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Computational Exploration and Molecular Docking Analysis of Mycobacterium Tuberculosis RPFB Protein

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Abstract
The RpfB protein, a vital component of bacterial cell wall metabolism, is particularly significant in the context of Mycobacterium tuberculosis, the causative agent of tuberculosis. Within this pathogen, RpfB plays a pivotal role in cell growth, division, and virulence, contributing to the survival and persistence of M. tuberculosis within the host. As a member of the Resuscitation-Promoting Factor (Rpf) family, RpfB is crucial for reactivating dormant cells, a process essential for M. tuberculosis to establish latent infections and evade host immune responses. Through its enzymatic activity, RpfB facilitates peptidoglycan remodeling and cell wall synthesis in M. tuberculosis, influencing bacterial physiology and pathogenicity. Elucidating the molecular mechanisms by which RpfB operates in M. tuberculosis not only enhances our understanding of bacterial persistence but also unveils potential targets for novel antimicrobial interventions against tuberculosis, a global health threat of immense significance**.** The vulnerability of *Mycobacterium tuberculosis* to various drugs and its persistence has stood as a hurdle in the race against eradication of the pathogenicity of the bacteria. Identification of novel antituberculosis compounds is highly demanding as the available drugs are resistant. The ability of the bacteria to surpass the body's defenses and adapt itself to survive for disease reactivation is contributed by secreted proteins called resuscitating promoting factors (Rpfs). These factors aid in virulence and resuscitation from dormancy of the bacteria. Sequence analysis of RpfB was performed and compounds were first screened for toxicity and high-throughput virtual screening eliminating the toxic compounds. To understand the mechanism of ligand binding and interaction, molecular docking was performed for the compounds passing through the filter resulting with better docking studies predicting the possible binding mode of the inhibitors to the protein.

Keywords: Resuscitation-Promoting Factor (Rpf), *Mycobacterium tuberculosis*, molecular docking.

INTRODUCTION

Tuberculosis is a persistent disease that spreads through populations like the persistent and sneaky shadow of nightfall. It is brought on by a little organism known as *Mycobacterium tuberculosis*, which has established itself as the world's thirteenth death harbinger. It captured 1.49 million people in

its icy grasp in 2020 alone, most of whom were from China, India, and Indonesia. Rumors suggested that COVID-19 would take a toll as well.

The fight against this ghost frequently occurs just under our noses; the lungs are its preferred target, but it can also besiege the kidneys or brain. However, not everyone who comes into contact with this enemy becomes sick; some people harbor it subtly, like latent seeds waiting for spring.

Traditionally, diagnosing this spectral invader has involved slowly and laboriously looking into body samples with the help of strong lenses and dyes. In current technology, there is hope since a group of nine neural networks trained on less magnified but more revealing images than ever promise astonishingly accurate results faster than ever before.

It becomes evident where our collective attention has lingered longest when experts map these murky waters over decades past through their articles on prevention or diagnosis, among other subjects. Imagine yourself at the edge of health and sickness, where every breath you take could lure invisible enemies closer. This is the domain of tuberculosis, an invisible battleground where there are silent battles taking place beneath both skin and bone.

If you business, you'll discover that no smell indicates the existence of *Mycobacterium tuberculosis*; instead, only labs replete with acrid antiseptics allude to conflicts fought outside of sight. Touch discloses nothing but maybe a cold feeling as though one is traveling through shadows created by doubt rather than light, and sights are typical of any clinic unless they are studied via a microscope, which turns ordinary slides into dangerous environments.

This story highlights not only the unrelenting progression of tuberculosis throughout time but also humanity's ceaseless quest for control over diseases that remain hidden from view—a monument to perseverance in the face of hardship.

A bacteria called Mycobacterium tuberculosis, commonly referred to as Koch's bacillus, is the source of tuberculosis (TB). Robert Koch discovered this bacterium in 1882. It is resistant to Gramme staining because of a waxy layer of acid on its cell surface. For identification reasons, certain stains such as auramine or Ziehl-Neelsen are employed instead. It mostly affects the respiratory system and does best in conditions with elevated oxygen levels. Its growth rate allows it to divide every 18 hours, allowing it to persist in a state for long periods. M. Tuberculosis is known to cause several illnesses that affect different body parts in addition to tuberculosis (TB). Comprehending its pathophysiology and virulence characteristics is crucial for creating instruments, including diagnostics, vaccines, and therapies, to tackle the global

what are the current research efforts to combat tuberculosis caused by mycobacterium tuberculosis?

Mycobacterium tuberculosis-related TB is the subject of extensive and diverse research. These include the investigation of compounds discovered during the heyday of antibiotic discovery and the development of novel antitubercular drugs that target various facets of the biology of the bacterium. Host-directed therapy (HDT) is a potentially effective approach that attempts to interfere with the way Mycobacterium tuberculosis manipulates the host's processes. Benefits of this strategy include enhancing treatment effectiveness, adjusting tuberculosis care to each patient's unique clinical circumstances, and affecting immunological responses and memory development.

Resuscitation–promoting factor B Protein

Among the many diverse roles that protein RpfB plays in bacteria, its primary function is cell-level regulation in some gram-positive bacteria, including Streptomyces and Mycobacterium. The RpfB protein has the following important properties. The RpfB protein has the following important properties. The function of RpfB is to create fatty acyl-CoA derivatives, which are signaling molecules that aid in the transmission of genetic information. RpfB is a transferase enzyme. Function in quorum sensing: Fatty acyl-CoA derivatives produced by the bacterial protein RpfB are involved in quorum sensing, a cell-to-cell communication mechanism that allows bacteria to control their behavior in a given environment depending on population density. Control of cellular processes: A crucial element of control is the quorum sensing system, which is transmitted by RpfB mechanisms that regulate the creation of antibiotics, the differentiation of a species of bacteria's morphology, and the expression of virulence factors.

The significance of RpfB in Streptomyces lies in its involvement in the manufacturing of antibiotics as well as the generation of aerial hyphae, a component of spores involved in the development process. Streptomyces species are members of the well-known group of bacteria that create antibiotics. Significance in Mycobacterium: RpfB regulates cell dormancy in Mycobacterium genomes, which includes Mycobacterium TB for tuberculosis. This helps the bacteria survive and become more virulent when they reactivate. Microbiology, antibiotic compounding, and a class of pharmaceuticals meant for use as a treatment against bacterial infections are all heavily focused on the study of RpfB.

Role of RpfB protein in Mycobacterium tuberculosis

The primary factor in the pathogenicity and persistence of Mycobacterium tuberculosis (MTB), the causative agent of the terrible disease tuberculosis (TB), is the RpfB protein, a crucial component of the intricate regulatory apparatuses of MTB. The complex job of the Rpf system, of which RpfB is a component, is to develop tactics that will allow this extremely destructive organism to get past the host's immunological barriers, live, and cause persistent infections.

RpfB, a fatty acyl-CoA ligase enzyme, activates the quorum-sensing signaling system in the bacterial population by binding long-chain fatty acyl-CoA and non-specific signaling molecules together to form a complex quorum-sensing mechanism. This behavior path is important because it connects to the unexpected mechanism of M. tuberculosis, known as a transition from active to rest for the overnight latent TB infections.

M. tuberculosis can go into a dormant stage during a latent sickness, during which metabolic activity stops. This makes the germ immune-resistant and resistant to conventional anti-infective regimens. The RpfB protein plays a key role in the aforementioned scenario since it can synthesize the signal molecules that aid in the resuscitation of dormant bacilli and, consequently, the reactivation of the active TB disease in those who harbor a latent infection. The re-amplifying functionality is the cause of the high number of new cases, which makes tuberculosis the leading cause of global public health issues. Additionally, RpfB's and RPF systems' regulatory roles on the virulence factors that support the persistence and spread of M. tuberculosis underlie the chronicity of tuberculosis infection. They comprise activities which are involved in the cellular wall and acquire defensive systems enabling the pathogen to elude the mammalian immune and to persist in host cells and macabre tangles.

Above all, it has been demonstrated that RpfB-signaling participates in the mechanisms that produce very robust biofilms that are capable of withstanding both host immune responses and antimicrobial

treatments. These biofilms provide an environment that promotes the selection of highly antibiotic-tolerant bacteria and the horizontal transference of drug resistance by creating a microenvironment that supports these processes. Furthermore, RpfB plays a critical role in the restoration of dormant bacteria, which may allow tuberculosis to relax following antibiotic treatment. This is another major contributing element to the difficulty in eliminating the infection.

Following a thorough examination of the versatile function of RpfB in the pathophysiology

As M. tuberculosis persists, this protein becomes more familiar with the various therapeutic intervention strategies that are being considered. Techniques that disrupt RpfB activity or reveal its signaling pathways may be able to prevent latent bacilli from reactivating and reduce virulence. The seed tunneling method holds significant promise for enhancing therapeutic outcomes and reducing the global disease case count.

The bacteria that causes tuberculosis (TB), Mycobacterium tuberculosis, mostly enters the human body through the respiratory system. Once inside, it engages in a complex interaction with the immune system of the host, which may result in either a latent or an active disease. When an infected person coughs, sneezes, or even speaks, respiratory droplets are released into the air, starting the infection's sneaky journey. As a result, the microscopic aerosols containing live tuberculous bacteria linger in the atmosphere for extended periods of time, which makes it easier for them to disperse through the air and cause unintentional inhalation sby those nearby.

The bacteria enter the airways through inhalation and travel through their intricate branching to reach the alveoli, the actual air sacs in the lungs where gas exchange occurs. At this critical juncture, M. Alveolar macrophages, which are specialised immune cells that perform phagocytosis and eliminate inhaled infections, are the first line of defence against tuberculosis. However, M. tuberculosis has developed a variety of highly complex tactics to subvert this initial immune response, allowing it to survive and multiply even in the presence of macrophages that are designed to eradicate it.

To stop the merging of the phagosome with the lysosome—a digesting compartment loaded with reactive oxygen species and antimicrobial enzymes—TB Bacillus employs a technique known as phagosome maturation inhibition. By blocking this crucial stage of the phagocytic process, the bacteria are able to enter the macrophage and find a place of refuge where they are shielded from the host's harmful enzymes. Furthermore, M. tuberculosis can evade the recruitment of additional immune cells and postpone the start of the effective response by infiltrating the signalling pathways of macrophages. The M. tuberculosis germs can travel through the lymphatic and circulatory systems to other parts of the host's body after taking up residence in the alveolar macrophages. In reaction to this infection's rapid spread, Granulomas, highly ordered collections of immune cells, are produced by the host organism as part of a well-coordinated immunological response that aims to isolate and contain the invasive microorganisms.

The delicate balance between M's virulence and the host determines the outcome of this intricate host-germ interaction. TB and the effectiveness of the host's immune system. Sometimes the infection is contained by the immune system, which results in a latent TB state in which the bacteria live inside the granulomas, are metabolically dormant, and do not multiply. However, this hidden status is not a static state because people who have latent tuberculosis infection are always at risk of reactivation if their immune systems are compromised due to ageing, malnourishment, or immunosuppressive diseases like HIV/AIDS.

On the other hand, active tuberculosis disease may develop if the host's immune system is still unable to

stop bacterial proliferation and spread. In this case, M. tuberculosis proliferates unchecked, causing detrimental tissue damage primarily to the lungs. Thus, inhaling infectious respiratory droplets maintains the transmission cycle.

While the respiratory route is the main way that infections spread, there are other, less common, but still possible, pathways as well. These techniques include direct inoculation into the skin or mucous membranes by skin-to-skin contact or medical procedures, or intake of unpasteurized dairy food products carrying the bacteria.

M. tuberculosis and the host's immunity interact in a way akin to a well-balanced dance, with the outcome dictating whether the infection becomes dormant or active. The aforementioned cross-functional interaction serves as further evidence of the dynamic and formidable nature of tuberculosis, underscoring the need for novel therapeutic approaches and preventive measures to mitigate the destructive effects of the disease on a global scal

REVIEW OF LITERATURE

1. Isabelle Vergne, *et al.,* (2003) The key to the spread of tuberculosis and the related pandemic that affects billions of people globally is Mycobacterium tuberculosis's capacity to infiltrate host macrophages and live in a phagosome that does not mature into a phagolysosome. One way to look at tuberculosis is as a disease with a big organellar biogenesis and intracellular trafficking component. A basic understanding of phagolysosome biogenesis is also provided by the current understanding of the block in M. tuberculosis phagosome maturation. s
2. Mandeep Chouhan, *et al.,* (2023) Roughly 25% of people on the planet are infected with Mycobacterium tuberculosis (Mtb), of which only 5–10% go on to get active TB, while 90–95% of people still have latent Mtb infection. It is therefore the most serious threat to global health. According to reports, the resuscitation-promoting factor B (RpfB) plays a crucial role in reactivating latent tuberculosis infection to an active infection, making it an attractive potential target for tuberculosis medication discovery. Numerous attempts have been made to use in-silico methods to look into possible inhibitors against RpfB. In this study, microbially produced natural chemicals were investigated using a computational approach against the Mtb RpfB protein, which is a relatively economical method. Molecular docking, drug-likeness profiling, structure-based virtual screening (SBVS), and molecular screening.
3. Vivek Dhar Dwivedi,*et al.,* (2020)The World Health Organisation (WHO) has identified suppression of Mycobacterium tuberculosis (Mtb) as one of the main techniques for containing the disease. This goal is reinforced by the existence of a large reservoir of latently infected individuals. Numerous initiatives have been undertaken to investigate possible possibilities, including as de novo designs, medication repurposing, and phytomolecule evaluation. Investigating phytomolecules with established experimental support is a much quicker and less expensive method than alternative approaches. It's interesting to note that several of the phytomolecules have been identified as having anti-tuberculosis properties in the past.
4. Ming-Ming Shao,*et al.,* (2022) Understanding the processes of Mycobacterium tuberculosis (Mtb) infection involving T cell adaptive immunity requires a characterisation of T cell receptor (TCR) repertoires. Uncertainty surrounds the properties of TCR sequences and unique markers of T cell subsets in tuberculous patients. We identified 41,718 CD3+ T cells in tuberculous pleural effusions (TPEs) and paired blood samples, including 30,515 CD4+ T cells and 11,203 CD8+ T cells. We did

this by combining single-cell TCR sequencing (sc-TCR seq) with single-cell RNA sequencing (sc-RNA seq) and flow cytometry to characterise T cells in TPEs.

5. Fei Li,*et al.*, (2023) Mycobacterium tuberculosis (M. tuberculosis) is the causative agent of tuberculosis (TB), a chronic infectious disease. T cell counts normally decline and there is a steady depletion of these cells during lymphopenia. Immune responses may be impeded by lymphopenia, which can result in systemic immunosuppression and death. In most cases of severe and advanced tuberculosis (TB), lymphopenia is a prominent immunological aberration whose severity is related to the course of the disease. The fundamental mechanism is yet unknown, though. The pathophysiology of lymphopenia during M. tuberculosis infection is now mostly studied in relation to its effects on tissue redistribution, lymphocyte survival, and production.

MATERIALS AND METHOD

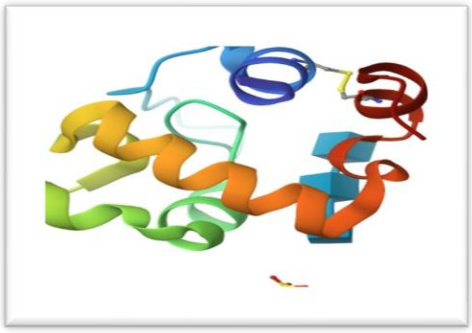
Biovia Discovery Studio 2021

Dassault Systems designed Biovia Discovery Studio, which is a powerful software suite that is used for drug discovery and life science research. Thanks to the extensive kit of devices at its disposal, researchers can model, simulate, visualize, and analyze biological systems in an accurate and efficient manner (Dassault Systems, n.d.). This multidisciplinary nature, which integrates structural biology, cheminformatics, bioinformatics, and molecular modeling, allows researchers to accelerate the drug discovery process with a single platform. Biovia Discovery Studio was used to illustrate the three-dimensional structure of a protein.

Swiss PDB Viewer

Swiss PDB Viewer (SPDBV) is a viewer and analyser of protein structures that was developed by the Swiss Institute of Bioinformatics. Researchers can model and rebuild protein structures in 3D, conduct protein alignments, calculate electrostatic potentials, and render photorealistic images with its user-friendly interface (Guex & Peitsch, 1997). The PDB Viewer of Swiss is utilized to eliminate water molecules, and heteroatoms, and minimize energy.

Cast-P (Active site finder):



Chain-A was the only chain chosen for additional RpfB protein docking. Using the Cast-P active site predictor, active sites in the protein chain were identified following the selection of the protein chain. The active site on chain-A of RpfB protein was found in the coordinates X: -13, Y: 0, Z: -6, with a grid box dimension of X: 40, Y: 40, Z: 40, with a spacing of 0.408 Å. After the identification of active sites on the chains of the proteins, the protein structures were saved in PDBQT format

Ligand preparation:

Ligands with inhibitory action against (Resuscitation–promoting factor B Protein, AP0639 Ligand) proteins were selected at random from the PubChem database https://pubchem.ncbi.nlm.nih.gov. Based on similarity we took five methods like this **(Pharmacophore**) and Two hundred compounds (200) ligands were obtained. Following the ligands extraction from the database, ADME and RO5 screenings were conducted on the ligands to verify their drug-likeness properties.

ss	NAME	LIGAND ID	MOLECU-LARFORMU-LA	M.WT	SMILE ID
1.	*Undefined*	CHEMBL295392	C20H29N3O5	391.47	CNC(=O)[C@H](Cc1ccc(OC)cc1)NC(=O)C1(CC(=O)NO)CCCCC1
2.	*Undefined*	CHEMBL299812	C19H27N3O5	377.44	CNC(=O)[C@H](Cc1ccc(OC)cc1)NC(=O)C1(CC(=O)NO)CCCC1
3.	*Undefined*	CHEMBL3828219	C19H29N3O5	379.46	CNC(=O)C(Cc1ccc(OC)cc1)NC(=O)C(CC(=O)NO)CC(C)C
4.	*Undefined*	CHEMBL20092002	C19H29N3O5	379.46	(=O)[C@H](Cc1ccc(OC)cc1)NC(=O)[C@@H](CC(=O)NO)CC(C)C CNC
5.	*Undefined*	CHEMBL296142	C20H31N3O5	393.48	CNC(=O)[C@H](Cc1ccc(OC)cc1)NC(=O)C(C)(CC(=O)NO)CC(C)C
6.	*Undefined*	CHEMBL417537	C20H31N3O5	393.48	(=O)[C@@H](Cc1ccc(CNCOC)cc1)NC(=O)[C@H](CC(C)C)[C@H](C)C(=O)NO
7.	*Undefined*	CHEMBL293003	C24H37N3O5	447.58	CNC(=O)[C@@H]1Cc2ccc(cc2)OCCCCCC[C@H](C(=O)NO)[C@@H](CC(C)C)C(=O)N1
8.	*Undefined*	CHEMBL302227	C22H33N3O5	419.52	CNC(=O)[C@@H]1Cc2ccc(cc2)OCCCC[C@@H](C(=O)NO)[C@@H](CC(C)C)C(=O)N1
9.	*Undefined*	CHEMBL207756	C20H29N3O5	391.47	CC[C@H](C(=O)NO)[C@H](C(=O)N1CCCC[C@H]1C(=O)NC)c1ccc(OC)cc1
10.	*Undefined*	CHEMBL62007	C23H35N3O5	433.55	CNC(=O)[C@@H]1Cc2ccc(cc2)OCCCCC[C@H](C(=O)NO)[C@@H](CC(C)C)C(=O)N1

11.	*Undefined*	CHEMBL45631	C21H31N3O5	405.50	CNC(=O)[C@H](Cc1ccc(OC)cc1)NC(=O)C1(CC(=O)NO)CCCc2ccccc21
12.	*Undefined*	CHEMBL46030	C22H27N3O5	413.47	CNC(=O)[C@H](Cc1ccc(OC)cc1)NC(=O)C(C)(CC(=O)NO)c1ccccc1
13.	*Undefined*	CHEMBL88520	C23H34N4O6	462.55	CNC(=O)CNC(=O)[C@@H]1Cc2ccc(cc2)OCCC[C@H](C(=O)NO)[C@@H](CC(C)C)C(=O)N1
14.	*Undefined*	CHEMBL49833	C24H29N3O5	439.51	CNC(=O)[C@H](Cc1ccc(OC)cc1)NC(=O)C1(CC(=O)NO)CCCc2ccccc21
15.	*Undefined*	CHEMBL85766	C21H32N4O5	420.51	CCCNC(=O)CCC[C@H](CC(=O)NO)C(=O)N[C@@H](Cc1ccccc1)C(=O)NC
16.	*Undefined*	CHEMBL48226	C21H25N3O5	399.45	CNC(=O)[C@H](Cc1ccc(OC)cc1)NC(=O)C(CC(=O)NO)c1ccccc1
17.	*Undefined*	CHEMBL433479	C23H27N3O5	425.49	CNC(=O)[C@H](Cc1ccc(OC)cc1)NC(=O)C1(CC(=O)NO)Cc2ccccc2C1
18.	*Undefined*	CHEMBL11306	C18H27N3O4	349.43	CNC(=O)[C@H](Cc1ccccc1)NC(=O)[C@@H](CC(=O)NO)CC(C)C
19.	*Undefined*	CHEMBL419751	C22H27N3O6	429.47	CNC(=O)[C@H](Cc1ccc(OC)cc1)NC(=O)[C@@H](CC(=O)NO)Cc1ccc(O)cc1
20.	*Undefined*	CHEMBL126122	C20H29N3O5	391.47	CC(C)C[C@H](CC(=O)NO)C(=O)N[C@@H](Cc1ccccc1)C(=O)N[C@@H](C)C=O
21.	*Undefined*	CHEMBL99103	C31H37N3O5	531.65	CNC(=O)[C@@H]1Cc2ccc(cc2)OCCCC[C@H](C(=O)NO)[C@@H](CCCc2ccccc3ccccc23)C(=O)N1
22.	*Undefined*	CHEMBL86797	C26H34N4O5	482.58	CNC(=O)[C@H](Cc1ccccc1)NC(=O)[C@H](CCCC(=O)NCCc1ccccc1)CC(=O)NO
23.	*Undefined*	CHEMBL98770	C29H39N3O6	525.65	CCOc1ccc(CCC[C@H]2C(=O)N[C@H](C(=O)NC)Cc3ccc(cc3)OCCCC[C@@

					H]2C(=O)NO)cc1
24.	*Undefined*	CHEMBL418292	C22H33N3O5	419.52	CNC(=O)[C@@H]1Cc2ccc(cc2)OCCCC[C@H](C(=O)NO)[C@@H](CC(C)C)C(=O)N1
25.	*Undefined*	CHEMBL64013	C28H37N3O5	495.62	CNC(=O)[C@@H]1Cc2ccc(cc2)OCCCC[C@H](C(=O)NO)[C@@H](CCCc2ccc(C)cc2)C(=O)N1
26.	*Undefined*	CHEMBL1790586	C30H45N5O7	587.72	CC[C@@H](C)[C@@H]1NC(=O)[C@@H](Cc2ccc(OC)cc2)NC(=O)[C@H](CCCCCN(O)C=O)NC(=O)[C@H]2CCCCN2C1=O
27.	*Undefined*	CHEMBL99283	C31H43N3O5	537.70	CNC(=O)[C@@H]1Cc2ccc(cc2)OCCCC[C@H](C(=O)NO)[C@@H](CCCc2cc(C)cc(C(C)C)c2)C(=O)N1
28.	*Undefined*	CHEMBL123571	C19H27N3O5	377.44	CC(C)C[C@H](CC(=O)NO)C(=O)N[C@@H](Cc1ccccc1)C(=O)NCC=O2
29.	*Undefined*	CHEMBL32839	C20H31N3O4	377.49	CNC(=O)[C@H](Cc1ccccc1)NC(=O)[C@H](CC(C)C)C(C)(C)C(=O)NO
30.	*Undefined*	CHEMBL318860	C27H34ClN3O5	516.04	CNC(=O)[C@@H]1Cc2ccc(cc2)OCCCC[C@H](C(=O)NO)[C@@H](CCCc2ccc(Cl)cc2)C(=O)N1
31.	*Undefined*	CHEMBL32730	C19H29N3O4	363.46	CNC(=O)[C@H](Cc1ccccc1)NC(=O)[C@H](CC(C)C)[C@H](C)C(=O)NO
32.	*Undefined*	CHEMBL124623	C23H35N3O5	433.55	CC(C)C[C@H](CC(=O)NO)C(=O)N[C@@H](Cc1ccccc1)C(=O)N[C@H](C=O)CC(C)C
33.	*Undefined*	CHEMBL313356	C22H34N4O5	434.54	CCCC(=O)NCCCC[C@H](CC(=O)NO)C(=O)N[C@@H](Cc1ccccc1)C(=O)NC
34.	*Undefined*	CHEMBL286295	C22H33N3O4	403.52	CNC(=O)[C@H](Cc1ccccc1)NC(=O)[C@H](CC(C)C)C1(C(=O)NO)CCCC1
35.	*Undefined*	CHEMBL452083	C18H27N3O4	349.43	CNC(=O)[C@H](Cc1ccccc1)NC(=O)[C@H](CC(=O

					)NO)CC(C)C
36.	*Undefined*	CHEMBL295257	C22H25N3O5	411.46	CNC(=O)[C@H](Cc1ccc(OC)cc1)NC(=O)C1(CC(=O)NO)Cc2ccccc21
37.	*Undefined*	CHEMBL318005	C29H39N3O7	541.65	CNC(=O)[C@@H]1Cc2ccc(cc2)OCCCC[C@H](C(=O)NO)[C@@H](CCCc2ccc(OC)c(OC)c2)C(=O)N1
38.	*Undefined*	CHEMBL410259	C24H31N3O5	441.53	CNC(=O)[C@H](Cc1ccccc1)NC(=O)[C@H](CCCCOc1ccccc1)CC(=O)NO
39.	*Undefined*	CHEMBL418291	C29H39N3O5	509.65	CCCc1ccc(CC[C@H]2C(=O)N[C@H](C(=O)NC)Cc3ccc(cc3)OCCCC[C@@H]2C(=O)NO)cc1
40.	*Undefined*	CHEMBL303298	C25H40N4O5	476.62	CC(C)C[C@H]1C(=O)N[C@H](C(=O)NCCN(C)C)Cc2ccc(cc2)OCCCC[C@@H]1C(=O)NO
41.	*Undefined*	CHEMBL66134	C24H37N3O5S	479.64	CSCCNC(=O)[C@@H]1Cc2ccc(cc2)OCCCC[C@H](C(=O)NO)[C@@H](CC(C)C)C(=O)N1
42.	*Undefined*	CHEMBL1790599	C29H43N5O7	573.69	CC[C@@H](C)[C@@H]1NC(=O)[C@@H](Cc2ccc(OC)cc2)NC(=O)[C@H](CCCCCN(O)C=O)NC(=O)[C@H]2CCCN2C1=O
43.	*Undefined*	CHEMBL99120	C29H39N3O7	541.65	CNC(=O)[C@@H]1Cc2ccc(cc2)OCCCC[C@H](C(=O)NO)[C@@H](CCCc2cc(OC)ccc2OC)C(=O)N1
44.	*Undefined*	CHEMBL35602	C21H31N3O4	389.50	C=CC[C@@H](C(=O)NO)[C@@H](CC(C)C)C(=O)N[C@@H](Cc1ccccc1)C(=O)NC
45.	*Undefined*	CHEMBL35348	C22H33N3O4	403.52	C=CC[C@](C)(C(=O)NO)[C@@H](CC(C)C)C(=O)N[C@@H](Cc1ccccc1)C(=O)NC
46.	*Undefined*	CHEMBL1790587	C29H43N5O7	573.69	CC[C@@H](C)[C@@H]1NC(=O)[C@@H](Cc2ccc(OC)cc2)NC(=O)[C@H](C

					CCCCC(=O)NO)NC(=O)[C@H]2CCCN2C1=O
47.	*Undefined*	CHEMBL1790596	C29H43N5O7	573.69	CC[C@@H](C)[C@@H]1NC(=O)[C@@H](Cc2ccc(OC)cc2)NC(=O)[C@H](CCCCCN(O)C=O)NC(=O)[C@@H]2CCCN2C1=O
48.	*Undefined*	CHEMBL433381	C22H33N3O5	419.52	CNC(=O)[C@@H]1CCc2ccc(cc2)OCCC[C@H](C(=O)NO)[C@@H](CC(C)C)C(=O)N1
49.	*Undefined*	CHEMBL289003	C22H33N3O4	403.52	C=CC[C@@](C)(C(=O)NO)[C@@H](CC(C)C)C(=O)N[C@@H](Cc1ccccc1)C(=O)NC
50.	*Undefined*	CHEMBL432079	C21H31N3O4	389.50	C=CC[C@H](C(=O)NO)[C@@H](CC(C)C)C(=O)N[C@@H](Cc1ccccc1)C(=O)NC
51.	*Undefined*	CHEMBL430838	C25H32N4O5		CNC(=O)[C@H](Cc1ccccc1)NC(=O)[C@H](CCCC(=O)NCc1ccccc1)CC(=O)NO
52.	*Undefined*	CHEMBL95718	C30H41N3O8	571.67	CNC(=O)[C@@H]1Cc2ccc(cc2)OCCCC[C@H](C(=O)NO)[C@@H](CCCc2cc(OC)c(OC)c(OC)c2)C(=O)N1
53.	*Undefined*	CHEMBL4544135	C26H37N5O5	499.61	CC(C)CC(CC(=O)NO)C(=O)N[C@@H](Cc1ccc2ccccc2c1)C(=O)N[C@@H](C)C(=O)NCCN
54.	*Undefined*	CHEMBL328090	C23H35N3O5	433.55	CNC(=O)[C@@H]1CCCc2ccc(cc2)OCCC[C@H](C(=O)NO)[C@@H](CC(C)C)C(=O)N1
55.	*Undefined*	CHEMBL327892	C19H29N3O5	379.46	CCCC[C@H](CN(O)C=O)C(=O)N[C@@H](Cc1ccc(O)cc1)C(=O)N(C)C
56.	*Undefined*	CHEMBL438964	C23H32N4O6	444.59	Coc1ccc([C@@H](C(=O)N2CCCCC2)[C@H](CN2C(=O)N©C©©C2=O)C(=O)NO)cc1

57.	*Undefined*	CHEMBL304243	C29H39N3O6	525.65	CNC(=O)[C@@H]1Cc2ccc(cc2)OCCCC[C@H](C(=O)NO)[C@@H](CCCCOCc2ccccc2)C(=O)N1
58.	*Undefined*	CHEMBL439330	C19H27N3O6	393.44	CNC(=O)[C@@H]1CCCCN1C(=O)[C@H](c1ccc(OC)cc1)[C@H](CO)C(=O)NO
59.	*Undefined*	CHEMBL284465	C24H35N3O4	429.56	C=CCC(CC=C)(C(=O)NO)[C@@H](CC©C)C(=O)N[C@@H](Cc1ccccc1)C(=O)NC
60.	*Undefined*	CHEMBL3827627	C23H37N3O4	419.57	CC©©NC(=O)C(NC(=O)C(CCCc1ccccc1)CC(=O)NO)C©©C
61.	*Undefined*	CHEMBL2372819	C29H38N6O6	566.66	NC(=O)[C@@H]1CCCCNC(=O)CC[C@H](NC(=O)[C@@H](N)Cc2ccc(O)cc2)C(=O)N[C@@H](Cc2ccccc2)C(=O)N1
62.	*Undefined*	CHEMBL382705	C19H26ClN3O4	395.89	CC[C@H](C(=O)NO)[C@H](C(=O)N1CCCC[C@H]1C(=O)NC)c1ccc(Cl)cc1
63.	*Undefined*	CHEMBL66532	C29H40N4O7S	588.73	CC©C[C@H]1C(=O)N[C@H](C(=O)NCCc2ccc(S(N)(=O)=O)cc2)Cc2ccc(cc2)OCCCC[C@@H]1C(=O)NO
64.	*Undefined*	CHEMBL3099019	C19H29N3O4	363.46	CNC(=O)[C@@H](CCc1ccccc1)NC(=O)[C@@H](CC(=O)NO)CC©C
65.	*Undefined*	CHEMBL279078	C23H35N3O4	417.55	CNC(=O)[C@H](Cc1ccccc2c1CCCC2)NC(=O)[C@H](CC©C)[C@H]©C(=O)NO
66.	*Undefined*	CHEMBL405102	C40H58N8O8	778.95	CC©[C@H](NC(=O)[C@@H](NC(=O)C1(NC(=O)[C@H](Cc2ccccc2)NC(=O)[C@H]©NC(=O)[C@@H](N)Cc2ccc(O)cc2)CCCCC1)C©C)C(=O)NCC(N)=O
67.	*Undefined*	CHEMBL99547	C33H38N2O5	542.68	Cc1ccc(CCC[C@H]2C(=O)N[C@H](C(=O)c3ccccc3)

					Cc3ccc(cc3)OCCCC[C@@H]2C(=O)NO)cc1
68.	*Undefined*	CHEMBL2048512	C19H29N3O4	363.46	CNC(=O)C(CCc1ccccc1)NC(=O)C(CC(=O)NO)CC©C
69.	*Undefined*	CHEMBL3828455	C20H31N3O4	377.49	CNC(=O)C(NC(=O)C(CCCc1ccccc1)CC(=O)NO)C©©C
70.	*Undefined*	CHEMBL3828521	C25H39N3O4	445.60	CC©©C(NC(=O)C(CCCc1ccccc1)CC(=O)NO)C(=O)NC1CCCCC1
71.	*Undefined*	CHEMBL252246	C19H25N3O3	343.43	O=C(NO)[C@H]1CC2(CC2)CN[C@@H]1C(=O)N1CCC(c2ccccc2)C1
72.	*Undefined*	CHEMBL326022	C17H25N3O4	335.40	NC(=O)[C@H](Cc1ccccc1)NC(=O)CCCCCCC(=O)NO
73.	*Undefined*	CHEMBL222830	C28H36N6O6	552.63	NC(=O)[C@H]1CCCC[C@@H](NC(=O)[C@@H](N)Cc2ccc(O)cc2)C(=O)NCC(=O)N[C@@H](Cc2ccccc2)C(=O)N1
74.	*Undefined*	CHEMBL2372817	C29H38N6O6	566.66	NC(=O)[C@@H]1CCC(=O)NCCCC[C@H](NC(=O)[C@@H](N)Cc2ccc(O)cc2)C(=O)N[C@@H](Cc2ccccc2)C(=O)N1
75.	*Undefined*	CHEMBL92954	C19H29N3O4	363.46	CCCC[C@H](CN(O)C=O)C(=O)N[C@@H](Cc1ccccc1)C(=O)N©C
76.	*Undefined*	CHEMBL208181	C25H37N5O7	519.60	CNC(=O)[C@@H](NC(=O)[C@H](c1ccc(OC)cc1)[C@H](CN1C(=O)N©C©©C1=O)C(=O)NO)C©©C
77.	*Undefined*	CHEMBL452372	C33H39N5O5	585.71	NC(=O)[C@H](Cc1ccccc1)NC(=O)[C@H](Cc1ccccc1)NC(=O)[C@@H]1CCCCN1C(=O)[C@@H](N)Cc1ccc(O)cc1
78.	*Undefined*	CHEMBL214869	C27H44N4O4	488.67	CCC[C@@H]1NC(=O)[C@@H](C©C)NC(=O)[C@@H](Cc2ccc(O)cc2)NCCCCCCCCNC1=O

79.	*Undefined*	CHEMBL146896	C15H20N2O4	292.34	Coc1ccc([C@]2©CCN([C@H]©C(=O)NO)C2=O)cc1
80	*Undefined*	CHEMBL338502	C19H30N2O3S	366.53	CNC(=O)[C@H](Cc1ccc(OC)cc1)NC(=O)C(CC©C)C©S
81.	*Undefined*	CHEMBL23051997	C28H36N6O6	552.63	NC(=O)[C@@H]1CCC(=O)NCCC[C@@H](NC(=O)[C@@H](N)Cc2ccc(O)cc2)C(=O)N[C@@H](Cc2ccccc2)C(=O)N1
82.	*Undefined*	CHEMBL3827566	C24H37N3O4	431.58	CC©©C(NC(=O)C(CCCc1ccccc1)CC(=O)NO)C(=O)NC1CCCC1
83.	*Undefined*	CHEMBL338231	C24H39N3O6	465.59	CCOC(OCC)[C@H]©NC(=O)[C@H](Cc1ccccc1)NC(=O)[C@@H](CC(=O)NO)CC©C
84.	*Undefined*	CHEMBL72511	C19H29N3O6	395.46	CNC(=O)[C@@H](NC(=O)[C@H](c1ccc(OC)cc1)[C@H](CO)C(=O)NO)C©©C
85.	*Undefined*	CHEMBL144049	C20H22N2O4	354.41	C[C@H](C(=O)NO)N1CC[C@@]©(c2ccc(Oc3ccccc3)cc2)C1=O
86.	*Undefined*	CHEMBL09072002	C28H37N3O5	495.62	CC(=O)N[C@@H](Cc1ccc(OC©=O)cc1)C(=O)N1CCC[C@@H]1C(=O)NC1C2CC3CC(C2)CC1C3
87.	*Undefined*	CHEMBL221698	C19H25N3O3	343.43	O=C(NO)[C@H]1CC2(CC2)CN[C@@H]1C(=O)N1CC[C@H](c2ccccc2)C1
88.	*Undefined*	CHEMBL2372200	C28H37N5O7	555.63	CC(=O)O.N[C@@H](Cc1ccc(O)cc1)C(=O)N[C@@H]1CCCCNC(=O)[C@H](Cc2ccccc2)NC(=O)CNC1=O
89.	*Undefined*	CHEMBL221537	C17H23N3O3	317.39	O=C(NO)[C@H]1CCCN[C@@H]1C(=O)N1CC[C@H](c2ccccc2)C1
90.	*Undefined*	CHEMBL156033	C21H32N2O5	392.50	CCCC[C@H](CN(O)C=O)C(=O)N[C@H](C(=O)c1ccc(OC)cc1)C©©C

91.	*Undefined*	CHEMBL1927270	C37H45N7O7	699.81	NC(=O)[C@@H]1CC(=O)NCCCC[C@@H](NC(=O)[C@@H](N)Cc2ccc(O)cc2)C(=O)N[C@@H](Cc2ccccc2)C(=O)N[C@@H](Cc2ccccc2)C(=O)N1
92.	*Undefined*	CHEMBL3143518	C32H45N5O5	579.74	CC©©c1cc(C[C@@H]2NC(=O)[C@@H](NC(=O)[C@@H](N)Cc3ccccc3)CCCCNC(=O)CCCNC2=O)ccc1O
93.	*Undefined*	CHEMBL2372196	C34H48N6O8	668.79	CC(=O)O.CC©C[C@H]1NC(=O)[C@H](Cc2ccccc2)NC(=O)CNC(=O)[C@H](NC(=O)[C@@H](N)Cc2ccc(O)cc2)CCCCNC1=O
94.	*Undefined*	CHEMBL2372207	C34H48N6O8	668.79	CC(=O)O.CC©C[C@@H]1NC(=O)[C@H](Cc2ccccc2)NC(=O)CNC(=O)[C@H](NC(=O)[C@@H](N)Cc2ccc(O)cc2)CCCCNC1=O
95.	*Undefined*	CHEMBL104838	C29H38N6O6	566.66	CN1C(=O)[C@H](NC(=O)[C@@H](N)Cc2ccc(O)cc2)CCCNC(=O)CC[C@@H](C(N)=O)NC(=O)[C@@H]1Cc1ccccc1
96.	*Undefined*	CHEMBL1774020	C26H32ClN3O3	470.01	Coc1ccc(CC(=O)N[C@H](Cc2ccc(Cl)cc2)C(=O)N[C@H]2C[C@H]3CC[C@@H](C2)N3C)cc1
97.	*Undefined*	CHEMBL3355779	C40H49N7O7	739.87	NC(=O)[C@@H]1CC(=O)N[C@H]2CC[C@@H](CC2)C[C@@H](NC(=O)[C@@H](N)Cc2ccc(O)cc2)C(=O)N[C@@H](Cc2ccccc2)C(=O)N[C@@H](Cc2ccccc2)C(=O)N1
98.	*Undefined*	CHEMBL438833	C29H39N5O5	537.66	CCCC[C@H](NC(=O)[C@@H]1CCCN1C(=O)[C@@H](N)Cc1ccc(O)cc1)C(=O)N[C@@H](Cc1ccccc1)C(N)=O
99.	*Undefined*	CHEMBL223552	C32H43N5O5	577.73	NC(=O)[C@H](Cc1ccccc1

					)NC(=O)[C@H](CC1CCCCC1)NC(=O)[C@@H]1CCCN1C(=O)[C@@H](N)Cc1ccc(O)cc1
100.	*Undefined*	CHEMBL263021	C32H38N6O6	602.69	NC(=O)[C@@H]1CCC(=O)NCCC[C@@H](NC(=O)[C@@H](N)Cc2ccc(O)cc2)C(=O)N[C@@H](Cc2ccc3ccccc3c2)C(=O)N1
101.	*Undefined*	CHEMBL242979	C32H43N5O5	577.73	NC(=O)[C@H](CC1CCCCC1)NC(=O)[C@H](Cc1ccccc1)NC(=O)[C@@H]1CCCN1C(=O)[C@@H](N)Cc1ccc(O)cc1
102.	*Undefined*	CHEMBL095728	C40H49N7O7	739.87	NC(=O)[C@@H]1CC(=O)N[C@H]2CC[C@H](CC2)C[C@@H](NC(=O)[C@@H](N)Cc2ccc(O)cc2)C(=O)N[C@@H](Cc2ccccc2)C(=O)N[C@@H](Cc2ccccc2)C(=O)N1
103.	*Undefined*	CHEMBL4169083	C26H37N3O3	439.60	CCOc1ccc(C[C@H](N)C(=O)N2CCC[C@@H]2C(=O)NC2C3CC4CC(C3)CC2C4)cc1
104.	*Undefined*	CHEMBL325810	C29H38N6O6	566.66	C[C@]1(Cc2ccccc2)NC(=O)[C@H](NC(=O)[C@@H](N)Cc2ccc(O)cc2)CCCNC(=O)CC[C@@H](C(N)=O)NC1=O
105.	*Undefined*	CHEMBL359424	C17H22N2O4	318.37	C=CCOc1ccc([C@]2(C)CCN([C@H](C)C(=O)NO)C2=O)cc1
106.	*Undefined*	CHEMBL4467160	C30H43N5O6	569.70	CC1CCCCC12NC(=O)[C@H](CCCCCC(=O)NO)NC(=O)[C@H]1CCCN1C(=O)[C@H](Cc1ccccc1)NC2=O
107.	*Undefined*	CHEMBL3143520	C31H43N5O5	565.72	CC(C)(C)Oc1ccc(C[C@@H]2NC(=O)[C@@H](NC(=O)[C@@H](N)Cc3ccccc3)CCCCNC(=O)CCNC2=O)cc1

108.	*Undefined*	CHEMBL4085033	C34H45N7O7	663.78	NC(=O)[C@@H]1CC(=O)NCCCC[C@@H](NC(=O)[C@@H](N)Cc2ccc(O)cc2)C(=O)N[C@@H](Cc2ccccc2)C(=O)N2CCC(CC2)C(=O)N1
109.	*Undefined*	CHEMBL329232	C35H42N2O8	618.73	COc1cc(CCC[C@H]2C(=O)N[C@H](C(=O)c3ccccc3)Cc3ccc(cc3)OCCCC[C@@H]2C(=O)NO)cc(OC)c1OC
110.	*Undefined*	CHEMBL94165	C19H28ClN3O4	397.90	CCCC[C@H](CN(O)C=O)C(=O)N[C@@H](Cc1ccc(Cl)cc1)C(=O)N(C)C
111.	*Undefined*	CHEMBL2372201	C33H46N6O8	654.77	CC(=O)O.CC(C)C[C@@H]1NC(=O)[C@H](Cc2ccccc2)NC(=O)CNC(=O)[C@H](NC(=O)[C@@H](N)Cc2ccc(O)cc2)CCCNC1=O
112.	*Undefined*	CHEMBL99318	C34H40N2O7	588.70	COc1cc(CCC[C@H]2C(=O)N[C@H](C(=O)c3ccccc3)Cc3ccc(cc3)OCCCC[C@@H]2C(=O)NO)cc(OC)c1
113.	*Undefined*	CHEMBL164062	C39H56N8O8	764.93	CC(C)[C@H](NC(=O)[C@@H](NC(=O)C1(NC(=O)[C@H](Cc2ccccc2)NC(=O)[C@H](C)NC(=O)[C@@H](N)Cc2ccc(O)cc2)CCCC1)C(C)C)C(=O)NCC(N)=O
114.	*Undefined*	CHEMBL274012	C35H42N6O6	642.76	N[C@@H](Cc1ccc(O)cc1)C(=O)N[C@H]1CCCCNC(=O)CNC(=O)[C@H]2CCCN2C(=O)[C@H](Cc2ccc3ccccc3c2)NC1=O
115.	*Undefined*	CHEMBL4074931	C34H45N7O7	663.78	NC(=O)[C@@H]1CC(=O)NCCCC[C@@H](NC(=O)[C@@H](N)Cc2ccc(O)cc2)C(=O)N[C@@H](Cc2ccccc2)C(=O)N2CCCC[C@H]2C(=O)N1

116.	*Undefined*	CHEMBL2372203	C32H44N6	640.74	CC(=O)O.CC(C)C[C@@H]1NC(=O)[C@@H](Cc2ccccc2)NC(=O)CNC(=O)[C@H](NC(=O)[C@@H](N)Cc2ccc(O)cc2)CCNC1=O
117.	*Undefined*	CHEMBL500212	C30H40N6O7	596.69	CC(=O)N[C@@H](Cc1ccc(O)cc1)C(=O)NCC(=O)NCC(=O)N[C@@H](Cc1ccccc1)C(=O)N[C@@H](CC(C)C)C(N)=O
118.	*Undefined*	CHEMBL53621	C21H34N2O3S	394.58	CCC(C)C(S)CC(C(=O)NC(Cc1ccc(O)cc1)C(N)=O)C(C)CC
119.	*Undefined*	CHEMBL157091	C23H34N2O5	418.53	COc1ccc(C(=O)[C@@H](NC(=O)[C@H](CC2CCCC2)CN(O)C=O)C(C)(C)C)cc1
120.	*Undefined*	CHEMBL4083221	C33H43N7O7	649.75	NC(=O)[C@@H]1CC(=O)NCCCC[C@@H](NC(=O)[C@@H](N)Cc2ccc(O)cc2)C(=O)N[C@@H](Cc2ccccc2)C(=O)N2CCC[C@H]2C(=O)N1
121.	*Undefined*	CHEMBL3765059	C35H42N6O7	658.76	N[C@@H](Cc1ccc(O)cc1)C(=O)N[C@@H]1CCCCNC(=O)CNC(=O)[C@H](Cc2ccc(O)cc2)NC(=O)[C@H](Cc2ccccc2)NC1=O
122.	*Undefined*	CHEMBL387816		495.58	C[C@H](NC(=O)[C@@H]1CCCN1C(=O)[C@@H](N)Cc1ccc(O)cc1)C(=O)N[C@@H](Cc1ccccc1)C(N)=O
123.	*Undefined*	CHEMBL286698	C29H45N3O4	499.70	C=CC[C@](C)(C(=O)NO)[C@@H](CC(C)C)C(=O)N[C@@H](CC1CCCCC1)C(=O)NCCc1ccccc1
124.	*Undefined*	CHEMBL563719	C31H35N5O5	557.65	NC(=O)[C@H](Cc1ccccc1)NC(=O)[C@H](Cc1ccccc1)NC(=O)[C@@H]1CCN1C(=O)[C@@H](N)Cc1ccc(O)cc1

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125.	*Undefined*	CHEMBL243200	C29H39N5O5	356.64	CCCC[C@H](NC(=O)[C@H](Cc1ccccc1)NC(=O)[C@@H]1CCCN1C(=O)[C@@H](N)Cc1ccc(O)cc1)C(N)=O
126.	*Undefined*	CHEMBL4095366	C34H45N7O7	663.78	NC(=O)[C@@H]1CC(=O)NCCCC[C@@H](NC(=O)[C@@H](N)Cc2ccc(O)cc2)C(=O)N[C@@H](Cc2ccccc2)C(=O)N2CCC[C@H](C2)C(=O)N1
127.	*Undefined*	CHEMBL105568	C28H36N6O6	552.63	NC(=O)[C@@H]1CCC(=O)NCCC[C@@H](NC(=O)[C@@H](N)Cc2ccc(O)cc2)C(=O)N[C@H](Cc2ccccc2)C(=O)N1
128.	*Undefined*	CHEMBL3828338	C17H15FN2O4	330.32	O=C(NO)C1CC(c2ccc(Oc3ccc(F)cc3)cc2)C(=O)N1
129.	*Undefined*	CHEMBL458592	C19H28N2O5	364.44	CCCCC[C@H](CC(=O)NO)C(=O)N[C@@H](Cc1ccccc1)C(=O)OC
130.	*Undefined*	CHEMBL440124	C22H35N3O4	405.54	CC(C)CC(CC(=O)NO)C(=O)C(CC(C)C)NC(=O)C(N)Cc1ccccc1
131.	*Undefined*	CHEMBL2371264	C30H41N5O5	551.69	CC(C)(C)c1cc(C[C@@H]2NC(=O)[C@@H](NC(=O)[C@@H](N)Cc3ccccc3)CCCCNC(=O)CNC2=O)ccc1O
132.	*Undefined*	CHEMBL15100	C30H38N6O6	578.67	N[C@@H](Cc1ccc(O)cc1)C(=O)N[C@H]1CCCNC(=O)CNC(=O)[C@H]2CCCN2C(=O)[C@H](Cc2ccccc2)NC1=O
133.	*Undefined*	CHEMBL1405007	C20H27N3O5	389.45	COc1ccc(CCN2C(=O)CC(N3CCC(C(N)=O)CC3)C2=O)cc1OC
134.	*Undefined*	CHEMBL98304	C32H34Br2N2O5	686.44	O=C(c1ccccc1)[C@@H]1Cc2ccc(cc2)OCCCC[C@H](C(=O)NO)[C@@H](CCCc2cc(Br)cc(Br)c2)C(=O)N1
135	*Undefined*	CHEMBL379434	C27H41N3O6	503.64	COc1cc([C@@H](C(=O)

		3			N2CCCC[C@H]2C(=O)NCCCC(N)=O)C2CCCCC2)cc(OC)c1OC
136.	*Undefined*	CHEMBL360194	C26H37N5O6	515.61	CC1(C)NC(=O)[C@H](CCCCCC(=O)NO)NC(=O)[C@H]2CCCN2C(=O)[C@H](Cc2ccccc2)NC1=O
137.	*Undefined*	CHEMBL2370207	C34H40N6O6	628.73	N[C@@H](Cc1ccc(O)cc1)C(=O)N[C@@H]1CCCNC(=O)CNC(=O)[C@@H]2CCCN2C(=O)[C@H](Cc2ccc3ccccc3c2)NC1=O
138.	*Undefined*	CHEMBL65493	C23H35N3O5	433.55	CC(C)C[C@H](CC(=O)NO)C(=O)N[C@H]1CCCCN(CCCOc2ccccc2)C1=O
139.	*Undefined*	CHEMBL2371340	C28H35N5O5	521.62	NC(=O)[C@H]1CCCN1C(=O)[C@@H](Cc1ccccc1)NC(=O)[C@@H]1CCCN1C(=O)[C@@H](N)Cc1ccc(O)cc1
140.	*Undefined*	CHEMBL3326665	C31H43N5O5	565.72	CN[C@@H](Cc1ccc(O)cc1)C(=O)N1CCCC1C(=O)N(C)[C@@H](Cc1ccccc1)C(=O)N[C@@H](CC(C)C)C(N)=O
141.	*Undefined*	CHEMBL290737	C23H29N5O	455.52	C[C@H](NC(=O)[C@@H](N)Cc1ccc(O)cc1)C(=O)N[C@@H](Cc1ccccc1)C(=O)NCC(N)=O
142	*Undefined*	CHEMBL388265	C26H33N5O5	495.58	C[C@H](NC(=O)[C@H](Cc1ccccc1)NC(=O)[C@@H]1CCCN1C(=O)[C@@H](N)Cc1ccc(O)cc1)C(N)=O
143.	*Undefined*	CHEMBL372682	C34H41N5O5	599.73	NC(=O)[C@H](Cc1ccccc1)NC(=O)[C@H](Cc1ccccc1)NC(=O)[C@@H]1CCCC[C@@H]1NC(=O)[C@@H](N)Cc1ccc(O)cc1
144.	*Undefined*	CHEMBL66039	C26H38N6O6	530.63	NC(=O)[C@@H]1CC(=O)NCCC[C@@H](NC(=O)[C@@H](N)Cc2ccc(O)cc2)C(=O)N[C@@H](C2CCC

					CC2)C(=O)N1
145.	*Undefined*	CHEMBL349816	C23H29N5O5	455.52	C[C@@H](NC(=O)[C@@H](N)Cc1ccc(O)cc1)C(=O)N[C@@H](Cc1ccccc1)C(=O)NCC(N)=O
146.	*Undefined*	CHEMBL2371339	C29H37N5O5	535.65	CN(C(=O)[C@@H]1CCCN1C(=O)[C@@H](N)Cc1ccc(O)cc1)[C@@H](Cc1ccccc1)C(=O)N1CCC[C@H]1C(N)=O
147.	*Undefined*	CHEMBL63972	C27H34N6O6	538.61	NC(=O)[C@@H]1CC(=O)NCCC[C@@H](NC(=O)[C@@H](N)Cc2ccc(O)cc2)C(=O)N[C@H](Cc2ccccc2)C(=O)N1
148.	*Undefined*	CHEMBL4475712	C19H20N2O4	340.38	Cc1cc(C[C@@H]2NC(=O)[C@H](Cc3ccc(O)cc3)NC2=O)ccc1O
149.	*Undefined*	CHEMBL3236076	C25H38N4O3	442.60	CN[C@@H](C)C(=O)N[C@H]1CCC[C@H]2C[C@H]3CCN(CCc4ccc(OC)cc4)C[C@H]3N2C1=O
150.	*Undefined*	CHEMBL2371336	C29H37N5O5	535.65	CN(C(=O)[C@@H]1CCCN1C(=O)[C@@H](N)Cc1ccc(O)cc1)[C@H](Cc1ccccc1)C(=O)N1CCC[C@@H]1C(N)=O
151.	*Undefined*	CHEMBL219104	C20H27N3O3	357.45	O=C(NO)[C@H]1CC2(CC2)CN[C@@H]1C(=O)N1CCC(c2ccccc2)CC1
152.	*Undefined*	CHEMBL323024	C29H38N6O6	566.66	Cc1ccccc1C[C@@H]1NC(=O)[C@H](NC(=O)[C@@H](N)Cc2ccc(O)cc2)CCCNC(=O)CC[C@@H](C(N)=O)NC1=O
153.	*Undefined*	CHEMBL280264	C32H37N5O5	571.68	N[C@@H](Cc1ccc(O)cc1)C(=O)N[C@H]1CCCNC(=O)[C@H]2CCCN2C(=O)[C@H](Cc2ccc3ccccc3c2)NC1=O
154.	*Undefined*	CHEMBL278891	C34H40N6O6	628.73	N[C@@H](Cc1ccc(O)cc1)C(=O)N[C@@H]1CCCNC(=O)CNC(=O)[C@H]2C

					CCN2C(=O)[C@H](Cc2ccc3ccccc23)NC1=O
155.	*Undefined*	CHEMBL242087	C28H37N5O5	523.63	CC(C)[C@H](NC(=O)[C@@H]1CCCN1C(=O)[C@@H](N)Cc1ccc(O)cc1)C(=O)N[C@@H](Cc1ccccc1)C(N)=O
156.	*Undefined*	CHEMBL283287	C29H37N5O5	535.65	CN(C(=O)[C@@H]1CCCN1C(=O)[C@@H](N)Cc1ccc(O)cc1)[C@@H](Cc1ccccc1)C(=O)N1CCC[C@@H]1C(N)=O
157.	*Undefined*	CHEMBL355367	C33H39N5O5	585.71	C[C@@H](c1ccccc1)[C@@H](NC(=O)[C@@H]1CCCN1C(=O)[C@@H](N)Cc1ccc(O)cc1)C(=O)N[C@@H](Cc1ccccc1)C(N)=O
158.	*Undefined*	CHEMBL59641	C22H32N4O5	287.33	CC(=O)N[C@@H](CC(C)C)C(=O)N[C@@H](Cc1ccccc1)C(=O)N[C@H](C=O)CCC(N)=O
159.	*Undefined*	CHEMBL2332717	C38H44N8O10	772.82	NC(=O)CC[C@@H]1NC(=O)[C@H](Cc2ccccc2)NC(=O)[C@H](Cc2ccc(O)cc2)NC(=O)[C@H](Cc2ccc(O)cc2)NC(=O)CNC(=O)[C@H](CC(N)=O)NC1=O
160.	*Undefined*	CHEMBL3794574	C32H43N3O6	565.71	COc1cc([C@@H](C(=O)N2CCCC[C@H]2C(=O)N[C@H](Cc2ccccc2)C(N)=O)C2CCCCC2)cc(OC)c1OC
161.	*Undefined*	CHEMBL2371359	C28H35N5O5	521.62	NC(=O)[C@@H]1CCCN1C(=O)[C@@H](Cc1ccccc1)NC(=O)[C@@H]1CCCN1C(=O)[C@@H](N)Cc1ccc(O)cc1
162.	*Undefined*	CHEMBL3621348	C24H36N4O5	460.58	CCC[C@H]1NC(=O)[C@@H](Cc2ccc(O)cc2)NC(=O)[C@@H](C)NC(=O)[C@@H](C(C)C)NC(=O)[C@H]1C
163	*Undefined*	CHEMBL447871	C34H41N5O5	599.73	NC(=O)[C@H](Cc1ccccc1

.					)NC(=O)[C@H](Cc1ccccc1)NC(=O)[C@@H]1CCCC[C@H]1NC(=O)[C@@H](N)Cc1ccc(O)cc1
164.	*Undefined*	CHEMBL423466	C33H39N5O5	585.71	C[C@@H](c1ccccc1)[C@H](NC(=O)[C@@H]1CCCN1C(=O)[C@@H](N)Cc1ccc(O)cc1)C(=O)N[C@@H](Cc1ccccc1)C(N)=O
165.	*Undefined*	CHEMBL3103451	C20H22Cl2N2O4	425.31	COc1ccc(CCNC(=O)CC(CC(=O)NO)c2ccc(Cl)cc2Cl)cc1
166.	*Undefined*	CHEMBL2372834	C21H30N6O6	462.51	NC(=O)[C@@H]1CCC(=O)NCCC[C@H](NC(=O)[C@@H](N)Cc2ccc(O)cc2)C(=O)NCC(=O)N1
167.	*Undefined*	CHEMBL416641	C27H29N3O4	459.55	C[C@@](Cc1ccccc1)(NC(=O)Cc1ccc(O)cc1)C(=O)NC(Cc1ccccc1)C(N)=O
168.	*Undefined*	CHEMBL526496	C32H44N4O5	564.73	CC(C)(C)c1cc(C[C@@H]2NC(=O)[C@@H](NC(=O)[C@@H](N)Cc3ccccc3)CCCCCC(=O)CCNC2=O)ccc1O
169.	*Undefined*	CHEMBL166108	C33H39N5O5	585.71	C[C@H](c1ccccc1)[C@@H](NC(=O)[C@@H]1CCCN1C(=O)[C@@H](N)Cc1ccc(O)cc1)C(=O)N[C@@H](Cc1ccccc1)C(N)=O
170.	*Undefined*	CHEMBL1253633	C33H39N5O5	585.71	NC(=O)[C@H](Cc1ccccc1)NC(=O)[C@H](Cc1ccccc1)NC(=O)C[C@H]1CCCN1C(=O)[C@@H](N)Cc1ccc(O)cc1
171.	*Undefined*	CHEMBL1927272	C33H43N7O7	649.75	NC(=O)[C@@H]1CC(=O)NCCCC[C@@H](NC(=O)[C@@H](N)Cc2ccc(O)cc2)C(=O)N[C@@H](Cc2ccccc2)C(=O)N2CCC[C@@H]2C(=O)N1
172.	*Undefined*	CHEMBL267708	C28H35N5O5	521.62	NC(=O)[C@H]1CCCN1C(=O)[C@H](Cc1ccccc1)NC(=O)[C@@H]1CCCN1C(

					=O)[C@@H](N)Cc1ccc(O)cc1
173.	*Undefined*	CHEMBL3827377	C27H37N3O4	467.61	CC(NC(=O)C(NC(=O)C(CCCc1ccccc1)CC(=O)NO)C(C)(C)C)c1ccccc1
174.	ENDO-MORPHIN 2	CHEMBL333357	C32H37N5O5	571.68	NC(=O)[C@H](Cc1ccccc1)NC(=O)[C@H](Cc1ccccc1)NC(=O)[C@@H]1CCCN1C(=O)[C@@H](N)Cc1ccc(O)cc1
175.	*Undefined*	CHEMBL2370620	C28H35N5O5	521.62	NC(=O)[C@@H]1CCCN1C(=O)[C@H](Cc1ccccc1)NC(=O)[C@H]1CCCN1C(=O)[C@@H](N)Cc1ccc(O)cc1
176.	*Undefined*	CHEMBL455743	C34H41N5O5	599.73	NC(=O)[C@H](Cc1ccccc1)NC(=O)[C@H](Cc1ccccc1)NC(=O)[C@H]1CCCC[C@@H]1NC(=O)[C@@H](N)Cc1ccc(O)cc1
177.	*Undefined*	CHEMBL2370199	C30H38N6O6	578.67	N[C@@H](Cc1ccc(O)cc1)C(=O)N[C@@H]1CCCNC(=O)CNC(=O)[C@@H]2CCCN2C(=O)[C@H](Cc2ccccc2)NC1=O
178.	*Undefined*	CHEMBL275670	C34H40N6O6	628.73	N[C@@H](Cc1ccc(O)cc1)C(=O)N[C@H]1CCCNC(=O)CNC(=O)[C@H]2CCCN2C(=O)[C@H](Cc2ccc3ccccc3c2)NC1=O
179.	*Undefined*	CHEMBL1927274	C33H43N7O7	649.75	NC(=O)[C@@H]1CCCCNC(=O)C[C@@H](NC(=O)[C@@H](N)Cc2ccc(O)cc2)C(=O)N[C@@H](Cc2ccccc2)C(=O)N2CCC[C@@H]2C(=O)N1
180.	*Undefined*	CHEMBL3827768	C28H39N3O4	481.64	CC(C)(NC(=O)C(NC(=O)C(CCCc1ccccc1)CC(=O)NO)C(C)(C)C)c1ccccc1
181.	*Undefined*	CHEMBL2414997	C31H42N6O6	594.71	CC(C)[C@H](NC(=O)[C@H](C)N)C(=O)N1CCC[C@H]1C(=O)N[C@@H](Cc1ccccc1)C(=O)N[C@@

					H](Cc1ccc(O)cc1)C(N)=O
182.	*Undefined*	CHEMBL2048248	C32H35N5O5	569.66	N[C@@H](Cc1ccc(O)cc1)C(=O)N1C[C@@H]2C[C@H]1C(=O)N[C@@H](Cc1ccccc1)C(=O)N[C@@H](Cc1ccccc1)C(=O)N2
183.	*Undefined*	CHEMBL2414998	C32H44N6O6	608.74	CN[C@@H](C)C(=O)N[C@H](C(=O)N1CCC[C@H]1C(=O)N[C@@H](Cc1ccccc1)C(=O)N[C@@H](Cc1ccc(O)cc1)C(N)=O)C(C)C
184.	*Undefined*	CHEMBL242089	C29H39N5O5	537.66	CC(C)C[C@H](NC(=O)[C@@H]1CCCN1C(=O)[C@@H](N)Cc1ccc(O)cc1)C(=O)N[C@@H](Cc1ccccc1)C(N)=O
185.	*Undefined*	CHEMBL58178	C30H35N5O5	545.64	C[C@H](NC(=O)[C@@H](N)Cc1ccc(O)cc1)C(=O)N[C@@H](Cc1ccccc1)C(=O)N[C@@H](Cc1ccccc1)C(N)=O
186.	*Undefined*	CHEMBL505975	C34H41N5O5	599.73	CN(C)C(=O)[C@H](Cc1ccccc1)NC(=O)[C@H](Cc1ccccc1)NC(=O)[C@@H]1CCCN1C(=O)[C@@H](N)Cc1ccc(O)cc1
1187.	MORPHICEPTIN	CHEMBL362991	C28H35N5O5	521.62	NC(=O)[C@@H]1CCCN1C(=O)[C@H](Cc1ccccc1)NC(=O)[C@@H]1CCCN1C(=O)[C@@H](N)Cc1ccc(O)cc1
188.	*Undefined*	CHEMBL242974	C32H37N5O6	587.68	NC(=O)[C@H](Cc1ccccc1)NC(=O)[C@H](Cc1ccc(O)cc1)NC(=O)[C@@H]1CCCN1C(=O)[C@@H](N)Cc1ccc(O)cc1
189.	*Undefined*	CHEMBL2171847	C34H36F3N5O7	683.68	N[C@@H](Cc1ccc(O)cc1)C(=O)N1C[C@@H]2C[C@H]1C(=O)N[C@H](Cc1ccccc1)C(=O)N[C@@H](Cc1ccccc1)C(=O)N2.O=C(O)C(F)(F)F

190.	*Undefined*	CHEMBL2171846	C34H36F3N5O7	683.68	N[C@@H](Cc1ccc(O)cc1)C(=O)N1C[C@@H]2C[C@H]1C(=O)N[C@H](Cc1ccccc1)C(=O)N[C@H](Cc1ccccc1)C(=O)N2.O=C(O)C(F)(F)F
191.	*Undefined*	CHEMBL33418	C27H35N3O4	465.59	C=CC[C@](C)(C(=O)NO)[C@@H](CC(C)C)C(=O)N[C@@H](Cc1ccccc1)C(=O)Nc1ccccc1
192.	*Undefined*	CHEMBL365984	C32H37N5O5	571.68	NC(=O)[C@H](Cc1ccccc1)NC(=O)[C@H](Cc1ccccc1)NC(=O)[C@H]1CCCN1C(=O)[C@@H](N)Cc1ccc(O)cc1
193.	*Undefined*	CHEMBL242984	C29H39N5O5	537.66	CC(C)C[C@H](NC(=O)[C@H](Cc1ccccc1)NC(=O)[C@@H]1CCCN1C(=O)[C@@H](N)Cc1ccc(O)cc1)C(N)=O
194.	*Undefined*	CHEMBL317264	C30H35N5O5	545.64	C[C@@H](NC(=O)[C@@H](N)Cc1ccc(O)cc1)C(=O)N[C@@H](Cc1ccccc1)C(=O)N[C@@H](Cc1ccccc1)C(N)=O
195.	*Undefined*	CHEMBL423794	C33H39N5O5	585.71	C[C@H](c1ccccc1)[C@H](NC(=O)[C@@H]1CCCN1C(=O)[C@@H](N)Cc1ccc(O)cc1)C(=O)N[C@@H](Cc1ccccc1)C(N)=O
196.	*Undefined*	CHEMBL154551	C27H37N3O4	467.61	C[C@@H](NC(=O)[C@@H](NC(=O)[C@H](CCCc1ccccc1)CC(=O)NO)C(C)(C)C)c1ccccc1
197.	*Undefined*	CHEMBL355141	C33H39N5O5	585.71	C[C@H](c1ccccc1)[C@@H](NC(=O)[C@H](Cc1ccccc1)NC(=O)[C@@H]1CCCN1C(=O)[C@@H](N)Cc1ccc(O)cc1)C(N)=O
198.	*Undefined*	CHEMBL390914	C28H37N5O5	523.63	CC(C)[C@H](NC(=O)[C@H](Cc1ccccc1)NC(=O)[C@@H]1CCCN1C(=O)[C@@H](N)Cc1ccc(O)cc1)C

					(N)=O
199.	*Undefined*	CHEMBL3828459	C28H39N3O4	481.64	CCC(NC(=O)C(NC(=O)C(CCCc1ccccc1)CC(=O)NO)C(C)(C)C)c1ccccc1
200.	*Undefined*	CHEMBL242981	C32H37N5O6	587.68	NC(=O)[C@H](Cc1ccc(O)cc1)NC(=O)[C@H](Cc1ccccc1)NC(=O)[C@@H]1CCCN1C(=O)[C@@H](N)Cc1ccc(O)cc1

Table 01: LIST OF INHIBITORS RETRIEVED FROM CHEMBL DATABASE:

VIRTUAL SCREENING:

A computerized technique, "virtual screening" is used during drug discovery process to find out the affinity of different chemical compound libraries to proteins or enzymes in order to bind with the target. To assess or rate the binding affinities of the compounds, each of them gets docked into a 3D structure of the main target. Second is the prioritization "hits" with the highest score for velocity and experimentation. Virtual screening is built on two approaches, i.e. structure-based screening (target structure is used) and ligand based screening (known active chemicals are used).

ADME & Ro5 Screening:

ADME testing is the examination of the absorption, distribution, metabolism, and excretion properties of the drug candidate. As it can generate estimates of drug absorption and toxicity for a certain chemical compound, it plays a central role in the discovery and development of new medications. In ADME screening, various tests that include in vitro and in silico techniques are used to determine a compound's tissue distribution, cell membrane absorption, enzyme metabolism, and excretion routes. These studies help in choosing drugs that have the best pharmacokinetic characteristics and also lower the probability of negative side effects. The productivity and accuracy of the ADME screening stage are of paramount importance to pharmaceutical programs (Wenlock et al. 2003).

The Lipinski Rule of 5 is a widely used screening method in drug discovery that assesses a compound's potential oral bioavailability. Christopher Lipinski developed the rule, which offers a set of guidelines based on four physicochemical characteristics: molecular weight, lipophilicity (logP), hydrogen bond donors, and hydrogen bond acceptors. The Lipinski Rule of 5 states that for a chemical to have sufficient oral bioavailability, it must have a molecular weight of less than 500 Daltons, a log value of no more than 5, no more than five hydrogen bond donors, and no more than 10 hydrogen bond acceptors. During the initial stages of drug discovery and optimisation, the Lipinski Rule of 5 screening is a valuable method that can be employed to identify compounds with promising drug-like characteristics. (Lipinski et al., 2001)

All ligands' 3D structures were retrieved in PDB format from Corina software in preparation for the RO5 screening. A ligand can be screened using the Lipinski rule of five (RO5), which has certain requirements. These include the ligand's molecular weight being less than 500, its Clog P value being less than 5, the number of hydrogen bond donors being less than 5, and the number of hydrogen bond acceptors being less than 10. The RO5 tool was used for this screening. 230 ligands were selected for docking with the ACE2 receptor, protease protein, and spike protein following screening using RO5

Chembl ID	LIPINSKI RULE OF 5	ADMET
1-CHEMBL295392	YES	yes
2-CHEMBL299812	YES	yes
3-CHEMBL3828219	YES	yes
4-CHEMBL20092002	NO	no
5-CHEMBL296142	yes	yes
6- CHEMBL417537	No	NO
7-CHEMBL293003	Yes	Yes
8- CHEMBL302227	Yes	Yes
9- CHEMBL207756	yes	Yes
10- CHEMBL62007	Yes	Yes
11-CHEMBL45631	yes	No
12- CHEMBL46030	Yes	Yes
13-CHEMBL88520	Yes	No
14-CHEMBL49833	yes	Yes
15- CHEMBL85766	Yes	No
16- CHEMBL48226	Yes	No
17- CHEMBL433479	Yes	Yes
18- CHEMBL11306	Yes	Yes
19- CHEMBL419751	yes	No
20- CHEMBL126122	yes	Yes
21- CHEMBL99103	yes	No
22- CHEMBL86797	yes	No
23- CHEMBL98770	No	No
24- CHEMBL418292	Yes	Yes
25- CHEMBL64013	Yes	Yes
26- CHEMBL1790586	No	No
27- CHEMBL99283	No	No
28- CHEMBL123571	Yes	Yes
29- CHEMBL32839	Yes	Yes
30- CHEMBL318860	No	No
31- CHEMBL32730	No	Yes
32- CHEMBL124623	yes	Yes
33- CHEMBL313356	Yes	No
34- CHEMBL286295	Yes	Yes
35- CHEMBL452083	Yes	Yes
36- CHEMBL295257	Yes	Yes
37- CHEMBL318005	no	No
38- CHEMBL410259	Yes	Yes
39- CHEMBL418291	No	no
40- CHEMBL303298	yes	Yes
41- CHEMBL66134	yes	No

42- CHEMBL1790599	No	No
43- CHEMBL99120	No	No
44- CHEMBL35602	Yes	Yes
45- CHEMBL35348	yes	Yes
46- CHEMBL1790587	No	No
47- CHEMBL1790596	No	No
48- CHEMBL433381	Yes	Yes
49- CHEMBL289003	Yes	Yes
50- CHEMBL432079	yes	Yes
51- CHEMBL430838	Yes	No
52- CHEMBL95718	No	No
53- CHEMBL4544135	yes	No
54- CHEMBL328090	yes	Yes
55- CHEMBL327892	yes	Yes
56- CHEMBL438964	Yes	No
57- CHEMBL304243	no	No
58- CHEMBL439330	yes	No
59- CHEMBL284465	yes	Yes
60- CHEMBL3827627	yes	yes
61- CHEMBL2372819	no	No
62- CHEMBL382705	yes	Yes
63- CHEMBL66532	no	No
64- CHEMBL3099019	yes	yes
65- CHEMBL279078	yes	Yes
66- CHEMBL405102	no	No
67- CHEMBL99547	no	No
68- CHEMBL2048512	yes	Yes
69- CHEMBL3828455	yes	Yes
70- CHEMBL3828521	yes	No
71- CHEMBL252246	yes	Yes
72- CHEMBL326022	Yes	No
73- CHEMBL222830	no	No
74- CHEMBL2372817	no	No
75- CHEMBL92954	yes	Yes
76- CHEMBL208181	no	No
77- CHEMBL452372	no	No
78- CHEMBL214869	yes	Yes
79- CHEMBL146896	yes	No
80- CHEMBL338502	yes	Yes
81-CHEMBL107580	no	No
82- CHEMBL3827566	yes	Yes

83- CHEMBL338231	yes	No
84- CHEMBL72511	yes	No
85- CHEMBL144049	yes	Yes
86-CHEMBL4161163	yes	No
87- CHEMBL221698	yes	Yes
88- CHEMBL2372200	no	No
89- CHEMBL221537	yes	Yes
90- CHEMBL156033	yes	Yes
91- CHEMBL1927270	no	No
92- CHEMBL3143518	no	No
93- CHEMBL2372196	no	No
94- CHEMBL2372207	no	No
95- CHEMBL104838	no	No
96- CHEMBL1774020	yes	yes
97- CHEMBL3355779	no	No
98- CHEMBL438833	no	No
99- CHEMBL223552	no	No
100- CHEMBL263021	no	No
101- CHEMBL242979	no	No
102-CHEMBL3355778	no	No
103- CHEMBL4169083	yes	Yes
104- CHEMBL325810	yes	No
105- CHEMBL359424	yes	No
106- CHEMBL4467160	no	No
107- CHEMBL3143520	no	No
108- CHEMBL4085033	no	No
109- CHEMBL329232	no	No
110- CHEMBL94165	yes	No
111- CHEMBL2372201	no	No
112- CHEMBL99318	no	No
113- CHEMBL164062	no	No
114- CHEMBL274012	no	No
115- CHEMBL4074931	no	No
116- CHEMBL2372203	no	No
117- CHEMBL500212	no	No
118-CHEMBL53621	yes	No
119- CHEMBL157091	yes	No
120- CHEMBL4083221	no	No
121- CHEMBL3765059	no	No
122- CHEMBL387816	no	No
123- CHEMBL286698	yes	No

124- CHEMBL563719	no	No
125- CHEMBL243200	no	No
126- CHEMBL4095366	no	No
127- CHEMBL105568	no	No
128- CHEMBL3828338	yes	Yes
129- CHEMBL458592	yes	No
130- CHEMBL440124	no	No
131- CHEMBL2371264	no	No
132- CHEMBL15100	no	No
133- CHEMBL1405007	yes	No
134- CHEMBL98304	no	No
135- CHEMBL3794343	no	No
136- CHEMBL360194	no	No
137- CHEMBL2370207	no	No
138- CHEMBL65493	yes	Yes
139- CHEMBL2371340	yes	No
140- CHEMBL3326665	no	No
141- CHEMBL290737	yes	No
142- CHEMBL388265	no	No
143- CHEMBL372682	no	No
144- CHEMBL66039	no	No
145- CHEMBL349816	no	No
146- CHEMBL2371339	no	No
147- CHEMBL63972	No	No
148- CHEMBL4475712	no	No
149- CHEMBL3236076	yes	yes
150- CHEMBL2371336	no	No
151- CHEMBL219104	yes	Yes
152- CHEMBL323024	no	No
153- CHEMBL280264	no	No
154- CHEMBL278891	no	No
155- CHEMBL242087	no	No
156- CHEMBL283287	no	No
157- CHEMBL355367	no	No
158- CHEMBL59641	yes	No
159- CHEMBL2332717	no	No
160- CHEMBL3794574	no	No
161- CHEMBL2371359	no	No
162- CHEMBL3621348	yes	No
163- CHEMBL447871	yes	No
164- CHEMBL423466	no	No

165- CHEMBL3103451	yes	Yes
166- CHEMBL2372834	no	No
167- CHEMBL416641	yes	No
168- CHEMBL526496	no	No
169- CHEMBL166108	no	No
170- CHEMBL1253633	nos	No
171- CHEMBL1927272	no	No
172- CHEMBL267708	no	No
173- CHEMBL3827377	yes	No
174- CHEMBL333357	no	No
175- CHEMBL2370620	no	No
176- CHEMBL455743	no	No
177- CHEMBL2370199	no	No
178- CHEMBL275670	no	No
179- CHEMBL1927274	no	No
180- CHEMBL3827768	yes	No
181- CHEMBL2414997	no	No
182- CHEMBL2048248	no	No
183- CHEMBL2414998	no	No
184- CHEMBL242089	no	No
185- CHEMBL58178	no	No
186- CHEMBL505975	no	No
187- CHEMBL362991	no	No
188- CHEMBL242974	no	No
189- CHEMBL2171847	no	No
190- CHEMBL2171846	no	No
191- CHEMBL33418	yes	No
192- CHEMBL365984	no	No
193- CHEMBL242984	no	No
194- CHEMBL317264	no	No
195- CHEMBL423794	no	No
196- CHEMBL154551	yes	No
197- CHEMBL355141	no	No
198- CHEMBL390914	no	No
199- CHEMBL3828459	yes	No
200- CHEMBL242981	no	No

Table 02 : ADMET & Ro5 SCREENED LIGANDS

Molecular Docking:

Molecular docking is a well-liked computer technique for forecasting and examining the affinity and binding mechanism of tiny molecules (ligands) to target proteins or macromolecular structures. It is applied in drug discovery and structural biology. It involves determining the energetics of the ligand as

well as its spatial arrangement within the protein binding site. Molecular docking is a crucial technique in the search for novel therapeutic opportunities because of its capacity to measure binding affinities, quantify the intensity of ligand-protein interactions, and evaluate binding poses. Molecular docking provides insights into the structural basis of ligand-receptor interactions, which helps with the creation and optimisation of new therapeutic drugs. (Trott and others, 2010)

Multiple molecule docking was carried out using a variety of docking software and sites, and the binding energy (Kcal/Mol) of the different software was compared. Using molecular docking with ARGUS LAB, CB-DOCK, and AUTODOCK, the lowest binding energy of the ligand interacting with the protein was found.

CB-Docking:

Ten spike protein ligands, ten protease protein ligands, and ten ACE2 receptor ligands were used for CB-DOCK docking. It's an internet docking platform. Online docking, also known as web-based docking, allows molecular docking investigations to be conducted remotely through a computer interface. It provides researchers with docking tools and resources without forcing them to install specialised software or perform time-consuming computations locally. Online docking platforms provide user-friendly interfaces that facilitate the setup of docking studies, submission of protein and ligand structures, and display of docking results. In order to predict the ligand and receptor binding affinities and modalities, these platforms often employ robust docking algorithms and scoring systems. Online docking systems offer greater user base accessibility, ease of use, and speed for collaborative research and drug development projects. Kim and colleagues, 2020).

S.No.	Ligand ID	CB-Dock Binding Energy (Kcal/mol)
1.	CHEMBL296142	-6.1
2.	CHEMBL293003	-5.6
3.	CHEMBL302227	-5.4
4.	CHEMBL207756	-6.6
5.	CHEMBL62007	-5.4
6.	CHEMBL46030	-6.7
7.	CHEMBL49833	-6.8
8.	CHEMBL433479	-6.6
9.	CHEMBL11306	-5.7
10.	CHEMBL126122	-5.9
11.	CHEMBL64013	-6.6
12.	CHEMBL32839	-5.9
13.	CHEMBL124623	-6.3
14.	CHEMBL286295	-5.3
15.	CHEMBL452083	-5.7
16.	CHEMBL410259	-6.5
17.	CHEMBL303298	-5.6
18.	CHEMBL35602	-6.1

19.	CHEMBL35348	-5.7
20.	CHEMBL433381	-6.5
21.	CHEMBL289003	-5.3
22.	CHEMBL432079	-5.7
23.	CHEMBL328090	-5.8
24.	CHEMBL327892	-6.1
25.	CHEMBL284465	-6.2
26.	CHEMBL3827627	-6.8
27.	CHEMBL382705	-6.2
28.	CHEMBL3099019	-6.2
29.	CHEMBL279078	-6.9
30.	CHEMBL2048512	-6.7
31.	CHEMBL3828455	-6.7
32.	CHEMBL252246	-6.9
33.	CHEMBL92954	-5.9
34.	CHEMBL214869	-6.8
35.	CHEMBL338502	-5.7
36.	CHEMBL3827566	-6.6
37.	CHEMBL144049	-6.4
38.	CHEMBL221698	-6.6
39.	CHEMBL221537	-6.1
40.	CHEMBL156033	5.5
41.	CHEMBL1774020	-6.5
42.	CHEMBL4169083	-6.7
43.	CHEMBL3828338	-6.6
44.	CHEMBL65493	-6.5
45.	CHEMBL3236076	-5.9
46.	CHEMBL219104	-6.9
47.	CHEMBL3103451	-6.4

Table 03: Docking values of top analogs via CB Dock

Argus Lab Docking:

Docking is made easier through a methodical procedure by the molecular modelling and drug design programme Argus Lab. The first step involves starting the software and loading the receptor and ligand structures in the relevant file formats. Optimise the structure of the receptor, make necessary adjustments to its protonation states, and fix any problems. In the same way, add hydrogen atoms to improve the ligand structure. Specify the search space and scoring functions for the docking parameters. To enable Argus Lab to investigate possible binding modes, start the docking calculation. Examine the data, finding interactions and binding locations. Analyse results with molecular graphics and adjust parameters as necessary to ensure accuracy. Create reports that summarise the top binding poses and scores after saving the results.In a thorough docking research, Argus Lab was used to dock 18 ligands that were found through target-based screening with the resuscitation-promoting factor B. Six ligands

showed a score higher than -10 kcal/mol, while the highest Argus Lab score recorded was -11.56 kcal/mol. This thorough approach helps with drug development and design by offering insightful information about possible interactions between the ligands and the resuscitation-promoting factor B protein.

S.No.	Ligand ID	Argus Lab Binding Energy (Kcal/mol)
1.	CHEMBL207756	-8.503
2.	CHEMBL46030	-10.168
3.	CHEMBL49833	-10.099
4.	CHEMBL433479	-9.720
5.	CHEMBL64013	-9.370
6.	CHEMBL410259	-9.761
7.	CHEMBL433381	-8.414
8.	CHEMBL3827627	-11.563
9.	CHEMBL279078	-9.758
10.	CHEMBL2048512	-10.122
11.	CHEMBL3828455	-10.462
12.	CHEMBL252246	-8.701
13.	CHEMBL214869	-8.500
14.	CHEMBL3827566	-11.375
15.	CHEMBL221698	-8.520
16.	CHEMBL4169083	-8.644
17.	CHEMBL3828338	-8.449
18.	CHEMBL219104	-8.314

Table 04: Docking values of top analogs via Argus Lab

AutoDock docking 4.0:

AutoDock is a well-liked software programme for virtual screening and molecular docking in the drug development industry. The Scripps Research Institute's AutoDock programme allows scientists to predict the binding sites of ligands, or tiny molecules, to specific proteins. It uses a scoring system based on energy estimates to evaluate and rank different ligand conformations at the protein binding site. AutoDock offers several functions for the ligand and receptor generation, parameterization, and docking result display. It has been successfully applied in several research to understand the interactions between ligands and proteins and to assist find potential drug candidates. (2009) Morris et al.

Docking with AUTODOCK was done with 6 Ligands of RpfB Protein

S. NO.	Ligand ID	AUTODOCK BINDING ENERGY
1.	CHEMBL46030	-7.38
2.	CHEMBL49833	-7.42
3.	CHEMBL3827627	-5.91
4.	CHEMBL2048512	-6.54

5.	CHEMBL3828455	-6.25
6.	CHEMBL3827566	-6.70

Table 05: Docking values of top analogs via Autodock 4.0

S. NO.	LIGAND ID	CB DOCK	ARGUS LAB	AUTODOCK
1.	CHEMBL46030	-6.7	-10.16	-7.38
2.	CHEMBL49833	-6.8	-10.09	-7.42
3.	CHEMBL3827627	-6.8	-11.56	-5.91
4.	CHEMBL2048512	-6.7	-10.12	-6.54
5.	CHEMBL3828455	-6.9	-10.46	-6.25
6.	CHEMBL3827566	-6.6	-11.37	-6.70

Table 00 : - DOCKING ANALYSIS OF RpfB PROTEIN

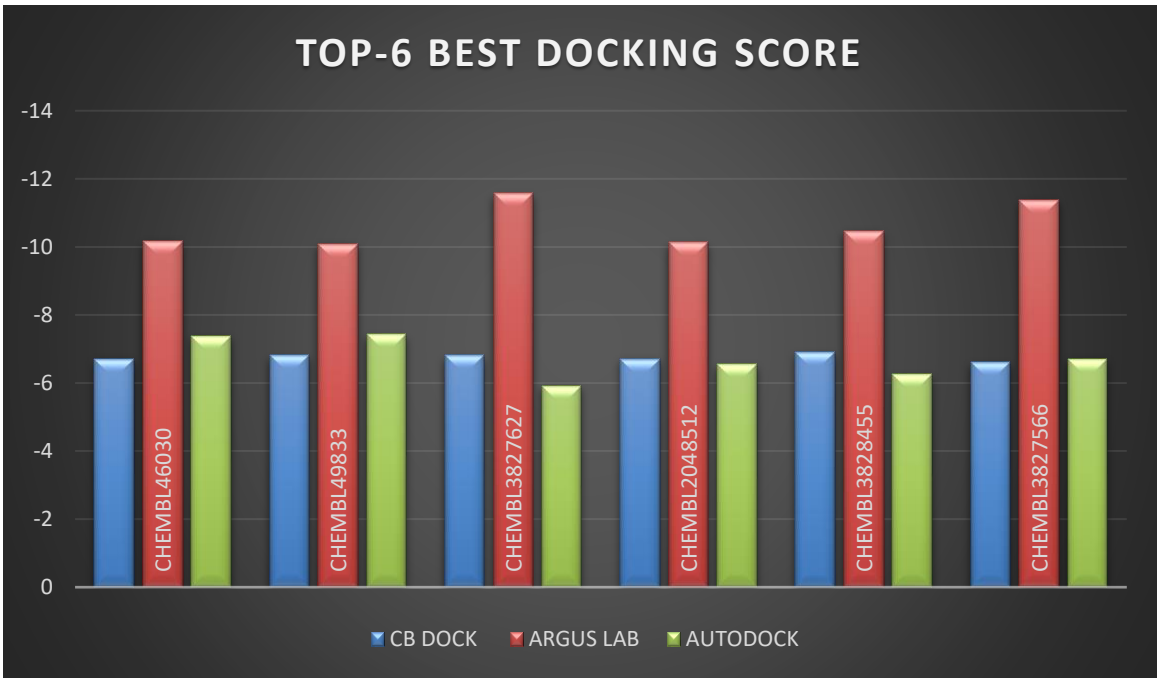

Fig 02: Inhibitors with binding affinity if RpfB Protein

RpfB Protein:

Following the conclusion of the docking study by Argus Lab, ligands surpassing the energy binding score threshold of >= -10 kcal/mol were chosen using a selective filtering procedure. After careful screening, six ligands were found to be part of a subset. These ligands were then the focus of more docking investigations with AutoDock 4.0. The aim of this phase was to refine the selection on the basis of superior binding energy scores, and all six of the top ligands showed remarkable scores that exceeded -11.0 kcal/mol.

CB-Dock-2 with top 48 ligands:

Further molecular docking studies were carried out using CB-Dock 2 after the Auto Dock 4.0 analyses. These studies focused on three important proteins associated with RpfB protein, the protease protein. CB-Dock 2 methodically investigated the binding interactions of the previously identified top 48 ligands

exhibiting highest binding scores with these proteins. The thorough investigation sought to shed light on the possible ligand-inhibitory effects on important viral proteins, such as the ACE2 receptor involved in host cell recognition, the protease protein necessary for viral replication, and the RofB protein in charge of host cell entry.

3D Structure Retrieval, Preparation, and Energy Minimization of RpfB Protein:

1. RpfB Protein:

Among the many diverse roles that protein RpfB plays in bacteria, its primary function is cell-level regulation in some gram-positive bacteria, including Streptomyces and Mycobacterium. The RpfB protein has the following important properties:The RpfB protein has the following important properties:The function of RpfB is to create fatty acyl-CoA derivatives, which are signalling molecules that aid in the transmission of genetic information. RpfB is a transferase enzyme. Function in quorum sensing: Fatty acyl-CoA derivatives produced by the bacterial protein RpfB are involved in quorum sensing, a cell-to-cell communication mechanism that allows bacteria to control their behaviour in a given environment depending on population density. Control of cellular processes: A crucial element of control is the quorum sensing system, which is transmitted by RpfB mechanisms that regulate the creation of antibiotics, the differentiation of a species of bacteria's morphology, and the expression of virulence factors

The significance of RpfB in Streptomyces lies in its involvement in the manufacturing of antibiotics as well as the generation of aerial hyphae, a component of spores involved in the development process. Streptomyces species are members of the well-known group of bacteria that create antibiotics. Significance in Mycobacterium: RpfB regulates cell dormancy in Mycobacterium genomes, which includes Mycobacterium TB for tuberculosis. This helps the bacteria survive and become more virulent when they reactivate.

Microbiology, antibiotic compounding, and a class of pharmaceuticals meant for use as a treatment against bacterial infections are all heavily focused on the study of RpfB.

Target based virtual screening:

The RpfB protein in Mycobacterium tuberculosis, its structure, and its potential as a therapeutic target are all covered in the search results. One resuscitation-promoting component that aids in the resuscitation of latent mycobacteria is the RpfB protein. The RpfB protein's crystal structure has been established, and research has been done on the molecules that cause inactivation. It has been demonstrated that Mycobacterium tuberculosis expresses the RpfB protein differently in host tissues, indicating the protein's significance in the pathophysiology of tuberculosis.

In terms of drug development, research has been done to find RpfB inhibitors in Gymnema sylvestre natural compounds. Potential RpfB inhibitors were found by the study using a computer-aided identification method that included molecular docking. Results indicated that Gymnema sylvestre benzamidine compounds exhibited strong binding affinity to the RpfB protein, suggesting their potential as RpfB inhibitors

Another study used a computational method to examine how naturally occurring chemicals produced from microbes inhibit RpfB.

Many natural substances that shown possible inhibitory activity against RpfB were found in the study, indicating that these substances could serve as lead compounds for the creation of novel anti-tuberculosis medications.

In conclusion, natural compounds obtained from Gymnema sylvestre and microbiologically produced natural compounds have demonstrated potential as RpfB inhibitors. The RpfB protein in Mycobacterium tuberculosis represents a prospective target for drugs. To confirm the effectiveness and safety of these chemicals as anti-tuberculosis medications, more research is required.

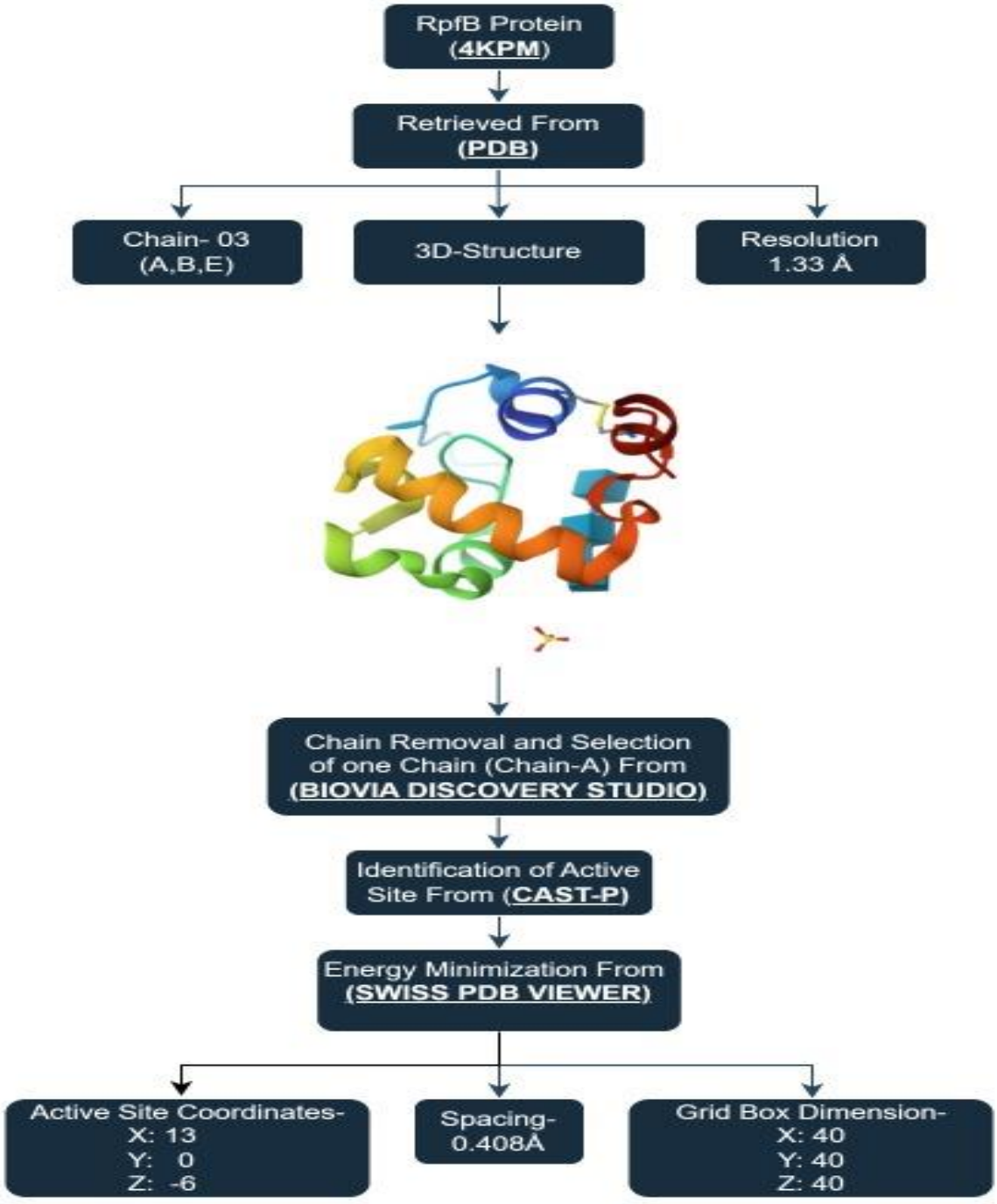

Fig. 03: Flow chart of RpfB Protein

Result & Discussion

Receptor based Screening Analysis Based on Targets

Following Swiss ADME studies on a ligand library comprising Pharmacophore, eighteen molecules demonstrated favorable ADME properties. Target-based screening (TBS) was used to select these

potential candidates based on their salient features, including optimal permeability of the blood-brain barrier (BBB) and optimal absorption of the human intestinal tract (HIA). Further analyses that emphasized the similarities between their medications included Lipinski's Rule of Five (RO5) and the Ghose, Veber, Egan, and Muegge factors.

This meticulous evaluation demonstrates the attempt to identify compounds with high ADME profiles, which raises the possibility that these compounds may be successfully converted into beneficial medicinal therapies.

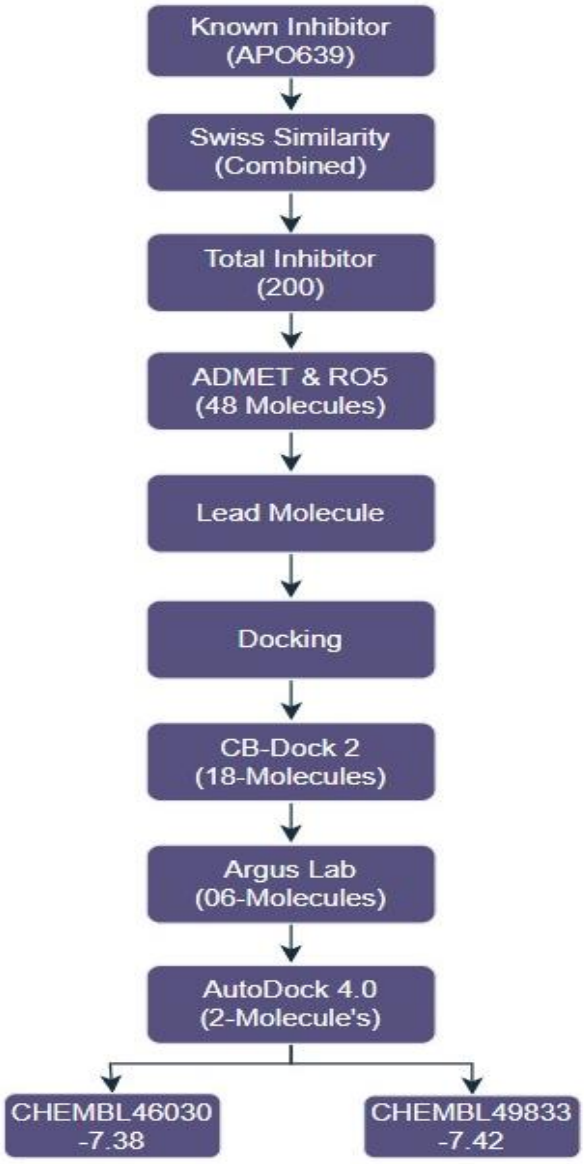

Fig 04: Flow chart of retrieving inhibitors of RpfB Protein

On the bases of CHEMBL1774020:

On the bases of boiled egg the analog CCHEMBL1774020 is found to have the most desirable values and properties and through Swiss similarity searching the top 15 molecules are identified to be the most similar those analogs are docked via autodock and the two best analogs are taken into consideration and after checking the biological activity of both the analogs the analog CHEMBL1774007 is considered as the best candidate for pharmacophore modification. After the necessary modification are made the new

analog is docked and the resulting value is -8.12 this will be our novel inhibitor.

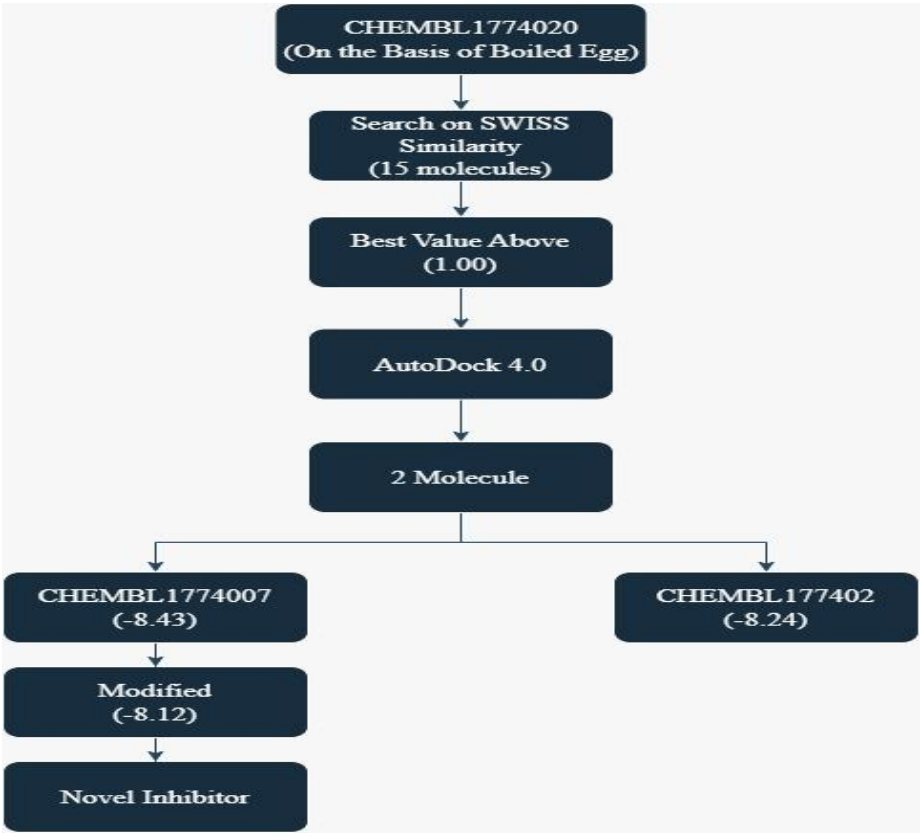

Fig. 05: Flow chart of inhibitors of CHEMBL1774020

The following are the complexes from the docking of the top analogs and modified analogs:

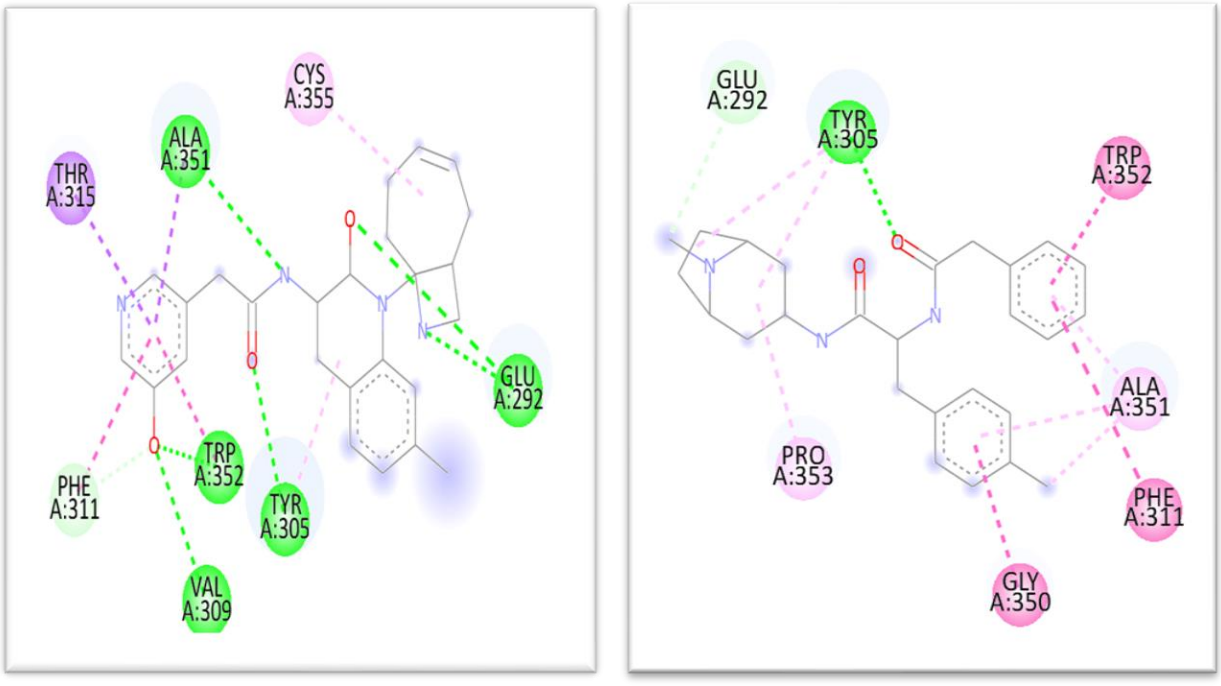

Fig 06 : 2D and 3D structure of best ligand(CHEMBL1774020)

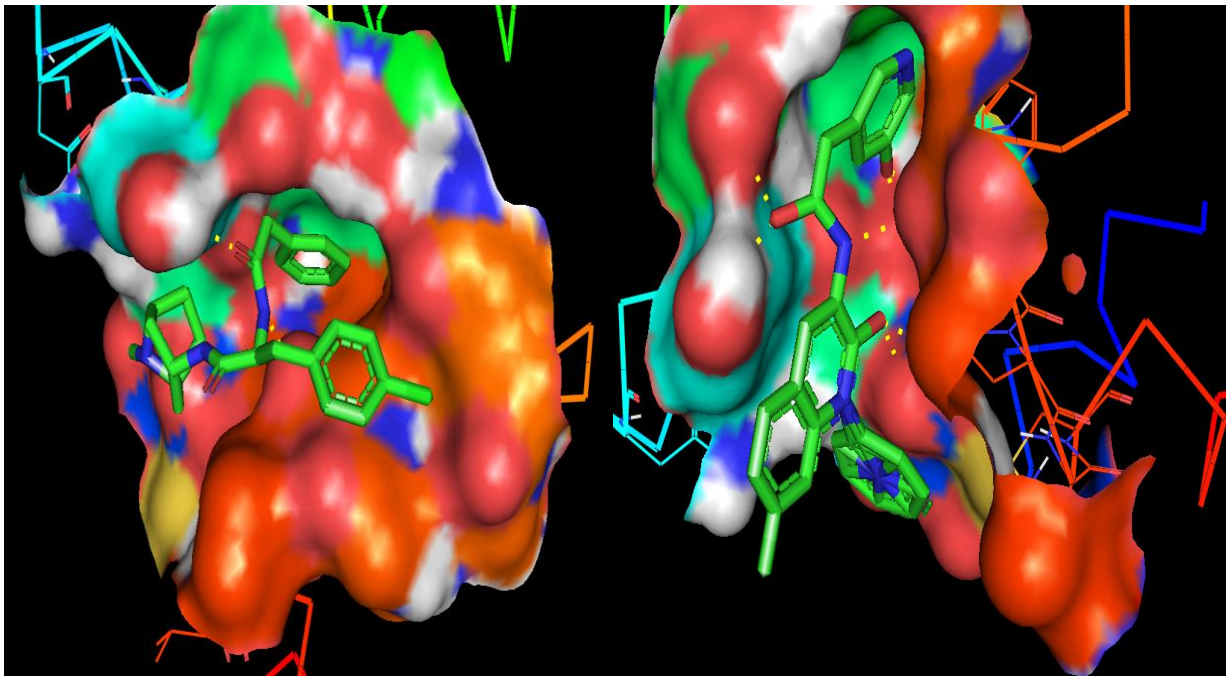

Fig 07: 2D and 3D structure of modified (CHEMBL1774020)

CONCLUSION

The analogue with the best delta G value was ultimately determined by all of the docking results, and since its pharmacophore kinetics analysis and RO5 analysis show that it has good biological properties, we can conclude that it is the best candidate to act as an inhibitor for the RpfB mutation.

From various screening methodologies and docking techniques we are able to deduce that the top analogs CHEMBL1774007 and CHEMBL1774020 are best candidates for being a possible hit then upon modification of said analogs we were able to further improve overall biological activity and essentially design a novel drug molecule that has desirable affinity toward the target protein and desirable biological activity as well however upon further analysis the best analog to inhibit the mutation of RpfB protein is CHEMBL1774020 since it has more favorable attributes which makes it the best potential hit molecule that combat against the mutation of RpfB protein.

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