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In Silico Drug Design and Molecular Docking Studies of Potent Inhibitors against Cathepsin-L (Ctsl) for Sars Disease

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Abstract

Severe acute respiratory syndrome (SARS) is a severe respiratory infection caused by a recently recognized corona virus (SARS-CoV). Newly innovative machinery for way in of SARS CoV hooked on target cells was reported. The ingress of SARS-CoV necessities for proteases in establishment of viral infection. Cathepsin – L (CTSL) is the prime enzyme concerned in access of virus. Inhibition of CTSL represents a prospective drug mark for SARS disease. MDL28170 (CID10152654) was recognized as a proficient natural inhibitor of CTSL mediated substrate cleavage. Founded on the ligand structure likeness to get analogous effective medicine like molecules, the PubChem Database was screened for analogous strong remedy like compounds as MDL28170. Virtual Screening and docking studies were intended for these molecules against CTSL protein with PyRx Virtual Screening tool and AutoDock Vena. The docking outcome showed that the compounds CID11496897, CID11795833, CID333247, CID501956 and CID11199915 were having highest binding energies like -7.4, -7.3, -7.1, 6.7 and -6.4. The current study indicates that the lead molecules have to be evaluated additional for improved prospective drug molecules.

Keywords: Cat-L; Virtual Screening; Docking, SMILES; H-bond

Introduction

A respiratory illness called "severe acute respiratory syndrome" (SARS) was first reported in Asia in November 2002. The illness spread to more than two dozen countries in North America, South America, Europe, and Asia within only a few months. Patients agony from SARS frequently commence having a high fever (>38°C or 100.4°F) with symptoms such as nuisance, depression, chills, severity, diarrhea, and body aches followed by emergent a dry (non-productive) cough and having [1] difficulty breathing that might be accompanied by or development to hypoxia, a stipulation in which there is inadequate oxygen accomplishment body tissues. Severe acute respiratory syndrome (SARS) is a respiratory disease in humans which is caused by [2] the SARS corona virus (SARS-CoV). It is frequently not awfully transmissible, with an average of 2-4 secondary cases stemming from each major case [3,4]. SARS-CoV is widening chiefly throughout the respiratory droplets in the perspective of close contact with especially ill people in the hospital or household selting (WHO, 2015). Recently new machinery for entry of SARS CoV into mark cells was reported by Simmons [5]. In their cram necessities for protease in establishment of viral infectivity and SARS-CoV employs a distinctive three step method in membrane fusion, connecting receptor binding and induces conformational changes in S glycol protein followed by Cathepsin L (CTSL) proteolysis and commencement of membrane fusion within endosomes. So CTSL is an alternate molecular marker for drug design against SARS. CTSL is one of the foremost cystein protease, commonly initiate throughout mammalian cell types and primarily functions in regular protein break down [6]. CTSL has also been implicated in a number of disease processes, such as epidermal homeostasis, hair follicle morphogenesis and cycling, extracellular matrix degradation and viral entry [6-10].

In this revision, MDL28170 is worn as the model in database penetrating based on the structure likeness for finding of new and effective drug candidates from the PubChem database. For finding out novel and vigorous with stumpy toxicity compounds by using sophisticated drug design techniques.

Materials and methods

Protein preparation

The x-ray crystal structure of CTSL combined with the ligand was obtained from protein data bank (PDB code 1LCF). The atomic coordinates of the CTSL protein was estranged and its geometry optimized by way of Argus Lab 4.0.1. The enzyme CTSL structure is shown in Figure 1.

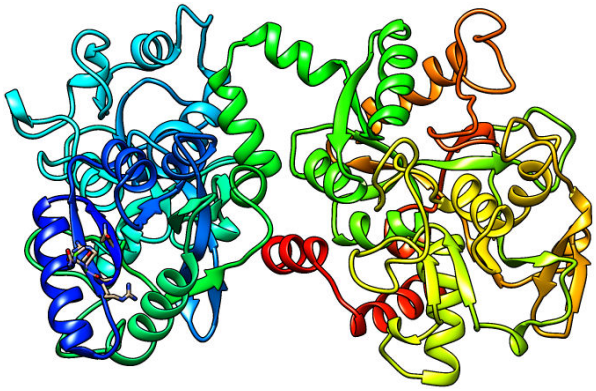

Figure 1: Cathepsin - L protein in cartoon model.

Ligand Preparation

The compound structure of MDL28170 [11], an amino terminal barren dipeptide aldehyde, is displayed in Figure 2, which was once employed as the inhibitor of calpain to defend rat erythrocyte membrane associated cytoskeletal proteins from proteolytic squalor (IC_{50}=1μM) [12]. The assay outcome of Simmons [5] recommends that MDL28170 can also inhibit CTSL meditated substrate cleavage with IC_{50} of 2.5 nmol/l through SARS virus admission. As a result, MDL28170 is worn as the model in PubChem database penetrating based on the structure likeness. The dataset contains 85 compound structures. All the atomic coordinates were changed to pdbqt set-up using Open Babel GUI © 2006 (developed by Chris Morley) [13].

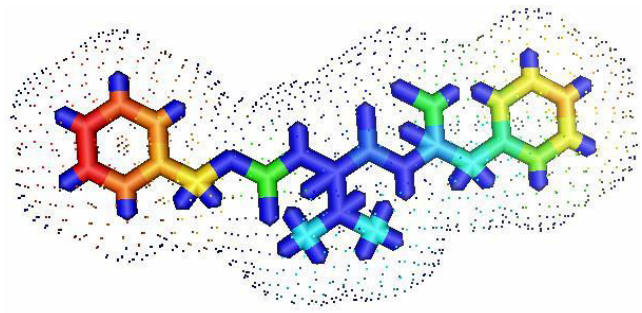

Figure 2: Structure of MDL 28170.

Binding site prediction

Active site of 1LCF was acknowledged by CASTp server (Computer Atlas of Surface Topology of protein) [14]. A latest program, CASTp, for mechanically locating and measuring protein pockets and cavities, is based on accurate computational geometry methods, as well as alpha form and distinct flow theory. CASTp detection and capacity of exterior available pockets as well as interior unapproachable cavities by locating, delineating and measuring hollow exterior regions on three-dimensional structure of proteins. The dimension includes the region and quantity of pocket or void by solvent accessible exterior model (Richards' surface) and by molecular exterior model (Connolly's surface), considered analytically. It can also be worn to revise exterior features and practical regions of proteins. CTSL (1LCF) of active site is shown in Figure 3.

Virtual Screening

The MDL 21870 medicine molecule was worn as a investigate query to regain molecules with new compound structures on PubChem database. PyRx virtual screening tool was worn to investigate the database. The regain molecules were preferred for docking studies in organize to revise the contacts with active site of CTSL.

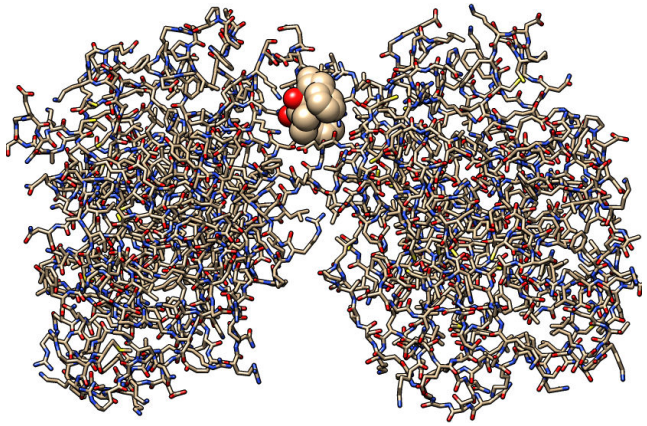

Figure 3: Active site of Cathepsin – L protein.

S.No	Compound	Binding energies (ΔG) k.cal/mol	H-bond residues	Active site residues	No. of H-bonds
1.	CID11496897	-7.4	Arg341	Val346, Glu337, Arg344, Glu329, Thr326, Gly387, Glu388, Asn330, Lys333, Arg332, Tyr65.	1
2.	CID11795833	-7.2	Arg341, Arg344, Asn330, Lys333	Thr326, Glu329, Arg602, Arg342, Gly387, Glu388, Val346, Glu337. Arg341, Arg344, Asn330, Lys333.	6
3.	CID333247	-7.1	Arg344, glu337, arg341, lys333	Arg341, Arg344, Glu337, Val346, Lys333, Arg602, Asn330, Thr326, Gln329, Arg342, Gly387, Glu388.	5
4.	CID501956	-6.7	Glu143	Ala161, Gly160, Asp162, Phr166, Leu331, Arg120, Leu119, Ile145, Arg332, Glu146, Trp138, Pro144, Glu143, Pro141, Pro142.	1
5.	CID11199915	-6.4	Arg341, arg344	Arg341, Arg344, Asn330, Lys333, Glu388, Thr326, Gln329, Arg602, Gly387, Arg342.	2

Table 1: The list of best leads and binding energies and molecular interactions of protein residues and ligands listed.

Molecular docking

For the docking of ligands into intention protein binding pockets [15] and to approximate the binding affinities of docked ligands, a molecular docking program AutoDock Vina [16] in PyRx Virtual screening tool (1.1.2) [17] was worn in this cram. Docking studies were performed on developed protein and screened MDL 21870 like

inhibitors. The protein PDB file was changed into the PDBQT format file containing the protein atom coordinates, partial charges and deliverance parameters and the ligands file (SDF) was distorted into PDBQT format. Auto Grid boxes (x, y, z coordinates 77.53, 51.05, 56.59) were predetermined around the active site of the protein. The look for was based on the Lamarckian genetic algorithm (LGA) and the obtained dock scores were reported in kcal/mol. The docking protocol utilized in the revise consisted of 10 autonomous runs per ligand. The outcome was analyzed on the source of ranked clusters of compound conformations. The various ligands binding energy values are shown in Table1.

Structural analysis and visualization

Protein and ligand interactions were analyzed and visualized through PyMol viewer tool (www.pymol.org).

Results and Discussion

Active site of the protein is determined by using Castp server followed by the water molecules, hetero atoms and ligands are detached as of target protein. The protein structure and predicted active site regions are shown in Figure 3. Thr326, Glu329, Arg602, Arg342, Gly387, Glu388, Val346, Glu337. Arg341, Arg344, Asn330, Lys333 are the active site residues which are play a considerable task in binding and catalytic activity in the active site of 1LCF.

Virtual screening is a capable approach in discovering inhibitors with new element scaffolds. Two-dimensional formation of MDL28170 was worn to investigate for analogous compounds in the PubChem database. Subsequently, roughly 4525 compounds were screened, and the entire compounds were saved for additional molecular docking study.

The mark protein CTSL (1ICF) three dimensional structure (3D) was in use as of the Protein Data Bank. AutoDock Vina was worn for the docking studies. The docking scores are scheduled in Table 1. In the ligand protein docking calculations, the most positive conformation for every ligand is chosen from 10 conformations. Hydrogen bonds are invented to construct vital aid to the connections between the ligand and protein. The docking outcome point out that there is one hydrogen bond for CID11496897 ligand to the 1ICF -7.4 kcal/mol binding energy with Arg341 residue. There are six hydrogen bonds interactions between CID11795833 ligand and 1ICF -7.2 kcal/mol binding energy with Arg341, Arg344, Asn330 and Lys333. There are five hydrogen bonds between CID333247 and protein -7.1 kcal/mol binding energy with Arg344, glu337, arg341, lys333 residues. There is one hydrogen bond between CID501956 and protein -6.7 kcal/mol binding energy with Glu143 residue. There are two H-bonds between CID11199915 ligand and protein (1ICF) -6.4 kcal/mol binding affinity with Arg341, arg344 residues. The links are shown in Table 1 and Figure 4 shows the graphical analysis of protein and ligands interactions.

Conclusions

In the current effort, we have searched for narrative and effective anti-CTSL inhibitors throughout Virtual Screening on PubChem database based on structural likeness of ligand (MDL21870). The recently acknowledged cysteine protease enzyme CTSL is a significant mark in the drug design for beneficial involvement of severe acute respiratory syndrome disease. Our effort outcome were steady with a model in which SARS-CoV employs a distinctive three-step method in membrane fusion, involving receptor binding and induced conformational changes in S glycoprotein followed by Cathepsin-L (CTSL) proteolysis and foundation of membrane fusion contained by endosomes. The inhibition of CTSL might avert the SARs.

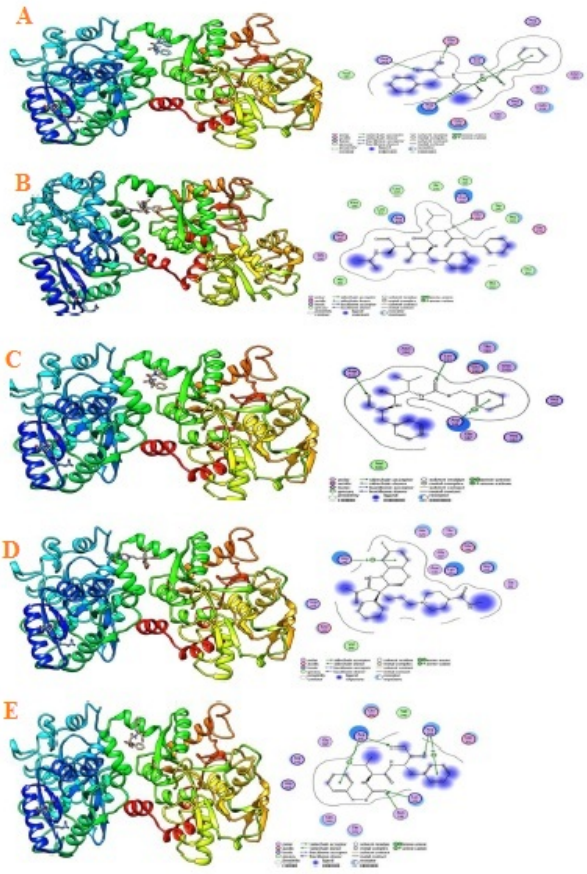

Figure 4: A: CID333247, **B:** CID 501956, **C:** CID 11199915, **D:** CID 11496897, **E:** CID 11795833.

Amongst screened compounds CID11496897, CID11795833, CID333247, CID501956 and CID11199915 encompass the maximum binding energies compared to MDL28170. For that reason, it is a positive drug molecule similar to MDL28170 against SARS disease. We expect that these investigations will be supportive for designing a novel and effective inhibitors against the severe acute respiratory syndrome disease.

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Conflict of Interest

The authors confirm that this article content has no conflicts of interest.

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