Regular Article

Synthesis and Biological Evaluation of Curcuminoid Derivatives

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Many curcuminoid derivatives have been reported to have multiple biological activities. The aim of this study was to improve the biological activity of curcuminoids by synthesizing 16 new derivatives which combined cinnamic acids with curcuminoids, and we also analyzed the structure–activity relationship of the new compounds. Almost all the new compounds showed encouraging activity, especially compound 7g. It had much better antioxidant activity than curcuminoids and Vitamin C (VC), and also had the most significant antibacterial activity, which was 5-folder better than ampicillin (one of the best marketed antibiotics) with a minimum inhibitory concentration (MIC) of 0.5 μg/mL against Gram-positive cocci (*Staphylococcus aureus* and *Streptococcus viridans*) as well as *Escherichia coli* and 0.6 μg/mL against *Enterobacter cloacae*. Compound 7g also showed the greatest anticancer activity with a much lower IC_{50}, which was 0.51 μM against MCF-7, 0.58 μM against HepG-2, 0.63 μM against LX-2, and 0.79 μM against 3T3. The results suggest that these compounds have promising potential as candidates for the treatment of cancer and thus further studies are warranted.

Key words curcuminoid derivative; cinnamic acid; anticancer; antibacterial; antioxidant; structure–activity relationship

Since thousands of years, natural products have been used to treat human cancers because of its significant biological properties and safeties. In the development of the new cancer drugs, the natural product-derived derivatives are of growing concern.[1–4] Among them, *Curcuma longa* L. has been used for hundreds of years as a flavor, color and preservative.[5] Curcuminoids *viz*. curcumin (CCM), demethoxycurcumin (DCM) and bisdemethoxycurcumin (BCM) are the yellow pigments of turmeric.[6] They are the major components of *Curcuma longa* L., which is used in the food industry, for cooking, and in folkloric remedies.[7] Many recent studies have shown that curcuminoids are nutriceutical compounds which possess a variety of biological activities, including antioxidant,[8–11] anti-inflammatory,[12–14] anticancer,[15–18] and anti-angiogensis.[19,20] Besides, they also have therapeutic properties against diseases such as cystic fibrosis, human immunodeficiency virus (HIV)[21] and Alzheimer's disease.[22] What's more, curcumin is nontoxic to humans up to a dose of 10 g/d with almost no adverse effects. It is considered to be a potential chemopreventive agent and has been used in clinical trials.[23] However, previous reports indicated that the utility of curcumin is limited by its color, lack of water solubility, and relatively low *in vivo* bioavailability. Hence, synthesis of "man-made" curcumin analogues which have no these problems is becoming challenging.[24–26] In this study, we aimed to synthesize a novel of curcumin derivatives to improve their biological activities.

In addition to curcuminoids, many other natural products such as isoferulic acid,[27] *trans*-3-hydroxylcinnamic acid,[28] *trans*-4-hydroxylcinnamic acid[29] and coumaric acid[30] also have apparent biological activities. To improve the potency of the curcuminoids without losing their apoptotic effect, we selected these active ingredients as starting materials to design and synthesize curcuminoid derivatives. Then we evaluated their antioxidant abilities, antibacterial activities and anticancer activities, respectively.

Results and Discussion

Chemistry To analyze the impact on the biological activities of hydroxyl and methoxy of curcuminoids, we took cinnamic acids as examples to react with CCM which have both hydroxyl and methoxy as well as react with BCM which has no methoxy. The curcuminoid derivatives of cinnamic acid (compounds **3a**–**d**) were obtained as outlined in Chart 1. We used acetic anhydride (Ac_2O) to protect hydroxyl with the method described in Chart 2 to obtain compounds **5a**–**c**. To decorate the parent curcuminoids, acetylated compounds were reacted with CCM or BCM to get new compounds **6a**–**l**, to get the final product (**7a**–**l**), CH_3ONa/methanol (MeOH) was used to hydrolyze the acetylated curcuminoid derivatives (compounds **6a**–**l**). All the newly synthetic compounds were purified by column chromatography and their structures were established by (^{1}H-NMR, ^{13}C-NMR and MS) analysis (shown in Experimental).

Antioxidant Activity As well-known mechanisms, the hydrogen atom or electron donation abilities of some pure compounds were measured by the bleaching of a purple colored methanol solution of the stable 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical, this spectrophotometric assay uses the stable radical, DPPH, as a reagent.[31] This method is quite simple and rapid for screening specific compounds. Thus, the antioxidant activity of all the test compounds (**3a**–**d**, **7a**–**l**, CCM, BCM, VC) was evaluated for their radical scavenging ability using the stable DPPH radical method. The assay was conducted at six different concentrations of test compounds (2.5, 5, 10, 20, 40, 80 μM) in a polar, homogenous medium. The antioxidant potency (DPPH FRSA %) was presented in μM concentrations as shown in Table 1.

The radical-scavenging assay obviously showed that compounds **7a**–**l** had much higher DPPH FRSA than curcuminoids. Besides, all of the test compounds, the best radical scavenger was compound **7g** (98.3%), whose scavenging abil-

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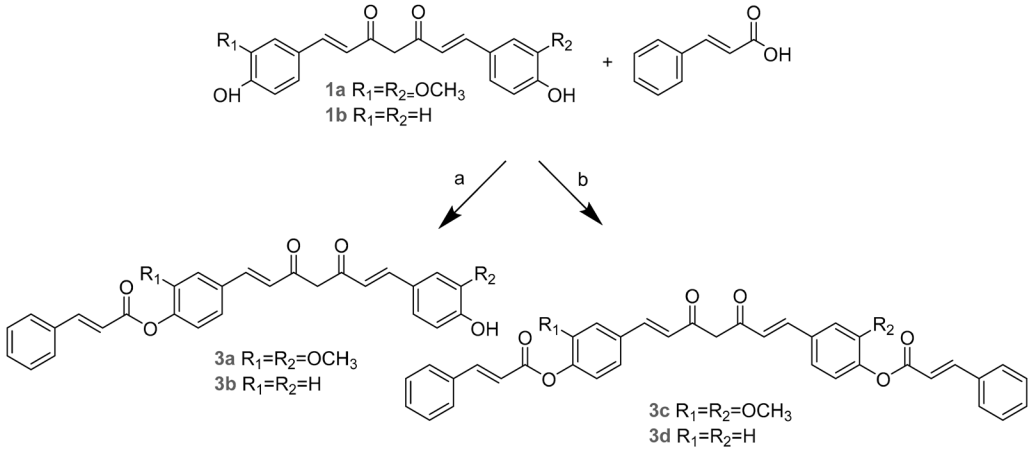


Reagents and conditions: a) EDCI, HOBT, DIEA, reflux, room temp.; b) $SOCl_2$, TEA, reflux.

Chart 1. Synthesis of Target Compounds **3a**–**d**

ity was about 1.65-folder higher than curcumin (59.1%) and was 1.7-folder higher than VC (57.6%) which was the standard compound. However, compounds **3a**–**d** which their active ingredients had no hydroxyl or methoxy had lower antioxidant activity with much lower DPPH FRSA. Besides, curcuminoid derivatives with two active ingredients had better antioxidant activity than the derivatives with only one active ingredient. Hence, the test compounds **7a**–**l** had great potential to be used as antioxidants.

Antibacterial Activity The antibacterial activities of all the target compounds were tested against Gram-positive cocci (*Staphylococcus* (*S.*) *aureus* and *Streptococcus viridans*) and Gram-negative bacilli (*Escherichia* (*E.*) *coli* and *Enterobacter cloacae*). The lowest concentration of the tested compounds in μg/mL which prevented *in vitro* growth of microorganism has been represented with minimum inhibitory concentration (MIC) shown in Table 2.

All the compounds **7a**–**l** showed better antibacterial activities than curcuminoids. The most encouraging results were obtained in the case of compound **7g** having an MIC of 0.5 μg/mL against *S. aureus*, 0.5 μg/mL against *S. viridans*, 0.5 μg/mL against *E. coli* and 0.6 μg/mL against *E. cloacae* respectively, while ampicillin, the best marked antibiotic, shows an MIC of 2.5 μg/mL. It is obviously that compound **7g** which had 2-hydroxyl and 4-methoxy was five times more effective than the ampicillin at similar concentrations and nearly twenty-one times more effective than CCM (10.3 μg/mL). On the other hand, the antibacterial activities of curcumin derivatives (**3a**, **c**, **7a**, **c**, **e**, **g**, **i**, **k**) were better than those of demethoxycurcumin derivatives (**3b**, **d**, **7b**, **d**, **f**, **h**, **j**, **l**). Besides, compounds **7g**–**l** which had two active ingredients had much better effect than **7a**–**f** which had only one active ingredient.

However the curcuminoid derivatives of cinnamic acid (**3a**–**d**) exhibited low antibacterial activities. In this group, compounds **3a** and **b** which had hydroxyl had relative good activity and the best activity was against *E. cloacae* with an MIC of 11 μg/mL. However, all this group compounds showed lower activity than curcuminoids (CCM and BCM). Besides, compound **3d** which had no hydroxyl or methoxy had the lowest activity with an MIC of 24 μg/mL while the MIC of CCM was only 10.3 μg/mL.

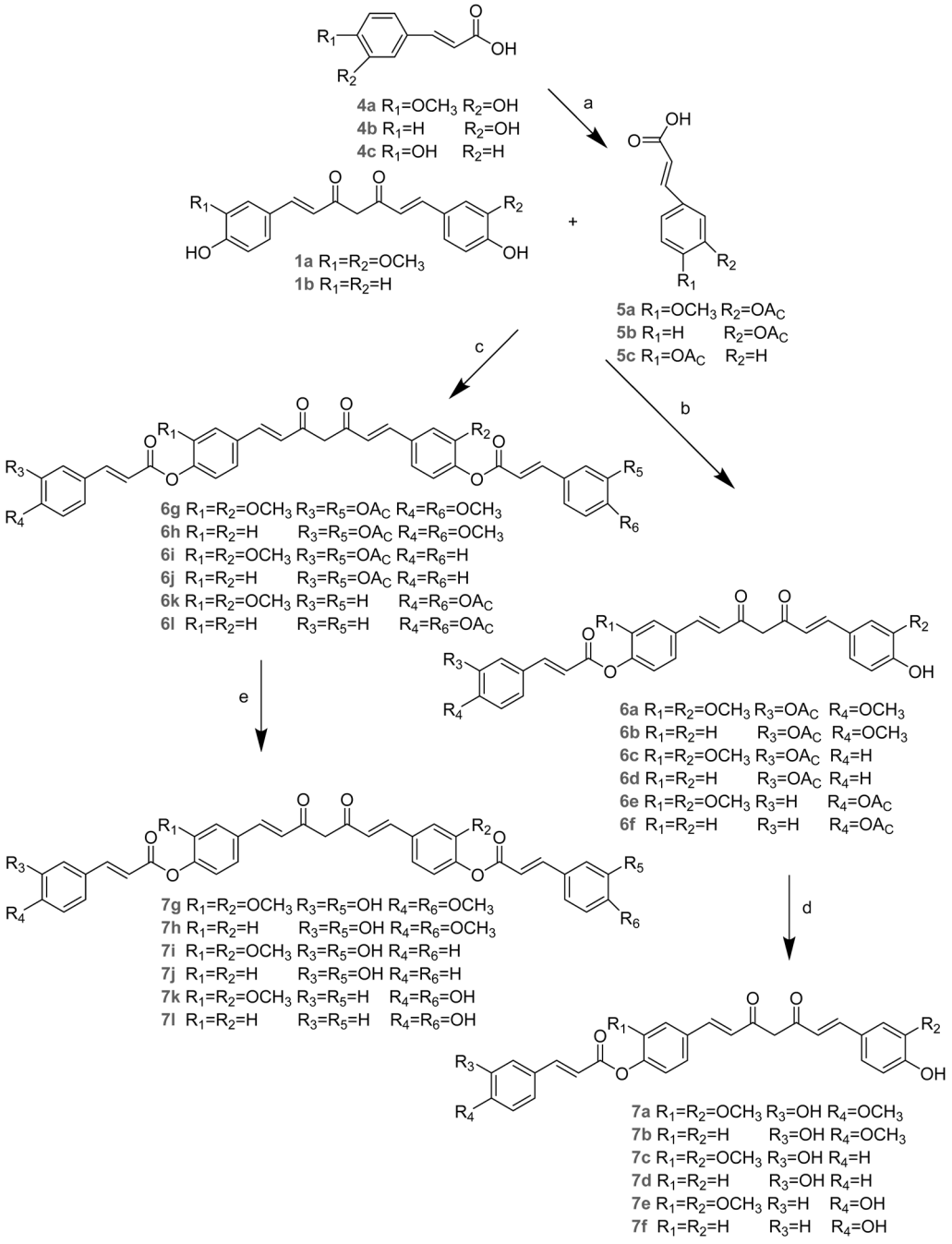
Anticancer Activity The inhibitory effects of curcuminoid derivatives on the growth of three lines of cultured tumor cells (LX-2, HepG-2 and MCF-7) and one line of normal cells (3T3) were evaluated by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. In each experiment, the drug doxorubicin (ADR) was used as positive control and the IC_{50} of curcuminoids (CCM and BCM) were also presented to compare the anticancer activities. The anticancer activity of curcuminoid derivatives were evaluated at varying concentrations which were from 1 to 50 μM. IC_{50} values of all the test compounds were presented in μM as shown in Table 3.

Almost all the newly synthetic curcuminoid derivatives exhibited much stronger inhibitory activity against LX-2, HepG-2, MCF-7 and relatively lower inhibitory activity against normal cells (3T3). As shown in Table 3, compound **7g** which had 2-hydroxyl and 4-methoxy exhibited an IC_{50} of 0.61 μM in MCF-7, 0.68 μM in HepG-2, 0.73 μM in LX-2 and 0.89 μM in 3T3, which was about thirteen three fold higher than curcuminoids (9.14–12.11 μM). On the other hand, the IC_{50} value of compound **7g** was almost the same as the positive control drug ADR.

The results shown in Table 3 indicated that compounds **3a**–**d** which their active ingredients had no hydroxyl or methoxy had no anticancer activity, while compounds **7a**–**l** which their active ingredients had hydroxyl and methoxy had much better anticancer activity than curcuminoids (CCM and BCM) and they also had lower activity against normal cells (3T3). What's more, the antitumor activity of CCM derivatives was much better than BCM derivatives. Curcuminoid derivatives with two active ingredients had much better activity than curcuminoid derivatives with one active ingredient. Hence, compounds having both hydroxyl and methoxy have great advantages and hold promise as prodrugs.

Structure–Activity Relationship Curcumin has two phenyl rings and substitutions at the 3 and 4 positions with methoxy and hydroxyl groups respectively. BCM has two phenyl rings and substitutions at the 4 position with hydroxyl. Research has shown that the biological activities are affected by 4-hydroxyl groups present on both phenyl rings of curcuminoids and 3-methoxy on phenyl rings of CCM.

In this study, cinnamic acids were used as the active ingredients to prepare new compounds which may hold promise as prodrugs with curcuminoids. Among them, the curcuminoid



Reagents and conditions: a) Ac_2O, DMAP, reflux, room temp.; b) EDCI, DMAP, reflux, room temp.; c) $SOCl_2$, DIEA, reflux; d) CH_3ONa, MeOH, reflux; e) CH_3ONa, MeOH, reflux.

Chart 2. Synthesis of Target Compounds **7a**–**l**

derivatives of cinnamic acid had no hydroxyl, what's more, their biological activities were lower than curcuminoids. But curcuminoid derivatives of isoferulic acid, *trans*-3-hydroxyl cinnamic acid and *trans*-4-hydroxyl cinnamic acid had hydroxyl, their biological activities were much better than curcuminoids. On the other hand, the derivatives (**7b**, **d**, **f**, **h**, **j**, **l**) which had no methoxy had relatively lower biological activities.

Hence, we attempt to summarize the structure–activity relationships:

1) Hydroxyl group is the major active group in tested compounds. To some extent, the more hydroxyl groups the substituent contains, the better biological activity the derivatives will have. In other words, the hydroxyl groups incorporated are helpful for the improvement of biological activity.
2) The absence of the methoxy group in curcuminoid derivatives leads to a decrease in the biological activity.
3) Positions of hydroxyl can cause difference in the biological activity.

Experimental

Materials and Methods Used reagents were bought from Aldrich Chemical Co. (Beijing, China) and used without further purification. The products were purified by column chromatography using silica gel (200–300 mesh). ^{1}H- and

Table 1. *In Vitro* DPPH Free Radical Scavenging Activity (FRSA) of the Target Compounds; CCM, Curcumin; BCM, Bisdemethoxycurcumin and VC

Compound	DPPH FRSA%					
	2.5 μM	5 μM	10 μM	20 μM	40 μM	80 μM
3a	1.3	2.6	4.3	7.1	8.2	9.2
3b	1.1	2.4	4	6.3	6.7	8.3
3c	0.3	0.7	0.9	2.4	3.9	6.2
3d	0.1	0.3	0.7	2.1	3.5	5.7
7a	8.2	15.4	32.7	71.6	82.3	92.9
7b	4.3	9.2	18.7	36.3	67.2	86.9
7c	7.1	13.9	27.5	57.6	78.6	90.3
7d	3.3	7.1	15.2	31.3	61.7	85.3
7e	7.1	14.2	28.6	59.3	80.9	92.1
7f	3.6	7.6	15.8	32.1	62.9	86.1
7g	11.4	20.3	43.1	88.2	92.6	98.3
7h	6.2	13.1	26.9	54.3	73.8	89.1
7i	9.1	17.5	37.2	81.3	83.6	93.4
7j	5.2	11.3	22.9	37.1	68.9	87.3
7k	9.3	18.1	40.2	83.5	90.1	97.2
7l	5.4	11.8	23.5	37.8	69.3	88.2
CCM	1.8	3.7	7.5	14.3	29.6	59.1
BCM	1.5	3.3	6.7	12.3	26.1	53.2
VC[a)]	1.7	3.5	6.5	13.1	28.4	57.6

a) Vitamin C (VC) was used in this study as reference.

Table 2. MIC Correlation Diagram of Curcuminoid Derivatives against Bacterial Strains

Compound	MIC[a)]			
	Gram-positive		Gram-negative	
	S. aureus	*S. viridans*	*E. coli*	*E. cloacae*
3a	13	12	14	11
3b	17	17	15	15
3c	20	18	18	18
3d	24	21	21	23
7a	0.9	0.9	0.8	0.9
7b	2.1	2.1	2.3	2.5
7c	1.2	1.3	1.2	1.2
7d	2.7	2.8	2.7	2.7
7e	1.1	1.2	0.9	0.9
7f	2.3	2.3	2.3	2.4
7g	0.5	0.5	0.5	0.6
7h	1.4	1.4	1.4	1.4
7i	0.6	0.6	0.8	0.8
7j	1.9	1.9	1.8	1.7
7k	0.6	0.7	0.7	0.7
7l	1.7	1.6	1.6	1.6
CCM	10.3	10.3	13.1	13.1
BCM	16.1	16.1	14.3	14.3
Amipicillin	2.5	2.5	3.2	3.2

a) MIC values were method in μg/mL. If MIC value of the test compound is over 200 μg/mL, it is regarded as inactive.

^{13}C-NMR spectra were recorded on Bruker-400 at room temperature with tetramethylsilane (TMS) as an internal standard and chloroform-d_3 ($CDCl_3$) or dimethyl sulfoxide (DMSO)-d_6 as solvents. Mass spectra were recorded with a MAT95 mass spectrometer (Finnigan). Melting points were measured with a micro melting point apparatus and are uncorrected. The reactions were monitored by analytical thin-layer chromatography TLC and the TLC was carried out on silica gel GF_{254}. The anhydrous solvents were dried and purified according to standard techniques before use. Gram-positive cocci (*S. aureus* and *S. viridans*), Gram-negative bacilli (*E. coli* and *E. cloacae*), cancer cells (LX-2, HepG-2 and MCF-7) and normal cells (3T3) were obtained from Expression Systems (Beijing, China).

Table 3. IC_{50} Values of Test Compounds against 3T3, LX-2, HepG-2 and MCF-7

Compound	IC_{50} (μM)[a)]			
	3T3	LX-2	HepG-2	MCF-7
3a	40	35	37	29
3b	>40	>40	>40	>40
3c	>40	>40	>40	>40
3d	>40	>40	>40	>40
7a	1.92	1.58	1.61	1.53
7b	5.88	4.86	4.72	4.75
7c	2.83	2.62	2.55	4.51
7d	5.75	5.46	5.51	5.44
7e	2.51	2.31	2.19	2.28
7f	5.31	5.21	5.33	5.19
7g	0.79	0.63	0.58	0.51
7h	3.61	3.32	3.39	3.38
7i	1.87	1.62	1.59	1.55
7j	4.84	4.61	4.59	4.52
7k	1.71	1.42	1.38	1.41
7l	4.35	4.12	4.27	4.33
CCM	9.51	9.14	9.44	9.28
BCM	12.11	11.93	11.63	11.64
ADR[b)]	0.53	0.51	0.49	0.47

a) IC_{50} is the drug concentration effective in inhibiting 50% of the cell growth measured by MTT method. If the IC_{50} of test compound is over 40 μM, it is regarded as inactive. *b*) The drug doxorubicin (ADR) was used as positive control in this study.

Isolation and Purification of Curcuminoids As curcuminoid powder contain three components named curcumin, demethoxycurcumin and bisdemethoxycurcumin. We separated them using silica gel (100 mesh). Briefly, putting dried silica gel (100 mesh) weigh 50 g dissolved in chloroform and filling them in a glass column of 5 cm internal diameter and 60 cm height. Then curcuminoid powder weighing 0.5 g was dissolved in 3 mL chloroform and was put on the silica gel column. Lastly, it was successively eluted with 500 mL of eluent (methanol–carbon tetrachloride–acetic acid=1 : 10 : 1). They were analyzed by TLC on silica gel plates and the pure fractions combined and solvents were removed to give pure components which were curcumin, demethoxycurcumin and bisdemethoxycurcumin, respectively.

General Procedure for the Synthesis of 3a and b To a solution of cinnamic acid (5 mmol) in chloroform (20 mL), HOBT (5 mmol) and DIEA (2 mL) were added and were stirred for 0.5 h at 0°C. Then, EDCI (5 mmol) was added and was still stirred at 0°C for 2 h. Afterwards, a chloroform solution (15 mL) of **1a** or **b** (3.5 mmol) was added to the mixture, which was allowed to be stirred at 0°C for 1 h, then was stirred for another 18 h at room temperature. The reaction was indicated by TLC and after it completed, the organic layer was washed by 1 M HCl solution and concentrated in the vacuum. The residue was purified by column chromatography on silica gel with methanol–carbon tetrachloride–acetic acid=1 : 10 : 1

to yield pure product (compounds **3a**, **b**).

Curcumin-Mono-cinnamic Acid (**3a**)

Yield 80%, yellow solid, mp 160–163°C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.83 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 4.57 (2H, s), 6.29 (1H, d, J=14.0 Hz), 6.81 (1H, d, J=6.9 Hz), 6.89 (2H, d, J=13.5 Hz), 6.94 (1H, d, J=7.2 Hz), 7.11 (1H, d, J=7.2 Hz), 7.13 (1H, s), 7.19 (1H, d, J=6.9 Hz), 7.25 (1H, s), 7.35 (1H, m), 7.42 (2H, m), 7.48 (1H, m, J=14.0 Hz), 7.54 (2H, ddd, J=7.1, 1.5, 0.9 Hz), 7.60 (2H, d, J=13.5 Hz), 9.21 (1H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 198.71, 164.24, 150.38, 149.03, 147.52, 147.11, 142.46, 138.18, 135.17, 130.37, 128.49, 128.51, 127.06, 126.61, 123.43, 122.87, 115.51, 114.74, 112.16, 111.07, 56.05, 55.73, 51.63; high resolution-electrospray ionization (HR-ESI)-MS m/z: 498.5301 $[M+H]^+$ (Calcd for $C_{30}H_{26}O_7$ 498.5310).

Bisdesmethoxycurcumin-Monocinnamic Acid (**3b**)

Yield 83%, yellow solid, mp 173–176°C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 4.57 (2H, s), 6.31 (1H, d, J=14.0 Hz), 6.70 (1H, s), 6.83 (1H, dd, J=7.2, 1.3 Hz), 6.89 (2H, d, J=13.5 Hz), 7.03 (1H, s), 7.16 (1H, dd, J=7.2, 1.3 Hz), 7.21 (1H, dd, J=6.9, 1.3 Hz), 7.31 (1H, m), 7.33 (1H, m), 7.38 (2H, m), 7.41 (1H, dd, J=6.9, 1.3 Hz), 7.45 (1H, m), 7.48 (1H, d, J=14.0 Hz), 7.54 (2H, ddd, J=7.1, 1.5, 0.9 Hz), 7.60 (2H, d, J=13.5 Hz), 9.21 (1H, s, OH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 198.71, 164.28, 156.43, 151.17, 147.83, 142.76, 135.42, 135.28, 134.31, 130.38, 129.04, 128.61, 128.45, 127.85, 121.22, 121.05, 120.73, 117.59, 115.51, 51.63; HR-ESI-MS m/z: 438.4786 $[M+H]^+$ (Calcd for $C_{28}H_{22}O_5$ 438.4790).

General Procedure for the Synthesis of 3c and d Excess thionyl chloride was added to a stirred, ice-cooled chloroform solution (20 mL) rapidly, which contains cinnamic acid (5 mmol). The resulting solution was stirred for 30 min at 0°C. Then dried the solution and unreacted thionyl chloride to give wanted chloride product. Afterwards, a chloroform solution (20 mL) of **1a** or **b** (2.5 mmol) was mixed with the product as well as Et_3N at 0°C and then was stirred for 24 h at room temperature. The reaction was indicated by TLC. After completion of the reaction, the mixture was washed with aqueous hydrochloric acid and then extraction. The organic layer was dried with anhydrous $MgSO_4$ and evaporated to dryness under vacuum. Purification by chromatography on silica gel (methanol–carbon tetrachloride–acetic acid=1 : 10 : 1.5) to give **3c** and **d** which are yellow solids.

Curcumin-Dicinnamic Acid (**3c**)

Yield 85%, yellow solid, mp 173–176°C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.83 (6H, s, OCH_3), 4.57 (2H, s), 6.29 (2H, d, J=14.0 Hz), 6.94 (2H, d, J=7.2 Hz), 6.89 (2H, d, J=13.5 Hz), 7.03 (2H, s), 7.11 (2H, d, J=7.2 Hz), 7.33(2H, m), 7.38 (4H, m), 7.48 (2H, d, J=14.0 Hz), 7.54 (4H, ddd, J=7.1, 1.5, 0.9 Hz), 7.60 (2H, d, J=13.5 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 198.71, 164.27, 150.87, 147.93, 142.87, 138.24, 135.13, 130.43, 128.52, 128.43, 127.87, 127.05, 126.63, 123.42, 115.41, 111.18, 55.75, 51.63; HR-ESI-MS m/z: 628.6768 $[M+H]^+$ (Calcd for $C_{39}H_{32}O_8$ 628.6770).

Bisdesmethoxycurcumin-Dicinnamic Acid (**3d**)

Yield 84%, yellow solid, mp 165–168°C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 4.57 (2H, s), 6.31 (2H, d, J=14.0 Hz), 6.89 (2H, d, J=13.5 Hz), 7.03 (2H, s), 7.21 (2H, dd, J=6.9, 1.3 Hz), 7.33 (2H, m), 7.38 (4H, m), 7.41 (2H, dd, J=6.9, 1.3 Hz), 7.45 (2H, m), 7.48 (2H, d, J=14.0 Hz), 7.54 (4H, ddd, J=7.1, 1.5, 0.9 Hz), 7.60 (2H, d, J=13.5 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 198.71, 164.27, 151.173, 147.93, 142.67, 135.15, 134.43, 130.8, 129.05, 128.52, 128.46, 127.91, 125.21, 121.16, 120.73, 115.47, 51.63; HR-ESI-MS m/z: 568.6247 $[M+H]^+$ (Calcd for $C_{37}H_{28}O_6$ 568.6250).

General Procedure for the Synthesis of 5a–c Three milliliter AC_2O was added to a pyridine solution (5 mL) of **4a**, **b** or **c** (5 mmol) and then the mixture was heated reflux for 8 h. Afterwards, the solution was washed with dilute aqueous sodium hydroxide and then extraction. The organic layer was dried with anhydrous magnesium sulfate ($MgSO_4$) and evaporated to dryness under vacuum. Lastly, the product was recrystallized from ethanol and then dried in vacuum to get **5a–c** which were white solids.

Acetylated Isoferulic Acid (**5a**)

Yield 92%, white solid, mp 120–123°C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 2.31 (3H, s), 3.83 (3H, s, OCH_3), 6.27 (1H, d, J=13.4 Hz), 6.93 (1H, d, J=7.2 Hz), 7.03 (1H, s), 7.33 (1H, d, J=7.2 Hz), 7.45 (1H, d, J=13.4 Hz), 12.05 (1H, s, OH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 171.47, 169.06, 150.58, 144.85, 141.43, 127.04, 126.68, 123.41, 116.49, 111.08, 55.78, 20.22; HRESI-MS m/z: 236.2231 $[M+H]^+$ (Calcd for $C_{12}H_{12}O_5$ 236.2230).

Acetylated *trans*-3-Hydroxylcinnamic Acid (**5b**)

Yield 87%, white solid, mp 122–125°C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 2.31 (3H, s), 6.27 (1H, d, J=13.4 Hz), 7.03 (1H, s), 7.21 (1H, dd, J=6.8, 1.7 Hz), 7.45 (1H, d, J=13.4 Hz), 7.48 (1H, m), 7.55 (1H, dd, J=6.8, 1.7 Hz), 12.05 (1H, s, OH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 171.5, 169.07, 151.13, 144.93, 134.45, 129.03, 125.26, 121.24, 120.75, 116.43, 20.22; HR-ESI-MS m/z: 206.1971 $[M+H]^+$ (Calcd for $C_{11}H_{10}O_4$ 206.1970).

Acetylated *trans*-4-Hydroxylcinnamic Acid (**5c**)

Yield 88%, white solid, mp 119–122°C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 2.31 (3H, s), 6.27 (1H, d, J=13.4 Hz), 7.28 (2H, d, J=7.8 Hz), 7.45 (1H, d, J=13.4 Hz), 7.62 (2H, d, J=7.8 Hz), 12.05 (1H, s, OH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 171.47, 169.06, 150.58, 144.13, 132.02, 129.69, 121.47, 116.48, 20.22; HR-ESI-MS m/z: 206.1971 $[M+H]^+$ (Calcd for $C_{11}H_{10}O_4$ 206.1970).

General Procedure for the Synthesis of 6a–f To a solution of **5a**, **b** or **c** (5 mmol) in chloroform (20 mL), DMAP (0.1 mmol) was added and was stirred for 0.5 h at 0°C. Then, 4.2 mmol EDCI was added and was still stirred at 0°C for 2 h. Afterwards, a chloroform solution (20 mL) of **1a** or **b** (3.5 mmol) was added to the mixture, which was allowed to be stirred 0°C for 1 h, then was stirred for another 18 h at room temperature. The reaction was indicated by TLC and after it completed, the mixture was washed with aqueous hydrochloric acid and then extraction. The organic layer was dried with anhydrous Na_2SO_4 and evaporated to dryness under vacuum. Purification by chromatography on silica gel (methanol–carbon tetrachloride–acetic acid=1 : 10 : 1) to give **6a–f** which are yellow solids.

Curcumin-Monoacetylated Isoferulic Acid (**6a**)

Yield 69%, yellow solid, mp 163–166°C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 2.31 (3H, s, $COCH_3$), 3.75 (6H, s, OCH_3), 3.86 (3H, s, OCH_3), 4.57 (2H, s), 6.31 (1H, d, J=14.0 Hz), 6.90 (1H, d, J=7.3 Hz), 6.89 (2H, d, J=13.5 Hz), 6.93 (1H, d, J=7.2 Hz), 6.94 (1H, d, J=7.2 Hz), 7.02 (1H, d, J=7.2 Hz), 7.03 (1H, s), 7.19 (1H, d, J=7.3 Hz), 7.23 (1H, s), 7.33 (1H, d, J=7.2 Hz), 7.48 (1H, d, J=14.0 Hz),7.60 (2H, d, J=13.5 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 198.71, 169.05,

164.28, 150.92, 149.33, 147.85, 147.07, 142.72, 141.48, 138.27, 130.38, 127.69, 127.05, 126.63, 123.48, 122.72, 115.43, 114.75, 112.20, 111.05, 56.15, 55.73, 51.70, 20.22; HR-ESI-MS *m/z*: 586.5929 $[M+H]^+$ (Calcd for $C_{33}H_{30}O_{10}$ 586.5930).

Bisdesmethoxycurcumin-Monoacetylated Isoferulic Acid (**6b**)

Yield 62%, yellow solid, mp 158–161°C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 2.31 (3H, s, $COCH_3$), 3.83 (3H, s, OCH_3), 4.57 (2H, s), 6.31 (1H, d, J=14.0 Hz), 6.70 (1H, s), 6.83 (1H, dd, J=7.2, 1.3 Hz), 6.89 (2H, d, J=13.5 Hz), 6.93 (1H, d, J=7.2 Hz), 7.03 (1H, s), 7.16 (1H, dd, J=7.2, 1.3 Hz), 7.21 (1H, dd, J=6.9, 1.3 Hz), 7.31 (1H, m), 7.33 (1H, d, J=7.2 Hz), 7.41 (1H, dd, J=6.9, 1.3 Hz), 7.45 (1H, m), 7.48 (1H, d, J=14.0 Hz), 7.60 (2H, d, J=13.5 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 198.71, 169.05, 164.88, 158.32, 151.17, 150.92, 147.85, 142.72, 141.48, 135.34, 134.46, 130.38, 129.05, 127.07, 126.63, 125.28, 121.18, 120.73, 117.55, 115.43, 115.13, 111.05, 55.73, 51.63, 20.22; HR-ESI-MS *m/z*: 526.5412 $[M+H]^+$ (Calcd for $C_{31}H_{26}O_8$ 526.5410).

Curcumin-Monoacetylated *trans*-3-Hydroxylcinnamic Acid (**6c**)

Yield 61%, yellow solid, mp 162–165°C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 2.31 (3H, s, $COCH_3$), 3.83 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 4.57 (2H, s), 6.31 (1H, d, J=14.0 Hz), 6.89 (2H, d, J=13.5 Hz), 6.90 (1H, d, J=7.3 Hz), 6.94 (1H, d, J=7.2 Hz), 7.02 (1H, d, J=7.2 Hz), 7.03 (2H, s), 7.19 (1H, d, J=7.3 Hz), 7.21 (1H, dd, J=7.5, 2.3 Hz), 7.23 (1H, s), 7.48 (1H, d, J=14.0 Hz), 7.51 (1H, m), 7.55 (1H, dd, J=7.5, 2.3 Hz), 7.60 (2H, d, J=13.5 Hz), 9.21 (1H, s, OH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 198.71, 169.07, 164.28, 151.17, 150.92, 149.33, 147.92, 147.07, 142.72, 138.27, 134.46, 130.38, 129.05, 127.69, 127.07, 126.63, 125.28, 123.48, 122.83, 120.72, 115.43, 114.75, 112.16, 111.05, 56.15, 55.73, 51.63, 20.22; HR-ESI-MS *m/z*: 556.5671 $[M+H]^+$ (Calcd for $C_{32}H_{28}O_9$ 556.5670).

Bisdesmethoxycurcumin-Monoacetylated *trans*-3-Hydroxylcinnamic Acid (**6d**)

Yield 69%, yellow solid, mp 157–160°C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 2.31 (3H, s, $COCH_3$), 4.57 (2H, s), 6.31 (1H, d, J=14.0 Hz), 6.70 (1H, s), 6.83 (1H, dd, J=7.2, 1.3 Hz), 6.89 (2H, d, J=13.5 Hz), 7.03 (2H, s), 7.16 (1H, dd, J=7.2, 1.3 Hz), 7.21 (1H, dd, J=7.5, 2.3 Hz), 7.31 (1H, m), 7.41 (1H, dd, J=6.9, 1.3 Hz), 7.45 (1H, m), 7.48 (1H, d, J=14.0 Hz), 7.55 (1H, dd, J=7.5, 2.3 Hz), 7.60 (2H, d, J=13.5 Hz), 9.45 (1H, s, OH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 198.71, 169.07, 164.28, 158.32, 151.17, 147.85, 142.72, 135.34, 134.46, 130.38, 130.05, 129.05, 125.28, 121.18, 120.73, 117.55, 115.43, 115.13, 51.63, 20.22; HR-ESI-MS *m/z*: 496.5151 $[M+H]^+$ (Calcd for $C_{30}H_{24}O_7$ 496.5150).

Curcumin-Monoacetylated *trans*-4-Hydroxylcinnamic Acid (**6e**)

Yield 64%, yellow solid, mp 150–153°C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 2.31 (3H, s, $COCH_3$), 3.83 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 4.57 (2H, s), 6.31 (1H, d, J=14.0 Hz), 6.90 (2H, d, J=7.3 Hz), 6.89 (2H, d, J=13.5 Hz), 7.03 (2H, s), 7.19 (2H, d, J=7.3 Hz), 7.23 (1H, s), 7.28 (2H, d, J=7.8 Hz), 7.48 (1H, d, J=14.0 Hz), 7.60 (2H, d, J=13.5 Hz), 7.62 (2H, d, J=7.8 Hz), 9.21 (1H, s, OH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 198.71, 169.07, 164.28, 150.92, 150.58, 149.33, 147.92, 147.07, 142.72, 138.27, 132.02, 130.38, 129.63, 127.69, 127.07, 126.63, 123.48, 122.33, 121.47, 115.43, 114.75, 112.16, 111.05, 56.15, 55.73, 51.63, 20.22; HR-ESI-MS *m/z*: 556.5671 $[M+H]^+$ (Calcd for $C_{32}H_{28}O_9$ 556.5670).

Bisdesmethoxycurcumin-Monoacetylated *trans*-4-Hydroxylcinnamic Acid (**6f**)

Yield 58%, yellow solid, mp 152–155°C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 2.31 (3H, s), 4.57 (2H, s), 6.31 (1H, d, J=14.0 Hz), 6.83 (1H, dd, J=7.2, 1.3 Hz), 6.89 (2H, d, J=13.5 Hz), 7.03 (2H, s), 7.16 (2H, dd, J=7.2, 1.3 Hz), 7.21 (1H, dd, J=7.5, 2.3 Hz), 7.28 (2H, d, J=7.8 Hz), 7.45 (2H, m), 7.48 (1H, d, J=14.0 Hz), 7.60 (2H, d, J=13.5 Hz), 7.62 (2H, d, J=7.8 Hz), 9.45 (1H, s, OH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 198.71, 169.07, 164.28, 158.46, 151.17, 150.58, 147.92, 142.72, 135.34, 134.46, 132.02, 130.38, 130.08, 129.69, 129.05, 125.28, 121.47, 121.18, 121.01, 120.73, 115.43, 115.13, 51.63, 20.22; HR-ESI-MS *m/z*: 496.5151 $[M+H]^+$ (Calcd for $C_{30}H_{24}O_7$ 496.5150).

General Procedure for the Synthesis of 6g–l Ten milliliter thionyl chloride was added to a stirred, ice-cooled chloroform solution (20 mL) rapidly, which contains 5.3 mmol **5a**, **b** or **c** respectively. Then the resulting solution was stirred for 30 min at 0°C. Then dried the solution and unreacted thionyl chloride to give wanted chloride product. Afterwards, a chloroform solution (20 mL) of **1a** or **b** (2.5 mmol) was mixed with the product as well as Et_3N at 0°C and then was stirred for 24 h at room temperature. The reaction was indicated by TLC. After completion of the reaction, the mixture was washed with aqueous hydrochloric acid and then extraction. The organic layer was dried with anhydrous $MgSO_4$ and evaporated to dryness under vacuum. Purification by chromatography on silica gel (methanol–carbon tetrachloride–acetic acid=1 : 10 : 1.5) to give **6g–l** which are yellow solids.

Curcumin-Diacetylated Isoferulic Acid (**6g**)

Yield 56%, yellow solid, mp 157–160°C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 2.31 (6H, s, $COCH_3$), 3.75 (6H, s, OCH_3), 4.57 (2H, s), 6.31 (2H, d, J=14.0 Hz), 6.90 (2H, d, J=7.3 Hz), 6.89 (2H, d, J=13.5 Hz), 6.93 (2H, d, J=7.2 Hz), 7.03 (4H, s), 7.19 (2H, d, J=7.3 Hz), 7.33 (2H, d, J=7.2 Hz), 7.48 (2H, d, J=14.0 Hz), 7.60 (2H, d, J=13.5 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 198.71, 169.05, 164.28, 150.92, 147.85, 142.72, 141.48, 138.27, 130.38, 127.05, 126.63, 123.48, 115.43, 111.05, 55.73, 51.63, 20.22; HR-ESI-MS *m/z*: 804.7998 $[M+H]^+$ (Calcd for $C_{45}H_{40}O_{14}$ 804.8010).

Bisdesmethoxycurcumin-Diacetylated Isoferulic Acid (**6h**)

Yield 53%, yellow solid, mp 156–159°C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 2.31 (3H, s, OCH_3), 3.75 (6H, s, OCH_3), 4.57 (2H, s), 6.31 (1H, d, J=14.0 Hz), 6.89 (2H, d, J=13.5 Hz), 6.93 (1H, d, J=7.2 Hz), 7.03 (1H, s), 7.21 (2H, dd, J=6.9, 1.3 Hz), 7.33 (1H, d, J=7.2 Hz), 7.41 (2H, dd, J=6.9, 1.3 Hz), 7.45 (2H, m), 7.48 (1H, d, J=14.0 Hz), 7.60 (2H, d, J=13.5 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 198.71, 169.05, 164.28, 151.17, 150.92, 147.85, 142.72, 141.48, 134.38, 130.38, 129.05, 127.07, 126.63, 125.28, 123.54, 121.18, 120.73, 115.43, 111.05, 55.73, 51.63, 20.22; HR-ESI-MS *m/z*: 744.7485 $[M+H]^+$ (Calcd for $C_{43}H_{36}O_{12}$ 744.7490).

Curcumin-Diacetylated *trans*-3-Hydroxylcinnamic Acid (**6i**)

Yield 56%, yellow solid, mp 157–160°C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 2.31 (6H, s, $COCH_3$), 3.83 (6H, s, OCH_3), 4.57 (2H, s), 6.31 (2H, d, J=14.0 Hz), 6.89 (2H, d, J=13.5 Hz), 6.90 (2H, d, J=7.3 Hz), 7.03 (4H, s), 7.19 (2H, d, J=7.3 Hz), 7.21 (2H, dd, J=7.5, 2.3 Hz), 7.48 (2H, d, J=14.0 Hz), 7.50 (2H, m), 7.55 (2H, dd, J=7.5, 2.3 Hz), 7.60 (2H, d, J=13.5 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 198.71, 169.07, 164.28, 151.17, 150.92, 147.92, 142.72, 138.27, 134.46,

130.38, 129.05, 127.07, 126.63, 125.28, 121.24, 120.72, 115.43, 111.05, 55.73, 51.63, 20.22; HR-ESI-MS *m/z*: 744.7483 $[M+H]^+$ (Calcd for $C_{43}H_{36}O_{12}$ 744.7490).

Bisdesmethoxycurcumin-Diacetylated *trans*-3-Hydroxylcinnamic Acid (**6j**)

Yield 58%, yellow solid, mp 162–165°C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 2.31 (6H, s, $COCH_3$), 4.57 (2H, s), 6.31 (2H, d, J=14.0 Hz), 6.89 (2H, d, J=13.5 Hz), 7.03 (4H, s), 7.21 (4H, dd, J=7.5, 2.3 Hz), 7.41 (2H, dd, J=6.9, 1.3 Hz), 7.45 (2H, m), 7.48 (2H, d, J=14.0 Hz), 7.50 (2H, m), 7.55 (2H, dd, J=7.5, 2.3 Hz), 7.60 (2H, d, J=13.5 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 198.71, 169.07, 164.28, 151.17, 147.92, 142.72, 134.46, 130.38, 129.05, 125.28, 121.24, 120.72, 115.43, 51.83, 20.22; HR-ESI-MS *m/z*: 684.6964 $[M+H]^+$ (Calcd for $C_{41}H_{32}O_{10}$ 684.6970).

Curcumin-Diacetylated *trans*-4-Hydroxylcinnamic Acid (**6k**)

Yield 55%, yellow solid, mp 158–161°C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 2.31 (6H, s, $COCH_3$), 3.83 (6H, s, OCH_3), 4.57 (2H, s), 6.31 (2H, d, J=14.0 Hz), 6.90 (2H, d, J=7.3 Hz), 6.89 (2H, d, J=13.5 Hz), 7.03 (2H, s), 7.19 (2H, d, J=7.3 Hz), 7.28 (4H, d, J=7.8 Hz), 7.48 (2H, d, J=14.0 Hz), 7.60 (2H, d, J=13.5 Hz), 7.62 (4H, d, J=7.8 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 198.71, 169.07, 164.28, 150.88, 150.58, 147.92, 142.72, 138.27, 132.02, 130.38, 129.69, 127.07, 126.63, 123.48, 121.47, 115.43, 111.05, 55.73, 51.63, 20.22; HR-ESI-MS *m/z*: 744.7483 $[M+H]^+$ (Calcd for $C_{43}H_{36}O_{12}$ 744.7490).

Bisdesmethoxycurcumin-Diacetylated *trans*-4-Hydroxylcinnamic Acid (**6l**)

Yield 57%, yellow solid, mp 163–166°C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 2.31 (6H, s, $COCH_3$), 4.57 (2H, s), 6.31 (2H, d, J=14.0 Hz), 6.89 (2H, d, J=13.5 Hz), 7.03 (2H, s), 7.21 (2H, dd, J=7.5, 2.3 Hz), 7.28 (4H, d, J=7.8 Hz), 7.41 (2H, dd, J=6.9, 1.3 Hz), 7.45 (2H, m), 7.48 (2H, d, J=14.0 Hz), 7.60 (2H, d, J=13.5 Hz), 7.62 (4H, d, J=7.8 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 198.71, 169.07, 164.28, 151.17, 150.58, 147.92, 142.72, 134.46, 132.02, 130.38, 129.69, 129.05, 125.28, 121.47, 121.18, 120.73, 115.43, 51.63, 20.22; HR-ESI-MS *m/z*: 684.6964 $[M+H]^+$ (Calcd for $C_{41}H_{32}O_{10}$ 684.6970).

General Procedure for the Synthesis of 7a–l A solution of **6a–l** (2 mmol) in MeOH (10 mL) and sodium hydroxide solution (10 mL, 1 M) was stirred at room temperature overnight. The solvent was washed with aqueous hydrochloric and then was extracted with ethyl acetate. Lastly, the ethyl acetate was dried with anhydrous Na_2SO_4 and evaporated to dryness under vacuum to give **7a–l** which were yellow solids.

Curcumin-Monoisoferulic Acid (**7a**)

Yield 95%, yellow solid, mp 178–181°C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.75 (3H, s, OCH_3), 3.86 (6H, s, OCH_3), 4.57 (2H, s), 6.31 (1H, d, J=14.0 Hz), 6.90 (1H, d, J=7.3 Hz), 6.89 (2H, d, J=13.5 Hz), 6.94 (2H, d, J=7.2 Hz), 7.02 (2H, d, J=7.2 Hz), 7.03 (1H, s), 7.19 (1H, d, J=7.3 Hz), 7.23 (2H, s), 7.48 (1H, d, J=14.0 Hz), 7.60 (2H, d, J=13.5 Hz), 9.21 (2H, s, OH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 198.71, 164.28, 150.92, 149.33, 147.85, 147.07, 142.72, 138.27, 130.38, 127.69, 127.07, 126.63, 123.48, 122.72, 115.43, 114.75, 112.18, 111.05, 56.15, 55.73, 51.63; HR-ESI-MS *m/z*: 544.5562 $[M+H]^+$ (Calcd for $C_{31}H_{28}O_9$ 544.5560).

Bisdesmethoxycurcumin-Monoisoferulic Acid (**7b**)

Yield 97%, yellow solid, mp 173–176°C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.86 (3H, s, OCH_3), 4.57 (2H, s), 6.31 (1H, d, J=14.0 Hz), 6.83 (1H, dd, J=7.2, 1.3 Hz), 6.89 (2H, d, J=13.5 Hz), 6.94 (1H, d, J=7.2 Hz), 7.02 (1H, d, J=7.2 Hz), 7.03 (2H, s), 7.16 (1H, dd, J=7.2, 1.3 Hz), 7.21 (1H, dd, J=6.9, 1.3 Hz), 7.23 (1H, s), 7.31 (1H, m), 7.41 (1H, dd, J=6.9, 1.3 Hz), 7.45 (1H, m), 7.48 (1H, d, J=14.0 Hz), 7.60 (2H, d, J=13.5 Hz), 9.21 (1H, s, OH), 9.45 (1H, s, OH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 198.71, 164.28, 158.32, 151.17, 149.33, 147.85, 147.07, 142.72, 135.34, 134.38, 130.38, 130.04, 129.05, 127.69, 125.28, 122.72, 121.18, 120.73, 117.55, 115.43, 115.13, 114.75, 112.18, 56.15, 51.63; HR-ESI-MS *m/z*: 484.5040 $[M+H]^+$ (Calcd for $C_{29}H_{24}O_7$ 484.5040).

Curcumin-Mono-*trans*-3-hydroxylcinnamic Acid (**7c**)

Yield 94%, yellow solid, mp 186–189°C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.83 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 4.57 (2H, s), 6.31 (1H, d, J=14.0 Hz), 6.83 (1H, dd, J=7.5, 2.3 Hz), 6.89 (2H, d, J=13.5 Hz), 6.94 (2H, d, J=7.2 Hz), 7.02 (2H, d, J=7.2 Hz), 7.03 (2H, s), 7.16 (1H, dd, J=7.5, 2.3 Hz), 7.23 (1H, s), 7.31 (1H, m), 7.48 (1H, d, J=14.0 Hz), 7.60 (2H, d, J=13.5 Hz), 9.21 (1H, s, OH), 9.45 (1H, s, OH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 198.71, 164.28, 158.32, 150.92, 149.33, 147.92, 147.07, 142.72, 138.27, 135.34, 130.38, 130.05, 127.63, 127.07, 126.63, 123.48, 122.83, 121.18, 117.55, 115.43, 115.13, 114.75, 112.16, 111.05, 56.15, 55.73, 51.63; HR-ESI-MS *m/z*: 514.5297 $[M+H]^+$ (Calcd for $C_{30}H_{26}O_8$ 514.5300).

Bisdesmethoxycurcumin-Mono-*trans*-3-hydroxylcinnamic Acid (**7d**)

Yield 96%, yellow solid, mp 179–182°C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 4.57 (2H, s), 6.31 (1H, d, J=14.0 Hz), 6.70 (2H, s), 6.83 (1H, dd, J=7.5, 2.3 Hz), 6.89 (2H, d, J=13.5 Hz), 7.03 (1H, s), 7.16 (1H, dd, J=7.5, 2.3 Hz), 7.21 (2H, dd, J=7.5, 2.3 Hz), 7.31 (1H, m), 7.41 (2H, dd, J=6.9, 1.3 Hz), 7.45 (1H, m), 7.48 (1H, d, J=14.0 Hz), 7.60 (2H, d, J=3.5 Hz), 9.45 (2H, s, OH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 198.71, 164.28, 158.32, 151.17, 147.92, 142.72, 135.34, 134.46, 130.38, 129.05, 125.28, 121.18, 120.72, 117.55, 115.43, 115.13, 51.63; HR-ESI-MS *m/z*: 454.4773 $[M+H]^+$ (Calcd for $C_{28}H_{22}O_6$ 454.4780).

Curcumin-Mono-*trans*-4-hydroxylcinnamic Acid (**7e**)

Yield 94%, yellow solid, mp 174–177°C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.83 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 4.57 (2H, s), 6.31 (1H, d, J=14.0 Hz), 6.59 (2H, d, J=6.3 Hz), 6.90 (1H, d, 7.3 Hz), 6.89 (2H, d, J=13.5 Hz), 6.94 (1H, d, J=7.2 Hz), 7.02 (1H, d, J=7.2 Hz), 7.03 (2H, s), 7.19 (1H, d, J=7.3 Hz), 7.23 (1H, s), 7.45 (2H, d, J=6.3 Hz), 7.48 (1H, d, J=14.0 Hz), 7.60 (2H, d, J=13.5 Hz), 9.21 (1H, s, OH), 9.68 (1H, s, OH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 198.71, 164.28, 157.65, 149.33, 147.92, 147.01, 142.72, 138.27, 130.62, 130.38, 127.75, 127.07, 126.63, 123.48, 122.83, 115.72, 115.43, 114.75, 112.12, 111.05, 56.15, 55.73, 51.63; HR-ESI-MS *m/z*: 514.5297 $[M+H]^+$ (Calcd for $C_{30}H_{26}O_8$ 514.5300).

Bisdesmethoxycurcumin-Mono-*trans*-4-hydroxylcinnamic Acid (**7f**)

Yield 97%, yellow solid, mp 166–169°C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 4.57 (2H, s), 6.31 (1H, d, J=14.0 Hz), 6.59 (2H, d, J=6.3 Hz), 6.83 (1H, dd, J=7.2, 1.3 Hz), 6.89 (2H, d, J=13.5 Hz), 7.03 (2H, s), 7.16 (1H, dd, J=7.2, 1.3 Hz), 7.21 (1H, dd, J=7.5, 2.3 Hz), 7.31 (2H, m), 7.41 (1H, dd, J=6.9, 1.3 Hz), 7.45 (2H, d, J=6.3 Hz), 7.47 (1H, dd, J=6.9, 1.3 Hz), 7.60 (2H, d, J=13.5 Hz), 7.48 (1H, d, J=14.0 Hz), 9.45 (1H, s, OH), 9.68 (1H, s, OH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 198.71, 164.28, 158.46, 157.65, 151.17, 147.92, 142.72, 135.34, 134.46,

130.62, 130.38, 130.08, 129.05, 127.75, 125.83, 121.01, 120.73, 117.64, 115.72, 115.43, 51.63; HR-ESI-MS *m/z*: 454.4773 $[M+H]^+$ (Calcd for $C_{28}H_{22}O_6$ 454.4780).

Curcumin-Diisoferulic Acid (**7g**)

Yield 95%, yellow solid, mp 192–195°C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.75 (6H, s, OCH_3), 3.86 (6H, s, OCH_3), 4.57 (2H, s), 6.31 (2H, d, J=14.0 Hz), 6.90 (2H, d, J=7.3 Hz), 6.89 (2H, d, J=13.5 Hz), 6.94 (2H, d, J=7.2 Hz), 7.02 (2H, d, J=7.2 Hz), 7.19 (2H, d, J=7.3 Hz), 7.23 (2H, s), 7.48 (2H, d, J=14.0 Hz), 7.60 (2H, d, J=13.5 Hz), 9.21 (2H, s, OH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 198.71, 164.28, 150.92, 149.33, 147.85, 147.07, 142.72, 138.27, 130.38, 127.69, 127.07, 126.63, 123.48, 122.72, 115.43, 114.75, 112.18, 111.05, 56.15, 55.73, 51.63; HR-ESI-MS *m/z*: 720.7271 $[M+H]^+$ (Calcd for $C_{41}H_{36}O_{12}$ 720.7270).

Bisdesmethoxycurcumin-Diisoferulic Acid (**7h**)

Yield 93%, yellow solid, mp 194–197°C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.86 (6H, s, OCH_3), 4.57 (2H, s), 6.31 (2H, d, J=14.0 Hz), 6.89 (2H, d, J=13.5 Hz), 6.94 (2H, d, J=7.2 Hz), 7.02 (2H, d, J=7.2 Hz), 7.03 (2H, s), 7.21 (2H, dd, J=6.9, 1.3 Hz), 7.23 (2H, s), 7.41 (2H, dd, J=6.9, 1.3 Hz), 7.45 (2H, m), 7.48 (2H, d, J=14.0 Hz), 7.60 (2H, d, J=13.5 Hz), 9.21 (2H, OH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 198.71, 164.28, 151.17, 149.33, 147.85, 147.07, 142.72, 134.38, 130.38, 129.05, 127.69, 125.28, 122.72, 121.18, 120.73, 115.43, 114.75, 112.18, 56.15, 51.63; HR-ESI-MS *m/z*: 660.6746 $[M+H]^+$ (Calcd for $C_{39}H_{32}O_{10}$ 660.6750).

Curcumin-Di-*trans*-3-hydroxylcinnamic Acid (**7i**)

Yield 97%, yellow solid, mp 196–199°C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.83 (6H, s, OCH_3), 4.57 (2H, s), 6.31 (2H, d, J=14.0 Hz), 6.70 (2H, s), 6.83 (2H, dd, J=7.5, 2.3 Hz), 6.89 (2H, d, J=13.5 Hz), 6.90 (2H, d, J=7.3 Hz), 7.03 (2H, s), 7.16 (2H, dd, J=7.5, 2.3 Hz), 7.19 (2H, d, J=7.3 Hz), 7.31 (2H, m), 7.48 (2H, d, J=14.0 Hz), 7.60 (2H, d, J=13.5 Hz), 9.45 (1H, s, OH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 198.71, 164.28, 158.32, 150.92, 147.92, 142.72, 138.27, 135.34, 130.38, 130.05, 127.07, 126.63, 123.48, 121.18, 117.55, 115.43, 115.13, 111.05, 55.73, 51.63; HR-ESI-MS *m/z*: 660.6750 $[M+H]^+$ (Calcd for $C_{39}H_{32}O_{10}$ 660.6750).

Bisdesmethoxycurcumin-Di-*trans*-3-hydroxylcinnamic Acid (**7j**)

Yield 91%, yellow solid, mp 190–193°C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 4.57 (2H, s), 6.31 (2H, d, J=14.0 Hz), 6.70 (2H, s), 6.83 (2H, dd, J=7.5, 2.3 Hz), 6.89 (2H, d, J=13.5 Hz), 7.03 (2H, s), 7.16 (2H, dd, J=7.5, 2.3 Hz), 7.21 (2H, dd, J=7.5, 2.3 Hz), 7.31 (2H, m), 7.41 (2H, dd, J=6.9, 1.3 Hz), 7.45 (2H, m), 7.48 (2H, d, J=14.0 Hz), 7.60 (2H, d, J=13.5 Hz), 9.45 (2H, s, OH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 198.71, 164.28, 158.32, 151.17, 147.92, 142.72, 135.34, 134.46, 130.38, 130.05, 129.05, 125.28, 121.18, 121.14, 120.72, 117.55, 115.43, 115.13, 51.63; HR-ESI-MS *m/z*: 600.6228 $[M+H]^+$ (Calcd for $C_{37}H_{28}O_8$ 600.6230).

Curcumin-Di-*trans*-4-hydroxylcinnamic Acid (**7k**)

Yield 98%, yellow solid, mp 186–189°C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.83 (6H, s, OCH_3), 4.57 (2H, s), 6.31 (2H, d, J=14.0 Hz), 6.59 (4H, d, J=6.3 Hz), 6.90 (2H, d, J=7.3 Hz), 6.89 (2H, d, J=13.5 Hz), 7.03 (2H, s), 7.19 (2H, d, J=7.3 Hz), 7.45 (2H, d, J=6.3 Hz), 7.48 (2H, d, J=14.0 Hz), 7.60 (2H, d, J=13.5 Hz), 9.68 (1H, s, OH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 198.71, 164.28, 157.65, 150.88, 147.92, 142.72, 138.27, 130.62, 130.38, 127.75, 126.63, 123.48, 115.72, 115.43, 111.05, 55.73, 51.63; HR-ESI-MS *m/z*: 660.6750 $[M+H]^+$ (Calcd for $C_{39}H_{32}O_{10}$ 660.6750).

Bisdesmethoxycurcumin-Di-*trans*-4-hydroxylcinnamic Acid (**7l**)

Yield 92%, yellow solid, mp 180–183°C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 4.57 (2H, s), 6.31 (2H, d, J=14.0 Hz), 6.59 (4H, d, J=6.3 Hz), 6.89 (2H, d, J=13.5 Hz), 7.03 (2H, s), 7.21 (2H, dd, J=7.5, 2.3 Hz), 7.41 (2H, dd, J=6.9, 1.3 Hz), 7.45 (2H, d, J=6.3 Hz), 7.47 (1H, dd, J=6.9, 1.3 Hz), 7.48 (2H, d, J=14.0 Hz), 7.50 (2H, m), 7.60 (2H, d, J=13.5 Hz), 9.68 (1H, s, OH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 198.71, 164.28, 157.65, 151.17, 147.92, 142.72, 134.46, 130.62, 130.38, 129.05, 127.75, 125.28, 121.18, 120.73, 115.72, 115.43, 51.63; HR-ESI-MS *m/z*: 600.6228 $[M+H]^+$ (Calcd for $C_{37}H_{28}O_8$ 600.6230).

Antioxidant Method The antioxidant activity was determined by DPPH method. To be brief, 100 μL ethanol solutions of the test compound and VC (2.5, 5, 10, 20, 40, 80 μM) were added to 100 μL of ethanol solution of DPPH radicals (100 μM). Then the mixture was incubated at 25°C for 30 min. Lastly, the absorbance was recorded at 570 nm, using ethanol as a blank for correction. VC was used as references, and its concentration was maintained to that of the synthesized compounds. The experiment was carried out in triplicate, and the resulting values were averaged. The radical-scavenging activity (%) was calculated using the following formula:

$$\text{Radical-scavenging activity (\%)} = [(A_C - A_S) / A_C] \times 100\%$$

where A_C is the absorbance of the control and A_S is the absorbance of the tested sample after 30 min.

Antibacterial Method The antibacterial activity was tested by the drilling method. The *S. aureus*, *Bacilllus subtilis*, *E. coli* and *Pseudomonas aeruginosa* were activated for 2 h at optimum temperature. The resulting broth was diluted to 10^8 Colony Forming Unit (CFU)/mL. The stock solutions of the unJugates along with curcuminoids were prepared in DMSO and they were in different concenirations (1, 1.25, 2.5, 5, 10, 20, 40, 50 μg/mL). Then in each dish access 10^8 CFU/mL experimental strains for 100 mL and polee holes for 6 mm. Then add 10 μL the compounds, chloromycethin and sterile saline solution into the well, respecticely. Each solution was three parallel experinents alone. They were developed at an optimun incubation temperature for a growth cycle and then the diameter of each zone of inhibition was measured. The concentration in the hole showing the diameter within 6.2 mm has been reported as the MIC. As each test was performed in triplicate, the MIC reported represents the result of three repetitions.

Cytotoxicity Assay *in Vitro* The four lines of cells (3T3, LX-2, HepG-2 and MCF-7) were incubated at 37°C under a humidified atmosphere containing 5% CO_2 for 24 h with a density of 0.2×10^4 cells/well. Then the cells were cultured for another 48 h with various concentrations (1, 5, 10, 15, 20, 40, 50 μM) of the test compounds and ADR. After that, add 20 μL of 5 mg/mL MTT to the wells and go on culturing for 3 h in the same condition. Then 200 μL DMSO was added and the absorbance was measured at 570 nm with a microplate reader. And the cell viability (%) was calculated as the ratio of the number of surviving cells upon treatment with the test compounds compared to the blank.

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Conflict of Interest The authors declare no conflict of interest.

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