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Molecular docking analysis of beta-lactamase from *Salmonella* species with eicosane

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Abstract:
beta-lactamases of Salmonella Sp. belongs to a group of enzymes produced by bacteria which break the *beta-lactam* ring to inactivate the *beta-lactam* antibiotic. Therefore, it is of interest to document the molecular docking analysis of beta-lactamase from *Salmonella* species with eicosane. Hence, we document the molecular docking analysis data of beta-lactamase from *Salmonella* species with eicosane.

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Keywords: eicosane, beta-lactamase, metronidazole, drug docking

Background:

Several serovars of *Salmonella enterica* subspecies *enterica* cause salmonellosis in humans. Food is a large global reservoir of *Salmonella*. *Salmonella* is the 2nd top known bacteria that cause human gastero intestinal outbreaks especially with the species of *Salmonella enteritidis* and *Salmonella typhimurium*. *Salmonella* is the primary cause of infection in about half of the 1500 cumulative food borne infections that occurs in France every year. Salmonellosis is caused by non-typhoid *Salmonella* resulting in acute gastroenteritis. It is seen in 95% of cases by the intake of contaminated food specifically fresh fruit juices, meet and egg. It is also present in fresh products like fruits and vegetables which are contaminated by animal faeces **[1]**. The rising frequency of enterobacterial strains producing extended-spectrum lactamases is linked to ESBLs. Third-generation cephalosporins, penicillins, and monobactams are inactivated by these enzymes **[2 -3]**. ESBL development in bacteria that aren't generally known to display lactam resistance can provide useful information about resistance gene transfer and the significance of antimicrobial control methods in animal feed **[3 - 4]**. Even in the absence of selective pressure from antimicrobial drugs, the prevalence of ESBL carriage is likely to rise and spread to different enteric pathogens, as it did with ampicillin resistance **[5]** and, more recently, cephalosporin resistance in *Escherichia coli* **[6]**. All penicillin, cephalosporin, and mono lactam drugs are resistant to ESBL-producers **[7]**. ESBLs have developed plasmid-encoded enzyme families (TEM, SHV, cefotaxime (CTXM), and oxacillin (OXA), but they can also be encoded on the chromosome or be transposon-mediated depending on the bacterial species **[8]**. As in the case of TEM1, which hydrolyzes penicillins and first-generation cephalosporins **[9]**, this variety has aided the dissemination of these enzymes. ESBLs produced by *Enterobacteriaceae* species have spread around the world since the introduction of novel medicines that target beta-lactamases **[3 & 10]**. Powder samples of *Rhinacanthus nasutus* plant leaves were taken and ethanol extract was prepared using soxhlet apparatus. The concentrated and dried extract was then subjected to phytochemical analysis. The bioactive components were identified by performing GCMS analysis, which showed the presence of eicosane as one of the bioactive component in the plant extract. Known data shows that eicosane showed potential antibacterial activity **[11 – 12]**. Therefore, it is of interest to document the molecular docking analysis of beta-lactamase from *Salmonella* species with eicosane.

Methodology:

Protein modelling and visualizations:

The protein sequence of *beta-lactamase* (*Salmonella Sp*.) was used for domain analysis using PFAM (https://pfam.xfam.org/). Then, the sequence was used for homology modelling server using Swiss Model (https://swissmodel.expasy.org/). The modelled protein 3D structure was validated using ProCheck server (https://saves.mbi.ucla.edu/) and viewed with the molecular visualization Software, Discovery Studio Software.

3D structure prediction for drug:

We used *metronidazole*, (CID: 4173) retrieved from NCBI –PubChem (https://pubchem.ncbi.nlm.nih.gov/) and data for the GC–MS instrument test compound, *eicosane* (CID: 8222) to perform molecular drug docking analysis. The 2D drug like compounds was converted into the 3D structure using Cheminformatics protocols.

Molecular docking:

Molecular drug docking studies were performed using an automated molecular drug docking server, PatchDock (https://bioinfo3d.cs.tau.ac.il/PatchDock/). We docked the control drug (*metronidazole*) with *beta-lactamase* from *Salmonella Sp* and the test compound (*eicosane*) with *beta-lactamase* from *Salmonella Species* in order to compare the molecular binding affinities between the chemical molecules and the protein target.

Table 1: Results of Molecular drug docking (Patch dock server)

Microorganism target	Control drug	Test compound
beta-lactamase	(metronidazole)	(eicosane)
Salmonella Sp. (AAA75015.1)	-121.25 Kcal/mol	-211.04 Kcal/mol

Table 2: H-bond interaction – protein-ligand complex

GLN:202-ARG:198,LEU:204-GLN:200,GLN:205-ARG:201,ARG:218-VAL:208,ARG:218-ILE:227,SER::219-PRO:215,PHE:226-GLY:246,ARG:239,ASN:270,ARG:239-ASN:270,ALA:274-ASN:270,GLY:275-GLN271,GLY:277-ILE:273,ALA:278-ALA:274)	eicosane with beta- lactamase
ARG:79-ALA:75,ARG:79-VAL:76,GLY:139-ALA:136,PHE:149-GLY:143,GLN:150,ARG:239-ASN:270,ALA:274-ASN:270,GLY:275-GLN:271,GLY:277-ILE:273,ALA:278-ALA-274,GLN:150)	metronidazole with beta-lactamase

Results and Discussion:

The selected protein target was retrieved from NCBI database in FASTA format. The length of the Nucleotide sequence is 861 nt and corresponding amino acids sequence is 286 aa. The 3D structure of the target protein was developed using an automated homology modelling server named Swiss-Model. SWISS-MODEL server **[13 - 16]** converted the amino acid sequence of *beta-lactamase* from *Salmonella Sp* into 3D structure (**Figure 1, 2, 3 & 4**). The predicted structure was viewed using the molecular visualization tool, Discovery studio software. SWISS-MODEL **[1 - 4]** was used to analyse the molecular and structural details of b*eta-lactamase* for docking. SWISS-MODEL is a server for automated comparative modelling of three-dimensional (3D) protein structures. Waterhouse *et al*. **[13]** computed models by the SWISS-MODEL server homology modelling pipeline which is based on ProMod3, an in-house comparative modelling engine based on Open Structure. The modelled 3D protein was comprehensively evaluated using the ProCheck server **[6]** for the assessment of Ramachandran Plot. The 3D structure of the mutated protein was validated using ProCheck server **[17 - 18]**. **Figure** 6 shows the assessment of Ramachandran Plot which confirms that there is no error (90.5 %) in the modelled protein. Data shows that based on the molecular drug docking scores, the selected eicosane molecule is an efficient inhibitor of *beta-lactamase* (*Salmonella Sp*.) protein when compared to the control drug molecule metronidazole (**Table 1**).

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Figure 1: Protein domain prediction using the Pfam tool. It shows the functional domain regions (represented in green colour) present in beta lactamase enzyme

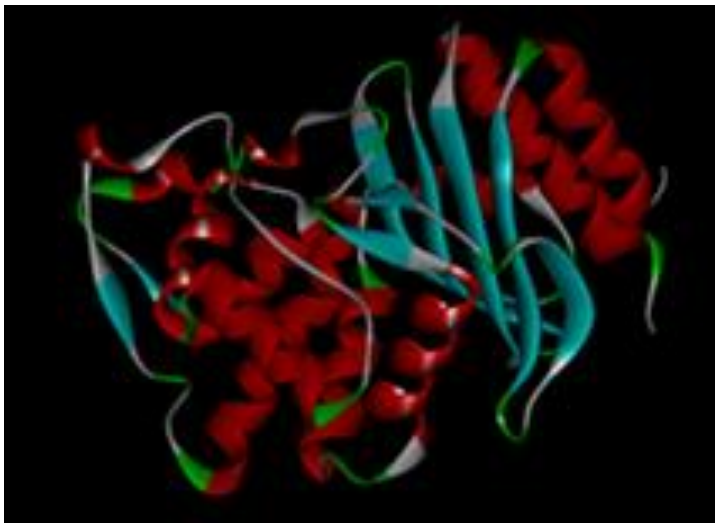

Figure 2: Protein modelling of the 3D structure for beta-lactamase. It shows the 3D view of the protein structure of *beta-lactamase (Salmonella typhimurium)* in secondary structure colour with solid ribbon model visualized using the Discovery Studio Software.

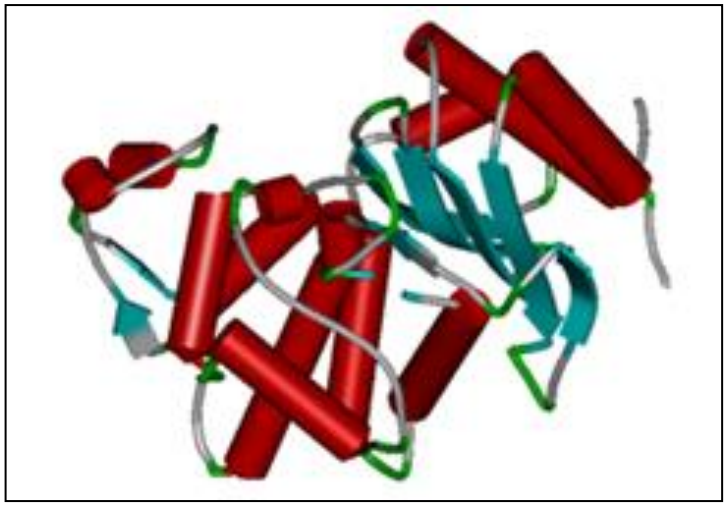

Figure 3: Protein Modellingof the 3D structure for beta-lactamase. It shows the 3D view of the protein structure of beta-lactamase (*Salmonella typhimurium*) with secondary structure colour with schematic model visualized using Discovery Studio Software.

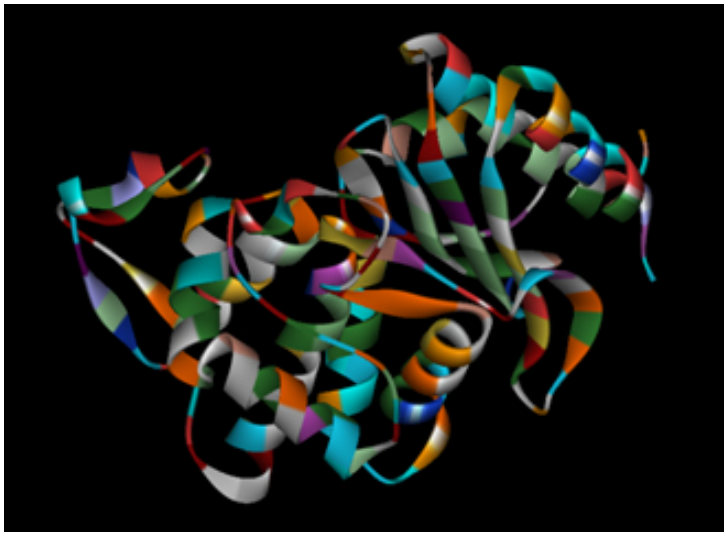

Figure 4: Protein Modelling: 3D structure of beta-lactamase. It shows the 3D view of the protein structure of beta-lactamase (*Salmonella typhimurium*) in secondary structure model with coloured amino acids residues visualized using the Discovery Studio Software.

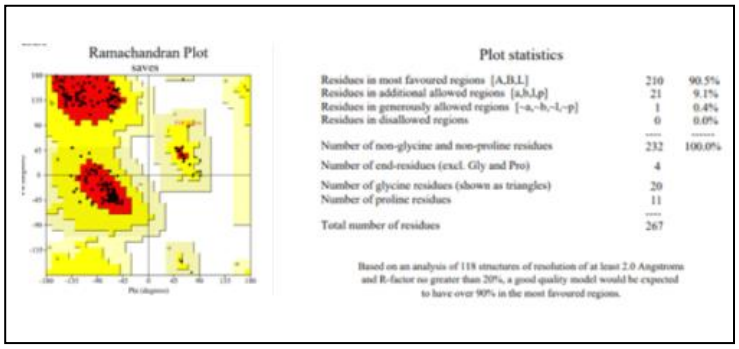

Figure 5: Protein Structure Validation: 3D structure of *beta-lactamase*. It shows the 3D view of the protein structure of beta-lactamase (*Salmonella typhimurium*) in space fill colour model with coloured atoms. The yellow coloured spacefill structure represents the functional domain regions with the respective amino acid positions. Assessment of Ramachandran Plot for the predicted mutated protein sequence of the modeled beta-lactamase Image not clear

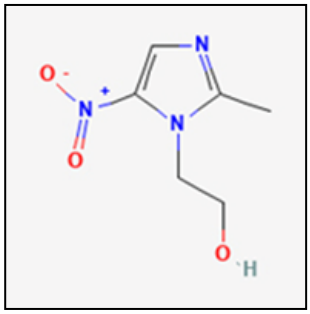

Figure 6: Cheminformatics data for the 2D Structure of metronidazole. It shows the 3D structure of metronidazole with coloured atoms: Grey-Carbon, Blue-Nitrogen, Yellow-Sulphur and White –Hydrogen using Discovery Studio Software.

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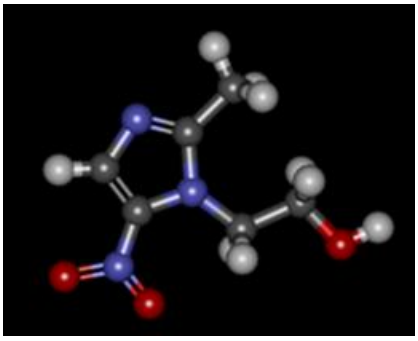

Figure 7: 3D structure of metronidazole. It shows the 3D structure of metronidazole with coloured atoms: Grey-Carbon, Blue-Nitrogen, Yellow-Sulphur and White – Hydrogen using Discovery Studio Software.

Figure 8: 2D structure of eicosane. It shows the 2D structure of eicosane using PubChem compound database.

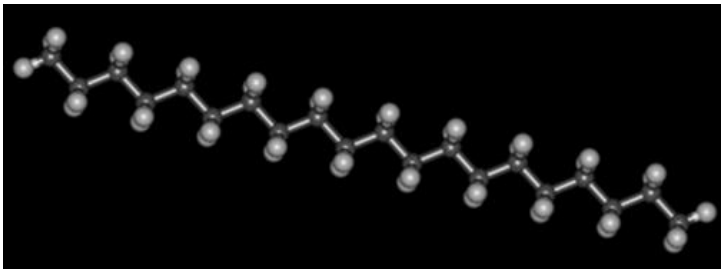

Figure 9: Cheminformatics data for the 3D Structure of eicosane. It shows the 3D structure of eicosane with coloured atoms: Grey-Carbon and White –Hydrogen using Discovery Studio Software.

Receptor	Ligand	Complex Type
Sol_typhi_betalac.pdb	Metronidazole.pdb	drug

Solution No	Score	Area	ACE
1	2482	273.10	-52.25
2	2442	270.10	-44.03
3	2270	243.90	-100.31
4	2230	241.90	-99.95
5	2216	248.80	-75.16
6	2214	239.10	-68.38
7	2214	250.80	-103.47
8	2214	234.20	-37.97
9	2204	259.90	-28.81
10	2202	271.20	-28.30
11	2200	248.70	-72.94
12	2196	267.60	17.59
13	2194	229.90	-105.03
14	2188	272.80	-53.03
15	2174	242.20	-91.34
16	2164	260.90	-44.38
17	2164	245.60	-64.68
18	2148	251.00	-80.44
19	2142	252.40	-121.25
20	2134	258.90	-102.37

Figure 10: Molecular docking data of beta-lactamase with metronidazole. It represents the PatchDock result page showing the drug docking score of the control drug, metronidazole with the modelled protein target, *beta-lactamase* (*Salmonella typhimurium*). The negatively high ACE (Atomic Contact Energy) value is -121.25 Kcal/mol.

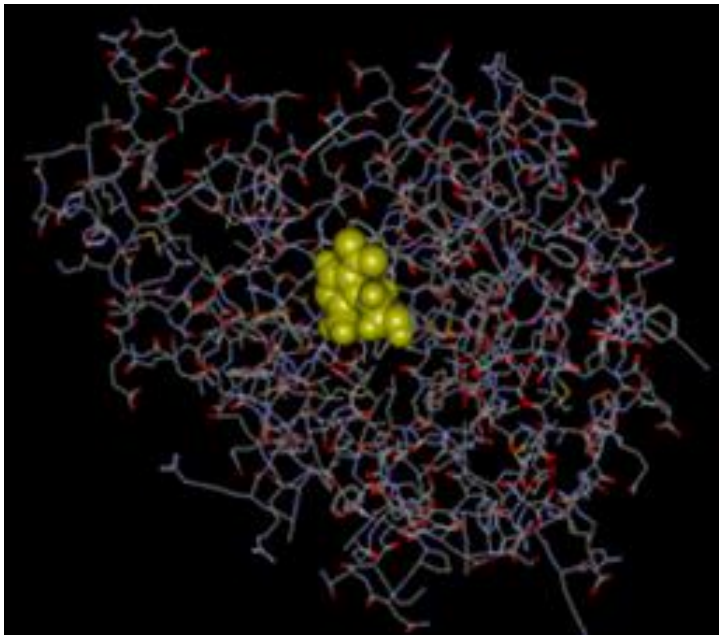

Figure 11: Molecular docking of beta-lactamase with metronidazole complex. It represents the existing drug molecule (metronidazole) docked with beta-lactamase protein structure. Yellow colour indicates metronidazole in space-filling model using Discovery Studio Software.

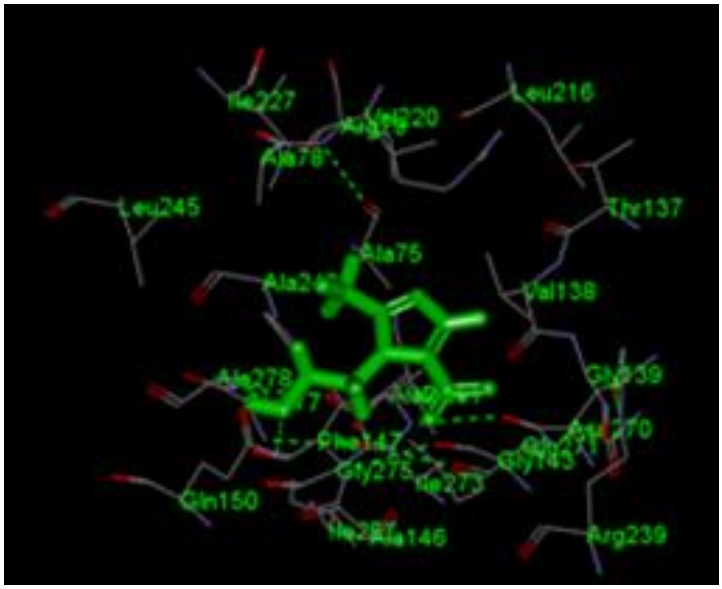

Figure 12: Molecular docking 3D structure of beta-lactamase with metronidazole complex. It represents the existing drug molecule docked with beta-lactamase protein structure with drug binding amino acids labels. Green colour indicates metronidazole in Stick model using Discovery Studio Software

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Receptor	Ligand	Complex Type	C
Sol_tyohi_betalac.pdb	Eicosane.pdb	drug	4

Solution No	Score	Area	ACE
1	4910	586.20	-43.43
2	4592	554.40	-99.65
3	4584	540.80	-114.00
4	4524	577.50	-50.52
5	4440	524.50	-110.56
6	4400	559.50	-157.37
7	4380	480.30	-102.26
8	4352	534.50	-98.94
9	4330	542.40	-70.40
10	4328	473.40	-93.83
11	4294	471.00	-100.33
12	4234	549.40	-149.84
13	4224	552.40	-150.55
14	4212	501.10	-102.36
15	4208	435.20	-51.85
16	4202	543.70	-70.18
17	4188	435.10	-48.34
18	4182	484.80	-74.18
19	4176	547.00	-211.04
20	4148	511.00	-141.13

Figure 13: Molecular docking data of beta-lactamase with eicosane. It represents the PatchDock result page showing the drug docking score of the control drug, **eicosane** with the modelled protein target, *beta-lactamase* (*Salmonella typhimurium*). The negatively high ACE (Atomic Contact Energy) value is -211.04 Kcal/mol.

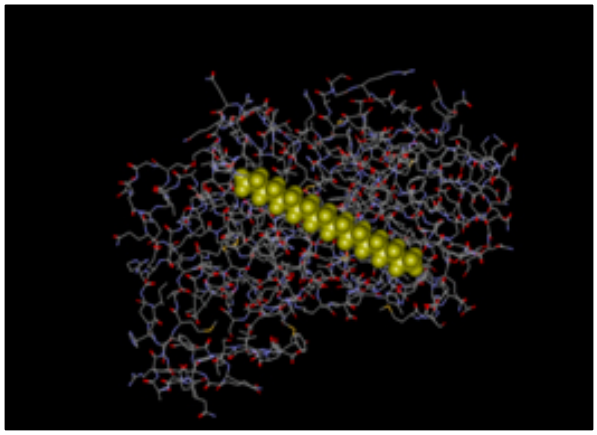

Figure 14: Molecular docking of beta-lactamase with eicosane **complex.** It represents the existing drug molecule (eicosane) docked with beta-lactamase protein structure. Yellow colour indicates eicosane in space-filling model using Discovery Studio Software.

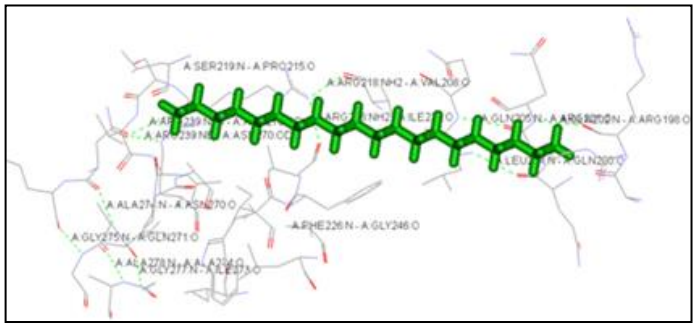

Figure 15: Molecular docking of 3D structure for beta-lactamase with eicosane complex. It represents the test drug molecule, eicosane docked with beta-lactamase protein structure with drug binding amino acids labels. Green colour indicates eicosane in Stick model using Discovery Studio Software

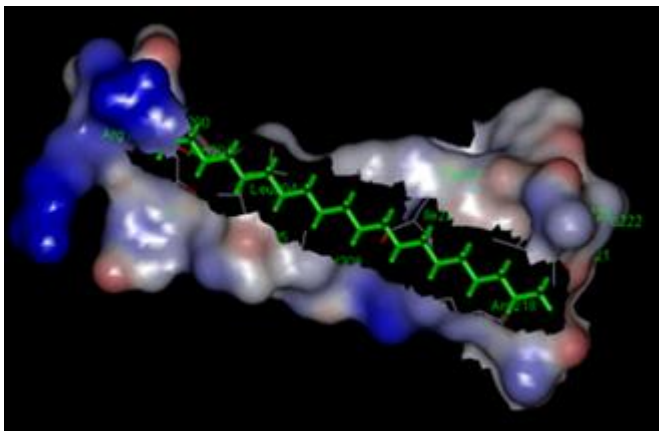

Figure 16: Molecular docking of 3D structure for beta-lactamase with eicosane complex. It represents the test molecule (eicosane) docked with beta-lactamase protein structure in *Van Der Waals* model -1 view with drug binding amino acids labels. Green colour indicates eicosane in Stick model using Discovery Studio Software.

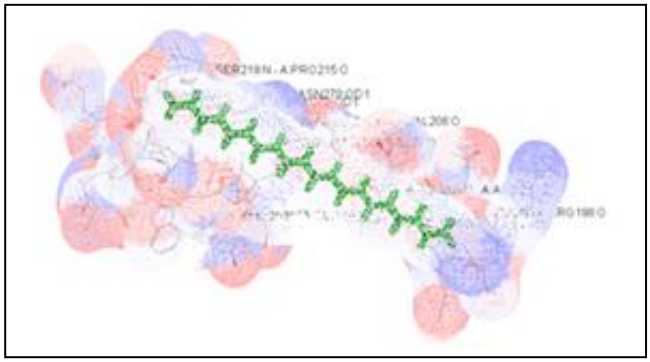

Figure 17: Molecular docking of 3D structure for beta-lactamase with eicosane complex. It represents the test molecule (eicosane) docked with beta-lactamase protein structure in *Van Der Waals* model -2 view with drug binding amino acids labels. Green colour indicates eicosane in Stick model using Discovery Studio Software.

Figure 7 shows the 2D structure of metronidazole and **Figure** 8 represents the 3D structure of the metronidazole. Similarly, we show the 2D and 3D structure of eicosane in **Figure** 9 and 10, respectively. The conversion of 2D to 3D structure is one of the primary steps in drug docking procedure. We used Discovery Studio Software to perform automated 2D to 3D conversion for molecular docking using PatchDock. We ranked the remaining candidates as per a geometric shape complementarity score **[19 – 20]**. The PatchDock results of *eicosane* drug with *beta-lactamase* protein show an atomic contact energy value of -211.04 Kcal/mol (**Figure** 11). Whereas, that of the existing drug molecule, *metronidazole* with *beta-lactamase* protein is -121.25 Kcal/mol (**Figure** 9). **Figure** 11 **& 12** shows that binding between the target protein and the control drug. **Figures 13 to 16** show that *eicosane* is a potential inhibitor of *beta-lactamase* (*Salmonella Sp.*) protein. Interestingly, it was proved clinically that the domain region of

beta-lactamase is found between 41 – 259 amino acids positions. Data show that eicosane directly binds within the range of the domain activity region of beta-lactamase (202-274 positions).

Conclusion:

We document the molecular docking of beta-lactamase from *Salmonella* species with eicosane compared to *metronidazole* for further consideration.

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