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Natural products-based insecticidal agents 5. Design, semisynthesis and insecticidal activity of novel 4′-substituted benzenesulfonate derivatives of 4-deoxypodophyllotoxin against *Mythimna separata* Walker in vivo

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ABSTRACT

In an attempt to find the effective phytopesticides, eight novel 4′-substituted benzenesulfonate derivatives of 4-deoxypodophyllotoxin were synthesized and preliminarily tested against the pre-third-instar larvae of *Mythimna separata* Walker in vivo at the concentration of 1 mg/mL. Among all of the tested analogs, compounds **5a**, **5c**, **5d**, and **5h** showed the higher insecticidal activity than 4-deoxypodophyllotoxin. Especially **5a** exhibited the most potent insecticidal activity compared with toosendanin, a commercial insecticide derived from *Melia azedarach*.

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. Therefore, it is highly desirable to develop the pest management methods from natural products. Podophyllotoxin (**1**, Fig. 1) is naturally occurring aryltetralin lignan, and its derivatives such as etoposide and teniposide are currently applied in the chemotherapy for small cell lung cancer, testicular carcinoma, Kaposi's sarcoma, and human immunodeficiency virus (HIV).[1–3] On the other hand, compound **1** was also found to possess insecticidal activity.[4–6] More recently, 4β-benzenesulfonamides of podophyllotoxin,[7] 4α-esters of 2-chloropodophyllotoxin (**2**),[8] and 4′-aromatic esters of 4-deoxypodophyllotoxin (**3**)[9] have been designed and prepared from compound **1** in our research group, and some analogs have displayed more potent insecticidal activity than **1**. Therefore, in this Letter we want to investigate the effect of substituted benzenesulfonates groups at the C-4′ position of 4-deoxypodophyllotoxin on the insecticidal activity.

As shown in Scheme 1, 4′-demethyl-4-deoxypodophyllotoxin (**4**) was prepared from podophyllotoxin (**1**) by catalytic hydrogenolysis in the presence of 10% palladium/carbon, followed by regioselective 4′-demethylation of 4-deoxypodophyllotoxin with dry hydrobromide (**3**).[10] Eight novel 4′-substituted benzenesulfonate derivatives of 4-deoxypodophyllotoxin (**5a**–**h**) were then synthesized by the reaction of **4** with the corresponding substituted benzenesulfonyl chlorides in the presence of triethylamine. The structures of the target molecules were well characterized by ^{1}H NMR, MS, HR-MS, optical rotation, and IR.[11]

The insecticidal activity of compounds **3**, **4**, and **5a**–**h** against the pre-third-instar larvae of *Mythimna separata* Walker was assessed at the concentration of 1 mg/mL by leaf-dipping method.[9] Toosendanin, a commercial insecticide derived from *Melia azedarach*, was used as a positive control.

As shown in Table 1, it was found that the corresponding corrected mortality rates caused by these derivatives after 30 d were higher than those after 10 d and 20 d. For example, the corrected mortality rate of **5d** against *M. separata* after 10 d was only 3.3%, after 20 d the corresponding mortality rate was increased to 20.7%, but after 30 d it was sharply increased to 42.9%, which was 13 times of the mortality rate after 10 d. That is, these compounds, different from those conventional neurotoxic insecticides, such as organophosphates, carbamates and pyrethroids, showed delayed insecticidal activity.[7–9] Meanwhile, the symptoms of the tested *M. separata* were also characterized by the same way as our previous reports.[7–9] For example, the movement of the *M. separata* treated by these compounds decreased greatly after 24 h, and after 48 h some of them were becoming immobilized and loss of body liquid. 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

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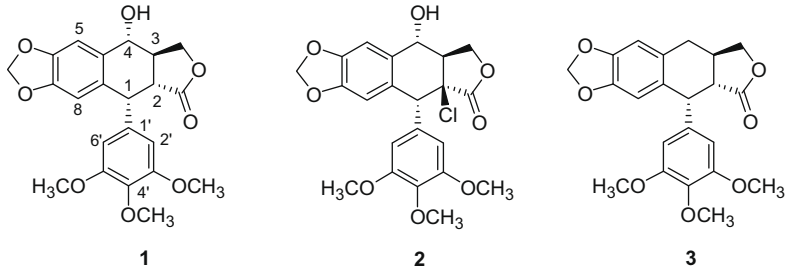
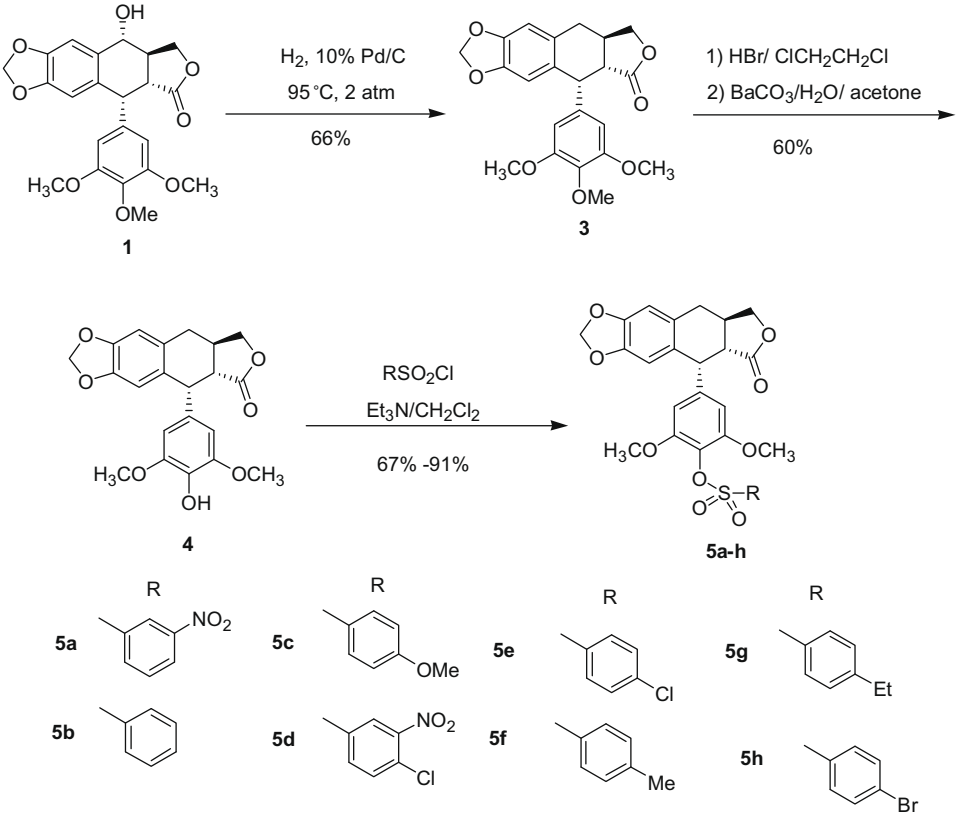


Figure 1. Chemical structures of podophyllotoxin (**1**), 2-chloropodophyllotoxin (**2**), and deoxypodophyllotoxin (**3**).



Scheme 1.

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.

Table 1
Insecticidal activity of **5a**–**h** against *Mythimna separata* Walker in vivo

Compounds	Corrected mortality rate (%)		
	10 d	20 d	30 d
5a	26.7 (±4.7)	27.6 (±8.2)	60.7 (±4.7)
5b	16.7 (±4.7)	13.8 (±4.7)	35.7 (±8.2)
5c	33.3 (±9.4)	37.9 (±8.2)	46.4 (±8.2)
5d	3.3 (±4.7)	20.7 (±12.5)	42.9 (±9.4)
5e	10.0 (±7.4)	10.3 (±4.7)	25.0 (±8.2)
5f	3.3 (±4.7)	10.3 (±5.8)	21.4 (±9.4)
5g	13.3 (±4.7)	27.6 (±8.2)	35.7 (±0)
5h	20.0 (±0)	31.0 (±4.7)	50.0 (±8.2)
3	16.7 (±4.7)	20.7 (±4.7)	39.3 (±4.7)
4	10.0 (±0)	13.8 (±4.7)	21.4 (±4.7)
Toosendanin	30.0 (±8.2)	34.5 (±4.7)	46.4 (±8.2)

Through a comparative study between the insecticidal activity and the chemical structures of 4′-substituted benzenesulfonate derivatives of 4-deoxypodophyllotoxin (**5a**–**h**), some interesting results were obtained as follows: (1) The methyl group on the 4′ position of **3** was necessary for its insecticidal activity. That is, when the 4′-methyl group of **3** was removed to give **4**, the corresponding insecticidal activity of **4** would reduce to some degree. For example, the corrected mortality rates of **3** and **4** against *M. separata* after 10, 20, and 30 d were 16.7/10.0%, 20.7/13.8%, and 39.3/21.4%, respectively. (2) The electronic effect of the substituent groups on the 4′-benzenesulfonate′s ring of 4-deoxypodophyllotoxin to insecticidal activity was not obvious. For example, when the nitro group, methoxy group, or bromo atom was introduced on the 4′-benzenesulfonate′s ring of 4-deoxypodophyllotoxin, the insecticidal activity of the corresponding compounds would be increased as compared to **3** (**5a** 60.7%, **5c** 46.4%, **5d** 42.9%, and **5h** 50.0% vs **3** 39.3%); on the contrary, when the methyl group, ethyl group, or chlorine atom was

introduced on the 4′-benzenesulfonate's ring of 4-deoxypodophyllotoxin, the corresponding insecticidal activity was decreased as compared to **3** (**5e** 25.0%, **5f** 21.4%, and **5g** 35.7% vs **3** 39.3%). (3) Compound **5a** bearing the nitro group at the *meta* position on the 4′-benzenesulfonate's ring of 4-deoxypodophyllotoxin, whose corrected mortality rate against *M. separata* after 30 d was 60.7%, showed the most promising and best insecticidal activity as compared to **3** (39.3%) and toosendanin (46.4%). Especially compound **5a** exhibited the same potent insecticidal activity as 4′-deoxypodophyllotoxin nicotinate or isonicotinate.[9]

In conclusion, eight novel 4′-substituted benzenesulfonate derivatives of 4-deoxypodophyllotoxin were synthesized and preliminarily tested against the pre-third-instar larvae of *M. separata* Walker in vivo at the concentration of 1 mg/mL. Among all of the tested compounds, analogs **5a**, **5c**, **5d**, and **5h** showed the higher insecticidal activity than 4-deoxypodophyllotoxin. Especially **5a** exhibited the most potent insecticidal activity compared with toosendanin, a commercial insecticide derived from *M. azedarach.*

Acknowledgments

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10. *The representative procedure for the synthesis of compound* **4**: A mixture of 10% palladium/carbon (12.0 g) and podophyllotoxin (**1**, 16.0 g, 38.6 mmol) in acetic acid solution (150 mL) was stirred at 95 °C under 2 atm of hydrogen for 5 h. After filtration to remove the catalyst and evaporation of the solvent, the residue was purified by silica gel column chromatography to give the crude product, which was further purified by recrystallization from methanol to afford 9.8 g (66%) of **3** as a white solid. Then compound **3** (2 g, 50.2 mmol) was suspended in 1,2-dichloroethane (25 mL) and diethyl ether (2.5 mL) at 0 °C. A flow of dry hydrobromic acid was passed in the above solution. When the reaction was complete according to TLC analysis, water (25 mL), acetone (25 mL) and a little amount of $BaCO_3$ were added to the reaction mixture, which continued to stir for 0.5 h and extracted by EtOAc. Subsequently, the combined organic phase was washed by brine, dried over anhydrous Na_2SO_4, filtered, concentrated and purified by silica gel column chromatography to give 1.16 g (60%) of **4** as a khaki solid. *Compound* **3**: mp 165–167 °C; $[\alpha]_D^{20} = -116$ (*c* 1 mg/mL, $CHCl_3$); IR cm^{-1}: 2892, 2831, 1763, 1587, 1482, 1457, 1223, 1120, 925, 768; ^1H NMR (400 MHz, $CDCl_3$) δ: 6.67 (s, 1H, H-5), 6.52 (s, 1H, H-8), 6.34 (s, 2H, H-2′, 6′), 5.93 (d, *J* = 8.0 Hz, 2H, OCH_2O), 4.60 (s, 1H, H-1), 4.43 (m, 1H, H-11), 3.89 (m, 1H, H-11), 3.79 (s, 3H, 4′-OCH_3), 3.75 (s, 6H, 3′,5′-OCH_3), 3.06 (m, 1H, H-4), 2.71 (m, 3H, H-2, 3, 4); MS (EI), *m*/*z* (%) 398.1 (M^+, 100). *Compound* **4**: mp 246–248 °C; $[\alpha]_D^{20} = -130$ (*c* 0.4 mg/mL, $CHCl_3$); IR cm^{-1}: 2899, 2824, 1757, 1608, 1478, 1458, 1214, 1105, 922, 769; ^1H NMR (400 MHz, $CDCl_3$) δ: 6.66 (s, 1H, H-5), 6.51 (s, 1H, H-8), 6.35 (s, 2H, H-2′, 6′), 5.92 (m, 2H, OCH_2O), 5.39 (s, 1H, 4′-OH), 4.59 (d, *J* = 2.4 Hz, 1H, H-1), 4.42 (m, 1H, H-11), 3.88 (m, 1H, H-11), 3.78 (s, 6H, 3′,5′-OCH_3), 3.05 (m, 1H, H-4), 2.71 (m, 3H, H-2, 3, 4); MS (EI), *m*/*z* (%) 383.9 (M^+, 100).
11. *Spectral data for* **5a**: yellow solid, mp 115 °C; $[\alpha]_D^{20} = -48$ (*c* 4 mg/mL, $CHCl_3$); IR cm^{-1}: 2916, 2845, 1769, 1598, 1483, 1462, 1378, 1225, 1126, 929, 705; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.89 (s, 1H, H-2″), 8.48–8.51 (m, 1H, H-6″), 8.30–8.33 (m, 1H, H-4″), 7.74 (t, *J* = 8.0 Hz, 1H, H-5″), 6.67 (s, 1H, H-5), 6.50 (s, 1H, H-8), 6.36 (s, 2H, H-2′, 6′), 5.94 (dd, *J* = 1.2, 10 Hz, 2H, OCH_2O), 4.61 (d, *J* = 4.8 Hz, 1H, H-1), 4.46–4.50 (m, 1H, H-11), 3.90–3.95 (m, 1H, H-11), 3.61 (s, 6H, 3′,5′-OCH_3), 3.05–3.10 (m, 1H, H-4), 2.74–2.81(m, 3H, H-2, 3, 4); HRMS: Calcd for $C_{27}H_{27}N_2O_{11}S$ ($[M+NH_4]^+$), 587.1330; found, 587.1326. **5b**: white solid, mp 248–250 °C; $[\alpha]_D^{20} = -70$ (*c* 5.3 mg/mL, $CHCl_3$); IR cm^{-1}: 2881, 2838, 1765, 1596, 1484, 1460, 1373, 1227, 1129, 932, 755, 733; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.95 (d, *J* = 8.8 Hz, 2H, H-2″, 6″), 7.61 (t, *J* = 8.0 Hz, 1H, H-4″), 7.50 (t, *J* = 8.0 Hz, 2H, H-3″, 5″), 6.66 (s, 1H, H-5), 6.50 (s, 1H, H-8), 6.32 (s, 2H, H-2′, 6′), 5.93 (dd, *J* = 1.2, 9.6 Hz, 2H, OCH_2O), 4.59 (d, *J* = 4.8 Hz, 1H, H-1), 4.45–4.49 (m, 1H, H-11), 3.90–3.94 (m, 1H, H-11), 3.53 (s, 6H, 3′,5′-OCH_3), 3.04–3.09 (m, 1H, H-4), 2.68–2.80 (m, 3H, H-2, 3, 4); MS (ESI-TRAP), *m*/*z* (%) 525 ($[M+1]^+$, 100); HRMS: Calcd for $C_{27}H_{28}NO_9S$ ($[M+NH_4]^+$), 542.1479; found, 542.1469. **5c**: white solid, mp 94–96 °C; $[\alpha]_D^{20} = -47$ (*c* 3.6 mg/mL, $CHCl_3$); IR cm^{-1}: 2915, 2838, 1767, 1595, 1483, 1460, 1367, 1225, 1127, 929, 755; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.87 (d, *J* = 8.8 Hz, 2H, H-2″, 6″), 6.96 (d, *J* = 8.8 Hz, 2H, H-3″, 5″), 6.66 (s, 1H, H-5), 6.50 (s, 1H, H-8), 6.32 (s, 2H, H-2′, 6′), 5.93 (s, 2H, OCH_2O), 4.59 (d, *J* = 4.0 Hz, 1H, H-1), 4.45–4.49 (m, 1H, H-11), 3.88–3.94 (m, 1H, H-11), 3.88 (s, 3H, $C_6H_4OCH_3$), 3.57 (s, 6H, 3′,5′-OCH_3), 3.04–3.09 (m, 1H, H-4), 2.72–2.80 (m, 3H, H-2, 3, 4); MS (ESI-TRAP), *m*/*z* (%) 555 ($[M+1]^+$, 100); HRMS: Calcd for $C_{28}H_{30}NO_{10}S$ ($[M+NH_4]^+$), 572.1585; found, 572.1572. **5d**: yellow solid, mp 97–99 °C; $[\alpha]_D^{20} = -58$ (*c* 7 mg/mL, $CHCl_3$); IR cm^{-1}: 2903, 2844, 1769, 1597, 1483, 1462, 1379, 1225, 1127, 929, 752, 709; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.48 (d, *J* = 2.4 Hz, 1H, H-2″), 8.09 (dd, *J* = 2.0, 8.4 Hz, 1H, H-5″), 7.73 (d, *J* = 8.8 Hz, 1H, H-6″), 6.67 (s, 1H, H-5), 6.50 (s, 1H, H-8), 6.36 (s, 2H, H-2′, 6′), 5.94 (dd, *J* = 1.2, 10 Hz, 2H, OCH_2O), 4.61 (d, *J* = 4.8 Hz, 1H, H-1), 4.46–4.50 (m, 1H, H-11), 3.91–3.95 (m, 1H, H-11), 3.62 (s, 6H, 3′,5′-OCH_3), 3.05–3.11 (m, 1H, H-4), 2.65–2.81 (m, 3H, H-2, 3, 4); MS (ESI-TRAP), *m*/*z* (%) 604 ($[M+1]^+$, 93); HRMS: Calcd for $C_{27}H_{26}N_2O_{11}SCl$ ($[M+NH_4]^+$), 621.0940; found, 621.0943. **5e**: white solid, mp 114–116 °C; $[\alpha]_D^{20} = -57$ (*c* 3.9 mg/mL, $CHCl_3$); IR cm^{-1}: 2909, 2831, 1769, 1597, 1482, 1461, 1374, 1225, 1127, 930, 758; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.88 (d, *J* = 7.2 Hz, 2H, H-2″, 6″), 7.49 (d, *J* = 8.8 Hz, 2H, H-3″, 5″), 6.66 (s, 1H, H-5), 6.49 (s, 1H, H-8), 6.33 (s, 2H, H-2′, 6′), 5.93 (dd, *J* = 1.2, 9.6 Hz, 2H, OCH_2O), 4.59 (d, *J* = 4.8 Hz, 1H, H-1), 4.45–4.49 (m, 1H, H-11), 3.90–395 (m, 1H, H-11), 3.56 (s, 6H, 3′,5′-OCH_3), 3.04–3.09 (m, 1H, H-4), 2.65–2.80 (m, 3H, H-2, 3, 4); MS (ESI-TRAP), *m*/*z* (%) 559 ($[M+1]^+$, 61); HRMS: Calcd for $C_{27}H_{27}NO_9SCl$ ($[M+NH_4]^+$), 576.1090; found, 576.1087. **5f**: white solid, mp 97–99 °C; $[\alpha]_D^{20} = -50$ (*c* 4.2 mg/mL, $CHCl_3$); IR cm^{-1}: 2920, 2838, 1769, 1596, 1483, 1460, 1368, 1225, 1127, 929, 755; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.83 (d, *J* = 8.4 Hz, 2H, H-2″, 6″), 7.30 (d, *J* = 8.0 Hz, 2H, H-3″, 5″), 6.66 (s, 1H, H-5), 6.50 (s, 1H, H-8), 6.32 (s, 2H, H-2′, 6′), 5.93 (dd, *J* = 1.2, 9.2 Hz, 2H, OCH_2O), 4.59 (d, *J* = 4.8 Hz, 1H, H-1), 4.45–4.49 (m, 1H, H–11), 3.89–3.94 (m, 1H, H-11), 3.55 (s, 6H, 3′,5′-OCH_3), 3.04–3.09 (m, 1H, H-4), 2.66–2.80 (m, 3H, H-2, 3, 4), 2.45 (s, 3H, $C_6H_4CH_3$); MS (ESI-TRAP), *m*/*z* (%) 539 ($[M+1]^+$, 100); HRMS: Calcd for $C_{28}H_{30}NO_9S$ ($[M+NH_4]^+$), 556.1636; found, 556.1644. **5g**: white solid, mp 106–107 °C; $[\alpha]_D^{20} = -60$ (*c* 4.1 mg/mL, $CHCl_3$); IR cm^{-1}: 2917, 1770, 1596, 1483, 1460, 1369, 1225, 1127, 929, 755; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.85 (d, *J* = 8.4 Hz, 2H, H-2″, 6″), 7.33 (d, *J* = 8.4 Hz, 2H, H-3″, 5″), 6.66 (s, 1H, H-5), 6.50 (s, 1H, H-8), 6.32 (s, 2H, H-2′, 6′), 5.93 (dd, *J* = 1.2, 9.2 Hz, 2H, OCH_2O), 4.59 (d, *J* = 4.8 Hz, 1H, H-1), 4.45–4.49 (m, 1H, H-11), 3.90–3.94 (m, 1H, H-11), 3.54 (s, 6H, 3′,5′-OCH_3), 2.69–2.80 (m, 5H, H-2, 3, 4, $C_6H_4CH_2CH_3$), 1.25 (t, *J* = 7.6 Hz, 3H, $C_6H_4CH_2CH_3$); MS (ESI-TRAP), *m*/*z* (%) 553 ($[M+1]^+$, 100); HRMS: Calcd for $C_{29}H_{32}NO_9S$ ($[M+NH_4]^+$), 570.1792; found, 570.1797. **5h**: white solid, mp 96–98 °C; $[\alpha]_D^{20} = -53$ (*c* 3.6 mg/mL, $CHCl_3$); IR cm^{-1}: 2918, 2854, 1769, 1597, 1483, 1462, 1373, 1225, 1127, 930, 745; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.80 (d, *J* = 8.4 Hz, 2H, H-2″, 6″), 7.49 (d, *J* = 8.8 Hz, 2H, H-3″, 5″), 6.66 (s, 1H, H-5), 6.49 (s, 1H, H-8), 6.32 (s, 2H, H-2′, 6′), 5.93 (dd, *J* = 1.2, 9.6 Hz, 2H, OCH_2O), 4.59 (d, *J* = 4.8 Hz, 1H, H-1), 4.45–4.49 (m, 1H, H-11), 3.90–3.94 (m, 1H, H-11), 3.56 (s, 6H, 3′,5′-OCH_3), 3.04–3.09 (m, 1H, H-4), 2.65–2.80 (m, 3H, H-2, 3, 4); MS (ESI-TRAP), *m*/*z* (%) 603 ($[M+1]^+$, 100); HRMS: Calcd for $C_{27}H_{27}NO_9SBr$ ($[M+NH_4]^+$), 620.0584; found, 620.0578.