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ScienceDirect
*Chinese Journal of Natural Medicines* 2015, **13**(5): 0375–0382
**Chinese Journal of Natural Medicines**

# Synthesis and cytotoxic activities of *E*-resveratrol derivatives

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Available online 20 May 2015

**[ABSTRACT]** The present study was designed to synthesize derivatives of *E*-resveratrol and evaluate their cytotoxic activity *in vitro*. Different functional groups were conjugated with the phenolic hydroxyl group of *E*-resveratrol, and the double bond of *E*-resveratrol was reduced. The *in vitro* cytotoxicity of the synthetic derivatives was evaluated against three tumor cell lines (A549, LAC, and HeLa) using the MTT assay. Twenty-six *E*-resveratrol derivatives were synthesized and their structures were confirmed by $^1$H NMR, MS, IR, and elemental analyses. Compounds **1**−**6**, **12**, **15**−**21**, and **23**−**26** were reported for the first time. Among them, Compounds **1**, **2**, **4**, **5**, and **9**−**11**, showed significant cytotoxicity against tumor cells; especially, Compound **1** showed an $IC_{50}$ value of 4.38 μmol·L$^{-1}$ in the A549 cells which was 15-fold more active than *E*-resveratrol; Compound **9** showed an $IC_{50}$ value of 1.41 μmol·L$^{-1}$ in the HeLa cell line which was 90-fold more active than *E*-resveratrol, and close to adriamycin. The structure–activity relationships were also investigated. Compounds **1**, **2** and **9**−**11** may serve as potential lead compounds for the discovery of new anticancer drugs.

**[KEY WORDS]** *E*-resveratrol derivatives; Synthesis; Cytotoxic activity; Structure–activity relationships

**[CLC Number]** R284.3, R965 **[Document code]** A **[Article ID]** 2095-6975(2015)05-0375-08

## Introduction

The naturally occurring *E*-resveratrol and its various derivatives have attracted a great deal of attention due to their wide range of biological properties. *E*-resveratrol (3, 4', 5-trihydroxystilbene) is a stilbene-type polyphenolic natural product present in grapes and a variety of medicinal plants [1-7]. It is a naturally occurring phytoalexin which can be activated by adverse conditions of plants, protecting against fungal infections [8]. *E*-resveratrol possesses multiple biological activities that are beneficial to human health, including anticancer [9], anti-inflammatory [10], antibacterial antioxidant [11], anti-free radica [12], heart protecting [13], liver protecting [14], fatty acid synthase-inhibitory [15], nerve protecting [16], estrogenic [17], bone metabolism and endothelin antagonist [18], among others. Jang M *et al* reported the antitumor function of *E*-resveratrol in 1997 [19].

The usefulness of *E*-resveratrol, however, is limited by its instability upon exposure to light and oxygen. These stimuli may cause *trans-cis* transformation or oxidation that leads to a reduction in bioavailability and bioactivity. Recently, considerable attention has been focused on *E*-resveratrol derivatives. It has been reported that methylated *E*-resveratrol derivative $R_3$ is an effective neuroprotective agent against free radical-mediated oxidative stress triggered by 6-OHDA in SH-SY5Y cells [20]. Yang LM *et al* have synthesized a series of *E*-resveratrol derivatives with sulfur thalidomide substitutes that showed inhibitory activities against breast cancer and colon cancer [21]. It is reported that methylated *E*-resveratrol derivatives are more effective than *E*-resveratrol in the prevention and treatment of cancer [22]. Cardile V and others have synthesized methoxy derivatives of *E*-resveratrol and *E*-resveratrol esters, tested their cytotoxicity in human prostate cancer cells, and found that the activity of these derivatives was stronger than *E*-resveratrol [23-25]. It has been reported that polymethoxy-stilbene analogs, especially (*Z*)-3, 5, 4-trimethoxystilbene, exhibit strong anti-proliferative activity [26-27]. Stivala LA *et al* have reported a number of *E*-resveratrol derivatives which showed good anti-proliferative activity, suggesting that the 7-methoxycoumarin nucleus, together with the 3, 5-disubstitution pattern of the *trans*-

**[Received on]** 03-June-2014
**[Research funding]** This work was supported by the Cross-fund of Nanchang University.
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These authors have no conflict of interest to declare.

vinylbenzene moiety, are promising structural features to obtain excellent anticancer compounds endowed with a apoptosis-inducing capability [28].

Encouraged by the promising cytotoxic activity of the reported *E*-resveratrol derivatives, we designed and synthesized a series of *E*-resveratrol derivatives and evaluated their biological activities structure-activity relationships (SAR) in the present study. Our results indicated that some of the analogs can be developed as lead compounds as novel anticancer agents.

## Materials and Methods

### *Materials and instrumentation*

$^1$H NMR spectra were recorded with a Bruker Avance 600 FT-NMR spectrometer (Bruker Biospin Ltd., Bern, Switzerland) in the indicated solvents (TMS as internal standard). Mass spectra were obtained using Waters 2695-4000 spectrometer (Waters Ltd., Milford, Massachusetts, USA). IR spectra were obtained on a Nicolet 380 spectrometer (Thermo Nicole Ltd, Madison, Wisconsin, USA). All melting points are measured using an Electrothermal engineering 9200 apparatus (Electrothermal Engineering Ltd, Stone Staffordshire, UK). Elemental analyses were performed using a TQ-3A elemental analysis instrument (Elementar Ltd, Hanau, Germany).

All of the compounds synthesized were purified by column chromatography (CC) on silica gel 60 (200−300 mesh) and thin-layer chromatography (TLC) on silica gel 60 $F_{254}$ plates (250 μm; Qingdao Marine Chemical Company, Qingdao, China). Most chemicals and solvents were of analytical grade. *E*-resveratrol (98%) was purchased from Shanxi Sciphar Hi-tech Industry Co., Ltd. (Shanxi, China).

### *General procedures for the synthesis of compounds **1**−**25***

*E*-resveratrol (1.14 g, 5.00 mmol) was dissolved in acetone (100 mL), and $K_2CO_3$ (1.04 g, 7.54 mmol) was added. Then, $PhSO_2Cl$ (0.6 mL, 4.70 mmol) were slowly added and the reaction mixture was stirred at reflux temperature for 9 h. The resultant clear solution was filtered and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel; 9 : 1 chloroform/ethyl acetate elution) to give compound **1** (0.39 g, 22.5% yield) as white crystals: mp 152−153 ºC; IR (KBr) *v* 3 413, 3 059, 3 017, 1 600, 1 515, 1 449, 1 353, 1 298, 1 171, 1 090, 986, 959, 847, 808, 570 cm$^{-1}$; $^1$H NMR (600 MHz, $CDCl_3$) δ: 6.66 (1H, s, $C_5$-H), 6.73 (1H, s, $C_2$-H), 6.74 (1H, d, *J* = 16.4 Hz, CH=), 6.82 (1H, s, $C_6$-H) 6.83-6.84 (2H, d, *J* = 8.4 Hz, $C_3$′-H and $C_5$′-H), 6.88 (1H, d, *J* = 16.4 Hz, CH=), 7.35 (2H, d, *J* = 8.4 Hz, $C_2$′-H and $C_6$′-H), 7.54 (2H, dd, *J* = 7.6 Hz, Ar-H), 7.69 (1H, t, *J* = 7.6 Hz, Ar-H), 7.88 (2H, d, *J* = 7.6 Hz, Ar-H); ESI-MS *m/z* 369 $[M + H]^+$; Anal. $C_{20}H_{16}O_5S$, C 65.12, H 4.49 (Req C 65.20, H 4.38).

Following the general procedure, compound **2** was prepared from *E*-resveratrol as white crystals (33.1% yield): mp 94−95 ºC; IR (KBr) *v* 3 460, 1 615, 1 569, 1 501, 1 449, 1 370, 1 292, 1 192, 1 148, 1 091, 984, 972, 874, 750, 581 cm$^{-1}$; $^1$H NMR(600 MHz, $CDCl_3$) δ: 6.42 (1H, s, $C_5$-H), 6.66 (1H, s, $C_2$-H), 6.78 (1H, d, *J* = 16.4 Hz, CH=), 6.82 (1H, s, $C_6$-H), 6.84 (1H, d, *J* = 16.4 Hz, CH=), 6.94 (2H, d, *J* = 8.4 Hz, $C_3$′-H and $C_5$′-H), 7.32 (2H, d, *J* = 8.4 Hz, $C_2$′-H and $C_6$′-H), 7.54 (4H, t, *J* = 12.0 Hz, Ar-H), 7.66-7.69 (2H, m, Ar-H), 7.83−7.88 (4H, m, Ar-H); ESI-MS *m/z* 531 $[M + Na]^+$; Anal. $C_{26}H_{20}O_7S_2$, C 61.58; H 3.89 (Req C 61.40, H 3.96).

Following the general procedure, compound **3** was prepared from *E*-resveratrol as white crystals (96.3% yield) as a white crystal: mp 144−145 ºC; IR (KBr) *v* 3 079, 3 029, 1 611, 1 578, 1 500, 1 449, 1 383, 1 350, 1 304, 1 191, 1 089, 968, 866, 843, 771, 682, 633, 563 cm$^{-1}$; $^1$H NMR (600 MHz, $CDCl_3$) δ: 6.49 (1H, s, $C_4$-H), 6.79 (1H, d, *J* = 16.2 Hz, CH=), 6.84 (1H, d, *J* = 16.2 Hz, CH=), 6.98 (2H, d, *J* = 9.0 Hz, $C_3$′-H and $C_5$′-H), 7.04 (2H, s, $C_2$-H and $C_6$-H), 7.35 (2H, d, *J* = 9.0 Hz, $C_2$′-H and $C_6$′-H), 7.53−7.57 (6H, m, Ar-H), 7.69−7.71 (3H, m, Ar-H), 7.80 (4H, t, *J* = 8.4 Hz, Ar-H), 7.82 (2H, d, *J* = 8.4 Hz, Ar-H); ESI-MS *m/z* 687 $[M + K]^+$; Anal. $C_{32}H_{24}O_9S_3$, C 59.06, H 3.69 (Req C 59, H 3.73).

Following the general procedure, compound **4** was prepared from *E*-resveratrol as white crystals (30.9% yield): mp 152−154 ºC; IR (KBr) *v* 3 395, 3 249, 2 959, 2 929, 2 872, 1 605, 1 511, 1 459, 1 350, 1 306, 1 258, 1 168, 1 148, 1 038, 962, 831, 682 cm$^{-1}$; $^1$H NMR(600 MHz, $CDCl_3$) δ: 2.26 (2H, m, $CH_2$), 3.75 (2H, d, *J* = 6.3 Hz, $CH_2Cl$), 4.14 (2H, d, *J* = 6.3 Hz, $OCH_2$), 6.25 (1H, s, $C_4$-H), 6.55 (2H, s, $C_2$-H and $C_6$-H), 6.83 (1H, d, *J* = 16.2 Hz, CH=), 6.89 (2H, d, *J* = 8.4 Hz, $C_3$′-H and $C_5$′-H), 6.99 (1H, d, *J* = 16.2Hz, CH=), 7.42 (2H, d, *J* = 8.4 Hz, $C_2$′-H and $C_6$′-H); ESI-MS *m/z* 305 $[M + H]^+$; Anal. $C_{17}H_{17}ClO_3$, C 68.84, H 5.81 (Req C 67.00, H 5.62).

Following the general procedure, compound **5** was prepared from *E*-resveratrol as white crystals (47.9% yield): mp 94−95 ºC; IR (KBr) *v* 3 339, 3 015, 2 964, 2 934, 2 860, 1 600, 1 511, 1 441, 1 341, 1 251, 1 230, 1 164, 1 064, 957, 832, 676, 656 cm$^{-1}$; $^1$H NMR(600 MHz, $CDCl_3$) δ: 2.23−2.26 (4H, m, 2 × $CH_2$), 3.74−3.77 (4H, m, 2 × $CH_2Cl$), 4.12−4.15 (4H, m, 2 × $OCH_2$), 6.31 (1H, s, $C_4$-H), 6.57 (1H, s, $C_2$-H), 6.63 (1H, s, $C_6$-H), 6.86 (1H, d, *J* = 16.2 Hz, CH=), 6.89 (2H, d, *J* = 8.4 Hz, $C_3$′-H and $C_5$′-H), 7.01 (1H, d, *J* = 16.2 Hz, CH=), 7.42−7.43 (2H, d, *J* = 8.4 Hz, $C_2$′-H and $C_6$′-H); ESI-MS *m/z* 381 $[M + H]^+$; Anal. $C_{20}H_{22}C_{l2}O_3$, C 63.13, H 5.77 (Req C 63.00, H 5.82).

Following the general procedure, compound **6** was prepared from *E*-resveratrol as white crystals (53.1% yield): mp 88−89 ºC; IR (KBr) *v* 2 955, 2 930, 2 876, 1 587, 1 512, 1 439, 1 257, 1 165, 1 062, 955, 833, 677 cm$^{-1}$; $^1$H NMR(600 MHz, $CDCl_3$) δ: 2.23−2.27 (6H, m, 3 × $CH_2$), 3.76 (6H, t, *J* = 8.0 Hz, 3 × $CH_2Cl$), 4.14 (6H, t, *J* = 8.0 Hz, 3 × $OCH_2$), 6.38 (1H, s, $C_4$-H), 6.66 (2H, s, $C_2$-H and $C_6$-H), 6.88 (1H, d, *J* = 16.2 Hz, CH=), 6.90 (2H, d, *J* = 8.0 Hz, $C_3$′-H and $C_5$′-H), 7.03 (1H, d, *J* = 16.2 Hz, CH=), 7.43 (2H, d, *J* = 8.0 Hz, $C_2$′-H and $C_6$′-H); ESI-MS *m/z* 457 $[M + H]^+$; Anal. $C_{23}H_{27}Cl_3O_3$, C 60.51, H 6.01 (Req C 60.34, H 5.94).