Original Research Article

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

ABSTRACT

BACKGROUND

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.

AIM

The main aim of this study is

- To study the molecular docking and molecular dynamic studies of the different thiazolidine derivatives.
- To synthesise the compound based on the results produced in the molecular dynamics and molecular studies.
- To Characterise the synthesised compounds using FTIR, 1H NMR, 13C NMR and Mass Spectral studies.

PROCEDURE

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, 1H-NMR, 13C-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.

CONCLUSION

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 252nd 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 1-2, antifungal 1-2, antitubercular activity 3, anti-HIV 4, analgesic 5, anti inflammatory 5, and ulcerogenic activity 6. Isoniazid derivatives were reported to possess antimicrobial 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, 1H-NMR, 13C-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.7,8

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. 1H-NMR spectra were recorded on Bruker A VIII 500 MHz NMR Facility using DMSO-d6 as a solvent. The chemical shifts are reported as parts per million downfield from tetramethylsilane (Me4Si). 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 (C4S1,C12S1,C16S1):

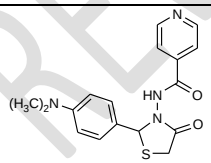
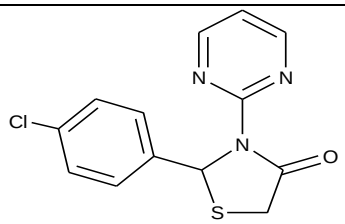
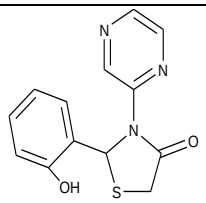
A mixture of Isoniazid 0.01mol)/ 2-amino pyrazine/ 2-amino pyrimidine, and substituted benzaldehyde (0.01mol) and a drop of acetic acid was dissolved in ethanol (25ml) and heated on a steam bath for 45-60 min or on a water bath for 2-3 hrs. The reaction mixture was allowed to stand at room temperature for 24h; the

product separated out was filtered, dried under vacuum and recrystallized by using warm ethanol.

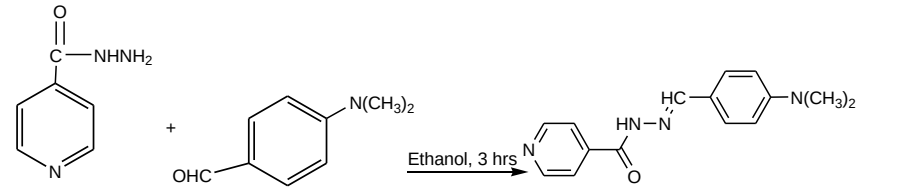
General Methods of Synthesis of Thiazolidine-4-one (C4S2,C12S2,C16S2):

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.

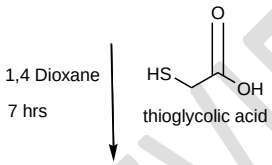
Table 1 : The Schiff bases and thiazolidine- 4-one derivatives were prepared by the method of S. Ramachandran *et al*..(10-12)

S.No	Aromatic Amine	Aromatic Aldehyde	Structure of Thiazolidine-4-one
1 C 4	isoniazid	Para dimethyl amino benzldehyde	 *N*-(2-(4-(dimethylamino)phenyl)-4-oxothiazolidin-3-yl)isonicotinamide **N-(2-(4-(dimethylamino)phenyl)-4-oxothiazolidin-3-yl)isonicotinamide**
2 C12	2-amino Pyrimidine	4-chloro benzaldehyde	 2-(4-chlorophenyl)-3-(pyrimidin-2-yl)thiazolidin-4-one **2-(4-chlorophenyl)-3-(pyrimidin-2-yl)thiazolidin-4-one**
3 C16	2- amino pyrazine	2-hydroxy benzaldehyde	 2-(2-hydroxyphenyl)-3-(pyrazin-2-yl)thiazolidin-4-one **2-(2-hydroxyphenyly)-3-(pyrazine-2-yl)thiazolidin-4-one**

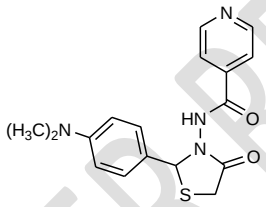
SCHEMES



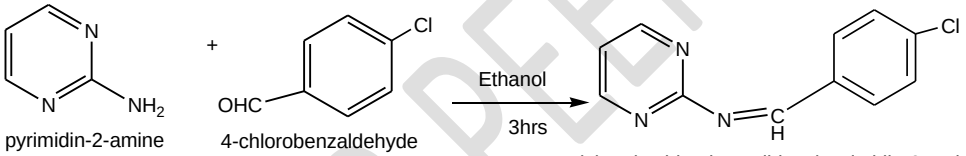
isonicotinohydrazide 4-(dimethylamino)benzaldehyde (*E*)-*N*'-(4-(dimethylamino)benzylidene)isonicotinohydrazide
C4S1



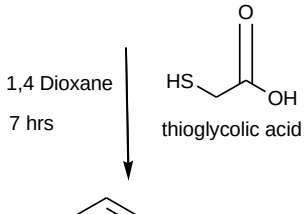
thioglycolic acid



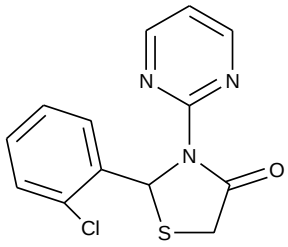
N-(2-(4-(dimethylamino)phenyl)-4-oxothiazolidin-3-yl)isonicotinamide
C4S1



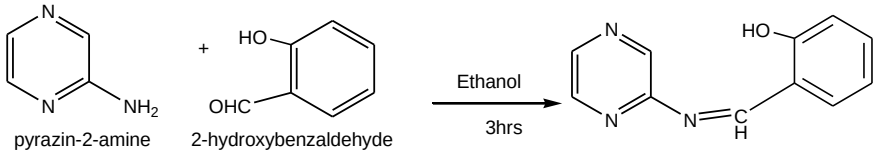
pyrimidin-2-amine 4-chlorobenzaldehyde (*Z*)-*N*-(4-chlorobenzylidene)pyrimidin-2-amine
C12S1



thioglycolic acid

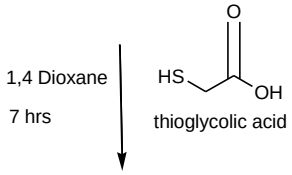


2-(2-chlorophenyl)-3-(pyrimidin-2-yl)thiazolidin-4-one
C12S2

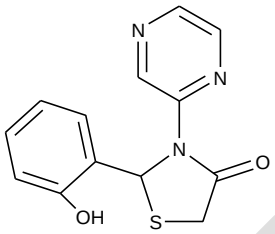


pyrazin-2-amine 2-hydroxybenzaldehyde

(*Z*)-2-((pyrazin-2-ylimino)methyl)phenol
C16S1



thioglycolic acid



2-(2-hydroxyphenyl)-3-(pyrimidin-2-yl)thiazolidin-4-one
C16S2

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 %	**Yield:** 65 %	**Yield:** 63 %
MELTING POINT	**Mp:** 120-123 °C	**Mp:** 119-120 °C	**Mp:** 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	**IR (KBr):** Amide NH (3414 cm^{-1}), Aromatic CH (3063, 2912 and 2834 cm^{-1}), Amide C=O (1731 cm^{-1}), Thiozolidine C=O (1648 cm^{-1}), Aromatic C=C (1571 cm^{-1}), C-N (1288 cm^{-1});	**IR (KBr):** Aromatic CH-3086,2994 and 2970cm^{-1}, Thiozolidine Carbonyl-1671cm^{-1}, Aromatic C=C-1528cm^{-1} and C-N-1285cm^{-1}	**IR (KBr):** Aromatic (3072, 2943, 2910 and 2788 cm^{-1}), Aromatic C=C (1530 cm^{-1}) Aromatic OH(3417 cm^{-1}), Thiozolidine C=O (1670 cm^{-1}), C-N (1285 cm^{-1}).;
H1NMR	**^{1}H NMR (400 MHz, DMSO-d_6)** δ 10.39 (s, 1H), 8.56 (d, J = 5.2 Hz, 2H), 7.68 (d, J = 5.1 Hz, 2H), 7.35 (d, J = 8.6 Hz, 2H), 6.76 (d, J = 8.8 Hz, 2H), 5.51 (s, 1H), 3.15 (s, 2H), 2.98 (s, 6H) ppm;	**^{1}H NMR (500 MHz, DMSO-d6)** δ 8.31 (d, *J* = 4.8 Hz, 2H), 7.67 (d, *J* = 8.4 Hz, 2H), 7.63 (d, *J* = 8.5 Hz, 2H), 7.08 (t, *J* = 8.5 Hz, 1H), 6.34 (s, 1H), 3.62 (s, 2H) ppm.	**^{1}H NMR (500 MHz, $CDCl_3$)** δ 12.97 (s, 1H), 8.67 (s, 1H), 8.54 (d, J = 2.5 Hz, 1H), 8.46 (dd, J = 2.3, 1.2 Hz, 1H), 7.64 (d, J = 5.1 Hz, 1H), 7.45 – 7.42 (m, 1H), 7.19 (s, 1H), 7.11 (d, J = 5.0 Hz, 1H), 6.99 – 6.95 (m, 1H), 3.91 (s, 2H) ppm;
C13NMR	**^{13}C NMR (101 MHz, DMSO-d_6)** δ 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;	**^{13}C NMR (126 MHz, DMSO-d6)** δ 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.	**^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.89, 162.02, 154.55, 145.39, 143.49, 142.12, 130.92, 129.90,126.04, 120.42, 118.84, 59.23, 34.35ppm;

MASS SPECTRA	HRMS (ESI) Anal.Calcd. for ($C_{17}H_{18}N_4O_2S$) (M+): 342.1150, found: 342.1120	HRMS (ESI) Anal.Calcd. for ($C_{13}H_{10}ClN_3OS$) (M+): 291.0233,found: 291.9865.	HRMS (ESI) Anal.Calcd. for ($C_{13}H_{11}N_3O_2S$) (M+): 273.0572,found: 273.1379.

4. MOLECULAR DOCKING AND MOLECULAR DYNAMICS STUDIES

MOLECULAR DOCKING STUDIES

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. The molecular docking approach can be used for the study of interaction (hydrogen bond, hydrophobic) between a protein and a small molecule at the atomic level. The docking process involves three basic steps: protein flexibility, ligand sampling, and scoring function. Synthetic organic chemistry plays an important role in anti-tubercular drug development.13

Insilico Docking studies means conducted or produced by means of computer modelling or computer simulation14. Molecular docking studies are used to determine the interaction of two molecules and to find the best orientation of ligand which would form a complex with overall minimum energy. The small molecule, known as ligand usually fits within protein's cavity which is predicted by the search algorithm.15

AutoDock is a popular non-commercial docking program that docks a ligand to its target protein and performs well (accurate and computationally fast). In this study we propose an easier user-friendly docking protocol for docking ligands with target protein that utilizes AutoDock and Cygwin for docking operations. Our analysis provides a detailed outline and advice for use of AutoDock, AutoDock Tools, its graphical interface and to analyze interaction complexes using computational docking. Autodock and cygwin tools was used to spread knowledge and make scientific research accessible to researchers who could not afford to buy software or pay high subscription fees of online docking servers. Thus we can claim that a researcher with no previous background in bioinformatics research would be able to perform molecular docking using Auto- Dock 4.2 program by following stepwise guidelines.

The Discovery Studio Visualizer is a free viewer that can be used to open data generated by other software in the Discovery Studio product line. ... It also provides a rich set of viewers for displaying plots and other graphical representations

of data Discovery Studio is a suite of software for simulating small molecule and macromolecule systems. It is developed and distributed by Accelrys

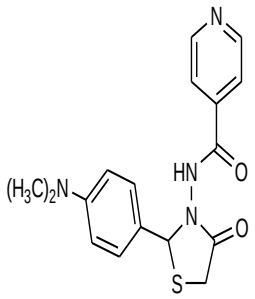
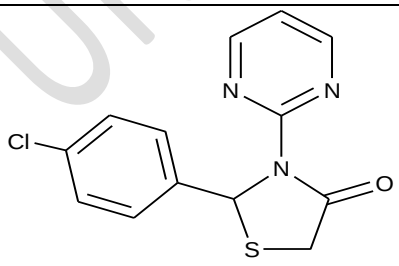
MOLECULAR DYNAMICS STUDIES (16,17)

Molecular dynamics (MD) is a computer simulation method for analyzing the physical movements of atoms and molecules. The atoms and molecules are allowed to interact for a fixed period of time, giving a view of the dynamic "evolution" of the system. In the most common version, the trajectories of atoms and molecules are determined by numerically solving Newton's equations of motion for a system of interacting particles, where forces between the particles and their potential energies are often calculated using interatomic potentials or molecular mechanics force fields. The method is applied mostly in chemical physics, materials science, and biophysics.16

Molecular dynamics (MD) simulations predict how every atom in a protein or other molecular system will move over time, based on a general model of the physics governing interatomic interactions17. These simulations can capture a wide variety of important biomolecular processes, including conformational change, ligand binding, and protein folding, revealing the positions of all the atoms at femtosecond temporal resolution. Importantly, such simulations can also predict how biomolecules will respond—at an atomic level—to perturbations such as mutation, phosphorylation, protonation, or the addition or removal of a ligand. MD simulations are often used in combination with a wide variety of experimental structural biology techniques, including x-ray crystallography, cryo-electron microscopy (cryo-EM), nuclear magnetic resonance (NMR), electron paramagnetic resonance (EPR), and Förster resonance energy transfer (FRET) 18,19

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

<table>
<tr><th>COMPOUND</th><th>COMPOUND NO</th><th>MOL WT</th><th>DOCKING STORE</th><th>MOLECULAR DYNAMICS
Hydrophobic and H-Bond interaction between Amino Acids</th></tr>
<tr><td> 
N-(2-(4-(dimethylamino)phenyl)-4-oxothiazolidin-3-yl)isonicotinamide</td><td>4</td><td>342.42</td><td>6.9</td><td>Hydrophobic Interactions
<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>
Hydrogen Bonds
<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></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td> 
2-(4-chlorophenyl)-3-(pyrimidin-2-yl)thiazolidin-4-one</td><td>12</td><td>291.76</td><td>6.3</td><td>Hydrophobic_Interactions
<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></td></tr>
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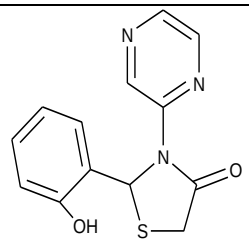
<td> 
2-(2-hydroxyphenyl)-3-(pyrazin-2-yl)thiazolidin-4-one</td>
<td>16</td>
<td>273.31</td>
<td>7.0</td>
<td>Hydrophobic Interactions :
<table><tr><th>Residue</th><th>Res-Pos</th><th>Chain</th></tr><tr><td>PRO</td><td>140</td><td>C</td></tr></table>Hydrogen Bonds
<table><tr><th>Residue</th><th>Res-Pos</th><th>Chain</th></tr><tr><td>ALA</td><td>81</td><td>A</td></tr></table></td>
</tr>
<tr>
<td>ISONIAZID</td>
<td>20</td>
<td></td>
<td>4.8</td>
<td>hydrophobic_interactions :
<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>hydrogen_bonds :
<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></td>
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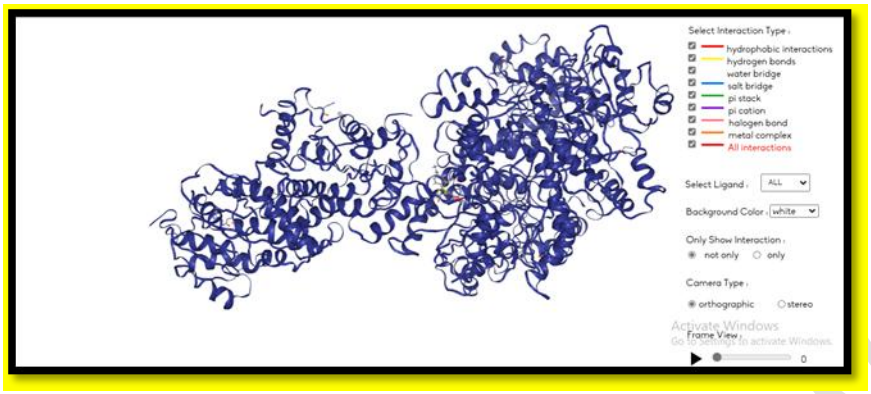

Figure 1 : Molecular Dynamics: Ligand – Protein Complex - Compound 4 (C4)

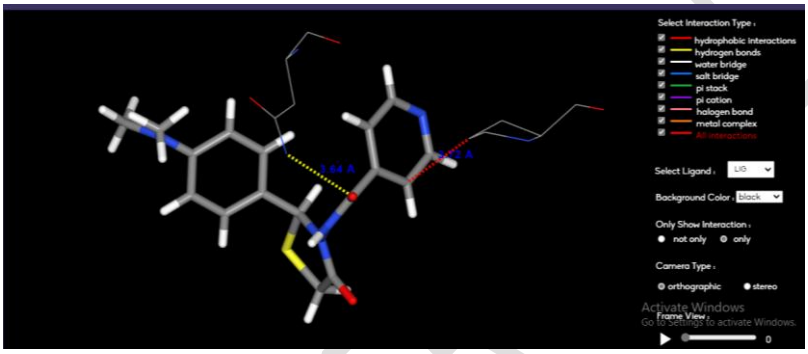

Figure 2 : Molecular Dynamics – Ligand – Protein Interaction - Compound 4 (C4)

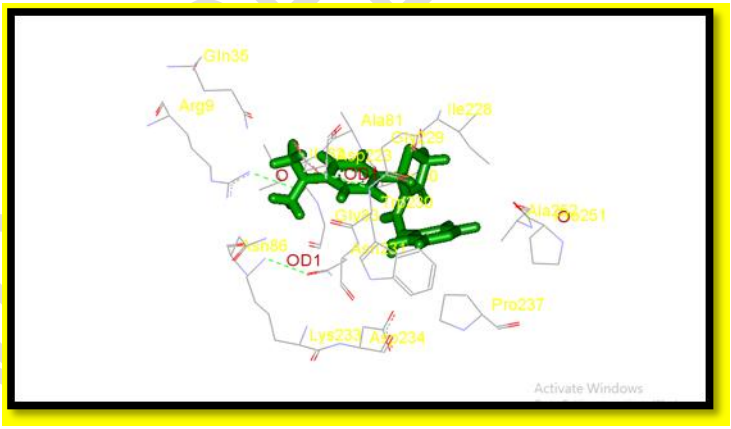

Figure 3 : MOLECULAR DRUG DOCKING

Drug –Protein interactions (C4 + 1BVR protein)

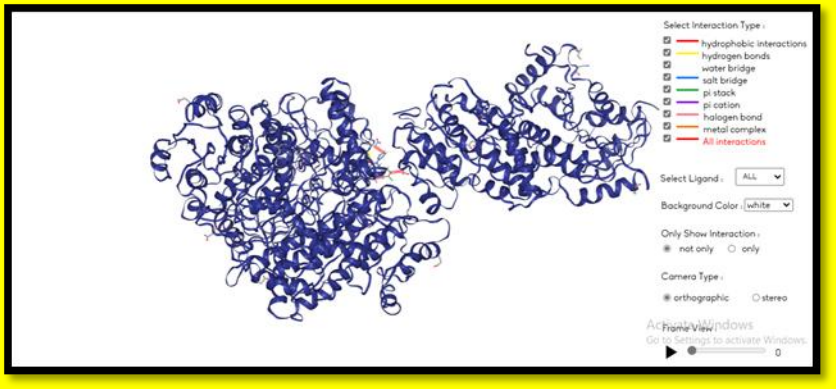

Figure 4 : Molecular Dynamics: Ligand – Protein Complex - Compound 12 (C12)

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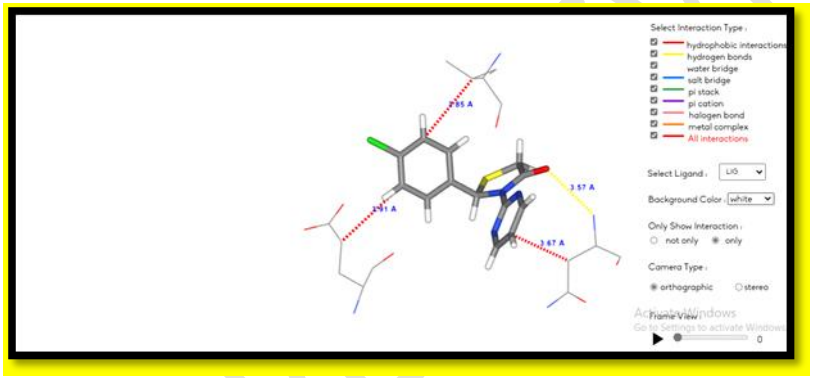

Figure 5 : Molecular Dynamics – Ligand – Protein Interaction - Compound 12 (C12)

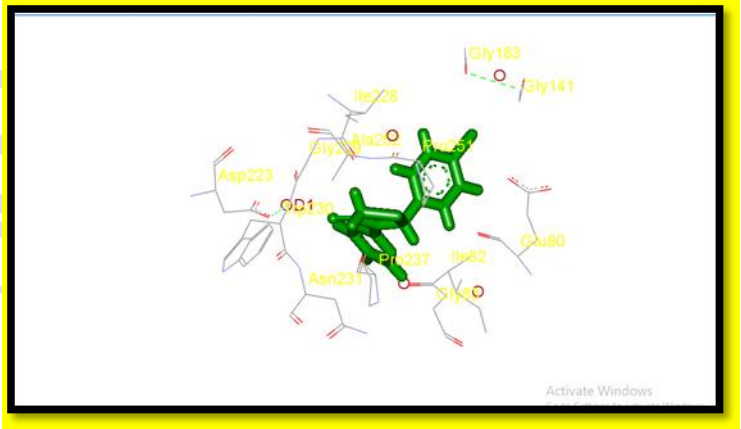

Figure 6 : MOLECULAR DRUG DOCKING

Drug –Protein interactions (C12 + 1BVR protein)

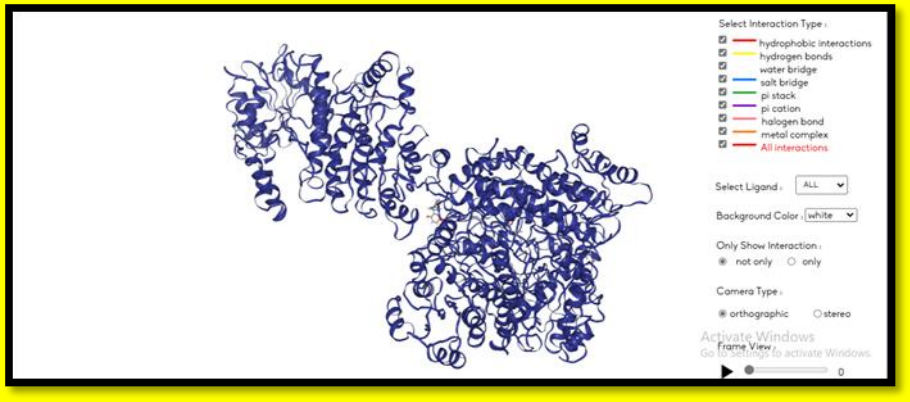

Figure 7 : Molecular Dynamics: Ligand – Protein Complex - Compound 16 (C16)

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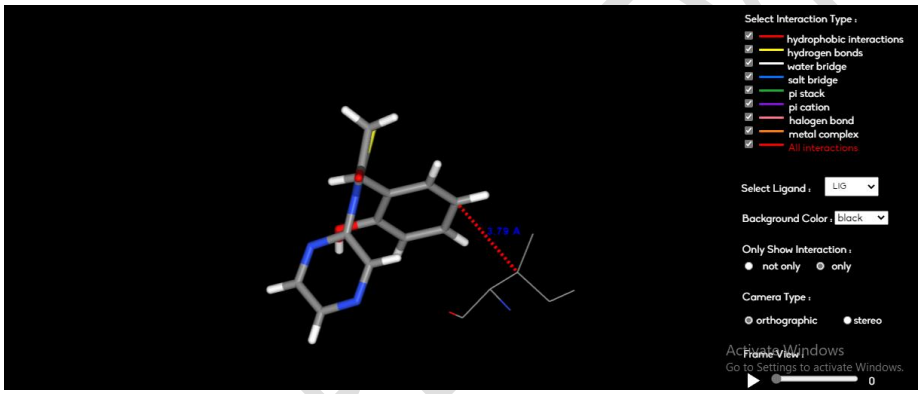

Figure 8 : Molecular Dynamics – Ligand – Protein Interaction - Compound 16 (C16)

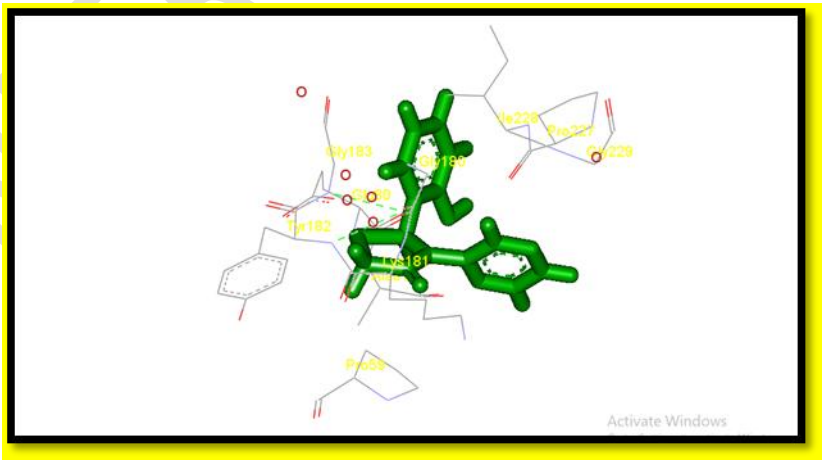

Figure 9 : MOLECULAR DRUG DOCKING

Drug –Protein interactions (C16 + 1BVR protein)

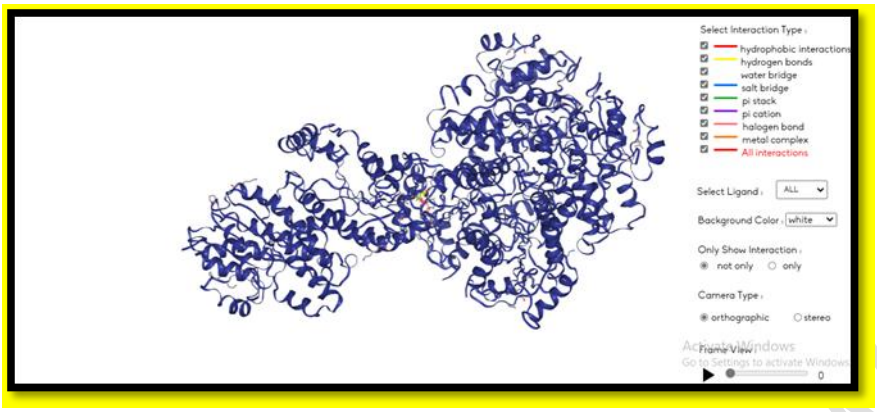

Figure 10 : Molecular Dynamics: Ligand – Protein Complex - Compound 20 (C20)

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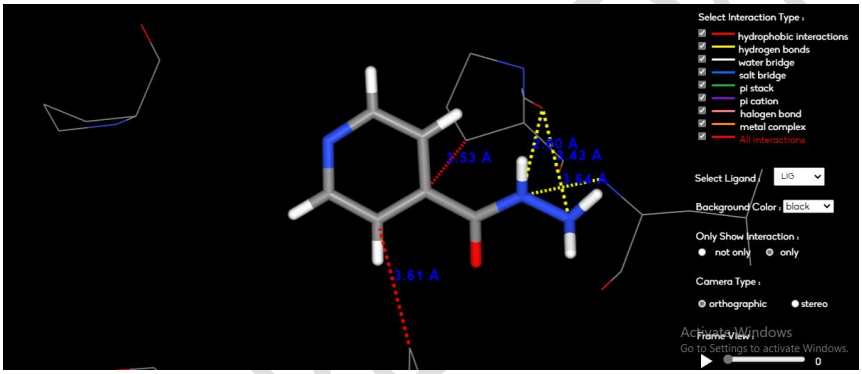

Figure 11: Molecular Dynamics – Ligand – Protein Interaction - Compound 20 (C20)

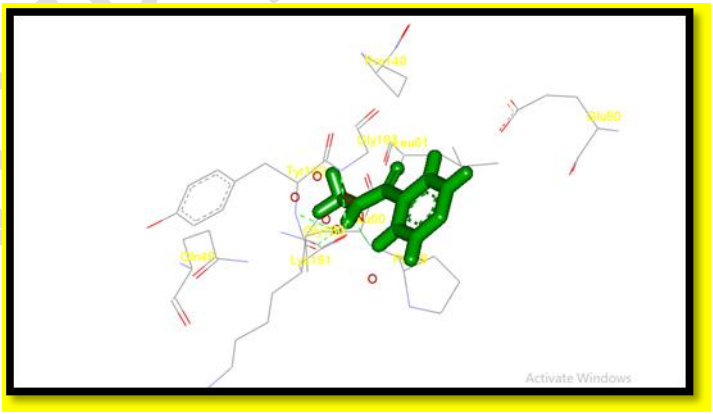

Figure 12 : MOLECULAR DRUG DOCKING

Drug –Protein interactions (C20 + 1BVR protein)

5. DISCUSSION

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 dlg files. The conformation by ranking was determined and the results were tabulated after viewing these dlg 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.

6. CONCLUSION

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. ACKNOWLEDGEMENT

The authors are immensely thankful to the organization Vels Institute of Science, Technology and Advanced Studies (VISTAS) for providing helpful support for the study.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest for this study.

FUNDING SUPPORT

The authors declare that they have no funding support for this study