

Electronic Supplementary information

Synthesis and biological evaluation of 4 β -benzoxazolepodophyllotoxin hybrids as DNA topoisomerase-II targeting anticancer agents

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List of Contents

1. Docking poses for 9a, 9c and 9f in DNA topoisomerase-II
2. Top 10 interaction poses of compound 9i
3. Experimental Section

1. Docking poses for 9a, 9c and 9f in DNA topoisomerase-II

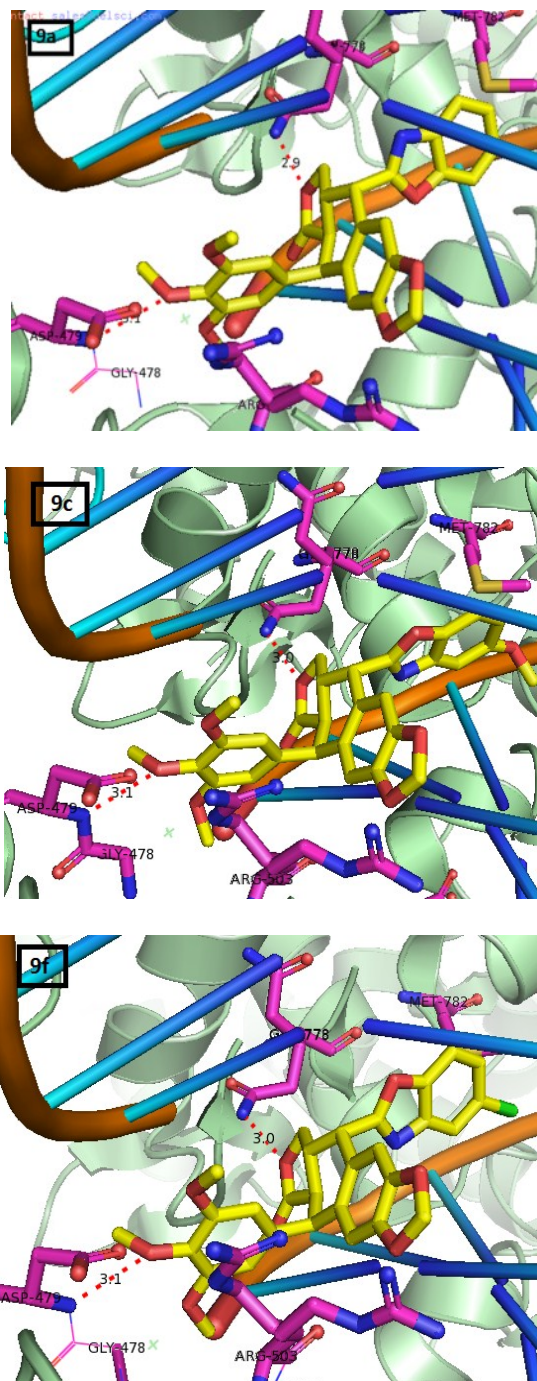


Fig. S1 Docking poses for 9a, 9c and 9f in DNA topoisomerase-II: The representative compounds were shown as yellow colour sticks, the interacted amino acid residues were represented as magenta sticks. The hydrogen bonding interactions with ASP-479 and GLN-778 were denoted as red dots. The protein DNA topoisomerase-II was shown as a pale green cartoon. PyMOL was used to visualize the docking poses.

2. Top 10 interaction poses of compound 9i

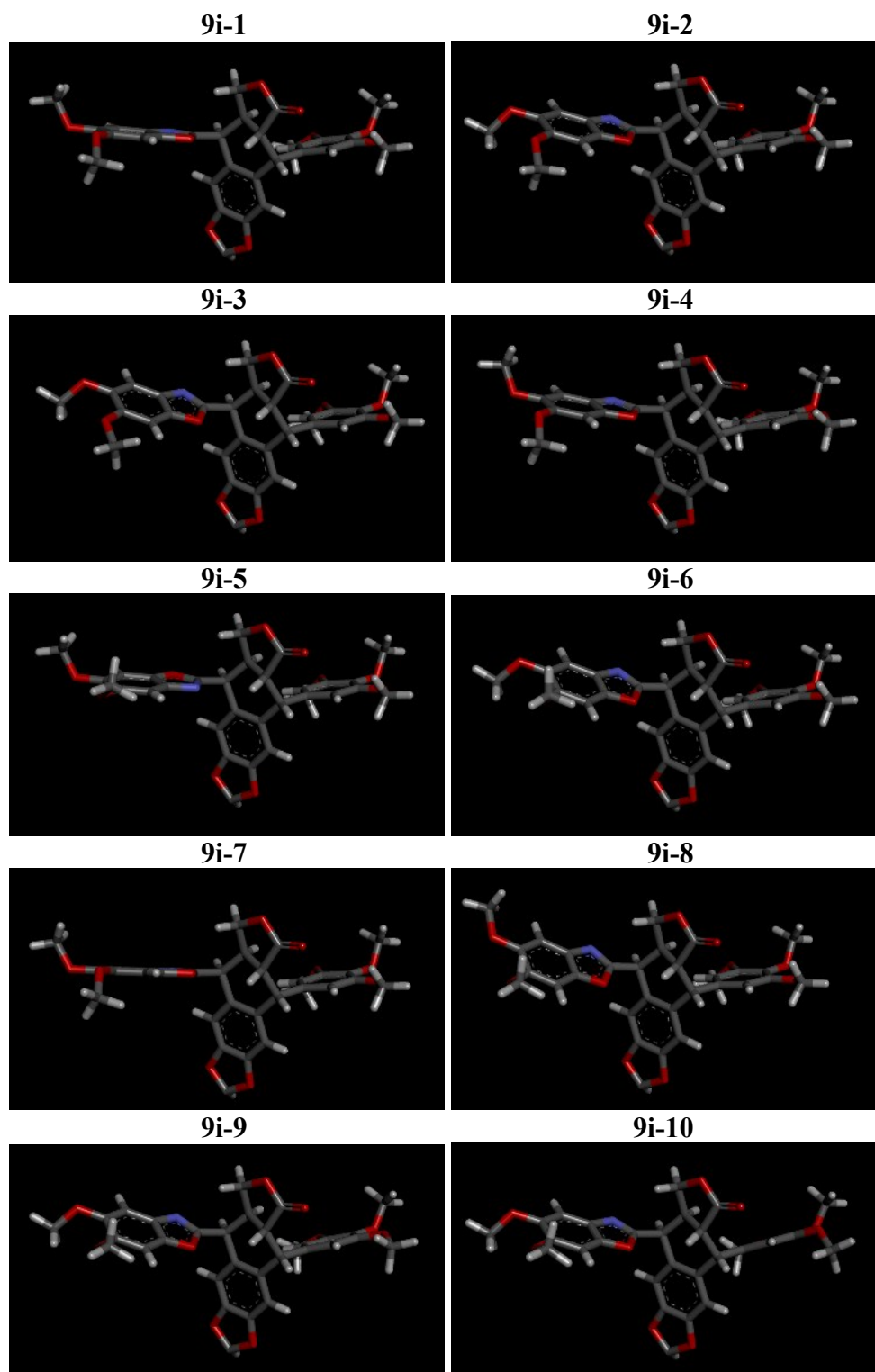


Fig. S2 The top 10 interaction poses of compound 9i

3. Experimental section

Chemicals and Reagents

All chemicals and reagents were obtained from Aldrich (Sigma–Aldrich, St. Louis, MO, USA), Lancaster (Alfa Aesar, Johnson Matthey Company, Ward Hill, MA, USA) and were used without further purification. Reactions were monitored by TLC, performed on silica gel glass plates containing 60 F-254, and visualization of TLC was achieved by UV light or iodine indicator. ¹H and ¹³C NMR (Nuclear Magnetic Resonance) spectra were recorded on Gemini Varian-VXR-unity (200 and 400 MHz) or Bruker UXNMR/XWIN-NMR (300 MHz) instruments. Chemical shifts (δ) are reported in ppm downfield from internal TMS standard. ESI spectra were recorded in Micro mass, Quattro LC using ESI+ software with capillary voltage 3.98 kV and ESI mode positive ion trap detector. Melting points were determined with an electro thermal melting point apparatus, and are uncorrected.

Spectral data

(5*R*,5*aR*,8*aR*,9*S*)-9-Hydroxy-5-(3,4,5-trimethoxyphenyl)-5,5*a*,6,8,8*a*,9-hexahydro[1,3]dioxolo[4',5':4,5]benzo[*f*]isobenzofuran-6-one (6)

To a solution of podophyllotoxin (**1**) (4.14 g, 10 mmol) in dry CH₃CN (100 mL), NaI (2.98 g, 20 mmol) was added and stirred for 5 minutes. To this stirred suspension, CH₃SO₃H (1.3 mL, 20 mmol) was added drop wise at 0 °C and stirring continued for another 30 min at room temperature. Then a mixture of H₂O/Me₂CO, v/v (1:1) and BaCO₃ (2.17 mg, 11 mmol) were added successively. After stirring for 30 min at room temperature, the solvent was evaporated and the residue was treated with 10% Na₂S₂O₃ solution and extracted with ethyl acetate. The organic layer was dried over anhydrous Na₂SO₄ and concentrated under vacuum to afford the crude product. This was purified by column chromatography (CH₂Cl₂/CH₃COCH₃, 92:8) to afford pure compound **7**, 3.52 g in 85% yield. Mp: 148–152 °C, [α]_D²⁵: – 64.0 (*c* = 1.0, CHCl₃); ¹H NMR (200 MHz, CDCl₃): δ 2.69–2.85 (m, 1H), 3.14–3.23 (dd, 1H, *J* = 14.3, 5.2 Hz), 3.73 (s, 6H), 3.76 (s, 3H), 4.26–4.39 (m, 2H), 4.55 (d, 1H, *J* = 5.2 Hz), 4.80 (d, 1H, *J* = 3.0 Hz), 5.95 and 6.01 (ABq, 2H, *J* = 7.3, 7.1 Hz), 6.21 (s, 2H), 6.52 (s, 1H), 6.84 (s, 1H); IR(KBr): 3513, 2921, 2849, 1764, 1589, 1504, 1479 cm⁻¹. MS (ESI): 413 [M-H]⁺.

(5*S*,5*aR*,8*aR*,9*R*)-8-Oxo-9-(3,4,5-trimethoxyphenyl)-5,5*a*,6,8,8*a*,9-hexahydro[1,3]dioxolo[4',5':4,5]benzo[*f*]isobenzofuran-5-carbonitrile (7)

To a solution of epipodophyllotoxin (7) (6 g, 14.4 mmol) in dry CHCl₃ (40 mL), was added dropwise BF₃·Et₂O (6.2 mL, 21.6 mmol), and trimethylsilyl cyanide (3.6 mL, 28.9 mmol) added to reaction mixture at -15 °C and stirred 6 hours. After completion of reaction, the solvent was evaporated and layer was dried over anhydrous Na₂SO₄ and concentrated under vacuum to afford the crude product. This was purified by column chromatography with ethyl acetate/hexane (2:8) to afford pure compound **8**, 5.90 g in 96% yield. ¹H NMR (400 MHz, CDCl₃): δ 2.71(dd, 1H, *J* = 11.6, 15.6 Hz), 2.87-2.97 (m, 1H), 3.76 (s, 6H), 3.89 (s, 3H), 4.23 (d, 1H, *J* = 7.80 Hz), 4.45-4.59 (m, 2H), 4.78 (d, 1H, *J* = 9.2 Hz), 6.13 (d, 2H, *J* = 19.4 Hz), 6.58 (s, 2H), 6.72 (s, 1H), 7.46 (s, 1H). MS (ESI): 424 [M+H]⁺.

(5*R*,5*aR*,8*aR*,9*S*)-9-(1,3-Benzoxazol-2-yl)-5-(3,4,5-trimethoxyphenyl)-5,5*a*,6,8,8*a*,9-hexahydro[1,3]dioxolo[4',5':4,5]benzo[*f*]isobenzofuran-6-one (9a)

A mixture of the nitrile (7) (200 mg, 4.72 mmol), 2-aminophenol (**8a**) (51 mg, 4.72 mmol), and Cu(OTf)₂ (20 mol% to 7) in chlorobenzene (2.0 mL) was stirred under reflux for 5 hours. Upon completion of the reaction, the chlorobenzene was removed under reduced pressure by an aspirator, and then the residue was purified by silica gel column chromatography (EtOAc/hexane, (2:8)) to afford corresponding compound **9a**, 212 mg in 87% yield. Mp: 161-163 °C, [α]_D²⁵ -81.8 (*c* 0.5 in CHCl₃), ¹H NMR (400 MHz, CDCl₃): δ 2.76(dd, 1H, *J* = 13.2, 14.6 Hz), 2.91-3.06 (m, 1H), 3.73 (s, 6H), 3.76 (s, 3H), 3.79-3.92 (m, 2H), 4.42 (t, 1H), 4.53 (d, 1H, *J* = 4.93 Hz), 5.93 (d, 2H, *J* = 13.9 Hz), 6.22 (s, 2H), 6.48 (s, 1H), 6.60 (s, 1H), 7.19-7.39 (m, 4H). ¹³C NMR (75 MHz, CDCl₃): δ 39.4, 40.7, 41.6, 43.3, 45.4, 55.7, 61.4, 65.8, 100.3, 106.5, 107.3, 107.8, 109.6, 117.8, 121.5, 123.8, 126.4, 133.7, 135.7, 136.8, 141.2, 144.7, 147.8, 149.6, 150.5, 165.6, 171.5. MS (ESI): 516 [M+H]⁺.

(5*R*,5*aR*,8*aR*,9*S*)-9-(6-Methoxy-1,3-benzoxazol-2-yl)-5-(3,4,5-trimethoxyphenyl)-5,5*a*,6,8,8*a*,9-hexahydro[1,3]dioxolo[4',5':4,5]benzo[*f*]isobenzofuran-6-one (9b)

The compound **9b** was prepared following the method described for the preparation of the compound **9a**, employing **7** (200 mg, 4.72 mmol), 2-amino-5-methoxyphenol (**8b**) (65 mg, 4.72 mmol), and Cu(OTf)₂ (20 mol% to **7**). The crude product was purified by column chromatography with ethyl acetate/hexane (3:7) to afford pure compound **9b**, 225 mg in 86% yield. Mp: 165-167 °C; [α]_D²⁵ -85.4 (*c* 0.5 in CHCl₃), ¹H NMR (400 MHz, CDCl₃): δ 2.81 (dd, 1H, *J* = 11.0, 12.2 Hz), 3.12-3.20 (m, 1H), 3.68 (s, 3H), 3.76 (s, 6H), 3.83 (s, 3H), 3.99 (t, 1H), 4.56-4.69 (m, 2H), 4.83 (d, 1H, *J* = 13.0 Hz), 5.98 (d, 2H, *J* = 15.01 Hz), 6.30 (s, 2H), 6.48 (s, 1H), 6.59 (s, 1H), 6.85-7.01 (m, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 37.6, 38.7, 39.4, 42.6, 45.4, 54.6, 55.6, 59.8, 66.5, 70.3, 94.3, 101.2, 106.4, 107.2, 107.9, 109.4, 119.6, 126.8, 133.5, 134.9, 135.7, 136.8, 144.7, 147.8, 150.8, 151.5, 156.8, 166.5, 171.2. MS (ESI): 546 [M+H]⁺.

(5R,5aR,8aR,9S)-9-(5-Methoxy-1,3-benzoxazol-2-yl)-5-(3,4,5-trimethoxyphenyl)-5,5a,6,8,8a,9-hexahydro[1,3]dioxolo[4',5':4,5]benzo[*f*]isobenzofuran-6-one (9c)

The compound **9c** was prepared following the method described for the preparation of the compound **9a**, employing **7** (200 mg, 4.72 mmol), 2-amino-4-methoxyphenol (**8c**) (65 mg, 4.72 mmol), and Cu(OTf)₂ (20 mol% to **7**). The crude product was purified by column chromatography with ethyl acetate/hexane (3:7) to afford pure compound **9c**, 219 mg in 85% yield. Mp: 170-172 °C; [α]_D²⁵ -86.6 (*c* 0.5 in CHCl₃), ¹H NMR (400 MHz, CDCl₃): δ 2.73 (dd, 1H, *J* = 14.02, 12.2 Hz), 2.89-2.96 (m, 1H), 3.72 (s, 3H), 3.79 (s, 6H), 3.89 (s, 3H), 3.98 (t, 1H), 4.78-4.89 (m, 2H), 5.03 (d, 1H, *J* = 3.02 Hz), 5.99 (d, 2H, *J* = 16.2 Hz), 6.27 (s, 2H), 6.39 (s, 1H), 6.44 (s, 1H), 6.67 (d, 1H, *J* = 8.40 Hz), 6.78-6.89 (m, 2H). ¹³C NMR (75 MHz, CDCl₃): δ 38.2, 39.1, 40.4, 42.4, 55.6, 56.7, 61.4, 66.5, 101.2, 102.8, 105.7, 106.5, 107.4, 107.7, 108.2, 108.7, 126.4, 133.8, 135.7, 137.3, 142.8, 144.6, 145.8, 148.3, 150.3, 152.2, 154.7, 166.5, 171.8. MS (ESI): 546 [M+H]⁺.

(5R,5aR,8aR,9S)-9-(6-Nitro-1,3-benzoxazol-2-yl)-5-(3,4,5-trimethoxyphenyl)-5,5a,6,8,8a,9-hexahydro[1,3]dioxolo[4',5':4,5]benzo[*f*]isobenzofuran-6-one (9d)

The compound **9d** was prepared following the method described for the preparation of the compound **9a**, employing **7** (200 mg, 4.72 mmol), 2-amino-5-nitrophenol (**8d**) (72 mg, 4.72 mmol), and Cu(OTf)₂ (20 mol% to **7**). The crude product was purified by

column chromatography with ethyl acetate/hexane (2:8) to afford pure compound **9d**, 229 mg in 87% yield. Mp: 173-175 °C; $[\alpha]_{\text{D}}^{25} -89.5$ (*c* 0.5 in CHCl₃), ¹H NMR (400 MHz, CDCl₃): δ 2.85 (dd, 1H, *J* = 13.2, 14.0 Hz), 3.10-3.18 (m, 1H), 3.76 (s, 6H), 3.84 (s, 3H), 3.96 (d, 1H, *J* = 9.02 Hz), 4.23-4.34 (m, 2H), 4.49 (d, 1H, *J* = 3.40 Hz), 5.98 (d, 2H, *J* = 17.1 Hz), 6.23 (s, 2H), 6.47 (s, 1H), 6.57 (s, 1H), 7.21 (d, 1H, *J* = 8.02 Hz), 7.79 (d, 1H, *J* = 9.0 Hz), 8.35 (s, 1H). ¹³C NMR (75 MHz, CDCl₃): δ 37.9, 39.4, 40.8, 43.6, 45.4, 55.5, 61.3, 68.7, 94.6, 101.3, 106.7, 107.5, 108.2, 118.9, 120.8, 126.8, 133.8, 136.3, 137.3, 140.6, 144.8, 146.7, 147.5, 149.8, 152.2, 166.5, 170.3. MS (ESI): 561 [M+H]⁺.

(5*R*,5*aR*,8*aR*,9*S*)-9-(5-Chloro-6-nitro-1,3-benzoxazol-2-yl)-5-(3,4,5-trimethoxyphenyl)-5,5*a*,6,8,8*a*,9-hexahydro[1,3]dioxolo[4',5':4,5]benzo[*f*]isobenzofuran-6-one (9e)

The compound **9e** was prepared following the method described for the preparation of the compound **9a**, employing **7** (200 mg, 4.72 mmol), 2-amino-4-chloro-5-nitrophenol (**8e**) (89 mg, 4.72 mmol), and Cu(OTf)₂ (20 mol% to **7**). The crude product was purified by column chromatography with ethyl acetate/hexane (2:8) to afford pure compound **9e**, 236 mg in 84% yield. Mp: 171-173 °C; $[\alpha]_{\text{D}}^{25} -92.3$ (*c* 0.5 in CHCl₃), ¹H NMR (400 MHz, CDCl₃): δ 2.91 (dd, 1H, *J* = 10.2, 13.2 Hz), 3.10-3.19 (m, 1H), 3.78 (s, 6H), 3.88 (s, 3H), 3.99 (d, 1H, *J* = 4.6 Hz), 4.35-4.44 (m, 2H), 4.67 (d, 1H, *J* = 5.70 Hz), 6.12 (d, 2H, *J* = 19.4 Hz), 6.45 (s, 2H), 6.57 (s, 1H), 6.68 (s, 1H), 7.31 (s, 1H), 8.42 (s, 1H). ¹³C NMR (75 MHz, CDCl₃): δ 38.5, 39.8, 40.6, 43.8, 56.7, 60.8, 66.4, 101.8, 104.6, 106.9, 107.5, 107.9, 121.6, 126.4, 129.8, 133.8, 135.8, 136.9, 140.5, 144.6, 145.7, 146.8, 147.6, 150.9, 165.9, 171.8. MS (ESI): 595 [M+H]⁺.

(5*R*,5*aR*,8*aR*,9*S*)-9-(5-Chloro-1,3-benzoxazol-2-yl)-5-(3,4,5-trimethoxyphenyl)-5,5*a*,6,8,8*a*,9-hexahydro[1,3]dioxolo[4',5':4,5]benzo[*f*]isobenzofuran-6-one (9f)

The compound **9f** was prepared following the method described for the preparation of the compound **9a**, employing **7** (200 mg, 4.72 mmol), 2-amino-4-chlorophenol (**8f**) (68 mg, 4.72 mmol), and Cu(OTf)₂ (20 mol% to **7**). The crude product was purified by column chromatography with ethyl acetate/hexane (2:8) to afford pure compound **9f**, 226 mg in 87% yield. Mp: 176-178 °C; $[\alpha]_{\text{D}}^{25} -93.4$ (*c* 0.5 in CHCl₃), ¹H NMR (400 MHz, CDCl₃):

δ 2.81 (dd, 1H, $J = 12.6, 9.3$ Hz), 3.09-3.19 (m, 1H), 3.74 (s, 6H), 3.83 (s, 3H), 3.98 (d, 1H, $J = 6.03$ Hz), 4.34-4.49 (m, 2H), 4.56 (d, 1H, $J = 4.03$ Hz), 5.97 (d, 2H, $J = 18.2$ Hz), 6.34 (s, 2H), 6.46 (s, 1H), 6.58 (s, 1H), 7.10-7.24 (m, 3H). ^{13}C NMR (75 MHz, CDCl_3): δ 37.8, 39.8, 40.5, 43.8, 56.8, 61.4, 101.4, 106.9, 107.4, 108.3, 110.6, 117.8, 123.7, 126.9, 127.4, 133.6, 137.3, 138.2, 138.8, 144.7, 146.3, 147.9, 152.4, 156.6, 166.8, 171.5. MS (ESI): 550 $[\text{M}+\text{H}]^+$.

(5R,5aR,8aR,9S)-9-(5,7-Dinitro-1,3-benzoxazol-2-yl)-5-(3,4,5-trimethoxyphenyl)-5,5a,6,8,8a,9-hexahydro[1,3]dioxolo[4',5':4,5]benzo[*f*]isobenzofuran-6-one (9g)

The compound **9g** was prepared following the method described for the preparation of the compound **9a**, employing **7** (200 mg, 4.72 mmol), 2-amino-4,6-dinitrophenol (**8g**) (94 mg, 4.72 mmol), and $\text{Cu}(\text{OTf})_2$ (20 mol% to **7**). The crude product was purified by column chromatography with ethyl acetate/hexane (2:8) to afford pure compound **9g**, 218 mg in 76% yield. Mp: 180-182 °C; $[\alpha]_{\text{D}}^{25} -96.2$ (c 0.5 in CHCl_3), ^1H NMR (400 MHz, CDCl_3): δ 2.87 (dd, 1H, $J = 4.5, 9.12$ Hz), 3.27-3.34 (m, 1H), 3.86 (s, 6H), 3.94 (s, 3H), 4.26 (d, 1H, $J = 8.21$ Hz), 4.56-4.68 (m, 2H), 4.75 (d, 1H, $J = 1.34$ Hz), 6.36 (d, 2H, $J = 13.3$ Hz), 6.78 (s, 2H), 6.83 (s, 1H), 6.95 (s, 1H), 8.23 (s, 1H), 8.54 (s, 1H). ^{13}C NMR (75 MHz, CDCl_3): δ 38.7, 40.5, 41.3, 57.2, 60.2, 66.8, 101.8, 106.4, 106.9, 107.8, 112.6, 118.5, 125.3, 133.7, 135.9, 137.4, 137.9, 138.9, 142.6, 143.6, 144.8, 147.8, 151.7, 156.3, 169.6, 170.2. MS (ESI): 606 $[\text{M}+\text{H}]^+$.

(5R,5aR,8aR,9S)-9-(5-Methyl-1,3-benzoxazol-2-yl)-5-(3,4,5-trimethoxyphenyl)-5,5a,6,8,8a,9-hexahydro[1,3]dioxolo[4',5':4,5]benzo[*f*]isobenzofuran-6-one (9h)

The compound **9h** was prepared following the method described for the preparation of the compound **9a**, employing **7** (200 mg, 4.72 mmol), 2-amino-4-methylphenol (**8h**) (58 mg, 4.72 mmol), and $\text{Cu}(\text{OTf})_2$ (20 mol% to **7**). The crude product was purified by column chromatography with ethyl acetate/hexane (2:8) to afford pure compound **9h**, 231 mg in 92% yield. Mp: 154-156 °C; $[\alpha]_{\text{D}}^{25} -58.5$ (c 0.5 in CHCl_3), ^1H NMR (400 MHz, CDCl_3): δ 2.39 (s, 3H), 2.56-2.67 (dd, 1H, $J = 6.2, 10.3$ Hz), 2.79-2.86 (m, 1H), 3.71 (s, 6H), 3.79 (s, 3H), 4.12 (d, 1H, $J = 10.4$ Hz), 4.27-4.35 (m, 2H), 4.69 (d, 1H, $J = 7.9$ Hz), 5.98 (d, 2H, $J = 23.4$ Hz), 6.24 (s, 2H), 6.36 (s, 1H), 6.45 (s, 1H), 6.67 (d, 1H, $J = 1.3$

Hz), 7.23 (s, 1H), 7.37 (d, 1H, $J = 9.03$ Hz). ^{13}C NMR (75 MHz, CDCl_3): δ 21.5, 37.9, 39.8, 40.7, 55.6, 59.7, 66.8, 101.2, 106.8, 107.5, 107.9, 108.8, 120.9, 126.8, 127.6, 129.8, 133.9, 135.8, 136.9, 139.8, 144.6, 145.9, 147.8, 151.4, 157.4, 166.8, 171.3. MS (ESI): 530 $[\text{M}+\text{H}]^+$.

(5*R*,5*aR*,8*aR*,9*S*)-9-(5,6-Dimethoxy-1,3-benzoxazol-2-yl)-5-(3,4,5-trimethoxyphenyl)-5,5*a*,6,8,8*a*,9-hexahydro[1,3]dioxolo[4',5':4,5]benzo[*f*]isobenzofuran-6-one (9i)

The compound **9i** was prepared following the method described for the preparation of the compound **9a**, employing **7** (200 mg, 4.72 mmol), 2-amino-4,5-dimethoxyphenol (**8i**) (80 mg, 4.72 mmol), and $\text{Cu}(\text{OTf})_2$ (20 mol% to **7**). The crude product was purified by column chromatography with ethyl acetate/hexane (3:7) to afford pure compound **9i**, 221 mg in 82% yield. Mp: 159-161 °C; $[\alpha]_{\text{D}}^{25} -97.3$ (c 0.5 in CHCl_3), ^1H NMR (400 MHz, CDCl_3): δ 2.61 (dd, 1H, $J = 4.9, 12.8$ Hz), 2.78-2.87 (m, 1H), 3.72 (s, 3H), 3.79 (s, 3H), 3.88 (s, 6H), 3.94 (s, 3H), 4.12 (d, 1H, $J = 12.5$ Hz), 4.34-4.49 (m, 2H), 4.58 (d, 1H, $J = 7.6$ Hz), 5.99 (d, 2H, $J = 17.6$ Hz), 6.19 (s, 2H), 6.45 (s, 1H), 6.54 (s, 1H), 6.65 (s, 1H), 6.69 (s, 1H). ^{13}C NMR (75 MHz, CDCl_3): δ 38.6, 39.8, 40.7, 43.6, 56.6, 56.9, 57.4, 60.5, 66.7, 95.8, 101.3, 102.9, 106.7, 107.5, 108.4, 126.7, 133.8, 137.3, 137.7, 137.9, 144.6, 146.7, 147.9, 148.5, 150.9, 153.6, 166.8, 171.3. MS (ESI): 576 $[\text{M}+\text{H}]^+$.

(5*R*,5*aR*,8*aR*,9*S*)-9-(5,6-Dimethyl-1,3-benzoxazol-2-yl)-5-(3,4,5-trimethoxyphenyl)-5,5*a*,6,8,8*a*,9-hexahydro[1,3]dioxolo[4',5':4,5]benzo[*f*]isobenzofuran-6-one (9j)

The compound **9j** was prepared following the method described for the preparation of the compound **9a**, employing **7** (200 mg, 4.72 mmol), 2-amino-4,5-dimethylphenol (**8j**) (65 mg, 4.72 mmol), and $\text{Cu}(\text{OTf})_2$ (20 mol% to **7**). The crude product was purified by column chromatography with ethyl acetate/hexane (2:8) to afford pure compound **9j**, 209 mg in 82% yield. Mp: 174-176 °C; $[\alpha]_{\text{D}}^{25} -74.5$ (c 0.5 in CHCl_3), ^1H NMR (400 MHz, CDCl_3): δ 2.34 (s, 3H), 2.39 (s, 3H), 2.61 (dd, 1H, $J = 12.4, 6.7$ Hz), 2.87-2.96 (m, 1H), 3.75 (s, 6H), 3.85 (s, 3H), 4.12 (d, 1H, $J = 11.8$ Hz), 4.45-4.57 (m, 2H), 4.79 (d, 1H, $J = 12.4$ Hz), 5.99 (d, 2H, $J = 23.5$ Hz), 6.34 (s, 2H), 6.56 (s, 1H), 6.67 (s, 1H), 7.23-7.37 (m, 2H). ^{13}C NMR (75 MHz, CDCl_3): δ 20.4, 37.9, 39.8, 40.4, 43.9, 56.8, 61.3, 68.4, 100.9,

106.7, 107.4, 107.9, 108.9, 123.7, 126.8, 131.8, 133.7, 137.4, 137.9, 138.3, 140.9, 144.6,
145.9, 147.8, 150.9, 158.7, 166.8, 170.1. MS (ESI): 544 [M+H]⁺.