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Review Article

Insilico Activity Prediction of Imidazole Derivatives

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ABSTRACT

Imidazole chalcones are highly promising synthetic antimicrobial agents that combine the reactive enone moiety of chalcones with the established heterocyclic azole (imidazole) ring. Together, these pharmacophores exhibit potent dual-action inhibition against a wide variety of human fungal and bacterial pathogens. Antifungal: The enone (α alpha, β beta)-unsaturated carbonyl) group acts as a Michael acceptor, binding to thiol groups of vital fungal proteins. This inhibits fungal cell wall biosynthesis, disrupting pathogens like *Candida albicans* and *Candida krusei*. Antibacterial: They target bacterial enzymes like DNA gyrase and MurA, proving highly effective against multidrug-resistant bacteria, notably Gram-positive strains like *Staphylococcus aureus*. In our Present research work we have chosen Lanosterol 14- α -demethylase, as targets to screen our proposed chemical structures for anti-bacterial and anti-microbial activity. The molecules were docked to the above said targets and the energy values obtained are as follows using the docking software. Depending on the energy values we have chosen the best three drug analogs they are Compound 3b { -8.0}, Compound 3e { -8.0}, Compound 3k -8.1}. We tried to improve the binding efficiency and steric compatibility. Several modifications were made to the probable functional groups which are interacting with receptor molecules. Analogs of this drug molecule were prepared using ACD-chem.-sketch and docking. The modified drugs is sketched using chem.-sketch were found to be better than the conventional drugs available. Drug likeliness performed in the software of molsoft. Where the drug analog using the "SMILES" notation which are generated by the chem.-sketch. By using the molinspiration online software, the drug analogs are undergone for their molecular properties like milogp, molecular formula, BBB score, druglikeliness, HBA, HBD, pKa, Volume, molecular weight, TPSA and Drug likeliness where some of the drug analogs have been shown the good druglikeliness.

INTRODUCTION

THE CHEMISTRY OF IMIDAZOLE

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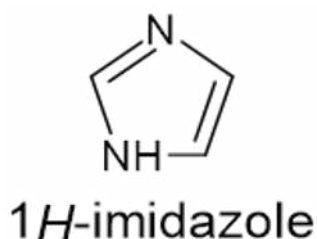
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Imidazole is a chemical with the method C₃N₂H₄. It is a white or colourless substance that evaporates in water to form a moderately basic mixture. It is an aromatic heterocycle categorised as a di-azole in chemistry, with non-adjacent nitrogen molecules in metasubstitution. The imidazole ring is found in many organic compounds, particularly alkaloids. This imidazole has the same 1,3-C₃N₂ ring but different substituents. This ring structure is found in several critical biological developing components, including histidine and the associated hormone histamine. Various medications, including antifungals, antibiotics in the nitroimidazole group, and the sedative midazolam, consist of an imidazole ring [6]. Imidazole is a planar 5-membered ring with two parallel tautomeric types due to hydrogen binding to one or both nitrogen atoms. Imidazole is a highly polar chemical with a dipole moment of 3.67 D and is very solvable in water. The existence of a planar ring containing 6 π electrons classifies the chemical as aromatic (FIG. 2). The following are some imidazole resonance structures:



Molecular Formula: C₃H₄N₂

Formula Weight: 68.079

TARGETS:

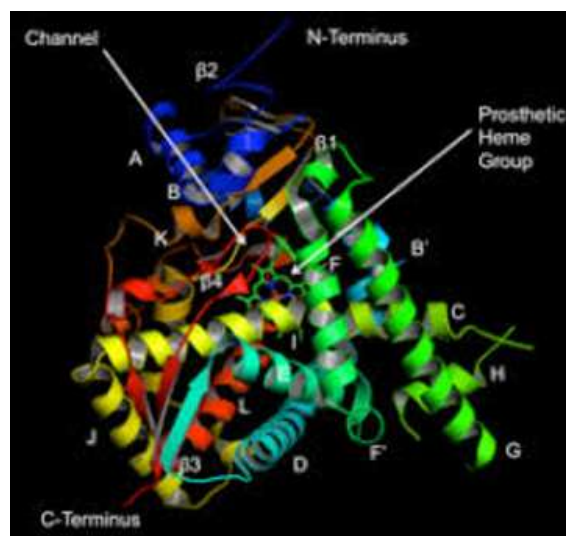


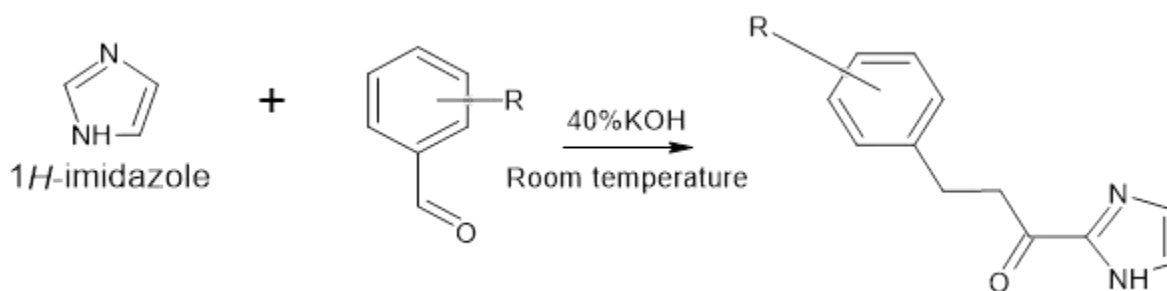
Figure 2 : Lanosterol 14-alpha-demethylase

Organism: Trypanosoma brucei

Code: 3gw9

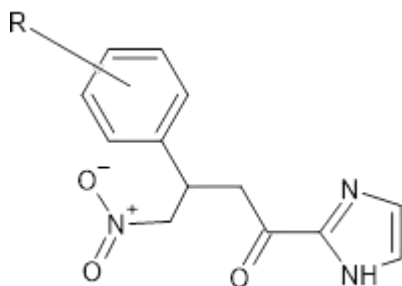
CHALCONES:

Chalcone is an aromatic ketone that forms the central core for a variety of important biological compounds, which are known collectively as chalcones. They show antibacterial, antifungal, antitumor and anti-inflammatory properties. They are also intermediates in the biosynthesis of flavonoids, which are substances widespread in plants and with an array of biological activities. Chalcones are also intermediates in the Auwers synthesis of flavones. Chalcones can be prepared by an aldol condensation between a benzaldehyde and an acetophenone in the presence of sodium hydroxide as a catalyst. This reaction has been found to work in without any solvent at all - a solid-state reaction. The reaction between substituted benzaldehydes and acetophenones has been used to demonstrate green chemistry in undergraduate chemistry education. In a study investigating green chemistry synthesis, chalcones were also synthesized from the same starting materials in high temperature water (200 to 350 degree centigrade).



Michael Adducts Imidazole chalcones:

Among all heterocyclic compounds, Michael Adducts Imidazole chalcones are one of the most important heterocyclic structures exhibiting remarkable pharmacological activities because it is an essential constituent of all cells. Michael Adducts Imidazole chalcones is a six-membered heterocyclic ring containing two nitrogen atoms at position 1 and 14 of the 5 and 6 membered rings.



Experimental work:

Step: 1

Preparation of Chalcone: -

- Equimolar mixture of Imidazole and different substituted aldehydes dissolved in 15ml of ethanol and added 40% KOH and stirred the entire reaction mixture for 6 hrs. Then the mixture is kept for overnight at room

temperature. Then pour the above mixture in crushed ice. Then acidified with HCl. The obtained chalcone was recrystallized from ethanol.

Step : 2

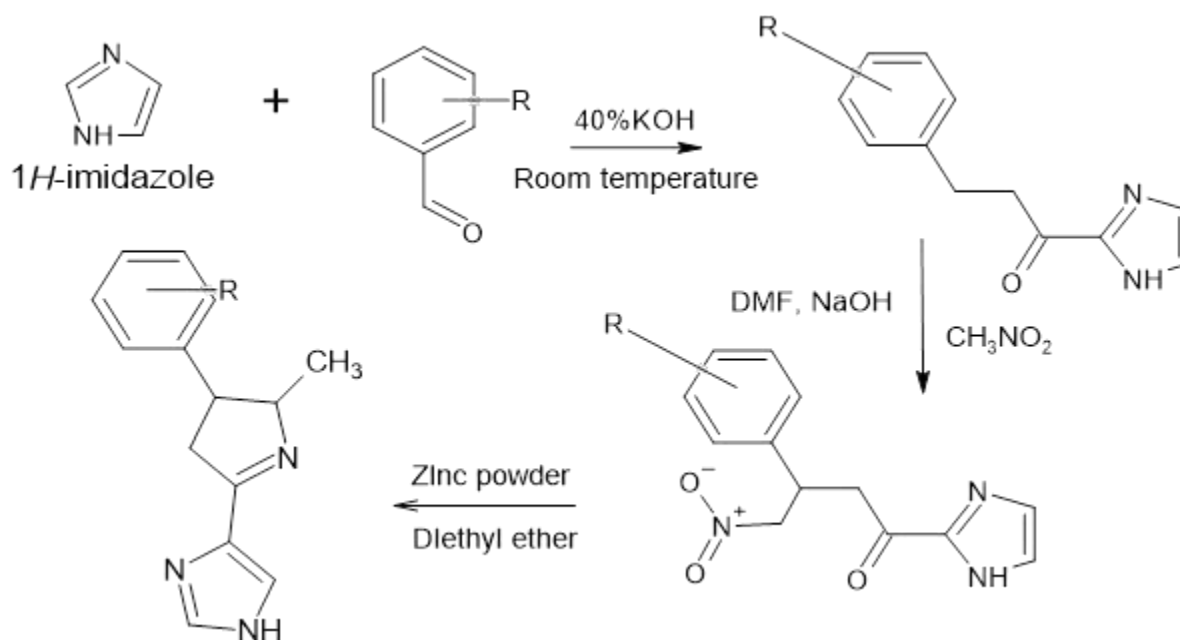
Preparation of Michael adducts:

- NaOH-1.0M was added to the stirred solution of chalcones (2.08g, 10mmol) at room temperature in DMF (10ml) and nitromethane (0.61g, 10mmol) the resulting mixture was stirred until the reaction was complete (TLC).

Step : 3

Reduction and ring cyclization:

- Then granular zinc (3.27g: 50mmol) was added to the mixture and was stirred at 80°C and conc. HCl (20ml) was added very slowly. The mixture was stirred at 80°C under the reducing conditions for about 90min, and then allowed to come room temperature. Neutralized with Saturated aqueous NaHCO_3 (30ml) and extracted with diethyl ether (3×20ml), filtered and concentrated. The crude product was purified by silica gel chromatography.



MATERIALS AND METHODS

Tools and Materials Used: - For our present study we used bioinformatics tools, biological database like PDB (protein data bank) and software like ACD chem. sketch, organic chemistry portal and molecule docking. ACD/chem. sketch is the powerful all-purpose chemical drawing and graphics package from ACD/labs developed to help chemist quickly and easily draw molecules, reactions, and schematic diagrams, calculate chemical properties and design professional reports and presentations. ACD chem. sketch can convert “SMILES” notations to structure and vice versa .PDB (protein data bank) is the single worldwide archive of structural data of biological macromolecules, established in Brookhaven national laboratories (BNL) in 1971. It contains

structural information of the macromolecules determined by X-ray crystallographic, NMR methods ect. Docking allows the scientist to virtually screen a database of compounds and predict the strongest binders based on various scoring functions. It explores ways in which two molecules, such as drugs and an enzyme or receptor fit together and docks to each other well, like pieces of a three-dimensional zigzag puzzle. The molecules binding to a receptor, inhibit its function, and thus act as drug. The collection of drug analogs and receptor complexes was identified via docking and their relative stabilities were evaluated using molecular dynamics and their binding affinities, using free energy simulations. All the parameters used for molecule docking are selected by default.

Table 1: Substitutions of Michael adducts thiazolidinedione derivatives and Smiles File

Sr. No.	Code	Substitutions	Smiles Notations
1	3a	4-Cl	<chem>Clc1ccc(cc1)C1CC(=NC1C)c1c[NH]cn1</chem>
2	3b	3-Cl	<chem>Clc1cc(ccc1)C1CC(=NC1C)c1c[NH]cn1</chem>
3	3c	2-Cl	<chem>Clc1cccc1C1CC(=NC1C)c1c[NH]cn1</chem>
4	3d	4-F	<chem>Fc1ccc(cc1)C1CC(=NC1C)c1c[NH]cn1</chem>
5	3e	3-F	<chem>Fc1cc(ccc1)C1CC(=NC1C)c1c[NH]cn1</chem>
6	3f	2-F	<chem>Fc1cccc1C1CC(=NC1C)c1c[NH]cn1</chem>
7	3g	4-NO ₂	<chem>O=[N+](O-)[O-]c1ccc(cc1)C1CC(=NC1C)c1c[NH]cn1</chem>
8	3h	4,3-NO ₂	<chem>O=[N+](O-)[O-]c1cc(ccc1[N+](=O)[O-])C1CC(=NC1C)c1c[NH]cn1</chem>



9	3i	4,3,2-NO ₂	<chem>O=[N+](O)c1c(c(ccc1[N+](=O)[O-]))C1CC(=NC1C)c1c[NH]cn1[N+](=O)[O-]</chem>
10	3j	4-COCH ₃	<chem>O=C(C)c1ccc(cc1)C1CC(=NC1C)c1c[NH]cn1</chem>
11	3k	4,3-COCH ₃	<chem>CC(=O)c1cc(ccc1C(=O)C)C1CC(=NC1C)c1c[NH]cn1</chem>

Result: Out of 11 proposed chemical structures only best three structures were selected and their energy values are tabulated below. Which were docked with the mentioned targets.

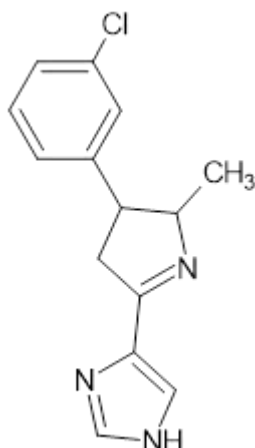
Table 2: Druglike properties predicted from Molsoft, Molinspiration Property calculator the following are the properties of Michael Adducts imidazole derivatives.

Sr. No	CODE	Mi logp	TPSA	Mol. formula	MW	HBA	HBD	pK _a	BBB score	Mol. volume	Drug-likeliness
1	3a	3.33	30.67A ²	C14 H14 Cl N3	259.09	2	1	5.86/8.28	5.33	236.94 A ³	0.40
2	3b	3.20	30.67 A ²	C14 H14 Cl N3	259.09	2	1	5.86 / 8.28	5.33	237.02 A ³	0.13
3	3c	3.19	30.67 A ²	C14 H14 Cl N3	259.09	2	1	5.86 / 8.28	5.33	236.73 A ³	0.04
4	3d	2.80	30.67 A ²	C14 H14 F N3	243.12	2	1	5.86 / 8.28	5.34	225.66 A ³	0.19
5	3e	2.73	30.67 A ²	C14 H14 F N3	243.12	2	1	5.86 / 8.28	5.34	225.74 A ³	0.05
6	3f	2.73	30.67 A ²	C14 H14 F N3	243.12	2	1	5.86 / 8.28	5.34	226.28 A ³	-0.22
7	3g	2.67	64.06 A ²	C14 H14 N4 O2	270.11	4	1	5.86 / 8.28	3.95	244.74 A ³	-0.31
8	3h	2.33	96.84 A ²	C14 H13 N5 O4	315.10	6	1	5.86 / 8.28	2.90	270.87 A ³	-0.56
9	3i	2.79	129.31 A ²	C14 H12 N6 O6	360.08	8	1	5.86 / 8.28	2.17	299.41A ³	-0.79
10	3j	2.34	44.50 A ²	C16 H17 N3 O	267.14	3	1	5.86 / 8.28	4.89	266.15 A ³	-0.21
11	3k	2.34	58.33 A ²	C18 H19 N3 O2	309.15	4	1	5.86 / 8.28	4.16	311.79 A ³	-0.20

Table 3: Docking score predicted from Mcule the following are the properties of Michael Adducts imidazole derivatives.

Sr. No	CODE	SUBSTITUTIONS	Drug-likeliness	Docking score
				Lanosterol 14-alpha-demethylase
1	3a	4-Cl	0.40	-7.2
2	3b	3-Cl	0.13	-8.0
3	3c	2-Cl	0.04	-7.9
4	3d	4-F	0.19	-7.3
5	3e	3-F	0.05	-8.0
6	3f	2-F	-0.22	-7.9
7	3g	4-NO ₂	-0.31	-7.3
8	3h	4,3-NO ₂	-0.56	-7.5
9	3i	4,3,2-NO ₂	-0.79	-7.6
10	3j	4-COCH ₃	-0.21	-7.8
11	3k	4,3-COCH ₃	-0.20	-8.1

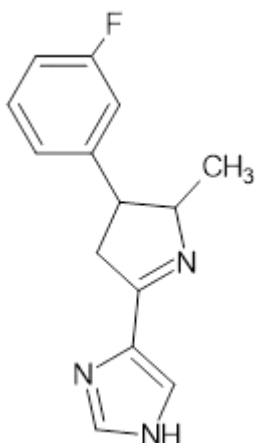


Ligand: 3b**Table 4:**

Sr. No.	Code	Substitutions
1	3a	4-Cl
2	3b	3-Cl
3	3c	2-Cl
4	3d	4-F
5	3e	3-F
6	3f	2-F
7	3g	4-NO ₂
8	3h	4,3-NO ₂
9	3i	4,3,2-NO ₂
10	3j	4-COCH ₃
11	3k	4,3-COCH ₃

Table 5: Docking score predicted from Mcule the following are the properties of Michael Adducts imidazole derivatives.

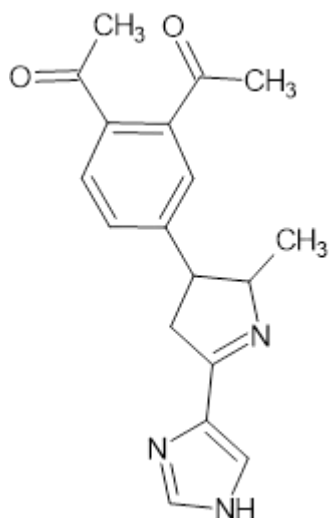
Sr. No	CODE	SUBSTITUTIONS	Druglikeliness	Docking score
				Lanosterol 14-alpha-demethylase
1	3a	4-Cl	0.40	-7.2
2	3b	3-Cl	0.13	-8.0
3	3c	2-Cl	0.04	-7.9
4	3d	4-F	0.19	-7.3
5	3e	3-F	0.05	-8.0
6	3f	2-F	-0.22	-7.9
7	3g	4-NO ₂	-0.31	-7.3
8	3h	4,3-NO ₂	-0.56	-7.5
9	3i	4,3,2-NO ₂	-0.79	-7.6
10	3j	4-COCH ₃	-0.21	-7.8
11	3k	4,3-COCH ₃	-0.20	-8.1

Ligand: 3e**Table 6:**

Sr. No.	Code	Substitutions
1	3a	4-Cl
2	3b	3-Cl
3	3c	2-Cl
4	3d	4-F
5	3e	3-F
6	3f	2-F
7	3g	4-NO ₂
8	3h	4,3-NO ₂
9	3i	4,3,2-NO ₂
10	3j	4-COCH ₃
11	3k	4,3-COCH ₃

Table 7: Docking score predicted from Mcule the following are the properties of Michael Adducts imidazole derivatives.

Sr. No	CODE	SUBSTITUTIONS	Druglikeliness	Docking score
				Lanosterol 14-alpha-demethylase
1	3a	4-Cl	0.40	-7.2
2	3b	3-Cl	0.13	-8.0
3	3c	2-Cl	0.04	-7.9
4	3d	4-F	0.19	-7.3
5	3e	3-F	0.05	-8.0
6	3f	2-F	-0.22	-7.9
7	3g	4-NO ₂	-0.31	-7.3
8	3h	4,3-NO ₂	-0.56	-7.5
9	3i	4,3,2-NO ₂	-0.79	-7.6
10	3j	4-COCH ₃	-0.21	-7.8
11	3k	4,3-COCH ₃	-0.20	-8.1

Ligand: 3k**Table 8:**

Sr. No.	Code	Substitutions
1	3a	4-Cl
2	3b	3-Cl
3	3c	2-Cl
4	3d	4-F
5	3e	3-F
6	3f	2-F
7	3g	4-NO ₂
8	3h	4,3-NO ₂
9	3i	4,3,2-NO ₂
10	3j	4-COCH ₃
11	3k	4,3-COCH ₃

Table 9: Docking score predicted from Mcule the following are the properties of Michael Adducts imidazole derivatives.

Sr. No	CODE	SUBSTITUTIONS	Drug-likeliness	Docking score
				Lanosterol 14-alpha-demethylase
1	3a	4-Cl	0.40	-7.2
2	3b	3-Cl	0.13	-8.0
3	3c	2-Cl	0.04	-7.9
4	3d	4-F	0.19	-7.3
5	3e	3-F	0.05	-8.0
6	3f	2-F	-0.22	-7.9
7	3g	4-NO ₂	-0.31	-7.3
8	3h	4,3-NO ₂	-0.56	-7.5
9	3i	4,3,2-NO ₂	-0.79	-7.6
10	3j	4-COCH ₃	-0.21	-7.8
11	3k	4,3-COCH ₃	-0.20	-8.1

CONCLUSION

Based on the literature it has been shown clearly that the compounds 3b,3e,3k have been used to target receptors where the compound 3b,3e and 3f on docking with the target produced an energy value of [-8.0], [-8.0] and [-8.1] respectively. Drug likeliness performed in the software of molsoft. Where the drug analog using the “SMILES” notation which are generated by the chem.-sketch.

By using the molinspiration online software, the drug analogs are undergone for their molecular properties like mollogp, molecular formula, BBB score, druglikeliness, HBA, HBD, pKa, Volume, molecular weight, TPSA and Drug likeliness, where some of the drug analogs have been shown the good druglikeliness.

Docking pose of proposed chemical structures:

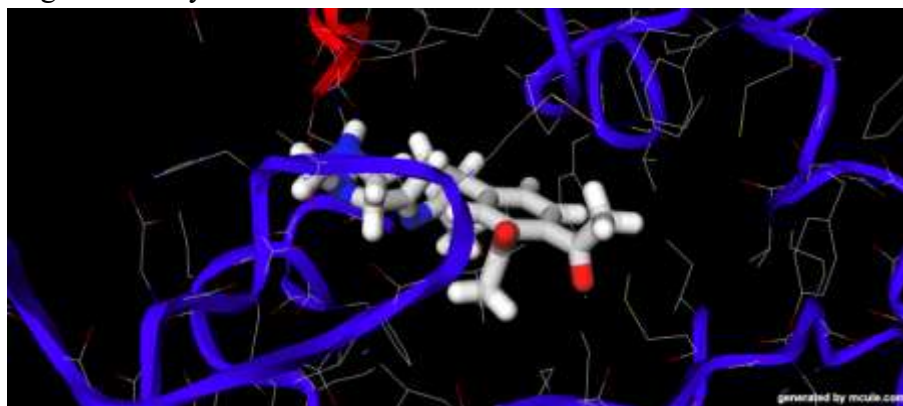


Figure 3: Docking pose of 3b with the target 3gw9

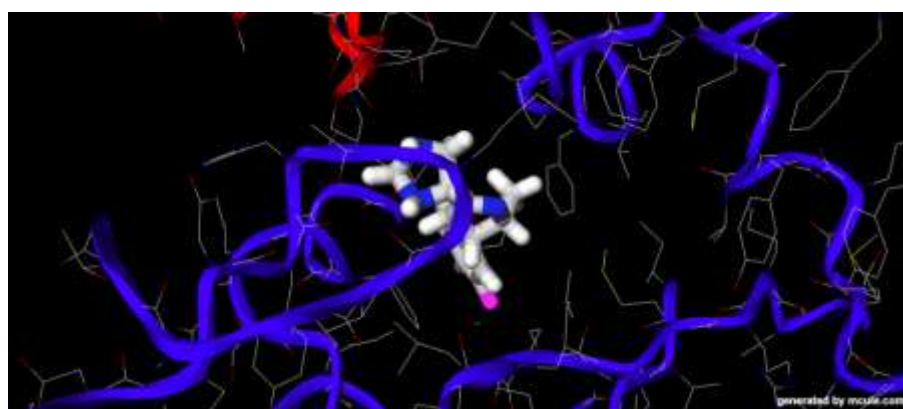


Figure 4: Docking pose of 3e with the target 3gw9

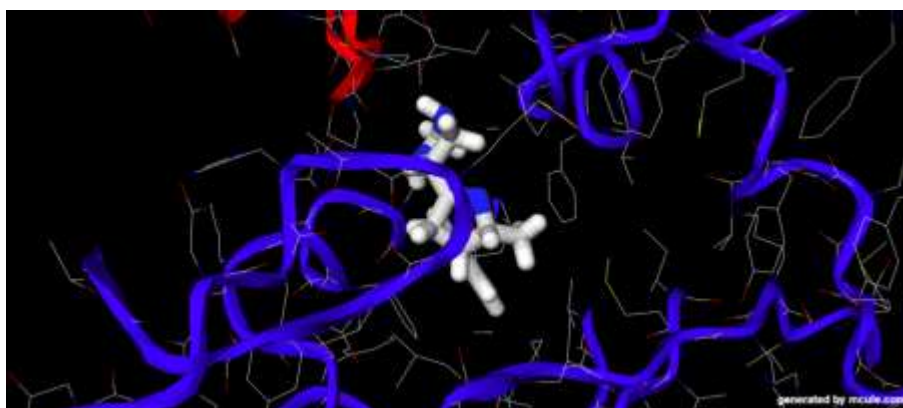


Figure 5: Docking pose of 3f with the target 3gw9

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I am grateful to my supervisor and co-supervisor who have imparted their knowledge about the subject to me to complete this project work. This would not have been a successful effort without their blissful insight and guidance.

I acknowledge from the bottom core of my heart, a great debt of gratitude to my beloved parents and colleagues inspiration without which it would not have been possible to accomplish this task.

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