Indian Journal of Chemistry
Vol. 61, August 2022, pp.866-869
DOI: 10.56042/ijc.v61i8.65050

Synthesis and spectral analysis of 5,7-dihydroxy-3-(4-hydroxybenzyl)-6,8-dimethylchroman-4-one

Zhen Lv*, Jifang Yang & Lu Han
College of Pharmacy, Qiqihar Medical University, Qiqihar-161006, China
*E-mail: pangmax27@163.com

Received 17 August 2021; accepted (revised) 19 July 2022

An efficient and concise synthetic route is designed based on 5,7-dihydroxy-3-(4-hydroxybenzyl)-6,8-dimethylchroman-4-one, an important active ingredient extracted from *Polygonatum Odoratum* (Mill.) Druce. In this regard, spectroscopic techniques such as ^{1}H and ^{13}C NMR and high-resolution mass spectrometry are also performed to confirm the final structure. Also, micro-infrared spectroscopy and micro-Raman spectroscopy are performed to further determine the structure of the compound.

Keywords: Homoisoflavonoid, Spectral analysis, Micro-infrared, Micro-Raman

Homoisoflavonoid is a phytochemical of considerable interest because of its positive effects on human health, and it is also encountered in a variety of plants, such as *Polygonatum Odoratum* (Mill.) Druce, *Polygonatumsibiricum* Delar. ex Redoute, etc.[1-3] Nguyen et al. (2006) demonstrated the cytotoxic activity of the carbon methylated hyperisoflavone at concentrations of 0.003-300 μmol L^{-1} against six human cancer cells (HCT15, T24S, MCF7, Bowes, A549 and K562), all of which had higher cytotoxic activity than the hydroxyl substituted hyperisoflavone.[4] Du Toit et al. determined the anti-inflammatory properties of diverse perhydroisoflavone compounds using cellular particle fractions, and discovered that most of the perhydroisoflavone compounds had anti-inflammatory activity.[5] Sabrina et al. determined the antiviral activity of multiple high hydrogen isoflavone compounds using an assay for virus replication in Buffalo green monkey cells. The results revealed substantial antiviral activity against coxsackie viruses and Echo30, and broad-spectrum inhibitory activity against HRV and EV viruses.[6]

In summary, homoisoflavonoid compounds possess many valuable biological activities. Currently, most of the scholars' studies have been acquired from plant extracts (Fig. 1). However, the extraction process suffers from the complexity of the separation and extraction process and low yield of the compounds. Research has shown that application of Jaspal's formaldehyde and diethylamine method to obtain 5,7-dihydroxy-3-(4-hydroxybenzyl)-6,8-dimethylchroman-4-one, but the yield is very low (1.6%).[7] In this paper, a synthetic route to obtain 5,7-dihydroxy-3-(4-hydroxybenzyl)-6,8-dimethylchroman-4-one from aldehyde and ketone as source material compounds by multi-step reactions is designed, which laid the foundation for further studies on the activity of the 5,7-dihydroxy-3-(4-hydroxybenzyl)-6,8-dimethylchroman-4-one (Scheme 1). Meanwhile, micro-infrared spectroscopy and micro-Raman spectroscopy were performed to further verify the structure of the target product and also to establish the spectral information of the target product.

Experimental Details[8-11]

All reagents and solvents were purchased from commercial sources (Energy, Shanghai, China) and used without further purification. All reactions dealing with air and moisture-sensitive compounds were carried out under an atmosphere of argon using flame-dried glassware and standard syringe techniques. Unless otherwise noted, all retail reagents and solvents were obtained from the commercial provider and used without further purification. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on Bruker 400 MHz spectrometers (Berlin, Germany). Chemical shifts were reported relative to internal tetramethylsilane (δ 0.00 ppm) or dimethyl sulfoxide (DMSO-d_6, δ 7.26 ppm) for ^{1}H and (DMSO-d_6, δ 77.00 ppm) for ^{13}C. High-resolution

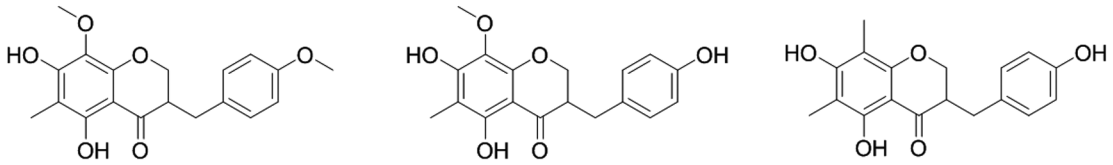
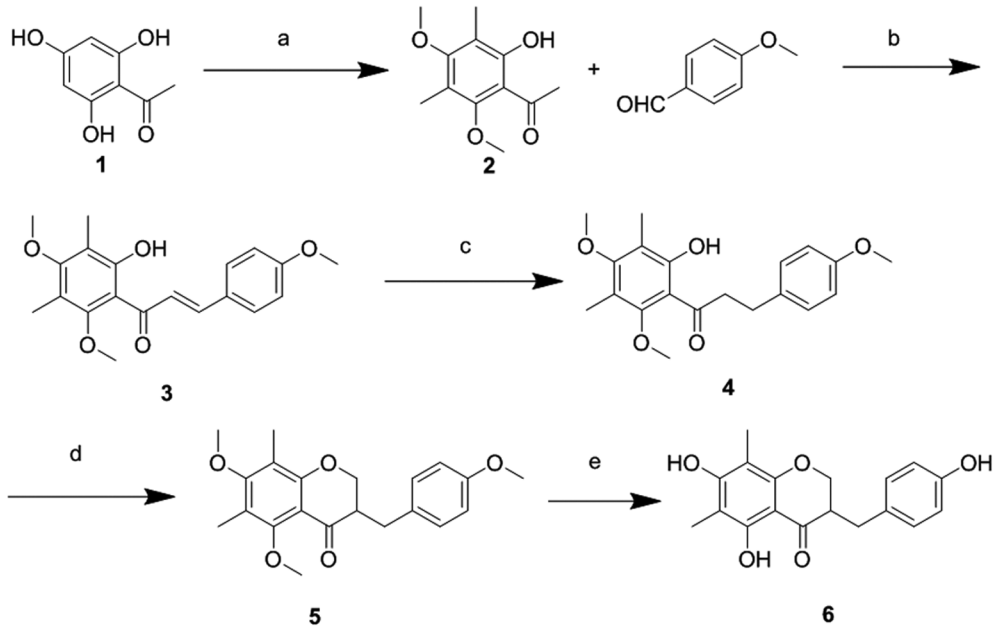


Fig. 1 — Three kinds ofhomoisoflavonoids with excellent biological activity are obtained by extracting and separating from plants (not mentioned in main manuscript)



Conditions:a. CH_3I, K_2CO_3, ketone, r.t. 4h; b. KOH/MeOH, MeOH, 80 °C, 4h; c. Zn, CH_3COOH, Ultrasonic, r.t. 0.5h; d. PFA, diethylamine, MeOH, 6h; e. $AlCl_3$, $C_2H_4Cl_2$, 12h.

Scheme 1 — Syhthesis of 5,7-dihydroxy-3-(4-hydroxybenzyl)-6,8-dimethylchroman-4-one

mass spectrometry (HRMS) was recorded on AB SCIEXTriple TOF 4600 spectrometer (USA). Micro-infrared spectroscopy was recorded on Thermo Fisher Nicolet iN10 Micro infrared spectroscopy (USA). Raman spectroscopy is performed by Thermo Fisher DXRxi Raman spectrometer (USA) to determine.

1-(2-hydroxy-4,6-dimethoxy-3,5-dimethylphenyl) ethan-1-one (2)

In a mixture of 1-(2,4,6-trihydroxyphenyl)ethan-1-one (compound **1**, 2 mmol) was dissolved in 10 mL ketone. CH_3I (4 mmol) and K_2CO_3(2 mmol) were added to the boiling acetone solution and the reaction was refluxed for 4h. The residue was poured into water and extracted with CH_2Cl_2. Afterwards, the combined organic layers were washed with water and dried over with Na_2SO_4, filtered, and concentrated under reduced pressure. Compound **2** was obtained.

(E)-1-(2-hydroxy-4,6-dimethoxy-3,5-dimethylphenyl)-3-(4-metho-xyphenyl)prop-2-en-1-one (3)

A mixture of compound **2** (2.4 mmol) and anisic aldehyde (2 mmol) were dissolvedin MeOH (40 mL) and KOH/MeOH (1 mL, 10 mmol%). The temperature was raisedto 80 °C and refluxed for 4 h. The reaction was cooled toroom temperature and adjusted to pH 3-4 with 1 M HCl. Then, it was filtered and washed with petroleum ether to give yellow solid (**compound 3**).

1-(2-hydroxy-4,6-dimethoxy-3,5-dimethylphenyl)-3-(4-metho-xyphenyl)propan-1-one (4)

Compound **3** (1 mmol) and Zn (10 mmol) were solubilized in CH_3COOH (10 mL) and ultrasonicated (400W) at room temperature for 0.5 h. The residue was poured into water and extracted with MeOH. Afterwards, the combined organic layers were washed with water and dried over with anhydrous

sodium sulfate, filtered, and concentrated under reduced pressure. Compound **4** was obtained by column chromatography (petroleum ether:ethyl acetate = 3:1 (v/v)).

5,7-dimethoxy-3-(4-methoxybenzyl)-6,8-dimethylchroman-4-one (5)

Compound **4** (2 mmol) was dissolved in MeOH (10 mL) and refluxed for 6 h with paraformaldehyde (0.01 g) and diethylamine (0.1 mL). MeOH was distilled off and the residue was dissolved in CH_2Cl_2. The organic layer was then washed with H_2O (3 x 20 mL) followed by dilute solution and the residue was dried with anhydrous sodium sulfate. The dried residue was subjected to column chromatography to obtain the compound **5** (petroleum ether:ethyl acetate = 8:1 (v/v)).

5,7-dihydroxy-3-(4-hydroxybenzyl)-6,8-dimethylchroman-4-one (6)

Compound **5** (2 mmol) was dissolved in dichloroethane (10.0 mL) and refluxed with anhydrous aluminum trichloride for 12 h, cooled to room temperature, extracted with CH_2Cl_2, the organic layer was then washed with water (3 x 20 mL) followed by dilute solution and the residue was dried with anhydrous sodium sulfate. The dried residue was subjected to column chromatography to obtain the target product (42%) (petroleum ether:acetone = 10:1 (v/v)). ^{1}H-NMR: (600 MHz, DMSO-d_6) δ4.26 (1H, J=11.36, 4.54 Hz, H-2), 4.07 (1H, J=11.36, 8.15 Hz, H-2), 2.92 (1H, H-3), 12.42 (1H, H-5), 9.64 (1H, H-7), 3.00 (1H, J=13.86, 4.92 Hz, H-9), 2.61 (1H, J=13.94, 9.55 Hz, H-9), 7.02 (1H, J=8.41 Hz, H-2'), 6.69 (1H, J=8.48Hz, H-3'), 9.24 (1H, H-4'), 6.69 (1H, J=8.48 Hz, H-5'), 7.02 (1H, J=8.41Hz, H-6'), 1.95 (3H, 6-CH3), 1.93 (3H, 8-CH3); 13C-NMR: (150 MHz, DMSO-d_6) δ 69.29(C-2), 46.07(C-3), 198(C-4), 101.62(C-4a), 159.14(C-5), 103.75(C-6), 162.76(C-7), 102.68(C-8), 157.79(C-8a), 31.67(C-9), 128.60(C-1'), 130.38(C-2'), 115.68(C-3'), 156.32(C-4'), 115.68(C-5'), 130.38(C-6'), 8.55(6-CH3), 8.09(8-CH3); LC-HRMS calcd. for $[C_{18}H_{18}O_5]^+$: 315.1154, found: 315.1205.

Micro-infrared spectroscopy

Liquid nitrogen was added to the micro-infrared spectrometer, and the MTC detector was cooled down. The instrument was turned on and preheated for 30 min, and then the instrument was put into stable working condition. A small amount of the target product was taken into the compacting device, compacted, and placed on the carrier platform. The microscope was adjusted to determine the test site, and the infrared spectrum was measured under the conditions of 4 cm^{-1} resolution, 64 scans, MTC detector, 400-4000 cm^{-1} scanning range, transmission method, and background collection before sampling.

Raman Spectroscopy

The machine was turned on to warm up, and waited till stable working condition. Very small amount of the target product powder was taken, transferred to the gold mirror, the powder was compacted into a thin sheet, and gold mirror was placed on the carrier platform. The microscope was adjusted to determine the test site, and Raman spectroscopy was performed on the microscope with a resolution of 4 cm^{-1}, laser power of 10.0 mW, 120 exposures, excitation light wavelength of 532 nm, exposure time of 0.17 s, and scan range of 100-3500 cm^{-1}.

Results and Discussion

Chemsitry

Synthetic steps that were adopted to furnish the final 5,7-dihydroxy-3-(4-hydroxybenzyl)-6,8-dimethylchroman-4-one (**6**) was drawn in Scheme 1. Significantly, we employed the Claisen-Schmidt reaction to obtain chalcone (**3**) from aldehydes and ketones under basic conditions. Other than that we combined the ultrasonication method mentioned in the literature to perform the hydrogenation reaction on compound **3** to obtain compound **4**. In the preparation of compound **5**, methanol was used as the reaction solvent and compound **4** was cyclized with paraformaldehyde in the presence of ethylenediamine. Finally, a demethylation reaction occurs in the presence of anhydrous aluminum trichloride to obtain the target product. Spectral details of the synthesized compounds are given in Supplementary Data.

Analysis

According to the characteristic peak pattern of aromatic hydrocarbon compounds, it is concluded that after the hydrogen bonding at -OH, the O-H^+ bond elongates and the electric dipole moment increases, which shows a strong and wide peak, so the absorption caused by the O-H stretching vibration (3750-3000 cm^{-1}) is at 3401 cm^{-1}; the absorption caused by the aromatic hydrogen stretching vibration (3100-3000 cm^{-1}) is at 3010 cm-1 The peak intensity (strong); due to the large electric dipole moment of

Table 1 — Main Peaks of Infrared spectrum of 5,7-dihydroxy-3-(4-hydroxybenzyl)-6,8-dimethylchroman-4-one

IR absorption peak position (cm^{-1})	Asssignment
3401	ν_{O-H}
3019	$\nu_{=CH}$
2926	ν_{-CH2}
2870	ν_{C-H}
1889	$\nu_{C=C}$
1636	$\nu_{C=O}$
1443	δ_{-CH3}
1288	ν_{C-O}
1131	$\beta_{=C-H}$
899	$\gamma_{=C-H}$
816	$\gamma_{=C-H}$

C=O, it shows a strong and wide band, which often becomes the first strong peak in the IR spectrum, so the absorption peak intensity (strong) at 1636 cm^{-1} is characteristic of the carbonyl stretching vibration (1650-1430 cm^{-1}); 1443 cm^{-1} is the absorption caused by the bending in the methyl plane (1470-1430 cm^{-1}), the peak intensity (medium); at 1131 cm^{-1}, there is an absorption peak caused by aromatic hydrogen in-plane bending vibration (1250-950 cm^{-1}), whose peak is usually weak and sharp; at 1288 cm-1 is the absorption caused by aromatic ether stretching vibration (1275-1210 cm^{-1}), peak intensity (medium); strong absorption peaks at 816 cm^{-1}, 899 cm^{-1} are the aromatic hydrogen in-plane bending vibration (910-650 cm^{-1}). Detailed information is shown in Table 1.

Raman spectroscopy of high isoflavone III shows that the Raman shifts are caused by CH stretching on the side chain of the benzene ring at 3062 cm^{-1}; the Raman shifts are caused by intramolecular antisymmetric CH_2 stretching (2929-2912 cm^{-1}) near 2928 cm^{-1}; the Raman shifts are caused by ring stretching of furan methylene or furan formyl near 1472 cm^{-1} (1480-1460 cm^{-1}) or intra-molecular CH_3 and CH_2 deformation (1473-1446 cm^{-1}); near 1380 cm^{-1}, intra-molecular CH_2 symmetric deformation (1385-1368 cm^{-1}); near 1289 cm^{-1}, 1239 cm^{-1}, intra-molecular CH_2 twisting and in-plane shaking (1310-1175 cm^{-1}); Raman shifts due to ring vibration of para-disubstituted benzene (1230-1200 cm^{-1}) around 1204 cm^{-1}; Raman shifts due to CC stretching (1150-950 cm^{-1}) around 1133 cm^{-1}; monosubstituted CH (1030-1015 cm^{-1}) or the ring vibration of the adjacent disubstituted benzene (1060-1020 cm^{-1}); the CC stretching (1150-950 cm^{-1}) around 967 cm^{-1}; the CC backbone stretching (905-837 cm^{-1}) around 854 cm^{-1}. The Raman shifts are caused by the ring vibration of para-disubstituted benzene (850-720 cm^{-1}) around 826 cm^{-1}. Detailed information is shown in Table 2.

Table 2 — Main Raman spectra peaks of 5,7-dihydroxy-3-(4-hydroxybenzyl)-6,8-dimethylchroman-4-one

Raman absorption peak position (cm^{-1})	Assignment
3063	ν_{C-H}
2928	ν_{CH2}
1472	δ_{CH3}、δ_{CH2}
1380	δ_{CH2}
1289	ρ_{CH2}
1230	ρ_{CH2}
1204	Benzene ring vibration
1133	ν_{C-C}
1022	δ_{C-H}
967	ν_{C-C}
854	$\nu_{C=C}$
826	Benzene ring vibration

Conclusion

In conclusion, 5,7-dihydroxy-3-(4-hydroxybenzyl)-6,8-dimethylchroman-4-one (**6**) was synthesized, and the structure was elucidated based on ^1H NMR, ^{13}C NMR,and HRMS data. Meanwhile, we also analyzed the compounds by micro-infrared spectroscopy and micro-Raman spectroscopy, and established the corresponding spectral information.

Supplementary Information

Supplementary information is available in the website http://nopr.niscair.res.in/handle/123456789/58776.

Acknowledgments

We gratefully acknowledge the financial support by Qiqihar Institute of Medical Sciences Project (QMSI2020M-09) and fundamental scientific research business expenses of colleges and universities in Heilongjiang Province (2020-KYYWF-0023).

References

1 Qian Y, Qu W, Liang J Y, et al, *Chin J Nat Med,* 8(3) (2010) 189.
2 Wang D M, Zhang J F, Li D W, *J Forest Sci*, 44(9) (2008) 621.
3 Nishida Y, Wada K, Toyohisa D, Tanaka T, Ono M & Yasuda S, *Nat Prod Res,* 27 (2013) 2360.
4 Nguyen A T, Fontaine J, Malonne H & Duez P, *Phytochemistry*, 67 (2006) 2159.
5 Toit K D, Elgorashi E E, Malan S F, Mulholland D A, Drewes S E & Staden J V, *S Afr J Bot,* 73 (2007) 236.
6 Tait S, Salvati A L, Desideri N & Fiore L, *Antiviral Res,* 72 (2006) 252.
7 Fujii M, Egawa K, Hirai Y, Kondo M, Akita H, Nose K, Toriizuka K & Ida Y, *Heterocycles*, 78 (2009) 207.
8 Shatokhin S S, Tuskaev V A, Gagieva S Ch & Oganesyan É T, *Russ Chem Bull*, 70 (2021) 1011.
9 Panja S K, Maiti S & Bandyopadhyay C, *J Chem Res,* 34 (2010) 555.
10 Basha G M, Yadav S K, Srinuvasarao R, Prasanthi S, Ramu T, Mangarao N & Siddaiah V, *Can J Chem,* 91 (2013) 763.
11 Hoshino Y, Tanaka H & Takeno N, *Bull Chem Soc Jpn*, 71 (1998) 2923.