Drug repurposing for COVID-19 using computational screening: Is Fostamatinib/ R406 a potential candidate? : Supplementary Document

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Basic Terminologies

1. **Protein-Protein Interaction Network (PPIN):** When one protein interacts with another protein, it forms a network-like structure known as PPIN. Generally, it is portrayed as a graph where proteins are represented as nodes, and their corresponding connecting edges represent their interactions. Mathematically, PPIN can be highlighted as a graph G_{nv}, which consists of vertices v (nodes) connected by edges e (links). Thus, $G_{nv} = (v, e)$ [1].

2. **Level-1 and Level-2 proteins:** In a PPIN, level-1 proteins of a node are those proteins that are in direct connection with that node, i.e., its immediate neighbors, whereas level-2 proteins are those proteins that are indirectly connected with level-1 proteins of that node, i.e., its indirect neighbors [1].

3. **Spreader nodes and spreader edges:** The viral infection gets mediated from one part of the PPIN to another through spreader nodes and edges [2]. Generally, in disease-specific PPIN models, at least two entities are involved: pathogen/Bait and host/Prey [3]. In this research work, SARS-CoV takes the role of the former while human the latter one. Viral proteins of SARS-CoV tend to target their corresponding interaction with human proteins, which target its next level of proteins. So, the establishment of interactions between SARS-CoV and human occurs through connected nodes and edges of PPIN. But mostly, these viral proteins try to interact more with the central/hub proteins rather than the other proteins [2]. Thus, proper identification of central nodes (i.e., spreader nodes) is required. It is also confirmed that the interaction is not possible without the edges connecting two spreader nodes. Thus, these connecting edges are called spreader edges.

4. **Spreadability index:** The spreadability index of node i [4] is defined as the ability of node i to mediate a viral infection in a PPIN. Three important network terminologies are involved in the spreadability index. They are 1) Edge ratio [5] 2) Neighborhood diversity [5] 3) Node Weight [6]. Mathematically it can be defined as:

   $$Spreadability\_index\ (i)\ = (Edge\ ratio\ (i)\ \times neighborhood\_diversity\ (i)\ ) + Node\ weight\ (w_i)$$

   Nodes having a high spreadability index are termed as spreader nodes, i.e., if the viral proteins establish interactions with these nodes, then the viral infection can be mediated to a more significant number of nodes in a much short amount of time compared to the other nodes in PPIN.

5. **MolDock Score:** MolDock is considered to be a new heuristic search algorithm. It combines differential evolution with a cavity prediction algorithm. The docking scoring function of MolDock is an extension of the piecewise linear potential (PLP). It includes new hydrogen bonding and electrostatic terms. As a result, MolDock has a very high docking accuracy for the identification of ligand-binding modes [7].

6. **ReRank Score:** The re-rank score is a linear combination of E-inter (steric, Van der Waals, hydrogen bonding, electrostatic) between the protein and the ligand and E-intra. (torsion, sp2-sp2, hydrogen bonding, Van der Waals, electrostatic) of the ligand weighted by pre-defined coefficients. The re-ranking procedure is adequate for identifying high-quality binding modes in place of more advanced scoring schemes [7].

Significance of choosing loss of smell as a major Covid-19 symptom

Several health symptoms like cough, fever, breathing difficulty, *loss of smell* etc., are studied in the proposed research work as highlighted in section 2.3 in the main manuscript. However, *"loss of smell"* is given higher preference in comparison to the other symptoms due to the following reason: 1) According to a correspondence published on April 15, 2020, in *The Lancet Infectious Diseases* [8], it was highlighted by the authors that though the reason of losing smell by COVID-19 patients was not discovered yet, their initial inspection suggests that loss of smell "*manifests either early in the disease process or in patients with mild or no constitutional symptoms.*" 2) Another correspondence published on June 04, 2020, in *The Lancet* [9], stated that "*after quantifying the sensitivity, specificity, positive predicted value, and negative predicted value of fever, cough, fever or cough, and loss of smell in 76 260 users of the COVID Symptom Study app who underwent the SARS-CoV-2 test (13 863 testing positive; 62 397 testing negative), they found that the predictive ability of loss of smell and taste to be higher than fever or persistent cough, which is in line with their previous finding that loss of smell and taste was the strongest predictor of having the virus* [10]*. Moreover, they found that the median duration of anosmia symptoms was 5 days, whereas the median duration of fever was only 2 days.*"

Table S1. List of significant research articles involving potential recommended drugs for COVID-19

SL. No.	Journal/Article name	Involved drugs	Report type	Drug Categorization	Results/Outcome
1	The Use of Anti-Inflammatory Drugs in the Treatment of People With Severe Coronavirus Disease 2019 (COVID-19): The Perspectives of Clinical Immunologists From China [11]	Glucocorticoids IL-6 antagonist JAK inhibitors Chloroquine (CQ)/ Hydroxychloroquine (HCQ)	Clinical	Anti-malarial Anti-inflammatory	Confirmation of the short-term efficacy of HCQ in the treatment of COVID-19
2	Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial [12]	HCQ Azithromycin	Clinical	Anti-viral Anti-inflammatory	A combination of the two is effective in the extermination of coronavirus.
3	Lianhuaqingwen exerts anti-viral and anti-inflammatory activity against novel coronavirus (SARS-CoV-2) [13]	Lianhuaqingwen (LH)	Laboratory test	Traditional Chinese Medicine	LH hinders the replication of SARS-COV-2
4	Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. [14]	HCQ	*In vitro* Cytotoxicity and antiviral	Anti-malarial Anti-inflammatory	HCQ can effectively stop the infection of SARS-CoV-2 *in vitro.*
5	Aminoquinolines Against Coronavirus Disease 2019 (COVID-19): Chloroquine or Hydroxychloroquine [15]	HCQ CQ Other medicinal agents	Opinion paper	Anti-malarial Anti-viral	Though both HCQ and CQ are beneficial, HCQ is safer in comparison to CQ
6	Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study [16]	Favipiravir (FPV)	Clinical	Anti-viral	FPV performs a faster clearance of viral infection with a better chance in chest imaging.
7	TH17 responses in cytokine storm of COVID-	Janus kinase 2 (JAK2)	*In vitro* study	Anti-inflammatory	JAK2 inhibitor Fedratinib can prevent the

	19: An emerging target of JAK2 inhibitor Fedratinib [17]	Fedratinib			deteriorating outcomes of TH17 associated cytokine storms in COVID-19.
8	In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) [18]	HCQ CQ	*In vitro* study	Anti-malarial	Inhibits COVID-19.
9	Coronavirus Disease 2019 (COVID-19) Pneumonia in a Hemodialysis Patient [19]	Lopinavir Ritonavir	Case study on Hemodialysis Patient	Anti-viral	Recovery symptoms noted though the combination of the drugs needs more testing.
10	Repurposing of clinically approved drugs for treatment of coronavirus disease 2019 in a 2019-novel coronavirus (2019-nCoV) related coronavirus model. [20]	Cepharanthine Selamectin Mefloquine	Cell culture and pangolin coronavirus modelling	Anti-inflammatory antineoplastic anti-parasitic	Reduction of cytopathic effects in cell culture.
11	Traditional Chinese Medicine for COVID-19 Treatment [21]	Qingfei paidu decoction	Case study	Traditional Chinese Medicine	Control COVID-19.
12	COVID-19: combining antiviral and anti-inflammatory treatments [22]	Baricitinib Fedratinib Ruxolitinib	*In silico*	Anti-inflammatory	Favourable in COVID-19 treatment.
13	The antiviral compound remdesivir potently inhibits RNA-dependent RNA polymerase from Middle East respiratory syndrome coronavirus. [23]	Remdesivir	*In vitro* study	Anti-viral	High effectiveness of remdesivir against RNA viruses in cell-based assays.
14	Virus against virus: a potential treatment for 2019-nCov (SARS-CoV-2) and other RNA viruses. [24]	CRISPR/Cas13d strategy	*In vitro* test	Other treatment/drugs	Capable of RNA virus treatment
15	Therapeutic options for the 2019 novel coronavirus (2019-nCoV) [25]	Remdesivir Umifenovir Oseltamivir ASC09F Other inhibitors	Opinion	Anti-viral	Biocontainment capability against covid-19.
16	Inhibitors of RAS Might Be a Good Choice for the Therapy of COVID-19 Pneumonia [26]	Renin-Angiotensin System (RAS) inhibitors	Opinion	Other treatment/drugs	ACEI and AT1R inhibitors could be used in patients with COVID-19 pneumonia to reduce the pulmonary inflammatory response and mortality.
17	Case of the Index Patient Who Caused Tertiary Transmission of Coronavirus Disease 2019 in Korea: the Application of Lopinavir/Ritonavir for the Treatment of COVID-19 Pneumonia Monitored by Quantitative RT-PCR. [27]	Lopinavir RitonavirA	Clinical	Anti-viral	Combat COVID-19 harmful effect.
18	Therapeutic strategies in an outbreak scenario to treat the novel coronavirus originating in Wuhan, China [28]	Angiotensin-converting enzyme 2	Opinion	Other treatment/drugs	Potentiality of ACE2-Fc to act as the neutralizing antibody which can be used for COVID-19 treatment.

19	Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. [29]	Remdesivir	*In vitro* study	Anti-viral	Drugs proved to be effective with Remdesivir and chloroquine.
		Ribavirin		Anti-malarial	
		Penciclovir			
		Nitazoxanide			
		Nafamostat			
		Remdesivir Favipiravir			
		Chloroquine			
20	Clinical characteristics and therapeutic procedure for four cases with 2019 novel coronavirus pneumonia receiving combined Chinese and Western medicine treatment. [30]	Lopinavir/ Ritonavir	Case study	Anti-viral	Effective treatment was observed.
		Arbidol			
		Shufeng Jiedu		Anti-malarial	
21	First case of 2019 novel coronavirus in the United States. [31]	Remdesivir	Case Study on a single patient	Anti-viral	The patient got recovered.
22	One highly suspected case of novel coronavirus pneumonia treated by Integrated Traditional Chinese and Western medicine and nucleic acid analysis. [32]	Traditional Chinese Medicine	Case Study on a single patient	Traditional Chinese Medicine	The patient got recovered.
23	COVID-19 in patients with HIV: clinical case series [33]	Darunavir	Case Study on a single patient	Anti-viral	Darunavir was proved to be ineffective against COVID-19 due to low affinity.
24	Favipiravir: Pharmacokinetics and Concerns About Clinical Trials for 2019-nCoV Infection [34]	Favipiravir	Opinion	Anti-viral	Recommendation for use in COVID-19. Needs more clinical confirmation.
25	Remdesivir for COVID-19: challenges of underpowered studies [35]	Remdesivir	Case study	Anti-viral	Effective against COVID-19.

Table S2. Few statistical analyses of genes in COVID-19 symptoms, risk factors and clinical outcome

Categorizations	Symptoms	Total no. of genes
COVID-19 symptoms [36]	Cough	270
	Fever	1743
	Dyspnea	323
	Pneumonia	1416
Risk factors [36]	Heart Disease	1964
	Kidney Disease	2131
	Lung Disease	1018
	Diabetes	5078
	Hypertension	1573
	Cancer	4747
Clinical Outcomes (Mild & Moderate Case) [36]	Lymphopenia	241
	Pulmonary infiltrate	43
Clinical Outcomes (Severe Case) [36]	Leukocytosis	179
	Neutrophilia	152
	Sepsis	1506
	Kidney injury	228
	Coagulopathy	21
	Thrombocytopenia	774
	Multiple organ failure	25

Table S3. Mapping of FDA drug of DrugBank with selected key genes of level-1

Level-1 Key Genes	Approved/Approved & Investigational Drug	
	Drug	**Drug ID**
PPIA	Cyclosporine	DB00091
	Copper	DB09130
ACE2	Hydroxychloroquine	DB01611
	Chloroquine	DB00608
EIF3F	No approved drug	
UBC	No approved drug	
PRKDC	Caffeine	DB00201
CDK2	Bosutinib	DB06616
CDK1	*Fostamatinib*	*DB12010*
PRKCA	D-alpha-Tocopherol acetate	DB14002
	Midostaurin	DB06595
	alpha-Tocopherol succinate	DB14001
	Phosphatidyl serine	DB00144
	Vitamin E	DB00163
	Tamoxifen	DB00675
	Ingenol mebutate	DB05013
AKT1	Arsenic trioxide	DB01169
TRAF6	No approved drug	

Table S4. Mapping of FDA drug of DrugBank with selected key genes of level-2

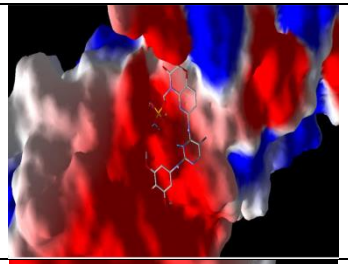
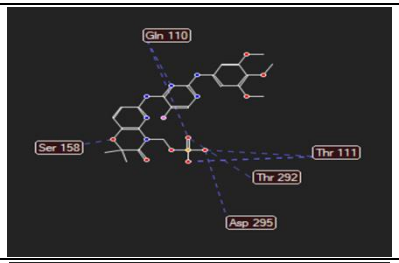
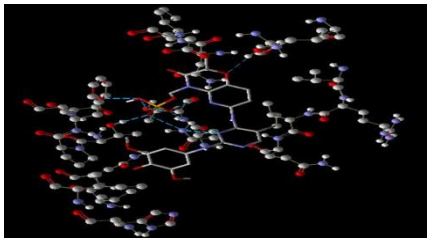
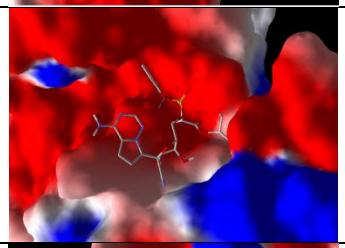
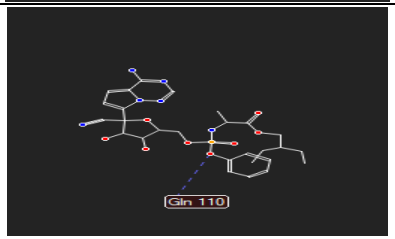
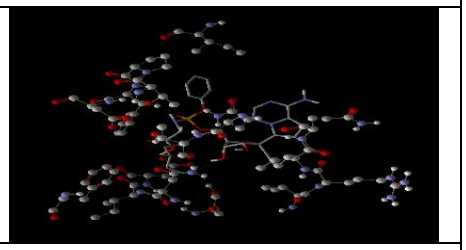
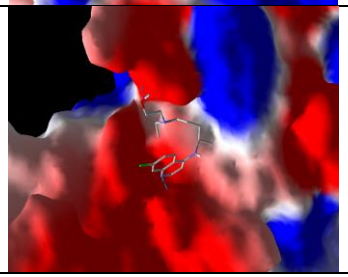
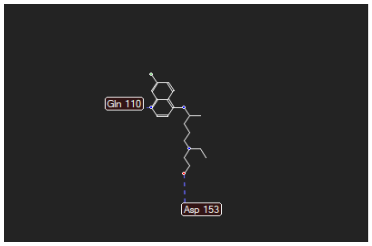
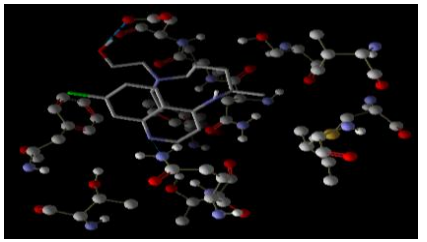
Level-2 Key Genes	Approved/Approved & Investigational Drug	
	Drug	**Drug ID**
APP	Aluminium phosphate	DB14517
	Dimercaprol	DB06782
	Copper	DB09130
	Florbetapir (18F)	DB09149
	Flutemetamol (18F)	DB09151
	Deferoxamine	DB00746
	Zinc	DB01593
	Zinc sulfate, unspecified form	DB14548
	Florbetaben (18F)	DB09148
	Zinc acetate	DB14487
	Aluminum acetate	DB14518
	Aluminium	DB01370
	Zinc chloride	DB14533
ELAVL1	No approved drug	
NTRK1	Entrectinib	DB11986
	Fostamatinib	*DB12010*
	Cenegermin	DB13926
	Amitriptyline	DB00321
	Imatinib	DB00619
	Regorafenib	DB08896
	Larotrectinib	DB14723
XPO1	Selinexor	DB11942
MEOX2	No approved drug	
GRB2	Pegademase	DB00061
EGFR	Lidocaine	DB00281
	Gefitinib	DB00317
	Fostamatinib	*DB12010*
	Zanubrutinib	DB15035
	Cetuximab	DB00002
	Erlotinib	DB00530
	Vandetanib	DB05294
	Osimertinib	DB09330
	Dacomitinib	DB11963
	Brigatinib	DB12267

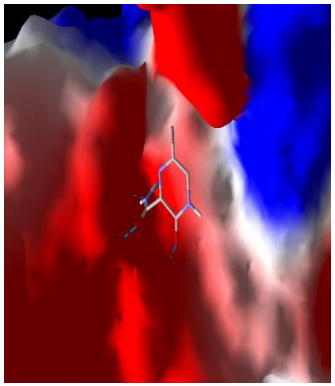
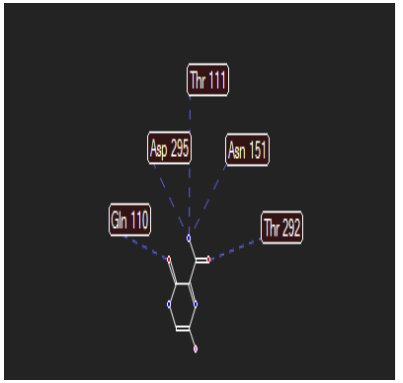
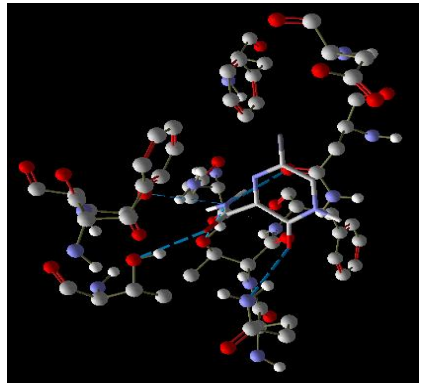
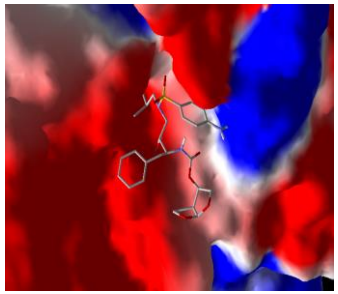
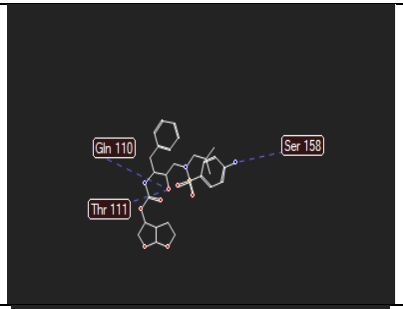
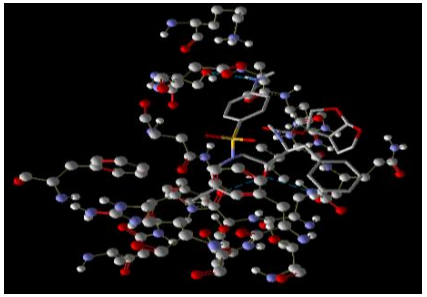
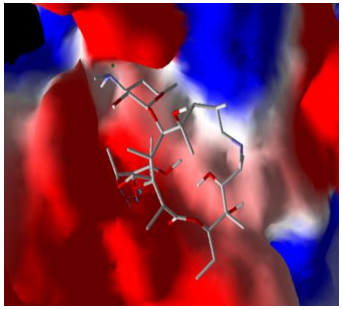
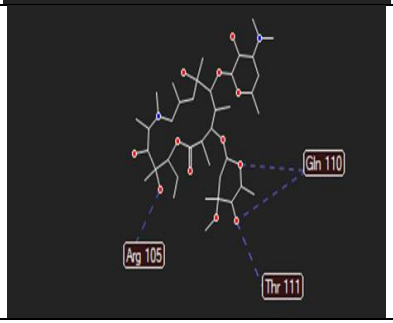
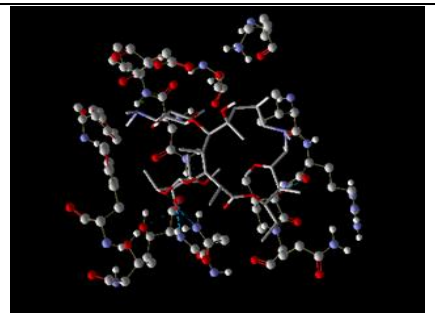
	Foreskin keratinocyte (neonatal)	DB10772
	Trastuzumab	DB00072
	Lapatinib	DB01259
	Panitumumab	DB01269
	Afatinib	DB08916
	Necitumumab	DB09559
	Neratinib	DB11828
TP53	Zinc acetate	DB14487
	Zinc chloride	DB14533
	Acetylsalicylic acid	DB00945
	Zinc	DB01593
	Zinc sulfate, unspecified form	DB14548
BAG3	No approved drug	
NXF1	No approved drug	

Table S5. Mapping of FDA drug of DrugBank with selected key genes of level-2 associated with "*loss of smell*" symptom of COVID19

Genes in L2 n-CoV	**Target drugs**	**DrugId**	**Approved**
DCC 2	N/A	N/A	N/A
EIF4G1	N/A	N/A	N/A
GIGYF2	N/A	N/A	N/A
HTRA2	N/A	N/A	N/A
LRRK2	Fostamatinib	DB12010	**TRUE**
PARK7	Copper	DB09130	**TRUE**
PINK1	N/A	N/A	N/A
PODXL	N/A	N/A	N/A
PTPN11	Dodecyltrimethylammonium	DB02779	FALSE
SNCA	Copper	DB09130	**TRUE**
UCHL1	Phenethyl Isothiocyanate	DB12695	FALSE
VPS35	N/A	N/A	N/A

Table S6. Best dock poses for potential COVID19 drugs and interactions of hydrogen bonds with respect to 6LU7

Drugs	Drug ID	Moldock score	Rerank Score	Best docked poses	H-bond interaction details best pose	H-bond interaction best pose
Fostamatinib	**DB12010**	**-140.495**	**-102.464**			
Remdesivir	DB14761	-134.19	-56.312			
Hydroxychloroquine	DB01611	-106.266	-69.417			

Favipiravir	DB12466	-62.855	-55.371			
Darunavir	DB01264	-128.798	-80.316			
Azithromycin	DB00207	-86.77	29.53			

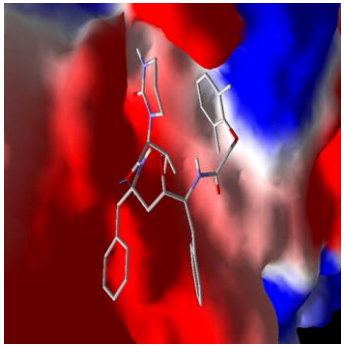
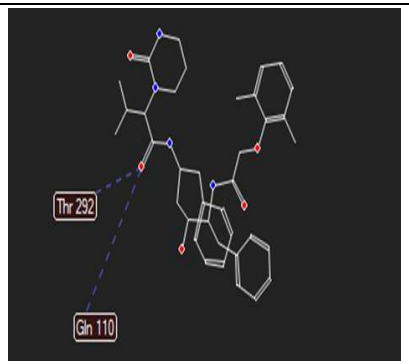
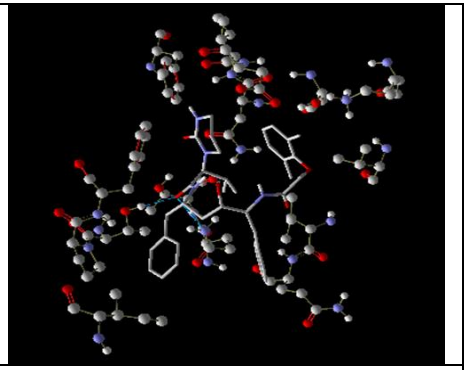
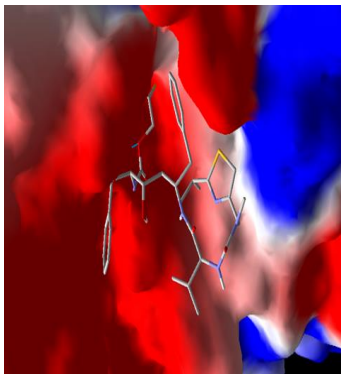
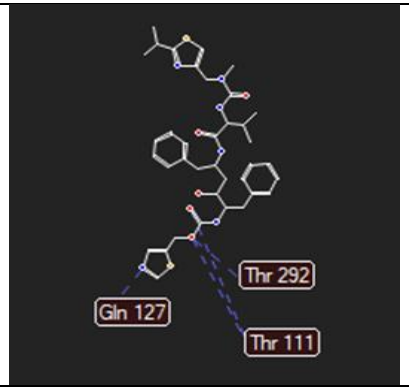
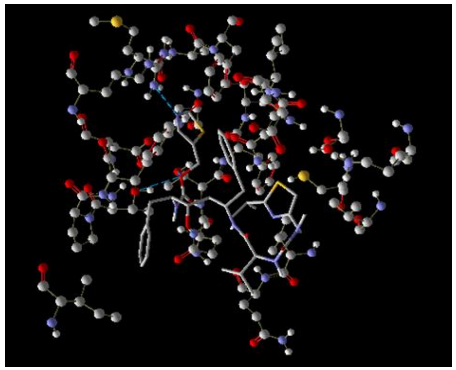
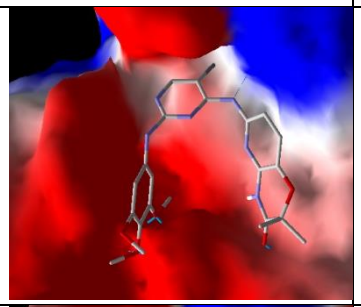
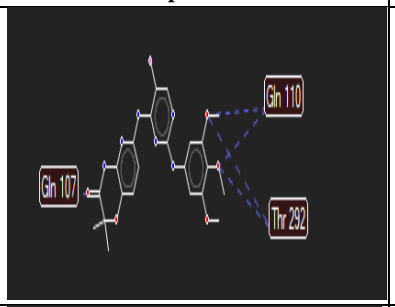
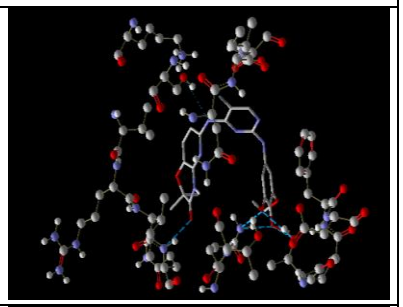
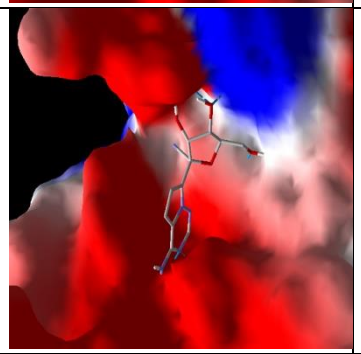
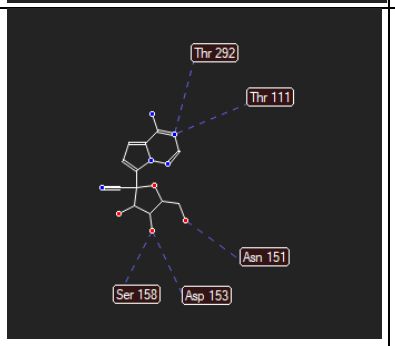
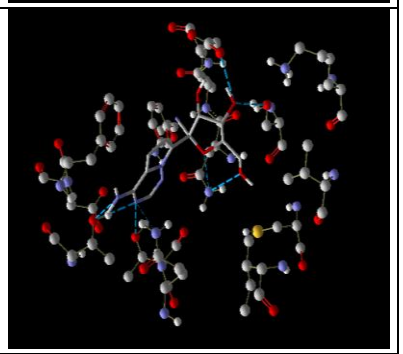
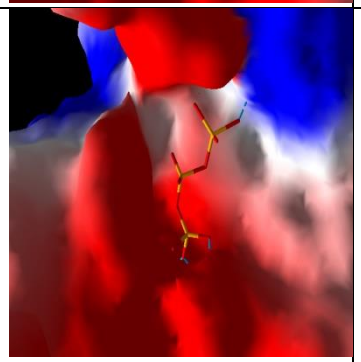
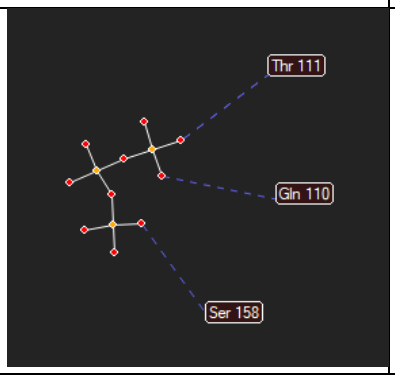
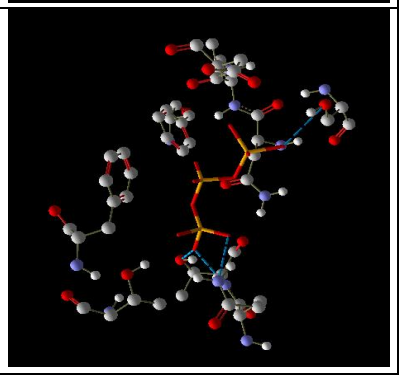
Lopinavir	DB01601	-83.09	-30.19			
Ritonavir	DB00503	-110.36	103.40			

Table S7. Best dock poses for active metabolites/promoieties of potential COVID-19 Prodrugs with respect to 6LU7

Prodrugs	Drug id	Active promoieties	Moldock Score	Rerank Score	Best docked poses	H-bond interaction details best pose	H-bond interaction best pose
Fostamatinib	**DB12010**	**R406 (using 3FQS)** [37, 38]	**-110.11**	**-93.83**			
Remdesivir	DB14761	GS-441524	-93.37	-76.07			
Favipiravir	DB12466	RdRp complex (6K32) [39, 40]	-50.72	-45.20			

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