Computational Study of Homochirality and Heterochirality and Drug Interactions with SARS COV-2 in Biological System

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Abstract: *Now a day, chiral discrimination has become a centre of research and it is more relevant for drug designing. Chiral drugs have been widely used in pharmaceutical industries; nearly 90% of them are racemates.Therefore, it is important to study the racemic drug in order to avoid formation of unwanted drug isomers. The concept of homochirality and heterochirality of amino acids is analysed in many research reports. The biomolecules of our ecological and biological system possess homochirality.Experimental studies have also shown that homochiral L-L amino acids are mostly manufactured in cells and are incorporated in proteins. Computational analysis of homochirality of amino acids and drug interactions with selective residues of corona virus has beenexplored using Gaussian software. In the current project, we have calculated their energy and explored their interaction with drugs such as Hydroxychloroquine and Dexamethasone. Since COVID -19 has caused global pandemic and these two drugs have emerged as a major breakthrough in treatment of COVID-19. Above mentioned drugs are generally used for treatment of rheumatic diseases. The interaction energy of drug with selected residue of amino acids from coronavirus has been calculated. Further, energy of amino acid dimer (L-L and D-L) has also been calculated. It has been found that decrease in energy leads to stability of the system.*

Keywords: **Betacoronavirus, Amino Acids, Hydroxychloroquine and Dexamethasone**

1. INTRODUCTION

In December 2019, outbreak of Coronavirus (COVID-19) from the seafood market of Wuhan, China brought the whole world in the current pandemic situation[1]. WHO have revealed **27,205,275** confirmed cases and **890,392** deaths worldwide on 8thseptember 2020. The COVID-19 is a massive health problem at present as it transmits irregularly and spread rapidly[2]. The most common symptoms of this deadly disease include fever, cough, and shortness of breath, headache and nausea. As COVID-19 virus is a member of *Beta*coronavirus and has 89.1% nucleotide similarity with SARS-CoV (severe acute respiratory syndrome coronavirus)[3].That is why some of the drugs that inhibit target sites of SARS-CoV may also work similarly for COVID-19 virus[4]. Scientists from all over the world are trying to develop new compounds to targets and overcome the proliferating threat of Betacoronavirus. Therefore, drug discovery is one of the ways that may pave us towards the cure of this virus. It is a multistep process with high attrition rate, high cost and slow speed development of a new molecule. It takes 10 to 12 years to design a new drug. Therefore, drug repurposing (It means use of old drugs for new purposes) is an alternative and attractive way for the new application of FDA approved drugs[5]. A Pubmed research with the keyword COVID-19 resulted in more than 900 publications from November 2019 to April 2020. Around the globe, the majority of research efforts are being mainly focused on finding the clinical manifestations and effective treatment options of COVID. It has been described in the literature that drugs approved by FDA (as shown in **Fig - 1)** namely **Chloroquine (CQ)** and **Hydroxychloroquine (HCQ)** are well known to prevent the viral infection. These

drugs are antimalarial and have shown activity against autoimmune disorders. Further these drugs have been reused for the treatment of a number of diseases such as HIV and rheumatoid arthritis etc[6]. Chloroquine and Hydroxychloroquine enhance the pH within the intracellular vacuoles and alter the biological processes such as protein degradation by hydrolases in the lysosome, assembly of macromolecules in the endosomes and posttranslational modification of proteins in the Golgi apparatus[7]. Same way Remdesivir and Arbidol are being used for the treatment of coronavirus because of antiviral property.

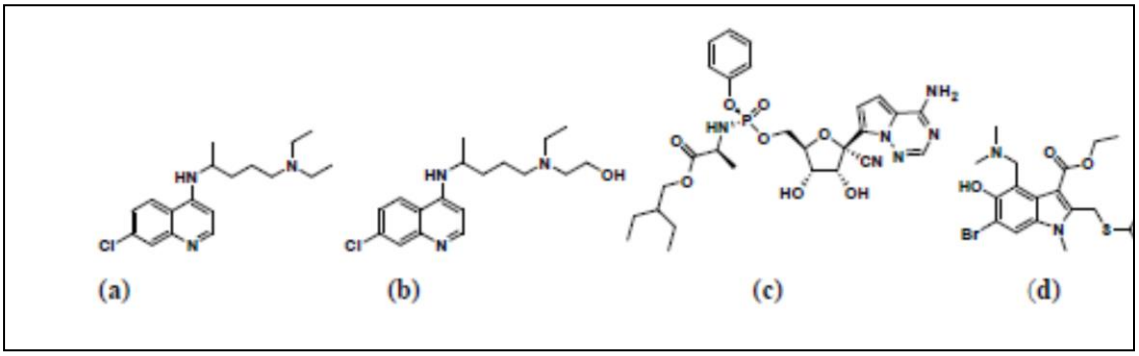


Fig - 1: Drugs used for treatment of Novel coronavirus: (a) Chloroquine (CQ),(b) Hydroxychloroquine (HCQ),(c) Remdesivir (RDV) (approved by FDA) and (d) Arbidol (ABD)

The corona virus (**Fig - 2**) enters in human cells through an interaction with angiotensin-converting enzyme[8]. Angiotensin converting enzyme 2- is a receptor for SARS CoV and it is expressed in human airway epithilia and lung parenchyma[9]. SARS COV-2 is a RNA virus and understanding of the proteins in SARS COV-2 helps for the designing of effective antiviral drugs[10-11]**.** SARS COV-2 has 11 genes and 11 ORFS (open reading frames).The first gene (ORF1ab) expresses a polyprotein. This ORF1ab polyprotein consists of 16 NSPs (non-structural proteins)[12]**.** The non-structural protein 12 (NSP12) also called RdRp (RNA dependent RNA polymerase) that copies viral RNA. Therefore, it plays a very important role in replication and transcription cycle of COVID-19 virus[13].The presence of NSP7 and NSP8 (Cofactors present in covid-19 virus) decreases the dissociation rate of NSP12 from RNA[13].

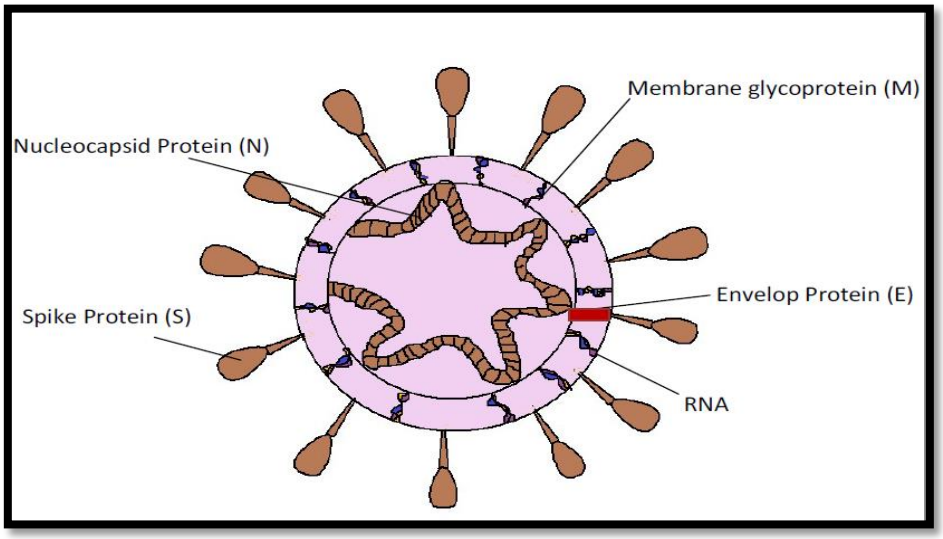


Fig -2: Schematic representation of SARS-CoV particle.

Identification of key protein residue or hotspots is necessary for drug designing. Once these hotspots are identified, binding interaction with adjacent areas of protein surface increases selectivity and improves affinity towards receptor site[14] (Liu X., *et al.*, 2018). Basically, amino acids are the building block of protein and most of the natural enzymes also contain the amino acids. Amino acids can occur in L- and D-forms, but usually L-forms are generally used by cells. Most of the biological reactions occur by chiral interactions. This is because the biological system is made up of D-carbohydrates and L-amino acids for e.g., our human odour receptors are basically chiral thus humans are able to find that D-asparagine tastes sweet whereas L-asparagine tastes bitter. D-amino acids are found in low levels in the human body [15-17].The ten essential amino acids are valine,leucine, isoleucine, phenylalanine, tryptophan, lysine, arginine, histidine, methionine and threonine. The branched-chain amino acid such as leucine acts as a precursor for muscle protein synthesis[18]. Therefore, chiral discrimination has become an emerging field due to its biological relevance. Molecules which have non superimposable mirror images, lack of plane of symmetry, lack of centre of symmetry and have improper axis of symmetry are said to be chiral and their mirror images are called enantiomers. Chirality is a distinctive feature of biological systems. Only one form of sugar and amino acid is present in biological system. This is homochirality i.e., the uniformity of chirality [19]. The importance of chirality for the functioning of human body, was discovered in 1960s when thalidomide, the chiral drug which was given to pregnant women to reduce morning sickness. Later on it was found that the (S)-enantiomer of the drug resulted in the birth defects whereas (R)-enantiomer of it was giving the desired effect[20].Chiral recognition is a powerful process in biological systems because many naturally occurring chiral molecules exist in the living system for e.g. Carbohydrates, Proteins, Amino Acids, Hormones[21-26]. The study of chiral recognition of compounds can be done by using different techniques such as nuclear magnetic resonance, capillary electrophoresis, circular dichroism, use of chiral reagents etc. [27-31].

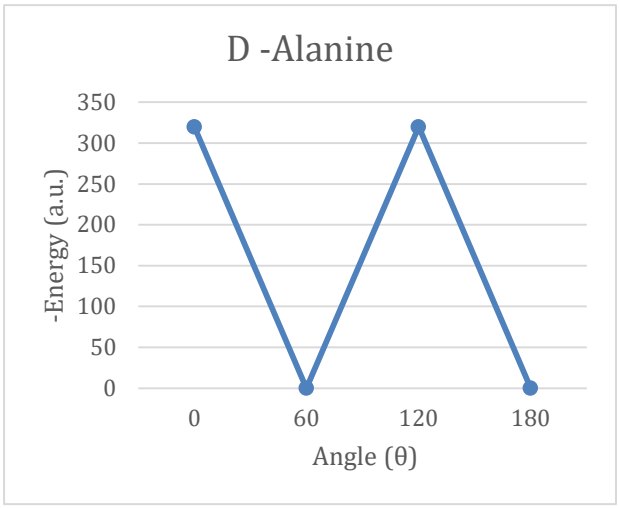
2. USE OF COMPUTATIONAL SOFTWARE

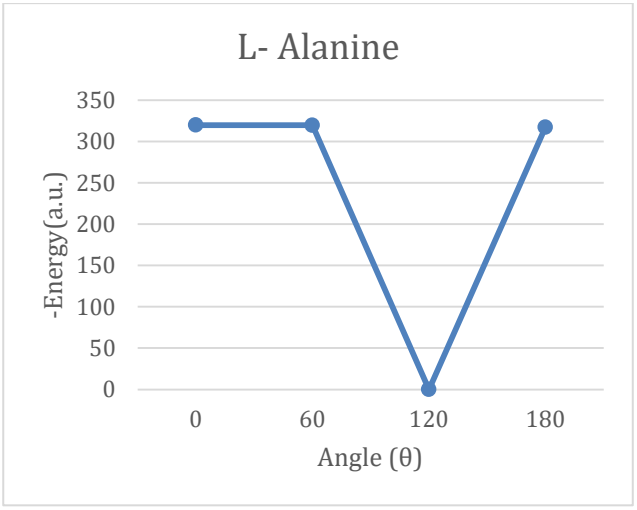
Chem Draw Ultra, Gaussian software and Swiss PDB viewer have been used for the designing of amino acids and drugs molecules. Various amino acid residues of coronavirus and drugs have taken from protein data bank (PDB). Gaussian software has been used for the calculation of single point energy bond length as well as for the optimization of various molecules. Hydroxychloroquine and Dexamethasone which have emerged as a major breakthrough in the treatment of coronavirus, are also studied in this project. We have studied the L-L and D-L interactions of various amino acids like alanine, phenylalanine, leucine, isoleucine, valine etc.

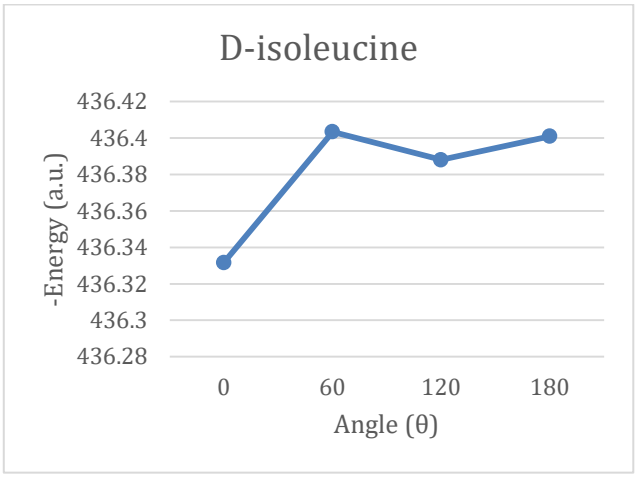
3. RESULT AND DISCUSSION

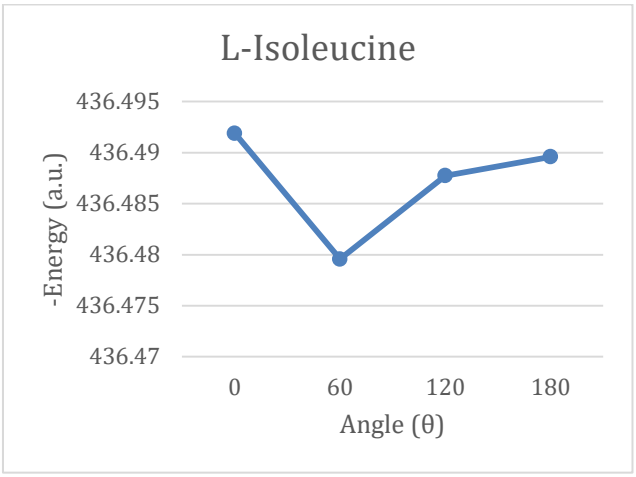
3.1 L-L AND L-D INTERACTION OF AMINO ACIDS

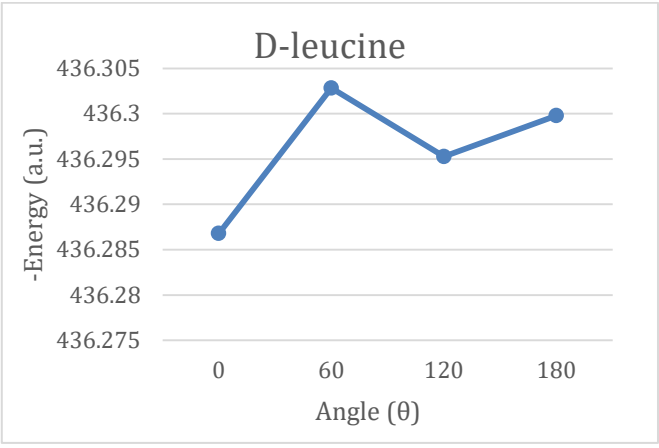
We have calculated energies of different 'L' and 'D' amino acids by varying dihedral angles and plotted them (**Chart - 1**) to obtain minimum energy of the system. The most stable structure displays highest negative energy value which is also reflected in the respective plots. We have also analysed the interaction of L-L and L-D system of the amino acids (Alanine, Valine, Isoleucine, Leucine and Phenylalanine respectively). Favourability of the interaction can be predicted from the energy value. The global minima of potential energy signify the most stable configuration of a molecule. From our results we interpret that L-L system is the most favourable one for the interaction because of its lower energy than L-D system. We have shown these results with the help of gauss view software which is given in **Fig - 3** with respective energy values.

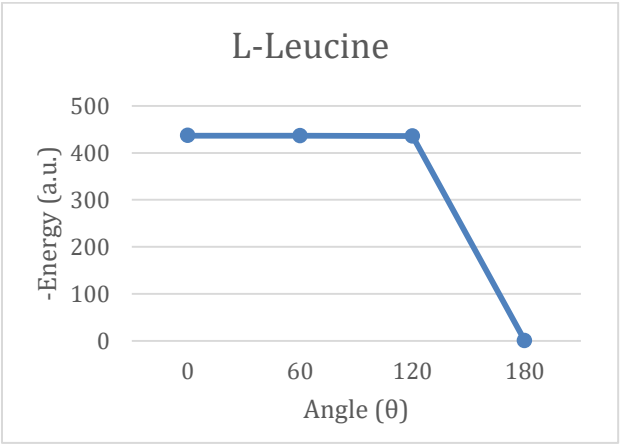

D -Alanine
-Energy (a.u.)
350
300
250
200
150
100
50
0
0
60
120
180
Angle (θ)


L- Alanine
-Energy(a.u.)
350
300
250
200
150
100
50
0
0
60
120
180
Angle (θ)


D-isoleucine
-Energy (a.u.)
436.42
436.4
436.38
436.36
436.34
436.32
436.3
436.28
0
60
120
180
Angle (θ)


L-Isoleucine
-Energy (a.u.)
436.495
436.49
436.485
436.48
436.475
436.47
0
60
120
180
Angle (θ)


D-leucine
-Energy (a.u.)
436.305
436.3
436.295
436.29
436.285
436.28
436.275
0
60
120
180
Angle (θ)


L-Leucine
-Energy (a.u.)
500
400
300
200
100
0
0
60
120
180
Angle (θ)

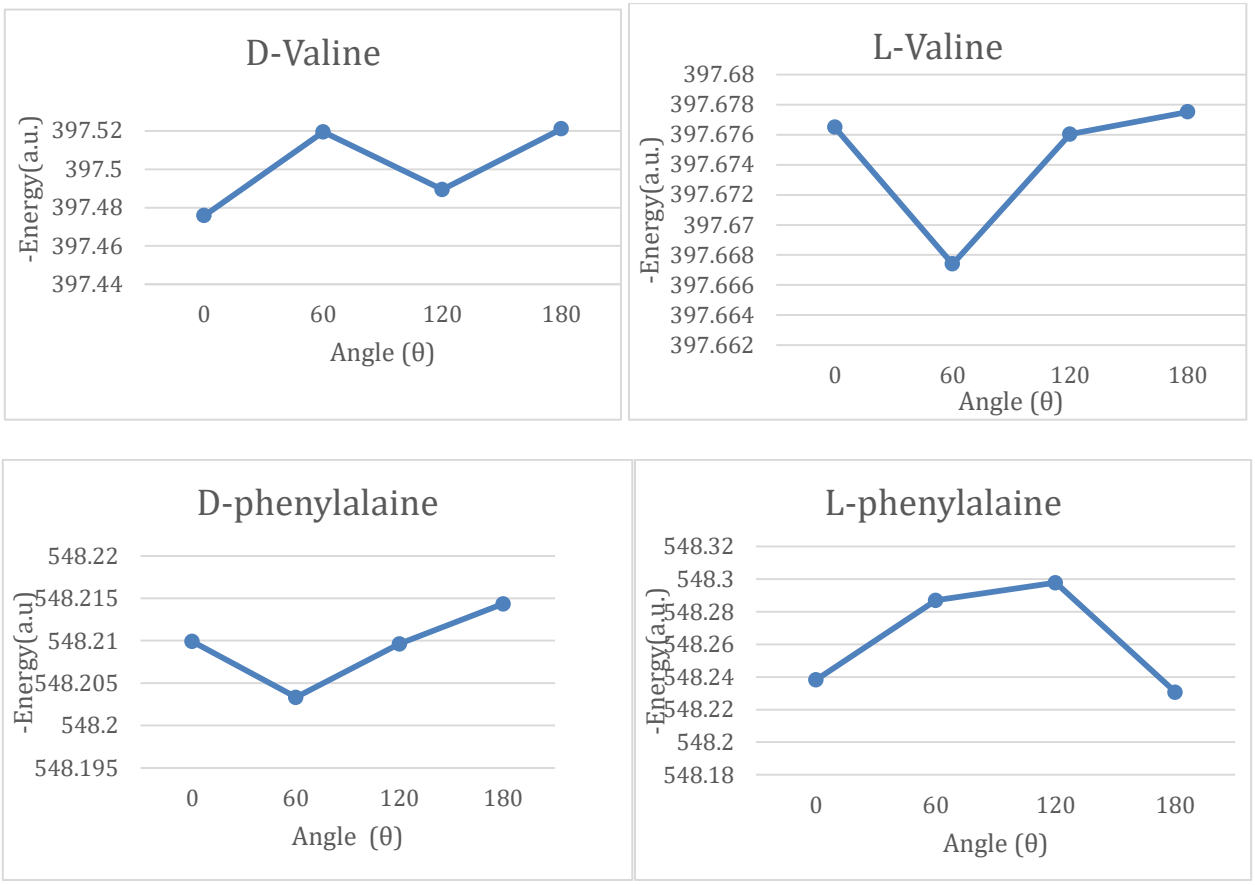
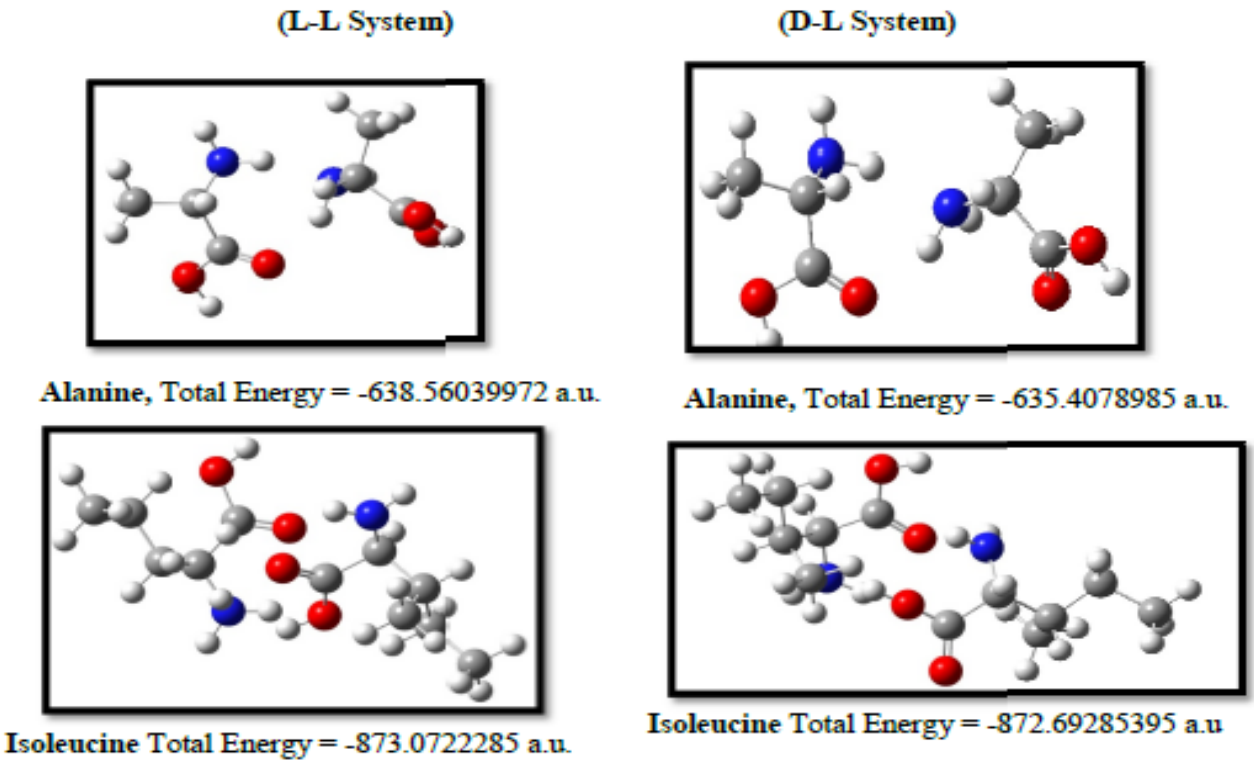


Chart - 1: Energy v/s dihedral angle plots of D- and L- amino acids of Alanine, Valine, Isoleucine, Leucine and Phenylalanine respectively.



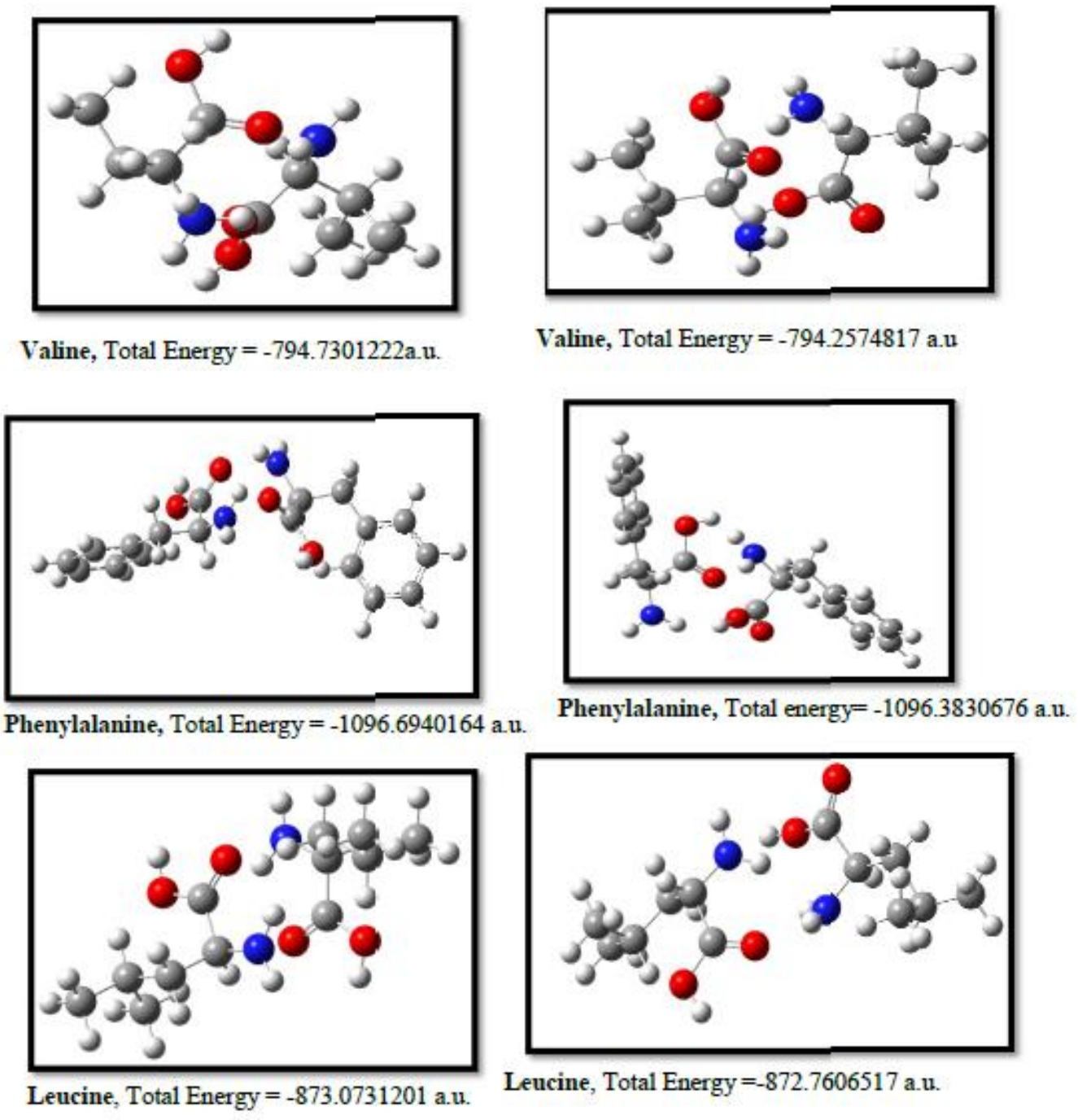


Fig - 3: Comparison of Energies of L-L and L-D systems of various Amino acids.

3.2 THE BINDING MODE ANALYSIS OF HYDROCHLOROQUINE AND DEXAMETHASONE WITH CORONAVIRUS

We have studied the interaction of two drugs Hydroxychloroquine (PDB ID 6LZG) and Dexamethasone (PDB ID 4UDC) respectively with novel coronavirus. We have also illustrated the respective structure of Hydroxychloroquine and Dexamethasone drug through Chem Draw. We have first optimized the drug molecules to obtain the most stable

configuration for interaction as shown in **Fig - 4**. Further, we have examined theirs interaction with coronavirus receptor ACE2 as shown in **Fig - 4 (c) and 4 (d).**

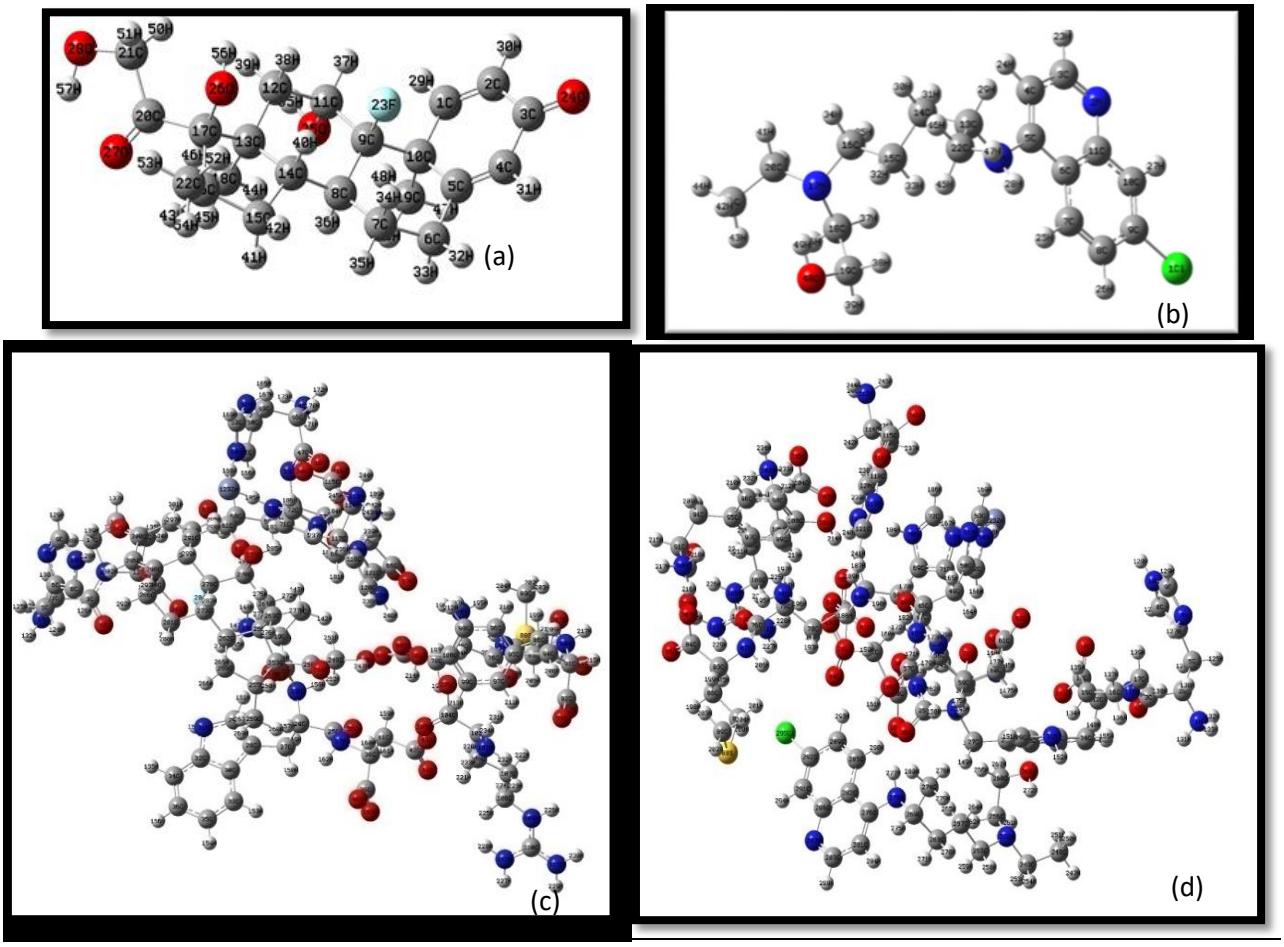


Fig - 4: Optimised structure of the drug and the interaction of Drug with covid-19 residue (a) Dexamethasone drug (b) Hydroxychloroquine (c) Dexamethasone drug interaction with 6LZG residue of virus (d) Hydroxychloroquine interaction with 6LZG residue of virus

Energies were calculated for protein residue of coronavirus with both drugs at different orientations as shown below

[Table 1].

Table 1: Depicts energy of various Hydroxychloroquine and Dexamethasone at different orientations

Table 1: PDB 6LZG of Covid-19 amino acid Residues interaction with (a) Hydroxychloroquine and (b) Dexamethasone.				
	(a)		**(b)**	
	Interacted residue in B chain and its Bond Length (Å)	**Energy (a.u.)**	**Interacted residue and its Bond Length(Å)**	**Energy(a.u.)**
1	His 374 (2.0302)	-9845.3922231	Asp 350 (1.13)	-9774.1703897

	Met 383 (1.94)		Trp 349 (2.35) Arg 393 (1.7)	
2	His 345 (2.44) Pro 346 (2.99) Trp (349)	-9845.43051711	Pro 346 (2.50) His 345 (2.12) Glu 375 (2.30)	-9774.4603535
3	His 401 (2.28) His 345 (2.56) Pro 346 (2.72)	-9845.4689241	Pro 346 (1.75) His 345 (2.2) Trp 349 (1.86) Ala 348 (2.26)	-9774.1358331
4	More Than 3	-9845.5721607	Pro 346 (1.96) His 345 (2.7) Trp 349 (1.86) Ala 348 (2.4)	-9774.5064833
5	His 378 (1.55) Glu 375 (2.37) Met 383 (2.3) Asp 382 (1.47)	-9845.5206218	Zn 704 (2.92) Pro 346 (1.54)	-9774.3949529
6	His 378 (2.11) Glu 375 (2.4) His 374 (2.59)	-9845.5025844	Zn 704 (1.699) Pro 346 (1.98) Trp 349 (1.18) His 378 (1.94) Glu 375 (1.98) His 374 (2.99)	-9773.9908217
7	Meth 383 (2.11) Trp 349 (2.39) Ala 348 (2.41) Asp 350 (2.9)	-9845.3979834	Trp 349 (3.0) Ala348 (2.9) Glu375 (2.48) Met 383 (2.11)	-9774.5639407

4. CONCLUSIONS

In our research study, we are able to anticipate two compelling results in the field of amino acids and their interaction. In first result, we are successfully able to demonstrate homochirality and heterochirality of amino acids using the quantum chemical model. As the outcome, it was observed that L-L amino acid systems are most favourable and stable because of more negative free energy than that of L-D systems.

Studies on drugs to be used for COVID-19 treatment are still an unsolved quest. SARS-CoV-2 uses the angiotensin-converting enzyme (ACE2) receptor to enter the human body. This receptor also has peptidase domain for amino acid interaction so in the second study, we have explored interaction of peptidase domain of this receptor with different drugs

moiety (Hydroxychloroquine and Dexamethasone). It is evidently seen that amino acid residues having bond distance <3 Å reflects significant interaction with drug molecule that helps us to predict the binding capacity of the particular drug (Table 1). The more the binding capacity of amino acid residue leads to inhibition of the action of the novel corona virus, thus potential to be used as antidote.

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