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MOLECULAR DOCKING STUDY OF ACYCLOVIR AND ITS DERIVATIVES AS POTENT INHIBITORS IN NOVEL COVID-19

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ABSTRACT: Novel coronavirus (nCovid-19) is a recent emerging, dangerous pathogen that has shaken the whole world. Present therapeutic strategies to deals with this infectious disease are only supportive. The discovery of a new drug within a short period of time is a great task. Structure predictions of several proteins associated with SARS-CoV-2, the virus that causes COVID-19, was made possible by Genomics. Docking is a computational method used in present days to identify a hit molecule by measuring the binding ability of molecular drugs within the binding pocket of the macromolecular target. In this study, we have selected five ligand molecules which are currently used as antiviral agents. The drugs selected are, namely, Acyclovir, Ganciclovir, Penciclovir, Valaciclovir, and deoxyguanosine. The protein with PDB id 6LU7 was retrieved from the protein data bank for the docking procedure. The 2D plot of interactions was obtained using discovery studio visualizer software, and energy calculations were done by summing up van der Waals, electrostatic, and Hydrogen bonding interactions. Acyclovir and its derivatives are found to be potential against nCovid-19 through molecular docking studies using iGEMDOCK. The scores obtained from the computational analysis indicated the best result for the antiviral drug, Ganciclovir, with a docking score of -96.21Kcal/mol.

INTRODUCTION: Novel Coronavirus (nCov-19) is a recent emerging deadly pathogen that originated in the city of Wuhan in china's Hubei Province. The symptoms of this disease are fever, severe respiratory illness, and Pneumonia [1]. The emerging virus is a new member of the beta coronavirus genus, which is closely related to SARS Coronavirus [2].

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Compared with the SARS Coronavirus, this nCov-19 virus is transmitted from human to human [3] though contact, and it is not an airborne disease.

Coronaviruses are classified into four subfamilies. They are alpha, beta, gamma and delta [4]. Alpha and beta coronaviruses originated from mammals like bats and gamma and delta originated from pigs and birds [5]. According to World Health Organization (WHO), as of 4th April 2020, there had been more than 1,118,562 cases around the world. The approximately death cases exceeded 1 lakh. Now discovery of new drug that can fight against Corona virus and rapid test for the early detection of corona affected patients is gaining much importance.

The conventional method of development of a new drug is done by *in-vitro* and *in-vivo* screening by trial and error method is a lengthy procedure to identify a hit molecule. Tools available in Bioinformatics and computational chemistry can be used for the identification of proper target and hit molecules, respectively. The challenge and threat posed by the growing pandemic of COVID-19, the Corona Virus can be abruptly stopped only by the discovery of a potent drug. Till now, there is no medicine for nCov-19. In the current work, we are repurposing the currently used antiviral agents in nCov-19, using molecular docking studies. Acyclovir is an antiviral drug which is a synthetic nucleoside analog used against the herpes virus, including Varicella-Zoster, Epstein-Barr virus [6], herpes simplex 1 and 2. Penciclovir is a guanosine analog that has antiviral action against various herpes infections [7]. Ganciclovir is also an antiviral medication that is used to treat cytomegalovirus infections [8]. Valaciclovir is used to treat outbreaks of herpes simplex or herpes zoster [9]. Deoxyguanosine is an antiretroviral agent. It inhibits viral DNA growth. For fast screening of the action of drugs, it is a usual practice to use a computation tool and do the *in-silico* analysis rather than moving directly into the *in-vitro* and *in-vivo* screening. Using a Molecular docking study, the binding affinity can be found out, and various binding interactions can be analyzed.

Structure of Ligands:

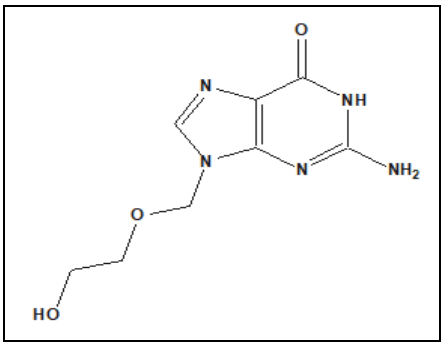

FIG. 1: ACYCLOVIR

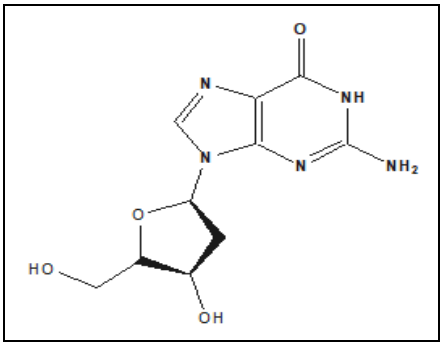

FIG. 2: DEOXYGUANOSINE

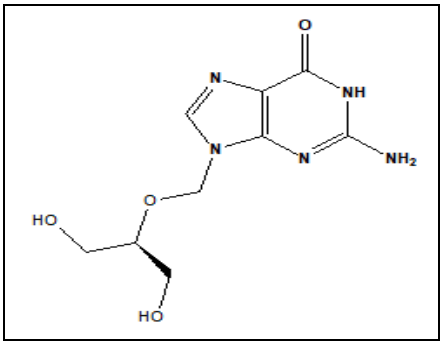

FIG. 3: GANCICLOVIR

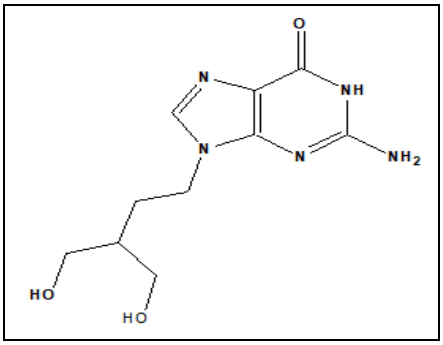

FIG. 4: PENCICLOVIR

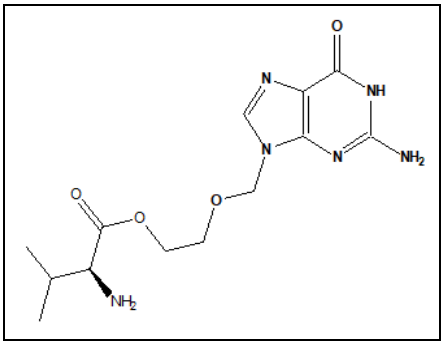

FIG. 5: VALACICLOVIR

Objective of Research: To study the binding affinity and binding interaction of Acyclovir and its derivatives which is currently used as antiviral agents with the molecular docking software iGEMDOCK.

MATERIALS AND METHODS:

Protein Data Bank: For the Molecular docking study, the structure of the protein that has to be inhibited is selected and retrieved from the Protein Data Bank. Thus the protein, having PDB ID: 6LU7, was retrieved. Docking studies were performed to determine the best pose of the protein-ligand binding interaction. It was done using iGEMDOCK v.2.1 program (Generic Evolutionary Method for Molecular Docking). It is a graphical-automatic drug design system for docking, screening and post analysis [10].

Structure Drawing Software: The Marvin sketch v5.3 was used for drawing 2D structures of the compounds. The geometry of the 2D structure was obtained by cleaning and saved as pdb format.

Visualizing software: Discovery studio visualizer 4.0 is a free viewer software. The Discovery studio visualizer gives functionality for visualizing and analyzing biological as well as chemical data. After the post-analysis, the 2D plot interaction diagram can be visualized.

Docking Procedure: All docking processes were carried out in Windows 7 software. The Novel covid-19 protein was downloaded from protein data bank with protein id: 6LU7 with resolution 2.16 A°. The water molecules were deleted, and the binding sites at $8A^{0}$ were identified. After loading the proteins and ligands, the output path was set. For docking, the standard docking parameters were used. Population size = 200, generations = 70 and number of solutions=2. Mod_ leg is a programme used to generate ligand list depending on user-selected ligands. Mod_ ga is used for the docking/ screening module. After the docking process, the best poses can be obtained and visualized using Discovery studio visualizer 4.0. The interaction data obtained includes summarized energy and individual energy terms. Fitness is the total energy of a predicted pose in the binding site. The total energy, van der Waals interactions (vdW), Hydrogen bonding (H-Bond), and Electrostatic interactions [11] (Elec) can also be obtained from the software. The Empirical scoring function of iGEMDOCK is estimated according to the equation;

$$\text{Fitness} = \text{vdW} + \text{HBond} + \text{Elec}$$

RESULTS AND DISCUSSION:

TABLE 1: DOCKING RESULTS OF ACYCLOVIR AND ITS DERIVATIVES

Ligand Name	Energy(kcl/mol)	VDW(kcl/mol)	HBond(kcl/mol)	Elec(kcl/mol)
Ganciclovir	-96.21	-56.56	-39.66	0
Deoxyguanosine	-93.19	-62.51	-30.68	0
Acyclovir	-89.64	-51.02	-38.62	0
Penciclovir	-89.64	-53.36	-36.28	0
Valaciclovir	-89.59	-47.97	-41.62	0

TABLE 2: COMMON TYPES OF H-BOND AND ELECTROSTATIC INTERACTIONS BETWEEN PROTEIN STRUCTURE WITH THE SELECTED LIGANDS

Ligand Name	Bond	Interaction of Amino acid residue
Ganciclovir	Hydrogen bonding	GLU A:166, SER A:144, CYS A:145
	Electrostatic interaction	ASN A:142
Deoxyguanosine	Hydrogen bonding	GLU A:166, SER A:144, HIS A: 163, CYS A: 145
Acyclovir	Hydrogen bonding	SER A:144, ASN A:142, GLY A:143, THR A:26
Penciclovir	Hydrogen bonding	GLU A:166, CYS A:145, MET A:165, HIS A:164, HIS A:163, SER A:144, LEU A:141
Valaciclovir	Hydrogen bonding	LYS A: 137, ARG A:131, GLU A:290, GLY A:127
	Electrostatic interaction	LYA A:5

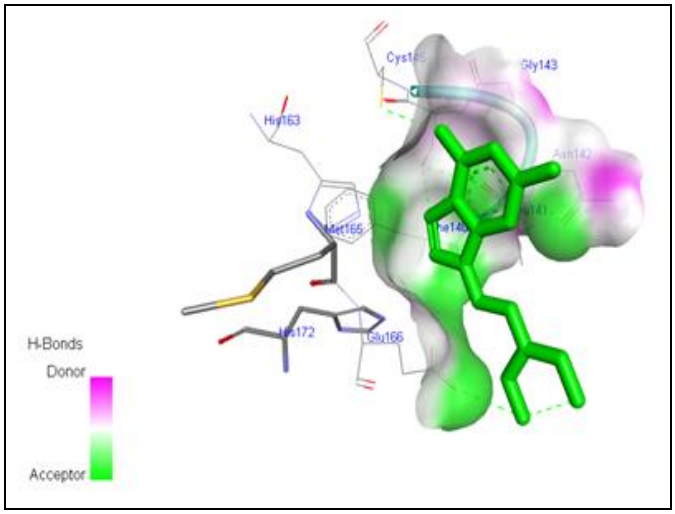

FIG. 6: DOCKING IMAGES OF GANCICLOVIR

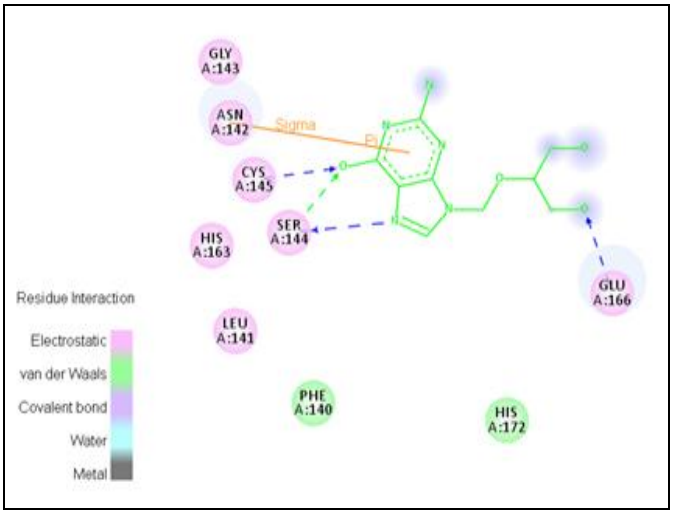

FIG. 7: 2D PLOT DIAGRAM OF GANCICLOVIR

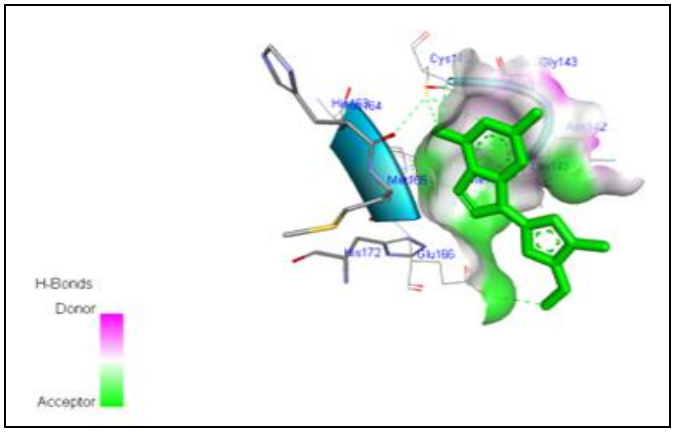

FIG. 8: DOCKING IMAGES OF DEOXYGUANOSINE

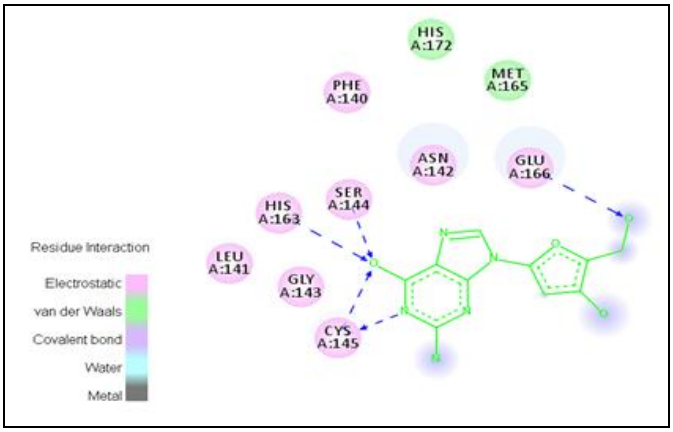

FIG. 9: 2D PLOT DIAGRAM OF DEOXYGUANOSINE

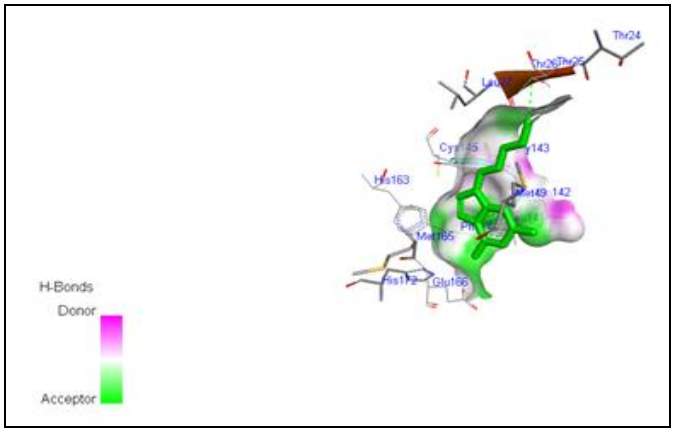

FIG. 10: DOCKING IMAGES OF ACYCLOVIR

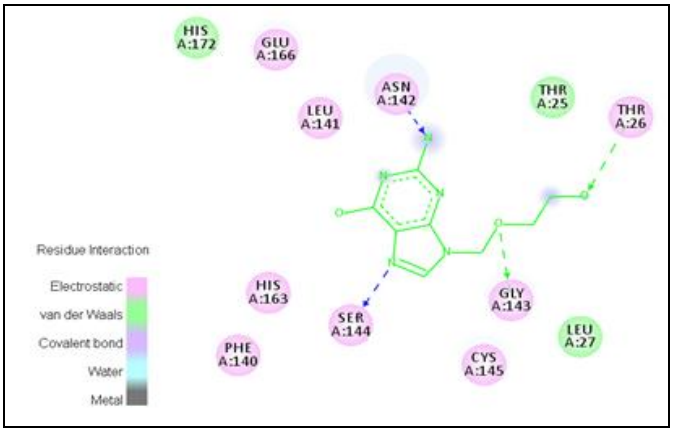

FIG. 11: 2D PLOT DIAGRAM OF ACYCLOVIR

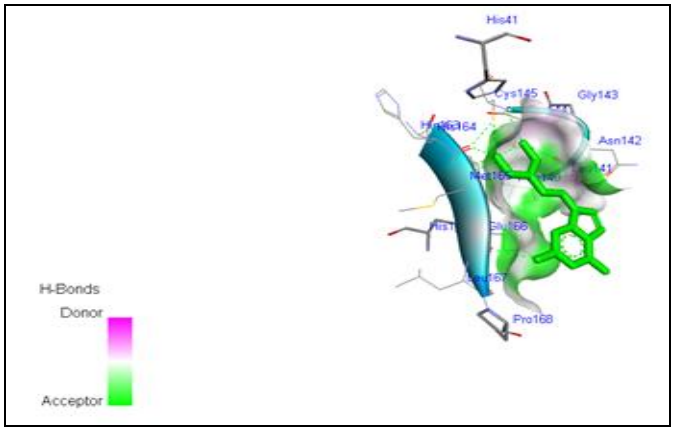

FIG. 12: DOCKING IMAGES OF PENCICLOVIR

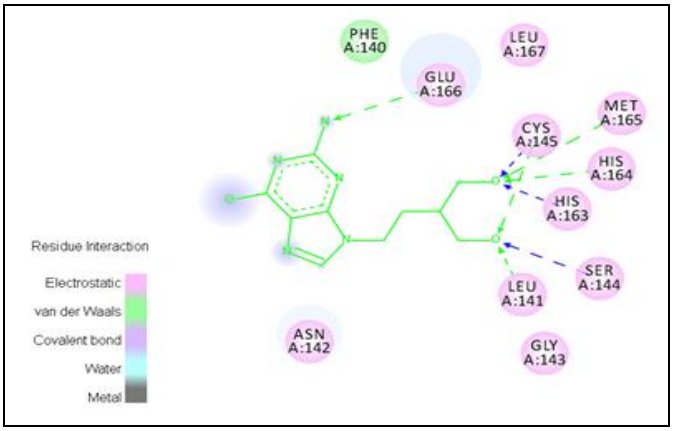

FIG. 13: 2D PLOT DIAGRAM OF PENCICLOVIR

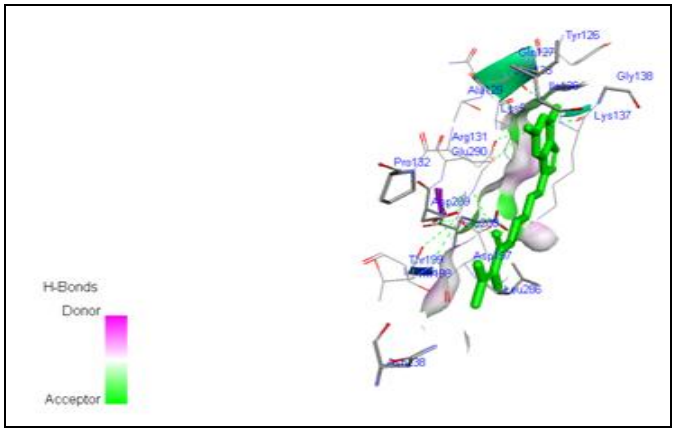

FIG. 14: DOCKING IMAGES OF VALACICLOVIR

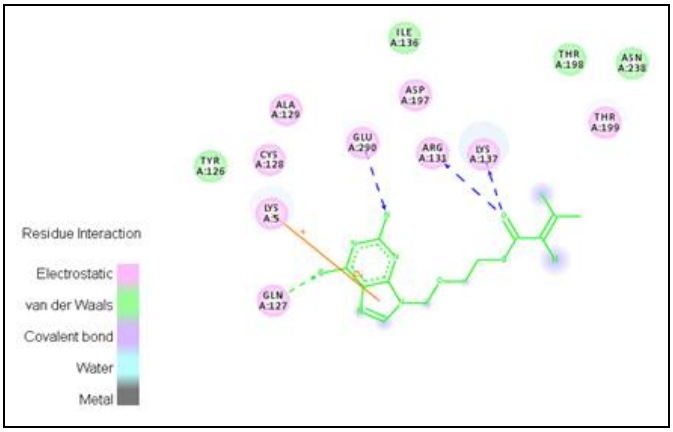

FIG. 15: 2D PLOT DIAGRAM OF VALACICLOVIR

Critical role during the disease propagation is played by mainly the Proteases of the novel Coronavirus, and hence it represents one of the crucial targets for drug discovery. The main protease domain (Mpro) has been reported to be a conserved target in favour of designing new inhibitors throughout the entire coronavirinae subfamily.

The docking results **Table 1** with Main proteases as the target, with all the five drugs, namely Acyclovir, Ganciclovir, Penciclovir, Valaciclovir and Deoxyguanosine, are shown. The maximum negative energy value indicates maximum interaction, and thus the activity of the drug is very high. It was observed that the drug Ganciclovir got a maximum negative docking score of -96.21 Kcal/mol, indicating this as the best of the five drugs *in-silico* screening procedure. The Deoxyguanosine also gave a good docking score of -93.19Kcal/mol. Acyclovir and Penciclovir had almost the same docking score of -89.64 Kcal/mol. The lowest docking score, -89.59 Kcal/mol, was given by the drug Valaciclovir. The best drug among the five derivatives is Ganciclovir, which exhibited effective interactions with amino acid residues like GLU A: 166, SER A: 144, CYS A: 145, ASN A: 14 through hydrogen bonding and van der Waals interactions. The drug Deoxyguanosine also had good interactions with amino acid residues, GLU A:166, SER A:144, HIS A:163, CYS A:145, and the drug Acyclovir had interactions with amino acids, ASN A:142, THR A:26, GLY A:143, SER A:144.

The drug Penciclovir also gave good amino acid interactions with LEU A: 141, SER A: 144, HIS A: 163, HIS A: 164, MET A: 165, CYS A: 145. The amino acids which interacted with the drug, Valaciclovir are LYS A: 5, GLU A: 290, ASG A: 131, and LYS A: 137. The evaluation of the hydrogen bond formed between the antiviral drug Acyclovir and its derivatives with the binding pocket of protein 6LU7 active site was then evaluated. It was found that most of the ligands showed hydrogen bond formation with SER A: 144, GLU A: 166, and CYS A: 145 amino acids. The 2D plot exhibiting various interactions are given in different color codes. The hydrogen bonding and Electrostatic interactions are depicted in **Table 2**.

CONCLUSION: On the basis of Molecular docking studies with iGEMDOCK, it was concluded that the above-mentioned ligands showed a higher negative energy score indicating a good binding affinity towards the target molecule. Among them, the Acyclovir derivative, Ganciclovir exhibited effective binding interactions with good docking scores. Deoxyguanosine also gave a better docking score.

The scores of all the drugs are comparable, indicating that these molecules can act as the best hit against the Main protease domain, which is the target of COVID-19. The molecular docking study of Acyclovir derivatives with the main protease revealed that Acyclovir and its derivatives are having good interaction in a favourable pose with the main protease, which was explained by the lowest binding energy. Thus, with the help of docking studies, the most active structures of the compounds may be designed with less time consumption and cost.

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CONFLICTS OF INTEREST: In this research article, there is no conflict of interest.

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