

## Design, Synthesis and molecular docking study of hybrids of quinazolin-4(3H)-one as anticancer agents

Diseño, síntesis y estudio de acoplamiento molecular de híbridos de quinazolino-na-tiazolidin-4-onas como agentes anticancerígenos

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### ABSTRACT

A series of 4-(2-(4-substituted phenyl)-4-oxoquinazolin-3(4H)-yl)-N-(2-(4-fluorophenyl)-4-oxo-5-(arylidene)thiazolidin-3-yl) benzamides (VIa-n) have been synthesized by condensation of N-(2-(4-fluorophenyl)-4-oxothiazolidin-3-yl)-4-(4-oxo-2-(4-substituted phenyl)quinazolin-3(4H)-yl)benzamides (Va-b) with various aryl/heteroaryl aldehydes using conventional methodology. All compounds were screened for their in vitro anticancer activity against the human breast cancer cell lines (MCF-7), human lung cancer cell lines (A549) using MTT assay method and doxorubicin is used as standard drug. Compound VIId, VIk and VIn showed high potency against A549 cell lines with  $IC_{50}$  values  $0.035 \pm 0.002 \mu M$ ,  $0.031 \pm 0.002 \mu M$  and  $0.030 \pm 0.002 \mu M$  respectively compared to  $0.023 \pm 0.002 \mu M$  showed by the standard. However, highest activity against MCF-7 cell lines was exhibited by Va, Vb, VIk and VIn with  $IC_{50}$  values between  $0.040 - 0.050 \mu M$ . All the remaining compounds showed moderate anticancer activity against both the MCF-7 and A549 cell lines. To understand the interactions with active binding site of receptor, molecular docking study was also performed.

**Keywords:** Quinazolin-4(3H)-one; Thiazolidin-4-one; Anticancer activity; Molecular docking.

### RESUMEN

Una serie de 2-(4-sustituido fenil)-4-oxoquinazolin-3(4H)-il)-N-(2-(4-fluorofenil)-4-oxo-5-(arilideno) tiazolidin-3-ilo) benzamidas (VIa-n) han sido sintetizadas por condensación de N-(2-(4-fluorofenil)-4-oxotiazolidin-3-il)-4-(4-oxo-2-(4-fenil sustituido) quinazolin-3(4H)-il) benzamidas (Va-b) con diversos aldehídos de arilo / heteroarilo usando metodología convencional. Todos los compuestos se cribaron para su actividad anticancerosa in vitro contra las líneas celulares de cáncer de mama humano (MCF-7), líneas celulares de cáncer de pulmón humano (A549) usando el método de ensayo MTT y se usa doxorubicina como fármaco estándar. El compuesto VIId, VIk y VIn mostraron alta potencia contra las líneas celulares A549 con valores  $IC_{50}$  de  $0.035 \pm 0.002 \mu M$ ,  $0.031 \pm 0.002 \mu M$  y  $0.030 \pm 0.002 \mu M$ , respectivamente, en comparación con  $0.023 \pm 0.002 \mu M$  mostrada por el estándar. Sin embargo, la actividad más alta contra líneas celulares MCF-7 fue exhibida por Va, Vb, VIk y VIn con valores de  $CI_{50}$  entre  $0.040 - 0.050 \mu M$ . Todos los compuestos restantes mostraron una actividad anticancerígena moderada contra las líneas celulares MCF-7 y A549. Para comprender las interacciones con el sitio de unión activa del receptor, también se realizó el estudio de acoplamiento molecular.

**Palabras clave:** Quinazolin-4(3H)-ona; Thiazolidin-4-one; Actividad anticancerosa; Atraje molecular.

## INTRODUCTION

Cancer is a disease of worldwide importance. Its incidence in the developed countries is increasing, and it occupies the second rank in the order of death causes<sup>1</sup>. Genotoxicity and cytotoxicity of anti-cancer drugs to the normal tissues is major problems in cancer therapy. However, cancer research always requires the discovery of new drugs that can kill the cancer cells or stop the growth of cancer cells more specifically and overcome the limitation of toxicity to normal tissue leading to many undesirable side effects<sup>2</sup>. Quinazoline derivatives have been identified as a new class of cancer chemotherapeutic agents with significant therapeutic efficacy against solid tumors<sup>3</sup>. Hybrid anti-cancer agents, which combine quinazoline and phenylquinoxaline moieties in one were reported and found to

possess enhanced cytotoxicity and specificity<sup>4</sup>. 4-Oxo-thiazolidine derivatives have occupied a unique place in the field of medicinal chemistry due to a wide range of biological activities<sup>5</sup>. 4-Thiazolidinones have been reported to inhibit tumor cell proliferation through inducing cell cycle arrest<sup>6</sup>. Recently 2-phenyl-(4-oxothiazolidin-3-yl)-quinazolin-4(3H)-one derivatives were found to possess potent activity against MCF-7 and HepG2 cell lines<sup>7</sup>. In our present study, we have designed and synthesized a new series of quinazolin-4(3H)-one and 4-thiazolidinone hybrid molecules as new anticancer agents with improved activity profile. In the process the C2 position of quinazolin-4(3H)-one was attached with substituted phenyl ring and the C5 position of 4-thiazolidinone substituted with various aryl and heteroaryl ring systems (Figure: 1).

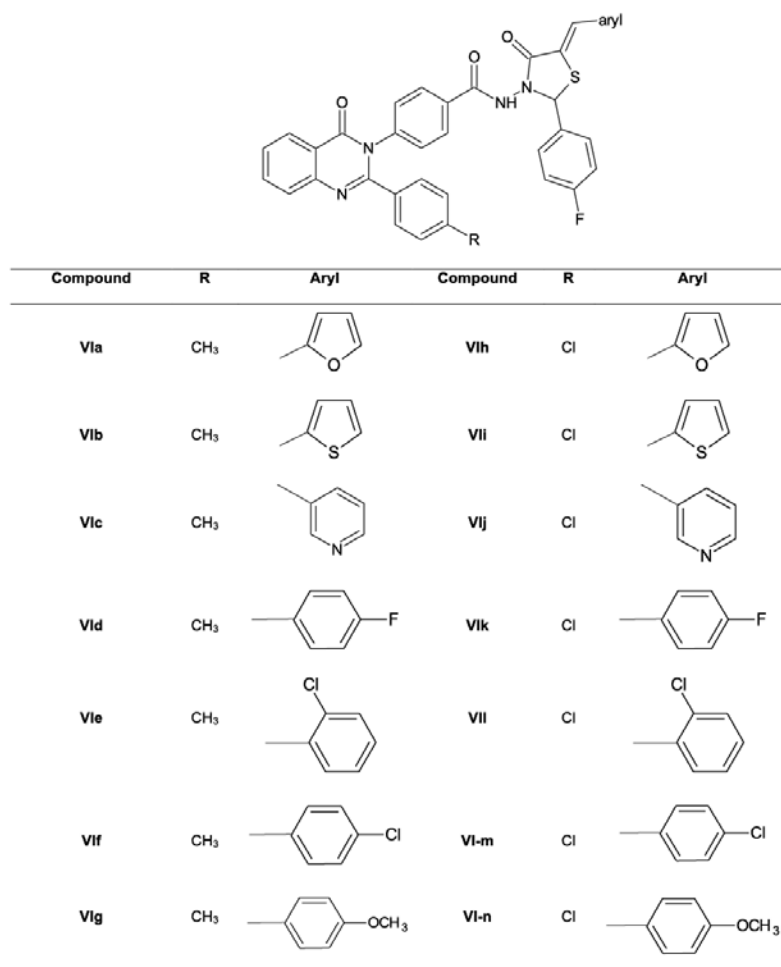
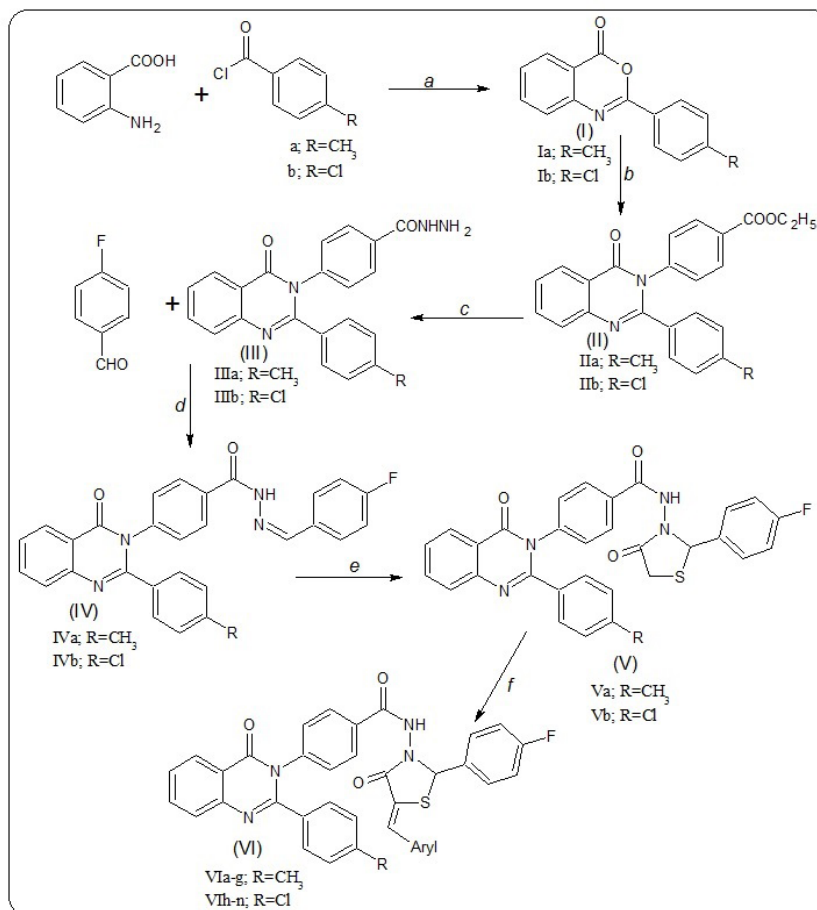


Figure 1: General structure of the synthesized compounds (VIa-n).



**Scheme 1:** Synthetic route of the final compounds (Via-n). (a) Pyridine; stirring at 15-20 °C, 1-2 hrs; (b) Ethyl 4-amino benzoate, heated on an oil bath at 180-200 °C for 25 min; (c)  $\text{NH}_2\text{-NH}_2\cdot\text{H}_2\text{O}$ , methanol, 3 hrs reflux; (d) Methanol, glacial acetic acid, 5 hrs reflux; (e)  $\text{HSCH}_2\text{COOH}$ , 1,4-dioxane, 6 hrs reflux; (f) Ar-CHO, 1,4-dioxane, glacial acetic acid, 8 hrs reflux.

## EXPERIMENTAL

All the chemicals and solvents were supplied by Sigma-Aldrich Pvt Ltd. The column chromatography was performed on silica gel 60-100 (Merk) for purification of the compounds using ethylacetate: hexane and chloroform: methanol in different ratios as mobile phase. Melting points were determined using MEL TEMP electrothermal apparatus. IR spectrum was acquired on Perkin Elmer FT-IR spectrometer. Both  $^1\text{H-NMR}$  and  $^{13}\text{C-NMR}$  spectra of the compounds were taken on Bruker Avance-II 400 NMR Spectrometer operating at 400 MHz and 100 MHz respectively at IICT, Hyderabad and Andhra University, Vishakapatnam. Mass spectra were recorded at IICT, Hyderabad. The elemental analysis was carried out using Elementar Vario Micro Cube at UCPSc, Kakatiya University, Warangal.

## Chemistry

Preparation of intermediate compounds 2-(4-substituted phenyl)benzo[d]1,3-oxazin-4-ones Ia-b were carried out according to the literature method<sup>8</sup>.

### Preparation of ethyl 4-[2-(4-substituted phenyl)-4-oxoquinazolin-3(4H)-yl] benzoate (IIa-b)

A mixture of compound (Ia-b) (0.01 mol) and ethyl 4-amino benzoate (0.012 mol) were fused at a temperature of 180-200°C for 25 min. After cooling, the reaction mixture was treated with methanol carefully portion wise the solid was separated by filtration, dried and recrystallized from ethanol to give the corresponding derivatives IIa & IIb. [(IIa, R =  $\text{CH}_3$ ;  $\text{C}_{24}\text{H}_{20}\text{N}_2\text{O}_3$ ; % Yield 63, M.P. 162-166°C); (IIb, R = Cl;  $\text{C}_{23}\text{H}_{17}\text{ClN}_2\text{O}_3$ ; % Yield 57, M.P. 186-190°C)].

### Preparation of 4-[2-(4-substituted phenyl)-4-oxoquinazolin-3(4H)-yl] benzohydrazide (IIIa-b)

A mixture of 4-[2-(4-substituted phenyl)-4-oxoquinazolin-3(4H)-yl] benzoates (IIa-b) (0.01 mol) and excess of hydrazine hydrate (99%, 0.015 mol) in methanol (20 ml) were transferred to a round bottom flask and refluxed for 3 h. After the reaction was completed, the reaction mixture was poured into crushed ice to afford dark brown precipitates. These precipitates were collected by filtration and washed with cold water. The resulting solids were recrystallized

from ethanol (99%) to give the corresponding hydrazides (IIIa & IIIb). [(IIIa, R = CH<sub>3</sub>; C<sub>22</sub>H<sub>18</sub>N<sub>4</sub>O<sub>2</sub>; % Yield 75, M.P. 182-186°C); (IIIb, R = Cl; C<sub>21</sub>H<sub>15</sub>ClN<sub>4</sub>O<sub>2</sub>; % Yield 68, M.P. 204-208°C)].

#### Preparation of N-(4-fluorobenzylidene)-4-(4-oxo-2-(4-substituted phenyl)-quinazolin-3(4H)-yl) benzohydrazide (IVa-b)

The compounds IVa & IVb were prepared by refluxing 4-[2-(4-substituted phenyl)-4-oxoquinazolin-3(4H)-yl] benzohydrazides (IIIa-b; 0.01 mol) and 4-fluorobenzaldehyde (0.012 mol) in methanol (30 ml) containing small amount of glacial acetic acid for 5 h. After the reaction was completed, the Schiff bases (IVa-b) were precipitated out. The precipitate was collected by filtration. The resulting solids were recrystallized from methanol. [(IVa, R = CH<sub>3</sub>; C<sub>29</sub>H<sub>21</sub>FN<sub>4</sub>O<sub>2</sub>; % Yield 58, M.P. 224-228°C; IVb, R = Cl; C<sub>28</sub>H<sub>18</sub>ClFN<sub>4</sub>O<sub>2</sub>; % Yield 53, M.P. 240-244°C)].

#### Preparation of N-(2-(4-fluorophenyl)-4-oxothiazolidin-3-yl)-4-(4-oxo-2-(4-substituted phenyl)-quinazolin-3(4H)-yl)benzamide (Va-b)

The synthesis of compounds (Va-b) was achieved by refluxing N-(4-fluorobenzylidene)-4-(4-oxo-2-(4-substituted phenyl)-quinazolin-3(4H)-yl) benzo hydrazides (IVa-b; 0.01 mol) and thioglycolic acid in 1,4 dioxan (20 ml) for 6 h. After the reaction was completed, the solution was poured into ice-cold aqueous solution of sodium bicarbonate to neutralize unreacted thioglycolic acid. The yellow to brown solids separated were filtered and then washed with cold water. The resulting solids were recrystallized from ethanol. [(Va, R = CH<sub>3</sub>; C<sub>31</sub>H<sub>23</sub>FN<sub>4</sub>O<sub>3</sub>S; % Yield 76, M.P. 190-194°C); (Vb, R = Cl; C<sub>30</sub>H<sub>20</sub>ClFN<sub>4</sub>O<sub>3</sub>S; % Yield 65, M.P. 214-218°C)].

#### General procedure for synthesis of N-(5-(aryl)-2-(4-fluorophenyl)-4-oxo thiazolidin-3-yl)-4-(4-oxo-2-(4-substituted phenyl)-quinazolin-3(4H)-yl) benzamides (VIa-n).

A mixture of a solution of N-(2-(4-fluorophenyl)-4-oxothiazolidin-3-yl)-4-(4-oxo-2-(4-substituted phenyl)-quinazolin-3(4H)-yl)benzamides (Va-b; 0.01 mol) and appropriate aryl aldehyde (0.01 mol) in 1,4 dioxane (20 ml) were added with a few drops of glacial acetic acid and refluxed for 8 h. After the reaction was completed, the reaction mixture was poured into crushed ice to afford a precipitate. This was collected by filtration, and then washed with cold water. The above procedure was applied to synthesize the arylidene derivatives VIa-n. All the derivatives were purified by column chromatography using mixture of ethyl acetate and hexane as mobile phase. (% Yield 54-71, M.P. 190-252°C).

#### N-(2-(4-fluorophenyl)-4-oxo-5-(furan-2-ylmethylene)-4-oxothiazolidin-3-yl)-4-(4-oxo-2-(p-tolyl) quinazolin-3(4H)-yl) benzamide (VIa)

<sup>1</sup>H - NMR: (400 MHz; DMSO-d<sub>6</sub>) δ (ppm): 2.28 (s, 3H, CH<sub>3</sub>); 5.79 (s, 1H, -N-CH-S-); 7.37-7.48 (m, 2H, H); 7.53-7.89 (m, 9H, H); 7.98-8.10 (m, 4H, H); 8.19-8.37 (m, 4H, Ar-H); 8.84 (s, 1H, -C=CH-Ar); 9.12 (s, 1H, -CO-NH-). <sup>13</sup>C - NMR: (100 MHz; DMSO-d<sub>6</sub>) δ (ppm): 168.24, 166.46, 163.87, 162.35, 157.87, 153.21, 147.82, 144.17, 139.78, 137.89, 137.50, 136.92, 133.78, 130.06, 129.84, 127.69, 126.75, 125.47, 124.97, 120.85, 116.12, 110.97, 108.74, 68.47, 19.43. IR: 3328.20 (N-H str); 3108.50, 3086.40 (C-H Ar); 2932.70 (C-H Ali); 1709.80 (C=O str); 1674.70 (C=O str); 1567.40 (C=N str); 1241.10 (C-F str). Mass (m/z) (ESI-MS): [M<sup>+</sup>] 629. C, H, N: Calcd. C-68.78, H-4.01, N-8.91; Found C-69.10, H-4.33, N-9.23.

#### N-(2-(4-fluorophenyl)-4-oxo-5-(thiophen-2-ylmethylene)-4-oxothiazolidin-3-yl)-4-(4-oxo-2-(p-tolyl) quinazolin-3(4H)-yl) benzamide (VIb)

<sup>1</sup>H - NMR: (400 MHz; DMSO-d<sub>6</sub>) δ (ppm): 2.23 (s, 3H, CH<sub>3</sub>); 5.88 (s, 1H, -N-CH-S-); 7.39-7.50 (m, 2H, Ar-H); 7.56-7.873 (m, 10H, Ar-H); 7.98-8.26 (m, 7H, Ar-H); 8.84 (s, 1H, -C=CH); 9.11 (s, 1H, -CO-NH-). <sup>13</sup>C - NMR: (100 MHz; DMSO-d<sub>6</sub>) δ (ppm): 166.27, 165.83, 162.17, 161.85, 157.74, 153.86, 149.25, 144.38, 139.78, 137.89, 137.50, 136.92, 135.47, 134.06, 131.64, 130.08, 129.65, 127.41, 126.35, 125.68, 124.16, 120.53, 116.92, 112.37, 110.74, 69.23, 19.78. IR: 3304.83 (N-H str); 3098.75, 3057.84 (C-H Ar); 2987.10 (C-H Ali); 1729.04 (C=O str); 1683.60 (C=O str); 1584.10 (C=N str); 1198.78 (C-F str). Mass (m/z) (ESI-MS): [M<sup>+</sup>] 645. C, H, N: Calcd. C-67.06, H-3.91, N-8.69; Found C-67.43, H-4.23, N-9.04.

#### N-(2-(4-fluorophenyl)-4-oxo-5-(pyridin-3-ylmethylene) thiazolidin-3-yl)-4-(4-oxo-2-(p-tolyl) quinazolin-3(4H)-yl) benzamide (VIc)

<sup>1</sup>H - NMR: (400 MHz; DMSO-d<sub>6</sub>) δ (ppm): 2.28 (s, 3H, CH<sub>3</sub>); 5.90 (s, 1H, -N-CH-S-); 7.41-7.64 (m, 8H, Ar-H); 7.72-7.84 (m, 2H, Ar-H); 7.94-8.12 (m, 4H, Ar-H); 8.19-8.28 (m, 2H, Ar-H); 8.76-8.92 (m, 4H, -C=CH & Ar-H); 9.26 (d, 2H, J=8.528, -CO-NH- & Ar-H). <sup>13</sup>C - NMR: (100 MHz; DMSO-d<sub>6</sub>) δ (ppm): 167.63, 164.75, 163.12, 160.09, 157.78, 150.09, 148.93, 147.81, 141.07, 137.82, 136.43, 135.04, 132.65, 132.48, 130.07, 129.61, 129.13, 127.28, 126.97, 125.65, 124.51, 124.03, 121.36, 117.18, 68.31, 19.62. IR: 3312.63 (N-H str); 3112.44, 3097.32 (C-H Ar); 2962.46 (C-H Ali); 1712.64 (C=O str); 1682.09 (C=O str); 1547.25 (C=N str); 1221.17 (C-F str). Mass (m/z) (ESI-MS): [M<sup>+</sup>] 640. C, H, N: Calcd. C-69.47, H-4.10, N-10.95; Found C-69.12, H-3.75, N-10.62.

***N*-(5-(4-fluorobenzylidene)-2-(4-fluorophenyl)-4-oxothiazolidin-3-yl)-4-(4-oxo-2-(*p*-tolyl) quinazolin-3(4H)-yl) benzamide (VI<sub>d</sub>)**

<sup>1</sup>H - NMR: (400 MHz; DMSO-*d*<sub>6</sub>) δ (ppm): 2.40 (s, 3H, CH<sub>3</sub>); 5.91 (s, 1H, -N-CH-S-); 7.22-7.32 (m, 3H, Ar-H); 7.48-7.56 (m, 2H, Ar-H); 7.68-7.76 (m, 5H, Ar-H); 7.98-8.08 (m, 4H, Ar-H); 8.30-8.38 (m, 3H, Ar-H); 8.61-8.72 (m, 3H, Ar-H); 8.87 (s, 1H, -C=CH); 9.26 (s, 1H, -CO-NH-). <sup>13</sup>C - NMR: (100 MHz; DMSO-*d*<sub>6</sub>) δ (ppm): 166.07, 164.82, 160.35, 157.21, 149.27, 140.18, 137.89, 134.12, 130.81, 129.84, 127.53, 126.96, 126.07, 124.85, 116.74, 72.48, 20.08. IR: 3298.90 (N-H str); 3096.73, 3042.52 (C-H Ar); 2943.89 (C-H Ali); 1720.36 (C=O str); 1671.37 (C=O str); 1586.10 (C=N str); 1198.95 (C-F str). Mass (*m/z*) (ESI-MS): [M<sup>+</sup>] 657. C, H, N: Calcd. C-69.50, H-3.99, N-8.53; Found C-69.18, H-3.67, N-8.21.

***N*-(5-(2-chlorobenzylidene)-2-(4-fluorophenyl)-4-oxothiazolidin-3-yl)-4-(4-oxo-2-(*p*-tolyl) quinazolin-3(4H)-yl) benzamide (VI<sub>e</sub>)**

<sup>1</sup>H - NMR: (400 MHz; DMSO-*d*<sub>6</sub>) δ (ppm): 2.39 (s, 3H, CH<sub>3</sub>); 5.81 (s, 1H, -N-CH-S-); 7.27-7.33 (m, 2H, Ar-H); 7.38-7.47 (m, 6H, Ar-H); 7.63-7.72 (m, 3H, Ar-H); 7.78-7.85 (m, 3H, Ar-H); 7.92-7.99 (m, 4H, Ar-H); 8.42-8.49 (m, 2H, Ar-H); 8.78 (s, 1H, -C=CH); 9.21 (s, 1H, -CO-NH-). <sup>13</sup>C - NMR: (100 MHz; DMSO-*d*<sub>6</sub>) δ (ppm): 165.13, 164.28, 161.39, 156.84, 149.27, 140.13, 137.46, 134.92, 133.27, 131.48, 130.12, 129.85, 129.36, 127.83, 126.75, 125.87, 125.26, 120.96, 115.82, 69.24, 19.82. IR: 3294.82 (N-H str); 3100.12, 3053.64 (C-H Ar); 2964.17 (C-H Ali); 1707.68 (C=O str); 1644.83 (C=O str); 1589.75 (C=N str); 1209.78 (C-F str). Mass (*m/z*) (ESI-MS): [M<sup>+</sup>] 673. C, H, N: Calcd. C-67.80, H-3.89, N-8.32; Found C-68.10, H-4.22, N-8.63.

***N*-(5-(4-chlorobenzylidene)-2-(4-fluorophenyl)-4-oxothiazolidin-3-yl)-4-(4-oxo-2-(*p*-tolyl) quinazolin-3(4H)-yl) benzamide (VI<sub>f</sub>)**

<sup>1</sup>H - NMR: (400 MHz; DMSO-*d*<sub>6</sub>) δ (ppm): 2.26 (s, 3H, CH<sub>3</sub>); 5.87 (s, 1H, -N-CH-S-); 7.38-7.62 (m, 5H, Ar-H); 7.79-8.10 (m, 8H, Ar-H); 8.17-8.33 (m, 4H, Ar-H); 8.43-8.60 (m, 3H, Ar-H); 8.90 (s, 1H, -C=CH); 9.26 (s, 1H, -CO-NH-). <sup>13</sup>C - NMR: (100 MHz; DMSO-*d*<sub>6</sub>) δ (ppm): 165.13, 164.28, 161.39, 156.84, 149.27, 140.13, 137.46, 134.92, 133.67, 130.97, 130.04, 129.85, 129.36, 127.83, 126.75, 125.87, 125.26, 120.96, 115.82, 69.24, 19.82. IR: 3289.12 (N-H str); 3111.45, 3097.24 (C-H Ar); 2978.10 (C-H Ali); 1718.05 (C=O str); 1665.85 (C=O str); 1578.42 (C=N str); 1208.63 (C-F str). Mass (*m/z*) (ESI-MS): [M<sup>+</sup>] 673. C, H, N: Calcd. C-67.80, H-3.89, N-8.32; Found C-68.14, H-4.23, N-8.64.

***N*-(2-(4-fluorophenyl)-5-(4-methoxybenzylidene)-4-oxothiazolidin-3-yl)-4-(4-oxo-2-(*p*-tolyl) quinazolin-3(4H)-yl) benzamide (VI<sub>g</sub>)**

<sup>1</sup>H - NMR: (400 MHz; DMSO-*d*<sub>6</sub>) δ (ppm): 2.18 (s, 3H, CH<sub>3</sub>); 3.90 (s, 3H, OCH<sub>3</sub>); 5.88 (s, 1H, -N-CH-S-); 7.07-7.22 (m, 4H, Ar-H); 7.25-7.36 (m, 2H, Ar-H); 7.43-7.68 (m, 6H, Ar-H); 7.73-7.89 (m, 3H, Ar-H); 7.92-8.07 (m, 3H, Ar-H); 8.26-8.40 (m, 2H, Ar-H); 8.82 (s, 1H, -C=CH); 9.24 (s, 1H, -CO-NH-). <sup>13</sup>C - NMR: (100 MHz; DMSO-*d*<sub>6</sub>) δ (ppm): 165.13, 164.28, 161.39, 156.84, 149.27, 140.13, 137.46, 134.92, 133.27, 131.48, 130.12, 129.85, 129.36, 127.83, 126.75, 125.87, 125.26, 120.96, 115.82, 69.24, 19.82. IR: 3278.20 (N-H str); 3104.50, 3082.40 (C-H Ar); 2923.70 (C-H Ali); 1711.45 (C=O str); 1680.35 (C=O str); 1574.56 (C=N str); 1217.24 (C-F str). Mass (*m/z*) (ESI-MS): [M<sup>+</sup>] 669. C, H, N: Calcd. C-70.04, H-4.37, N-8.38; Found C-69.65, H-4.06, N-8.02.

**4-(2-(4-chlorophenyl)-4-oxo quinazolin-3(4H)-yl)-N-(2-(4-fluorophenyl)-4-oxo-5-(furan-2-ylmethylene) thiazolidin-3-yl) benzamide (VI<sub>h</sub>)**

<sup>1</sup>H - NMR: (400 MHz; DMSO-*d*<sub>6</sub>) δ (ppm): 5.79 (s, 1H, -N-CH-S-); 7.56-7.83 (m, 11H, Ar-H); 7.98-8.14 (m, 3H, Ar-H); 8.20-8.49 (m, 5H, Ar-H); 8.83 (s, 1H, -C=CH); 9.11 (s, 1H, -CO-NH-). <sup>13</sup>C - NMR: (100 MHz; DMSO-*d*<sub>6</sub>) δ (ppm): 165.37, 164.10, 161.28, 157.06, 152.48, 149.24, 144.60, 138.18, 136.83, 135.46, 133.81, 129.56, 128.83, 127.63, 126.42, 125.06, 121.75, 116.54, 113.68, 110.35, 72.17. IR: 3386.75 (N-H str); 3189.60, 3046.32 (C-H Ar); 2934.61 (C-H Ali); 1708.13 (C=O str); 1676.02 (C=O str); 1591.52 (C=N str); 1175.18 (C-F str); 723.92 (C-Cl str). Mass (*m/z*) (ESI-MS): [M<sup>+</sup>] 649. C, H, N: Calcd. C-64.76, H-3.42, N-8.63; Found C-64.42, H-3.10, N-8.31.

**4-(2-(4-chlorophenyl)-4-oxoquinazolin-3(4H)-yl)-N-(2-(4-fluorophenyl)-4-oxo-5-(thiophen-2-ylmethylene) thiazolidin-3-yl) benzamide (VI<sub>i</sub>)**

<sup>1</sup>H - NMR: (400 MHz; DMSO-*d*<sub>6</sub>) δ (ppm): 5.79 (s, 1H, -N-CH-S-); 7.48-7.61 (m, 3H, Ar-H); 7.67-7.86 (m, 8H, Ar-H); 7.98-8.24 (m, 3H, Ar-H); 8.20-8.49 (m, 5H, Ar-H); 8.43-8.56 (m, 2H, Ar-H); 8.83 (s, 1H, -C=CH); 9.11 (s, 1H, -CO-NH-). <sup>13</sup>C - NMR: (100 MHz; DMSO-*d*<sub>6</sub>) δ (ppm): 165.42, 163.92, 161.15, 157.23, 148.94, 138.05, 136.70, 135.68, 133.76, 131.28, 130.65, 129.86, 128.73, 127.52, 126.75, 125.16, 121.28, 116.42, 71.85. IR: 3316.54 (N-H str); 3127.43, 3098.12 (C-H Ar); 2914.16 (C-H Ali); 1718.23 (C=O str); 1686.42 (C=O str); 1545.12 (C=N str); 1185.34 (C-F str); 726.21 (C-Cl str). Mass (*m/z*) (ESI-MS): [M<sup>+</sup>] 665. C, H, N: Calcd. C-63.20, H-3.33, N-8.42; Found C-63.57, H-3.70, N-8.79.



**4-(2-(4-chlorophenyl)-4-oxoquinazolin-3(4H)-yl)-N-(2-(4-fluorophenyl)-4-oxo-5-(pyridin-3-ylmethylene)thiazolidin-3-yl) benzamide (VIj)**

<sup>1</sup>H - NMR: (400 MHz; DMSO-d<sub>6</sub>) δ (ppm): 5.95 (s, 1H, -N-CH-S-); 7.42-7.59 (m, 3H, Ar-H); 7.69-7.83 (m, 3H, Ar-H); 7.92-8.11 (m, 4H, Ar-H); 8.18-8.30 (m, 3H, Ar-H); 8.43-8.62 (m, 3H, Ar-H); 8.78-8.90 (m, 3H, Ar-H); 9.04 (s, 1H, -C=CH); 9.24 (s, 1H, -CO-NH-). <sup>13</sup>C - NMR: (100 MHz; DMSO-d<sub>6</sub>) δ (ppm): 164.96, 163.84, 161.67, 160.43, 157.18, 151.60, 148.45, 139.12, 137.42, 136.74, 134.45, 132.87, 130.67, 129.52, 128.90, 127.45, 126.76, 125.38, 124.12, 121.60, 116.85, 72.10. IR: 3296.72 (N-H str); 3142.35, 3042.12 (C-H Ar); 2914.67 (C-H Ali); 1711.43 (C=O str); 1684.32 (C=O str); 1568.72 (C=N str); 1186.23 (C-F str); 734.02 (C-Cl str). Mass (*m/z*) (ESI-MS): [M<sup>+</sup>] 660. C, H, N: Calcd. C-65.50, H-3.51, N-10.61; Found C-65.15, H-3.16, N-10.26.

**4-(2-(4-chlorophenyl)-4-oxoquinazolin-3(4H)-yl)-N-(5-(4-fluorobenzylidene)-2-(4-fluorophenyl)-4-oxothiazolidin-3-yl) benzamide (VIk)**

<sup>1</sup>H - NMR: (400 MHz; DMSO-d<sub>6</sub>) δ (ppm): 5.87 (s, 1H, -N-CH-S-); 7.22-7.30 (m, 3H, Ar-H); 7.48-7.56 (m, 2H, Ar-H); 7.67-7.86 (m, 5H, Ar-H); 7.98-8.06 (m, 4H, Ar-H); 8.28-8.36 (m, 3H, Ar-H); 8.49-8.68 (m, 3H, Ar-H); 8.95 (s, 1H, -C=CH); 9.27 (s, 1H, -CO-NH-). <sup>13</sup>C - NMR: (100 MHz; DMSO-d<sub>6</sub>) δ (ppm): 165.57, 164.42, 161.82, 160.35, 157.21, 151.65, 149.27, 140.18, 137.89, 134.12, 130.81, 129.84, 127.53, 126.96, 126.07, 124.85, 116.74, 72.48. IR: 3316.05 (N-H str); 3118.40, 3074.32 (C-H Ar); 2925.46 (C-H Ali); 1712.18 (C=O str, amide); 1684.62 (C=O str); 1597.12 (C=N str); 1167.28 (C-F str); 728.14 (C-Cl str). Mass (*m/z*) (ESI-MS): [M<sup>+</sup>] 677. C, H, N: Calcd. C-65.63, H-3.42, N-8.27; Found C-66.01, H-3.78, N-8.64.

**N-(5-(2-chlorobenzylidene)-2-(4-fluorophenyl)-4-oxothiazolidin-3-yl)-4-(2-(4-chlorophenyl)-4-oxoquinazolin-3(4H)-yl) benzamide (VII)**

<sup>1</sup>H - NMR: (400 MHz; DMSO-d<sub>6</sub>) δ (ppm): 5.82 (s, 1H, -N-CH-S-); 7.37-7.46 (m, 6H, Ar-H); 7.63-7.74 (m, 3H, Ar-H); 7.80-7.85 (m, 3H, Ar-H); 7.92-8.00 (m, 4H, Ar-H); 8.23-8.30 (m, 2H, Ar-H); 8.48-8.56 (m, 2H, Ar-H); 8.76 (s, 1H, -C=CH); 9.21 (s, 1H, -CO-NH-). <sup>13</sup>C - NMR: (100 MHz; DMSO-d<sub>6</sub>) δ (ppm): 165.74, 164.12, 162.32, 161.08, 157.25, 149.37, 139.18, 137.89, 135.72, 133.56, 130.48, 130.48, 129.84, 128.90, 128.53, 126.76, 125.20, 121.38, 116.85, 72.15. IR: 3307.62 (N-H str); 3118.96, 3078.43 (C-H Ar); 2914.98 (C-H Ali); 1711.43 (C=O str); 1656.62 (C=O str); 1584.62 (C=N str); 1168.94 (C-F str); 727.49 (C-Cl str). Mass (*m/z*) (ESI-MS): [M<sup>+</sup>] 694. C, H, N: Calcd. C-64.07, H-3.34, N-8.08; Found C-64.39, H-3.66, N-8.40.

**N-(5-(4-chlorobenzylidene)-2-(4-fluorophenyl)-4-oxothiazolidin-3-yl)-4-(2-(4-chlorophenyl)-4-oxoquinazolin-3(4H)-yl) benzamide (VIIm)**

<sup>1</sup>H - NMR: (400 MHz; DMSO-d<sub>6</sub>) δ (ppm): 5.86 (s, 1H, -N-CH-S-); 7.38-7.61 (m, 5H, Ar-H); 7.80-8.08 (m, 8H, Ar-H); 8.16-8.32 (m, 4H, Ar-H); 8.40-8.62 (m, 3H, Ar-H); 8.90 (s, 1H, -C=CH); 9.28 (s, 1H, -CO-NH-). <sup>13</sup>C - NMR: (100 MHz; DMSO-d<sub>6</sub>) δ (ppm): 165.75, 164.12, 161.08, 157.20, 149.62, 139.86, 136.94, 135.78, 133.45, 131.40, 130.52, 129.76, 128.74, 128.62, 126.47, 125.26, 121.30, 116.74, 71.83. IR: 3365.16 (N-H str); 3123.46, 3074.13 (C-H Ar); 2945.08 (C-H Ali); 1712.78 (C=O str); 1672.61 (C=O str); 1584.52 (C=N str); 1178.07 (C-F str); 728.19 (C-Cl str). Mass (*m/z*) (ESI-MS): [M<sup>+</sup>] 694. C, H, N: Calcd. C-64.07, H-3.34, N-8.08; Found C-64.39, H-3.66, N-8.40.

**4-(2-(4-chlorophenyl)-4-oxoquinazolin-3(4H)-yl)-N-(2-(4-fluorophenyl)-5-(4-methoxybenzylidene)-4-oxothiazolidin-3-yl) benzamide (VIN)**

<sup>1</sup>H - NMR: (400 MHz; DMSO-d<sub>6</sub>) δ (ppm): 3.92 (s, 3H, Ar-OCH<sub>3</sub>); 5.88 (s, 1H, -N-CH-S-); 7.16-7.32 (m, 4H, Ar-H); 7.42-7.63 (m, 6H, Ar-H); 7.74-7.89 (m, 3H, Ar-H); 7.91-8.10 (m, 3H, Ar-H); 8.22-8.40 (m, 4H, Ar-H); 8.82 (s, 1H, -C=CH); 9.23 (s, 1H, -CO-NH-). <sup>13</sup>C - NMR: (100 MHz; DMSO-d<sub>6</sub>) δ (ppm): 165.80, 164.63, 162.17, 161.25, 160.10, 157.20, 149.62, 138.56, 136.42, 135.78, 134.23, 131.84, 130.52, 129.26, 128.94, 127.48, 126.67, 125.26, 124.53, 121.30, 116.74, 114.75, 71.90, 56.47. IR: 3345.17 (N-H str); 3139.60, 3086.32 (C-H Ar); 2932.61 (C-H Ali); 1712.84 (C=O str); 1694.02 (C=O str); 1572.32 (C=N str); 1164.18 (C-F str); 724.92 (C-Cl str). Mass (*m/z*) (ESI-MS): [M<sup>+</sup>] 689. C, H, N: Calcd. C-66.23, H-3.80, N-8.13; Found. C-65.87, H-3.44, N-7.87.

**Cell culture:** The MCF-7 and A549 cell lines were maintained in culture with MEM medium, supplemented with 10% FBS and the antibiotics penicillin/streptomycin (0.5 mg/ml); in atmosphere of 5% CO<sub>2</sub> and 95% air at 37°C. Stock solutions of synthesized compounds were made in DMSO and kept in aliquots at -20°C. For MTT assay, each test compound was weighed separately and dissolved in DMSO, made up the final concentration with media to 1 mg/ml and the cells were treated with series of concentrations from 10 to 100 μm.

**Molecular Docking**

Quinazolinone derivatives were reported to possess anticancer activity by inhibiting target enzyme phosphoinositide-3-OH kinase PI(3)K<sup>9,10</sup>. Hence, in the present study, the titled compounds were docked on the PI(3)K to understand the underlying mechanism. Docking studies were performed by Molegro Virtual Docker (MVD) program-

mer<sup>11</sup>. The 3D coordinates of crystal structure of phosphoinositide-3-OH kinase (PI(3)K) was obtained from protein data bank (PDB ID: 2WXQ) with resolution of 2.7 Å. The ligands were developed using Chem Draw Ultra 12.0. Ligands were further 3D optimized and saved in mol2 file format. MVD performs flexible ligand docking, so the optimal geometry of the ligand will be determined during the docking.

## RESULTS

### Synthesis of Compounds

The titled compounds (**VIa-n**) were synthesized by the reported multi-step reaction protocol<sup>12, 13</sup>. The synthetic

procedures were carried out as shown in **Scheme-1**. The starting materials (**Ia-b**) were prepared by the reaction of 5-chloroanthranilic acid with substituted benzoyl chlorides<sup>14</sup>, which were treated with ethyl-p-amino benzoate to give (**IIa-b**). The compounds (**IIIa-b**) were obtained by the reaction of (**IIa-b**) with hydrazine hydrate. Upon fusion of (**IIIa-b**) with 4-fluoro phenyl afforded the (**IVa-b**). The reaction of compounds (**IVa-b**) with thioglycolic acid gave (**Va-b**). The desired compounds (**VIa-n**) were obtained by refluxing the (**Va-b**) with various heteroaryl/ substituted aldehydes in 1,4 dioxane by adding few drops of glacial acetic acid. The target compounds were obtained in 54-71% yields (**Table: 1**).

**Table: 1** Physical data of the synthesized compounds

Sl. No.	Compound code	R	Aryl	Mol. Formula	Mol. Wt.	% Yield	R <sub>f</sub>	M. P. (°C)
1	VIa	CH <sub>3</sub>	2-Furan	C <sub>36</sub> H <sub>25</sub> FN <sub>4</sub> O <sub>4</sub> S	628.67	58	0.51	226-230
2	VIb	CH <sub>3</sub>	2-Thiophene	C <sub>36</sub> H <sub>25</sub> FN <sub>4</sub> O <sub>3</sub> S <sub>2</sub>	644.74	67	0.67	208-212
3	VIc	CH <sub>3</sub>	3-Pyridine	C <sub>37</sub> H <sub>26</sub> FN <sub>5</sub> O <sub>3</sub> S	639.70	54	0.35	222-228
4	VI d	CH <sub>3</sub>	4-Fluoro phenyl	C <sub>38</sub> H <sub>26</sub> F <sub>2</sub> N <sub>4</sub> O <sub>3</sub> S	656.70	71	0.74	230-234
5	VIe	CH <sub>3</sub>	2-Chloro phenyl	C <sub>38</sub> H <sub>26</sub> ClFN <sub>4</sub> O <sub>3</sub> S	673.15	69	0.61	202-206
6	VI f	CH <sub>3</sub>	4-Chloro phenyl	C <sub>38</sub> H <sub>26</sub> ClFN <sub>4</sub> O <sub>3</sub> S	673.15	62	0.53	194-198
7	VIg	CH <sub>3</sub>	4-Methoxy phenyl	C <sub>39</sub> H <sub>29</sub> FN <sub>4</sub> O <sub>4</sub> S	668.74	60	0.47	190-194
8	VIh	Cl	2-Furan	C <sub>35</sub> H <sub>22</sub> ClFN <sub>4</sub> O <sub>4</sub> S	649.09	56	0.29	244-248
9	VIi	Cl	2-Thiophene	C <sub>35</sub> H <sub>22</sub> ClFN <sub>4</sub> O <sub>3</sub> S <sub>2</sub>	665.16	62	0.41	232-236
10	VIj	Cl	3-Pyridine	C <sub>36</sub> H <sub>23</sub> ClFN <sub>5</sub> O <sub>3</sub> S	660.12	56	0.52	240-244
11	VIk	Cl	4-Fluoro phenyl	C <sub>37</sub> H <sub>23</sub> ClF <sub>2</sub> N <sub>4</sub> O <sub>3</sub> S	677.12	69	0.36	248-252
12	VII	Cl	2-Chloro phenyl	C <sub>37</sub> H <sub>23</sub> Cl <sub>2</sub> FN <sub>4</sub> O <sub>3</sub> S	693.60	63	0.68	226-230
13	VI m	Cl	4-Chloro phenyl	C <sub>37</sub> H <sub>23</sub> Cl <sub>2</sub> FN <sub>4</sub> O <sub>3</sub> S	693.60	61	0.46	218-222
14	VI n	Cl	4-Methoxy phenyl	C <sub>38</sub> H <sub>26</sub> ClFN <sub>4</sub> O <sub>4</sub> S	689.15	57	0.53	212-216

### MTT assay

Cell viability was evaluated by the MTT Assay with three independent experiments with five concentrations of compounds. MCF-7 and A549 cells were seeded in 96 well plates at a density of 5X10<sup>3</sup> cells/well. The cultures were treated with a series of concentration of 10-100 µg/ml of test and standard compounds and incubated at 37°C for 48 hrs., followed by addition of MTT solution (5 mg/ml) to each plate and were incubated at 37°C for 3 hrs. At the end of incubation time, precipitates are formed as a result of the

reduction of the MTT salt to chromophore formazan crystals by the cells with metabolically active mitochondria. The optical density of solubilized crystals in DMSO was measured at 570 nm on a microplate reader<sup>15, 16</sup>. Percentage growth inhibition was calculated using the following formula. Results were indicated with mean and standard deviation (M±S.D.) of three independent experiments and were documented in **Table: 2**.

$$\% \text{ Inhibition} = \frac{100 (\text{Control} - \text{Treatment})}{\text{Control}}$$

**Table: 2** Anticancer activity of synthesized compounds (VIa-n)

Sl. No.	Compound	R	Aryl	IC <sub>50</sub> (μM)	
				MCF-7	A549
1	Va	CH <sub>3</sub>	----	0.053±0.003	0.065±0.002
2	Vb	Cl	----	0.048±0.004	0.055±0.002
3	VIa	CH <sub>3</sub>	2-Furanyl	0.074±0.003	0.064±0.001
4	VIb	CH <sub>3</sub>	2-Thiophenyl	0.116±0.002	0.140±0.002
5	VIc	CH <sub>3</sub>	3-Pyridinyl	0.075±0.002	0.125±0.002
6	VIId	CH <sub>3</sub>	4-Fluorophenyl	0.066±0.003	0.035±0.002
7	VIe	CH <sub>3</sub>	2-Chlorophenyl	0.093±0.002	0.135±0.002
8	VIIf	CH <sub>3</sub>	4-Chlorophenyl	0.079±0.003	0.123±0.002
9	VIg	CH <sub>3</sub>	4-Methoxyphenyl	0.066±0.002	0.042±0.003
10	VIh	Cl	2-Furanyl	0.063±0.002	0.040±0.003
11	VIi	Cl	2-Thiophenyl	0.099±0.003	0.109±0.002
12	VIj	Cl	3-Pyridinyl	0.065±0.003	0.092±0.002
13	VIk	Cl	4-Fluorophenyl	0.054±0.003	0.031±0.003
14	VIl	Cl	2-Chlorophenyl	0.075±0.002	0.106±0.002
15	VIIm	Cl	4-Chlorophenyl	0.066±0.002	0.093±0.002
16	VIIn	Cl	4-Methoxyphenyl	0.055±0.002	0.030±0.002
17	Standard	---	---	0.028±0.002	0.023±0.002
Standard: Doxorubicin					

## DISCUSSION

Structures of synthesized compounds were ascertained by IR, NMR and Mass spectral studies. Elemental analysis results were in good agreement ( $\pm 0.4\%$ ) with the calculated values. The mass spectra ESI-MS showed molecular ion peak at  $M^+$  corresponding to exact molecular weight of the respective compound. The IR spectral data of quinazolin-4(3H)-one-thiazolidinone derivatives (VIa-n) showed characteristic absorption bands. The vibration frequencies of N-H stretching were found in the range of 3386-3278  $\text{cm}^{-1}$ ; C=O stretching bands were observed in the range of 1729-1707  $\text{cm}^{-1}$  and 1686-1644  $\text{cm}^{-1}$  whereas C-F stretching at 1241-1164  $\text{cm}^{-1}$ . The  $^1\text{H-NMR}$  spectra of all compounds showed a singlet in the range of  $\delta$  9.28 - 9.09 ppm corresponding to amide ( $-\text{CO-NH}-$ ) proton. The proton of thiazolidinone-5-arylidene substitution ( $-\text{C}=\text{CH}-\text{Ar}-$ ) appeared as singlet between  $\delta$  8.95- 8.76 ppm; whereas thiazolidinone ring ( $-\text{N}-\text{CH}-\text{S}-$ ) proton appeared as singlet between  $\delta$  5.91-5.79 ppm. The substituents of phenyl rings  $-\text{CH}_3$  (VIa-g) and  $-\text{OCH}_3$  (VIg & VIIn) appeared as singlet signals between  $\delta$  2.38-2.18 ppm and  $\delta$  3.90-3.92 ppm respectively.  $^{13}\text{C-NMR}$  spectra of VIa-n showed signals at frequencies in the range of  $\delta$  167-158 ppm associated with

C=O of quinazolinone, thiazolidinone and amide. Further, the aliphatic carbons of  $\text{CH}_3$  and  $\text{OCH}_3$  appeared at  $\delta$  ~20 ppm and  $\delta$  ~57 ppm respectively. All the other carbons of aromatic and hetero aromatic rings were observed in the region at  $\delta$  110-165 ppm.

### Anticancer evaluation

The results revealed that all the tested compounds exhibited moderate to excellent activity against MCF-7 and A549 cell lines. The compounds **Va** and **Vb** with methyl and chloro substitution exhibited the highest potency against both the cell lines greater than that of their corresponding arylidene derivatives (VIa-n). Compound **Vb** showed IC<sub>50</sub> of 0.048±0.004  $\mu\text{M}$  and 0.055±0.002  $\mu\text{M}$  against MCF-7 and A549 cell lines respectively compared to the IC<sub>50</sub> of 0.027±0.002  $\mu\text{M}$  and 0.023±0.002  $\mu\text{M}$  exhibited by the standard doxorubicin. Among the arylidene derivatives compound **VIk** (R = Cl; Ar = 4-F-C<sub>6</sub>H<sub>4</sub>), **VIIn** (R = Cl; Ar = 4-OCH<sub>3</sub>-C<sub>6</sub>H<sub>4</sub>) and **VIId** (R = CH<sub>3</sub>; Ar = 4-F-C<sub>6</sub>H<sub>4</sub>) showed significant activity with IC<sub>50</sub> values 0.031±0.003  $\mu\text{M}$ , 0.030±0.002  $\mu\text{M}$  and 0.035±0.002  $\mu\text{M}$  respectively against A549 cell lines, as compared to 0.023±0.002  $\mu\text{M}$  showed by the standard doxorubicin. In addition, the arylidene derivatives **VIk** and **VIIn** also showed high potency against

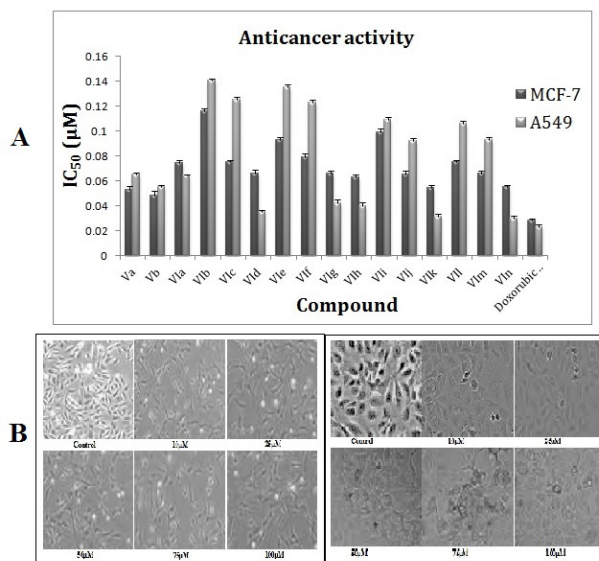


MCF-7 cell lines with  $IC_{50}$  values  $0.054 \pm 0.003 \mu\text{M}$  and  $0.055 \pm 0.002 \mu\text{M}$  respectively. Among the arylidene derivatives, the compounds with 4-fluorophenyl substitution on C5 position of 4-thiazolidinone (**VId** & **VIk**) showed greater potency against both cell lines than the other with aryl and hetero aryl substitutions. The anticancer activity of synthesized derivatives and inhibition of growth of cell by **VIk** were depicted in **Figure 2**.

### Molecular docking study

The lowest energy docked conformation of the ligands **Vib**, **VII** and **VIn** revealed that the compounds bind with an overall binding energy of  $-62.964 \text{ kcal/mol}$ ,  $-81.968 \text{ kcal/mol}$ ,  $-65.086 \text{ kcal/mol}$  making intimate contacts with the residues of active site of the target enzyme phosphoinositide-3-OH kinase (PI(3)K) through significant bonded and non-bonded interactions with higher docking scores  $-74.602$ ,  $-99.037$  and  $-76.787$  respectively (**Table 3**). The ligand **VII** showed three hydrogen bonding interaction with His-716, Arg-720, Lys-712 with high docking score (Figure: 3), whereas the ligand **Vib** with least anticancer activity showed three H-bond interactions with Arg-720, His-716. The ligand **VIn** which showed high potency also showed one hydrogen bond interaction with Arg-720. The compounds **VIk** and **Vd**, which exhibited highest activity

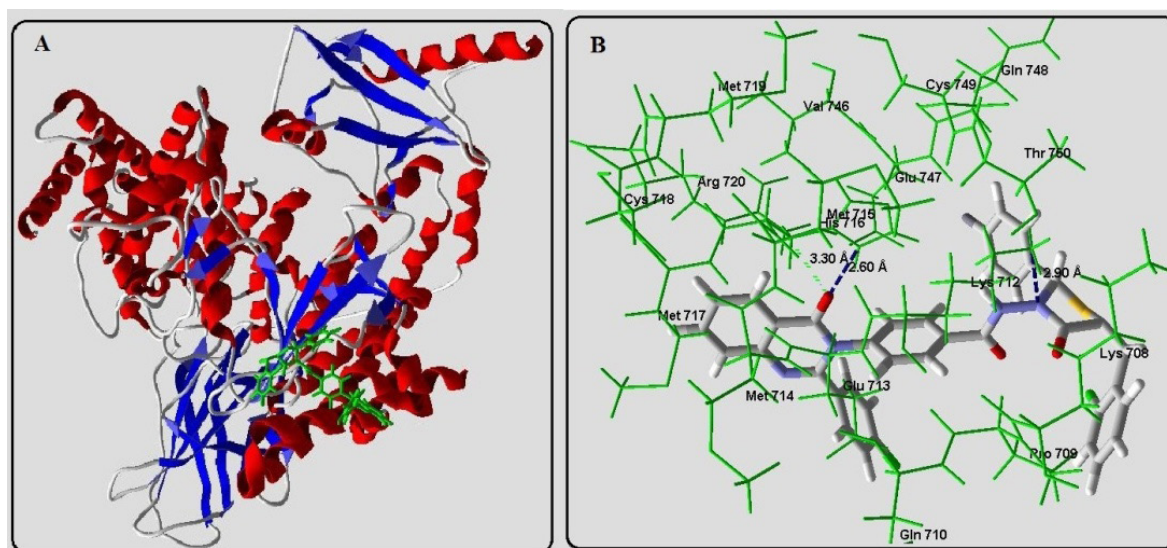
against A549 cell lines and MCF-7 cell lines showed least docking scores, indicating that the cytotoxicity of the most active compound may due to other mechanism than the inhibition of PI(3)K enzyme.



**Figure 2:** (A) Comparing the  $IC_{50}$  ( $\mu\text{M}$ ) of all synthesized compounds and (STD) on the MCF-7 and A549 cells. The data represented as mean  $\pm$  S.D. (B) Dose dependant inhibition of MCF-7 and A549 cells by compound **VIk**, representing the images of one out of three experiments

**Table: 3** Molecular docking results: molecular docking scores, docking energies and H- bond interactions & distances of compounds with target PI(3)K (PDB ID: 2WXQ)

Sl. No.	Compound	Docking score	Re-rank score	Binding energy	H-Bond & Distance
1	Va	-25.527	-21.056	-14.382	----
2	Vb	-19.88	-13.748	-5.943	----
3	Vla	-47.131	-35.503	-41.105	----
4	Vlb	-74.602	-57.884	-62.964	Arg 720; N(7)-6=3.44Å; His 716; N(7)-6=3.48Å & N(7)-9=3.58Å
5	Vlc	-16.32	0.068	-14.902	----
6	Vld	-25.525	-19.874	-13.936	----
7	Vle	-38.777	-32.843	-22.84	----
8	Vlf	-25.533	-20.745	-14.051	----
9	Vlg	-73.171	-61.666	-59.036	Glu 713; N(7)-24=2.60Å Gln 710; N(7)-6=3.45Å
10	Vlh	-51.067	-43.871	-36.627	----
11	Vli	-25.807	-18.079	-15.17	----
12	Vlj	-56.474	-47.974	-41.384	----
13	Vlk	-20.918	-15.237	-9.425	----
14	Vll	-99.037	-60.212	-81.968	His 716; O(8)-10=2.60Å Arg 720; O(8)-10=3.30Å Lys 712; N(7)-27=2.90Å
15	Vlm	-20.918	-17.458	-13.87	----
16	Vln	-76.787	-62.39	-65.086	Arg 720; N(7)-6=3.44Å



**Figure 3:**(A) Docking orientation of compound VII with the target enzyme (B) Compound VII forming H-Bond interactions with amino acid residues of the target enzyme PI(3)K

## CONCLUSIONS

The present study revealed a new series of N-(2-(4-fluoro phenyl)-4-oxothiazolidin-3-yl)-4-(4-oxo-2-[(4-substituted phenyl)-quinazolin-3(4H)-yl]) benzamide derivatives were successfully synthesized and analyzed by various spectral methods. All the purified compounds were screened for their *in vitro* anti-cancer activity against MCF-7 and A549 cell lines. Compounds **Va**, **Vb**, **VId**, **VIh**, **VIk** and **VIIn** exhibited potent anticancer activity with  $IC_{50}$  range of 0.030-0.070  $\mu$ M against MCF-7 and A549 cell lines. Docking results indicate that anticancer activity of the title compounds is not due to inhibition of PI(3)K enzyme.

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