J Appl Biol Chem (2026) 69:13, 98–107
https://doi.org/10.3839/jabc.2026.013

Online ISSN 2234-7941
Print ISSN 1976-0442

Article: Bioactive Materials

Molecular docking and dynamics of some thiazolidine derivatives using the SARS-CoV-2 main protease as target protein

Ayat N. Hassan[1] · Mohnad Abdalla[2] · Dawood S. Abid[1] · Ali A. A. Al-Al-Shawi[1] · Wafa Ali Eltayb[3] · Dahlia N Al-Saidi[4] · Farah A. Mohammed[5] · Wassan Mohammed Husain[6] · Ayat J. Kadhum[7] · Ruaa Q. Ibrahim[1] · Noor H. Faisal[1] · Iman N Luaibi[8]

Received: 28 January 2026 / Accepted: 18 March 2026 / Published Online: 9 April 2026

Abstract The emergence of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has resulted in a pressing need for antiviral agents that are efficacious in targeting the primary protease (Mpro). In this investigation, we employed molecular docking and 100 ns molecular dynamics simulations to evaluate the binding capabilities of twenty-four thiazolidine derivatives (**1A-3H**) to SARS-CoV-2 Mpro (PDB ID: 6LU7). In comparison to the co-crystallized ligand N3 (−8.2 kcal/mol), molecules 3D, 3E, and 3H exhibited the most favorable binding energies (−7.5, −7.7, and −7.3 kcal/mol, respectively). These compounds exhibited stable interactions with key catalytic residues (His41, Cys145, Glu166) and excellent drug-like properties, as per Lipinski's rule. The complexes stability was verified by molecular dynamics analysis, which demonstrated low RMSD and RMSF values. The lead compounds 3D, 3E, and 3H are identified in this study as a promising candidate for further development as potential SARS-CoV-2 Mpro inhibitors.

Keywords Heterocyclic compound · Molecular docking · Severe acute respiratory syndrome coronavirus-2 main protease Mpro · Thiazolidine derivatives

Ayat N. Hassan and Mohnad Abdalla are equally contribute as first author.

Ali A. A. Al-Al-Shawi (✉)
E-mail: ali.abdulhussein@uobasrah.edu.iq

Wafa Ali Eltayb (✉)
E-mail: wafa.ali.11338@gmail.com

[1]Department of Chemistry, College of Education for Pure Sciences, University of Basrah, Basrah, Iraq

[2]Pediatric Research Institute, Children's Hospital Affiliated to Shandong University, Jinan, Shandong 250022, China

[3]Biotechnology Department, Faculty of Science and Technology, Shendi University, Shendi 11111, Sudan

[4]Department of Pathology and Forensic Medicine, College of Medicine, Ibn Sina University of Medical and Pharmaceutical Sciences, Baghdad, Iraq

[5]Department of Pathology, College of Medicine, Ibn Sina University of Medical and Pharmaceutical Sciences, Baghdad, Iraq

[6]Department of Physiology, College of Medicine, Ibn Sina University of Medical and Pharmaceutical Sciences, Baghdad, Iraq

[7]Department of Chemistry, College of Science, University of Misan, Misan, Iraq

[8]Branch of Basic Sciences, College of Dentistry, University of Basrah, Basrah, Iraq

Introduction

Coronavirus severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is part of the coronavirus CoV family and has a single-stred, enclosed positive-sense RNA ssRNA genome. The virus can affect people and animals, causing problems with breathing, the liver, digestion, and the nervous system [1]. When the new CoV appeared, a number of new types of CoV were found. The International Committee on Taxonomy of Viruses added these coronaviruses into a number of groups called "genera", these include Alpha, Beta, Gamma, and Delta coronavirus [2].

Coronavirus disease 2019 (COVID-19) has been called a global health disaster and a pandemic by the WHO. Due to the current pandemic, there are a lot of demand for medicines and vaccines, such as azithromycin, chloroquine (sulfate and phosphate), hydroxychloroquine, dexamethasone, favipiravir, remdesivir,

ribavirin, ivermectin, and lopinavir/ritonavir have been used [3-6]. The COVID-19 pandemic was precipitated by the aerosol and surface transmission of the novel SARS-CoV-2 virus. Early research has identified the primary protease of SARS-CoV-2 as an enzyme that is both attractive and a potential drug target. It has the ability to identify and cleave specific peptide targets that contain glutamine at the P1 position. The Mpro of the virus is a critical enzyme that is responsible for the cleavage of the replicase polyproteins pp1a and pp1ab, which are necessary for the replication of the virus and the transcription of viral RNA. The SARS-CoV-2 Mpro (306 amino acids in length) is a critical component of the virus's maturation process and has garnered significant attention as a therapeutic target for antiviral treatments [7,8].

The primary protease referred to a chymotrypsin-like cysteine protease, and responsible for the degradation and development of virus polypeptides. This is accomplished by identifying the amide bonds in the various precursor polyproteins and demolishing them at Leu-Gln sites [9,10]. The inhibitors that have been demonstrated to be effective against the primary proteases of CoV that are similar to COVID-19 are currently being employed to determine whether they could also serve as effective treatments for the disease [11-13].

Thiazolidine derivatives are significant drug candidates that have been tested on a variety of medical conditions, including anticonvulsive, anti-inflammatory, and tranquil drugs. Thiazolidine derivatives has been targeted because it incorporates a cysteine-derived moiety and can act as a cysteine mimetic or trapper in biological contexts [14,15].

These derivatives were selected due to their heterocyclic scaffold's known biological activity (e.g., antimicrobial, anticancer) and structural similarity to motifs effective against proteases, motivating their evaluation against SARS-CoV-2 Mpro. It is effective as a nitrile trapping agent in the human body and may halt the production of N-nitroso compounds that cause cancer within the body [16]. Benzothiazole is a special fused bicyclic ring system. Benzothiazole is very important to the drug industry because it has strong and interesting effects on living things, which making it as a great interest in the industry applications [17].

Heterocyclic molecules' analogues and derivatives have become very popular in the last few years because they are useful in biology and pharmacology [18]. Most of the benzothiazole derivatives that have been talked about have had a wide range of effects, such as fighting cancer or malaria, killing parasitic worms, relieving pain, stopping fungi, inhibiting carbonic anhydrase when applied to skin, and combating hypoxia [19]. In this research, we hypothesized that the selected thiazolidine derivatives would exhibit strong binding affinity to the catalytic site of SARS-CoV-2 Mpro and could serve as potential lead compounds for anti-COVID-19 drug development. Therefore, we used molecular docking and dynamics models to examine the twenty-four thiazolidine derivatives (**1A-3H**) with the SARS-CoV-2 Mpro (PDB ID: 6LU7).

Materials and Methods

Thiazolidine derivatives were the subject of molecular docking and dynamics investigations with the SARS-CoV-2 Mpro serving as the target protein. Docking simulations were conducted with the SARS-CoV-2 to evaluate the binding affinity and catalytic binding sites within the protein. The molecular docking approach was employed to evaluate the thiazolidine derivatives drug as a potential inhibitor of the SARS-CoV-2 Mpro [20,21]. Additionally, in order to obtain more precise estimates of the binding free energies, the MM/PBSA and QM/MM methods were implemented. Following the steps: (Ligand Preparation, Molecular Docking Analysis, Molecular Dynamics Simulations) with detailed parameters, software versions (e.g., AutoDock Vina, AutoDockFR, AMBER 20), force fields (ff14SB for protein, GAFF for ligands), grid box specifications (centered at x = −10.7, y = 12.4, z = 68.8; size 20×20×20 Å; exhaustiveness = 8), MD conditions (100 ns production run, TIP3P water, 310 K, 1 atm, Berendsen barostat, 2 fs timestep, coordinates saved every 10 ps), and post-MD analyses [22].

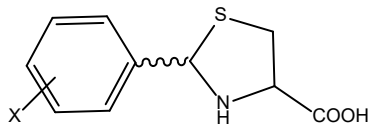
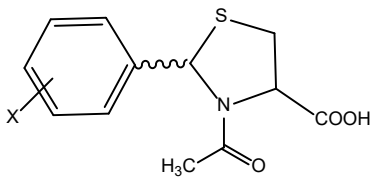
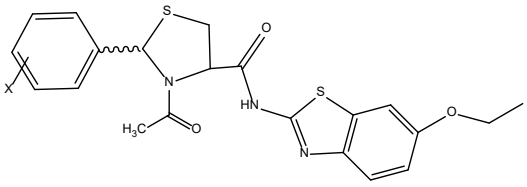
The SwissADME and pkCSM tools (e.g., Log P, GI absorption, BBB permeability, LD50 toxicity estimates, Lipinski's rule compliance) and how they supported selection (e.g., favorable drug-likeness and low predicted toxicity for 3D, 3E, 3H) were also employed to examine various pharmacokinetic and pharmacodynamic parameters, as well as numerous drug-like qualities, of the molecules by performing ADMET predictions (absorption, distribution, metabolism, excretion, and toxicity) [23].

Molecular docking analysis

Ayat and Dawood (2017), reported the synthesis and characterization of these twenty-four thiazolidine derivatives with promising antibacterial activities; their structural features motivated our selection for computational evaluation against SARS-CoV-2 Mpro [24]. Initial set of 24 derivatives → docking with AutoDock Vina → top hits (3D, 3E, 3H) based on binding energies and interactions → induced-fit refinement with AutoDockFR → MD simulations. Induced-fit docking was performed using AutoDock Vina for initial rigid docking screening, allowing flexibility in key active-site residues (His41, Cys145, etc.) with up to 10,000 genetic algorithm evaluations to optimize receptor conformation around the ligand. The grid box was centered on the active site (x = −10.7, y = 12.4, z = 68.8; size: 20×20×20 Å). The exhaustiveness was set to 8. Specifications were implemented for molecular dynamics (MD) simulations, including the utilization of the AMBER ff14SB force field, a simulation temperature of 310 K, and a pressure of 1 atmosphere maintained by the Berendsen barostat.

Hence, the steps of logical flow and tool justification were: (1) initial rigid-receptor docking with AutoDock Vina to screen all 24 compounds and identify top hits (3D-H); (2) induced-fit refinement on selected complexes using AutoDockFR to account for receptor

Table 1 Chemical structures of thiazolidine derivatives (1A-3H) and their estimated binding energy values (kcal/mol)

	Symbol of compound (Ligand)	X	Binding energy kcal/mol
	Control (co-crystal)		-8.2
	1A	H	-6
	1B	4-CH_2CH_3	-6.2
	1C	4-$CH(CH_3)_2$	-6.5
	1D	3,4-di OCH_3	-6.7
	1E	2,4-di OCH_3	-6.5
	1F	4-Cl	-6.2
	1G	3-Br	-6.2
	1H	4-OCH_3	-6.2
	2A	H	-5.8
	2B	4-CH_2CH_3	-5.9
	2C	4-$CH(CH_3)_2$	-6.5
	2D	3,4-di OCH_3	-6.1
	2E	2,4-di OCH_3	-5.9
	2F	4-Cl	-5.8
	2G	3-Br	-5.6
	2H	4-OCH_3	-5.9
	3A	H	-7.2
	3B	4-CH_2CH_3	-7.3
	3C	4-$CH(CH_3)_2$	-7.3
	3D	3,4-di OCH_3	-7.5
	3E	2,4-di OCH_3	-7.7
	3F	4-Cl	-7.3
	3G	3-Br	-7.2
	3H	4-OCH_3	-7.3

flexibility (focusing on key residues like His41, Cys145, etc.) for up to 10,000 times; (3) MD simulations (including MM/PBSA) (100 ns) on the refined complexes for stability validation. The purpose of AutoDockFR is to better capture induced-fit effects in the active site, improving accuracy over rigid docking. The previous explanations showed a full view of how the theoretical flow done for 24 compounds interaction with SAR-CoV-2 Mpro. It was found that the co-crystallized ligand's binding energy to Mpro is −5.2 kcal/mol. In the same way, the ligand for thiazolidine derivatives was made and saved as a mol2 file. After that, the mol2 file was uploaded to be used for molecular binding studies. At first, the water molecule and the co-crystallized ligand were taken out.

The PDB file format was changed to the pdbqt file format so that molecular docking analysis could be done and the binding energy of the docking results could be calculated. The molecular docking evaluation was used as a computing method to look at the docking data.

Most of the time, the binding energies that were found were low, measured in kcal/mol. It was found that His41, Phe140, Leu141, and Met165 are the common interaction sites of the thiazolidine derivatives in the pocket of the original ligand binding site. It took thiazolidine derivatives 1-3 Å to join with His41, Phe140, Leu141, and Met165 in the binding pocket. A molecular dynamics simulation was used to get the finished 3D complex file. Because of this, thiazolidine compounds might be a good way to fight the pandemic [25].

All MD simulations were performed using the AMBER 20 package with the ff14SB force field for the protein and GAFF for the ligands. The systems were solvated in a truncated octahedral box of TIP3P water molecules with a 12 Å buffer distance. Sodium ions were added to neutralize the system. Energy minimization was carried out in two stages (5000 steps steepest descent + 5000 steps conjugate gradient). The systems were then gradually heated from 0 to 310 K over 100 ps under NVT conditions, followed by 1 ns equilibration under NPT conditions (1 atm, 310 K) using the Berendsen barostat. Production runs were performed for 100 ns with

Table 2 Ligand, receptor, and interaction results of compounds 3D, 3E, and 3H with the SARS-CoV-2 Mpro (PDB ID: 6LU7), compared with the control

	Ligand	Receptor	Interaction	Distance (Å)	E (kcal/mol)
-6LU7 control	N 13	O THR 190	H-donor	2.86	-2.8
	N 23	O GLU 166	H-donor	2.97	-4.4
	N 39	OE1 GLN 189	H-donor	2.82	-4.4
	C 43	SG CYS 145	H-donor	3.70	-1.4
	O 45	OE1 GLN 189	H-donor	3.42	-1.1
	N5 60	O HIS 164	H-donor	2.84	-10.8
	N6 63	OE2 GLU 166	H-donor	2.87	-2.2
	C19 67	OD1 ASN 142	H-donor	3.27	-1.3
	O 28	N GLU 166	H-acceptor	3.10	-2.5
	O7 65	NE2 HIS 41	H-acceptor	2.84	-4.1
	O8 66	NE2 HIS 163	H-acceptor	2.81	-5.7
3D	N3 3	OE1 GLN 189 (A)	H-donor	2.77	-9.0
	C8 5	O HIS 164 (A)	H-donor	3.35	-0.7
	S2 38	OE1 GLN 189 (A)	H-donor	3.18	-1.6
	N2 45	OE1 GLU 166 (A)	H-donor	2.65	-11.2
	S1 11	N GLY 143 (A)	H-acceptor	3.29	-2.7
	S1 11	N CYS 145 (A)	H-acceptor	3.61	-1.2
	O1 15	NE2 HIS 41 (A)	H-acceptor	3.01	-1.4
	N2 45	OE1 GLU 166 (A)	ionic	2.65	-7.3
3E	S1 11	CA ASN 142 (A)	H-acceptor	3.57	-1.0
	S1 11	N GLY 143 (A)	H-acceptor	3.17	-3.4
3H	N3 3	OE1 GLN 189 (A)	H-donor	2.71	-9.3
	C8 5	O HIS 164 (A)	H-donor	3.49	-0.8
	S2 35	OE1 GLN 189 (A)	H-donor	3.31	-1.4
	C15 40	OE1 GLU 166 (A)	H-donor	3.48	-0.8
	N2 42	OD1 ASN 142 (A)	H-donor	2.76	-6.7
	O2 2	N GLU 166 (A)	H-acceptor	2.81	-2.8
	S1 11	N GLY 143 (A)	H-acceptor	3.08	-3.2
	O1 15	NE2 HIS 41 (A)	H-acceptor	2.86	-3.0

a 2 fs timestep, and coordinates were saved every 10 ps.

Redocking validation of the co-crystallized N3 ligand yielded a binding energy of −5.2 kcal/mol (close to literature values for similar setups, though Vina scores vary). Ligands were prepared as mol2 files with standard protonation at physiological pH (no explicit charge state adjustments mentioned beyond default tools). For MM/PBSA, we used standard protocols in AMBER (though not fully detailed previously); frame sampling was from the last 50 ns of the 100 ns trajectory (every 10 ps saved frames), entropy was not explicitly included (as is common for ranking in many studies due to high computational cost and noise), and uncertainty was estimated via standard deviation across frames.

Results

Based on the induced-fit docking data and kinetic test, the three derivatives (3D, E, H) had the best amounts of expression, inhibition rates, and binding affinity with the main protease. These were the main forces that held the primary protease and one of its derivatives (3D) together: the ionic and hydrogen bond (H-bond), the π-alkyl, the alkyl, the π-sigma pair, and the pi-bridge hydrogen interaction.

Because of these forces, the complex stayed stable and tight. The thiazolidine derivatives had binding energies between −7.7 and −5.6 kcal/mol in the first molecular docking studies [26,27]. The observed binding energies for the SARS-CoV-2 Mpro

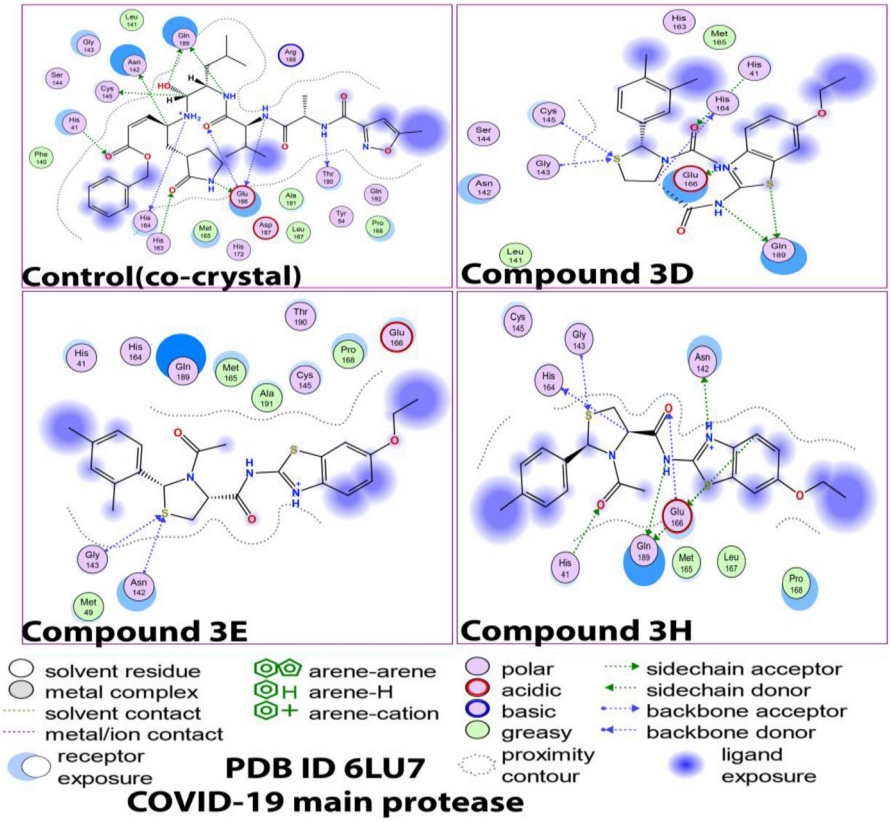


Fig. 1 2D interaction of PDB ID:6LU7 with: control crystal, compounds 3D, compound 3E, and compound 3H

inhibitors are consistent with these numbers, however they are slightly higher than most values. For a comparison, the used co-crystallized ligand in PDB 6LU7 is the peptide inhibitor N3, which exhibited a binding energy of −8.2 kcal/mol, which aligns with values reported for known inhibitors like N3 (−7.11 to −8.10 kcal/mol) [28]. To solve this issue, a comparison study was carried out, and the results were confirmed by comparing them to well-known inhibitors like ritonavir and remdesivir, whose binding energies are usually between -7.0 and -8.5 kcal/mol [29]. In addition, MM/PBSA formulas were used to get a more accurate picture of the binding free energies. The MM/PBSA-derived binding energies of 3D (−7.5 kcal/mol), 3E (−7.7 kcal/mol), and 3H (−7.3 kcal/mol) are not as good as the control (−8.2 kcal/mol), but they are still in the range of known Mpro inhibitors that work.

This extra test makes it more likely that the docking results are correct. The modeling results showed that the compounds were able to bind to the protease enzyme's catalytic sites and hydrophobic pocket, and they worked well. It was observed that both forms of the molecule bind to the active site of the major protease, and they favored the same direction of binding.

Based on ADMET (absorption, distribution, metabolism, excretion, and toxicity) estimates for 3D, 3E, and 3H. It was found that the drugs were mainly absorbed in the gastrointestinal tract (Log P ~3-3.4), couldn't cross the blood-brain barrier, and weren't very harmful (LD50>500 mg/kg). Table 1, shows the chemical structures of thiazolidine derivatives (1A-3H) along with the binding energies (kcal/mol).

Table 2, shows 3D, 3E, and 3H where they like to attach to the protein. As shown in Tables 1 and 2, the thiazolidine derivative (3D) may be able to stop the SARS-CoV-2 Mpro.

Both Figs. 1 and 2 displays how drug molecules (3D, E, H) interaction with the main enzyme in two and three dimensions. The ligand preparation choice was used to make the 3D structure of this medicine molecule better and less stiff. The RMSD number showed us the accurate of compound.

The numbers for the standard deviation show that the molecule is now more stable and that the ligand synthesis works. Before and after the contact, the compound had an RMSD value of 0.2702 and a value of 3.7647. This proves that the molecule was well made. These numbers were found using an RMSD value with a standard deviation of 0.35.

Figures 1 and 2 show that amino acids His 41 and His 164 bonded strongly with the carbonyl oxygen of 3D, while amino acids Cys 145 and Gly 143 bonded strongly with the heterocyclic sulfur atom, and amino acid Gln 189 bonded strongly with the heterocyclic sulfur and amid nitrogen atoms. Amino acid Glu 166 bonded strongly with

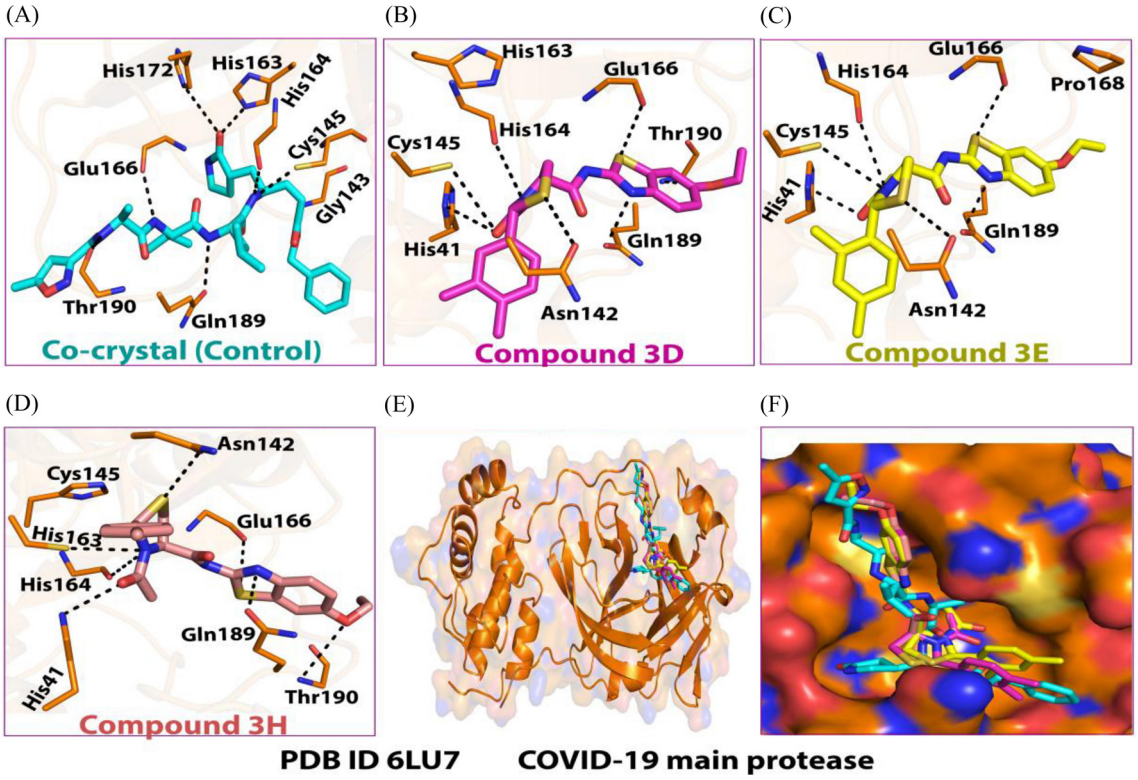


Fig. 2 3D interaction of PDB ID:6LU7 with: control crystal, compounds 3D, compound 3E, and compound 3H

the heterocyclic imine hydrogen, and amino acid His 164 bonded strongly with the carbon atom (C4) of the thiazolidine ring. In 3E, amino acids Gly 143 and Asn 142 made a strong bond with the protein's irregular sulfur atom, as shown in Figs. 1 and 2.

It didn't break Lipinski's rule of five, which is made up of molecular weight and hydrogen bonds between donors and recipients, Fig. 3. To compare with the control (1A), Table 2 and Fig. 3B show that 3D has four H-donors (2.77, 3.35, 3.18, and 2.65 Å distance) and three H-acceptors (3.29, 3.61, and 3.01 Å distance), as well as ionic contact (2.65 Å distance). In Table 2, the control is shown in Fig. 3A. Figure 3C is then compared to 3E, which shows two H-acceptor interactions with distances of 3.57 and 3.17 Å. Figure 3A shows that 3H has five interactions with H-donors (2.71, 3.49, 3.31, 3.48, 2.76 Å distance) and three interactions with H-acceptors (2.81, 3.08, 2.86 Å distance) compared to the control, Table 2 and Fig. 3D.

We used a method to guess how the synthesized chemicals would connect with the main protein crystallographic binding residue, Figs. 4 and 5 [30]. The 3D contact with the protein has an RMSD value of 1.4-1.2 Å, while the control RMSD value was 1.2 Å. This information is shown in Fig. 4B. The RMSD value for the 3E contact with the protein in Fig. 4C is 1.2 -0.2 Å, which is less than the control value of 1.2 Å. The RMSD value for the control was 1.2 Å, but the RMSD value for the 3H contact with the protein is 1.2-0.8 Å, as shown in Fig. 4D. The RMSF results in Fig. 5C show a study of the 3E-protein interaction that is similar to the control in some ways. His 41 is an example of a 3H amino acid, which polarized and attached to 3H's carbonyl oxygen. Another example is Asn 142, which polarized and bound to the heterocyclic imine hydrogen. Other examples are Gln 189, which polarized and bound to the amid group and carbon atom (C4) of benzothiazole, Glu 166, which polarized and bound to the carbonyl oxygen and carbon atom (C4) of benzothiazol, His 164, which showed polar binding, and Gly 143, which polarized and bound to the heterocyclic sulfur atom of 3H.

Figure 5B shows that the RMSF results for the 3D-protein interaction are the same as those for the control. This finding shows that ligand binding in the active region of the protein stays stable during molecular modeling. The RMSF results in Fig. 5D show a study of the 3H-protein interaction that is somewhat similar to the control. During the simulation time, the hydrogen bond had a big effect on how stable these compounds were. The RMSF changes in 3D, 3E, and 3H were similar to those in the control group (0.5-1.0 Å), which shows that the binding is stable. This makes it possible to get a better idea of how the protein and ligand move together.

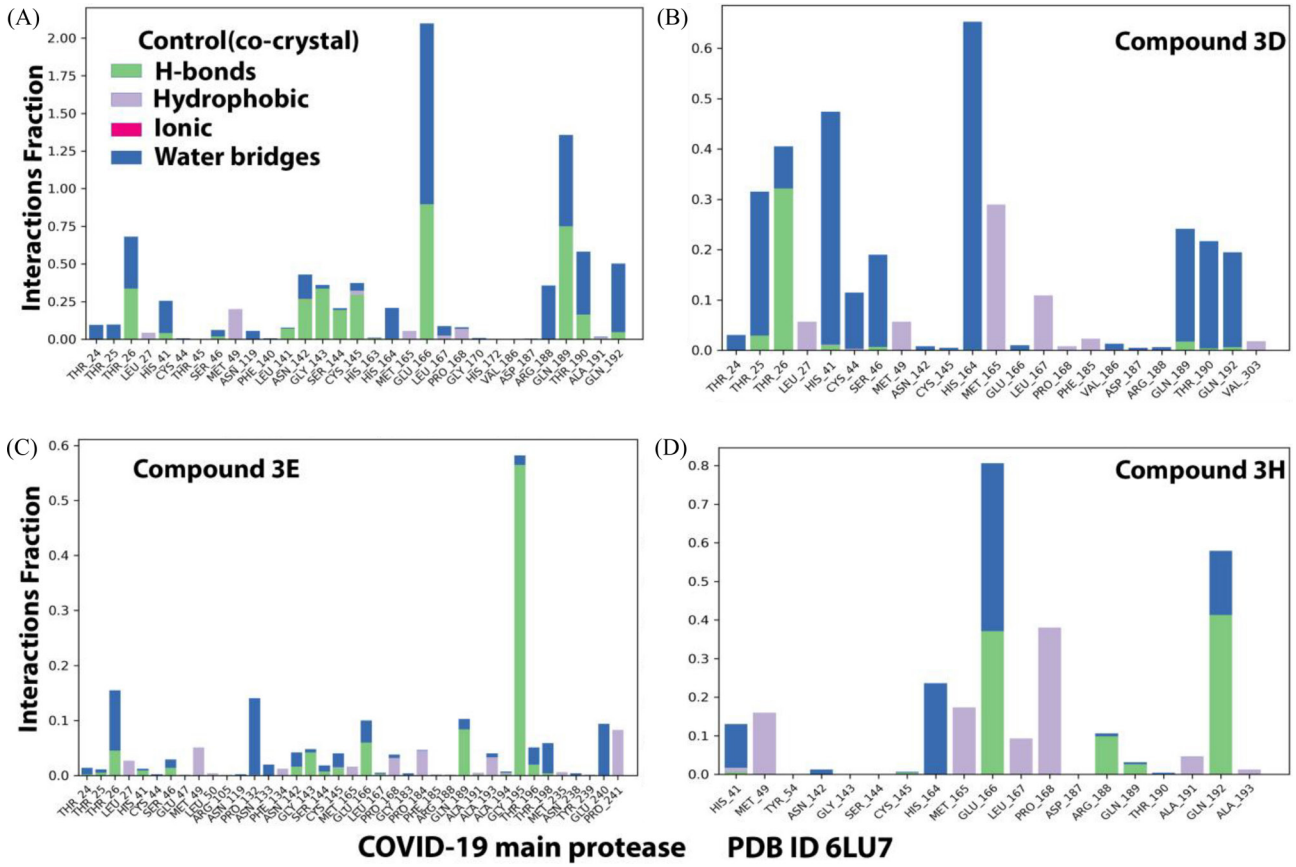


Fig. 3 Interaction fractions of PDB ID:6LU7 with: control crystal, compounds 3D, compound 3E, and compound 3H

Discussion

COVID-19 is a deadly disease caused by the SARS-CoV-2 virus that is quickly spreading around the world and is now a major threat to all people. Ritonavir, remdesivir, hydroxychloroquine, and camostat mesylate are drugs used an antiviral quality. The focus of scientific research has changed toward developing new ways to treat ailments and discovering new drugs that can help. This is because we require effective medications immediately away. It is crucial to investigate whether additional substances, such as rhinacanthin-A, -I, -O, -V, and -G from *Rhinacanthus nasutus* leaf extracts and thiazolidine derivatives that have been developed to target the SARS-CoV-2, can facilitate the healing process. This can be accomplished by employing molecular docking and dynamics models to observe the manner in which they alter the binding sites [26].

Because they can stop a lot of different receptors and enzymes, thiazolidine heterocyclic parts have been helpful in the process of creating new drugs. We used molecular docking and molecular dynamics to examine the thiazolidine derivatives as a drug to fight SARS-CoV-2 Mpro infections. The molecular docking was used to examine and identify the synthesized thiazolidine derivatives that stopped the main protease and know the binding and interaction [32].

The molecular dynamics models were used to identify the best inhibitors that showed good binding at the docking spot. As expected, the simulations demonstrated that the compounds under investigation functioned properly. It was discovered that both versions of the molecule attach to the protease's main active site and do so in a comparable manner. The R-enantiomer of the molecule appears to have the potential to prevent the enzyme from performing its function. More research is needed to determine their potential utility in medication production [33,34].

Based on the molecular docking studies, the thiazolidine derivative 3D was the most drug-like of the ligands, which made it the best choice for binding. The catalytic residues of the SARS-CoV-2 Mpro active site were better at targeting in 3D. Hydrogen bonds with residues His41 and Gly143 showed the blocked active sites. MM/PBSA calculations used to get a better idea of the binding free energies. The new binding free energies are between −6.8 and −7.5 kcal/mol. It found that thiazolidine 3D could be used to make a number of new main protease inhibitors. The 3D-SARS-CoV-2 complex was simulated in molecular dynamics for 100 ns [29,31].

The RMSD (root mean square deviation), Rg (radius of gyration), and binding free energy found that the 3D and the binding region of the SARS-CoV-2 Mpro were stable and could interact with each

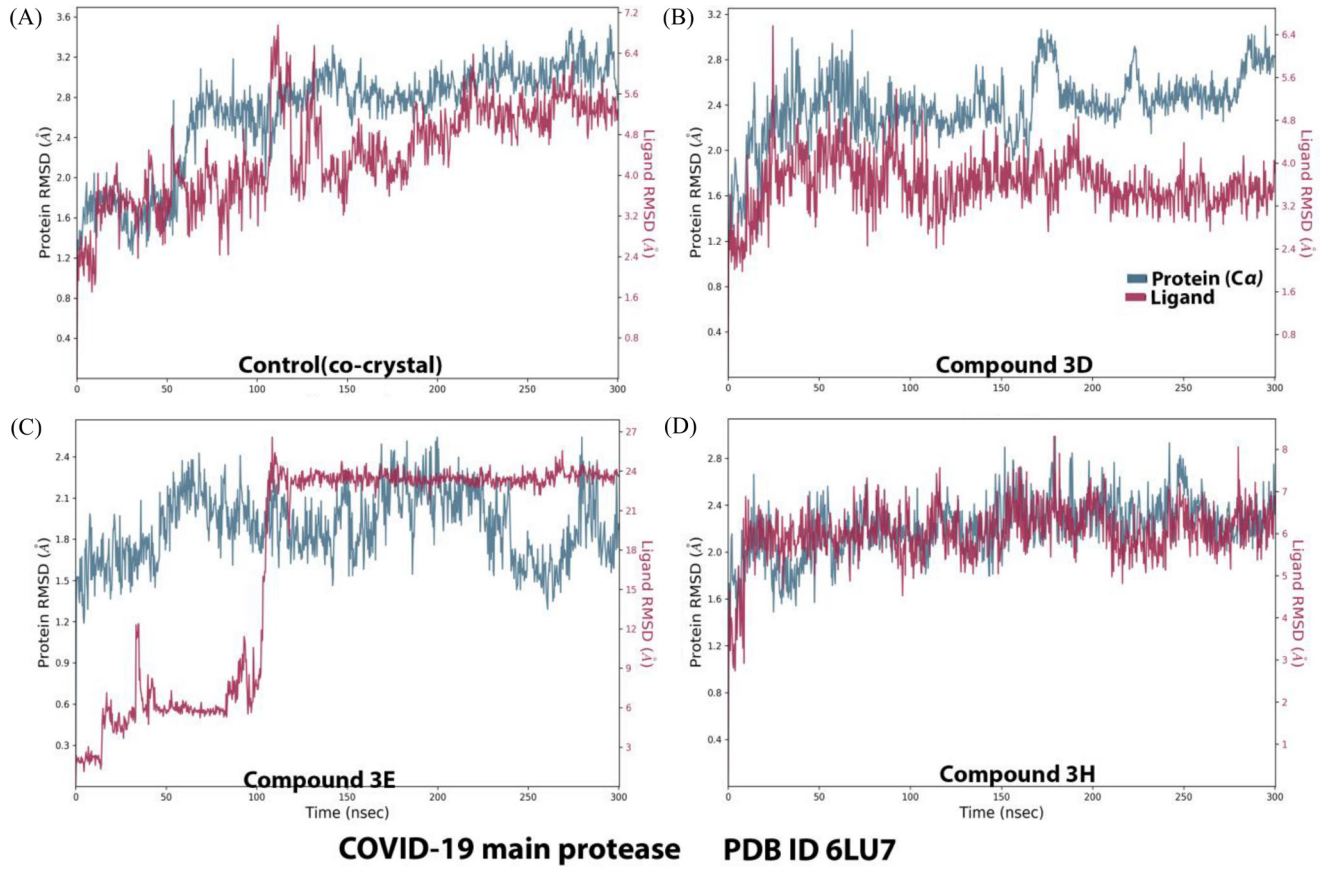


Fig. 4 RMSD analysis of PDB ID:6LU7 with: control crystal, compounds 3D, compound 3E, and compound 3H

other. From the data, the compound 3D could be useful for early studies in the future. In vitro testing of 3D ability to stop SARS-CoV-2 is needed to make it even more certain that it could be the best protease inhibitor for treating COVID-19. Computational methods have a huge impact on how quickly new drugs are found or drugs are moved around in the evaluation process [32,33].

With this computational method, hits that are active in the body can be found among thousands or millions of molecules. It also uses basic methods like molecular dynamics, molecular docking, and QSAR (quantitative structure–activity relationship), and find molecules that are like drugs. A big part of drug design is molecular docking, which lets molecules aim for a certain spot while looking at a lot of possible ligands [35].

Molecular dynamics offers numerous physical interactions between proteins and ligands, including hydrogen bonds, hydrophobic interactions, and solvent accessibility, facilitating the quantification of binding affinities. Molecular dynamics simulations and molecular docking are both helpful and unique ways to explore how well proteins and ligands stick together. The integration of induced-fit docking with molecular dynamics analysis may yield evaluation outcomes compared to the use of either method in isolation [36].

The thiazolidine derivative [3D: 3-acetyl-2-(3,4-dimethoxyphenyl)-N-(6-ethoxybenzo[d]thiazol-2-yl) thiazolidine-4-carboxamide] sticks to the target receptor and stops SARS-CoV-2 Mpro. The best possible relative binding strength was found in the molecular docking models [37]. It was clear that 3D-Mpro was a stable complex by looking at its molecular dynamics. It fit well in the active spot and stopped Mpro. The binding energies for compounds 3D, 3E, and 3H are about the same (−7.3 to −7.7 kcal/mol) as those of some well-known Mpro inhibitors, such as N3 (−7.11 to −8.10 kcal/mol), ritonavir (−7.0 to −8.5 kcal/mol), and remdesivir derivatives. Also, the MM/PBSA free energies (−7.5 to −7.7 kcal/mol) are similar to what is usually seen for strong non-covalent Mpro inhibitors that are being studied right now [28-30]. Because of the encouraging results from molecular docking results, the thiazolidine derivative (3D) is a promising option for additional biological research aimed at inhibiting the replication of the SARS-CoV-2 Mpro. This finding could aid future research and lead to the discovery of medications that inhibit the SARS-CoV-2 Mpro [38].

Although the binding energies are not as high as the control, they nonetheless exhibit strong interactions and should be investigated further. During 100 ns MD simulations, molecules 3D, 3E, and 3H exhibited low RMSD values (1.2-1.4 Å), indicating high stability

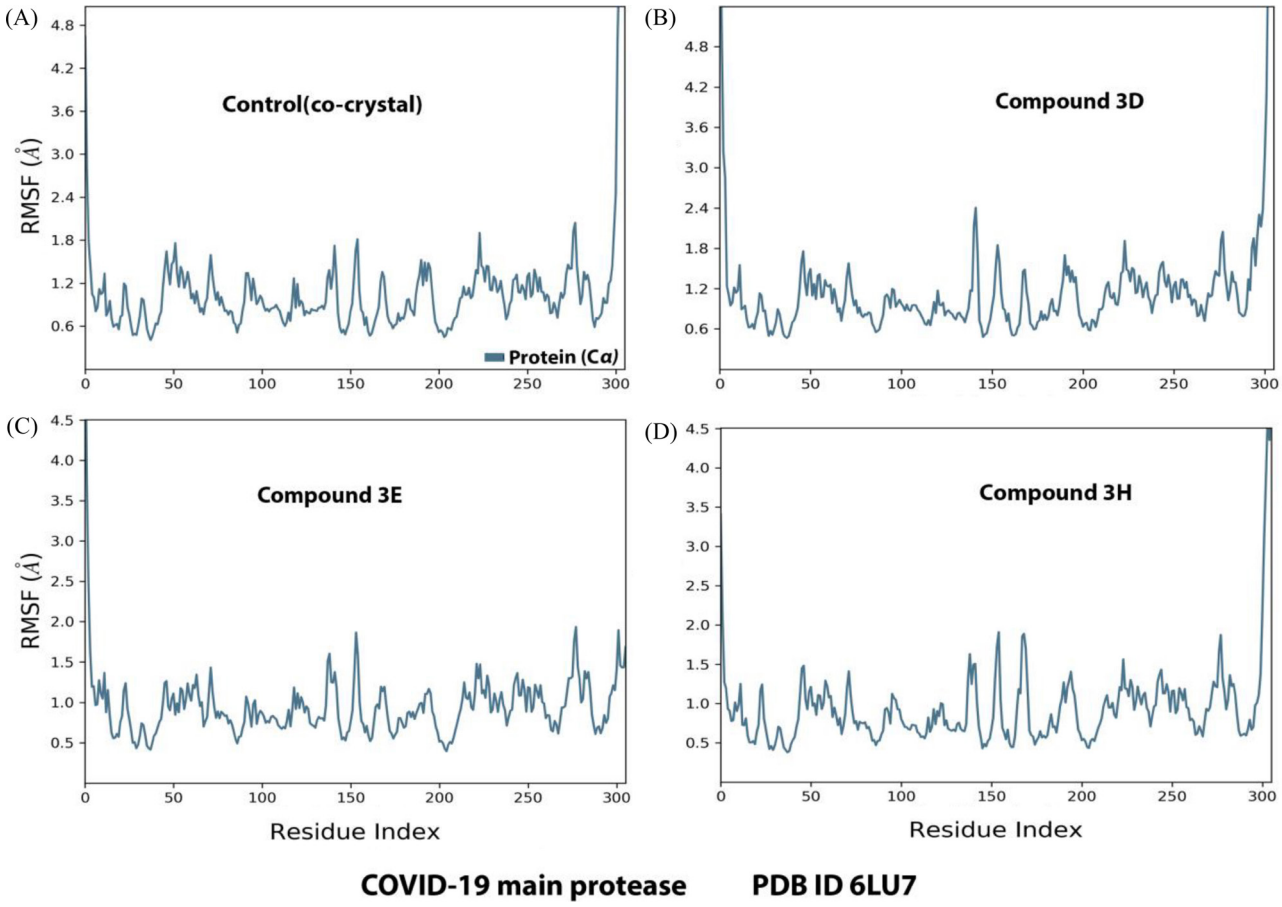


Fig. 5 RMSF analysis of PDB ID:6LU7 with: control crystal, compounds 3D, compound 3E, and compound 3H

of the ligand-protein complexes. These findings, together with the fact that the MM/PBSA binding free energies are positive, indicate that the chemicals remain in touch with the catalytic dyad (His41-Cys145), likely limiting Mpro proteolytic activity.

We now emphasize that results are computational predictions only, binding energies/MM-PBSA values are approximate (typical ranges for known Mpro inhibitors are −6 to −9 kcal/mol in docking and variable in MM/PBSA), and limitations include lack of experimental validation, approximations in scoring functions, and no entropy contributions in MM/PBSA. We highlight the need for in vitro/in vivo testing of hits like 3D.

Among twenty-four thiazolidine derivatives (**1A-3H**), the molecular docking scores were shown to be lower for 3D, 3E, and 3H. The RMSD and RMSF data, 2D and 3D structures, indicated that compound 3D may be able to inhibit the SARS-CoV-2 Mpro, and further investigation as a model for developing novel medications to combat COVID-19.

Acknowledgments The authors would like to thank their affiliations to support their works.

Funding This research was funded by the authors affiliations.

Availability of data and material The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate Not applicable

Competing interests The authors declare that they have no competing interests

References

1. Singhal T (2020) A Review of Coronavirus Disease-2019 (COVID-19). Indian J Pediatr 87(4): 281–286. doi: 10.1007/s12098-020-03263-6
2. Liu Y, Gayle AA, Wilder-Smith A, Rocklöv J (2020) The reproductive number of COVID-19 is higher compared to SARS coronavirus. J Travel Med 27(2): taaa021. doi: 10.1093/jtm/taaa021
3. Kamaz Z, Al-jassani MJ, Umar H (2020) Screening of common herbal medicines as promising direct inhibitors of Sars-Cov-2 in silico. Annu Res Rev Biol 35(8): 53–67. doi: 10.9734/arrb/2020/v35i830260
4. Anjorin AA (2020) The coronavirus disease 2019 (COVID-19) pandemic:

a review and an updata on cases in Africa. Asian Pac J Trop Med 13: 1–6. doi: 10.4103/1995-7645.281612
5. Abosheasha MA, El-Gowily AH (2021) Superiority of cilostazol among antiplatelet FDA-approved drugs against COVID 19 M^{pro} and spike protein: Drug repurposing approach. Drug Dev Res 82(2): 217–229. doi: 10.1002/ddr.21743
6. Li G, Fan Y, Lai Y, Han T, Li Z, Zhou P, Pan P, Wang W, Hu D, Liu X, Zhang Q, Wu J (2020) Coronavirus infections and immune responses. J Med Virol 92(4): 424–432. doi: 10.1002/jmv.25685
7. Jin Z, Du X, Xu Y, Deng Y, Liu M, Zhao Y, Zhang B, Li X, Zhang L, Peng C, Duan Y, Yu J, Wang L, Yang K, Liu F, Jiang R, Yang X, You T, Liu X, Yang X, Bai F, Liu H, Liu X, Guddat LW, Xu W, Xiao G, Qin C, Shi Z, Jiang H, Rao Z, Yang H (2020) Structure of M^{pro} from SARS-CoV-2 and discovery of its inhibitors. Nature 582(7811): 289–293. doi: 10.1038/s41586-020-2223-y
8. Shan T, Li LY, Yang JM, Cheng Y (2023) Role and clinical implication of autophagy in COVID-19. Virol J 20(1): 125. doi: 10.1186/s12985-023-02069-0
9. Chiu KH, Sridhar S, Yuen KY (2023) Preparation for the next pandemic: challenges in strengthening surveillance. Emerg Microbes Infect 12(2): 2240441 doi: 10.1080/22221751.2023.2240441
10. Pushpakom S, Iorio F, Eyers PA, Escott KJ, 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. Nat Rev Drug Discov 18(1): 41–58. doi: 10.1038/nrd.2018.168
11. Afanamol MS, Dinesh AD, Ali KS, Vengamthodi A, Rasheed A (2023) Drug repurposing by in silico prediction of cyclizine derivatives as anti-hyperlipemic agents. In Silico Pharmacol 11(1): 27. doi: 10.1007/s40203-023-00164-2
12. Song Z, Hu Y, Ren Z, Wang G, Liu S, Zheng S, Yang L, Zhao R (2022) Optimal Management of the Public and Patients by Pharmacists in the Era of COVID-19: An Evidence-Based Review and Practical Recommendations. Front Public Health 9: 758325. doi: 10.3389/fpubh.2021.758325
13. Kartritzky AR, C. Rees (1984) Comprehensive Heterocyclic Chemistry. Vol. 6, 1st Edition, Pergamon Press, Oxford
14. Önen Bayram FE, Sipahi H, Acar ET, Kahveci Ulugöl R, Buran K, Akgün H (2016) The cysteine releasing pattern of some antioxidant thiazolidine-4-carboxylic acids. Eur J Med Chem 114: 337–344. doi: 10.1016/j.ejmech.2016.03.019
15. Ershov AY, Lagoda IV, Mokeev MV, Yakimovich SI, Zerova IV, Pakalnis VV, Shamanin VV (2008) Thiosalicyloylhydrazones of Alyphatic Aldehydes and Their Cyclization into 1,3,4-Benzothiadiazepine Derivatives. Chem Heterocycl Compd 44: 356–359. doi: 10.1007/s10593-008-0052-2
16. Musaddiq S, Imran Shahzad M, Firdous F, Iqbal A, Tanveer M, Ashraf A, Aslam S, Khakwani S (2020) Thiazolidines: Potential anti-viral agents against avian influenza and infectious bronchitis viruses. Vet Res Forum 11(4): 415–421. doi: 10.30466/vrf.2018.91264.2211
17. Albakhit SDY, Ali S H, Ibrahim S Q, Majeed KR, Faisal NH, Al-Shawi AAA, Hussein KA, Mohsein OA, Eltayb WA, Mamoun R, Abdalla M (2025) Molecular Docking and Dynamics of 2,5-Pyrrolidinedione Analogue Using the SARS-CoV-2 Main Protease as Target Protein. Infect Epidemiol Microbiol 11(3): 269–283. doi: 10.61882/iem.11.3.269
18. AbdulJabar LA, Al-Shawi AAA, Mutlaq DZ (2021) Anti-liver and anti-breast cancer activities of 2-thioxo-4-imidazolidinone derivatives. Med Chem Res 30: 1943–1953. doi:10.1007/s00044-021-02769-8
19. Al-Shawi AA, Hameed MF, Hussein KA (2020) Perspective Study of Exploring Some Medicinal Plants to Manage the Pandemic COVID-19. Eur J Med Health Sci 2(4). doi:10.24018/ejmed.2020.2.4.374
20. Magro G (2020) COVID-19: Review on latest available drugs and therapies against SARS-CoV-2. Coagulation and inflammation cross-talking. Virus Res 286: 198070. doi: 10.1016/j.virusres.2020.198070
21. Modjarrad K, Moorthy VS, Ben Embarek P, Van Kerkhove M, Kim J, Kieny MP (2016) A roadmap for MERS-CoV research and product development: report from a World Health Organization consultation. Nat Med 22(7): 701–705. doi: 10.1038/nm.4131
22. Abdalla M, El-Arabey AA, Gai Z (2023) Hypertension is still a moving target in the context of COVID-19 and post-acute COVID-19 syndrome. J Med Virol 95(1): e28128. doi: 10.1002/jmv.28128
23. Zhang Y, Tang LV (2021) Overview of Targets and Potential Drugs of SARS-CoV-2 According to the Viral Replication. J Proteome Res 20(1): 49–59. doi: 10.1021/acs.jproteome.0c00526
24. Ayat NH, Dawood SA (2017) Preparation, Characterization and Biological Activity Study of some New Thiazolidine Derivatives. J Basrah Res ((Sci)) 43(1) A
25. Abdalla M, Rabie AM (2023) Dual computational and biological assessment of some promising nucleoside analogs against the COVID-19-Omicron variant. Comput Biol Chem 104: 107768. doi: 10.1016/j.compbiolchem.2022.107768
26. Li X, Song Y (2023) Structure and function of SARS-CoV and SARS-CoV-2 main proteases and their inhibition: A comprehensive review. Eur J Med Chem 260: 115772. doi: 10.1016/j.ejmech.2023.115772
27. Abdalla M, El-Arabey AA, Gai Z (2023) Interplay between LPL and GPIHBP1 in COVID-19 patients: a possible mechanism for post-recovery cardiomyopathy. Hum Cell 36(6): 2270-2272. doi: 10.1007/s13577-023-00953-z
28. Majchrzak M, Poręba M (2022) The roles of cellular protease interactions in viral infections and programmed cell death: a lesson learned from the SARS-CoV-2 outbreak and COVID-19 pandemic. Pharmacol Rep 74(6): 1149–1165. doi: 10.1007/s43440-022-00394-9
29. van de Sand L, Bormann M, Alt M, Schipper L, Heilingloh CS, Steinmann E, Todt D, Dittmer U, Elsner C, Witzke O, Krawczyk A (2021) Glycyrrhizin Effectively Inhibits SARS-CoV-2 Replication by Inhibiting the Viral Main Protease. Viruses 13(4): 609. doi: 10.3390/v13040609
30. Hu Q, Xiong Y, Zhu GH, Zhang YN, Zhang YW, Huang P, Ge GB (2022) The SARS-CoV-2 main protease (M^{pro}): Structure, function, and emerging therapies for COVID-19. MedComm 3(3): e151. doi: 10.1002/mco2.151
31. Al-Shawi AAA, El-Arabey AA, Mutlaq DZ, Eltayb WA, Iriti M, Abdalla M (2023) Study on Molecular Anti-tumor Mechanism of 2-Thiohydantoin Derivative based on Molecular Docking and Bioinformatic Analyses. Curr Top Med Chem 23(6): 440–452. doi: 10.2174/1568026623666230106121527
32. Arya R, Kumari S, Pandey B, Mistry H, Bihani SC, Das A, Prashar V, Gupta GD, Panicker L, Kumar M (2021) Structural insights into SARS-CoV-2 proteins. J Mol Biol 433(2): 166725. doi: 10.1016/j.jmb.2020.11.024
33. Naser NM, Mutlaq DZ, Al-Shawi AA, Modafer Y, Dawoud RA, Abdalla M (2024) Synthesis, characterization, antibacterial, and molecular docking and dynamics studies of novel 2-thioxoimidazolidin-4-one analogue. Chem Afr 7(8): 4193–210. doi: 10.1007/s42250-024-01040-y
34. Gorkhali R, Koirala P, Rijal S, Mainali A, Baral A, Bhattarai HK (2021) Structure and Function of Major SARS-CoV-2 and SARS-CoV Proteins. Bioinform Biol Insights 15: 11779322211025876. doi: 10.1177/11779322211025876
35. El-Arabey AA, Abdalla M, Abd-Allah AR (2020) SnapShot: TP53 status and macrophages infiltration in TCGA-analyzed tumors. Int Immunopharmacol 86: 106758. doi: 10.1016/j.intimp.2020.106758
36. V'kovski P, Kratzel A, Steiner S, Stalder H, Thiel V (2021) Coronavirus biology and replication: implications for SARS-CoV-2. Nature Rev Microbiol 19(3): 155–170. doi: 10.1038/s41579-020-00468-6
37. Bahadur Gurung A, Ajmal Ali M, Al-Hemaid F, El-Zaidy M, Lee J (2022) *In silico* analyses of major active constituents of fingerroot (Boesenbergia rotunda) unveils inhibitory activities against SARS-CoV-2 main protease enzyme. Saudi J Biol Sci 29(1): 65–74. doi: 10.1016/j.sjbs.2021.11.053
38. Nazir F, John Kombe Kombe A, Khalid Z, Bibi S, Zhang H, Wu S, Jin T (2024) SARS-CoV-2 replication and drug discovery. Mol Cell Probes 77: 101973. doi: 10.1016/j.mcp.2024.101973