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NEW MONOMERIC AND DIMERIC HYDROLYZABLE TANNINS FROM *TAMARIX NILOTICA*¹

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Abstract – Two new ellagitannin monomers, nilotinins M2 (**4**) and M3 (**5**), two new dimers, nilotinins D4 (**6**), D5 (**7**), and a known dimer (**8**), were isolated from an aqueous acetone extract of dried leaves of *Tamarix nilotica* (Ehrenb.) Bunge. Structures of **4–7** were determined based on spectral data and chemical correlations with known tannins. The known dimer **8** was isolated from a plant extract for the first time; its ¹H and ¹³C assignments are also reported here.

INTRODUCTION

Early studies on tannins from tamaricaceous plants revealed the occurrence of a unique class of hydrolyzable tannins with vast structural diversity, including those with hellinoyl, dehydrodigalloyl (DHDG), isodehydrodigalloyl (isoDHDG), and macrocyclic structures.^{2–7} We have recently investigated tannin constituents of *T. nilotica* grown in Egypt (Tamaricaceae) and reported the isolation of a new ellagitannin monomer, nilotin M1, three new dimers, nilotinins D1 (**1**), D2, and D3, and six known ellagitannins, hirtellin A, remurin A (**2**), remurin B, gemin D, hippomanin A, and 1,3-di-O-galloyl-4,6-O-(S)-hexahydroxydiphenoyl-β-D-glucose (**3**) (Figure 1).¹ Continued investigation of tannins from this plant species led to the isolation of two additional unique ellagitannin monomers (**4**, **5**), and three dimers (**6–8**) belonging to three different types of tannins. This paper deals with these five tannins.

[†]Dedicated to Professor Emeritus Akira Suzuki, Hokkaido University, on the occasion of his 80th birthday.

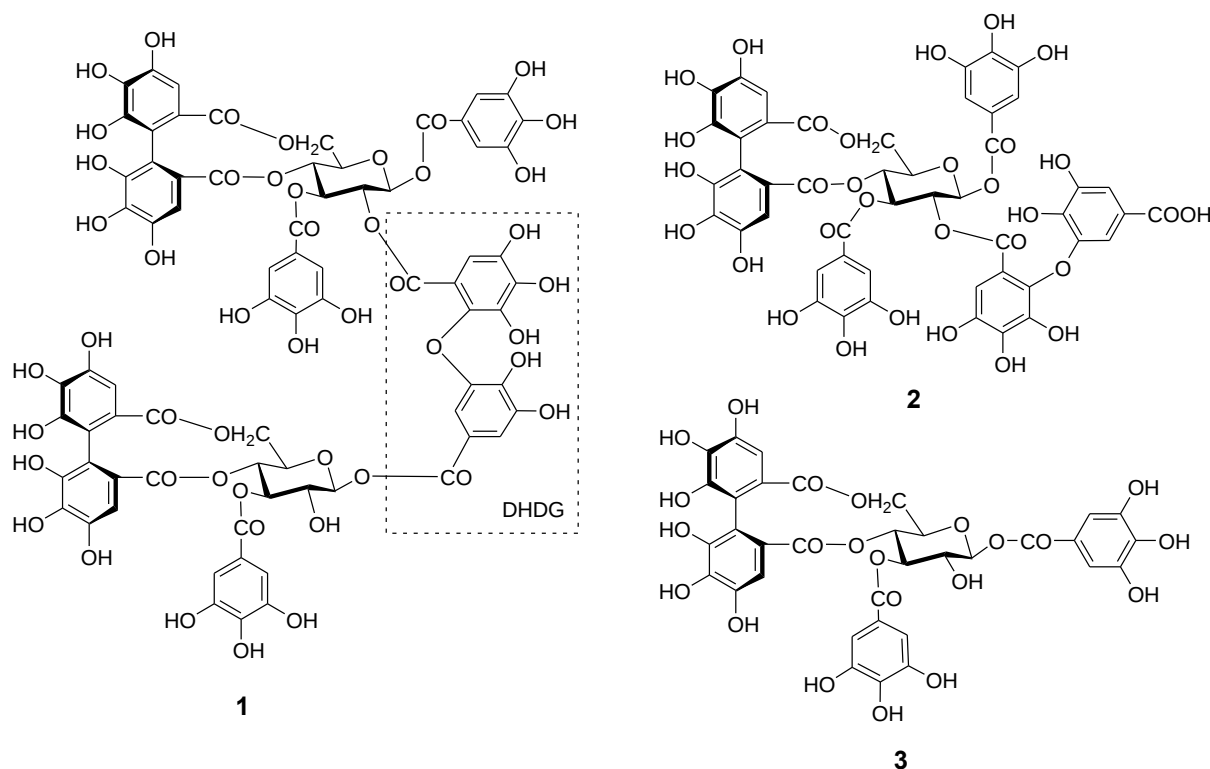


Figure 1. Previously reported hydrolyzable tannins isolated from *Tamarix nilotica*.¹

RESULTS AND DISCUSSION

The eluate with 40% aq. MeOH from a Dia-ion HP-20 column of a concentrated extract of the dried leaves of *T. nilotica* was subjected to a combination of column chromatography on Toyopearl HW-40, Sephadex LH-20, and MCI-gel CHP-20P, followed by preparative reverse-phase HPLC, to afford ellagitannins (**4–8**) (Figures 2 and 3).

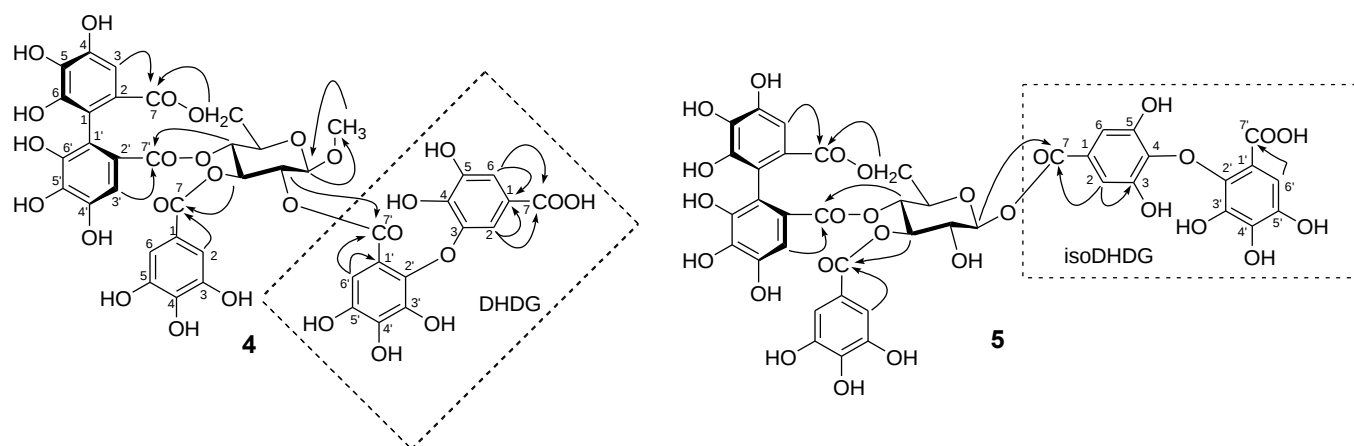


Figure 2. Structures of new monomeric hydrolyzable tannins, **4** and **5**.

The arrows (H→C) indicate HMBC correlations.

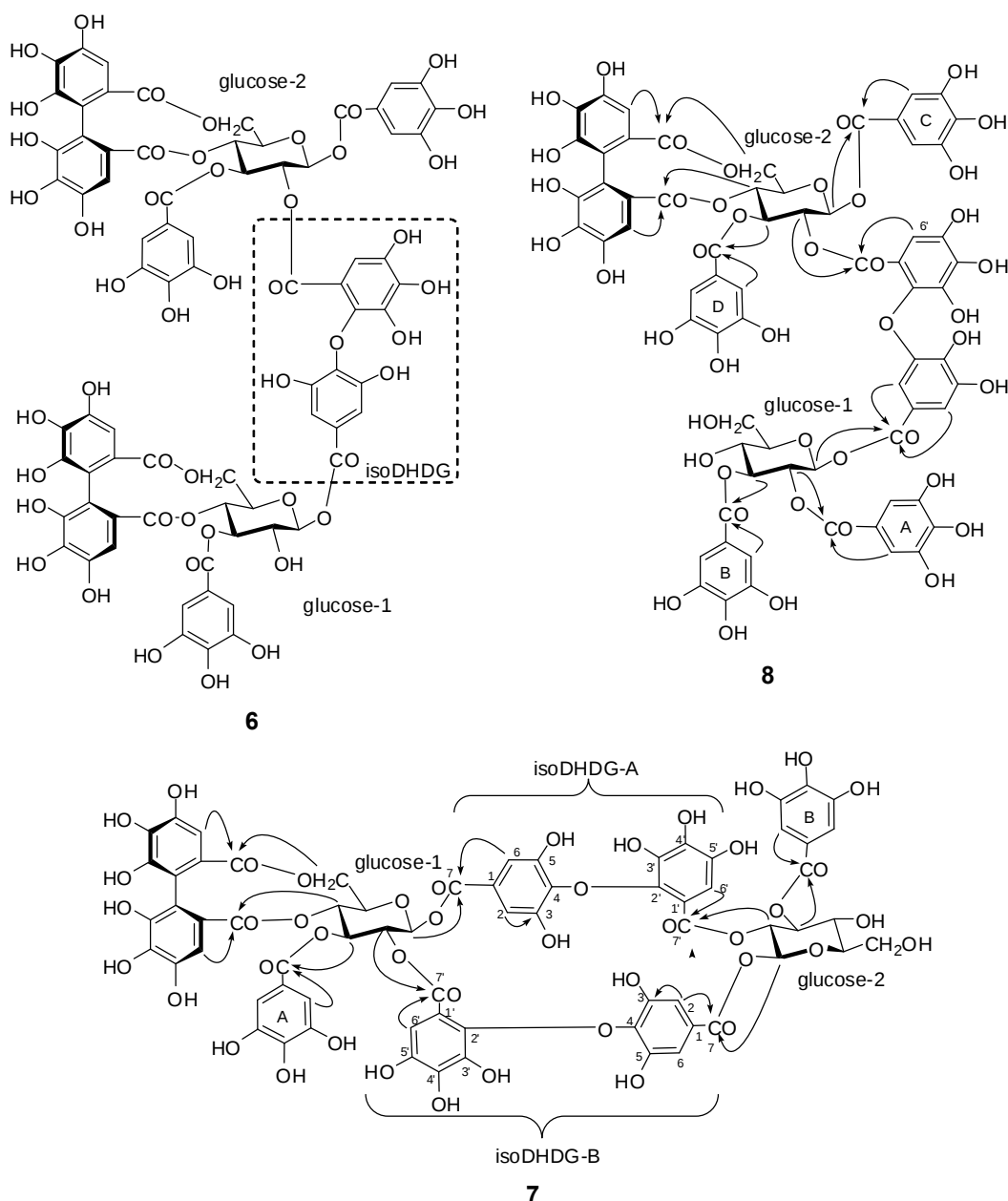


Figure 3. Structures of new dimeric hydrolyzable tannins, **6-8**.

The arrows (H→C) in formulae **7** and **8** indicate HMBC correlations.

Structure of nilotin M2

Nilotin M2 (**4**) was isolated as an off-white amorphous powder. Its ^1H NMR spectrum displayed a pair of *m*-coupled signals [δ 7.24, 6.62 (each 1H, d, $J = 2.0$ Hz)], and a 1H singlet (δ 7.05), which is the characteristic pattern for a DHDG unit.^{1,3} The spectrum also displayed a 2H singlet (δ 6.92), and two 1H singlets (δ 6.60 and 6.48), which indicate the presence of a galloyl and a hexahydroxydiphenoyl (HHDP) groups, respectively.¹⁻⁷ A system of seven aliphatic proton signals (δ 5.41–3.83) with large coupling constants ($J_{1,2} = 8$ Hz, $J_{2,3} = J_{3,4} = J_{4,5} = 10$ Hz) indicated a β -glucose core with a *C1* conformation (Table 1).

Table 1. ^1H NMR spectral data of glucose cores of **4-8** (600 MHz, acetone- d_6 - D_2O , 9:1, J in Hz).

	4	5	6	7	8
Glucose-1					
H-1	4.00, d ($J = 8$)	5.87, d ($J = 8$)	5.89, d ($J = 8$)	6.05, d ($J = 8$)	5.90, d ($J = 8$)
H-2	5.15, dd ($J = 8, 10$)	4.00, dd ($J = 8, 10$)	4.03, dd ($J = 8, 10$)	5.531, dd ($J = 8, 10$)	5.35, dd ($J = 8, 10$)
H-3	5.41, t ($J = 10$)	5.45, t ($J = 10$)	5.46, t ($J = 10$)	5.73, t ($J = 10$)	5.523, t ($J = 10$)
H-4	5.00, t ($J = 10$)	5.03, t ($J = 10$)	5.05, t ($J = 10$)	5.17, t ($J = 10$)	3.91, t ($J = 10$)
H-5	4.00, dd ($J = 6.5, 10$)	4.33, dd ($J = 6.5, 10$)	4.34, dd ($J = 6.5, 10$)	4.44, dd ($J = 6.5, 10$)	3.80, ddd ($J = 2, 5.5, 10$)
H-6	5.23, dd ($J = 6.5, 13$)	5.26, dd ($J = 6.5, 13$)	5.26, dd ($J = 6.5, 13$)	5.29, dd ($J = 6.5, 13$)	4.00 dd ($J = 2, 12$)
	3.83, d ($J = 13$)	3.81, d ($J = 13$)	3.82, d ($J = 13$)	3.83, d ($J = 13$)	3.85, dd ($J = 5.5, 12$)
Glucose-2					
H-1			6.04, d ($J = 8$)	5.94, d ($J = 8$)	5.44, d ($J = 8$)
H-2			5.63, dd ($J = 8, 10$)	5.32, dd ($J = 8, 10$)	5.521, dd ($J = 8, 10$)
H-3			5.76, t ($J = 10$)	5.530, t ($J = 10$)	5.60, t ($J = 10$)
H-4			5.19, t ($J = 10$)	3.91, t ($J = 10$)	5.11, t ($J = 10$)
H-5			4.45, dd ($J = 6.5, 10$)	3.72, ddd ($J = 2, 5.5, 10$)	4.24, dd ($J = 6.5, 10$)
H-6			5.29, dd ($J = 6.5, 13$)	3.87, dd ($J = 2, 12$)	5.26, dd ($J = 6.5, 13$)
			3.84, d ($J = 13$)	3.75, dd ($J = 5.5, 12$)	3.81, d ($J = 13$)

Additionally, the aliphatic region of the spectrum also displayed a 3H singlet signal (δ 3.07), ascribable to a methoxy group. The high resolution (HR) ESIMS of **4** exhibited an $[\text{M} + \text{Na}]^+$ ion peak, corresponding to a molecular formula of $\text{C}_{42}\text{H}_{32}\text{O}_{27}$, consistent with the structural moieties. The presence of these constructing units of **4** was further confirmed by corresponding carbon peaks (Table 2 and experimental section) in the ^{13}C NMR spectrum. A large difference in chemical shifts of the H-6 *gem*-protons (δ 5.23 and 3.83) indicated the location of the HHDP group at O-4/O-6 of the glucose core. An upfield shift (δ 4.00) of the resonance of the glucose anomeric proton relative to that of a related monomer, remurin A (**2**) (δ 5.53),^{1,3} suggested methylation, rather than galloylation, of the glucose O-1. A methoxy group at C-1 of

Table 2. ^{13}C NMR spectral data of the glucose cores of **4**, **5**, **7**, and **8** (151 MHz, acetone- d_6 - D_2O , 9:1).

	4	5	7	8
Glucose-1				
C-1	102.9	95.9	93.4	93.3
C-2	72.6	72.0	72.0	71.9
C-3	73.9	75.6	73.4	75.9
C-4	70.8	70.6	70.6	68.8
C-5	71.9	72.7	72.8	78.2
C-6	63.2	63.2	63.1	61.6
Glucose-2				
C-1			93.2	93.5
C-2			72.1	71.6
C-3			76.3	73.5
C-4			68.8	70.5
C-5			78.1	72.8
C-6			61.4	63.0

the glucose core was demonstrated by a heteronuclear multiple-bond coherence (HMBC) correlation of its proton signal (δ 3.07) with the glucose anomeric carbon peak (δ 102.9) and correlations of the glucose anomeric proton signal with both the glucose anomeric carbon and the methoxy carbon (δ 56.9). In the HMBC spectrum, correlations of the DHDG singlet signal [δ 7.05 (H-6')] with the glucose H-2 signal (δ 5.15) via a common carbonyl carbon peak [δ 164.5 (C-7')] substantiated the location of the DHDG unit at O-2 of the glucose core. On the other hand, correlations of the remaining proton signals [δ 7.24 (H-6) and 6.62 (H-2)] of the DHDG unit with a carboxyl carbon peak [δ 168.1 (C-7)], combined with the absence of correlation with any of the glucose proton signals to this carbon confirmed an identical orientation of the DHDG unit in **4** to that in **2**. Similarly, the location of the galloyl group at O-3 of the glucose core was also evidenced by two HMBC correlations of the galloyl proton signal (δ 6.92) and the glucose H-3 signal (δ 5.41) with the common carbonyl carbon peak (δ 166.9). Correlations among the HHDP proton signals (δ 6.60 and 6.48) and the glucose H-4 (δ 5.00) and H-6 (δ 5.23) signals through the common ester carbonyl carbon peaks (δ 167.8) and (δ 168.4), respectively, were also observed (Figure 2). The HMBC spectrum also substantiated the assignments of the carbon signals in Table 2 and in the experimental section. The CD spectrum of **4** showed a positive Cotton effect in the short wavelength region, indicating the *S* configuration of the HHDP group.⁸ Based on these data, nilotinin M2 was assigned structure **4**. The occurrence of methyl glucoside, the sugar core in nilotinin M2, as a natural compound in higher plants has been reported,^{9,10} while 1-*O*-methyl derivative of a *C*-glycosidic tannin has been suggested to be an artifact.¹¹ Although nilotinin M2 may be an artifact, this is the first report of methylated ellagitannins in tamaricaceous plants.

Structure of nilotinin M3

Nilotinin M3 (**5**) was isolated as an off-white amorphous powder and exhibited an $[M + Na]^+$ ion peak in HRESIMS, indicating its molecular formula to be $C_{41}H_{30}O_{27}$. Its 1H NMR spectrum exhibited a 2H (7.16), and a 1H (δ 6.90) singlets, which are characteristic of an isoDHDG unit.^{1,4,5} The spectrum also showed the proton signals at δ 7.03 (2H, s; galloyl), and δ 6.60 and 6.47 (each 1H, s; HHDP) in the aromatic region.⁵ The presence of seven aliphatic signals in the range δ 5.87–3.82, with coupling constants identical to those of **4**, indicated a β -glucose core with a *C1* conformation (Table 1). The presence of these acyl units as well as the glucose core was also confirmed by their carbon signals shown in Table 2 and the experimental section. The appearance of the H-2 signal of the glucose core in the higher field (δ 4.00) relative to that of **4** (δ 5.15) indicates an unacylated OH-2 of the glucose core of **5**. The 1H - 1H COSY data for **5** revealed resonances of H-6 *gem*-protons at δ 5.26 and 3.81 indicating the location of the HHDP group at O-4/O-6 of the glucose core. In the ^{13}C NMR spectrum of **5**, a carbon peak at δ 150.7 was assigned to isoDHDG C-3 (C-5), because C-3 (C-5) of an isoDHDG unit resonates at lower field shift than the C-3 (C-5) of the usual galloyl (at around δ 145.7), which is attributed to the formation of the ether linkage at the *p*-hydroxyl group in the isoDHDG moiety.¹ Consequently, a 2H singlet signal (δ 7.16) was assigned to the isoDHDG moiety (H-2, H-6) based on the two-bond HMBC correlation of the proton signal with the carbon peak (δ 150.7) of C-3 (C-5) of the same moiety (see the formula **5** in Figure 2).¹ The correlations of this aromatic proton signal with the glucose H-1 signal (δ 5.87) via the common ester carbonyl carbon [δ 165.3 (C-7)] substantiated the location of the isoDHDG unit at O-1 of the glucose core. A carbonyl carbon peak (δ 170.7) was assigned to the isoDHDG unit (C-7') based on the HMBC connectivity of its 1H singlet [δ 6.90 (H-6')] with this carbon signal. The absence of correlation between any of the glucose proton signals and this carbon confirmed the orientation of the isoDHDG unit, as shown in **5** (Figure 2). Placements of the galloyl and HHDP groups on the glucose core were further confirmed by the HMBC correlations, as represented by the arrows in Figure 2. A positive Cotton effect, $[\theta]_{237} +9.3 \times 10^4$ in the CD spectrum of **5**, indicated the *S* configuration of the HHDP group. Based on these data, structure **5** was proposed for nilotinin M3. This is the first reported monomeric ellagitannin with an isoDHDG unit at the anomeric center of its glucose core.

Structure of nilotinin D4

Nilotinin D4 (**6**) was isolated as an off-white amorphous powder. Its molecular formula was determined to be $C_{75}H_{54}O_{48}$ by HRESIMS. The 1H NMR spectrum of **6** exhibited proton signals δ 7.07, 7.04, 7.02, 6.97 (each 2H, s), and δ 6.77 (1H, s) attributable to three galloyl groups and an isoDHDG unit. Additionally, proton signals at δ 6.61, 6.60, 6.48, and 6.47 were assignable to two HHDP groups. In the aliphatic region of the spectrum, two seven-spin systems with large coupling constants (Table 1) were

characteristic of two β -glucose cores with *C1* conformations. The ^1H - ^1H COSY data indicated that one (glucose-2) of these glucose cores was fully acylated, whereas the hydroxyl group at C-2 of the other (glucose-1) was unacylated, as indicated by the H-2 resonance at higher field (δ 4.03) relative to the corresponding signal of glucose-2. Two HHDP moieties in the molecule were assigned to be at O-4/O-6 of the glucose cores, in a way analogous to those in **4** and **5**. The identical chemical shifts of the glucose-1 proton signals to those of nilotinin M3 (**5**; Table 1) suggested the presence of **5** in the dimeric structure of **6**. Based on these data, structure **6** was assumed to be a structure isomeric to **1**, through replacement of the DHDG linking unit in **1** with the isoDHDG in **6**. Because modification of the less stable isoDHDG unit into the more stable DHDG one through the Smiles rearrangement under weak alkaline conditions has been reported for some hydrolyzable tannins,^{1,4,5} this reaction was applied to **6**. Conversion of **6** into **1**, as shown in the experimental section, satisfied structure **6** for nilotinin D4, including the *S* configuration of the HHDP units. Nilotinin D4 was presumed to be biologically derived from the co-existing monomers **3** (Figure 1) and **5** (Figure 2) through an esterification of the free carboxyl group of the isoDHDG unit of **5** with the glucose OH-2 of **3**.

Structure of nilotinin D5

Nilotinin D5 (**7**) was isolated as an off-white amorphous powder. Its dimeric molecular formula was established as $\text{C}_{68}\text{H}_{50}\text{O}_{44}$ by HRESIMS, along with the spectral data shown below. The aromatic region of the ^1H NMR spectrum of **7** exhibited eight signals due to two galloyl groups [δ 7.13 and 7.03 (each 2H, s)], an HHDP group [δ 6.61 and 6.49 (each 1H, s)], and two isoDHDG units [δ 6.770 and 6.769 (each 2H, s), and 6.51 and 6.493 (each 1H, s)]. In the aliphatic region of the spectrum, signals of two glucose cores (Table 1) having β -configuration and adopting *C1* conformations were seen. The ^{13}C NMR spectrum exhibited aromatic, carbonyl, and aliphatic carbon peaks consistent with these units (see Table 2 and the experimental section). An HHDP unit in **7** locates O-4/O-6 of glucose-1, as indicated by the large chemical shift difference between H-6 methylene protons (δ 5.29 and 3.83), whereas OH-4 and OH-6 of glucose-2 were assigned to be unacylated based on the upfield shifts (δ 3.75–3.91) of H-4 and H-6. Thus, the remaining acyl groups should be at O-1–O-3 of each glucose core. The HMBC spectrum of **7** showed correlations of galloyl proton signals (δ 7.13 and 7.03) with signals of H-3 of glucose-2 (δ 5.32) and H-3 of glucose-1 (δ 5.73) through the ester carbonyl carbons (δ 167.3 and 167.0), respectively. Consequently, **7** was assigned to have a macrocyclic structure in which each of the two isoDHDG units links between O-1 of one glucose core and O-2 of the other glucose core. The mode of the attachments of the isoDHDG units in **7** was confirmed by the HMBC connectivities of two 2H singlet signals (δ 6.769 and 6.770) of the isoDHDG units (H-2, H-6) with H-1 of glucose-1 (δ 6.05) and H-1 of glucose-2 (δ 5.94) through the common ester carbonyl carbons (δ 164.8 and 165.2) (C-7), respectively. Similarly, connectivities of the

two ^1H singlet signals (δ 6.51 and 6.493) of the isoDHDG units (H-6') with H-2 of glucose-2 (δ 5.32) and H-2 of glucose-1 (δ 5.531) through the respective ester carbonyl carbons (δ 166.7 and 166.8) (C-7') were consistent with this attachment mode. The other HMBC correlations explained by the arrows in Figure 3 were also consistent with the proposed structure. The atropisomerism of the chiral HHDP group in **7** was determined to be *S* based on the strong, positive Cotton effect at 236 nm in the CD spectrum. Nilotinin D5 is therefore represented by structure **7**, which corresponds to a des-HHDP derivative of tamarixinin B (**9**)⁵ (Figure 4), where O-4/O-6 of one of the glucose cores are unacylated. The *Mr* of **7**, demonstrated by an $[\text{M} + \text{Na}]^+$ ion peak at m/z 1593, was 302 mass units (HHDP) less than **9**. This is consistent with the structural correlation.

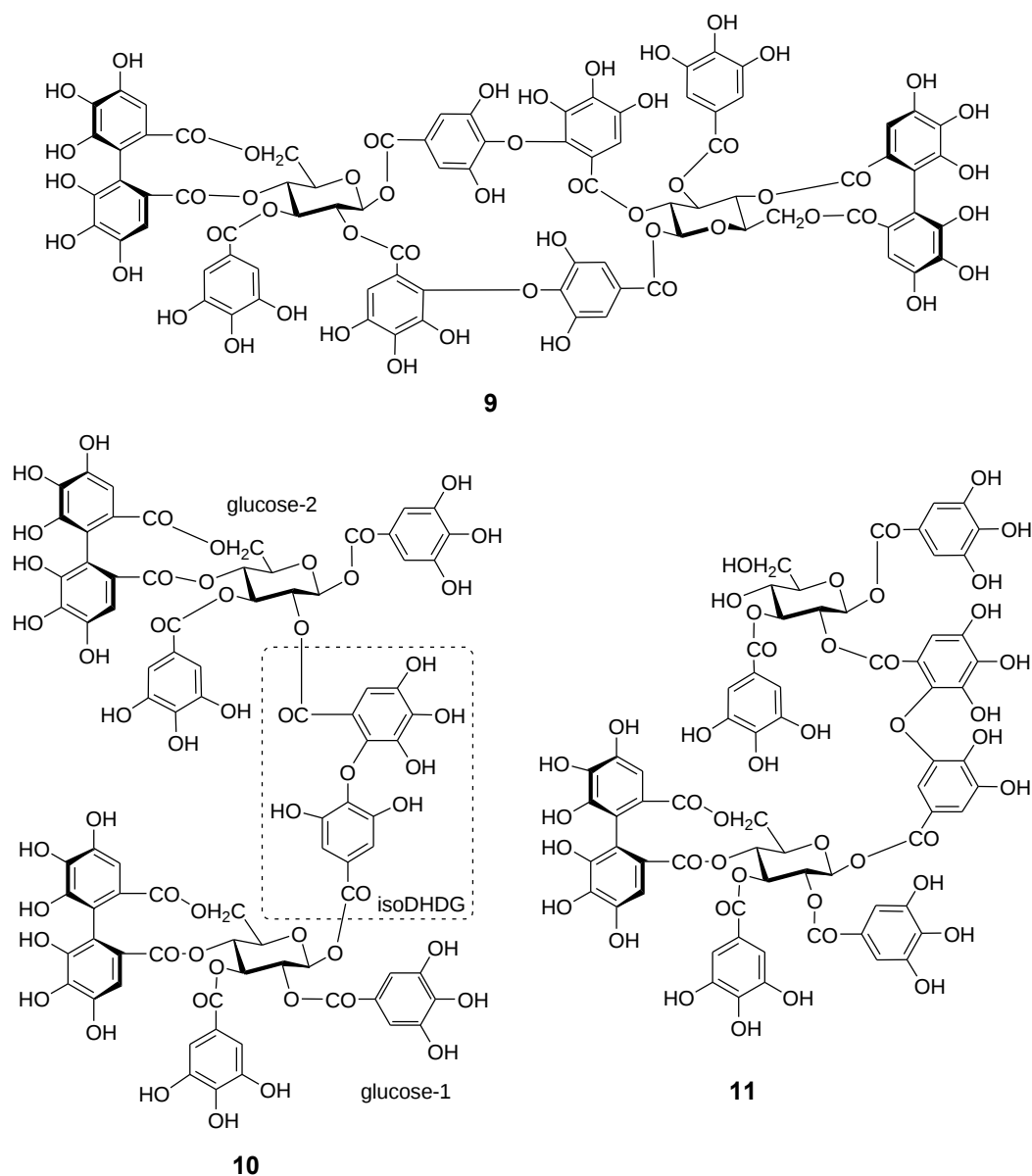


Figure 4. Structures of hydrolyzable tannins, **9-11**.

The isoDHDG 1H singlets (H-6') in **7** resonated at δ 6.51 and 6.493, which is shifted upfield (*ca.* 0.4 ppm) relative to the corresponding proton signals of the isoDHDG units in the linear tannins **5**, **6**, and tamarixinin C (**10**) (Figure 4) (δ 6.84).⁵ Further, the corresponding protons of the isoDHDG units in **9** also showed analogous upfield shifts (δ 6.54).⁵ The upfield shifts of the isoDHDG 1H singlets in **7** and **9** could be attributed to the shielding effect of the aromatic ring, bearing two protons, of the isoDHDG units in these macrocyclic structures.

Structure of nilotinin D6

Nilotinin D6 (**8**) was isolated as an off-white amorphous powder, for which the molecular formula, C₆₈H₅₂O₄₄, was established by HRESIMS, along with the spectral data below. The ¹H NMR spectrum of **8** showed the presence of four galloyl groups [δ 7.028, 6.97, 6.94, 6.93 (each 2H, s)], a DHDG unit [δ 7.11 and 6.37 (each 1H, d, *J* = 2Hz), and 7.027 (1H, s)], an HHDP group [δ 6.58 and 6.50 (each 1H, s)], and two glucose cores in the β -configuration and the *C1* confirmation (Table 1). These are the same structural units as in hirtellin G (**11**) (Figure 4).⁶ The ¹³C NMR spectral data (Table 2 and experimental section) of **8** are consistent with these units. The ¹H-¹H COSY data listed in Table 1 indicated the location of the HHDP group at O-4/O-6 of glucose-2. The HMBC spectrum of **8** exhibited correlations of the DHDG proton signals [δ 7.11, 6.37 (each 1H, d) and 7.027 (1H, s)] and the galloyl-C (see formula in Figure 3) proton signal (δ 6.97) with H-1 of glucose-1 (δ 5.90), H-2 of glucose-2 (δ 5.521) and H-1 of glucose-2 (δ 5.44) through a non-differentiated cluster of ester carbonyl carbon peaks (δ 164.7, 3C). Resonance of the glucose-2 anomeric proton showed an upfield shift (δ 5.44) relative to that of glucose-1 (δ 5.90), which is explained by the anisotropic effect of the galloyl part, bearing an isolated proton (H-6'), of the DHDG unit at O-2 of glucose-2.³ The binding mode of the DHDG unit in **8** was thus determined to be identical to that in **11**. Other important HMBC correlations are shown by the arrows in Figure 3 and are consistent with structure **8**. The CD spectrum of **8** indicated the *S* configuration of the HHDP group. Based on these data, structure **8**, a regioisomer of **11** concerning the position of the HHDP group, was assigned for nilotinin D6. Although the ¹H NMR spectral data for **8** are identical to those reported for a hydrolysate from hirtellin A (hydrolysate-2),⁶ its physicochemical data, including [α]_D, UV, and CD, as well as the detailed aromatic proton and full carbon assignments, are reported for the first time in this paper. Similar to other tamaricaceous plants,²⁻⁷ *T. nilotica* produces DHDG, isoDHDG, and macrocyclic ellagitannins. This emphasizes the chemotaxonomic importance of these tannins.

EXPERIMENTAL

General procedures. HRESIMS were performed using a Bruker MicroTOF-Q spectrophotometer with positive ion mode. FABMS was performed using an Auto Spec OA-Tof spectrophotometer.

m-Nitrobenzyl alcohol was used as the matrix agent. Normal-phase HPLC was conducted on a YMC-Pack SIL A-003 (YMC, Japan) column (4.6 i.d. $\times$ 250 mm) developed with *n*-hexane–MeOH–tetrahydrofuran–formic acid (47:39:13:1) containing oxalic acid (450 mg/L; flow rate, 1.5 mL/min; 280 nm UV detection) at room temperature. Analytical reverse-phase HPLC was performed on a YMC-Pack ODS-A A-303 (YMC) column (4.6 i.d. $\times$ 250 mm) developed with 0.01 M H₃PO₄–0.01 M KH₂PO₄–MeOH (2:2:1; flow rate, 1 mL/min; 280 nm UV detection) at 40 °C. Preparative reverse-phase HPLC was performed on a YMC-Pack ODS-A A-324 (YMC) column (10 i.d. $\times$ 300 mm) developed with 0.01 M H₃PO₄–0.01 M KH₂PO₄–MeOH (2:2:1; flow rate, 2 mL/min; 280 nm UV detection) at 40 °C. The plant materials (*T. nilotica*), other instruments, and chromatographic methods used in this study have been described previously.¹

Extraction and isolation. The 40% MeOH fraction (10.4 g), previously obtained from a 70% aq. acetone homogenate of the dried leaves of *T. nilotica* (200 g), was chromatographed over a Toyopearl HW-40 column (coarse grade, 2.2 i.d. $\times$ 43 cm) with 70% EtOH, 70% EtOH–70% acetone (9:1 $\rightarrow$ 8:2 $\rightarrow$ 7:3 $\rightarrow$ 5:5, v/v), and 70% acetone, collecting 1000-drop fractions (Tfrs). Separation of the respective fractions was achieved by monitoring either normal- or reverse-phase HPLC. The 70% EtOH eluate (Tfrs. 70–97, 240 mg) was applied to MCI gel CHP-20P column (1.1 i.d. $\times$ 22 cm) eluted with aqueous MeOH (10% $\rightarrow$ 20% $\rightarrow$ 25% $\rightarrow$ 30% $\rightarrow$ 40%, v/v). Nilotinin D6 (**8**) (2 mg) was purified from the 25% MeOH eluates (26 mg) by preparative HPLC. Tfrs. 98–190 (1.7 g) was further chromatographed over Sephadex LH-20 column (2.2 i.d. $\times$ 32 cm) with 70% EtOH, collecting 700-drop fractions, and yielded Sfrs. Sfrs. 46–59 (216 mg) was rechromatographed on the same column with 70% EtOH followed by preparative HPLC purification to give nilotinin D5 (**7**) (4 mg). Tfrs. 191–218 (285 mg) was subjected to column chromatography over MCI gel CHP-20P (1.1 i.d. $\times$ 35 cm) eluted with H₂O $\rightarrow$ aqueous MeOH (10% $\rightarrow$ 20% $\rightarrow$ 30% $\rightarrow$ 40%, v/v). The 40% MeOH eluate was purified by preparative HPLC giving nilotinin D4 (**6**) (2 mg). In a separate experiment and guided by the first one, extraction and fractionation for the same dried leaves (1 kg) was carried out. Nilotinins M2 (**4**) (7.2 mg) and M3 (**5**) (15 mg) were purified from a MCI-gel fraction (20% MeOH eluate from MCI chromatography of the 70% EtOH eluate from the Toyopearl chromatography) by preparative HPLC. Additionally, enrichment of **7** (7 mg) and **8** (4 mg) from the corresponding fractions was achieved.

Nilotinin M2 (4): An off-white amorphous powder, $[\alpha]_D^{27} +31.2$ (*c* 1.0, MeOH). FABMS *m/z*: 991 [*M* + Na]⁺. HRESIMS *m/z*: 991.10463 [*M* + Na]⁺ (calcd. for C₄₂H₃₂O₂₇ + Na, 991.10232). UV $\lambda_{\max}$ (MeOH) nm (log ϵ): 220 (4.90), 273 (4.56). CD (MeOH): $[\theta]_{237} +8.2 \times 10^4$, $[\theta]_{265} -3.2 \times 10^4$, $[\theta]_{283} +2.2 \times 10^4$. ¹H NMR (acetone-*d*₆–D₂O, 9:1) δ : 7.24 (1H, d, *J* = 2.0 Hz, DHDG H-6), 7.05 (1H, s, DHDG H-6'), 6.92 [2H,

s, galloyl H-2,H-6), 6.62 (1H, d, $J = 2.0$ Hz, DHDG H-2), 6.60 (1H, s, HHDP H-3), 6.48 (1H, s, HHDP H-3'), 3.07 (3H, s, -OCH₃), glucose protons (Table 1). ¹³C NMR (acetone-*d*₆-D₂O, 9: 1) δ : 56.9 (-OCH₃), 107.1 (DHDG C-2), 107.7 (HHDP C-3'), 107.8 (HHDP C-3), 110.1 (2C, galloyl C-2, C-6), 110.2 (DHDG C-6'), 111.9 (DHDG C-6), 113.8 (DHDG C-1'), 115.6 (HHDP C-1), 115.8 (HHDP C-1'), 120.0 (galloyl C-1), 121.9 (DHDG C-1), 125.5, 126.1 (HHDP C-2, C-2'), 136.2 (HHDP C-5), 136.5 (HHDP C-5'), 136.6 (DHDG C-2'), 139.1 (DHDG C-4), 139.3 (galloyl C-4), 140.4 (DHDG C-3'), 140.5 (DHDG C-4'), 143.4 (DHDG C-5'), 144.3 (2C, HHDP C-6, C-6'), 145.1, 145.2 (HHDP C-4, C-4'), 145.7 (2C, galloyl C-3, C-5), 146.2 (DHDG C-5), 148.0 (DHDG C-3), 164.6 (DHDG C-7'), 166.9 (galloyl C-7), 167.8 (HHDP C-7'), 168.1 (DHDG C-7), 168.4 (HHDP C-7), glucose carbons (Table 2).

Nilotinib M3 (5): An off-white amorphous powder, $[\alpha]_D^{25} -5.4$ (c 1.0, MeOH). FABMS m/z : 977 [M + Na]⁺. HRESIMS m/z : 977.08857 [M + Na]⁺ (calcd. for C₄₁H₃₀O₂₇ + Na 977. 08667). UV $\lambda_{\max}$ (MeOH) nm (log ϵ): 217 (5.05), 266 (4.70). CD (MeOH): $[\theta]_{237} +9.3 \times 10^4$, $[\theta]_{261} -3.2 \times 10^4$, $[\theta]_{285} +1.6 \times 10^4$; ¹H NMR (acetone-*d*₆-D₂O, 9:1) δ : 7.16 (2H, s, isoDHDG H-2, H-6), 7.03 (2H, s, galloyl H-2, H-6), 6.90 (1H, s, isoDHDG H-6'), 6.60 (1H, s, HHDP H-3), 6.47 (1H, s, HHDP H-3'), glucose protons (Table 1). ¹³C NMR (acetone-*d*₆-D₂O, 9: 1) δ : 107.7 (HHDP C-3'), 107.8 (HHDP C-3), 108.2 (isoDHDG C-6'), 110.1 (2C, galloyl C-2, C-6), 110.8 (2C, isoDHDG C-2, C-6), 115.0 (isoDHDG C-1'), 115.7, 115.8 (HHDP C-1, C-1'), 120.8 (galloyl C-1), 125.4 (isoDHDG C-1), 125.7, 126.1 (HHDP C-2, C-2'), 136.2 (HHDP C-5), 136.4 (HHDP C-5'), 139.0 (galloyl C-4), 139.1 (isoDHDG C-4'), 139.61 (isoDHDG C-4), 139.4, 139.65 (isoDHDG C-2', C-3'), 142.3 (isoDHDG C-5'), 144.27, 144.29 (HHDP C-6, C-6'), 145.13 (HHDP C-4'), 145.15 (HHDP C-4), 145.7 (2C, galloyl C-3, C-5), 150.7 (2C, isoDHDG C-3, C-5), 165.3 (isoDHDG C-7), 167.1 (galloyl C-7), 167.9 (HHDP C-7'), 168.3 (HHDP C-7), 170.7 (isoDHDG C-7'), glucose carbons (Table 2).

Nilotinib D4 (6): An off-white amorphous powder, $[\alpha]_D^{24} +11.8$ (c 1.0, MeOH). FABMS m/z : 1745 [M + Na]⁺. HRESIMS m/z : 1745.16764 [M + Na]⁺ (calcd. for C₇₅H₅₄O₄₈ + Na, 1745.16767). UV $\lambda_{\max}$ (MeOH) nm (log ϵ): 220 (5.37), 274 (5.09). CD (MeOH): $[\theta]_{237} +3.2 \times 10^5$, $[\theta]_{263} -8.5 \times 10^4$, $[\theta]_{287} +3.8 \times 10^4$. ¹H NMR (acetone-*d*₆-D₂O, 9: 1) δ : 7.07, 7.04, 7.02, 6.97 [each 2H, s, galloyl (H-2, H-6) $\times$ 3 and isoDHDG (H-2, H-6)], 6.77 (1H, s, isoDHDG H-6'), 6.61, 6.60, 6.48, 6.47 [each 1H, s, HHDP (H-3, H-3') $\times$ 2], glucose protons (Table 1).

Nilotinib D5 (7): An off-white amorphous powder, $[\alpha]_D^{26} +11.2$ (c 1.0, MeOH). ESIMS m/z : 1593 [M + Na]⁺. HRESIMS m/z : 1593.15579 [M + Na]⁺ (calcd. for C₆₈H₅₀O₄₄ + Na, 1593.15672). UV $\lambda_{\max}$ (MeOH) nm (log ϵ): 218 (5.38), 276 (5.04). CD (MeOH): $[\theta]_{236} +1.5 \times 10^5$, $[\theta]_{265} -6.0 \times 10^4$, $[\theta]_{294} +3.0 \times 10^4$; ¹H

NMR (acetone- d_6 -D₂O, 9: 1) δ : 7.13 [2H, s, galloyl-B (H-2, H-6)], 7.03 [2H, s, galloyl-A (H-2, H-6)], 6.770, 6.769 [each 2H, s, isoDHDG (H-2, H-6) $\times$ 2], 6.61 (1H, s, HHDP H-3), 6.51 (1H, s, isoDHDG-A H-6'), 6.493 (1H, s, isoDHDG-B H-6'), 6.49 (1H, s, HHDP H-3'), glucose protons (Table 1). ¹³C NMR (acetone- d_6 -D₂O, 9: 1) δ : 107.2, 107.3 [isoDHDG (C-6') $\times$ 2], 107.7 (HHDP C-3'), 107.9 (HHDP C-3), 110.0 [2C, galloyl-B (C-2, C-6)], 110.1 [2C, galloyl-A (C-2, C-6)], 110.2, 110.6 [each 2C, isoDHDG (C-2, C-6) $\times$ 2], 115.6 (HHDP C-1), 116.0 (HHDP C-1'), 116.1, 116.3 [isoDHDG (C-1') $\times$ 2], 120.1 (galloyl-A C-1), 120.8 (galloyl-B C-1), 122.8, 123.2 [isoDHDG (C-1) $\times$ 2], 125.4, 126.1 (HHDP C-2, C-2'), 136.3 (HHDP C-5), 136.6 (HHDP C-5'), 138.4 [2C, isoDHDG (C-4') $\times$ 2], 138.5 [2C, isoDHDG (C-4) $\times$ 2], 138.6, 138.7, 139.6, 139.7, 141.5, 141.6 [isoDHDG (C-2', C-3', C-5') $\times$ 2], 139.2 (galloyl-B C-4), 139.4 (galloyl-A C-4), 144.3 (2C, HHDP C-6, C-6'), 145.2 (2C, HHDP C-4, C-4'), 145.8 [2C, galloyl-A (C-3, C-5)], 145.9 [2C, galloyl-B (C-3, C-5)], 149.0 [4C, isoDHDG (C-3, C-5) $\times$ 2], 164.8 (isoDHDG-A C-7), 165.2 (isoDHDG-B C-7), 166.7 (isoDHDG-A C-7'), 166.8 (isoDHDG-B C-7'), 167.0 (galloyl-A C-7), 167.3 (galloyl-B C-7), 167.8 (HHDP C-7'), 168.3 (HHDP C-7), glucose carbons (Table 2).

Nilotin D6 (8): An off-white amorphous powder, $[\alpha]_D^{23} +83.1$ (c 1.0, MeOH). ESIMS m/z : 1595 [M + Na]⁺. HRESIMS m/z : 1595.17064 [M + Na]⁺ (calcd. for C₆₈H₅₂O₄₄ + Na, 1595.17237). UV $\lambda_{\max}$ (MeOH) nm (log ϵ): 218 (5.17), 278 (4.84). CD (MeOH): $[\theta]_{238} +1.0 \times 10^5$, $[\theta]_{263} -1.0 \times 10^4$, $[\theta]_{286} +2.7 \times 10^4$. ¹H NMR (acetone- d_6 -D₂O, 9: 1) δ : 7.11 (1H, d, J = 2 Hz, DHDG H-6), 7.028 (2H, s, galloyl-B H-2, H-6), 7.027 (1H, s, DHDG H-6'), 6.97 (2H, s, galloyl-C H-2, H-6), 6.94 (2H, s, galloyl-D H-2, H-6), 6.93 (2H, s, galloyl-A H-2, H-6), 6.58 (1H, s, HHDP H-3), 6.50 (1H, s, HHDP H-3'), 6.37 (1H, d, J = 2 Hz, DHDG H-2), glucose protons (Table 1). ¹³C NMR (acetone- d_6 -D₂O, 9: 1) δ : 106.9 (DHDG C-2), 107.8 (HHDP C-3'), 107.9 (HHDP C-3), 110.1 (DHDG C-6'), 109.9, 110.0, 110.2, 110.3 [each 2C, galloyl (C-2, C-6) $\times$ 4], 112.7 (DHDG C-6), 113.4 (DHDG C-1'), 115.7 (HHDP C-1), 115.9 (HHDP C-1'), 119.1, 119.84, 119.87, 120.1, 120.8 [DHDG C-1, and galloyl (C-1) $\times$ 4], 125.4, 126.0 (HHDP (C-2, C-2')), 136.3 (HHDP C-5), 136.6 [2C, HHDP C-5', DHDG C-2'], 139.0, 139.25, 139.34, 139.8 (2C) [galloyl (C-4) $\times$ 4 and DHDG C-4], 140.2, 140.7 (DHDG C-3', C-4'), 143.4 (DHDG C-5'), 144.4 [2C, HHDP (C-6, C-6')], 145.1, 145.2 [HHDP (C-4, C-4')], 145.7, 145.77, 145.78, 145.81 [each 2C, galloyl (C-3, C-5) $\times$ 4], 145.9 (DHDG C-5), 147.8 (DHDG C-3), 164.7 [3C, DHDG (C-7, C-7') and galloyl-C (C-7)], 166.2 (galloyl-A C-7), 166.77 (galloyl-B C-7), 166.82 (galloyl-D C-7), 167.8 (HHDP C-7'), 168.3 (HHDP C-7), glucose carbons (Table 2).

Isomerization of nilotin D4 (6) into nilotin D1 (1): A solution of **6** (0.7 mg) in a phosphate buffer (pH 7.4; 200 μ L) was incubated for 1 h at 40 °C. The reaction mixture was acidified with 1 N HCl and passed

through a Sep-Pak C18 cartridge. After the cartridge was washed with water, the adsorbed material was recovered with MeOH. The MeOH was evaporated to give **1** (0.5 mg), which was determined by co-chromatographic analyses with samples isolated from the plant on normal-phase and reverse-phase HPLC, $[\alpha]_D$, and the ^1H -NMR spectral comparison.

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