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Synthesis and Biological Evaluation of 1,3,4-Oxadiazole Fused Resveratrol Derivatives as Anticancer Agents

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A novel target compounds (**9a-j**) were design and synthesized and characterized by ^{1}H & ^{13}C NMR, ESI-MS spectral analysis. Further, these were tested for their anticancer activity against three human cancer cell lines such as MCF-7, MDA MB-231 (breast), A549 (Lung) and adriamycin was used as positive control. Among ten compounds, two compounds like **9b** and **9j** were showed a significant anticancer activity compared to control drug.

Keywords: 1,3,4-Oxadiazoles, Resveratrol, Combretastatin A-4, Zibotentan, Anticancer activity.

INTRODUCTION

Resveratrol (Fig. 1) is a biological active naturally occurring compound and was isolated in 1940 from the roots of white hellebore [1]. Resveratrol is a naturally occurring polyphenol produced by various plant species and possesses a broad variety of pharmacological activities and acts as a protective substance to avoid the environmental or insect damage. It also persuades many systems in the body and is therefore considered as a multitarget molecule. Resveratrol (**1**) is a hydrophilic molecule containing three hydroxyl groups and its half life is only 8-14 min which affects its bioavailability and efficiency. It is available in grapevines, pines, pomegranates, soy beans and in peanuts [2] and was showed a different pharmacological activities such as anticancer [3], anti-inflammatory [4], antibacterial [5], antifungal [6], heart protecting [7], antiviral [8], estrogenic [9], liver protecting [10], platelet anti-aggregating [11], nerve protecting [12], endothelin antagonist and bone metabolism [13]. Combretastatin A-4 (**2**) is one of the naturally occurring scaffold and was isolated from *Combretum caffrum* [14,15]. It shows anticancer cancer activity by inhibit tubulin polymerization [16].

On the other hand, 1,3,4-oxadiazoles are small heterocyclic compounds and many researchers have attracted due to its significant biological activities, which were demonstrated a wide range of biological properties including antitumoral [17], antibacterial [18], antiviral [19], antitubercular [20], insecticidal [21], antifungal [22,23], inflammatory [24], analgesic [25], anti-HIV [26], tyrosinase inhibitors [27] and anticonvulsant

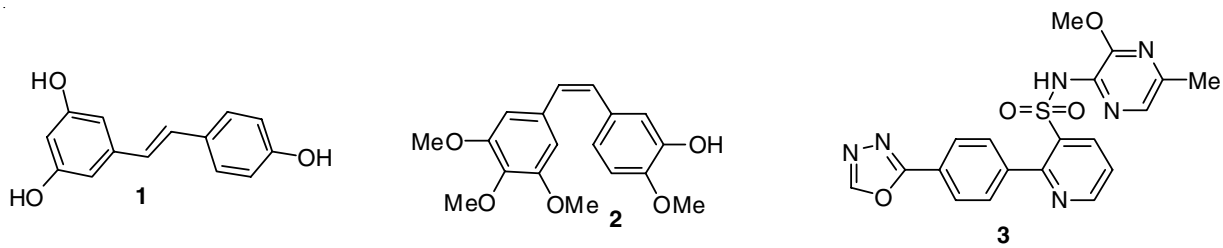


Fig. 1

[28], antimicrobial activity [29] and human serum albumin [30] activities [31]. The 1,3,4-oxadiazole unit containing zibotentan (**3**) is a anticancer drug used for treatment of cancer [32].

In recent years, design of hybrid molecules comprising two pharmacophores in one molecule has gained much interest. The hybrid molecules are classified as linked, merged and fused hybrid depending upon the incorporation of starting molecules. Resveratrol has also been combined with other biologically active compounds by using hybrid molecular techniques. Current modifications in the resveratrol deal with the improvement of pharmacokinetic properties in addition to the enhancement of pharmacological activities [33]. Resveratrol with oxadiazole hybrid molecules demonstrated multiple activities [34]. Enchanting into account the above results, we have designed and synthesized a novel series of oxadiazole fused resveratrol (**9a-j**) derivatives and were characterized by ^{1}H & ^{13}C NMR, ESI-MS spectral analysis. Further, all the newly synthesized compounds were evaluated for their *in vitro* anticancer activity.

EXPERIMENTAL

All chemicals and reagents were obtained from Aldrich (Sigma-Aldrich, St. Louis, USA), Lancaster (Alfa Aesar, Johnson Matthey Company, Ward Hill, USA) and used without further purification. Reactions were monitored by TLC, performed on silica gel glass plates containing 60 F_{254} and visualization on TLC wasachieved by UV light or iodine indicator. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker UXNMR/XWIN-NMR and Varian (400 MHz, 300 MHz)instrument.Chemical shifts (δ) are reported in ppm downfield from internal TMS standard. ESI spectra were recorded on Micro mass, QuattroLC using ESI+ software with capillary voltage 3.98 kV and ESI mode positive ion trap detector. Melting points were determined with an electrothermal melting point apparatus and are uncorrected.

(*E*)-Ethyl 2-(4-(3,5-dimethoxystyryl)phenoxy)acetate (6): (*E*)-4-(3,5-Dimethoxystyryl)phenol (**4**) (10 g, 39.04 mmol) was dissolved in 30 mL of DMF, followed by slowly addition of ethyl bromoacetate (**5**) (7.82 g, 46.84 mmol) and K_2CO_3 (10.79 g, 78.08 mmol). The reaction mixture was stirred at room temperature for 6 h. After completion of the reaction, K_2CO_3 was removed by filtration then extracted with ethyl acetate and washed with water and brine solution. The ethyl acetate layer was evaporated under vacuum to afford crude product. The crude product was purified by column chromatography with ethyl acetate/hexane (2:8) to afford pure compound **6**, 12.1 g (90.6%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.78 (t, 3H), 3.76 (s, 6H), 4.46 (q, 2H), 4.76 (s, 2H), 6.36 (s, 1H), 6.72 (d, 2H, *J* = 8.36 Hz), 6.75 (s, 2H), 7.05 (d, 1H, *J* = 16.3 Hz), 7.20 (d, 1H, *J* = 16.3 Hz), 7.50 (d, 2H, *J* = 8.36 Hz);MS (ESI): 343 $[M+H]^+$.

(*E*)-2-(4-(3,5-Dimethoxystyryl)phenoxy)acetohydrazide (7): A mixture of compound (**6**) (11 g, 32.1mmol) and hydrazine hydrochloride (6.4 g,128.4 mmol) in ethanol (100 mL) was refluxed for 6 h. The crude product was obtained after distilling off the ethanol and add cold water (100 mL) to get this product (**7**) was employed in the next step without further purification to give compound **7**. Yield: 8.6 g (83.1%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.76 (s, 6H), 4.76 (s, 2H), 6.36 (s, 1H), 6.72 (d, 2H, *J* = 8.4 Hz), 6.75 (s, 2H), 7.06 (d, 1H, *J* = 16.4 Hz), 7.21 (d, 1H, *J* = 16.4 Hz), 7.52 (d, 2H, *J* = 8.4 Hz), 7.67 (t, 2H), 8.36 (bs, 2H); MS (ESI): 329 $[M+H]^+$.

(*E*)-2-((4-(3,5-Dimethoxystyryl)phenoxy)methyl)-5-phenyl-1,3,4-oxadiazole (9a): Compound **7** (500 mg, 1.52 mmol) was dissolved in DMF (5mL) and add $POCl_3$ (5 mL) and benzoic acid (**9a**) (204 mg, 1.67 mmol). The reaction mixture was heated to 80 ºC for 6 h. After completion of reaction, neutralized with aqueous Na_2CO_3 (35 mL) and then workup with ethyl acetate (2 × 50 mL) and washed with water(25 mL) and brine solution(25 mL). The organic layer dried it with Na_2SO_4 and evaporated. The crude compound was purified by column chromatography with ethyl acetate/hexane (4:6) to afford pure compound **9a**. Yield: 410 mg (65%); m.p. 210-212 ºC, ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.76 (s, 6H), 4.90 (s, 2H), 6.37 (s, 1H), 6.73-6.79 (m, 4H), 7.07 (d, 1H, *J* = 16.4 Hz), 7.21 (d, 1H, *J* = 16.4 Hz), 7.53-7.60 (m, 5H), 7.76 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 57.4, 67.5, 100.5, 110.5, 115.7, 127.5, 128.7, 129.6, 130.5, 130.6, 131.5, 131.8, 139.6, 139.8, 159.5, 161.4, 162.6, 163.8; MS (ESI): 415 $[M+H]^+$.

(*E*)-2-((4-(3,5-Dimethoxystyryl)phenoxy)methyl)-5-(3,4,5-trimethoxyphenyl)-1,3,4-oxadiazole (9b): Mixed the compound **7** (500 mg, 1.52 mmol) with 3,4,5-trimethoxybenzoic acid (**8b**) (354 mg, 1.67 mmol) in DMF (5mL) and added $POCl_3$ (5 mL) and the crude product was purified by column chromatography with ethyl acetate/hexane (3:7) to afford pure compound **9b**. Yield: 420 mg (55%), m.p.: 218-220 ºC, ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.76 (s, 6H), 3.84 (s, 6H), 3.86 (s, 3H), 4.90 (s, 2H), 6.37 (s, 1H), 6.72-6.80 (m, 4H), 7.07 (d, 1H, *J* = 16.4 Hz), 7.21 (d, 1H, *J* = 16.4 Hz), 7.52 (d, 2H, *J* = 8.36 Hz), 7.64 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 57.6, 58.5, 61.4, 67.5, 100.5, 105.6, 110.5, 115.6, 126.4, 127.7, 129.6, 131.5, 139.6, 139.8, 142.5, 155.6, 159.6, 161.7, 162.4, 163.6; MS (ESI): 505 $[M+H]^+$.

(*E*)-2-((4-(3,5-Dimethoxystyryl)phenoxy)methyl)-5-(4-methoxyphenyl)-1,3,4-oxadiazole (9c): Mixed compound **7** (500 mg, 1.52 mmol) with 4-methoxybenzoic acid (**8c**) (254 mg, 1.67 mmol) in DMF (5 mL) and added $POCl_3$ (5 mL) and the crude product was purified by column chromatography with ethyl acetate/hexane (4:6) to afford pure compound **9c**. Yield: 450 mg (66%), m.p.: 213-215 ºC, ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.76 (s, 6H), 3.86 (s, 3H), 4.90 (s, 2H), 6.38 (s, 1H), 6.73-6.80 (m, 4H), 7.05 (d, 2H, *J* = 8.27 Hz), 7.07 (d, 1H, *J* = 16.4 Hz), 7.21 (d, 1H, *J* = 16.4 Hz), 7.52 (d, 2H, *J* = 8.36 Hz), 7.65 (d, 2H, *J* = 8.27 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 57.6, 61.4, 67.5, 100.6, 105.6, 110.7, 115.6, 117.6, 118.8, 124.7, 127.5, 129.6, 131.7, 139.5, 139.8, 159.5, 161.4, 162.4, 162.7, 163.8; MS (ESI): 445 $[M+H]^+$.

(*E*)-2-(4-Chlorophenyl)-5-((4-(3,5-dimethoxystyryl)-phenoxy)methyl)-1,3,4-oxadiazole (9d): Mixed compound **7** (500 mg, 1.52 mmol) with 4-chlorobenzoic acid (**8d**) (264 mg, 1.67 mmol) in DMF (5 mL) and added $POCl_3$ (5 mL) and the crude product was purified by column chromatography with ethyl acetate/hexane (3:7) to afford pure compound **9d**. Yield: 520 mg (76.4%) m.p.: 219-221 ºC, ^{1}H NMR (400 MHz,

DMSO-d_6): δ 3.76 (s, 6H), 4.91 (s, 2H), 6.38 (s, 1H), 6.73-6.81 (m, 4H), 7.07 (d, 1H, *J* = 16.4 Hz), 7.21 (d, 1H, *J* = 16.4 Hz), 7.52 (d, 2H, *J* = 8.4 Hz), 7.67-7.76 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 57.6, 67.6, 100.7, 110.7, 115.6, 127.6, 128.6, 129.4, 129.8, 131.4, 131.7, 138.5, 139.6, 139.7, 159.6, 161.4, 162.6, 163.8; MS (ESI): 449 $[M+H]^+$.

(*E*)-2-(4-Bromophenyl)-5-((4-(3,5-dimethoxystyryl)-phenoxy)methyl)-1,3,4-oxadiazole (9e): Mixed compound **7** (500 mg, 1.52 mmol) with 4-bromobenzoic acid (**8e**) (335 mg, 1.52 mmol) in DMF (5 mL) and added $POCl_3$ (5 mL) and the crude product was purified by column chromatography with ethyl acetate/hexane (2:8) to afford pure compound **9e**. Yield: 565 mg (75%), m.p. 226-228 ºC, ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.76 (s, 6H), 4.91 (s, 2H), 6.38 (s, 1H), 6.72-6.80 (m, 4H), 7.07 (d, 1H, *J* = 16.4 Hz), 7.21 (d, 1H, *J* = 16.4 Hz), 7.53 (d, 2H, *J* = 8.40 Hz), 7.63 (d, 2H, *J* = 8.46 Hz), 7.77 (d, 2H, *J* = 8.46 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 57.6, 67.8, 100.8, 110.6, 115.7, 126.5, 126.8, 127.6, 127.8, 129.2, 129.7, 131.4, 133.6, 139.6, 139.7, 159.5, 161.5, 162.7, 163.8; MS (ESI): 494 $[M+H]^+$.

(*E*)-2-((4-(3,5-Dimethoxystyryl)phenoxy)methyl)-5-(4-fluorophenyl)-1,3,4-oxadiazole (9f): Mixed compound **7** (500 mg, 1.52 mmol) with 4-fluorobenzoic acid (**8f)** (234 mg, 1.67 mmol) in DMF (5mL) and added $POCl_3$ (5 mL) and the crude product was purified by column chromatography with ethyl acetate/hexane (4:6) to afford pure compound **9f**. Yield: 450 mg (68%) m.p.: 216-218 ºC, ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.76 (s, 6H), 4.91 (s, 2H), 6.38 (s, 1H), 6.72-6.80 (m, 4H), 7.07 (d, 1H, *J* = 16.4 Hz), 7.21 (d, 1H, *J* = 16.4 Hz), 7.33 (d, 2H, *J* = 8.37 Hz), 7.52 (d, 2H, *J* = 8.4 Hz), 7.65 (d, 2H, *J* = 8.37 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 57.5, 67.8, 100.8, 110.7, 115.7, 117.5,126.5, 126.7, 127.6, 129.7, 131.7, 139.6, 139.7, 159.6, 160.4, 161.5, 162.7, 163.8; MS (ESI): 433 $[M+H]^+$.

(*E*)-2-((4-(3,5-Dimethoxystyryl)phenoxy)methyl)-5-(4-nitrophenyl)-1,3,4-oxadiazole (9g): Mixed compound **7** (500 mg, 1.52 mmol) with 4-nitrobenzoic acid (**8g)** (279 mg, 1.67 mmol) in DMF (5mL) and added $POCl_3$ (5 mL) and the crude product was purified by column chromatography with ethyl acetate/hexane (3:7) to afford pure compound **9g**. Yield: 550 mg (78%), m.p.: 230-232 ºC, ^{1}H NMR (400 MHz, DMSO-d_6): *d*3.76 (s, 6H), 4.92 (s, 2H), 6.38 (s, 1H), 6.73-6.80 (m, 4H),7.07 (d, 1H, *J* = 16.4 Hz), 7.21 (d, 1H, *J* = 16.4 Hz), 7.53 (d, 2H, *J* = 8.39 Hz), 7.68 (d, 2H, *J* = 8.50 Hz), 8.15 (d, 2H, *J* = 8.50 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 57.6, 67.8, 100.8, 110.7, 115.6, 116.7, 124.5, 126.8, 127.7, 129.5, 131.6, 136.9, 139.6, 139.8, 149.7, 159.7, 161.5, 162.6, 163.8; MS (ESI): 460 $[M+H]^+$.

(*E*)-2-((4-(3,5-dimethoxystyryl)phenoxy)methyl)-5-(*p*-tolyl)-1,3,4-oxadiazole (9h): Mixed compound **7** (500 mg, 1.52 mmol) with 4-methylbenzoic acid (**8h)** (227 mg, 1.67 mmol) in DMF (5 mL) and added $POCl_3$ (5 mL) and the crude product was purified by column chromatography with ethyl acetate/hexane (2:8) to afford pure compound **9h**. Yield: 410 mg (63%), m.p.: 216-218 ºC, ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.48 (s, 3H), 3.76 (s, 6H), 4.92 (s, 2H), 6.36 (s, 1H), 6.72-6.79 (m, 4H), 7.07 (d, 1H, *J* = 16.4 Hz), 7.21 (d, 1H, *J* = 16.4 Hz), 7.29 (d, 2H, *J* = 8.35 Hz), 7.52 (d, 2H, *J* = 8.4 Hz), 7.65 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 26.7, 57.4, 67.5, 100.5, 110.4, 115.4, 126.6, 127.6, 128.3, 129.2, 131.3, 132.5, 139.5, 139.5, 141.5, 159.5, 161.3, 162.4, 163.7; MS (ESI): 429 $[M+H]^+$.

(*E*)-2-((4-(3,5-Dimethoxystyryl)phenoxy)methyl)-5-(4-(trifluoromethyl)phenyl)-1,3,4-oxadiazole (9i): Mixed compound **7** (500 mg, 1.52 mmol) with 4-(trifluoromethyl)-benzoic acid (**8i)** (317 mg, 1.67 mmol) in DMF (5 mL) and added $POCl_3$ (5 mL) and the crude product was purified by column chromatography with ethyl acetate/hexane (3:7) to afford pure compound **9i**. Yield: 450 mg (61%), m.p.: 220-222 ºC, ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.76 (s, 6H), 4.92 (s, 2H), 6.38 (s, 1H), 6.73-6.80 (m, 4H), 7.07 (d, 1H, *J* = 16.4 Hz), 7.21 (d, 1H, *J* = 16.4 Hz), 7.53 (d, 2H, *J* = 8.39 Hz), 7.76 (d, 2H, *J* = 8.5 Hz), 8.16 (d, 2H, *J* = 8.5 Hz);^{13}C NMR (100 MHz, DMSO-d_6): δ 57.4, 67.3, 100.6, 110.6, 115.7, 121.3, 127.5, 128.6, 129.4, 130.5, 130.8, 131.4, 133.6, 139.6, 139.8, 159.5, 161.4, 162.8, 163.9; MS (ESI): 483 $[M+H]^+$.

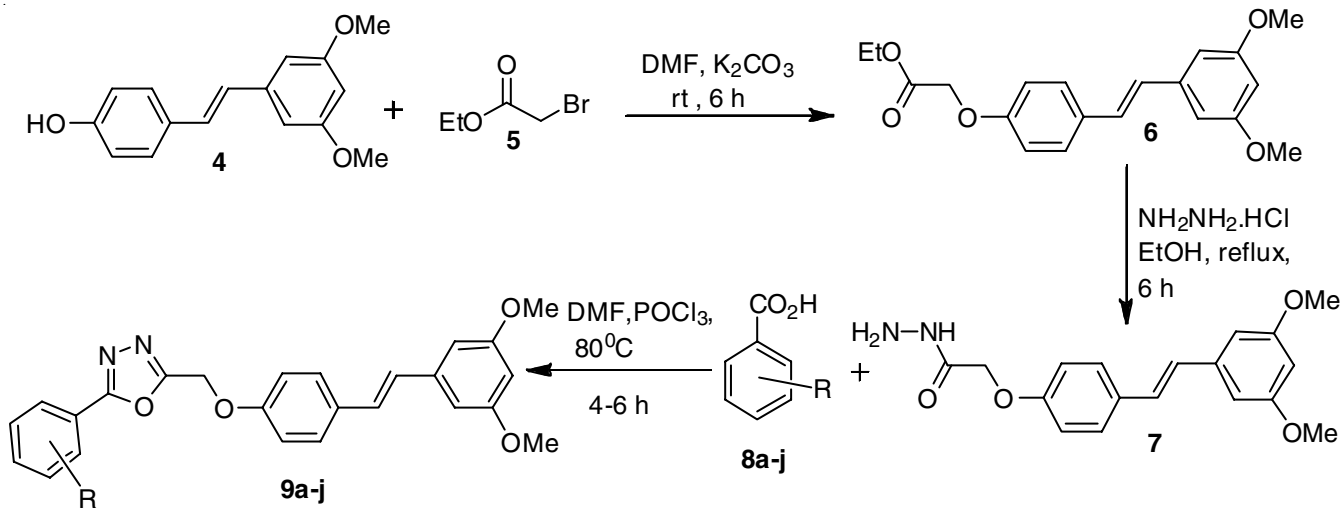
(*E*)-4-(5-((4-(3,5-Dimethoxystyryl)phenoxy)methyl)-1,3,4-oxadiazol-2-yl)benzonitrile (9j): Mixed compound **7** (500 mg, 1.52 mmol) with 4-cyanobenzoic acid (**8j)** (245 mg, 1.52 mmol) in DMF (5 mL) and added $POCl_3$ (5 mL) and the crude product was purified by column chromatography with ethyl acetate/hexane (3:7) to afford pure compound **9j**. Yield: 540 mg (81%), m.p.: 232-234 ºC, ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.76 (s, 6H), 4.94 (s, 2H), 6.38 (s, 1H), 6.74-6.80 (m, 4H), 7.07 (d, 1H, *J* = 16.4 Hz), 7.21 (d, 1H, *J* = 16.4 Hz), 7.53 (d, 2H, *J* = 8.39 Hz), 7.79 (d, 2H, *J* = 8.53 Hz), 8.18 (d, 2H, *J* = 8.53 Hz);^{13}C NMR (100 MHz, DMSO-d_6): δ 57.4, 67.4, 100.8, 110.6, 115.4, 115.8, 119.6, 127.4, 128.6, 129.3, 131.5, 134.6, 134.9, 139.5, 139.8, 159.4, 161.7, 162.8, 163.9; MS (ESI): 440 $[M+H]^+$.

MTT assay: The cytotoxic activity of the compounds was determined using MTT assay. A 1×10^4 cells/well were seeded in 200 mL DMEM, supplemented with 10% FBS in each well of 96-well microculture plates and incubated for 24 h at 37 º C in a CO_2 incubator. Compounds were diluted to the desired concentrations in culture medium and added to the wells with respective vehicle control. After 48 h of incubation, 10 mL of MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) (5 mg/mL) was added to each well and the plates were further incubated for 4 h. Then the supernatant from each well was carefully removed, formazon crystals were dissolved in 100 mL of DMSO and absorbance at5 40 nm wavelength was recorded.

RESULTS AND DISCUSSION

This newly synthesized target compounds (**9a-j**) are outlined in **Scheme-I**. Compound **4** was reacted with ethyl bromoacetate (**5**) in DMF, K_2CO_3 at room temperature for 6 h to afford pure compound **6**. This intermediate **6** was then reacted with hydrazine hydrochloride in ethanol at reflux for again 6 h to afford acid hydrazide intermediate **7**, then this intermediate **7** was coupled with different types of aromatic acids (**8a-j**) in phosphoryl chloride ($POCl_3$) at reflux for 4-6 h to afford pure final compounds (**9a-j**) in good yield.

***in vitro* Cytotoxicity**: All the newly compounds (**9a-j**) were screened for their anticancer activity against three human



9a; R = H
9b; R = 3,4,5-trimethoxy
9c; R = 4-methoxy
9d; R = 4-chloro
9e; R = 4-bromo
9f; R = 4-fluoro
9g; R = 4-nitro
9h; R = 4-methyl
9i; R = 4-trifluoro
9j; R = 4-cyano

8a; R = H
8b; R = 3,4,5-trimethoxy
8c; R = 4-methoxy
8d; R = 4-chloro
8e; R = 4-bromo
8f; R = 4-fluoro
8g; R = 4-nitro
8h; R = 4-methyl
8i; R = 4-trifluoro
8j; R = 4-cyano

Scheme-I

cancer cell lines (MCF-7, A549 and MDA MB-231) by MTT assay and these results are summarized in Table-1, adriamycin used as control drug. Most of the compounds were showed good anticancer activity on respected cell lines. Among them compounds **9b** and **9j** were showed more potent activity than positive control.

TABLE-1
CYTOTOXICITY ACTIVITY OF COMPOUNDS (**9a-j**) IN (IC_{50}, μM)

Compound	MCF-7	A549	MDA MB-231
9a	3.78	9.56	Not active
9b	1.56	0.11	1.22
9c	4.77	Not active	Not active
9d	10.4	18.9	Not active
9e	3.56	14.3	19.4
9f	2.89	17.2	Not active
9g	12.9	5.44	7.23
9h	13.9	12.6	32.6
9i	4.55	Not active	8.22
9j	0.45	1.11	1.98
Adriamycin	3.12	2.10	3.41

Docking analysis: Molecular docking studies were performed on compound **9b** against tubulin structures (Fig. 2). Glide standard precision (SP) docking has been employed and the lead compounds docked in the colchicines binding pocket of tubulin (PDB code: 3E22) [35].

It is well studied that colchicine binding site is generally present at the interface of α,β-tubulin heterodimers [36]. The α- and β-subunits of tubulin are shown as green cartoons and the interacting amino acid residues are represented as violet sticks. Compound **9b** is docked in the colchicine binding site and exhibit the oxygen linker, which showed a strong hydrogen

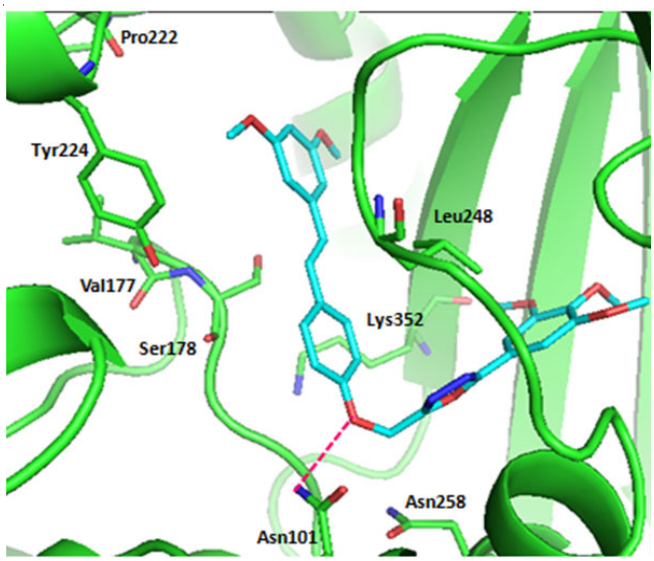


Fig. 2. Molecular docking poses of compound **9b** at the colchicine binding site of tubulin

bonding with NH of the Asn101 (O…NH, distance 2.74 Å), the binding pose is surrounded by the amino acid residues Asn101, Val177, Ser178, Ala180, Pro222, Tyr224 in the α-subunit and Gln247, Leu248, Asn258, Lys352, Ala354 in the β-subunit with a dock score of -7.41 kcal/mol.

Conclusion

In summary, a series of oxadiazole fused resveratrol (**9a-j**) derivatives were synthesized and characterized. All these derivatives were evaluated for their anticancer activity against human cancer cell lines (MCF-7, MDA MB-231 and A549). Among them, compounds **9b** and **9j** were revealed more potent anticancer activity than adriamycin.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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