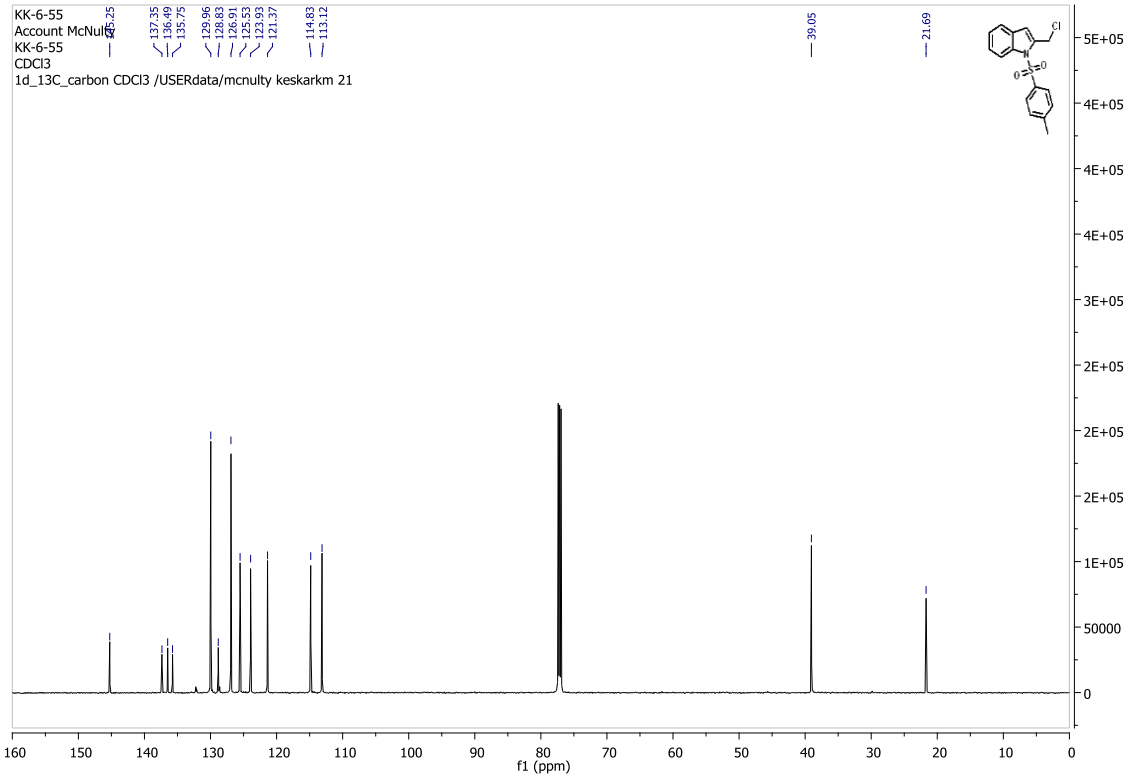




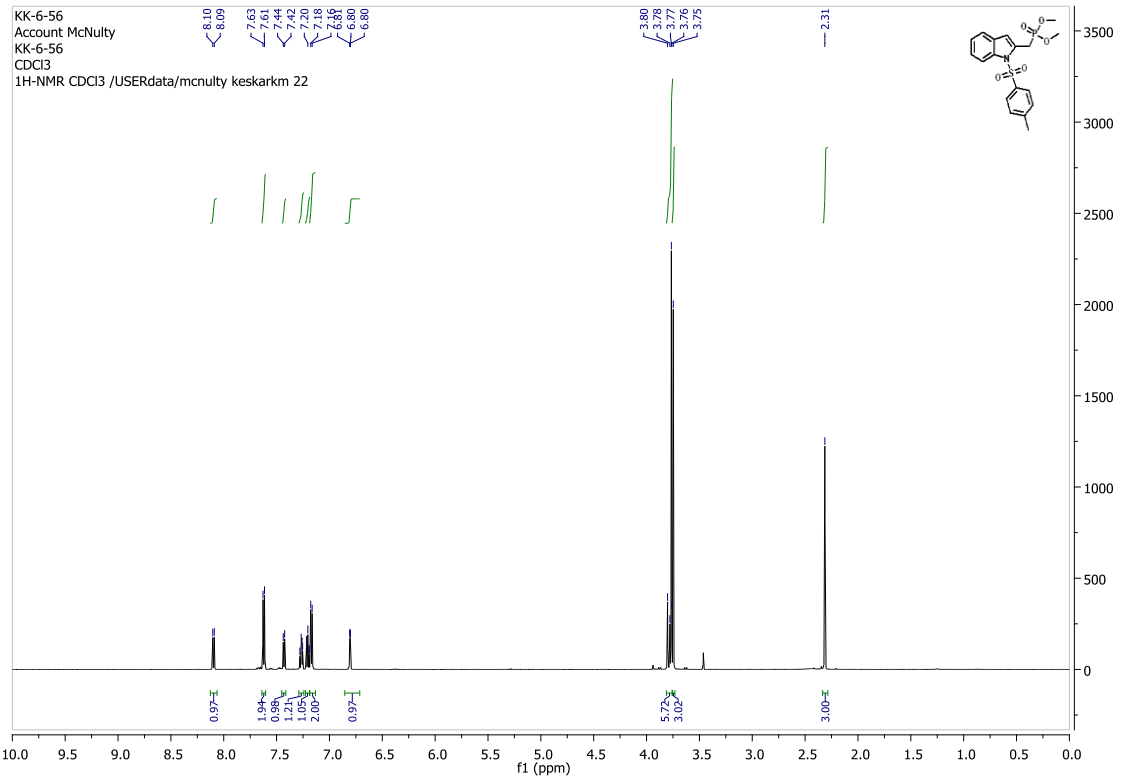
(1-tosyl-1H-indol-2-yl)methanol: (9) See spectra in ref 2

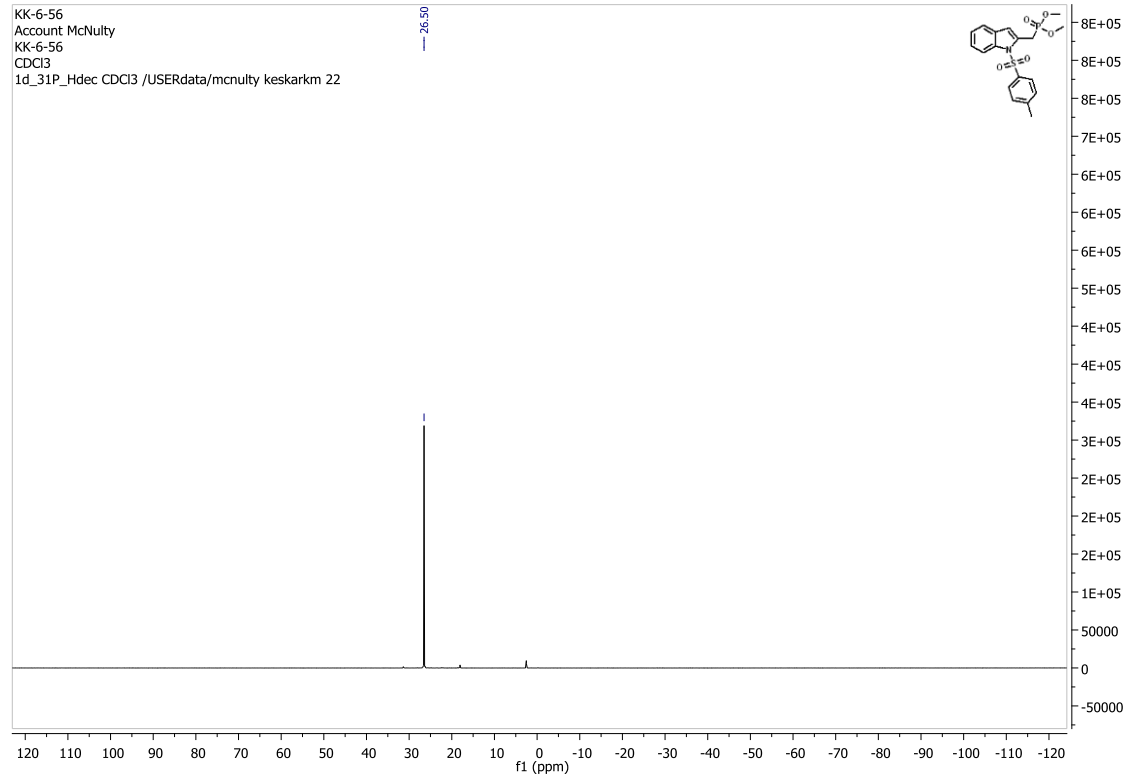
2-(chloromethyl)-1-tosyl-1H-indole: (10)

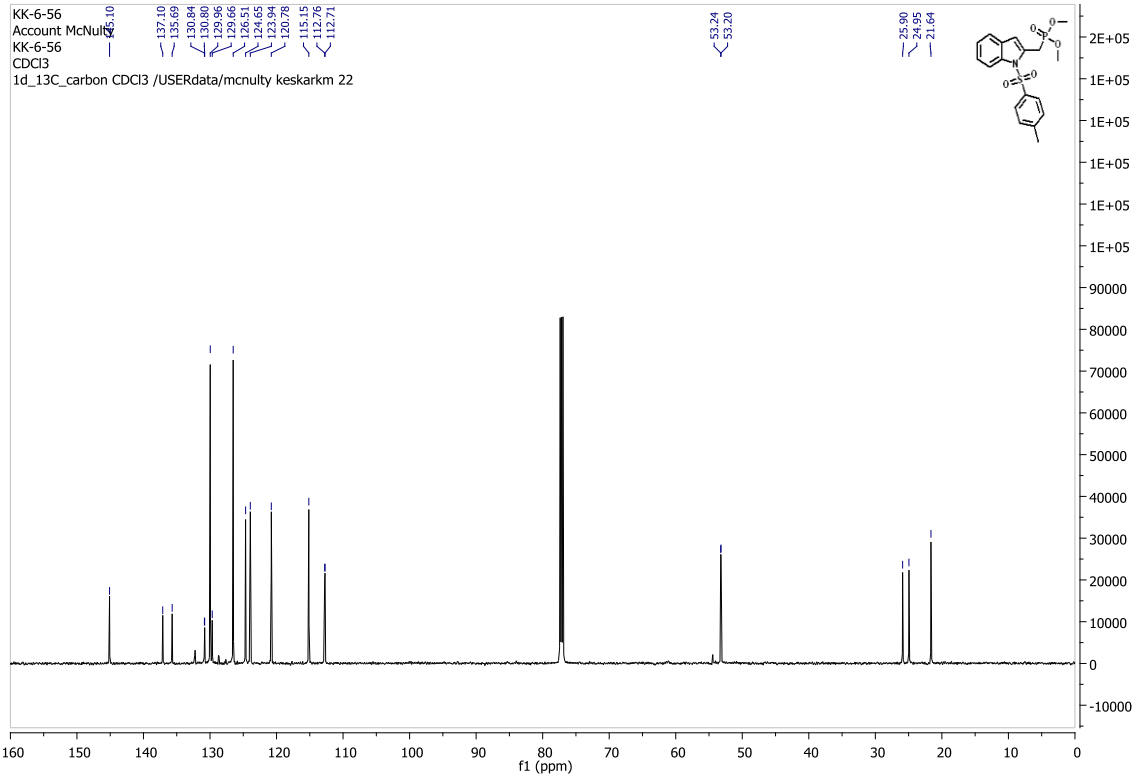




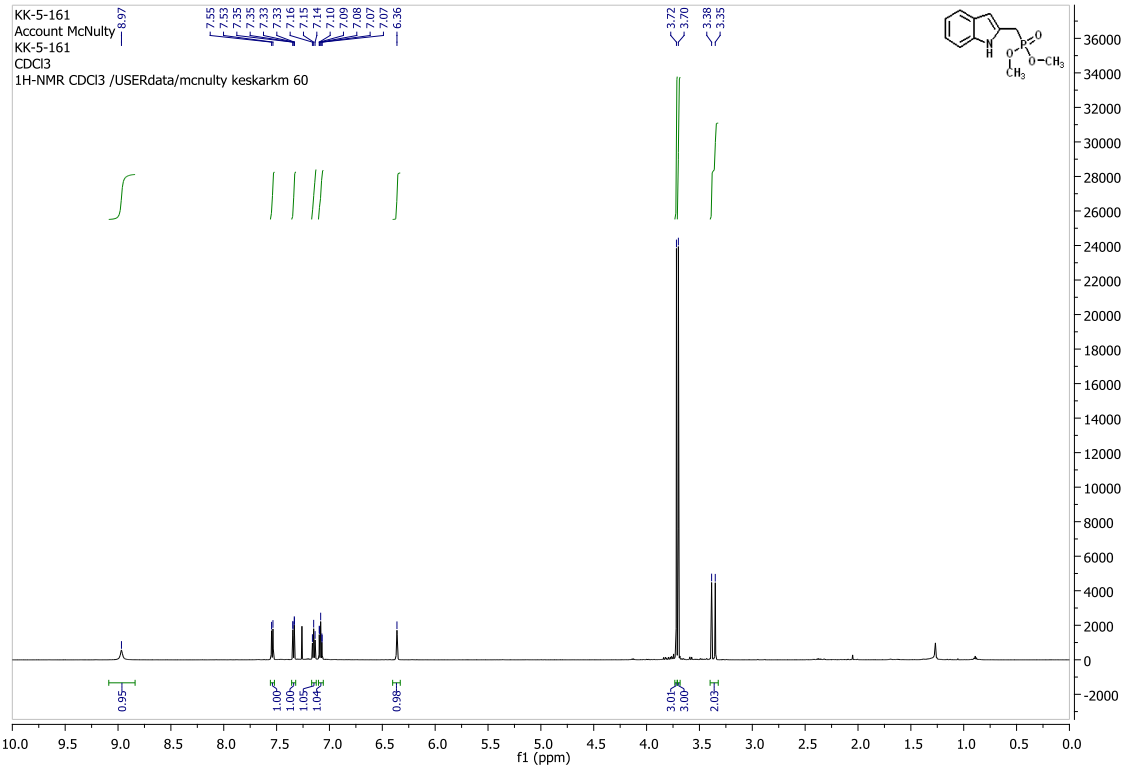
Dimethyl (1-tosyl-1H-indol-2-yl)methylphosphonate: (11)

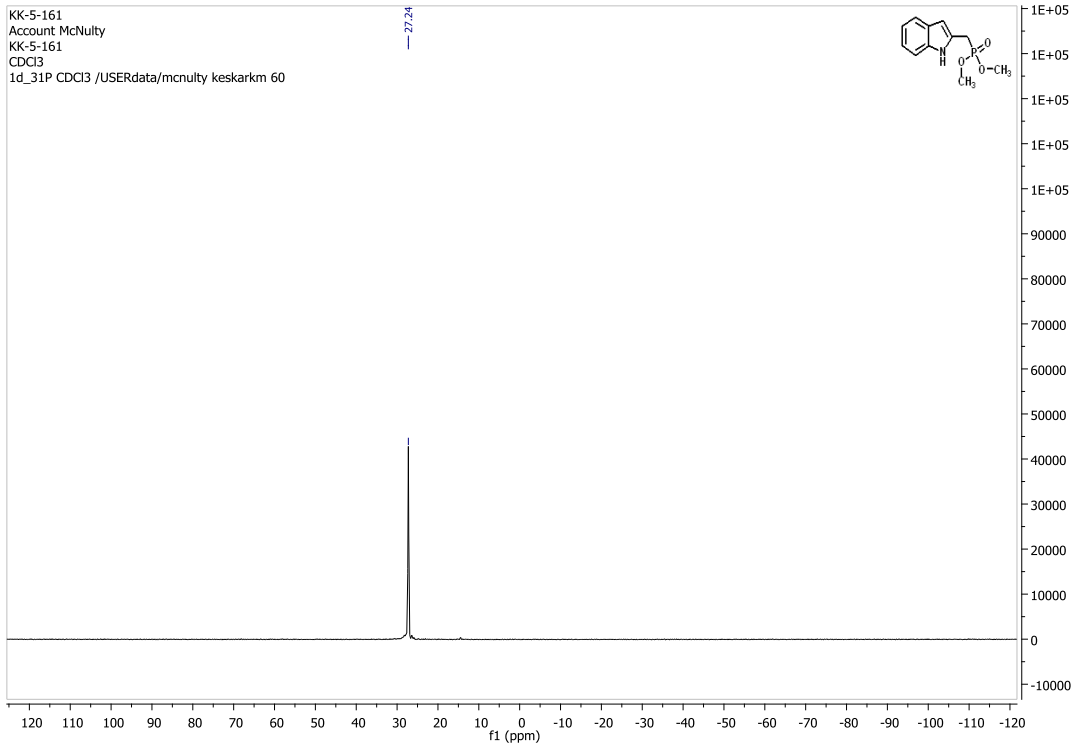






Dimethyl (1H-indol-2-yl)methylphosphonate: (12)

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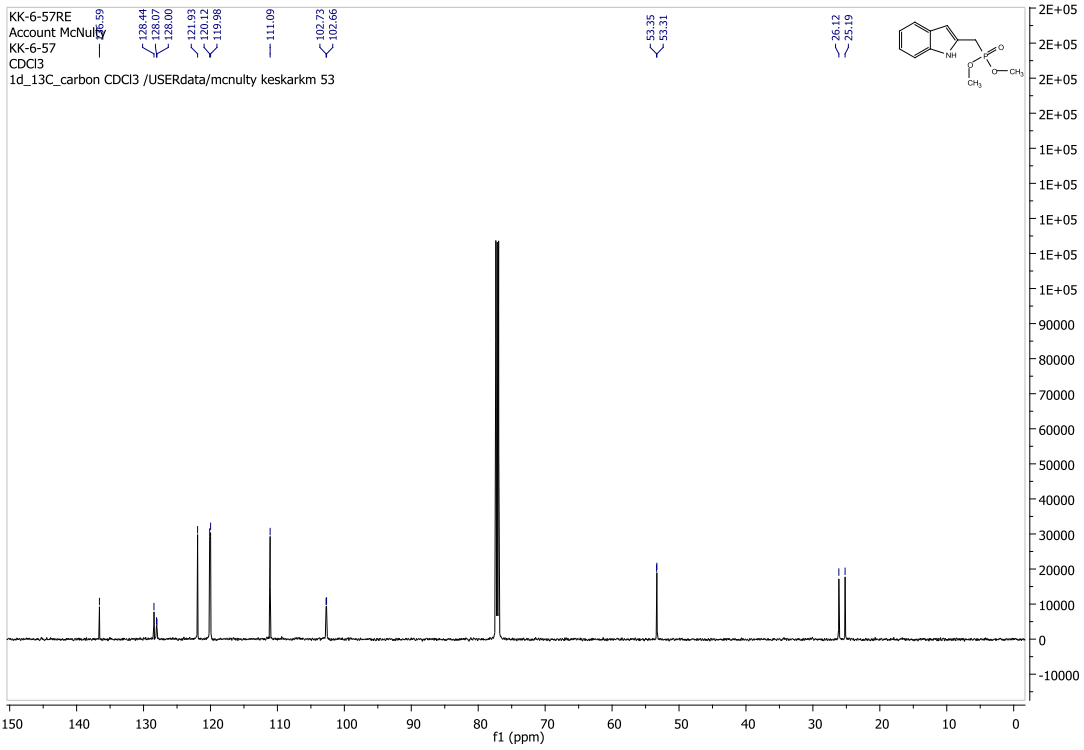
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120.12
119.98
111.09
102.73
102.66
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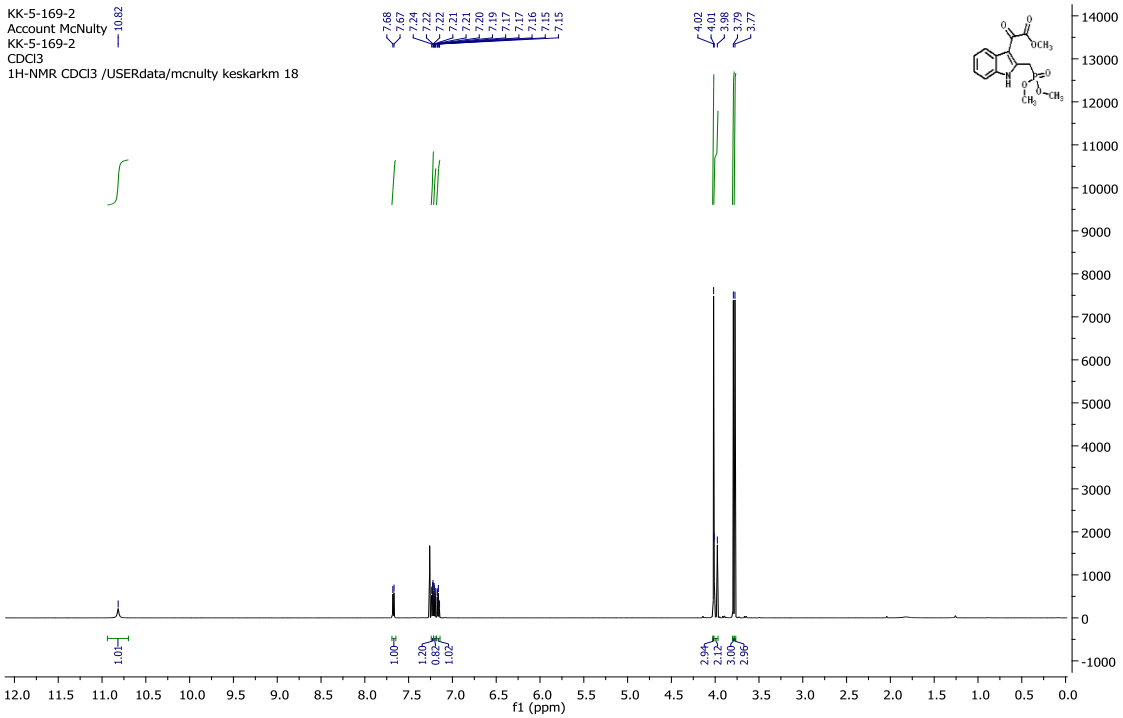
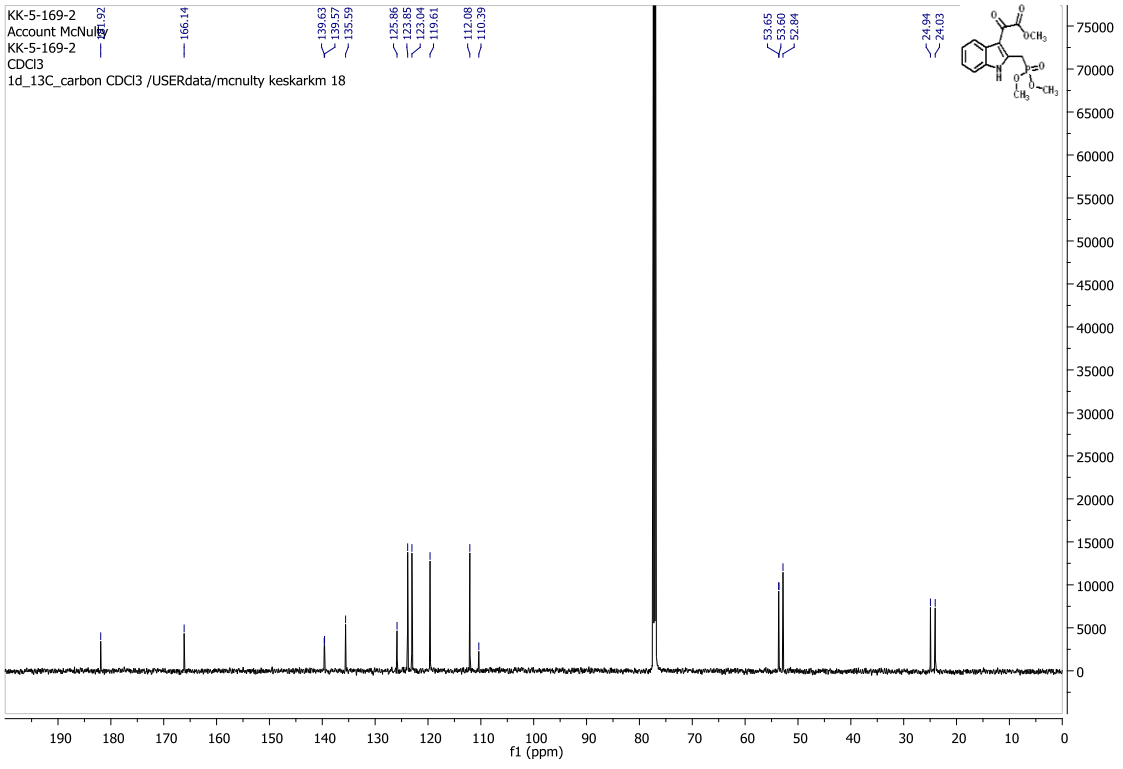
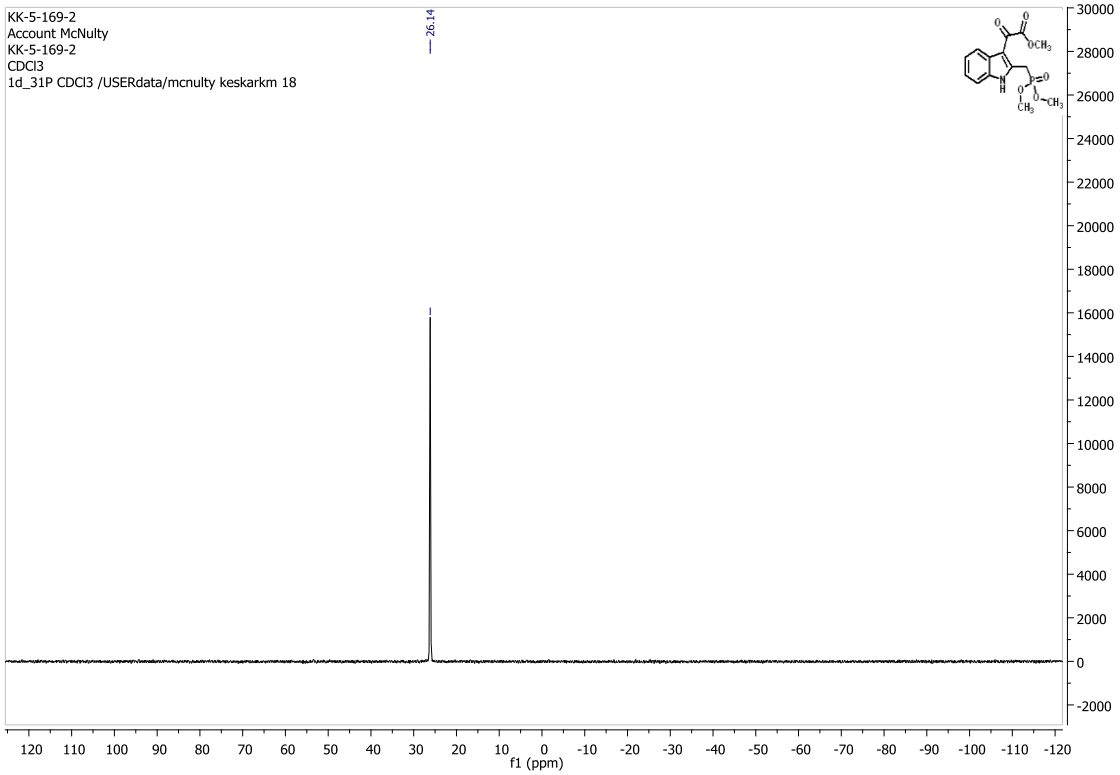
25.19
f1 (ppm)

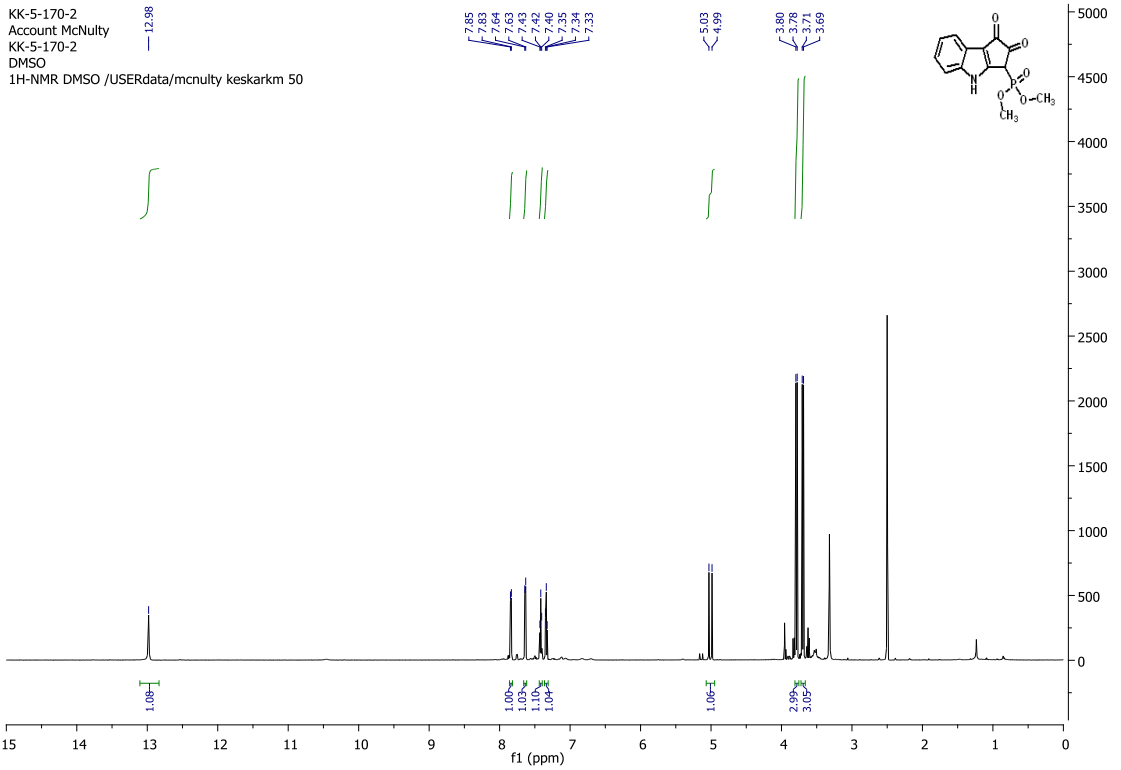
Methyl 2-(2-((dimethoxyphosphoryl)methyl)-1H-indol-3-yl)-2-oxoacetate: (14)

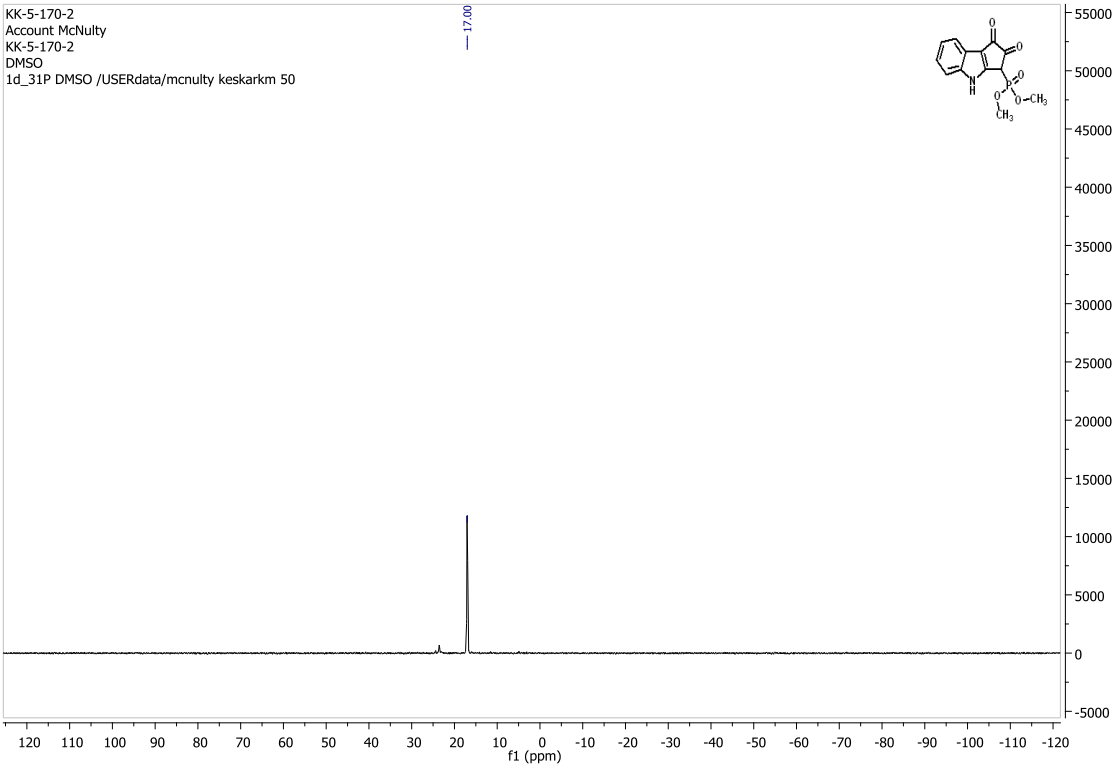






Dimethyl 1,2-dioxo-1,2,3,4-tetrahydrocyclopenta[b]indol-3-ylphosphonate: (15)

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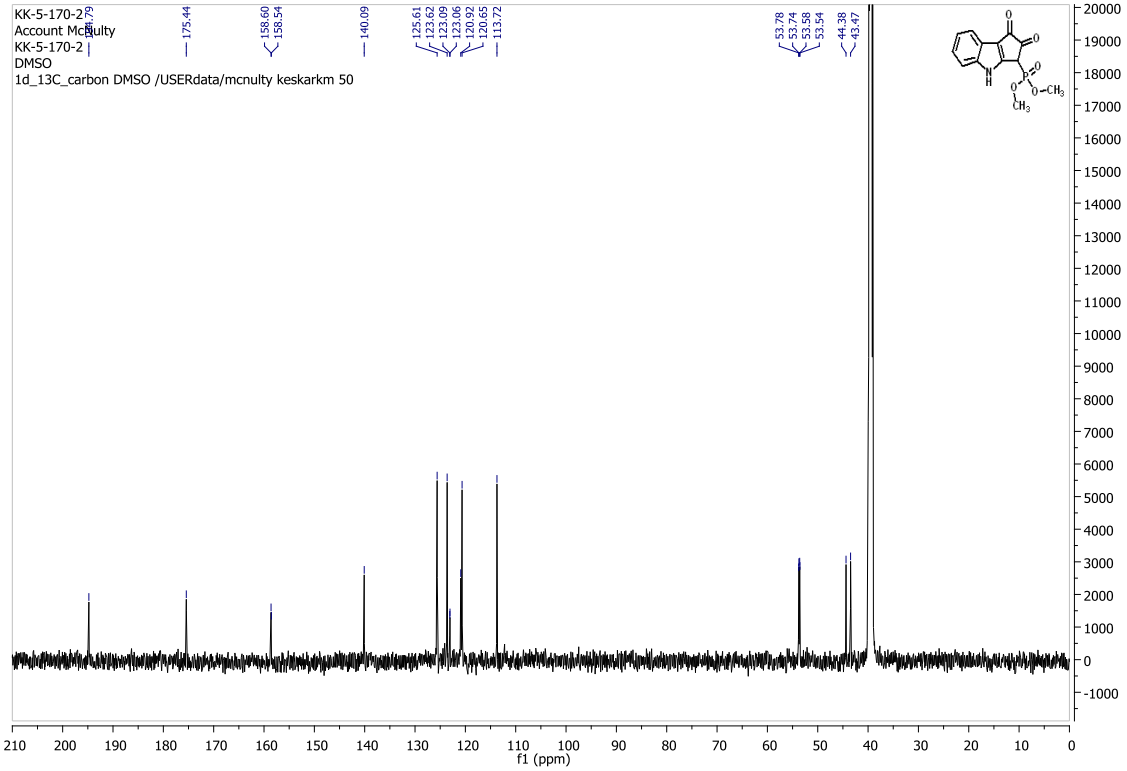
f1 (ppm)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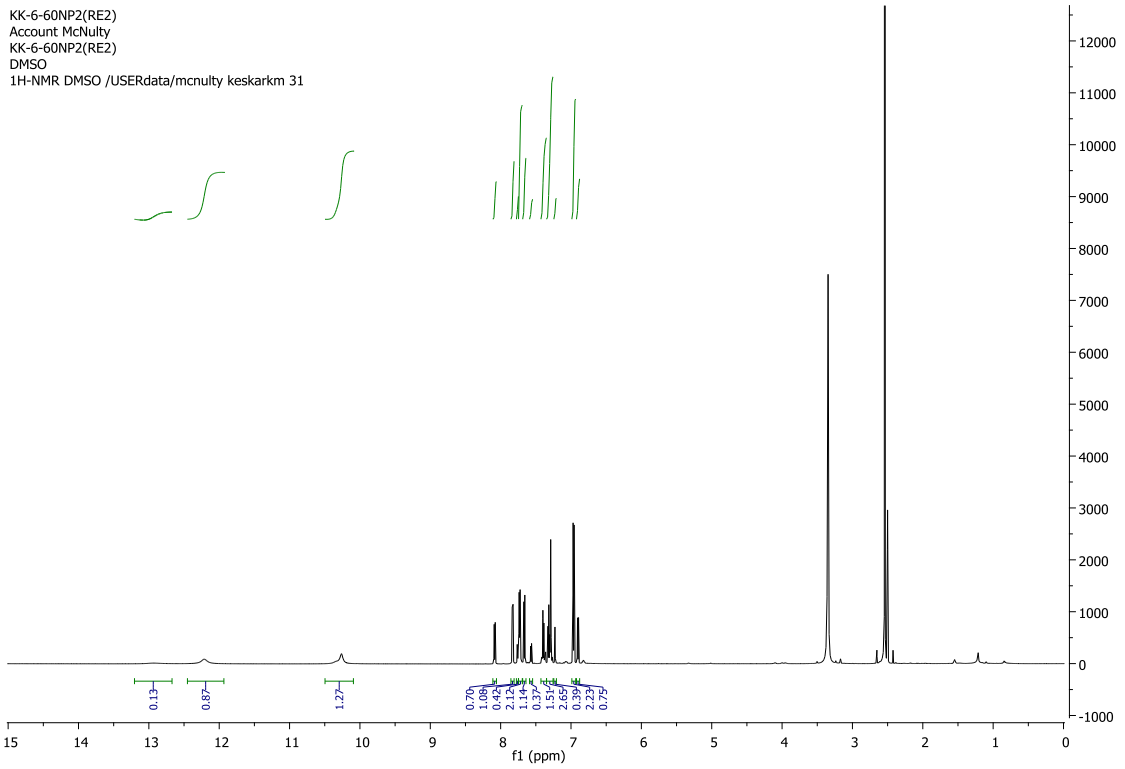
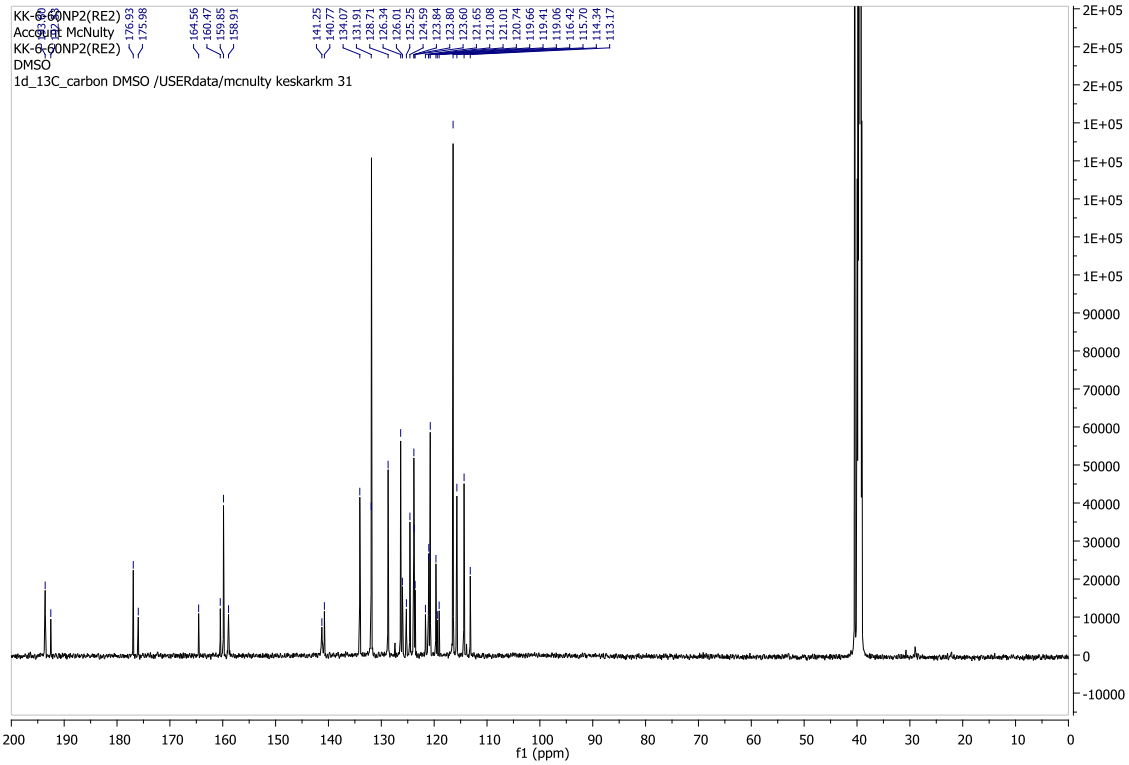
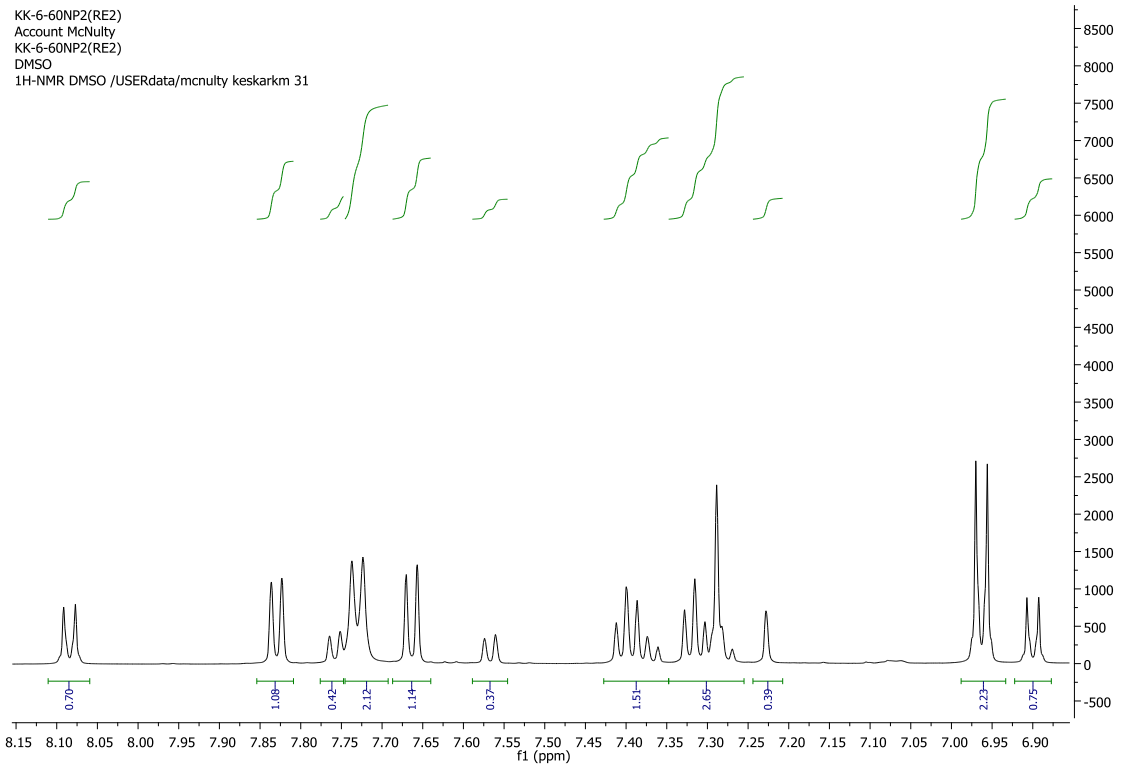
44.38
43.47
f1 (ppm)

Nostodione A: (1)

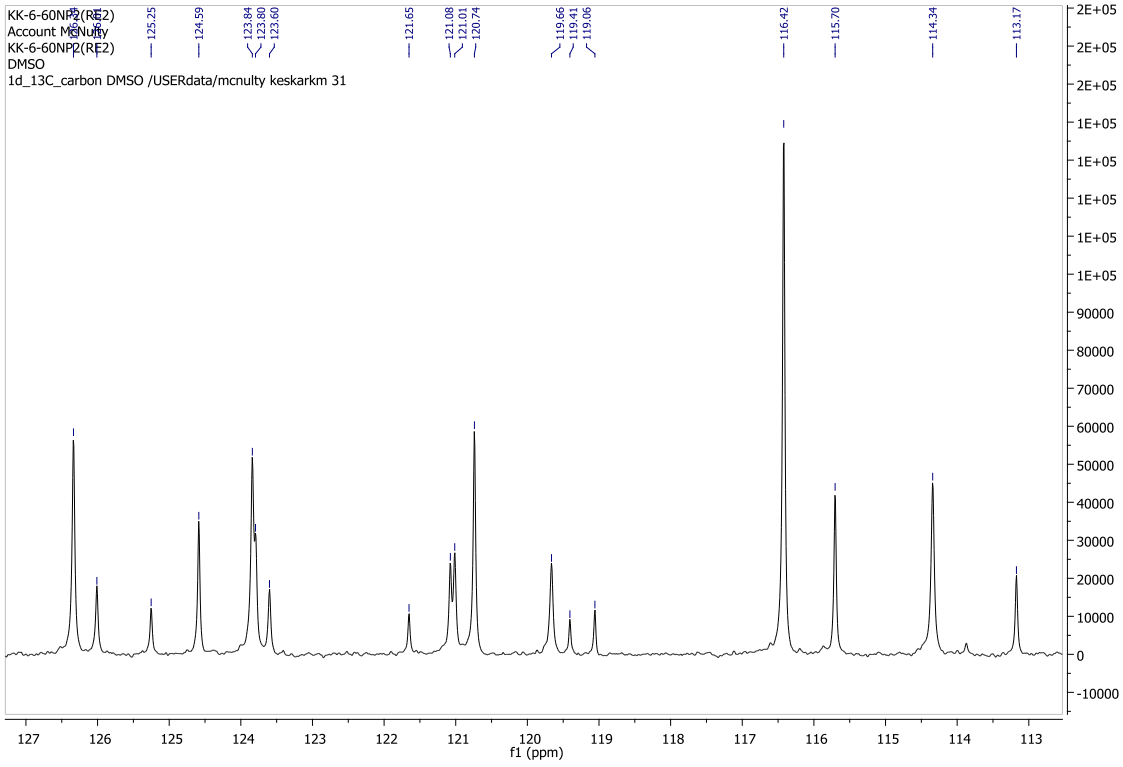




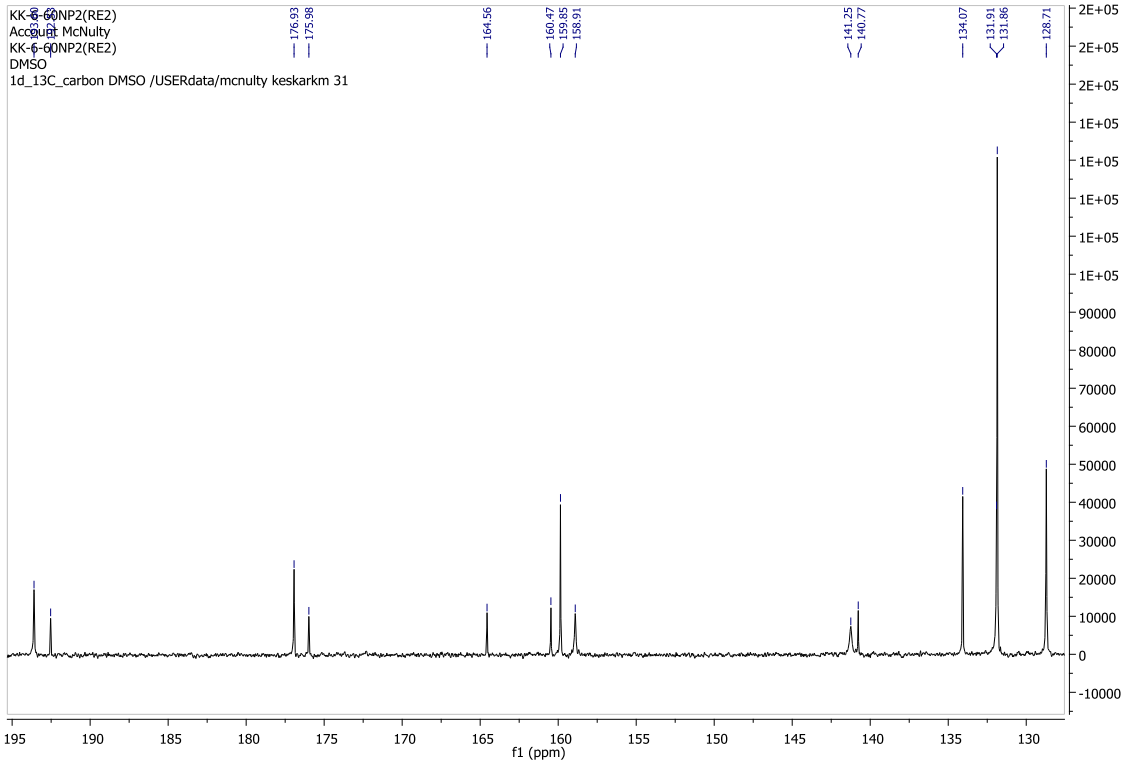
Nostodione A: (1) *(Aromatic Region zoomed - ^{1}H-NMR)*



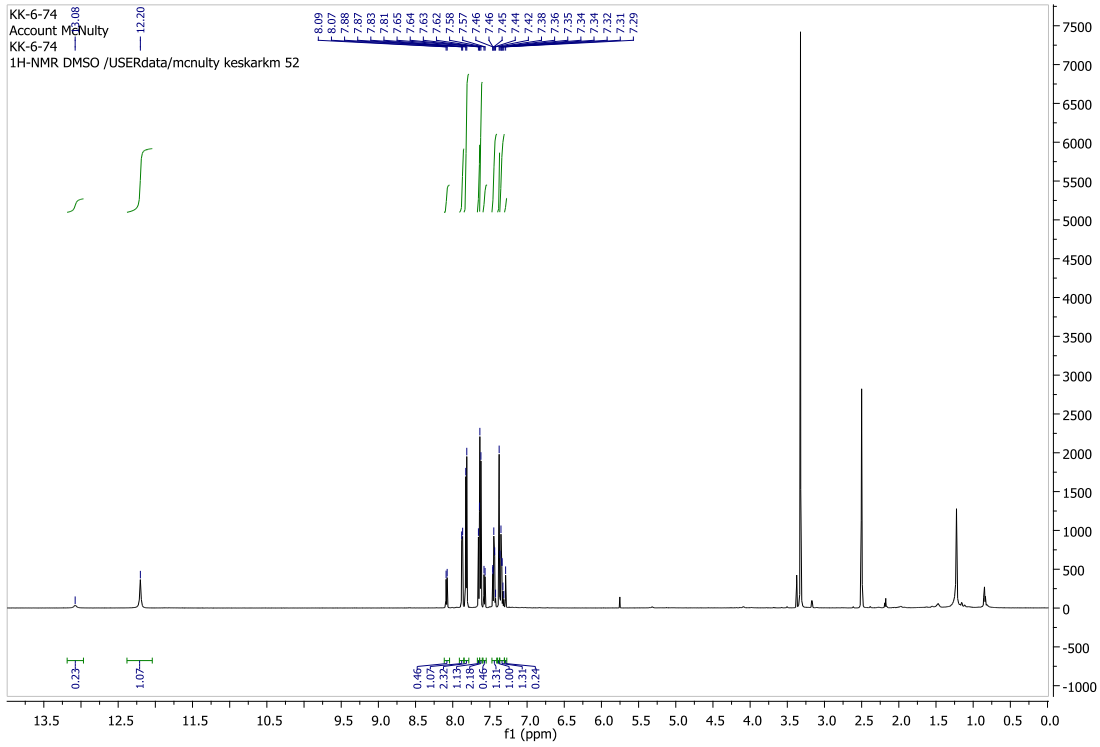
Nostodione A: (1) *(127 ppm-112 ppm zoomed - ^{13}C-NMR)*

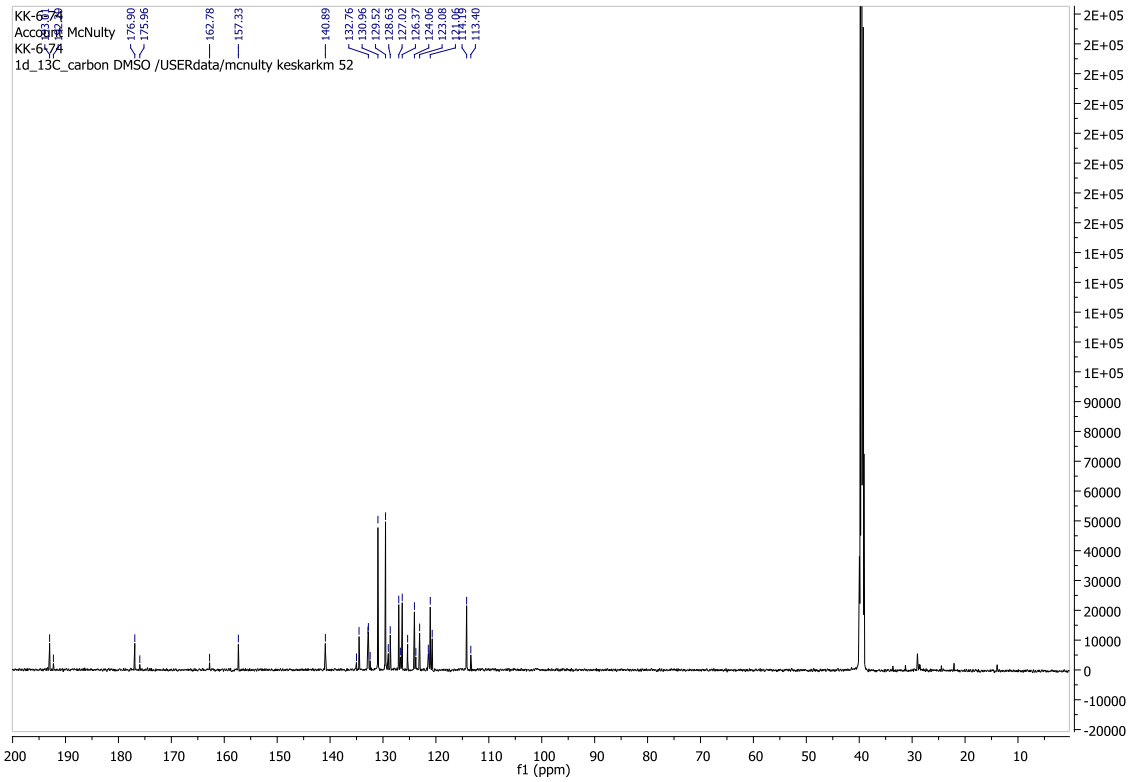


Nostodione A: (1) *(195 ppm-128 ppm zoomed - ^{13}C-NMR)*



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

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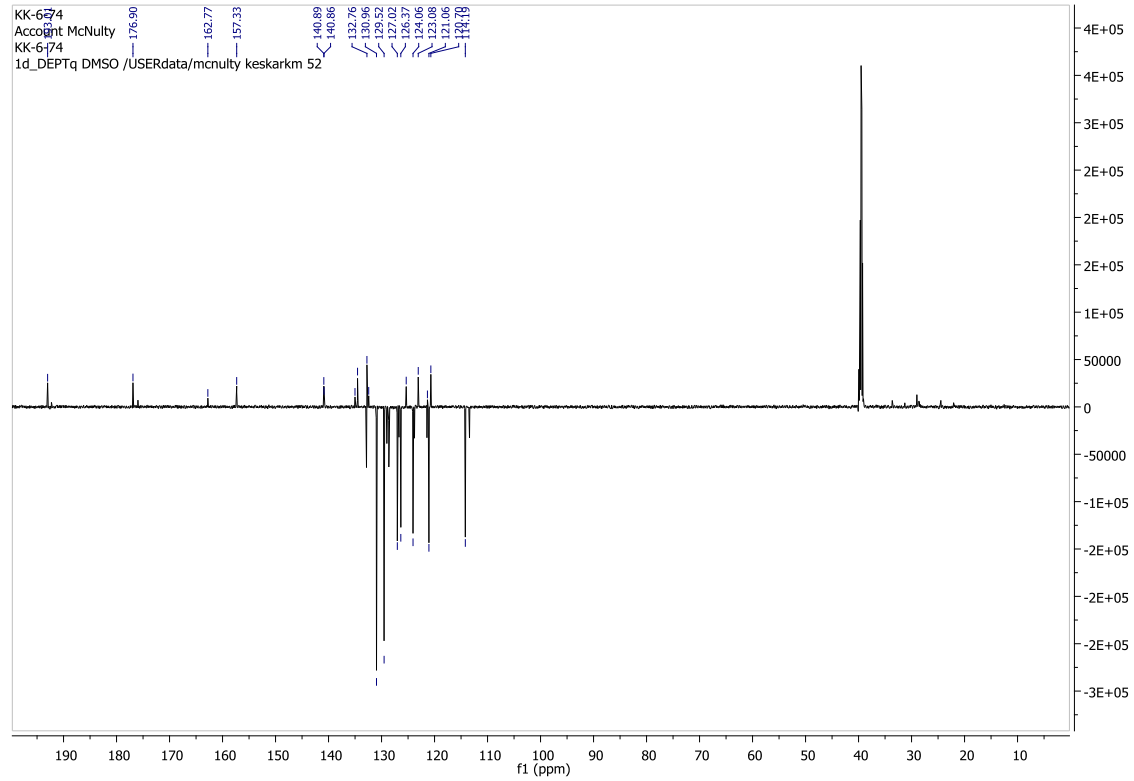
124.06
123.08
113.40
f1 (ppm)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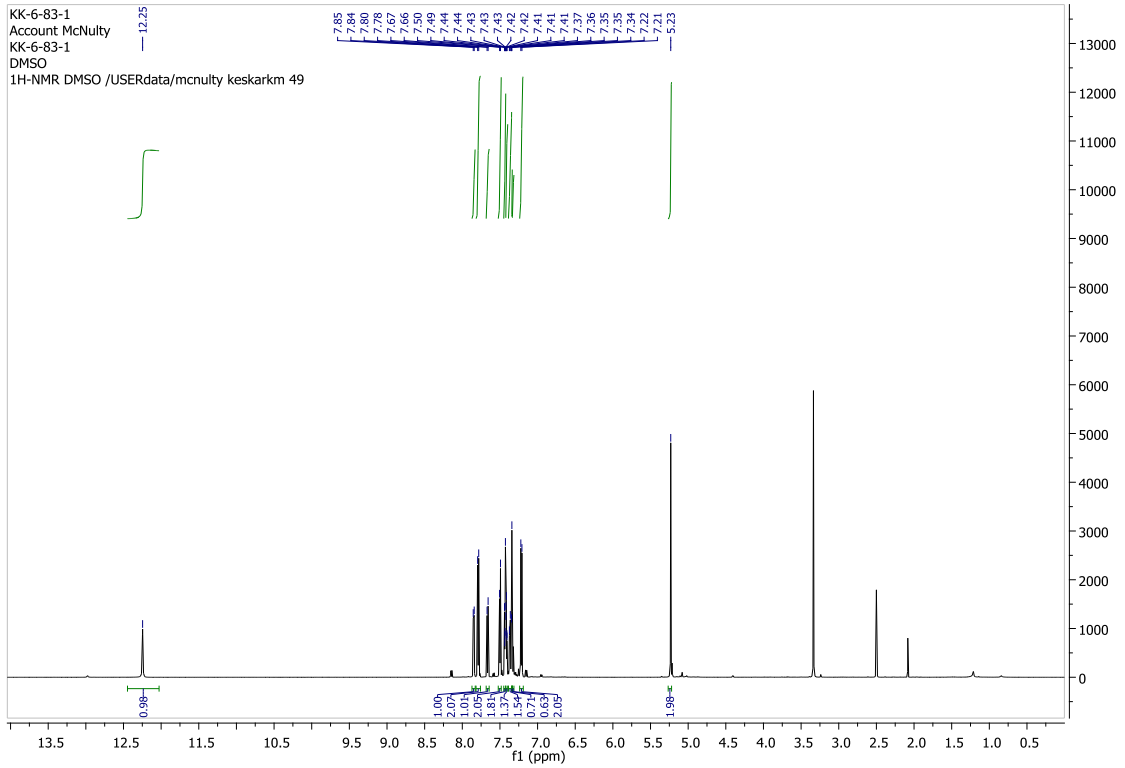
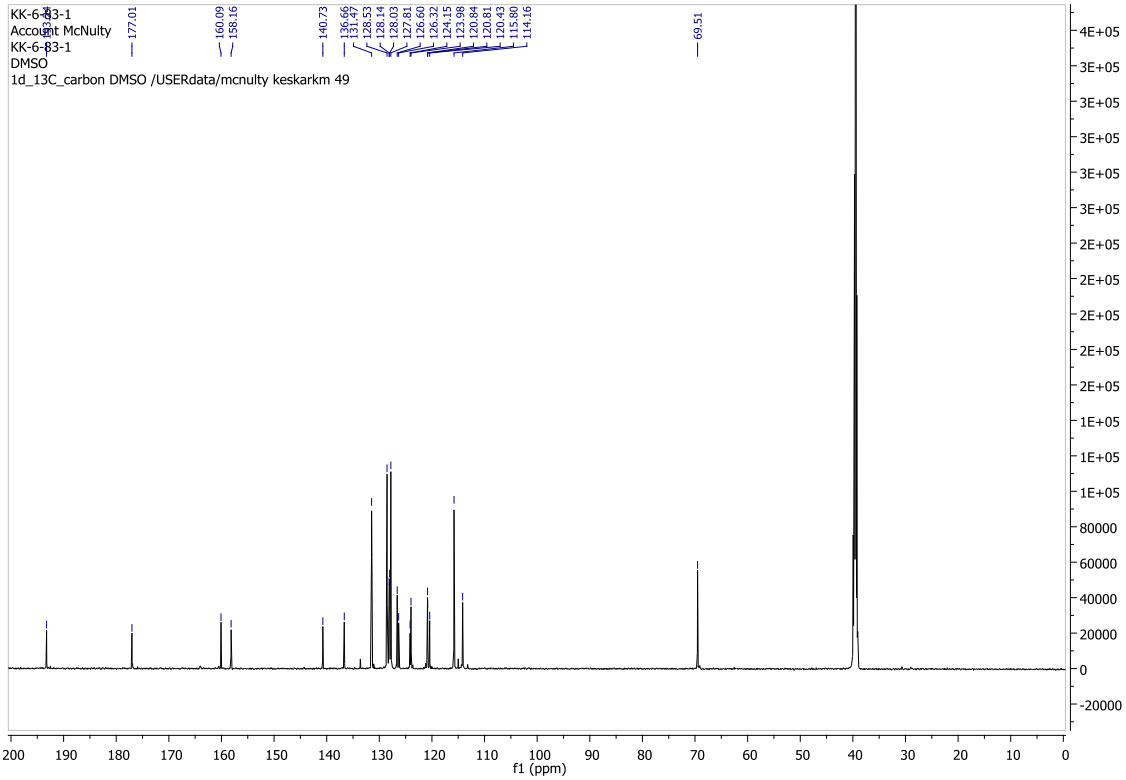
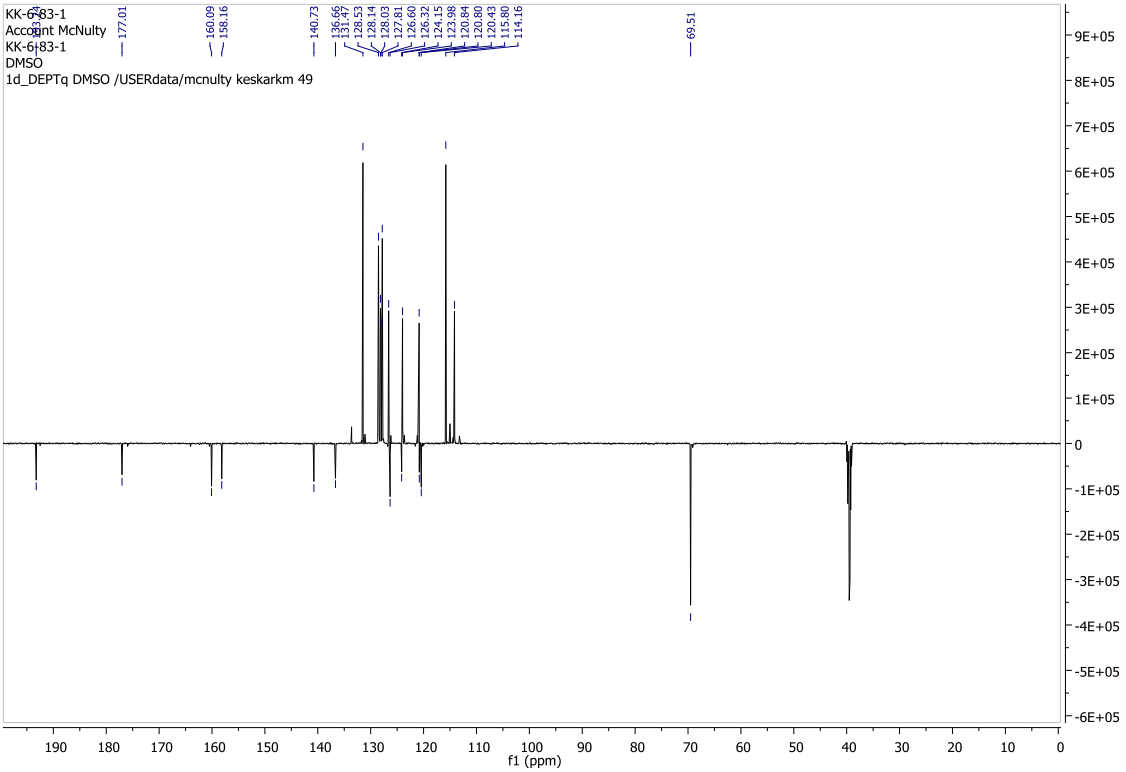
157.33
140.89
140.86
132.76
130.96
129.52
127.02
126.37
124.06
123.08
121.06
f1 (ppm)

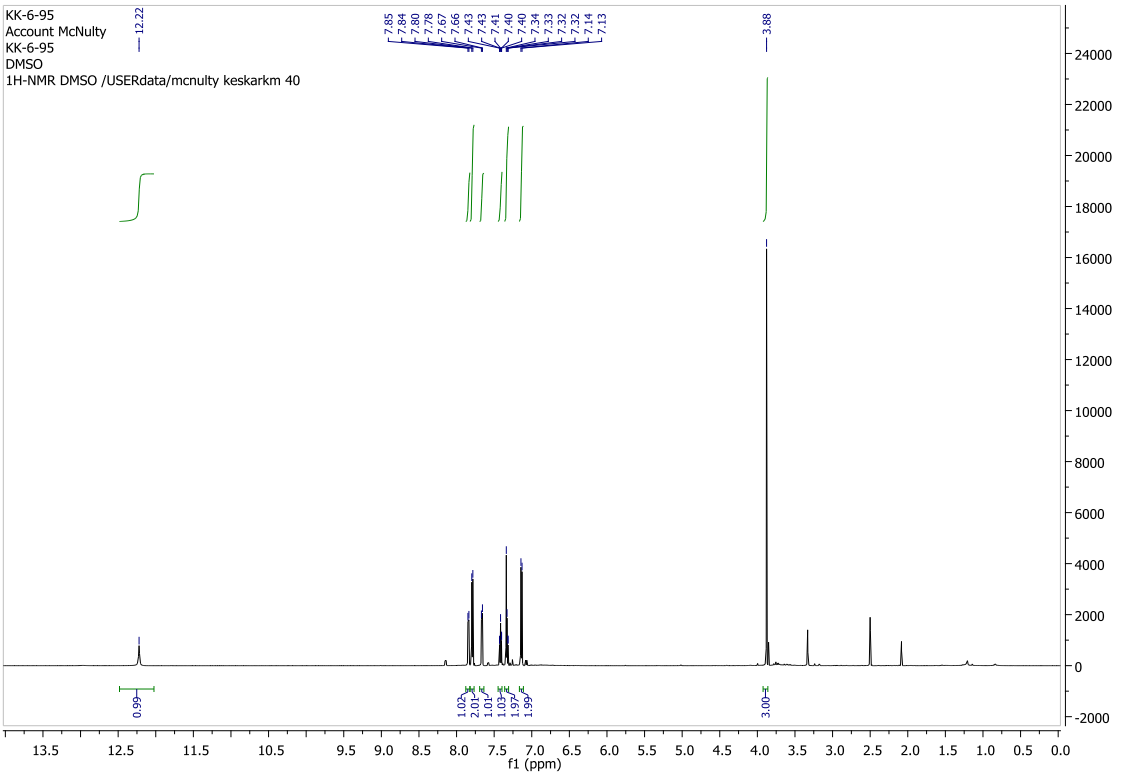
3-(4-(benzyloxy)benzylidene)cyclopenta[b]indole-1,2(3H,4H)-dione: (18)

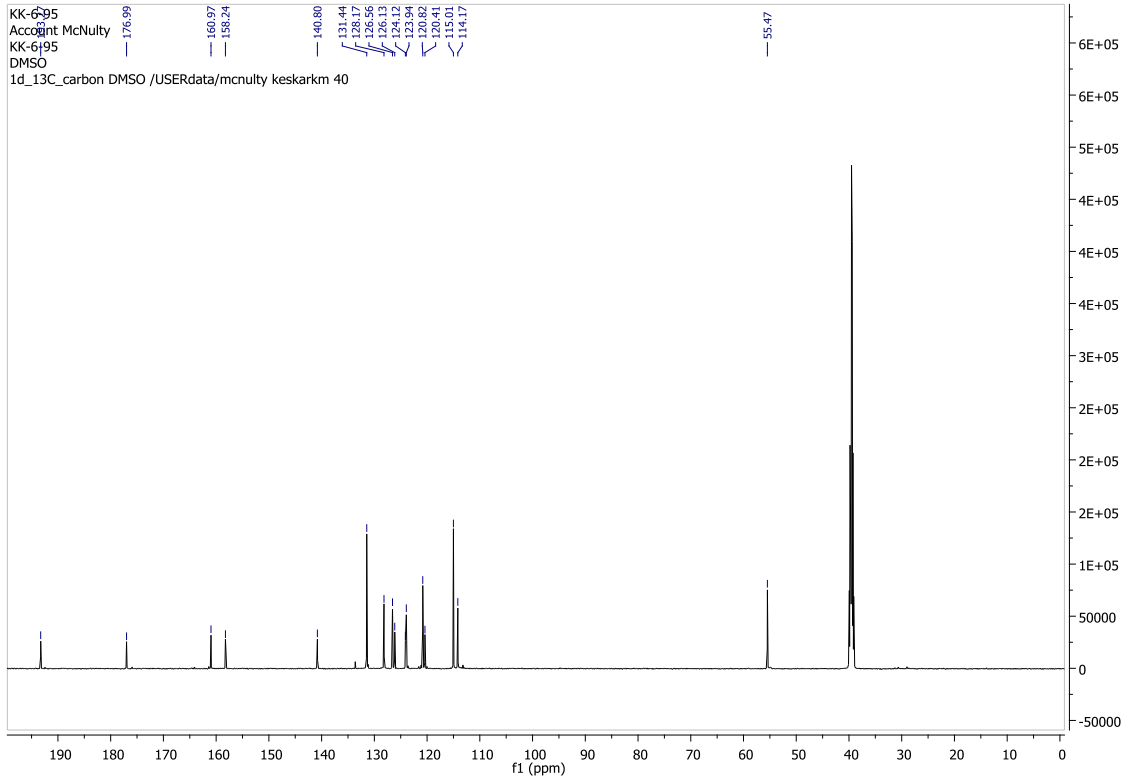






3-(4-methoxybenzylidene)cyclopenta[b]indole-1,2(3H,4H)-dione: (19)

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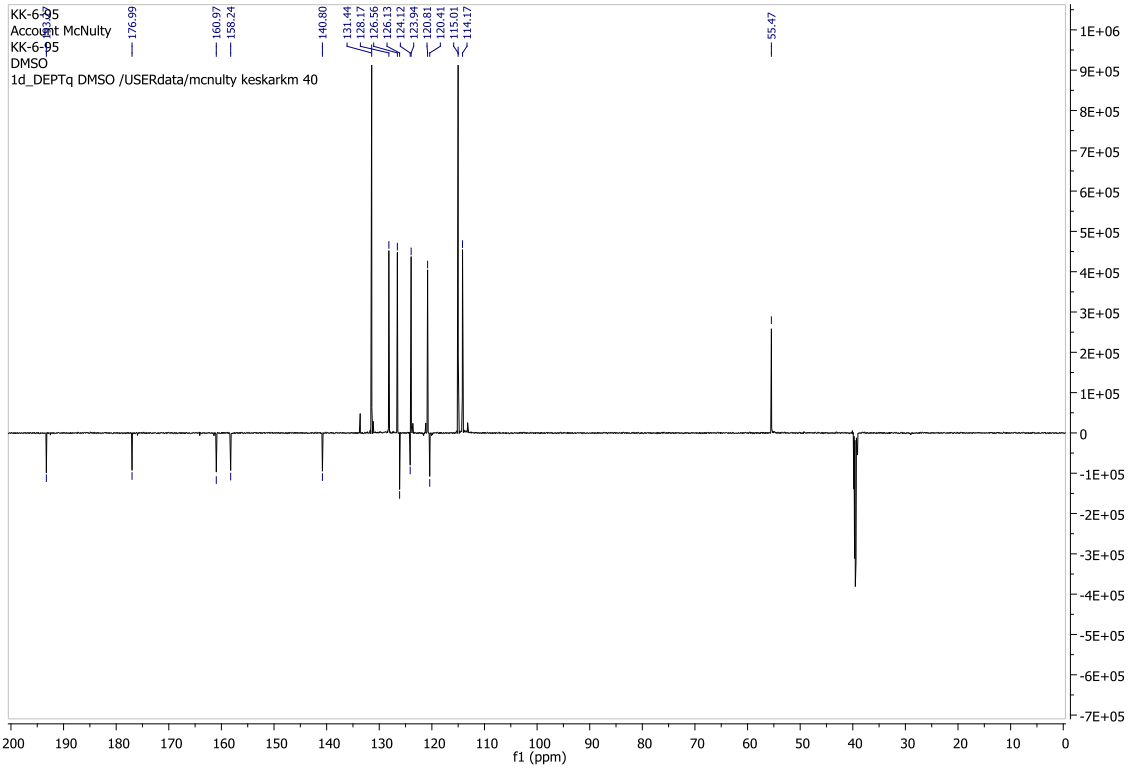
120.41
115.01
114.17
55.47
f1 (ppm)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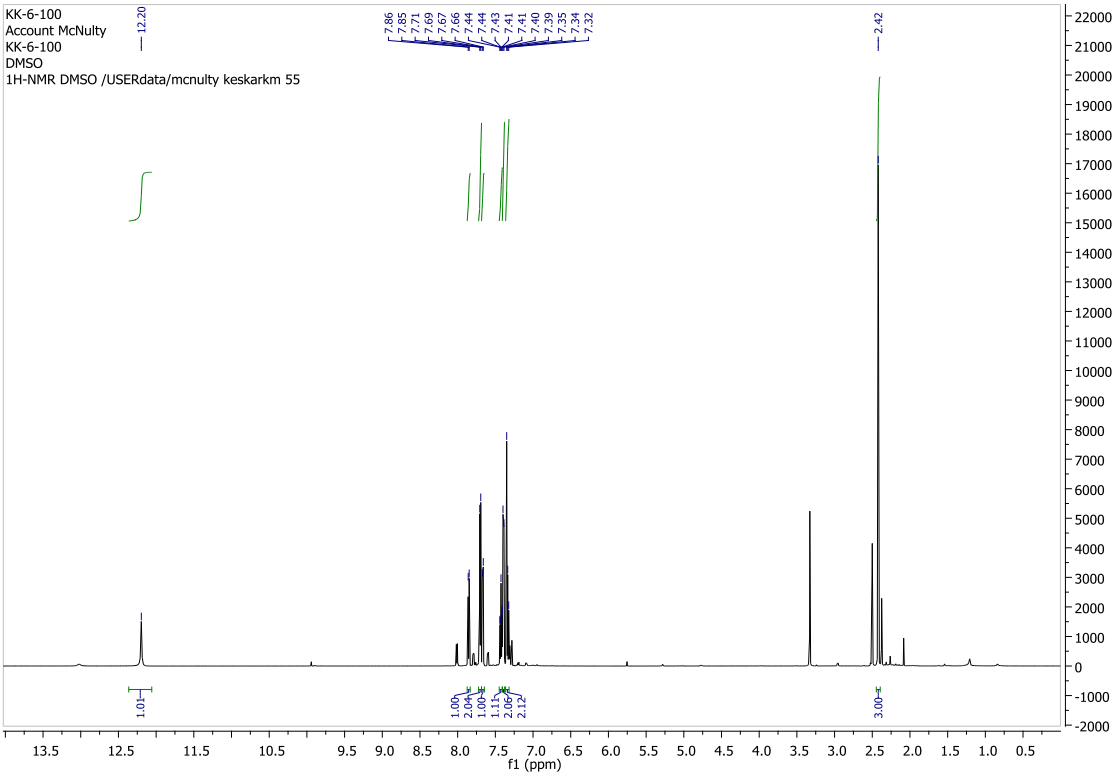
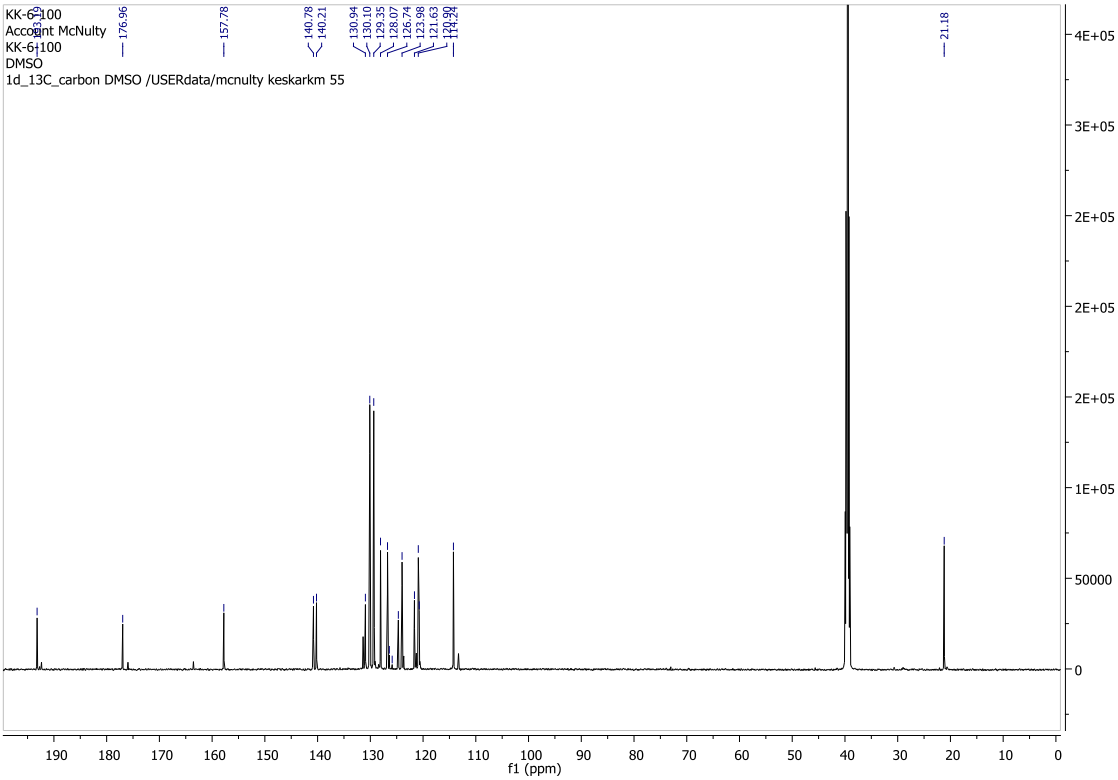
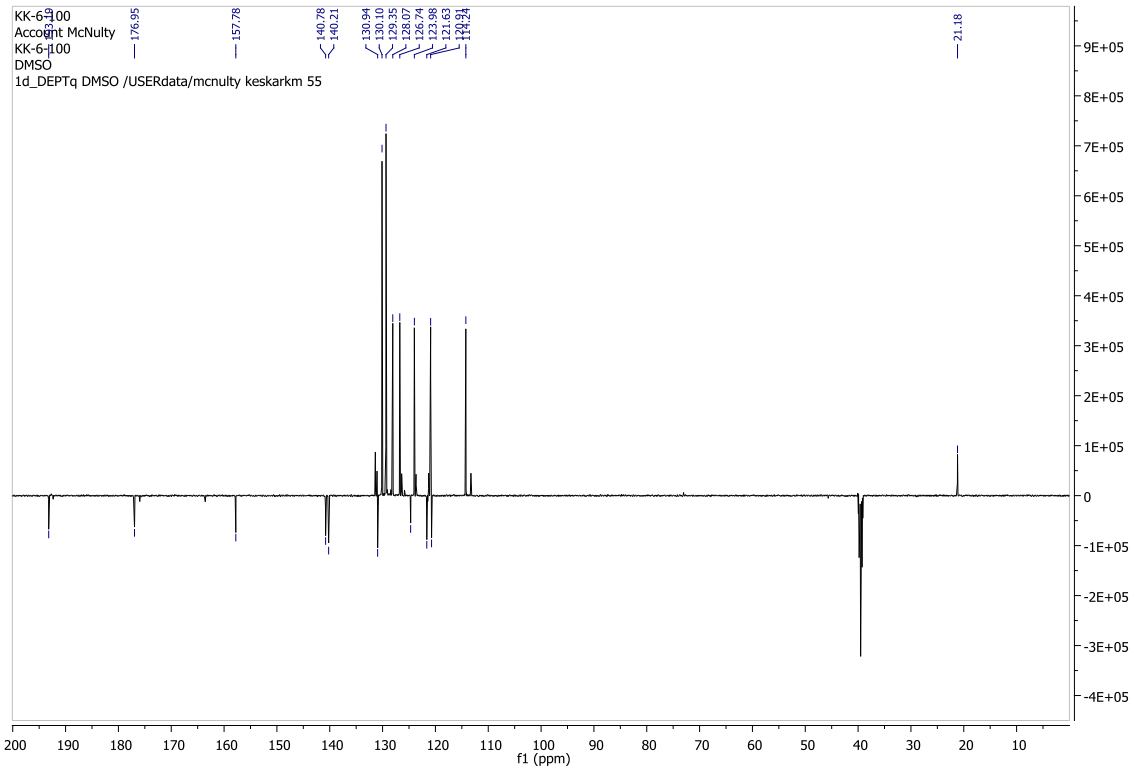
140.80
131.44
128.17
126.56
126.13
124.12
123.94
120.81
120.41
115.01
114.17
55.47
f1 (ppm)

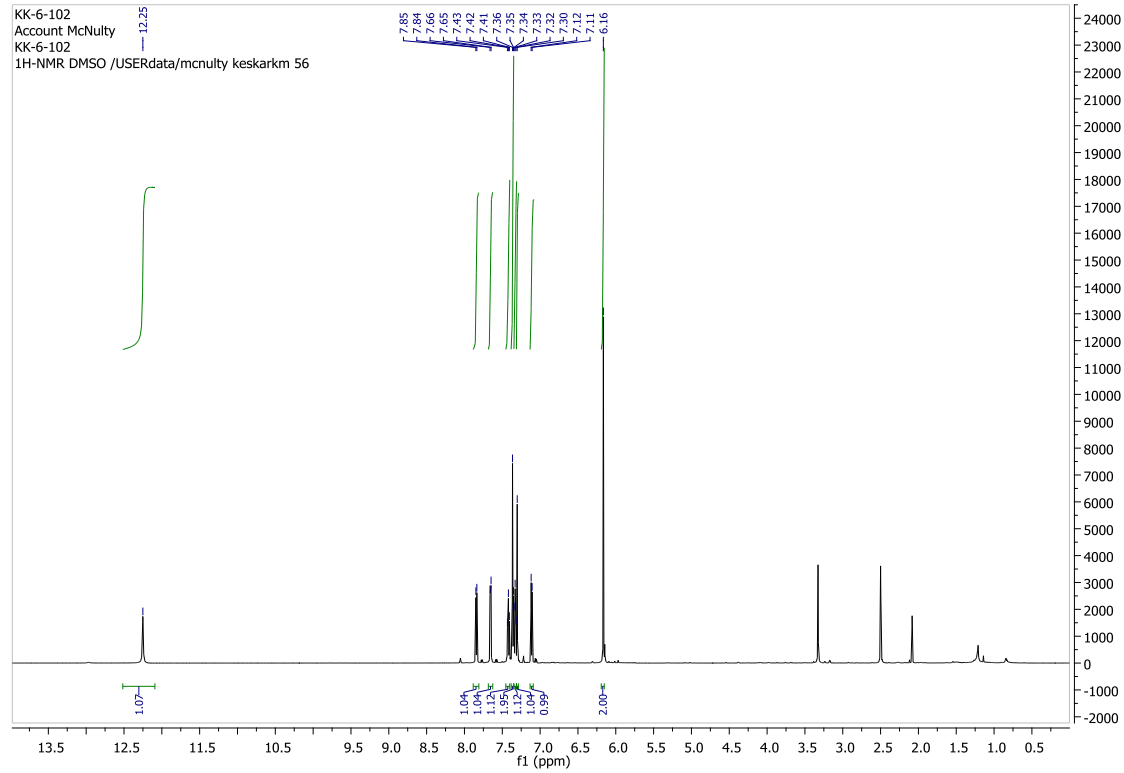
3-(4-methylbenzylidene)cyclopenta[b]indole-1,2(3H,4H)-dione: (20)

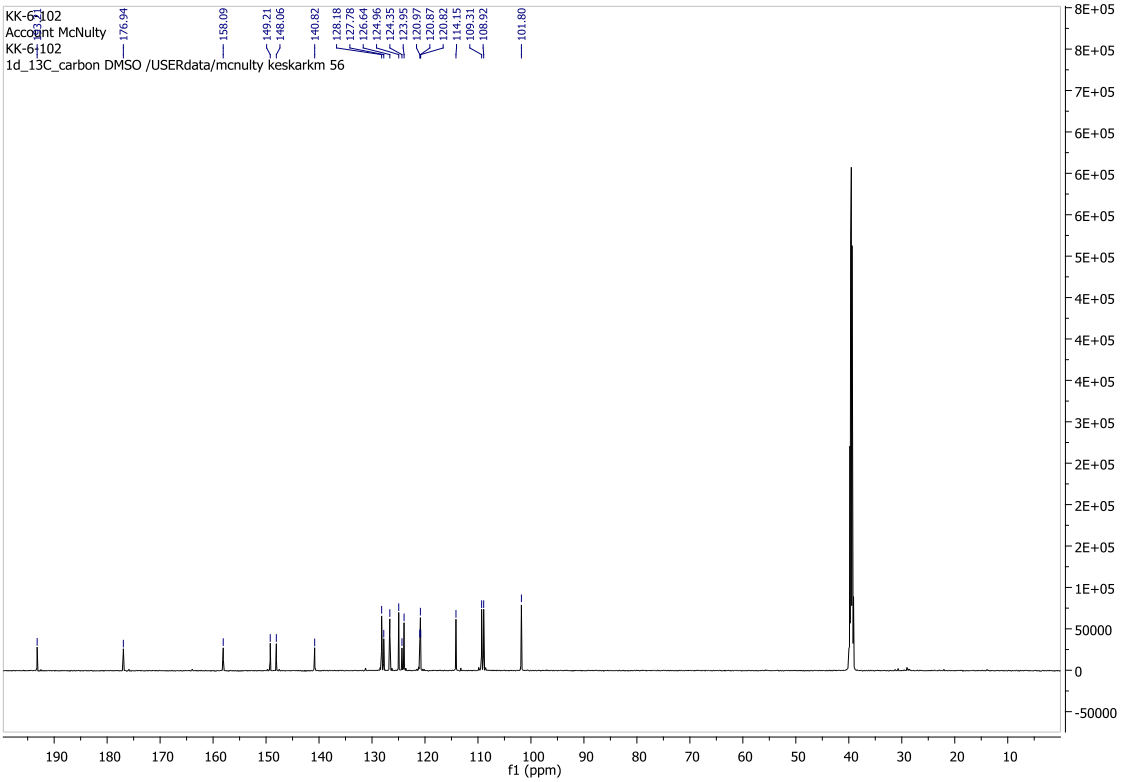






3-(benzo[d][1,3]dioxol-5-ylmethylene)cyclopenta[b]indole-1,2(3H,4H)-dione: (21)

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KK-6-102
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149.21
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140.82
128.18
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124.96
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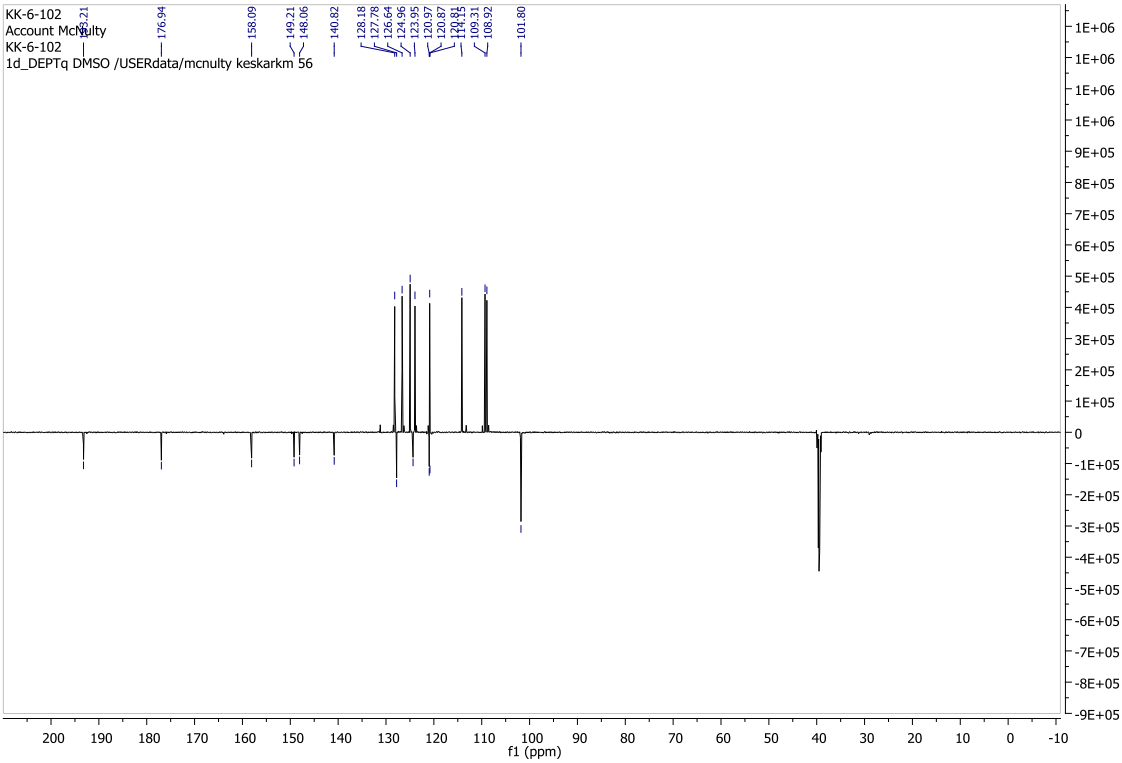
120.97
120.87
120.82
114.15
109.31
108.92
101.80
f1 (ppm)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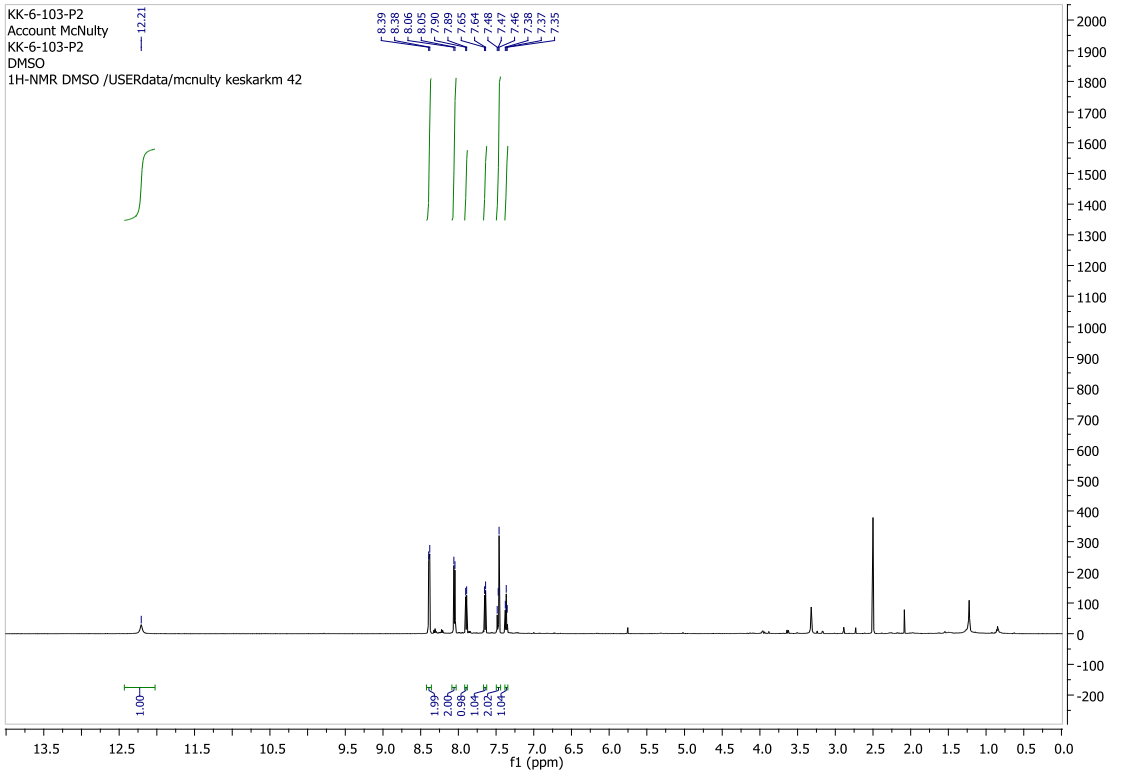
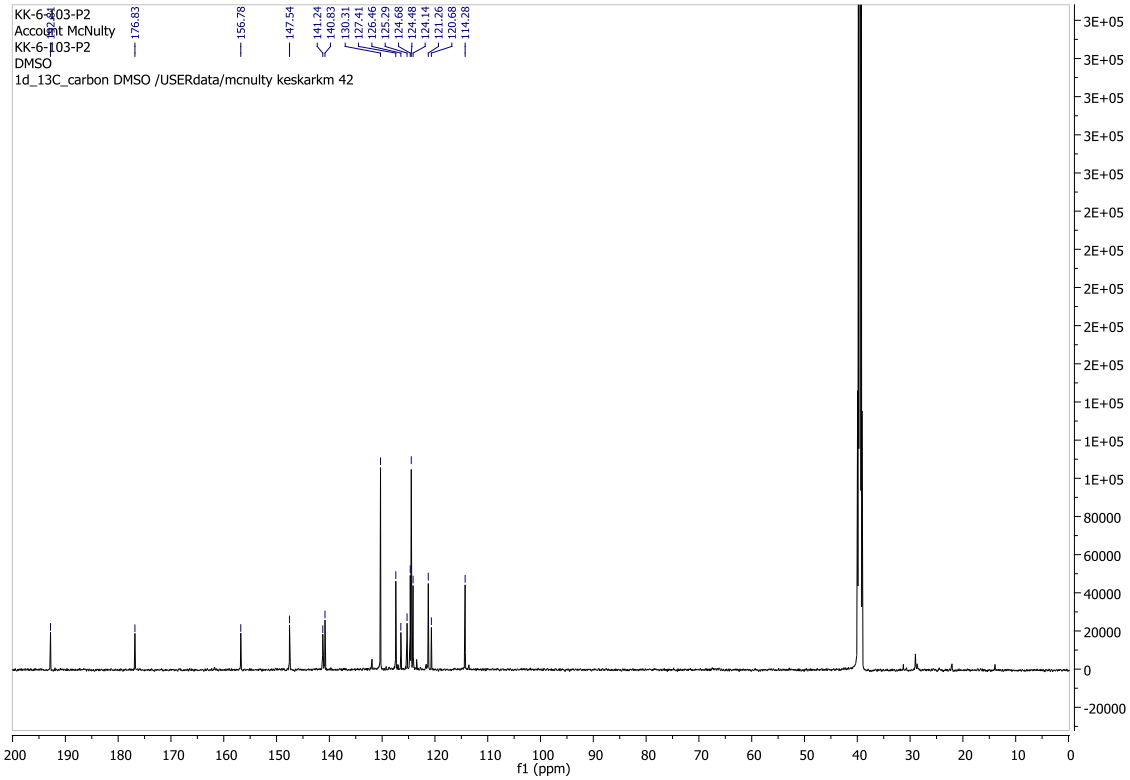
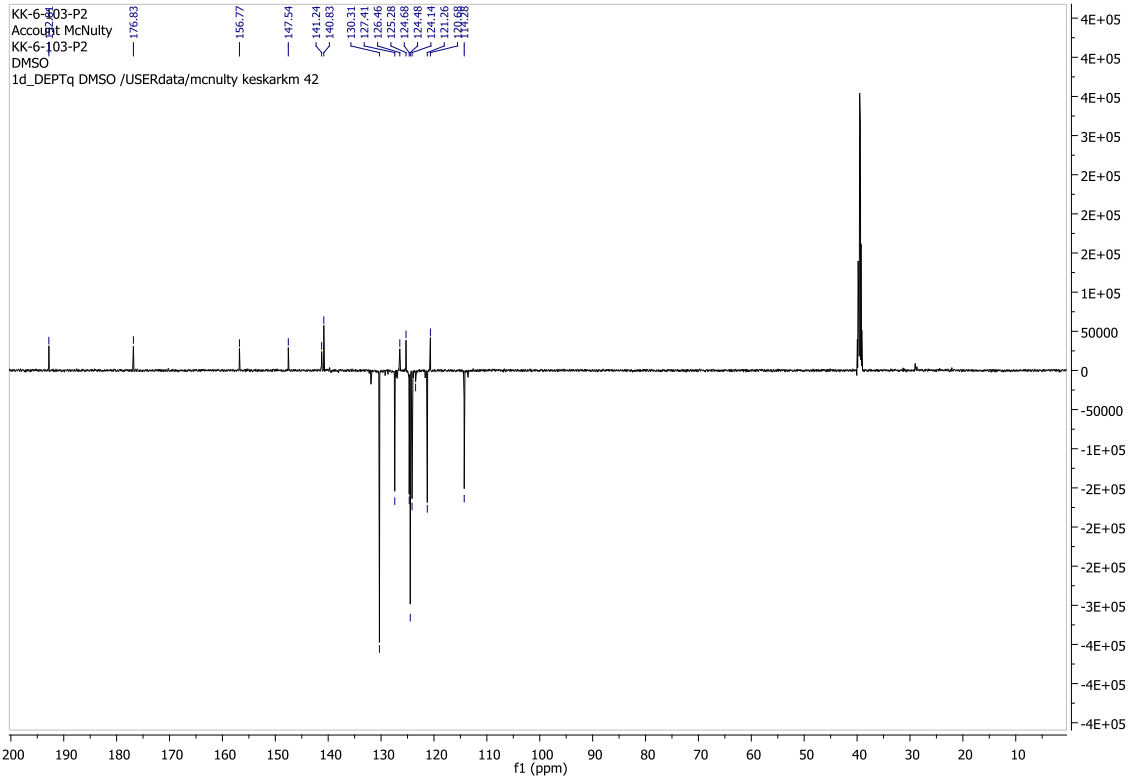
158.09
149.21
148.06
140.82
128.18
127.78
126.64
124.96
123.95
120.97
120.87
120.81
114.15
109.31
108.92
101.80
f1 (ppm)

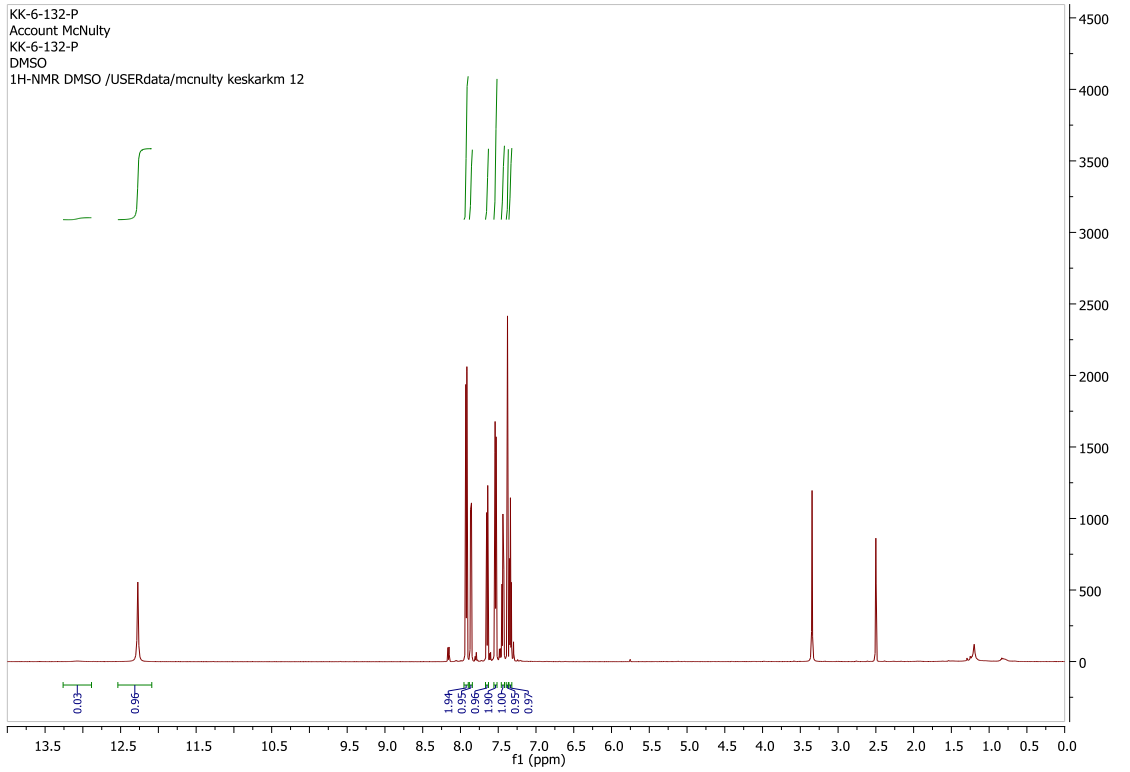
3-(4-nitrobenzylidene)cyclopenta[b]indole-1,2(3H,4H)-dione: (22)



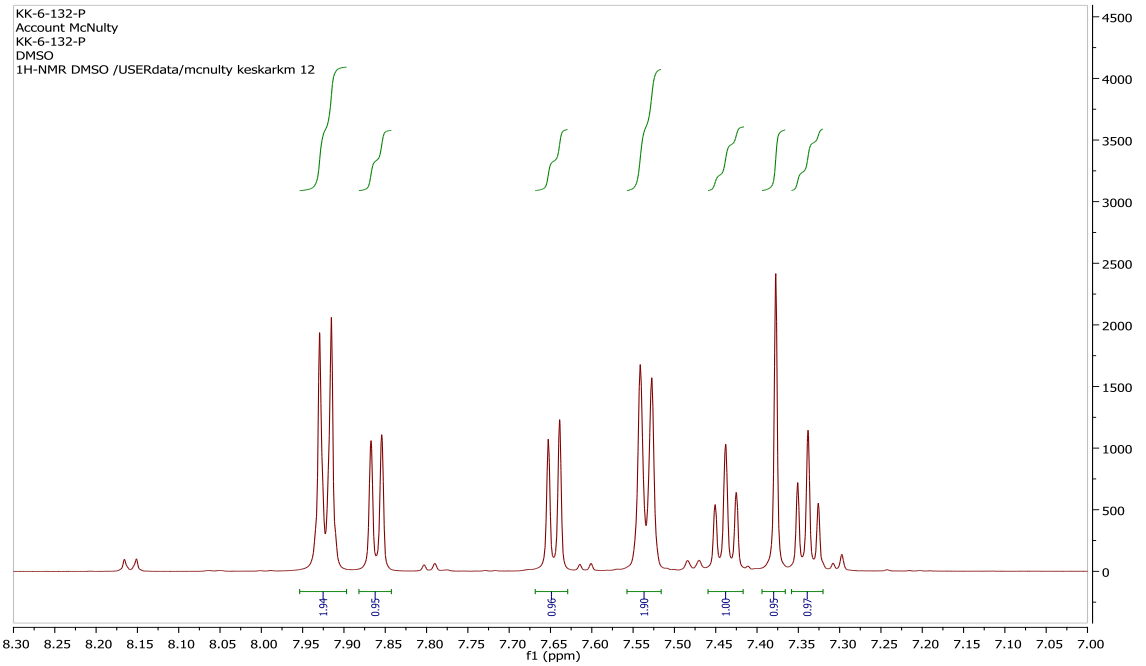


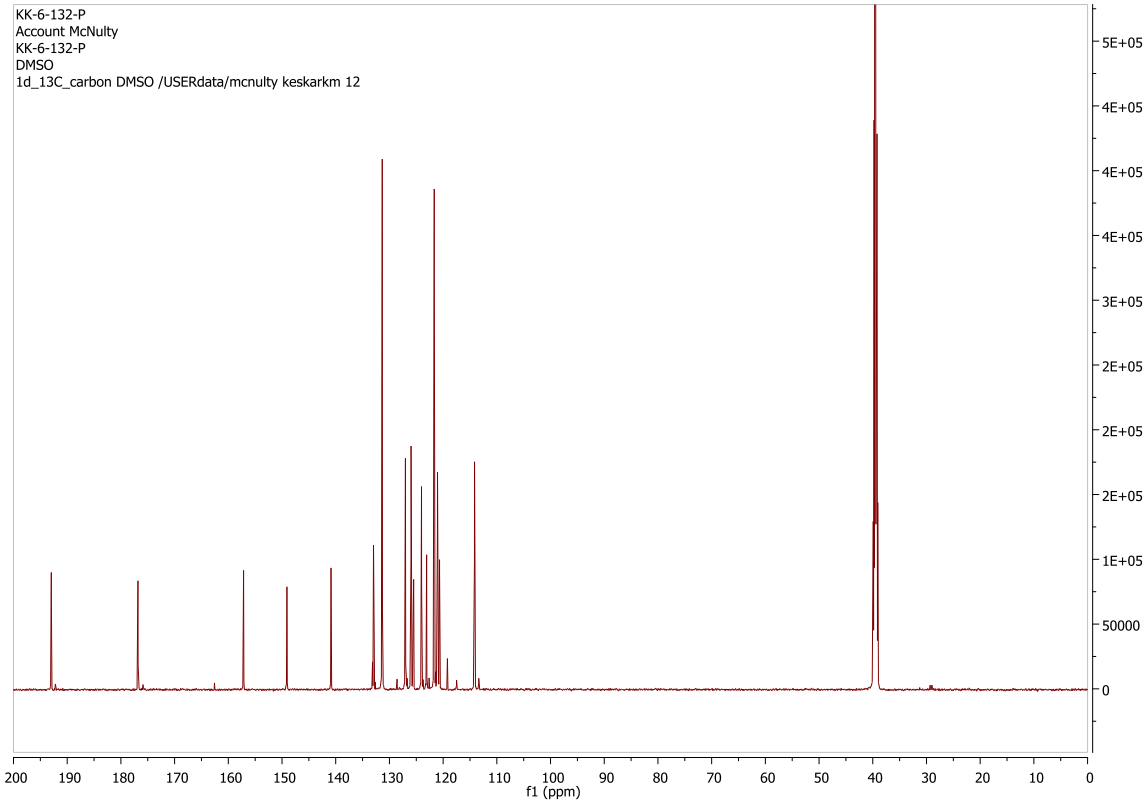


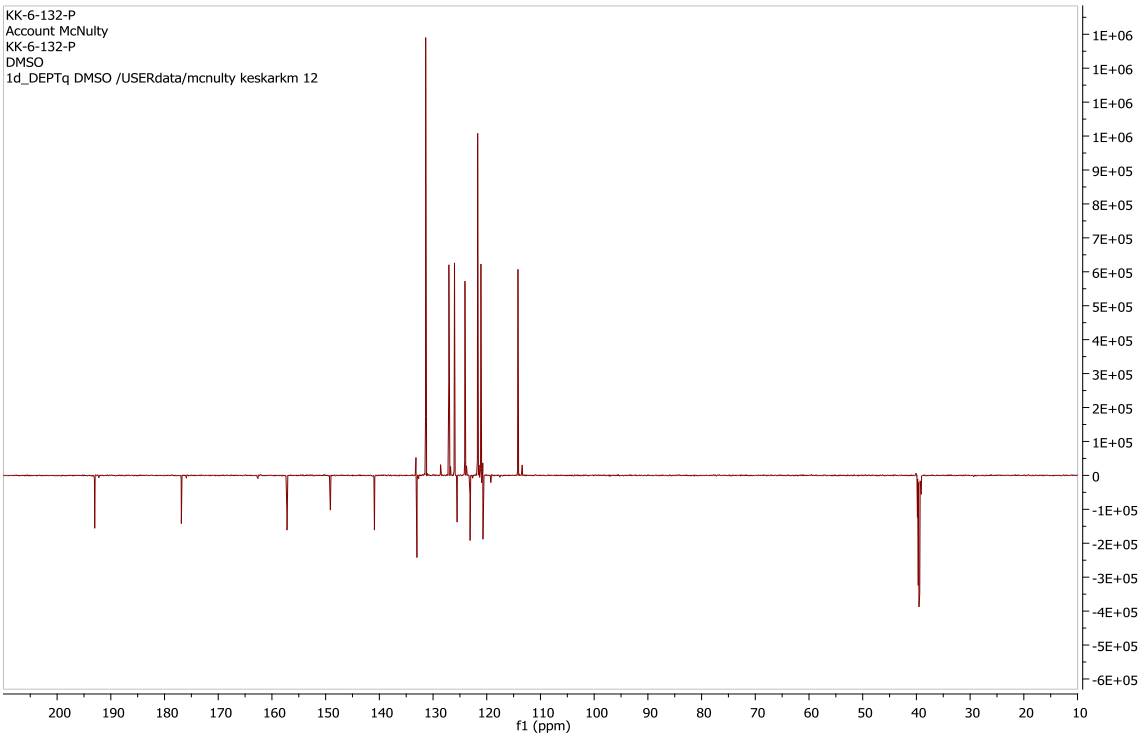
3-(4-(4-(trifluoromethoxy)phenoxy)benzylidene)cyclopenta[b]indole-1,2(3H,4H)-dione (23)



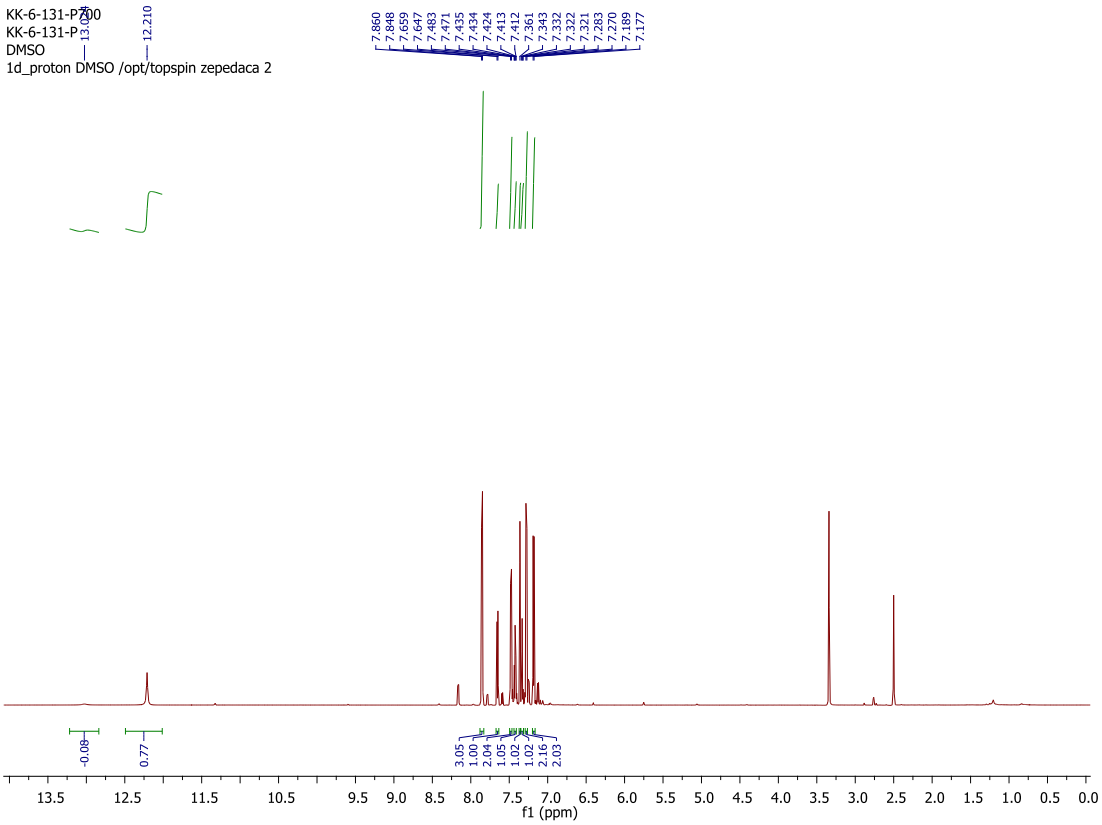
^{1}H NMR (Zoom 8.3 ppm-7.0 ppm)



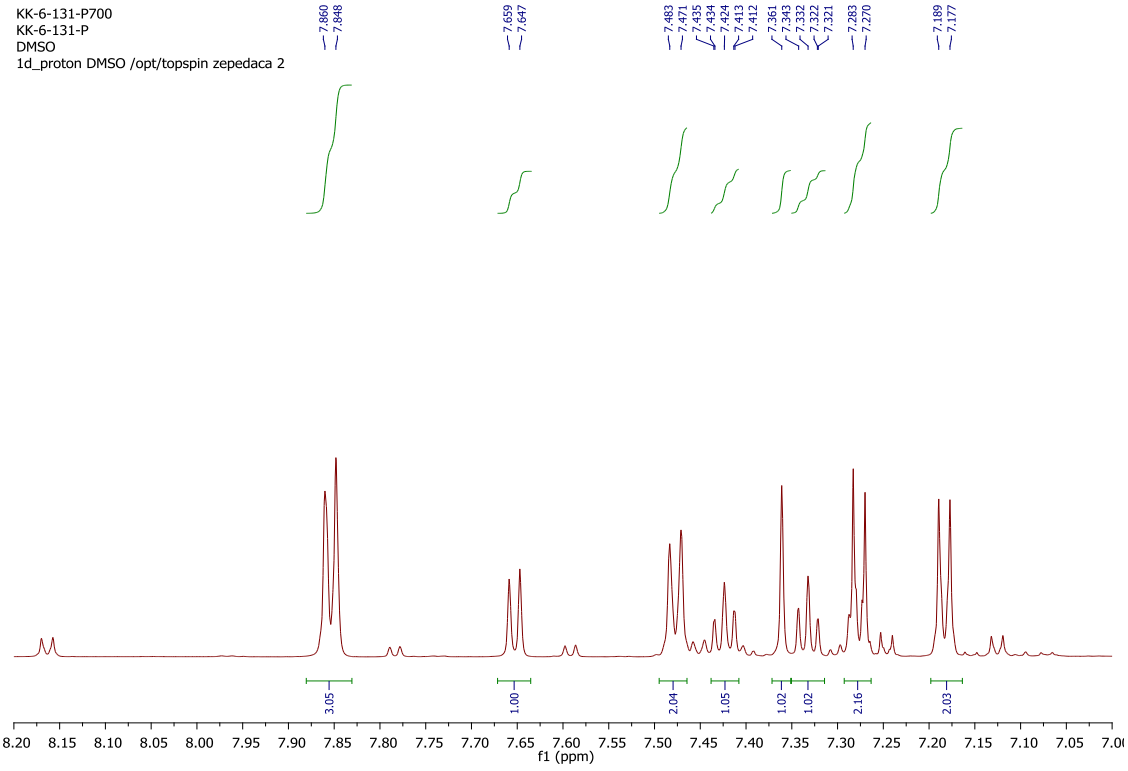


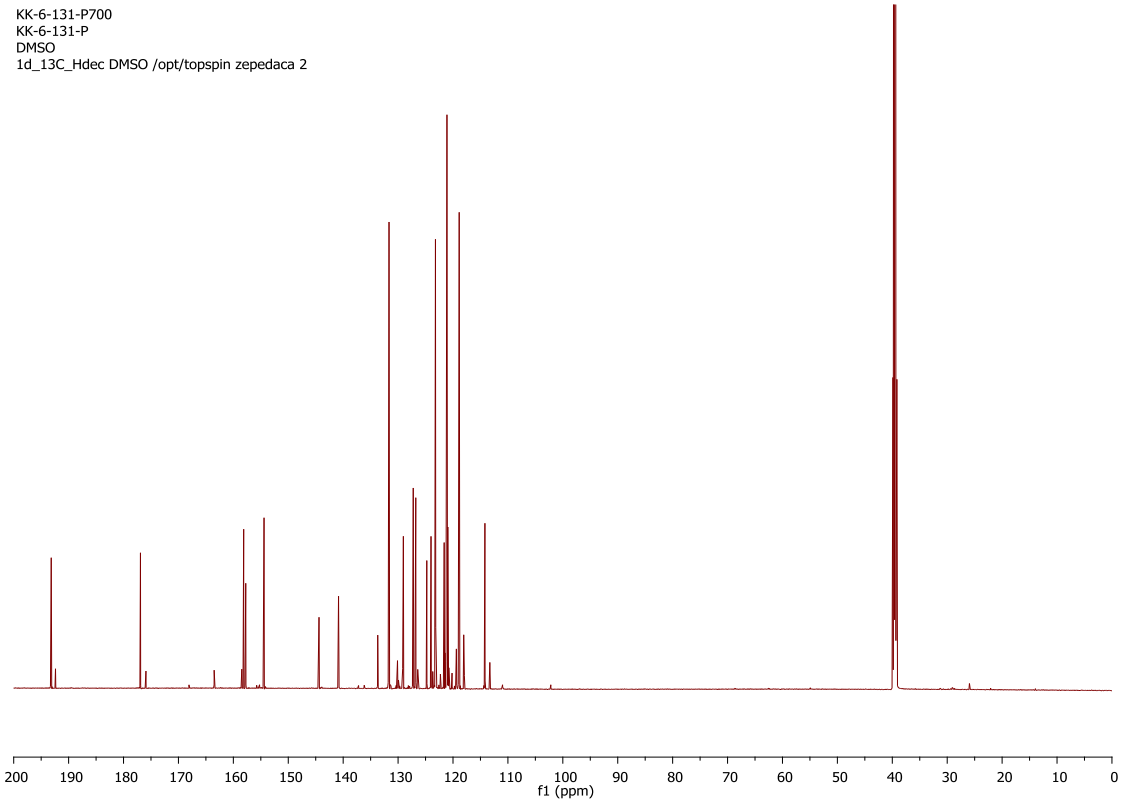


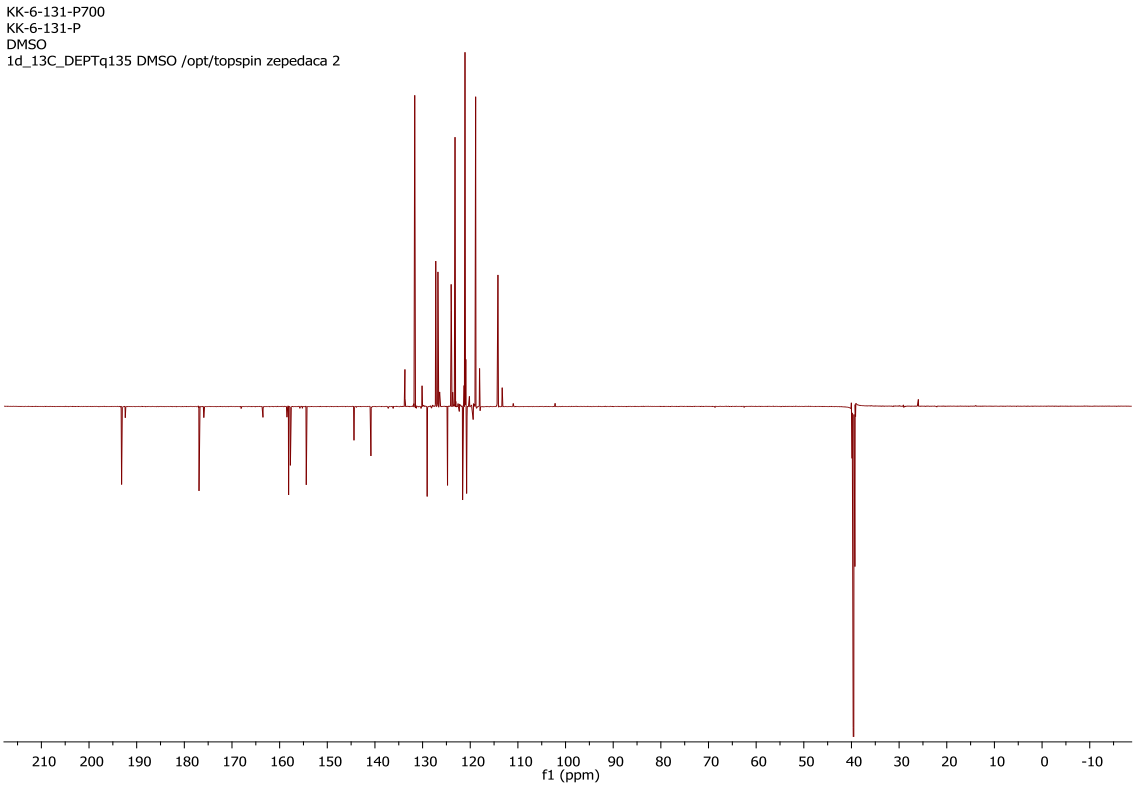
3-(4-(trifluoromethoxy)benzylidene)cyclopenta[b]indole-1,2(3H,4H)-dione (24)



^{1}H NMR (Zoom 8.3 ppm-7.0 ppm)







References:

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2. J. McNulty and K. Keskar, *Eur. J. Org. Chem*., **2014**, 1622.
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5. P. Das, X. Deng, L. Zhang, M. G. Roth, B. M. A. Fontoura, M. A. Philips and J. K. De Brabander, ACS Med. Chem. Lett., **2013**, *4*, 517.

Crystal structure report for sample (19) having molecular formula $C_{19}H_{13}NO_3$ was submitted for X-ray analysis with <u>KK695RE3</u> code

Crystal Structure Report for KK695RE3

A specimen of $C_{19}H_{13}NO_3$, approximate dimensions 0.020 mm x 0.196 mm x 0.470 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured.

The integration of the data using an orthorhombic unit cell yielded a total of 8332 reflections to a maximum θ angle of 25.52° (0.82 Å resolution), of which 2671 were independent (average redundancy 3.119, completeness = 99.3%, R_{int} = 7.37%, R_{sig} = 7.45%) and 1638 (61.33%) were greater than $2\sigma(F^2)$. The final cell constants of a = 13.823(4) Å, b = 7.673(2) Å, c = 27.213(7) Å, volume = 2886.3(13) $Å^3$, are based upon the refinement of the XYZ-centroids of reflections above 20 σ(I). The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.8142 and 1.0000.

The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group P b c a, with Z = 8 for the formula unit, $C_{19}H_{13}NO_3$. The final anisotropic full-matrix least-squares refinement on F^2 with 238 variables converged at R1 = 5.57%, for the observed data and wR2 = 13.16% for all data. The goodness-of-fit was 1.016. The largest peak in the final difference electron density synthesis was 0.189 $e^-/Å^3$ and the largest hole was -0.280 $e^-/Å^3$ with an RMS deviation of 0.052 $e^-/Å^3$. On the basis of the final model, the calculated density was 1.396 g/cm^3 and F(000), 1264 e^-.

Table 1. Sample and crystal data for KK695RE3.

Identification code	KK695RE3	
Chemical formula	$C_{19}H_{13}NO_3$	
Formula weight	303.30 g/mol	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal size	0.020 x 0.196 x 0.470 mm	
Crystal system	orthorhombic	
Space group	P b c a	
Unit cell dimensions	a = 13.823(4) Å	α = 90°
	b = 7.673(2) Å	β = 90°
	c = 27.213(7) Å	γ = 90°
Volume	2886.3(13) $Å^3$	
Z	8	
Density (calculated)	1.396 g/cm^3	
Absorption coefficient	0.095 mm^{-1}	
F(000)	1264	

Table 2. Data collection and structure refinement for KK695RE3.

Theta range for data collection	2.10 to 25.52°
Index ranges	-16<=h<=12, -9<=k<=9, -24<=l<=32
Reflections collected	8332
Independent reflections	2671 [R(int) = 0.0737]
Max. and min. transmission	1.0000 and 0.8142
Structure solution technique	direct methods
Structure solution program	SHELXT (Sheldrick 2014)
Refinement method	Full-matrix least-squares on F^2

Refinement program	SHELXL-2014/6 (Sheldrick, 2014)	
Function minimized	$\Sigma\ w(F_o^2 - F_c^2)^2$	
Data / restraints / parameters	2671 / 0 / 238	
Goodness-of-fit on F^2	1.016	
Final R indices	1638 data; I>2σ(I)	R1 = 0.0557, wR2 = 0.1127
	all data	R1 = 0.1062, wR2 = 0.1316
Weighting scheme	$w=1/[\sigma^2(F_o^2)+(0.0635P)^2+0.0418P]$ where $P=(F_o^2+2F_c^2)/3$	
Largest diff. peak and hole	0.189 and -0.280 eÅ^{-3}	
R.M.S. deviation from mean	0.052 eÅ^{-3}	

Table 3. Atomic coordinates and equivalent isotropic atomic displacement parameters (Å^2) for KK695RE3.

U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x/a	y/b	z/c	U(eq)
O21	0.61862(14)	0.7762(3)	0.74203(7)	0.0424(6)
O23	0.33051(11)	0.1731(2)	0.49002(6)	0.0324(5)
O24	0.39953(12)	0.3758(3)	0.57018(7)	0.0349(5)
N1	0.65901(15)	0.2166(3)	0.46106(8)	0.0260(6)
C2	0.58013(17)	0.2503(3)	0.48805(9)	0.0235(6)
C3	0.49871(17)	0.1796(3)	0.46521(9)	0.0236(6)
C4	0.53000(17)	0.0972(3)	0.42099(9)	0.0238(6)
C5	0.48480(19)	0.0075(4)	0.38281(10)	0.0296(7)
C6	0.5404(2)	0.9444(4)	0.34482(10)	0.0326(7)
C7	0.6410(2)	0.9672(4)	0.34477(10)	0.0353(7)
C8	0.6872(2)	0.0570(4)	0.38178(10)	0.0346(7)
C9	0.63137(18)	0.1220(4)	0.41943(9)	0.0256(6)
C11	0.41641(17)	0.2126(3)	0.49497(9)	0.0256(6)

C12	0.45327(18)	0.3175(3)	0.53934(10)	0.0264(6)
C13	0.56157(17)	0.3389(3)	0.53403(9)	0.0234(6)
C14	0.62726(19)	0.4285(3)	0.56099(9)	0.0253(6)
C15	0.62157(18)	0.5170(3)	0.60762(9)	0.0250(6)
C16	0.5486(2)	0.4938(4)	0.64281(11)	0.0342(7)
C17	0.69637(18)	0.6307(4)	0.61991(10)	0.0267(6)
C18	0.5509(2)	0.5798(4)	0.68677(11)	0.0377(7)
C19	0.69900(19)	0.7202(4)	0.66382(10)	0.0289(7)
C20	0.62524(19)	0.6961(4)	0.69747(9)	0.0303(7)
C22	0.6899(2)	0.9007(4)	0.75424(11)	0.0487(9)

Table 4. Bond lengths (Å) for KK695RE3.

O21-C20	1.362(3)	O21-C22	1.412(3)
O23-C11	1.233(3)	O24-C12	1.207(3)
N1-C2	1.340(3)	N1-C9	1.398(3)
N1-H10	0.89(3)	C2-C3	1.395(3)
C2-C13	1.447(4)	C3-C11	1.419(3)
C3-C4	1.426(4)	C4-C5	1.394(4)
C4-C9	1.415(3)	C5-C6	1.376(4)
C5-H5A	0.96(3)	C6-C7	1.402(4)
C6-H6A	0.98(3)	C7-C8	1.378(4)
C7-H7A	0.98(3)	C8-C9	1.376(4)
C8-H8A	0.98(3)	C11-C12	1.538(4)
C12-C13	1.513(3)	C13-C14	1.354(4)
C14-C15	1.442(4)	C14-H14A	0.99(3)
C15-C17	1.394(4)	C15-C16	1.402(4)
C16-C18	1.366(4)	C16-H3A	0.96(3)
C17-C19	1.378(4)	C17-H17A	0.97(3)
C18-C20	1.392(4)	C18-H18A	1.01(3)
C19-C20	1.383(4)	C19-H19A	0.99(3)
C22-H22C	0.98	C22-H22B	0.98
C22-H22A	0.98		

Table 5. Bond angles (°) for KK695RE3.

C20-O21-C22	117.9(2)	C2-N1-C9	108.8(2)
C2-N1-H10	124.6(17)	C9-N1-H10	126.6(17)
N1-C2-C3	109.7(2)	N1-C2-C13	135.2(2)
C3-C2-C13	115.1(2)	C2-C3-C11	108.8(2)
C2-C3-C4	107.7(2)	C11-C3-C4	143.5(2)
C5-C4-C9	119.2(2)	C5-C4-C3	135.4(2)
C9-C4-C3	105.4(2)	C6-C5-C4	118.9(2)
C6-C5-H5A	123.1(16)	C4-C5-H5A	118.0(16)
C5-C6-C7	120.7(3)	C5-C6-H6A	121.3(16)
C7-C6-H6A	117.9(16)	C8-C7-C6	121.5(3)
C8-C7-H7A	121.0(16)	C6-C7-H7A	117.5(16)
C9-C8-C7	117.7(3)	C9-C8-H8A	120.7(16)
C7-C8-H8A	121.6(16)	C8-C9-N1	129.6(2)
C8-C9-C4	121.9(2)	N1-C9-C4	108.4(2)
O23-C11-C3	131.7(2)	O23-C11-C12	122.3(2)
C3-C11-C12	106.0(2)	O24-C12-C13	129.4(2)
O24-C12-C11	122.4(2)	C13-C12-C11	108.0(2)
C14-C13-C2	126.0(2)	C14-C13-C12	131.8(2)
C2-C13-C12	101.9(2)	C13-C14-C15	132.8(2)
C13-C14-H14A	113.8(15)	C15-C14-H14A	113.4(15)
C17-C15-C16	116.7(2)	C17-C15-C14	117.8(2)
C16-C15-C14	125.5(2)	C18-C16-C15	121.3(3)
C18-C16-H3A	121.2(17)	C15-C16-H3A	117.4(17)
C19-C17-C15	122.6(3)	C19-C17-H17A	122.9(16)
C15-C17-H17A	114.4(16)	C16-C18-C20	120.7(3)
C16-C18-H18A	120.3(16)	C20-C18-H18A	118.8(16)
C17-C19-C20	119.2(3)	C17-C19-H19A	121.6(15)
C20-C19-H19A	119.2(15)	O21-C20-C19	125.4(2)
O21-C20-C18	115.2(2)	C19-C20-C18	119.4(3)
O21-C22-H22C	109.5	O21-C22-H22B	109.5

H22C-C22-H22B	109.5	O21-C22-H22A	109.5
H22C-C22-H22A	109.5	H22B-C22-H22A	109.5

Table 6. Torsion angles (°) for KK695RE3.

C9-N1-C2-C3	0.0(3)	C9-N1-C2-C13	179.3(3)
N1-C2-C3-C11	178.5(2)	C13-C2-C3-C11	-1.0(3)
N1-C2-C3-C4	-0.2(3)	C13-C2-C3-C4	-179.7(2)
C2-C3-C4-C5	-179.1(3)	C11-C3-C4-C5	3.0(6)
C2-C3-C4-C9	0.3(3)	C11-C3-C4-C9	-177.6(3)
C9-C4-C5-C6	0.5(4)	C3-C4-C5-C6	179.9(3)
C4-C5-C6-C7	1.0(4)	C5-C6-C7-C8	-1.8(5)
C6-C7-C8-C9	0.9(5)	C7-C8-C9-N1	179.9(3)
C7-C8-C9-C4	0.7(4)	C2-N1-C9-C8	-179.1(3)
C2-N1-C9-C4	0.2(3)	C5-C4-C9-C8	-1.4(4)
C3-C4-C9-C8	179.0(3)	C5-C4-C9-N1	179.2(2)
C3-C4-C9-N1	-0.3(3)	C2-C3-C11-O23	-178.9(3)
C4-C3-C11-O23	-1.0(6)	C2-C3-C11-C12	1.4(3)
C4-C3-C11-C12	179.3(3)	O23-C11-C12-O24	-4.5(4)
C3-C11-C12-O24	175.2(2)	O23-C11-C12-C13	178.9(2)
C3-C11-C12-C13	-1.4(3)	N1-C2-C13-C14	5.9(5)
C3-C2-C13-C14	-174.8(2)	N1-C2-C13-C12	-179.2(3)
C3-C2-C13-C12	0.1(3)	O24-C12-C13-C14	-1.0(5)
C11-C12-C13-C14	175.3(3)	O24-C12-C13-C2	-175.5(3)
C11-C12-C13-C2	0.8(3)	C2-C13-C14-C15	-177.3(3)
C12-C13-C14-C15	9.4(5)	C13-C14-C15-C17	-165.4(3)
C13-C14-C15-C16	17.1(5)	C17-C15-C16-C18	0.4(4)
C14-C15-C16-C18	177.9(3)	C16-C15-C17-C19	-1.3(4)
C14-C15-C17-C19	-179.0(2)	C15-C16-C18-C20	1.3(5)
C15-C17-C19-C20	0.5(4)	C22-O21-C20-C19	3.4(4)
C22-O21-C20-C18	-177.6(3)	C17-C19-C20-O21	-179.8(3)
C17-C19-C20-C18	1.2(4)	C16-C18-C20-O21	178.8(3)
C16-C18-C20-C19	-2.1(5)		

Table 7. Anisotropic atomic displacement parameters (Å^2) for KK695RE3.

The anisotropic atomic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U_{11} + ... + 2 h k a^* b^* U_{12}]$

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O21	0.0404(12)	0.0582(14)	0.0285(11)	-0.0063(10)	0.0017(9)	-0.0160(11)
O23	0.0116(9)	0.0470(13)	0.0385(11)	-0.0006(10)	-0.0016(8)	-0.0024(9)
O24	0.0174(10)	0.0500(13)	0.0372(11)	-0.0052(10)	0.0046(8)	0.0030(9)
N1	0.0124(10)	0.0365(14)	0.0292(13)	-0.0025(11)	0.0006(9)	-0.0025(10)
C2	0.0137(12)	0.0265(14)	0.0302(15)	0.0031(12)	0.0005(11)	0.0019(12)
C3	0.0169(12)	0.0254(14)	0.0286(15)	0.0001(12)	-0.0004(11)	0.0015(12)
C4	0.0162(13)	0.0268(15)	0.0286(15)	0.0033(12)	-0.0028(11)	0.0000(11)
C5	0.0202(14)	0.0365(16)	0.0322(17)	0.0063(14)	-0.0037(13)	-0.0027(13)
C6	0.0300(16)	0.0390(18)	0.0288(16)	-0.0030(14)	-0.0012(13)	-0.0047(14)
C7	0.0300(16)	0.0460(19)	0.0299(16)	-0.0061(15)	0.0049(13)	-0.0041(15)
C8	0.0233(15)	0.0458(19)	0.0347(17)	-0.0048(15)	0.0040(13)	-0.0060(14)
C9	0.0192(13)	0.0315(16)	0.0263(15)	0.0000(13)	-0.0008(11)	-0.0020(12)
C11	0.0174(13)	0.0291(16)	0.0302(15)	0.0050(12)	-0.0027(12)	0.0004(12)
C12	0.0171(12)	0.0305(16)	0.0318(16)	0.0061(13)	0.0007(12)	0.0017(12)
C13	0.0154(13)	0.0287(15)	0.0262(15)	0.0020(13)	0.0006(11)	0.0013(11)
C14	0.0159(12)	0.0267(15)	0.0334(16)	0.0023(13)	0.0003(12)	-0.0002(12)
C15	0.0183(13)	0.0290(15)	0.0279(15)	0.0045(13)	-0.0032(11)	0.0034(12)
C16	0.0252(15)	0.0443(18)	0.0330(17)	-0.0014(15)	-0.0011(13)	-0.0121(14)
C17	0.0165(13)	0.0349(16)	0.0288(16)	0.0021(13)	-0.0004(12)	0.0007(12)
C18	0.0282(15)	0.054(2)	0.0306(16)	0.0003(16)	0.0037(13)	-0.0141(15)
C19	0.0207(13)	0.0349(17)	0.0312(15)	0.0018(13)	-0.0028(12)	-0.0046(13)
C20	0.0287(14)	0.0376(17)	0.0247(15)	0.0013(13)	-0.0035(12)	-0.0025(13)
C22	0.0445(19)	0.057(2)	0.0447(19)	-0.0138(17)	-0.0018(15)	-0.0166(18)

Table 8. Hydrogen atomic coordinates and isotropic atomic displacement parameters ($Å^2$) for KK695RE3.

	x/a	y/b	z/c	U(eq)
H10	0.7190(19)	0.248(4)	0.4692(9)	0.031
H5A	0.416(2)	-0.010(3)	0.3848(9)	0.036
H6A	0.5114(19)	-0.122(4)	0.3176(10)	0.039
H7A	0.677(2)	-0.078(4)	0.3165(10)	0.042
H8A	0.757(2)	0.077(4)	0.3812(9)	0.042
H14A	0.6915(19)	0.439(3)	0.5449(9)	0.03
H3A	0.497(2)	0.416(4)	0.6347(10)	0.041
H17A	0.747(2)	0.641(4)	0.5951(10)	0.032
H18A	0.503(2)	0.550(4)	0.7134(11)	0.045
H19A	0.752(2)	0.804(3)	0.6714(9)	0.035
H22C	0.6767	0.9478	0.7870	0.073
H22B	0.7538	0.8452	0.7541	0.073
H22A	0.6888	0.9955	0.7301	0.073

Table 9. Hydrogen bond distances (Å) and angles (°) for KK695RE3.

	Donor-H	Acceptor-H	Donor-Acceptor	Angle
N1-H10···O23	0.89(3)	1.99(3)	2.848(3)	160.(2)
C8-H8A···O24	0.98(3)	2.40(3)	3.254(3)	146.(2)