In sillico Molecular Docking study of Isatin and Acetophenone derivatives as Antimicrobial Agent

ABSTRACT: The heterocyclic molecule isatin (1H-indole-2,3-dione) and its derivatives form a significant family of chemicals that can be employed as building blocks for the manufacture of pharmaceuticals. In the computational method known as docking, different software tools produce different positions at which ligands attach to their receptors. With the help of the Molegro virtual docker software (Version 6.0) and the PDB 3ACX, the present study attempts to perform a high-throughput in silico screening of 27 developed isatin and acetophenone-based derivatives. The docking results showed mol dock scores of -103.345 and one hydrogen bond interaction for the standard drug Ampicillin, on the other hand, the isatin and acetophenone-based derivatives YDA 27, YDA 26, YDA 25, YDA 17 and YDA 7 exhibited excellent mol dock scores and docking scores ranging from -104.23 to -121.126. Apart from the mol dock score, most of the studied compounds observed excellent hydrogen bonding with amino acids of PDB. Compound YDA 27, YDA 26, YDA 25, YDA 17 and YDA 7 showed 3 to 7 hydrogen bond interactions, however, the standard drug Ampicillin showed H-bond interaction with 1 amino acid Val 133 and Val 137. The results of the present study confirmed the significant antimicrobial potential of some designed isatin and acetophenone-based derivatives based on their mol dock values and other parameters when studied in silico, and the data obtained will give data that supports and provides perspectives in future research to develop an effective antimicrobial agent from these derivatives.

KEYWORDS: Antimicrobial agent, Docking study, Isatin, Ampicillin, In sillico.

INTRODUCTION

The world's population suffered severe suffering from infectious diseases over the past 20 years due to multi-drug resistance, which is typically the result of over-expression and widespread usage of a multidrug efflux system. Due to their rapid spread, severity, and resistance to existing antimicrobial medicines, microbial infections are the second leading cause of death worldwide, behind cardiac arrest[1]. Antimicrobials operating at the cell wall level are the most selective, and bactericidal, and have a high therapeutic index because they cause cell lysis by inhibiting peptidoglycan formation. There is a wide variety of antibiotics that can work in the cytoplasmic, membrane, and parietal stages of peptidoglycan production. When peptidoglycan production occurs in its last (parietal) phase, -lactams act fully outside of the cell membrane[2]. The ability of antimicrobial medicines to treat infectious disorders brought on by a variety of contagious strains (bacteria, fungi, parasites, and viruses) makes them crucial medications for the health of both people and animals. The rise of infectious diseases and current clinical resistance make treating infections a crucial and challenging problem[1]. The use of antimicrobial drugs is essential for the effective management of infectious illnesses. The development of novel antimicrobial medicines is crucial for many types of reasons,

despite the fact that several different medication classes have been used to treat human infections[3].In the last ten years, the development of resistance in organisms that are common human diseases has grown. Methicillin/oxacillin-resistant Staphylococcus aureus, intermediate and vancomycin-resistant Staphylococcus aureus, vancomycin-resistant Enterococcus, extended-spectrum beta-lactamase-producing gram-negative bacilli, carbapenem-resistant Klebsiella pneumoniae, and Pseudomonas and Acinetobacter strains are a few examples[4]. Antibiotics are employed in the treatment of bacterial infections. There are more microorganisms that are resistant to antibiotics, which limits their effectiveness. Bacterial resistance is seen as a public health problem because of the high rates of morbidity and death and elevated treatment costs[1].

Isatin, which has an indole ring structure common to many medicines and natural compounds, is a significant "privileged scaffold". It is an inorganic substance that serves as an adaptable chemical building block for the combinatorial library synthesis of compounds with potential therapeutic profiles[2]. Isatin and its derivatives have a wide range of pharmacological effects, including sedative, antibacterial[5], antiviral[6], antifungal[7], anti-inflammatory[8], antiangiogenic[9], anticancer[10], anticonvulsant[11], anti-HIV[12], antitubercular[13]. Linne Erdman and Auguste Laurent first isolated isatin from indigo dye in 1941. Nitric acid and chromic acid were used to oxidise the indigo, producing vivid orange monoclinic crystals of isatin as a byproduct[14].

For in silico screening, molecular docking is a reliable and efficient approach. In the process of developing rational drugs, it is becoming more and more important. Docking is a computer process for locating a ligand that is suitable for the binding site of a protein and fits it both energetically and geometrically. To put it another way, it is the study of how two or more molecules, such as a protein and a ligand, fit together[15].A computer method called molecular docking aids in the prediction and conformation of receptor-ligand complexes, in which the receptor can be either a protein or a nucleic acid. Multiple locations for the ligand in the receptor binding compartment might be produced using this dock system[16].

MATERIAL AND METHODS:

Method: For this work, we included the usage of tools such as Molegro Virtual Docker 6.0 and Chemdraw, as well as biological resources including PubChem, Drug Bank, PDB (Protein Data Bank), and PubChem. According to The Protein Data Bank (2000), Brookhaven National Laboratories (BNL) started the PDB (Protein Data Bank) in 1971, making it the only library of structural data on biological macromolecules in the world. It has macromolecule structural data that was derived using techniques like X-ray crystallography and NMR. With a reasonable library of practical compounds, Arguslab provides strong on-screen molecular construction capabilities. An independent research group called Molinspiration focuses on creating and using contemporary cheminformatics approaches, particularly in relation to the Internet.

Methodology:

Software Methodology: In the current molecular docking investigation, the Molegro Virtual Docker (MVD) 6.0 software and Graphical User Interface (GUI) tools were used to create a grid, determine the dock score, and assess conformers. MolDock docking was used to carry out the molecular docking. A cavity identification technique is used by Molegro's virtual docker to find potential drug-binding sites that have an active area.

Protein crystal structure and ligands are imported into the worksheet. To guarantee that MVD will handle all preparation, all features under the "Protein and Ligand Preparation" tab have been set to "Always." By choosing the 'preparation' and 'detect cavities' parameters, the binding site on the protein was predicted. To ensure precise binding of newly created pharmaceuticals, reference ligands and docking templates of reference medications are set. By selecting the minimum grid resolution and 10 posture generation, docking is created. The ideal binding energy values were discovered.

Preparation of Protein Structure: The Crystal structure of the C (30) carotenoid dehydrosqualene synthase from Staphylococcus aureus complexed with BPH-673 is downloaded from RCSB Protein Data Bank. The PDB repository is usually the main source of protein target structures for docking studies with the number rapidly increasing for many years. Currently, there are over 190,000 PDB entries of protein structures. The 3D structure of the protein target can be downloaded (either in an SDF or PDB file format) from this database for docking studies Organism: Staphylococcus aureus, the Sequence length of 3ACX is 293, and the protein 3ACX has a single chain i.e., chain A.3ACX is the PDB id of the target protein[17].

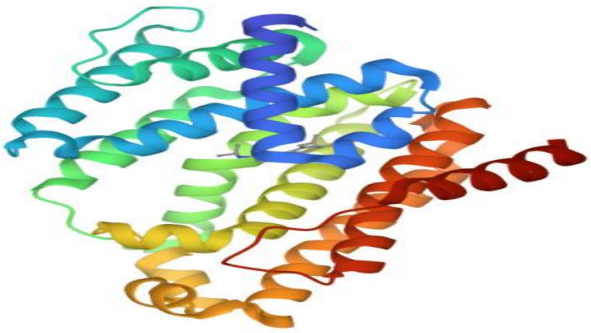

Figure 1. Crystal structure of carotenoid dehydrosqualene synthase 3(ACX)

Preparation of Ligand Structure: The structures of the ligand were drawn using ChemDraw Professional 16.0, copied to Chem3D 16.0 to create a 3D model and, finally subjected to energy minimization using molecular mechanics (MM2) and such energy-minimized structures are considered for docking. The resulting structures were subsequently uploaded into the workspace of the docking programme Molegro Virtual Docker 6.0. The molecule can be incorporated into the MVD using MDL (sdf/sd/mol/mdl) file format which contains bonding formation. In this step, the preparation of

molecules was assigned bonds, bond order and hybridization, charges, explicit hydrogens, and flexible torsion in ligands.

Docking Simulation: A useful method for understanding the relations between macromolecular structure and function is molecular simulation. The most common applications of molecular simulation are to assess stability, examine stability of a model structure, and study the stable and static interaction between the ligand and the protein. With 27 synthetic ligands of 2-phenylquinoline-4-carboxylic acid-based derivatives YDA1-YDA27 produced from isatin and acetophenone reported to have carotenoid dehydrosqualene synthase inhibitory activity, the ligand-protein inverse docking simulation approach was carried out using the MVD programme.

RESULTS AND DISCUSSION: The score was determined using the total number of hydrogen bond interactions, the mol dock score, and the re-rank score after comparing the interactions of the standard and test compounds. The ligands' negative docking values demonstrate a stable binding interaction among the receptor and the ligands.

Good antimicrobial activity was demonstrated by all hypothetical compounds. Out of 27 compounds, compounds (YDA 27, YDA 26, YDA 25, YDA 17 and YDA 7) have been identified to have excellent antimicrobial activity. Table-1 shows the results of the docking for 27 compounds.

Table 1. Results of hypothetical compounds checked for docking studies

Sr. No.	M.V.D Name	Moldock Score	Rerank	Hydrogen Bond	Docking Score
1	Unknown 1	-94.9176	-71.4825	-4.20791	-95.7508
2	Unknown1_1	-99.2199	-79.3332	-3.42784	-101.092
3	Unknown1_2	-98.3254	-85.8187	-5.66972	-104.136
4	Unknown1_3	100.721	-81.01	-3.548	-102.576
5	Unknown1_4	-102.117	-80.489	0	-100.517
6	Unknown1_5	-104.012	-83.7507	-5.73256	-102.918
7	Unknown1_6	-112.16	-86.6198	-8.8865	-121.126
8	Unknown1_7	-104.3258	-85.5308	-2.10598	-103.658

9	Unknown1_8	-105.921	-87.9428	-2.6584	109.357
10	Unknown1_9	-112.037	-85.7516	-5.3657	-112.985
11	Unknown1_10	-99.8295	-79.1619	-5.94116	-99.8239
12	Unknown1_11	-96.5892	-75.1176	-6.31408	-99.6681
13	Unknown1_12	-101.658	-78.105	-4.6574	-102.974
14	Unknown1_13	-112.313	-88.2594	0	-108.535
15	Unknown1_14	-107.069	-82.5717	-5.46289	-105.033
16	Unknown1_15	-120.204	-89.8608	-3.21039	-121.049
17	Unknown1_16	-121.6547	-89.0815	-5.69541	-120.941
18	Unknown1_17	-109.324	-72.6609	-3.08218	-109.756
19	Unknown1_18	-106.252	-74.895	0	-104.003
20	Unknown1_19	-103.767	-75.9262	-2.04066	-108.529
21	Unknown1_20	-120.019	-89.2329	-3.20438	-120.845
22	Unknown1_21	-120.158	-89.3031	-3.16249	-111.421
23	Unknown1_22	-106.01	-76.5253	0	-103.542
24	Unknown1_23	-111.333	-80.5477	-3.20264	-111.691
25	Unknown1_24	-119.7895	-71.8984	-5.32976	-124.969
26	Unknown1_25	-120.113	-84.7041	-5.71964	-121.206
27	Unknown1_26	-121.3548	-84.911	-5.88574	-123.065
28	Standard drug	-103.345	-77.9226	-2.04116	-104.864

In comparison to the standard drug (Amoxicillin), a total of six compounds had a good moldock score, docking score and a fair number of H-bond interactions. Based on their docking scores, compounds YDA 27, YDA 26, YDA 25, YDA 17 and YDA 7 could be considered the greatest antimicrobial agents.

Table 2. Selected Derivatives with good Moldock score, docking score and hydrogen bonding

Sr. No.	M.V.D Name	Moldock score	Rerank	Hydrogen bond	Docking Score
1	YDA 27	-121.3548	-84.911	-5.88574	-123.065
2	YDA 26	-120.113	-84.7041	-5.71964	-121.206
3	YDA 25	-119.7895	-71.8984	-5.32976	-124.969
4	YDA 17	-121.6547	-89.0815	-5.69541	-120.941
5	YDA 7	-112.16	-86.6198	-8.8865	-121.126

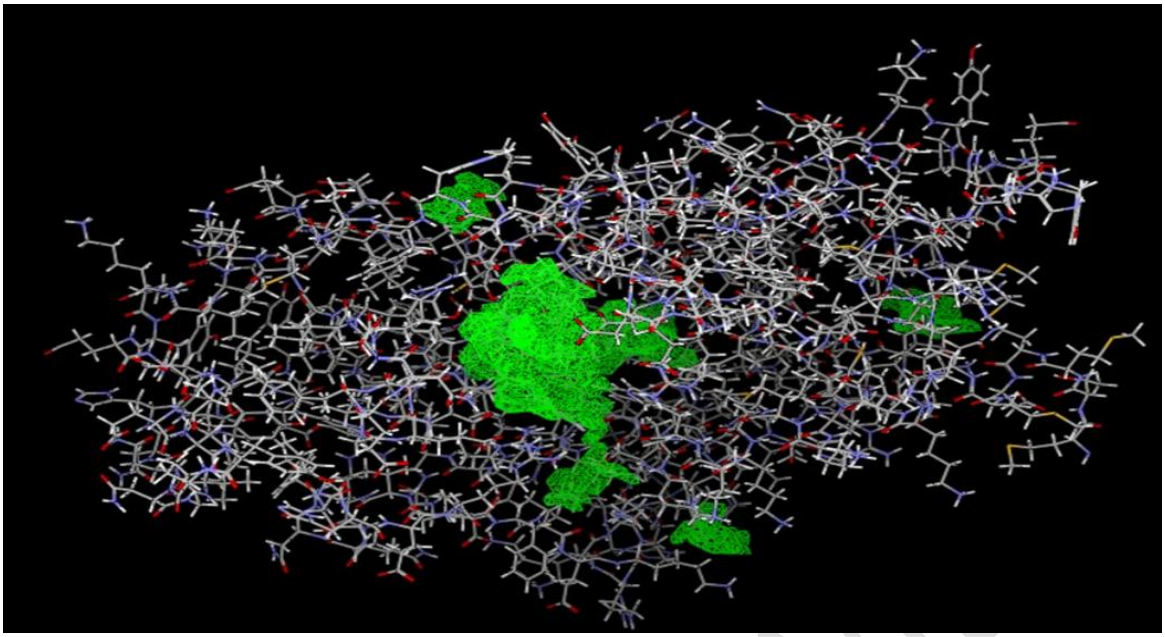

Figure 2. Five cavities detected in Molegro virtual docker in 3ACX

- Cavity [Vol= 444.904]
- Cavity [Vol= 36.28]
- Cavity [Vol=25.872]
- Cavity [Vol=32.672]
- Cavity [Vol=28.016]

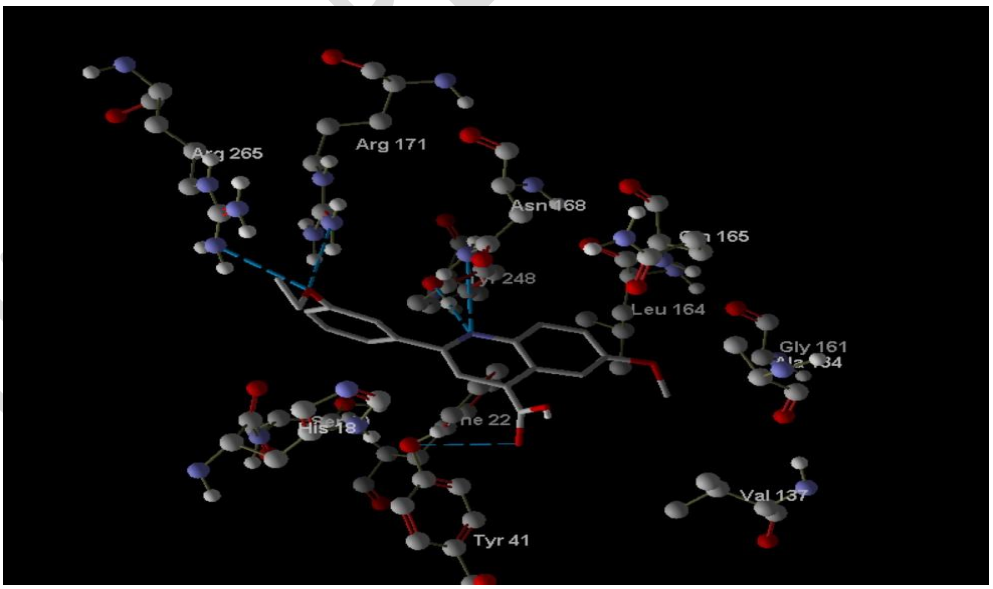

Figure 3. Interaction of compound YDA 27 with 3ACX

Compound YDA 27 showed hydrogen bond interactions with amino-acids Arg 265, Arg171, Asn 168, Tyr 248 and steric interaction Tyr 41, His 18, Lu 164, Tyr 248.

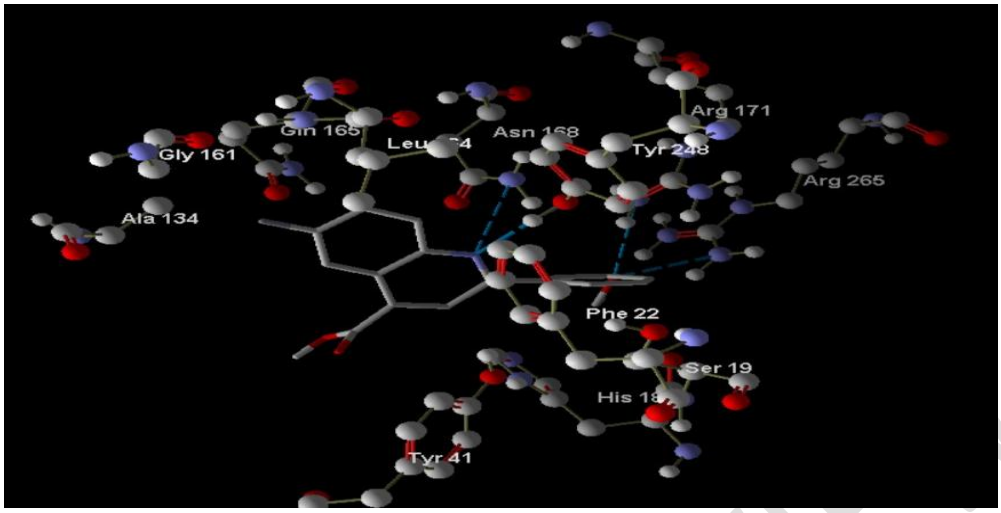

Figure 4. Interaction of compound YDA 26 with 3ACX

Compound YDA 26 showed hydrogen bond interactions with amino-acids Asn 267, Arg 174, Asn 165, Tyr 248 and steric interaction Arg 265, Tyr 248, Leu 164, Ala 134, Tyr 41 and His 18.

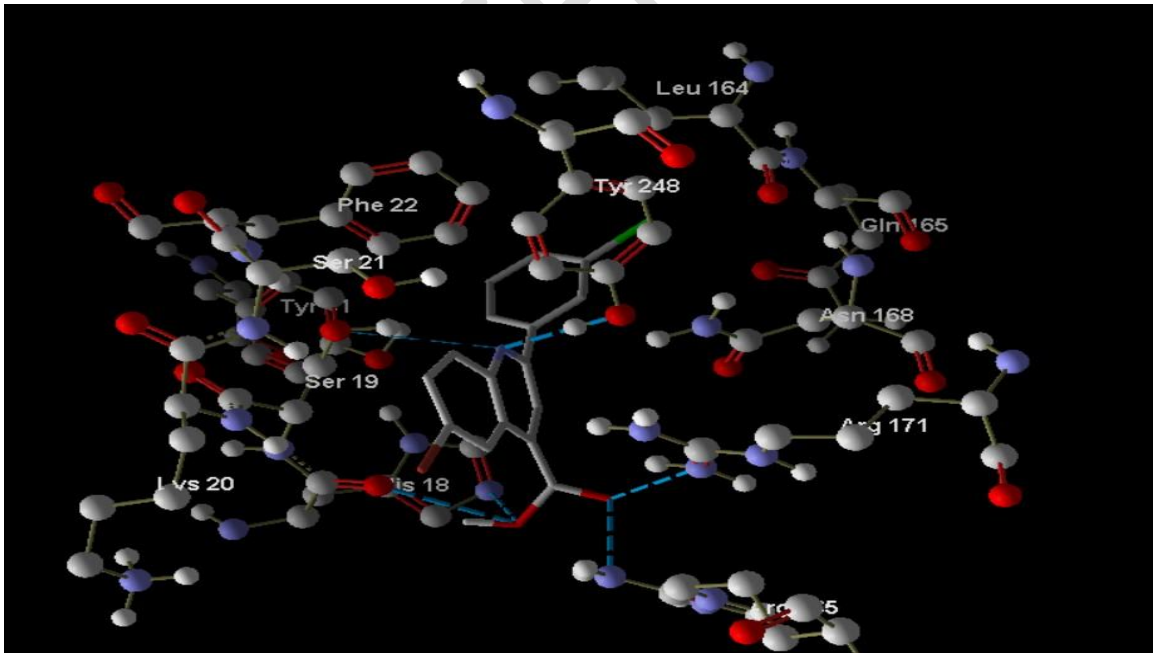

Figure 5. Interaction of compound YDA 25 with 3ACX

Compound YDA 25 showed hydrogen bond interactions with amino-acids Arg 265, Arg 171, His 18, Ser 19 and steric interaction Tyr 41, Tyr 248, Ser 19 and His 18.

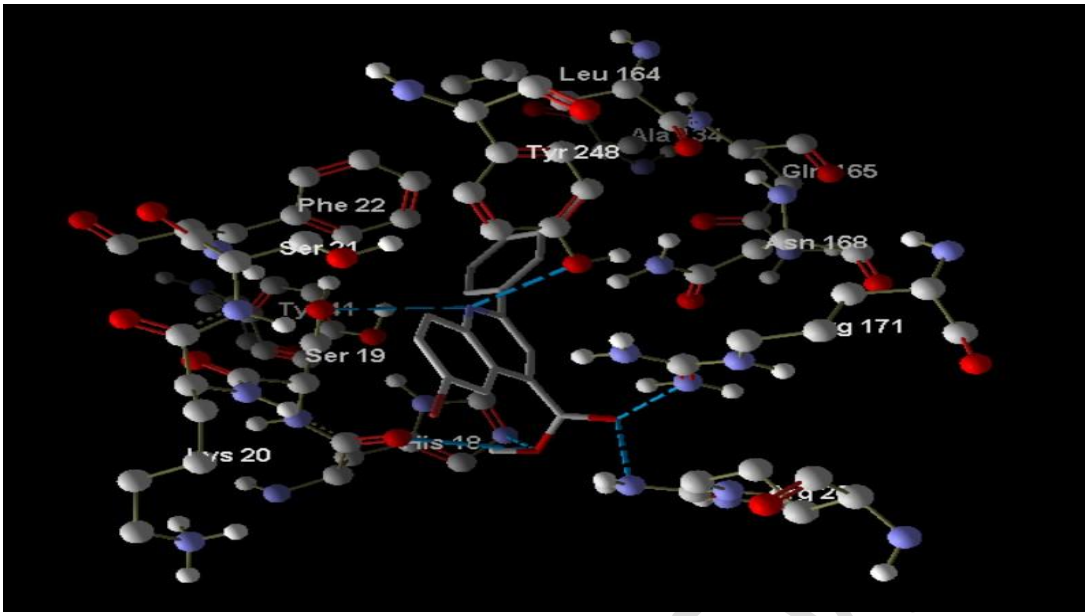

Figure 6. Interaction of compound YDA 17 with 3ACX

Compound YDA 17 showed hydrogen bond interactions with amino-acids Arg 171, Arg 265, His 18, Ser 19, Tyr 248 and steric interaction Tyr 41, Tyr 248 and Ser 19.

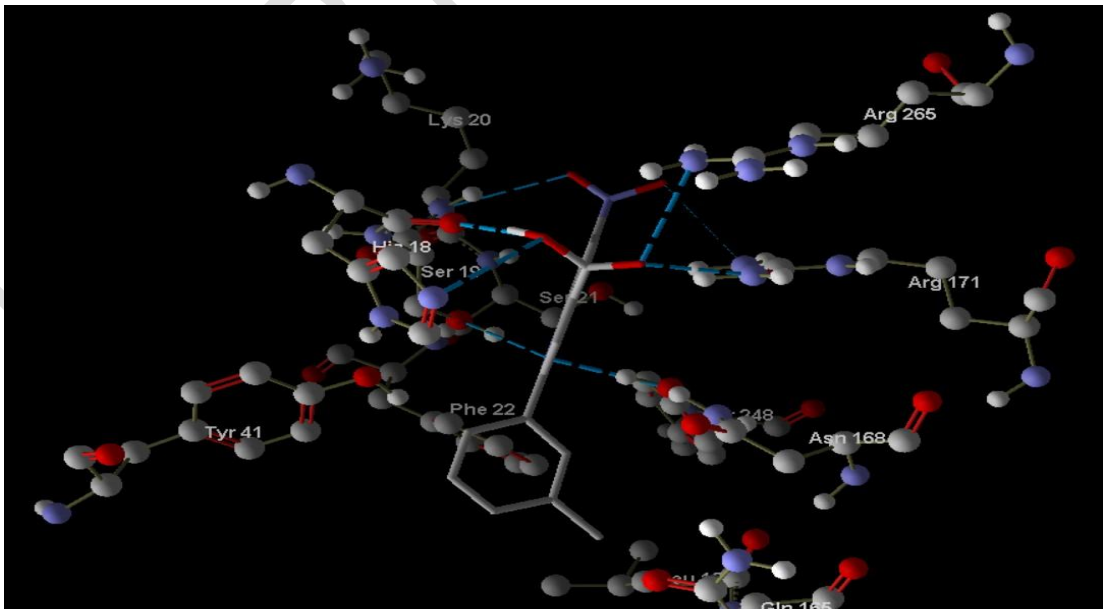

Figure 7. Interaction of compound YDA 7 with 3ACX

Compound YDA 7 showed hydrogen bond interactions with amino-acids Arg 171, Arg 265, His 18, Lys 20, Tyr 248, Ser 19 and steric interactions Tyr 41, Tyr 248, Ser 19, Tyr 248 and Ser 19.

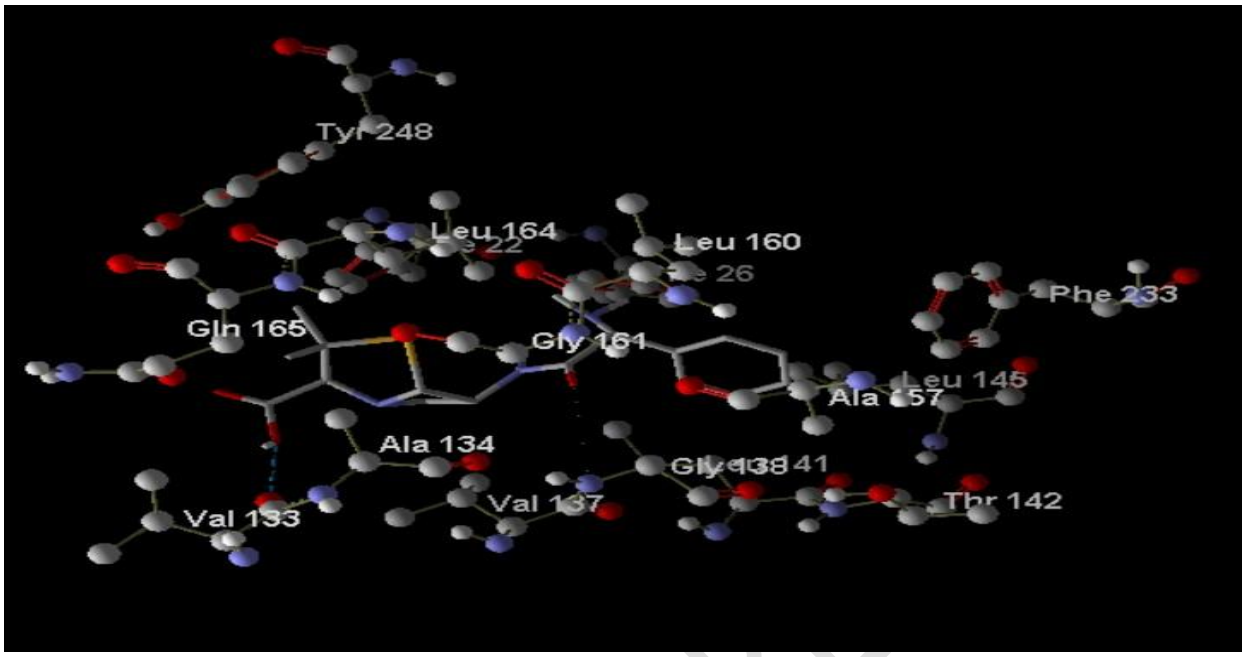

Figure 8. Standard drug Ampicillin showed interactions with amino acids Val 133, Val 137, Ala 134, Gln 165, Gly 161, Leu 164.

CONCLUSION: We have learned how the carotenoid dehydrosqualene synthase enzyme is inhibited by isatin and acetophenone based derivatives through docking studies. These studies are extremely useful in producing specific compounds that effectively block enzymes. From a greater perspective, it was also investigated how much receptor structure affects how drugs work. Thus, it can be concluded that the mentioned isatin and acetophenone derivatives, which were discovered using in silico methods in the present work, might be very important, especially as antibacterial agents.

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