https://doi.org/10.46344/JBINO.2022.v11i04.12

IN-SILICO ACTIVITY OF WARFARIN, CAFFEINE AND ETISOMICIN AS INHIBITORS OF HEPATITIS C VIRUS NS5B POLYMERASE

Iqra Aziz, Atika Yousaf, Syed Bilal Hussain, Muhammad Imran Qadir*

Institute of Molecular Biology and Biotechnology, Bahauddin Zakariya University, Multan, Pakistan

Email Id : mrimranqadir@hotmail.com

ABSTRACT

Objective: Hepatitis C (HCV) is a contagious disease and recent treatments confirm the requirement for new HCV drugs. Many artificial analogues targeting 'HCV serine protease' and 'RNA-based RNA polymerase' arrived early in the clinic. The experimental data included warfarin and other analogues to evaluate a distinct inhibitor of the HCV NS5B RdRp polymerase. The purpose of the study was to find an inhibitor of such proteins.**Method:** Warfarin and other analogues are included in the NS5B receiver using Auto vina dock software. In the dock calculation they provide the correlation and RMSD values.**Result:** In total 3 compounds were incorporated and gave consistency values between -6.8 to -7.6 (kcal / mol) respectively.**Conclusion:** From the docking study of the 3 compounds, a few of them have shown excellent affinity for receptors and therefore, can be considered for further studies.

Key Words: NS5B polymerase, warfarin, Anti-HCV, Caffeine, Etisomicin, virtual screening

INTRODUCTION

Visual examination of composite libraries has been commonplace since the discovery of contemporary medications. The development of a suitable molecule of targeted cellular fishing molecules allows researchers to discern between binding and non-binding bonds to huge chemical reserves while also reducing the number of compounds that must be tested.[1] During the visual test, the primary site of each molecule is identified and scored points using the same point-finding function that was used to calculate the prediction mode binding. [2] A specified number of compounds are chosen for testing in the tests at the end of the test process. Docking is therefore a visual and auditing technique that uses poorly structured and positive chemicals on a location that binds protein to negative and low score points. A huge number of active chemicals are likely to be concentrated in the component of high-scoring computers.[3]

Hepatitis C virus nonstructural protein (NS5B) is a viral protein discovered in the virus (HCV). It increases the polymerization of ribonucleoside triphosphates (rNTP) during RNA replication and has the critical function of reproducing the RNA of the HCV virus utilising a viral positive RNA fibre as a model. Based on the identical sequence of BK, multiple crystalline structures of NS5B polymerase in various crystalline forms have been determined (HCV-BK, genotype 1). The right hand, with its fingers, palm, and thumb, can depict the structure. The protein's palm structure contains the active surrounding environment, which is different from NS5B.[4-7]

An effort was made to develop warfarin and a few other compounds as well as to study the inhibitory effect of molecules in order to detect potential NS5B inhibitors. The research results are reported here.

MATERIALS AND METHODS

Materials

In the present study, various biological sites, bioinformatics tools and software were used. The software used and the tools are presented in Table 1.

Table 1: Software used for the study

Software	Utility
Discovery Studio 4.1	For refine the protein, removing ligand from protein and for modification
AutoDockTools-1.5.6	2D structure of ligand, generate 3D modles
Auto dock vina	Docking software
PyMOL	For open ligand, for interaction of protein and ligand
MedChem_Designer 3.0	For ADMET properties

Method

Structural Assessment of the Protein

By using the Discovery Studio, remove the ligand from the structure of protein NS5B. In this study, protein acts as a receptor. Make the grid box of protein and set the dimensions of(x, y and z). Note the (x, y and z) centers then put the values in conf file of vina.

Docking

Docking allows screening a database of compounds and calculating the strongest binders based totally on various capabilities. It explores ways in which two

molecules, inclusive of pills and an enzyme it together and to every other properly. The molecule may also bind to the receptor and alter their function. The interplay of drug and receptor complex turned into identified via docking and their relative stabilities have been evaluated with the aid of autodock_vina and evaluated their binding affinities.

in this look at, NS5B as receptor and caffeine, warfarin, etisomicin, have been taken as ligands. Docking examine was achieved between receptor and ligands by using the Autodock_vina. The structure of NS5B changed into taken by the protein data bank. All water molecules and ligand were removed from the receptor for docking research. The systems of the molecules under research had been sketched using the PyMOL.

The visualization and evaluation of the protein shape became made and the docking evaluation of the proposed compounds with receptor performed by way of docking software Autodock_vina.

Ligands

By using the discovery studio open the ligand and modify them.

In warfarin O1 changed with C1, O2 changed with N2 and O4 changed with H4 as shown in figure 1. Then set the number of torsions in the ligand.

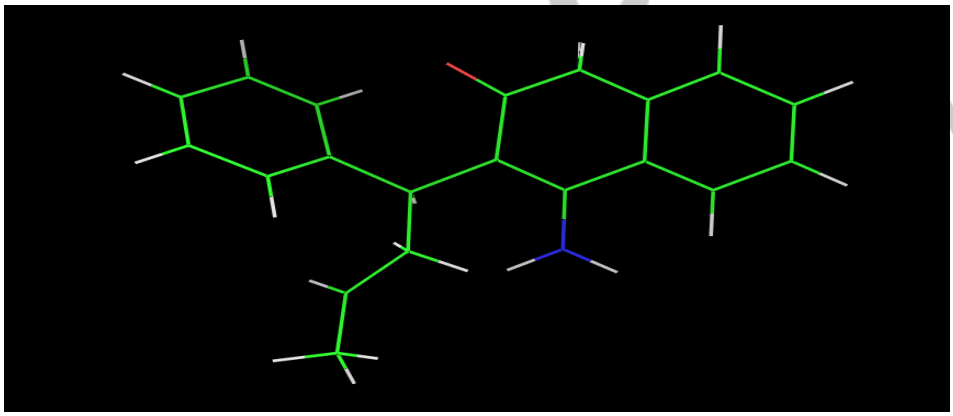


Fig 1: Modified ligand 1.

In Etisomicin O7 changed with C7, O1 changed with C1 and O5 changed with N5 as shown in fig 2. Then set the number of torsions in the ligand.

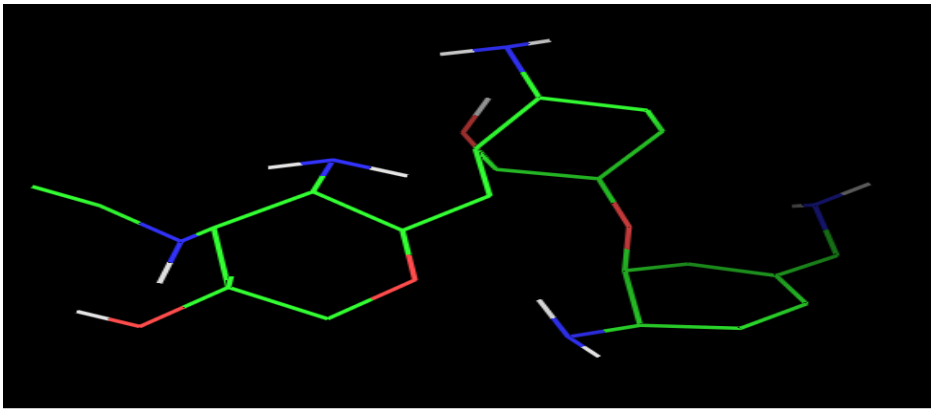


Fig 2: Modified ligand 2

In Caffeine N3 changed with C3, N5 changed with C5 and O2 changed with N2 as shown in fig 3. Then set the number of torsions in the ligand.

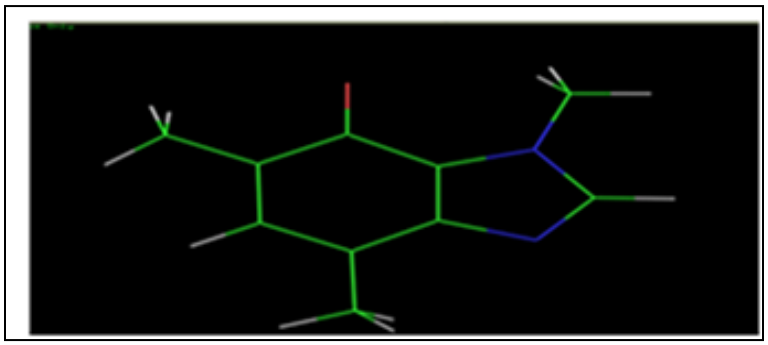
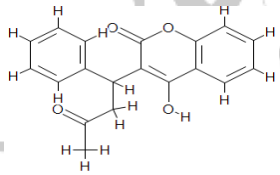
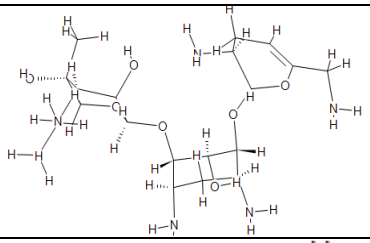
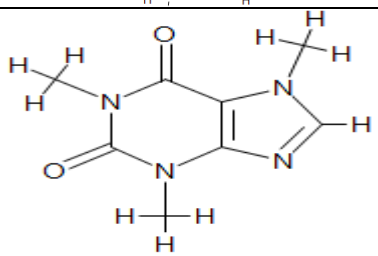


Fig 3: Modified ligand 3

CID of the original ligands along with their modifications are given in table 2.

Table 2: CID of the original ligands along with their modifications

Name	CID	Structure	R1	R2	R3
Warfarin	**54678486**		**O1 to C1**	**O2 to N2**	**O4 to H4**
Etisomicin	**70689320**		**O7 to C7**	**O5 to N5**	**N9 to H9**
Caffeine	**2519**		**N3 to C3**	**N5 to C5**	**O2 to H2**

RESULTS & DISCUSSION

Docking studies

Warfarin, caffeine, etisomicin and their changed structures were docked to the receptor then their affinity and RMSD

values had been taken by way of the docking software autodock_vina. The consequences of docking look at are supplied in table 4. The affinity values of the 4 compounds have been discovered in the variety of -6.8 to -7.6(Kcal/mol) the receptor ligand interactions of compounds had been provided in Fig A, Fig B, Fig C respectively. Therefore, may also prove to be capacity as hepatitis C virus drug candidate furnished, they fulfill different sequential phases of examine.

Ligand

After the docking of receptor and modified ligand the results shown in Fig 4, Fig 5, Fig 6.

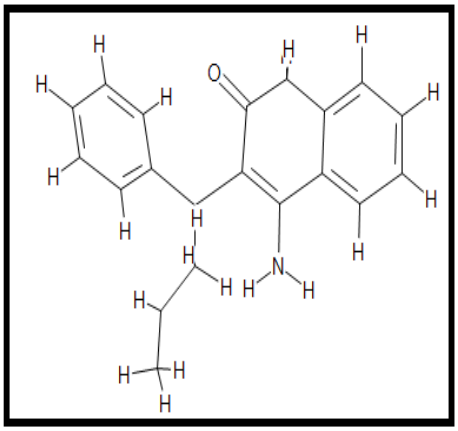


Fig 4: Ligand-1

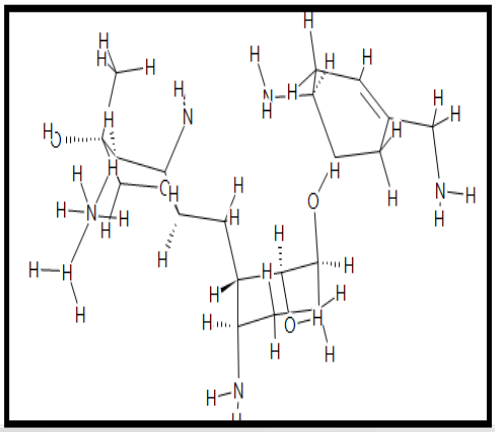


Fig 5: Ligand-2

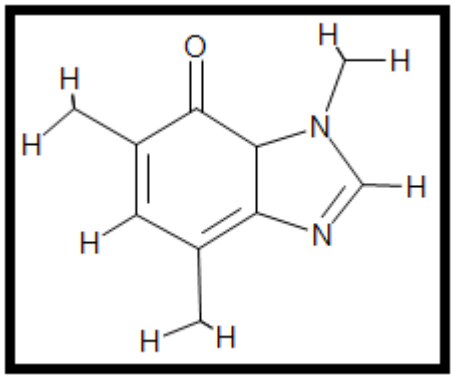


Fig 6: Ligand-3

Structural Assessment of Protein

The 3 compounds were docked with the non-structural protein NS5B and the results shown in the table 2. The protein binds with the Ligand-1, Ligand-2, and Ligand-3. The interaction of protein and ligand were shown in the below figures**.**

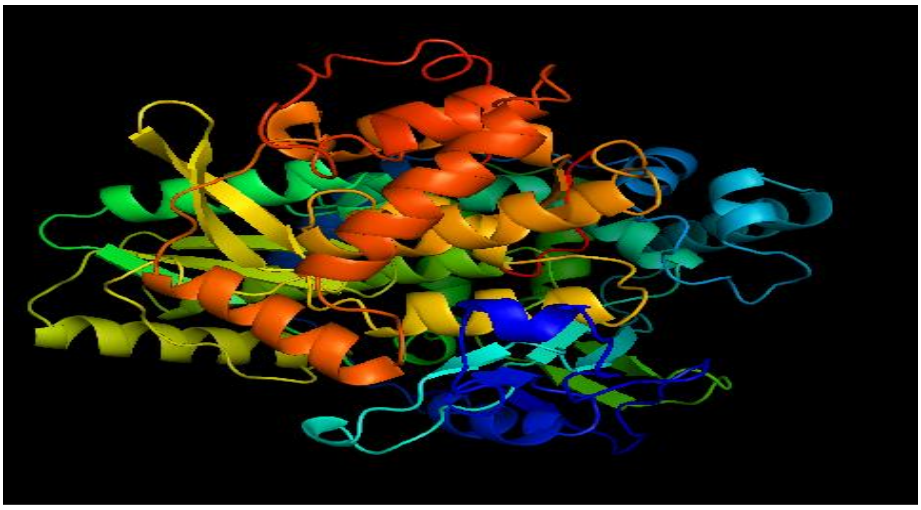


Fig 8: It shows the three dimension structure of NS5B (without ligand)

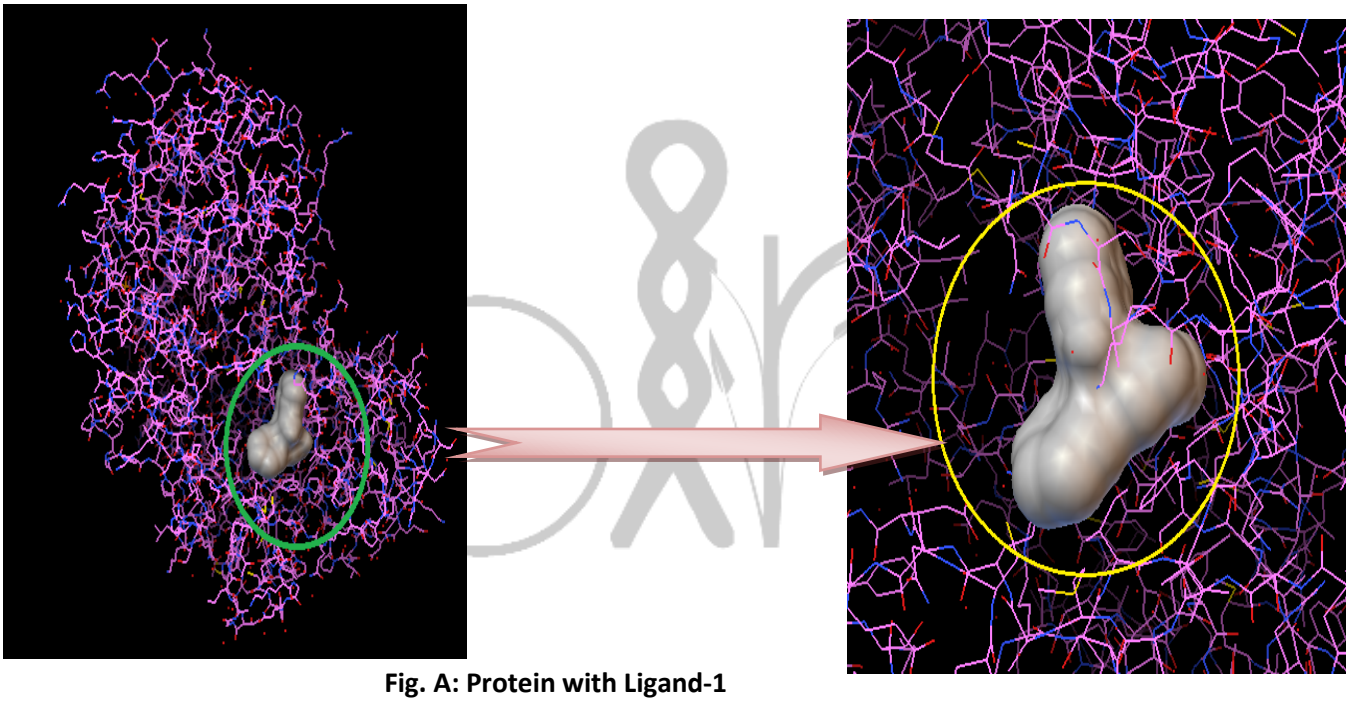


Fig. A: Protein with Ligand-1

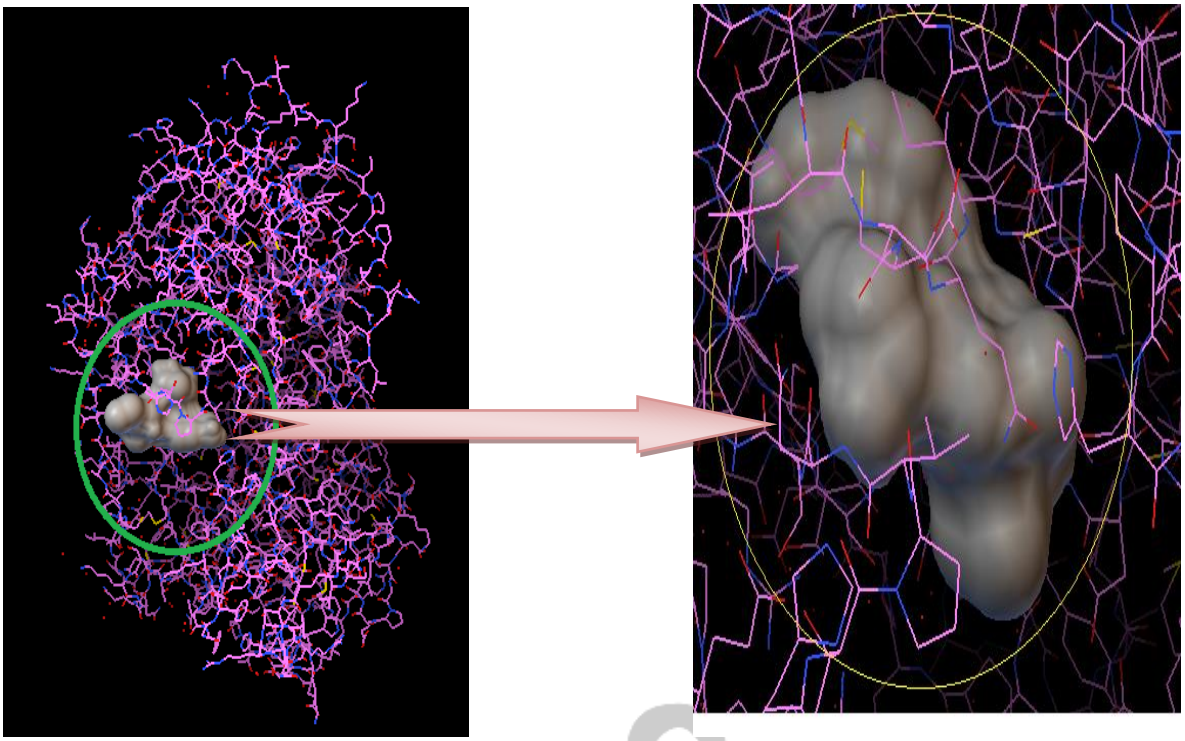


Fig. B: Protein with Ligand-2

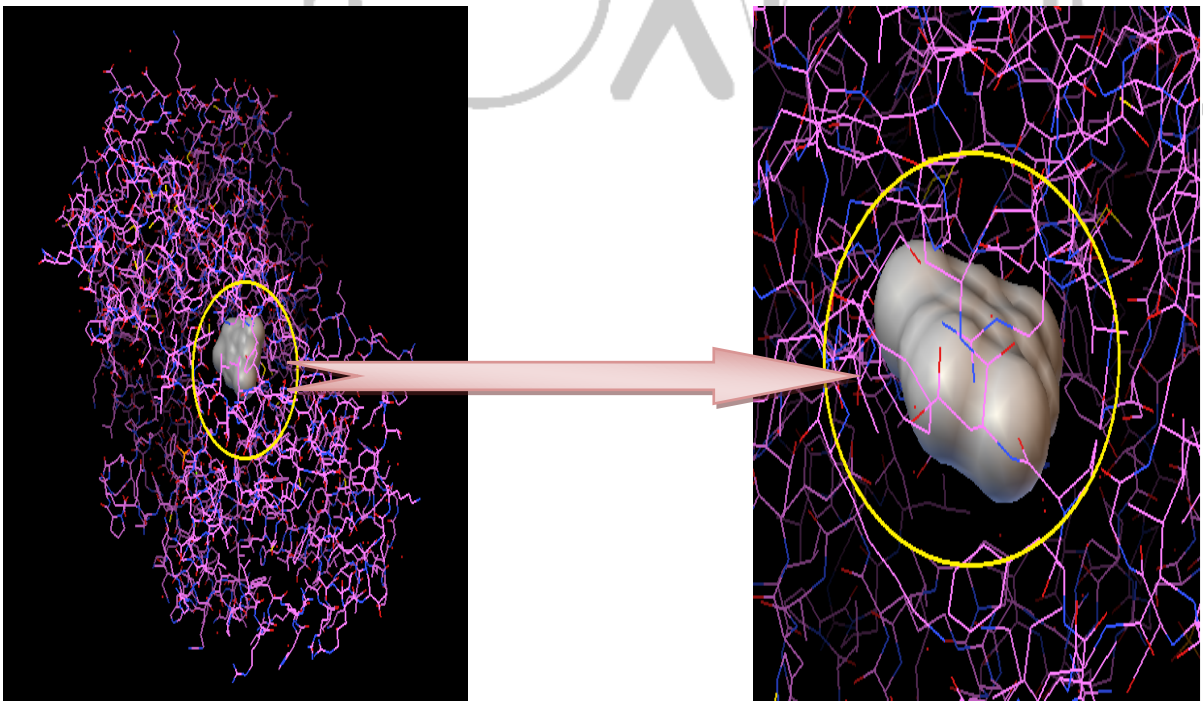


Fig. C: Protein with Ligand-3

Table 4: It shows chemical features and their affinities

Compounds	Affinity (kcal/mol)
Ligand-1	-6.8
Ligand-2	-7.1
Ligand-3	-7.6

ADMET Properties

ADMET properties of the ligands are given in table 5.

Table 5: ADMET Properties

Attributes	Ligand1	Ligand2	Ligand3
Structure Name	54678486	70689320	2519
MlogP	3.678	-0.977	0.752
S+logP	4.212	-1.234	0.851
S+logD	4.211	-4.895	0.751
RuleOf5	0.000	1.000	0.000
RuleOf5_Code		Hb	
MWt	291.395	441.618	176.219
M_NO	2.000	9.000	3.000
T_PSA	43.090	175.030	32.670
HBDH	2.000	11.000	0.000

CONCLUSION

In this study, docking of warfarin and other analogs was carried out. The affinity obtained were -6.8 to -7.6 respectively.

REFRENCES

1. Mayhoub, A. S. (2012). Hepatitis C RNA-dependent RNA polymerase inhibitors: A review of structure–activity and resistance relationships; different scaffolds and mutations. Bioorganic & medicinal chemistry, 20(10), 3150-3161.
2. Yuan, G. (2017). Design, synthesis, methodology development, and evaluation of PET imaging agents targeting cancer and CNS disorders (Doctoral dissertation, Northeastern University).
3. Beaulieu, P. L. (2007). Non-nucleoside inhibitors of the HCV NS5B polymerase: progress in the discovery and development of novel agents for the treatment of HCV infections. Current opinion in investigational drugs (London, England: 2000), 8(8), 614-634.
4. Beaulieu, P. L., Bös, M., Bousquet, Y., DeRoy, P., Fazal, G., Gauthier, J., ... & Kukolj, G. (2004). Non-nucleoside inhibitors of the hepatitis C virus NS5B polymerase: discovery of benzimidazole 5-carboxylic amide derivatives with low-nanomolar

potency. Bioorganic & medicinal chemistry letters, 14(4), 967-971.

5. Kukolj, G., McGibbon, G. A., McKercher, G., Marquis, M., Lefebvre, S., Thauvette, L., ... & Beaulieu, P. L. (2005). Binding site characterization and resistance to a class of non-nucleoside inhibitors of the hepatitis C virus NS5B polymerase. Journal of Biological Chemistry, 280(47), 39260-39267.
6. Behrens, S. E., Tomei, L., & De Francesco, R. (1996). Identification and properties of the RNA-dependent RNA polymerase of hepatitis C virus. The EMBO journal, 15(1), 12-22.
7. Beaulieu, P. L., Boïs, M., Cordingley, M. G., Chabot, C., Fazal, G., Garneau, M., ... & Kukolj, G. (2012). Discovery of the first thumb pocket 1 NS5B polymerase inhibitor (BILB 1941) with demonstrated antiviral activity in patients chronically infected with genotype 1 hepatitis C virus (HCV). Journal of medicinal chemistry, 55(17), 7650-7666.