

INHIBITORY EFFECT OF NATURAL COMPOUNDS ON SARS-COV-2 RNA-DEPENDENT RNA POLYMERASE THROUGH COMPUTER AIDED DRUG DESIGN

(Submitted in partial fulfillment of the requirements Under Bachelor of technology
degree in Biotechnology)

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APRIL – 2021



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BONAFIDE CERTIFICATE

This is to certify that this Project Report is the bonafide work of MERUVA PADMASRI (37230045) & ORIMPATI VENKATA SAITEJA (37230051) who carried out the project entitled **INHIBITORY EFFECT OF NATURAL COMPOUNDS ON SARS-COV-2 RNA-DEPENDENT RNA POLYMERASE THROUGH COMPUTER AIDED DRUG DESIGNS** under the supervision of DR. SABITHA.Y PhD, MANAGING DIRECTOR AT CIENCIA LIFE SCIENCE, Hyderabad from JANUARY 5TH TO MARCH 6ST

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DECLARATION

I MERUVA PADMASRI (37230045) hereby declare that the Project Report entitled **“INHIBITORY EFFECT OF NATURAL COMPOUNDS ON SARS-COV-2 RNA-DEPENDENT RNA POLYMERASE THROUGH COMPUTER AIDED DRUG DESIGN”** done by me under the guidance of Dr. PRABAVATHY (Internal) and Dr. Sabitha.Y (External), Managing director at ciencia life science, Hyderabad is submitted in partial fulfillment of the requirements for the award of Bachelor of Engineering in Biotechnology.

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ACKNOWLEDGEMENT

We are pleased to acknowledge our sincere thanks to Board of Management of SATHYABAMA for their kind encouragement in doing this project and for completing it successfully. I am grateful to them.

We convey our thanks to Dr.V. Ramesh Kumar PhD, Head of the Department, and Department of Biotechnology for providing me necessary support and details at the right time during the progressive reviews.

We would like to express our sincere and deep sense of gratitude to our Guide Dr. SABITHA.Y PhD, MANAGING DIRECTOR AT CIENCIA LIFE SCIENCE, HYDERABAD for his valuable guidance, suggestions and constant encouragement paved way for the successful completion of my project work.

A special thanks to our Year coordinator Dr. Renuga Devi PhD for her assistance in the preparation the intern report.

I wish to express my thanks to all Teaching and Non-teaching staff members of the Department of Biotechnology who were helpful in many ways for the completion of the project.

ABSTRACT

In October of 2019, the first case of severe acute respiratory syndrome corona virus 2, or SARS-CoV-2, had taken place in Wuhan, China. Since then, it instigated tens of millions of cases and claimed more than a million lives. As the world screeched to a halt due to the global lockdown, the race to a vaccine had started.

SARS-CoV-2 is a RNA virus that is positive-sense, single stranded, and sizeable, with their genome being one of the largest to date in the category of RNA viruses. Its symptoms vary but mainly include fatigue, cough, shortness of breath, and loss of taste and smell, with the severest being the development of acute respiratory distress syndrome, which can cause septic shock, multiple organ failure and blood clots. However, it can also spread through asymptomatic transmission where people do not show symptoms yet remain infected. The actual spread is caused by respiratory droplets or aerosols, when breathing, coughing, sneezing, and usually occurs when a person is in close proximity when an infected person.

Corona virus have an enzyme named RNA Dependent RNA polymerase which is a core protein, encoded into genomes of RNA viruses, that helps to catalyze the replication of RNA from an existing RNA template. There are many possible protein targets within the corona virus strands, most notably the spike, nucleocapsid, membrane, and envelope proteins but in this investigation, RdRp was taken as the target to limit the replication of the corona virus. Hence in this study we selected natural products and compounds derived from herbs to inhibit RNA dependent RNA polymerase and help in the treatment of SARS-CoV-2.

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LIST OF ABBREVIATIONS

SARS	Severe acute respiratory syndrome
CoV	Coronavirus disease
RdRp	RNA dependent RNA polymerase
MERS	Middle East respiratory syndrome

CHAPTER 1

Introduction

Over the previous twenty years, Covids (CoV's) have been related with critical sickness episodes in East Asia and the Middle East. The serious intense respiratory disorder (SARS) and the Middle East respiratory conditions (MERS) started to arise in 2002 and 2012, separately. As of now, a novel Covid, the extreme intense respiratory disorder Covid 2 (SARS-CoV-2), causing the Coronavirus Disease 2019 (COVID-19), has arisen in late 2019, which has represented a worldwide wellbeing danger with its progressing pandemic in numerous nations and regions (Rodriguez-Morales AJ et al,2019).

Wellbeing laborers overall are as of now putting forth attempts to control further illness episodes brought about by the novel CoV (initially named 2019-nCoV) that was first distinguished in Wuhan City, Hubei Province, China, on December twelfth, 2019. On February eleventh, 2020, the World Health Organization (WHO) reported the authority assignment for this momentum CoV-related infection to be "Coronavirus", brought about by the SARS-CoV-2. The essential bunch of patients was discovered to be associated with the Huanan South China Seafood Market in Wuhan (Gralinski LE and Menachery VD,2019). CoVs have a place with the family Coronaviridae (subfamily Coronavirinae), the individuals from which taint an expansive scope of hosts, delivering side effects and sicknesses going from a typical cold to extreme and at last lethal diseases like SARS, MERS, and, as of present, COVID-19. The SARS-CoV-2 is considered as one of the seven individuals from the CoV family that contaminate people (Zhang D et al,2020), and it has a place with the very heredity of CoVs that causes SARS; nonetheless, this novel infection is hereditarily particular. Until 2020, six CoVs were known to contaminate people incorporate HCoV-229E, HCoV-NL63, HCoV-OC43, HCoV-HKU1, SARS-CoV, and MERS-CoV. In spite of the fact that SARS-CoV and MERS-CoV have brought about flare-ups with high mortality, others remain related with gentle upper-respiratory lot diseases (Cui J et al,2

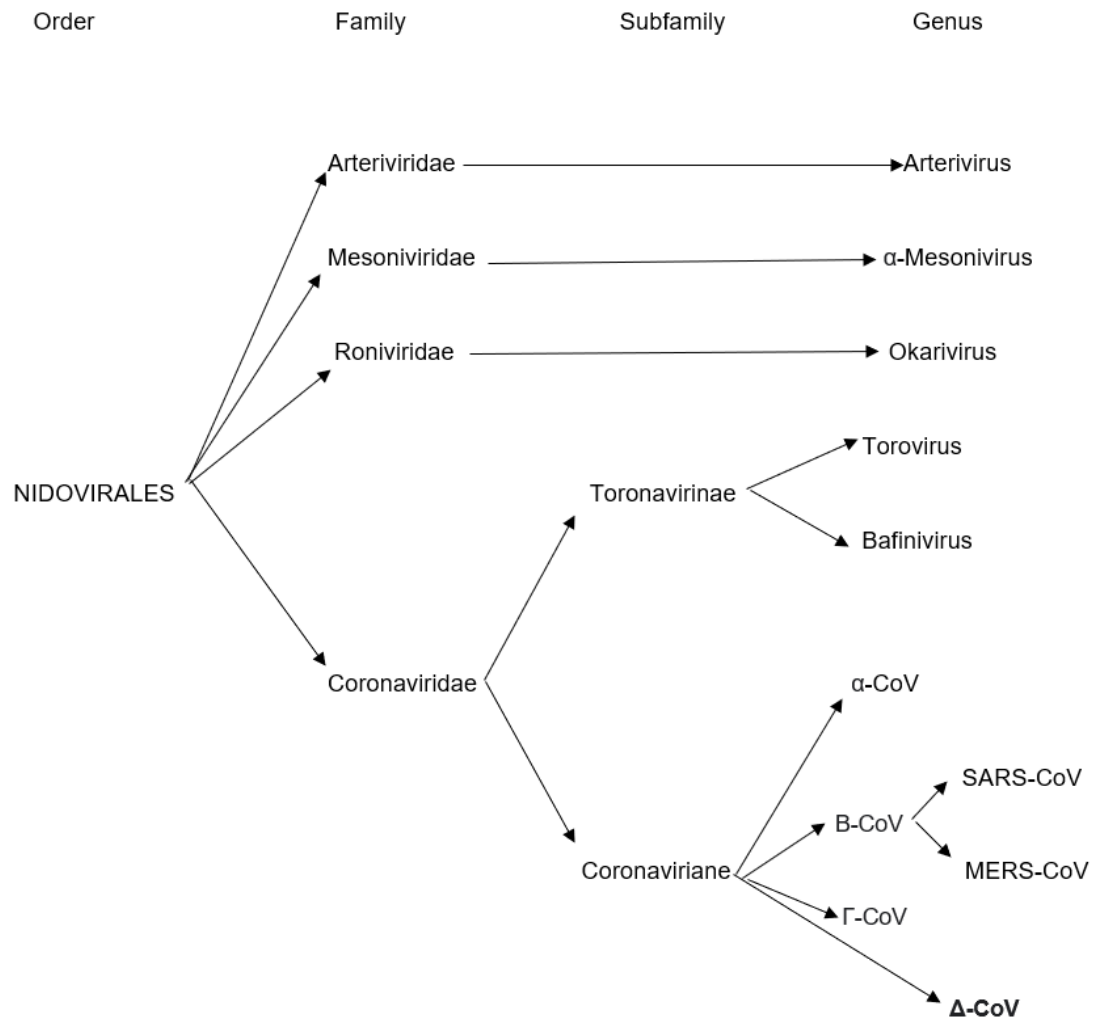


Figure: 1.1: Classification of coronaviruses.

Recently advanced CoVs are accordingly representing a critical danger to worldwide general wellbeing. In the course of recent many years, the current development of COVID-19 is the third CoV flare-up in people (Munster VJ et al,2020). It is no happenstance that Fan et al. anticipated potential SARS-or MERS-like CoV episodes in China following microorganism transmission from bats (Zhou P et al,2019). The COVID-19 that arose in China spread quickly all through the country and thusly to different nations. Because of the seriousness of this episode and the capability of spreading on a worldwide scale, the WHO announced a "worldwide wellbeing crisis"

on January 31st, 2020. Thusly, on March eleventh, 2020, a pandemic circumstance was announced. As of now, we are not in a situation to adequately treat COVID-19 since neither affirmed immunizations nor explicit antiviral medications for treating human CoV contaminations are accessible (Lu H,2020; Manickam Met al, 2020). Most countries are as of now putting forth attempts to forestall further spreading of this conceivably destructive infection by actualizing preventive and control procedures.

This Virus is exhibited as a respiratory problem and its brooding period is 2 to 14 days (Lauer et al., 2020). Its side effects are:

- Dry hack
- Fever
- Shortness of breath
- Runny nose
- Sore throat
- Muscle joint torments
- Diarrhea
- Loss of faculties like smell and taste at times.

The Covid is communicated and spread in the accompanying cases:

- Person getting in contact with the drops or discharges of somebody wheezing or hacking and glide down the respiratory lot.
- Physical contact with the infection through hands and taking it to the mouth.

1.1 RNA DEPENDENT RNA POLYMERASE ACTIVITY FOR SARS-CoV:

This polypeptide is autoproteolytically severed into four subunits, named nonstructural proteins (nsP) 1-4, which structure the replication complex. The nsP1 is the compound answerable for covering the viral mRNA and a layer related protein (Garvin et al. 2020). The nsP2 has RNA helicase, triphosphatase exercises and is an auto protease answerable for dividing the nonstructural polypeptide. The nsP4 is a RNA-subordinate,

RNA polymerase. The capacity of nsP3 stays obscure, notwithstanding, it is the solitary viral protein phosphorylated by obscure cell kinases. The nsP3 contains a full scale or X space that ties ADP-ribose and is exceptionally saved with homologues in rubella infection, hepatitis E infection and Corvids, including extreme intense respiratory condition (SARS) infection. Goran et al. (2020) comment the protease area of viral nsP2 protein severs the nsP1234 polyprotein replication complex into practical proteins.

During replication of SARS-CoV genome, the positive strand of RNA genome is interpreted into a less strand by the cleavage moderate nsP123 and nsP4. Cleavage between nsP2/3 causes a format iii change from negative strand to positive strand (Hozhabri et al. 2020). Albeit the nonstructural protein 2/3 is fundamental for RNA replication, its capacity in viral replication is as yet not surely knew. Here we report the precious stone design of infection antecedent type of nsP2/3 at 2.94Å goal. Joyce Kelly et al. (2020) comments the design of nsP2/3 protein comprises of four unmistakable spaces, which are the protease area, methyltransferase like space, large scale space and zinc restricting area. Shockingly, nsP3 contains a novel collapsing with a formerly uncharacterized zinc coordination site (Kousar et al. 2020). Furthermore, the cleavage site somewhere in the range of nsP2 and nsP3 is covered the two proteins and not open for proteolysis.

Besides, the circle interfacing the full scale and zinc-restricting areas connects with and causes a design move in the nsp2 protease space. Ju et al. (2020) noticed impressive contrasts between the pre-cleavage and post-cleavage types of nsp2/3. The design recommends that a conformational change in nsP2/3 is needed all together for the nsP2 protease to access the nsP2/3 cleavage site. The capacity of the MT like area in nsP2/3 protein is not notable. Kandeel et al. (2020) show the tertiary construction of the second space of Sindbis nsP2/3 has high comparability to the design of the VEEV nsP2 C-terminal space with a z-score of 26.7%. Both the nsP2/3 second space and the VEEV nsP2 C-terminal area are like the methyltransferase group of chemicals. Albeit the Sindbis nsP2/3 second space has a fundamentally the same as design to the

VEEVnsP2 area, the principle primary distinction is in the association between the β 2 sheet and β 3 sheet.

The RMSD between the Sindbis nsP2/3 MT like area and the VEEV nsP2 MT like space is 0.667. On account of the VEEV nsP2 area, it contains an additional short β sheet and α helix between the β 2 sheet and β 3 sheet. The MT like space in Sindbis nsP2/3 has a critical tertiary design which is like proteins having a place with the S-adenosyl-L-methionine (SAM)- subordinate methyltransferases superfamily (Lawrence et al. 2020). This family incorporates methyltransferases from a wide assortment of life forms, including RNA polymerase NS5 and the E. coli heat stun protein FtsJ RNA methyltransferase. Notwithstanding, S-adenosyl-L-methionine restricting site between Sindbis nsP2/3 MT like space and FtsJ methyltransferase area showed low similitude among singular buildup and the generally underlying arrangement was exceptionally poor in restricting site (Loureiro et al. 2020).

Additionally, this area has 13% grouping personality with the ribosomal RNA enormous subunit methyltransferase J, ribosomal RNA methyltransferase and the E. coli heat stun protein FtsJ RNA methyltransferase. In a past report of Luo et al. (2020), succession likeness between alphavirus nsP2 and 2'- O-methyltransferase (2'- O-MT) proposes that this space is enzymatically dormant. The basic center SAM-subordinate methyltransferase superfamily crease was portrayed as having seven abandoned β sheets and three helices on each side as sandwiched structure. The β sheets of seven strands are masterminded in the request 3-2-1-4-5-7-6 with antiparallel to different strands (Machitani et al. 2020). One of the α helix layers comprises of a solitary helix that is 5 buildups in length. The Sindbis nsP2/3 second area has a tertiary design like SAM subordinate methyltransferase structures (e.g., VEEV nsP2 C-terminal space, FtsJ, and RNA polymerase NS5). The entirety of the β strands between the nsP2 and FtsJ adjust well. Be that as it may, the spine arrangement, when contrast is poor.

The SAM substrate restricting destinations show no critical comparability to one another. In view of past underlying investigations of full-scale area in alphavirus, the center β sheet and the places of the α helices are all around saved inside the designs of large-scale areas (Mittal et al. 2020). Arrangement personality between 160 amino

corrosive deposits of the nsP3 large scale area and the CHIKV full scale space was exceptionally high with 57% character and z-score of 31. Clearly, the most firmly related designs to the nsP3 large scale space are the CHIKV and VEEV nsP3 large scale area just as the putative phosphatase of *Escherichia coli* full scale space. The RMSDs among the alphavirus full scale spaces are somewhere in the range of 0.8 and 1.1 Å for 160 amino acids. The Sindbis nsP3 full scale space had critical primary and utilitarian similitude to a putative poly protein of *E. coli*, center histone large scale H2A (Ogunyemi et al. 2020). The replication polyprotein of SARS-CoV large scale area just as other alphavirus full scale areas like CHIKV and VEEV large scale area

1.2 PHYTOCHEMICALS DRUG AGAINST NOVEL CORONAVIRUS:

Phytochemicals are synthetic mixtures that happen normally in plant sources. Phyto means plant, so phytochemicals mean chemicals found in plants and plant products, they are usually secondary metabolites. Plants are one of the medicinal therapeutic active compound sources that have been widely used as treatments for several diseases caused by microbe causes disease. Furthermore, purified natural products and traditional herbal medicines may guide the development of more effective substances based on their structure and desired activities. There are many plant bioactive substances cited to have activities as an antifungal, antibacterial, and antiviral. The naturally occurring compounds that have been recognized to have antiviral activity can be used as a starting point to identify probable bioactive substance candidates against SARS-CoV2. Molecular docking can be utilized to foresee how the receptor protein interfaces with bioactive mixtures (ligands). Several prior studies have been carried out to find bioactive substances of plants that have the potential to inhibit and/or to reduce viruses' proliferation. Recently researchers

demonstrated that nelfinavir (a selective inhibitor of HIV protease), by using molecular docking, is a drug candidate for the possible treatment of COVID-19 by inhibiting the main protease (Mpro). The accessible data on phytogetic mixtures or concentrates that may have restorative potential and show antiviral abilities to repress Covids, expecting to help in recommending a normally based medication for SARS-CoV-2. (Attia et al. 2020).

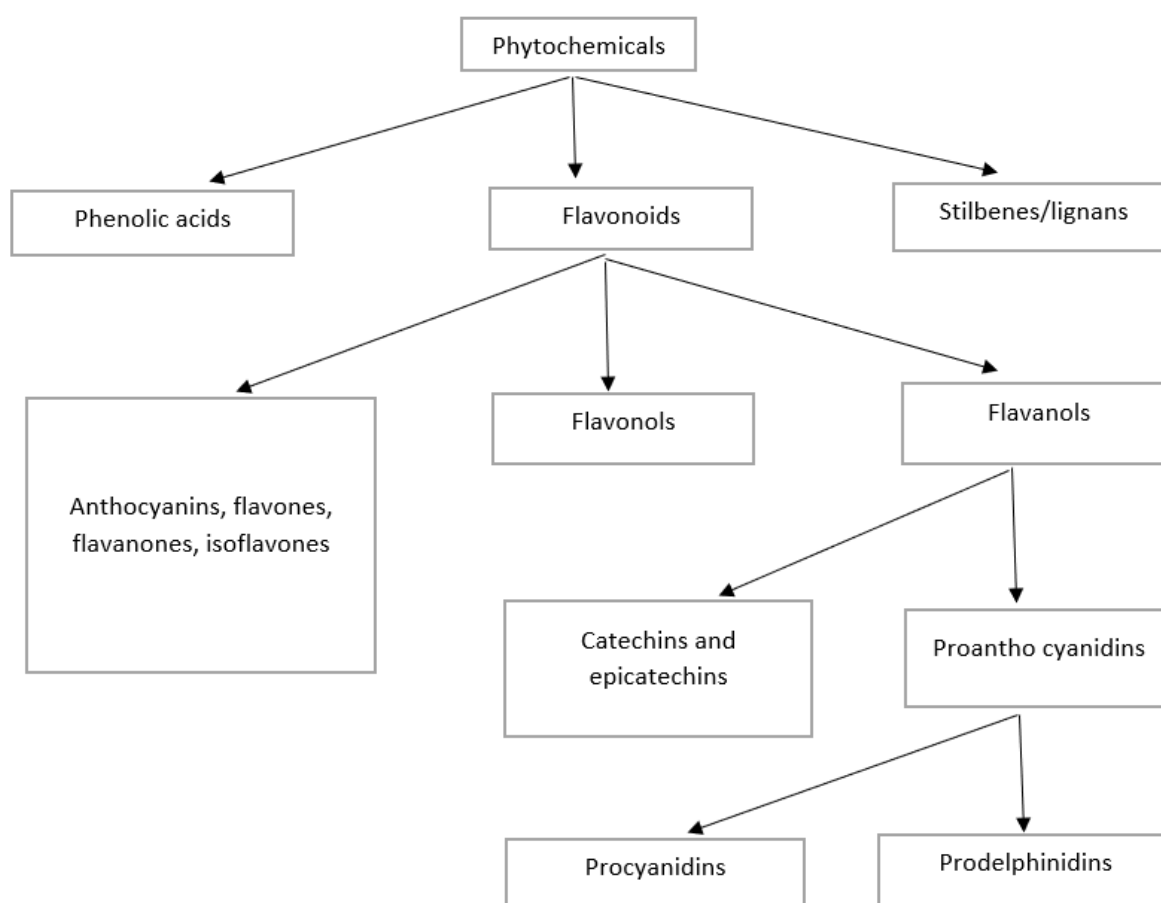


Figure:1.2: Classification of phytochemicals.

1.3 INSILICO ANALYSIS:

In science and other trial sciences, an insilico test is one performed on PC or by means of PC reenactment. The expression is pseudo-Latin for "in silicon", alluding to silicon in

central processors. It was instituted in 1987 as a mention to the Latin expressions *in vivo*, *in vitro*, and *in situ*, which are generally utilized in science (particularly frameworks science). The last expressions allude, individually, to tests done in living organic entities, outside living creatures, and where they are found in nature.

In silico concentrate in medication is thought to can possibly speed the pace of disclosure while diminishing the requirement for costly lab work and clinical preliminaries. One approach to accomplish this is by delivering and screening drug up-and-comers all the more adequately. In 2010, for instance, utilizing the protein mooring calculation EADock (see Protein-ligand mooring), specialists discovered possible inhibitors to a catalyst related with malignant growth action *in silico*. Half of the atoms were subsequently demonstrated to be dynamic inhibitors *in vitro*. This methodology varies from utilization of costly high-throughput screening (HTS) automated labs to actually test a large number of different accumulates a day regularly with a normal hit rate on the request for 1% or less with still less expected to be genuine leads following further test.

For instance, the method was used for a medication repurposing concentrate to look for expected remedies for COVID-19 (SARS-CoV-2)

In this way *in silico* examination decreases the expense and time on specific explores and clears profoundly successful and effective approach to parcel of medication planning and discovery. It likewise gives huge data to the researcher through the information base accessible and diminishes the time and cost for the medication disclosure measure.

1.4 MOLECULAR DOCKING:

The methodology of protein-ligand docking is inherited from earlier work in small molecule conformational sampling and macromolecular energy calculations [R. Pearlman,1993]. Calculating the accurate protein-ligand interactions is the key principle behind structure-based drug discovery [R. D. Cramer, D. E. Patterson et al,1988]. Predicting ligand conformation within the active site of a protein/receptor is termed as

molecular docking. In general, there are two key components of molecular docking [A. R. Leach, V. J. Gillet, 2003]:

- Accurate pose prediction or binding conformation of the ligand inside the binding site of the target protein.
- Accurate binding free energy prediction, which later is used to rank order the docking poses.

The docking algorithm usually carries out the first part of the docking (predicting binding conformation) and the scoring function associated with the docking program carries out the second part that is binding free energy calculations.

Pose prediction: Docking algorithm usually perform pose predictions. Identifying molecular features, which are responsible for molecular recognition or pose prediction are very complex and often difficult to understand and even more so, when simulated on a computer [H. Decornez, J. R. Furr et al, 2004].

The challenges and difficulties in the protein-ligand docking are mainly due to the involvement of many degrees of freedom

- Translational and rotational (in relation to each other) involves six degrees of freedom.
- Conformational degrees of freedom (Protein and ligand)

The challenge of various docking algorithms lies in sampling these translational, rotational and conformational degrees of freedom accurately and further finding the ligand conformation which best matches the receptor conformation. Furthermore, the sampling has to be quick enough to allow evaluating number of compounds in a given a docking experiment.

Activity prediction: After the pose prediction by the docking algorithm, the immediate step in the docking process is activity prediction, which is also termed as scoring. Docking score is achieved by the scoring functions associated with the particular docking software. Scoring functions are designed to calculate the biological activity by estimating the interactions between the compound and protein target. During the early stages of the docking experiments, scoring was performed based the simple shape and electrostatic complementarities. However, currently, the docking conformers are often treated with sophisticated scoring methods that include the Van der Waals interactions, electrostatic interactions, solvation effects and entropic effects [H.Gohlke,G. Klebe, 2002].

CHAPTER – 2

REVIEW OF LITERATURE

Coronavirus (CoVs) are basic human and creature microorganisms causing a scope of organ pathologies including respiratory, gastrointestinal, and cerebrum infections. The endemic CoV species record for 33% of gentle respiratory contaminations around the world can be developed by computer aided designs. Computer aided molecular docking studies the best fit of two or more molecular structures, such as drug, enzyme or protein. Docking is a computer aided design technique that predicts interaction between enzyme and its ligands. The phytochemicals influenced by ethnomedicinal information and in-vitro research promise a medicinal possibility for SARS-CoV.

T. Joshi et al, (2020) conducted virtual screening of phytochemicals, to find novel compounds that act against novel corona virus. So, he created a phytochemical library of 11 plants which have antiviral, antifungal, and antibacterial activity. These phytochemicals were subjected to virtual screening against molecular targets such as main protease (Mpro) and Angiotensin. from each target 10 compounds were that

had low binding energy when compared to reference molecule. Results obtained from this study suggest that Absinthin, Quercetin 3-glucuronide-7-glucoside and quercetin 3-vicianoside compounds act against corona virus according to binding energy score and these compounds can be used as antiviral drug.

Satyam Singh et al, (2020) collected plant derived polyphenols that plays a major role in maintaining immune homeostasis. These poly phenols act by inhibiting the RdRp of other viruses by docking in the catalytic pocket of RdRp. Investigation reveals that EGCG, theaflavin (TF1), (TF2a), (TF2b), TF3, hesperidin, quercetagenin, and myricetin bound strongly to the active site of RdRp. Results obtained from this study proved that EGCG, TF1, TF2a, TF2b, TF3 can inhibit RdRp and shows an effective the ray against covid-19.

Tok et al, (2017) has identified the classification and genome organization of coronaviruses and he describes the structure and function of these proteins in the replication and transcription mechanism from a more biophysical point of view by using molecular modeling methods. This information aid to understand the replication and transcription mechanism of the CoV.

Attia et al, (2020) has discovered the Virtual computer docking models have that been widely used by researcher to investigators to screen the inhibition activities for prospective phytochemical agents against several binding sites of coronaviruses, including S protein, RNA-dependent RNA polymerase, papain-like protease (PLpro), and 3CLpro. The antiviral potential of several substances such as sabadinine and aurantiamide acetate as these compounds could inhibit or bind to critical proteins found in SARS-CoV. Virtual screening docking will predict the hihibit of the antiviral agents against the coronavirus by using the computer aided drug design.

Prachi Singh et al, (2020) has worked on RdRp, as it serves as a classical target for the inhibition of coronavirus infection. He performed molecular docking of 69 different phytochemical compounds obtained from different herbs with RdRp. This work shows that phytochemical constituents obtained from *Withania somnifera* root extract, *Hyssopus officinalis* and *Camellia sinensis* leaf extract have greater binding capacity towards RdRp enzyme. These constituents' amino acid residue in NTP entry and to recognition site and also the metal ion cofactor chelating site of SARS-CoV-2. Results obtained from the study reveal the development of targeted therapy using phytochemical for treating covid-19 and other potential SARS coronaviruses.

Jiansheng et al, (2020) evaluated that Remdesivir and chloroquine has the ability to inhibit the replication of SARS-CoV-2. In addition to it, protease inhibitor such as camostat mesylate has been demonstrated to inhibit Calu-3 infection with SARS-CoV-2 and prevents the entry of SARS-2-spike protein into the lung cells. The study discusses about the viability and challenges in targeting RdRp and proteinase. By knowing the structural and functional relationship of S-protein of SARS-CoV-2 helps in inhibition of interaction between S-protein and ACE-2. Results reveal that helps in treating Covid-19 by targeting the RdRp.

Naun lobo-Galo et al, (2020) has searched for FDA approved drugs that can potentially inhibit essential viral enzymes. Disulfiram as well as its metabolites and captopril can be as antiviral drugs against covid-19. Though captopril cannot be recommended medication for anti-covid therapy because it induces the expression of viral cell receptors such as ACE-2 thus making the patient more susceptible to infection. But Disulfiram, an alcoholism-averting drug can be used as even at higher doses for antiviral treatment. Result reveals that catalytic Cys 145 of SARS-CoV-2 mp can be blocked and inactivated by Disulfiram and its thiol-reactive derivatives metabolites.

Neda shaghaghi et al, (2020) has worked on plant derivatives such as protease inhibitors and compounds, mainly terpenoids as they are effective on controlling the virus-induced infections. From the databases such as PubChem and Protein Data Bank (PDB) the structure of terpene compounds and protease was obtained, and then molecular docking was done by using Molegro virtual docker (MVD) software. The main

aim this research is to provide bioinformatical study of Covid-19 inhibition terpenoid compounds results this study reveals that these compounds have inhibitory activity against novel Corona virus.

Liang et al, performed MD simulation to demonstrate the binding stability of an α -ketoamide inhibitor inside the SARS-CoV-2 main protease. In this rapidly evolving pandemic, repurposing existing drugs and evaluating commercially available inhibitors against the druggable targets of SARS-CoV-2 should be an effective strategy to accelerate the drug discovery process. Consequently, taking advantage of the availability of the X-ray crystal structure of 3CLpro in complex with the inhibitor N3 (PDB code 6LU7)³⁶, he performed a docking-based virtual screening of the protease inhibitor database MEROPS⁴⁶ (<https://www.ebi.ac.uk/merops/>) to identify potential 3CLpro inhibitors. Molecular docking and dynamic simulations were carried out to study the binding interactions of the inhibitor compounds with 3CLpro. Binding energy calculations were performed using the molecular mechanics Poisson Boltzmann surface area (MM-PBSA) method to evaluate the binding affinity of the compounds and to identify residues important for binding with 3CLpro. The results of the modeling study were carefully analyzed to identify commercially available potential 3CLpro inhibitors.

Olubiyi et al, (2020) state, three out of four CoV major primary proteins and here and there a non-major underlying protein can be found on the CoV envelope. These are the spike (S) protein, film (M) protein, envelope (E) protein, and hemagglutinin esterase (HE). The nucleocapsid (N) proteins partners with the CoV genome and, through its cooperation's with oneself collected M proteins, lives inside the viral molecule. Along with the CoV genomic RNA, these primary proteins structure a virion. CoV sub genomic RNAs are produced by joining of the 5' pioneer (red box) arrangement to different downstream destinations. CoV non-underlying qualities comprises of the 5' 66% of the RNA genome, though primary qualities are situated inside the 3' one-third. During viral replication, non-primary qualities are communicated as polyproteins, while underlying qualities are communicated by each subgenomic RNAs.

Shawan Mohammad Mahfuz et al, (2021) comment it is partially because of the blunder inclined RNA-dependent RNA polymerase (RdRp), whose replacement rate has been arrived at the midpoint of two $\sim 10^{-4}$ every year for each site, with much higher rates for certain hypervariable areas (for example S protein), at 0.6×10^{-2} for each site each year. Another patron for CoV versatility is the RNA recombination during viral replication, through the cycle of RdRp format exchanging. Along with a huge genome size endures higher genome varieties, and the age of sub genomic RNAs during viral replication. Sabri et al. (2020) note it hoists the pace of homologous recombination between various viral genealogies, CoVs are prepared to do rapidly adjusting to a wide scope of organic specialties.

Chitranshi et al, (2020) zeroed in on three particular phases of the CoV life cycle: (1) CoV molecule cell restricting; (2) CoV molecule cell section; (3) CoV cell-to-cell spread, where the disease passes straightforwardly from a tainted cell to an adjoining sound cell through cell-cell combination, or syncytia development. For RNA protein, recognized its connection with have sialic acids, utilizing an infection like molecule (VLP) framework. The cooperation with sialic acids, and not with the protein receptor, is liable for most of the molecule restricting interceded by the S protein. Also, the S-sialic corrosive collaboration aids JHM-CoV passage into different objective cells, just as the resulting cell-to-cell spread, both in the presence and nonattendance of the protein receptor. For the S protein of SARS-CoV,

Hozhabri et al, (2020) initially tracked down that viral particles negligibly require S, protein receptor, and protease for combination. Furthermore, like JHM, MERS S-sialic corrosive connection is adequate for cell-cell combination. Finally, we distinguished single-nucleotide changes in both S protein-sialic corrosive restricting S space as that gave raised cell-restricting and cell-cell combination capacities. In general, these discoveries uncover parts for sialic acids in infection cell restricting, viral S protein-

coordinated cell-cell combination, and resultant spread of CoV diseases. This examination features unmistakable CoV receptor restricting space exercises in the contamination cycle and raises the likelihood that the lectinlike properties of numerous CoVs are answerable for simple CoV zoonotic transmission and intercellular spread inside tainted life forms.

Coronaviruses are positive-sense, single-stranded RNA (ssRNA) infections that contain the biggest genome of all RNA infections, which goes from 24 to 32 kilobases (kb). The 5' 66% of the CoV genome encodes the different non-primary proteins, and is communicated as a polyprotein. The 3' 33% of the CoV genome encodes the underlying and adornment proteins, whose articulations result from the age of viral subgenomic RNAs (Kousar et al. 2020). CoVs are phylogenetically sorted under the request Nidovirales and are subcategorized into four gatherings (alpha-, beta-, gamma-, and delta-). CoVs are wrapped infections, which means the develop virion comprises of a furthest layer comprised of a lipid bilayer got from the host film, advanced with transmembrane viral proteins. The observation of Luo et al. (2020) helped clarified the explanation a few creatures (bats, camels) could be tainted. On the side of this, he saw that versatile S space A progressions upgrade viral connection, straightforwardly featuring a job have sialo sides can fill in as an advertiser of productive cross-species transmissions.

CHAPTER - 3

AIM AND OBJECTIVE

AIM:

To identify the inhibitory effect of phytochemical compounds on SARS-CoV-2 of RNA dependent RNA polymerase through computer aided drug design.

OBJECTIVE:

- Collection of phytochemical constituents from various plants with antiviral activity based on the literature survey.
- Identification of protein (RNA dependent RNA polymerase) on SARS-CoV-2.
- Identifying, depicting and validating binding zones for the proteins of RNA dependent RNA polymerase (PDB ID: 6M71).
- Prediction of ADME properties for collected phytochemical constituents.
- Performing molecular docking of RdRp (RNA dependent RNA polymerase) protein of SARS-CoV-2 with the collected phytochemical constituents.

CHAPTER – 4

MATERIALS AND METHODS

4.1 MATERIALS:

4.1.1. Software's:

1. RCSB PDB.
2. UCSF Chimera.
3. Modeller.
4. SWISS ADME.
5. iGem dock.
6. Auto dock vina.
7. Pre ADMET.
8. Discovery studio.

4.1.2. DATA BASES:

1. UNIPROT: Universal Protein Resource Knowledge Base.
UNIPROT ID – P0DTD1 (R1AB_SARS 2).
Total sequence length of SARS-CoV-2 is 7096.

Sequence length of RdRp (RNA dependent RNA polymerase) is 4393 – 5324.

2. RCSB PDB – Research Collaboratory for Structural Bioinformatics Protein Data.

PDB ID – 6M71 (SARS-CoV-2 RNA dependent RNA polymerase with cofactors).

```
>6M71_1|Chain A|RNA-directed RNA polymerase |Severe acute respiratory  
syndrome coronavirus 2 (2697049)  
SADAQSFLNRVCGVSAARLTPCGTGTSTDVVYRAFDIYNDKVAGFAKFLKTNCCRFQEKDEDDNLIDSYFV  
VKRHTFSNYQHEETIYNLLKDCPAVAKHDFKFRIDGDMVPHISRQRLTKYTMADLVYALRHFDENCDTL  
KEILVTYNCCDDYFNKKDWYDFVENPDILRVYANLGERVRQALLKTVQFCDAMRNAGIVGVLTLDNQDLN  
GNWYDFGDFIQTPGSGVPVVDSSYSLMLPILTLTRALTAESHVDTDLTKPYIKWDLKLYDFTEERLKLFD  
RYFKYWDQTYHPNCVNCDDRCILHCANFNVLSTVFPPTSFGPLVRKIFVDGVFPVVSSTGYHFRELGVVH  
NQDVNLHSSRLSFKELLVYAADPAMHAASGNLLLDKRTTCFSVAALTNNVAFQTVKPGNFNKDFYDFAVSK  
GFFKEGSSVELKHFFFAQDGNAAISDYDYRYRNLPMTCDIRQLLFVVEVVDKYFDCYDGGCINANQVIVNN  
LDKSAGFPFNKWKARLYYDSMSYEDQDALFAYTKRNVIPITITQMNLYAISAKNRARTVAGVSICTMTN  
RQFHQKLLKSIAATRGTAVVIGTSKFYGGWHNMLKTVYSDVENPHLMGWDYPKCDRAMPNMLRIMASIVLA  
RKHTTCCSLSHRFYRLANCAQVLESMVMCGGSLYVKPGGTSSGDATTAYANSVFNICQAVTANVNALLST  
DGNKIADKYVRNLQHRLYECLYRNRDVTDFVNEFYAYLRKHFSMMILSDDAVVCFNSTYASQGLVASIKN  
FKSVLYYQNNVFMSEAKCWTETDLTKGPHEFCSQHTMLVKQGGDYVYLPYPDPSPRILGAGCFVDDIVKTDG  
TLMIERFVSLAIDAYPLTKHPNQEYADVFLYLQYIRKLHDELTDGHMLDMYSVMLTNDNTSRYWEPEFYEA  
MYTPHTVLQHHHHHHHHHH  
>6M71_2|Chain C | Non-structural protein 7|Severe acute respiratory  
syndrome coronavirus 2 (2697049)  
SKMSDVKCTSVVLLSVLQQLRVESSSKLWAQCVQLHNDILLAKDTTEAFEKMSVLLSVLLSMQGAVDINKL  
CEEMLDNRATLQ  
>6M71_3|Chains B, D | Non-structural protein 8|Severe acute respiratory  
syndrome coronavirus 2 (2697049)  
AIASEFSSLPSYAAFATAQEAYEQAVANGDSEVVLLKLLKKSINVAKSEFDRDAAMQRKLEKMAQAMTQMY  
KQARSEDKRAKVTSAMQTMLFTMLRKLDNDALNNIINNARDGCVPLNIIPLTTAAKLMVVIPDYNTYKNTC  
DGTTFYASALWEIQQVVDADSKIVQLSEISMDNSPNLAWPLIVTALRANSVAVKLQ.
```

Figure: 4.1: Sequence of RNA dependent RNA polymerase (FASTA Format).

4.2 METHODS:

4.2.1 Collection of phytochemical constituents:

Based on the literature survey 1005 phytochemical constituents of plants were collected.

4.2.2 PDB (Protein data bank):

The Protein Data Bank (PDB) is a crystallographic database for the three-dimensional basic information of extensive organic atoms, for example, proteins and nucleic acids. The information, normally acquired by X-ray crystallography, NMR spectroscopy or, progressively, cryo-electron microscopy. The PDB is a key asset in zones of basic science, for example, basic genomics. The crystal structure of COVID-19 RdRp (RNA dependent RNA polymerase) (PDB ID: 6M71) was obtained from protein data bank.

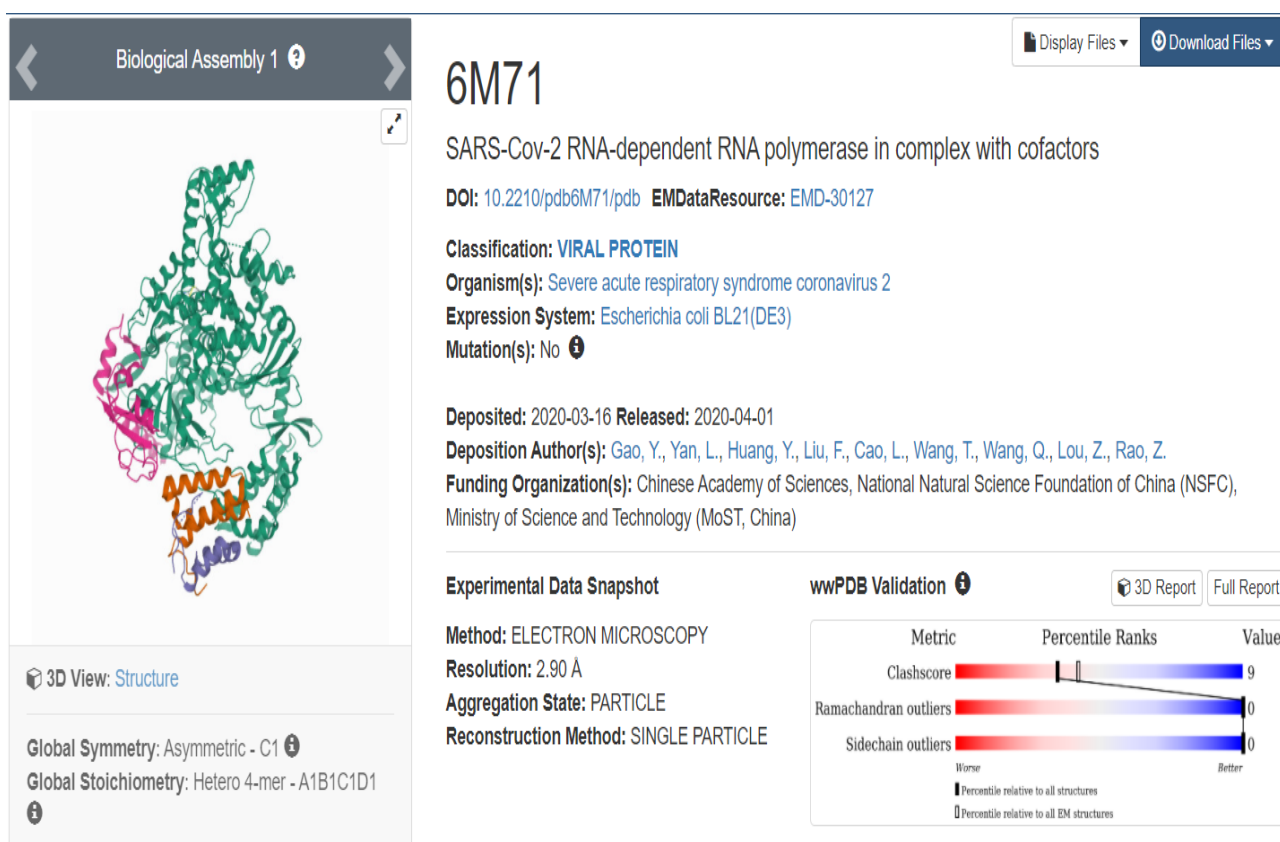


Figure: 4.2: 6M71 protein retrieved from PDB.



Figure: 4.3: 3D structure of RdRp (RNA dependent RNA polymerase).

4.2.3 UCSF Chimera:

UCSF Chimera is an extensible program for intelligent perception and investigation of atomic designs and related information, including thickness maps, supramolecular gatherings, succession arrangements, docking results, directions, and conformational troupes. High grade pictures can be made.

4.2.4 Modeller:

Modeller is a PC program that models three-dimensional constructions of proteins and their gatherings by fulfillment of spatial limitations. Modeller is most habitually utilized for homology or similar protein structure displaying. Modeller provides an arrangement of a succession to be demonstrated with known related constructions and Modeller will consequently compute a model with all non-hydrogen particles. Using UCSF Chimera, the protein loops of RdRp protein (PDB ID:6M71) were designed by modeller tool.



Figure: 4.4: RNA dependent RNA polymerase protein (Chain A).

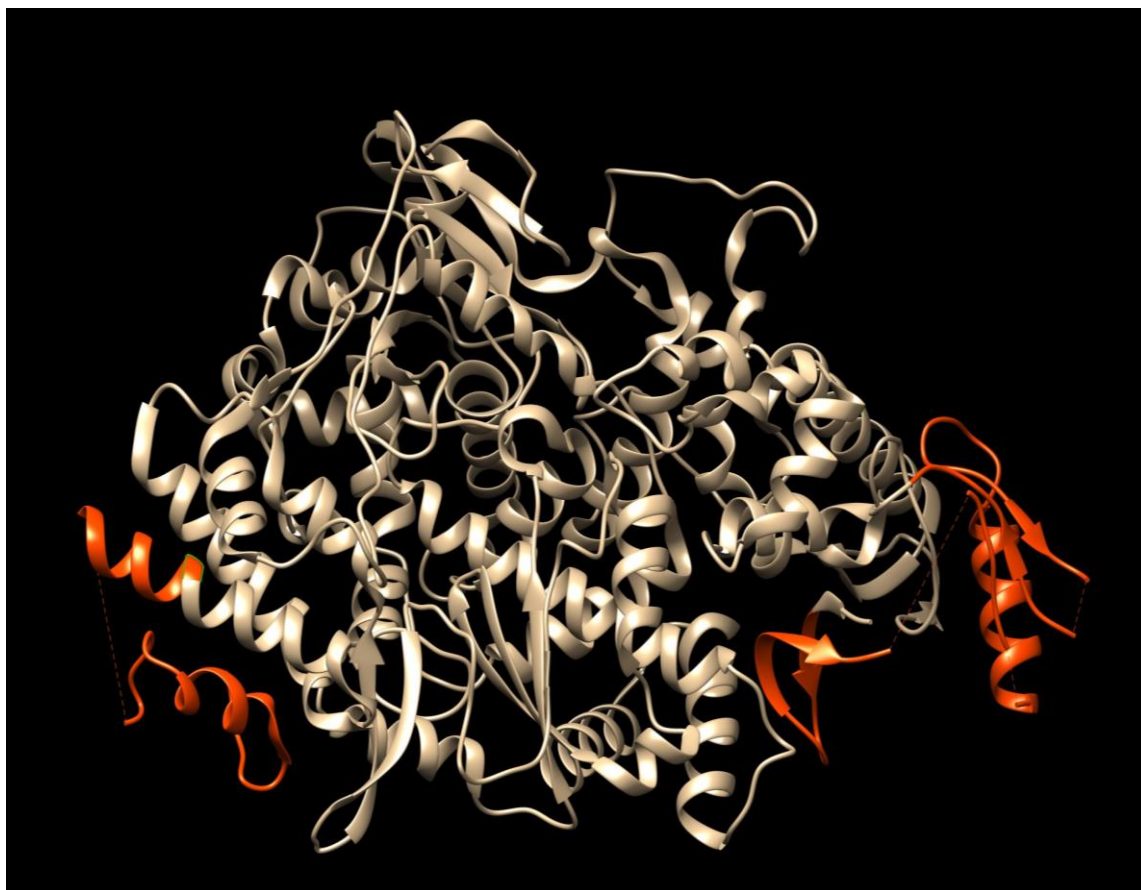


Figure: 4.5: RNA dependent RNA polymerase protein with loops.

4.2.5 PubChem:

PubChem is a database of compound molecules and their activities against natural examines. The framework is kept up by the National Centre for Biotechnology Information (NCBI), a segment of the National Library of Medicine, which is a piece of the United States National Institutes of Health (NIH). PubChem can be gotten to for nothing through a web user interface. A large number of compound structures and distinct datasets can be openly downloaded by means of FTP. PubChem contains substance depictions and little particles with less than 1000 molecules and 1000 bonds. In excess of 80 database merchants add to the developing PubChem database. The SDF structures of all collected 1005 phytochemical constituents were retrieved from

PubChem data base. The phytochemical compounds were converted into PDB format and conformational energies of all ligands were minimized using UCSF Chimera.

4.2.6 SwissADME:

This site permits use to register phytochemical descriptors just as to forecast ADME boundaries, pharmacokinetic properties, drug like nature and restorative science neighborliness of one or numerous little particles to help drug revelation. We got ADME properties of all 1005 drugs like compounds from this server. Out of 1005 compounds 577 compounds were predicted based on Lipinski rule of five.

4.2.7 Molecular Docking:

Molecular docking is a key device in structural molecular biology and computer-based drug design. The objective of ligand-protein docking is to anticipate the overwhelming binding mode of a ligand with a protein of known three-dimensional structure. Fruitful docking strategies seek high-dimensional spaces viably and utilize a scoring capacity that effectively positions competitor dockings. Docking can be utilized to perform virtual screening on expansive libraries of mixes, rank the outcomes, and propose auxiliary theories of how the ligands restrain the objective, which is precious in lead enhancement.

4.2.8 Igem dock:

Structure-based virtual screening and post-screening examination are new assignments in computer-based drug delivery. Joining these two strategies to successfully diminish the false positives from an extensive compound database is considered as a key advance to finding the lead mixes. In this consider, we have built up a graphical-programmed medicate disclosure framework, called Igemdock, for coordinating docking, screening, post-investigation, and perception.

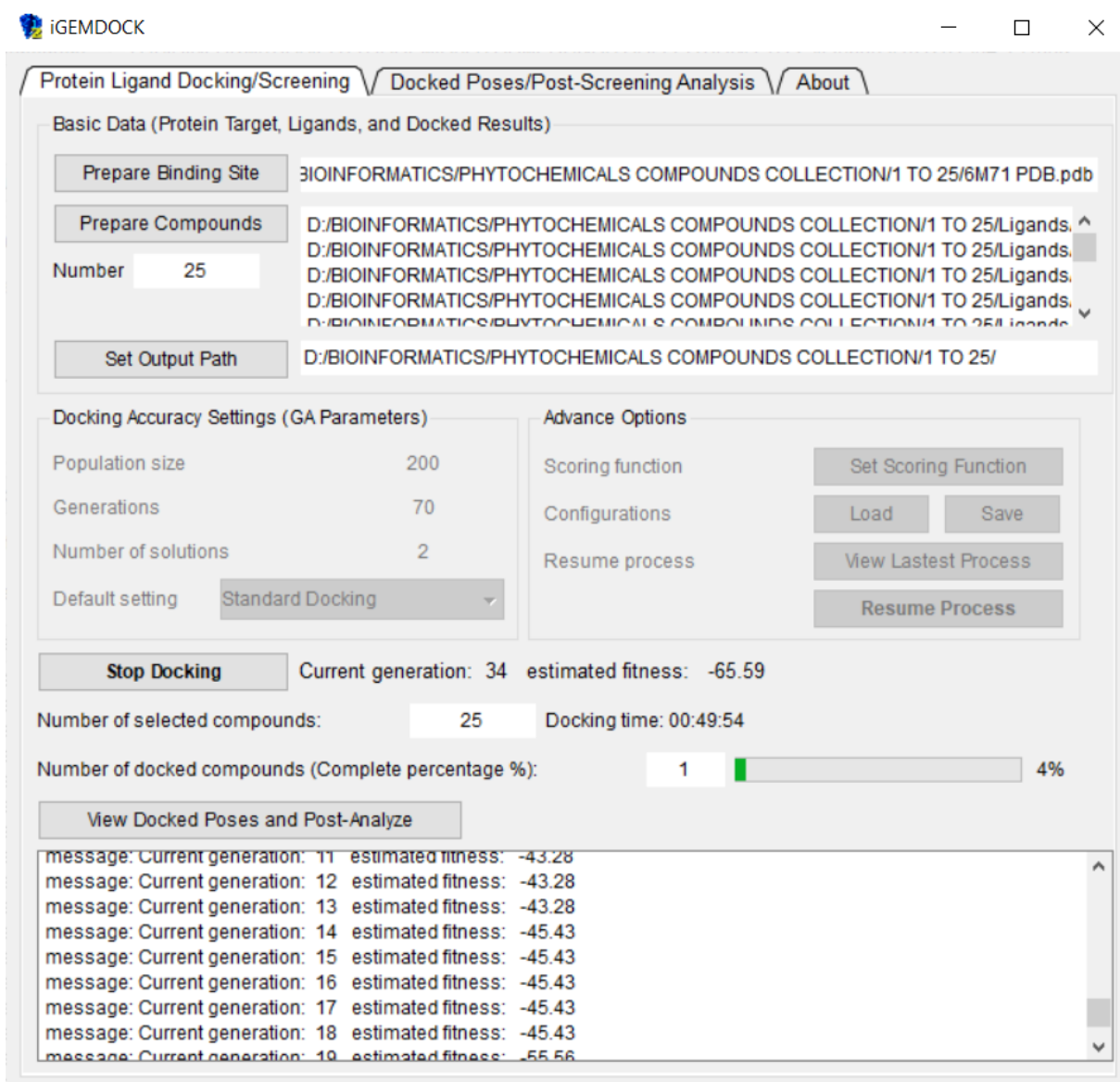


Figure: 4.6: Igem dock.

4.2.9 Auto dock vina:

Auto Dock is an automated method for processing the interaction of ligands with bio macromolecular targets. The inspiration for this work emerges from issues in the outline of bioactive mixes, and specifically the field of PC supported medication plan. Advance in bimolecular x-ray crystallography keeps on giving vital protein and nucleic corrosive structures. These structures could be focuses for bioactive operators in the control of creature and plant maladies, or basically key to the comprehension of

central parts of science, by using auto dock vina as secondary docking program, we get the best molecular interacting inhibitors.

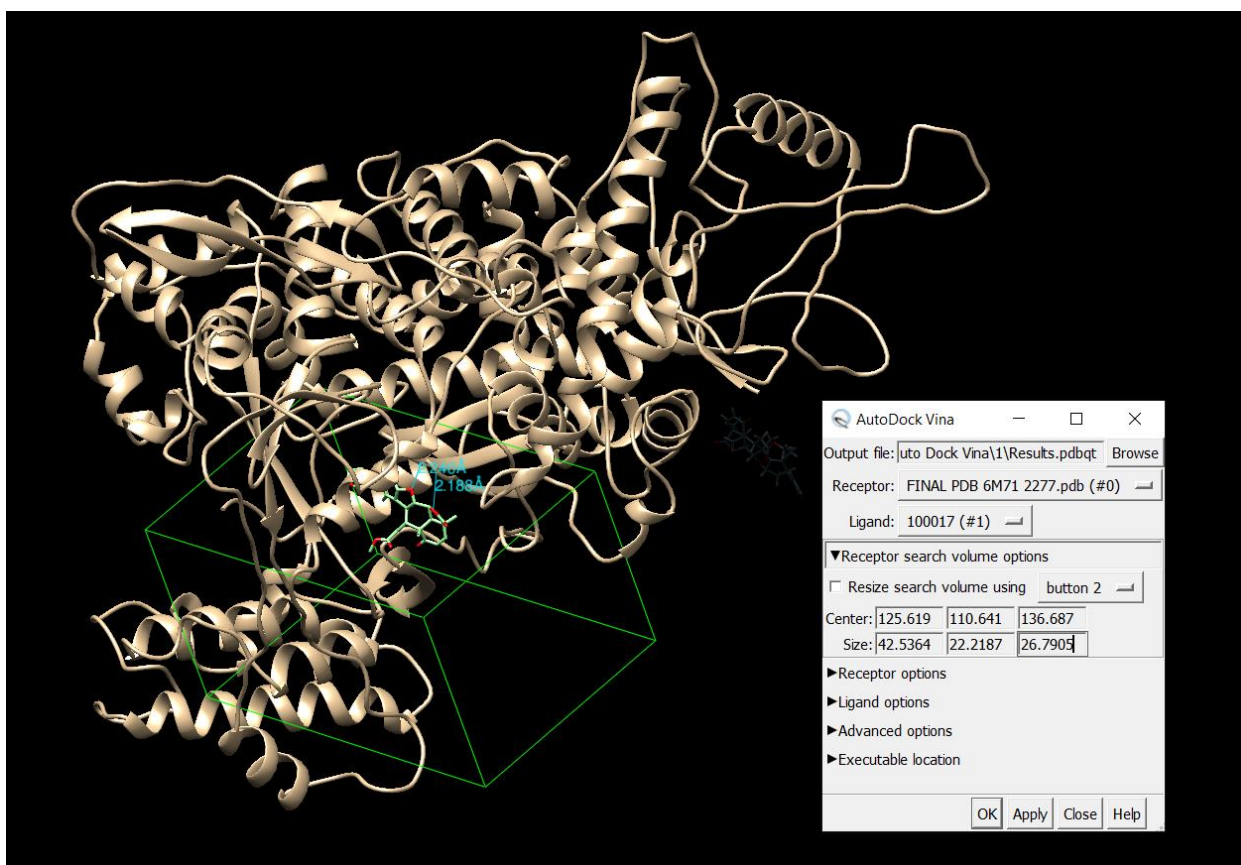


Figure: 4.7: Auto dock vina.

4.2.10 PreADMET:

PreADMET is an electronic application for anticipating ADME information and building drug-like library utilizing in silico method. A critical bottleneck stays in the medication revelation system, specifically in the later phases of lead disclosure, is examination of the ADME and unmistakable poisonousness properties of medication competitors. More than half of the applicants flopped because of ADME/Tox lacks during improvement. To keep away from this disappointment at the improvement a bunch of in vitro ADME/Tox screens has been executed in most drug organizations with the point of disposing of mixtures in the disclosure stage that are probably going to flop sometime

later. Despite the fact that the beginning phase in vitro ADME decreases the likelihood of the disappointment at the improvement stage, it is as yet tedious and asset serious. Consequently, we depict another electronic application called PreADMET, which has been created in light of a requirement for quick forecast of medication similarity and ADME/Tox information.

4.2.11 DISCOVERY STUDIO:

Discovery studio is a set-up of programming for reproducing little atom and macromolecule systems. Structure-based Design Includes devices for piece-based situation and refinement, receptor-ligand docking and posture refinement, anew plan.

BIOVIA Discovery Studio is a US-based programming organization with European and Japanese portrayal. Particularly in the fields of medication disclosure and materials science, it offers programming for synthetic studies. Discovery Studio is an exhaustive programming suite for breaking down and demonstrating atomic designs, arrangements, and other information of significance to life science analysts. The item incorporates usefulness for review and altering information alongside devices for performing essential information investigation.

The Discovery Studio Client is a work area application that can be utilized to get to all the usefulness in Discovery Studio. The Discovery Studio Visualizer is a free watcher that can be utilized to open information created by other programming in the Discovery Studio product offering. It is intended to offer an intelligent climate for review and altering sub-atomic designs, successions, X-beam reflection information, contents, and other information. It additionally gives a rich arrangement of watchers for showing plots and other graphical portrayals of information. The application runs on Windows and Linux and is a completely coordinated work area climate.

4.3 Methodology:

UCSF chimera was used to visualize the receptor, ligand structures, hydrogen-bonding network, and bond lengths and to render images. The PubChem database online server was used to identify three dimensional structures of phytochemical compounds for molecular docking in order inhibit the RdRp protein (RNA dependent RNA polymerase) of SARS-CoV-2. Igem dock software was the primary docking program used in this study for virtual screening with quick docking. A receptor (PDB ID: 6M71) and ligands were prepared for virtual screening by adding the hydrogen atoms and by removing all water molecules that were co-crystallized with this target protein. The addition of hydrogen atoms ensures an accurate determination of the ionization states of amino acid residues. The energy of the protein structure was then minimized using the USCF Chimera, and the obtained structure was saved in a PDB file format for further studies. Additionally, ligands were prepared by first removing the hybridization errors in the molecules and then adding the missing hydrogen bonds in order to check the fidelity of all bonds in the compounds. All prepared compounds were saved in the mol format for further docking studies after a geometry optimization stage with the energy-scoring grid box was centered at the active ligand binding site location and its dimensions were set to 60 Å along each axis (x, y, and z). The grid spacing was 0.40 Å, and the default atomic salvation parameters were used. The grid was assigned such that the active site of 6M71 was enclosed by the three-dimensional grid box. “A score” scoring function with all docking parameters set to the default values was selected as the docking engine in auto dock vina (navneet Chauhan et al, 2016). Toxicity prediction was determined by using Pre ADMET, for the best compounds.

CHAPTER - 5

RESULT AND DISCUSSION:

SARS-CoV-2 have a protein named RNA dependent RNA polymerase (RdRp) (PDB ID: 6M71) which is consider as core protein that helps to catalyze the replication of RNA from an existing RNA template. This protein actively involves in replication of virus and hence, this protein was selected in order to limit the replication of coronavirus. The RdRp protein was retrieved from PDB, this protein has breaks by using modeller the breaks were cleared and the protein was saved in PDB format further studies.

5.1 Validation of designed protein (PDB ID: 6M71) by modeller:

- DOPE (Discrepe optimize protein energy) and GA341 are statical potentials used to assess homology models quality in protein structure prediction.
- The best GA341 score is near to 1 or 1 as it ranges from 0 to 1 while the lowest DPOE value is considered to be best one for the better model.
- It is better to consider the DOPE value and specifically lowest DOPE value instead of GA341 score.
- Hence, we considering model 1.1 with GA341 value as 1.00 and the lowest DOPE value -1.04.

Based on DOPE value model 1.1 was considered as the best model.



Figure: 5.1: Final protein obtained after loop designing by modeller.

5.2 SWISS ADME:

From collected 1005 phytochemicals or ligands, 577 compounds have shown best activities.

ADME studies for 577 compounds:

Table: 5.1: 577 compounds predicted from SWISSADME.

S. N O:	Pubchem ID	Formula	MW	Rotatable bonds	H-bond acceptors	H-bond donors	MR	TPSA	iLOGP
1	443143	C ₁₃ H ₂₄ N ₂ O	224.34	4	3	2	74.01	41.13	2.71

2	12306 778	C13H24N2 O	224 .34	4	3	1	74. 1	32. 34	2.8 7
3	12015 43	C13H24N2 O	224 .34	4	3	0	74. 2	23. 55	3.0 9
4	44093 3	C8H15NO	141 .21	2	2	0	45. 47	20. 31	2.0 9
5	92987	C8H15NO	141 .21	2	2	1	45. 37	29. 1	2.0 5
6	8424	C8H15NO	141 .21	0	2	1	44. 31	23. 47	1.8 4
7	14106 343	C36H36N2 O7	608 .68	3	9	2	171 .39	100 .93	4.1 1
8	16167 1	C28H38O6	470 .6	2	6	2	127 .53	96. 36	3.6 2
9	21679 023	C28H38O5	454 .6	2	5	2	128 .08	83. 83	4.0 9
1 0	21679 022	C28H38O6	470 .6	2	6	3	129 .28	104 .06	3.4
1 1	23266 147	C28H36O5	452 .58	3	5	2	127 .57	83. 83	3.4 4
1 2	23266 146	C28H36O5	452 .58	2	5	2	127 .57	83. 83	3.7 5
1 3	21679 034	C28H38O5	454 .6	2	5	2	128 .08	83. 83	4.9 8
1 4	10128 1365	C28H38O6	470 .6	3	6	3	129 .21	104 .06	3.2 1
1 5	10128 1364	C28H38O6	470 .6	2	6	2	127 .49	96. 36	3.5 6
1 6	13588 7	C28H40O7	488 .61	2	7	4	130 .92	124 .29	3.5 8
1 7	11491 1	C17H17N	235 .32	0	1	0	78. 97	3.2 4	2.7 9

1 8	44201 2	C20H22O7	374 .38	1	7	1	89. 54	98. 5	2.0 9
1 9	18828 9	C20H22O6	358 .39	1	6	1	90. 1	85. 97	2.1 1
2 0	24721 165	C20H22O6	358 .39	1	6	1	90. 1	85. 97	2.1 1
2 1	73337	C20H24NO 4	342 .41	2	4	2	101 .87	58. 92	- 0.5 9
2 2	44206 8	C20H22O7	374 .38	1	7	1	89. 54	98. 5	2.0 9
2 3	19009	C21H22NO 4	352 .4	4	4	0	101 .8	40. 8	0.1
2 4	63777 5	C11H12O5	224 .21	4	5	2	58. 12	75. 99	1.6 3
2 5	16771 8	C20H26NO 4	344 .42	4	4	2	102 .87	58. 92	- 0.3 1
2 6	5417	C21H25NO 4	355 .43	4	5	0	103 .99	40. 16	3.6 7
2 7	10092 6540	C15H22O3	250 .33	1	3	1	69. 63	49. 83	2.5 9
2 8	10191 6313	C25H34O9	478 .53	4	9	4	118 .47	138 .82	2.9 2
2 9	17738 4	C21H32O7	396 .47	4	7	4	100 .93	116 .45	3.0 1
3 0	15215 479	C19H22O5	330 .37	1	5	1	86. 28	76. 74	2.2 6
3 1	12220 6355	C21H26O8	406 .43	3	8	2	97. 66	118 .73	2.7

3	63966		354				102	86.	2.9
2	5	C21H22O5	.4	6	5	3	.53	99	3
3			122				33.	37.	0.9
3	126	C7H6O2	.12	1	2	1	85	3	9
3			138				35.	57.	0.8
4	135	C7H6O3	.12	1	3	2	42	53	5
3	10398		222				70.	20.	3.1
5	656	C15H26O	.37	1	1	1	72	23	5
3	16246		344				91.	98.	3.0
6	4	C18H16O7	.32	4	7	2	44	36	7
3	18832		314				84.	89.	2.5
7	3	C17H14O6	.29	3	6	2	95	13	6
3			164				49.	29.	2.3
8	3314	C10H12O2	.2	3	2	1	06	46	7
3			198				48.	86.	1.2
9	13250	C9H10O5	.17	3	5	3	6	99	1
4	11726		360				93.	118	2.6
0	019	C18H16O8	.31	4	8	3	47	.59	9
4	63025		330				86.	109	2.5
1	3	C17H14O7	.29	3	7	3	97	.36	8
4	63752		162				47.	26.	
2	0	C10H10O2	.19	3	2	0	43	3	2.3
4			178				53.	18.	2.6
3	7127	C11H14O2	.23	4	2	0	53	46	5
4			168				41.	66.	
4	8468	C8H8O4	.15	2	4	2	92	76	1.4
4	63722		486				138	94.	2.4
5	9	C30H46O5	.68	1	5	3	.31	83	9
4	20522		434				120	87.	4.2
6	538	C25H22O7	.44	7	7	1	.4	36	4

4	69941		178				49.	46.	1.6
7	4	C10H10O3	.18	3	3	1	6	53	8
4	44258		312				87.	57.	3.2
8	3	C18H16O5	.32	4	5	0	4	9	1
4			149				43.	49.	1.0
9	76955	C8H7NO2	.15	0	2	2	76	33	6
5	52816		302				78.	131	1.8
0	38	C15H10O7	.24	1	7	5	03	.36	7
5	52816		302				78.	131	1.9
1	42	C15H10O7	.24	1	7	5	03	.36	4
5	22017		219				58.	79.	
2	520	C11H9NO4	.19	2	4	2	02	39	1.4
5	37906	C22H29NO	355				102	73.	2.8
3	3	3	.47	0	4	2	.17	48	5
5	13846	C16H17Br	321				83.	37.	3.6
4	145	O2	.21	6	2	1	57	3	8
5	23424	C26H51N5	465				141	113	4.7
5	567	O2	.72	23	3	3	.82	.81	7
5	30826	C14H9ClO	276				73.	54.	3.5
6	99	2S	.74	3	2	0	27	54	8
5	10200	C19H24ClN	397				99.	85.	
7	848	O6	.85	3	7	1	98	3	2.8
5	13959		584				160	114	3.8
8	7845	C34H48O8	.74	2	8	3	.71	.68	5
5	64382		154				50.	20.	2.7
9	0	C10H18O	.25	4	1	1	4	23	5
6			196				60.	26.	3.0
0	8294	C12H20O2	.29	6	2	0	17	3	8
6	42608	C22H43NO	369				113	86.	4.2
1	352	3	.58	14	4	4	.11	71	9

6 2	18534 7	C8H8O3	152 .15	0	3	1	37. 84	46. 53	1.3 7
6 3	64981	C21H24O6	372 .41	7	6	1	100 .6	74. 22	2.8
6 4	53210 18	C15H18O2	230 .3	0	2	0	67. 48	26. 3	2.8 8
6 5	14448 070	C15H20O2	232 .32	0	2	0	67. 95	26. 3	2.6 5
6 6	15594 8	C15H20O3	248 .32	0	3	1	69. 15	46. 53	2.3 7
6 7	17417 4	C17H23NO 3	289 .37	5	4	1	84. 51	49. 77	2.8 5
6 8	72185	C21H30O2	314 .46	2	2	2	97. 53	40. 46	3.2 5
6 9	52816 05	C15H10O5	270 .24	1	5	3	73. 99	90. 9	2.4 3
7 0	44269 4	C17H16O4	284 .31	3	4	1	82. 95	47. 92	3.0 5
7 1	18988 5	C12H9ClN2	216 .67	0	1	0	63. 51	17. 82	2.2 4
7 2	18988 4	C12H8Cl2N 2	251 .11	0	1	0	68. 52	17. 82	2.4 1
7 3	18988 3	C12H8Cl2N 2O	267 .11	0	1	1	71. 35	37. 79	2.3 7
7 4	64685	C10H18O	154 .25	0	1	1	46. 6	20. 23	2.2 9
7 5	52813 61	C17H19N3	265 .35	1	2	1	87. 46	31. 92	2.6 2
7 6	21669 866	C26H33Cl O10	540 .99	6	10	1	129 .65	137 .96	2.4 1

7	18352	C20H13Br	421				107	97.	2.2
7	8	N4O2	.25	3	3	4	.33	56	6
7	46115	C19H23NO	297				93.	46.	2.9
8	0	2	.39	4	2	1	57	17	8
7	44297		384				122	29.	
9	0	C26H44N2	.64	2	2	1	.52	26	4.4
8			370				106	68.	3.8
0	64972	C22H26O5	.44	2	5	1	.11	9	3
8									-
1	54606	C11H14Ca	282				56.	89.	37.
	827	O6	.3	5	6	1	74	9	62
8	52804		284				78.	79.	
2	48	C16H12O5	.26	2	5	2	46	9	2.4
8		C20H16N2	348				95.	81.	2.4
3	24360	O4	.35	1	5	1	31	42	9
8	19781	C20H19NO	353				96.	60.	3.2
4	0	5	.37	0	6	1	12	39	1
8	52816		254				71.	70.	2.2
5	07	C15H10O4	.24	1	4	2	97	67	7
8			154				49.	17.	2.4
6	7794	C10H18O	.25	5	1	0	91	07	9
8			198				60.	26.	3.2
7	9017	C12H22O2	.3	7	2	0	61	3	9
8	54877	C16H15NO	301				84.	80.	2.5
8	72	5	.29	2	5	2	01	92	2
8	52832		446				122	95.	4.7
9	18	C25H34O7	.53	16	7	0	.37	97	7
9	10332		258				68.	66.	1.9
0	730	C15H14O4	.27	2	4	2	3	76	6
9	52843	C18H21NO	299				86.	41.	2.8
1	71	3	.36	1	4	1	74	93	8

9 2	11958 6	C13H10O4	230 .22	1	4	0	63. 71	52. 58	2.4 3
9 3	46112 8	C22H26O5	370 .44	2	5	1	106 .11	68. 9	3.8 3
9 4	92765	C24H27NO 3	377 .48	3	4	0	117 .48	30. 93	4.0 6
9 5	12886 1	C15H11O6	287 .24	1	6	5	76. 17	114 .29	- 2.5 9
9 6	10128 1345	C24H42N2 O	374 .6	2	3	3	112 .54	58. 28	3.8 4
9 7	52817 08	C15H10O4	254 .24	1	4	2	71. 97	70. 67	1.7 7
9 8	16078	C21H30O2	314 .46	4	2	1	97. 91	29. 46	3.9
9 9	13077 4	C21H20N4 S	360 .48	3	3	0	111 .47	62. 19	3.4 9
1 0 0	8550	C32H38N2 O8	578 .65	9	9	1	159 .03	108 .55	4.7 7
1 0 1	13526 3040	C28H30N2 O3	442 .55	8	3	2	130 .27	67. 4	3.9 8
1 0 2	43692 70	C23H34O4	374 .51	1	4	2	104 .76	66. 76	3.0 9
1 0 3	24633 0	C15H12O6	288 .25	1	6	4	72. 73	107 .22	1.4 7

104	100492	C21H16O7	380.35	3	7	1	99.78	83.45	2.84
105	24829009	C38H44N2O8	656.76	5	10	2	187.24	118	4.4
106	681	C8H11NO2	153.18	2	3	3	42.97	66.48	1.27
107	5281855	C14H6O8	302.19	0	8	4	75.31	141.34	0.79
108	9294	C10H15NO	165.23	3	2	2	49.79	32.26	2.25
109	13855381	C20H28O4	332.43	1	4	2	91.48	70.67	2.15
110	91469	C15H14O3	242.27	1	3	2	69.13	49.69	1.95
111	440735	C15H12O6	288.25	1	6	4	73.59	107.22	1.62
112	184887	C14H16BrN3O2S	370.26	0	4	3	91.15	99.81	2.26
113	128900	C14H16BrN3O2S	370.26	0	4	3	91.15	99.81	1.9

1 1 4	18488 8	C14H16Br N3OS	354 .27	0	3	2	89. 13	79. 58	2.4 4
1 1 5	18488 9	C14H16Br N3OS	354 .27	0	3	2	89. 13	79. 58	2.4 6
1 1 6	16430 0	C23H30O5	386 .48	4	5	2	108 .65	83. 83	3.2 3
1 1 7	40305	C21H20NO 4	350 .39	3	4	1	104 .05	51. 8	- 0.5 5
1 1 8	44585 8	C10H10O4	194 .18	3	4	2	51. 63	66. 76	1.6 2
1 1 9	99956 72	C21H28O2	312 .45	1	2	2	97. 32	40. 46	3
1 2 0	10087 772	C21H26O3	326 .43	0	3	1	94. 93	46. 53	3.2 6
1 2 1	92023 653	C7H14O7S	242 .25	2	7	3	48. 68	121 .67	0.4 7
1 2 2	52815 41	C14H12O4	244 .24	3	4	0	68. 27	56. 51	2.8 1
1 2 3	30018 11	C30H48O4	472 .7	6	4	3	139 .6	77. 76	4.0 4

1 2 4	53177 56	C21H20O6	368 .38	4	6	3	104 .2	100 .13	2.8 2
1 2 5	53177 64	C20H18O6	354 .35	3	6	4	99. 73	111 .13	2.5 6
1 2 6	14579	C10H14O5	214 .22	4	5	4	53. 02	90. 15	1.4 2
1 2 7	52814 04	C12H10N2	182 .22	0	1	1	58. 57	28. 68	1.7 5
1 2 8	52809 53	C13H12N2 O	212 .25	1	2	1	65. 06	37. 91	2.0 7
1 2 9	68094	C12H10N2 O	198 .22	0	1	2	61. 39	48. 65	1.6 8
1 3 0	72281	C16H14O6	302 .28	2	6	3	78. 06	96. 22	2.2 4
1 3 1	10361 056	C22H30O4	358 .47	3	4	1	102 .64	63. 6	3.2 6
1 3 2	10177	C16H10N2 O2	262 .26	1	3	2	80. 62	65. 45	2.1 3
1 3 3	10256	C9H7NO	145 .16	1	1	1	43. 69	32. 86	1.1 2

1 3 4	45524 8	C25H24O5	404 .46	1	5	1	116 .97	68. 9	3.7 3
1 3 5	72412	C25H24O5	404 .46	1	5	1	116 .97	68. 9	3.7 3
1 3 6	45525 2	C25H22O5	402 .44	1	5	0	116 .23	65. 74	3.4 3
1 3 7	45525 0	C25H24O5	404 .46	1	5	1	116 .97	68. 9	3.7 3
1 3 8	5254	C25H22O5	402 .44	1	5	0	116 .23	65. 74	3.4 3
1 3 9	13543 3966	C20H18N2 O4	350 .37	3	5	1	100 .33	73. 58	3.1 3
1 4 0	10800 314	C14H12O4	244 .24	1	4	1	66. 59	55. 76	2.4 6
1 4 1	72304	C15H10O2	222 .24	1	2	0	67. 92	30. 21	2.5 1
1 4 2	10197 4031	C30H52O3	460 .73	4	3	3	139 .92	60. 69	4.6 5
1 4 3	53185 85	C20H18O6	354 .35	3	6	4	99. 73	111 .13	3

1 4 4	63827 8	C15H12O4	256 .25	3	4	3	72. 32	77. 76	2.0 2
1 4 5	68079	C13H10O5	246 .22	2	5	0	65. 24	61. 81	2.4 9
1 4 6	10336 876	C20H28O4	332 .43	1	4	2	91. 48	70. 67	1.8 3
1 4 7	3806	C10H6O3	174 .15	0	3	1	46. 27	54. 37	1.4 7
1 4 8	15998 2	C22H18O7	394 .37	4	7	0	104 .25	72. 45	3.4
1 4 9	44288 2	C21H16O6	364 .35	3	6	0	97. 76	63. 22	3.1 5
1 5 0	49317 3	C22H18O7	394 .37	4	7	0	104 .25	72. 45	3.4 4
1 5 1	3828	C14H12O5	260 .24	2	5	0	70. 21	61. 81	2.6 3
1 5 2	53189 98	C21H22O4	338 .4	6	4	2	100 .39	66. 76	2.9 4
1 5 2	12285 1	C21H20O7	384 .38	3	7	3	103 .42	109 .36	2.6 1

1 5 3	11482 9	C15H12O4	256 .25	1	4	2	69. 55	66. 76	1.7 3
1 5 4	72378	C16H17NO 4	287 .31	0	5	2	78. 4	62. 16	2.0 6
1 5 5	73659	C30H48O4	472 .7	1	4	3	137 .82	77. 76	3.5 5
1 5 6	30839 36	C7H8O3	140 .14	1	3	2	36. 98	49. 69	1.4 8
1 5 7	52816 70	C15H10O7	302 .24	1	7	5	78. 03	131 .36	1.4 7
1 5 8	52888 26	C17H19NO 3	285 .34	0	4	2	82. 27	52. 93	2.3 8
1 5 9	11060 358	C25H43NO 10	517 .61	10	10	3	128 .17	134 .17	3.3 9
1 6 0	10409 312	C24H42O5	410 .59	5	5	2	115 .8	75. 99	3.7 5
1 6 1	44585 437	C25H44O5	424 .61	5	5	2	120 .35	75. 99	3.7 9
1 6 2	4501	C21H18NO 4	348 .37	2	4	0	101 .6	40. 8	- 0.1 6

1 6 3	4374	C11H17NO	179 .26	3	2	1	54. 69	23. 47	2.4
1 6 4	53520 72	C21H21NO 4	351 .4	2	5	2	105 .66	73. 91	3.1 3
1 6 5	24198 103	C20H22CIN O4	375 .85	2	5	0	104 .38	40. 16	0
1 6 6	44281 3	C22H22O9	430 .4	5	9	4	108 .56	138 .82	2.7 7
1 6 7	34354 7	C18H11NO 4	305 .28	1	5	0	83. 17	57. 65	2.1 9
1 6 8	51359 6	C19H19NO 4	325 .36	1	5	1	92. 09	51. 16	2.7 3
1 6 9	4680	C20H21NO 4	339 .39	6	5	0	97. 16	49. 81	3.4 8
1 7 0	31161	C16H12O7	316 .26	2	7	4	82. 5	120 .36	1.2 5
1 7 1	67249	C15H11Cl O5	306 .7	1	5	4	80	94. 06	- 4.5 2
1 7 2	64509 48	C30H40O4	464 .64	16	4	4	142 .2	80. 92	5.6 7

1 7 3	46036 7	C22H29Br O3	421 .37	3	3	2	110 .79	57. 53	3.1 8
1 7 4	46036 8	C24H32O4	384 .51	5	4	2	113 .18	66. 76	3.4 6
1 7 5	64980	C29H46O4	458 .67	2	4	2	132 .78	74. 6	3.3 8
1 7 6	10205	C11H8O3	188 .18	0	3	1	51. 07	54. 37	1.7 9
1 7 7	10607	C22H22O8	414 .41	4	8	1	103 .85	92. 68	2.9 4
1 7 8	10160 9799	C17H28N4 O	304 .43	9	2	2	96. 41	84. 71	2.5 6
1 7 9	38283 1	C30H48O4	472 .7	1	4	3	138 .11	77. 76	3.5 8
1 8 0	11512 7	C27H44O6	464 .63	5	6	5	128 .54	118 .22	3.4 2
1 8 1	73360	C18H21NO 5	331 .36	1	6	1	88. 91	60. 39	2.4 8
1 8 2	72	C7H6O4	154 .12	1	4	3	37. 45	77. 76	0.6 6

1 8 3	12114 129	C30H50O3	458 .72	0	3	2	135 .53	49. 69	4.3 2
1 8 4	7028	C10H15NO	165 .23	3	2	2	49. 79	32. 26	2.2 5
1 8 5	7047	C9H7N	129 .16	0	1	0	41. 74	12. 89	1.7 3
1 8 6	11833 660	C20H32O2	304 .47	5	2	0	93. 69	34. 14	3.4
1 8 7	13943 700	C20H30O2	302 .45	4	2	0	93. 22	34. 14	3.2 5
1 8 8	52809 54	C35H42N2 O9	634 .72	11	10	1	175 .23	117 .78	4.8 8
1 8 9	5770	C33H40N2 O9	608 .68	10	10	1	165 .52	117 .78	4.3 9
1 9 0	10343 634	C24H32O8	448 .51	5	8	3	114	122 .52	2.3 6
1 9 1	10623 605	C27H34O6	454 .56	5	6	2	122 .69	100 .9	2.9 2
1 9 2	11729 855	C27H34O5	438 .56	4	5	1	121 .53	80. 67	3.2 3

1 9 3	11385 155	C27H36O5	440 .57	4	5	2	122 .79	83. 83	2.9 8
1 9 4	30003 22	C17H21NO 4	303 .35	5	5	1	83. 48	62. 3	2.7 4
1 9 5	52816 97	C15H10O6	286 .24	1	6	4	76. 01	111 .13	2.0 8
1 9 6	50399 1	C18H24O6	336 .38	7	6	4	92. 2	115 .06	3.1 1
1 9 7	50399 2	C18H24O6	336 .38	5	6	3	90. 26	104 .06	2.8 4
1 9 8	50399 3	C18H24O6	336 .38	5	6	3	90. 26	104 .06	1.8 7
1 9 9	53213 17	C20H21NO 4	339 .39	2	5	0	97. 07	40. 16	3.5 3
2 0 0	54593 08	C19H23NO 4	329 .39	2	5	1	94. 12	59	2.7 3
2 0 1	42608 235	C28H39Cl O9	555 .06	8	9	2	139 .14	131 .89	3.6 5
2 0 2	14060 358	C22H29Cl O7	440 .91	2	7	2	110 .25	110 .13	2.2 1

203	72978	C25H24O5	404 .46	1	5	1	116 .97	68. 9	3.7 3
204	13855 380	C20H28O4	332 .43	1	4	2	91. 48	70. 67	2.1 5
205	21672 083	C27H34O5	438 .56	4	5	1	121 .53	80. 67	3.2 3
206	10917 156	C27H34O5	438 .56	4	5	1	121 .53	80. 67	3.2 3
207	99281 12	C22H32O3	344 .49	1	3	1	102 .08	38. 69	3.8 7
208	10006 7	C22H26O8	418 .44	6	8	2	107 .89	95. 84	3.5 2
209	99729 13	C18H18O5	314 .33	4	5	2	85. 91	83. 83	2.4 7
210	46607 6	C19H20O3	296 .36	6	3	2	89. 52	49. 69	2.8 2
211	46607 7	C19H22O5	330 .37	7	5	4	92. 36	90. 15	2.4 8
212	72386	C13H8S2	228 .33	0	0	0	70. 74	50. 6	3.5 7

2 1 3	10984 902	C30H53Br O7	605 .64	7	7	3	153 .79	97. 61	5.1 2
2 1 4	72457	C20H14N4 O2	342 .35	3	3	4	99. 63	97. 56	1.8 4
2 1 5	45285 5	C21H24O7	388 .41	7	7	2	101 .8	94. 45	3.0 6
2 1 6	73549	C15H8N2O 2	248 .24	0	3	0	70. 77	51. 96	1.9 5
2 1 7	14371 275	C9H11N3O 2	193 .2	2	3	4	54. 49	104 .86	0.8 7
2 1 8	64818 23	C28H40O6	472 .61	10	6	2	135 .88	93. 06	3.9 9
2 1 9	64818 22	C28H40O6	472 .61	10	6	2	135 .88	93. 06	3.9 9
2 2 0	98175 50	C14H11N7 O	293 .28	1	4	3	83. 15	127 .98	0.8 1
2 2 1	18460 6	C30H53Br O7	605 .64	7	7	3	153 .79	97. 61	5.1 2
2 2 2	6716	C13H10O4	230 .22	1	4	0	63. 71	52. 58	2.4 4

2									
2	26523		470				127	96.	3.3
3	7	C28H38O6	.6	3	6	2	.49	36	9
2									
2	11294		470				127	96.	3.6
4	368	C28H38O6	.6	2	6	2	.53	36	8
2									
2	14236		454				126	76.	3.9
5	711	C28H38O5	.6	2	5	1	.33	13	1
2									
2	10155	C28H39Cl	523				135	124	4.0
6	9583	O7	.06	2	7	4	.75	.29	1
2									
2	30175		486				128	116	3.5
7	1	C28H38O7	.6	2	7	3	.77	.59	5
2									
2	12407		372				102	93.	3.2
8	2	C21H24O6	.41	10	6	2	.17	06	1
2									
2	30338		283				88.	40.	
9	36	C18H35O2	.47	16	2	0	47	13	4.3
2									
3	15927		300				71.	119	1.1
0	8	C14H20O7	.3	5	7	5	78	.61	6
2									
3	52881		454				140	60.	4.6
1	49	C30H46O3	.68	7	3	3	.88	69	3
2									
3		C12H17N4	265				73.	104	
2	1130	OS	.35	4	3	2	26	.15	-1.6

233	442630	C28H50N2O4	478.71	0	6	2	146.37	76.66	4.77
234	854019	C10H12N2O	176.22	1	2	0	53.33	33.2	1.63
235	31256	C6H12O2	116.16	2	2	1	32.36	37.3	1.52
236	51283	C3H7NO2	89.09	1	3	2	21.01	63.32	0.33
237	7193	C12H16O2	192.25	5	2	0	56.95	26.3	2.89
238	30011	C14H22Cl2N2O2	321.24	8	2	2	86.25	42.77	0
239	442649	C9H10N2	146.19	1	2	0	48.52	25.25	1.85
240	3931	C18H32O2	280.45	14	2	1	89.46	37.3	4.14
241	5202	C10H12N2O	176.22	2	2	3	52.8	62.04	1.18
242	12305270	C28H50N2O4	478.71	0	6	2	146.37	76.66	4.77

2 4 3	9396	C6H12ClO 4P	214 .58	6	4	0	47. 2	54. 57	2.8
2 4 4	8723	C5H12O	88. 15	2	1	1	27. 31	20. 23	1.8
2 4 5	15241 411	C10H20O3	188 .26	5	3	3	53. 27	60. 69	2.2 2
2 4 6	26613	C8H16O3	160 .21	6	3	2	43. 5	57. 53	1.7 4
2 4 7	52806 78	C10H18O2	170 .25	5	2	2	51. 6	40. 46	2.3 1
2 4 8	27354 73	C8H8N2OS	180 .23	3	1	2	49. 94	87. 21	1.3 6
2 4 9	1030	C3H8O2	76. 09	1	2	2	18. 86	40. 46	1
2 5 0	44489 9	C20H32O2	304 .47	14	2	1	98. 13	37. 3	4.6 4
2 5 1	52811 19	C14H26O2	226 .36	11	2	1	70. 71	37. 3	3.3 9
2 5 2	12035	C5H9NO3S	163 .19	4	3	2	38. 85	105 .2	0.6 5

2 5 3	13682 8302	C18H18N2 O2	294 .35	1	2	1	88. 65	47. 16	2.5 7
2 5 4	16724	C10H14O	150 .22	1	1	0	47. 32	17. 07	2.2 7
2 5 5	10197 7	C10H20O	156 .27	5	1	1	50. 87	20. 23	2.7 2
2 5 6	52845 43	C18H23NO 3	301 .38	1	4	1	87. 21	41. 93	2.9 5
2 6 7	359	C6H6O3	126 .11	0	3	3	32. 51	60. 69	0.6 6
2 5 8	52817 17	C14H12O4	244 .24	2	4	4	69. 9	80. 92	1.4 4
2 5 9	68077	C20H20O7	372 .37	6	7	0	100 .38	76. 36	3.7 1
2 6 0	53790 265	C12H19N3 O4	269 .3	6	4	0	70. 82	78. 53	2.8 1
2 6 1	72303	C18H18O2	266 .33	5	2	2	84. 14	40. 46	2.9 6
2 6 2	11272 0	C4H9NO2	103 .12	3	3	1	25. 33	52. 32	1.3 6

2 6 3	70699 355	C35H58O6	574 .83	8	6	4	165 .14	99. 38	4.2 3
2 6 4	64130 1	C9H8O2	148 .16	2	2	1	43. 56	37. 3	1.3 1
2 6 5	52805 35	C9H10O2	150 .17	2	2	2	44. 52	40. 46	1.5 1
2 6 6	11149 005	C13H14O4	234 .25	6	4	0	63. 74	52. 6	2.7 9
2 6 7	52803 43	C15H10O7	302 .24	1	7	5	78. 03	131 .36	1.6 3
2 6 8	52808 63	C15H10O6	286 .24	1	6	4	76. 01	111 .13	1.7
2 6 9	10237 107	C24H24O3	360 .45	8	3	0	108 .21	35. 53	3.6 5
2 7 0	53185 17	C20H30O5	350 .45	3	5	3	95. 21	86. 99	2.4 5
2 7 1	98480 24	C26H40O8	480 .59	7	8	4	125 .27	125 .68	3.2 7
2 7 2	57083 51	C20H28O4	332 .43	3	4	2	93. 58	66. 76	2.8 5

2 7 3	11666 871	C20H30O3	318 .45	4	3	1	92. 89	46. 53	3.3 4
2 7 4	63754 2	C9H8O3	164 .16	2	3	2	45. 13	57. 53	0.9 5
2 7 5	52804 60	C10H8O4	192 .17	1	4	1	51	59. 67	1.8 6
2 7 6	323	C9H6O2	146 .14	0	2	0	42. 48	30. 21	1.7 5
2 7 7	16051 1	C12H14N2 O2	218 .25	4	3	3	62. 26	65. 12	1.4 2
2 7 8	338	C7H6O3	138 .12	1	3	2	35. 42	57. 53	1.1 3
2 7 9	44535 4	C20H30O	286 .45	5	1	1	94. 67	20. 23	3.8 9
2 8 0	54670 067	C6H8O6	176 .12	2	6	4	35. 12	107 .22	0.3 9
2 8 1	65036	C6H10OS2	162 .27	5	1	0	45. 88	61. 58	1.9 5
2 8 2	87310	C6H11NO3 S	177 .22	5	4	2	43. 24	99. 6	0.5 5

283	2758	C10H18O	154 .25	0	1	0	47. 12	9.2 3	2.5 8
284	6549	C10H18O	154 .25	4	1	1	50. 44	20. 23	2.7
285	44219 5	C28H38N2 O4	466 .61	6	6	2	142 .58	63. 19	4.4 6
286	10219	C29H40N2 O4	480 .64	7	6	1	147 .05	52. 19	4.6 7
287	65380	C28H36N2 O4	464 .6	6	6	1	142 .88	63. 52	4.1 9
288	72341	C29H37N3 O3	475 .62	5	5	3	147 .95	69. 75	3.9 2
289	16532 7	C29H37N3 O3	475 .62	5	5	3	147 .95	69. 75	3.9 2
290	16500 3	C29H37N3 O2	459 .62	5	4	2	145 .92	49. 52	4.4 6
291	44216 6	C19H29NO 4	335 .44	5	5	2	98. 39	62. 16	3.2
292	44215 9	C29H37N3 O3	475 .62	5	5	3	147 .95	69. 75	4.2 5

293	56842090	C9H11NO	149.19	0	2	1	42.83	33.12	1.53
294	442157	C19H18N2O4	338.36	2	5	2	95	84.58	2.56
295	10853265	C19H18N2O3	322.36	2	4	1	94.85	62.66	2.79
296	46695	C11H15NO2	193.24	1	3	2	59.11	41.49	2.26
297	12302705	C28H38N2O4	466.61	6	6	2	142.58	63.19	4.46
298	158671	C18H27NO3	305.41	4	4	2	91.9	52.93	3.09
299	101946255	C18H19NO2	281.35	1	3	1	86.54	32.7	2.91
300	101946254	C18H19NO2	281.35	1	3	1	86.54	32.7	2.91
301	46229104	C20H22N2O3	338.4	2	4	1	99.39	50.8	2.97
302	72340	C21H24N2O3	352.43	2	4	1	103.47	54.56	3.2

3 0 3	11953 926	C22H29N2 O4	385 .48	3	4	3	113 .15	78. 79	-0.5
3 0 4	10314 057	C20H22N2 O2	322 .4	2	3	1	99. 91	41. 57	3.1 5
3 0 5	23274 110	C12H13Cl O2	224 .68	3	2	0	60	26. 3	2.6 1
3 0 6	30852 57	C12H16O2	192 .25	3	2	0	55. 91	26. 3	2.6 8
3 0 7	52803 78	C16H12O4	268 .26	2	4	1	76. 43	59. 67	2.4 9
3 0 8	2236	C17H11NO 7	341 .27	3	7	1	89. 79	110 .81	1.9 6
3 0 9	11946 5	C17H12O5	296 .27	2	5	1	80. 97	64. 99	2.3 7
3 1 0	53320 351	C17H13NO 4	295 .29	2	4	1	82. 1	70. 78	2.3
3 1 1	96709	C18H13NO 7	355 .3	4	7	0	94. 11	99. 81	2.9 9
3 1 2	42608 203	C15H24O	220 .35	0	1	1	66. 14	20. 23	2.8 7

3 1 3	92812	C15H26O	222 .37	0	1	1	68. 82	20. 23	3.0 8
3 1 4	15559 789	C15H22O	218 .33	0	1	0	65. 18	17. 07	2.6 9
3 1 5	15905 5	C10H16O	152 .23	0	1	0	45. 64	17. 07	2.1 2
3 1 6	22384	C15H25NO 5	299 .36	6	6	3	81. 14	90. 23	2.3 4
3 1 7	10793 8	C15H25NO 5	299 .36	6	6	3	81. 14	90. 23	2.3 4
3 1 8	11470 3	C14H16O3	232 .28	2	3	0	67. 25	35. 53	2.6 2
3 1 9	54877 90	C28H34O5	450 .57	6	5	0	132 .63	46. 15	5.3 3
3 2 0	28619	C12H14O2	190 .24	1	2	0	57. 05	18. 46	2.7 4
3 2 1	12565	C13H16O3	220 .26	2	3	0	63. 55	27. 69	2.9 6
3 2 2	72815	C22H24O9	432 .42	8	9	0	113 .36	94. 82	4.1 3

3 2 3	72344	C21H22O8	402 .39	7	8	0	106 .87	85. 59	3.9 6
3 2 4	14565 9	C20H20O7	372 .37	6	7	0	100 .38	76. 36	3.6 6
3 2 5	10089 586	C19H16O7	356 .33	4	7	0	93. 46	76. 36	3.4 6
3 2 6	68904 3	C9H8O4	180 .16	2	4	3	47. 16	77. 76	0.9 7
3 2 7	44497 2	C4H4O4	116 .07	2	4	2	24. 41	74. 6	0.3 2
3 2 8	52817 58	C12H16O3	208 .25	4	3	0	60. 82	27. 69	3.0 2
3 2 9	63682 2	C12H16O3	208 .25	4	3	0	60. 82	27. 69	3.0 2
3 3 0	10248	C12H16O3	208 .25	5	3	0	60. 02	27. 69	2.8 9
3 3 1	15490 41	C10H12O2	164 .2	2	2	1	49. 86	29. 46	2.3 8
3 3 2	85343 3	C10H12O2	164 .2	2	2	1	49. 86	29. 46	2.3 8

3									
3			262				69.	63.	2.1
3	23205	C15H18O4	.3	0	4	1	32	6	1
3									
3	30329		264				69.	63.	2.1
4	10	C15H20O4	.32	0	4	1	79	6	7
3									
3	44559		362				94.	89.	2.3
4	333	C20H26O6	.42	3	6	1	64	9	5
3									
3	10019		324				81.	93.	1.9
5	140	C17H24O6	.37	2	6	2	65	06	9
3									
3			290				74.	110	1.4
6	9064	C15H14O6	.27	1	6	5	33	.38	7
3									
3			290				74.	110	1.4
7	72276	C15H14O6	.27	1	6	5	33	.38	7
3									
3		C8H10N4O	194				52.	61.	1.7
8	2519	2	.19	0	3	0	04	82	9
3									
3	52816		316				82.	120	2.2
9	91	C16H12O7	.26	2	7	4	5	.36	3
3									
4	44239		274				72.	90.	1.6
0	7	C15H14O5	.27	1	5	4	31	15	2
3									
4		C20H18NO	336				94.	40.	
1	2353	4	.36	2	4	0	87	8	0

3 4 2	4970	C20H19NO 5	353 .37	0	6	0	97. 49	57. 23	3.1 9
3 4 3	5154	C20H14NO 4	332 .33	0	4	0	94. 68	40. 8	- 0.0 4
3 4 4	2703	C21H18NO 4	348 .37	2	4	0	101 .6	40. 8	0.2 2
3 4 5	30851 81	C21H19NO 6	381 .38	5	6	1	105 .25	77. 46	2.8 6
3 4 6	30847 08	C19H16NO 4	322 .33	1	4	1	90. 41	51. 8	- 0.3 4
3 4 7	98570	C21H23NO 5	369 .41	2	6	0	104 .41	57. 23	3.3 8
3 4 8	72322	C19H14NO 4	320 .32	0	4	0	87. 95	40. 8	- 0.1 7
3 4 9	72323	C20H20NO 4	338 .38	3	4	1	97. 33	51. 8	- 0.1 5
3 5 0	72310	C20H20NO 4	338 .38	3	4	1	97. 33	51. 8	- 0.0 9
3 5 1	11066	C20H17NO 5	351 .35	2	5	0	96. 81	58. 92	3.3 1

3 5 2	10983	C6H13N3	127 .19	2	1	2	39. 58	64. 4	1.3 3
3 5 3	8343	C24H38O4	390 .56	16	4	0	116 .3	52. 6	4.7 7
3 5 4	44293 5	C11H10N2 O2	202 .21	0	3	1	56. 09	55. 12	1.6 7
3 5 5	15872 0	C11H10N2 O3	218 .21	0	4	2	58. 11	75. 35	1.5 2
3 5 6	44293 4	C11H12N2 O2	204 .23	0	3	2	64. 13	56. 06	1.4
3 5 7	9210	C8H6N2	130 .15	0	2	0	39. 54	25. 78	1.6 2
3 5 8	6780	C14H8O2	208 .21	0	2	0	59. 75	34. 14	1.9 4
3 5 9	44453 9	C9H8O2	148 .16	2	2	1	43. 11	37. 3	1.5 5
3 6 0	227	C7H7NO2	137 .14	1	2	2	37. 81	63. 32	1.0 4
3 6 1	996	C6H6O	94. 11	0	1	1	28. 46	20. 23	1.2 4

3 6 2	13220	C9H17NO	155 .24	0	2	1	50. 26	29. 1	2.0 8
3 6 3	6773	C15H10O2	222 .24	0	2	0	64. 72	34. 14	2.2
3 6 4	30340 34	C20H24N2 O2	324 .42	4	4	1	99. 73	45. 59	3.3 6
3 6 5	370	C7H6O5	170 .12	1	5	4	39. 47	97. 99	0.2 1
3 6 6	525	C4H6O5	134 .09	3	5	3	26. 05	94. 83	- 0.0 1
3 6 7	44563 9	C18H34O2	282 .46	15	2	1	89. 94	37. 3	4.2 7
3 6 8	57386 859	C20H18N2 O5	366 .37	7	5	4	101 .26	111 .65	2.3 1
3 6 9	1110	C4H6O4	118 .09	3	4	2	24. 89	74. 6	0.3 2
3 7 0	10805 8	C30H36O9	540 .6	8	9	0	138 .81	118 .34	3.9 5
3 7 1	44715 635	C28H34O7	482 .57	6	7	0	128 .17	92. 04	3.8 8

3 7 2	73900 4	C11H8CIN3 OS2	297 .78	5	2	2	76. 74	114 .35	2.4 6
3 7 3	15727 7	C26H32O7	456 .53	4	7	2	119 .63	106 .2	4.0 2
3 7 4	10001 7	C27H30O7	466 .52	4	7	0	120 .99	92. 04	3.5 1
3 7 5	11119 228	C18H24O2	272 .38	0	2	1	82. 44	37. 3	2.8 6
3 7 6	43167 3	C20H27NO 3	329 .43	0	4	3	92. 5	63. 93	2.4 1
3 7 7	44173 5	C22H33NO 5	391 .5	2	6	2	106 .21	79. 23	2.6 5
3 7 8	64737 64	C24H39NO 4	405 .57	5	5	1	115 .69	66. 84	3.9 1
3 7 9	25157 5	C22H26N2 O4	382 .45	3	5	1	109 .96	63. 79	3.4 8
3 8 0	10128 9617	C22H33NO 4	375 .5	2	5	1	105 .04	59	3.0 8
3 8 1	10168 5340	C21H27NO 4	357 .44	0	5	2	98. 66	77. 84	1.9 1

3 8 2	15870 6	C20H28O3	316 .43	0	3	1	88. 88	46. 53	2.6 9
3 8 3	7428	C8H8O5	184 .15	2	5	3	43. 79	86. 99	0.9 6
3 8 4	12285 0	C15H12O6	288 .25	1	6	4	72. 73	107 .22	1.4 2
3 8 5	932	C15H12O5	272 .25	1	5	3	71. 57	86. 99	1.7 5
3 8 6	44146 7	C11H19NO 6	261 .27	4	7	4	59. 48	123 .17	0.9 5
3 8 7	68085	C12H9NO2	199 .21	1	3	0	58. 01	35. 26	2.3 8
3 8 8	33470 4	C14H14O4	246 .26	1	4	1	67. 45	59. 67	2.5 5
3 8 9	64502 30	C19H24O5	332 .39	7	5	2	94. 13	79. 9	3.0 9
3 9 0	52814 26	C9H6O3	162 .14	0	3	1	44. 51	50. 44	1.4 4
3 9 1	6760	C14H13NO 4	259 .26	3	5	0	70. 99	53. 72	2.7 8

3 9 2	10212	C16H14O4	270 .28	3	4	0	77. 5	52. 58	3.0 5
3 9 3	69502	C16H14O4	270 .28	2	4	1	78	63. 58	2.6 2
3 9 4	6199	C11H6O3	186 .16	0	3	0	52. 26	43. 35	2.0 1
3 9 5	10094 9562	C20H24N2 O2	324 .42	2	2	2	98. 71	48. 63	2.6 5
3 9 6	16755 1	C22H36O3	348 .52	15	3	2	107 .69	57. 53	4.1 9
3 9 7	15875 260	C18H26O4	306 .4	11	4	1	89. 6	55. 76	4.1 5
3 9 8	10159 3045	C27H32O9	500 .54	4	9	1	123 .78	124 .8	2.8 1
3 9 9	65188	C14H12O3	228 .24	0	3	0	66. 61	39. 44	2.6 2
4 0 0	15499 92	C15H26O	222 .37	4	1	1	72. 36	20. 23	3.4 6
4 0 1	15506 07	C19H22O3	298 .38	6	3	0	91. 29	39. 44	3.9 6

4 0 2	44288 7	C23H25NO 4	379 .45	4	4	4	115 .58	93. 55	3.8 2
4 0 3	15286 416	C24H27NO 4	393 .48	4	4	3	120 .49	82. 69	3.7
4 0 4	10128 1327	C27H30O9	498 .52	4	9	0	122 .82	121 .64	3.0 1
4 0 5	10131 6727	C26H28O8	468 .5	1	8	1	115 .52	115 .57	2.1 6
4 0 6	10658	C11H6O3	186 .16	0	3	0	52. 26	43. 35	2.0 3
4 0 7	985	C16H32O2	256 .42	14	2	1	80. 8	37. 3	3.8 5
4 0 8	52811 26	C18H30O2	278 .43	13	2	1	88. 99	37. 3	4.0 6
4 0 9	64408 56	C13H12O2	200 .23	2	2	0	59. 27	26. 3	2.3 3
4 1 0	73202	C15H12O5	272 .25	1	5	3	70. 71	86. 99	1.7 5
4 1 1	36959 8	C18H16O4	296 .32	2	4	1	86. 37	59. 67	3.2

4 1 2	18055 0	C17H16O4	284 .31	1	4	2	79. 48	66. 76	2.6 5
4 1 3	54888 01	C26H32O8	472 .53	2	8	2	118 .77	115 .43	3.2 3
4 1 4	21768 173	C26H34O8	474 .54	4	8	3	122 .15	134 .27	2.3 8
4 1 5	10104 9584	C26H34O8	474 .54	2	8	3	119 .73	118 .59	3.0 7
4 1 6	5971	C4H5NS	99. 15	2	1	0	30. 03	44. 45	1.9 3
4 1 7	53658 13	C5H5NOS	127 .16	2	2	0	35. 04	61. 52	1.9 5
4 1 8	10132 4856	C30H48O4	472 .7	1	4	2	136 .7	58. 92	4.2 9
4 1 9	14018 346	C18H14O6	326 .3	1	6	2	87. 36	89. 13	2.9 9
4 2 0	14018 348	C17H12O6	312 .27	0	6	3	82. 63	100 .13	2.4 7
4 2 1	13940 643	C18H16O7	344 .32	1	7	3	86. 43	105 .45	2.2 3

4 2 2	15081 178	C18H14O7	342 .3	1	7	3	89. 38	109 .36	2.5 6
4 2 3	11537 197	C17H12O7	328 .27	0	7	4	84. 65	120 .36	2.0 6
4 2 4	12004 175	C17H10O7	326 .26	0	7	3	87. 07	121 .11	2.0 1
4 2 5	5962	C6H14N2O 2	146 .19	5	4	3	38. 14	89. 34	0.9 8
4 2 6	6137	C5H11NO2 S	149 .21	4	3	2	38. 22	88. 62	1.1 7
4 2 7	16087 5	C17H17NO 2	267 .32	1	3	2	82. 59	41. 49	2.5 8
4 2 8	345	C7H8O6	188 .13	4	6	3	40. 6	111 .9	0
4 2 9	52804 43	C15H10O5	270 .24	1	5	3	73. 99	90. 9	1.8 9
4 3 0	52804 45	C15H10O6	286 .24	1	6	4	76. 01	111 .13	1.8 6
4 3 1	68071	C15H12O4	256 .25	1	4	2	69. 55	66. 76	2.1 1

4 3 2	29025	C10H14O	150 .22	0	1	0	45. 42	17. 07	2.1 9
4 3 3	61126	C10H16O	152 .23	0	1	1	46. 38	20. 23	2.2 6
4 3 4	63756 6	C10H18O	154 .25	4	1	1	50. 4	20. 23	2.7 5
4 3 5	6989	C10H14O	150 .22	1	1	1	48. 01	20. 23	2.3 2
4 3 6	10364	C10H14O	150 .22	1	1	1	48. 01	20. 23	2.2 4
4 3 7	53433 123	C14H8O3	224 .21	0	3	0	61. 08	51. 21	1.3 9
4 3 8	52817 44	C18H23NO 6	349 .38	1	7	2	92. 62	96. 3	2.4 8
4 3 9	52817 50	C18H23NO 5	333 .38	0	6	1	91. 46	76. 07	3.0 3
4 4 0	52809 06	C18H25NO 5	335 .39	0	6	1	91. 93	76. 07	2.8 3
4 4 1	11904 0	C18H27NO 6	353 .41	1	7	2	93. 6	96. 3	2.8 6

4									
4	11903		488				139	97.	2.8
2	4	C30H48O5	.7	2	5	4	.24	99	9
4									
4	69569		488				139	97.	3.1
3	689	C30H48O5	.7	1	5	4	.24	99	6
4									
4			164				52.	9.2	2.7
4	14104	C11H16O	.24	2	1	0	48	3	7
4									
4	91820	C10H13NO	227				57.	104	0.9
5	550	3S	.28	5	3	1	9	.05	7
4									
4			60.				13.	37.	0.6
6	176	C2H4O2	05	0	2	1	5	3	3
4									
4			172				51.	37.	
7	2969	C10H20O2	.26	8	2	1	96	3	2.5
4									
4	15489	C18H27NO	305				90.	58.	3.1
8	43	3	.41	10	3	2	52	56	5
4									
4	16883	C17H27NO	293				86.	58.	2.8
9	6	3	.4	10	3	2	19	56	2
4									
5	30843	C19H31NO	321				95.	58.	3.6
0	36	3	.45	12	3	2	8	56	6
4									
5	64425	C19H29NO	319				95.	58.	3.6
1	66	3	.44	11	3	2	33	56	7

4									
5			270				70.	94.	1.8
2	3220	C15H10O5	.24	0	5	3	78	83	1
4									
5	12406		254				68.	74.	1.9
3	2	C15H10O4	.24	0	4	2	76	6	4
4									
5			284				70.	111	1.3
4	10168	C15H8O6	.22	1	6	3	75	.9	7
4									
5			228				71.	37.	3.3
5	11005	C14H28O2	.37	12	2	1	18	3	2
4									
5	10447		306				81.	69.	3.0
6	866	C17H22O5	.35	5	5	0	43	67	5
4									
5	52809		278				88.	37.	3.3
7	34	C18H30O2	.43	13	2	1	99	3	6
4									
5	96951		368				102	93.	3.2
8	6	C21H20O6	.38	8	6	2	.8	06	7
4									
5	54694		338				96.	83.	2.7
9	24	C20H18O5	.35	7	5	2	31	83	8
4									
6	53154		308				89.	74.	1.7
0	72	C19H16O4	.33	6	4	2	82	6	5
4									
6	22216		458				121	117	2.8
1	0	C26H34O7	.54	3	7	3	.48	.2	8

4 6 2	795	C3H4N2	68. 08	0	1	1	18. 59	28. 68	0
4 6 3	52804 50	C18H32O2	280 .45	14	2	1	89. 46	37. 3	4.1 4
4 6 4	5610	C8H11NO	137 .18	2	2	2	40. 95	46. 25	1.3 6
4 6 5	91439	C27H44O3	416 .64	0	3	1	122 .07	38. 69	4.4
4 6 6	92095	C27H44O3	416 .64	0	3	1	122 .07	38. 69	4.4
4 6 7	44201 4	C24H34O7	434 .52	6	7	0	111 .78	83. 59	3.8 1
4 6 8	5281	C18H36O2	284 .48	16	2	1	90. 41	37. 3	4.3
4 6 9	52818 77	C26H36O8	476 .56	8	8	4	127 .87	133 .52	3.7 2
4 7 0	62852 8	C18H16O5	312 .32	4	5	0	87. 4	57. 9	3.2 8
4 7 1	8815	C10H12O	148 .2	3	1	0	47. 04	9.2 3	2.4 7

4 7 2	63756 3	C10H12O	148 .2	2	1	0	47. 83	9.2 3	2.5 5
4 7 3	66957 732	C20H24O2	296 .4	5	2	1	94. 58	29. 46	4.6 5
4 7 4	53168 79	C14H18O	202 .29	4	1	0	66. 59	9.2 3	3.4 3
4 7 5	11230	C10H18O	154 .25	1	1	1	48. 8	20. 23	2.5 1
4 7 6	64284 32	C10H14O	150 .22	3	1	0	48. 96	17. 07	2.4 8
4 7 8	64284 31	C10H14O	150 .22	3	1	0	48. 96	17. 07	2.4 8
4 7 9	52845 07	C15H26O	222 .37	7	1	1	74	20. 23	3.6 4
4 8 0	68081	C16H14O4	270 .28	3	4	0	77. 5	52. 58	3.0 7
4 8 1	33306	C16H14O5	286 .28	3	5	0	76. 98	65. 11	3
4 8 2	2355	C12H8O4	216 .19	1	4	0	58. 75	52. 58	2.2 9

4 8 3	4114	C12H8O4	216 .19	1	4	0	58. 75	52. 58	2.2 2
4 8 4	65090	C11H6O4	202 .16	0	4	1	54. 28	63. 58	1.6 9
4 8 5	11906 6	C19H22O4	314 .38	3	4	1	91. 05	59. 67	3.4 7
4 8 6	44429 171	C19H22O3	298 .38	6	3	0	91. 29	39. 44	3.9 3
4 8 7	64398 23	C21H18O6	366 .36	5	6	0	100 .23	78. 88	3.5 4
4 8 8	45267 954	C15H20O6	296 .32	0	6	2	69. 95	93. 06	1.5
4 8 9	17965 1	C26H30O8	470 .51	1	8	0	116 .17	104 .57	2.8 7
4 9 0	44181 2	C26H30O8	470 .51	1	8	1	117 .89	115 .57	2.5 3
4 9 1	54586 00	C25H32O8	460 .52	1	8	2	114 .56	118 .73	2.8 9
4 9 2	6854	C12H9N	167 .21	0	0	1	55. 8	15. 79	1.8 2

4 9 3	44178 674	C19H17NO 4	323 .34	2	4	1	89. 86	63. 85	2.6 6
4 9 4	44178 760	C19H17NO 3	307 .34	2	3	1	90. 38	51. 32	2.8 8
4 9 5	13175 1786	C16H19NO 8	353 .32	11	9	2	81. 48	135 .31	1.8 5
4 9 6	99516	C27H44O3	416 .64	0	3	1	122 .07	38. 69	4.4
4 9 7	99474	C27H42O3	414 .62	0	3	1	121 .59	38. 69	4.4 1
4 9 8	10639	C16H12O5	284 .26	1	5	2	75. 25	83. 83	2.4 9
4 9 9	62852	C14H28O6	292 .37	9	6	4	74. 12	99. 38	1.4 2
5 0 0	97560	C15H10O5	270 .24	0	5	3	70. 78	94. 83	2.2 4
5 0 1	10151	C15H10O5	270 .24	0	5	3	70. 78	94. 83	2.2 2
5 0 2	12444 971	C16H12O6	300 .26	1	6	3	77. 28	104 .06	2.3 6

5 0 3	10207	C15H10O5	270 .24	1	5	3	69. 92	94. 83	1.9 5
5 0 4	10208	C15H10O4	254 .24	0	4	2	68. 76	74. 6	2.2 2
5 0 5	72537	C15H12O5	272 .25	1	5	2	75. 49	79. 9	2.8 5
5 0 6	10446 798	C16H16O5	288 .3	1	5	3	78. 35	86. 99	2.4 7
5 0 7	16071 7	C16H12O5	284 .26	1	5	2	75. 25	83. 83	2.0 5
5 0 8	91746 921	C21H28O5 Si2	416 .62	5	5	0	116 .85	53. 99	4.2 4
5 0 9	52319 80	C15H12O5	272 .25	1	5	2	75. 49	79. 9	2.7 9
5 1 0	62763 8	C16H16O6	304 .29	1	6	3	79. 43	96. 22	2.4 4
5 1 1	15538 1	C19H18O7	358 .34	4	7	1	92. 71	91. 29	2.9 5
5 1 2	15501 1	C17H14O7	330 .29	2	7	3	83. 77	113 .29	2.1 9

5 1 3	15538 0	C18H16O7	344 .32	3	7	2	88. 24	102 .29	2.6
5 1 4	10680	C15H10O2	222 .24	1	2	0	67. 92	30. 21	2.5 5
5 1 5	7172	C9H13NO2	167 .21	3	3	3	47. 01	52. 49	1.5 2
5 1 6	4581	C8H11NO2	153 .18	2	3	3	42. 11	66. 48	1.0 1
5 1 7	9727	C9H13NO	151 .21	3	2	2	45. 85	32. 26	1.8 6
5 1 8	44301 3	C22H22O8	414 .41	4	8	1	103 .85	92. 68	2.9 4
5 1 9	18202 6	C16H14O7	318 .28	1	7	5	79. 72	127 .45	1.8 3
5 2 0	13185 2604	C16H14O7	318 .28	1	7	5	79. 72	127 .45	1.4 5
5 2 1	43953 3	C15H12O7	304 .25	1	7	5	74. 76	127 .45	1.3
5 2 2	62693 1	C36H38N2 O6	594 .7	2	8	2	177 .14	83. 86	4.5 6

5 2 3	62852 0	C37H40N2 O6	608 .72	3	8	1	181 .6	72. 86	4.7 7
5 2 4	22169 421	C23H19N	309 .4	4	1	0	100 .65	12. 89	3.3 2
5 2 5	53157 73	C18H16O8	360 .31	4	8	3	93. 47	118 .59	2.9 8
5 2 6	3893	C12H24O2	200 .32	10	2	1	61. 57	37. 3	2.7
5 2 7	44563 8	C16H30O2	254 .41	13	2	1	80. 32	37. 3	3.5 3
5 2 8	10444 703	C15H20O3	248 .32	3	3	1	71. 01	54. 37	2.1 9
5 3 0	7293	C3H8N2O	88. 11	2	1	2	22. 73	41. 13	1
5 3 1	99656 63	C15H10O6	286 .24	1	6	4	76. 01	111 .13	1.0 6
5 3 2	14585 8	C15H11O	207 .25	1	1	0	66. 06	13. 14	- 0.6 8
5 3 3	15687 5	C20H18O8	386 .35	4	8	2	98. 82	107 .59	3

5 3 4	11464 176	C21H20O9	416 .38	5	9	2	105 .31	116 .82	3.1 8
5 3 5	13965 876	C21H20O9	416 .38	5	9	2	105 .31	116 .82	3.0 1
5 3 6	10208 8154	C29H34O7	494 .58	0	7	4	132 .39	124 .27	3.5 3
5 3 7	10891 721	C16H22O5	294 .34	4	5	2	78. 07	83. 83	2.1 5
5 3 8	31289	C9H18O	142 .24	7	1	0	45. 58	17. 07	2.4 4
5 3 9	91750 943	C13H22O	194 .31	0	1	0	60. 77	9.2 3	2.9 1
5 4 0	9895	C10H16O	152 .23	1	1	0	47. 54	17. 07	2.2 3
5 4 1	44210 6	C14H18N2 O2	246 .3	4	2	1	69. 5	55. 92	- 1.6 5
5 4 2	5570	C7H7NO2	137 .14	1	2	0	35. 05	44. 01	- 3.1 1
5 4 3	54878 55	C17H14O7	330 .29	3	7	3	86. 97	109 .36	2.5 1

5 4 4	5862	C3H7NO2S	121 .16	2	3	2	28. 94	102 .12	0.3 7
5 4 5	6305	C11H12N2 O2	204 .23	3	3	3	57. 36	79. 11	0.9 4
5 4 6	6410	C4H10O2	90. 12	1	2	1	24. 04	29. 46	1.5 8
5 4 7	424	C4H7NO4	133 .1	3	5	3	27. 59	100 .62	- 0.1 4
5 4 8	602	C3H7NO2	89. 09	1	3	2	21. 01	63. 32	0.3 3
5 4 9	750	C2H5NO2	75. 07	1	3	2	16. 21	63. 32	0.3 7
5 5 0	63830 9	C15H8O3	236 .22	0	3	0	69. 76	43. 35	2.5 6
5 5 1	52818 13	C16H10O7	314 .25	1	7	3	82. 32	113 .27	1.9 2
5 5 2	54896 05	C15H8O7	300 .22	0	7	4	77. 85	124 .27	1.6 3
5 5 3	89594	C10H14N2	162 .23	1	2	0	53. 13	16. 13	2.1 4

5									
5			123				31.	50.	0.8
4	938	C6H5NO2	.11	1	3	1	2	19	6
5									
5			150				47.	17.	2.2
5	7439	C10H14O	.22	1	1	0	32	07	7
5									
5			152				49.	17.	2.4
6	63801 1	C10H16O	.23	4	1	0	44	07	7
5									
5			156				50.	20.	2.7
7	8842	C10H20O	.27	5	1	1	87	23	2
5									
5			196				60.	26.	2.8
8	15490 26	C12H20O2	.29	6	2	0	13	3	3
5									
5			386				110	83.	3.2
9	10198 9995	C23H30O5	.48	5	5	2	.55	83	4
5									
6			386				110	83.	3.1
0	11728 770	C23H30O5	.48	5	5	2	.55	83	5
5									
6			218				71.	20.	3.2
1	12283 6	C15H22O	.33	4	1	1	57	23	4
5									
6			358				93.	78.	
2	21575 210	C20H22O6	.39	3	6	0	87	9	2.7
5									
6			358				93.	78.	
3	13167 6067	C20H22O6	.39	3	6	0	87	9	2.7

5 6 4	10158 49	C22H18N2 O3	358 .39	5	4	1	105 .12	64. 36	3.3 3
5 6 5	15747 9	C20H28O5	348 .43	1	5	4	93. 51	97. 99	1.9 2
5 6 6	15231 941	C25H24O5	404 .46	3	5	3	119 .16	90. 9	3.5 1
5 6 7	15231 942	C25H24O6	420 .45	2	6	3	118 .38	100 .13	3.3 3
5 6 8	52803 71	C11H6O4	202 .16	0	4	1	54. 28	63. 58	1.7
5 6 9	13314 5	C20H24O3	312 .4	9	3	1	93. 45	46. 53	3.5 8
5 7 0	44197 5	C21H24N2 O3	352 .43	2	4	1	103 .47	54. 56	3.2
5 7 1	92114	C24H27NO 4	393 .48	4	5	0	119 .16	40. 16	4.0 4
5 7 2	16174 9	C22H23NO 4	365 .42	2	5	2	109 .37	62. 16	3.4
5 7 3	16059 7	C17H15NO 2	265 .31	0	3	1	80. 13	30. 49	2.7 6

5 7 4	10146	C19H21NO 2	295 .38	2	3	0	91. 96	21. 7	3.2 2
5 7 5	64406 59	C18H19NO 4	313 .35	7	4	3	88. 98	78. 79	2.5 8
5 7 6	72511 85	C15H20O3	248 .32	0	3	0	69. 34	38. 83	2.4 9
5 7 7	44227 9	C15H20O3	248 .32	0	3	1	69. 41	46. 53	2.5 8

5.3 Igem dock:

Igem docking has been done for the compounds (577 ligands) which have shown best activity from SWISS ADME studies.

Based on total energy values 10 best ligands were predicted from igem dock results.

Table:5.2: Docking results of Igem dock.

S. No:	Ligands	Total energy	VDW	HBond	Elec	Aver Con Pair
1	Nimbolide	-142.31	-125.9	-16.38	0	23.735
2	Atisenol	-135.975	-131.3	-4.622	0	41.608

3	Acarbidine A	- 135.772	- 110.0	-25.01	- 0.712	24.545
4	4-Epi- Scopadulcic acid B	- 133.606	- 117.8	-15.54	- 0.259	25.625
5	Glycoside	- 132.925	- 103.8	-29.03	0	25.272
6	Petrosynol	- 129.608	- 126.1	-3.42	0	22.441
7	DiFurocumenonol	- 127.786	- 102.9	-24.80	0	22.472
8	Di (2-ethylhexyll phthalate)	- 121.491	- 104.1	-17.34	0	23
9	Stigmasteryl glucoside	- 121.349	-94.3	-27.00	0	20.756
10	Tinocordioside	- 119.657	-86.2	-33.40	0	24.147

5.4 Auto dock vina:

Auto dock vina is considered best molecular docking software for the prediction of protein ligand interaction. For further more clarification, molecular docking has been

done for the 10 ligands which have shown best activity in igem dock. By using discovery studio 2D structures of protein ligand docking was visualization.

Table: 5.3: Docking results of auto dock vina.

S. NO:	Ligands	Score	HBonds (All)
1	Nimbolide	-6.9	4
2	Atisenol	-1	0
3	Acarnidine A	-5	4
4	4-Epi-Scopadulcic acid B	-7	3
5	Glycoside	-7.9	2
6	Petrosynol	-5	3
7	DiFurocumenonol	-8	1
8	Di (2-ethylhexyll phthalate)	-4.4	1
9	Stigmasteryl glucoside	-8	5
10	Tinocordioside	-7.7	4

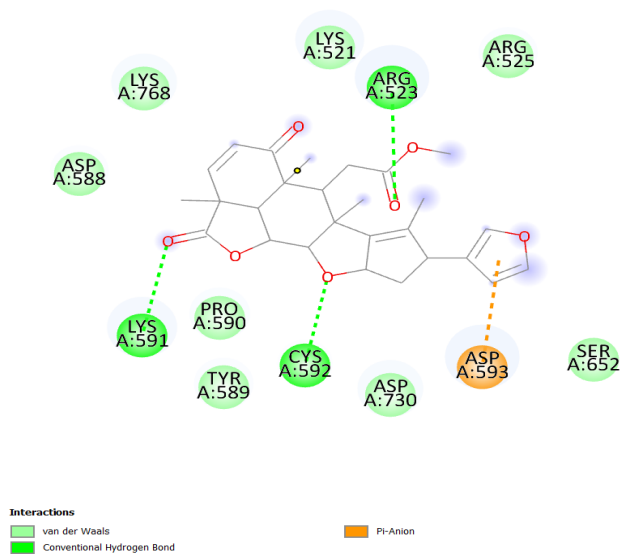


Figure: 5.2: 2D docking diagram of Nimbolide.

(The Interacting residues are LYS A:591, ARG A:523).

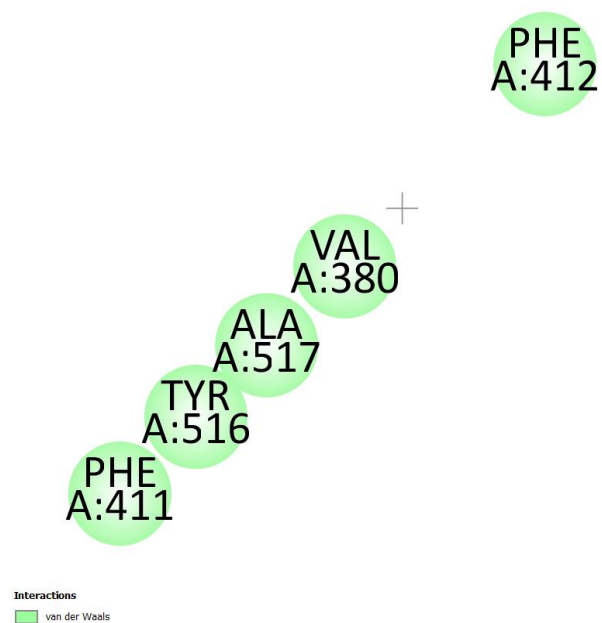


Figure: 5.3: 2D docking diagram of Atisenol.

(There are no interacting residues).

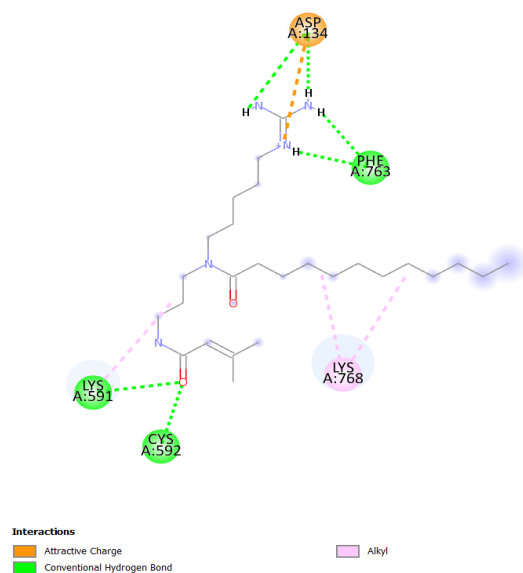


Figure: 5.4: 2D docking diagram for Acarnidine A.

(The interacting residues are LYS A:591, CYS A: 592, PHE A:763).

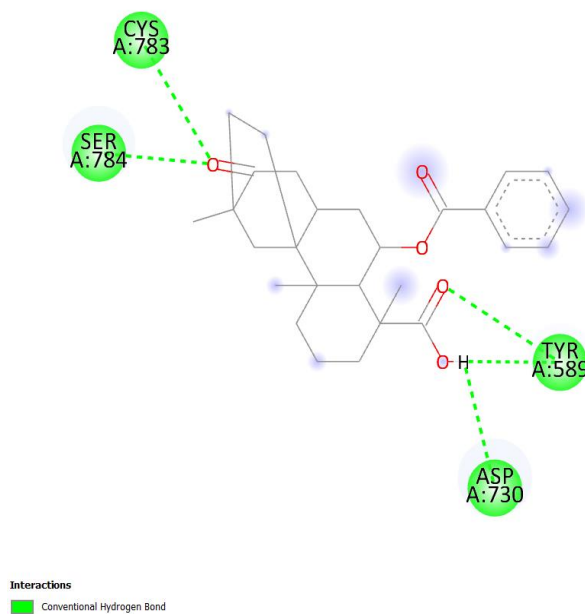


Figure: 5.5: 2D docking diagram of 4-Epi-Scopadulcic acid B.

(The interacting residues are TYR A:589, ASP A:730, CYS A:783, SER A:784).

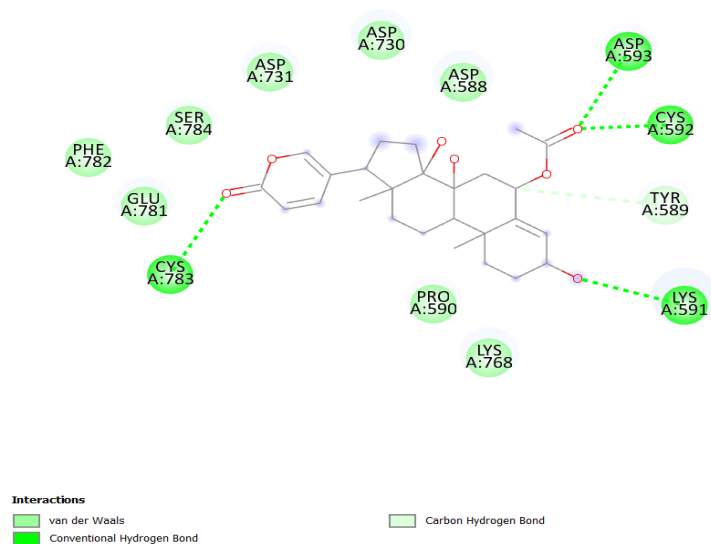


Figure: 5.6: 2D docking diagram of Glycoside.

(The interacting residues are CYS A:783, ASP A: 593, CYS A592, LYS A: 591).

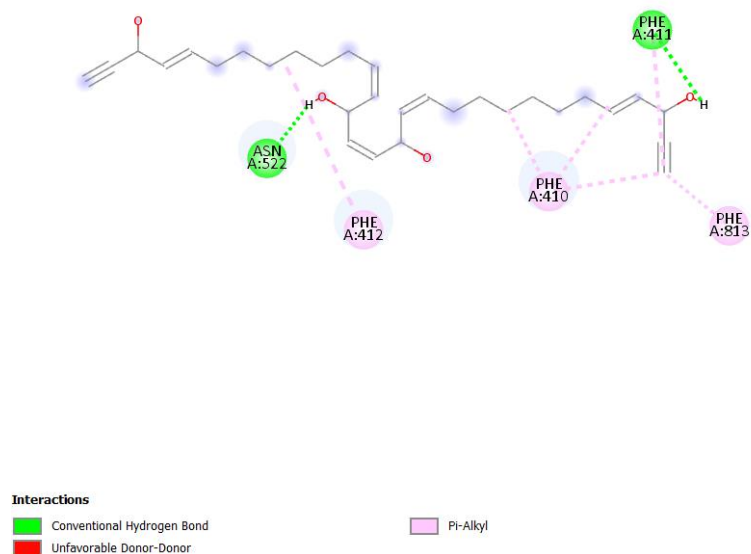


Figure: 5.7: 2D docking diagram of Petrosynol.

(The interacting residues are ASN A:522, PHE A:411).

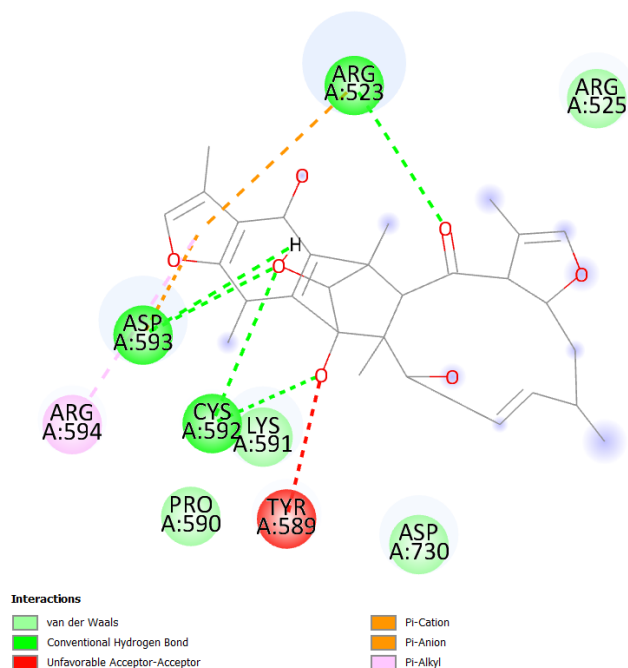


Figure: 5.8: 2D docking diagram of DiFurocumenonol.

(The interacting residues are ASP A:593, CYS A:592, ARG A:523).

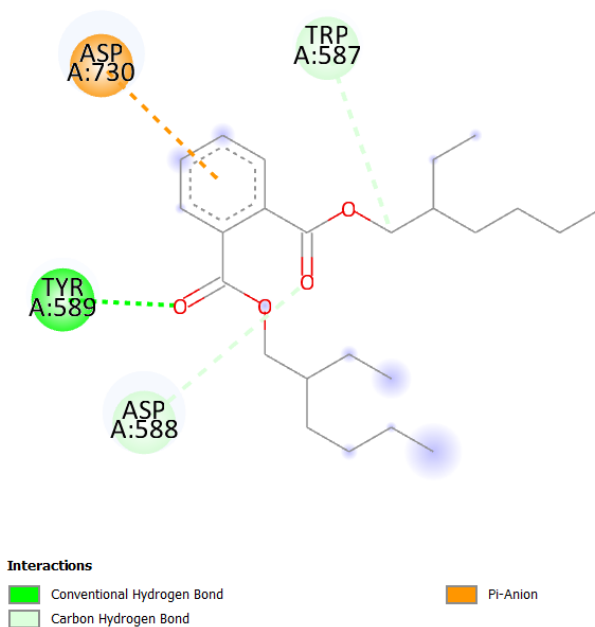


Figure: 5.9: 2D docking diagram of di (2-ethylhexyl phthalate).

(The interacting residues are TYR A:589).

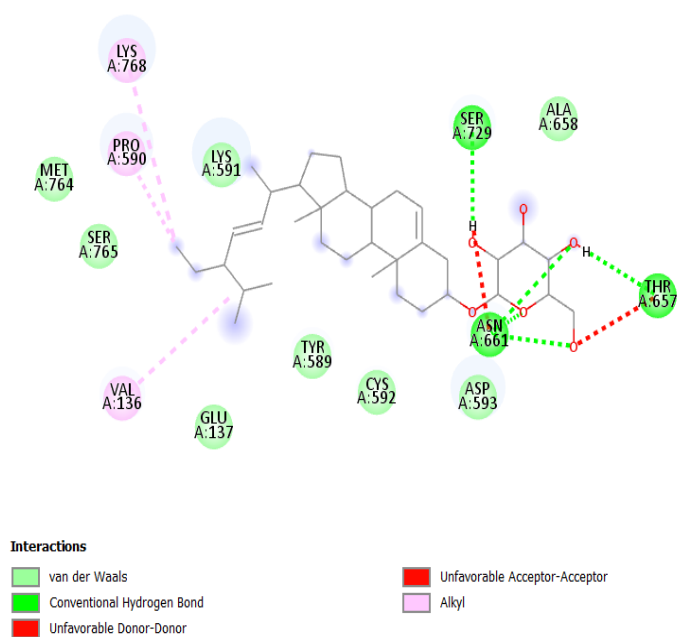


Figure 5.10: 2D docking diagram of Stigmasteryl glucoside.

(The interacting residues are SER A:729, THR A:657, ASN A:661).

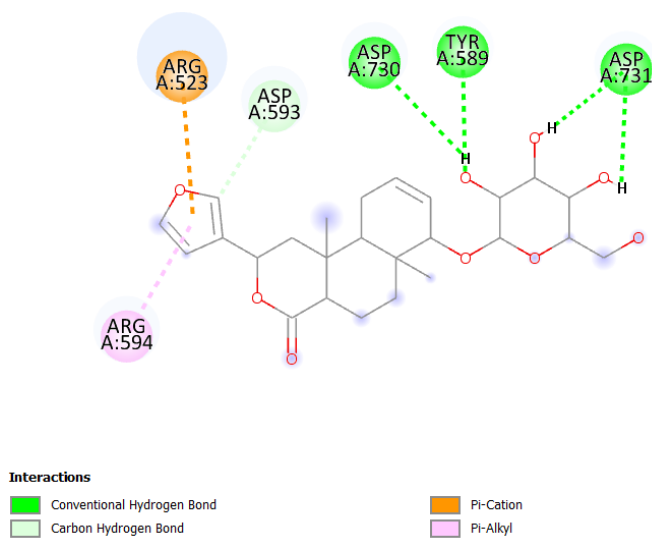


Figure 5.11: 2D docking diagram of Tinocordioside.

(The interacting residues are ASP A: 730, TYR A: 589, ASP A: 731).

5.5 Pre ADMET:

Pre ADMET studies have been predicted for the 10 ligands which have shown best activity in molecular docking.

Table: 5.4: Toxicity study for nimbolide (PubChem ID:100017).

ID	Value
Algae_at	0.0497192
Ames_test	Mutagen
Carcino_Mouse	Negative
Carcino_Rat	Positive
Daphnia_at	0.119767
Herg_inhibition	Medium_risk
Medaka_at	0.0267873
Minnow_at	0.0291986
TA100_10RLI	Negative
TA100_NA	Negative
TA1535_10RLI	Negative
TA1535_NA	Negative

Table: 5.5: Toxicity for Atisenol (PubChem ID:158706).

ID	Value
Algae_at	0.0279957
Ames_test	Mutagen
Carcino_Mouse	Negative
Carcino_Rat	Positive
Daphnia_at	0.0467814
Herg_inhibition	Low_risk
Medaka_at	0.00354532
Minnow_at	0.00233662
TA100_10RLI	Negative
TA100_NA	Negative
TA1535_10RLI	Negative
TA1535_NA	Negative

Table: 5.6: Toxicity study for Acarnidine A (PubChem ID:23424567).

ID	Value
Algae_at	0.00182811
Ames_test	Mutagen
Carcino_Mouse	Negative
Carcino_Rat	Negative
Daphnia_at	0.00793671
Herg_inhibition	low_risk
Medaka_at	0.000136492
Minnow_at	0.000187799
TA100_10RLI	Negative
TA100_NA	Negative
TA1535_10RLI	Negative
TA1535_NA	Negative

Table: 5.7: Toxicity study for 4-Epi-scopadulcicacid B (PubChem ID:10917156).

ID	Value
Algae_at	0.0110571
Ames_test	Non-mutagen
Carcino_Mouse	Negative
Carcino_Rat	Positive
Daphnia_at	0.0117719
Herg_inhibition	medium_risk
Medaka_at	0.000297565
Minnow_at	0.000725258
TA100_10RLI	Negative
TA100_NA	Negative
TA1535_10RLI	Negative
TA1535_NA	Negative

Table: 5.8: Toxicity study for glycoside (PubChem ID:222160).

ID	Value
Algae_at	0.0280174
Ames_test	Non-mutagen
Carcino_Mouse	Positive
Carcino_Rat	Positive
Daphnia_at	0.405665
Herg_inhibition	low_risk
Medaka_at	0.274653
Minnow_at	0.193217
TA100_10RLI	Negative
TA100_NA	Negative
TA1535_10RLI	Negative
TA1535_NA	Negative

Table: 5.9: Toxicity study for petrosynol (PubChem ID: 6450948).

ID	Value
Algae_at	0.00036304
Ames_test	Non-mutagen
Carcino_Mouse	Positive
Carcino_Rat	Negative
Daphnia_at	0.000328783
Herg_inhibition	Ambiguous
Medaka_at	3.11656e-007
Minnow_at	9.09235e-007
TA100_10RLI	Negative
TA100_NA	Negative
TA1535_10RLI	Negative
TA1535_NA	Negative

Table: 5.10: Toxicity study for Difurocumenonol (PubChem ID:102088154).

ID	Value
Algae_at	0.0109875
Ames_test	Mutagen
Carcino_Mouse	Negative
Carcino_Rat	Positive
Daphnia_at	0.0771906
Herg_inhibition	Medium_risk
Medaka_at	0.0124812
Minnow_at	0.0187343
TA100_10RLI	Negative
TA100_NA	Negative
TA1535_10RLI	Negative
TA1535_NA	Negative

Table: 5.11: Toxicity study for Di (2-ethylhexyl phthalate) (PubChem ID:8343).

ID	Value
Algae_at	0.00168846
Ames_test	Non-mutagen
Carcino_Mouse	Positive
Carcino_Rat	Positive
Daphnia_at	0.00206869
Herg_inhibition	Low_risk
Medaka_at	8.83508e-006
Minnow_at	5.92727e-006
TA100_10RLI	Negative
TA100_NA	Negative
TA1535_10RLI	Negative
TA1535_NA	Negative

Table: 5.12: Toxicity study for stigmasteryl glucoside (PubChem ID :70699355).

ID	Value
Algae_at	0.000837866
Ames_test	Non-mutagen
Carcino_Mouse	Positive
Carcino_Rat	Negative
Daphnia_at	0.0115317
Herg_inhibition	Low_risk
Medaka_at	0.000288052
Minnow_at	9.46483e-005
TA100_10RLI	Negative
TA100_NA	Negative
TA1535_10RLI	Negative
TA1535_NA	Negative

Table: 5.13: Toxicity study for tinocordioside (PubChem ID:101916313).

ID	Value
Algae_at	0.031922
Ames_test	Mutagen
Carcino_Mouse	Positive
Carcino_Rat	Positive
Daphnia_at	0.480405
Herg_inhibition	Medium-risk
Medaka_at	0.378125
Minnow_at	0.479823
TA100_10RLI	Negative
TA100_NA	Negative
TA1535_10RLI	Negative
TA1535_NA	Negative

SUMMARY AND CONCLUSION

In October of 2019, the primary instance of severe acute respiratory syndrome corona virus 2, or SARS-CoV-2, had occurred in Wuhan, China. SARS-CoV-2 is a RNA virus that is positive-sense, single stranded, and sizeable, with their genome being one of the biggest to date in the class of RNA viruses. Covid have a protein named RNA Dependent RNA polymerase which is a central protein, encoded into genomes of RNA infections, that assists with catalyzing the replication of RNA from a current RNA layout. There is numerous conceivable protein focuses inside the Covid strands, most strikingly the spike, nucleocapsid, membrane, and envelope proteins. Hence in this study, RdRp was taken as the objective to restrict the replication of the Corona virus. Consequently, in this study we have selected phytochemical compounds (1005 phytochemical compounds) based on published literature to repress RNA dependent RNA polymerase and help in the treatment of SARS-CoV-2. Swiss ADME studies were predicted for the collected phytochemical compounds, based on Lipinski's rule of five the phytochemical compounds (577 compounds) were filtered. For InSilco analysis molecular docking was performed to know which of the compounds from the collected phytochemicals have high binding affinity towards the target enzyme (RNA dependent RNA polymerase) which is responsible for the replication of corona virus. Igem dock and auto dock vina tools were used for docking and docking simulations were made for the collected ligands. 577 compounds were docked with the target enzyme RNA dependent RNA polymerase (PDB ID: 6M71). Based on the binding energy values best compounds were predicted, which

showed great binding affinity which are Nimbolide, Acarnidine A, 4-Epi-Scopadulcic acid B, Glycoside, Petosynol, Difurocumenonol, Di (2-ethylhexyl phthalate), Stigmasteryl glucoside, Tinocordioside. The docked ligands were tested for toxicology studies using PreADMET tool. By comparing the docking score (binding energy) and toxicology studies three best ligands were predicted which can be considered as potential drug candidates out of the all docked ligands, they are Nimbolide, Stigmasteryl glucoside, Tinocordioside.

The conclusion of this study is, the ligands which are predicted after comparing the results of molecular docking and toxicity studies helps to inhibit RNA dependent RNA polymerase (RdRp) protein in SARS-CoV-2.

The present study if we take for further research work will definitely yield fruitful results.

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