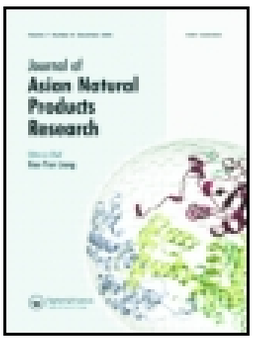

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Design, synthesis of novel C-3′-N-sulfonyl modified taxane analogues from 1-deoxybaccatin VI and their impact on anti-HCC activity

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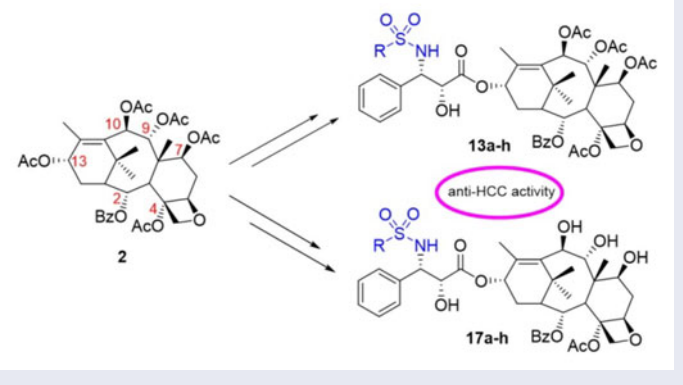
ABSTRACT

A new series of C-3′-N-sulfonyl paclitaxel analogs were designed and synthesized from 1-deoxybaccatin VI and their structures were confirmed by ^{1}H NMR, ^{13}C NMR and high resolution MS. The synthesized compounds were evaluated for their *in vitro* anti-Hepatocellular carcinoma (HCC) activity against human hepatoma (HepG2) cell line. Bioassay results showed that compounds **17c**, **17d** and **17f** exhibited more potent inhibitory activity against HepG2 cell line in comparison with paclitaxel. It is suggested that paclitaxel analogs containing the C-3′-N-sulfonyl could be considered as a precursor structure for further synthesis of more potent analogues.



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Paclitaxel; 1-deoxybaccatin VI; synthesis; anti-HCC activity; 3′-N-sulfonyl

1. Introduction

Hepatocellular carcinoma (HCC) is a rapidly fatal disease with a third highest mortality rate among all cancers [1]. Although several therapeutic approaches and systemic drugs including gemcitabine and octreotide have been used for patients with

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advanced HCC, the prognosis of these patients is not favorable yet [2]. Therefore, it is necessary to develop new drugs for the treatment of advanced HCC.

Paclitaxel (**1**), a diterpenoid natural compound originally isolated from the bark of *Taxus brevifolia*, is one of the most important antitumor agents, has been used for therapy of different types of cancers, including breast, gastric, ovarian, and non-small cell lung carcinomas (Figure 1) [3–6]. Mechanistically, paclitaxel blocks cell cycle and induces cell death by stabilizing microtubules and disrupting microtubule disruption in cell division [7]. There are some reports on the activity of paclitaxel against HCC *in vitro* and *in vivo*. Iesalnieks reported that paclitaxel promoted liver graft survival in rats and inhibited HCC growth *in vitro* and was a potentially useful drug for transplant patients with liver cancer [8]. Okano indicated the growth inhibition of liver cancer cells by paclitaxel and the involvement of extracellular signal-regulated kinase and apoptosis [9]. Additionally, paclitaxel has also been reported to possess significant growth inhibitory effects on HCC in nude mice [10]. These results suggest that paclitaxel could be a promising candidate with excellent therapeutic efficacy for HCC therapy. Thus, further exploration of the effects of paclitaxel analogues in HCC could be fruitful for the discovery of new candidates for the treatment of advanced HCC.

A large number of structure-activity relationship (SAR) studies of paclitaxel have revealed that the C-1 hydroxy group is not necessary for the activity of paclitaxel [11]. Deoxygenation of the C-1-hydroxyl group of paclitaxel had been reported to be a difficult procedure [12,13]. Thus, development of a procedure for synthesis of 1-deoxypaclitaxel analogs will be very significant. 1-Deoxybaccatin VI **2** (Figure 1) that possesses the typical tetracyclic taxoid core while lacking the C-1 hydroxy group is readily available from *Rehd. var. mairei* in good yield [14]. Hence, the development of a method using 1-deoxybaccatin VI as the starting material for preparation of new active taxoids will be of value. Structure-activity studies also indicate that the C-13 side chain is essential for antitumor activity, and the stereochemistry of the side chain at the C-2′ and C-3′ is crucial for biological activity [15]. It is reported that analogues without 3′-N-acyl groups are significantly less active than paclitaxel, and aliphatic and heteroaromatic 3′-N-acyl analogs are slightly more active than paclitaxel [16,17]. In our previous study, the novel C-3′-N-acyl modified 1-deoxybaccatin VI taxane analogues **3** and **4** (Figure 1) had been synthesized, and biologically tested results showed these two compounds have good activities against HepG2 cell line [18].

The sulfonamides constitute an important class of drugs, with antibacterial, antiparasitic, anti-inflammatory, diuretic, hypoglycemic, anti-epileptic, antithyroid and anticancer activities among others [19]. A large number of sulfonamide derivatives have been reported to have remarkable antitumor activity *in vitro* and *in vivo* [20], which provide guidance for designing paclitaxel analogs with sulfonamide groups. Three new 3′-N-tert-butylsulfonyl docetaxel analogues **5–7** (Figure 1) were synthesized and shown to exhibit potent cytotoxicities against human tumor cell lines Eca-109, SKOV3, SMMC-7721, HCT-8, PC3, MCF-7, HeLa and KB [17]. Thus, according to the bioisosteric [21] nature of oxygen and sulfur atoms and the rapid metabolism of sulfur atoms in the body (oxidation to sulfoxide or sulfone), the carbonyl group at the C-3′-N is replaced by a sulfone group. Sixteen novel C-3′-N-sulfonyl modified 1-

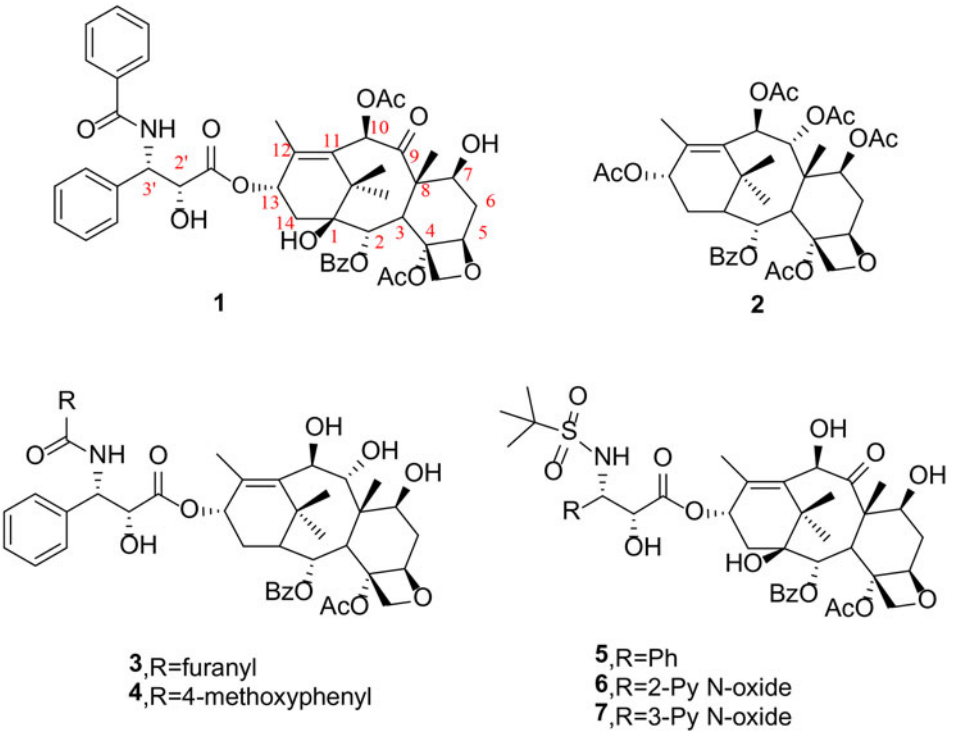


Figure 1. Structures of compounds **1–7**.

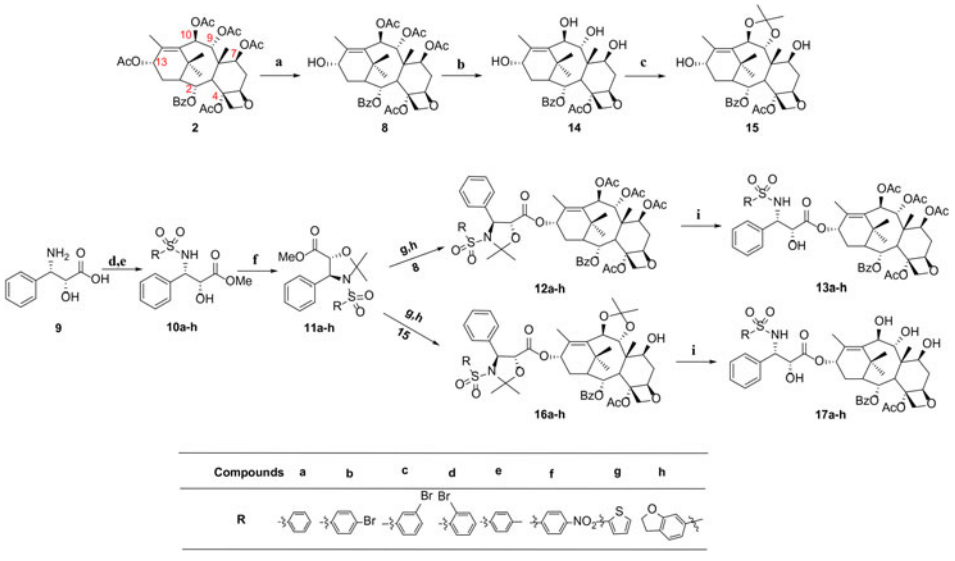
deoxybaccatin VI taxane analogues were designed, synthesized and evaluated for anti-HCC activity.

2. Results and discussion

2.1. Chemistry

As previously reported, paclitaxel side chains were synthesized by different methods [22–24]. Among them, it is preferred to synthesize an oxazolidine side chain precursor by using commercially available material (2 R, 3S)-3-phenylisoserine **9** as starting material. As depicted in Scheme 1, compound **9** was transformed into sulfonamides **10a-h** with sulfonyl chloride after formation of the methyl ester. Cyclic protection using methoxypropene in the presence of a catalytic amount of pyridinium para toluenesulfonate (PPTS) afforded the oxazolidine side chain precursors **11a–h** in 80–90% yields.

The synthesis of compounds **13a-h** is shown in Scheme 1. Treatment of 1-deoxybaccatin VI **2** with Red-Al at -20 °C gave 13-deacetyl-1-deoxybaccatin VI **8** in 77% yield, that was proved to be a very efficient way for the synthesis of analogues retaining the C-7, C-9, and C-10 acetoxyl groups [21]. Then the side chain intermediates **11a-h** were coupled with **8** after saponification in the presence of dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) at 50 °C to provide the corresponding cyclic ester intermediates **12a-h** in 85%-95% yields. After hydrolysis of the acetonide protecting groups of side chain, the final products **13a-h** were afforded.



Scheme 1. The synthetic route of compounds **13a-h** and **17a-h**. Reagents and conditions: (a) Red-Al, THF, -20 °C, 0.5 h; (b) $NH_2NH_2{\cdot}H_2O$, EtOH, rt, 82%; (c) 2,2-dimethoxypropane, montmorillonite K10, CH_2Cl_2, rt, 97%; (d) $SOCl_2$, MeOH, 0 °C to rt, overnight; (e) sulfonyl chloride, THF, sat.$NaHCO_3$, 0 °C to rt, 2 h, 80-90%; (f) 2-methoxypropene, PPTS, toluene, 2 h, 90 °C, 80-90%;(g) KOH, MeOH, rt, 2 h; (h) **8** or **15**, DCC, DMAP, toluene, 50 °C, 2 h, 80- 90%; (i) formic acid, rt, 4 h, 25-35%.

To compare with these compounds **13a-h** with three acetoxyl groups on the parent skeleton, we also synthesized a series of 1-deoxypaclitaxel analogues bearing different substituted groups at the C-3′-N-sulfonyl position and three hydroxyls at the C-7, C-9 and C-10 positions in similar method. The synthesis of the compounds **17a-h** is illustrated in Scheme 1. Starting from compound **8**, which was transformed to 7,9,10,13-tetradeacetylbaccatin VI **14** upon treatment with hydrazine hydrate in ethanol. Subsequently, the C-9 and C-10 hydroxyl groups were selectively protected with 2,2-dimethoxypropane catalyzed by montmorillonite K10 to give compound **15** in 97% yield. Then the side chain intermediates **11a-h** were coupled with **15** after saponification in the presence of DCC and DMAP at 50 °C to provide the corresponding intermediates **16a-h** in 85%-95% yields. After removing the acetonide protecting group of **16a-h** with formic acid at room temperature for 4 h, the final products **17a-h** were afforded.

2.2. Cytotoxicity to HepG2 cell line

In our previous study, we had found that the C-3′-N-acyl modified 1-deoxybaccatin VI taxane analogues **3** and **4** mentioned in the introduction had good anti-HCC activities, especially compound **3** which exhibited a 2.5-fold higher cytotoxicity than paclitaxel to the HepG2 cell line [18]. Therefore, we explore whether C-3′-N-sulfonyl modified taxane analogs we synthesized also have good activities against that cell line. The *in vitro* anti-HCC activities of paclitaxel and the newly synthesized compounds **13a-h** and **17a-h** were assayed for effect in HepG2 cell line by CCK-8 method in series of bioassay. The inhibitory activities (IC_{50}) are summarized in Table 1.

Table 1. Cytotoxicity (IC_{50}[a]) values against HepG2 for paclitaxel and its analogues 13a-h and 17a-h.

Compounds	IC_{50}(nM) HepG2[b]	Compounds	IC_{50}(nM) HepG2[b]
13a	72.72	**17a**	95.31
13b	>100	**17b**	**33.03**
13c	>100	**17c**	**3.82**
13d	>100	**17d**	**5.04**
13e	**52.68**	**17e**	**40.71**
13f	154.97	**17f**	**13.01**
13g	>100	**17g**	>100
13h	64.34	**17h**	>100
paclitaxel	46.47		

[a]Cytotoxicity (IC_{50}) was assayed by CCK-8 method under which growing human tumor cell lines were exposed for 48 h.
[b]Hepatoma cell line.

As reported in Table 1, anti-HCC activities of six derivates were found in the range of 3.82–52.68 nM. Among them, three compounds **17c**, **17d** and **17f** showed potent cytotoxicity with IC_{50} values of 3.82 nM, 5.04 nM and 13.01 nM, respectively, and they were 5–12 times more cytotoxic than paclitaxel against HepG2 cell line. These three compounds also showed better anti-HCC activities than the novel C-3′-N-acyl modified 1-deoxybaccatin VI taxane analogs **3** and **4** [18]. The result indicated that compounds **17c**, **17d** and **17f** may be potential anti-HCC products and demonstrated the rationality and correctness we originally design. Another three compounds **17 b**, **17e**, **13e** exhibited an activity almost similar to standard reference paclitaxel with IC_{50} value of 46.47 nM. Whereas other compounds (**13a-d**, **13f-h**, **17a** and **17 g-h**) showed low toxicity against the tested liver carcinoma cells. Moreover, compounds **17 b-f** have higher cytotoxicity than **13 b-f**. In comparison with their structures, compounds **17 b-f** have the three hydroxyl groups at the C-7, C-9 and C-10 positions instead of the acetoxyl group of compound **13 b-f**. As illustrated by the results above, these 1-deoxypaclitaxel analogues with three hydroxyls at the C-7, C-9 and C-10 positions would be valuable for enhancing the anti-HCC activity.

Based on the above-mentioned anti-HCC study, we selected compounds **17 b-d**, **17f** to further investigate its *in vitro* cell growth inhibitory activity against human lung cancer cell line A549 and its resistant cell line A549/T. The *in vitro* antitumor activities were evaluated by MTT method. As shown in Table 2, compound **17d** showed comparable activity to paclitaxel against A549 and A549/T cell lines with IC_{50} values of 0.093 μM and 1.454 μM respectively. However, compounds **17 b, 17c** and **17f** exhibited weak activity compared to paclitaxel against A549 and A549/T cell lines. The preliminary tests showed that C-3′-N-sulfonyl-modified taxane analogue **17d** also exhibited potent anti-lung cancer activity.

In conclusion, we synthesized some C-3′-N-sulfonyl modified paclitaxel analogues to investigate the effect of the C-3′-N sulfonyl substituents for anti-HCC activity. The compounds **17 b-f** showed remarkable anti-HCC activity. Among them, compounds **17c** and **17d** are the most potent compounds presenting IC_{50} values on HepG2 cells of 3.82 and 5.04 nM compared to 46.47 nM of paclitaxel. Our findings show that the substituents of the sulfonyl group at the C-3′-N position have a significant effect on the anti-HCC activity. At the same time, compound **17d** showed comparable activity

Table 2. Cytotoxicity (IC_{50}[a]) values for paclitaxel and its analogues **17b–d**, **17f**.

	Compounds				
IC_{50}(μM)	17b	17c	17d	17f	Paclitaxel
A549[b]	>10	>10	0.093 ± 0.018	>10	0.020 ± 0.001
A549/T[c]	>10	>10	1.454 ± 0.508	>10	1.406 ± 0.167

[a]Cytotoxicity (IC_{50}) was assayed by MTT method under growing human tumor cell lines were exposed for 72 h.
[b]Human lung cancer cell line.
[c]Human lung cancer resistant cell line.

to paclitaxel against A549 and A549/T cell lines. The IC_{50} values of two series **17 b-f** and **13 b-f** could lead to the conclusion that 1-dexoypaclitaxel analogues with three hydroxyls at the C-7, C-9 and C-10 positions have a conspicuous enhancement in anti-HCC activity. Therefore, this may be an important orientation in finding candidates from C-3′-N-sulfonyl modified paclitaxel analogues that can be used in liver cancer treatment in the future.

3. Experimental

Experimental procedure, 1H NMR, 13C NMR data of compounds 8, 13a-h, 14, 15, 17a-h are available in Supplementary data.

3.1. General experimental procedures

All reported yields are obtained after column chromatography or thin-layer chromatography (TLC). Column chromatography was performed with silica-gel H (Qingdao Marine Chemical Inc., Qingdao, China). TLC was conducted on silica gel GF254 plates (Qingdao Marine Chemical Factory, Qingdao, China). The NMR spectra were measured with a Bruker Avance/AV 500 MHz (^{13}C: 125.7 MHz, ^{1}H: 500 MHz) spectrometer (Bruker BioSpin AG, Fallanden, Switzerland). ^{1}H and ^{13}C NMR spectra were recorded with tetramethylsilane as internal standard in $CDCl_3$. Chemical shifts (δ) are given in ppm. MSs were recorded on a Thermo Finnigan LCQ Advantage Mass spectrometer (Agilent Technologies Singapore(sale)pte, Singapore). All chemicals were dried or purified according to standard procedures prior to use.

3.2. General procedure for the synthesis of compounds 17c and 17d

HCOOH (>98%, 5 ml) was added to compounds **16c-d**, and the reaction mixture was stirred at room temperature for 4 h. Then the resulting solution was neutralized by addition of saturated $NaHCO_3$. After extracted with EtOAc, the combined organic phase was washed with brine, dried over anhydrous Na_2SO_4. The crude products was purified by thin layer chromatography, yielding products **17c-d** as white solid.

3.2.1. 3′-N-Debenzoyl-N-(3-bromo)-phenylsulfonyl-9(R)-dihydro-10-deacetyl-9,10-dihydroxy-1-deoxypaclitaxel (17c)

White solid. Yield 33%. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.12 (d, $J = 6.0$, Hz, 2 H, Ph-H), 7.58-7.48 (m, 2 H, Ph-H), 7.47-7.35 (m, 4 H, m-Br-Ph-H), 7.14-6.95 (m,

6 H, Ph-H), 6.47 (t, $J = 8.42$ Hz, 1 H, 13-H), 6.44 (dd, $J = 9.6$, 3.2 Hz, 1 H, 2-H), 6.03-5.90 (m, 1 H, 3'-H), 5.14 (d, $J = 6.9$ Hz, 1 H, 2'-H), 5.01-4.94 (m, 2 H, 5-H and 10-H), 4.49-4.40 (m, 2 H, 20-H and 9-H), 4.29 (d, $J = 8.0$ Hz, 1 H, 20-H), 4.19 (t, $J = 8.8$ Hz, 1 H, 7-H), 4.06 (br, 1 H), 2.15 (s, 3 H, CH_3CO), 2.10 (d, $J = 4.8$ Hz, 1 H, 3-H), 2.08-2.06 (m, 2 H, 14-H and 6-H), 1.89 (d, $J = 6.6$ Hz, 1 H, 1-H), 1.86 (s, 3 H, CH_3), 1.82 (s, 3 H, CH_3), 1.74-1.68 (m, 2 H, 14-H and 6-H), 1.29 (s, 3 H, CH_3), 1.27 (s, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 171.4, 165.7 142.2, 139.8, 135.2, 130.1, 130.0, 129.9, 128.5, 128.4, 127.1, 126.9, 125.2, 122.6, 99.6, 99.5, 78.9, 75.8, 71.3, 69.3, 65.3, 59.4, 53.5, 47.5, 45.2, 42.6, 42.0, 38.3, 37.7, 36.3, 29.7, 26.2, 25.6, 21.3, 20.3, 18.3, 17.6, 17.4, 16.1, 15.7, 14.2, 13.6. HR-ESI-MS: *m/z* 912.2220 $[M + H]^+$ (calcd for $C_{44}H_{51}BrNO_{13}S$, 912.2264).

3.2.2. 3′-N-Debenzoyl-N-(2-bromo)-phenylsulfonyl-9(R)-dihydro-10-deacetyl-9,10-dihydroxy-1-deoxypaclitaxel (17d)

White solid. Yield 28%. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.07-8.05 (m, 2 H, Ph-H), 7.65(t, $J = 1.8$ Hz, 1 H, Ph-H), 7.54-7.51 (m, 1 H, Ph-H), 7.45-7.37 (m, 4 H, Ph-H), 7.11 (d, $J = 7.0$ Hz, 3 H, o-Br-Ph-H), 7.06-7.03 (m, 3 H, Ph-H), 6.06 (t, $J = 8.6$ Hz, 1 H, 13-H), 5.76 (dd, $J = 8.4$, 3.7 Hz, 1 H, 2-H), 5.66 (d, $J = 6.7$ Hz, 1 H, 3′-H), 5.32 (d, $J = 6.0$ Hz, 1 H, 2'-H), 5.07 (d, $J = 8.3$ Hz, 1 H, 5-H), 4.83 (d, $J = 9.6$ Hz, 1 H, 10-H), 4.52 (d, $J = 9.8$ Hz, 1 H, 9-H), 4.23 (d, $J = 8.5$ Hz, 1 H, 20-H), 4.17 (t, $J = 8.7$ Hz, 1 H, 7-H), 4.03 (d, $J = 8.2$ Hz, 1 H, 20-H), 3.65 (d, $J = 5.9$ Hz, 1 H, 3-H), 2.12-2.07 (m, 2 H, 14-H and 6-H), 2.01 (s, 3 H, CH_3CO), 1.92 (d, $J = 6.1$ Hz, 1 H, 1-H), 1.82 (s, 3 H, CH_3), 1.79 (s, 3 H, CH_3), 1.64-1.60 (m, 2 H, 14-H and 6-H), 1.26 (s, 3 H, CH_3), 1.25 (s, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 171.2, 165.5, 144.0, 142.0, 136.1, 135.2, 133.5, 130.1, 129.3, 128.5, 128.4, 128.2, 127.1, 125.3, 124.3, 122.6, 75.0, 74.2, 71.9, 71.9, 59.7, 67.1, 66.9, 55.9, 52.2, 51.0, 50.0, 48.2, 47.5, 45.3, 40.3, 31.9, 30.4, 29.8, 26.3, 22.7, 21.2, 18.4, 17.6, 17.1, 16.1, 15.7, 14.1, 13.6. HR-ESI-MS: *m/z* 912.2232 $[M + H]^+$ (calcd for $C_{44}H_{51}BrNO_{13}S$, 912.2264).

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Disclosure statement

No potential conflict of interest was reported by the authors.

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