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## **Synthesis, molecular docking and anticancer activity of novel 1,3-thiazolidin-4-ones**

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## ABSTRACT

**Background:** Cancer is a major cause of death all over the globe. Controlling cell division by inhibition of mitosis is the most successful clinical strategy for cancer treatment. The development of novel anticancer agents is the most important area in medicinal chemistry and drug discovery research. Thiazolidine is the multifunctional nucleus which shows a number of pharmacological activities like anticancer, anti-inflammatory, antioxidant, antibacterial, antifungal, antidiabetic, antihyperlipidemic and antiarthritic. **Methods:** In a present study series of 2-substituted-3-(1H-benzimidazole-2-yl)-thiazolidin-4-ones were designed, synthesized by the microwave-assisted system, and characterized by melting point, IR, <sup>1</sup>H NMR, and mass spectroscopy. All the newly synthesized compounds were examined for their *in vitro* anticancer activity against breast cancer cell line MCF-7 by Sulforhodamine B (SRB) assay. **Results:** The compounds AB-12 (GI<sub>50</sub>: 28.5 µg/ml) and AB-6 (GI<sub>50</sub>: 50.7 µg/ml) exhibited significant cell growth inhibitory activity. **Conclusion:** These results indicate that compound AB-12 and AB-6 as related polo-like kinase 1 inhibitors compounds could be lead compounds for further development of anticancer agents.

**Keywords:** Anticancer activity, MCF-7 cell line, Molecular Modelling, Polo-like kinase 1 inhibitors, Synthesis, Thiazolidine-4-one

## Introduction

Cancer is a disease in which normal body cells transformed into tumour cells without any control. As per World Health Organization (WHO) cancer is second most mortality cause worldwide. Lung cancer and breast cancer are the most dangerous as compared with the other type of cancers. Approximately 2.09 million cases and 6, 27,000 deaths occurred due to the breast cancer in 2018<sup>1, 2</sup>. Polo-like kinase 1 (PLK1) is from family of serine/threonine protein kinase which is basically available in eukaryotic cells<sup>3</sup>. PLK1 is a most studied member from the PLK family and which play important role in the cell cycle progression. This is required for the regulation of various steps involve in cell cycle<sup>4, 5</sup>. Overexpression of (PLK1) may cause carcinogenesis and is a specific target for prevention of various steps involve in cancer cell growth like mitosis, spindle formation, centrosome maturation, mitotic entry, mitotic exit, chromatin segregation and cytokinesis<sup>6, 7</sup>. Currently more than 51 kinase inhibitors are approved for the management of cancer<sup>8</sup>. At present situation some PLK1 inhibitors are in preclinical and clinical trials<sup>9</sup>.

Literature survey shows diversity in the biological response of 1, 3-thiazolidine-4-ones like anticancer<sup>10</sup>, anti-inflammatory<sup>11</sup>, antioxidant<sup>12</sup>, antibacterial<sup>13</sup>, antifungal<sup>14</sup>, antidiabetic<sup>15</sup> and antihyperlipidemic<sup>16</sup> activity. By preventing PLK1 overexpression we can prevent carcinogenesis. Some Thiazolidine analogues used to inhibit polo-like kinase enzyme for treatment of cancer. In the present study, we propose to synthesize a series of 1, 3 thiazolidine-4-ones, structural elucidation and molecular docking studies, followed by screening for their anticancer activity by Sulforhodamine B (SRB) assay on breast cancer cell line MCF-7.

## **Materials and methods**

### ***General***

The synthesized compounds were purified using flash chromatography. Physical constant (Melting point) was determined by Gallenkamp electric melting point apparatus. Thin layer chromatography (TLC, Silica gel 60 F254, Merck) was used to monitor the progress, amount of untreated starting material and assess the purity of the compounds that were detected under UV light and iodine vapour. All synthesized compounds were characterized by <sup>1</sup>H NMR and IR and mass spectroscopy. IR spectra (KBr discs) were recorded on Jasco Infrared Affinity-1 spectrophotometer. <sup>1</sup>H NMR, spectra recorded in DMSO-d<sub>6</sub> by using Bruker 500 MHz spectrometers (Bruker Bioscience, Billerica, MA, USA) 500 MHz in chloroform (CDCl<sub>3</sub>) and dimethyl sulfoxide (DMSO-d<sub>6</sub>) used as a solvent, tetramethylsilane (TMS) was used as an

internal standard. Chemical shifts are shown as  $\delta$  values (ppm). Signals are shown as s (singlet), d (doublet), t (triplet), q (quintet) or m (multiplet). Mass spectral data were recorded by using a Waters Q-TOF premier mass spectrometer. Mass spectra of most of the compounds show molecular ion as  $(M+1)^+$ . The elemental analysis were done by Elemental analyser (Exeter Analytical Inc. model: CE 440) for CHN analysis. The chemicals were purchased commercially from Sigma Aldrich, S. D. Fine chemicals, Loba Chemicals and Spectrochem Chemicals.

***General method for the synthesis of 2-substituted-3-(1H-benzoimidazol-2-yl)-thiazolidin-4-ones (AB-1 to AB-13)***

A mixture of 2-aminobenzimidazole (0.01 mol), substituted aldehydes (0.01mol), thioglycolic acid (0.01mol) and sodium hydroxide in ethanol (10 ml) was placed in a round bottom flask. The mixtures were stirred well and then allow for microwave irradiation in the microwave synthesis system (CEM, USA) at 30W for 30 min. After cooling, the mixture was dissolved into ethyl acetate and water. The ethyl acetate layer was dried. The crude product was purified by flash chromatography (BUCHI, Switzerland). The completion of the reaction was monitored by thin layer chromatography and the mobile phase used was ethyl acetate: petroleum ether (2:1).

***3-(1H-Benzoimidazol-2-yl)-2-phenyl-thiazolidin-4-one (AB-1)***

White solid; Yield 67%;  $R_f$  value 0.63; M.P.:110-113°C; FT-IR: (KBr, $\text{cm}^{-1}$ ): 3481, 3073, 2560, 1704, 1664, 1308;  $^1\text{H}$  NMR (500 MHz, DMSO): 7.26-7.70 (m, 4H, Ar-H), 5.00 (s, 1H, NH), 5.92 (s, 1H, CH), 3.33 (s, 2H,  $\text{CH}_2$ ), 7.06-7.14 (m, 5H, Ar-H); MS (ESI):  $m/z$  296.08  $(M+1)^+$ ; Anal. Calcd for  $\text{C}_{16}\text{H}_{13}\text{N}_3\text{OS}$ ; C, 65.06; H, 4.44; N, 14.23; found C, 65.11; H, 4.49; N, 14.25.

***3-(1H-Benzoimidazol-2-yl)-2-(4-chloro-phenyl)-thiazolidin-4-one (AB-2)***

Brown solid; Yield 54%;  $R_f$  value 0.68; M.P.:141-144°C; FT-IR: (KBr, $\text{cm}^{-1}$ ): 3481, 3073, 2560, 1704, 1664, 1308, 605;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ): 7.26-7.70 (m, 4H, Ar-H), 7.00-7.15 (m, 4H, Ar-H); 5.92 (s, 1H, CH), 5.00 (s, 1H, NH), 3.33 (s, 2H,  $\text{CH}_2$ ), MS (ESI):  $m/z$  330.04  $(M+1)^+$ ; Anal. Calcd for  $\text{C}_{16}\text{H}_{12}\text{ClN}_3\text{OS}$ ; C, 58.27; H, 3.67; N, 12.74. found C, 58.32; ; H, 3.70; N, 12.76.

**3-(1H-Benzoimidazol-2-yl)-2-(2-nitro-phenyl)-thiazolidin-4-one (AB-3)**

Black solid; Yield 60%;  $R_f$  value 0.51; M.P.:152-154°C; FT-IR: (KBr, $\text{cm}^{-1}$ ): 3481, 3073, 2560, 1704, 1664, 1308, 1535;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ): 7.26-7.70 (m, 4H, Ar-H), 5.00 (s, 1H, NH), 5.92 (s, 1H, CH), 3.33 (s, 2H,  $\text{CH}_2$ ), 7.32-8.07 (m, 4H, Ar-H); MS (ESI):  $m/z$  341.06 ( $\text{M}+1$ ) $^+$ ; Anal. Calcd for  $\text{C}_{16}\text{H}_{12}\text{N}_4\text{O}_3\text{S}$ ; C, 56.46; H, 3.55; N, 16.46. found C, 56.50; H, 3.57; N, 16.51.

**3-(1H-Benzoimidazol-2-yl)-2-(2-chloro-phenyl)-thiazolidin-4-one (AB-4)**

Brown solid; Yield 47%;  $R_f$  value 0.67; M.P.:157-159°C; FT-IR: (KBr, $\text{cm}^{-1}$ ): 3481, 3073, 1704, 2560, 1664, 1308, 605;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ): 7.26-7.70 (m, 4H, Ar-H), 5.00 (s, 1H, NH), 5.92 (s, 1H, CH), 3.33 (s, 2H,  $\text{CH}_2$ ), 7.00-7.15 (m, 4H, Ar-H); MS (ESI):  $m/z$  330.04 ( $\text{M}+1$ ) $^+$ ; Anal. Calcd for  $\text{C}_{16}\text{H}_{12}\text{ClN}_3\text{OS}$ ; C, 58.27; H, 3.67; N, 12.74. found C, 58.30; H, 3.71; N, 12.77.

**3-(1H-Benzoimidazol-2-yl)-2-(3-chloro-phenyl)-thiazolidin-4-one (AB-5)**

Yellow solid; Yield 64%;  $R_f$  value 0.55; M.P.:167-169°C; FT-IR:(KBr, $\text{cm}^{-1}$ ): 3481, 3073, 2560, 1704, 1664, 1308, 605;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ): 7.26-7.70 (m, 4H, Ar-H), 5.00 (s, 1H, NH), 5.92 (s, 1H, CH), 3.33 (s, 2H,  $\text{CH}_2$ ), 6.94-7.08 (m, 4H, Ar-H); MS (ESI):  $m/z$  330.04 ( $\text{M}+1$ ) $^+$ ; Anal. Calcd for  $\text{C}_{16}\text{H}_{12}\text{ClN}_3\text{OS}$ ; C, 58.27; H, 3.67; N, 12.74. found C, 58.32; H, 3.72; N, 12.78.

**3-(1H-Benzoimidazol-2-yl)-2-(3-bromo-phenyl)-thiazolidin-4-one (AB-6)**

Yellow solid; Yield 67%;  $R_f$  value 0.59; M.P.:184-186°C; FT-IR: (KBr, $\text{cm}^{-1}$ ): 3481, 3073, 2560, 1704, 1664, 1308, 585;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ): 7.26-7.70 (m, 4H, Ar-H), 5.00 (s, 1H, NH), 5.92 (s, 1H, CH), 3.33 (s, 2H,  $\text{CH}_2$ ), 7.00-7.24 (m, 4H, Ar-H); MS (ESI):  $m/z$  373.99 ( $\text{M}+1$ ) $^+$ ; Anal. Calcd for  $\text{C}_{16}\text{H}_{12}\text{BrN}_3\text{OS}$ ; C, 51.35; H, 3.23; N, 11.23. found C, 51.39; H, 3.27; N, 11.27.

**3-(1H-Benzoimidazol-2-yl)-2-(4-nitro-phenyl)-thiazolidin-4-one (AB-7)**

Brown solid; Yield 42%;  $R_f$  value 0.63; M.P.:176-178°C; FT-IR: (KBr, $\text{cm}^{-1}$ ): 3481, 3073, 2560, 1704, 1664, 1308, 1535;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ): 7.26-7.70 (m, 4H, Ar-H), 5.00 (s, 1H, NH), 5.92 (s, 1H, CH), 3.33 (s, 2H,  $\text{CH}_2$ ), 7.32-8.07 (m, 4H, Ar-H); MS (ESI):  $m/z$  341.06

(M+1)<sup>+</sup>; Anal. Calcd for C<sub>16</sub>H<sub>12</sub>N<sub>4</sub>O<sub>3</sub>S; C, 56.46; H, 3.55; N, 16.46. found C, 56.51; H, 3.59; N, 16.50.

**3-(1H-Benzoimidazol-2-yl)-2-pyridin-2-yl-thiazolidin-4-one (AB-8)**

Brown solid; Yield 46%; R<sub>f</sub> value 0.61; M.P.:170-172°C; FT-IR: (KBr,cm<sup>-1</sup>): 3481, 3073, 2560,1704, 1664, 1308; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): 7.26-7.70 (m, 4H, Ar-H), 5.00 (s, 1H, NH), 5.92 (s, 1H, CH), 3.33 (s, 2H, CH<sub>2</sub>), 7.29-8.64 (m, 4H, Ar-H); MS (ESI): m/z 297.07 (M+1)<sup>+</sup>; Anal. Calcd for C<sub>15</sub>H<sub>12</sub>N<sub>4</sub>O<sub>3</sub>S; C, 60.79; H, 4.08; N, 18.91. found C, 60.83; H, 4.13; N, 18.93.

**3-(1H-Benzoimidazol-2-yl)-2-(3-methoxy-phenyl)-thiazolidin-4-one (AB-9)**

Yellow solid; Yield 45%; R<sub>f</sub> value 0.61; M.P.:179-181°C; FT-IR: (KBr,cm<sup>-1</sup>): 3481, 3073, 2560,1704, 1664, 1308, 1245; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): 7.26-7.70 (m, 4H, Ar-H), 5.00 (s, 1H, NH), 5.92 (s, 1H, CH), 3.33 (s, 2H, CH<sub>2</sub>), 3.73 (s, 3H, Ar-OCH<sub>3</sub>), 6.57-7.03 (m, 4H, Ar-H); MS (ESI): m/z 326.09 (M+1)<sup>+</sup>; Anal. Calcd for C<sub>17</sub>H<sub>15</sub>N<sub>3</sub>O<sub>2</sub>S; C, 62.75; H, 4.65; N, 12.91. found C, 62.79; H, 4.69; N, 12.94.

**3-(1H-Benzoimidazol-2-yl)-2-(4-dimethylamino-phenyl)-thiazolidin-4-one (AB-10)**

Brown solid; Yield 49%; R<sub>f</sub> value 0.55; M.P.:245-247°C; FT-IR: (KBr,cm<sup>-1</sup>): 3481, 3073, , 2560, 1704,1664, 1308; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): 7.26-7.70 (m, 4H, Ar-H), 5.00 (s, 1H, NH), 5.92 (s, 1H, CH), 3.33 (s, 2H, CH<sub>2</sub>), 2.85 (s, 6H, Ar-N-2CH<sub>3</sub>), 6.47-6.88 (m, 4H, Ar-H); MS (ESI): m/z 339.12 (M+1)<sup>+</sup>; Anal. Calcd for C<sub>18</sub>H<sub>18</sub>N<sub>4</sub>OS; C, 63.88; H, 5.36; N, 16.56. found C, 63.91; H, 5.38; N, 16.60.

**3-(1H-Benzoimidazol-2-yl)-2-(3-nitro-phenyl)-thiazolidin-4-one (AB-11)**

Yellow solid; Yield 40%; R<sub>f</sub> value 0.65; M.P.:174-176°C; FT-IR: (KBr,cm<sup>-1</sup>): 3481, 3073, 2560, 1704, 1664, 1535, 1308; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): 7.26-7.70 (m, 4H, Ar-H), 5.00 (s, 1H, NH), 5.92 (s, 1H, CH), 3.33 (s, 2H, CH<sub>2</sub>), 7.40-8.00 (m, 4H, Ar-H); MS (ESI): m/z 341.06 (M+1)<sup>+</sup>; Anal. Calcd for C<sub>16</sub>H<sub>12</sub>N<sub>4</sub>O<sub>3</sub>S; C, 56.46; H, 3.55; N, 16.46. found C, 56.50; H, 3.58; N, 16.49.

**3-(1H-Benzoimidazol-2-yl)-2-(4-methoxy-phenyl)-thiazolidin-4-one (AB-12)**

Brown solid; Yield 56%;  $R_f$  value 0.62; M.P.:168-170°C; FT-IR: (KBr,  $\text{cm}^{-1}$ ): 3481, 3073, 2560, 1704, 1664, 1308, 1245;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ): 7.26-7.70 (m, 4H, Ar-H), 5.00 (s, 1H, NH), 5.92 (s, 1H, CH), 3.33 (s, 2H,  $\text{CH}_2$ ), 3.73 (s, 3H, Ar- $\text{OCH}_3$ ), 6.65-6.95 (m, 4H, Ar-H); MS (ESI):  $m/z$  326.09 ( $\text{M}+1$ )<sup>+</sup>; Anal. Calcd for  $\text{C}_{17}\text{H}_{15}\text{N}_3\text{O}_2\text{S}$ ; C, 62.75; H, 4.65; N, 12.91. found C, 62.77 ; H, 4.70; N, 12.96.

### ***3-(1H-Benzoimidazol-2-yl)-2-(2-hydroxy-phenyl)-thiazolidin-4-one (AB-13)***

Yellow solid; Yield 67%;  $R_f$  value 0.69; M.P.:133-135°C; FT-IR: (KBr,  $\text{cm}^{-1}$ ): 3481, 3073, 2560, 1704, 1664, 1308;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ): 7.26-7.70 (m, 4H, Ar-H), 5.00 (s, 1H, NH), 5.92 (s, 1H, CH), 3.33 (s, 2H,  $\text{CH}_2$ ), 5.0 (s, 1H, Ar-OH), 6.61-6.90 (m, 4H, Ar-H); MS (ESI):  $m/z$  312.07 ( $\text{M}+1$ )<sup>+</sup>; Anal. Calcd for  $\text{C}_{16}\text{H}_{13}\text{N}_3\text{O}_2\text{S}$ ; C, 61.72; H, 4.21; N, 13.50. found C, 61.76; H, 4.24; N, 13.54.

### ***Molecular docking studies***

Docking procedure aims to identify the correct binding poses and binding interaction within the binding site of the protein. Molecular docking is performed with VLife MDS software. The crystal structure of Polo-like kinase 1 (PDB entry code-2rku) was extracted from protein data bank database (<http://www.rcsb.org/pdb>). The 2D structures were drawn and converted into 3D structures. The 3D structure was optimized by using optimization tool up to the rms gradient of 0.01 using MMFF. Protein structure was optimized. Cavity no.1 is selected for docking procedure. The active site of protein was defined as all atoms within 5Å radius. Docking studies were performed by batch docking to get docking score and interactions between ligand and target protein.

### ***Anticancer activity (Sulforhodamine B assay)***

Anticancer activity of the synthesized compounds was tested by using SRB assay on MCF-7 human breast cancer cell line. The medium used for growing the cell line contains 2 mM L-glutamine and 10 % fetal bovine serum. The experiment was carried out in 96 well microtiter plates in 100  $\mu\text{L}$  at plating densities, depending on the double time of separate cell line. An inoculated plate was incubated at a temperature of 37°C, 5 % carbon dioxide and 95 % air and 100 % relative humidity for a time period of 24 hours. The synthesized compounds were not added in the plates at that time.

The synthesized compound was dissolved in dimethyl sulfoxide (DMSO) and solution with a concentration of 100 mg/ml was prepared. The prepared solution diluted up to 1 mg/ml by using water and this solution was stored frozen before further procedure. At the time of actual compound addition aliquots of frozen concentrated (1 mg/ml) was diluted to 100, 200, 400 and 800 µg /ml with complete medium. Aliquots of 10 µl of dilutions of the synthesized compounds was added into the microtiter wells which already containing 90 µl of a medium. The resultant final concentration of the compound was 10, 20, 40 and 80 µg /ml<sup>17</sup>.

The microtiter plate was incubated in the standard condition for 48 hours and the process was finished by addition of cold trichloroacetic acid (TCA). Trichloroacetic acid (TCA) was added for the washing of stain. The cell line was fixed *in situ* by slow addition in 50 µl of trichloroacetic acid (30 % w/v) and incubated at 4°C for 60 minutes. The upper layer of the solution was discarded and plate was washed five times with water and finally air dried. The 50 µl sulforhodamine B (SRB) solutions at 0.4 % w/v were prepared. After that 1% acetic acid was added to well for removal of unbound dye. Microtiter plates were incubated at room temperature for 20 minutes. The staining unbound dye was removed by five times washing with the water. All plates were air-dried. Bound dye stain was eluted with 10 mM trizma base. Absorbance was measured at a wavelength of 540 nm and reference wavelength of 690 nm. Percentage of growth was calculated. Growth of plates of synthesized compounds and control well was compared<sup>18</sup>.

Percentage growth = Average absorbance of the test well / average absorbance of the control wells x 100

## Results and Discussion

### Chemistry

A series of 2-substituted-3-(1H-benzimidazol-2-yl)-thiazolidin-4-ones was synthesized by using microwave system as per outlined in Figure 1. All compounds were obtained in appreciable yield and their physicochemical characteristics. Synthesized compounds primarily analysed by thin layer chromatography and melting point. The formation of final compounds was analysed on the basis of NMR, IR and Mass spectral characteristics.

### Docking studies



The docking studies were carried out to check docking score and interactions between ligand and PLK1 enzyme molecule. The molecular docking was carried out by the Biopredicta tool of VLife MDS software version 4.4. The X-ray crystal structure of PLK1 was obtained from the protein data bank (PDB ID: 2rku). The docking and scoring was performed using the default parameters of the Biopredicta program. Compounds under study shows interaction with amino acids of protein PLK1, and the compounds with phenyl ring containing *para*-methoxy groups shown to exhibit good binding interaction and elucidate the good docking score (-5.75), the phenyl ring containing *meta*-bromo groups shows better docking score (-4.82) than the phenyl ring containing *ortho*-nitro and *para*-nitro groups. The dock scores (kcal/moles) of all compounds were shown in Table 1. The nitrogen atom of benzimidazole ring forms hydrophobic bonding with amino acid residues LEU523B, ILE542B, and VAL411B. The electron withdrawing group (bromine) substituted on phenyl ring at *meta* position (AB-6) forms as hydrophobic bonding with amino acid residues LEU511B, LEU523B, VAL411B, GLN531B, VAL530B, ILE542B as well as hydrogen bonding with amino acid residues LEU525B, HIS524B, SER529B and LEU541B. The electron-donating group (methoxy) substituted on phenyl ring at *para* position (AB-12) forms hydrophobic bonding with amino acid residues TRP410B, GLN531B, ILE542B, VAL530B, LEU525B, LEU523B, VAL411B as well as hydrogen bonding with amino acid residues HIS524B, SER529B, LEU541B. The interactions of the standard compounds were compared with the series of compounds shown in figure. The binding site of interactions between the most active synthesized compound AB-12 with the polo-like kinase 1 (PLK 1) was recorded in Fig. 1. The binding interaction of the synthesized compound AB-12 at the binding sites showed 7 hydrophobic bonding with the amino acid residues. According to molecular modeling studies thiazolidine-4-ones are the good inhibitor of PLK1.

### ***Anticancer activity***

The anticancer activity of compounds (AB-1 to AB-13) was determined by sulforhodamine (SRB) assay with MCF-7 cell lines for breast cancer. The anticancer drug Adriamycin was used as the reference standard. Results are summarized in Table 1 and are expressed as GI<sub>50</sub> µg/ml (50% growth inhibitory concentration) values. The compounds AB-12 (GI<sub>50</sub>: 28.5 µg/ml) and AB-6 (GI<sub>50</sub>: 50.7 µg/ml) exhibited significant cell growth inhibitory activity.

Anticancer activity by SRB assay method and molecular docking study shows similar results in some extent.

### ***Structure activity relationship (SAR)***

The substitution of methoxy group on the phenyl ring at *para* position (**AB-12**) increases the anticancer activity as compared with *meta*-substitution (**AB-9**). The *ortho*-chlorophenyl compounds (**AB-4**) are more active than *meta* and *para*-chlorophenyl compounds (**AB-5 & AB-2**) against cancer cell line. The *ortho*-chlorophenyl (**AB-4**) and *meta*-bromophenyl compounds (**AB-6**) are having comparable anticancer activity. The substitution of nitro group on the *ortho* position of phenyl ring (**AB-3**) shows better anticancer activity than the *meta* and *para* nitro phenyl analogues (**AB-11 & AB-7**). The unsubstituted phenyl derivatives (**AB-1**) found to be less active against the cancer cell line.

### **Conclusion**

The experimental and molecular docking data results found in good correlation and demonstrated that compound AB-12 and AB-6 showing good anticancer activity against breast cancer cell line MCF-7. Molecular docking studies also suggest that the activity of the compounds may be due to the inhibition of polo-like kinase 1. These results indicate that compound AB-12 and AB-6 as related polo-like kinase 1 inhibitors compounds could be lead compounds for further development of anticancer agents.

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### **Conflict of interest**

The authors have declared no conflicts of interest.

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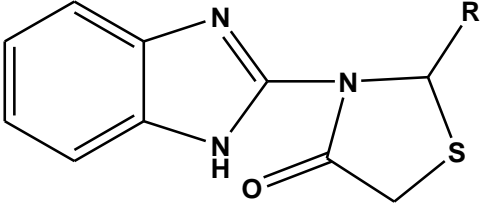
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**Table 1** Binding free energy and key interactions at the binding site of PLK1 and GI<sub>50</sub> value (µg/ml) on MCF-7 human breast cancer cell line

<b>BINDING FREE ENERGY AND KEY INTERACTIONS AT THE BINDING SITE</b>	
	<b>GI<sub>50</sub> (µg/ml)</b>

Compounds	-R	Docking score	Hydrophobic bonding	Hydrogen bonding	MCF-7 cell lines
AB-1	-C <sub>6</sub> H <sub>5</sub>	-3.80	VAL411B, LEU523B, GLN531B, ILE542B, VAL530B	LEU525B, SER529B, VAL533B, HIS524B, LEU535B	>80
AB-2	4-Cl-C <sub>6</sub> H <sub>5</sub>	-4.17	LEU523B, ILE542B, VAL411B, LEU511B, VAL530B, LEU525B	LEU525B, HIS524B, LEU541B, GLN531B, SER529B	>80
AB-3	2-NO <sub>2</sub> -C <sub>6</sub> H <sub>5</sub>	-4.14	VAL530B, LEU525B, LEU523B, GLN531B, ILE542B, VAL411B	SER529B, HIS524B, LEU525B, LEU541B	53.7
AB-4	2-Cl-C <sub>6</sub> H <sub>5</sub>	-4.21	LEU523B, GLN531B, ILE542B, VAL530B, VAL411B	LEU541B, SER529B, HIS524B, LEU525B	53.1
AB-5	3-Cl-C <sub>6</sub> H <sub>5</sub>	-3.74	LEU511B, LEU523B, LEU525B, VAL411B, VAL530B, GLN531B, ILE542B	HIS524B, SER529B, LEU541B	>80
AB-6	3-Br-C <sub>6</sub> H <sub>5</sub>	-4.82	LEU511B, LEU523B, VAL411B, GLN531B, VAL530B, ILE542B	LEU525B, HIS524B, SER529B, LEU541B	50.7
AB-7	4-NO <sub>2</sub> -C <sub>6</sub> H <sub>5</sub>	-3.96	TRP410B, ILE542B, VAL530B, LEU525B, VAL411B, GLN531B	LEU543B, LEU541B, SER529B, HIS524B, LEU523B	>80
AB-8	-C <sub>5</sub> H <sub>4</sub> N	-3.86	TRP410B, GLN531B, VAL411B, ILE542B, VAL530B, LEU525B	ASN533B, LEU523B, LEU541B, LEU543B, SER529B, HIS524B	79.5
AB-9	3-OCH <sub>3</sub> -C <sub>6</sub> H <sub>5</sub>	-3.75	VAL411B, GLN531B, ILE542B, VAL530B, LEU523B, LEU525B,	HIS524B, SER529B, LEU543B, LEU541B	64.2
AB-10	4-N-(CH <sub>3</sub> ) <sub>2</sub> -C <sub>6</sub> H <sub>5</sub>	-4.45	ILE542B, GLN531B, VAL411B, LEU523B, VAL530B	TYR510B, HIS524B, SER529B, LEU541B	>80

<b>AB-11</b>	3-NO <sub>2</sub> -C <sub>6</sub> H <sub>5</sub>	-4.09	ILE542B, GLN531B, LEU523B, VAL530B, LEU525B	LEU511B, LEU541B, VAL411B, SER529B, HIS524B	>80
<b>AB-12</b>	4-OCH <sub>3</sub> -C <sub>6</sub> H <sub>5</sub>	-5.75	TRP410B, GLN531B, ILE542B, VAL530B, LEU525B, LEU523B, VAL411B	HIS524B, SER529B, LEU541B	28.5
<b>AB-13</b>	2-OH-C <sub>6</sub> H <sub>5</sub>	-3.70	LYS540B, TRP410B, GLN531B, ILE542B, VAL411B, LEU525B, VAL530B	ASN533B, LEU543B, LEU541B, SER529B, LEU523B	>80
<b>ADR</b>	-	-6.12	LEU543B, MET377B, VAL530B, LEU523B, LEU525B, VAL411B	THR551B, GLN531B, LEU525B, GLY528B, GLN426B, LEU541B, SER412B	<10

**ADR: Adriamycin, Adriamycin was used as standard anticancer drug.**

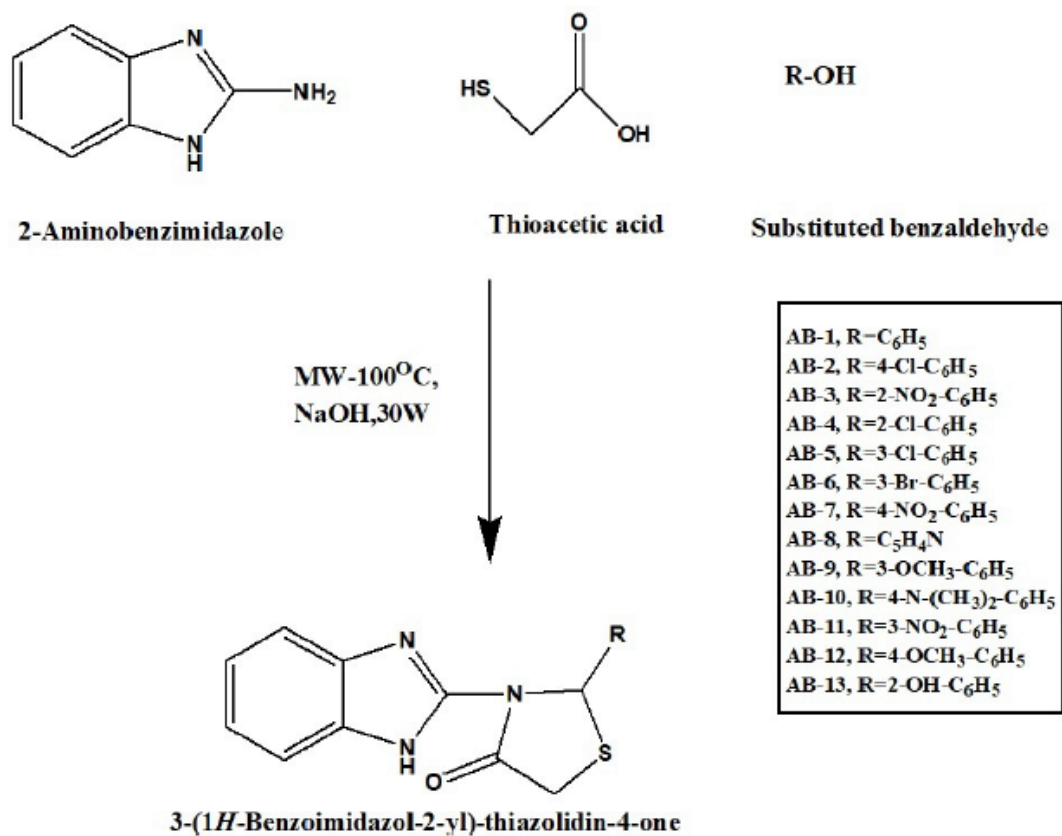


Fig. 1 Synthesis of 2-substituted-3-(1*H*-benzoimidazol-2-yl)-thiazolidin-4-ones.

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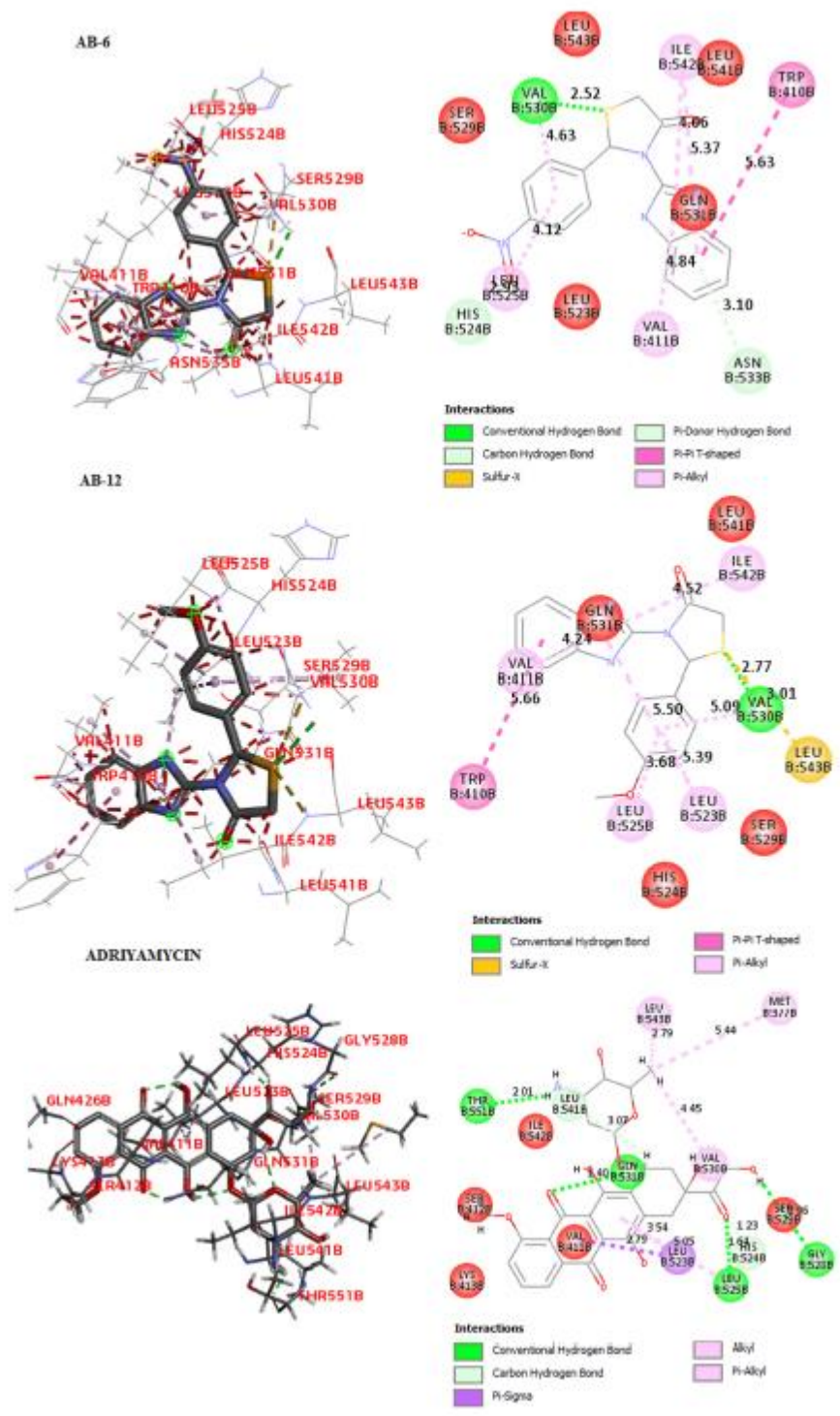


Fig. 2 Molecular docking of synthesized compounds (AB-12, AB-6 and Standard Adriamycin) fitted with polo like kinase 1 (PLK 1) and along with possible hydrogen and hydrophobic bonding interactions.

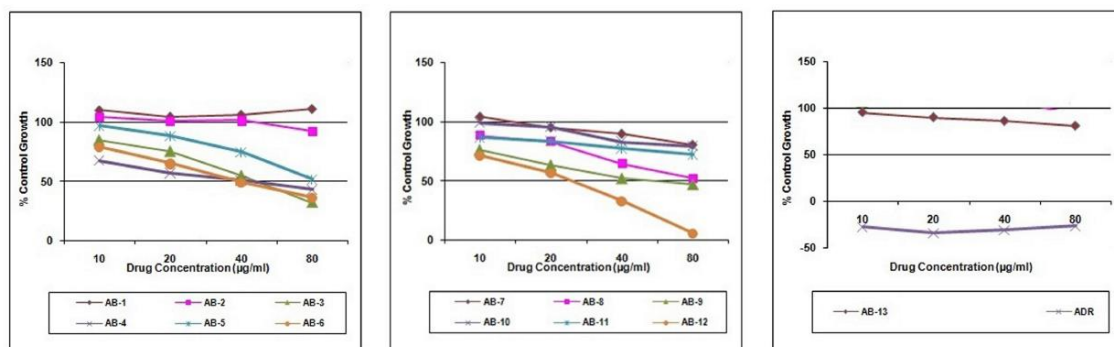


Fig. 3 Cell cytotoxicity determined by sulforhodamine B assay. The title compound (AB-1 to AB-13) tested with various concentrations on MCF-7 (Human breast cancer cell line) and compared with standard drug of Adriamycin. Graph showed growth curve of human breast cancer cell line MCF-7.

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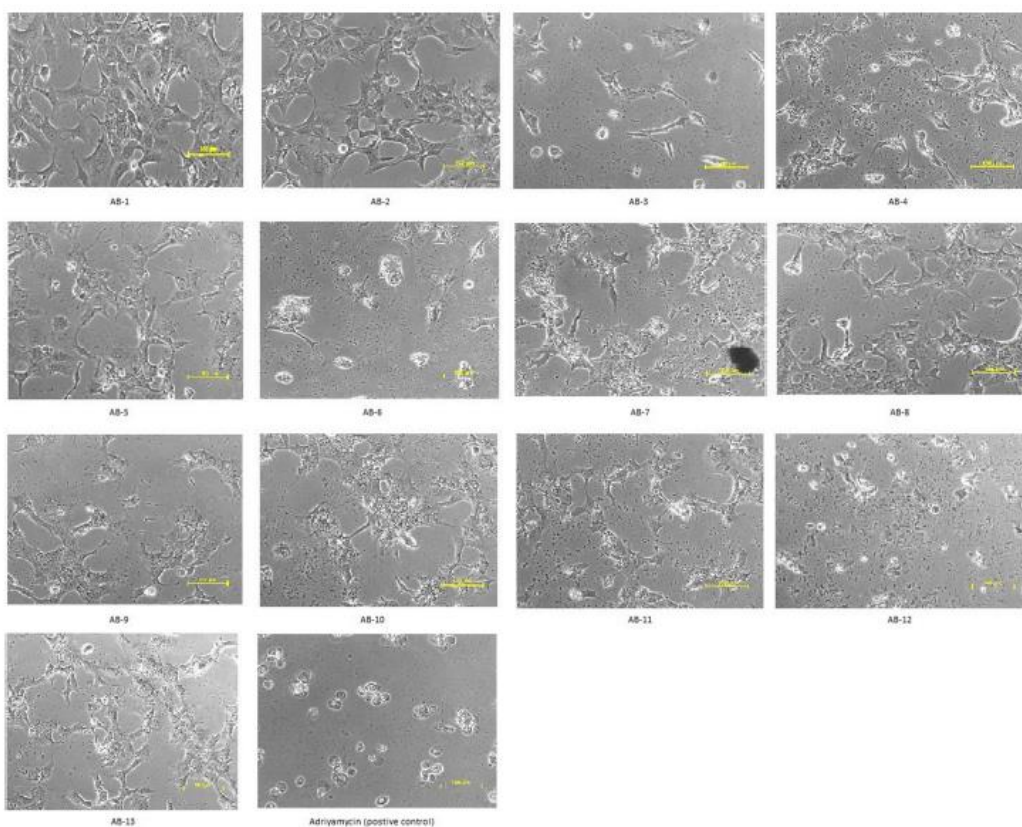


Fig. 4 Morphological changes of the human breast cancer cell line MCF-7 after treatment. MCF-7 cells were treated with title compounds (AB-1 to AB-13) for 48 h and the morphological changes of cells were observed under a transmission electron micrograph.