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Short communication

Synthesis and cytotoxic evaluation of a series of resveratrol derivatives modified in C2 position

Xian-Feng Huang, Ban-Feng Ruan, Xiao-Ting Wang, Chen Xu, Hui-Ming Ge, Hai-Liang Zhu*, Ren-Xiang Tan*

Institute of Functional Biomolecules, State Key Laboratory of Pharmaceutical Biotechnology, Nanjing University, Nanjing 210093, People's Republic of China

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Abstract

Eleven C2-substituted derivatives of resveratrol (*trans*-3,4′,5-trihydroxystilbene, RES) were prepared by partial synthesis from RES and evaluated for their cytotoxic activities against a human nasopharyngeal epidermoid tumor cell line KB. Among them, compounds **2** and **3** were more active than 5-fluorouracil (5-FU), an anticancer drug, and compound **5f** exhibited similar activity to 5-FU. On the basis of the biological results, structure–activity relationships were discussed.

Keywords: Resveratrol derivatives; Nasopharyngeal; Antitumor activities; Structure–activity relationships

1. Introduction

Resveratrol (*trans*-3,4′,5-trihydroxystilbene, RES, **1**), a phytoalexin with a stilbene structure is present in medicinal plants, grape skin, peanuts, and red wine [1]. Stilbene-based compounds are widely represented in nature and have become of particular interest to chemists and biologists because of their wide range of biological activities [2–5]. RES has been discovered as a potential cancer chemopreventive agent based on its striking inhibitory effects on cellular events associated with cancer initiation, promotion, and progression [6]. In addition to the anticancer-promoting activity, RES has displayed in vitro growth inhibition in a number of human cancer cell lines [7]. The simplicity of resveratrol, associated with its interesting anticancer activity, offers promises for the rational design of new chemotherapeutic agents. However, due to its photosensitivity and metabolic instability [8–10], RES itself cannot be used as an antitumor drug. Therefore, modifications of RES, keeping its stilbene backbone, are necessary.

Recently, many RES derivatives by total synthesis have been reported, as well as the activities including ceramide-mediated proapoptotic, antineoplastic, apoptosis-inducing, antifungal, antihyperglycemic and lipid modulating [11–14]. These totally synthesized RES analogues mainly focused on changing the replaced groups and its positions on two aromatic rings of RES. However, there are few reports about partially synthesized derivatives starting from RES [15]. In this paper, 11 new compounds were prepared by convenient synthesis methods (Scheme 1) and first reported. Their cytotoxic activities against a human nasopharyngeal epidermoid tumor cell line KB were also evaluated.

2. Chemistry

Though many totally synthesized RES analogues in the last five years were reported, there are few derivatives that are partially synthesized [15]. Compound **2** was isolated from plants [16], but was not easily available in the market. In our laboratory, at the beginning compound **2** was synthesized by the

* Corresponding authors. Tel.: +86 25 8359 2085; fax: +86 25 8330 2728.
E-mail addresses: zhuhl@nju.edu.cn (H.-L. Zhu), rxtan@nju.edu.cn (R.-X. Tan).

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direct treatment of RES with $(CH_3)_2SO_4$ in 10% NaOH solution under nitrogen atmosphere in order to prevent the oxidation of compound **1**. Better yield (88%) of methylation of RES was obtained by using CH_3I instead of $(CH_3)_2SO_4$. Because $(CH_3)_2SO_4$ is a much cheaper methylated agent than CH_3I, the former was preferred. Vilsmeier formylation of compound **2** by treatment with slight excess of $POCl_3$ in DMF at 0 °C yielded aldehyde **3**. The Vilsmeier reaction conditions were investigated and two procedures were used: compound **2** was dissolved in *N*,*N*-dimethylformamide (DMF) or *N*-methylformanilide (MFA) and $POCl_3$ was added slowly to the solution. The reaction mixtures were monitored by TLC. After compound **2** disappeared, the mixtures were added to ice–water, followed by extraction with $CHCl_3$. When the solvent was changed from DMF to MFA the product mixture was more complex and the yield was lower. A side chain containing nitrogen atoms is a common structural feature of many classes of drugs. So in the next step, condensation reaction of compound **3** with a series of amines containing various functional groups (tyramine, morpholine, furfurylamine, etc.), which are cheap and available easily in the market afforded the Schiff bases (Fig. 1). Reduction of the latter with $NaBH_4$ afforded the corresponding saturated alkyl amines (Fig. 2). Although the marked deepening of the color indicated a progressive formation of the chromophore C=N– as the reaction mixtures were heated, only two Schiff bases, compounds **4a** and **4b**, were isolated (Fig. 1). In most instances, no crystal products of Schiff bases could be obtained.

3. Pharmacological evaluation and discussion

The cytotoxic activities of the compounds against a human nasopharyngeal epidermoid tumor cell line KB are summarized in Table 1. The results indicate that methylation of three hydroxyl groups of compound **1** can remarkably improve the antitumor activity. This modification is likely to make the compounds more lipophilic, which may increase the permeability of the cell membrane. As a result, all of the derivatives showed higher potency against KB than RES. When the C2 H of the phenyl ring of compound **2** was replaced by a –CHO group, the activity was not influenced in a significant way (IC_{50} of compounds **2** and **3** = 10.3 and 9.2 μM, respectively), then the –CHO of compound **3** was reduced and this modification considerably decreased the cytotoxic activity, implying

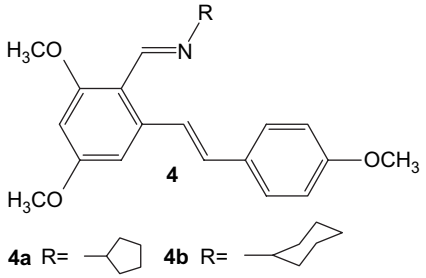


Fig. 1. Structures of compounds **4a** and **4b**.

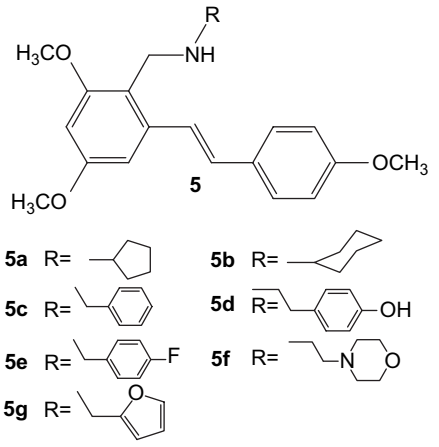


Fig. 2. Structures of compounds **5a**–**5g**.

electron-withdrawing effect of –CHO in compound **3** is essential for its cytotoxicity. In another modification, the –CHO on site C2 was replaced with a series of groups containing nitrogen atoms (**4a** and **4b**, **5a**–**5g**). Among the compounds, compounds containing alkyl ring amino side chains (**4a**, **4b**, **5a**, **5b**, and **5f**) showed better activities against KB than those containing aromatic ring amino side chains (**5c**, **5d**, **5e**, and **5g**). This result may be explained because the former had better lipophilicity than the latter. Two Schiff bases (**4a** and **5a**) exhibited similar activity with their reduced products (**4b** and **5b**). When the alkyl ring was morpholine the compound (**5f**, IC_{50} = 13.1 μM) showed the highest cytotoxic activity, which was even comparable with 5-fluorouracil (IC_{50} = 13.4 μM). However, it remains to be further investigated as to how the change of side chains influences the cytotoxic activity. In conclusion, among all the synthesized RES analogues, compounds **2** and **3** were more active than 5-fluorouracil (5-FU) and compound **5f** exhibited similar activity to 5-FU. In addition, the lipophilicity was found to play a very important role in the cytotoxic potency and compounds **2** and **3** had a common feature of polar structure. These results provided us a better understanding of the preliminary structure–activity relationships of resveratrol as a potential antitumor agent, the design and the synthesis of RES derivatives with superior activities.

Table 1
Cytotoxic activities of compounds **1**–**6** against a human nasopharyngeal epidermoid tumor cell line KB

Compound	IC_{50} (μM)	Compound	IC_{50} (μM)
1	82.8 ± 1.55	**5c**	28.8 ± 2.6
2	10.3 ± 0.59	**5d**	29.8 ± 1.4
3	9.2 ± 0.37	**5e**	31.7 ± 0.74
4a	17.2 ± 0.7	**5f**	13.1 ± 0.67
4b	18.9 ± 1.2	**5g**	30.3 ± 1.5
5a	15.1 ± 0.46	**6**	43.3 ± 0.6
5b	17.2 ± 0.54	5-FU	13.4 ± 0.2

IC_{50} = 50% inhibitory concentration represents the mean ± S.D. from dose–response curves of at least three experiments.

4. Conclusions

In summary, a –CHO was first introduced into the phenyl ring of RES and 11 new compounds were prepared and first reported. Their cytotoxic activities against a human nasopharyngeal epidermoid tumor cell line KB were evaluated. Compounds **2** and **3** showed more potent inhibitory activities than 5-fluorouracil and compound **5f** also exhibited similar activity to it. At present we are exploring de-methylation of these RES derivatives selectively and economically, and expected that these modifications may result in more potent anticancer agents.

5. Experimental protocols

5.1. Chemistry

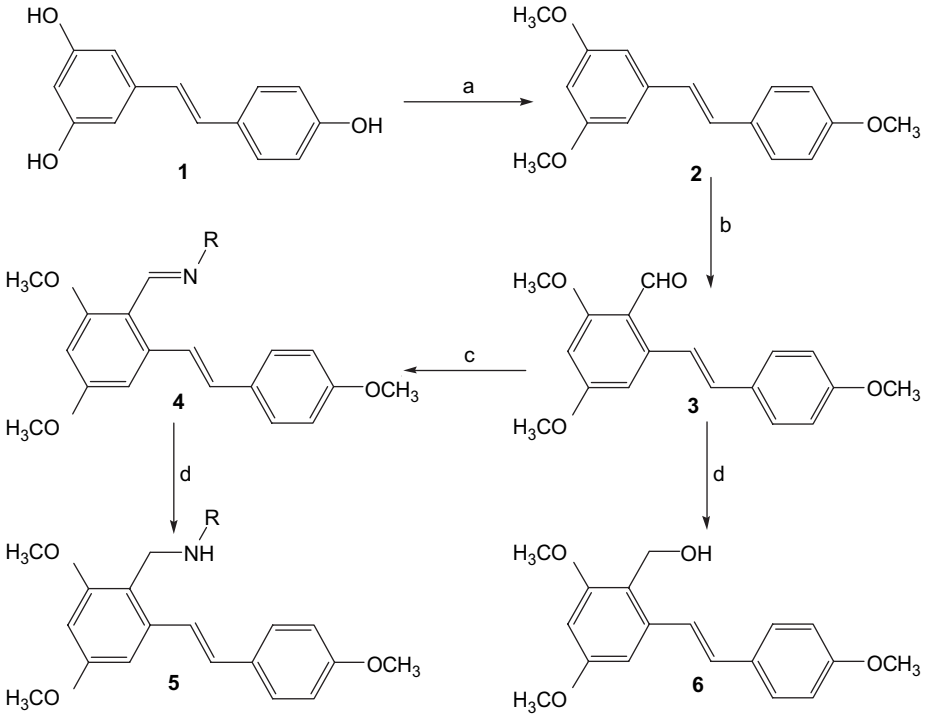
RES was bought from Xi'an Mingzhu Company, Xi'an China. ^{1}H NMR and ^{13}C NMR spectra were recorded at 300 and 500 MHz on Bruker spectrometers in DMSO-d_6. MS spectra were recorded with a mariner system 5304 mass spectrometer. Melting points were obtained by using a Boetius micro melting point apparatus. Elemental analyses were performed on a CHN–O-Rapid instrument. Flash-column chromatographies were performed on silica gel Merck Kieselgel 60 (230–400 mesh). Thin-layer chromatographies were performed on silica gel plates (GF_{254}, Merk); spots were detected visually by ultraviolet irradiation (254 nm).

5.2. Experimental procedure for the synthesis of trans-3,4′,5-trimethoxystilbene (2)

Dimethyl sulfate (4.9 ml) was dropped into a solution of 456 mg (2 mmol) of compound **1** in 5 ml of aq NaOH (10%) under an atmosphere of nitrogen while cooling with an ice–water bath, keeping the dropping velocity at which the temperature of the reaction solution was under 40 °C. The mixture was stirred for 2 h, and extracted with 10 ml of EtOAc twice. The organic layer was washed with water, dried over Na_2SO_4, and evaporated under vacuum. Purification by silica gel afforded compound **2** (colorless crystalline, 410 mg, 1.52 mmol, yield 76%). Mp: 54–56 °C, ESI MS: 271.3 $[M+H]^+$, ^{1}H NMR (DMSO-d_6): 3.77 (s, 9H), 6.39 (s, 1H), 6.74 (s, 2H), 6.94 (d, 2H, $J = 8.4$ Hz), 7.02 (d, 1H, $J = 16.4$ Hz), 7.21 (d, 1H, $J = 16.4$ Hz), 7.53 (d, 2H, $J = 8.4$ Hz) (Scheme 1).

5.3. Experimental procedure for the synthesis of trans-2-formyl-3,4′,5-trimethoxystilbene (3)

To a solution of 270 mg (1 mmol) of compound **2** in 5 ml of DMF was added dropwise 200 μl (0.21 g, 1.0 mmol) of $POCl_3$ while cooling with an ice–water bath. The reaction mixture was stirred for 30 min at room temperature. The solution was added to a mixture of ice and water, and the yellow solution was extracted with three 10 ml portions of dichloromethane. The combined organic layers were washed with water, dried over anhydrous sodium sulfate, filtered,



Scheme 1. Synthesis of the resveratrol analogs. Reagents and conditions: (a) $(CH_3)_2SO_4$, 10% NaOH, 0–40 °C, 76%; (b) $POCl_3$, DMF, 0 °C, 69%; (c) RNH_2, ethanol, reflux, 94–95%; (d) $NaBH_4$, ethanol, 40 °C, 74–95%.

evaporated, and recrystallized from dichloromethane, and afforded **3** (yellow solid, 206 mg, 0.69 mmol, yield 69%). Mp: 108–109 °C, ESI MS: 299.3 $[M+H]^+$, ^{1}H NMR (DMSO-d_6): 3.78 (s, 3H), 3.90 (s, 3H), 3.92 (s, 3H), 6.63 (s, 1H), 6.91 (s, 1H), 6.97 (d, 2H, $J=7.9$ Hz), 7.21 (d, 1H, $J=16.2$ Hz), 7.50 (d, 2H, $J=7.9$ Hz), 7.95 (d, 1H, $J=16.2$ Hz), 10.41 (s, 1H). Anal. Calc for $C_{18}H_{18}O_4$: C, 72.74; H, 6.08%. Found: C, 72.56; H, 6.11%.

5.4. General experimental procedure for the synthesis of ***4a*** and ***4b***

Compound **2** (1 mmol) was dissolved in 5 ml of ethanol/dichloromethane (1:1), amine was added to the solution. The reaction mixture was refluxed for 30 min, and cooled to room temperature, and afforded the crystal products.

5.4.1. Synthesis of 2-(N-cyclopentyliminomethyl)-3,4′, 5-trimethoxystilbene (***4a***)

Colorless crystals, yield 94%, mp: 108–109 °C, ESI MS: 366.3 $[M+H]^+$, ^{1}H NMR (DMSO-d_6): 1.63 (m, 4H), 1.85 (m, 2H), 1.88 (m, 2H), 3.31 (m, 1H), 3.77 (s, 3H), 3.82 (s, 3H), 3.86 (s, 3H), 6.53 (d, 1H, $J=1.6$ Hz), 6.91 (d, 1H, $J=1.6$ Hz), 6.94 (d, 2H, $J=8.5$ Hz), 7.10 (d, 1H, $J=16.4$ Hz), 7.43 (d, 2H, $J=8.5$ Hz), 8.08 (d, 1H, $J=16.4$ Hz), 8.61 (s, 1H). Anal. Calc for $C_{23}H_{27}NO_3$: C, 75.59; H, 7.45; N, 3.83%. Found: C, 75.36; H, 7.39; N, 3.86%.

5.4.2. Synthesis of 2-(N-cyclohexyliminomethyl)-3,4′, 5-trimethoxystilbene (***4b***)

Colorless crystals, yield 95%, mp: 145–146 °C, ESI MS: 380.3 $[M+H]^+$, ^{1}H NMR (DMSO-d_6): 1.22–1.60 (m, 6H), 1.63–1.79 (m, 4H), 3.17 (m, 1H), 3.77 (s, 3H), 3.82 (s, 3H), 3.86 (s, 3H), 6.53 (d, 1H, $J=1.9$ Hz), 6.92 (d, 1H, $J=1.9$ Hz), 6.95 (d, 2H, $J=8.6$ Hz), 7.10 (d, 1H, $J=16.4$ Hz), 7.43 (d, 2H, $J=8.6$ Hz), 8.07 (d, 1H, $J=16.4$ Hz), 8.64 (s, 1H). Anal. Calc for $C_{24}H_{29}NO_3$: C, 75.96; H, 7.70; N, 3.69%. Found: C, 76.17; H, 7.61; N, 3.63%.

5.5. General experimental procedure for the synthesis of ***5a–5g***

Compound **2** (1 mmol) was dissolved in 5 ml of ethanol/dichloromethane (1:1), amine was added to the solution. The reaction mixture was refluxed for 30 min, and cooled to room temperature. $NaBH_4$ of 0.5 mmol was added to the reaction solution slowly, and stirred at room temperature for 2 h. The mixture was evaporated under vacuum, and dissolved in dichloromethane (5 ml). The solution was washed with saturated NaCl solution and water, respectively, dried over anhydrous sodium sulfate, and evaporated. Purification by silica gel afforded pure products.

5.5.1. Synthesis of 2-(N-cyclopentylaminomethyl)-3,4′, 5-trimethoxystilbene (***5a***)

White powder, yield 82%, mp: 46–48 °C, ESI MS: 368.2 $[M+H]^+$, ^{1}H NMR (DMSO-d_6): 1.38 (m, 2H), 1.45 (m, 2H), 1.61 (m, 2H), 1.71 (m, 2H), 1.38 (m, 2H), 3.06 (m, 1H), 3.73 (s, 6H), 3.77 (s, 2H), 3.80 (s, 3H), 3.92 (s, 3H), 6.47 (s, 1H), 6.81 (s, 1H), 6.95 (d, 2H, $J=8.3$ Hz), 7.11 (d, 1H, $J=16.2$ Hz), 7.37 (d, 1H, $J=16.2$ Hz), 7.52 (d, 2H, $J=8.3$ Hz). Anal. Calc for $C_{23}H_{29}NO_3$: C, 75.17; H, 7.95; N, 3.81%. Found: C, 75.12; H, 8.08; N, 3.76%.

5.5.2. Synthesis of 2-(N-cyclohexylaminomethyl)-3,4′, 5-trimethoxystilbene (***5b***)

White powder, yield 86%, mp: 58–60 °C, ESI MS: 382.2 $[M+H]^+$, ^{1}H NMR (DMSO-d_6): 1.05–1.22 (m, 6H), 1.63 (m, 2H), 1.84 (m, 2H), 2.42 (m, 2H), 3.77 (m, 8H), 3.80 (s, 3H), 6.47 (d, 1H, $J=1.9$ Hz), 6.80 (d, 1H, $J=1.9$ Hz), 6.95 (d, 2H, $J=8.5$ Hz), 7.11 (d, 1H, $J=16.3$ Hz), 7.37 (d, 1H, $J=16.3$ Hz), 7.51 (d, 2H, $J=8.5$ Hz). Anal. Calc for $C_{24}H_{31}NO_3$: C, 75.56; H, 8.19; N, 3.67%. Found: C, 75.61; H, 8.16; N, 3.72%.

5.5.3. Synthesis of 2-(N-benzylaminomethyl)-3,4′, 5-trimethoxystilbene (***5c***)

White powder, yield 78%, mp: 71–73 °C, ESI MS: 390.2 $[M+H]^+$, ^{1}H NMR (DMSO-d_6): 3.77 (s, 3H), 3.80 (s, 3H), 3.84 (s, 3H), 4.11 (m, 2H), 4.23 (m, 2H), 6.55 (d, 1H, $J=2.0$ Hz), 6.89 (d, 1H, $J=2.0$ Hz), 6.98 (d, 2H, $J=8.7$ Hz), 7.18 (d, 2H, $J=8.7$ Hz), 7.45–7.48 (m, 3H), 7.52–7.58 (m, 4H). Anal. Calc for $C_{25}H_{27}NO_3$: C, 77.09; H, 6.99; N, 3.60%. Found: C, 77.21; H, 7.06; N, 3.62%.

5.5.4. Synthesis of 2-(N-(2-(4-hydroxyphenyl)ethyl) aminomethyl)-3,4′,5-trimethoxystilbene (***5d***)

White powder, yield 74%, mp: 164–165 °C, ESI MS: 420.2 $[M+H]^+$, ^{1}H NMR (DMSO-d_6): 2.59 (t, 2H, $J=7.0$ Hz), 2.71 (t, 2H, $J=7.0$ Hz), 3.73 (s, 3H), 3.75 (s, 2H), 3.78 (s, 3H), 3.80 (s, 3H), 3.80 (s, 3H), 6.45 (d, 1H, $J=2.0$ Hz), 6.61 (d, 2H, $J=8.6$ Hz), 6.82 (d, 2H, $J=2.0$ Hz), 6.94 (m, 2H), 6.96 (m, 2H), 7.10 (d, 1H, $J=16.2$ Hz), 7.32 (d, 1H, $J=16.2$ Hz), 7.49 (d, 2H, $J=8.6$ Hz), 9.15 (s, 1H). Anal. Calc for $C_{26}H_{29}NO_4$: C, 74.44; H, 6.97; N, 3.34%. Found: C, 74.32; H, 7.07, N, 3.28%.

5.5.5. Synthesis of 2-(N-(4-fluorobenzyl) aminomethyl)-3,4′,5-trimethoxystilbene (***5e***)

White powder, yield 88%, mp: 77–79 °C, ESI MS: 408.2 $[M+H]^+$, ^{1}H NMR (DMSO-d_6): 3.66 (s, 3H), 3.69 (s, 3H), 3.84 (m, 5H), 4.13 (s, 2H), 6.31 (d, 1H, $J=2.1$ Hz), 6.55–6.57 (m, 3H), 6.76 (d, 2H, $J=8.7$ Hz), 6.96 (d, 2H, $J=8.7$ Hz), 7.28–7.32 (m, 2H), 7.53–7.57 (m, 2H). Anal. Calc for $C_{25}H_{26}FNO_3$: C, 73.69; H, 6.43; N, 3.44%. Found: C, 73.56; H, 6.63; N, 3.49%.

5.5.6. Synthesis of 2-(N-(2-(morpholin-4-yl)ethyl) aminomethyl)-3,4′,5-trimethoxystilbene (***5f***)

White powder, yield 87%, mp: 86–88 °C, ESI MS: 413.5 $[M+H]^+$, ^{1}H NMR (DMSO-d_6): 2.23 (m, 4H), 2.35 (t, 2H, $J=5.9$ Hz), 2.62 (t, 2H, $J=5.9$ Hz), 3.40 (m, 4H), 3.77 (s, 6H), 3.79 (s, 2H), 3.81 (s, 3H), 3.80 (s, 3H), 6.48 (d, 1H, $J=2.1$ Hz), 6.82 (d, 1H, $J=2.1$ Hz), 6.95 (d, 2H,

$J = 8.7$ Hz), 7.13 (d, 1H, $J = 16.2$ Hz), 7.32 (d, 1H, $J = 16.2$ Hz), 7.55 (d, 2H, $J = 8.7$ Hz). Anal. Calc for $C_{24}H_{32}N_2O_4$: C, 69.88; H, 7.82; N, 6.79%. Found: C, 69.67; H, 7.73; N, 6.77%.

*5.5.7. Synthesis of 2-(N-(furan-2-yl) methylaminomethyl)-3,4′,5-trimethoxystilbene (**5g**)*

White powder, yield 84%, mp: 70–72 °C, ESI MS: 380.4 $[M + H]^+$, ^{1}H NMR (DMSO-d_6): 3.70 (s, 2H), 3.72 (s, 2H), 3.77 (s, 3H), 3.78 (s, 3H), 3.81 (s, 3H), 3.80 (s, 3H), 6.28 (d, 1H, $J = 2.9$ Hz), 6.52 (m, 1H), 6.48 (d, 1H, $J = 2.0$ Hz), 6.82 (d, 1H, $J = 2.0$ Hz), 6.96 (d, 2H, $J = 8.6$ Hz), 7.09 (d, 1H, $J = 16.3$ Hz), 7.25 (d, 1H, $J = 16.3$ Hz), 7.46 (d, 2H, $J = 8.6$ Hz), 7.58 (m, 1H). Anal. Calc for $C_{23}H_{25}NO_4$: C, 72.80; H, 6.64; N, 3.69%. Found: C, 72.75; H, 6.81; N, 3.73%.

*5.6. Experimental procedure for the synthesis of 2-(hydroxymethyl)-3,4′,5-trimethoxystilbene (**6**)*

$NaBH_4$ (0.5 mmol) was added to a solution of 1.0 mmol of compound **2** in 5 ml of ethanol, and stirred at room temperature for 2 h. The mixture was evaporated under vacuum, and dissolved in dichloromethane (5 ml). The solution was washed with saturated NaCl solution and water, respectively, dried over anhydrous sodium sulfate, and evaporated. Purification by silica gel afforded pure products of compound **6**. White powder, yield 93%, mp: 96–97 °C, ESI MS: 323.1 $[M + Na]^+$, ^{1}H NMR (DMSO-d_6): 3.77 (s, 3H), 3.78 (s, 3H), 3.81 (s, 3H), 4.56 (s, 2H), 6.46 (d, 1H, $J = 2.1$ Hz), 6.84 (d, 1H, $J = 2.1$ Hz), 6.96 (d, 2H, $J = 8.8$ Hz), 7.13 (d, 1H, $J = 16.3$ Hz), 7.45 (d, 1H, $J = 16.3$ Hz), 7.53 (d, 2H, $J = 8.4$ Hz). Anal. Calc for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71%. Found: C, 71.83; H, 6.68%.

5.7. Cytotoxicity study using KB cells

The cytotoxicity was evaluated as described elsewhere [17] with some modifications. Briefly, target tumor cells were grown to log phase in RPMI 1640 medium supplemented with 10% fetal bovine serum. After diluting to 2×10^4 cells ml^{-1} with the complete medium, 100 μl of the obtained cell suspension was added to each well of 96-well culture plates. The subsequent incubation was permitted at 37 °C, 5% CO_2 atmosphere for 24 h before the cytotoxicity assessments. Tested samples at pre-set concentrations were added to 6 wells with 5-fluorouracil co-assayed as a positive reference. After 48 h exposure period, 40 μl of PBS containing 2.5 mg ml^{-1} of MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) was added to each well. And 4 h later 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} value was defined as the concentration at which 50% survival of cells was allowed.

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