Structure-Based Screening of Novel Lichen Compounds for SARS *Coronavirus* Main protease (*M^{pro}*) and Angiotensin-Converting Enzyme 2 (ACE2) inhibitory potentials as multi-target inhibitors of COVID-19

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Abstract

Outbreak of SARS-CoV-2 and massing death caused by it all over world has imposed great concern on scientific community to develop potential drugs to combat with Coronaviruas disease 19 (COVID-19). In this regard, lichen metabolites may offer a vast reservoir for discovery of anti-viral drug candidates. Therefore to find novel compounds against COVID-19, we created a library of 412 lichen compounds and subjected to virtual screening against two molecular targets; SARS-CoV-2 target- Main protease (Mpro) and host cell target- Angiotensin-converting enzyme 2 (ACE2). All the ligands were virtually screened, and 80 compounds were found to have better docking score with both the targets. These compounds were assessed for druglikeness analysis where 27 compounds were found to fit well for redocking studies. The results of redocking by X-Score showed that 7 out of 27 compounds were found to have high affinities with Mpro as well ACE2 which reflect that these compounds can function as dual inhibitors. Molecular docking, druglikeness, X-Score and toxicity analysis resulting seven novel lichen compounds (Orcynyllecanorate, Siphulin, Fremontol, Gyrophoric acid, Rhizocarpic acid, Ovoic acid, and Umbilicatic acid) with Mpro and ACE2 multi-target activities and they can be used as hit compounds to develop potential antiviral agents against SARS-CoV-2. These lichen compounds may be a suitable candidate for further experimental analysis.

Introduction

Recently, Novel Coronavirus (SARS-CoV-2) is spreading very rapidly all over the world and causing an ongoing outbreak of COVID-19, a serious and often fatal respiratory tract infection. COVID-19 has created an emergency in India and all around the world. The SARS-CoV-2, previously named as 2019 novel coronavirus (2019-nCoV), is a positive-sense, single-strand RNA coronavirus. According to worldometers report, about 81,285 people in China have been infected with coronavirus and 3,287 deaths since its emergence in the city of Wuhan, Hubei province. The outbreak of coronaavirus is increasing day by day. By now, more than 18,04,128 people have been diagnosed, and more than 1,12,223 deaths have been recorded from worldwide from COVID-19, according to World Health Organization (WHO) figures till 13 April, 2020.

Due to its disseminating rate and fatality, COVID-19 is declared as pandemic disease by WHO and the whole world is fighting against it at war level. Every day a new case is coming from a different part of the world but China is only one country that is recovering every day by this disease which started in December 2019 and 74051 cases are recovered till now (Zhang et al. 2020). After China, USA and Italy has been affected most from the coronavirus followed by Spain, Germany Iran, and France. The outbreak of corona is also affecting India and till date 13 April 2020, total 8,447 total cases and 273 death reports from COVID-19.

Although appropriate vaccines and antiviral agents can effectively prevent and treat the COVID-19 infection but no effective drugs or vaccines that target the SARS-CoV-2 have been developed yet. This situation is putting the whole world under high pressure to develop of novel vaccine or drug against it. On the date, March 17, 2020, the USA reported starting vaccine trial against COVID-19 but it will take more than one year to come in markets. Therefore, effective treatment or control mechanism is needed to prevent Coronavirus (Huang et al. 2020). Consequently, to develop new drugs against COVID-19, we have conducted computational screening of compounds from lichen species which natural treasure for many type pharmacologically active compounds against coronavirus. Many lichen species have been reported to have antiviral, antibacterial and antifungal activity etc (Ingolfssdottir 2002; Molnar and Farkas 2009). Various scientific reports have suggested that lichen metabolites may a valuable treasure for anti-viral drug candidates (Esimone et al. 2009; Fazio et al. 2007; Molnar and Farkas 2009). Hence we were curious whether lichen compounds can also prevent SARS-CoV-2 or not and carried out virtual screening to find out potential anti-SARS-CoV-2 agents.

For the control of viral replication, inhibition of replication of viral genomic material is a good strategy for potential antiviral drug discovery (De Clercq 2002). Given that SARS-CoV-2 is a (+) SS RNA virus, its main protease (Mpro) cut two replicase polyproteins, which is required to mediate viral replication and transcription, Mpro can be used as molecular target for drug discovery. Thus by inhibiting the Mpro protein, virus replication could be stopped. Another protein named spike protein of SARS-CoV-2 can directly bind to angiotensin-converting enzyme 2 (ACE2) receptor of the host cell and mediates entry into the host cells, which could be targeted to stop infection (Wan et al. 2020). This is because the inhibition of ACE2 catalytic pocket by small molecules could change the conformation of ACE2 resulting in blockage SARS-CoV-2 entry in host cell (Towler et al. 2004). Therefore we selected two enzymes viral Mpro and human ACE2 receptor as drug targets to quickly identify novel inhibitors of SARS-CoV-2. To achieve this aim, 412 lichen compounds were selected for molecular docking using AutoDock Vina, based on literature search, to explore their binding modes with Mpro and ACE2. Furthermore, all screened hits were subjected to drug likeness investigation based on physiochemical properties using DruLiTo tool. The common screened compounds having druglike property and high binding affinity with both target proteins were taken for redocking using X-Score. Further, all screened hits were subjected for extensive toxicity analysis using the OSIRIS Property Explorer and resulting non-toxic compounds were further proceeded to study their antiviral activity by AVCpred server. Protein-ligand molecular interaction of compounds with remarkable inhibitory characteristics against the selected target proteins were viewed with PyMOL and LigPlus to gain structural insight into the binding interaction, including the types of bonding interaction and the amino acids involved in such interactions, compared to the their respective standard inhibitors. Finally all screened compounds were used for ligand-based pharmacophore studies to analyze common pharmacophore between the screened compounds and reference compounds (Figure 1).

Materials And Methods

2.1. Construction of library

Text mining analysis by using DLAD4U, PubTator and Carrot2 servers showed that several lichen spp. have anti-viral properties. Hence to screen anti-viral compounds against coronavirus, a library of 412 Lichen compounds was built in-house by collecting information from scientific literature (Huneck and Yoshimura 1928) and Herbal Net Digital Repository database [<http://herbalnet.healthrepository.org/>]. The compounds with known 2D structures in PubChem [<https://pubchem.ncbi.nlm.nih.gov>] and ChemSpider databases [<http://www.chemspider.com>] were considered to create the library.

2.2. Receptors Preparation

The COVID-19 main protease (Mpro) and Human ACE2 were selected as the target protein (Receptor) in this study. The X-ray crystal structure of COVID-19 Mpro covalently attached with their non-peptide inhibitor D3F (PDB ID-2GZ7) and human ACE2 covalently attached with its inhibitor XX5 (PDB ID-1R4L) were retrieved from the Protein Data Bank [<http://www.rcsb.org/pdb/home/home.do>] (Lu et al. 2006; Towler et al. 2004). Additional ligands, water molecules and ions were removed from the protein molecule using PyMOL software. After that, the addition of hydrogen atoms to both the receptor molecules was carried out by using AutoDockTools (ADT). Thereafter, non-polar hydrogens were merged while polar hydrogen were added to each protein. The process was repeated for both proteins and subsequently saved into dockable pdbqt format for molecular docking analysis(Figure 2).

2.3. Ligand preparation

The 3D structure of reference molecules, D3F and XX5 which was co-crystallized with protein 2GZ7 and 1R4L respectively were retrieved from the respective protein from Protein Data Bank in SDF format. The 3D structure of each ligand (lichen compound) was obtained from various online resources and compound databases e.g. PubChem, ZINC, and CHEM SPIDER in mol or SDF format. The compounds were converted to mol2 chemical format using Open babel. Polar hydrogen charges were assigned and the nonpolar hydrogens were merged by using Autodock tools. Finally, the compounds were further converted to the dockable pdbqt format.

2.4 Molecular Docking

In order to achieve the mode of interaction of Lichen compounds with the binding pocket of COVID-19 Mpro and human ACE2, molecular docking was performed by using AutoDock Vina software in PyRx platform (GUI version 0.8). Firstly docking was performed with reference molecules of respective proteins to validate docking protocol. Using PyRx software, the grid box centered for 2GZ7 was X= -24.86, Y= -43.82, and Z= 2.08 and the dimensions of the grid box were set as 59.87 × 31.93 × 42.32Å and for 1R4L was X= 45.52, Y= 8.49, and Z= 32.68 and the dimensions of the grid box were set as 36.24 × 35.80 × 45.41Å. After validation of the docking protocol, virtual screening was conducted by rigid docking into the active site of each protein. The binding modes were clustered through the root mean square deviation (RMSD) among the coordinates of the ligand atoms. The compounds were then ranked by their binding affinity Scores. Thereafter, molecular interaction between Mpro and ACE2 and compounds with binding

affinity higher than that of respective reference compounds (standard inhibitors) were viewed with PyMOL.

2.5 Drug Likness analysis and toxicity prediction

The pharmacological significance of any compound is based on its drug bioavailability or drug-likeness which is calculated based on certain physicochemical properties. Therefore, all ligands were evaluated for its druglike nature by DruLiTo software. Lipinski's rule of five (RO5) which was considered as an empirical thumb rule for evaluating the druggability of small molecules was used to filter the compounds based on their drug-likness property (Lipinski 2000).

2.6 Docking validation

The best molecules from molecular docking, drug-likeness were re docked using the X-SCORE program (Wang, Lai, & Wang, 2002). X-Score is a scoring function to calculate the binding affinity of the ligand molecules toward their target protein. The same binding pocket was selected for docking studies that was used in virtual screening. Two different kinds of files required in X-Score is a receptor structure file (in pdb format) and a ligand structure file (in mol2 format). Both the structure files were used as an input file to carry out X-score analysis. After that binding energy of the protein-ligand complex was calculated by using the X-score command. All default parameters of X-Score were used. The X-Score program uses three scoring functions viz. HP Score, HM Score, and HS Score. The final X-Score = (HP Score + HM Score + HS Score).

2.7 Toxicity risk and antiviral activity prediction

The compounds having druglike property and good binding affinity with both receptors were taken for the extensive toxicity analysis using the OSIRIS Property Explorer (Halgren et al. 2004). All the screened compounds that were drug-like and nontoxic were further proceeded to study their antiviral activity and percentage inhibition of several viruses by using AVCpred server (Qureshi et al. 2016).

2.8 Visualization

PyMOL was used to visualize the docked pose of screened compounds at the active site of the receptor. The 2D interactions of the protein-ligand complexes were performed by LigPlot+ v.1.4.5 program to identify the interactions of an amino acid between protein and ligand complexes. LigPlot depicted hydrophobic bonds, hydrogen bonds, and their bond lengths in each docked pose.

2.9 Pharmacophore Study

All screened compounds were finally used for ligand-based pharmacophore studies. To analyze the important pharmacophore features in reference compounds as well as screened compounds, the pharmacophore models were generated by using Pharmit web server (<http://pharmit.csb.pitt.edu/>). After

that common pharmacophore between the screened compounds and reference compounds were analyzed.

Result And Discussion

The molecular docking, virtual screening (VS), the assessment of physicochemical properties and bioavailability of lead compounds play a crucial role in searching of novel and potential lead molecules to the protein targets associated with human diseases (Mishra et al. 2018; Peterson et al. 2019). However, the feasibility of large-scale virtual screening mainly depends on deciding the accurate target, selection of suitable chemical compound dataset and the critical assessment of pharmacokinetic profiles of lead molecules (Verma et al. 2018). We employed virtual screening of compounds from lichen compounds library for the viral target 2GZ7 and human target 1R4L involve in COVID-19. Molecular docking, drug-likeness, toxicity, and pharmacophore analysis of lead molecules showed fifteen promising hits that can be evaluated as antiviral molecules to control the global health crisis of COVID-19 (Figure 1).

3.1 Virtual Screening

Before conducting virtual screening, molecular docking protocol was validated by docking the reference ligands, D3F and XX5 into their binding pocket obtained from crystal structure of target proteins, 2GZ7 and 1R4L respectively. The docked ligands were superimposed to compare with co-crystallized ligands. The result revealed that both the docked reference molecules, D3F as well as XX5 were completely superimposed with that of co-crystallized reference molecule and both ligands showed interaction with the same amino acid residues by hydrogen as well as hydrophobic bonds as found in the crystal structure of 2GZ7 and 1R4L respectively (Figure 3). Thus, this protocol was considered good enough for reproducing the docking results similar to X-ray crystal structure and therefore can be applied for further docking experiments.

The virtual screening of all lichen compounds ($n = 412$) was performed by molecular docking in the active site of both target proteins using AutoDock Vina. From molecular docking, a total of 80 compounds were screened which showed binding energy ranging from -14.5 to -7.6 kcal mol⁻¹ against 2GZ7 and -17.6 to -9.4 kcal mol⁻¹ against 1R4L. The binding energy of reference molecule, D3F was -7.50 kcal mol⁻¹ and of XX5 was -9.3 kcal mol⁻¹ (Table 1). All screened hits showed lower and significantly better binding energy against both the target proteins in comparison to their respective reference molecules. The molecular docking result suggest that screened compounds may have the same mechanism of action as the reference molecules. Then, all these 80 compounds and the reference compounds were further employed for Drug-likeness prediction.

3.2 Drug Likness analysis

It has been reported that drug molecules showing good binding affinity with the target protein may fail in clinical trial at advanced stages of drug discovery due to lack of druglikeness i.e. drugability, bioavailability, and solubility (Hoelder et al. 2012). Hence we analyzed drug likness of screened

compounds using DruLiTo software. DruLiTo can calculate more than 23 physicochemical properties which are important for evaluating the drug-likeness of a molecule. Here, the drug-likeness was measured under the empirical thumb rule of drug-likeness i.e. Lipinski rule of 5. According to Lipinski's RO5, that most "drug-like" molecules have $\text{Log P} \leq 5$, molecular weight ≤ 500 , number of hydrogen bond acceptors ≤ 10 , and number of hydrogen bond donors ≤ 5 . Among the eighty compounds, twenty seven compounds showed better pharmacokinetics and successfully passed in RO5 evaluation. The compounds which show better pharmacokinetics and satisfy the fundamental RO5 are accepted as drug-like molecules. As per the RO5 filter, the drug-likeness result of hit compounds is shown in Table 2.

3.3 Docking validation

X-Score is normally used to validate the binding energies of the protein-ligand complex. Thus, we used X-Score to re-validate the binding energies of screened hits. Out of 27, seven compounds were finally screened by X-Score. The X-Score associated Binding energy of reference compounds and seven screened hits against both the target protein are compiled in Table 1. Among the seven molecules, Fremontol shows the highest X-Score with both Mpro as well as ACE2 followed by Gyrophoric acid and Ovoic acid. All the screened hit shows good X-Score as compare to reference molecules, FLC and 3np.

3.4 Toxicity risk and antiviral activity prediction

The US Food and drug administration toxicity risk predictor tool OSIRIS and AdmetSAR server used to predict the toxicity of screened compounds (Mabkhot et al. 2016). OSIRIS predicted various toxicity risks properties such as tumorigenicity, mutagenicity, irritation, and reproductive development toxicity. The results of OSIRIS prediction for all seven hit compounds are summarized in Table 3. The drug-score show ranges between 0 to 1, where the value 1 indicates the good possibility of a compound to be drug molecule, whereas, the score value 0 indicates that compounds having no possibilities of drug candidates. The toxicity test shows that reference molecule, D3f have a medium risk for reproductive toxicity. Reference molecule XX5 as well as all the screened hits are non-AMES toxic and show no risk of reproductive toxicity, irritation, tumorigenicity, and mutagenicity.

All the seven bioactive compounds those have good binding affinity, drug-like and non-toxic are further proceeded to predict their antiviral activity and percentage inhibition of several viruses like General (26 viruses), Human Immunodeficiency Virus (HIV), Hepatitis C Virus (HCV), Hepatitis B Virus (HBV), Human Herpes Virus (HHV) by using AVCpred web server. The percentage inhibition values suggested that all the hit compounds can be used to develop antimicrobial drugs for treating viral infections (Table 4).

Thus, considering the molecular docking, drug-likeness, toxicity and antiviral activity prediction results we observed that seven lichen compounds viz. Orcinyllecanorate, Siphulin, Fremontol, Gyrophoric acid, Rhizocarpic acid, Ovoic acid, and Umbilicaric acid may be exploited as promising drug candidates for the development of antiviral drug molecules against COVID-19.

3.5 Visualization

The 2D interactions of the screened ligands as well as reference compounds, in the active sites of the receptor, were visualized by using LigPlot+ v.1.4.5 software. The Reference molecule **D3F** shows interaction with the several residues of 2GZ7 and forms two hydrogen bonds with His41 and Gln192 and four hydrophobic bonds with Glu166, Asp187, His164, and Arg188 and yields the binding energy is $-7.5 \text{ kcal mol}^{-1}$. Other hit compounds also interact with the active site residues of 2GZ7 receptor (Figure 4 & Supplementary Table S1). Similarly, the Reference molecule **XX5** shows active interaction with the several residues of 1R4L and forms six hydrogen bonds with Thr371, His345, His505, Arg273, Tyr515, and Pro346, and yields the binding energy $-9.3 \text{ Kcal.mol}^{-1}$. Additionally, the 1R4L-**XX5** complex also exhibits hydrophobic interactions with Glu375, His378, Tyr510, Phe504, Glu402, and Agr514. Other hit compounds also interacted with the active site residues of 1R4L receptor (Figure 5 & Supplementary Table S1).

From the analysis of 2D molecular interaction between protein-ligand complexes, we observed that most of the hit compounds show common interaction and are involved in H-bond interaction and hydrophobic interaction with the same residue as shown in Supplementary Table S1 which suggested the crucial role of hydrogen and hydrophobic interactions to hold the ligand at the active site of target protein.

3.6 Pharmacophore Study

Pharmacophore features which are important the biological activity are useful in drug discovery. Therefore, we used Pharmit server to analyze important pharmacophore features of hit compounds and reference molecules. For that, seven hit compounds, and both reference molecules were subjected to ligand-based pharmacophore modeling. The Pharmit server predicted several pharmacophore features like hydrogen-bond acceptor, hydrogen-bond donor, aromatic ring and hydrophobic group, positive and and negative ion etc which may be useful to understand specific activity of molecules.

The common pharmacophores from the reference molecule (**D3F**) showed six hydrogen bond acceptors, six hydrophobic groups, two aromatic rings, two positive ions and two negative ions (Figure 6(a)). Second reference molecule (**XX5**) showed six hydrogen bond acceptor (Yellow), one hydrogen bond donor (White), five hydrophobic groups (Green), two aromatic rings (Purple) and two negative ions (Red) (Figure 6(b)) and seven screened molecules showed two hydrogen bond acceptor (Yellow), two hydrophobic groups (Green), two aromatic rings (Purple) (Figure 6(c)). Two hydrogen bond acceptors (Yellow), two hydrophobic groups (Green) and two aromatic rings (Purple) were common pharmacophores in all structures that are useful for binding with receptors.

Conclusion

COVID-19 becomes a global concern, due to widespread outbreaks and lack of treatment. Therefore, it is necessary to find and evaluate treatment methods more quickly. In this case, computational methods are very effective and helpful. In this study, we employed various computational methods, virtual screening, drug-likeness analysis, toxicity prediction, antiviral activity and pharmacophore analysis for the identification of novel lead molecules as potential inhibitors for Mpro and ACE2, the protein belongs to

COVID-19. Here, we used a broad library of lichen compounds for screening purposes. Based on molecular docking, and binding affinity a total 80 hit molecules were selected as lead compounds against Mpro (2GZ7) and ACE2 (1R4L). Using the extensive pharmacokinetic drug-likeness analysis we obtained 27 compounds which followed the Lipinski's RO5. The X-Score, toxicity and antiviral activity predicted seven compounds that were non AMES-toxic and having no mutagenicity, tumorigenicity and other effects, as well as they all, are antiviral compounds. These observations suggested that these lichen compounds may be explored as a novel lead molecule for the rapid development of suitable drug candidates against COVID-19.

Declaration

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Conflict of interest

The authors declare that there is no competing interest in this work.

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Tables

Table 1- Summary of Molecular Docking and X-Score between molecular targets and screened hits.

S. No.	Name of Common Hit Compound	Compound ID	Binding Affinity with Molecular Targets of COVID-19 (kcal mol ⁻¹)			
			2GZ7		1R4L	
			AutoDock Vina	X-Score	AutoDock Vina	X-Score
1	Reference		-7.5	-8.21	-9.3	-9.2
2	Orcinyllecanorate	CID 101642999	-8	-8.65	-10.8	-9.91
3	Siphulin	CID 21676270	-7.9	-8.63	-9.5	-9.65
4	Fremontol	CID 5487269	-8.3	-9.41	-9.6	-9.26
5	Gyrophoric acid	CID 135728	-8.7	-9.21	-10.1	-9.2
6	Rhizocarpic acid	CID 54733074	-8.2	-8.82	-10.2	-9.88
7	Ovoic acid	CID 14647824	-8.8	-9.14	-10.1	-9.25
8	Umbilicaric acid	CID 12444590	-8.3	-9.08	-10	-9.22

Table 2- The parameters showing different types of physiochemical properties of screened hits.

S. No.	Name of Compound	Mw	LogP	HBA	HBD	Solubility (LogS)	Lipinski Rule Violation	Drug-likeness alert
1	Reference D3f (2GZ7)	403.93	2.387	7	0	-6.67	0	Accepted
2	Reference XX5 (1R4L)	450.88	0	2	0	-3.07	0	Accepted
3	Orcinyllecanorate	424.12	3.604	8	4	-4.4	0	Accepted
4	Siphulin	426.17	4.65	7	4	-5.03	0	Accepted
5	Fremontol	422.17	4.968	6	4	-4.74	0	Accepted
6	Gyrophoric acid	468.11	3.566	10	5	-4.42	0	Accepted
7	Rhizocarpic acid	469.15	4.483	7	2	-4.22	0	Accepted
8	Ovoic acid	482.12	3.458	10	4	-4.73	0	Accepted
9	Umbilicaric acid	482.12	3.458	10	4	-4.73	0	Accepted

Table 3- Toxicity profile of the screened hits by OSIRIS and AdmetSAR server.

S. No.	Name of Compound	Toxicity	Mutagenic	Tumerogenic	Irritant	Reproductive effect	Drug score
1	Reference D3f (2GZ7)	Non - toxic	No risk	No risk	No risk	Medium risk	0.18
2	Reference XX5 (1R4L)	Non - toxic	No risk	No risk	No risk	No risk	0.4
3	Orcinyllecanorate	Non - toxic	No risk	No risk	No risk	No risk	0.13
4	Siphulin	Non - toxic	No risk	No risk	No risk	No risk	0.27
5	Fremontol	Non - toxic	No risk	No risk	No risk	No risk	0.24
6	Gyrophoric acid	Non - toxic	No risk	No risk	No risk	No risk	0.13
7	Rhizocarpic acid	Non - toxic	No risk	No risk	No risk	No risk	0.36
8	Ovoic acid	Non - toxic	No risk	No risk	No risk	No risk	0.34
9	Umbilicaric acid	Non - toxic	No risk	No risk	No risk	No risk	0.36

Table 4- antiviral activity of screened hits showing percentage inhibition of various viruses.

S. No.	Name of Compound	General Virus	HBV	HCV	HHV	HIV
	Reference (D3F)	62.56	27.49	35	49.32	74.15
1	Reference (XX5)	56.63	23.1	43.214	35.02	70.08
2	Orcinyllecanorate	47.38	23.81	58.93	52.63	61.09
3	Siphulin	32.25	18.91	44.51	46.78	64.23
4	Fremontol	36.99	20.45	65.6	47.91	56.37
5	Gyrophoric acid	47.58	20.29	59.07	51.53	61.16
6	Rhizocarpic acid	51.5	22.36	42.85	61.82	71.57
7	Ovoic acid	52.96	20.24	46.37	51.4	60.49
8	Umbilicaric acid	47.68	20.24	54.72	51.41	61.29

Figures

Figure 1

Figure 1- Schematic representation of various steps of the methodology.

Figure 2

Figure 2- X-ray crystal structure of COVID-19 Mpro (a) and human ACE2 (b) covalently linked to their inhibitors.

Figure 3

Figure 3- The superimposition of the docked D3F (a) and XX5 (b) with its X-ray crystal structure. Light blue and dark blue colour indicates Docked and Experimental ligand respectively. The dotted lines and attached residues indicates H-bond and H-bonding residues and residues present in the half circle

represent the hydrophobic bond forming residues and red circle shows the Superimposed interacting residues.

Figure 4

Figure 4- 2D Interactions of D3F (a) and screened compounds (b-g) with the active site of Mpro. The 2D ligand structures are represented as thick purple sticks and the residues of the binding site as brown sticks and those involved in the hydrophobic interactions are depicted with the red eye-lashes and hydrogen bond showed by green (—) line.

Figure 6

Figure 6- Common pharmacophore for reference molecule, D3F (a) and XX5 (b) and all screened compounds (c).

Supplementary Files

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