World Journal of Pharmaceutical and Life Sciences
WJPLS
www.wjpls.org
SJIF Impact Factor: 6.129

INSILICO STUDY OF QUINAZOLINE-4-ONE ON SARS-COV 3CL PROTEASE

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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 Artierividae 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 fastest-evolving 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 3D-structure. 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 co-crystallized 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.

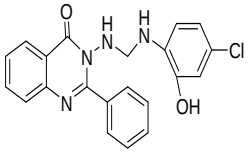
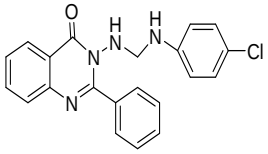
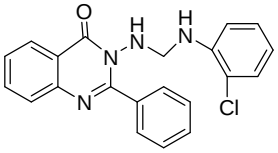
The binding energy of each ligand against 3CL PRO macromolecule was predicted using auto dock vina, which is one of the most commonly used docking software .in the docking procedure eight binding pose were obtained, and the binding bose with the highest binding energy corresponding to the RMSD value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

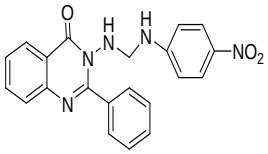
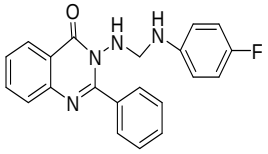
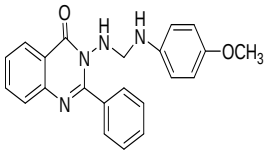
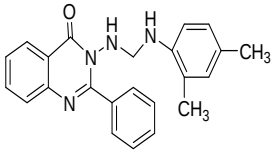
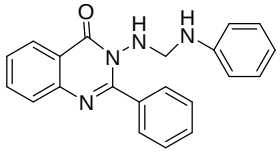
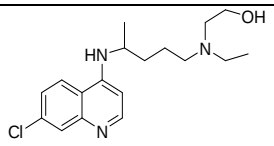
From selected compound library QC1 (-8.8 kcal/mol) showed the highest binding energy. The selected libraries of quinazolinone series, however, showed better binding energy than the hydroxy chloroquine which is used as reference compound. In particular, almost all the compounds showed the excellent binding 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		-8.6
QC6		-8.3
QC7		-8.6
QC8		-8.3
Ref		-6.8

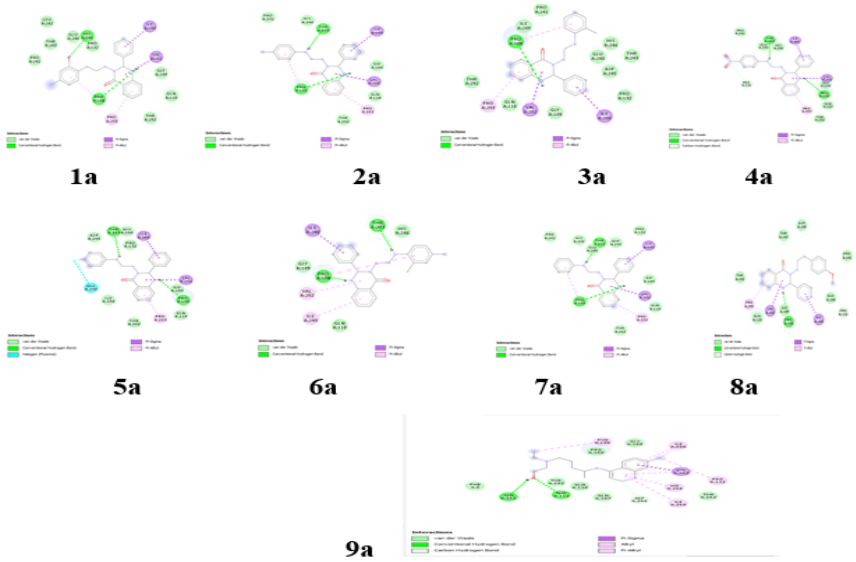


Fig.1: 2D Stereo view of compound QC1 on enzyme 3CL Pro 6M2N.

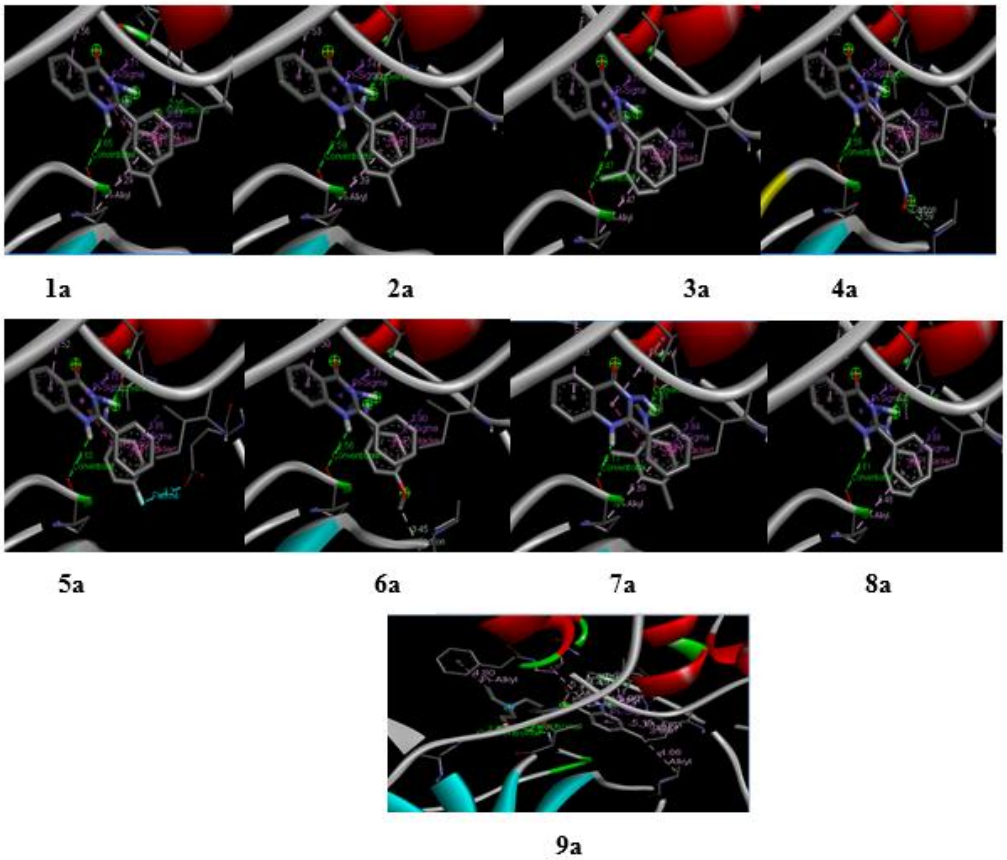


Fig.2: 3D Stereo view of compound QC1 on enzyme 3CL Pro 6M2N.

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 GLU A : 240 THR A : 243 PRO A :241 THR A : 292 GLN A : 110 GLN A : 109	HIS A : 26 PRO A : 108	PRO A :293 PRO A : 108	ILE A : 200 VAL A:202
QC2	PRO A :241 HIS A :p246 THR A :292 GLN A :110 GLY A :109	THR A :243 PRO A :108	PRO A :293 PRO A : 108	VAL A:202 ILE A :200

QC3	PRO A :241 ILE 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 : 293 PRO A : 108	VAL A:202 ILE A :200
QC4	PRO A :241 GLU A : 240 HIS A : 246 GLY 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 :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 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 :249	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	THR A :243 PRO A :108	PRO A : 293 PRO A : 108	VAL A:202 ILE A :200
REF	PHE A : 8 THR A : 292 GLN A : 110 GLN A : 107 THR A : 243 GLY A : 109 PRO A :108	ASN A : 151 THR A : 111 ASP A : 245	PRO A : 132 HIS A : 246 ILE A : 249	VAL A : 202

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.

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