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Natural products-based insecticidal agents 6. Design, semisynthesis, and insecticidal activity of novel monomethyl phthalate derivatives of podophyllotoxin against *Mythimna separata* Walker in vivo

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ABSTRACT

To discover the more potent analogs, 12 novel monomethyl phthalate derivatives of podophyllotoxin were synthesized and preliminarily tested against the pre-third-instar larvae of *Mythimna separata* Walker in vivo at the concentration of 1 mg/mL. Compounds **8e**–**i** showed the higher insecticidal activity than podophyllotoxin. Especially **8g** exhibited the most potent insecticidal activity compared with toosendanin, a commercially available insecticide derived from *Melia azedarach*. The structure–activity relationships demonstrated that *trans*-lactone, 4β-substitution, 2β-chlorine substitution, and 4′-methoxy group were the important structural properties of podophyllotoxins for good insecticidal activity.

The routine use of a wide variety of synthetic insecticides in agriculture has now become an accepted practice, however, the use of these chemicals over the years has resulted in the development of resistance in insect pest populations and environmental problems. Plant secondary metabolites result from the interaction between plants and environment (life and non-life) during the long period of evolution in plants. Consequently, the discovery of new insecticidal compounds from plant secondary metabolites, followed by using them as the lead-compounds for further modification has been one of the important ways for the research and development of new pesticides. Podophyllotoxin (**1**, Fig. 1), a naturally occurring aryltetralin lignan, besides its use as the lead-compound for the generation of potent anticancer drugs,[1] exhibited the interesting insecticidal activity.[2–4]

More recently, 4β-benzenesulfonamides of podophyllotoxin,[5] 4α-esters of 2β-chloropodophyllotoxin,[6] and 4′-aromatic esters/substituted benzenesulfonates of 4-deoxypodophyllotoxin[7,8] have been designed and prepared from **1** in our research group, and some derivatives have showed more potent insecticidal activity than **1**. However, to the best of our knowledge, it has never been investigated the effect of the configurations of C-2 and C-4, and the methoxy group at the C-4′ position of podophyllotoxin on the insecticidal activity. Meanwhile, introduction of the phthalate groups to the molecule would usually increase toxicity,[9,10] therefore, in this Letter we introduced the monomethyl phthalate (MMP) groups to podophyllotoxins for their insecticidal activity studies.

As shown in Scheme 1, picropodophyllotoxin (**2**) was prepared from **1** in the presence of absolute ethanol and 10% aqueous sodium acetate, followed by recrystallization from absolute ethanol.[11] Epipodophyllotoxin (**3**) was obtained when **1** reacted with NaI and $BF_3{\cdot}Et_2O$ in dry CH_3CN, followed by treatment with acetone, H_2O and anhydrous $BaCO_3$.[12] 2β-Chloropodophyllotoxin (**4**) and 4β-aminopodophyllotoxin (**5**) were synthesized according to our previous methods.[6,13] Subsequently, 4′-demethylepipodophyllotoxin (**6**) was prepared by the reaction of **1** with NaI and $MeSO_3H$ in dry CH_2Cl_2, followed by treatment with acetone, H_2O and anhydrous $BaCO_3$.[14] Finally, we introduced MMP substituents (**7**) to podophyllotoxin derivatives (**1–6**) via the ester or amido bond. As outlined in Scheme 2, compounds **1–6** reacted smoothly with **7** in the presence of diisopropylcarbodiimide (DIC) and 4-dimeth-

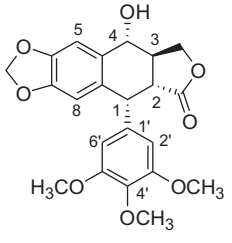

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Figure 1. Chemical structure of podophyllotoxin (**1**).

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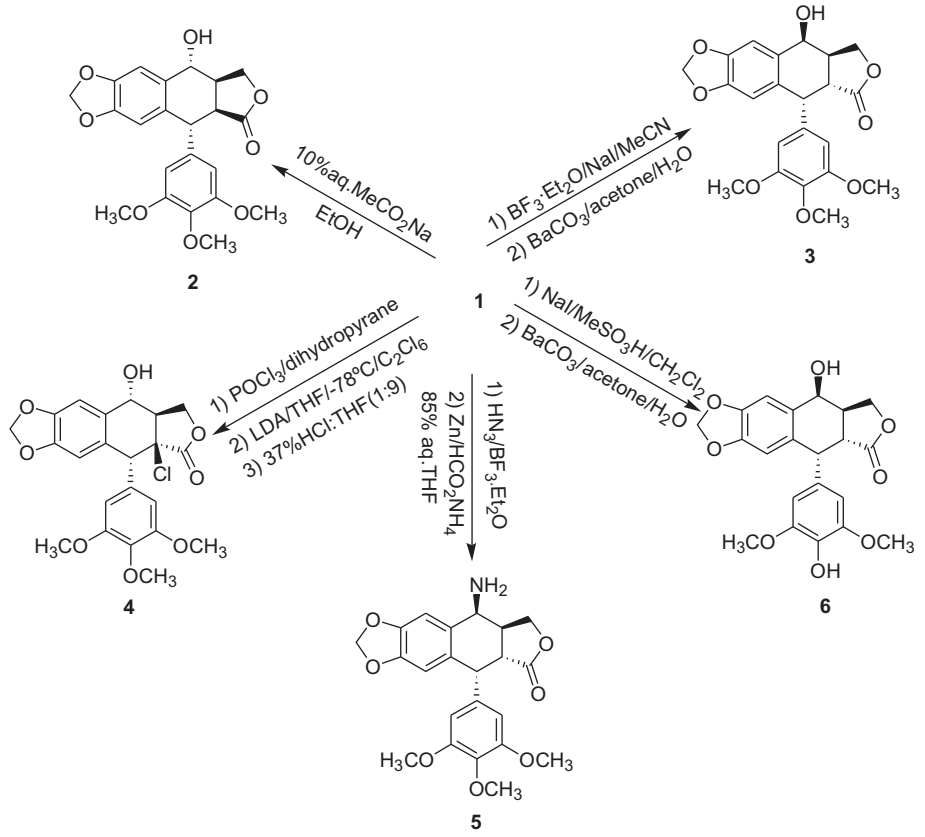
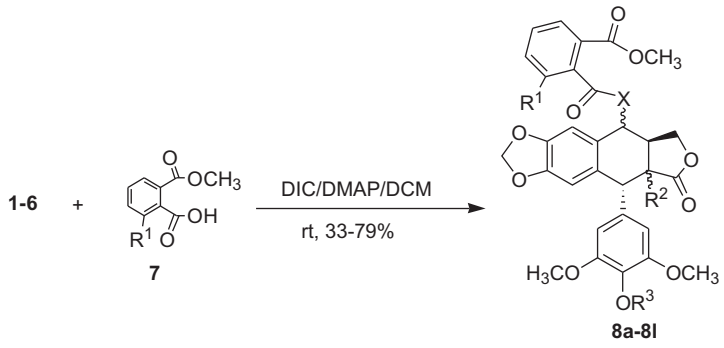
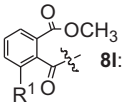
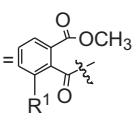


Scheme 1. Synthesis of podophyllotoxin derivatives **2**–**6**.



8a: R^1 = H, X = α-O, R^2 = β-H, R^3 = CH_3; **8b**: R^1 = NO_2, X = α-O, R^2 = β-H, R^3 = CH_3;
8c: R^1 = H, X = α-O, R^2 = α-H, R^3 = CH_3; **8d**: R^1 = NO_2, X = α-O, R^2 = α-H, R^3 = CH_3;
8e: R^1 = H, X = β-O, R^2 = β-H, R^3 = CH_3; **8f**: R^1 = NO_2, X = β-O, R^2 = β-H, R^3 = CH_3;
8g: R^1 = H, X = α-O, R^2 = β-Cl, R^3 = CH_3; **8h**: R^1 = NO_2, X = α-O, R^2 = β-Cl, R^3 = CH_3;
8i: R^1 = H, X = β-NH, R^2 = β-H, R^3 = CH_3; **8j**: R^1 = NO_2, X = β-NH, R^2 = β-H, R^3 = CH_3;

8k: R^1 = H, X = β-O, R^2 = β-H, R^3 =  **8l**: R^1 = NO_2, X = β-O, R^2 = β-H, R^3 = 

Scheme 2. Synthesis of target compounds **8a**–**l**.

ylaminopyridine (DMAP) at room temperature to afford the target compounds **8a–l** in 33–79% yields. The structures of **8a–l** were well characterized by ^{1}H NMR, MS, HRMS, and mp.[15]

The insecticidal activity of compounds **8a**–**l** against the pre-third-instar larvae of *Mythimna separata* Walker was assessed at the concentration of 1 mg/mL by leaf-dipping method.[7] Toosendanin, a commercially available insecticide derived from *Melia azedarach*, was used as a positive control.

As shown in Table 1, it indicated that the corresponding corrected mortality rates caused by these compounds after 33 d were higher than those after 10 d and 20 d. That is, these compounds, different from those conventional neurotoxic insecticides, such as

Table 1
Insecticidal activity of **8a–l** against *M. separata* in vivo at 1 mg/mL

Compounds	Corrected mortality rate (%)		
	10 d	20 d	33 d
8a	16.6 (± 4.7)	24.1 (± 9.4)	35.7 (± 0.0)
8b	6.6 (± 4.7)	6.9 (± 0.0)	21.4 (± 4.7)
8c	10.0 (± 8.1)	10.3 (± 9.4)	17.8 (± 4.7)
8d	13.3 (± 4.7)	13.7 (± 9.4)	14.2 (± 8.1)
8e	10.0 (± 8.1)	20.6 (± 4.7)	38.5 (± 4.7)
8f	10.0 (± 8.1)	17.2 (± 14.1)	42.8 (± 9.4)
8g	16.6 (± 12.4)	31.0 (± 17.0)	53.5 (± 9.4)
8h	30.0 (± 8.1)	41.3 (± 4.7)	46.4 (± 8.1)
8i	6.6 (± 9.4)	10.3 (± 4.7)	42.8 (± 9.4)
8j	10.0 (± 8.1)	20.6 (± 4.7)	35.7 (± 8.1)
8k	16.6 (± 4.7)	17.2 (± 8.1)	21.4 (± 12.4)
8l	16.6 (± 4.7)	20.6 (± 4.7)	28.5 (± 4.7)
1	16.6 (± 9.4)	20.6 (± 4.7)	35.7 (± 8.1)
Toosendanin	30.0 (± 14.1)	31.0 (± 9.4)	50.0 (± 12.4)

organophosphates, carbamates, and pyrethroids, exhibited delayed insecticidal activity.[5–8] For example, the corrected mortality rate of **8i** against *M. separata* after 10 d was only 6.6%, after 20 d the corresponding mortality rate was increased to 10.3%, but after 33 d it was sharply increased to 42.8%, which was more than six times of the mortality rate after 10 d. On the other hand, the symptoms of the tested *M. separata* were also characterized by the same way as our previous reports.[5–8] After 24 h the movement of the *M. separata* treated by these compounds decreased greatly, and some of them were becoming immobilized and loss of body liquid after 48 h. Some of the treated *M. separata* showed moulting disturbances or deformities. For example, the pupation of the larvae and the adult emergence of *M. separata* were inhibited by these compounds, therefore, the stage from the larvae to adulthood of *M. separata* was prolonged as compared to the control group. Moreover, many larvae of the treated groups molted to abnormal pupae, which could not reach adulthood and died during the stage of pupation because they were not able to remove their pupal skin.

Among all the tested derivatives, compounds **8e–i** showed the higher insecticidal activity than **1**. Especially **8g** exhibited the more potent insecticidal activity than toosendanin (53.5% for **8g** vs 50.0% for toosendanin). Through a comparative study on the general relationship between the chemical structures of **8a–l** and the insecticidal activity (SAR), some interesting results were found as follows: (1) The *trans*-lactone derivatives were more active than the *cis*-lactone ones. That is, the inversion of configuration of the lactone would reduce the insecticidal activity. For example, corrected mortality rates after 33 d of **8a** and **8b** were 35.7% and 21.4%, respectively; while corrected mortality rates of the corresponding *cis*-lactone ones **8c** and **8d** were 17.8% and 14.2%, respectively. (2) The β configuration of the substituents at the C-4 position was very important for their insecticidal activity. That is, the insecticidal activity of 4α-substituted podophyllotoxins was less potent than the 4β-substituted ones (35.7% for **8a** vs 38.5% for **8e**; 21.4% for **8b** vs 42.8% for **8f**). (3) The C-2 substitution of the podophyllotoxin by chlorine could enhance the insecticidal activity as our previous reports.[6] For example, the 2β-chloropodophyllotoxin analogs **8g** and **8h** exhibited the more potent activity than the corresponding podophyllotoxin ones **8a** and **8b** (53.5% for **8g** vs 35.7% for **8a**; 46.4% for **8h** vs 21.4% for **8b**). (4) The ester bond at the C-4 position could be replaced with the amido bond, and the corresponding compounds still showed the potent insecticidal activity (38.5% for **8e** vs 42.8% for **8i**; 42.8% for **8f** vs 35.7% for **8j**). (5) The methyl group at the C-4′ position of **8e** or **8f** was necessary for its insecticidal activity. When the 4′-methyl group of **8e** or **8f** was substituted by other group (*o*-(methoxycarbonyl)benzoyl or 2-(methoxycarbonyl)-6-nitrobenzoyl) to give **8k** or **8l**, the corresponding insecticidal activity after 33 d of **8k** or **8l** would reduce to some degree (38.5% for **8e** vs 21.4% for **8k**; 42.8% for **8f** vs 28.5% for **8l**). (6) In general, introduction of the nitro group on the MMP would decrease the activity of the corresponding compounds (**8a** vs **8b**; **8c** vs **8d**; **8g** vs **8h**; **8i** vs **8j**). (7) All in all, some important structural properties of podophyllotoxins for good insecticidal activity were the *trans*-lactone, 4β-substitution, 2β-chlorine substitution, and 4′-methoxy group.

In summary, twelve novel monomethyl phthalate derivatives of podophyllotoxin were synthesized and preliminarily tested against the pre-third-instar larvae of *M. separata* in vivo at the concentration of 1 mg/mL. Among all the tested derivatives, compounds **8e–i** showed the higher insecticidal activity than podophyllotoxin. Especially **8g** exhibited the most potent insecticidal activity compared with toosendanin, a commercially available insecticide derived from *M. azedarach*. SAR indicated that *trans*-lactone, 4β-substitution, 2β-chlorine substitution, and 4′-methoxy group were the important structural properties of podophyllotoxins for good insecticidal activity. It will pave the way for the design and development of podophyllotoxin derivatives as insecticidal agents in the future.

Acknowledgments

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15. *Spectral data for compound* **8a**: 40% yield, white solid, mp 97–101 °C; $[\alpha]_D^{24} = -114.3$ (*c* 2.1 mg/mL, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.85 (dd, *J* = 7.2, 1.2 Hz, 1H), 7.67 (dd, *J* = 7.2, 1.2 Hz, 1H), 7.55–7.63 (m, 2H), 6.91 (s, 1H, H-5), 6.55 (s, 1H, H-8), 6.39 (s, 2H, H-2′, 6′), 6.13–6.15 (m, 1H, H-4), 5.97 (d, *J* = 2.0 Hz, 2H, OCH_2O), 4.63–4.69 (m, 2H, H-1, H-11), 4.32–4.37 (m, 1H, H-11), 3.85 (s, 3H, CO_2CH_3), 3.80 (s, 3H, 4′-OCH_3), 3.71 (s, 6H, 3′, 5′-OCH_3), 2.99–3.00 (m, 2H, H-2, H-3); EI-MS *m*/*z* (%): 576 (M^+, 9); HRMS-ESI: calcd for $C_{31}H_{32}NO_{11}$ ($[M+NH_4]^+$), 594.1970; found, 594.1973. *Compound* **8b**: 56% yield, light yellow, mp 106–109 °C; $[\alpha]_D^{24} = -119.1$ (*c* 2.1 mg/mL, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.41 (d, *J* = 8.0 Hz, 1H), 8.33 (d, *J* = 8.0 Hz, 1H), 7.73 (t, *J* = 8.0 Hz, 1H), 6.83 (s, 1H, H-5), 6.59 (s, 1H, H-8), 6.42 (s, 2H, H-2′, 6′), 6.13 (d, *J* = 8.0 Hz, 1H, H-4), 6.00 (d, *J* = 8.4 Hz, 2H, OCH_2O), 4.65 (d, *J* = 3.2 Hz, 1H, H-1), 4.43–4.47 (m, 1H, H-11), 4.25–4.30 (m, 1H, H-11), 3.89 (s, 3H, CO_2CH_3), 3.80 (s, 3H, 4′-OCH_3), 3.77 (s, 6H, 3′, 5′-OCH_3), 2.96–2.98 (m, 2H, H-2, H-3); EI-MS *m*/*z* (%): 621 (M^+, 3); HRMS-ESI: calcd for $C_{31}H_{31}N_2O_{13}$ ($[M+NH_4]^+$), 639.1821; found, 639.1822. *Compound* **8c**: 70% yield, white solid, mp 70–72 °C; $[\alpha]_D^{24} = -42.9$ (*c* 4.2 mg/mL, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.76–7.78 (m, 1H), 7.50–7.56 (m, 2H), 7.37–7.39 (m, 1H), 6.91 (s, 1H, H-5), 6.58 (s, 1H, H-8), 6.35 (s, 2H, H-2′, 6′), 5.95–6.00 (m, 3H, H-4, OCH_2O), 4.46–4.51 (m, 3H, H-1, H-11), 3.81 (s, 3H, CO_2CH_3), 3.77 (s, 3H, 4′-OCH_3), 3.53 (s, 6H, 3′, 5′-OCH_3), 3.28–3.29 (m, 2H, H-2, H-3); EI-MS *m*/*z* (%): 576 (M^+, 2); HRMS-ESI: calcd for $C_{31}H_{32}NO_{11}$ ($[M+NH_4]^+$), 594.1970; found, 594.1966. *Compound* **8d**: 76% yield, light yellow, mp 127–128 °C; $[\alpha]_D^{24} = 100$ (*c* 4.2 mg/mL, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.29 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.49 (t, *J* = 8.0 Hz, 1H), 7.25–7.27 (m, 1H), 6.91 (s, 1H, H-5), 6.72 (s, 1H, H-8), 6.36 (s, 2H, H-2′, 6′), 5.99 (dd, *J* = 10.0, 1.2 Hz, 2H, OCH_2O), 5.94 (d, *J* = 3.2 Hz, 1H, H-4), 4.52–4.56 (m, 2H, H-1, H-11), 4.16–4.20 (m, 1H, H-

11), 3.97 (s, 3H, CO_2CH_3), 3.82 (s, 3H, 4′-OCH_3), 3.68 (s, 6H, 3′, 5′-OCH_3), 3.55–3.58 (m, 1H, H-3), 3.22–3.27 (m, 1H, H-2); ESI-MS *m*/*z* (%): 639 ($[M+NH_4]^+$, 100); HRMS-ESI: calcd for $C_{31}H_{31}N_2O_{13}$ ($[M+NH_4]^+$), 639.1821; found, 639.1826. *Compound* **8e**: 79% yield, white solid, mp 96–99 °C; $[\alpha]_D^{24} = -61$ (*c* 4.1 mg/mL, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.75–7.77 (m, 1H), 7.61–7.64 (m, 1H), 7.54–7.57 (m, 2H), 7.05 (s, 1H, H-5), 6.56 (s, 1H, H-8), 6.36 (d, *J* = 3.6 Hz, 1H, H-4), 6.30 (s, 2H, H-2′, 6′), 5.98 (dd, *J* = 9.6, 1.2 Hz, 2H, OCH_2O), 4.67 (d, *J* = 5.2 Hz, 1H, H-1), 4.42–4.47 (m, 1H, H-11), 4.13–4.18 (m, 1H, H-11), 3.81 (s, 3H, CO_2CH_3), 3.80 (s, 3H, 4′-OCH_3), 3.75 (s, 6H, 3′, 5′-OCH_3), 3.21–3.26 (m, 1H, H-3), 3.07–3.13 (m, 1H, H-2); EI-MS *m*/*z* (%): 576 (M^+, 3); HRMS-ESI: calcd for $C_{31}H_{32}NO_{11}$ ($[M+NH_4]^+$), 594.1970; found, 594.1965. *Compound* **8f**: 76% yield, light yellow, mp 140–142 °C; $[\alpha]_D^{24} = -114$ (*c* 5.7 mg/mL, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 8.39 (d, *J* = 8.4 Hz, 1H), 8.28 (d, *J* = 8.0 Hz, 1H), 7.70 (t, *J* = 8.0 Hz, 1H), 6.89 (s, 1H, H-5), 6.60 (s, 1H, H-8), 6.37 (d, *J* = 3.2 Hz, 1H, H-4), 6.29 (s, 2H, H-2′, 6′), 6.00 (d, *J* = 6.8 Hz, 2H, OCH_2O), 4.72 (d, *J* = 5.2 Hz, 1H, H-1), 4.38–4.42 (m, 1H, H-11), 3.87–3.95 (m, 1H, H-11), 3.80 (s, 3H, 4′-OCH_3), 3.75 (s, 9H, CO_2CH_3, 3′, 5′-OCH_3), 3.25–3.30 (m, 1H, H-3), 3.07–3.11 (m, 1H, H-2); ESI-MS *m*/*z* (%): 622 ($[M+H]^+$, 100); HRMS-ESI: calcd for $C_{31}H_{31}N_2O_{13}$ ($[M+NH_4]^+$), 639.1821; found, 639.1816. *Compound* **8g**: 59% yield, white solid, mp 205–207 °C; $[\alpha]_D^{24} = -151.7$ (*c* 2.9 mg/mL, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.87–7.89 (m, 1H), 7.56–7.65 (m, 3H), 6.93 (s, 1H, H-5), 6.56 (s, 1H, H-8), 6.43 (s, 2H, H-2′, 6′), 6.23 (d, *J* = 8.8 Hz, 1H, H-4), 5.99 (s, 2H, OCH_2O), 4.80 (s, 1H, H-1), 4.62–4.74 (m, 2H, H-11), 3.83 (s, 3H, CO_2CH_3), 3.79 (s, 3H, 4′-OCH_3), 3.69 (s, 6H, 3′, 5′-OCH_3), 3.26–3.32 (m, 1H, H-3); ESI-MS *m*/*z* (%): 611 ($[M+H]^+$, 3); HRMS-ESI: calcd for $C_{31}H_{31}NO_{11}Cl$ ($[M+NH_4]^+$), 628.1580; found, 628.1587. *Compound* **8h**: 60% yield, light yellow, mp 147–149 °C; $[\alpha]_D^{24} = -96.6$ (*c* 2.9 mg/mL, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 8.41 (d, *J* = 8.4 Hz, 1H), 8.31 (d, *J* = 7.6 Hz, 1H), 7.73 (t, *J* = 8.0 Hz, 1H), 6.88 (s, 1H, H-5), 6.60 (s, 1H, H-8), 6.47 (s, 2H, H-2′, 6′), 6.25 (d, *J* = 9.2 Hz, 1H, H-4), 6.01 (d, *J* = 10.8 Hz, 2H, OCH_2O), 4.83 (s, 1H, H-1), 4.56–4.61 (m, 1H, H-11), 4.42–4.46 (m, 1H, H-11), 3.90 (s, 3H, CO_2CH_3), 3.79 (s, 3H, 4′-OCH_3), 3.76 (s, 6H, 3′, 5′-OCH_3), 3.18–3.32 (m, 1H, H-3); ESI-MS *m*/*z* (%): 673 ($[M+NH_4]^+$, 100); HRMS-ESI: calcd for $C_{31}H_{30}N_2O_{13}Cl$ ($[M+NH_4]^+$), 673.1431; found, 673.1429. *Compound* **8i**: 60% yield, white solid, mp 115–119 °C; $[\alpha]_D^{24} = -56.7$ (*c* 3.0 mg/mL, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.91(dd, *J* = 7.6, 1.2 Hz, 1H), 7.42–7.57 (m, 3H), 7.02 (s, 1H, H-5), 6.50 (s, 1H, H-8), 6.29 (s, 2H, H-2′, 6′), 6.10 (d, *J* = 6.4 Hz, 1H, H-4), 5.95–5.98 (m, 2H, OCH_2O), 5.38 (dd, *J* = 6.4, 4.4 Hz, 1H, NH), 4.51–4.56 (m, 2H, H-1, H-11), 4.23–4.28 (m, 1H, H-11), 3.92 (s, 3H, CO_2CH_3), 3.79 (s, 3H, 4′-OCH_3), 3.74 (s, 6H, 3′, 5′-OCH_3), 2.99–3.06 (m, 1H, H-3), 2.90–2.95 (m, 1H, H-2); ESI-MS *m*/*z* (%): 576 ($[M+H]^+$, 100); HRMS-ESI: calcd for $C_{31}H_{30}NO_{10}$ ($[M+H]^+$), 576.1864; found, 576.1870. *Compound* **8j**: 53% yield, light yellow, mp 177–178 °C; $[\alpha]_D^{24} = -20$ (*c* 1.0 mg/mL, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 8.18–8.20 (m, 1H), 7.87–7.89 (m, 1H), 7.63 (t, *J* = 8.0 Hz, 1H), 6.84 (s, 1H, H-5), 6.59 (d, *J* = 7.2 Hz, 1H, H-4), 6.51 (s, 1H, H-8), 6.26 (s, 2H, H-2′, 6′), 5.97–5.99 (m, 2H, OCH_2O), 5.36 (dd, *J* = 7.6, 4.4 Hz, 1H, NH), 4.57 (d, *J* = 5.2 Hz, 1H, H-1), 4.44–4.48 (m, 1H, H-11), 3.92–3.97 (m, 4H, H-11, CO_2CH_3), 3.76 (s, 3H, 4′-OCH_3), 3.73 (s, 6H, 3′, 5′-OCH_3), 2.98–3.04 (m, 1H, H-3), 2.89–2.94 (m, 1H, H-2); ESI-MS *m*/*z* (%): 621 ($[M+H]^+$, 100); HRMS-ESI: calcd for $C_{31}H_{29}N_2O_{12}$ ($[M+H]^+$), 621.1715; found, 621.1711. *Compound* **8k**: 33% yield, white solid, mp 118–120 °C; $[\alpha]_D^{24} = -28.6$ (*c* 1.4 mg/mL, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 8.02–8.04 (m, 1H), 7.84 (d, *J* = 7.2 Hz, 1H), 7.54–7.71 (m, 6H), 6.92 (s, 1H, H-5), 6.56 (s, 1H, H-8), 6.47 (s, 2H, H-2′, 6′), 6.16 (d, *J* = 8.0 Hz, 1H, H-4), 5.98 (d, *J* = 2.0 Hz, 2H, OCH_2O), 4.68–4.71 (m, 2H, H-1, H-11), 4.33–4.38 (m, 1H, H-11), 3.85 (s, 3H, CO_2CH_3), 3.87 (s, 3H, CO_2CH_3), 3.68 (s, 6H, 3′, 5′-OCH_3), 2.99–3.02 (m, 2H, H-2, H-3); ESI-MS *m*/*z* (%): 742 ($[M+NH_4]^+$, 100); HRMS-ESI: calcd for $C_{39}H_{36}NO_{14}$ ($[M+NH_4]^+$), 742.2130; found, 742.2136. *Compound* **8l**: 49% yield, light yellow, mp 134–135 °C; $[\alpha]_D^{24} = -64.3$ (*c* 2.8 mg/mL, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 8.56–8.58 (m, 1H), 8.39–8.42 (m, 2H), 8.30 (d, *J* = 7.6 Hz, 1H), 7.73 (t, *J* = 8.0 Hz, 2H), 6.85 (s, 1H, H-5), 6.60 (s, 1H, H-8), 6.50 (s, 2H, H-2′, 6′), 6.16 (d, *J* = 9.2 Hz, 1H, H-4), 6.00–6.02 (m, 2H, OCH_2O), 4.70 (d, *J* = 4.4 Hz, 1H, H-1), 4.46–4.50 (m, 1H, H-11), 4.28–4.32 (m, 1H, H-11), 3.95 (s, 3H, CO_2CH_3), 3.88 (s, 3H, CO_2CH_3), 3.72 (s, 6H, 3′, 5′-OCH_3), 2.93–3.06 (m, 2H, H-2, H-3); ESI-MS *m*/*z* (%): 832 ($[M+NH_4]^+$, 100); HRMS-ESI: calcd for $C_{39}H_{34}N_3O_{18}$ ($[M+NH_4]^+$), 832.1832; found, 832.1836.