# Compounds from *Acorus tatarinowii*: Determination of Absolute Configuration by Quantum Computations and cAMP Regulation Activity

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A new cadinane-type sesquiterpenoid, tatarinowin A (**1**), two phenylpropanoids, tatarinoids A (**2**) and B (**3**), and a trinorlignan, tatarinoid C (**4**), along with 15 known compounds including two pairs of mixtures were isolated from the rhizome of *Acorus tatarinowii*. The absolute configurations of **1**−**4** were established by computation of specific rotation values. The isolated compounds were evaluated for their cAMP regulatory activity by the AlphaScreen assay.

The rhizome of *Acorus tatarinowii* Schott (Araceae) has been used as a famous traditional Chinese medicine for the treatment of central nervous system related diseases.[1] Plants of the genus *Acorus* are known to produce various sesquiterpenoids[2−4] and phenylpropanoids[4−7] as major constituents, and some of these compounds were found to possess anticonvulsive,[8] spasmolytic,[9] neuroprotective,[10] and antigermination effects.[4] Previous studies on *A. tatarinowii* revealed the presence of mono-, sesqui-, and diterpenoids, phenylpropanoids, flavonoids, and amides.[11−14] In the course of our search for bioactive compounds from traditional Chinese medicine, 19 compounds were isolated from the rhizome of this plant. The absolute configurations of compounds **1**−**4** were assigned by quantum calculations. Except for **2**, the other compounds were evaluated for their cAMP regulatory activity by the AlphaScreen assay.
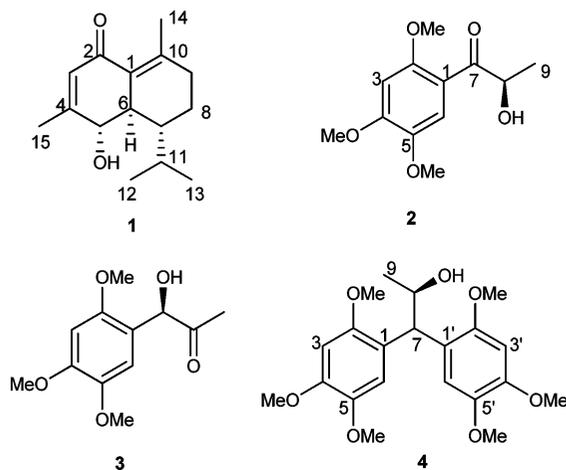


Compound **1** was isolated as a colorless gum. The molecular formula was determined as $C_{15}H_{22}O_2$ by HRESIMS (*m/z* found 235.1704 [M + H]+, calcd 235.1698). The IR spectrum showed absorption bands for hydroxy (3428 cm$^{-1}$) and α,β-unsaturated carbonyl groups (1656 cm$^{-1}$).[15] The ^{1}H NMR spectrum showed

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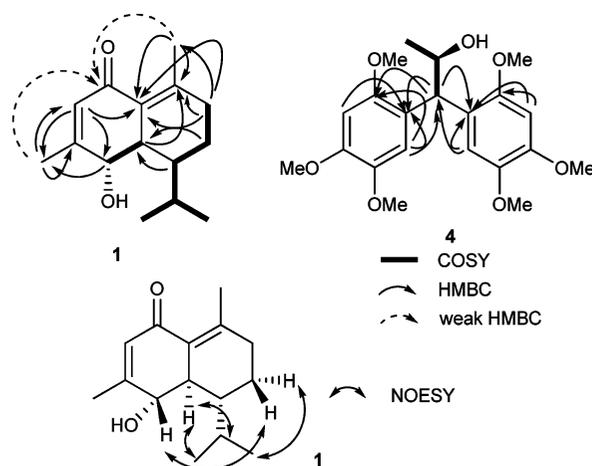
**Figure 1.** Key 2D NMR correlations of compounds **1** and **4**.

signals for an olefinic proton at δ 5.88 (s, H-3), an oxymethine proton at δ 4.15 (d, *J* = 10.3 Hz), four methyl groups at δ 0.92 (d, *J* = 6.6 Hz, H$_3$-12), 0.93 (d, *J* = 6.6 Hz, H$_3$-13), 1.95 (s, H$_3$-14), and 2.00 (s, H$_3$-15), and signals with complex coupling patterns attributable to two aliphatic methylene and three methine protons. The ^{13}C NMR and DEPT spectra showed 15 carbon resonances including four methyl, two methylene, five methine, and four quaternary carbons (one carbonyl and three olefinic carbons). These spectroscopic data indicated **1** to be a cadinane-type sesquiterpene with an α,β-unsaturated carbonyl group.[15] The [1]H−^{1}H COSY spectrum displayed correlations between H-5 and H-6 as well as between H-12 or H-13 and H-7, H-7 and H-8, and H-8 and H-9, consistent with two fragments shown with bold lines in Figure 1. The locations of the functional groups and the assembly of compound **1** were done by HMBC data. The HMBC spectrum showed correlations of H-9/C-1, C-10, C-14 and H-14/C-1, C-10, indicative of a partial structure comprising C-9−C-10−C-1 with a methyl group (C-14) attached at C-10 (Figure 1). HMBC correlations of H-15/C-3, C-4, and C-5 suggested a methyl group (C-15) linked at C-4. A carbonyl group was positioned at C-2 due to its chemical shift, diagnostic IR absorption, and characteristic and weak HMBC correlations of H-14, H-15/C-2. Finally, the linkage of C-6 with C-7 and C-1 was supported by HMBC correlations of H-7, H-8/C-6 and H-6/C-10 (weak), respectively. The above evidence allowed the elucidation of the planar structure of **1**. The relative configuration of **1** was determined by the NOESY correlations (Figure 1) of H-6/H-11, H-12, H-8a/H-12, and H-8b/H-5, which

implied that H-5 and H-6 and H-6 and H-7 are both in *trans* relationships. H-6 resonating as a doublet (d, $J = 10.3$ Hz) and showing no COSY cross-peaks with H-7 indicated a ca. 90° dihedral angle between H−C-6−H−C-7 and further confirmed that H-5 and H-6 are *trans* oriented. The absolute configuration of **1** was clarified using density functional theory (DFT) methods.[16] The stable conformations with relative 5*S*, 6*R*, 7*R* configuration were analyzed, and six stable geometries were obtained at the B3LYP/6-31G(d) and B3LYP/6-31+G(d) levels, respectively, using previously reported methods.[17−19] The conformational searches were performed using the HyperChem package via the Amber force field. The geometries with relative energies in the range 0−6 kcal/mol were selected for further optimization with DFT methods. The structures were then used in optical rotation calculations at the B3LYP/aug-cc-pVDZ level in the gas phase. The computed specific rotation value was +26.4 when the B3LYP/6-31G(d)-optimized energy was used, +31.5 when the B3LYP/6-31+G(d)-optimized energy was used, and +42.1 when the single-point energy (SPE) at the B3LYP/aug-cc-pVDZ level was used in the gas phase. The experimental specific rotation of **1** was +20.3, similar to the computed value. The difference between the experimental specific rotation and the computed values might be attributable to the limited basis sets, lack of explicit solvation, vibrational averaging, etc.[16b] Since the relative configuration of **1** was determined, the absolute configuration should be 5*S*, 6*R*,7*R*. The structure of **1** was thus determined as (5*S*,6*R*,7*R*)-2-oxocadinan-1(10),3-dien-5-ol, named tatarinowin A.

Compound **2** was isolated as a colorless gum, with a molecular formula of $C_{12}H_{16}O_5$ determined by HRESIMS (*m/z* found 263.0883 [M + Na]$^+$, calcd 263.0895). The UV spectrum showed absorptions at 234, 271, and 329 nm, indicating the presence of phenyl and carbonyl moieties in **2**.[20] The IR absorptions were indicative of hydroxy (3446 cm$^{-1}$), carbonyl (1650 cm$^{-1}$), and phenyl groups (1605, 1515 cm$^{-1}$). The $^1H$ and $^{13}C$ NMR spectra of **2** were similar to those of 1-(2,4,5-trimethoxyphenyl)propane-1,2-dione (**2a**),[4] differing from **2a** only in the location of a carbonyl group (C-8), which was reduced to a hydroxymethine group. The $^1H$ NMR splitting patterns of H-8 ($\delta_H$ 5.13, 1H, q, $J = 6.8$ Hz) and H-9 ($\delta_H$ 1.34, 3H, d, $J = 6.8$ Hz) and the HMBC correlations of H-6, H-8, and H-9/C-7 further supported the presence of 7-carbonyl and 8-hydroxy functionalities. The absolute configuration of C-8 was clarified using the matrix method.[21] The calculated det(D) value for the *R* isomer of **2** was −8.96, and the experimental value was −6.85 in CHCl$_3$. The calculated $k_0$ value was +0.76 (−6.85/−8.96), indicating an 8*R* absolute configuration. This conclusion was confirmed using the DFT method, which is an expensive method for analyzing acyclic chiral compounds because many conformations must be examined. (*R*)-**2** was analyzed at the B3LYP/6-31+G(d) level, and approximately 40 stable conformations with relative energies from 0 to 2.5 kcal/mol were found. To reduce the computational time, a total of 22 geometries with relative energy data of 0−2.0 kcal/mol were used for the computation of the specific rotation at the B3LYP/aug-cc-pVDZ level. The predicted specific rotation value was −24.2 when the B3LYP/6-31+G(d)-optimized energy was used and −23.1 when the SPEs at the B3LYP/aug-cc-pVDZ level were used in the gas phase. The sign of the computed specific rotation was negative, which agreed with the sign of the recorded value. However, there was a large error in the computed specific rotation values when compared to the recorded value, which might be attributable to the causes proposed for compound **1**. Collectively, the structure of **2** was determined to be (2*R*)-1-(2,4,5-trimethoxyphenyl)propan-2-ol-1-one and given the trivial name tatarinoid A.

Compound **3** was isolated as a colorless gum, and HRESIMS (*m/z* found 263.0906 [M + Na]$^+$, calcd 263.0895) suggested that **3** has the same molecular formula as **2**. The $^1H$ and $^{13}C$ NMR spectra of **3** were similar to those of **2**, differing in that the functionalities at C-7 and C-8 are reversed. This was also supported by the two observed proton singlets for H-7 ($\delta_H$ 5.38, s) and H-9 ($\delta_H$ 2.02, s) in **3**. The configuration of **3** was also assigned using the matrix method.[21] Because it has many stable conformations, its specific rotation was not predicted with the DFT methods, but instead with the economical matrix method. The calculated det(*D*) value for the *R* isomer was −6.89, and the experimental value was −4.77 in CHCl$_3$. The computed $k_0$ was +0.69 (−4.77/−6.89), close to that of **2** (+0.76), indicating the 7*R* absolute configuration of **3**.[21] Consequently, the structure of **3** was shown to be (1*R*)-1-(2,4,5-trimethoxyphenyl)propan-1-ol-2-one, having the trivial name tatarinoid B. It was noted that compounds **2** and **3** are probably in equilibrium with each other via enediol intermediates.

The molecular formula of **4** was determined to be $C_{21}H_{28}O_7$ by its HRESIMS (*m/z* found 415.1735 [M + Na]$^+$, calcd 415.1732). The IR spectrum showed absorptions for hydroxy (3440 cm$^{-1}$) and phenyl groups (1511 cm$^{-1}$). The $^1H$ NMR spectrum showed the presence of one methyl doublet (H-9), one oxymethine proton (H-8), one proton resonance at $\delta$ 4.57 (d, $J = 5.9$ Hz, H-7), six *O*-methyl groups, and four aromatic protons. By comparing the $^1H$ and $^{13}C$ signals of **4** with those of **2** in the aromatic region, it was evident that two 2,4,5-trimethoxyphenyl units are present in **4**. The $^1H$−$^1H$ COSY spectrum indicated that H-8 correlates with H-7 and H-9. The HMBC correlations of H-6 and H-6′/C-7 suggested two 2,4,5-trimethoxyphenyl units connected via C-7. Because the compound has so many stable conformations, no specific rotation value was computed with the DFT methods, but the configuration of **4** was also clarified using the matrix method.[21] The calculated det(*D*) value for the *R* isomer was −20.80, and the measured value was −10.16 in CHCl$_3$. The computed $k_0$ was +0.50 (−10.16/−20.80). The $k_0$ value is also similar to the value for **2** (+0.76) and **3** (+0.69). This indicated that the absolute configuration at C-8 is *R*. Consequently, compound **4** was determined to be (2*R*)-1,1-di(2,4,5-trimethoxyphenyl)propan-2-ol, having the trivial name tatarinoid C.

Known compounds were identified as 1-(2,4,5-trimethoxyphenyl)propan-2-one (**5**),[22] asaraldehyde (**6**),[22] 1-(2,4,5-trimethoxyphenyl)propan-1,2-dione (**7**),[22] 1-(2,4,5-trimethoxyphenyl)propan-1-one (**8**),[22] (*Z*)-3-(2,4,5-trimethoxyphenyl)acrylaldehyde (**9**),[22] *cis*-asarone,[22] *trans*-asarone,[22] (*Z*)-1,2-dimethoxy-4-(prop-1-enyl)benzene,[22] 1-(3,4-dimethoxyphenyl)propan-2-one,[22] acoronene,[22] epiacoronene,[22] isocalamediol,[22] 2-hydroxyacorenone,[22] 2-acetaxyacorenone,[22] and calamensesquiterpenone[23] by comparison with literature data.

Cyclic adenosine monophosphate (cAMP) is an important second messenger, regulating many biological processes. In humans, cAMP affects not only the higher-order of thinking but also neurogenesis, memory, emotional disorders, and cognitive function. Because the rhizomes of *A. tatarinowii* are used to treat neuropsychiatric diseases, we evaluated the cAMP-regulating activity of all the compounds isolated from this plant, with the exception of compound **2**, using the AlphaScreen assay. The results showed that compounds **4**−**9** have weak activity or cause an upward trend in cAMP levels at concentrations of 50 $\mu$M ($P < 0.05$) in N1E-115 neuroblastoma cells (Figure 2), whereas the isolated sesquiterpenoids showed no activity in this assay (data not shown).

2,4,5-Trimethoxyphenylpropanoids are characteristic constituents of *A. tatarinowii* and exhibit antiepileptic activity.[24] However, most of the previous reports have not clarified the absolute configurations at the flexible chains of 2,4,5-trimethoxyphenylpropanoids.[4,25,26] In general, the low concentrations of natural products make it difficult to determine their configurations with conventional chemical methods.[27,28] In such cases, quantum calculation[29] is an effective and economical method that provides useful data for direct comparisons without material consumption. In the present study, quantum computations were successfully used to determine the absolute configurations of the new isolates and should be useful in addressing the issue of the absolute configurations of this class of compounds.
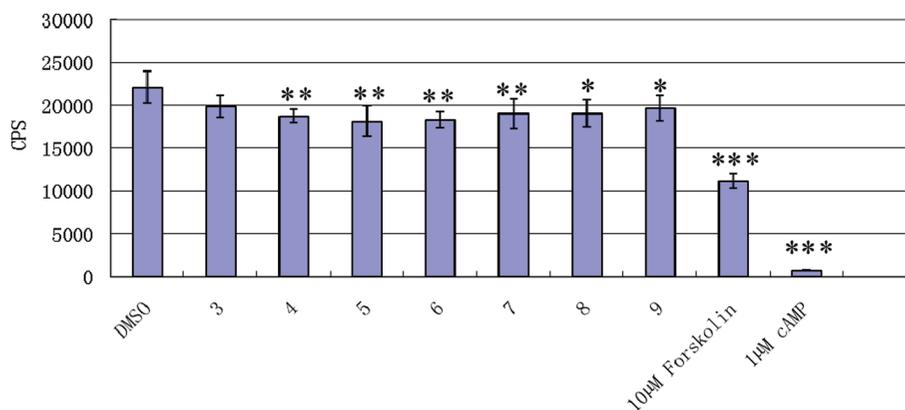
**Figure 2.** cAMP regulation activity of compounds **3−9**. $*p < 0.05$; $**p < 0.01$; $***p < 0.001$. y-axis units are AlphaScreen counts per second (cps). Bars represent means, and vertical lines represent the standard error of the mean.

## Experimental Section

**General Experimental Procedures.** Optical rotations were measured using a Horiba SEPA-300 polarimeter. UV spectra were recorded on a Shimadzu UV-2401PC spectrometer. IR spectra were obtained on a Tensor 27 spectrometer with KBr pellets. NMR spectra were recorded on a Bruker AV-400 or a DRX-500 spectrometer with TMS as an internal standard. EIMS and FABMS were measured on a Finnigan-4510 spectrometer and a VG Autospec-3000 spectrometer. HRESIMS were determined with an API QSTAR Pulsar 1 spectrometer. Silica gel (200−300 mesh, Qingdao Marine Chemical, Inc., People's Republic of China), RP-18 gel (40−63 $\mu$m, Daiso, Co., Japan), and Sephadex LH-20 (Amersham Biosciences, Sweden) were used for column chromatography. Spots on TLC plates (silica gel GF$_{254}$, Qingdao Marine Chemical, Inc., People's Republic of China) were detected under UV radiation and by heating after spraying with 10% $H_2SO_4$ in EtOH.

**Plant Material.** The rhizome of *A. tatarinowii* was purchased from Yunnan Corporation of Materia Medica, Yunnan Province, People's Republic of China, and identified by Mr. Hong-Yan Sun, at Yunnan Corporation of Materia Medica. A voucher specimen (CHYX0001) was deposited at the State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Sciences, People's Republic of China.

**Extraction and Isolation.** The dried and powdered rhizomes of *A. tatarinowii* (50 kg) were extracted with boiling $H_2O$ (2 × 100 L) and then EtOH (1 × 100 L). The extracts were combined to give a dark brown residue (4.7 kg), which was suspended in $H_2O$ followed by successive partitioning with EtOAc and *n*-BuOH (each 3 × 6 L). The EtOAc-soluble extract was separated by column chromatography. Detailed isolation procedures are given in the Supporting Information.

**Tatarinowin A (1):** colorless gum; $[\alpha]^{27}_D$ +20.3 (*c* 0.13, MeOH); UV (MeOH) $\lambda_{max}$ (log $\varepsilon$) 282 (3.67), 235 (4.04) nm; IR (KBr) $\nu_{max}$ 3428, 2968, 2926, 2907, 1656, 1630, 1618, 1272, 1090, 1013 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 5.88 (1H, s, H-3), 4.15 (1H, d, $J =$ 10.3 Hz, H-5), 2.57 (1H, d, $J =$ 10.3 Hz, H-6), 2.16 (1H, m, H-9a), 2.00 (3H, s, H-15), 1.95 (3H, s, H-14), 1.86 (1H, m, H-9b), 1.74 (1H, m, H-8a), 1.65 (1H, m, H-7), 1.57 (1H, m, H-11), 1.53 (1H, m, H-8b), 0.93 (3H, d, $J =$ 6.6 Hz, H-13), 0.92 (3H, d, $J =$ 6.6 Hz, H-12); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 192.6 (C-2), 161.4 (C-4), 143.9 (C-10), 128.9 (C-3), 128.7 (C-1), 74.3 (C-5), 48.0 (C-6), 38.7 (C-7), 29.3 (C-9), 27.2 (C-11), 21.7 (C-13), 20.6 (C-8, C-14), 20.3 (C-12), 19.9 (C-15); EIMS *m/z* 234 [M]$^+$ (100), 219 (31), 205 (39), 191 (93), 163 (93), 149 (54), 145 (59), 91 (62), 77 (41), 69 (39); HRESIMS *m/z* [M + H]$^+$ 235.1704 (calcd for C$_{15}$H$_{23}$O$_2$, 235.1698).

**Tatarinoid A (2):** colorless gum; $[\alpha]^{27}_D$ −6.9 (*c* 0.21, CHCl$_3$); UV (MeOH) $\lambda_{max}$ (log $\varepsilon$) 329 (3.84), 271 (3.92), 234 (4.14) nm; IR (KBr) $\nu_{max}$ 3446, 2936, 2849, 1650, 1605, 1515, 1468, 1271, 1222, 1115, 1025 cm$^{-1}$; $^1$H and $^{13}$C NMR data, see Table 1; EIMS *m/z* 240 [M]$^+$ (7), 197 (15), 195 (100); HRESIMS *m/z* [M + Na]$^+$ 263.0883 (calcd for C$_{12}$H$_{16}$O$_5$Na, 263.0895).

**Tatarinoid B (3):** colorless gum; $[\alpha]^{27}_D$ −4.8 (*c* 0.32, CHCl$_3$); UV (MeOH) $\lambda_{max}$ (log $\varepsilon$): 293 (3.45) nm; IR (KBr) $\nu_{max}$: 3450, 2936, 2853, 1717, 1514, 1465, 1304, 1238, 1212, 1032 cm$^{-1}$; $^1$H and $^{13}$C NMR data, see Table 1; FABMS *m/z* 240 [M]$^+$ (13), 223 (100), 197 (42); HRESIMS *m/z* [M + Na]$^+$ 263.0906 (calcd for C$_{12}$H$_{16}$O$_5$Na, 263.0895).

**Table 1.** NMR Data of Compounds **2**$^a$ and **3**$^b$

| no. | **2** | | **3** | |
|---|---|---|---|---|
| 1 | 114.9 | | 119.7 | |
| 2 | 154.5 | | 153.1 | |
| 3 | 96.1 | 6.48, s | 99.3 | 6.71, s |
| 4 | 155.2 | | 151.8 | |
| 5 | 143.5 | | 144.8 | |
| 6 | 113.0 | 7.47, s | 114.2 | 6.87, s |
| 7 | 201.4 | | 75.3 | 5.38, s |
| 8 | 72.7 | 5.13, q (6.8) | 209.4 | |
| 9 | 21.1 | 1.34, d (6.8) | 25.5 | 2.02, s |
| 2-OCH$_3$ | 56.2 | 3.96, s | 56.9 | 3.84, s |
| 4-OCH$_3$ | 56.1 | 3.92, s | 56.7 | 3.86, s |
| 5-OCH$_3$ | 56.3 | 3.88, s | 57.3 | 3.76, s |

$^a$ In CDCl$_3$ at 500 MHz for $^1$H and 125 MHz for $^{13}$C. $^b$ In methanol-$d_4$ at 500 MHz for $^1$H and 125 MHz for $^{13}$C.

**Tatarinoid C (4):** colorless gum; $[\alpha]^{27}_D$ −10.2 (*c* 0.17, CHCl$_3$); UV (MeOH) $\lambda_{max}$ (log $\varepsilon$) 292 (3.99) nm; IR (KBr) $\nu_{max}$: 3440, 2929, 2850, 1511, 1464, 1208, 1034 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.07 (1H, s, H-6), 6.91 (1H, s, H-6′), 6.52 (1H, s, H-3), 6.49 (1H, s, H-3′), 4.57 (2H, m, H-7, H-8), [4.57 (1H, d, $J =$ 5.9 Hz, H-7) and 4.53 (1H, m, H-8) recorded at 500 MHz in acetone-$d_6$], 3.86, 3.85, 3.82, 3.79, 3.78, 3.77 (each 3H, s, OC$H_3$), 1.18 (3H, d, $J =$ 5.3 Hz, H-9); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 152.1 (C-2), 151.4 (C-2′), 148.1 (C-4), 147.3 (C-4′), 142.8 (C-5′), 140.3 (C-5), 122.9 (C-1′), 121.3 (C-1), 113.6 (C-6, C-6′), 98.3 (C-3), 98.2 (C-3′), 69.6 (C-8), 56.8, 56.7, 56.6, 56.6, 56.0, 56.0 (6 × OC$H_3$), 45.8 (C-7), 21.6 (C-9); FABMS *m/z* 392 [M]$^+$ (43), 347 (100), 225 (49), 69 (93); HRESIMS *m/z* [M + Na]$^+$ 415.1735 (calcd for C$_{21}$H$_{28}$O$_7$Na, 415.1732).

**AlphaScreen cAMP Assay.** [30] See Supporting Information.

**Supporting Information Available:** The isolation procedures of all the isolates. Structures of known compounds. Quantum calculations of compounds **1** and **2**. The AlphaScreen cAMP assay. This material is available free of charge via the Internet at http://pubs.acs.org.

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