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SYNTHESIS AND STRUCTURE OF SOME PHENOXYACETIC ACID DERIVATIVES FROM CURCUMIN AND MONOCARBONYL CURCUMIN ANALOGS

Duong Quoc Hoan*, Dam Thi Uyen, Pham Thi Yen, Nguyen Hien

Department of Chemistry, Hanoi National University of Education

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Abstract

Curcumin is well known as an anticancer agent, but many studies have revealed poor absorption, low water solubility and rapid metabolism of curcumin that severely curtails its bio-availability. In this paper, curcumin was converted to curcumin derivative containing oxazole **A1**. Two monocarbonyl curcumin analogs **B1** and **C1** were synthesized successfully from vanillin. Then, the replacement of the phenolic hydrogen of compounds **A1**, **B1**, and **C1** with ethyl monochloroacetate gave acetate ester derivatives **A2**, **B2**, and **C2** followed by hydrolysis in methanol and LiOH to give phenoxy acetic acid derivatives **A3**, **B3**, and **C3** in high yields. Their structures were determined with spectroscopic methods such as IR, and NMR spectra. Biological activities as well as the synthesis of other derivatives from these compounds are in progress.

Keywords. Curcumin, monocarbonyl curcumin analogs, oxazole, phenoxyacetic acid derivatives, ethyl monochloroacetate.

1. INTRODUCTION

Curcumin, (1E,6E)-1,7-bis-(3-hydroxy-4-methoxyphenyl)-1,6-heptadiene-3,5-dione (Figure 1) is an important bioactive component in the traditional herb *Curcuma Longa*. It has been used in many Asia countries as a food additive, cosmetic, and a traditional herbal medicine. For example, in Vietnam, the *Curcuma Longa* has been used to serve as food for women after parturition to recover their matrix, and mixed with honey into a paste against stomach ulcers. In basic cancer researches, beneficial effects of curcumin have been shown in prostate cancer cells [1] ovarian cancer cells [2.], and gastric carcinoma cells [3]. On the other hand, some recent researches have shown that curcumin has revealed small solubility in water (< 0.1 mg/ml), poor absorption [4] and rapid metabolism that curtails its bioavailability [5]. In order to overcome these limitations, curcumin has been converted to its derivatives or mimicked the 1,3-diketone with monocarbonyl group for improving bio-activities [6].

Recently, the phenoxyacetic acid pharmacophore has been used in hypolipidemic agents. They are worked as lipid-lowering drugs. Especially, the combination of the phenoxyacetic acid pharmacophore moiety and a heterocyclic part such as pyrimidine, isoxazol, thiazole, morpholine... have shown high potent hyperlipidemic activity [7]. Based on the literatures, initially, scaffold was designed as illustrated in figure 1. The target compounds were designed by combining linkers of oxazole ring or monocarbonyl groups with the pharmacophore groups.

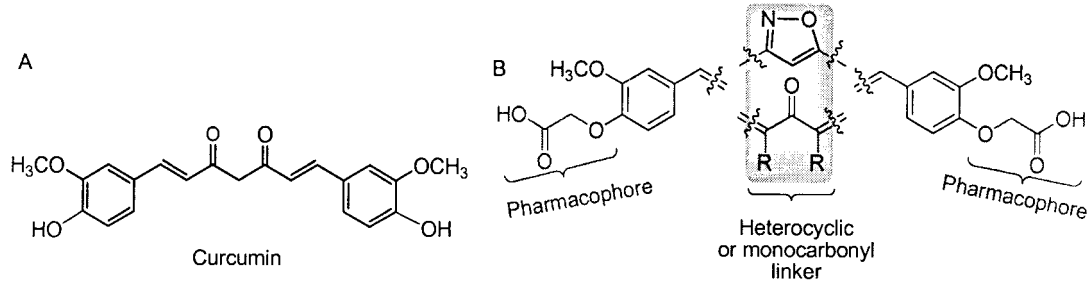


Figure 1: Structures of curcumin and designed target compounds

The oxazole heterocyclic linker was achieved by the reaction of curcumin and hydroxyl amine under basic conditions. The monocarbonyl linker was synthesized by the condensation reaction of cyclohexanone or acetone with vanillin. Replacement of the hydrogen in the phenolic groups furnished the target compounds.

2. EXPERIMENTAL

2.1. Chemicals and equipment

Solvents and other chemicals were purchased from Sigma-Aldrich, Merck, Vinachem, and Shanghai Fine Chemicals were used as received, unless indicated. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 500 NMR spectrometer in $CDCl_3$. Chemical-shift data for each signal were reported in ppm units. IR spectra were recorded on a Mattson 4020 GALAXY Series FT-IR. Mass spectra were obtained from Mass Spectrometry Facility of Temple University on an Agilent 6210 TOF mass spectrometer.

2.2. Synthetic procedure

2.2.1. Synthesis of compound A1

Hydroxylamine hydrochloride (5 g, 72 mmol) and pyridine (5.5 mL, 72 mmol) were added to a stirred solution of curcumin (5 g, 13.6 mmol) in ethanol (100 mL) and held at reflux for 48 h. After completion of the reaction (TLC), the mixture was cooled to ambient temperature, and the solvent was evaporated *in vacuo* to give the crude product. The crude product was dissolved in ethyl acetate (100 mL), and washed with 5% HCl solution (2 x 20 mL). The organic mother liquid was dried over anhydrous sodium sulfate and evaporated *in vacuo* to yield the title compound as a pale yellow solid in 90% yield, mp. 189-190 °C.

2.2.2. Synthesis of compound A2

Anhydrous K_2CO_3 (170 mg, 1.23 mmol) was added to a stirred solution of compound **A1** (150 mg, 0.41 mmol) in acetone (10 mL) and stirred at ambient temperature for 30 min. Ethyl chloroacetate (1.04 mL, 0.82 mmol, 1.145 g/mL) was 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 **A2** as a lemon-colored solid (209 mg, 95%), mp. 214-215 °C. ^{13}C-NMR ($CDCl_3$, 125 MHz) δ (ppm):168.74, 168.68, 168.38, 162.05, 149.86(2C), 148.40, 148.15, 135.25, 134.53, 130.50, 130.15, 120.68, 120.53, 114.87, 114.05, 111.78, 110.10, 109.79, 98.00, 66.44, 66.39, 61.43, 61.41, 56.05, 56.00, 14.18(2C).

2.2.3. Synthesis of compound A3

To a solution of compound **A2** (268 mg, 0.05 mmol) in MeOH/water (4/1, 10 mL) was added lithium hydroxide (6 mg, 0.25 mmol, 5 equivalent). The reaction mixture was stirred at reflux temperature. The progress of the reaction was monitored by thin-layer chromatography (TLC). Workup of the reaction involved acidifying to pH 4-5 with 5 % HCl. The residue after crystallization with 96 % ethanol provided the title compound as a a lemon-colored solid in nearly quantitative yield (~240 mg), mp. 219 °C.

^{13}C-NMR (125 MHz, $CDCl_3$), δ (ppm):168.90, 168.15, 162.55, 162.12, 149.00, 148.27, 148.08, 136.00, 134.32, 129.25, 128.91, 124.55, 124.16, 121.13, 120.76, 113.81, 113.90, 111.52, 110.15 (2C), 98.30, 64.86 (2C), 55.62(2C).

2.2.4. Synthesis of compound B1

To suspension of vanillin (15.2 g, 0.1 mol) in cyclohexanone (10 mL, 0.1 mol) were stirred until a clear solution was obtained; then concentrated hydrochloric acid (2.0 mL) was added in 5 min while stirring, followed by stirring for further 2 h. After standing for 2 days, the mixture was treated with cold AcOH/water (1: 1) and filtered. The solid material was washed first with cold ethanol, then with hot water and dried in vacuum to give the title compound **B1 as** a yellow solid after re-crystallization from methanol in 86 %, mp. 186-187 °C.

2.2.5. Synthesis of compound B2

Following the procedure for the synthesis of compound **A2** from **B1** (0.15 g, 0.41 mmol), K_2CO_3 (170 mg, 1.23 mmol), ethyl acetate (1.04 mL, 0.82 mmol), and NaI (0.15 g, 1 mmol) gave compound **B2** as a yellow solid in 80 % after re-crystallization from ethanol, mp. 199-200 °C. ^{13}C-NMR ($CDCl_3$) δ (ppm) (125 MHz): 189.97 (1C), 168.65 (2C), 149.19(2C), 147.76(2C), 136.56(2C), 134.96(2C), 130.41(2C), 123.49(2C), 114.49(2C), 113.54(2C), 66.27(2C), 61.38(2C), 56.00(2C), 28.43(2C), 22.94(2C), 14.13(2C).

*2.2.6. Synthesis of compound **B3***

Following the procedure for the synthesis of compound **A3** from B2 (2.15 g, 4 mmol), LiOH (0.2 g, 2 mmol), and methanol/water (4/1, 30 mL) gave compound **B3** as a pale yellow solid in 82% yield, mp. 229-230 °C. ^{13}C-NMR ($CDCl_3$, 125 MHz) δ (ppm): 189.02, 169.64(2C), 148.23(2C), 147.18(2C), 135.68(2C), 134.13(2C), 129.14(2C), 122.92(2C), 113.53(2C), 112.42(2C), 65.02(2C), 55.22(2C), 27.65 (2C), 22.17. Exact mass: cald. for [$C_{26}H_{26}NaO_9^+$], 505.1469, found 505.1432.

*2.2.7. Synthesis of compound **C1***

Following the procedure for the synthesis of compound **B1** from vanillin (2 g, 0.013 mol), acetone (2.48 mL, 0.065 mol), and concentrated hydrochloric acid (2.0 mL) gave the title compound **C1** as a dark blue solid after re-crystallization from methanol in 68 %, mp. 167-168 °C.

*2.2.8. Synthesis of compound **C2***

Following the procedure for the synthesis of compound **A2** from **C1** (0.13 g, 0.41 mmol), K_2CO_3 (170 mg, 1.23 mmol), ethyl acetate (1.04 mL, 0.82 mmol), and NaI (0.15 g, 1 mmol) gave compound **C2** as a yellow solid in 88 % after re-crystallization from ethanol, mp. 184-185 °C. ^{13}C-NMR ($CDCl_3$, 125 MHz) δ (ppm): 18.60, 168.50 (2C), 149.78 (2C), 149.48(2C), 142.84 (2C), 129.28 (2C), 124.20(2C), 122.52(2C), 113.68 (2C), 110.98 (2C), 66.22 (2C), 61.49 (2C), 56.07 (2C), 14.17 (2C).

*2.2.9. Synthesis of compound **C3***

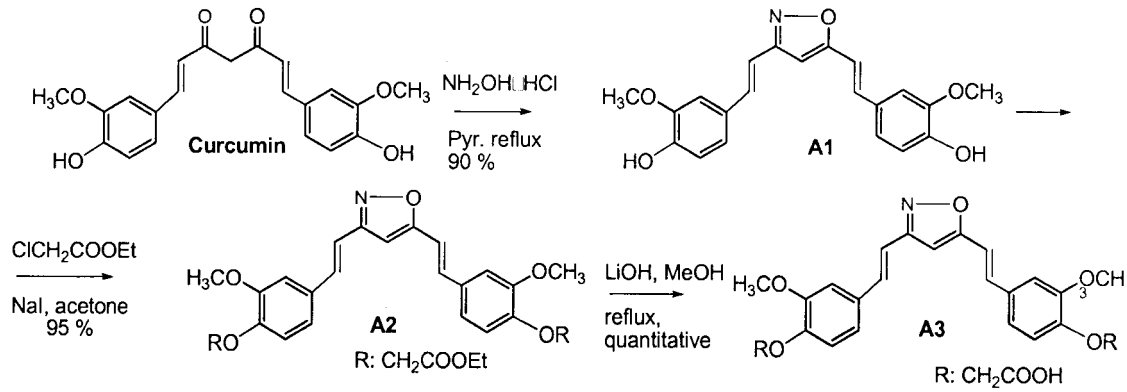
Following the procedure for the synthesis of compound **A3** from C2 (0.46 g, 1 mmol), LiOH (0.048 g, 2 mmol), and methanol/water (4/1, 10 mL) gave compound **C3** as a brown solid in 82% yield, 249-250 °C. ^{13}C-NMR ($CDCl_3$, 125 MHz) δ (ppm): 188.36, 170.07 (2C), 149.35 (2C), 149.32 (2C), 142.61 (2C), 128.60 (2C), 123.75 (2C), 122.40 (2C), 112.99 (2C), 110.50 (2C), 65.49 (2C), 55.74 (2C).

3. RESULTS AND DISCUSSION

3.1. Synthesis

3.1.1 Synthesis of curcumin derivatives containing isoxazole ring

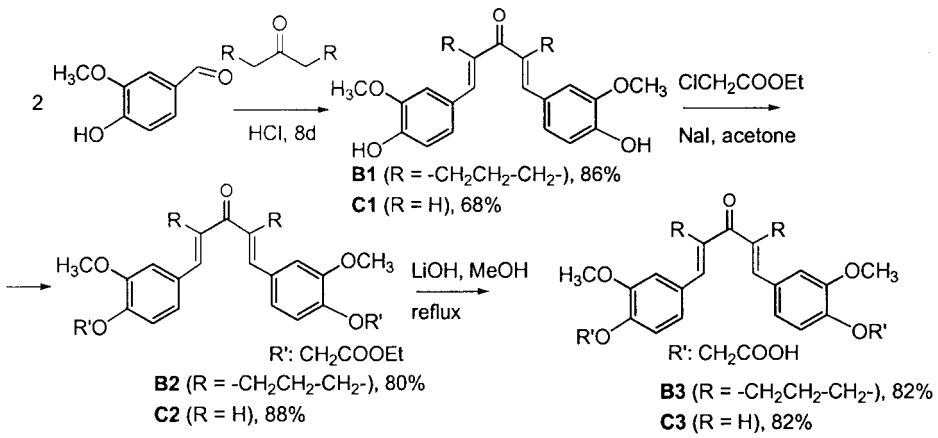
Curcumin, a commercially available compound. was converted to compound **A1** [6] in 90 % yield. Replacement of the hydrogen atom of phenolic hydroxyl group was tried based on the reaction of eugenol and monochloroacetic acid in basic condition, but it failed. It worked with ethyl monochloacetate but the yield was low (< 5%). In presence of NaI as a catalyst, the ethyl phenoxyacetate was obtained with exelent yield (95%). The hydrolysis of **A2** in methanol with lithium hydroxide gave **A3** in quantitative yield.



Scheme 1: Synthesis of curcumin derivatives containing an oxazole ring

3.1.2. Synthesis of monocarbonylcurcumin analogs

The synthesis of monocarbonyl curcumin analogs (Scheme 2) were based on the condensation reaction of vanillin and ketones following Sadjiman's protocol [9], giving **B1** and **C1** in high yields. The sequent reactions were carried out as shown in Scheme 1. These two phenolic hydroxyl groups were replaced by an ethyl acetate to give compounds **B2** and **C2**. **B2** and **C2** were treated with lithium hydroxide in methanol to furnish the derivatives of acetic acids **B3** and **C3**, respectively.



Scheme 2: Synthesis of monocarbonyl curcumin analogs

3.2. Structure of synthesized compounds

The known compound such as **A1**, **B1**, and **C1** were purified until the recorded m.ps were constant. Compound **A3** is known as well, but its NMR spectra were recorded to confirm compounds in sequence later on (publishing soon). Indeed, the structures of new compounds **A2**, **B2**, **B3**, **C2**, and **C3** were elucidated by NMR and MS techniques.

IR data are shown in Table 1. All compounds have vibrations of C-H bonds in range of 2728-3159 cm^{-1}, and weak, or medium vibrations of C=C, C=N bonds in the range of 1428-1658 cm^{-1}. Importantly, the esters **A2**, **B2**, and **C2** have strong C=O vibrations in the range of 1750-1759 cm^{-1} while the acids **A3**, **B3**, and **C3** have strong vibrations in the range of 1733-1736 cm^{-1} that are smaller than vibrations of C=O bond of these acids. Besides, the acids **A3**, **B3**, and **C3** have a broadened (br) vibration of O-H belonging to the carboxylic groups [10]. Thus, it is demonstrated that the replacement reaction of the hydrogen in the phenolic hydroxyl groups and hydrolysis of the ester groups were successful.

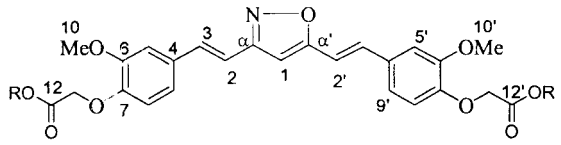
Table 1: IR data of the synthesized compounds

Comp.	ν_{OH}	ν_{C-H}	$\nu_{C=O}$	$\nu_{C=C, C=N}$
A2	-	3100, 2979, 2852	1750	1658,1592, 1512, 1428
A3	3470 (br)	2958, 2932, 2843	1736	1652, 1590, 1510, 1426
B2	-	2984, 2928, 2872	1753	1655, 1588, 1510, 1419
B3	3450 (br)	2943, 2872, 2779	1733	1650, 1582, 1508, 1412
C2	-	3159, 2939, 2839	1759	1660, 1584, 1511, 1420
C3	3473 (br)	2917, 2846, 2728	1734	1630, 1589, 1508, 1417

Because the compounds in group B and C have symmetric structures, compound **B3** was selected to record its exact mass. The result matched well with the expected structure. The assignment of the protons and carbons in NMR spectra was based on some unpublished 2D NMR analysis results of some derivatives from the studied compounds in this paper. ^{13}C-NMR data were listed at the end of synthesis part for each compound (see experimental). "2C" means there are two carbon atoms having the same chemical shift. ^{1}H-NMR data were listed in Table 2 and Table 3. The written numbers on each compound is used for NMR analysis. The esters **A2**, **B2**, and **C2** have peaks at 168 ppm; 66 ppm; 61 ppm; and 14 ppm associated with the carbon atoms in the $-CH_2COOCH_2CH_3$ moiety. After hydrolysis, the peaks at 61 ppm and 14 ppm were disappeared. This fact is in good agreement with the IR analysis above.

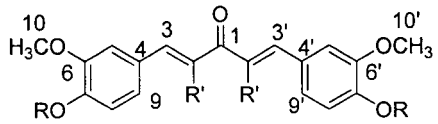
^{1}H-NMR spectra also show that the introduction of $-CH_2COOCH_2CH_3$ in esters **A2**, **B2**, and **C2** was successful where the appearances of singlet peaks at 4.7 ppm for two protons O-CH_2-CO, quartet peaks at 4.2 for two protons O-CH_2-C of ethyl groups, and triplet peaks at 1.29 ppm for methyl groups. The hydrolysis of the esters removed the ethyl group, hence the peaks at 4.2 ppm and 1.29 ppm disappeared. This information is a good support for the IR and ^{13}C-NMR data above.

Table 2: ^{1}H-NMR data of curcumin derivative containing oxazole ring



Comp.	R	H2, H2'	H3, H3'	H5, H5'	H8, H8'	H9, H9'	H10, H10'	H11 H11'	H13, H13'	H14 H14'
A2	14 13 CH_3CH_2-	6.83 (d, *J*16, 2H)	7.28 (d, *J*16, 2H)	7.05 (s, 2H)	7.02 (d, *J*8, 2H)	7.11 (d, *J* 8, 2H)	3.95 (s, 6H)	4.71 (s, 4H)	4.27 (q, *J*7, 4H)	1.29(t, *J*7, 6H)
A3	H	6.82 (d, *J*16, 2H)	7.27 (d, *J*16, 2H)	7.02 (s, 2H)	7.01 (d, *J*8, 2H)	7.12 (d, *J*8, 2H)	3.90 (s, 6H)	4.70 (s, 4H)	-	-

Table 3: ^{1}H-NMR data of curcumin derivative containing monocarbonyl group



Comp.	R, R', R'	H2, H2'	H3, H3'	H5, H5'	H8, H8'	H9, H9'	H10, H10'	Ha	Hc, Hd	Hy	Hx, Hx'
B2	a b c d -$CH_2COOCH_2CH_3$ H_2C CH_2 x' y x	-	7.72 (s, 2H)	7.03 (s, 2H)	7.05 (d,*J* 8.5, 2H)	6.83 (d,*J* 8.5, 2H)	3.91 (s, 2H) -	4.72 (s)	4.26 (q, *J*7.5); 1.28 (t, *J* 7)	1.82 (m, 4H) 0.85 (m, 2H)	2.92 (t,*J* 5.5, 4H)
B3	a b k -CH_2COOH H_2C CH_2 x' y x	-	7.68 (s, 2H)	7.04 (s, 2H)	6.87 (d,*J* 8.5, 2H)	7.04 (s, 2H)	3.90 (s, 2H)	4.68 (s)	-	1.82 (m, 4H) 0.85 (m, 2H)	2.92 (t,*J* 5.5, 4H)
C2	a b c d -$CH_2COOCH_2CH_3$ R' = H	6.95 (d, *J*15.5, 2H)	7.67 (d, *J*15.5, 2H)	7,16 (s, 2H)	7.17 (d, *J*7, 2H)	6.82 (d, *J*7, 2H)	3.95 (s, 2H) -	4.73 (s)	4.27(q, *J* 7); 1.29 (t, *J*7)	-	-
C3	a b k -CH_2COOH R' = H	6.97 (d, *J*15.5, 2H)	7.67 (d, *J*15.5, 2H)	7.38 (s, 2H)	7.38 (s, 2H)	6.84 (d, *J*8.5, 2H)	3.95 (s, 2H)	4.7 (s)	-	-	-

Signals of the two pairs H2, H2' and H3, H3' in compounds **A2**, **A3**, **C2**, and **C3** reveal the *trans* isomers since the splitting constants are 15.5 Hz. The two pairs of H8, H8' and H9, H9' (ortho position to each other) have splitting constants of about 8.5 ppm. Compounds B2 and B3 do not have H2 and H2' protons, hence allowing to confirm H2, H2' and H3, H3' in the other compounds.

4. CONCLUSION

The synthesis of 9 compounds based on modified curcumin, in which the pharmacophore group and oxazole or ketone linkers were successfully combined, is a promising solution to overcome the curcumin's biological limitations. The hydrogens of phenolic groups were replaced by a -CH_2COOEt group to form three esters **A2**, **B2**, and **C2**. The hydrolysis of these esters gave three acids **A3**, **B3**, and **C3** in good yields. All the reactions were carried out under normal conditions. The structures of six compounds were determined by IR and NMR spectra. The structure of compound **B3** was further checked with exact mass spectrum. Biological activities of the synthesized are being investigated.

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Corresponding author: **Duong Quoc Hoan**
Department of Chemistry
Hanoi National University of Education Hanoi, Vietnam
E-mail: hoandq@hnue.edu.vn; Tel: 0986778213.