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The Molecular Docking and Molecular Dynamics Simulation of Some HIV-1 protease Inhibitors For the treatment of Coronavirus Disease-19

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ABSTRACT

In this manuscript; Molecular dynamics simulation was tested on COVID -19 main protease (PDB: 6LU7) with the docking studies have been employed using autodock-vina-1.1.2-4 and autodock- mgltools-1.5.6 (flex) programs to evaluate the interactions. HIV-1 Protease is a prerequisite for viral replication. In this manuscript; Molecular dynamics simulation was tested on COVID -19 main protease (PDB: 6LU7) with the docking studies have been employed using autodock-vina-1.1.2-4 and autodock- mgltools-1.5.6 (flex) programs to evaluate the interactions. Regular and Flexible docking approaches were run. Molecular dynamics simulation was tested on COVID -19 main protease (PDB: 6LU7) with molecule 7. Drug-likeness descriptors of compounds such as logP (partition coefficient), H-Bond Acceptor (HBA), H-Bond Donor (HBD), number of Rotable Bond (nRB), and nHB calculated by DruLiTo. In the molecular docking study, the maximum binding affinity of -5.9 kcal/mol was obtained between each of COVID -19 main protease (PDB: 6LU7) enzyme systems and the geometric-optimized molecules, representing a strong interaction. The reference molecule PRD_002214 of Mpro forms four hydrogen bonds with Glu 166, Phe 140, Gln 189, His 163, and some hydrophobic bonds. In this study, molecules 7 (Amprenavir) and 15 were presented as the most stable ones that may be introduced for further investigations, including clinical experiments.

Keywords: Molecular Docking; Molecular dynamics simulation; COVID-19; Autodock-vina; Gromacs

1. INTRODUCTION

There are several molecular level targets for investigation on HIV-1 cycle. The Main protease (Mpro) that cuts two replicase polyproteins resulting in matured proteins that are required to mediate viral replication and transcription. We selected Mpro, protease as a target to inhibit virus replication [1-6].

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Today, the infection by COVID-19 spread to all of countries. We want to treat infections of coronavirus. Computational methods can be employed for design drugs. Where there is no alternative medicine, such a drug repurposing strategy is attractive [7-11].

Different software algorithms use various approaches, such as rigid or flexible proteins. Biological assays must confirm the computational findings. Docking calculations can be validated by re-docking ligands that are co-crystallized in the receptor structures. Molecular dynamics (MD) simulation delivers information for explaining the experimental data. Molecular docking has been used in drug design. It is used for ligand- receptor complex and the study of binding energy. The equilibration was confirmed by the root mean squared deviations (RMSDs) of the backbone atoms.

RMSD values should be less than 2.0 Å. Root mean squared deviation was used for two sets of N atoms on c and d coordinates.

$$\text{RMSD} = \sqrt{\frac{1}{N}\sum_1^N (Xci - Xdi)^2 + (Yci - Ydi)^2 + (Zci - Zdi)^2}$$

Molecular dynamics (MD) simulation delivers information for explaining the experimental data [12-14]. Ubuntu 2018.1 operating system (64-bit) with 16GB memory was used for all computational work.

It was found that the protease activity of HIV is similar between SARS-CoV and SARS-CoV-2, and HIV protease inhibitors could hinder the replication of SARS-CoV virus. In attempts to screen anti-SARS-CoV drugs, it was revealed that many potential drugs identified by molecular simulation or other experimental methods were HIV protease inhibitors in spite of the structures of Mpro and HIV protease being different.

Wei Yu et al. have studied Computational Simulation of HIV Protease Inhibitors to the Main Protease (Mpro) in 2021 [15-19]. Our study might be beneficial for the molecular design for the development of new small-molecule drugs as lead compounds as specific treatments for COVID-19.

2. MATERIALS AND METHODS

2.1. Protein Receptors Preparation

The 3D structure of Mpro from COVID-19 (Brookhaven Protein Data Bank (PDB) ID 6LU7) was obtained from http://www.rcsb.org [20]. The clean input file was generated using GROMACS. The inhibitor N3 was bound to the structure of the complex.

2.2. Ligand Preparation

The Ligand structure was drawn using Marvin Sketch software and the docking studies were performed using the Vina program to evaluate the interactions. Flexible docking approaches were run for each docking run and the presented results in Fig.1. The docking was validated by re-docking the reference molecules of the active site of protein structure. Grid spacing was set to 0.375 Å. Center grid box values were set to x= -14.100, y=-12.636, and z=-70.776. The active site is the target for an enzyme's inhibition. The active site of the protease was predicted using the MetaPocket 2.0 online server.

2.3. Drug Likness Activity

Drug-likeness descriptors of compounds calculated by the DruLiTo program.

2.4. Visualization

The LigPlot+ v.1.4.5 program depicts hydrogen bonds. The figures of molecules were shown in Fig. 2.

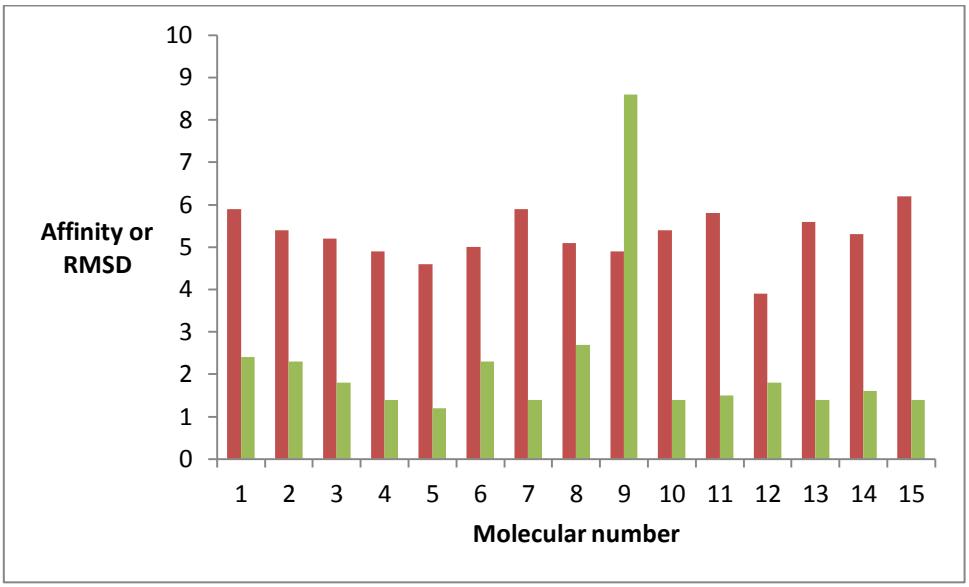


Fig. 1. The RMSD lb and Affinity for COVID-19 main protease (PDB:6LU7), calculated by autodock-mgl tools-1.5.6(flex) program with co- crystal

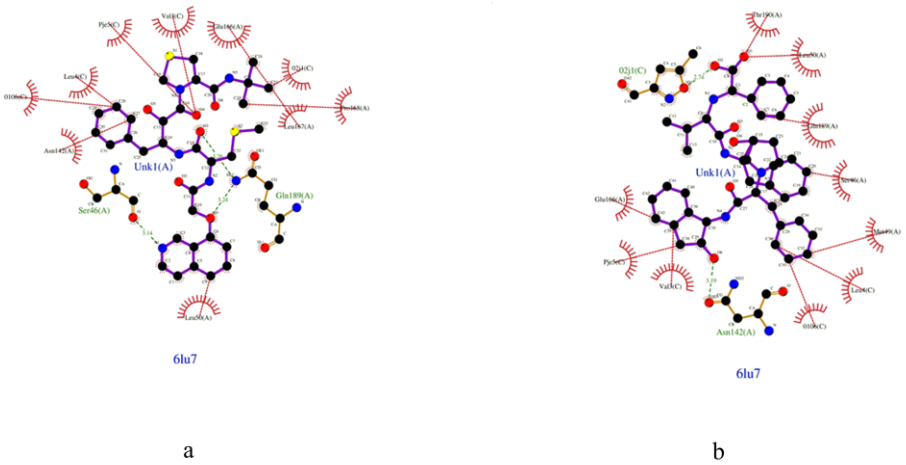


Fig. 2. The docking COVID-19 main protease (PDB: 6LU7) - molecules visualized by LigPlot+ v.1.4.5 program (a: Molecule 1,b: Amprenavir)

2.5. Molecular Dynamics Simulation

The molecular dynamics simulation was carried out using GROMACS (version 2018.1), where the force field was GROMO S96 54 A5 and n steps were equal to 20 ns. The required itp and gro files were obtained from PRODRG 2.5. Ubuntu 2018.1 operating system (64-bit) with 16GB memory was used for all computational work.

3. RESULTS AND DISCUSSION

Molecular docking and molecular dynamics simulation studies were done on HIV-1 protease inhibitors using autodock-vina-1.1.2-4 and Gromacs (2018.1) software. Docking studies against COVID - 19 main protease (PDB: 6LU7) revealed that molecules were suitably docked on 6LU7 (−3.9 to −6.2 kcal/mol). The structure of amprenavir is shown in Fig. 3.

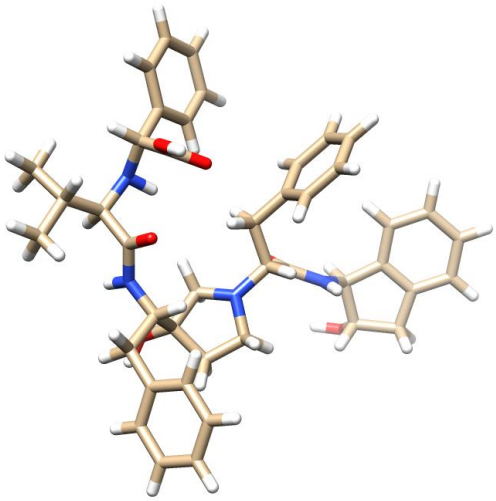


Fig. 3. The structure of Amprenavir

In COVID- 19 main protease (PDB: 6LU7) of docking poses with a minimum RMSD l. b value of 1.225Å it means the binding mode has been correctly done. In addition, some key residues such as Leu 27, His 41, Asp 51, Tyr 118, and Phe 140 in COVID - 19 main protease (PDB: 6LU7) in A branch appeared in the binding cavity .

The maximum affinity towards COVID -19 main protease (PDB: 6LU7) macromolecule belonged to molecules 7 and 15.

The 2D interactions of complexes were visualized by using Lig- Plot+ v.1.4.5 software (Figure 3). The reference molecule PRD_002214 of Mpro shows four hydrogen bonds with Glu 166, Phe 140, Gln 189, His 163, and some hydrophobic bonds.

Molecule 1 forms hydrogen bonds with Gln 189 (A), and Ser 46(A). Molecule 2: Asn 84 (A), Gly 183 (A), and Phe 185 (A). Molecule 3: Ser 46(A). Molecule 4: Gln 189 (A), and Leu4 (C). Molecule 5: Ser 46 (A). Molecule 6: Glu 166 (A), and Pro 168 (A) Molecule 7: N3, Asn 142 (A). Molecule 8: Asn 142(A). Molecule 9: Gln 189 (A).Molecule 10: Leu 50(A), and Ser 46(A). Molecule 11: N3, and Gln 189(A). Molecule 12: N3, and Gln 189(A). Molecule 13: N3, and Gln 189(A). Molecule 15: N3, and Gln 189 (A).

Drug-likeness descriptors of compounds such as logP, H-Bond Acceptor (HBA), HBD, nRB, and nHB calculated by DruLiTo are shown in Table 1. Log P refers to the partition coefficient of the ligand that ideally ranges between 5.6 and -0.4. All the ligands are showing Log P values between these ranges. The permeability and the value of Log p (experimental) were given from literatures.

The RMSD in molecular dynamics simulation is shown in Fig. 4. In the light of Fig. 4 it can be said that the RMSD and interactions results well confirms the Docking quality and results.

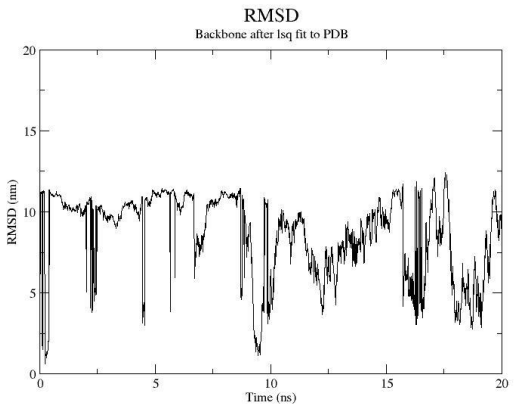
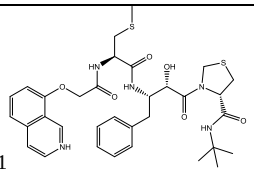
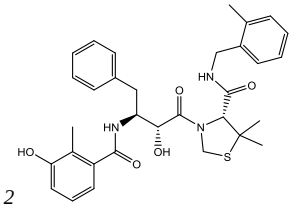
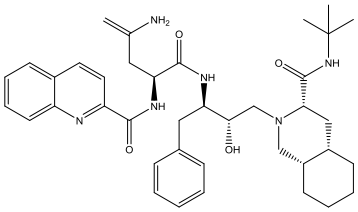
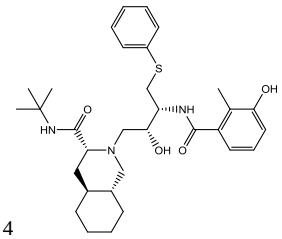
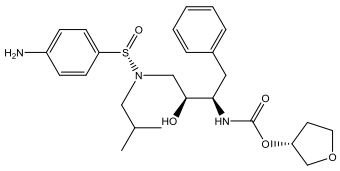
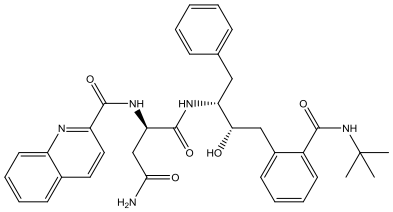
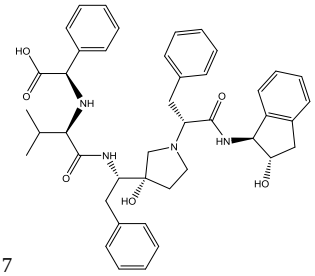
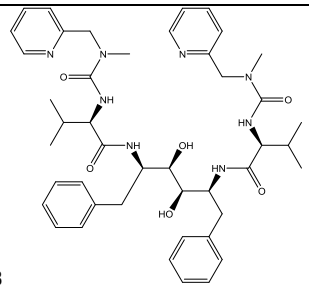
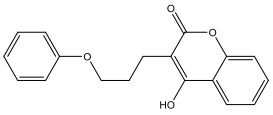
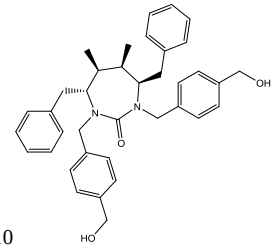
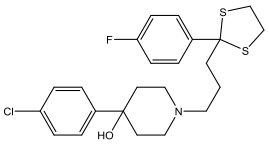
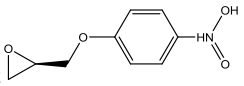
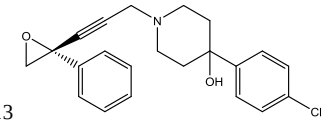
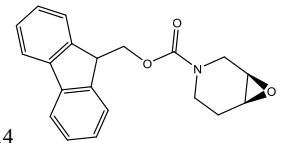
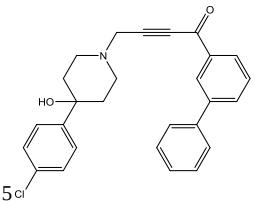


Fig. 4. The RMSD of molecular dynamics calculated by gromacs of the COVID-19 main protease (PDB: 6LU7) - molecule 7.

Table 1. Drug-likeness descriptors of compounds 1-15, calculated by DruLiTo software

Molecule	MW	Log P	HBA	HBD	nRB	nHB	TPSA	Log p ref.	Caco2 Permeability
 1	668.26	2.03	11	5	18	16	187.67		
 *2*	575.25	2.51	8	4	12	12	144.27		
3 	668.41	3.35	10	5	16	15	149.15	4.7[a],1.9[d]	-6.26[b]
 4	567.31	3.94	7	4	12	11	127.2	3.88[c], 2.9[d]	-
5  6	489.23	0.34	8	3	13	11	133.33		
	609.3	1.19	10	5	16	15	162.98		
 7	718.37	3.25	10	6	17	16	151.23	1.7[d]	-12[e]

Molecule	MW	Log P	HBA	HBD	nRB	nHB	TPSA	Log p ref.	Caco2 Permeability
 8	794.45	1.13	14	6	25	20	188.06		
 9	296.1	2.37	4	1	5	5	55.76		
 10	562.32	3.36	5	2	10	7	64.01		
 11	451.12	2.79	2	1	6	3	74.07		
 12	197.07	0.79	2	2	4	4	59.16		
 13	367.13	1.66	3	1	3	4	36		
 14	321.14	2.56	4	0	4	4	42.07		
 15	429.15	3.85	3	1	4	4	40.54		

a: BIOBYTE STARLIST (2009), b: **URL:** http://www.drugbank.ca/drugs/DB01232, c: chemaxon, d: [4], e: [3]

4. CONCLUSION

The calculated RMSD and molecule-receiver interactions showed a high agreement between molecular docking and molecular dynamic simulations. In molecular docking study, amprenavir and the structure 15 exhibit as maximum affinity and minimum RMSD that may be introduced for further investigations, including clinical experiments. The predicted binding will also be useful for the treatment of COVID-19. With the Lig-Plot softare, molecule amprenavir forms hydrogen bonds with N3, Asn 142(A).

5. ACKNOWLEDGMENT

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مجله شیمی فیزیک و شیمی نظری
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داکینگ مولکولی و شبیه سازی دینامیک مولکولی تعدادی از بازدارنده های HIV-1 پروتئاز برای درمان بیماری کووید-۱۹

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چکیده

1پروتئاز برای تکثیر ویروسی لازم است.مطالعات داکینگ با استفاده از برنامه اتوداک وینا و mgltools-1.5.6 انجام شده است. انواع منظم و انعطاف پذیر داکینگ انجام شده است. بررسی شبیه سازی دینامیک مولکولی COVID -19 main protease (PDB: 6LU7) روی مولکول ۷ انجام شده است. توصیف کننده ای چون nHB, logP, HBA, HBD, nRB بوسیله برنامه DruLiTo محاسبه شده اند. در مطالعات داکینگ مولکولی بالاترین افینیتی 5.9 kcal/mol- بود که نشان دهنده برهم کنش قوی است. در مولکول مرجع Mpro PRD_002214 ٤ پیوند هیدروژنی با Glu 166, Phe 140, Gln 189, His 163 وتعدادی برهمکنش هیدروفوبیک وجود داشت. بر اساس این بررسی‌ها مولکول های آمپرناویر و مولکول ۱۵ بعنوان ترکیبات پایدار برای بررسی های بیشتر و آزمایشات کلینیکی پیشنهاد می‌گردد.

کلید واژه‌ها: داکینگ مولکولی؛ شبیه سازی دینامیک مولکولی؛ کووید-۱۹؛ آتوداک وینا، گروماکس.

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