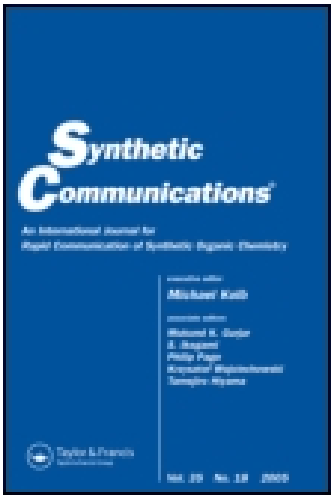

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Synthesis and Evaluation of Coumarin-Resveratrol Hybrids as 15-Lipoxygenaze Inhibitors

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SYNTHESIS AND EVALUATION OF COUMARIN–RESVERATROL HYBRIDS AS 15-LIPOXYGENAZE INHIBITORS

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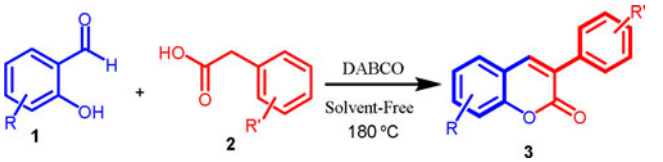
GRAPHICAL ABSTRACT



Abstract *A series of coumarin–resveratrol hybrids, 3-arylcoumarin derivatives* ***3a–u****, were synthesized through the intermolecular condensation reaction of various salicylaldehydes and phenylacetic acids in the presence of 1,4-diazabicyclo[2.2.2]octane under solvent-free conditions. All the synthesized compounds were screened for their inhibitory potency*

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*against soybean 15-lipoxygenase. Among them, three compounds (**3c**, **3j**, and **3q**) showed good enzyme-inhibitory activities.*

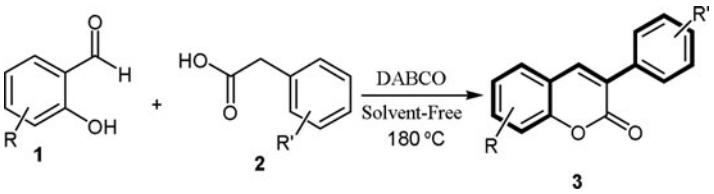
Keywords: 3-Arylcoumarins; DABCO; salicylaldehyde; solvent-free; soybean 15-lipoxygenase

INTRODUCTION

Coumarin (2*H*-chromen-2-one) and its derivatives are some of the most important O-heterocycles and are extensively found in various bioactive natural and synthetic products.[1] They are effective pharmacophores, widely used for the design and synthesis of novel bioactive compounds.[2] Accordingly, different biological activities such as anticoagulation and cardiovascular activities (warfarin)[3] and antimicrobial activities (novobiocin and clorobiocin)[4] have been reported. They also possess anticancer,[5] anti-inflammatory and antioxidant,[6] antiviral (inhibitor of HIV-1 protease and integrase),[7] and enzyme-inhibition effects.[8] At this juncture, 3-arylcoumarins have attracted lots attention because of their biological properties.[9] Their antiproliferative,[10] antioxidant,[11] and monoamine oxidase A inhibitor activities[12] have been reported in the literature.

Various classical methods such as Perkin,[13] Pechmann,[14] Knoevenagel,[15] Wittig,[16] and Kostanecki–Robinson reactions[17] have been used for the synthesis of 3-arylcoumarin derivatives. One of the most common methods for the construction of 3-arylcoumarins is based on the reaction of 2-hydroxyacetophenones/2-hydroxybenzaldehydes with phenylacetic acids. For this purpose, various catalysts or reagents such as 1,1-carbonyldiimidazole[18] and cyanuric chloride/*N*-methyl morpholine[19] and use of two-phase system conditions[20] have been utilized. However, most of these methods suffer from different limitations and disadvantages such as poor yields of the products, use of expensive and toxic reagents, formation of by-products, and long reaction time. In view of this, there is already a considerable demand for developing new synthetic approaches to 3-arylcoumarins.

In continuation of our efforts to develop efficient methods for the synthesis of novel heterocyles as well as bioactive compounds,[21] herein we report a simple, efficient, and general method for the preparation of 3-aryl coumarins **3** as coumarin-resveratrol hybrids through the reaction of salicylaldehydes **1** and phenylacetic acids **2** in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) under solvent-free conditions (Scheme 1). Also, considering the ability of 3-aryl coumarins to inhibit soybean lipoxygenase (LO),[18] all compounds were evaluated for their inhibitory activity against soybean 15-lipoxygenase.



Scheme 1. Synthesis of 3-arylcoumarins **3** in the presence of DABCO.

RESULTS AND DISCUSSION

Chemistry

Focusing on the efficiency of DABCO as an organocatalyst base in different organic transformations such as protection of carbohydrates,[22] Heck reaction,[23] synthesis of isothiocyanates[24] and isoxazolines,[25] alcohol oxidation,[26] and oxa-Michael–Henry reaction for the formation of 3-nitrochromenes,[27] we decided to conduct the reaction in the presence of DABCO (Scheme 1).

Initially, we selected the reaction of salicylaldehyde and phenylacetic acid as a model reaction. Next, different conditions such as temperatures, solvents, and the amounts of DABCO were tested to obtain the optimal conditions (Table 1).

Different solvents such as EtOH, MeOH, toluene, tetrahydrofuran (THF), and dimethylformamide (DMF) were examined. It was found that using solvent-free conditions led to the best results in terms of reaction time and yield. As shown in Table 1, the best yield (90%) was obtained for a molar ratio of phenylacetic acid/salicylaldehyde/DABCO 1:0.5:3 (Table 1, entry 5) at 180 °C. It should be noted that lower temperatures gave the corresponding product in very poor yield.

With the optimized reaction conditions, we conducted the reaction of a wide spectrum of salicylaldehyde and phenylacetic acid derivatives under the optimized condition (Table 2). All substrates possessing electron-rich as well as electron-poor substituents underwent DABCO- promoted reaction to afford the title compounds **3** in good yields (61–93%). However, the best results were related to the salicylaldehyde series with no substituent (Table 2, entries 1–7).

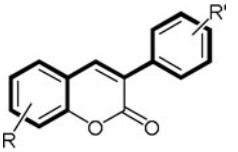
The plausible mechanism for the formation of 3-aryl coumarins **3** has been shown in Scheme 2. Initially, the acidic proton of phenacylacetic acid derivative **2** is captured by DABCO to form the salt **4**. Then, it would be attacked by hydroxyl group of salicylaldehyde derivative **1** to afford the related ester **5**, which was separated and characterized during our investigations. Activation of methylene protons (**6**) in the presence of DABCO followed by the intermolecular cyclization (**7**) and dehydration gives 3-aryl coumarin derivatives **3**.

Table 1. Investigation of various conditions for the reaction of salicylaldehyde and phenylacetic acid

Entry	Molar ratio of phenylacetic acid/salicylaldehyde/DABCO	Solvent	Time (min)	Temperature (°C)	Yield (%)[a]
1	1:1:1.5	—	120	180	55
2	1:1:2	—	120	180	65
3	1:0.5:2	—	110	180	65
4	1:0.5:2.5	—	100	180	75
5	1:0.5:3	—	90	180	90
6	1:0.5:3	—	90	140	10
7	1:0.5:3	—	90	110	5
8	1:0.5:3	—	90	rt	0
9	1:0.5:3	EtOH	90	Reflux	40
10	1:0.5:3	MeOH	90	Reflux	25
11	1:0.5:3	DMF	120	130	70
12	1:0.5:3	THF	120	Reflux	55
13	1:0.5:3	Toluene	120	Reflux	50

[a]Isolated yields.

Table 2. Synthesis of 3-arylcoumarine derivatives **3**



3

Entry	R	R′	Product **3**	Time (min)	Yield (%)[a]
1	H	H	**3a**	90	90
2	H	3,4-diOMe	**3b**	100	81
3	H	4-Cl	**3c**	95	88
4	H	4-OMe	**3d**	100	85
5	H	4-NO_2	**3e**	90	93
6	H	2,4-diCl	**3f**	95	86
7	H	4-F	**3g**	90	91
8	2-OMe	H	**3h**	115	79
9	2-OMe	3,4-diOMe	**3i**	120	74
10	2-OMe	4-Cl	**3j**	115	78
11	2-OMe	4-OMe	**3k**	120	75
12	2-OMe	4-NO_2	**3l**	110	80
13	2-OMe	2,4-diCl	**3m**	120	78
14	2-OMe	4-F	**3n**	110	80
15	3,4,5-triOMe	H	**3o**	115	67
16	3,4,5-triOMe	3,4-diOMe	**3p**	120	61
17	3,4,5-triOMe	4-Cl	**3q**	120	65
18	3,4,5-triOMe	4-OMe	**3r**	120	63
19	3,4,5-triOMe	4-NO_2	**3s**	115	72
20	3,4,5-triOMe	2,4-diCl	**3t**	120	65
21	3,4,5-triOMe	4-F	**3u**	115	70

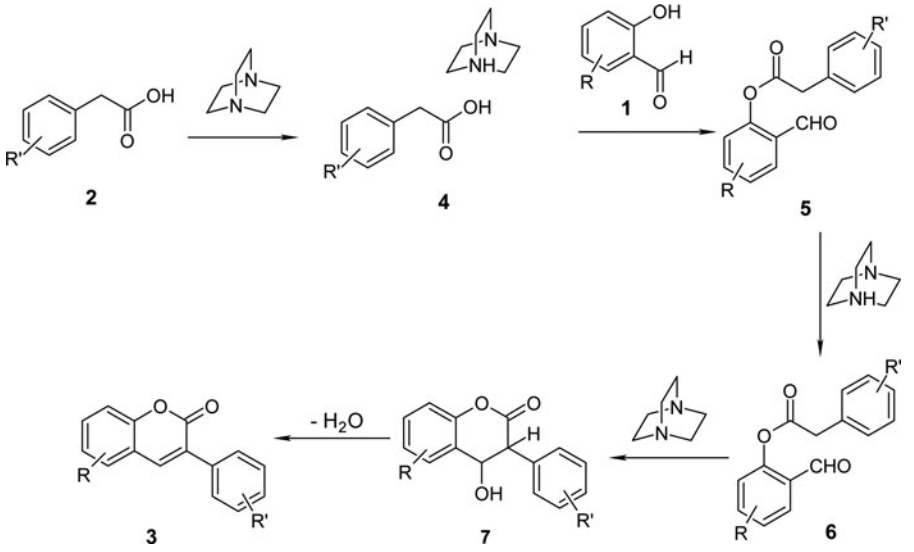
[a]Isolated yields.

Pharmacology

15-LOX inhibition assay. Inhibitory activity of the target compounds **3a–u** on soybean 15-lipoxygenase was studied by the spectrophotometric assay method described in the literature.[28] Quercetin was used as the reference compound and all results are summarized in Table 3.

Among the tested compounds, compounds **3b**, **3d**, **3i**, **3k**, **3p**, and **3r** showed no lipoxygenase inhibitory activity and other derivatives exhibited moderate activity. It seems that 3-aryl coumarins bearing *p*-chlorophenyl at the 3-position showed better activities and the introduction of the methoxy groups to any positions of the synthesized compounds did not improve inhibitory activity against soybean 15-lipoxygenase.

In conclusion, we developed a simple and efficient method for the synthesis of 3-aryl coumarines via the reaction of salicylaldehydes and phenylacetic acids in the presence of DABCO under solvent-free conditions. The advantages of this method compared to previously reported methods include the use of safe base, solvent-free



Scheme 2. Plausible mechanism for the preparation of 3-aryl coumarin **3**.

Table 3. Structures and inhibition of soybean lipoxygenase (LO) at 100 μM for coumarins **3a–u** in comparison with quercetin

Entry	R	R′	Product **3**	Inhibition of LO (%) at 100 μM
1	H	H	**3a**	18
2	H	3,4-diOMe	**3b**	No[a]
3	H	4-Cl	**3c**	22
4	H	4-OMe	**3d**	No
5	H	4-NO_2	**3e**	7.5
6	H	2,4-diCl	**3f**	15
7	H	4-F	**3g**	17.5
8	2-OMe	H	**3h**	17
9	2-OMe	3,4-diOMe	**3i**	No
10	2-OMe	4-Cl	**3j**	23
11	2-OMe	4-OMe	**3k**	No
12	2-OMe	4-NO_2	**3l**	8
13	2-OMe	2,4-diCl	**3m**	14.6
14	2-OMe	4-F	**3n**	16
15	2,3,4-triOMe	H	**3o**	18.3
16	2,3,4-triOMe	3,4-diOMe	**3p**	No
17	2,3,4-triOMe	R4-Cl	**3q**	27
18	2,3,4-triOMe	4-OMe	**3r**	No
19	2,3,4-triOMe	4-NO_2	**3s**	6.2
20	2,3,4-triOMe	2,4-diCl	**3t**	12.7
21	2,3,4-triOMe	4-F	**3u**	21.6
22	Quercetin			100

[a]No activity.

conditions, elimination of toxic reagents and organic solvents, simple workup, and good yield of products. Also, all products were evaluated against soybean 15-lipoxygenase activities and most of them showed moderate activity.

EXPERIMENTAL

All reagents and solvents were purchased from Merck. Melting points are uncorrected and were determined with a Kofler hot-stage apparatus (Reichert, Vienna, Austria). ^{1}H and ^{13}C NMR spectra were measured using 400 and 500 spectrometers in $CDCl_3$; chemical shifts (δ) are reported in parts per million (ppm); and coupling constant (*J*) values are presented in hertz (Hz). The IR spectra were obtained on a Nicolet Magna FTIR 550 spectrophotometer (potassium bromide disks). The elemental analysis was carried out using Elementar Analysen system (Vario EL).

Synthesis of 3-Arylcoumarins: General Procedure

2-Hydroxy-3,4,5-trimethoxybenzaldehyde (**1c**) was synthesized from 2,3,4-trimethoxy benzaldehyde according to the literature.[29] A mixture of salicylaldehyde derivative **1** (0.5 mmol), phenylacetic acid derivative **2** (1 mmol), and DABCO (3 mmol) was heated at 180 °C for the appropriate time (Table 1). After the completion of the reaction (monitored by thin-layer chromatography, TLC), it was diluted with ice water and extracted with dichloromethane (3 × 15 ml). The organic layer was dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. The crude product was recrystallized from ethanol to give the pure compound. All the products were characterized using ^{1}H NMR, ^{13}C NMR, and CHN analysis.

6,7,8-Trimethoxy-3-(4-nitrophenyl)-2*H*-chromen-2-one (3s)

Yield: 72%, yellow crystals, mp 269–271 °C. IR (KBr): 1733 (C=O) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.91 (s, 3H, OCH_3), 4.02 (s, 3H, OCH_3), 4.08 (s, 3H, OCH_3), 6.74 (s, 1H, H_5), 7.48 (d, *J* = 8.8 Hz, 2H, $H_{2'}$, $H_{6'}$), 7.77 (s, 1H, H_4), 8.43 (d, *J* = 8.8 Hz, 2H, $H_{3'}$, $H_{5'}$). ^{13}C NMR (100 MHz, CDCl3): δ = 56.3, 61.6, 61.9, 103.7, 115.0, 123.0, 125.6, 130.0, 131.6, 133.7, 140.0, 141.0, 142.6, 145.9, 150.3, 160.0. Anal. calcd. for $C_{18}H_{15}NO_7$: C, 60.51; H, 4.23; N, 3.92. Found: C, 60.37; H, 4.41; N, 4.21.

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SUPPORTING INFORMATION

Supplemental data for this article can be accessed on the publisher's website.

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