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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

Wei Shen and Jianfeng Mao contributed equally to this work.

W. Shen · J. Mao · J. Sun · C. Zhang (✉)
Center for Drug Discovery, School of Pharmacy,
China Pharmaceutical University, Nanjing 210009,
People's Republic of China
e-mail: zhangcancpu@yahoo.com.cn

M. Sun
Department of Pharmaceutics, School of Pharmacy,
China Pharmaceutical University, Nanjing 210009,
People's Republic of China

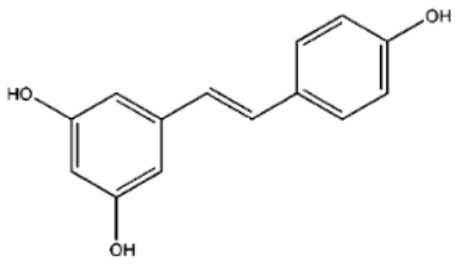


**Fig. 1** Structure of *trans*-resveratrol

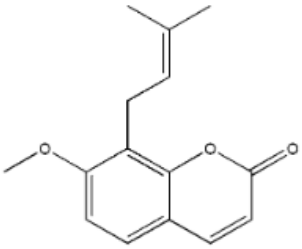


**Fig. 2** Osthole

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

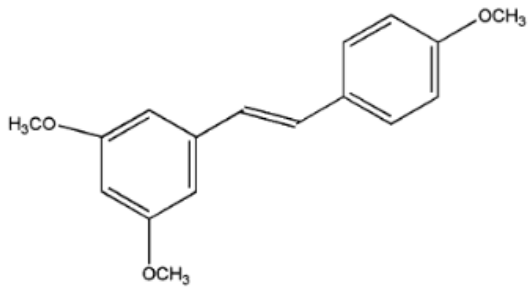


**Fig. 4** *Trans*-3,4′,5-trimethoxyresveratrol

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

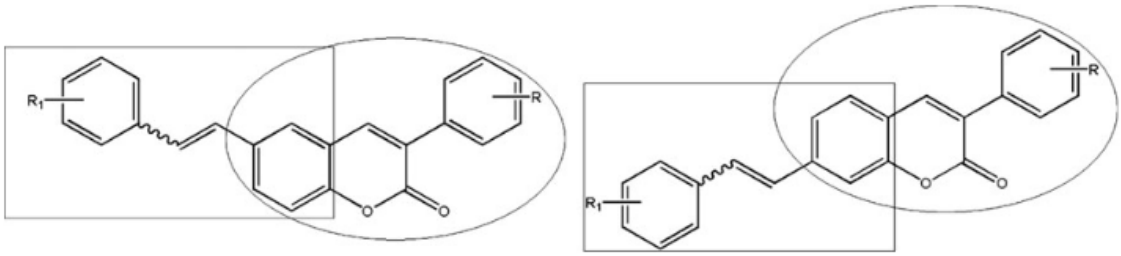


**Fig. 3** Target compounds