Supporting Information

Total Synthesis of the Antitumor Natural Product Polycarcin V and Evaluation of its DNA Binding Profile

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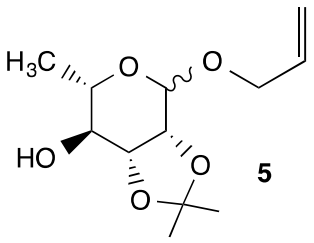
General Methods. Distilled water was used in all of the experiments. Organic extracts were dried over Na_2SO_4, filtered, and concentrated using a rotary evaporator at aspirator pressure (20-30mmHg). Chromatography refers to flash chromatography and was carried out on SiO_2 (silica gel 60, 230-400 mesh). ^1H and ^{13}C NMR spectra were measured in $CDCl_3$ at 400 MHz and 100 MHz, respectively, using Me_4Si as internal standard. Chemical shifts are reported in ppm downfield (δ) from Me_4Si.



5

A solution of L-rhamnose (8 g, 48.7 mmol) and allyl alcohol (88 mL, 0.55 M) was treated with 5 drops of sulfuric acid and stirred at 85°C for 3 hrs. The reaction was then neutralized with 12 M NH_4OH and diluted in toluene. The solution was concentrated *in vacuo*. The crude allyl glycoside was dissolved in 2,2-dimethoxypropane (29.8 mL, 244 mmol, 5 eq). To this solution *p*-TsOH (14 mg, 3.9 mmol, 0.08 eq) was added and the reaction was stirred for 10 min at room temperature. The mixture was diluted with CH_2Cl_2 and quenched with saturated sodium bicarbonate solution (10 mL). The organic layer was washed with brine (10 mL) and dried over anhydrous Na_2SO_4. After filtration the solvent was concentrated *in vacuo* to furnish a crude oil. Purification by silica gel chromatography (10:1 → 4:1 hexanes: ethyl acetate) afforded acetal **5** (10.7 g, 44 mmol, 90% yield).

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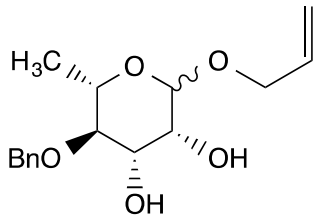
^{1}H NMR: (400 MHz, $CDCl_3$)

5.97-5.87 (m, 1H); 5.32 (d, *J*=16.0 Hz, 1H); 5.23 (d, *J*=16.1 Hz, 1H); 5.04 (s, 1H); 4.24-4.17 (m, 2H); 4.11 (t, *J*=12.2 Hz, 1H); 4.05-3.99 (ddd, *J*=1.3, 8.8, 14.8 Hz, 1H); 3.74-3.66 (m, 1H); 3.45-3.44 (m, 1H); 2.50 (br s, 1H); 1.54 (s, 3H); 1.37 (s, 3H), 1.31 (d, *J*= 8.2 Hz, 3H).

^{13}C NMR: (100 MHz, $CDCl_3$)

133.6; 117.8; 109.5; 96.3; 78.4; 75.8; 74.5; 68.0; 66.0; 28.0; 26.1; 17.5.

HRMS (ESI): calculated for $C_{12}H_{20}NaO_5$: 267.1208; found $(M+Na)^+$: 267.1260



6

Compound **5** (5 g, 20.5 mmol) was dissolved in DMF (77.3 mL, 0.26 M) and NaH (2.64 g, 66 mmol, 3.2 eq) and imidazole (150 mg, 2.2 mmol, 0.09 eq) were added at 0 °C. The mixture was stirred for 15 min at room temperature. BnBr (3.5 mL, 29 mmol, 1.45 eq) and TBAI (0.8 g, 0.1 eq) were then added to the reaction mixture. The reaction was stirred for 14 hours at room temperature. The reaction was placed in an ice bath and quenched with saturated sodium bicarbonate solution (30 mL); then ethyl acetate (30 mL) was added. The phases were separated and the organic phase was washed with brine. The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo.* The crude product was purified by silica gel chromatography (99:1 → 20:1 hexanes: ethyl acetate) to furnish a yellow oil. The benzylated allyl glycoside (6.2 g, 18.5 mmol) was then dissolved in MeCN (18.5 mL, ~1M) and a spatula tip (20 mg) of $BiCl_3$ was added, followed by 20 drops of water. The reaction was stirred for 14 hours at room temperature. The mixture was quenched with saturated sodium bicarbonate solution (10 mL) and EtOAc (10 mL) was added. The phases were separated and the organic extracts were washed with brine and dried over Na_2SO_4. The organic layer was filtered and concentrated *in vacuo* to provide a crude oil. Diol **6** (4.8 g, 16.3 mmol, 80% yield) was obtained after purification by silica gel chromatography (10:1 → 3:1 hexanes: ethyl acetate).

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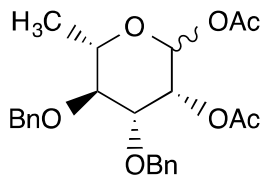
^{1}H NMR: (400 MHz, $CDCl_3$)

7.43-7.42 (m, 5H); 5.96-5.86 (m, 1H); 5.32 (dd, *J*=2.0, 16.0 Hz, 1H); 5.21 (dd, *J*=2.8, 12.1 Hz, 1H); 4.91 (d, *J*=15.0 Hz, 1H); 4.84 (s, 1H); 4.69 (d, *J*=12.0 Hz, 1H); 4.22-4.15 (m, 2H); 4.05-3.95 (m, 3H); 3.84-3.78 (m, 2H); 3.47 (t, *J*=9.6 Hz, 1H); 1.39 (d, *J*=6.2 Hz, 3H)

^{13}C NMR: (100 MHz, $CDCl_3$)

138.5; 133.9; 128.5; 128.0; 127.8; 117.3; 98.9; 81.6; 75.0; 71.7; 71.3; 68.0; 67.5; 18.0.

HRMS (ESI): calculated for $C_{16}H_{22}NaO_5$: 317.1365; found $(M+Na)^+$: 317.1423



7

Compound **6** (4.4 g, 15.1 mmol) was dissolved in toluene (15.1 mL, 1.0 M) and treated with Bu_2SnO (4.1 g, 16.4 mmol, 1.1eq). The mixture was refluxed at 110 °C for 2 hrs. After the reaction was cooled to 65 °C, BnBr (2 mL, 16.8 mmol, 1.1eq.) and TBAI (6.14 g, 16.6 mmol 1.1eq.) were added to the solution. The reaction mixture was then stirred for 14 hrs at 65 °C. Saturated sodium bicarbonate solution (10 mL) was added, and after the reaction was cooled in an ice bath, the solids were vacuum filtered and washed with EtOAc (20 mL). The filtrate phases were separated and the organic layer was washed with brine and dried over anhydrous Na_2SO_4. The organic phase was filtered and concentrated *in vacuo* to afford a crude oil. The product was purified by silica gel column chromatography (10:1 → 6:1 hexanes: ethyl acetate) to afford the 3,4-di-*O*-benzyl allyl glycoside (5.3 g, 13.8 mmol), which was dissolved in acetic anhydride (5 mL) and pyridine (5 mL). After a catalytic amount of DMAP (20 mg) was added, the mixture was stirred at room temperature for five hours and concentrated *in vacuo*.

The crude acetate ester was dissolved in acetic anhydride (42 mL), and acetic acid (14 mL) and 12M H_2SO_4 (0.1 mL) were added and the mixture was stirred for 1 hr. The reaction mixture was diluted with diethyl ether (50 mL) and carefully quenched with saturated sodium bicarbonate solution (10 mL). The organic layer was washed with saturated sodium bicarbonate solution and brine and dried over anhydrous Na_2SO_4. The organic layer was filtered and concentrated *in vacuo* to afford a crude oil. Purification by silica gel chromatography (99:1 → 10:1 hexanes: ethyl acetate) afforded **7** (4.1g, 10.6 mmol 70% overall yield).

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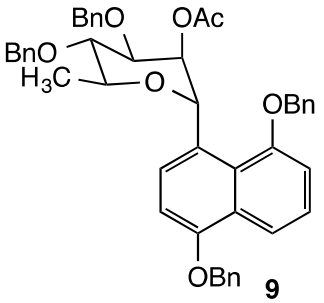
^{1}H NMR: (400 MHz, $CDCl_3$)

7.40-7.31 (m, 10H); 6.08 (d, *J*= 2.0 Hz, 1H); 5.43 (q, *J*=1.6 Hz, 1H); 4.91 (d, *J*=10.7 Hz, 1H); 4.79 (d, *J*=11.2 Hz, 1H); 4.68 (d, *J*=10.7 Hz, 1H); 4.61 (d, *J*=11.1 Hz, 1H); 3.99 (dd, *J*=3.3, 12.0 Hz, 1H); 3.91-3.84 (m, 1H); 3.55 (t, *J*= 9.5 Hz, 1H); 2.21 (s, 3H); 2.12 (s, 3H); 1.40 (d, *J*=6.2 Hz, 3H)

^{13}C NMR: (100 MHz, $CDCl_3$)

170.0; 168.5; 138.3; 137.8; 128.5; 128.4; 128.1; 128.0; 127.9; 127.8; 91.2; 79.5; 77.7; 75.6; 71.9; 70.1; 67.9; 20.9; 20.8; 18.1

HRMS (ESI): calculated for $C_{24}H_{28}NaO_7$: 451.1733; found $(M+Na)^+$: 451.1785



9

Acetate sugar **7** (1 g, 2.3 mmol) was combined with 1,5-dibenzyloxynaphthalene **8** (2.4 g, 6.9 mmol, 3 eq)[1] and the mixture was dissolved in anhydrous CH_2Cl_2 (33.7 mL, 0.07 M). The solution was stirred under argon for 2 hrs with 4.4 g of 4 Å molecular sieves. To this solution TMSOTf (1.27 mL, 6.9 mmol, 3 eq) was added dropwise. After 5 min of stirring, TLC indicated completion consumption of **7**. The reaction was then quenched with saturated sodium bicarbonate (10 mL). The solids were filtered and the product was extracted with CH_2Cl_2 (2x50 mL), and the combined organic layers were dried over Na_2SO_4. The solvent was filtered and concentrated *in vacuo* to give a crude oil. Purification by flash chromatography (99:1 → 8:1 hexanes: ethyl acetate) afforded **9** (1.1 g, 1.62 mmol, 70% yield).

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^{1}H NMR: (400 MHz, $CDCl_3$)

8.12 (d, *J*=9.3 Hz, 1H); 7.75 (d, *J*=8.3 Hz, 1H); 7.58 (m, 4H); 7.50-7.35 (m, 16H); 7.28 (m, 2H); 7.23 (m, 2H); 7.06 (d, *J*=7.1 Hz, 1H); 6.93 (d, *J*=8.4 Hz, 1H); 6.03 (s, 1H); 5.82 (d, *J*=4.3 Hz, 1H); 5.32-5.16 (m, 4H); 4.93 (d, *J*=11.3 Hz, 1H); 4.65 (d, *J*=11.3 Hz, 1H); 4.47(d, *J*=11.0 Hz, 1H); 4.03 (d, *J*=11.0 Hz, 1H); 3.50-3.41 (m, 2H); 2.99 (dd, *J*=3.4, 6.7 Hz, 1H); 1.85 (s, 3H); 1.47 (d, *J*=5.6 Hz, 3H)

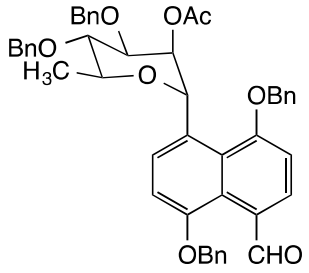
^{13}C NMR: (100 MHz, $CDCl_3$)

170.0; 155.5; 153.7; 139.2; 138.4; 137.2; 136.3; 129.1; 129.0; 128.6; 128.4; 128.3; 128.0; 127.9; 127.9; 127.6; 127.5; 127.4; 127.4; 126.3; 125.5; 124.7; 123.5; 116.0; 107.8; 105.1; 81.7; 80.3; 76.3; 75.5; 74.7; 71.1; 71.1; 70.3; 70.2; 20.8; 18.6

HRMS (ESI): calculated for $C_{46}H_{44}NaO_7$: 731.2985; found $(M+Na)^+$: 731.2937

$[\alpha]^{25}_D$: -75.6° (c 0.018, CH_2Cl_2)

[1](a) Edleson-Averbukh, M.; Etinger, A.; Mandelbaum, A. *J. Chem. Soc., Perk. Trans.* 2, **1999**, *6*, 1095. (b) Batcho, A.D.; Leimgruber, W. *Org. Synth.* 1990, *Coll. Vol. VII,* 34.



10

C-glycoside **9** (6.8 g, 9.6 mmol) was dissolved in toluene (10.0 mL, 1M) and treated with DMF (7.7 mL, 100 mmol, 10 eq). To this mixture $POCl_3$ (9.3 mL, 100 mmol, 10 eq) was added dropwise at 0 °C. The reaction was refluxed at 110 °C under argon for 6 hrs. The reaction mixture was then cooled to 0 °C and diluted with CH_2Cl_2 (10 mL). 1N aqueous sodium hydroxide solution (300 mL, 1M) was slowly added until the aqueous layer became basic. The organic layer was separated, dried over Na_2SO_4, and concentrated *in vacuo*. Purification by silica gel chromatography (10:1 → 4:1 hexanes: ethyl acetate) furnished **10** (4.9 g, 6.7 mmol, 70% yield).

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^{1}H NMR: (400 MHz, $CDCl_3$)

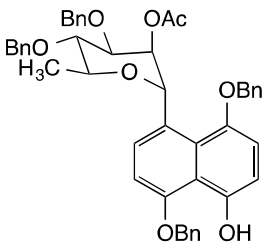
10.89 (s, 1H); 7.86 (d, *J*=8.2 Hz, 1H); 7.81 (d, *J*=8.1 Hz, 1H); 7.55 (m, 2H); 7.47-7.32 (m, 14H); 7.25 (m, 2H); 7.20 (m, 3H); 7.15 (m, 2H); 5.97 (s, 1H); 5.74 (d, *J*=4.3 Hz, 1H); 5.30-5.18 (m, 3H); 4.89 (d, *J*=11.2 Hz, 1H); 4.61 (d, *J*=11.3 Hz, 1H); 4.40 (d, *J*=11.0 Hz, 1H); 4.03 (d, *J*=11.0 Hz, 1H); 3.43-3.40 (m, 2H); 2.90 (dd, *J*=3.4, 6.6 Hz, 1H); 1.83 (s, 3H); 1.42 (d, *J*=5.6 Hz, 3H)

^{13}C NMR: (100 MHz, $CDCl_3$)

194.3; 169.9; 159.0; 154.4; 139.1; 138.2; 135.9; 135.2; 129.5; 129.3; 129.2; 129.1; 128.9; 128.8; 128.4; 128.3; 128.3; 127.8; 127.6; 127.5; 127.5; 126.6; 126.0; 125.3; 124.0; 108.2; 107.0; 81.5; 80.1; 77.3; 76.0; 75.6; 74.7; 71.5; 71.3; 71.1; 70.1; 20.7; 18.6

HRMS (ESI): calculated for $C_{47}H_{44}NaO_8$: 759.2934; found $(M+Na)^+$: 759.2967

$[\alpha]^{25}_D$: -76.5° (c 0.016, CH_2Cl_2)



11

Aldehyde **10** (49.3 mg, 0.07 mmol) was dissolved in THF (1.3 mL) and MeOH (2.8 mL). The solution was treated with 30% aqueous H_2O_2 (0.57 mL) and 3 drops of H_2SO_4. After the reaction was stirred for 1 hr, Et_2O (4.2 mL) was added to the mixture. An aqueous solution of $NaHSO_3$ (341 mg) in water (11.3 mL) was then added to the reaction at 0 °C. The aqueous layer was extracted with Et_2O (250 mL) and the combined organic layers were dried over Na_2SO_4. The organic layer was filtered and concentrated *in vacuo* to give a crude oil. Column chromatography (10:1 → 7:1 hexanes: ethyl acetate) purification afforded naphthol **11** (44.6 mg, 0.064 mmol, 92%).

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^{1}H NMR: (400 MHz, $CDCl_3$)

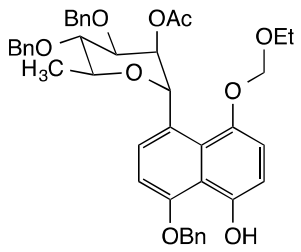
9.58 (s, 1H); 7.60 (d, *J*=8.4 Hz, 1H); 7.55 (m, 4H); 7.51-7.40 (m, 13 H); 7.39-7.28 (m, 5H); 7.00 (d, *J*=8.5 Hz, 1H); 6.96 (d, *J*=8.5 Hz, 1H); 6.86 (d, *J*=8.4 Hz, 1H); 6.07 (s, 1H); 5.87 (d, *J*=3.2 Hz, 1H); 5.28 (s, 2H); 5.13 (s, 2H); 4.96 (d, *J*=11.1 Hz, 1H); 4.65 (d, *J*=11.2 Hz, 1H); 4.50 (d, *J*=11.0 Hz, 1H); 4.06 (d, *J*=11.0 Hz, 1H); 3.6-3.4 (m, 2H); 2.99 (dd, *J*=3.4, 6.7 Hz, 1H); 1.91 (s, 3H); 1.50 (d, *J*=5.6 Hz, 3H)

^{13}C NMR: (100 MHz, $CDCl_3$)

169.9; 154.7; 149.3; 148.5; 139.2; 138.4; 136.5; 135.2; 129.1; 128.9; 128.8; 128.7; 128.2; 128.1; 128.1; 127.9; 127.5; 127.4; 125.7; 125.1; 116.6; 109.9; 109.8; 105.7; 81.6; 80.2; 77.5; 77.2; 76.9; 76.1; 75.5; 74.6; 71.8; 71.7; 71.1; 70.3; 20.8; 18.7.

HRMS (ESI): calculated for $C_{46}H_{44}NaO_8$: 747.2934; found $(M+Na)^+$: 747.2991

$[\alpha]^{25}_D$: -84.7° (c 0.006, CH_2Cl_2)



13

Naphthol **11** (1 g, 1.3 mmol) was dissolved with CH_3CN (4 mL, 0.3M). To this mixture an aqueous solution of ceric ammonium nitrate (1.8 g, 3.9 mmol, 2.5 eq) in water (1 mL) was added. The reaction mixture turned bright yellow, at which point TLC indicated complete consumption of **11**. The reaction was then quenched with water (5 mL). The aqueous layer was extracted with CH_2Cl_2 (5 mL) and combined organic layers were washed with saturated NaCl solution (5 mL). Concentration *in vacuo* gave a crude intermediate quinone. Due to the light sensitivity of the compound, the quinone was immediately dissolved with Et_2O and DCM (26 mL, 0.05M, 3:1) and transferred to a separatory funnel; then a freshly prepared 20% sodium dithionite solution (30 mL) was mixed with the organic solution and the biphasic mixture was shaken vigorously for 15 min. As the bright yellow organic layer turned dark brown, TLC showed complete consumption of the quinone. The organic layer was then concentrated *in vacuo* to afford **12** (660.1 mg, 1.04 mmol, 80% yield overall). The crude red oil was quickly filtered through a silica gel column (CH_2Cl_2) and concentrated *in vacuo*.

To a solution of diol **12** (1 g, 1.57 mmol) in THF (1.57 mL, 1 M) at -78°C, NaHMDS (1 M solution in THF, 1.6 mL, 3.2 mmol, 2 eq) was added. Then chloromethyl ethyl ether (0.2 mL, 1.88 mmol, 1.2 eq) was added and the reaction was stirred at -78°C for 5 min. At this point TLC indicated consumption of the starting material. The reaction was diluted with EtOAc (10 mL), quenched with sodium bicarbonate (10 mL), and the organic layer was washed with brine (10 mL). The organic extract was dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to afford a brown oil, which was purified by silica gel chromatography (10:1 → 7:1 hexanes: ethyl acetate) to provide **13** (707 mg, 1.02 mmol, 65% yield).

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^{1}H NMR: (400 MHz, $CDCl_3$)

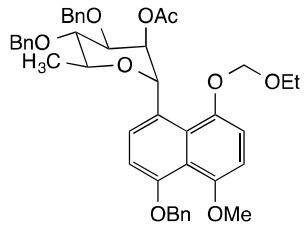
9.66 (s, 1H); 7.86 (d, *J*= 8.5 Hz, 1H); 7.54-7.38 (m, 18H); 7.27 (d, *J*= 8.4Hz, 1H); 6.96 (d, *J*=8.5 Hz, 1H); 6.90 (d, *J*=8.5 Hz, 1H); 6.16 (d, *J*=3.1 Hz, 1H); 6.04 (s, 1H); 5.33 (d, *J*=7.8 Hz, 1H); 5.26-5.16 (m, 4H); 4.98 (d, *J*=11.4 Hz, 1H); 4.85 (d, *J*=11.0 Hz, 1H); 4.74 (d, *J*=11.4 Hz, 1H); 4.08 (dd, *J*=3.1, 6.2 Hz, 1H); 3.84- 3.73 (m, 4H); 2.02 (s, 3H); 1.64 (d, *J*=5.6 Hz, 3H); 1.34 (t, *J*=7.0 Hz, 3H).

^{13}C NMR: (100 MHz, $CDCl_3$)

170.1; 154.8; 150.0; 147.0; 138.7; 138.2; 135.2; 129.0; 128.9; 128.5; 128.2; 128.1; 127.9; 127.8; 127.7; 127.4; 126.9; 125.7; 125.5; 116.5; 113.1; 110.2; 105.5; 94.9; 82.1; 80.8; 76.6; 76.1; 75.7; 71.8; 71.3; 70.5; 64.8; 20.8; 18.7; 15.3.

HRMS (ESI): calculated for $C_{42}H_{44}NaO_9$: 715.2883; found $(M+Na)^+$: 715.2936

$[\alpha]^{25}_D$: -57.8°(c=0.0028 , CH_2Cl_2)



14a

Naphthol **13** (0.7 g, 1.01 mmol) was dissolved in THF (1.02 mL, 1 M) at -78°C and treated with NaHMDS (1M in THF, 1.02 mL, 1.02 mmol, 1 eq) at -78 °C. To this mixture Me_2SO_4 (0.09 mL, 1.12 mmol, 1.1 eq) was added at -78 °C. The reaction was warmed to room temperature and stirred for 1 hr. Saturated sodium bicarbonate solution (10 mL) was then added and the mixture was extracted with EtOAc (10 mL) and washed with brine (10mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to yield a brown oil. Silica gel column chromatography (9:1 hexanes: ethyl acetate) furnished **14a** (0.65 g, 0.92 mmol, 91% yield).

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^{1}H NMR: (400 MHz, $CDCl_3$)

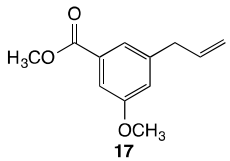
7.85 (d, *J*= 8.4 Hz, 1H); 7.66 (m, 2H); 7.50-7.35 (m, 13H); 7.23 (d, *J*=8.4 Hz, 1H); 7.02 (d, *J*= 8.5 Hz, 1H); 6.84 (d, *J*=8.5 Hz, 1H); 6.06 (d, *J*=3.0 Hz, 1H); 5.99 (s, 1H); 5.34 (d, *J*=6.8 Hz, 1H); 5.23 (s, 2H); 5.17 (d, *J*= 6.8 Hz, 1H); 5.10 (d, *J*=10.7 Hz, 1H); 4.92 (d, *J*= 11.3 Hz, 1H); 4.79 (d, *J*=11.4 Hz, 1H); 4.67 (d, *J*= 11.5 Hz, 1H); 4.00 (dd, *J*= 3.1, 6.3 Hz, 1H); 3.93 (s, 3H); 3.80-3.65 (m, 4H); 1.96 (s, 3H); 1.58 (d, *J*=5.6 Hz, 3H); 1.31 (t, *J*=7.0 Hz, 3H)

^{13}C NMR: (100 MHz, $CDCl_3$)

170.0; 155.6; 152.6; 148.4; 138.6; 138.1; 137.6; 128.4; 128.3; 128.2; 128.1; 128.0; 127.9; 127.8; 127.7; 127.5; 127.1; 126.8; 126.5; 126.4; 126.3; 120.0; 110.7; 108.9; 107.0; 94.5; 82.0; 80.7; 75.9; 75.6; 71.8; 71.1; 70.3; 64.7; 57.2; 20.7; 18.6; 15.2

HRMS (ESI): calculated for $C_{43}H_{46}NaO_9$: 729.3040; found $(M+Na)^+$: 729.3003

$[\alpha]^{25}_D$: -43.6° (c=0.005, CH_2Cl_2)



17

Phenol **16** was prepared from **15** according to a literature procedure.[2] Phenol **16** (5.5 g, 30 mmol) was dissolved in pyridine (5 mL) and CH_2Cl_2 (32 mL, 0.1M). To this mixture a solution of Tf_2O (6.2 ml, 36 mmol, 1.2 eq) in CH_2Cl_2 (~13 mL) was added at 0°C. The reaction mixture was stirred for 1 hr and quenched with saturated $NaHCO_3$ (10 mL). The aqueous layer was extracted with CH_2Cl_2 (10 mL). The organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was rapidly filtered through a pad of silica gel (CH_2Cl_2) and concentrated *in vacuo* to provide a quantitative recovery of the corresponding aryl triflate.

To the triflate (0.5 g, 1.6 mmol) in 12.5 mL DMF, anhydrous LiCl (0.3 g, 6.4 mmol, 4 eq) was added. To this mixture $(Ph_3P)_2PdCl_2$ (112 mg, 0.16 mmol, 10 mol%) and allytributyltin (1ml, 3.18 mmol, 2 eq) were added. The suspension was heated at 100°C for 3 hrs, at which point TLC indicated complete consumption of the starting material. The reaction was cooled and stopped by adding water (10 mL) and ethyl ether (10 mL). The aqueous phase was extracted with diethyl ether (50 mL). The combined ether extracts were washed with brine (10 mL) and saturated $NaHCO_3$ (10 mL) and dried over anhydrous sodium sulfate and concentrated *in vacuo*. Silica gel column chromatography (10:1 → 5:1 hexanes: ethyl acetate) afforded **17** (0.27 g, 1.3 mmol, 80%).

See spectra on page S28

^{1}H NMR: (400 MHz, $CDCl_3$)

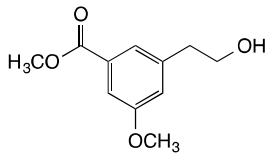
7.41 (s, 1H); 7.34 (s, 1H); 6.85 (s, 1H); 5.92-5.82 (m, 1H); 5.06 (m, 1H); 5.02 (s, 1H); 3.82 (s, 3H); 3.74 (s, 3H); 3.31 (d, *J*= 7.8 Hz, 2H)

^{13}C NMR: (100 MHz, $CDCl_3$)

166.5; 159.6; 141.6; 136.5; 131.2; 122.0; 119.4; 116.1; 111.6; 55.0; 51.6; 39.7.

HRMS (ESI): calculated for $C_{12}H_{14}NaO_3$: 229.0841; found 229.0822 $(M+Na)^+$

[2] Nawrat, C.C.; Palmer, L.I.; Blake, A.J.; Moody, C.J. *J. Org. Chem.* **2013**, *78*, 5587.



18

Compound **17** (0.10 g, 0.49 mmol) was dissolved in acetone and *t*-BuOH (1:1, 1 mL, 0.5 M) and treated with OsO_4 (20 µL, 4% solution in water) and *N*-methylmorpholine-*N*-oxide (0.5 mL, 50% solution in H_2O) and stirred for 5 hrs at room temperature. EtOAc (10 mL) was added and the layers were separated; the organic extracts were washed with saturated $NaHCO_3$ (5 mL) and brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The diol intermediate was dissolved in acetone and pH 6.5 phosphate buffer (1:3, 20 mL) and treated with KIO_4 (0.200 g, 1.0 mmol, 2 eq). After 3 hours at room temperature the reaction was stopped by adding water (5 mL) and CH_2Cl_2 (10 mL) and the layers were separated; the organic phase was washed with brine (10 mL) and saturated sodium bicarbonate (10 mL) and concentrated *in vacuo*. The crude intermediate aldehyde was immediately dissolved in MeOH (~10 mL), treated with $NaBH_4$ (37.8 mg, 1.0 mmol, 2eq) and stirred for 10 min. At this time saturated sodium bicarbonate solution (5 mL) and EtOAc (10 mL) was added and the layers were separated. The organic phase was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude alcohol compound was purified by silica gel chromatography (10:1 → 2:1 hexanes: ethyl acetate) to afford **18** (66.3 mg, 0.33 mmol, overall 67%) as a colorless oil.

See spectra on page S29

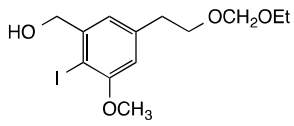
^{1}H NMR: (400 MHz, $CDCl_3$)

7.37 (s, 1H); 7.25 (s, 1H); 6.85 (s, 1H); 3.75 (s, 3H); 3.71 (t, *J*=10.2 Hz, 2H); 3.66 (s, 3H); 3.34 (br, 1H); 2.73 (t, *J*= 6.4 Hz, 2H)

^{13}C NMR: (100 MHz, $CDCl_3$)

167.0; 159.5; 140.7; 131.1; 122.4; 120.1; 111.7; 62.9; 55.1; 51.9; 38.8

HRMS (ESI): calculated for $C_{11}H_{14}NaO_4$: 233.0790; found $(M+Na)^+$: 233.0842



21

To alcohol **18** (1 g, 4.8 mmol) in CH_2Cl_2 (9.5 mL, 0.5 M) was added DIEA (2.1 mL, 12.1 mmol, 2.5 eq) followed by chloromethyl ethyl ether (0.75 ml, 7.2 mmol, 1.5 eq) at 0°C. The reaction was stirred for 5 hours at room temperature and then saturated $NaHCO_3$ (10 mL) and ether (50 mL) was added. The layers were separated and the organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was dissolved in CH_2Cl_2 (20 mL) and rapidly filtered through a pad of silica gel and concentrated *in vacuo*. To ester **19** (1 g, 3.7 mmol) in dry Et_2O (37 mL, 0.1 M) was added $LiAlH_4$ (292.4 mg, 8.4 mmol, 2.25 eq) in four small portions with caution. The reaction mixture was stirred for 10 min and stopped by carefully adding water (0.3 mL), 15% NaOH (0.3 mL) and water (0.9 mL) dropwise. After the residual $LiAlH_4$ was quenched, the resulting white solids were diluted with EtOAc (20 mL) and the mixture was filtered through celite; the filtrate was then concentrated *in vacuo*. The crude product was purified by silica gel chromatography (10:1 → 2:1 hexanes: ethyl acetate) to afford **20** (876.0 mg, 3.6 mmol, 98% yield).

To a suspension of **20** (3 g, 12.5 mmol) in anhydrous diethyl ether (125 mL, 0.1M) was slowly added *n*-BuLi (37.5 mL, 37.5 mmol, 3eq, 1M solution in hexanes) at 0°C and the solution turned light brown. This reaction was stirred for 1 hour at room temperature. The mixture was then cooled in an ice bath and an additional portion of *n*-BuLi (12.5 mL, 12.5 mmol, 1eq, 1M solution in hexanes) was added to the reaction, which was then stirred for an additional 3 hours. To the dark red reaction solution, I_2 (16 g, 62.5 mmol, 5eq) in THF (5 mL) was added at 0°C. The reaction was titrated to colorless and turned dark brown (excess of iodine) and stirred for an additional hour. The residual iodine was scavenged by addition of saturated sodium thiosulfate solution (10 mL) and the product was extracted with EtOAc (20 mL). The organic layer was washed with saturated $NaHCO_3$ (10 mL) and brine (10 mL) and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (10:1 → 4:1 hexanes: ethyl acetate) to give **21** (2.98 g, 8.1 mmol, 65% yield) as a light yellow oil. Starting material **20** (~0.3 g, 1.3 mmol, ~10%) was also recovered.

See spectra on page S30

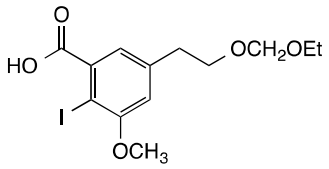
^{1}H NMR: (400 MHz, $CDCl_3$)

6.99 (s, 1H); 6.65 (s, 1H); 4.67-4.64 (m, 4H); 3.89 (s, 3H); 3.78 (t, *J*=6.8 Hz, 2H); 3.53 (q, *J*= 7.2 Hz, 2H); 2.89 (t, *J*=6.8 Hz, 2H); 2.59 (br, 1H); 1.18 (t, *J*=8.0 Hz, 3H)

^{13}C NMR: (100 MHz, $CDCl_3$)

157.8; 144.3; 140.8; 121.3; 110.8; 95.0; 86.4; 69.4; 68.1; 63.3; 56.5; 36.1; 15.1

HRMS (ESI): calculated for $C_{13}H_{19}INaO_4$: 389.0226; found $(M+Na)^+$: 389.0222



22

Iodo alcohol **21** (2 g, 5.46 mmol) was dissolved in CH_2Cl_2 (10 mL, 0.5M) and PCC (2.35 g, 10.9 mmol, 2eq) and KOAc (1.07 g, 10.9 mmol, 2eq) was added. After 2 hours, the reaction was diluted with EtOAc (20 mL) and filtered through a celite cake. The combined eluates were concentrated *in vacuo* to give a dark-brown oil. The crude aldehyde was dissolved in CH_2Cl_2 (10 mL) and rapidly flushed through a pad of silica gel and concentrated *in vacuo*. The aldehyde was dissolved in *t*-BuOH (~55 mL, ~0.1M). To this mixture, a solution of $NaClO_2$ (~800 mg, 8.2 mmol, ~1.5eq) and NaH_2PO_4 (~980 mg, 8.2 mmol, ~1.5eq) in water (8 mL) was added and the reaction was stirred for 1 hr. The reaction was stopped by the addition of water (5 mL) and CH_2Cl_2 (20 mL), and the layers were separated and the organic phase was washed with brine (10 mL). The CH_2Cl_2 extracts were dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude carboxylic acid was diluted in diethyl ether (20 mL). To this solution, saturated aqueous $NaHCO_3$ (10 mL) was added and the layers were separated; the aqueous layer was acidified with 1M HCl (12 mL) and extracted with DCM (20 mL). The combined extracts were collected and concentrated under reduced pressure to give carboxylic acid **22** (1.6 g, 4.4 mmol, overall 80%).

See spectra on page S31

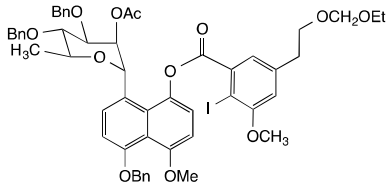
^{1}H NMR: (400 MHz, $CDCl_3$)

10.60 (br, 1H); 7.22 (s, 1H); 6.78 (s, 1H); 4.61 (s, 2H); 3.78 (s, 3H); 3.74 (m, 2H); 3.44 (q, *J*=7.2 Hz, 2H); 2.88 (t, *J*=6.8 Hz, 2H); 1.08 (t, *J*=8 Hz, 3H)

^{13}C NMR: (100 MHz, $CDCl_3$)

171.7; 158.7; 141.0; 137.4; 123.7; 114.6; 94.9; 84.3; 67.8; 63.4; 56.8; 35.8; 15.0

HRMS (ESI): calculated for $C_{13}H_{17}INaO_5$: 403.0018; found 403.0095 $(M+Na)^+$



23

Intermediate **14a** (0.65 g, 0.9 mmol) was dissolved in CH_2Cl_2 (9 mL, 0.1M). To the mixture a freshly prepared 10% HCl (1 mL, 0.1 eq) solution in methanol was added. The reaction was stirred at room temperature for 8 hrs and stopped by adding saturated sodium bicarbonate (10 mL) solution. The aqueous solution was extracted with CH_2Cl_2 (2x10 mL). The combined CH_2Cl_2 extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude naphthol. The crude oil was then flushed through a silica gel column (CH_2Cl_2) and concentrated *in vacuo* to give compound **14b** (0.55 g, 0.85 mmol, 95%). **14b** was found to be unstable when exposed to light and air. **14b** (0.55 g, 0.85 mmol), **22** (0.52 g, 1.29 mmol, 1.5 eq) and EDC (200 mg, 1.29 mmol) were immediately mixed and dissolved in CH_2Cl_2 (15 mL, 0.1M). To this solution, DMAP (15.8 mg, 0.13 mmol, 0.1eq) was added and the reaction mixture was stirred for 15 hrs. The reaction was stopped by the addition of saturated $NaHCO_3$ (10 mL). The resulting aqueous solution was extracted with CH_2Cl_2 (20 mL). The combined organic solution was washed with brine (10 mL), concentrated under reduced pressure and purified through silica gel column (10:1 → 4:1 hexanes: ethyl acetate) to obtain ester **23** (0.84 g, 0.83 mmol, 98%).

See spectra on page S32

^{1}H NMR: (400 MHz, $CDCl_3$)

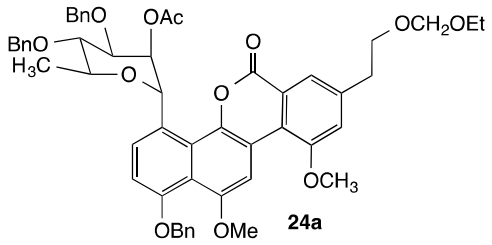
7.79 (d, *J*=8.4 Hz, 1H); 7.60-6.93 (m, 2H); 7.50- 7.20 (m, 18H); 6.97 (d, 8.4 Hz, 1H); 6.93 (d, 8.3 Hz, 1H); 6.81 (s, 1H); 5.85 (d, *J*=3.5 Hz, 1H); 5.36 (s, 1H); 5.21 (s, 2H); 4.80 (d, *J*=11.8 Hz, 1H); 4.63-4.51 (m, 5H); 3.97 (s, 3H); 3.75-3.72 (m, 5H); 3.51 (q, *J*=7.2 Hz, 2H); 3.44-3.40 (m, 2H); 2.85 (t, *J*=6.7 Hz, 2H); 2.73 (dd, *J*=3.3, 6.7 Hz, 1H); 1.76 (s, 3H); 1.27 (d, *J*=5.5 Hz, 3H); 1.18 (t, *J*=7.0 Hz, 3H)

^{13}C NMR: (100 MHz, $CDCl_3$)

169.6; 166.8; 158.9; 156.2; 156.1; 142.3; 139.4; 139.1; 138.4; 137.4; 128.4; 128.3; 128.2; 128.1; 127.9; 127.8; 127.6; 127.5; 127.4; 127.1; 126.8; 124.6; 122.9; 121.2; 119.8; 114.5; 108.6; 105.5; 95.0; 83.7; 82.7; 79.9; 76.7; 75.9; 75.8; 75.7; 74.6; 71.7; 71.6; 69.6; 67.4; 63.3; 56.6; 35.9; 20.6; 18.5; 15.2

HRMS (ESI): calculated for $C_{53}H_{55}INaO_{12}$: 1033.2636; found $(M+Na)^+$: 1033.2626

$[\alpha]^{25}_D$: -32.5° (c=0.0004, CH_2Cl_2)



24a

To ester **23** (145 mg, 0.143 mmol) in DMA (16 mL, 0.01M), $(Ph_3P)_2PdCl_2$ (16 mg, 0.05 mmol, 25 mol%) and KOAc (87 mg, 0.6 mmol, 3eq) were added and the mixture was heated to 120°C for 5 hrs. After the reaction was cooled, the resulting dark brown solution was diluted with Et_2O (20 mL). The mixture was successively washed with saturated sodium bicarbonate (10 mL) and brine (10 mL). The combined ether extracts were concentrated under *in vacuo* and the crude product was purified by silica gel chromatography. The resulting product was re-purified by silica gel chromatography (10:1 → 2:1 hexanes: ethyl acetate) to furnish **24a** as light yellow oil (81.0 mg, 0.092 mmol, 64%).

See spectra on page S33

^{1}H NMR: (400 MHz, $CDCl_3$)

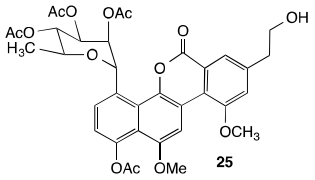
8.55 (s, 1H); 8.01 (s, 1H); 7.94 (d, *J*=8.4 Hz, 1H); 7.70 (m, 2H); 7.62 (d, *J*=8.5 Hz, 2H); 7.54 (m, 1H); 7.46-7.26 (m, 21H); 7.08 (d, *J*= 8.4 Hz, 1H); 6.33 (d, *J*=3.4 Hz, 1H); 6.14 (s, 1H); 5.24 (s, 2H); 5.03 (d, *J*=11.5 Hz, 1H); 4.83 (d, *J*= 11.4 Hz, 1H); 4.75-4.69 (m, 4H); 4.57 (dd, *J*=3.4, 6.7 Hz, 1H); 4.12 (s, 3H); 4.01 (s, 3H); 3.90 (t, *J*=6.6 Hz, 2H); 3.62-3.54 (m, 4H); 3.07 (t, *J*=6.4 Hz, 2H); 1.92 (s, 3H); 1.50 (d, *J*=5.6 Hz, 3H); 1.20 (t, *J*=7.0 Hz, 3H)

^{13}C NMR: (100 MHz, $CDCl_3$)

170.2; 160.3; 157.4; 155.1; 153.3; 141.5; 141.3; 138.9; 138.5; 137.3; 132.0; 128.4; 127.8; 127.4; 127.0; 124.0; 122.9; 122.4; 122.1; 120.8; 119.0; 118.2; 114.7; 109.7; 105.1; 95.1; 95.0; 81.9; 80.5; 76.6; 75.9; 75.2; 75.0; 71.6; 70.5; 67.7; 67.5; 63.3; 56.8; 56.7; 56.4; 36.5; 36.2; 24.6; 20.9; 18.6; 15.1

HRMS (ESI): calculated for $C_{53}H_{54}NaO_{12}$: 905.3513; found $(M+Na)^+$: 905.3458

$[\alpha]^{25}_D$: -40.0° (c=0.0008, CH_2Cl_2)



In the presence of the Pearlman's catalyst $Pd(OH)_2$ (20% on C, 5 mg), a solution of compound **24a** (15 mg, 0.017 mmol) in MeOH (4 mL) and THF (1 mL) was stirred under H_2 at room temperature for 8 hrs. The mixture was filtered through a Celite cake and washed with EtOAc (20 mL). The solvent was concentrated *in vacuo* to give a crude tetraol as bright yellow oil. This compound was dissolved in pyridine (5 mL, 0.003 M), to which was added Ac_2O (0.75 mL) and a catalytic amount of DMAP (5 mg). After the mixture was stirred for 3h at room temperature, the reaction was stopped by the addition of a small amount of MeOH (2 mL). The mixture was diluted with Et_2O (5 mL) and washed successively with saturated sodium bicarbonate (5 mL) and Cu_2SO_4 solution (5 mL), dried (over Na_2SO_4), and concentrated *in vacuo*. The residue was purified by silica gel chromatography (2:1 ~ 1:4 Hexanes: Ethyl Acetate) to give pure tetraacetate **24b** (8 mg, 0.0108 mmol, 64%) as bright yellow foam.

To a solution of tetraacetate ether **24b** (45 mg, .060 mmol) in CH_2Cl_2 (4.5 mL, 0.01M) was added a solution of TMSBr (51.3 mg, 0.335 mmol, 5.6 eq) in CH_2Cl_2 (0.5 mL) at -78°C. The reaction mixture was gradually warmed to -10 °C over 3 hrs, and the stirring was continued for 30 min at this temperature. The reaction was stopped by the addition of saturated aqueous $NaHCO_3$ (10 mL) and the mixture was extracted with EtOAc (10 mL). The combined organic extracts were washed with brine (10 mL), dried over sodium sulfate and concentrated under reduced pressure. The resulting yellow oil was purified by silica gel column chromatography (1:1 → 1:5 hexanes: ethyl acetate) to give primary alcohol **25** (37 mg, 0.055 μmol, 91%).

See spectra on page S34

^{1}H NMR: (400 MHz, $CDCl_3$)

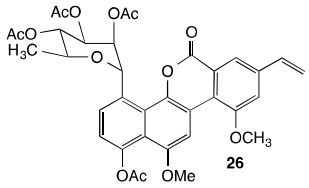
8.52 (s, 1H); 8.03 (s, 1H); 8.01 (d, *J*=8.4 Hz, 1H); 7.26 (d, *J*=8.2 Hz, 1H); 7.18 (d, *J*=8.2 Hz, 1H); 6.40 (s, 1H); 6.00 (d, *J*=3.4 Hz, 1H); 5.73 (dd, *J*= 3.4, 6.7 Hz, 1H); 5.25 (t, *J*= 16.1 Hz, 1H); 5.15 (s, 1H); 4.03-3.80 (m, 8H); 3.42 (s, 1H); 3.00 (t, *J*=7.0 Hz, 2H); 2.40 (s, 3H); 2.13 (s, 3H); 1.97 (s, 3H); 1.88 (s, 3H); 1.39 (d, *J*=6.4 Hz, 3H)

^{13}C NMR: (100 MHz, $CDCl_3$)

173.0; 172.5; 172.4; 162.5; 160.0; 153.9; 148.7; 143.9; 134.2; 131.6; 130.3; 125.9; 125.2; 125.1; 123.0; 122.7; 121.1; 117.5; 110.0; 107.5; 77.3; 75.1; 74.6; 73.9; 65.6; 59.0; 58.9; 41.6; 25.3; 23.6; 23.3; 23.1; 20.6; 17.9; 16.7

HRMS (ESI): calculated for $C_{35}H_{36}NaO_{14}$: 703.2003; found $(M+Na)^+$: 703.1940

$[\alpha]^{25}_D$: -96.8° (c=0.007, CH_2Cl_2)



26

To a solution of alcohol **25** (7.7 mg, 0.011 mmol) in THF (0.1 mL, 0.1M) was added *o*-nitrophenyl selenocyanate (26 mg, 0.11 mmol, 10 eq) and *n*-Bu_3P (21 mg, 0.11 mmol, 10 eq) at room temperature. After the mixture was stirred for 10 min, a 30% aqueous hydrogen peroxide solution was added (0.089 mL) at 0°C, and after being stirred for 30 min at room temperature, the reaction mixture was concentrated under reduced pressure and diluted with MeOH (5 mL). The resulting bright yellow solids were filtered and residual methanol solution was concentrated *in vacuo* (5 minutes) to give crude polycarcin V tetraacetate **26**. The product was purified by silica gel column chromatography (2:1 → 1:2 hexanes: ethyl acetate) to give **26** (4.3 mg, 0.0063 mmol, 57%), which was isolated by azeotroping the column fractions with CCl_4 and concentration *in vacuo* for 5 minutes before dissolving the sample in $CDCl_3$ for NMR.

See comparison spectra on pages S35- S37 and HMBC page S38

^{1}H NMR: (400 MHz, $CDCl_3$)

8.55 (s, 1H); 8.23 (s, 1H); 8.01 (d, *J*=8.4 Hz, 1H); 7.39 (s, 1H); 7.19 (d, *J*=8.4 Hz, 1H); 6.82 (dd, *J*=8.7, 17.3 Hz, 1H); 6.41 (s, 1H); 6.00 (d, *J*=3.0 Hz, 1H); 5.97 (d, *J*=17.5 Hz, 1H); 5.74 (dd, *J*=3.4, 9.9 Hz, 1H); 5.47 (d, *J*=10.8 Hz, 1H); 5.24 (t, *J*=7.2 Hz, 1H); 4.13 (s, 3H); 4.01 (s, 3H); 3.94 (qd, *J*=6.1, 7.0 Hz, 1H); 2.40 (s, 3H); 2.12 (s, 3H); 1.97 (s, 3H); 1.88 (s, 3H); 1.39 (d, *J*= 6.1 Hz, 3H)

^{13}C NMR: (100 MHz, $CDCl_3$)

169.4; 168.9; 168.8; 168.7; 158.8; 156.6; 150.3; 145.0; 140.5; 138.0; 134.2; 130.7; 127.7; 122.7; 122.6; 122.3; 121.7; 119.6; 119.5; 119.2; 115.6; 113.8; 113.5; 104.8; 73.7; 71.4; 70.9; 70.2; 55.4; 55.0; 21.6; 20.0; 18.7.

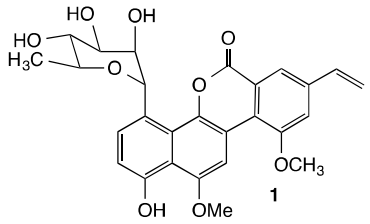
HRMS (ESI): calculated for $C_{35}H_{34}NaO_{13}$: 685.1897; found $(M+Na)^+$: 685.1924

$[\alpha]^{25}_D$: -61° (c=0.0007, CCl_4)

Naturally isolated polycarcin V **1** (1.5 mg, 0.003 mmol) was dissolved in pyridine (0.4 mL)/Ac_2O (0.4 mL) and stirred at rt for 3 h. After the solvent was removed under reduced pressure, the residue was dissolved in MeOH (0.5 mL) and then subjected to preparative reverse-phase HPLC (Phenomenex fusion RP, 20 × 250 mm, flow-rate 12 mL/min) using a gradient system solvent A (H_2O), solvent B (acetonitrile); 40% B (10 min) to 100% B in 30 min to yield 1.9 mg (95%).

^{1}H NMR: (600 MHz, $CDCl_3$, Spectrum was referenced to $CDCl_3$.)
8.51 (s, 1H); 8.20 (d, 1.5 Hz, 1H); 7.99 (d, *J*=8.2 Hz, 1H); 7.36 (d, *J*=1.5 Hz, 1H); 7.16 (d, *J*=8.2 Hz, 1H); 6.79 (dd, *J*=10.8, 17.6 Hz, 1H); 6.39 (s, 1H); 5.98 (d 3.4, 1H); 5.97 (d, *J*=17.6 Hz, 1H); 5.72 (dd, *J*=3.4, 9.6 Hz, 1H); 5.45 (d, *J*=10.8 Hz, 1H); 5.22 (t, *J*=9.6 Hz, 1H); 4.08 (s, 3H); 3.98 (s, 3H); 3.94 (qd, *J*=6.2, 9.6 Hz, 1H); 2.38 (s, 3H); 2.10 (s, 3H); 1.95 (s, 3H); 1.86 (s, 3H); 1.38 (d, *J*= 6.2 Hz, 3H)

^{13}C NMR: (150 MHz, $CDCl_3$, Spectrum was referenced to $CDCl_3$.)
170.4; 169.9; 169.8; 169.7; 159.8; 157.6; 151.3; 146.0; 141.5; 139.0; 135.3; 131.7; 127.7; 123.7; 123.3; 122.7; 120.53; 120.48; 120.2; 116.7; 114.8; 114.5; 104.8; 74.7; 72.5; 72.0; 71.3; 56.4; 56.3; 20.9; 20.7; 20.5; 18.0.
HRMS (ESI): calculated for $C_{35}H_{35}O_{13}$: 663.2072; found $(M+H)^+$: 663.2075
$[\alpha]^{25}_D$: -124° (*c*=0.18, CCl_4)



1

Tetraacetate **26** (3.4 mg, 5.3 μmol) was dissolved with MeOH (1.2 mL, 0.01M). To the solution was treated with NaCN (1 mg). The mixture was stirred for 20 hrs at room temperature and was then diluted with 9:1 $CHCl_3$:MeOH. The mixture was concentrated *in vacuo* and then loaded onto a silica gel column. Elution with 9:1 $CHCl_3$:MeOH gave synthetic **1** (2.0 mg, 4 μmol, 77%).

See spectra on page S39 and comparison of natural and synthetic data on page S40.

^{1}H NMR: (400 MHz, $CDCl_3$)

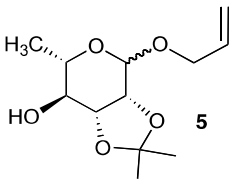
9.71 (s, 1H); 8.44 (s, 1H); 7.96 (s, 1H); 7.80 (d, *J*=7.8 Hz, 1H); 7.71 (s, 1H); 6.95 (d, *J*=7.8 Hz, 1H); 6.93 (m, 1H); 6.13 (d, *J*=17.4 Hz, 1H); 5.82 (s, 1H); 5.49 (d, *J*=10.8 Hz, 1H); 4.80 (m, 1H); 4.45 (m, 1H); 4.14 (s, 3H); 4.09 (s, 3H); 4.05 (m, 1H); 4.01 (m, 1H); 3.78 (m, 1H); 3.30-3.40 (m, 1H); 3.22 (s, 1H); 1.27 (d, *J*= 6.7 Hz, 3H).

^{13}C NMR: (100 MHz, $CDCl_3$)

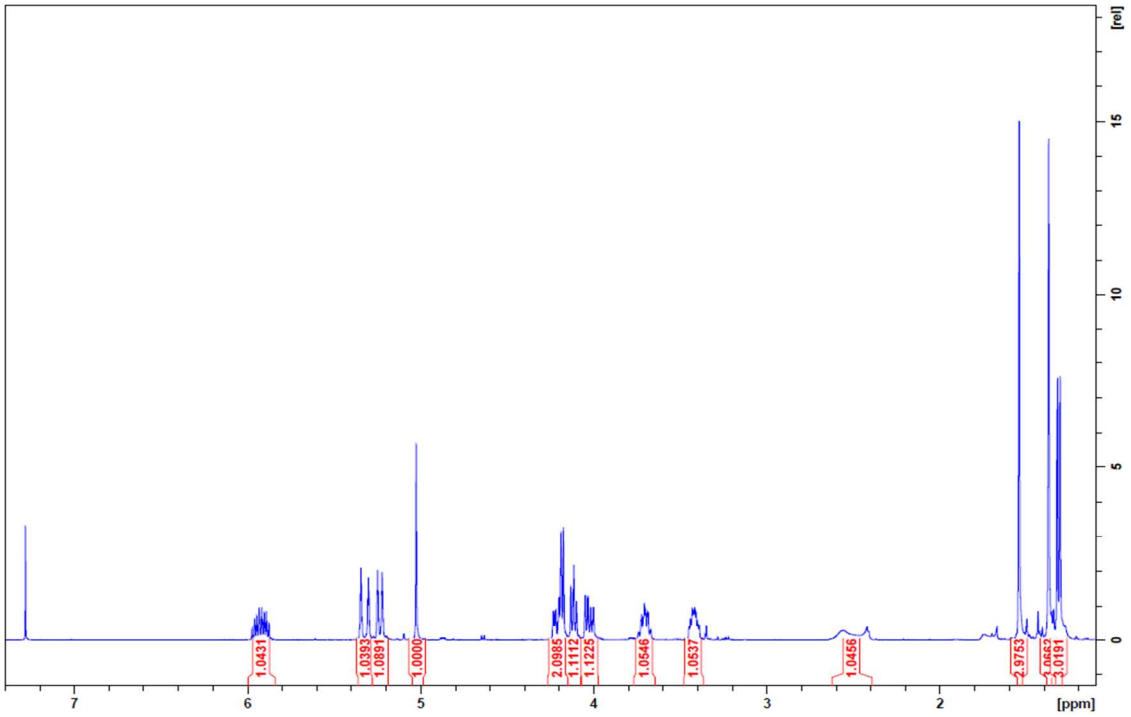
159.8; 157.9; 153.2; 152.5; 142.2; 139.3; 135.6; 130.4; 127.4; 122.9; 122.3; 121.2; 119.6; 117.7; 115.2; 114.5; 114.0; 112.5; 101.9; 77.9; 77.0; 75.1; 73.2; 72.0; 56.7; 55.7; 18.9.

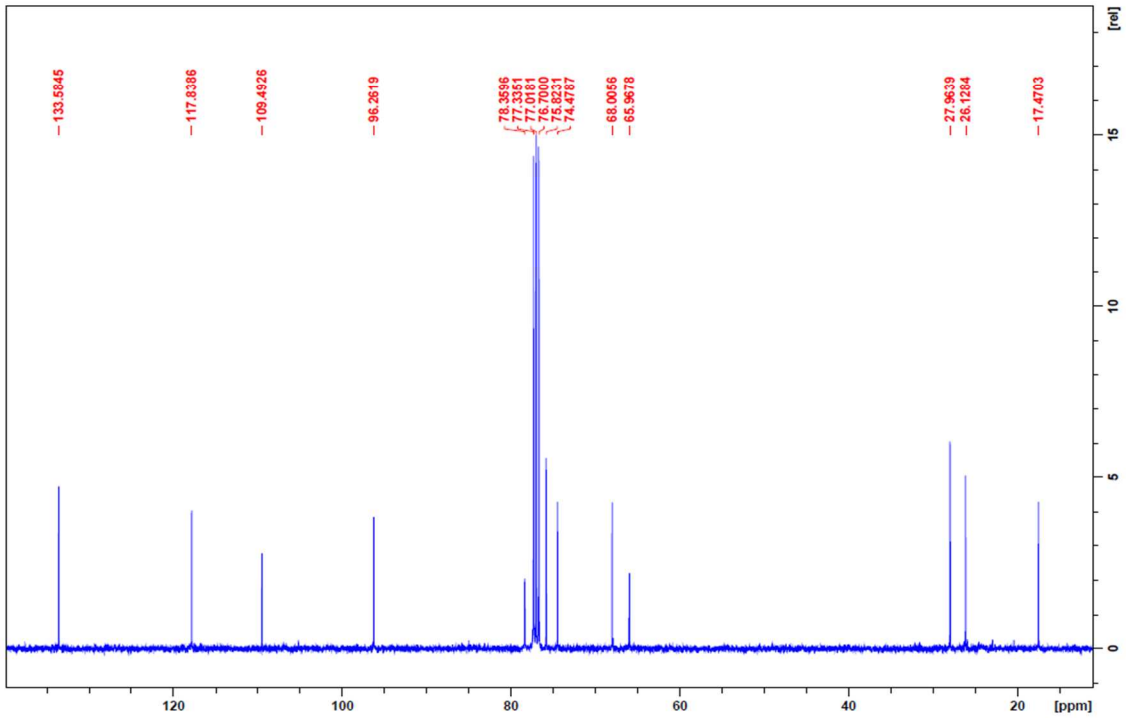
HRMS (ESI): calculated for $C_{27}H_{26}NaO_9$: 517.1475; found 517.1528 $(M+Na)^+$:

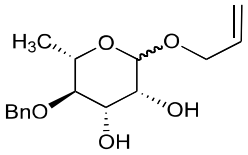
$[\alpha]^{25}_D$: -84.2° (c=0.0007, CH_3OH)



^{1}H (400 MHz) and ^{13}C NMR (100 MHz) spectra

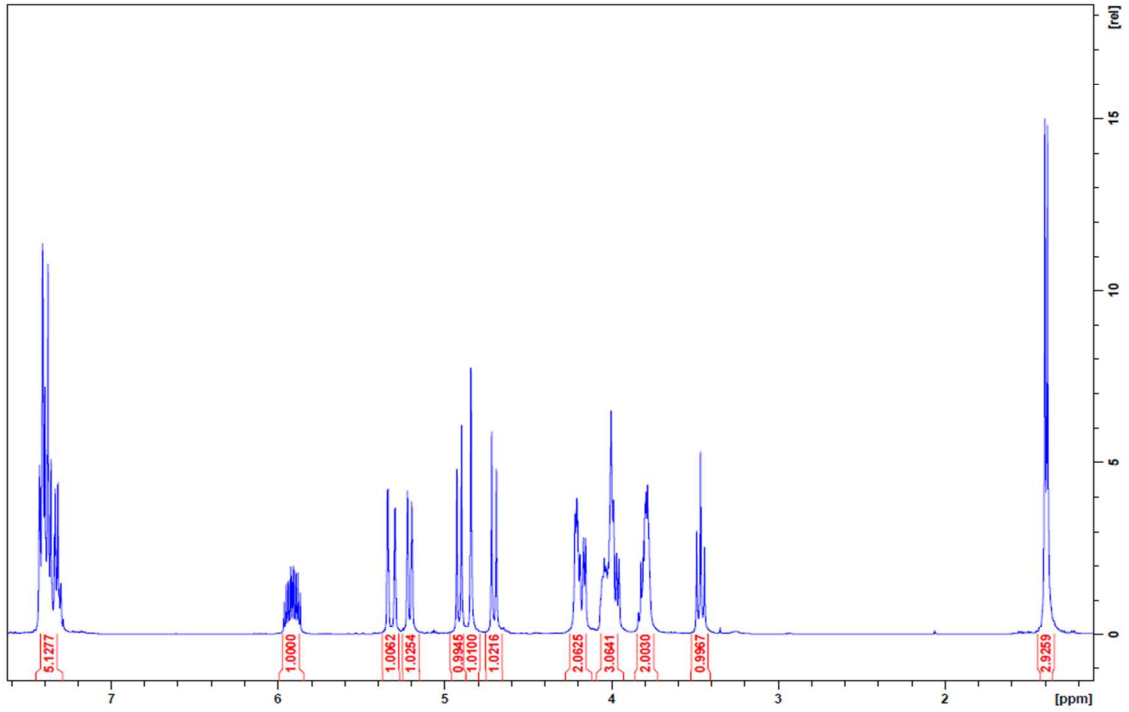


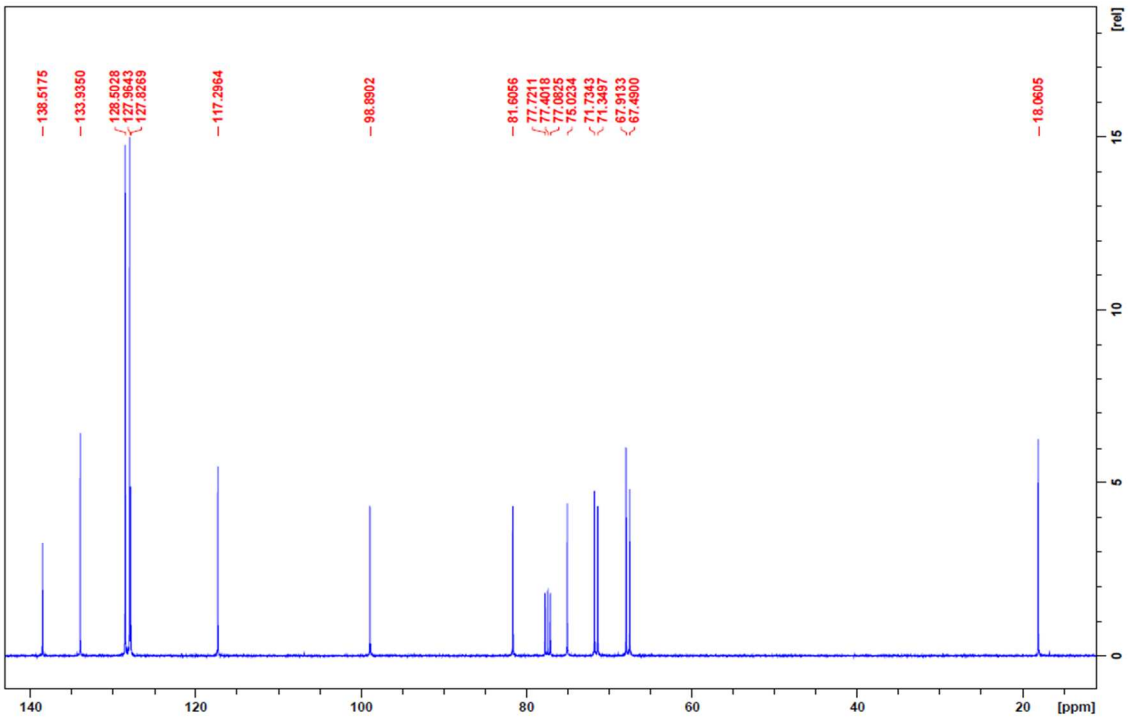


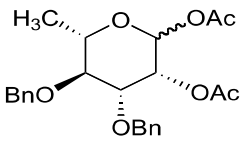


6

^{1}H (400 MHz) and ^{13}C NMR (100 MHz) spectra

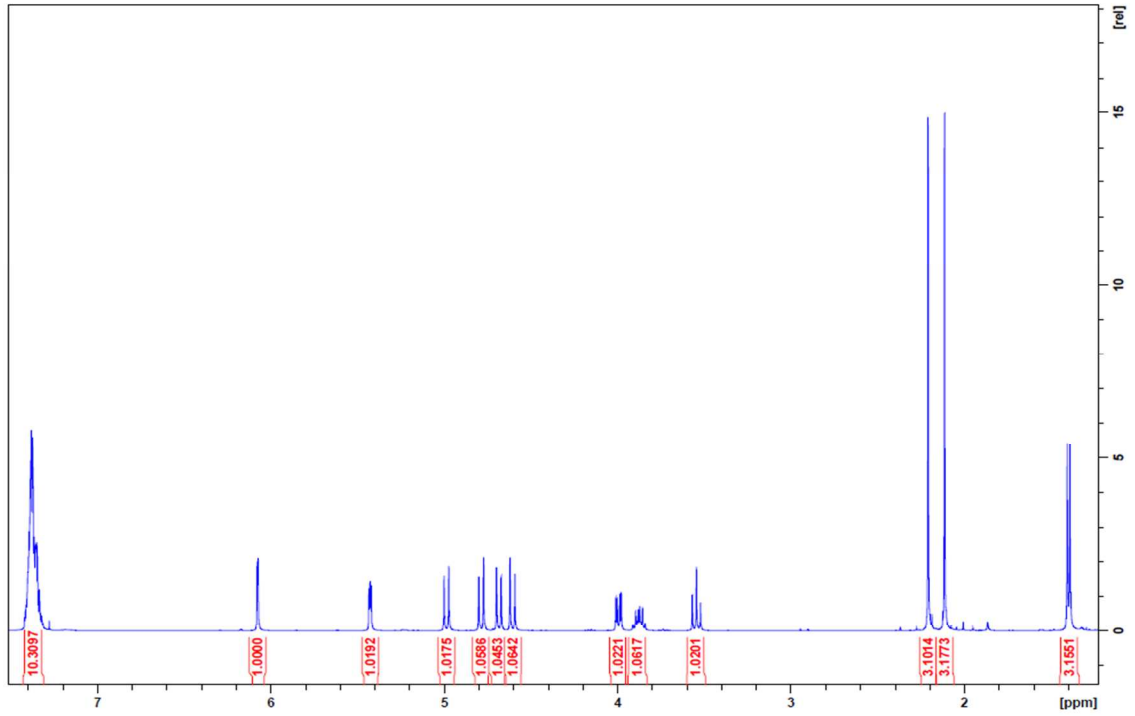


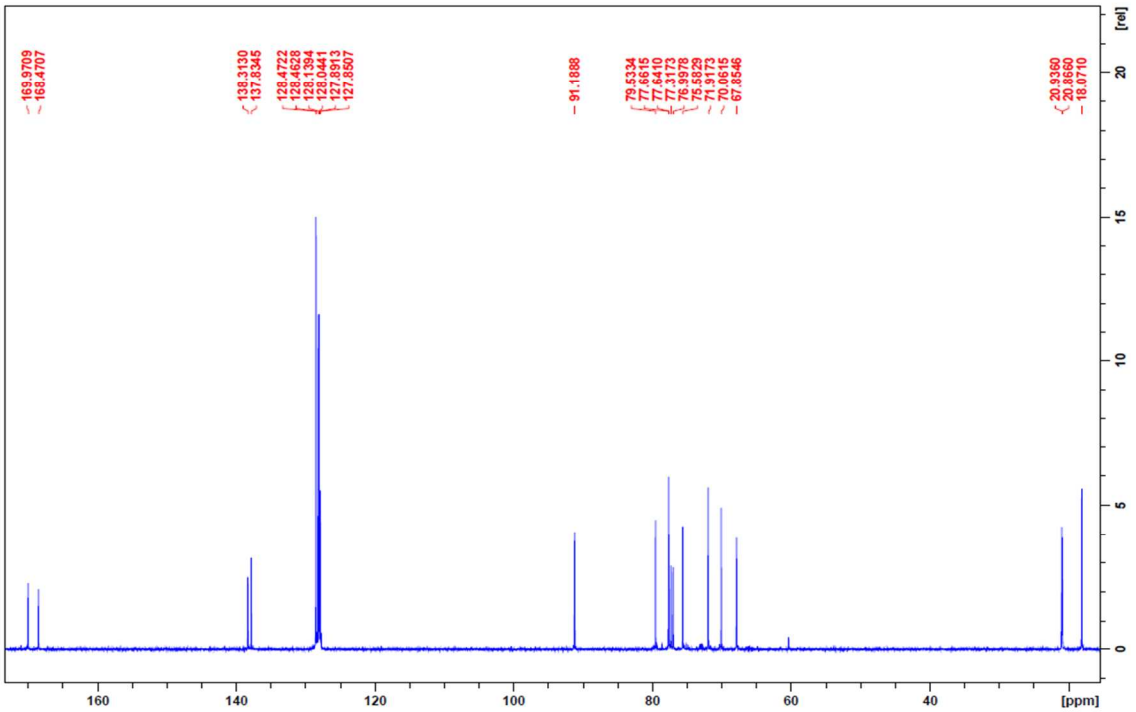


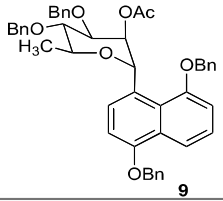


7

^{1}H (400 MHz) and ^{13}C NMR (100 MHz) spectra

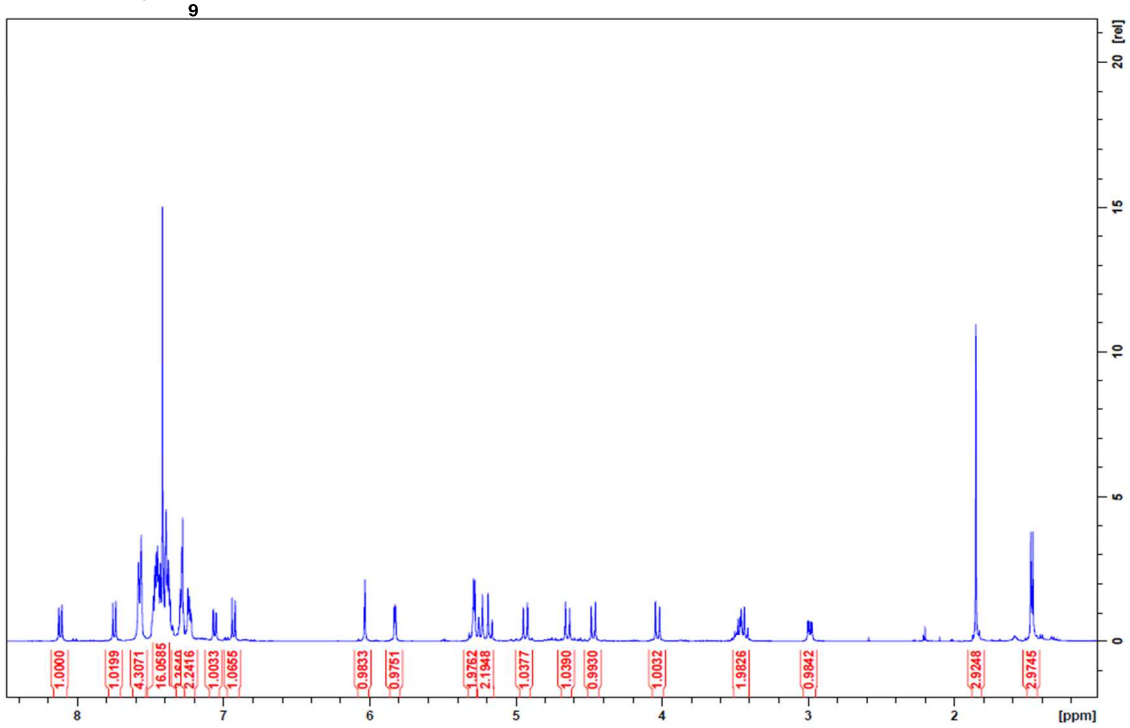


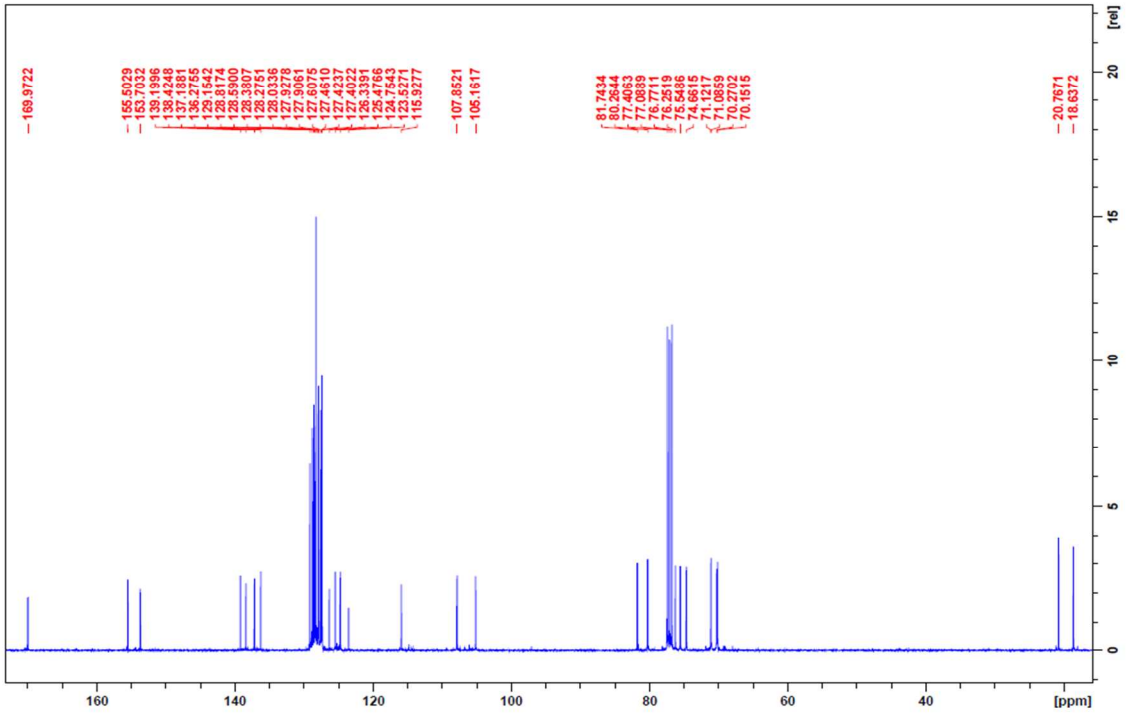


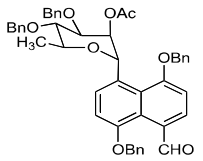


9

^{1}H (400 MHz) and ^{13}C NMR (100 MHz) spectra

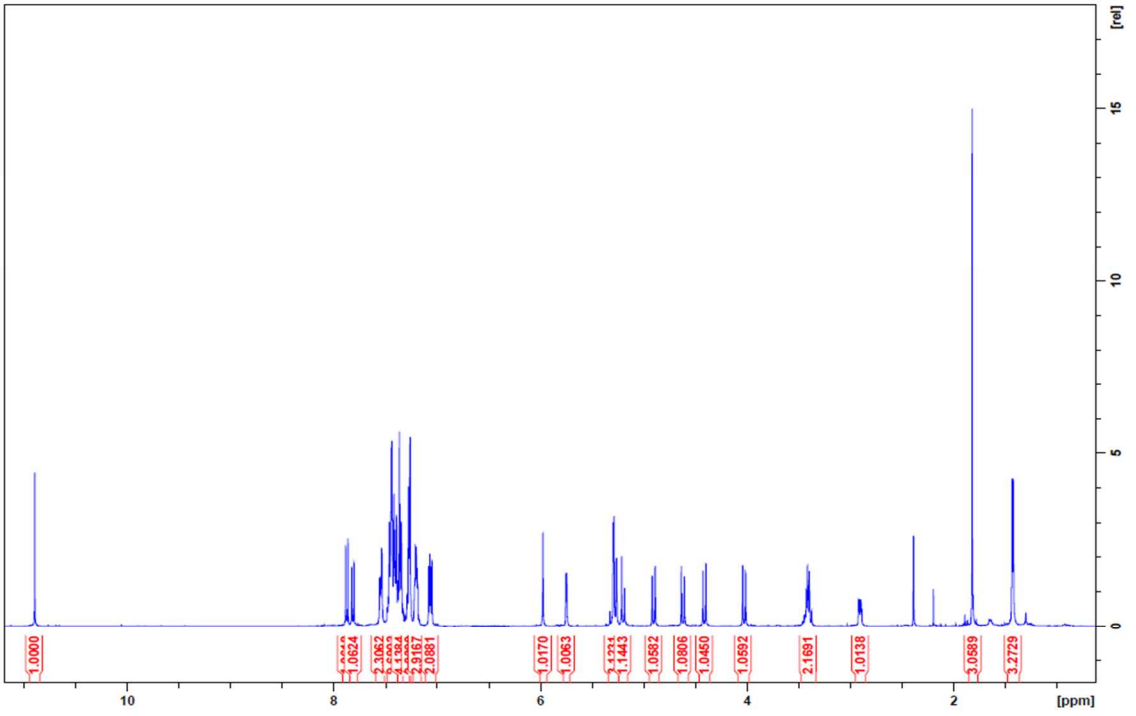


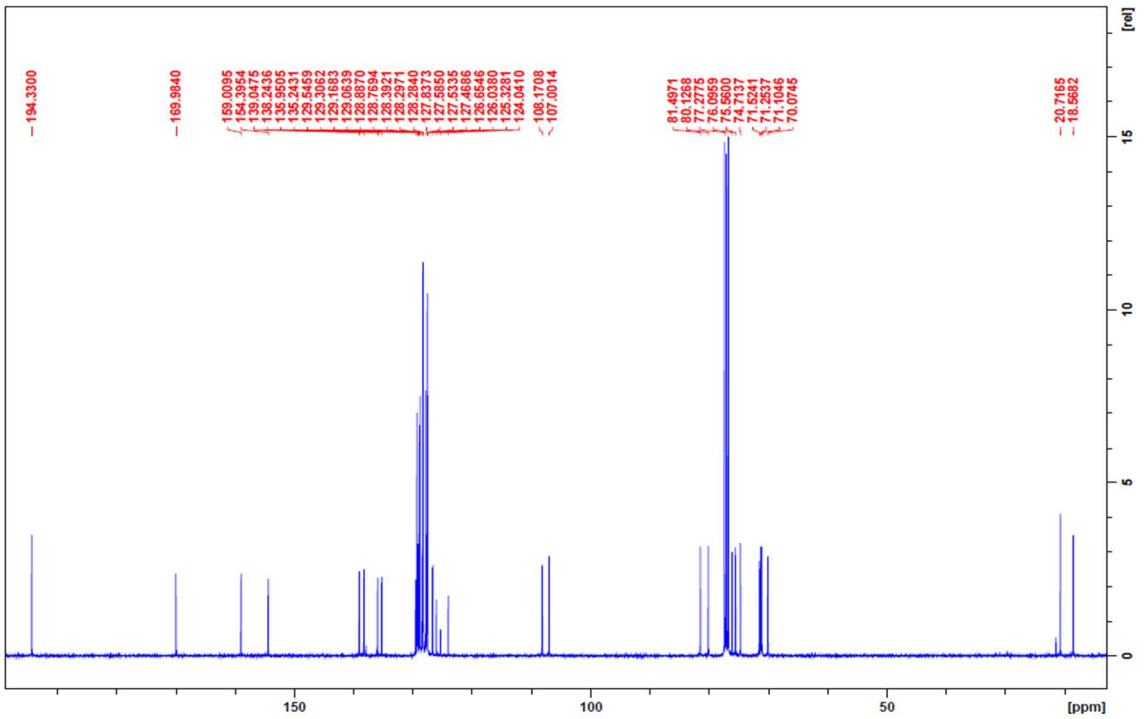


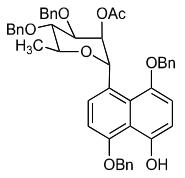


10

^{1}H (400 MHz) and ^{13}C NMR (100 MHz) spectra

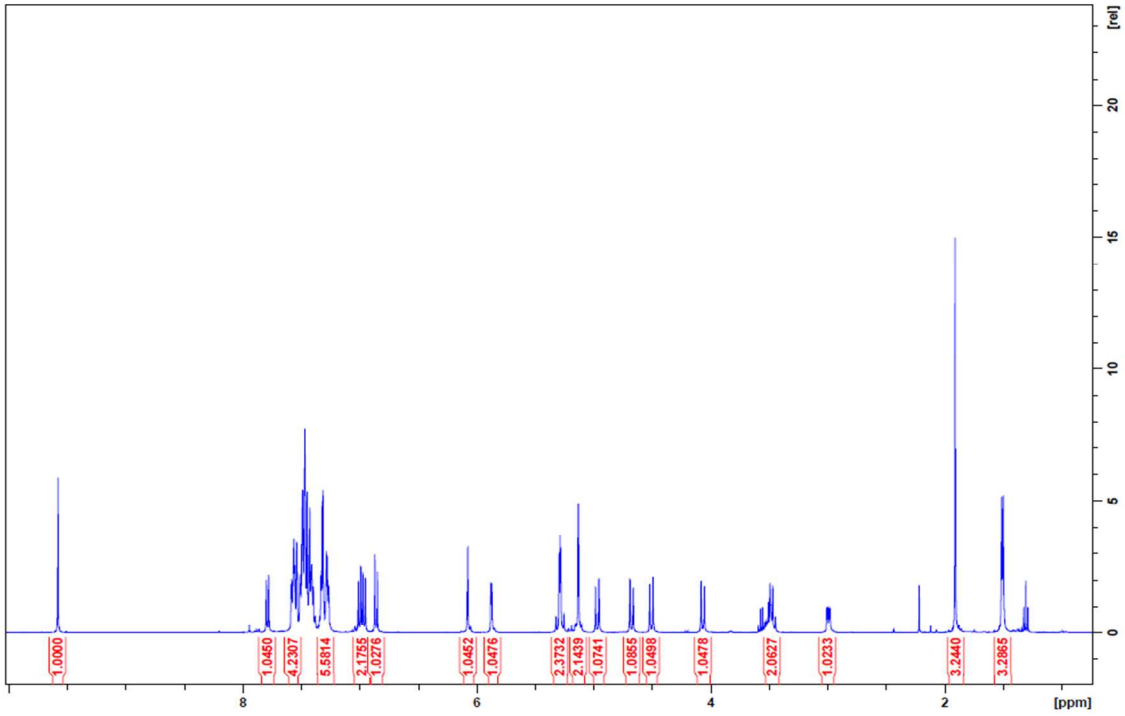


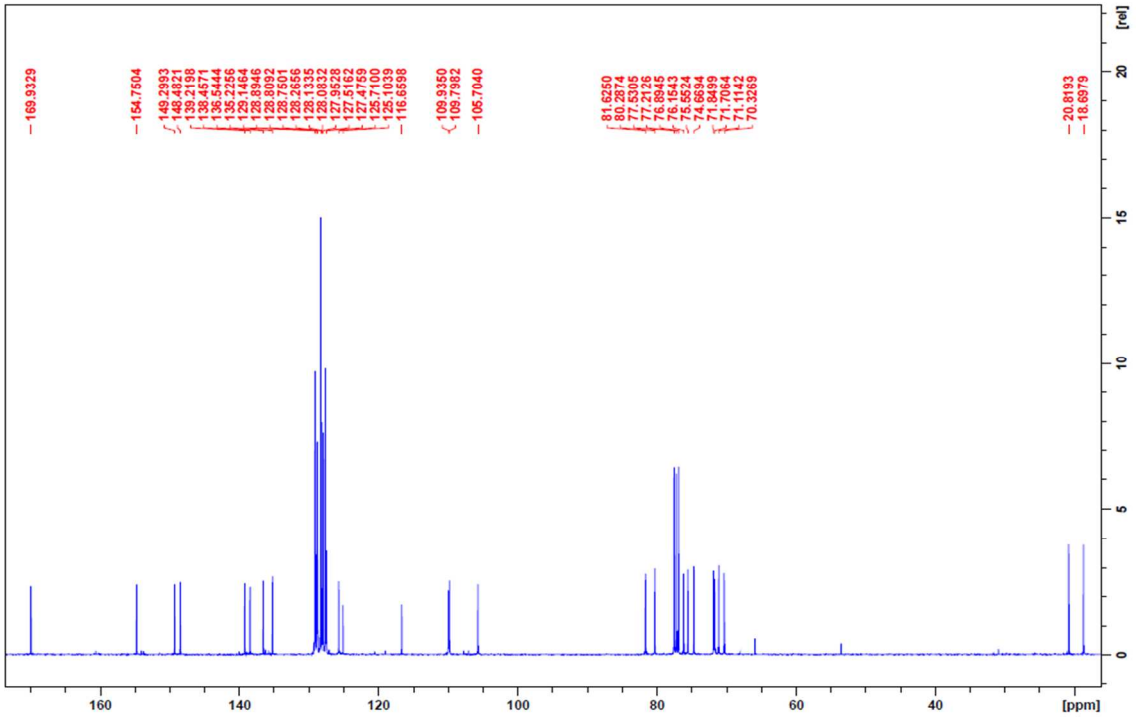


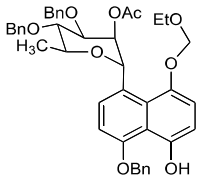


11

^{1}H (400 MHz) and ^{13}C NMR (100 MHz) spectra

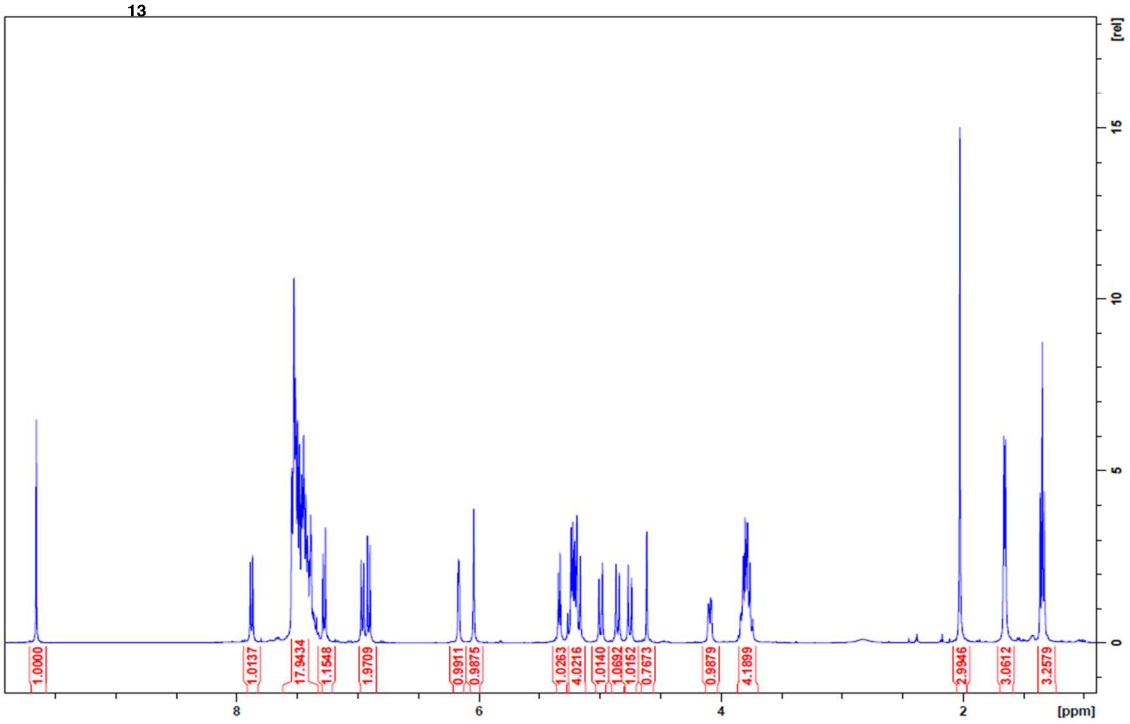


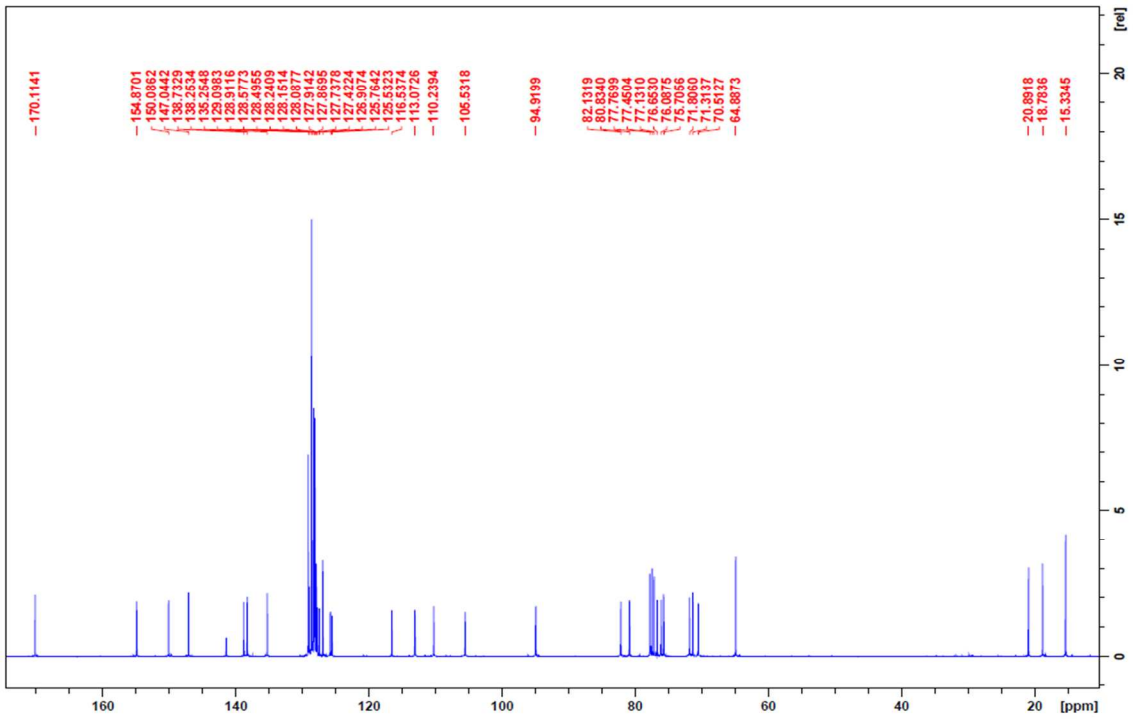


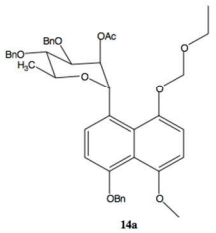


13

^{1}H (400 MHz) and ^{13}C NMR (100 MHz) spectra

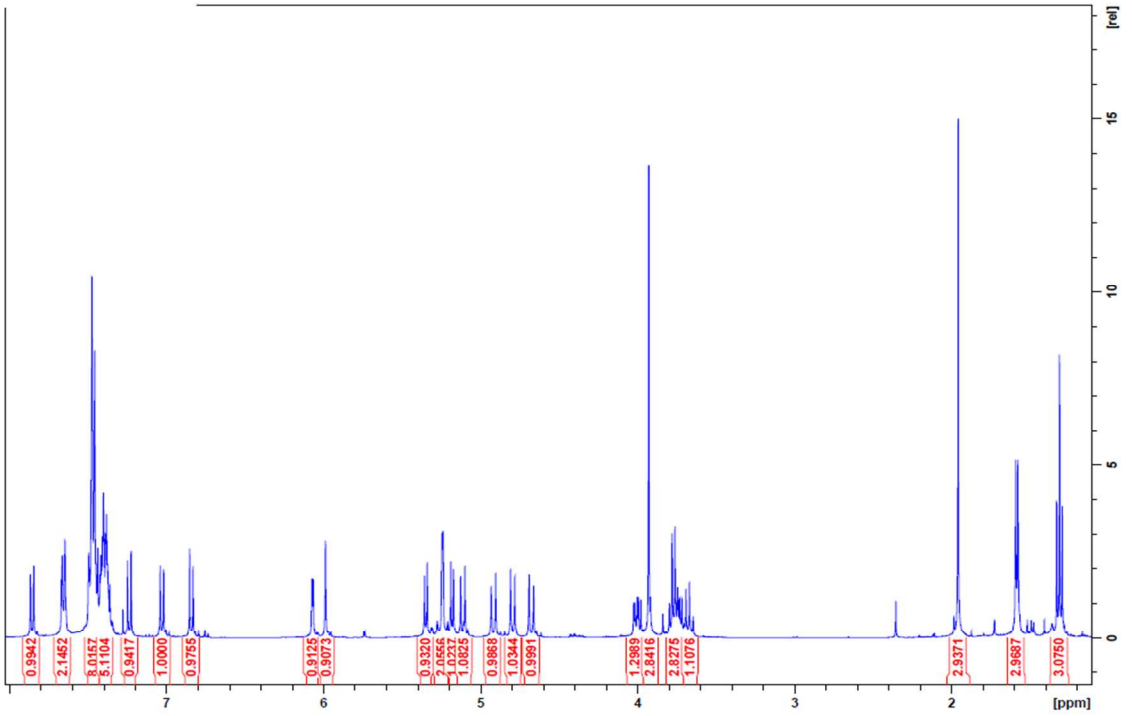


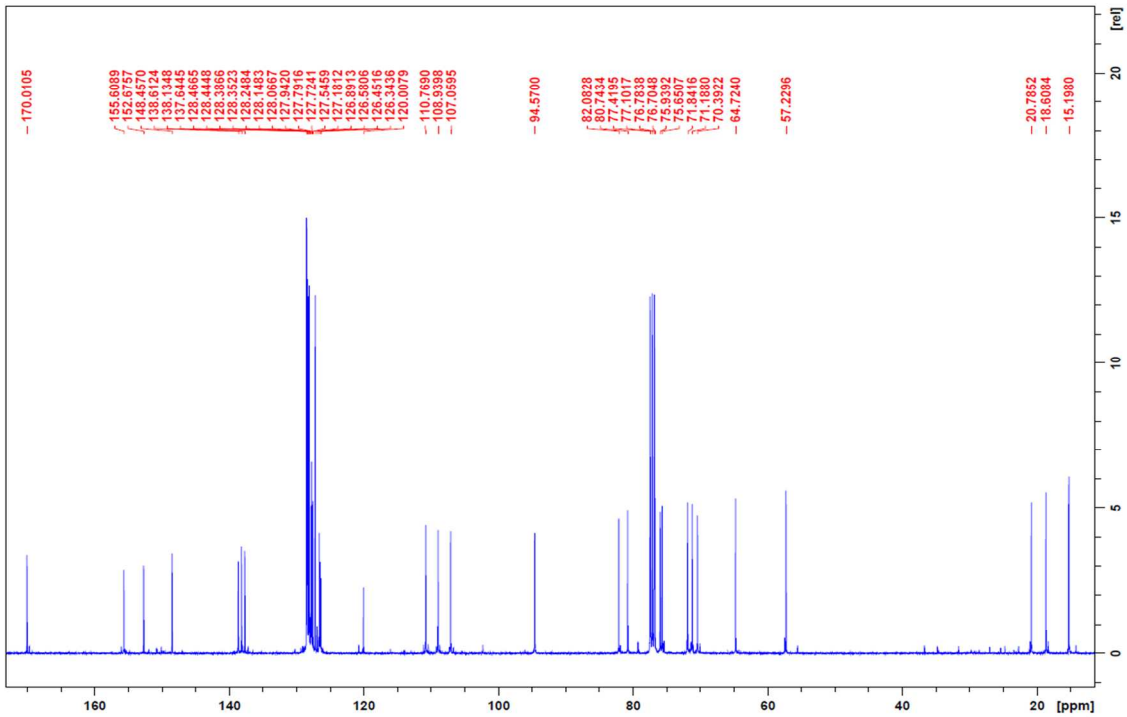


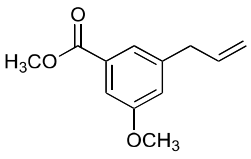


14a

^{1}H(400 MHz) and ^{13}C NMR (100 MHz) spectra

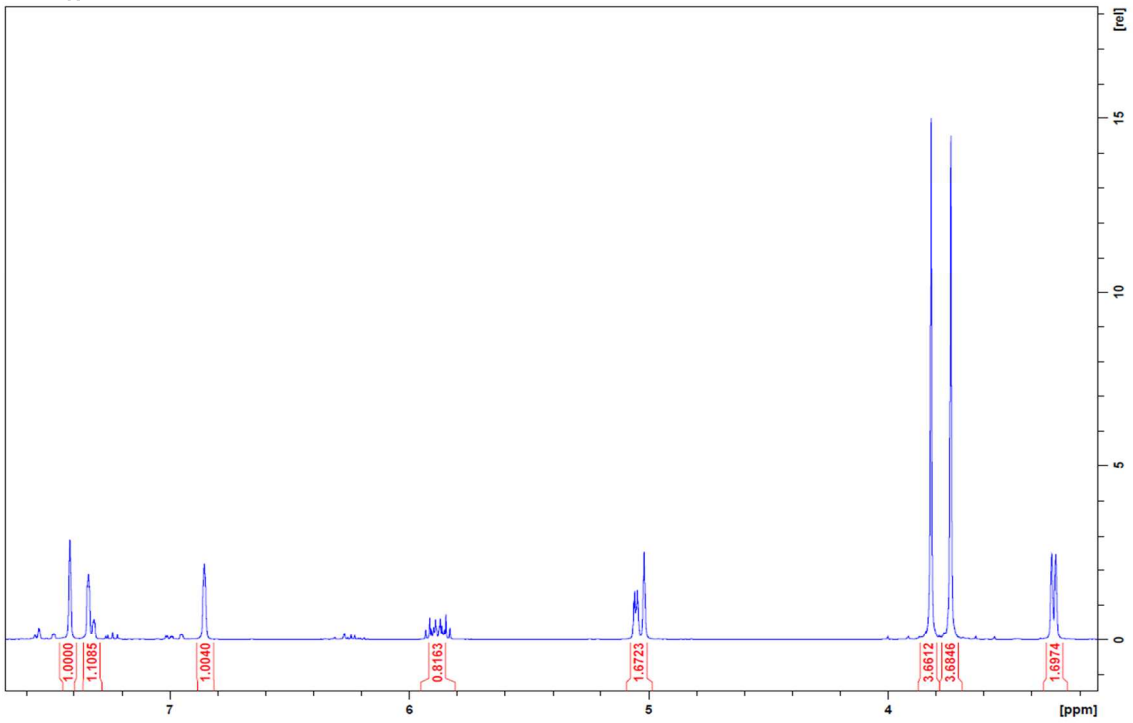


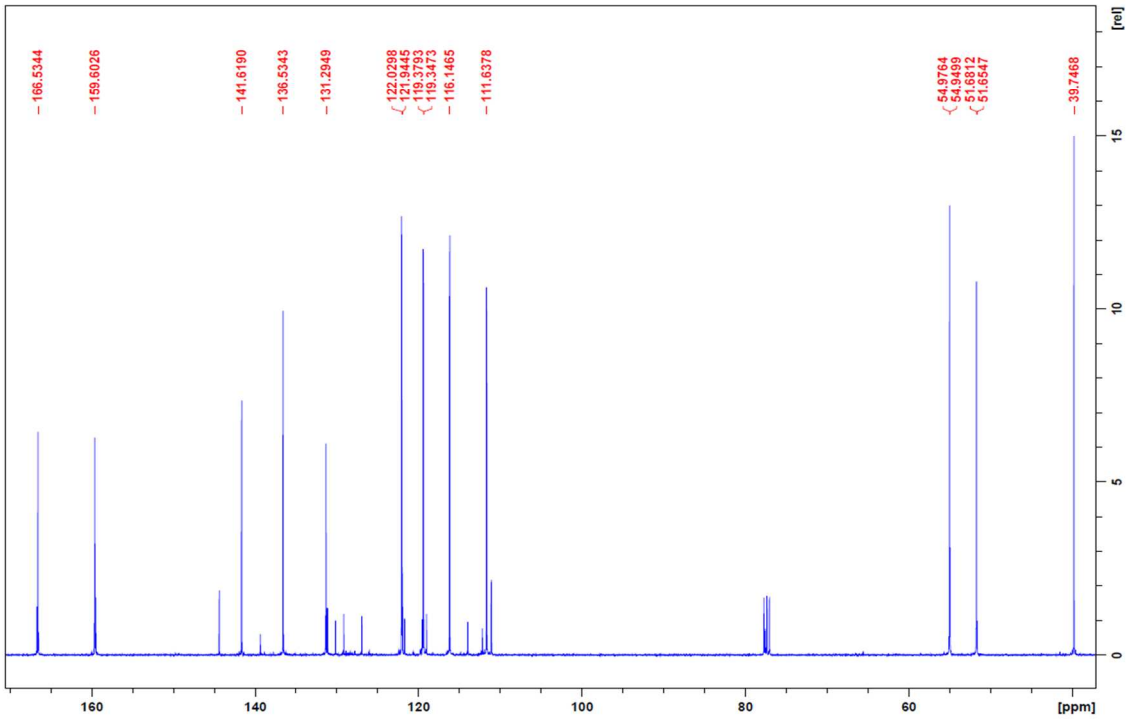


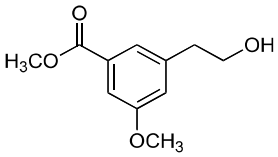


17

^{1}H(400 MHz) and ^{13}C NMR (100 MHz) spectra

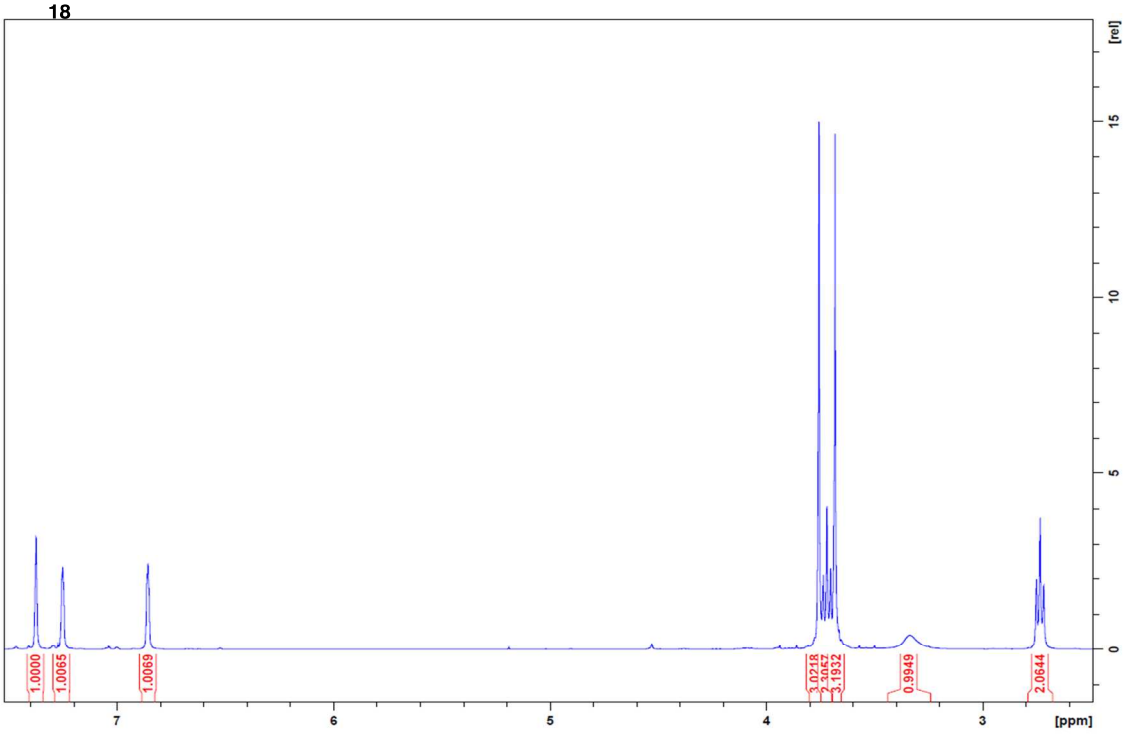


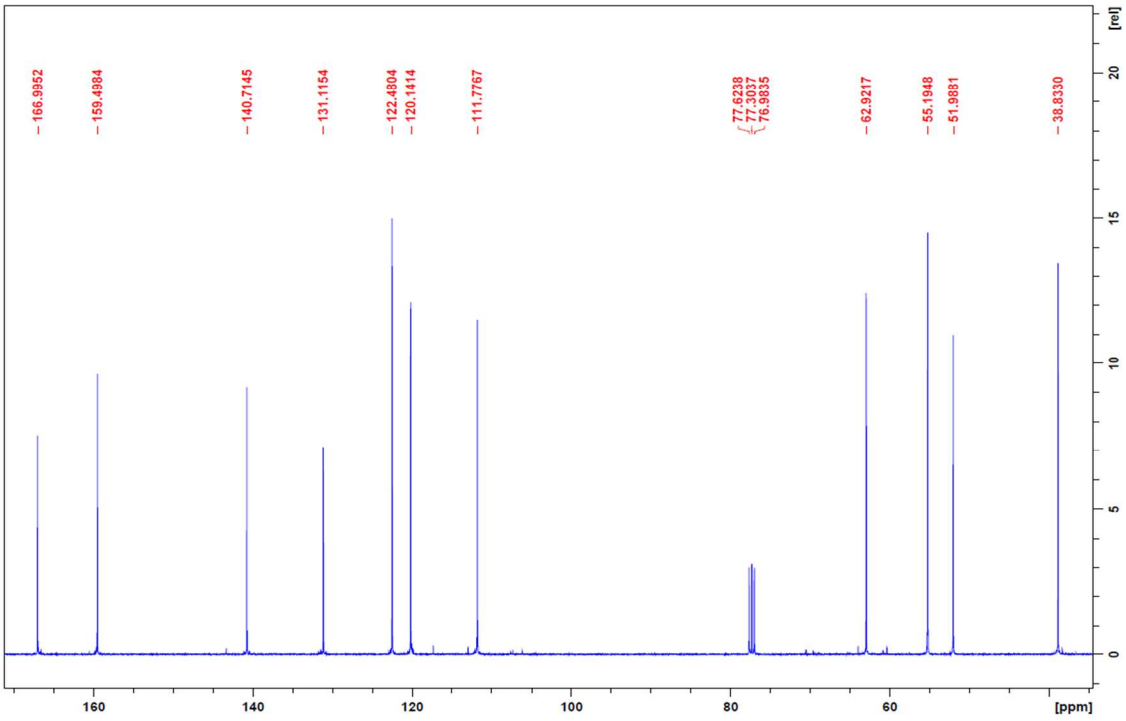


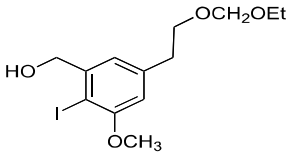


18

^{1}H(400 MHz) and ^{13}C NMR (100 MHz) spectra

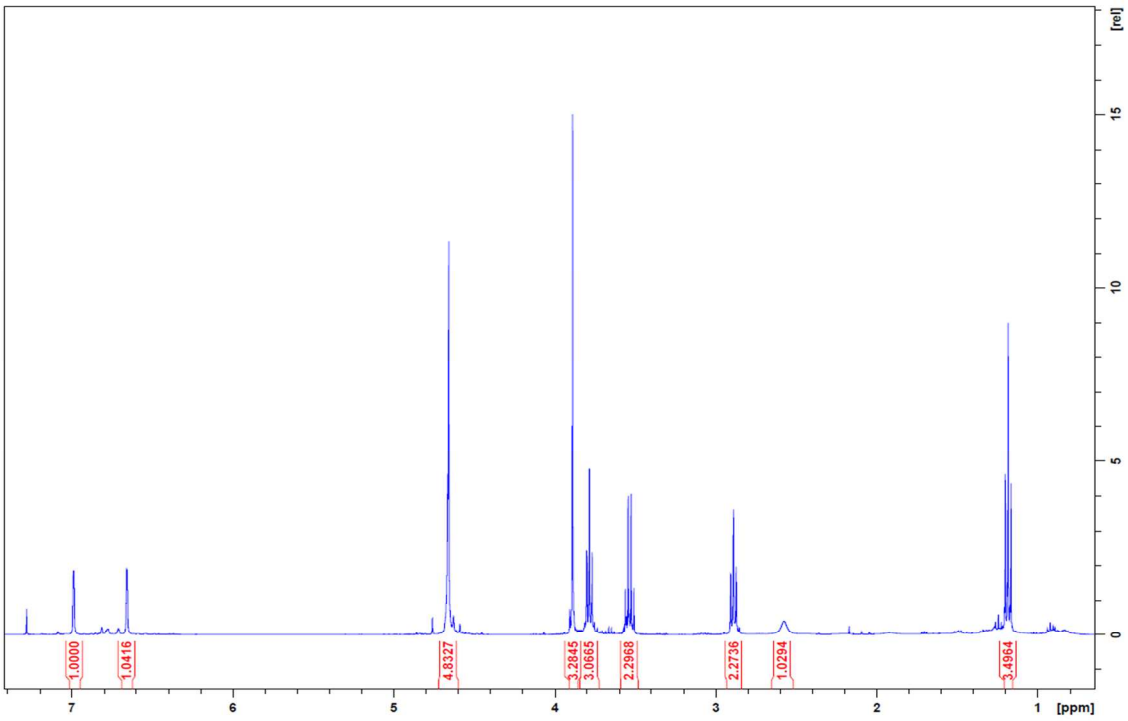


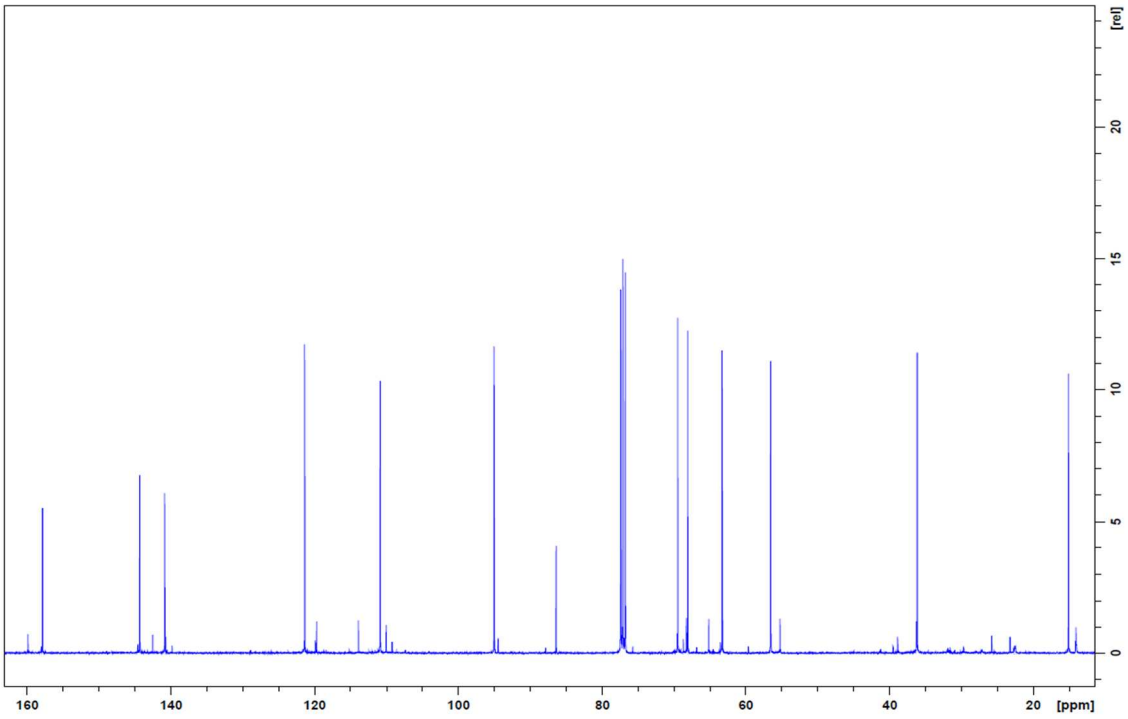


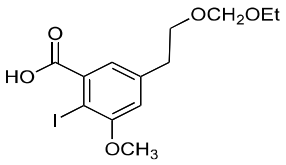


21

^{1}H(400 MHz) and ^{13}C NMR (100 MHz) spectra

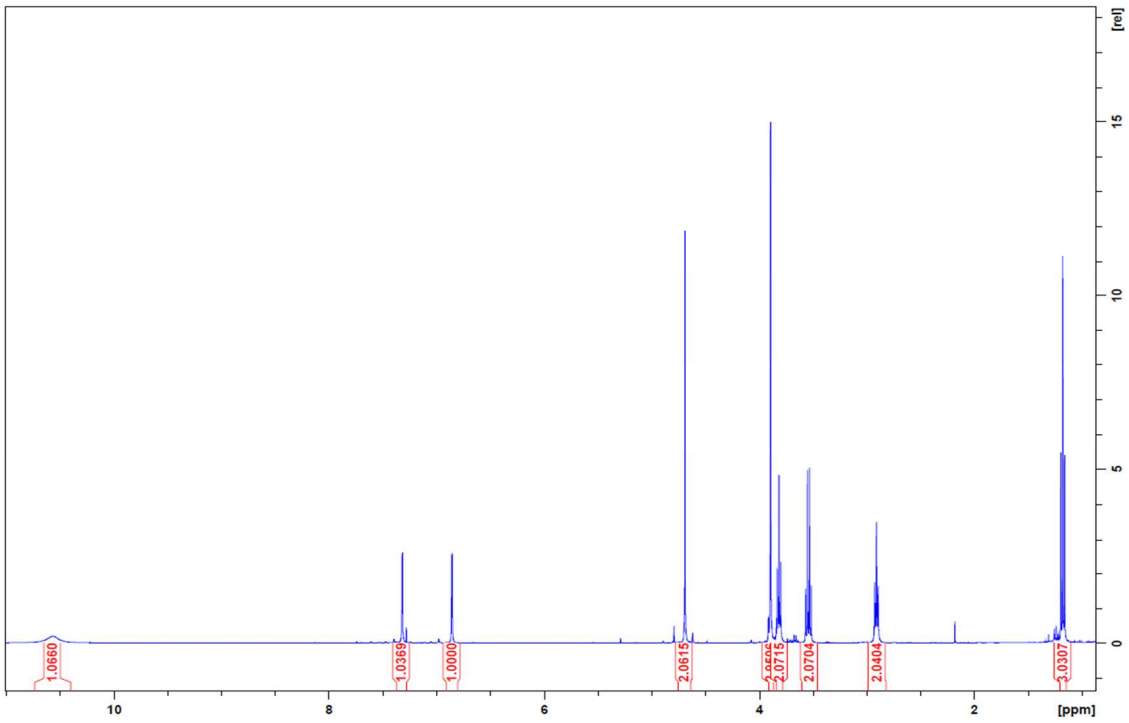


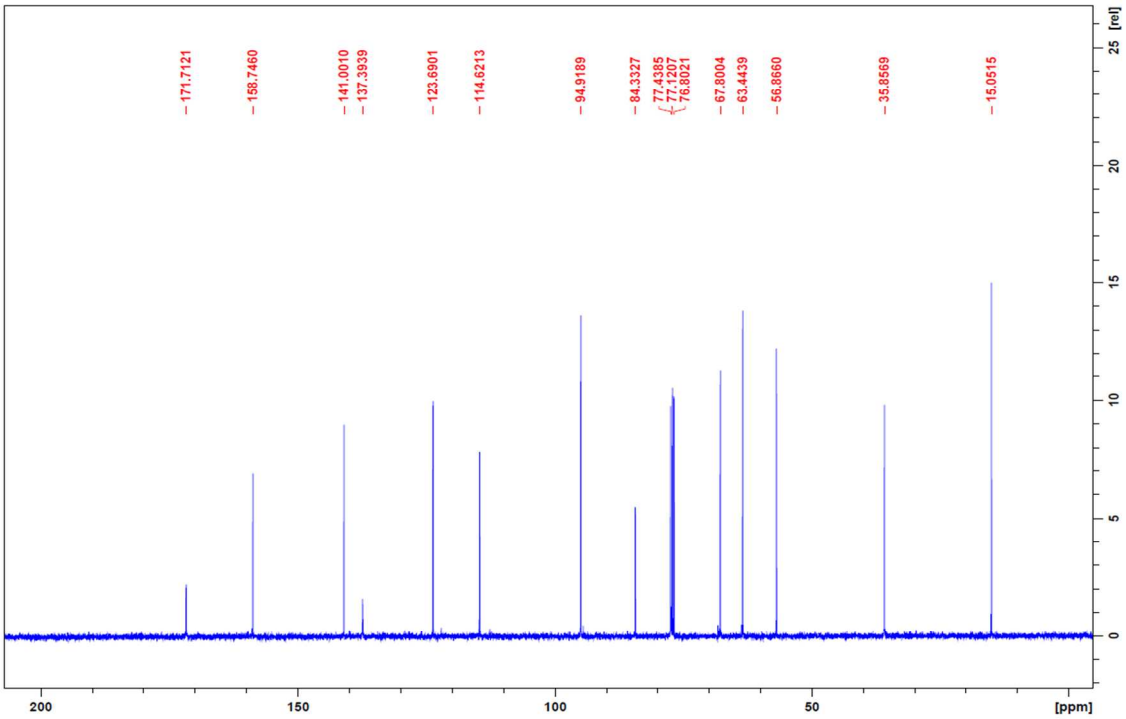


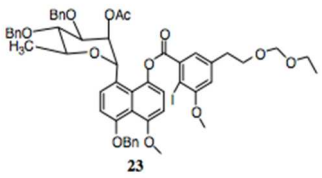


22

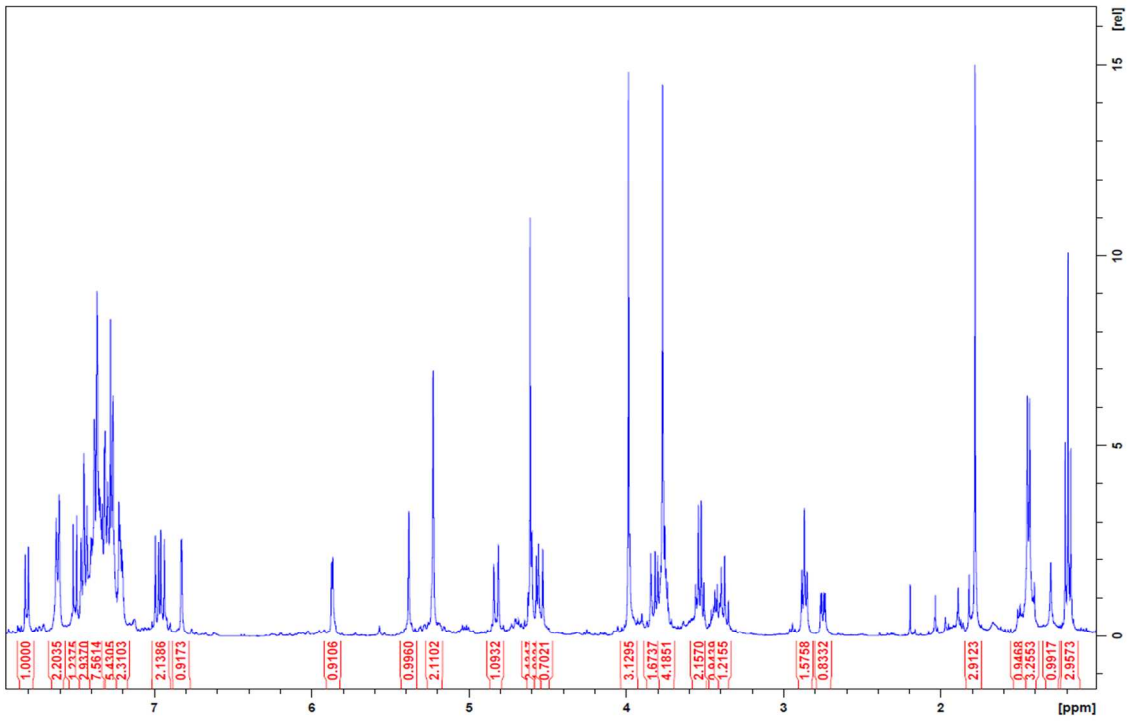
^{1}H(400 MHz) and ^{13}C NMR (100 MHz) spectra

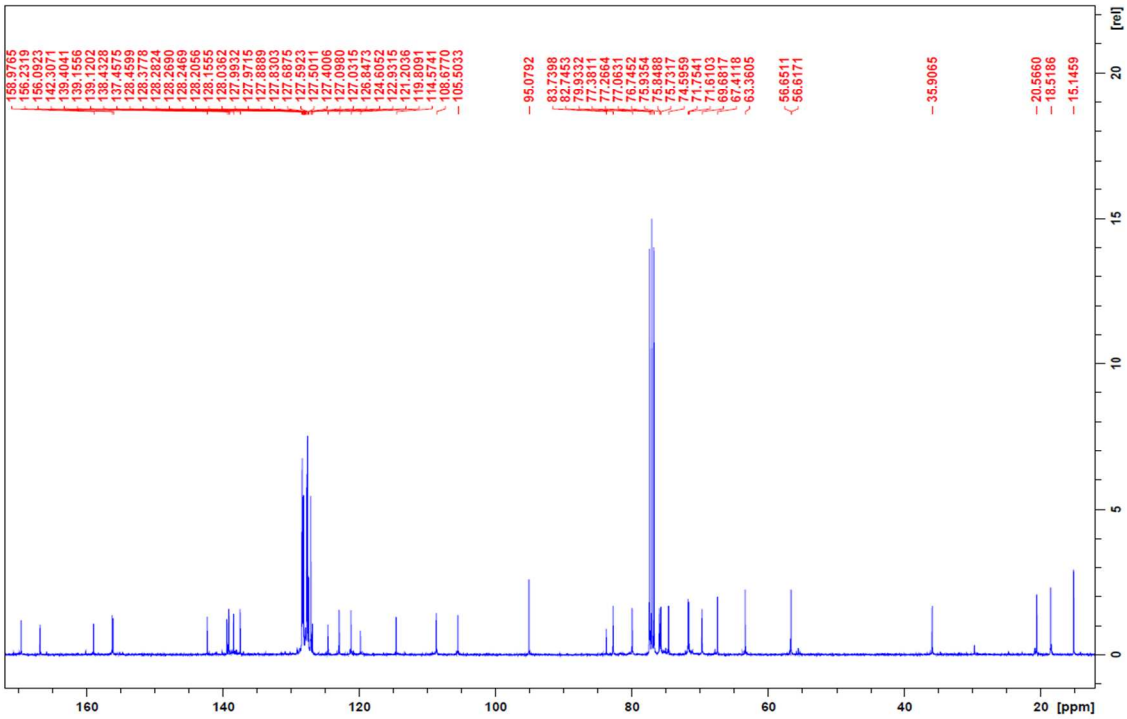


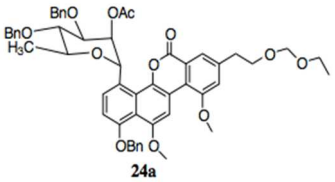




^{1}H(400 MHz) and ^{13}C NMR (100 MHz) spectra

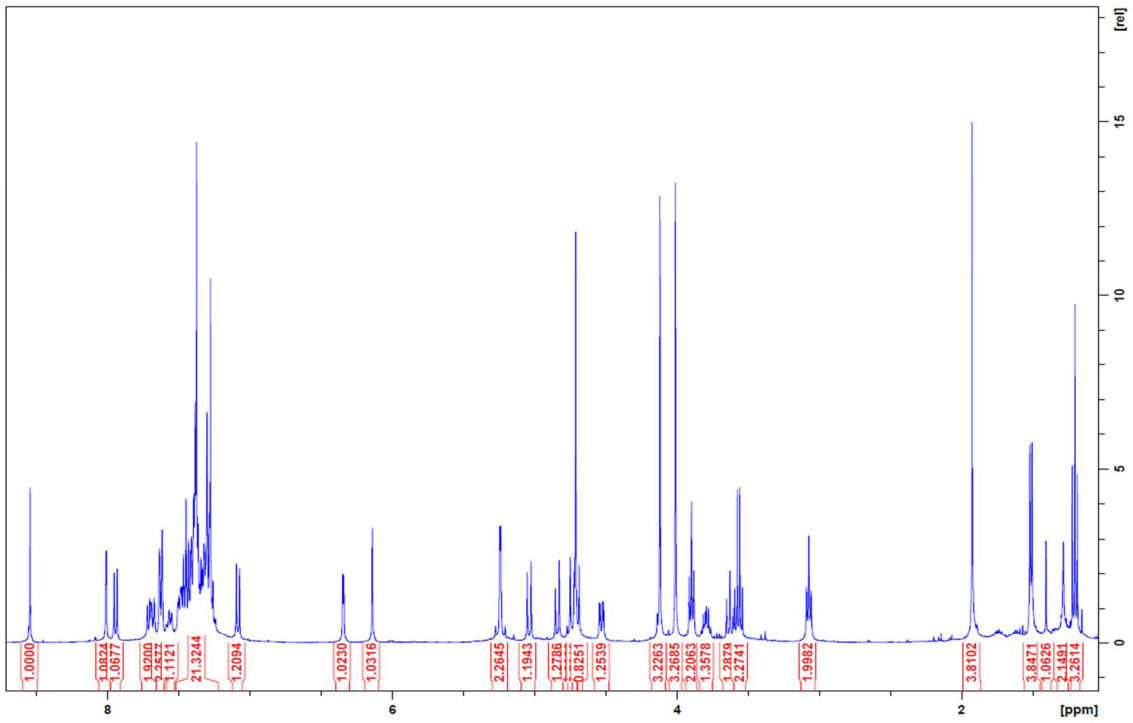


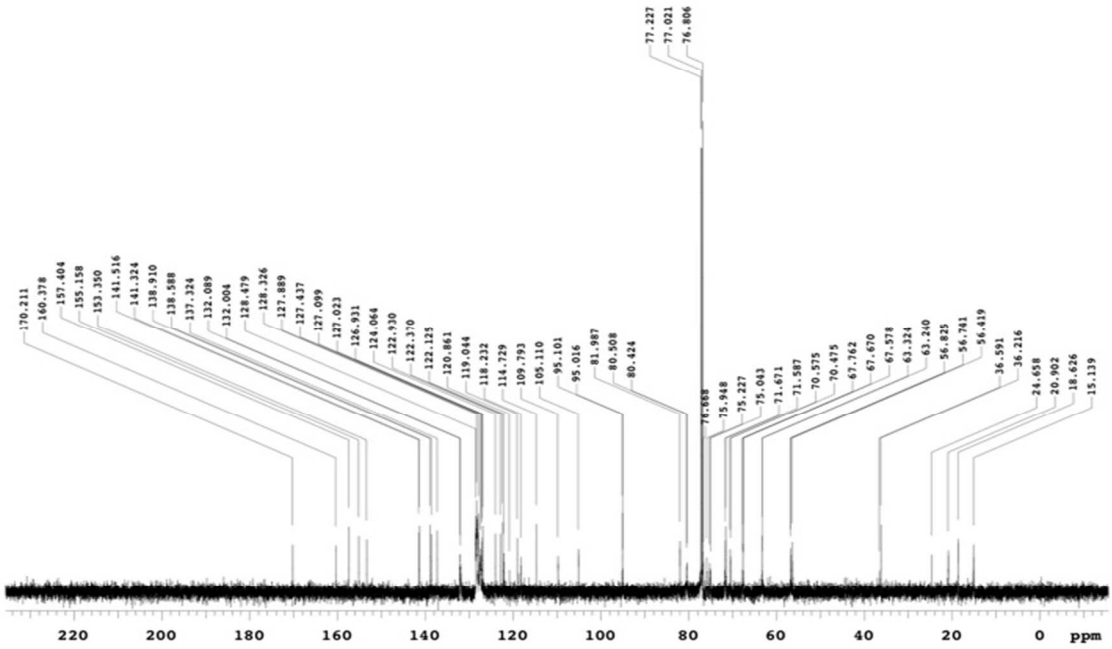


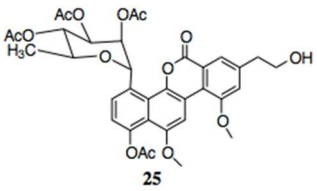


24a

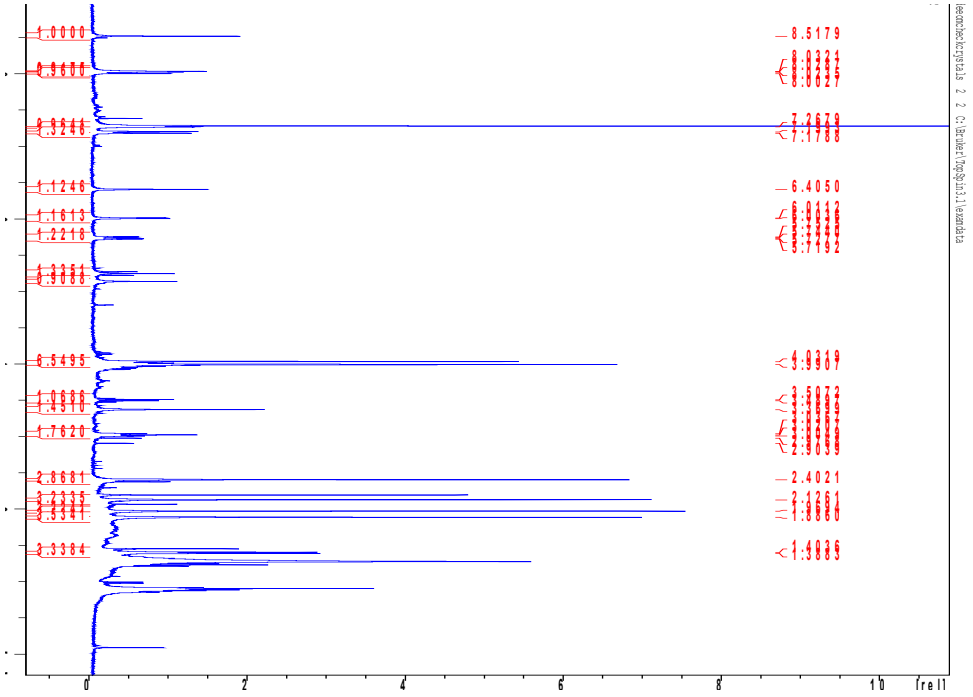
^{1}H(400 MHz) and ^{13}C NMR (100 MHz) spectra

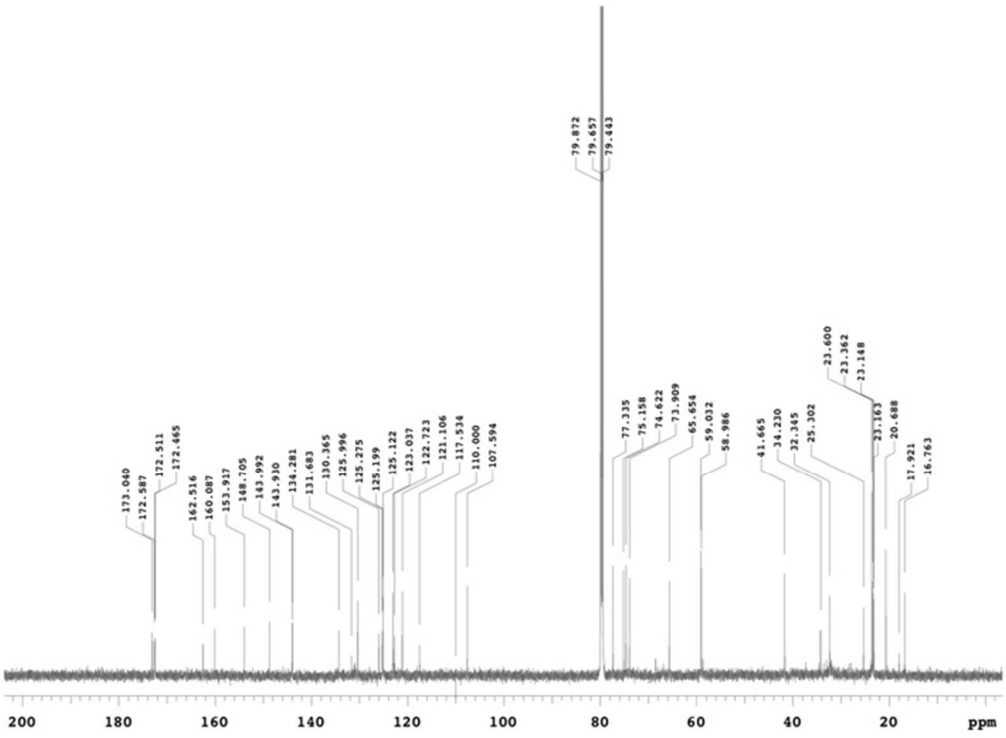


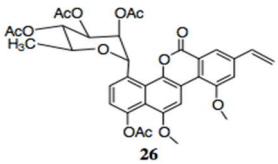




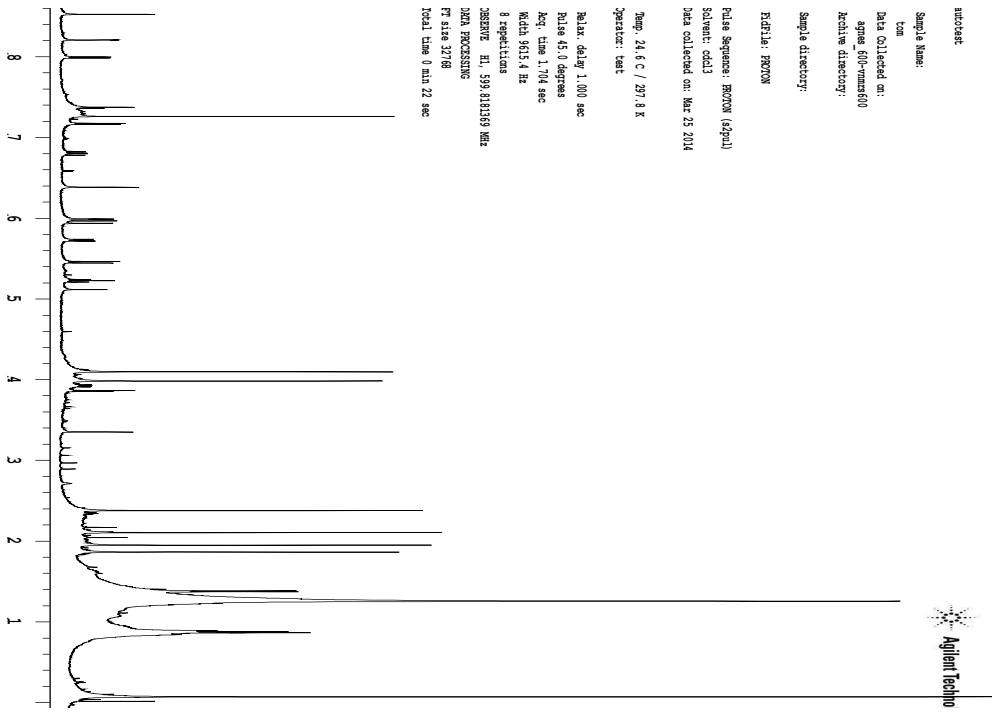
^{1}H(400 MHz) and ^{13}C NMR (100 MHz) spectra

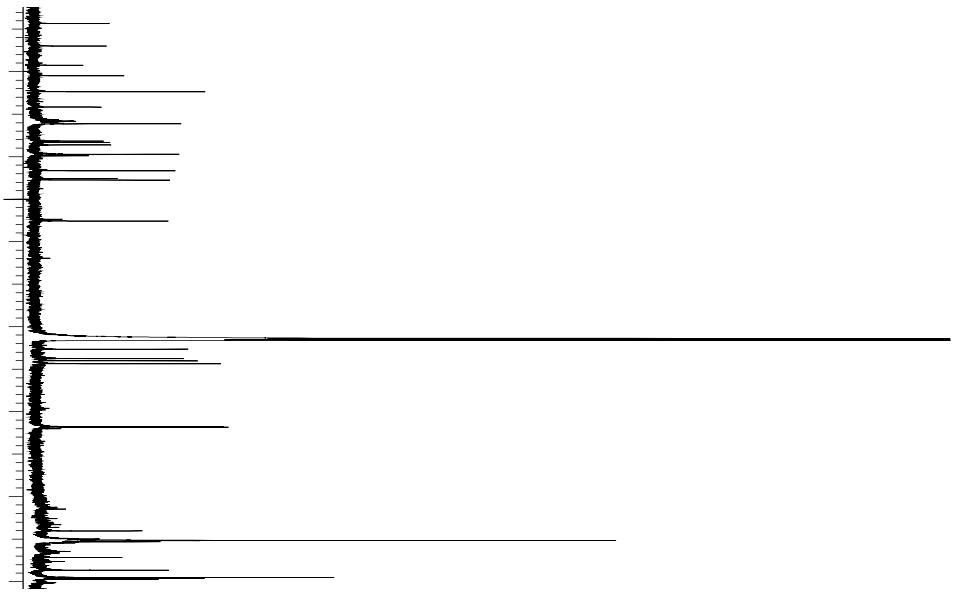


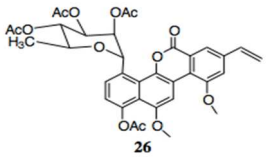




^{1}H(400 MHz) and ^{13}C NMR (100 MHz) spectra

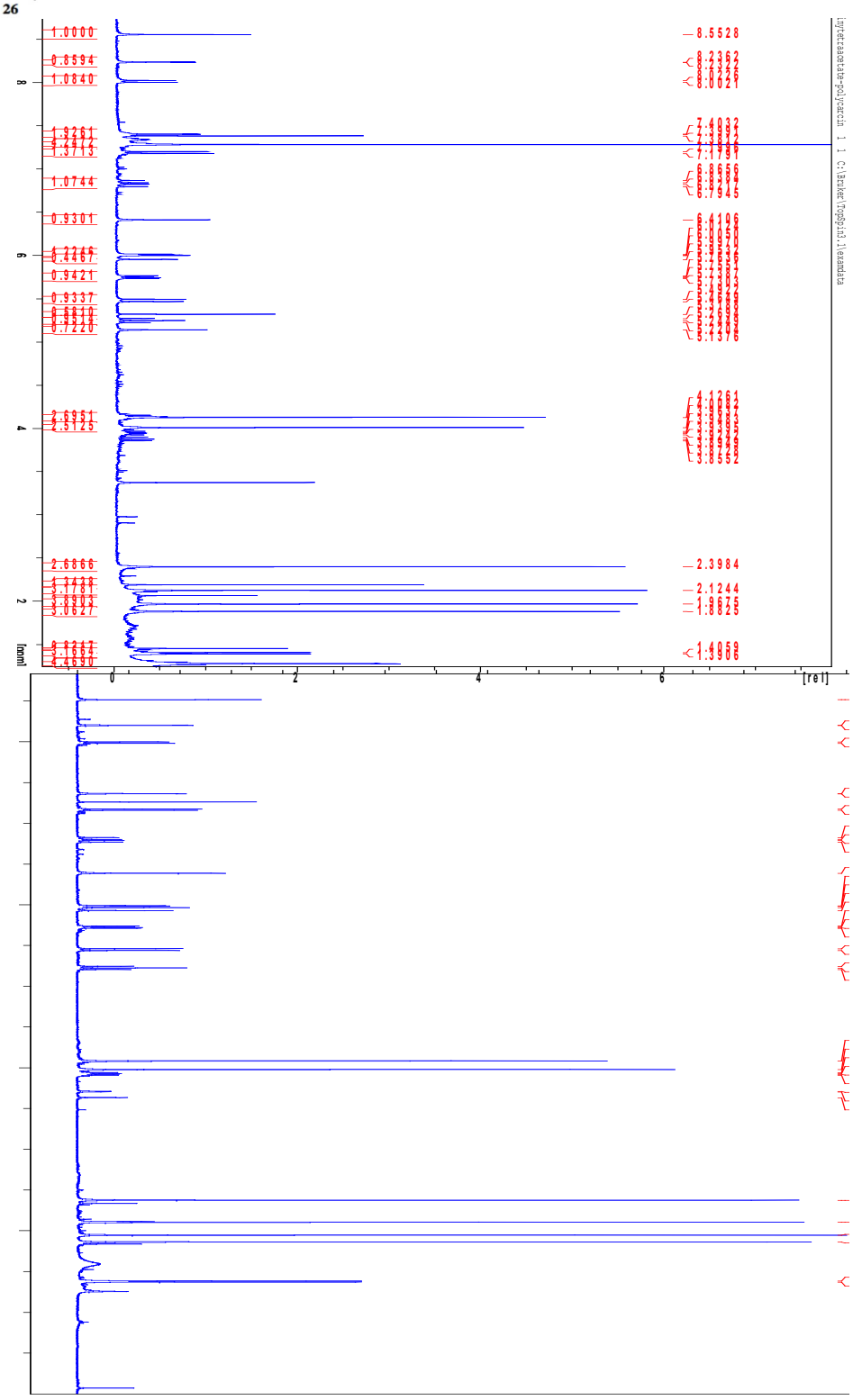


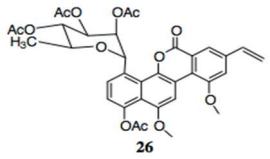




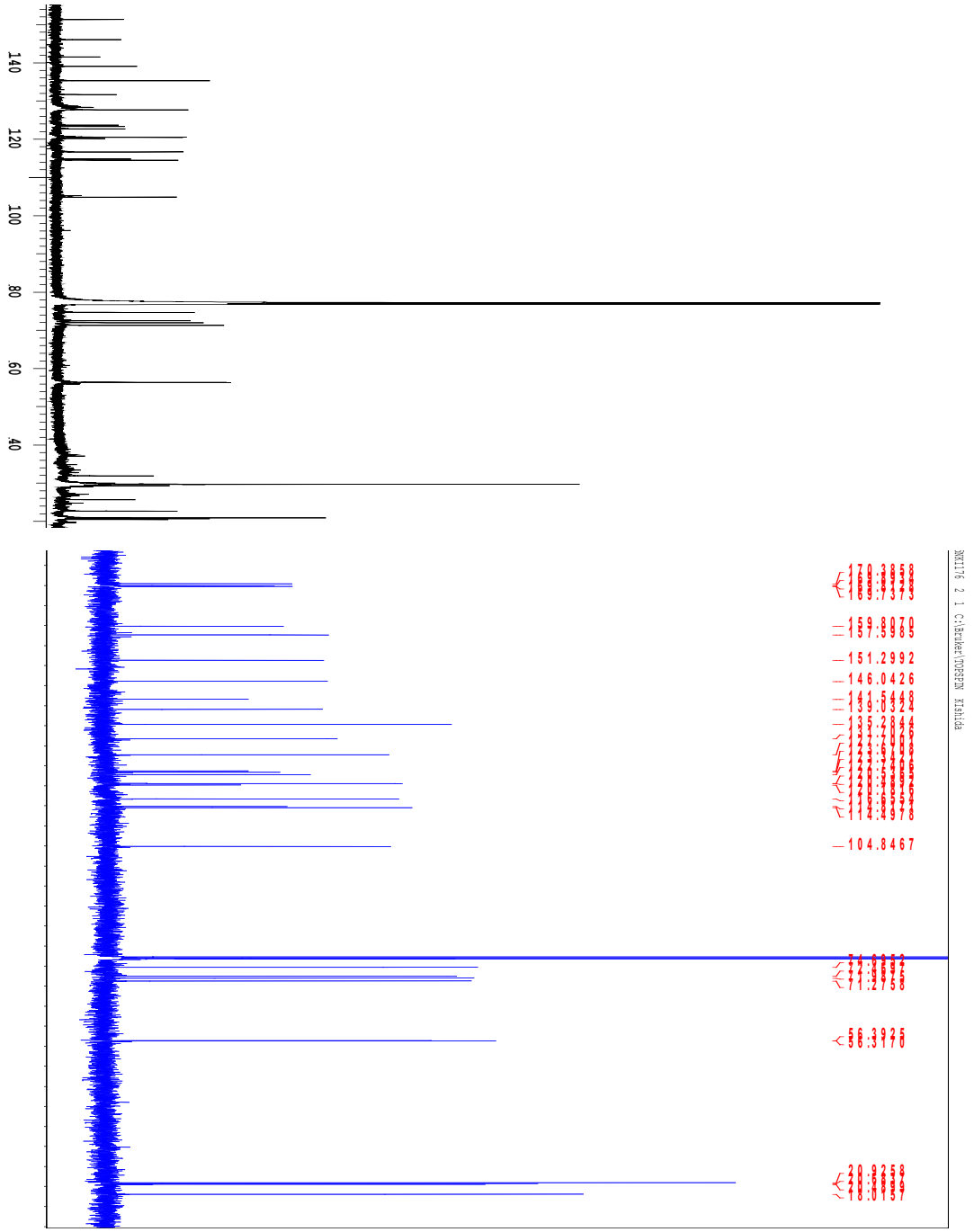
26

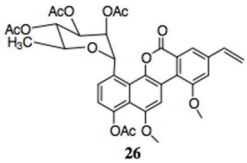
^{1}H NMR Comparison **26** (top-synthetic; bottom-natural)



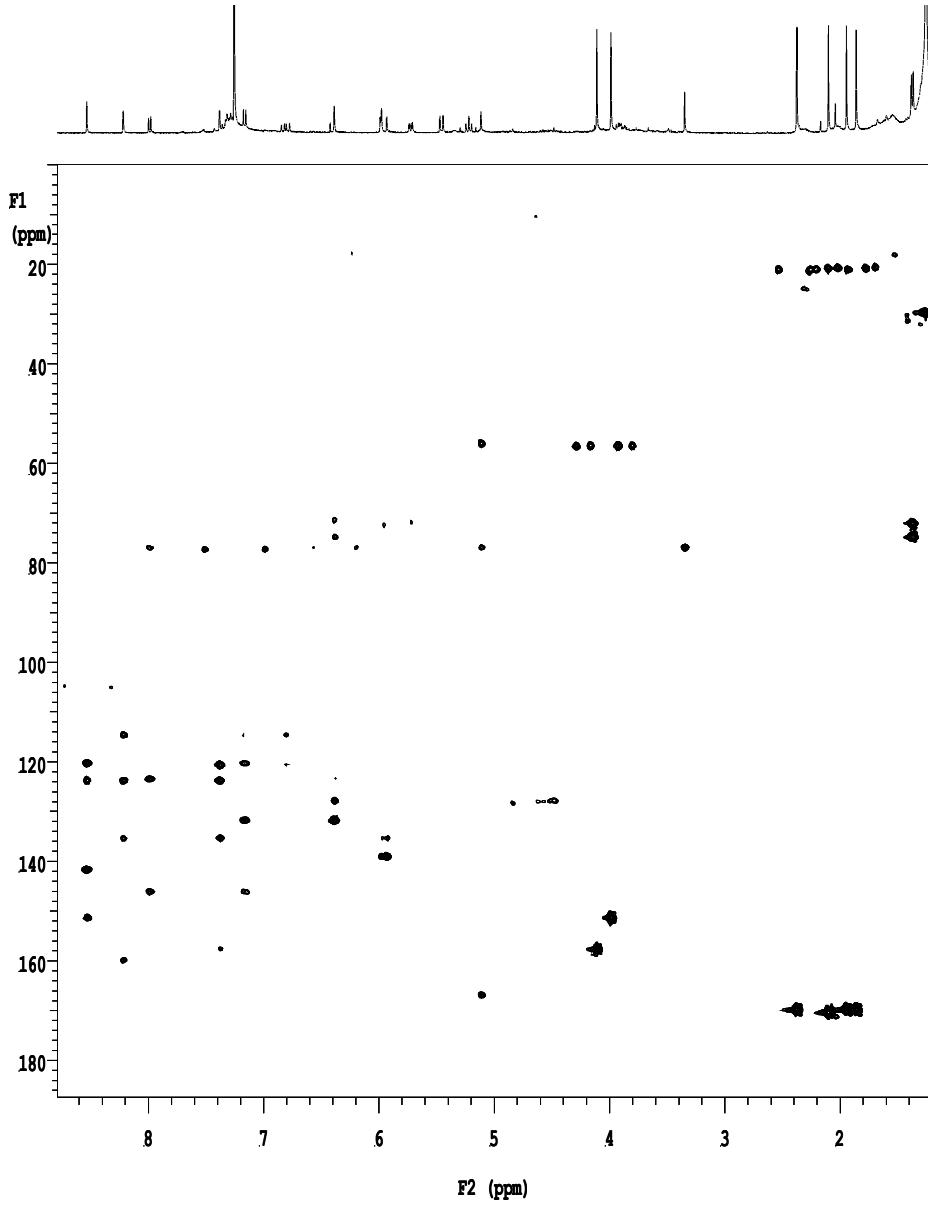


comparison: **26** ^{13}C NMR (150 MHz) synthetic-top; natural-bottom

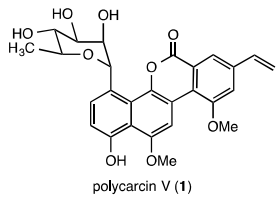




HMBC **26**

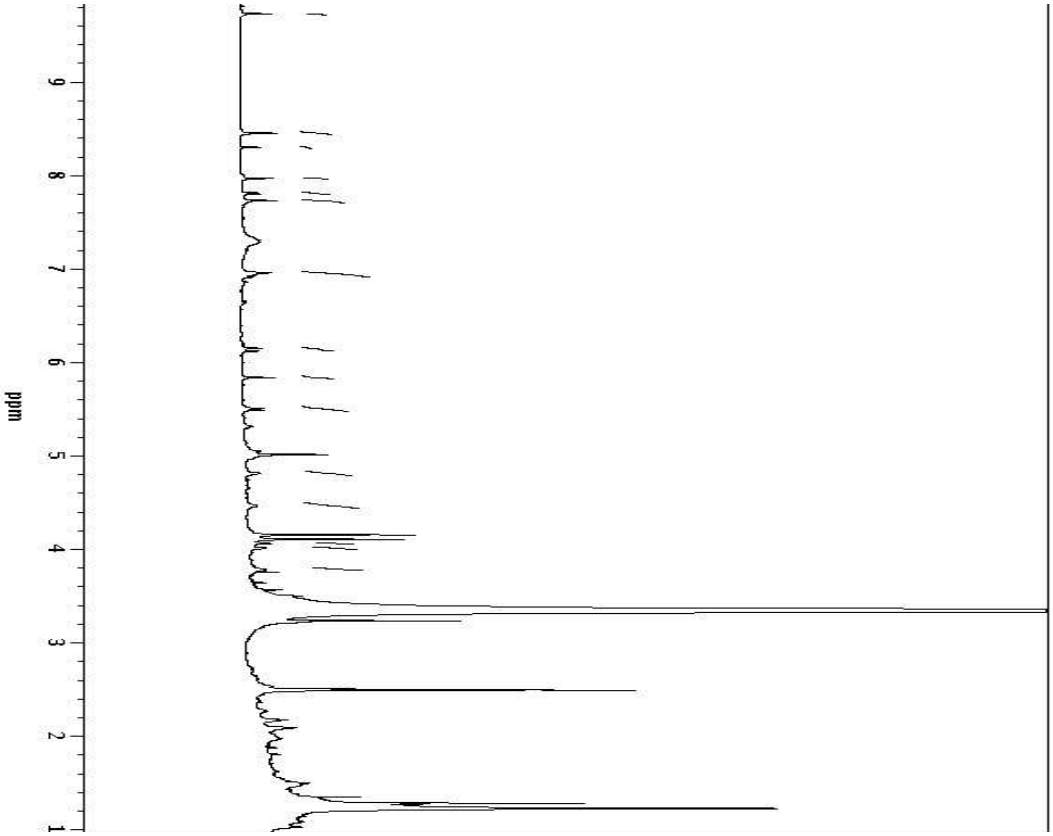


Plotname: --Not assigned--



polycarcin V (**1**)

^{1}H(600 MHz) and ^{13}C (150 MHz) NMR (DMSO-d6)



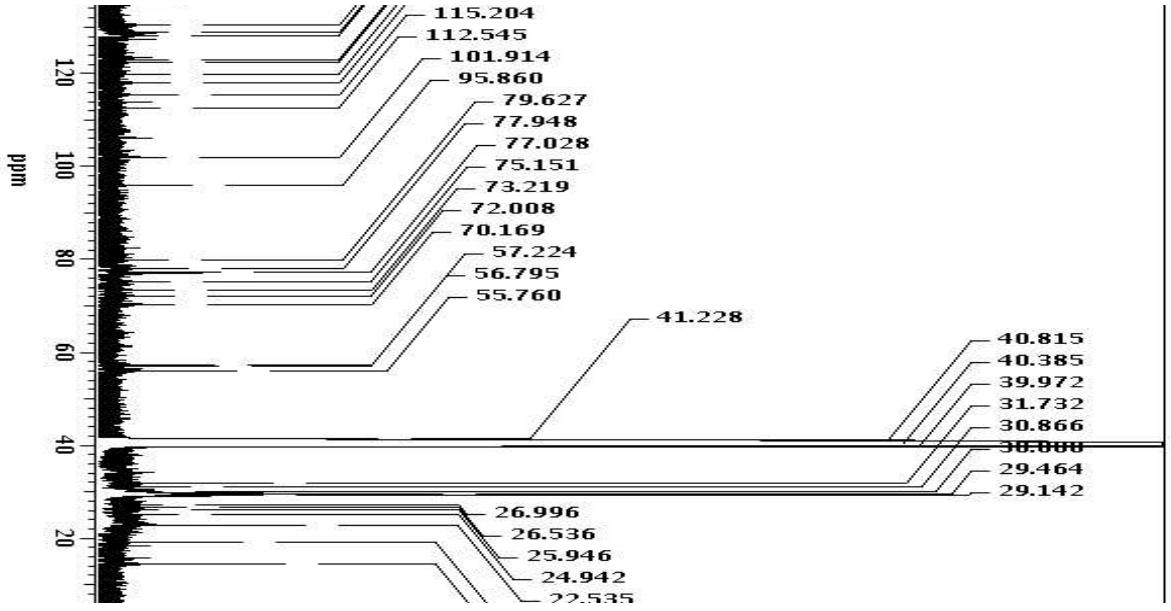
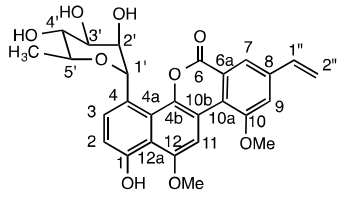


Table comparing ^{1}H and ^{13}C data for Natural and Synthetic polycarcin V



polycarcin V (**1**)

No.	**1** natural (125, 500MHz) δ_C	δ_H(*J* in Hz)	**1** synthetic (150, 600MHz) δ_C	δ_H(*J* in Hz)
1	152.8		153.2	
2	112.0	6.96 (d, 8.4)	112.5	6.95 (d, 7.8)
3	129.9	7.78 (d, 8.4)	130.4	7.80 (d, 7.8)
4	126.7		127.4	
4a	121.8		121.2	
4b	141.8		142.2	
6	159.4		159.8	
6a	122.4		122.3	
7	119.1	7.97 (d, 1.5)	119.6	7.96 (s)
8	138.8		139.3	
9	114.6	7.73 (d, 1.5)	114.5	7.71 (s)
10	157.4		157.9	
10a	122.8		122.9	
10b	113.2		114.0	
11	101.4	8.45 (s)	101.9	8.44 (s)
12	152.0		152.5	
12a	114.9		115.2	
10-OMe	56.7	4.16 (s)	56.7	4.14 (s)
12-OMe	56.5	4.11 (s)	55.7	4.09 (s)
1’	77.5	5.84 (brs)	77.9	5.82 (s)
2’	71.6	4.06 (dd, 5.9, 3.7)	72.0	4.05 (m)
3’	76.4	3.78 (m)	77.0	3.78 (m)
4’	72.8	3.31 (m)	73.2	3.30-
5’	74.7	3.36 (m)	75.1	3.40 (DMSO)
6’	18.5	1.28 (d, 6.4)	18.9	1.27 (d, 6.7)
1”	135.2	6.94 (dd, 11.0, 17.6)	135.6	6.93 (m)
2”	117.3	6.13 (d, 17.6);	117.7	6.13 (d, 17.4)
		5.50 (d, 11.0)		5.49 (d, 10.8)
1-OH		9.72 (s)		9.71 (s)
2’-OH		3.98 (d, 5.9)		4.01 (m)
3’-OH		4.42 (d, 5.9)		4.45 (m)
4’-OH		4.77 (d, 5.1)		4.80 (m)

DNA binding studies

DNA preparation:

Calf thymus (CT) DNA and Salmon Testes (ST) DNA were purchased from CALBIOCHEM. Solutions of CT DNA and ST DNA were prepared in 10mM Tris-EDTA buffer at pH 7.1 (as described in Jenkins: Jenkins, T.C. Optical Absorbance and Fluorescence Techniques for Measuring DNA-Drug Interactions. In *Methods in Molecular Biology, Drug-DNA Interaction Protocols;* Fox, K.R., Ed. Humana: Totowa, 1997; Vol 90, pp.195-217) and gave a 1.82:1 absorbance ratio (CT DNA) or a 1.84:1 absorbance ratio (ST DNA) at 260 nm and 280 nm. The concentration of the DNA was determined using 8452A HP Diode Array Spectrophotometer (ε_{260} = 6600 M^{-1} cm)[22]. The solution pH was measured using Beckman 350 pH meter.

PV preparation:

PV (1.2 mg) was dissolved in 0.4 mL DMSO to make s stock solution that was diluted with 10mM Tris-EDTA to the desired working concentrations (see below). The final concentrations of PV were then determined using 8452A HP Diode Array Spectrophotometer (ε_{398} = 12,200 M^{-1} cm; see reference 5, main text).

Fluorescence studies were performed on a Perkin Elmer Luminescence Spectrometer (LS 50B). The maximum emission wavelength of PV was 470 nm when the excitation wavelength was 380 nm and the excitation and emission monochromators slits were set to 10 nm; the scan speed was 200 nm/min.

Changes in fluorescence intensity at 470 nm were monitored as a function of increasing DNA concentration in solutions containing a constant concentration of PV:

1. CT-DNA (trial 1)

Utilizing the stock solutions of PV and CT DNA prepared above, 13 separate solutions of PV+DNA were prepared (total volume = 2 mL) with [PV]=0.39 μM in each and final CT DNA concentrations of: 0.00 nM, 0.50 nm, 1.00 nm, 2.50 nm, 5.00 nm, 10.00 nm, 12.50 nm, 25.00 nm, 49.70 nm, 99.40 nm, 100.00 nm, 250.00 nm, and 500.00 nm.

2. CT-DNA (trial 2)

Utilizing the stock solutions of PV and CT DNA prepared above, 18 separate solutions of PV+DNA were prepared (total volume = 2 mL) with [PV]=0.46 μM in each and final CT DNA concentrations of: 0.00 nM, 0.41 nm, 1.03 nm, 2.58 nm, 3.10 nm, 5.16 nm, 10.33 nm, 13.92 nm, 18.88 nm, 24.85 nm, 49.70 nm, 51.70 nm, 89.50 nm, 103.40 nm, 155.10 nm, 206.76 nm, 258.50 nm, and 516.90 nm.

Fluorescence spectra were recorded from 370 nm to 620 nm after an equilibration period of 2 min. The fluorescence of the fully bound drug was estimated using a plot of fluorescence intensity at 470 nm against DNA concentration and extrapolating to infinite DNA concentration. The fraction of free and bound drug to DNA in solution was then calculated at each DNA concentration to yield r, the number of drug bound per base pair and C, the free drug concentration. The resulting data were then plotted as r/C vs r and analyzed by nonlinear regression based on the treatment of McGhee and von Hippel (Eq. 4), where r is the concentration of the bound drug per nucleotide concentration, C is the concentration of the free drug in solution, *K* is the binding constant for an isolated bound ligand and n is the number of base pairs occupied per bound drug.

$$r/C = K(1 - nr)\,[(1 - nr)/1-(n-1)\,r]^{n-1}$$

The Scatchard plots (r/C vs r) for PV in 10mM Tris-EDTA buffer are shown in Fig. 5. The curvature of the plots could indicate interaction between binding sites, according to the neighbor exclusion model (see reference 26, main text). Plot curvature may also indicate that individual binding sites may have different intrinsic binding constants.

3. polydAdT•polydAdT

Utilizing the stock solutions of PV and polydAdT•polydAdT prepared as above, 13 separate solutions of PV+DNA were prepared (total volume = 2 mL) with [PV]=0.9 μM in each and final DNA concentrations of: 0.00, 11 nm, 22 nm, 54 nm, 151 nm, 436 nm, 680 nm, 1058 nm, 1436 nm, 1814 nm, 1890 nm, 4320 nm and 9720 nm.

4. polydGdC•polydGdC

Utilizing the stock solutions of PV and CT DNA prepared above, 18 separate solutions of PV+DNA were prepared (total volume = 2 mL) with [PV]=0.9 μM in each and final DNA concentrations of: 0.00, 13 nm, 66 nm, 185 nm, 251 nm, 317 nm, 515 nm, 792 nm, 1230 nm, 1760 nm, 3520 nm, 4310 nm, 5280 nm, 12320 nm, 17860 nm, and 43520 nm.

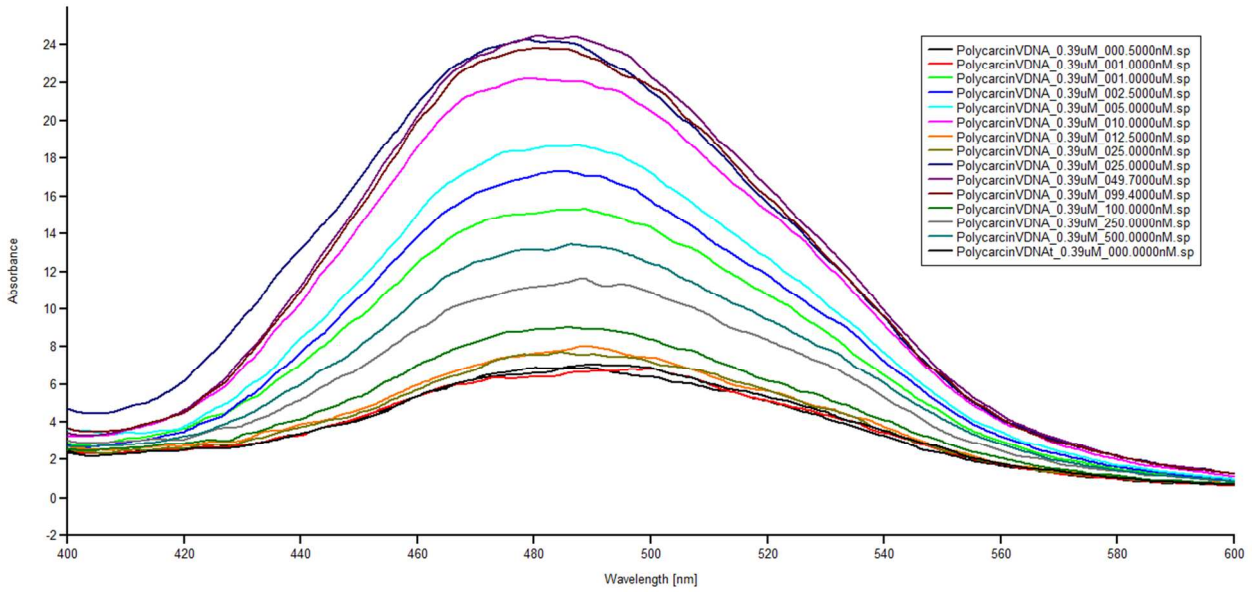


Fig.1 Fluorescence spectra of PV in the presence of varying concentrations of CT-DNA, [PV] = 3.9 x 10^{-7} mol L^{-1}, [CT-DNA] = 0-5.00 x 10^{-7} mol L^{-1}

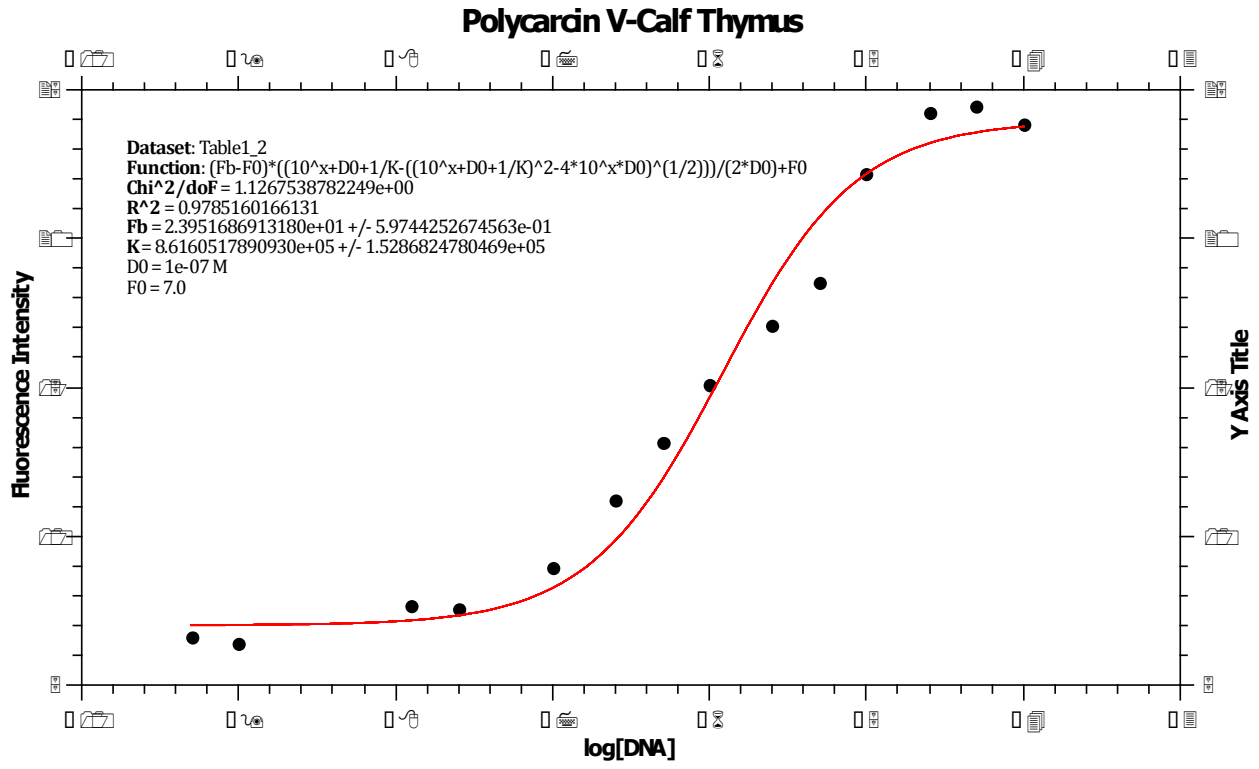


Fig.2 Least Squares Fitting analysis of fluorescence spectra of PV in the presence of varying concentrations of CT-DNA, [PV] = 3.9 x 10^{-7} mol L^{-1}, [CT DNA] = 0-5.00 x 10^{-7} mol L^{-1}

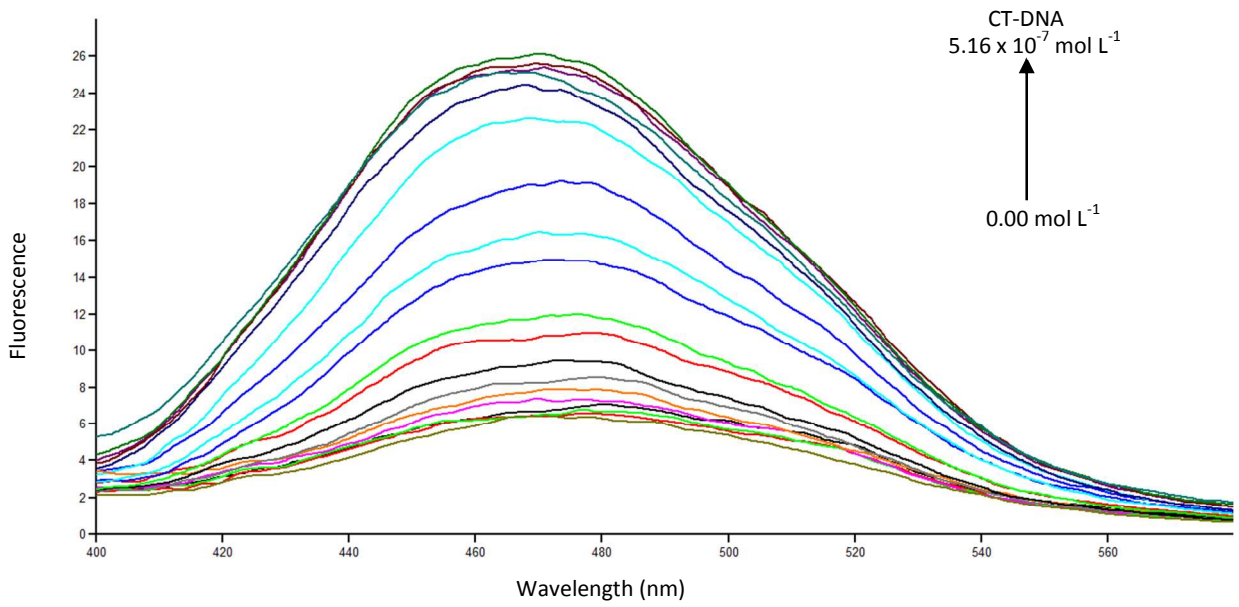


Fig.3 Fluorescence spectra of PV in the presence of varying concentrations of CT-DNA, [PV] = 4.60 x 10^{-7} mol L^{-1}, [CT-DNA] = 0-5.16 x 10^{-7} mol L^{-1}

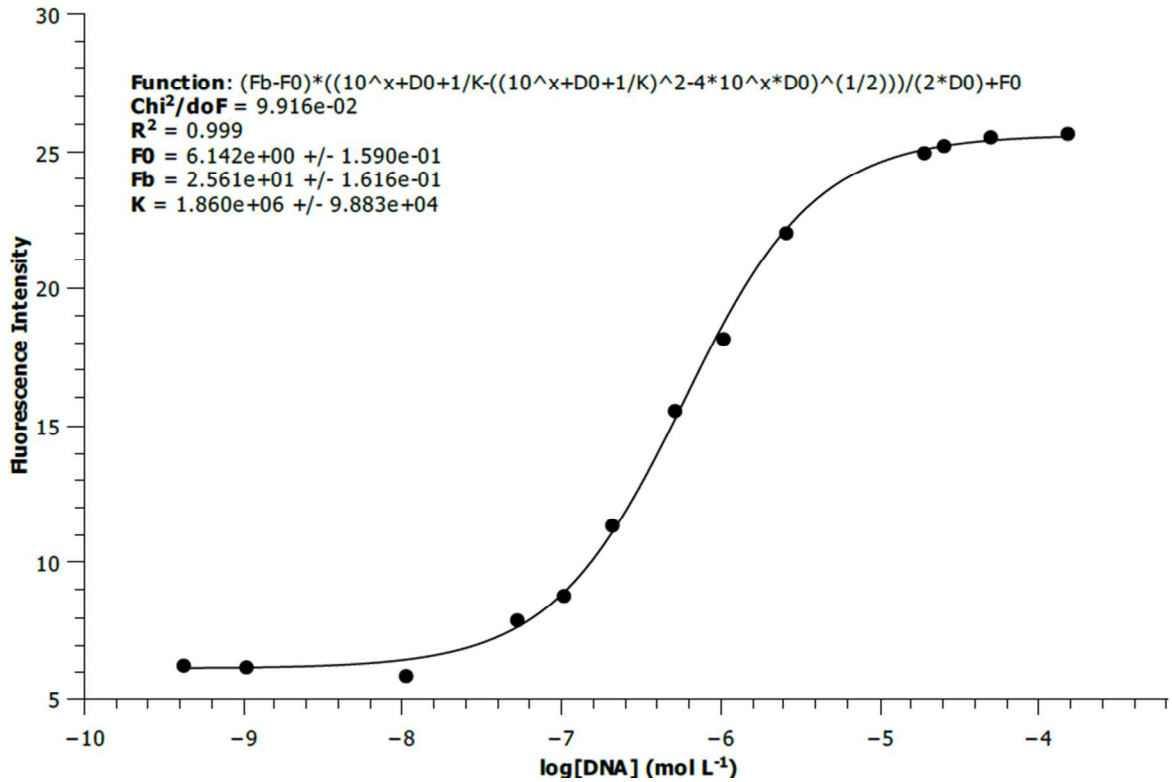


Fig.4 Least Squares Fitting analysis of fluorescence spectra of PV in the presence of varying concentrations of CT-DNA, [PV] = 4.60 x 10^{-7} mol L^{-1}, [CT DNA] = 0-5.16 x 10^{-7} mol L^{-1}

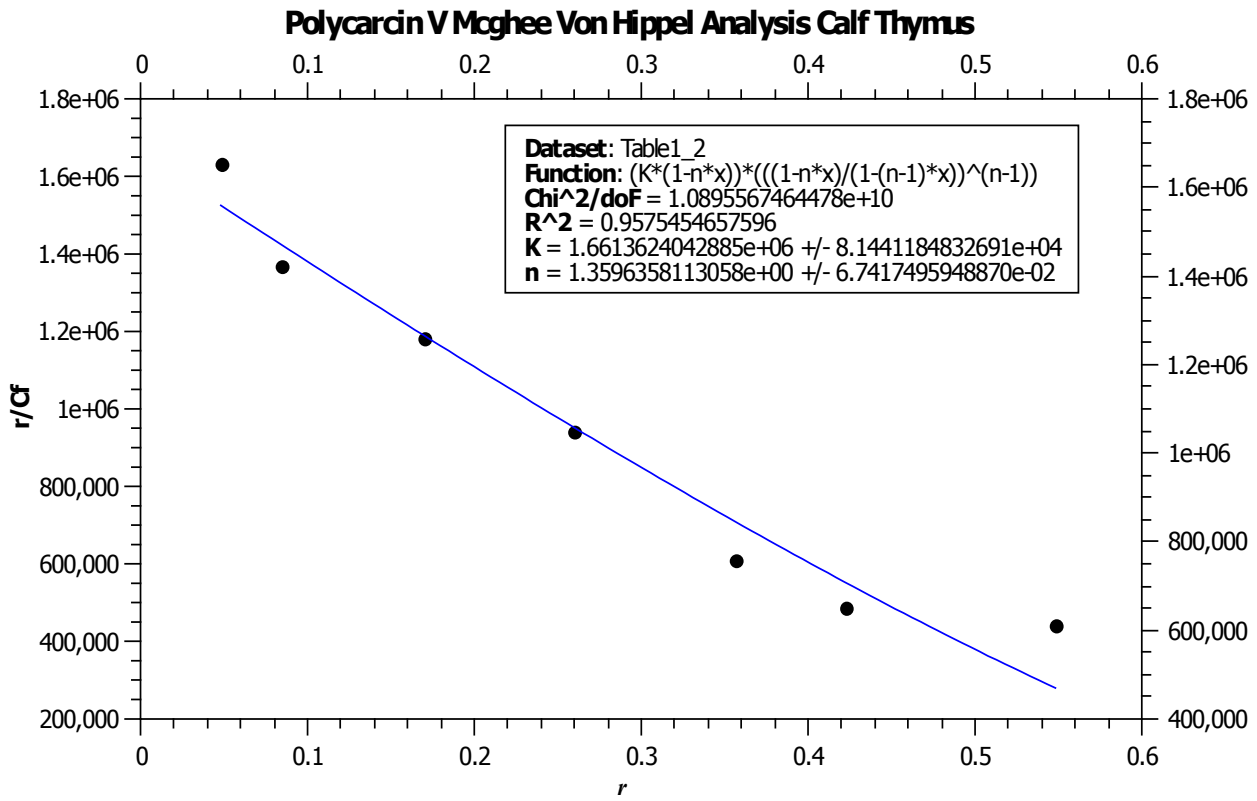
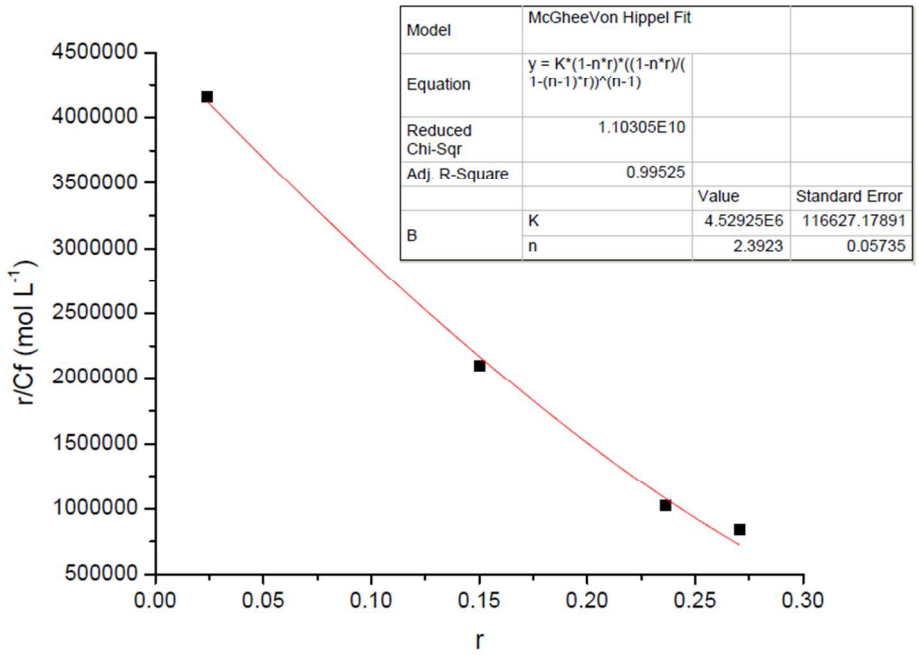


Fig.5 Scatchard plots of r/C_f vs. r analyzed by nonlinear regression based on the treatment of McGhee and von Hippel McGhee-Von Hippel.



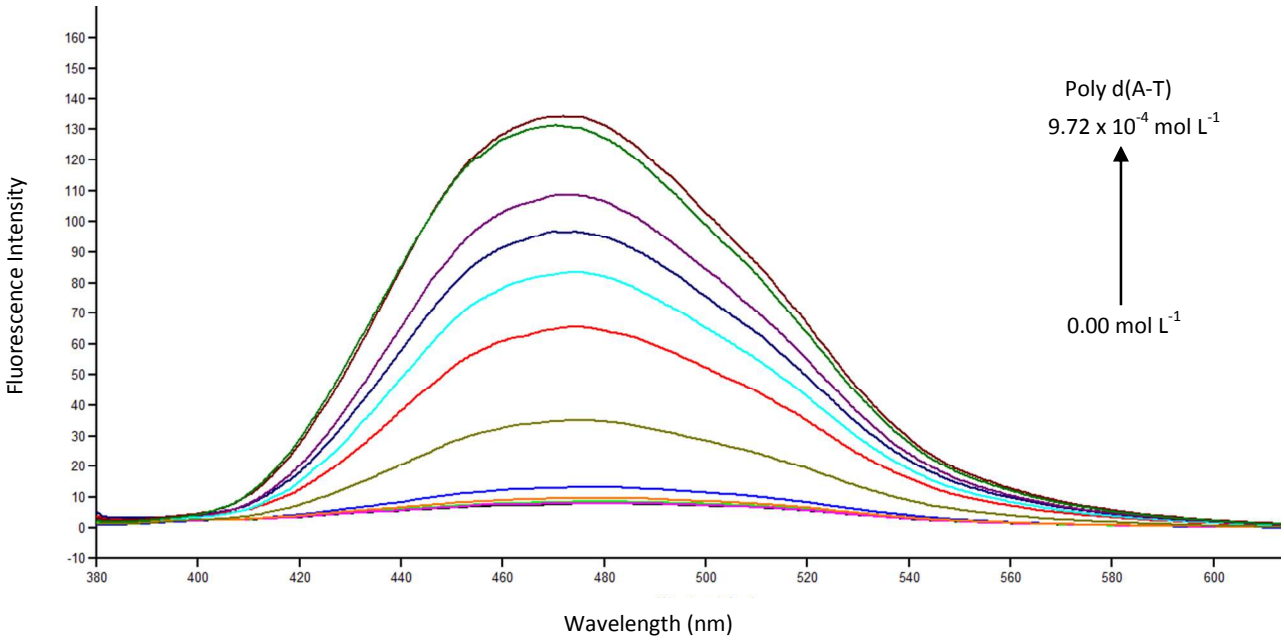


Fig. 6 Fluorescence spectra of PV in the presence of varying concentrations of poly dAdT•polydAdT, [PV] = 9.00 x 10^{-7} mol L^{-1}, [DNA] = 0.00, 0.11, 0.22, 0.54, 1.51, 4.36, 6.80, 10.58, 14.36, 18.14, 18.90, 43.20, and 97.20 x 10^{-7} mol L^{-1}

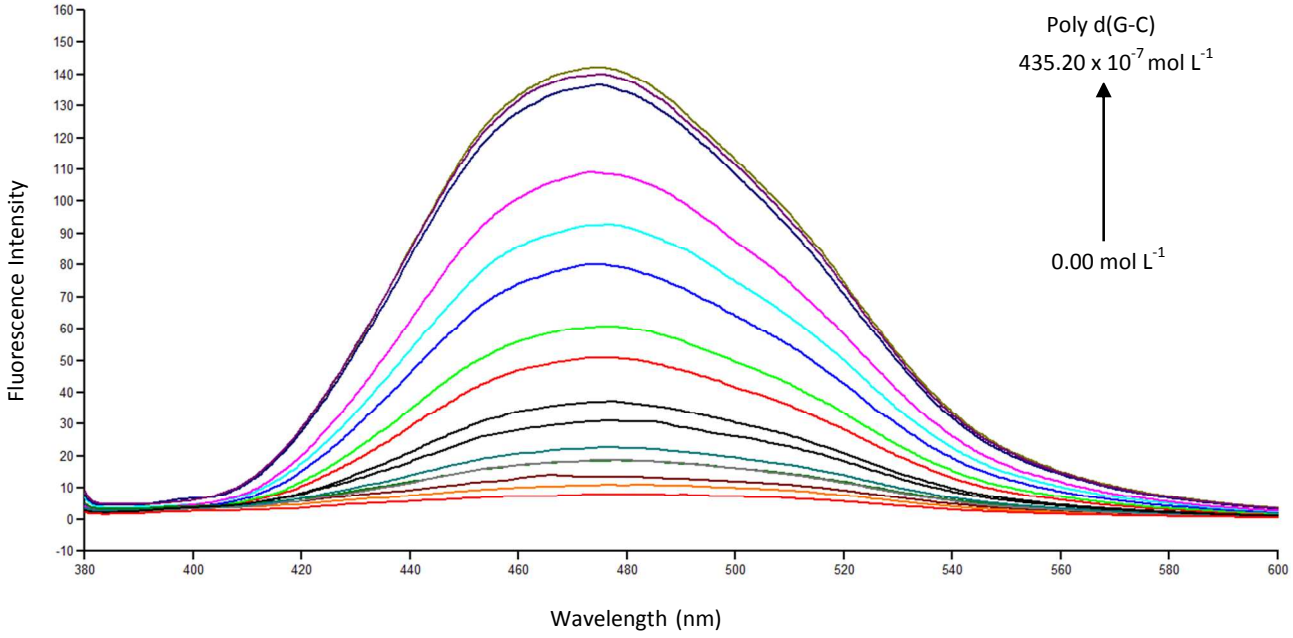


Fig. 7 Fluorescence spectra of PV in the presence of varying concentrations of poly dGdC•polydGdC, [PV] = 9.00 x 10^{-7} mol L^{-1}, [DNA] = 0.00, 0.13, 0.66, 1.85, 2.51, 3.17, 5.15, 7.92, 12.30, 17.60, 35.20, 43.10, 52.80, 123.20, 178.60, and 435.20 x 10^{-7} mol L^{-1}

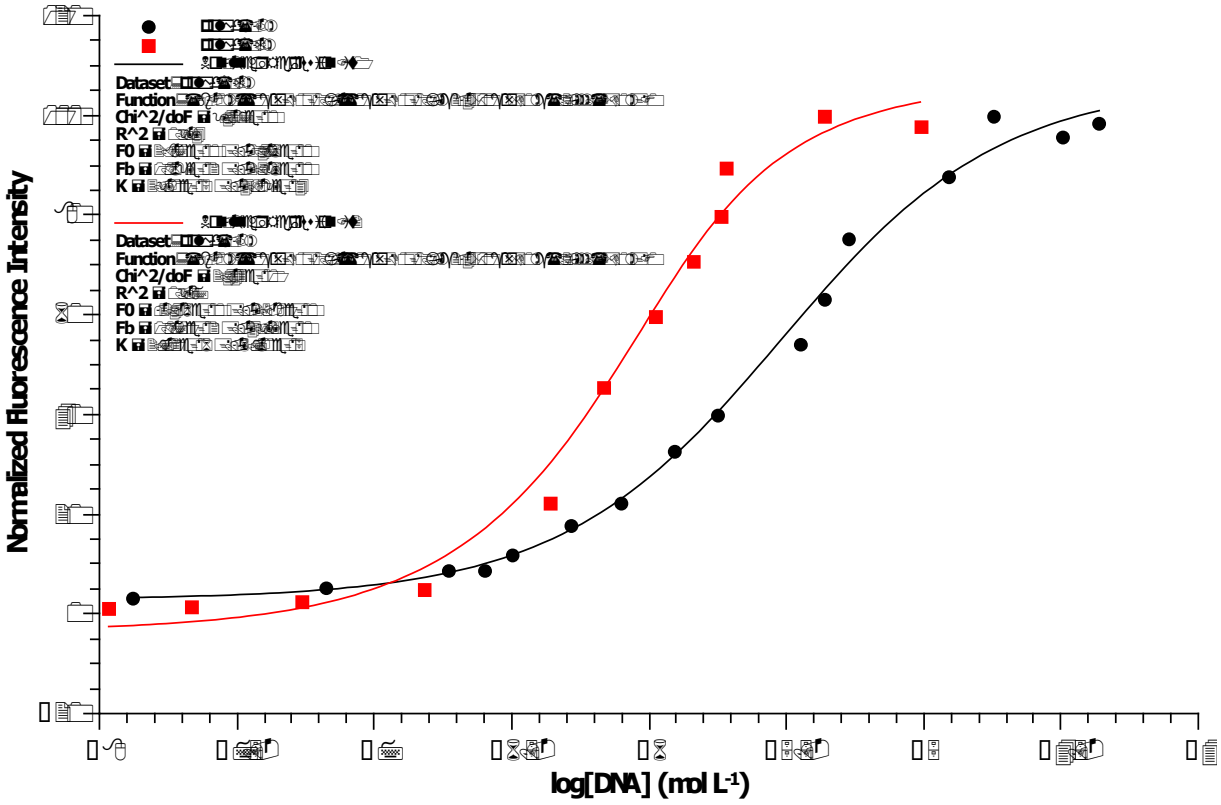


Fig 8. Comparison of the binding of polycarcin V to poly (dA-dT)$_2$ and poly (dG-dC)$_2$. **1** shows ~10-fold higher affinity for poly (dA-dT)$_2$.

DNA thermal denaturation experiments

DNA thermal denaturation experiments were conducted using 8452A HP Diode Array Spectrophotometer connected to 89090A Peltier Temperature Controller.

a. A stock solution of Salmon Testes DNA (9.84 mM) was diluted with 10mM Tris-EDTA buffer to give a working concentration of 19.7 μM. This solution (2 mL) was placed in a quartz cuvette and absorbance readings were taken in 1°C increments for temperatures ranging from 26 ˚C to 90 ˚C with heating at a rate of 1˚C/min and absorbance monitoring at 260 nm.

b. 2mL of a solution containing Salmon Testes DNA (19.7 μM) and PV (0.96 μM) prepared from the corresponding stock solutions noted above was placed in a quartz cuvette and absorbance readings were taken in 1°C increments for temperatures ranging from 26 ˚C to 90 ˚C

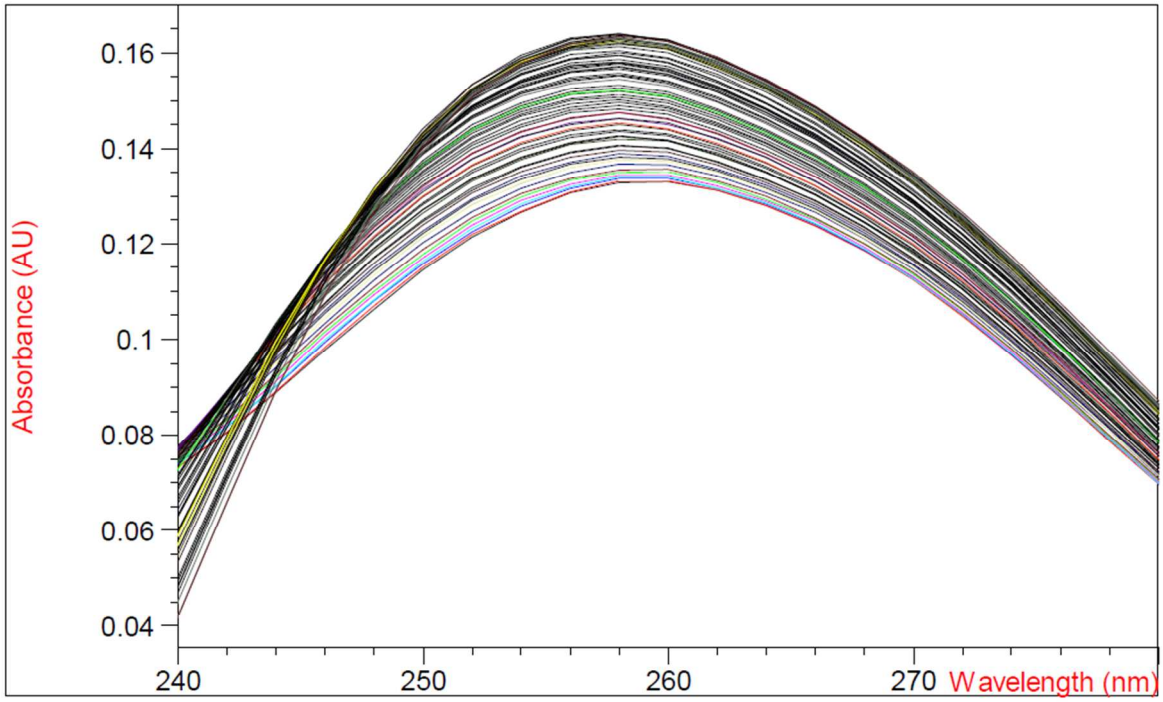


Fig.9 ST DNA denaturation in the absence of PV; [ST DNA] = 1.97 x 10^{-5} mol L^{-1}; Temperature Range: 26 ˚C - 90 ˚C

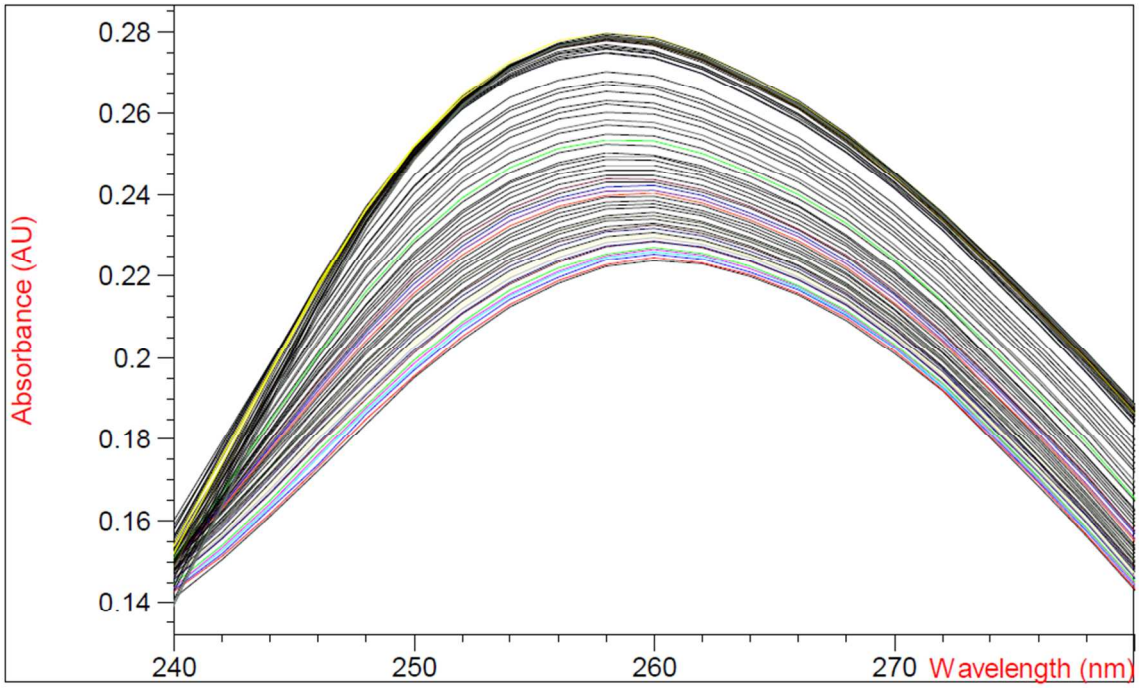


Fig.10 ST DNA denaturation in the presence of PV; [PV] = 9.64 x 10^{-7} mol L^{-1}; [ST DNA] = 1.97 x 10^{-5} mol L^{-1}; Temperature Range: 26 ˚C - 90 ˚C

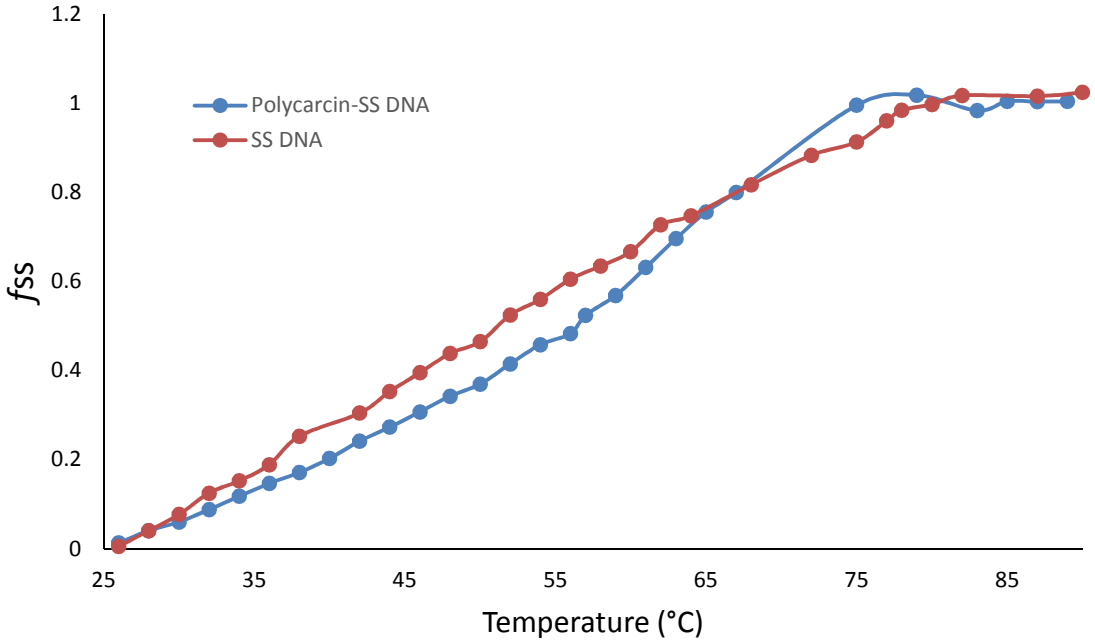


Fig. 11 Melting curve of ST DNA in the absence and presence of PV; [PV] = 9.64 x 10^{-7} mol L^{-1}; [ST DNA] = 1.97 x 10^{-5} mol L^{-1} ; f_{ss} = (A-A_0)/ (A_f-A_0), where $\mathbf{A_0}$ is the initial absorbance intensity, **A** is the absorbance intensity corresponding to its temperature, and $\mathbf{A_f}$ is the final absorbance intensity.

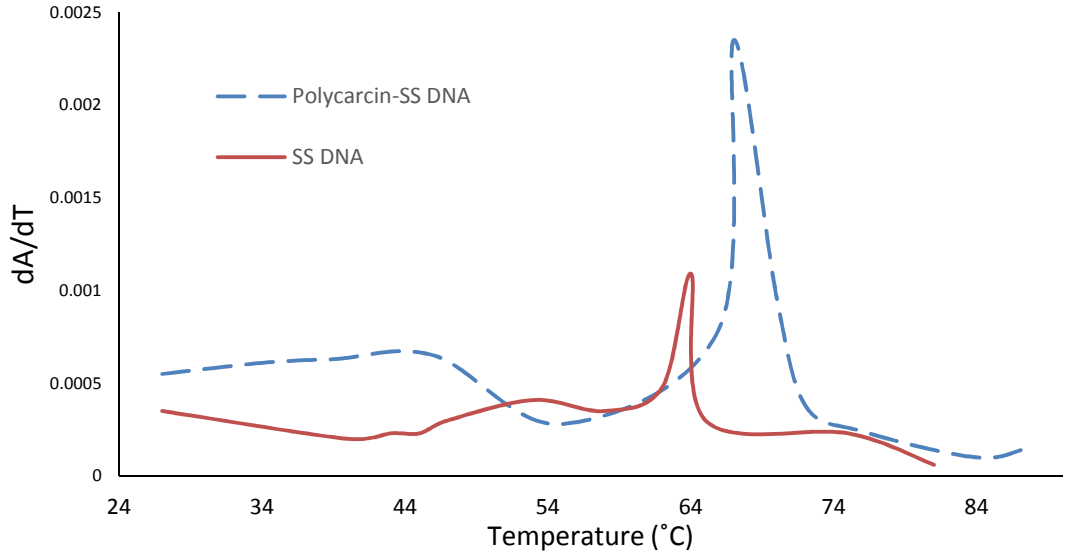


Fig. 12 ST DNA denaturation first derivative; [PV] = 9.64 x 10^{-7} mol L^{-1}; [ST DNA] = 1.97 x 10^{-5} mol L^{-1} ;T_m (ST DNA)=64 °C; T_m (ST DNA + PV)= 67 °C.