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ORIGINAL ARTICLE **OPEN ACCESS**

Repurposing of Drugs for the Treatment of Cystic Fibrosis: A Computational Approach

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ABSTRACT
The CFTR gene mutation that results in anomalies in the CFTR protein channel, which oversees ion movement across the membrane, is the cause of the disease cystic fibrosis. There are currently some common medications that act as CFTR modulators available to treat the condition, including ivacaftor, tezacaftor, lumacaftor, and elexacaftor. In addition to these medications, the condition is managed symptomatically. Since there is no effective treatment for the condition, the study looked for medications from the FDA and ZINC databases that could be used to treat CF. The target protein 7SVD and the ligands were used in molecular docking studies. The drug repurposing technique gave us two medicines from each database Glimepiride and ZINC000085531303 that, based on their affinity scores, met the requirements to be the most potent candidates among the other drug candidates. To determine the typical interactions of each drug candidate with the target, the various forms of interactions between the functional groups of the ligand and the amino acid residues were evaluated. The top ten drug candidates also underwent ADMET studies to determine if they satisfied the essential molecular, absorption, metabolism, excretion, and toxicity characteristics. The research mentioned above assists us in eliciting the required therapeutic and pharmacological effects necessary for treating CF. To comprehend the structural and dynamic characteristics of the ligand-receptor complexes under research, molecular dynamic simulation studies were also carried out. As a result, we were able to identify two medications that could be used in future research. As a result, this study gave us a greater chance to develop medications to treat cystic fibrosis patients.
Keywords: *CFTR, Drug repurposing, Cystic Fibrosis, Molecular Dynamics.*

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INTRODUCTION

Cystic fibrosis is a major lifespan shortening genetic disorder. It causes abnormal transport of salt and water across the cells in the body resulting in the build-up of mucus and organ dysfunction. The following introduction covers epidemiology, risk factors, pathophysiology, signs, symptoms, diagnosis, prevention, and treatment. The cause of cystic fibrosis is a mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. The CFTR gene encodes a protein that is responsible for regulating the movement of sodium and chloride ions across epithelial cell membranes [1,2]. A defective protein is caused by mutations in one or both copies of the gene. When the transport of ions is disrupted, thick mucus is produced throughout the body, resulting in respiratory insufficiency as well as a variety of other systemic blockages and abnormalities. Infection is caused by bacterial colonisation of the respiratory tract, which is most typically caused by Pseudomonas, Haemophilus influenzae, and Staphylococcus aureus. Chronic infection can trigger an inflammatory response that is both overwhelming and repeated, leading to airway damage. CFTR function can be disrupted by different types of mutation, which eventually results in complete loss of protein synthesis or normal apical membrane protein expression with poor conductance of ions [3-5]. All mutations result in increased salt resorption into the cellular space and decreased chloride secretion. Increased salt reabsorption also enhances water reabsorption, causing mucus secreted on epithelium linings to thicken and secretion in exocrine tissues to become more viscous. Mucus plugging with obstructive diseases occurs as mucus secretions thicken in the organ system [6]. The most usually affects sinuses, sweat glands, lungs, pancreas, intestines, biliary and hepatic systems. Sinus and lung illnesses are caused by obstruction of the sinus ostia and lung airways due to

thicker mucus production. The cascade influences the inflammatory response, and the airways in the lungs do not receive adequate ventilation, which can be fatal. When secretions thicken the pancreatic duct, it causes large-spectrum blockage and pancreatic symptoms of CF [7-9]. When the enzymes attack the pancreatic tissues, the pancreas auto digests, causing pancreatitis and eventually endocrine pancreatic failure. If the biliary ducts get clogged with high viscosity secretions, the biliary and hepatic systems are damaged. It is possible to develop obstructive cirrhosis and post-hepatic hyperbilirubinemia. Meconium ileus in infants usually obstructs the intestines [10]. Constipation is caused by dehydration of the intestinal contents. Sweat glands contrast all CFTR-channel-containing tissues. Chloride ions travel from extracellular to intracellular space, and sodium ions are reabsorbed to maintain the ionic potential. This causes re-absorption of water [11]. When the chloride channel fails to reabsorb chloride, sodium ions leak onto the skin's surface, causing fluid loss. The combination of sodium and chloride produces salt, which is pathognomonic for cystic fibrosis. Most of these genetic changes have not been identified. Respiratory symptoms include wheezing, breathlessness, a persistent cough with thick mucus, inflamed nasal passages, stuffy nose, haemoptysis, pneumothorax etc.Digestive symptoms include severe constipation, foul-smelling stool, intestinal blockages in newborns, hypersplenism, exocrine pancreatic insufficiency characterized by chronic diarrhoea [12-14]. Other symptoms include salty tasting skin, clotting disorders, poor weight gain and growth due to malnutrition and psychosocial problems [15].

The current therapeutics mainly focuses on correcting the functional and structural abnormalities of CFTR protein. Elexacaftor, ivacaftor, tezacaftor, lumacaftor are the drugs used in modulator therapy which may be given in specific combinations that offer treatment to the underlying cause of the disease. Orkambi is a combination of lumacaftor and ivacaftor [16-19]. Antibiotics such as tobramycin, levofloxacin, ciprofloxacin, azithromycin, colistin, aztreonam, cephalexin, amoxicillin, doxycycline, roscovitine fight acute and chronic bacterial sinus and pulmonary infections. Aerosolized medications such as humidified oxygen, dornase alfa and 3-6% hypertonic saline help loosen secretions by reducing viscoelasticity [20] Airway inflammation can be controlled by NSAIDs, inhaled and systemic steroids and cromolyn. During CF exacerbations, β-2 adrenergic agonists and corticosteroids are used to treat acute hyperresponsiveness [21,22]. Nasal steroids like fluticasone propionate reduce nasal inflammation. Sinus surgery alleviates nasal obstruction and limits further infections [16, 23,24]. Pancreatic insufficiency is treated by pancreatic enzyme replacement therapy (PERT) consisting of different combinations of amylases, proteases, and lipases, such asliprotamase (Anthera AN-EPI3332), burlulipase, pancrelipase etc. Enteric treatments such as ORS, stool softeners, osmotic laxatives, mucolytics, prokinetics, hyperosmolar contrast enemas, balanced electrolyte intestinal lavage solutions containing diatrizoatemeglumine and diatrizoate sodiumare used to improve symptoms such as intestinal dysbiosis, inflammation and blockages in CF [24]. The most prevalent non-pulmonary consequence of cystic fibrosis is diabetes, which is treated with oral antidiabetic medications, insulin injections, and pumps. Bisphosphonates can be taken orally or intravenously to help people with cystic fibrosis enhance their bone mineral density. To avoid poor growth, growth hormones are injected, or a feeding tube is placed to provide supplemental nutrients. Male infertility can be treated by testicular sperm extraction and intracytoplasmic sperm injection, while female infertility can be treated using assisted reproduction techniques such as embryo transfer or third-party reproduction [25].

Certain compounds with corrector, modifier or potentiator activities under clinical trials are 4PBA (sodium 4-phenylbutarate), VRT-532, N6022, Ataluren (PTC124), Riociguat, QBW251, N91115(Cavosonstat), QR-010, CTP656, PGM169/GL67A,PTI428, Duramycin (Moli1901/Lancovutide), PDE5 inhibitors, Cysteamine in combination with epigallocatechin gallate, triple therapy of GLPG1837, GLPG2222 and GLPG2665.Other approaches include modulation of proteostasis; use of chemical and pharmacological chaperones such as curcumin, thapsigargin, Bortezomib, Miglustat, Corr-4a, VRT-325 and VRT-532; gene editing using various types of nucleases.Anti-inflammatory compounds to reduce inflammation include Andecaliximab, α-1 anti-trypsin, POL6014, LAU-7b, CTX-4430, elastase inhibitor AZD9668, JBT-101, some of which are under clinical trials.Agents used to rehydrate airway secretions and mucus clearance include AZD5634, SPX-101, OrPro (ORP-100), OligoG (Alginate Oligosaccharide), VX-371 (P10370029), GSK2225745, bronchitol etc.AquADEKs-2 and Oral Glutathione are used as antioxidants [12,26].

In the rehabilitation process, occupational therapy makes use of energy conservation techniques (ECT) such as ergonomic principles, diaphragmatic and pursed lip breathing. Massage therapy, chest physiotherapy, flutter valve therapy, positive expiratory pressure therapy, mechanical devices for chest wall oscillation (percussion vest), manual chest percussion, high-frequency vest-assisted chest compression, intrapulmonary percussive ventilation, biphasic cuirass ventilation, collateral ventilation, and associated clearance mode are used to dislodge secretions and provide short-term airway clearance. Non-invasive customised masks and bi-level positive airway pressure (BiPAP) ventilators are used to

maintain blood oxygen levels in patients with advanced illness. Aerobic exercise can help with aerobic exercise capacity, lung function, and overall health [27]. The ultimate treatment available for CF patients having severe bronchiectasis, end-stage lung disease and <30% of forced expiratory volume is lung transplant, which providesa median survival of 4.7 to 7.8 years. Drug repurposing aims to uncover new uses of the approved, discontinued, failed, shelved, abandoned or investigational drug compounds for different diseases. In this study, the drugs from FDA and ZINC databases were reprofiled to find indications for the treatment of cystic fibrosis. A customized way to deal with treatment might address the best method for testing the viability of up-and-comer drugs in CF. The repositioning methodology in CF could be seen as an overall technique for the adjuvant treatment of other uncommon inconsequential illnesses [26,27].

Hence the present work focusses to identify novel molecules to inhibit cystic fibrosis transmembrane conductance regulator for the treatment of cystic fibrosis through the application of computational tools.

MATERIAL AND METHODS

Structure of Ligands

The chemical structure of each ligand was obtained from FDA and ZINC data library. FDA database is a collection of information on drugs, including biological products, approved for use by humans in the US. ZINC database is a curated collection of commercially accessible chemical compounds that is utilized by investigators at research universities, pharma, and biotech companies for virtual screening.

Structure of protein

The Research Collaboratory for Structural Bioinformatics Protein Data Bank (RCSB PDB) http://www.rcsb.org/pdb, a database for three-dimensional structural data of big biological molecules like proteins and nucleic acids, provided the typical structure file for the target protein. The usual structure file from the PDB is unsuitable to use directly in molecular modelling calculations. Water molecules, metal ions, a co-crystallized ligand, and co-factors are all possible additions to a normal PDB structure file. Purification was then carried out using CHARMM-GUI, a web-based platform that allows users to interactively build complicated systems and prepare their inputs [27,28].

Receptor grid generation

It necessitates a well-prepared structure, which includes all atoms with the proper bond ordering and formal charges. Favorable interaction between ligand molecule(s) and a receptor molecule (usually protein), is discovered using AUTODOCK. Continuing the shape and features of receptors, which are represented on a grid by various sets of fields that give increasingly accurate ligand pose scoring. The settings in each tab of the receptor grid generation panel helps to define the structure of the receptor by omitting any co-crystallized ligands, choosing the location and size of the active site as represented by receptor grids, and setting the AUTODOCK constant. Thus, a grid area can be generated around the binding site of the receptor [27, 28].

Ligand Docking

AUTODOCK VINA is used to do ligand docking. AUTODOCK VINA looks for a good match between ligand molecule(s) and a receptor molecule (usually protein). Each ligand is a single molecule, whereas the receptor has many molecules. AUTODOCK VINA was run in either flexible or rigid docking mode, with the latter generating conformations for each input ligand automatically. In flexible docking, ligand posture refers to the combination of a ligand's position and orientation relative to the receptor, as well as its shape. The AUTODOCK VINA-generated ligand pose is subjected to a series of filters in a hierarchy, which assess ligand-receptor interaction. Initial filters assess the ligand's spatial fit to a particular active site. A grid-based technique is used to assess complementarity of ligand-receptor interactions. The final scoring is then completed [28].

Procedure for docking

The usual structure file for the target protein was received from the Protein Data Bank (RCSB) and purified with CHARM-GUI [27]. The experiment was carried out using the application AUTODOCK VINA. The protein preparation wizard was used to create full length substrate complex dimmer coordinates for AUTODOCK VINA calculations. The P-PreP script creates a new receptor file containing neutralized residues. Finally, the software was allowed to run to begin the docking process, in which each ligand was made to connect with the active site present in the target protein's active pocket. [28-29]

Visualization

For visualization, the pdbqt file obtained from docking is combined with the protein structure. The 2D and 3D structures of the complexes are visualized in Maestro software or BioVia Discovery Studio for studying ligand interactions and improved presentation [29].

ADMET studies

The downloaded 2D structures of ligands were uploaded in CACTUS, an online SMILES translator (http;//cactus.nci.nih.gov/translate/). The SMILES generated was copied and pastedin pkCSM website (http;//biosig.unimelb.edu.au/pkcsm/) to carry out ADMET analysis of the ligand. The results were useful in determining its efficacy and toxicity [30].

Molecular dynamics

MD was performed using the Desmond module of Schrödinger developed by D.E Shaw research group (Academic license, Version 2020-1) 1 through the system's builder panel; the orthorhombic simulation box was prepared with the Simple Point-Charge (SPC) explicit water model in such a way that the minimum distance between the protein surface and the solvent surface is 10 Å. Complexes docked with receptors were solvated with the orthorhombic TIP3P water model 2. Neutralization of the solvated system was accomplished by counterions and limiting the salt concentration in the physiological system to 0.15 M. The receptor-ligand complex system was designated with the OPLS AA force field 3.

Two seconds of relaxation time was used for the reversible Reference System Propagation Algorithm (r-RESPA) integrator 4, Nose-Hoover chain thermostat 5 and Martyna-Tobias-Klein barostat. The final production of MD simulations was performed using the equilibrated system. This MD simulation was set to run for 100 ns with 310 K temperature at 1.0 bar pressure with NPT (Isothermal-Isobaric ensemble, constant temperature, constant pressure, constant number of particles) ensemble at default settings 6 for relaxation before simulation. The MD simulation was performed with the MD simulation tool, with the simulation time set to 100 ns. Furthermore, the .out file was used to view the trajectories and create a movie [30,31]. The .out cmsfile was imported and the movie was exported at a higher resolution (1280x1024) with better quality. The trajectory was written with 1000 frames during the complete MD simulation. The protein backbone frames were aligned to the backbone of the initial frame to better understand the complex's stability during MD simulation. Finally, after loading the .out file and selecting the Root Mean Square Deviation (RMSD) and Root Mean Square Fluctuation (RMSF) in the analysis type to oblique, the simulation interaction diagram and the results were analyzed [31].

RESULT

Molecular Docking

The protein target selected for the study was the co-crystallized complex of phosphorylated human cystic fibrosis transmembrane conductance regulator (CFTR) with ATP/Mg and Lumacaftor (VX-809) with the expression system being homo sapiens. The protein data bank (PDB) ID for the target is 7SVD**.** (PDB DOI: 10.2210/pdb7SVD/pdb). The target protein along with the drug candidates selected from FDA database was uploaded in the software mentioned and molecular docking was performed.

Based on the docking results, the topmost drug candidates with the highest scores were considered for further study, as they showed an acceptable level of binding. The selected drug candidates include glimepiride, eletriptan, trospium, ergocalciferol, olmesartan, valsartan, indinavir, nelfinavir, adapalene and dicoumarol. The docking scores obtained were -9.0, -8.9, -8.8, -8.4, -8.3, -8.2, -8.1, -8.0, -7.9 and -7.9 respectively. The range of the docking scores lies between -9.0 and -7.9. Higher the negative value of the docking score, higher is the binding affinity. Therefore these scores indicate the repurposability of the drug candidates. Based on the scores obtained, we can say that glimepiride (-9.0) and eletriptan (-8.9) can be the most suitable candidates for drug repurposing. A similar molecular docking analysis was conducted for the same target protein and drug candidates selected from zinc database. The top ten drug candidates with the highest scores which were considered for further study include ZINC000085531303, ZINC000000822120, ZINC000085531085, ZINC000253505810, ZINC000085531281, ZINC000085878218, ZINC000085569126, ZINC000085531275, ZINC000085531238 and ZINC000085531248. The docking scores obtained were -13.0, -11.9, -11.9, -11.8, -11.5, -11.5, -11.4, -11.3, -11.1 and -10.9 respectively. The range of the docking scores lies between -13.0 and -10.9. These scores indicate the repurposability of the drug candidates. Since the docking score value is proportional to the binding affinity, we can say that ZINC000085531303 (-13.0) and ZINC000085531248 (-10.9) can be the most suitable candidates for drug repurposing.

Molecular docking results for FDA drug database

Table 1: Molecular docking results for FDA drug database

Sl. No.	Compound name	Docking scores
1	Glimepiride	-9
2	Eletriptan	-8.9
3	Trospium	-8.8
4	Ergocalciferol	-8.4
5	Olmesartan	-8.3
6	Valsartan	-8.2
7	Indinavir	-8.1
8	Nelfinavir	-8
9	Adapalene	-7.9
10	Dicoumarol	-7.9

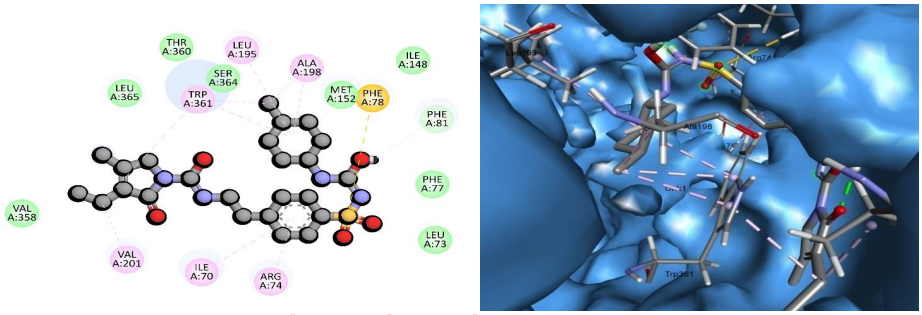

Fig 1: 7SVD-Glimepiride complex – 2D & 3D interactions

Molecular Docking Results for Zinc Database

Table 2: Molecular docking results for ZINC database

Sl. No.	Compound name	Docking scores
1	ZINC000085531303	-13
2	ZINC000000822120	-11.9
3	ZINC000085531085	-11.9
4	ZINC000253505810	-11.8
5	ZINC000085531281	-11.5
6	ZINC000085878218	-11.5
7	ZINC000085569126	-11.4
8	ZINC000085531275	-11.3
9	ZINC000085531238	-11.1
10	ZINC000085531248	-10.9

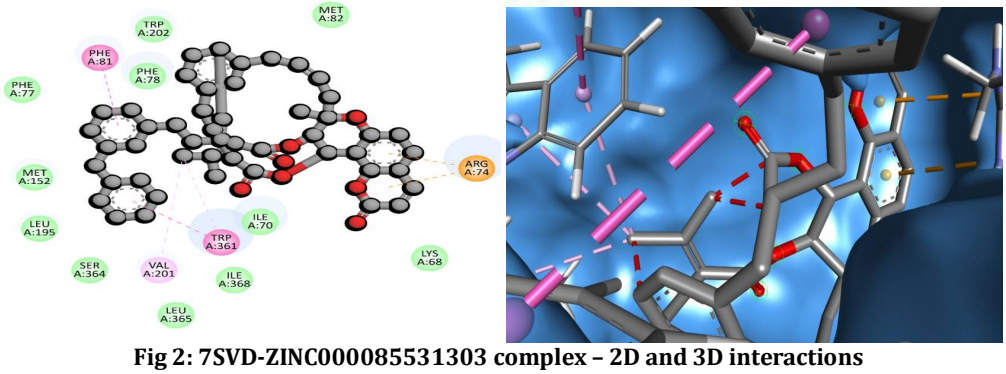

Fig 2: 7SVD-ZINC000085531303 complex – 2D and 3D interactions

From the above given type of interactions, it is noticeable that the common amino acids residues involved for interactions are ILE (isoleucine), PHE (phenylalanine), LEU (leucine), VAL (valine), THR (threonine), TRP (tryptophan), ARG (arginine), TYR (tyrosine) and HIS (histidine).

ADMET Analysis for FDA Database Drugs

Table 3: Molecular properties of FDA approved repurposable drugs

Descriptor	Molecular Weight	LogP	Rotatable Bonds	Acceptors	Donors	Surface Area
Glimepiride	490.626	3.074	7	5	3	200.954
Eletriptan	104.152	0.984	0	0	0	48.265
Trospium	396.659	7.641	5	1	1	179.611
Ergocalciferol	392.519	3.7697	4	3	1	172.254
Olmesartan	446.511	3.6566	8	7	3	190.684
Valsartan	435.528	4.1617	10	5	2	187.211
Indinavir	613.803	2.8669	11	7	4	266.218
Nelfinavir	567.796	4.74762	9	6	4	242.67
Adapalene	412.529	6.6814	4	2	1	182.601
Dicoumarol	336.299	2.9014	2	6	2	139.738

The ADMET analysis mainly deals with various parameters such as absorption, distribution, metabolism, excretion and toxicity including molecular properties for a given set of drugs under investigation or study. The drug candidates for which ADMET properties were investigated are glimepiride, eletriptan, trospium, ergocalciferol, olmesartan, valsartan, indinavir, nelfinavir, adapalene and dicoumarol among FDA approved drugs; ZINC000085531303, ZINC000000822120, ZINC000085531085, ZINC000253505810, ZINC000085531281, ZINC000085878218, ZINC000085569126, ZINC000085531275, ZINC000085531238 and ZINC000085531248 among ZINC database drugs. The molecular properties analyzed include molecular weight, log p value, number of rotatable bonds, number of hydrogen bond donors and acceptors, and surface area of the molecule. The most potent drug candidate in FDA DB, glimepiride showed 64% of absorption in human intestine; -0.3 log L/kg of steady state volume of distribution; no metabolism by most of the CYP family enzymes; 0.7 log ml/min/kg of total clearance and no AMES toxicity. The most potent drug candidate in ZINC DB, ZINC000085531303showed 100% of absorption in human intestine; -0.9 log L/kg of steady state volume of distribution; no metabolism by most of the CYP family enzymes; 0.7 log ml/min/kg of total clearance and no AMES toxicity.

Molecular dynamics simulation

Molecular dynamics (MD) is a computer simulation method to analyze the physical movements of atoms and molecules, during their interaction for a fixed time. The analysis is done by using Newton's equation of motion. The top two compounds glimepiride and eletriptan were selected for molecular dynamic simulations because they had the most binding affinity with the target 7SVD and better predicted ADMET properties. Molecular dynamic simulation was carried out for 100.102 nanoseconds at 300 kelvin temperature for the two above mentioned drugs with the target separately. MD simulations generate trajectories that depict the motions of atoms by giving atomic coordinates at specified time intervals. Macromolecule dynamics can then be analyzed by calculation of measures such as root mean square deviation (RMSD) and root mean square fluctuation (RMSF). Simulation of MD helps visualize the action of Protein-Ligand complexes (PLCs) at the target's binding site region under physiological conditions.

Protein-Ligand RMSD

RMSD measures the average change in displacement of a selection of atoms for a particular frame with respect to a reference frame. It describes the molecule's overall discrepancy with respect to a reference conformation and gives an indication on the stability of protein- ligand complex. RMSD is plotted against time to assess the variations in structural conformations.

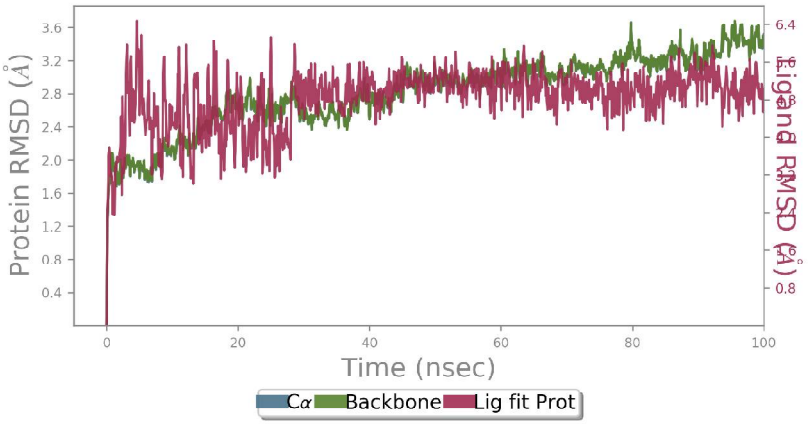

Fig 3: Protein-Ligand RMSD of 7SVD-Glimepiride complex

The complex of 7SVD and glimepiride initially showed fluctuations that were higher than RMSD of protein ranging 1.6-3.4A from 2 to 40ns. The RMSD of the complex overlapped with that of protein from 41 to

65ns. At the end of the simulation i.e., 70 to 100ns, RMSD values of complex were lesser than that of the protein and stabilized around 2.84A indicated that the complex system has equilibrated, and the simulation may be long enough for rigorous analysis.

Eletriptan

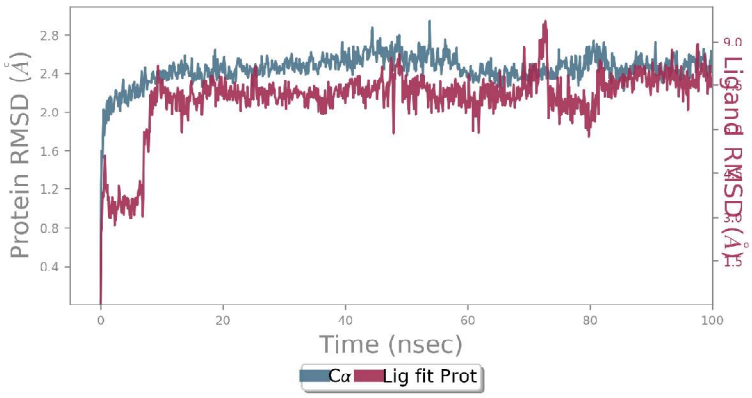

Fig 4: Protein-Ligand RMSD of 7SVD-Eletriptan complex

The complex of 7SVD and eletriptan initially showed fluctuations ranging 0.8-2.2A till 10ns. The RMSD of the complex stabilised around 2.1A for the major portion of the simulation with a variation at 70ns. At the end of the simulation i.e., 85 to 100ns, RMSD values of complex slightly overlapped with that of the protein. This indicates that the complex system has equilibrated, and the simulation may be long enough for rigorous analysis.

Protein RMSF

RMSF is a measure of individual residue flexibility. It measures the movement of a particular residue during a simulation. A plot of RMSF vs. residue number indicates the amino acids in the protein structure which contribute the most to a molecular motion. It helps to analyze changes in the behaviour of amino acid residues of target protein after ligand binding.

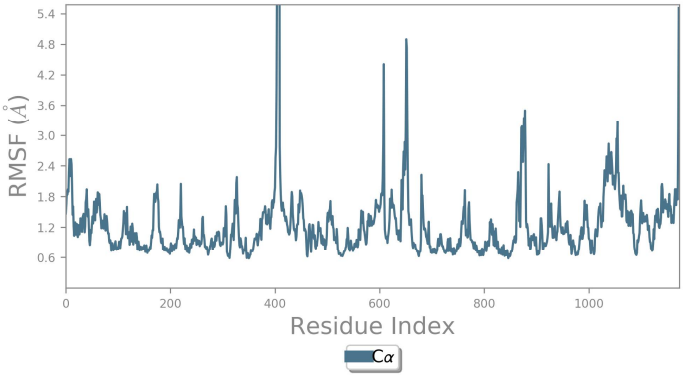

Fig 5: Protein RMSF of 7SVD-Glimepiride

On this plot, peaks indicate areas of the protein that fluctuate the most during the simulation. In the examined glimepiride-7SVD complex, the amino acid residues showed major fluctuations at 400, 600, 650, 850 for the entire simulation. However, the values of RMSF are below 5. This shows that ligand binding did not stimulate any major effects on the flexibility of the protein.

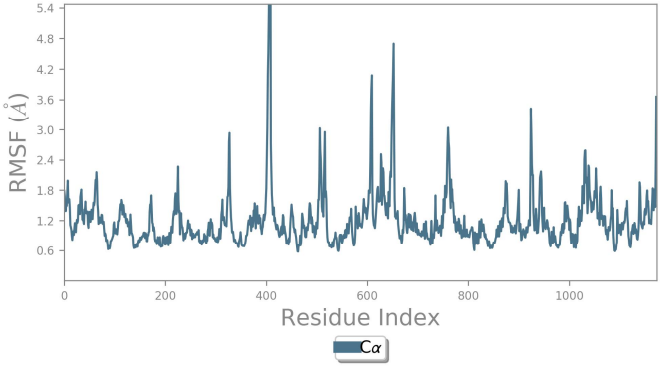

Fig 6: Protein RMSF of 7SVD-Eletriptan

In the examined eletriptan-7SVD complex, the amino acid residues showed major fluctuations at 400, 600, 650 for the entire simulation. However, the values of RMSF are below 5Ao. This shows that ligand binding did not stimulate any major effects on the flexibility of the protein.

Protein-Ligand Contacts (PLCs)

Protein-ligand interactions were monitored for the entire simulation. Each interaction has subtypes, which can be explained by simulation interactions diagram panel. These contacts are classified into four types as hydrogen bonding, hydrophobic contacts, ionic or polar interactions and water bridges.

The stacked bar charts provide a schematic of detailed interactions.

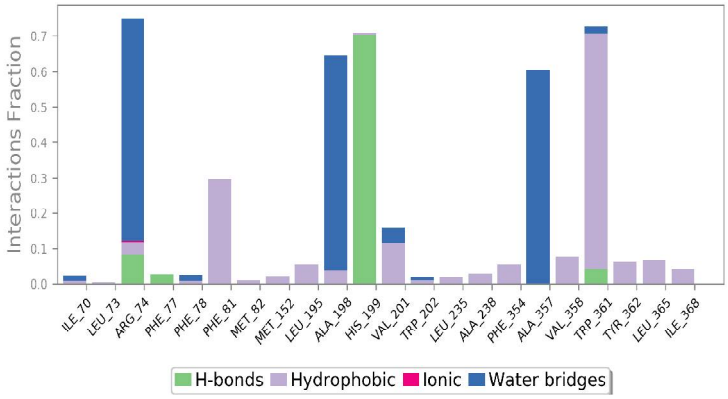

Fig 7: PLC of 7SVD-Glimepiride

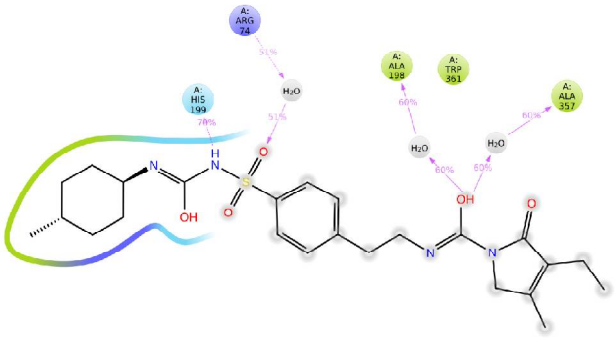

Fig 8: Structure showing protein-glimepiride interactions

Hydrogen bonding interaction fractions of the ligand glimepiride with amino acid residues are as follows: 0.09 (9%) with ARG 74, 0.02 (2%) with PHE 77, 0.7 (70%) with HIS 199, and 0.05 (5%) with TRP 361. The percentage suggests the simulation time, the interaction was maintained.

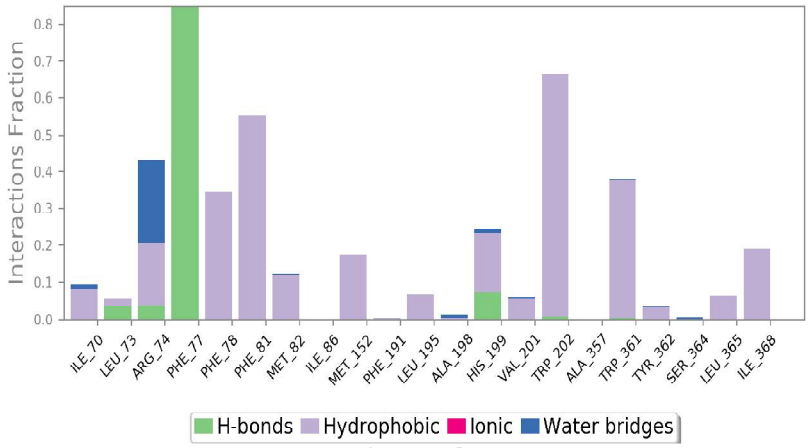

Fig 9: PLC of 7SVD-Eletriptan

Hydrogen bonding interaction fractions of the ligand eletriptan with amino acid residues are as follows: 0.05 (5%) with LEU 73, 0.05 (5%) with ARG 74, and 0.08 (8%) with HIS 199. The percentage suggests the simulation time the interaction was maintained.

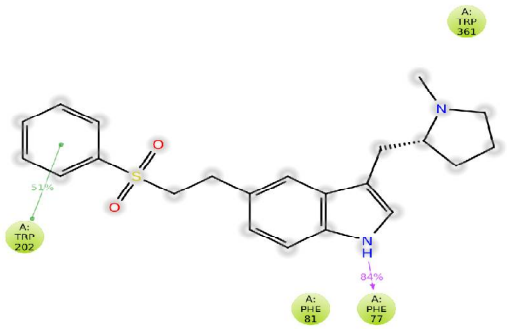

Fig 10: Structure showing protein-eletriptan interactions

CONCLUSION

Cystic fibrosis is a disease caused by the mutation of CFTR gene that causes abnormalities in the CFTR protein channel responsible for ion movement across the membrane. To correct the abnormality, some standard drugs such as ivacaftor, tezacaftor, lumacaftor, elexacaftor are available at present, which work as CFTR modulators. Apart from these drugs, the disease is treated through symptomatic management. Since there is no proper cure for the disease, the study aimed to find the drugs from FDA and ZINC database that prove to be repurposable for CF. Molecular docking studies with the target protein 7SVD and the ligands was conducted. The drug repurposing strategy provided us with two drugs from each database, namely Glimepiride and ZINC000085531303 that matched the criteria to be the most potent candidates among the rest of the drug candidates, based on their affinity scores. The various types of interactions between the functional groups of ligand and the amino acid residues were assessed to identify the common interactions of each drug candidate with the target. ADMET studies were also carried out for the ten topmost drug candidates to check if they have the necessary molecular, absorption, metabolism, excretion, and toxicity parameters. The above studies help us to elicit the desired pharmacological and therapeutic actions essential for treating CF. Furthermore, molecular dynamic simulation studies were conducted to understand the structural and dynamic aspects of the ligand-receptor complexes under study. In conclusion, we have found two drugs with repurposability, which can be employed for further studies. Therefore, this study provided us with a better chance of therapeutics to treat the patients suffering from cystic fibrosis.

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CONFLICT OF INTEREST

The authors declare that no conflict of interest.

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