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# MOLECULAR MODELING AND DOCKING OF SUBSTITUTED BENZIMIDAZOLE NUCLEOSIDES AS POTENTIAL ANTIVIRAL AGENTS

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***Abstract:*** The aim of this work is to establish a structure- activity relationship analysis of a series of benzimidazole derivatives and evaluate their binding mode. Benzimidazole derivatives were designed and evaluated for their antiviral activity against maize dwarf mosaic virus. Through molecular modeling the representation of 3D structures of antiviral molecules is done with the help of computerized techniques based on theoretical methods and experimental data. MDMV is targeted for the analysis as it infectivity on plants shows low or stunned growth in plants and its leaves thereby making a heavy loss to commercial value of the plant. MDMV is pathogenic plant virus of potyviridae family and its strains are A, C, D, E, and F which shows severe implications on plant leaves which turn into a mosaic pattern. The viral protein was modeled by homology modeling by selecting templates from the PDB database through alignment searching. The activity sites were identified in the target protein structure as cavities within the tool for docking studies. The docking studies were performed with the series of modeled molecules of 4-Floro-1-H (β-D-ribofuranosyl), 4-Chloro-1-H (β-D-ribofuranosyl), 4-Methylketon-1-H (β-D-ribofuranosyl), 4-Monochloromethyl-1-H (β-D-ribofuranosyl) benzimidazole nucleoside in which interaction between protein and ligand was analyzed.

**Keywords**- Molecular docking; benzimidazole nucleosides; molecular modeling; MDMV.

## I. Introduction

Molecular modeling has become a valuable and essential tool to medicinal chemists in the drug design process. Molecular modeling describes the generation, manipulation or representation of three- dimensional structures of molecules and associated physico-chemical properties. It involves a range of computerized techniques based on theoretical chemistry methods and experimental data to predict molecular and biological properties. Depending on the context and the rigor, the subject is often referred to as 'molecular graphics', 'molecular visualizations', 'computational chemistry', or 'computational quantum chemistry'. No protein is an island but exerts its function through the recognition of other molecular partners (Salmaso, 2018). Ligand-protein interactions are involved in many biological processes with consequent pharmaceutical implications. It consists in the generation of a number of possible conformations/orientations, i.e., poses, of the ligand within the protein binding site. For this reason, the availability of the three- dimensional structure of the molecular target is a necessary condition; it can be an experimentally solved structure. Models are central for understanding of

Chemistry. Molecular modeling allows us to do and teach chemistry better by providing better tools for investigating, interpreting, explaining and discovering new phenomena.

The term molecular modeling is often used synonymously with the term computational chemistry. Computational chemistry is a broader term, referring to any use of computers to study chemical systems. Some chemists use the term computational quantum chemistry to refer to the use of computers to perform electronic structure calculations, where the electrons in a chemical system are calculated.[1]

The approaches can be classified roughly into two categories: de novo design and docking[2].

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## II. Molecular Docking

In the field of molecular modeling, docking is a method which predicts the preferred orientation of one molecule to a second when bound to each other to form a stable complex. Knowledge of the preferred orientation in turn may be used to predict the strength of association or binding affinity between two molecules using for example scoring functions.

The associations between biologically relevant molecules such as proteins, nucleic acids, carbohydrates, and lipids play a central role in signal transduction.

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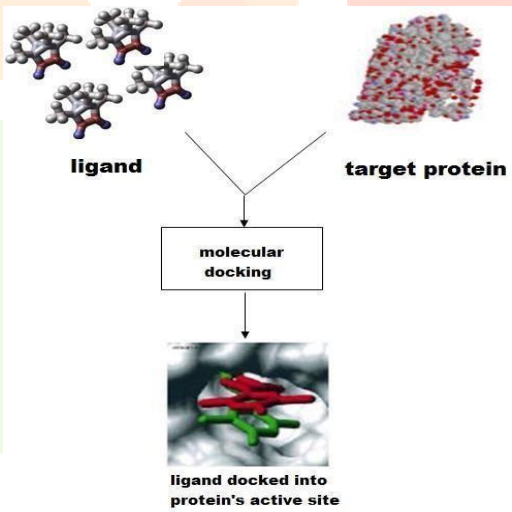



Docking is frequently used to predict the binding orientation of small molecule drug candidates to their protein targets in order to in turn predict the affinity and activity of the small molecule. Hence docking plays an important role in the rational design of drugs. Given the biological and pharmaceutical significance of molecular docking, considerable efforts have been directed towards improving the methods used to predict docking.[4]

Molecular docking can be thought of as a problem of "lock-and- key", where one is interested in finding the correct relative orientation of the "key" which will open up the "lock" (where on the surface of the lock is the key hole, which direction to turn the key after it is inserted, etc.). Here, the protein can be thought of as the "lock" and the ligand can be thought of as a "key". Molecular docking may be defined as an optimization problem, which would describe the "best-fit" orientation of a ligand that binds to a particular protein of interest. However, since both the ligand and the protein are flexible, a "hand-in-glove" analogy is more appropriate than "lock-and-key".5

During the course of the process, the ligand and the protein adjust their conformation to achieve an overall "best-fit" and this kind of conformational adjustments resulting in the overall binding is referred to as "induced-fit".6

## III. Benzimidazole Nucleosides Series

In this regard we have design a series of benzimidazole nucleoside and so designed molecules were then docked with virus proteins and their free energy was calculated which are as follows-

| SR.NO | STRUCTURE | CHEMICAL NAME | Energy level |
|---|---|---|---|
| 1. | | **4-Floro-1-H (β-D-ribofuranosyl) Benzimidazole** | -108.50 |
| 2. | | **4-Chloro-1-H D-ribofuranosyl) Benzimidazole** | -106.98 |
| 3. | | **ıylketon-1-H (β-D- ribofuranosyl) Benzimidazole** | -104.78 |
| 4. | | **4-Monochloromethyl- 1- H(β-D-ribofuranosyl) Benzimidazole** | -103.02 |

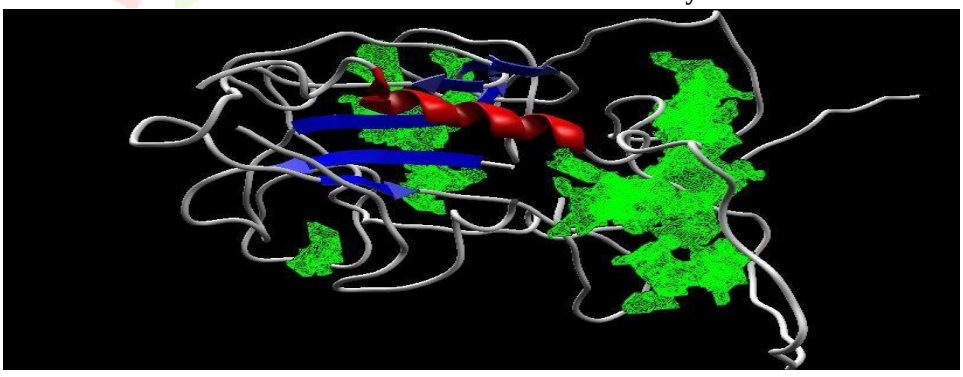
**Table 1: Docking interaction of ligand with MDMV (protein)**

| S.no. | Residue | Hydrogen Bonding | Residue element |
|---|---|---|---|
| 3-m | Lys21 Gln203 Lys20 Glu19 Asn16 Ala17 | 6 | N(7)<br>O(8)<br>N(7)<br>O(8)<br>N(7)<br>O(8) |
| 3-l | Gln203 Lys20 Glu19 Asn16 Ala17 Lys21 | 6 | O(8)<br>N(7)<br>O(8)<br>N(7)<br>O(8)<br>N(7) |
| 3-o | Asn205 Lys14 Asn205 Tyr110 Asn111 Gln203 | 6 | O(8)<br>N(7)<br>N(7)<br>O(8)<br>O(8)<br>N(7) |
| 3-p | Gln203 Asn205 Tyr110 Asn111 Lys14 | 5 | N(7)<br>N(7)<br>O(8)<br>O(8)<br>N(7) |

## V. Materials and Methods

**Protein modeling-** The viral protein was modeled by homology modeling by selecting templates from the PDB data bank through alignment searching. Target sequence was compared with the templates and then structure was modeled with the tool. Five structures were modeled in which the best model was identified with respect to least dope score. The activity sites were identified in the target protein structure as cavities within the tool for docking studies. Protein data bank is a data base which provides 3D structural information of large biological molecules such as protein and nucleic acids. Paymol and Rasmol are computer software which is used for molecular graphics visualization and mainly to depict and explore biological macromolecule structures, such as those found in the PDB (Protein Data Bank).

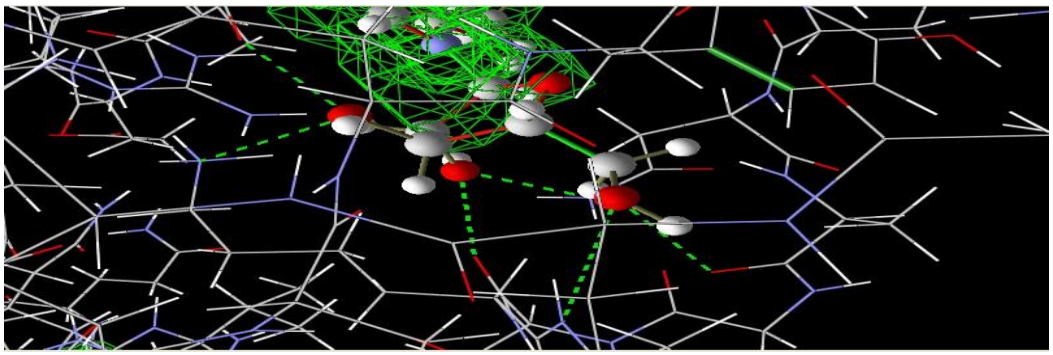
**Protein structure of MDMV with its cavity**



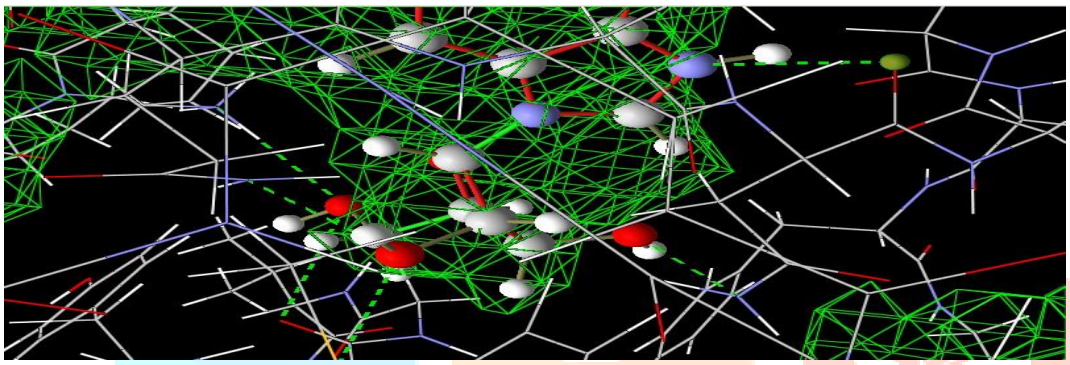
**Ligand designing-** Ligand designing was carried out using Marvin software. Ligand designing study and conformation alignment study of benzimidazole nucleosides were performed in order to understand the biological activity, mechanism of action of antiviral molecule (benzimidazole nucleoside) and mode of action of target (MDMV).

**Molecular docking-** Molecular docking was performed using Molegro Virtual Docker software. Docking studies was performed in order to explore the detailed of interaction between ligand (benzimidazole nucleoside) and target protein of MDMV. Protein structure was imported and the active sites were generated in the target protein of MDMV as cavity. Then ligand was docked within the active site of target protein.

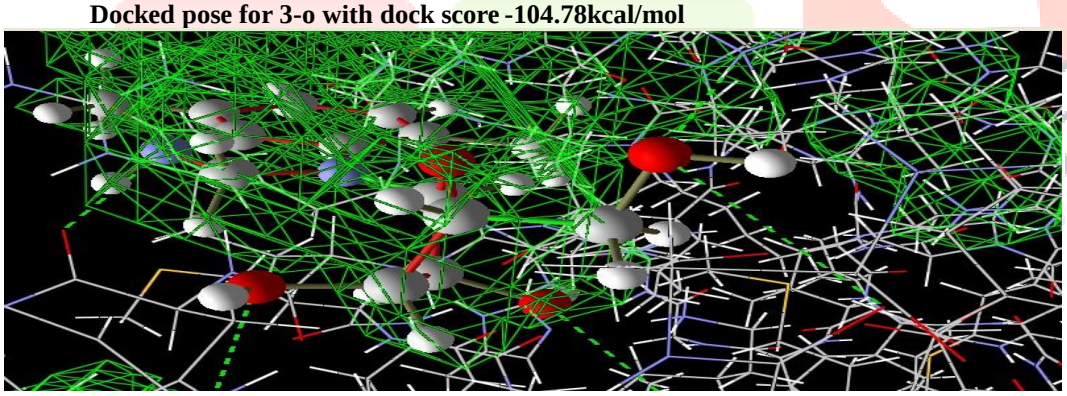
**Docked pose for 3-m with dock score -108.50kcal/mol**



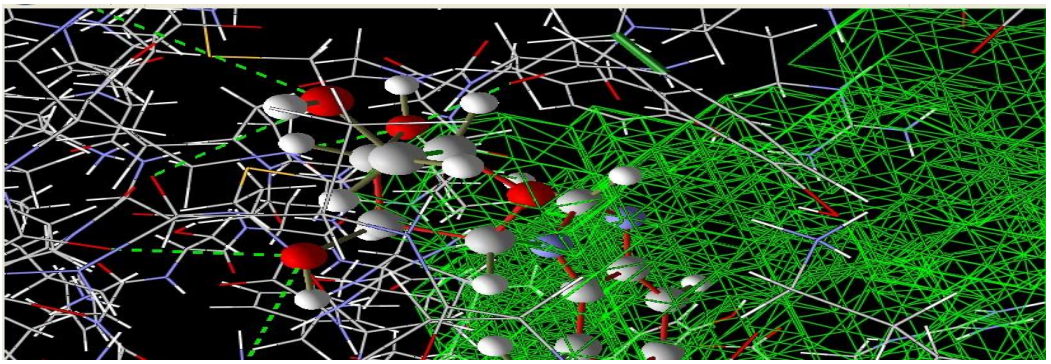
**Docked pose for 3-l with dock score -106.98kcal/mol**



**Docked pose for 3-o with dock score -104.78kcal/mol**



**Docked pose for 3-p with dock score -103.02kcal/mol**



## V. Conclusion

Benzimidazole nucleosides represent a very interesting and promising class of modified nucleosides having a narrow specificity towards viral targets and high potential for further structural modifications. The elucidation of the mechanism of action in in vitro systems and the exact identification of cellular targets will allow researchers to design drugs with high antiviral activity and low systemic toxicity.

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