PREPARING AND EVALUATING THE ANTIOXIDANT OF AN ACID DERIVATIVE FROM A MONOCARBONYL CURCUMIN ANALOG OF CYCLOPENTANONE

DUONG QUOC HOAN*, NGUYEN QUYNH CHI**, NGUYEN HIEN*

ABSTRACT

*The monocarbonyl curcumin analog derivatives of cyclopentanone have been interested since these have various biological activities. Chalcone **2** was a product of the aldol condensation between vanillin and cyclopentanone in moderate yield. The Williamson ether synthesis was employed to form an ester **3** form the chalcone **2** in good yield. The hydrolysis reaction of compound **3** was carried out successfully forming compound **4**. Structures of new compounds **3** and **4** were determined with IR, NMR and MS spectra. Compound **4** was not against DPPH free radical.*

Keywords: curcumin, monocarbonyl curcumin analog, cyclopentanone.

TÓM TẮT

Tổng hợp và khảo sát khả năng chống oxi hóa của một dẫn xuất axit của hợp chất monocacbonyl tương tự curcumin từ xiclopentanon

*Dẫn xuất của hợp chất monocacbonyl tương tự curcumin của xiclopentanon được quan tâm nhiều do chúng có hoạt tính sinh học phong phú. Hợp chất **2** là sản phẩm của phản ứng ngưng tụ andol hóa giữa vanillin và xiclopetanon với hiệu suất khá. Phản ứng tổng hợp ete Williamson được sử dụng để chuyển hóa hợp chất **2** thành dẫn xuất ester **3** với hiệu suất khá cao. Phản ứng thủy phân este **3** trong môi trường kiềm tạo thành hợp chất đích axit **4**. Cấu trúc của hai hợp chất mới **3** và **4** được xác định nhờ nghiên cứu phổ IR, NMR và MS. Hợp chất **4** không thể hiện hoạt tính chống oxy hóa với gốc DPPH.*

Từ khóa: curcumin, monocarbonyl curcumin analog, xiclopentanon.

1. Introduction

The modification of curcumin has been improving recently [5]. The monocarbonyl curcumin analog derivatives of cyclopentanone have been interested since these derivatives have a broad range of biological activities. Interestingly, the cyclopentanone ring plays an important role in the structures becoming a good antioxidant which is opened to form a radical [3]. Moreover, some derivatives were reported as good anti-tumors [3].

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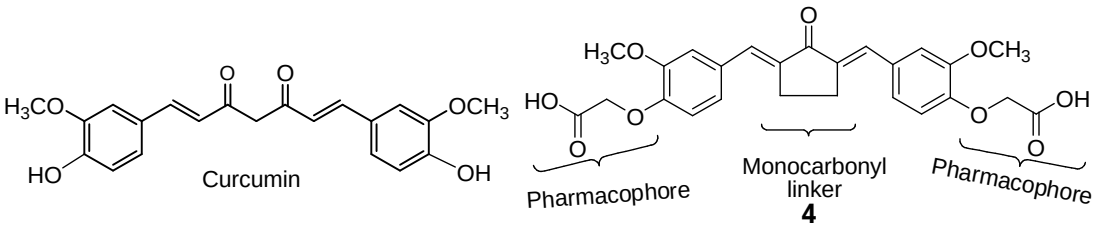


Figure 1. *Design the target structure **4** from curcumin*

Recently, the phenoxyacetic acid pharmacophores are well known in hypolipidemic agents because it could work as lipid-lowering drugs [4]. Therefore, the target compound **4** was designed by retaining the cyclopentanone linkers with the pharmacophore groups. The benzene ring is kept the same as in curcumin, but the hydroxyl group was attached a pharmacophore CH_2COOH group, Figure 1.

2. Content

2.1. Experimental section

Solvents and other chemicals were purchased from Sigma-Aldrich, Merck were used as received, unless indicated. The ^{1}H NMR and ^{13}C NMR spectra were recorded on the Bruker Avance 500 NMR spectrometer in deuterated solvents. Chemical-shift data for each signal was reported in ppm units. IR spectra were recorded on the Mattson 4020 GALAXY Series FT-IR. Mass spectra were obtained from Mass Spectrometry Facility of The Vietnam Academy of Science and Technology on LC-MSD-Trap-SL spectrometer.

2.2. Synthetic procedure

*2.2.1. Synthesis of (2E,5E)-2,5-bis(4-hydroxy-3-methoxybenzylidene) cyclopentanone (**2**)*

To a solution of vanillin (3.0 g, 20 mmol, 152 g/mol) and cyclopentanone (0.9 mL, 10 mmol, 84.12 g/mol, 0.95 g/mL) in absolute ethanol (10 mL) was added concentrated HCl (2 ml). The mixture was further stirred for 2 h, and then stood at r.t. for 8 d. A portion of distilled water (100 mL) was then poured into the dark viscous solution. Brown gel was washed with cold HOAc and water (1/1) until yellow solid formed. Re-crystallization of the crude product in 96 % ethanol gave title product **2** (5.3 g, 352.38 g/mol, mp. 212-214 °C) in 75%.

2.2.2. Synthesis of Ethyl-2-{4-((E)[(3E)-3-({[4-(2-ethoxycarbonylethoxy)]-3-methoxyphenyl}methylidene)-2-oxidanylidene-cyclopentylidene]methyl)-2-methoxy phenoxy}acetate ***(3)***

Anhydrous K_2CO_3 (690 mg, 5 mmol, 138.2 g/mol) was added to a stirred solution of compound **2** (352 mg, 1 mmol, 352.3 g/mol) in acetone (10 mL) and stirred at ambient temperature for 30 min. Ethyl chloroacetate (0.45 mL, 2.4 mmol, 1.145 g/mL, 122.55 g/mol) and NaI (75 mg, 0.5 mmol , 150 g/mol) were added. The reaction mixture was heated at 60-70 °C for 12 h, then cooled to room temperature and filtered.

The insoluble residue was extracted with acetone (3x 3 mL). The combined organic extracts were evaporated *in vacuo* and the crude produced was purified by recrystallization from hot EtOAc/n-hexane to yield the title compound **3** as a lemon-colored solid (446 mg, 85%, 524.56 g/mol, mp. 130-131 °C). IR (cm^{-1}): 3100, 2970, 2902, 2833, 1757, 1718, 1675, 1586, 1513, 1211. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm): 7.48 (s, 1H), 7.27 (d, J = 2.0 Hz, 1H), 7.24 (dd, J = 2.0, 8.0 Hz, 1H), 7.01 (d, J = 8.5 Hz, 1H), 4.76 (s, 2H), 4.27 (q, J = 7.5 Hz, 2H), 3.93 (s, 3H), 3.13 (s, 2H), 1.3 (t, J = 7.5 Hz, 3H). ^{13}C-NMR (MeOD, 125 MHz) δ (ppm): 195.01, 170.62, 151.32, 150.60, 137.69, 134.86, 131.83, 125.81, 116.61, 116.17, 67.62, 62.37, 56.99, 27.42, 14.39 (C14 and C14').

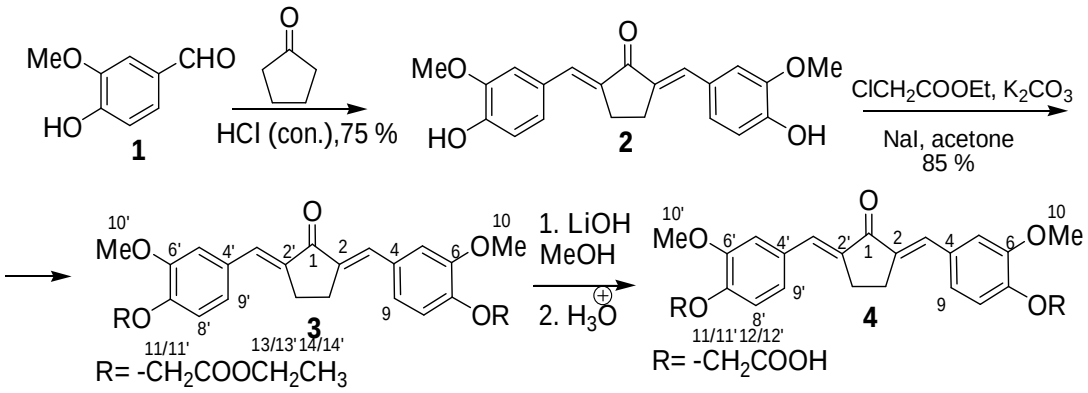
*2.2.3. Synthesis of 2-{4-((E)[(3E)-3-({[4-(2-carboxyethoxy)]-3-methoxyphenyl} methylidene)-2-oxidanylidene-cyclopentylidene]methyl)-2-methoxyphenoxy}acetic acid (**4**)*

To a solution of compound **3** (262 mg, 0.05 mmol, 524.56 g/mol) in MeOH/water (4/1, 10 mL) was added lithium hydroxide (6 mg, 0.25 mmol). The reaction mixture was stirred at reflux temperature until all solid was dissolved completely. The the reaction mixture was further refluxed for 10 min. Workup of the reaction involved acidifying to pH 4-5 with 5% HCl. Then the title product **4** was collected in quantitative yield (230 mg, 468 g/mol, mp. 239-240 °C). IR (cm^{-1}): 3600-3100 (br.), 3100, 2992, 2948, 2849, 1733, 1672, 1618, 1583, 1583, 1514, 1241. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm): 7.36 (s, 1H), 7.24 (d, J = 1,5 Hz, 1H), 7.18 (dd, J = 2,0, 8.5 Hz, 1H), 6.94 (d, J = 8.5 Hz, 1H), 4.51 (s, 1H), 3.86 (s, 3H), 3.07 (s, 2H). ^{13}C-NMR ($CDCl_3$, 125 MHz) δ (ppm): 195.01, 170.62, 151.32, 150.60, 137.69, 134.86, 131.83, 125.81, 116.61, 116.17, 67.62, 62.37, 56.99, 27.42, 14.39. MS (ESI): cald. for $[M+H]^+$ $[C_{25}H_{25}O_9]^+$: 469.46, found 469.00; $[M-H]^-$ cald. for $[C_{25}H_{23}O_9]^-$: 467.45, found 467.45.

3. Results and Discussion

3.1. Synthesis

Vanillin (**1**) was activated with acidic condition to condense with cyclopentanone. This reaction took 8 days. The most important to carry out successfully the reaction was work up step. As the reaction finished, a brown gel was collected. To get compound **2**, a mixture of solvent HOAc and water was used to wash the gel until the yellow solid was formed. The solid was re-crystallized in 96 % ethanol forming long yellow needle crystal in 75% yield.



Scheme 1. *Synthesis of the target compound*

The Williamson ether synthesis gave ester derivative **3** in 85%. It was not successful to boil the reaction mixture in water bath. So it was heated directly on a hot place for 72 h. Monitoring the progress of the reaction could follow two ways. Besides TLC method, an extract of solution was treated with sodium hydroxide solution whether the solution was turned brown color meaning the reaction was not completed due to present of phenol in compound **2**. Purification of compound **3** was simplified since the un-reacted compound **2** became phenolate in basic solution that can dissolve in water well but compounds **3** could not. The hydrolysis was quite simple and followed procedure in ref. [1].

3.2. Structure determination

IR spectrum of compound **3** showed the vibration of the carbonyl group of an ester group at 1757 cm^{-1}, another vibration at 1718 cm^{-1} belongs to carbonyl conjugated with double bond C=C. In addition, compound **3** was treated with lithium hydroxide solution in methanol to give acetic acid derivative **4**. Hence, on the IR spectrum of compound **4**, there are two important vibrations of carboxylic group. The broad vibration at range 3600 ÷ 3100 cm^{-1} indicates the vibration of O-H bond. The other vibration at 1733 cm^{-1} is for C=O bond in the carboxylic group that is lower than vibration of carbonyl in the ester group expectedly.

Compound **3** and **4** were recorded NMR spectra. As mentioned above, compounds **2**, **3** and **4** are symmetrical so signals of protons and carbons appear a half except resonance of C1 (Scheme 1). For example, ^{1}H NMR spectrum of compound **3** showed H3/H3' as a singlet at δ 7.48 ppm due to no adjacent protons. Proton H5/H5' is at meta position of proton H9/H9' and para position of proton H8/H8' so it is a doublet peak at δ 7.27 ppm with splitting constant is 2 Hz. Proton H8/H8' is a doublet peak at δ 7.01 ppm with splitting constant 8.5 Hz due to at ortho position of proton H9/H9' and para position of proton H5/H5'. Double double peak at δ 7.24 ppm with splitting constant 2.0 Hz, and 8.0 Hz is for H9/H9' because it is at *ortho* and *meta* position with H8/H8' and H5/H5'. Interestingly, Hx/Hx' appears only as a single peak at at δ 3.13

ppm. Besides, H10/H10' is a single peak at δ 3.93 ppm. The most important peaks indicating the success of the Williamson ether reaction are peaks at δ 4.76 ppm for H11/H11'; at δ 4.27 ppm and at δ 1.30 ppm for methylene and methyl groups. On the ^{13}C NMR of compound **3**, there are two signals for carbonyl carbons at δ 195.01 ppm for C1 and at δ 170.62 ppm for carbonyl ester. In addition, there are eight carbons for benzene ring and alkene at range of δ 151.32 ÷ 116.17 ppm. There are also 5 signals for 5 aliphatic carbons such as δ 67.62 for methylene –OCH_2-CO- (C11), δ 62.37 ppm for another methylene –O-CH_2CH_3, δ 56.99 ppm for C10, δ 27.42 ppm for methylene Cx,x', δ 14.39 ppm for methyl group. Thus, IR, ^{1}H NMR and ^{13}C NMR data are matched each other.

Since the target compound **4** has symmetrical structure mass spectral method is an important datum to elucidate the real structure. Therefore, compound **4** was recorded mass spectral method. It was found that compound **4** has molecular weight 468 g/mol matching with calculation of $C_{25}H_{24}O_9$. Hence, calculation of $[M+H]^+$ ($[C_{25}H_{25}O_9]^+$) is 469.46 au and found 469.00 au; calculation of $[M-H]^-$ ($[C_{25}H_{23}O_9]^-$) is 467.45 au, found 467.45 au. The ^{1}H and ^{13}C NMR spectra of compound **4** are cleaner than those of compound **3** due to the missing of ethyl group [6].

3.3. Bioactivity test

Bioactivity tests were followed by the Broth dilution method [2]. All tests were screened in the Laboratory of applied biochemistry of The Vietnam Academy of Science and Technology. Compound **4** was selected to test antioxidant activities.

4. Conclusion

In conclusion, a target molecule **4** was designed based on combination of cyclopentanone, aromatic and pharmacophore moieties. The aldol condensation reaction, the Williamson ether synthesis and hydrolysis were used to yield the target product **4**. Structures of two new compounds were determined with IR, NMR and MS spectra. Compound **4** was selected to test anti oxidant activities. The result showed that it was not against DPPH free radical.

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