Supporting Information

Synthesis and antiproliferative activity of 6-naphthylpterocarps
Ádám Szappanos, a,b Attila Mándi,* a Katalin Gulácsi, a† Erika Lisztes, c Balázs István Tóth, c Tamás Bíró, d Sándor Antus, a Tibor Kurtán* a

aDepartment of Organic Chemistry, University of Debrecen, P. O. Box 400, 4002 Debrecen, Hungary Fax: +36-52-512-744
bDoctoral School of Chemistry, University of Debrecen, Egyetem tér 1, 4032 Debrecen, Hungary
cDepartment of Physiology, Faculty of Medicine, University of Debrecen, Debrecen, Hungary
dDepartment of Immunology, Faculty of Medicine, University of Debrecen, Debrecen, Hungary

†deceased

Dedicated in honor and to the memory of Prof. Koji Nakanishi

E-mail: kurtan.tibor@science.unideb.hu.

Table of Contents

1 Experimental Section for Previously Reported Derivatives ........................................................................5

1.1 General Procedure for the Preparation of Chalcone Analogues (12a-d) .................................................. 5

1.2 General Procedure for the Synthesis of 4-Chromanone Derivatives (13a-d) .............................................. 6

1.3 General Procedure for the Preparation of 2H-chromenes (7a-d) .............................................................. 7

1.4 General Procedure for the Synthesis of Chroman-4-ol derivatives (14a-d) .................................................. 8

1.5 References of known compounds .............................................................................................................. 9

2 NMR and IR Spectra ................................................................................................................................. 10

Figure S1. 1H NMR (400 MHz) spectrum of 9a in CDCl3 .............................................................................. 10

Figure S2. 13C NMR (100 MHz) spectrum of 9a in CDCl3 ........................................................................... 11

Figure S3. COSY spectrum of 9a in CDCl3 .................................................................................................. 12

Figure S4. HSQC spectrum of 9a in CDCl3 .................................................................................................. 13

Figure S5. NOESY spectrum of 9a in CDCl3 ................................................................................................. 14

Figure S6. IR spectrum of 9a recorded as KBr disc ....................................................................................... 15

Figure S7. 1H NMR (360 MHz) spectrum of 9b in CDCl3 .............................................................................. 16

Figure S8. 13C NMR (90 MHz) spectrum of 9b in CDCl3 ............................................................................. 17

Figure S9. IR spectrum of 9b recorded as KBr disc ....................................................................................... 18

Figure S10. 1H NMR (400 MHz) spectrum of 9c in CDCl3 .......................................................................... 19
Figure S11. $^1$H NMR (400 MHz) spectrum of 9e in CDCl$_3$ ................................................................. 20
Figure S12. IR spectrum of 9c recorded as KBr disc ............................................................................. 21
Figure S13. $^1$H NMR (360 MHz) spectrum of 9d in CDCl$_3$ ................................................................. 22
Figure S14. $^1$C NMR (90 MHz) spectrum of 9d in CDCl$_3$ ................................................................. 23
Figure S15. IR spectrum of 9d recorded as KBr disc ............................................................................. 24
Figure S16. $^1$H NMR (360 MHz) spectrum of 10a in CDCl$_3$ ................................................................. 27
Figure S17. $^1$C NMR (90 MHz) spectrum of 10a in CDCl$_3$ ................................................................. 28
Figure S18. IR spectrum of 10a recorded as KBr disc ............................................................................. 29
Figure S19. $^1$H NMR (400 MHz) spectrum of 10b in CDCl$_3$ ................................................................. 30
Figure S20. $^1$C NMR (100 MHz) spectrum of 10b in CDCl$_3$ ................................................................. 31
Figure S21. IR spectrum of 10b recorded as KBr disc ............................................................................. 32
Figure S22. $^1$H NMR (360 MHz) spectrum of 10c in CDCl$_3$ ................................................................. 33
Figure S23. $^1$C NMR (90 MHz) spectrum of 10c in CDCl$_3$ ................................................................. 34
Figure S24. IR spectrum of 10c recorded as KBr disc ............................................................................. 35
Figure S25. $^1$H NMR (400 MHz) spectrum of 10d in CDCl$_3$ ................................................................. 36
Figure S26. $^1$C NMR (100 MHz) spectrum of 10d in CDCl$_3$ ................................................................. 37
Figure S27. IR spectrum of 10d recorded as KBr disc ............................................................................. 38
Figure S28. $^1$H NMR (360 MHz) spectrum of 7a in CDCl$_3$ ................................................................. 39
Figure S29. $^1$C NMR (90 MHz) spectrum of 7a in CDCl$_3$ ................................................................. 40
Figure S30. IR spectrum of 7a recorded as KBr disc ............................................................................. 41
Figure S31. $^1$H NMR (360 MHz) spectrum of 7b in CDCl$_3$ ................................................................. 42
Figure S32. $^1$C NMR (90 MHz) spectrum of 7b in CDCl$_3$ ................................................................. 43
Figure S33. IR spectrum of 7b recorded as KBr disc ............................................................................. 44
Figure S34. $^1$H NMR (360 MHz) spectrum of 7c in CDCl$_3$ ................................................................. 45
Figure S35. $^1$C NMR (90 MHz) spectrum of 7c in CDCl$_3$ ................................................................. 46
Figure S36. $^1$H NMR (360 MHz) spectrum of 7d in CDCl$_3$ ................................................................. 47
Figure S37. $^1$C NMR (90 MHz) spectrum of 7d in CDCl$_3$ ................................................................. 48
Figure S38. $^1$H NMR (360 MHz) spectrum of 14a in CDCl$_3$ ................................................................. 49
Figure S39. $^1$C NMR (90 MHz) spectrum of 14a in CDCl$_3$ ................................................................. 50
Figure S40. $^1$H NMR (360 MHz) spectrum of 14b in CDCl$_3$ ................................................................. 51
Figure S41. $^1$C NMR (90 MHz) spectrum of 14b in CDCl$_3$ ................................................................. 52
Figure S42. $^1$H NMR (400 MHz) spectrum of 14c in CDCl$_3$ ................................................................. 53
Figure S43. $^1$C NMR (100 MHz) spectrum of 14c in CDCl$_3$ ................................................................. 54
3 Antiproliferative activity experiments

4 Chiral HPLC-ECD Spectra
Figure S74. HPLC-UV and –ECD traces of 10b on Chiralpak IA column with hexane/2-propanol 80:20 eluent monitored at 270 nm...

Figure S75. HPLC-ECD spectra of the first- [(6S,12S), black] and second-eluting [(6R,12R), red] enantiomers of 10b...  

Figure S76. HPLC-UV and –ECD traces of 10c on Chiralpak IA column with hexane/2-propanol 80:20 eluent monitored at 310 nm...

Figure S77. HPLC-ECD spectra of the first- [(6R,12R), black] and second-eluting [(6S,12S), red] enantiomers of 10c...  

Figure S78. HPLC-UV and –ECD traces of 10d on Chiralpak IA column with hexane/2-propanol 80:20 eluent monitored at 250 nm...

Figure S79. HPLC-ECD spectra of the first- [(6R,12R), black] and second-eluting [(6S,12S), red] enantiomers of 10d...

Figure S80. HPLC-UV trace of 13a on Chiralpak IC column with hexane/2-propanol 75:25 eluent...

Figure S81. HPLC-ECD spectra of the first- [(2S), black] and second-eluting [(2R), red] enantiomers of 13a...

Figure S82. HPLC-UV trace of 13b on Chiralpak IC column with hexane/2-propanol 75:25 eluent...

Figure S83. HPLC-ECD spectra of the first- [(2S), black] and second-eluting [(2R), red] enantiomers of 13b...

Figure S84. HPLC-UV trace of 13c on Chiralpak IC column with hexane/2-propanol 75:25 eluent...

Figure S85. HPLC-ECD spectra of the first- [(2S), black] and second-eluting [(2R), red] enantiomers of 13c...

Figure S86. HPLC-UV trace of 13d on Chiralpak IC column with hexane/2-propanol 75:25 eluent...

Figure S87. HPLC-ECD spectra of the first- [(2S), black] and second-eluting [(2R), red] enantiomers of 13d...

Figure S88. HPLC-UV trace of 7a on Chiracle OD column with hexane/2-propanol 95:5 eluent monitored at 260 nm...

Figure S89. HPLC-ECD spectra of the first- [(2R), black] and second-eluting [(2S), red] enantiomers of 7a...

Figure S90. HPLC-UV trace of 7b on Chiralpak IA column with hexane/2-propanol 95:5 eluent monitored at 280 nm...

Figure S91. HPLC-ECD spectra of the first- [(2S), black] and second-eluting [(2R), red] enantiomers of 7b...

Figure S92. HPLC-UV trace of 7c on Chiralpak IA column with hexane/2-propanol 95:5 eluent monitored at 270 nm...

Figure S93. HPLC-ECD spectra of the first- [(2S), black] and second-eluting [(2R), red] enantiomers of 7c...

Figure S94. HPLC-UV trace of 7d on Chiralcel OD column with hexane/2-propanol 95:5 eluent monitored at 225 nm...

Figure S95. HPLC-ECD spectra of the first- [(2S), black] and second-eluting [(2R), red] enantiomers of 7d...

Figure S96. Effect of pterocarpan derivatives on the viability and proliferation of tumorigenic cell lines...

Figure S97. B3LYP/TZVP PCM/CHCl₃ torsional angle scans of 9a and 9b...
1 Experimental Section for Previously Reported Derivatives

1.1 General Procedure for the Preparation of Chalcone Analogues (12a-d)

2-Hydroxyacetophenone 11a (1 g, 7.34 mmol) or 4-benzyloxyacetophenone 11b was dissolved in ethanol (50 mL) under stirring. Then NaOH (0.88 g; 22.02 mmol, with a minimum amount of water) was added and the solution was stirred for 5 min. To this solution, the aromatic aldehyde (8.81 mmol) was added and stirring was continued at room temperature for 24 h. The reaction was monitored by TLC. After completion of the reaction, the mixture was poured over crushed ice and acidified with 10 % HCl solution. The separated solid was filtered off and washed with water. The crude product was dried and recrystallized from ethanol to obtain the product in pure form.

\[
\text{(E)-1-(2-Hydroxyphenyl)-3-(1-naphthyl)prop-2-en-1-one (12a):} \quad \text{yellow crystals, 1.68 g (84 %), mp 107-109}^\circ \text{C, } ^1\text{H NMR (360 MHz, CDCl}_3 \text{)} \delta: 6.95 (t, J = 7.9 Hz, 1 H, 5'-H), 7.04 (d, J = 8.3 Hz, 1 H, 3'-H), 7.55 (m, 4 H, 4'-H, 3''-H, 6'''-H, 7''''-H), 7.72 (d, J = 15.5 Hz, 1 H, 2-H), 7.93 (m, 4 H, 2''-H, 4''-H, 5''-H, 8''-H), 8.26 (d, J = 8.3 Hz, 1 H, 6'-H), 8.76 (d, J = 15.1 Hz, 1 H, 3-H), 12.87 (s, 1 H, OH). ^{13}\text{C NMR (90 MHz, CDCl}_3 \text{)} \delta: 118.8 (C-3'), 119.0 (C-5'), 120.1 (C-1'), 122.8 (C-2), 123.5 (C-8''), 125.4 (C-2''), 125.5 (C-3''), 126.5 (C-6''), 127.2 (C-7''), 128.9 (C-6''), 129.8 (C-4''), 131.3 (C-5''), 131.9 (C-8a''), 132.1 (C-4a''), 133.8 (C-1''), 136.6 (C-1), 136.8 (C-2''), 193.6 (C-1). HRMS (ESI) calculated for C_{19}H_{14}NaO_2 [M + Na]^+: 297.0886, found 297.0887.
\]

\[
\text{(E)-1-(2-Hydroxyphenyl)-3-(2-naphthyl)prop-2-en-1-one (12b):} \quad \text{yellow crystals, 1.86 g (93 %), mp 150-152}^\circ \text{C, } ^1\text{H NMR (360 MHz, CDCl}_3 \text{)} \delta: 6.95 (t, J = 7.2 Hz, 1 H, 5'-H), 7.02 (d, J = 8.3 Hz, 1 H, 3'-H), 7.52 (m, 3 H, H-3'', 6''-H, 7''''-H), 7.75 (m, 2 H, 3-H, 4'-H), 7.84 (m, 3 H, 4''-H, 5''-H, 8''-H), 7.93 (d, J = 8.3 Hz, 1 H, 6'-H), 8.03 (m, 2 H, 2-H, 1''-H), 12.88 (s, 1 H, OH). ^{13}\text{C NMR (90 MHz, CDCl}_3 \text{)} \delta: 118.1 (C-3''), 118.4 (C-2), 119.6 (C-1), 119.6 (C-5''), 123.1 (C-3''), 126.4 (C-6''), 127.1 (C-7''), 127.3 (C-5''), 128.2 (C-1''), 128.3 (C-8''), 129.2 (C-4''), 130.6 (C-6''), 131.6 (C-2''), 132.8 (C-4a''), 134.0 (C-8a''), 135.9 (C-4''), 145.0 (C-3), 163.1 (C-2''), 193.1 (C-1). HRMS (ESI) calculated for C_{19}H_{14}NaO_2 [M + Na]^+: 297.0886, found 297.0886.
\]
1.2 General Procedure for the Synthesis of 4-Chromanone Derivatives (13a-d)

To the stirred solution of chalcone derivatives 12a-d (1 g, 3.62 mmol) in ethanol (50 mL), sodium acetate solution (4 g in 10 mL water) was added and the reaction mixture was refluxed for 5 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure, and extracted with ethyl acetate. The combined organic layers were washed with water, dried over MgSO₄, filtered and solvent was evaporated under reduced pressure. The residue was triturated with cold diethyl ether. The precipitate was filtered and dried on air.

(±)-2-(1-Naphthyl)chromanone (13a): white crystals, 506 mg (51 %), mp 99-101 °C, ¹H NMR (360 MHz, CDCl₃) δ: 3.05 (dd, J = 16.9, 2.8 Hz, 1 H, 3-Hₐ), 3.24 (m, 1 H, 3-Hₖ), 6.19 (dd, J = 13.3, 2.8 Hz, 1 H, 2-H), 7.08 (m, 2 H, 6-H, 8-H), 7.53 (m, 4 H, 7-H, 2’-H, 3’-H, 7’-H), 7.75 (d, J = 6.8 Hz, 1 H, 4’-H), 7.89 (m, 2 H, 5’-H, 6’-H), 8.00 (m, 2 H, 5-H, 8’-H). ¹³C NMR (90 MHz, CDCl₃) δ: 43.9 (C-3), 76.8 (C-2), 118.2 (C-8), 121.1 (C-4a), 121.7 (C-6), 122.7 (C-8’), 123.8 (C-3’), 125.9 (C-7’), 126.6 (C-2), 127.1 (C-5), 129.0 (C-4’), 129.3 (C-5’), 130.1 (C-8a’), 133.8 (C-4a’), 134.1 (C-1), 136.2 (C-7), 161.7 (C-8a), 192.2 (C-4). HRMS (ESI) calculated for C₁₉H₁₄NaO₂ [M + Na]⁺: 297.0886, found 297.0885.

(S)-13a: t_R = 5.93 min on Chiralpak IC column (hexane/2-propanol 75:25), HPLC-ECD λ [nm] (ϕ): 336 (6.27), 267sh (5.09), 247sh (6.67), 228 (84.87), 223 (−35.63), 218sh (−22.55).

(R)-13a: t_R = 8.67 min on Chiralpak IC column (hexane/2-propanol 75:25), HPLC-ECD λ [nm] (ϕ): 336 (6.16), 267sh (4.48), 247sh (−6.74), 228 (−85.15), 223 (37.94), 218sh (26.31).

(±)-2-(2-Naphthyl)chromanone (13b): white crystals, 675 mg (68 %) mp 108-110 °C, ¹H NMR (360 MHz, CDCl₃) δ: 2.90 (dd, J = 16.5, 2.5 Hz, 1 H, 3-Hₐ), 3.09 (m, 1 H, 3-Hₖ), 5.56 (dd, J = 13.3, 2.2 Hz, 1 H, 2-H), 7.05 (m, 2 H, 6-H, 8-H), 7.50 (m, 4 H, 7-H, 6’-H, 7’-H, 8’-H), 7.88 (m, 5 H, 5-H, 1’-H, 3’-H, 4’-H, 5’-H). ¹³C NMR (90 MHz, CDCl₃) δ: 44.5 (C-3), 79.6 (C-2), 118.1 (C-8), 120.9 (C-4a), 121.6 (C-6), 123.6 (C-3’), 125.3 (C-1’), 126.5 (C-4’, C-6’), 127.0 (C-7’), 127.7 (C-5), 128.1 (C-5’), 128.7 (C-8a’), 133.0 (C-4a’), 136.0 (C-2’), 136.1 (C-7), 161.4 (C-8a), 191.8 (C-4). HRMS (ESI) calculated for C₁₉H₁₄NaO₂ [M + Na]⁺: 297.0886, found 297.0885.

(S)-13b: t_R = 7.57 min on Chiralpak IC column (hexane/2-propanol 75:25), HPLC-ECD λ [nm] (ϕ): 340 (1.86), 313 (−3.81), 249 (−14.60).

(R)-13b: t_R = 8.92 min on Chiralpak IC column (hexane/2-propanol 75:25), HPLC-ECD λ [nm] (ϕ): 340 (−1.50), 313 (2.74), 249 (2.66), 231 (−2.63), 210 (−14.60).
1.3 General Procedure for the Preparation of $2H$-chromenes (7a-d)

Method A

To the stirred solution of chroman-4-ol analogues 14a-d (100 mg, 0.36 mmol) in acetone (10 mL), 1% HCl solution (20 µL) was added dropwise at room temperature. The reaction was refluxed for 1 h and the conversion was checked by TLC. After completion, the reaction mixture was diluted with water (10 mL) and ethyl-acetate (10 mL) was added. The organic layer was separated and dried over magnesium sulfate. Removal of the solvent under reduced pressure afforded the crude material as orange oil. The residue was purified by column chromatography on silica gel using hexane/ethyl acetate 6:1 as eluent.

Method B

A three necked flask was charged with cerium chloride heptahydrate (4.35 g, 11.68 mmol) and ethanol (15 mL). The mixture was stirred at room temperature under nitrogen to obtain a clear solution. THF (15 mL) was added followed by the addition of the chalcone analogues 12a-d (1 g, 3.65 mmol). The reaction was cooled to approximately 2 °C (internal temperature), after which sodium borohydride (2.49 g, 65.8 mmol) was added in portions. The reaction was monitored by TLC. When the starting material disappeared, the mixture was quenched by the slow addition of 5 wt % citric acid solution. When the vigorous gas release had subsided, the mixture was refluxed for an additional 20 min, and then extracted with ethyl acetate. The solid material in the aqueous layer was dissolved by adding 1 M HCl (5 mL) and the aqueous phase was extracted with ethyl acetate. The combined organic layers were washed with saturated sodium bicarbonate and brine. The pH value of the final aqueous wash was ca 4–5. The organic layer was dried over MgSO₄. Removal of solvent afforded the crude product as orange oil, which was purified by column chromatography on silica using hexane/ethyl acetate 6:1 as eluent.

(±)-2-(1-Naphthyl)-$2H$-chromene (7a):³ colorless oil, 547 mg (58 %), $^1$H NMR (360 MHz, CDCl₃) δ: 5.88 (dd, $J = 9.7, 3.2$ Hz, 1 H, 3-H), 6.61 (m, 2 H, 2-H, 4-H), 6.77 (d, $J = 7.9$ Hz, 1 H, 8-H), 6.88 (m, 1 H, 6-H), 7.07 (m, 2 H, 5-H, 7-H), 7.41 (t, $J = 7.2$ Hz, 1 H, 3'-H), 7.52 (m, 2 H, 6'-H, 7'-H), 7.63 (d, $J = 6.9$ Hz, 1 H, 2'-H), 7.81 (d, $J = 7.9$ Hz, 1 H, 5'-H), 7.86 (d, $J = 9$ Hz, 1 H, 4'-H), 8.29 (d, $J = 8.3$ Hz, 1 H, 8'-H). $^{13}$C NMR (90 MHz, CDCl₃) δ: 74.7 (C-2), 116.0 (C-8), 121.2 (C-6), 121.5 (C-4a), 123.9 (C-4), 124.7 (C-3), 124.8 (C-6’), 125.2 (C-8’), 125.6 (C-5’), 125.7 (C-3’), 126.2 (C-2’), 126.6 (C-7’), 128.7 (C-4’), 129.0 (C-5’), 129.3 (C-7), 130.8 (C-8a’), 134.0 (C-4a’), 135.3 (C-1’), 153.4 (C-8a).

(R)-7a: $t_R = 10.67$ min on Chiralcel OD column (hexane/2-propanol 95:5), HPLC-ECD $\lambda$ [nm] (ϕ): 314sh (3.11), 283 (5.14), 258sh (6.69), 227 (32.55), 214 (39.27).

(S)-7a: $t_R = 11.33$ min on Chiralcel OD column (hexane/2-propanol 95:5), HPLC-ECD $\lambda$ [nm] (ϕ): 314sh (−3.67), 283 (−5.49), 258sh (6.43), 227 (32.40), 214 (−44.47).
(±)-2-(2-Naphthyl)-2H-chromene (7b): \(^3\) colorless oil, 424 mg (45 %), \(^1\)H NMR (360 MHz, CDCl\(_3\)) \(\delta\): 5.82 (dd, \(J = 9.7, 3.2\) Hz, 1 H, 3-H), 6.06 (s, 1 H, 2-H), 6.54 (dd, \(J = 9.7, 1.1\) Hz, 1 H, 4-H) 6.79 (d, \(J = 7.9\) Hz, 1 H, 8-H), 6.86 (t, \(J = 7.2\) Hz, 1 H, 6-H), 7.00 (dd, \(J = 7.2, 1.1\) Hz, 1 H, 3’-H), 7.10 (m, 1 H, 7-H), 7.46 (m, 2 H, 6’-H, 7’-H), 7.57 (dd, \(J = 8.6, 1.4\) Hz, 1 H, 8’-H), 7.82 (m, 4 H, 5-H, 1’-H, 5’-H, 8’-H). \(^1\)C NMR (90 MHz, CDCl\(_3\)) \(\delta\): 77.2 (C-2), 116.0 (C-8), 121.2 (C-6), 121.3 (C-4a), 124.2 (C-4), 124.9 (C-1’), 126.0 (C-5), 126.2 (C-6’, C-7’), 126.6 (C-3’), 127.7 (C-8’), 128.2 (C-5’), 128.6 (C-4’), 129.5 (C-7), 133.2 (C-4a’), 133.3 (C-8a’), 138.0 (C-2’), 153.2 (C-8a).

(S)-7b: \(t_R = 3.31\) min on Chiralpak IA column (hexane/2-propanol 95:5), HPLC-ECD \(\lambda\) [nm] (\(\phi\)): 315 (–11.60), 259 (–26.40), 235 (10.60), 220 (–21.50), 209 (64.35).

(R)-7b: \(t_R = 3.57\) min on Chiralpak IA column (hexane/2-propanol 95:5), HPLC-ECD \(\lambda\) [nm] (\(\phi\)): 315 (8.95), 259 (21.64), 235 (–9.41), 220 (20.21), 209 (–65.49).

1.4 General Procedure for the Synthesis of Chroman-4-ol derivatives (14a–d)

To the stirred solution of flavanone analogues 13a–d (500 mg, 1.81 mmol) in ethanol (30 mL), NaBH\(_4\) (103 mg, 2.72 mmol) was added at room temperature. The reaction was monitored by TLC and after completion, the reaction mixture was diluted with water (20 mL), acidified with 10 % HCl solution (pH 6) and extracted with ethyl acetate. The combined organic layers were dried over anhydrous MgSO\(_4\), filtered and concentrated. The residue was purified by column chromatography on silica gel using hexane/ethyl acetate 2:1 as eluent.

(±)-2-(1-Naphthyl)chroman-4-ol (14a): \(^4\) white crystals, 345 mg (69 %), mp 117-119 ºC, \(^1\)H NMR (360 MHz, CDCl\(_3\)) \(\delta\): 2.21 (m, 2 H, 3-Ha, OH), 2.57 (dd, \(J = 12.9, 6.1\) Hz, 1 H, 3-Hb), 5.10 (dd, \(J =\) 9.7, 6.1 Hz, 1 H, 4-H), 5.80 (d, \(J = 11.5\) Hz, 1 H, 2-H), 6.90 (d, \(J = 7.9\) Hz, 1 H, 8-H), 6.97 (t, \(J = 7.2\) Hz, 1 H, 6-H), 7.19 (t, \(J = 6.8\) Hz, 1 H, 7-H), 7.49 (m, 4 H, 2’-H, 3’-H, 6’-H, 7’-H), 7.66 (d, \(J = 7.2\) Hz, 1 H, 5-H), 7.82 (m, 2 H, 5-H, 4’-H), 7.98 (m, 1 H, 8’-H). \(^1\)C NMR (90 MHz, CDCl\(_3\)) \(\delta\): 38.9 (C-3), 66.0 (C-4), 73.9 (C-2), 116.8 (C-8), 121.1 (C-6), 122.8
(C-6’), 123.5 (C-7’), 125.5 (C-8’), 125.7 (C-3’), 126.0 (C-4a), 126.4 (C-4’), 127.1 (C-2’), 128.7 (C-5), 129.0 (C-5’), 129.2 (C-7), 130.3 (C-8a’), 133.8 (C-4a’), 135.7 (C-1’), 154.6 (C-8a). HRMS (ESI) calculated for C_{19}H_{16}NaO_{2} [M + Na]^+: 299.1043, found 299.1043.

1.5 References of known compounds

Figure S1. $^1$H NMR (400 MHz) spectrum of 9a in CDCl$_3$
**Figure S2.** $^{13}$C NMR (100 MHz) spectrum of 9a in CDCl₃
Figure S3. COSY spectrum of 9a in CDCl₃
Figure S4. HSQC spectrum of 9a in CDCl₃
Figure S5. NOESY spectrum of 9a in CDCl$_3$
Figure S6. IR spectrum of 9a recorded as KBr disc
Figure S7. $^1$H NMR (360 MHz) spectrum of 9b in CDCl$_3$
Figure S8. $^{13}$C NMR (90 MHz) spectrum of 9b in CDCl$_3$
Figure S9. IR spectrum of 9b recorded as KBr disc
Figure S10. $^1$H NMR (400 MHz) spectrum of 9c in CDCl$_3$
Figure S11. $^{13}$C NMR (100 MHz) spectrum of 9c in CDCl$_3$
Figure S12. IR spectrum of 9c recorded as KBr disc
Figure S13. $^1$H NMR (360 MHz) spectrum of 9d in CDCl$_3$. 
Figure S14. $^{13}$C NMR (90 MHz) spectrum of 9d in CDCl$_3$
Figure S15. IR spectrum of 9d recorded as KBr disc
Figure S13. $^1$H NMR (400 MHz) spectrum of 17 in CDCl$_3$
Figure S14. $^{13}$C NMR (100 MHz) spectrum of 17 in CDCl$_3$
Figure S16. $^1$H NMR (360 MHz) spectrum of 10a in CDCl$_3$
Figure S17. $^{13}$C NMR (90 MHz) spectrum of 10a in CDCl$_3$
Figure S18. IR spectrum of 10a recorded as KBr disc
Figure S19. \(^1\)H NMR (400 MHz) spectrum of 10b in CDCl\(_3\)
Figure S20. $^{13}$C NMR (100 MHz) spectrum of 10b in CDCl$_3$
Figure S21. IR spectrum of 10b recorded as KBr disc
Figure S22. $^1$H NMR (360 MHz) spectrum of 10c in CDCl$_3$
Figure S23. $^{13}$C NMR (90 MHz) spectrum of 10c in CDCl$_3$
Figure S24. IR spectrum of 10c recorded as KBr disc
Figure S25. $^1$H NMR (400 MHz) spectrum of 10d in CDCl$_3$
Figure S26. $^{13}$C NMR (100 MHz) spectrum of 10d in CDCl$_3$
Figure S27. IR spectrum of 10d recorded as KBr disc
Figure S28. $^1$H NMR (360 MHz) spectrum of 7a in CDCl$_3$. 
Figure S29. $^{13}$C NMR (90 MHz) spectrum of 7a in CDCl$_3$
Figure S30. IR spectrum of 7a recorded as KBr disc
Figure S31. $^1$H NMR (360 MHz) spectrum of 7b in CDCl$_3$
Figure S32. $^{13}$C NMR (90 MHz) spectrum of 7b in CDCl$_3$
Figure S33. IR spectrum of 7b recorded as KBr disc
Figure S34. $^1$H NMR (360 MHz) spectrum of 7c in CDCl$_3$
Figure S35. $^{13}$C NMR (90 MHz) spectrum of 7c in CDCl$_3$. 
Figure S36. $^1$H NMR (360 MHz) spectrum of 7d in CDCl$_3$
Figure S37. $^{13}$C NMR (90 MHz) spectrum of 7d in CDCl$_3$
Figure S38. $^1$H NMR (360 MHz) spectrum of 14a in CDCl$_3$
Figure S39. $^{13}$C NMR (90 MHz) spectrum of 14a in CDCl$_3$
Figure S40. $^1$H NMR (360 MHz) spectrum of 14b in CDCl$_3$
Figure S41. $^{13}$C NMR (90 MHz) spectrum of 14b in CDCl$_3$
Figure S42. $^1$H NMR (400 MHz) spectrum of 14c in CDCl$_3$
Figure S43. $^{13}$C NMR (100 MHz) spectrum of 14c in CDCl$_3$
Figure S44. COSY spectrum of 14c in CDCl₃
Figure S45. HSQC spectrum of 14c in CDCl₃
Figure S46. $^1$H NMR (360 MHz) spectrum of 14d in CDCl$_3$
Figure S47. $^{13}$C NMR (90 MHz) spectrum of 14d in CDCl$_3$
Figure S48. $^1$H NMR (360 MHz) spectrum of 13a in CDCl$_3$
Figure S49. $^{13}$C NMR (90 MHz) spectrum of 13a in CDCl₃
Figure S50. $^1$H NMR (360 MHz) spectrum of 13b in CDCl$_3$
Figure S51. $^{13}$C NMR (90 MHz) spectrum of 13b in CDCl$_3$
Figure S52. $^1$H NMR (360 MHz) spectrum of 13c in CDCl$_3$
Figure S53. $^{13}$C NMR (90 MHz) spectrum of 13c in CDCl$_3$
**Figure S54.** $^1$H NMR (360 MHz) spectrum of 13d in CDCl$_3$
Figure S55. $^{13}$C NMR (90 MHz) spectrum of 13d in CDCl$_3$
Figure S56. $^1$H NMR (360 MHz) spectrum of 12a in CDCl$_3$
Figure S57. $^{13}$C NMR (90 MHz) spectrum of 12a in CDCl$_3$
Figure S58. $^1$H NMR (360 MHz) spectrum of 12b in CDCl$_3$
Figure S59. $^{13}$C NMR (90 MHz) spectrum of 12b in CDCl$_3$
Figure S60. $^1$H NMR (400 MHz) spectrum of 12c in CDCl$_3$
Figure S61. $^{13}$C NMR (100 MHz) spectrum of 12c in CDCl$_3$
Figure S62. $^1$H NMR (400 MHz) spectrum of 12d in CDCl$_3$
Figure S63. $^{13}$C NMR (100 MHz) spectrum of 12d in CDCl$_3$
3 Antiproliferative activity experiments

**Figure S64.** Concentration-dependent effect of 9a on the viability of A2780 cells. Cells were treated daily for 3 days, subjected for MTT assay and IC$_{50}$ value was determined as described in the Experimental section. Green line indicates the value of negative control treated with equal amount of vehicle solvent (DMSO) and blue line represents the effect of 1 µg/ml doxorubicin used as positive control. Data are presented as Mean±SEM, N=4 at each data point.
Figure S6. Concentration-dependent effect of 9a on the viability of WM35 cells. Cells were treated daily for 3 days, subjected for MTT assay and IC\textsubscript{50} value was determined as described in the Experimental section. Green line indicates the value of negative control treated with equal amount of vehicle solvent (DMSO) and blue line represents the effect of 1 µg/ml doxorubicin used as positive control. Data are presented as Mean±SEM, N=4 at each data point.
Figure S66. Concentration-dependent effect of 9b on the viability of A2780 cells. Cells were treated daily for 3 days, subjected for MTT assay and IC₅₀ value was determined as described in the Experimental section. Green line indicates the value of negative control treated with equal amount of vehicle solvent (DMSO) and blue line represents the effect of 1 µg/ml doxorubicin used as positive control. Data are presented as Mean±SEM, N=4 at each data point.
**Figure S67.** Concentration-dependent effect of 9b on the viability of WM35 cells. Cells were treated daily for 3 days, subjected for MTT assay and IC50 value was determined as described in the “Experimental” section. Green line indicates the value of negative control treated with equal amount of vehicle solvent (DMSO) and blue line represents the effect of 1 µg/ml doxorubicin used as positive control. Data are presented as Mean±SEM, N=4 at each data point.
4 Chiral HPLC-ECD Spectra

**Figure S68.** HPLC-UV and –ECD traces of 9c on Chiralpak IA column with hexane/2-propanol 80:20 eluent monitored at 250 nm.

**Figure S69.** HPLC-ECD spectra of the first- [((6S,6aR,11aR), black] and second-eluting [((6R,6aS,11aS), red] enantiomers of 9c.
**Figure S70.** HPLC-UV and –ECD traces of 9d on Chiralpak IA column with hexane/2-propanol 80:20 eluent monitored at 310 nm.

**Figure S71.** HPLC-ECD spectra of the first- [(6S,6aR,11aR), black] and second-eluting [(6R,6aS,11aS), red] enantiomers of 9d.
Figure S72. HPLC-UV and –ECD traces of 10a on Chiralpak IA column with hexane/2-propanol 95:5 eluent monitored at 270 nm.

Figure S73. HPLC-ECD spectra of the first- [(6S,12S), black] and second-eluting [(6R,12R), red] enantiomers of 10a.
Figure S74. HPLC-UV and –ECD traces of 10b on Chiralpak IA column with hexane/2-propanol 80:20 eluent monitored at 270 nm.

Figure S75. HPLC-ECD spectra of the first- [(6S,12S), black] and second-eluting [(6R,12R), red] enantiomers of 10b.
Figure S76. HPLC-UV and –ECD traces of 10c on Chiralpak IA column with hexane/2-propanol 80:20 eluent monitored at 310 nm.

Figure S77. HPLC-ECD spectra of the first- [(6R,12R), black] and second-eluting [(6S,12S), red] enantiomers of 10c.
**Figure S78.** HPLC-UV and –ECD traces of **10d** on Chiralpak IA column with hexane/2-propanol 80:20 eluent monitored at 250 nm.

**Figure S79.** HPLC-ECD spectra of the first- [(6R,12R), black] and second-eluting [(6S,12S), red] enantiomers of **10d**.
**Figure S80.** HPLC-UV trace of **13a** on Chiralpak IC column with hexane/2-propanol 75:25 eluent.

**Figure S81.** HPLC-ECD spectra of the first- [(2S), black] and second-eluting [(2R), red] enantiomers of **13a**.
Figure S82. HPLC-UV trace of 13b on Chiralpak IC column with hexane/2-propanol 75:25 eluent.

Figure S83. HPLC-ECD spectra of the first- [(2S), black] and second-eluting [(2R), red] enantiomers of 13b.
**Figure S84.** HPLC-UV trace of 13c on Chiralpak IC column with hexane/2-propanol 75:25 eluent.

**Figure S85.** HPLC-ECD spectra of the first- [(2S), black] and second-eluting [(2R), red] enantiomers of 13c.
Figure S86. HPLC-UV trace of 13d on Chiralpak IC column with hexane/2-propanol 75:25 eluent.

Figure S87. HPLC-ECD spectra of the first- [(2S), black] and second-eluting [(2R), red] enantiomers of 13d.
Figure S88. HPLC-UV trace of 7a on Chiralcel OD column with hexane/2-propanol 95:5 eluent monitored at 260 nm.

Figure S89. HPLC-ECD spectra of the first- [(2R), black] and second-eluting [(2S), red] enantiomers of 7a.
Figure S90. HPLC-UV trace of 7b on Chiralpak IA column with hexane/2-propanol 95:5 eluent monitored at 280 nm.

Figure S91. HPLC-ECD spectra of the first- [(2S), black] and second-eluting [(2R), red] enantiomers of 7b.
Figure S92. HPLC-UV trace of 7c on Chirlpak IA column with hexane/2-propanol 95:5 eluent monitored at 270 nm.

Figure S93. HPLC-ECD spectra of the first- [(2S), black] and second-eluting [(2R), red] enantiomers of 7c.
**Figure S94.** HPLC-UV trace of 7d on Chiralcel OD column with hexane/2-propanol 95:5 eluent monitored at 225 nm.

**Figure S95.** HPLC-ECD spectra of the first- [(2S), black] and second-eluting [(2R), red] enantiomers of 7d.
Figure S96. Effect of pectrocarpan derivatives on the viability and proliferation of tumorigenic cell lines.

Effect of pectrocarpans on the viable cell number of A2780 ovarian carcinoma (A), and WM35 melanoma (B). 50 μM solution of each compound was applied daily, for 3 days. Control cells were treated with equal amount of vehicle solvent (DMSO). Data are presented as Mean±SEM, N = 4 at each data point.*p<0.05; **p<0.01; ***p<0.001 compared to the vehicle treated control on the same day using ANOVA and Dunnett post-hoc test.
Figure S97. B3LYP/TZVP PCM/CHCl₃ torsional angle scans around the C-6–C-1’ bond ($\omega_{O-5,C-6,C-1',C-8a'}$ torsional angle) of (6R,6aS,11aS)-9a (blue curve) and the C-6–C-2’ bond ($\omega_{O-5,C-6,C-2',C-1'}$ torsional angle) of (6R,6aS,11aS)-9b (pink curve). Relative energy (kJ mol$^{-1}$) is plotted as a function of torsional angles.