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Tectonoelins, new norlignans from a bioactive extract of *Tectona grandis*

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ABSTRACT

A phytochemical study on the most bioactive extract from *Tectona grandis* led to the isolation of two new norlignans, tectonoelin A and tectonoelin B, together with ten known compounds. The structures of the compounds were determined by a combination of 1D and 2D NMR techniques. This is the first time that this type of compound (C8–C8′ linkage norlignans) has been isolated from a dicotyledon. The general bioactivities of the isolated compounds have been studied using etiolated wheat coleoptiles. The activities showed that the isolated lignans and norlignans should be part of the defence mechanisms of this plant.

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1. Introduction

Forest species' produce large amounts of non-wood forest products (NWFPs) in which bioactive substances are present in high percentages. These compounds can be transported to the ground by exudation from roots or leaching of the aerial parts. The increased forest area is not only a source of wood as forestry systems provide an excellent opportunity to explore the properties of these species in the control of weeds, insects and nematodes or for the improvement of grounds and as a source of bioactive products in Pharmacology.

Tectona grandis L.f. (teak) is a native tree from tropical countries of Asia. Teak wood is one of the most valuable and better known woods and it has a large number of applications in the timber industry due to its beautiful surface and its resistance to termite and fungal damage (Sumthong et al., 2008). Research on this plant has led to interest in terms of Allelopathy because teak has been successfully used in agroforestry systems (system taungya) and in crop rotation in India, Costa Rica, Venezuela and Cuba (Raets, 1965; Betancourt, 1983; Mishra and Prasad, 1980; Wiersum, 1982). Furthermore, phytotoxic effects on maize, bean, mountain rice and peanut have been reported (Jayakumar et al., 1987; Krishna et al., 2003).

In order to study the potential use of this species as a source of natural herbicide models and/or bioactive compounds, we continued our systematic allelopathic and phytochemical studies on leaves from teak (NWFPs). Previously, we reported the isolation of apocarotenoids, terpenoids and quinones from bioactive extracts of leaves of *T. grandis* (Macías et al., 2008, 2010; Lacret et al., 2011). As a continuation of this research, we report here the isolation and structure elucidation of two new norlignans and ten known compounds (six lignans and four phenolic compounds), which are shown in Fig. 1. The general bioactivities of the isolated compounds were studied using etiolated wheat coleoptile. Norlignans are found mainly in conifers, monocotyledons and a few species of dicotyledons (Chang et al., 1997; Kawazoe et al., 1999; Ning et al., 2005; D'Abrosca et al., 2006; Lee et al., 2010; Mohamed et al., 2010; Wang et al., 2010). This is the first time that lignans and norlignans have been isolated from *T. grandis*.

2. Results and discussion

The study of the allelopathic potential of *T. grandis* and its possible use as a source of natural herbicide models was initiated with the phytochemical study of (i) the DCM/H_2O extract obtained from the aqueous extract and (ii) the DCM extract obtained by direct maceration of the dry leaves. Both extracts were selected on the basis of the bioactivity levels shown in the wheat coleoptile bioassay (Macías et al., 2008).

The chromatographic study of the DCM/H_2O active extract allowed us to isolate four phenolic compounds (**1**–**4**) and eight lignans (**5**–**12**) (Fig. 1). The spectroscopic data of **1**–**10** were identical to those previously reported for acetovanillone (**1**) (Knapp et al., 1972), *E*-isofuraldehyde (**2**) (Macías et al., 2004),

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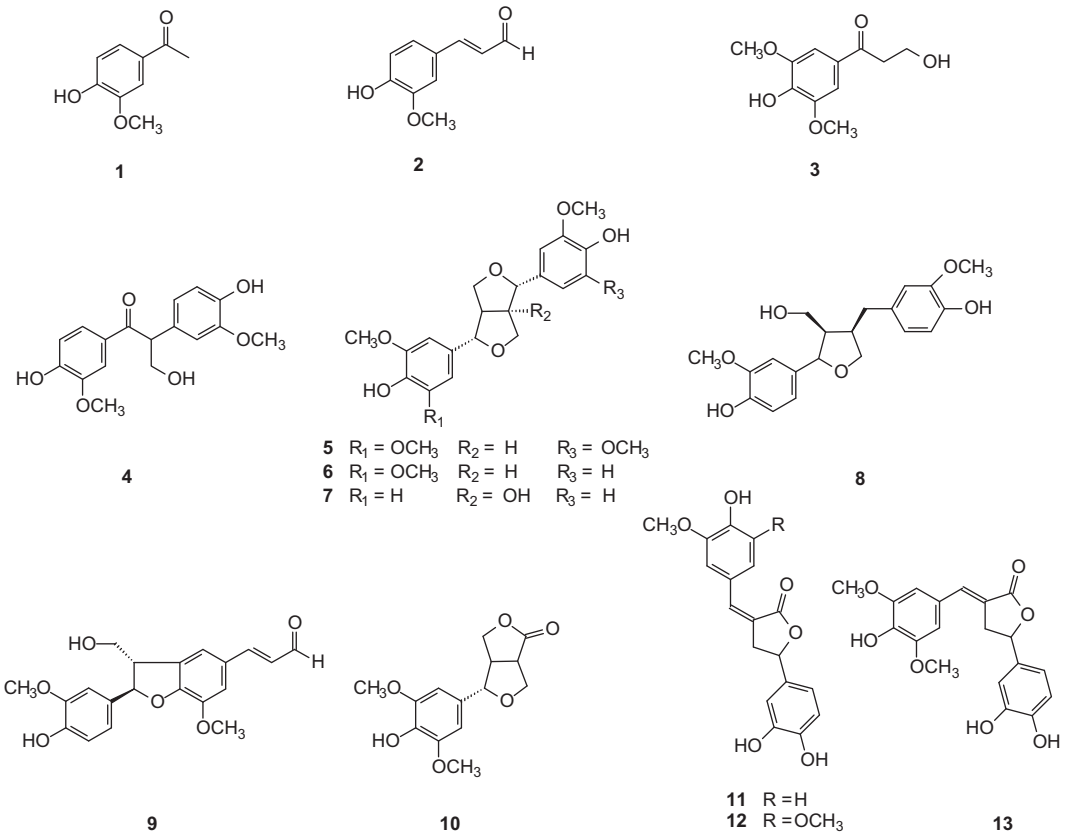

Fig. 1. Compounds isolated from *Tectona grandis*.

3-hydroxy-1-(4-hydroxy-3,5-dimethoxyphenyl)propan-1-one (**3**) (Jones et al., 2000), evofolin A (**4**) (Wu et al., 1995), syringaresinol (**5**) (Macías et al., 2004), medioresinol (**6**) (Macías et al., 2004), 1-hydroxypinoresinol (**7**) (Tsukamoto et al., 1984), lariciresinol (**8**) (Macías et al., 2004), balaphonin (**9**) (Haruna et al., 1982) and zhebeiresinol (**10**) (Chiji et al., 1986). All of these compounds were isolated for the first time from *T. grandis*. Compounds **11** and **12** are also described for the first time in the literature.

2.1. Tectonoelin A (11)

11 was isolated from the DCM/H_2O extract as a brown oil. The molecular formula was determined to be $C_{18}H_{16}O_6$ from the molecular ion peak at *m*/*z* 328.0948 (calc. 328.0947) in the HR-EIMS. The IR absorptions at 3429, 1735, and 1607 cm^{-1} indicated the presence of hydroxyl groups, ester group and double bonds, respectively.

The ^{1}H NMR spectrum contained signals for one aromatic methoxy group at δ 3.85 (3H, s) and six aromatic protons as two groups of signals. The first group of signals was at δ 6.77 (1H, *d*, *J* = 8.0 Hz, H-5′), δ 6.78 (1H, *d*, *J* = 2.0 Hz, H-2′) and δ 6.68 (1H, *dd*, *J* = 8.0 Hz, *J* = 2.0 Hz, H-6′) and the second group was at δ 6.87 (1H, *d*, *J* = 8.0 Hz, H-5), δ 7.06 (1H, *bs*, H-2) and δ 7.04 (1H, *dd*, *J* = 8.0 Hz, *J* = 2.0 Hz, H-6), indicating the presence of two 1,3,4-trisubstituted benzenic rings.

Other signals were assigned to one methylene at δ 3.07 (1H, *ddd*, *J* = 17.6 Hz, *J* = 8.4 Hz, *J* = 3.0 Hz, H-8′a) and δ 3.62 (1H, *ddd*, *J* = 17.6 Hz, *J* = 8.4 Hz, *J* = 3.0 Hz, H-8′b) and one methine at δ 5.48 (1H, *dd*, *J* = 8.4 Hz, *J* = 6.0 Hz, H-7′) bonded to oxygen. Additionally, a signal was observed for a downfield olefinic proton at δ 7.45 (1H, *t*, *J* = 3.0 Hz, H-7), suggesting the presence of a trisubstituted double bond attached to an electron withdrawing group.

The ^{1}H NMR-2D-COSY spectrum of **11** showed the presence of the fragment –CH=C–CH_2–CH–(O)–. Thus, the geminal system that gave signals at δ 3.07 (H-8′a) and δ 3.62 (H-8′b) showed a coupling with the signals at δ 7.45 (H-7) and δ 5.48 (H-7′).

All of the signals and their correlations suggested the presence of a nor-7-ene-lignan-9,7′-lactone. This proposal was further supported by the similarity of the spectroscopic data to those reported for other analogous compounds (D'Abrosca et al., 2006).

The ^{13}C NMR spectrum contained 18 signals as follows: 1 methyl, 1 methylene, 8 methines and 8 quaternary carbons, according to an HSQC experiment. Twelve of these signals were due to aromatic carbons that belonged to the two 1,3,4-trisubstituted benzenic rings. Three signals were due to sp^2 carbons, with the two at δ 122.8 and 138.4 belonging to the double bond. The last signal, at δ 174.9, was consistent with the presence of a carbonyl group.

The HMBC experiment confirmed the presence of a γ-lactone, with correlations observed between H-7′ (δ 5.48), H-8′a (δ 3.07) and H-8′b (δ 3.62) with C-9 (δ 174.9) as well as H-7 (δ 7.45) with C-8′ (δ 37.2), C-1 (δ 127.9), C-2 (δ 114.6), C-3 (δ 149.1) and C-8 (δ 122.5) (Fig. 2).

The stereochemistry of the double bond at C-7 and C-8 was deduced from the NOE effects observed on irradiation of H-8′a and H-8′b with H-7 and H-7′. The relative position of the rings was confirmed by NOE effects between protons H-8′ (2H) and H-2′, H-5′ and H-6′. Compound **11** was therefore (7*Z*)-9′nor-3′,4,4′-trihydroxy-3-methoxylign-7-ene-9,7′-lactone. This compound has not been described previously in the literature and we have named this compound tectonoelin A.

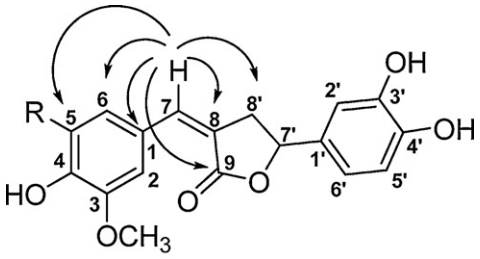

Fig. 2. HMBC correlations observed for compounds **11** and **12**.

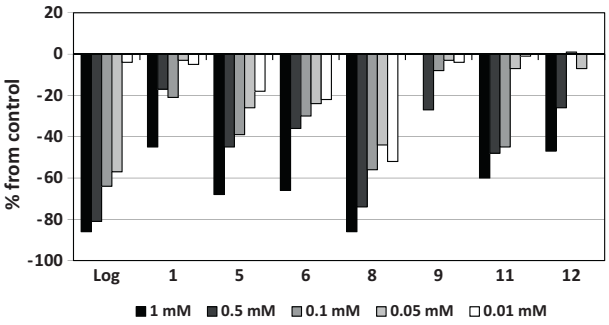

Fig. 3. Bioactivities obtained in the etiolated wheat coleoptile bioassay.

2.2. Tectonoelin B (12)

12 was obtained from the DCM/H_2O extract as a brown oil. The molecular formula was determined to be $C_{19}H_{18}O_7$ from the molecular ion peak at *m/z* 358.1053 (calc. 358.1053) in the HR-EIMS. The IR absorptions at 3438, 1727 and 1626 cm^{-1} indicated again the presence of the same functional groups, hydroxyl, ester and double bonds.

The ^1H NMR spectrum of **12** was very similar to that of tectonoelin A (**11**), which would indicate that it was a derivative of tectonoelin A. The most significant difference between the two spectra was the chemical shift and multiplicity of the signals due to protons on one of the rings (δ 6.78, 2H, *s*, H-2, H-6 and δ 3.83, *s*, 2 × OCH_3). The data suggested that these two compounds differ in the presence of one extra methoxyl group in **12**, which must be located at C-5. The correlation observed in the g-HMBC experiment between the methoxyl groups at δ 3.83 (6H, *s*) and the signals at δ 108.9 and δ 149.3 confirmed the positions of methoxyl groups at C-3 and C-5. On the other hand, the NOE effect between H-7 and H-8′ confirmed a *Z* stereochemistry for the double bond.

On the basis of these data the structure suggested for this compound was (7*Z*)-9′nor-3′,4,4′-trihydroxy-3,5-dimethoxylign-7-ene-9,7′-lactone, as shown in Fig. 1. An isomer isolated from *Cestrum parqui* has been described in the literature, i.e. **13** (D'Abrosca et al., 2006). The differences observed between the spectroscopic data of compound **12** and its isomer **13** suggested that the stereochemistry of the double bond of these compounds should be different [^{13}C NMR spectrum, δ: 129.2 (C-1), 109.5 (C-2), 133.6 (C-4), 133.6 (C-8), 123.3 (C-1′), 81.1 (C-7′)], as shown in Fig. 1. This is the first time that compound **12** has been isolated and we have named it tectonoelin B.

Norlignans are unusual compounds and most of them have been found in the heartwood of coniferous trees (Castro et al., 1996). Compounds **11** and **12** can be included in the group with a C8–C8′ linkage type, which is particularly rare (Suzuki and Umezawa, 2007). This kind of compound has been obtained from conifers (Erdtman and Harmatha, 1979; D'Abrosca et al., 2006). However, this is the first time that compounds of this type (C8–C8′ linkage norlignans) have been isolated from a dicotyledon – although teak is a timber tree – and, more importantly, from the leaves, which is in full even more uncommon.

2.3. Bioassay results

Etiolated wheat coleoptiles bioassay is a rapid test that is sensitive to a wide range of bioactive substances (Cutler et al., 2000; Cutler, 1984; Jacyno and Cutler, 1993). Twelve compounds were isolated from *T. grandis* and, as dictated by the available quantities of these compounds, the bioactivities of the C_6C_2 phenolic **1**, four known lignans (**5**, **6**, **8** and **9**) and tectonoelins (**11** and **12**) were evaluated (Fig. 3). The highest concentration tested was 10^{-3} M. The results obtained showed that compounds **5**, **6**, **8** and **11** have good levels of activity. The most active compound was **8**, which gives values of around −85% at 10^{-3} M. Compounds **5**, **6** and **11** showed inhibition effects of between −70 and −60% at the highest concentration. The activities observed for **5** and **8** were consistent with those previously reported for these compounds (Macías et al., 2004). Compounds **5** and **6** have a tetrahydrofurofuranic skeleton and the only structural difference is the presence of an additional methoxyl group. This difference has very little influence on the bioactivity observed. In the case of the new compounds, tectonoelins A (**11**) and B (**12**), which have a norlignan skeleton, the presence of an additional methoxyl group in **12** seems to decrease the bioactivity levels in comparison with **11**.

These activities show that the isolated lignans and norlignans should form part of the defence mechanism of this plant and contribute to the success of this species in a variety of agroecosystems.

3. Experimental

3.1. General

IR spectra (KBr) were recorded on a Perkin-Elmer FT-IR Spectrum 1000 or a Mattson 5020 spectrophotometer. NMR spectra were run on Varian INOVA 400 and Varian INOVA 600 spectrometers. Chemical shifts are given in ppm with respect to residual ^1H signals of $CHCl_3$-d_1 and methanol-d_4 (δ 7.25 and 3.30, respectively), and ^{13}C signals are referenced to the solvent signal (δ 77.00 and 49.00, respectively). Optical rotations were determined using a Perkin-Elmer model 241 polarimeter (on the sodium D line). HRMS were obtained on a VG AUTOESPEC mass spectrometer (70 eV). HPLC was carried out on a Merck-Hitachi instrument with RI detection, using three different Merck LiChrospher columns: RP-18 (10 μm, 250 mm × 10 mm), RP-18 (5 μm, 250 mm × 4 mm) SI 60 (5 μm, 250 mm × 4 mm) and SI 60 (10 μm, 250 mm × 10 mm).

3.2. Plant material

Leaves of *T. grandis* L.f. were collected between the months February and March (2003) in Ciudad de La Habana and were identified by MsC. Lutgarda González. Voucher specimen (80613) were deposited at the Jardín Botánico de Cuba.

3.3. Extraction and isolation

Dried leaves of *T. grandis* (5 kg) were extracted with water (35 L) for 24 h at room temperature in the dark. The aqueous solution was extracted with CH_2Cl_2 and then with EtOAc at room

Table 1
^{1}H NMR and ^{13}C NMR spectral data for compounds **11** and **12** (in CD_3OD).

H/C	**11**		**12**	
	^{1}H NMR	^{13}C NMR	^{1}H NMR	^{13}C NMR
1		127.9 *s*		126.9 *s*
2	7.06 *bs*	114.6 *d*	6.78 *s*	108.9 *d*
3		149.1 *s*		149.3 *s*
4		150.1 *s*		139.2 *s*
5	6.87 *d* (*J* = 8.0 Hz)	116.7 *d*		149.3 *s*
6	7.04 *d* (*J* =8.0, 2.0 Hz)	125.9 *d*	6.78 *s*	108.9 *d*
7	7.45 *t* (*J* = 3.0 Hz)	138.1 *d*	7.42 *t* (*J* = 3.0 Hz)	138.4 *d*
8		122.5 *s*		122.8 *s*
9		174.9 *s*		174.9 *s*
1′		133.3 *s*		133.2 *s*
2′	6.78 *d* (*J* = 2.0 Hz)	113.9 *d*	6.78 *d* (*J* = 2.0 Hz)	113.9 *d*
3′		146.7[a] *s*		146.9[a] *s*
4′		146.8[a] *s*		146.7[a] *s*
5′	6.77 *d* (*J* = 8.0 Hz)	116.4 *d*	6.76 *d* (*J* = 8.4 Hz)	116.4 *d*
6′	6.68 *d* (*J* = 8.0, 2.0 Hz)	118.8 *d*	6.68 *d* (*J* = 8.4, 2.0 Hz)	118.9 *d*
7′	5.48 *dd* (*J* = 8.0, 6.0 Hz)	80.6 *d*	5.46 *dd* (*J* = 8.4, 6.0 Hz)	80.6 *d*
8a′	3.07 *ddd* (*J* = 17.6, 8.4, 3.0 Hz)	37.2 *t*	3.10 *m*	37.2 *t*
8b′	3.62 *ddd* (*J* = 17.4, 8.4, 3.0 Hz)		3.60 *ddd* (*J* = 17.6, 8.4, 2.8 Hz)	
OCH_3	3.85 *s*	56.4 *q*	2 × 3.83 *s*	56.8 *q*

[a] Signals may be interchanged.

temperature. Details of the extraction procedure and the bioassays on the extract have been described previously (Macías et al., 2008).

The DCM/H_2O extract (8.8 g) was chromatographed on silica gel (160 g) using hexane/ethyl acetate mixtures of increasing polarity, acetone and methanol to yield twelve fractions: A_1–L_1.

Fraction E_1 (0.750 g, hexane/ethyl acetate, 17:3–4:1) was subjected to CC on Sephadex LH-20 using n-hexane/chloroform/methanol (3:1:1) to afford 11 fractions ($E_1$1–$E_1$11). Fraction $E_1$5 (72 mg) was separated by CC on silica gel using hexane/ethyl acetate mixtures to yield compound **1** (2.0 mg). Fraction $E_1$7 (54 mg) was purified by C-18 HPLC (water/methanol, 1:1) to yield **2** (1.0 mg).

Fraction H_1 (0.734 g, hexane/EtOAc, 3:2–2:3) was subjected to CC on Sephadex LH-20 using n-hexane/chloroform/methanol (3:1:1) to yield compound **11** (60 mg).

Fraction I_1 (0.719 g, hexane/EtOAc, 1:4) was subjected to CC on silica gel using chloroform/acetone mixtures of increasing polarity and methanol to afford ten fractions: $I_1$1–$I_1$10. Fraction $I_1$2 (0.055 g) was purified by silica gel HPLC to yield **5** (8.6 mg), **6** (5.0 mg) and **10** (2.6 mg). The largest fraction, $I_1$6 (0.300 g), was purified by CC on silica gel using hexane/acetone mixtures to afford ten fractions: $I_1$6A–$I_1$6J. Further purification of fraction $I_1$6I (0.058 g) by C-18 HPLC (water/methanol, 9:11) yielded **8** (20.0 mg), **9** (8.0 mg) and **4** (3.0 mg). Fraction $I_1$6H (0.028 g) was purified by RP-18 HPLC (water/methanol, 2:3) to yield **9** (5.0 mg) and **7** (3.4 mg). Fraction $I_1$7 (0.112 g) was purified using hexane/chloroform/methanol (3:1:1) on Sephadex LH-20 to afford compound **12** (27.0 mg).

Fraction J_1 (1.730 g, hexane/EtOAc, 1:4) was subjected to CC on Sephadex LH-20 using hexane/chloroform/methanol (3:1:1) to afford four fractions ($J_1$1–$J_1$4). Fraction $J_1$4 (0.400 g) was subjected to CC on silica gel using chloroform/acetone mixtures (10–100% acetone) to afford 6 fractions. Further purification of $J_1$4A (0.077 g) by C-18 HPLC (water/methanol, 3:2) yielded compound **3** (3.0 mg).

3.3.1. Tectonoelin A (11)

Brown oil; $[\alpha]_D^{25} = 0$ (*c* 0.10, CH_3OH); IR ν_{max} (KBr): 3438 (OH), 1727 (C=O), 1626 (C=C) cm^{-1} ^{1}H NMR and ^{13}C NMR data, see Table 1; EIMS *m*/*z* (rel. int.): 328 $[M]^+$; HREIMS *m*/*z* 328.0948 (calc. for $C_{18}H_{16}O_6$ *m*/*z* 328.0947).

3.3.2. Tectonoelin B (12)

Brown oil; $[\alpha]_D^{25} = -10$ (*c* 0.10, CH_3OH); IR ν_{max} (KBr): 3429 (OH), 1735 (C=O), 1607 (C=C) cm^{-1};. ^{1}H NMR and ^{13}C NMR data, see Table 1; EIMS *m*/*z* (rel. int.): 358 $[M]^+$; HREIMS *m*/*z* 358.1053 (calc. for $C_{19}H_{18}O_7$ *m*/*z* 358.1053).

3.4. Coleoptiles bioassay

Wheat seed (*Triticum aestivum* L. cv. Duro) were sown in 15 cm diameter Petri dishes moistened with water and grown in the dark at 22 ± 1 °C for 3 days (Hancock et al., 1964). The roots and caryopses were removed from the shoots. The latter were placed in a Van der Weij guillotine and the apical 2 mm were cut off and discarded. The next 4 mm of the coleoptiles were removed and used for bioassays. All manipulations were performed under a green safelight (Nitsch and Nitsch, 1956). Compounds were predissolved in DMSO and diluted to the final bioassay concentration with a maximum of 0.1% DMSO. Parallel controls were also run.

Crude extracts, fractions or pure compounds to be assayed for biological activity were added to test tubes. Each assay was carried out in duplicate. Phosphate-citrate buffer (2 ml) containing 2% sucrose (Nitsch and Nitsch, 1956) at pH 5.6 was added to each test tube. Five coleoptiles were placed in each test tube (three tubes per dilution) and the tubes were rotated at 0.25 rpm in a roller tube apparatus for 24 h at 22 °C in the dark. The coleoptiles were measured by digitalization of their images. Data were statistically analyzed using Welch's test (Martín Andrés and Luna del Castillo, 1990). Data are presented as percentage differences from control. Thus, zero represents the control; positive values represent stimulation of the studied parameter, and negative values represent inhibition.

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