Comparative Docking analysis of rational drugs against COVID-19 Main Protease

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Abstract:-

COVID-19, a new strain of coronavirus (CoV), was identified in Wuhan, China, in 2019. No specific therapies are available, and investigations regarding COVID-19 treatment are lacking. Crystallised COVID-19 main protease (Mpro), which is a potential drug target. The present study aimed to assess drugs found in literature as potential COVID-19 Mpro inhibitors, using a molecular docking study. Molecular docking was performed using Autodock 4.2, with the Lamarckian Genetic Algorithm, to analyse the probability of docking. The docking was cross-validated using Swiss Dock. COVID-19 Mpro was docked with several compounds, and docking was analysed by Biovia Discovery Studio 2020. Quinine and hydroxychloroquine were used as standards for comparison. The binding energies obtained from the docking of 6LU7, 2GTB with screened drugs viz., Quinine, Artesunate, Clotrimazol, Artemether, Quercetin, Mefloquine, ciprofloxacin, clindamycin, cipargamin, SJ-733 were in between -7.0 to -9.6 kcal/mol. On consideration of similar binding energy obtained from Autodock vina and SWISSDock and interaction residue pattern specifically (GLU 166,CYS 145, CYS44 and MET 49 residue) for SJ-733 & JPC-3210 may represent potential treatment options, and appeared to have the best potential to act as COVID-19 Mpro inhibitors. However, further research is necessary to investigate their potential medicinal use against CoV.

Keywords: Drugs, Docking, Protease, Corona Virus, Autodock

Introduction:-

Coronaviruses (CoVs) are an etiologic agent of severe infections in both humans and animals, which may cause disorder not only within the respiratory tract but also within the alimentary canal and systemically. Previous studies of CoVs have reported that CoVs can infect certain species of animals, including mammals, avian species, and reptiles. Consistent with the present situational report from WHO, released on April 7, 2020, 12,79,722 COVID-19 cases are confirmed globally, China, the number of confirmed cases reached 83,071, including 66 new cases, and 3340 deaths. Outside of China, 395 cases were confirmed in 150 countries, (1). Currently, no specific therapies for COVID-19 are available, and investigations regarding the treatment of COVID-19 are lacking(2). The current line of treatment includes antimalarial drug (3). However, the measures that are implemented

remain limited to preventive and supportive therapies designed to stop further complications and organ damage (2). Researchers have successfully crystallised the most protease (Mpro)/chymotrypsin-like protease (3CLpro) from COVID-19, which has been structured and repositioned within the Protein Data Bank (PDB) and is accessible by the general public. This protease represents a possible target for the inhibition of CoV replication (4). The drugs were selected from drug bank on the basis of the literature survey. The findings of this study will provide other researchers with opportunities to spot the proper drug to combat COVID-19.

Methods

Macromolecules/ Proteins:

The 3-dimensional (3D) structures were obtained from PubChem and Drugbank (https://pubchem.ncbi.nlm.nih.gov/), in .sdf format. PubChem is a chemical substance and biological activities repository consisting of three databases, including substance, compound, and bioassay databases (5).

COVID-19 3clpro/Mpro (PDB ID: 6LU7) and 3clpro/Mpro (PDB ID: 2GTB) (4) structures were obtained from PDB (https://www.rcsb.org/), in .pdb format. PDB is an archive for the crystal structures of biological macromolecules, worldwide . The 6LU7 protein contains two chains, A and B, which form a homodimer. Chain A was used for macromolecule preparation. The native ligand for 6LU7 is n-[(5-methylisoxazol-3yl)carbonyl]alanyl-l-valyl-n~1~-((1r,2z)-4-(benzyloxy)-4-oxo-1-{[(3r)-2-oxopyrrolidin-3yl]methyl}but-2-enyl)-l-leucinamide whearas of 2GTB is aza-peptide epoxide.

Drug likeness

Drug-like properties were calculated using Lipinski's rule of five(6), which proposes that molecules with poor permeation and oral absorption have molecular weights > 500, C logP > 5, more than 5 hydrogen-bond donors, and more than 10 acceptor groups (7,8) Adherence with Lipinski's rule of five as calculated using SWISSADME prediction (http://www.swissadme.ch/).

Active Site identification

The amino acids in the active site of a protein were determined using meta pocket (https://projects.biotec.tu-dresden.de/metapocket/) accessed on 6th April,2020 and Biovia Discovery studio client 2020 (*Dassault Systèmes BIOVIA, Discovery Studio Modeling Environment, Release 2017, San Diego: Dassault Systèmes, 2016*).

Molecular docking

Ligand optimisation was performed by marvin sketch and saved in .mol2 format. Autodock version 4.2 used for protein optimisation, by removing water and other atoms, and then adding a polar hydrogen group. Autodock 4.2 was supported by Autodock tools, MGL tools, and Rasmol. Autogrid then determined the native ligand position on the binding site by arranging the grid coordinates (X, Y, and Z). Ligand tethering of the protein was performed by regulating the genetic algorithm (GA) parameters, using 10 runs of the GA criteria(9,10).

The drugs which shows better non covalent interaction and binding energy as compared to standard drugs, quinine and hydroxychloroquine were selected further for cross validation on swiss dock work bench accessed on 8th April,2020 (11). The docking analyses was performed by Biovia Discovery studio client 2020(*Dassault Systèmes BIOVIA, Discovery Studio Modeling Environment, Release 2017, San Diego: Dassault Systèmes, 2016*).

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Results :

The Lipinski filter data is added as supplementary material.

Table 1: Binding energy and amino acid interaction table between compounds and 6LU7

Sr. No.	Drug Name	Chemical formula	Autodock (KJ/mol)	Interaction	Swiss Dock (KJ/mol)	Interaction
1	SJ-733	$C_{24}H_{16}F_4N_4O_2$	-8.7	1] Electrostatic Interaction: GLU166, MET165,ASP187, CYS145, HIS164 2]Van der waals interaction:NIL	-8.4	1] Electrostatic Interaction:GLU166, MET49, ASN142 2]Van der waals interaction: PHE140
2	Tafenoquine	$C_{24}H_{28}F_3N_3O_3$	-8.3	1] Electrostatic Interaction: THR190, GLN192 2]Van der waals interaction: PRO168,LEY141, ARG188	-9.0	1] Electrostatic Interaction: HIS164, ASN142, THR26, MET165 2]Van der waals interaction: LEu141,
3	Cipargamin	$C_{19}H_{14}Cl_2FN_3O$	-8.2	1] Electrostatic Interaction:HIS41, HIS164, CYS145, THR190 2]Van der waals interaction: PRO168, MET165	-7.8	1] Electrostatic Interaction:GLY143, LEU141, SER144, CYS145, MET165 2]Van der waals interaction:HIS172
4	Clotrimazol	$C_{22}H_{17}ClN_2$	-8.2	1] Electrostatic Interaction:NIL 2]Van der waals interaction:ARG188, HIS41, CYS145,MET165	-7.6	1] Electrostatic Interaction:MET165,ASN142, GLY143 2]Van der waals interaction:MET49,CYS145, LEU141
5	Mefloquine	$C_{17}H_{16}F_6N_2O$	-8.1	1] Electrostatic Interaction: HIS41, TYR54, CYS145, HIS164, MET49 2]Van der waals interaction: NIL	-9.3	1] Electrostatic Interaction: ASP187, ARG188, MET49, MET165, GLU166, ASN142(bumps) 2]Van der waals interaction: LEU141(Bumps)
6	Artesunate	$C_{19}H_{28}O_8$	-7.9	1] Electrostatic Interaction:	-8.6	1] Electrostatic Interaction: PHE140, GLY143 2]Van der

				GLU166, THR26 2]Van der waals interaction: HIS41, MET49, MET165		waals interaction: LEU27
7	Artemether	$C_{16}H_{26}O_5$	-7.7	1] Electrostatic Interaction:ASP187, HIS41, CYS145 2]Van der waals interaction: MET165,	-7.8	1] Electrostatic Interaction: LEU141, CYS145 2]Van der waals interaction: MET49, MET165
8	JPC-3210	$C_{21}H_{26}F_4N_2O$	-7.6	1] Electrostatic Interaction: GLU166,CYS145, THR26,THR24, GLY143 2]Van der waals interaction: MET49,MET165, HIS41, THR25	-8.6	1] Electrostatic Interaction:MET49, MET165, HIS41, GLU166, ARG188, ASP187 2]Van der waals interaction: NIL
9	Artenimol	$C_{15}H_{24}O_5$	-7.6	1] Electrostatic Interaction: HIS41 2]Van der waals interaction: MET165	-7.4	1] Electrostatic Interaction:CYS145, GLY143 2]Van der waals interaction:MET165, MET49
10	Quercetin	$C_{15}H_{10}O_7$	-7.6	1] Electrostatic Interaction:THR190, ARG188, GLN192, GLU166, MET165, HIS163, SER144, CYS145, GLY143, LEU141 2]Van der waals interaction:NIL	-7.2	1] Electrostatic Interaction: GLU166, MET165,, MET49, GLY143, CYS145 2]Van der waals interaction:ASN142
11	Ciprofloxacin	$C_{17}H_{18}FN_3O_3$	-7.5	1] Electrostatic Interaction:GLY143, SER144, CYS145, GLU166, THR190, 2]Van der waals interaction:ARG188, HIS41, MET49	-9.6	1] Electrostatic Interaction: ARG188, ASP187, MET49, GLN189, MET165, GLU166, CYS145, PHE140, LEU141(Bumps) 2]Van der waals interaction:NIL
12	Artemisinin	$C_{15}H_{22}O_5$	-7.5	1] Electrostatic Interaction: HIS41 (bumps_ H bonds), GLN189 2]Van der waals interaction:MET165	-7.3	1] Electrostatic Interaction: MET49, GLY143, MET165, CYS145, 2]Van der waals interaction: LEU27
13	Clindamycin	$C_{18}H_{33}ClN_2O_5S$	-7.4	1] Electrostatic Interaction: GLY143, CYS145, GLU166, THR190,MET165 2]Van der waals interaction:HIS41, MET49,PRO168	-8.7	1] Electrostatic Interaction:THR24,MET49, THR26, LEU27, GLY143, 2]Van der waals interaction:HIS164
14	Quinine	$C_{20}H_{24}N_2O_2$	-7.3	1] Electrostatic Interaction: SER144, CYS145, GLU166, HIS41 2]Van der waals interaction: HIS163	-8.3	1] Electrostatic Interaction: GLU166, GLN189, ASN142(red) 2]Van der waals interaction:MET49

Table 2: Binding energy and amino acid interaction table between compounds and 2GTB

Sr. No.	Drug Name	Chemical formula	Autodock (KJ/mol)	Interaction	Swiss Dock (KJ/mol)	Interaction
1	SJ-733	$C_{24}H_{16}F_4N_4O_2$	-8.3	1] Electrostatic Interaction:GLU166 , THR190, ASN142 2]Van der Waals Interaction:MET165 , LEU167, ALA191,PRO168	-8.9	1] Electrostatic Interaction:HIS41, MET49, GLU166 2]Van der Waals Interaction:CYS145, ASP187
2	Tafenoquin e	$C_{24}H_{28}F_3N_3O_3$	-7.3	1] Electrostatic Interaction:GLN192	-9.0	1] Electrostatic Interaction:CYS145,

				, HIS163, GLU166 2]Van der Waals Interaction:LEU141, PRO168, MET165		ASN142, THR26 2]Van der Waals Interaction: MET49
3	Cipargamin	$C_{19}H_{14}Cl_2FN_3O$	-7.0	1] Electrostatic Interaction: GLN192, 2]Van der Waals Interaction:MET165, LEU167, PRO168	-7.8	1] Electrostatic Interaction: HIS41, MET165, ASN142, MET49, GLY143 2]Van der Waals Interaction:LEU141,
4	Clotrimazol	$C_{22}H_{17}ClN_2$	-7.2	1] Electrostatic Interaction: NIL 2]Van der Waals Interaction: GLN189, GLU166, LEU167, PRO168, MET165	-7.6	1] Electrostatic Interaction: GLY143 CYS145 2]Van der Waals Interaction:MET49,HIS164
5	Mefloquine	$C_{17}H_{16}F_6N_2O$	-6.3	1] Electrostatic Interaction: LEU167, GLU166 2]Van der Waals Interaction: MET165, PRO168,	-8.0	1] Electrostatic Interaction:MET49, HIS41,HIS164, MET165 2]Van der Waals Interaction: NIL
6	Artesunate	$C_{19}H_{28}O_8$	-7.7	1] Electrostatic Interaction:GLY143, GLU166, PRO168, MET165 2]Van der Waals Interaction: NIL	-8.1	1] Electrostatic Interaction: GLU166, ASP187, MET165 2]Van der Waals Interaction: CYS145
7	Artemether	$C_{16}H_{26}O_5$	-7.3	1] Electrostatic Interaction: GLU166 2]Van der Waals Interaction: CYS145, MET49, HIS41	-7.6	1] Electrostatic Interaction: MET165, GLU166 2]Van der Waals Interaction: CYS145
8	JPC-3210	$C_{21}H_{26}F_4N_2O$	-7.6	1] Electrostatic Interaction:HIS163, GLU166, CYS145, PHE140, LEU141 2]Van der Waals Interaction:MET49, HIS41, CYS44	-8.3	1] Electrostatic Interaction:CYS44, HIS41, ASP187, MET49, MET165, GLU166, ARG188 2]Van der Waals Interaction: NIL
9	Artenimol	$C_{15}H_{24}O_5$	-7.6	1] Electrostatic Interaction: GLU166, MET165 2]Van der Waals Interaction: HIS41,CYS145,	-7.5	1] Electrostatic Interaction: MET49, GLU166 2]Van der Waals Interaction:CYS145
10	Quercetin	$C_{15}H_{10}O_7$	-7.6	1] Electrostatic Interaction:GLU166 ,HIS163, SER144, LEU141, ASN142, HIS41, CYS44, THR25 2]Van der Waals Interaction: MET49	-7.9	1] Electrostatic Interaction: GLY143, CYS145, MET49, MET165, GLU166, PHE140, LEU141, ASN142 2]Van der Waals Interaction: NIL
11	Ciprofloxacin	$C_{17}H_{18}FN_3O_3$	-6.3	1] Electrostatic Interaction: HIS41,TYR54, THR25 2]Van der Waals Interaction:MET49, CYS145	-8.1	1] Electrostatic Interaction:CYS145, GLY143,ASP187 2]Van der Waals Interaction:MET165
12	Artemisinin	$C_{15}H_{22}O_5$	-7.8	1] Electrostatic Interaction:GLU166, MET165 2]Van der Waals Interaction:CYS145 HIS41	-7.6	1] Electrostatic Interaction:MET49, GLu166 2]Van der Waals Interaction:CYS145
13	Clindamycin	$C_{18}H_{33}ClN_2O_5S$	-7.8	1] Electrostatic Interaction:SER144, HIS163, THR190, PRO168, LEU167, GLU166 2]Van der Waals	-9.0	1] Electrostatic Interaction: MET165 2]Van der Waals Interaction:MET49, CYS145

				Interaction:HIS172, MET165,		
14	Quinine	$C_{20}H_{24}N_2O_2$	-6.9	1] Electrostatic interaction: THR190, MET165, GLU166 2]Van der waals interaction: PHE185, PRO168, HIS164	-8.5	1]Electrostatic interaction: GLU166 , ASN142, PHE1402]Van der waals interaction:MET165, CYS145

The visualization of the various non covalent interactions between compounds and active site residues of 6LU7 (Fig 1a to fig 14b).

*H-Bonds are depicted by Green, Electrostatic is dark yellow, Hydrophobic are represented by pink shades, Halogen interaction by Cyan

6lu7 interaction with Quinine

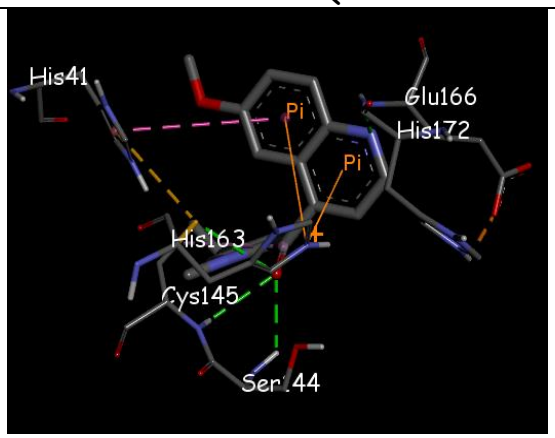

Figure 1 a : Autodock Vina Output

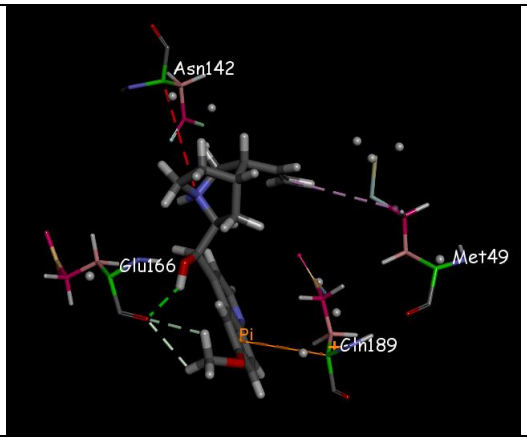

Figure 1 b: SwissDock Output

6lu7 interaction with Artesunate

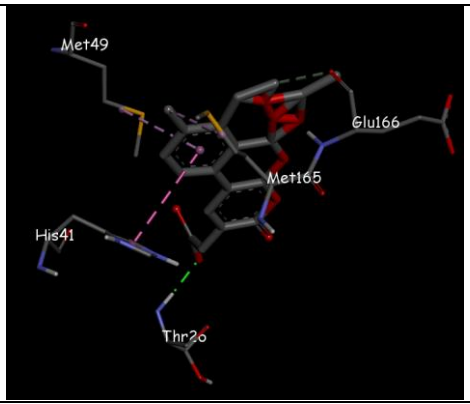

Figure 2a :AutoDock Vina Output

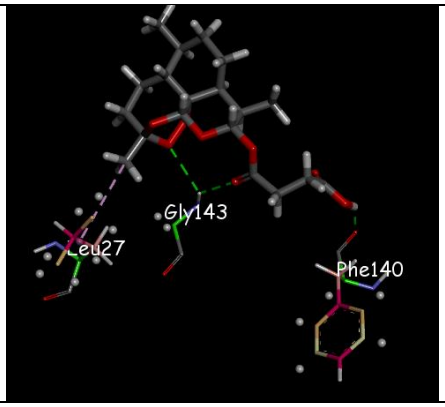

Figure 2b: SwissDock Output

6lu7 interaction with Clotrimazol

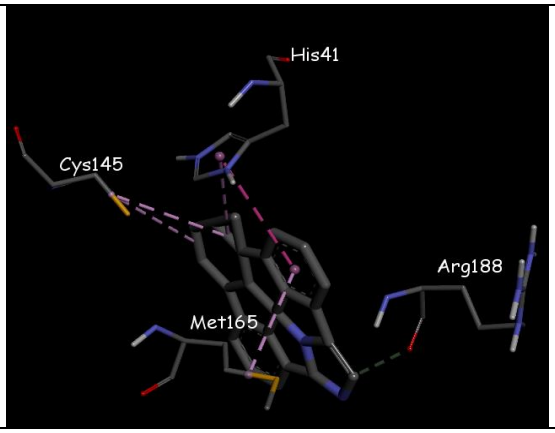

Figure 3a:AutoDock Vina Output

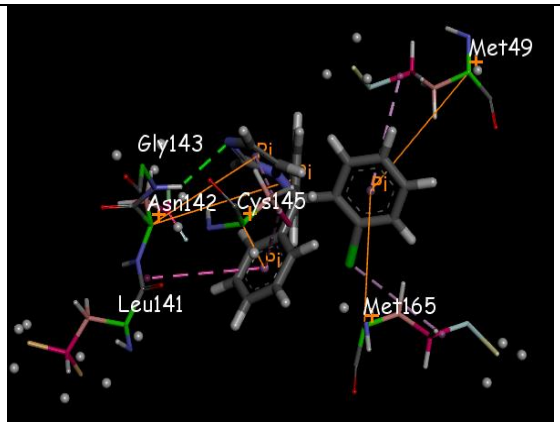

Figure 3b: SwissDock Output

6lu7 interaction with Artemether

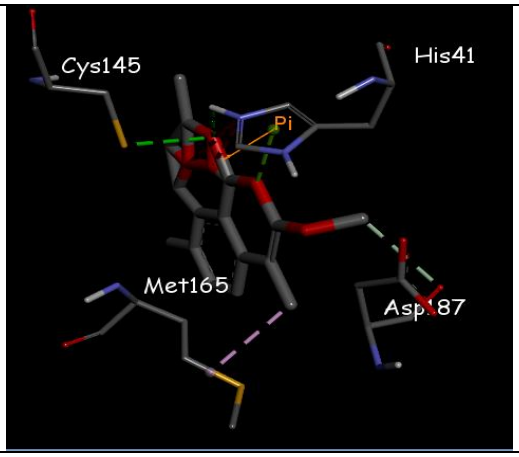

Figure 4a:AutoDock Vina Output

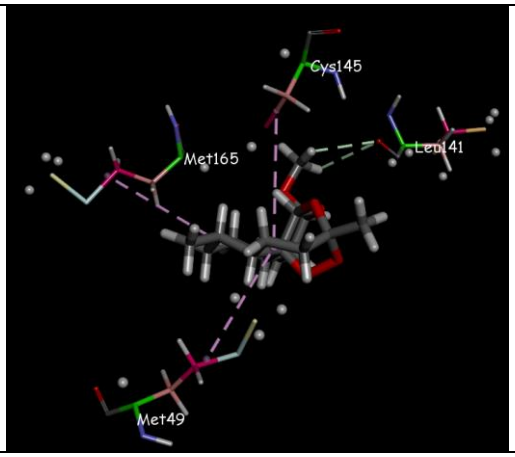

Figure 4b: SwissDock Output

6lu7 interaction with Quercetin

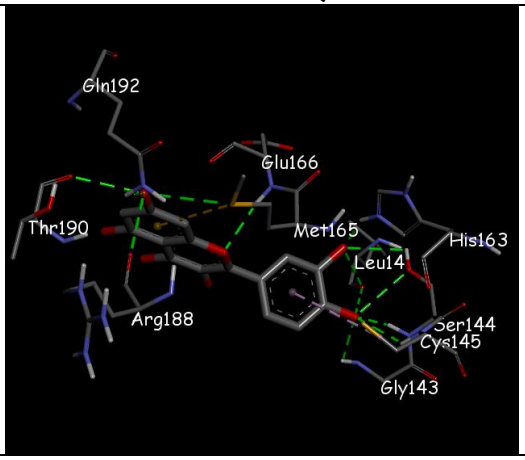

Figure 5a :AutoDock Vina Output

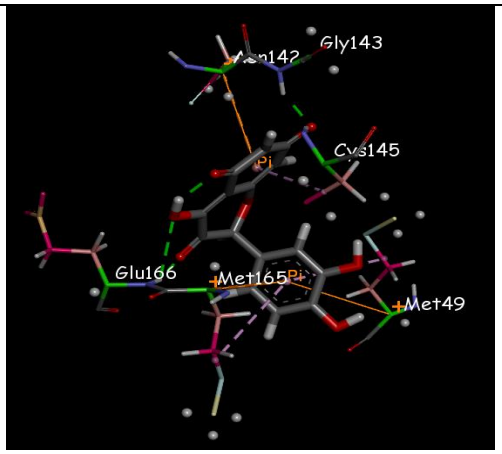

Figure 5b: SwissDock Output

6lu7 interaction with Mefloquine	
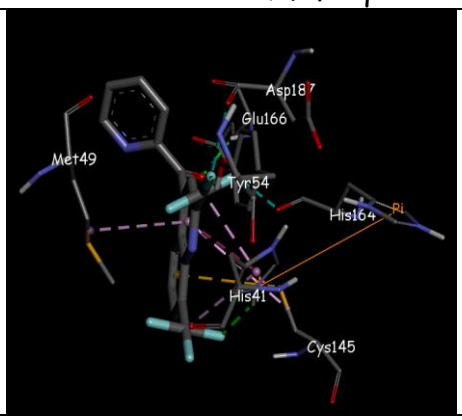	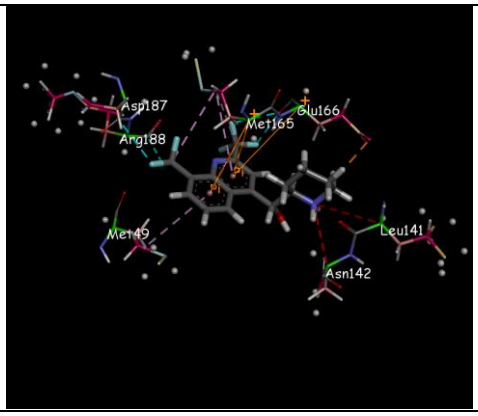
Figure 6a:AutoDock Vina Output	Figure 6b: SwissDock Output

6lu7 interaction with Ciprofloxacin	
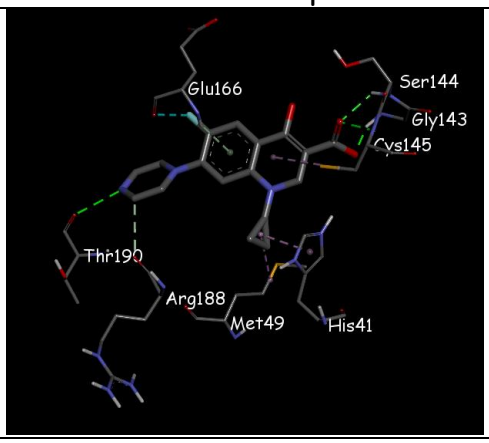	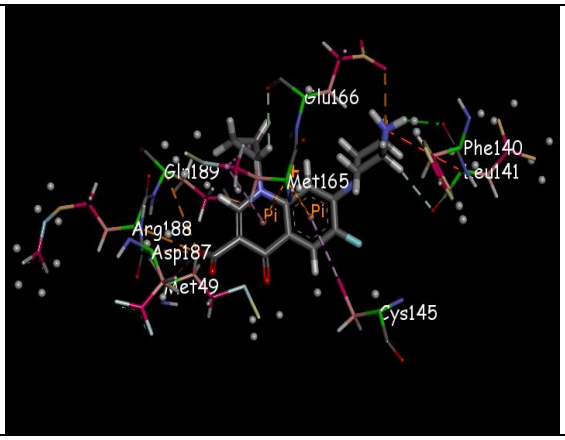
Figure 7a: :AutoDock Vina Output	Figure 7b: SwissDock Output

6lu7 interaction with Clindamycin

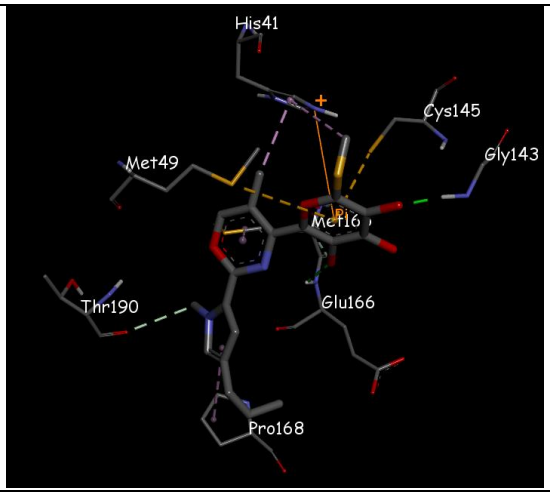	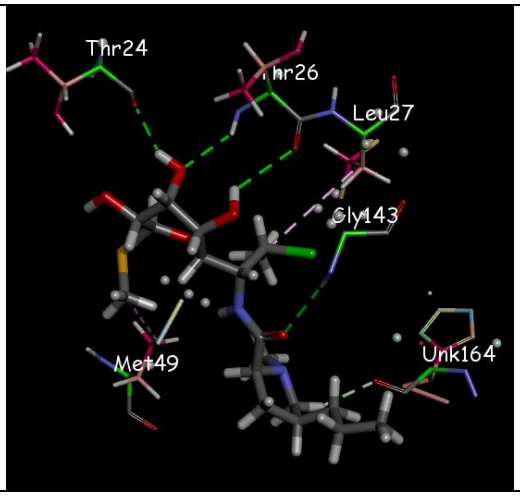
Figure 8a:AutoDock Vina Output	Figure 8b: SwissDock Output

6lu7 interaction with Cipargamin	
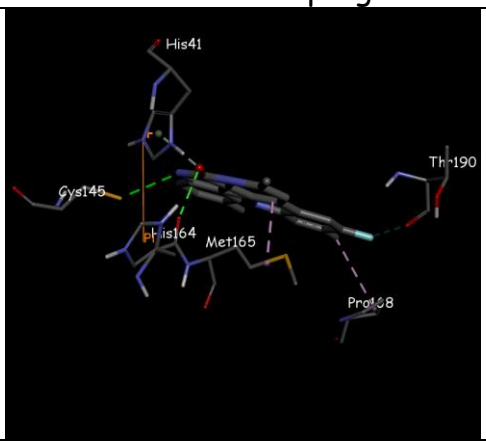	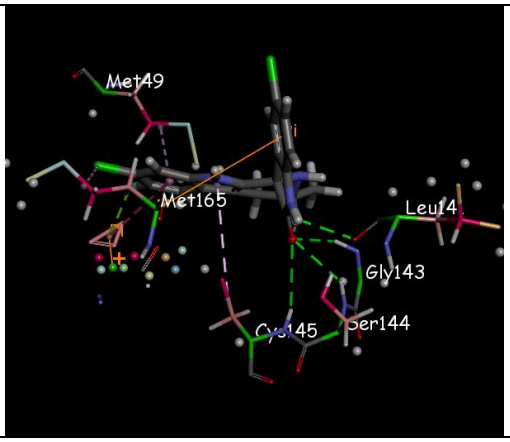
Figure 9a:AutoDock Vina Output	Figure 9b: SwissDock Output

6lu7 interaction with SJ-733	
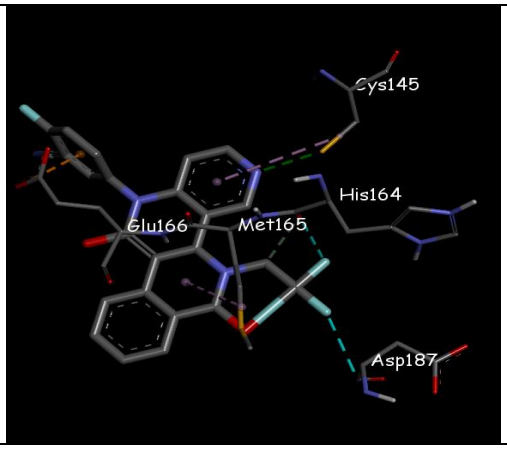	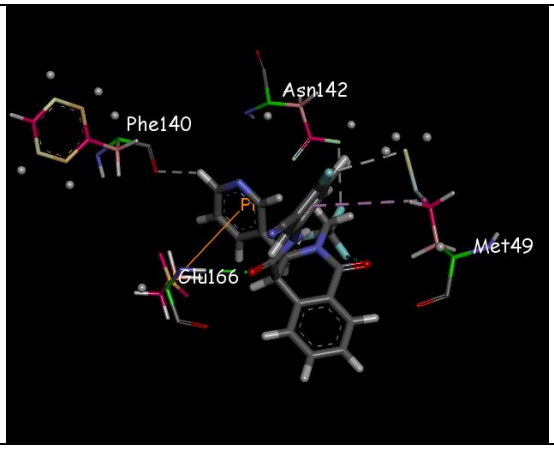
Figure 10a:AutoDock Vina Output	Figure 10b: SwissDock Output

6lu7 interaction with Tafenoquine

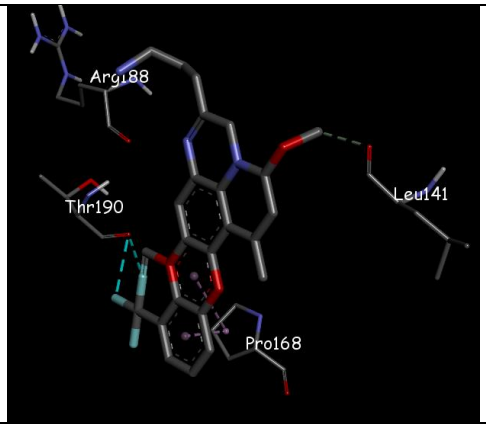	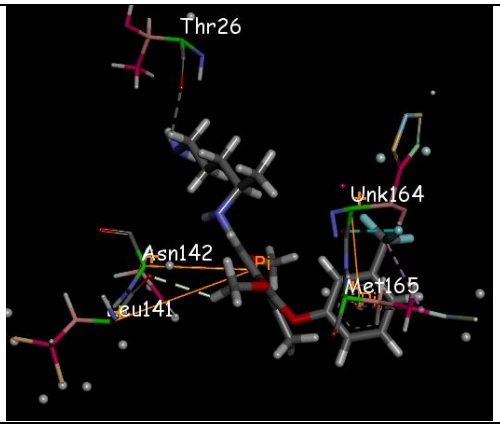
Figure 11a:AutoDock Vina Output	Figure 11b: SwissDock Output

6lu7 interaction with Artenimol	
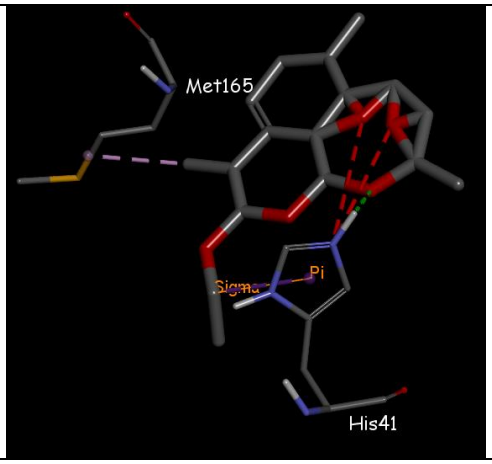	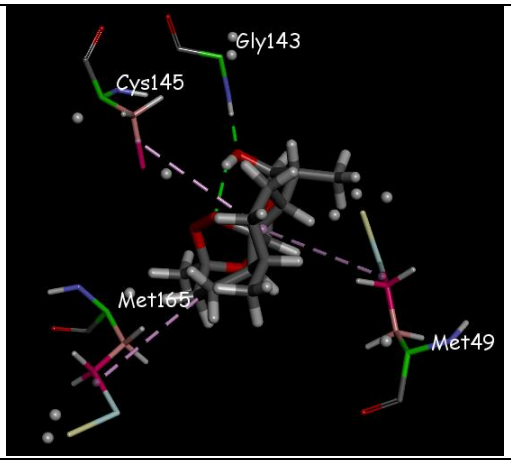
Figure 12a:AutoDock Vina Output	Figure 12b: SwissDock Output

6lu7 interaction with JPC-3210	
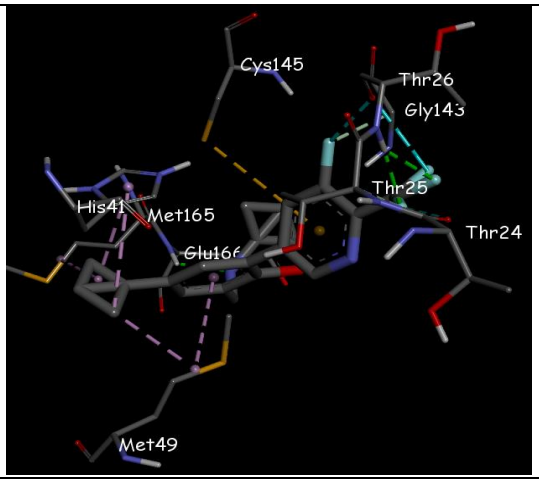	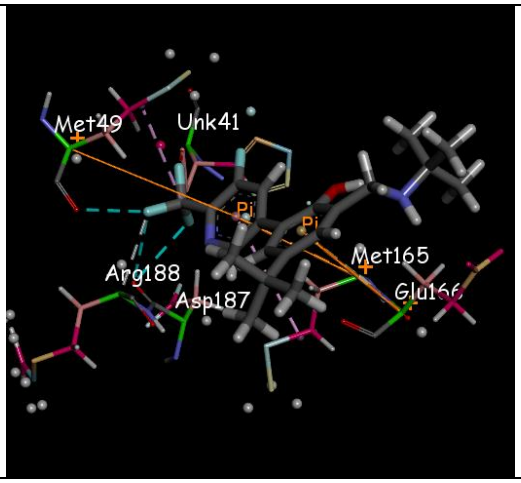
Figure 13a:AutoDock Vina Output	Figure 13b: SwissDock Output

6lu7 interaction with Artemisinin

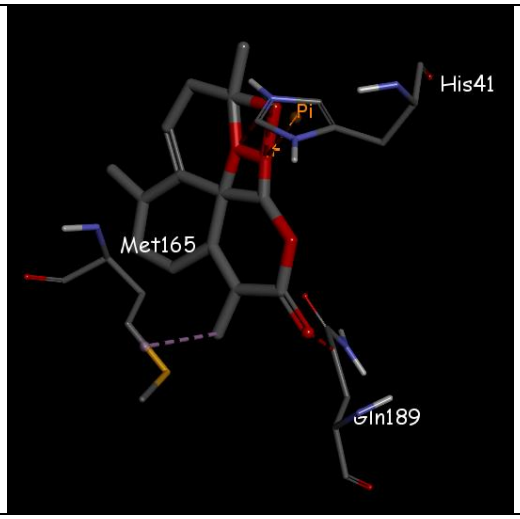	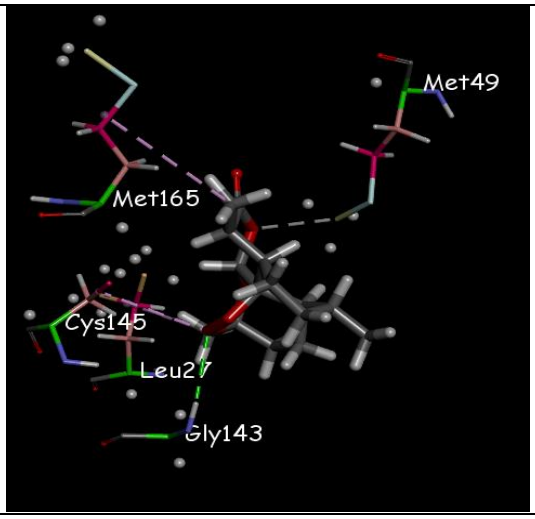
Figure 14a:AutoDock Vina Output	Figure 14b: SwissDock Output

The visualization of the various non covalent interactions between compounds and active site residues of 2GTB (Fig 15a to fig 28b).

2GTB interaction with Quinine	
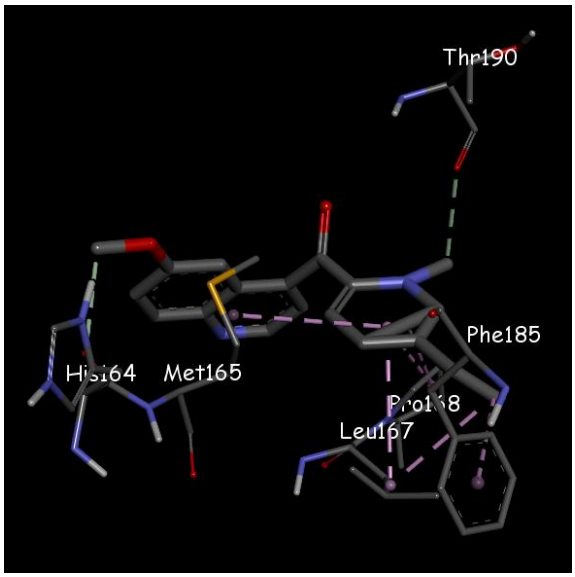	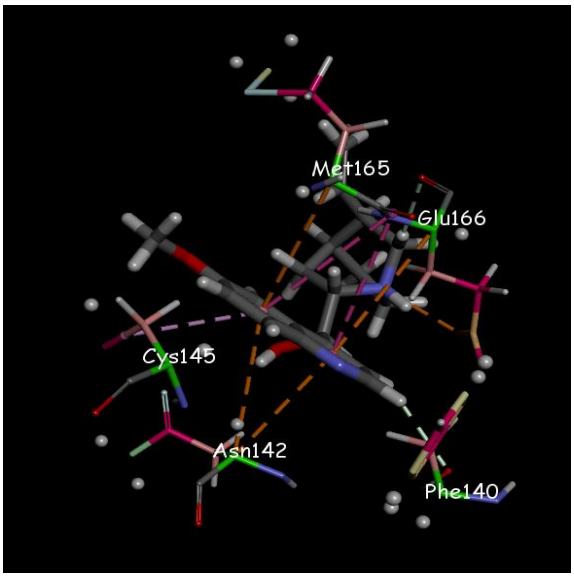
Figure 15a:AutoDock Vina Output	Figure 15b: SwissDock Output

2GTB interaction with Artesunate

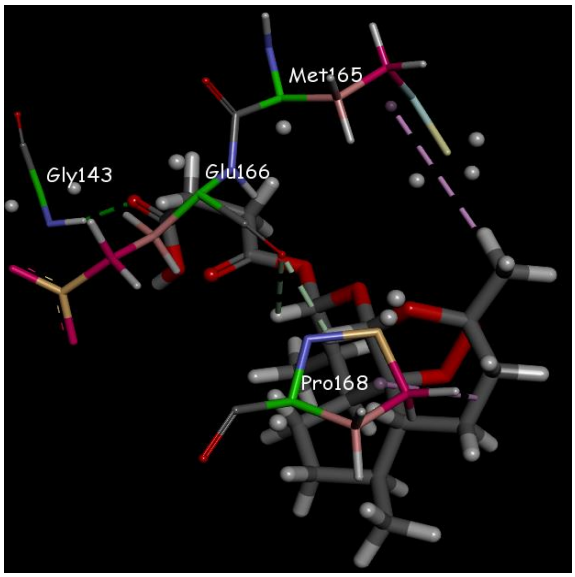	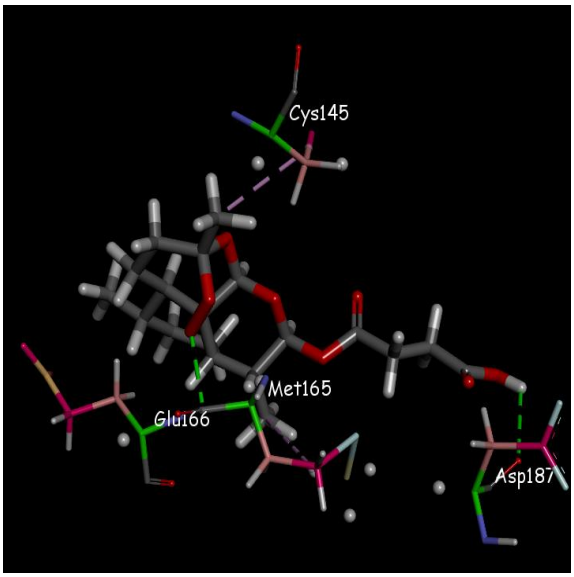
Figure 16a:AutoDock Vina Output	Figure 16b: SwissDock Output

2GTB interaction with Clotrimazol	
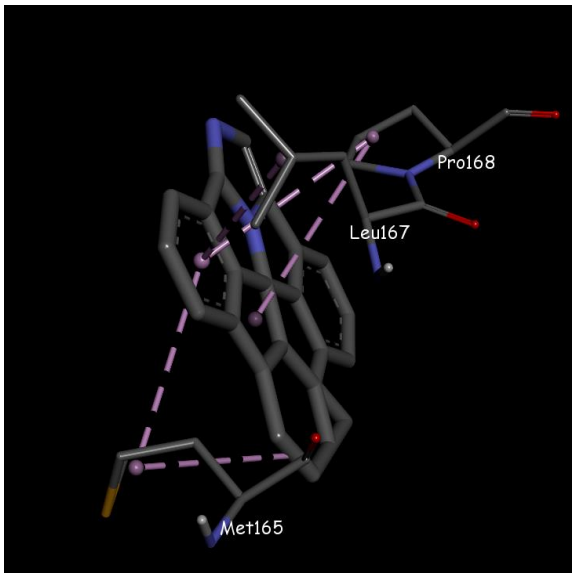	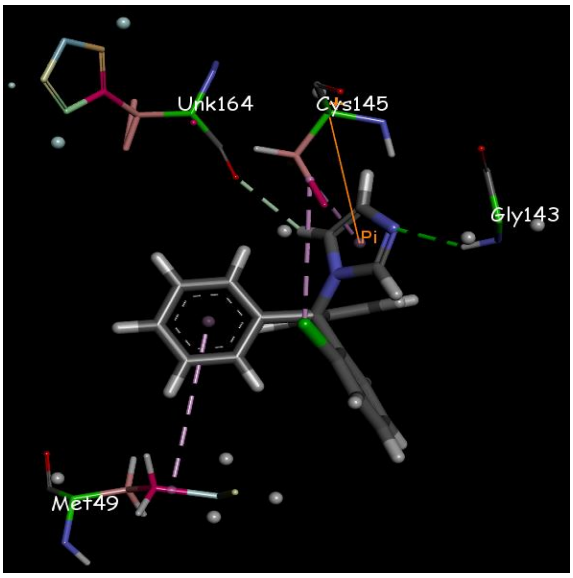
Figure 17a:AutoDock Vina Output	Figure 17b: SwissDock Output

2GTB interaction with Artemether

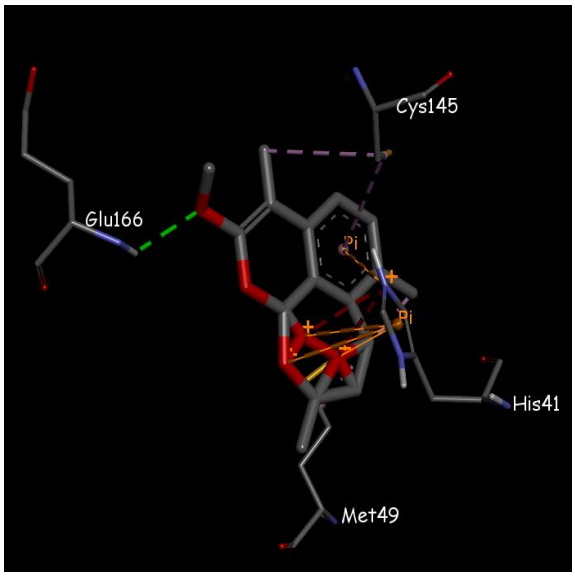	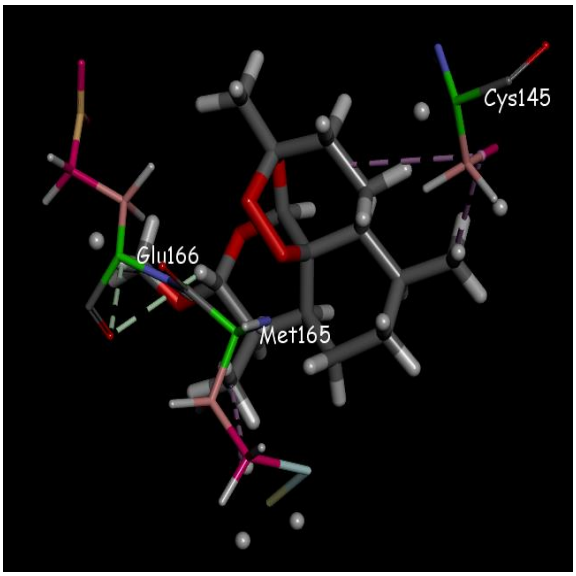
Figure 18a:AutoDock Vina Output	Figure 18b: SwissDock Output

2GTB interaction with Quercetin	
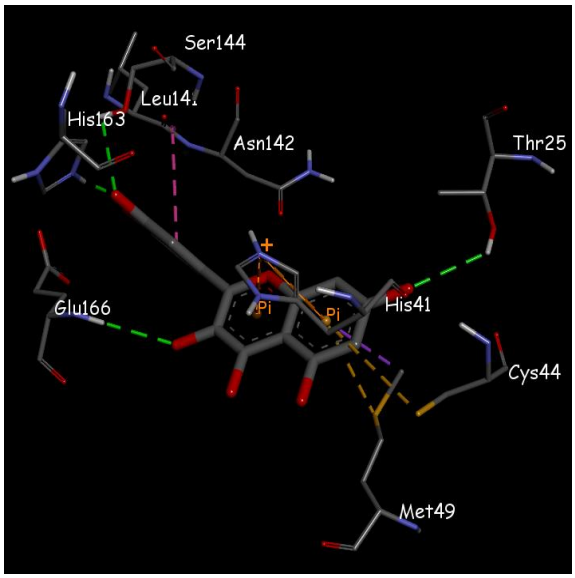	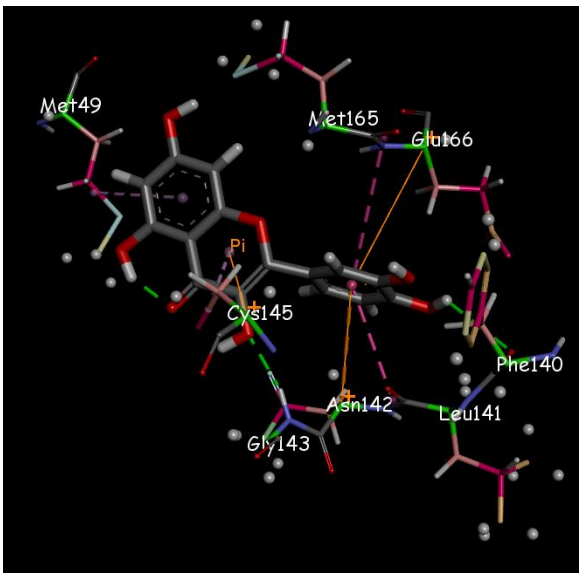
Figure 19a:AutoDock Vina Output	Figure 19b: SwissDock Output

2GTB interaction with Mefloquine

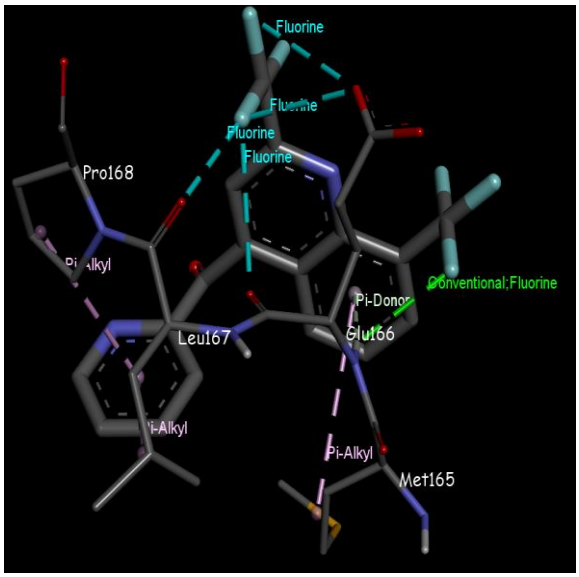	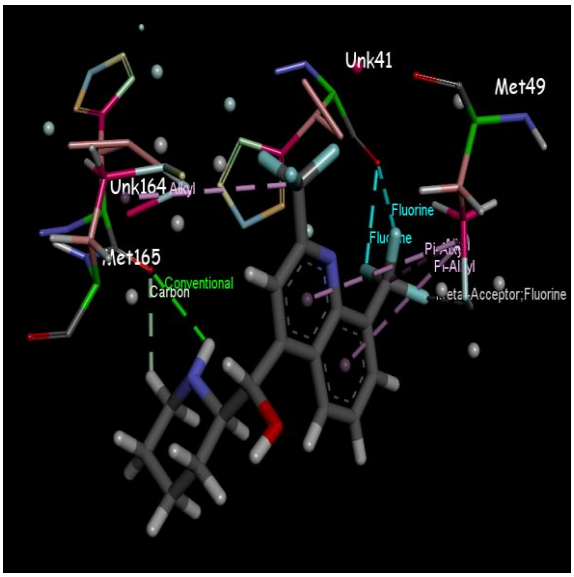
Figure 20a:AutoDock Vina Output	Figure 20b: SwissDock Output

2GTB interaction with Ciprofloxacin	
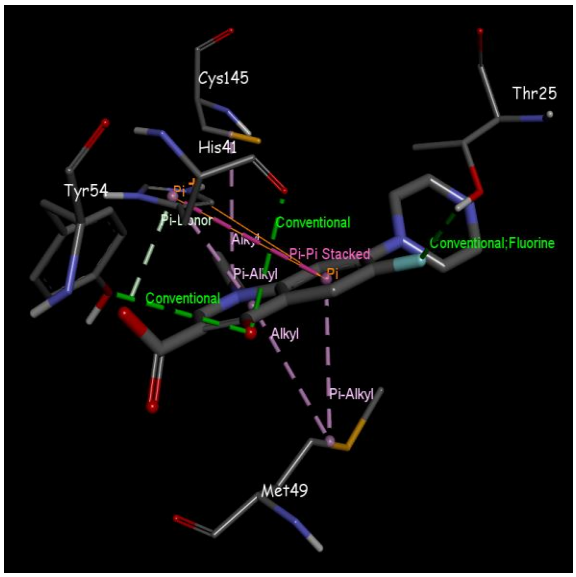	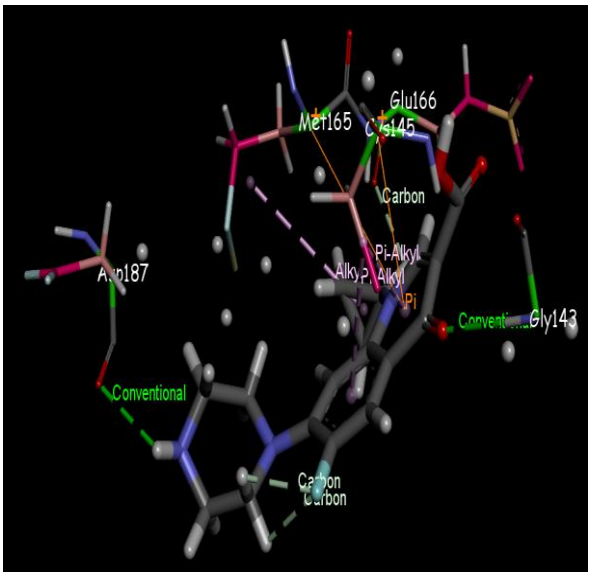
Figure 21 a:AutoDock Vina Output	Figure 21b: SwissDock Output

2GTB interaction with Clindamycin

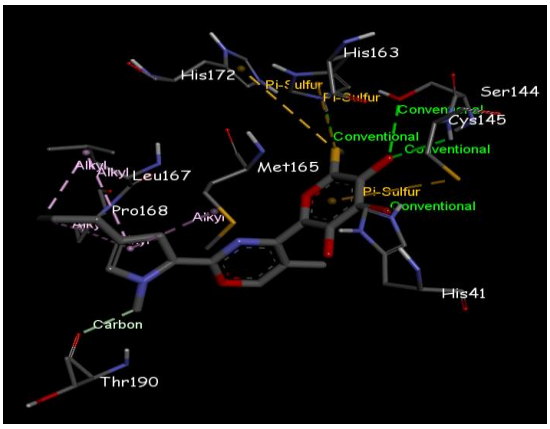	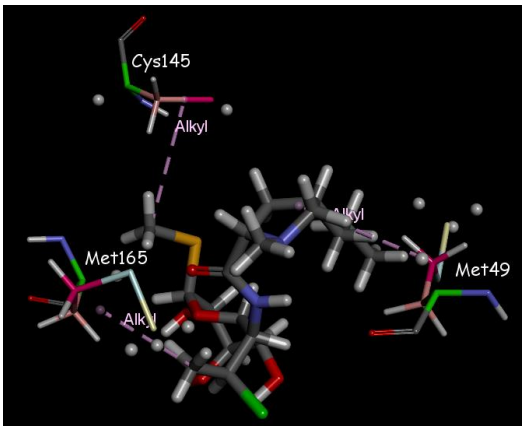
Figure 22a:AutoDock Vina Output	Figure 22b: SwissDock Output

2GTB interaction with Cipargamin	
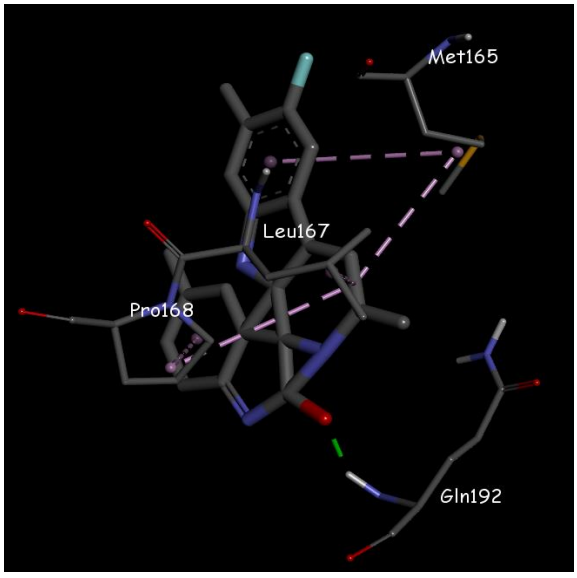	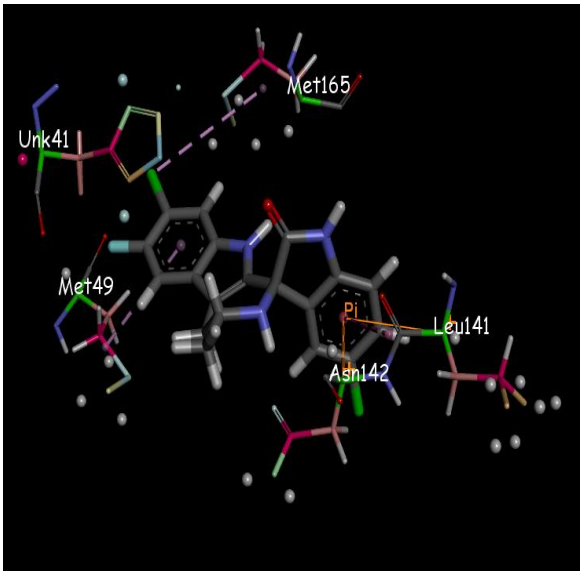
Figure 23a:AutoDock Vina Output	Figure 23b: SwissDock Output

2GTB interaction with SJ-733

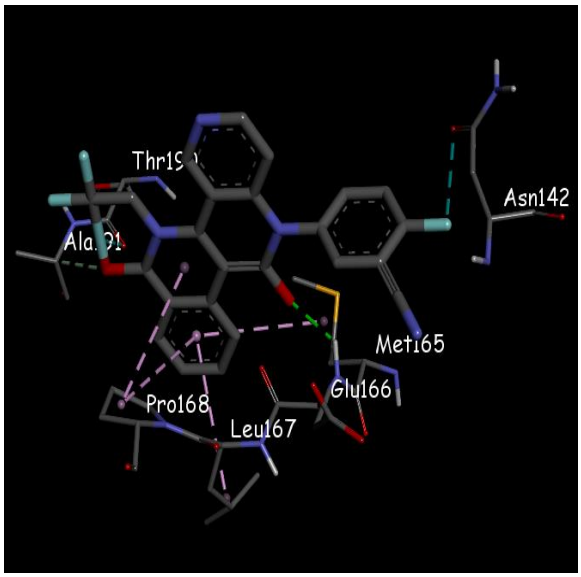	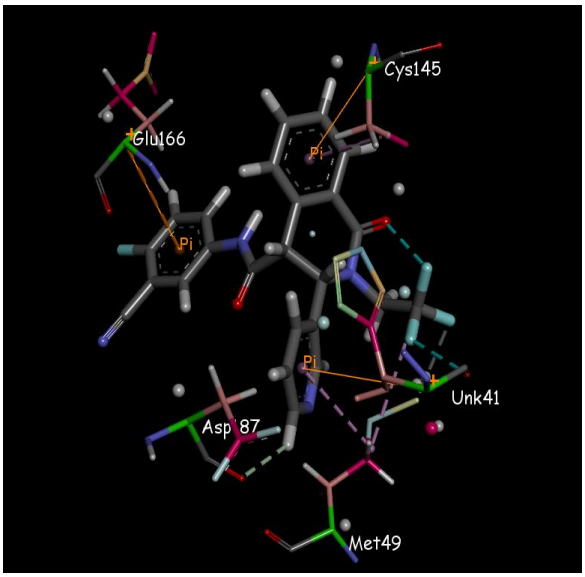
Figure 24a:AutoDock Vina Output	Figure 25b: SwissDock Output

2GTB interaction with Tafenoquine	
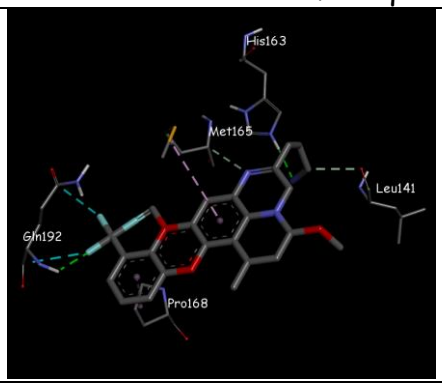	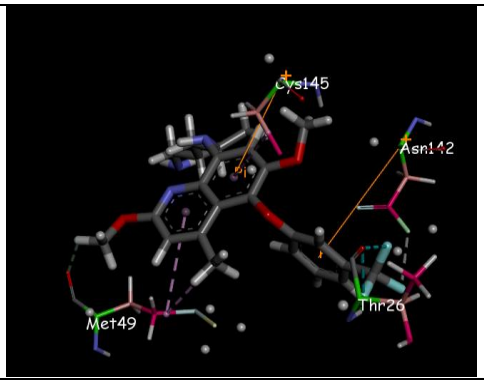
Figure 25a:AutoDock Vina Output	Figure 25b: SwissDock Output

2GTB interaction with Artenimol

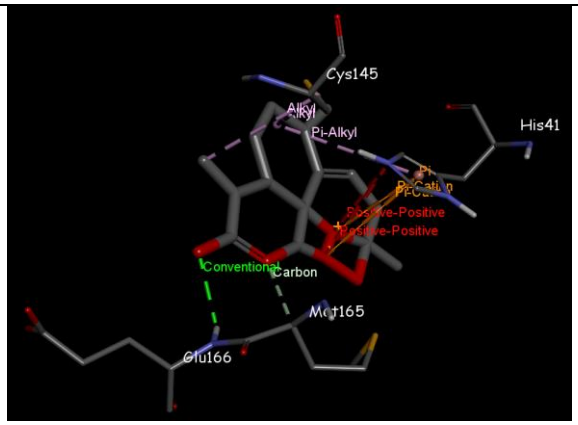	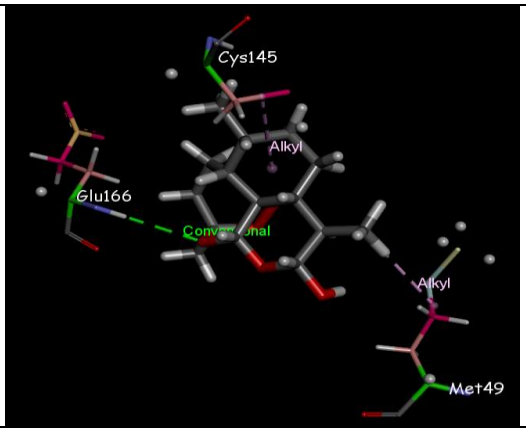
Figure 26a:AutoDock VinaOutput	Figure 26b: SwissDock Output

2GTB interaction with JPC-3210	
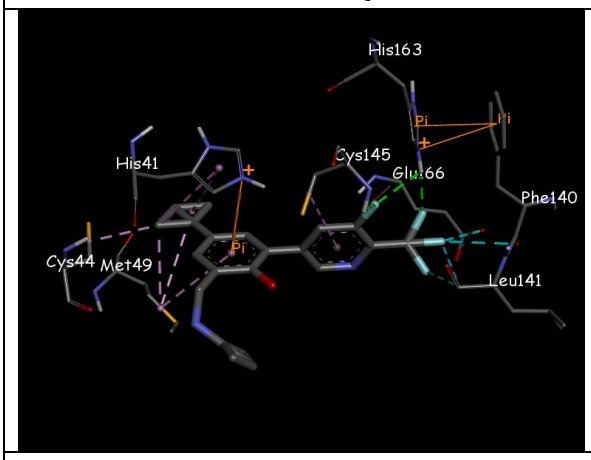	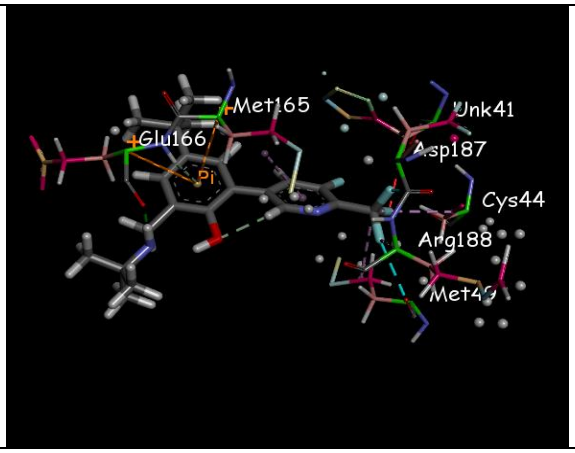
Figure 27a:AutoDock Vina Output	Figure 27b: SwissDock Output

2GTB interaction with Artemisinin	
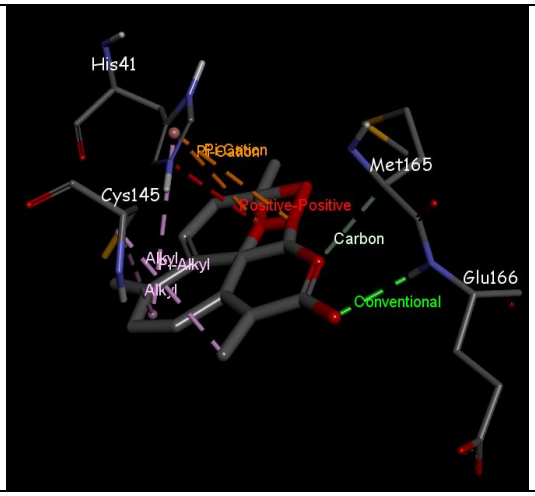	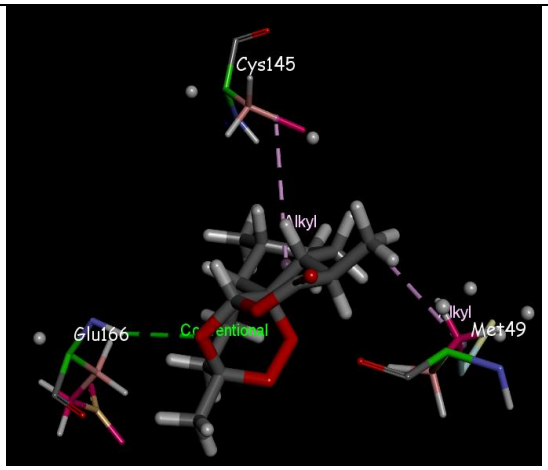
Figure 28a: Autodock Vina Output	Figure 28b: SwissDock Output

Discussion:

CoV infections affect the respiratory, digestive, liver, and central nervous systems of humans and animals (12). this study focused on the most proteases in CoVs (3CLpro/Mpro), especially PDB ID 6LU7, and 2GTB as potential target proteins for COVID-19 treatment 6LU7 is that the Mpro in COVID-19 . that has been structured and repositioned in PDB and has been accessible by the general public since early February 2020. The Mpro of 2019-nCov shares 96% similarity with the Mpro of the SARS-CoV (13),(14). The Mpro in CoV is important for the proteolytic maturation of the virus and has been examined as a possible target protein to stop the spread of infection by inhibiting the cleavage of the viral polyprotein(15). The invention of the Mpro protease structure in COVID-19 provides an excellent opportunity to spot potential drug candidates for treatment. Proteases represent potential targets for the inhibition of CoV replication, and therefore the refore the protein sequences of the SARS-CoV Mpro and the 2019-nCoV Mpro are 96% identical, and therefore the active sites in both proteins remain free from mutations. The Mpro amino acids GLU166, CYS 44, CYS145, SER 144 and MET49 are predicted to play roles in drug interactions (16). The disruption of protease activity can cause various diseases; thus, commonly, host proteases are often used as potential therapeutic targets. In many viruses, proteases play essential roles in viral replication; therefore, proteases are often used as protein targets during the event of antiviral therapeutics (17).

Conclusion:

In summary, basing on the structural information of clinical effective medicines for 2019-nCoV, we have predicted a list of commercial medicines which may function as inhibitors for 2019-nCoV by targeting its main protease Mpro. Compared to Quinine and hydroxycloroquinine, most of these predicted drugs could form more hydrogen bounds with 2019-nCoV Mpro, . The binding pockets of these drugs on Mpro are conserved between SARS-CoV Mpro and 2019-nCoV Mpro, indicating the potential of these drugs to function as inhibitors for other coronaviruses with similar Mpro binding sites and pocket structures.

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