In silico Molecular Docking study approach with Multi potent anti-viral and anti-malarial drugs for COVID-19 main protease key enzyme responsible for mediating viral replication and transcription

Pradeep H K[1*], Girish Bolakatti[2], Rakesh N R[3], Gurumurthy H [4] , Thimmasetty J[5]
Dipti H patel[6]

[1] Dept. of Pharmaceutics, GM Institute of Pharmaceutical Sciences and Research, Davangere, Karnataka, India
[2] Dept. of Chemistry, GM Institute of Pharmaceutical Sciences and Research, Davangere, Karnataka, India
[3, 4] Dept. of Biotechnology GM Institute of Technology, PB Road, Davangere, Karnataka, India
[5] Dept. of Pharmaceutics, Bapuji Pharmacy College, Davangere, Karnataka, India
[6] Dept. of Pharmaceutics, Parul Institute of Pharmacy, Vododara, Gujarat, India

*Correspondence author: - GM Institute of Pharmaceutical Sciences and Research, Davangere, Karnataka, India

ABSTRACT: The horrendous Covid-19 affected throughout the world, the first time in the history of human being this disease caused terrible impinge on the wellbeing of mankind. Since its inception from Wuhan, China till today "2019-nCoV" caused more than millions of deaths were confirmed from more than 75 million confirmed cases. At present no drug is available for the treatment of novel coronavirus infection. Only emergency approved vaccines were available. New drug discovery is a complex process which required long term to get Food Drug Administration approval, right now only available option is repurposing the approved drugs to treat Covid-19. In the present investigation, we systematically studied interaction of anti-viral (38) and anti-malarial (18) drugs on protease ofCovid-19 (PDB: 6LU7) the docking was performed on Molecular Operating Environment (MOE) 2019.01 computer-aided molecular design software. Among the investigated antiviral drugs (38) and anti-malarial (18), the potential binding force was predicted. The drug compounds such as hydroxychloroquine (-6.80 kcal/mol), atovaquone (-7.13kcal/mol), amodiaquine (-7.03 kcal/mol), elvitegravir (-7.21 kcal/mol),oseltamivir (-6.74 kcal/mol), and favipiravir (-4.24 kcal/mol) showed fairbinding energy values during MOE docking studies.

Keywords: Covid-19, 6LU7, Molecular docking, Antiviral drugs, Anti-malarial drugs

1. Introduction

The pandemic nCov-19 outbreak has not only raised global health concern but it also created an insatiable appetite for drug inventors. The national health commission of china has concluded the transmission of Wuhan outbreak nCov-19 from human to human on January 20th 2020. According to the present situation report from World Health Organisation (WHO), more than 75 million confirmed cases were reported covering majority of the countries worldwide.

The first COVID-19 case was reported[1] in Wuhan city, in December 2019 the province Hubei reports[2-3] severe pneumonia in China, especially in Wuhan. The causative organism caused the disease was soon identified as a novel corona virus, which is closely related to severe acute respiratory syndrome corona virus (SARS-CoV). Later on, the International Committee on the Taxonomy of Viruses the virus was renamed as severe acute respiratory syndrome coronavirus 2

(SARS-CoV-2). [4-5] The availability of protein structure SARS Cov-2 at early stage, crystal structure of 3CLpro is now available from PDB (pdb code: 6LU7) which enable us to use encoded protein homology model directly. The accuracy of homologous modelling was verified by aligning computational structures of SARS-CoV-2 3CLpro which was constructed from SARS-CoV 3CLpro.[6]

Corona viruses belong to zoonotic group. Zoonotic means the viruses capable of transmitting from animals to humans.[7] These corona viruses were characterized in 1960s which acts causative agents for upper respiratory tract infections in children's. Since 2003, as a minimum five new human coronaviruses were diagnosed, together with the extreme acute breathing syndrome coronavirus, which prompted vast morbidity and mortality.[8] corona viruses, were in spotlight when SARS become an epidemic.

Epidemiology of corona virus shows that severe respiratory infections in mild temperate and high during the winter and spring. And fall during the summer. Analysing the data they contribute overall 35% of severe respiratory infections during epidemics. An estimate of 15% adult cold produced by corona viruses.[9]

The name corona name arrived because of having crown like shape on the cellular membrane. The different types of corona viruses were shown in figure 1. Among all the types of corona first four types were commonly infected by human beings. These viruses having capacity to evolve in new form when they infect animals and transmit to human and becoming a new human corona virus, mainly ERS- CoV, SARS- CoV, SARS- CoV2 (COVID -19).[10]

The pandemic COVID-19 infection is spreading through the globe in an uncontrollable speed and right now the best available approach for rapid development of medicines for treating SARS CoV-2 is to find out the ability of already marked antiviral drugs or any other approved drugs which may effectively eradicate COVID-19 disease.

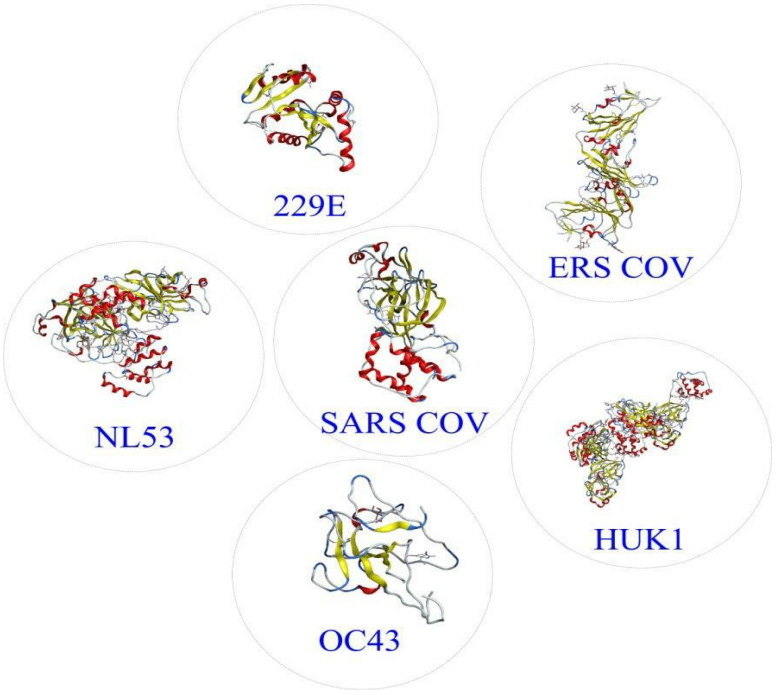

Figure 1 Types of Corona Virus Reported

The present study predicts array of anti-viral and anti-malarial drugs that may inhibit novel corona viruses and provides drug innovators with information on compounds that may be effectively binds

with pharmacophoric group of the target. The figure 2 shows docking approach of anti-viral and anti-malarial on COVID-19 protease. Subsequent validation of anti-viral effects of these drugs on SARS- CoV2 (COVID-19) through clinical studies will provide useful information for clinical treatment of novel corona virus infection.

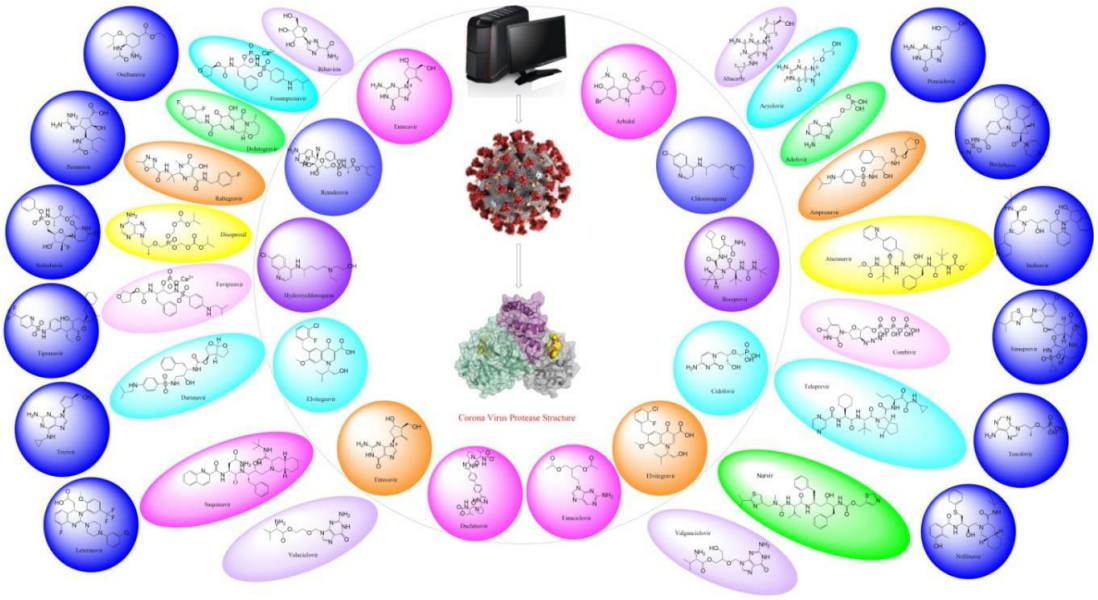

Figure 2 Molecular Docking of 6LU7 (From COVID-19) with anti-viral and anti-malarial drugs.

2. Material and Methods

2.1. Molecular Modeling platform

The computation studies were performed using integrated computer aided molecular design platform MOE 2019.01 gold software (Chemical Computing Group).

2.2. Preparation of ligand and energy minimization

All the Ligand molecules were constructed through molecular builder of MOE 2019.01 gold software, then they are subjected for energy minimization using Amber 10 force field with gradient 0.1 RMS kcal/mol. Total USFDA approved 38 anti-viral and 19 anti-malarial drugs were selected to perform the molecular docking studies to predict interaction between ligand and COVID 19 protease.[11-13] The list of drugs selected for docking studies are shown in the **Table no 1.**

Sl. No	Drugs	Class	Sl. No	Drugs
1	Amodiaquine	Antimalerial	10	Mefloquine
2	Artemether		11	Piperaquine
3	Atovaquone		12	Primaquine
4	Chloroquine		13	Proguanil
5	Clindamycin		14	Pyrimethamine
6	Dapsone		15	Pyronaridone

7	Doxycycline		16	Quinine
8	Hydroxychloroquine		17	Sulfadoxine
9	Lumefantrine		18	Sulfalene
1	Abacavir	Antiviral	21	Lopinavir
2	Acyclovir		22	Nelfinavir
3	Adefovir		23	Norvir
4	Amprenavir		24	Oseltamavir
5	Arbidol		25	Penciclovir
6	Atazanavir		26	Premivir
7	Beclabuvir		27	Ralttegravir
8	Boceprevir		28	Remdesivir
9	Cidofovir		29	Ribaverin
10	Combivir		30	Ritonavir
11	Daclatasavir		31	Saquinavir
12	Darunavir		32	Simeprevir
13	Disoproxil		33	Sofosbuvir
14	Elvitegravir		34	Telaprevir
15	Entacavir		35	Tenofovir
16	Famciclovir		36	Tipranavir
17	Favipiravir		37	Trizivir
18	Fosampiravir		38	Valaganciclovir
19	Indinavir		39	Valaciclovir
20	Lotermovir			

Table No. 1: List of selected drugs for docking study

2.3. Extraction of protein and preparation of macromolecule

To fight with COVID-19 the protease crystal structure of main protein chain is downloaded from RCSB protein (http://www.rscb.org) data bank (PDB entry: 6LU7, released dated 05-02-2020). The crystallographic structures of both viral protein (6LU7) and drugs were selected for the study were subjected for the preparation step, based on energy minimisation (EM) with default parameters such as GBVI/WSA dG (force field based on scoring function) and solvation method was employed. Refinement was carried out down to a Root mean square (RMS) gradient of 0.01kcal/mol/Å The alignment produced by the MOE align program module with default parameters were set. All drugs were taken for study docked with 6LU7. After each time docking the ligand structure is correlated with data base viewer file through browsing in MOE module.

2.4. Binding site Analysis

Through MOE 2019.01 the binding sites of the ligand molecule were identified through geometric approach which helps to calculate binding sites in protein, starting from its three dimensional structure. The analysis of binding sites is not based on any energy models. Binding sites were analysed through MOE binding site finder module, confirmed binding sites defined by the co-crystallised ligands in the holo forms of investigated protein.

2.5 Computational Docking

In-Silico screening with MOE dock programme, a part of simulation module of gold scoring is used. The method opted for docking triangular matcher which is standard method and well defined for binding sites. With Triangle Matcher the poses are generated by superposing triplets of ligand atoms and triplets of receptor site points. The receptor site points are alpha spheres centres that represent locations of tight packing. Thirty complexes were generated for each tested ligand. Duplicate complexes were then removed: poses are considered as duplicates if the same set of ligand-receptor atom pairs are involved in hydrogen bond interactions and the same set of ligand atom receptor residue pairs are involved in hydrophobic interactions. The accepted poses were scored according to the London dG scoring function, which estimates the binding free energy of the ligand from a given pose shown in **Table No. 2**

3. Results and Discussion

3.1. Topological Polar Surface Area in Sq Å

Topological polar surface area (TPSA) for given molecule is the surface sum total polar atoms or molecules, which mainly constituent of oxygen and nitrogen, along with attached hydrogen. It is one of the best ability parameter considered for the optimization of the drug moieties. A TPSA value of less than 90 angstroms squared is usually preferred for consideration in this studies the 4 out of 6 top drug have shown the fulfilling value Hydroxychloroquine TPSA: 48.39, Atovaquone: 54.39 Amodiaquine: 48.39 and Elvitegravir 87.07 Sq Å.

3.2. Molecular Weight in g/mol

It is made sure that the molecular weight (MW) of a compound must be under 500 Dalton to allow skin absorption. Larger molecules cannot pass the corneal layer. According to Lipinski's rule of 5, a small molecule drug should have its molecular mass less than 500 daltons i.e., 500 g/mol which is showing to be promising drug molecule the top 4 Drugs in this studies have shown to obey this value for their consideration Hydroxychloroquine 335.88, Atovaquone: 366.84, Amodiaquine: 355.87 Elvitegravir: 447.89 Oseltamavir: 312.41 and Favipiravir: 156.10 g/mol

3.3. Number of Hydrogen-Bond Accept

The number of hydrogen bond acceptors in the drug molecule is again suggested by simplified for of Lipinski's Rule of Five. It is counted by considering the count by basic atoms like nitrogen and oxygen. Larger the hydrogen bond acceptors lesser the membrane permeability due to the addition extra energy required to break H-Bonds in aqueous and lipid medium of cell membrane. The maximum value for hydrogen bond acceptors is 10. This studies the top 5 drug have shown the fulfilling value less than 10 i.e., Hydroxychloroquine: 3 Atovaquone:3 Amodiaquine: 3, Elvitegravir:2, Oseltamavir:0 and Favipiravir: 4

3.4. Number of Hydrogen-Bond Donor

The number of hydrogen bond donors in the drug molecule is again suggested by simplified for of Lipinski's rule of five. It is counted by considering the count being the count of NH, NH2, nH and OH larger the hydrogen bond donors lesser the membrane permeability due to the addition extra energy required to break H-bonds in aqueous and lipid medium of cell membrane. The maximum value for hydrogen bond donors is 5. In this study the top 5 drug have shown the fulfilling value less than 5 i.e., Hydroxychloroquine: 2, Atovaquone:1, Amodiaquine: 2, Elvitegravir:1, Oseltamavir: 0 and Favipiravir: 1

3.5. Docking parameters

3.5.1. Interacting Amino Acids with Distance in Å

Docking simulation and interaction with amino acids with drug molecules will spend some amount of Energy during docking is calculation. The study of the interaction mechanism between hydrophobic amino acids are capable of both activating and inhibiting protein activity based on energy and close they are connected. In this study top drugs have come in contact with maximum number of amino acids as Hydroxychloroquine: MET(3.68), GLN(3.96), GLN(4.59). Atovaquone: GLY (3.01), SER (2.89), GLN (4.16). Amodiaquine: THR(3.53), LEU (2.89), HIS (3.91), GLN (2.59). Elvitegravir: LEU (3.10), SER (3.08), HIS (4.15). Oseltamavir: HIS (3.77) and Favipiravir: GLN (3.10)

3.5.2. Molecular Superimposition Value through RMSD in Å Square

Docking Process with its RMSD value is found with the best docked conformation before altering the drug reference conformation. Generally, the lower RMSD value is achieved in docking experiment with iterations better the docking pose corresponds to the binding mode of the ligand. A preferred threshold of 2 to 2.5 angstrom has been considered. In this study with maximum of 5 poses of top 6 drugs have promised to show those values Hydroxychloroquine: 1.02, Atovaquone: 2.66, Amodiaquine: 1.65, Elvitegravir: 0.93, Oseltamavir: 1.13 and Favipiravir: 1.58 Å Sq

3.5.3. Refinement/Configuration and Minimization Energy in kcal/mol

Energy minimization of biological macromolecules is one of the key process in molecular docking which will initiate receptor and some ligand flexibility. Generally rigid body minimization of bond lengths and bond angles of small-molecules do not change significantly during the docking. In receptor and ligand molecules interaction they have association through covalent chemical bonds and other non-physical for of associate. Usually docking will have an optimization procedure, to which we will refer to all atoms can move freely and rely on energy minimization procedure. In this study different energy optimization of top 39 Drugs is shown in **Table No. 3**

3.5.4. Docking Score in kcal/mol

The process and key parameter of classifying which ligands could be more potent and likely to interact more significantly to a particular receptor based on the predicted free-energy of binding i.e., docking score are predicted values of the free energy of protein-ligand binding, In general, approximately 25-30 % of drug molecules studied *in-silico* turn out to be effective and potent drug molecules to the studied receptor molecules. In this study the 5 top most drugs have shown promising binding affinity which is expressed in terms of docking score as following Hydroxychloroquine: -6.80 kcal/mol; Atovaquone: -7.13 kcal/mol; Amodiaquine: -7.03 kcal/mol; Elvitegravir: -7.21 kcal/mol), Oseltamavir: -6.74 kcal/mol and Favipiravir: -4.24 kcal/mol.

Sl. No.	Compound	Mol Weight in g/mol	No. of H-Bond Accept	No. of H-Bond Donar	Amino Acids with Distance in Å	Docking Score in kcal/mol
1.	Amodiaquine	355.87	3	2	THR(3.53)	-7.03

					LEU (2.89) HIS (3.91) GLN (2.59)	
2.	Artemether	298.37	5	0	GLY (2.88)	-6.18
3.	Atovaquone	366.84	3	1	GLY (3.01) SER (2.89) GLN (4.16)	-7.13
4.	Chloroquine	319.88	2	1	NA	-6.97
5.	Clindamycine	424.99	6	4	HIS (3.02) GLN (3.36)	-7.50
6.	Dapsone	248.31	2	2	HIS (3.73)	-5.28
7.	Doxycycline	444.44	9	6	GLY (3.22) HIS (3.68)	-7.22
8.	Hydroxychloroquine	335.88	3	2	MET(3.68) GLN(3.96) GLN (4.59)	-6.80
9.	Lumefantrine	528.96	2	1	GLU (3.71) GLU (4.20) GLN (3.70) GLN (4.03)	-7.95
10.	Mefloquine	378.32	3	2	HIS (3.16) GLN (3.66)	-6.74
11.	Piperaquine	535.52	4	0	GLU (4.41) GLN (3.54)	-7.57
12.	Primaquine	259.35	3	2	ARG (3.64) HIS (4.04)	-6.47
13.	Proguanil	253.74	2	3	NA	-6.15
14.	Pyrimethamine	248.72	2	2	GLN (3.51)	-5.62
15.	Pyronaridine	518.06	5	2	HIS (3.79) GLU (4.63)	-8.57
16.	Quinine	324.42	4	1	NA	-6.59
17.	Sulfadoxine	310.32	7	2	HIS (3.15) MET (4.20) GLN (4.17)	-6.62
18.	Sulfalene	280.31	4	2	MET (4.27) GLN (4.21)	-6.22

Table No. 2 : Anti-Malarial Drugs with Number of H-Bond interacting with the receptor 6LU7 viral protein

Sl. No.	Compound	Mol Weight in g/mol	No. of H-Bond Accept	No. of H-Bond Donar	Amino Acids with Distance in Å	Final Docking Score in kcal/mol
1.	Abacavir	286.34	1	1	GLU (2.95) HIS (2.96)	-6.71
2.	Acyclovir	225.21	0	2	GLU (2.99) MET (3.54)	-5.64
3.	Adefovir	273.19	1	1	PHE (3.08) GLN (3.29) MET (4.20) GLU (3.74)	-6.16
4.	Amprenavir	505.64	0	1	MET (4.22)	-8.10
5.	Arbidol	477.42	0	1	THR (3.42)	-7.69
6.	Atazanavir	551.68	0	2	MET (3.79) GLU (3.05) HIS (4.53)	-9.35
7.	Beclabuvir	659.85	0	0	GLU (4.26)	-9.24
8.	Boceprevir	519.69	0	1	CYS (4.25)	-8.5
9.	Cidofovir	279.19	1	3	MET (4.34) LEU (3.18) HIS (3.50) GLY (3.47)	-5.96
10.	Combivir	507.18	4	2	MET (4.01) ASN (3.54) HIS (2.90) MET (3.29) ARG (3.53)	-8.51
11.	Daclatasavir	738.89	0	0	THR (4.70) GLY (4.11) GLN (3.53)	-9.30
12.	Darunavir	547.67	1	0	HIS (2.84)	-8.27
13.	Disoproxil	519.45	0	2	THR (3.27) MET (3.78)	-8.64
14.	Elvitegravir	447.89	2	1	LEU (3.10) SER (3.08) HIS (4.15)	-7.21
15.	Entacavir	277.28	0	0	HIS (3.90) MET (3.52)	-6.00

					GLN (3.90)	
16.	Famciclovir	321.34	1	0	CYS (3.30)	-6.93
17.	Favipiravir	156.1	4	1	GLN (3.10)	-4.24
8.	Fosampiravir	583.60	3	1	MET (3.56, 3.27) HIS (3.01) HIS (2.92)	-8.58
19	Indinavir	613.80	1	1	THR (3.06) ASN (3.89)	-9.07
20	Lotermovir	572.56	1	0	HIS (3.05)	-7.51
21	Lopinavir	628.81	5	4	MET (3.96) HIS (4.19) THR (4.36) GLN (4.09)	-8.81
22	Nelfinavir	567.79	1	1	ASN (3.12) GLU (2.86)	-9.17
23	Norvir	720.96	1	0	MET (3.34) THR (4.12)	-10.04
24	Oseltamavir	312.41	0	0	HIS (3.77)	-6.74
25	Penciclovir	253.26	1	1	MET (4.27, 4.79) SER (2.97) HIS (3.79)	-6.31
26	Premivir	328.41	1	0	GLY (3.14)	-6.94
27	Ralttegravir	444.42	2	0	HIS (3.11) CYS (3.00) THR (3.91) GLN (3.54)	-7.45
28	Remdesivir	602.58	0	2	GLU (3.12) THR (3.13) HIS (3.84)	-8.44
29	Ribaverin	244.21	0	1	MET (3.00) HIS (4.07 MET (3.62)	-5.63
30	Ritonavir	720.96	6	4	MET (4.28) HIS (4.00)	-9.61
31	Saquinavir	670.85	1	1	GLU (3.24) SER (2.97)	-9.20
32	Simeprevir	749.95	0	2	ASN (3.30) PHE (2.92)	-9.06
33	Sofosbuvir	529.46	4	0	HIS (3.05)	-9.20

					GLU (3.07, 2.88) CYS (2.98)	
34	Telaprevir	679.86	1	2	THR (3.29) MET (3.47) GLY (3.26)	-9.06
35	Tenofovir	287.22	1	0	HIS (2.91)	-6.47
36	Tipranavir	602.67	0	0	GLN (3.60)	-7.63
37	Trizivir	286.34	1	1	ARG (3.11) HIS (3.37) GLU (4.29)	-6.57
38	Valagancic lovir	354.37	2	0	SER (3.00) GLU (3.45)	-7.22
39	Valaciclov ir	324.34	1	1	HIS (3.01, 3.97) SER (3.00) ASN (4.07) GLY (4.40)	-6.90

Table No. 3: Ligand interaction properties of anti-viral drugs shown Docking Energy Values with the receptor 6LU7 along with the Amino acid along with thier distance of Interaction

Best Preferred Top Most	Drug Name	Based on best Parameter Values	Docking Score S_kcal/mol
1.	Hydroxychloroquine	Energy minimization in kcal/mol: -80.71 Refinement energy in kcal/mol: -34.42 Energy for receptor configuration in kcal/mol: -24. 68 Topological polar surface area TPSA in Å Sq : 48.39 RMSD in Å: 1.02	-6.80
2.	Atovaquone	Energy minimization in kcal/mol: -65.12 Refinement energy in kcal/mol: -33.3 Energy for receptor configuration in kcal/mol: 75.52 Topological polar surface area TPSA in Å Sq : 54.39 RMSD in Å: 2.66	-7.13
3.	Amodiaquine	Energy minimization in kcal/mol: -60.77 Refinement energy in kcal/mol: -37.29 Energy for receptor configuration in kcal/mol: -33.64 Topological polar surface area TPSA in Å Sq : 48.39	-7.03

		RMSD in Å: 1.65	
4.	Elvitegravir	Energy minimization in kcal/mol: -88.01 Refinement energy in kcal/mol: -39.98 Energy for receptor configuration in kcal/mol: 27.73 Topological polar surface area TPSA in Å Sq : 87.07 RMSD in Å: 0.97	-7.21
5.	Oseltamavir	Energy minimization in kcal/mol: -55.14 Refinement energy in kcal/mol: -33.12 Energy for receptor configuration in kcal/mol: -5.32 Topological polar surface area TPSA in Å Sq : 90.65 RMSD in Å: 1.13	-6.74
6.	Favipiravir	Energy minimization in kcal/mol: -63.56 Refinement energy in kcal/mol: -17.14 Energy for receptor configuration in kcal/mol: -14.28 Topological polar surface area TPSA in Å Sq : 91.93 RMSD in Å: 1.58	-4.24

Table No. 4 : Showing Best 6 Drugs for the Studied Target 6LU7 viral protein

Conclusion

The criterions of selecting only as the most 6 preferred and acceptable drug based on their physico-chemical an universal drug properties along with the main docking energy scoring functions when involved during *in-silico* docking studies with triangle matching receptor-ligand movement during the docking phenomena with the rigid receptor molecule 6LU7 with London dG and GBVI/WSA dG as the scoring function with MOE docking process with 5 best filtered poses of 30 maximum. The most promising 6 drug compound **Table No. 4** like Hydroxychloroquine (-6.80 kcal/mol), Atovaquone (-7.13 kcal/mol), Amodiaquine (-7.03 kcal/mol), Elvitegravir (-7.21 kcal/mol), Oseltamavir (-6.74 kcal/mol) and Favipiravir (-4.24 kcal/mol) showed fair binding energy values during MOE docking studies with active participation of amino acid residues from the receptor 6LU7 viral protein which are likely to be MET, GLN, GLY, SER, THR, LEU and HIS. The inhibition property of the above studied drugs may warrant further investigations through *in vitro* and *in vivo* model.

References:

1. R. Hussin, N.B. Siddappa, The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak, J. Autoimmun. (2020) 102433, https://doi.org/10.1016/j.jaut.2020.102433.

2. Cynthia, Z. Qiongqiong, L. Yingzhu, et al., Research and Development on therapeutic agents and vaccines for COVID-19 and related human coronavirus diseases, ACS Cent. Sci. (2020), https://doi.org/10.1021/acscentsci.0c00272.
3. A. Bogoch, A. Watts, C. Thomas-Bachli, et al., Pneumonia of unknown etiology in Wuhan, China: potential for international spread via commercial air travel, J. Trav. Med. (2020), https://doi.org/10.1093/jtm/taaa008.
4. Wu, F., Zhao, S., Yu, B., Chen, Y. M., Wang, W., Song, Z. G., Hu, Y., Tao, Z. W., Tian, J. H., Pei, Y. Y., Yuan, M. L., Zhang, Y. L., Dai, F. H., Liu, Y., Wang, Q. M., Zheng, J. J., Xu, L., Holmes, E. C., and Zhang, Y. Z. (2020) A new coronavirus associated with human respiratory disease in China, *Nature*.
5. Jiang, S., Xia, S., Ying, T., and Lu, L. (2020) A novel coronavirus (2019-nCoV) causing pneumonia-associated respiratory syndrome, *Cellular & molecular immunology*.
6. Canrong Wu, Yang Liu, Yueying Yang, Peng Zhang, Wu Zhong, Yali Wang, Qiqi Wang, Yang Xu, Mingxue Li, Xingzhou Li, Mengzhu Zheng, Lixia Chen, Hua Li. Analysis of therapeutic targets for SARS-CoV-2 and discovery of potential drugs by computational methods. *Acta Pharmaceutica Sinica B. In* Press, Journal Pre-proof, Available online 27 February 2020.
7. https://www.labmanager.com/lab-health-and-safety/covid-19-a-history-of coronavirus-22021 Dated 23-03-2020
8. The Pediatric Infectious Disease Journal • Volume 24, Number 11, November 2005, S223 to s227.
9. McIntosh K, Kapikian AZ, Turner HC, Hartley JW, Parrott RH, Chanock RM. Seroepidemiologic studies of coronavirus infection in adults and children. Am J Epidemiol. 1970;91:585–592
10. https://www.cdc.gov/coronavirus/types.html Dated 23-03-2020
11. E.D. Clercq, G. Li, Approved antiviral drugs over the past 50 years, Clin. Microbiol. Rev. 29 (3) (2016) 695–747.
12. M.J. David, Clinical trials of antiviral agents, J. Antimicrob. Chemother. 29 (2) (1992) 97–103.
13. Tse, E.G., Korsik, M. & Todd, M.H. The past, present and future of anti-malarial medicines. *Malar J* **18,** 93 (2019). https://doi.org/10.1186/s12936-019-2724-z
14. A Computational Approach to Evaluate the Androgenic Affinity of Iprodione, Procymidone, Vinclozolin and Their Metabolites Galli CL, Sensi C, Fumagalli A, Parravicini C, Marinovich M, et al. (2014) A Computational Approach to Evaluate the Androgenic Affinity of Iprodione, Procymidone, Vinclozolin and Their Metabolites. PLOS ONE 9(8): e104822. https://doi.org/10.1371/journal.pone.0104822
15. Meng, X.Y.; Zhang, H.X.; Mezei, M.; Cui, M. Molecular docking: A powerful approach for structure-based drug discovery. *Curr. Comput. Aided Drug Des.* **2011**, *7*, 146–157.
16. Lopez-Vallejo, F.; Caulfield, T.; Martínez-Mayorga, K.; Giulianotti, M.A.; Houghten, R.A.; Nefzi, A.; Medina-Franco, J.L. Integrating virtual screening and combinatorial chemistry for accelerated drug discovery. *Comb. Chem. High Throughput Screen.* **2011**, *14*, 475–487.
17. Huang, S.Y.; Zou, X. Advances and challenges in protein-ligand docking. *Int. J. Mol. Sci.* **2010**, *11*, 3016–3034.