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Molecular docking studies and theoretical investigation of anti-novel corona activity of chloroquine and its derivatives

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Abstract
In quest of some anti-Novel corona activity drugs, molecular docking studies with PDB ID 6LU7 were carried out using certain well known chloroquine and its derivatives viz Hydroxychloroquine Mefloquine. Molecular docking has been done in order to search the best drug candidate among chloroquine derivatives. The molecular dockings were done in Argus lab. Molecular docking studies revealed that chloroquine found effectively inhibit the recently emerged novel coronavirus . The docking score for chloroquine, Hydroxychloroquine Mefloquine found to be -8.55665, -8.30357, -7.98409 respectively. Chloroquine is found to be best drug candidate among its derivatives with docking score of -8.55665.
Keywords: Novel coronavirus; Molecular docking, antimalarial drugs, chloroquine.

Introduction

Recent advances on the development of drug designing against novel corona virus have been the interest for many authors [1-5]. COVID-19 pandemic caused by SARS-CoV-2. Recently a new world health crisis threatening the public with spread of COVID-19. Since December 2019, this viral disease was emerged in Hunan seafood market at Wuhan, South China and rapidly spread throughout the world. It is unavoidable that the novel coronavirus epidemic will have a considerable impact on the economy and society.

According to WHO this infectious disease was named as Novel Coronavirus-Infected Pneumonia (NCIP) and the virus had been named 2019 novel coronavirus (2019-nCoV). On 11th Feb 2020, the (WHO) officially renamed the clinical condition COVID-19 (a shortening of Corona Virus Disease-19) The newly emergence of a novel human coronavirus (2019-nCoV) of zoonotic origin has recently been identified in patients with acute respiratory disease. These Coronaviruses are a large family of viruses which cause disease in animals or humans. This virus is genetically similar to SARS coronavirus and bat SARS-like coronaviruses[6]. Coronaviruses are large, enveloped, positive-strand RNA viruses that are named for the crown-like spikes on their surface[7].

The seven coronaviruses that can infect people have been classified in Table1.

Table1. Types of coronaviruses.

1	229E (alpha coronavirus)
2	NL63 (alpha coronavirus)
3	OC43 (beta coronavirus)
4	HKU1 (beta coronavirus)
5	MERS-CoV (the beta coronavirus that causes MiddleEast Respiratory Syndrome, or MERS)
6	SARS-CoV (the beta coronavirus that causes severe acute respiratory syndrome, or SARS)
7	2019 Novel Coronavirus (2019-nCoV)

The following two ways are generally exit for the treating viral infections. The first way is to find small molecules that stop viruses replicating by interfering with viral proteins and the second way is to use the same weapons that our bodies use antibodies which are large proteins that bind to viruses for their destruction.

Literature survey revealed that there are seven coronaviruses which produce infection in people around the world but commonly people get infected with these four human coronaviruses: 229E, NL63, OC43, and HKU1[8].

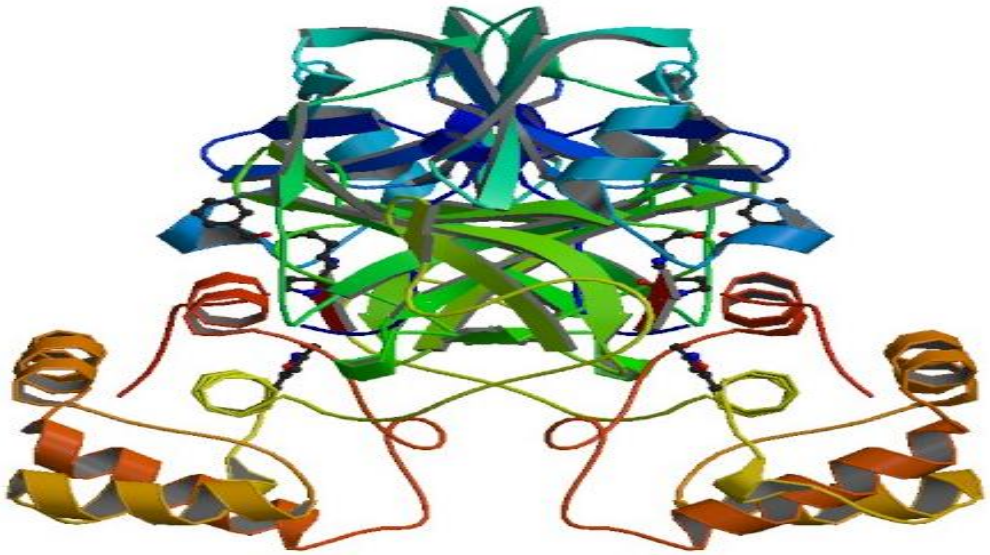
Chloroquine is a 9-aminoquinoline, a well-known compound since 1934 with interesting biochemical properties and has been explored against several viral infections[9] Recent report reviled that Chloroquine and hydroxychloroquine as an effective antiviral therapeutic treatment against COVID-19 with faster recovery time[10] .

When Azithromycin added to hydroxychloroquine, significant virus elimination was observed[11] . On the other hand, United States Centers for Disease Control and Prevention (US CDC) research also shows that chloroquine is a potential prophylactic (preventative) measure against coronavirus[12]. Since, Chloroquine is an inexpensive, and globally available drug without any serious side effects against malaria, autoimmune and various other conditions, it's being considered as one of the hope as immediate treatment or at least as preventive measure[13]. However, it is still under cautious view; as treating COVID-19 with chloroquine might have fatal side effects in long term[14]. Presently, it is undergoing further validating studies globally[15]. chloroquine or hydroxychloroquine does have the potential to lead mutation(s) in the virus, which can be either beneficial or harmful to humans has also been reported[16]. Based on the positive results of Chloroquine against coronavirus, a group of researchers from Standford University are considering designing chloroquine analogs with more nitrogens[17]. They found that the property of nitrogens to interact with hydrogens makes it harder and harder for the endosome to become acidified, consequently disrupting viral replication. Recent studies also revealed that Chloroquine found effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro[18-20].

This led the present authors to under the molecular docking studies and theoretical investigation of anti-novel corona activity of chloroquine and its derivatives.

Material and Methods

The molecular docking studies were done on the PDB ID 6LU7 by downloading it on the Argus Lab. The protein PDB ID 6LU7 was downloaded from site RCSB.org. It is a dimer of two identical subunits that together form two active sites. The protein fold is similar to serine proteases like trypsin, but a cysteine amino acid and a nearby histidine perform the protein-cutting reaction and an extra domain stabilizes the dimer. This structure has a peptide-like inhibitor bound in the active site



The molecular docking studies were carried out on Argus Lab software with some selected chloroquine and its derivatives viz Hydroxychloroquine Mefloquine

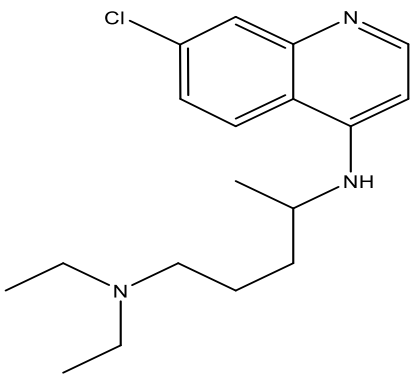
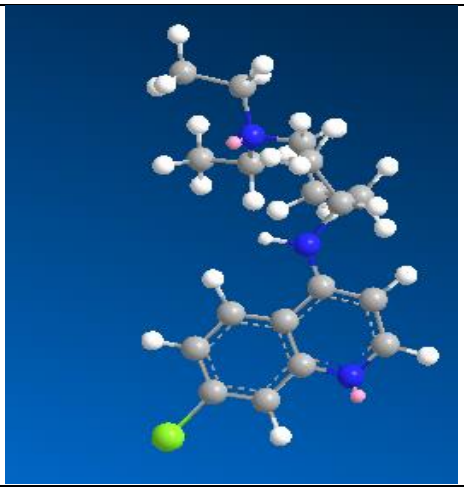
Methods for Molecular Docking:

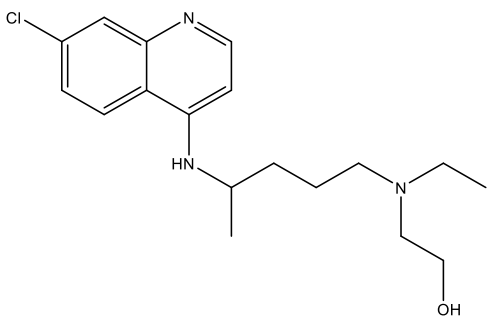
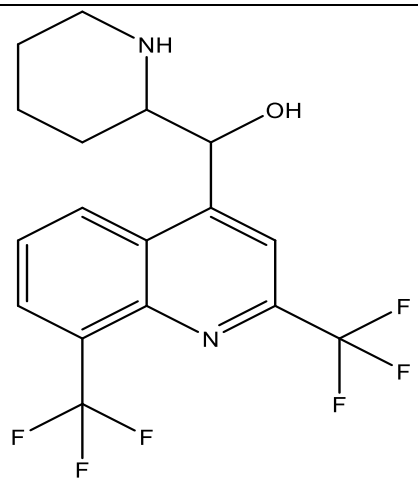
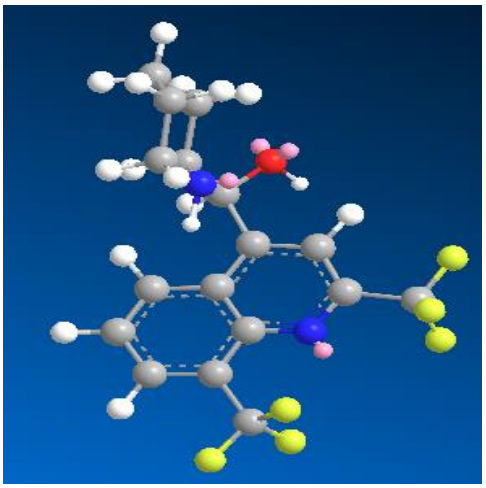
At first protein docked protein was imported form ArgusLab4.0. It contains the inhibitor pdb from the original X-ray structure. This file was save as a separate from the protein target file. The of selected drug candidates hydrochloroquinine and its derivatives were drawn in chemdraw software and then exported to ChemDraw3D software and the structures were optimized for minimize the energy. Then the ligand was imported on the same Argus interface. The hydrogen's in ligand was deleted and the molecule was optimized by using UFF method. The selected ligands were optimized for single point calculation using UFF method. The molecular docking were carried out on Argus lab and The binding pattern was visualized on Chimera software.

Results and discussion

The chemical structure, and optimized structure of some chloroquine and its derivatives have been summarized in Table2.

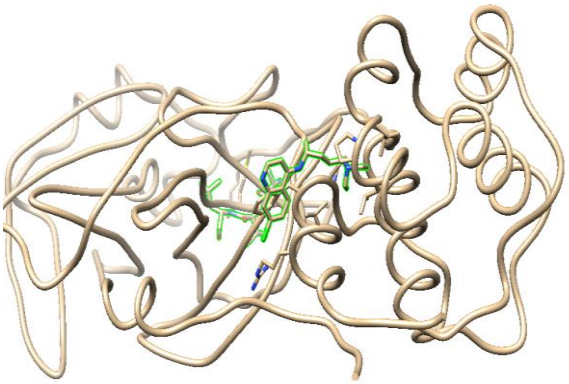
Table2. Chemical Structures and optimized structures of Drug candidates

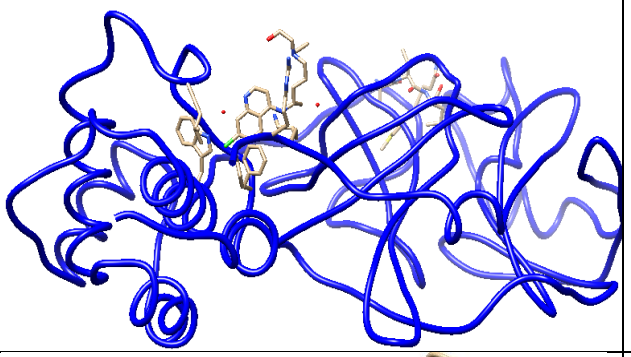
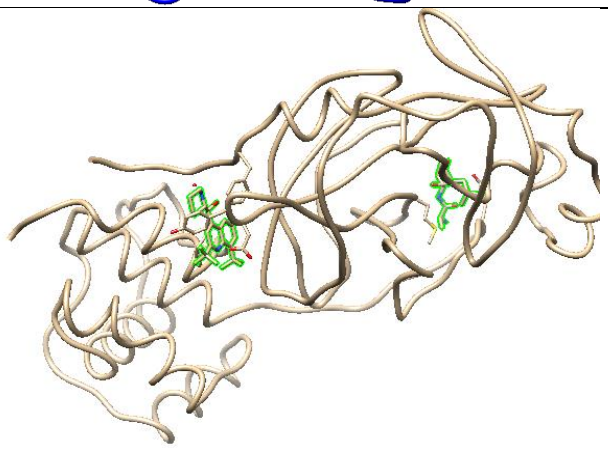
	Name chemical Structure of the drug	3D Structure
1	 **Chloroquine**	

2	 **Hydroxychloroquine**	
3	 **Mefloquine**	

The results of molecular docking in the form of negative binding energy were obtained after the completion of the calculation. The chimera software was used to import the best docking pose of protein-ligand. The docking score for chloroquine, Hydroxychloroquine Mefloquine against PDB ID 6LU7 found to be -8.55665, -8.30357, -7.98409 respectively . From the Table it is clear that Chloroquine is the best among its derivatives with docking score of -8.55665. The docking scores of the chloroquine derivatives and the ligand protein interaction poses appear in Table 3.

Table3. The docking score and pose of Chloroquine, Hydroquine and Mefloquine against Corona Virus PDB ID. 6LU7

	Name of the drug	Chemical Structure	Docking score (kcal/mol)
	Chloroquine		-8.55665

	Hydroxychloroquine		-8.30357
	Mefloquine		-7.98409

Conclusion:

The molecular docking studies have been carried out in order to predict the most effective drug candidates among chloroquine and its derivatives. The chloroquine and its derivatives viz chloroquine, Hydroxychloroquine Mefloquine were found to be effective drug against Novel corona virus with PDB ID 6LU7.

.Chloroquine shows best docking score among selected drug candidate against Novel Corona virus.

References:

[1]Zhou P, Yang X-L, Wang X-G, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020;579:270–3.

[2]Wang C, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern. The Lancet 2020;395:470–3.

[3] Coronavirus disease 2019 https://www.who.int/emergencies/ diseases/novel-coronavirus-2019 Accessed: 2020-04-14.

[4]AR Sahin, A Erdogan, PM Agaoglu, Y Dineri, AY Cakirci, ME Senel, 2019 novel coronavirus (COVID-19) outbreak: a review of the current literature, EJMO 2020; 4(1) 1-7.

[5] Entedar AJ Alsaadi & Ian M Jones, Membrane binding proteins of coronaviruses , Future Virol. (2019) 14(4), 275–286.

[6] Roujian Lu etal. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding, www.thelancet.com Published online January 29, 2020.

[7] Cherry, James; Demmler-Harrison, Gail J.; Kaplan, Sheldon L.; Steinbach, William J.; Hotez, Peter J. (2017). Feigin and Cherry's Textbook of Pediatric Infectious Diseases. Elsevier Health Sciences. p. PT6615. ISBN 978-0-323-39281-5.

[8] Killerby ME, Biggs HM, Haynes A, Dahl RM, et al. Human coronavirus circulation in the United States 2014 – 2017external icon. Journal of Clinical Virology. Vol 101; 2018 Apr; 101:52-6.

[9]Canadian rheumatology association Canadian Consensus Conference on hydroxychloroquine. J Rheumatol. 2000;27:2919–2921

[10]Khuroo M. S. (2020). Chloroquine and hydroxychloroquine in coronavirus disease 2019 (COVID-19). Facts, fiction and the hype: a critical appraisal. *International journal of antimicrobial agents*, *56*(3), 106101.
[11] Gautret, Philippe, et al. "Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial." International Journal of Antimicrobial Agents (2020): 105949.
[12]Khuroo, Mohammad Sultan. "Chloroquine and hydroxychloroquine in coronavirus disease 2019 (COVID-19). Facts, fiction and the hype: a critical appraisal." *International journal of antimicrobial agents* vol. 56,3 (2020): 106101. doi:10.1016/j.ijantimicag.2020.106101
[13]Liu, J., Cao, R., Xu, M. *et al.* Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. *Cell Discov* **6,** 16 (2020).
[14]Cortegiani A, Ingoglia G, Ippolito M, Giarratano A, Einav S. A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19. J Crit Care. 2020 Mar 10.
[15] Singh, R., Vijayan, V. Chloroquine: A Potential Drug in the COVID-19 Scenario. *Trans Indian Natl. Acad. Eng.* **5,** 399–410 (2020)
[16] Wang, M., Cao, R., Zhang, L. et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res 30, 269–271 (2020).
[17] **.** James M. Todaro, Gregory J. Rigano: An Effective Treatment for Coronavirus (COVID-19) March 13, 2020, 1-15
[18] Cortegiani A, Ingoglia G, Ippolito M, Giarratano A, Einav S (March 2020). "A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19". Journal of Critical Care. 57: 279–283.
[19]Li G, De Clercq E. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). Nature reviews. Drug discovery 2020;19:149–50.
[20]Edwards CJ. Hydroxychloroquine and coronavirus disease 19. Lupus. 2020 Jun;29(7):669-670