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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

# Synthesis and biological evaluation of resveratrol–coumarin hybrid compounds as potential antitumor agents

**Wei Shen · Jianfeng Mao · Juan Sun · Minjie Sun · Can Zhang**

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**Abstract** Eighteen resveratrol–coumarin hybrid compounds (6 or 7-styryl-3-phenylcoumarin) were designed, synthesized and thirteen compounds were evaluated for their antitumor activities against MCF-7, HCT-28, and K562 tumor cell lines. Among them, compounds **2Z**, **2E**, **5E**, and **7E** showed varying degrees of growth inhibition of the above cell lines ($IC_{50}$: 3.78–19.16 μmol/L). On the basis of the biological results, structure–activity relationships were obtained and discussed.

**Keywords** Resveratrol · Coumarin · Wittig reaction · Perkin reaction · Antitumor activity

## Introduction

Resveratrol (*trans*-3,4′,5-trihydroxystilbene, RV) (Fig. 1) is a phytoalexin which is present in a number of plant species. Many researches on the biological activities of resveratrol have been reported including antioxidation (Fauconneau *et al.*, 1997), antiplatelet aggregation (Pace-Asciak *et al.*, 1995), cardioprotective activity (Mokni *et al.*, 2007), antitumor activity (Bishayee *et al.*, 2010), anti-obesity, and anti-diabetic activity (Szkudelska and Szkudelski, 2010). One of the most striking biological activities of RV, which has been extensively investigated, is its antitumor property, and it was discovered as a promising cancer chemopreventive agent on account of its outstanding inhibition on cellular events associated with cancer initiation, promotion, and progression (Jang *et al.*, 1997). It has been documented that RV can modulate various signal transduction pathways resulting in the prevention of the carcinogenesis from diverse aspects. Several transcription factors such as NF-KB, AP-1, cyclooxygenase, and kinases can be targeted by RV (Athar *et al.*, 2009). However, its low bioavailability and rapid clearance from the circulation restrict it to behaving as an antitumor drug (Jiang, 2008).

On the other hand, coumarins which present another large family of natural and synthetic origin showing numerous biological effects such as anti-HIV, antitumor, antibacterial, antioxidation, and so on have a skeleton of benzopyrone (Pengsuparp *et al.*, 1996; Elinos-Báeza *et al.*, 2005; Cottiglial *et al.*, 2001; Torresa *et al.*, 2006). For example, osthole showed significant antiproliferative activity against some tumor cell lines in vitro (Fujioka *et al.*, 1999) (Fig. 2).

Bearing in mind the antitumor activity of RV and coumarin derivates and the similarity of the skeletons between these two series of compounds, we designed a series of compounds which combined two RV molecules by a skeleton of benzopyrone in which one double bond is fixed to the trans isomeric form by the ring of pyrone and the other remained as *cis–trans* isomerism (Fig. 3). It was reported that methylation of the hydroxyl groups in the RV (*trans*-3,4′,5-trimethoxyresveratrol, TMRV) (Fig. 4) can enhance its antitumor activity (Cardile *et al.*, 2005), so we used the methoxyl groups instead of hydroxyl groups in the same position as those in the RV fragment. In this way, 18

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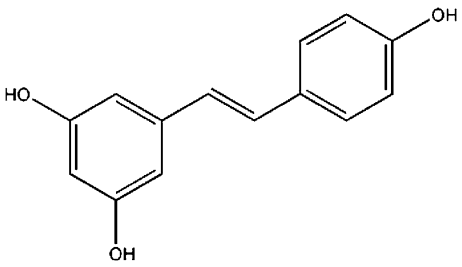



**Fig. 1** Structure of *trans*-resveratrol

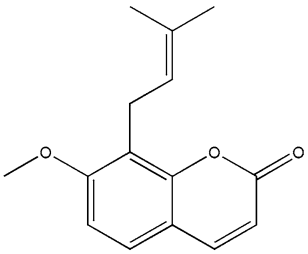


**Fig. 2** Osthole

new resveratrol–coumarin hybrids based on replacing the methoxyl groups in different positions of two benzene rings were prepared by convenient synthesis methods and first reported. 13 of these compounds' in vitro antitumor activity was evaluated against MCF-7, HCT-28, and K562 tumor cell lines and the structure–activity relationships were discussed.

## Results and discussion

### Chemistry

The synthesis of the resveratrol–coumarin hybrid compounds (Scheme 1) was started with methyl-substituted phenol (the compound **1**). The compound **2** was synthesized by the Duff reaction involving direct treatment of the compound **1** and hexamine in glycerol and boric acid under 150–160 °C. It was found that the Remier–Tiemann reaction was not valid here due to the orienting effect of the substitute group on the benzene ring. The Perkin reaction was accomplished to form the compound **6** and two

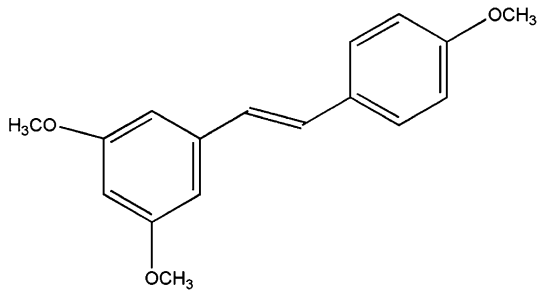



**Fig. 4** *Trans*-3,4′,5-trimethoxyresveratrol

conditions were investigated: The compound **2** reacted with phenylacetyl chloride in acetone when potassium carbonate existed or reacted with arylacetic acid when acetic anhydride and triethylamine existed. The latter condition resulted in a better yield. The compound **5** was synthesized by bromination of the compound **3** with *N*-bromosuccinimide (NBS) in benzene followed by formylation with hexamine. Subsequently, the final products (Tables 1, 2) were synthesized by treatment of the compound **5** with phosphorus ylides (the compound **8**) formed by the reaction of triphenyl phosphine with corresponding benzylchloride, and the *E* and *Z* isomers were isolated by column chromatography.

### Biological activity and discussion

The cytotoxic activities of the 13 new compounds against MCF-7, HCT-28, and K562 tumor cell lines are summarized in Table 3. The results indicated that compounds **3Z–7Z** showed no inhibition activity to these three tumor cell lines. Compound **3E** only exhibited cytotoxic activity against MCF-7 tumor cell line. Compounds **6E**, **8Z**, and **8E** have no inhibition activity against K562 tumor cell line. Compounds **2Z**, **2E**, **5E**, and **7E** showed varying degrees of growth inhibition of all test tumor cell lines ($IC_{50}$: 3.78–19.16 μmol/L).

Compound **7E** shows the most activity against MCF-7 cell lines ($IC_{50}$: 4.23 μmol/L; TMRV $IC_{50}$: 8.41 μmol/L). Compound **2E** is the most active compound against HCT-28 cell lines ($IC_{50}$: 3.78 μmol/L; TMRV $IC_{50}$: 4.83 μmol/L). Compound **2Z** exhibits the most activity

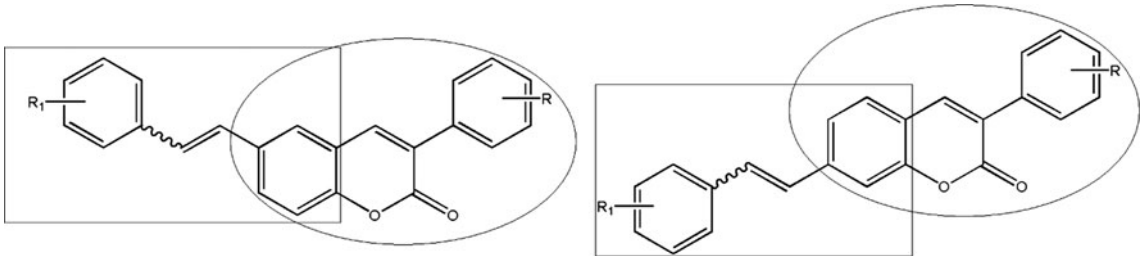
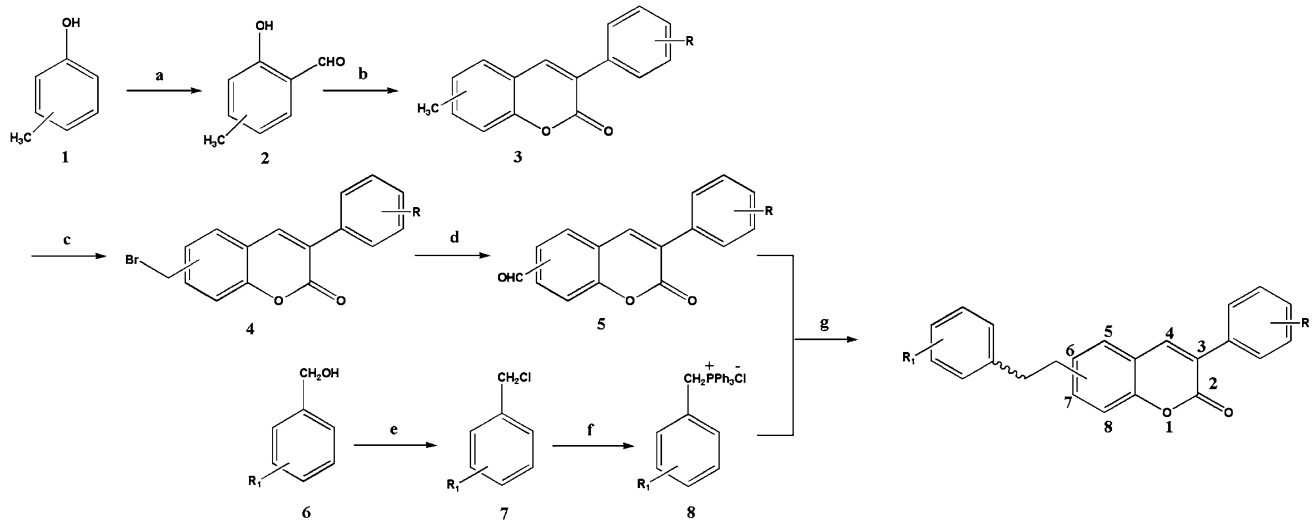
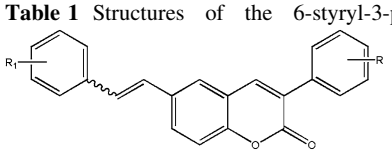



**Fig. 3** Target compounds



**Scheme 1** Synthesis of resveratrol–coumarin hybrid compounds. Reagents and conditions **a** hexamine, glycerol, boric acid, 150–160 °C; **b** substituted phenylacetic acid, triethylamine, acetic anhydride reflux; **c** NBS, benzene, reflux for 6 h; **d** hexamine, 50 % AcOH, reflux; **e** $SOCl_2$, 0–10 °C; **f** triphenyl phosphine, chloroform, reflux for 2 h; **g** 50 % NaOH, $CH_2Cl_2$, 0 °C

**Table 1** Structures of the 6-styryl-3-phenylcoumarin derivates

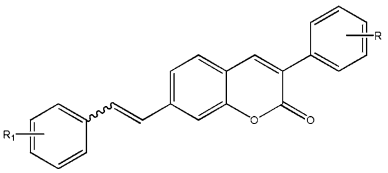


| Compound | Configuration | $R$ | $R_1$ |
|---|---|---|---|
| **2Z** | *Z* isomer | H | 4-$OCH_3$ |
| **2E** | *E* isomer | H | 4-$OCH_3$ |
| **3Z** | *Z* isomer | H | 3,5-$OCH_3$ |
| **3E** | *E* isomer | H | 3,5-$OCH_3$ |
| **4Z** | *Z* isomer | 4-$OCH_3$ | H |
| **5Z** | *Z* isomer | 4-$OCH_3$ | 3,5-$OCH_3$ |
| **5E** | *E* isomer | 4-$OCH_3$ | 3,5-$OCH_3$ |
| **6Z** | *Z* isomer | 3,4-$OCH_3$ | H |
| **6E** | *E* isomer | 3,4-$OCH_3$ | H |
| **7Z** | *Z* isomer | 3,4-$OCH_3$ | 4-$OCH_3$ |
| **7E** | *E* isomer | 3,4-$OCH_3$ | 4-$OCH_3$ |
| **8Z** | *Z* isomer | 3,4-$OCH_3$ | 3,5-$OCH_3$ |
| **8E** | *E* isomer | 3,4-$OCH_3$ | 3,5-$OCH_3$ |

against k562 cell lines ($IC_{50}$: 3.79 μmol/L; TMRV $IC_{50}$: 6.39 μmol/L). In one certain cell line, each compound reveals more potent cytotoxic activity than TMRV, respectively.

Among all thirteen resveratrol–coumarin hybrid compounds, the cytotoxic activities of the *trans*-6-substituted styryl hybrid compounds were more active than *cis*-6-substituted styryl hybrid compounds. All the *trans* form hybrid compounds showed inhibition activities to the MCF-7 tumor cell line and exhibited a certain extent of specificity. Among the *cis* form hybrid compounds, only **2Z** and **8Z** showed inhibition activities. It may be explained by the fact that most *cis* form hybrid compounds

**Table 2** Structures of the 7-styryl-3-phenylcoumarin derivates



| Compound | Configuration | $R$ | $R_1$ |
|---|---|---|---|
| **9E** | *E* isomer | H | 4-$OCH_3$ |
| **10E** | *E* isomer | H | 3,5-$OCH_3$ |
| **11E** | *E* isomer | 4-$OCH_3$ | H |
| **12E** | *E* isomer | 4-$OCH_3$ | 4-$OCH_3$ |
| **13E** | *E* isomer | 4-$OCH_3$ | 3,5-$OCH_3$ |

(**3Z–7Z**) cannot bind to the receptor, while the *trans* form hybrid compounds could be fixed in the receptor. These results suggested to us that the steric conformation of the double bond at the 6 position should be a very important factor for the inhibition activity of these compounds. Meanwhile, 4-methoxyl group on the benzene ring was found to play a very important role in the cytotoxic potency, while 3,5-methoxyl group is unnecessary. These results provided us a better understanding of the structure activity relationships of resveratrol–coumarin hybrid compounds as a potential antitumor agent. Further studies are being undertaken in our group to explore more resveratrol–coumarin hybrid compounds.

## Conclusions

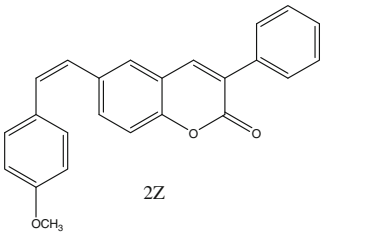
The synthesis of the resveratrol–coumarin hybrid compounds (Scheme 1) was started with methyl-substituted

**Table 3** $IC_{50}$ (μmol/L) of resveratrol–coumarin hybrid compounds on three tumor cell lines

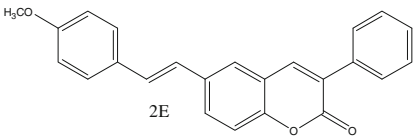
| Compound | MCF-7 | HCT-28 | K562 |
|---|---|---|---|
| TMRV | 8.41 | 4.83 | 6.39 |
| **2Z** | 10.89 | 10.65 | 3.79 |
| **2E** | 7.32 | 3.78 | 13.02 |
| **3Z** | N/A | N/A | N/A |
| **3E** | 13.50 | N/A | N/A |
| **4Z** | N/A | N/A | N/A |
| **5Z** | N/A | N/A | N/A |
| **5E** | 11.23 | 19.16 | 11.53 |
| **6Z** | N/A | N/A | N/A |
| **6E** | 14.50 | 10.75 | N/A |
| **7Z** | N/A | N/A | N/A |
| **7E** | 4.23 | 7.14 | 8.76 |
| **8Z** | 9.00 | 13.46 | N/A |
| **8E** | 7.41 | 10.09 | N/A |

$IC_{50}$ represents the half maximal (50 %) inhibitory concentration

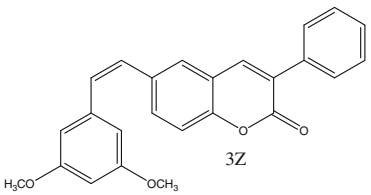
N/A represents that the compound shows no growth inhibition effect on the cell line



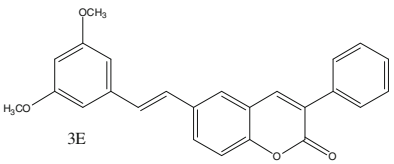

2Z



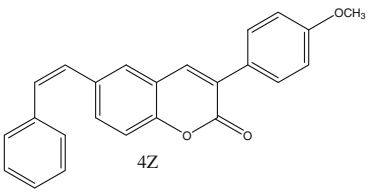

2E



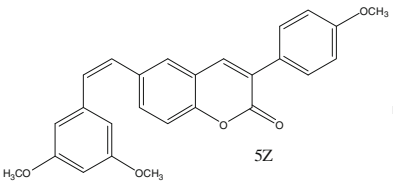

3Z



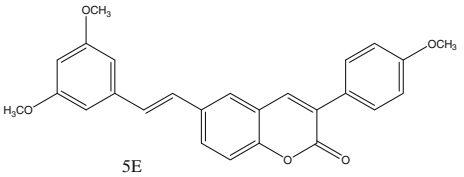

3E




4Z

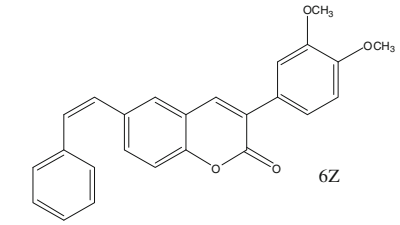



5Z

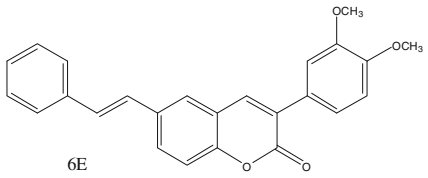



5E

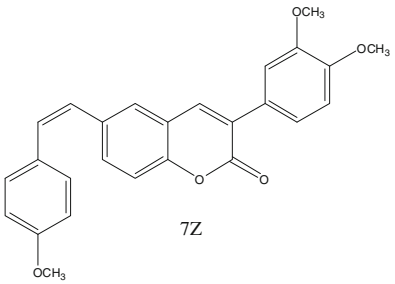
**Table 3** continued



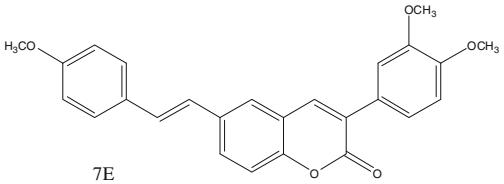

6Z



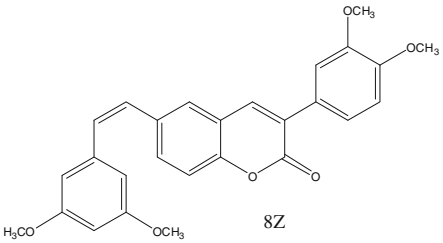

6E



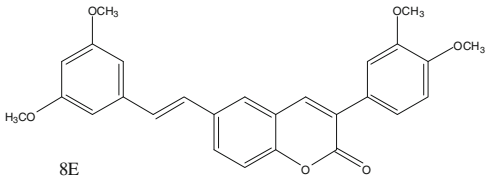

7Z



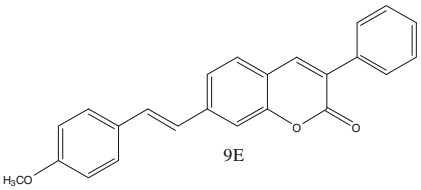

7E



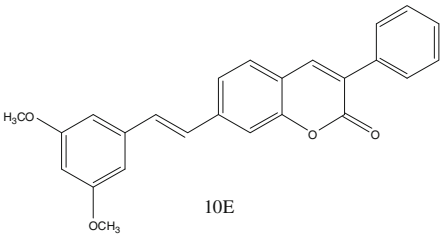

8Z



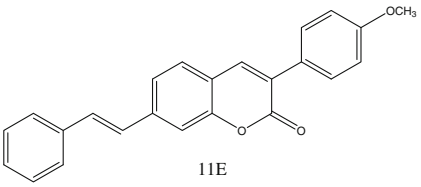

8E



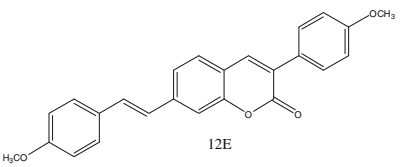

9E



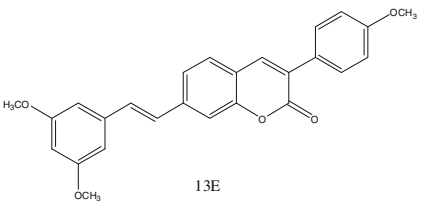

10E



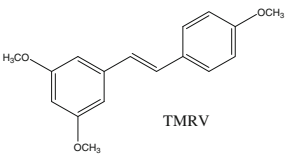

11E




12E




13E




TMRV

phenol (the compound **1**). The compound **2** was further synthesized by the Duff reaction involving direct treatment of the compound **1** and hexamine in glycerol and boric acid under 150–160 °C. The Remier–Tiemann reaction was found invalid here due to the orienting effect of the substitute group on the benzene ring. The Perkin reaction was accomplished to form the compound **6** and two scenarios were investigated: the compound **2** reacted either with phenylacetyl chloride in acetone when potassium carbonate existed or arylacetic acid when acetic anhydride and triethylamine existed. The latter condition resulted in a better yield. The compound **5** was synthesized by bromination of the compound **3** with *N*-bromosuccinimide (NBS) in benzene followed by formylation with hexamine. Subsequently, the final products (Tables 1, 2) were synthesized by treatment of the compound **5** with phosphorus ylides (the compound **8**) formed by the reaction of triphenyl phosphine with corresponding benzylchloride, and the *E* and *Z* isomers were isolated by column chromatography.

In summary, eighteen hybrid compounds with resveratrol–coumarin skeleton were synthesized and first reported. Their cytotoxic activities against MCF-7, HCT-28, and K562 tumor cell lines were evaluated. Compounds **2Z**, **2E**, **5E,** and **7E** showed varying degrees of growth inhibition of these three tumor cell lines. Due to the poor solubility of the compounds containing 7-styryl-3-phenylcoumarin skeleton, the in vitro antitumor activities of these compounds were not evaluated. At present, we are exploring demethylation or glycosylation after demethylation (via a linker-like succinate (Biasutto *et al.*, 2009) of these compounds to increase their solubility, and comparing antitumor activities to the demethylation products of the 6-styryl-3-phenylcoumarin derivates. These modifications were expected to produce some compounds with potentially higher antitumor activities and complete the structure–activity relationships.

## Experimental

### Chemistry

3,4-Dimethoxyphenylacetic acid hydrazide (99.6 %) was purchased from Zhejiang Liaoyuan Pharmaceutical Co. Ltd. (China). 2-Chloro-1-methylpyridiniumiodide (99.4 %) was obtained from Suzhou Highfine Biotech Co. Ltd. (China). 3,5-Dimethoxybenzaldehyde (99.93 %) was provided by Jiangsu Yadong Chemicals Co. Ltd. (China). 4-Methoxyphenylacetic acid (99.2 %) was supplied by Liyang Organo Synthesis Chemical Co. Ltd. (China). 4-Methoxybenzyl alcohol (99 %) was purchased from Shanghai Jiachen Chemicals Co. Ltd. (China). Other reagents were used as purchased unless otherwise stated. Reactions were monitored by TLC using silica gel GHLF uniplates from Yantai Huiyou Silica Gel Development Co. Ltd. (China) visualized under long- and short-wave UV irradiation along with staining with phosphomolybdic acid/heat, iodine, or $KMnO_4$. Solvent extracts were dried over anhydrous sodium sulfate unless otherwise stated. Where appropriate, the crude products were separated by column chromatography on silica gel (230–400 mesh) from Qingdao Haiyang Chemical Co. Ltd. (China).

Melting points are uncorrected and were determined employing an RY-1 apparatus from Tianjin Analytical Instrument Factory (China). The $^1$H-NMR spectra were recorded employing Bruker AV-300 or AV-500 instruments using a deuterated solvent and were referenced to either TMS or the solvent. The reported figures are given as ppm. Infrared spectra were recorded on a FT-IR spectrophotometer employing Nicolet Impact 410 instrument using thin KBr disks prepared under high pressure or liquid films prepared with $CH_2Cl_2$. Mass spectra were recorded employing Agilent 1100 LC–MS instrument. Elemental analyses were determined employing Vario EL III instrument (German).

### General experimental procedure for the synthesis of **2a–b**

To a three-neck round-bottomed flask, glycerol (148 mL) and boric acid (43.2 g, 0.70 mol) were added; the mixture was heated to 170 °C and maintained for 0.5 h. Then, it was cooled to 150 °C, and hexamine (30.8 g, 0.22 mol) and compound **1** (21.6 g, 0.20 mol) were added without delay. The reaction mixture was maintained at 150–160 °C for 10 min, then cooled to 110 °C rapidly. A solution of concentrated sulfuric acid (36.8 ml) in water (124 mL) was added, and the mixture was stirred for 1 h. The product was obtained by steam distillation.

*2-Hydroxy-5-methylbenzaldehyde* ***(2a)*** (yield 27 %); yellow solid; mp 56 °C; $^1$H-NMR (300 MHz, $CDCl_3$, $\delta$ppm): 10.83 (s, 1H, –OH), 9.85 (s, 1H, –CHO), 7.33–7.35 (m, 2H, 4-H, 6-H), 6.89 (d, 1H, $J = 9.0$ Hz, 3-H), 2.33 (s, $-CH_3$).

*2-Hydroxy-4-methylbenzaldehyde* ***(2b)*** (Yield 16.1 %); colorless needle crystal; mp 60 °C; $^1$H-NMR (300 MHz, $CDCl_3$, $\delta$ppm): 10.98 (s, 1H, –OH), 9.76 (s, 1H, –CHO), 7.36 (d, 1H, $J = 7.8$ Hz, 6-H), 6.76 (d, 1H, $J = 8.1$ Hz, 5-H), 6.73 (s, 1H,3-H), 2.31 (s, $-CH_3$).

### General experimental procedure for the synthesis of **3a–e**

*Method A* To a three-neck round-bottomed flask, compound **2** (4 g, 30 mmol), sodium carbonate (15 g, 141.5 mol), and acetone (300 mL) were added; then, a solution of

phenylacetyl chloride (8.1 mL) in acetone (50 mL) was added dropwise. The reaction mixture was refluxing for 6 h, and then cooled to room temperature. After evaporated under vacuum, 200 ml water was added to the residue to give a white solid. The resulting precipitate was filtered, washed, and dried. Recrystallization from alcohol afforded crystal products.

*Method B* To a three-neck round-bottomed flask, compound **2** (7.8 g, 58 mmol), 4-methoxyphenylacetic acid (9.6 g, 58 mmol), acetic anhydride (23.7 g, 232 mmol), and triethylamine (11.7 g, 116 mmol) were added. The reaction mixture was refluxing for 6 h. Then, the reflux device was changed into a distillation device. The reaction mixture was distilled until no distillate came out, then cooled, and anhydrous diethyl ether (50 mL) was added to give a yellow solid. The resulting precipitate was filtered, washed, and dried. Recrystallization from alcohol afforded crystal products.

*3-(4-Methoxyphenyl)-6-methylcoumarin (**3a**)* (Yield 95 %); Method A; colorless needle crystal; mp 146–147 °C; $^1$H-NMR (300 MHz, $CDCl_3$, $\delta$ppm): 7.75 (s, 1H, 4-H), 7.24–7.71 (m, 8H, Ar–H), 2.42 (s, 3H, $-CH_3$).

*7-Methyl-3-phenylcoumarin (**3b**)* (Yield 97 %); Method A; colorless needle crystal; mp 174–176 °C; $^1$H-NMR (500 MHz, $CDCl_3$, $\delta$ppm): 7.72 (s, 1H, 4-H), 7.04–7.64 (m, 8H, Ar–H), 2.41 (s, 3H, $-CH_3$).

*3-(4-Methoxyphenyl)-6-methylcoumarin (**3c**)* (Yield 81 %); Method B; yellow needle crystal; mp 151–152 °C; $^1$H-NMR (300 MHz, $CDCl_3$, $\delta$ppm): 7.72(s, 1H, 4-H), 7.68 (d, 2H, $J = 9$ Hz, C-2′ and C-6′-H), 7.24–7.33 (m, 3H, C-5, 7 and 8-H), 6,99 (d, 2H, $J = 9$ Hz, C-3′ and C-5′-H), 3.87 (s, 3H, $-OCH_3$), 2.43 (s, 3H, $-CH_3$).

*3-(3, 4-Dimethoxyphenyl)-6-methylcoumarin (**3d**)* (Yield 73.6 %); Method B; Yellow needle crystal; mp: 156–158 °C, $^1$H-NMR (300 MHz, $CDCl_3$, $\delta$ppm): 7.69 (s, 1H), 7.22–7.31 (m, 5H), 6.92 (d, $J = 8.3$ Hz, 1H), 3.92 (s, 3H), 3.91 (s, 3H), 2.40 (s, 3H).

*3-(4-Methoxyphenyl)-7-methylcoumarin (**3e**)* (Yield 50 %); Method B; light yellow needle crystal; mp 169–172.5 °C; $^1$H-NMR (300 MHz, $CDCl_3$, $\delta$ppm): 7.71 (s, 1H, 4-H), 7.65 (d, $J = 8.6$ Hz, 2H), 7.38 (d, $J = 7.8$ Hz 1H), 7.14 (s, 1H), 7.08 (d, $J = 7.8$ Hz, 1H), 6.96 (d, $J = 8.6$ Hz, 2H), 3.84 (s, 3H, $-OCH_3$), 2.45 (s, 3H, $-CH_3$).

General experimental procedure for the synthesis of **4**

Compound **3** (4 mmol), *N*-bromosuccinimide (4.4 mmol), and benzoyl peroxide (1 % mmol) were refluxing in benzene (20 mL) for 6 h. The mixture was evaporated under vacuum, and the residue was washed by hot water (50 mL) and ethanol (5 mL) in turn and dried. The crude solid 6 or 7-bromomethyl-3-substituted phenylcoumarin needed no further purification and was used directly for the next step.

General experimental procedure for the synthesis of **5a–e**

Compound **4** (2.5 mmol) and hexamine (5 mmol) were refluxing in 50 % acetic acid (40 mL) for 4 h. Then, concentrated hydrochloric acid (20 mL) was added, and the mixture continued refluxing for 15 min, was cooled, and poured into ice water (200 mL) to give the solid. The solid was filtered, dried, purified by flash chromatography.

*6-Formyl-3-phenylcoumarin (**5a**)* (Yield 70 %); white solid; mp 206–208 °C; $^1$H-NMR (300 MHz, $CDCl_3$, $\delta$ppm): 10.06 (s, 1H, –CHO), 8.05–8.10 (m, 2H, C-5 and C-7-H), 7.90 (s, 1H, C-4-H), 7.49–7.73 (m, 6H, C-8 and Ar–H).

*6-Formyl-3-(4-methoxyphenyl)coumarin (**5b**)* (Yield 69 %); white solid; mp 193–194 °C; $^1$H-NMR (300 MHz, $CDCl_3$, $\delta$ppm): 10.05 (s, 1H, –CHO), 7.84–8.08 (m, 2H, C-5 and C-7-H), 7.84 (s, 1H, C-4-H), 7.67–7.72 (m, 2H, C′-2 and C′-6-H), 7.49 (d, 1H, $J = 8.4$ Hz, C-8-H), 6.98–7.02 (m, 2H, C′-3 and C′-5-H), 3.87 (s, 3H, $-OCH_3$).

*6-Formyl-3-(3,4-dimethoxy-phenyl)coumarin (**5c**)* (Yield 65 %); yellow solid; mp 196–197 °C; $^1$H-NMR (300 MHz, $CDCl_3$, $\delta$ppm): 10.06 (s, 1H, –CHO), 8.02–8.10 (m, 2H, C-5 and C-7-H), 7.86 (s, 1H, C-4-H), 7.51 (d, 1H, $J = 8.4$ Hz, C-8-H), 7.26–7.32 (m, 2H, C′-2 and C′-6-H), 6.97 (s, 1H, $J = 9.0$ Hz), 3.96 (s, 3H, $-OCH_3$), 3.95 (s, 3H, $-OCH_3$).

*7-Formyl-3-phenylcoumarin (**5d**)* (Yield 61 %); white solid; mp 187–188 °C; $^1$H-NMR (500 MHz, $CDCl_3$, $\delta$ppm): 10.10 (s, 1H, –CHO), 7.81–7.85 (m, 3H), 7.70–7.74 (m, 3H), 7.44–7.50 (m, 3H).

*7-Formyl-3-(4-methoxyphenyl)coumarin (**5e**)* (Yield 71.4 %); yellow solid; mp 214–215 °C; $^1$H-NMR (500 MHz, $CDCl_3$, $\delta$ppm): 10.09 (s, 1H, –CHO), 7.67–7.82 (m, 6H), 7.00 (m, 2H), 3.87 (s, 3H).

General experimental procedure for the synthesis of **7a–b**

Compound **6** (7.6 g, 45.2 mmol) was dissolved in diethyl ether (34 mL), and then thionyl dichloride (10.8 g, 90.4 mmol) in diethyl ether (34 mL) was added dropwise under 0 °C, and was continuously stirred for 2 h. Then, 50 mL water was added, and the organic layer was separated. The water layer was extracted with diethyl ether (50 mL × 3), and the organic layers were combined, dried, filtered, and evaporated to afford the products. The resulting crude products, 4-methoxybenzyl chloride (**7a**) and 3,5-dimethoxylbenzyl chloride (**7b**), were used as a starting compound in the subsequent step without purification.

General experimental procedure for the synthesis of **8a–c**

*Method A* Triphenyl phosphine (44 mmol) and the compound **7** (40 mmol) were refluxing in trichloromethane for 3–4 h, then cooled to room temperature, and poured into anhydrous diethyl ether (160 ml). The mixture was stirred fiercely under 0 °C to give a white solid. The solid was filtered and dried.

*Method B* Triphenyl phosphine (44 mmol) and benzyl chloride (40 mmol) were refluxing in trichloromethane for 3–4 h, then cooled to the room temperature, and poured into anhydrous diethyl ether (160 ml). The mixtures were stirred fiercely under 0 °C to give a white solid. The solid was filtered and dried.

*4-Methoxybenzyl triphenylphosphonium chloride (**8a**)* (Yield 95.6 %); white solid; mp 246–248 °C; $^1$H-NMR (300 MHz, $CDCl_3$, δppm): 3.69 (s, 3H), 5.30 (d, 2H, $J = 13.8$ Hz), 6.76 (d, 2H, $J = 8.1$ Hz), 6.96 (d, 2H, $J = 8.4$ Hz), 7.19–7.92 (m, 15H).

*3,5-Dimethoxybenzyltriphenylphosphoniumchloride (**8b**)* (Yield 94.8 %); white solid; mp: 263–265 °C; $^1$H-NMR (300 MHz, $CDCl_3$, δppm): 3.51 (s, 6H), 5.33 (d, 2H, $J = 14.4$ Hz), 6.28–6.29 (d, $J = 2.4$ Hz, 3H), 7.60–7.78 (m, 15H).

*Benzyl triphenylphosphonium chloride (**8c**)* (Yield 96.8 %); white solid; mp 330–332 °C; $^1$H-NMR (300 MHz, $CDCl_3$, δppm): 5.40 (d, 2H, $J = 14.4$ Hz), 7.04–7.21 (m, 5H), 7.56–7.76 (m, 15H).

General experimental procedure for the synthesis of the resveratrol–coumarin hybrid compounds (**2Z–13E**)

*Method A* Compound **5** (1 mmol), compound **8** (1.1 mmol), potassium carbonate (1.54 mmol), and water (28 μL) were refluxing in 1,4-dioxane (6.6 mL) for 6 h. The reaction mixture was cooled to educe the solid and filtered to isolate the *E* isomer. Then, the filtrate was evaporated under reduced pressure and isolated by column chromatography to obtain the *Z* isomer.

*Method B* Compound **5** and compound **8** were solved in dichloromethane and 50 % sodium hydroxide solution (5 mL) was added under 0 °C. The reaction mixture was maintained for 40 min. Then, 50 ml water was added, and the organic layer was separated. The water layer was extracted with trichloromethane (20 mL × 3), and the organic layers were combined, dried, filtered, and evaporated to afford the crude products. The *Z* isomer and *E* isomer were isolated by column chromatography.

*Cis-6-(4-methoxystyryl)-3-phenylcoumarin (**2Z**)* (Yield 19.8 %); Method A was used in combination with **5a** and **8a** ($R_f$: 0.28, chloroform: petroleum ether = 3:2); yellow lamellar crystal; mp 183–185 °C; IR (KBr) v($cm^{-1}$): 3055, 2830, 1717, 1604, 1510, 1447, 1356, 1253, 1176, 1108, 963, 786, 696; $^1$H-NMR (300 MHz, $CDCl_3$, δppm): 7.63 (s, 1H, H-4), 7.60–7.62 (m, 2H, H-5 and H-7), 7.25–7.38 (m, 5H, H-phenyl), 7.09–7.20 (m, 3H), 6.67–6.72 (m, 2H), 6.55 (d, $J = 12$ Hz, 1H), 6.44 (d, $J = 12$ Hz, 1H), 3.73 (s, 3H, $OCH_3$); MS (ESI) *m/z*: 355.2 ($M^+ + 1$). Anal. Calcd for $C_{24}H_{18}O_3$: C, 81.34; H, 5.12. Found: C, 81.58; H, 5.16.

*Trans-6-(4-methoxystyryl)-3-phenylcoumarin (**2E**)* (Yield 16.9 %); Method A was used in combination with **5a** and **8a**; yellow lamellar crystal; mp 231–232 °C ($R_f$: 0.22, chloroform: petroleum ether = 3:2); IR (KBr) v($cm^{-1}$): 3048, 2989, 2935, 1712, 1604, 1510, 1447, 1388, 1249, 1177, 1117, 1031, 963, 831, 789, 718, 706; $^1$H-NMR (500 MHz, $CDCl_3$, δppm): 7.82 (s, 1H, H-4), 7.71–7.73 (m, 2H, H-5 and H-7), 7.60–7.68 (m, 2H), 7.42–7.48 (m, 5H), 7.08 (d, $J = 16.3$ Hz, 1H), 6.99 (d, $J = 16.3$ Hz, 1H), 6.91–6.93 (m, 2H), 3.84 (s, 3H, $OCH_3$); MS (ESI) *m/z*: 355.2 ($M^+ + 1$). Anal. Calcd for $C_{24}H_{18}O_3$: C, 81.34; H, 5.12. Found C, 81.62; H, 5.14.

*Cis-6-(3,5-dimethoxystyryl)-3-phenylcoumarin (**3Z**)* (Yield 13.0 %); Method A was used in combination with **5a** and **8b** ($R_f$: 0.37, acetic ether: petroleum ether = 1:5); white solid; mp 151–152 °C; IR (KBr) v($cm^{-1}$): 3003, 2948, 2826, 1723, 1589, 1485, 1462, 1392, 1330, 1232, 1194, 1154, 1110, 960, 850, 788, 705; $^1$H-NMR (300 MHz, $CDCl_3$, δppm): 7.71 (s, 1H, H-4), 7.68–7.69 (m, 2H), 7.43–7.50 (m, 5H), 7.25 (d, $J = 8.7$ Hz, 1H), 6.66 (d, $J = 12.3$ Hz, 1H), 6.61 (d, $J = 12.3$ Hz, 1H), 6.41–6.42 (d, $J = 2.2$ Hz, 2H), 6.36–6.38 (m, 1H), 3.69 (s, 6H, 2 × $OCH_3$); MS (ESI) *m/z*: 385.2 ($M^+ + 1$). Anal. Calcd for $C_{25}H_{20}O_4$: C, 78.11; H, 5.24. Found: C, 78.37; H, 5.17.

*Trans-6-(3,5-dimethoxystyryl)-3-phenylcoumarin (**3E**)* (Yield 26.0 %); Method A was used in combination with **5a** and **8b** ($R_f$: 0.31, acetic ether: petroleum ether = 1:5); yellow lamellar crystal; mp 170–172 °C; IR (KBr) v($cm^{-1}$): 3048, 2989, 2934, 2830, 1721, 1592, 1454, 1358, 1317, 1296,1275, 1204, 1156, 1148, 1106, 1069, 951, 785, 697; $^1$H-NMR (300 MHz, $CDCl_3$, δppm): 7.83 (s, 1H, H-4), 7.63–7.73 (m, 4H), 7.43–7.50 (m, 3H), 7.37 (d, $J = 8.4$ Hz, 1H), 7.14 (d, $J = 16.2$ Hz, 1H), 6.07 (d, $J = 16.3$ Hz, 1H), 6.68–6.69 (d, $J = 2.1$ Hz, 2H), 6.43(m, 1H), 3.85 (s, 6H, 2 × $OCH_3$); MS (ESI) *m/z*: 385.2 ($M^+ + 1$). Anal. calcd for $C_{25}H_{20}O_4$: C, 78.11; H, 5.24. Found: C, 77.86; H, 5.26.

*Cis-3-(4-methoxyphenyl)-6-styrylcoumarin (**4Z**)* (Yield 14.1 %); Method B was used in combination with **5b** and **8c**; colorless lamellar crystal; mp 140–142 °C; IR (KBr) v($cm^{-1}$): 3049, 2956, 2939, 2830, 1715, 1607, 1513, 1250, 1181, 1110, 931, 824, 782, 693; $^1$H-NMR (300 MHz, $CDCl_3$, δppm): 7.67 (s, 1H, H-4), 7.62–7.68 (m, 2H), 7.20–7.40 (m, 8H), 6.97–7.00(d, $J = 8.7$ Hz, 2H), 6.71 (d, $J = 12$ Hz, 1H), 6.62 (d, $J = 12$ Hz, 1H), 3.87 (s, 3H,

$OCH_3$); MS (ESI) *m/z*: 355.2 ($M^+ + 1$). Anal. Calcd for $C_{24}H_{18}O_3$: C, 81.34; H, 5.12. Found: C, 81.05; H, 5.10.

*Cis-6-(3,5-dimethoxystyryl)-3-(4-methoxyphenyl)coumarin (**5Z**)* (Yield 19.3 %); Method B was used in combination with **5b** and **8b** ($R_f$: 0.21, acetic ether: petroleum ether = 1:5); yellow solid; mp 125–127 °C; IR (KBr) v($cm^{-1}$): 3049, 2935, 2834, 1712, 1597, 1456, 1388, 1250, 1158, 1110, 832, 794, 683; $^1$H-NMR (300 MHz, $CDCl_3$, δppm): 7.69 (s, 1H), 7.63–7.68 (m, 2H), 7.22–7.44 (m, 3H), 6.99–7.01 (d, $J = 8.8$ Hz, 2H), 6.65 (d, $J = 12$ Hz, 1H), 6.61 (d, $J = 12$ Hz, 1H), 6.36–6.42 (m, 3H), 3.88 (s, 3H, $OCH_3$), 3.69 (s, 6H, 2 × $OCH_3$); MS (ESI) *m/z*: 415.2 ($M^+ + 1$). Anal. Calcd for $C_{26}H_{22}O_5$: C, 75.35; H, 5.35. Found: C, 75.62; H, 5.37.

*Trans-6-(3,5-dimethoxystyryl)-3-(4-methoxyphenyl)coumarin (**5E**)* (Yield 16.9 %); Method B was used in combination with **5b** and **8b** ($R_f$: 0.15, acetic ether: petroleum ether = 1:5); yellow solid; mp 194–195 °C; IR (KBr) v($cm^{-1}$): 3068, 3033, 2961, 2921, 2840, 1720, 1592, 1459, 1425, 1385, 1250, 1152, 1108, 1065, 949, 832, 804, 686; $^1$H-NMR (300 MHz, $CDCl_3$, δppm): 7.77 (s, 1H), 7.60–7.71 (m, 4H), 7.34 (d, $J = 8.6$ Hz, 1H), 7.11 (d, $J = 16.3$ Hz, 1H), 7.03 (d, $J = 16.3$ Hz, 1H), 6.98–7.01 (m, 2H), 6.68 (d, $J = 2.2$ Hz, 2H), 6.42–6.43 (m, 1H), 3.86 (s, 3H, $OCH_3$), 3.84 (s, 6H, 2 × $OCH_3$); MS (ESI) *m/z*: 415.2 ($M^+ + 1$). Anal. Calcd for $C_{26}H_{22}O_5$: C, 75.35; H, 5.35. Found: C, 75.08; H, 5.38.

*Cis-3-(3,4-dimethoxyphenyl)-6-styrylcoumarin (**6Z**)* (Yield 36.7 %); Method B was used in combination with **5c** and **8c** ($R_f$: 0.31, acetic ether: petroleum ether = 1:5); yellow solid; mp 91–92 °C; IR (KBr) v($cm^{-1}$): 3010, 2904, 2834, 1707, 1600, 1518, 1468, 1445, 1384, 1263, 1170, 1151, 1101, 1018, 815, 776, 696; $^1$H-NMR (500 MHz, $CDCl_3$, δppm): 7.62 (s, 1H), 7.36–7.39 (m, 2H), 7.20–7.29 (m, 8H), 6.92 (d, $J = 8.4$ Hz, 1H), 6.69 (d, $J = 12.1$ Hz, 1H), 6.60 (d, $J = 12.1$ Hz, 1H), 3.93 (s, 3H, $OCH_3$), 3.92 (s, 3H, $OCH_3$); MS (ESI) *m/z*: 385.2 ($M^+ + 1$). Anal. Calcd for $C_{25}H_{20}O_4$: C, 78.11; H, 5.24. Found: C, 78.42; H, 5.20.

*Trans-3-(3,4-dimethoxyphenyl)-6-styrylcoumarin (**6E**)* (Yield 24.0 %);Method B was used in combination with **5c** and **8c** ($R_f$: 0.24, acetic ether: petroleum ether = 1:5); yellow solid; mp 197–198 °C; IR (KBr) v($cm^{-1}$): 3003, 2967, 2925, 2825, 1716, 1518, 1259, 1102, 1026, 807, 759, 699; $^1$H-NMR (500 MHz, $CDCl_3$, δppm): 7.79 (s, 1H, H-4), 7.52–7.69 (m, 4H), 7.25–7.40 (m, 6H), 7.12 (s, 2H), 6.95 (d, $J = 8.3$ Hz, 1H), 3.95 (s, 3H, $OCH_3$), 3.94 (s, 3H, $OCH_3$); MS (ESI) *m/z*: 385.2 ($M^+ + 1$). Anal. Calcd for $C_{25}H_{20}O_4$: C, 78.11; H, 5.24. Found: C, 77.90; H, 5.22.

*Cis-3-(3,4-dimethoxyphenyl)-6-(4-methoxystyryl)coumarin (**7Z**)* (Yield 16.7 %); Method B was used in combination with **5c** and **8a** ($R_f$: 0.25, acetic ether: petroleum ether = 1:5); yellow solid; mp 90–92 °C; IR (KBr) v($cm^{-1}$): 3007, 2962, 2835, 1709, 1606, 1514, 1456, 1391, 1360, 1255, 1101, 1025, 819, 772; $^1$H-NMR (500 MHz, $CDCl_3$, δppm): 7.69 (s, 1H), 7.43–7.47 (m, 2H), 7.20–7.34 (m, 5H), 6.97 (d, $J = 8.4$ Hz, 1H), 6.81–6.83 (m, 2H), 6.65 (d, $J = 12.1$ Hz, 1H), 6.56 (d, $J = 12.1$ Hz, 1H), 3.98 (s, 3H, $OCH_3$), 3.97 (s, 3H, $OCH_3$), 3.83 (s, 3H, $OCH_3$); MS (ESI) *m/z*: 415.2 ($M^+ + 1$). Anal. Calcd for $C_{26}H_{22}O_5$: C, 75.35; H, 5.55. Found: C, 75.11; H, 5.37.

*Trans-3-(3,4-dimethoxyphenyl)-6-(4-methoxystyryl)coumarin (**7E**)* (Yield 15.9 %); Method B was used in combination with **5c** and **8a**; yellow solid ($R_f$: 0.19, acetic ether: petroleum ether = 1:5); mp 172–173 °C; IR (KBr) v($cm^{-1}$): 3006, 2959, 2942, 2844, 1735, 1605, 1513, 1466, 1384, 1258, 1092, 1019, 831, 818, 774; $^1$H-NMR (500 MHz, $CDCl_3$, δppm): 7.79 (s, 1H), 7.59–7.66 (m, 2H), 7.46–7.47 (m, 2H), 7.29–7.35 (m, 3H), 7.08 (d, $J = 16.3$ Hz, 1H), 6.98 (d, $J = 16.3$ Hz, 1H), 6.91–6.96 (m, 3H), 3.96 (s, 3H, $OCH_3$), 3.94 (s, 3H, $OCH_3$), 3.84 (s, 3H, $OCH_3$); MS (ESI) *m/z*: 415.2 ($M^+ + 1$). Anal. Calcd for $C_{26}H_{22}O_5$: C, 75.35; H, 5.55. Found: C, 75.61; H, 5.32.

*Cis-3-(3,4-dimethoxyphenyl)-6-(3,5-dimethoxystyryl)coumarin (**8Z**)* (Yield 23.6 %); Method B was used in combination with **5c** and **8b** ($R_f$: 0.22, acetic ether: petroleum ether = 1:5); yellow solid; mp 114–115 °C; IR (KBr) v($cm^{-1}$): 3049, 3003, 2933, 2833, 1708, 1590, 1515, 1454, 1388, 1255, 1154, 1108, 1058, 1025, 852, 820, 790, 744, 685; $^1$H-NMR (500 MHz, $CDCl_3$, δppm): 7.65 (s, 1H), 7.40–7.42 (t, 2H), 7.21–7.29 (m, 3H), 6.93 (d, $J = 8.4$ Hz, 1H), 6.62 (d, $J = 12.2$ Hz, 1H), 6.59 (d, $J = 12.2$ Hz, 1H), 6.39–6.40 (d, $J = 1.7$ Hz, 2H), 6.34–6.35 (t, 1H), 3.94 (s, 3H, $OCH_3$), 3.93 (s, 3H, $OCH_3$), 3.67 (s, 6H, 2 × $OCH_3$); GC–MS *m/z*: 444.1 ($M^+ + 1$). Anal. Calcd for $C_{27}H_{24}O_6$: C, 72.96; H, 5.44. Found: C, 72.71; H, 5.42.

*Trans-3-(3,4-dimethoxyphenyl)-6-(3,5-dimethoxystyryl)coumarin (**8E**)* (Yield 43.9 %); Method B was used in combination with **5c** and **8b** ($R_f$: 0.14, acetic ether: petroleum ether = 1:5); yellow solid; mp 178–179 °C; IR (KBr) v($cm^{-1}$): 3033, 2996, 2961, 2843, 1713, 1591, 1450, 1390, 1255, 1148, 1100, 1026, 980, 808, 681, 630; $^1$H-NMR (500 MHz, $CDCl_3$, δppm): 7.79 (s, 1H), 7.62–7.68 (m, 2H), 7.29–7.36 (m, 3H), 7.10 (d, $J = 16.2$ Hz, 1H), 7.04 (d, $J = 16.2$ Hz, 1H), 6.95 (d, $J = 8.3$ Hz, 1H), 6.67–6.68 (d, $J = 2.1$ Hz, 2H), 6.42–6.43 (t, 1H), 3.96 (s, 3H, $OCH_3$), 3.94 (s, 3H, $OCH_3$), 3.84 (s, 6H, 2 × $OCH_3$); MS (ESI) *m/z*: 445.2 ($M^+ + 1$). Anal. Calcd for $C_{27}H_{24}O_6$: C, 72.96; H, 5.44. Found: C, 72.52; H, 5.46.

*Trans-7-(4-methoxystyryl)-3-phenylcoumarin (**9E**)* (Yield 42.4 %);Method A was used in combination with **5d** and **8a**; yellow solid; mp 192–192.5 °C; IR (KBr) v($cm^{-1}$): 3067, 3017, 2953, 2829, 1721, 1598, 1511, 1446, 1383, 1251, 1175, 1134, 977, 827, 784, 694, 621; $^1$H-NMR (300 MHz, $CDCl_3$, δppm): 7.79 (s, 1H), 7.71–7.74 (q, 2H), 7.41–7.52 (m, 8H), 7.20 (d, $J = 16.2$ Hz, 1H), 7.01

(d, $J = 16.2$ Hz, 1H), 6.92–6.98 (d, $J = 18.9$ Hz, 2H), 3.85 (s, 3H, $OCH_3$); MS (ESI) *m/z*: 355.2 ($M^+ + 1$). Anal. Calcd for $C_{24}H_{18}O_3$: C, 81.34; H, 5.12. Found: C, 81.70; H, 5.12.

*Trans-7-(3,5-dimethoxystyryl)-3-phenylcoumarin* ***(10E)*** (Yield 36.5 %); Method A was used in combination with **5d** and **8b**; yellow solid; mp 188 °C; IR (KBr) v($cm^{-1}$): 3046, 2832, 1724, 1606, 1479, 1383, 1322, 1299, 1203, 1110, 1065, 950, 818, 783, 676, 629; $^1$H-NMR (300 MHz, $CDCl_3$, δppm): 7.81(s, 1H), 7.71–7.74 (q, 2H), 7.36–7.54 (m, 6H), 7.18 (d, $J = 16.2$ Hz, 1H), 7.11 (d, $J = 16.2$ Hz, 1H), 6.70–6.71 (d, $J = 2.1$ Hz, 2H), 6.45–6.46 (t, 1H), 3.86 (s, 6H, 2 × $OCH_3$); MS (ESI) *m/z*: 385.2 ($M^+ + 1$). Anal. Calcd for $C_{25}H_{20}O_4$: C, 78.11; H, 5.24. Found: C, 78.39; H, 5.24.

*Trans-(-3-(4-methoxyphenyl)-7-styrylcoumarin* ***(11E)*** (Yield 14.1 %); Method B was used in combination with **5e** and **8c**; amber solid, mp 218–222 °C; IR (KBr) v($cm^{-1}$): 3039, 2956, 2836, 1712, 1607, 1383, 1250, 1183, 1140, 1032, 827, 779, 692, 625; $^1$H-NMR (300 MHz, $CDCl_3$, δppm): 7.79 (s, 1H), 7.70–7.71 (q, 2H), 7.58–7.61 (d, $J = 7.2$ Hz, 2H), 7.35–7.52 (m, 6H), 7.28 (d, $J = 16.2$ Hz, 1H), 7.17 (d, $J = 16.2$ Hz, 1H), 7.00–7.03 (d, $J = 8.4$ Hz, 2H), 3.86 (s, 3H, $OCH_3$); MS (ESI) *m/z*: 355.2 ($M^+ + 1$). Anal. Calcd for $C_{24}H_{18}O_3$: C, 81.34; H, 5.12. Found: C, 81.60; H, 5.10.

*Trans-3-(4-methoxyphenyl)-7-(4-methoxystyryl)coumarin* ***(12E)*** (Yield 18.2 %);Method B was used in combination with **5e** and **8a**; yellow solid, mp 217–218 °C; IR (KBr) v($cm^{-1}$): 3024, 3010, 2833,1706, 1605, 1513, 1456, 1383, 1253, 1175, 1031, 825, 778, 624; $^1$H-NMR (300 MHz, $CDCl_3$, δppm): 7.67(s, 1H), 7.60–7.63 (d, 2H), 7.28–7.44 (m, 5H), 7.04–7.15 (d, $J = 31.8$ Hz, 2H), 6.93 (d, $J = 16.2$ Hz, 1H), 6.87 (d, $J = 16.2$ Hz, 1H), 6.87–6.92 (d, $J = 16.2$ Hz, 2H), 3.78 (s, 6H, 2 × $OCH_3$); MS (ESI) *m/z*: 385.2 ($M^+ + 1$). Anal. Calcd for $C_{25}H_{20}O_4$: C, 78.11; H, 5.24. Found: C, 77.83; H, 5.25.

*Trans-7-(3,5-dimethoxystyryl)-3-(4-methoxyphenyl)coumarin* ***(13E)*** (Yield 48.3 %); Method B was used in combination with **5e** and **8b**; yellow solid, mp 198–199 °C; IR (KBr) v($cm^{-1}$): 3075, 3035, 2989, 2835, 1708, 1599, 1429, 1384, 1250, 1204, 1150, 1106, 1060, 842, 832, 775, 686, 633. $^1$H-NMR (300 MHz, $CDCl_3$, δppm): 7.68 (s, 1H), 7.58–7.64 (d, 2H), 7.37–7.44 (m, 3H), 7.10 (d, $J = 16.2$ Hz, 1H), 7.02 (d, $J = 16.2$ Hz, 1H), 6.90–6.93 (d, $J = 8.7$ Hz, 2H), 6.63–6.64 (d, $J = 2.1$ Hz, 2H), 6.30–6.37 (m, 1H), 3.78 (s, 9H, 3 × $OCH_3$); MS (ESI) *m/z*: 415.2 ($M^+ + 1$). Anal. Calcd for $C_{26}H_{22}O_5$: C, 75.35; H, 5.35. Found: C, 75.60; H, 5.33.

### General experimental procedure for the synthesis of TMRV

Compound **8a** (2.62 g, 6.3 mmol) and 3,5-dimethoxybenzaldehyde (0.8 g, 4.8 mmol) were solved in dichloromethane and 50 % sodium hydroxide solution (5 mL) was added at 0 °C. The reaction mixtures were maintained for 40 min. Then, 50 mL water was added, and the organic layer was separated. The water layer was extracted with trichloromethane (20 mL × 3), and the organic layers were combined, dried, filtered, and evaporated to afford the crude products. The *E* isomer was isolated by column chromatography (PE: EA = 20:1).

*Trans-3,4′,5-trimethoxystilbene (TMRV)* (Yield 30.8 %); white solid; mp 61–62 °C; IR (KBr) v($cm^{-1}$): 2931, 2831, 1591, 1511, 1458, 1425, 1250, 1154, 961, 822; $^1$H-NMR (300 MHz, $CDCl_3$, δppm): 7.45 (d, $J = 8.8$ Hz, 2H, H-2′,6′), 7.04 (d, $J = 16.4$ Hz, 1H), 6.91 (d, $J = 16.4$ Hz, 1H), 6.90 (d, $J = 8.7$ Hz, 2H, H-3′,5′), 6.65 (s, 2H, H-2,6), 6.38 (s, 1H, H-4), 3.83 (s, 9H, $OCH_3$); MS (ESI) *m/z*: 271.1 ($M^+ + 1$). Anal. Calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.76; H, 6.69.

### MTT assay

The cytotoxicity was evaluated by MTT assay using KB cells, HCT-28 cells, and MCF-7 cells (Mo *et al.*, 2011). First, target tumor cells which were grown well were diluted to $5 \times 10^4$ cells $ml^{-1}$. Then, 200 μl of the obtained cell suspension was added to each well of 96-well culture plates. The suspension was incubated at 37 °C, 5 % $CO_2$ atmosphere in DMEM + 10 % calf serum for 24 h before the tested compounds at pre-set concentration in DMSO were added. After 48 h incubation, MTT (5 mg/mL) was added to each well and reacted for 4 h. The medium was replaced by 150 μl DMSO to solubilize the purple formazan crystals produced. The absorbance at 570 nm of each well was measured on an ELISA plate reader. And the $IC_{50}$ was calculated by a dose of Logarithmic linear regression analysis.

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