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On the structure of the bioactive constituent from ayurvedic medicine *Salacia reticulata*: revision of the literature

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ABSTRACT

The reported structure of a potent α-glucosidase inhibitor **7** isolated recently from ayurvedic medicine *Salacia reticulata* was found incorrect, and the compound was proved to be de-O-sulfated kotalanol **4**. Discussion and detailed analysis of the spectral data leading to the revised structure are presented.

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From the roots and stems of *Salacia* species plants, which have traditionally been used for the treatment of diabetes in Sri Lanka, India, and Thailand, the authors had isolated highly potent α-glucosidase inhibitors, salacinol (**1**) and kotalanol (**2**).[1] Their structures are quite unique, bearing thiosugar sulfonium sulfate inner salt that comprises 1-deoxy-4-thio-D-arabinofranosyl cation and 1-deoxyaldosyl-3-sulfate anion as shown in Figure 1. Their α-glucosidase inhibitory activities are potent,[1] and have been revealed to be as high as those of voglibose and acarbose, which are widely used clinically these days. De-O-sulfated analogs (**3** and **4**), which were readily derived by the acidic methanolysis, were also found to be as potent as the original sulfates (**1** and **2**).[2] Because of the intriguing structure and high α-glucosidase inhibitory activities, much attention has been focused on them, and intensive studies on the structure-activity relationships (SAR) have been reported.[3] Additionally, we isolated recently another thiosugar analogs, ponkolanol (**5**) and salaprinol (**6**) from the same species of plant,[2b] and absolute stereochemistry of **6** has been successfully determined on the basis of the single crystal X-ray crystallographic analysis.[4]

Very recently, Ozaki and co-workers[5a] reported the isolation of another highly potent α-glucosidase inhibitor from *S. reticulata*, and presented a polyhydroxylated 13-membered cyclic sulfoxide structure (**7**) for the inhibitor. However, the ^{1}H and ^{13}C NMR spectroscopic properties of the inhibitor **7** reported are quite similar to those of the de-O-sulfated kotalanol methyl sulfate (**4a**) we had reported (Table 1).

Reexamination and comparison of their spectral data with those of **4a** concluded that the presented structure **7** was incorrect, and the compound they isolated was proved to be de-O-sulfated kotalanol (**4**).

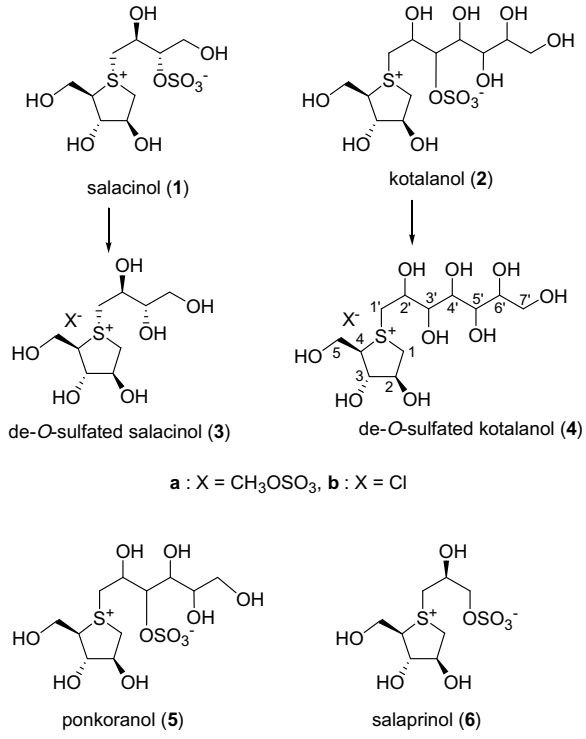

Figure 1.

As shown in Table 1, all the ^{13}C chemical shifts reported are in good correlation to those of **4a** with deviations of 3.8 or 3.9 ppm, which would be caused by the different standard employed. Therefore, it is reasonable and proper that these two compounds are

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Table 1
^{1}H and ^{13}C NMR data for compounds **7** and **4a** in D_20 (δ in ppm and J in Hz)

Compound **7** (400 MHz and 100 MHz) lit.[5a] an internal standard: acetone			Compound **4**[a] (600 MHz and 150 MHz) an external standard: DSS			$_\Delta\delta_H$[b]	$_\Delta\delta_C$[b]
	δ_H[a]	δ_C[a]		δ_H	δ_C		
H-2a	3.79–3.75 (2H, m)	46.9	H-1a	3.87 (dd, J = 12.7, 4.5)	50.8	0.12	3.9
H-2b			H-1b	3.91 (dd, J = 12.7, 3.1)			
H-3	4.59 (q, J = 3.4)	75.8	H-2	4.72–4.75 (m)	79.7	0.15	3.9
H-4	4.28 (t, J = 3.4)	76.4	H-3	4.43 (t-like, J = ca. 2.6)	80.2	0.15	3.8
H-5	3.94 (m)	68.8	H-4	4.07–4.10 (m)	72.66	0.15	3.9
H-6a	3.78 (dd, J = 13.2, 2.2)	58.0	H-5a	3.92 (dd, J = 10.5, 2.9)	61.9	0.14	3.9
H-6b	3.96 (dd, J = 13.2, 4.6)		H-5b	4.12 (dd, J = 10.5, 4.8)		0.16	
H-13a	3.63 (dd, J = 13.4, 8.8)	49.3	H-1′a	3.78 (dd, J = 13.4, 9.1)	53.1	0.15	3.8
H-13b	3.82 (dd, J = 13.4, 3.2)		H-1′b	3.97 (dd, J = 13.4, 3.1)		0.15	
H-12	4.07 (dt, J = 8.8, 2.4)	66.3	H-2′	4.22 (ddd, J = 9.6, 9.1, 3.1)	70.1	0.15	3.8
H-10	3.73 (t, J = 9.5)	66.9	H-3′	3.86 (dd-like, J = ca. 9.6, 1.2)	70.7	0.13	3.8
H-9	3.49 (t, J = 9.5)	68.0	H-4′	3.64 (dd, J = 9.4, 1.2)	71.8	0.15	3.8
H-11	3.72 (br d, J = 9.5)	70.4	H-5′	3.87 (d-like, J = ca. 9.4)	74.3	0.15	3.9
H-7	3.79 (dt, J = 6.6, 2.2)	68.9	H-6′	3.94 (td, J = 6.4, 1.0)	72.72	0.15	3.8
H-8a	3.51 (2H, d, J = 6.6)	62.0	H-7′a	3.66 (2H, d-like, J = 6.4)	65.9	0.15	3.9
H-8b			H-7′b				
				3.71 (s, $CH_3OSO_3^-$)	58.1		

[a] The order of the signals of **7** was rearranged according to the assignment of **4a**.
[b] Deviations of the chemical shift between **7** and **4a** in D_2O.

considered to be the same or having the very similar structure with each other.

Thus, the major mistakes by Ozaki and co-workers are the assignments for the four methylene carbons. Of the four peaks due to methylene carbons, they assigned the peaks at δ_C 58.0 and δ_C 62.0 to the carbons C6 and C8 in the structure **7**, respectively, as shown in Figure 2. However, this type of carbon, namely –CH(OH)CH_2CH(OH)– structure, is known to resonate normally at around 40 ppm.[6] When the deviation ($\Delta\delta_C$) of 3.9 is taken into account, chemical shifts of these two peaks are consistent with two peaks (δ_C 61.9 and δ_C 65.9) which had been reasonably ascribed to C5 and C7′ of **4a** by us, and the chemical sifts were in good accordance with those of de-O-sulfated salacinol[7] (**3a**).

The ^{1}H NMR spectrum reported[5a] is also in good accordance with that of **4a** as shown in Figure 3. In their interpretation of the spectroscopic properties, there appear apparent discrepancies especially concerning the vicinal coupling constants and coupling patterns for many protons, some of which are listed below: between H-11 (J = 9.5 Hz) and H-12 (J = 8.8 or 2.4 Hz), between H-12 (J_{12-13a} = 2.4 Hz) and H-13b (J_{13b-12} = 3.2 Hz), between H-6b (J_{6b-7} = 4.6 Hz) and H-7 (J_{7-6b} = 6.6 Hz), between H-8 (J_{8-9} = 6.6 Hz) and H-9 (J_{9-8} = 9.5 Hz), doublet for H-8, and triplet for H-9 are the unlikely interpretation for the structure **7** (Table 1).

It is also impossible to construct the structure **7** on the basis of their 2D NMR spectra which were recorded at 400 MHz in D_2O.

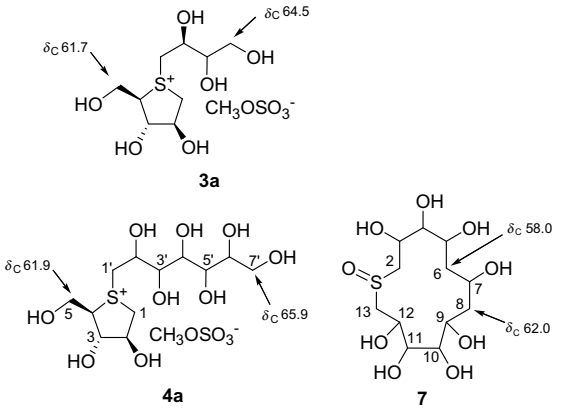

Figure 2.

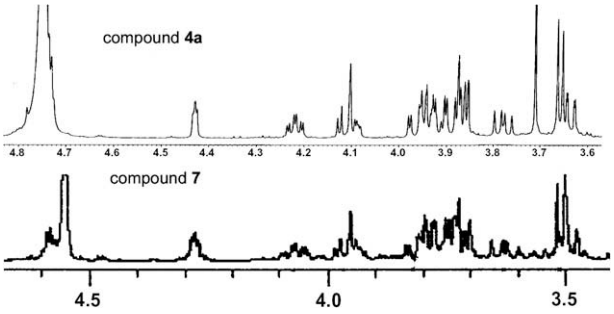

Figure 3. ^{1}H NMR spectrum of **4a** (600 MHz) and **7** (400 MHz)[5a] in D_2O.

In our study using a 600 MHz ^{1}H NMR spectrometer, the signals due to H-3′ (H-10 for **7**) and H-5′ (H-11 for **7**), which were observed at δ_H 3.86 and δ_H 3.87, respectively, were hardly distinguishable. Thus, it was almost impossible to clarify which of the two protons correlated to the H-2′ (H-12 for **7**) on the basis of ^{1}H–^{1}H-COSY studies.

On the other hand, these signals due to H-3′ and H-5′ were found well distinguishable when the spectrum of **4a** was recorded in pyridine-d_5,[8] where the corresponding signals were observed at δ_H 4.84 and δ_H 4.94, respectively. To ascertain our assignments, 2D NMR studies were conducted for the solution in pyridine-d_5 (Fig. 4) in this study. The ^{1}H–^{1}H-COSY spectrum showed cross-peaks due to two partial structures written in bold lines shown in Figure 5. Especially, the cross-peak observed between H-3′ (H-10 for **7**) and H-2′ (H-12 for **7**) proved that the partial structure composed of these carbons presented by Ozaki was incorrect. HMBC long-range correlation between H-1 and C4 supported the presence of the sulfonium thiosugar moiety of **4a**. The connectivity of the thiosugar moiety with the side chain was also supported by correlations H-1–C1′, H-1′–C1, and H-1′–C4 (Fig. 4). In addition to this, reasonable NOEs were detected between the appropriate signals as shown in Figure 5.

Previously, we reported that the exchange of the counter anion caused no significant influence on the NMR spectroscopic properties as shown in Figure 6.[2a] It is difficult to speculate the counter anion from the reported evidences, the inhibitor would possess a non-protic counter anion such as Cl^- or SO_4^{2-}, which might arise from the ion exchange reaction or hydrolysis of methyl sulfate

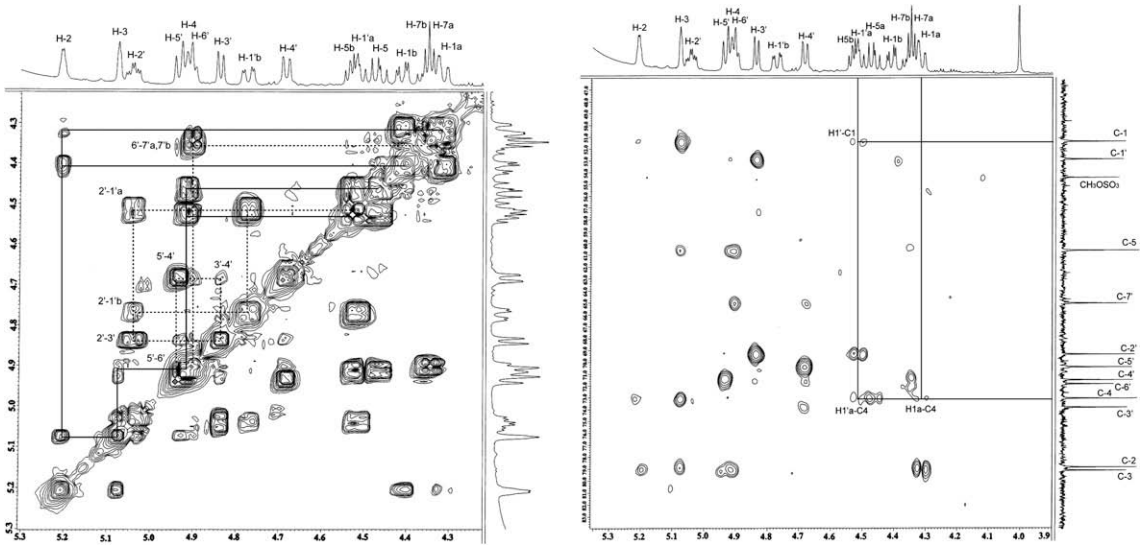

Figure 4. ^{1}H–^{1}H COSY and $^{1}HMBC$ spectra (600 MHz) of **4a** in pyridine-d_5.

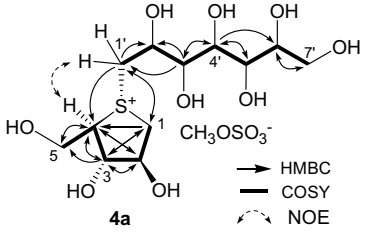

Figure 5. Correlations observed in COSY and HMBC experiments of in **4a** pyridine-d_5.

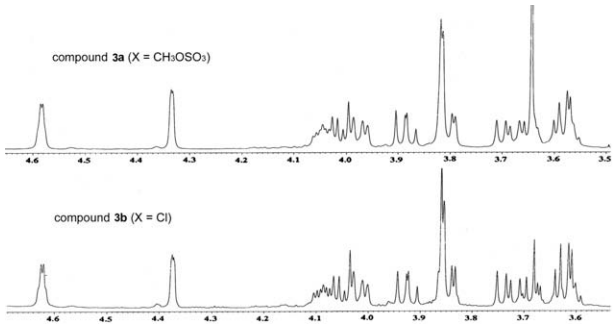

Figure 6. ^{1}H NMR spectra of **3a** and **3b** in CH_3OD.

anion during the isolation process of the inhibitor. Incidentally, **4a** showed distinct peaks at δ_H 3.71 and δ_C 58.1, corresponding to $CH_3OSO_3^-$ in the ^{1}H NMR and ^{13}C NMR spectra, respectively.

FAB mass spectrum of **4a** in the positive mode showed a peak at *m/z* 345. Although Ozaki and co-workers assigned this peak as the quasi-molecular ion peak $[M+H]^+$, it is also reasonable to ascribe this peak to the sulfonium cation moiety. In the negative ion mode, **4a** showed the distinct peak due to methyl sulfate anion at *m/z* 111.

In summary, examination and careful comparison of the ^{1}H and ^{13}C NMR spectroscopic properties of the isolated inhibitor with those of de-O-sulfated kotalanol **4a** concluded that the compound isolated by Ozaki et al. was de-O-sulfated kotalanol.

Acknowledgments

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7. Compound **3a**: ^{1}H NMR (500 MHz, D_2O, external standard: DSS) δ (ppm) 3.63 (dd-like, J = 11.2, 5.4, H-4′a), 3.71–3.75 (m, H-3′), 3.73 (3H, s, $CH_3OSO_3^-$), 3.73–3.77 (m, H-4′b), 3.76 (dd, J = 13.2, 9.2, H-1′a), 3.868 (dd, J = 13.2, 3.8, H-1a), 3.872 (dd, J = 13.2, 3.4, H-1′b), 3.92 (dd, J = 13.2, 3.2, H-1b), 3.93 (dd, J = 11.8, 8.9, H-5a), 4.08 (ddd, J = 8.9, 4.9, 2.6, H-4), 4.12 (dd, J = 11.8, 4.9, H-5b), 4.13–4.17 (m, H-2′), 4.44 (dd-like, J = 3.2, 2.6, H-3), 4.74 (ddd-like, J = 3.8, 3.2, 3.2, H-2); ^{13}C NMR (125 MHz, D_2O, external standard: DSS) δ (ppm) 50.8 (C-1), 52.1 (C-1′), 58.0 ($CH_3OSO_3^-$), 61.7 (C-5), 64.5 (C-4′), 70.1 (C-2′), 72.5 (C-4), 76.0 (C-3′), 79.5 (C-2), 80.1 (C-3).
8. Compound **4a**: ^{1}H NMR (600 MHz, pyridine-d_5) δ (ppm) 4.00 (3H, s, CH_3SO_3), 4.31 (dd, J = 12.7, 1.9, H-1a), 4.33 (dd, J = 10.8, 6.0, H-7′a), 4.36 (dd, J = 10.8, 6.2, H-7′b), 4.41 (dd, J = 12.7, 3.6, H-1b), 4.47 (dd, J = 11.7, 9.1, H-5a), 4.52 (dd, J = 12.8, 8.3, H-1′a), 4.54 (dd, J = 11.7, 5.7, H-5b), 4.68 (dd, J = 9.1, 1.0, H-4′), 4.77 (dd, J = 12.8, 3.3, H-1′b), 4.84 (br d, J = 8.0, H-3′), 4.90–4.93 (m, H-4), 4.91 (ddd, J = 6.2, 6.0, 1.0, H-6′), 4.94 (br d, J = 9.1, H-5′), 5.04 (ddd, J = 8.3, 8.0, 3.3, H-2′), 5.08 (dd-like, J = ca. 2.2, 1.9, H-3), 5.21 (ddd-like, J = ca. 3.6, 1.9, 1.9, H-2); ^{13}C NMR (150 MHz, pyridine-d_5) δ (ppm) 51.2 (C-1), 52.7 (C-1′), 54.3 ($CH_3OSO_3^-$), 60.4 (C-5), 64.9 (C-7′), 69.2 (C-2′), 70.2 (C-5′), 71.3 (C-4′), 71.7 (C-6′), 72.9 (C-4), 73.7 (C-3′), 78.7 (C-2), 78.9 (C-3).