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Research paper

Computational Identification of Potential Antiviral Agents Against Monkeypox Virus

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ABSTRACT

This study introduces a drug repurposing approach for monkeypox virus using molecular docking and molecular dynamics (MD) simulations to screen clinically approved drugs for other diseases. Potential candidates were analyzed with AutoDock software in two categories: (1) DNA polymerase inhibitors and (2) RNA polymerase inhibitors. Docking analysis identified seven promising compounds—five DNA polymerase and two RNA polymerase inhibitors—showing strong affinity toward monkeypox targets. MD simulations further confirmed their binding stability. Among them, etravirine (−8.04 kcal/mol) and valaciclovir (−7.57 kcal/mol) exhibited the highest affinity to DNA polymerase active sites at residues ASP347 and ASP462. Moreover, emetine dihydrochloride (−7.17 kcal/mol) demonstrated the strongest binding to the catalytic site of RNA polymerase. Consequently, etravirine and emetine dihydrochloride are proposed as potential therapeutics against monkeypox. Since these compounds are already approved by the U.S. Food and Drug Administration (FDA) for other viral infections, extensive safety testing and high development costs can be avoided, making this repurposing strategy an efficient and cost-effective option for managing monkeypox infection.

Keywords: *Monkeypox Virus, Etravirine, Molecular Docking, Molecular Dynamics Simulation, Drug Repurposing*

I. INTRODUCTION

Monkeypox virus belongs to the Orthopox virus family that includes vaccinia, cowpox, variola, and camelpox viruses and it was accepted by the World Health Organization (WHO) that the virus is the dominant infectious type of Orthopox genus after smallpox eradication (McCollum & Damon, 2014). WHOa reported a monkeypox case in UK on May 7, 2022 and although the disease was known as an endemic infection for Nigeria and Democratic Republic of Congo, hundreds of monkeypox cases were confirmed in UK, USA and other European countries recently (Bunge et al., 2022; Okyay et al., 2022). Two major classes of monkeypox virus were identified as Congo and West African-based clades (Likos et al., 2005). Monkeypox infection from Congo class was shown to have severe symptoms in patients with a case fatality ratio (CFR) of up to around 10% which was reported by WHO. Besides, a recent epidemic caused by the monkeypox

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virus was claimed to be resulted from West African class that has nearly 1% mortality rate (Okyay et al., 2022). Most clinical features of human monkeypox infection reflect those of smallpox and the first syndrome of the infection is accompanied by generally headache and fatigue. Before and with the development of the rash, many patients have maxillary, cervical, or inguinal lymphadenopathy (Brown & Leggat, 2016; Kao, 2003; Ye et al., 2019). On the other hand, lymphadenopathy is not a primary syndrome of smallpox, lymphadenopathy occurrence from monkeypox infection may be an implication of a higher immune response to the infection compared to the smallpox virus (Damon, 2011).

Despite technological advances and the increase in disease knowledge, the development of therapeutic strategies and drug discoveries that can be transferred from these technologies has been less than expected (Ashburn & Thor, 2004; Scannell et al., 2012). The global pharmaceutical industry is facing various obstacles including high attrition rates to provide fast and accurate treatment options for patients because of higher costs and the length of time to get ready a new drug to the market (Pammolli et al., 2011; Pushpakom et al., 2019). Drug repurposing which is also called reprofiling, repositioning or re-tasking is an approach to establish new applications for approved drugs that are used for a different scope of original treatment (Breckenridge & Jacob, 2019). There are many advantages of this strategy to develop a completely new treatment option for a known drug formulation. The most important advantage of the drug repurposing is to have lower failure risk because the re-tasked drug has already been analyzed to be adequately safe for clinical treatments and it is unlikely to fail in efficacy trials in the aspect of safety. Furthermore, time-consuming procedures for drug development are not a problem for the drug trials because of formulation development, safety assessments and preclinical analyses will have already been accomplished. Also, there is lower costs for new drug development because investments have already been done for the approved drug (Caufriez et al., 2022; Kast et al.,2022; Ozdemir et al., 2022).

Moreover, one of the fastest strategies for drug repurposing is in silico approaches to understand possible applications of a known drug formulation in different diseases by using computational simulations (Halder et al., 2023; Wu et al., 2022). Molecular docking analysis is a widely used approach to investigate ligand-protein and protein-protein interactions without using any in vivo or in vitro experiment and it is thought that the molecular docking analysis has higher accuracy (nearly 90%) compare to other computational biology calculations (Jayaram et al., 2012; Singh et al., 2011). There were several drug repurposing studies for the COVID-19 pandemics via the use of molecular docking analyses and potential drug candidates were defined which gave promising results (Fadlalla et al., 2022; Kumar et al., 2022; Jalalvand et al., 2022; Lazniewski et al., 2022). Previous studies reported that the vaccine used to eradicate smallpox could also be effective in controlling monkeypox infection. Because both monkeypox and smallpox belong to the same genus, the vaccinia vaccine could offer up to 85% protection and alleviate disease symptoms. Besides, obligatory smallpox vaccination was ended around 1970s and this would result in a decrease in vaccine immunity in the people who were vaccinated by that time (Hutin et al., 2001; McCollum & Damon, 2014). Therefore, new drug formulations are needed to prevent the spread of the monkeypox virus and the fastest possible way for identifying potential drug candidates for the disease is drug repurposing via computational simulations.

The primary aim of this study was to identify potential antiviral drug candidates against the monkeypox virus through an in silico drug repurposing strategy, utilizing computational methods to evaluate the binding affinities and dynamic interactions of clinically approved drugs with DNA and RNA polymerase targets of the virus. By utilizing a drug repurposing strategy, it is possible to eliminate the expensive and time-consuming drug development process to classify effective drug formulations against the monkeypox virus. Also, binding affinities of individual atoms and functional groups on the potential drug candidates against DNA and RNA polymerases were discussed in detail to aid for new drug discoveries. Finally, results of these study would give insight into effective drug types and structures to fight against the possible monkeypox epidemic and proposed drugs might be a starting point for eliminating monkeypox infection from our lives.

II. MATERIAL AND METHOD

DNA polymerase and RNA polymerase protein sequences were obtained from National Center for Biotechnology Information (NCBI) database with accession numbers ADX22900 and QNI40512, respectively. Amino acid sequences in FASTA format were used in NCBI protein-protein Basic Local Alignment Search Tool (blastp) to compare other polymerases in the different organisms to find the closest protein structures that can be found in Protein Data Base (PDB) in the crystal structure. Docking investigations were performed using Auto Dock software (Turkez et al., 2023; Arslan et al., 2023; Gouleni

et al., 2023), AutoDock 4.2.6 was downloaded from 'The Scripps Research Institute's official website (http://autodock.scripps.edu/) , with Phyton 3.10.5 and MGLTools 1.5.7, the software uses the genetic algorithm (GA) in the optimization step and it runs 10 times in the GA processes, in accordance with the previously published protocol26.

MD simulation were performed using Groningen Machine for Chemical Simulations (Gromacs) software (Gromacs-2023.3) downloaded freely from website (https://www.gromacs.org/, accessed on 19 October 2023). The obtained simulation results in data files have been visualized using Qtgrace visualization software downloaded freely from website (https://sourceforge.net/projects/qtgrace/). In the MD simulation process, we have done the energy minimization (EM) before simulation. The flow is as follows, first EM along with the force field for 5000 input steps, followed by two stage equilibration, viz., nvt/npt, then we have performed the MD simulation.

Due to the lack of the DNA and RNA protein structures of the monkeypox virus, it has been considered that 5N2E (DNA polymerase) and 6RFL (DNA-dependent RNA polymerase subunit rpo147) protein structures from the vaccinia virus would be suitable templates for the monkeypox virus. 5N2E and 6RFL protein structures were obtained from the Protein Data Bank (RCSB PDB, https://www.rcsb.org/). The structure of the drugs considered in this study was obtained from the National Library of Medicine (PubChem, https://pubchem.ncbi.nlm.nsih.gov/). In the docking process, water molecules were deleted from the protein structures and then, hydrogen atoms were added to the proteins at the beginning of the docking process using the AutoDock molecular modeling software. For the DNA polymerase, the whole protein was included in the grit and for the RNA polymerase, the whole rpo147 subunit as the catalytic part of the enzyme was included in the grit. Calculations were performed three times and ligand interactions with the active site for the DNA polymerase (168, 268, 166, 462, 458th amino acids) were confirmed. Also, non-homologous amino acid residues were checked for interaction involvements and active sites of the enzymes to not interfere with our results.

The obtained docking results using AutoDock were analyzed by the Protein-Ligand Interaction Profiler (plip-tool.biotec.tu-dresden.de) online software to monitor the distance between ligand and amino acid residues in detail. Finally, PyMol software (pymol.org) was utilized to obtain 3-dimensional residual interaction plots and also the LigPlot software (Version 4.5.3, https://www.ebi.ac.uk/thornton-srv/software/LIGPLOT) was performed to obtain data related to interactions between protein and ligand in 2-dimensional sketches (Laskowski & Swindells, 2011; Yuan et al., 2017). Finally, the binding affinities of each individual atom and functional group on the protein structures were analyzed from the resulting output obtained from AutoDock software. Also, protein structures of RNA and DNA polymerase that were used in the study were defined experimentally (Electron Microscopy and X-Ray Diffraction analyses) (Grimm et al., 2019; Tarbouriech et al., 2017). Thus, force field minimization was not performed to avoid the loss of interaction sites on the proteins. Although full force field minimization was not performed, attempts were made to lower the local energies of the ligand positions (e.g. by local fine-tuning) in the molecular docking process using Autodock. Ligand structures were obtained from PubChem (https://pubchem.ncbi.nlm.nih.gov) website and ligand structures were drawn by using Chem3D version 20.1.1. Prior to docking, the most biologically relevant tautomeric and protonation states of the ligands at physiological pH (7.4) were determined based on literature data and structural analysis, to ensure accurate representation of the active molecular forms during the docking calculations. Lowing energy conformations for ligand sites were calculated from output data of AutoDock by using the formula below;

Estimated Free Energy of Binding = [= (1) +(2)]

(1) Final Intermolecular Energy, vdW + Hbond + desolv Energy, Electrostatic Energy
(2) Free Energy Change

III. RESULTS AND DISCUSSIONS

There was no protein structure of DNA and RNA polymerases in PDB database for the monkeypox virus. Thus, NCBI protein-protein alignment search (blastp) was used to find the closest DNA and RNA polymerases for the monkeypox virus. According to the results, the closest DNA polymerase for the monkeypox virus was found to belong vaccinia virus with a 98.61% identity (Table 1). Also, NCBI blastp search showed that the closest RNA polymerase for monkeypox was found to belong to Cowpox virus with a 99.61% identity but, again there was no information about protein structure in PDB database for cowpox

virus RNA polymerase. Besides, vaccinia virus RNA polymerase was found to have 99.30% identical amino acid sequence with monkeypox polymerase (Table 2). Thus, vaccinia RNA polymerase protein structure was downloaded from PDB database for Molecular Docking investigations.

Table 1. NCBI protein-protein alignment (blastp) analysis for monkeypox virus DNA polymerase amino acid sequence.

Description	Scientific Name	Percent Identity	Accession Length	Accession
DNA polymerase	Vaccinia virus Ankara	98.61%	1006	CAM58235.1
CPXV075 protein	Cowpox virus	98.51%	1006	AGY97242.1
DNA polymerase	Buffalopox virus	98.31%	1006	AVO21083.1
RPXV054	Rabbitpox virus	98.31%	1006	AAS49767.1
HSPV066	Horsepox virus	97.91%	1006	ABH08169.1
DNA polymerase	Taterapox virus	97.91%	1006	YP_717373.1
DNA polymerase	Camelpox virus	97.51%	1006	NP_570451.1
DNA polymerase	Variola virus	97.51%	1005	ABF25828.1
DNA polymerase	Ectromelia virus ERPV	97.12%	1006	AFH54611.1
DNA polymerase	Ectromelia virus	97.02%	1006	NP_671567.1
DNA polymerase	Akhmeta virus	96.63%	1010	QEQ49620.1
DNA polymerase	Raccoonpox virus	93.33%	1005	YP_009143372.1
DNA polymerase	Skunkpox virus	93.43%	1005	YP_009282757.1

Table 2. NCBI protein-protein alignment (blastp) analysis for monkeypox virus RNA polymerase amino acid sequence.

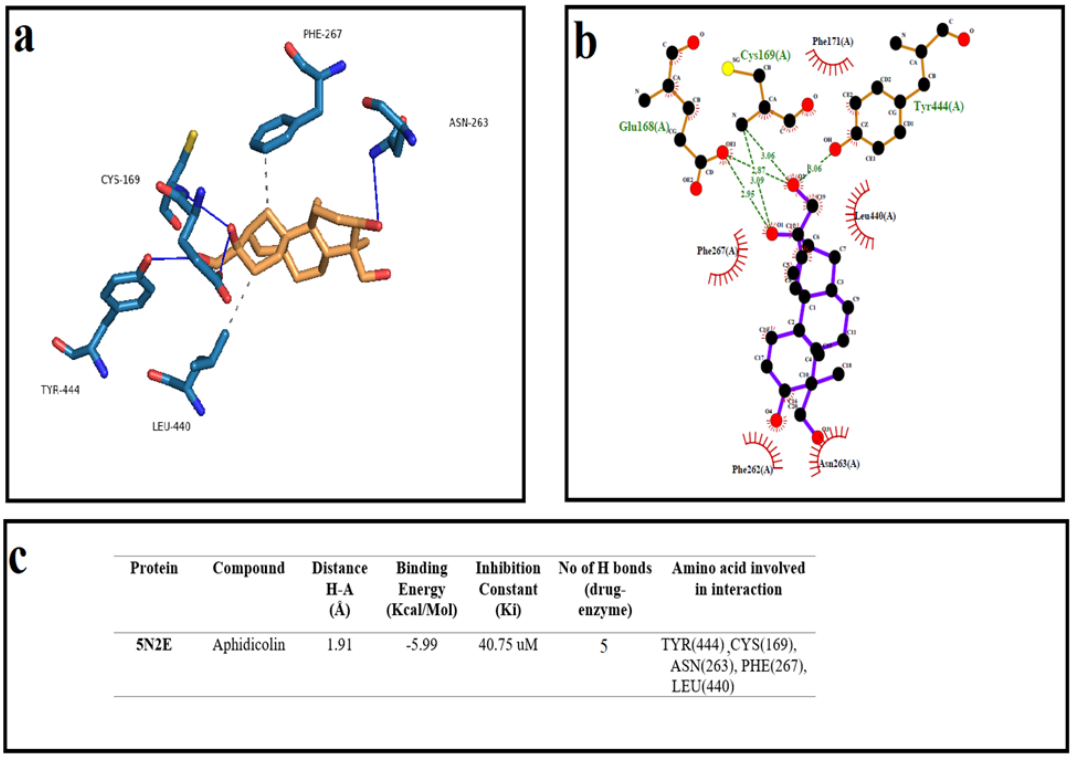
Description	Scientific Name	Percent Identity	Accession Length	Accession
CPXV109 protein	Cowpox virus	99.61%	1286	AGY99173.1
DNA-dependent RNA polymerase subunit rpo147	Vaccinia virus	99.30%	1286	YP_232980.1
DNA-dependent RNA polymerase subunit rpo147	Buffalopox virus	99.22%	1286	AVO21111.1
CMLV096	Camelpox virus	99.14%	1286	NP_570486.1
DNA-dependent RNA polymerase subunit rpo147	Taterapox virus	99.30%	1286	YP_717407.1
DNA-dependent RNA polymerase subunit rpo147	Variola virus	99.14%	1286	ABF23456.1
putative J6R protein	Orthopoxvirus Abatino	99.14%	1286	YP_010085766.1
M6R protein	Variola minor virus	99.07%	1286	CAB54683.1
RPXV087	Rabbitpox virus	99.07%	1286	AAS49800.1
TPA: DNA-dependent RNA polymerase subunit RPO147	Horsepox virus	99.07%	1286	DAD53466.1
EVM082	Ectromelia virus	98.99%	1286	NP_671600.1
RNA polymerase subunit	Akhmeta virus	98.68%	1286	YP_010085554.1
RNA polymerase 147 subunit	Orthopoxvirus Tena Dona	97.67%	1286	APA31992.1
RNA polymerase	Volepox virus	96.11%	1286	YP_009281845.1
RNA polymerase	Skunkpox virus	96.19%	1286	YP_009282791.1
RNA polymerase subunit RPO147 protein	Raccoonpox virus	96.35%	1286	YP_009143406.1
DNA-dependent RNA polymerase subunit rpo147	Murmansk poxvirus	90.90%	1286	YP_009408276.1
DNA-dependent RNA polymerase subunit rpo147	Yokapox virus	88.18%	1285	YP_004821431.1

Table 2 (cont). NCBI protein-protein alignment (blastp) analysis for monkeypox virus RNA polymerase amino acid sequence.

RNA polymerase subunit	Eptesipox virus	82.52%	1285	YP_009408026.1
RNA polymerase subunit RPO147	Hypsugopox virus	81.82%	1285	QDJ95084.1
RNA polymerase subunit	Lumpy skin disease virus	80.57%	1285	AYV61204.1
m68R	Myxoma virus	81.61%	1286	AQT37618.1
gp068R	Rabbit fibroma virus	81.13%	1286	NP_051957.1
RNA polymerase subunit RPO147	Deerpox virus W-848-83	81.75%	1286	YP_227455.1

For molecular docking analysis, literature was searched to choose potential candidate drugs for the treatment of monkeypox infection. It was found that DNA and RNA polymerase inhibitory drugs could give better results for viral infections. Thus, 11 DNA polymerase and 10 RNA inhibitor drugs were chosen as candidate drugs for monkeypox infection. A total of 21 candidate drugs were investigated by using molecular docking analysis to determine their efficiency in polymerase binding affinity. Results put forth that 5 candidate drugs (Aphidicolin, Entecavir, Tecovirimat, Valaciclovir and Etravirine) showed higher affinity to DNA polymerase enzyme and 2 candidate drugs (Bmh-21 and Emetine Dihydrochloride) were found to have higher affinity to RNA polymerase enzyme.

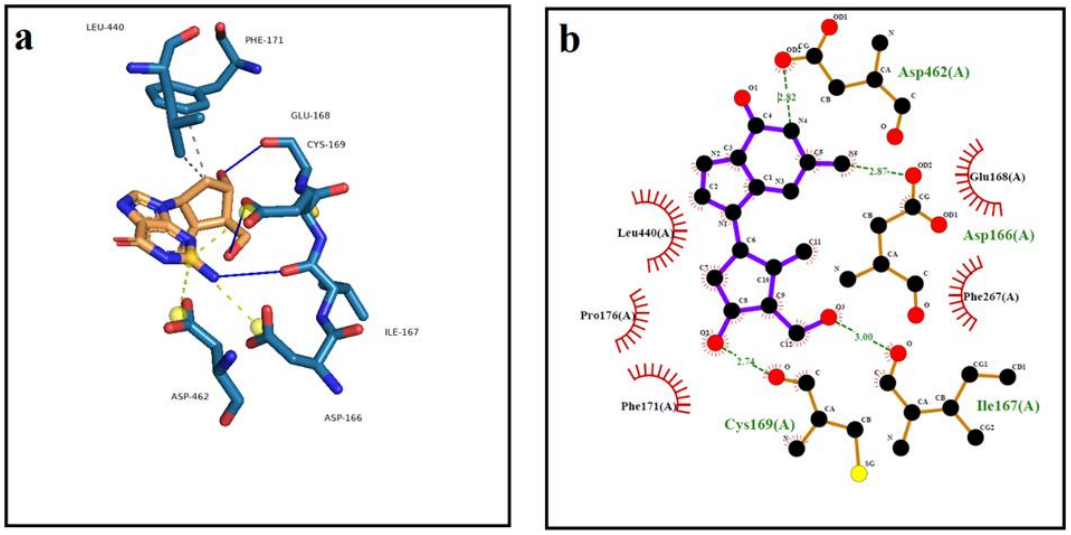
Molecular docking analyses on DNA polymerase enzyme showed that Aphidicolin had one of the highest binding affinities with -5.99 binding energy (Kcal/mol). Also, aphidicolin makes 5 hydrogen bonds to DNA polymerase with a distance of 1.91 Å and the inhibition constant of aphidicolin was found as 40.75 μM (Figure 1). Moreover, entecavir was investigated to have a high affinity against DNA polymerase with -6.64 Kcal/mol binding energy. The inhibition constant of entecavir was calculated as 13.59 μM with an atomic distance of 1.99 Å. It was found that entecavir formed three hydrogen bonds to DNA polymerase on the active site of the enzyme (ASP166, GLU168 and ASP462) (Figure 2). Docking analysis of tecovirimat also yielded good results compared to other candidate drugs with -6.70 Kcal/mol binding energy, 12.37 μM of inhibition constant, and atomic distance of 1.99 Å. On the other hand, tecovirimat was shown to have 2 hydrogen bonds against the DNA polymerase enzyme (Figure 3). Furthermore, valaciclovir was investigated to have one of the highest affinities to DNA polymerase with -7.57 Kcal/mol binding energy among the other candidate drugs. Moreover, valaciclovir was shown to have a low inhibition constant of 2.83 μM. Although it has only 2 hydrogen bonds on DNA polymerase, there were 2 interactions with the active site of the enzyme (ASP462 and GLU168) (Figure 4). It was found that rilpivirine docked to DNA polymerase with -7.96 Kcal/mol binding energy and have 1.45 μM inhibition constant against the enzyme. Also, rilpivirine was investigated to bind the DNA polymerase catalytic site at amino acid residues of GLU168 and ASP462 (Figure 5). Etravirine was found to have the lowest binding energy against the enzyme with -8.04 Kcal/mol ratio and inhibition constant of 1.28 μM. It was also observed that etravirine can dock to the catalytic site of the DNA polymerase at the amino acid residue of ASP462 (Figure 6). Delavirdine and nevirapine showed similar binding scores against DNA polymerase enzyme with -6,32 Kcal/mol and -6.21 Kcal/mol, respectively. On the other hand, these drugs did not dock to the enzyme on its catalytic site (Figure 7 and 8).



c

Protein	Compound	Distance H-A (Å)	Binding Energy (Kcal/Mol)	Inhibition Constant (Ki)	No of H bonds (drug-enzyme)	Amino acid involved in interaction
5N2E	Aphidicolin	1.91	-5.99	40.75 uM	5	TYR(444),CYS(169), ASN(263), PHE(267), LEU(440)

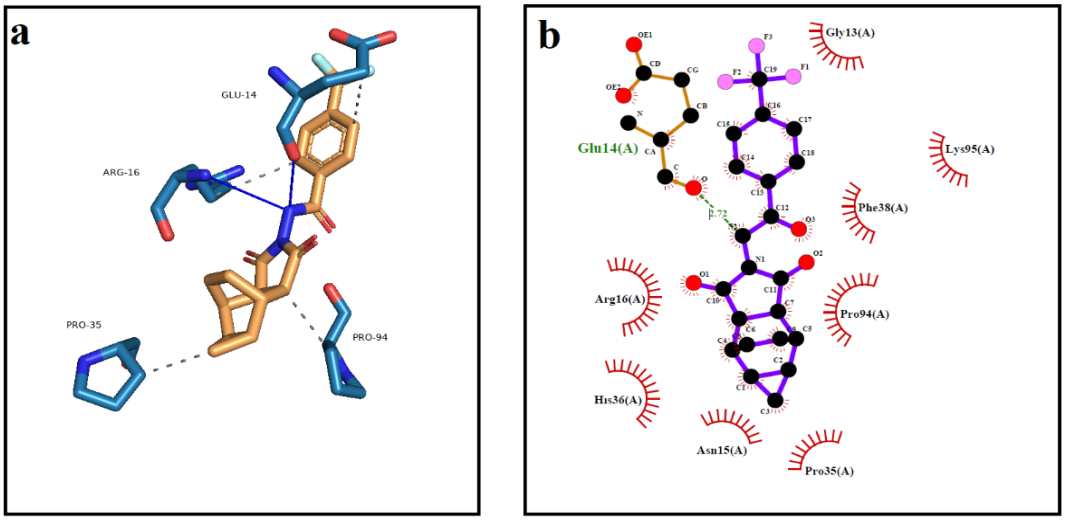
Figure 1. The Best docking conformation of DNA Polymerase (5N2E) with Aphidicolin obtained by a- PyMol-blue line and dashed gray show the Hydrogen(H)-bonds and Hydrophobic Interaction respective, b- LigPlot, and c- the table of binding information.



c

Protein	Compound	Distance H-A (Å)	Binding Energy (Kcal/Mol)	Inhibition Constant (Ki)	No of H bonds (drug-enzyme)	Amino acid involved in interaction
5N2E	Entecavir	1.99	-6.64	13.59 uM	3	ASP(166), ILE(167), GLU(168), CYS(169), PHE(171), LEU(440), ASP(462)

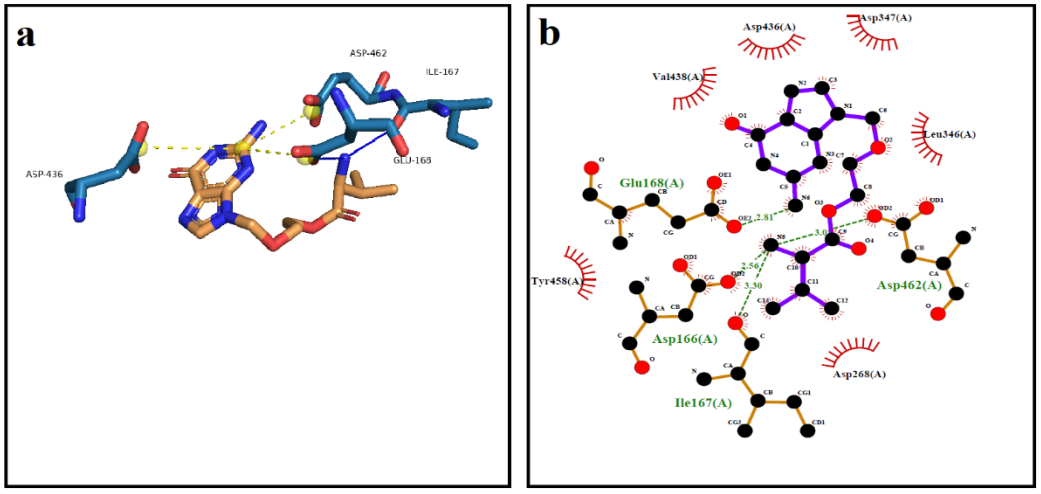
Figure 2. The Best docking conformation of DNA Polymerase (5N2E) with Entecavir obtained by a- PyMol-blue line and dashed gray show the Hydrogen(H)-bonds and Hydrophobic Interaction respective, b- LigPlot, and c- the table of binding information.



c

Protein	Compound	Distance H-A (Å)	Binding Energy (Kcal/Mol)	Inhibition Constant (Ki)	No of H bonds (drug-enzyme)	Amino acid involved in interaction
5N2E	Tecovirimat	1.99	-6.70	12.37 uM	2	GLU(14), ARG(16), PRO(35), PRO(94),

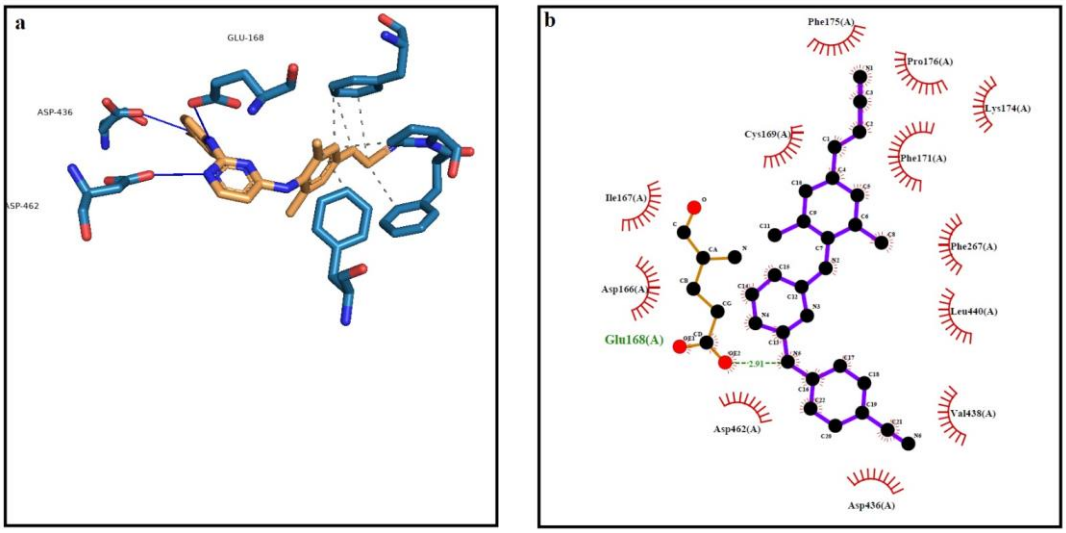
Figure 3. The Best docking conformation of DNA Polymerase (5N2E) with Tecovirimat obtained by a-PyMol-blue line and dashed gray show the Hydrogen(H)-bonds and Hydrophobic Interaction respective, b- LigPlot, and c- the table of binding information.



c

Protein	Compound	Distance H-A (Å)	Binding Energy (Kcal/Mol)	Inhibition Constant (Ki)	No of H bonds (drug-enzyme)	Amino acid involved in interaction
5N2E	Valaciclovir	2.72	-7.57	2.83 uM	2	ASP(436), ASP(462), ILE(167), GLU(168)

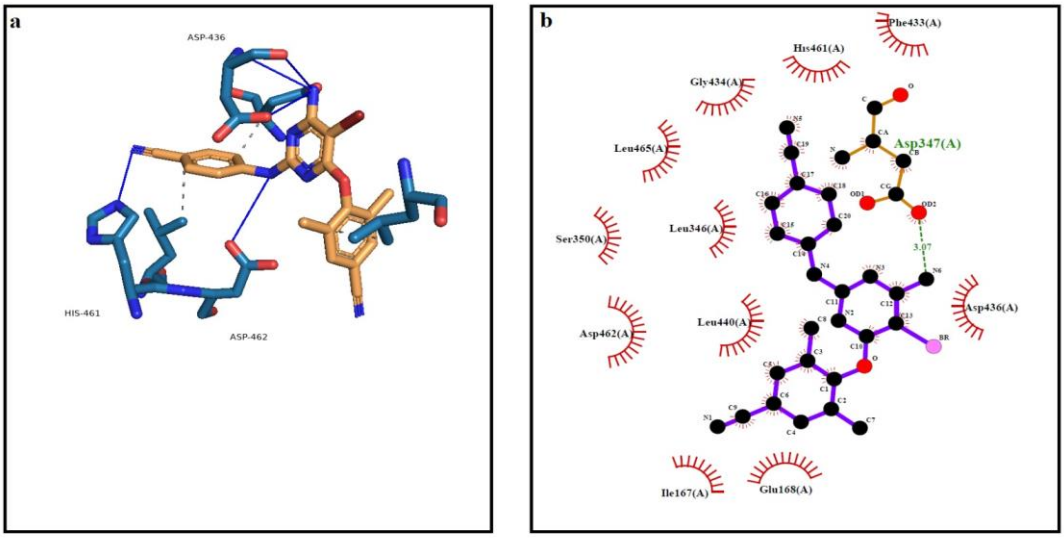
Figure 4. The Best docking conformation of DNA Polymerase (5N2E) with Valaciclovir obtained by a-PyMol-blue line and dashed gray show the Hydrogen(H)-bonds and Hydrophobic Interaction respective, b- LigPlot, and c- the table of binding information.



c

Protein	Compound	Distance H-A (Å)	Binding Energy (Kcal/Mol)	İnhibition Constant (Ki)	No of H bonds (drug-enzyme)	Amino acid involved in interaction
5N2E	Rilpivirine	1.91	-7.96	1.45 uM	3	GLU (168), ASP(436), ASP(462)

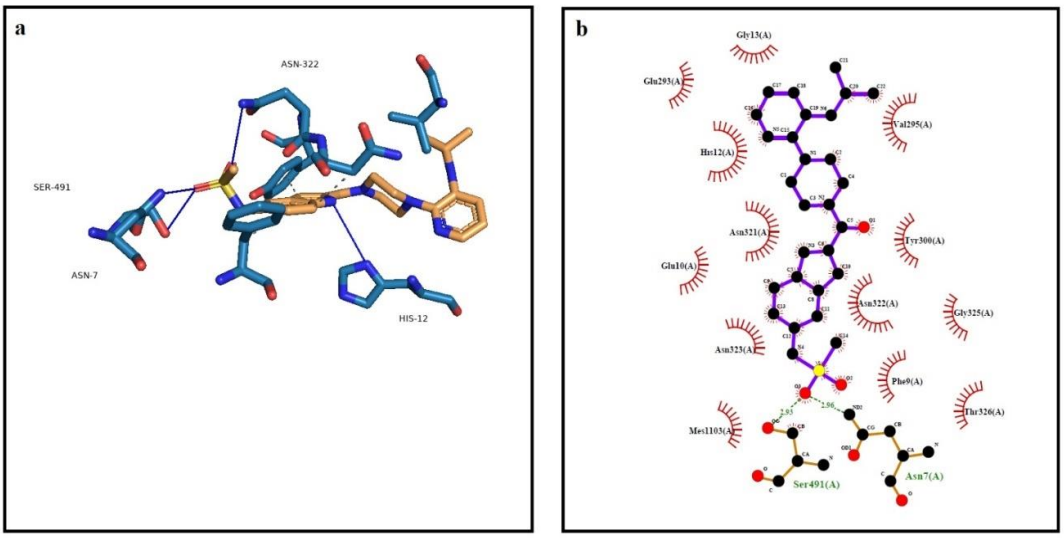
Figure 5. The Best docking conformation of DNA Polymerase (5N2E) with Rilpivirine obtained by a- PyMol-blue line and dashed gray show the Hydrogen(H)-bonds and Hydrophobic Interaction respective, b- LigPlot, and c- the table of binding information.



c

Protein	Compound	Distance H-A (Å)	Binding Energy (Kcal/Mol)	İnhibition Constant (Ki)	No of H bonds (drug-enzyme)	Amino acid involved in interaction
5N2E	Etravirine	2.14	-8.04	1.28 uM	5	ASP(436)(3), ASP(462), HIS(461)

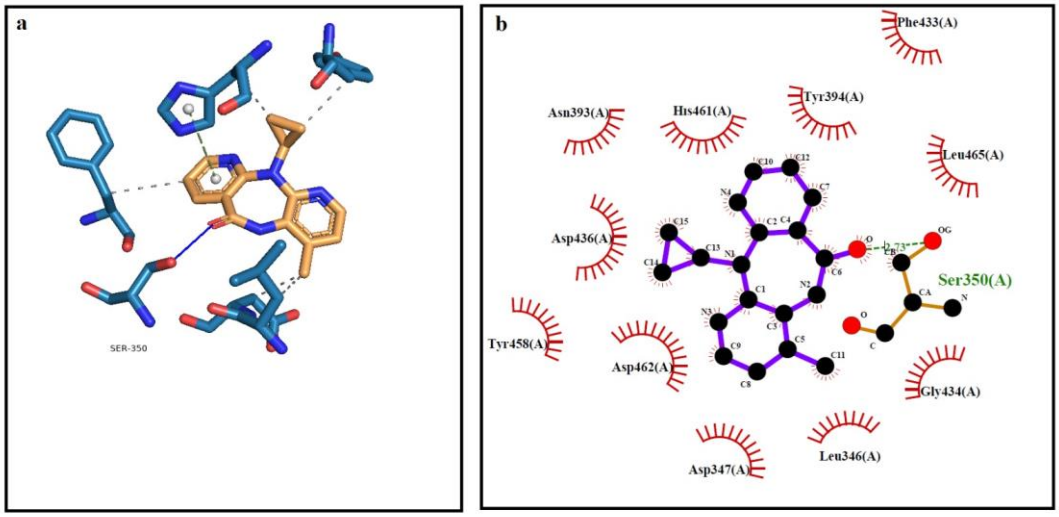
Figure 6. The Best docking conformation of DNA Polymerase (5N2E) with Etravirine obtained by a- PyMol-blue line and dashed gray show the Hydrogen(H)-bonds and Hydrophobic Interaction respective, b- LigPlot, and c- the table of binding information.



c

Protein	Compound	Distance H-A (Å)	Binding Energy (Kcal/Mol)	İnhibition Constant (Ki)	No of H bonds (drug-enzyme)	Amino acid involved in interaction
5N2E	Delavirdine	1.99	-6.32	23.32 uM	4	ASN(7), HIS(12), ASN (322), SER (491)

Figure 7. The Best docking conformation of DNA Polymerase (5N2E) with Delavirdine obtained by a- PyMol-blue line and dashed gray show the Hydrogen(H)-bonds and Hydrophobic Interaction respective, b- LigPlot, and c- the table of binding information.



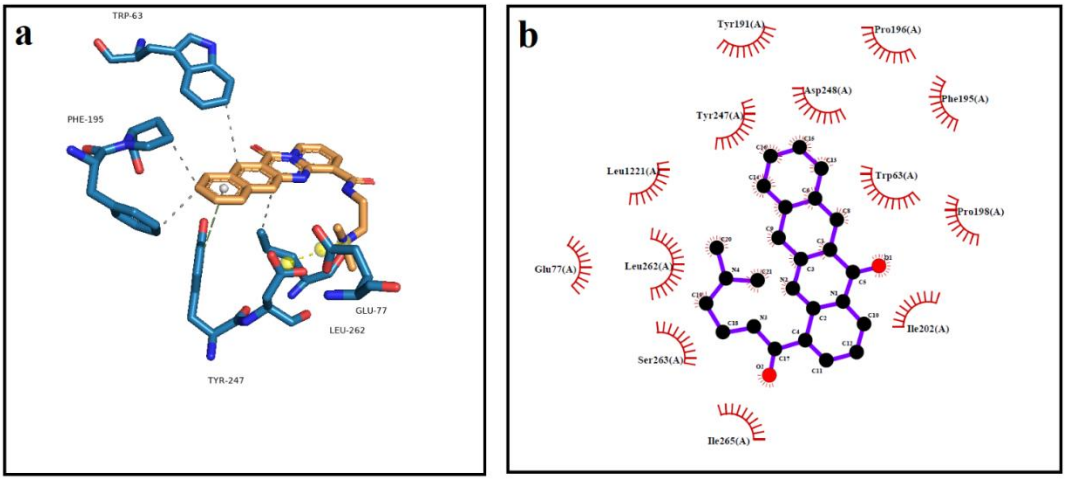
c

Protein	Compound	Distance H-A (Å)	Binding Energy (Kcal/Mol)	İnhibition Constant (Ki)	No of H bonds (drug-enzyme)	Amino acid involved in interaction
5N2E	Nevirapine	1.85	-6.21	28.14 uM	1	SER (350)

Figure 8. The Best docking conformation of DNA Polymerase (5N2E) with Nevirapine obtained by a- PyMol-blue line and dashed gray show the Hydrogen(H)-bonds and Hydrophobic Interaction respective, b- LigPlot, and c- the table of binding information.

Furthermore, molecular docking analyses on RNA polymerase showed that there are 2 possible candidate drugs for the treatment of monkeypox infection. Bmh-21 and Emetine Dihydrochloride exhibited

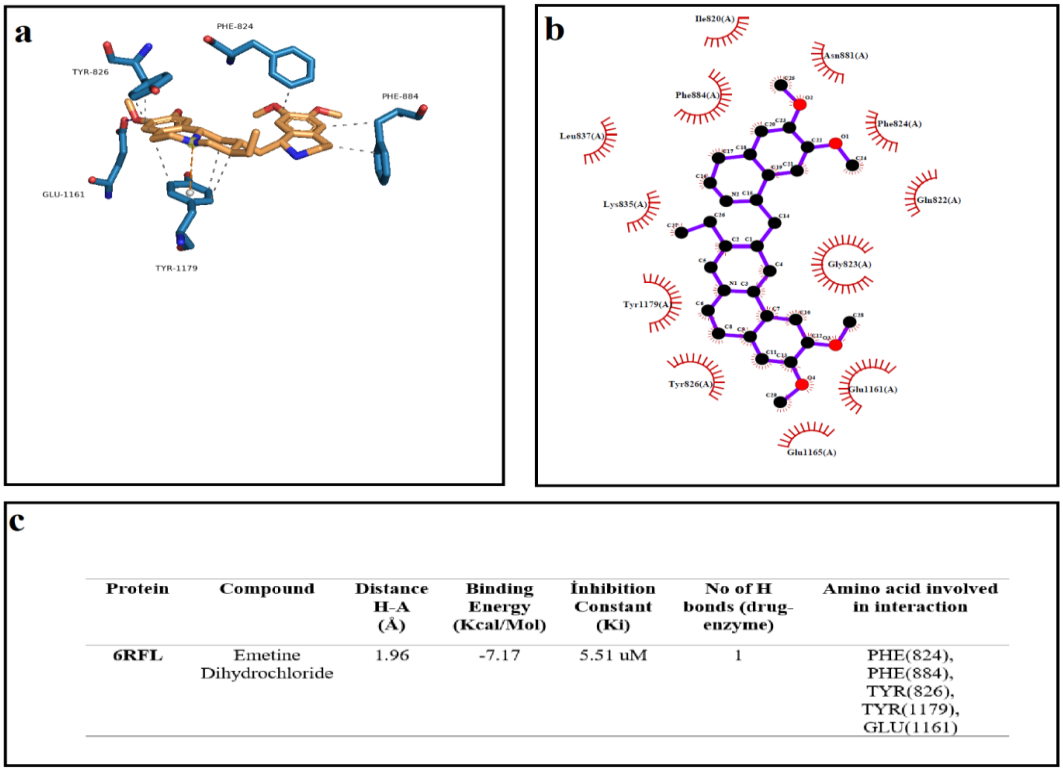
stronger affinity against RNA polymerase enzyme with -5.68 Kcal/mol and 7.17 Kcal/mol binding energy, respectively. Bmh-21 was shown to form only hydrophobic interactions to RNA polymerase on 5 different amino acid residues (TRP63, GLU77, TYR247, LEU262 and PHE195) with 69.04 µM inhibition constant (Figure 9). Besides, emetine dihydrochloride was shown to have the highest affinity among other candidates with the lowest binding energy of -7.17 Kcal/mol and have 1 hydrogen bond and 4 hydrophobic interactions (PHE824, PHE884, TYR826, TYR1179 and GLU1161) to RNA polymerase enzyme (Figure 10). Molecular docking results of other candidate drugs were summarized in Table 3 in respect to their binding energy (Kcal/mol), inhibition constant (Ki), distance H-A (Å), no of H bonds (drug-enzyme) and amino acid involved in the interaction. Also, nonhomologous amino acid residues for DNA polymerase (60, 311, 383, 384, 438, 477, 479, 533, 717, 752, 780, 963) and RNA polymerase (27, 258, 305, 633, 611, 630, 1112, 1161, 1280) of vaccinia virus were investigated to not involved in interactions between ligands and proteins. Which shows a small percentage of differences between monkeypox virus and vaccinia virus amino acid sequences do not interfere with our results (Supplementary data 1 and 2).



c

Protein	Compound	Distance H-A (Å)	Binding Energy (Kcal/Mol)	Inhibition Constant (Ki)	No of H bonds (drug-enzyme)	Amino acid involved in interaction
6RFL	Bmh-21	-	-5.68	69.04 uM	-	TRP(63), GLU(77), TYR(247), LEU(262), PHE(195)

Figure 9. The Best docking conformation of RNA Polymerase (6RFL) with Bmh-21 obtained by a- PyMol-blue line and dashed gray show the Hydrogen(H)-bonds and Hydrophobic Interaction respective, b- LigPlot, and c- the table of binding information.



c

Protein	Compound	Distance H-A (Å)	Binding Energy (Kcal/Mol)	İnhibition Constant (Ki)	No of H bonds (drug-enzyme)	Amino acid involved in interaction
6RFL	Emetine Dihydrochloride	1.96	-7.17	5.51 uM	1	PHE(824), PHE(884), TYR(826), TYR(1179), GLU(1161)

Figure 10. The Best docking conformation of RNA Polymerase (6RFL) with Emetine Dihydrochloride obtained by a- PyMol-blue line and dashed gray show the Hydrogen(H)-bonds and Hydrophobic Interaction respective, b- LigPlot, and c- the table of binding information.

Table 3. Other drug candidates that can be used in monkeypox treatment.

Protein	Compound	Distance H-A (Å)	Lowest Binding Energy (Kcal/mol)	Inhibition Constant (Ki)	No of H bonds (drug-enzyme)	Amino acid involved in interaction
5N2E	Cidofovir	2.07	-2.19	24.70 mM	5	GLU (70)(2), ILE (72), GLU (521), ARG (519)
5N2E	Foscamet	1.96	-3.90	1.37 mM	5	ARG (832)(4), LYS (837)
5N2E	Ganciclovir	3.38	-4.72	346.32 uM	3	ASP (166), GLU (168), ASP (462)

Table 3 (cont). Other drug candidates that can be used in monkeypox treatment.

5N2E	Famciclovir	2.57	-4.87	268.18 uM	1	CYS (169)
5N2E	Bromovinyldeoxyuridin	2.96	5.03	204.58 uM	2	LYS (404), LEU (420)
5N2E	Acyclovir	1.96	5.19	155.65 uM	1	GLU (1161)
5N2E	Valganciclovir	1.82	-5.44	102.71 uM	6	ASN (393) (2), TYR (394), GLY (434), ASP (462)
5N2E	Penciclovir	1.94	-5.64	73.44 uM	3	ILE (167), CYS (169) (2)
5N2E	Vidarabine	1.42	-2.52	14.27 mM	4	PHE (318), PHE (328), ASP (330), SER (333)
5N2E	Trifluridine	2.91	3.84	1.54 mM	5	ASP (69), GLU (70)(2), THR (71), GLU (521), GLN (524)
5N2E	Idoxuridine	2.14	-4.18	862.93 uM	4	SER (177), VAL (178), PHE (267), ASN (274)
5N2E	Telbivudine	1.94	-4.31	688.91 uM	3	ILE (72), THR (522), GLN (524)
5N2E	Lamivudine	2.11	-4.90	257.63 uM	5	VAL (41), THR (103), PHE (107), ASN (109), TRP (112)

Table 3 (cont). Other drug candidates that can be used in monkeypox treatment.

6RFL	Ribavirin	2.05	-3.33	3.65 mM	7	ILE (1232), ASN (1233), LYS (1243), ASN (1246), GLY (1250), LYS (1253)
6RFL	Methisazone	2.23	-4.50	504.93 uM	3	SER (1207), LYS (1210), ASP (1234)
6RFL	Bms-986094	3.14	-3.14	4.99 mM	6	GLN (822), SER (827), GLN (828), LYS (829), TYR (1144), GLU (1161)
6RFL	Remdesivir	1.83	-3.28	3.92 mM	16	ARG (120), GLN (125), LYS (127), ILE (127), SER (163), LYS (175), LYS (187), GLN (192), TYR (234), HIS (252), TYR (281), ARG (370), CYS (372), LYS (378)
6RFL	Vaccainia	1.96	-3.80	1.64 mM	3	THR (577), ASP (580), ASP (658)
6RFL	Eidd-193	1.99	-3.82	1.58 mM	9	ARG (687), ASP (689), GLY (690), SER (740), HIS (947), THR (949)
6RFL	Molnupiravir	1.90	3.93	1.32 mM	7	ARG (1043), PHE (1047), VAL (1049), ALA (1092), ASN (1094)
6RFL	Gs-441524	1.85	4.03	1.10 mM	7	ARG (97), LYS (127) (2), LYS (141), ASN (153), LEU (155), ASP (156)

Table 3 (cont). Other drug candidates that can be used in monkeypox treatment.

6RFL	Favipiravir	2.0	4.48	1.55 mM	6	LYS (269), ARG (274), THR (754), ARG (757), PHE (1214)
6RFL	Galidsivir dihydrochloride	2.86	-4.67	378.58 uM	3	SER (416), CYS (417), PHE (440)

Atom-based binding energies of Molecular docking data of the candidate antiviral drugs were also investigated, and the active sites of molecules for binding to DNA and RNA polymerase enzymes were determined in order to contribute to the discovery of possible antiviral drugs against monkeypox infection. As a result of analyses, it was found that the most active site of valacyclovir was the valine part and it was observed that especially nitrogen-bound hydrogens contribute to the reduction of the total binding energy for DNA polymerase enzyme. Furthermore, literature data correlate our results with respect to molecular activity. It was shown that valacyclovir was derived from acyclovir molecules to enhance the enzyme inhibitory properties and also modifications increased the absorption of the compound significantly (Fife et al., 1997; Kleymann, 2004; MacDougall & Guglielmo, 2004; Wu et al., 2009). When the atom-based binding energies of entecavir, another acyclovir-derived antiviral drug, were examined, it was observed that oxygen and hydrogen atoms in the hydroxyl groups attached to the cyclopentane ring, which resembles the deoxyribose structure, contributed to molecular affinity to the enzyme, and the binding energies of nitrogen and hydrogen in the guanine part were investigated to responsible for the total binding energy of the molecule. Moreover, it was observed that nitrogen and oxygen, especially in the amide groups, provide higher affinity to the enzyme with low binding energy and formed a large part of the active site of the tecovirimat compound. Also, a recent study on the monkeypox virus supports our result that tecovirimat was reported as a potential antiviral agent against the infection and claimed to be a good candidate for monkeypox treatment (Adler et al., 2022; Nakoune & Olliaro, 2022). According to our results, the other antiviral agent that can be used for monkeypox infection was aphidicolin. It was observed that hydroxyl groups on the aphidicolin molecule greatly contribute its binding affinity to DNA polymerase enzyme and oxygen and hydrogen atoms on the functional group decrease its binding energy against the enzyme (Figure 11).

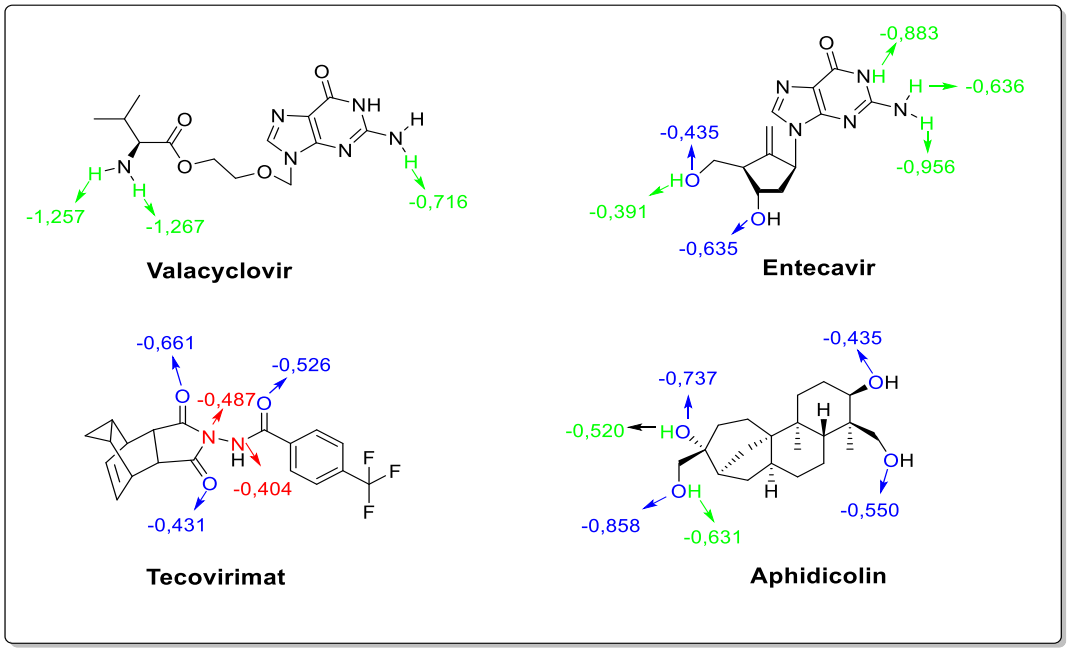


Figure 11. Individual binding energies of each atom on candidate drugs against DNA polymerase enzyme.

Molecular Docking analyses for the RNA polymerase enzyme showed that the binding energies of 2 antiviral drug candidates were significantly low that can be potential agents for the monkeypox treatment. When the atomic-based binding energies of emetine were examined, it was seen that the oxygen atoms of the methoxy groups are the highest contributors to the binding affinity of the compound against the RNA polymerase enzyme. Also, previous studies support our results that methoxy groups are the main structural requirement for Emetine's biological activities (Akinboye & Bakare, 2011; Zhou et al., 2005). Besides, previous studies showed that structural modifications were performed to enhance the biological activity of BMH-21 as an antiviral agent and preliminary information was given for the active site of the compound (Colis et al., 2014). Accordingly, it was observed that binding energies related to nitrogen atoms in the molecule significantly contributed to enzyme affinity. It was also observed that the primary binding mechanism could occur through hydrophobic interactions between oxygen atoms in the pyrimidine ring and the carbons in the 1 and 2 positions of the naphthalene part of the compound (Figure 12). The molecular docking results revealed that the RMSD values were below 2 Å, indicating that the docked conformations are highly similar to the reference structures.

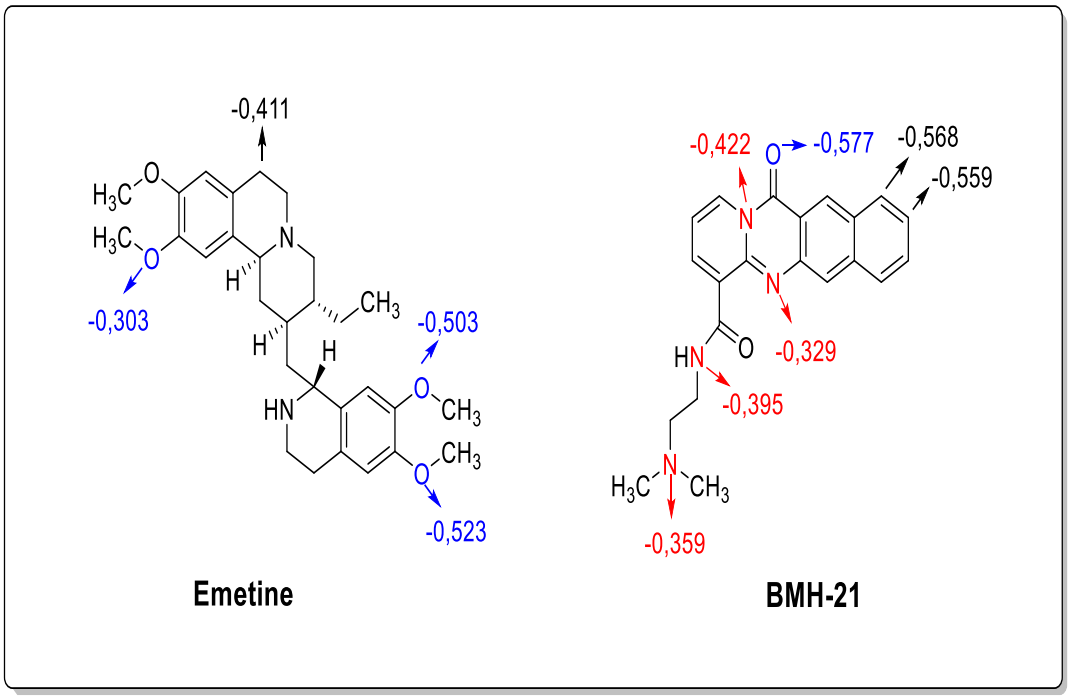


Figure 12. Individual binding energies of each atom on candidate drugs against RNA polymerase enzyme.

A. Molecular Dynamics (MD) Simulation

Molecular Dynamics (MD) simulation stands as a powerful computational tool in forecasting the dynamic trajectory of interacting particles, such as atoms and molecules. Its significance has notably surged in modern drug development, offering the capability to anticipate the intricate behavior of biomolecules, particularly proteins, with atomic precision and high temporal granularity. The fundamental concept underlying MD simulations involves computing the forces acting on each atom due to the entirety of other atoms within a biomolecular system. Newton's laws of motion are subsequently employed to predict the spatial coordinates of each atom over time. In the realm of drug development, MD simulations prove invaluable for assessing how a biomolecular system reacts to specific perturbations, such as the detachment of a ligand from a protein structure determined experimentally (Aswathy et al., 2024). The selection of the complex with the most favorable binding energy sets the stage for an in-depth MD simulation study. This analysis seeks to unravel the stability of the ligand-protein compound, scrutinizing its dynamics over a substantial period, often extending up to 100 nanoseconds (Hansson et al., 2002). In the molecular dynamics simulation process, the Optimized Potentials for Liquid Simulations All Atom (OPLS-AA) force field has been considered.

Root Mean Square Deviation (RMSD) and Root Mean Square Fluctuation (RMSF) analyses were used to evaluate the structural resistance of the MD-simulated compound. Figure 13 (a, b, c, d) below visually

summarizes these findings. Inspection of the RMSD profile of the complex reveals a remarkable constancy over a period of 100 nanoseconds (Martínez, 2015). A lower RMSD indicates a greater stability. The RMSDs of the two complexes exhibited stability at approximately 0.32- 0.27 nm and 1.00- 0.86 nm, respectively, while the 5N2E (DNA polymerase)-Etravirine compound was in the range of 0.3 nm (3 Å) with minimal fluctuations and the 6RFL (DNA-dependent RNA polymerase subunit rpo147)-Emetine compound was in the range of 0.85 nm with minimal fluctuations. It is a valuable indicator of stereo chemical stability for 5N2E-Etravirine, which is a key feature for molecular interactions. In conclusion, 5N2E-Etravirine and relatively 6RFL-Emetine showed favorable structural stability during MD simulation. Focusing on more in-depth dynamics for 5N2E-Etravirine, the RMSD values remained consistently below 3 Å throughout the simulation, reflecting the robustness of the complex. Notably, within each nanosecond window, the RMSD fluctuations were consistently confined to less than 1 Å. This nuanced observation underscores the marginal impact of ligand binding on the overall structural stability, affirming the enduring robustness of the ligand-protein complex throughout the 100 nanoseconds simulation.

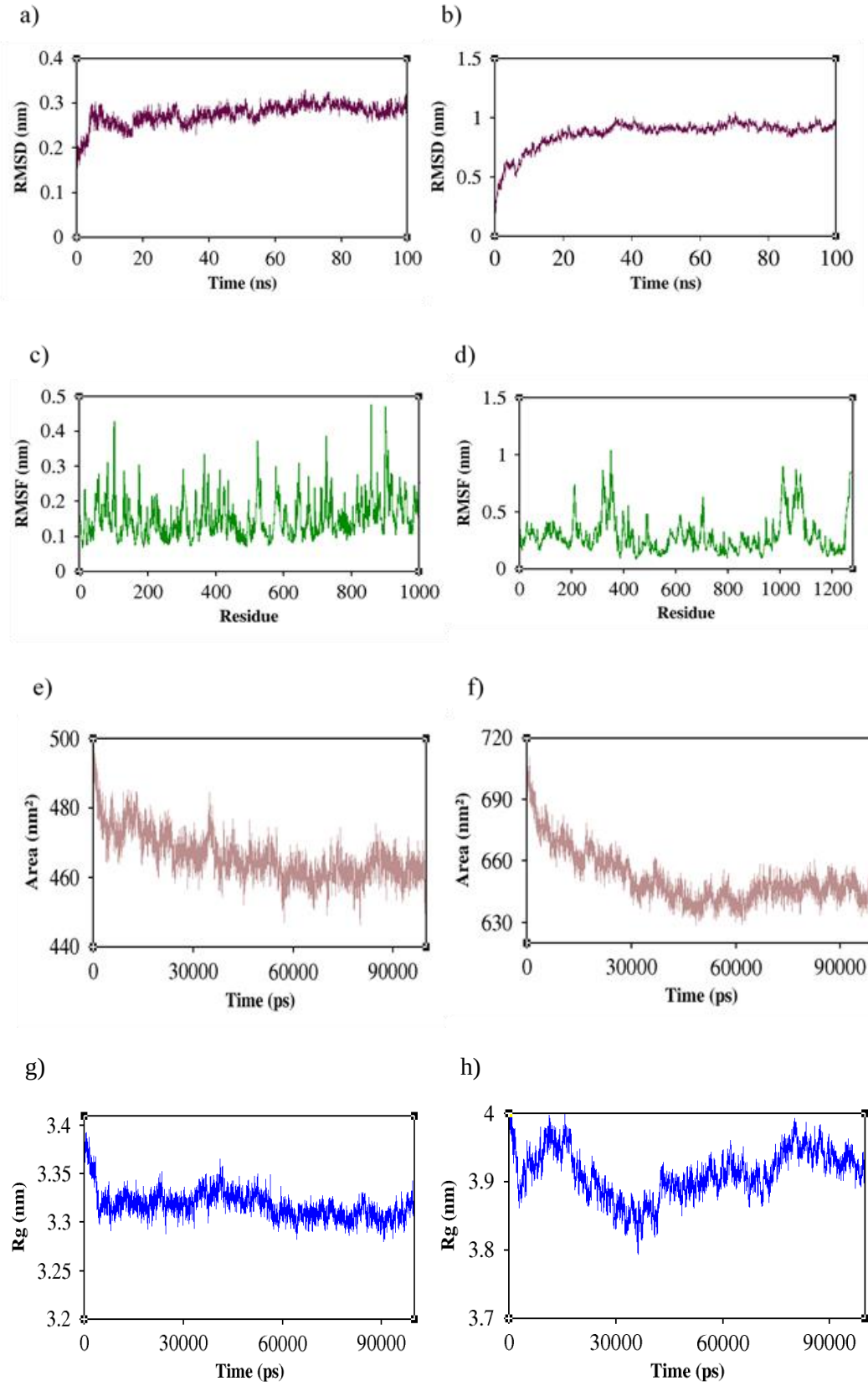
Beyond the investigation into Root Mean Square Deviation (RMSD), an additional layer of scrutiny was applied through Root Mean Square Fluctuation (RMSF) analysis. This examination sought to elucidate the extent of variations in amino acid residues within the docked complex. RMSF is often used to describe the structural adaptability of each protein residue. Lower RMSF offers less flexibility, which is mainly related to the interactions between protein and ligand. Notably, the docked complex with superior attributes consistently exhibited the lowest RMSF values. Post-ligand binding, the complexes exhibited a sustained RMSF profile, signifying a remarkable stability in the overall composition at the residue level. The RMSF values, representing the typical atomic shifts within the complex during the simulation, demonstrated a predominant stability, consistently remaining below 3 Å for 5N2E-Etravirine and below 5 Å for 6RFL-Emetine. While some initial fluctuations were observed, the overall trend highlighted that the core composition of the complex remained largely unaltered despite the dynamic process of ligand binding. This resilience at the residue level further underscores the robust and enduring nature of the complex structure following the binding event. As shown in Figure 13 (c and d), the RMSF values of all residues in 5N2E-Etravirine and 6RFL-Emetine were lower than 0.4 nm and 0.5 nm, respectively, except for some fluctuations, revealing the favorable stability of the protein residues during MD simulation and the promising binding affinity between the two proteins and the ligands Etravirine and Emetine.

The investigation into the protein-ligand complex extended to the Solvent Accessible Surface Area (SASA) analysis, a pivotal examination shedding light on structural changes. This analysis holds particular significance in unraveling how the complex engages with its environment, specifically interacting with solvent molecules. By gauging alterations in the protein's surface accessibility, the SASA analysis offered insights into potential shifts in its structure (Boroujeni et al., 2021). The SASA plot unveiled a consistent structural profile, suggesting that the introduction of the ligand did not lead to any substantial expansion of the protein volume. In Figure 13 (e and f), the SASA values prove that the structural consistency of the complex remains, maintaining a level below 480 $(nm)^2$ and 690 $(nm)^2$ for 5N2E-Etravirine and 6RFL-Emetine, respectively, regardless of minimal waves.

In scrutinizing the robustness of the complex post-Molecular Dynamics (MD) simulation, attention was directed toward the radius of gyration (Rg) as a crucial metric. Serving as a key gauge for the compactness of molecular structures, lower Rg values signify a more condensed and stable complex (Amani et al., 2011). The Rg analysis provided profound insights into the overarching architecture of the complex. Throughout the simulation, the Rg fluctuations of the two complexes consistently maintained a low profile, underscoring their enduring compactness and stability. The calculated Rg values hover around 3.3 nm and 3.92 nm for 5N2E-Etravirine and 6RFL-Emetine, providing numerical evidence of sustained robustness of the two complexes. This corroborates the proposition that the complex, engendered through the intricate interplay of ligand and protein binding, not only retains stability at the atomic and residue levels but also preserves a notably compact and well-structured state. This observation solidifies the narrative of the complex as a strong entity in the molecular landscape, further accentuating its resilience in the dynamic milieu of molecular interactions.

Finally, DSSP analysis was performed to determine whether the secondary structure of 5N2E-Etravirine and 6RFL-Emetine was stable during the MD simulation. As shown in Figure 13 (i and j), no detectable changes were found in the secondary structural elements of 5N2E-Etravirine and 6RFL-Emetine proteins, suggesting proper structural stability of the two protein-ligand complexes.

The exhaustive scrutiny of the protein-ligand complex, employing a diverse array of structural assessments encompassing RMSD, RMSF, SASA, Rg, and secondary structural analyses, collectively unveils a compelling narrative of its extraordinary stability and adaptability for diverse applications.


a)
RMSD (nm)
Time (ns)
b)
RMSD (nm)
Time (ns)
c)
RMSF (nm)
Residue
d)
RMSF (nm)
Residue
e)
Area (nm²)
Time (ps)
f)
Area (nm²)
Time (ps)
g)
Rg (nm)
Time (ps)
h)
Rg (nm)
Time (ps)

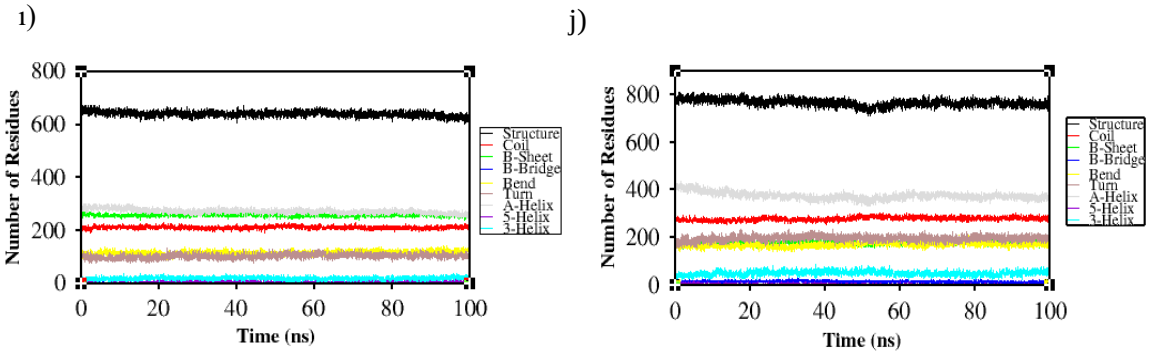


Figure 13. MD simulation of Etravirine and Emetine ligands in complex with 5N2E and 6RFL proteins with respectively. a), b) RMSD of 5N2E- Etravirine and 6RFL- Emetine complexes. c), d) RMSF of 5N2E-Etravirine and 6RFL-Emetine complexes. e), f) SASA of 5N2E-Etravirine and 6RFL-Emetine complexes. g), h) Rg of 5N2E-Etravirine and 6RFL-Emetine complexes. ı), j) Secondary structural analysis of 5N2E-Etravirine and 6RFL-Emetine complexes.

In addition to docking studies, these MD simulation results also reveal that the molecules mentioned above are potent drug candidates for Monkeypox disease.

As the world approaches the end of the COVID-19 pandemic, we may face a new epidemic, the monkeypox virus infection. Also, valuable experiences were obtained from the COVID-19 pandemic that new strategies should be constituted for upcoming pandemics to prepare global public health systems for evading negative impacts on economic and social areas. Recently, human monkeypox cases emerged and the number of reported case numbers increasing steadily in Europe and USA (Petersen et al., 2019; Zumla et al., 2022). New approaches must be used to deal with this latest epidemic before it gets out of control. One of the fastest strategies in drug discovery studies for a new disease is drug repurposing of the previous disease by using disease similarities and mechanism comparisons. For this purpose, previous viral infections are analyzed and similarities and treatment options are compared to choose the fittest drug candidates for suitable applications (Iorio et al., 2010; Hegde et al., 2015; Chiang & Butte, 2009). Different computational-based approaches can be used to repurpose known drugs into a whole different disease with a good level of treatment success. One of the strongest computer-aided drug discovery method is molecular docking analyses (Chen et al., 2020; Meng et al., 2011; Pagadala et al., 2017). In the present study, molecular docking investigations were used to identify possible candidate drugs for the monkeypox infection and nucleic acid synthesis mechanisms of the virus were targeted to determine the mode of action of the drugs.

Before the molecular docking analyses, nucleic acid synthesis enzymes were targeted for the monkeypox virus. On the other hand, there were no 3D structure models in the PDB database for DNA and RNA polymerases. Thus, the closest protein structures for monkeypox were identified by using protein-protein blast analyses of NCBI database. It was found that both DNA and RNA polymerases from the vaccina virus were close enough to monkeypox enzymes to use as template enzymes for drug targeting. Also, it was known that the smallpox vaccine was developed by using vaccinia virus information and it was claimed that the smallpox vaccine should be effective against monkeypox infection about 85% (McCollum & Damon, 2014; Moss, 1991; Neff, 2002). From this information, it was thought that vaccinia virus DNA and RNA polymerases were suitable templates for drug targeting in monkeypox virus drug screening. After drug targets were identified, a literature search was performed for potential drug candidates for these enzymes. It was determined from hundreds of antiviral agents that 21 potential drugs were chosen as DNA and RNA polymerase inhibitor candidates to be investigated in molecular docking analyses. From these analyses, 5 potential DNA inhibitors and 2 potential RNA inhibitors for monkeypox were identified with a higher affinity to enzymes from other candidate drugs.

According to molecular docking analysis, the best DNA polymerase inhibitors for the monkeypox virus are aphidicolin, entecavir, tecovirimat, valaciclovir and etravirine molecules. Previous studies showed that aphidicolin has great antiviral potential against different virus species through the DNA polymerase inhibition mechanism. Aphidicolin is especially effective against the herpes virus and it is an FDA-approved drug for the treatment of herpes infection (Michaelis et al., 2002; Normand et al., 2021; Pedrali-Noy & Spadari, 1979). Another potential antiviral molecule proposed in this study against monkeypox infection is entecavir. The antiviral potential of entecavir through inhibition of DNA polymerase activity was validated against the hepatitis B virus in different studies (Honkoop & de Man, 2003; Mazzucco et al., 2008). Moreover, molecular docking analyses on tecovirimat put forth that it could be a good candidate drug for

monkeypox treatment because of its high affinity against DNA polymerase enzyme. It was claimed that entecavir application has a high potential in infections of the orthopoxvirus family including the monkeypox virus (Adalja & Inglesbv, 2019; Yu & Raj, 2019). In the present study, the valaciclovir molecule was found to have a good DNA polymerase inhibitory property compare to other drug candidates with the lowest binding energy of -7.57 Kcal/mol. Valaciclovir is a highly effective antiviral agent that targets viral nucleic acid synthesis through inhibiting the DNA polymerase enzyme. Valaciclovir is especially recommended to use against hepatitis B and herpes virus infections (Laube et al., 2004; Shiraki, 2018; Snoeck, 2000). Moreover, molecular docking investigations on etravirine showed that it has the most potent DNA polymerase inhibitor among other candidate drugs with -8.04 Kcal/mol binding energy. Etravirine is FDA approved antiviral drug used for HIV treatment because of its DNA and RNA-dependent polymerase inhibitory activity. Etravirine has also been shown that it does not inhibit DNA polymerase enzymes (Croxtall, 2012; Schrijvers, 2013). However, the statement refers specifically to the lack of inhibitory activity against human DNA polymerases, while in this study, molecular docking results suggest that etravirine could exhibit binding affinity to the monkeypox virus DNA polymerase, which possesses distinct structural and functional properties. Therefore, our findings proposed a potential novel interaction that warrants further experimental validation.

Additionally, docking investigations of RNA polymerase enzyme displayed 2 highly potent drugs against monkeypox infection. It was found that Bmh-21 and emetine dihydrochloride molecules show a significant affinity and possible inhibitory properties against the monkeypox RNA polymerase enzyme. The bmh-21 molecule was shown to inhibit RNA polymerase enzyme selectively and this compound was claimed to inhibit tumor growth via the transcriptomic inhibition that can be used as an antiviral agent through RNA polymerase targeting (Jacobs et al., 2022; Peltonen et al., 2014; Wei et al., 2018). On the other hand, emetine dihydrochloride was hypothesized to have the highest affinity and inhibitory capacity against monkeypox RNA polymerase enzyme with the binding energy of -7.17 Kcal/mol. Previous studies showed that emetine is a highly effective antiviral agent that can prevent viral replication in both RNA and DNA viruses through inhibiting transcriptomic mechanisms and it was proposed to have an inhibitory effect on SARS-CoV2 (Choy et al., 2020; Khandelwal et al., 2017). Although tecovirimat is already recognized as an FDA-approved antiviral agent specifically targeting Orthopoxviruses, including monkeypox virus (MPXV), its binding affinity in our molecular docking analysis was observed to be lower than that of etravirine and valaciclovir. Tecovirimat showed a binding energy of -6.70 kcal/mol against DNA polymerase, whereas etravirine and valaciclovir exhibited more favorable energies of -8.04 and -7.57 kcal/mol, respectively. Similarly, emetine, which targets RNA polymerase, demonstrated a binding affinity of -7.17 kcal/mol, outperforming tecovirimat in terms of predicted interaction strength. These findings suggest that, while tecovirimat is an established antiviral with proven efficacy in vivo through inhibition of the VP37 protein involved in viral egress, the newly proposed candidates may offer additional or complementary mechanisms of action, particularly by targeting the viral replication machinery directly. Literature reports also support the strong inhibitory potential of etravirine and emetine against viral polymerases in other viruses, highlighting their potential for repurposing. Therefore, while tecovirimat remains a cornerstone in current MPXV treatment approaches, the inclusion of DNA/RNA polymerase-targeting agents may enhance therapeutic efficacy, reduce viral load more effectively, or help mitigate resistance when used in combination therapy (Arslan et al., 2023; Gouleni et al., 2023; Turkez et al., 2023).

IV. CONCLUSION

In this study, we aimed to identify potential drug candidates for the treatment of monkeypox infection through an in silico drug repurposing approach. To achieve this, the literature was thoroughly reviewed to select potent DNA and RNA polymerase inhibitors that are already approved and used in clinical settings for other viral diseases. By employing a drug repurposing strategy, we sought to overcome the time and cost barriers associated with the de novo development of antiviral therapies during potential epidemics. Our molecular docking and molecular dynamics simulation analyses identified several promising antiviral agents against monkeypox virus targets. Specifically, valaciclovir and etravirine were determined to have the strongest binding affinities to the active site of DNA polymerase, while emetine exhibited significant binding affinity to the RNA polymerase enzyme, suggesting its potential to interfere with the viral transcription process. Based on these findings, valaciclovir, etravirine, and emetine emerge as promising candidates for repositioning as therapeutic agents against monkeypox virus infection. Given that these drugs have already passed clinical safety evaluations for other indications, their repurposing could facilitate faster clinical deployment following efficacy validation. However, it should be noted that the inhibition constants observed in this study, although indicative of potential antiviral activity, were at the micromolar level, which may not be optimal for clinical application without further optimization. Moreover, as

molecular docking and simulation approaches provide only preliminary, predictive insights, the efficacy of these candidates must be confirmed through comprehensive in vitro and in vivo experimental studies. Future work should focus on experimental validation of these findings, including enzyme inhibition assays, viral replication studies in cell cultures, and eventually preclinical animal studies, to confirm the therapeutic potential of the identified compounds against monkeypox virus. If validated, this approach may serve as a model for rapid therapeutic development against future emerging viral threats.

In addition to the computational findings, the biological implications of the identified compounds should be emphasized to strengthen the translational relevance of this study. The observed high binding affinities of etravirine and valaciclovir to the DNA polymerase, and emetine to the RNA polymerase, suggest a potential inhibition of monkeypox virus (MPXV) replication machinery. Such inhibition could plausibly result in a significant reduction of viral load in infected cells, which is a critical step in halting disease progression and transmission. However, despite these promising in silico results, clinical translation may encounter several challenges. These include the pharmacokinetic limitations of the proposed drugs in targeting viral reservoirs, potential off-target effects due to structural similarities between viral and host polymerases, and the possibility of drug resistance development. Moreover, the effectiveness of these compounds in reducing MPXV transmission in vivo, particularly in human populations with variable immune status, remains uncertain. Therefore, future studies should focus on validating the antiviral activity of these drugs through robust in vitro assays, animal models, and ultimately, well-designed clinical trials to assess both efficacy and safety profiles in the context of MPXV infection.

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Conflict of Interest Disclosure: The author/authors declare no conflict of interest.

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Plagiarism Statement: This article has been evaluated for plagiarism and no instances of plagiarism were detected.

Availability of Data and Materials: Data sharing is not applicable to this study.

Use of AI Tools: The author/authors declare that no Artificial Intelligence (AI) tools were used in the creation of this article.

REFERENCES

Adalja, A., & Inglesby, T. (2019). Broad-spectrum antiviral agents: a crucial pandemic tool. *Expert Review of Anti-Infective Therapy*, *17*(7), 467-470. https://doi.org/10.1080/14787210.2019.1635009

Adler, H., Gould, S., Hine, P., Snell, L. B., Wong, W., Houlihan, C. F., Osborne, J. C., Rampling, T., Beadsworth, M. B. J., Duncan, C. J. A., Dunning, J., Fletcher, T. E., Hunter, E. R., Jacobs, M., Khoo, S. H., Newsholme, W., Porter, D., Porter, R. J., Ratcliffe, L., … Price, N. M. (2022). Clinical features and management of human monkeypox: A retrospective observational study in the UK. *The Lancet Infectious Diseases, 22*(8), 1153-1162. https://doi.org/10.1016/S1473-3099(22)00228-6

Akinboye, E. S., & Bakare, O. (2011). Biological activities of emetine. *The Open Natural Products Journal*, *411*(8), 8-15. https://doi.org/10.2174/1874848101104010008

Amani, A., York, P., de Waard, H., & Anwar, J. (2011). Molecular dynamics simulation of a polysorbate 80 micelle in water. *Soft Matter*, *7*(6), 2900-2908. https://doi.org/10.1039/C0SM00965B

Arslan, M. E., Türkez, H., Sevim, Y., Selvitopi, H., Kadi, A., Öner, S., & Mardinoğlu, A. (2023). Costunolide and parthenolide ameliorate MPP+ induced apoptosis in the cellular Parkinson's disease model. *Cells*, *12*(7), Article 992. https://doi.org/10.3390/cells12070992

Ashburn, T. T., & Thor, K. B. (2004). Drug repositioning: Identifying and developing new uses for existing drugs. *Nature Reviews Drug Discovery*, *3*, 673-683. https://doi.org/10.1038/nrd1468

Aswathy, S. V., Joe, I. H., Rameshkumar, K. B., & Ibrahim, J. M. (2024). Insights into the role of RAHB and IHB interactions for the structure-activity relationship of caged xanthone morellic acid: Spectroscopic and DFT exploration, molecular docking, and molecular dynamics simulation studies as an antituberculosis agent. *Journal of Molecular Structure*, *1303*(1), Article 137429. https://doi.org/10.1016/j.molstruc.2023.137429

Boroujeni, M. B., Dastjerdeh, M. S., Shokrgozar, M., Rahimi, H., & Omidinia, E. (2021). Computational driven molecular dynamics simulation of keratinocyte growth factor behavior at different pH conditions. *Informatics in Medicine Unlocked*, *23*(1), Article 100514. https://doi.org/10.1016/j.imu.2021.100514

Breckenridge, A., & Jacob, R. (2019). Overcoming the legal and regulatory barriers to drug repurposing. *Nature Reviews Drug Discovery*, *18*, 1-2. https://doi.org/10.1038/nrd.2018.92

Brown, K., & Leggat, P. (2016). Human monkeypox: Current state of knowledge and implications for the future. *Tropical Medicine and Infectious Disease, 1*(1), Article 8. https://doi.org/10.3390/tropicalmed1010008

Bunge, E. M., Hoet, B., Chen, L., Lienert, F., Weidenthaler, H., Baer, L. R., & Steffen, R. (2022). The changing epidemiology of human monkeypox—A potential threat? A systematic review. *PLoS Neglected Tropical Diseases*, *16*(2), Article e0010141. https://doi.org/10.1371/journal.pntd.0010141

Caufriez, A., Tabernilla, A., Van Campenhout, R., Cooreman, A., Leroy, K., Sanz Serrano, J., Kadam, P., dos Santos Rodrigues, B., Lamouroux, A., Ballet, S., & Vinken, M. (2022). Effects of drugs formerly suggested for COVID-19 repurposing on pannexin1 channels. *International Journal of Molecular Sciences*, *23*(10), Article 5664. https://doi.org/10.3390/ijms23105664

Chen, G., Seukep, A. J., & Guo, M. (2020). Recent advances in molecular docking for the research and discovery of potential marine drugs. *Marine Drugs*, *18*(11), Article 545. https://doi.org/10.3390/md18110545

Chiang, A. P., & Butte, A. J. (2009). Systematic evaluation of drug–disease relationships to identify leads for novel drug uses. *Clinical Pharmacology & Therapeutics*, *86*(5), 507-510. https://doi.org/10.1038/clpt.2009.103

Choy, K. T., Wong, A. Y. L., Kaewpreedee, P., Sia, S. F., Chen, D., Hui, K. P. Y., Chu, D. K. W., Chan, M. C. W., Cheung, P. P. H., Huang, X., Peiris, M., & Yen, H. L. (2020). Remdesivir, lopinavir, emetine, and homoharringtonine inhibit SARS-CoV-2 replication in vitro. *Antiviral Research*, *178*, Article 104786. https://doi.org/10.1016/j.antiviral.2020.104786

Colis, L., Ernst, G., Sanders, S., Liu, H., Sirajuddin, P., Peltonen, K., DePasquale, M., Barrow, J. C., & Laiho, M. (2014). Design, synthesis, and structure–activity relationships of pyridoquinazolinecarboxamides as RNA polymerase I inhibitors. *Journal of Medicinal Chemistry*, *57*(11), 4950-4961. https://doi.org/10.1021/jm5004842

Croxtall, J. D. (2012). Etravirine: A review of its use in the management of treatment-experienced patients with HIV-1 infection. *Drugs*, *72*(6), 847-869. https://doi.org/10.2165/11209110-000000000-00000

Damon, I. K. (2011). Status of human monkeypox: Clinical disease, epidemiology and research. *Vaccine*, *29* (Suppl 4), D54-D59. https://doi.org/10.1016/j.vaccine.2011.04.014

Fadlalla, M., Ahmed, M., Ali, M., Elshiekh, A. A., & Yousef, B. A. (2022). Molecular docking as a potential approach in repurposing drugs against COVID-19: A systematic review and novel pharmacophore models. *Current Pharmacology Reports*, *8*(3), 212-226. https://doi.org/10.1007/s40495-022-00285-w

Fife, K. H., Barbarash, R. A., Rudolph, T., Degregorio, B., Roth, R., & Valaciclovir International Herpes Simplex Virus Study Group (1997). Valaciclovir versus acyclovir in the treatment of first-episode genital herpes infection: results of an international, multicenter, double-blind, randomized clinical trial. *Sexually Transmitted Diseases*, *24*(8), 481-486. https://doi.org/10.1097/00007435-199709000-00007

Gouleni, N., Di Rienzo, A., Yılmaz, A., Selvitopi, H., Arslan, M. E., Mardinoglu, A., Turkez, H., Di Stefano, A., Vassiliou, S., & Cacciatore, I. (2023). Novel styryl-thiazole hybrids as potential anti-Alzheimer's agents. *RSC Medicinal Chemistry*, *14*(11), 2315-2326. https://doi.org/10.1039/d3md00308f

Grimm, C., Hillen, H. S., Bedenk, K., Bartuli, J., Neyer, S., Zhang, Q., Hüttenhofer, A., Erlacher, M., Dienemann, C., Schlosser, A., Urlaub, H., Böttcher, B., Szalay, A. A., Cramer, P., & Fischer, U. (2019). Structural basis of poxvirus transcription: Vaccinia RNA polymerase complexes. *Cell*, *179*(7), 1537-1550.e19. https://doi.org/10.1016/j.cell.2019.11.024

Halder, D., Das, S., Joseph, A., & Jeyaprakash, R. S. (2023). Molecular docking and dynamics approach to *in silico* drug repurposing for inflammatory bowel disease by targeting TNF alpha. *Journal of Biomolecular Structure and Dynamics*, *41*(8), 3462-3475. https://doi.org/10.1080/07391102.2022.2050948

Hansson, T., Oostenbrink, C., & van Gunsteren, W.F.V. (2002). Molecular dynamics simulations. *Current Opinion in Structural Biology*, *12*(2), 190-196. https://doi.org/10.1016/S0959-440X(02)00308-1

Hegde, R. N., Parashuraman, S., Iorio, F., Ciciriello, F., Capuani, F., Carissimo, A., Carrella, D., Belcastro V., Subramanian, A., Bounti, L., Persico, M., Carlile, G., Galietta, L., Thomas, D. Y., Di Bernardo, D., & Luini, A. (2015). Unravelling druggable signalling networks that control F508del-CFTR proteostasis. e*Life*, *4*, Article e10365. https://doi.org/10.7554/elife.10365

Honkoop, P., & de Man, R. A. (2003). Entecavir: A potent new antiviral drug for hepatitis B. *Expert Opinion on Investigational Drugs*, *12*(4), 683-688. https://doi.org/10.1517/13543784.12.4.683

Hutin, Y. J., Williams, R. J., Malfait, P., Pebody, R., Loparev, V. N., Ropp, S. L., Rodriguez, M., Knight, J. C., Tshioko, F. K., Khan, A. S., Szczeniowski, M. V., & Esposito, J. J. (2001). Outbreak of human monkeypox, Democratic Republic of Congo, 1996 to 1997. *Emerging Infectious Diseases*, *7*(3), 434-438. https://doi.org/10.3201/eid0703.017311

Iorio, F., Isacchi, A., Di Bernardo, D., & Brunetti-Pierri, N. (2010). Identification of small molecules enhancing autophagic function from drug network analysis. *Autophagy*, *6*(8), 1204-1205. https://doi.org/10.4161/auto.6.8.13551

Jacobs, R. Q., Huffines, A. K., Laiho, M., & Schneider, D. A. (2022). The small-molecule BMH-21 directly inhibits transcription elongation and DNA occupancy of RNA polymerase I *in vivo* and *in vitro*. *Journal of Biological Chemistry*, *298*(1), Article 101450. https://doi.org/10.1016/j.jbc.2021.101450

Jalalvand, A., Khatouni, S. B., Najafi, Z. B., Fatahinia, F., Ismailzadeh, N., & Farahmand, B. (2022). Computational drug repurposing study of antiviral drugs against main protease, RNA polymerase, and spike proteins of SARS-CoV-2 using molecular docking method. *Journal of Basic and Clinical Physiology and Pharmacology*, *33*(1), 85-95. https://doi.org/10.1515/jbcpp-2020-0369

Jayaram, B., Singh, T., Mukherjee, G., Mathur, A., Shekhar, S., & Shekhar, V. (2012). Sanjeevini: A freely accessible web-server for target directed lead molecule discovery. *BMC Bioinformatics, 13* (Suppl 17), S7. https://doi.org/10.1186/1471-2105-13-S17-S7

Kao, A. (2003). Diagnosis and management of smallpox. *AMA Journal of Ethics*, *5*(2), 51-53. https://doi.org/10.1001/virtualmentor.2003.5.2.cprl1-0302

Kast, R. E., Alfieri, A., Assi, H. I., Burns, T. C., Elyamany, A. M., Gonzalez-Cao, M., Karpel-Massler, G., Marosi, C., Salacz, M. E., Sardi, I., Van Vlierberghe, P., Zaghloul, M. S., & Halatsch, M. E. (2022). Mdact: A new principle of adjunctive cancer treatment using combinations of multiple repurposed drugs, with an example regimen. *Cancers*, *14*(10), Article 2563. https://doi.org/10.3390/cancers14102563

Khandelwal, N., Chander, Y., Rawat, K. D., Riyesh, T., Nishanth, C., Sharma, S., Jindal, N., Tripathi, B. N., Barua, S., & Kumar, N. (2017). Emetine inhibits replication of RNA and DNA viruses without generating drug-resistant virus variants. *Antiviral Research*, *144*, 196-204. https://doi.org/10.1016/j.antiviral.2017.06.006

Kleymann, G. (2004). Discovery, SAR and medicinal chemistry of herpesvirus helicase primase inhibitors. *Current Medicinal Chemistry-Anti-Infective Agents*, *3*(1), 69-83. https://doi.org/10.2174/1568012043354242

Kumar, S., Kovalenko, S., Bhardwaj, S., Sethi, A., Gorobets, N. Y., Desenko, S. M., & Rathi, B. (2022). Drug repurposing against SARS-CoV-2 using computational approaches. *Drug Discovery Today*, *27*(7), 2015-2027. https://doi.org/10.1016/j.drudis.2022.02.004

Laskowski, R. A., & Swindells, M. B. (2011). LigPlot+: Multiple ligand–protein interaction diagrams for drug discovery. *Journal of Chemical Information and Modeling*, *51*(10), 2778-2786. https://doi.org/10.1021/ci200227u

Laube, I., Boehler, A., Renner, E. L., & Speich, R. (2004). Valaciclovir for chronic hepatitis B virus infection after lung transplantation. *Infection*, *32*(1), 51-53. https://doi.org/10.1007/s15010-003-3094-5

Lazniewski, M., Dermawan, D., Hidayat, S., Muchtaridi, M., Dawson, W. K., & Plewczynski, D. (2022). Drug repurposing for identification of potential spike inhibitors for SARS-CoV-2 using molecular docking

and molecular dynamics simulations. *Methods*, *203*, 498-510. https://doi.org/10.1016/j.ymeth.2022.02.004

Likos, A. M., Sammons, S. A., Olson, V. A., Frace, A. M., Li, Y., Olsen-Rasmussen, M., Davidson, W., Galloway, R., Khristova, M. L., Reynolds, M. G., Zhao, H., Carroll, D. S., Curns, A., Formenty, P., Esposito, J. J., Regnery, R. L., & Damon, I. K. (2005). A tale of two clades: Monkeypox viruses. *Journal of General Virology*, *86*(10), 2661-2672. https://doi.org/10.1099/vir.0.81215-0

MacDougall, C., & Guglielmo, B. J. (2004). Pharmacokinetics of valaciclovir. *Journal of Antimicrobial Chemotherapy*, *53*(6), 899-901. https://doi.org/10.1093/jac/dkh244

Martínez, L. (2015). Automatic identification of mobile and rigid substructures in molecular dynamics simulations and fractional structural fluctuation analysis. *PLOS ONE*, *10*(3), e0119264. https://doi.org/10.1371/journal.pone.0119264

Mazzucco, C. E., Hamatake, R. K., Colonno, R. J., & Tenney, D. J. (2008). Entecavir for treatment of hepatitis B virus displays no in vitro mitochondrial toxicity or DNA polymerase gamma inhibition. *Antimicrobial Agents and Chemotherapy, 52*(2), 598-605. https://doi.org/10.1128/aac.01122-07

McCollum, A. M., & Damon, I. K. (2014). Human monkeypox. *Clinical Infectious Diseases*, *58*(2), 260-267. https://doi.org/10.1093/cid/ciu196

Meng, X. Y., Zhang, H. X., Mezei, M., & Cui, M. (2011). Molecular docking: A powerful approach for structure-based drug discovery. *Current Computer-Aided Drug Design*, *7*(2), 146-157. https://doi.org/10.2174/157340911795677602

Michaelis, M., Langer, K., Vogel, J. U., Kreuter, J., Rabenau, H., Doerr, H. W., & Cinatl, J. (2002). In vitro antiviral activity of aphidicolin and its derivates. *Arzneimittelforschung*, *52*(5), 393-399. https://doi.org/10.1055/s-0031-1299904

Moss, B. (1991). Vaccinia virus: A tool for research and vaccine development. *Science*, *252*(5013), 1662-1667. https://doi.org/10.1126/science.2047875

Nakoune, E., & Olliaro, P. (2022). Waking up to monkeypox. *BMJ*, *377*, Article o1321. https://doi.org/10.1136/bmj.o1321

Neff, J. M., Lane, J. M., Fulginiti, V. A., & Henderson, D. A. (2002). Contact vaccinia—transmission of vaccinia from smallpox vaccination. *JAMA*, *288*(15), 1901-1905. https://doi.org/10.1001/jama.288.15.1901

Normand, C., Fortier, C., Thieulent, C., Marcillaud-Pitel, C., Pronost, S., & Hue, E. (2021, September). In vitro evaluation of nine antiviral compounds for their potential effect against equid herpesvirus-4. *In* Proceedings of the 11th International Equine Infectious Diseases Conference*, 53*(S56), Article 60. https://doi.org/10.1111/evj.89_13495

Okyay, R. A., Bayrak, E., Kaya, E., Şahin, A. R., Koçyiğit, B. F., Taşdoğan, A. M., Avcı, A., & Sümbül, H. E. (2022). Another epidemic in the shadow of COVID-19 pandemic: A review of monkeypox. *Eurasian Journal of Medical Oncology*, *6*(2), 95-99. https://doi.org/10.14744/ejmo.2022.2022

Ozdemir, E. S., Le, H. H., Yildirim, A., & Ranganathan, S. V. (2022). In silico screening and testing of FDA-approved small molecules to block SARS-CoV-2 entry to the host cell by inhibiting spike protein cleavage. *Viruses*, *14*(6), Article 1129. https://doi.org/10.3390/v14061129

Pagadala, N. S., Syed, K., & Tuszynski, J. (2017). Software for molecular docking: A review. *Biophysical Reviews*, *9*(2), 91-102. https://doi.org/10.1007/s12551-016-0247-1

Pammolli, F., Magazzini, L., & Riccaboni, M. (2011). The productivity crisis in pharmaceutical R&D. *Nature Reviews Drug Discovery*, *10*, 428-438. https://doi.org/10.1038/nrd3405

Pedrali-Noy, G., & Spadari, S. (1979). Effect of aphidicolin on viral and human DNA polymerases. *Biochemical and Biophysical Research Communications, 88*(4), 1194-1202. https://doi.org/10.1016/0006-291X(79)91106-9

Peltonen, K., Colis, L., Liu, H., Trivedi, R., Moubarek, M. S., Moore, H. M., Bai, B., Rudek, M. A., Bieberich, C. J., & Laiho, M. (2014). A targeting modality for destruction of RNA polymerase I that possesses anticancer activity. *Cancer Cell*, *25*(1), 77-90. https://doi.org/10.1016/j.ccr.2013.12.009

Petersen, E., Abubakar, I., Ihekweazu, C., Heymann, D., Ntoumi, F., Blumberg, L., Asogun, D., Mukonka, V., Lule, S. A., Bates, M., Honeyborne, I., Mfinanga, S., Mwaba, P., Dar, O., Vairo, F., Mukhtar, M., Kock, R., McHugh, T. D., Ippolito, G., & Zumla, A. (2019). Monkeypox—Enhancing public health preparedness for an emerging lethal human zoonotic epidemic threat in the wake of the smallpox post-eradication era. *International Journal of Infectious Diseases*, *78*, 78-84. https://doi.org/10.1016/j.ijid.2018.11.008

Pushpakom, S., Iorio, F., Eyers, P. A., Escott, K. J., Hopper, S., Wells, A., Doig, A., Guilliams, T., Latimer, J., McNamee, C., Norris, A., Sanseau, P., Cavalla, D., & Pirmohamed, M. (2019). Drug repurposing: Progress, challenges and recommendations. *Nature Reviews Drug Discovery*, *18*(1), 41-58. https://doi.org/10.1038/nrd.2018.168

Scannell, J. W., Blanckley, A., Boldon, H., & Warrington, B. (2012). Diagnosing the decline in pharmaceutical R&D efficiency. *Nature Reviews Drug Discovery*, *11*, 191-200. https://doi.org/10.1038/nrd3681

Schrijvers, R. (2013). Etravirine for the treatment of HIV/AIDS. *Expert Opinion on Pharmacotherapy*, *14*(8), 1087-1096. https://doi.org/10.1517/14656566.2013.787411

Shiraki, K. (2018). Antiviral drugs against alphaherpesvirus. *Advances in Experimental Medicine and Biology,* 1045, 103-122. https://doi.org/10.1007/978-981-10-7230-7_6

Singh, T., Biswas, D., & Jayaram, B. (2011). AADS-An automated active site identification, docking, and scoring protocol for protein targets based on physicochemical descriptors. *Journal of Chemical Information and Modeling*, *51*(10), 2515-2527. https://doi.org/10.1021/ci200193z

Snoeck, R. (2000). Antiviral therapy of herpes simplex. *International Journal of Antimicrobial Agents*, *16*(2), 157-159. https://doi.org/10.1016/S0924-8579(00)00233-8

Tarbouriech, N., Ducournau, C., Hutin, S., Mas, P. J., Man, P., Forest, E., Hart, D. J., Peyrefitte, C. N., Burmeister, W. P., & Iseni, F. (2017). The vaccinia virus DNA polymerase structure provides insights into the mode of processivity factor binding. *Nature Communications*, *8*(1), Article 1455. https://doi.org/10.1038/s41467-017-01542-z

Turkez, H., Arslan, M. E., Selvitopi, H., Kadi, A., Oner, S., & Mardinoglu, A. (2023). Drug synergism of anticancer action in combination with favipiravir and paclitaxel on neuroblastoma cells. *Medicina*, *60*(1), Article 82. https://doi.org/10.3390/medicina60010082

Ye, F., Song, J., Zhao, L., Zhang, Y., Xia, L., Zhu, L., Kamara, I. L., Ren, J., Wang, W., Tian, H., Wu, G., & Tan, W. (2019). Molecular evidence of human monkeypox virus infection, Sierra Leone. *Emerging Infectious Diseases*, *25*(6), 1220-1222. https://doi.org/https://doi.org/10.3201/eid2506.180296

Yuan, S., Chan, H. S., & Hu, Z. (2017). Using PyMOL as a platform for computational drug design. *Wiley Interdisciplinary Reviews: Computational Molecular Science*, *7*(2), Article e1298. https://doi.org/10.1002/wcms.1298

Yu, J., & Raj, S. M. (2019). Efficacy of three key antiviral drugs used to treat orthopoxvirus infections: A systematic review. *Global Biosecurity*, *1*(1), Article 28. https://doi.org/10.31646/gbio.12

Wei, T., Najmi, S. M., Liu, H., Peltonen, K., Kucerova, A., Schneider, D. A., & Laiho, M. (2018). Small-molecule targeting of RNA polymerase I activates a conserved transcription elongation checkpoint. *Cell Reports*, *23*(2), 404-414. https://doi.org/10.1016/j.celrep.2018.03.066

Wu, J., Hu, B., Lu, S., Duan, R., Deng, H., Li, L., He, L., Zhao, Y., Wang, J., & Yu, Z. (2022). Identification of raloxifene as a novel α-glucosidase inhibitor using a systematic drug repurposing approach in combination with cross molecular docking-based virtual screening and experimental verification. *Carbohydrate Research*, *511*, Article 108478. https://doi.org/10.1016/j.carres.2021.108478

Wu, Z., Drach, J. C., Prichard, M. N., Yanachkova, M., Yanachkov, I., Bowlin, T. L., & Zemlicka, J. (2009). L-valine ester of cyclopropavir: A new antiviral prodrug. *Antiviral Chemistry and Chemotherapy*, *20*(1), 37-46. https://doi.org/10.3851/IMP782

Zhou, Y. D., Kim, Y. P., Mohammed, K. A., Jones, D. K., Muhammad, I., Dunbar, D. C., & Nagle, D. G. (2005). Terpenoid tetrahydroisoquinoline alkaloids emetine, klugine, and isocephaeline inhibit the activation of hypoxia-inducible factor-1 in breast tumor cells. *Journal of Natural Products*, *68*(6), 947-950. https://doi.org/10.1021/np050029m

Zumla, A., Valdoleiros, S. R., Haider, N., Asogun, D., Ntoumi, F., Petersen, E., & Kock, R. (2022). Monkeypox outbreaks outside endemic regions: Scientific and social priorities. *The Lancet Infectious Diseases*, *22*(7), 929-931. https://doi.org/10.1016/S1473-3099(22)00354-1