

Original Article



Structure-based In-silico Screening Reveals Promising Repurposed Drugs for Targeting Monkeypox Virus Proteins

Mahdi Amirzadeh¹ , Ali Jabbarzadeh² , Shahed Ahmadi^{1*} , Mehroo Ahmadi³ , Mousa Ahmadi⁴

1. Department of Clinical Pharmacy, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

2. Department of Medicinal Chemistry, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

3. Institute for Cognitive Science Studies, Tehran, Iran.

4. Department of Infectious Disease, Faculty of Medicine, AJA University of Medical Sciences, Tehran, Iran.

* Corresponding Author:

Shahed Ahmadi

Address: Department of Clinical Pharmacy, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Phone: +98 (912) 0849978

E-mail: shahedahmadi@sbmu.ac.ir



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ABSTRACT

Background: Monkeypox (mpox) has re-emerged as a significant global health concern, with outbreaks prompting public health emergencies. Despite the availability of vaccines and a few non-specific antivirals, no targeted therapy has been approved for pox, underscoring the urgent need for novel treatment strategies.

Objectives: This study aimed to identify potential high-affinity drug candidates against mpox by repurposing existing compounds using structure-based molecular docking. It focused on five essential viral proteins involved in the virus's replication and pathogenesis.

Methods: Five mpox viral proteins—A48R (thymidylate kinase), A50R (DNA ligase), D13L (capsid protein), F13L (envelope protein), and I7L (cysteine protease)—were modeled using AlphaFold2 and prepared using Chimera and PyRx software. Over 300 compounds with known antiviral activity were screened using molecular docking with AutoDock Vina. The binding energies and protein-ligand interactions were analyzed using PyMOL and Discovery Studio. Top candidates were selected based on binding affinity, pharmacokinetics, and safety profiles.

Results: Several repurposed drugs demonstrated superior binding affinities compared to known inhibitors. Notably, baicalin (-10.0 kcal/mol) for A48R, ledipasvir (-10.3 kcal/mol) for A50R and I7L, and suramin (-13.2 and -10.7 kcal/mol) for D13L and F13L outperformed reference compounds. These drugs also exhibited favorable pharmacokinetic properties and established safety profiles.

Conclusion: This in silico drug repurposing approach highlights promising candidates for further investigation of mpox. The findings offer a foundation for experimental validation and support accelerated therapeutic development for emerging poxvirus threats.

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Introduction

The zoonotic infection of monkeypox (mpox) was the latest cause of declared public health emergency by the [World Health Organization \(WHO\)](#) in August 2024 [1]. Mpoxvirus (MPXV) is a double-stranded DNA virus in the viral family of poxviridae, subfamily of chordopoxvirinae, and orthopoxvirus genus. Many animals, such as African rodents (e.g. African pouched rats, squirrels, and dormice), mice, prairie dogs (*Cynomys ludovicianus*), and non-human primates (e.g. chimpanzees, baboons (*Papio cynocephalus*), mangabeys, and jerboas), can hosts of mpox [2]. The reservoir host of this virus has not yet been identified.

Mpox infection presentations start with prodromal symptoms after an incubation period of 5-41 days [3]. The most prevalent manifestations, according to meta-analysis, are chills and fever, lymphadenopathy, lethargy, pruritus, myalgia, abdominal pain, pharyngitis, respiratory symptoms, nausea or vomiting, scrotal or penile edema, and conjunctivitis [4]. More than 85% of infected individuals in the 2022 outbreak showed skin lesions [4], mostly fluid-filled with high viral load, from whom the polymerase chain reaction (PCR) samples were taken to diagnose the virus [5]. Pregnant and breastfeeding females, younger than eight years old individuals, and any immunocompromised patients are at risk of severe infection [6, 7].

In many studies, three generations of smallpox vaccines have shown protection against mpox infections [8, 9]. ACAM2000, a second-generation vaccine based on Dryvax (first-generation), was approved by the U.S. [Food and Drug Administration \(FDA\)](#) in August 2024 for urgent use in the mpox outbreak [10]. The third-generation, modified vaccinia Ankara-Bavarian Nordic, a non-replicating, live, attenuated vaccine, was prequalified as the first vaccine against pox by the [WHO](#) on 13 September, 2024 and can be used in immunocompromised patients [11]. Tecovirimat (TPOXX), cidofovir, and brincidofovir are not specific medications against MPXV; however, they can be effective in preventing severe complications and mortality due to mpox infection [12]. New specific medications can play an essential role in decreasing the disease burden. Drug repurposing is one of the best methods for achieving this aim. Drug repurposing concerns discovering new indications for existing drugs, which is a quicker and often more economical method to find new treatments. Infectious diseases start by identifying potential targets, such as viral proteins or host factors critical for the pathogen's life cycle.

Molecular docking studies simulate the interaction between drugs and viral proteins and support prioritizing candidate drugs that may inhibit the key functions of viruses. In this study, by reviewing selected papers, we established five MPXV proteins: A48R (thymidylate kinase), A50R (DNA ligase), D13L (viral capsid protein), F13L (EEV formation protein), and I7L (protease), and evaluated existing drugs' affinity to them.

Materials and Methods

The protein sequences were obtained from a prior study by Lam et al. [13]. Using the [AlphaFold2 Protein Structure Prediction Database](#) via the ChimeraX 1.8 program, 3D structures of the proteins were modeled, and models with the highest per-residue accuracy of the structure (pLDDT) of 100 were chosen for docking analysis [14-16]. All proteins had high structural accuracy in their binding site. We further prepared the models using Chimera software, version 1.17.1 [17]. Hydrogen atoms and charges were added to the structures, and structure minimization was performed using the steepest descent steps and update interval set to 1000 and 100, respectively.

More than 300 ligands with previously proven antiviral properties were identified for the in-silico study against the mpox virus. The 3D structure of the ligands was downloaded from the [PubChem](#) database, in SDF format [18]. For compounds without an available 3D structure, the 3D structure was prepared by running an MM2 calculation on the 2D structure of the ligand using Chem3D Pro software [19].

This study used Autodock Vina within the PyRx software to determine the ligands' affinity to target proteins [20, 21]. First, the protein structure was loaded into the software and then converted to PDBQT format. The ligand molecules were then loaded into the software, and further energy minimization and format change to PDBQT were performed. The binding site of the target proteins was identified based on the literature [13, 22]. The grid box center for A48R was (x,y,z: +5.5,-3.6,-5.9) and the diameter was (x,y,z: 26,26,26), center for A50R was (x,y,z: -14.4,-8.2,-13) and the diameter was (x,y,z: 26,25,26), center for D13L was (x,y,z: +16.7,+17,+14.2) and the diameter was (x,y,z: 37,37,37), center for F13L was (x,y,z: +6,+5.1,+3.4), and the diameter was (x,y,z: 31,29,31), center for I7L was (x,y,z: +6.3,+6.6,-18), and the diameter was (x,y,z: 33,41,37). Exhaustiveness was set to 8. The protein-ligand interactions in the docked structures were visualized and analyzed using PyMOL and Biovia Discovery Studio, which provided both 3D and 2D representations [23, 24] (Table 1).

Table 1. Protein sequences of the target protein

Proteins	Sequence
A48R	MSRGALIVFEGLDKSGKTTQCMNIMESIPANTIKYLNFPQRSTVTGKMIDDYLTRKKTYNHDHVNLLFCANRWEFASFIQEQLQGITLIVDRYAFSGVAYAAAGKASMTLSKSYESGLPKPDLVIFLESGSKEINRNVGEEIYEDVTFQKQVLQYKKMIEEGDIHWQIISSEFEEDVKKELIKNIVIEAHTVTGPVQQLWM
A50R	MTSLREFRKLCCDIYHASGYKEKSLIRDFITDRDDTDYLIILKLLPGLDDRMYNMNDKQIIKLYSIIFKQSQEDMLQDLGYGYIGDTIRTFKENTEIRPRDKSILTLLEEDSFLTLLSSVTKEHQIKLTDIASYCTCNDLKCYMLIDKDLKIKAGPRYYLNAISPHAYDYFRKSNLKEIENAAKQNLDSISISYMT-PINPMLAESCDSYNAFKKFPSPGMFAEYKYDGERYQYHKNNNEFAFFSRNMKPYLSHKYDYLKEYIPKAFKATSIYLDSEIYLDENHYPLPFGSLGIHK-KKEYKNSNMCLFYFDCLYFDGDMTDIPLYERRSFLKDVMEIPNRIYFSELTNISNESQLTDYLDALTRKLEGLYLDKINGVYEPGKRRLHKIKRDYLNESGMADSAADLYLGAYYGKGGKGGIMAYFLMGCYDDESGKHKTCTCSGHDNTLRYLQDQLTMYKINKDPKKIPEHLVYNKIYIPDFYDDPQKQSIHEISGAETSSKSHANGISIRFPRFTRIREDKTHKESTHLNDLYNLTKSLNSYI
D13L	Chain A: MNNTIINSLIGGDDSIKRSNVFAVDSQIPTLYMPQYISLSGVMTNDGPDNQAIASFEIRDQYITALNHLVLSLELPEVKGMGRFGYVPYVGYKCINHV-SISSCNGVIWEIEGEEYNNCINNTIALKHSYGSSSELNDISGLTPNDTIKEPSTVYVYIKTPFDVEDTFSSKLSDSKITVTVTFNPVSDIVIRDSDFDFTF-NKEFVYVPELSFIGYVMVKNVQIKPSFIEKPRRVIGQINQPTATVTEVHAATSLSVYTKPYYGNTDNKFISYPGYSQDEKDYIDAYVSRLLDDLIVSDGPP-TGYPESAIEVEVPEDGIVSIQDADVYVVIDNVDPDNMSVYLHTNLLMFGTRKNSFIYNISKKFSAITGTYSDATKRTIFAHISHSINIIDTSIPVSLWTSQRN-VYNGDNRSAESKAKDLFINDPFIKIDFKNKTDIISRLVRFNGDVLVSENGPISRIYNELLTKSNNGTRTLTFNFTP KIFFRPTTITANVSRGKDLSVRV-VYSTMDVNHPIYVQKQLVVVNCNDLYKVSVDQGVSTIKIMGDN Chain B: MNNTIINSLIGGDDSIKRSNVFAVDSQIPTLYMPQYISLSGVMTNDGPDNQAIASFEIRDQYITALNHLVLSLELPEVKGMGRFGYVPYVGYKCINHV-SISSCNGVIWEIEGEEYNNCINNTIALKHSYGSSSELNDISGLTPNDTIKEPSTVYVYIKTPFDVEDTFSSKLSDSKITVTVTFNPVSDIVIRDSDFDFTF-NKEFVYVPELSFIGYVMVKNVQIKPSFIEKPRRVIGQINQPTATVTEVHAATSLSVYTKPYYGNTDNKFISYPGYSQDEKDYIDAYVSRLLDDLIVSDGPP-TGYPESAIEVEVPEDGIVSIQDADVYVVIDNVDPDNMSVYLHTNLLMFGTRKNSFIYNISKKFSAITGTYSDATKRTIFAHISHSINIIDTSIPVSLWTSQRN-VYNGDNRSAESKAKDLFINDPFIKIDFKNKTDIISRLVRFNGDVLVSENGPISRIYNELLTKSNNGTRTLTFNFTP KIFFRPTTITANVSRGKDLSVRV-VYSTMDVNHPIYVQKQLVVVNCNDLYKVSVDQGVSTIKIMGDN Chain C: MNNTIINSLIGGDDSIKRSNVFAVDSQIPTLYMPQYISLSGVMTNDGPDNQAIASFEIRDQYITALNHLVLSLELPEVKGMGRFGYVPYVGYKCINHV-SISSCNGVIWEIEGEEYNNCINNTIALKHSYGSSSELNDISGLTPNDTIKEPSTVYVYIKTPFDVEDTFSSKLSDSKITVTVTFNPVSDIVIRDSDFDFTF-NKEFVYVPELSFIGYVMVKNVQIKPSFIEKPRRVIGQINQPTATVTEVHAATSLSVYTKPYYGNTDNKFISYPGYSQDEKDYIDAYVSRLLDDLIVSDGPP-TGYPESAIEVEVPEDGIVSIQDADVYVVIDNVDPDNMSVYLHTNLLMFGTRKNSFIYNISKKFSAITGTYSDATKRTIFAHISHSINIIDTSIPVSLWTSQRN-VYNGDNRSAESKAKDLFINDPFIKIDFKNKTDIISRLVRFNGDVLVSENGPISRIYNELLTKSNNGTRTLTFNFTP KIFFRPTTITANVSRGKDLSVRV-VYSTMDVNHPIYVQKQLVVVNCNDLYKVSVDQGVSTIKIMGDN
F13L	MWPFASYPAGAKCRLYETLPENMDFRSDHLTTFECFNEITLAKKIYIASFCCNPLSTTRGALIFDKLKEYSEKGIKIYLLDERGKRNELGELQSHSPDIN-FITYNIDKNNYGLLLGCFWYSODERCYYGNASFTGGSIHTIKTLGVYSYDYPPLATDLRRRFDTFKAFNSAKNSHLNLCSAACCLPYSTAYHIKNPIG-GYFFDSDPEHLGYSRDLTDYVIDKLKSAKTSIDIEHLAIYPTRYDGNSSYWPDIYNSIIIEAANRGYKIRLLYGNWDKNDYYSMATARSLDALCYQNDL-SYKYFTIQNNTKLLIYDDEYHITSANFDGTHYQNHGFYSFNSIDKQLYSKAKKIFERDWYSSHSKSLKI
I7L	MERYTOLVISKIPELGFTNLLCHISLAGLCSNIDYSKFLTCNCGYVVEKYDKSTTAGKYSCIPIGMMLELVESGHLRPNSSDELQKKELTDELTRYHSI-YDYFELPTSIPLAYFFKPQLREKYSAIDFSQMDLKIDDLSRKGIHTGENPKYKMKIEPERGAWMSNRSIKNLYSQFAYGSEYDIYGQFDMRFLNSLAI-HEKFDAMFNKHLSYILDKIKSSTRFYMFYCYLSLHKKYIYDKQLVSYFSDGNGNIPTEFHYYNNFYFYSFGDNFTNHRHSYLDNTNCDIDYLFRR-FECTFGAKIGCINYEYNQLESECGHFISLPHILCTRTPPKSFKSLKYYTFKFLADKKHTLFSILFNQDLSLYITETDNAGLKEYKRMKEHTKSINICYD-KLTTKLNRIYDODE

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Results

Molecular docking was conducted against five key Monkeypox virus (MPXV) proteins — A48R, A50R, D13L, F13L, and I7L — to identify high-affinity repurposed drug candidates. Binding energies and interaction profiles were evaluated using AutoDock Vina, PyMOL, and Discovery Studio, and compared with known reference inhibitors where available.

For A48R (thymidylate kinase), no clinically established inhibitor has been previously reported, making this target a novel therapeutic focus. Among all screened molecules, baicalin demonstrated the strongest binding affinity (−10.0 kcal/mol), forming multiple hydro-

gen bonds with key catalytic residues, including Lys18, Asp92, and Glu146 involved in nucleotide substrate recognition. Eluxadoline (−9.9 kcal/mol), danoprevir (−9.8 kcal/mol), nilotinib (−9.8 kcal/mol), and rilpivirine (−9.7 kcal/mol) also showed strong interactions, suggesting that compounds with flavonoid or antiviral scaffolds may competitively interfere with thymidine phosphorylation and disrupt viral nucleotide metabolism.

For A50R (DNA ligase), ledipasvir produced the highest binding affinity (−10.3 kcal/mol), markedly stronger than the reference inhibitor mitoxantrone (−5.9 kcal/mol). Ledipasvir interacted with residues Lys112, Glu224, and Tyr276 within the ATP-binding region, indicating possible inhibition of DNA strand-sealing. Oth-

er high-affinity molecules included paritaprevir (−10.0 kcal/mol), elbasvir (−10.0 kcal/mol), lumacaftor (−9.9 kcal/mol), and olaparib (−9.8 kcal/mol). These findings suggest that antiviral compounds originally developed for hepatitis C may inhibit MPXV ligase activity due to conserved enzymatic motifs.

For D13L (major capsid protein), suramin exhibited the greatest affinity (−13.2 kcal/mol), significantly surpassing rifampicin (−8.1 kcal/mol), a known control compound. Suramin formed extensive electrostatic and hydrogen-bond interactions with residues Arg235, Asp288, and Lys342 at the hexameric interface critical for capsid assembly. Hypericin (−12.9 kcal/mol), ergotamine (−12.6 kcal/mol), irinotecan (−12.0 kcal/mol), and paritaprevir (−11.9 kcal/mol) also showed robust binding patterns, implying potential disruption of viral particle formation and structural stability.

For F13L (envelope protein responsible for extracellular virion formation), suramin again demonstrated the strongest binding affinity (−10.7 kcal/mol), outperforming the FDA-approved anti-orthopoxvirus agent tecovirimat (−7.9 kcal/mol). Suramin formed hydrogen bonds with Ser250, Asp283, and Tyr305 within the phospholipase-like catalytic region involved in membrane wrapping and virion egress. Hypericin (−10.6 kcal/mol), paritaprevir (−10.1 kcal/mol), nilotinib (−10.1 kcal/mol), and avacopan (−9.7 kcal/mol) also bound favorably, indicating strong potential to inhibit extracellular enveloped virion maturation.

For I7L (cysteine protease), ledipasvir showed the highest affinity (−10.5 kcal/mol), exceeding the known inhibitor TTP-6171 (−8.1 kcal/mol). Ledipasvir interacted with catalytic residues Cys328 and His210 and exhibited π - π stacking with nearby aromatic residues, suggesting effective competitive inhibition. Velpatasvir (−9.9 kcal/mol), ergotamine (−9.8 kcal/mol), paritaprevir (−9.7 kcal/mol), and ivermectin (−9.4 kcal/mol) also demonstrated favorable binding. These results highlight that HCV NS5A-inhibitor classes may serve as potent MPXV protease inhibitors due to structural similarity within viral enzymatic pockets.

Collectively, suramin showed the strongest binding to structural proteins (D13L and F13L), while ledipasvir demonstrated the highest affinity toward enzymatic targets (A50R and I7L). Baicalin emerged as the top-performing natural compound against A48R. These findings indicate that a subset of clinically approved antiviral and anti-parasitic drugs exhibit strong binding to multiple

MPXV targets, supporting their potential for rapid repurposing and further experimental validation (Figure 1).

Discussion

Most mpox-infected patients recovered without antiviral therapy, just for supportive care, such as nonsteroidal anti-inflammatory drugs (NSAIDs), lidocaine gel, and amitriptyline-based creams for painful lesions [25]. No specific antiviral against mpox is currently available. Three non-specific mpox antivirals are TPOXX (oral capsule, I.V. injectable vial), cidofovir (I.V. solution), and brincidofovir (oral tablets and suspensions). TPOXX inhibits VP37 protein and blocks its interaction with Rab9 GTPase and TIP47, preventing enveloped virions formation [26]. Cidofovir's active form can inhibit viral DNA synthesis by inhibiting DNA polymerase 3'-5' exonuclease activity, after two steps of phosphorylation [27]. Brincidofovir acts in the same mechanism as cidofovir, after hydrolysis of its hexadecyloxypropyl group. Although the FDA approves vaccinia immunoglobulin (VIGIV) for treating complications from vaccinia vaccination, the CDC permits using VIGIV to treat other orthopoxviruses during outbreaks. However, VIGIV has no proven benefit in treating mpox, and its efficacy against MPXV infection is unknown [28].

The side effects and less favorable pharmacokinetic profile of available antivirals can be addressed through nanodrug delivery. Nano drugs offer a wider therapeutic window and sustained release. Topical nano- and micro-antivirals have improved permeability. For example, in a study by Priyanka et al., the TPOXX gel formulation showed an enhanced cumulative permeation rate, which can be very effective on mpox lesions by facing viruses with a high concentration of this anti-orthopoxvirus drug [29]. Conjugating antiviral nanoparticles with target ligands can guide drugs to areas with high viral load. Lipophilic drug nanoparticles can be systemically administered due to altered properties [30].

Drug repurposing, or drug repositioning, aims to identify new therapeutic uses for existing drugs, including those already approved for a different indication. This approach can significantly reduce the time and cost of drug development as repurposed drugs have already been tested for safety and efficacy in humans during their initial approval [31]. Molecular docking is a computational technique that plays a crucial role in new drug discovery by predicting small molecules' binding orientation and affinity to their target proteins.

Table 2. Target protein model accuracy, reference inhibitors, and docking scores of the novel repurposable compounds

Gene	pLDDT Score (%)	In-vitro Proven Drug	Compounds		Binding Energy (Kcal/mol)
			Name	Current Indication [35]	
A48R	96.5	-	Baicalin	Antibacterial, antiviral, antioxidant, and hepatoprotective [36]	-10.0
			Eluxadolone	Miscellaneous agent, treatment of IBS with diarrhea	-9.9
			Danoprevir	HCV NS3/4A protease inhibitor	-9.8
			Nilotinib	Kinase inhibitors; chronic phase treatment of CML	-9.8
			Rilpivirine	NNRTI; treatment of HIV-1	-9.7
A50R	88.8	Mitoxantrone	Mitoxantrone (control)	Chemotherapy agent; treatment of MS	-5.9
			Ledipasvir	Anti-HCV	-10.3
			Paritaprevir	Anti-HCV	-10.0
			Elbasvir	Anti-HCV	-10.0
			Lumacaftor	Treatment of cystic fibrosis	-9.9
			Olaparib	PARP inhibitor; treatment of ovarian cancer	-9.8
D13L	88.8	Rifampicin	Rifampicin (control)	Anti-bacterial	-8.1
			Suramin	Antiprotozoal	-13.2
			Hypericin	-(Believed to have antimicrobial activity)	-12.9
			Ergotamine	Treatment of migraines (with/without aura and cluster headache)	-12.6
			Irinotecan	Topoisomerase inhibitor; treatment of colon, rectum, and pancreatic carcinoma	-12.0
			Paritaprevir	Anti-HCV	-11.9
F13L	89.8	Tecovirimat	Tecovirimat (control)	Anti-VP37; anti-poxviridae	-7.9
			Suramin	Antiprotozoal	-10.7
			Hypericin	-(Believed to have antimicrobial activity)	-10.6
			Paritaprevir	Anti-HCV ^c	-10.1
			Nilotinib	Kinase inhibitors; chronic phase treatment of CML	-10.1
			Avacopan	C5aR antagonist; treatment of ANCA-associated vasculitis	-9.7
I7L	93.3	TTP6171 (1)	TTP6171 (control)	17L protease inhibitor	-8.1
			Ledipasvir	Anti-HCV	-10.5
			Velpatasvir	Anti-HCV	-9.9
			Ergotamine	Treatment of migraines	-9.8
			Paritaprevir	Anti-HCV	-9.7
			Ivermectin	Antiprotozoal	-9.4

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Abbreviations: IBS: Irritable bowel syndrome; HCV: Hepatitis C virus; CML: Chronic myeloid leukemia; NNRTI: Non-nucleoside reverse transcriptase inhibitor; MS: Multiple sclerosis; C5Ar: Complement 5a receptor, ANCA: Anti-neutrophil cytoplasmic antibody.

Note: In-vitro-proven drugs are considered a control, according to Lam et al's study [13]. Lumacaftor: is used in combination with ivacaftor, for treating cystic fibrosis in *F508del* mutation homozygous patients in the *CFTR* gene.

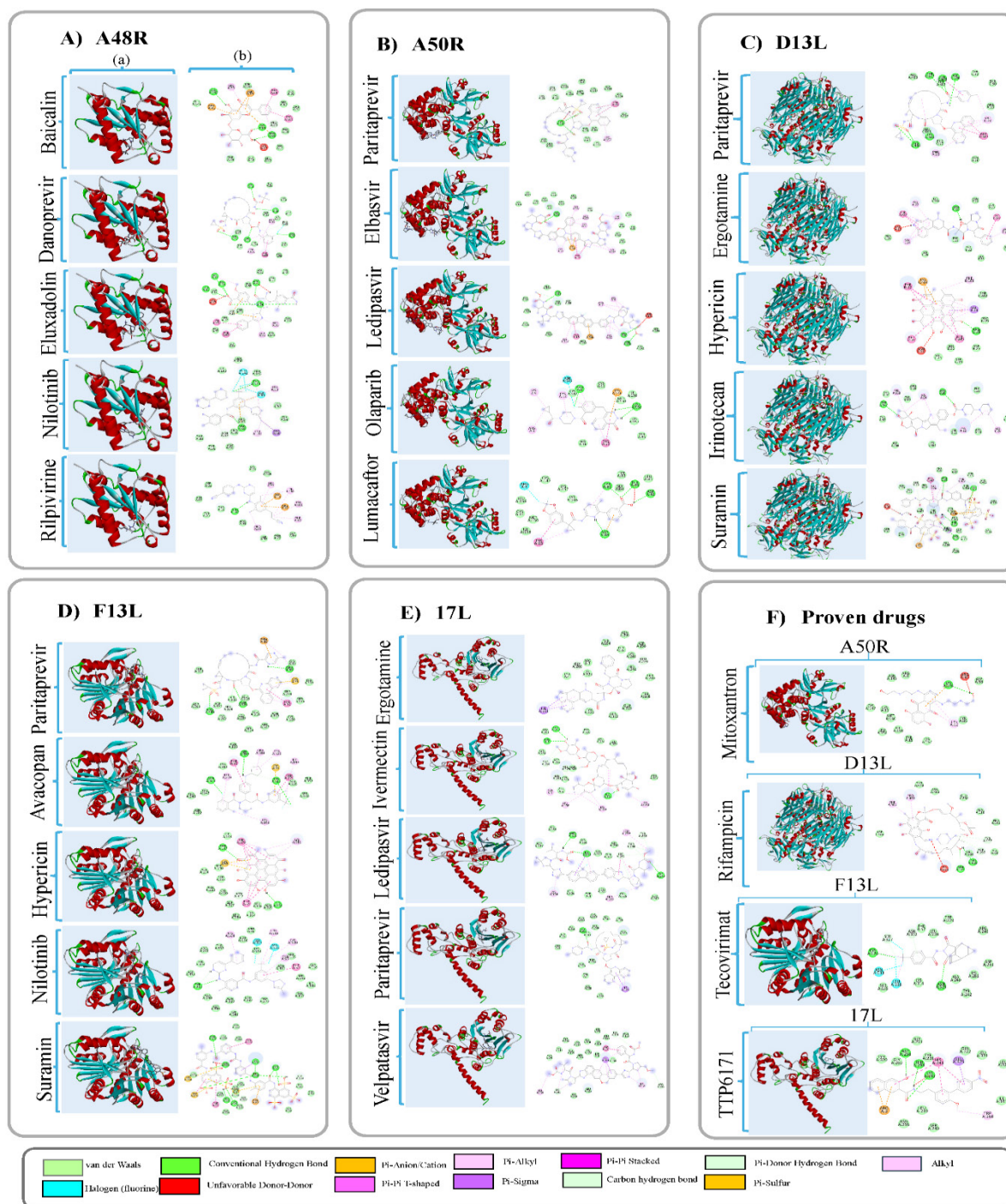


Figure 1. 3D (a) and 2D (b) structural view of the protein-ligand interactions in the best binding mode of the ligands in the A) A48R, B) A50R, C) D13L, D) F13L, and E) 17L binding sites 3D and 2D structural view of the protein -control drug interactions is demonstrated in F) Proven drugs

According to previous studies, we considered five viral proteins. A48R, which no drugs have targeted to date, is thymidylate kinase and is involved in the phosphorylation of thymidine and halogenated deoxyuridine monophosphate analogs. Lem et al. studied north-methanocarbathymidine (N-MCT) (a thymidine analog) and rutaecarpine (a cyclooxygenase-2 [COX-2] inhibitor), with bond energies of -7 and -9 Kcal/mol, respectively, as having the highest affinity to A48R [13]. MPXV DNA ligase (A50R), major capsid protein (D13L), envelope protein (F13L), and cysteine proteinase (I7L) were also targeted in our study. A molecular docking study was conducted to evaluate the potential binding capability of the chosen compounds to the A48R, A50R, D13L, F13L, and I7L active sites. The results were compared with those of previously recognized protein inhibitors to determine whether the affinity of the newly repurposed compound was acceptable (Table 2). Eventually, we selected the top 5 best compounds for each target. A48R was the only protein with no reference inhibitor. The selected compounds for A50R, ledipasvir, with an energy bond of -10.3 Kcal/mol, had a considerably higher affinity than mitoxantrone. Ledipasvir is a safe anti-hepatitis C virus (HCV) with no contraindications, and it is usually used in combination with sofosbuvir [32, 33]. Suramin is an anti-trypanosomiasis agent with the highest affinity to D13L, with a docking score of -13.2 Kcal/mol. Suramin also shows a binding energy of -10.3 Kcal/mol to F13L, higher than the only approved anti-poxviridae drug, TPOXX. TTP-6171 is the only non-covalent I7L protease inhibitor reported in many papers [34]. Our study suggests that ledipasvir for I7L protease with higher affinity to the I7L protease than TTP-6171.

Conclusion

Infectious diseases are among the most challenging public health and macroeconomic issues. Frequent resistance has been reported in bacteria, protozoa, fungi, and viruses on the one hand. On the other hand, the mutations that occur in different pathogens, especially viruses, require health researchers to look for different antimicrobial drugs. Also, no effective antiviral treatment is available for many viral families, such as Flaviviridae (dengue virus, Zika virus, yellow fever virus, and Powassan virus), Filoviridae (Marburg virus), Paramyxoviridae (Nipah virus), and Togaviridae (chikungunya virus). Therefore, research in antiviral drug development can benefit this field. One of these viruses is the mpox virus, which African countries are experiencing new outbreaks of clade 1 of this DNA virus.

In this manuscript, we first made a general review of mpox infection. Then, we used molecular docking evaluation for each of the five mpox viral proteins. We evaluated five of the best compounds with higher affinity and pharmacological and pharmacokinetics properties, which are prone to side effects. We reported that our proposed first drug had a higher affinity for each protein than the current drugs targeting that protein. Our study can motivate researchers to investigate the preclinical and clinical efficacy of the proposed drugs against the mpox virus in animal and human models.

Limitation

The ultimate efficacy of these proposed compounds will be outside of the in-silico atmosphere and requires further pharmacological and pharmacokinetic research to determine para-clinical and clinical efficacy and effective dosage. However, the significant advantage of drug repurposing is that the approval cost of them is significantly reduced by proving the safety profile of these drugs. Also, in this study, we used drugs reported to have antiviral efficacy in at least one in-silico, in-vitro, or in-vivo study. Therefore, only a limited number of ligands were used in this study. In addition, this study did not use other essential proteins in the virus, such as E9L, H5R, B1R, F10L, E8L, and A6R, which are known to play a crucial role in the virus's replication and survival. Thus, more comprehensive studies are needed to obtain a complete list of effective drugs for all known viral proteins.

Ethical Considerations

Compliance with ethical guidelines

This study did not involve any human participants or animal subjects. All experiments were conducted using computational and laboratory-based formulation methods only. Therefore, ethical approval and an institutional review board (IRB) code were not required for this research.

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Authors' contributions

Conceptualization: Shahed Ahmadi and Mousa Ahmadi; Data collection: Shahed Ahmadi, Mousa Ahmadi, and Mahdi Amirzadeh; Investigation: Shahed Ahmadi and Ali Jabbarzadeh; Writing: All authors.

Conflict of interest

The authors declared no conflict of interest.

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