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Research Article

In silico comparative analysis of HIV protease inhibitors effect on 2019-nCoV coronavirus $3CL_{pro}$

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Abstract

The novel coronavirus 2019-nCoV has become a bane to mankind and spread worldwide and infected many people. Thus, there is an urgent need of a cure for the severe pneumonia disease caused by this virus. In this study, *in silico* comparative analysis has been done for HIV protease inhibitors on coronavirus $3CL_{pro}$ protein which has shown the major interactions and common amino acid residues involved in interactions. The amino acid interaction analysis has revealed two amino acids ARG4, LYS5 to be the major amino acids targets among selected ligands. The binding energy analysis has also revealed Cobicistat as one of these best suited ligand for $3CL_{pro}$.

More Information

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Keywords: 2019-nCoV; Protease inhibitors; Pneumonia; $3CL_{pro}$; Interaction analysis; Ligands

Introduction

The outbreak of novel coronavirus has caused major loss of human lives and many lives are still at risk. 2019-nCoV is an enveloped, positive-sense, single-stranded RNA beta-coronavirus [1]. Corona viruses can infect respiratory, gastrointestinal, hepatic and central nervous system of human [2], livestock, birds, bats [3], mouse, and many other wild animals [4]. Similar to SARS and MERS, non-structural proteins encoded by 2019-nCoV genome are 3-chymotrypsin-like protease ($3CL_{pro}$), papain-like protease (PL_{pro}), RNA-dependent RNA polymerase (RdRp) and helicase, structural proteins spike glycoprotein [1]. $3CL_{pro}$ protein is considered as one of the main target for 2019-nCoV and the urgent need of cure has made it more prominent. In this study, the $3CL_{pro}$ has been considered as a target and HIV protease inhibitors (ligands) were comparatively analyzed in order to reveal the interactions and important amino acids involved in such interactions, so as to make it easier to identify drug-targets.

Methodology

Protein preparation

The three dimensional crystal structure of 2019-nCoV coronavirus protein 3CLpro (Pdb id: 6lu7) was obtained from RCSB PDB (https://www.rcsb.org/structure/). The ligand groups and water molecules already present were removed out in order to make this structure suitable for further interactions with other ligands.

Ligand preparation

The HIV protease inhibitors has been scanned for the selected coronavirus protein structure. Three ligands Lopinavir [5], Cobicistat [6], Amprenavir, Atazanavir, Indinavir and Saquinavir [7] were selected from the literature review. The chemical structures for these ligands were obtained from PubChem in SDF format and were converted to PDB format for further interactions analysis.

HIV protease inhibitors and $3CL_{pro}$ interactions

The selected ligands were docked to coronavirus protein 3CLpro using Autodock tool 1.5.6 [8]. Autodock is an automated docking tool to predict how the small molecule or substrate bind to a specific target protein. The protein and ligand PDB formatted files were converted to PDBQT formats followed by docking using Lamarckian genetic algorithm and a total of ten conformations for each ligand docking were observed with their binding energies to find out the best lead compound among them. The protein ligand interactions were obtained followed by the identification of interacting amino acid residues of coronavirus protein 3CLpro to chemical groups with their respective ligands.

Results and discussion

The docking analysis of 3CLpro and target ligands revealed

the interaction types in three ligands. The docking studies involving $3CL_{pro}$ with ligands such as Lopinavir, Cobicistat, Amprenavir, Atazanavir, Indinavir and Saquinavir were done to seek greater insight about the amino acid residues of MATE interacting with the specified ligands (Figure 1).

The interaction analysis revealed the occurrence of two amino acid residues ARG4 and LYS5 in interactions with selected ligands which conferred these two amino acid residues to be major drug target sites (Table 1).

The binding energies for ligands and $3CL_{pro}$ interactions were observed and analyzed comparatively. The lowest binding energy among the selected drugs; Cobicistat, Lopinavir, Amprenavir, Atazanavir, Indinavir and Saquinavir was found to be associated with Cobicistat which conferred it as one of the best suited ligand for $3CL_{pro}$ (Table 2). However, Cobicistat lacks the enzyme inducing activity and thus requires the co-administered drugs with close monitoring of dose adjustments while treating the patients.

Conclusion

The novel coronavirus 2019-nCoV has caused major loss to human lives, socially and economically as well. The urgent cure is the need of hour for this disease. The results observed from present studies has revealed the ligand with lowest binding energy 'Cobicistat' among the selected ligands which confers it to be one of the best suited ligand for $3CL_{pro}$. Cobicistat and Ritonavir are structural analogues of each other but Ritonavir has major limitations like poor water solubility which corresponds to difficulty in its co-formulation and drug interactions. Furthermore, the switching between Cobicistat-based drug and Ritonavir-based drug treatment may produce significant problems among the patients. In order to avoid these limitations, only cobicistat has been taken under consideration in this study. The common amino acids ARG4 & LYS5 in the docking studies confirmed these two amino acids as main targets. The amino acid residues involved in interaction with novel coronavirus protein $3CL_{pro}$ also revealed the common interactions which shall further help scientists to find out the new target sites and lead compounds for novel coronavirus 2019-nCoV.

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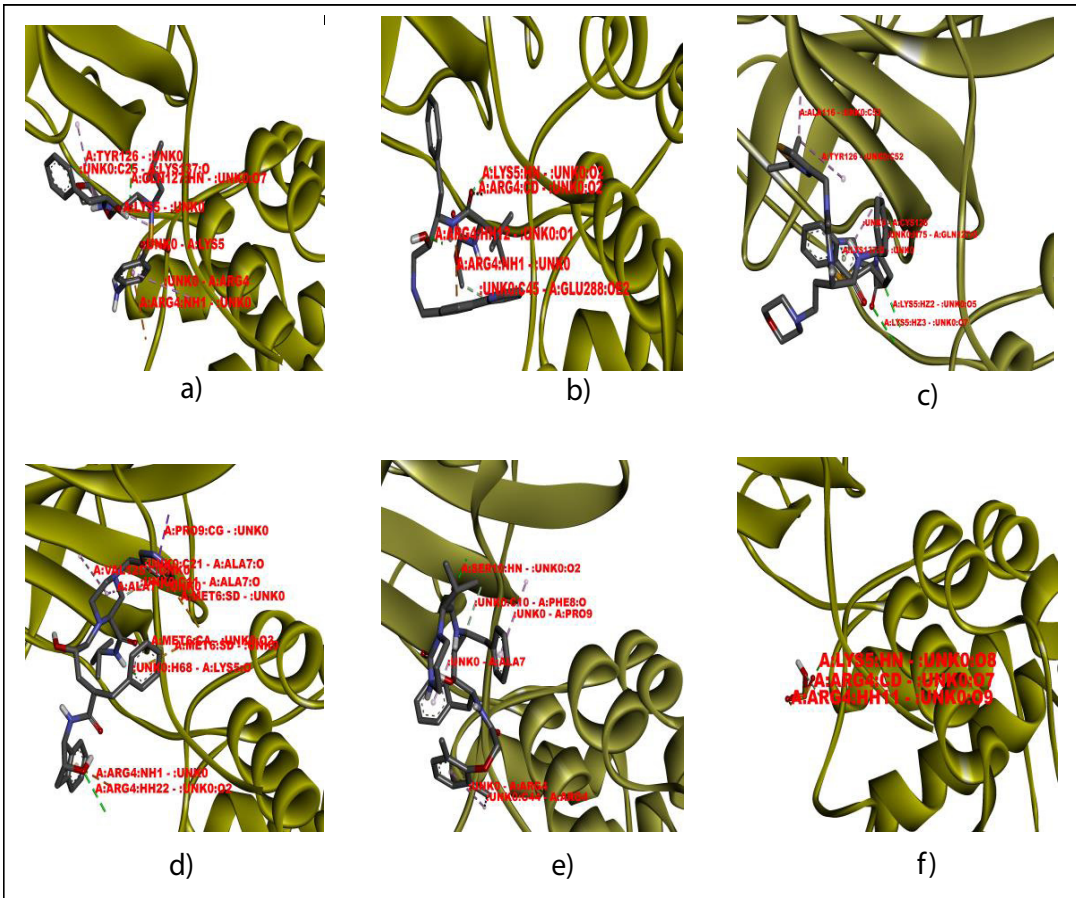

Figure 1: Interactions involved in docking of $3CL_{pro}$ protein with ligands (a) Amprenavir (b) Atazanavir (c) Cobicistat (d) Indinavir (e) Lopinavir and (f) Saquinavur.

Table 1: Amino acid residues involved in interaction of $3CL_{pro}$ to ligands.

	Amino acids	Distance	Bond type
Amprenavir	GLN127	2.69155	Hydrogen bond
	LYS137	3.38047	Hydrogen bond
	ARG4	4.1211	Electrostatic
	LYS5	5.46553	Hydrophobic
	TYR126	4.82572	Hydrophobic
	ARG4	5.4604	Hydrophobic
	LYS5	5.33228	Hydrophobic
Atazanavir	ARG4	2.10606	Hydrogen bond
	LYS5	2.17532	Hydrogen bond
	ARG4	3.7109	Hydrogen bond
	GLU288	3.68988	Hydrogen bond
	ARG4	3.88505	Electrostatic
Indinavir	ARG4	3.01365	Hydrogen bond
	LYS5	1.96033	Hydrogen bond
	MET6	3.46698	Hydrogen bond
	ALA7	3.41241	Hydrogen bond
	ALA7	3.23456	Hydrogen bond
	ARG4	3.41559	Electrostatic
	PRO9	3.91164	Hydrophobic
	MET6	5.23667	Other
	MET6	5.90228	Other
	ALA7	5.10413	Hydrophobic
	VAL125	4.90336	Hydrophobic
Saquinavir	ARG4	1.91972	Hydrogen bond
	LYS5	1.91442	Hydrogen bond
	ARG4	2.779	Hydrogen bond
Cobicistat	LYS5	2.82	Hydrogen bond
	LYS5	2.83	Hydrogen bond
	GLN127	1.97	Hydrogen bond
	LYS137	2.76	Other
	ALA116	3.26	Hydrophobic
	TYR126	4.84	Hydrophobic
	CYS128	5.06	Hydrophobic
Lopinavir	SER10	2.04	Hydrogen bond
	PHE8	3.51	Hydrogen bond
	ARG4	3.54	Hydrophobic
	ALA7	4.64	Hydrophobic
	ARG4	4.64	Hydrophobic
	PRO9	4.64	Hydrophobic

Table 2: Binding energies for ligands docked with 2019-nCoV coronavirus $3CL_{pro}$ protein.

Ligand	Binding energy
Cobicistat	-2.41
Amprenavir	-2.36
Lopinavir	-2.33
Indinavir	-2.01
Atazanavir	-1.07
Saquinavir	1.16

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