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Design, synthesis and antitumor activity of a series of novel coumarin–stilbenes hybrids, the 3-arylcoumarins

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Abstract

A series of novel coumarin–stilbenes hybrids called 3-arylcoumarins were synthesized via Perkin reaction and evaluated as potential antitumor agents. The results showed that some compounds exhibited *in vitro* activity against KB, KV, MCF-7, MCF-7/ADR cell lines to some extent. Compound **3a** showed remarkable effect against KB tumor cells with an IC_{50} value of 5.18 μmol/L.

Keywords: Perkin reaction; 3-Arylcoumarin; *Trans*-stilbene; Antitumor activity

Trans-stilbenes are an important family of plant secondary metabolites derived from the phenylpropanoid pathway, and have been found in a number of plant species [1]. Many *trans*-stilbenes, including resveratrol, oxyresveratrol, pterostilbene, piceatannol and isorhapotigenin exhibit high levels of biological activities and are renowned for protection properties against cancer, heart diseases, stroke, Alzheimer's disease, inflammations, infections and so on [2–4]. Studies also proved that stilbenes like resveratrol can activate SIRT1 and resulting in anti-aging effects in numerous organisms [5]. Although the skeleton of *trans*-stilbenes bear the resemblance to isoflavones, flavones and coumarins, which are related with each other in biosynthesis, implying a good opportunity for crosswise structure modification of these compounds (Fig. 1), few compounds have been documented concerning about the medicinal chemistry until recently. Vilar et al. reported the synthesis of a series of coumarin–resveratrol hybrids by Pechmann and Perkin reaction with yields of 27.3–42%. Pharmacological tests showed the new hybrids possess more potent vasorelaxant and platelet antiaggregatory activity than that of resveratrol [6]. The results indicated that further chemical and biological studies of coumarin–stilbenes hybrids would be worthy to do in the future.

As a continuation of our work on the chemistry of stilbene derivatives, we herein report the design and synthesis of a series of novel coumarin–stilbenes hybrids **4**, namely 3-arylcoumarins, which the *trans* double bond of the stilbenes were locked by a six-membered benzopyrone ring, with satisfactory yields (74–93%). Structurally, these 3-arylcoumarins bear close resemblance to the distinguished parent *trans*-stilbenes such as resveratrol, oxyresveratrol,

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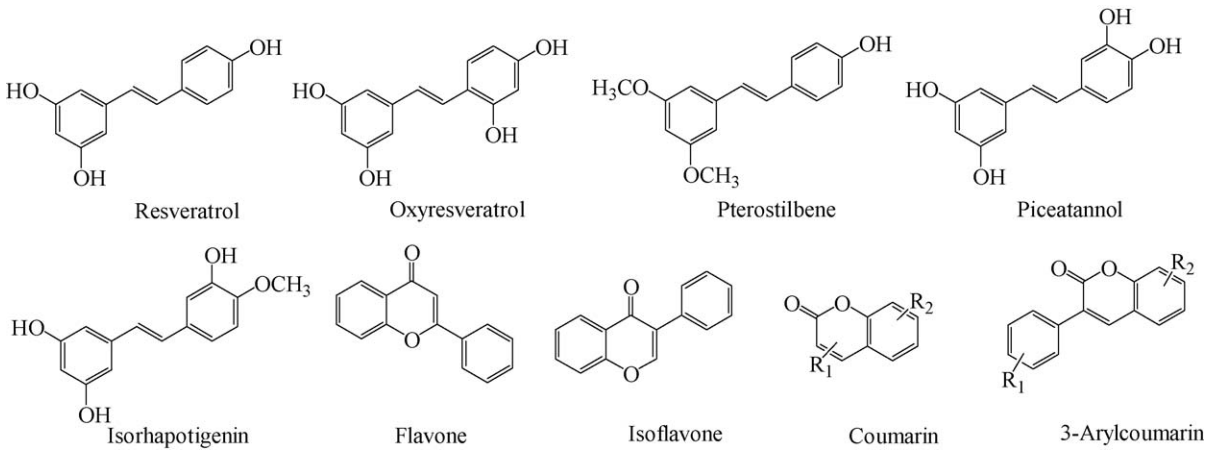


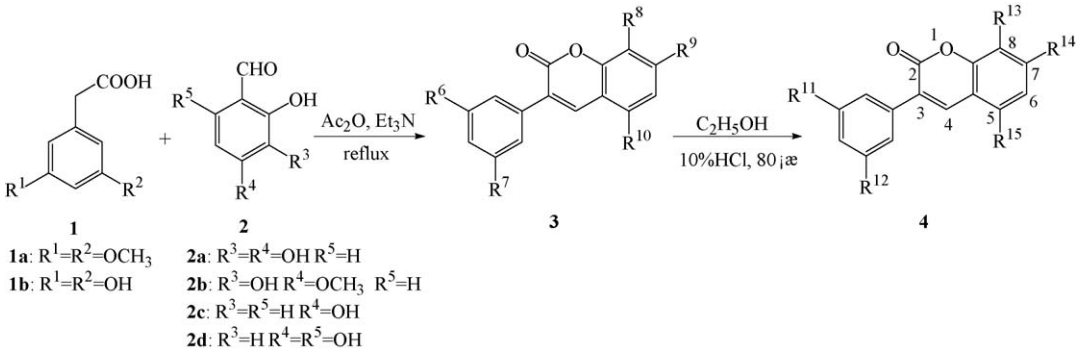
Fig. 1. Structure similarities between *trans*-stilbenes, (*iso*) flavones and 3-arylcoumarins.

pterostilbene, piceatannol and isorhapotigenin in terms of skeleton and hydroxyl substitution pattern. Cytotoxicities of the compounds were evaluated against four human cancer cell lines (KB, KV, MCF-7, MCF-7/ADR) by MTT assays, and compound **3a** was found to be a promising candidate with potent anticancer activity.

Preparation of the compounds **3** and **4** was shown in Scheme 1. Treatment of substituted phenyl acetic acid **1** and *ortho*-hydroxylbenzaldehyde **2** in the presence of acetic anhydride and triethylamine for 8–12 h at 110 °C resulted in acetylated 3-arylcoumarin **3** in 74–93% isolated yields. Compounds **4** were obtained by hydrolysis of **3** in the presence of 10% hydrochloric acid in ethanol at 80 °C in 90–95% yields. The Structures of these compounds were conformed by ^{1}H NMR, ^{13}C NMR, EI/ESI-MS, IR spectra (Table 1).

The synthesized compounds were evaluated for their inhibitory effects on the proliferation of tumor cells *in vitro* by MTT assays (Table 2). The concentrations required to inhibit growth by 50% (IC_{50}) were calculated from survival curves using the Bliss method [8]. Among the prepared compounds, compound **3a**, **3d** and **4a** which were characterized by a 7, 8-dihydroxy group or 7, 8-diacetyloxy group exhibited apparent activity. Especially, compound **3a** was found to possess the most potent activity with an IC_{50} value of 5.18 μmol/L against KB cell lines. It is worth mentioning that compound **3a** and **4a** showed more potent inhibitory effects against MCF-7/ADR cell lines (IC_{50} = 11.94, 11.11 μmol/L, respectively) than normal MCF-7 cell lines (IC_{50} = 21.43, 22.94 μmol/L, respectively), implying a remarkable anti-MDR properties endowed with these compounds.

In conclusion, a series of novel 3-arylcoumarins were synthesized and their anticancer activities were evaluated for four types cell lines. Among them, **3a**, **3d** and **4a** exhibited remarkable cytotoxic activity *in vitro*. Particularly, compound **3a** showed the most potent activity with an IC_{50} value of 5.18 μmol/L against KB cell lines. The results suggested that 3-arylcoumarins which possessing 7, 8-dihydroxy group or 7, 8-diacetyloxy group may be beneficial to cytotoxicities. Further structural modification aiming at discovering more potent compounds is under way in our laboratory.



Scheme 1. Synthesis of 3-arylcoumarins.

Table 1
The substituents, melting points and yields of compound **3** and **4**.

Entry1	R^6	R^7	R^8	R^9	R^{10}	Yield[a] (%)	M_p (°C)
3a	OCH_3	OCH_3	OAc	OAc	H	77	155–156
3b	OCH_3	OCH_3	OAc	OCH_3	H	93	159–161
3c	OCH_3	OCH_3	H	OAc	H	91	162–164
3d	OAc	OAc	OAc	OAc	H	75	168–170
3e	OAc	OAc	OAc	OCH_3	H	76	204–206
3f	OAc	OAc	H	OAc	H	74	189–191
3g	OAc	OAc	H	OAc	OAc	88	236–238

Entry2	R^{11}	R^{12}	R^{13}	R^{14}	R^{15}	Yield[a] (%)	M_p (°C)
4a	OCH_3	OCH_3	OH	OH	H	90	128–130 (lit. [7]:128–130)
4b	OCH_3	OCH_3	OH	OCH_3	H	93	165–167
4c	OCH_3	OCH_3	H	OH	H	95	221–223
4d	OH	OH	OH	OH	H	91	>280
4e	OH	OH	OH	OCH_3	H	90.5	249–251
4f	OH	OH	H	OH	H	90	>280
4g	OH	OH	H	OH	OH	94	>280

[a] Isolated yield.

Table 2
In vitro cytotoxic activity of tested compounds against KB, KV, MCF-7, MCF-7/ADR cell lines.

Compounds	Cell lines IC_{50} (μmol/L)			
	KB	KV	MCF-7	MCF-7/ADR
3a	5.18	13.96	21.43	11.94
3b	>100	>100	>100	>100
3c	>100	>100	>100	>100
3d	29.15	33.85	30.77	39.23
3e	>100	>100	>100	>100
3f	>100	>100	>100	>100
3g	>50	ND	>50	ND
4a	9.747	17.20	22.94	11.11
4b	>100	>100	>100	>100
4c	>100	>100	>100	>100
4d	>100	>100	>100	>100
4e	>100	>100	>100	>100
4f	>50	ND	>50	ND
4g	>50	ND	>50	ND

ND: not determined.

1. Experimental

All melting points were determined on SGW X-4 melting-point apparatus and uncorrected. IR spectra were recorded on an Analect RFX-65A IR spectrometer. ^1H NMR and ^{13}C NMR were obtained from a Brucker DRX-400 MHz spectrometer with TMS as an internal standard. MS analyses were performed using a Shimadzu GCMS-QP5050A and Thermo GCMS-MAT95XP mass spectrometer.

*1.1. Preparation of acetoxylated 3-arylcoumarins **3a–g***

To a solution of *ortho*-hydroxybenzaldehyde **2** (10 mmol) and substituted phenyl acetic acid **1** (10 mmol) in acetic anhydride (70 mmol), triethylamine (50 mmol) was added. The mixture was heated at 110 °C and stirred for 8–12 h. After cooling, it was poured into ice-water, stirred and stored for several hours. A yellow solid was precipitated, filtrated and washed with water, dried in air, then recrystalized from ethyl acetate.

7, 8-Diacetoxy-3-(3′, 5′-dimethoxyphenyl)coumarin ***3a***: IR(KBr): 3006, 2965, 2935, 2838, 1783, 1725, 1594, 1494, 1457, 1425, 1365, 1344, 1309, 1259, 1203, 1157, 1105, 1064, 1039, 1010, 923, 885, 835, 771, 744, 715; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.32(s, 3H, 7-OAc), 2.40(s, 3H, 8-OAc), 3.80(s, 6H, 3′, 5′-OCH_3), 6.49(t, 1H, J = 2.0 Hz, 4′-ArH), 6.77(d, 2H, J = 2.0 Hz, 2′,6′-ArH), 7.10(d, 1H, J = 8.4 Hz, 5-H), 7.38(d, 1H, J = 8.4 Hz, 6-H), 7.75(s, 1H, 4-H); EI-MS *m/z*: 398(M^+), 356(M^+-Ac), 314(M^+-2Ac).

1.2. Preparation of hydroxylated 3-arylcoumarins ***4a–g***

Compound **3** (1.25 mmol) was added to a solution of 10% HCl(15 mL) and ethanol(5 mL). The mixture was heated at 80 °C and stirred for 8–12 h. After cooling, it was poured into ice-water, a light yellow solid was precipitated, filtrated, washed with cold distilled water, and dried under vacuum, then recrystallized from ethanol and water.

7, 8-Dihydroxy-3-(3′, 5′-dimethoxyphenyl)coumarin ***4a***: IR(KBr): 3426, 3345, 2964, 2836, 1691, 1598, 1511, 1459, 1425, 1346, 1299, 1257, 1203, 1153, 1114, 1066, 1031, 966, 923, 854, 819, 773, 734, 703; ^{1}H NMR (400 MHz, CD_3COCD_3-d_6): δ 3.80(s, 6H, 3′, 5′-OCH_3), 6.49(t, 1H, J = 2.0 Hz, 4′-ArH), 6.87(d, 1H, J = 8.4 Hz, 6-H), 6.89(d, 2H, J = 2.0 Hz, 2′, 6′-ArH), 7.10(d, 1H, J = 8.4 Hz, 5-H), 8.04(s, 1H, 4-H); ^{13}C NMR(400 MHz, CD_3COCD_3-d_6):δ 55.6, 100.7, 107.5, 113.4, 114.1, 120.3, 123.8, 132.4, 138.2, 142.1, 143.9, 149.9, 160.3, 161.5; EI-MS *m/z:* 314(M^+), 286, 256.

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