Supporting Information

In vitro antischistosomal activity of 2-aroyl-benzofuran derivatives against *Schistosoma mansoni*

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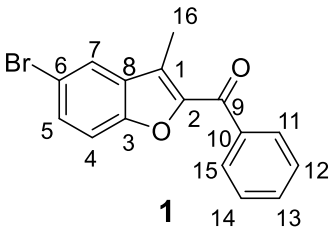
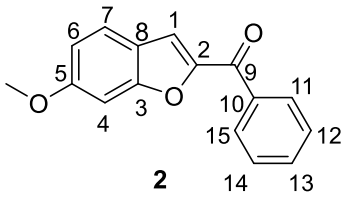
Experimental

^{1}H and ^{13}C NMR experiments were performed on a Bruker Avance DRX400 spectrometer (Karlsruhe, Germany, 400.13 MHz for 1H and 100.61 MHz for ^{13}C). A direct 5-mm probe head (BBO) was used for $^{13}C\{^{1}H\}$ NMR experiments and an inverse 5-mm probe head (BBI) was used for other experiments. Experiments were performed at 300 K and the concentrations for all samples were in the range of 10-15 mg mL^{-1}, in $CDCl_3$ using tetramethylsilane (TMS) as an internal reference.

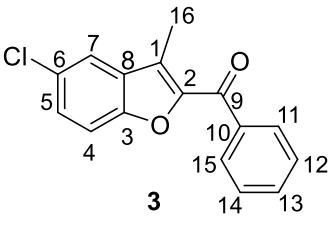
Mass spectra were recorded on triple quadrupole MS equipment (QqQ) Xevo TQS (Waters, Milford, MA, USA) equipped with Z-spray operating in the positive ion mode and Acquiti-H class UPLC system. The sample was dissolved in methanol/water (9:1, v/v) at a concentration of 0.5 mg mL^{-1} and infused directly into the ESI source by using a Harvard Apparatus system (model 1746, Houston, MA, USA) at a flow rate of 5 µL min^{-1}. The capillary voltage was 3.20 kV, and the gas flow was 700 L/h (0.15 V). The desolvation temperature was set at 250°C.



(5-bromo-3-methyl-2-benzofuranyl)-phenyl-methanone (1). Yellow powder, 55% yield, mp. 102-104°C. IR (KBr pellet, **Fig. S1**), ν_{max}/ cm^{-1}: 3088 (C_{sp2}–H), 1644 (C=O), 1879 (C=C), 1271 (C–O), 714 (C-Br). ^{1}H NMR (400 MHz, $CDCl_3$, **Fig. S2**): δ_H 2.60 (3 H, *s*, H16), 7.42 (1 H, *d*, *J* = 8.5 Hz, H5), 7.53 (2 H, *m*, H12=H14), 7.58 (1 H, *m*, H13), 7.63 (1 H, *s*, H7), 7.82 (1 H, *d*, *J* = 8.5 Hz, H4), 8.06 (2 H, *d*, *J* = 7.5 Hz, H11=H15). ^{13}C NMR (100 MHz, $CDCl_3$, **Fig. S3**): δ_C 9.9 (C16), 113, 7 (C5), 116.4 (C6), 124.0 (C4), 125.8 (C1), 128.3 (C12=C14), 129.7 (C11=C15), 131.0 (C8), 131.1 (C13), 132.8 (C7), 137.6 (C3), 149.1 (C10), 153.8 (C2), 185.7 (C9). ESI(+)-MS/MS of *m/z* 315 ($C_{16}H_{12}BrO_2^+$), E_{lab} = 10 eV (**Fig. S4**): 315 (19%, $[M+H]^+$), 237 (100%, $[M+H-C_6H_6]^+$), 209 (2%, $[M+H-C_6H_6-CO]^+$), 193 (2%, $[M+H-C_6H_6-CO_2]^+$), 181 (8%, $[M+H-C_6H_6-2CO]^+$), 105 (19%, $C_6H_5CO^+$), 102 (11%, $[M+H-C_6H_6-2CO-Br]^{\bullet+}$), 77 (6%, $C_6H_5^+$).

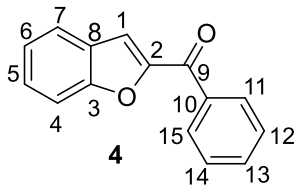


(6-methoxy-2-benzofuranyl)phenyl-methanone (2). Dark yellow powder. 66% yield, mp. 67-69 °C. IR (KBr pellet, **Fig. S5**), ν_{max}/ cm^{-1}: 3014 (C_{sp2}–H), 1649 (C=O), 1524 (C=C), 1273 (C–O), 1200 (C–O). ^{1}H NMR (400 MHz, $CDCl_3$, **Fig. S6**): δ_H 3.83 (3H, s, H16), 6.96 (1H, *d*, *J* = 7.7 Hz, H6), 7.22 (1H, *sl* , H4), 7.29 (1 H, *m*, H1), 7.52 (2H, *m,* H12=H14), 7.55 (1H, *m,* H13), 7.61 (1H, *d*, *J* = 7.7 Hz, H7), 8.07 (2H, *m,* H11=H15). ^{13}C NMR (100 MHz, $CDCl_3$, **Fig. S7**): δ 56.0, (C16), 109.6 (C4), 109.8 (C6), 115.0 (C8), 116.2 (C1), 124.6 (C7), 128.5 (C12=C14), 129.6 (C11=C15), 132.8 (C13), 137.2 (C10), 145.8 (C2), 146.2 (C5), 152.7 (C3), 183.9 (C9). ESI(+)-MS/MS of *m/z* 253 ($C_{16}H_{13}O_3^+$), E_{lab} = 10 eV (**Fig. S8**): 253 ($[M+H]^+$, 23%), 175 (100%, $[M+H-C_6H_6]^+$), 160 (1%, $[M+H-C_6H_6-CH_3]^{\bullet+}$), 147 (4%, $[M+H-C_6H_6-CO]^+$), 131 (2%, $[M+H-C_6H_6-CO_2]^+$), 119 (43%, $[M+H-C_6H_6-2CO]^+$), 105 (98%, $C_6H_5CO^+$), 89 (19%, $[M+H-C_6H_6-2CO-CH_2O]^+$), 77 (30%, $C_6H_5^+$).



(5-chloro-3-methyl-2-benzofuranyl)phenyl-methanone (3). Pale yellow powder, 59% yield, mp. 105-107°C, IR (KBr pellet, **Fig. S9**): ν_{max}/ cm^{-1}: 3435 (O–H), 3088 (C_{sp2}–H), 1642 (C=O), 1561 (C=C), 1273 (C–O), 1170 (C–O). ^{1}H NMR (400 MHz, $CDCl_3$, **Fig. S10**): δ_H 2.62 (3H, s, H16), 7.47 (2H, *m*, H12=H14), 7.54 (2H, *m*, H14), 7.62 (1H, *d*, *J* = 7.4 Hz, H7), 7.68 (1H, *d*, *J* = 8.5 Hz, H4), 8.08 (2H, *d,* *J* = 7.6 Hz, H11=H15). ^{13}C NMR (100 MHz, $CDCl_3$, **Fig. S11**): δ_C 9.5 (C16), 113.0 (C4), 120.5 (C7), 125.6 (C5), 128.1 (C1), 128.3

(C6), 128.8 (C12=C14), 129.4 (C11=C15), 130.2 (C13), 132.5 (C8), 137.2 (C10), 149.0 (C2), 152.2 (C3), 185.4 (C9). ESI(+)-MS/MS of *m/z* 271 ($C_{16}H_{13}ClO_2^+$), E_{lab} = 10 eV (**Fig. S12**): 271 (11%, $[M+H]^+$), 193 (100%, $[M+H-C_6H_6]^+$), 165 (4%, $[M+H-C_6H_6-CO]^+$), 149 (5%, $[M+H-C_6H_6-CO_2]^+$), 137 (13%, $[M+H-C_6H_6-2CO]^+$), 105 (25%, $C_6H_5CO^+$), 102 (11%, $[M+H-C_6H_6-2CO-Cl]^{\bullet+}$), 77 (6%, $C_6H_5^+$).



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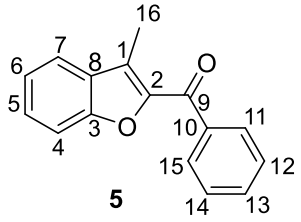
2-benzofuranylphenyl-methanone (4). Dark yellow powder, 70% yield, mp. 90-92°C; IR (KBr pellet, **Fig. S13**), ν_{max}/ cm^{-1}: 3144 (C_{sp2}–H), 1642 (C=O), 1546 (C=C), 1297 (C–O), 1188 (C–O). 1H NMR (400 MHz, $CDCl_3$, **Fig. S14**): δ_H 7.33 (1H, *m,* H6), 7.49-7.55 (4 H, *m*, H5, H6, H7, H8), 7,64 (2 H, *m,* H12=H14), 7.73 (1 H, *m*, H13), 8.05 (2 H, *d, J* = 7.3 Hz, H11=H15). ^{13}C (100 MHz, $CDCl_3$, **Fig. S15**): δ_C 112.5 (C4), 123.2 (C7), 123.9 (C6), 127.0 (C5), 128.3 (C8), 128.5 (C12=C14), 129.4 (C11=15), 131.1 (C1), 132.8 (C13), 137.2 (C10), 152.2 (C2), 156.0 (C3), 184.3 (C9). ESI(+)-MS/MS of *m/z* 223 ($C_{15}H_{11}O_2^+$), E_{lab} = 10 eV (**Fig. S16**): 223 (8%, $[M+H]^+$), 145 (100%, $[M+H-C_6H_6]^+$), 117 (2%, $[M+H-C_6H_6-CO]^+$), 105 (62%, $C_6H_5CO^+$), 101 (2%, $[M+H-C_6H_6-CO_2]^+$), 89 (28%, $[M+H-C_6H_6-2CO]^+$), 77 (21%, $C_6H_5^+$).



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(3-methyl-2-benzofuranyl)phenyl-methanone (5). Orange powder, 52% yield, mp. 80-82°C; IR (KBr pellet, **Fig. S17**), ν_{max}/ cm^{-1}: 3062 (C_{sp2}–H), 1642 (C=O), 1563 (C=C), 1291 (C–O), 1264 (C–O). ^1H NMR (400 MHz, $CDCl_3$ **Fig. S18**): δ_H 2.66 (3 H, s, H16), 7.34 (1H, *m*, H6), 7.50 (1H, *m*, H5), 7.55 (2H, *m,* H12=H14), 7.62 (1H, *d, J* = 7.9 Hz, H4), 7.70 (1 H, *d*, *J* = 7.8 Hz, H7), 8.11 (2H, *d, J* = 7.0 Hz, H11=H15). ^{13}C NMR (100 MHz, $CDCl_3$, **Fig. S19**): δ_C 10.2 (C16), 112.4 (C4), 121.6 (C7), 123.5 (C5), 128.4 (C6), 129.0 (C1), 129.6 (C8), 130.6 (C12=14), 132.4 (C13), 136.3 (C11=C15), 137.7 (C10), 148.2 (C2), 154.1 (C3), 185.7 (C9). ESI(+)-MS/MS of *m/z* 237 ($C_{16}H_{13}O_2^+$), E_{lab} = 10 eV (**Fig. S20**): 237 (8%, $[M+H]^+$), 159 (100%, $[M+H-C_6H_6]^+$), 131 (6%, $[M+H-C_6H_6-CO]^+$), 115 (4%, $[M+H-C_6H_6-CO_2]^+$), 105 (29%, $C_6H_5CO^+$), 103 (21%, $[M+H-C_6H_6-2CO]^+$), 77 (12%, $C_6H_5^+$).

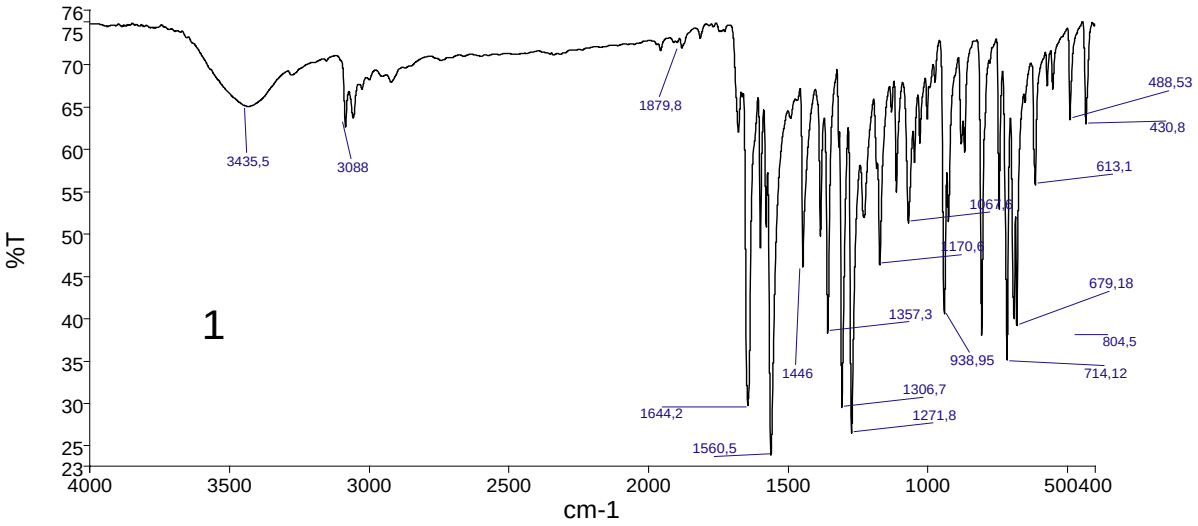

Figure S1. Infrared spectrum of compound **1** (KBr pellet).

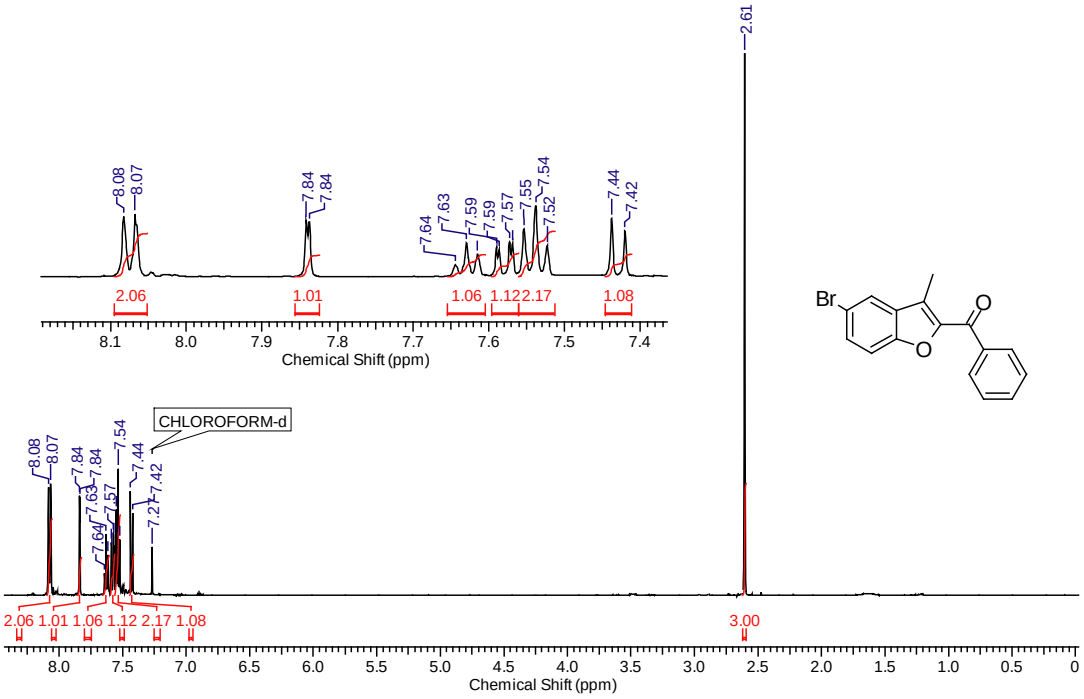

Figure S2 ^{1}H NMR spectrum of compound **1** (400 MHz, $CDCl_3$).

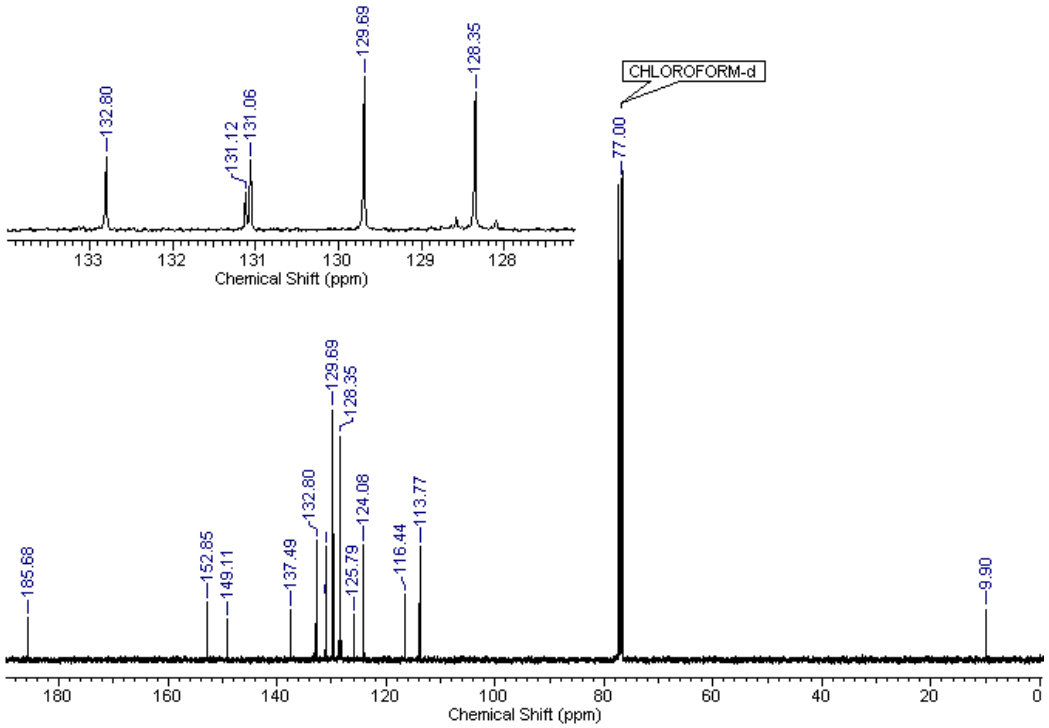

Figure S3. ^{13}C NMR spectrum of compound **1** (100 MHz, $CDCl_3$).

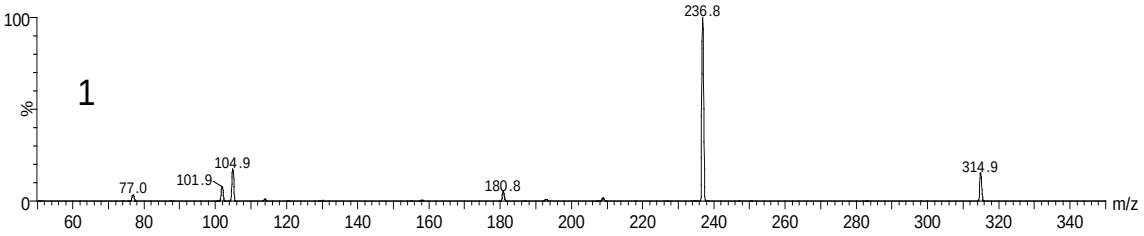

Figure S4. ESI(+)-MS/MS spectrum of protonated compound **1** (*m/z* 315) (QqQ, E_{lab} = 10 eV)

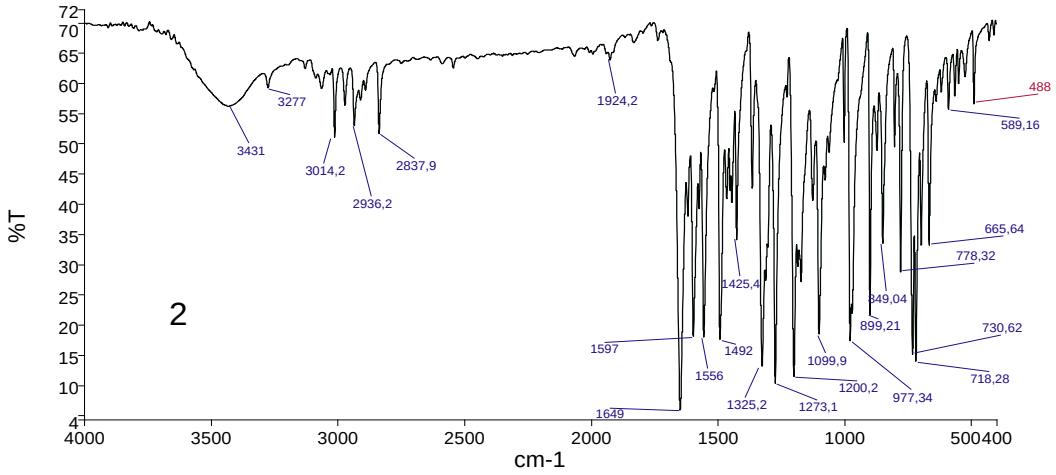

Figure S5. Infrared spectrum of compound **2** (KBr pellet)

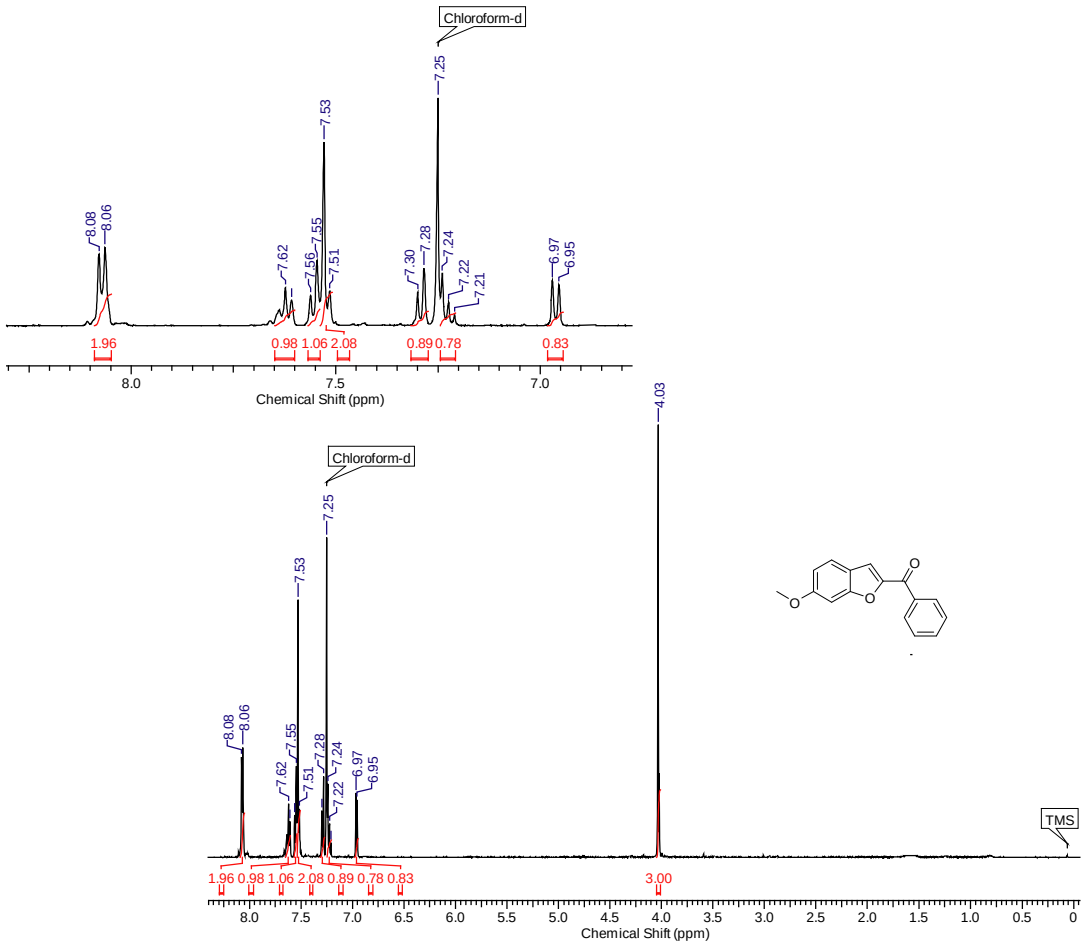

Figure S6. ^{1}H NMR spectrum of compound **2** (400 MHz, $CDCl_3$)

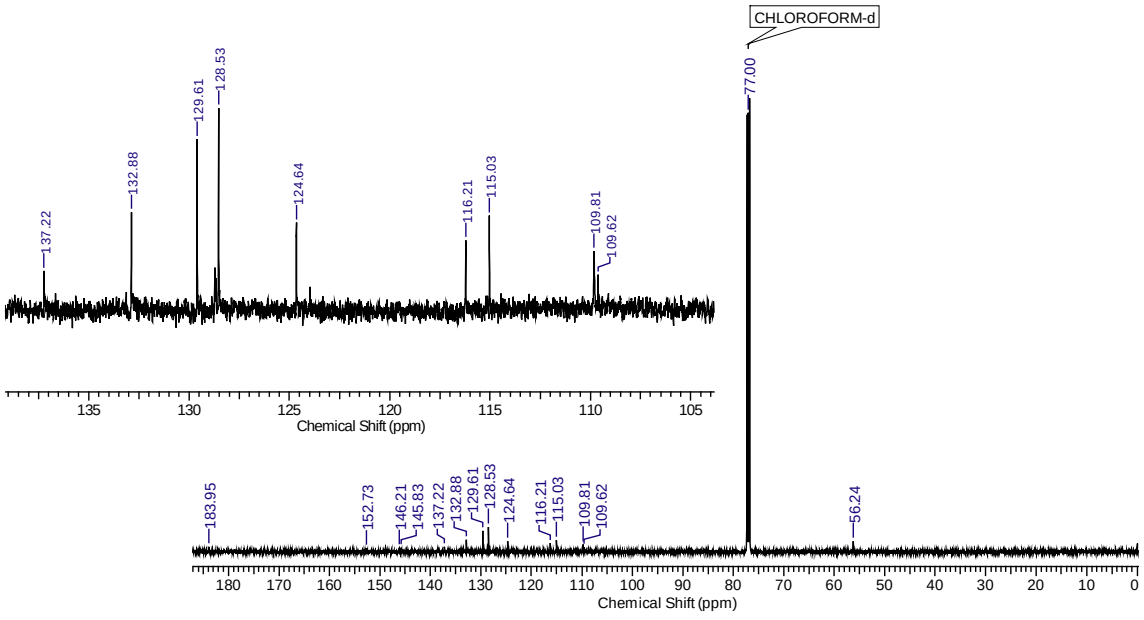

Figure S7. ^{13}C NMR spectrum of compound **2** (100 MHz, $CDCl_3$).

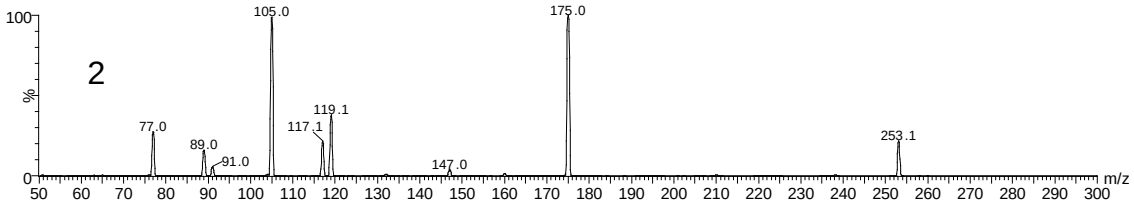

Figure S8. ESI(+)-MS/MS spectrum of protonated compound **2** (*m/z* 253) (QqQ, E_{lab} = 10 eV)

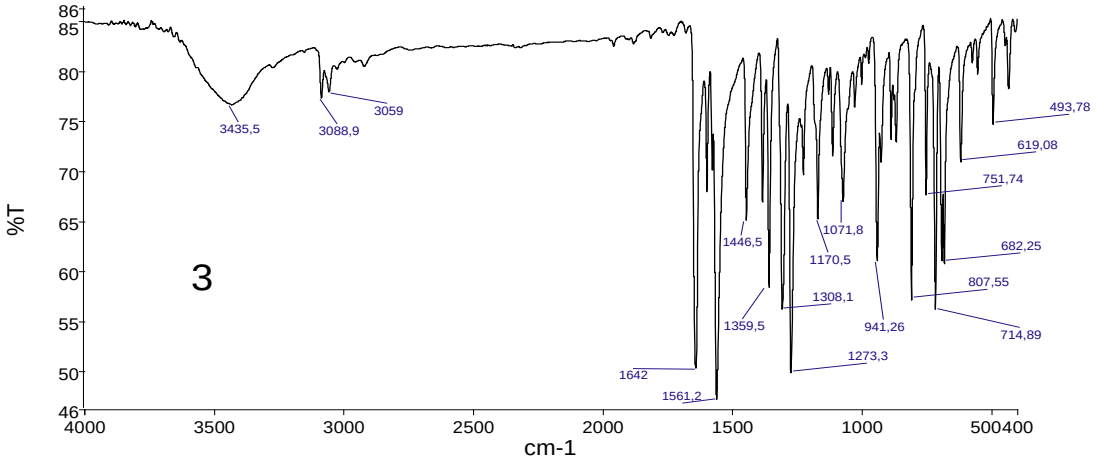

Figure S9. Infrared spectrum of compound **3** (KBr pellet).

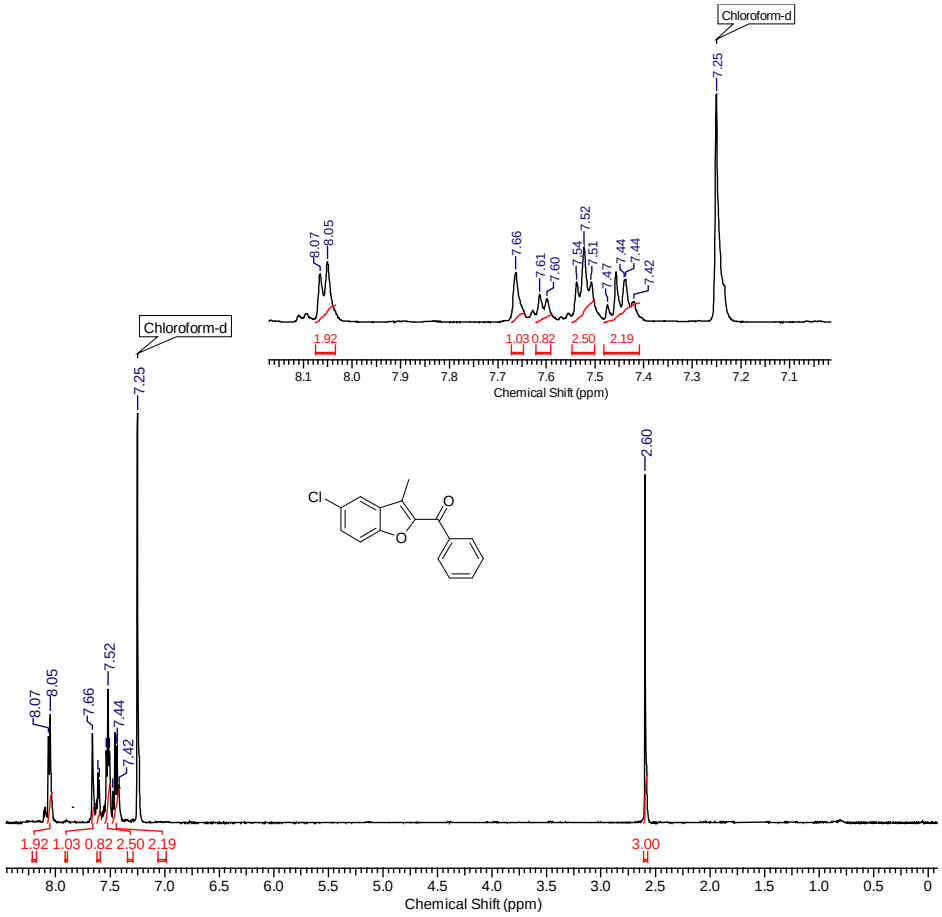

Figure S10. ^{1}H NMR spectrum of compound **3** (400 MHz, $CDCl_3$).

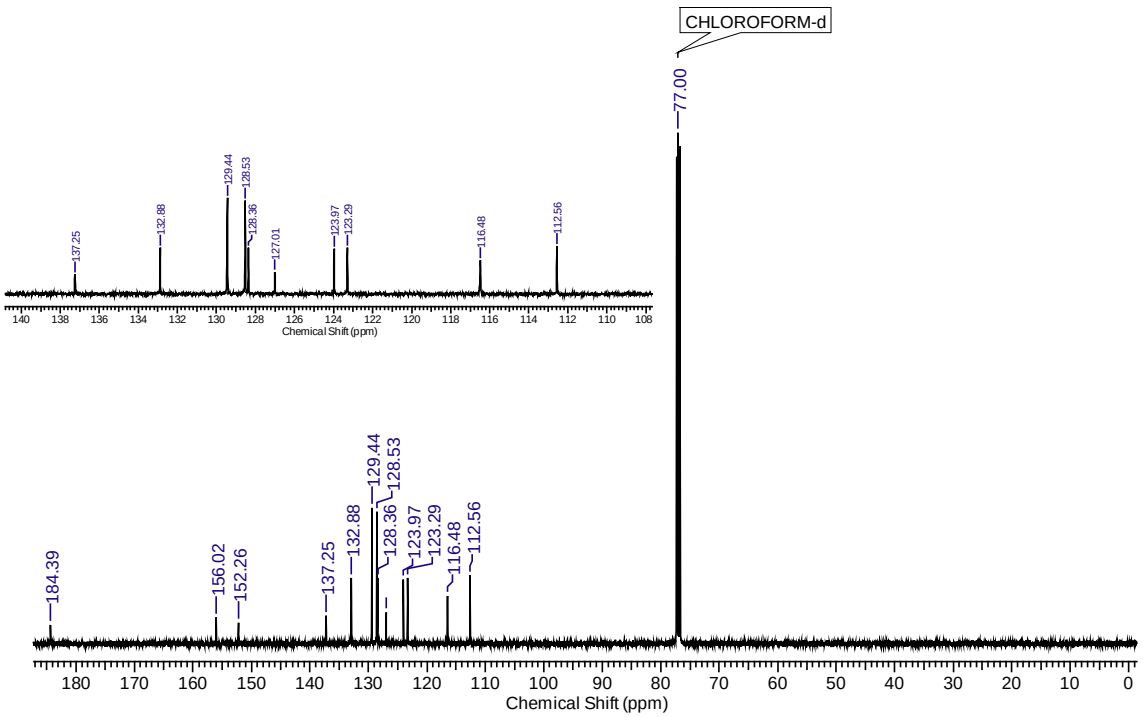

Figure S11 ^{13}C NMR spectrum of compound **3** (100 MHz, $CDCl_3$)

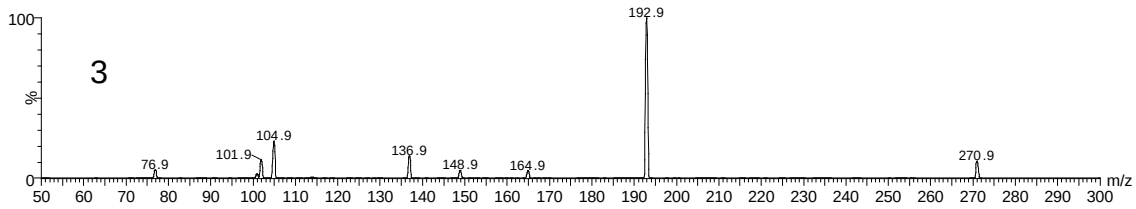

Figure S12. ESI(+)-MS/MS spectrum of protonated compound **3** (*m/z* 271) (QqQ, E_{lab} = 10 eV)

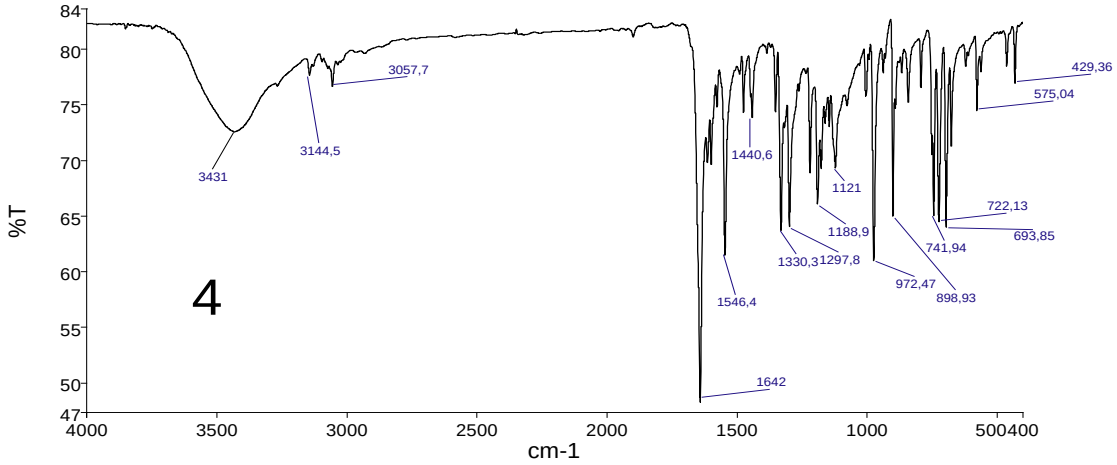

Figure S13. Infrared spectrum of compound **4** (KBr pellet)

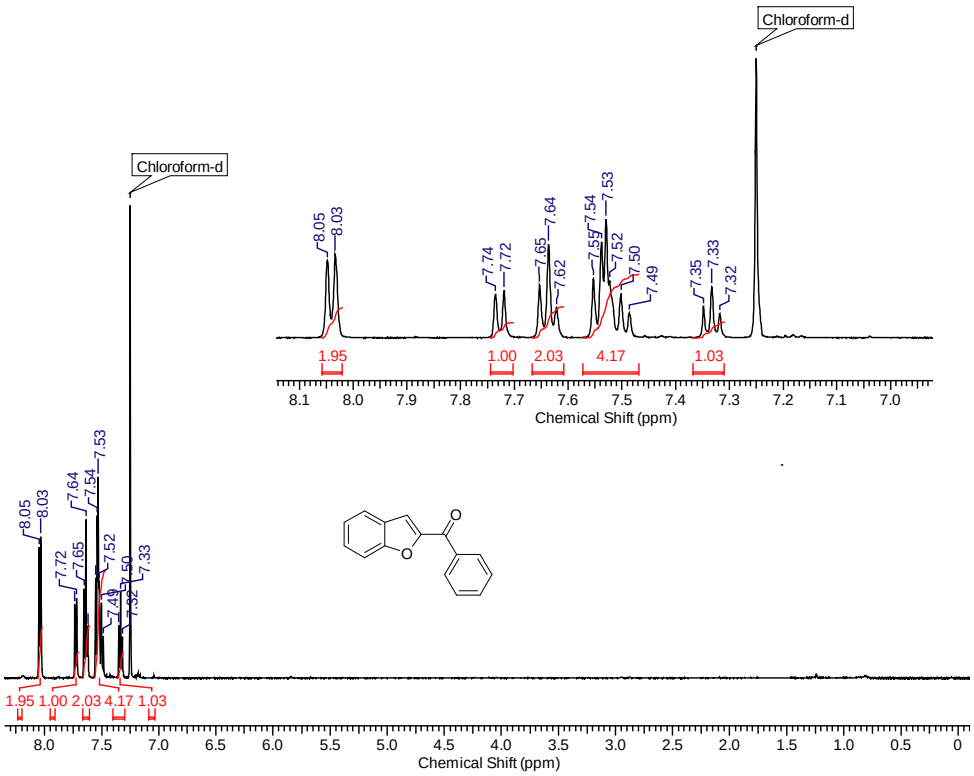

Figure S14. ^{1}H NMR spectrum of compound **4** (400 MHz, $CDCl_3$)

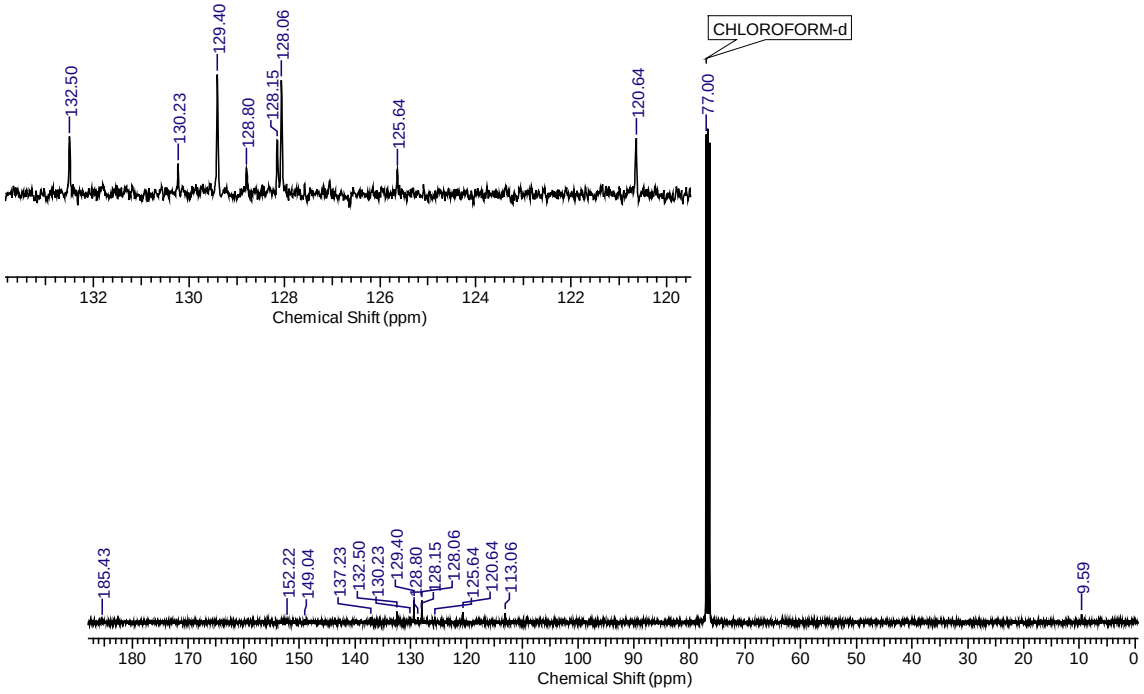

Figure S15 ^{13}C NMR spectrum of compound **4** (100 MHz, $CDCl_3$)

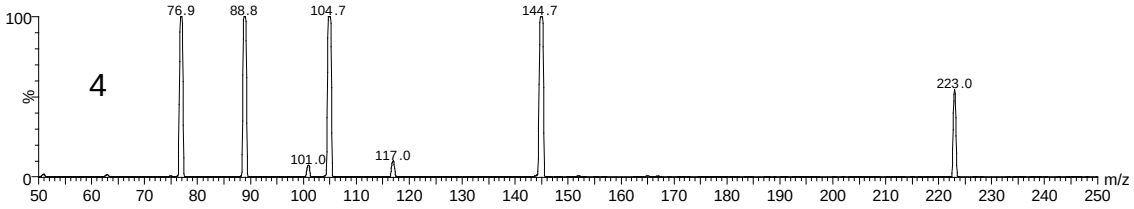

Figure S16. ESI(+)-MS/MS spectrum of protonated compound **4** (*m/z* 223) (QqQ, E_{lab} = 10 eV)

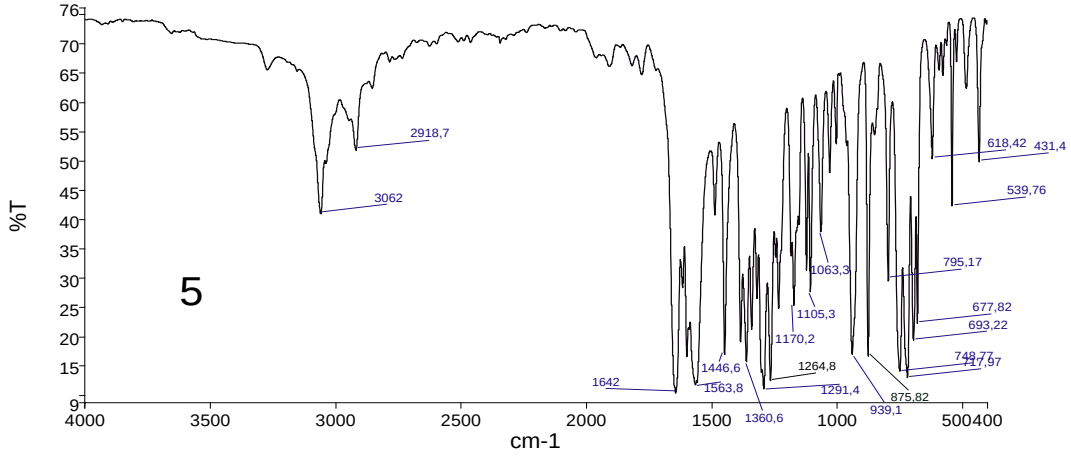

Figure S17 Infrared spectrum of compound **5** (KBr pellet)

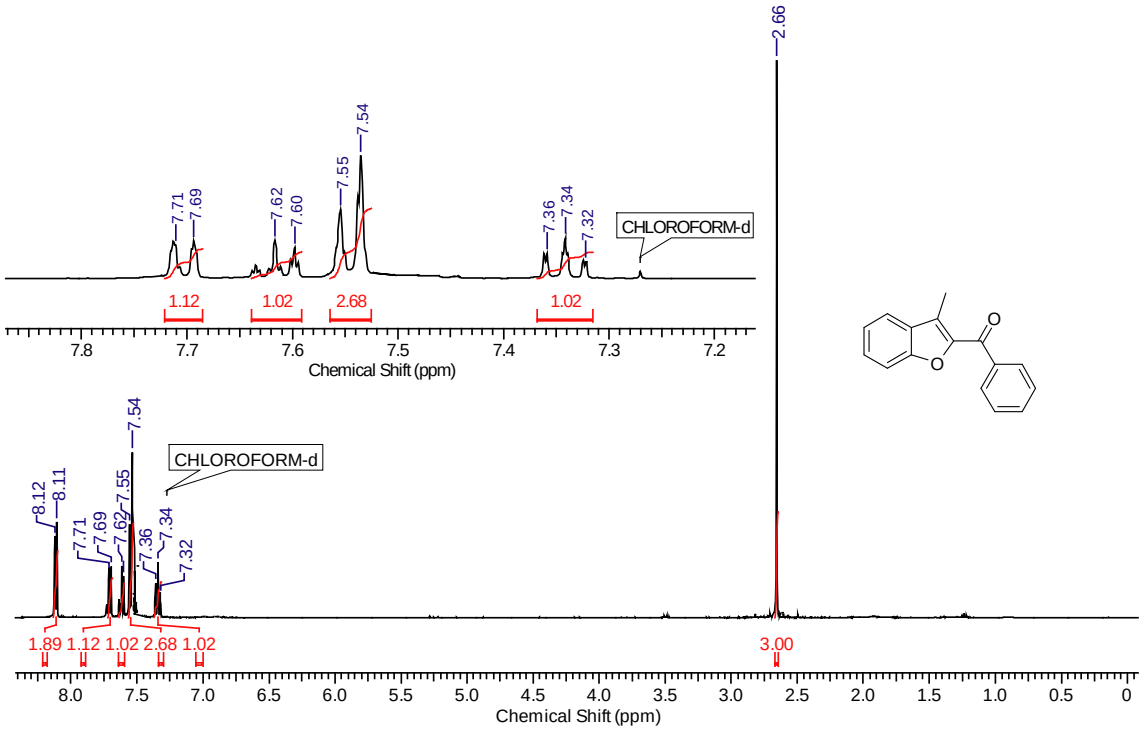

Figure S18. ^{1}H NMR spectrum of compound **5** (400 MHz, $CDCl_3$)

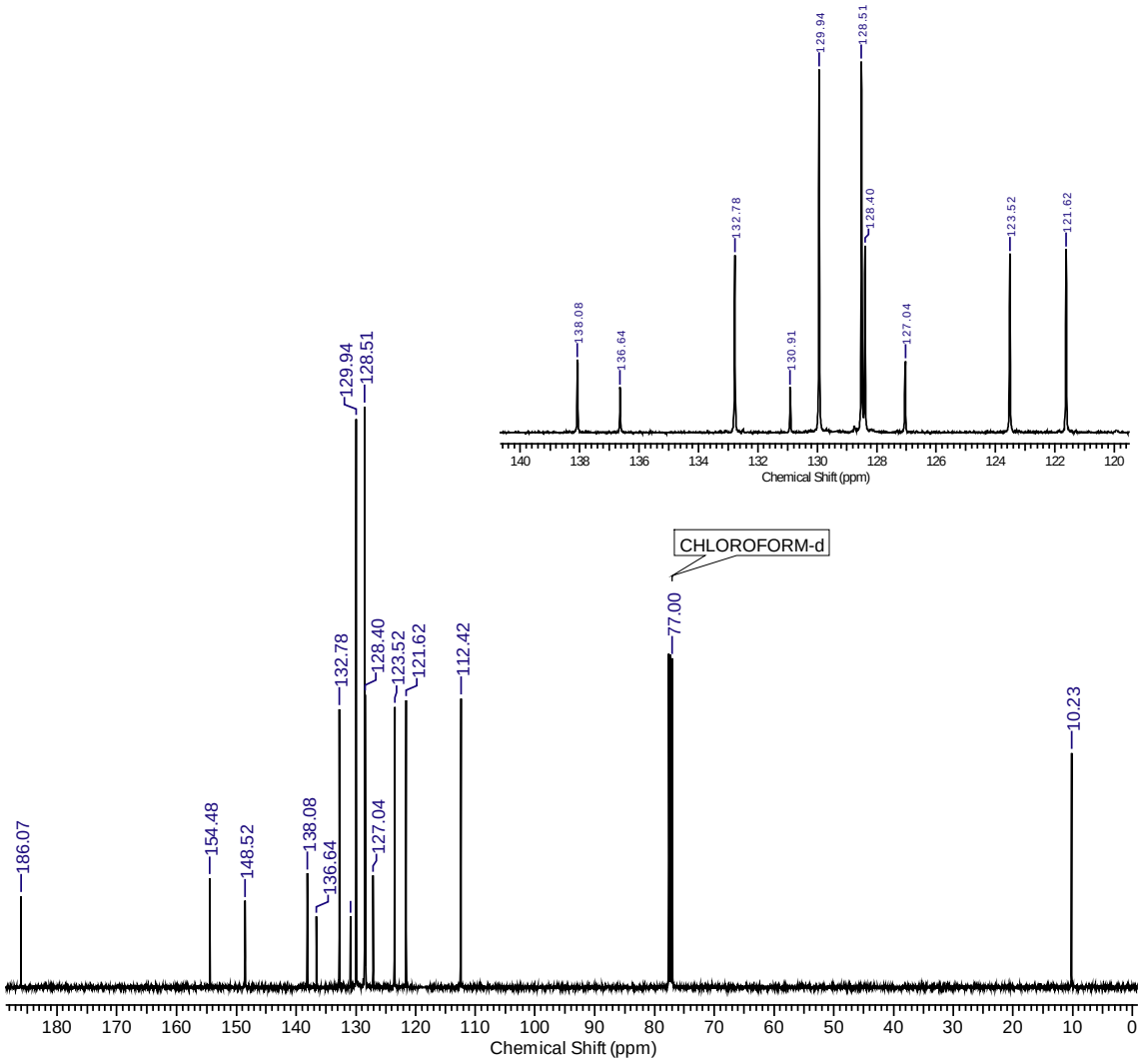

Figure S19. ^{13}C NMR spectrum of compound **5** (100 MHz, $CDCl_3$)

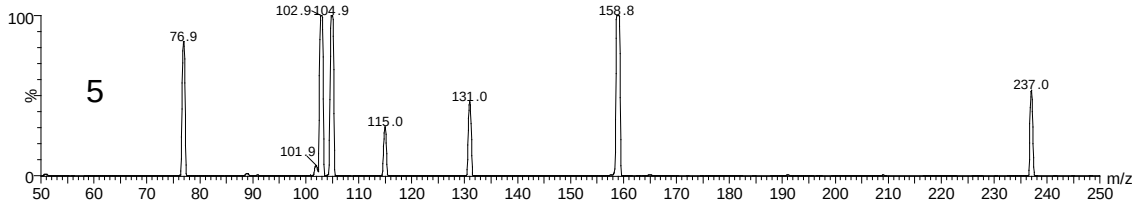

Figure S20. ESI(+)-MS/MS spectrum of protonated compound **5** (*m/z* 237) (QqQ, E_{lab} = 10 eV)

Table S1. *In vitro* antischistosomal effects of compounds **1–5** on *Schistosoma mansoni* tested at a concentration of 12.5 µg/mL

Concentration	Time of incubation (h)	Dead worms (%)	Motor activity	
			Decreased	Minimal
0.1%DMSO[a]	24	0±0	0±0	0±0
	48	0±0	0±0	0±0
	72	0±0	0±0	0±0
1	24	0±0	0±0	0±0
	48	0±0	0±0	0±0
	72	0±0	0±0	0±0
2	24	0±0	0±0	0±0
	48	0±0	0±0	0±0
	72	0±0	0±0	0±0
3	24	0±0	0±0	0±0
	48	0±0	0±0	0±0
	72	0±0	0±0	0±0
4	24	0±0	0±0	0±0
	48	0±0	0±0	0±0
	72	0±0	0±0	0±0
5	24	0±0	0±0	0±0
	48	0±0	0±0	0±0
	72	0±0	0±0	0±0
PZQ[b] (1.6 µM)				

[a] Negative control; [b] Positive control; PZQ: praziquantel

Table S2. *In vitro* antischistosomal effects of compounds **1–5** on *Schistosoma mansoni* tested at a concentration of 25 µg/mL

Concentration	Time of incubation (h)	Dead worms (%)	Motor activity	
			Decreased	Minimal
0.1%DMSO[a]	24	0±0	0±0	0±0
	48	0±0	0±0	0±0
	72	0±0	0±0	0±0
1	24	0±0	0±0	0±0
	48	0±0	0±0	0±0
	72	0±0	0±0	0±0
2	24	0±0	0±0	0±0
	48	0±0	0±0	0±0
	72	0±0	0±0	0±0
3	24	0±0	0±0	0±0
	48	0±0	0±0	0±0
	72	0±0	0±0	0±0
4	24	0±0	0±0	0±0
	48	0±0	0±0	0±0
	72	0±0	0±0	0±0
5	24	0±0	0±0	0±0
	48	0±0	0±0	0±0
	72	0±0	0±0	0±0
PZQ[b] (1.6 µM)				

[a] Negative control; [b] Positive control; PZQ: praziquantel

Table S3. *In vitro* antischistosomal effects of compounds **1–5** on *Schistosoma mansoni* tested at a concentration of 50 µg/mL

Concentration	Time of incubation (h)	Dead worms (%)	Motor activity	
			Decreased	Minimal
0.1%DMSO[a]	24	0±0	0±0	0±0
	48	0±0	0±0	0±0
	72	0±0	0±0	0±0
1	24	0±0	0±0	0±0
	48	0±0	0±0	0±0
	72	0±0	0±0	0±0
2	24	0±0	0±0	0±0
	48	0±0	0±0	0±0
	72	0±0	0±0	0±0
3	24	0±0	0±0	0±0
	48	0±0	0±0	0±0
	72	0±0	0±0	0±0
4	24	0±0	0±0	0±0
	48	0±0	0±0	0±0
	72	0±0	0±0	0±0
5	24	0±0	0±0	0±0
	48	0±0	0±0	0±0
	72	0±0	0±0	0±0
PZQ[b] (1.6 µM)				

[a] Negative control; [b] Positive control; PZQ: praziquantel

Table S4. *In vitro* antischistosomal effects of compounds **1–5** on *Schistosoma mansoni* tested at a concentration of 100 µg/mL

Concentration	Time of incubation (h)	Dead worms (%)	Motor activity	
			Decreased	Minimal
0.1%DMSO[a]	24	0±0	0±0	0±0
	48	0±0	0±0	0±0
	72	0±0	0±0	0±0
1	24	0±0	0±0	0±0
	48	0±0	0±0	0±0
	72	0±0	0±0	0±0
2	24	0±0	0±0	0±0
	48	0±0	0±0	0±0
	72	0±0	0±0	0±0
3	24	0±0	0±0	0±0
	48	0±0	0±0	0±0
	72	0±0	0±0	0±0
4	24	0±0	0±0	0±0
	48	0±0	0±0	0±0
	72	0±0	0±0	0±0
5	24	0±0	0±0	0±0
	48	0±0	0±0	0±0
	72	0±0	0±0	0±0
PZQ[b] (1.6 µM)				

[a] Negative control; [b] Positive control; PZQ: praziquantel