Chapter 146
Design and Synthesis of Resveratrol Analogs

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Abstract Resveratrol (3,5,4′-trihydroxy-trans-stilbene), a naturally occurring hydroxystilbene, is considered as an essential anti-oxidative and possessing chemopreventive properties, and is found in various medical plants. It has been proven that resveratrol is a Sirt1 activator and kinds of biological activities. In this paper, we designed and synthesized a series of resveratrol derivatives through a five-step synthetic procedure. Total 11 resveratrol derivatives were prepared from two kinds of hydroxybenzoic acid by methylation and reduction followed by bromination and reaction with triethyl phosphate to get methoxylated diethyl benzylphosphonates, then condensation with a series of aromatic aldehydes by Wittig-Horner reaction to offer the desired compounds in overall yield of about 17.2–48.5 %. These synthesized compounds were characterized on the basis of 1H NMR.

Keywords Resveratrol analogs · Synthesis · Sirt1 activator · Wittig-Horner reaction

146.1 Introduction

Resveratrol (3,5,4′-trihydroxystilbene) was identified as one ingredient of red wine, which could cause the so-called "French paradox" [1]. This compound, which is a naturally occurring phytoalexin produced by a wide range of plants in response to environmental stress or pathogenic attack, was first isolated from the roots of the white hellebore lily Veratrum grandiflorum by O. Loes in 1940 [2]. Since the discovery of its cardioprotective activity in 1992, resveratrol research has steadily accelerated.

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In past years, there have been a large of reports about resveratrol that exerts a variety of biological activities. Among the most significant activities of resveratrol are its cancer chemo-preventive properties [3, 4], antioxidant [5], antibacterial, and anti-inflammatory activities [6–8]. Some of these have been reported to inhibit LDL oxidation in human [9], in addition to its blocking of platelet aggregation [10] and vasorelaxing activities [11]. In yeast assays, resveratrol was also found to significantly mimic calorie restriction by stimulating Sirt2 which is the most homologic homolog of Sirt1 of mammalian and extended lifespan by 70 % [12].

In recent years, a large number of papers have been published on resveratrol, which report a wide range of novel discoveries, such as new extraction methods, new applications [13–15], and resveratrol analogs [16–18]. This intrigued us to prepare its analogs and their derivatives. In order to increase its stability and water-solubility, we designed and synthesized some methoxylated analogs of resveratrol. The methoxylation of hydroxyl groups results in an increase in lipophilicity and a loss of hydrogen bond donor property. These changes will influence bioavailability, susceptibility to metabolism, and possibly the pharmacological profile of the resulting analog.

146.2 Experimental

146.2.1 Materials and Measurements

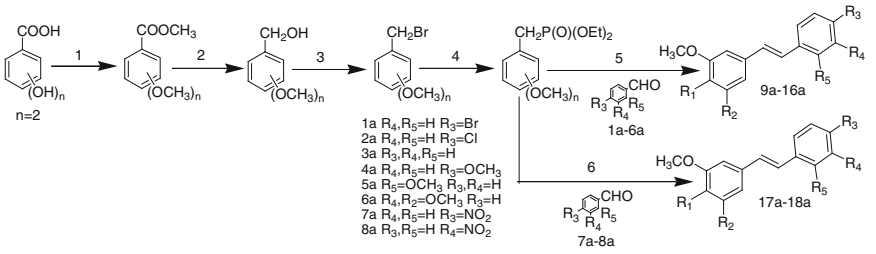
^{1}H NMR spectra was obtained at Bruker AM-400 NMR spectrometer using $CDCl_3$ as the solvent except where otherwise specified, the chemical shifts are reported in δ values (ppm) relative to Me_4Si line as internal standard and J values are reported in Hertz. Unless otherwise stated, reagents and solvents were of reagent grade and used as obtained from commercial sources without further purification. Dichloromethane was distilled from CaH_2, THF from sodium prior to use and DMF were dried over anhydrous sodium sulfate. Reaction temperatures were controlled by oil bath with temperature modulator and dewars. Thin layer chromatography (TLC) was performed using E. Merck silica gel 60 GF_{254} precoated plates (0.25 mm). Silica gel (particle size 200–400 mesh) was used for flash chromatography.

146.2.2 General Procedures

The route to prepare the resveratrol analogs was presented in Scheme 146.1.

146.2.2.1 General Procedure 1 (Gp 1) for the Preparation of Aromatic Esters from Hydroxybenzoic Acid

In a round-bottomed flask, to a well-stirred suspension of a mixture of hydroxybenzoic acid (1 eq.), freshly powered anhydrous K_2CO_3 (5 eq.), and



Scheme 146.1 Synthetic pathway for stilbenes 9a–18a. Reagents and conditions: *1* $(CH_3O)_2CO$, Bu_4NBr, DMF, K_2CO_3, reflx; *2* $LiAlH_4$, THF, 0 °C; *3* PBr_3, CH_2Cl_2, rt; *4* $P(O)(OEt)_3$, reflux; *5* NaH, ArCHO, THF, 0 °C; *6* CH_3ONa, ArCHO, DMF, 100 °C

tetrabutylammonium bromide (0.5 eq.) in DMF (10 ml) was added dimethyl carbonate (50 ml, 30 eq.) at room temperature. After the mixture was stirred at 140 °C for 38 h, the dimethyl carbonate was removed under reduced pressure and water (80 ml) was added to the residue. The resulted mixture was extracted with ethyl acetate and the organic layer was washed with water and brine, dried over anhydrous sodium sulfate. The solvent was concentrated in vacuo to yield the pure product as a white solid in moderate yield aromatic esters.

146.2.2.2 General Procedure 2 (Gp 2) for the Preparation of Aromatic Alcohol from Aromatic Esters

$LiAlH_4$ (0.5 eq.) was added slowly to a solution of aromatic esters (1 eq.) in THF (50 mL) at 0 °C for 1 h. The reaction mixture was stirred for 10 h at room temperature. Ice water (10 mL) was added slowly to the reaction mixture and stirred for 10 min, followed by concentrated 2 M HCl to neutralize the base. The reaction mixture was extracted with ethyl acetate, and the ethyl acetate layer was washed with water and brine, dried over anhydrous sodium sulfate. The solvent was removed in vacuo to yield the pure product in good yield aromatic alcohol.

146.2.2.3 General Procedure 3 (Gp 3) for the Preparation of Benzyl Bromine from Aromatic Alcohol

A solution of tribromophosphine (3 eq.) in CH_2Cl_2 (15 mL) was added dropwise to a solution of aromatic alcohol (1 eq.) in CH_2Cl_2 (30 mL) at 0 °C. The reaction mixture was stirred for 2 h and then warmed up to room temperature. After 4 h, the solution was poured into 50 mL ice water and stirred for 10 min. Then the organic layer was washed with water and aq $NaHCO_3$ (3 × 20 mL), dried over anhydrous sodium sulfate, and evaporated to yield the pure product as a solid benzyl bromine.

146.2.2.4 General Procedure 4 (Gp 4) for the Preparation of Methoxylated Diethyl Benzylphosphonates from Benzyl Bromine (Arbuzov Rearrangement)

A mixture of bromide (1 eq.) and triethyl phosphite (2 mL 5 eq.) was stirred at 135 °C for 3 h [19]. Triethyl phosphate (2 mL 5 eq.) was added again and stirred another 4 h. After the reaction was completely finished, the mixture was cooled to room temperature and purified by distillation at 4×10^{-3} bar and 120 °C to yield yellow oils methoxylated diethyl benzylphosphonates. The crude product was used directly for the next step without further purification.

146.2.2.5 General Procedure 5 (Gp 5) for Synthesis of Compounds 9a–16a (Wittig-Hornor Condensation)

Methoxylated diethyl benzylphosphonates (1 eq.) in the round-bottomed flask was added dropwise to a suspension of NaH (4 eq.) in THF (20 mL) at 0 °C and stirred for 1 h [20]. Then the mixture was treated with aromatic carboxaldehyde (1a–6a) (1 eq.) at 0 °C for 2 h. The reaction mixture was warmed up to room temperature and further stirred for 15 h. The solution was poured into 150 mL ice water, neutralized with 2 M HCl, and extracted with ethyl acetate. The ethyl acetate layer was washed with water and brine, dried over anhydrous sodium sulfate, and concentrated. The crude product purified by crystallization or flash column chromatography to afford (E)-stilbenes.

146.2.2.6 General Procedure 6 (Gp 6) for the Nitro Groups and Stilbenes (Compounds 17a–18a)

To a stirred suspension of CH_3ONa (3 eq.), DMF (25 mL) was added dropwise to the corresponding methoxylated diethyl benzylphosphonate (1 eq.) at 0 °C in a round-bottomed flask and the mixture was stirred for 1 h. Then the corresponding benzaldehyde (7a–8a) (1 eq.) were added. The mixture was stirred at room temperature for 1 h, then heated to 100 °C under argon for 10 h. The solution was poured into 150 mL ice water, the precipitate as filtered off and recrystallized from diluted or pure ethanol to afford the nitro groups and stilbenes.

146.2.3 Syntheses

146.2.3.1 3,5-Dimethoxyl-4′-bromo-trans-stilbene (9a)

This compound was prepared in 59.2 % yield by following GP 4 and 5. White solid: 1H NMR (400 MHz CDCl3): δ/ppm 7.47 (d, $J = 8.4$ Hz, 2H), 7.36

(d, $J = 8.4$ Hz, 2H), 7.01(s, 2H), 6.65 (d, $J = 2.4$ Hz, 2H), 6.41 (t, $J = 2.2$ Hz, 1H), 3.83 (s, 6H).

146.2.3.2 3,5-Dimethoxyl-4′-chloro-trans-stilbene (10a)

This compound was prepared in 65.8 % yield by following GP 4 and 5. White solid: ^{1}H NMR (400 MHz $CDCl_3$): δ/ppm 7.42 (d, $J = 8.4$ Hz, 2H), 7.32 (d, $J = 8.4$ Hz, 2H), 7.01 (d, $J = 1.6$ Hz, 2H), 6.65 (d, $J = 2.4$ Hz, 2H), 6.41 (t, $J = 2.4$ Hz, 1H), 3.83 (s, 6H).

146.2.3.3 3,5-Dimethoxyl-trans-stilbene (11a)

This compound was prepared in 45.6 % yield by following GP 4 and 5. White solid: ^{1}H NMR (400 MHz $CDCl_3$): δ/ppm 7.55 (d, $J = 7.6$ Hz, 2H), 7.40 (t, $J = 7.6$ Hz, 2H), 7.31 (t, $J = 7.2$ Hz, 1H), 7.14 (d, $J = 16.4$ Hz, 1H), 7.08 (d, $J = 16.4$ Hz, 1H), 6.73 (d, $J = 2$ Hz, 2H), 6.45 (t, $J = 2.4$ Hz, 1H), 3.87 (s, 6H).

146.2.3.4 3,5,4′-Trimethoxyl-trans-stilbene (12a)

This compound was prepared in 37.1 % yield by following GP 4 and 5. White solid: ^{1}H NMR (400 MHz $CDCl_3$): δ/ppm 7.44 (d, $J = 8.4$ Hz, 2H), 7.04 (d, $J = 16$ Hz, 1H), 6.91 (t, $J = 6.4$ Hz, 3H), 6.65 (s, 2H), 6.37 (s, 1H), 3.83 (s, 9H).

146.2.3.5 3,5,2′-Trimethoxyl-trans-stilbene (13a)

This compound was prepared in 46.2 % yield by following GP 4 and 5. White solid: ^{1}H NMR (400 MHz $CDCl_3$): δ/ppm 7.57 (d, $J = 7.6$ Hz, 2H), 7.45 (d, $J = 16.4$ Hz, 1H), 7.22–7.26 (m, 1H), 7.04 (d, $J = 16.4$ Hz, 1H), 6.96 (t, $J = 7.2$ Hz, 1H), 6.90 (d, $J = 8.4$ Hz, 1H), 6.69 (d, $J = 2$ Hz, 2H), 6.38 (t, $J = 2.4$ Hz, 1H), 3.88 (s, 3H), 3.83 (s, 6H).

146.2.3.6 3,5,2′,3′-Tetramethoxyl-trans-stilbene (14a)

This compound was prepared in 48.8 % yield by following GP 4 and 5. White solid: ^{1}H NMR (400 MHz $CDCl_3$): δ/ppm 7.42 (d, $J = 16.4$ Hz, 1H), 7.23 (d, $J = 9.2$ Hz, 1H), 7.06 (t, $J = 9.2$ Hz, 1H), 7.05 (d, $J = 16.4$ Hz, 1H), 6.84 (d, $J = 9.6$ Hz, 1H), 6.70 (d, $J = 2$ Hz, 2H), 6.4 (t, $J = 2.4$ Hz, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.84 (s, 6H).

146.2.3.7 3,4,2′-Trimethoxyl-trans-stilbene (15a)

This compound was prepared in 44.9 % yield by following GP 4 and 5. White solid: ^{1}H NMR (400 MHz $CDCl_3$): δ/ppm 7.58 (d, $J = 9.2$ Hz, 1H), 7.33 (d, $J = 16.4$ Hz, 1H), 7.21 (t, $J = 4.8$ Hz, 1H), 7.10 (d, $J = 1.6$ Hz, 1H), 7.06 (d, $J = 16.4$ Hz, 1H), 7.05 (d, $J = 8.4$ Hz, 1H), 6.96 (t, $J = 7.6$ Hz, 1H), 6.90 (d, $J = 8$ Hz, 1H), 6.85 (d, $J = 8.4$ Hz, 1H), 3.95 (s, 3H), 3.90 (d, $J = 1.2$ Hz, 6H).

146.2.3.8 3,4,2′,3′-Tetramethoxyl-trans-stilbene (16a)

This compound was prepared in 37.6 % yield by following GP 4 and 5. White solid: ^{1}H NMR (400 MHz $CDCl_3$): δ/ppm 7.31 (d, $J = 16.4$ Hz, 1H), 7.22 (d, $J = 9.6$ Hz, 1H), 7.09 (d, $J = 16.4$ Hz, 1H), 7.09 (s, 1H), 7.08 (t, $J = 6.4$ Hz, 1H), 7.04 (d, $J = 8$ Hz, 1H), 6.87 (d, $J = 8.8$ Hz, 1H), 6.83 (d, $J = 9.6$ Hz, 1H), 3.95 (s, 3H), 3.91 (s, 3H), 3.89 (s, 3H), 3.86 (s, 3H).

146.2.3.9 3,5-Dimethoxyl-4′-nitro-trans-stilbene (17a)

This compound was prepared in 76.5 % yield by following GP 4 and 6. Yellow solid: ^{1}H NMR (400 MHz $CDCl_3$): δ/ppm 8.22 (d, $J = 8.4$ Hz, 2H), 7.63 (d, $J = 8.8$ Hz, 2H), 7.20 (d, $J = 16.4$ Hz, 1H), 7.11 (d, $J = 16.4$ Hz, 1H), 6.96 (t, $J = 7.2$ Hz, 1H), 6.70 (s, 2H), 6.46 (t, $J = 2$ Hz, 1H), 3.85 (s, 6H).

146.2.3.10 3,5-Dimethoxyl-3′-nitro-trans-stilbene (18a)

This compound was prepared in 78.3 % yield by following GP 4 and 6. Orange solid: ^{1}H NMR (400 MHz $CDCl_3$): δ/ppm 8.36 (s, 1H), 8.09 (d, $J = 9.6$ Hz, 1H), 7.79 (d, $J = 8$ Hz, 1H), 7.52 (t, $J = 8$ Hz, 1H), 7.16 (d, $J = 16.4$ Hz, 1H), 7.09 (d, $J = 16.4$ Hz, 1H), 6.69 (d, $J = 2.4$ Hz, 2H), 6.45 (t, $J = 2.4$ Hz, 1H), 3.84 (s, 6H).

146.2.3.11 3,5-Dimethoxy-4′-amino-trans-stilbene (19a)

Ferric chloride hexahydrate (0.1 g) and activated carbon (1 g) were added to a solution of compound 17a (1.42 g, 5 mmol) in ethanol (55 mL). Then the reaction mixture was heated to 80 °C and hydrazine hydrate (9 mL, 15 mmol) was added dropwise to the mixture. The mixture was stirred under reflux for 5 h. The mixture was filtered and the solvent was removed. Water was added to the residue and the aqueous layer was extracted by ethyl acetate and the organic layer was washed by brine, and dried over anhydrous sodium sulfate. The solvent was evaporated in

vacuo to provide a yellow solid that was recrystallized from ethyl acetate and hexane to yield a pure yellow solid (1.09 g, 85.6 %): ^{1}H NMR (400 MHz $CDCl_3$): δ/ppm 7.33 (d, $J = 8.4$ Hz, 2H), 7.00 (d, $J = 16.4$ Hz, 1H), 6.84 (d, $J = 16.4$ Hz, 1H), 6.67 (d, $J = 8.4$ Hz, 2H), 6.63 (d, $J = 2.4$ Hz, 2H), 6.36 (t, $J = 2.4$ Hz, 1H), 3.82 (s, 6H), 3.75 (br, 2H).

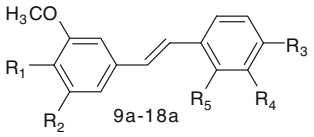
146.3 Results and Discussion

In this work, we used the Wittig-Horner reaction to synthesize resveratrol derivatives. It was found that Wittig-Horner reaction is much better in forming double bond of resveratrol due to its mild reaction conditions, simple manipulation, high purity, and yield than Perkin or Heck reaction.

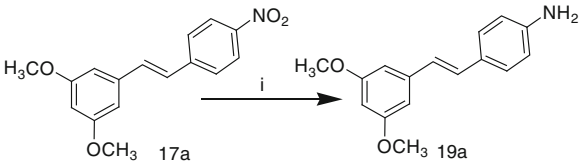
In this work, methoxylated analogs of resveratrol were synthesized through 3,5-dihydroxybenzoic acid or 3,4-trihydroxybenzoic acid followed by aromatic esters formation in moderate yield, which was reduced with $LiAlH_4$ to alcohol, and subsequent treatment with tribromophosphine afforded benzyl bromine in about 85.0 %. With Wittig-Horner reaction methoxylated diethyl benzylphosphonates were obtained by refluxing benzyl bromine with $P(OEt)_3$, which was condensed with ArCHO in CH_3ONa/DMF or NaH/THF to give compounds 9a–18a, only the trans isomer was obtained. Compounds 9a–18a were prepared according to Scheme 146.1 and the structures of these compounds were listed in Table 146.1. The nitro group of the analog 17a was reduced to provide the amine derivatives 19a in satisfactory yields (Scheme 146.2).

It is reported that some methylated derivatives of resveratrol show better potential antifungal, anti-proliferative, anticancer, and other activities than resveratrol. For instance, compound 12a was reported to inhibit invasion of human

Table 146.1 Chemical structures of compounds 9a–18a



Compound	R_1	R_2	R_3	R_4	R_5
9a	H	OCH_3	Br	H	H
10a	H	OCH_3	Cl	H	H
11a	H	OCH_3	H	H	H
12a	H	OCH_3	OCH_3	H	H
13a	H	OCH_3	H	H	OCH_3
14a	H	OCH_3	H	OCH_3	OCH_3
15a	OCH_3	H	H	H	OCH_3
16a	OCH_3	H	H	OCH_3	OCH_3
17a	H	OCH_3	NO_2	H	H
18a	H	OCH_3	H	NO_2	H



Scheme 146.2 Synthetic pathway for stilbenes 19a. Reagents and conditions: (i) $FeCl_3/C$, H_2NNH_2, EtOH, reflux

lung adenocarcinoma cells [21]. In addition, compound 19a also displayed potent QR2 inhibitory activity [22] and compound 11a possesses potent NQO1 induction activity [23] and other articles reported that they have inhibitory activity of prostaglandin E2 [24]. So the biological activities of these resveratrol derivatives lead us to synthesize novel derivatives and further study their other biological activities such as anti-diabetes.

146.4 Conclusion

In summary, we designed and synthesized some methoxylated analogs of resveratrol. The synthetic route is a five-step convenient procedure via Wittig-Horner reaction which is the key step to prepare resveratrol derivatives including compounds 9a–18a in overall yield 17.2–48.5 %. The compounds 17a–18a were prepared in 76.5–78.3 % yield by following GP 4 and 6, however, yield would be a range from 35.5 to 37.6 % by following GP 4 and 5. It was possible that compounds 7a–8a could cause Cannizzaro reaction when the reactions took GP 5, resulting in lower yield. The analogs 17a were reduced by hydrazine hydrate to get the compound 19a in yield 85.0 %.

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References

1. Richard JL (1987) Coronary risk factors: The French paradox. Arch Mal Coeur Vaiss 80:17–21
2. Takaoka MJ (1940) Of the phenolic substances of white hellebore. J Faculty Sci 3:1–16
3. Kopp P (1998) Resveratrol, a phytoestrogen found in red wine. A possible explanation for the conundrum of the 'French paradox'? Eur J Endocrinol 138:619–620
4. Jang M, Pezzuto JM (1999) Cancer chemopreventive activity of resveratrol. Drugs Exp Clin Res 25:65–771
5. Stivala LA, Savio M, Carafoli F et al (2001) Specific structural determinants are responsible for the antioxidant activity and the cell cycle effects of resveratrol. J Biol Chem 276:22586–22594
6. Daroch F, Hoeneisen M, Gonzalez CL et al (2001) In vitro antibacterial activity of Chilean red wines against Helicobacter pylori. Microbios 104:79–85

7. Wang WB, Lai HC, Hsueh PR et al (2006) Inhibition of swarming and virulence factor expression in Proteus mirabilis by resveratrol. J Med Microbiol 55:1313–1321
8. Zaidi SF, Ahmed K, Yamamoto T et al (2009) Effect of resveratrol on Helicobacter pylori-induced interleukin-8 secretion, reactive oxygen species generation and morphological changes in human gastric epithelial cells. Biol Pharm Bull 32:1931–1935
9. Arichi H, Kimura Y, Okuda H et al (1982) Effects of stilbene components of the roots of Polygonum cuspidatum on lipid metabolism. Chem Pharm Bull (Tokyo) 30:1766–1770
10. Pace-Asciak CR, Hahn S, Diamandis EP et al (1996) The red wine phenolics trans-resveratrol and quercetin block human platelet aggregation and eicosanoid synthesis: implications for protection against coronary heart disease. Clin Chim Acta 235:207–219
11. Chen CK, Pace-Asciak CR (1996) Vasorelaxing activity of resveratrol and quercetin in isolated rat aorta. Gen Pharmacol 27:363–366
12. Howitz KT, Bitterman KJ, Cohen HY et al (2003) Small molecule activators of sirtuins extend Saccharomyces cerevisiae lifespan. Nature 425:191–196
13. Wang RH, Sengupta K, Li C et al (2008) Impaired DNA damage response, genome instability, and Tumorigenesis in SIRT1 mutant mice. Cancer Cell 14:312–323
14. Rocha-Gonzalez HI, Ambriz-Tututi M, Granados-Soto V (2008) Resveratrol: a natural compound with pharmacological potential in neurodegenerative diseases. CNS Neurosci Ther 14:234–247
15. Vieira de Almeida LM, Pineiro CC, Leite Marina MC et al (2008) Protective effects of resveratrol on hydrogen peroxide induced toxicity in primary cortical astrocyte cultures. Neurochem Res 33:8–15
16. Ali HA, Kondo K, Tsuda Y (1992) Synthesis and nematocidal activity of hydroxystilbenes. Chem Pharm Bull 40:1130–1136
17. Thakkar K, Geahlen RL, Gushman M (1993) Synthesis and protein-tyrosine kinase inhibitory activity of polyhydroxylated stilbene analogs of piceatannol. J Med Chem 36:2950–2955
18. Murias M, Handler N, Erker T et al (2004) Resveratrol analogues as selectivecyclooxygenase-2 inhibitors: synthesis and structure—activity relationship. Bioorg Med Chem 12:5571–5578
19. Bhattacharya Alok K, Thyagarajan G (1981) Michaelis-Arbuzov rearrangement. Chem Rev 81:415–430
20. Cristau HJ, Darviche F, Torreilles E (1998) Mechanistic investigations of the formation of TTF derivatives via the phosphonate way. Tetrahedron Lett 39:2103–2106
21. Yang YT, Weng CJ, Ho CT et al (2009) Resveratrol analog-3,5,4′-trimethoxy-trans-stilbene inhibits invasion of human lung adenocarcinoma cells by suppressing the MAPK pathway and decreasing matrix metalloproteinase-2 expression. Mol Nutr Food Res 53:407–416
22. Sun B, Hoshino J, Jermihov K et al (2010) Design, synthesis, and biological evaluation of resveratrol analogues as aromatase and quinone reductase 2 inhibitors for chemoprevention of cancer. Bioorg Med Chem 18:5352–5366
23. Park EJ, Min HY, Park HJ et al (2011) Nuclear factor E2-related factor 2-mediated induction of NAD(P)H:quinone oxidoreductase 1 by 3,5-dimethoxy-trans- stilbene. J Pharmacol Sci 116:89–96
24. Park EJ, Min HY, Ahn YH et al (2004) Synthesis and inhibitory effects of pinosylvin derivatives on prostaglandin E2 production in lipopolysaccharide-induced mouse macrophage cells. Bioorg Med Chem Letters 14:5895–5898