A New Synthetic Approach to Coumestan Derivatives

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A new method for the preparation of coumestan derivatives was described involving an intramolecular palladium-catalyzed ring closure reaction of coumarins obtained from condensation of substituted *o*-hydroxyphenylacetic acid and *o*-hydroxybenzaldehyde.

Keywords Coumestan derivatives, palladium(II) chloride, coumarins

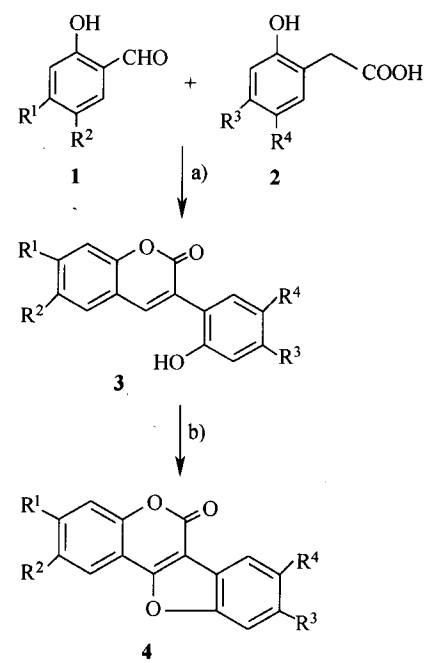
Introduction

Since the isolation of wedelolatone as the active principle of *wedelia calandu-laceae* and *eclipia prostrata*[1] that are widely used as traditional medicine for the treatment of liver disorders including liver cirrhosis and infective heptatitis both in China and India,[2] a series of coumestans, 6*H*-benzofuro[3, 2-c][1]benzopyran-6-ones were discovered from natural sources.[3] They possess a variety of biological activities, such as estrogenic, antibacterial, insecticidal and phytodexine activities.[4] Structurally coumestans can be regarded as a fused polynuclear ring system bearing furan ring and cyclic lactone moiety. The wide range of biological functions of coumestan derivatives and their common lactonic structures has aroused much interest in their structure-activity relationship analysis and synthetic studies. For the purpose to examine the structural effect of coumestans on their biological activity, some fluorine-containing coumestan derivatives and their precursors coumarins were prepared.

Results and discussion

Several syntheses of the coumestan system are known.[5] Our synthetic route leading to coumestans, 6H-benzofuro[3, 2-c][1]benzopyran-6-ones, is based on the following sequence of reactions, as shown in Scheme 1. As the starting compounds in the Scheme 1, substituted salicylaldehydes (**1**) were prepared from corresponding *p*-methoxyphenol, *p*-fluorophenol,[6] and resorcinol[7] *via* Reimer-Tiemann reaction, while the substituted phenylacetic acids (**2**) were synthesed by Willgenedt reaction[8] of substituted acetophenones that were obtained by Friedel-Crafts reaction.[9]

Scheme 1



R^1=H, OH; R^2=H, OCH_3, F; R^3=H, CF_3; R^4=H, CH_3
Conditions and reagents: a), CH_3COONa, $(CH_3CO)_2O$, CH_3COOH, reflux; b), $PdCl_2$, DMF, 150°C.

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The key intermediates, 3-(2-hydroxyphenyl)-coumarins (**3a-j**), were prepared by Perkin reaction.[5i] Thus, treatment of *o*-hydroxyphenylacetic acids with *o*-hydroxybenzaldehydes in the presence of acetic acid, acetic anhydride and sodium acetate afforded the corresponding coumarins **3** in high yields (Table 1).

Table 1 Compounds **3** prepared

Compounds	R^1	R^2	R^3	R^4	m.p.(℃)	Yield (%)
3a	H	H	H	H	212—213	89
3b	H	H	H	CH_3	138—140	90
3c	H	H	CF_3	H	213—215	92
3d	H	OCH_3	H	H	144—145	85
3e	H	OCH_3	H	CH_3	144—146	82
3f	H	OCH_3	CF_3	H	210—212	89
3g	H	F	CF_3	H	222—223	91
3h	OH	H	H	H	201—202	90
3i	OH	H	H	CH_3	182—183	90
3j	OH	H	CF_3	H	232—233	84

The cyclization of *o*-allylic phenols by palladium salts has been reported for the syntheses of cyclic ethers.[10] Unfortunately, our trials on the cyclization of **3a** as model reaction, using catalysts such as $Pd(OAc)_2$, $Pd_2(dba)_3 \cdot CHCl_3$, or $PdCl_2(PhCN)_2$, were unsuccessful and little or no product **4a** could be isolated. However, when **3a** was heated in water-methanol (1:4, *V*:*V*) solution with the catalysis of $PdCl_2$, **4a** was obtained in 35% yield along with 63% of starting material **3a** recovered. When **3a** was treated with $PdCl_2$ in DMF at 150℃ for 24 h, **4a** was achieved in 62% yield. We then applied this reaction condition to other substrates and the corresponding coumestans **4** were prepared in moderate yield (32—62%) (Table 2). The reaction conditions are simple. In addition, the reaction is insensitive to oxygen and moisture, which makes it easy to operate.

The formation of coumestans **4** is expected to be in accord with the well-known reactions of olefins with alcohols in the presence of palladium derivatives.[11] The reaction mechanism could be postulated as the coordination of the double bond in **3** with palladium dichloride followed by intramolecular attack by OH group and subsequent elimination of HPdX.[12]

In summary, we described a new approach to the preparation of substituted coumestan derivatives *via* intramolecular palladium-catalyzed ring closure. All the new compounds were characterized by their ^1H NMR, mass spectral data and elemental analyses. To the best of our knowledge, most of these compounds have not been reported, and their biological activities are currently being studied.

Table 2 Compounds **4** prepared

Compounds	R^1	R^2	R^3	R^4	m.p.(℃)	Yield (%)
4a	H	H	H	H	180—182	62
4b	H	H	H	CH_3	189—191	54
4c	H	H	CF_3	H	157—158	56
4d	H	OCH_3	H	H	155—156	50
4e	H	OCH_3	H	CH_3	172—173	50
4f	H	OCH_3	CF_3	H	167—169	42
4g	H	F	CF_3	H	158—159	50
4h	OH	H	H	H	253—255	40
4i	OH	H	H	CH_3	280—281	33
4j	OH	H	CF_3	H	265—266	30

Experimental

Melting points are uncorrected. IR spectra were taken on a Shimadzu-440 spectrometer. ^{1}H NMR spectra were recorded on a Bruker AM-300 or JEOL-90Q. Chemical shifts for ^{1}H NMR spectra are reported in δ value downfield from TMS. ^{19}F NMR spectra were obtained on a Varian EM 360A spectrometer using CF_3COOH as an external standard, positive for downfield shifts. EIMS data were obtained on a HP5989A mass spectrometer.

2-Hydroxy-4-trifluoromethylphenylacetic acid (**2c**)

A mixture of 2-hydroxy-4-trifluoromethylacetophenone[13] (1.8 g, 8.8 mmol), morpholine (2.783 g, 31.9 mmol) and sulfur (0.893 g, 27.9 mmol) was heated at 140℃ for 4 h. The resulting mixture was then cooled down, diluted with chloroform (15 mL) and washed successively with water (15 mL), hydrochloric acid (2 mol/L, 16 mL) and water (15 mL). After removal of solvent, the crude morpholide was hydrolyzed by boiling with 8.8 mL of aqueous sodium hydroxide solution (20%) for 8 h. After cooled down and acidified (pH 1) with concentrated hydrochloric acid, the mixture was boiled with celite and filtered. The filtrate was kept at 0℃ for 12 h. Filtration of the solution gave a light-yellow solid as the product **2c** (0.757 g, m.p. 133—135℃). Extraction of the filtrate with ether, drying and evaporation of the solvent gave 0.253 g of **2c** (m.p. 131—133℃). The combined yield was 52%. ^{1}H NMR (90 MHz, acetone-d_6) δ: 6.95 (d, J = 9 Hz, 1H, H-5), 6.73 (s, 1H, H-3), 6.68 (d, J = 9 Hz, 1H, H-6), 3.24 (s, 2H, CH_2); ^{19}F NMR (acetone-d_6/TFA) δ: −14.4 (s); IR (KBr) ν: 3326 (OH), 1738 (C=O), 1112 (C—F) cm^{-1}; MS (EI) m/z(%): 220 (M^+, 7.07), 202 (M^+ − H_2O, 100), 175 (M^+ − COOH, 14.03); Anal. calcd for $C_9H_7F_3O_3$: C 49.10, H 3.20; found C 49.03, H 3.16.

Preparation of 3-(2-hydroxyphenyl) coumarins (**3a—j**)

The general procedure for the preparation of 3-(2-hydroxyphenyl) coumarins was as follows: A mixture of *o*-hydroxybenzaldehyde (1 mmol), *o*-hydroxyphenylacetic acid (1.0 mmol), acetic anhydride (2.4 mmol), sodium acetate (5.0 mmol), and acetic acid (4 mL) was heated under refluxed for 24 h. After removal of the acetic acid, 30 mL of water was added to the resulting mixture, and the precipitates were collected by filtration. The crude product was purified by column chromatography on silica gel using EtOAc-petroleum ether (1:10, V:V) as the eluent. Upon evaporation of solvent, pure coumarin derivatives were obtained as light-yellow crystalline compounds.

3-(2-Hydroxyphenyl)-2H-benzopyran-2-one (**3a**) m.p. 212—213℃. (lit.[14] m.p. 212—213℃); ^{1}H NMR (90 MHz, DMSO-d_6) δ: 7.72 (s, 1H, H-4), 6.60—7.60 (m, 8H, Ar-H); IR (KBr) ν: 3300 (OH), 1700 (C=O) cm^{-1}; MS (EI) m/z(%): 238 (M^+,100), 221 (M^+ − OH, 23.67).

3-(2-Hydroxy-5-methylphenyl)-2H-benzopyran-2-one (**3b**) m.p. 138—140℃; ^{1}H NMR (90 MHz, acetone-d_6) δ: 8.53 (s, H, OH), 8.02 (s, 1H, H-4), 6.94—7.71 (m, 7H, Ar-H), 2.31 (s, 3H, CH_3); IR (KBr) ν: 3399 (OH), 1710 (C=O) cm^{-1}; MS (EI) m/z(%): 252 (M^+, 100), 253 (M^+ + 1, 21.58), 235 (M^+ − OH, 11.78); HRMS calcd for $C_{16}H_{12}O_3$ 252.07864, found 252.08140.

3-(2-Hydroxy-4-trifluoromethylphenyl)-2H-benzopyran-2-one (**3c**) m.p. 213—215℃; ^{1}H NMR (90 MHz, acetone-d_6) δ: 8.11 (s, 1H, OH), 7.25—7.78 (s, 8H, Ar-H); ^{19}F NMR (acetone-d_6/TFA) δ: −14.2; IR (KBr) ν: 3338 (OH), 1674 (C=O), 1106 (C—F) cm^{-1}; MS (EI) m/z(%): 306 (M^+, 100), 307 (M^+ + 1, 31.06), 289 (M^+ − OH, 21.83); Anal. calcd for $C_{16}H_9F_3O_3$: C 62.80, H 3.00; found C 62.58, H 3.17.

3-(2-Hydroxyphenyl)-6-methoxy-2H-benzopyran-2-one (**3d**) m.p. 144—145℃; ^{1}H NMR (90 MHz, acetone-d_6) δ: 7.91 (s, 1H, OH), 6.71—7.21 (m, 8H, Ar-H), 3.96 (s, 3H, OCH_3); IR (KBr) ν: 3323 (OH), 1714 (C=O) cm^{-1}; MS (EI) m/z(%): 268 (M^+, 100), 269 (M^+ + 1, 27.40), 251 (M^+ − OH, 7.95), 240 (M^+ − CO, 37.81); HRMS calcd for C_{16}-H_{12} O_4: 268.07356, found 268.07634.

3-(2-Hydroxyl-5-methylphenyl)-6-methoxy-2H-

benzoran-2-one (**3e**) m.p. 144—146℃; ^{1}H NMR (90 MHz, acetone-d_6) δ: 8.11 (s, 1H, OH), 7.90 (s, 1H, H-4), 6.79—7.40 (m, 6H, Ar-H), 3.87 (s, 3H, OCH_3), 2.28 (s, 3H, CH_3); IR (KBr) ν: 3197 (OH), 1714 (C=O) cm^{-1}; MS (EI) *m/z*(%): 282 (M^+, 100), 265 (M^+ - OH, 6.64), 254 (M^+ - CO, 49.75); HRMS calcd for $C_{17}H_{14}O_4$: 282.08921, found 282.09285.

3-(2-*Hydroxyl*-4-*trifluoromethylphenyl*)-6-*methoxy*-2*H*-*benzopyran*-2-*one* (**3f**) m.p. 210—212℃; ^{1}H NMR (90 MHz, acetone-d_6) δ: 7.72 (s, 1H, OH), 6.62—7.47 (m, 7H, Ar-H), 3.54 (s, 3H, OCH_3); ^{19}F NMR (acetone-d_6/TFA) δ: -14.4; IR (KBr) ν: 3331 (OH), 1683, 1668 (C=O), 1108 (C—F) cm^{-1}; MS (EI) *m/z*(%): 336 (M^+, 100), 337 (M^+ + 1, 18.12), 308 (M^+ - CO, 34.45); Anal. calcd for $C_{17}H_{11}F_3O_4$: C 60.72, H 3.30, found C 60.59, H 3.53.

6-*Fluoro*-3-(2-*hydroxy*-4-*trifluoromethylphenyl*)-2*H*-*benzopyran*-2-*one* (**3g**) m.p. 222—223℃; ^{1}H NMR (90 MHz, acetone-d_6) δ: 7.66 (s, 1H, OH), 6.76—7.20 (m, 7H, Ar-H); ^{19}F NMR (acetone-d_6/TFA) δ: -14.4 (s), 42.2 (s); IR (KBr) ν: 3345 (OH), 1671 (C=O), 1141, 1119 (C—F) cm^{-1}; MS (EI) *m/z*(%): 324 (M^+,100), 307 (M^+ - OH, 14.73); HRMS calcd for $C_{16}H_8F_4O_3$: 324.04096, found: 324.03731.

7-*Hydroxy*-3-(2-*hydroxyphenyl*)-2*H*-*benzopyran*-2-*one* (**3h**) m.p. 201—202℃; ^{1}H NMR (90 MHz, acetone-d_6) δ: 7.96 (s, 1H, OH), 6.86—7.64 (m, 9H, Ar-H); IR (KBr) ν: 3289 (OH), 1691 (C=O) cm^{-1}; MS (EI) *m/z*(%): 254 (M^+,100), 237 (M^+ - OH, 15.81), 226 (M^+ - CO, 44.68); HRMS calcd for $C_{15}H_{10}O_4$: 254.05791, found 254.05799.

7-*Hydroxy*-3-(2-*hydroxy*-5-*methylphenyl*)-2*H*-*benzopyran*-2-*one* (**3i**) m.p. 182—183℃; ^{1}H NMR (90 MHz, acetone-d_6) δ: 7.90 (s, 1H, OH), 6.82—7.57 (m, 8H, Ar-H); IR (KBr) ν: 3307 (OH), 1684 (C=O) cm^{-1}; MS (EI) *m/z*(%): 268 (M^+, 100), 251 (M^+ - OH, 12.55), 240 (M^+ - CO, 42.21); HRMS calcd for $C_{16}H_{12}O_4$: 268.07356, found 268.06971.

7-*Hydroxy*-3-(2-*hydroxy*-4-*trifluoromethylphenyl*)-2*H*-*benzopyran*-2-*one* (**3j**) m.p. 232—233℃; ^{1}H NMR (90 MHz, acetone-d_6) δ: 7.85 (s, 1H, OH), 6.67—7.25 (m, 8H, Ar-H); ^{19}F NMR (acetone-d_6/TFA) δ: -15 (s); IR (KBr) ν: 3319 (OH), 1680 (C=O), 1120 (C—F) cm^{-1}; MS (EI) *m/z*(%): 322 (M^+, 100), 305 (M^+ - OH, 19.64), 303 (M^+ - F, 7.08); HRMS calcd for $C_{16}H_9F_3O_4$: 322.04530, found 322.04573.

Preparation of coumestan derivatives (**4a—j**)

The general procedure for the cyclization of 3-(2-hydroxyphenyl)coumarins was as follows: To a solution of 3-(2-hydroxyphenyl)coumarins (0.25 mmol) in DMF (10 mL) were added palladium dichloride (0.25 mmol) and sodium acetate (3.39 mmol). The mixture was then heated at 150℃ for 24 h. After being cooled down to room temperature, the resulting mixture was filtered off. Water (50 mL) was added to the filtrate and the resulting mixture was extracted with ether (6 × 20 mL). The combined organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using EtOAc-petroleum ether (1:8, *V*:*V*) as the eluent. Upon removing of solvent, pure coumestan derivatives were obtained as light-yellow crystalline compounds.

6*H*-*Benzofuro*[3,2-*c*][1]*benzopyran*-6-*one* (**4a**) m.p. 180—182℃ (lit.[5h] m.p. 179—181℃); ^{1}H NMR (90 MHz, $CDCl_3$) δ: 7.95—8.15 (m, 2H, H-7, H-4), 7.25—7.72 (m, 6H, Ar-H); IR (KBr) ν: 1735 (C=O), 1625 (C=C) cm^{-1}; MS (EI) *m/z* (%): 236 (M^+, 100), 208 (M^+ - CO, 28.87).

8-*Methyl*-6*H*-*benzofuro*[3,2-*c*][1]*benzopyran*-6-*one* (**4b**) m.p. 189—191℃; ^{1}H NMR (90 MHz, $CDCl_3$) δ: 7.36—8.08 (m, 7H, Ar-H), 2.53 (s, 3H, CH_3); IR (KBr) ν: 1734 (C=O), 1631 (C=C) cm^{-1}; MS (EI) *m/z*(%): 250 (M^+, 100), 249 (M^+ - 1, 53.99), 222 (M^+ - CO, 5.90); Anal. calcd for $C_{16}H_{10}O_3$: C 76.80, H 4.03, found 76.65, H 4.08.

9-*Trifuoromethyl*-6*H*-*benzofuro*[3,2-*c*][1]*benzopyran*-6-*one* (**4c**) m.p. 157—158℃; ^{1}H NMR (90 MHz, $CDCl_3$) δ: 7.38—8.22 (m, 6H, Ar-H),

7.19—7.28 (m, 1H, Ar-H); ^{19}F NMR ($CDCl_3$/TFA) δ: −16.3 (s); IR (KBr) ν: 1748 (C=O), 1120 (C—F) cm^{-1}; MS (EI) *m/z*(%): 304 (M^+, 100), 305 (M^+ + 1, 23.22), 285 (M^+ − F, 6.02), 276 (M^+ − CO, 23.65); HRMS calcd for $C_{16}H_7F_3O_3$ 304.03473, found 304.02996.

2-Methoxy-6H-benzofuro[3,2-*c*][1]*benzopyran-6-one* (**4d**) m.p. 156—157℃ (lit.[15] m.p. 154—156℃); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.90—8.11 (m, 1H, Ar-H), 7.02—7.58 (m, 6H, Ar-H), 3.83 (s, 3H, OCH_3); IR (KBr) ν: 1739 (C=O), 1567 (C=C) cm^{-1}; MS (EI) *m/z*(%): 266 (M^+, 100), 267 (M^+ + 1, 18.37), 251 ($M^+ - CH_3$, 62.19).

2-Methoxy-8-methyl-6H-benzofuro[3,2-*c*][1]*benzopyran-6-one* (**4e**) m.p. 172—173 ℃; ^{1}H NMR (90 MHz, $CDCl_3$) δ: 7.91 (s, 1H, H-7), 7.51 (d, *J* = 8.5 Hz, 1H, H-4), 7.36 (d, *J* = 8.5 Hz, 1H, H-3), 7.35—7.41(m, 1H, H-1), 7.16—7.26 (m, 1H, H-10), 7.14 (dd, *J* = 3.0, 9.0 Hz, 1H, H-9), 3.93 (s, 3H, OCH_3), 2.50 (s, 3H, CH_3); IR (KBr) ν: 1732 (C=O), 1594 (C=C) cm^{-1}; MS (EI) *m/z*(%): 280 (M^+, 100), 281 (M^+ + 1, 22.04), 265 ($M^+ - CH_3$, 47.98); HRMS calcd for $C_{17}H_{12}O_4$: 280.07356, found 280.07474.

2-Methoxy-9-trifuoromethyl-6H-benzofuro[3,2-*c*][1]*-benzopyran-6-one* (**4f**) m.p. 167—169℃; ^{1}H NMR (90 MHz, $CDCl_3$) δ: 8.23 (d, *J* = 8.2 Hz, 1H, H-7), 7.93 (s, 1H, H-10), 7.73 (d, *J* = 8.2 Hz, 1H, H-8), 7.43 (d, *J* = 9.0 Hz, 1H, H-4), 7.41 (s, 1H, H-1), 7.21 (dd, *J* = 9.0, 3.0 Hz, 1H, H-3), 3.95 (s, 3H, OCH_3); ^{19}F NMR ($CDCl_3$/TFA) δ: −16.7 (s); IR (KBr) ν: 1738 (C=O), 1118 (C—F) cm^{-1}; MS (EI) *m/z*(%): 334 (M^+, 100), 319 ($M^+ - CH_3$, 64.04), 315 (M^+ − F, 4.57); HRMS calcd for $C_{17}H_9F_3O_4$ 334.04530, found 334.04144.

2-Fluoro-9-trifluoromethyl-6H-benzofuro[3,2-*c*][1]*-benzopyran-6-one* (**4g**) m.p. 158—159℃; ^{1}H NMR (90 MHz, $CDCl_3$) δ: 7.19—8.26 (m, 6H, Ar-H); ^{19}F NMR ($CDCl_3$/TFA) δ: −16.8 (s), 37.5 (s); IR (KBr) ν: 1747 (C=O), 1168, 1124 (C—F) cm^{-1}; MS (EI) *m/z*(%): 322 (M^+, 100), 303 (M^+ − F, 5.34), 294 (M^+ − CO, 27.61); Anal. calcd for $C_{16}H_6F_4O_3$: C 59.60, H 1.90; found C 59.55, H 2.02.

3-Hydroxy-6H-benzofuro[3,2-*c*][1]*benzopyran-6-one* (**4h**) m.p. 253—255℃; ^{1}H NMR (90 MHz, acetone-d_6) δ: 6.61—7.59 (m, 8H, Ar-H and OH); IR (KBr) ν: 3343 (OH), 1721 (C=O) cm^{-1}; MS (EI) *m/z*(%): 252 (M^+, 100), 224 (M^+ − CO, 20.70); Anal. calcd for $C_{15}H_8O_4$: C 71.40, H 3.20; foundC 71.38, H 3.50.

3-Hydroxy-8-methyl-6H-benzofuro[3,2-*c*][1]*benzopyran-6-one* (**4i**) m.p. 280—281℃; ^{1}H NMR (300 MHz, acetone-d_6) δ: 7.93 (d, *J* = 8.6 Hz, 1H, H-2), 7.80 (s, 1H, H-7), 7.64 (d, *J* = 8.6 Hz, 1H, H-1), 7.31—7.36 (m, 1H, Ar-H), 6.97—7.05 (m, 2H, Ar-H), 2.51 (s, 3H, CH_3); IR (KBr) ν: 3260 (OH), 1710 (C=O) cm^{-1}; MS (EI) *m/z*(%): 266 (M^+, 100), 265 (M^+ − 1, 55.26), 251 ($M^+ - CH_3$, 3.46); HRMS calcd for $C_{16}H_{10}O_4$: 266.05791, found 266.06253.

3-Hydroxy-9-trifluoromethyl-6H-benzofuro[3,2-*c*][1]*-benzopyran-6-one* (**4j**) m.p. 265—266℃; ^{1}H NMR (90 MHz, acetone-d_6) δ: 7.52—8.02 (m, 4H, Ar-H), 6.77—6.90 (m, 2H, Ar-H); ^{19}F NMR (acetone-d_6/TFA) δ: −16.4 (s); IR (KBr) ν: 3211 (OH), 1723 (C=O), 1122 (C—F) cm^{-1}; MS (EI) *m/z*(%): 320 (M^+, 100), 321 (M^+ + 1, 22.94), 69 (CF_3^+, 6.15); HRMS calcd for $C_{16}H_7F_3O_4$: 320.02965, found 320.03131.

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