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The convenient synthesis and evaluation of the anticancer activities of new resveratrol derivatives

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Abstract

In the present study we report the simple synthesis and antitumour activity of novel stilbene derivatives **13**–**22**. The key synthetic strategies involved Wadsworth-Horner-Emmons condensation and coupling reactions in high yields. All compounds showed significant growth inhibition on human tumour cell lines, with the most potent compound (**19**) exhibiting an IC_{50} of 5.7 μM – 11.4 μM *in vitro*.

Keywords: *Stilbene derivatives, Wadsworth-Horner-Emmons reaction, anticancer activity*

Introduction

Naturally occurring resveratrol (*trans*-3,4,5′-trihydroxystilbene, see Figure 1) isolated from grapes is the most representative compound of stilbene analogues, and it exhibits a wide range of intriguing biological activities, such as antibacterial [1], antitumour [2], antiviral [3], antioxidant [4], and antihypertensive [5] activities, and it inhibits the activity of platelet–activating factor (PAF) [6], Ca^{2+} channels [7] and cAMP phosphodiesterase [8] Furthermore, stilbene moieties have the potential to be useful intermediates for many industrial products and may have numerous agrochemical applications, such as in liquid crystals [9], color photography [10], dyestuffs [11], and herbicides [12]. These stilbene derivatives have received a great deal of attention from synthetic chemists, biologists, and pharmacologists due to their various pharmacological activities and unique structural features, such as the bis–phenyl groups between *E*-olefin or *Z*-olefin. Since it was first isolated as a constituent of the roots of white hellebore in 1940, several novel synthetic approaches and medicinal developments involving stilbene derivatives that have two different aryl groups or identical aryl groups have been reported in the literature [13]. Recent laboratory studies indicate that resveratrol and its analogues have promising therapeutic activities for various cancers, including breast, prostate, lung, and colon cancer [14].

The Nakamura group [15] recently reported the synthesis and biological evaluation of boronic acid containing *cis*-stilbenes as apoptotic tubulin polymerization inhibitors. The Macchia and Ghidoni groups [16] introduced resveratrol analogues with high ceramide-mediated proapoptotic activity on human breast cancer cells. Likhitwitayawuid and co-workers [17] chemically transformed oxyresveratrol (*trans*-2,4,3′,5′-tetrahydroxystilbene) into a potent tyrosinase inhibitor and a strong cytotoxic agent. The Andrus

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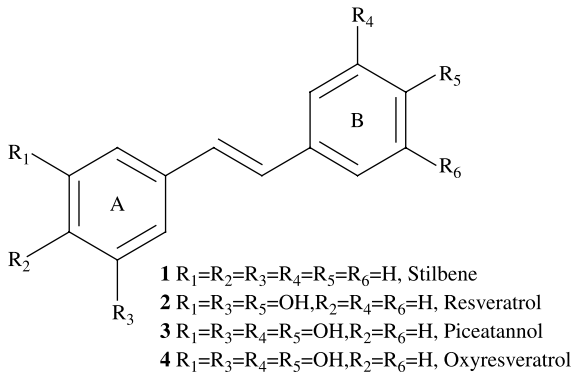


Figure 1. Chemical structures of *trans*-stilbene and its analogues.

group [18] recently developed a technique for the synthesis of polyhydroxylated ester analogues of the stilbene resveratrol using decarbonylative Heck couplings. The Simoni group [19] reported the synthesis of resveratrol analogues, which are stilbene-based agents that show anticancer activity on HL60 leukemic cells with a non-specific phase mechanism.

In a preliminary article [20], we reported the design, synthesis, and biological activity of resveratrol derivatives as protein tyrosine phosphatase 1B inhibitors. In a continuation of our medicinal chemistry program aimed at the efficient synthesis of new stilbene derivatives and the evaluation of their cytotoxicities, we describe the simple synthesis of ten novel stilbene derivatives based on resveratrol and determined the anticancer properties of each derivative. We used the SRB assay for the growth inhibition (IC_{50}) of six tumour cell lines *in vitro*. In the present study, we report the convenient synthesis and evaluation of the anticancer activities of novel stilbene derivatives **13**–**22**.

Experimental

General

All other commercial reagents and solvents were used as received without further purification. Reaction solvents were distilled from calcium hydride for dichloromethane and from sodium metal and benzophenone for tetrahydrofuran. The reactions were monitored and the R_f values determined using analytical thin layer chromatography (TLC) with Merck silica gel 60, F-254 precoated plates (0.25 mm thickness). Spots on the TLC plates were visualized using ultraviolet light (254 nm), a basic potassium permanganate solution or cerium sulfate/ammonium dimolybdate/sulfuric acid solution followed by heating on a hot plate. Flash column chromatography was performed with Merck silica gel 60 (230–400 mesh). ^{1}H NMR spectra were recorded on Bruker DPX-250 or Varian Unity-Inova 500 Spectrometers. Proton chemical shifts are reported in ppm (δ) relative to internal tetramethylsilane (TMS, δ 0.00) or with the solvent reference relative to TMS employed as the internal standard ($CDCl_3$, δ7.26 ppm; d_4-CD_3OD, δ3.31 ppm). Data are reported as follows: Chemical shift {multiplicity [singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m)], coupling constants [Hz], integration}. ^{13}C NMR spectra were recorded on Bruker DPX-250 (62.9 MHz) or Varian Unity-Inova 500 (125.8 MHz) spectrometers with complete proton decoupling. Carbon chemical shifts are reported in ppm (δ) relative to TMS with the respective solvent resonance as the internal standard ($CDCl_3$, δ 77.0 ppm; d_4-CD_3OD, δ 49.0 ppm). Infrared (IR) spectra were recorded on a Nicolet Model Impact FT-IR 400 spectrometer. Data are reported in wave numbers (cm^{-1}). High resolution mass spectrometer (HRMS) was recorded on an Applied Biosystems 4700 proteomics analyzer spectrometer.

Synthesis

*(E)-{2-[3,4-Bis-(tert-butyldimethylsilanyloxy)-phenyl] etheny}-benzoic acid methyl ester (**8**)*

Method A. To a solution of **30** (1.0 g, 3.5 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise a suspension of NaH (10 mg, 60% dispersion in parafilm liquid, washed successively with *n*-pentane) in dry CH_2Cl_2 (5 mL) at 0 °C and stirred for 1 h. A solution of protecting aldehyde 14 (1.0 g, 2.7 mmol) in CH_2Cl_2 (5 mL) was added dropwise and stirred at room temperature for 15 h. The reaction mixture was quenched by slow addition of water (10 mL) and extracted with ethyl acetate (30 mL × 2). The combined organic layer was washed with $NaHCO_3$ and brine. The organic layer was dried (anhydrous $MgSO_4$), filtered and concentrated under reduced pressure. The crude product was purified by flash silica chromatography (hexanes/ethyl acetate, 5/1, v/v) to yielded stilbene **8** (1.4 g, 80%) as a white solid. $R_f = 0.41$ (hexanes/ethyl acetate, 10:1, v/v), IR $\nu_{max}cm^{-1}$ ($CHCl_3$) 2941, 2854, 1729, 1672, 1601, 1515, 1464, 1429, 1281, 1179, 1113 ^{1}H-NMR (250 MHz, $CDCl_3$) δ 8.02 (d, 2H, $\mathcal{J} = 8.2$ Hz, aromatic H), 7.55 (d, 2H, $\mathcal{J} = 8.2$ Hz, aromatic H), 7.13 (d, 1H, $\mathcal{J} = 16.0$ Hz, vinyl CH), 7.00 (m, 3H, aromatic H), 6.94 (d, 1H, $\mathcal{J} = 16.0$ Hz, vinyl CH), 6.84 (m, 1H, aromatic H), 3.91(s, 3H, OCH_3), 1.01–0.99 (m, 18H, *tert*-butyl H), 0.23–0.22 (m, 12H, dimethyl H); ^{13}C-NMR (63 MHz, $CDCl_3$) δ 167.3, 147.5, 143.0, 132.3, 130.9, 130.5, 130.4, 130.0, 128.1, 126.4, 126.0, 122.8, 121.7, 121.6, 120.8, 52.4, 26.3 (3), 26.2 (3), 18.9, 18.7, −3.7 (2), −3.87 (2). HRMS (FAB) 499.2230 *m/z*: ($[M + H]^+$, obsd), 499.2622 (calcd for $C_{28}H_{42}O_4Si_2$)

Method B. To a solution of **30** (1.0 g, 3.5 mmol) in dry THF (5 mL) was added dropwise a suspension of *n*-BuLi (2.2 mL, 1.6 M in THF) in dry THF (5 mL) at 20 °C and stirred for 1 h. A solution of protecting aldehyde 14 (1.0 g, 2.7 mmol) in CH_2Cl_2 (5 mL) was

added dropwise and stirred at room temperature for 12 h. The reaction mixture was quenched by slow addition of water (10 mL) and extracted with ethyl acetate (30 mL × 2). The combined organic layer was washed with $NaHCO_3$ and brine. The organic layer was dried (anhydrous $MgSO_4$), filtered and concentrated under reduced pressure. The crude product was purified by flash silica chromatography (hexane/ethyl acetate, 15/1, v/v) to yielded stilbene **8** (1.5 g, 86%) as a white solid.

*(E)-4-{2-[3,4-Bis-(tert-butyldimethylsilanyloxy)-phenyl] -etheny}-benzoic acid (**10**)*

Method A. To a solution of oxalyl chloride (0.08 g, 0.62 mmol) in dichloromethane (20 mL) was added and stirred for 1 h. Alcohol **16** (0.29 g, 0.61 mmol) in dichloromethane (3 mL) was added dropwise at −78 °C, and resulting mixture was stirred for 45 min. The reaction mixture was quenched by slow addition of triethylamine (0.31 g, 3.1 mmol) at −78 °C, and the reaction mixture was allowed to warm to 0 °C. After 15 min, ether (30 mL) was added followed by saturated aqueous NH_4Cl solution (30 mL). The organic layer was separated, and aqueous phase was extracted with ether (20 mL). The combined organic layer was washed with brine (30 mL), dried over anhydrous MgSO4, filtered, and concentrated under reduced pressure to yield the aldehyde (0.25 g, 89%).

Method B. To a solution of alcohol **9** (0.29 g, 0.61 mmol) in dichloromethane (20 mL) were added molecular sieves (0.29 g, 4 Å, powdered) and 4-methylmorpholine *N*-oxide (0.11 g, 0.92 mmol), followed by addition of tetrapropylammonium perruthenate(0.011 g, 0.031 mmol) at 0 °C. The resulting mixture was stirred for 15 min. The reaction mixture was filtered through a short pad of silica (hexanes/ethyl acetate, 10/1, v/v) to give aldehyde (0.26 g, 90%). Then, to a stirred solution of aldehyde (89 mg, 0.19 mmol) in *tert*-butanol (3 mL) and 2-methyl-2-butene (5 mL) was added a solution of $NaClO_2$ (52mg, 0.57 mmol) and NaH_2PO_4 (0.2 g, 1.70 mmol) in water (1 mL) at 0 °C and the mixture was stirred at 0 °C for 16 h. The reaction mixture was diluted with ethyl acetate (10 mL), washed with brine (10 mL). The organic phase was separated, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture was purified by flash chromatography (silica gel, hexanes/ethyl acetate, 1/1, v/v) to yield pure acid **18** (88 mg, 96%). $R_f = 0.26$ (hexanes/ethyl acetate, 2:1, v/v), IRυ_{max} ($CHCl_3$) 2928, 2855, 1681, 1605, 1595, 1564, 1513, 1421, 1286, 1251, 1177, 1126, 916, 837 $cm^{-1;1}$ H-NMR (250 MHz, DMSO) δ 7.98 (d, 2H, $\mathcal{J} = 8.0$ Hz, aromatic H), 7.75 (d, 2H, $\mathcal{J} = 8.1$ Hz, aromatic H), 7.41 (d, 1H, $\mathcal{J} = 16.2$ Hz, vinyl CH), 7.23 (3H, m, aromatic H, vinyl CH), 6.94 (d, 1H, aromatic H), 1.02–1.01(m, 18H, *tert*-butyl H), 0.25–0.24 (m, 12H, dimethyl H); ^{13}C-NMR(63 MHz, DMSO) δ167.6, 147.1, 146.8, 131.3, 131.1, 130.2 (2), 129.6, 126.7 (2), 126.0, 121.5, 120.9, 119.9, 26.2 (6), 18.7 (2), −3.7 (4). HRMS (FAB) 484.1861 *m/z*: ($[M]^+$, obsd), 484.2465 (calcd for $C_{27}H_{40}O_4Si_2$).

*General procedure for the amide coupling of acid with various amines (**12a**–**12j**)*. A stirred solution of acid **18** (0.1 g, 0.21 mmol), HATU (236 mg, 0.62 mmol) in CH_2Cl_2 (5 mL) was added appropriate amines (**19a**–**19n**) at room temperature, and the reaction mixture was stirred at same temperature for 16 h. The reaction mixture was quenched with slow addition of water (5 mL), extracted with ethyl acetate (10 mL) and washed with brine (10 mL) an anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give crude product, which was purified by flash silica chromatography to afford pure amide derivatives. The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give crude product, which was purified by flash silica chromatography to afford pure amide derivatives.

*(E)-4-{2-[3,4-Bis-(tert-butyldimethylsilanyloxy)-phenyl]vinyl}-N-allylbenzamide (**12a**)*. Yield: 66%. $R_f =$ 0.89 (hexanes/ethyl acetate, 1:1, v/v); IR υ_{max} ($CHCl_3$) 3324, 2928, 2857, 1638, 1607, 1596, 1542, 1510, 1472, 1421, 1299, 1253, 1124, 992, 962, 907, 839, 781 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ7.79 (d, 2H, $\mathcal{J} = 8.3$ Hz, aromatic H), 7.54 (d, 2H, $\mathcal{J} = 8.3$ Hz, aromatic H), 6.84 (d, 2H, $\mathcal{J} = 8.8$ Hz, aromatic H), 6.01–5.86 (m, 1H, vinyl CH), 5.30–5.15 (m, 2H, vinyl CH), 4.10 (t, 2H, $\mathcal{J} = 5.7$ Hz, N-CH_2), 1.02–1.01 (m, 18H, *tert*-butyl H), 0.23–0.21 (m, 12H, dimethyl H); ^{13}C NMR (63 MHz, $CDCl_3$) δ167.1, 147.5, 147.2, 141.0, 134.4, 132.8, 130.6, 127.5 (2), 126.4 (2), 125.6, 121.3, 120.4, 119.4, 116.7, 42.5, 26.1 (3), 26.0 (3), 18.6 (2), −4.0 (4). HRMS (FAB) 524.2736 *m/z*: ($[M + H]^+$, obsd), 524.2938 (calcd for $C_{30}H_{45}NO_3Si_2$).

*(E)-4-{2-[3,4-Bis-(tert-butyldimethylsilanyloxy)-phenyl]vinyl}-N-decylbenzamide (**12b**)*. Yield: 73%. $R_f =$ 0.23 (hexanes/ethyl acetate, 5:1, v/v); IR υ_{max}($CHCl_3$) 3320, 2928, 2856, 1634, 1608, 1957, 1548, 1511, 1471, 1421, 1298, 1253, 1221, 1164, 1125, 982, 953, 907, 839, 782 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ7.77 (d, 2H, $\mathcal{J} = 8.2$ Hz, aromatic H), 7.52 (d, 2H, $\mathcal{J} = 8.2$ Hz, aromatic H), 7.08–6.98 (m, 3H, aromatic H, vinyl CH), 6.93 (d, 1H, $\mathcal{J} = 16.3$ Hz, vinyl CH), 6.83 (d, 1H, $\mathcal{J} = 8.8$ Hz, aromatic H), 3.46–3.39 (m, 2H, *N*-CH_2), 1.60–1.58 (m, 2H, alkyl chain), 1.60–1.58 (m, 12H, alkyl chain), 1.02–0.97 (m, 18H, *tert*-butyl H), 0.93–0.88 (m, 5H, alkyl chain), 0.23–0.22 (m, 12H, dimethyl H); ^{13}C NMR (63 MHz, $CDCl_3$) δ167.3, 147.5, 147.2, 140.8, 133.2, 130.7, 130.5, 127.4 (2), 126.1 (2), 125.7, 121.3, 120.4, 119.4, 40.6, 32.0, 29.8, 29.7 (2), 29.5, 29.4, 27.1, 26.1 (3), 26.0 (3), 22.8, 18.6 (2), 14.2, −4.0 (4). HRMS (FAB) 624.4006 *m/z*:

([M + H]$^+$, obsd), 624.4190 (calcd for $C_{37}H_{61}NO_3Si_2$)

(E)-4-{2-[3,4-Bis-(tert-butyldimethylsilanyloxy)-phenyl]vinyl}-N-[3-(2-oxopyrrolidin-1-yl)propyl]benzamide (***12c***). Yield: 50%. $R_f = 0.54$ (CH_2Cl_2/Methanol, 10:1, v/v); IR υ_{max} ($CHCl_3$) 3329, 2954, 2929, 2857, 1667, 1607, 1510, 1471, 1295, 1253, 1229, 1124, 981, 906, 840, 782 cm$^{-1;}$ ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.92 (d, 2H, $\mathcal{J} = 8.0$ Hz, aromatic H), 7.54 (d, 2H, $\mathcal{J} = 8.0$ Hz, aromatic H) 7.08–6.99 (m, 3H, aromatic H, vinyl CH), 6.93 (d, 1H, $\mathcal{J} = 16.3$ Hz, vinyl CH), 6.83 (d, 1H, $\mathcal{J} = 8.8$ Hz, aromatic H), 3.41–3.39 (m, 6H, NH-CH_2, CH_2N-CH_2), 2.44–2.41 (m, 2H, pyrrolidone H), 2.09–2.04 (m, 2H, pyrrolidone H), 1.78–1.69. (m, 2H, -CH_2), 1.01–0.98 (m, 18H, *tert*-butyl H), 0.23–0.21 (m, 12H, dimethyl H); ^{13}C NMR (63 MHz, $CDCl_3$) δ176.4, 166.9, 147.4, 147.1, 140.7, 132.8, 130.8, 130.3, 127.6 (2), 126.3 (2), 125.9, 121.3, 120.4, 119.4, 39.7, 35.7, 31.0, 29.8, 26.3, 26.3 (6), 18.6 (2), 18.1, −3.9 (4). HRMS (FAB) 609.3529 *m/z*: ([M + H]$^+$, obsd), 609.3466 (calcd for $C_{34}H_{52}N_2O_4Si_2$).

(E)-4-{2-[3,4-Bis-(tert-butyldimethylsilanyloxy)-phenyl]vinyl}phenyl-cyclohexylamide (***12d***). Yield: 61%. $R_f = 0.83$ (hexanes/ethyl acetate, 2:1, v/v); IR υ_{max} ($CHCl_3$) 3313, 2928, 2856, 1630, 1541, 1510, 1463, 1298, 1254, 1124, 982, 907, 839, 782 cm$^{-1;}$ ^{1}H NMR (250 MHz, $CDCl_3$) δ7.36 (d, 2H, $\mathcal{J} = 8.20$ Hz, aromatic H), δ7.52 (d, 2H, $\mathcal{J} = 8.09$ Hz, aromatic H), 7.08–6.80 (m, 5H, aromatic H, vinyl CH), 3.99–3.96 (m, 1H, NH-CH), 2.04–1.99 (m, 2H, cyclohexane), 1.78–1.63 (m, 4H, cyclohexane), 1.26–1.18 (m, 4H, cyclohexane), 1.02–0.99 (m, 18H, *tert*-butyl H), 0.23–0.22 (m, 12H, dimethyl H); ^{13}C NMR (63 MHz, $CDCl_3$) δ166.4, 147.5, 147.2, 140.7, 133.5, 130.7,130.5, 127.4 (2), 126.2 (2), 125.7, 121.3, 120.4, 119.4, 48.8, 33.4 (2), 25.7, 26.1 (6), 25.1 (2), 18.6 (2), −3.9 (4). HRMS (FAB) 566.3291 *m/z*: ([M + H]$^+$, obsd), 566.3407 (calcd for $C_{33}H_{51}NO_3Si_2$).

(E)-4-{2-[3,4-Bis-(tert-butyldimethylsilanyloxy)-phenyl]vinyl}-N-[(furan-2-yl)methyl]benzamide (***12e***). Yield: 91%. $R_f = 0.63$ (hexanes/ethyl acetate, 2:1, v/v); IR υ_{max} ($CHCl_3$) 3318, 2929, 2857, 11641, 1606, 1596, 1510, 1471, 1421, 1299, 1253, 1220, 1125, 982, 906, 839, 781 cm$^{-1;}$ ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.79 (d, 2H, $\mathcal{J} = 8.3$ Hz, aromatic H), 7.54 (d, 2H, $\mathcal{J} = 8.3$ Hz, aromatic H), 7.39–7.37 (m, 1H, furfuran H), 7.10–6.81 (m, 5H, aromatic H, vinyl CH), 6.35–6.30 (m, 2H, furfuran H), 4.66 (d, 2H, $\mathcal{J} = 5.4$ Hz, N-CH_2), 1.01–1.00 (m, 18H, *tert*-butyl H), 0.23–0.19 (m, 12H, dimethyl H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 167.0, 151.4, 147.6, 147.2, 142.4, 141.1, 132.5, 130.7, 130.6, 127.6 (2), 126.4 (2), 125.6, 121.3, 120.5, 119.4, 110.6, 107.8, 37.1, 26.1 (6), 18.6 (2), −4.0 (4). HRMS (FAB)568.3083 *m/z*: ([M + H]$^+$, obsd), 568.3200 (calcd for $C_{32}H_{49}NO_4Si_2$).

(E)-4-{2-[3,4-Bis-(tert-butyldimethylsilanyloxy)-phenyl]vinyl}-N-(2-fluoro)-benzamide (***12f***). Yield: 50%. $R_f = 0.85$ (hexanes/ethyl acetate, 1:1, v/v); IR υ_{max} ($CHCl_3$) 3333, 2957, 2929, 2895, 2858, 1647, 1610, 1594, 1487, 1421, 1315, 1204,1277, 1237, 1124, 985, 967, 909, 839, 857, 781 cm$^{-1;}$ ^{1}H NMR (250 MHz, $CDCl_3$) δ7.78 (d, 2H, $\mathcal{J} = 8.3$ Hz, aromatic H), δ 7.51 (d, 2H, $\mathcal{J} = 8.3$ Hz, aromatic H), 7.43–7.37 (m, 1H, aromatic H) 7.27–7.21 (m, 1H, aromatic H), 7.21–6.80 (m, 7H, aromatic H, vinyl CH), 4.69 (d, 2H, $\mathcal{J} = 5.8$ Hz), 1.02–0.99 (m, 18H, *tert*-butyl H), 0.23–0.22 (m, 12H, dimethyl H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 167.2, 147.5, 147.2, 141.1, 132.5, 130.6, 130.5, 130.4, 129.5, 129.3, 127.5 (2), 126.4 (2), 125.6, 121.3, 120.5, 119.4, 115.6, 115.3, 38.1, 26.1 (6), 18.6 (2), −3.9 (4). HRMS (FAB) 592.2626 *m/z*: ([M + H]$^+$, obsd), 592.3000 (calcd for $C_{34}H_{46}NO_3Si_2$).

(E)-ethyl-3-(4-{2-[3,4-Bis-(tert-butyldimethylsilanyloxy)-phenyl]vinyl})-benzamino benzoate (***12g***). Yield: 73%. $R_f = 0.37$ (hexanes/ethyl acetate, 5:1, v/v), IR υ_{max} ($CHCl_3$) 3336, 2930, 2858, 1721, 1652, 1596, 1546, 1512, 1488, 1472, 1433, 1299, 1253, 1223, 1165, 1124, 982, 906, 840, 782, 757 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ8.19–8.08 (m, 2H, aromatic H), 7.87–7.80 (m, 3H, aromatic H), 7.57 (d, 2H, $\mathcal{J} = 8.3$ Hz, aromatic H), 7.46 (t, $\mathcal{J} = 7.9$ Hz, aromatic H), 7.12–7.00 (m, 3H, aromatic H, vinyl CH), 6.94 (d, 1H, $\mathcal{J} = 16.3$ Hz, vinyl CH), 6.85 (d, 1H, $\mathcal{J} = 8.8$ Hz, aromatic H), 4.39 (2H, $\mathcal{J} = 7.13$ Hz, O-CH_2), 1.40 (m, $\mathcal{J} = 7.13$ Hz, CH_3), 1.02–1.00 (m, 18H, *tert*-butyl H), 0.24–0.23 (m, 12H, dimethyl H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 166.4, 165.8, 147.6, 147.2, 141.5, 138.4, 132.77, 131.3, 131.0, 129.2, 127.7 (2), 126.5 (2), 125.5, 125.4, 124.9, 121.3 (2), 120.5, 119.5, 61.2, 26.1, 26.0, 18.6 (6), 14.4 (2), −3.9 (4). HRMS (FAB) 632.3063 *m/z*: ([M + H]$^+$, obsd), 632.3149 (calcd for $C_{36}H_{49}NO_5Si_2$).

(E)-4-{2-[3,4-Bis-(tert-butyldimethylsilanyloxy)-phenyl]vinyl}-N,N-(1-benzoyl)-piperazinamide (***12h***). Yield: 74%. $R_f = 0.56$ (CH_2Cl_2/Methanol, 10:1, v/v); IR ν_{max} ($CHCl_3$) 2955, 2928, 2857, 1633, 1511, 1461, 1422, 1287, 1252, 1125, 1003, 906, 839, 782 cm$^{-1;}$ ^{1}H NMR (250 MHz, $CDCl_3$) δ7.54 (d, 2H, $\mathcal{J} = 8.0$ Hz, aromatic H), 7.41–7.38 (m, 7H, aromatic H), 7.07–8.80 (m, 5H, aromatic H, vinyl CH), 3.66 (s, 8H, piperazine H), 1.02–1.00 (m, 18H, *tert*-butyl H), 0.23–0.22 (m, 12H, dimethyl H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 170.8, 170.7, 147.5, 147.1, 139.8, 135.2, 133.4, 130.6, 130.4, 130.2, 128.7 (2), 127.8 (2), 127.2 (2), 126.4 (2), 125.6, 121.3, 120.3, 119.4, 26.0 (6), 18.6 (2), −4.0 (4). HRMS (FAB) 657.3398 *m/z*: ([M + H]$^+$, obsd), 657.3466 (calcd for $C_{33}H_{52}N_2O_4Si_2$).

*(E)-4-{2-[3,4-bis-(tert-butyl-dimethyl-silanyloxy) phenyl]vinyl}-(4-methylpiperidin-1-yl)methanone (**12i**)*. %Yield: 63%. $R_f = 0.72$ (hexanes/ethyl acetate, 1:1, v/v), IR υ_{max} ($CHCl_3$) 2954, 2927, 2857, 1635, 1568, 1508, 1471, 1458, 1425, 1303, 1275, 1251, 1124, 970, 906, 839, 782 $cm^{-1;}$ ^1H NMR (250 MHz, $CDCl_3$) δ7.51 (d, 2H, $J = 8.2$ Hz, aromatic H), 7.39 (d, $J = 8.2$ Hz, aromatic H), 7.05–6.98 (m, 3H, aromatic H, vinyl CH), 6.92 (d, 1H, $J = 16.3$ Hz, vinyl CH), 6.84 (d, 1H, $J = 8.8$ Hz, aromatic H), 4.67 (s, 1H, piperidine H), 3.90 (s, 1H, piperidine H), 2.96–2.82 (m, 2H, piperidine H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 170.31, 147.34, 147.14, 139.00, 135.04, 130.83, 129.83, 127.54 (2), 126.3 (2), 125.9, 121.3, 120.3, 119.4, 31.3 (2), 29.8, 26.1 (6), 21.9 (2), 18.6 (2), −3.9 (4). HRMS (FAB) 566.3105 *m/z*: ($[M + H]^+$, obsd), 566.3407 (calcd for $C_{33}H_{51}NO_3Si_2$)

*(E)-(4-{2-[3,4-Bis-(tert-butyl-dimethyl-silanyloxy) phenyl]vinyl}-(4-benzylpiperidin-1-yl)methanone (**12j**)*. Yield: 85%. $R_f = 0.65$ (hexanes/ethyl acetate, 2:1, v/v); IR ν_{max} ($CHCl_3$) 2951, 2929, 2884, 2857, 1721, 1632, 1512, 1471, 1429, 1293, 1253, 1164, 1126, 982, 840, 782 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ7.53 (d, 2H, $J = 8.1$ Hz, aromatic H), 7.41 (d, $J = 8.2$ Hz, aromatic H), 7.32–7.27 (m, 2H, aromatic H), 7.23–7.14 (m, 3H, aromatic H), 7.08–7.00 (m, 3H, aromatic H), 6.93 (d, 1H, $J = 16.4$ Hz, vinyl CH), 6.84 (d, 1H, $J = 8.8$ Hz, aromatic H), 4.71 (s, 1H, piperidine H), 3.80 (s, 1H, piperidine), 2.92–2.74 (m, 2H, piperidine H), 2.60 (d, 2H, $J = 6.7$ Hz, CH_2-Ph), 1.81–1.66 (m, 4H, piperidine H), 1.38–1.28 (m, 1H, piperidine H), 1.02–1.00 (m, 18H, *tert*-butyl H), 0.23–0.20 (m, 12H, dimethyli H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 170.2, 147.3, 147.1, 140.0, 139.0, 134.8, 130.8, 129.8, 129.1 (2), 128.4 (2), 127.5 (2), 126.2 (2), 125.9, 121.3, 120.2, 119.35, 43.1, 38.4, 26.0 (6), 18.6, 18.5, −4.0 (4). HRMS (FAB) 642.3265 *m/z*: ($[M + H]^+$, obsd), 642.3720 (calcd for $C_{39}H_{55}NO_3Si_2$).

*General procedure for the preparation of deprotected dihydroxy stilbenes (**13**–**22**)*

Method A. To a stirred solution of **12a**–**12j** (0.10 mmol) in dry THF (5 mL) was added dropwise TBAF (0.25 mmol, 0.25 ml, 1 M solution in THF) at 0 °C under nitrogen atmosphere and the mixture was stirred at room temperature for 30 min. The reaction mixture was quenched with water and acidified with 10% HCl. The mixture is diluted with ethyl acetate (10 mL) and washed with brine (7 mL). The organic phase was separated, and the aqueous phase was extracted with ethyl acetate (2 × 10 mL). The combined organic phases were washed with brine (15 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to yield dihydroxy stilbenes, which were purified by flash column chromatography (silica gel, CH_2Cl_2/Methanol, 15/1–10/1, v/v) to give **13**–**22**.

Method B. To a stirred solution of **12a**–**12j** (0.10 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise TFA (1mL) at room temperature under nitrogen atmosphere and the mixture was stirred for 1 h. The residue TFA was removed by reduced pressure. The resulting mixture was purified by flash column chromatography (silica gel, CH_2Cl_2/Methanol, 15/1-10/1, v/v) to give 13–22.

*(E)-4-[2-(3,4-Dihydroxyphenyl)vinyl]-N-allylbenz amide (**13**)*. Yield: 64%. $R_f = 0.06$ (CH_2Cl_2/Methanol, 20:1, v/v); ^1H NMR (250 MHz, CD_3OD) δ 7.82 (d, 2H, $J = 8.3$ Hz, aromatic H), 7.57 (d, 2H, $J = 8.2$ Hz, aromatic H), 7.20–6.89 (m, 4H, aromatic H, vinyl CH), 6.63 (d, 1H, $J = 8.2$ Hz, aromatic H), 6.01–5.86 (m, 1H, vinyl CH), 5.27–5.11 (m, 2H, vinyl CH), 4.00–3.98 (m, 2H, N-CH_2); ^{13}C NMR (63 MHz, CD_3OD) δ 169.7, 147.1, 146.6, 142.8, 135.6, 133.4, 132.1, 130.6, 128.7 (2), 127.1 (2), 125.5, 120.7, 116.4, 116.2, 114.1, 43.2.; HRMS (FAB): *m/z* 296.1238 ($[M + H]^+$, obsd), 296.1208 (calcd for $C_{18}H_{17}NO_3$).

*(E)-4-[2-(3,4-Dihydroxyphenyl)vinyl]-N-decylbenz amide (**14**)*. Yield: 60%. $R_f = 0.47$ (CH_2Cl_2/Methanol, 10:1, v/v); IR ν_{max} ($CHCl_3$) 3317, 2951, 2923, 2851, 1734, 1630, 1602, 1541, 1524, 1466, 1439, 1269, 963, 859 $cm^{-1;}$ ^1H NMR (250 MHz, CD_3OD) δ 7.79 (d, 2H, $J = 8.3$ Hz, aromatic H), 7.58 (d, 2H, $J = 8.3$ Hz, aromatic H), 7.17 (d, 1H, $J = 16.3$ Hz, vinyl CH), 7.05–6.89 (m, 3H, aromatic H, vinyl CH), 6.77 (d, 1H, $J = 8.2$ Hz, aromatic H), 3.39–3.36 (m, 2H, N-CH_2), 1.62–1.59 (m, 2H, alkyl chain), 1.34–1.29 (m, 12H, alkyl chain), 1.00–0.87 (m, 5H, alkyl chain); ^{13}C NMR (63 MHz, CD_3OD) δ169.7, 147.10, 146.59, 142.7, 133.8, 132.1, 130.2, 128.7 (2), 127.0 (2), 125.5, 120.7, 116.4, 114.1, 41.1, 33.1, 30.2 (2), 30.5, 30.5 (2), 28.1, 23.7, 14.5: HRMS (FAB): *m/z* 396.2532 ($[M + H]^+$, obsd), 396.2460 (calcd for $C_{25}H_{33}NO_3$).

*(E)-4-[2-(3,4-Dihydroxyphenyl)vinyl]-N-[3-(2-oxo pyrrolidin-1-yl)propyl]benzamide (**15**)*. Yield: 66%. $R_f = 0.41$ (CH_2Cl_2/Methanol, 10:1, v/v); IR ν_{max} ($CHCl_3$) 3444, 2924, 2958, 2853, 1732, 1646, 1455, 1383, 1242, 1123, 1086, 1025 $cm^{-1;}$ ^1H NMR (250 MHz, CD_3OD) δ 7.82 (d, 2H, $J = 8.4$ Hz, aromatic H), 7.59 (d, 2H, $J = 8.4$ Hz, aromatic H), 7.17 (d, 1H, $J = 16.3$ Hz, vinyl CH), 7.05–6.89 (m, 3H, aromatic H, vinyl CH), 6.77 (d, 1H, $J = 8.2$ Hz, aromatic H), 3.51–3.46 (m, 2H, NH-CH_2,), 3.40–3.29 (m, 4H, CH_2N-CH_2), 2.40–2.36 (m, 2H, pyrrolidone H), 2.11–2.02 (m, 2H, pyrrolidone H), 1.87–1.80 (m, 2H, CH_2); ^{13}C NMR (63 MHz, CD_3OD) δ 178.1, 169.8, 147.1, 146.6, 142.8, 133.5, 132.2, 130.6, 128.7 (2), 127.1 (2), 125.5, 120.7, 116.5, 114.1, 41.2, 38.1, 32.0, 30.8, 27.9, 18.8: HRMS (FAB): *m/z* 380.1146 ($[M]^+$, obsd), 380.1736 (calcd for $C_{22}H_{24}N_2O_4$).

*(E)-4-[2-(3,4-Dihydroxyphenyl)-vinyl]phenyl-cyclohexylamide (**16**)*. Yield: 63%. $R_f = 0.28$ (CH_2Cl_2/Methanol, 10:1, v/v); IR υ_{max} ($CHCl_3$) 3393, 2930, 2854, 1724, 1628, 1603, 1526, 1507, 1447, 1374, 1257 cm^{-1}; ^1H NMR (250 MHz, CD_3OD) δ7.78 (d, 2H, $J = 8.3$, aromatic H),7.55 (d, 2H, $J = 8.3$, aromatic H), 7.15 (d, 1H, $J = 16.3$ Hz, vinyl CH), 7.04–6.89 (m, 3H, aromatic H, vinyl CH), 6.78 (d, 1H, $J = 8.2$ Hz, aromatic H), 3.87–3.85 (m, 1H, NH-CH), 2.02–1.93 (m, 2H, cyclohexane), 1.79–1.66 (m, 4H, cyclohexane), 1.42–1.35 (m, 4H, cyclohexane); ^{13}C NMR (63 MHz, $CDCl_3$) δ160.2, 138.1, 137.6, 133.6, 125.0, 123.0, 121.6, 120.9, 119.7 (2), 118.0 (2), 116.5, 111.7, 107.5, 105.1, 41.5, 24.7 (2), 17.6, 17.4 (2): HRMS (FAB): *m/z* 338.1785 ($[M + H]^+$, obsd), 338.1678 (calcd for $C_{21}H_{23}NO_5$).

*(E)-4-[2-(3,4-Dihydroxyphenyl)vinyl]-N-[(furan-2-yl)methyl]benzamide (**17**)*. Yield: 73%. $R_f = 0.1$ (CH_2Cl_2/Methanol, 20:1, v/v); IR ν_{max} ($CHCl_3$) 3431, 2924, 2958, 2853, 1726, 1634, 1601, 1523, 1442, 1289, 1189, 1112, 1043, 1101 $cm^{-1;}$ ^1H NMR (250 MHz, CD_3OD) δ 7.81 (d, 2H, $J = 8.4$ Hz, aromatic H), 7.55 (d, 2H, $J = 8.4$ Hz, aromatic H), 7.42 (m, 1H, furfuran H), 7.15 (d, 1H, $J = 16.3$ Hz, vinyl CH), 7.05–6.88 (m, 3H, aromatic H, vinyl CH), 6.78 (d, 1H, $J = 8.2$ Hz, aromatic H), 6.35–6.28 (m, 2H, furfuran H), 4.55 (m, 2H, NCH_2); ^{13}C NMR (63 MHz, CD_3OD) δ169.7, 153.2, 147.1, 146.6, 143.2, 142.8, 133.2, 130.6, 128.8 (2), 127.0 (2), 125.4, 120.7, 116.4, 114.1, 111.4, 108.1, 37.6: HRMS (FAB): *m/z* 336.1097 ($[M + H]^+$, obsd), 335.1158 (calcd for $C_{20}H_{17}NO_4$).

*(E)-4-[2-(3,4-Dihydroxyphenyl)vinyl]-N-(2-fluoro)-benzamide (**18**)*. Yield: 64%. $R_f = 0.28$ (CH_2Cl_2/Methanol, 10:1, v/v); IR ν_{max} ($CHCl_3$) 3349, 2924, 2853, 1726, 1636, 1601, 1541, 1505, 1456, 1374, 1270, 1190, 1108, 962, 757 $cm^{-1;}$ ^1H NMR (250 MHz, CD_3OD) δ 7.83 (d, 2H, $J = 8.0$, aromatic H), 7.57 (d, 2H, $J = 8.6$ Hz, aromatic H), 7.42–7.23 (m, 3H, aromatic H) 7.15–6.89 (m, 6H, aromatic H, vinyl CH), 6.78 (d, 1H, $J = 8.1$ Hz, aromatic H), 4.63 (s, 2H, CH_2);^{13}C NMR (63 MHz, CD_3OD) δ170.0, 147.1, 146.6, 142.9, 133.3, 132.2, 130.6, 130.2, 130.0, 128.8 (2), 128.3, 127.1 (2), 125.5, 125.3, 120.7, 116.5, 116.3, 115.9, 114.1, 38.3: HRMS (FAB): *m/z* 364.1 ($[M + H]^+$, obsd), 364.1271 (calcd for $C_{22}H_{18}FNO_3$).

*(E)-Ethyl-3-{4-[2-(3,4-dihydroxyphenyl)vinyl]}-benz amino benzoate (**19**)*. Yield: 74%. $R_f = 0.26$ (CH_2Cl_2/Methanol, 10:1, v/v); IR ν_{max} 3345, 2924, 2853, 1716, 1651, 1598, 1544, 1437, 1290, 1259, 1108, 1112, 1025, 1002, 957, 756 $cm^{-1;}$ ^1H NMR (250 MHz, CD_3OD) δ 8.40–8.39 (m, 1H, aromatic H), 7.99–7.90 (m, 3H, aromatic H), 7.80 (d, 1H, $J = 8.3$ Hz, aromatic H), 7.63 (d, 2H, $J = 8.3$ Hz, aromatic H), 7.49 (t, 1H, $J = 7.9$ Hz, aromatic H), 7.20 (d, 1H, $J = 16.3$ Hz, vinyl CH), 7.06–6.90 (m, 3H, aromatic H, vinyl CH), 6.78 (d, 1H, $J = 8.2$ Hz, aromatic H), 4.41 (q, 2H, $J = 7.1$ Hz, O-CH_2), 1.42 (t, 3H, $J = 7.1$ Hz, CH_3); ^{13}C NMR (63 MHz, CD_3OD) δ 168.6, 167.8, 147.2, 146.6, 143.2, 140.4, 133.7, 130.5, 132.6, 132.2, 129.9 (2), 129.1 (2), 127.1, 126.5, 126.2, 125.4, 123.0, 120.8, 116.5, 114.1, 62.3, 14.6: HRMS (FAB): *m/z* 404.1436 ($[M + H]^+$, obsd), 404.1420 (calcd for $C_{24}H_{21}NO_5$).

*(E)-4-[2-(3,4-Dihydroxyphenyl)vinyl]-N,N-(1-benzoyl)-piperazinamide (**20**)*. Yield: 64%. $R_f = 0.46$ (CH_2Cl_2/Methanol, 10:1, v/v); IR ν_{max} ($CHCl_3$) 3403, 2924, 2853, 1734, 1560, 1508, 1460, 1431, 1372, 1256, 1002 $cm^{-1;}$ ^1H NMR (250 MHz, CD_3OD) δ 7.60 (d, 2H, $J = 8.1$ Hz, aromatic H), 7.46–7.39 (m, 7H, aromatic H), 7.15 (d, 1H, $J = 16.3$ Hz, vinyl CH), 7.03–6.88 (m, 3H, aromatic H, vinyl CH), 6.77 (d, 1H, $J = 8.1$ Hz, aromatic H), 3.91–3.61 (m, 8H, piperazine H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 172.8 (2), 147.1, 146.6, 141.6, 136.4, 134.2, 131.9, 131.4, 130.6, 129.8 (2), 128.8 (2), 128.2 (2), 127.2 (2), 125.4, 120.6, 116.4, 114.1, 30.8 (4): HRMS (FAB): *m/z* 429.1660 ($[M + H]^+$, obsd), 429.1736 (calcd for $C_{26}H_{24}N_2O_4$).

*(E)-4-[2-(3,4-Dihydroxy-phenyl)vinyl]-(4-methylpiperidin-1-yl)methanone (**21**)*. $R_f = 0.49$ (CH_2Cl_2/Methanol, 10:1, v/v), IR υ_{max} ($CHCl_3$) 3408, 2957, 2924, 2854, 1736, 1601, 1508, 1446, 1373, 1273, 1251, 1197, 1114, 1045, 969 $cm^{-1;}$ ^1H NMR (250 MHz, CD_3OD); δ7.58 (d, 2H, $J = 8.0$ Hz, aromatic H), 7.37 (d, 2H, $J = 8.0$ Hz, aromatic H), 7.17–6.88 (m, 4H, aromatic H, vinyl CH), 6.77 (d, 1H, $J = 8.2$ Hz, aromatic H), 4.61–4.65 (m, 1H, piperidine H), 3.59–3.50 (m, 1H, piperidine H), 2.83–2.78 (m, 2H, piperidine H), 1.72–1.67 (m, 4H, piperidine H), 1.26 (s, 3H, -CH_3); ^{13}C NMR (63 MHz, CD_3OD) δ172.4, 147.0, 146.6, 141.1, 135.3, 130.7, 131.7, 128.4 (2), 127.1 (2), 125.6, 120.6, 116.5, 114.0. 32.2, 22.0: HRMS (FAB): *m/z* 348.1210 ($[M + Na]^+$, obsd), 348.1314 (calcd for $C_{19}H_{19}NO_4$).

*(E)-4-[2-(3,4-Dihydroxy-phenyl)vinyl]-(4-benzylpiperidin-1-yl)methanone (**22**)*. Yield: 68%. $R_f = 0.46$ (CH_2Cl_2/Methanol, 10:1, v/v); IR υ_{max} ($CHCl_3$) 3395, 2923, 2851, 1593, 1558, 1445, 1838, 1237, 1086, 1021, 963 cm^{-1}; ^1H NMR (250 MHz, CD_3OD) δ7.59 (d, 2H, $J = 8.2$ Hz, aromatic H), 7.37 (d, $J = 8.2$ Hz, aromatic H), 7.32–7.27 (m, 2H, aromatic H), 7.23–7.14 (m, 3H, aromatic H), 7.29–6.88 (m, 9H, aromatic H), 6.77 (d, 1H, $J = 8.2$ Hz, aromatic H), 4.37 (m, 1H, piperidine H), 3.57 (m, 1H, piperidine H), 2.71–2.60 (2H, piperidine H), 2.60 (d, 2H, $J = 6.6$ Hz, CH_2-Ph), 1.74–1.55 (m, 4H, piperidine H), 1.21–1.18 (m, 1H, piperidine H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 168.8, 145.9, 145.5, 140.1, 138.7, 134.5, 130.1, 129.0 (2), 128.4, 128.2 (2), 127.3 (2), 125.9 (2), 124.1, 118.9, 115.7, 113.5, 42.1, 37.6: HRMS (FAB): *m/z* 414.2081 ($[M + H]^+$, obsd), 414.1991 (calcd for $C_{27}H_{27}NO_3$).

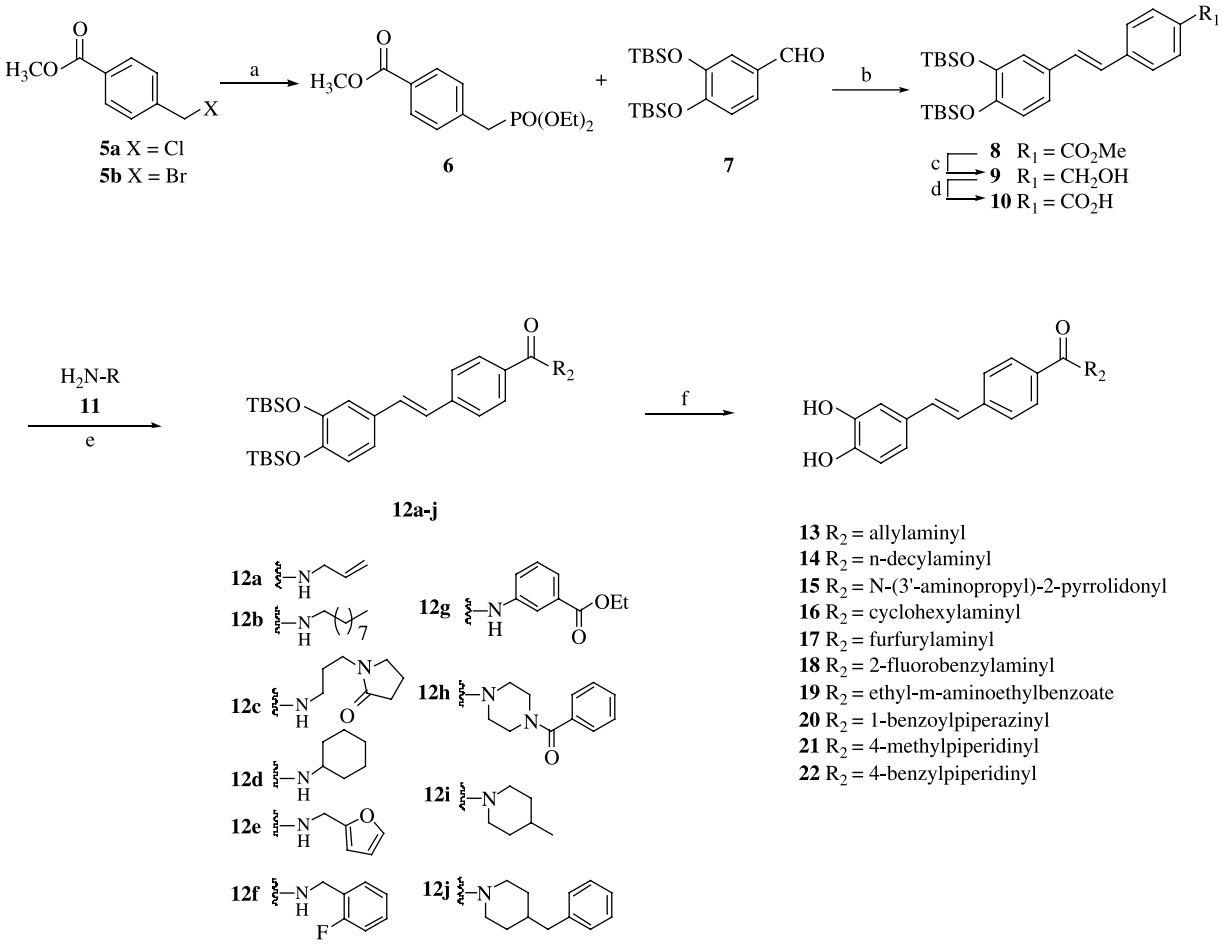
Measurement of anticancer activity

Human cancer cell lines of the lung (A549), the ovarian (SK-OV-3), the melanoma (SK-MEL-2), the brain (XF498) and the colon (HCT15) were used for cytotoxicity test in vitro using SRB (sulforhodamin B) assay [21]. They were maintained as stocks in RPMI 1640 (Gibco) supplemented with 10% fetal bovine serum (Gibco). Cell cultures were passaged once or twice weekly by using trypsin-EDTA to detach the cells from their culture flasks. The rapidly growing cells were harvested, counted, and incubated at the appropriate concentration ($1-2 \times 10^4$ cells/well) in 96-well plates. After incubation for 24 h, the compounds dissolved in culture medium were applied to the culture wells in triplicate and incubated for 48 h at 37°C under 5% CO_2 /95% air atmosphere in a humidified incubator. The culture cells were fixed with 10% cold TCA and stained with 0.4% SRB dissolved in 1% acetic acid. After solublizing the bound stain with 10 mM of unbuffered Trisma base solution (pH 10.5) using gyratory shaker, the absorbance at 520 nm was measured spectrophotometrically in a microplate reader. Cytotoxic activity was evaluated by measuring the concentration of a compound which was required to inhibit the protein synthesis by 50% (IC_{50}) and compared with that of adriamycin.

Results and discussion

Chemistry

A series of stilbene derivatives (**13**–**22**) was prepared in 6 steps (Scheme 1) using commercially available methyl 4-(chloro or bromomethyl)benzoate (**5a** or **5b**) as a starting material. Compounds **5a** and **5b** were converted to phosphonate 6 by treatment with triethyl phosphite at 160 °C for 3 h in 85% yield [22] Compound **6** was coupled with freshly prepared aldehyde 7 through a Wadsworth-Horner-Emmons reaction in order to obtain ester **8** in good yield. The *n*-butyllithium (*n*-BuLi) used as a base resulted in the production of ester **8**, mostly the *E* isomer, while sodium hydride (NaH, 60% dispersion) afforded ester



Scheme 1. Reagents and conditions: (a) $P(OEt)_3$, 160 °C, 3 h, 85%; (b) **7**, *n*-BuLi (1.3 equiv), THF, −20 °C, 1 h; then rt, 12 h, 86%, or **7**, NaH (1.3 equiv), CH_2Cl_2, 0 °C, 16 h, 80% (*E*:*Z* = 25:1); (c) DIBAL-H (2.5equiv), CH_2Cl_2, −78 °C, 1 h, 77%; (d) DMSO, $(COCl)_2$, TEA, CH_2Cl_2, −78 °C, 1 h, 89% or TPAP (5 mol %), NMO, THF, rt 30 min, 90%, then $NaClO_2$ (3.0 equiv), NaH_2PO_4 (3.0 equiv), 2-methyl-2-butene, *t*-BuOH, 0 °C, 16 h, 96%; (e) HATU (1.5 equiv), CH_2Cl_2, rt, 16 h, 50%–91%; (f) 20% TFA, CH_2Cl_2, rt, 1 h, 50–80%, or TBAF (2.5 equiv), THF, 0 °C, 30 min, (64%–73%).

Table I. *In vitro* anticancer activity of new stilbene derivatives **13**–**22**.

Compounds	IC_{50} (μM)[a]				
	A549[b]	SK-OV-3	SK-MEL-2	XF-498	HCT-15
13	–	36.6	–	56.5	–
14	16.4	21.7	14.2	19.7	21.2
15	27.9	20.2	26.0	25.8	20.0
16	10.4	**6.8**	12.4	13.6	17.2
17	25.6	26.2	22.4	28.0	16.4
18	12.7	9.1	16.2	15.7	21.5
19	**8.7**	**5.7**	10.4	11.4	14.4
20	20.8	21.2	16.8	14.9	16.1
21	–	21.6	–	21.6	–
22	45.7	26.8	43.0	25.4	47.4
Resveratrol[c]	36.9	42.6	41.4	32.1	35.6
Adriamycin[d]	2.8	4.3	2.6	2.1	7.6

[a] IC_{50}: Concentration that produces 50% inhibition of proliferation after 72 h of incubation; [b] Cell lines: A549: Human lung tumour, SK-OV-3: Human ovarian tumour, SK-MEL-2: Human melanoma tumour, XF 498: Human brain tumour, HCT-15: Human colon tumour; [c] Resveratrol: Reference compound; [d] Adriamycin: Standard compound.

8 in a 25:1 ratio of *E*:*Z*, respectively, which were cleanly separated by flash column chromatography. The reduction of ester **8** by diisobutylaluminum hydride (DIBAL-H) in dichloromethane afforded alcohol **9** in 77% yield. The oxidation of alcohol **9** through Swern oxidation [23] or tetrapropylammonium perruthenate (TPAP)/*N*-methylmorpholine (NMO) [24] gave aldehydes in 89% and 90% yields, respectively, which was subsequently treated with sodium chlorite ($NaClO_2$) and sodium dihydrogen phosphate (NaH_2PO_4) in *t*-BuOH to give acid **10** in high yield. Acid **10** was coupled with several amines [allyl amine, *N*-decyl amine, *N*-(3′-aminopropyl)-2-pyrrolidone, *N*-cyclohexyl amine, furfuryl amine, 2-fluorobenzylamine, ethyl-*m*-aminoethylbenzoate, 1-benzoylpiperazine, 4-methylpiperidine, 4-benzylpiperidine] in the presence of 2-(7-aza-1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluroniumhexafluorophosphate (HATU)/CH_2Cl_2 [25] to afford amides **12a**–**j**, which were subjected to the removal of TBS from dihydroxy groups to produce new *trans*-stilbene derivatives **13**–**22** in good yields (Scheme 1).

Biological activity

The *in vitro* cytotoxicities of stilbene derivatives **13**–**22** were evaluated against five human cancer cell lines, A549 (non-small cell lung carcinoma), SK-OV-3 (ovarian carcinoma), SK-MEL-2 (melanoma), XF498 (CNS carcinoma) and HCT-15 (colon carcinoma) using the SRB (sulforhodamine B) method (Table I). Compounds **16** and **19** showed more cytotoxic activity than the other compounds, and the cytotoxic activity of compound **19** was especially superior to that of resveratrol against the human tumour cell lines tested. The IC_{50} value of compound **19** was 5.7 μM against the SK-OV-3, whereas that of adriamycin was 4.3 μM (Table I).

Conclusion

A series of new stilbene derivatives **13**–**22** was prepared, and the anticancer activities of the derivatives were evaluated *in vitro*. The synthetic strategies involved the use of the well-known Wadsworth-Horner-Emmons condensation and coupling reactions. We found that compound **19** exhibited the most potent anticancer activity with an IC_{50} value of 5.7 μM-14.4 μM, and compound **16** and **19** showed efficacies comparable to the anticancer activity of adriamycin *in vitro* in the SK-OV-3 cell line.

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