Supporting Information

Semisynthesis and Quantitative Structure-Activity Relationship (QSAR) Study of Novel Aromatic Esters of 4′-Demethyl-4-deoxypodophyllotoxin as Insecticidal Agents

Hui Xu,*[,a] Juan-Juan Wang,[a] Hui-Jun Sun,[b] Min Lv,[a] Xuan Tian,[b] Xiao-Jun Yao,*[,b] Xing Zhang[a]

[a]*Laboratory of Pharmaceutical Design and Synthesis, College of Life Sciences, Northwest A&F University, Yangling 712100, Shannxi Province, P. R. China*

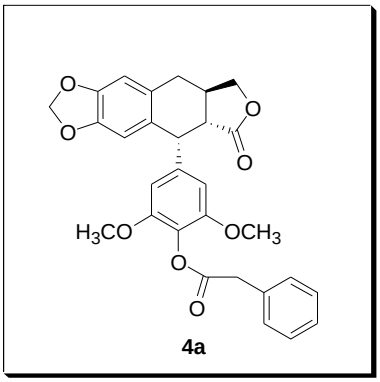
[b]*Department of Chemistry, Lanzhou University, Gansu Province, P. R. China*

To whom correspondence should be addressed. Tel: +86(0)29-87091952. Fax: +86(0)29-87091952. E-mail: orgxuhui@nwsuaf.edu.cn; xjyao@lzu.edu.cn

Synthetic Procedures. All reagents and solvents were of reagent grade or purified according to standard methods before use. Analytical thin-layer chromatography (TLC) and preparative thin-layer chromatography (PTLC) were performed with silica gel plates using silica gel 60 GF_{254} (Qingdao Haiyang Chemical Co., Ltd.). Melting points were determined on a digital melting-point apparatus and were uncorrected.

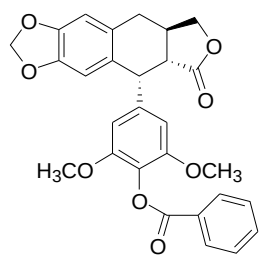
Infrared spectra (IR) were recorded on a Thermo Nicolet Nexus FTIR-8700 spectrometer. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on a Bruker Avance DMX 400 MHz instrument using TMS as internal standard and $CDCl_3$ as solvent. High-resolution mass spectra (HR-MS) and electrospray iontrap mass spectrometry (ESI-TRAP-MS) were carried out with APEX II Bruker 4.7T AS and Bruker ESI-TRAP Esquire 3000 plus mass spectrometry instruments, respectively.

General Synthetic Procedure for Aromatic Esters of 4′-Demethyl-4-deoxypodophyllotoxin (4a-4o). A mixture of the corresponding acid (0.3 mmol), diisopropylcarbodiimide (DIC, 0.3 mmol), 4-dimethylaminopyridine (DMAP, 0.1 mmol), and **3** (0.25 mmol) in dried dichloromethane (10 mL) was stirred at 0 °C. When the reaction was complete according to TLC analysis, the resulting suspension was filtered, and water (25 mL) was added to the solution of the above mixture, which was extracted with dichloromethane (30 mL × 4). Then the organic phase were combined, dried over anhydrous Na_2SO_4, concentrated in vacuo and purified by PTLC to give the pure products in 38−93% yields.



4a

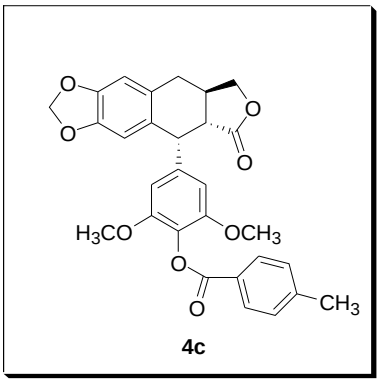
Data for ***4a***: R_f = 0.52 (petroleum ether/ethyl acetate, 1:1). Yield: 93%. White solid, mp 223—225 °C; $[\alpha]^{20}_D$ = -79° (*c* 0.29 mg/mL, $CHCl_3$); IR cm^{-1}: 2921, 2849, 1779, 1759, 1597, 1482, 1459, 1224, 1122, 928, 774, 731; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.38 (d, J = 7.2 Hz, 2H, H-2″, 6″), 7.32 (m, 2H, H-3″, 5″), 7.28 (d, J = 7.6 Hz, 1H, H-4″), 6.65 (s, 1H, H-5), 6.51 (s, 1H, H-8), 6.35 (s, 2H, H-2′, 6′), 5.92 (dd, J = 1.2 Hz, J = 8.0 Hz, 2H, OCH_2O), 4.61 (d, J = 4.4 Hz, 1H, H-1), 4.42 (m, 1H, H-11), 3.88 (m, 3H, H-11 and $\underline{CH_2}C_6H_5$), 3.62 (s, 6H, 3′, 5′-OCH_3), 3.03 (m, 1H, H-4), 2.69 (m, 3H, H-2, 3, 4); MS (ESI-TRAP), *m/z* (%) 525 ($[M+Na]^+$, 25). HRMS: Anal. Calcd for $C_{29}H_{30}NO_8$ ($[M+NH_4]^+$), 520.1966; found, 520.1960.



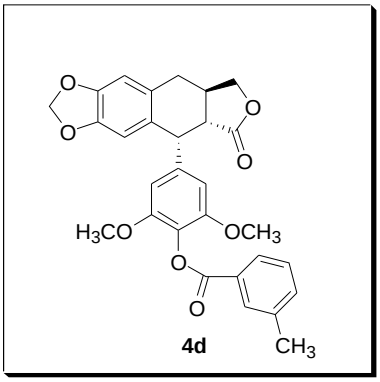
4b

Data for ***4b***: R_f = 0.7 (dichloromethane/acetone, 50:1). Yield: 71%. White solid, mp 256—258 °C; $[\alpha]^{20}_D$ = -80° (*c* 0.26 mg/mL, $CHCl_3$); IR cm^{-1}: 2921, 2849, 1761, 1738, 1597, 1486, 1454, 1230, 1128, 928, 771, 706; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.19 (d, J = 7.6 Hz, 2H, H-2″, 6″), 7.59 (t, J = 7.6 Hz, 1H, H-4″), 7.46 (t, J = 7.6 Hz, 2H, H-3″, 5″), 6.68 (s, 1H, H-5), 6.59 (s, 1H, H-8), 6.43 (s, 2H, H-2′, 6′), 5.94 (d, J = 7.6 Hz, 2H, OCH_2O), 4.67 (s, 1H, H-1), 4.46 (m, 1H, H-11), 3.89 (m, 1H, H-11), 3.69 (s, 6H, 3′, 5′-OCH_3), 3.07 (m, 1H, H-4), 2.76 (m, 3H, H-2, 3, 4); MS (ESI-TRAP), *m/z* (%) 511 ($[M+Na]^+$, 39). HRMS: Anal. Calcd for $C_{28}H_{28}NO_8$ ($[M+NH_4]^+$), 506.1809; found,

506.1802.

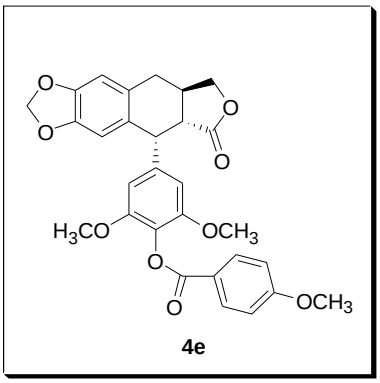


Data for ***4c***: R_f = 0.5 (dichloromethane/acetone, 50:1). Yield: 89%. White solid, mp 246–247 °C; $[\alpha]^{20}_D$ = -74° (*c* 0.3 mg/mL, $CHCl_3$); IR cm^{-1}: 2923, 2850, 1761, 1736, 1597, 1486, 1458, 1229, 1129, 927, 747; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.08 (d, J = 8.0 Hz, 2H, H-2″, 6″), 7.27 (d, J = 7.6 Hz, 2H, H-3″, 5″), 6.67 (s, 1H, H-5), 6.56 (s, 1H, H-8), 6.42 (s, 2H, H-2′, 6′), 5.94 (d, J = 7.2 Hz, 2H, OCH_2O), 4.67 (s, 1H, H-1), 4.46 (m, 1H, H-11), 3.88 (m, 1H, H-11), 3.68 (s, 6H, 3′, 5′-OCH_3), 3.07 (m, 1H, H-4), 2.76 (m, 3H, H-2, 3, 4), 2.43 (s, 3H, $C_6H_4\underline{CH_3}$); MS (ESI-TRAP), *m/z* (%) 525 ($[M+Na]^+$, 36). HRMS: Anal. Calcd for $C_{29}H_{30}NO_8$ ($[M+NH_4]^+$), 520.1966; found, 520.1967.

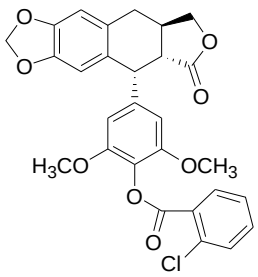


Data for ***4d***: R_f = 0.6 (dichloromethane/acetone, 40:1). Yield: 84%. White solid, mp 253–254 °C; $[\alpha]^{20}_D$ = -76° (*c* 0.22 mg/mL, $CHCl_3$); IR cm^{-1}: 2920, 2849, 1762, 1734,

1596, 1485, 1459, 1229, 1128, 927, 739; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.01 (s, 1H, H-2″), 7.99 (d, J = 8.8Hz, 1H, H-6″), 7.35 (m, 2H, H-4″, 5″), 6.67 (s, 1H, H-5), 6.56 (s, 1H, H-8), 6.42 (s, 2H, H-2′, 6′), 5.94 (dd, J = 1.2 Hz, J = 8.4 Hz, 2H, OCH_2O), 4.66 (d, J = 3.2 Hz, 1H, H-1), 4.46 (m, 1H, H-11), 3.91 (m, 1H, H-11), 3.69 (s, 6H, 3′, 5′-OCH_3), 3.07 (m, 1H, H-4), 2.76 (m, 3H, H-2, 3, 4), 2.42 (s, 3H, $C_6H_4\underline{CH_3}$); MS (ESI-TRAP), *m/z* (%) 525 ([M+Na]$^+$, 37). HRMS: Anal. Calcd for $C_{29}H_{30}NO_8$ ([M+NH_4]$^+$), 520.1966; found, 520.1960.

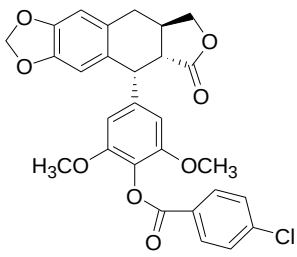


Data for ***4e***: R_f = 0.55 (dichloromethane/acetone, 50:1). Yield: 38%. White solid, mp 263–265 ^{o}C; $[\alpha]^{20}_D$ = -76° (c 0.32 mg/mL, $CHCl_3$); IR cm^{-1}: 2921, 2850, 1762, 1731, 1598, 1485, 1460, 1227, 1130, 925, 764; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.14 (d, J = 8.8 Hz, 2H, H-2″, 6″), 6.95 (d, J = 8.4 Hz, 2H, H-3″, 5″), 6.67 (s, 1H, H-5), 6.56 (s, 1H, H-8), 6.42 (s, 2H, H-2′, 6′), 5.94 (m, 2H, OCH_2O), 4.67 (s, 1H, H-1), 4.46 (m, 1H, H-11), 3.91 (m, 1H, H-11), 3.88 (s, 3H, $C_6H_4O\underline{CH_3}$), 3.68 (s, 6H, 3′, 5′-OCH_3), 3.07 (m, 1H, H-4), 2.76 (m, 3H, H-2, 3, 4); MS (ESI-TRAP), *m/z* (%) 541 ([M+Na]$^+$, 31). HRMS: Anal. Calcd for $C_{29}H_{30}NO_9$ ([M+NH_4]$^+$), 536.1915; found, 536.1926.



4f

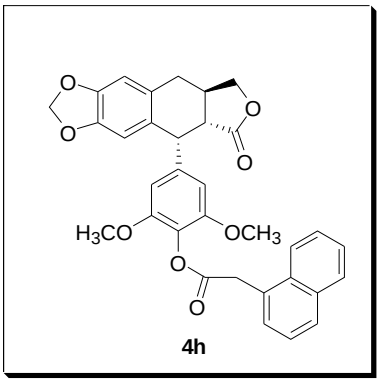
Data for ***4f***: R_f = 0.57 (dichloromethane/acetone, 80:1). Yield: 72%. White solid, mp 236–237 °C; $[\alpha]^{20}_{D}$ = -75° (*c* 0.34 mg/mL, $CHCl_3$); IR cm^{-1}: 2918, 2848, 1761, 1736, 1598, 1485, 1457, 1228, 1129, 924, 742; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.10 (dd, *J* = 1.6 Hz, *J* = 7.6 Hz, 1H, H-6″), 7.46 (m, 2H, H-4″, 5″), 7.34 (m, 1H, H-3″), 6.68 (s, 1H, H-5), 6.55 (s, 1H, H-8), 6.43 (s, 2H, H-2′, 6′), 5.94 (dd, *J* = 1.2 Hz, *J* = 8.0 Hz, 2H, OCH_2O), 4.66 (d, *J* = 3.6 Hz, 1H, H-1), 4.46 (m, 1H, H-11) 3.91 (m, 1H, H-11), 3.72 (s, 6H, 3′, 5′-OCH_3), 3.07 (m, 1H, H-4), 2.76 (m, 3H, H-2, 3, 4); MS (ESI-TRAP), *m/z* (%) 545 ($[M+Na]^+$, 36). HRMS: Anal. Calcd for $C_{28}H_{27}NO_8Cl$ ($[M+NH_4]^+$), 540.1420; found, 540.1419.



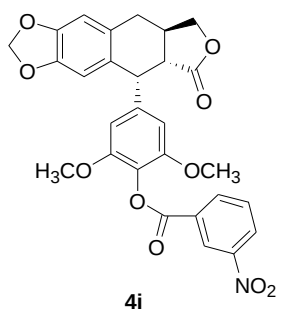
4g

Data for ***4g***: R_f = 0.64 (dichloromethane/acetone, 80:1). Yield: 66%. White solid, mp 246–248 °C; $[\alpha]^{20}_{D}$ = -71° (*c* 0.21 mg/mL, $CHCl_3$); IR cm^{-1}: 2923, 2850, 1762, 1740, 1597, 1485, 1462, 1229, 1129, 928, 753; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.12 (d, *J* =

8.8 Hz, 2H, H-2″, 6″), 7.44 (d, J = 8.4 Hz, 2H, H-3″, 5″), 6.67 (s, 1H, H-5), 6.55 (s, 1H, H-8), 6.42 (s, 2H, H-2′, 6′), 5.94 (m, 2H, OCH_2O), 4.66 (d, J = 3.6 Hz, 1H, H-1), 4.46 (m, 1H, H-11), 3.91 (m, 1H, H-11), 3.68 (s, 6H, 3′, 5′-OCH_3), 3.07 (m, 1H, H-4), 2.76 (m, 3H, H-2, 3, 4); MS (ESI-TRAP), *m/z* (%) 545 ($[M+Na]^+$, 62). HRMS: Anal. Calcd for $C_{28}H_{27}NO_8Cl$ ($[M+NH_4]^+$), 540.1420; found, 540.1409.

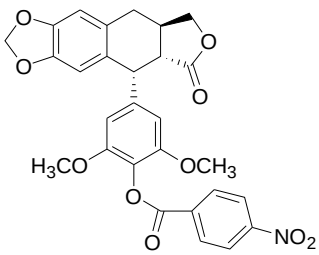


Data for ***4h***: R_f = 0.42 (dichloromethane/acetone, 80:1). Yield: 38%. White solid, mp 196 °C; $[\alpha]^{20}_D$ = -65° (*c* 0.35 mg/mL, $CHCl_3$); IR cm^{-1}: 2921, 2845, 1761, 1597, 1484, 1459, 1227, 1120, 928, 792, 776; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.12 (d, J = 8.8 Hz, 1H, H-8″), 7.85 (d, J = 7.2 Hz, 1H, H-5″), 7.78 (d, J = 8.0 Hz, 1H, H-4″), 7.41 (m, 4H, H-2″, 3″, 6″, 7″), 6.64 (s, 1H, H-5), 6.48 (s, 1H, H-8), 6.31 (s, 2H, H-2′, 6′), 5.91 (d, J = 5.6 Hz, 2H, OCH_2O), 4.59 (d, J = 4.0 Hz, 1H, H-1), 4.39 (m, 1H, H-11), 4.33 (s, 2H, $\underline{CH_2}C_{10}H_8$), 3.86 (m, 1H, H-11), 3.55 (s, 6H, 3′, 5′-OCH_3), 3.01 (m, 1H, H-4), 2.69 (m, 3H, H-2, 3, 4); MS (ESI-TRAP), *m/z* (%) 575 ($[M+Na]^+$, 31). HRMS: Anal. Calcd for $C_{33}H_{32}NO_8$ ($[M+NH_4]^+$), 570.2122; found, 570.2112.



4i

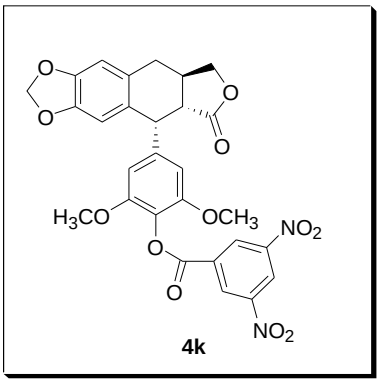
Data for ***4i***: R_f = 0.45 (dichloromethane/acetone, 80:1). Yield: 90%. Pale yellow solid, mp 137—138 °C; $[\alpha]^{20}_D$ = -72° (*c* 0.29 mg/mL, $CHCl_3$); IR cm^{-1}: 2915, 2848, 1746, 1600, 1482, 1459, 1225, 1125, 929, 716; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.03 (s, 1H, H-2″), 8.50 (dd, J = 1.2 Hz, J = 8.0 Hz, 1H, H-6″), 8.45 (m, 1H, H-4″), 7.68 (t, J = 7.6 Hz, 1H, H-5″), 6.68 (s, 1H, H-5), 6.56 (s, 1H, H-8), 6.44 (s, 2H, H-2′, 6′), 5.95 (d, J = 8.8 Hz, 2H, OCH_2O), 4.67 (d, J = 3.2 Hz, 1H, H-1), 4.47 (m, 1H, H-11), 3.93 (m, 1H, H-11), 3.70 (s, 6H, 3′, 5′-OCH_3), 3.08 (m, 1H, H-4), 2.77 (m, 3H, H-2, 3, 4); MS (ESI-TRAP), *m/z* (%) 556 ($[M+Na]^+$, 65). HRMS: Anal. Calcd for $C_{28}H_{27}O_{10}N_2$ ($[M+NH_4]^+$), 551.1660; found, 551.1666.



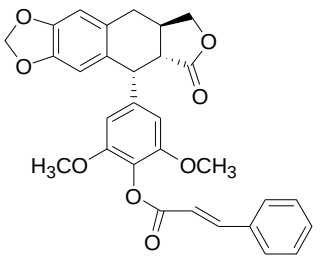
4j

Data for ***4j***: R_f = 0.45 (dichloromethane/acetone, 80:1). Yield: 66%. Yellow solid, mp 133—134 °C; $[\alpha]^{20}_D$ = -63° (*c* 0.48 mg/mL, $CHCl_3$); IR cm^{-1}: 2918, 2850, 1771, 1743, 1600, 1482, 1461, 1225, 1126, 929, 770, 715; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.35 (dd,

J = 2.0 Hz, J = 6.8 Hz, 2H, H-3″, 5″), 8.31 (dd, J = 2.0 Hz, J = 6.8 Hz, 2H, H-2″, 6″), 6.68 (s, 1H, H-5), 6.55 (s, 1H, H-8), 6.44 (s, 2H, H-2′, 6′), 5.94 (dd, J= 1.2 Hz, J = 8.4 Hz, 2H, OCH_2O), 4.67 (d, J = 4 Hz, 1H, H-1), 4.46 (m, 1H, H-11), 3.92 (m, 1H, H-11), 3.69 (s, 6H, 3′, 5′-OCH_3), 3.07 (m, 1H, H-4), 2.73 (m, 3H, H-2, 3, 4); MS (ESI-TRAP), *m/z* (%) 556 ($[M+Na]^+$, 37). HRMS: Anal. Calcd for $C_{28}H_{27}O_{10}N_2$ ($[M+NH_4]^+$), 551.1660; found, 551.1662.

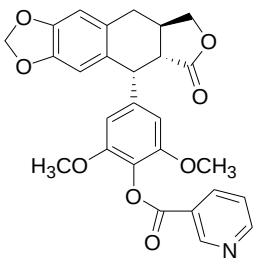


Data for ***4k***: R_f = 0.45 (dichloromethane/acetone, 100:1). Yield: 90%. Yellow solid, mp 272—274 °C; $[\alpha]^{20}_D$ = -73° (c 0.29 mg/mL, $CHCl_3$); IR cm^{-1}: 2918, 2850, 1753, 1600, 1485, 1460, 1227, 1133, 924, 771, 716; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.30 (d, J = 2.0 Hz, 2H, H-2″, 6″), 9.26 (t, J = 2.0 Hz, 1H, H-4″), 6.69 (s, 1H, H-5), 6.56 (s, 1H, H-8), 6.46 (s, 2H, H-2′, 6′), 5.94 (dd, J = 0.8 Hz, J = 9.2 Hz, 2H, OCH_2O), 4.68 (d, J = 4 Hz, 1H, H-1), 4.48 (m, 1H, H-11), 3.93 (m, 1H, H-11), 3.70 (s, 6H, 3′, 5′-OCH_3), 3.09 (m, 1H, H-4), 2.74 (m, 3H, H-2, 3, 4); MS (ESI-TRAP), *m/z* (%) 601 ($[M+Na]^+$, 100). HRMS: Anal. Calcd for $C_{28}H_{26}O_{12}N_3$ ($[M+NH_4]^+$), 596.1511; found, 596.1518.



4l

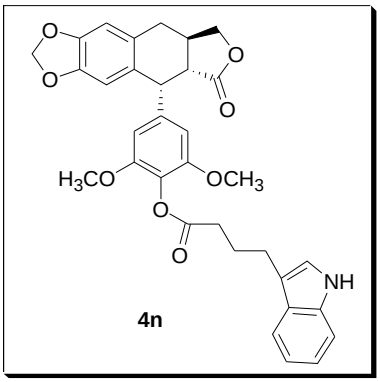
Data for ***4l***: R_f = 0.53 (dichloromethane/acetone, 100:1). Yield: 85%. White solid, mp 142–144 °C; $[\alpha]^{20}_D$ = -81° (*c* 0.19 mg/mL, $CHCl_3$); IR cm^{-1}: 2922, 2850, 1761, 1735, 1595, 1486, 1454, 1228, 1123, 925, 764; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.83 (d, J = 16.0 Hz, 1H, —CH═CH—C_6H_5), 7.56 (m, 2H, H-3″, 5″), 7.39 (m, 3H, H-2″, 4″, 6″), 6.67 (d, J = 16.0 Hz, 1H, —CH═CH—C_6H_5), 6.67 (s, 1H, H-5), 6.55 (s, 1H, H-8), 6.41 (s, 2H, H-2′, 6′), 5.93 (d, J = 8.4 Hz, 2H, OCH_2O), 4.66 (s, 1H, H-1), 4.46 (m, 1H, H-11), 3.90 (m, 1H, H-11), 3.71 (s, 6H, 3′, 5′-OCH_3), 3.07 (m, 1H, H-4), 2.75 (m, 3H, H-2, 3, 4); MS (ESI-TRAP), *m/z* (%) 537 ($[M+Na]^+$, 23). HRMS: Anal. Calcd for $C_{30}H_{30}NO_8$ ($[M+NH_4]^+$), 532.1966; found, 532.1959.



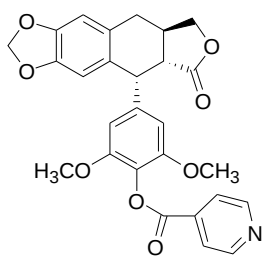
4m

Data for ***4m***: R_f = 0.32 (dichloromethane/acetone, 15:1). Yield: 91%. White solid, mp 259–260 °C; $[\alpha]^{20}_D$ = -73° (*c* 0.43 mg/mL, $CHCl_3$); IR cm^{-1}: 2922, 2850, 1761, 1741, 1595, 1485, 1460, 1228, 1125, 928, 734; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.38 (s, 1H,

H-2″), 8.82 (d, J = 3.6 Hz, 1H, H-6″), 8.42 (m, 1H, H-4″), 7.41 (m, 1H, H-5″), 6.68 (s, 1H, H-5), 6.55 (s, 1H, H-8), 6.44 (s, 2H, H-2′, 6′), 5.94 (m, 2H, OCH_2O), 4.66 (d, J = 3.6 Hz, 1H, H-1), 4.46 (m, 1H, H-11), 3.88 (m, 1H, H-11), 3.69 (s, 6H, 3′, 5′-OCH_3), 3.06 (m, 1H, H-4), 2.73 (m, 3H, H-2, 3, 4); MS (ESI-TRAP), *m/z* (%) 512 ($[M+Na]^+$, 100). HRMS: Anal. Calcd for $C_{27}H_{27}O_8N_2$ ($[M+NH_4]^+$), 490.1496; found, 490.1487.



Data for ***4n***: R_f = 0.4 (dichloromethane/acetone, 100:1). Yield: 64%. White solid, mp 106–107 °C; $[\alpha]^{20}_D$ = -6 8 ° (c 0.45 mg/mL, $CHCl_3$); IR cm^{-1}: 2919, 2850, 1759, 1598, 1482, 1457, 1224, 1124, 929, 743; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.94 (s, 1H, NH), 7.63 (d, J = 8.0 Hz, 1H, H-4″), 7.34 (d, J = 8.0 Hz, 1H, H-7″), 7.16 (t, J = 7.2 Hz, 1H, H-6″), 7.08 (t, J = 7.2 Hz, 1H, H-5″), 7.03 (d, J = 2.0 Hz, 1H, H-2″), 6.66 (s, 1H, H-5), 6.53 (s, 1H, H-8), 6.38 (s, 2H, H-2′, 6′), 5.92 (dd, J = 0.8 Hz, J = 7.6 Hz, 2H, OCH_2O), 4.63 (d, J = 3.6 Hz, 1H, H-1), 4.43 (m, 1H, H-11), 3.89 (m, 1H, H-11), 3.68 (s, 6H, 3′, 5′-OCH_3), 3.04 (m, 1H, H-4), 2.89 (t, J = 7.2 Hz, 2H, $\underline{CH_2}(CH_2)_2$–indole), 2.71 (m, 3H, H-2, 3, 4), 2.63 (t, J = 7.2 Hz, 2H, $(CH_2)_2\underline{CH_2}$–indole), 2.11 (m, 2H, $CH_2\underline{CH_2}CH_2$–indole); MS (ESI-TRAP), *m/z* (%) 592 ([M+Na]+, 94). HRMS: Anal. Calcd for $C_{33}H_{35}O_8N_2$ ($[M+NH_4]^+$), 587.2388; found, 587.2386.



4o

Data for ***4o***: R_f = 0.44 (dichloromethane/acetone, 15:1). Yield: 53%. White solid, mp 208–210 ^{o}C; $[\alpha]^{20}_{D}$ = -84° (*c* 0.24 mg/mL, $CHCl_3$); IR cm^{-1}: 2922, 2850, 1762, 1745, 1600, 1485, 1463, 1227, 1132, 927, 771, 753; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.82 (d, J = 5.6 Hz, 2H, H-2″, 6″), 7.99 (dd, J = 1.6 Hz, J = 4.8 Hz, 2H, H-3″, 5″), 6.68 (s, 1H, H-5), 6.55 (s, 1H, H-8), 6.43 (s, 2H, H-2′, 6′), 5.94 (dd, J = 1.2 Hz, J = 8.0 Hz, 2H, OCH_2O), 4.66 (d, J = 4 Hz, 1H, H-1), 4.47 (m, 1H, H-11), 3.88 (m, 1H, H-11), 3.69 (s, 6H, 3′, 5′-OCH_3), 3.07 (m, 1H, H-4), 2.72 (m, 3H, H-2, 3, 4); MS (ESI-TRAP), *m/z* (%) 512 ($[M+Na]^+$, 46). HRMS: Anal. Calcd for $C_{27}H_{27}O_8N_2$ ($[M+NH_4]^+$), 490.1496; found, 490.1493.