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Synthesis, Characterization and Cytotoxic Study of 2-Hydroxy Benzothiazole Incorporated 1,3,4-Oxadiazole Derivatives

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A SERIES of fifteen 1, 3, 4-oxadiazoles derived from 2-hydroxy benzothiazole have been synthesized and screened for the anticancer activity. Different aromatic acids were used for this library for generating structure activity relationship. The *in vitro* cytotoxicity was done against MCF-7 breast cancer cells. The synthesized compounds showed variable cytotoxic effects. Four compounds showed potent cytotoxic effect with IC_{50} varies from 1.8µM/mL to 4.5µM/mL. Other compounds showed moderate to lower cytotoxicity. 2-(5-((benzo[d]thiazol-2-yloxy)-methyl)-1,3,4-oxadiazol-2-yl)phenol was the most potent compound which showed a cytotoxicity effect (IC_{50} 1.8 ± 0.02 µM/mL) comparable to the standard drug Doxirubicin (IC_{50} 1.2 ± 0.005 µM/mL). From the result it was observed that aromatic ring activating groups such as methyl and hydroxyl, enhances the cytotoxicity effect, whereas aromatic ring deactivating groups such as nitro group showed moderate cytotoxicity against MCF-7 breast cancer cell line.

Keywords: 2-hydroxy benzothiazole, 1,3,4-oxadiazole, anticancer, SRB assay.

Introduction:

Cancer is an abnormal and uncontrolled cell growth which accounts for large number of deaths [1,2]. The available treatment such as radiation treatment, chemotherapy are associated with undesirable side effects [3,4].Therefore, there is an urgent need to develop new and safer anticancer agents for treatment.

In recent years, heterocyclic compounds have emerged as a potent scaffold in medicinal chemistry [5]. Several heterocyclic compounds containing nitrogen, oxygen and sulphur have been synthesized as anti-cancer and anti-viral agents [6]. Benzothiazole, one of the most important heterocyclic compounds is present in many marketed drugs like Ethoxzolamide, Frentizole, Riluzole, etc. This moiety is known to have various pharmacological activities like antimicrobial, anticancer, antitumor, antidiabetic, antimalarial, antihelmintic, antitubercular, antileishmanial and anti-inflammatory [7-18]. On the other hand, 1, 3, 4-oxadiazole contains nitrogen and oxygen in its skeleton which imparts higher efficiency against various diseases [19]. Various biological activity of 1, 3, 4-oxadiazole derivatives have been reported such as antidiabetic, antimicrobial, antiviral, antitubercular, anti-inflammatory and anticancer [20-25]. 1, 3, 4-oxadiazole pharmacophore is present in many drugs such as Zibotentan (anticancer), Raltegravir (antiretroviral), tiodazosin and nesapidil (antihypertensive drugs)[26].

Considering the biological importance of 1, 3, 4-oxadiazole and benzothiazole, we have conjugated the two heterocycles under one construct for better bioactivities (Fig. 1). The present work reports the designing and synthesis of 1, 3, 4-oxadiazole clubbed benzothiazole derivatives with promising anticancer activity against MCF-7 breast cancer cell line.

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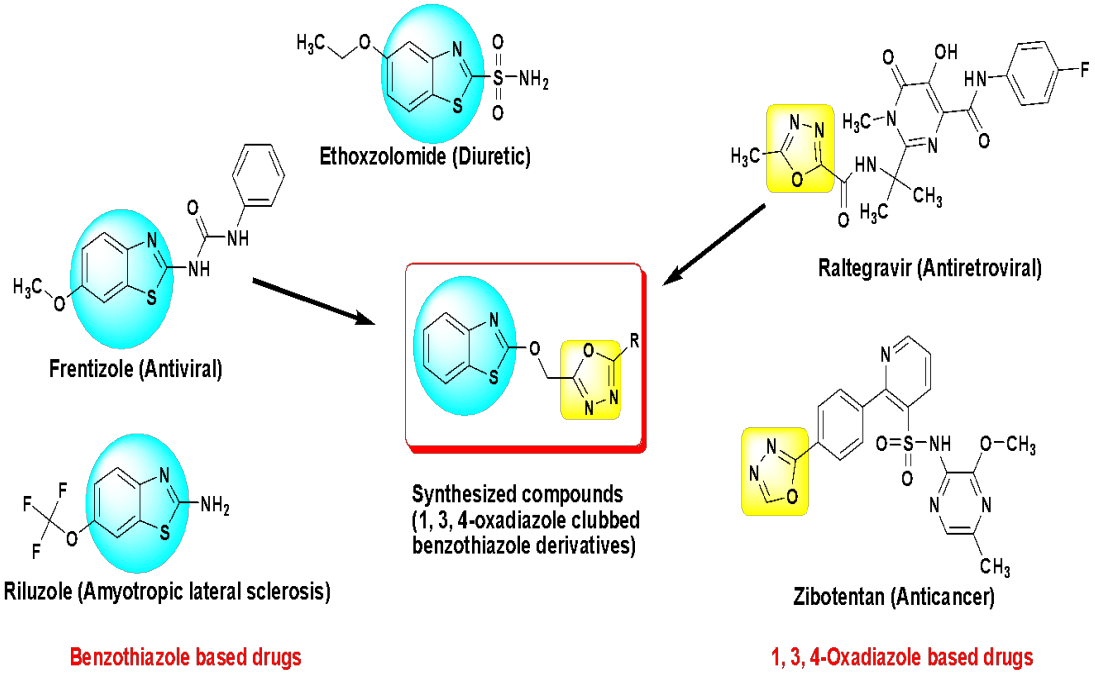


Fig. 1. Drug based designing of 1, 3, 4-oxadiazole derivatives

Experimental

Chemistry

All the chemicals used in the present work were of reagent grade and procured from Sigma Aldrich (Germany) and Loba (India). The starting material 2-hydroxy benzothiazole (**1**) was purchased from Sigma Aldrich. IR spectra were done on thermos scientific iS-50 by ATR method. NMR spectra were performed on a Bruker 300 MHz and 850 MHz instruments using solvents $CDCl_3$ or DMSO-d_6. Tetramethylsilane (TMS) was used as an internal standard. Chemical shift and coupling constant are provided in Hertz (Hz) and parts per million (ppm), respectively. Thermo scientific-LCQ Fleet (LCF10605) using electron spray ionization method was used for recording the mass spectra and provided in m/z. Melting points were recorded by using automatic melting point (Stuart SMP40). Elemental analysis was performed on LEECO Elementar Elemental Analyzer. The elemental analysis data were reported in % standard and were within ±0.4% of the calculated values.

Synthesis of ethyl 2-(benzo[d]thiazol-2-yloxy) acetate (2)

2-Hydroxy benzothiazole (**1**) (10 g, 66.2 mmol) was charged in 250 mL round bottom flask followed by addition of acetone (150 mL) and stirred to get clear solution. To this clear solution, anhydrous potassium carbonate (9.0 g, 66.2 mmol) was added and reaction mass was kept under stirring. After 30 min, ethyl chloroacetate (8.07 g, 66.2 mmol) was added and refluxed for 10-12 hrs. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mass was filtered and filtrate was concentrated to 50 mL, cooled and poured on to the crushed ice and extracted with dichloromethane. Dichloromethane was dried over anhydrous sodium sulphate, concentrated and finally crystallized by adding little petroleum ether to give white crystals. Yield: 94%; white crystals; m.p. 49.8-50 °C; IR (ATR, cm^{-1}): 3060 (C-H aromatic), 2973 (C-H aliphatic), 1671 (C=N of benzothiazole), 1663 (C=O), 1183 (C-O of benzothiazole), 1049 (C-O), 705 (C-S). ^{1}H NMR (850 MHz, DMSO-d_6) δ (ppm): 1.21 (t, *J*=6.8 Hz, 3H, -CH_3), 4.17 (q, *J*=6.8 Hz, 2H, -O-CH_2 of ethyl ester), 4.84 (s, 2H, -O-CH_2-), 7.23 (tt, *J*=0.85 Hz, 8.5 Hz, 1H, Ar-H), 7.31 (d, *J*=8.5 Hz, 1H, Ar-H), 7.36 (tt, *J* = 0.85 Hz, 8.5 Hz 1H, Ar-H), 7.68 (dd, *J* = 0.85 Hz, 7.6 Hz, 1H, Ar-H). ^{13}C NMR (213 MHz, DMSO-d_6) δ (ppm): 14.03 (-CH_3), 43.43 (-O-$\underline{C}H_2$-CH_3), 61.46 (-O-CH_2-), 111.41 (Ar-C), 121.12 (Ar-C), 123.04 (Ar-C), 123.53 (Ar-C), 126.75 (Ar-C), 136.76 (Ar-C), 167.43 (-C=N), 169.21 (C=O); ESI +ve MS (m/z): 238.00 $[M+H]^+$.

Synthesis of 2-(benzo[d]thiazol-2-yloxy) acetohydrazide (3)

To the solution of ethyl 2-(benzo[d]thiazol-2-yloxy) acetate (**2**) (8.0 g, 3.3 mmol) in ethanol (100ml), hydrazine monohydrate (1.68 g, 3.3 mmol) was added and refluxed for 7-8 hrs. After completion of the reaction monitored by TLC, the reaction mass was cooled and solid product was separated out. It was filtered and crystallized with ethanol to give 2-(benzo[d] thioazol-2-yloxy)acetohydrazide (**3**) as a white crystals. Yield: 88%; white crystals; m.p. 207-208 °C; IR (ATR, cm^{-1}): 3311 (NH_2), 3222 (NH), 3040 (C-H aromatic), 2986 (C-H aliphatic), 1680 (C=N of benzothiazole), 1653 (C=O), 1188 (C-O of benzothiazole), 1053 (C-O), 714 (C-S). ^{1}H NMR (850 MHz, DMSO-d_6) δ (ppm): 4.31 (s, 2H, -NH_2), 4.56 (s, 2H, -O-CH_2-), 7.16-7.21 (m, 2H, Ar-H), 7.34-7.35 (m, 1H, Ar-H), 7.65-7.66 (m, 1H, Ar-H), 9.45 (s, 1H, -N-H). ^{13}C NMR (213 MHz, DMSO-d_6) δ (ppm): 43.31 (-O-CH_2), 111.41 (Ar-C), 121.21 (Ar-C), 122.83 (Ar-C), 123.25 (Ar-C), 126.54 (Ar-C), 137.30 (Ar-C), 165.40 (C=N), 169.14 (C=O); ESI +ve MS (m/z): 224.00 $[M+H]^+$.

General procedure for the synthesis of 1,3,4-oxadiazole derivatives (4-18)

A mixture of 2-(benzo[d]thiazol-2-yloxy) acetohydrazide (**3**) (0.2 mmol) and different substituted aromatic acids (0.2 mol) in $POCl_3$ (10 mL) was refluxed for 8-12 hrs. After completion of the reactions monitored by TLC, the reaction mixture were cooled, poured on to crushed ice and neutralized with $NaHCO_3$ solution. The solid material that precipitated out was filtered, washed with water (50ml X 3), dried and finally purified either by recrystallization with dichloromethane or methanol or column chromatography using *n*-hexane-ethylacetate as eluents

2-((5-phenyl-1,3,4-oxadiazol-2-yi)methoxy) benzo[d]thiazole (4)

Yield: 57%; white powder; m.p. 258-259 °C; IR (ATR, cm^{-1}): 3068 (C-H aromatic), 2956 (C-H aliphatic), 1668 (C=N of benzothiazole), 1591 (C=N of oxadiazole), 1512, 1488, 1475, 1336, 1272, 1245, 1188, 1024, 746 (C-S). ^{1}H NMR (850 MHz, DMSO-d_6) δ (ppm): 4.82 (s, 2H, -O-CH_2-), 7.27-7.31 (m, 2H, Ar-H), 7.44-7.45 (m, 1H, Ar-H), 7.55 (t, *J* = 8.5 Hz, 2H, Ar-H), 7.62-7.64 (m, 1H, Ar-H), 7.73-7.76 (m, 1H, Ar-H), 7.91-7.92 (m, 2H, Ar-H). ^{13}C NMR (213 MHz, DMSO-d_6) δ (ppm): 43.25 (-O-CH_2-), 111.54 (Ar-C), 121.17 (Ar-C), 122.87 (Ar-C), 123.38 (Ar-C), 126.6 (Ar-C), 127.47 (Ar-C), 127.66 (Ar-C), 128.54 (Ar-C), 128.70 (Ar-C), 131.98 (Ar-C), 132.22 (Ar-C), 137.11 (Ar-C), 165.52 (C=N of oxadiazole), 165.58 (C=N of oxadiazole), 169.23 (C=N of benzothiazole); ESI +ve MS (m/z): 310$[M+H]^+$; Anal. Calc. for $C_{16}H_{11}O_2N_3S$: C, 62.12; H, 3.58; O, 10.34; N, 13.58; S, 10.37. Found: C, 62.10; H, 3.59; O, 10.35; N, 13.56; S, 10.36.

2-((5-(2-chlorophenyl)-1,3,4-oxadiazol-2-yl) methoxy)benzo[d]thiazole (5)

Yield: 54%; white crystals; m.p. 167-168 °C; IR (ATR, cm^{-1}): 3050 (C-H aromatic), 2986 (C-H aliphatic), 1697 (C=N of benzothiazole), 1592 (C=N of oxadiazole), 1582, 1473, 1457, 1423, 1321, 1176, 1044, 715(C-S). ^{1}H NMR (850 MHz, DMSO-d_6) δ (ppm): 5.62 (s, 2H, -O-CH_2-), 7.26 (t, *J* = 7.6 Hz, 1H, Ar-H), 7.41 (t, *J* = 8.5 Hz, 1H, Ar-H), 7.48 (d, *J* = 8.5 Hz, 1H, Ar-H), 7.56 (t, *J* = 7.6 Hz, 1H, Ar-H), 7.65 (t, *J* =7.6 Hz, 1H, Ar-H), 7.69 (d, *J* = 8.5 Hz, 1H, Ar-H), 7.72 (d, *J* = 7.6 Hz, 1H, Ar-H), 7.93 (d, *J* = 7.6 Hz, 1H, Ar-H). ^{13}C NMR (213MHz, DMSO-d_6) δ (ppm): 36.96 (-O-CH_2-), 111.71 (Ar-C), 121.27 (Ar-C), 122.21 (Ar-C), 123.18 (Ar-C), 123.84 (Ar-C), 126.87 (Ar-C), 127.99 (Ar-C), 131.19 (Ar-C), 131.37 (C Ar-C), 131.83 (Ar-C), 133.53 (Ar-C), 136.22 (Ar-C), 162.05 (C=N of oxadiazole), 162.89 (C=N of oxadiazole), 169.08 (C=N of benzothiazole); ESI +ve MS(m/z): 344 $[M+H]^+$, 346 $[M+2+H]^+$; Anal. Calc. for $C_{16}H_{10}ClO_2N_3S$: C, 55.90; H, 2.93; O, 9.31; N, 12.22; S, 9.33. Found: C, 55.88; H, 2.94; O, 9.32; N, 12.21; S, 9.32. IR, ^{1}H, ^{13}C NMR and mass spectra for product 5 are provided in supplementary file.

2-((5-(4-bromophenyl)-1,3,4-oxadiazol-2-yi) methoxy)benzo[d]thiazole (6)

Yield: 63%; white powder; m.p. 219-220 °C; IR (ATR, cm^{-1}), 3035 (C-H aromatic), 2869 (C-H aliphatic), 1677 (C=N of benzothiazole), 1590 (C=N of oxadiazole), 1495, 1473, 1331, 1187, 1069, 1023, 1010, 744, 716 (C-S). ^{1}H NMR (850 MHz, DMSO-d_6) δ (ppm): 5.56 (s, 2H, -OCH_2-), 7.03 (d, *J* = 8.5 Hz, 2H, Ar-H), 7.45 (d, *J* = 7.65 Hz, 1H, Ar-H), 7.82-7.87 (m, 4H, Ar-H), 8.06 (d, *J* = 8.5 Hz, 1H. Ar-H). ^{13}C NMR (213 MHz, DMSO-d_6) δ (ppm): 43.24 (-O-CH_2-), 111.52 (Ar-C), 121.17 (Ar-C), 122.88 (Ar-C), 123.39 (Ar-C), 125.79 (Ar-C), 127.60 (Ar-C), 128.55 (Ar-C), 129.77 (Ar-C), 131.33 (Ar-C), 131.63 (Ar-C), 131.72 (Ar-C), 137.10 (Ar-C), 164.66 (C=N of oxadiazole), 164.69 (C=N of oxadiazole), 169.18 (C=N of benzothiazole); ESI +ve MS (m/z): 387 $[M+H]^+$, 389$[M+2+H]^+$; Anal. Calc. for

$C_{16}H_{10}BrO_2N_3S$: C, 49.50; H, 2.60; O, 8.24; N, 10.82; S, 8.26. Found: C, 49.52; H, 2.60; O, 8.26; N, 10.80; S, 8.23.

2-(5-((benzo[d]thiazol-2-yloxy)-methyl)-1,3,4-oxadiazol-2-yl)phenol(7)

Yield: 63%; white powder; m.p. 111-113 °C; IR (ATR, cm^{-1}): 3261 (Ar-OH), 3070 (C-H aromatic), 2987 (C-H aliphatic), 1779 (C=N of benzothiazole), 1541 (C=N of oxadiazole), 1507, 1473, 1288, 1245, 1193, 1156, 1050, 745 (C-S).^{1}H NMR (850 MHz, DMSO-d_6) δ (ppm): 5.64 (s, 2H, -O-CH_2-), 7.27-7.31 (m, 1H, Ar-H), 7.42-7.44 (m, 1H, Ar-H), 7.52-7.54 (m, 3H, Ar-H), 7.70-7.74 (m, 1H, Ar-H), 7.79-7.83 (m, 2H, Ar-H), 10.51 (s, 1H, Ar-OH).^{13}C NMR (213MHz, DMSO-d_6) δ (ppm): 43.24 (-O-CH_2-), 111.68 (Ar-C), 122.86 (Ar-C), 123.18 (Ar-C), 123.37 (Ar-C), 123.81 (Ar-C), 126.59 (Ar-C), 126.87 (Ar-C), 129.47 (Ar-C), 132.21 (Ar-C), 132.52 (Ar-C), 136.27 (Ar-C), 164.84 (C=N of oxadiazole), 165.63 (C=N of oxadiazole), 169.06 (C=N of benzothiazole); ESI +ve MS (m/z): 326 $[M+H]^+$; Anal. Calc. for $C_{16}H_{11}O_3N_3S$: C, 59.07; H, 3.41; O, 14.75; N, 12.92; S, 9.86. Found: C, 59.09; H, 3.42; O, 14.77; N, 12.90; S, 9.85.

3-(5-((benzo[d]thiazol-2-yloxy)methyl)-1,3,4-oxadiazol-2-yl)benzenamine (8)

Yield: 55%; white crystals; m.p. 214-216 °C; IR (ATR, cm^{-1}): 3274 (NH_2), 3060 (C-H aromatic), 2988 (C-H aliphatic), 1651 (C=N of benzothiazole), 1587 (C=N of oxadiazole), 1473, 1434, 1329, 1196, 1052, 894, 742 (C-S). ^{1}H NMR(850 MHz, DMSO-d_6) δ (ppm): 4.77 (s, 2H, -O-CH_2-), 6.76 (d, J = 6.8 Hz, Ar-H), 7.10-7.26 (m, 2H, Ar-H), 7.50-7.74 (m, 1H, Ar-H), 7.98-8.02 (m, 1H, Ar-H), 8.29-8.43 (m, 2H, Ar-H), 10.30 (s, 2H, Ar-NH_2). ^{13}C NMR (213 MHz, DMSO-d_6) δ (ppm): 43.27 (-O-CH_2-), 111.58 (Ar-C), 121.17 (Ar-C), 122.5 (Ar-C), 123.39 (Ar-C), 123.72 (Ar-C), 126.6 (Ar-C), 128.7 (Ar-C), 128.97 (Ar-C), 131.27 (Ar-C), 132.92 (Ar-C), 135.4 (Ar-C), 135.65 (Ar-C), 149.03 (Ar-C), 165.53 (C=N of oxadiazole), 165.84 (C=N of oxadiazole), 169.24 (C=N of benzothiazole); ESI +ve MS (m/z): 325 $[M+H]^+$;Anal. Calc. for $C_{16}H_{12}O_2N_4S$: C, 59.25; H, 3.73; O, 9.87; N, 17.27; S, 9.89. Found: C, 59.26; H, 3.74; O, 9.88; N, 17.25; S, 9.88.

2-((5-p-tolyl-1,3,4-oxadiazol-2-yl)methoxy) benzo[d]thiazole (9)

Yield: 68%; white powder; m.p. 225-226 °C; IR (ATR,cm^{-1}): 3060 (C-H aromatic), 2984 (C-H aliphatic), 1651 (C=N of benzothiazole), 1593 (C=N of oxadiazole), 1489, 1473, 1192, 1042, 829, 746 (C-S). ^{1}H NMR (850 MHz, DMSO-d_6) δ (ppm): 2.35 (s, 3H, Ar-CH_3), 4.76 (s, 2H, -O-CH_2-), 7.21-7.24 (m, 2H, Ar-H),7.29 (d, J =8.5 Hz, 2H, Ar-H), 7.37-7.41 (m, 1H, Ar-H), 7.66-7.68 (m, 1H, Ar-H), 7.76 (d, J =8.5 Hz, 2H, Ar-H). ^{13}C NMR (213 MHz, DMSO-d_6) δ (ppm): 21.04 (Ar-CH_3), 43.24 (-O-CH_2-), 111.54 (Ar-C), 121.16 (Ar-C), 122.86 (Ar-C), 123.37 (Ar-C), 126.59 (Ar-C), 127.67 (Ar-C), 129.21 (Ar-C), 130.09 (Ar-C), 137.11 (Ar-C), 142.0 (Ar-C), 165.41 (C=N of oxadiazole), 165.58 (C=N of oxadiazole), 169.22 (C=N of benzothiazole); ESI +ve MS (m/z): 324 $[M+H]^+$; Anal. Calc. for $C_{17}H_{13}O_2N_3S$: C, 63.14; H, 4.05; O, 9.90; S, 9.92. Found: C, 63.12; H, 4.03; O, 9.91; N, 12.97; S, 9.91.

2-((5-m-tolyl-1,3,4-oxadiazol-2-yl)methoxy) benzo[d]thiazole(10)

Yield: 65%; white powder; m.p. 179-180 °C; IR (ATR, cm^{-1}): 3039 (C-H aromatic), 2915 (C-H aliphatic), 1670 (C=N of benzothiazole), 1584 (C=N of oxadiazole), 1473, 1183, 1025, 761 (C-S). ^{1}H NMR (850 MHz, DMSO-d_6) δ (ppm): 2.41 (s, 3H, Ar-CH_3), 4.81 (s, 2H, -O-CH_2), 7.27-7.32 (m, 2H, Ar-H), 7.42-7.45 (m, 3H, Ar-H), 7.70-7.74 (m, 2H, Ar-H), 7.78-7.79 (m, 1H, Ar-H). ^{13}C NMR (213 MHz, DMSO-d_6) δ (ppm): 20.93 (Ar-CH_3), 43.24 (-O-CH_2-), 111.54 (Ar-C), 121.16 (Ar-C), 122.86 (Ar-C), 123.18 (Ar-C), 124.57 (Ar-C), 126.59 (Ar-C), 128.04 (Ar-C), 128.59 (Ar-C), 132.21 (Ar-C), 132.52 (Ar-C), 137.11 (Ar-C), 137.85 (Ar-C), 165.54 (C=N of oxadiazole), 165.63 (C=N of oxadiazole), 169.22 (C=N of benzothiazole); ESI +ve MS (m/z): 324 $[M+H]^+$; Anal. Calc. for $C_{17}H_{13}O_2N_3S$: C, 63.14; H, 4.05; O, 9.90; N, 12.99; S, 9.92. Found: C, 63.12; H, 4.06; O, 9.92; N, 12.97; S, 9.91.

2-((5-(3-chlorophenyl)-1,3,4-oxadiazol-2-yl) methoxy)benzo[d]thiazole (11)

Yield: 69%; white crystals; m.p. 235-236 °C; IR (ATR, cm^{-1}): 3037 (C-H aromatic), 2976 (C-H aliphatic), 1655 (C=N of benzothiazole), 1594 (C=N of oxadiazole), 1582, 1473, 1334, 1244, 1157, 1048, 744 (C-S). ^{1}H NMR (850 MHz, DMSO-d_6) δ (ppm): 4.77 (s, 2H, -O-CH_2-), 7.21-7.25 (m, 2H, Ar-H), 7.37-7.39 (m, 1H, Ar-H), 7.54 (t, J = 8.5 Hz, 1H, Ar-H), 7.64-7.68 (m, 2H, Ar-H), 7.82 (d, J = 8.5 Hz, 1H, Ar-H), 7.89 (t, J = 1.7 Hz, 1H, Ar-H). ^{13}C NMR (213 MHz, DMSO-d_6) δ (ppm): 43.25(-O-CH_2), 111.52 (Ar-C), 121.18 (Ar-C), 122.89 (Ar-C), 123.40 (Ar-C), 126.22 (Ar-C), 126.60 (Ar-C), 127.27 (Ar-C), 130.65 (Ar-C), 131.84 (Ar-C), 133.36 (Ar-C), 137.10 (Ar-C), 164.12 (C=N of oxadiazole), 165.50 (C=N

of oxadiazole), 169.24 (C=N of benzothiazole); ESI +ve MS (m/z): 344 $[M+H]^+$, 346 $[M+2+H]^+$; Anal. Calc. for $C_{16}H_{10}ClO_2N_3S$: C, 55.90; H, 2.93; O, 9.31; N, 12.22; S, 9.33. Found: C, 55.88; H, 2.92; O, 9.32; N, 1.23; S, 9.32.

2-((5-(3-nitrophenyl)-1,3,4-oxadiazol-2-yl) methoxy)benzo[d]thiazole (12)

Yield: 57%; white powder; m.p. 180-181°C; IR (ATR, cm^{-1}): 3038 (C-H aromatic), 2986 (C-H aliphatic), 1673 (C=N of benzothiazole), 1605, 1527 (C=N of oxadiazole), 1473, 1343 (NO_2), 1286, 1189, 1024, 746 (C-S). ^{1}H NMR (850 MHz,DMSOd_6) δ (ppm): 4.79 (s, 2H, -O-CH_2-), 7.22-7.26 (m, 2H, Ar-H), 7.38-7.40 (m, 1H, Ar-H), 7.68 (dd, *J* = 0.85 Hz, 7.6 Hz, 1H, Ar-H), 7.82 (t, *J* = 7.6 Hz, 1H, Ar-H), 8.30 (d, *J* = 8.5 Hz, 1H, Ar-H), 8.42-8.44 (m, 1H, Ar-H), 8.69 (t, *J*= 1.7 Hz, 1H, Ar-H). ^{13}C NMR (213 MHz, DMSO-d_6) δ (ppm): 43.25 (-O-CH_2), 111.50 (Ar-C), 121.19 (Ar-C), 122.25 (Ar-C), 122.91 (Ar-C), 123.41 (Ar-C), 126.62 (Ar-C), 130.50 (Ar-C), 133.55 (Ar-C), 137.10 (Ar-C), 147.85 (Ar-C), 163.48 (C=N of oxadiazole), 165.53 (C=N of oxadiazole), 169.25 (C=N of benzothiazole); ESI +ve MS (m/z): 355 $[M+H]^+$;Anal. Calc. for $C_{16}H_{10}O_4N_4S$: C, 54.23; H, 2.84; O, 18.06, N, 15.81; S, 9.05. Found: C, 54.25; H, 2.84; O, 18.07; N, 15.80; S, 9.05.

2-(5-((benzo[d]thiazol-2-yloxy)methyl)-1,3,4-oxadiazol-2-yl)benzenethiol (13)

Yield: 56%; white crystals; m.p. 243-244°C; IR (ATR, cm^{-1}): 3050 (C-H aromatic), 2988 (C-H aliphatic), 2567 (Ar-SH), 1668 (C=N of benzothiazole), 1587 (C=N of oxadiazole), 1473, 1269, 1197, 897, 741 (C-S). ^{1}H NMR (850 MHz, DMSO-d_6) δ (ppm): 3.17 (s, 1H, Ar-SH), 4.80 (s, 2H, -O-CH_2-), 7.38-7.50 (m, 4H, Ar-H), 7.61-7.79 (m, 2H, Ar-H), 8.01-8.05 (m, 1H, Ar-H), 8.23-8.24 (m, 1H, Ar-H). ^{13}C NMR (213 MHz, DMSO-d_6) δ (ppm): 43.175 (-O-CH_2-), 111.31 (Ar-C), 123.68 (Ar-C), 123.86 (Ar-C), 124.04 (Ar-C), 126.32 (Ar-C), 128.73 (Ar-C), 131.80 (Ar-C), 132.0 (Ar-C), 135.69 (Ar-C), 137.49 (Ar-C), 140.69 (Ar-C), 141.72 (Ar-C), 161.72 (C=N of oxadiazole), 161.99 (C=N of oxadiazole), 167.14 (C=N of benzothiazole); ESI +ve MS (m/z): 342 $[M+H]^+$; Anal. Calc. for $C_{16}H_{11}O_2N_3S_2$: C, 56.29; H, 3.25; O, 9.37; N, 12.31; S, 18.78. Found: C, 56.27; H, 3.26; O, 9.38; N, 12.30; S, 18.79.

2-((5-o-tolyl-1,3,4-oxadiazol-2-yl)methoxy) benzo[d]thiazole (14)

Yield: 63%; white powder; m.p. 282-283 °C; IR (ATR, cm^{-1}): 3060 (C-H aromatic), 2987 (C-H aliphatic), 1670 (C=N of benzothiazole), 1592 (C=N of oxadiazole), 1489, 1473, 1176, 1044, 746 (C-S). ^{1}H NMR (850 MHz, DMSO-d_6) δ (ppm): 2.41 (s, 3H, Ar-CH_3), 4.80 (s, 2H, -O-CH_2-), 7.27-7.32 (m, 4H, Ar-H),7.40-7.49 (m, 2H, Ar-H), 7.54-7.57 (m, 1H, Ar-H), 7.77 (dd, *J* = 0.85 Hz, 7.6 Hz, 1H, Ar-H). ^{13}C NMR (213 MHz, DMSO-d_6) δ (ppm): 21.24 (Ar-CH_3), 43.21 (-O-CH_2-), 111.71 (Ar-C), 121.27 (Ar-C), 122.19 (Ar-C), 123.17 (Ar-C), 123.81 (Ar-C), 126.86 (Ar-C), 127.36 (Ar-C), 130.88 (Ar-C), 131.74 (Ar-C), 131.83 (Ar-C), 134.59 (Ar-C), 136.26 (Ar-C), 164.94 (C=N of oxadiazole), 165.45 (C=N of oxadiazole), 169.07 (C=N of benzothiazole); ESI +ve MS (m/z): 324 $[M+H]^+$; Anal. Calc. for $C_{17}H_{13}O_2N_3S$: C, 63.14; H, 4.05; O, 9.90; N, 12.99; S, 9.92. Found: C, 63.11; H, 4.05; O, 9.91; N, 13.00; S, 9.91.

2-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl) methoxy)benzo[d]thiazole (15)

Yield: 63%; white powder; m.p. 223-225 °C; IR (ATR, cm^{-1}): 3035 (C-H aromatic), 2981 (C-H aliphatic), 1667 (C=N of benzothiazole), 1522 (C=N of oxadiazole), 1472, 1335 (NO_2), 1249, 1022, 747 (C-S). ^{1}H NMR (850 MHz, DMSO-d_6) δ (ppm): 4.79 (s, 2H, -O-CH_2-), 7.22-7.26 (m, 2H, Ar-H), 7.38 (t, *J* = 7.6 Hz, 1H, Ar-H), 7.68 (d, *J* = 7.6 Hz, 1H, Ar-H), 8.08 (d, *J* = 8.5 Hz, 2H, Ar-H), 8.34 (d, *J* = 8.5 Hz, 2H, Ar-H). ^{13}C NMR (213 MHz, DMSO-d_6) δ (ppm): 43.24 (-O-CH_2-), 111.50 (Ar-C), 121.18 (Ar-C), 122.90 (Ar-C), 123.40 (Ar-C), 123.78 (Ar-C), 126.60 (Ar-C), 129.04 (Ar-C), 137.09 (Ar-C), 137.83 (Ar-C), 149.46 (Ar-C), 163.96 (C=N of oxadiazole), 165.51 (C=N of oxadiazole), 169.24 (C=N of benzothiazole); ESI +ve MS (m/z): 355 $[M+H]^+$; Anal. Calc. for $C_{16}H_{10}O_4N_4S$: C, 54.23; H, 2.84; O, 18.06; N, 15.81; S, 9.05. Found: C, 54.20; H, 2.84; O, 18.07; N, 15.82; S, 9.05.

2-((5-((1H-indol-3-yl)methyl)-1,3,4-oxadiazol-2-yl)methoxy)benzo[d]thiazole (16)

Yield: 56%; yellow crystals; m.p. 172-173 °C; IR (ATR, cm^{-1}): 3254 (C-H aromatic), 2987 (C-H aliphatic), 1669 (C=N of benzothiazole), 1592 (C=N of oxadiazole), 1540, 1473, 1242, 1177, 1044, 745 (C-S). ^{1}H NMR (850 MHz, DMSO-d_6) δ (ppm): 3.17 (s, 2H, -CH_2), 4.86 (s, 2H, -O-CH_2-), 6.97-7.73 (m, 9H, Ar-H), 11.21 (s, 1H, NH); ^{13}C NMR (213 MHz, DMSO-d_6) δ (ppm): 23.42 (-CH_2), 43.44 (-O-CH_2-), 111.44 (Ar-C), 121.86 (Ar-C), 123.98 (Ar-C), 124.38 (Ar-C), 125.89 (Ar-C), 126.45 (Ar-C), 128.34 (Ar-C), 128.59 (Ar-C), 132.58 (Ar-C), 132.64 (Ar-C), 137.11 (Ar-C), 137.75 (Ar-C), 145.67 (Ar-C),

165.44 (C=N of oxadiazole), 165.72 (C=N of oxadiazole), 169.68 (C=N of benzothiazole); ESI +ve MS (m/z): 363 $[M+H]^+$; Anal. Calc. for $C_{19}H_{14}O_2N_4S$: C, 62.97; H, 3.89; O, 8.83; N, 15.46; S, 8.85. Found: C, 62.95; H, 3.90; O, 8.84; N, 15.46; S, 8.84.

2-((5-((2,4-dichlorophenoxy)methyl)-1,3,4-oxadiazol-2-yl)methoxy)benzo[d]thiazole (17)

Yield: 54%; white crystals; m.p. 243-244 °C; IR (ATR, cm^{-1}): 3070 (C-H aromatic), 2988 (C-H aliphatic), 1668 (C=N of benzothiazole), 1586 (C=N of oxadiazole), 1473, 1460, 1269, 1234, 1187, 1093, 1052, 898, 739 (C-S). ^{1}H NMR (850 MHz, DMSO-d_6) δ (ppm): 4.71 (s, 2H, -O-CH_2-), 4.74 (s, 2H, -O-CH_2-), 7.07 (d, *J* = 9.5 Hz, 1H, Ar-H), 7.16-7.22 (m, 2H, Ar-H), 7.27-7.37 (m, 2H, Ar-H), 7.49 (s, 1H, Ar-H), 7.56-7.58 (m, 1H, Ar-H). ^{13}C NMR (213 MHz, DMSO-d_6) δ (ppm): 43.55 (-O-CH_2-), 43.74 (-O-CH_2-), 111.88 (Ar-C), 121.58 (Ar-C), 123.00 (Ar-C), 123.31 (Ar-C), 123.81 (Ar-C), 127.03 (Ar-C), 128.07 (Ar-C), 128.44 (Ar-C), 129.43 (Ar-C), 129.85 (Ar-C), 130.02 (Ar-C), 137.51 (Ar-C), 165.47 (C=N of oxadiazole), 165.87 (C=N of oxadiazole), 169.62 (C=N of benzothiazole); ESI +ve MS (m/z): 408 $[M+H]^+$, 410 $[M+2+H]^+$; Anal. Calc. for $C_{17}H_{11}Cl_2O_3N_3S$: C, 50.01; H, 2.72; O, 11.76; N, 10.29; S, 7.85. Found: C, 49.98; H, 2.71; O, 11.77; N, 10.30; S,7.85.

2-((5-styryl-1,3,4-oxadiazol-2-yl)methoxy) benzo[d]thiazole (18)

Yield: 58%; white crystals; m.p. 192-193 °C; IR (ATR, cm^{-1}): 3067 (C-H aromatic), 2983 (C-H aliphatic), 1600 (C=N of benzothiazole), 1577 (C=N of oxadiazole), 1538, 1508, 1484, 1449, 1403, 1312, 1289, 1217, 1160, 1126, 1089, 1067, 1047, 1024, 744 (C-S). ^{1}H NMR (850 MHz, DMSO-d_6) δ (ppm): 5.55 (s, 2H, -O-CH_2-), 7.25-7.27 (m, 1H, Ar-H), 7.31-7.33 (m, 1H, Ar-H), 7.40-7.45 (m, 5H, Ar-H), 7.53-7.57 (m, 1H, Ar-H), 7.72-7.73 (m, 1H, Ar-H), 7.76 (d, *J* = 6.8 Hz, 2H, -C=CH). ^{13}C NMR (213 MHz, DMSO-d_6) δ (ppm): 37.02 (-O-CH_2-), 109.75 (Ar-C), 111.66 (Ar-C), 121.26 (Ar-C), 123.18 (Ar-C), 123.81 (Ar-C), 126.88 (Ar-C), 127.96 (Ar-C), 128.99 (Ar-C), 130.13 (Ar-C), 134.47 (Ar-C), 136.27 (Ar-C), 139.28 (C=C), 160.91 (C=N of oxadiazole), 164.75 (C=N of oxadiazole), 169.05 (C=N of benzothiazole); ESI +ve MS (m/z): 336 $[M+H]^+$;Anal. Calc. for $C_{18}H_{13}O_2N_3S$: C, 64.46; H, 3.91; O, 9.54; N, 12.53; S, 9.56. Found: C, 64.44; H, 3.90; O, 9.55; N,12.54; S, 9.57.

Anticancer activity

Cell culture

Breast adenocarcinoma cells (MCF-7) used was obtained from the American type culture collection (ATCC). The cells were maintained in RPMI-1640 in a humidified atmosphere of 5% CO_2 at 37 °C. The cells were supplemented with antibiotic penicillin (100 units/mL) and heat activated fetal bovine serum (10% v/v) [27].

Cytotoxic study

The cytotoxicity of the target compounds were evaluated against MCF-7 cells using sulphorhodamine B assay (SRB). The healthy cells were cultured in 96 well tissue culture plate (3000 cells/well). The cells were cultured before 24 hrs of the testing of the target compounds. The 96 well culture plate were exposed to the five different concentration (0.01, 0.1, 1, 10 and 100 μM/mL); untreated cells were consider as control. The plate was incubated for 72 hrs and subsequently fixed with TCA (10% w/v) for 1hr at 4 °C. The cells were washed for several times and were stained by 0.4% (w/v) SRB solution for 10 min in dark place. Stained cells were dried overnight, dissolved in *tris*-HCl and the intensity of color was measured in microplate reader at 540 nm. IC_{50} (dose of the drug which reduces survival to 50%) value of the tested compounds were obtained from the linear plot between viability percentage of tumor cells and compounds concentration using Sigmaplot 12.0 software [28].

Results and Discussion

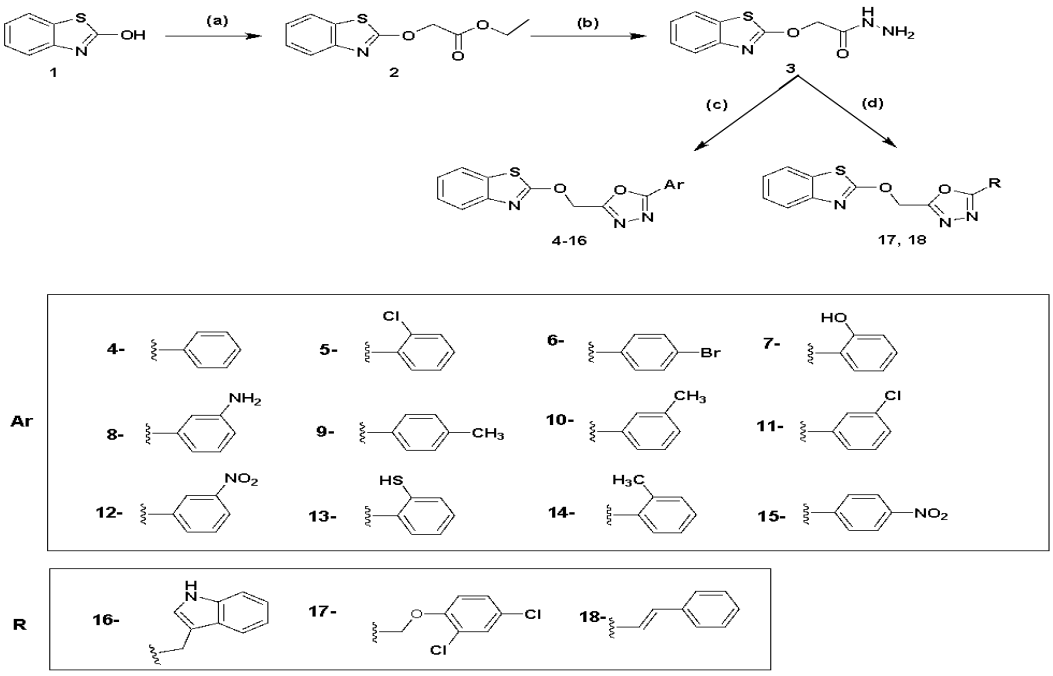
Chemistry

A series of fifteen new 1,3,4-oxadiazole clubbed benzothiazole heterocycles (**4-18**) have been synthesized according to the synthetic route described in scheme 1. Reaction of 2-hydroxy benzothiazole (**1**) with ethyl chloroacetate in presence of dry acetone and anhydrous potassium carbonate yielded ethyl 2-(benzo[d]thiazol-2-yloxy)acetate (**2**)**.** Reaction of compound **(2)** with hydrazine monohydrate in absolute ethanol yielded a key intermediate 2-(benzo[d]thiazol-2-yloxy) acetohydrazide (**3**). This key intermediate (**3**) was reacted with different aromatic acids and substituted phenoxy acetic acids in presence of dehydrating agent $POCl_3$ to give the target compounds (**4-18**)**.** Proposed structures of the compounds were confirmed by different analytical techniques such as IR, ^{1}H NMR, ^{13}C NMR, elemental analyses and mass spectrometry. The spectral data confirmed the proposed structures of the synthesized compounds.

Formation of ethyl 2-(benzo[d]thiazol-2-yloxy) acetate (**2**) was confirmed by the presence of a strong absorption band at 1671 cm^{-1} for C=N of benzothiazole ring, 1663 cm^{-1} for carbonyl carbon and 1049 cm^{-1} for C-O of the ester group. The ^1H NMR showed a quartet of two protons at δ 4.17 and a triplet for three protons at δ 1.21 which is typical for ethyl ester. The methylene group was observed as a singlet at δ 4.84 for two protons in ^1H NMR and at δ 61.46 in ^{13}C NMR. Beside this, the presence of two triplet of triplet integrating for one proton each at 7.23 (*J*=0.85 Hz, 8.5 Hz), 7.36 (*J* = 0.85 Hz, 8.5 Hz), one doublet at 7.31 (*J*=8.5 Hz) for one proton and a doublet of doublet integrating for one proton at 7.68 (*J* = 0.85 Hz, 7.6 Hz) supported the aromatic protons of benzothiazole ring. Finally formation of compound (**2**) was confirmed by mass spectrometry which exhibited the molecular ion peak at 238 $(M+H)^+$. Formation of hydrazide (**3**) was supported by the presence of absorption bands at 3311 and 3222 cm^{-1} for NH_2 and NH, respectively and a carbonyl carbon stretching at 1653 in the IR spectrum. The disappearance of signals of ethyl protons of the ester and appearance of broad singlet at δ 9.45 for one proton (-NH) and other broad singlet at δ 4.31 for two protons (NH_2) in ^1H NMR spectrum further supported the conversion of compound (**2**) to (**3**). The structure of compound (**3**) was further supported by the mass spectrometry which exhibited molecular ion peak at 224 $(M+H)^+$. The formation of target compounds (**4-18**) was confirmed by the disappearance of bands of NH-NH_2 and of hydrazidic carbonyl group indicating the conversion of hydrazide into oxadiazole ring as observed from the stretching of oxadiazole ring at 1522-1594 cm^{-1} for C=N in IR spectra. Further structure confirmation was done by ^{13}C NMR which exhibited two additional signals in the range δ 160-165 for C=N of the oxadiazole ring and one signal in the range δ 167-169 for C=N of benzothiazole ring. Finally, all the target compounds were confirmed by the mass spectral data.

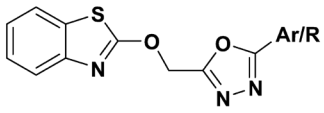
Anticancer activity

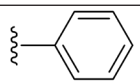
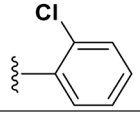
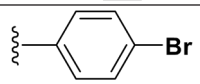
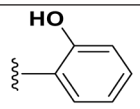
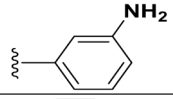
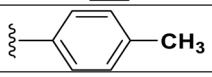
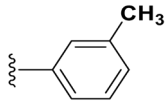
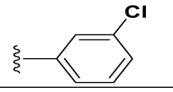
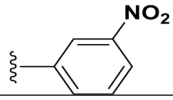
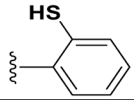
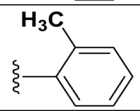
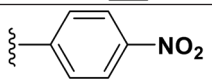
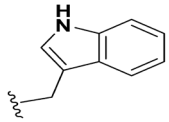
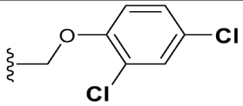
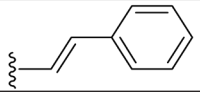
The target compounds (4-18) were screened for the anticancer activity against Breast adenocarcinoma cell line (MCF-7) using Sulphorhodamine B assay (SRB). The results are presented in Table 1, Fig. (2). The results showed that the synthesized derivatives revealed variable activity. Four compounds (7, 10, 13, 14) showed potent cytotoxic profile. 2-(5-((benzo[d]thiazol-2-yloxy)-methyl)-1,3,4-oxadiazol-2-yl)phenol was the most potent compound which showed IC_{50} value 1.8 ± 0.2 µM/mL which was comparable to standard drug, Doxirubicin having IC_{50} 1.2 ± 0.005 µM/mL. Compounds (2-((5-m-tolyl-**1,3,4**-oxadiazol-2-yl)methoxy)benzo[d]thiazole, 2-(5-((benzo[d]hiazol-2-yloxy) methyl)-1,3,4-



Scheme 1. Synthesis of benzothiazole linked 1,3,4-oxadiazole derivatives

TABLE 1: The IC_{50} (µM/mL) of the synthesized compounds (4-18) against MCF-7 cells.



Compound	Ar / R	IC_{50} (µM/mL)
* Dox.		1.2 ± 0.005
4		119.1 ± 4.02 (N A)
5		135.1 ± 2.1 (N A)
6		50.5 ± 2.7
7		1.8 ± 0.2
8		95.1 ± 1.3
9		6.4 ± 0.9
10		4.5 ± 0.2
11		20.6 ± 0.1
12		15.8 ± 0.8
13		4.3 ± 0.3
14		3.4 ± 0.4
15		7.5 ± 1
16		10.4 ± 0.6
17		6.9 ± 0.4
18		8.6 ± 1.3

* Dox: Doxirubicin (standard drug)

oxadiazol-2-yl)benzene thiol and 2-((5-o-tolyl-1,3,4-oxadiazol-2-yl)methoxy)benzo[d]thiazole) exhibited IC_{50} 4.5 ± 0.2 µM/mL, 4.3 ± 0.3 µM/mL and 3.4 ± 0.4 µM/mL, respectively. Fig. (3). It was observed from the results that the presence of substituent at ortho position showed potent cytotoxicity.

Compounds (9, 11, 12, 15, 16, 17 and 18) have moderate cytotoxicity effect on breast cancer (MCF-7) with IC_{50} ranging from 6.4-8.6 µM/mL. Compound (2-((5-p-tolyl-1,3,4-oxadiazol-2-yl)methoxy)benzo [d]thia zole, 2-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl) methoxy)benzo[d]thiazole, 2-((5-((2,4-dichloro

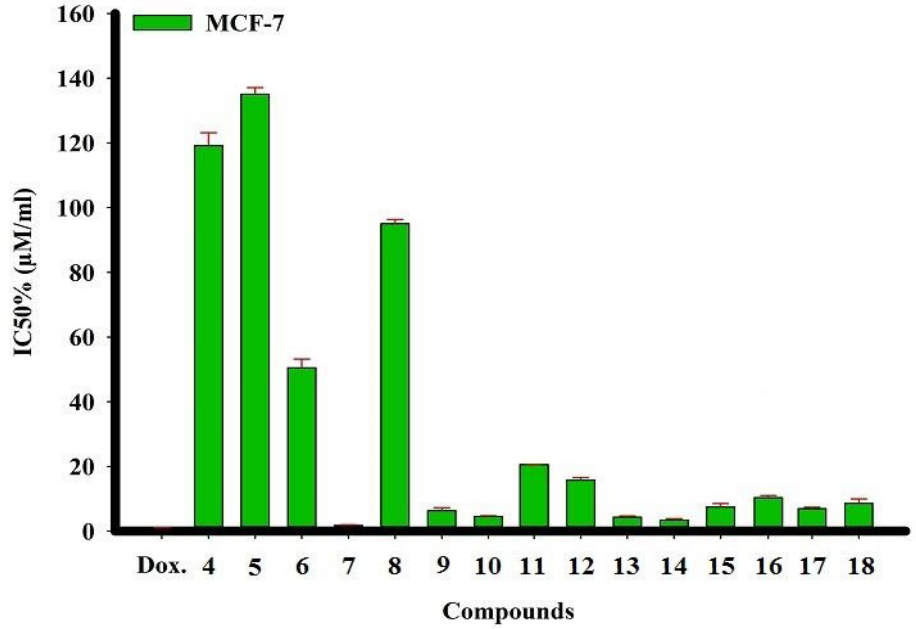


Fig. 2. IC_{50}% of the synthesized compounds against MCF-7. Dox-Doxorubicin.

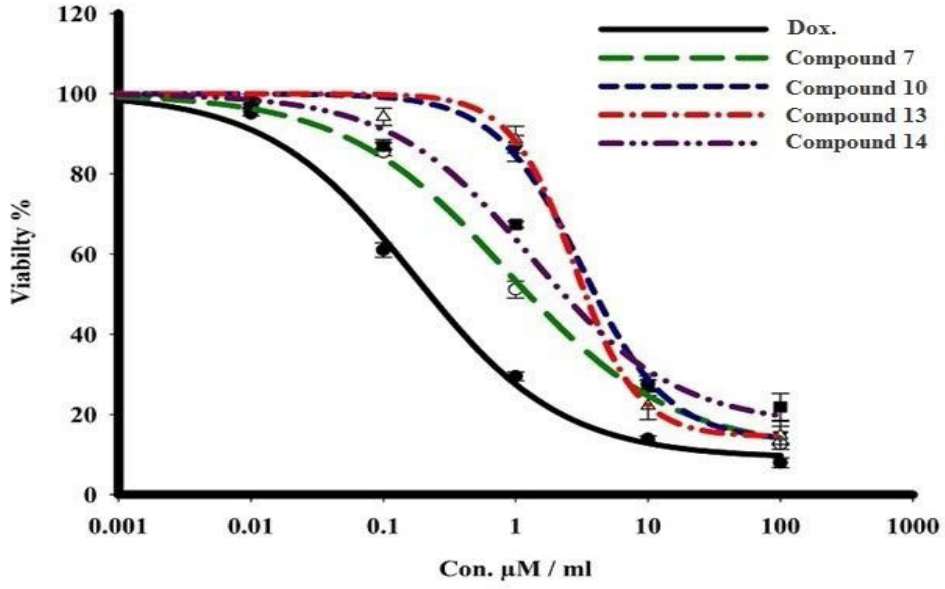


Fig. 3. Dose-response curve of active compounds (7, 10, 13, 14) in MCF-7. Viability of cell was determined using SRB-U SulphoRhodamine-B assay. Data are expressed as mean ± S.D (n=3). Dox = Doxorubicin.

phenoxy) methyl)-1,3,4-oxadiazol-2-yl) methoxy)benzo[d]thiazole and 2-((5-styryl-1,3,4-oxadiazol-2-yl) methoxy) benzo [d]thiazole) revealed IC_{50} 6.4 ± 1.0 µM/mL, 6.9 ± 0.4 µM/mL and 8.6 ± 1.3 µM/mL, respectively. Beside this, 2-((5-(4-bromophenyl)-1,3,4-oxadiazol-2-yi) methoxy)benzo[d]thiazole and 3-(5-((benzo[d] thiazol-2-yloxy)methyl)-1,3,4-oxadiazol-2-yl) benzenamine showed lower cytotoxic effect towards MCF-7 cells with 50.5 µM/mL and 95.1 µM/mL respectively. Some compounds were found to be inactive against the cell line. 2-((5-phenyl-1,3,4-oxadiazol-2-yi)methoxy)benzo[d]thiazole and 2-((5-(2-chlorophenyl)-1,3,4-oxadiazol-2-yl)methoxy)benzo[d]thiazole did not showed cytotoxicity. From the results it was observed that aromatic ring activating groups such as methyl and hydroxy enhances the cytotoxic effect whereas aromatic ring deactivating group such as nitro showed moderate cytotoxicity against MCF-7 cancer cells.

Conclusion

A library of fifteen 1,3,4-oxadiazole incorporated benzothiazole heterocycles have been synthesized and confirmed by different analytical techniques. The synthesized derivatives were screened for cytotoxic against MCF-7 cells. The synthesized compounds showed variable cytotoxic effects. Some compounds showed potent anticancer activity with IC_{50} in the range of 1.8-4.5 µM/mL. While some compounds showed moderate to low cytotoxicity. 2-(5-((benzo[d] thiazol-2-yloxy)-methyl)-1,3,4-oxadiazol-2-yl) phenol was the most potent compound which exhibited cytotoxicity on MCF-7 cell with IC_{50} value of 1.28 µM/mL which was comparable to standard drug Doxirubicin with IC_{50} value of 1.2 µM/mL. From the results it was observed that electron donating groups such as methyl and hydroxyl resulted in enhancement of the cytotoxic effect against MCF-7 cells.

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تحضير، توصيف ودراسة سمية ٢-هيدروكسي بينزوثيازولمدموجة مع مشتقات ١،٣،٤-أكساديازول

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تم تحضير خمسة عشر أوكسادايزولمشتقة من ٢-هيدروكسي بنزوثيازولواختبار نشاطها كمضاد للسرطان وقد تم استخدام أحماض عطرية مختلفة من أجل هذا التصنيع. ولربط العلاقة بين البنية والنشاط ،قد عمل فحص السمية الخلوية مخبرياً ضدعخلايا سرطان الثدي MCF-7، حيث أظهرت المركبات المحضرة تأثيراً سمياً مختلفاً ، أربع مركبات أظهرت تأثيراً قوياً للسمية الخلوية وكانت قيم IC_{50} مختلفة و بمعدل يتراوح بين ١,٨ ميكروميتر إلى ٤,٥ ميكروميتر بينما باقي المركبات أظهرت تأثيراً متوسط إلى منخفض ، المركب ٧ كان المركب الأكثر فاعلية والذي أظهر تأثيراً (IC_{50} ١,٨ ± ٠,٠٢) مقارنة بالدواء القياسيدوكسيروبيسين (IC_{50} ١,٢ ± ٠,٠٠٥).

لوحظ من النتائج أن المجموعات المنشطة مثل الميثيل والهيدروكسيل للحلقة العطرية تعزز من سمية المركب ضد الخلايا السرطانية وفي المقابل المجموعات المثبطة للحلقة العطرية مثل مجموعة النيتروأظهرت سمية خلوية متوسطة تجاه خلايا سرطان الثدي MCF-7.