Cytotoxic Xanthones from *Psorospermum molluscum* from the Madagascar Rain Forest[△]

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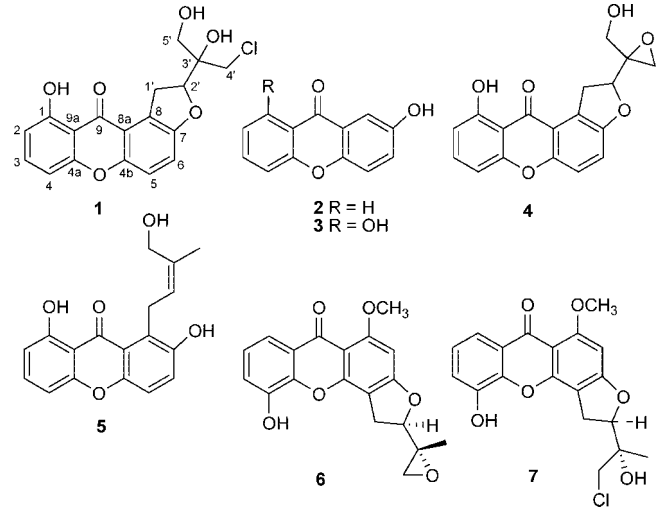
Two new cytotoxic xanthones were isolated from extracts of the Madagascar rain forest plant *Psorospermum* cf. *molluscum* using bioassay-guided fractionation with the *Escherichia coli* SOS chromotest. The structures of the new dihydrofuranoxanthones, designated 3′,4′-deoxy-4′-chloropsoroxanthin-(3′,5′-diol) (**1**) and psoroxanthin (**4**), were determined on the basis of 2D-NMR, MS, and UV spectroscopic data and are structurally related to the psorospermins, a known class of plant antitumor agents. A new hydroxyprenylated xanthone (**5**) is also described. Xanthones **1** and **4** showed selective *in vitro* cytotoxicity against ABAE cells (bovine endothelial cell line).

In our search for new biologically active compounds from the Madagascar and Suriname rain forests as part of the International Cooperative Biodiversity Group (ICBG) program, we selected for further evaluation extracts of the plant *Psorospermum* cf. *molluscum* (Pers.) Hochr. (Hypericaceae), which displayed cytotoxic and DNA repair activities. Described herein are the isolation and structure determination of two new cytotoxic and DNA-reactive xanthones from this Madagascar plant.

The plant material was collected in the Fianarantsoa area of Madagascar.[1] The dichloromethane−methanol extracts of the wood stems and roots were initially treated separately. These were shown to have nearly identical HPLC-UV profiles and demonstrated potent cytotoxicity in a panel of mammalian tumor cell lines (mean IC_{50} ranges from 0.2 to 4 μg/mL).[2] In particular there was a clear selective *in vitro* cytotoxicity observed against ABAE cells (bovine endothelial cell line, 0.03 μg/mL). As the endothelial cell selectivity was suggestive of potential antiangiogenic utility, coupled with the relatively rare occurrence of DNA reactivity in plant extracts, these extracts received priority for isolation studies. As a result, extensive fractionation of both extracts yielded two new cytotoxic dihydrofuranoxanthones, psoroxanthin chlorohydrin (**1**) and psoroxanthin (**4**), and a new hydroxyprenylated xanthone (**5**).

The crude extracts as received were subjected to a modified "Kupchan" liquid–liquid partitioning sequence,[3] followed by gel partition chromatography (Sephadex LH-20) and/or silica gel vacuum liquid chromatography. The fractionation was guided initially by TLC-bioautography using the *Escherichia coli* SOS PQ37 chromotest assay, a DNA reactivity assay.[4] More precise localization of the peak of SOS activity was later made possible using HPLC biogram methodology.[5] In this manner, analytical HPLC was used to further fractionate the SOS-active sample into 96-deep-well plates. The fraction collection utilized a time-based protocol, resulting in a direct relationship between a well's position in the plate and a corresponding area on the HPLC chromatogram. Subsequent bioassay of all fractions using the SOS chromotest revealed activity correlated with an extremely minor cluster of peaks (i.e., barely detectable by UV) in the chromatogram. Final purification of the SOS-active complex was achieved after repeated reversed-phase HPLC. In this manner, fractionation of *P. molluscum* wood stem extract yielded a new SOS-active compound, psoroxanthin chlorohydrin (**1**). Also identified in the extract by NMR, UV, and MS were the known 2-hydroxyxanthone (**2**) and 1,7-dihydroxyxanthone (**3**).[6,7] Likewise, fractionation of *P. molluscum* root extract yielded a second new SOS-active compound, psoroxanthin (**4**), plus a new prenylated xanthone, 8-(4′-hydroxyprenyl)-1,7-dihydroxyxanthone (**5**), and again 2-hydroxyxanthone (**2**).



Compound **1** was isolated from the wood stem extract as a yellow, amorphous solid (4.8 mg). The MS spectrum obtained in positive mode utilizing electrospray ionization (+ESI) indicated that **1** was monochlorinated with a molecular mass of 362 Da. Its molecular formula was established as $C_{18}H_{15}O_6Cl$ by high-resolution accurate mass analysis (HR +ESI) ($[M + H]^+$ at *m/z* 363.0634, calcd 363.0635), indicating 11 degrees of unsaturation in the molecule. Its UV spectrum (λ_{max} 243, 264, 292, 325, 396 nm) was highly similar to that of 1,7-dihydroxyxanthone, a known xanthone found in this extract.[7] The ^{1}H NMR spectrum (DMSO-d_6) featured a hydrogen-bonded hydroxyl proton singlet (δ 12.59), five ortho-coupled aromatic signals (one proton each) at δ 7.71 (t, J = 8.3 Hz), 7.44 (d, J = 9.0 Hz), 7.37 (d, J = 9.0 Hz), 7.03 (d, J = 8.0 Hz), and 6.78 (d, J = 8.5 Hz), a methine triplet resonance at δ 5.04 (J = 9.3 Hz), two methylene signals, δ 3.84, (2H, s) and 3.75 (2H, dd, J = 9.0, 3.0 Hz), and a methylene pair, δ 3.53, 3.46 (J = 11.0 Hz). In the ^{13}C spectrum, 13 of the 18 signals were consistent with a 1,7-dioxyxanthone moiety within the molecule.[7c] The

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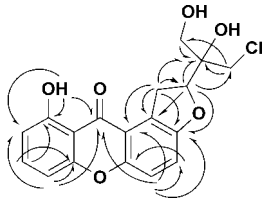

Figure 1. HMBC correlations for **1**.

additional five signals were attributed to an isoprenoid unit, and these included three methylene carbons (δ 61.2, 46.4, 31.1), one methine (δ 85.2), and one quaternary carbon (δ 74.7). On the basis of a series of 2D-NMR experiments including HMQC and HMBC (Figure 1, Table 1), structure **1** was proposed. In particular, long-range proton−carbon correlations were observed between one of the methylene pairs, H1′ (δ 3.75) of the isoprenoid unit to C7 (δ 156.0), C8 (δ 125.5), and C8a (δ 117.0), thus establishing linkage of the isoprenoid unit to C8 of the 1,7-dioxyxanthone system. Furthermore, two three-bond proton−carbon correlations between H2′ (δ 5.04) and C7 (δ 156.0) and C8 (δ 125.5) support the presence of a dihydrofuran ring fused at C7 and C8 of the xanthone ring system (Figure 1). The structural assignment of compound **1** is corroborated by HR +ESI MS/MS data, where a key loss of 110 Da, i.e., [$C_3H_7O_2Cl$], was observed (Figure 2), resulting in a product ion at *m/z* 253.0499 ([M − $C_3H_7O_2Cl$]$^+$, calcd 253.0501). Thus compound **1**, named 3′,4′ deoxy-4′-chloropsoroxanthin-(3′,5′-diol), is essentially a highly substituted isoprenoid (prenylated) derivative of 1,7-dihydroxyxanthone.

The second, highly potent SOS-active xanthone **4** was isolated by repeated HPLC of the enriched SOS-active fraction from the root extract in extremely low yield (<0.1 mg). The +ESI MS spectrum indicated that **4** has a molecular mass of 326 Da. Its molecular formula was established as $C_{18}H_{14}O_6$ by HR +ESI ([M + H]$^+$ at *m/z* 327.0867, calcd 327.0869), indicating 12 degrees of unsaturation in the molecule. Its HPLC-UV spectrum (λ_{max} 242, 265, 292, 325, 396 nm) was essentially identical to that of **1**, indicative of a structural analogue having the 1,7-dioxyxanthone chromophore.[7] To achieve a superior NMR spectrum free of background impurity and solvent signals, the sample was analyzed in a LC-NMR experiment. In this manner, the ^{1}H NMR spectrum of the separated peak (D_2O−CD_3CN, 7:3, mobile phase) featured five ortho-coupled aromatic signals (one proton each), as observed in **1**, at δ 7.62 (t, J = 8.4 Hz), 7.32 (d, J = 8.4 Hz), 7.23 (d, J = 9.0 Hz), 6.94 (d, J = 8.4 Hz), and 6.71 (J = 8.4 Hz), a methine resonance at δ 5.08 (dd, J = 10.2, 7.8 Hz), a methylene doublet, δ 3.71, (2H, J = 7.2 Hz), and a methylene pair: (δ 3.85, 1H, dd, J = 18.0, 10.2 Hz; 3.63, 1H, dd, J = 17.2, 7.2 Hz). A second methylene pair (δ 2.98, 1H, d, J = 4.8 Hz; 2.86, 1H, d, J = 4.2 Hz) was highly indicative of an epoxide moiety in the molecule. The structural assignment of compound **4** is corroborated by HR +ESI MS/MS data, where a key loss of 74 Da, i.e., [$C_3H_6O_2$], was observed, resulting in a product ion at *m/z* 253.0500 ([M − $C_3H_6O_2$]$^+$, calcd 253.0501) (Figure 3). Detailed carbon−proton NMR correlation experiments were not possible due to very limited quantities available; nonetheless, the protonated carbon assignments were made possible from an HMQC experiment (Table 1). Thus, on the basis of consideration of UV data and by analogy to compound **1**, for which it was possible to acquire a more complete 2D carbon−proton NMR data set, the structure for psoroxanthin (**4**) was proposed. Due to their very low yields, the stereochemistries of **1** and **4** were not determined in this investigation.

In the course of HPLC isolation of psoroxanthin (**4**), a later eluting peak (**5**) was collected (0.8 mg). The +ESI MS spectrum indicated that **5** has a molecular mass of 312 Da. Its molecular formula was established as $C_{18}H_{16}O_5$ by HR +ESI ([M + H]$^+$ at *m/z* 313.1088, calcd 313.1076), indicating 11 degrees of unsaturation in the molecule. Its UV spectrum (λ_{max} 240, 264, 292, 320, 390 nm) was again nearly identical to that of **1** and **4**, indicative of a structural analogue having the 1,7-dioxyxanthone chromophore.[7] As in the case of **1**, long-range proton−carbon correlations were observed between the C1′ methylene protons (δ 4.03) of the isoprenoid side chain unit to C7 (δ 152.3), C8 (δ 127.1), and C8a (δ 119.1), again establishing linkage of this unit to C8 of the xanthone system. A 4′-hydroxyprenyl moiety (i.e., (*Z*)-2-methylbut-2-en-1-ol) was deduced from COSY, HMQC, and HMBC NMR spectra. In addition, the *Z*-configuration was supported from a 1D NOESY experiment, where irradiation of H2′ (δ 5.22) led to NOE enhancement of the methyl group signal H5′ (δ 1.62). The structure of **5** is thus 8-(4′-hydroxyprenyl)-1,7-dihydroxyxanthone.

The SOS-active compounds **1** and **4** were evaluated for *in vitro* cytotoxicity in a panel of tumor cell lines. In particular, **1** showed selectivity against bovine endothelial cells (ABAE; Table 2).

Psoroxanthin (**4**) is, in all likelihood, a biogenetically derived oxidation product of 8-(4′-hydroxyprenyl)-1,7-dihydroxyxanthone (**5**). On the other hand, one cannot rule out the possibility that the chlorohydrin 3′,4′-deoxy-4′-chloropsoroxanthin-(3′,5′-diol) (**1**) is an artifact of the isolation process since dichloromethane and chloroform were used in the early stages of purification.[8] Regardless of whether or not **1** is a true natural product, however, its interesting tumor cell cytotoxicity profile warrants further examination. The dihydrofuranoxanthones **1** and **4** in the present study are structurally related to the psorospermins (i.e., epoxide **6** and its chlorohydrin counterpart (**7**)) isolated from *Psorospermum febrifugum*.[9] The psorospermins were reported to have potent *in vivo* activity against P388 mouse leukemia, and mechanism of action studies have focused on their interaction with the topoisomerase II-DNA complex.[10] Large-scale reisolation and/or synthetic studies will be required for stereochemical determination and further biological evaluation of psoroxanthins **1** and **4**.

Experimental Section

General Experimental Procedures. NMR spectra were obtained on a Bruker DRX 500 MHz spectrometer equipped with a 5 mm TXI cryoprobe, or a Varian Inova 600 MHz spectrometer with a 5 mm triple resonance cold probe. Proton and carbon chemical shifts are reported in ppm relative to DMSO at δ_H 2.49 and δ_C 39.6. LC-NMR on an enriched psoroxanthin (**4**) sample was conducted with a Varian Inova 600 MHz instrument, using a YMC ODS-AQ (C18) HPLC column, 4.6 × 150 mm, 3 μm, and mobile phase D_2O−CD_3CN, 7:3, isocratic, 1.2 mL/min flow rate. Low-resolution MS and MS/MS measurements were performed by +ESI on a Thermo Scientific Finnigan SSQ7000 (single quadrupole MS), TSQ7000 (triple quadrupole MS), or LCQ Classic (ion trap MS). High-resolution MS data were determined by HR +ESI on a Thermo Scientific Finnigan MAT900 (magnetic sector MS, polypropylene glycol reference) or Orbitrap (hybrid ion trap-Fourier transform MS). IR spectra were recorded with a Perkin-Elmer System 2000 FT-IR instrument (thin film-NaCl). UV spectra were obtained using a Hewlett-Packard 8452A diode array spectrophotometer. Optical rotation data were recorded with an Autopol IV automatic polarimeter (Rudolf Research Analytical). CD data were recorded with a Jasco J-720 spectropolarimeter. Sephadex LH-20 (Pharmacia Biotech) and LiChroprep Si 60, 25–40 μm (EM Separations) were used for column chromatography. HPLC (C18) conditions: Analytical: Agilent HP-1100, Waters Corp. X-Terra 5 μm (C18) column, 4.6 × 150 mm; mobile phase: 0.01 N potassium phosphate buffer pH 3.5−acetonitrile gradient, flow rate 1.2 mL/min. UV 254 nm;[5b] Preparative: Beckman System Gold workstation, YMC ODS-A 5 μm (C18) column, 20 × 100 mm. For TLC biogram (SOS) analyses, silica gel plates (Analtech, 0.25 mm) with chloroform−methanol mixtures (i.e., 95:5 v/v) as the mobile phase were used. For HPLC biogram (SOS) analyses, fractions were collected into Beckman 96-deep-well plates using a Gilson 215 liquid handler and dried under a nitrogen stream prior to bioassay. Methods for the *E. coli* SOS chromotest and tumor cell cytotoxicity assays have been described previously.[2,4]

Plant Material. The plant *Psorospermum* cf. *molluscum* (Pers.) Hochr. (Hypericaceae) (vernacular name Fanterana) was collected by botanists from the Missouri Botanical Gardens (St. Louis, MO) under the direction of Chris Birkinshaw, from an area of Madagascar known

Table 1. NMR Spectral Data for Xanthones **1**, **4**, and **5** in DMSO-d_6[a]

	1		**4**		**5**	
position	^{13}C[b]	^{1}H[b,c] (J, Hz)	^{13}C[b]	^{1}H[b,c,d] (J, Hz)	^{13}C[b]	^{1}H[b,c] (J, Hz)
1	160.8				155.6	
1-OH		12.59 (1H, s)				12.96 (1H, s)
2	109.5	6.78 (1H, d, (8.5))	110.5	6.72 (1H, d, (8.2))	110.1	6.71 (1H, d, (8.0))
3	137.2	7.71 (1H, t, (8.3))	138.3	7.64 (1H, t, (8.3))	137.4	7.63 (1H, t, (8.2)
4	107.0	7.03 (1H, d, (8.0))	108.0	6.96 (1H, d, (8.4))	107.3	6.94 (1H, d, (8.5))
4a	155.9				162.0	
4b	150.2				151.7	
5	117.0	7.44 (1H, d, (9.0))	118.4	7.38 (1H, d, (8.7))	117.1	7.36 (1H, m)
6	117.3	7.37 (1H, d, (9.0))	118.0	7.30 (1H, d, (8.8))	124.7	7.36 (1H, m)
7	156.0				152.3	
8	125.5				127.1	
8a	117.0				119.1	
9	182.7				185.0	
9a	108.3				109.5	
1′	31.1	3.75 (2H, dd, (9.0, 3.0))	33.8	3.63 (1H, m) 3.85 (1H, m)	25.3	4.03 (2H, d, (6.9))
2′	85.2	5.04 (1H, t, 9.3)	83.8	5.10 (1H, dd, (10.2, 7.8))	124.6	5.22 (1H, t, 6.9)
3′	74.7				136.0	
4′	46.4	3.84 (2H, s)	48.0	2.74 (1H, d, (5.0)) 2.86 (1H, d, (5.0))	60.5	4.17 (2H, s)
5′	61.2	3.46 (1H, d, 11.0) 3.53 (1H, d, 11.0)	61.6	3.57 (1H, m) 3.60 (1H, m)	27.0	1.62 (3H, s)

[a] Assignments based on HMQC, HMBC. [b] Chemical shifts (δ) in ppm. [c] s: singlet, d: doublet, t: triplet, dd: doublet of doublets, m: multiplet. [d] HMQC data were acquired on an enriched sample of **4** prior to LC-NMR.

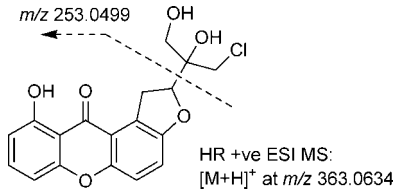

Figure 2. MS/MS fragmentation of **1**.

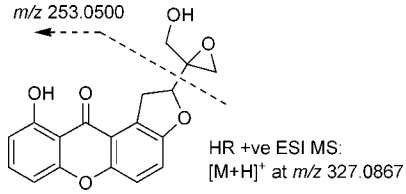

Figure 3. MS/MS fragmentation of **4**.

Table 2. Cytotoxicity Data for Xanthones **1** and **4** (IC_{50}'s (μM))

cell line	**1**	**4**
A2780	0.042	0.33
HCT-116	0.068	1.0
ABAE	0.004	0.102
SKBR3	2.0	not tested

as Fianarantsoa, in the vicinity of the Ranomafana National Park, at a height of 1200 m in June 1996. Voucher samples (NCI collection numbers Q66V4221 (roots), Q66V4223 (wood stems)) are held at Missouri Botanical Gardens and at the National Herbarium, Smithsonian Institution, Washington, D.C.

Extract Preparation. The plant parts (roots, wood stems) were separated and air-dried, ground in a ball mill, and extracted at room temperature by soaking overnight in dichloromethane−methanol, 1:1 (v/v), followed by methanol. The extracts from each plant part were pooled, dried under vacuum, and stored at −20 °C. The dried extracts N92955 (roots) and N94711 (wood stems) were shipped to BMS-Wallingford for isolation studies.

Isolation. The crude extract from wood stems (1.0 g) was dissolved in methanol–water, 9:1 (100 mL), and extracted three times with equal volumes of *n*-hexane. The aqueous methanol layer was diluted with 20 mL of water to give a 3:1 methanol–water ratio and extracted three times with equal volumes of toluene. The aqueous methanol phase was further diluted with 18 mL of water to give a 65:35 methanol–water ratio, and then extracted three times with presaturated chloroform. TLC bioautography of all fractions using the SOS chromotest revealed prominent zones of inhibition in the toluene extract (71 mg). The remaining available extract (8 g) was processed as above, giving 706 mg of additional toluene extract. The toluene extracts were pooled and subjected to silica gel VLC. The extract was preadsorbed onto 2 g of Merck LiChroprep silica gel 60 (25–40 μm) and applied to a 2.5 × 15 cm fritted filter funnel packed with 15 g of silica gel. Elution using house vacuum was carried out with hexane, followed by 3:1, 1:1, and 1:3 hexane−chloroform, then chloroform, and then 98:2 (2 times), 95:5, and 90:10 v/v chloroform−methanol (all 100 mL fractions). TLC bioautography revealed strong SOS activity in the initial 98:2 chloroform−methanol fraction (198 mg). This fraction (75 mg portion) was subjected to repeated preparative C18 HPLC, using a mobile phase of 0.01% aqueous trifluoroacetic acid (TFA)−acetonitrile, 60:40, with a concave gradient to acetonitrile over a period of 20 min, flow rate 20 mL/min, UV detection 254 nm. This afforded the new psoroxanthin chlorohydrin **1** (10 min peak, 4.8 mg), as well as 2-hydroxyxanthone **2** (4.6 min peak, 6.6 mg), and 1,7-dihydroxyxanthone **3** (7.8 min peak, 22.4 mg).

The crude extract from roots (11 g) was dissolved in 9:1 methanol–water (100 mL) and extracted three times with equal volumes of *n*-hexane. The aqueous methanol layer was diluted with 38 mL of water to give a 65:35 methanol–water ratio and extracted three times with equal volumes of presaturated chloroform. The SOS-active chloroform extract (1.47 g) was subjected to Sephadex LH-20 chromatography using 1:1 chloroform−methanol eluant. The SOS-active fractions were pooled (422 mg) and further chromatographed by silica gel VLC as previously described. The peak of SOS activity was in the chloroform fraction (11.9 mg), and this was subjected to preparative HPLC as previously described, affording 2-hydroxyxanthone (**2**) (4.4 min peak, 2.6 mg) and 8-(4′-hydroxyprenyl)-1,7-dihydroxyxanthone (**5**) (10.5 min peak, 0.8 mg). The peak of SOS activity was detected in a minor, broad peak (7.9−9.1 min, 0.2 mg). Final purification of this SOS-active peak in the course of an LC-NMR experiment afforded psoroxanthin (**4**) (<0.1 mg). Known xanthones **2** and **3** were identified by comparison of their UV, NMR, and MS spectra with published data.[6,7]

Psoroxanthin chlorohydrin (3′,4′-deoxy-4′-chloropsoroxanthin-3′,5′-diol) (1): yellow solid; $[\alpha]_D^{20}$ −103 (*c* 0.08, MeOH); UV (MeOH) λ_{max} 243 (ϵ 23 200), 264 (29 800), 292 (4400), 325 (3400), 396 (4600); CD λ nm ($\Delta\epsilon$) (MeOH) 240 (−4.5), 262 (−4.3), 290 (0), 329 (−0.6), 403 (−0.3); IR ν_{max} 3445, 2936, 1642, 1605, 1585, 1478, 1462, 1365, 1337, 1278, 1219, 1056, 1038, 978, 816, 759 cm^{-1}; ^{1}H and ^{13}C NMR, see Table 1; HR +ESI MS, $C_{18}H_{15}O_6Cl$, $[M + H]^+$ at *m*/*z* 363.0634, calcd 363.0635.

Psoroxanthin (4): yellow solid; HPLC-UV (aqueous CH_3CN) λ_{max} 242, 265, 292, 325, 396 nm; ^1H and ^{13}C NMR, see Table 1; HR +ESI MS, $C_{18}H_{14}O_6$, $[M + H]^+$ at *m*/*z* 327.0867, calcd 327.0869.

8-(4′-hydroxyprenyl)-1,7-dihydroxyxanthone (5): yellow solid; UV (MeOH) λ_{max} 240 (ϵ 17 500), 264 (21 100), 292 (4500), 320 (2800), 390 (3600); IR ν_{max} 3389, 2966, 1683, 1645, 1603, 1486, 1463, 1384, 1291, 1265, 1225, 1153, 1057, 981, 818, 758 cm^{-1}; ^1H and ^{13}C NMR, see Table 1; HR +ESI MS, $C_{18}H_{16}O_5$, $[M + H]^+$ at *m*/*z* 313.1088, calcd 313.1076.

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Supporting Information Available: Complete NMR spectral data for compounds **1**, **4**, and **5** are available free of charge via the Internet at http://pubs.acs.org.

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