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Original Research Paper

Chemistry

MOLECULAR MODELING AND DOCKING STUDIES OF BENZIMIDAZOLE NUCLEOSIDES WITH FLUORO GROUP AS MDMV INHIBITOR

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ABSTRACT A series of benzimidazole nucleosides with fluoro group was designed and screened for their antiviral activity against maize dwarf mosaic virus. In the present work docking analysis of Antiviral Benzimidazole nucleosides were performed to understand the structural features responsible for their potent antiviral activity against MDMV. MDMV was selected as target for analysis as it affect on maize plant causing low growth in plant and its leaves showed mosaic pattern. Docking of benzimidazole nucleoside (5-(6-fluoro-1H-1,3-benzodiazol-1-yl)-2-(hydroxymethyl)oxolan-3-ol) with MDMV showed hydrogen bond interactions with GLU19, ALA17, ASN16. Docking analysis of 5-(6-fluoro-1H-1,3-benzodiazol-1-yl)-2-(hydroxymethyl)oxolan-3-ol with 6-fluoro group 1-d on the aromatic ring showed good antiviral activity with good dock score, however, lower than the molecule, 2-(4-fluoro-1H-1,3-benzodiazol-1-yl)-5-(hydroxymethyl)oxolane-3,4-diol with 4-fluoro group 1-g and 2-(5-fluoro-1H-1,3-benzodiazol-1-yl)-5-(hydroxymethyl)oxolane-3,4-diol with 5-fluoro group 1-h.

KEYWORDS : Amolecular Modeling; Molecular Docking; Benzimidazole Nucleosides; Mdmv.

Introduction:

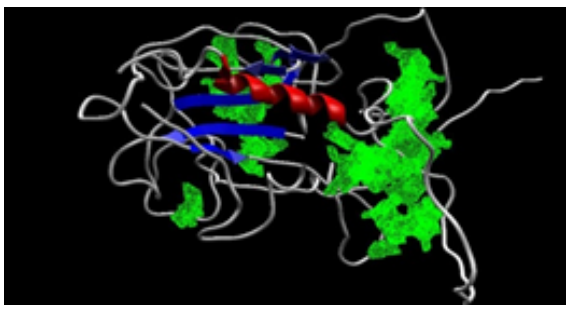
In recent year the synthesis of benzimidazole[1] and its derivative has attracted the attention of many organic chemists because of its broad spectrum biological activity. The ability to control virus diseases of plants with chemicals would be valuable addition to existing control strategies. In recent 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 inhabit multiplication and spread of virus, be selective enough not to harm the host but have broad spectrum antiviral activity against a number of virus diseases. Numerous compounds have been identified which can inhabit the growth of virus. Most inhibitory compounds are nucleosides and their many substituted derivatives. Benzimidazoles are pharmaceutical agent possessing a variety of biological such as antiviral[2,3], antifungal[4], antimicrobial[5,6], and antibacterial[7,8]. Some derivatives of benzimidazole can act as anti HIV agent[9], [10] and anticancer agent[11] and as inhibitors for the hepatitis B and C viruses[12]. Some benzimidazoles were also tested as anti inflammatory[13] and analgesic activity[14]. Several benzimidazole nucleosides with fluoro group showed antiviral activity against MDMV. Biologically synthesized organo fluorines have been found in microorganisms and plants, but not animals[15].Insertion of fluorine atom(s) in to the molecule of heterocyclic compounds leads is a significant increase in biological activity. The fluoro and difluoro benzimidazoles are component parts of modified nucleosides [16]. The man made carbon fluorine bonds are commonly found pharmaceuticals and agrichemicals, because it adds stability to the carbon frame work, also, the relatively small size of fluorine is convenient as fluorine acts as an approximate bioisosteares of the hydroxyl group[17]. Introducing the carbon fluorine bond to organic compounds is the major challenge for medicinal chemists using organo fluorine chemistry, as the carbon fluorine bond increases the probability of having successful drug by about a factor of ten[18]. An estimated 20% of pharmaceuticals and 30-40% agrichemicals are organo fluorines, including several of the top drugs. Maize dwarf mosaic virus is a member of genus Potyvirus in the family Potyviridae and caused by various strains of the Maize dwarf mosaic virus. MDMV is closely related to Sugarcane mosaic virus (SCMV) [19] which is caused by strain B and Johnsongrass mosaic virus (J GMV) [20,21] Sorghum mosaic virus (SrMV), Zea mosaic virus (ZeMV). Symptoms of maize dwarf mosaic virus disease vary widely depending on virus strain, host range and infection time [22]. Generally, maize plant infected with MDMV show chlorotic spotting on young leaves which may eventually turn in to a mosaic or mottle pattern [23]. Computer aided drug design is one of these tools which can be used increase the speed and efficiency of drug discovery process[24]

. As per previous study for chloro 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. Simultaneously the molecule of fluoro group were docked with the protein molecule of MDMV so that the nobel drug molecule can be analysed in the ascending order of dock score Arora et al., 2015.

Materials and methods- Protein modeling-

The modeling of viral protein is done by homology modeling by selecting templates from the PDB databank 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. Pymol and Rasmol are computer software which is used for molecular graphics visualization and mainly to depict and explore biological mecromolecule structures, such as those found in the PDB (Protein Data Bank).

Protein structure of MDMV with its cavities

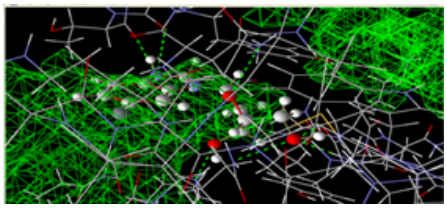


Ligand designing- Ligand designing was performed using Marvin software. Ligand designing study and confirmation alignment studies of benzimidazole nucleosides were performed in order to understand the biological activity, mechanism of actions of antiviral molecule (benzimidazole nucleoside) and mode of interaction with target (MDMV).

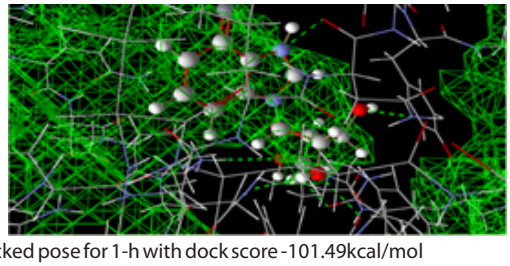
Molecular docking- Molecular docking was performed using Molegro Virtual Docker software. Docking studies were performed

in order to investigate the detailed of interaction between benzimidazole nucleosides (ligand) and target protein of MDMV. Protein structure was imported and the active sites were generated in the target protein of MDMV as cavities. Then ligand was docked within the target protein (MDMV) active site. Docking studies of benzimidazole nucleosides showed hydrogen bond interaction as GLU19, ALA17, ASN16.

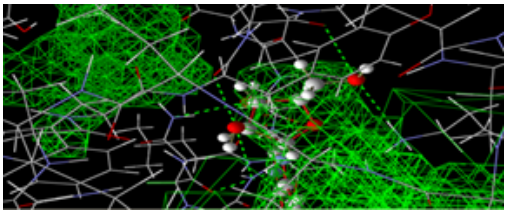
Docked pose for 1-d with dock score -103.27kcal/mal.



Docked pose for 1-g with dock score -101.59kcal/mol.



Docked pose for 1-h with dock score -101.49kcal/mol



Result - A series of benzimidazole nucleosides 1a-1j designed by us were used for molecular docking studies on the active sites of protein (MDMV). We report our results from a study of changing the position of fluoro group on the aromatic ring of benzimidazole nucleoside. Dock score are summarized in table 1. Residues involved in docking studied are given in table 2

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

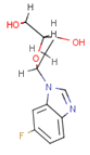
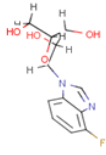
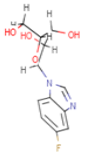
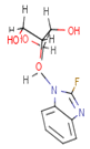
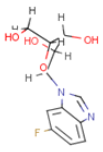
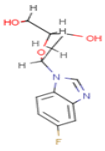
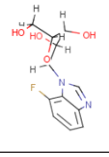
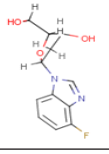
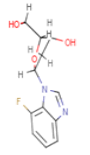
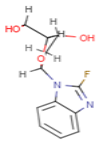
	Molecule structure	Molecule name	Dock score (kcal/mol)
1-d		5-(6-fluoro-1H-1,3-benzodiazol-1-yl)-2-(hydroxymethyl)oxolan-3-ol	-103.27
1-g		2-(4-fluoro-1H-1,3-benzodiazol-1-yl)-5-(hydroxymethyl)oxolane-3,4-diol	-101.59
1-h		2-(5-fluoro-1H-1,3-benzodiazol-1-yl)-5-(hydroxymethyl)oxolane-3,4-diol	-101.59
1-f		2-(2-fluoro-1H-1,3-benzodiazol-1-yl)-5-(hydroxymethyl)oxolane-3,4-diol	-98.42
1-i		2-(6-fluoro-1H-1,3-benzodiazol-1-yl)-5-(hydroxymethyl)oxolane-3,4-diol	-97.64
1-c		5-(5-fluoro-1H-1,3-benzodiazol-1-yl)-2-(hydroxymethyl)oxolan-3-ol	-96.24
1-j		2-(7-fluoro-1H-1,3-benzodiazol-1-yl)-5-(hydroxymethyl)oxolane-3,4-diol	-95.94
1-b		5-(4-fluoro-1H-1,3-benzodiazol-1-yl)-2-(hydroxymethyl)oxolan-3-ol	-93.82
1-e		5-(7-fluoro-1H-1,3-benzodiazol-1-yl)-2-(hydroxymethyl)oxolan-3-ol	-92.95
1-a		5-(2-fluoro-1H-1,3-benzodiazol-1-yl)-2-(hydroxymethyl)oxolan-3-ol	-89.25

Table 2: Docking interaction of ligand with MDMV

S. no.	Residue	HB	Residue element	Bond length	Bond energy
1-d	Glu19 Ala17 Asn16	3	O(8) O(8) N(7)	3.00316 3.15281 3.04893	2.5 2.2 2.4
1-g	Asn205 Asn205 Tyr110 Asn111 Gln203 Lys14	6	O(8) N(7) O(8) O(8) N(7) N(7)	3.29767 3.34623 2.72468 2.95625 3.00632 3.08842	1.5 1.2 2.5 2.5 2.1 0.2
1-h	Gln203 Glu188 Arg204 Arg204 Arg204	5	O(8) O(8) N(7 N(7) N(7)	2.66332 2.87902 3.1952 3.09134 2.72777	2.2 2.5 2.0 2.5 2.5

Discussion- In this paper, the antiviral activities of benzimidazole nucleosides against MDMV were investigated. A series of benzimidazole nucleosides were designed and antiviral activity of benzimidazole nucleoside against MDMV was evaluated by using

MVD software. Docking of benzimidazole nucleoside in to the active site of protein (MDMV) reveals that some interesting facts like benzimidazole nucleoside interact with MDMV through hydrogen bonding and vander Waal's interaction. Among the series 1-d and 1-g were found to be most potent which are suitable for synthesis predicting for promising antiviral activity.

Conclusion-

The objective of this study is to design fluoro benzimidazole nucleosides and their derivative using structure activity relationship of similar literature molecules for better antiviral activity against MDMV along with to correlate antiviral of designed fluoro benzimidazole derivatives with respect to subsequent change in position of fluoro group and to identify which could show better antiviral activity. The molecule 5-(6-fluoro-1H-1,3-benzodiazol-1-yl)-2-(hydroxymethyl)oxolan-3-ol with 6-fluoro group 1-d on the aromatic ring was found to be most potent having binding energy -103.27 kcal/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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