Research Artícle

World Journal of Pharmaceutical and Life Sciences WJPLS

www.wjpls.org

SJIF Impact Factor: 6.129



Kavitha K.*¹, Mohan S.¹, Srinivasan N.³, Suresh R.³ and Vismaya K. V.²

¹Department of Pharmaceutical Chemistry, Karpagam College of Pharmacy, Coimbatore, Tamil Nadu. India. ²Department of Pharmaceutical Chemistry, Nehru College of Pharmacy, Thrissur, Kerala. India. ³Department of Pharmacy, Faculty of Engineering and Technology, Annamalai University, Annamalai Nagar, Tamil Nadu. India.

Corresponding Author: Kavitha K. Department of Pharmaceutical Chemistry, Karpagam College of Pharmacy, Coimbatore, Tamil Nadu. India.

Article Received on 16/03/2021

Article Revised on 06/04/2021

Article Accepted on 26/04/2021

ABSTRACT

In the world wide presently severe panics caused by Severe Acute respiratory syndrome (SARS), Middle East respiratory syndrome – coronavirus.and Middle-East Respiratory Syndrome-Corona virus. Think about that, the researchers targeting these viruses have been required. Assortment literature quinazolinone derivatives exhibited antiviral activity and Corona viruses (Co-Vs) have been raising targets of some quinazolinone. The antiviral activity of quinazolinone against CoVs is assumed directly caused by inhibiting 3C-like protease (3CLpro). In this, we applied a newly designed quinazolinone compounds to systematically investigate binding affinity of compounds against SARS-CoV 3CLpro. The interaction of the newly designed compounds QC1-QC8 against 6M2N enzyme five quinazolinone an induced-fit docking analysis indicated are more involved in binding affinity. The present study aimed at studies showed with the systematic analysis, the newly designed potential quinazolinone are suggested to be templates to design functionally improved inhibitors quinazolinone.

KEYWORDS: SARS-CoV, Quinazolin-4-one, auto dock vina, binding score, 3CL Pro.

INTRODUCTION

Respiratory Syndrome (SARS) caused by the novel corona virus SARS-CoV and bird flu caused by avian influenza (H5N1) virus have emerged as two important infectious diseases with pandemic potential. Both infections crossed the species barrier to infect humans. Quinazoline derivatives represent one of the most active classes of compounds possessing a wide spectrum of biological activity.^[1]

Corona viruses (CoVs) are single-stranded RNA viruses with huge, enveloped and positive mind that can infect both animals and humans.^[2] CoVs, along with Artierivirdae and Roniviridae, belong to the Coronaviridae family in the order Nidovirales. These CoVs can infect various hosts, including avian, swine and humans. Human corona viruses (HCoVs) represent a major group of CoVs associated with various respiratory diseases from common cold to serious pneumonia and bronchiolitis.^[3]

Today, HCoVs are documented as one of the fastestevolving viruses derived from their, characteristic high genomic nucleotide replacement rates and recombination.^[4] Severe Acute Respiratory Syndrome (SARS), the first established atypical pneumonia in

china's Guangdong province, has spread to several countries. The majority of common symptoms of SARS include coughing, high fever (>38C), chills, convusions, dizziness, headaches, and progressive radiographic changes of the chest and lymphopenia.^[5] the harshness of the disease shows a death shows a death rate of about 3% to 6%, although this rate could rise up to 43% to 55% for senior citizens older than 60years.^[6] the primary epidemic of SARS was eventually controlled, but a SARS CoV-like virus was detected in Chinese bats.^[7,8] Besides, a recent pandemic of middle east respiratory syndrome (MERS) caused by a novel corona virus MERS-CoV raises fear of possible recurrence of SARS or related unsafe diseases.^[9,10] Since there is no vaccine and effective therapy for these viral infections, developing anti-SARS drugs against future outbreaks remains a Since there is no vaccine and effective therapy for these viral infections, developing anti-SARS drugs against future outbreaks remains a frightening Challenge.

SARS-and MERS-CoVs genomes include two open reading frames ORF1a and ORF1b translated to two particular viral polyproteins pp1a and pp1a by host ribosome. ORF1a encodes two cysteine proteases, a papain-like protease (PLpro) and a 3CL-like protease (3CLPro). While PLpro cuts the first three cleavage sites of its polyproteins,3CLpro is responsible for cleavage of the lasting 11 locations resulting in release of a total of 16 non-structural proteins (nsp) in both SARS-and MERS-CoVs.the homodimeric form of 3CLpros is active in the presence of substrates. The crystal structures of both 3CLpros showed so as to each monomer is composed of three structural domains: domains I and II form a chymotrypsin-like structural design with a catalytic cysteine and are connected to a third C-Terminal domain via a long loop.^[11] In the proteolytic site, all 3CL pros prefer glutamine at P1 position and leucine, basic residues, small hydrophobic residues at P2, P3 and P4 Positions, respectively.^[12] At P10 and P20 positions, small residues are required nevertheless; P30 Position shows no strong preference. Since the auto cleavage process is important for viral propagation, 3CLpro is a good drug target for anti-corona viral infection.

In this study, we engaged molecular docking method, to investigate SARS-CoV 3CLpro inhibitory compounds. Although, molecular level studies have not been much reported for SARS-CoV. Hence, we performed the docking analysis of with newly designed quinazolinone Ligands. Among, we try to work out a structural and functional relationship of quinazolin 4 one important to binding with SARS-CoV 3CLpro. The information can be applied to develop newly designed compounds after wet lab synthesis with better results in invitro and in vivo analysis.

Molecular Docking Analysis^[14,15] Introduction

Auto Dock Tools (ADT) is a program package of automated docking tools and designed to predict how small molecules bind to a target protein of known 3Dstructure. Auto Dock vina was used to identify the binding modes of designed compounds library responsible for the activity to find the binding energies of those compounds in the active sites. Also the position of the ligand in the enzyme binding site can be visualized by discovery studio visualizer. It can be useful for developing potential drug candidates and also for knowing the binding nature. The designed libraries were afforded for prediction of anti-viral activity on crystal structure of SARS CoV3L Pro (6M2N) by molecular docking study.

MATERIALS AND METHODS

Software required

Molecular graphics laboratory (MGL) tools and Auto Dock vina PyRx virtual screening tool was downloaded from www.scripps.edu, ChemSketch was downloaded from www.acdlabs.com, biovia Discovery studio visualizer was downloaded from https://www.3dsbiovia. com/biovia-discovery. The Mol file of Ligand to PDB format translation was carried out by using Chem 3D Pro 8.0 and protein to PDB format translation was carried out carried out by Molecular operating environment (MOE) were used.

METHODOLOGY

Computer Aided drug design is one of the tool which plays a vital role in understanding the structure activity relationship, binding energy, interaction between the protein and ligand, binding affinity etc. On this program, Auto dock was widely used in evaluating the binding studies of our designed compound on targeted enzyme. The binding energy of the synthesised compounds (QC1-QC8) on the crystal structure of SARS CoV 3CL Pro [PDB ID: 6M2N] were obtained from Protein Data Bank (http://www. rcsb.org/pdb) place at Brookhaven National Laboratory in 1971.

Preparation of macromolecule

The 3D crystal of structure of SARS Co A in Complex Novel Inhibitors of 3CL Protease enzyme (PDB Code: 6M2N) was retrieved from the RSCB protein data bank. The dock preparation tool of molecular operating environment (MOE) for Mac was used to prepare the enzyme for docking. Ultimately, python prescription (PyRx) 0.8 for Mac was used to save the macromolecule in pdbqt format, which contains hydrogen atoms in all polar residues.

Ligand preparation

The 2D chemical structures of the Ligands were prepared using chembiodraw for Mac (Cambridge, MA, USA).The 2D chemical structures were converted into the respective 3D structures using the open Babel of Pyrx0.8.

Docking Validation

The ligand from the active site of the crystal structure of SARS- CoA was removed from using MOE molecular operating environment for Mac .after the ligand was redocked, the alignment between the docked ligand and the ligand from the crystal structure was using Mac biovia studio viewer.

Receptor Grid Generation

Receptor grid generation requires a "prepared" structure: an all atom structure with appropriate bond orders and formal charges. Auto Dock searches for favourable interactions between one or more ligand molecules and a receptor molecule, usually a protein. The shape and properties of the receptor are represented on a grid by several different sets of fields that provide progressively more accurate scoring of the ligand poses. The options in each tab of the Receptor Grid Generation panel allow defining the receptor structure by excluding any cocrystallized ligand that may be present, determine the position and size of the active site as it will be represented by receptor grids, and set up Auto Dock constraints. A grid area was generated around the binding site of the receptor.

Docking Analysis

Docking **was** performed using PyRx auto dock vina. The results were quantified in terms of free binding energy. The highest binding energy values corresponding to the

RMSD value of zero were considered as the binding affinity value of the Ligands. The [post dock analysis was made using biovia discovery studio visualizer.

The prepared crystal structures of ligand and active site of various enzymes such as crystal structure of [PDB ID: 6M2N] were subjected to Auto dock Vina for measuring the binding energies. The docking grid box was set at approx. above 90 90 90 and genetic algorithm (GA) with default settings was employed for the studies. In the search parameter, number of runs and the other settings were left as default. The results of docking calculations seen in the output were in word format.

The position and orientation of Ligands in protein receptor and the interaction with amino acids that bound to the ligand were analyzed and visualized with Auto Dock tools. During the docking process the top ten conformations were simulated for each of the compound after the minimization of the energy.

The binding energy of each ligand against 3CL PRO macromolecule was predicted using auto dock vina, which is one of the most commonly used docking software .in the docking procedure eight binding pose were obtained, and the binding bose with the highest binding energy corresponding to the RMSD value of zero was considered as the binding affinity of the ligand.

From selected compound library QC1 (-8.8 kcal/mol) showed the highest binding energy. The selected libraries of quinazolinone series, however, showed better binding energy than the hydroxy chloroquine which is used as

reference compound. In particular, almost all the compounds showed the excellent binding score (-8.3 to -8.8 kcal/mol) library of quinazolinones. The amino acid residues interacting with the selected libraries of quinazolinone derivatives and all molecules showed hydrogen bond interactions, many having Vander walls attraction with different amino acid residues in the binding site. In general, all the libraries of quinazolinones were found to have more binding affinity than the chloroquine. This is due to an increased number of hydrogen bond, vanderwalls attraction with the amino acids of the binding site. The most active compound was which showed hydrogen bond interactions over the enzyme although pialkyl interactions, also pi-sigma interactions were analysed.

RESULT AND DISCUSSION

The docking poses were obtained according to their docking parameters and their corresponding binding pockets. These evaluations should be helpful for understanding the binding interactions over the targeted enzyme. Molecular docking studies of quinazoline- 4[one derivatives were carried out, the docking scores of these compounds libraries fall within the range of -8.3 -8.8 kcal/mol which showed at table -1 All the Compound were found to strongly inhibit the SARS CoV 3CL Protease enzyme by totally the efficient site in target protein, the result of docking analysis is showed that all the docked Ligands have lower energy value (high binding energy value) compared to the hydroxy chloroquine as a reference drug with it binding energy value of -6.37 kcal/mol.

Table 1: Docking result and interacting sites of tested compounds library of 6M2N.

Compound code	Structure of Tested compound13	Binding score-(kcal/mol)
QC1		-8.8
QC2		-8.6
QC3		-8.5

QC4		-8.6
QC5	O H H N N N F F	-8.6
QC6	N H O OCH3	-8.3
QC7	CH ₃	-8.6
QC8	N, N	-8.3
Ref		-6.8

WJAHR 1307



Fig.1: 2D Stereo view of compound QC1 on enzyme 3CL Pro 6M2N.

93

www.wjpls.org	Vol 7, Issue 5, 2021.	ISO 9001:2015 Certified Journal	
---------------	-----------------------	---------------------------------	--



Fig.2: 3D Stereo view of compound QC1 on enzyme 3CL Pro 6M2N.

Moreover the various interaction value of QC1 to QC8 & REF libraries which showed at table-2. & Fig-1. Depict the best low binding energy (high binding energy values) for the docked Ligands. Among the 8 Ligands that were docked with the enzyme SAR Co V 3CL Pro, the disubstituted chlorine & hydroxy group ligand QC1 showed the most potent with the high docked score of - 8.8 kcal/mol. The mono substituted electron withdrawing group ligand QC3, QC2, QC4 & QC5 the best docked score of -8.5 & -8.6 kcal/mol, further ,the di

substituted electron donating methyl group ligand QC7 the best docked score of -8.6 while monosustituted electron donating methoxy group ligand QC6 -8.3kcal/mol and ligand QC8 with docked score of -8.3 kcal/mol respectively, the docked ligand configuration display Hydrogen bond and electrostatic interaction, Pi alkyl & Pi sigma interactions present in table-2.. These interactions indicated that Ligands bind deep in the core of active site where the reference ligand binds.

Table 2: Docking result and various interaction of tested compounds on 3CL Pro 62MN.

code	VDW	H-Bond	Pi-alkyl	Pi-sigma
QCI	LEU A :242	HIS A : 26	PRO A :293	ILE A : 200
	GLU A : 240	PRO A : 108	PRO A : 108	VAL A:202
	THR A : 243			
	PRO A :241			
	THR A : 292			
	GLN A : 110			
	GLN A : 109			
QC2	PRO A :241	THR A :243	PRO A :293	VAL A:202
	HIS A :p246	PRO A :108	PRO A : 108	ILE A :200
	THR A :292			
	GLN A :110			
	GLY A :109			

Construction THE A :249 THR A : 292 GLN A : 110 GLY A : 109 PRO A : 132 ASP A : 245 THR A : 243 GLU A : 240 HIS A :246 PRO A : 108 PRO A : 108 HIS A : 243 GLU A : 240 HIS A : 246 GLY A : 109 GLN A : 110 THR A : 292 PRO A : 243 PRO A : 293 PRO A : 293 HIS A : 246 PRO A : 132 GLY A : 109 GLN A : 110 THR A : 292 PRO A : 293 PRO A : 293 PRO A : 293 HIS A : 246 PRO A : 132 GLY A : 109 GLN A : 110 THR A : 292 VAL A:202 HIE A : 200 PRO A : 108 PRO A : 132 GLY A : 109 GLN A : 110 THR A : 292 HIE A : 249 QC6 ASP A : 245 THR A : 249 HIS A : 246 PRO A : 108 GLN A : 110 THR A : 292 HIE A : 249 PRO A : 108 PRO A : 293 HIS A : 246 PRO A : 108 FRO A : 109 GLN A : 110 THR A : 243 PRO A : 109 GLN A : 110 THR A : 243 PRO A : 108 FRO	0C3	PRO A :241	PRO A :108	PRO A : 293	VAL A:202
THR A: 292 GLN A: 110 GLY A: 109 PRO A: 312 ASP A: 245 THR A: 243 GLU A: 240 HIS A: 246 THR A: 243 PRO A: 293 VAL A:202 VAL A:202 ILE A: 200 GLN A: 110 THR A: 292 QC4 PRO A: 241 GLU A: 240 PRO A: 240 GLY A: 109 GLN A: 110 THR A: 292 THR A: 243 PRO A: 108 PRO A: 293 PRO A: 293 VAL A: 202 ILE A: 200 QC5 ASP A: 245 PRO A: 132 GLY A: 109 GLN A: 110 THR A: 292 THR A: 243 PRO A: 108 PRO A: 108 PRO A: 109 GLN A: 110 THR A: 292 PRO A: 293 VAL A: 202 ILE A: 200 QC6 THR A: 292 ILE A: 249 PRO A: 108 PRO A: 108 GLN A: 110 GLN A: 110 GLN A: 110 GLN A: 241 ASP A: 245 THR A: 243 PRO A: 293 PRO A: 293 VAL A: 202 ILE A: 200 QC6 THR A: 292 HIS A: 246 PRO A: 241 ASP A: 245 THR A: 243 PRO A: 108 PRO A: 108 PRO A: 293 VAL A: 202 ILE A: 200 QC7 GLY A: 109 GLU A: 240 ASP A: 245 PRO A: 132 GLY A: 109 GLN A: 110 THR A: 243 PRO A: 108 PRO A: 293 VAL A: 202 ILE A: 200 QC8 PRO A: 241 HIS A: 246 GLU A: 240 ASP A: 245 PRO A: 132 GLY A: 109 GLN A: 110 THR A: 292 PRO A: 132 PRO A: 132 GLY A: 109 GLN A: 110 THR A: 243 PRO A: 132 GLY A: 109 GLN A: 110 GLN A: 110 GLN A: 110 GLN A: 110 GLN A: 107 THR A: 243 GLY A: 109 PRO A: 108 PRO A: 132 PRO A: 124 PRO A: 124 REF PHE A: 8 THR A: 243 GLY A: 109 PRO A: 108 PRO A: 132 PRO A: 132 PRO A: 132 PRO A: 108 PRO A: 245 PRO A: 132 PRO A: 245	200	ILE A $\cdot 249$	1110 111100	$PROA \cdot 108$	ILE A $\cdot 200$
GLN A : 110 GLY A : 109 PRO A :132 ASP A : 245 THR A : 243 GLU A : 240 HIS A :246 PRO A : 293 VAL A:202 ILE A :200 QC4 PRO A : 240 HIS A : 246 GLY A : 109 GLN A : 110 THR A : 242 GLY A : 109 GLN A : 110 THR A : 292 PRO A : 293 VAL A:202 ILE A :200 QC5 ASP A : 245 HIS A : 246 PRO A : 132 GLY A : 109 GLN A : 110 THR A : 292 PRO A : 132 PRO A : 293 VAL A:202 ILE A : 200 QC5 ASP A : 245 HIS A : 246 PRO A : 108 GLN A : 110 THR A : 292 ILE A : 249 PRO A : 108 PRO A : 108 GLN A : 110 THR A : 292 ILE A : 249 PRO A : 108 GLN A : 110 THR A : 243 PRO A : 293 VAL A:202 ILE A : 200 QC6 GLY A : 109 GLU A : 240 PRO A : 241 ASP A : 245 THR A : 243 PRO A : 108 PRO A : 108 PRO A : 293 VAL A: 202 ILE A : 200 QC7 GLY A : 109 GLU A : 240 ASP A : 245 PRO A : 108 PRO A : 108 PRO A : 203 ULE A : 200 QC8 PRO A : 241 HIS A : 244 GLY A : 109 GLN A : 110 THR A : 242 PRO A : 108 PRO A : 108 ILE A : 200 QC8 PRO A : 132 GLY A : 109 GLN A : 110 THR A : 243 GLY A : 109 GLN A : 110 GLN A : 110 GLN A : 107 THR A : 243 GLY A : 109 PRO A : 108 PRO A : 132 PRO A : 232		THR $A \cdot 292$		1100 111 100	122 11.200
GLY A: 109 PRO A: 132 ASP A: 245 THR A: 243 GLU A: 240 HIS A: 246 PRO A: 132 PRO A: 293 VAL A:202 ILE A: 200 QC4 PRO A: 241 GLU A: 240 HIS A: 246 THR A: 243 PRO A: 108 PRO A: 293 VAL A:202 ILE A: 200 QC5 ASP A: 245 HIS A: 246 PRO A: 110 THR A: 292 THR A: 243 PRO A: 132 PRO A: 293 VAL A:202 ILE A: 200 QC5 ASP A: 245 HIS A: 246 PRO A: 132 GLY A: 109 GLN A: 110 THR A: 292 PRO A: 108 PRO A: 108 PRO A: 293 VAL A:202 ILE A: 200 QC6 THR A: 292 ILE A: 249 PRO A: 108 GLN A: 110 GLN A: 1246 PRO A: 108 PRO A: 293 VAL A: 202 ILE A: 200 QC7 GLY A: 109 GLU A: 240 PRO A: 241 ASP A: 245 THR A: 243 PRO A: 108 PRO A: 108 PRO A: 108 PRO A: 108 ILE A: 200 QC8 PRO A: 241 HIS A: 246 GLU A: 240 ASP A: 245 PRO A: 110 GLN A: 110 THR A: 292 PRO A: 108 PRO A: 108 PRO A: 108 PRO A: 108 ILE A: 200 REF PHE A: 8 THR A: 243 GLY A: 109 FRO A: 108 PRO A: 132 FRA : 109 FRO A: 108 PRO A: 132 FRA : 109 FRO A: 108 VAL A: 249 REF PHE A: 8 THR A: 243 GLY A: 109 FRO A: 108 PRO A: 122 FRA : 109 FRO A: 108 PRO A: 122 FRA : 109 FRO A: 108 VAL A: 249		$GLN A \cdot 110$			
ORD A : 132 ASP A : 245 THR A : 243 GLU A : 240 HIS A : 246 GLU A : 240 HIS A : 246 GLU A : 240 HIS A : 246 GLU Y A : 109 GLN A : 110 THR A : 292 PRO A : 293 PRO A : 293 CC5 VAL A:202 ILE A : 200 VAL A: 200 HIS A : 245 PRO A : 132 GLY A : 109 GLN A : 110 THR A : 292 ILE A : 249 RC6 PRO A : 293 PRO A : 293 CC5 VAL A:202 ILE A : 200 VAL A: 200 ILE A : 200 CC5 QC5 ASP A : 245 PRO A : 109 GLN A : 110 THR A : 292 ILE A : 249 RC6 THR A : 243 PRO A : 108 THR A : 292 ILE A : 249 RC6 PRO A : 108 PRO A : 293 ILE A : 200 CC5 VAL A: 202 ILE A : 200 CC6 QC6 THR A : 292 HIR A : 292 ILE A : 249 RC7 PRO A : 108 GLY A : 109 GL A : 110 GLY A : 109 FRO A : 241 HIS A : 246 THR A : 243 CC7 PRO A : 108 FRO A : 108 FRO A : 293 CC7 VAL A: 202 ILE A : 200 CC6 QC7 GLY A : 109 GL A : 240 PRO A : 241 HIS A : 246 GL A : 100 GL A : 240 ASP A : 245 FRO A : 108 FRO A : 108		$GLY A \cdot 109$			
ASP A: 1245 GLU A: 243 GLU A: 240 HIS A: 246 THR A: 243 GLU A: 240 PRO A: 293 VAL A:202 ILE A: 200 QC4 PRO A: 241 GLU A: 240 PRO A: 109 GLN A: 110 THR A: 292 THR A: 243 PRO A: 132 GLY A: 109 GLN A: 110 THR A: 292 PRO A: 123 PRO A: 233 VAL A:202 ILE A: 200 QC5 ASP A: 245 PRO A: 132 GLY A: 109 GLN A: 110 THR A: 292 THR A: 243 PRO A: 108 GLN A: 110 THR A: 292 PRO A: 108 PRO A: 293 VAL A:202 ILE A: 200 QC6 THR A: 292 ILE A: 249 PRO A: 108 GLN A: 110 GLN A: 110 GLN A: 110 GLN A: 240 PRO A: 241 ASP A: 245 THR A: 243 PRO A: 108 GLN A: 109 GLN A: 109 GLN A: 109 GLU A: 240 PRO A: 241 ASP A: 245 THR A: 243 PRO A: 108 PRO A: 293 VAL A: 202 ILE A: 240 PRO A: 241 ASP A: 245 PRO A: 108 QC6 PRO A: 241 HIS A: 246 GLU A: 240 PRO A: 108 PRO A: 108 PRO A: 108 ILE A: 200 QC7 GLY A: 109 HIS A: 246 GLU A: 240 ASP A: 245 PRO A: 108 PRO A: 108 PRO A: 108 ILE A: 200 QC8 PRO A: 241 HIS A: 246 GLU A: 240 ASP A: 245 PRO A: 108 PRO A: 108 PRO A: 108 ILE A: 200 REF PHE A: 8 THR A: 292 GLN A: 110 GLN A: 110 GLN A: 110 GLN A: 110 GLN A: 110 GLN A: 110 GLN A: 107 THR A: 243 GLY A: 109 PRO A: 108 PRO A: 132 PRO A: 132 PRO A: 132 PRO A: 132 PRO A: 132 PRO A: 134		PRO A ·132			
India 1:220 GLU A: 240 HIS A: 246 THR A: 243 PRO A: 200 PRO A: 201 HIS A: 246 QC4 THR A: 241 PRO A: 240 HIS A: 246 PRO A: 109 GLY A: 109 GLY A: 109 GLN A: 110 THR A: 292 PRO A: 108 PRO A: 132 PRO A: 293 VAL A:202 ILE A: 200 QC5 ASP A: 245 PRO A: 132 GLY A: 109 GLN A: 110 THR A: 292 THR A: 243 PRO A: 108 PRO A: 293 VAL A:202 ILE A: 200 QC6 THR A: 292 HIE A: 249 PRO A: 108 PRO A: 108 PRO A: 293 VAL A: 202 ILE A: 200 QC6 THR A: 292 HIE A: 249 PRO A: 108 GLN A: 110 GLY A: 109 GLU A: 240 PRO A: 241 PRO A: 108 A: 246 PRO A: 108 CN A: 200 PRO A: 293 VAL A: 202 ILE A: 200 QC7 GLY A: 109 GLU A: 240 PRO A: 241 FRO A: 108 THR A: 243 PRO A: 108 PRO A: 202 ILE A: 240 ILE A: 200 QC8 PRO A: 241 HIS A: 246 GLV A: 100 GLN A: 110 THR A: 292 PRO A: 108 FRO A: 108 ILE A: 200 ILE A: 200 ILE A: 200 QC8 PRO A: 323 GLY A: 109 GLN A: 110 THR A: 292 PRO A: 108 FRO A: 108 PRO A: 108 FRO A: 108 ILE A: 200 REF PHE A: 8 THR A: 243 GLY A: 109 PRO A: 108 ASN A: 151 THR A: 246 ILE A: 249 VAL A: 202 REF PHE A: 8 THR A: 109 PRO A: 108 ASN A: 245 ILE A: 249 A: 202		$\Delta SP \Delta \cdot 245$			
GLU A: 240 HIS A: 246 THR A: 243 PRO A: 293 VAL A: 202 QC4 PRO A: 240 GLU A: 240 HIS A: 246 GLV A: 109 GLN A: 110 THR A: 292 PRO A: 108 PRO A: 132 GLY A: 109 GLN A: 110 THR A: 292 PRO A: 293 VAL A: 202 QC5 ASP A: 245 HIS A: 246 PRO A: 132 GLY A: 109 GLN A: 110 THR A: 292 THR A: 243 PRO A: 108 PRO A: 293 VAL A: 202 QC6 THR A: 292 THR A: 243 PRO A: 108 PRO A: 293 VAL A: 202 QC6 THR A: 292 PRO A: 108 PRO A: 293 VAL A: 202 QC6 THR A: 292 PRO A: 108 PRO A: 293 VAL A: 202 QC6 THR A: 292 PRO A: 108 PRO A: 293 VAL A: 202 QC6 THR A: 243 PRO A: 108 PRO A: 293 VAL A: 202 QC7 GLY A: 109 HIS A: 240 ASP A: 243 PRO A: 108 PRO A: 108 ILE A: 200 QC8 PRO A: 241 HIS A: 246 GLV A: 110 THR A: 292 THR A: 243 PRO A: 108 PRO A: 108 ILE A: 200 REF PHE A: 8 THR A: 110 GLN A: 110 THR A: 243 GLY A: 109 PRO A: 108 PRO A: 132 PRO A: 132 PRO A: 132 VAL REF PHE A: 8 THR A: 243 GLY A: 109 PRO A: 108		THR $A \cdot 243$			
BIS A : 246 THR A : 243 PRO A : 293 VAL A:202 QC4 PRO A : 240 PRO A : 108 PRO A : 293 UAL A:202 GL X A : 109 GL X A : 109 PRO A : 132 PRO A : 293 UAL A:202 QC5 ASP A : 245 THR A : 243 PRO A : 132 PRO A : 293 VAL A:202 QC5 ASP A : 245 THR A : 243 PRO A : 108 PRO A : 293 VAL A:202 QC6 GLY A : 109 GLN A : 110 FIR A : 243 PRO A : 108 PRO A : 293 VAL A:202 QC6 THR A : 292 PRO A : 108 PRO A : 293 VAL A:202 QC6 THR A : 243 PRO A : 108 PRO A : 293 VAL A:202 QC6 THR A : 243 PRO A : 108 ILE A : 200 ILE A : 200 GLV A : 109 GLN A : 110 GLN A : 110 ILE A : 200 ILE A : 200 QC7 GLY A : 109 PRO A : 108 PRO A : 293 VAL A:202 QC8 PRO A : 246 THR A : 243 PRO A : 108 ILE A : 200 GLY A : 109 GLN A : 110 <t< td=""><td></td><td>$GLUA \cdot 240$</td><td></td><td></td><td></td></t<>		$GLUA \cdot 240$			
QC4 PRO A :241 GLU A : 240 HIS A : 246 GLV A : 109 GLN A : 110 THR A : 292 THR A : 243 PRO A : 108 PRO A : 132 PRO A : 293 VAL A:202 ILE A :200 QC5 ASP A :245 HIS A : 246 PRO A : 109 GLN A : 110 THR A : 292 THR A : 243 PRO A : 108 GLN A : 110 THR A : 292 PRO A : 108 PRO A : 293 VAL A:202 ILE A : 200 QC6 THR A : 292 GLN A : 110 GLN A : 120 PRO A : 293 PRO A : 293 VAL A:202 ILE A : 200 QC6 THR A : 292 GLY A : 109 GLU A : 240 ASP A : 245 THR A : 243 PRO A : 108 PRO A : 108 PRO A : 293 VAL A : 200 QC7 GLY A : 109 GLU A : 240 ASP A : 245 THR A : 243 PRO A : 108 PRO A : 108 ILE A : 200 QC8 PRO A : 241 HIS A : 246 GLU A : 240 ASP A : 245 PRO A : 108 PRO A : 108 PRO A : 108 ILE A : 200 REF PRC A : 107 THR A : 292 THR A : 292 THR A : 110 GLN A : 110 GLN A : 110 GLN A : 110 FHR A : 243 GLY A : 109 PRO A : 108 PRO A : 132 PRO A : 108 VAL A : 202		HIS A ·246			
QC4 FRO A 1240 FRO A 1105 FRO A 1255 FRO A 1255 FRO A 1255 GL X : 109 GL X : 100 PRO A : 132 ILE A :200 ILE A :200 QC5 ASP A :245 THR A :243 PRO A : 293 VAL A:202 HIS A :246 PRO A :108 PRO A : 293 VAL A:202 GL Y A :109 GL Y A :109 FRO A :108 ILE A :200 GL X : 110 THR A :292 PRO A :108 PRO A : 293 VAL A:202 ILE A :249 PRO A :108 PRO A : 293 VAL A:202 QC6 THR A : 292 PRO A :108 PRO A : 293 VAL A:202 QC6 THR A : 292 PRO A :108 PRO A : 293 VAL A:202 QC7 GL X : 110 GLN A :110 PRO A : 293 ILE A : 200 QC7 GL Y A : 109 PRO A :108 PRO A : 202 ILE A : 200 QC8 PRO A :241 THR A :243 PRO A : 108 ILE A :200 QC8 PRO A :241 THR A :243 PRO A : 108 ILE A :200 QC8 PRO A :241 PRO A :108 PRO A : 108 ILE A :200 GL Y A :109 GL	0C4	PRO A ·241	THR A $\cdot 243$	$PRO A \cdot 293$	VAL A·202
HIS A: 246 GLY A: 109 GLN A: 110 THR A: 292 PRO A: 132 HIS A: 246 GLY A: 109 GLN A: 110 PRO A: 132 VAL A:202 QC5 ASP A: 245 HIS A: 246 PRO A: 132 GLY A: 109 GLN A: 110 THR A: 292 PRO A: 108 PRO A: 293 VAL A:202 QC6 THR A: 292 HIS A: 249 PRO A: 108 PRO A: 293 VAL A:202 QC6 THR A: 292 GLY A: 109 GLU A: 110 GLV A: 109 GLU A: 240 PRO A: 241 ASP A: 245 THR A: 243 PRO A: 108 PRO A: 293 VAL A:202 QC7 GLY A: 109 GLU A: 240 PRO A: 241 ASP A: 245 THR A: 243 PRO A: 108 THR A: 243 PRO A: 108 VAL A: 202 ILE A: 200 QC7 GLY A: 109 GLU A: 240 PRO A: 241 ASP A: 245 PRO A: 132 GLY A: 109 GLN A: 110 THR A: 292 PRO A: 108 PRO A: 108 PRO A: 108 PRO A: 108 ILE A: 200 QC8 PRO A: 241 HIS A: 246 GLU A: 240 ASP A: 245 PRO A: 108 PRO A: 108 PRO A: 108 VAL A: 202 QC8 PRO A: 241 HIS A: 246 GLU A: 240 ASP A: 245 PRO A: 108 PRO A: 108 ILE A: 200 QC8 PRO A: 241 HIS A: 246 GLU A: 240 ASP A: 245 PRO A: 108 PRO A: 108 ILE A: 249 QC8 PRO A: 132 HIS A: 246 GLU A: 240 ASP A: 245 PRO A: 108 PRO A: 132 PRO A: 108 A: 202 REF PHE A: 8 THR A: 292 PRO A: 108 ASN A: 151 HIS A: 246 A: 202 A: 202 <td>QC7</td> <td>$GLUA \cdot 240$</td> <td>111111111111111111111111111111111111</td> <td>11011.275</td> <td>$IIFA \cdot 200$</td>	QC7	$GLUA \cdot 240$	111111111111111111111111111111111111	11011.275	$IIFA \cdot 200$
GLY A : 109 GLN A : 100 GLY A : 109 GLN A : 110 THR A: 292 PRO A : 293 VAL A:202 QC5 ASP A : 245 PRO A : 108 PRO A : 293 VAL A:202 HIS A : 246 PRO A : 109 GLN A : 110 ILE A : 200 ILE A : 200 GLY A : 109 GLN A : 110 PRO A : 108 PRO A : 293 VAL A:202 ILE A : 249 ILE A : 249 ILE A : 200 ILE A : 200 QC6 GLN A : 110 GLN A : 110 GLN A : 110 ILE A : 200 GLY A : 109 GLN A : 110 GLN A : 110 ILE A : 200 GLY A : 109 GLN A : 110 GLN A : 100 ILE A : 200 GC7 GLY A : 109 PRO A : 108 PRO A : 108 ILE A : 200 QC8 PRO A : 241 THR A : 243 VAL A : 202 ILE A : 200 QC8 PRO A : 241 THR A : 243 PRO A : 108 ILE A : 200 QC8 PRO A : 241 THR A : 243 PRO A : 108 ILE A : 200 QC8 PRO A : 241 THR A : 243 PRO A : 108 ILE A : 200 QC8 PRO A : 122 THR A : 108		HIS A $\cdot 246$	$\frac{1}{2}$		ILL / 1.200
GLN A: 110 THR A: 292 THR A: 243 PRO A: 1245 PRO A: 132 GLY A: 109 GLN A: 110 THR A: 292 PRO A: 293 VAL A: 202 ILE A: 200 QC5 ASP A: 245 PRO A: 132 GLY A: 109 GLN A: 110 THR A: 292 PRO A: 108 GLN A: 110 THR A: 292 PRO A: 108 GLN A: 110 GLN A: 109 GLU A: 240 PRO A: 241 THR A: 243 PRO A: 108 PRO A: 108 GLU A: 240 PRO A: 245 THR A: 243 PRO A: 108 PRO A: 108 THR A: 243 VAL A: 202 ILE A: 200 QC7 GLY A: 109 GLU A: 240 PRO A: 241 HIS A: 245 THR A: 243 PRO A: 108 THR A: 243 PRO A: 108 PRO A: 293 ILE A: 200 QC8 PRO A: 241 HIS A: 246 GLY A: 100 GLU A: 240 ASP A: 245 PRO A: 132 GLY A: 100 THR A: 292 PRO A: 108 THR A: 243 PRO A: 108 PRO A: 108 ILE A: 200 REF PHE A: 8 THR A: 243 GLY A: 100 THR A: 243 GLY A: 100 FRO A: 108 ASN A: 151 PRO A: 132 THR A: 245 PRO A: 108 PRO A: 132 HIS A: 246 A: 202 VAL REF PHE A: 8 THR A: 243 GLY A: 100 FRO A: 108 ASN A: 151 HIS A: 246 A: 202 A: 202 REF PHE A: 8 THR A: 243 GLY A: 109 PRO A: 108 ASN A: 245 HIS A: 245 A: 202		$GIYA \cdot 109$	1 KO A . 152		
THR A: 292 PRO A: 245 THR A: 243 PRO A: 293 VAL A: 202 QC5 ASP A: 245 PRO A: 108 PRO A: 293 VAL A: 202 ILE A: 109 GLY A: 109 PRO A: 108 PRO A: 293 VAL A: 202 QC6 THR A: 292 PRO A: 108 PRO A: 293 VAL A: 202 QC6 THR A: 292 PRO A: 108 PRO A: 293 VAL A: 202 QC6 THR A: 292 PRO A: 108 PRO A: 293 VAL A: 202 QC6 THR A: 292 PRO A: 110 GLN A: 110 ILE A: 200 GLY A: 109 PRO A: 108 PRO A: 203 VAL A: 202 PRO A: 241 ASP A: 245 THR A: 243 VAL A: 202 QC7 GLY A: 109 PRO A: 108 VAL A: 202 HIS A: 246 THR A: 243 VAL A: 202 QC8 PRO A: 240 PRO A: 108 ILE A: 249 QC8 PRO A: 110 THR A: 243 PRO A: 108 ILE A: 200 GLY A: 109 GLN A: 110 THR A: 243 PRO A: 108 ILE A: 200 GLY A: 109		$GIN \Delta \cdot 110$			
QC5 ASP A : 245 HIS A : 246 PRO A : 132 GLY A : 109 GLN A : 110 THR A : 292 ILE A : 249 THR A : 243 PRO A : 108 PRO A : 293 VAL A: 202 ILE A : 200 QC6 THR A : 292 GLY A : 109 GLU A : 110 GLY A : 109 GLU A : 240 PRO A : 293 PRO A : 293 VAL A: 202 ILE A : 240 QC6 THR A : 292 GLY A : 109 GLU A : 240 PRO A : 241 ASP A : 245 THR A : 243 PRO A : 108 GLU A : 240 PRO A : 241 PRO A : 108 PRO A : 202 ILE A : 200 ILE A : 200 QC7 GLY A : 109 HIS A : 246 PRO A : 108 THR A : 243 PRO A : 108 PRO A : 293 ILE A : 200 QC8 PRO A : 241 HIS A : 246 THR A : 243 PRO A : 108 PRO A : 108 PRO A : 108 ILE A : 200 QC8 PRO A : 241 HIS A : 246 THR A : 243 PRO A : 108 PRO A : 108 PRO A : 108 ILE A : 200 QC8 PRO A : 241 HIS A : 246 GLV A : 109 GLN A : 110 THR A : 292 THR A : 151 PRO A : 108 PRO A : 108 PRO A : 108 ILE A : 200 REF PHE A : 8 THR A : 100 GLN A : 107 THR A : 243 GLY A : 109 PRO A : 108 ASN A : 151 PRO A : 132 HIE A : 249 VAL		THR $\Delta \cdot 292$			
QCS HIS A:246 PRO A:132 GLY A:109 GLN A:110 THR A:292 ILE A:249 PRO A:108 FRO A:293 ILE A:200 QC6 THR A: 292 GLY A:109 GLV A:110 GLV A:109 GLU A:240 PRO A:241 ASP A:245 PRO A:108 GLN A:110 PRO A:293 VAL A:202 ILE A:200 QC7 GLY A:109 GLY A:109 GLV A:240 PRO A:108 PRO A:241 PRO A:108 HIS A:246 ILE A:200 QC7 GLY A:109 GLU A:240 PRO A:108 PRO A:241 PRO A:108 HIS A:246 ILE A:200 QC8 PRO A:241 HIS A:246 THR A:243 PRO A:108 PRO A:293 PRO A:293 VAL A:202 ILE A:200 QC8 PRO A:241 HIS A:246 THR A:243 PRO A:108 PRO A:108 ILE A:200 QC8 PRO A:241 HIS A:246 THR A:243 PRO A:108 PRO A:293 PRO A:108 VAL A:202 REF PHE A: 8 THR A:292 ASN A:151 THR A:245 PRO A:132 PRO A:132 VAL REF PHE A: 8 THR A:292 ASN A:151 PRO A:132 PRO A:132 VAL REF PHE A: 8 THR A:292 ASN A:151 PRO A:132 PRO A:145 A:202 REF PHE A:8 THR A:292 ASN A:151 PRO A:132 PRO A:108 A:202 REF PHE A:243 GLN A:107 THR A:243 GLN A:107 ASP A:245 ASP A:245 ASP A:245	0C5	ASP A ·245	THR A ·243	$PRO A \cdot 293$	VAL A·202
PRO A :132 GLY A :109 FRO A :132 GLY A :109 GLN A :110 THR A :292 PRO A :108 PRO A : 293 VAL A:202 ILE A :249 GLN A :110 GLN A :110 GLN A :100 ILE A :200 QC6 THR A : 292 PRO A :108 PRO A : 293 VAL A:202 GLV A :109 GLN A :110 GLN A :110 ILE A :200 QC7 GLY A :109 PRO A :108 PRO A :108 ILE A :200 QC8 PRO A :241 THR A :243 PRO A :108 ILE A :200 QC8 PRO A :241 THR A :243 PRO A :108 ILE A :200 QC8 PRO A :241 THR A :243 PRO A : 108 ILE A :200 QC8 PRO A :241 THR A :243 PRO A : 108 ILE A :200 QC8 PRO A :241 THR A :243 PRO A : 108 ILE A :200 GLV A :109 GLN A :100 PRO A :108 ILE A :200 ILE A :200 GLV A :109 GLN A :100 PRO A :108 ILE A :200 ILE A :200 GLN A :100 GLN A :100 FRO A : 108 ILE A :200 ILE A :200 REF PHE A	QC3	HIS A $\cdot 246$	$\frac{1110}{108}$	11011.275	$IIFA \cdot 200$
Image: CLY A : 109 GLN A : 110 GLN A : 110 THR A : 292 ILE A : 249 PRO A : 108 QC6 THR A : 292 GLN A : 110 GLN A : 110 GLY A : 109 FRO A : 108 PRO A : 241 ASP A : 245 THR A : 243 PRO A : 108 QC7 GLY A : 109 HIS A : 246 THR A : 243 QC8 PRO A : 241 HIS A : 246 PRO A : 108 GLY A : 109 PRO A : 108 GLU A : 240 PRO A : 108 PRO A : 108 PRO A : 293 VAL A: 202 ILE A : 200 QC8 PRO A : 241 PRO A : 108 PRO A : 108 GLY A : 109 PRO A : 108 GLY A : 109 PRO A : 108 GLY A : 109 PRO A : 122 REF PHE A : 8 ASP A : 245 FRO A : 132 GLN A : 107 THR A : 243 GLN A :		PRO A ·132	1 KO 11 .100		ILL / 1.200
GLN A: 110 THR A: 292 ILE A: 249 PRO A: 108 PRO A: 293 VAL A: 202 QC6 THR A: 292 GLN A: 110 GLY A: 109 GLU A: 240 PRO A: 241 ASP A: 245 THR A: 243 GLN A: 110 PRO A: 293 VAL A: 202 QC7 GLY A: 109 HIS A: 246 PRO A: 108 THR A: 243 PRO A: 108 VAL A: 202 ILE A: 200 QC8 PRO A: 241 HIS A: 246 THR A: 243 PRO A: 108 PRO A: 293 VAL A: 202 VAL A: 202 QC8 PRO A: 241 HIS A: 246 THR A: 243 PRO A: 108 PRO A: 293 PRO A: 108 VAL A: 202 QC8 PRO A: 241 HIS A: 246 THR A: 243 PRO A: 108 PRO A: 108 PRO A: 108 ILE A: 200 QC8 PRO A: 241 HIS A: 246 THR A: 243 PRO A: 108 PRO A: 108 ILE A: 200 QC8 PRO A: 241 HIS A: 246 THR A: 243 PRO A: 108 PRO A: 108 ILE A: 200 QC8 PRO A: 122 GLY A: 109 GLN A: 110 THR A: 292 THR A: 111 HIS A: 246 GLN A: 110 THR A: 292 YAL A: 202 REF PHE A: 8 GLN A: 110 GLN A: 107 THR A: 243 GLY A: 109 PRO A: 108 ILE A: 249 YAL REF PHE A: 107 PRO A: 108 ILE A: 249 A: 202		$GIY A \cdot 109$			
QC6 THR A : 292 ILE A : 249 PRO A : 108 GLN A : 110 GLN A : 110 PRO A : 293 GLN A : 200 VAL A: 202 ILE A : 200 QC6 THR A : 292 GLN A : 109 GLU A : 240 PRO A : 241 ASP A : 245 THR A : 243 PRO A : 108 PRO A : 109 PRO A : 108 VAL A : 200 QC7 GLY A : 109 HIS A : 246 PRO A : 108 THR A : 243 PRO A : 108 ILE A : 200 QC8 PRO A : 241 HIS A : 246 THR A : 243 PRO A : 108 PRO A : 293 PRO A : 202 VAL A: 202 QC8 PRO A : 241 HIS A : 246 THR A : 243 PRO A : 108 PRO A : 108 ILE A : 200 QC8 PRO A : 241 HIS A : 246 THR A : 243 PRO A : 108 PRO A : 108 ILE A : 200 QC8 PRO A : 241 HIS A : 246 THR A : 243 PRO A : 108 PRO A : 108 ILE A : 200 QC8 PRO A : 241 HIS A : 246 THR A : 243 PRO A : 108 PRO A : 108 ILE A : 200 QC8 PRO A : 241 HIS A : 245 PRO A : 120 THR A : 243 PRO A : 108 PRO A : 108 ILE A : 200 REF PHE A : 8 GLN A : 110 GLN A : 110 FIR A : 243 GLY A : 109 PRO A : 108 A : 202 VAL A : 202 REF PHE A : 100 PRO A : 108 ILE A : 249 ILE A : 249 A : 202		$GINA \cdot 110$			
ILE A :249 PRO A :108 PRO A : 293 VAL A:202 QC6 THR A : 292 GLN A :110 GLN A :110 ILE A :200 GLY A :109 GLN A :110 GLN A :110 ILE A :200 ILE A :200 QC6 THR A :240 PRO A :108 PRO A :201 ILE A :200 ASP A :241 ASP A :245 THR A :243 PRO A :108 ILE A :200 QC7 GLY A :109 PRO A :108 PRO A :108 VAL A :202 UE A :246 THR A :243 VAL A :202 ILE A :200 QC8 PRO A :241 THR A :243 PRO A : 293 VAL A:202 UE A :240 ASP A :245 PRO A :108 PRO A : 203 ILE A :200 QC8 PRO A :241 THR A :243 PRO A : 108 ILE A :200 QC8 PRO A :241 THR A :243 PRO A : 108 ILE A :200 QC8 PRO A :241 THR A :243 PRO A : 108 ILE A :200 GLV A :109 GLN A :110 THR A :245 PRO A : 132 VAL GLY A : 109 GLN A : 107 THR A		THR A $\cdot 292$			
QC6 THR A : 292 GLN A :110 GLY A :109 GLU A :240 PRO A :241 ASP A :245 THR A :243 PRO A :108 GLN A :110 PRO A : 293 VAL A:202 ILE A :200 QC7 GLY A :109 HIS A :246 PRO A :108 THR A :243 PRO A :108 VAL A :202 ILE A :200 ILE A : 200 QC7 GLY A :109 HIS A :246 PRO A :108 THR A :243 PRO A :108 VAL A :202 ILE A :200 ILE A : 200 QC8 PRO A :241 HIS A : 246 GLU A :240 ASP A :245 PRO A :132 GLY A :109 GLN A :110 THR A :292 PRO A : 108 PRO A : 108 ILE A : 200 REF PHE A : 8 THR A : 292 GLN A : 110 GLN A : 110 GLN A : 110 GLN A : 110 GLN A : 107 THR A : 243 GLY A : 109 PRO A :108 PRO A : 132 VAL VAL REF PHE A : 8 THR A : 292 GLN A : 107 THR A : 243 GLY A : 109 PRO A : 108 ASN A : 151 ILE A : 249 PRO A : 202		ILE A $\cdot 249$			
QC0 INK A : 510 GLN A : 110 GLY A : 109 GLU A : 240 PRO A : 241 ASP A : 245 THR A : 243 GLN A : 110 ILE A : 200 QC7 GLY A : 109 HIS A : 246 UC8 PRO A : 108 THR A : 243 PRO A : 108 VAL A : 202 ULE A : 249 ILE A : 200 QC8 PRO A : 241 HIS A : 246 GLU A : 240 ASP A : 245 PRO A : 108 THR A : 243 PRO A : 108 PRO A : 108 VAL A : 202 ILE A : 249 VAL A : 202 ILE A : 249 QC8 PRO A : 241 HIS A : 246 GLU A : 240 ASP A : 245 PRO A : 103 THR A : 243 PRO A : 108 PRO A : 108 ILE A : 200 QC8 PRO A : 241 HIS A : 246 GLU A : 240 ASP A : 245 PRO A : 102 THR A : 243 PRO A : 108 VAL A: 202 ILE A : 200 REF PHE A : 8 THR A : 292 GLN A : 110 GLN A : 110 GLN A : 110 GLN A : 107 THR A : 243 GLY A : 109 PRO A : 108 ASP A : 245 ILE A : 249 VAL A : 202 REF PHE A : 8 THR A : 202 GLN A : 107 THR A : 243 GLY A : 109 PRO A : 108 ASP A : 245 ILE A : 249 VAL	006	THR A \cdot 292	PRO A ·108	$PROA \cdot 293$	VAL A·202
GLY A :109 GLY A :109 GLY A :109 Final Activity GLU A :240 PRO A :241 ASP A :245 Final Activity THR A :243 PRO A :108 PRO A :108 ILE A : 200 QC7 GLY A :109 PRO A :108 VAL A :202 HIS A :246 THR A :243 VAL A :202 QC8 PRO A :241 THR A :243 PRO A : 209 QC8 PRO A :241 THR A :243 PRO A : 202 HIS A : 246 THR A :243 PRO A : 202 GLU A :240 ASP A :245 PRO A :108 ILE A :200 GLY A :109 GLN A :110 PRO A :108 PRO A : 108 ILE A :200 REF PHE A : 8 ASN A : 151 PRO A : 132 VAL GLN A :110 ASP A : 245 ILE A : 249 A : 202 REF PHE A : 8 ASN A : 151 PRO A : 132 VAL GLN A : 110 ASP A : 245 ILE A : 249 A : 202 GLN A : 107 THR A : 243 GLY A : 109 ILE A : 245 A : 202 PRO A : 108 PRO A : 108 ILE A : 249 A : 202 ILE A : 249	QCO	$GLN A \cdot 110$	GLN A ·110	11011.275	$ILE A \cdot 200$
GLU A :240 PRO A :241 ASP A :245 HIR A : 243 PRO A :108 ILE A : 200 QC7 GLY A :109 PRO A :108 VAL A :202 ILE A : 200 HIS A :246 THR A :243 VAL A :202 ILE A :249 QC8 PRO A :241 THR A :243 PRO A : 293 VAL A:202 HIS A :246 THR A :243 PRO A : 108 ILE A : 200 QC8 PRO A :241 THR A :243 PRO A : 108 ILE A : 200 QC8 PRO A :241 THR A :243 PRO A : 108 ILE A : 200 GLU A :240 ASP A :245 PRO A :108 PRO A : 108 ILE A : 200 GLY A :109 GLN A :110 THR A :292 PRO A : 132 VAL REF PHE A : 8 ASN A : 151 PRO A : 132 VAL GLN A : 110 ASP A : 245 ILE A : 249 A : 202 REF PHE A : 8 ASN A : 245 ILE A : 249 A : 202 REF PHE A : 8 ASP A : 245 ILE A : 249 A : 202 GLN A : 110 ASP A : 245 ILE A : 249 A : 202 ILE A : 249 GLN A : 108 PRO A :		$GLY A \cdot 109$	GLIVIIII		122 11.200
PRO A :241 ASP A :245 THR A: 243 PRO A :108 QC7 GLY A :109 PRO A :108 HIS A :246 THR A :243 VAL A :202 ILE A :249 ILE A :249 QC8 PRO A :241 THR A :243 HIS A :246 THR A :243 PRO A : 293 GLY A :109 PRO A :108 PRO A : 108 GLY A :109 PRO A :108 PRO A : 108 GLY A :109 GLN A :110 THR A : 292 REF PHE A : 8 ASN A : 151 THR A : 292 THR A : 111 HIS A : 243 GLY A : 109 GLN A : 110 ASP A : 245 GLN A : 107 THR A : 243 GLN A : 107 ASP A : 245 FIR A : 243 GLY A : 109 PRO A : 108 ILE A : 249		GLUA ·240			
ASP A :243 PRO A :108 PRO A :108 ILE A : 200 QC7 GLY A :109 PRO A :108 VAL A :202 ILE A : 249 QC8 PRO A :241 THR A :243 PRO A :293 VAL A:202 ULE A :240 PRO A :108 PRO A :108 ILE A :200 QC8 PRO A :241 THR A :243 PRO A : 293 VAL A:202 ULE A :240 ASP A :245 PRO A :108 PRO A : 108 ILE A :200 GLV A :240 ASP A :245 PRO A :108 PRO A : 108 ILE A :200 GLV A :240 ASP A :245 PRO A :108 PRO A : 108 ILE A :200 GLY A :109 GLN A :110 THR A : 245 PRO A : 132 VAL REF PHE A : 8 ASN A : 151 PRO A : 132 VAL GLN A :110 ASP A : 245 ILE A : 249 A : 202 REF PHE A : 8 ASP A : 245 ILE A : 249 A : 202 REF PRO A :107 THR A : 243 ILE A : 249 A : 202 GLN A : 107 THR A : 243 ILE A : 249 A : 202 PRO A :108 PRO A :108 ILE A : 249 A : 202		PRO A ·241			
THR A: 243 PRO A:108 PRO A:108 ILE A: 200 QC7 GLY A:109 PRO A:108 THR A: 243 ILE A:202 QC8 PRO A:241 THR A:243 PRO A: 293 VAL A:202 QC8 PRO A:241 THR A:243 PRO A: 293 VAL A:202 ILE A:249 PRO A: 240 PRO A: 108 PRO A: 108 ILE A:200 QC8 PRO A:245 PRO A: 108 PRO A: 108 ILE A:200 GLY A:109 GLN A:110 PRO A:108 PRO A: 108 ILE A:200 REF PHE A:8 ASN A: 151 PRO A: 132 VAL GLN A:110 THR A: 245 ILE A: 246 A: 202 GLN A:110 ASP A: 245 ILE A: 249 A: 202 REF PHE A:8 ASN A: 151 PRO A: 132 VAL GLN A: 110 ASP A: 245 ILE A: 249 A: 202 GLN A: 107 THR A: 243 ILE A: 249 A: 202 GLY A: 109 PRO A:108 ILE A: 249 A: 202		ASP A :245			
QC7 GLY A :109 HIS A :246 PRO A :108 THR A :243 PRO A :108 VAL A :202 ILE A :249 ILE A : 200 QC8 PRO A :241 HIS A : 246 GLU A :240 ASP A :245 PRO A :108 THR A :243 PRO A :108 PRO A : 293 PRO A : 108 VAL A:202 ILE A :240 ASP A :245 PRO A :132 GLY A :109 GLN A :110 THR A :292 PRO A : 108 PRO A : 108 ILE A : 200 REF PHE A : 8 THR A : 292 ASN A : 151 THR A : 245 PRO A : 132 HIS A : 246 ILE A : 240 VAL REF PHE A : 8 THR A : 292 GLN A : 110 GLN A : 110 GLN A : 107 THR A : 243 GLY A : 109 PRO A :108 ASN A : 245 ILE A : 249		THR A: 243			
CC HIS A :246 THR A :243 VAL A :202 QC8 PRO A :241 THR A :243 PRO A : 293 VAL A :202 HIS A :246 PRO A :108 PRO A : 293 VAL A :202 GLU A :240 ASP A :245 PRO A :108 PRO A : 108 ILE A :200 GLY A :109 GLN A :110 THR A :292 PRO A : 132 VAL A :202 REF PHE A : 8 ASN A : 151 PRO A : 132 VAL GLN A :110 THR A : 245 ILE A : 246 A : 202 REF PHE A : 8 ASN A : 151 PRO A : 132 VAL GLN A : 110 ASP A : 245 ILE A : 246 A : 202 A : 202 REF PHE A : 8 ASN A : 245 ILE A : 249 A : 202 GLN A : 110 ASP A : 245 ILE A : 249 A : 202 GLN A : 107 THR A : 243 ILE A : 249 A : 202 GLY A : 109 PRO A :108 ILE A : 249 ILE A : 249	OC7	GLY A :109	PRO A :108	PRO A :108	ILE A : 200
QC8 PRO A :241 THR A :243 PRO A : 293 VAL A:202 ILE A :240 ASP A :246 PRO A :108 PRO A : 108 ILE A :200 GLU A :240 ASP A :245 PRO A :108 PRO A : 108 ILE A :200 GLY A :109 GLN A :110 PRO A :132 PRO A :132 PRO A : 132 PRO A : 108 REF PHE A : 8 ASN A : 151 PRO A : 132 VAL GLN A : 110 THR A : 292 THR A : 246 A : 202 REF PHE A : 8 ASN A : 151 PRO A : 132 VAL GLN A : 110 ASP A : 245 ILE A : 249 A : 202 REF PHE A : 8 ASN A : 245 ILE A : 249 A : 202 REF PHE A : 100 ASP A : 245 ILE A : 249 A : 202 GLN A : 107 THR A : 243 GLY A : 109 PRO A : 108 ILE A : 249		HIS A :246	THR A :243	VAL A :202	
QC8 PRO A :241 HIS A : 246 GLU A :240 ASP A :245 PRO A :108 THR A :243 PRO A :108 PRO A : 293 PRO A : 108 VAL A:202 ILE A :200 GLY A :109 GLN A :110 THR A :292 GLY A :109 GLN A :110 PRO A : 132 PRO A : 132 VAL A:202 PRO A : 108 REF PHE A : 8 THR A : 292 ASN A : 151 THR A : 246 GLN A : 110 PRO A : 132 ASP A : 246 A : 202 VAL REF PHE A : 8 THR A : 292 GLN A : 107 THR A : 243 GLY A : 109 PRO A :108 ASP A : 245 ILE A : 249 VAL				ILE A :249	
HIS A : 246 PRO A :108 PRO A : 108 ILE A :200 GLU A :240 ASP A :245 PRO A :108 PRO A : 108 ILE A :200 GLY A :109 GLN A :110 PRO A :132 PRO A :132 PRO A :108 ILE A :200 REF PHE A : 8 ASN A : 151 PRO A : 132 VAL THR A : 292 THR A : 111 HIS A : 246 A : 202 REF PHE A : 8 ASP A : 245 ILE A : 249 GLN A : 110 ASP A : 245 ILE A : 249 VAL GLN A : 107 THR A : 243 ILE A : 243 ILE A : 249 GLY A : 109 PRO A :108 ILE A : 249 ILE A : 249	0C8	PRO A :241	THR A :243	PRO A : 293	VAL A:202
GLU A :240 ASP A :245 FRO A :132 FRO A :132 GLY A :109 GLN A :110 FRO A :132 FRO A :132 REF PHE A : 8 ASN A : 151 PRO A : 132 VAL THR A : 292 THR A : 111 HIS A : 246 A : 202 REF PHE A : 8 ASP A : 245 ILE A : 249 A : 202 REF PHE A : 8 ASP A : 245 ILE A : 249 A : 202 REF PHE A : 107 THR A : 243 ILE A : 249 A : 202 GLY A : 109 PRO A :108 ILE A : 249 ILE A : 249 ILE A : 249	200	HIS A : 246	PRO A :108	PRO A : 108	ILE A :200
ASP A :245 PRO A :132 GLY A :109 GLN A :110 THR A :292 REF PHE A : 8 THR A : 292 THR A : 292 THR A : 292 THR A : 292 GLN A :110 GLN A : 110 GLN A : 110 GLN A : 110 GLN A : 107 THR A : 243 GLY A : 109 PRO A :108		GLU A :240			
PRO A :132 PRO A :132 GLY A :109 GLN A :110 THR A :292 PRO A : 151 REF PHE A : 8 THR A : 292 THR A : 151 GLN A : 110 ASN A : 151 GLN A : 110 ASP A : 245 GLN A : 107 THR A : 243 GLY A : 109 PRO A : 108		ASP A :245			
GLY A :109 GLN A :110 THR A :292 THR A :151 REF PHE A : 8 THR A : 292 THR A : 111 HIS A : 246 A : 202 GLN A : 110 ASP A : 245 GLN A : 107 THR A : 243 GLY A : 109 FRO A : 108		PRO A :132			
GLN A :110 GLN A :110 THR A :292 THR A :10 REF PHE A : 8 THR A : 292 THR A : 151 GLN A : 110 ASN A : 151 GLN A : 110 ASP A : 245 GLN A : 107 THR A : 243 GLY A : 109 FRO A : 108		GLY A :109			
THR A :292 PRO A : 132 VAL REF PHE A : 8 ASN A : 151 PRO A : 132 VAL THR A : 292 THR A : 111 HIS A : 246 A : 202 GLN A : 110 ASP A : 245 ILE A : 249 A : 202 GLN A : 107 THR A : 243 ILE A : 249 A : 202 GLY A : 109 PRO A :108 ILE A : 249 ILE A : 249		GLN A :110			
REF PHE A : 8 ASN A : 151 PRO A : 132 VAL THR A : 292 THR A : 111 HIS A : 246 A : 202 GLN A : 110 ASP A : 245 ILE A : 249 A : 202 GLN A : 107 THR A : 243 ILE A : 249 A : 202 GLY A : 109 PRO A :108 ILE A : 249 ILE A : 249		THR A :292			
THR A : 292 THR A : 111 HIS A : 246 A : 202 GLN A : 110 ASP A : 245 ILE A : 249 A : 202 GLN A : 107 THR A : 243 ILE A : 249 A : 202 GLY A : 109 PRO A :108 A : 108 A : 202	REF	PHE A : 8	ASN A : 151	PRO A : 132	VAL
GLN A : 110 ASP A : 245 ILE A : 249 GLN A : 107 THR A : 243 ILE A : 249 PRO A : 109 PRO A :108 ILE A : 249		THR A : 292	THR A : 111	HIS A : 246	A : 202
GLN A : 107 THR A : 243 GLY A : 109 PRO A :108		GLN A : 110	ASP A : 245	ILE A : 249	
THR A : 243 GLY A : 109 PRO A :108		GLN A : 107			
GLY A : 109 PRO A :108		THR A : 243			
PRO A :108		GLY A : 109			
		PRO A :108			

CONCLUSION

In the present We have selected the compound library of quinazolin -4- one followed by investigate SAS-CoV 3CL Pro binding interaction by docking study using the library, a number of quinazolin 4 one with a better range of binding score were detected. Insilico study data shows the most potent with the high docking score - 8.8kcal/mol. depending upon the docking scores of the compound were selected and further studies. The study suggests that, the selected libraries exhibit the significant

activity against SAR –CoV 3CL Protease enzyme which may be useful to develop better inhibitory quinazolin-4-one derivatives.

REFERENCES

1. N.C.Desai, Amit Dodiya, Niraj Shihory synthesis and antimicrobial activity of novel quinazolinonethiazolidine-quinoline compounds., Journal of Saudi chemical society, 2013; 17: 259-267.

- Lai MM, Cavanagh D. the molecular biology of corona viruses. Adv virus Res., 1997; 48: 1-100.
- Mesel-Lemoine M, Millet J, and Vidalain P-O et al. A Human corona virus responsible for the common cold massively kills dentritic cells but not monocytes. J Virol., 2012; 86: 7577-87.
- De Wit E, Van Doremalen N, Falzarano D, Munster VJ. SARS and MERS :recent insights into emerging corona viruses. Nat Rev Microbial, 2016; 14: 523-34.
- Drosten C, Gunther S, Preiser W, et al. Identification of a novel corona virus in patients with severe acute respiratory syndrome. N Engl J Med, 2003; 348: 1967-76.
- 6. Donnelly CA,Ghani AC, Leung GM, et al Epidemiological determinants of spread of causal agent of severe acute respiratory syndrome in Hong kong.lancet, 2003; 361: 1761-6.
- Li W, Shi Z, Yu M, et al Bats are natural reservoirs of SARS like corona viruses. science, 2005; 310: 676-9.
- 8. Lan JT, Yang X, Pang E, et al SARS- related perceptions in Hong kong.Emerg infect Dis., 2013; 11: 417-24.
- Ren Z, Yan L, Zhang N, et al. The newly emerged SARS-Like Corona virus HCo V-EMC also has an "Achilles heel". Current effective inhibitor targeting a 3C-Like protease .protein Cell., 2013; 4: 248-50
- Kilianski A, Mielech AM, Deng X, Baker SC. Assessing activity and inhibition of middle East respiratory syndrome corona virus papain like and 3C Like protease using luciferasebased biosensors Virol., 2013; 87: 11955-62.
- 11. Neddle D, Lountos GT, Waugh DS. Structures of the Middle East respiratory syndrome corona virus 3C like Protease reveals insights into substrate specificity. Acta Crrystallography, 2015; 71: 1102-11.
- 12. Chunck CP, Chow HF, Wan DC,Wong KB Profiling of substrate specificities of 3C like proteases from group 1,2a,2b, and 3 corona viruses.PLoS onem 2011; 6: e27228.
- Kavitha K, Srinivasan N, Haribabu Y, Suresh R Synthesis and molecular docking study of novel 2phenyl quinazoline-4(-3H)-one Derivative as Cox-2 Inhibitor.,Indo American journal of pharmaceutical sciences., 2019; 06(02): 4032-4037.
- 14. KK.Rajasekhar ,ND Nizamuddin abdrrahman Shemsu surur ,yennus Tadesse Mekonnen synthesis, characterization, anti tubercular and anti bacterial activity, and molecular docking of 2,3-di substituted quinazolinone derivative. Research and reports in medicinal chemistry, 2016; 6: 15-26.
- 15. Sako Mirzaie, Majid Monajjemi, Mohammad Sajeed Hakhamaneshi, Fardin Fathi, Mostafa Jamalan Combined 3D QSAR on Multi acting quinazoline derivatives as HER2 Kinase inhibitors., EXCLI Journal, 2013; 12: 130-143.