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Synthesis and Anti-Cancer Activities of Resveratrol Derivatives

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Abstract

A novel series of resveratrol derivatives were synthesized according to Wittig-Horner reaction with 3,5-dihydroxybenzyl alcohol or 3,5-dimethoxybenzyl alcohol or 4-hydroxybenzyl alcohol as raw material and the inhibitory activities on breast carcinoma (MDA-MB-231) and gastric carcinoma cell lines (SGC-7901) *in vitro* were evaluated by the standard methyl thiazole tetrazolium (MTT) method. The result of biological test shows that some of resveratrol derivatives possess stronger anti-cancer activities than 5-FU. Compound 5c shows the strongest activity against breast carcinoma (MDA-MB-231) and gastric carcinoma cell lines (SGC-7901) with IC_{50} value of 50.19 ± 1.02 μM, 122.68.27 ± 2.04 μM, compared to that IC_{50} value of 5-FU is 98.59±3.61 μM,156.74±6.16 μM, respectively.

Keywords

Resveratrol Derivatives, Wittig-Horner Reaction, MTT Method, Breast Carcinoma, Gastric Carcinoma

1. Introduction

Cancer is the term used for diseases in which abnormal cells divide without control and are able to invade other tissues. All cancers begin in cells, when the DNA of a cell becomes damaged or changed, it will produce muta-

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tions that will affect normal cell growth and division. In recent years, cancer has become one of the main causes of death to the human being [1]. The incidences of breast cancer and gastric cancer are increasing rapidly. Breast cancer, the top cancer in women in the global, is particularly spreading in China at an amazing rate, and it has become a leading cause of cancer-related death worldwide [2]. In 2014, an estimated 235,030 new cases have been diagnosed, and 40,430 deaths from breast cancer occurred [3]. Gastric cancer is also one of the major causes of cancer death worldwide, with almost 990,000 cases detected annually. The incidences of gastric cancer vary with geographic location, and they are the highest in Eastern Asia including China, Japan and Korea [4]. Despite its prevalence, there is still no curative modality for late-diagnosed gastric cancer. The mechanism of carcinogenesis is complex and poorly understood. Nobili S. *et al*. [5] believed that gastric cancer appeared by the accumulation of both genetic and epigenetic changes, while de Souza C. R. *et al*. [6] said that it was influenced by both infection with *Helicobacter pylori* and genetic factors. The incident of cancer is higher and higher, and the treatment of cancer is imminent, so finding the best method for the treatment of cancer is the primary task for us. Chemotherapy is one of the major approaches of all the measures of cancer treatment. It has always been the focus in the research of anti-cancer candidates with high efficacy, low toxicity, and minimum side effects from nature plants.

Resveratrol (3,5,4'-trihydroxy-*trans*-stilbene, **Figure 1**) was originally isolated by Takaoka from the roots of *hellebore* in 1940 [7], and later, from the roots of Japanese *knotweed* in 1963, a plant used in traditional Chinese medicine. It attracted wider attention only in 1992 when its presence in wine was suggested as the explanation for cardioprotective effects [8]. Gradually, resveratrol was also found in Liliaceous, Polygonaceae, Leguminosae, Asmyrtaceae 21 families, 31 genera and 72 species of plants [9]. It was also reported to possess remarkable activities of anti-cancer [10], anti-bacterial [11], anti-aging [12], anti-inflammatory [13], and anti-oxidant [14]. The anti-oxidative and anti-inflammatory effects of resveratrol play a critical role in the therapeutic processing, evidence has revealed that resveratrol acts as a free radical scavenger; it promotes nitric oxide production, increases HDL cholesterol, and inhibits platelet coagulation and vasodilation [15]. These biological effects may explain the strange phenomenon "French paradox", a decreased incidence of cardiovascular diseases in moderate consumers of red wines despite an intake of a high-fat diet [16].

Although resveratrol possesses a series of pharmacological activities, its therapeutic application is still limited due to its short biological half-life (8 - 14 min) [17]. Experiments have proved that the enterohepatic recirculation and rapid first pass metabolism lead to its poor systemic bioavailability [18]. Since the last few years, significant progress has been made in studying the biological effects of resveratrol and the analogues. Cushman M. *et al*. [19] tested the activity of 70 different resveratrol analogues as aromatase for chemotherapy cancer. The aromatase inhibitory activities of some analogues were much more effective than the lead compound resveratrol. From the structure-activity relationship of resveratrol study, it was proved that the lipophilic groups introduced in the structure help to improve the bioactivity. With this concept in mind, we introduce lipophilic group to ring A or B, and alkylate the instability of the hydroxyl in order to provide lead compounds for independent innovation of anti-cancer drugs by designing and synthesizing a series of new and trifluoromethyl resveratrol derivatives and evaluating the anti-cancer to breast carcinoma (MDA-MB-231) and gastric carcinoma cell lines (SGC-7901).

2. Materials and Methods

^{1}H NMR spectra were recorded with an Agilent Technologies 400/54 Premium shielded spectrometer (400 MHz). ^{19}F NMR spectra were recorded with an Agilent Technologies 400/54 Premium shielded (376 MHz). ^{13}C NMR spectra were recorded with an Agilent Technologies 400/54 Premium shielded (101 MHz) spectrometer.

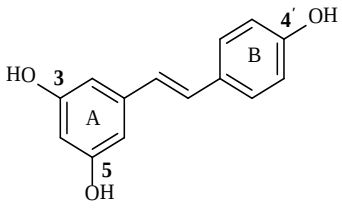


Figure 1. Structure of resveratrol.

MS was recorded with a Hewlett-Packard HP-5989A spectrometer. Infrared spectra were measured with a Perkin-Elmer 983 spectrometer. Melting point was detected by DSC-Q2000. Unless otherwise noted, reagents were commercially available analytical grade materials used as supplied, without further purification.

General procedures for the preparation of compounds 5a ~ 5c

The synthetic route of resveratrol derivatives **5a ~ 5c** is shown in Scheme 1. To obtain the product *via* four-step reaction by using commercially available 3,5-dimethoxylbenzyl alcohol as the starting material. First, the raw material (2.5 g, 15 mmol) was dissolved in DCM (15 mL) and stirred at 0˚C, then a solution of phosphorous bromide (1.5 mL, 16 mmol) in the presence of DCM (10 mL) was added drop wise at the condition of ice-salt bath for 2 h. The resulting mixture was poured into ice-water (40 mL), separating the organic layer, washing it with saturated brine to neutral pH. Dried and evaporated solvent under vacuum. The mixture was filtered through silica gel to get a white needle crystal compound **2** (3,5-dimethoxybenzyl bromide), yield 85%. A solution of compound **2** (1.5 g, 6.5 mmol) and triethylphosphite (1.5 mL, 8.7 mmol) was stirred at 130˚C for 5 h. Vacuum distilling to remove excess triethylphosphite to get colorless oil compound **3** (3,5-dime-thoxybenzyl phosphonate). Next, in the same reacting three-necked bottle, after sodium methanolate (1.1 g, 20.5 mmol) in DMF (7 mL) stirring at 0˚C for 30 min, the fluorine-substituted benzaldehyde **4a ~ 4c** (6.6 mmol) was added under ice-salt bath condition for 2 h and room temperature over night. The resulting mixture was poured into ice-water (30 mL), white solid precipitation appeared and then it was washed till neutral and recrystallize with ethyl alcohol (95%) to get white crystal compound **5a ~ 5c**.

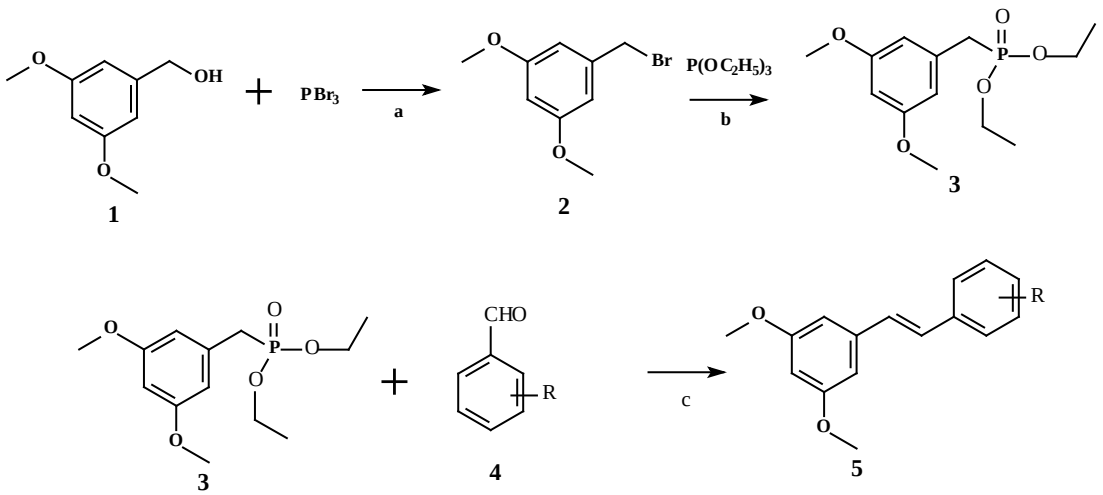
General method for synthesis of compounds 10a - 10c

Compounds **10a ~ 10c** were obtained as shown in Scheme 2. A solution of hydroxy-substituted benzyl alcohol (50 mmol) into acetone (50 mL) and potassium carbonate (150 mmol) as base was stirred at room temperature for 30 min and then bromoalkane was added at refluxing temperature for 18 ~ 48 h. The mixture was filtered to remove potassium carbonate. Filtrate was evaporated under vacuum to give the compound **7** (alkoxy-substituted benzyl alcohol). Longer alkyl chains resulted in longer reaction times. The next steps for these compounds **10a ~ 10c** were similar to the synthesis of compounds **5a ~ 5c**.

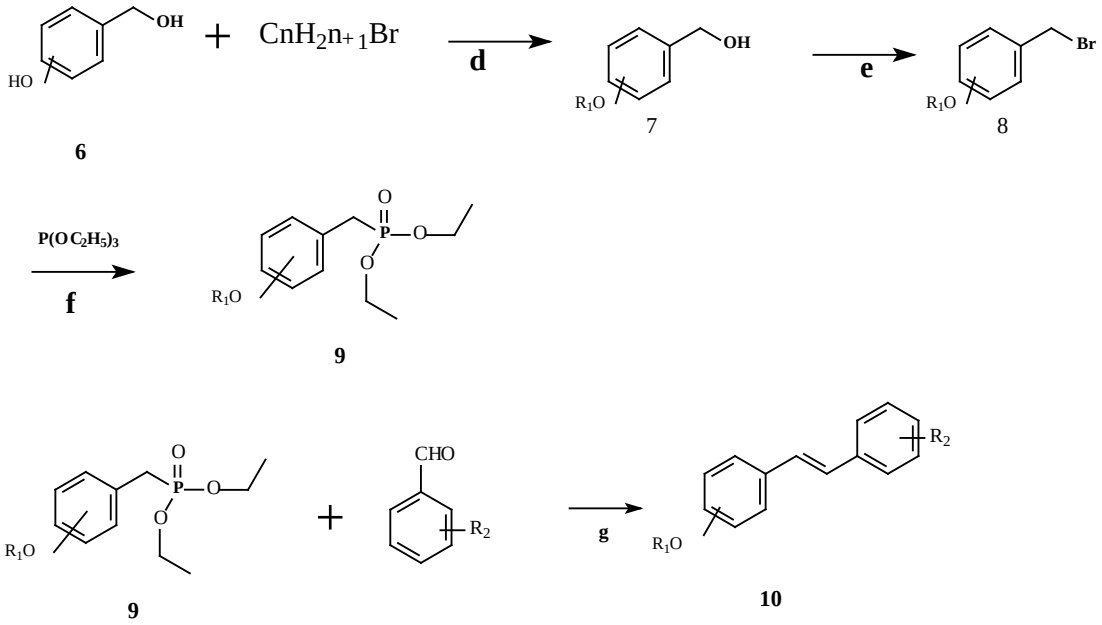
All the new compounds were characterized by detailed spectroscopic analysis.

5a (*trans*-3,5-dimethoxy-2'-fluoro-4'-methoxy stilbenes)

White solid, yield 31%, m.p. 59.7˚C ~ 60.3˚C. IR υ_{max} (cm^{-1}), 832, 962, 1032, 1066, 1290, 1457, 1506, 1597, 1620, 2837, 2938. ^{19}F NMR (376 MHz, $CDCl_3$) δ −115.51 (dd, J = 12.5, 8.8 Hz). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (t, J = 8.8 Hz, 1H), 7.17 (d, J = 16.5 Hz, 1H), 6.97 (d, J = 16.5 Hz, 1H), 6.71 (dd, J = 8.7, 2.5 Hz, 1H), 6.66 (d, J = 2.2 Hz, 2H), 6.63 (dd, J = 12.6, 2.5 Hz, 1H), 6.39 (t, J = 2.2 Hz, 1H), 3.83 (s, 6H), 3.82 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.32 (s), 160.94 (s), 160.30 (d, J = 11.2 Hz), 159.84 (s), 139.58 (s), 128.53 (d, J = 4.8 Hz), 127.65 (d, J = 5.6 Hz), 121.25 (d, J = 3.1 Hz), 117.56 (d, J = 12.5 Hz), 110.48 (d, J = 2.9 Hz), 104.40 (s), 101.58 (d, J = 26.0 Hz), 99.91 (s), 55.47 (d, J = 22.7 Hz). HRMS(EI), Calcd. for, $C_{17}H_{17}O_3F$, 288.1162, Found, 288.1158.



Scheme 1. Synthetic steps of compounds 5a ~ 5c. Reagents and conditions, a) DCM, ice salt bath, 2 h to room temperature, 2 h, b) 130˚C, 5 h, c) DMF, MeONa, 0˚C to room temperature, overnight.



Scheme 2. Synthetic steps of compounds 10a ~ 10c. Reagents and conditions, d) Acetone, reflux, 18 ~ 48 h, e) PBr_3, DCM, ice salt bath, 2 h to room temperature, 2h, f) 130˚C, 5 h, g) DMF, MeONa, 0˚C to room temperature, overnight.

5b (*trans*-3,5-diethoxy-3'-fluoro-4'-methoxy stilbenes)

White solid, yield 35%, m.p. 59.9˚C ~ 62.3˚C. IR υ_{max} (cm^{-1}), 683, 827, 958, 1065, 1155, 1204, 1459, 1518, 1591, 2838, 2937. ^{19}F NMR (376 MHz, $CDCl_3$) δ −135.24 (dd, J = 12.4, 8.5 Hz). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (dd, 12.4, 8.5 Hz, 1H), 7.18 (d, J = 8.5 Hz, 1H), 6.98 (d, J = 16.2 Hz, 1H), 6.92 (d, J = 8.5 Hz, 1H), 6.88 (d, J = 16.2 Hz, 1H), 6.64 (d, J = 2.2 Hz, 2H), 6.39 (t, J = 2.2 Hz, 1H), 3.91 (s, 3H), 3.83 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.96 (s), 153.74 (s), 151.29 (s), 147.29 (d, J = 11.1 Hz), 139.15 (s), 130.68 (d, J = 6.6 Hz), 127.86 (s), 127.72 (d, J = 2.5 Hz), 123.02 (d, J = 3.2 Hz), 113.48 (s), 113.28 (d, J = 2.6 Hz), 104.43 (s), 99.90 (s), 56.25 (s), 55.34 (s). HRMS(EI), Calcd. for, $C_{17}H_{17}O_3F$, 288.1162, Found, 288.1158.

5c (*trans*-3,5-diethoxy-4'-((trifluoromethyl)thio) stilbenes)

White solid, yield 37%, m.p. 96.1˚C ~ 96.7˚C. ^{19}F NMR (376 MHz, $CDCl_3$) δ −42.84 (s, 3F). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 8.3 Hz, 2H), 7.54 (d, J = 8.3 Hz, 2H), 7.12 (d, J = 16.3 Hz, 1H), 7.06 (d, J = 16.3 Hz, 1H), 6.68 (d, J = 2.2 Hz, 2H), 6.43 (t, J = 2.2 Hz, 1H), 3.84 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.01 (s), 139.77 (s), 138.62 (s), 136.63 (s), 131.07 (s), 128.01 (s), 127.59 (s), 127.36 (s), 122.93 (d, J = 2.1 Hz), 104.82 (s), 100.47 (s), 55.38 (s). HRMS(EI), Calcd. for, $C_{17}H_{15}F_3O_2S$, 340.0745, Found, 340.0747.

10a (*trans*-3,5-diethoxy-2'-fluoro-4'-methoxy stilbenes)

White solid, yield 28%, m.p. 57.3˚C ~ 58.2˚C. IR υ_{max} (cm^{-1}), 835, 962, 1106, 1170, 1290, 1444, 1506, 1532, 1619.2933, 2979. ^{19}F NMR (376 MHz, $CDCl_3$) δ −115.55 (dd, J = 12.8, 8.7 Hz). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (t, J = 8.7 Hz, 1H), 7.15 (d, J = 16.4 Hz, 1H), 6.95 (d, J = 16.4 Hz, 1H), 6.70 (dd, J = 8.7, 2.4 Hz, 1H), 6.63 (dd, J = 12.8, 2.3 Hz, 3H), 6.37 (t, J = 2.3 Hz, 1H), 4.05 (q, J = 7.0 Hz, 4H), 3.81 (s, 3H), 1.42 (t, J = 7.0 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.30 (s), 160.25 (t, J = 5.2 Hz), 159.82 (s), 139.46 (s), 128.63 (d, J = 4.7 Hz), 127.61 (d, J = 5.6 Hz), 121.03 (d, J = 3.1 Hz), 117.63 (d, J = 12.6 Hz), 110.46 (d, J = 2.9 Hz), 104.98 (s), 101.57 (d, J = 26.0 Hz), 100.79 (s), 63.49 (s), 55.56 (s), 14.85 (s). HRMS(EI), Calcd. for $C_{19}H_{21}O_3F$, 316.1475, Found, 316.1469.

10b (*trans*-3,5-n-dipropoxy-2'-fluoro-4'-methoxy stilbenes)

White solid, yield 21%, m.p. 58.3˚C ~ 60.2˚C. IR υ_{max} (cm^{-1}), 831, 962, 1066, 1197, 1290, 1445, 1506, 1596, 1619, 2876, 2964. ^{19}F NMR (376 MHz, $CDCl_3$) δ −115.55 (dd, J = 12.4, 8.7 Hz). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (t, J = 8.7 Hz, 1H), 7.16 (d, J = 16.5 Hz, 1H), 6.96 (d, J = 16.5 Hz, 1H), 6.70 (dd, J = 8.7, 2.4 Hz, 1H), 6.63 (dd, J = 12.4, 2.2 Hz, 3H), 6.38 (t, J = 2.2 Hz, 1H), 3.94 (t, J = 6.6 Hz, 4H), 3.81 (s, 3H), 1.88 - 1.75 (m, 4H), 1.04 (t, J = 7.4 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.30 (s), 160.45 (s), 160.23 (d, J = 11.2 Hz), 159.82

(s), 139.42 (s), 128.68 (d, *J* = 4.7 Hz), 127.61 (d, *J* = 5.6 Hz), 121.00 (d, *J* = 3.1 Hz), 117.66 (d, *J* = 12.6 Hz), 110.46 (d, *J* = 2.9 Hz), 104.97 (s), 101.57 (d, *J* = 26.0 Hz), 100.82 (s), 69.57 (s), 55.57 (s), 22.62 (s), 10.56 (s). HRMS(EI), Calcd. for, $C_{21}H_{25}O_3F$, 344.1788, Found, 344.1782.

10c (*trans*-4-ethoxy-3'-fluoro-4'-methoxy stilbenes)

White solid, yield 27%, m.p. 160.0˚C ~ 160.6˚C. IR υ_{max} (cm^{-1}), 526, 649, 734, 909, 1025, 1161, 1285, 1442, 1517, 1604, 2842, 2983. ^{19}F NMR (376 MHz, $CDCl_3$) δ −135.43 (dd, *J* = 12.6, 8.8 Hz). ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.8 Hz, 1H), 7.24 (d, *J* = 1.9 Hz, 1H), 7.15 (d, *J* = 8.4 Hz, 1H), 6.94 (d, *J* = 8.4 Hz, 1H), 6.90 (d, *J* = 2.0 Hz, 1H), 6.87 (d, *J* = 2.0 Hz, 1H), 4.06 (q, *J* = 7.0 Hz, 2H), 3.91 (s, 3H), 1.43 (t, *J* = 7.0 Hz, 3H).13C NMR (101 MHz, cdcl3) δ 158.63 (s), 153.78 (s), 151.34 (s), 146.82 (d, *J* = 11.1 Hz), 131.34 (d, *J* = 6.6 Hz), 129.77 (s), 127.55 (d, *J* = 2.4 Hz), 125.00 (d, *J* = 2.4 Hz), 122.53 (d, *J* = 3.3 Hz), 114.67 (s), 113.35 (d, *J* = 2.3 Hz), 113.08 (d, *J* = 18.7 Hz), 63.47 (s), 56.29 (s), 14.81 (s). HRMS(EI), Calcd. for $C_{17}H_{17}O_2F$, 272.1213, Found, 272.1215.

2.1. Anti-Cancer Assays

The *in vitro* anti-cancer activities of flourine-substituted resveratrol derivatives were studied on human cells breast carcinoma (MDA-MB-231) and gastric carcinoma cell lines (SGC-7901) by applying the MTT assay as described by Mosmann [20]. Briefly, cells were seeded at a density of 10^4 cells/well in 96-well microtiter plates and incubated in 5% CO_2 at 37˚C for 24 h. The tested compounds at indicated concentrations were added to culture medium, and the cell cultures were continued for another 48 h. After 48 h, cell survival was determined by the addition of an MTT solution (5 mg/mL MTT in PBS). We calculated optical density (OD) at 570 nm with EX-800 Eliasa IC_{50}, calculated by OD, was used to evaluate the effect on the cell proliferation. All of the compounds were tested three times in each of the cell lines.

2.2. Anticancer Activity

MTT assay is dependent on NAD(P)H-dependent oxidoreductase enzymes largely in the cytosolic compartment of the cell [21]. Therefore, reduction of MTT depends on the cellular metabolic activity due to NAD(P)H flux. *In vitro* MTT assays were done through the same method as previously work described [22]. The synthesized compounds **5a ~ 5c** and **10a ~ 10c** were evaluated by MTT-based assay using breast cancer cell lines (MDA-MB-231) and gastric carcinoma cell lines (SGC-7901) with 5-FU and resveratrol as the positive control. The IC_{50} represents the concentration of a drug that can induce the death of 50% cancer cells *in vitro*. The given values are mean values of three experiments (**Table 1**).

As summarized in **Table 1**, these synthetic resveratrol derivatives exhibited a remarkable different inhibitory activity against two cancer cell lines. Compound **5c** shows the strongest activity against breast carcinoma (MDA-MB-231) and gastric carcinoma cell lines (SGC-7901) with IC_{50} value of 50.19 ± 1.02 μM, 122.68 ± 2.04

Table 1. The anticancer activities of resveratrol derivatives *in vitro*.

Compound	Molecular weight	IC_{50} (μM)	
		MDA-231	SGC-7901
5a	288.11	66.23 ± 0.96	184.54 ± 1.24
5b	288.11	51.27 ± 0.84	---
5c	340.17	50.19 ± 1.02	122.68 ± 2.04
10a	316.14	440.22 ± 0.78	284.5 ± 2.36
10b	344.17	57.08 ± 0.32	---
10c	272.12	64.06 ± 0.27	---
5-FU	262.19	98.59 ± 0.74	156.74 ± 2.64
Resveatrol	228.24	153.32 ± 0.64	184.3 ± 1.38

IC_{50} = compound concentration required to inhibit tumor cell proliferation by 50%. Data are expressed as the mean ± SE from the dose-response curves of at least three independent experiments. ---, promotes the growth of cancer cells.

μM, compared to IC_{50} value of 5-FU is (98.59 ± 3.61 μM, 156.74 ± 6.16 μM, respectively). Moreover, **5c** is little better than resvertarol where the difference is about 3-fold. All the compounds except **10a** have shown good anti-breast cancer activity than 5-FU and resveratrol which prove that these series of resveratrol derivatives possess visible anti-cancer activity.

3. Conclusion

In summary, **6** new resveratrol derivatives were successfully synthesized. Most of the synthetic compounds indicated higher activities than resveratrol and 5-FU. From the results, compound **5c** was identified as the most effective candidate item against breast cancer and gastric carcinoma cells lines. It is expected that the pharmacological studies described in this article will promote the design of new therapeutic drugs for the clinical treatment of breast cancer and gastric carcinoma. It shows the potentiality as a therapeutic for humans.

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