MOLECULAR MODELING, DOCKING AND ANTIVIRAL STUDIES OF BENZIMIDAZOLE NUCLEOSIDE AS POSSIBLE MDMV INHIBITORS

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Abstract – A series of benzimidazole nucleosides with methyl group was designed and evaluated their antiviral activity against maize dwarf mosaic virus. MDMV was selected as target for analysis as it affect on maize showed low growth in plant and its leaves turn into mosaic pattern. Molecular docking studies were performed on benzimidazole nucleosides in the active site of maize dwarf mosaic virus to study the binding mode analysis of these benzimidazole nucleosides. Results generated from this study indicate that all compound docked into the different site of maize dwarf mosaic virus and showing good docking score. Docking analysis of 2-(hydroxymethyl)-5-(7-methyl-1H-1,3-benzodiazole-1-yl)oxolane-3,4-diol with 7-methyl group at the 7 position 3-m on the aromatic ring showed good antiviral activity with good dock score, however lower than the molecule 2-(hydroxymethyl)-5-(6-methyl-1H-1,3-benzodiazol-1-yl)oxolane-3,4-diol with 6-methyl group at 6 position 3-l and 2-(4,6-dimethyl-1H-1,3-benzodiazol-1-yl)-5-(hydroxymethyl)oxolane-3,4-diol with 4,6-dimethyl group at 4,6 position 3-o.

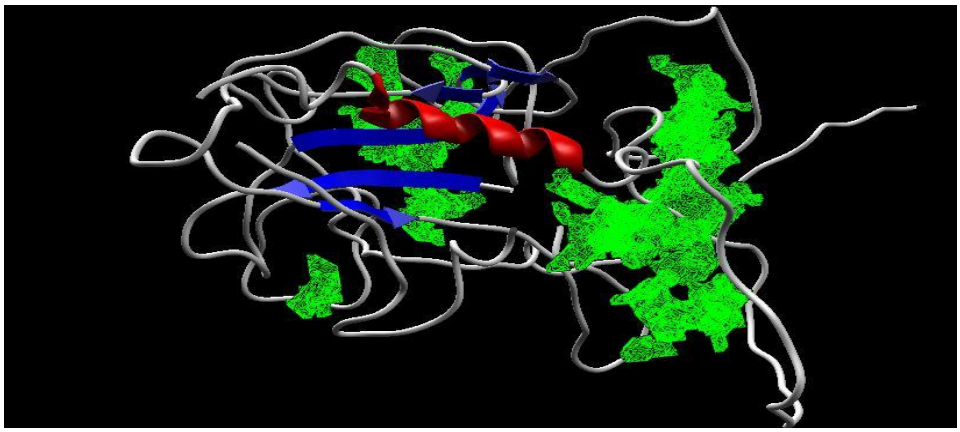
Keywords- Molecular docking; benzimidazole nucleosides; molecular modeling; MDMV.

Introduction- Benzimidazole is an important hetrocyclic aromatic organic compound which is bi-cyclic in nature and play important role in medicinal chemistry (R. Walia et al., 2011). Different derivatives of benzimidazole possessing a variety of pharmaceutical activities such as antiviral (H.C.Gupta et al., 2010, Erik De Clercq et al., 2004), antibacterial (Sivakumar et al., 2006, T S. Chitre et al., 2011), antifungal (Mehendale Nitin P et al., 2012), anticancer (Mohammed Hadi Al Dauh et al.2012), anti-inflammatory (S.M. Sondhi et al., 2002), analgesic (CS Kavitha et al., 2010), antimicrobial (V. Chidambaranathan et al., 2015, Fatmah A. S. Alasmary et al., 2015, Rakhi Rajput et al.,2012), and antidiabetic (Pattan S et al., 2005). Some derivatives of benzimidazole can act as inhibitors for the hepatitis B and C viruses (Mahmoud EIHefnawi et al., 2012,) and as anti HIV agent (A Chimirri et al., 2001, Swastika Ganguly et al., 2013). These biological activities of this compound depend upon the functional group attached on the benzimidazole moiety (Periyasamy Selvam et al., 2010). Maize dwarf mosaic virus is a viral disease of maize. The ability to control virus diseases of plant with chemical would be valuable addition to existing control strategies. In recent time, the major limitation to progress in this field is the difficulty in identifying antiviral chemicals. The requirement of a useful antiviral chemical include ability to inhibit multiplication and spread of virus, be selective enough not to harm the host but have broad spectrum antiviral activity against a number of viral disease. Numerous compounds have been identified which can inhibit the growth of virus. Most inhibitory compounds are nucleosides and their many substituted derivatives. The methyl group plays an important role in the drug designing and most commonly occurring carbon fragments in small molecule drugs. Methyl group can modulate both biological and physical properties of molecule and also improves the metabolic stability (Cheryl S. Leung et al., 2013). 2-methoxycarbonylamino derivatives showed good antiprotozoal activity against some protozoan parasites such as *Giardia lamblia* and *Entamoeba* and 2-methyl and 2-amino benzimidazole derivatives showed antibacterial activity against Gram negative bacteria *Pseudomonas aeruginosa* (Sanja O. Podunavac Kuzmanovic et al., 2009). 2-methyl benzimidazole showed antioxidant activity (Saini et al., 2016). Maize dwarf mosaic virus is a member of Potyviridae family within the genus of Potyvirus and caused by various strains such as A, C, D, E and F. Maize dwarf mosaic virus is closely related to sugarcane mosaic virus (SCMV) (Jinlong Guo et al., 2014), johnsongrass mosaicvirus (JGMV) (D. L. Seifers et al., 2000, M.Tosic et al., 1990), sorghum mosaic virus (SrMV) and zea mosaic virus (ZeMV). Some other viruses have been shown infect to maize such as maize chlorotic mottle virus (MCMV) and maize chlorotic dwarf virus (MCDV) (Maathavi Kannan et al., 2018). Among all the maize infecting viruses MDMV is the most common disease. Symptoms of MDMV disease vary widely depending on virus strain, infection time and host range (MM Jarjees et al., 1983). Significant variation of mosaic pattern may be produced by maize dwarf mosaic virus in corn. Maize plant infected with MDMV initially show chorotic spotting on young leaves as the disease progresses which may eventually turn in to a mottle or mosaic pattern (R.W.Toler et al., 1985). Generally drug design

is a creative science, special technology and a synthesis of scientific knowledge, experience, intuition and aesthetics (Prakash Prajapat et al., 2018). Computer aided drug design is one of these tool which can be used to provide the information for the drug discovery process and also increase the efficiency of drug discovery process (M. Thakur et al., 2012). As per previous study for chloro group and fluoro group against MDMV, the molecule that were identified 2-(5-chloro-1H-1,3-benzodiazol-1-yl)-5-(hydroxymethyl)oxolane-3,4-diol w.r.t to their docking score -107.39 (Arora et al., 2015) and the molecule with fluoro group that were identified 5-(6-fluoro-1H-1,3-benzodiazol-1-yl)-2-(hydroxymethyl)oxolan-3-ol w.r.t to their docking score -103.27 (Deval et al., 2018).

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).

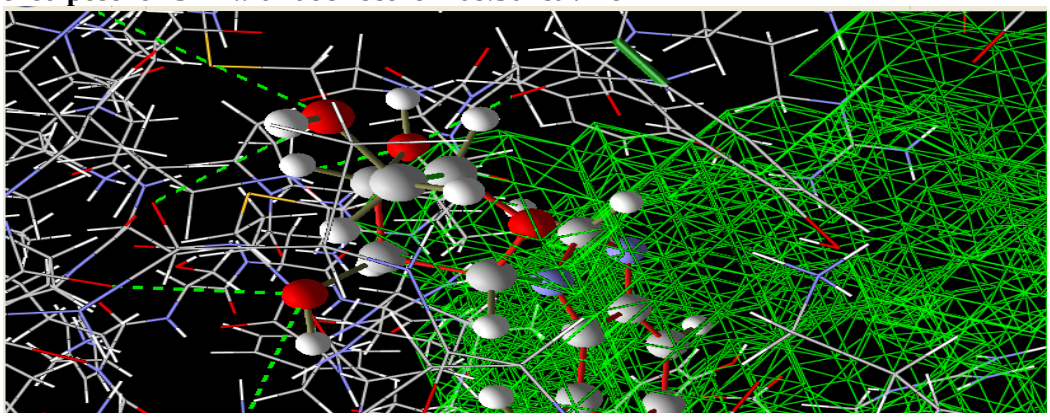


Protein structure of MDMV with its cavity

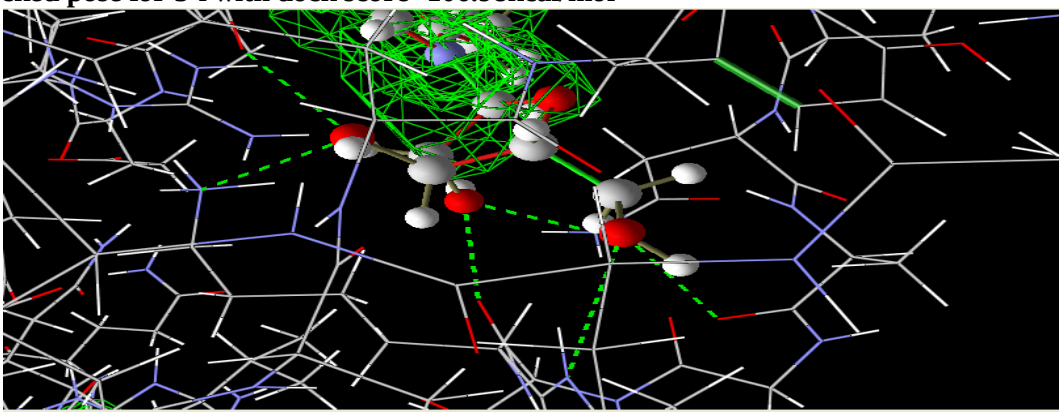
Ligand designing- Ligand designing was carried out using Marvin software. Ligand designing study and conformation alignment study of benzimidazole nucleosides were performed in order to understand the biological activity, mechanism of action of antiviral molecule (benzimidazole nucleoside) and mode of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

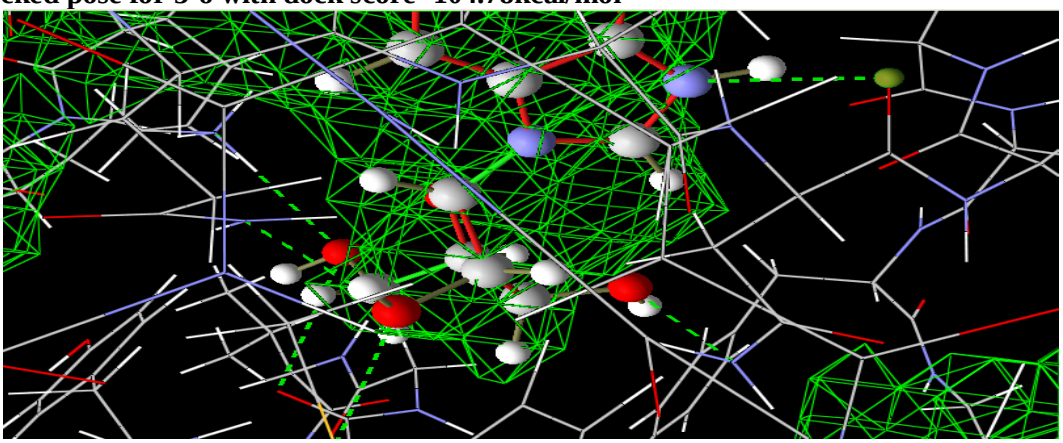
Docked pose for 3-m with dock score -108.50kcal/mol



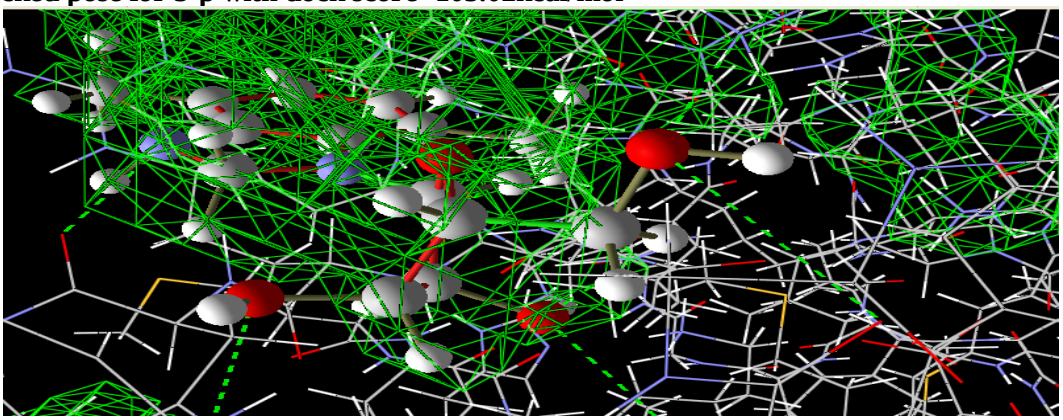
Docked pose for 3-l with dock score -106.98kcal/mol



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

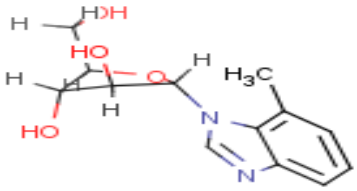
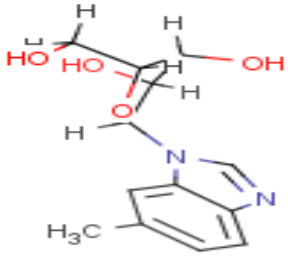
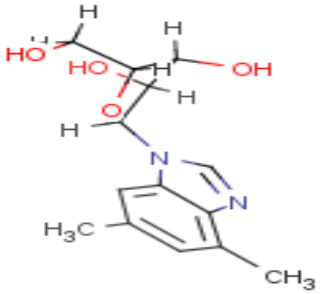
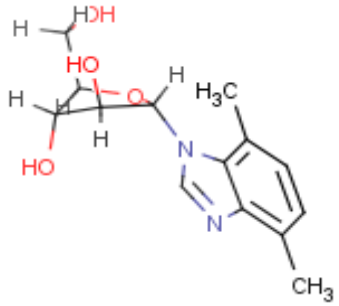
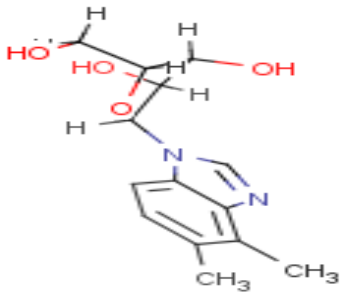
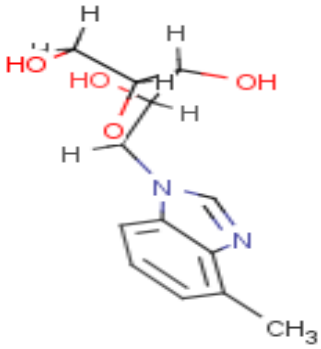


Docked pose for 3-p with dock score -103.02kcal/mol



Result and discussion- Our target molecules were based on benzimidazole nucleosides. We designed a series of benzimidazole nucleosides 3a-3p were used for molecular docking studies on the active sites of protein (MDMV). Among the series of benzimidazole nucleosides, there are two groups of condense carbohydrate molecules were developed i.e one is deoxyribose and other is ribose. It is possible to design the potential MDMV inhibitors by changing the position of methyl group on the aromatic ring of benzimidazole nucleoside. Antiviral activities of benzimidazole nucleosides against MDMV were evaluated by using MVD software. Docking of benzimidazole nucleoside into the active site of protein (MDMV) reveals that some interesting features like benzimidazole nucleoside interact with protein of MDMV through hydrogen bonding. Among the series 3-m and 3-l with methyl group at the position 7 and 6 respectively were found to be most potent which are suitable for predicting for promising antiviral activity. Dock scores and residues involved in docking studies are summarized in table 1 and table 2 respectively.

Table 1: Interaction energy value (kcal/mol) between ligand and protein (MDMV)

	Molecule structure	Molecule name	Dock score kcal/mol
3-m		2-(hydroxymethyl)-5-(7-methyl-1H-1,3-benzodiazol-1-yl)oxolane-3,4-diol	-108.50
3-l		2-(hydroxymethyl)-5-(6-methyl-1H-1,3-benzodiazol-1-yl)oxolane-3,4-diol	-106.98
3-o		2-(4,6-dimethyl-1H-1,3-benzodiazol-1-yl)-5-(hydroxymethyl)oxolane-3,4-diol	-104.78
3-p		2-(4,7-dimethyl-1H-1,3-benzodiazol-1-yl)-5-(hydroxymethyl)oxolane-3,4-diol	-103.06
3-n		2-(4,5-dimethyl-1H-1,3-benzodiazol-1-yl)-5-(hydroxymethyl)oxolane-3,4-diol	-102.29
3-j		2-(hydroxymethyl)-5-(4-methyl-1H-1,3-benzodiazol-1-yl)oxolane-3,4-diol	-101.68

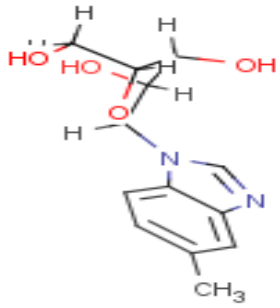
3-k		2-(hydroxymethyl)-5-(5-methyl-1H-1,3-benzodiazol-1-yl)oxolane-3,4-diol	-101.21

Table 2: 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)** **O(8)** **N(7)** **O(8)** **N(7)** **O(8)**
3-l	**Gln203** **Lys20** **Glu19** **Asn16** **Ala17** **Lys21**	**6**	**O(8)** **N(7)** **O(8)** **N(7)** **O(8)** **N(7)**
3-o	**Asn205** **Lys14** **Asn205** **Tyr110** **Asn111** **Gln203**	**6**	**O(8)** **N(7)** **N(7)** **O(8)** **O(8)** **N(7)**
3-p	**Gln203** **Asn205** **Tyr110** **Asn111** **Lys14**	**5**	**N(7)** **N(7)** **O(8)** **O(8)** **N(7)**
3-n	**Asn205** **Tyr110** **Asn111** **Gln203** **Asn205**	**5**	**N(7)** **O(8)** **O(8)** **N(7)** **O(8)**

Conclusion- Aim of this study is to design a series 3a-3p of benzimidazole nucleosides with methyl group for better antiviral activity against MDMV along with to correlate antiviral of designed methyl benzimidazole nucleoside with respect to subsequent change in position of methyl group and to identified which could show better antiviral activity. In the present study benzimidazole nucleoside was successfully docked into the active site of target protein (MDMV) for drug interaction study to have a track in the ongoing race between drug development and new agrichemicals especially new compound which are more important for the discovery of new hits using molecular methods. The molecule 2-(hydroxymethyl)-5-(7-methyl-1H-1,3-benzodiazol-1-yl)oxolane-3,4-diol with methyl group 3-m at 7 position on the aromatic ring was found to be most potent having binding energy -108.50kcal/mol. The results of the *in silico* studies reveal that the molecule is potential candidate for lower inhibitor for maize dwarf mosaic virus which calls for wet lab trials.

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