Available online www.worldscientificnews.com

World Scientific News

An International Scientific Journal

WSN 208 (2025) 36-52 EISSN 2392-2192

Molecular Docking Study of Substituted Camphor- Hydrazide and Isatin-Based Compounds

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ABSTRACT

Drug discovery is an intensive and costly process, and computational approaches such as molecular docking can significantly accelerate the identification of promising lead molecules. In this study, molecular docking investigations were performed on previously synthesized camphor hydrazide (MBL-101 to MBL-106) and Isatin-based (MMP-01 to MMP-12) derivatives against ATP-dependent DNA ligase from bacteriophage (PDB ID: 1a0i) using Molegro Virtual Docker (MVD). The native ATP ligand exhibited the strongest binding affinity, with a MolDock score of –190.482 kcal/mol and a re-rank score of –114.713 kcal/mol. Among the synthesized ligands, MBL-103 (–116.521 kcal/mol) and MBL-106 (–112.338 kcal/mol) demonstrated the highest binding affinities, forming multiple hydrogen bond interactions with key residues such as Arg39, Tyr35, Ile33, and Ala11. These interactions were further stabilized by favorable steric contacts, suggesting strong potential activity. In contrast, most MMP derivatives displayed weaker or unfavorable docking scores, with positive re-rank values in some cases, indicating poor binding. Overall, MBL-103 and MBL-106 emerged as the most promising candidates, warranting further in vitro and in vivo evaluation. These findings highlight the utility of in-silico docking in prioritizing compounds for drug discovery pipelines and support the potential of camphor hydrazide derivatives as inhibitors of ATP-dependent DNA ligase.

***Keywords*:** camphor, Isatin, molecular docking, ATP-dependent DNA ligase from bacteriophage

(Received 21 August 2025; Accepted 17 September 2025; Date of Publication 4 October 2025)

1. INTRODUCTION

The discovery and development of new drugs is a complex, expensive, and time-consuming process for pharmaceutical and biotechnology industries. The journey from initial lead identification to the approval of a single therapeutic agent often requires years of research and substantial financial investment. In recent years, computational approaches have gained significant attention in drug discovery due to their ability to predict biological activity, reduce experimental costs, and accelerate the design of novel drug candidates. Among the in-silico methods, molecular docking has emerged as a powerful technique for understanding protein–ligand interactions at the molecular level. Docking predicts the most favorable orientation of a ligand when bound to a target protein, thereby providing insights into binding affinity, stability of the complex, and possible molecular interactions. This approach plays a critical role in structure-based drug design, enabling researchers to prioritize compounds before advancing to labor-intensive experimental validation.

DNA ligases are essential enzymes involved in DNA replication, recombination, and repair processes. The ATP-dependent DNA ligase from bacteriophage (PDB ID: 1a0i) is an important target due to its role in catalyzing the formation of phosphodiester bonds, which are crucial for maintaining genomic integrity. Inhibiting DNA ligase activity can disrupt DNA repair pathways, making it a potential target for antimicrobial and anticancer drug development.

Camphor hydrazide and Isatin-based derivatives represent two structurally diverse classes of bioactive compounds with reported pharmacological significance. Hydrazide derivatives are known for their antimicrobial, anticancer, and antiviral activities, whereas Isatin-based compounds have demonstrated wide biological potential, including antibacterial and antitumor properties. Considering their diverse biological activity, these scaffolds offer an attractive starting point for the development of new ligase inhibitors. In the present study, we investigated the molecular interactions of a series of previously synthesized camphor hydrazide derivatives (MBL-101 to MBL-106) [1] and Isatin-based derivatives (MMP-01 to MMP-12) [2] with the ATP-dependent DNA ligase (1a0i) using Molegro Virtual Docker (MVD) software, as shown in **Figure 1**. The docking simulations aimed to identify the most promising candidates with high binding affinity and favorable molecular interactions, thereby providing a basis for further experimental validation.

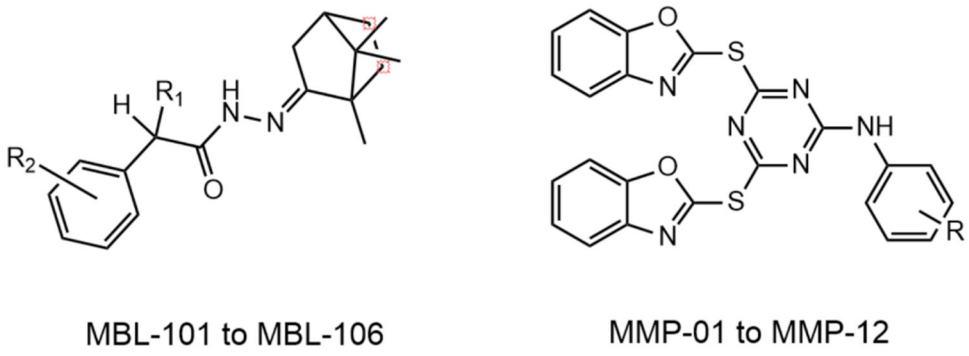

Figure 1. Substituted camphor hydrazide (MBL-101 to MBL-106) and Isatin-based (MMP-01 to MMP-12) compounds.

2. COMPUTATIONAL STUDY

Computational studies were carried out using Molegro Virtual Docker (MVD) software. MVD is a high-quality docking program that uses advanced optimization techniques, combined with an intuitive user interface designed for efficiency and productivity. It is an integrated platform for predicting protein-ligand interactions, handling all aspects of the docking process, from molecule preparation and identification of potential binding sites on the target protein to predicting the binding modes of the ligands [3].

3. RESULTS AND DISCUSSION

The docking scores represent the predicted binding affinities of different camphor and Isatin derivatives within the binding site of the ATP-dependent DNA ligase from bacteriophage 1a0i is given in **Table 1**. The native ATP ligand has the best MolDock score (-190.482 kcal/mol) and re-rank score (-114.713 kcal/mol). This suggests it has the strongest binding affinity to the protein. Among the newly synthesized ligands, MBL-103 has the best MolDock score (-116.521 kcal/mol), followed by MBL-106 (-112.338 kcal/mol) and MMP-04 (-109.474 kcal/mol). A lower docking score indicates better binding affinity.

Table 1. Docking results for the titled compounds.

Ligand	**MolDock score** (kcal/mol)	**Rerank score** (kcal/mol)	**H Bond** (kcal/mol)	**Hydrogen Bonds Interaction**	**Steric Interaction**
MBL-101	-57.8553	-26.3073	-1.47332	Ala 11	Ala 11, Lys 10
MBL-102	-96.5945	-85.0908	-2.5000	Arg 39	Lys 232, Arg 39, Glu 32, Ile 33, Lys 222
MBL-103	-116.521	-96.9624	-10.6146	Arg 39, Tyr 35, Ile 33, Ala 11	Arg 39, Tyr 35, Ile 33, Ala 11, Trp 236, Phe 9
MBL-104	-69.7221	-38.5742	-2.48792	Arg 39	Arg 39
MBL-105	-98.8628	-85.4864	-2.27678	Arg 55	Glu 93, Arg 55
MBL-106	-112.338	-85.8396	-8.07364	Tyr 149, Arg 39, Tyr 35	Lys 10, Trp 236, Tyr 149, Arg 39, Tyr 35, Ile 33, Glu 32, Lys 222
MMP-01	-83.948	-68.2470	-4.39602	Lye 238, Arg, 39	Lye 238, Arg, 39, Tyr 149, Ile 33, Glu 32, Lys 222
MMP-02	-40.0586	7.67119	-8.03478	Ala 11	Ala 11, Lys 10
MMP-03	-12.7079	35.6910	-8.25548	Arg 55, Lys 222	Arg 55, Lys 222, Tyr 149, Ile 33, Ile 220, Arg 39
MMP-04	-109.474	-73.9616	-4.11848	Lye 222,	Lye 222, Glu 32, Glu 93, Ile 220, Glu 242, Lys 240

MMP-05	63.4663	199.605	-6.83554	Tyr 149, Arg 39, Arg 55	Tyr 149, Arg 39, Arg 55, Ile 220, Lys 10, Ala 11
MMP-06	28.9665	156.602	-5.58857	Arg 55, Lys 222	Arg 55, Lys 222, Lys 238, Ile 33 Tyr 149
MMP-07	33.0914	150.652	-10.5688	Lys 34, Arg 55, Arg 39, Tyr 35	Lys 34, Arg 55, Arg 39, Tyr 35, Lye 34, Lys 10, Tyr 149, Ile 33, Glu 32
MMP-08	-32.7292	4.32884	-7.20269	Arg 55, Lys 222	Arg 55, Lys 222, Lye 10, Arg 39, Ile 33, Tyr 149
MMP-09	53.6211	190.115	-11.0374	Arg 55, Arg 39, Tyr 35	Arg 55, Arg 39, Tyr 35, Glu 32, Ile 33, Tyr 149,
MMP-10	18.6654	90.2774	-7.04716	Tyr 149, Arg 55	Tyr 149, Arg 55, Ile 220, Arg 39
MMP-11	24.6841	156.314	-9.39883	Arg 55, Arg 39, Tyr 35	Arg 55, Arg 39, Tyr 35, Lys 10, Tyr 149, Glu 32, Ile 33
MMP-12	-37.3484	18.199	-7.39972	Arg 55, Arg 39, Lys 222	Arg 55, Arg 39, Lys 222, Lys 232, Ile 33, Tyr 149, Ala 11
ATP Ligand	-190.482	-114.713	-15.2384	Lys 222, Glu 32, Tyr 35, Ala 11, Lys 10, Arg 55	Lys 222, Glu 32, Tyr 35, Ala 11, Lys 10, Arg 55, Phe 9, Ile 33, Arg 39

Ligands with highly negative MolDock and re-rank scores are considered more active toward the target protein. MBL-103 and MBL-106 show the strongest activity among the synthesized ligands due to their highly negative MolDock and re-rank scores. Hydrogen bond contributions also play a key role in stability. MBL-103 and MBL-106 form several hydrogen bonds with crucial residues such as Arg 39, Tyr 35, and Ile 33, enhancing their binding potential. ATP shows extensive interactions, including Lys 222, Glu 32, Tyr 35, and Arg 39, which explains its superior docking scores compared to the synthesized ligands. Ligands like MMP-02 and MMP-03 have positive re-rank scores, indicating unfavorable binding. These ligands are less likely to exhibit strong activity towards the protein. The molecular docking studies provided insight into the binding interactions of the most active camphor and Isatin derivatives. Figure 2 illustrate the surface view (a) with cavities in protein 1a0i and protein preparation (b). The interactions of the titled compounds are depicted in **Figure 3** to **Figure 25**.

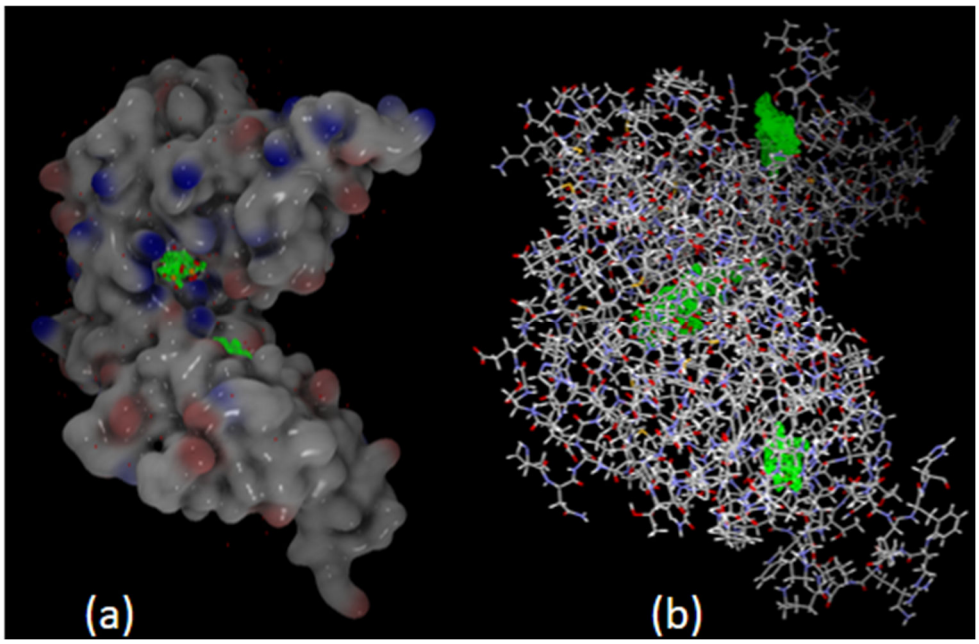

Figure 2. Cavities in protein 1a0i surface view (a) and protein preparation (b) with ATP ligand.

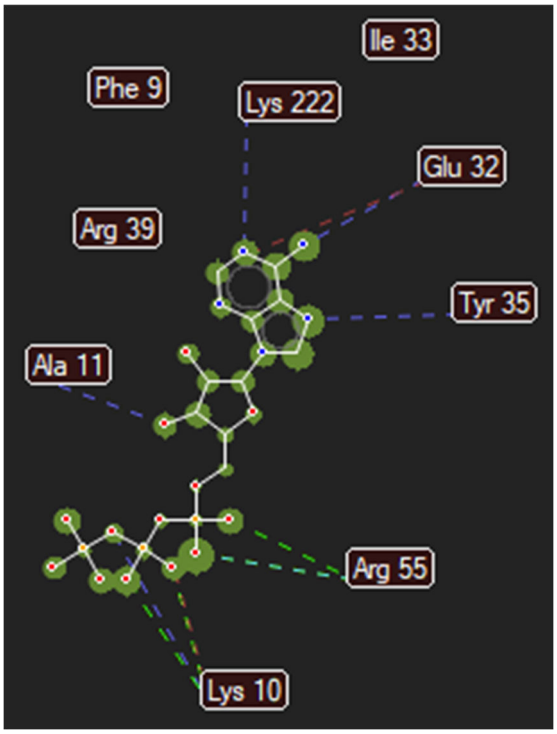

Figure 3. ATP ligands, hydrogen, and steric interaction.

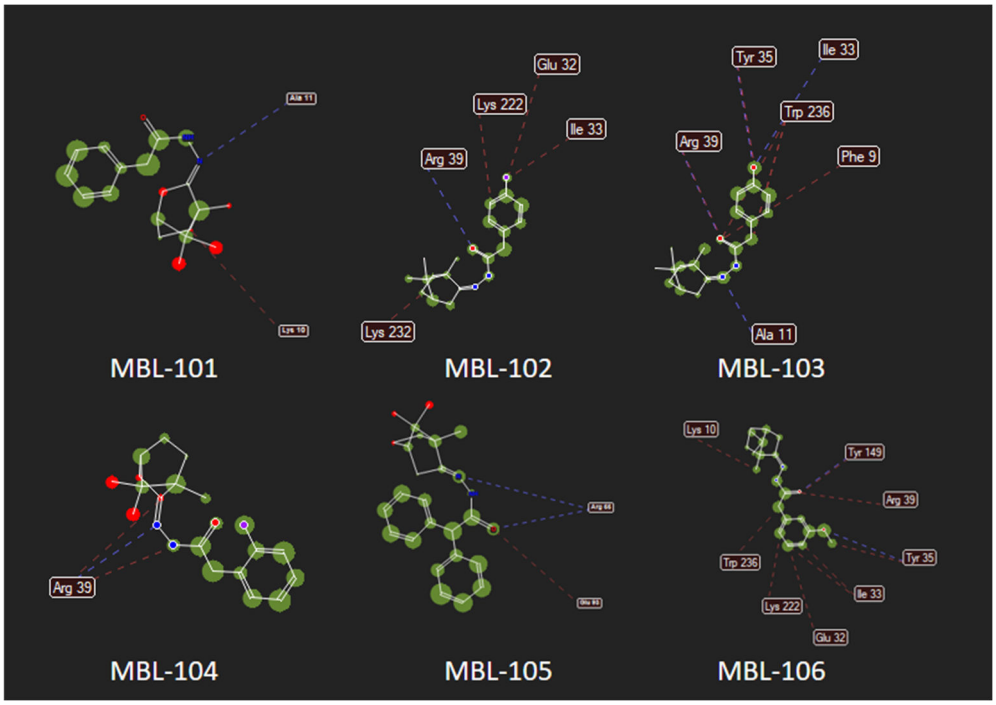

Figure 4. MBL series ligands, hydrogen, and steric interaction.

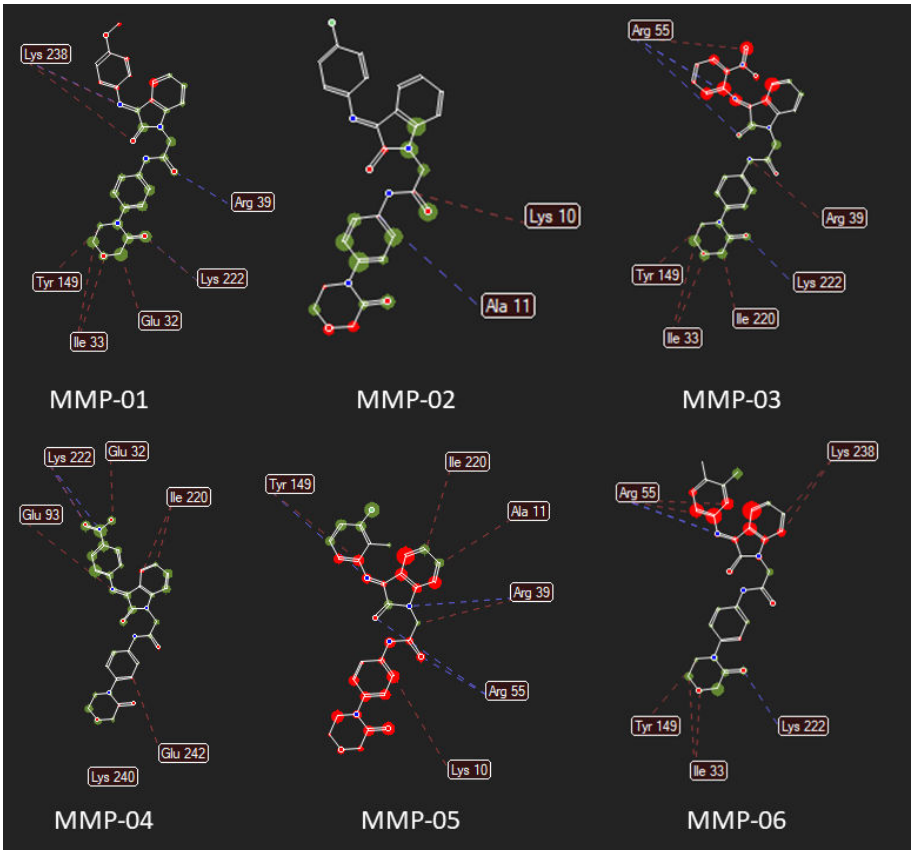

Figure 5. MMP-01 to MMP-06 ligands' hydrogen and steric interaction .

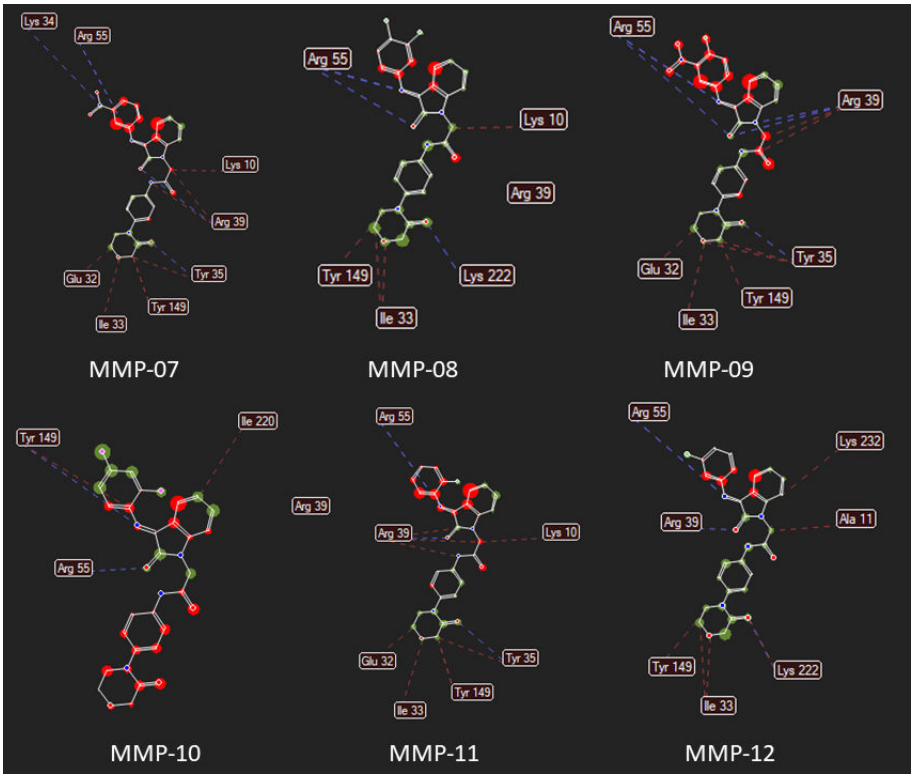

Figure 6. MMP-07 to MMP-12 ligands' hydrogen and steric interaction .

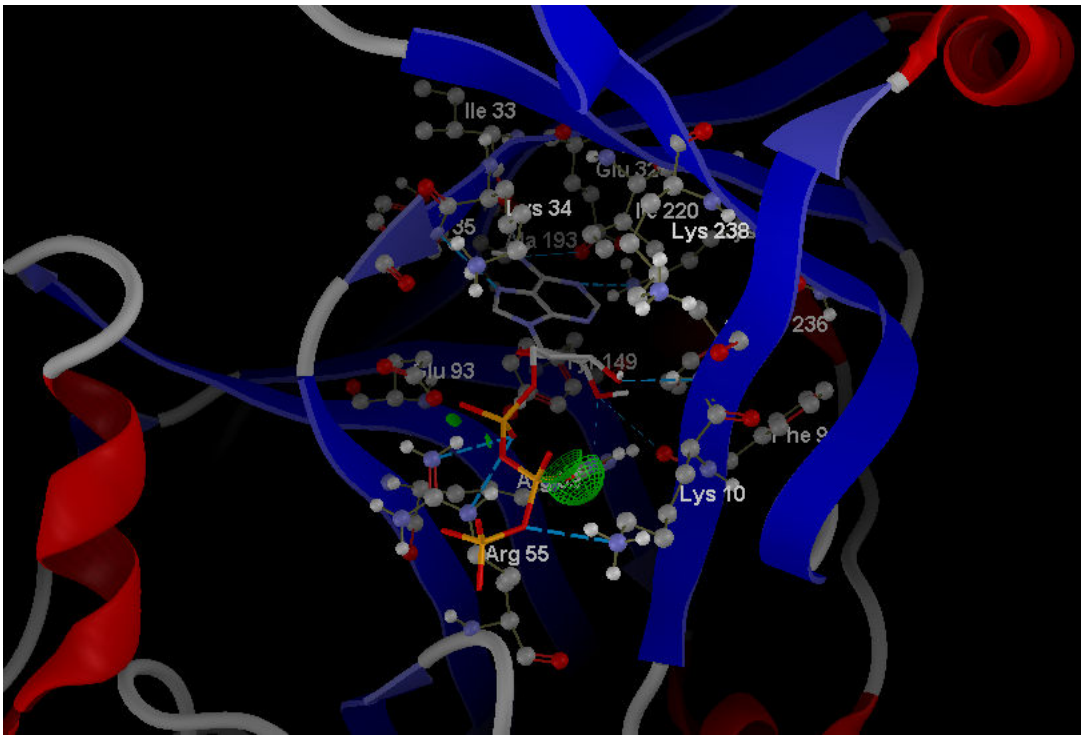

Figure 7. ATP ligand hydrogen interaction with 1a0i protein.

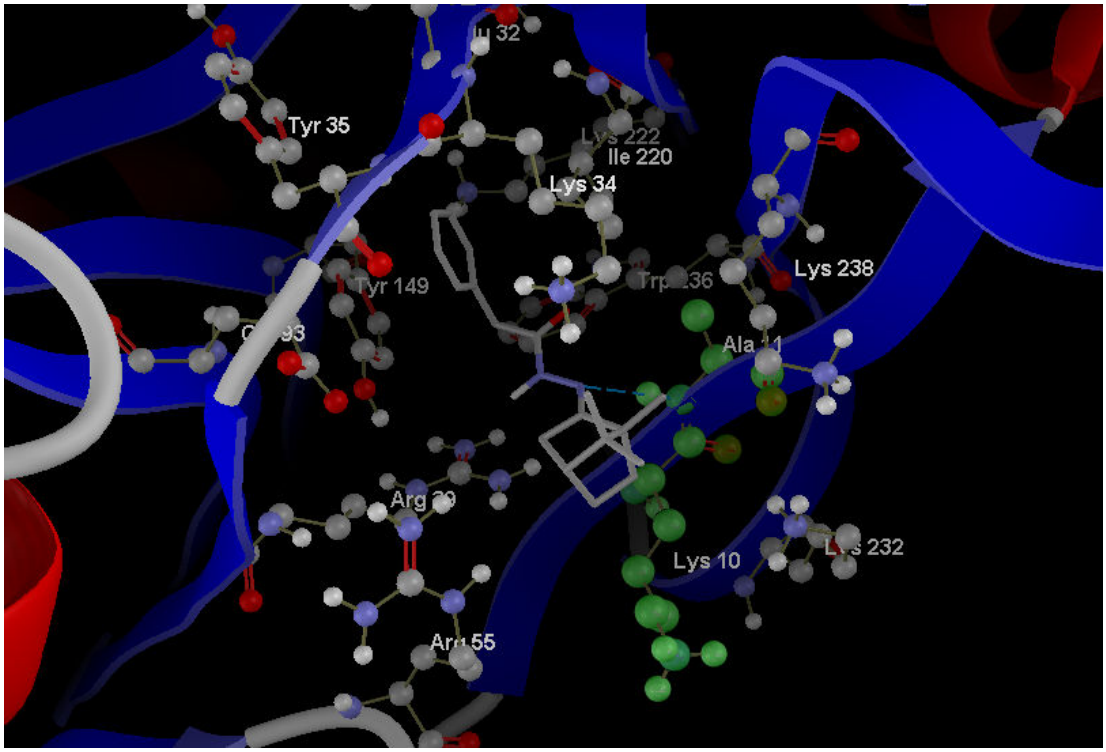

Figure 8. MBL-101 ligand hydrogen interaction with 1a0i protein.

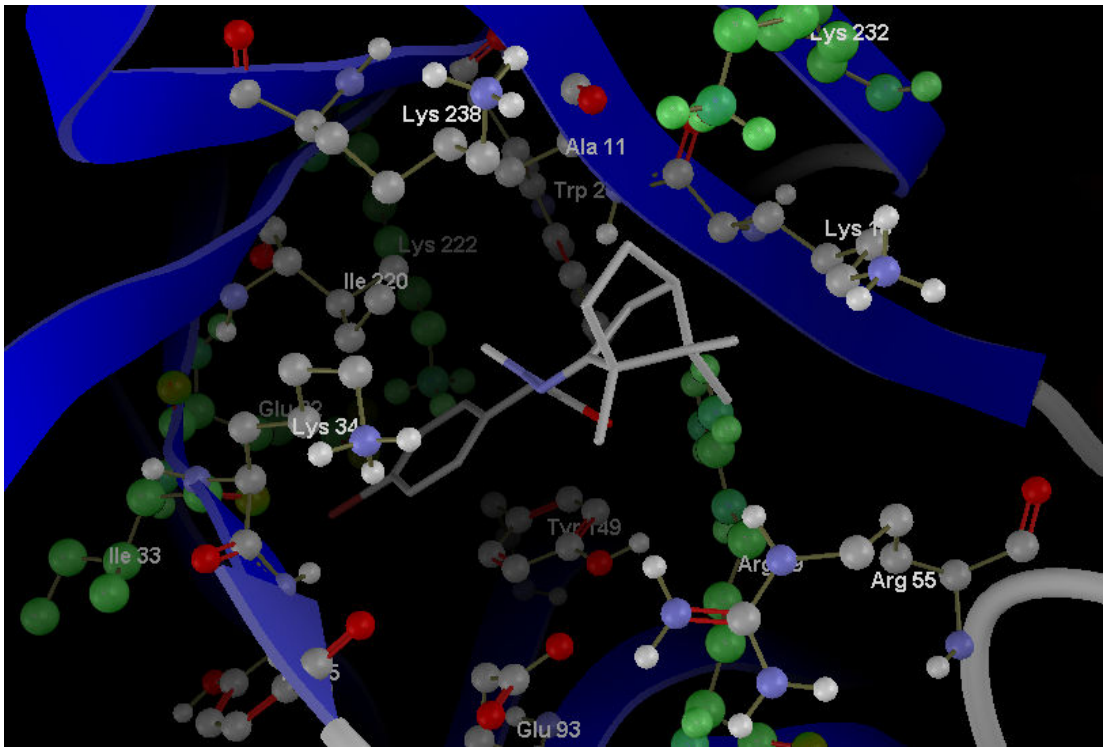

Figure 9. MBL-102 ligand hydrogen interaction with 1a0i protein.

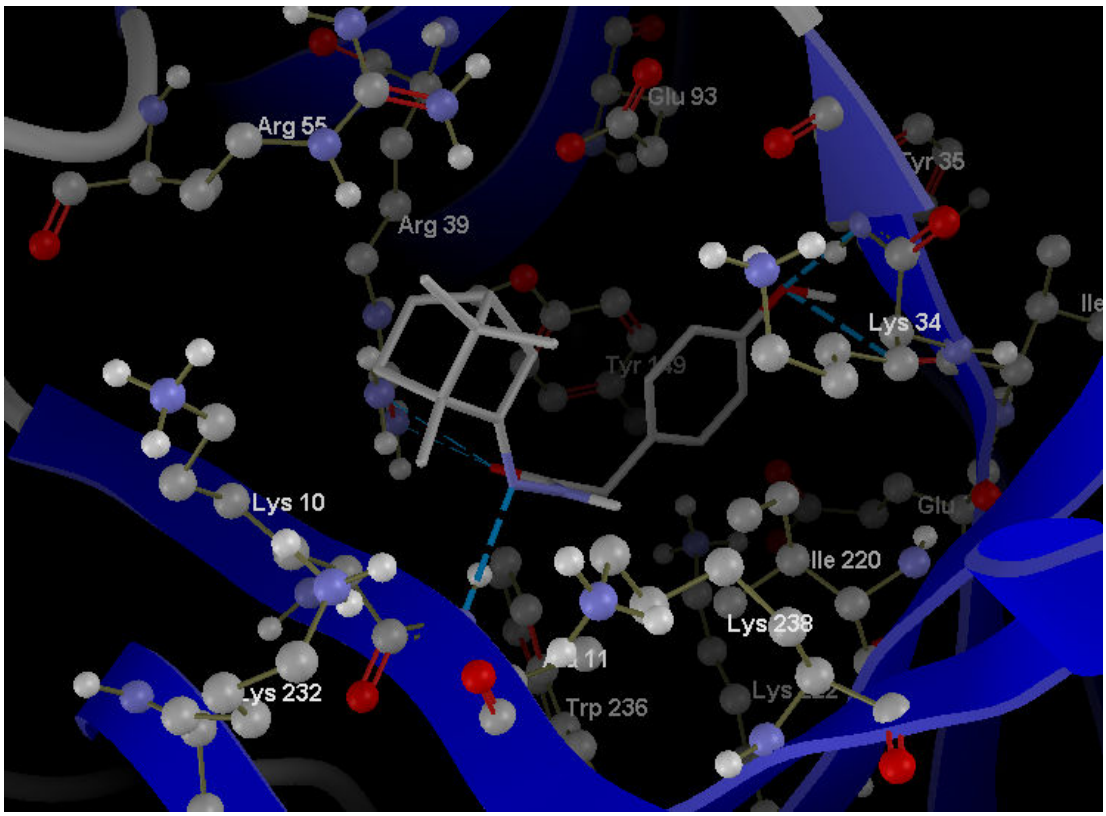

Figure 10. MBL-103 ligand hydrogen interaction with 1a0i protein.

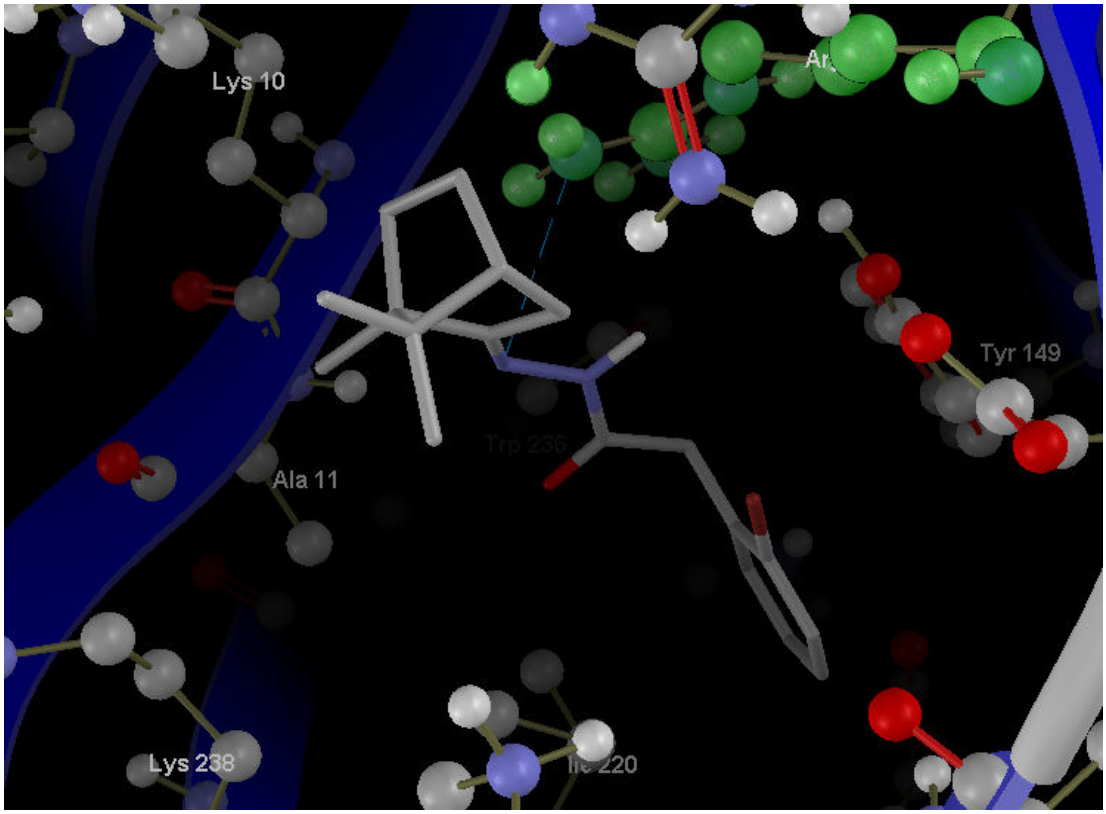

Figure 11. MBL-104 ligand hydrogen interaction with 1a0i protein.

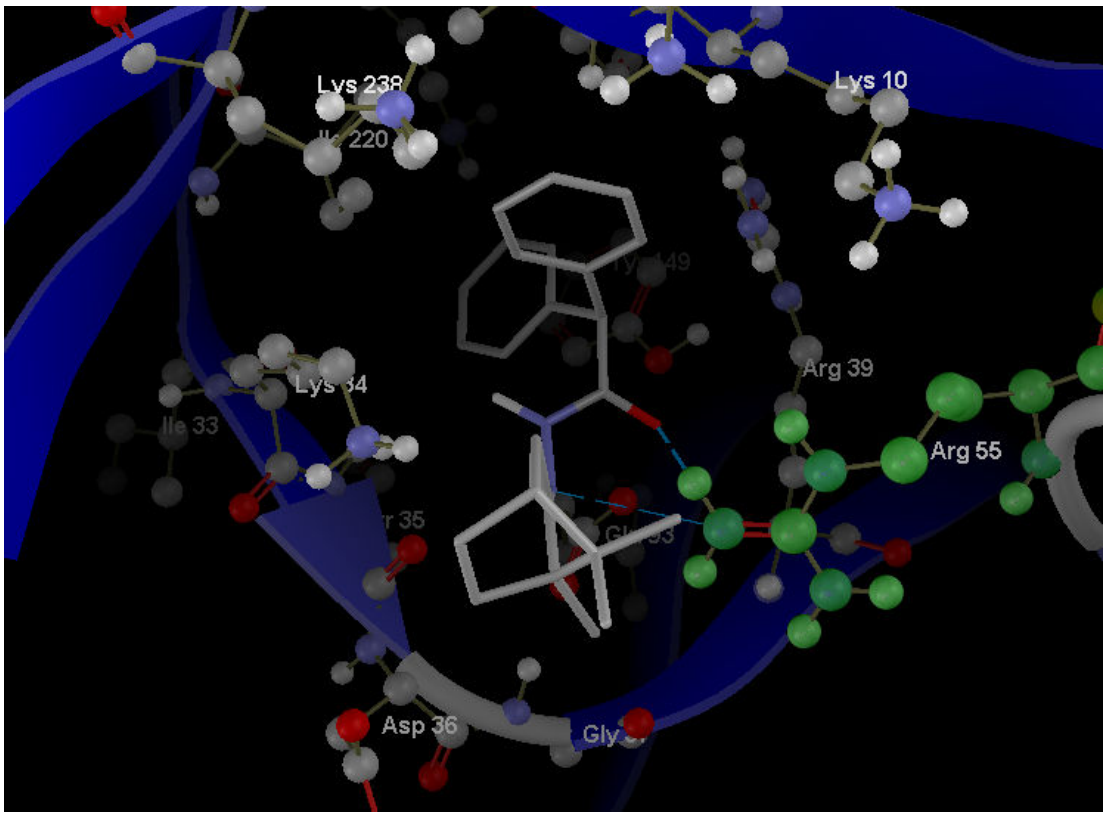

Figure 12. MBL-105 ligand hydrogen interaction with 1a0i protein.

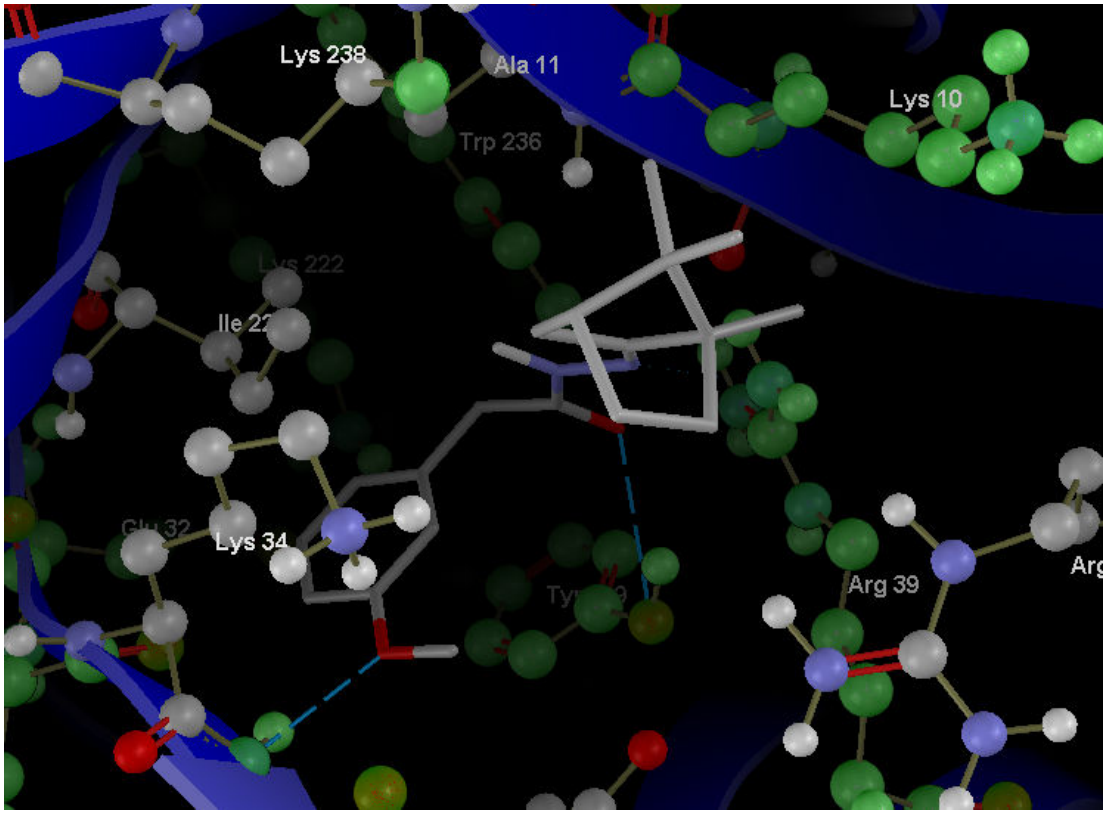

Figure 13. MBL-106 ligand hydrogen interaction with 1a0i protein.

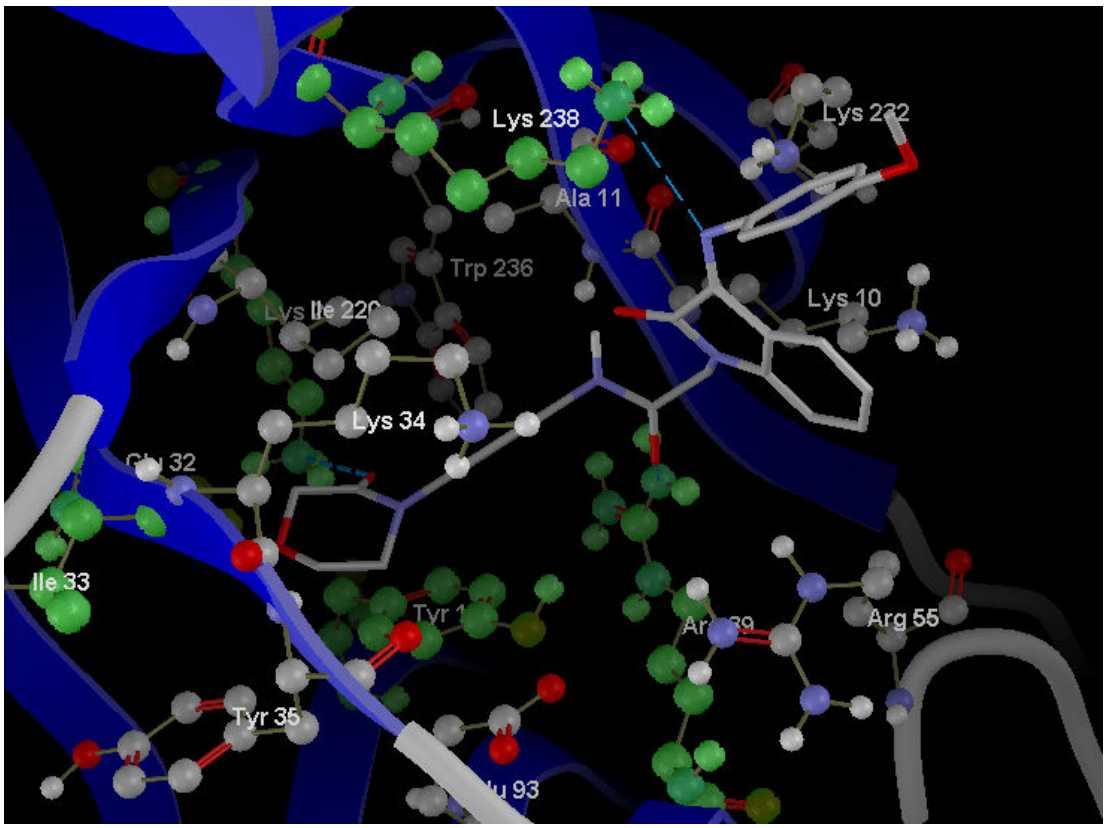

Figure 14. MMP-01 ligand hydrogen interaction with 1a0i protein.

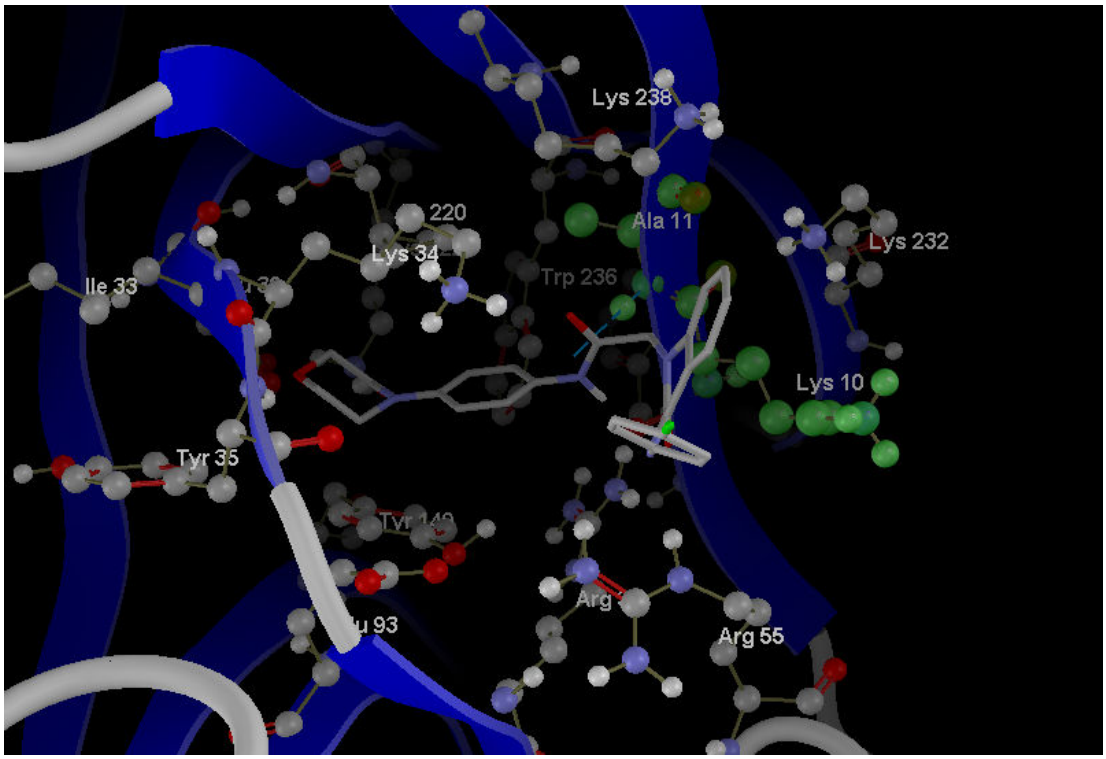

Figure 15. MMP-02 ligand hydrogen interaction with 1a0i protein.

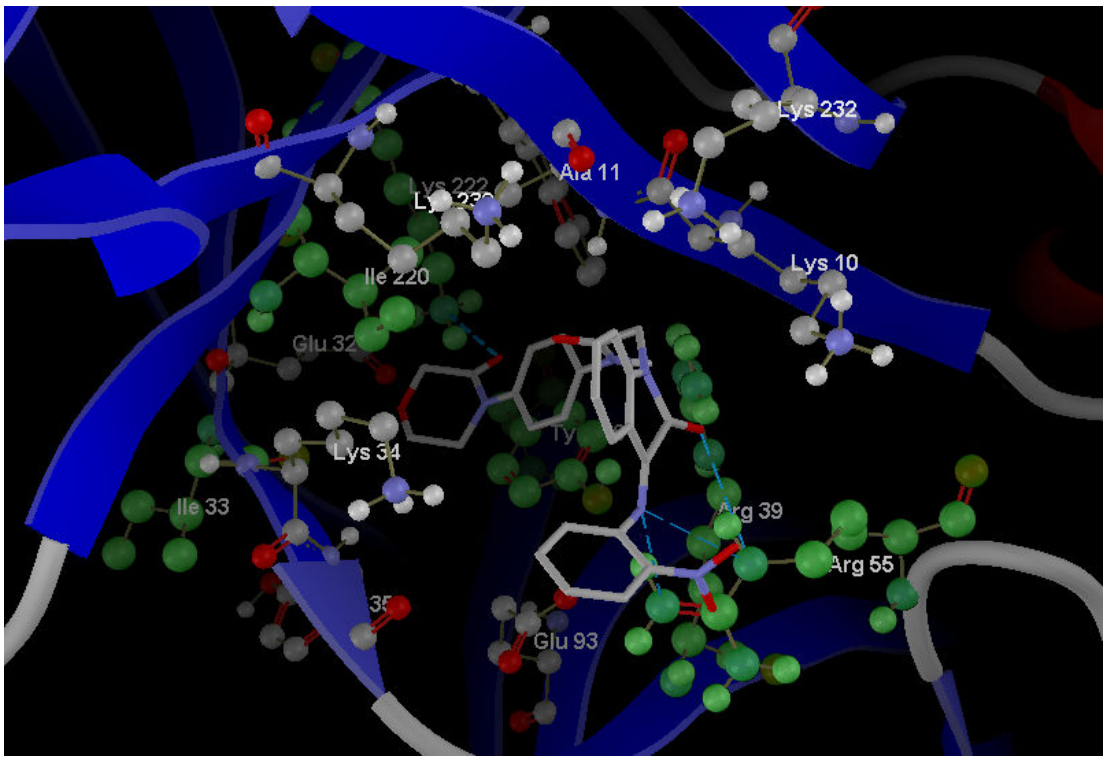

Figure 16. MMP-03 ligand hydrogen interaction with 1a0i protein.

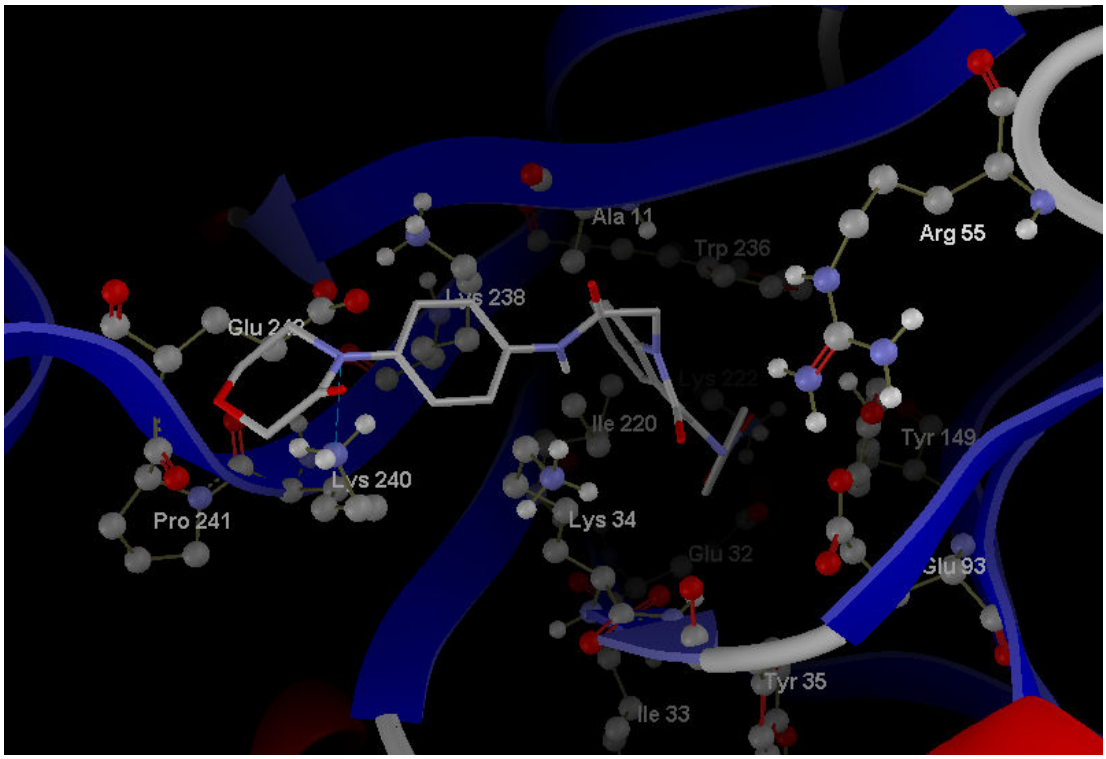

Figure 17. MMP-04 ligand hydrogen interaction with 1a0i protein.

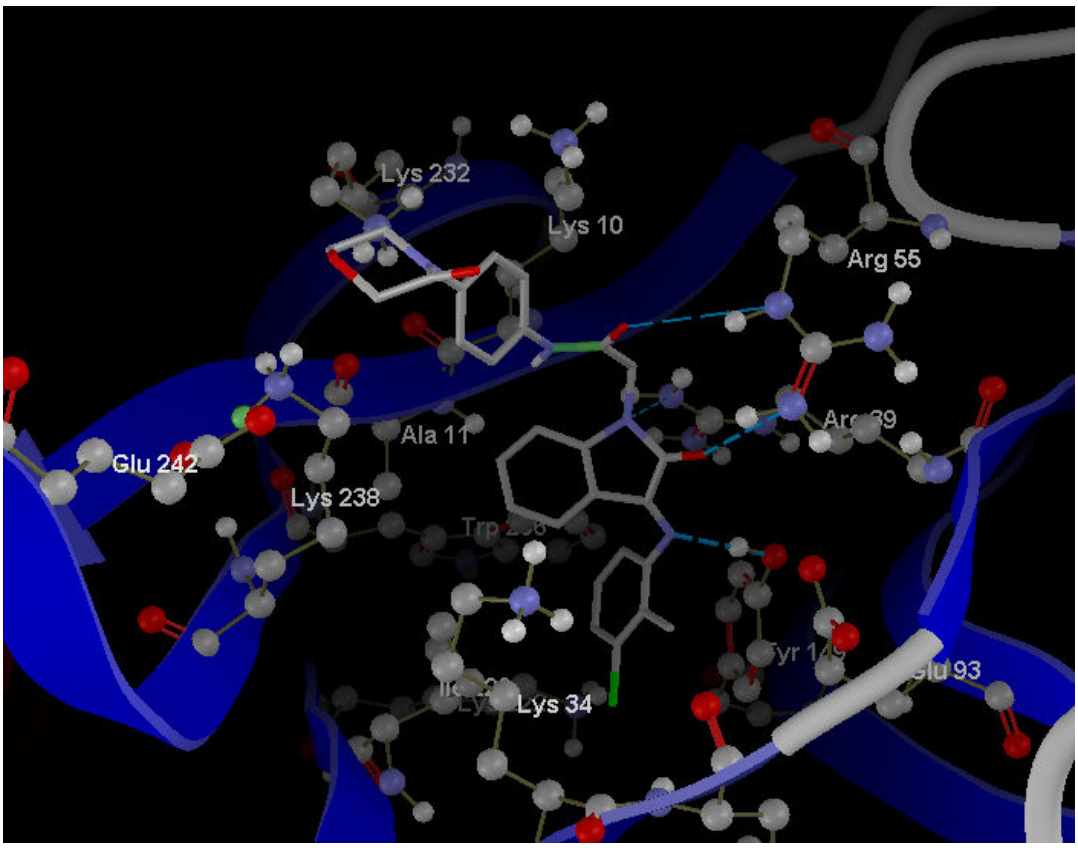

Figure 18. MMP-05 ligand hydrogen interaction with 1a0i protein.

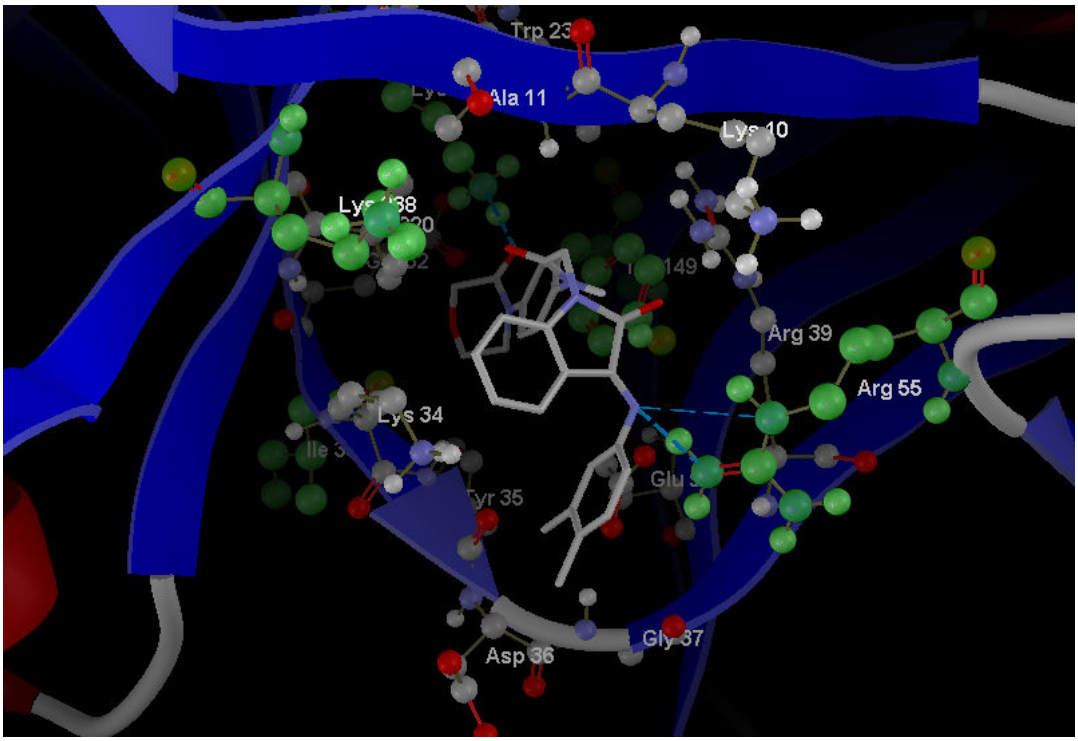

Figure 19. MMP-06 ligand hydrogen interaction with 1a0i protein.

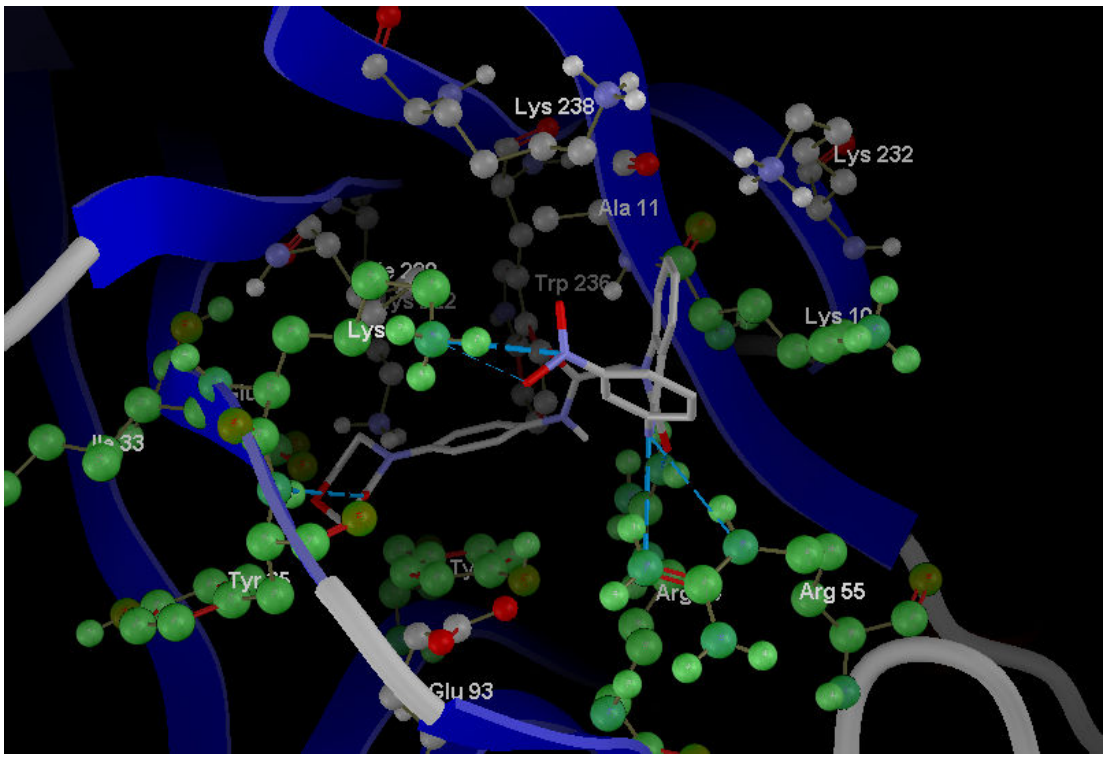

Figure 20. MMP-07 ligand hydrogen interaction with 1a0i protein.

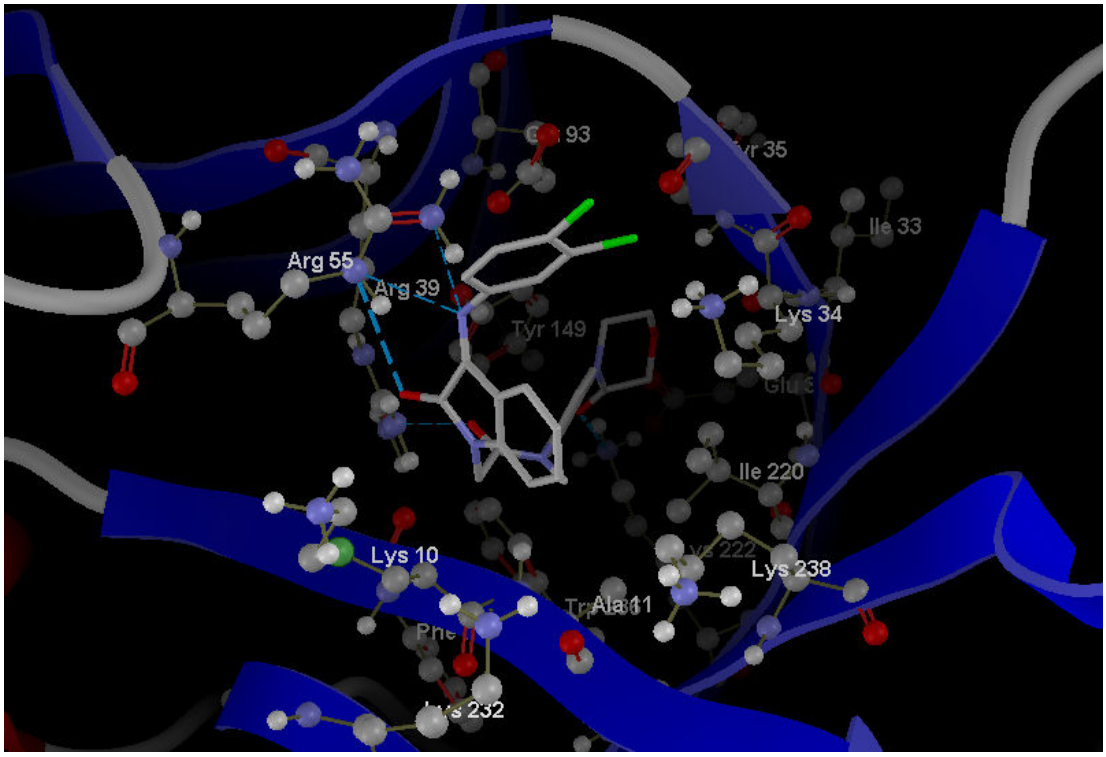

Figure 21. MMP-08 ligand hydrogen interaction with 1a0i protein.

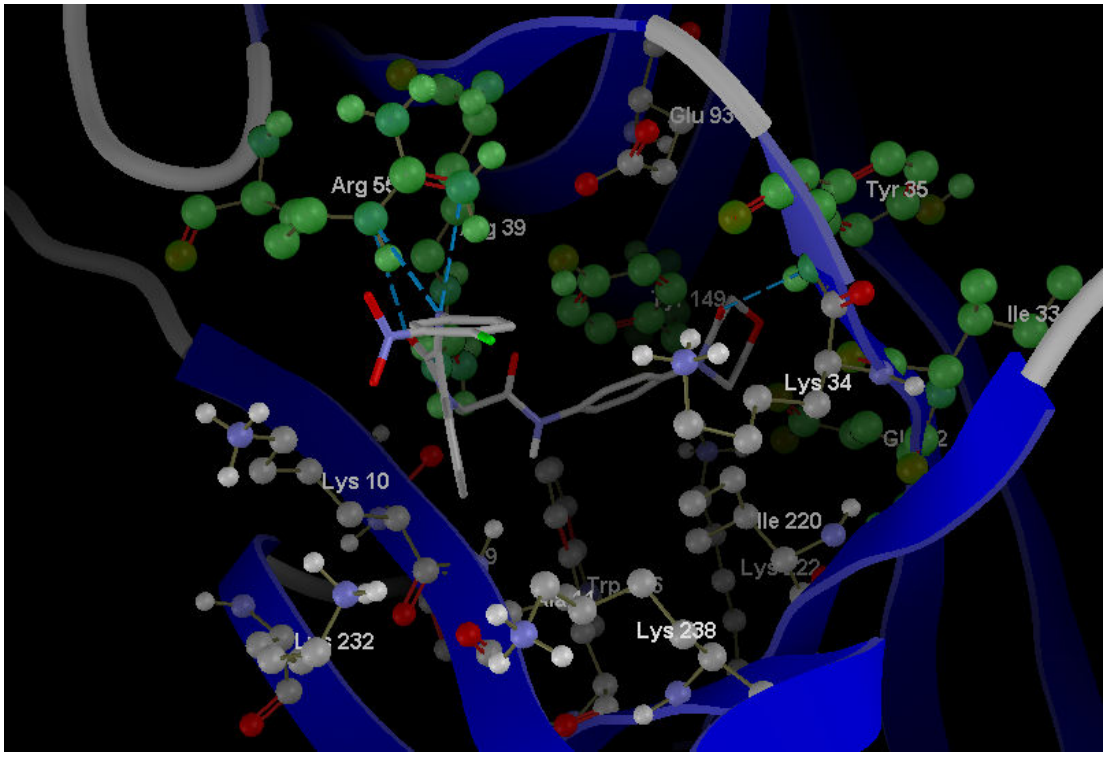

Figure 22. MMP-09 ligand hydrogen interaction with 1a0i protein.

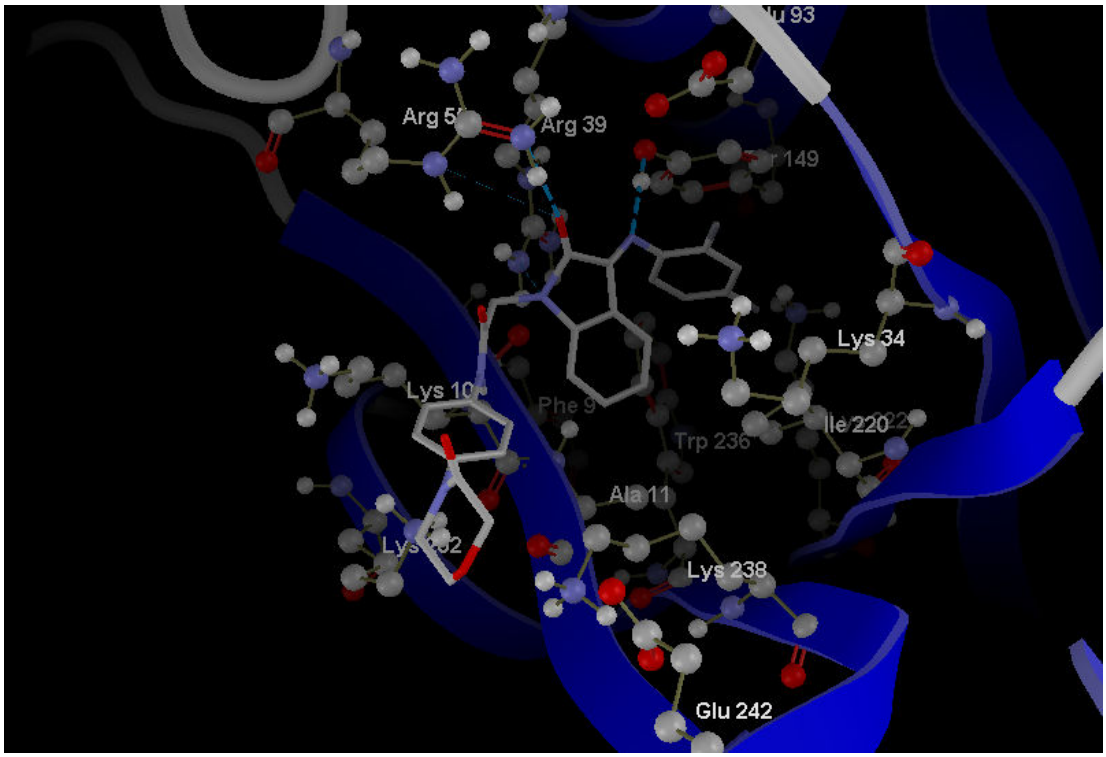

Figure 23. MMP-10 ligand hydrogen interaction with 1a0i protein.

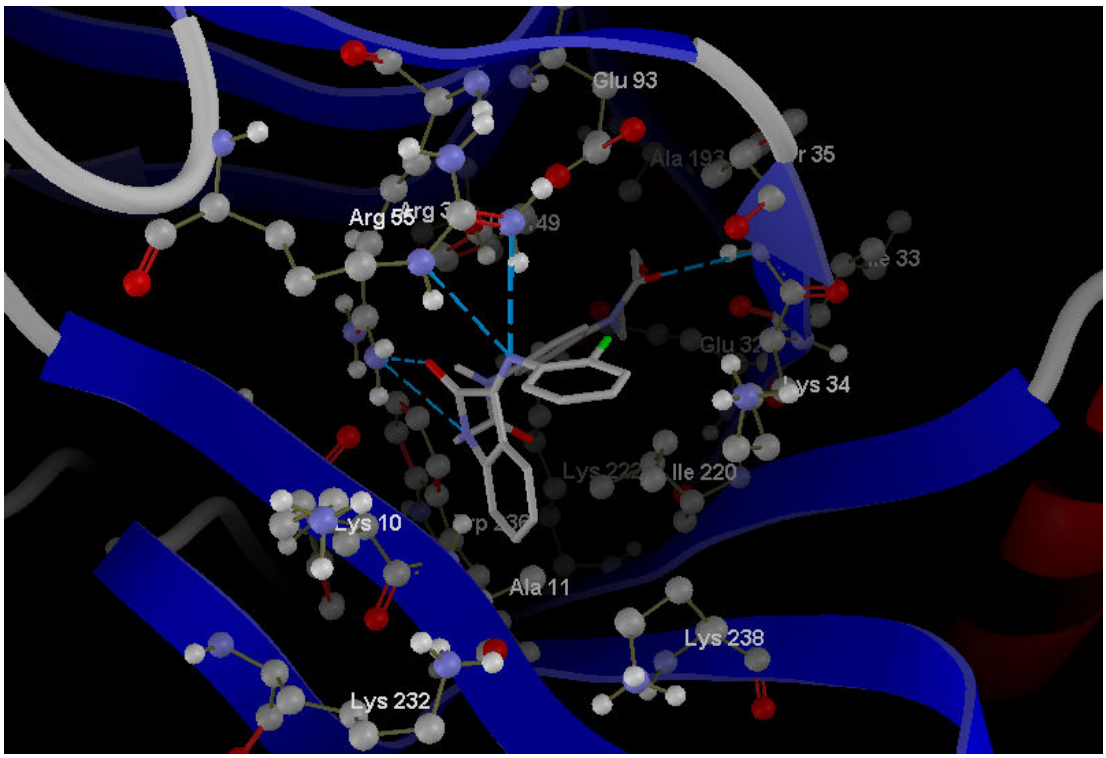

Figure 24. MMP-11 ligand hydrogen interaction with 1a0i protein.

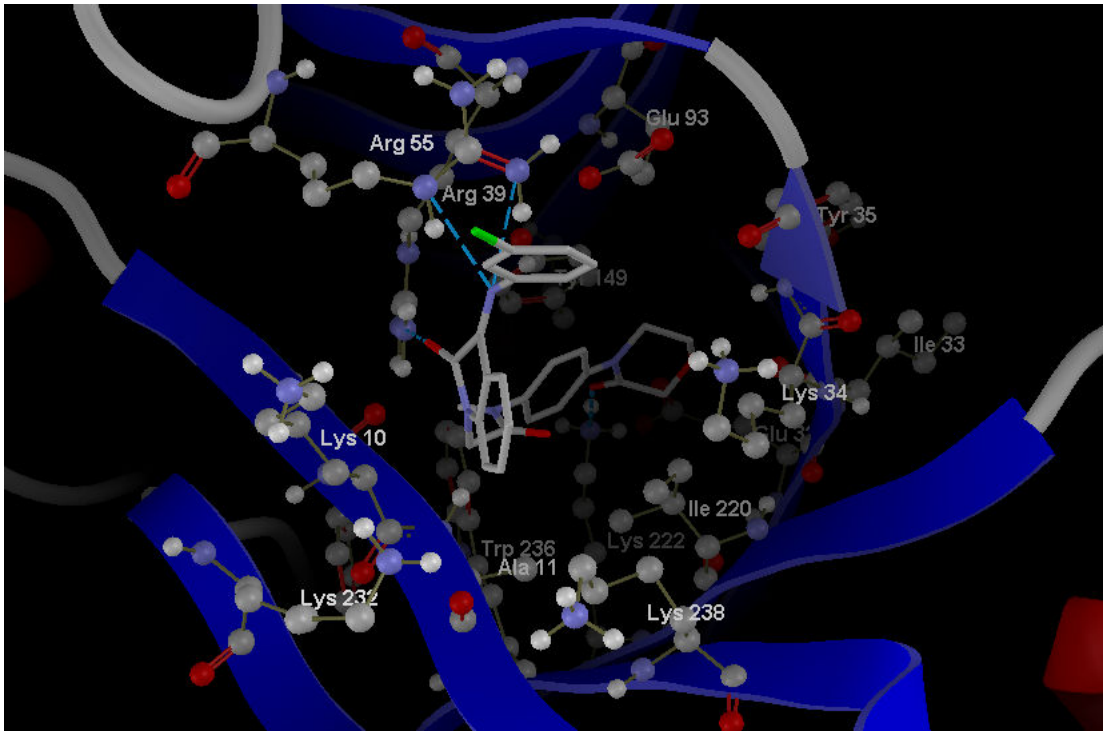

Figure 25. MMP-12 ligand hydrogen interaction with 1a0i protein.

4. CONCLUSION

The native ATP ligand exhibits the strongest binding affinity, as expected. Among the synthesized ligands, MBL-103 and MBL-106 are the most active due to their strong MolDock scores, multiple hydrogen bond interactions, and favorable re-rank scores. These ligands are promising candidates for further experimental validation. MMP series ligand exhibits very low binding affinity compared to MBL-103 and MBL-106. These findings not only provide structural insights into ligand–protein interactions but also establish a basis for the rational design and optimization of new ligase inhibitors with potential therapeutic applications.

Acknowledgement

Authors are thankful to Department of Chemistry, H. & H. B. Kotak Institute of Science, Rajkot, for laboratory support and facility.

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