

## Original Research Article

### **MOLECULAR DOCKING AND MOLECULAR DYNAMIC STUDIES, SYNTHESIS, CHARACTERISATION OF THIAZOLIDINE-4-ONE DERIVATIVES**

#### Abstract

Antibacterial, antifungal, anticancer, antitubercular, anti-HIV, analgesic, anti-inflammatory, and ulcerogenic activities have all been documented for thiazolidine derivatives. Molecular docking has become a crucial step in the drug discovery process, with the goal of predicting the binding mechanism and affinity of the protein-ligand complex. AutoDock is a popular non-commercial docking tool that successfully docks ligands to their target proteins (accurate and computationally fast). The Discovery Studio Visualizer is a free viewer that may be used to open data produced by other Discovery Studio tools.

In two phases, a new series of Thiazolidine-4-one derivatives was created. The production of Schiff base is the first step, followed by the condensation of Schiff base with Chloro acetyl chloride and subsequent cyclisation steps. FTIR, <sup>1</sup>H-NMR, <sup>13</sup>C-NMR, and Mass Spectroscopy were used to characterise the chemical structures of the produced compounds.

1BVR protein that was taken from the protein database website

The structures were drawn using Chem draw Ultra 8.0 and Biovia draw 2018. Using the Smiles Online Translator, it was stored in Mol format and then converted to PDB format. The Cygwin toolings were used to log all of the files.

The conformation was computed using a ranking system. This indicates whether the molecule has strong ligand binding energy, hydrogen bonding, and hydrophobic interaction with the receptor. According to the findings, thiazolidine-4-one derivatives have antitubercular efficacy when used in conjunction with the Enoyl-acyl carrier protein (enoyl-ACP) reductase enzyme.

For the docking analysis it indicates if the compound has strong ligand binding energy, hydrogen bonding, and hydrophobic binding with the receptor shows good activity. Using Auto dock 4.2 it was found out that Among the above 20 compounds

(including the control compound), C2, C5, C6, C8, C11. C13, C15 and C17 directly bind with the functional domain (*Casein kinase II phosphorylation site*) of the amino acid (252 to 255). The above compounds bind at the 252<sup>nd</sup> position of the Chain C, where Alanine is present (The target protein, 1BVR () contains ABCDEF chains).

**KEYWORDS:** Molecular docking, Thiazolidine-4-one derivatives, antitubercular activity, Enoyl-acyl carrier protein. Antibacterial, ,Chloroacetyl chloride, Schiff Base.

## 1.INTRODUCTION

Azetidinone and Thiazolidinone derivatives were reported to possess antibacterial <sup>1-2</sup>, antifungal <sup>1-2</sup>, antitubercular activity <sup>3</sup>, anti-HIV <sup>4</sup>, analgesic <sup>5</sup>, anti inflammatory <sup>5</sup>, and ulcerogenic activity <sup>6</sup>. Isoniazid derivatives were reported to possess antimicrobial <sup>7</sup> activities. Therefore it was envisaged that compounds containing both the chemical moieties would result in compounds of interesting biological activities.

In this present study, a new series of Thiazolidine-4-one derivative were synthesized in two steps. The first step is the formation of Schiff base and the second step is the condensation of Schiff base with Chloro acetyl chloride and cyclisation processes. The chemical structures of the synthesized compounds were confirmed using FTIR, <sup>1</sup>H-NMR, <sup>13</sup>C-NMR and Mass Spectroscopy.

Molecular docking has become an important process in the course of drug discovery and docking aims to predict the binding mode and binding affinity of the protein-ligand complex.

Insilico Docking studies means conducted or produced utilizing computer modeling or computer simulation. Based on the literature survey, one enzyme was selected for the insilico docking studies namely the Enoyl-acyl carrier protein (enoyl-ACP) reductase enzyme. The protein would be downloaded from the Protein database and the necessary studies would be done systematically and methodically.<sup>7,8</sup>

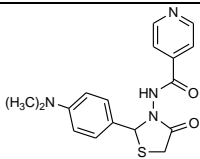
2.Chemistry: The melting points were taken in an open capillary tube and are uncorrected. The FTIR spectra of the compounds were recorded on Win-Bommen B-104 IR Spectrophotometer with KBr pellets. <sup>1</sup>H-NMR spectra were recorded on Bruker A VIII 500 MHz NMR Facility using DMSO-d<sub>6</sub> as a solvent. The chemical shifts are reported as parts per million downfield from tetramethylsilane (Me<sub>4</sub>Si). The mass spectra was also done. The purity of the compounds was checked by TLC on precoated aluminum sheets (Silica gel 60 F254) using benzene and alcohol as mobile phase and visualized by iodine vapors

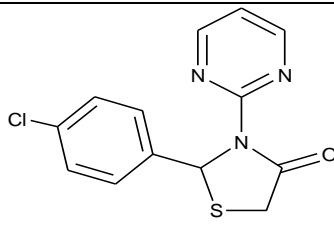
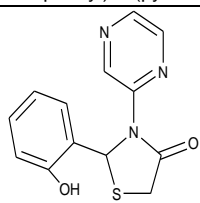
### 3. General Methods of Synthesis of Thiazolidine-4-one derivatives 9,10,11,12

**General Methods of Synthesis of Schiff Bases (C<sub>4</sub>S<sub>1</sub>,C<sub>12</sub>S<sub>1</sub>,C<sub>16</sub>S<sub>1</sub>):** A mixture of Isoniazid 0.01mol/ 2-amino pyrazine/ 2-amino pyrimidine, and substituted benzaldehyde (0.01mol) and a drop of acetic acid was dissolved in ethanol (25ml) and heated on a steam bath for 45-60 min or on a water bath for 2-3 hrs. The reaction mixture was allowed to stand at room temperature for 24h; the product separated out was filtered, dried under vacuum and recrystallized by using warm ethanol.

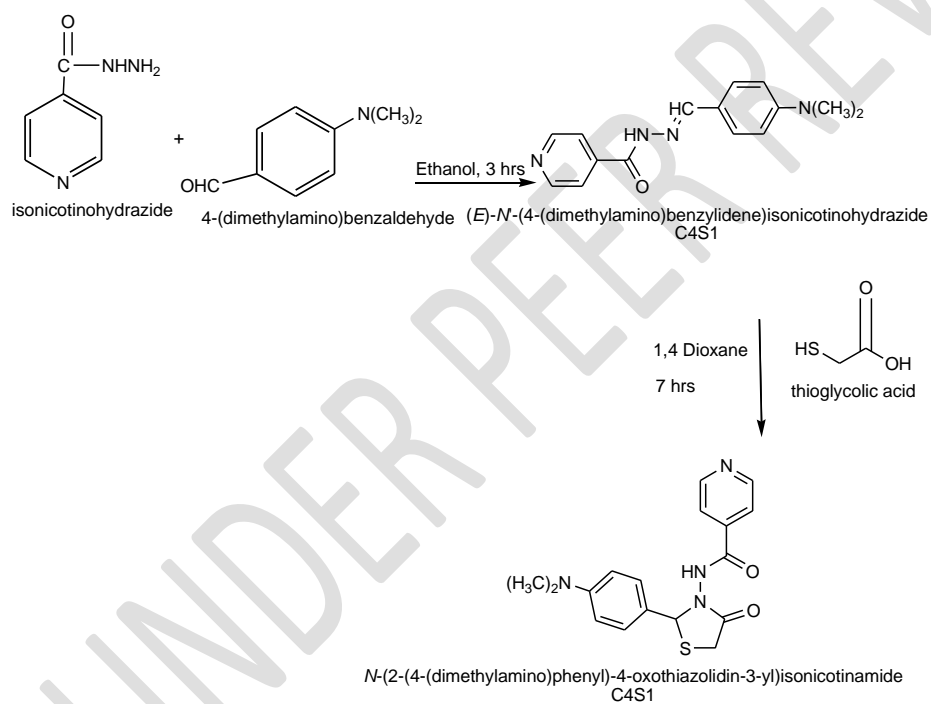
**General Methods of Synthesis of Thiazolidine-4-one (C<sub>4</sub>S<sub>2</sub>,C<sub>12</sub>S<sub>2</sub>,C<sub>16</sub>S<sub>2</sub>):** To a mixture of Schiff's base (0.01mol) and thioglycolic acid (0.01mol) dissolved in 1, 4 dioxane (20ml), anhydrous zinc chloride (0.004 mol) was added and refluxed for 8h. The reaction mixture was cooled, filtered, washed with water; vacuum dried and recrystallized using absolute ethanol.

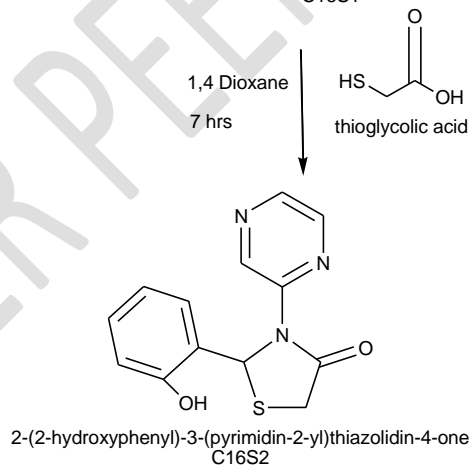
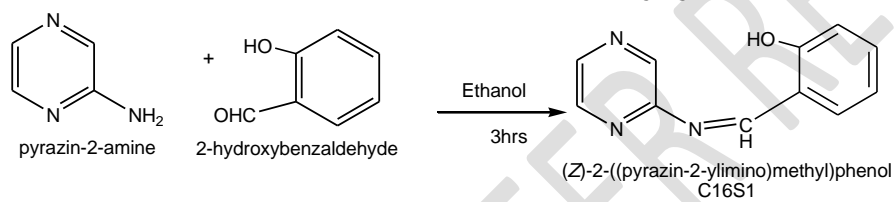
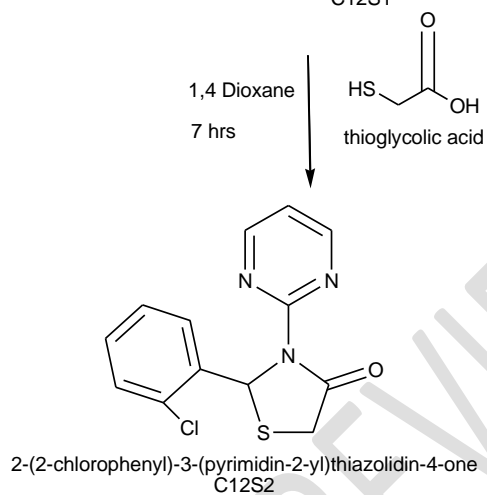
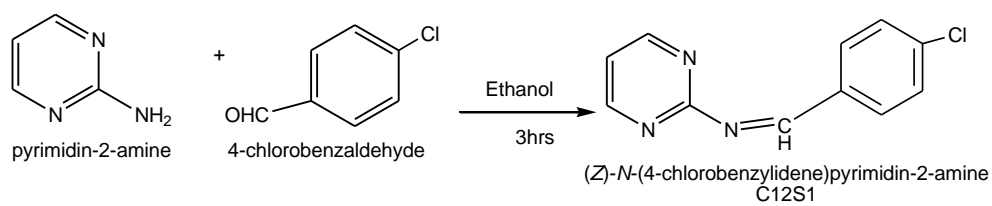
Table 1 : The Schiff bases and thiazolidine- 4-one derivatives were prepared by the method of S. Ramachandran *et al.*.

S.No	Aromatic Amine	Aromatic Aldehyde	Structure of Thiazolidine-4-one
1 C 4	isoniazid	Para dimethyl amino benzldehyde	 <chem>CN(C)c1ccc(cc1)C2N(C(=O)Nc3ccncc3)SC2=O</chem> <i>N</i> -(2-(4-(dimethylamino)phenyl)-4-oxothiazolidin-3-yl)isonicotinamide

2 C12	2-amino Pyrimidine	4-chloro benzaldehyde	 <p>2-(4-chlorophenyl)-3-(pyrimidin-2-yl)thiazolidin-4-one</p>
3 C16	2- amino pyrazine	2-hydroxy benzaldehyde	 <p>2-(2-hydroxyphenyl)-3-(pyrazin-2-yl)thiazolidin-4-one</p>

## SCHEMES





## RESULTS

Table 2 . INTERPRETATION DETAILS OF ALL THE FOUR SYNTHESISED COMPOUNDS

S2 stands for Step 2 Product

PARAMETER	C4S2 Structure 5	C12S2 Structure 3	C16S2 Structure 16
YIELD	56 %	<b>Yield:</b> 65 %	<b>Yield:</b> 63 %
MELTING POINT	<b>Mp:</b> 120-123 °C	<b>Mp:</b> 119-120 °C	<b>Mp:</b> 140-142 °C
RF VALUE	0.50	0.44	0.41
RF SOLVENT SYSTEM	(H:EtOAc/1:2)	(H:EtOAc/1:1)	(H:EtOAc/1:1)
FTIR	<b>IR (KBr):</b> Amide NH ( $3414\text{ cm}^{-1}$ ), Aromatic CH ( $3063$ , $2912$ and $2834\text{ cm}^{-1}$ ), Amide C=O ( $1731\text{ cm}^{-1}$ ), Thiozolidine C=O ( $1648\text{ cm}^{-1}$ ), Aromatic C=C ( $1571\text{ cm}^{-1}$ ), C-N ( $1288\text{ cm}^{-1}$ );	<b>IR (KBr):</b> Aromatic CH- $3086, 2994$ and $2970\text{ cm}^{-1}$ , Thiozolidine Carbonyl- $1671\text{ cm}^{-1}$ , Aromatic C=C- $1528\text{ cm}^{-1}$ and C-N- $1285\text{ cm}^{-1}$	<b>IR (KBr):</b> Aromatic ( $3072$ , $2943$ , $2910$ and $2788\text{ cm}^{-1}$ ), Aromatic C=C ( $1530\text{ cm}^{-1}$ ) Aromatic OH( $3417\text{ cm}^{-1}$ ), Thiozolidine C=O ( $1670\text{ cm}^{-1}$ ), C-N ( $1285\text{ cm}^{-1}$ );
H1NMR	<b><math>^1\text{H}</math> NMR (400 MHz, DMSO-<math>d_6</math>)</b> $\delta$ 10.39 (s, 1H), 8.56 (d, $J = 5.2\text{ Hz}$ , 2H), 7.68 (d, $J = 5.1\text{ Hz}$ , 2H), 7.35 (d, $J = 8.6\text{ Hz}$ , 2H), 6.76 (d, $J = 8.8\text{ Hz}$ , 2H), 5.51 (s, 1H), 3.15 (s, 2H), 2.98 (s, 6H) ppm;	<b><math>^1\text{H}</math> NMR (500 MHz, DMSO-<math>d_6</math>)</b> $\delta$ 8.31 (d, $J = 4.8\text{ Hz}$ , 2H), 7.67 (d, $J = 8.4\text{ Hz}$ , 2H), 7.63 (d, $J = 8.5\text{ Hz}$ , 2H), 7.08 (t, $J = 8.5\text{ Hz}$ , 1H), 6.34 (s, 1H), 3.62 (s, 2H) ppm.	<b><math>^1\text{H}</math> NMR (500 MHz, <math>\text{CDCl}_3</math>)</b> $\delta$ 12.97 (s, 1H), 8.67 (s, 1H), 8.54 (d, $J = 2.5\text{ Hz}$ , 1H), 8.46 (dd, $J = 2.3$ , $1.2\text{ Hz}$ , 1H), 7.64 (d, $J = 5.1\text{ Hz}$ , 1H), 7.45 – 7.42 (m, 1H), 7.19 (s, 1H), 7.11 (d, $J = 5.0\text{ Hz}$ , 1H), 6.99 – 6.95 (m, 1H), 3.91 (s, 2H) ppm;
C13NMR	<b><math>^{13}\text{C}</math> NMR (101 MHz, DMSO-<math>d_6</math>)</b> $\delta$ 169.54, 162.10, 150.72, 150.32, 141.30, 133.13, 129.13, 122.89, 112.24, 60.89, 40.19, 34.77 ppm;	<b><math>^{13}\text{C}</math> NMR (126 MHz, DMSO-<math>d_6</math>)</b> $\delta$ 172.48, 159.46, 159.38, 157.25, 141.28, 134.58, 129.82, 129.89, 128.64, 128.61, 114.76, 65.50, 35.13 ppm.	<b><math>^{13}\text{C}</math> NMR (101 MHz, <math>\text{CDCl}_3</math>)</b> $\delta$ 169.89, 162.02, 154.55, 145.39, 143.49, 142.12, 130.92, 129.90, 126.04, 120.42, 118.84, 59.23, 34.35 ppm;

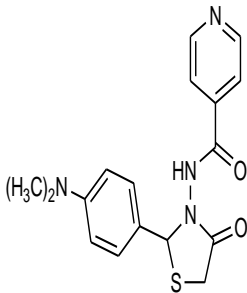
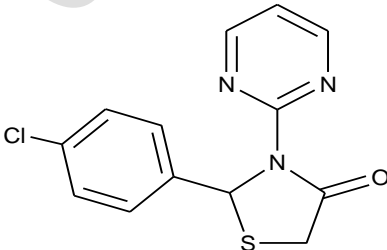
MASS SPECTRA	HRMS (ESI) Anal.Calcd. for (C <sub>17</sub> H <sub>18</sub> N <sub>4</sub> O <sub>2</sub> S) (M <sup>+</sup> ): 342.1150, found: 342.1120	HRMS (ESI) Anal.Calcd. for (C <sub>13</sub> H <sub>10</sub> ClN <sub>3</sub> OS) (M <sup>+</sup> ): 291.0233,found: 291.9865.	HRMS (ESI) Anal.Calcd. for (C <sub>13</sub> H <sub>11</sub> N <sub>3</sub> O <sub>2</sub> S) (M <sup>+</sup> ): 273.0572,found: 273.1379.
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UNDER PEER REVIEW

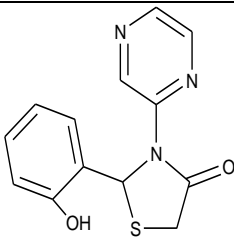
#### 4. MOLECULAR DOCKING AND MOLECULAR DYNAMICS STUDIES

The lists of Thiazolidine-4-one structures and the standard compounds were shown in Table No 3

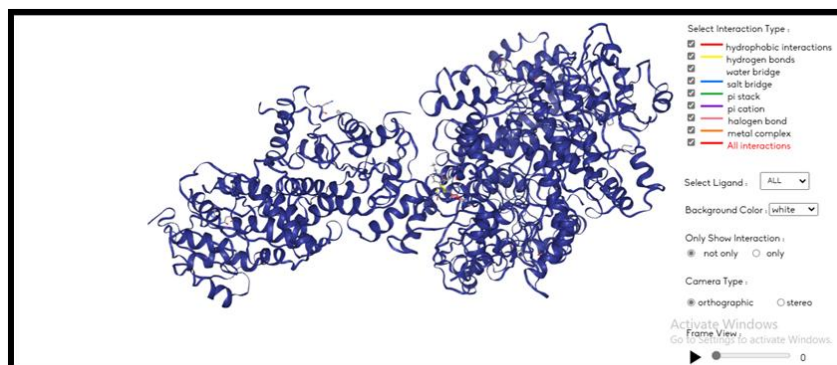
**Table 3 -COMPLETE ANALYSIS OF THE COMPOUNDS INVOLVING THE MOLECULAR DOCKING**

COMPOUND	COM POU ND NO	MOL WT	DOC KING STOR E	MOLECULAR DYNAMICS												
<div> <i>N</i>-(2-(4-(dimethylamino)phenyl)-4-oxothiazolidin-3-yl)isonicotinamide</div>	4	342.42	6.9	<div>Hydrophobic and H-Bond interaction between Amino Acids</div> <div>Hydrophobic Interactions</div> <table><tr><th>Residue</th><th>Res-Pos</th><th>Chain</th></tr><tr><td>PRO</td><td>237</td><td>F</td></tr></table> <div>Hydrogen Bonds</div> <table><tr><th>Residue</th><th>Res-Pos</th><th>Chain</th></tr><tr><td>ASN</td><td>231</td><td>F</td></tr></table>	Residue	Res-Pos	Chain	PRO	237	F	Residue	Res-Pos	Chain	ASN	231	F
Residue	Res-Pos	Chain														
PRO	237	F														
Residue	Res-Pos	Chain														
ASN	231	F														
<div> 2-(4-chlorophenyl)-3-(pyrimidin-2-yl)thiazolidin-4-one</div>	12	291.76	6.3	<div>Hydrophobic_Interaction s</div> <table><tr><th>Residue</th><th>Res-Pos</th><th>Chain</th></tr><tr><td>ILE</td><td>228</td><td>F</td></tr></table>	Residue	Res-Pos	Chain	ILE	228	F						
Residue	Res-Pos	Chain														
ILE	228	F														



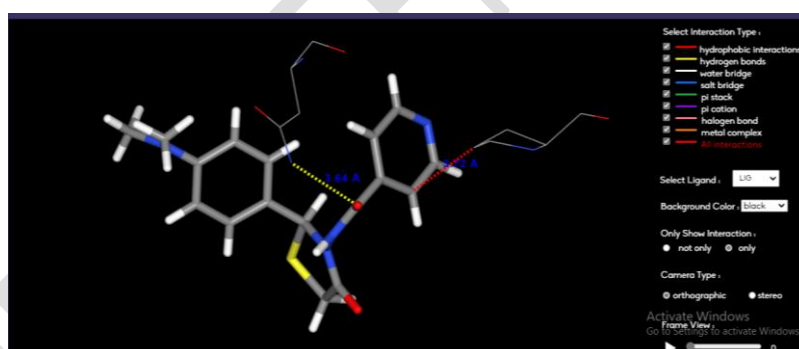
<div><p>2-(2-hydroxyphenyl)-3-(pyrazin-2-yl)thiazolidin-4-one</p></div>	16	273.31	7.0	<div>Hydrophobic Interactions :</div> <div><table><tr><th>Residue</th><th>Res-Pos</th><th>Chain</th></tr><tr><td>PRO</td><td>140</td><td>C</td></tr></table><div>Hydrogen Bonds</div><table><tr><th>Residue</th><th>Res-Pos</th><th>Chain</th></tr><tr><td>ALA</td><td>81</td><td>A</td></tr></table></div>	Residue	Res-Pos	Chain	PRO	140	C	Residue	Res-Pos	Chain	ALA	81	A						
Residue	Res-Pos	Chain																				
PRO	140	C																				
Residue	Res-Pos	Chain																				
ALA	81	A																				
ISONIAZID	20		4.8	<div>hydrophobic_interactions :</div> <div><table><tr><th>Residue</th><th>Res-Pos</th><th>Chain</th></tr><tr><td>PRO</td><td>59</td><td>A</td></tr><tr><td>PRO</td><td>140</td><td>C</td></tr></table><div>hydrogen_bonds :</div><table><tr><th>Residue</th><th>Res-Pos</th><th>Chain</th></tr><tr><td>LEU</td><td>60</td><td>A</td></tr><tr><td>LYS</td><td>181</td><td>C</td></tr></table></div>	Residue	Res-Pos	Chain	PRO	59	A	PRO	140	C	Residue	Res-Pos	Chain	LEU	60	A	LYS	181	C
Residue	Res-Pos	Chain																				
PRO	59	A																				
PRO	140	C																				
Residue	Res-Pos	Chain																				
LEU	60	A																				
LYS	181	C																				

**Figure 1 : Molecular Dynamics: Ligand – Protein Complex - Compound 4 (C4)**



The above picture represents the entire protein structure of compound 4 complex with hydrophobic interactions retrieved using MolADI server.

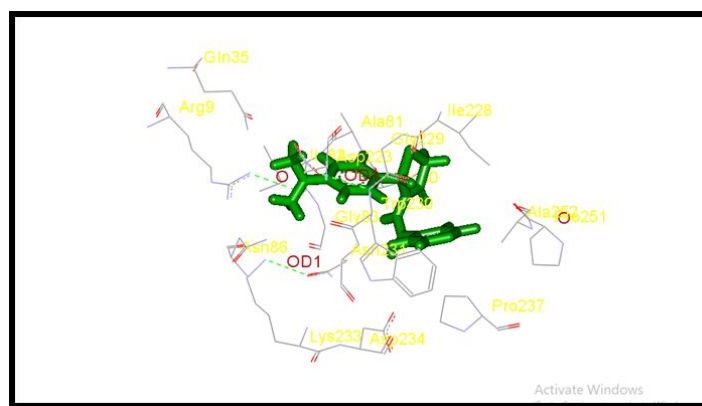
**Figure 2 : Molecular Dynamics – Ligand – Protein Interaction - Compound 4 (C4)**



The above picture represents the entire protein structure of compound 4 complex with hydrophobic interactions. (Red dotted lines indicate the hydrophobic interaction between compound 4 and the target protein.)

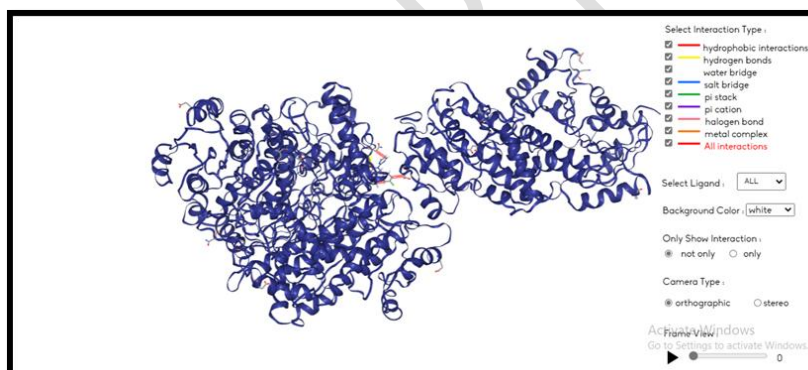
**Figure 3 : MOLECULAR DRUG DOCKING**

Drug –Protein interactions (C4 + 1BVR protein)



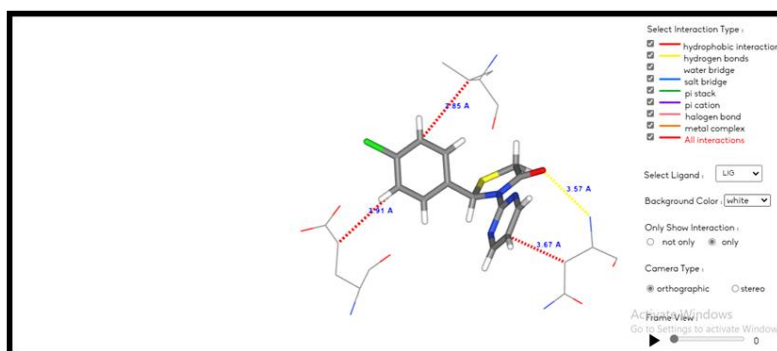
The above picture shows the intra molecular interaction between the drug-protein complex with the respective amino acids labels and H- Bond acceptor atoms

**Figure 4 : Molecular Dynamics: Ligand – Protein Complex - Compound 12 (C12)**



The above picture represents the entire protein structure of compound 12 complex with hydrophobic interactions retrieved using MolADI server.

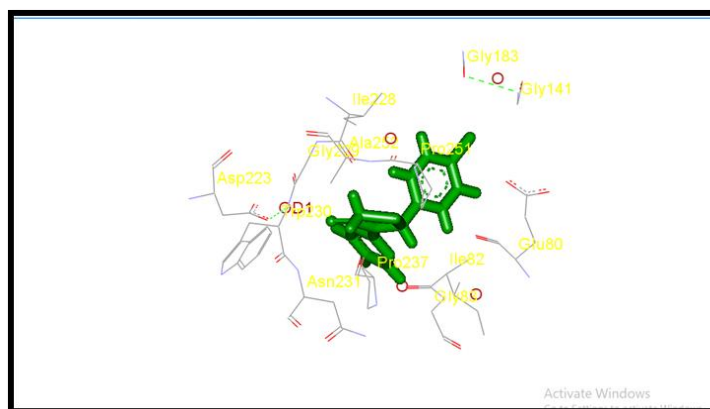
**Figure 5 : Molecular Dynamics – Ligand – Protein Interaction - Compound 12 (C12)**



The above picture represents the entire protein structure of compound 12 complex with hydrophobic interactions. (Red dotted lines indicate the hydrophobic interaction between compound 12 and the target protein.)

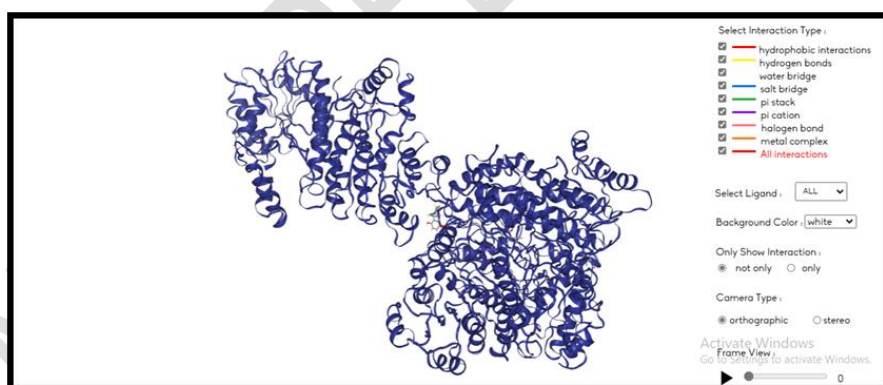
**Figure 6 : MOLECULAR DRUG DOCKING**

Drug –Protein interactions (C12 + 1BVR protein)



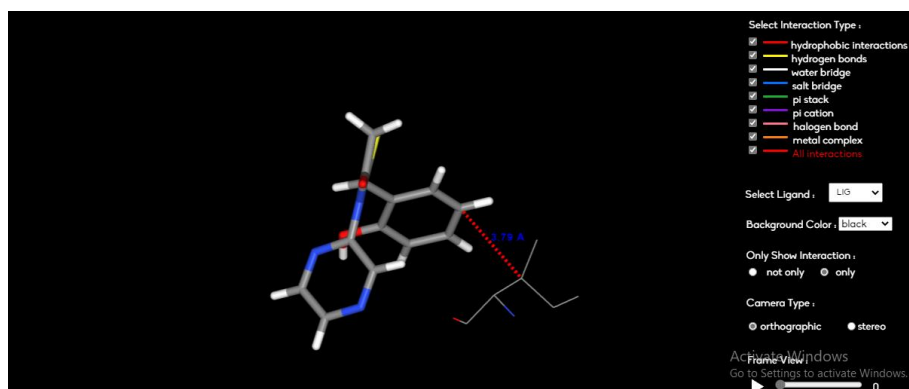
The above picture shows the intra molecular interaction between the drug-protein complex with the respective amino acids labels and H- Bond acceptor atoms.

**Figure 7 : Molecular Dynamics: Ligand – Protein Complex - Compound 16 (C16)**



The above picture represents the entire protein structure of compound 16 complex with hydrophobic interactions retrieved using MolADI server.

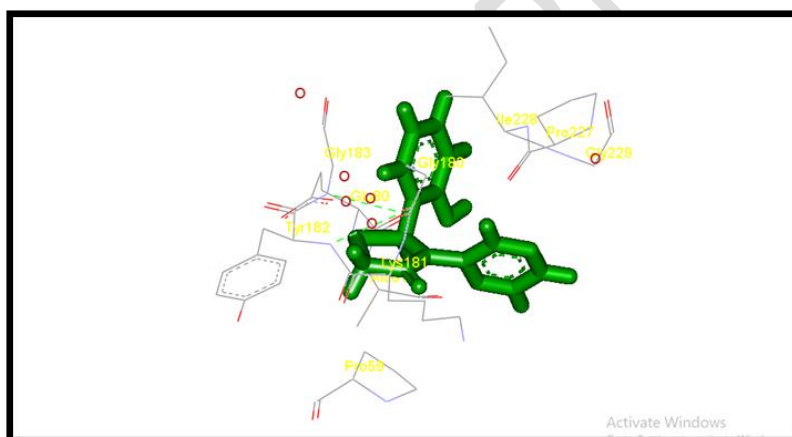
**Figure 8 : Molecular Dynamics – Ligand – Protein Interaction - Compound 16 (C16)**



The above picture represents the entire protein structure of compound 16 complex with hydrophobic interactions. (Red dotted lines indicate the hydrophobic interaction between compound 16 and the target protein.)

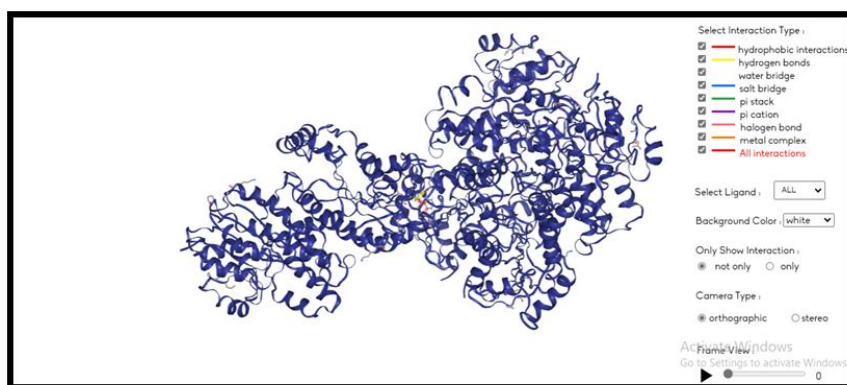
**Figure 9 : MOLECULAR DRUG DOCKING**

Drug –Protein interactions (C16 + 1BVR protein)



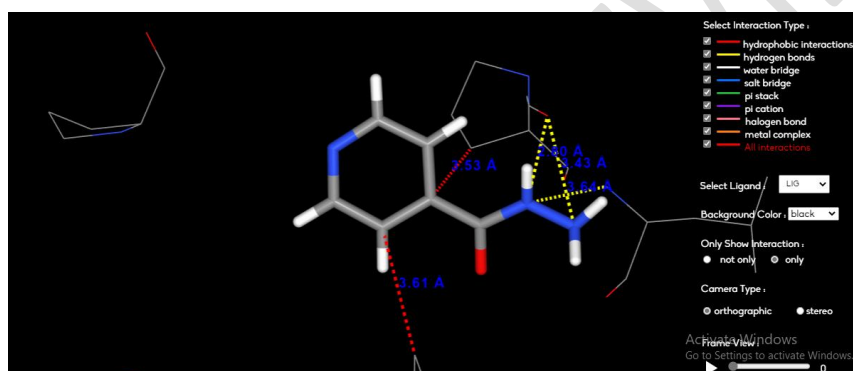
The above picture shows the intra molecular interaction between the drug-protein complex with the respective amino acids

**Figure 10 : Molecular Dynamics: Ligand – Protein Complex - Compound 20 (C20)**



The above picture represents the entire protein structure of compound 20 complex with hydrophobic interactions retrieved using MolADI server.

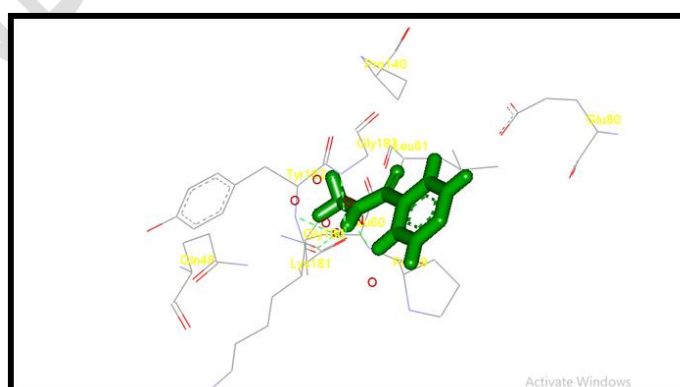
**Figure 11: Molecular Dynamics – Ligand – Protein Interaction - Compound 20 (C20)**



The above picture represents the entire protein structure of compound 20 complex with hydrophobic interactions. (Red dotted lines indicate the hydrophobic interaction between compound 20 and the target protein.)

**Figure 12 : MOLECULAR DRUG DOCKING**

Drug –Protein interactions (C20 + 1BVR protein)



The above picture shows the intra molecular interaction between the drug-protein complex with the respective amino acids labels and H- Bond acceptor atoms.

## 5. DISCUSSION AND CONCLUSION

The current study examines the synthesis of Thiazolidine-4-one derivatives as well as their antibacterial properties. S.Ramachandran et al approach was used to make the thiazolidine derivatives. TLC was used to confirm reaction completion, and recrystallization was used to purify the produced chemicals. Based on the spectrum data, the structures of the produced compounds were assigned. The thiazolidine-4-one compounds' infrared nuclear magnetic resonance spectra revealed the predicted frequencies and signals.

AutoDock is a popular non-commercial docking tool that successfully docks ligands to their target proteins (accurate and computationally fast). In this paper, we present a more user-friendly docking methodology for docking ligands with target proteins, which makes use of AutoDock and Cygwin. The Discovery Studio Visualizer is a free viewer that may be used to open data produced by other Discovery Studio tools.

Various search engines, such as Google general, Google scholar, and SciFinder databases, were used to conduct a comprehensive search of the literature

1BVR was the protein that was taken from the Protein database website. Using the Smiles Online Translator, it was stored in Mol format and then converted to PDB format.

- All of the files were logged in Cygwin tools, and the various properties were checked before the docked files were saved as dlz files. The conformation by ranking was determined and the results were tabulated after viewing these dlz files in visual mode on the Discovery studio website. In general, ten conformations were considered based on their ranking. This indicates whether the molecule has strong ligand binding energy, hydrogen bonding, and hydrophobic interaction with the receptor.

If the molecule has a high ligand binding energy, hydrogen bonding, and hydrophobic interaction with the receptor, the docking analysis indicates that it is active. Using Auto dock 4.2, it was discovered that C2, C5, C6, C8, C11, C13, C15, and C17 directly bind to the functional domain (Casein kinase II phosphorylation site) of the amino acid (including the control molecule) (252 to 255). The aforementioned chemicals bind to Alanine at the 252nd position of Chain C (the target protein, 1BVR ()), comprises ABCDEF chains).

## 7. REFERENCES

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