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FACILE SYNTHESIS OF 2-ARYL(GUAIAZULEN-1-YL)METHYLKOJIC ACID DERIVATIVES VIA BENZYLATION

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Abstract – A facile and efficient one-pot procedure for the preparation of 2-aryl(guaiazulen-1-yl)methylkojic acid derivatives by a catalyst-free, benzylation of guaiazulene with kojic acid-substituted benzylic alcohols under mild conditions in good yield is reported.

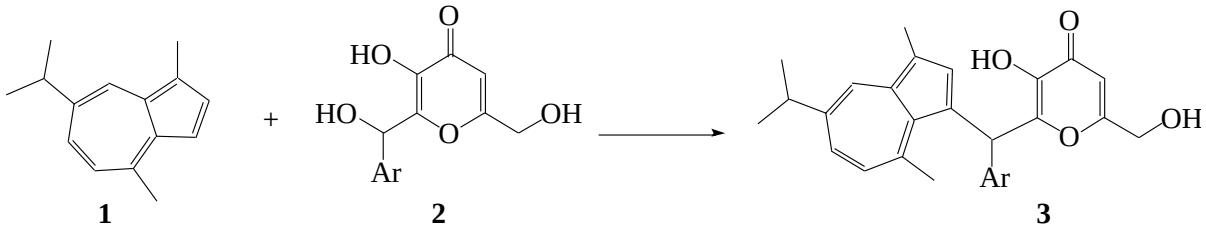
Kojic acid (5-hydroxy-2-hydroxymethyl-4-pyrone) is a natural product that has been isolated from various strains of microorganisms such as *Penicillium*, *Aspergillus*, and *Gluconacetobacter*.[1] It has been known as an additive to prevent browning of food materials in the food industry, as an antioxidant in order to preserve their freshness and to inhibit discoloration.[2] Kojic acid and its analogues, one of the important kind of heterocyclic compounds, possess signifcant bioactivities such as antifungal,[3] anti-neoplastic,[4] anti HIV,[5] anti-inflammatory,[6] antioxidative,[7] anti-diabetic,[8] and tyrosinase inhibitory activities.[9] Therefore, the synthesis of kojic acid derivatives has aroused great interest in the organic and medicinal communities.

Guaiazulene is a known active component of the essential oil of *Guaiacum officinalis* L., and there are a number of reports describing the anti-allergenic and anti-inflammatory activities.[10] Azulene derivatives have attracted interest in medicine as antiulcer drugs,[11] anticancer agents,[12] and as antioxidant therapeutics for neurodegenerative conditions.[13] A variety of heterocycle-fused and substituted azulenes have so far been obtained on the viewpoints of chemical properties and physiological activities by several methods.[14]

Since the past few decades, several azulenylmethanes were prepared by the condensation reaction of azulenes with aryl aldehydes under acidic conditions.[15] Inparticular, the methyl cations, which were stabilized by three or two azulene rings, exhibited extraordinary thermodynamic stabilities.

In recent years, benzylic alcohols and their derivatives have received considerable attention as carbon electrophiles capable of reacting with various carbon, oxygen and sulfur nucleophiles.[16] As part of a

continuing effort in our laboratory toward the development of azulene chemistry,[17] we became interested in exploring the reactivity and synthetic application of guaiazulene[18] to 2-aryl(guaiazulen-1-yl)methyl-kojic acid derivatives (**3**) by a catalyst-free, benzylation of guaiazulene (**1**) with kojic acid-substituted benzylic alcohols (**2**) under mild conditions (**Scheme 1**).



1 **2** **3**

Scheme 1. One-pot synthesis of 2-aryl(guaiazulen-1-yl)methylkojic acid derivatives

First, to optimize the conditions, we initially evaluated the benzylation reaction of guaiazulene (**1**) with 3-hydroxy-2-(hydroxy(phenyl)methyl)-6-(hydroxymethyl)-4*H*-pyran-4-one (**2a**) (Scheme 2). The reaction mixture, which was composed of a 1:1 mixture of **1** and **2a**, was tested under a variety of different conditions. The effects of solvent and temperature were evaluated for this reaction, and the results are summarized in Table 1.

The initial reaction of guaiazulene (**1**) and 3-hydroxy-2-(hydroxy(phenyl)methyl)-6-(hydroxymethyl)-4*H*-pyran-4-one (**2a**) stirred for 24 h at 25 °C in dichloromethane (Table 1, Entry 1). After the reaction was completed, the mixture was purified by flash column chromatography to give pure product, 2-(guaiazulene-1-yl)(phenyl)methyl-3-hydroxy-6-(hydroxymethyl)-4*H*-pyran-4-one (**3a**), whose structure was characterized by ^{1}H NMR, ^{13}C NMR, IR, MS spectra and elemental analysis.

After the above observation, we also examined the influence of solvents such as toluene, MeCN, EtOH, and DMF without catalysts provided the desired product **3a** in 52–68% yield (Table 1, entries 2–6). In order to make the reaction more efficient, next we employed the model reaction in AcOH at 100 °C, and to our delight the desired product was obtained in 74% yield within 2 h (Table 1, entry 5). Inspired by these results, the model reaction was performed in AcOH at 70 °C to furnish the desired product **3a** in 84% yield within 3 h (Table 1, entry 8). From these optimization results, we found that AcOH (at 70 °C) is the most effective solvent media for this one-pot synthesis of 2-(guaiazulen-1-yl)(phenyl)methyl-3-hydroxy-6-(hydroxymethyl)-4*H*-pyran-4-one (**3a**).

In addition, the previous work reported successful preparation of 2-aryl(guaiazulen-1-yl)methylkojic acid derivatives in refluxing NH_4OAc solution.[19] However, this method suffer from such disadvantages as long reaction times and low yield.

Table 1. Optimizing the reaction condititions for the synthesis of **3a***

Entry	Solvent	Temperature	Time (h)	Yield (%)
1	CH_2Cl_2	25	24	38
2	CH_2Cl_2	40	12	52
2	MeCN	80	10	63
3	EtOH	80	8	68
4	DMF	100	5	65
5	AcOH	100	2	74
6	toluene	100	12	46
7	AcOH	80	2	80
8	AcOH	70	3	84
9	AcOH	60	5	80
10	AcOH	25	24	54

* Reaction conditions: guaiazulene (**1**, 1.0 mmol) and benzylic alcohol (**2a**, 1.0 mmol), solvent (20 mL).

Next, with this optimized procedure in hand, a range of 2-aryl(guaiazulen-1-yl)methylkojic acid derivatives were synthesized by the one-pot condensation of guaiazulene with 3-hydroxy-2-(hydroxy-(aryl)methyl)-6-(hydroxymethyl)-4*H*-pyran-4-ones (see Table 2).

Table 2. Synthesis of 2-aryl(guaiazulen-1-yl)methyl kojic acid derivatives **3**

Entry	Ar	Time (h)	Product (**3**)	Yield (%)
1	C_6H_5	3	**3a**	84
2	4-MeC_6H_4	3	**3b**	85
3	3,4,-$(Me)_2C_6H_3$	3	**3c**	88
4	2-$MeOC_6H_4$	4	**3d**	80
5	4-$MeOC_6H_4$	3	**3e**	86
6	3,4-$(MeO)_2C_6H_3$	3	**3f**	90
7	3,4,5-$(MeO)_3C_6H_2$	2	**3g**	92
8	4-ClC_6H_4	4	**3h**	84
9	3-$NO_2C_6H_4$	5	**3i**	80
10	4-pyridine	3	**3j**	87

It was found that phenyl groups, bearing either electron-withdrawing or electron-donating groups, were tolerated under the reaction conditions, leading to the final products in satisfactory yields (up to 92%). To the best of our knowledge, this new procedure provides the first example of an efficient synthesis for the 2-aryl(guaiazulen-1-yl)methylkojic acid derivatives. The structures of all the synthesized compounds were established by IR, NMR, MS spectroscopy and elemental analysis.

In summary, we have demonstrated for the efficient method for the synthesis of 2-aryl(guaiazulen-1-yl)methylkojic acid derivatives by a catalyst-free, benzylation of guaiazulene with kojic acid-substituted benzylic alcohols under mild conditions in good yield. This approach offers an effective route for the construction of heteroarylazulene frameworks in a one-step process from commercially available starting materials.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. The NMR spectra were recorded with a Bruker Avance 400 spectrometer (400 MHz for ^{1}H and 100 MHz for ^{13}C) using TMS an internal reference. IR spectra were measured on Shimadzu FTIR-8300 spectrophotometer. C, H and N analyses were performed by a HP-MOD 1106 microanalyzer. LC-MS analyses were performed on waters Q-TOF micro mass spectrometer. The preparation of kojic acid-substituted benzylic alcohols (**2**)[20] were according to the literature procedure. All other chemicals used in this study were commercially available.

General procedure for the preparation of 2-aryl(guaiazulen-1-yl)methylkojic acid derivatives. A mixture of guaiazulene **1** (1 mmol) and appropriate 3-hydroxy-2-(hydroxy(aryl)methyl)-6-(hydroxymethyl)-4*H*-pyran-4-one **2** (1 mmol) was dissolved in AcOH (25 mL) and the reaction was heated at 70 °C. After completion monitored by TLC, the reaction mixture was allowed to cool to room temperature, and then water (40 mL) was added to the mixture. EtOAc (50 mL) was added to the mixture. The organic layer was washed with brine (50 mL), dried over anhydrous Na_2SO_4 and evaporated to dryness. The residue was recrystallized from isopropanol to afford the corresponding products **3a-j**.

2-[(Guaiazulen-1-yl)(phenyl)methyl]-3-hydroxy-6-(hydroxymethyl)-4*H*-pyran-4-one (3a): Blue crystals. mp 218-220 °C; IR (KBr): *v* 3379, 3168, 1654 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.28 (d, J = 6.8 Hz, 6H), 2.54 (s, 3H), 2.69 (s, 3H), 3.04-3.07 (m, 1H), 4.21-4.25 (m, 2H), 5.64 (s, 1H), 6.32 (s, 1H), 6.79 (s, 1H), 7.05 (d, J = 7.2 Hz, 1H), 7.17-7.19 (m, 2H), 7.26-7.29 (m, 3H), 7.31 (d, J = 7.2 Hz, 1H), 7.55 (s, 1H), 8.09 (s, 1H), 9.16 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.1, 167.7, 144.8, 139.4, 138.7, 137.8, 137.4, 134.5, 133.5, 133.0, 132.8, 132.3, 130.9, 128.8, 127.1, 124.3, 123.6, 117.9, 116.7, 58.0, 47.7, 37.6, 34.0, 27.7, 19.6, 13.2. MS (ESI) *m*/*z*: 429 [M+H]$^{+}$. *Anal*. Calcd for $C_{28}H_{28}O_4$: C 78.48, H 6.59. Found: C 78.53, H 6.62.

2-[(Guaiazulen-1-yl)(4-methylphenyl)methyl]-3-hydroxy-6-(hydroxymethyl)-4*H*-pyran-4-one (3b):

Blue crystals. mp 228-230 °C; IR (KBr): *v* 3363, 3175, 1658 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.27 (d, *J* = 6.8 Hz, 6H), 2.23 (s, 3H), 2.54 (s, 3H), 2.89 (s, 3H), 3.02-3.05 (m, 1H), 4.22-4.25 (m, 2H), 5.67 (s, 1H), 6.34 (s, 1H), 6.77 (s, 1H), 6.91-6.95 (m, 3H),7.06 (d, *J* = 8.0 Hz, 2H), 7.23 (d, *J* = 7.2 Hz, 1H), 7.57 (s, 1H), 8.09 (s, 1H), 9.15 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.1, 167.7, 152.4, 144.8, 141.5, 140.1, 139.6, 139.5, 138.1, 135.8, 135.3, 134.1, 132.6, 129.4, 128.7, 127.6, 124.8, 124.7, 109.5, 59.9, 56.5, 42.6, 37.2, 26.9, 24.8, 21.0, 13.3. MS (ESI) *m*/*z*: 443 $[M+H]^+$. *Anal*. Calcd for $C_{29}H_{30}O_4$: C 78.71, H 6.83. Found: C 78.53, H 6.62.

2-[(3,4-Dimethylphenyl)(guaiazulen-1-yl)methyl]-3-hydroxy-6-(hydroxymethyl)-4*H*-pyran-4-one (3c): Blue crystals. mp 234-236 °C; IR (KBr): *v* 3352, 3164, 1661 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.27 (d, *J* = 6.8 Hz, 6H), 2.11 (s, 3H), 2.14 (s, 3H), 2.54 (s, 3H), 2.89 (s, 3H), 3.02-3.05 (m, 1H), 4.22-4.25 (m, 2H), 5.64 (s, 1H), 6.31 (s, 1H), 6.72 (s, 1H), 6.86 (d, *J* = 10.8 Hz, 1H), 6.89-6.91 (m, 2H), 7.01-7.03 (m, 1H), 7.34 (d, *J* = 10.2 Hz, 1H), 7.56 (s, 1H), 8.09 (s, 1H), 9.09 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.1, 167.6, 152.5, 144.8, 141.4, 140.1, 139.6, 138.0, 136.5, 135.2, 134.6, 134.0, 132.6, 129.9, 129.8, 127.5, 126.3, 124.8, 124.6, 109.4, 59.9, 56.4, 42.5, 37.2, 26.9, 24.8, 19.9, 19.4, 18.9, 13.3. MS (ESI) *m*/*z*: 457 $[M+H]^+$. *Anal*. Calcd for $C_{30}H_{32}O_4$: C 78.92, H 7.06. Found: C 78.83, H 7.04.

2-[(Guaiazulen-1-yl)(2-methoxyphenyl)methyl]-3-hydroxy-6-(hydroxymethyl)-4*H*-pyran-4-one (3d): Blue crystals. mp 227-229 °C; IR (KBr): *v* 3360, 3172, 1655 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.27 (d, *J* = 6.8 Hz, 6H), 2.52 (s, 3H), 2.81 (s, 3H), 3.03-3.05 (m, 1H), 3.71 (s, 3H), 4.15-4.17 (m, 2H), 5.60 (s, 1H), 6.29 (s, 1H), 6.81-6.88 (m, 3H), 6.95-6.98 (m, 2H), 7.20-7.23 (m, 1H), 7.34 (d, *J* = 10.8 Hz, 1H), 7.44 (s, 1H), 8.07 (s, 1H), 8.85 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.1, 167.3, 156.4, 152.6, 145.2, 141.2, 139.8, 139.5, 137.9, 135.3, 134.0, 132.4, 130.6, 130.5, 128.4, 127.4, 124.8, 124.2, 120.7, 111.3, 109.4, 59.9, 56.1, 37.8, 37.2, 36.2, 26.3, 24.8, 13.2. MS (ESI) *m*/*z*: 459 $[M+H]^+$. *Anal*. Calcd for $C_{29}H_{30}O_5$: C 75.96, H 6.59. Found: C 76.02, H 6.61.

2-[(Guaiazulen-1-yl)(4-methoxyphenyl)methyl]-3-hydroxy-6-(hydroxymethyl)-4*H*-pyran-4-one (3e): Blue crystals. mp 190-192 °C; IR (KBr): *v* 3362, 3164, 1658 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.38 (d, *J* = 6.8 Hz, 6H), 2.69 (s, 3H), 3.04 (s, 3H), 3.14-3.16 (m, 1H), 3.80 (s, 3H), 4.34-4.39 (m, 2H), 5.82 (s, 1H), 6.49 (s, 1H), 6.89 (s, 1H), 6.95-6.70 (m, 3H), 7.11 (d, *J* = 8.8 Hz, 2H), 7.45 (d, *J* = 9.6 Hz, 1H), 7.72 (s, 1H), 8.27 (s, 1H), 9.27 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.1, 167.6, 158.1, 152.5, 144.9, 141.4, 140.1, 139.4, 138.0, 135.2, 134.5, 132.6, 129.9, 129.1, 127.5, 125.0, 124.6, 114.2, 109.5, 59.9, 55.4, 42.2, 37.2, 26.9, 24.8, 19.1, 13.3. MS (ESI) *m*/*z*: 459 $[M+H]^+$. *Anal*. Calcd for $C_{29}H_{30}O_5$: C 75.96, H 6.59. Found: C 76.04, H 6.62.

2-[(3,4-Dimethoxyphenyl)(guaiazulen-1-yl)methyl]-3-hydroxy-6-(hydroxymethyl)-4*H*-pyran-4-one (3f): Blue crystals. mp 202-204 °C; IR (KBr): *v* 3365, 3167, 1656 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.27 (d, *J* = 6.8 Hz, 6H), 2.54 (s, 3H), 2.89 (s, 3H), 3.02-3.04 (m, 1H), 3.68 (s, 3H), 3.76 (s, 3H),

4.20-4.23 (m, 2H), 5.66 (s, 1H), 6.31 (s, 1H), 6.72-6.76 (m, 2H), 6.86-6.89 (m, 2H), 7.01 (d, *J* = 8.8 Hz, 1H), 7.37 (d, *J* = 9.6 Hz, 1H), 7.56 (s, 1H), 8.09 (s, 1H), 9.10 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 174.2, 167.6, 152.6, 149.0, 147.8, 144.9, 141.3, 140.1, 139.4, 138.1, 135.2, 134.9, 132.61, 132.0, 131.9, 129.1, 127.5, 125.0, 124.6, 121.2, 112.6, 111.9, 109.5, 60.0, 55.8, 55.7, 42.6, 37.2, 26.9, 24.7, 19.1, 13.2. MS (ESI) *m*/*z*: 489 $[M+H]^+$. *Anal*. Calcd for $C_{30}H_{32}O_6$: C 73.75, H 6.60. Found: C 73.79, H 6.63.

2-[(Guaiazulen-1-yl)(3,4,5-trimethoxyphenyl)methyl]-3-hydroxy-6-(hydroxymethyl)-4*H*-pyran-4-one (3g): Blue crystals. mp 221-223 °C; IR (KBr): *ν* 3358, 3162, 1659 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 1.27 (d, *J* = 6.8 Hz, 6H), 2.54 (s, 3H), 2.97 (s, 3H), 3.04-3.06 (m, 1H), 3.62 (s, 9H), 4.24-4.28 (m, 2H), 5.66 (s, 1H), 6.31 (s, 1H), 6.43 (s, 2H), 6.70 (s, 1H), 6.93 (d, *J* = 9.6 Hz, 1H), 7.34 (d, *J* = 9.6 Hz, 1H), 7.58 (s, 1H), 8.08 (s, 1H), 9.14 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 174.1, 167.5, 153.2, 152.1, 144.9, 141.3, 140.1, 139.5, 138.2, 138.1, 136.5, 135.2, 134.1, 132.5, 127.6, 124.7, 124.6, 109.6, 106.5, 103.7, 60.4, 60.0, 56.3, 43.0, 37.2, 27.2, 24.8, 13.3. MS (ESI) *m*/*z*: 519 $[M+H]^+$. *Anal*. Calcd for $C_{31}H_{34}O_7$: C 71.80, H 6.61. Found: C 71.83, H 6.64.

2-[(4-Chlorophenyl)(guaiazulen-1-yl)methyl]-3-hydroxy-6-(hydroxymethyl)-4*H*-pyran-4-one (3h): Blue crystals. mp 235-237 °C; IR (KBr): *ν* 3362, 3158, 1654 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 1.34 (d, *J* = 6.8 Hz, 6H), 2.59 (s, 3H), 2.96 (s, 3H), 3.05-3.07 (m, 1H), 4.30-4.34 (m, 2H), 5.34 (s, 1H), 6.87-6.93 (m, 2H), 7.01 (d, *J* = 8.8 Hz, 2H), 7.21 (d, *J* = 8.8 Hz, 2H), 7.35 (d, *J* = 9.6 Hz, 1H), 7.47-7.53 (m, 2H), 7.73 (s, 1H), 8.14 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 174.4, 167.8, 151.7, 144.9, 140.4, 138.8, 138.2, 135.1, 134.1, 133.0, 132.4, 130.9, 129.9, 128.8, 128.5, 127.8, 124.9, 122.8, 113.8, 65.6, 37.7, 30.5, 27.3, 24.6, 19.2, 13.8. MS (ESI) *m*/*z*: 463 $[M+H]^+$. *Anal*. Calcd for $C_{28}H_{27}ClO_4$: C 72.64, H 5.88. Found: C 72.68, H 5.80.

2-[(Guaiazulen-1-yl)(3-nitrophenyl)methyl]-3-hydroxy-6-(hydroxymethyl)-4*H*-pyran-4-one (3i): Blue crystals. mp 221-223 °C; IR (KBr): *ν* 3367, 3162, 1659 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 1.28 (d, *J* = 6.8 Hz, 6H), 2.55 (s, 3H), 2.90 (s, 3H), 3.06-3.08 (m, 1H), 4.19-4.22 (m, 2H), 5.62 (s, 1H), 6.30 (s, 1H), 7.53-7.65 (m, 4H), 7.78-7.80 (m, 1H), 7.84 (s, 1H), 8.25 (s, 1H), 9.43 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 174.3, 168.2, 151.0, 149.6, 148.2, 144.6, 143.9, 141.8, 140.6, 139.2, 138.2, 135.5, 134.5, 133.1, 130.4, 128.0, 125.1, 123.2, 122.9, 120.9, 109.3, 59.8, 42.9, 37.2, 27.0, 24.8, 18.9, 13.4. MS (ESI) *m*/*z*: 474 $[M+H]^+$. *Anal*. Calcd for $C_{28}H_{27}NO_6$: C 71.02, H 5.75, N 2.96. Found: C 71.04, H 5.78, N 2.98.

2-[(Guaiazulen-1-yl)(pyridin-4-yl)methyl]-3-hydroxy-6-(hydroxymethyl)-4*H*-pyran-4-one (3j): Blue crystals. mp 212-214 °C; IR (KBr): *ν* 3354, 3160, 1653 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): *δ* 1.27 (d, *J* = 6.8 Hz, 6H), 2.53 (s, 3H), 2.84 (s, 3H), 3.02-3.05 (m, 1H), 4.15-4.19 (m, 2H), 5.61 (s, 1H), 6.31 (s, 1H), 6.81-6.88 (m, 3H), 6.96-6.98 (m, 2H), 7.21-7.24 (m, 1H), 7.33 (d, *J* = 10.8 Hz, 1H), 7.45 (s, 1H), 8.07 (s, 1H), 8.86 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): *δ* 174.1, 167.3, 152.6, 145.2, 141.3, 139.8, 139.6, 137.9, 135.3, 134.0, 132.4, 130.6, 130.5, 128.4, 127.4, 124.9, 124.2, 109.4, 59.9, 56.1, 37.8, 37.2,

26.3, 24.8, 13.3. MS (ESI) *m*/*z*: 430 $[M+H]^{+z}$. *Anal*. Calcd for $C_{27}H_{27}NO_4$: C 75.50, H 6.34, N 3.26. Found: C 75.53, H 6.36, N 3.27.

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